Descending motor pathways and the spinal motor system. Limbic and non-limbic components

Descenderende motorische baansystemen en het spinale motorische systeem. Limbische en niet limbische componenten

Proefschrift

Ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de Rector Magnificus
Prof. Dr. C.J. Rijnvos
en volgens besluit van
het College van Dekanen.

De openbare verdediging zal plaats vinden op
woensdag 19 september 1990 om 15.45 uur

door

Gerrit Holstege

Geboren te Warnsveld

PROMOTIECOMMISSIE

Promotoren:

Prof. Dr. H. Collewijn

Prof. Dr. J. Voogd

Overige leden:

Prof. Dr. R. Nieuwenhuys
Afd. Anatomie,
Katholieke Universiteit Nijmegen

Prof. Dr. H.J. Ralston III
Dept. Anatomy,
University of California San Francisco

Het schrijven van dit proefschrift werd mede mogelijk gemaakt door een NASA Grant (NCC 2-491) aan Gert Holstege.

Ontwerp omslag: R.D.E. Oxenaar

Aan Marianne

Aan Henne, Floor en Gert Jan

Dit proefschrift is identiek aan het laatste hoofdstuk van een in 1991 te verschijnen deel van Progress in Brain Research: "Role of the forebrain in sensation and behavior", (Ed. G. Holstege), Elsevier Science Publishers B.V. Amsterdam Nederland.

Dit deel van Progress in Brain Research zal de voordrachten bevatten van de sprekers op het congres, gehouden op 26 en 27 mei 1989 op NASA/Ames Research Center, Moffett Field California, ter gelegenheid van het afscheid van William R. Mehler als senior scientist op NASA/Ames.

De lay-out van dit proefschrift werd vervaardigd op een Apple Macintosh IIci computer met behulp van het programma Pagemaker en Adobe Illustrator 88.

Table of Contents

A. Introduction

For a thorough understanding of the descending pathways of the motor system originating in the forebrain, knowledge about the anatomy and function of the structures in the more caudally located parts of the central nervous system is indispensable. In this paper an overview will be presented of these caudal structures in brainstem and spinal cord as far as they concern the motor system, (sections 1 to 3). After that the descending pathways belonging to the so-called somatic motor system are reviewed (section 4). Finally, a summary of the many newly discovered pathways related to the limbic system will be given (section 5). In the Conclusions section a concept will be presented, which subdivides the multitude of motor pathways into three motor systems. In this concept the motoneurons will be considered to belong to the peripheral motor system, (motor unit, which is the motoneuronal cell body-motor axon-muscle). The first motor system consists of the interneurons involved in motor reflex pathways. The second motor system contains the pathways of the so-called somatic motor system, while the third motor system comprises the motor pathways related to the limbic system. The second and third motor systems act upon the neurons of the first motor system and to a limited extent directly on motoneurons, but not on each other. The importance and strength of the third motor system, which, untill recently, was virtually unknown, will be emphasized.

B. Description of the spinal motor system and the descending motor pathways

1. Somatic and autonomic motoneurons in spinal cord and brainstem

1a. Somatic motoneurons in the spinal cord

The somatic motoneurons innervate striated muscles of body and limbs. They are located in the ventral part of the ventral horn of the spinal cord, called lamina IX by Rexed (1952; 1954). The motoneurons innervating one particular muscle form a group, occupying a circumscribed portion of lamina IX. Rostrocaudally such a cell group can extend from one segment, (for example the medial gastrocnemius and soleus motor nuclei in the cat, which are located within the confines of the L7 spinal segment (Burke et al., 1977), up to 19 segments (the longissimus dorsi muscle motoneuronal cell group, which, according to Holstege et al., (1987), extends from C8 to L5). The motoneuronal cell groups can be subdivided into a medial and a lateral motor column. The medial motor column is present throughout the length of the spinal cord and its motoneurons innervate the axial muscles, which include the neck muscles. In the cat the lateral motor column is only present at the levels C5 to the upper half of T1 (cervical enlargement) and from L4 to S1 (lumbosacral enlargement). Motoneurons in the cervical and lumbosacral lateral column innervate the muscles of the fore- and hind-limbs respectively.

The axial musculature, innervated by motoneurons in the medial motor column, consists of epaxial and hypaxial muscles. The epaxial muscles are innervated by branches of the dorsal rami of a spinal nerve and the hypaxial muscles by branches of the ventral rami. In the ventral horn, motoneurons innervating epaxial muscles are always located ventral to the motoneurons innervating hypaxial muscles (Sprague, 1948; Smith and Hollyday, 1983). The epaxial muscles function as extensors and lateral flexors of the head and vertebral column. They also fix the vertebral column and some of them (the rotators) rotate the vertebral column about its longitudinal axis.

1a 1. **Upper cervical cord.** Motoneurons in the upper cervical cord innervate the neck muscles. Epaxial neck muscles are the biventer cervicis, complexus, the suboccipitally located rectus dorsalis capitis major, medius and minor, the obliquus capitis cranialis and caudalis, the splenius and longissimus capitis. They are mainly involved in extension or elevation of the head, al-

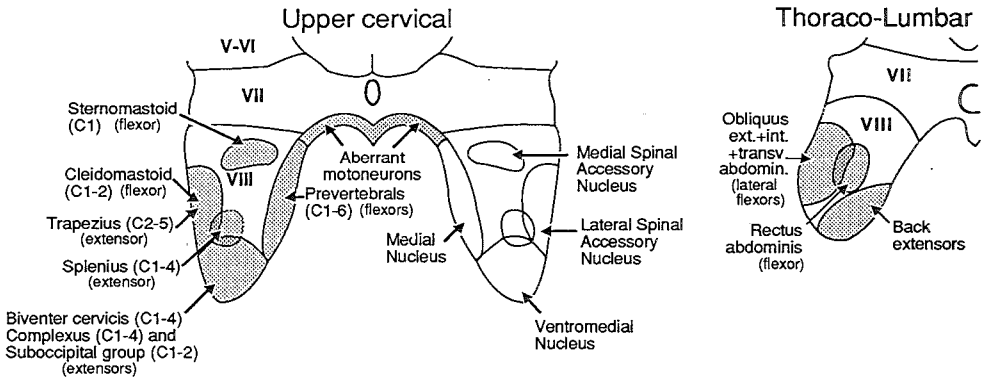


Fig. 1: Schematic representation of the combined C1-4 and T10-L2 spinal segments. The motoneuronal cell groups innervating specific neck and axial muscles are shown. The general action of these muscles and the precise cervical cord location of the neck muscle motoneurons are also indicated. It must be emphasized that the cell groups not only contain motoneurons but also interneurons, (from Holstege and Cowie, 1989).

though unilateral contraction of the biventer cervicis, complexus and splenius muscles draws the head dorsally and laterally. Examples of hypaxial neck muscles are the prevertebral muscles (longus capitis, rectus capitis ventralis and rectus capitis lateralis), the sterno- and cleidomastoid muscles and the trapezius. All hypaxial muscles are involved in ventral and lateral flexion of head and neck. The upper portion of the trapezius muscle, the clavotrapezius, overlies all dorsal neck muscles and acts as an extensor and rotator of the head. All three superficial muscles are innervated by the spinal accessory nerve. Several reports exist on the location of the neck muscle motoneuronal cell groups in the cat, which are summarized by Holstege and Cowie (1989). Figure 1 gives an overview of the location of these motoneurons in the upper cervical ventral horn, indicating that the epaxial muscle motor cell groups are situated ventral to the hypaxial muscle motoneurons. Holstege and Cowie (1989) have emphasized the fact that the action, structure and fiber composition of the clavotrapezius, splenius and cleidomastoid muscles (Richmond and Abrahams, 1975) appear best suited to produce rapid or phasic torsional movements of the head such as might occur during orienting movements (Callister et al., 1987). On the other hand, the biventer cervicis, occipitoscapularis, semispinalis cervicis and rectus capitis dorsalis and probably also the prevertebral muscles, are all involved in more tonic aspects of head position (Richmond and Abrahams, 1975; Richmond et al., 1985a,b; Roucoux et al., 1985). Note that the subdivision of the neck muscles into muscles involved in phasic (orienting) and tonic (head position) function does not follow the subdivision into epaxial and hypaxial muscles, but motoneurons innervating phasic muscles are always located lateral to the motoneurons innervating tonic muscles (Fig. 1). Such a functional subdivision is important, because the descending pathways project differently to the upper cervical ventral horn (see section 4 a 2).

1a 2. **Phrenic nucleus.** The phrenic nucleus occupies a special position among the somatic motoneuronal cell groups, because its motoneurons innervate the diaphragm. Although the diaphragm is an axial muscle, it plays an essential role in respiration, which function is virtually independent of that of the other axial muscles. In the cat the phrenic nucleus is located in the ventromedial part of the ventral horn at the level of the most caudal portion of C4 and throughout the rostro-caudal extent of C5 and C6 (Duron et al., 1979). Phrenic motoneurons at the C5 level preferentially innervate the costal region of the diaphragm, while those in the C6 portion of the nucleus innervate the crural region (Duron et al., 1979). There are almost no muscle spindles in the diaphragm (Duron et al., 1978) or g-motoneurons in the phrenic nucleus. Propriospinal projections to the phrenic nucleus have not convincingly been demonstrated anatomically (see section 2 c 5), but the nucleus receives a great number of afferent fibers from specific brainstem areas (see section 3 a 1). Sterling and Kuypers (1967) found a remarkable high number of rostro-caudally ori-

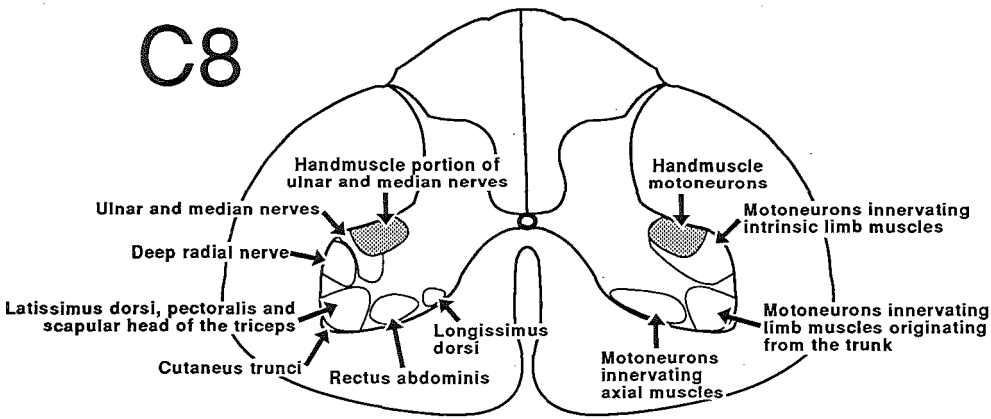


Fig. 2. Schematic overview of the location of the motoneuronal cell groups at the C8 level in the cat. The left side of the scheme shows the cell groups, the location of which has been studied using retrograde degeneration or tracing techniques (Sterling and Kuypers, 1967; Fritz et al., 1986a,b; Holstege et al., 1987 and Mc Curdy et al., 1987). On the right side of the scheme a more general subdivision into four motoneuronal cell groups has been made.

ented dendrites within the phrenic nucleus, and the cell somata were elongated in a rostro-caudal direction (Cameron et al., 1983). On the other hand, Cameron et al. (1983), using intracellular HRP staining techniques, confirmed that the majority of the dendrites extended rostro-caudally within the phrenic motor column, and showed some dendrites of phrenic motoneurons extending in dorsolateral and dorsomedial directions. Many of the dorsomedial dendrites cross the midline in the anterior commissure or through the central gray. The dorsolaterally directed dendrites form bundles upon entering the lateral funiculus with the dendrites from other phrenic motoneurons (Cameron et al., 1983).

1a 3. **Cervical enlargement.** At the level of the C5 to T1 spinal segments in the cat the medial motor column is located in the ventral portion of the ventral horn. Only very few retrograde tracing studies exist about the exact location of the medial column motoneurons at this level. The epaxial muscle motoneurons, for example those innervating the longissimus dorsi, are located in the medial part of this area, while hypaxial muscle motoneurons such as those innervating the most rostral rectus abdominis, are located just lateral to the longissimus neurons (Holstege et al., 1987). Muscles with their origin at the vertebral column (latissimus dorsi) or chest (pectoralis and deltoid muscles), but with insertion on the humerus, produce forelimb movements (Crouch, 1969). Therefore they are not considered axial, but limb muscles. Sterling and Kuypers (1967) call them girdle muscles. Their motoneurons take part in the lateral motor column and are located in the ventral part of the ventral horn, lateral to the axial muscle motoneurons, but ventral to the intrinsic limb muscle motoneurons (Sterling and Kuypers, 1967; Holstege et al., 1987) (Fig. 2). A very special place is occupied by a cell group in the most ventrolateral part of the ventral horn, named nucleus X by Giovanelli Barilari and Kuypers (1969) or ventral motor nucleus by Matsushita and Ueyama (1973). Only recently (Baulac and Meininger, 1981; Haase and Hrycyshyn,1985 and Theriault and Diamond, 1988b in the rat; Krogh and Towns, 1984 in the dog; Holstege et al., 1987 in the cat) this cell group has been demonstrated to contain motoneurons innervating the cutaneus trunci or cutaneus maximus muscle, which extends over the thoracic and abdominal regions of the body, covering the underlying muscles like a veil (see section 2 c 4). Motoneurons innervating muscles intrinsic to the forelimb are located more dorsally in the ventral horn, and the motoneurons innervating the most distal (hand-) muscles are located most dorsally (Fritz et al., 1986a,b; McCurdy et al., 1987) (Fig. 2). The difference in location between proximal and distal muscle motoneurons is nicely shown by Sterling and Kuypers (1967), who noted that the motoneurons of the

scapular head of the triceps muscle were located more ventral in the ventral horn than those innervating the medial and lateral heads of this muscle, which are intrinsic to the forelimb.

1a 4. **Thoracic and upper lumbar spinal cord.** At thoracic and upper lumbar levels, in rat and cat all the motoneurons belong to the medial motor column. Many of them innervate the epaxial extensor muscles of the trunk, and are located in greatly overlapping cell columns in the ventromedial portion of the ventral horn, largely segregated from the overlapping cell groups of the motoneurons innervating the hypaxial muscles which lie dorsolateral in the ventral horn (Brink et al., 1979; Smith and Hollyday, 1983; Miller, 1987; Holstege et al., 1987, Fetcho, 1987, Lipski and Martin-Body, 1987; Fig. 1). The hypaxial muscles include the abdominal (external and internal abdominal oblique, the transversus abdominis and the rectus abdominis) and the internal and external intercostal muscles. The abdominal muscles are involved in postural functions such as flexion and bending of the trunk, but they also play an important role in increasing the intra-abdominal pressure during defecation, vomiting and forced expiration (see Holstege et al., 1987 for review). Except for those innervating the rectus abdominis muscle, abdominal muscle motoneurons are scarce at upper thoracic levels, but are very numerous at low thoracic and upper lumbar segments (Holstege et al., 1987; Miller, 1987; Fig. 3). In the cat, at low thoracic and upper lumbar levels, the motoneuronal cell group innervating the rectus abdominis muscle (a medial hypaxial flexor) is located medial to the cell column of motoneurons innervating the other abdominal muscles, but dorsal to the epaxial muscle motoneurons (Miller, 1987; Holstege et al., 1987; Fig. 3). The intercostal muscles (internal and external) are inserted between adjacent ribs and their contraction decreases the distance between these ribs. The inter-

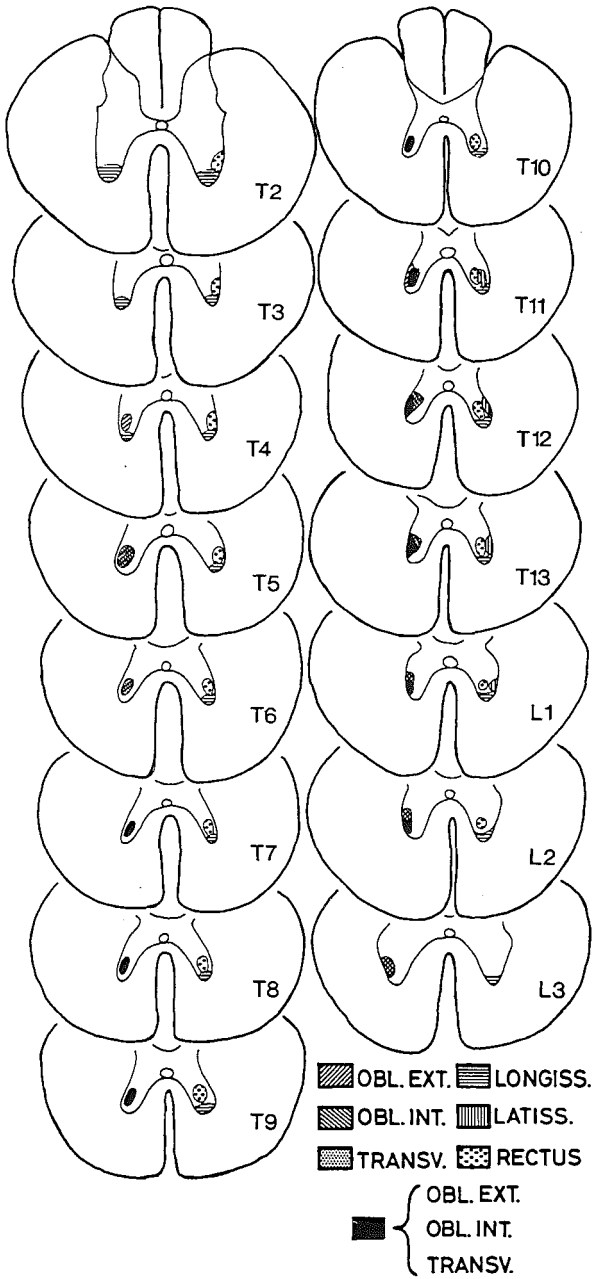


Fig. 3. Location of the motoneuronal cell groups innervating the hypaxial abdominal and latissimus dorsi muscles and the epaxial longissimus dorsi muscle (from Holstege et al., 1987).

costal muscles are important for posture control, but they play a role in respiration also. Until recently it was generally been held that the external intercostal muscles are inspiratory in nature, while the internal intercostal muscles are expiratory. A recent study of Lipski and Martin-Body (1987) confirmed that all external intercostal motoneurons were inspiratory, but they also found that at upper thoracic levels three times as many internal intercostal motoneurons were inspiratory than expiratory. Apparently at upper thoracic levels expiratory motoneurons are scarce, since only a limited number of abdominal muscle motoneurons, which are all expiratory, was present at these levels (Holstege et al., 1987; Fig. 3). Conversely, at low thoracic levels all internal intercostal motoneurons were expiratory (47% of the total intercostal motoneuronal population). At these levels only very few external intercostal motoneurons were expiratory (5% of the total intercostal motoneuronal population), while 48% were non-respiratory (Lipski and Martin-Body, 1987). Furthermore the location of the expiratory intercostal motoneurons at low thoracic levels overlaps greatly with the location of the expiratory abdominal muscle motoneurons, which are quite numerous at these levels (Lipski and Martin-Body, 1987; Holstege et al., 1987; Miller, 1987). In conclusion, inspiratory motoneurons are mainly located at upper thoracic levels, and expiratory motoneurons at low thoracic and upper lumbar levels.

1a 5. **Lumbosacral enlargement.** The location of the motoneuronal cell groups at the lumbosacral enlargement (L4 to S1 in the cat) is very similar to the one of the cervical enlargement. The study of Romanes (1951) is still the most extensive on this subject, although there exist more recent retrograde HRP tracing studies of Burke et al. (1977) on the location of the medial gastrocnemius and soleus motor nuclei and Horcholle-Bossavitet al. (1988) on the location of the peroneal motoneuronal cell groups. The position of the motoneuronal cell groups in the lumbosacral enlargement is very similar to that of the motoneurons in the cervical enlargement. For example, in both enlargements the motoneurons innervating the distal muscles of the limbs are located in the dorsal portions of the ventral horn, while those innervating proximal limb muscles occupy a more ventral position. Furthermore, the motoneurons of the most distal muscles are always located in the caudal part of the enlargement, for example at the level C8-T1 for the small hand-muscle motoneuronal cell groups and at the level L7-S1 for the small foot-muscle motoneurons. Trunk muscle motoneurons are always located within the medial column (Brink et al., 1979).

1a 6. **Nucleus of Onuf.** Onufrowicz (1899), who called himself Onuf, described a group X in the ventral horn of the human sacral spinal cord, extending from the caudal S1 to the rostral S3 segments. According to Onuf, motoneurons in his nucleus X would be involved in erection and ejaculation, but they would also innervate the striated muscles of the urethral and anal sphincters. Romanes (1951) in the cat described a homologous cell group in the caudal half of the first and the rostral half of the second sacral segment and called it group Y. The cell group is now known as nucleus of Onuf (Fig. 4). Later retrograde HRP tracing studies in the cat (Sato et al., 1978; Mackel, 1979; Kuzuhara et al., 1980; Ueyama et al., 1984; Holstege and Tan, 1987) demonstrated that Onuf motoneurons, via the pudendal nerve, innervate the striated muscles of the pelvic floor, including the urethral and anal sphincters. Within Onuf's nucleus the dorsomedial motoneurons innervate the anal sphincter, while the ventrolateral motor cells innervate the urethral sphincter (Sato et al., 1978; Kuzuhara et al., 1980; Holstege and Tan, 1987; Pullen, 1988). The motoneurons in the nucleus of Onuf are characterized by their dense packing, their relatively small size (however, see Pullen, 1988), and their numerous longitudinal dendrites (Dekker et al., 1973). Although in cat (Sato et al., 1978; Mackel, 1979; Kuzuhara et al., 1980; Ueyama et al., 1984; Holstege and Tan, 1987), monkey (Roppolo et al., 1985) and man (Schrøder, 1981) Onuf's nucleus consists of a single motoneuronal pool, in rat it consists of two spatially separate motoneuronal groups, with those innervating the anal sphincter being located at the medial gray border just ventral to lamina X (Schrøder, 1980; McKenna and Nadelhaft, 1986). There is evidence that Onuf motoneurons belong to a separate class of motoneurons. On the one hand they are somatic motoneurons, because they innervate striated muscles and are under voluntary control, but on the other hand they are autonomic motoneurons because; 1: cytoarchitectonically they resemble autonomic motoneurons (Rexed, 1954; Fig. 4); 2: they have an intimate relationship with sacral parasympathetic motoneurons (Holstege and Tan, 1987; Nadelhaft et al., 1980; Rexed, 1954); 3: they receive direct hypotha-

lamic afferents (Holstege, 1987; Holstege and Tan, 1987) and 4: unlike the somatic motoneurons, but similar to the autonomic motoneurons, they are well preserved in the spinal cords of patients who have died from amyotrophic lateral sclerosis (ALS), (Mannen et al., 1977; 1982). Because the sacral autonomic (parasympathetic) motoneurons innervating the bladder are also spared in ALS patients, bladder and sphincter functions remain intact until the latest stages of the disease.

1b. Autonomic motoneurons in the spinal cord

1b 1. Sympathetic preganglionic motoneurons

The sympathetic motoneurons project to the chromaffin cells of the adrenal gland, and to the postganglionic neurons in the sympathetic trunk, the sympathetic chain of ganglion cells, in which the peripheral sympathetic system originates. In the rat the superior, middle and inferior (stellate) cervical ganglia receive their input from preganglionic motoneurons in the T1-T5 spinal segments, with a minor contribution of C8 and T6-T7 segments (Strack et al., 1988). The adrenal gland receives its sympathetic input from preganglionic cells in the T5 to T11 segments, with the emphasis on T8. The celiac, aortico-renal and superior mesenteric ganglia receive their main input from the T8 to T12 segments and the inferior mesenteric ganglion from the T13-L2 segments (Strack et al., 1988). About 25% of the preganglionic cells in the T1-T5 segments projecting to the cervical ganglia are located in the lateral funiculus, around 70% in the intermediolateral cell column (IML) and a total of 5% in the central autonomic cell group (CA) around the central canal (Rexed's (1954) lamina X) and in the area in between the IML and CA, called the intercalated nucleus (Strack et al., 1988; Fig. 5). The number of preganglionic motoneurons in the lateral funiculus, projecting to the other ganglia is much less numerous (≈5%), while, with the exception of the inferior mesenteric ganglion, ≈90% of the preganglionic motoneurons are located in the IML. Around 70% of the preganglionic motoneurons projecting to the inferior mesenteric ganglion are located in the central autonomic nucleus and ≈25% in the IML. In the cat it is known that the sympathetic preganglionic motoneurons are segmentally organized (Rubin and Purves, 1980; Kuo et al., 1980). In the caudal C8 and rostral T1 segments of the cat preganglionic motoneurons

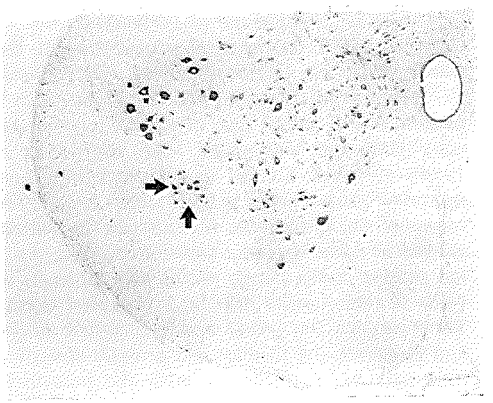


Fig. 4. Brightfield photomicrograph of the ventral horn of a section through the left ventral horn of the S1 spinal segment in the cat. The arrows indicate the nucleus of Onuf, (from Holstege and Tan, 1987).

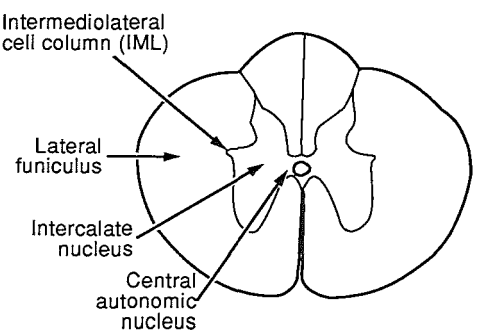


Fig. 5. Schematic drawing of a transverse section of the third thoracic segment of the spinal cord of the cat. The 4 different locations of sympathetic motoneurons are indicated.

are exclusively located in the dorsolateral funiculus (Henry and Calaresu, 1972; Chung et al., 1979). The highest concentration of neurons in the IML is at the T1-T2 and at the L3-L4 levels (Henry and Calaresu, 1972). In the lumbar cord the IML continues until the L4 level (Henry and Calaresu, 1972), but sympathetic motoneurons may also be present in the lateral part of the L5 intermediate zone (Jänig and McLachlan, 1986; Morgan et al., 1986), although not all cats have sympathetic motoneurons as caudal as L5 (Morgan et al., 1986). Many of them traverse the inferior mesenteric ganglia to make synaptic connections with terminal ganglia of the pelvic plexus as well as in the walls of their targets (bladder and genital organs). They run via the pelvic and hypogastric nerves, and innervate the bladder and genitals directly or indirectly via connections with the paravesical ganglia of the parasympathetic system Elbadawi, 1982). Sympathetic fibers have inhibitory effects on the detrusor muscle of the bladder and excitatory effects on the smooth musculature of the urethra and base of the bladder.

1b 2. **Parasympathetic preganglionic motoneurons.** The parasympathetic preganglionic motoneurons in the sacral cord of the cat (S2 and S3 segments) innervate the detrusor muscle of the bladder and the colon. The motoneurons are organized into two groups, a lateral band of neurons, dorsoventrally oriented in the lateral part of lamina VII and a more medial group of neurons, the dorsal band, mediolaterally oriented in the lateral part of lamina V (Nadelhaft et al., 1980). The urinary bladder is innervated mainly by the lateral band of cells and the colon mainly by the dorsal band cells (Morgan et al., 1979; Holstege and Tan, 1987).

1c. Somatic motoneurons in the brainstem

The motoneurons innervating the muscles of the head, such as the facial, chewing, tongue, pharynx and extra-ocular muscles are all located in the brainstem. They do not form a continuous rostrocaudal band of motoneurons such as in the spinal cord, but are subdivided into several distinct motoneuronal cell groups.

1c 1. **Extra-ocular muscle and retractor bulbi motoneuronal cell groups.** The extra-ocular muscles are innervated by motoneurons in the oculomotor, trochlear and abducens nuclei, all of which are located dorsomedially in the tegmentum. The oculomotor nucleus is located in the rostral mesencephalon, the trochlear nucleus in the caudal mesencephalon and the abducens nucleus in the ponto-medullary transition zone. The oculomotor nucleus contains motoneurons innervating the ipsilateral medial rectus, inferior rectus and inferior oblique muscles and the contralateral superior rectus and levator palpebrae. Trochlear motoneurons innervate the contralateral superior oblique, and abducens motoneurons innervate the ipsilateral lateral rectus muscle (see Evinger, 1988 for review).

The accessory abducens or retractor bulbi nucleus in the cat is a loosely arranged motoneuronal cell group, just dorsal to the superior olivary complex (Fig. 6). The nucleus contains a total of about 100 (Grant et al., 1979; Spencer et al., 1980) motoneurons. They innervate the retractor bulbi muscle, an extraocular muscle divided into four slips, which attach themselves on the eyeball behind and beside the inferior and superior recti muscles. The four slips are thinner and shorter than the other extra-ocular muscles. Retractor bulbi muscles are present in most vertebrates, but not in apes and humans (Bolk et al., 1938). The functional role of the retractor bulbi muscles is purely eye -protection: it retracts the eyeball, forcing the intraorbital fat against the base of the nictitating membrane and causing the latter to sweep across the eyeball (Bach-y-Rita, 1971). This event is also called the nictitating membrane response. The retractor bulbi muscles do not contract independently of the orbicularis oculi (McCormick et al., 1982).

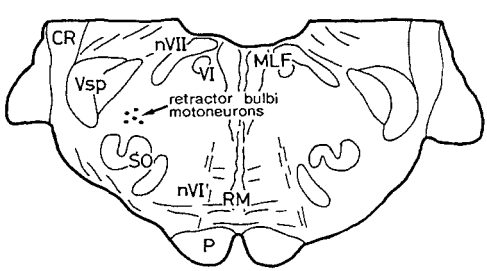


Fig. 6. Schematic drawing of a transverse section through the caudal brainstem at the level of the abducens (VI) and superior olivary nucleus (SO). The black dots indicate the position of the small accessory abducens or retractor bulbi nucleus, which consists of ≈100 motoneurons, (from Holstege et al. 1986b).

1c 2. **Jaw-closing and opening muscle motoneurons.** In the cat the jaw-closing muscles masseter, temporalis and medial pterygoid muscles as well as the lateral pterygoid muscle, which is not a jaw closing muscle, are innervated by motoneurons in the dorsolateral two thirds of the motor trigeminal nucleus. The jaw-opening muscle motoneurons (anterior digastric and mylohyoid) are located in the ventromedial one third of this nucleus (Mizuno, et al., 1975; Batini et al., 1976). This region also contains the motoneurons innervating the tensor veli palatini (Keller et al., 1983). In the cat the posterior digastric muscle motoneurons, which send their axons via the facial nerve, are located in two separate small cell groups, one dorsal to the superior olivary complex and just medial to the VII nerve and one dorsal to the facial nucleus (Grant et al., 1981). The latter region also contains stylohyoid muscle motoneurons (Shohara and Sakai, 1983).

1c 3. **Facial muscle motoneurons.** Motoneurons in the facial nucleus innervate the various facial muscles. In the cat the lateral and ventrolateral facial subnuclei contain the motoneurons innervating the muscles of the upper and lower mouth respectively. Motoneurons in the dorsomedial facial subnucleus innervate the ear or pinna muscles, and the dorsal portion of the facial nucleus (intermediate facial subnucleus) contains motoneurons innervating the muscles around the eye (Papez, 1927; Courville, 1966a; Kume et al., 1978; Fig. 7). In other mammals slight variations in this subdivision are present (Komiyama et al., 1984 in the mouse; Hinrichsen and Watson, 1984;

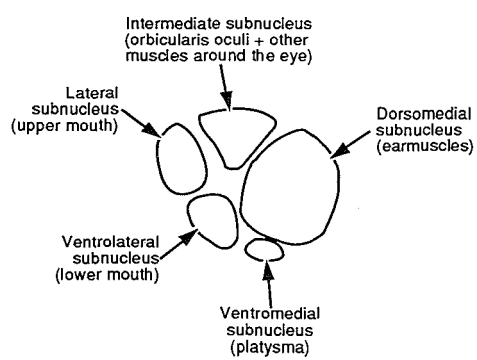


Fig. 7. Schematic drawing of a transverse section through the left facial nucleus. The different facial subnuclei and the muscle innervated by the motoneurons in these subnuclei are indicated.

Klein and Rhoades, 1985 and Friauf and Herbert, 1985 in the rat; Dom et al., 1973 in the opossum; Provis, 1977 in the brush-tailed possum; Holstege and Collewijn, 1982 in the rabbit; Satoda et al., 1987 in the Japanese monkey). The facial nucleus contains mainly motoneurons, only a few non-motoneuronal cells have been detected. They project to the cerebellar flocculus (Røste, 1989).

1c 4. **Middle ear muscle motoneurons.** In the cat, motoneurons innervating the tensor tympani, which send their axons via the motor trigeminal nerve, are located just ventral to the motor trigeminal nucleus (Lyon, 1975; Mizuno et al., 1982; Keller et al., 1983; Friauf and Baker, 1985). Stapedius motoneurons, which send their axons via the facial nerve, are located in cell clusters around the traditional borders of the facial nucleus as well as dorsal to the lateral superior olivary nucleus (Lyon, 1978; Shaw and Baker, 1983; Joseph et al., 1985). In the squirrel monkey stapedius motoneurons are located ventromedial to the facial nucleus (Thompson et al., 1985). Recently it has been shown (McCue and Guinan, 1988; Guinan et al. 1989) in the cat that there is a spatial segregation of function within the stapedius motoneurons.

1c 5. **Somatic motoneurons belonging to the nucleus ambiguus.** In the cat the somatic motoneurons in the nucleus ambiguus innervate the laryngeal, pharyngeal and soft palate muscles. The nucleus extends for a distance of 5 to 6 mm caudally from the facial nucleus. Laryngeal motoneurons are located in the caudal two thirds of the nucleus and lie dispersed in the ventrolateral part of the reticular formation. Motoneurons innervating pharynx and soft palate form a compact cell group, the dorsal group of the nucleus ambiguus. It is located 1.5 to 2.5 mm caudal to the facial nucleus. Pharyngeal motoneurons are also located in the more loosely arranged retrofacial part of the nucleus, situated just caudal to the facial nucleus. Furthermore, the retrofacial part of the nucleus ambiguus contains motoneurons innervating the cricothyroid muscles and the upper portion of the esophagus (Lawn, 1966; Yoshida et al., 1981; Holstege et al., 1983; Davis and Nail, 1984). In the rat the oesophagus motoneurons are located in a compact cell group (Bieger and Hopkins, 1987), but in this animal certain palatal and upper pharyngeal muscles are absent (Cleaton-Jones, 1972; Bieger and Hopkins, 1987), which might simplify the motoneuronal arrangement in this species.

1c 6. **Tongue muscle motoneurons.** Motoneurons innervating the intrinsic and extrinsic tongue muscles are located in the hypoglossal nucleus, which also contains motoneurons innervating the geniohyoid muscles (Uemura et al., 1979; Miyazaki et al., 1981). In the cat the geniohyoid muscle motoneurons are located in the most ventral portion of the rostral two thirds of the hypoglossal nucleus. The other extrinsic tongue muscle motoneurons (genioglossus, hyoglossus, and styloglossus) are located laterally in the hypoglossal nucleus. The intrinsic muscle motoneurons, which send their axons via the medial branch of the hypoglossal nerve, are located medially and ventrally in the nucleus, while the intrinsic muscle motoneurons, which send their axons via the lateral branch, are located in the dorsal portions of the nucleus (Uemura et al., 1979). This relatively complicated subdivision of the hypoglossal nucleus makes it impossible to subdivide the hypoglossal nucleus into tongue protrusion and a tongue retraction regions and further anatomic and physiological study is necessary to unravel a more precise subdivision within this motoneuronal pool.

1d. Autonomic (parasympathetic) preganglionic motoneurons in the brainstem

1d 1. **Preganglionic motoneurons innervating iris and lens via the ciliary ganglion.** Parasympathetic preganglionic motoneurons in the vicinity of the oculomotor nucleus innervate the ipsilateral ciliary ganglion, whose neurons control the iris and lens (ciliary body). Some may bypass the ciliary ganglion to innervate the iris or ciliary body directly (see Evinger, 1988 for review). All these preganglionic motoneurons are involved in the pupillary light reflex. In the cat the preganglionic motoneurons lie in the ipsilateral central gray dorsal to the oculomotor nucleus and in the tegmental area ventral to the oculomotor nucleus (Loewy et al., 1978; Toyoshima et al., 1980; Strassman et al., 1987). In the monkey (Burde and Loewy, 1980) the preganglionic motoneurons are located in the Edinger-Westphal nucleus and in the nucleus of Perlia, located between the somatic motoneuronal oculomotor nuclei (Olszewski and Baxter, 1954).

1d 2. **Preganglionic motoneurons innervating salivatory and lacrimal glands.** The parasympathetic motoneurons innervating the parotid gland, via the minor petrosal nerve and the otic ganglion, as well as those innervating the submandibular and sublingual salivatory glands, via the chorda tympani, are all intermingled in the lateral tegmental field dorsal to the facial nucleus (Contreras et al., 1980 in the rat; Nomura and Mizuno, 1981, 1982; Hosoya et al., 1983 and Tramonte and Bauer, 1986 in the cat). The motoneurons innervating the lacrimal gland, via the greater petrosal nerve, are located slightly more rostrally and ventrally in the lateral tegmentum (Contreras et al., 1980).

1d 3. **Preganglionic motoneurons innervating the visceral organs.** The parasympathetic motoneurons innervating the visceral organs (lung, heart, stomach and intestine) via the vagus nerve are located mainly in the dorsal vagal nucleus and in the ventral part of the medullary lateral tegmental field, i.e. the area of the nucleus ambiguus and retroambiguus (Nosaka et al., 1979; Weaver, 1980; Kalia and Mesulam, 1980a,b; Kalia, 1981; Hopkins and Armour, 1982). A few neurons are present in the lateral tegmentum between both cell groups and in the upper cervical ventral horn (Kalia and Mesulam, 1980a,b). There is extensive overlap between the location of the neurons innervating the different viscera, although Hopkins and Armour (1982) and Plecha et al. (1988) indicate that almost 90% of the preganglionic neurons innervating the heart are located in the area of the nucleus ambiguus. It has always been difficult to give a precise description of the nuclei ambiguus and retroambiguus, because both nuclei consist of many different populations of motor (autonomic and somatic) and premotor cells. In the cat the only portion of the nucleus ambiguus that can easily be recognized as such in non-experimental Nissl sections is its dorsal group, containing motoneurons innervating pharynx and soft palate (Lawn, 1966; Yoshida et al., 1981; Holstege et al., 1983; Davis and Nail, 1984). Furthermore the caudal half of the nucleus retroambiguus (NRA), located at the border between gray and white matter at medullary levels caudal to the hypoglossal nucleus, forms a reasonably well circumscribed nucleus (Fig. 8; Kalia and Mesulam (1980a,b) reported that this nucleus contains vagal nerve parasympathetic preganglionic motoneurons. However, from their drawings the impression is gained that the parasympathetic neurons are not located within the confines of the nucleus retroambiguus, but just medial to it. The nucleus itself contains interneurons involved in expiration related sys-

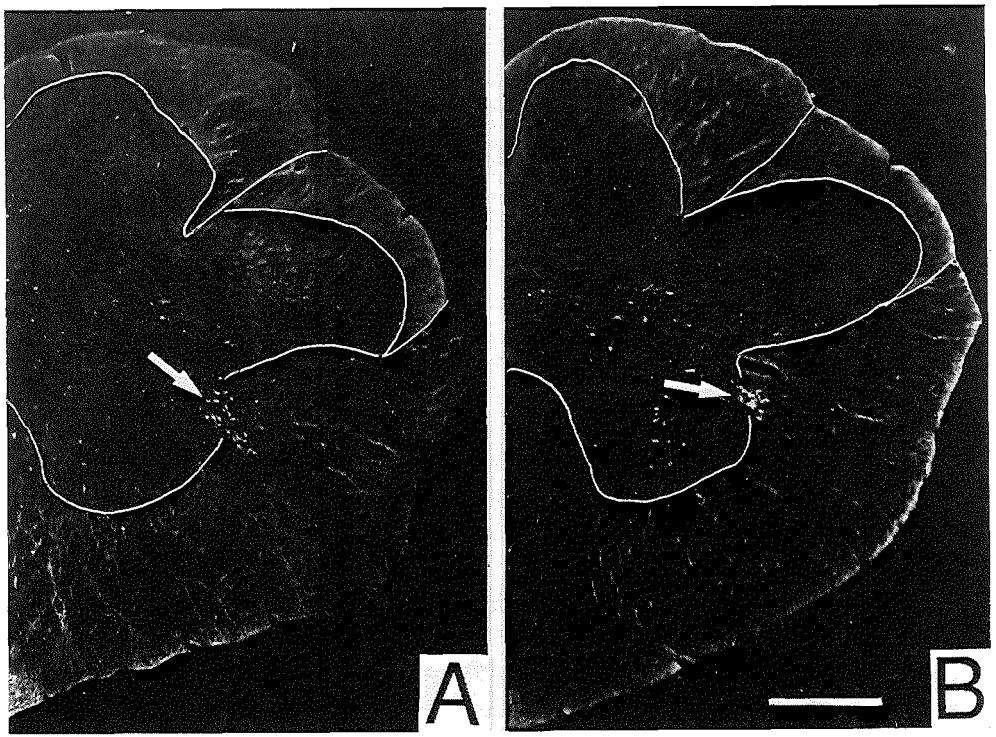


Fig. 8. Darkfield photomicrographs showing the HRP labeled neurons in the contralateral NRA (arrows) at the level of the caudal medulla (A) and medullospinal transition (B) after injection of HRP in the ipsilateral T1 spinal cord. Bar represents 1 mm.

tems (see section 3a). The fact that all other portions of the nuclei ambiguus and retroambiguus consist of neurons more or less scattered within the lateral tegmental field, makes a description of afferents to these nuclei practically useless without a precise identification of the motoneurons involved.

2. Local projections to motoneurons

2a. Recurrent motoneuronal axon collateral projections to motoneurons

Recurrent collaterals of motoneurons innervating limb muscles terminate directly on local motoneurons innervating the same or synergistic muscles (Cullheim and Kellerth, 1978). Furthermore, motoneuronal axon collaterals project directly on local interneurons (Renshaw cells). Renshaw cells are located in the ventral horn medial to the motor nuclei (Jankowska and Lindström, 1971; Van Keulen, 1979; Fig. 9). They have an inhibitory effect on the same or synergistic a and g motoneuronal cell groups from which they receive their afferents. This phenomenon is known as recurrent inhibition (see Baldissera et al., 1981 for review). Renshaw cells project via propriospinal pathways in the ventral funiculus (Fig. 9). Recurrent inhibition is especially strong in motoneuronal cell groups innervating proximal limb muscles, less strong in muscles of more distal parts of the limb (wrist or ankle) and absent in motoneuronal cell groups innervating the most distal limb musculature such as those innervating the phalanges of the forelimb (Hahne et al., 1988) or the small foot-muscles of the hindlimb (Cullheim and Kellerth, 1978). Apparently recurrent

inhibition is primarily concerned with control of the proximal muscles (limb position), rather than of the distal ones (movements of the digits).

2b. Muscle spindle afferent projections to motoneurons

2b 1. **Muscle spindle afferent projections to motoneurons in the spinal cord.** In the spinal cord group Ia muscle spindle afferents have an excitatory effect on motoneurons, innervating the same or synergistic muscle groups (Mendell and Henneman, 1971). Muscle spindles project directly (Brown and Fyffe, 1978; Ishizuka et al., 1979) or via interneurons (Jankowska et al., 1981) onto motoneurons. The Ia afferent projection system exists in proximal as well as in distal limb muscle control (Ishizuka et al., 1979; Fritz et al., 1978; 1984). Ia muscle spindle afferents not only have an excitatory effect on motoneurons, but also on the so-called Ia inhibitory interneurons which in turn have an inhibitory effect on motoneurons innervating muscles, antagonistic to the muscle from which the Ia muscle spindle afferents are derived. The Ia inhibitory interneurons are located in lamina VII of the spinal intermediate zone and project to the antagonist muscle motoneurons, mainly via propriospinal pathways (Jankowska and Lindström, 1972; Fig. 9). Thus, the Ia afferents of a specific muscle excite the motoneurons of the same (homonymous) and synergistic muscles, and, via Ia inhibitory interneurons, inhibit the motoneurons of the antagonistic muscles (see Henneman and Mendell, 1981 and Baldissera et al., 1981 for reviews). Ia afferents also have an inhibitory influence on homonymous and synergistic muscle motoneurons (Fetz et al., 1979), but this inhibition is mediated by

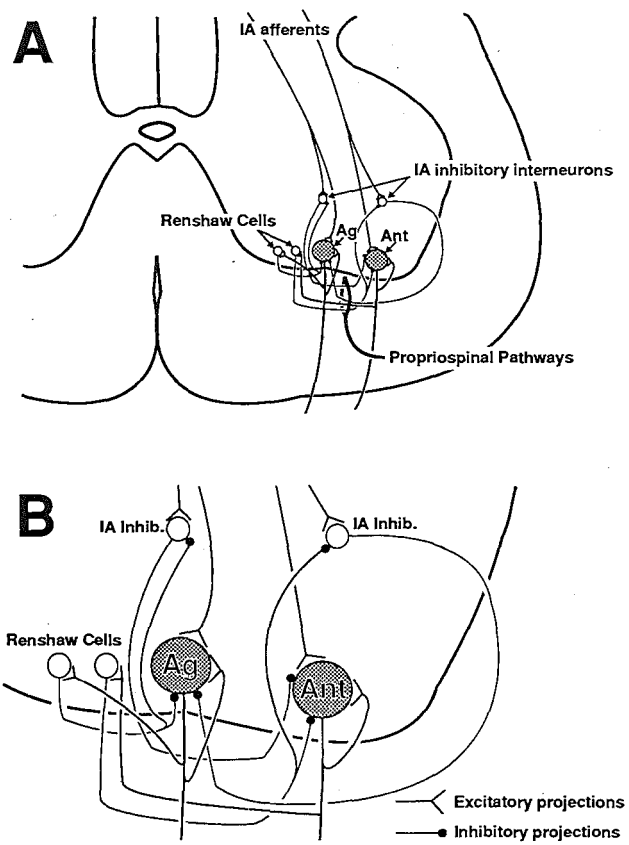


Fig. 9. In A a schematic drawing of the L7 ventral horn showing the recurrent axon collaterals, Renshaw cells, Ia inhibitory interneurons and Ia afferents of two motoneurons innervating an agonist (Ag) and an antagonist (Ant) muscle respectively. Note that many of the neurons project via propriospinal pathways. In B a magnified view of the different projections is shown. Note that the motoneurons receive inhibitory input from their own axon collaterals and Renshaw cells as well as from the Ia inhibitory interneurons from the antagonist muscle. Excitatory input is derived from Ia afferents. It is known, (Cullheim and Kellerth, 1978), that recurrent axon collaterals of a proximal muscle motoneuron projects directly onto the somata or dendrites of other motoneurons innervating the same or synergistic muscles. Although indicated as such in the schematic drawing, it is not sure whether a motoneuron projects to its own dendrites or soma.

interneurons and not by direct projections to motoneurons.

2b 2. **Muscle spindle afferent projections to motoneurons in the brainstem.** The neuronal cell bodies of the muscle spindle afferents are located in spinal ganglia outside the central nervous system. However, the ganglion cells of the muscle spindle afferents of the mouth closing muscles are located within the central nervous system. They are called mesencephalic trigeminal neurons and are mainly large-diameter globular cells with one process, although some of them are of smaller diameter. The mesencephalic trigeminal neurons, which combined form the mesencephalic trigeminal nucleus, are located at pontine and mesencephalic levels in the border area between periaqueductal gray (PAG) and the dorsally and laterally adjoining tegmentum. The peripheral processes of these cells first descend through the so-called mesencephalic trigeminal tract (Fig. 10A), and then via the motor root of the trigeminal nerve to the sensory receptors in the mouth closing muscles. The sensory signals are derived from the muscle spindles in the mouth closing muscles as well as from pressure receptors at the base of the teeth, the temporomandibular joint, gums and tongue. The muscle spindle afferents are located throughout the rostrocaudal extent of the mesencephalic trigeminal nucleus, while the pressure receptor ganglion cells are present in the caudal half of the nucleus. After a ^{3}H-leucine injection involving the rostral mesencephalic trigeminal nucleus, Holstege and Cowie (in preparation) found that the proximal processes pass caudally, first via the mesencephalic trigeminal tract (Fig. 10A), but at levels caudal to the motor trigeminal nucleus in the so-called Probst (1899) tract, which can be followed until the upper segments of the cervical cord (figs. 10C-F). From this tract some fibers are distributed to the dorsolateral two thirds of the motor trigeminal nucleus (Fig. 10B), which contains mouth closing muscle motoneurons (see section 1 c 2). Although the termination of muscle spindle afferents in the motor trigeminal nucleus was not very strong, it was more pronounced than the very weak projection reported by Luschei (1987). The detection of only a limited muscle spindle projection to the mouth closing motoneurons is in agreement with the finding of Appenteng et al. (1978), who triggered mouth closing muscle spindle afferents in the mesencephalic trigeminal nucleus. They found that the muscle spindles produced monosynaptic excitatory post synaptic potentials in only a small proportion of the mouth closing motoneurons. Much denser projections than to the motor trigeminal nucleus were found to the supratrigeminal and intertrigeminal regions (Fig. 10B), located just dorsal and lateral to the motor trigeminal nucleus (see also Luschei, 1987 and Shigenaga et al., 1988). Further caudally, Holstege and Cowie (in preparation) found that muscle spindle afferents in the Probst tract terminate only to a very limited extent at levels around the facial nucleus (Fig. 10C), but strongly in the dorsal portion of the lateral tegmentum at the level of the hypoglossal nucleus (Fig. 10E). No labeled fibers were found in the trigeminal, solitary or hypoglossal nuclei. Projections to these nuclei may be derived from neurons in more caudal portions of the mesencephalic trigeminal nucleus receiving peri-oral pressure receptor afferents (Sirkin and Feng, 1987). Neurons in the dorsal portion of the lateral tegmentum at the level of the hypoglossal nucleus project to the hypoglossal nucleus and to the ventromedial one third of the motor trigeminal nucleus (Holstege and Kuypers, 1977; Holstege et al., 1977; Holstege and Blok, 1986), which area contains mouth opening muscle motoneurons (see section 1 c 2; Fig. 11). Interneurons, which receive mouth closing muscle spindle afferents and project to mouth opening motoneurons, might serve as Ia inhibitory interneurons for the mouth closing motoneurons. However, after stimulating mouth closing muscle afferent fibers, Kidokoro et al. (1968) could not demonstrate such inhibitory effects in the antagonist digastric muscle motoneurons.

2c. Propriospinal pathways

2c 1. **Projections from interneurons.** With the exception of the Ia afferents, no direct primary afferent projections exist to the motoneurons. For example, stimulation of Ib tendon organ afferents of a specific muscle produces inhibition of the motoneurons of the same and synergistic muscles and excitation of motoneurons of antagonist muscles. These effects are mediated via excitation of interneurons in the intermediate zone, mainly laminae V and VI, which in turn project, via propriospinal pathways, to motoneurons (Czarkowska et al., 1976). Jankowska and McCrea (1983) demonstrated that both the excitatory and inhibitory interneuronal pathways to motoneurons are shared by Ia and Ib afferents.
Other primary afferents are derived from the skin

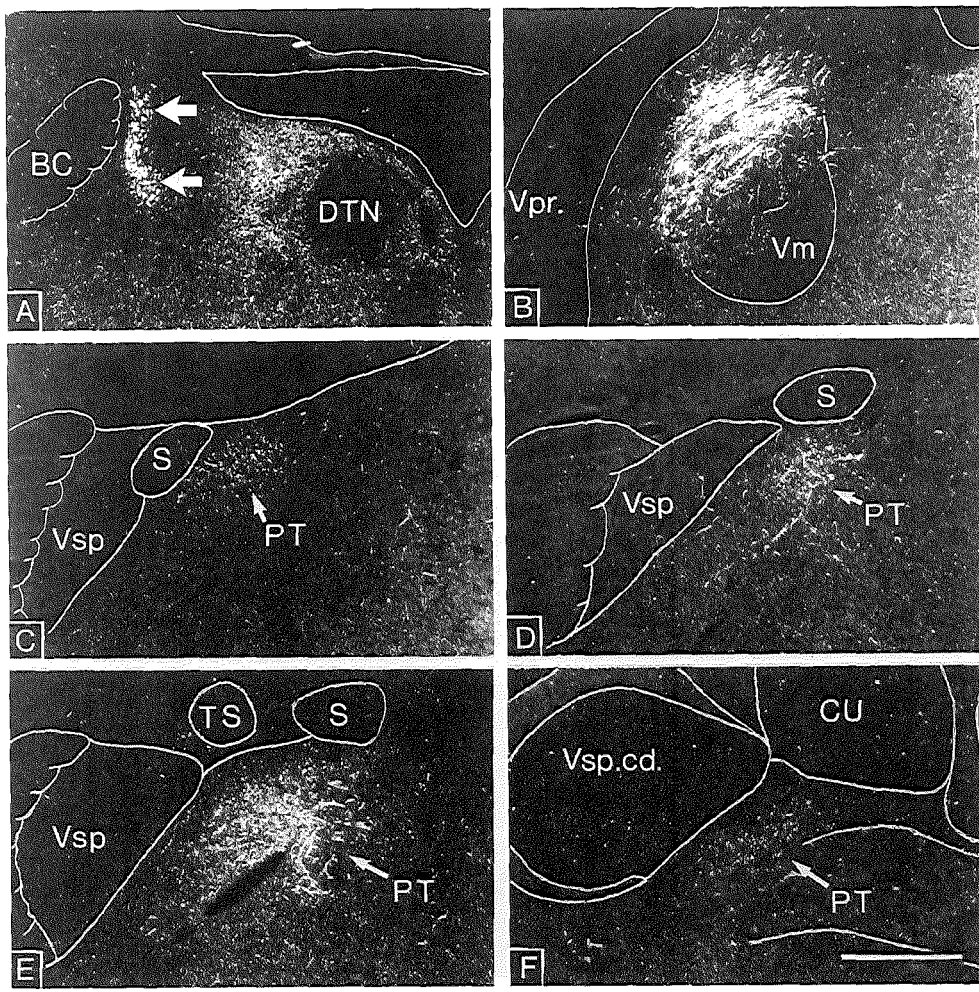


Fig. 10. Darkfield photomicrographs of the labeled fibers in the mesencephalic trigeminal tract (A) or Probst tract (Figs. C-F) after an injection of ^{3}H-leucine in the dorsolateral part of the pretentorial PAG and adjoining tegmentum, including the mes. V neurons at that level. Note the light projections to the dorsolateral two thirds of the motor trigeminal nucleus, the virtual absence of projections around the level of the facial nucleus, and the strong projections to the lateral tegmental field at the level of the hypoglossal nucleus (E).

and joints, and the group II and III muscle afferents. Their reflex pathways to motoneurons always include interneurons. In hindlimb segments of the cat the minimum linkage in reflex pathways from cutaneous afferents to motoneurons is trisynaptic (Lundberg, 1975), although in case of the forelimb disynaptic pathways seem to exist. The last order interneurons, projecting to the motoneurons, enter the funiculus at the same rostrocaudal level as their cell body is located. Within the funiculus they run rostrally and/or caudally to reenter the spinal gray at the level of their target motoneurons (Jankowska and Roberts, 1972). For such local pathways especially those parts of the dorsolateral, ventrolateral and ventral funiculi are involved, which border the gray matter. These parts are called fasciculi proprii or propriospinal pathways. Anatomic studies (Sterling and Kuypers,

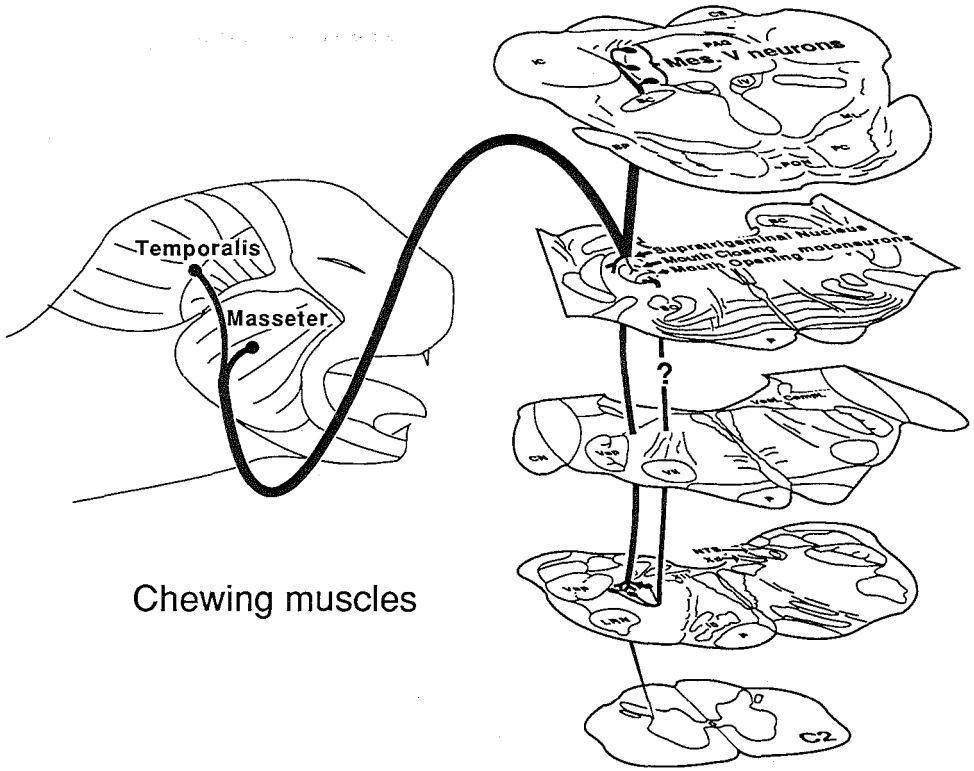


Fig. 11. Schematic drawing of the organization of the mesencephalic trigeminal nucleus and tract. The strongest projections from the Probst tract is at the level of the hypoglossal nucleus. Other tracing studies have indicated that neurons in this area project strongly to the mouth opening motoneurons in the motor trigeminal nucleus, but whether these neurons at the level of the hypoglossal nucleus play the role of Ia inhibitory neurons remains to be elucidated.

1968; Rustioni et al., 1971; Molenaar et al., 1974; Molenaar, 1978) have indicated that the interneurons, located in different areas of the intermediate zone, project to different motoneuronal cell groups. Interneurons in the lateral part of laminae V and VI project via the dorsolateral funiculus to the dorsolateral motoneuronal cell group in the cervical or lumbosacral enlargement, which innervate distal limb muscles. Interneurons in the central part of the intermediate zone project via the ventrolateral funiculus to the ventrolateral motoneuronal cell group, innervating proximal limb muscles. Interneurons in the medial part of the intermediate zone, (medial part of lamina VII and lamina VIII) project via the ventral funiculus, to the medial motoneuronal cell groups, innervating the axial and proximal muscles (Fig. 12). Within the cervical or lumbosacral enlargements such projections go from rostral to caudal and from caudal to rostral (Molenaar and Kuypers, 1978).

2c 2. **Projections from propriospinal neurons.** According to Baldissera et al. (1981) there is a functional difference between interneurons and propriospinal neurons. Interneurons are intercalated in reflex pathways of limb segments, while propriospinal neurons are located outside the limb segments, but project into them. The C3-C4 neurons which relay supraspinal motor information to a-motoneurons in the C5-T1 spinal cord (Illert

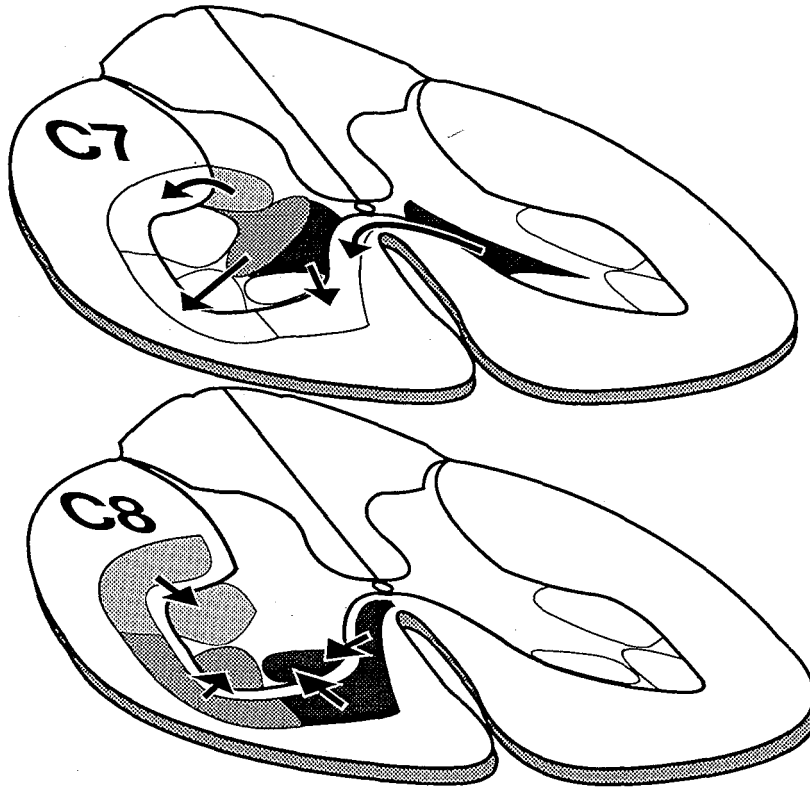
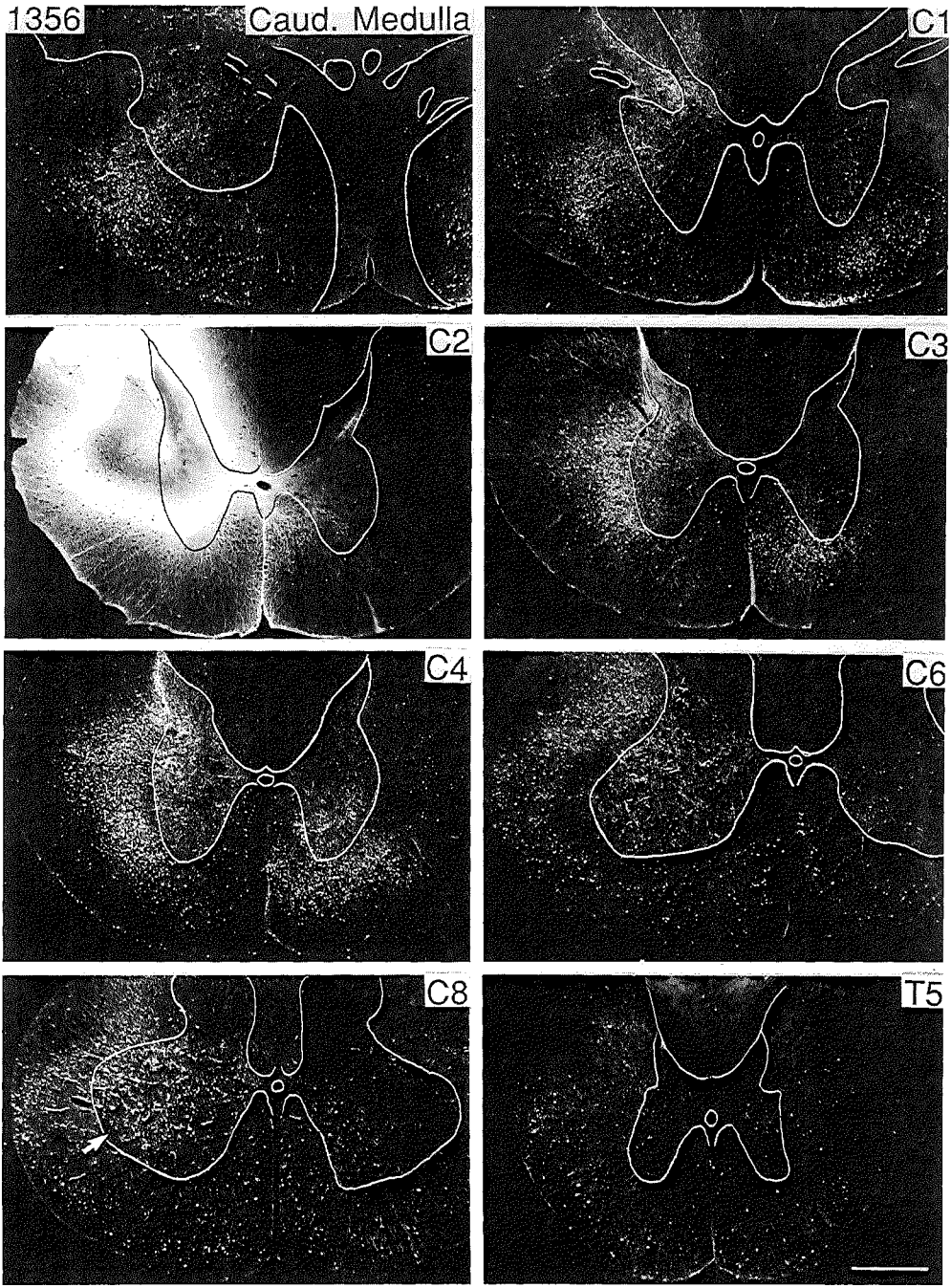


Fig. 12. Schematic illustration of the projections from interneurons in the C7 intermediate zone (laminae V-VII) via the propriospinal pathways to the motoneurons at the C8 level. Note that the neurons in the dorsolateral part of the intermediate zone project to the dorsolaterally located motoneuronal cell group innervating distal limb muscles. The interneurons in the central part of the intermediate zone project to motoneurons in the ventrolateral ventral horn, which innervate proximal limb muscles. Interneurons in the medial part of the intermediate zone on both sides of the spinal cord project to the motoneurons in the medial part of the ventral horn. These motoneurons innervate axial muscles. Note also that the C7 propriospinal fibers at the level of C8 are shifted to a slightly more peripheral position in the funiculus.

et al., 1978) are examples of propriospinal neurons. Illert et al. (1978) demonstrated that, after a complete transection of the corticospinal tract at the level of C5, disynaptic excitatory postsynaptic potentials (EPSP's) in forelimb muscle motoneurons can still be evoked by stimulation of the contralateral pyramid or red nucleus, while they were abolished after a corticospinal tract transection at the level of C2. Alstermark et al., 1987b, using intra-axonal injections of horseradish peroxidase, demonstrated C3-C4 propriospinal projections to a-motoneurons and interneurons in

Fig. 13. On the right. Darkfield photomicrographs of the caudal medulla oblongata and 7 different levels of the cervical and upper thoracic cord after injection of ^{3}H-leucine in the lateral two thirds of the intermediate zone of the C2 spinal gray matter. Note the strong projections to the motoneuronal cell groups in the C6 and C8 ventral horn. Note also that from the injection site the descending propiospinal fibers gradually move to more peripheral parts of the funiculi. The arrow in C8 points to the CTM motor nucleus, which does not receive descending propriospinal pathways. Bar represents 1 mm.


1356
Caud. Medulla
C1
C2
C3
C4
C6
C8
T5

the C6-T1 spinal cord. Molenaar (1978) using the retrograde HRP technique found that only a limited number of labeled neurons in the C2-C4 intermediate zone projected to a-motoneurons in the C5-T1 spinal cord, but Holstege (1988b) and Holstege and Blok (1989), using the anterograde autoradiographic tracing technique, demonstrated that neurons in the intermediate zone of C2 project heavily to the C6-T1 motoneuronal cell groups (Fig. 13), with the exception of the cutaneus trunci muscle motoneurons (see later). Thus, not only C3-C4, but also C2 propriospinal neurons project to the C5-T1 a-motoneurons. With regard to the functional importance of the upper cervical propriospinal projections to motoneurons, Alstermark et al. (1981; 1987b) demonstrated that the propriospinal neurons, driven by cortico- and/or rubrospinal fibers, can produce target reaching movements in cats. During this movement the paw is brought in contact with the food. However, direct activation of the C5-T1 inter- and motoneurons from the cortico- and/or rubrospinal tracts can also produce target reaching movements (Alstermark, 1987b). Such direct activation is essential for food taking movements in cats, consisting of toe grasping and paw supination. Thus the upper cervical propriospinal neurons, when properly stimulated, can produce target reaching movements, but not the more precise food taking movements.

2c2 a. **Propriospinal neurons as rhythm generators.** During the scratch reflex (one limb) or locomotion (all four limbs) the limbs perform rhythmic movements, which are independent of the afferent signals from that limb. The main characteristics of the rhythmic movements of a limb are determined by its so-called spinal generator. During the scratch reflex only one generator is active, during locomotion, all four of them. The spinal generators consist of interneurons, which lie mainly in the lateral part of laminae V, VI and VII over the whole length of the cervical or lumbosacral enlargement. Renshaw cells and Ia inhibitory interneurons are not responsible for the basic pattern of rhythmic changes, (see Gelfand et al., 1988 for review). Grillner (1981) hypothesized that the spinal generator of a limb consists of several rhythm generators, each controlling one joint. The regulation of the rhythm generators is performed by means of tonic commands coming from higher brain centers. In all likelihood the diffuse descending systems, originating in the ventromedial medulla oblongata and projecting to all parts of the intermediate zone and motoneuronal cell groups, play an important role in this regulation (see further sections 5 b 1 and 5 c 1 c).

2c 3. **Long propriospinal projections.** As pointed out in section 1, the column of motoneurons innervating axial muscles extends from the caudal medulla oblongata (neck muscles) to the sacral cord (lower back muscles). Since they are often simultaneously active during certain proximal body movements, long propriospinal projections are necessary to coordinate such axial movements. Giovanelli Barilari and Kuypers (1969) and Molenaar and Kuypers (1978) have shown that there exist direct reciprocal connections between the cervical and lumbosacral spinal cord. The great majority of the neurons giving rise to such long propriospinal projections are located in the medial part of the intermediate zone (lamina VIII and adjoining VII). They project bilaterally, but mainly ipsilaterally via the ventral funiculus, and probably play a role in establishing a functional unity of the axial and proximal musculature. A smaller number of neurons in the dorsolateral part of the cervical intermediate zone and a few in lamina I (Molenaar and Kuypers, 1978) send axons via the dorsolateral funiculus to the lumbar cord. The function of these projections is less clear, although it is known that stimulation of forelimb afferents evokes a sequence of excitation and inhibition in hindlimb motoneurons (for example to a-motoneurons of the flexor digitorum longus muscle (Schomburg et al., 1975)). In summary, long propriospinal pathways are probably involved in the coordination of axial muscle activity as well as in the coordination between fore- and hindlimbs.

Comparing the density of the short and long propriospinal projections, it is important to note that an injection of ^{3}H-leucine in the intermediate zone of a portion of the C2 or C6 intermediate zone produces many fibers terminating in the C8-T1 motoneuronal cell groups (Holstege, 1988b; Fig. 13; Holstege and Blok, 1989), but only very few in the lumbar cord (Holstege, 1988b). After an injection of ^{3}H-leucine in the L7 spinal cord, which produces heavy labeling in for example the inferior olive, only very few labeled fibers were found in the medial part of the C8 intermediate zone (Holstege unpublished observations). Thus, the long propriospinal projections are much weaker than the short propriospinal and interneuronal projections to motoneurons. It remains to be determined whether the coordination between fore-

and hindlimbs relies entirely on the relatively weak long propriospinal projections, or on other projection systems as well.

2c 4. **Specific propriospinal projections.** Giovanelli Barilari and Kuypers (1969) and Ueyama and Matsushita (1973) have demonstrated an ipsilateral projection from the thoracolumbar spinal cord to a specific motoneuronal cell group in the most ventrolateral portion of the C8-T1 ventral horn. The cell group was called "group X" by Giovanelli Barilari and Kuypers (1969) and "ventral motor nucleus" by Matsushita and Ueyama (1973), indicating that it was not known which muscle was innervated by these motoneurons. It was later demonstrated (see section 1 a 3) that the motoneurons in this cell group innervate the cutaneus trunci muscle (CTM). The CTM is a thin broad sheet of skeletal muscle just beneath the skin. It does not contain muscle spindles and receives its afferents from the overlying skin. Bilateral contraction of the muscle can easily be triggered by pinching the skin or in the cat by gentle displacement of the fur (CTM-reflex). The afferent information for this reflex is conveyed via the cutaneous nerves, which are segmentally organized. Physiological studies have shown that long ascending propriospinal pathways, originating in the thoracolumbar cord, exist between the cutaneous afferents and the CTM motor nucleus (Krogh and Denslow, 1979; Theriault and Diamond, 1988a). Holstege and Blok (1989) in their study on the specific descending pathways to the CTM motor nucleus, combined the anatomic findings of Giovanelli Barilari and Kuypers (1969) and Ueyama and Matsushita, 1973 with the more recent physiological findings and produced a schematic diagram of the anatomy of the CTM reflex (Fig. 14).

2c 5. **Absence of propriospinal projections to certain motor nuclei**

2c5 a. **CTM motor nucleus.** Short propriospinal pathways exist for almost all motoneuronal cell groups. However, the CTM motor nucleus, in contrast to the surrounding motoneuronal cell groups in the cervical enlargement, does not seem

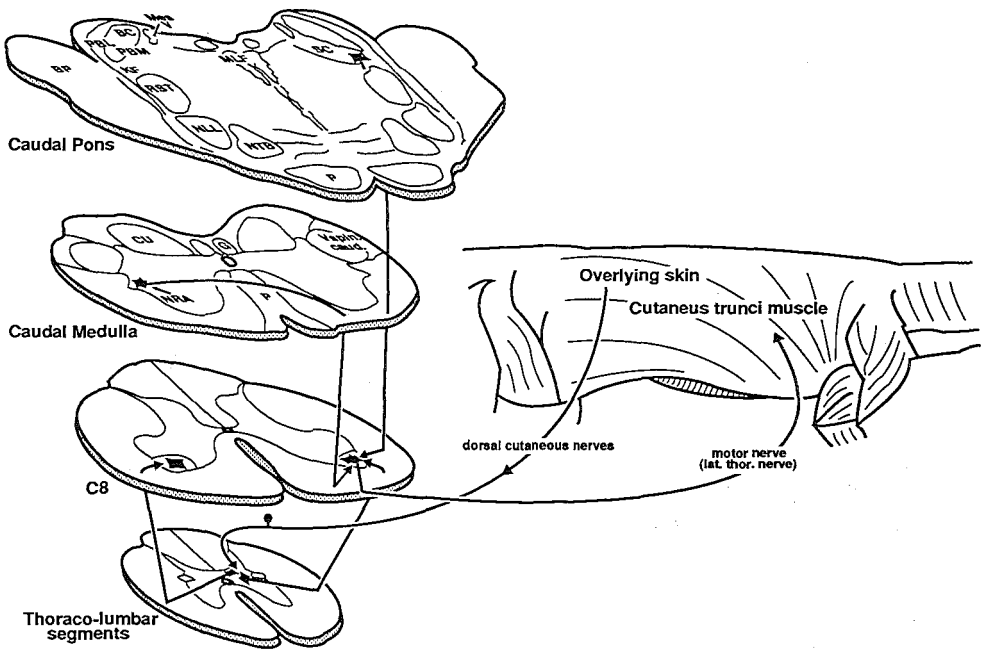


Fig. 14. Schematic representation of the pathways involved in the CTM reflex and the specific supraspinal projections to the CTM motor nucleus.

to receive projections from cervical interneurons (Holstege and Blok, 1989), although many from more caudal regions (see section 2 c 4 and Fig. 14). The lack of descending propriospinal pathways to the CTM motor nucleus is not surprising. CTM motoneurons are involved in totally different movements than the other motoneurons in the ventrolateral portion of the C8-upper T1 ventral horn, which innervate the muscles of the forelimb. The propriospinal afferent pathways from the cervical cord are mainly concerned with coordination of movements of the forelimb, in which the CTM does not play a role.

2c5 b. **Phrenic nucleus.** A second cell group that seems to receive only a small number of propriospinal fibers (if any) is the phrenic nucleus. Holstege (1988b) observed, in cases with relatively large injections of triated leucine in the C1 and C2 spinal cord, strong projections to the C5-T1 motoneuronal cell groups, but only very weak (if any) projections to the phrenic nucleus (Fig. 15). This observation is not unimportant, because Aoki et al. (1980) have reported that neurons in the C1-C2 intermediate zone generate a spontaneous respiratory rhythm in cats two hours after a C1 spinal transection, but not after a C3 transection. On the other hand, Lipski and Duffin (1986) studied the C1-C2 propriospinal inspiratory neurons, but could not find any evidence for synaptic connections between these cells and the phrenic motoneurons. They suggested a disynaptic pathway involving segmental interneurons, but Holstege (unpublished observations), in a case with a large triated leucine injection in the segmental interneuronal zone at the upper C6 level, could not find well defined projections to the ipsi- or contralateral phrenic nucleus. Thus, it remains to be resolved how the C1-C2 inspiratory interneurons of Aoki et al. (1980) control phrenic motoneurons. Possibly, propriospinal neurons in the thoracic cord project to the phrenic nucleus, because stimulation in spinal cats of the afferent fibers of the internal and external intercostal muscles elicits a polysynaptic reflex excitation of phrenic motoneurons, followed by a depression of spontaneous phrenic motor activity (Decima et al., 1969).

2c5 c. **Onuf's nucleus.** The third motoneuronal cell group which does not seem to receive propriospinal projections from more rostral levels is the nucleus of Onuf (Rustioni et al., 1971; Holstege and Tan, 1987) (Fig. 16). Similar to the descending propriospinal pathways to the CTM motor nucleus, the lack of descending interneuronal or propiospinal projections to Onuf's nucleus is not unexpected, because Onuf motoneurons are involved in completely different movements than the hindlimb innervating motoneurons surrounding Onuf's nucleus. The propriospinal afferent pathways from the lumbar cord are mainly concerned with coordination of movements of the hindlimb, in which Onuf's nucleus does not play a role.

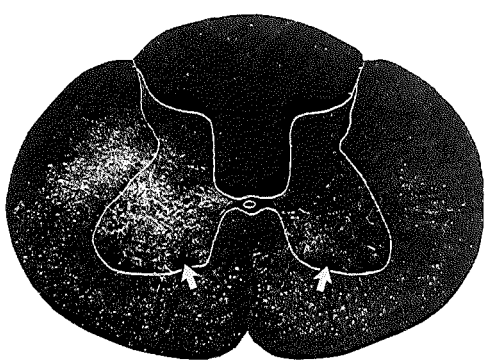


Fig. 15. Darkfield photomicrograph of a tranverse section of the C6 spinal cord after an injection of ^{3}H-leucine at the level of C2 (Fig. 13 C2). The arrows indicate the area of the phrenic nuclei, receiving virtually no labeled fibers from the C2 intermediate zone.

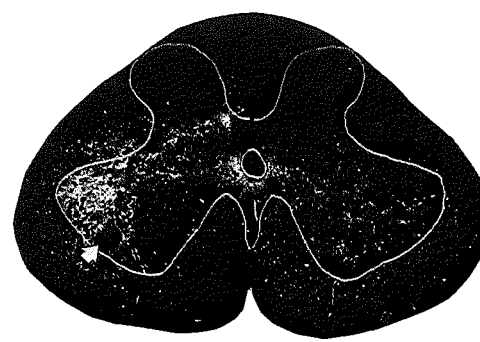


Fig. 16. Darkfield photomicrograph of a transverse section through the S1 spinal cord of the cat after an injection of ^{3}H-leucine at the level of L7. The arrow points to the nucleus of Onuf, receiving no labeled fibers from the L7 intermediate zone (from Holstege and Tan, 1987).

However, Onuf motoneurons, innervating the pelvic floor muscles, have a very strong relationship with skin afferents. Stimulation of the perianal skin gives rise to simultaneous reflex reactions of the anal, urethral and bulbocavernosus muscle (Pedersen, 1985). The afferent fibers enter the spinal cord via the pudendal nerve, in the cat in the segments S1, S2 and upper S3 (Ueyama et al., 1984), in the monkey in the segments L7 to S2 (Roppolo et al., 1985) and in humans in the segments S1 to S4 (Pedersen, 1985). In general the strongest afferent input enters the cord one segment caudal to the level of the nucleus of Onuf. Predictably, but not yet demonstrated, there exist projections from interneurons in the caudal sacral cord to the Onuf motoneurons, similar to the ascending projections from the thoracolumbar cord to the CTM motor nucleus.

The CTM, phrenic and Onuf's nuclei not only have in common that they receive only very few, if any, descending propriospinal fibers, but also that for all three of them the muscles they innervate contain only very few, if any muscle spindles, (see Theriault and Diamond, 1988a for the CTM motor nucleus, Duron et al., 1978 for the phrenic nucleus and Todd, 1964 and Gosling et al., 1981 for Onuf's nucleus). Furthermore all three motor nuclei have an exceptionally large number of longitudinally running dendrites within their nuclei (Dekker et al., 1973), and all three receive specific afferent projections from supraspinal structures (see section 3).

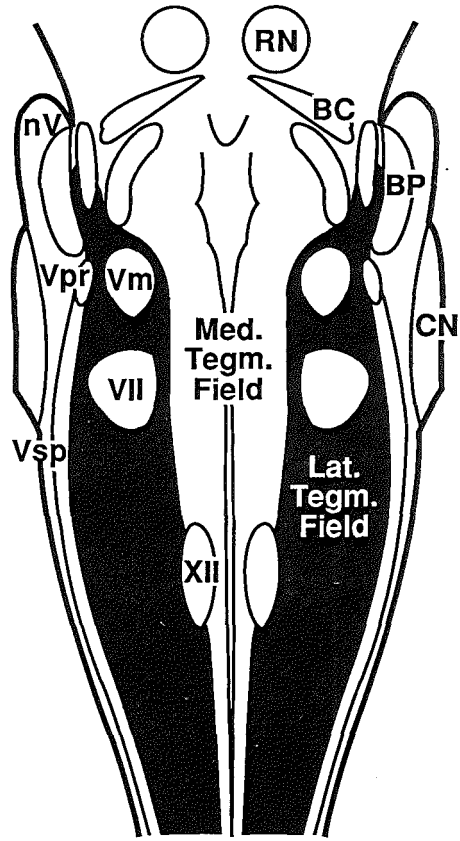


Fig. 17 Schematic drawing of the subdivision of the bulbar reticular formation into a medial and lateral tegmental field. The lateral tegmental field can be considered as the rostral extension of the spinal intermediate zone, containing interneurons for the motoneurons in brainstem and spinal cord. The medial tegmental field gives rise to descending pathways involved in postural and orienting movements and in level setting of all neurons in the spinal cord.

2d. **Propriobulbar pathways**

The organization of the interneuronal projections to the trigeminal (V), facial (VII), ambiguus (X) and hypoglossal (XII) motor nuclei in the brainstem is not fundamentally different from the interneuronal and propriospinal projections in the spinal cord. This is not the case for the projections to the extra-ocular motor nuclei of the oculomotor, trochlear and abducens nerves and the ear mucle motoneurons in the facial nucleus, which form part of specific, mainly medially located premotor systems controlling eye-, head- and ear movements (see section 4a).

Going rostrally from the level of C1, the spinal intermediate zone (laminae V to VIII) is called reticular formation (subnuclei reticulares dorsalis and ventralis of Meessen and Olszewski, 1949). It contains interneurons projecting to the motoneurons in the upper cervical cord (Holstege, 1988b) and to the V, VII, X and XII motor nuclei (Holstege and Kuypers, 1977 and Holstege et al., 1977). Rostral to the level of the obex the reticular formation can be subdivided into a medial and a lateral tegmental field (Fig. 17). The lateral tegmental field extends rostrally into the parabrachial nuclei and the nucleus Kölliker-Fuse, and can be considered as the rostral extension of the spinal intermediate zone (Holstege et al., 1977).

For example, the projections from the red nucleus and motor cortex in cat and monkey to the bulbar lateral tegmental field are continuous with the projections to the intermediate zone of the spinal cord (see section 4b). At medullary levels the bulbar lateral tegmental field involves the so-called parvocellular reticular formation, the lateral paragigantocellular reticular nucleus of Olszewski and Baxter (1954), (see also Martin et al., 1990) and the intermediate reticular nucleus, as defined by Paxinos and Watson (1986) in the rat. The lateral tegmental field adjoins the hypoglossal nucleus ventrolaterally, the facial nucleus dorsomedially and surrounds the nucleus ambiguus. At pontine levels the lateral tegmental field comprises area h of Meessen and Olszewski (1949), which surrounds the motor trigeminal nucleus, and the ventral part of the parabrachial nuclei and the nucleus Kölliker-Fuse. In general, interneurons located medially in the lateral tegmental field project bilaterally to the V, VII and XII motor nuclei, while neurons located laterally project ipsilaterally (Holstege et al., 1977). The medial tegmental field at the levels of pons and medulla is involved in eye-head coordination and gives rise to long descending pathways to the spinal cord, involved in regulating axial and proximal body movements (see section 4 a) or level setting systems (section 5 b 1).

2d 1. **Interneuronal projections to the motor trigeminal nucleus.** In the cat almost all afferent projections to the motor trigeminal nucleus are derived from the bulbar lateral tegmental field. There are only 3 exceptions; 1) the few afferents from the mesencephalic trigeminal ganglion cells to the mouth closing motoneurons (see section 3 b 2); 2) fibers from the upper medullary ventromedial tegmentum, which project diffusely to all motoneuronal cell groups including the motor trigeminal nucleus (see section 5 b 1) and 3) the motor cortex in monkey and humans, but not in cat, (Kuypers, 1958a,b,c).
Interneurons projecting to the motor trigeminal nucleus are not uniformly distributed throughout the lateral tegmental field. The mouth opening motoneurons receive their strongest projections from neurons in the lateral tegmentum at levels caudal to the obex (Holstege and Blok, 1986; Holstege, 1989). The mouth closing motoneurons receive their afferent projections mainly from neurons in more rostral parts of the lateral tegmental field, i.e. from the level of the hypoglossal nucleus rostrally until the supratrigeminal nuclei and the area of the ventral parabrachial nuclei and nucleus Kölliker-Fuse (Holstege and Kuypers, 1977 and Holstege et al., 1977; Mizuno et al., 1983; Holstege and Blok, 1986, Travers and Norgren, 1983).
Furthermore, Holstege et al. (1983) demonstrated a very specific projection pattern, originating from neurons located just dorsal and dorsomedial to the superior olivary complex. These neurons project contralaterally to mouth opening motoneurons in the trigeminal nucleus, the geniohyoid motoneurons in the hypoglossal nucleus and soft palate and pharynx motoneurons in the dorsal group of the nucleus ambiguus (Fig. 18). The authors suggest that this projection pattern might play a role in the coordination of the first (buccopharyngeal) phase of swallowing. Physiological studies (Doty and Bosma, 1956; Miller, 1972) had demonstrated that the mylohyoid, geniohyoid and palatopharyngeal muscles were inhibited immediately prior to the swallowing act, which led Holstege et al. (1983) to speculate that this inhibition might be due to action of the pontine cell group.

2d 2. **Interneuronal projections to the hypoglossal nucleus.** The afferents to the hypoglossal nucleus

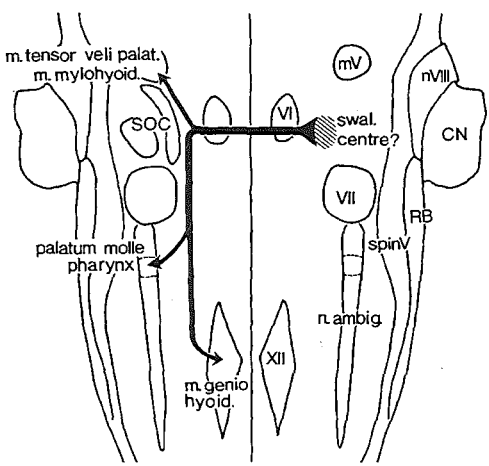


Fig. 18. Schematic drawing of the projections originating from neurons located just dorsomedial to the superior olivary complex. On the left side are indicated the muscles involved, on the right side the nuclei in which the motoneurons are located that innervate these muscles. It is suggested that this projection pattern might be involved in the first phase of swallowing.

are organized in largely the same way as those to the motor trigeminal motoneurons, which suggests that a strong relationship exists between the motor control of tongue and jaw movements. With the exception of some diffuse projections originating in the medullary ventromedial tegmentum and some primary afferent fibers from the C1-C3 dorsal roots (Holstege and Kuypers, 1977) all afferent projections to the hypoglossal nucleus are derived from the bulbar lateral tegmental field (Holstege et al., 1977; Travers and Norgren, 1983). Different levels of the lateral tegmental field project to different portions of the hypoglossal nucleus (Holstege unpublished results). For instance, interneurons in the respiration related caudal part of the lateral tegmentum project to other parts of the hypoglossal nucleus (see also Sica et al., 1984) than interneurons in the rostral part of the lateral tegmental field, which are involved in coordinating mouth closing movements. However, the functional importance of these differences is difficult to assess, because, although some anatomic subdivisions have been described (see section 1 c 6) within the hypoglossal nucleus of the cat, thorough knowledge about a functional subdivision (for example a different location in the hypoglossal nucleus for tongue protrusion and tongue retraction motoneurons) is still lacking. Only combined anatomic and physiological studies can reveal the meaning of the observed anatomic differences in projections to the hypoglossal nucleus, (see for example the projection from the NRA to the hypoglossal nucleus in Fig. 22).

2d 3. **Interneuronal projections to the facial nucleus.** The lateral tegmental field projects heavily to the facial nucleus. However, these projections differ strongly for each of the subnuclei, and will, therefore, be described for each subnucleus separately.

2d3 a. **Interneuronal projections to the ear- and platysma muscle motoneuronal cell groups.** The only portion of the lateral tegmental field projecting to the dorso- and ventromedial subnuclei, which contain ear and platysma muscle motoneurons respectively (Fig. 7), is its most caudal part, i.e. the area of the nucleus retroambiguus (NRA) (Holstege et al., 1977; Travers and Norgren, 1983; Holstege and Blok, 1989). These neurons probably form the rostral extent of a group of interneurons in the cervical cord projecting to the pinna- and platysma muscle motoneurons in the facial nucleus, because similar projections to the pinna muscle motoneuronal cell group are derived from the dorsal horn and intermediate zone at the level C1-C4 (Mehler, 1969; Holstege and Kuypers, 1977; Nakano et al., 1986). These fibers ascend bilaterally (Holstege et al., 1977), (and not only contralaterally as suggested by Nakano et al., 1986), to terminate mainly ipsilaterally in the dorsomedial and ventromedial facial subnuclei (ear- and platysma muscle motoneuronal cell groups). The platysma muscle motoneurons receive their afferents from the C1-C6 spinal cord (Mehler, 1969; Holstege and Kuypers, 1977). The ascending projections probably represent a similar pathway as the ascending propriospinal projections to the CTM motor nucleus (see section 2 c 4). Neither the CTM nor the external ear and platysma muscles contain muscle spindles and these muscles use the overlying skin for there proprioceptive information. Afferent fibers from the skin overlying the external ear and platysma muscles reach the central nervous system via the auriculotemporal branch of the trigeminal nerve, and the C2-C4 dorsal root fibers (pinna muscles) or the C2-C6 dorsal root fibers (platysma muscle). The fibers of the auriculotemporal nerve terminate in the dorsal portion of the C1-C3 dorsal horn (Panneton and Burton, 1981; Shigenaga et al., 1986), and the C2-C6 dorsal roots fibers terminate mainly on interneurons in the C2-C6 dorsal horn (Pfaller and Arvidsson, 1988). Such first order interneurons may project directly to the pinna and platysma muscle motoneurons in the facial nucleus (Holstege and Kuypers, 1977), but second order interneurons may also be involved. There exist other projections to the dorsomedial facial subnucleus, but they are derived from areas related to eye-head coordination, see section 4a).

2d3 b. **Interneuronal projections to the orbicularis oculi and retractor bulbi muscle motoneuronal cell groups and the neuronal organization of the blink reflex.** As for the ear and platysma muscles, the orbicularis oculi muscle does not contain muscle spindles and uses the overlying skin for its proprioception. The skin overlying the orbicularis oculi muscle and the cornea is innervated by the ophthalmic branch of the trigeminal nerve, the proximal fibers of which terminate in the ventral part of the spinal trigeminal nucleus (Panneton and Burton, 1981). Neurons in the ventral part part of the spinal trigeminal nucleus project to the blink motoneurons, which are the orbicularis oculi and retractor bulbi motoneu-

ronal cell groups (Takeuchi et al., 1979; Panneton and Martin, 1983; Holstege et al., 1986a,b; see sections 1 c 1 and 1 c 3). These disynaptic connections between trigeminal nerve afferents on the one hand and orbicularis oculi and retractor bulbi motoneurons on the other probably represent the R1 component of the blink reflex.

The blink reflex consists of two different reflexes; the orbicularis oculi reflex and the nictitating membrane response. The orbicularis oculi reflex in the cat consists of two EMG components (R1 and R2) (Lindquist and Martensson, 1970) and has latencies of 9-12 msec (R1) and 15-25 msec (R2). R1 is ipsilateral in all vertebrates; R2 is bilateral in humans (Kugelberg, 1952), but ipsilateral in cats (Hiraoka and Shimamura, 1977). The nictitating membrane response, which is the retraction of the eyeball by the retractor bulbi muscles, also consists of two components similar to the orbicularis oculi reflex (Guégan and Horcholle-Bossavit, 1981). The nictitating membrane response is used in studying conditioned reflexes, because it provides the experimenter with a high degree of control over the sensory consequences of the unconditioned stimulus (Gormezano et al., 1962). Although the R1 reflex is disynaptic in mammals, in the lizard primary trigeminal afferents seem to project directly on retractor bulbi motoneurons (Barbas-Henry and Wouterlood,1988), suggesting that in the lizard the R1 reflex is monosynaptic.

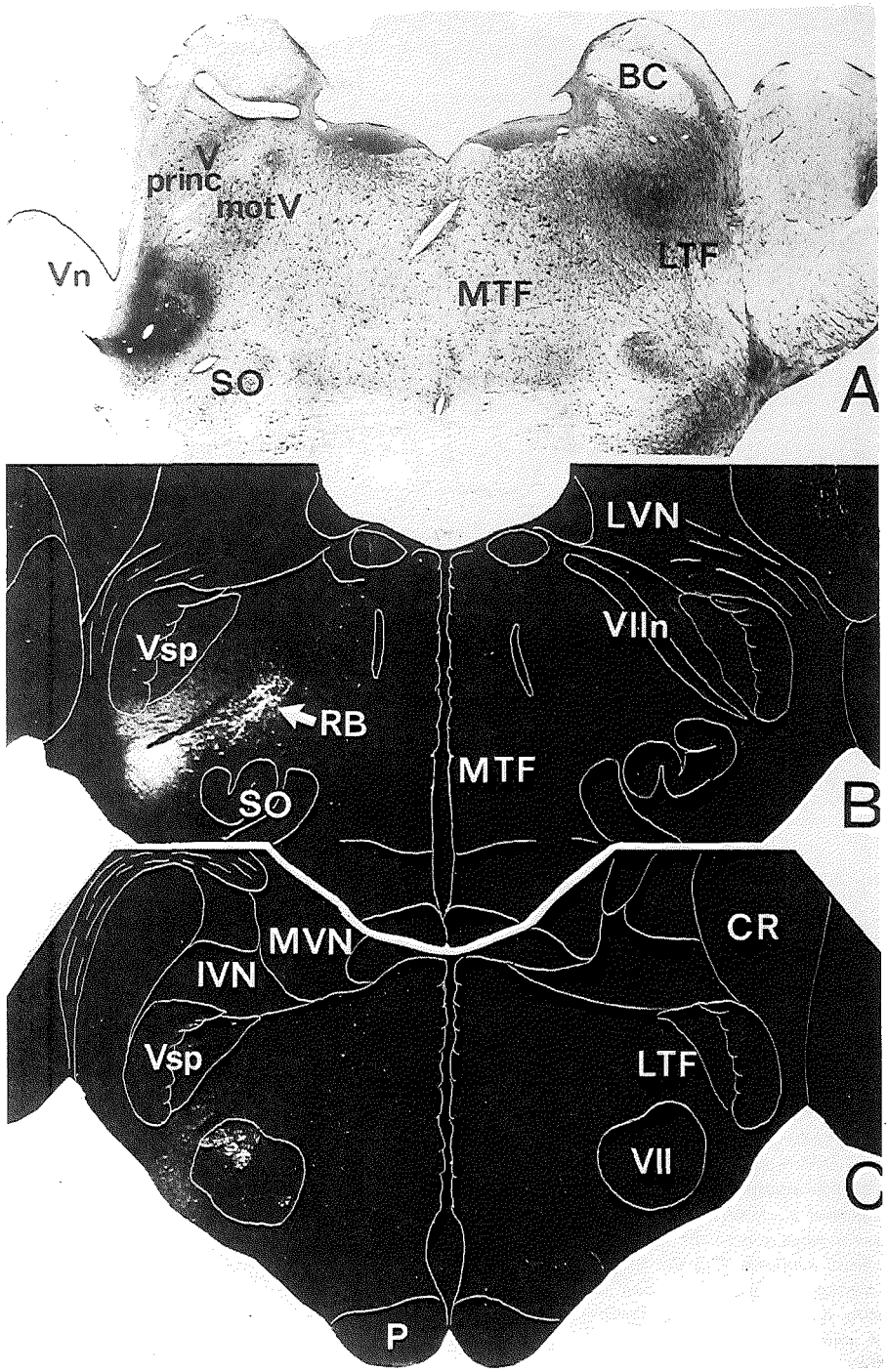
Holstege et al., (1986a,b) demonstrated a strong and specific ipsilateral projection to the blink motoneuronal cell groups from the ventrolateral pontine tegmental field, which they called the pontine blink premotor area (Fig. 19). It must be emphasized that this region, which forms part of the lateral tegmental field, lies outside the spinal trigeminal nucleus. It means that this projection cannot play a role in the disynaptic R1 component of the blink reflex.

Holstege et al. (1986a,b) also demonstrated specific projections from an area in the medial tegmentum at levels of the hypoglossal nucleus to the blink motoneuronal cell groups, which they called the medullary blink premotor area (Fig. 20). This region is not part of the lateral tegmental field, but belongs to the dorsal part of the medullary medial tegmentum, which plays an important role in eye- and neck muscle motor control (see section 4a). A similar projection to the retractor bulbi motoneuronal cell group has been described in the rabbit (Harvey et al., 1984). Holstege et al. (1986b) also observed projections from the medullary blink premotor area to the pontine blink premotor area (Fig. 20 A,B). The projections from the medullary blink premotor area were mainly bilateral, but some ipsilateral projections were also observed (Holstege et al. 1988). Like the pontine blink premotor area, the medullary blink premotor area is not located in the spinal trigeminal nucleus and thus cannot be involved in the disynaptic organization of the R1 blink reflex component.

Both the pontine and medullary blink premotor areas are probably involved in the R2 blink reflex component because 1) The R2 reflex component is not disynaptic, but multisynaptic (Kugelberg, 1952; Lindquist and Martensson, 1970; Hiraoka and Shimamura, 1977; Ongerboer de Visser and Kuypers, 1978), and the response consists of several spikes (Berthier and Moore, 1983; Kugelberg, 1952); 2) The R2 blink reflex component, according to Shahani and Young (1972), is responsible for actual closure of the eyelids. For such a motor performance, strong projections to the blink motoneurons are necessary. Holstege et al. (1986a,b) found such connections only from the pontine and medullary blink premotor areas; 3) The medullary blink premotor area projects specifically to the pontine blink premotor area, indicating that both areas are involved in the same neuronal organization. For a description of the afferent projections to the pontine blink premotor area (from red nucleus, pretectum and medullary blink premotor area) and the medullary blink premotor area (from the superior colliculus and pontine medial tegmentum), which may play an important role in the R2 reflex, see Holstege et al. (1986b; 1988 and Fig. 21).

There are also projections to the orbicularis oculi motoneurons that do not project to the retractor bulbi motoneurons. Such projections are derived from all levels of the bulbar lateral tegmental field from caudal medulla to the ventral parabrachial nuclei and nucleus Kölliker-Fuse (Holstege et al., 1986a). They probably play an important role in the relay of the cortical and lateral limbic control of the muscles around the eye.

Fig. 19. On the right. Brightfield (A) and darkfield (B and C) photomicrographs of a case with an injection of 3H-leucine in the caudal pontine ventrolateral tegmental field, not involving the trigeminal nucleus. Note the dense ipsilateral distribution of labeled fibers to the RB motoneuronal area (B) and the intermediate facial subnucleus (C), (from Holstege et al. 1986b)


BC
V
princ
motV
Vn
LTF
MTF
SO
A
LVN
VIIn
Vsp
RB
MTF
SO
B
MVN
CR
IVN
Vsp
LTF
VII
C
P

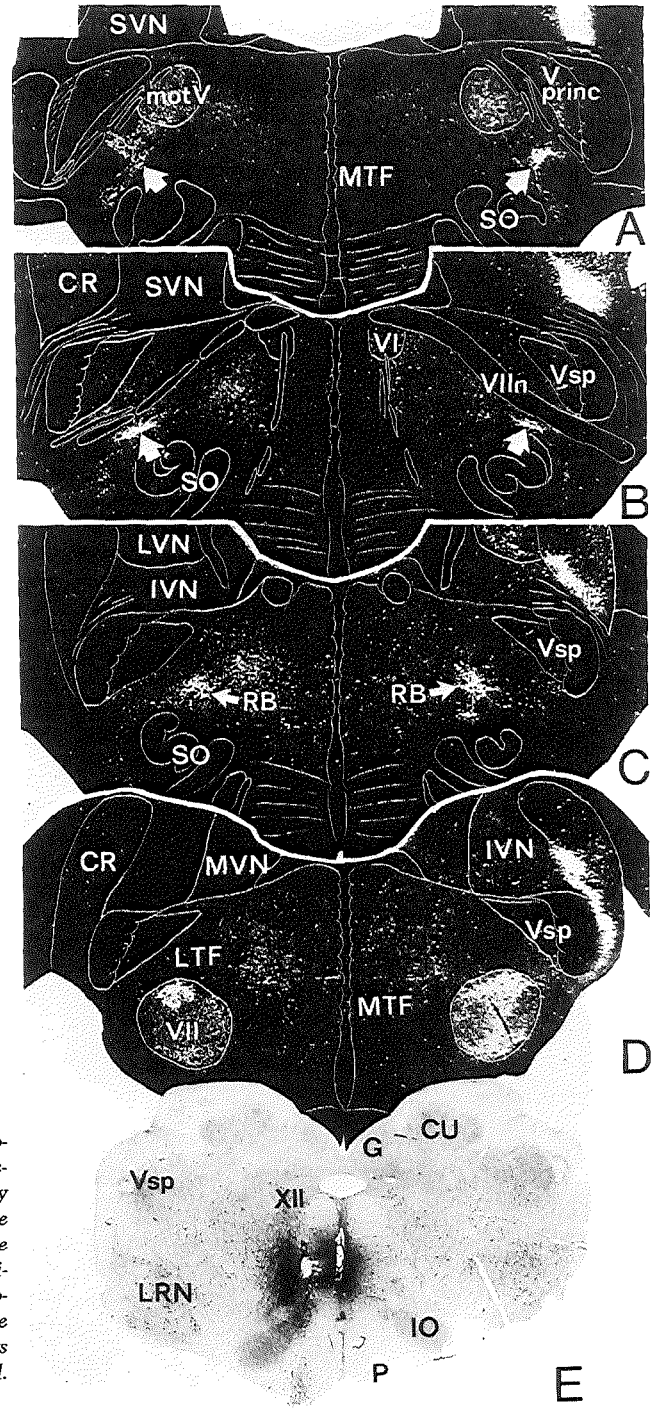


Fig. 20. Darkfield and brightfield photomicrographs of a case with an injection of ^{3}H-leucine in the medullary medial tegmentum at the level of the hypoglossal nucleus. Note the dense bilateral projection to the intermediate facial subnuclei (D), the RB motoneuronal cell group (C), and the pontine premotor blink area (arrows in A and B), (from Holstege et al. 1986b).

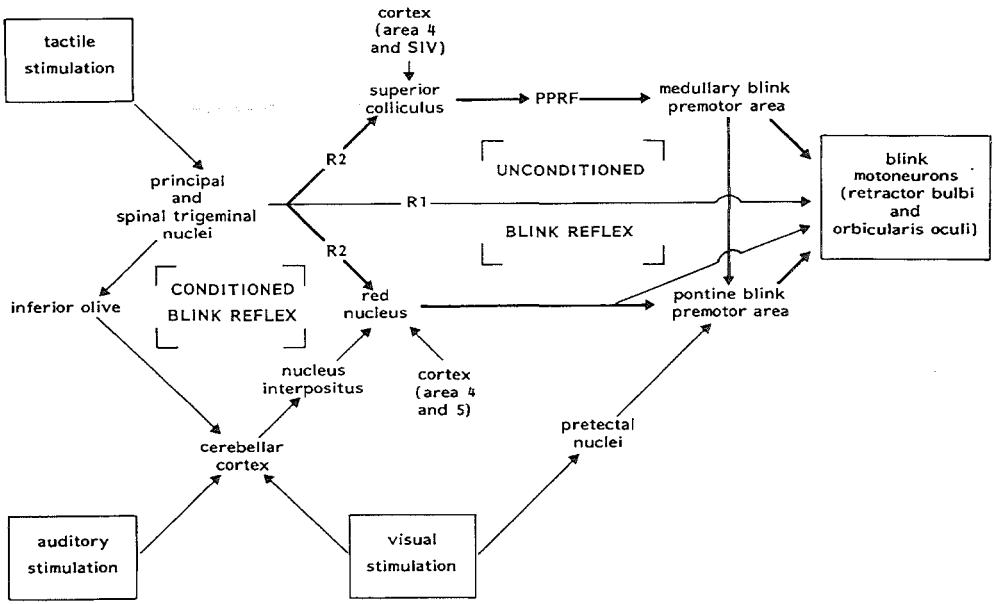


Fig. 21. Schematic representation of the pathways possibly involved in the anatomic framework of the R1 and R2 blink reflex components, (from Holstege et al. 1986b).

2d3 c. **Interneuronal projections to the motoneurons of the peri-oral muscles.** Peri-oral muscles, like the other facial muscles, do not contain muscle spindles and depend on the overlying skin for their proprioception. According to Shigenaga et al. (1986) the afferent information of the peri-oral skin terminates in the rostral portion of the caudal spinal trigeminal nucleus, just caudal to the obex. However, peri-oral muscle motoneurons, located in the lateral and ventrolateral facial subnuclei, receive only a limited number of afferents from interneurons in the caudal spinal trigeminal nucleus itself, but very many from interneurons in the lateral tegmentum medially adjoining the caudal spinal trigeminal nucleus (Holstege et al., 1977; Erzurumlu et al. 1980; Takeuchi et al., 1979; Panneton and Martin, 1983; Travers and Norgren, 1983). Although afferent projections to the peri-oral muscle motoneurons are derived from all levels of the lateral tegmental field, very strong projections originate in the most rostral portion of this area, the ventral parabrachial nuclei and the nucleus Kölliker-Fuse (Holstege et al., 1977; Takeuchi et al., 1979; Panneton and Martin, 1983; Travers and Norgren, 1983). Thus, similar to the organization of the afferents to the other facial muscle motoneurons, mainly second order neurons in the lateral tegmental field (intermediate zone) give rise to direct projections to motoneurons. Naturally, such second order interneurons receive also afferents from other sources, such as motor cortex, red nucleus and limbic system. Finally, neurons in the area of the NRA project mainly contralaterally to the ventrolateral facial subnucleus, innervating the muscles of the lower part of the mouth. Possibly, these projections take part in the expiration related system, which also projects mainly contralaterally to the mouth opening, pharynx, soft palate, and abdominal muscle motoneurons (Holstege, 1989).

2d 4. **Interneuronal projections to the dorsal group of the nucleus ambiguus.** Most subgroups of the nucleus ambiguus of the cat consist of motoneurons scattered in the ventrolateral part of the medullary lateral tegmental field. In the cat only one subgroup, the dorsal group, is so compact that it can be easily recognized in Nissl stained

sections (section 1 c 5). The dorsal group contains motoneurons innervating pharynx and soft palate. Direct projections to the dorsal group of the nucleus ambiguus have only been demonstrated to originate from a small number of areas. A light, but distinct projection is derived from a cell group dorsomedial to the superior olivary complex (see section 2 d 1). From studying a large number of cases the impression was gained that all other projections to the dorsal group of the nucleus ambiguus are derived from neurons in caudal parts of the medullary lateral tegmental field. From these projections, those from the caudal NRA are most numerous, especially contralaterally (Holstege, 1989; Fig. 22). Various studies have claimed that the nucleus ambiguus receives projections from the PAG and hypothalamus (Jürgens and Pratt, 1979; Mantyh, 1983; Saper et al., 1976; Ter Horst et al., 1984), but in none of these studies the precise subgroup of the nucleus ambiguus has been indicated. With respect to the dorsal group, it has been demonstrated that it receives no afferents from the PAG (Holstege, 1989), the hypothalamus (Holstege, 1987b), or amygdala and bed nucleus of the stria terminalis (Holstege et al. 1985). Furthermore, the impression was gained

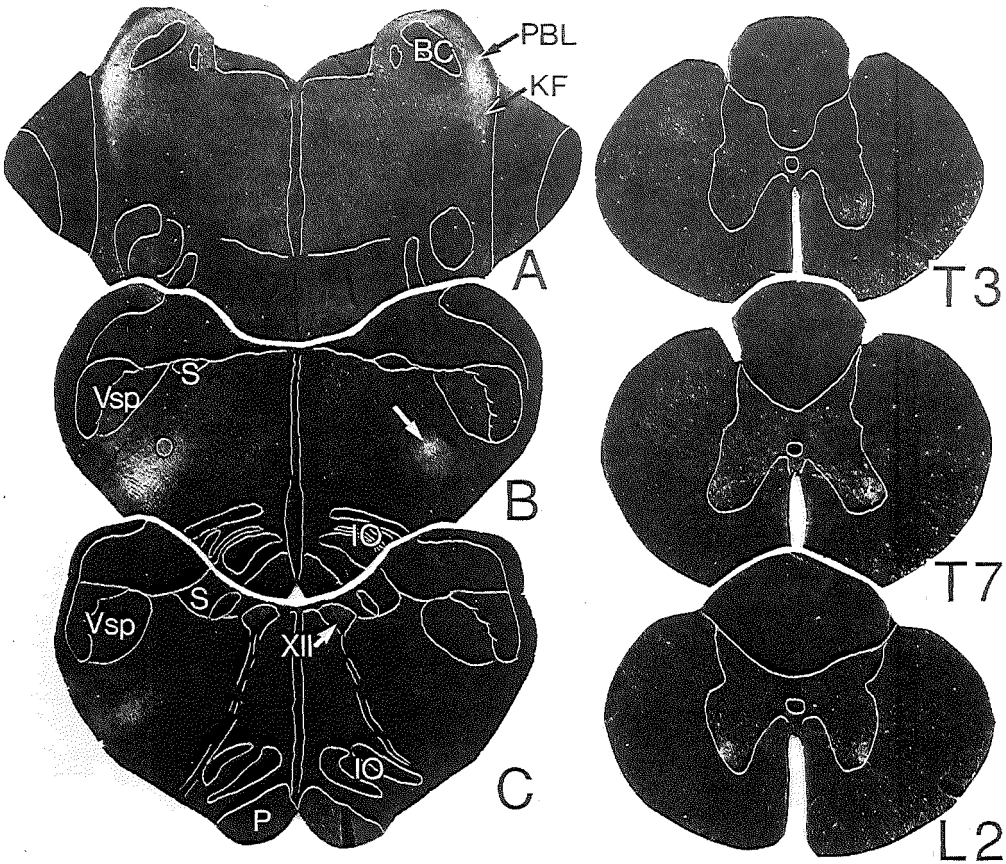


Fig. 22. Darkfield photographs of the caudal brainstem (A to C) and 3 segments (T3, T7 and L2) of the spinal cord after a relatively small injection of ^{3}H-leucine in the caudal NRA. Note the strong bilateral projections to the lateral parabrachial nuclei and nucleus Kölliker-Fuse in A and the very strong projection to the contralateral dorsal group of the nucleus ambiguus in B (arrow). The projection to the ipsilateral dorsal group (in circle) is weaker. Note further the bilateral projection to the dorsal part of the hypoglossal nucleus in C and the strong projections to the intercostal and abdominal motoneuronal cell groups in the spinal cord, (from Holstege, G., 1989).

that neither the ventral parabrachial nuclei/nucleus Kölliker-Fuse complex nor the lateral solitary nucleus project to the dorsal group (Holstege and Van Krimpen, 1986). These negative findings emphasize the importance of the caudal medullary lateral tegmental field, and especially the NRA as interneuronal link to the pharynx and soft palate motoneurons. The caudal NRA is strongly involved in expiration related activities (see section 3 a) and that is probably also true for its projection to the pharynx motoneurons in the dorsal group of the nucleus ambiguus, because it has been shown that the pharynx muscles are involved in expiratory activities (Sherrey and Megirian, 1975).

3. Bulbospinal interneurons projecting to motoneurons

In section 2 d it has been stated that the bulbar lateral tegmental field can be considered as the rostral continuation of the spinal intermediate zone. However, the bulbar lateral tegmental field not only contains interneurons for the motoneuronal cell groups V, VII, X and XII in the brainstem, but also for certain cell groups in the spinal cord, especially those involved in respiration, abdominal pressure, micturition and blood pressure.

3a. **Pathways involved in respiratory control.** Chemoreceptors in the carotid body and the pulmonary stretch receptors form the most important peripheral afferents for the respiratory system. From the carotid body, which senses arterial blood gases and pH, fibers terminate in the dorsomedial subnuclei of the solitary tract (Berger, 1980). These fibers have there cell bodies in the petrosal ganglion and pass via the glossopharyngeal and carotid sinus nerve. The pulmonary stretch receptors are located in the smooth muscle of the trachea, main bronchi and intrapulmonary airways. Peripheral afferent fibers innervating all these receptors, arise from cell bodies in the nodose ganglion and project to the nuclei of the solitary tract (Donoghue et al., 1982). The organization of the CTM and ear reflex pathways (sections 2c 4 and 2d3 a) indicate that the premotor interneurons are located close to the incoming afferent fibers. The same is true for the premotor interneurons of the respiratory motor output system. They are located in the caudal medulla, where the vagal nerve enters the brainstem, and not in the spinal cord. Therefore, the medullary projections to the respiratory motoneurons should not be considered as a specific supraspinal control system, but as a propriobulbospinal system.
Physiological studies have demonstrated that the brainstem neurons can be subdivided into inspiratory and expiratory neurons, although in the dorsolateral pons some inspiratory-expiratory phase-spanning neurons exist (see Feldman, 1986 for review). From the inspiratory neurons 50-90% project to the spinal cord, while almost all expiratory neurons project to the cord. The spinal cord projecting inspiratory neurons send excitatory fibers to the phrenic nucleus, while the expiratory neurons send excitatory fibers to the abdominal muscle motor nuclei. The expiratory fibers in the Bötzinger complex send inhibitory fibers to the phrenic nucleus. The importance of these pathways is exemplified by the finding that a transection at the spino-medullary junction completely abolishes respiratory movements of diaphragm, rib cage and abdominal muscles (St. John et al., 1981).

3a 1. **Projections to the phrenic nucleus.** The phrenic nucleus, containing motoneurons innervating the diaphragm, is by far the most important motor nucleus for inspiratory activity. Although the phrenic nucleus receives only a limited number of descending propriospinal afferent connections (see section 2 c 5), it receives very strong descending monosynaptic connections from four sources in the caudal brainstem:

3a1 a. **Projections from the ventrolateral nucleus of the solitary tract.** Physiological studies have pointed out the existence of direct monosynaptic excitatory inputs from the ventrolateral solitary nucleus (called dorsal respiratory group by investigators of the respiratory system) to the phrenic nucleus (Cohen et al., 1974; Hilaire and Monteau, 1976; Davies et al., 1985a,b). Pulmonary vagal afferents terminate in the medial and dorsolateral subnuclei of the solitary tract nucleus and to a limited extent to the ventrolateral solitary nucleus (Donoghue et al., 1982; Berger and Averill, 1983). The neurons in the ventrolateral solitary nucleus, projecting to the phrenic nucleus, can be subdivided into R_a and R_b neurons. Pulmonary stretch receptors inhibit the R_a neurons and excite the R_b neurons (Von Baumgarten et al., 1957). The excitation of the R_b neurons is at least in part monosynaptic, but monosynaptic connectivity

between pulmonary stretch receptors and the R_a neurons could not be demonstrated (Averill et al., 1984; Berger et al., 1985). Both R_a and R_b neurons have been shown to drive the spinal inspiratory neurons (phrenic and external intercostal) monosynaptically (Fedorko et al., 1983; Lipski et al., 1983; Lipski and Duffin, 1986).

Using anterograde tracing techniques, Loewy and Burton, (1978) and Holstege, G. and Kuypers, (1982) demonstrated such direct connections anatomically. Their finding was confirmed by Rikard-Bell et al., (1984) and Onai and Miura, (1986) using retrograde tracing techniques. According to Holstege (unpublished results), a contingent of labeled fibers crossed the midline just rostral to the obex and descended contralaterally via the dorsolateral, but mainly ventral funiculi until low thoracic levels. From these fibers, many terminate on both the somata and dendrites of the phrenic motoneurons at caudal C4 to C6 levels. Phrenic motoneuronal dendrites extend far into the lateral and ventrolateral funiculi and the medial and dorsal parts of the ventral funiculus (Cameron et al., 1983). The terminations on the phrenic motoneurons are so strong that terminations on the more distal portions of the dendrites are easily recognizable (Fig. 23). The projection to the contralateral phrenic motoneurons is slightly stronger than to the ipsilateral one. Part of the fibers terminating on ipsilateral phrenic motoneurons travel through the ipsilateral ventral funiculus. However, the impression is gained (Holstege, unpublished results) that the majority of the fibers terminating in the ipsilateral phrenic nucleus, descend via the contralateral ventral funiculus (Fig. 23), and recross in the ventral commissure of the C5-C6 spinal level. This idea is further supported by the finding that a C2 hemi-infiltration with HRP resulted in only a few labeled neurons in the ipsilateral and many in the contralateral ventrolateral solitary nucleus (Holstege unpublished results).

The R_a and R_b neurons not only receive afferent information from the pulmonary stretch receptors, but also from neurons in other parts of the solitary nucleus and from neurons in other parts of the brainstem (e.g. the Bötzinger neurons, see section 3 a 1 c) and limbic system (see sections 5 d 2; 5 d 4 and 5 e).

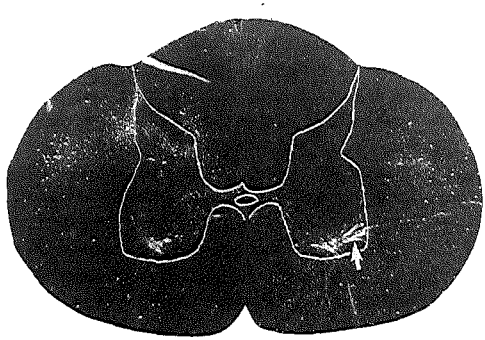


Fig. 23. Darkfield photomicrograph of a section through the C5 segment of the spinal cord in the cat, after a ^{3}H-leucine injection in the area of the lateral solitary nucleus on the left side. Note the strong bilateral projections to the phrenic motor nuclei and the heavy projection to the distal dendrites of the phrenic motoneurons on the contralateral side (arrow). Note also that almost all descending fibers in the ventral and ventrolateral funiculi are contralateral.

3a1 b. **Projections from the para-ambiguus nucleus/rostral NRA.** Physiological studies have demonstrated that at levels around the obex, in the area of the nucleus ambiguus, a group of premotor respiratory interneurons is located. This group is called the rostral retroambiguus or paraambiguus or by scientists working in the respiratory system the ventral respiratory group. The rostral part of this group, (rostral to the obex), contains mainly inspiratory neurons, while the caudal portions, (caudal to the obex) contain mainly expiratory neurons. Especially at levels around the level of the obex the inspiratory and expiratory neurons are intermingled. Some of the inspiratory neurons maintain mono-, di-, or oligosynaptic excitatory projections to phrenic motoneurons (Merrill, 1970; Cohen et al., 1974; Davies et al., 1985a,b) and, similar to the neurons in the ventrolateral solitary nucleus, they form a source of drive to inspiratory motoneurons (phrenic and external intercostal). Holstege, G. and Kuypers, (1982) and Holstege et al. (1984b) were the first to demonstrate that neurons in this area indeed projected to the somata and dendrites of the phrenic motoneurons at caudal C4 to C6 levels, in an almost identical manner as the neurons in the ventrolateral solitary nucleus. Later anterograde (Feldman et al., 1985; Yamada et al., 1988) and retrograde (Rikard-Bell et al., 1984; Onai and Miura, 1986) tracing studies confirmed their findings. Holstege, (unpublished observations), observed a rostrocaudal difference in the pathways to the phrenic and the intercostal motoneurons. The rostral portion of the rostral NRA project mainly

via the dorsolateral and lateral funiculus, the caudal portions of the rostral NRA (at levels around the obex) project mainly via the ventral funiculus. Similar to the projections from the ventrolateral solitary nucleus, a substantial portion of the fibers terminating in the ipsilateral phrenic nucleus seems to be derived from the contralateral ventral funiculus, recrossing in the ventral commissure of the C5 and C6 segments (Holstege, unpublished results). The most caudal part of the NRA does not project to the phrenic nucleus (Holstege, 1989). There exist many different opinions about how many inspiratory neurons in the ventrolateral tegmentum project monosynaptically to the phrenic nucleus. Estimations range from 2-7% (Fedorko et al., 1983) via 25% (Merrill, 1974) and 28% (Sears et al., 1985) to 61% (Hilaire and Monteau, 1976). All other projections would be di- or oligosynaptic. In contrast to the physiological studies, anatomic tracing studies give the impression that most of the rostral retroambiguus/para-ambiguus projections to the phrenic nucleus are monosynaptic. They show specific pathways to the phrenic nucleus and very few projections to other portions of the cervical gray.

The finding of Holstege G. and Kuypers, (1982); Feldman et al. (1985) and Holstege, G. (1989) that neurons in the caudal NRA also project to the phrenic nucleus, (according to Holstege, G. (1989) only the most caudal portion of the NRA does not project to the phrenic nucleus), seem to contradict the physiological findings of Merrill, (1970). Merrill found no electrophysiologically identified expiratory neuron in the caudal NRA, which project to the phrenic nucleus. However, caudal NRA neurons, projecting to phrenic motoneurons may not be involved in expiration, but in vomiting, coughing and other abdominal straining activities. During vomiting and coughing the phrenic motoneurons are simultaneously active with the abdominal muscle motoneurons. Miller et al. (1987) found that neurons in the caudal NRA control vomiting, during which strong contractions of the abdominal muscle motoneurons take place. However, they also found that only one third of the expiratory neurons in the caudal NRA are active during vomiting. By making lesions in the upper cervical spinal cord, Newsom Davis and Plum (1972) were able to achieve a considerable reduction of the diaphragmatic component of the cough response, without any reduction of the diaphragmatic activity during rhythmic breathing. Furthermore, Newsom Davis (1970) showed that the descending pathways involved in producing hiccups in man was largely distinct from those concerned with rhythmic breathing.

3a1 c. **Projections from the Bötzinger complex.** The ventrolateral part of the lateral tegmental field of the medulla just caudal to the facial nucleus contains a group of neurons, called the Bötzinger complex. The name Bötzinger was chosen by participants at a symposium on the nucleus tractus solitarius in Heidelberg in honor of a German vineyard (Feldman, 1986). According to anterograde tracing studies of Holstege et al., (1984b); Ellenberger and Feldman, (1988) and Otake et al. (1988), Bötzinger neurons give rise to a specific bilateral projection to somata and dendrites of the phrenic nucleus by way of the contralateral dorsolateral funiculus. It was difficult to assess whether there were also descending fibers in the ipsilateral dorsolateral funiculus terminating in the ipsilateral phrenic nucleus, but the impression was gained that the ipsilateral phrenic nucleus receives fibers via the contralateral dorsolateral funiculus, recrossing at the C5/C6 level. Furthermore, Bötzinger neurons project bilaterally, but mainly contralaterally to the lateral solitary nucleus, and ipsilaterally to the NRA. Physiological studies have demonstrated that Bötzinger neurons are expiratory neurons, which, during the expiratory phase, monosynaptically inhibit the phrenic motoneurons (Merrill and Fedorko, 1984) as well as the inspiratory neurons in the ventrolateral solitary nucleus (Merrill et al., 1983) and rostral NRA (Fedorko and Merrill, 1984). It has been suggested that the Bötzinger projections to the caudal NRA are excitatory (see Long and Duffin, 1986 for review).

3a1 d. **Projections from the ventrolateral parabrachial nuclei and nucleus Kölliker-Fuse.** A fourth source of phrenic nucleus afferents is the ventrolateral part of the parabrachial nuclei, including the area of the nucleus Kölliker-Fuse. This area was called pontine pneumotaxic center (Lumsden, 1923; Bertrand and Hugelin, 1971; Bertrand et al., 1974), but presently called pontine respiratory group by respiratory system investigators. According to anterograde tracing results of Holstege, G. and Kuypers, (1982), neurons in this area give rise to specific bilateral, but mainly ipsilateral projections to the somata and dendrites of the phrenic motoneurons (Fig. 24). Similar results were obtained by Rikard-Bell et al. (1984), using retrograde tracing techniques, but questioned by Onai and Miura (1986), who, after injecting HRP

in the phrenic nucleus observed only sparse labeling in the dorsolateral pontine tegmentum. The last authors explained their failure to identify neurons in the dorsolateral pons by suggesting that the projections of this area to the phrenic nucleus were disynaptic, having a synaps in the NRA. However, transneuronal transport is difficult to obtain with the anterograde triated leucine tracing technique (Grafstein and Laureno, 1973). It can only be observed in the case of extremely dense projections to certain areas, in which the silver grains are not only located *around*, but also *over* the cell bodies. An example is the retinal projection to the superior colliculus (Collewijn and Holstege, 1984), but even then the transneuronal fiber labeling is very weak. In none of the cases with dorsolateral pontine injections, silver grains were found *over* the cell bodies of the NRA (Holstege, unpublished observations), which excludes the possibility of labeling disynaptic projections from the dorsolateral pons to the phrenic nucleus.

Electrical stimulation in the area of the ventrolateral parabrachial nuclei and nucleus Kölliker-Fuse elicits different respiratory effects, depending on the phase, intensity and precise site of the stimulus. Stimulation in the dorsolateral pons (Cohen, 1971) revealed that dorsally in this area strong inspiratory facilitatory effects were obtained, while ventrally in this area, i.e. medial to the rubrospinal tract strong expiratory facilitatory effects were observed. The neurons projecting to the phrenic nucleus are located in the area between the inspiratory and expiratory facilitatory regions and at present it is unclear whether they have an excitatory or inhibitory effect on the phrenic motoneurons. Lesions in the dorsolateral pontine tegmentum produce so-called inspiratory apneusis, i.e. the inspiratory phase continues for abnormal length (Lumsden, 1923), which can sometimes lead to death by asphyxia. Later studies (Von Euler et al., 1976) demonstrated that a rise of body temperature causes a progressive shortening of apneustic duration after apneusis-promoting lesions in the area of the parabrachial nuclei and nucleus Kölliker-Fuse. Although the dorsolateral pons does not seem to contain the pneumotaxic centre, it exerts strong excitatory influence on the inspiratory switch-off mechanisms. Furthermore it may play an important role in the coordination of the respiratory functions with cardiovascular control functions (Mraovitch et al., 1982; Connelly and Wurster, 1985), also because neurons in the same dorsolateral pontine area project very strongly to the T1-T3 intermediolateral cell column (Holstege, G. and Kuypers, 1982).

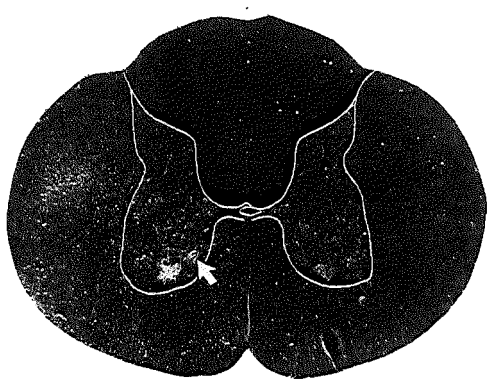


Fig. 24. Darkfield photomicrograph of a section through the C5 segment of the spinal cord in the cat, after a ^{3}H-leucine injection in the area of the ventral parabrachial nuclei and nucleus Kölliker-Fuse. Note on the left the strong ipsilateral projections to the phrenic nucleus and to the distal dendrites of the phrenic motoneurons (arrow). Note on the right the limited projection to the contralateral phrenic nucleus.

3a 2. **Projections to the intercostal motoneurons**

As indicated in section 1 a 4, the intercostal motoneurons in the upper thoracic cord are mainly inspiratory and at caudal thoracic levels expiratory. Physiological studies of Davies et al. (1985a,b) and Duffin and Lipski, (1987) have demonstrated that the inspiratory brainstem neurons in the ventrolateral solitary nucleus and in the area of the rostral retroambiguus/para-ambiguus not only project to the phrenic nucleus, but also to the intercostal motoneurons. Moreover, Davies et al. (1985a,b) found inspiratory neurons, that project to both the phrenic and intercostal motoneurons. The ventrolateral solitary nucleus projects contralaterally to the upper thoracic ventral horn (Fig. 25) but fibers are scarce at mid-thoracic levels and absent beyond the level of T11 (Holstege, G. and Kuypers, 1982; Holstege, unpublished results). Merrill and Lipski, (1987) studied the retroambiguus projections to the external and internal intercostal motoneurons physiologically. They concluded that monosynaptic connections are rare (≈4%) and that most of them go via segmental interneurons, which would produce synchronized discharge of intercostal motoneurons. Anatomic tracing results of Holstege, G. and Kuypers, (1982) demonstrate that neurons in the area of the NRA

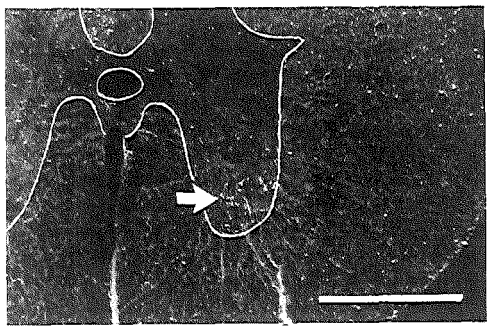


Fig. 25. Darkfield photomicrograph of a section through the T3 segment of the spinal cord in the cat, after a ^{3}H-leucine injection in the area of the lateral solitary nucleus on the left side. Note the projection in the contralateral ventral horn to motoneurons, probably innervating inspiratory intercostal muscles. Bar represents 1 mm.

just rostral to the obex project mainly contralaterally to large portions of the upper thoracic ventral horn, containing inter- and motoneurons. At caudal thoracic levels, however, the projections are very strong in the abdominal muscle motoneuronal cell groups. These projections are probably derived from expiratory neurons in the NRA. Projections from the Bötzinger complex to intercostal or abdominal muscle motoneurons were not observed, although Bongianni et al. (1988) have found inhibitory effects on the inspiratory external intercostal motoneurons, of stimulation in the Bötzinger cell group. The dorsolateral pontine neurons, giving rise to specific projections the phrenic nucleus, were not found to project to the inspiratory intercostal motoneurons (Holstege, unpublished results). The projections to the expiratory intercostal motoneurons are much more difficult to assess, because these motoneurons are intermingled with expiratory abdominal muscle motoneurons in the caudal thoracic cord. In all likelihood the expiratory intercostal motoneurons receive the same projections from the expiratory medullary neurons as the abdominal muscle motoneurons (see next section).

3a 3. **Projections to the cutaneus trunci, abdominal muscle and pelvic floor motor nuclei**

Abdominal muscles not only play a role in the expiration phase of respiration, but also in straining of the abdomen in relation to coughing, vomiting, hiccups, parturition and defecation. Abdominal muscle motoneurons, located in the T5 to L3 spinal cord (see section 1 a 4) receive strong monosynaptic afferent projections from the expiration related interneurons in the rostral as well as caudal parts of the NRA. Anatomic studies of Holstege, G. and Kuypers, (1982); Feldman et al. (1985) and Holstege G. (1989) show that the NRA gives rise to fibers, which cross the midline at the caudal medullary levels and travel via the contralateral ventral funiculus, to terminate on the somata and dendrites of the abdominal muscle motoneurons bilaterally, with a slight contralateral preponderance (Fig. 22). Holstege, G. (1989) and Holstege (unpublished observations) also observed that the caudal part of the rectus abdominis muscle motoneuronal cell column, which is located medial to the motoneurons innervating the other abdominal muscles (Holstege et al., 1987; Miller, 1987; Fig. 3), does not receive NRA projections. Apparently, the rectus abdominis muscle is not involved in abdominal straining related activities, which is in agreement of the finding of Ninane et al. (1988), that in the dog the rectus abdominis, unlike the other abdominal muscles, does not show phasic expiratory electromyographic (EMG) activity during respiration.

Thus, retrograde and anterograde tracing studies indicate that specific brainstem projections to the abdominal muscle motoneurons originate only in the NRA (from levels around the obex until C1). However, within the confines of the NRA neurons have different functions. Some are specifically involved in expiration and some others in vomiting and/or coughing or other abdominal straining activities. Only one third of the neurons seems to be active in more than one of these functions. The abdominal muscles also play a role in posture control. However, the supraspinal posture control areas are located in other parts of the brainstem (see section 4 a) and do not involve the NRA.

The CTM motor nucleus also receives afferent fibers from the NRA, suggesting that the CTM is also involved in abdominal straining activities (Holstege and Blok, 1989; Fig.14). Moreover, neurons in the ventral parabrachial nuclei and nucleus Kölliker-Fuse, which also send fibers to the ipsilateral phrenic nucleus and T1-T3 intermediolateral cell column, project to the ipsilateral CTM motor nucleus (Holstege and Blok, 1989; Fig.14). It remains to be determined whether the pontine projection to the CTM motor nucleus is respiration related.

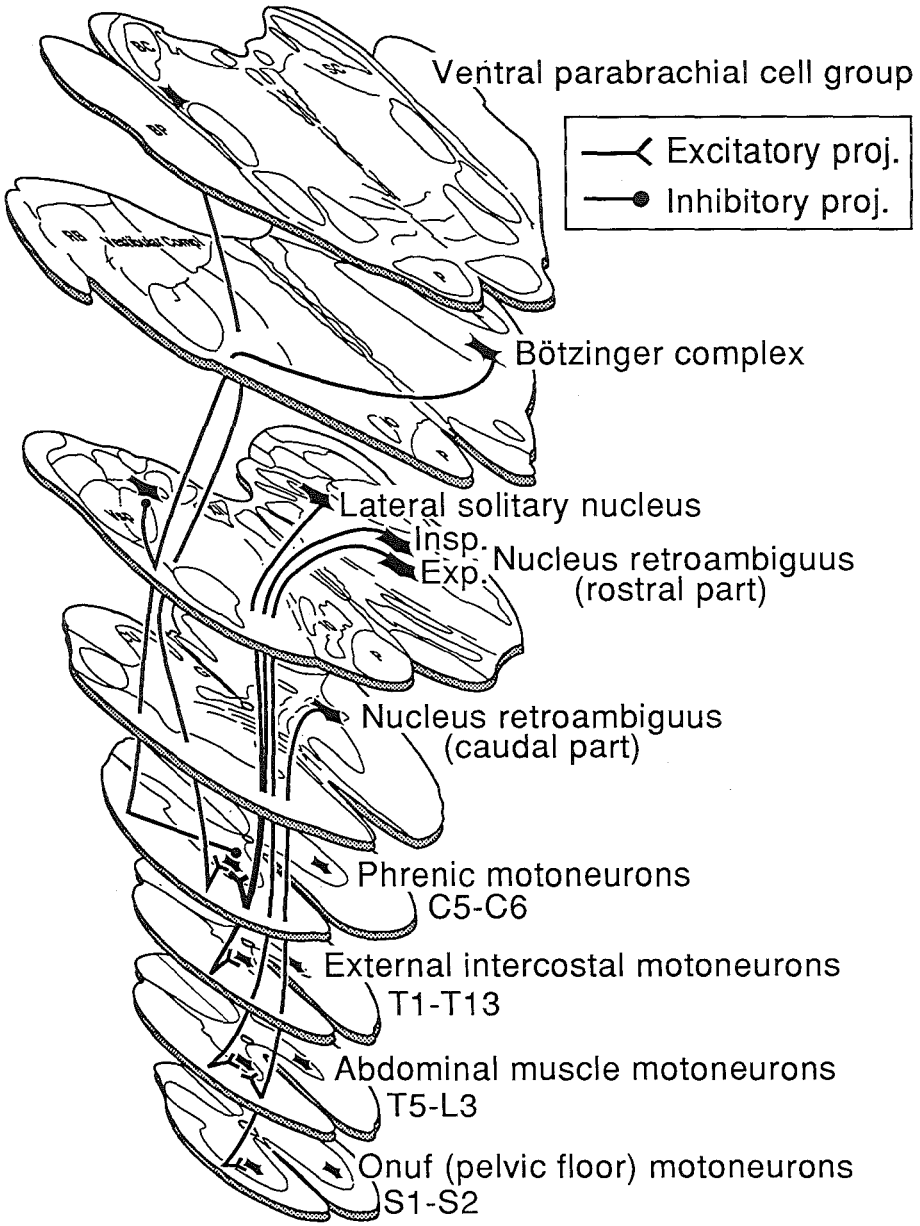


Fig. 26. Schematic overview of the pathways controlling respiration and abdominal pressure. Note that from the descending pathways originating in the medulla, only the contralateral ones are indicated, although there exist to a limited extent some ipsilateral pathways.

A relatively small number of neurons in the most caudal portion of the caudal NRA project to the nucleus of Onuf, bilaterally but with a contralateral preponderance (Holstege and Tan, 1987). The involvement of the Onuf nucleus in this projection suggest that the pelvic floor also plays a role in abdominal straining and that neurons in the caudal NRA coordinates abdominal straining via direct projections to all abdominal wall muscle motoneurons, i.e. diaphragm, abdominal muscles and pelvic floor. Fig. 26 gives an schematic overview of the pathways controlling respiration and abdominal pressure

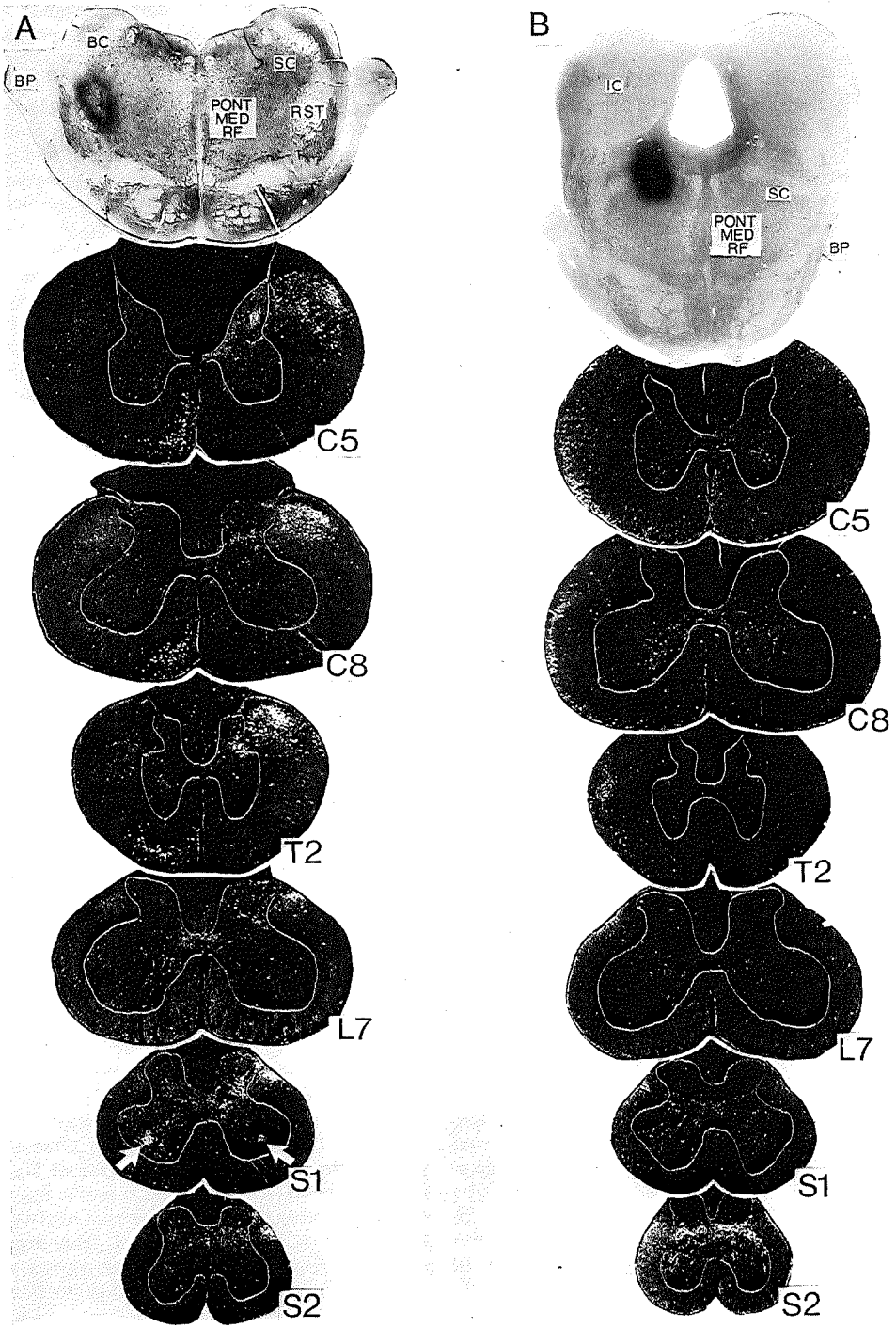
3b. **Pathways involved in micturition control.**

The brainstem, via its long descending pathways to the sacral cord, is vital for coordinating muscle activity of bladder and bladder-sphincter, during normal micturition. The importance of the brainstem in micturition control is best shown by patients with spinal cord injuries above the sacral level. They have great difficulty in emptying the bladder because of uncoordinated actions of the bladder and sphincter (detrusor-sphincter dyssynergia). Such disorders never occur in patients with neurologic lesions rostral to the pons, which indicates that the coordinatory neurons are located in the pontine tegmentum (Blaivas, 1982). Barrington showed as early as 1925 that these neurons are probably located in the dorsolateral part of the pontine tegmentum, because bilateral lesions in this area in the cat produced inability to empty the bladder. Later studies of Nathan and Smith (1958) supported this finding, which led to the concept that micturition can be considered as a spino-bulbo-spinal reflex.

Recent anatomic studies in the rat (Loewy et al., 1979), opossum (Martin et al., 1979b); cat (Holstege et al., 1979; 1986c) and monkey (Westlund and Coulter, 1980) have shown that neurons in the dorsolateral pontine tegmentum, medial to the locus coeruleus, project directly and specifically to the sacral intermediolateral cell group (parasympathetic motoneurons) as well as to the sacral intermediomedial cell group, but not to the nucleus of Onuf (Fig. 27). The nucleus of Onuf receives specific projections from neurons in more lateral parts of the dorsolateral pontine tegmental field (Holstege et al., 1979; 1986c). The dorsolateral pontine tegmentum does not project to the sacral parasympathetic motoneurons (Fig. 27). In order to differentiate between the two different areas in the dorsolateral pons, Holstege et al. (1986c) called them the M- (medial) and L- (lateral) regions. The M-region probably corresponds with Barrington's (1925) area. Neither the M- nor the L-region projects to the lumbar intermediolateral (sympathetic) cell groups.

Electric stimulation in the M-region produces an immediate and sharp decrease in the urethral pressure and pelvic floor EMG, followed after about two seconds by a steep rise in the intravesical pressure (Holstege et al., 1986c), mimicking complete micturition (Fig. 28). The decrease in the urethral pressure cannot be caused by a direct M-region projection to the nucleus of Onuf, because such a projection does not exist (Holstege et al., 1979,1986c). A study of Griffiths et al. (1989) suggests that the M- and L-regions may have reciprocal inhibitory connections. Stimulation in the L-region results in strong excitation of the pelvic floor musculature and an increase in the urethral pressure (Holstege et al., 1986c; Fig. 29). Bilateral lesions in the M-region result in a long period of urinary retention, during which detrusor activity is depressed and the bladder capacity increases. Bilateral lesions in the L-region give rise to inability to store urine. The urethral pressure decreases and due to absence of the inhibitory influence of the L-region on the M-region detrusor activity increases. The result is that the urine is expelled prematurely because of a combination of increased detrusor activity and decreased urethral pressure. Outside the episodes of detrusor activity the urethral pressure is not depressed below normal values (Griffiths et al., 1989). These observations suggest that during the filling phase the L-region has a continuous excitatory effect on the nucleus of Onuf, which inhibits urethral relaxation coupled with detrusor contraction. When micturition takes place, the M-region excites, via a direct pathway, the sacral parasympathetic motoneurons, but at the same time the M-region inhibits the L-region, which disinhibits sphincter relaxation so that micturition can take place.

Although patients with neurological lesions in the brain rostral to the pons never experience detrusor-sphincter dyssynergia, they suffer from lack of control of the initiation of micturition. This raises the question of what determines the beginning of the micturition act. Obviously, precise information about the degree of bladder filling is conveyed to supraspinal levels, but specific sacral projections to the pontine micturition center have not been demonstrated. This suggests that other structures, rostral to the pontine micturition center, determine the initiation of mic-


A
BC
SC
BP
PONT
MED
RF
RST
C5
C8
T2
L7
S1
S2
B
IC
SC
PONT
MED
RF
BP
C5
C8
T2
L7
S1
S2

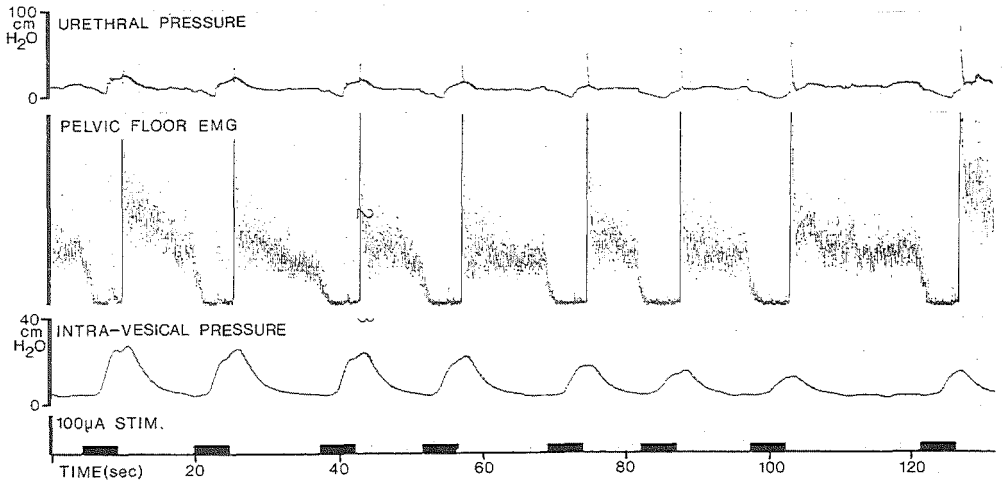


Fig. 28. Recordings of urethral pressure, pelvic floor EMG, intravesical pressure, and stimulus timing during M-region stimulation in the cat. Note the immediate fall in urethral pressure and pelvic floor EMG after the beginning of the stimulus and the steep rise in the intravesical pressure about two seconds after the beginning of the stimulus. This pattern mimics complete micturition (from Holstege et al. 1986).

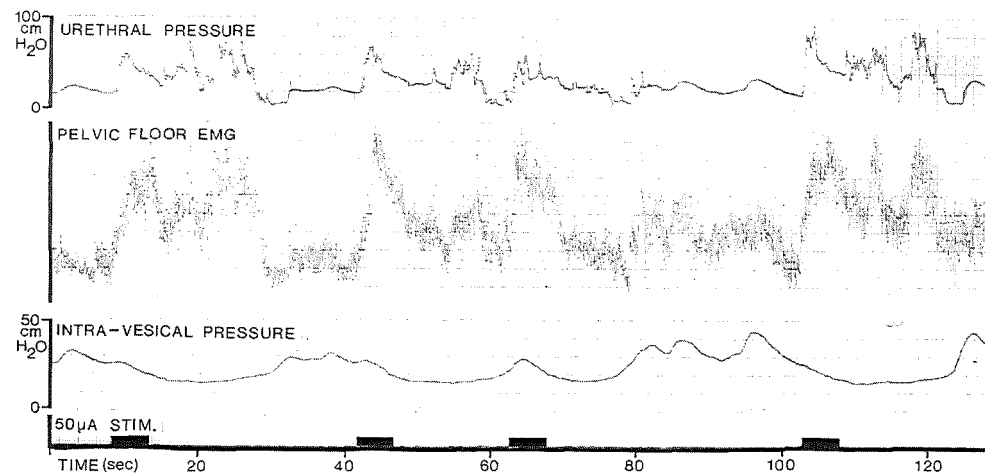
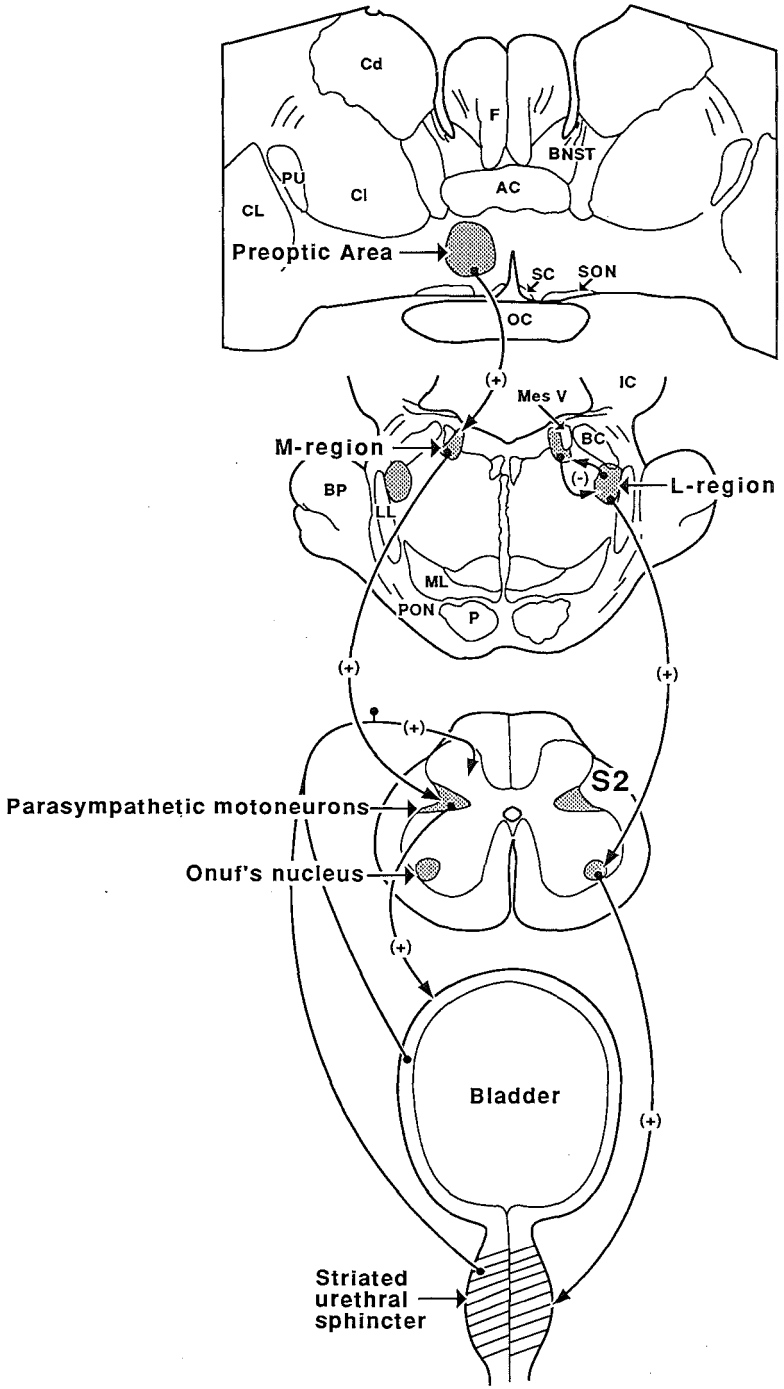


Fig. 29. Recordings of urethral pressure, pelvic floor EMG, intravesical pressure, and stimulus timing during L-region stimulation in the cat. At the beginning of each period of stimulation there is an immediate increase in the urethral pressure and the pelvic floor EMG. Note that the spontaneous detrusor contractions tend to be inhibited by the stimulation (from Holstege et al. 1986).

Fig. 27. On the left. Brightfield photomicrographs of autoradiographs showing the tritiated leucine injection areas and darkfield photomicrographs showing the spinal distributions of labeled fibers after an injection in the L-region (on the left) and after an injection in the M-region (on the right) in the cat. Note the pronounced projection to the nucleus of Onuf (arrows in the S1 segment) in the case with an injection in the L-region (left). Note also the dense distribution of labeled fibers to the sacral intermediolateral (parasympathetic motoneurons) and intermediomedial cell groups after an injection in the M-region (S2 segment on the right).


Cd
F
BNST
PU
Cl
AC
CL
Preoptic Area
SC
SON
OC
(+)
Mes V
IC
M-region
BC
(-)
L-region
BP
LL
ML
PON
P
(+)
(+)
(+)
S2
Parasympathetic motoneurons
Onuf's nucleus
(+)
Bladder
(+)
Striated
urethral
sphincter

turition. Such structures would be expected to project specifically to the M-region of the pontine micturition center. Many clinical studies indicate that cortical (the medial frontal gyrus and anterior cingulate lobe) as well as subcortical structures (septum, preoptic region of the hypothalamus, and amygdala) are involved in control of the beginning of micturition. Experimentally, the only structure that has been demonstrated to project specifically to the M-region is the preoptic area in the cat (Holstege, 1987b; section 5 d 4). Stimulation in this area produces micturition-like contractions (Grossman and Wang, 1956), but it is not known whether it determines the beginning of micturition. It is possible that regions other than the preoptic area also project to the M-region. Furthermore, the fact that the pelvic floor, including the intrinsic external urethral sphincter, is under voluntary control, suggests that direct cortical projections to the nucleus of Onuf may exist. However, such projections have not been demonstrated convincingly. Figure 30 gives a schematic overview of the spinal and supraspinal structures involved in micturition control and their role in the neuronal framework of micturition.

3c. Pathways specifically involved in cardiovascular control

The spinal cord motoneurons involved in cardiovascular control are the sympathetic motoneurons in the intermediolateral cell column (IML) (see section 1 b 1). Afferent projections to these neurons originate in several parts of the medulla and pons. Strong afferent projections originate in the nucleus raphe magnus and pallidus, but these structures project diffusely to all parts of the spinal gray matter and not specifically to the IML. They are probably involved in level setting mechanisms of all spinal cord neurons (see section 5 b). Physiological studies have indicated that the neurons specifically controlling cardiovascular functions are located in the ventrolateral part of the lateral tegmental field between inferior olive and facial nucleus. In several studies this area is referred to as the VLM (ventrolateral medulla), a large area extending from the level of the superior olivary nucleus to the most caudal extent of the lateral reticular nucleus. Although the whole area contains neurons which project to the IML (Loewy et al., 1981; Ross et al., 1984; Ciriello et al., 1986), the strongest projections are derived from the an area in the rostral VLM, at the level of the caudal pole of the facial nucleus and just caudal to this nucleus. This area, some parts of which are located close to the ventrolateral surface of the medulla, is also called the subretrofacial nucleus. Subretrofacial neurons must not be mistaken by cells belonging to the Bötzinger complex, which are located in the retrofacial nucleus, dorsal and medial to the subretrofacial nucleus, and project to the phrenic nucleus (see section 3 a 1 c). An injection of tritiated leucine in this area shows thin labeled fibers descending in the lateral funiculus to terminate in the IML throughout its total length (T1-L4) bilaterally, but at upper thoracic levels mainly ipsilaterally (Holstege, unpublished results; Fig. 31). The neurons in the subretrofacial nucleus take part in the rostral sympatho-excitatory VLM area, which is essential for the maintenance of the vasomotor tone and reflex regulation of the systemic arterial blood pressure (see Ciriello et al., 1986 for review). At least part of the cells in this area projecting to the IML contain substance P and phenylethanolamine N-methyltransferase, which catalyzes the synthesis of adrenalin (Lorenz et al., 1985). Lovick (1987) and Dampney and McAllen (1988) have shown that neurons in the rostral part of the subretrofacial nucleus project specifically to the IML neurons, innervating the kidney and adrenal medulla, while neurons in the caudal part of the subretrofacial nucleus innervate more caudal parts of the IML, with neurons innervating the hindlimb. Neurons in more caudal portions of the VLM, i.e. around the obex, have sympatho-inhibitory effects, probably by inhibiting neurons in the rostral VLM by means of release of nor-adrenalin (Ciriello et al., 1986).

Other bulbar areas projecting directly to the IML are the solitary nucleus (Loewy and Burton, 1978) and the lateral parabrachial nuclei and nucleus Kölliker-Fuse (Holstege, G. and Kuypers, 1982). The latter area projects specifically to the rostral (T1-T3) portion of the IML, but the significance of these projections, and whether or not they play a role in cardiovascular control remains to be determined.

Fig. 30. On the left.
Schematic representation of the spinal and supraspinal structures involved in micturition control. Excitatory pathways are indicated by "(+)", inhibitory projections by "(-)". (From Holstege and Griffiths, 1990).

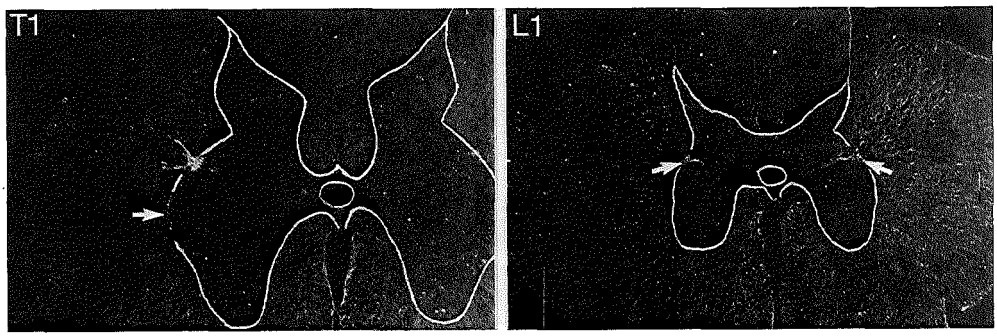


Fig. 31. Darkfield photomicrographs of a section through the T1 (left) and L1 (right) spinal segments after an injection of ^{3}H-leucine in the ventrolateral medulla (VLM) just caudal to the facial nucleus. The injection included the subretrofacial nucleus. Note the specific projections to the IML mainly ipsilaterally at T1, bilaterally at L1 (arrows). The arrow in T1 points to labeled fibers terminating on distal dendrites of the preganglionic motoneurons. Note also the specificity of the projection and the absence of other descending pathways

4. Descending pathways of somatic motor control systems

As pointed out in section 1a, the somatic motoneurons in the cervical and lumbosacral enlargements of the spinal cord can be subdivided into lateral and medial columns. At upper cervical, thoracic and upper lumbar levels all motoneurons belong to the medial column. Motoneurons

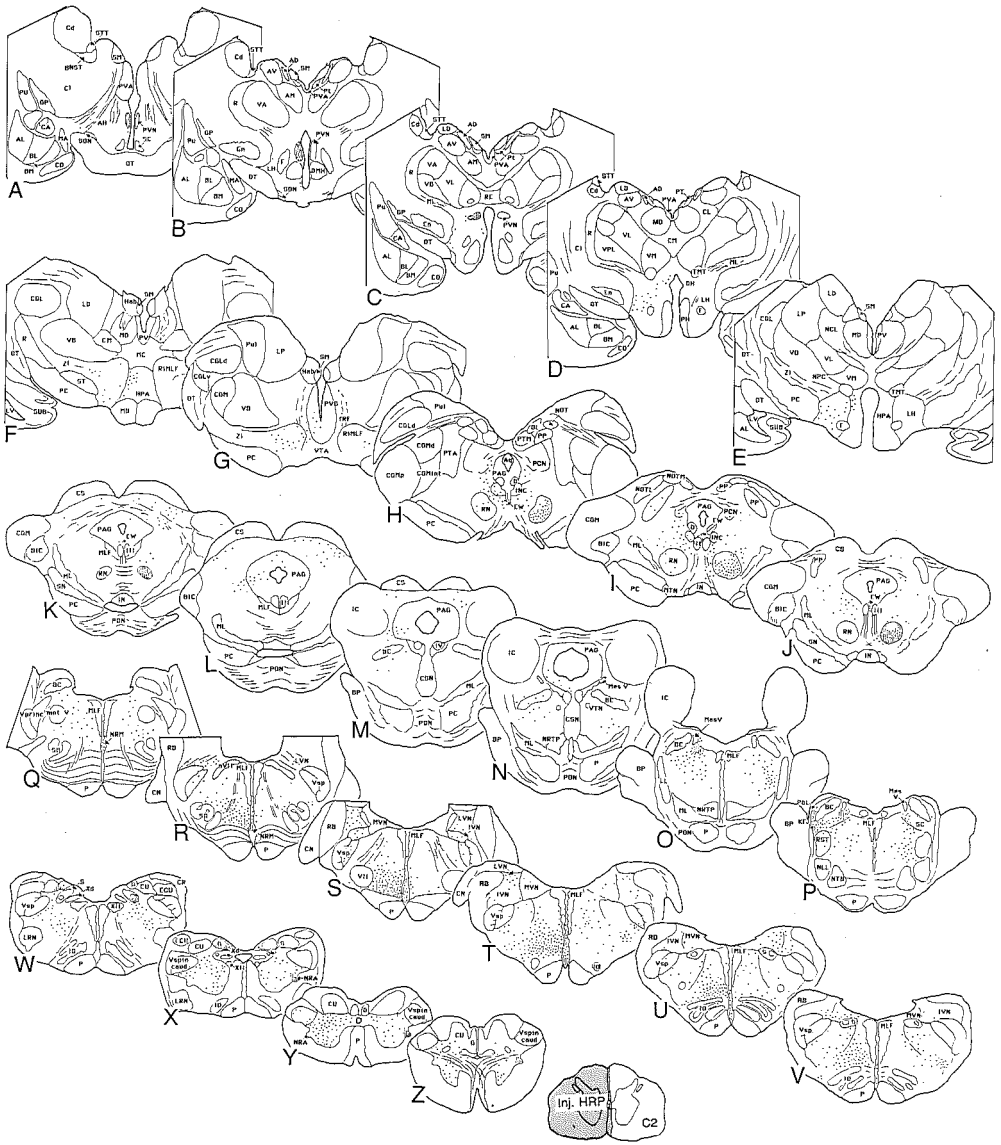
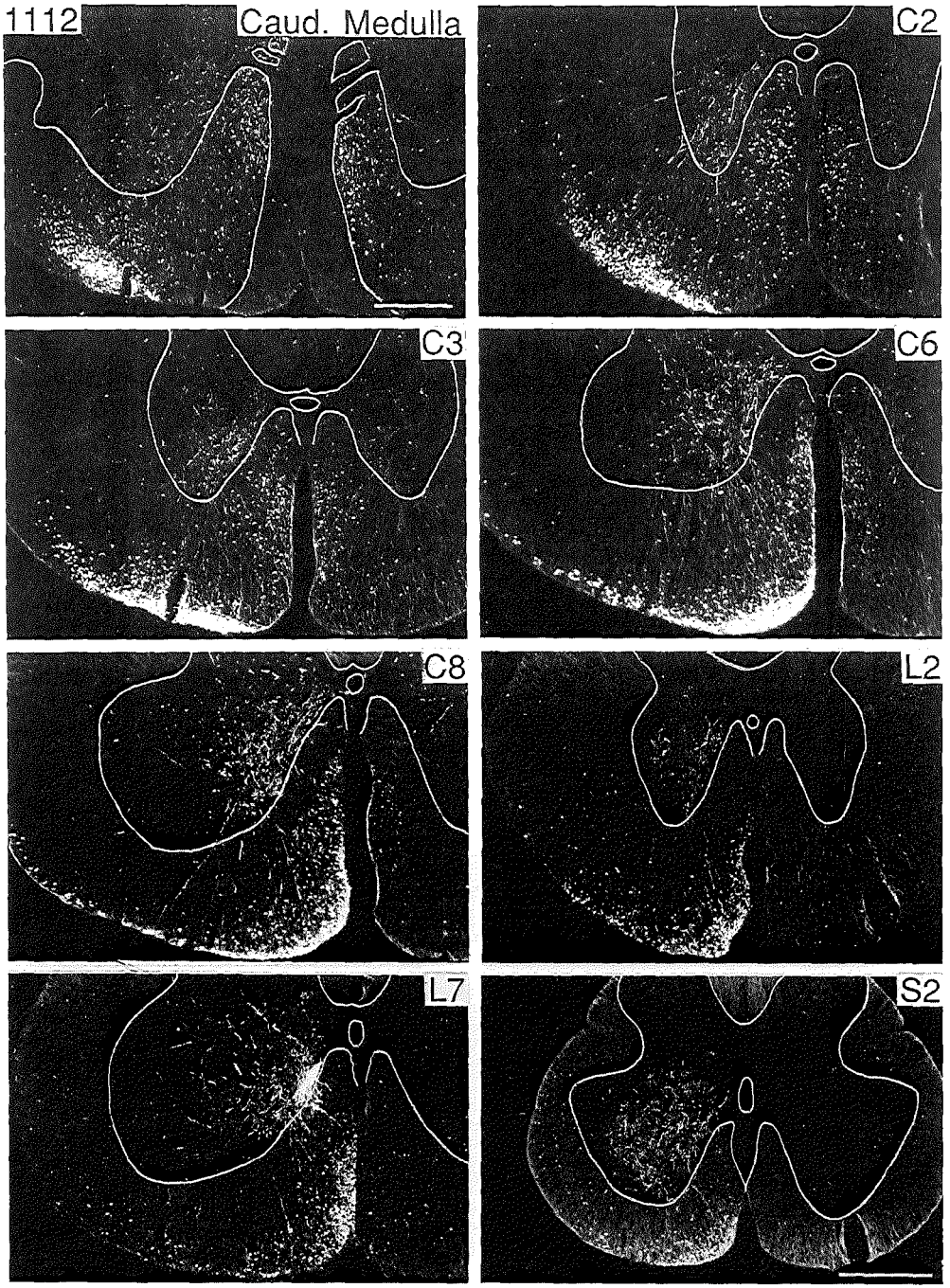


Fig. 32. Schematic representation of the distribution of the HRP labeled neurons in brainstem and diencephalon of the cat after hemi-infiltration of HRP in the C2 spinal cord. (From Holstege, 1988a).


1112
Caud. Medulla
C2
C3
C6
C8
L2
L7
S2

in the lateral motor column innervate the distal extremity muscles, i.e. the fore- and hindpaws in the cat (hands and feet in primates) and the distal portions of the fore- and hindlegs. Motoneurons in the medial column innervate proximal and axial musculature, such as muscles of neck, shoulder, trunk, hip and back. A similar mediolateral organization appears to exist in the propriospinal pathways (section 2c 1) and in the descending pathways belonging to the somatic motor system. The medial motor column receives afferents mainly from cell groups in the brainstem which project via the ventral funiculus of the spinal cord (Petras, 1967; Holstege, G. and Kuypers, 1982; Holstege, 1988b). They form the medial descending system. The lateral motor column receives its supraspinal fiber afferent projections mainly from red nucleus and cerebral motor cortex via the dorsolateral funiculus (lateral descending system) (Nyberg-Hansen and Brodal, 1964; Petras, 1967; Kuypers and Brinkman, 1970; Armand et al., 1985; Holstege, 1987a; Holstege and Tan, 1988). They represent the lateral descending system.

4a. The medial descending system

The function of the medial system is maintenance of erect posture (antigravity movements), integration of body and limbs, synergy of the whole limb and orientation of body and head (Kuypers, 1981). Within the medial system most of the proximal and axial muscles are simultaneously active, which explains why they are mutually connected via long propriospinal systems (section 2c 3) and why supraspinal structures, projecting to inter- and motoneurons of the proximal and axial muscles are not clearly somatotopically organized. In order to control orientation of body and head, the medial system also determines the position of the eyes in space, which includes the position of the head on the trunk and the position of the eyes in the orbit. The following brainstem cell groups belong to the medial system: Field H of Forel, the interstitial nucleus of Cajal and surrounding reticular formation (INC-RF), the intermediate and deep layers of the superior colliculus, a cell group in the lateral PAG and adjacent tegmentum, the pontine and upper medullary medial tegmentum, a cell group in the contralateral medullary medial tegmental field and the lateral, medial and inferior vestibular nuclei (Fig. 32). They all project (directly or indirectly) to the oculomotor nuclei in the brainstem (section 1c 1) (see Büttner-Ennever and Büttner, 1988 for review) and to the neck muscle inter- and motoneurons in the first five cervical segments of the spinal cord (section 1a 1) (Holstege, 1988b).

4a 1. **Pathways involved in regulating axial and proximal body movements.** Neurons in the pontine and upper medullary medial tegmentum and in the lateral vestibular nucleus (LVN) send a large number of fibers via the ventral funiculus to laminae VIII and the adjoining part of VII throughout the length of the spinal cord (Jones and Yang (1985) in the rat; Martin et al. (1979c) in the opossum; Nyberg-Hansen and Mascitti (1964); Nyberg-Hansen, (1965); Petras, (1967); Holstege, G. and Kuypers, (1982) and Holstege, (1988b) in the cat; Fig. 33). With respect to the neurotransmitters involved in the long reticulo- and vestibulospinal pathways, Kimura et al. (1981), utilizing a polyclonal antibody, reported that the large neurons in the pontine and medullary medial tegmentum and in the LVN were choline acetyl transferase (ChAT) positive, i.e. contained acetylcholine. On the other hand, Jones and Beaudet (1987) utilizing a monoclonal antibody did not find these neurons ChAT positive, but found that some other (smaller) neurons in the inferior and medial vestibular nuclei contained ChAT. Thus, it remains to be determined whether or not the long medially descending systems contain acetylcholine as a neurotransmitter.

The function of the long medially descending systems is nicely illustrated by experiments of Lawrence and Kuypers (1968a,b) in the monkey. They made, after pyramidotomy, (interruption of the

Fig. 33. On the left.

Darkfield photomicrographs of the caudal medulla and 7 different levels of the spinal cord in a cat with a ^{3}H-leucine injection in the vestibular complex (lateral vestibular nucleus, rostrodorsal portion of the inferior vestibular nucleus and cell group y). Note the heavily labeled lateral vestibulospinal tract fibers in the ventral part of the ipsilateral ventral funiculus gradually passing medially. Note also the medial vestibulospinal tract fibers on both sides in the dorsal part of the ventral funiculus of the cervical cord. Note further the dense projections to the medial part of the ipsilateral ventral horn throughout the length of the spinal cord and the very strong fiber terminations in a small area at the L7 level. This area contains many neurons projecting to the inferior olive (Armstrong and Schild, 1979). (From Holstege, 1988b).

corticospinal fibers at the level of the medulla oblongata), a bilateral lesion of the upper medullary medial tegmentum. The lesion not only destroyed the spinal cord projecting neurons in the upper medulla, but also interrupted all the fibers descending medially in the brainstem, e.g. the ponto-, tecto-, interstitio- and vestibulospinal fibers. Such lesions produced monkeys with postural changes of trunk and limbs, inability to right themselves, and a severe deficit in the steering of axial and proximal limb movements. On the other hand picking up pieces of food with the hand was considerably less impaired. Recovery was slow and when the animals were able to walk, they had great difficulty in avoiding obstacles and frequently veered from course. In the examining chair the animals had no problem to pick up pieces of food from a board with their hands and bring them to the mouth. Unlike the animals in which the medial system is intact, they did not orient themselves to the approaching food, but followed the food only with their eyes.

4a 2. **Pathways involved in regulating eye- and head movements.** The medial system brainstem structures can be subdivided into cell groups steering vertical eye- and head movements and those steering horizontal eye- and head movements. Examples of the first group are the interstitial nucleus of Cajal and adjacent reticular formation (INC-RF) and Field H of Forel, which includes the rostral interstitial nucleus of the MLF (Büttner-Ennever et al., 1982; Holstege and Cowie, 1989). For the horizontal eye and head movements, the superior colliculus and the pontine and medullary medial tegmental field are most important (Büttner-Ennever and Holstege, 1986).

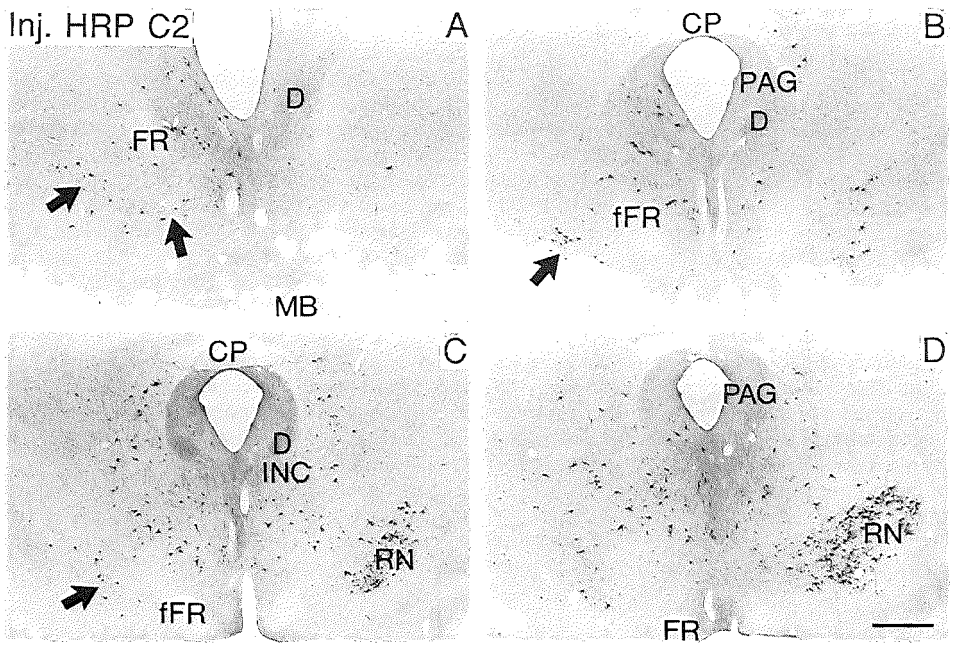


Fig. 34. Brightfield photomicrographs of transverse sections of the ventral part of the rostral mesencephalon in a cat with a left hemi-infiltration of HRP in the C2 spinal cord. Note the scattered HRP labeled neurons in the caudal Field H of Forel (arrows in A, B and C). Note also the many HRP labeled neurons in the reticular areas surrounding the INC in C and D. Many of these neurons are located contralaterally, but some of them may be labeled because the hemi-infiltration extended slightly into the contralateral ventral funiculus of the C2 segment. Note further the many labeled rubrospinal neurons on the contralateral side in B, C and D and one labeled neuron in A. Bar represents 1 mm. (From Holstege and Cowie, 1989).

4a2 a.. **Projections of Field H of Forel and interstitial nucleus of Cajal and surrounding areas (INC-RF).** Neurons in Field H of Forel and interstitial nucleus of Cajal, projecting to the extraocular muscle motoneurons, are mainly located in the so-called rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), (Graybiel, 1977; Büttner-Ennever and Büttner, 1978), and in the interstitial nucleus of Cajal (INC), (Carpenter et al., 1970; Graybiel and Hartwieg, 1974). The major portion of the spinally projecting neurons are not located in the riMLF or INC proper but in adjacent areas, i.e. the ventral and lateral parts of the caudal third of the Field H of Forel and in the INC-RF (Zuk et al., 1983; Spence and Saint-Cyr, 1988; Holstege, 1988b; Holstege and Cowie, 1989; Figs. 32 and 34).

Neurons in caudal Field H of Forel project to the pontine and upper medullary medial tegmental field (Büttner-Ennever and Holstege, 1986), and via the ventral part of the ventral funiculus, to the lateral part of the upper cervical ventral horn (Holstege, 1988b; Holstege and Cowie, 1989; Fig. 35). This area contains the laterally located motoneuronal cell groups, innervating cleidomastoid, clavotrapezius and splenius muscles (see section 1 a 1; Fig. 1). At lower cervical levels labeled fibers are distributed to the medial part of the ventral horn. Projections from the caudal Field H of Forel to thoracic or more caudal spinal levels are sparse (Holstege, 1988b; Holstege and Cowie, 1989).

Neurons in the INC-RF, together with a few neurons in the area of the nucleus of the posterior commissure, project bilaterally to the medial part of the upper cervical ventral horn, via the dorsal part of the ventral funiculus (Holstege, 1988b; Holstege and Cowie, 1989). This area includes motoneurons innervating prevertebral flexor muscles and some of the motoneurons of the biventer cervicis and complexus muscles (Section 1 a 1; Fig. 1). Further caudally, labeled fibers are distributed to the medial part of the ventral horn (laminae VIII and adjoining VII) similar to the projections of Field H of Forel. A few INC-RF neurons project to low thoracic and lumbosacral levels (Holstege and Cowie, 1989).

Stimulation in the riMLF and adjacent areas produces vertical saccadic eye and fast head movements (Hassler, 1972; Büttner et al., 1977), and lesions in this area, including the H-field of Forel, result in vertical gaze paralysis (Büttner-Ennever et al., 1982; Brandt and Dieterich, 1987). On the other hand, stimulation in the INC-RF was shown

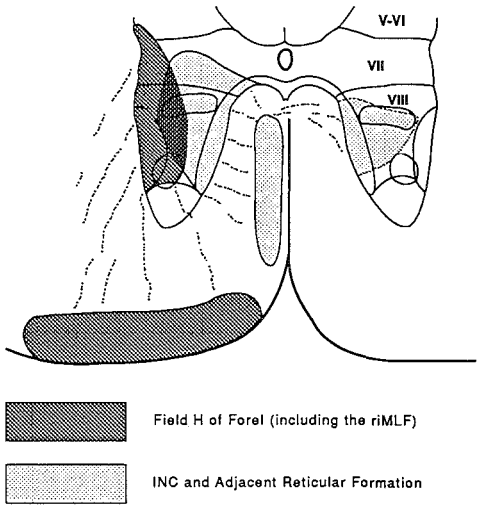


Fig. 35. Schematic drawing showing the pathways as well as the termination zones of the projections originating in caudal Field H of Forel and in the INC-RF. Note that the neurons in the caudal Field H of Forel project to more lateral parts of the ventral horn than the neurons of the INC-RF. Note also that the ventromedial nucleus (see Fig. 1) does not receive direct afferent connections from this part of the brainstem. (From Holstege and Cowie, 1989).

to cause ocular torsion, head tilt and head rotation in the frontal plane to the ipsilateral side (Anderson, 1981; Fukushima et al., 1978). Unilateral electrolytic and kainic acid lesions and temporary (procaine) lesions in the INC-RF produce deficits in the vertical vestibulo-ocular and vestibulocollic reflexes (Anderson, 1981), as well as head tilt to the opposite side (Hyde and Toczek, 1962). Bilateral lesions result in dorsiflexion of the head (Fukushima et al., 1978). These physiological observations suggest that the riMLF is primarily involved in eye and head **movement** control, while the INC-RF is mainly concerned with eye and head **position**. The differences in the spinal cord projections from these two areas may form the anatomic framework for the differences in neck muscle control.

4a2 b. **Projections from the colliculus superior.** Retrograde tracing studies indicate that the neurons in the superior colliculus, projecting to the spinal cord, are mainly located in the lateral portion of its intermediate and deep layers on the

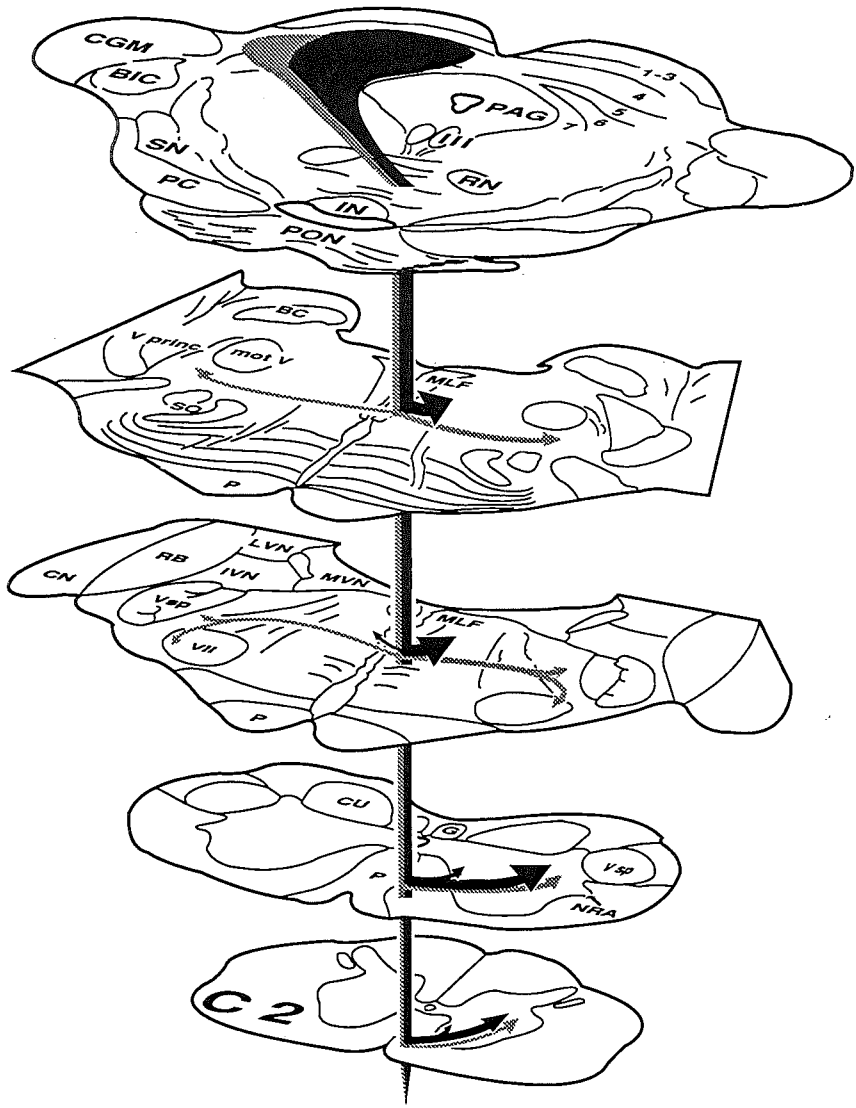
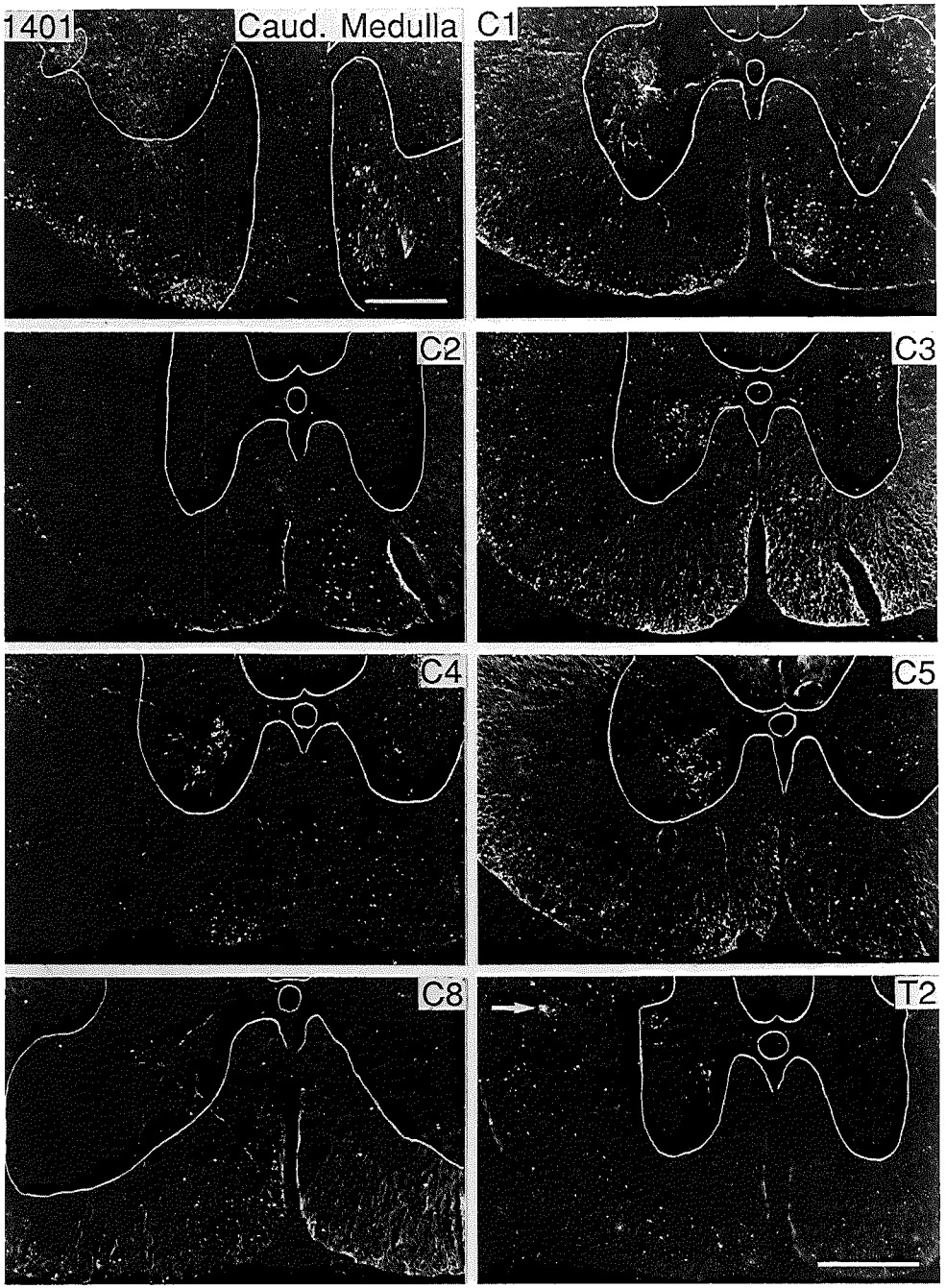


Fig. 36. Schematic drawing of the contralaterally descending pathways of the intermediate and deep layers of the superior colliculus to the caudal brainstem. Note the strong projections to the dorsal two thirds of the contralateral pontine and medullary medial tegmental field and the small ipsilateral fiber distribution to this area, mainly at the level of the facial nucleus. Note also that at caudal medullary and upper cervical levels the main contralateral projection is to the lateral part of the intermediate zone, although there exists a small component terminating more medially. Furthermore, originating mainly in the lateral part of the superior colliculus, a specific component is indicated in gray, descending medially with the contralateral tecto-bulbo-spinal tract. The fibers of this component terminate in the lateral tegmental field and lateral facial subnuclei bilaterally, with an ipsilateral preponderance. (From Holstege and Cowie, in preparation)

contralateral side. Anterograde tracing studies (Nyberg-Hansen, 1964a; Petras, 1967; Coulter et al., 1979; Huerta and Harting, 1982; Holstege, 1988b and Cowie and Holstege, in preparation) show that from the superior colliculus a stream of thick diameter fibers pass lateral and ventral to the PAG and cross the midline via the dorsal tegmental decussation. On the contralateral side the fibers descend in a medial position through the caudal mesencephalon, pons and medulla into the ventromedial funiculus of the spinal cord (Fig. 36), where they continue until the level of C4 and a few until C5-C6. In the pons and medulla many fibers terminate in the medial tegmental field and in the upper cervical cord in the lateral part of the intermediate zone (Fig. 36). The main projection in the spinal cord is on interneurons, which corresponds with the findings of Anderson et al. (1971) who reported disynaptic excitatory tecto-motoneuronal projections and only a few monosynaptic ones. Cowie and Holstege (in preparation) have demonstrated that there exists a lateral component of this medially descending system, which projects to the lateral tegmental field of caudal pons and medulla (section 2 d) and to the lateral facial subnuclei (Holstege et al., 1984a; Fig. 36). Roucoux et al. (1980) found that stimulation of the anterior part of the CS evokes eye saccades, which were retinotopic and the accompanying head movements were slow and of small amplitude. At intermediate collicular levels SC stimulation produced goal directed eye saccades and synchronous head movements, which were fast and of large amplitude. At posterior collicular levels stimulation evoked goal directed head movements.

4a2 c. **Spinal projections from the lateral periaqueductal gray (PAG) and adjacent mesencephalic tegmentum.** Retrograde tracing results of Castiglioni et al. (1978) in the monkey, Martin et al. (1979c) in the opossum; Huerta and Harting (1982) and Holstege, (1988a,b) in the cat have demonstrated a spinally projecting group of neurons in the lateral PAG and adjacent mesencephalic tegmentum at levels caudal to the RN (Fig. 32 L,M). According to anterograde tracing studies of Martin et al. (1979c) and Holstege, (1988b), these neurons project to the spinal cord via the central tegmental tract into the ventral and ventrolateral funiculi of the spinal cord. Although some continue until the upper lumbar cord, they are sparse beyond the T3 level. A few descending labeled fibers are observed in the dorsolateral funiculus. At the level of the C1 segment labeled fibers terminate in the lateral part of the intermediate zone and at the C2-C4 levels in more central parts of it (Fig. 37). Further caudally labeled fibers terminate in the medial part of the ventral horn (laminae VIII and adjoining VII). Some labeled fibers, probably derived from the fibers descending in the dorsolateral funiculus, terminate in lamina X and the upper thoracic intermediolateral cell column (Fig. 37). It is not known whether this cell group is involved in eye and head movement control, but exactly this region has been shown to project to an eye movement related area of the central mesencephalic reticular formation (cMRF), (see Büttner-Ennever and Büttner, 1988). Furthermore, stimulation in this area produces horizontal conjugate saccadic eye movements, which are different from eye movements, elicited in the deep layers of the superior colliculus (Robinson, 1972 in the monkey, Collewijn, 1975 in the rabbit). Such an involvement of the PAG and adjacent tegmentum in eye and head movements is interesting, because this area receives its main afferents from limbic structures (Hopkins and Holstege, 1978; Holstege et al., 1985; Holstege, 1987b). It implies that these neurons in the lateral PAG and adjacent mesencephalic tegmentum could provide an interaction between the limbic and oculomotor system, which does not occur at "immediate" premotor levels (Büttner-Ennever and Holstege, 1986).

4a2 d. **Spinal projections from the pontine and medullary medial tegmental field.** In section 4a it has been indicated that this area maintains long descending projections to the central and medial parts of the intermediate zone (laminae VII and VIII) of the spinal cord. However, at the level of the upper cervical cord, fibers terminate in the lateral and central parts (laminae V-VIII) of the ventral horn. The pontine and upper medullary medial tegmentum plays an important role in the oculomotor control system. The region includes the so-called paramedian pontine reticular formation (PPRF), which is a physiological entity, whose complete anatomic limits are still obscure. It contains many specific cell groups, such as long-lead bursters, short-lead bursters and omnipause neurons, all known to be essential for the generation of saccades (Raphan and Cohen, 1978; Fuchs et al., 1985; Büttner-Ennever and Büttner, 1988). The pontine and upper medullary projections to the upper cervical cord are similar to the spinal projections from other saccade related areas, such


1401
Caud. Medulla
C1
C2
C3
C4
C5
C8
T2

as the area of the rostral iMLF and the superior colliculus and all 3 regions have strong reciprocal connections (see Büttner-Ennever and Büttner, 1988 for review). Neurons in this region have been reported to receive afferent impulses from the labyrinth (Peterson et al., 1984), cerebellum (Eccles et al., 1975) and superior colliculus (Grantyn et al., 1980). Grantyn et al. (1987) also demonstrated that pontine reticulospinal neurons, on their way to the spinal cord, give off collaterals to the abducens nucleus, facial nucleus, nucleus prepositus hypoglossi and medial vestibular nucleus. This illustrates the close relationship between the oculomotor, neck and axial musculature control systems.

Retrograde tracing results (Holstege, 1988b) have revealed a cell group in the dorsal half of the contralateral medullary medial tegmentum at the level of the inferior olive (Fig. 32 T,U). Anterograde tracing studies of Büttner-Ennever and Holstege (1986) and Holstege, (1988b) demonstrated that these neurons project through the contralateral ventral funiculus, but only until the level of C5. The fibers, which remain close to the ventral horn, terminate densely in the motoneuronal cell groups of the C1-C4 segments. The impression was gained that this projection represents one of the strongest direct brainstem projections to neck muscle motoneurons.

The pontine and medullary medial tegmental projections have been extensively investigated physiologically by Peterson et al. (1978,1979) and Peterson (1979,1980), who subdivided the pontine and medullary medial tegmentum in 5 different zones. Holstege, (1988b), comparing the anatomic observations with the physiological results of Peterson, concluded that the anatomic tracing studies confirm some of the physiological "tracing" results of Peterson (1979,1980), but many differences still exist and need to be resolved.

4a2 e. **Spinal projections from the vestibular nuclei.** In section 4 a it has been indicated that the lateral vestibular nucleus and the pontine and upper medullary medial tegmentum maintain long descending projections to the central and medial parts of the intermediate zone (laminae VII and VIII) of the spinal cord. In the upper cervical cord, the lateral vestibulospinal tract (LVST) descends through the ventral part of the ipsilateral ventral funiculus. They terminate, unlike the fibers from the medial tegmentum, in the medial and central and not lateral parts of the ventral horn at the level of the upper cervical cord (Fig. 33). Two other bundles of vestibulospinal fibers descended via the ipsi- and contralateral MLF into the medial part of the upper cervical ventral funiculi (Nyberg-Hansen, 1964b; Nyberg-Hansen and Mascitti, 1964, and Petras, 1967; Holstege and Kuypers,1982 and Holstege, 1988b). They belong to the medial vestibulospinal tract, which originates in the lateral, medial and inferior vestibular nuclei. Medial vestibulospinal fibers terminate in the medial part of the ventral horn also. The contralateral medial vestibulospinal tract does not descend beyond cervical levels (Fig. 33). Whether the ipsilateral medial vestibulospinal tract descends beyond cervical levels is difficult to assess, because its fibers join the lateral vestibulospinal tract at low cervical levels. During their descent through the brainstem, the vestibulospinal fibers did not project significantly to the caudal pontine and medullary medial tegmental field, which suggests that these two areas have different functions within the medial system.

Stimulation in the lateral vestibular nucleus (LVN) produces mono- and polysynaptic excitatory postsynaptic potentials (EPSP's) in head extensor muscle motoneurons (Wilson and Yoshida, 1969a) and in back muscle motoneurons (Wilson et al., 1970). LVN stimulation also produces some monosynaptic EPSP's in hindlimb extensor muscles, but polysynaptic EPSP's are much more common (Grillner et al., 1970; Wilson and Yoshida, 1969a). Stimulation in the LVN also resulted in disynaptic inhibition of flexor muscles via Ia inhibitory interneurons located in the ventral part of the intermediate zone (Hultborn, 1976). On the

Fig. 37. On the left.

Darkfield photomicrographs of the caudal medulla and 7 different levels of the spinal cord in a cat with an injection of ^{3}H-leucine involving the lateral PAG, the laterally adjoining mesencephalic tegmentum and deep layers of the superior colliculus. Note the ipsilateral fibers derived from the lateral PAG and adjoining tegmentum descending in the ventral and ventrolateral funiculi and terminating in the lateral part of the C1 and the central and/or medial parts of the C2-T1 ventral horn. Note also the projection to lamina X and the upper thoracic intermediolateral cell column, derived from fibers descending in the dorsolateral funiculus (arrow in T2). Note further the tectospinal fibers in the contralateral ventral funiculus, distributing labeled fibers to the lateral (C1-C3) or central (C4-C5) parts of the intermediate zone. Bar represents 1 mm, (from Holstege, 1988b).

other hand, stimulation in the MVN evokes monosynaptic inhibition of neck (Wilson and Yoshida, 1969b) and back motoneurons (Wilson et al., 1970). These inhibitory effects are mediated via the MVST (Akaike et al., 1973). In short, the LVST excites neck, axial and extensor muscle motoneurons and inhibits flexor muscles. The MVST inhibits neck- and axial muscle motoneurons.

4a2 f. **Concluding remarks regarding the descending pathways involved in regulating head movements.** Figure 38 gives an overview of the white matter location of all the descending pathways belonging to the medial descending system in the upper cervical and low thoracic spinal cord. Only the pontine medial tegmental field and the lateral vestibulospinal tract, and to a limited extent the interstitiospinal tract, descend throughout the length of the spinal cord.

At upper cervical levels, the INC-RF and the vestibular nuclei project mainly to the *medial* portion of the upper cervical intermediate zone, in which area the prevertebral muscle and some biventer cervicis and complexus muscle motoneurons are located (Abrahams and Keane, 1984; Fig. 1). These muscles may be specifically involved in

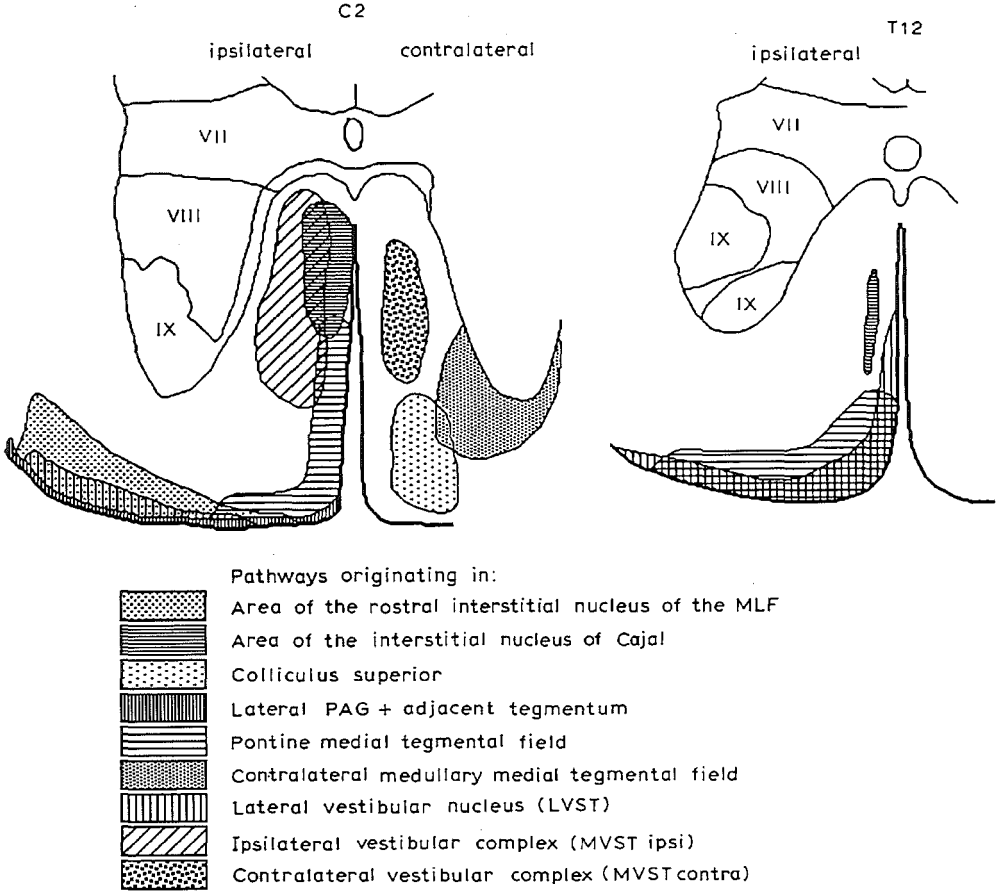


Fig. 38. Schematic representation of the spinal white matter location of the various descending pathways, specifically involved in control of neck and axial muscle inter- and motoneurons. On the left a drawing of the C2 spinal segment and on the right a drawing of the T12 spinal segment. It must be emphasized that this scheme does not give any indication about the number of fibers belonging to the different descending pathways. It must also be noted that many other descending fiber systems pass through the same areas as indicated in the drawing (for example propiospinal, reticulospinal and corticospinal fibers), (from Holstege, 1988b).

head position, although until now such an involvement has only been described for the biventer cervicis, occipitoscapularis, semispinalis cervicis and rectus capitis (Richmond et al., 1985; Roucoux et al., 1985). In accordance with this concept, both INC-RF and vestibular nuclei are known to be strongly involved in eye position and head posture. On the other hand, the main spinal projection of the caudal Field H of Forel, superior colliculus, lateral PAG and adjacent tegmentum, and pontine medial tegmental field is to the *lateral* parts of the upper cervical ventral horn, which contains motoneurons innervating cleidomastoid, trapezius and splenius muscles. The latter group of muscles appear best suited to produce rapid or phasic torsional movements of the head such as might occur during orienting movements (Callister et al., 1987). It would correspond with the observation that stimulation in the caudal Field H of Forel, superior colliculus and pontine medial tegmental field produces eye saccades and fast head movements.

In summary, a concept is put forward (Holstege, 1988b) in which the medial somatic system structures are subdivided into two groups; one that controls tonic eye- and head position, and one that produces saccadic eye- and fast head movements.

4b. The lateral descending system

The lateral component of the voluntary motor system produces independent flexion-biased movements of the extremities, in particular of the elbow and hand (Kuypers, 1981). The two most important constituents are the rubro- and corticospinal tracts. Vertebrates without extremities, such as snakes and sharks, do not have a rubro- or corticospinal tract, indicating that the presence of such tracts is related to the presence of limbs or limb like structures (Ten Donkelaar, 1988). Both red nucleus and motor cortex are somatotopically organized, containing regions such as a face area projecting to the face motor- and premotor neurons in caudal pons and medulla, an arm or foreleg area projecting to the cervical cord, and a hindleg portion sending fibers to the lumbosacral cord (Kuypers, 1981; Armand et al., 1985; Holstege, 1987a; Holstege and Tan, 1988). There are differences between the organization of the rubro- and corticospinal tract, which depend for an important part on the species involved.

4b 1. **The rubrobulbar and rubrospinal system.** There are two different descending pathways from the red nucleus to the caudal brainstem; 1) a mainly contralateral pathway, which sends fibers to the premotor interneurons in the lateral tegmental field (section 2d), the dorsal column nuclei, precerebellar structures other than the inferior olive, and to the spinal cord; 2) an ipsilateral fiber system which terminates on neurons in the inferior olive. Many of the neurons in the red nucleus projecting via the contralateral rubrobulbospinal system are of large diameter and are located in the caudal portions of the red nucleus, while the rubro-olivary neurons are of smaller diameter and are located in the rostral parts of the red nucleus. The caudal part of the red nucleus is usually called magnocellular red nucleus, while the rostral part of the red nucleus is called parvocellular red nucleus. In the cat neurons projecting to both the spinal cord and inferior olive do not exist (Huisman et al., 1982). The subdivision in magno- an parvocellular red nucleus leads to confusion because in the cat the parvocellular (rostral) red nucleus not only contains neurons projecting to the inferior olive, but also neurons projecting to the spinal cord (Holstege and Tan, 1988). Furthermore there exist important species differences regarding the relation magnocellular-parvocellular red nucleus. Therefore, Holstege and Tan (1988) proposed a new subdivision of the red nucleus based on the projections of the neurons located in it: a rubrobulbospinal red nucleus and a rubro-olivary red nucleus. It must be emphasized that the rubro-olivary neurons form part of a much larger projection system, (see section 4 b 1 b).

4b1 a. **The rubrobulbospinal projections.** The rubrobulbospinal red nucleus is somatotopically organized in such a way that neurons in its dorsal part project to the bulbar lateral tegmental field and facial nucleus (Kuypers et al., 1962; Martin et al., 1974; Holstege and Tan, 1988), neurons in the dorsomedial red nucleus project to the cervical cord and neurons in the ventrolateral red nucleus to the lumbosacral cord (Pompeiano and Brodal, 1957; Murray and Gurule, 1979; Huisman et al., 1982; Holstege and Tan, 1988). In accordance with the somatotopic organization, only very few red nucleus neurons project to both the cervical and lumbar cord (Huisman et al., 1982). All projections are contralateral except for a few ipsilaterally descending fibers, projecting to the intermediate zone of the cervical cord (Holstege, 1987a). The red nucleus also projects to the interpositus nucleus in the cerebellum (Huisman et al., 1982)

and to some precerebellar structures in the caudal brainstem, such as the nucleus corporis pontobulbaris, lateral reticular nucleus and external cuneate nucleus (Edwards, 1972; Martin et al., 1974; Holstege and Tan, 1988). Furthermore, neurons in the dorsomedial (foreleg) part of the red nucleus send fibers to the cuneate nucleus, while neurons in the ventrolateral (hindleg) part of the red nucleus project to the gracile nucleus (Edwards, 1972; Martin et al., 1974; Holstege and Tan, 1988). It has been demonstrated that the projections to the interpositus nucleus are collaterals from rubrobulbospinal fibers (Huisman et al., 1982). In all likelihood, this is also true for the red nucleus projections to the precerebellar structures in the brainstem and dorsal column nuclei (see Anderson, 1971), which would correspond with the finding that the latter projections are somatotopically organized (Holstege and Tan, 1988).

In the spinal cord the rubrospinal fibers descend via the dorsolateral funiculus and terminate on interneurons in the lateral parts of the intermediate zone (laminae V to VII) and to a limited extent directly to motoneurons. Interneurons receiving rubrospinal fibers receive afferents from other sources also, such as peripheral nerves, propriospinal neurons, and reticulo- and corticospinal tracts. Furthermore, rubrospinal fibers terminate on both first and last order interneurons (Hongo et al., 1969; see also Jankowska, 1988 for review). Apparently the red nucleus uses all the interneurons involved in the reflex pathways in the spinal cord (see section 2). Rubrospinal fibers also terminate on interneurons in the upper cervical cord (Holstege et al., 1988b). Upper cervical motoneurons innervate the neckmuscles, which belong to the medial system. Although a red nucleus effect on neck muscles cannot be excluded, it is more likely that the great majority of these projections terminate on interneurons, which in turn project to motoneurons in the lower cervical cord, innervating distal muscles of the forelimb (Holstege, 1988b, see section 2 c 2). The neurotransmitter utilized by the rubrospinal neurons is not precisely known. According to Kimura et al. (1981) all rubrospinal cells in the red nucleus contain choline acetyl tranferase (ChAT), indicating that they use acetylcholine as a neurotransmitter. However, Jones and Beaudet (1987) did not find ChAT positive neurons in the red nucleus.

Although the red nucleus projections to motoneurons are mostly indirect, physiological studies in cat (Shapovalov and Karamyan, 1968) and monkey (Shapovalov et al., 1971; Shapovalov and Kurchavyi, 1974; Cheney, 1980; Cheney et al., 1988) have demonstrated direct red nucleus projections to spinal motoneurons. Anatomically however, there was only evidence for direct red nucleus projections to motoneurons in the facial nucleus (Courville, 1966b; Edwards, 1972; Martin et al., 1974; Holstege et al., 1984a; Holstege and Tan, 1988). Only recently, Holstege (1987a; Fig. 39); Robinson et al. (1987) and McCurdy et al. (1987) demonstrated that the red nucleus in the cat projects directly to a specific group of motoneurons in the dorsolateral part of the C8-T1 ventral horn, innervating forelimb digit muscles (see section 1 a 3). One year later, Holstege et al. (1988; Figs. 40 and 41) at the light microscopical level and Ralston et al. (1988) at the electron microscopical level revealed rubro-motoneuronal projections in the monkey, which were more extensive than in the cat. These projections involved all distal limb muscle motoneuronal cell groups in the cervical and lumbosacral enlargements. Projections to the axial or proximal muscle motoneurons were never observed. The predominant population of rubromotoneuronal contacts were terminals containing rounded synaptic vesicles, forming asymmetric contacts with motoneuronal somata and primary dendrites. Only occasional terminals with flattened or pleomorphic vesicles were present (Ralston et al., 1988). Gibson et al. (1985) and Cheney et al. (1988) studied the red nucleus projections to flexors and extensor motoneurons of the wrist and fingers in the monkey

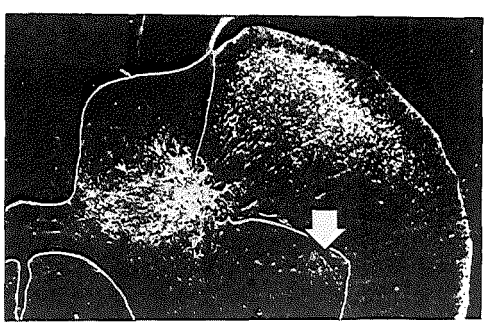


Fig. 39. Darkfield photomicrograph of the contralateral C8 spinal segment of a cat with an injection of ^{3}H-leucine in the dorsomedial (forepaw area) part of the rubrospinal red nucleus. Note the strong projections to the dorsal and lateral intermediate zone and the specific projection to the most dorsolateral portion of the motoneuronal cell group (arrow). Bar represents 1 mm. (From Holstege, 1987a).

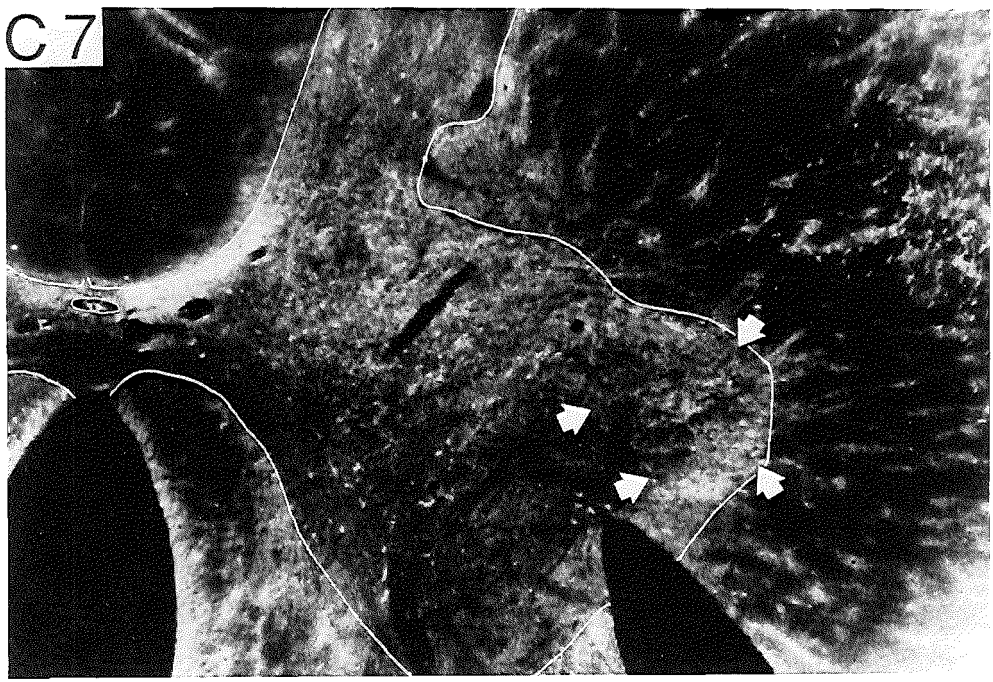


Fig. 40. Darkfield photographs of the C7 spinal cord of a monkey after an injection of WGA-HRP in the caudal red nucleus and adjacent areas. The labeling in the gray matter represents anterograde labeled rubrospinal fibers. Note that in C7 labeled fibers terminate in the intermediate zone and in the dorsolateral motoneuronal cell groups innervating distal forelimb muscles, i.e. muscles involved in movements of wrist and digits.

and observed a strong preference for facilitation of extensor muscles (see also Cheney et al. this volume). Martin and Ghez, (1988) in the cat studied the differential contributions of the motor cortex and red nucleus neurons to the initiation of a targeted limb response and to the control of trajectory. They concluded that both the motor cortex and the red nucleus contributed to the initiation of the motor responses, but that only the motor cortex is involved in the proper scaling of targeted responses.

Direct red nucleus projections to the motoneurons in the intermediate subgroup of the facial nucleus (orbicularis oculi motoneurons) have been described by many authors, and a projection to the dorsal part of the dorsomedial facial subnucleus (pinna muscle motoneurons) by Courville, (1966b) and Holstege et al. (1984a). However, the literature is not clear about the red nucleus projections to the lateral facial subnuclei (containing peri-oral muscle motoneurons). Martin and Dom (1970) in the opossum, Edwards (1972) and Robinson et al. (1987) in the cat and Miller and Strominger (1973) in the monkey, have reported such projections, but Courville, (1966b) and Holstege et al. (1984a) found only fibers of passage and no terminations in this motoneuronal cell group. In a recent study in the cat Holstege and Ralston (1989) at the electron microscopical level observed only occasional terminals in the peri-oral muscle motoneuronal cell group after large injections of WGA-HRP in the red nucleus. On the other hand, abundant terminals (at least 200 times as many as in the lateral and ventrolateral facial subnuclei) were present in the orbicularis oculi and pinna muscle motoneuronal cell groups, indicating that the red nucleus fibers observed among the peri-oral muscle motoneurons were fibers of passage. Figure 42 gives an overview of the rubrobulbospinal projections.

The red nucleus may have a function in motor learning (Tsukahara, 1981). Schmied et al. (1988), studied the participation of the red nucleus in motor initiation, by training cats to release or not

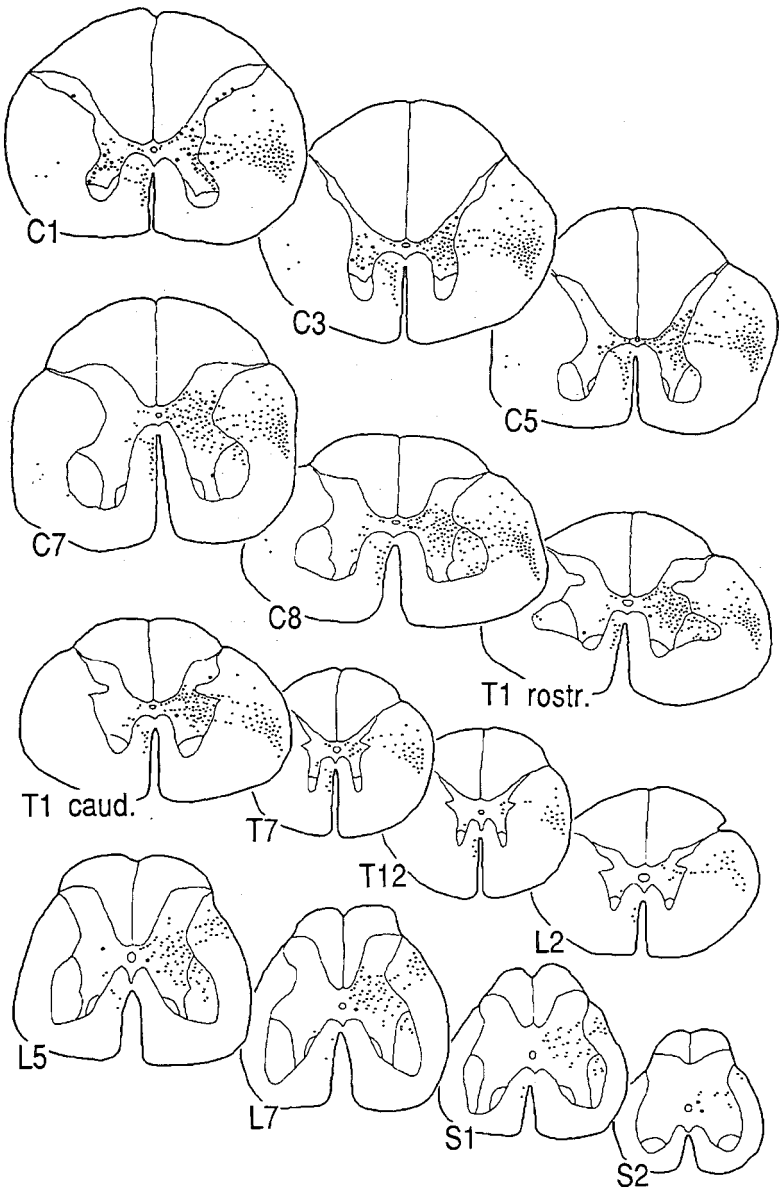


Fig. 41. Schematic representation of the labeled fibers (small dots) in the spinal cord of a monkey with an injection of WGA-HRP in the rubrospinal red nucleus. The injection-site extended into the area of the interstitial nucleus of Cajal (INC-RF). The retrogradely labeled neurons are indicated with large dots. Note the contralateral projections to the intermediate zone throughout the length of the spinal cord and to the lateral motoneuronal cell groups in the cervical and lumbosacral enlargements. Note also the ipsilateral (interstitiospinal) fibers in the ventral funiculus on the ipsilateral side. Note further the very few ipsilateral rubrospinal fibers, some of which terminate in the lateral motoneuronal cell groups in rostral T1, (from Holstege et al. 1988).

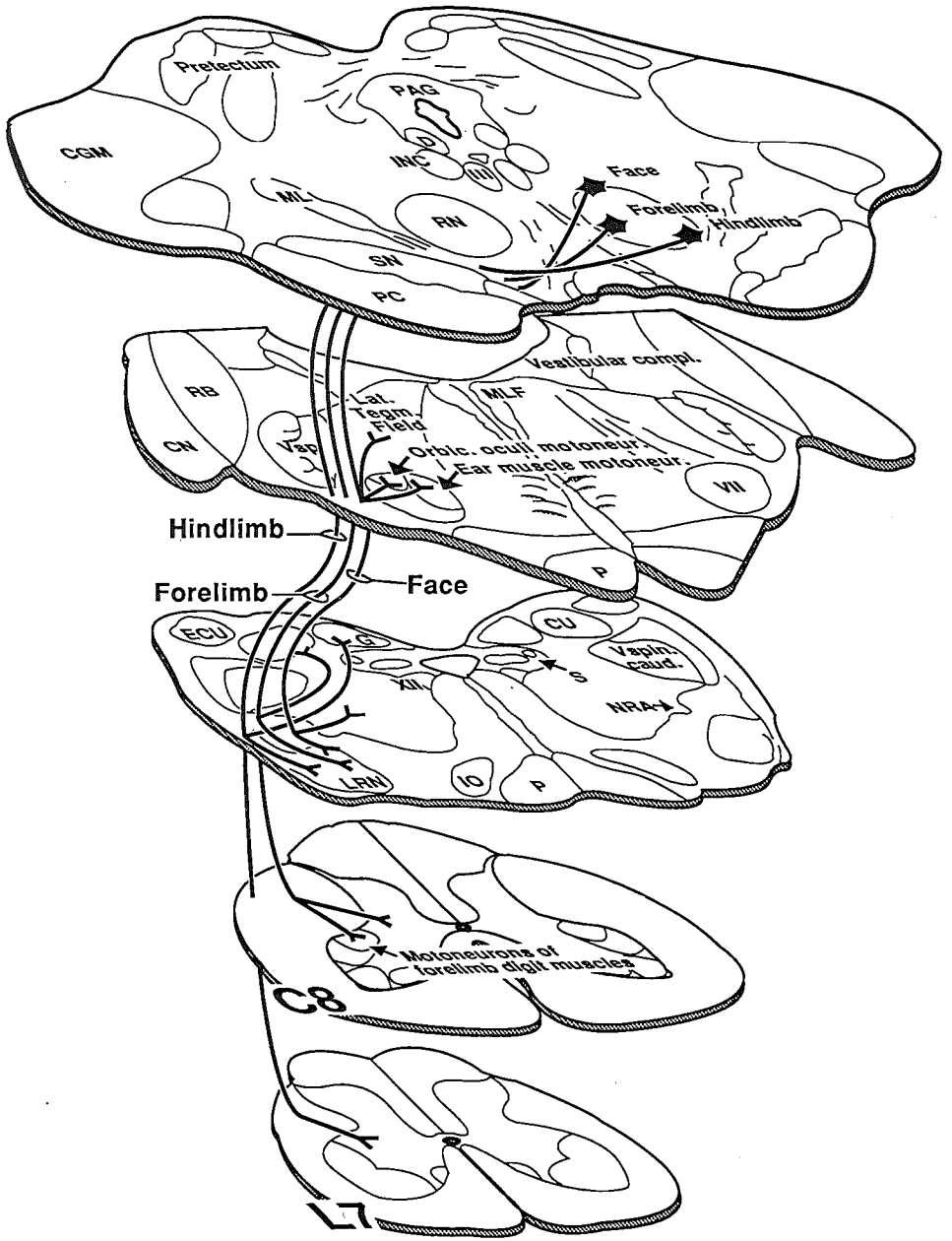


Fig. 42. Schematic overview of the rubrobulbospinal projections in the cat. In the monkey the rubrobulbospinal projections are almost identical, with the exception of more extensive projections to the motoneuronal cell groups (see fig. 41).

release a lever with its forepaw in response to a certain auditory signal, while other auditory signals were no-go cues. The results led them to propose that the red nucleus responses to a sensory signal depend on its triggering significance, and thus be modifiable by training. In this regard the role of the red nucleus in the conditioned blink reflex is interesting. The conditioned blink reflex or nictitating membrane response (NMR) is a learned response. When a neutral stimulus (visual or auditory) is repeatedly followed by an airpuff to the cornea, the animal will soon develop reflex blinking (i.e. NMR and closure of the eyelids) to the neutral stimulus alone. The reflex pathway goes via the trigeminal nucleus, inferior olive (Yeo et al., 1986), cerebellar cortex (lobule VI), (Yeo et al., 1985b), nucleus interpositus (Yeo et al., 1985a) and red nucleus to the orbicularis oculi and retractor bulbi motoneurons (Holstege et al., 1986a,b). In the latter pathway the pontine blink premotor area may also play a role (Holstege et al., 1986b). It has been demonstrated that lesioning the red nucleus abolishes the conditioned blink reflex (Rosenfield and Moore, 1983) and recently it has been reported that injecting GABA in the red nucleus has also this effect (Haley et al., 1988). The face area of the red nucleus not only receives afferents from the interpositus nucleus, but also directly from the trigeminal nuclei (Holstege et al., 1986b). These projections might be involved in the R2 component of the unconditioned blink reflex, in which the pontine blink premotor area may also be involved (see section 2 d 3 b).
As the evolutionary scale is climbed, the rubrospinal red nucleus becomes smaller, and in humans only very few rubrospinal neurons seem to exist, which do not descend further than C3 (see Nathan and Smith, 1982 for review). The most likely reason for such a regression is the development of the corticospinal tract, which is extremely well developed in humans and might render the rubrospinal tract redundant (see Massion, 1988). It remains to be determined whether this is also true for the contralateral rubrobulbar projections

4b1 b. **The rubro-olivary projections.** The rubro-olivary projections form part of a large mesencephalo-olivary projection system. In the cat, many neurons in the nucleus of Darkschewitsch, nucleus accessorius medialis of Bechterew, the area of the interstitial nucleus of Cajal, rostral red nucleus and Field H of Forel all contribute to the fiber projections to the inferior olive. Somewhat surprising is that the termination pattern of all these structures is very similar (Saint-Cyr and Courville, 1982; Oka, 1988; Holstege and Tan, 1988; Fig. 43). Although the upper mesencephalic projections to the inferior olive, including the rubro-olivary ones, are already quite extensive in the cat, climbing the evolutionary scale to humans, the rubro-olivary red nucleus, its projections to the inferior olive via the central tegmental tract as well as the inferior olive itself becomes larger (Nathan and Smith, 1982). In all likelihood, this is due to the enormous growth of the cerebral cortex, because rubro-olivary projections play an important role in the relay cerebral cortex-cerebellum. According to Kuypers and Lawrence (1967) and Humphrey et al. (1984) in the monkey, both the rubrospinal and rubro-olivary neurons receive afferents from the precentral (motor) cortex. However, the projection to the rubro-olivary neurons is much stronger and originate not only in the precentral gyrus, but also in the premotor and supplementary motor areas. It has been demonstrated (Gibson et al., 1985; Cheney et al., 1988) that the discharge of most rubrospinal neurons precede the onset of movement. Part of this discharge might be elicited by cortical projections to the rubrobulbospinal neurons, which are partly collaterals of corticospinal fibers (Humphrey and Reitz, 1976). Another, (possibly stronger) source of input might be the projections from various motor and premotor cortical areas via the rubro-olivary neurons and the cerebellum, i.e. via the circuit rubro-olivary neurons-inferior olive-cerebellar cortex-deep cerebellar nuclei-rubrobulbospinal red nucleus. A similar pathway exists for the conditioned blink reflex (trigeminal nuclei-inferior olive-cerebellar cortex-deep cerebellar nuclei-face part of the rubrobulbospinal red nucleus). Such a concept, (the cortico-rubrospinal red nucleus projections go via the cerebellum) would provide the anatomic framework for the observation that the rubrospinal red nucleus is so heavily involved in conditioned motor responses (Schmied et al., 1988).

4b 2. **The corticobulbar and corticospinal pathways.** The enormous outgrowth of the cerebral cortex in humans, compared to other mammals, is also reflected In the motor cortico-bulbospinal tract, which in primates but especially humans is the most important descending pathway within the somatic motor system. The motor cortex is somatotopically organized with a foreleg area projecting to the cervical cord, a hindleg area projecting to the lumbosacral cord (Armand et al.,

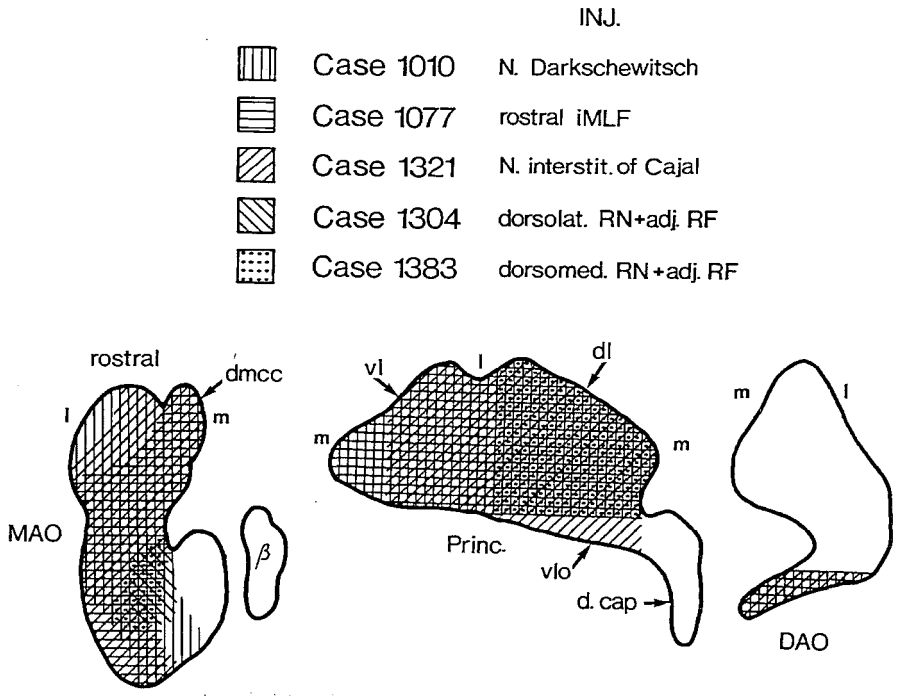


Fig. 43. Schematic diagram of the unfolded inferior olive after Brodal (1940), illustrating the extent of the projections of the rostral mesencephalon. Note the strong overlap of the fiber distributions in the cases with injections of ^{3}H-leucine in the rostral iMLF and Field H of Forel (case 1077), the nucleus of Darkschewitsch and the INC-RF. Note the relatively small contribution of the more caudally located injection sites (cases 1304 and 1383). Injections in the most caudal portion of the red nucleus did not produce labeling in the inferior olive. (From Holstege and Tan, 1988). l=lateral; m=medial; MAO=medial accessory olive; dmcc=dorsomedial cell column; b=nucleus Beta; vl=ventrolateral; dl=dorsolateral; Princ.=principal inferior olive; vlo= ventrolateral outgrowth; d. cap=dorsal cap; DAO= dorsal accessory olive.

1985) and a face area projecting to the lateral tegmental field of caudal pons and medulla (Kuypers, 1958c; Holstege, unpublished results). In cat, monkey, apes, and humans the motor cortex not only projects mainly contralaterally to the laterally located interneurons in the spinal cord, but, in contrast to the red nucleus, also bilaterally to more medially located interneurons (lamina VIII). These projections are derived from the so-called common zone. In the cat this area is located in the medial part of the motor cortex next to area 6 and extends caudally between the fore- and hindleg areas (Armand and Kuypers, 1980). Stimulation in the area tends to carry the representations of axial movements, i.e. neck, trunk and proximal forelimb movements (Nieoullon and Rispal-Padel, 1976). Strictly speaking, this cortical projection system belongs to the medial descending system, but is presented together with the other corticospinal projections, because it represent a relatively small portion of the descending corticospinal tract. Not surprisingly, neurons in the common zone, possibly via collaterals of the corticospinal fibers, project to the pontine and upper medullary medial tegmental field, one of the most important parts of the medially-descending system (see sections 4 a 1 and 4 b 5-6).

In the monkey (Kuypers, 1958b; Ralston and Ralston, 1985), but not in the cat (Armand et al., 1985) there exist direct cortical projections to motoneurons, innervating the most distal muscles of the extremities. Ralston and Ralston (1985)

found electron microscopically that two thirds of the corticomotoneuronal terminals contained round vesicles, suggesting excitatory effects on the motoneuron, and one third pleomorphic or flattened vesicles, suggesting inhibitory effects. It is questionable, however, whether there exist monosynaptic inhibitory corticomotoneuronal connections, but disynaptic connections have been demonstrated (Landgren et al., 1962; see also Cheney et al. this volume). Jankowska et al., (1975), stimulating the motor cortex in monkeys, observed EPSP's with response latencies of 0.6-1.0 ms, indicating monosynaptic contact. The rubro- and corticospinal tract in the monkey are very similar, but there are some differences; 1) the motor cortex projects also to more medial parts of the intermediate zone; 2) corticospinal fibers are at least 100 times more numerous than the rubrospinal ones (Holstege et al., 1988). For the differences between the cortico-motoneuronal and

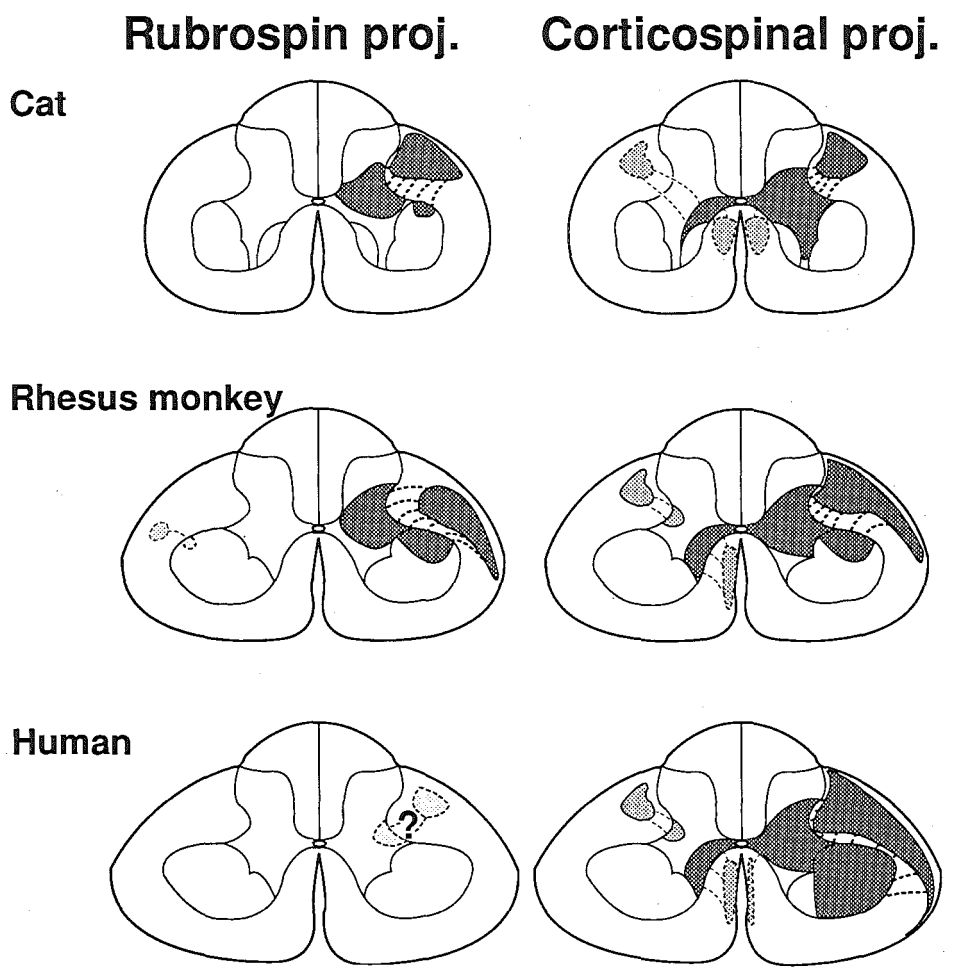


Fig. 44. Schematic representation of the rubrospinal and corticospinal projections in cat, rhesus monkey and human at the level of C8. The gray areas in the white matter represent the descending pathways, those in the gray matter represent termination zones. Dark gray areas represent strong projections, lighter gray areas represent light projections.

rubro-motoneuronal cells, see Cheney et al. (this volume). In chimpanzees and humans direct cortico-motoneuronal projections are more extensive than in the monkey and terminate also on motoneurons, innervating more proximal muscles of the body (Kuypers, 1958a,b; Schoen, 1964). However, the degeneration findings of Kuypers, 1964 and Schoen, 1964, do not reveal corticospinal projections to the medial motoneuronal cell column in chimpanzee and human. It is possible that more modern tracing techniques in the chimpanzee would reveal direct cortical projections to medial column motoneurons, but such studies have not yet been done. Since the corticospinal and rubrospinal systems are so similar, it is not surprising that collaterals of the corticospinal tract terminate in the magnocellular red nucleus in a somatotopically organized manner (Kuypers, 1981; Holstege unpublished observations).

Behavioral studies on the lateral system of Lawrence and Kuypers (1968a,b) in the monkey have demonstrated that immediately after pyramidotomy, (interruption of the corticospinal fibers at the level of the medulla oblongata), the animals can sit, walk, run and climb, but cannot pick up pieces of food with their hands. After some recovery they regain this capacity, but individual finger movements such as the thumb and index finger precision grip do not return. In pyramidotomized monkeys, the red nucleus as well as the cortico-rubral fibers are still intact and the recovery of hand movements is probably related to the rubrospinal tract taking over many of the functions of the corticospinal tract. Ablation of the precentral motor cortex in adult monkeys, (thus lesioning the corticospinal as well as the cortico-rubral fibers) results in a stronger deficit, i.e. a flaccid paresis of the contralateral extremity muscles. In chimpanzee and humans (patients with stroke or tumor interrupting the cortico-bulbospinal fibers) this flaccid paresis is more severe than in monkeys and much more than in cats. The reason for this difference probably is that the rubrospinal neurons in monkey and cat are much more numerous than in chimpanzee and humans. Correspondingly, if in a monkey a bilateral pyramidotomy is combined with an interruption of the rubrospinal tract on one side, the motor deficit on that side is much more pronounced. The monkey is able to sit up, walk and climb, but in the examining chair the fingers and wrist of the arm ipsilateral to the side of the rubrospinal lesion are noticeably limp. In reaching for food, the hand is brought to the food by turning the arm in the shoulder.

Figure 44 gives a summary on the rubro- and corticospinal pathways, based on the findings of Kuypers, 1964; Schoen, 1964; Kuypers and Brinkman, 1970; Kuypers, 1973; Kuypers, 1981; Ralston and Ralston, 1985; Armand et al. 1985; Holstege, 1987a; Holstege et al., 1988. The corticospinal fibers become more and more numerous and control larger parts of the spinal gray, going from cat, via monkey to human, which is not true for the rubrospinal tract. The enormous predominance of the corticospinal tract over the rubrospinal tract in humans leads to great clinical problems in stroke patients with interruption of the corticospinal tract in the internal capsule. Recovery from such a lesion is much more difficult than in monkeys or cats with similar lesions, because humans do not have the disposal over a well developed rubrospinal tract.

5. Descending pathways involved in limbic motor control systems

5a. Introduction

It is well known that hemiplegic patients with damage to corticobulbar fibers, resulting in a complete central paresis of the lower face on one side, are able to smile a spontaneously, for example when they enjoy a joke. On the other hand, in cases with postencephalitic parkinsonism, patients are able to show their teeth, whistle, frown, i.e. there is no facial palsy, but the patients' emotions are not reflected in their countenance and they have a stiff, masklike facial expression (poker face). Patients with irritative pontine lesions sometimes suffer from non-emotional laughter and crying, and patients with pseudo-bulbar palsy (for example with lesions in the mesencephalon) often suffer from uncontrollable fits of crying or laughter. Such fits are usually devoid of feeling of grief, joy, or amusement; they may even be accompanied by entirely incompatible emotions. Fits of crying and laughter may occur in the same patients, other patients show only one of them (Poeck, 1969; Rinn, 1984). Crying and laughter belong to an expressive behavior, which in animals is called vocalization. It has been shown in many different species that stimulation in the caudal part of the periaqueductal gray (PAG) produces vocalization. Recently Holstege, G. (1989) has demonstrated that vocalization is based on a specific final common pathway, originating from a distinct group of neurons in the PAG that project to the nucleus retroambiguus, which in turn has direct access to all vocalization motoneurons (section 3 a 3-4; see Holstege, G. 1989). In all likelihood, in humans this projection forms the anatomical framework for laughing and crying. The vocalization neurons in the PAG receive their afferents from structures belonging to the limbic system, but not from the voluntary system (section 4). All this clinical and experimental evidence shows that there exists a complete dissociation between the voluntary and emotional or limbic innervation of motoneurons.

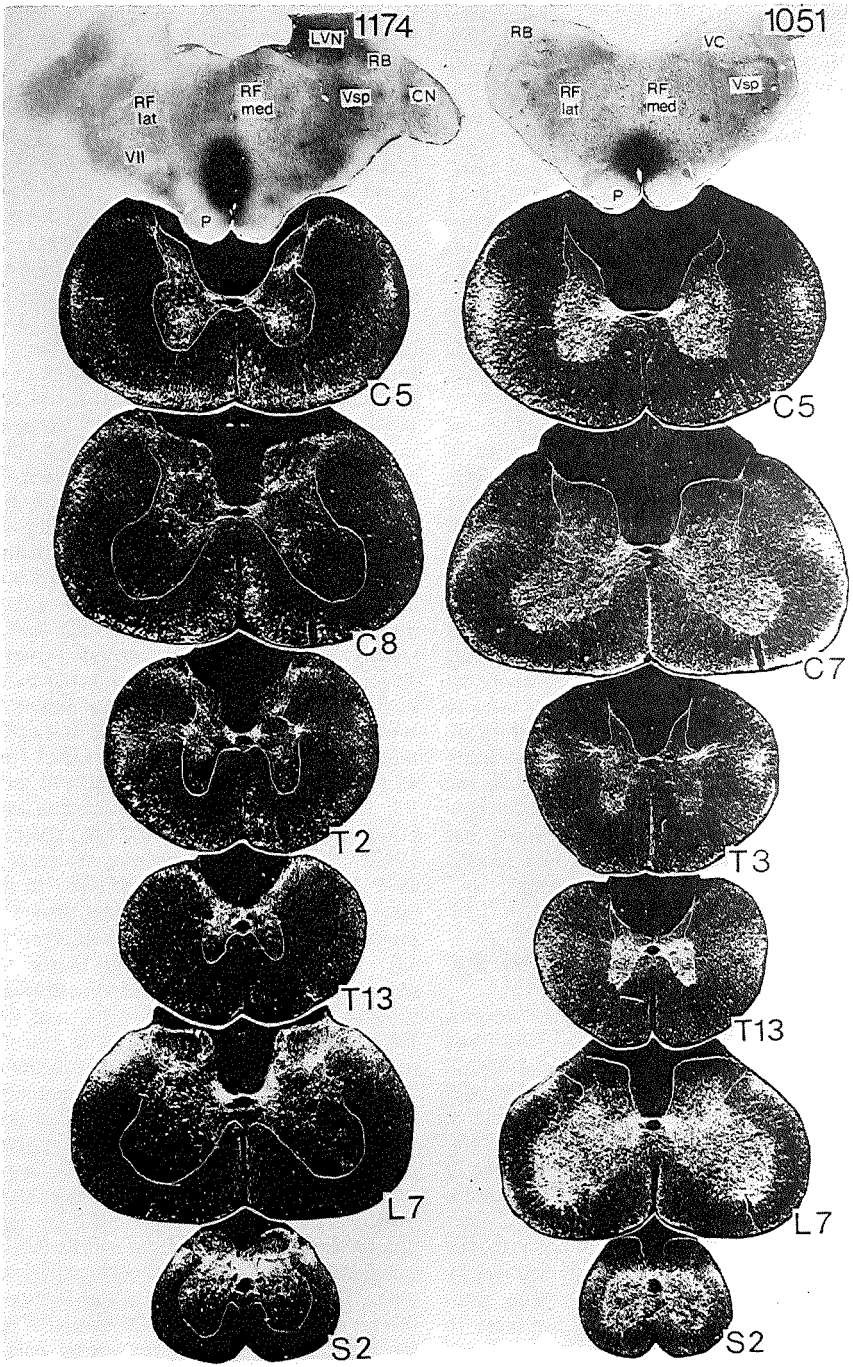
The limbic system is closely involved in the elaboration of emotional experience and expression (MacLean, 1952) and is associated with a wide variety of autonomic, visceral and endocrine functions. The limbic system consists of several cortical and subcortical structures, although there is no agreement on exactly which structures belong to it. Some authors argue that the use of the term limbic system should be abandoned (for example Brodal, 1981). Nevertheless, many scientists still use it and they consider the cingulate, insular, entorhinal, piriform, hippocampal, retrosplenial and orbitofrontal cortex to belong to the limbic system. Subcortical regions usually included in the limbic system are the hypothalamus and the pre-optic region, the amygdala, the bed nucleus of the stria terminalis, the septal nuclei, and the anterior and mediodorsal thalamic nuclei. As early as 1958, Nauta pointed out that the limbic system has extremely strong reciprocal connections with mesencephalic structures such as the periaqueductal gray (PAG) and the laterally and ventrally adjoining tegmentum, (Nauta's limbic system-midbrain circuit). More recent findings strongly support Nauta's concept and has led Holstege, (1990) to consider the mesencephalic periaqueductal gray (PAG) and large parts of the lateral and ventral mesencephalic tegmentum to belong to the limbic system. Nieuwenhuys, (1985; see also Nieuwenhuys et al. 1988), introduces the term *"core of the neuraxis"* for *"a set of neuromediator-rich centers and pathways, which corresponds partly with the limbic system"*. Nieuwenhuys' core not only involves major parts of the limbic system as defined earlier, but also the ventral parts of the striatum, the thalamic midline nuclei, the parabrachial nuclei, the dorsal vagal complex, the superficial zones of the spinal trigeminal nucleus and of the spinal dorsal horn, and the spinal substantia intermedia centralis. Furthermore Nieuwenhuys (see Nieuwenhuys et al. 1988) introduces the medial and lateral paracore zones. The medial paracore is constituted by the series of raphe nuclei, which extends throughout the brain stem. The lateral paracore consists of the lateral tegmentum of mesencephalon, pons and medulla. It comprizes the substantia nigra, the locus coeruleus and subcoeruleus (A6 group), the nucleus Kölliker-Fuse, and the bulbar lateral tegmental field as defined by Holstege et al. (1977).

Although it is well known that the limbic system exerts a strong influence on somatic and autonomic motoneurons, lesion-degeneration studies did not reveal strong limbic projections to levels caudal to the mesencephalon. This led to the idea that the limbic pathways to caudal brainstem and spinal cord were multisynaptic (Nauta, 1958;

Nauta and Domesick, 1981). Since 1975 this view changed dramatically mainly because new tracing techniques became available, such as retrograde tracing using horseradish peroxidase (HRP) (LaVail and LaVail, 1972; Mesulam, 1978), anterograde autoradiographic (Lasek et al., 1968; Cowan et al., 1972) and immuno-histochemical fiber-tracing techniques. Kuypers and Maisky (1975), using the retrograde HRP technique, demonstrated direct hypothalamo-spinal pathways in the cat. Subsequently, the autoradiographic tracing technique has revealed many new limbic system pathways to caudal brainstem and spinal cord. One of the most interesting of these projections are the limbic system projections to the nucleus raphe magnus (NRM) and pallidus (NRP) as well as to the adjacent ventral part of the caudal pontine and medullary reticular formation (the caudal part of the medial paracore of Nieuwenhuys et al., 1988). These findings are important, because NRM, NRP and adjoining reticular formation in turn project diffusely, but very strongly to all parts of the gray matter throughout the length of the spinal cord. There exist also strong limbic projections to the pontine paralemniscal region and to the area of the locus coeruleus and/or nucleus subcoeruleus, which take part in the lateral paracore of Nieuwenhuys et al. (1988), and also these areas in turn project diffusely to the spinal gray throughout its total length. Therefore, the diffuse brainstem-spinal projections will be discussed in the framework of the descending limbic motor control systems. It should be kept in mind that almost all projections presented in this section have been discovered in the last 15 years.

5b. Pathways projecting diffusely to the spinal gray matter

5b 1. **Projections from the nuclei raphe magnus (NRM), pallidus (NRP) and obscurus (NRO) and the ventral part of the caudal pontine and medullary medial reticular formation.** Retrograde HRP results (Kuypers and Maisky, 1975; Tohyama et al., 1979; Holstege, G. and Kuypers, 1982; Holstege, 1988b) indicate that a great number of neurons in the nuclei raphe magnus and pallidus and ventral part of the caudal pontine and medullary medial reticular formation project to the spinal cord (Fig. 32). It was also demonstrated by means of retrograde double labeling tracing techniques that many of these neurons project to cervical as well as lumbar levels of the spinal cord and to the caudal spinal trigeminal nucleus (Martin et al.,1981b; Hayes and Rustioni, 1981; Huisman et al., 1982; Lovick and Robinson, 1983). Basbaum et al. (1978), using the autoradiographic tracing technique, were the first to demonstrate in the cat that the NRM projects to the marginal layer of the caudal spinal trigeminal nucleus and in the spinal cord to laminae I, II, V, VI and VII, and to the thoracolumbar intermediolateral cell column. Similar projections were observed from the tegmentum located next to the NRM, i.e. the ventral part of the medial tegmental field at the level of the facial nuclei, also called the nucleus reticularis magnocellularis. The results of Basbaum et al. (1978) were confirmed in the opossum and rat (Martin et al.,1981a; 1985) and in the cat (Holstege et al., 1979; Holstege, G. and Kuypers, 1982; Fig. 45 left). Moreover, Holstege, G. and Kuypers (1982) demonstrated that the NRM and adjoining tegmentum project to the sacral intermedial and intermediolateral cell column. Furthermore they showed that the rostral portion of the NRM and adjoining reticular formation does not project specifically to laminae I and V, but to all laminae of the dorsal horn. Another very important finding was that the NRP and its adjoining reticular formation does not project to the dorsal horn of caudal medulla and spinal cord, but to all other parts of the spinal gray matter, i.e. the intermediate zone and the somatic and autonomic motoneuronal cell groups of the spinal cord (Fig. 45 right) and to the motoneuronal cell groups V, VII, X and XII in the caudal brainstem (Holstege, J.C. and Kuypers, 1982 in the rat; Martin et al., 1979a; 1981a in the opossum; Holstege et al., 1979, Holstege, G. and Kuypers, 1982 in the cat). Such projections have also been shown in the monkey, (Holstege, unpublished observations, Fig. 46). In the rat the projections to the somatic motoneurons have also been demonstrated at the ultrastructural level (Holstege J.C and Kuypers, 1982, 1987). Further caudally, at the level of rostral pole of the hypoglossal nucleus, the medullary medial reticular formation projects mainly to the somatic motoneuronal cell groups, and to a lesser extent to the intermediate zone (Holstege, G. and Kuypers, 1982). Caudal NRM and rostral NRP also project to the thoracolumbar and sacral intermediolateral cell groups (IML), i.e. the autonomic (sympathetic and parasympathetic) preganglionic motoneuronal cell groups (Fig. 45). The rostral NRM and adjacent reticular formation and the ventral part of the medullary medial reticular formation at the level of the rostral pole of the hypoglossal nucleus do not project to the IML.


1174
LVN
RB
RF lat
RF med
Vsp
CN
VII
P
C5
C8
T2
T13
L7
S2
1051
RB
VC
RF lat
RF med
Vsp
P
C5
C7
T3
T13
L7
S2

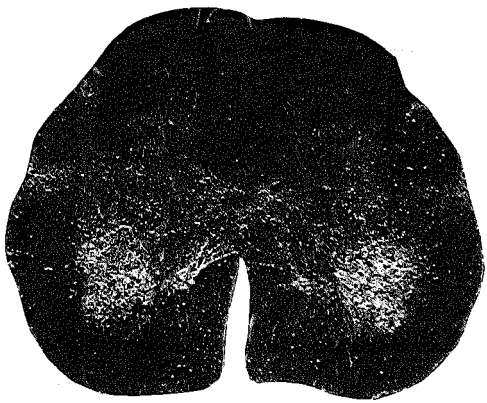


Fig. 46. Darkfield photomicrograph of a section through the lumbar spinal cord in the monkey, after injection of ^{3}H-leucine in the ventral part of the medullary medial tegmental field. Note the diffuse projections to the motoneuronal cell groups.

Summarizing, NRM, NRP and NRO, with their adjoining reticular formation, send fibers throughout the length of the spinal cord, giving off collaterals to all spinal levels. These descending systems are extremely diffuse and are not topographically organized. Furthermore, a strong heterogeneity exists in these projections, in which 1) the rostral NRM and adjoining reticular formation project to all parts of the dorsal horn; 2) the caudal NRM and adjoining reticular formation project mainly to laminae I and V and the autonomic motoneuronal cell groups; 3) the NRP, NRO and ventromedial medulla projects to the intermediate zone and the ventral horn, including the autonomic and somatic motoneuronal cell groups and 4) the ventral part of the medial reticular formation at the level of rostral pole of the hypoglossal nucleus projects mainly to the somatic motoneuronal cell groups.

Physiological studies are consistent with the anatomy of the descending pathways outlined above. Electrical stimulation in the NRM inhibits neurons in the caudal spinal trigeminal nucleus (Hu and Sessle, 1979; Lovick and Wolstencroft, 1979; Sessle et al., 1981) and spinal dorsal horn (Engberg et al., 1968; Fields et al., 1977, Willis et al., 1977). More recently, stimulation in the NRM was found to produce an inhibitory postsynaptic potential (IPSP) in neurons in laminae I and II of the dorsal horn at a latency consistent with a monosynaptic connection (Light et al., 1986). Not only NRM stimulation, but also stimulation in the adjacent ventral part of the caudal pontine and/or upper part of the medullary medial reticular formation produces inhibition of neurons in the dorsal horn (Fields et al., 1977; Akaike et al., 1978).

The diffuse organization of NRP, NRO and ventromedial medulla projections to the motoneuronal cell groups suggests that they do not steer specific motor activities such as movements of distal (arm, hand or leg) or axial parts of the body, but have a more global effect on the level of activity of the motoneurons. Stimulation of the raphe nuclei has a facilitory effect on motoneurons (Cardona and Rudomin, 1983). There exist many different neurotransmitter substances in this area, of which serotonin the best known. Serotonin plays a role in the facilitation of motoneurons, probably directly by acting on the Ca2+ conductance or indirectly by reduction of K+ conductance of the membrane of the motoneuron (McCall and Aghajanian, 1979; White and Neuman, 1980; VanderMaelen and Aghajanian, 1982; Hounsgaard et al., 1986). Thus serotonin enhances the excitability of the motoneurons for inputs from other sources, such as red nucleus or motor cortex (McCall and Aghajanian, 1979). In mammals, there are many serotonergic fibers around the motoneurons (Steinbusch, 1981 and Kojima, 1983b in the rat, Kojima et al., 1982 in the dog, Kojima, 1983a in the monkey). The cell bodies of these serotonergic fibers are mainly located in the NRP, and to a limited extent in the NRO, but not in the NRM (Alstermark et al.,

Fig. 45: On the left.
Brightfield photomicrographs of autoradiographs showing tritiated leucine injection sites in the raphe nuclei and darkfield photomicrographs showing the distributions of the labeled fibers in the spinal cord. On the left an injection is shown in the caudal NRM and adjoining reticular formation. Note that labeled fibers are distributed mainly to the dorsal horn (laminae I, the upper part of II and V), the intermediate zone and the autonomic motoneuronal cell groups. On the right the injection is placed in the NRP and immediately adjoining tegmentum. Note that the labeled fibers are not distributed to the dorsal horn, but very strongly to the ventral horn (intermediate zone and autonomic and somatic motoneuronal cell groups, (from Holstege, G. and Kuypers, 1982).

1987a).

Not only serotonin, but, at least in the rat, several peptides are also present in the spinally projecting neurons in the ventromedial medulla and NRP and NRO. Many neurons contain substance P, thyrotropin releasing hormone (TRH), somatostatin, methionine (M-ENK) and leucine-enkephalin (L-ENK), while a relatively small number contains vasoactive intestinal peptide (VIP) and cholecystokinin (CCK). It has been demonstrated that most of these peptides coexist to a variable extent with serotonin in the same neuron (Chan Palay et al., 1978; Hökfelt et al., 1978; Hökfelt et al., 1979; Johansson et al., 1981; Hunt and Lovick, 1982; Bowker et al., 1983; Mantyh and Hunt, 1984; Taber-Pierce et al. 1985; Helke et al., 1986; Léger et al., 1986; Bowker et al., 1988). Johansson et al. (1981) have also demonstrated the coexistence of serotonin, substance P and TRH in one and the same neuron. This coexistence of serotonin with different peptides not only occurs in the neuronal cell bodies, but also in their terminals in the ventral horn, (Pelletier et al., 1981; Bowker, 1986; Wessendorf and Elde, 1987). According to Hökfelt et al. (1984), at the ultrastructural level, serotonin, substance P and TRH is stored in the terminal in dense core or granular vesicles, terminals with such vesicles are called G-type terminals (G=granular). Ulfhake et al., (1987) has recently shown that some of the G-type terminals lack synaptic specialization, suggesting that the content of dense core vesicles may be released at non-synaptic sites of the terminal membrane.

It must be emphasized that a major portion of the diffuse descending pathways to the dorsal horn and the motoneuronal cell groups is not derived from serotonergic neurons (Bowker et al., 1982; Johannessen et al., 1984). At the light microscopical level, Holstege, G. and Kuypers, (1982) showed in the cat that the appearance of the labeling in the motoneuronal cell groups after tritiated leucine injections in the area of the ventral nucleus raphe pallidus, with more than 90% serotonergic neurons, or in the laterally adjacent medullary medial tegmentum, with almost no serotonergic neurons (Wiklund et al., 1981), was clearly different (Fig. 47). This suggests that non-serotonergic neurons terminate differently in the motoneuronal cell groups than the fibers of the serotonergic neurons, which may or may not contain other peptides as well. One possible neurotransmitter is acetylcholine, since some of the neurons in the ventromedial medulla are ChAT positive (Jones and Beaudet, 1987). Another candidate is somatostatin, which is present in many of the neurons in especially the more caudal portions of the ventromedial medulla, and in some of the more dorsally located giant cells in the medial tegmentum. Somatostatin containing neurons are not very numerous in the raphe nuclei (Taber-Pierce et al. 1985) and coexists to a small extent with serotonin (Bowker et al. 1988). Electrophoresis of somatostatin in the brain always produces an inhi-

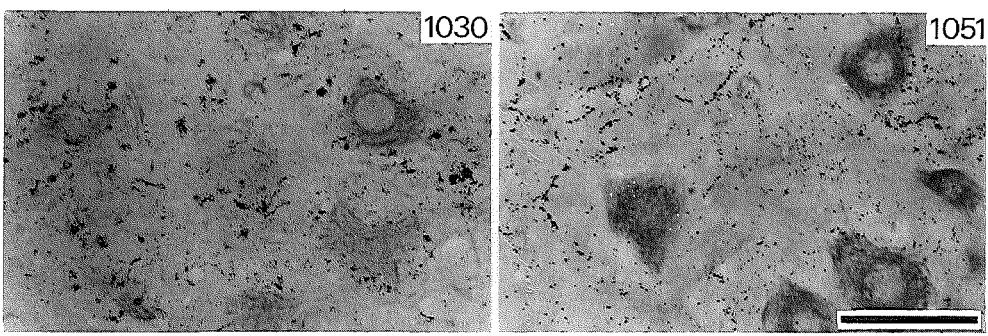


Fig. 47. Brightfield photomicrographs of autoradiographs in the somatic motoneuronal cell groups of the L7 ventral horn in the cat after injections of ^{3}H-leucine in the ventral part of the medullary medial tegmentum. On the left the injection was made at the level just rostral to the hypoglossal nucleus, not involving the raphe nuclei. Note the dominance of clusters of silver grains in the motoneuronal cell groups. On the right the injection was made in the NRP (see Fig. 45 right side). Note that the silver grains are located in strings and not in clusters. These distinct termination patterns probably represent differences in functions and/or neurotransmitter content. Bar represents 0.1 mm. (From Holstege, G. and Kuypers, 1982).

bition of the neurons in the injection-site, which suggests a generalized inhibitory role for somatostatin in the central nervous system. Also GABA may play an important role in these non-serotonergic pathways. Holstege, J.C. (1989) in the rat showed that after injection of WGA-HRP in the ventromedial medulla, 40% of the labeled terminals in the L5-L6 lateral motoneuronal cell group were also labeled for GABA. Of the double labeled terminals ≈80% contained flattened vesicles, indicating an inhibitory function (Krnjévic and Schwartz, 1966). Holstege, J.C. (1989) also found that ≈10% of the labeled terminals containing GABA were of the so-called G-type, which probably contain serotonin and/or peptides such as substance P, TRH or enkephalin-like substances (Pelletier et al., 1981; Holstege, J.C. and Kuypers, 1987). This corresponds with the finding of Belin et al. (1983) and Millhorn et al. (1988), who demonstrated colocalization of serotonin and GABA in neurons in the ventral medulla in the rat. Thus, there exist spinally projecting neurons in the ventromedial medulla that contain serotonin as well as GABA. Nicoll (1988) has found that 5HT1A and GABA-B receptors are coupled to the same ion channel. The functional implication of these findings is that some terminals, taking part in this diffuse descending system, may have inhibitory as well as facilitatory effects on the postsynaptic element (i.e. the motoneuron), although the majority is probably either facilitatory or inhibitory. Spinal motoneurons display a bistable behavior, i.e. they can switch back and forth to a higher excitable level (Hounsgaard et al., 1984; 1986; 1988; Crone et al., 1988). Bistable behavior disappears after spinal transection, but reappears after subsequent intravenous injection of the serotonin precursor 5-hydroxy-tryptophan. Thus, intact descending pathways are essential for this bistable behavior of motoneurons and serotonin is one of the neurotransmitters involved in switching to a higher level of excitation. Possibly, GABA may be involved in switching to a lower level of excitation.

In summary, the diffuse descending pathways originating in the ventromedial medulla, including the nucleus raphe pallidus and obscurus, have very general and diffuse facilitatory or inhibitory effects on motoneurons and probably also on interneurons in the intermediate zone. Although most of the terminals have either a facilitatory or an inhibitory function, recent results suggest that there also exist terminals with both facilitatory and inhibitory functions

5b 2. **Projections from the dorsolateral pontine tegmental field (A7 cell group).** Retrograde HRP and anterograde autoradiographic tracing studies (Martin et al., 1979b in the opossum; Holstege, J.C. and Kuypers, 1982, 1987 in the rat; Holstege et al., 1979 and Holstege, G. and Kuypers, 1982 in the cat; Westlund and Coulter, 1980 in the monkey) show that a large number of neurons in the locus coeruleus in the rat or the nucleus subcoeruleus and ventral part of the parabrachial nuclei in the cat project diffusely to all parts of the spinal gray matter. The diffuse dorsolateral pontine projections to the somatic motoneurons have also been demonstrated at the E.M. level (Holstege J.C. and Kuypers, 1987). In the brainstem some fibers terminate in the NRM and rostral NRP (Holstege, 1988a; Fig. 48). Many neurons in the locus coeruleus, subcoeruleus and the parabrachial nuclei contain noradrenaline (Westlund and Coulter, 1980; Jones and Friedman, 1983; Jones and Beaudet, 1987) or acetylcholine (Kimura et al., 1981; Jones and Beaudet, 1987). Neurons containing both neurotransmitters have not been reported. The diffuse projection from this area to the spinal cord is at least in part noradrenergic, since lesioning the dorsolateral pontine tegmental field, the number of noradrenergic terminals in the spinal gray matter was reduced by 25-50% in the dorsal horn and by 95% in the ventral horn (Nygren and Olson, 1977). In addition some serotonergic neurons are present in the dorsolateral pontine tegmental field (Wiklund et al., 1981), and they also project to the spinal cord (Lai and Barnes, 1985).

Electrical stimulation in the area of the locus coeruleus/subcoeruleus in rat (Chan et al., 1986) and cat (Fung and Barnes, 1987) produces a decrease in input resistance and a concurrent non-selective enhancement in motoneuron excitability, indicative of an overall facilitation of motoneurons. Furthermore there is evidence that in the rat noradrenergic fibers derived from the locus coeruleus and descending via the ventrolateral funiculus have an inhibitory effect on nociception (Jones and Gebhart, 1987).

In conclusion, neurons in the area of locus coeruleus/subcoeruleus project diffusely to all parts of the spinal gray throughout the length of the spinal cord. They have an inhibitory effect on nociception and a facilitory effect on motoneurons, an influence which is strikingly similar to that obtained after stimulation in NRM and NRP and their adjacent reticular formation.

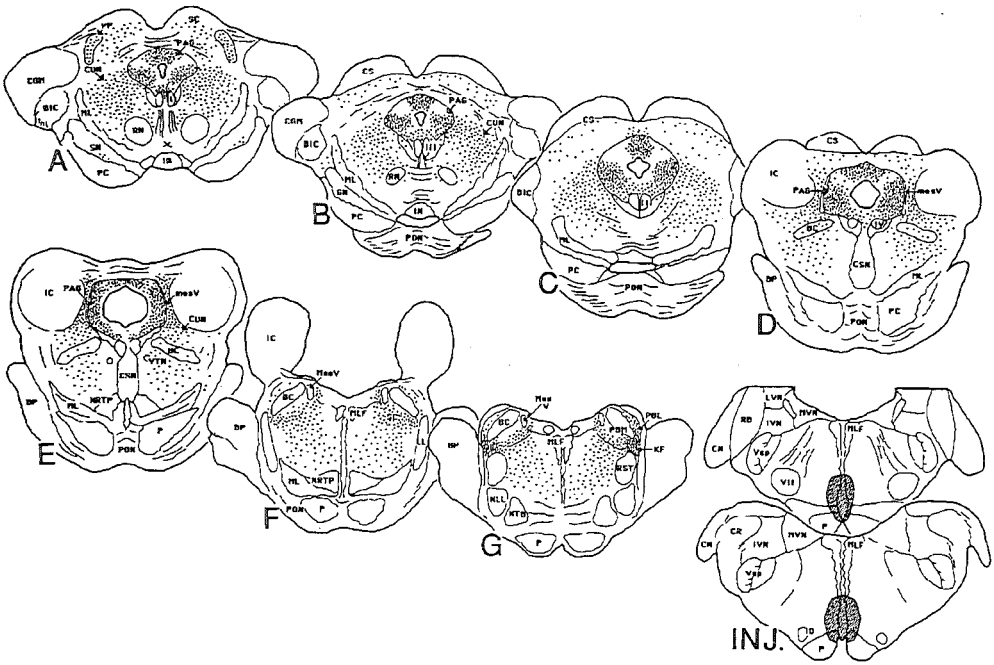


Fig. 48. Schematic drawings of HRP-labeled neurons in mesencephalon and pons after injection of HRP in the NRM/NRP region. Note the dense distribution of labeled neurons in the PAG (except its dorsolateral part) and the tegmentum ventrolateral to it. Note also the distribution of labeled neurons in the area of the ventral parabrachial nuclei and the nucleus Kölliker-Fuse (from Holstege, 1988a).

5b 3. **Projections from the pontine lateral tegmentum (paralemniscal reticular formation).** According to retrograde HRP (Fig. 32) and fluorescent tracing studies (Martin et al. 1979b; Holstege and Kuypers 1982; Huisman et al., 1982) the pontine lateral tegmental field contains a cluster of neurons, which projects contralaterally throughout the length of the spinal cord with a high degree of collateralization. Anterograde autoradiographic tracing studies (Martin et al., 1979b; Holstege et al., 1979; Holstege G. and Kuypers, 1982; Carlton et al., 1985 and Tan and Holstege, 1986) revealed that fibers originating in this area cross just beneath the floor of the fourth ventricle, and descend through the lateral reticular formation of caudal pons and medulla into the contralateral dorsolateral funiculus of the spinal cord (Fig. 27 right). In the brainstem caudal to the obex, labeled fibers from the pontine lateral tegmental field were distributed to the marginal layer of the caudal spinal trigeminal nucleus and, at the level of C1-C2, a very strong bilateral projection was observed to the lateral cervical nucleus, a small group of cells lying just lateral to the dorsal horn of the C1-C2 spinal cord (Westman 1968). Labeled fibers were distributed throughout the length of the spinal cord to lamina I, the outer part of II, but the strongest projections were to the lateral parts of laminae V and VI. Almost nothing is known about the function of this well defined contralateral pathway. The fact that it is contralateral, that it is located in the dorsolateral funiculus and that it terminates in laminae V and V suggest a motor function, similar to the rubrospinal tract. On the other hand, the additional projections to laminae I and II and the lateral cervical nucleus and the fact that it is highly collateralized suggest a function in nociception control. In this respect it may be noted that electrical stimulation in the paralemniscal cell group generated a powerful descending inhibition of nociception (Carstens et al., 1980), although it must be kept in mind that

many descending fiber systems on their way to the NRM and adjacent tegmentum pass through the paralemniscal area.

5b 4. **Projections from the rostral mesencephalon/caudal hypothalamus (A11 cell group).** Skagerberg and Lindvall (1985) in the rat demonstrated that dopamine containing neurons in the A11 cell group projected throughout the length of the spinal cord. The A11 cell group is located in the border region of rostral mesencephalon and dorsal and posterior hypothalamus, extending dorsally along the paraventricular gray of the caudal thalamus. Skagerberg and Lindvall (1985) were not able to determine in which specific parts of the spinal gray matter the A11 dopaminergic fibers terminated. Skagerberg et al. (1982) had demonstrated dopaminergic terminals in the intermediolatyeral cell column, but Yoshida and Tanaka (1988), using anti-dopamine serum found dopamine-immunoreactive fibers *"throughout the whole gray matter at any level of the spinal cord"*. Final proof that these dopaminergic fibers originate exclusively in the A11 neurons is still lacking. However, none of the other dopaminergic cell groups (A8 to A10 and A12 to A14) project to the spinal cord (Skagerberg and Lindvall, 1985; see also Albanese et al. 1986), which strongly suggests that the A11 cell group is the only source of the dopaminergic fibers in the spinal cord.
The distribution of the dopaminergic fibers in the spinal gray strongly resembles that of the noradrenergic fibers in the spinal cord, originating in the A5 and A7 cell groups. Therefore the possibility of labeling dopamine as a precursor of noradrenalin must be kept in mind, (for discussion see Yoshida and Tanaka, 1988). Functionally there is also a resemblance between noradrenergic and dopaminergic fiber projections to the spinal cord. Infusion of dopamine in the spinal cord increases (sympathetic) motoneuron activity (Simon and Schramm, 1983) and has an inhibitory effect on noxious input to the spinal cord (Jensen and Smith, 1982; Jensen and Yaksh, 1984).

5c. Projections from the mesencephalon to caudal brainstem and spinal cord

In recent years specific information became available about the anatomy and function of the descending projections of the mesencephalon in relation to emotional behavior. Stimulation in the mesencephalon has been shown to result in pain inhibition, vocalization, aggressive behavior, blood pressure changes, lordosis and locomotion. Many of the neurons involved in these functions are located in the PAG, but neurons in the mesencephalic tegmentum lateral and ventral to the PAG also play a role.

5c 1. **Descending projections to the NRM, NRP and ventral part of the caudal pontine and medullary medial tegmentum**
Retrograde HRP tracing studies (Abols and Basbaum, 1981; Holstege, 1988a) indicate that an enormous number of HRP labeled neurons in the PAG and laterally and ventrolaterally adjoining areas project to NRM, NRP and ventral part of the caudal pontine and medullary medial tegmentum (Fig. 48). Anterograde (autoradiographic) tracing studies (Jürgens and Pratt, 1979; Mantyh, 1983; Holstege, 1988a; Fig. 49) show that different parts of the PAG and adjacent tegmentum project in the same basic pattern to the caudal brainstem. The descending mesencephalic fibers pass ipsilaterally through the mesencephalic and pontine lateral tegmental field, but gradually shift ventrally and medially at caudal pontine levels. They terminate mainly ipsilaterally in the ventral part of the caudal pontine and medullary medial reticular formation and in the NRM (Fig. 49). On their way to the medulla they give off fibers to the area of the locus coeruleus and nucleus subcoeruleus and the paralemniscal cell group. Neurons in the ventrolateral portion of the caudal PAG and the ventrally adjoining mesencephalic tegmentum send fibers to the NRP (Fig. 49 left). There exists a mediolateral organization within the descending mesencephalic pathways. The main projection of the medially located neurons, i.e. neurons in the medial part of the dorsal PAG, is to the medially located NRM and immediately adjacent tegmentum. On the other hand, neurons in the lateral PAG, the laterally adjacent tegmentum and the intermediate and deep layers of the superior colliculus project mainly laterally to the ventral part of the caudal pontine and upper medullary medial tegmentum with virtually no projections to the NRM (Holstege, 1988a). Figure 50 from Cowie and Holstege, (1990) is a schematic diagram, showing this mediolateral organization in the descending pathways from the dorsal mesencephalon.

5c1 a. **Involvement of the descending mesencephalic projections in control of nociception**
In animals (see Besson and Chaouch, 1987 and Willis, 1988 for reviews) as well as in humans

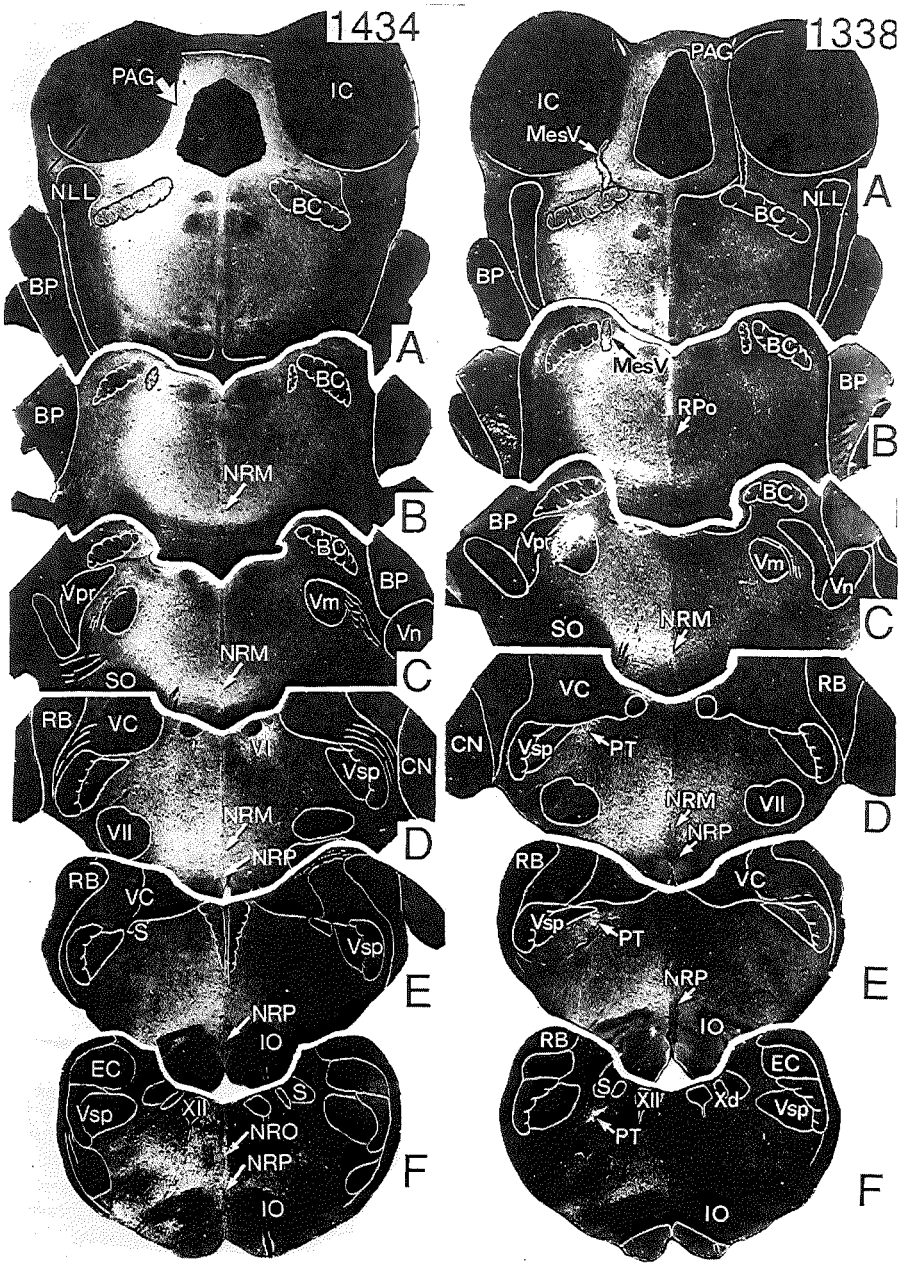


Fig. 49. Darkfield photomicrographs of the brainstem in the cases 1434 and 1338 with injections in respectively the ventrolateral PAG and more rostrally in the lateral PAG. Note the strong projections to the NRM and the ventral part of the medial tegmentum of caudal pons and medulla in both cases. Note that in case 1434, but not in case 1338 labeled fibers were also distributed to the NRP (from Holstege, 1988a).

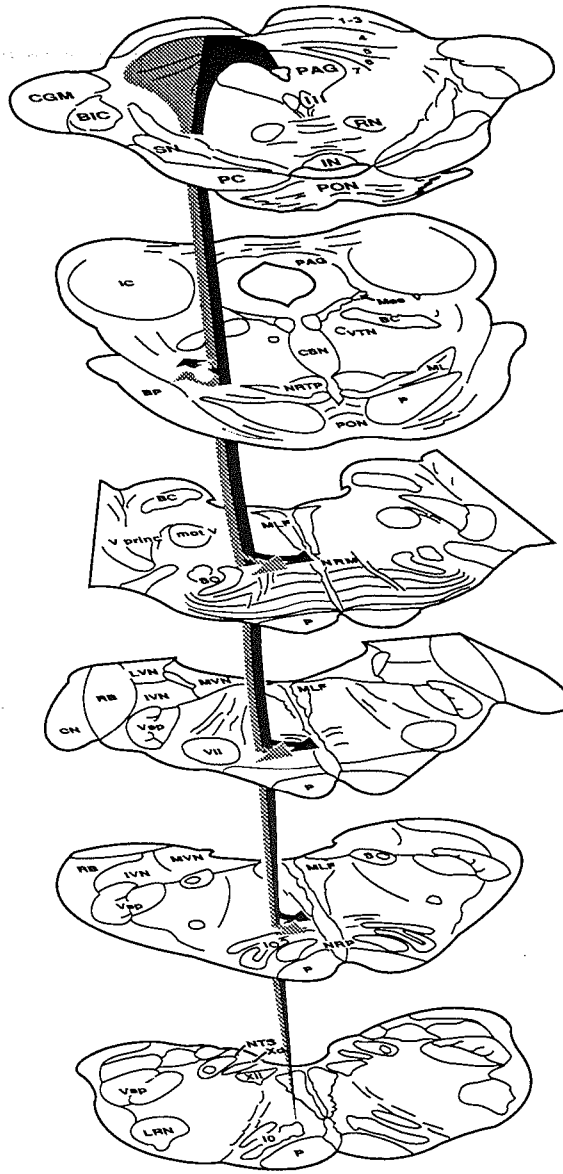


Fig. 50. Schematic representation of the ipsilateral descending pathway, originating from the intermediate and deep layers of the superior colliculus and dorsal PAG. The mediolateral organization of this descending system is illustrated. The lateral (gray) component projects to the lateral aspects of the ventral part of the medial tegmentum of caudal pons and medulla oblongata. The medial (black) component projects to the medial aspects of the medial tegmentum, including the NRM. A similar mediolateral organization exists for the descending pathways originating in more ventral part of the mesencephalic tegmentum, (from Cowie and Holstege, 1990).

(Hosobuchi, 1988; Meyerson, 1988) the PAG is well known for its involvement in the supraspinal control of nociception. The strong impact on nociception is partly mediated via its projections to the NRM and adjacent reticular formation, because in cases with reversible blocks of the NRM and adjacent tegmentum, PAG stimulation results in reduced analgesic effects (Gebhart et al., 1983; Sandkuhler and Gebhart, 1984). However, the analgesic effects do not completely disappear after blocking the NRM and adjacent tegmentum, which suggests that other brainstem regions also play a role. In this respect the PAG projections to the paralemniscal cell group are of interest, since part of the antinociceptive action of the PAG may be exerted through this pathway (see section 5 b 3).

5c1 b. **Involvement of the descending mesencephalic projections in the lordosis reflex**

Stimulation in the PAG also facilitates the lordosis reflex (Sakuma and Pfaff, 1979a,b). Lordosis, a curvature of the vertebral column with ventral convexity, is an essential element of female copulatory behavior in rodents. The lordosis reflex is facilitated by stimulation of the ventromedial hypothalamic nucleus (Pfaff and Sakuma, 1979a,b) and the PAG (Sakuma and Pfaff, 1979a,b). Stimulation of the L1 through S1 dermatomes is sufficient for eliciting the lordosis reflex, but several studies suggested that it was oestrogen dependent, i.e. would only occur when copulation can result in fertilization. This led to the concept that the lordosis reflex cannot be produced in the absence of facilatory forebrain influences. However, it was recently demonstrated that the lordosis reflex can also be elicited in decerebrate rats (Rose and Flynn, 1989). It is also known that descending fibers in the ventrolateral funiculus play a role in the facilitation of the reflex (Kow et al., 1977). It is not possible that these fibers originate from neurons in the ventromedial hypothalamic nucleus or the PAG, because none of the two structures projects directly to the lumbosacral spinal cord (Holstege, 1987b; Holstege, 1988a).

Perhaps, the lordosis reflex should be considered as a spinal reflex, in which the L1-S1 cutaneous input from flank, rump, tailbase and perineum serves as the afferent loop, and the fibers of the back and axial muscle motoneurons form the efferent loop. Both loops are interconnected by spinal interneurons and short and long propriospinal pathways. Neurons in the dorsal two thirds of the pontine and upper medullary medial tegmentum may coordinate the back and axial muscle inter- and motoneuronal activity via their descending pathways through the ventral funiculus of the spinal cord (see section 4 a 1). These neurons receive afferents from the PAG, although their number is much lower than the PAG fibers terminating in the ventral parts of the medial tegmentum (Fig. 49). However, lordosis behaviour occurs only when the membrane excitability of the motoneurons is high. This level of excitability is determined by descending pathways, which originate in the ventral part of the medullary medial tegmentum and project diffusely to all inter- and motoneuronal cell groups in the ventral horn throughout the length of the spinal cord (section 5 b 1). The ventral part of the medial tegmental field receives its afferents from PAG and anteromedial hypothalamus, but not from the ventromedial hypothalamic nucleus (see Fig. 54). Thus, a concept is put forward in which the ventromedial hypothalamic nucleus controls the lordosis reflex by means of its projections to the dorsal and ventral parts of the caudal pontine and medullary medial tegmentum, using the anteromedial hypothalamus and the PAG as relay structures. Neurons in the dorsal two thirds of the medial tegmentum coordinate the back and axial muscle motoneuronal activity while the medullary ventromedial tegmentum increases the excitability of the motoneurons to such a level that cutaneous L1-S1 afferent stimulation, which is otherwise ineffective, results in lordosis. Actually, during oestrus the female rat shows several forms of stressful behavior, characterized by frequent locomotion and other stress like phenomena (Pfaff, 1980). It is well known in mammals that various forms of stress, whether it is aggression, fear or sexual arousal, set the motor system at a "high" level. In such circumstances spinal reflexes such as the lordosis reflex can easily be elicited. Pfaff (1980) points to the lateral vestibulospinal tract to play an important role in lordosis behavior, although the lateral vestibular nucleus does not receive afferents from the hypothalamus or PAG. Lesions in the lateral vestibular nucleus led to decreases in lordosis (Modianos and Pfaff, 1979). In this respect it should be recalled that the lateral vestibulospinal tract has an important influence on all axial movements, thus including the lordosis movements. The question remains whether the lateral vestibular nucleus is specifically involved in lordosis behavior.

5c1 c. **Involvement of the descending mesencephalic projections in locomotion**

Just lateral to the brachium coniunctivum, just ventral to the cuneiform nucleus and just rostral to the parabrachial nuclei is located the so-called pedunculopontine nucleus. The area contains many ChAT positive neurons (Jones and Beaudet, 1987). Stimulation in the pedunculopontine nucleus induces locomotion in cats (Shik et al., 1966), which is the reason that this area is also termed the mesencephalic locomotor region (MLR). The MLR not only comprises the pedunculopontine nucleus, but extends into the cuneiform nucleus, which is located just dorsal to the pedunculopontine nucleus. Garcia Rill and Skinner, (1988) found that during locomotion neurons in the cuneiform nucleus were related preferentially to rhythmic (bursting) activity, while neurons in the pedunculopontine nucleus are preferentially related to the onset or termination of cyclic episodes (on/off cells).

Anatomical studies (Moon Edley and Graybiel, 1983; Holstege, unpublished results) revealed that the descending projections from this area are organized similar to those from the PAG and adjacent tegmentum. The mainly ipsilateral fiberstream first descends laterally in the mesencephalon and upper pons and then gradually shifts medially to terminate bilaterally, but mainly ipsilaterally in the ventral part of the caudal pontine and medullary medial tegmental field (see also Garcia Rill and Skinner, 1987b). Only sparse projections exist to the nucleus raphe magnus and almost none to the dorsal portions of the caudal pontine and medullary medial tegmentum. By means of low-amplitude (<70 μA), high frequency (5-60 Hz) stimulation or via injection of cholinergic agonists in this same area, Garcia Rill and Skinner (1987a) were able to elicit locomotion in the ventral portion of the caudal pontine and medullary medial tegmentum. They also demonstrated that the locomotion in the medioventral medulla could control or override the stepping frequency induced by the mesencephalic locomotor region. Moreover, Garcia Rill and Skinner, (1987b) reported that ≈35% of the cells in this area project through the ventrolateral funiculus of the C2 spinal cord and half of these cells received short latency orthodromic input from the mesencephalic locomotor region. Somewhat surprising was that they also found such cells as far rostral as the caudal pontine ventral tegmentum. The latter area, according to the anatomic findings, only projects to the dorsal horn via the dorsolateral funiculus and not to the intermediate zone or ventral horn via the ventrolateral funiculus. Nevertheless, the findings of Garcia Rill and Skinner, (1987a,b) indicate that locomotion, elicited in the mesencephalic locomotor region, is based on the projections from this area to the medial part of the ventral medullary medial tegmentum and on the diffuse projections from the latter area to the rhythm generators in the spinal cord.

The afferent connections of the mesencephalic locomotor area are derived from lateral parts of the limbic system, such as the bed nucleus of the stria terminalis, central nucleus of the amygdala and lateral hypothalamus (Moon Edley and Graybiel, 1983). Strong projections are also derived from the entopeduncular nucleus, subthalamic nucleus and the substantia nigra pars reticulata, but motor cortex projections to the MLR are very scarce (Moon Edley and Graybiel, 1983). These findings indicate that the MLR is influenced by extrapyramidal and lateral limbic structures, and virtually not by somatic motor structures. This corresponds with the fact that the descending projections from the MLR terminate in the ventromedial part of the caudal pontine and medullary tegmental field, which area receives afferents from many other limbic system related areas, but not from the somatic motor structures.

Another area, stimulation of which produces locomotion is the so-called subthalamic locomotor region, which seems to correspond with the caudal hypothalamus (see Armstrong, 1986 and Gelfand et al., 1988 for reviews). After bilateral lesions in the subthalamic locomotor region the cat cannot walk spontaneously for 7-10 days, and neither food nor nociceptive stimuli evoke locomotion, although the animal eats food which it can reach without making a step or responds by aggression to pain. Stimulation of the MLR during this period elicits locomotion. The animal walks or runs depending on the strength of stimulation without bumping the walls of the room. Lesioning the MLR, with an intact subthalamic locomotor region does not interfere essentially with motor activity (Sirota and Shik, 1973). In this respect it is important to note that the subthalamic locomotor region (caudal hypothalamus) not only projects to the MLR but also directly to the ventral part of the caudal pontine and medullary medial tegmental field (see section 5 d 3).

The last region in which locomotion can be elicited is the so called pontomedullary locomotor strip, located in the lateral tegmental field of pons

and medulla. This non-continuous tract consists of mainly short propriobulbar axons (Shik, 1983) and probably must be considered as the rostral extent of the spinal interneurons involved in stepping (see section 2 d).

5c 2. **PAG projections to the ventrolateral medulla; involvement in blood pressure control**
In section 3 c it has been shown that neurons in the rostral part of the ventrolateral tegmental field of the medulla (subretrofacial nucleus) are essential for the maintenance of the vasomotor tone and reflex regulation of the systemic arterial blood pressure. Neurons in the rostral part of the subretrofacial nucleus project specifically to the IML neurons, innervating the kidney and adrenal medulla, while neurons in the caudal part of it innervate more caudal parts of the IML, with neurons innervating the hindlimb (Lovick, 1987; Dampney and McAllen, 1988). In a recent study Carrive et al. (1989) have been shown that neurons in the dorsal portions of the caudal half of the PAG have an excitatory effect on the neurons in the subretrofacial nucleus (increase of blood pressure), while neurons in the ventral part of the PAG have an inhibitory effect (decrease of blood pressure). The same authors have also shown that neurons in the subtentorial portion of the PAG project to the rostral part of the subretrofacial nucleus, which neurons send fibers to the IML motoneurons that innervate the kidney and adrenal medulla. On the other hand, neurons in the caudal part of the pretentorial PAG project to the caudal subretrofacial nucleus, which in turn project to IML motoneurons innervating the hindlimb. In conclusion, there exists a precise organization in the mesencephalic control of blood pressure in different parts of the body. All these projections take part in a descending system involved in the elaboration of emotional motor activities. For an extensive review of this control system, see Richard Bandler et al., (1990).

5c 3. **PAG projections to the nucleus retroambiguus; involvement in vocalization**
In many different species, from leopard frog to chimpanzee (see Holstege, G., 1989 for review), stimulation in the caudal PAG results in vocalization, i.e. the nonverbal production of sound. In humans laughing and crying are probably examples of vocalization (see section 5a). Holstege, G. (1989) has demonstrated that a specific group of neurons in the lateral and to a limited extent in the dorsal part of the caudal PAG send fibers to the NRA in the caudal medulla (Fig. 51). The cell group in the PAG differs from the smaller cells projecting to the raphe nuclei and adjacent tegmentum or the larger cells projecting to the spinal cord. The NRA in turn projects to the somatic motoneurons innervating the pharynx, soft palate, intercostal and abdominal muscles and probably the larynx (see section 3 a 3-4; Fig. 52). Direct PAG projections to these somatic motoneurons do not exist (Holstege, 1989). In all likelihood, the projection from the PAG to the NRA forms the final common pathway for vocalization, because

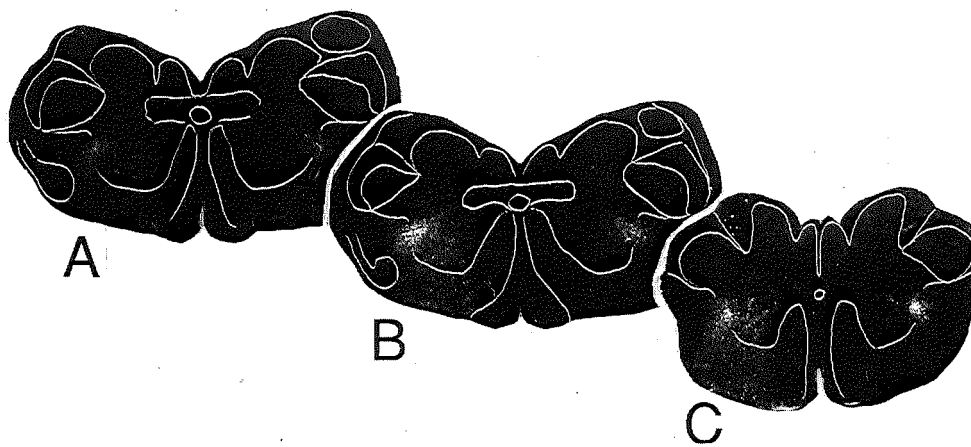


Fig. 51. Darkfield photographs of the caudal medulla in a cat (1434, see also fig. 48 left) with an injection of ^{3}H-leucine in the ventrolateral part of the caudal PAG. Note the strong bilateral projections to the NRA, (from Holstege, G., 1989).

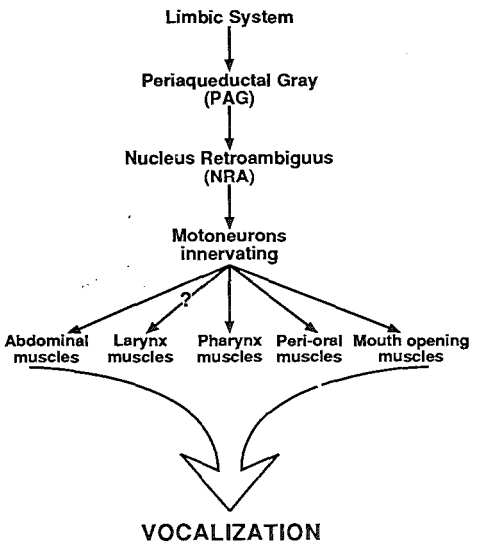


Fig. 52. Schematic representation of the pathways for vocalization from the limbic system to the vocalization muscles, (from Holstege, G., 1989).

DeRosier et al., (1988) found that during vocalization the NRA neurons were more closely related to the vocalization muscle EMG than the PAG. This finding is important, because it shows that a specific expressive motor activity (fixed action pattern) such as vocalization is based on a distinct descending pathway, suggesting that all the other specific motor activities displayed during expressive behavior are based on separate descending pathways.

5c 4. **PAG projections to the spinal cord**

Only limited PAG projections to the spinal cord exist (Fig. 32 L-N). Some neurons in the lateral PAG and laterally adjacent tegmentum send fibers through the ipsilateral ventral funiculus of the cervical spinal cord to terminate in laminae VIII and the adjoining part of VII (Martin et al., 1979c; Holstege, 1988a,b; see section 4 a 2 c). A very few fibers descend ipsilaterally in the lateral funiculus to terminate in the T1-T2 IML (Holstege, 1988a,b). The projections to the spinal cord may play a role in the defensive behavior observed by Bandler and Carrive (1988), stimulating the PAG. For example, the projection to the medial part of the intermediate zone of the cervical cord may be involved in the contralateral head turning movements as part of defensive behavior, while the projection to the T1-T2 IML may produce the pupil dilation described by Bandler and Carrive (1988).

Figure 53 gives a schematic overview of the descending projections from the PAG and pedunculopontinepontine and cuneiform nuclei to the caudal brainstem and spinal cord, including the functions in which these projections might be involved.

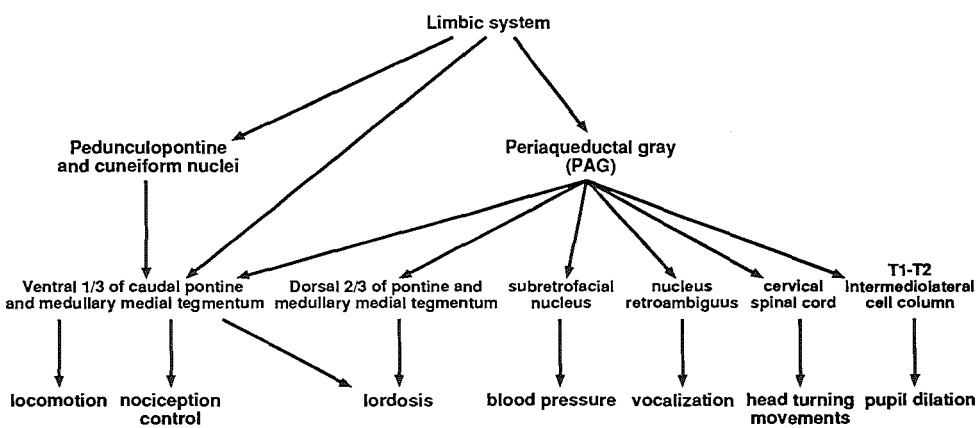


Fig. 53. Schematic overview of the descending projections from the PAG and pedunculopontine and cuneiform nuclei to different regions of the caudal brainstem and spinal cord. The functions in which each of the projections might be involved are also indicated. It should be emphasized that these functional interpretations are only tentative.

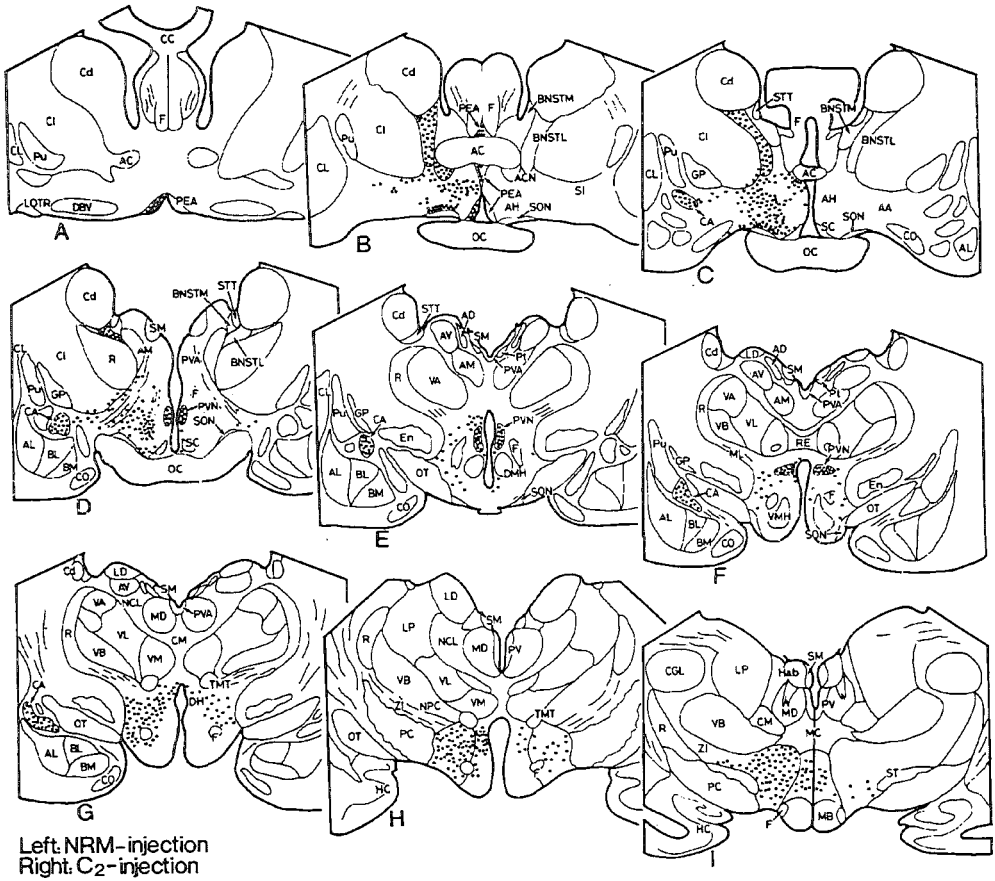


Fig. 54. Schematic drawing of HRP neurons in the hypothalamus, amygdala and bed nucleus of the stria terminalis. On the left the pattern of distribution of labeled neurons in after a large injection of HRP in the NRM, rostral NRP and adjoining tegmentum is indicated. On the right the pattern of distribution of HRP-labeled neurons after hemi-infiltration of HRP in the C2 spinal segment is shown. (From Holstege, 1987b).

5d. Projections from the hypothalamus to caudal brainstem and spinal cord

The descending hypothalamic projection systems differ greatly, depending on which part of the hypothalamus is considered. In this section the hypothalamus will be subdivided into the anterior hypothalamus, the paraventricular hypothalamic nucleus, the posterior hypothalamus and the lateral hypothalamus.

5d 1. **Projections from the anterior hypothalamus/preoptic area.** According to retrograde HRP studies in the rat, opossum, and cat (Kuypers and Maisky, 1975; Saper et al., 1976; Crutcher et al., 1978; Basbaum et al., 1978 and Holstege, 1987b) neurons in the anterior hypothalamus/preoptic area project strongly to the caudal brainstem, but not to the spinal cord (Fig. 54). Neurons in the medial part of the anterior hypothalamus project (via a medial fiber stream, see large arrows in Fig. 55) to the PAG, the dorsal and superior central raphe nuclei in the pontine tegmentum, and to the ventromedial tegmentum of caudal pons and medulla, including the NRM and NRP (Figs. 55 and 56B).

The anterior hypothalamus receives afferent fiber

connections from caudal brainstem structures such as the lateral parabrachial nucleus, the solitary nucleus, and neurons in the ventrolateral medulla (Berk and Finkelstein, 1981; Saper and Levisohn, 1983), which suggests that it is involved in cardiovascular regulation. Moreover, application of cholinergic drugs in the anterior hypothalamus results in an emotional aversive response, which includes defense posture and autonomic (e.g., cardiovascular) manifestations (Brudzynski and Eckersdorf, 1984; Tashiro et al., 1985).

5d 2. **Projections from the paraventricular hypothalamic nucleus (PVN).** Using the retrograde HRP method in the cat, Kuypers and Maisky (1975) were the first to demonstrate PVN projections to the spinal cord (Fig. 54). Their findings were later confirmed by Hancock (1976) in the rat, Crutcher et al. (1978) in the opossum, Blessing and Chalmers (1979) in the rabbit, Holstege (1987b) in the cat, and Kneisley et al. (1978) in the monkey. The PVN is best known for its projections to the hypophysis, but Hosoya and Matsushita (1979) and Swanson and Kuypers (1980) have shown that the neurons projecting to the hypophysis differ from the ones projecting to the spinal cord. According to Holstege (1987b), the PVN neurons in the cat send their fibers to the caudal brainstem and spinal cord via the medial forebrain bundle and more caudally via a well defined pathway through the lateral part of the mesencephalon and upper pons. At this level they gradually shift medially, filtering through (but not terminating in) the pontine nuclei, to arrive in a very peripheral position lateral to the pyramidal tract (Fig. 58). The PVN fibers descend further into the lateral and dorsolateral funiculus of the spinal cord throughout its total length (Fig. 57). Via this pathway the PVN sends fibers to the NRM, rostral NRP and adjoining reticular formation (Figs. 58 and 56D), and specific parts of the medullary lateral tegmental field (Holstege, 1987b; Fig. 58 D-I). In this area lie parasympathetic motoneurons (see section 1 d) and the noradrenergic brainstem nuclei A1 and A2. Specific projections have been demonstrated to the nor-adrenergic A5 area and to the parasympathetic motoneurons in the salivatory nuclei, (Hosoya et al. 1990). Furthermore, PVN fibers terminate in mainly the rostral half of the solitary nucleus (Figs. 58 E-G), in all parts of the dorsal vagal nucleus (Swanson and Kuypers, 1980 in the rat; Berk and Finkelstein, 1983 in the pigeon and Holstege, 1987b in the cat; Fig. 58G), and in the area postrema (Hosoya and Matsushita, 1981 in the rat; Holstege, 1987b in the cat; Fig. 58H).

According to the autoradiographic tracing findings of Holstege (1987b; Fig. 57), in the spinal cord the PVN projects bilaterally, but mainly ipsilaterally, to lamina X next to the central canal, the thoracolumbar (T1-L4) intermediolateral (sympathetic) motoneuronal cell group, and to the sacral intermediomedial and intermediolateral (parasympathetic) motoneuronal cell groups. The projections to the sympathetic intermediolateral cell column at the levels L2, L3 and upper L4 are especially strong and extensive. Finally, the PVN projects to the nucleus of Onuf (Holstege, 1987b; Holstege and Tan, 1987). One might speculate, in view of the strong PVN projections to the L2-L4 intermediolateral sympathetic motoneurons, the sacral intermediolateral parasympathetic motoneurons and the nucleus of Onuf (Fig. 57 bottom left), that the PVN might play a role in sexual activity and/or control of the uterus contractions in pregnant women (see Holstege and Tan, 1987 for a review). On the other hand, the PVN projects to all preganglionic motoneurons (sympathetic and parasympathetic), which suggests a more general function, for example a similar function as the hormone ACTH. According to Strack et al. 1989, the PVN neurons projecting to the upper thoracic IML are located more medially in the PVN than the neurons projecting to the caudal thoracic and upper lumbar IML, which suggests that there exist some specificity within the PVN spinal pathways (see also Loewy, this volume). The PVN sends its fibers to lamina I of the caudal spinal trigeminal nucleus and throughout the length of the spinal cord (Holstege, 1987b, Fig. 57). This, together with the fact that stimulation in the area of the PVN produces inhibition of spinal dorsal horn neuronal responses to noxious skin heating (Carstens, 1982), suggests a role of the PVN in nociception control mechanisms.

The PVN contains a large number of transmitter substances such as oxytocin, vasopressin, somatostatin, dopamine, methionine-enkephalin, leucine-enkephalin, neurotensin, cholecystokinin, dynorphin, substance P, glucogen, renin, and corticotropin releasing factor (see Swanson and Sawchenko, 1983 for a review). Swanson (1977) and Nilaver et al. (1980) traced a pathway containing neurophysin (a carrier protein for oxytocin and vasopressin) from the PVN through the MFB to the caudal brainstem and spinal cord, distributing fibers to the parabrachial nuclei, the nucleus of

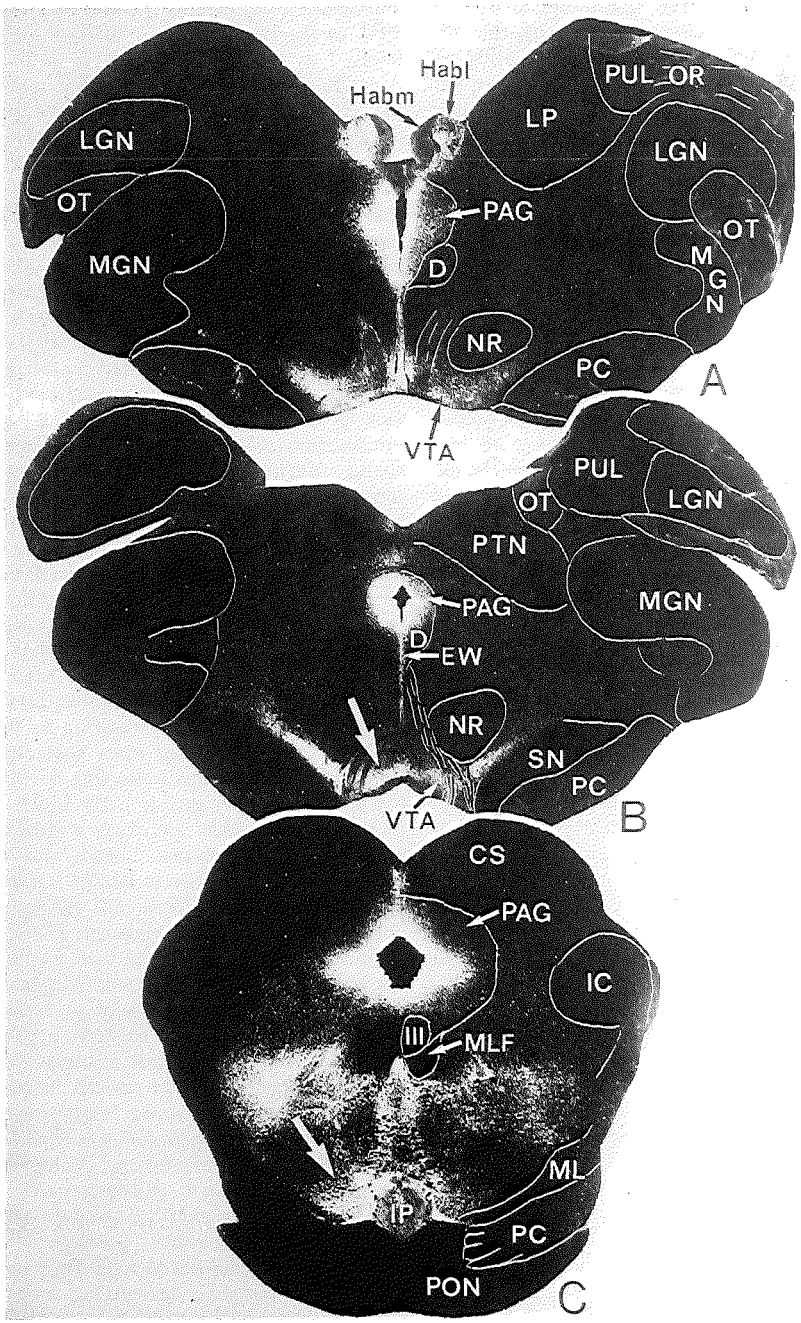
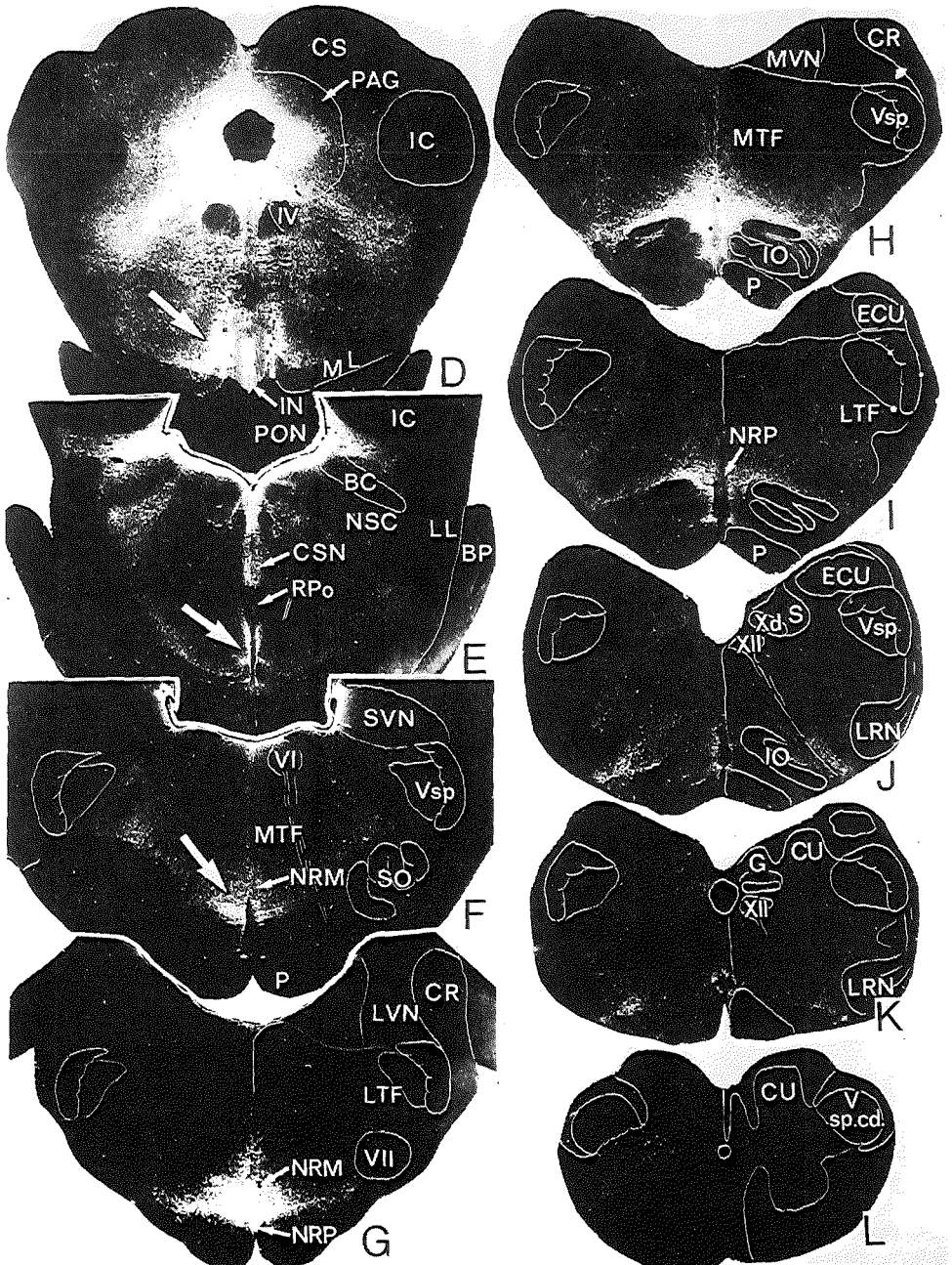


Fig. 55. Darkfield photomicrographs of the brainstem in a case with a ^{3}H-leucine injection in the medial part of the anterior hypothalamic area. Note the strong projections, via a medial fiberstream (see large arrows in B



to F) to the medially located NRM/NRP and to the ventral part of the caudal pontine and upper medullary medial tegmentum. Note also that only the most rostral part of the NRP receives labeled fibers. (From Holstege, 1987b).

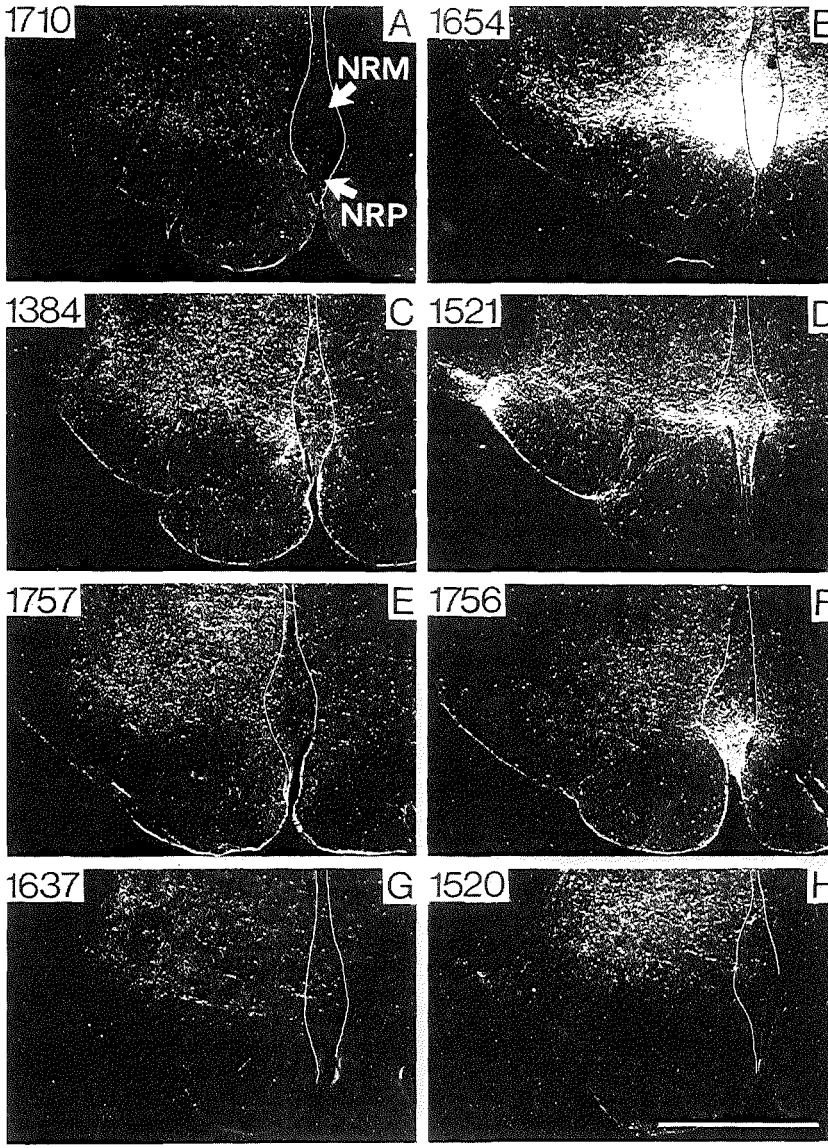


Fig. 56. Darkfield photomicrographs of the NRM, rostral NRP and adjoining tegmental field at the level of the facial nucleus in 8 cases with injections in the lateral hypothalamic area (A, C and E), the medial part of the anterior hypothalamic area (B), the PVN of the hypothalamus (D), the medial part of the caudal hypothalamus (F), the central nucleus of the amygdala (G) and bed nucleus of the stria terminalis (H). Note the relative small number of labeled fibers in the NRM/NRP after lateral injections in the limbic system (A, E, G and H) and the strong projections to the NRM/NRP after medial injections in the limbic system (B, D and F). The injection in C involved the lateral hypothalamus but extended into the medial hypothalamus, which explains the labeled fibers in NRM/NRP in this case. Bar represents 2 mm. (From Holstege, 1987b).

the solitary tract, the dorsal vagal nucleus and the thoracic intermediolateral cell column and Rexed's laminae I and X. Similar oxytocinergic brainstem projections were found by Hermes et al. (1988) in the garden dormouse, but they also reported oxytocinergic fibers terminating in the nuclei raphe magnus, pallidus and obscurus. Furthermore, Holstege and Van Leeuwen in the cat (unpublished observations) observed oxytocinergic and vasopressinergic fibers in the nucleus of Onuf and the sacral intermediolateral (parasympathetic) cell group. Oxytocin and vasopressin in the spinal cord are only derived from the PVN (Hawthorn et al., 1985), but according to Sawchenko and Swanson (1982) only 20% of the PVN-spinal neurons contain oxytocin or vasopressin and another 5% contain tyrosine hydroxylase (presumably dopamine) and met-enkephalin. Therefore, other neuro-active substances must be involved in this PVN-caudal brainstem/spinal pathway.

The PVN is believed to play an important role in cardiovascular regulation as well as in the feeding mechanism. Feeding behavior in satiated rats can be elicited by injecting clonidine (a noradrenergic agonist) intraperitoneally or in the PVN itself (McCabe et al., 1984). The neural circuitry for this feeding system is believed to start in the noradrenergic neurons of the locus coeruleus (A6 nucleus) that project to the PVN by way of the dorsal pons and dorsal midbrain (Leibowitz and Brown, 1980). The PVN neurons in turn innervate neurons in the dorsal vagal nucleus, which play a crucial role in the noradrenaline-elicited eating response (Sawchenko et al., 1981).

5d 3. **Projections from the medial part of the posterior hypothalamic area.** Retrograde tracing studies have demonstrated that the posterior hypothalamus projects to the spinal cord (Kuypers and Maisky, 1975 and Holstege, 1987b in the cat; Fig. 54; Saper et al., 1976; Hancock, 1976 and Hosoya, 1980, in the rat) as well as to the NRM and NRP (Holstege, 1987b). Anterograde autoradiographic tracing studies have revealed that the posterior hypothalamic area sends fibers via a medial pathway to the caudal raphe nuclei and adjoining reticular formation (Hosoya, 1985; Holstege, 1987b). The caudal hypothalamic projections to the NRM are weaker and those to the NRP are much stronger than the PVN projections to this area (compare figs. 56D (=PVN) and 56F (= caudal hypothalamus). The posterior hypothalamus also projects to the caudal parts of the NRP, which region does not receive afferents from the PVN or other hypothalamic areas (Holstege, 1987b).

The medial part of the posterior hypothalamus sends fibers into the lateral funiculus of the spinal cord, where they terminate in the upper thoracic intermediolateral cell column and in lamina X throughout the length of the spinal cord (Holstege, 1987b). There seems to exist a rostrocaudal organization in the medial hypothalamic projections to the raphe nuclei and spinal cord, in which the rostral portion of the hypothalamus projects to the rostral parts of the raphe nuclei (i.e. the NRM and the rostral NRP), while the caudal hypothalamus projects to all parts of the NRP and to the spinal cord. Functionally, such differences in projections may be important, because NRM and NRP project to different parts of the spinal gray.

The dorsomedial region of the caudal hypothalamus plays an important role in temperature regulation, and it contains the primary motor center for the production of shivering (Stuart et al. 1961). Shivering is an involuntary response of skeletal muscles which are usually under voluntary control and all skeletal muscle groups can participate (Hemingway 1963). Shivering does not take place in spinalized animals, indicating that supraspinal mechanisms, i.e. the caudal hypothalamus control this activity. On the other hand, the rhythm of the shiver is probably determined in the spinal cord under the control of the proprioceptive inflow (Birzis and Hemingway, 1957). Possibly the strong caudal hypothalamic projections to the NRP and adjacent tegmentum plays an important role in this "shivering pathway", similar to its role in the descending pathways involved in locomotion, which is also a rhythmical activity.

5d 4. **Projections from the lateral hypothalamic area.** Functional and anatomical studies on the lateral hypothalamus have always been difficult, because the fibers of the medial forebrain bundle pass through it. This important fiber bundle not only contains fibers originating in the lateral hypothalamus, but also in many other areas, and stimulation or lesions in this area not only affect lateral hypothalamic neurons, but also fibers derived from many other limbic structures (cf. Nieuwenhuys et al., 1982 for a review). Retrograde HRP studies (Saper et al., 1976; Hosoya, 1980 and Holstege, 1987b) reveal that many neurons in the more caudal portions of the lateral hypothalamus project to the spinal cord. Autora-

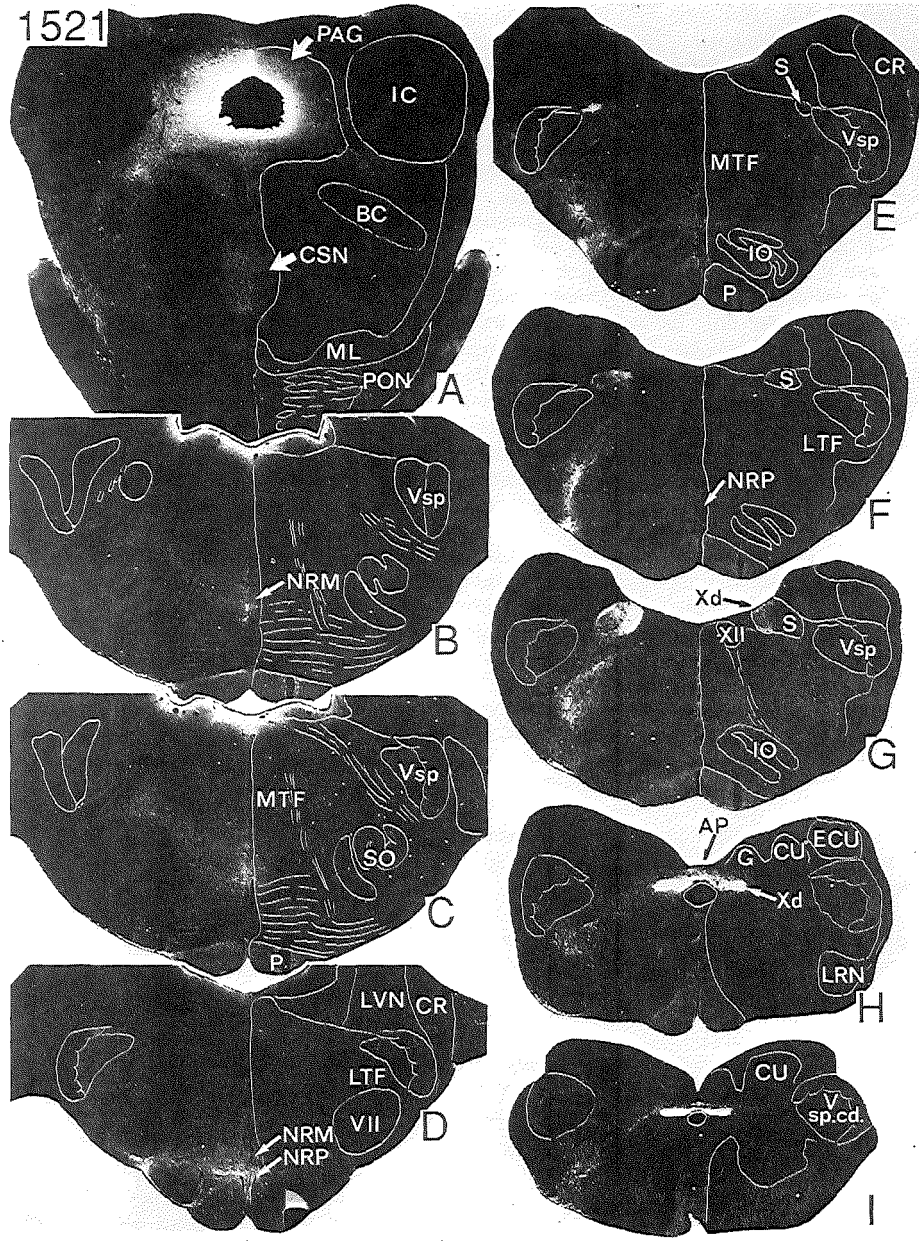


Fig. 57. Darkfield photomicrographs of 9 brainstem sections of a cat with an injection of ^{3}H-leucine in the area of the PVN of the hypothalamus. Note the distinct descending pathway in the area next to the pyramidal tract and its fiber distribution to the NRM/NRP, dorsal vagal nucleus, area postrema and rostral solitary complex. (From Holstege, 1987b).

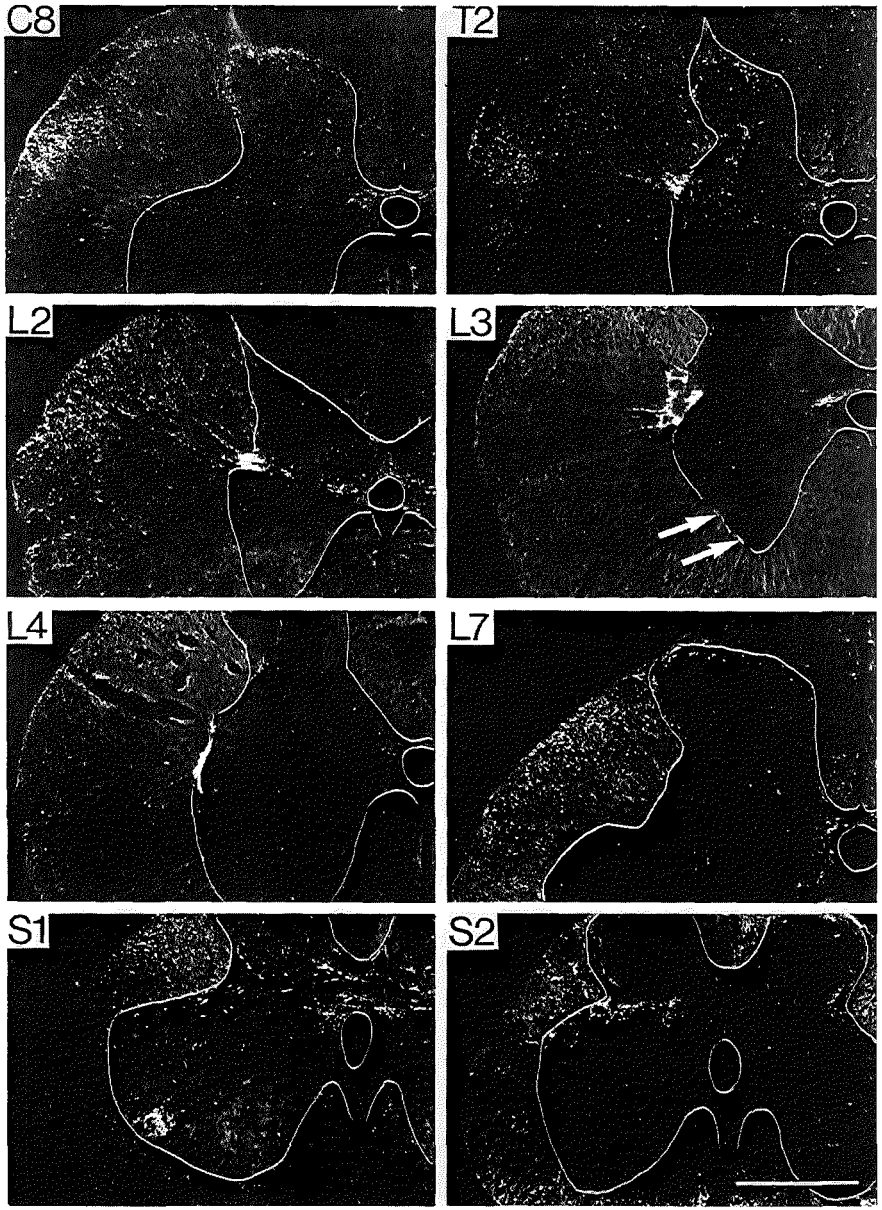


Fig. 58. Darkfield photomicrographs of the spinal cord of the same cat as illustrated in fig. 57, with a ^{3}H-leucine injection in the area of the PVN of the hypothalamus. Note the projection to lamina I (C8, T2 and L7), the sympathetic intermediolateral cell group (T2, L2, L3 and L4), the nucleus of Onuf (S1) and the parasympathetic intermediomedial and intermediolateral cell group (S2). The arrows in L3 probably indicate projections to distal dendrites of the motoneurons located in the sympathetic intermediolateral cell group. (From Holstege, 1987b).

diographic tracing studies (Berk, 1987 in the pigeon; Hosoya and Matsushita, 1981 and Berk and Finkelstein, 1982 in the rat; Holstege, 1987b in the cat), which do not label fibers of passage (Lasek et al., 1968; Cowan et al., 1972), show that the lateral hypothalamus sends fibers to the PAG, the cuneiform nucleus, the parabrachial nuclei and nucleus Kölliker-Fuse, the nucleus subcoeruleus, the locus coeruleus, the caudal pontine and medullary lateral tegmental field, (as defined by Holstege et al., 1977, see section 2 d), and to the ventral part of the caudal pontine and medullary medial tegmentum. Only very few fibers terminate in the area of the NRM and none in the NRP (Fig. 56 A and E). Some fibers terminate in the periphery of the dorsal vagal nucleus and in the rostral half of the solitary nucleus. The rostral portion of the lateral hypothalamus also projects strongly to the area just ventral and medial to the mesencephalic trigeminal tract, probably representing Barrington's (1925) nucleus or the M-region of Holstege et al. (1986c). This last area is strongly involved in micturition control (section 3 b), and an anterior hypothalamic projection to it corresponds with the observation of Grossman and Wang (1956) that stimulation of the preoptic area, which, according to Bleier (1961) is the same as the anterior part of the anterior hypothalamic area, produces micturition-like bladder contractions. Only the caudal portion of the lateral hypothalamus sends fibers throughout the length of the spinal cord via the lateral and dorsolateral funiculi to the intermediate zone, lamina X and the thoracolumbar sympathetic intermediolateral cell column. Köhler et al. (1984) have demonstrated that at least part of the lateral hypothalamo-spinal neurons contain αMSH, and that some of the spinally projecting cells also send fibers to the hippocampus.

The lateral hypothalamic projection to the caudal pontine and medullary lateral tegmental field and to the intermediate zone throughout the length of the spinal cord is interesting, since the caudal brainstem lateral tegmentum can be considered as the rostral continuation of the spinal intermediate zone (see section 2 d). No direct lateral hypothalamic projections exist to the oculomotor, trochlear, trigeminal, abducens, facial and hypoglossal nerve motor nuclei, nor to the retractor bulbi motoneuronal cell group, dorsal group of the nucleus ambiguus or the interneurons in the nucleus retroambiguus. On the other hand, the many parasympathetic motoneurons located in the caudal brainstem lateral tegmentum, such as those innervating the salivatory glands (Hosoya et al., 1983), receive lateral hypothalamic afferents. In summary, the lateral hypothalamus has direct access to autonomic motoneurons in brainstem and spinal cord, and indirect access, via premotor interneurons, to the somatic motoneurons of brainstem and spinal cord.

Many of the brainstem motoneurons are involved in activities such as swallowing, chewing and licking. It is interesting that the lateral hypothalamus is involved in feeding and drinking behavior (Grossman et al., 1978) as well as in salivation (Epstein, 1971). It is probably also involved in cardiovascular control (Stock et al., 1981) and defense behavior (see next section).

5e. Projections from amygdala and bed nucleus of the stria terminalis to caudal brainstem and spinal cord

Hopkins and Holstege (1978), using the autoradiographical tracing method, were the first to describe direct projections from the central nucleus of the amygdala (CA) to the caudal brainstem and first cervical spinal segment. HRP injections in the dorsomedial medulla of Schwaber et al. (1980) and in the NRM and NRP by Holstege et al. (1985) revealed many HRP-labeled neurons in the CA and in the lateral part of the bed nucleus of the stria terminalis (BNSTL). A continuum of HRP labeled neurons was observed in both studies extending from the CA dorsomedially along the medial border of the internal capsule into the BNSTL. Such a distribution pattern is suggestive of a nucleus split into two different parts by the fibers of the internal capsule in the same way as the caudate nucleus and the putamen. As early as 1923 Johnston considered the central and medial amygdaloid nuclei and the BNST as a single anatomic entity, and many others have accepted this concept (see De Olmos et al., 1985, Holstege et al., 1985 and Heimer et al. 1990, this volume). In agreement with this concept is that both areas (CA and BNSTL) receive afferents from the same brainstem structures such as the solitary nuclei (Ricardo and Koh, 1978 in the rat, however see Russchen et al.,1982 in the cat and Beckstead et al.,1980 in the monkey) and parabrachial nuclei (Saper and Loewy, 1980). In addition, both areas contain neurons with the same neuropeptides, for example neurotensin, substance P, cholecystokinin, vasoactive intestinal polypeptide, enkephalin, somatostatin and dynorphin. Some of these neurons have also been shown to project to the

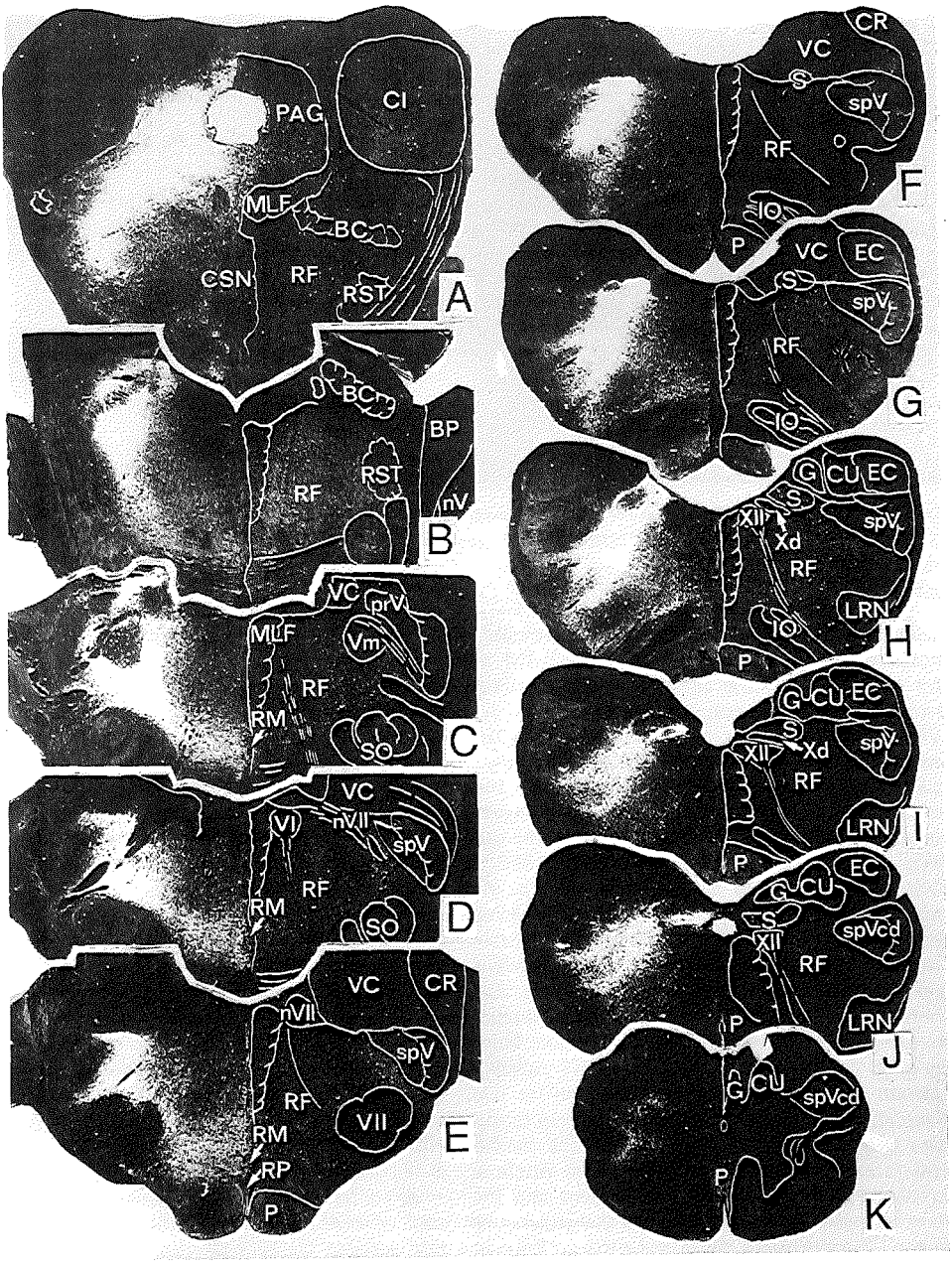


Fig. 59. Darkfield photomicrographs of 11 brainstem sections of a cat with an injection of 3H-leucine in the bed nucleus of the stria terminalis. Note the strong projection to the PAG, with the exception of its dorsolateral part. Note also the strong projection to the bulbar lateral tegmental field and the projection to the ventral part of the caudal pontine and upper medullary medial tegmentum. (From Holstege et al., 1985).

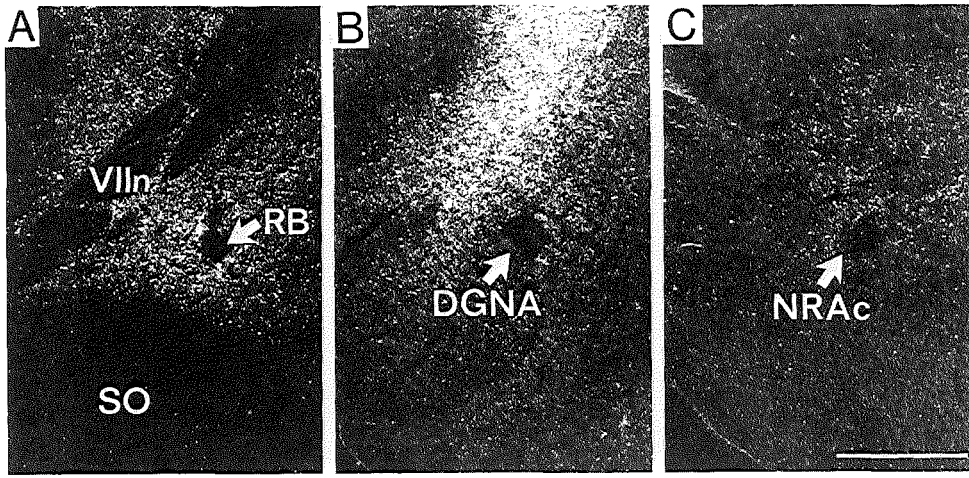


Fig. 60. Darkfield photomicrographs of 3 different rostrocaudal levels of the lateral tegmental field in a cat with an injection centered on the central nucleus of the amygdala. Note the absence of labeled fibers in the motor nucleus of the retractor bulbi motor nucleus (A), the dorsal group of the nucleus ambiguus (B) and the caudal nucleus retroambiguus (C). Bar represents 1mm.

brainstem (cf. Price et al., 1987, for review). Moreover, the projections from CA and BNST to the caudal brainstem are virtually identical (Hopkins and Holstege, 1978; Holstege et al., 1985). Both structures send many fibers to the lateral hypothalamic area, and via the medial forebrain bundle, into the lateral part of the mesencephalon, pons, and medulla oblongata (amygdala: Hopkins and Holstege, 1978 in the cat; Price and Amaral, 1981 in the monkey; BNST: Holstege et al., 1985 in the cat; Fig. 59). At mesencephalic levels fibers were distributed from this fiber bundle to the PAG (except its dorsolateral part), the ventrolaterally adjoining nucleus cuneiformis and pedunculopontine nucleus, and the mesencephalic lateral tegmental field, including the paralemniscal nucleus. Part of these fibers (at least those derived from the BNST) probably contain vasopressin as a neurotransmitter (De Vries and Buijs, 1983). In the pons, fibers terminate laterally in the tegmentum, i.e. the medial and lateral parabrachial nuclei, the nucleus Kölliker-Fuse, the nucleus subcoeruleus and the locus coeruleus. With respect to the projections to the locus coeruleus, Price and Amaral (1981) in the monkey did not observe fibers terminating in the nucleus itself, but just lateral to it. At the level of the motor trigeminal nucleus some fibers branch off from the lateral descending fiber bundle, passing ventrally and medially to terminate in the ventral part of the caudal pontine and upper medullary medial tegmentum. A few fibers terminate in the NRM, but none in the NRP (Fig. 56 G-H). At medullary levels many fibers terminate in the lateral tegmental field as defined by Holstege et al. (1977) (section 2 b) as well as in the rostral and caudal parts of the solitary nucleus and the peripheral parts of the dorsal vagal nucleus. In the same way as the projections from the hypothalamus, no direct projections exist from CA and BNST to the oculomotor, trochlear, trigeminal, abducens, facial and hypoglossal motor nuclei, and also none to the motoneurons in the nucleus retractor bulbi and dorsal group of the nucleus ambiguus, nor to the interneurons in the nucleus retroambiguus (Fig.60). Both CA and BNSTL send a few fibers to the intermediate zone of the C1 spinal cord, but not beyond that level. This corresponds with the finding that a hemi-infiltration of HRP at the level of C2 does not produce HRP labeled neurons in CA or BNSTL, (Holstege et al., 1985; Holstege, 1987b). Thus, there is no evidence for amygdaloid projections to the spinal cord other than to the intermediate zone of the first cervical segment (Mizuno et al., 1985; Sandrew et al., 1986).

A great similarity exists between the caudal brainstem projections originating in the CA and BNSTL on the one hand and the lateral hypothalamic area on the other. All three areas have very strong

mutual connections. Neurons in CA and BNSTL receive many afferent fibers from other (basolateral and basomedial) amygdaloid nuclei (Krettek and Price, 1978), but these connections are not reciprocal (see also Price et al., 1987 for review). Apparently, both CA and BNSTL serve as "output nuclei" for other parts of the amygdala/bed nucleus of the stria terminalis complex to reach the caudal brainstem. The lateral hypothalamus also may have this function, although its afferent connections are less clearly defined, mainly because of the many fibers of passage in the medial forebrain bundle.

The direct projections from CA, BNSTL and the lateral hypothalamus to the caudal brainstem lateral tegmental field may form the anatomic framework of the final output of the defense response of the animal. Electrical stimulation in the amygdala (especially the basal and central nuclei), bed nucleus of the stria terminalis, lateral hypothalamus, and PAG elicits defensive behavior (Fernandez de Molina and Hunsperger, 1962; Bandler et al., 1990). In fact there exists a column of electrical stimulation sites from CA, BNST, lateral hypothalamus, and PAG through the lateral mesencephalic tegmentum into the lateral tegmentum of the caudal brainstem, which elicits defensive behavior (Abrahams et al., 1960, Coote et al., 1973). Kaada (1972) gives an excellent description of the defense response in cats. The initial phase of such a response is arrest of all spontaneous ongoing activities, and the whole attitude of the animal changes to one of attention. The arousal is followed by orienting or searching movements towards the contralateral side, frequently accompanied by sniffing, swallowing, chewing, and by twitching of the ipsilateral facial musculature. Later in the defense reaction the cat retracts its head and crouches with the ears flattened to a posterior position. The cat growls or hisses, the pupils are dilated and there is piloerection, elevation of blood pressure with bradycardia, increased rate of breathing, alteration of gastric motility and secretion. On stronger stimulation an "affective" attack may take place, in which the cat strikes with its paw with claws unsheathed, in a series of swift, accurate blows. If the stimulus continues, the cat will bite savagely. Many of the activities in the beginning of the defense response are coordinated in the caudal brainstem lateral tegmental field. The observation that part of this behavior appears to be ipsilateral corresponds with the predominantly ipsilateral projection of CA, BNSTL and lateral hypothalamus to the caudal brainstem lateral tegmentum. Edwards and Flynn (1972) have shown that during the strike movement in the "affective" attack, a pure facilitation of the pyramidal tract neurons of the ipsilateral motor cortex takes place. In addition there are mainly facilitatory influences at the motoneuronal level in the spinal cord, which might be the result of the CA, BNST, lateral hypothalamus, and mesencephalic projections to the ventral part of the medullary medial reticular formation, which in turn projects diffusely to all motoneuronal cell groups in the spinal cord.

Figure 61 gives a schematic overview of the descending projections to the caudal brainstem from hypothalamus, amygdala and BNST. Similar to the descending projections from the mesencephalon, there is a mediolateral organization within this descending system in which the medial hypothalamus forms the medial, and the lateral hypothalamus, amygdala and BNST the lateral component. The PVN, with its direct projections to all preganglionic (sympathetic and parasympathetic) motoneurons in brainstem and spinal cord, occupies a separate position within this framework.

5 f Projections from the prefrontal cortex to caudal brainstem and spinal cord

In recent years it has been shown that the prefrontal cortex projects directly to the caudal brainstem. Most of these studies are done in the rat, in which the medial frontal cortex sends fibers to the solitary nuclei (NTS), the dorsal parts of the parabrachial nuclei, the PAG and the superior colliculus (Van der Kooy et al. 1984; Neafsy et al. 1986; Terreberry and Neafsy 1987). The insular cortex projects also to the NTS and PAG (Ruggiero et al., 1987; Neafsy et al. 1986). Ruggiero et al. (1987) also found that electrical stimulation of the rat's insular cortex leads to elevation of arterial pressure and cardioacceleration. Also in the rat projections from the infralimbic cortex to the spinal cord have been reported by Hurley-Gius et al.(1986). After WGA-HRP injections in this part of the cortex, they observed labeled fibers descending contralaterally in the base of the dorsal column and bilaterally in the dorsolateral funiculi. These fibers terminated in laminae I and IV-V throughout the length of the spinal cord and a few in the intermediolateral cell column. Projections from the prefrontal cortex to the NRM, NRP and adjacent tegmentum have not been described. In animals other than the rat studies on the prefrontal cortical projections to the brainstem are extremely

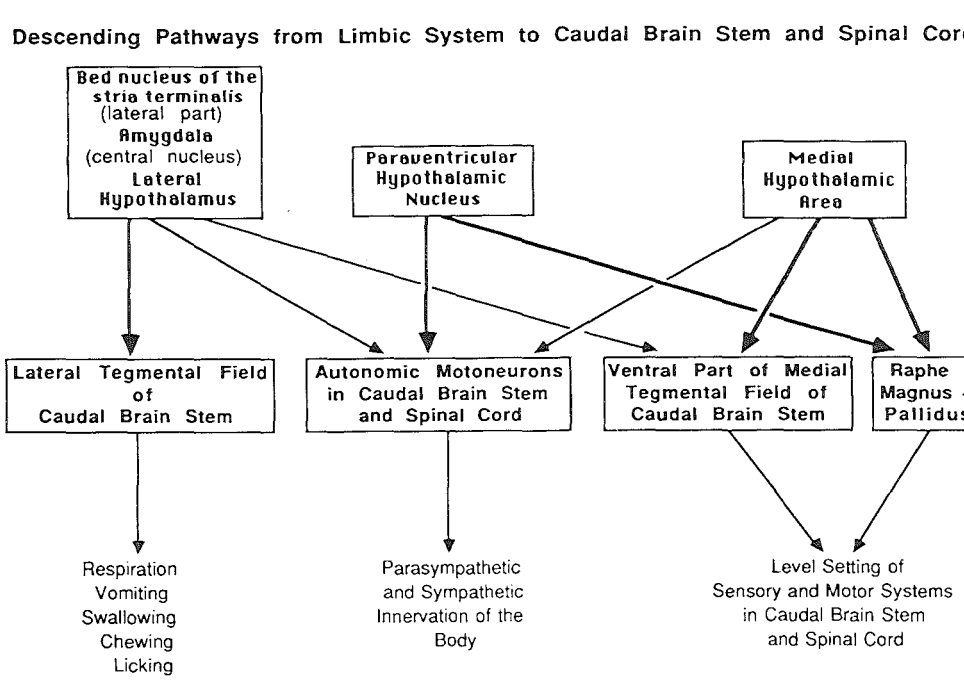


Fig. 61. Schematic overview of the mediolateral organization of the limbic system pathways to brainstem and spinal cord and its possible functional implications. The strongest projections are indicated by thick arrows. (From Holstege, 1988a).

scarce. In the cat, Willett et al. (1986), by means of the WGA-HRP method, found that the orbital gyrus, anterior insular cortex and infralimbic cortex project to the nucleus tractus solitarius. In the monkey, Arnsten and Goldman-Rakic (1984), using the anterograde autoradiographic tracing technique, demonstrated that the dorsolateral and dorsomedial prefrontal cortex projects to the locus coeruleus and nucleus raphe centralis superior. They did not observe labeled fibers beyond the level of the locus coeruleus, and suggested that frontal cortical fibers to more caudal brainstem areas do not exist. It must be emphasized that Arnsten and Goldman-Rakic (1984) in their autoradiographic tracing study used survival times of only 24-48 hours. However, much longer survival times are necessary to adequately label the fibers over longer distances (see Holstege 1987b for an extensive review of the use of the autoradiographic tracing technique). Therefore, in the light of the findings in rat and cat, it is extremely unlikely that the frontal cortex in the monkey does not project to the caudal brainstem. In section 4b it has been pointed out that there exist major differences between cat, monkey and humans in respect to the projections and the functions of the motor cortex. The motor cortex in primates has taken over many of the "motor tasks", performed by brainstem structures in rat and cat. This might also be the case for the frontoorbital cortical projections in primates.

C. Conclusions

An enormous number of new studies have been published in the last 10 years on the descending motor pathways to caudal brainstem and spinal cord and about the physiological and pharmacological properties of them. Nevertheless all the new pathways seem to belong to one of three major motor systems in the central nervous system, which determine the activity of the somatic and autonomic motoneurons. In this concept the motoneuronal cell columns themselves are not considered a central motor system, but the beginning of the peripheral motor system (motoneuronal cell body-motor nerve-muscle).

1. The first motor system

The first system (fig. 62) is formed by the premotor interneuronal projections to the motoneurons. These neurons receive direct or indirect afferent information from the periphery via peripheral afferent nerves and from the second and/or third motor system. They are of paramount importance for determining the final output of the motoneurons. It is not always true that these interneurons are located close to their target motoneurons. For example those involved in back-musculature control travel over large distances through the spinal cord. Also the interneurons involved in the cutaneus trunci muscle (CTM) reflex send their fibers over large distances, because part the afferent information for the CTM reflex enters the spinal cord far from where the CTM motoneurons are located.

As has been pointed out in section 2 d, the bulbar lateral tegmental field can be considered as the rostral extent of the spinal intermediate zone. Correspondingly this area contains interneurons, not only for the brainstem motoneurons of the cranial nerves V, VII, X and XII, but also for some motoneuronal cell groups in the spinal cord. Also these interneurons belong to the first system. Examples are the medullary interneurons projecting to the phrenic and other respiratory related motoneuronal cell groups. Since most of the afferent information from the respiratory organs does not enter the central nervous system via the spinal cord, but via the brainstem (vagal nerve), it is natural that the interneurons involved are located in the region of entrance. The author of this paper reckons the micturition related interneurons in the dorsolateral pons also to this system. They are of enormous importance for micturition, because via their long descending pathways they determine whether bladder and bladder-sphincter function synergistically. The question arises why these neurons are located so far from their target motoneurons. In that respect it is important to realize that micturition is strongly correlated with the emotional state of the individual. Therefore, the micturition interneurons need to receive afferent information from the limbic system, which is available in the dorsolateral pons, but not in the sacral cord. The interneurons involved in blood-pressure control and projecting to the sympathetic motoneurons in the intermediolateral cell column of the thoracolumbar cord are located in the ventrolateral medulla. Their afferent information enters the central nervous system via the brainstem (vagal nerve), while afferent information from the limbic system, which plays an extremely important role in determining the level of the blood pressure, is also available.

The bulbar lateral tegmental field corresponds with the caudal part of Nieuwenhuys' paracore (Nieuwenhuys et al.,1988), mainly because it receives many afferent connections from the lateral limbic system and because it contains adrenergic (C1 and C2) and nor-adrenergic (A1-A6) cell groups. However, the great majority of the neurons in the bulbar lateral tegmental field serve as interneurons for motoneurons in caudal brainstem and spinal cord. Although it is true that many of them play a role in the generation of so-called fixed action patterns, such as biting, swallowing and licking, which can be elicited in the limbic system, the same interneurons also receive many afferents from second system structures such as motor cortex and red nucleus. In the present concept the interneurons in the bulbar lateral tegmental field belong to the first and not to the third system.

In summary, the first motor system is formed by the interneuronal projections to the motoneurons. They are present in the caudal brainstem, the spinal cord, and between brainstem and spinal cord.

2. The second motor system

The second motor system (fig. 62) is discussed in section 4. The projections of this system have been studied for some time, mainly because they exist of thick fibers, which could be detected with the lesion-degeneration techniques in the nineteenfifties and sixties. The fibers of this system terminate to only a limited extent directly on mo-

toneurons, but for the most part on the interneurons of the first motor system. Kuypers was the first to point out the mediolateral organization within this system. The medial component originates mainly in the brainstem (dorsal two thirds of the pontine and medullary medial tegmentum, vestibular nuclei, superior colliculus, interstitial nucleus of Cajal and caudal Field H of Forel), descends medially in the ventral funiculus of the spinal cord and terminates on inter- and to a lesser extent motoneurons of the medial motor column in the spinal cord. The medial motor column controls eye- and neck-movements and axial and proximal body movements. The function of the medial system is maintenance of erect posture (antigravity movements), integration of body and limbs, synergy of the whole limb and orientation of body and head (Kuypers, 1981). On the other hand, the lateral component of this second motor system is formed by laterally descending fibersystems, terminating in laterally located inter- and to a more limited extent motoneurons in caudal brainstem and spinal cord (the lateral motor column). These systems are represented by the the rubrospinal tract, (in humans of minor importance) and the lateral corticospinal tract, (in humans extremely well developed). The lateral motor column in the spinal cord innervates the distal body musculature, i.e. those of the distal limbs. The lateral component of the voluntary motor system produces independent flexion-biased movements of the extremities, in particular of the elbow and hand (Kuypers, 1981).

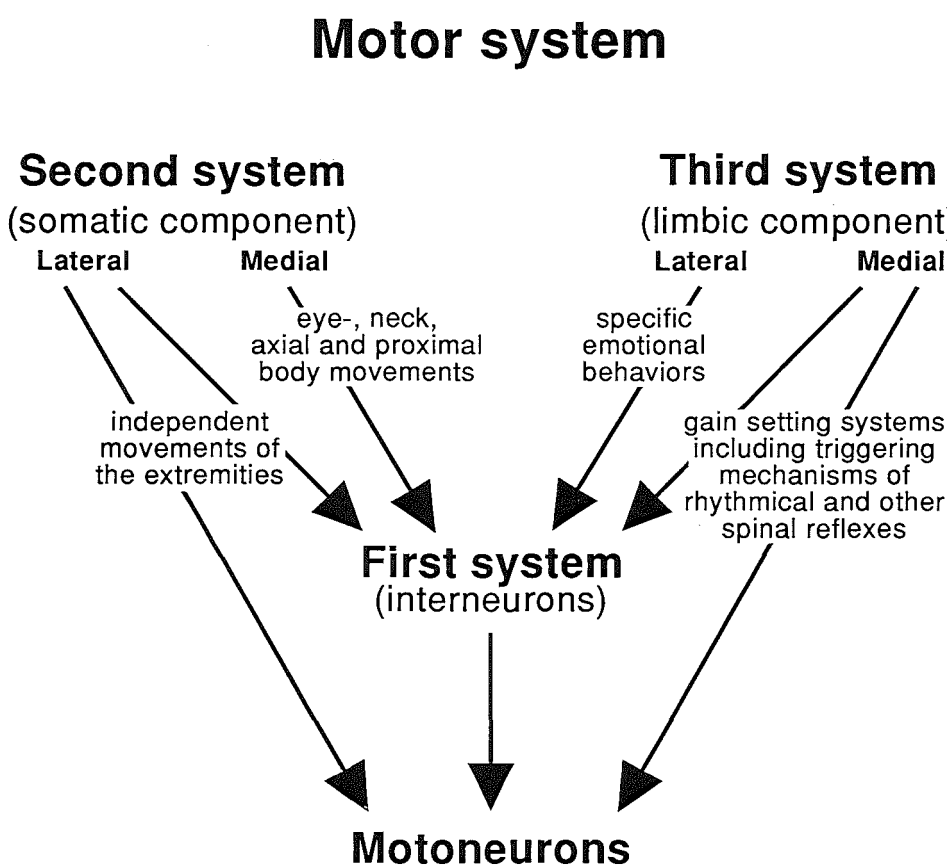


Fig. 62. Schematic overview of the three subdivisions of the motor system.

3. The third motor system

The third motor system (fig. 62) is discovered only recently. Although there was clinical evidence that a separate motor system had to exist, anatomical studies did not find any evidence for such a system. In the last 15 years that has changed drastically. It appeared that modern tracing techniques were able to demonstrate a large number of new pathways. They all consisted of thin fibers, which was the reason that the lesion-degeneration techniques were not able to demonstrate them earlier. The development of the immunohistochemical techniques has revealed a large number of neurotransmitters or neuromodulators within the central nervous system. Interestingly, with the exception of acetylcholine, glutamate and aspertate, all these new monoamines and peptides were found in the third motor system.

The third motor system, which largely corresponds with the core and medial paracore of Nieuwenhuys et al. (1988), is strongly connected with the limbic system and systematically skips the areas belonging to the second one, such as red nucleus, interstitial nucleus of Cajal and other peri-oculomotor areas, the dorsal two thirds of the caudal brainstem medial tegmentum, vestibular nuclei or precerebellar structures as pontine nuclei, inferior olive or lateral reticular nucleus. Reversely, the second motor system does not overlap in its projections with the third motor system. An exception on this rule are the monaminergic projections originating in the raphe nuclei and locus coeruleus/subcoeruleus complex. These structures, which belong to the third system, send fibers to many structures in the central nervous system, including some belonging to the second system (e.g. the inferior olive and cerebellum).

A mediolateral organization is present within the third motor system. The medial component originates in the medial portions of hypothalamus and in the mesencephalon and terminates in the area of locus coeruleus/subcoeruleus and in the ventral part of the caudal pontine and medullary medial tegmental field. The latter structures determine the final output of this system. The lateral component originates laterally in the limbic system, i.e. in the lateral hypothalamus, central nucleus of the amygdala and bed nucleus of the stria terminalis. These structures project to the lateral tegmental field of caudal pons and medulla, but not to the somatic motoneurons in this area. In how far the prefrontal cortex plays a role within these systems remains to be determined.

There are some exceptions on this general subdivision into medial and lateral third motor systems; 1) Within the PAG and lateral adjacent tegmentum, some specific groups of neurons exist, projecting to areas outside the caudal brainstem ventromedial tegmental field, such as the nucleus retroambiguus, cervical spinal cord or subretrofacial nucleus. These neurons are probably related to specific functions, such as vocalization, head movements involved in emotional behavior or blood pressure control. They may serve as final common pathways for especially the lateral component of the third motor system. 2) Some of the fibers of the lateral component of the third descending system terminate in the ventromedial tegmentum at levels around the facial nucleus. Neurons in this area in turn project diffusely to the dorsal horn of the spinal cord. Via these fibers the lateral component structures may have some control over nociception.

The functional implications of the third system motor pathways differ, depending on whether they belong to the medial or lateral system. The medial system, via its projections to the locus coeruleus/nucleus subcoeruleus and NRM and NRP/NRO and the diffuse coeruleo- and raphespinal pathways, has a global effect on the level of activity of the somatosensory and motoneurons in general by changing their membrane excitability. In other words, the emotional brain has a great impact on the sensory as well as on the motor system. In both systems it sets the gain or level of functioning of the neurons. The emotional state of the individual determines this level. For example it is well known that many forms of stress, such as aggression, fear and sexual arousal, induce analgesia, while at the same time the motor system is set at a "high" level and motoneurons can easily be excited by the second motor system. In this concept the brainstem structures, which project diffusely to all parts of the spinal cord, can be considered as tools for the limbic system controlling spinal cord activity. The diffuse descending system is also used to trigger rhythmical (locomotion, shivering) or other (lordosis) in essence spinal reflexes. Whether functions such as locomotion, shivering and lordosis use different or the same diffuse pathways from the caudal brainstem to the spinal cord is not yet clear. If they use the same pathways, the differences lie in the function of the spinal generators for each of these functions.

The lateral component of the third motor system project to the caudal brainstem lateral tegmental

field, which contains first motor system interneurons involved in specific functions such as respiration, vomiting, swallowing, chewing, and licking. These activities are displayed in the beginning of flight or defense response and can be easily elicited by stimulation of the lateral parts of the limbic system. Therefore it seems that the lateral component of the third motor systems is involved in more specific activities, related to emotional behavior.

It is intriguing that both the medial and lateral components of the second and third motor systems are involved in similar activities. The medial components are involved in general activities such as in integration of body and limbs and orientation of body and head for the second system and level setting of neurons for the third system. On the other hand, the lateral components are involved in specific activities such as independent movements of the extremities for the second motor system and blood pressure and respiration control, vocalization, vomiting, swallowing, chewing, and licking for the third motor system.

D. Acknowledgements

This work was supported by NASA Grant NCC 2-491 to Gert Holstege. The author thanks Drs. Han Collewijn, R. Nieuwenhuys and J. Voogd for reading the manuscript and their comments. Furthermore he thanks his brother Joan Holstege for the helpful discussions and suggestions about the text on the diffuse descending pathways.

E. Abbreviations

AA	anterior amygdaloid nucleus
AC	anterior commissure
ACN	nucleus of the anterior commissure
AD	anterodorsal nucleus of the thalamus
AH	anterior hypothalamic area
AL	lateral amygdaloid nucleus
AM	anteromedial nucleus of the thalamus
AP	area postrema
Aq	aqueduct of Sylvius
AV	anteroventral nucleus of the thalamus
BC	brachium conjunctivum
BIC	brachium of the inferior colliculus
BL	basolateral amygdaloid nucleus
BM	basomedial amygdaloid nucleus
BNST	bed nucleus of the stria terminalis
BNSTL	lateral part of the bed nucleus of stria terminalis
BNSTM	medial part of the bed nucleus of the stria terminalis
BP	brachium pontis
CA	central amygdaloid nucleus
CC	corpus callosum
Cd	caudate nucleus
CGL	lateral geniculate body
CGLd	lateral geniculate body (dorsal part)
CGLv	lateral geniculate body (ventral part)
CGM	medial geniculate body
CGMd	medial geniculate body, dorsal part
CGMint	medial geniculate body, interior division
CGMp	medial geniculate body, principal part
CI	capsula interna
CL	claustrum
CL	nucleus centralis lateralis of the thalamus
CM	centromedian thalamic nucleus
CN	cochlear nuclei
CO	cortical amygdaloid nucleus
CP	posterior commissure
CR	corpus restiforme
cru	cruciate sulcus
CS	superior colliculus
CSN	nucleus raphe centralis superior
CU	nucleus cuneatus
CUN	cuneiform nucleus
D	nucleus of Darkschewitsch
DBV	nucleus of the diagonal band of Broca
DGNA	dorsal group of the nucleus ambiguus
DH	dorsal hypothalamic area
DMH	dorsomedial hypothalamic nucleus
DTN	dorsal tegmental nucleus
EC	external cuneate nucleus
ECU	external cuneate nucleus
En	entopeduncular nucleus
E W	nucleus Edinger-Westphal
F	fornix
fRF	fasciculus retroflexus
G	nucleus gracilis
GP	globus pallidus
Hab	habenular nucleus
Habl	lateral habenular nucleus
Habm	medial habenular nucleus
HC	hippocampus
HPA	posterior hypothalamus area
IC	inferior colliculus
IN	interpeduncular nucleus

I N C	interstitial nucleus of Cajal
IO	inferior olive
IP	interpeduncular nucleus
IVN	inferior vestibular nucleus
KF	nucleus Kölliker-Fuse
Latiss	latissimus dorsi muscle
LD	nucleus lateralis dorsalis of the thalamus
LGN	lateral geniculate nucleus
LH	lateral hypothalamic area
LL	lateral lemniscus
LONGISS	longissimus dorsi muscle
LOTR	lateral olfactory tract
LP	lateral posterior nucleus of the thalamus
LRN	lateral reticular nucleus
LTF	lateral tegmental field
LV	lateral ventricle
LVN	lateral vestibular nucleus
MA	medial amygdaloid nucleus
MB	mammillary body
MC	nucleus medialis centralis of the thalamus
MD	nucleus medialis dorsalis of the thalamus
MesV	mesencephalic trigeminal tract
ML	medial lemniscus
MLF	medial longitudinal fasciculus
motV	motor trigeminal nucleus
MTF	medial tegmental field
mV	motor trigeminal nucleus
MVN	medial vestibular nucleus
M T N	medial terminal nucleus
NCL	nucleus centralis lateralis
NLL	nucleus of the lateral lemniscus
NOT	nucleus of the optic tract
NOTL	lateral nucleus of the optic tract
NOTM	medial nucleus of the optic tract
NPC	nucleus paracentralis of the thalamus
NTB	nucleus of the trapezoid body
NR	red nucleus
NRA	nucleus retroambiguus
NRAc	caudal nucleus retroambiguus
NRM	nucleus raphe magnus
NRP	nucleus raphe pallidus
NRTP	nucleus reticularis tegmenti pontis
NSC	nucleus subcoeruleus
NTB	nucleus of the trapezoid body
nVI	abducens nerve
nVII	facial nerve
nVIII	vestibulocochlear nerve
OBL. EXT.	external oblique abdominal muscle
OBL. INT.	internal oblique abdominal muscle
OC	optic chiasm
OL	olivary pretectal nucleus
OR	optic radiation
OT	optic tract
P	pyramidal tract
PAG	periaqueductal gray
PbL	lateral parabrachial nucleus
PBM	medial parabrachial nucleus
TMT	mammillothalamic tract
PC	pedunculus cerebri
PCN	nucleus of the posterior commissure
PEA	anterior part of periventricular hypothalamic nucleus
P H	periventricular hypothalamic nucleus
PON	pontine nuclei
PONTMedRF	pontine medial reticular formation
PP	posterior pretectal nucleus

Pt	parataenial nucleus of the thalamus
PT	Probst tract
P T A	anterior pretectal nucleus
PTM	medial pretectal nucleus
Pu	putamen
Pul	pulvinar nucleus of the thalamus
PV	posterior paraventricular nucleus of the thalamus
PVA	paraventricular nucleus of the thalamus (anterior part)
P V G	periventricular gray
PVN	paraventricular hypothalamic nucleus
R	reticular nucleus of the thalamus
RB	restiform body
RB	retractor bulbi motor nucleus
RE	nucleus reuniens of the thalamus
RECTUS	rectus abdominis muscle
RF	reticular formation
RFmed	medial reticular formation
RFlat	lateral reticular formation
RiMLF	rostral interstitial nucleus of the MLF
RM	nucleus raphe magnus
RN	red nucleus
Rpo	nucleus raphe pontis
RST	rubrospinal tract
S	solitary complex
SC	suprachiasmatic nucleus
SC	nucleus subcoeruleus
SI	substantia innominata
SM	stria medullaris
SN	substantia nigra
SO	superior olivary complex
SON	supraoptic nucleus
spin V	spinal trigeminal complex
S T	subthalamic nucleus
STT	stria terminalis
SUB	subiculum
VII	facial nucleus
SVN	superior vestibular nucleus
Transv.	transversus abdominis muscle
TMT	mammillothalamic tract
TS	tract of the solitary nucleus
VA	ventroanterior nucleus of the thalamus
VB	ventrobasal complex of the thalamus
VC	vestibular complex
VL	ventrolateral nucleus of the thalamus
VM	ventromedial nucleus of the thalamus
VMH	ventromedial nucleus of the hypothalamus
VPL	nucleus ventralis posterolateralis of the thalamus
VTA	ventral tegmental area of Tsai
VTN	ventral tegmental nucleus
ZI	zona incerta
III	oculomotor nucleus
IV	trochlear nucleus
Vm	motor trigeminal nucleus
Vn	trigeminal nerve
Vpr.	principal trigeminal nucleus
Vprinc.	principal trigeminal nucleus
Vsp.	spinal trigeminal complex
V sp.cd.	spinal trigeminal complex pars caudalis
Vspin.caud.	spinal trigeminal complex pars caudalis
VI	abducens nucleus
VII	facial nucleus
VIIn	facial nerve
XII	hypoglossal nucleus

F. Conclusies

Gedurende de laatste 10 jaar zijn een enorm aantal publicaties verschenen over de afdalende motorische banen naar de lagere hersenstam en ruggemerg en over hun fysiologische en farmacologische eigenschappen. Niettemin kunnen al deze nieuwe baansystemen worden ondergebracht bij een van 3 grote motorische subsystemen in het centraal zenuwstelsel, die de activiteit van de somatische en autonome motoneuronen bepalen. In dit concept worden de motoneuronen zelf niet beschouwd tot het centraal zenuwstelsel, maar tot het perifere zenuwstelsel te behoren.

1. Het eerste motorische systeem.

Het eerste motorische systeem wordt gevormd door de premotorische interneuronale projecties naar de motoneuronen. Deze interneuronen ontvangen directe of indirecte afferente informatie vanuit de periferie via perifere afferente zenuwen en van het tweede en/of derde motorische systeem. Deze interneuronen zijn van enorm belang voor het bepalen van de uiteindelijke activiteit van de motoneuronen. Het is niet altijd zo dat deze interneuronen vlakbij de motoneuronen gelegen zijn waarop zij projecteren. Bijvoorbeeld de interneuronen die betrokken zijn bij de controle over de rugmusculatuur verlopen over lange afstanden binnen het ruggemerg. Ook de interneuronen betrokken bij de cutaneus trunci spier (CTS) reflex sturen hun vezels over grote afstanden, omdat een deel van de afferente informatie voor de CTS reflex het ruggemerg binnentreedt op grote afstand van de CTS motoneuronen.

Zoals in hoofdstuk 2d wordt uiteengezet, kan het bulbaire laterale tegmentale veld worden beschouwd als het rostrale vervolg van de spinale intermediaire zone. Daarom bevat dit gebied niet alleen de interneuronen voor de motoneuronen van de V, VII, X en XII hersenzenuwen, maar ook voor een aantal motoneuronale celgroepen in het ruggemerg. Ook deze interneuronen behoren tot het eerste systeem. Voorbeelden zijn de medullaire interneuronen die naar de nucleus phrenicus en andere bij de ademhaling betrokken spinale motoneuronale celgroepen projecteren. Omdat het merendeel van de afferente informatie van de ademhalingsorganen het centraal zenuwstelsel niet via het ruggemerg maar via de hersenstam (nervus vagus) binnenkomt, is het begrijpelijk dat de betrokken interneuronen in het gebied van de binnenkomende afferente zenuw zijn gelegen. De auteur van deze publicatie rekent de interneuronen in het dorsolaterale ponsgebied betrokken bij de mictie-controle ook tot het eerste systeem. Deze interneuronen zijn van overwegend belang voor het verloop van de normale mictie, omdat zij, via hun lange descenderende banen de samenwerking (synergie) van de blaas en zijn sphincter bepalen. Dit werpt de vraag op waarom deze interneuronen zo ver van hun motoneuronen in het sacrale ruggemerg zijn afgelegen. Wat dat betreft is het van belang zich te realiseren dat de mictie sterk onder invloed staat van de emotionele hoedanigheid van het individu. Daarom staan de mictie interneuronen onder sterke invloed van het limbisch systeem, dat het dorsolaterale ponsgebied gemakkelijk maar het sacrale ruggemerg vrijwel niet kan bereiken. De interneuronen betrokken bij de bloeddrukcontrole en die naar de sympathische motoneuronen in het thoracolumbale ruggemerg projecteren, zijn gelegen in de ventrolaterale medulla. Hun perifere afferente informatie komt het centraal zenuwstelsel binnen via de hersenstam (nervus vagus), terwijl andere afferenten afkomstig zijn van het limbisch systeem, dat een zeer grote invloed uitoefent op de vaststelling van de hoogte van de bloeddruk.
Het bulbaire laterale tegmentale veld komt overeen met het caudale deel van Nieuwenhuys' paracore (Nieuwenhuys et al. 1988), voornamelijk omdat het vele afferente verbindingen ontvangt vanuit het laterale limbische systeem en omdat het adrenerge (C1 en C2) en nor-adrenerge (A1-A6) celgroepen bevat. Het grootste deel van de interneuronen in de bulbaire laterale tegmentale veld zijn interneuronen die naar motoneuronen in lagere hersenstam en ruggemerg projecteren. Hoewel deze laatste interneuronen een belangrijke rol spelen bij de totstandkoming van de zogenaamde vastliggende actiepatronen (fixed action patterns), zoals bijten, slikken en likken, die in het limbisch systeem opgewekt kunnen worden, ontvangen dezelfde interneuronen ook afferenten van structuren behorend bij het tweede systeem, zoals motor cortex en nucleus ruber. In het in dit proefschrift gepresenteerde concept behoren de interneuronen in het bulbaire laterale tegmentum tot het eerste en niet tot het derde systeem (wat wel het geval is in het concept van Nieuwenhuys et al. 1988).
Samenvattend wordt het eerste systeem gevormd door de interneuronale projecties naar de motoneuronen. Deze bevinden zich in de lagere hersenstam, het ruggemerg en tussen hersenstam en ruggemerg.

2. Het tweede motorische systeem.

Het tweede motorische systeem wordt behandeld in hoofdstuk 4. De projecties behorend bij dit systeem worden al betrekkelijk lang bestudeerd, voornamelijk omdat ze uit dikke vezels bestaan, die konden worden opgespoord met de lesie-degeneratietechnieken uit de vijftiger en zestiger jaren van deze eeuw. De vezels van dit systeem eindigen slechts in beperkte mate direkt op motoneuronen, maar vooral op interneuronen behorende bij het eerste systeem. Kuypers (1981) was de eerste die erop wees dat er een mediolaterale organisatie bestond in dit systeem. De mediale component heeft zijn oorsprong voornamelijk in de hersenstam (dorsale tweederde van het pontine en medullaire mediale tegmentum, vestibulaire kernen, colliculus superior , interstitiale kern van Cajal en het caudale veld H van Forel). Deze component zendt zijn vezels door het mediale deel van de ventrale funiculus van het ruggemerg en eindigt op inter- en in beperkte mate op motoneuronen van de mediale motor kolom in het ruggemerg.

De mediale motor kolom verzorgt oog- en nekbewegingen en axiale en proximale lichaamsbewegingen. De functie van de mediale component van het mediale systeem is handhaving van de rechtopstaande houding (antigraviditeitsbewegingen), integratie van de bewegingen van romp en ledematen, synergie van de ledematen en orientatiebewegingen van lichaam en hoofd.

De laterale component van het tweede motorische systeem daarentegen wordt gevormd door lateraal descenderende vezelsystemen, eindigend op lateraal gelegen inter- en in beperkte mate motoneuronen in de lagere hersenstam en ruggemerg (de laterale motor kolom). Tot de laterale component behoren de rubrospinale baan (bij de mens van beperkt belang) en de laterale corticospinale baan (in de mens zeer sterk ontwikkeld). De laterale motor kolom in het ruggemerg innerveert voornamelijk de distale lichaamsspieren, d.w.z. die van de uiteinden van de ledematen. De laterale component van het voluntaire motorische systeem brengt onafhankelijke, vooral flexieachtige bewegingen van de extremiteiten tot stand, in het bijzonder die van elleboog en hand (Kuypers, 1981).

3. Het derde motorische systeem.

Het derde motorische systeem is pas recent ontdekt. Hoewel er klinische aanwijzingen waren dat een dergelijk systeem eigenlijk wel moest bestaan, kon anatomisch een dergelijk systeem niet aangetoond worden. Dat is gedurende de laatste 15 jaar dramatisch veranderd. Met behulp van moderne vezelopsporingstechnieken kon het bestaan van een groot aaantal nieuwe descenderende banen worden aangetoond. Deze bestonden alle uit dunne vezels, hetgeen de reden was dat ze met de lesie-degeneratie vezelsopsporingstechnieken niet konden worden aangetoond. Omdat verschillende histochemische technieken zijn ontwikkeld heeft men een groot aantal neurotransmitters of neuromodulatoren binnen het centraal zenuwstelsel kunnen aantonen. Van belang daarbij is dat, met uitzondering van acetylcholine, glutamaat en aspertaat, al deze nieuwe monoamines en peptiden zich in het derde systeem bevinden.

Het derde motorische systeem, dat grotendeels overeenkomt met het "core" en "medial paracore" van Nieuwenhuys et al. (1988), is sterk verbonden met het limbisch systeem en slaat systematisch de structuren behorend tot het tweede systeem over (zoals nucleus ruber, interstitiale kern van Cajal en andere peri-oculomotorische gebieden, het dorsale 2/3 deel van het mediale tegmentum van de lagere hersenstam, de vestibulaire kernen of precerebellaire structuren als pontine kernen, onderste olijf of laterale reticulaire kernen). Anderzijds overlappen de projecties van het tweede motorische systeem niet met die van het derde. Een uitzondering op deze regel vormen de monoaminerge projecties die ontstaan in de raphe kernen en het locus coeruleus/subcoeruleus complex. Deze structuren, die tot het derde systeem behoren, zenden vezels naar vele structuren in het centraal zenuwstelsel, inclusief een aantal behorend tot het tweede systeem (b.v. onderste olijf en cerebellum).

Er bestaat een mediolaterale organisatie binnen het derde motorische systeem. De mediale component ontstaat in de mediale delen van de hypothalamus en in het mesencephalon en eindigt in het gebied van de locus coeruleus/subcoeruleus en in het ventrale deel van het caudale pontine en medullaire mediale tegmentale veld. De laatste structuren bepalen het uiteindelijke effect van de mediale component. De laterale component ontstaat in laterale structuren van het limbisch systeem, d.w.z. in de laterale hypothalamus, centrale kern van de amygdala en de bed nucleus van de stria terminalis. Deze structuren projecteren naar het laterale tegmentale veld van caudale pons en medulla, maar niet naar de somatische motoneuronen in dit gebied. In hoeverre de

prefrontale cortex een rol speelt binnen deze systemen is nog onduidelijk. Er zijn enkele uitzonderingen op deze algemene onderverdeling in mediale en laterale componenten van het derde motorische systeem:
1) Binnen het periaqueductale grijs (PAG) en het lateraal aangrenzende tegmentale veld bestaan een aantal specifieke groepen neuronen, die naar gebieden projecteren buiten het ventromediale tegmentale veld van de caudale hersenstam, zoals de nucleus retroambiguus, cervicale ruggemerg of nucleus subretrofacialis. Deze neuronen zijn waarschijnlijk aan specifieke functies verbonden, zoals vocalisatie, hoofdbewegingen als onderdeel van emotioneel gedrag of bloeddrukbeheersing. Ze dienen waarschijnlijk als de "final common pathway" voor in het bijzonder de laterale component van het derde systeem.
2) Enkele vezels van de laterale component van het derde descenderende systeem eindigen in het ventromediale tegmentum ter hoogte van de facialis kern. Op hun beurt projecteren neuronen in dit gebied diffuus naar de dorsale hoorn van het ruggemerg. Via deze vezels kunnen de laterale componentstructuren enige controle uitoefenen over nociceptie.
De functionele implicaties van het derde motor systeem verschillen naar gelang zij tot het mediale dan wel laterale systeem behoren. Het mediale systeem, via zijn projecties naar de locus coeruleus/subcoeruleus en nucleus raphe magnus, pallidus en obscurus met aangrenzende gebieden en de diffuse (sub-)coeruleo- en raphe spinale banen, hebben een algemeen effect op het activiteitsniveau van de somatosensibele en motoneuronen door hun membraan-excitabiliteit te veranderen. Met andere woorden, het emotionele brein heeft grote invloed op zowel het sensibele als motorische systeem. In beide systemen bepaalt het het niveau van functioneren van de neuronen. De emotionele hoedanigheid van het individu bepaalt dus dit niveau. Het is bijvoorbeeld algemeen bekend dat vele vormen van "stress", zoals agressie, angst en sexuele opwinding analgesie opwekken, terwijl op hetzelfde moment het motorische systeem op een hoog niveau wordt gezet en de motoneuronen gemakkelijk kunnen worden aangedreven door het tweede motorische systeem. In dit concept kunnen de hersenstamstructuren, die diffuus naar alle delen van het ruggemerg projecteren, worden beschouwd als werktuigen voor het limbisch systeem om ruggemergsactiviteit te controleren. Het diffuse descenderende systeem wordt ook gebruikt om rhythmische (locomotie, huiveren of rillen) of andere (lordose) in principe spinale reflexen op te wekken. Onbekend is of functies als locomotie, huiveren/rillen en lordose gebruik maken van verschillende of dezelfde diffuse baansystemen. Als ze dezelfde baansystemen gebruiken liggen de verschillen in de functie van de spinale generatoren voor ieder van deze functies. De laterale component van het derde motorische systeem projecteert naar het laterale tegmentale veld van de lagere hersenstam die interneuronen bevat behorend bij het eerste motorische systeem en die betrokken zijn bij specifieke functies zoals ademhaling, braken, slikken, kauwen en likken. Deze activiteiten kan men waarnemen in het begin van de vlucht of afweer respons en kunnen gemakkelijk worden opgewekt door stimulatie in het laterale deel van het limbische systeem. Daarom lijkt het dat de laterale component van het derde motorische systeem betrokken is bij meer specifieke activiteiten, verbonden aan emotioneel gedrag.
Het is intrigerend dat zowel de mediale als laterale componenten van de tweede en derde motorische systemen betrokken zijn bij soortgelijke activiteiten. De mediale componenten zijn betrokken bij algemene activiteiten zoals wat betreft het tweede systeem de integratie van romp- en ledemaatbewegingen en lichaams- en hoofdorientatie en wat het derde systeem betreft het bepalen van de neuron-activiteit in het algemeen. Aan de andere kant zijn de laterale componenten betrokken bij meer specifieke activiteiten zoals onafhankelijke bewegingen van de extremiteiten wat betreft het tweede motorische systeem en bloeddruk, ademhalingsbeheersing, vocalisatie, braken, slikken, kauwen en likken wat betreft het derde motorische systeem.

G. References

Abols, I. A., and Basbaum, A. I. (1981) Afferent connections of the rostral medulla of the cat: a neural substrate for midbrain-medullary interactions in the modulation of pain. J. Comp. Neurol. 201: 285-297

Abrahams, V. C.; Hilton, S. M., and Zbrozyna, A. (1960) Active muscle vasodilatation produced by stimulation of the brain stem: its significance in the defence reaction. J. Physiol. 154: 491-513

Abrahams, V. C., and Keane, J. (1984) Contralateral, midline and commissural motoneurons of neck muscles: a retrograde HRP study in the cat. J. Comp. Neurol. 223: 448-456

Akaike, T.; Fanardjian, V. V.; Ito, M., and Ohno, T. (1973) Electrophysiological analysis of the vestibulospinal reflex pathway in the rabbit. II. Synaptic actions upon spinal neurons. Exp. Brain Res. 17: 497-515

Akaike, A.; Shibata, T.; Satoh, M., and Takagi, H. (1978) Analgesia induced by microinjection of morphine into, and electrical stimulation of, the nucleus reticularis paragigantocellularis of rat medulla oblongata. Neuropharmacol. 17: 775-778

Albanese, A.; Altavista, M. C., and Rossi, P. (1986) Organization of central nervous system dopaminergic pathways. J. Neural. Transm. 22 (Suppl.): 3-17

Alstermark, B.; Kimmel, H., and Tantisira, B. (1987) Monosynaptic raphespinal and reticulospinal projection to forelimb motoneurons in cats. Neurosci. Lett. 74: 286-290

Alstermark, B.; Kummel, H.; Pinter, M. J., and Tantisira, B. (1987) Branching and termination of C3-C4 propriospinal neurones in the cervical spinal cord of the cat. Neurosci. Lett. 74: 291-296

Alstermark, B.; Lundberg, A.; Norsell, U., and Sybirska, E. (1981) Integration in descending motor pathways controlling the forelimb in the cat. 9. Differential behavioural defects after spinal cord lesions interrupting defined pathways from higher centers to motoneurones. Exp. Brain Res. 42: 299-318

Anderson, J. H. (1981) Ocular torsion in the cat after lesions of the interstitial nucleus of Cajal. Ann. NY Acad. Sci. 374: 865-871

Anderson, M. E. (1971) Cerebellar and cerebral inputs to physiologically identified efferent cell groups in the red nucleus of the cat. Brain Res. 30: 49-66

Anderson, M. E.; Yoshida, M., and Wilson, V. J. (1971) Influence of superior colliculus on cat neck motoneurons. J. Neurophysiol. 34: 898-907

Aoki, M.; Mori, S.; Kawahara, K.; Watanabe, H., and Ebata, N. (1980) Generation of spontaneous respiratory rhythm in high spinal cats. Brain Res. 202: 51-63

Appenteng, K.; O'Donovan, M. J.; Somjen, G., and Stephens, J. A. (1978) The projection of jaw elevator muscle spindle afferents to fifth nerve motoneurones in the cat. J. Physiol. (Lond.) 279: 409-424

Armand, J., and Kuypers, H. G. J.M. (1980) Cells of origin of crossed and uncrossed corticospinal fibers. A quantitative horseradish peroxidase study. Exp. Brain Res. 42: 299-318

Armand, J.; Holstege, G., and Kuijpers, H. G. J.M. (1985) Differential corticospinal projections in the cat. An autoradiographical tracing study. Brain Res. 343: 351-355

Armstrong, D. M. (1986) Supraspinal contributions to the initiation and control of locomotion in the cat. Prog. Neurobiol. 26: 273-361

Armstrong, D.M. and Schild, R.F. (1979) Spino-olivary neurones in the lumbo-sacral cord of the cat demonstrated by retrograde transport of horseradish peroxidase. Brain Res. 168: 176-179

Arnsten, A. F. T., and Goldman-Rakic, P. S. (1984) Selective prefrontal cortical projections to the region of the locus coeruleus and raphe nuclei in the rhesus monkey. Brain Res. 306: 9-18

Averill, D. B.; Cameron, W. E., and Berger, A. J. (1984) Monosynaptic excitation of dorsal medullary respiratory neurons by slowly adapting pulmonary stretch receptors. J. Neurophysiol. 52: 771-785

Bach-y-Rita, P. (1971) Neurophysiology of eye movements. In: The control of eye movements, (Paul Bach-y-Rita and Carter C. Collins Eds) Academic Press, New York pp. 7-45

Baldissera, F.; Hultborn, H., and Illert, M. (1981) Integration in spinal neuronal systems. In: Handbook of Physiology, Section I, The Nervous System, Vol. II, Motor Systems (Ed. R.E. Burke) Washington American Physiological Society. 509-595

Bandler, R., and Carrive, P. (1988) Integrated defence reaction elicited by excitatory amino acid microinjection in the midbrain periaqueductal grey region of the unrestrained cat. Brain Res. 439: 95-106

Bandler, R., Carrive, P. and Zhang, S.P. (1990) Integration of somatic and autonomic reactions within the midbrain periaqueductal grey: Viscerotopic, somatotopic and functional organization. In: "Role of the forebrain in sensation and behavior" G. Holstege (Ed.) Elsevier Amsterdam, Progr. Brain Res. in press

Barbas-Henry, H., and Wouterlood, F. G. (1988) Synaptic connections between primary trigeminal afferents and accessory abducens motoneurons in the monitor lizard varanus-exanthematicus. J. Comp. Neurol. 267: 387-397

Barrington, F. J. F. (1925) The effect of lesions of the hind- and mid-brain on micturition in the cat. Quart. J. Exp. Physiol. Cogn. Med. 15: 81-102

Basbaum, A. I.; Clanton, C. H., and Fields, H. L. (1978) Three bulbospinal pathways from the rostral medulla of the cat: an autoradiographic study of pain modulating systems. J. Comp. Neurol. 178: 209-224

Batini, C.; Buisseret-Delmas, C., and Corvisier, J. (1976) Horseradish peroxidase localization of masticatory muscle motoneurons in cat. J. Physiol. 72: 301-309

Baulac, M., and Meininger, V. (1981) Organisation des motoneurones des muscles pectoraux chez le chat.

Contribution à l'étude de l'arc axillaire (Achselbogen). Acta Anat. 109: 209-217

Baumgarten, R.von ; Baumgarten, C.von , and Schäfer, K. P. (1957) Beitrag zur Lokalisationsfrage bulboreticularer respiratorischer Neurone der Katze. Pflügers Archiv 264: 217-227

Beckstead, R. M.; Morse, J. R., and Norgren, R. (1980) The nucleus of the solitary tract in the monkey: projections to the thalamus and brain stem nuclei. J. Comp. Neurol. 190: 259-282

Belin, M. F.; Nanopoulos, D.; Didier, M.; Aguera, M.; Steinbusch, H.; Verhofstad, A.; Maitre, M., and Pujol, J. -F (1983) Immunohistochemical evidence for the presence of gamma-aminobutyric acid and serotonin in one nerve cell. A study on the raphe nuclei of rat using antibodies to glutamate decarboxylase and serotonin. Brain Res. 275: 329-339

Berger, A. J. (1977) Dorsal respiratory group neurons in the medulla of cat: spinal projections, responses to lung inflation and superior laryngeal nerve stimulation. Brain Res. 135: 231-254

Berger, A. J. (1980) The distribution of the cat's carotid sinus nerve afferent and efferent cell bodies using the horseradish peroxidase technique. Brain Res. 190: 309-320

Berger, A. J., and Averill, D. B. (1983) Projection of single pulmonary stretch receptors to solitary tract region. J. Neurophysiol. 49: 819-830

Berk, M. L. (1987) Projections of the lateral hypothalamus and bed nucleus of the stria terminalis to the dorsal vagal complex in the pigeon. J. Comp. Neurol. 260: 140-156

Berk, M. L., and Finkelstein, J. A. (1981) Afferent projections to the preoptic area and hypothalamic regions in the rat brain. Neuroscience 6 no. 8: 601-624

Berk, M. L., and Finkelstein, J. A. (1982) Efferent connections of the lateral hypothalamic area of the rat: an autoradiographic investigation. Brain Res. Bull. 8: 511-526

Berk, M. L., and Finkelstein, J. A. (1983) Long descending projections of the hypothalamus in the pigeon, columba livia. J. Comp. Neurol. 220: 127-137

Berthier, N. E., and Moore, J. W. (1983) The nictitating membrane response: an electrophysiological study of the abducens nerve and nucleus and the accessory abducens in rabbit. Brain Res. 258: 201-211

Bertrand, F., and Hugelin, A. (1971) Respiratory synchronizing function of nucleus parabrachialis medialis: pneumotaxic mechanisms. J. Neurophysiol. 34: 189-207

Bertrand, F.; Hugelin, A., and Vibert, J. F. (1974) A stereologic model of pneumotaxic oscillator based on spatial and temporal distributions of neuronal bursts. J. Neurophysiol. 37: 91-107

Besson, J-M. and Chaouch, A. (1987) Peripheral and spinal mechanisms of nociception. Physiological Reviews 67: 67-186

Bieger, D., and Hopkins, D. A. (1987) Viscerotopic representation of the upper alimentary tract in the medulla oblongata in the rat: the nucleus ambiguus. J. Comp. Neurol. 262: 546-562

Birzis, L., and Hemingway, A. (1957) Shivering as a result of brain stimulation. J. Neurophysiol. 20: 91-99

Blaivas, J. G. (1982) The neurophysiology of micturition: a clinical study of 550 patients. J. Urol. 127: 958-963

Bleier, R.(1961) The hypothalamus of the cat: a cytoarchitectonic atlas in the Horsley-Clarke co-ordinate system. Baltimore J. Hopkins Press

Blessing, W. W., and Chalmers, J. P. (1979) Direct projection of catecholamine (presumably dopamine) containing neurons from hypothalamus to spinal cord. Neurosci. Lett. 11: 35-41

Bolk, L.; Groppert, E.; Kallius, E., and E. Lubosch, W. (1938) Handbuch der vergleichende Anatomie den Wirbeltiere. Urban & Schwarzenberg, Berlin

Bongianni, F.; Fontana, G., and Pantaleo, T. (1988) Effects of electrical and chemical stimulation of the Bötzinger complex on respiratory activity in the cat. Brain Res. 445: 254-261

Bowker, R. M. (1986) Serotonergic and peptidergic inputs to the primate ventral spinal cord as visualized with multiple chromagens on the same tissue section. Brain Res. 375: 345-350

Bowker, R. M.; Westlund, K. N.; Sullivan, M. C., and Coulter, J. D. (1982) Organization of serotonergic projections to the spinal cord. Progr. Brain Res. 57: 239-265

Bowker, R. M.; Westlund, K. N.; Sullivan, M. C.; Wilber, J. F., and Coulter, J. D. (1983) Descending serotonergic, peptidergic and cholinergic pathways from the raphe nuclei: A multiple transmitter complex. Brain Res. 288: 33-48

Bowker, R. M.; Abbott, L. C., and Dilts, R. P. (1988) Peptidergic neurons in the nucleus raphe magnus and the nucleus gigantocellularis: their distributions, interrelationships, and projections to the spinal cord. In: "Pain Modulation" (H.L. Fields and J.M. Besson Eds.) Elsevier Amsterdam Progr. Brain Res. 77: 95-127

Brandt, T., and Dieterich, M. (1987) Pathological eye-head coordination in roll: tonic ocular tilt reaction in mesencephalic and medullary lesions. Brain 110: 649-666

Brink, E. E.; Morrell, J. I., and Pfaff, D. W. (1979) Localization of lumbar epaxial motoneurons in the rat. Brain Res. 170: 23-43

Brodal, A. (1940) Experimentelle untersuchungen über die olivocerebellare Lokalisation. Z. Gesamte Neurol. Psychiatr. 169: 1-153

Brodal, A. (1981) Neurological Anatomy in Relation to Clinical Medicine. Third Edition, Oxford University Press, Inc.

Brown, A. G., and Fyffe, R. E. W. (1978) The morphology of group Ia afferent fibre collaterals in the spinal

cord of the cat. J. Physiol. 274: 111-128

Brudzynski, S. M., and Eckersdorf, B. (1984) Inhibition of locomotor activity during cholinergically-induced emotional-aversive response in the cat. Behav. Brain Res. 14: 247-253

Burde, R. M., and Loewy, A. D. (1980) Central origin of oculomotor parasympathetic neurons in the monkey. Brain Res. 198: 434-440

Burke, R. E.; Strick, P. L.; Kanda, K.; Kim, C. C., and Walmsley, B. (1977) Anatomy of medial gastrocnemius and soleus motor nuclei in cat spinal cord. J. Neurophysiol. 40: 667-680

Büttner-Ennever, J. A., and Büttner, U. (1978) A cell group associated with vertical eye movements in the rostral mesencephalic reticular formation of the monkey. Brain Res. 151: 31-48

Büttner-Ennever, J. A., and Büttner, U. (1988) The reticular formation. In: Neuroanatomy of the oculomotor system, (ed.) Büttner-Ennever, J.A.,Elsevier Science Publishers BV, Amsterdam, New York, Oxford 119-176

Büttner-Ennever, J. A.; Büttner, U.; Cohen, B., and Baumgarter, G. (1982) Vertical gaze paralysis and the rostral interstitial nucleus of the medial longitudinal fasciculus. Brain 105: 125-149

Büttner-Ennever, J., and Holstege, G. (1986) Anatomy of premotor centers in the reticular formation controlling oculomotor, skeletomotor and autonomic motor systems. Progr. Brain Res. 64: 89-98

Büttner, U.; Büttner-Ennever, J. A., and Henn, V. (1977) Vertical eye movement related unit activity in the rostral mesencephalic reticular formation of the alert monkey. Brain Res. 130: 239-253

Callister, R. J.; Brichta, A. M., and Peterson, E. H. (1987) Quantitative analysis of cervical musculature in rats: histochemical composition and motor pool organization. II. deep dorsal muscles. J. Comp. Neurol. 255: 369-385

Cameron, W. E.; Averill, D. B., and Berger, A. J. (1983) Morphology of cat phrenic motoneurons as revealed by intracellular injection of horseradish peroxidase. J. Comp. Neurol. 219: 70-80

Cardona, A., and Rudomin, P. (1983) Activation of brainstem serotoninergic pathways decreases homosynaptic depression of monosynaptic responses of frog spinal motoneurons. Brain Res. 280: 373-378

Carlton, S. M.; Chung, J. M.; Leonard, R. B., and Willis, W. D. (1985) Funicular trajectories of brainstem neurons projecting to the lumbar spinal cord in the monkey (Macaca fascicularis): A retrograde labeling study. J. Comp. Neurol. 241: 382-404

Carpenter, M. B.; Harbison, J. W., and Peter, P. (1970) Accessory oculomotor nuclei in the monkey: projections and effects of discrete lesions. J. Comp. Neurol. 140: 131-154

Carrive, P.; Bandler, R., and Dampney, R. A. L. (1989) Viscerotopic control of regional vascular beds by discrete groups of neurons within the midbrain periaqueductal gray. Brain Res. 493: 385-390

Carstens, E. (1982) Inhibition of spinal dorsal horn neuronal responses to noxious skin heating by medial hypothalamic stimulation in the cat. J. Neurophysiol. 48: 808-822

Carstens, E.; Klumpp, D., and Zimmermann, M. (1980) Differential inhibitory effects of medial and lateral midbrain stimulation on spinal neuronal discharges to noxious skin heating in the cat. J. Neurophysiol. 43: 332-342

Castiglioni, A. J.; Gallaway, M. C., and Coulter, J. D. (1978) Spinal projections from the midbrain in monkey. J. Comp. Neurol. 178: 329-346

Chan, J. Y. H.; Fung, S. J.; Chan, S. H. H., and Barnes, C. D. (1986) Facilitation of lumbar monosynaptic reflexes by locus coeruleus in the rat. Brain Res. 369: 103-109

Chan Palay, V.; Jonsson, G., and Palay, S. L. (1978) Serotonin and substance P coexist in neurons of the rat's central nervous system. Proc. Natl. Acad. Sci. 75: 1582-1586

Cheney, P. D. (1980) Response of rubromotoneuronal cells identified by spiketriggered averaging of EMG activity in awake monkeys. Neurosci. Lett. 17: 137-143

Cheney, P. D.; Mewes, K., and Fetz, E. E. (1988) Encoding of motor parameters by corticomotoneuronal (CM) and rubromotoneuronal (RM) cells producing postspike facilitation of forelimb muscles in the behaving monkey. Beh. Brain Res. 28: 181-191

Chung, K.; Chung, J. -M; LaVelle, F. W., and Wurster, R. D. (1979) Sympathetic neurons in the cat spinal cord projecting to the stellate ganglion. J. Comp. Neurol. 185: 23-31

Ciriello, J.; Caverson, M. M., and Polosa, C. (1986) Function of the ventrolateral medulla in the control of the circulation. Brain Res. Rev. 11: 359-391

Cleaton-Jones, P. (1972) Anatomical observations on the soft palate of the albino rat. Anat. Anz. 131: 419-424

Cohen, M. I. (1971) Switching of the respiratory phases and evoked phrenic responses produced by rostral pontine electrical stimulation. J. Physiol. 217: 133-258

Cohen, M. I.; Piercey, M. F.; Gootman, P. M., and Wolotsky, P. (1974) Synaptic connections between medullary inspiratory neurons and phrenic motoneurons as revealed by cross-correlation. Brain Res. 81: 319-324

Collewijn, H. (1975) Oculomotor areas in the rabbit's midbrain and pretectum. J. Neurobiol. 6: 3-22

Collewijn, H., and Holstege, G. (1984) Effects of neonatal and late unilateral enucleation on optokinetic responses and optic nerve projections in the rabbit. Exp. Brain Res. 57: 138-150

Connelly, C. A., and Wurster, R. D. (1985) Sympathetic rhythms during hyperventilation-induced apnea. Am. J. Physiol. 249: R424-431

Contreras, R. J.; Gomez, M. M., and Norgren, R. (1980) Central origins of cranial nerve parasympathetic neurons in the rat. J. Comp. Neurol. 190: 373-395

Coote, J. H.; Hilton, S. M., and Zbrozyna, A. W. (1973) The ponto-medullary area integrating the defence reaction in the cat and its influence on muscle blood flow. J. Physiol. 229: 257-274

Coulter, J. D.; Bowker, R. M.; Wise, S. P.; Murray, E. A.; Castiglioni, A. J., and Westlund, K. N. (1979) Cortical, tectal and medullary descending pathways to the cervical spinal cord. Progr. Brain Res. 50: 263-279

Courville, J. (1966) The nucleus of the facial nerve; the relation between cellular groups and peripheral branches of the nerve. Brain Res. 1: 338-354

Courville, J. (1966) Rubrobulbar fibres to the facial nucleus and the lateral reticular nucleus (nucleus of the lateral funiculus). An experimental study in the cat with silver impregnation methods. Brain Res. 1: 317-337

Cowan, W. M.; Gottlieb, D. I.; Hendrickson, A. E.; Price, J. L., and Woolsey, T. A. (1972) The autoradiographic demonstration of axonal connections in the central nervous system. Brain Res. 37: 21-51

Cowie, R. J. and Holstege, G. (1990) Dorsal mesencephalic projections to pons, medulla oblongata and spinal cord in the cat. Limbic and non-limbic components. Neuroscience (submitted)

Crone, C.; Hultborn, H.; Kiehn, O.; Mazieres, L., and Wigstrom, H. (1988) Maintained changes in motoneuronal excitability by short-lasting synaptic inputs in the decerebrate cat. J. Physiol. 405: 321-343

Crouch, J. E. (1969) Text-Atlas of Cat Anatomy. Philadelphia, Lea and Febiger

Crutcher, K. A.; Humbertson, A. O. jr., and Martin, G. F. (1978) The origin of brainstem spinal pathways in the North American Opossum (Didelphis virginiana). Studies using the horseradish peroxidase. J. Comp. Neurol. 179: 169-194

Cullheim, S., and Kellerth, J. -O (1978) A morphological study of the axons and recurrent axon collaterals of cat a-motoneurones supplying different functional types of muscle unit. J. Physiol. 281: 301-314

Czarkowska, J.; Jankowska, E., and Sybirska, E. (1976) Axonal projections of spinal interneurones excited by group I afferents in the cat, revealed by intracellular staining with horseradish peroxidase. Brain Res. 118: 115-118

Dampney, R. A. L., and McAllen, R. M. (1988) Differential control of sympathetic fibres supplying hindlimb skin and muscle by retrofacial neurones in the cat. J. Physiol. (Lond.) 395: 41-56

Davies, J. G. McF.; Kirkwood, P. A., and Sears, T. A. (1985) The detection of monosynaptic connexions from inspiratory bulbospinal neurones to inspiratory motoneurones in the cat. J. Physiol. (London) 368: 33-62

Davies, J. G. McF.; Kirkwood, P. A., and Sears, T. A. (1985) The distribution of monosynaptic connexions from inspiratory bulbospinal neurones to inspiratory motoneurones in the cat. J. Physiol. 368: 63-87

Davis, P. J., and Nail, B. S. (1984) On the location and size of laryngeal motoneurons in the cat and rabbit. J. Comp. Neurol. 230: 13-32

Decima, E. E.; Von Euler, C., and Thoden, U. (1969) Intercostal-to-phrenic reflexes in the spinal cat. Acta physiol. scand. 75: 568-579

Dekker, J. J.; Lawrence, D. G., and Kuypers, H. G. J.M. (1973) The location of longitudinally running dendrites in the ventral horn of the cat spinal cord. Brain Res. 51: 319-325

De Olmos, J. S.; Alheid, G. F., and Beltramino, C. A. (1985) Amygdala. In: G. Paxinos, (Ed.) The Rat Nervous System, Academic Press, Sydney pp. 223-334

DeRosier, E. A.; West, R. A., and Larson, C. R. (1988) Comparison of single unit discharge properties in the periaqueductal gray and nucleus retroambiguus during vocalization in monkeys. Soc. Neurosci. Abstr. 14: 1237

Dom, R.; Falls, W., and Martin, G. F. (1973) The motor nucleus of the facial nerve in the opossum (Didelphis marsupialis virginiana). Its organization and connections. J. Comp. Neurol. 152: 373-402

ten Donkelaar, H. J. (1988) Evolution of the red nucleus and rubrospinal tract. Behav. Brain Res. 28: 9-20

Donoghue, S.; Garcia, M.; Jordan, D., and Spyer, K. M. (1982) The brain-stem projections of pulmonary stretch afferent neurons in cats and rabbits. J. Physiol. (London) 322: 352-364

Doty, R. W., and Bosma, J. F. (1956) An electromyographic analysis of reflex deglutition. J. Neurophysiol. 19: 44-60

Duffin, J., and Lipski, J. (1987) Monosynaptic excitation of thoracic motoneurones by inspiratory neurones of the nucleus tractus solitarius in the cat. J. Physiol. 390: 415-431

Duron, B.; Jung-Caillol, M. C., and Marlot, D. (1978) Myelinated nerve fiber supply and muscle spindles in the respiratory muscles of cat: a quantitative study. Anat. Embryol. 152: 171-192

Duron, B.; Marlot, D.; Lamicol, N.; Jung-Caillol, M. C., and Macron, J. M. (1979) Somatotopy in the phrenic motor nucleus of the cat as revealed by retrograde transport of horseradish peroxidase (HRP). Neurosci. Lett. 14: 159-163

Eccles, J. C.; Nicoll, R. A.; Schwartz, W. F.; Táboríková, H., and Willey, T. J. (1975) Reticulospinal neurons with and without monosynaptic inputs from cerebellar nuclei. J. Neurophysiol. 38: 103.

Edwards, S. B. (1972) Descending projections of the midbrain reticular formation of the cat: an experimental study using a "protein transport", tracing method. Anat. Rec. 172: 305

Edwards, S. B., and Flynn, J. P. (1972) Corticospinal control of striking in centrally elicited attack behavior. Brain Res. 41: 51-65

Elbadawi, A. (1982) Neuromorphologic basis of vesicourethral function: I. histochemistry, ultrastructure, and function of intrinsic nerves of the bladder and

urethra. Neurourol. Urodyn. 1: 3-50

Ellenberger, H. H., and Feldman, J. L. (1988) Monosynaptic transmission of respiratory drive to phrenic motoneurons from brainstem bulbospinal neurons in rats. J. Comp. Neurol. 269: 47-57

Engberg, I.; Lundberg, A., and Ryall, R. W. (1968) Reticulospinal inhibition of interneurones. J. Physiol. 194: 225-236

Epstein, A. N. (1971) The lateral hypothalamic syndrome: its implications for the physiological psychology of hunger and thirst. In E.Stellar and J.M. Sprague (Eds.): Progress in Physiological Psychology, Vol. 4. New York: Academic Press. pp. 263-317

Erzurumlu, R. S.; Bates, C. A., and Killackey, H. P. (1980) Differential organization of thalamic projection cells in the brain stem trigeminal complex of the rat. Brain Res. 198: 427-434

Euler, C.von; Martilla, I.; Remmers, J. E., and Trippenbach, T. (1976) Effects of lesions in the parabrachial nucleus on the mechanisms for central and reflex termination of inspiration in the cat. Acta Physiol. Scand. 96: 324-337

Evinger, C. (1988) Extraocular motor nuclei: location, morphology and afferents. In: Neuro-anatomy of the oculomotor system (Ed. Büttner-Ennever) Elsevier, Amsterdam, New York, Oxford 81-117

Fedorko, L., and Merrill, E. G. (1984) Axonal projections from the rostral expiratory neurones of the Bötzinger complex to medulla and spinal cord in the cat. J. Physiol. 350: 487-496

Fedorko, L.; Merrill, E. G., and Lipski, J. (1983) Two descending medullary inspiratory pathways to phrenic motoneurons. Neurosci. Lett. 43: 285-291

Feldman, J. L. (1986) Neurophysiology of breathing in mammals. In: F.E. Bloom (Ed.): Handbook of Physiology, Sect. 1: The Nervous System, vol. IV. Intrinsic Regulatory Systems of the Brain. Bethesda, Md: American Physiological Soc. 463-524

Feldman, J. L.; Loewy, A. D., and Speck, D. F. (1985) Projections from the ventral respiratory group to phrenic and intercostal motoneurons in cat: An autoradiographic study. J. Neuroscience 5: 1993-2000

Fernandez de Molina, A., and Hunsperger, R. W. (1959) Central representation of affective reactions in forebrain and brain stem: electrical stimulation of amygdala, stria terminalis, and adjacent structures. J. Physiol. 145: 251-265

Fernandez de Molina, A., and Hunsperger, R. W. (1962) Organization of the subcortical system governing defense and flight reactions in the cat. J. Physiol. (London) 160: 200-213

Fetcho, J. R. (1987) A review of the organization and evolution of motoneurons innervating the axial musculature of vertebrates. Brain Res. Rev. 12: 243-280

Fetz, E. E.; Jankowska, E.; Johannisson, T., and Lipski, J. (1979) Autogenetic inhibition of motoneurones by impulses in group Ia muscle spindle afferents. J. Physiol. 293: 173-197

Fields, H. L.; Basbaum, A. I.; Clanton, C. H., and Anderson, S. D. (1977) Nucleus raphe magus inhibition of spinal cord dorsal horn neurons. Brain Res. 126: 441-453

Friauf, E., and Baker, R. (1985) An intracellular HRP-study of cat tensor tympani motoneurons. Exp. Brain Res 57: 499-511

Friauf, E., and Herbert, H. (1985) Topographic organization of facial motoneurons to individual pinna muscles in rat and bat. J. Comp. Neurol. 240: 161-170

Fritz, N.; Illert, M., and Reeh, P. (1986) Location of motoneurones projecting to the cat distal forelimb. II. Median and ulnar motornuclei. J. Comp. Neurol. 244: 302-312

Fritz, N.; Illert, M., and Saggau, P. (1986) Location of motoneurones projecting to the cat distal forelimb. I. Deep radial motornuclei. J. Comp. Neurol. 244: 286-301

Fritz, N.; Illert, M., and Saggau, P. (1978) Monosynaptic convergence of group I muscle afferents from the forelimb onto interosseus motoneurones. Neurosci. Lett. Suppl. I: S 95

Fritz, N.; Illert, M.; de la Motte, S., and Reeh, P. (1984) Pattern of monosynaptic Ia connections from forelimb nerves onto median and ulnar motoneurones. Neurosci. Lett. 18: S264

Fuchs, A. F.; Kaneko, C. R. S., and Scudder, C. A. (1985) Brainstem control of saccadic eye movements. Ann. Rev. Neurosci. 8: 307-337

Fukushima, K.; Pitts, N. G., and Peterson, B. W. (1978) Direct excitation of neck motoneurons by interstitiospinal fibers. Exp. Brain Res. 33: 565-583

Fung, S. J., and Barnes, C. D. (1987) Membrane excitability changes in hindlimb motoneurons induced by stimulation of the locus coeruleus in cats. Brain Res. 402: 230-242

Garcia-Rill, E., and Skinner, R. D. (1987) The mesencephalic locomotor region. I. Activation of a medullary projection site. Brain Res. 411: 1-12

Garcia-Rill, E., and Skinner, R. D. (1987) The mesencephalic locomotor region. II. Projections to reticulospinal neurons. Brain Res. 411: 13-20

Garcia-Rill, E., and Skinner, R. D. (1988) Modulation of rhythmic function in the posterior midbrain. Neurosci. 27: 639-654

Gebhart, G. F.; Sandkühler, J.; Thalhammer, J. G., and Zimmermann, M. (1983) Quantitative comparision of inhibition in spinal cord of nociceptive information by stimulation in periaqueductal gray or nucleus raphe magnus of the cat. J. Neurophysiol. 50: 1433-1445

Gelfand, I. M.; Orlovsky, G. N., and Shik, M. L. (1988) Locomotion and scratching in tetrapods. In: Neural control of rhythmic movements in vertebrates. A.H. Cohen, S. Rossignol, S. Grilner (Eds.) John Wiley and Sons Inc. New York pp.167-199

Gibson, A. R.; Houk, J. C., and Kohlerman, N. J. (1985) Magnocellular red nucleus activity during different types of limb movement in the macaque monkey. J. Physiol. 358: 527-549

Giovanelli Barilari, M. S., and Kuypers, H. G. J.M. (1969) Propriospinal fibers interconnecting the spinal enlargements in the cat. Brain Res. 14: 321-330

Gormezano, I.; Schneiderman, N.; Deaux, E., and Fuentes, I. (1962) Nictitating membrane: classical conditioning and extinction in the albino rabbit. Science 138: 33-34

Gosling, J. A.; Dixon, J. S.; Critchley, H. O. D., and Thompson, S. (1981) A comparative study of the human external sphincter and periurethral levator ani muscle. Br. J. Urol. 53: 35-41

Grafstein, B., and Laureno, R. (1973) Transport of radioactivity from eye to visual cortex in the mouse. Exp. Neurol. 39: 44-57

Grant, K.; Guéritaud, J. P.; Horcholle-Bossavit, G., and Tyc-Dumont, S. (1979) Anatomical and electrophysiological identification of motoneurones supplying the cat retractor bulbi muscle. Exp. Brain Res. 34: 541-550

Grant, K.; Guegan, M., and Horcholle-Bossavit, G. (1981) The anatomical relationship of the retractor bulbi and posterior digastric motoneurones to the abducens and facial nuclei in the cat. Arch. Ital. Biol. 119: 195-207

Grantyn, A.; Ong-Meang Jacques, V., and Berthoz, A. (1987) Reticulo-spinal neurons participating in the control of synergic eye and head movements during orienting in the cat. Exp. Brain Res. 66: 355-377

Grantyn, R.; Baker, R., and Grantyn, A. (1980) Morphological and physiological identification of excitatory pontine reticular neurons projecting to the cat abducens nucleus and spinal cord. Brain Res. 198: 221-229

Graybiel, A. M. (1977) Direct and indirect preoculomotor pathways of the brain stem: an autoradiographic study of the pontine reticular formation in the cat. J. Comp. Neurol. 175: 37-78

Graybiel, A. M., and Hartwieg, E. A. (1974) Some afferent connections of the oculomotor complex in the cat: an experimental study with tracer techniques. Brain Res. 81: 543-551

Griffiths, D.; Holstege, G.; Dalm, E., and de Wall, H. (1989) Control and coordination of bladder and urethral function in the brain stem of the cat. Neurourol. and Urodynam. in press:

Grillner, S. (1981) Control of locomotion in bipeds, tetrapods, and fish. In: Handbook of Physiology, Section I, The Nervous System, Vol. II, Motor Systems (Ed. R.E. Burke) Washington, American Physiological Society 2, part 2: 1179-1236

Grillner, S.; Hongo, T., and Lund, S. (1970) The vestibulospinal tract. Effects on alpha motoneurons in the lumbosacral spinal cord in the cat. Exp. Brain Res. 10: 94-120

Grossman, R. G., and Wang, S. C. (1956) Diencephalic mechanism of control of the urinary bladder of the cat. Yale J. Biol. and Med. 28: 285-297

Grossman, S. P.; Dacey, D.; Halaris, A. E.; Collier, T., and Routtenberg, A. (1978) Aphagia and adipsia after preferential destruction of nerve cell bodies in hypothalamus. Science 202: 537-539

Guégan, M., and Horcholle-Bossavit, G. (1981) Reflex control of the retractor bulbi muscle in the cat. Pflügers Arch. 389: 143-148

Guinan Jr., J. J.; Joseph, M. P., and Norris, B. E. (1989) Brainstem facial-motor pathways from two distinct groups of stapedius motoneurons in the cat. J. Comp. Neurol. 287: 134-144

Haase, P., and Hrycyshyn, A. W. (1985) Labelling of motoneurons supplying the cutaneous maximus in the rat, following injection of the triceps brachii muscle with horseradish peroxidase. Neurosci. Lett. 60: 313-318

Hagg, S., and Ha, H. (1970) Cervicothalamic Tract in the Dog. J. Comp. Neurol. 139: 357-374

Hahne, M.; Illert, M., and Wietelmann, D. (1988) Recurrent inhibition in the cat distal forelimb. Brain Res. 456: 188-192

Haley, D. A.; Thompson, R. F., and Madden, J. IV (1988) Pharmacological analysis of the magnocellular red nucleus during classical conditioning of the rabbit nictitating membrane response. Brain Res. 454: 131-139

Hancock, M. B. (1976) Cells of origin of hypothalamospinal projections in the rat. Neurosci. Lett. 3: 179-184

Harvey, J. A.; Land, T., and McMaster, S. E. (1984) Anatomical study of the rabbit's corneal-VIth nerve reflex: connections between cornea, trigeminal sensory complex, and the abducens and accessory abducens nuclei. Brain Res. 301: 307-321

Hassler, R. (1972) Supranuclear structures regulating binocular eye and head movements. Bibl. ophthal. 82: 207-219

Hawthorn, J.; Ang, V. T. Y., and Jenkins, J. S. (1985) Effects of lesions in the hypothalamic paraventricular, supraoptic and suprachiasmatic nuclei on vasopressin and oxytocin in the rat brain and spinal cord. Brain Res. 346: 51-57

Hayes, N. L., and Rustioni, A. (1981) Descending projections from brainstem and sensorimotor cortex to spinal enlargements in the cat. Exp. Brain Res. 41: 89-107

Heimer, L.; de Olmos, J.;Alheid, G.F. and Zaborsky, L. (1990) "Peristroika" in the basal forebrain; Opening the border between neurology and psychiatry. In: "Role of the forebrain in sensation and behavior" G. Holstege (Ed.) Elsevier Amsterdam, Progr. Brain Res. in press

Helke, C. J.; Sayson, S. C.; Keeler, J. R., and Charlton, C. G. (1986) Thyrotropin-releasing hormone-immunoreactive neurons project from the ventral medulla to the intermediolateral cell column: partial coexistence with serotonin. Brain Res. 381: 1-7

Hemingway, A. (1963) Shivering. Phys. Reviews 43: 397-422

Henneman, E., and Mendell, L. M. (1981) Functional organization of motoneuron pool and its inputs. In: Handbook of Physiology, Section I, The Nervous System, Vol. II, Motor Systems (Ed. R.E. Burke) Washington American Physiology Society. 423-507

Henry, J. L., and Calaresu, F. R. (1972) Topography and numerical distribution of neurons of the thoraco-lumbar intermediolateral nucleus in the cat. J. Comp. Neurol. 144: 205-214

Hermes, M. L.; Buijs, R. M.; Masson-Pevet, M., and Pevet, P. (1988) Oxytocinergic innervation of the brain of the garden dormouse (Eliomys quercinus L.). J. Comp. Neurol. 273: 252-262

Hilaire, G., and Monteau, R. (1976) Connexions entre les neurones inspiratoire bulbaires et les motoneurones phrénique et intercosteaux. J. Physiol. (Paris) 72: 987-1000

Hinrichsen, C. F. L., and Watson, C. D. (1984) The facial nucleus of the rat: Representation of facial muscles revealed by retrograde transport of HRP. Anat. Rec. 209: 407-415

Hiraoka, M., and Shimamura, M. (1977) Neural mechanisms of the corneal blinking reflex in cats. Brain Res. 125: 265-275

Hökfelt, T.; Ljungdahl, A.; Steinbusch, H.; Verhofstad, A.; Nilsson, G.; Brodin, E.; Pernow, B., and Goldstein, M. (1978) Immunohistochemical evidence of substance P-like immunoreactivity in some 5-hydroxytryptamine-containing neurons in the rat central nervous system. Neuroscience 3: 517-538

Hökfelt, T.; Terenius, T.; Kuypers, H. G. J.M., and Dann, O. (1979) Evidence for enkephalin immunoreactivity neurons in the medulla oblongata projecting to the spinal cord. Neurosci. Lett. 14: 55-61

Hökfelt, T.; Skirboll, L.; Rehfeld, J. F.; Goldstein, M.; Markey, K., and Dann, O. (1980) A subpopulation of mesencephalic dopamine neurons projecting to limbic areas contains a cholecystokinin-like peptide: evidence from immunohistochemistry combined with retrograde tracing. Neuroscience 5: 2093-2124

Hökfelt, T.; Johansson, O., and Goldstein, M. (1984) Chemical neuroanatomy of the brain. Science 225: 1326-1334

Holstege, G. (1987a) Anatomical evidence for an ipsilateral rubrospinal pathway and for direct rubrospinal projections to motoneurons in the cat. Neurosci. Lett. 74: 269-274

Holstege, G. (1987b) Some anatomical observations on the projections from the hypothalamus to brainstem and spinal cord: an HRP and autoradiographic tracing study in the cat. J. Comp. Neurol. 260: 98-126

Holstege, G. (1988a) Direct and indirect pathways to lamina I in the medulla oblongata and spinal cord of the cat. In: H.L.Fields and J.M. Besson (Eds.): Descending brainstem controls of nociceptive transmission. Elsevier Amsterdam Progr. Brain Res. vol. 77 pp. 47-94.

Holstege, G. (1988b) Brainstem-spinal cord projections in the cat, related to control of head and axial movements. In: Neuroanatomy of the oculomotor system (Ed. J. Büttner-Ennever) Elsevier Amsterdam chapter 11: 429-468

Holstege, G. (1988c) Anatomical evidence for a strong ventral parabrachial projection to nucleus raphe magnus and adjacent tegmental field. Brain Res. 447: 154-158

Holstege, G. (1989) An anatomical study on the final common pathway for vocalization in the cat. J. Comp. Neurol. 284: 242-252

Holstege, G. (1990) Subcortical limbic system projections to caudal brainstem and spinal cord. In: The human nervous system, Ed. G. Paxinos, Acad. Press Sydney - Tokyo. in press:

Holstege, G., and Blok, B. (1986) The afferent projections of the motor trigeminal nucleus in the cat. An autoradiographical tracing study. Neurosci. Lett. 26: S. 435

Holstege, G., and Blok, B. (1989) Descending pathways to the cutaneus trunci muscle motoneuronal cell group in the cat. J. Neurophysiol. in press:

Holstege, G., and Collewijn, H. (1982) The efferent connections of the nucleus of the optic tract and the superior colliculus in the rabbit. J. Comp. Neurol. 209: 139-175

Holstege, G., and Cowie, R. J. (1989) Projections from the rostral mesencephalic reticular formation to the spinal cord. Exp. Brain Res. 75: 265-279

Holstege, G., and Griffiths, D. (1990) Neuronal organization of micturition In: The human nervous system, Ed. G. Paxinos Acad. Press Sydney - Tokyo, in press

Holstege, G., and Kuypers, H. G. J.M. (1977) Propriobulbar fibre connections to the trigeminal, facial and hypoglossal motor nuclei I. An anterograde degeneration study in the cat. Brain 100: 239-264

Holstege, G., and Kuypers, H. G. J.M. (1982) The anatomy of brain stem pathways to the spinal cord in the cat. A labeled amino acid tracing study. Progr. Brain Res. 57: 145-175

Holstege, G., and Ralston, D. D. (1989) Rubrofacial projections in the cat. An anterograde L.M. and E.M. study utilizing WGA-HRP as a tracer. Soc. Neurosci. Abstr. 15: p. 389

Holstege, G., and Tan, J. (1987) Supraspinal control of motoneurons innervating the striated muscles of the pelvic floor including urethral and anal sphincters in the cat. Brain 110: 1323-1344

Holstege, G., and Tan, J. (1988) Projections from the red nucleus and surrounding areas to the brainstem and spinal cord in the cat. An HRP and autoradiographical tracing study. Beh. Brain Res. 28: 33-57

Holstege, G., and Van Krimpen, L. (1986) Afferent connections to the pharynx and soft palate motoneuronal cell group. An autoradiographical study in the cat. Neurosci. Lett. Suppl. 26: S437

Holstege, G.; Blok, B. F., and Ralston, D. D. (1988) Anatomical evidence for red nucleus projections to motoneuronal cell groups in the spinal cord of the monkey. Neurosci. Lett. 95: 97-101

Holstege, G.; Kuypers, H. G. J.M., and Boer, R. C. (1979) Anatomical evidence for direct brain stem projections to the somatic motoneuronal cell groups and autonomic preganglionic cell groups in cat spinal cord. Brain Res. 171: 329-333

Holstege, G.; Kuypers, H. G. J.M., and Dekker, J. J. (1977) The organization of the bulbar fibre connections to the trigeminal, facial and hypoglossal motor nuclei. II. an autoradiographic tracing study in cat. Brain 100: 265-286

Holstege, G.; Meiners, L., and Tan, K. (1985) Projections of the bed nucleus of the stria terminalis to the mesencephalon, pons, and medulla oblongata in the cat. Exp. Brain Res. 58: 379-391

Holstege, G.; van Ham, J. J., and Tan, J. (1986a) Afferent projections to the orbicularis oculi motoneuronal cell group. An autoradiographical tracing study in the cat. Brain Res. 374: 306-320

Holstege, G.; Van Neerven, J., and Evertse, F. (1984b) Some anatomical observations on axonal connections from brain stem areas physiologically identified as related to respiration. Neurosci. Lett. Suppl. 18: S83

Holstege, G.; Van Neerven, J., and Evertse, F. (1987) Spinal cord location of the motoneurons innervating the abdominal, cutaneous maximus, latissimus dorsi and longissimus dorsi muscles in the cat. Exp. Brain Res. 67: 179-194

Holstege, G.; Graveland, G.; Bijker-Biemond, C., and Schuddeboom, I. (1983) Location of motoneurons innervating soft palate, pharynx and upper esophagus. Anatomical evidence for a possible swallowing center in the pontine reticular formation. An HRP and autoradiographical tracing study. Brain Behav. Evol. 23: 47-62

Holstege, G.; Griffiths, D.; De Wall, H., and Dalm, E. (1986c) Anatomical and physiological observations on supraspinal control of bladder and urethral sphincter muscles in the cat. J. Comp. Neurol. 250: 449-461

Holstege, G.; Tan, J.; van Ham, J., and Bos, A. (1984a) Mesencephalic projection to the facial nucleus in the cat. An autoradiographic tracing study. Brain Res. 311: 7-22

Holstege, G.; Tan, J.; van Ham, J. J., and Graveland, G. A. (1986b) Anatomical observations on the afferent projections to the retractor bulbi motoneuronal cell group and other pathways possibly related to the blink reflex in the cat. Brain Res. 374: 321-334

Holstege, J. C. (1989) Ultrastructural evidence for GABA-ergic brainstem projections to spinal motoneurons. Soc. Neurosci. Abstr. 15 part 1: p. 308

Holstege, J. C., and Kuypers, H. G. J.M. (1982) Brain stem projections to spinal motoneuronal cell groups in rat studied by means of electron microscopy autoradiography. Progr. Brain Res. 57: 177-183

Holstege, J. C., and Kuypers, H. G. J.M. (1987) Brainstem projections to lumbar motoneurons in rat-I. An ultrastructural study using autoradiography and the combination of autoradiography and horseradish peroxidase histochemistry. Neuroscience 21: 345-367

Hongo, T.; Jankowska, E., and Lundberg, A. (1969) The rubrospinal tract. I. Effects on alpha-motoneurons innervating hindlimb muscles in cats. Exp. Brain Res. 7: 344-364

Hopkins, D. A., and Armour, J. A. (1982) Medullary cells of origin of physiologically identified cardiac nerves in the dog. Brain Res. Bull. 8: 359-365

Hopkins, D. A., and Holstege, G. (1978) Amygdaloid projections to the mesencephalon, pons, and medulla oblongata in the cat. Exp. Brain Res. 32: 529-547

Horcholle-Bossavit, G.; Jami, L.; Thiesson, D., and Zytnicki, D. (1988) Motor nuclei of peroneal muscles in the cat spinal cord. J. Comp. Neurol. 277: 430-40

ter Horst, G. J.; Luiten, P. G. M., and Kuipers, F. (1984) Descending pathways from hypothalamus to dorsal motor vagus and ambiguus nuclei in the rat. J. Auton. Nerv. Syst. 11: 59-75

Hosobuchi, Y. (1988) Current issues regarding subcortical electrical stimulation for pain control in humans. In: "Nociception control" (H.L. Fields and J.M. Besson Eds.) Elsevier Amsterdam Progr. Brain Res. 77: 189-192

Hosoya, Y. (1980) The distribution of spinal projection neurons in the hypothalamus of the rat, studied with the HRP method. Exp. Brain Res. 40: 79-87

Hosoya, Y. (1985) Hypothalamic projections to the ventral medulla oblongata in the rat, with special reference to the nucleus raphe pallidus: a study using autoradiographic and HRP techniques. Brain Res. 344: 338-350

Hosoya, Y., and Matsushita, M. (1979) Identification and distribution of the spinal and hypophyseal projection neurones in the paraventricular nucleus of the rat. A light and electron microscopic study with the HRP method. Exp. Brain Res. 35: 315-331

Hosoya, Y., and Matsushita, M. (1981) Brainstem projections from the lateral hypothalamic area in the rat, as studied with autoradiography. Neurosci. Lett. 24: 111-116

Hosoya, Y.; Matsushita, M., and Sugiura, Y. (1983) A direct hypothalamic projection to the superior salivatory nucleus neurons in the rat. A study using anterograde autoradiographic and retrograde HRP methods. Brain Res. 266: 329-334

Hosoya, Y.; Sugiura, Y.; Ito, R., and Kohno, K. (1990) Descending projections from the hypothalamic paraventricular nucleus to the A5 area, including the superior salivatory nucleus in the rat, using anterograde and retrograde transport techniques. Exp. Brain Res. in press:

Hounsgaard, J.; Hultborn, H.; Jespersen, B., and Kiehn, O. (1984) Intrinsic membrane properties causing a bistable behavior of a-motoneurons. Exp. Brain Res. 55: 391-394

Hounsgaard, J.; Hultborn, H., and Kiehn, O. (1986)

Transmitter-controlled properties of a-motoneurones causing long-lasting motor discharge to brief excitatory inputs. Progr. Brain Res. 64: 39-49

Hounsgaard, J.; Hultborn, H.; Jespersen, B., and Kiehn, O. (1988) Bistability of alpha-motoneurons in the decebrate cat and in the acute spinal cat after intravenous 5-hydroxytryptophan. J. Physiol. 405: 345-367

Hu, J. W., and Sessle, B. J. (1979) Trigeminal nociceptive and non-nociceptive neurones: brain stem intranuclear projections and modulation of orofacial, periaqueductal gray and nucleus raphe magnus stimuli. Brain Res. 170: 547-553

Huerta, M. F., and Harting, J. K. (1982) Tectal control of spinal cord activity: neuroanatomical demonstration of pathways connecting the superior colliculus with the cervical spinal cord. Progr. in Brain Res 57: 293-328

Huisman, A. M.; Kuypers, H. G. J.M., and Verburgh, C. A. (1982) Differences in collateralization of the descending spinal pathways from red nucleus and other brain stem cell groups in cat and monkey. Progr. Brain Res. 57: 185-217

Hultborn, H. (1976) Transmission in the pathway of reciprocal 1a inhibition to motoneurons and its control during the tonic stretch reflex. In: S. Homma (Ed.). Understanding the Stretch Reflex. Progr. Brain Res. 44: 235-255

Humphrey, D. R., and Reitz, R. R. (1976) Cells of origin of corticorubral projections from the arm area of primate cortex and their presynaptic actions in the red nucleus. Brain Res. 110: 219.

Humphrey, D. R.; Gold, R., and Reed, D. J. (1984) Sizes, laminar and topographic origins of cortical projections to the major divisions of the red nucleus in the monkey. J. Comp. Neurol. 225: 75-94

Hunt, S. P., and Lovick, T. A. (1982) The distribution of serotonin, met-enkephalin and b-lipotropin-like immunoreactivity in neuronal perikarya of the cat brainstem. Neurosci. Lett. 30: 139-145

Hurley-Gius, K. M.; Cechetto, D. F., and Saper, C. B. (1986) Spinal connections of the infralimbic autonomic cortex. Soc. Neurosc. Abstr. 12: pp. 538

Hyde, J. E., and Toczek, S. (1962) Functional relation of interstitial nucleus to rotatory movements evoked from zona incerta stimulation. J. Neurophysiol. 25: 455-466

Illert, M.; Lundberg, A.; Padel, Y., and Tanaka, R. (1978) Integration in descending motor pathways controlling the forelimb in the cat. 5. Properties of and monosynaptic excitatory convergence on C3-C4 propriospinal neurones. Exp. Brain Res. 33: 101-130

Ishizuka, N.; Mannen, H.; Hongo, T., and Sasaki, S. (1979) Trajectory of group Ia afferent fibers stained with horseradish peroxidase in the lumbosacral spinal cord of the cat: three dimensional reconstructions from serial sections. J. Comp. Neurol. 186: 189-213

Jänig, W., and McLachlan, E. M. (1986) Identification of distinct topographical distributions of lumbar sympathetic and sensory neurons projecting to end organs with different functions in the cat. J. Comp. Neurol. 246: 104-112

Jankowska, E. (1988) Target cells of rubrospinal tract fibres within the lumbar spinal cord. Behav. Brain Res. 28: 91-96

Jankowska, E., and Lindström, S. (1971) Morphological identification of Renshaw cells. Acta Physiol. Scand. 81: 428-430

Jankowska, E., and Lindström, S. (1972) Morphology of interneurones mediating Ia reciprocal inhibition of motoneurones in the spinal cord of the cat. J. Physiol. 226: 805-823

Jankowska, E.; McCrea, D., and Mackel, R. (1981) Oligosynaptic excitation of motoneurones by impulses in group Ia muscle spindle afferents in the cat. J. Physiol. 316: 411-425

Jankowska, E., and McCrea, D. A. (1983) Shared reflex from Ib tendon organ afferents and Ia muscle spindle afferents in the rat. J. Physiol. 338: 99-111

Jankowska, E.; Padel, Y., and Tanaka, R. (1975) Projections of pyramidal tract cells to alpha motoneurons innervating hindlimb muscles in the monkey. J. Physiol. (Lond.) 249: 637-667

Jankowska, E., and Roberts, W. J. (1972) An electrophysiological demonstration of the axonal projections of single spinal interneurones in the cat. J. Physiol. 222: 597-622

Jensen, T. S., and Smith, D. F. (1982) Dopaminergic effects on tail-flick response in spinal rats. Europ. J. Pharmacol. 79: 129-133

Jensen, T. S., and Yaksh, T. L. (1984) Effects of an intrathecal dopamine agonist, apomorphine, on thermal and chemical evoked noxious responses in rats. Brain Res. 296: 285-293

Johannessen, J. N.; Watkins, L. R., and Mayer, D. J. (1984) Non-serotonergic origins of the dorsolateral funiculus in the rat ventral medulla. J. Neuroscience 4: 757-766

Johansson, O.; Hökfelt, T.; Pernow, B.; Jeffcoate, S. L.; White, N.; Steinbusch, H. W. M.; Verhofstad, A. A. J.; Emson, P. C., and Spindel, E. (1981) Immunohistochemical support for three putative transmitters in one neuron: coexistence of 5-hydroxytryptamine, substance P- and thyrotropin releasing hormone-like immunoreactivity in medullary neurons projecting to the spinal cord. Neuroscience 6: 1857-1881

Johnston, J. B. (1923) Further contributions to the study of the evolution of the forebrain. J. Comp. Neurol. 35: 337-481

Jones, B. E., and Beaudet, A. (1987) Distribution of acetylcholine and catecholamine neurons in the cat brainstem: A choline acetyltransferase and tyrosine hydroxylase immunohistochemical study. J. Comp. Neurol. 261: 15-32

Jones, B. E., and Friedman, L. (1983) Atlas of catecholamine perikarya, varicosities and pathways in the brainstem of the cat. J. Comp. Neurol. 215: 382-396

Jones, B. E., and Yang, T. -Z (1985) The efferent

projections from the reticular formation and the locus coeruleus studied by anterograde and retrograde axonal transport in the rat. J. Comp. Neurol. 242: 56-92

Jones, S. L., and Gebhart, G. F. (1987) Spinal pathways mediating tonic, coeruleospinal, and raphe-spinal descending inhibition in the rat. J. Neurophysiol. 58: 138-159

Joseph, M. P.; Guinan, J. J. jr.; Fullerton, B. C.; Norris, B. E., and Kiang, N. Y. S. (1985) Number and distribution of stapedius motoneurons in cats. J. Comp. Neurol. 232: 43-54

Jürgens, U., and Pratt, R. (1979) The cingular vocalization pathway in the squirrel monkey. Exp. Brain Res. 34: 499-510

Kaada, B. (1972) Stimulation and regional ablation of the amygdaloid complex with reference to functional representation. In: B.E. Eleftheriou (Ed.): The Neurobiology of the Amygdala. Plenum Press New York. pp.145-204

Kalia, M. (1981) Brain stem localization of vagal preganglionic neurons. J. Autonomic Nerv. Syst. 3: 451-481

Kalia, M., and Mesulam, M. M. (1980a) Brain stem projections of sensory and motor components of the vagus complex in the cat: II. laryngeal, tracheobronchial, pulmonary, cardiac and gastrointestinal branches. J. Comp. Neurol. 193: 467-508

Kalia, M., and Mesulam, M. M. (1980b) Brain stem projections of sensory and motor components of the vagus complex in the cat: I. The cervical vagus and nodose ganglion. J. Comp. Neurol. 193: 435-465

Keller, J. T.; Saunders, M. C.; Ongkiko, C. M.; Johnson, J.; Frank, E.; Van Loveren, H., and Tew, J. M. jr. (1983) Identification of motoneurons innervating the tensor tympani and tensor veli palatini muscles in the cat. Brain Res. 270: 209-215

van Keulen, L. C. M. (1979) Axon trajectories of Renshaw cells in the lumbar spinal cord of the cat as reconstructed after intracellular staining with horseradish peroxidase. Brain Res. 167: 157-163

Kidokoro, Y.; Kubota, K.; Shuto, S., and Sumino, R. (1968) Possible interneurons responsible for reflex inhibition of motoneurons of jaw-closing muscles from the inferior dental nerve. J. Neurophysiol. 31: 709-716

Kimura, H.; McGeer, P. L.; Peng, J. H., and McGeer, E. G. (1981) The central cholinergic system studied by choline acetyltransferase immunohistochemistry in the cat. J. Comp. Neurol. 200: 151-201

Klein, B. G., and Rhoades, R. W. (1985) Representation of Whisker follicle intrinsic musculature in the facial motor nucleus of the rat. J. Comp. Neurol. 232: 55-69

Kneisley, L. W.; Biber, M. P., and LaVail, J. H. (1978) A study of the origin of brain stem projections to monkey spinal cord using retrograde transport method. Exp. Neurol. 60: 116-139

Köhler, C.; Haglund, L., and Swanson, L. W. (1984) A diffuse aMSH-immunoreactive projection to the hippocampus and spinal cord from individual neurons in the lateral hypothalamic area and zona incerta. J. Comp. Neurol. 223: 501-514

Kojima, M.; Takeuchi, Y.; Goto, M., and Sano, Y. (1982) Immunohistochemical study on the distribution of serotonin fibers in the spinal cord of the dog. Cell Tissue Res. 226: 477-491

Kojima, M.; Takeuchi, Y.; Goto, M., and Sano, Y. (1983a) Immunohistochemical study on the localization of serotonin fibers and terminals in the spinal cord of the monkey (Macaca fuscata). Cell Tissue Res. 229: 23-36

Kojima, M.; Takeuchi, Y.; Kawata, M., and Sano, Y. (1983b) Motoneurons innervating the cremaster muscle of the rat are characteristically densely innervated by serotonergic fibers as revealed by combined immunohistochemistry and retrograde fluorescence DAPI-labeling. Anat. Embryol. 168: 41-49

Komiyama, M.; Shibata, H., and Suzuki, T. (1984) Somatotopic representation of facial muscles within the facial nucleus of the mouse. Brain Behav. Evol. 24: 144-151

Kow, L. -M; Montgomery, M. O., and Pfaff, D. W. (1977) Effects of spinal cord transections on lordosis reflex in female rats. Brain Res. 123: 75-88

Krettek, J. E., and Price, J. L. (1978) A description of the amygdaloid complex in the rat and cat with observations on intra-amygdaloid axonal connections. J. Comp. Neurol. 178: 225-280

Krnjévic, K., and Schwartz, S. (1966) Is gamma-aminobutyric acid an inhibitory transmitter? Nature 211: 1372-1374

Krogh, J. E., and Denslow, J. S. (1979) The cutaneus trunci muscle in spinal reflexes. Electromyogr. clin. neurophysiol. 19: 157-164

Krogh, J. E., and Towns, L. C. (1984) Location of the cutaneus trunci motor nucleus in the dog. Brain Res. 295: 217-225

Kugelberg, E. (1952) Facial reflexes. Brain 75: 385-396

Kume, M.; Uemura, M.; Matsuda, K.; Matsushima, K., and Mizuno, N. (1978) Topographical representation of peripheral branches of the facial nerve within the facial nucleus: An HRP study in the cat. Neurosci. Lett. 8: 5-8

Kuo, D. S.; Yamasaki, D. S., and Krauthamer, G. M. (1980) Segmental organization of sympathetic preganglionic neurons of the splanchinc nerve as revealed by retrograde transport of horseradish peroxidase. Neurosci. Lett. 17: 11-17

Kuypers, H. G. J.M. (1958) An anatomical analysis of cortico-bulbar connections to the pons and lower brain stem in the cat. J. Anat. (Lond.) 92: 198-218

Kuypers, H. G. J.M. (1958) Corticobulbar connections to the pons and lower brain stem in man. An anatomical study. Brain 81: 364-388

Kuypers, H. G. J.M. (1958) Some projections from the peri-central cortex to the pons and lower brain stem in monkey and chimpanzee. J. Comp. Neurol. 110: 221-

255

Kuypers, H. G. J.M. (1964) The descending pathways to the spinal cord, their anatomy and function. Organization of the Spinal Cord (J.C. Eccles and J.P.Schadé, eds.) Elsevier Amsterdam, Progr. Brain Res. 11: 178-200

Kuypers, H. G. J.M. (1973) The anatomical organization of the descending pathways and their contributions to motor control especially in primates. New Developments in EMG and Clinical Neurophysiology 3: 38-68

Kuypers, H. G. J.M. (1981) Anatomy of the descending pathways. In: Handbook of Physiology, Section I, The Nervous System, Vol. II, Motor Systems (Ed. R.E. Burke) Washington American Physiological Society 597-666

Kuypers, H. G. J.M., and Brinkman, J. (1970) Precentral projections to different parts of the spinal intermediate zone in the rhesus monkey. Brain Res. 24: 29-48

Kuypers, H. G. J.M., and Lawrence, D. G. (1967) Cortical projections to the red nucleus and the brain stem in the rhesus monkey. Brain Res. 4: 151-188

Kuypers, H. G. J.M., and Maisky, V. A. (1975) Retrograde axonal transport of horseradish peroxidase from spinal cord to brain stem cell groups in the cat. Neurosci. Lett. 1: 9-14

Kuypers, H. G. J.M.; Fleming, W. R., and Farinholt, J. W. (1962) Subcorticospinal projections in the rhesus monkey. J. Comp. Neurol. 118: 107-137

Kuzuhara, S.; Kanazawa, I., and Nakanishi, T. (1980) Topographical localization of the Onuf's nuclear neurons innervating the rectal and vesical striated sphincter muscles: a retrograde fluorescent double labeling in cat and dog. Neurosci. Lett. 16: 125-130

Lai, Y. -Y, and Barnes, C. D. (1985) A spinal projection of serotonergic neurons of the locus coeruleus in the cat. Neurosci. Lett. 58: 159-164

Landgren, S.; Phillips, C. G., and Porter, R. (1962) Minimal synaptic actions of pyramidal impulses on some alpha motoneurons of the baboon's hand and forearm. J. Physiol. (Lond.) 161: 91-111

Lasek, R.; Joseph, B. S., and Whitlock, D. G. (1968) Evaluation of a radioautographic neuroanatomical tracing method. Brain Res. 8: 319-336

Lavail, J. H., and Lavail, M. M. (1972) Retrograde axonal transport in the central nervous system. Science 176: 1416-1417

Lawn, A. M. (1966) The nucleus ambiguus of the rabbit. J. Comp. Neurol. 127: 307-320

Lawrence, D. G., and Kuypers, H. G. J.M. (1968a) The functional organization of the motor system in the monkey. I. The effects of bilateral pyramidal lesions. Brain 91: 1-14

Lawrence, D. G., and Kuypers, H. G. J.M. (1968b) The functional organization of the motor system in the monkey II. The effects of lesions of the descending brainstem pathways. Brain 91: 15-36

Léger, L.; Charnay, Y.; Dubois, P. M., and Jouvet, M. (1986) Distribution of enkephalin-immunoreactive cell bodies in relation to serotonin-containing neurons in the raphe nuclei of the cat: immunohistochemical evidence for the coexistence of enkephalins and serotonin in certain cells. Brain Res. 362: 63-73

Leibowitz, S. F., and Brown, L. L. (1980) Histochemical and pharmacological analysis of noradrenergic projections to the paraventricular hypothalamus in relation to feeding stimulation. Brain Res. 201: 289-314

Light, A. R.; Casale, E. J., and Menetrey, D. M. (1986) The effects of focal stimulation in nucleus raphe magnus and periaqueductal gray on intracellularly recorded neurons in spinal laminae I and II. J. Neurophysiol. 56 no. 3: 555-571

Lindquist, C., and Martensson, A. (1970) Mechanisms involved in the cat's blink reflex. Acta Physiol. Scand. 80: 149-159

Lipski, J.; Kubin, L., and Jodkowski, J. (1983) Synaptic action of Rb neurons on phrenic motoneurons studied with spike-triggered averaging. Brain Res. 288: 105-118

Lipski, J., and Duffin, J. (1986) An electrophysiological investigation of propriospinal inspiratory neurons in the upper cervical cord of the cat. Exp. Brain Res. 61: 625-637

Lipski, J., and Martin-Body, R. L. (1987) Morphological properties of respiratory intercostal motoneurons in cats as revealed by intracellular injection of horseradish peroxidase. J. Comp. Neurol. 260: 423-434

Loewy, A. D., and Burton, H. (1978) Nuclei of the solitary tract: efferent projections to the lower brain stem and spinal cord of the cat. J. Comp. Neurol. 181: 421-450]

Loewy, A. D.; Saper, C. B., and Baker, R. P. (1979) Descending projections from the pontine micturition center. Brain Res. 172: 533-539

Loewy, A. D.; Saper, C. B., and Yamodis, N. D. (1978) Re-evaluation of the efferent projections of the Edinger-Westphal nucleus in the cat. Brain Res. 141: 153-159

Loewy, A. D.; Wallach, J. H., and McKellar, S. (1981) Efferent connections of the ventral medulla oblongata in the rat. Brain Res. Rev. 3: 63-80

Long, S., and Duffin, J. (1986) The neural determinants of respiratory rhythm. Progr. Neurobiol. 27: 101-182

Lorenz, R. G.; Saper, C. B.; Wong, D. L.; Ciaranello, R. D., and Loewy, A. D. (1985) Co-localization of substance P and phenylethanolamine-n-methyltransferase-like immunoreactivity in neurons of ventrolateral medulla that project to the spinal cord: potential role in control of vasomotor tone. Neurosci. Lett. 55: 255-260

Lovick, T. A. (1987) Differential control of cardiac and vasomotor activity by neurones in nucleus paragigantocellularis lateralis in the cat. J. Physiol. (Lond.) 389: 23-35

Lovick, T. A., and Robinson, J. P. (1983) Bulbar raphe neurones with projections to the trigeminal nucleus caudalis and the lumbar cord in the rat: A fluorescence double-labelling study. Exp. Brain Res. 50: 299-309

Lovick, T. A., and Wolstencroft, J. H. (1979) Inhibitory effects of nucleus raphe magnus on neuronal responses in the spinal trigeminal nucleus to nociceptive compared to non-nociceptive inputs. Pain 7: 135-145

Lumsden, T. (1923) Observations on the respiratory centres in the cat. J. Physiol. (London) 57: 153-160

Lundberg, A. (1975) Control of spinal mechanisms from the brain. In: The Nervous System. The Basic Neurosciences. (Ed. D.B. Tower). New York Raven. vol.I: 253-265

Luschei, E. S. (1987) Central projections of the mesencephalic nucleus of the fifth nerve: An autoradiographic study. J. Comp. Neurol. 263: 137-145

Lyon, M. J. (1975) Localization of the efferent neurons of the tensor tympani muscle of the newborn kitten using horseradish peroxidase. Exp. Neurol. 49: 439-455

Lyon, M. J. (1978) The central location of the motor neurons to the stapedius muscle in the cat. Brain Res. 143: 437-444

Mackel, R. (1979) Segmental and descending control of the external urethral and anal sphincters in the cat. J. Physiol. 294: 105-123

MacLean, P. D. (1952) Some psychiatric implications of physiological studies on frontotemporal portion of limbic system. EEG Clin. Neurophysiol. 4: 407-418

Mannen, T.; Iwata, M.; Toyokura, Y., and Nagashima, K. (1977) Preservation of a certain motoneurone group of the sacral cord in amyotrophic lateral sclerosis: its clinical significance. J. Neurol. Neurosurg. Psych. 40: 464-469

Mannen, T.; Iwata, M.; Toyokura, Y., and Nagashima, K. (1982) The Onuf's nucleus and the external anal sphincter muscles in amyotrophic lateral sclerosis and Shy-Drager Syndrome. Acta Neurophathol. 58: 255-260

Mantyh, P. W. (1983) Connections of midbrain periaqueductal gray in the monkey. II. Descending efferent projections. J. Neurophysiol. 49: 582-595

Mantyh, P. W., and Hunt, S. P. (1984) Evidence for cholecystokinin-like immunoreactive neurons in the rat medulla oblongata which project to the spinal cord. Brain Res. 291: 49-54

Martin, G. F.; Cabana, T., and Humbertson, A. O. Jr. (1981a) Evidence for collateral innervation of the cervical and lumbar enlargements of the spinal cord by single reticular and raphe neurons. Studies using fluorescent markers in double-labelling experiments on the North American opossum. Neurosci. Lett. 24: 1-6

Martin, G. F.; Cabana, T.; Humbertson, A. O. Jr.; Laxson, L. C., and Panneton, W. M. (1981b) Spinal projections from the medullary reticular formation of the North American Opossum: Evidence for connectional heterogeneity. J. Comp. Neurol. 196: 663-682

Martin, G. F., and Dom, R. (1970) Rubrobulbar projections of the opossum (Didelphis virginiana). J. Comp. Neurol. 139: 199-214

Martin, G. F.; Dom, R.; Katz, S., and King, J. S. (1974) The organization of projection neurons in the opossum red nucleus. Brain Res. 78: 17-34

Martin, G. F.; Holstege, G., and Mehler, W. R. (1990) The reticular formation of the pons and medulla. In; The Human Nervous System (Ed. G. Paxinos) Academic Press in press:

Martin, G. F.; Humbertson, A. O. Jr.; Laxson, C., and Panneton, W. M. (1979a) Evidence for direct bulbospinal projections to laminae IX, X and the intermediolateral cell column. Studies using axonal transport techniques in the North American opossum. Brain Res. 170: 165-171

Martin, G. F.; Humbertson, A. O. Jr.; Laxson, C., and Panneton, W. M. (1979b) Dorsolateral pontospinal systems. Possible routes for catecholamine modulation of nociception. Brain Res. 163: 333-339

Martin, G. F.; Humbertson, A. O. Jr.; Laxson, L. C.; Panneton, W. M., and Tschismadia, I. (1979c) Spinal projections from the mesencephalic and pontine reticular formation in the north american opossum: A study using axonal transport techniques. J. Comp. Neurol. 187: 373-401

Martin, G. F.; Vertes, R. P., and Waltzer, R. (1985) Spinal projections of the gigantocellular reticular formation in the rat. Evidence for projections from different areas to laminae I and II and lamina IX. Exp. Brain Res. 58: 154-162

Martin, J. H., and Ghez, C. (1988) Red nucleus and motor cortex: parallel motor systems for the initiation and control of skilled movement. Behav. Brain Res. 28: 217-223

Massion, J. (1988) Red nucleus: past and future. Behav. Brain Res. 28: 1-8

Matsushita, M., and Ueyama, T. (1973) Ventral motor nucleus of the cervical enlargement in some mammals; its specific afferents from the lower cord levels and cytoarchitecture. J. Comp. Neurol. 150: 33-52

McCabe, J. T.; deBellis, M., and Leibowitz, S. F. (1984) Clonidine-induced feeding: Analysis of central sites of action and fiber projections mediating this response. Brain Res. 309: 85-104

McCall, R. B., and Aghajanian, G. K. (1979) Serotonergic facilitation of facial motoneuron excitation. Brain Res. 169: 11-29

McCormick, D. A.; Lavond, D. G., and Thompson, R. F. (1982) Concomitant classical conditioning of the rabbit nictitating membrane and eyelid responses: correlations and implications. Physiol. and Behav. 28: 769-775

McCue, M. P., and Guinan Jr., J. J. (1988) Anatomical and functional segreration in the stapedius motoneuron pool of the cat. J. Neurophysiol. 60: 1160-1180

McCurdy, M. L.; Hansma, D. I.; Houk, J. C., and Gibson, A. R. (1987) Selective projections from the cat red nucleus to digit motor neurons. J. Comp. Neurol. 265: 367-379

McKenna, K. E., and Nadelhaft, I. (1986) The organiza-

tion of the pudendal nerve in the male and female rat. J. Comp. Neurol. 248: 532-549

Meessen, H., and Olszewski, J. (1949) A Cytoarchitectonic Atlas of the Rhombencephalon of the Rabbit. S. Karger, Basel New York

Mehler, W. (1969) Some neurological species differences - A posteriori. Ann. N.Y. Acad. Sci. 167: 424-468

Meyerson, B. A. (1988) Problems and controversies in PVG and sensory thalamic stimulation as treatment for pain. In: "Nociception control" (H.L. Fields and J.M. Besson Eds.) Elsevier Amsterdam Progr. Brain Res. 77: 175-188

Mendell, L. M., and Henneman, E. (1971) Terminals of single Ia fibers: location, density, and distribution within a pool of 300 homonymous motoneurons. J. Neurophysiol. 34: 171-187

Merrill, E. G. (1974) Finding a respiratory function for the medullary respiratory neurons. In: Essays on the Nervous System (Eds. R. Bellairs and E.G. Gray) Clarendon, Oxford 451-486

Merrill, E. G. (1970) The lateral respiratory neurones of the medulla: their associations with nucleus ambiguus, nucleus retroambigualis, the spinal accessory nucleus and the spinal cord. Brain Res. 24: 11-28

Merrill, E. G., and Fedorko, L. (1984) Monosynaptic inhibition of phrenic motoneurons: A long descending projection from Bötzinger neurons. Neuroscience 4 no. 9: 2350-2353

Merrill, E. G., and Lipski, J. (1987) Inputs to intercostal motoneurons from ventrolateral medullary respiratory neurons in the cat. J. Neurophysiol. 57 no. 4: 1837-1853

Merrill, E. G.; Lipski, J.; Kubin, L., and Fedorko, L. (1983) Origin of expiratory inhibition of nucleus tractus solitarius inspiratory neurones. Brain Res. 263: 43-51

Mesulam, M. (1978) Tetramethyl benzidine for horseradish peroxidase neurohistochemistry: a non-carcinogenic blue reaction-product with superior sensitivity for visualizing neural afferents and efferents. J. Histochem. and Cytochem. 26: 106-117

Miller, A. J. (1972) Characteristics of the swallowing reflex induced by peripheral nerve and brain stem stimulation. Exp. Neurol. 34: 210-222

Miller, A. D. (1987) Localization of motoneurons innervating individual abdominal muscles of the cat. J. Comp. Neurol. 256: 600-606

Miller, A. D.; Tan, L. K., and Suzuki, I. (1987) Control of abdominal and expiratory intercostal muscle activity during vomiting: role of ventral respiratory group expiratory neurons. J. Neurophysiol. 57: 1854-1866

Miller, R. A., and Strominger, N. L. (1973) Efferent connections of the red nucleus in the brainstem and spinal cord of the rhesus monkey. J. Comp. Neurol. 152: 327-346

Millhorn, D. E.; Hökfelt, T.; Seroogy, K., and Verhofstad, A. A. J. (1988) Extent of colocalization of serotonin and GABA in neurons of the ventral medulla onblongata in rat. Brain Res. 461: 169-174

Miyazaki, T.; Yoshida, Y.; Hirano, M.; Shin, T., and Kanaseki, T. (1981) Central location of the motoneurons supplying the thyrohyoid and the geniohyoid muscles as demonstrated by horseradish peroxidase method. Brain Res. 219: 423-427

Mizuno, N.; Konishi, A., and Sato, M. (1975) Localization of masticatory motoneurons in the cat and rat by means of retrograde axonal transport of horseradish peroxidase. J. Comp. Neurol. 164: 105-116

Mizuno, N.; Nomura, S.; Konishi, A.; Uemura-Sumi, M.; Takahashi, O.; Yasui, Y.; Takada, M., and Matsushima, R. (1982) Localization of motoneurons innervating the tensor tympani muscles: an horseradish peroxidase study in the guinea pig and cat. Neurosci. Lett. 31: 205-208

Mizuno, N.; Yasui, Y.; Nomura, S.; Itoh, K.; Konishi, A.; Takada, M., and Kudo, M. (1983) A light and electron microscopic study of premotor neurons for the trigeminal motor nucleus. J. Comp. Neurol. 215: 290-299

Mizuno, N.; Takahashi, O.; Satoda, T., and Matsushima, R. (1985) Amygdalospinal projections in the macaque monkey. Neurosci. Lett. 53: 327-330

Modianos, D. and Pfaff, D.W. (1979) Medullary reticular formation lesions and lordosis reflex in female rats. Brain Res. 171: 334-338

Molenaar, I. (1978) The distribution of propriospinal neurons projecting to different motoneuronal cell groups in the cat's brachial cord. Brain Res. 158: 203-206

Molenaar, I., and Kuypers, H. G. J.M. (1978) Cells of origin of propriospinal, ascending supraspinal and medullospinal fibers. A HRP study in cat and Rhesus monkey. Brain Res. 152: 429-450

Molenaar, I.; Rustioni, A., and Kuypers, H. G. J.M. (1974) The location of cells of origin of the fibers in the ventral and the lateral funiculus of the cat's lumbosacral cord. Brain Res. 78: 239-254

Moon Edley, S., and Graybiel, A. M. (1983) The afferent and efferent connections of the feline nucleus tegmenti pedunculopontine, pars compacta. J. Comp. Neurol. 217: 187-216

Morgan, C.; De Groat, W. C., and Nadelhaft, I. (1986) The spinal distribution of sympathetic preganglionic and visceral primary afferent neurons that send axons into the hypogastric nerves of the cat. J. Comp. Neurol. 243: 23-40

Morgan, C.; Nadelhaft, I., and De Groat, W. C. (1979) Location of bladder preganglionic neurons within the sacral parasympathetic nucleus of the cat. Neurosci. Lett. 14: 189-195

Mraovitch, S.; Kumada, M., and Reis, D. J. (1982) Role of the nucleus parabrachialis in cardiovascular regulation in cat. Brain Res. 232: 57-75

Murray, H. M., and Gurule, M. E. (1979) Origin of the rubrospinal tract of the rat. Neurosci. Lett. 14: 19-25

Nadelhaft, I.; De Groat, W. C., and Morgan, C. (1980)

Location and morphology of parasympathetic preganglionic neurons in the sacral spinal cord of the cat revealed by retrograde axonal transport of horseradish peroxidase. J. Comp. Neurol. 193: 265-281

Nakano, K.; Tokushige, A.; Hasegawa, Y., and Kohno, M. (1986) An autoradiographic study of the spinofacial projection in the monkey. Brain Res. 372: 338-344

Nathan, P. W., and Smith, M. C. (1958) The centrifugal pathway for micturition within the spinal cord. J. Neurol. Neurosurg. Psychiat. 21: 177-189

Nathan, P. W., and Smith, M. C. (1982) The rubrospinal and central tegmental tracts in man. Brain 105: 223-269

Nauta, W. J. H. (1958) Hippocampal projections and related neural pathways to the mid-Brain in the cat. Brain 80: 319-341

Nauta, W. J. H., and Domesick, V. B. (1981) Ramifications of the limbic system. In: S. Matthysse (ed): Psychiatry and the Biology of the Human Brain: A Symposium Dedicated to Seymour S. Kety. Amsterdam: Elsevier North Holland, Inc., pp.165-188

Neafsy, E. J.; Hurley-Gius, K. M., and Arvanitis, D. (1986) The topographical organization of neurons in the rat medial frontal, insular and olfactory cortex projecting to the solitary nucleus, olfactory bulb, periaqueductal gray and superior colliculus. Brain Res. 377: 261-270

Newsom Davis, J. (1970) An experimental study of hiccup. Brain 93: 851-872

Newsom Davis, J., and Plum, F. (1972) Separation of descending spinal pathways to respiratory motoneurons. Exp. Neurol. 34: 78-94

Nicoll, R. A. (1988) The coupling of neurotransmitter receptors to ion channels in the brain. Science 241: 545-551

Nieoullon, A., and Rispal-Padel, L. (1976) Somatotopic localization in cat motor cortex. Brain Res. 105: 405-422

Nieuwenhuys, R. (1985) Chemoarchitecture of the brain. Springer, Berlin, Heidelberg New York, Tokyo, 246 p.

Nieuwenhuys, R.; Geeraedts, L. M. G., and Veening, J. (1982) The medial forebrain bundle of the rat. I. General introduction. J. Comp. Neurol. 206: 49-81

Nieuwenhuys, R.; Voogd, J., and Van Huijzen, C. (1988) The Human Central Nervous System. 3rd. revised edition, Springer, Berlin, Heidelberg New York, Tokyo, 437 p.

Nilaver, G.; Zimmerman, E. A.; Wilkins, J.; Michaels, J.; Hoffman, D., and Silverman, A. (1980) Magnocellular hypothalamic projections to the lower brain stem and spinal cord of the rat. Neuroendocrinology 30: 150-158

Ninane, V.; Gilmartin, J. J., and De Troyer, A. (1988) Changes in abdominal muscle length during breathing in supine dogs. Respir. Physiol. 73: 31-41

Nomura, S., and Mizuno, N. (1982) Central distribution of afferent and efferent components of the glossopharyngeal nerve: An HRP study in the cat. Brain Res. 236: 1-13

Nomura, S., and Mizuno, N. (1981) Central distribution of afferent and efferent components of the chorda tympani in the cat as revealed by horseradish peroxidase. Brain Res. 214: 229-237

Nosaka, S.; Yamamoto, T., and Yasunaga, K. (1979) Localization of vagal cardioinhibitory preganglionic neurons within rat brain stem. J. Comp. Neurol. 186: 79-93

Nyberg-Hansen, R. (1965) Sites and mode of termination of reticulo-spinal fibers in the cat. An experimental study with silver impregnation methods. J. Comp. Neurol. 124: 71-100

Nyberg-Hansen, R. (1964a) The location and termination of tectospinal fibers in the cat. Exp. Neurol. 9: 212-227

Nyberg-Hansen, R. (1964b) Origin and termination of fibers from the vestibular nuclei and descending in the Medial Longitudinal Fasciculus. An experimental study with silver impregnation methods in the cat. J. Comp. Neurol. 122: 355-367

Nyberg-Hansen, R., and Brodal, A. (1964) Sites and mode of termination of rubrospinal fibres in the cat. J. Anat. Lond. 98: 235-253

Nyberg-Hansen, R., and Mascitti, T. A. (1964) Sites and mode of termination of fibres of the vestibulospinal tract in the cat. An experimental study with silver impregnation methods. J. Comp. Neurol. 122: 369-387

Nygren, L. G., and Olson, L. (1977) A new major projection from locus coeruleus: the main source of noradrenergic nerve terminals in the ventral and dorsal columns of the spinal cord. Brain Res. 132: 85-93

Oka, H. (1988) Functional organization of the parvocellular red nucleus in the cat. Behav. Brain Res. 28: 233-240

Olszewski, J. and Baxter, D.(1954) Cytoarchitecture of the Human Brain Stem, Switzerland, J.B. Lippincott Company

Onai, T., and Miura, M. (1986) Projections of supraspinal structures to the phrenic motor nucleus in cats studied by a horseradish peroxidase microinjection method. J. Auton. Nerv. Syst. 16: 61-77

Ongerboer de Visser, B. W., and Kuypers, H. G. J.M. (1978) Late blink reflex changes in lateral medullary lesions. Brain 101: 285-295

Onufrowicz, B. (1899) Notes on the arrangement and function of the cell groups in the sacral region of the spinal cord. J. Nerv. and Mental Diseases 26: 498-504

Otake, K.; Sasaki, H.; Ezure, K., and Manabe, M. (1988) Axonal projections from Bötzinger expiratory neurons to contralateral ventral and dorsal respiratory groups in the cat. Exp. Brain Res. 72: 167-177

Panneton, W. M., and Burton, H. (1981) Corneal and periocular representation within the trigeminal sen-

sory complex in the cat studied with transganglionic transport of horseradish peroxidase. J. Comp. Neurol. 199: 327-344

Panneton, W. M., and Martin, G. F. (1983) Brainstem projections to the facial nucleus of the opossum. Brain Res. 267: 19-33

Papez, J. W. (1927) Subdivisions of the facial nucleus. J. Comp. Neurol. 43: 159-191

Paxinos, G., and Watson, C. (1986) The Rat Brain in Stereotaxic Coordinates (Second Edition) Academic Press San Diego.

Pedersen, E. (1985) The anal reflex. In: Coloproctology and the Pelvic Floor Pathophysiology and Management (Eds. M.M. Henry and M. Schwash) 104-111

Pelletier, G.; Steinbusch, H. W. M., and Verhofstad, A. A. J. (1981) Immunoreactive substance P and serotonin present in the same dense core vesicles. Nature 293: 71-72

Peterson, B. W. (1979) Reticulospinal projections to spinal motor nuclei. Ann. Rev. Physiol. 41: 127-140

Peterson, B. W. (1980) Participation of pontomedullary reticular neurons in specific motor activity. In: J.A. Hobson and M.A.B. Brazier (Eds.), The Reticular Formation Revisited. Raven Press, New York. pp. 171-192

Peterson, B. W.; Fukushima, K.; Hirai, N.; Schor, R. H., and Wilson, V. J. (1984) Responses of vestibulospinal and reticulospinal neurons to sinusoidal vestibular stimulation. J. Neurophysiol. 43: 1236-1251

Peterson, B. W.; Pitts, N. G.; Fukushima, K., and Mackel, R. (1978) Reticulospinal excitation and inhibition of neck motoneurons. Exp. Brain Res. 32: 471-489

Peterson, B. W.; Pitts, N. G., and Fukushima, K. (1979) Reticulospinal connections with limb and axial motoneurons. Exp. Brain Res. 36: 1-20

Petras, J. M. (1967) Cortical, tectal and tegmental fiber connections in the spinal cord of the cat. Brain Res. 6: 275-324

Pfaff, D.W. (1980) Estrogens and brain function. Neuronal analysis of a hormone-controlled mammalian reproductive behavior. Springer-Verlag New York Heidelberg Berlin pp. 281

Pfaff, D. W., and Sakuma, Y. (1979a) Deficit in the lordosis reflex of female rats caused by lesions in the ventromedial nucleus of the hypothalamus. J. Physiol. 288: 203-211

Pfaff, D. W., and Sakuma, Y. (1979b) Facilitation fo the lordosis refles of female rats from the ventromedial nucleus of the hypothalamus. J. Physiol. 288: 189-203

Pfaller, K., and Arvidsson, J. (1988) Central distribution of trigeminal and upper cervical primary afferents in the rat studied by anterograde transport of horseradish peroxidase conjugated to wheat germ agglutinin. J. Comp. Neurol. 268: 91-108

Plecha, D. M.; Randall, W. C.; Geis, G. S., and Wurtser, R. D. (1988) Localization of vagal preganglionic somata controlling sinoatrial and atrioventricular nodes. Am. J. Physiol. 255: R703-708

Poeck, K. (1969) Pathophysiology of emotional disorders associated with brain damage. In: P.J. Vinken & G.W. Bruyn (eds.) Handbook of clinical neurology (Vol. 3) Amsterdam: North-Holland pp. 343-367

Pompeiano, O., and Brodal, A. (1957) Experimental demonstration of a somatotopical origin of rubrospinal fibers in the cat. J. Comp. Neurol. 108: 225-252

Price, J. L., and Amaral, D. G. (1981) An autoradiographic study of the projections of the central nucleus of the monkey amygdala. J. Neuroscience 1 no. 11: 1242-1259

Price, J. L.; Russchen, F. T., and Amaral, D. G. (1987) The limbic region. II: The amygdaloid complex. In: Handbook of Chemical Neuroanatomy. Björklund, A.,Hökfelt, T.,Swanson, L.W. (Eds.) Vol. 5. Integrated Systems of the CNS. Part I Hypothalamus, Hippocampus,Amygdala, Retina Elsevier Science Publishers, Amsterdam 279-388

Provis, J. (1977) The organization of the facial nucleus of the brush-tailed possum (Trichosurus vulpecula). J. Comp. Neurol. 172: 177-188

Pullen, A. H. (1988) Quantitative synaptology of feline motoneurones to external anal sphincter muscle. J. Comp. Neurol. 269: 414-424

Ralston, D. D., and Ralston, H. J. III (1985) The terminations of corticospinal tract axons in the macaque monkey. J. Comp. Neurol. 242: 325-337

Ralston, D. D.; Milroy, A. M., and Holstege, G. (1988) Ultrastructural evidence for direct monosynaptic rubrospinal connections to motoneurons in Macaca mulatta. Neurosci. Lett. 95: 102-106

Raphan, T., and Cohen, B. (1978) Brain stem mechanisms for rapid and slow eye movements. Annu. Rev. Physiol. 40: 527-552

Rexed, B. (1952) The cytoarchitectonic organization of the spinal cord in the cat. J. Comp. Neurol. 96: 415-496

Rexed, B. (1954) A cytoarchitectonic atlas of the spinal cord in the cat. J. Comp. Neurol. 100: 297-380

Ricardo, J. A., and Koh, E. T. (1978) Anatomical evidence of direct projections from the nucleus of the solitary tract to the hypothalamus, amygdala, and other forebrain structures in the rat. Brain Res. 153: 1-26

Richmond, F. J. R., and Abrahams, V. C. (1975) Morphology and enzyme histochemistry of dorsal muscles of the cat neck. 1312-1321

Richmond, F. J. R.; Loeb, G. E., and Reesor, D. (1985a) Electromyographic activity in neck muscles during head movements in the alert, unrestrained cat. Soc. Neurosci. Abstr. 11: 83

Richmond, F. J. R.; MacGillis, D. R. R., and Scott, D. A. (1985b) Muscle-fiber compartmentalization in cat splenius muscles. J. Neurophysiol. 53: 868-885

Rikard-Bell, G. C.; Bystrzycka, E. K., and Nail, B. S. (1984) Brainstem projections to the phrenic nucleus: a HRP study in the cat. Brain Res. Bull. 12: 469-77

Rinn, W. E. (1984) The neurophysiology of facial expression: a review of the neurological and psychological mechanisms for producing facial expressions. Psychol. Bull. 95: 52-77

Robinson, D. A. (1972) Eye movements evoked by collicular stimulation in the alert monkey. Vision Res. 12: 1795-1808

Robinson, F. R.; Houk, J. C., and Gibson, A. R. (1987) Limb specific connections of the cat magnocellular red nucleus. J. Comp. Neurol. 257: 553-577

Romanes, G. J. (1951) The motor cell columns of the lumbo-sacral spinal cord of the cat. J. Comp. Neurol. 94: 313-363

Roppolo, J. R.; Nadelhaft, I., and de Groat, W. C. (1985) The organization of pudendal motoneurons and primary afferent projections in the spinal cord of the rhesus monkey revealed by horseradish peroxidase. J. Comp. Neurol. 234: 475-488

Rose, J.D. and Flynn, F.W. (1989) Lordosis can be elicited in chronically-decerebrate rats by combined lumbosacral and vagino-cervical stimulation. Soc. Neurosci. Abstr. 15: p. 1100

Rosenfield, M. E. and Moore, J.W. (1983) Red nucleus lesions disrupt the classically conditioned nictitating membrane response in rabbits. Behav. Brain Res. 10: 393-398

Ross, C. A.; Ruggiero, D. A.; Park, D. H.; Joh, T. H.; Sved, A. F.; Fernandez-Pardal, J.; Saavedra, J. M., and Reis, D. J. (1984) Tonic vasomotor control by the rostral ventrolateral medulla: effect of electrical or chemical stimulation of the area containing C1 adrenaline neurons on arterial pressure, heart rate and plasma catecholamines and vasopressin. J. Neurosci. 4: 474-494

Røste, G. K. (1989) Non-motoneurons in the facial and motor trigeminal nuclei projecting to the cerebellar flocculus in the cat. A fluorescent double-labelling and WGA-HRP study. Exp. Brain Res. 75: 295-305

Roucoux, A.; Guitton, D., and Crommelinck, M. (1980) Stimulation of the superior colliculus in the alert cat II. Eye and head movements evoked when the head is unrestrained. Exp. Brain Res. 39: 75-85

Roucoux, A.; Crommelinck, M.; Decostre, M. F., and Crémieux, J. (1985) Gaze shift related neck muscle activity in trained cats. Soc. Neurosci. Abstr. 11: 83

Rubin, E., and Purves, D. (1980) Segmental organization of sympathetic preganglionic neurons in the mammalian spinal cord. J. Comp. Neurol. 192: 163-175

Ruggiero, D. A.; Mraovitch, S.; Granata, A. R.; Anwar, M., and Reis, D. J. (1987) A role of insular cortex in cardiovascular function. J. Comp. Neurol. 257: 189-207

Russchen, F. T. (1982) Amygdalopetal projections in the cat: II. Subcortical afferent connections. A study with retrograde tracing techniques. J. Comp. Neurol. 207: 157-176

Rustioni, A.; Kuypers, H. G. J.M., and Holstege, G. (1971) Propriospinal projections from the ventral and lateral funiculi to the motoneurons in the lumbosacral cord of the cat. Brain Res. 34: 255-275

Saint-Cyr, J. A., and Courville, J. (1982) Descending projections to the inferior olive from the mesencephalon and superior colliculus in the cat. Exp. Brain Res. 45: 333-348

Sakuma, Y., and Pfaff, D. W. (1979a) Facilitation of female reproductive behavior from mesencephalic central gray in the rat. Am. J. Physiol. 237: R278-R284

Sakuma Y., and Pfaff, D. W. (1979b) Mesencephalic mechanisms for integration of female reproductive behavior in the rat. Am. J. Physiol. 237: R285-R290

Sandkuhler, J., and Gebhart, G. F. (1984) Characterization of inhibition of a spinal nociceptive reflex by stimulation medially and laterally in the midbrain and medulla in the pentobarbital-anesthetized rat. Brain Res. 305: 67-76

Sandrew, B. B.; Edwards, D. L.; Poletti, C. E., and Foote, W. E. (1986) Amygdalospinal Projections in the Cat. Brain Res. 373: 235-239

Saper, C. B., and Levisohn, D. (1983) Afferent connections of the median preoptic nucleus in the rat: Anatomical evidence for a cardiovascular integrative mechanism in the anteroventral third ventricular (AV3V) region. Brain Res. 288: 21-31

Saper, C. B.; Loewy, A. D.; Swanson, L. W., and Cowan, W. M. (1976) Direct hypothalamo-autonomic connections. Brain Res. 117: 305-312

Saper, C. B., and Loewy, A. D. (1980) Efferent connections of the parabrachial nucleus in the rat. Brain Res. 197: 291-317

Sato, M.; Mizuno, N., and Konishi, A. (1978) Localization of motoneurons innervating perineal muscles: a HRP study in cat. Brain Res. 140: 149-154

Satoda, T.; Takahashi, O.; Tashiro, T.; Matsushima, R.; Uemura-Sumi, M., and Mizuno, N. (1987) Representation of the main branches of the facial nerve within the facial nucleus of the Japanese monkey (Macaca fuscata). Neurosci. Lett. 78: 283-287

Sawchenko, P. E.; Gold, R. M., and Leibowitz, S. F. (1981) Evidence for vagal involvement in the eating elicited by adrenergic stimulation of the paraventricular nucleus. Brain Res. 225: 249-269

Sawchenko, P. E., and Swanson, L. W. (1982) Immunohistochemical identification of neurons in the paraventricular nucleus of the hypothalamus that project to the medulla or to the spinal cord in the rat. J. Comp. Neurol. 205: 260-272

Schmied, A.; Amalric, M.; Dormont, J. F.; Conde H., and Farin, D. (1988) Participation of the red nucleus in motor initiation: unit recording and cooling in cats. Behav. Brain Res. 28: 207-216

Schoen, J. H. R. (1964) Comparative aspects of the descending fibre systems in the spinal cord. In: Organization of the Spinal Cord, (J.C. Eccles and J.P. Schadé, eds.) Progr. Brain Res. 11: 203-222

Schomburg, E. D.; Meinck, H. -M, and Haustein, J. (1975) A fast propriospinal inhibitory pathway from forelimb afferents to motoneurones of hindlimb flexor digitorum longus. Neurosci. Lett. 1: 311-314

Schrøder, H. D. (1981) Onuf's nucleus X: A morphological study of a human spinal nucleus. Anat. Embryol. 162: 443-453

Schrøder, H. D. (1980) Organization of the motoneurons innervating the pelvic muscles of the rat. J. Comp. Neurol. 192: 567-587

Schwaber, J. S.; Knapp, B. S., and Higgins, G. (1980) The origin and extent of direct amygdala projections to the region of the dorsal motor nucleus of the vagus and the nucleus of the solitary tract. Neurosci. Lett. 20: 15-21

Sears, T. A.; Kirkwood, P. A., and Davies, J. G. McF. (1985) Cross-correlation analysis of connections between bulbospinal neurones and respiratory motoneurones. In: Neurogenesis of Central Respiratory Rhytm. (Eds. A.L. Bianchi and M. Denavit-Saubie) MTP Press Limited Lancaster. 216-222

Sessle, B. J.; Hu, J. W.; Dubner, R., and Lucier, G. E. (1981) Functional properties of neurons in cat trigeminal subnucleus caudalis (medullary dorsal horn) II: Modulation of responses to noxious and nonnoxious stimuli by periaqueductal gray, nucleus raphe magnus, cerebral cortex and afferent influences and effect of naloxone. J. Neurophysiol. 45: 193-207

Shahani, B. T., and Young, R. R. (1972) Human orbicularis oculi reflexes. Neurology (Minneap.) 22: 149-154

Shapovalov, A. I., and Karamyan, O. A. (1968) Short-latency interstitiospinal and rubrospinal synaptic influences on alpha-motoneurons. Bull. Eksp. Biol. Med. 66: 1297-1300

Shapovalov, A. I.; Karamyan, O. A.; Kurchavyi, G. G., and Repina, Z. A. (1971) Synaptic actions evoked from the red nucleus on the spinal alpha-motoneurons in the rhesus monkey. Brain Res. 32: 325-348

Shapovalov, A. I., and Kurchavyi, G. G. (1974) Effects of trans-membrane polarization and TEA injection on monosynaptic actions from motor cortex, red nucleus and group Ia afferents on lumbar motoneurons in the monkey. Brain Res. 82: 49-67

Shaw, M. D., and Baker, R. (1983) The locations of stapedius and tensor tympani motoneurons in the cat. J. Comp. Neurol. 216: 10-19

Sherrey, J. H., and Megirian, D. (1975) Analysis of the respiratory role of pharyngeal constrictor motoneurons in the cat. Exp. Neurol. 49: 839-851

Shigenaga, Y.; Chen, I. C.; Suemune, S.; Nishimori, T.; Nasution, I. D.; Yoshida, A.; Sato, H.; Okamoto, T.; Sera, M., and Hosoi, M. (1986) Oral and facial representation within the medullary and upper cervical dorsal horns in the cat. J. Comp. Neurol. 243: 388-408

Shigenaga, Y.; Yoshida, A.; Mitsuhiro, Y.; Doe, K., and Suemune, S. (1988) Morphology of single mesencephalic trigeminal neurons innervating periodontal ligament of the cat. Brain Res 448: 331-8

Shik, M. L. (1983) Action of the brain stem locomotor region on spinal stepping generators via propriospinal pathways. In Spinal Cord Reconstruction, C.C. Kao, R.P. Bunge, and P.J. Reier, eds. Raven Press, New York. pp. 421-434

Shik, M. L.; Severin, F. V., and Orlovski, G. N. (1966) Control of walking and running by means of electrical stimulation of the mid-brain. Biophysics 11: 756-765

Shohara, E., and Sakai, A. (1983) Localization of motoneurons innervating deep and superficial facial muscles in the rat: A horseradish peroxidase and electrophysiologic study. Exp. Neurol. 81: 14-33

Sica, A. L.; Cohen, M. I.; Connelly, D. F., and Zhang, H. (1984) Hypoglossal motoneuron responses to pulmonary and superior laryngeal afferent inputs. Respir. Physiol. 56: 339-357

Simon, O. R., and Schramm, L. P. (1983) Spinal superfusion of dopamine excites renal sympathetic nerve activity. Neuropharmacology 22: 287-293

Sirkin, D. W., and Feng, A. S. (1987) Autoradiographic study of descending pathways from the pontine reticular formation and the mesencephalic trigeminal nucleus in the rat. J. Comp. Neurol. 256: 483-93

Sirota, M. G., and Shik, M. L. (1973) The cat locomotion elicited through the electrode implanted in the midbrain. Sechenov Physiol. J. (Leningrad) 59: 1314-1321

Skagerberg, G.; Björklund, A.; Lindvall, O., and Schmidt, R. H. (1982) Origin and termination of the diencephalospinal dopamine system in the rat. Brain Res. Bull. 9: 237-244

Skagerberg, G., and Lindvall, O. (1985) Organization of diencephalic dopamine neurones projecting to the spinal cord in the rat. Brain Res. 342: 340-351

Smith, C. L., and Hollyday, M. (1983) The development and postnatal organization of motor nuclei in the rat thoracic spinal cord. J. Comp. Neurol. 220: 16-28

Spence, S. J., and Saint-Cyr, J. A. (1988) Comparative topography of projections from the mesodiencephalic junctions to the inferior olive, vestibular nuclei, and upper cervical cord in the cat. J. Comp. Neurol. 268: 357-374

Spencer, R. F.; Baker, R., and McCrea, R. A. (1980) Localization and morphology of cat retractor bulbi motoneurons. J. Neurophysiol. 43: 754-771

Sprague, J. M. (1948) A study of motor cell localization in the spinal cord of the rhesus monkey. Am. J. Anat. 82: 1-26

Steinbusch, H. W. M. (1981) Distribution of serotonin-immunoreactivity in the central nervous system of the rat: cell-bodies and terminals. Neuroscience 6 no. 4: 557-618

Sterling, P., and Kuypers, H. G. J.M. (1967) Anatomical organization of the brachial spinal cord of the cat. II. The motoneuron plexus. Brain Res. 4: 16-32

Sterling, P., and Kuypers, H. G. J.M. (1968) Anatomical organization of the brachial spinal cord of the cat. III.

The propriospinal connections. Brain Res. 7: 419-443

St. John, W. M.; Barltlett, Jr D.; Knuth, K. v., and Hwang, J-C (1981) Brain stem genesis of automatic ventilatory patterns independent of spinal mechanisms. J. Appl. Physiol. 51: 204-210

Stock, G.; Rupprecht, U.; Stumpf, H., and Schlör, K. H. (1981) Cardiovascular changes during arousal elicited by stimulation of amygdala, hypothalamus and locus coeruleus. J. Auton. Nerv. Syst. 3: 503-510

Strack, A. M.; Sawyer, W. B.; Marubio, L. M., and Loewy, A. D. (1988) Spinal origin of sympathetic preganglionic neurons in the rat. Brain Res. 455: 187-191

Strack, A. M.; Sawyer, W. B.; Hughes, J.H., Platt, K.B., and Loewy, A. D. (1989) A general pattern of CNS innervation of the sympathetic outflow demonstrated by transneuronal pseudorabies viral infections. Brain Res. 491: 156-162f

Strassman, A.; Mason, P.; Eckenstein, F.; Baughman, R. W., and Maciewicz, R. (1987) Choline acetyltransferase immunocytochemistry of Edinger-Westphal and ciliary ganglion afferent neurons in the cat. Brain Res. 423: 293-304

Stuart, D. G.; Kawamura, Y., and Hemingway, A. (1961) Activation and suppression of shivering during septal and hypothalamic stimulation. Exp. Neurol. 4: 485-506

Swanson, L. W. (1977) Immunohistochemical evidence for a neurophysin-containing autonomic pathway arising in the paraventricular nucleus of the hypothalamus. Brain Res. 128: 346-353

Swanson, L. W., and Kuypers, H. G. J.M. (1980) The paraventricular nucleus of the hypothalamus: cytoarchitectonic subdivisions and organization of projections to the pituitary, dorsal vagal complex, and spinal cord as demonstrated by retrograde fluorescence double labeling methods. J. Comp. Neurol. 194: 555-570

Swanson, L. W., and Sawchenko, P. E. (1983) Hypothalamic integration: Organization of the paraventricular and supraoptic nuclei. Ann. Rev. Neurosci. 6: 269-324

Taber-Pierce, E.; Lichtenstein, E., and Feldman, S. C. (1985) The somatostatin systems of the guinea-pig brainstem. Neuroscience 15: 215-235

Takeuchi, Y.; Nakano, K.; Uemura, M.; Matsuda, K.; Matsushima, R., and Mizuno, N. (1979) Mesencephalic and pontine afferent fiber system to the facial nucleus in the cat: a study using the horseradish peroxidase and silver impregnation techniques. Exp. Neurol. 66: 330-343

Tan, J., and Holstege, G. (1986) Anatomical evidence that the pontine lateral tegmental field projects to lamina I of the caudal spinal trigeminal nucleus and spinal cord and to the Edinger-Westphal nucleus in the cat. Neurosci. Lett. 64: 317-322

Tashiro, N.; Tanaka, T.; Fukumoto, T.; Hirata, K., and Nakao, H. (1985) Emotional behavior and arrhytmias induced in cats by hypothalamic stimulation. Life Science 36: 1087-1094

Terreberry, R. R., and Neafsey, E. J. (1987) The rat medial frontal cortex projects directly to autonomic regions of the brainstem. Brain Res. Bull. 19: 639-649

Theriault, E., and Diamond, J. (1988a) Intrinsic organization of the rat cutaneus trunci motor nucleus. J. Neurophysiol. 60: 463-477

Theriault, E., and Diamond, J. (1988b) Nociceptive cutaneous stimuli evoke localized contractions in a skeletal muscle. J. Neurophysiol. 60: 446-462

Thompson, G. C.; Igarashi, M., and Stach, B. A. (1985) Identification of stapedius muscle motoneurons in squirrel monkey and bush baby. J. Comp. Neurol. 231: 270-279

Todd, J. K. (1964) Afferent impulses in the pudendal nerves of the cat. Q. J. Exp. Physiol. 49: 258-267

Tohyama, M.; Sakai, K.; Salvert, D.; Touret, M., and Jouvet, M. (1979) Spinal projections from the lower brain stem in the cat as demonstrated by the horseradish peroxidase technique. I. Origins of the reticulospinal tracts and their funicular trajectories. Brain Res. 173: 383-405

Toyoshima, K.; Kawana, E., and Sakai, H. (1980) On the neuronal origin of the afferents to the ciliary ganglion in cat. Brain Res. 185: 67-76

Tramonte, R., and Bauer, J. (1986) The location of the preganglionic neurons that innervate the submandibular gland of the cat. A horseradish peroxidase study. Brain Res. 375: 381-384

Travers, J. B., and Norgren, R. (1983) Afferent projections to the oral motor nuclei in the rat. J. Comp. Neurol. 220: 280-298

Tsukahara, N. (1981) Classical conditioning mediated by the red nucleus in the cat. J. Neurosci. 1: 72-79

Uemura, M.; Matsuda, K.; Kume, M.; Takeuchi, Y.; Matsushima, R., and Mizuno, N. (1979) Topographical arrangement of hypoglossal motoneurons: An HRP study in the cat. Neurosci. Lett. 13: 99-104

Ueyama, T.; Mizuno, N.; Nomura, S.; Konishi, A.; Itoh, K., and Arakawa, H. (1984) Central distribution of afferent and efferent components of the pudendal nerve in cat. J. Comp. Neurol. 222: 38-46

Ulfhake, B.; Arvidsson, U.; Cullheim, S.; Hokfelt, T.; Brodin, E.; Verhofstad, A., and Visser, T. (1987) An ultrastructural study of 5-hydroxytryptamine-, thyrotropin-releasing hormone- and substance P-immunoreactive axonal boutons in the motor nucleus of spinal cord segments L7-S1 in the adult cat. Neuroscience 23: 917-929

Van der Kooy, D.; Koda, L. Y.; McGinty, J. F.; Gerfen, C. R., and Bloom, F. E. (1984) The organization of projections from the cortex, amygdala, and hypothalamus to the nucleus of the solitary tract in rat. J. Comp. Neurol. 224: 1-24

VanderMaelen, C. P., and Aghajanian, G. K. (1982) Serotonin-induced depolarization of rat facial motoneurons in vivo: comparison with amino acid transmitters. Brain Res. 239: 139-152

de Vries, G. J., and Buijs, R. M. (1983) The origin of the vasopressinergic and oxytocinergic innervation of the rat with special reference to the lateral septum. Brain Res. 273: 307-317

Weaver, Fr C. (1980) Localization of parasympathetic preganglionic cell bodies innervating the pancreas within the vagal nucleus and nucleus ambiguus of the rat brain stem: evidence of dual innervation based on the retrograde axonal transport of horseradish peroxidase. J. Auton. Nerv. Syst. 2: 61-71

Wessendorf, M. W., and Elde, R. (1987) The coexistence of serotonin- and substance P-like immunoreactivity in the spinal cord of the rat as shown by immunofluorescent double labeling. J. Neuroscience 7: 2352-2363

Westlund, K. N., and Coulter, J. D. (1980) Descending projections of the locus coeruleus and subcoeruleus/medial parabrachial nuclei in monkey: axonal transport studies and dopamine-ß-hydroxylase immunocytochemistry. Brain Res. Rev. 2: 235-264

Westman, J. (1968) The lateral cervical nucleus in the cat. I. A Golgi study. Brain Res. 10: 352-368

White, S. R., and Neuman, R. S. (1980) Facilitation of spinal motoneurone excitability by 5-hydroxytryptamine and noradrenaline. Brain Res. 188: 119-127

Wiklund, L.; Léger, L., and Persson, M. (1981) Monoamine cell distribution in the cat brain stem. A fluorescence histochemical study with quantification of indolaminergic and locus coeruleus cell groups. J. Comp. Neurol. 203: 613-647

Willett, C. J.; Gwyn, D. G.; Rutherford, J. G., and Leslie, R. A. (1986) Cortical projections to the nucleus of the tractus solitarius: An HRP study in the cat. Brain Res. Bull. 16: 497-505

Willis, W. D. (1988) Anatomy and physiology of descending control of nociceptive resposes of dorsal horn neurons: comprehensive review. In: "Pain Modulation" (H.L. Fields and J.M. Besson Eds.) Elsevier Amsterdam Progr. Brain Res. 77: 1-29

Willis, W. D.; Haber, L. H., and Martin, R. F. (1977) Inhibition of spinothalamic tract cells and interneurons by brain stem stimulation in the monkey. J. Neurophysiol. 40: 968-982

Wilson, V. J., and Yoshida, M. (1969a) Comparison of effects of stimulation of Deiters' nucleus and medial longitudinal fasciculus on neck, forelimb, and hindlimb motoneurons. J. Neurophysiol. 32: 743-758

Wilson, V. J., and Yoshida, M. (1969b) Monosynaptic inhibition of neck motoneurons by the medial vestibular nucleus. Exp. Brain Res. 9: 365-380

Wilson, V. J.; Yoshida, M., and Schor, R. H. (1970) Supraspinal monosynaptic excitation and inhibition of thoracic back motoneurons. Exp. Brain Res. 11: 282-295

Yamada, H.; Ezure, K., and Manabe, M. (1988) Efferent projections of inspiratory neurons of the ventral respiratory group. A dual labeling study in the rat. Brain Res. 455: 283-294

Yeo, C. H.; Hardiman, M. J., and Glickstein, M. (1985a) Classical conditioning of the nictitating membrane response of the rabbit: I. Lesions of the cerebellar nuclei. Exp. Brain Res. 60: 87-98

Yeo, C. H.; Hardiman, M. J., and Glickstein, M. (1985b) Classical conditioning of the nictitating membrane response of the rabbit: III. Connections of cerebellar lobule HVI. Exp. Brain Res. 60: 114-126

Yeo, C. H.; Hardiman, M. J., and Glickstein, M. (1986) Classical conditioning of the nictitating membrane response of the rabbit: IV. Lesions of the inferior olive. Exp. Brain Res. 63: 81-92

Yoshida, M., and Tanaka, M. (1988) Existence of new dopaminergic terminal plexus in the rat spinal cord: assessment by immunohistochemistry using anti-dopamine serum. Neurosci. Lett. 94: 5-9

Yoshida, Y.; Miyazaki, O.; Hirano, M.; Shin, T.; Totoki, T., and Kanaseki, T. (1981) Localization of efferent neurons innervating the pharyngeal constrictor muscles and the cervical esophagus muscle in the cat by means of the horseradish peroxidase method. Neurosci. Lett. 22: 91-95

Zuk, A.; Rutherford, J. G., and Gwyn, D. G. (1983) Projections from the interstitial nucleus of Cajal to the inferior olive and to the spinal cord in cat: a retrograde fluorescent double-labeling study. Neurosci. Lett. 38: 95-103

H. Verantwoording

Dit proefschrift bevat niet één studie, maar is een overzichtsartikel over de bouw van het motorisch systeem. Het werd geschreven op NASA/Ames Research Center in de tweede helft van 1989 als laatste hoofdstuk van een in 1991 te verschijnen deel van Progress in Brain Research. Het schrijven van dit hoofdstuk werd mogelijk gemaakt door een verlenging van mijn NASA-grant. Dank is verschuldigd aan Bill Mehler, Peter Ralston, Joan Danellis en Cindy Bollens, die mij in deze periode met raad en daad hebben bijgestaan.

Een groot deel van de inhoud van dit hoofdstuk is gebaseerd op eigen werk, waaraan een groot aantal personen hebben meegewerkt, zoals hoogleraren, student-assistenten (zie de co-auteurs bij de verschillende artikelen) en technische medewerkers. Bij het noemen van de betrokkenen beperk ik mij tot die personen, die meer dan normale invloed hebben gehad bij het totstandkomen van de verschillende publikaties. In alfabetische volgorde zijn dat: Corrie Bijker-Biemond, Han Collewijn, Eddy Dalm, Mevr. Holstege-Jacobs, Edith Klink, Hans Kuypers en A.M. Vreugdenhil.

Corrie Bijker-Biemond heeft vooral gedurende het begin van de zeventiger jaren een enorme inspanning geleverd om de op dat moment nieuwe autoradiografische tracing techniek tot een goedlopende routine techniek te maken. Dit is wonderwel gelukt, vooral door Corrie's nauwgezette en langdurige inspanningen. Nooit zal ik de periode vergeten, waarin we met de dip- dan wel ontwikkelsessies om half vijf 's ochtends begonnen en om tien uur 's avonds eindigden. Het ging daarbij om 5 à 800 object-glazen. Zoals met zovele technieken waren we enige jaren later in staat zonder moeite 3 à 4000 glazen te verwerken tussen 9 uur 's ochtends en 6 uur 's avonds.

Han Collewijn heeft mij in het begin van de tachtiger jaren kunnen overtuigen dat de autoradiografische resultaten en mijn ideeën daarover zo slecht nog niet waren. Hij heeft daarmee een zeer belangrijke rol in mijn wetenschappelijke leven gespeeld.

Wanneer men in het buitenland een wetenschapper tegen kwam, die ooit op de afdeling neuroanatomie had vertoefd, was steevast de eerste vraag: "Hoe gaat het met Eddie". Dalm had met zijn kundigheid bij de operaties zoveel indruk op deze collega's gemaakt dat hij daardoor wereldwijde faam heeft verworven. Het had soms wel als nadeel dat het voor beginnende onderzoekers soms moeilijk was de operatietechnieken onder de knie te krijgen. Het proefdier was open en dicht voordat ze het goed en wel in de gaten hadden. Het succes van het urologische deel van het onderzoek is voor een groot deel gekomen door de enorme inspanningen van Eddie.
Last, but not least was Eddie Dalm in tijden van spanningen in staat zichzelf te blijven.

Mijn moeder, Mevr. Holstege-Jacobs, heeft in de periode dat mij slechts weinig technische hulp ter beschikking werd gesteld, geholpen door thuiswerk te verrichten in de vorm van het opslepen van vele duizenden coupes op objectglaasjes. Ze bestaan nog steeds en worden door vele verschillende wetenschappers bestudeerd.

Edith Klink heeft altijd klaar gestaan om bij het administratieve deel van het werk te helpen, ook als dat soms slecht uitkwam. Vooral dat laatste is belangrijk geweest.

Hans Kuypers, in de periode 1969-1984 hoofd van de afdeling neuro-anatomie in Rotterdam, heeft de meeste invloed op mijn wetenschappelijk denken gehad. De wijze waarop hij de resultaten altijd in het totale systeem wist te plaatsen was onnavolgbaar. Terecht heeft Kuypers daar wereldfaam mee verworven. Het is daarom bijzonder jammer dat hij niet in staat was "school te maken", omdat bijna alle medewerkers hun carrière in de kliniek wensten voort te zetten. Persoonlijk ben ik er trots op te behoren tot de Nauta-Kuypers school.

Mijn schoonvader, de heer A.M. Vreugdenhil, heeft ook vele jaren thuiswerk verricht. Dit "thuiswerk" (vele tienduizenden coupes) heeft enorm bijgedragen aan het uiteindelijke resultaat, omdat de vele experimenten anders histologisch niet verwerkt hadden kunnen worden en dat zou zeer vele publikaties hebben gescheeld.

Aan alle bovengenoemden bijzonder veel dank. Tenslotte wil ik mijn dank uitspreken aan Jan Voogd en Han Collewijn dat ik dit hoofdstuk als proefschrift heb kunnen indienen.

I. Curriculum Vitae

Geboortedatum en plaats
7 april, 1948; Warnsveld, Nederland

Persoonlijke omstandigheden
Gehuwd (10/4/'73) met Marianne G. Vreugdenhil. Kinderen: Henne, (geboren 14/11/'75); Floor (22/1/'77) en Gert Jan (25/5/'78).

Opleiding:
sept.'66-sept.'71
doctoraal examen Medische Faculteit Rotterdam

jan.'74-april '75
artsexamen Erasmus Universiteit Rotterdam

april 75-april '76
assistentschap neurochirurgie Academisch Ziekenhuis Dykzigt Rotterdam

Wetenschappelijke ervaring
jan. 1990- heden
Universitair Hoofddocent afd. Anatomie en Embryologie Rijksuniversiteit Groningen

juni 1987-jan. 1990
Visiting Associate Professor, Dept. Anatomy University of California San Francisco, School of Medicine

febr.1987-juni 1987
National Research Council (NRC) Associate, NASA/Ames Reseach Center Moffett Field CA.

jan. 1982-febr.1987
Wetenschappelijk hoofdmedewerker, Afdeling Anatomie, Erasmus Universiteit Rotterdam

apr. 1977-jan. 1982
Wetenschappelijk medewerker, Afdeling Anatomie, Erasmus Universiteit Rotterdam

sept. 1971-jan. 1974
FUNGO wetenschappelijk medewerker, Afdeling Anatomie, Erasmus Universiteit Rotterdam

Studiebeurzen en toelagen
Februari 1987
Senior fellowship of the National Research Council

1 juni 1987 tot 1 jan. 1990
NASA Grant (NCC 2-491) "The neuro-anatomical substrate of vomiting".

April 1989
Beurs van de National Science Foundation om een een top level neuroscience symposium "Role of the forebrain in sensation and behavior" te organiseren. Deze bijeenkomst werd gehouden in mei 1989 at NASA/Ames Research Center, ter ere van Dr. W.R. Mehler.
De "proceedings" zullen worden gepubliceerd als hoofdstukken in een deel van de serie Progress in Brain Research, (Elsevier Amsterdam)

Maart 1990
Alberta Heritage Scholarship Award. Deze award houdt in een tenure full professorship aan de Medical School te Edmonton Alberta Canada en ruim voldoende geld om een eigen laboratorium op te starten. Bij het schrijven van dit proefschrift was het nog niet zeker of deze award zal worden geaccepteerd.