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## Descending pathways from hypothalamus to dorsal motor vagus and ambiguous nuclei in the rat

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### Abstract

The anatomical pathways between the hypothalamus and cell groups of the lower medulla that are involved in the neural control of endocrine pancreas activity were investigated. As part of this control system the descending pathways originating from lateral, dorsomedial and ventromedial hypothalamic nuclei towards the dorsal motor vagus and ambiguous nuclei, were studied by retrograde transport of horseradish peroxidase. Very small injections of the tracer, by means of the iontophoretic delivery method, were placed in the dorsal motor vagus, ambiguous and solitary tract nucleus as well as in the various nuclei of the medullary reticular formation. Subsequent retrograde labeling was studied in the hypothalamus and the brainstem. The appearance of considerable retrograde labeling in mesencephalic periventricular grey and rostral mesencephalic reticular formation indicated a possible role for these structures as intermediates in an indirect hypothalamo-medullary control circuitry. This led us to extend the peroxidase injections to these mesencephalic areas after which the hypothalamus was investigated for retrograde labeling. All data combined indicated the existence of three descending pathways, direct and indirect, between hypothalamus and the parasympathetic motor nuclei of the lower medulla.

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## Introduction

There is a considerable amount of evidence that the central nervous system plays a crucial role in maintaining blood glucose levels within narrow limits in order to provide the living cell with a constant glucose concentration to meet its metabolic demands. It has become obvious that blood glucose homeostasis is achieved by sensitive mechanisms in the control of the release of hormones from the pancreatic islets of Langerhans.

Studies on the neural control of hormone release from the pancreas have been focused mainly on structures in the hypothalamus and the peripheral branches of the sympathetic and parasympathetic divisions of the autonomic nervous system. Several authors have reported dramatic effects on glucose, insulin and glucagon blood levels following experimental manipulation of the lateral (lh) and ventromedial (vmh) hypothalamic nuclei [5,13,19,37,39,40]. In summary, electrical or chemical stimulation of the lh elicits an insulin release from the pancreas, but does not change glucagon levels [19,37,39,40], whereas stimulation of the vmh leads to an increase of glucagon secretion and minor changes in insulin levels. Likewise it was reported that vagal nerve stimulation results in insulin secretion [4,6,20] and splanchnic nerve stimulation in glucagon release and suppression of insulin secretion [7,8]. The effect of blocking agents like atropin [20] or hexamethonium [39] further supports the theory that insulin and glucagon secretion are under control of parasympathetic and sympathetic autonomous components, respectively.

In the present study we have attempted to elucidate the structural nature of the pathways between hypothalamus and pancreas that form the anatomical substrate for the physiological processes described above. The study will be dealing with the anatomical structure of descending direct and indirect pathways originating from certain hypothalamic nuclei to the pancreas innervating centers in the medulla oblongata such as dorsal motor vagus (dmnX) and ambiguus (amb) nuclei [11,26]. As relevant to pancreatic endocrine secretion control from the hypothalamus, we have considered the vmh and lh for reasons described above. Furthermore we have included in this study descending efferents from the dorsomedial hypothalamic nucleus (dmh) since we found a considerable number of reciprocal relations between this nucleus and lh and vmh [27], which has been confirmed in part by more recent studies [21]. Furthermore, an increasing number of studies indicate a role for the dmh in the control of body weight and food intake [1,43]. As will become clear from the following description the investigations are mainly aimed at the possible parasympathetic component of the underlying physiological mechanisms.

The present investigation with the aid of retrograde transport of HRP showed that descending pathways to the lower medulla originating from lh, dmh and vmh could be divided into direct and indirect circuitry to the medulla. It was found that the dmnX and amb receive only minor direct connections from the hypothalamus, but that the hypothalamic efferents predominantly run via the parvocellular reticular formation (rpc) of the lower medulla. Also indirect connections were found between hypothalamus and medulla, that synaps within the mesencephalic central grey (sgc) and adjacent tegmentum before they terminate within the rpc. Those connections

also do not reach the dmX and amb directly but are mediated by the parvocellular reticular formation.

## Materials and Methods

As stated in the introductory section the present study consists of two parts, firstly, the descending hypothalamic and mesencephalic connections to the medulla oblongata and secondly, descending hypothalamic connections to intermediate mesencephalic structures as part of indirect descending pathways.

### *Experimental Group 1. Descending projections to the medulla oblongata*

As was described earlier [26], pancreas innervating cell groups were localized in the dmX and amb. Descending pathways to these motor nuclei and adjacent structures like the nucleus of the solitary tract (nst) and medullary reticular formation were investigated. To reveal the precise target of descending afferents from the hypothalamus to the medulla region, small micro-iontophoretic deposits of HRP were made through glass micropipettes in 60 male Wistar rats. This was done in such a way that most of the medullary structures mentioned above received the tracer. This method is believed to produce the smallest practicable HRP deposits with a minimal risk of tissue damage in order to minimize the labeling of passing fibers [16] (Fig. 1). Forty cases proved to give satisfactory results and were used in this study.

In all cases, animals weighing approximately 300 g were anaesthetized with ether and placed in a Kopf stereotaxic apparatus using the coordinates of Pellegrino et al. [31]. Beveled glass micropipettes with tip diameters from 10–15  $\mu\text{m}$  were filled with a 10% HRP (Sigma, type VI) in 0.01 M NaCl solution and so placed as to permit injection into a variety of medullary structures located between 5.0 and 7.0 mm posterior to interaural line coordinates according to De Groot [15] and Pellegrino et al. [31]. After positioning of the pipette, a positive current of 0.8–1.0  $\mu\text{A}$  was applied to the capillary by a constant current source (Midgard CS-3) for 20 min at a 7 s on/7 s off cycle to prevent polarization. After iontophoresis the pipette was maintained in its original position for at least 10 min, which prevents HRP leaking from the capillary tip during retraction. After a survival time of 24 h the animals were perfused transcardially under deep ether anaesthesia with 50 ml of a prerinse consisting of 0.8% NaCl, 0.4% sucrose and 0.4% D-glucose in 0.05 M phosphate buffer (pH 7.4) to which 10 IU heparine/ml was added. The prerinse was followed by 300 ml fixative solution consisting of 0.5% paraformaldehyde, 1.5% glutaraldehyde, 4.0% sucrose in phosphate buffer. The brains were removed and stored overnight in a 30% phosphate buffered sucrose solution at 4°C. After quick freezing in dry ice the tissue was sectioned at 40  $\mu\text{m}$  on a cryostat microtome and sections stained according to the benzidine · 2HCl procedure [12]. After mounting the sections with a chromalum gelatin solution, they were dried and counterstained with neutral red/safranin-O. Until examination the slides were stored at 4°C in the dark to prevent eventual fading of the HRP deposits. Every second section was examined and representative sections were plotted.

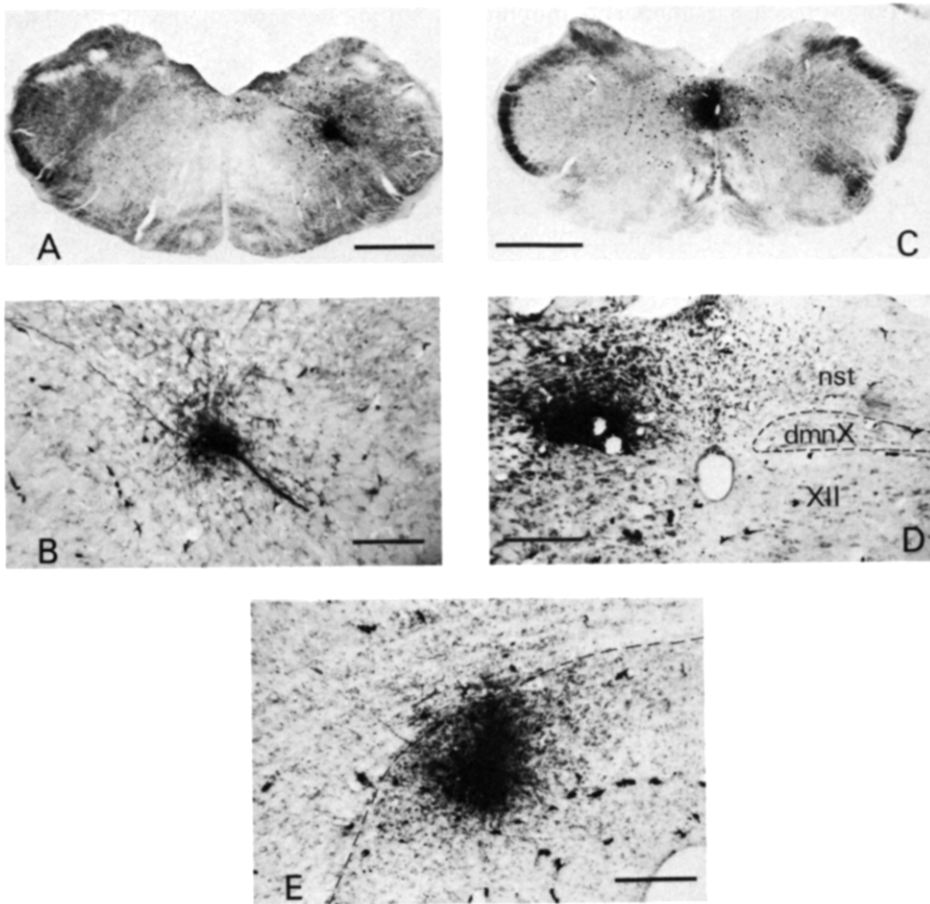


Fig. 1. A–E. Photomicrographs of iontophoretic injections of horseradish peroxidase in the various structures described in this study. All sections were tested for peroxidase according to the benzidine-di hydrochloride procedure of De Olmos and Heimer [12]. A, photomicrograph of an HRP injection in the parvocellular reticular formation of the lower medulla. Scale bar = 1 mm; B, the same tracer deposit as shown in Fig. 1A at higher magnification. Bar = 300  $\mu$ m; C, shows an injection spot of peroxidase in the dorsal motor nucleus of the vagal nerve. Scale bar = 1 mm; D, photomicrograph of an injection of tracer in the dorsal motor vagus nucleus (dmnX) on the left side of the brain. The open circle in the centre of the photograph represents the central canal. Bar = 200  $\mu$ m; E, photomicrograph of an injection of HRP in the dorsal aspects of the mesencephalic periaqueductal grey. The white area at the bottom right gives the position of the aqueduct. Scale bar = 250  $\mu$ m.

*Experimental Group 2. Descending projections to the periaqueductal central grey and adjacent tegmentum*

In the course of the study of projections from the hypothalamus the existence of an indirect hypothalamo-medullary circuit, especially from the vmh, became more and more obvious. For various reasons to be explained later, structures in the mesencephalic periaqueductal grey (sgc) and adjacent tegmentum appeared as

candidates for intermediary structures in such an indirect circuit. Thus we started a second group of experiments applying iontophoretic injections of tracer in the sgc and the surrounding tegmentum at the level of the oculomotor complex (Fig. 1). This experimental group consisted of 16 successful cases out of 20 experiments on 300 g male Wistar rats. The procedures followed were similar to those described for experimental group one. The animals survived 24 h and were fixed and treated histologically as described above. The brains were examined after being treated by the benzidine · 2HCl method [12] and representative sections documented.

## Results

### *Experimental Group 1. Descending projections to the medulla oblongata*

After analysis of the results of 40 microinjections in the medullary region, we were able to discriminate between three groups of experiments that revealed pathways related to hypothalamic descending connections. The first group consists of injections into the dmX and surrounding tissue including the nst; a second group of injections into the amb, and a third group of injections into the rpc situated just dorsal to the nucleus ambiguus. Each group of data will be described by a representative case.

### *Descending projections to the dmX (Fig. 2)*

It proved to be difficult, if not impossible, to produce HRP deposits confined to the dmX, due to the extremely narrow dorso-ventral limits of this nucleus. Determination of projections to a certain area, however, can be obtained by combining the results of adjacent injections covering a common structure.

In Fig. 2 a survey is given of retrograde labeling following an injection that covers the dmX but also a part of the adjacent nst. At the level of the injection, labeling occurred in the area postrema (ap), contralateral dmX, nst and nucleus raphe obscuris (ro). Labeling of the bilateral reticular formation was in most cases confined to somata in the rpc and in the vicinity of the nst. Ipsilaterally, some retrograde transport was observed to cells in the lateral reticular nucleus (rl) adjacent to the amb. More rostrally, at the level of the nucleus locus coeruleus (lc), bilateral labeling, although sparse, occurred in the dorsolateral nucleus of the periventricular grey and in the parabrachial nuclei (pb). At the mesencephalic level, predominantly ipsilateral labeling was observed in a circumscribed area of the sgc in its central aspects, apart from some HRP-positive somata in the dorsal raphe nucleus (rd). At the hypothalamic level, retrograde transport of HRP was found to medium-sized, multipolar cells in the more caudal parts of the lh mainly in its ventral and lateral aspects and in the corpus mammillare. More anterior in the hypothalamus, few cells became labeled in the dmh, arcuate nucleus (arc) and perifornical nucleus (pf). Most conspicuous was the strong labeling bilaterally of numerous cells in both parvo- and magnocellular parts of the paraventricular nucleus (pv). Furthermore, cells were found labeled in the anterior hypothalamus and in the central nucleus of the amygdaloid body (ac). It is worth mentioning that we never found any cellular labeling in the vmh after injections in the dmX area.

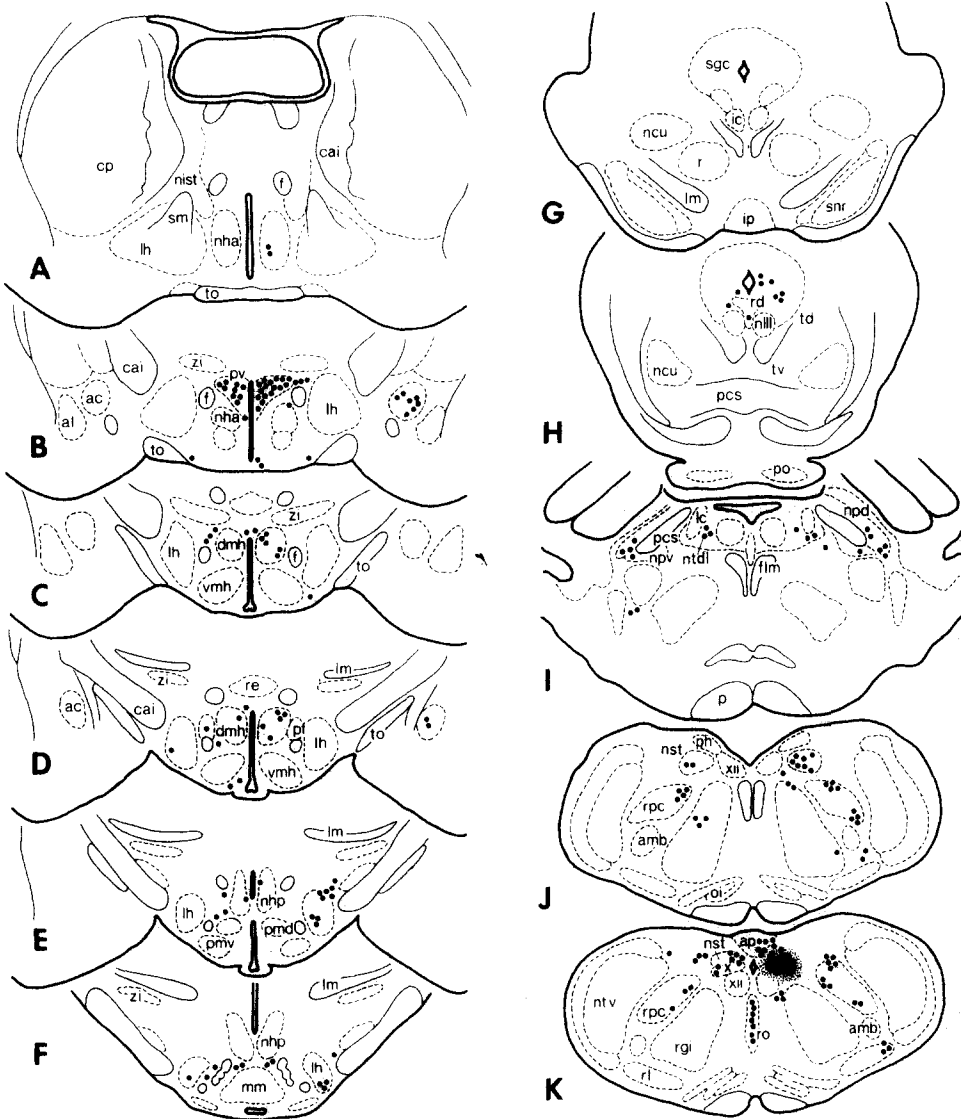


Fig. 2. Series of transverse sections from anterior (A) to posterior (K) showing the distribution of retrogradely labeled cells indicated by solid black dots following an HRP injection in the dorsal motor vagus nucleus. Abbreviations: aa, anterior amygdaloid nucleus; ac, central amygdaloid nucleus; amb, nucleus ambiguus; ap, area postrema; dmh, dorsomedial hypothalamic nucleus;  $h_2$ , Forell's field 'h<sub>2</sub>'; h<sub>1</sub>, lateral habenular nucleus; lc, locus coeruleus; lh, lateral hypothalamic area; ncu, cuneiform nucleus; nha, anterior hypothalamic nucleus; nhp, posterior hypothalamic nucleus; nist, interstitial nucleus of stria terminalis; npd, dorsal parabrachial nucleus; npl, lateral mammillary nucleus, pars posterior; npv, ventral parabrachial nucleus; nsc, suprachiasmatic nucleus; nst, solitary tract nucleus; ntd, dorsal tegmental nucleus, pars lateralis; pf, perifornical nucleus; pmd, dorsal premammillary nucleus; pmv, ventral premammillary nucleus; pv, paraventricular nucleus; rd, dorsal raphe nucleus; rgi, nucleus reticularis gigantocellularis; rl, lateral reticular nucleus; ro, nucleus raphe obscuris; rpc, nucleus reticularis parvocellularis; sd, dorsal septal nucleus; sgc, substantia grisea centralis; sl, lateral septal nucleus; snr, substantia nigra, pars reticulata; vmh, ventromedial hypothalamic nucleus; zi, zona incerta; X, dorsal motor vagus nucleus. Remaining abbreviations according to Palkovits and Jacobowitz [30].

*Descending projections to the nucleus ambiguus and surrounding tissue (Fig. 3)*

With regard to HRP injections confined to the region of the amb, the same problems occur as after dmnx injections. Because of the extremely limited size of the amb, that merely appears as a cluster of approximately 20 cells in transverse sections with a nucleus diameter of about 100  $\mu$ m, amb injections always impinge on some of the surrounding reticular formation. Combining the results of various injections that

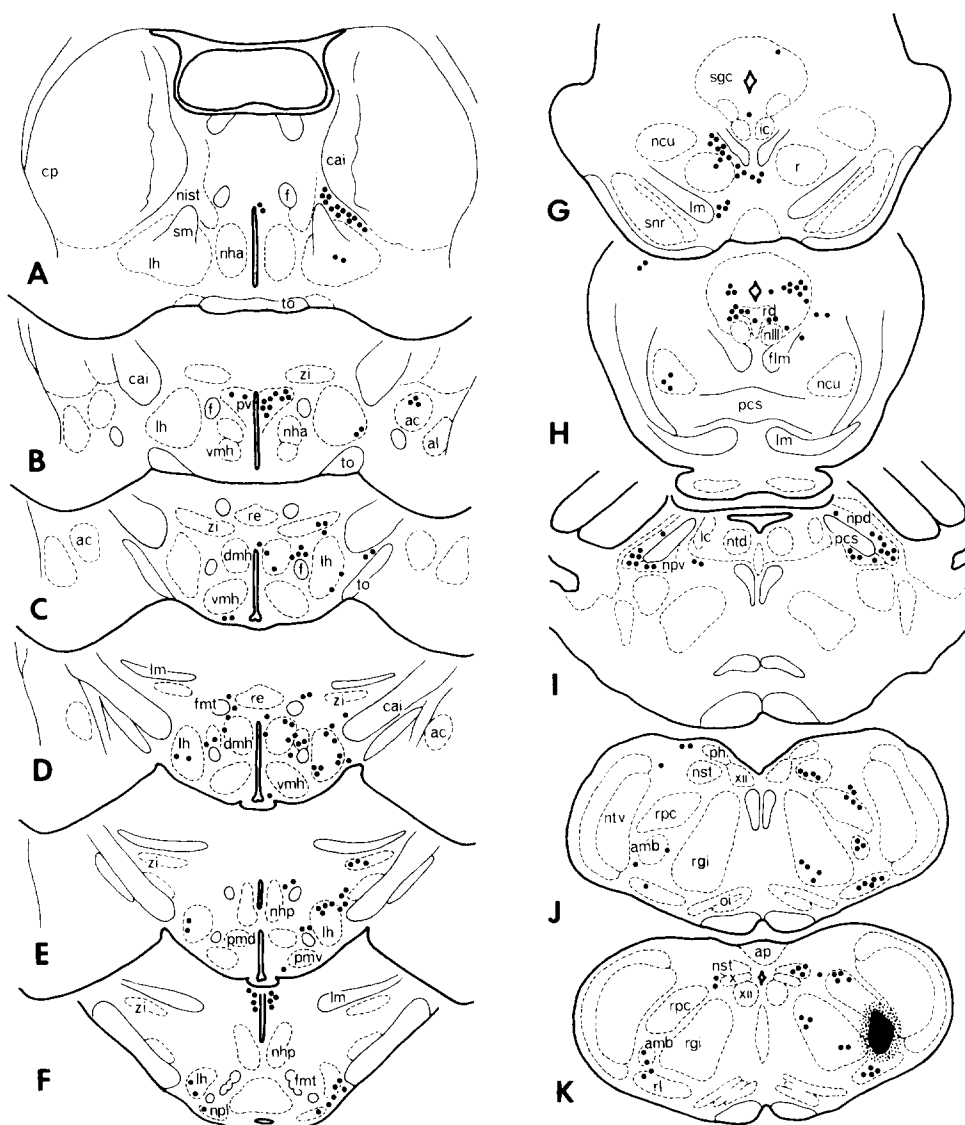


Fig. 3. Diagrammatic charting of transverse sections from anterior (A) to posterior (K) giving the distribution of HRP-positive somata resulting from an HRP injection in the nucleus ambiguus.

had the amb in common demonstrated the same phenomena as described for *dmnX* injections. The amb also is the recipient of information from only a minor proportion of hypothalamic cell populations. As will be outlined in the following description, most of the descending hypothalamic connections are directed towards the surrounding reticular formation rather than to the amb proper. In Fig. 3 the results are presented from an injection in the amb that also covered part of the adjacent *rpc*.

At the injection level, predominantly ipsilateral labeling occurred in the *nst*, *rpc*, gigantocellular (*rgi*) and lateral reticular (*rl*) nuclei, and some cells in the contralateral amb. This same type of labeling was observed throughout the longitudinal extent of the lower medulla. More rostrally, at the locus coeruleus level, HRP-positive somata appeared bilaterally in the dorsal (*npd*) and ventral (*npv*) (or lateral and medial, respectively) parabrachial nuclei. As was the case after *dmnX* injections, specific cell groups in the *sgc* at oculomotor levels became labeled. At this level also retrograde labeling occurred of contralateral deep superior collicular (*cs*) cells. Slightly more rostral we found a large group of tegmental cells that were HRP-positive lying between the nucleus ruber (*r*) and the fasciculus longitudinalis medialis (*flm*). In the hypothalamus, positively reacting somata were found in the peripheral aspects of the entire longitudinal extent of the *lh*, predominantly ipsilateral. Furthermore precipitates were observed in cells of the *dmh*, *pf*, retrochiasmatic area (*rca*), *arc* and zona incerta (*zi*) [9]. This labeling, however, as after *dmnX* injections was never very dense. At the anterior diencephalic pole we found a considerable amount of labeling in the *pv* although far less numerous than after *dmnX* injections. At the same transverse level some sparse labeling could be seen in the *ac*. More conspicuous was the labeling of a cell group in the ipsilateral bed nucleus of the stria terminalis (*nist*).

*Descending projections to the parvocellular nucleus of the medullary reticular formation (rpc) (Fig. 4)*

As was concluded from the labeling in the *rpc* after amb and *dmnX* injections, the *rpc* proved to be a major candidate for an intermediary structure between direct and indirect descending hypothalamic efferents and the parasympathetic motor nuclei of the lower medulla. Compared with HRP injections in other parts of the reticular formation, it was demonstrated that the *rpc* is the major, if not the only, recipient of descending pathways from the hypothalamic nuclei under study to the reticular formation. Furthermore, the hypothalamic retrograde labeling was always far more numerous and diverse after *rpc* injections than after injections in the *dmnX* or amb which will be exemplified by an injection as given in Fig. 4.

From posterior to anterior we observed HRP-positive somata, although never very numerous in the *nst* and *rl* bilaterally. On the same side of the injection, some transport occurred to somata in the *rgi* and to cells in the contralateral *rpc*. Continuing rostrally, abundant labeling appeared in the parabrachial nuclei bilaterally, apart from some scattered somata in the lateral medulla and some cells in the *lc*. At mesencephalic levels, a considerable amount of labeled cells appeared in various segments of the *sgc*, deep layers of the contralateral *cs*, cuneiform nucleus (*ncu*), lateral pool of the substantia nigra (*sn*) and in dorsal and ventral aspects of





At anterior hypothalamic levels, HRP deposits were detected in the ipsilateral nist.

In summary, the majority of lh descending connections are aimed at the rpc with a concentration of the projection at rpc levels adjacent to the ambiguous nucleus. Compared to the projections from vmh and dmh, the lh projection is relatively widespread. Lateral hypothalamic labeling also occurred after tracer injections in the

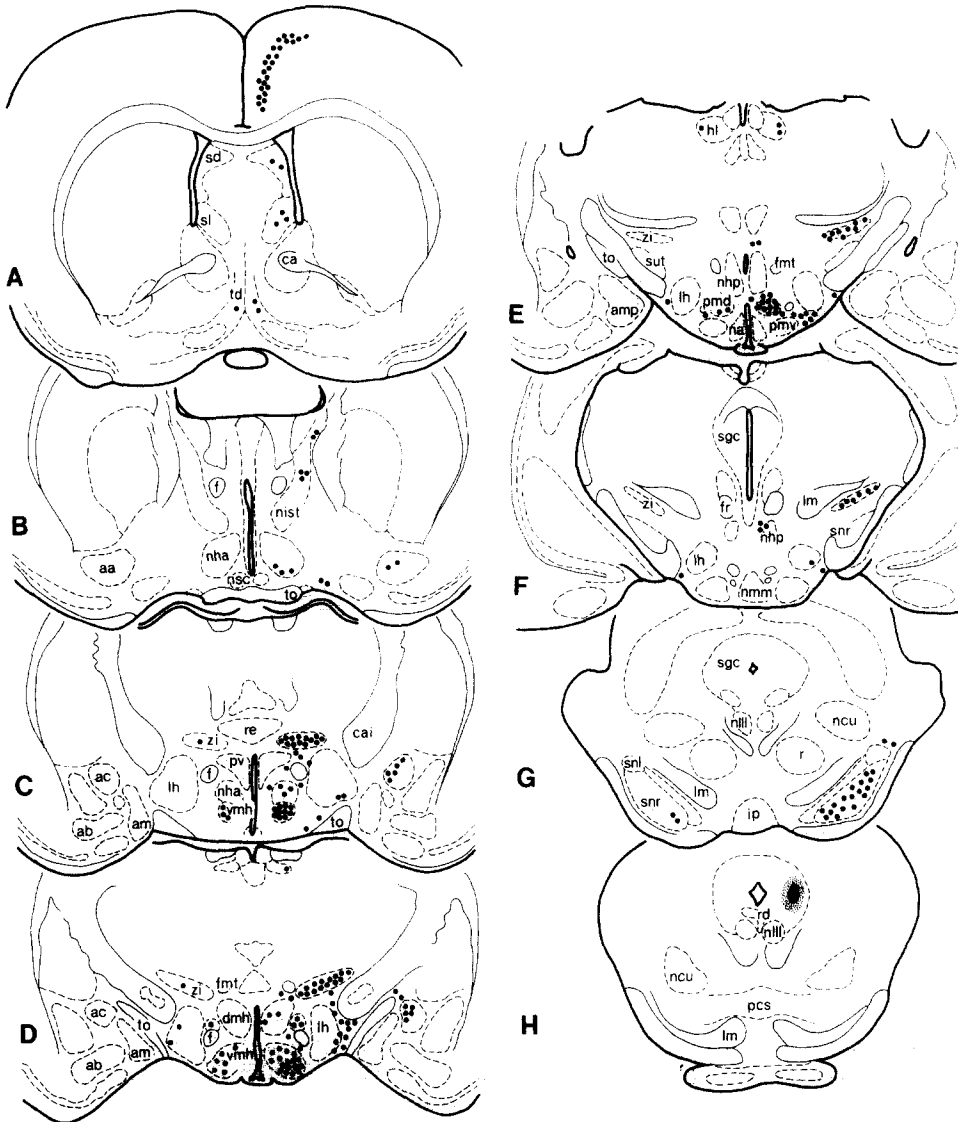


Fig. 5. Series of transverse sections from anterior (A) to posterior (H) indicating retrograde labeling with HRP following a tracer injection in the central aspects of the mesencephalic periventricular grey. Brain sections anterior to the injection site are shown to demonstrate descending connections.

rgi, nst, nucleus hypoglossus (XII), dmnX and the area surrounding the nst. A considerable portion of the lh projection appears to be contralateral.

It may be concluded from our HRP experiments that the medullary projection field of the vmh is far more restricted. The terminal field of the vmh projection is almost exclusively limited to the rpc with a minor projection to the nst. Although of minor importance, a small proportion of the vmh projection is of contralateral origin.

The direct projection of the dmh to the medulla is also very limited and aimed at the rpc and adjacent reticular tissue and at the nst and dmnX. The dmh projection consists in part of a contralateral component.

*Experimental Group 2. Descending projections to the periaqueductal grey and the adjacent mesencephalic tegmentum*

The results from the first group of experiments strongly suggested the possibility of a mesencephalic intermediary relay in descending hypothalamic pathways. After HRP injections in the lower medullary regions we consistently observed well circumscribed retrograde labeling in the sgc and several areas in the rostral reticular formation of the adjacent tegmentum. This led us to start a second series of HRP injections in these particular mesencephalic structures with special attention to the hypothalamic labeling resulting from such injections. The results of these experiments will be exemplified by two injections, one in the sgc and one in the mesencephalic reticular formation (Figs. 5 and 6).

*Descending projections to the periventricular grey (Fig. 5)*

At the level of the injection, labeled somata were detected in the pars reticulata of the substantia nigra (snr) predominantly on the ipsilateral side. More anterior at hypothalamic levels very strong and numerous labeling could be observed especially in the zi, dorsal premammillary nucleus (pmd) and vmh with strong emphasis on labeling ipsilateral to the injection site. Although far less numerous, HRP-positive somata were also present in dmh and lh and in the pf. Labeling in the lh was conspicuously limited to its ventral and lateral aspects. At the same transverse level, some retrograde labeling occurred in the ac. At more anterior levels, some HRP-positive cells were detected in the retrochiasmatic area, preoptic nuclei, nist, diagonal band of Broca and lateral nuclei of the septum (sl). Moreover, fairly large numbers of cells were observed in the medial aspects of the frontal cortex.

*Descending projections to the rostral mesencephalic reticular formation (Fig. 6)*

Injections in the ventral tegmentum adjacent to the sgc resulted in some striking differences as compared to the sgc injections. At mesencephalic levels, a number of HRP-positive cells occurred in the sn ipsilaterally and in deeper layers of the contralateral cs. At hypothalamic levels, labeled cells were recorded in the pmh, lh and zi. Dorsomedial and ventromedial hypothalamic nuclei, however, were almost completely devoid of labeled cells. Labeling in the lh was confined to its ventral and lateral subdivisions.

The hypothalamo-mesencephalic connections may be summarized as follows. The

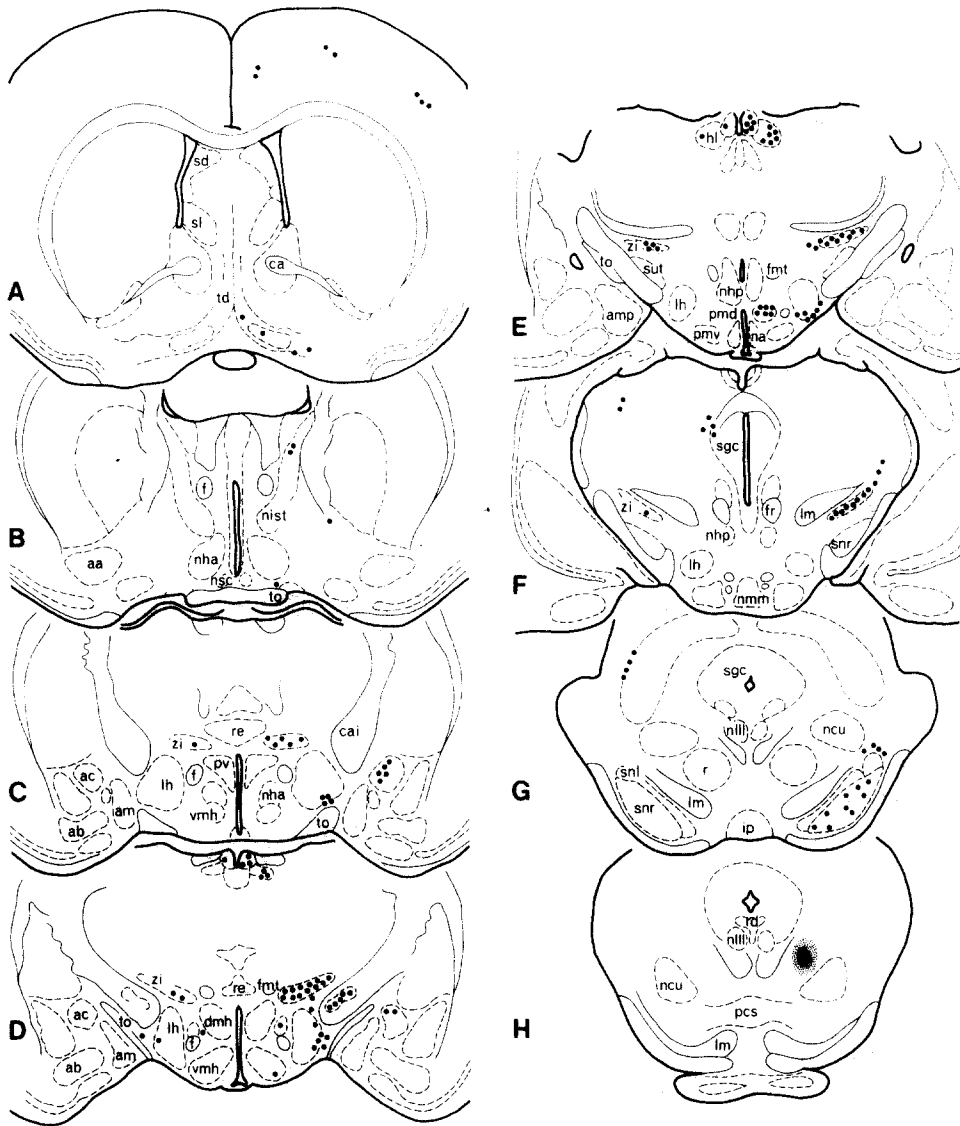


Fig. 6. Charting of transverse brain sections from anterior (A) to posterior (H) with HRP labeled cells resulting from an HRP deposit in the ventral tegmental area.

mesencephalic projection pattern of the lh is characterized by a rather diffusely organized projection to the more ventrolateral aspects of the sgc and a terminal field in the ventral tegmentum. Also dorsal tegmental fields just ventral to the cs are recipients of lh input. Only few of the descending lh connections to the sgc seem to originate from the contralateral lh. The mesencephalic projection of the vmh shows

some striking features. The projection is almost entirely aimed at the dorsal quadrant of the sgc with only some minor termination fields in the dorsal aspects of the tegmentum. Moreover, the vmh projection apparently is not only circumscribed but very dense as well. This vmh projection shows considerable contrast with the mesencephalic termination field of dmh. The dmh projection is rather limited and diffusely aimed at a dorsoventral column within the sgc.

## Discussion

In the present study we investigated the central connections between lateral, dorsomedial and ventromedial nuclei of the hypothalamus and cell groups in the lower brainstem that innervate the endocrine pancreas. These connections, presumed to be part of the anatomical substrate for the autonomic system control of hormone release from the endocrine pancreas, consist of one direct and two indirect circuits (Fig. 7).

The direct circuit is made up of fiber connections originating from cell groups in lh and dmh and projecting to the dmnX and amb. The two latter nuclei reportedly contain the preganglionic parasympathetic cell groups that innervate the endocrine pancreas  $\beta$ -cells [11,26]. The number of cells that may form the direct circuit is, however, rather limited. From the retrograde labeling of hypothalamic cells after dmnX and amb injections, respectively, it must be concluded that each of the parasympathetic medullary motor nuclei receive projections from partly different cell groups in lh and dmh. Apparently more extensive, but also more complex, are the indirect pathways between hypothalamus and medulla oblongata. One indirect pathway consists of efferent projections from lh, dmh and vmh, upon the rpc in the

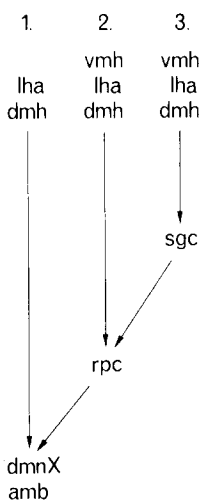


Fig. 7. Diagram with the 3 descending pathways between lateral, dorsomedial and ventromedial hypothalamic nuclei and the parasympathetic motor nuclei of the lower medulla as described in this paper.

lower medulla. The rpc on its turn was shown to maintain short projections to both dmnX and amb.

The second indirect circuit consists of hypothalamus projections to the mesencephalic sgc and ventral tegmentum, projections that appear to be very numerous for the vmh in particular. These mesencephalic structures give rise to projections upon the medullary rpc, although some of the mesencephalic efferents also seem to reach the dmnX and amb directly. From the rpc the mesencephalic projections can be relayed to the vagal and ambiguous motor cell groups.

In previous reports lh efferents projecting directly to the parasympathetic motor nuclei in the lower medulla have been described in autoradiographic material [17,33]. However, as a result of the large size of the tracer injections employed by these authors it proved to be difficult to localize specifically the cell groups in the lh that give rise to the descending medullary connections. Hypothalamus connections directly aimed at the dmnX have also been identified in retrograde transport studies [32]. These authors, however, describe the pv as the only hypothalamic locus of retrogradely labeled somata after dmnX injections of HRP, but do not describe labeling in other nuclei of the hypothalamus.

As part of the circuitry between hypothalamus and the dmnX/amb complex we described the projection from the rpc to the vagal and ambiguous motor nuclei. These rpc connections were also described by Rogers et al. [32], although these projections in our material appear to be more extensive. It was shown in our experiments that the ventrolateral aspect of the rpc is a source of afferents to the dmnX and amb, whereas the ventrolateral rpc also seems to be a major recipient of efferent connections from lh, dmh and vmh.

Hypothalamic projections to the lower medulla originating from lh, vmh and dmh have been reported before by various authors using retrograde transport techniques [23,38]. In all of these studies, however, the observed hypothalamic labeling was based on extremely large tracer injections in the lower medulla that did not permit a precise delineation of the terminal areas. On the other hand, several autoradiographic investigations of descending vmh and lh projections did not include brainstem levels posterior to the locus coeruleus in their analysis [22,34,35]. Saper et al. [33] and Hosoya and Matsushita [17], however, studied lh projections extending into the medulla oblongata and reported terminations in the rpc, which is compatible with our observations.

The existence of an indirect circuit between hypothalamus and medulla that relays in mesencephalic structures is supported by several previous investigations. Evidence for sgc and ventral tegmentum projections of vmh and lh is presented by autoradiographic studies [17,22,33–35] and has also been confirmed by retrograde transport experiments [14,29,36]. The midbrain sgc projections to the lower medulla have recently been described in detail for monkey [10,28] and show a considerable resemblance with our observations in rat.

### *Functional considerations*

Although we were able to identify various anatomical pathways between hypothalamus and the preganglionic parasympathetic cell groups of dmnX and amb,

their functional significance needs further elucidation.

As has been documented in the introductory section, the physiological effects in terms of hormone release from the pancreas after stimulation of the hypothalamic nuclei on the one hand and of vagus and splanchnic nerves on the other hand are well-known. Much less evidence is available on the functional role of structures between hypothalamus and the peripheral autonomic nervous system.

Recently it was demonstrated that electrical stimulation of the dmNX [18] and of the amb [3] result in markedly increased levels of plasma insulin. It appeared, however, that the sites of stimulation in the study of Bereiter et al. [3] on amb stimulation were not localized in the ambiguous nucleus but rather in the more dorsally situated rpc. These physiological findings strongly indicate that the rpc is an important relay structure in the brain circuitry involved in the control of the endocrine pancreas.

Such direct functional evidence is not yet available for the mesencephalic intermediary structures that were identified in this investigation. Lesion experiments performed at mesencephalic tegmental areas adjacent to the sgc are reported to result in changes of body weight and hyperphagia [2,24]. Although no data are available on changes in insulin levels after such lesions, it was shown that lesions in the vmh result in hyperphagia together with a simultaneous hyperinsulinemia [5]. These effects of vmh lesions in plasma insulin levels suggest the possibility of equal effects of mesencephalic tegmental lesions. It has to be taken into account, however, that the mesencephalic hyperphagia may be the result of damage to ascending rather than to descending fiber systems.

The present study revealed descending fiber systems specifically aimed at dmNX and amb and can therefore be regarded as parasympathetic pathways. Sympathetic control of the endocrine pancreas is relayed through preganglionic cell groups located in thoracic levels of the spinal cord [26]. The fiber systems projecting to these sympathetic areas are currently being studied with anterograde transport techniques.

It should be born in mind, however, that both dmNX and amb contain preganglionic neurons aimed at various target organs in the alimentary tract and viscera, which indicates a multimodal function for dmNX and amb. The presence of preganglionic cells in dmNX and amb aimed at pharyngeal [42], laryngeal [25] or cardiac muscle tissue [41] point at a role of vagus and ambiguous motor nuclei in the control of cardiovascular and alimentary motor functions. Consequently, the pathways described in the present paper cannot exclusively be related to the central control of the endocrine pancreas. Further experiments are needed to clarify in detail how the described circuitry is involved in the regulation of endocrine pancreatic functions.

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