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Arterial Baro- And Chemoreceptor Projections To The Amygdala In The Cat

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ARTERIAL BARO- AND CHEMORECEPTOR PROJECTIONS TO THE AMYGDALA IN THE CAT

by

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Department of Physiology

Submitted in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

Faculty of Graduate Studies

The University of Western Ontario

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A B S T R A C T

There is some preliminary evidence in the literature suggesting that cardiovascular afferent information projects to the amygdala. In the present study baro- and chemoreceptor input to the amygdala was investigated with electrophysiological experiments in chloralose-anesthetized cats and with the neuroanatomical tracing method of retrograde transport of horseradish peroxidase.

To test the possibility that afferent information from carotid sinus and aortic depressor nerves projects to the amygdala, spontaneously active units in the amygdala were monitored for changes in firing frequency during electrical stimulation of the buffer nerves. Stimulation of the carotid sinus and aortic depressor nerves altered the firing frequency of 30% (73/241) and 20% (50/251), respectively, of the units. The majority of the responsive units were located in the central and lateral nuclei of the amygdala.

The possibility of the existence of separate projections to the amygdala of baro- and chemoreceptors was tested by monitoring changes in the firing frequency of spontaneously discharging units during baroreceptor activation and chemoreceptor activation. Chemoreceptor and baroreceptor activation altered the firing frequency of 23% (35/154) and 16% (24/154), respectively, of the units. The units responsive to chemoreceptor activation were located primarily in the dorsomedial amygdala while those responsive to baroreceptor activation were located primarily in the ventrolateral amygdala.

To investigate afferent connections to nuclei of the amygdala that have been shown electrophysiologically to receive inputs from baro- and chemoreceptors, small discrete deposits of horseradish peroxidase

were placed in the central and lateral nuclei of the amygdala. Horseradish peroxidase deposits in the medial part of the central nucleus of the amygdala labelled neurons in the ipsilateral hypothalamus, primarily in the paraventricular and ventromedial nuclei. The parabrachial nucleus also was shown to project to the central nucleus. Horseradish peroxidase deposits in the lateral nucleus labelled few neurons in the ipsilateral hypothalamus.

To investigate the possibility that the parabrachial nucleus has a key role in receiving cardiovascular input and relaying this information to the forebrain and in turn sending control signals to cardiovascular effectors, spontaneously firing units in the parabrachial nuclei were monitored for changes in firing frequency during electrical stimulation of the carotid sinus and aortic depressor nerves, central nucleus of the amygdala and paraventricular nucleus of the hypothalamus. In the ipsilateral parabrachial nucleus 34% (64/189) and 24% (18/185), respectively, of the units responded to carotid sinus and aortic depressor nerve stimulation. Stimulation of the central nucleus of the amygdala and paraventricular nucleus of the hypothalamus antidromically and orthodromically activated units in the parabrachial nucleus, of which approximately half also responded to buffer nerve stimulation.

The possibility that both the paraventricular nucleus of the hypothalamus and the parabrachial nucleus relay cardiovascular information to the amygdala was tested by monitoring changes in firing frequency of amygdalar units to electrical stimulation of the paraventricular nucleus of the hypothalamus and parabrachial nucleus and then to baro- and chemoreceptor activation. Nineteen percent (27/140) of the units

responded to stimulation of the paraventricular nucleus of the hypothalamus, of which 33% also responded to chemoreceptor activation and none to baroreceptor activation. Thirty-one percent (46/150) of the units responded to stimulation of the parabrachial nucleus, of which 24% also responded to chemoreceptor activation and 4% responded to baroreceptor activation.

From these results a model is proposed indicating that cardiovascular information to the amygdala could be important in control of behavior such that chemoreceptor input to the dorsomedial amygdala is an important component of behavioral arousal while the baroreceptor input to the ventrolateral amygdala inhibits this system. In addition, this study has demonstrated that the parabrachial nucleus plays a key role in relaying cardiovascular information to the forebrain and in receiving converging descending forebrain information and ascending cardiovascular input. It is suggested that the parabrachial nucleus then sends an integrated signal to autonomic and respiratory effectors. Finally, both the paraventricular nucleus of the hypothalamus and the parabrachial nucleus were demonstrated to be likely sites of relay of cardiovascular afferent information from the medulla to the amygdala.

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I wish to thank Dr. G. J. Mogenson, in whose department this research was done, and the members of my advisory committee for their guidance and constructive criticisms.

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INTRODUCTION

The amygdala is known to be involved in a number of behavioral responses including the defence reaction, sleep, arousal, learning, feeding and sexual behaviors, territoriality, aggression and rage. These behavioral responses are associated with concomitant autonomic and respiratory responses (Kaada, 1972). For example, the autonomic and respiratory changes of the defence reaction elicited by stimulation of the dorsomedial amygdala include an increase in blood pressure and heart rate with vasoconstriction in the mesenteric and renal vascular beds, skeletal muscle vasodilation and hyperventilation (Hilton and Zbrozyna, 1963; Stock et al., 1978; Stock et al., 1981; Timms, 1981).

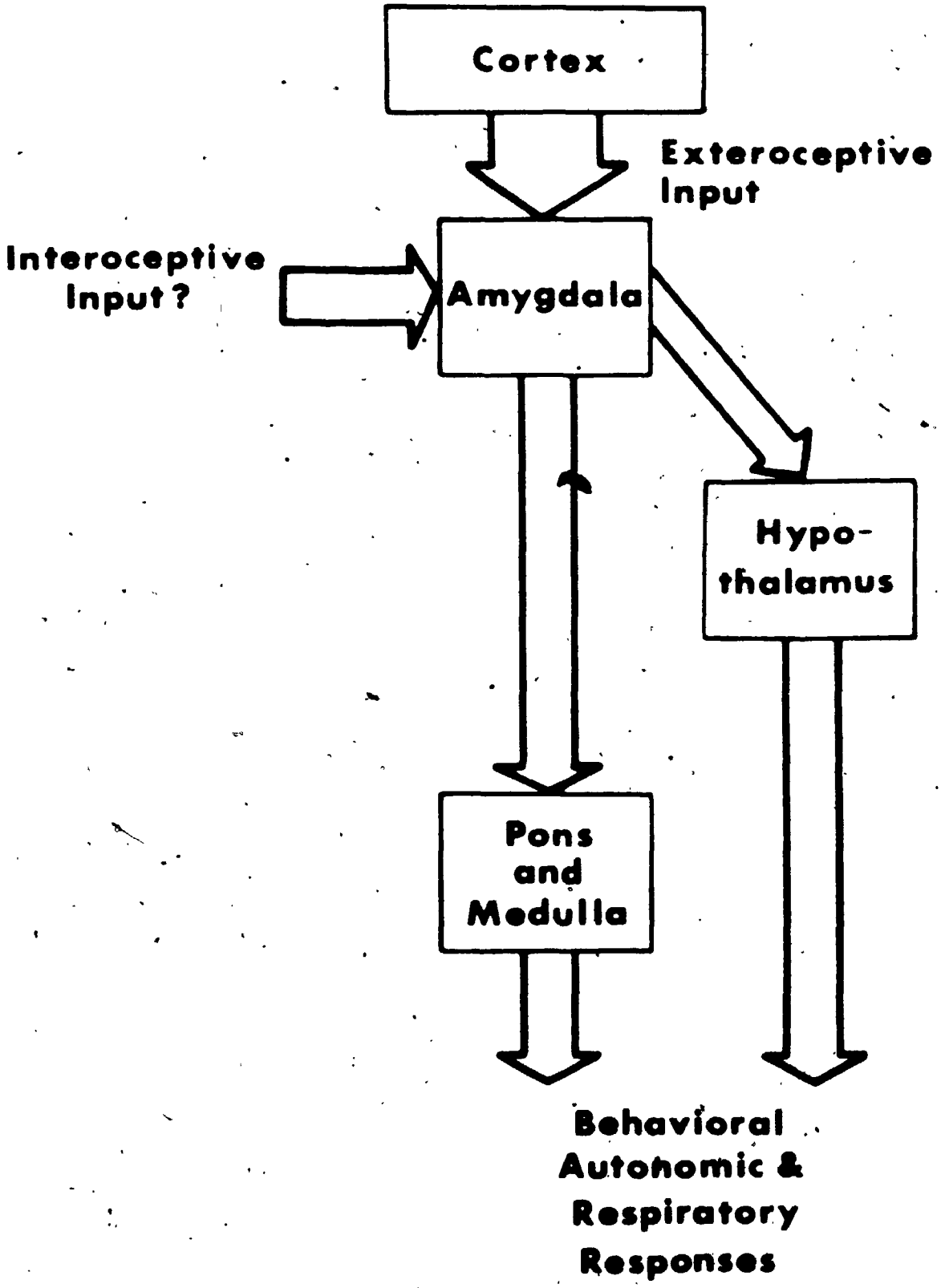
The classical view of the function of the amygdala is that it relays information from cortical to subcortical structures (Fonberg, 1968; Gloor, 1978; Fig. 1). It has been demonstrated both neuroanatomically and electrophysiologically that the amygdala receives a large input from the cerebral cortex, particularly the insular and temporal regions and that the amygdala is a major site of convergence of all exteroceptive sensory modalities (Femano, 1983; Gloor, 1960; Gloor, 1978; Goddard, 1972; Turner et al., 1980). Furthermore, the amygdala has extensive connections with structures in the basal telencephalon and hypothalamus which provide the anatomical substrate for the role of the amygdala as a modulator of functions governed by the hypothalamus (Eleftheriou, 1972; Kapp and Kesner, 1981). Although most of the early literature indicated that the vegetative responses

are mediated via direct ventral amygdalo-hypothalamic pathways, there was some evidence that pathways controlling respiratory and cardiovascular variables can also bypass the hypothalamus (Kaada, 1951; Gloor, 1960). Indeed it has been demonstrated more recently that the amygdala has direct projections to respiratory and cardiovascular control nuclei of the pons and medulla (Hopkins and Holstege, 1978; Takeuchi et al., 1982; Price and Amaral, 1981; Schwaber et al., 1980; Schwaber et al., 1982). Thus, the amygdala appears to integrate highly processed exteroceptive sensory information from the cortex to elicit the appropriate behavioral, autonomic and respiratory reactions from the hypothalamus or other subcortical structures in response to signals from the environment (Gloor, 1960; Gloor, 1978; Fig. 1).

Although there have been many investigations of exteroceptive projections to the amygdala, there are few studies demonstrating interoceptive inputs to the amygdala. The notion that interoceptive inputs may play a significant role in the function of this limbic structure has been suggested by the demonstration of vagal afferent projections to the amygdala (Dell and Olson, 1951; Radna and MacLean, 1981). In addition, there is some evidence indicating that cardiovascular afferent information in the carotid sinus nerve projects to the amygdala (Hockman et al., 1972; Hockman and Livingston, 1970). Thus, the amygdala may integrate multimodal exteroceptive inputs and information about the current status of blood pressure and blood gases before sending out the control signals which alter the cardiovascular system to produce the changes appropriate to the behavior. However there is no information on where in the amygdala the cardio-

FIGURE 1

Simplified diagram of descending control of the function of the amygdala. The amygdala integrates highly processed exteroceptive sensorty information from the cortex and in turn projects to the hypothalamus and other subcortical areas to elicit the appropriate behavioral, autonomic and respiratory reactions in response to signals from the external environment. It is not known whether interoceptive information projecting to the amygdala plays a significant role in its function.


Cortex
Exteroceptive Input
Interoceptive Input?
Amygdala
Hypo-thalamus
Pons and Medulla
Behavioral Autonomic & Respiratory Responses

vascular afferents project, what their function is, or the route taken from the medulla.

There is some evidence which suggests that cardiovascular inputs to the amygdala play an important role in the function of this limbic structure. First, it has been demonstrated that activation of baro- and chemoreceptors elicits behavioral and autonomic responses similar to those elicited by stimulation of the amygdala. Activation of chemoreceptors can elicit responses such as arousal, cortical desynchronization, defence and rage behaviors, increased blood pressure and heart rate, vasoconstriction in the mesenteric vasculature, skeletal muscle vasodilation and hyperventilation which are similar to those elicited by stimulation of the dorsomedial amygdala (Baccelli et al., 1965; Bizzi et al., 1961; Blanco et al., 1983 a & b; Bowes et al., 1981; Hilton, 1977; Hilton and Joels, 1965; Hugelin et al., 1959; Marshall, 1977; Marshall, 1981; Miller and Tenney, 1975). On the other hand, activation of baroreceptors elicits responses such as sleep, cortical synchronization, inhibition of defence and rage behaviors, decrease in blood pressure and heart rate, and hypoventilation which are similar to those elicited by stimulation of the ventrolateral amygdala (Baccelli et al., 1965; Bartorelli et al., 1960; Bonvallet et al., 1954; Brunner et al., 1982; Hilton, 1977; Koch, 1932; Marshall, 1981). Additional evidence has indicated that the amygdala may be necessary for the full expression of the responses to activation of baro- and chemoreceptors (Baccelli et al., 1965; Marshall, 1981; Timms, 1982).

A second reason for suggesting that cardiovascular inputs to

the amygdala may have an important role in its function is based on the results of experiments demonstrating that different behavioral states such as sleep, arousal, defence and fighting, in which the amygdala is known to have an important role, can modify cardiovascular reflexes (Conway et al., 1983; Folkow, 1979; Hilton, 1975; Smith et al., 1980; Smyth et al., 1969; Stock et al., 1983; Zanchetti, 1971). It has also been demonstrated that stimulation of the amygdala can modify baroreceptor reflexes (Gebber and Klevans, 1972; Stock et al., 1983). Thus, it is possible that baro- and chemoreceptor inputs are relayed to the amygdala and that the amygdala in turn affects reflex cardiovascular responses.

Neuroanatomical evidence has indicated some of the possible routes afferent cardiovascular information might follow to the amygdala. It is known that the primary site of termination of buffer nerves is in the nucleus of the solitary tract (Ciriello et al., 1981; Davies and Kalia, 1981). The route by which this cardiovascular input might project to regions of the brain rostral to the medulla was previously thought to be via a multisynaptic reticular relay system (Miura and Reis, 1969; Hockman et al., 1972). However, recent advances in neuroanatomical tracing methods such as the orthograde transport of labelled amino acids and retrograde transport of horseradish peroxidase have demonstrated more direct routes from the medulla to the amygdala. In the rat, but not in the cat and monkey, it has been shown that the nucleus of the solitary tract, the primary site of termination of baro- and chemoreceptors projects directly to the amygdala (Ricardo and Koh, 1978). The nucleus of the solitary tract also has direct projections in several species

to the hypothalamus and parabrachial nuclei, which in turn project directly to the amygdala (Loewy and Burton, 1978; Ottersen, 1981; Ricardo and Koh, 1978; Russchen, 1982; Saper and Loewy, 1980).

In summary, the amygdala is involved in many behaviors with concomitant autonomic and respiratory changes. The classical view of the function of the amygdala is that it receives multimodal exteroceptive inputs and in turn sends integrated signals to the hypothalamus and other subcortical areas to produce the appropriate behavioral, autonomic and respiratory responses. There is little evidence for interoceptive inputs to the amygdala, in particular cardiovascular information, although a review of the literature suggests that baro- and chemoreceptor inputs may have an important role in the function of the amygdala in control of behavioral and autonomic responses. Finally, it is not known what route is taken by the cardiovascular information to the amygdala. The purpose of the experiments to be described was to examine in detail cardiovascular afferent inputs to the amygdala, to determine where in the amygdala they project, what the function is and the possible relay sites. The results obtained in these experiments were used to suggest a model by which the cardiovascular input to the amygdala and the amygdala's connections with other subcortical structures function in control of autonomic and respiratory changes during the various behaviors in which the amygdala is involved.

HISTORICAL REVIEW

A. The Amygdala

1. Anatomy

The amygdala is a subcortical limbic structure located in the dorsomedial portion of the temporal lobes. Based on anatomical, ontogenetic and phylogenetic studies, the amygdala was originally divided into basolateral and corticomedial groups of nuclei (Holmgren, 1925; Johnston, 1923). In this division the lateral and medial and lateral basal nuclei were included in the basolateral component while the corticomedial portion included the cortical, medial and central nuclei. Later the central nucleus was subdivided into two parts: the anterior amygdaloid area and the central nucleus, resulting in the division of the amygdala into basolateral, corticomedial and anterior components (Fox, 1940; Gurdjian, 1928).

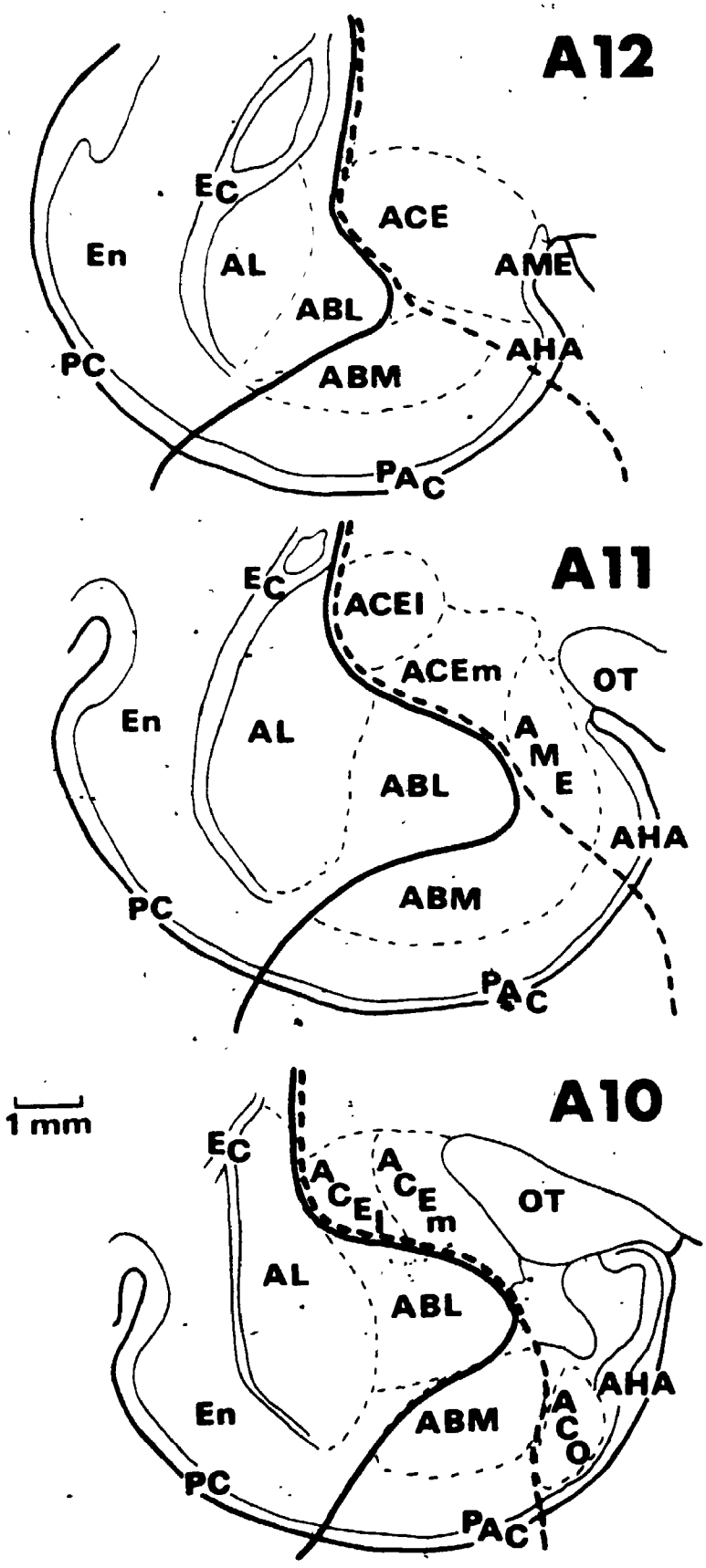
In addition, based on fiber projections, the medial parvocellular part of the basal nucleus was included in the medial division of the amygdala (Kaada, 1972). However, on the basis of histochemistry and anatomy, Hall (1972), suggested that the medial portion of the basal nucleus is not part of either the basolateral or the medial subdivisions. This anatomical subdivision of the amygdala into basolateral and medial components corresponds to the basolateral and dorsomedial subdivisions demonstrated by stimulation and ablation studies for many responses including arousal, defence, mating and ingestive behaviors, cardiovascular, respiratory and endocrine

effects (Fonberg, 1968; 1974; 1975; 1981; Fonberg and Delgado, 1969; Hilton and Zbrozyna, 1963; Kaada, 1972; Morin et al., 1952). The subdivisions of the nuclei of the amygdala in the cat are shown in Fig. 2.

The current views about the topography of nuclei within the amygdala of the cat have been reviewed by Hall (1972), Krettek and Price (1978) and Price (1981), and are summarized below. The lateral nucleus is the largest and is bordered by the external capsule. It has three subdivisions: the magnocellular shell on the lateral edge adjacent to the external capsule, the body with medium-sized cells which has a densely packed dorsolateral portion, and a sparser ventromedial portion (Krettek and Price, 1978). There are two distinct parts to the basal nucleus, the magnocellular basolateral nucleus and the parvocellular basomedial nucleus. The central nucleus is in the dorsal portion of the amygdaloid complex ventral to the globus pallidus. In the rat it is further subdivided into a lateral parvocellular division and a medial magnocellular component (Fox, 1940; Hall, 1972; Krettek and Price, 1978). Projections to the lower brain stem from this nucleus arise only from the medial portion (Hopkins and Holstege, 1978). The medial nucleus is a parvocellular nucleus in the anterior portion of the amygdala ventral and lateral to the optic tract (Fox, 1940; Krettek and Price, 1978). The cortical nucleus is found only in the rostral portion of the amygdala and receives direct projections from the olfactory bulb (Krettek and Price, 1978; Price, 1973).

FIGURE 2

Subdivision of the nuclei of the amygdala in the cat shown in 3 transverse sections from 12 to 10 mm rostral to the interaural line. Nuclear boundaries determined from the photomicrographs of Krettek and Price (1978). Heavy dashed line indicates the original basolateral and corticomedial subdivisions of the nuclei based on anatomical, ontogenetic and phylogenetic studies. The heavy solid line indicates the current subdivision of the nuclei of the amygdala into basolateral and dorsomedial components based on fiber projections and stimulation and ablation studies. ABl and ABm, basolateral and basomedial nuclei of the amygdala; ACEl and ACEm, lateral and medial parts of the central nucleus of the amygdala; ACO, AL and AME, cortical, lateral and basal nuclei of the amygdala; AHA, amygdalo-hippocampal area; EC, external capsule; En, endopiriform nucleus; OT, optic tract, PAC, periamygdaloid cortex; PC, perpiriform cortex.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2. Functional implications of connections of the amygdala

The classical view of the amygdala is that it functionally relates exteroceptive sensory input of the cerebral cortex to behavioral and autonomic functions of the hypothalamus and other subcortical regions. Cortical projections to the amygdala were first demonstrated in 1956 by Whitlock and Nauta. It is now known that the heaviest cortical projections arise primarily from insular and temporal regions as well as from the prepiriform, infralimbic, perirhinal and entorhinal cortices (Aggleton et al., 1980; Cranford et al., 1976; Herzog and Van Hoesen, 1976; Klinger and Gloor, 1960; Mufson et al., 1981; Ottersen, 1982; Russchen, 1982; Turner et al., 1980; Venning, 1978).

A number of studies have demonstrated that a variety of exteroceptive inputs project to the amygdala (Bobbin et al., 1979; Creutzfeldt et al., 1963; Machne and Segundo, 1956; O'Keefe and Bouma, 1969; Sanghera et al., 1979; Sawa and Delgado, 1963). In a thorough study, Turner, Mishkin and Knapp (1980) demonstrated that auditory, visual, gustatory and somesthetic sensory systems contain areas which project to the amygdala but not to more central limbic structures in the basal forebrain and hypothalamus, suggesting that any influences of sensory systems on emotions are likely to involve relays through the amygdala. With the exception of the olfactory system, only highly processed sensory information projects to the amygdala.

The amygdala projects to the hypothalamus by two main pathways. The corticomedial division of the amygdala projects primarily by the stria terminalis while the ventroamygdalofugal pathway contains

fibers with projections from the basolateral area of the amygdala (Cowan et al., 1965; De Olmos, 1972; Egger, 1972; Lammers, 1972). The projection from the amygdala to the hypothalamus is primarily to the ventromedial nucleus but also to other areas including the lateral hypothalamus, supraoptic, dorsomedial and paraventricular nuclei (Gloor, 1955; Krettek and Price, 1978; Pittman et al., 1981; Price and Amaral, 1981; Renaud, 1976).

It has been demonstrated that the projections from the amygdala to the hypothalamus are important for the function of the amygdala. This is supported by the evidence that hypothalamic lesions are effective in abolishing the responses due to stimulation or ablation of the amygdala (Kling and Hutt, 1958; Schlafani et al., 1970; White and Fisher, 1969). The modulatory role of the amygdala on hypothalamic function is suggested by the results of experiments in which stimulation of the dorsomedial amygdala was shown to elicit responses in hypothalamic units opposite to those of basolateral stimulation (Dreifuss et al., 1968; Gloor, 1972; 1978). In a review of electrophysiological studies of connections between amygdala and hypothalamus, Egger (1972) concluded that the amygdala acts as an intermediate zone between the cortex and the hypothalamus, modulating and timing functions which are controlled by the hypothalamus.

In addition to the projections to the hypothalamus, many recent neuroanatomical studies have demonstrated direct connections from the amygdala to other brain stem structures. These observations support the suggestion made by previous investigators that respiratory and cardiovascular changes elicited from the amygdala are not mediated by amygdalo-hypothalamic pathways but bypass the hypothalamus

(Kaada, 1951; Gloor, 1960). Indeed it has been demonstrated that the central nucleus of the amygdala projects directly to brain stem nuclei such as the parabrachial nucleus, the nucleus of the solitary tract and the dorsal motor nucleus of the vagus which are important nuclei in respiratory and cardiovascular control (Hopkins and Holstege, 1978; Hopkins et al., 1981; Krettek and Price, 1978; Price and Amaral, 1981; Schwaber et al., 1980; Schwaber et al., 1982).

Investigations using lesions or the recording of electrical activity in the amygdala also have provided evidence that contributes to an understanding of the possible function of the amygdala. Lesions of the amygdala do not seriously impair neuroendocrine or autonomic regulation but they do disrupt the ability to select behaviors appropriate to a given situation (Gloor, 1960; Kling et al., 1979; Schreiner and Kling, 1953; Summers and Kaleber, 1963; Weiskranz, 1956). It has also been demonstrated that electrical activity in the amygdala of unrestrained monkeys is correlated with the type of stimulus received from other monkeys (Kling et al., 1979). The highest levels of activity occurred under conditions in which the subject was receiving a threat or sexual inspection; stimuli which precede behaviors such as flight, defence or mounting (Kling et al., 1979). Furthermore, in monkeys receiving the same stimulus from other members of a group there is a reduction in the electrical activity of the amygdala in animals with lesions in the temporal neocortex compared with unlesioned animals (Kling, 1981).

3. Sleep and arousal

The most common response to stimulation of the amygdala in the anesthetized animal is the orienting response (Kaada, 1972; Ursin and Kaada, 1960 a & b). This response is characterized by the complete cessation of all ongoing activities and is followed by arousal associated with cortical desynchronization (Kreindler and Steriade, 1964; Ursin and Kaada, 1960 a). The amygdala appears to be essential for some components of the orienting reaction. Bagshaw and Benzies (1968) demonstrated that amygdalectomy in monkeys prevented the galvanic skin response, increased heart rate and increased respiratory rate components of the orienting response elicited by presentation of an auditory signal. The orienting and arousal responses are the initial phases of the defence reaction and are elicited primarily from the dorsomedial amygdala including the dorsal portion of the medial basal nucleus, the central nucleus and the region dorsal to the optic tract (Kreindler and Steriade, 1964).

Stimulation in the ventrolateral areas does not elicit the orienting response and arousal. Indeed, some investigators have produced a decrease in arousal and neocortical synchronization by stimulation in the lateral and ventral parts of the amygdala and surrounding neocortex (Caruthers, 1969; Kaada, 1951; Kreindler and Steriade, 1964; Sterman and Clemente, 1962). This response can include inhibitory effects on somamotor reflexes, respiration and blood pressure (Kaada, 1972).

4. Defence reaction

In 1928 Bard demonstrated that rage is readily elicited or

occurs spontaneously in decorticate cats. This led to investigations of the diencephalic and mesencephalic mechanisms of this phenomenon. Ranson and Magoun in 1933 and Magoun et al., in 1937 obtained hissing and spitting in cats by electrical stimulation of the central gray matter and hypothalamus. Hess (1957) elicited an affective defence reaction by stimulation of the hypothalamus in cats. This reaction included hissing, flattening of the ears, lowering of the head, dilation of the pupils and piloerection. The region concerned with these patterns of behavior was thought to be an unbroken field comprising portions of the central gray matter, the preoptic area, the hypothalamus and the midbrain (Fernandez de Molina and Hunsperger, 1959). That this response could also be elicited from the amygdala was demonstrated by MacLean and Delgado in 1953. Since then, the results of other investigators have indicated that the response is elicited from the dorsomedial amygdala (Fernandez de Molina and Hunsperger, 1959; 1962; Fonberg, 1968; Hilton and Zbrozyna, 1963; Timms, 1981; Zbrożyna, 1972).

The functionally distinct ventrolateral amygdala has effects on the defence reaction opposite to that of the dorsomedial amygdala. Stimulation in the ventrolateral amygdala reduces or even abolishes conditioned classical defence response (Fonberg, 1963; 1968). In addition, electrical stimulation of the basolateral amygdala inhibits hypothalamically induced attack behavior (Egger and Flynn, 1963). Thus, the role of the amygdala in the defence reaction further supports the concept of the dorsomedial amygdala as an activator and the ventrolateral amygdala as an inhibitor.

It has been suggested that the response from the amygdala

is mediated through the hypothalamus for the following two reasons. First, the response elicited by stimulation of the amygdala is similar to that of stimulation of the hypothalamus and the response from the hypothalamus has a more abrupt onset and greater magnitude than that from the amygdala (Stock et al., 1981). Finally, the amygdala defence reaction appears to be mediated by the hypothalamus because it is abolished by lesions in the hypothalamus (Fernandez de Molina and Hunsperger, 1962).

A number of studies have shown that bilateral removal of the amygdala results in increased docility (Gloor, 1960; Goddard, 1964; Kaada, 1972) whereas others have shown increased aggressive behavior (Bard and Rioch, 1937; Bard and Mountcastle, 1947; Kaada, 1972; Spiegel et al., 1940; Wood, 1958). It has not been possible to correlate lesions producing defence and rage or inhibition of these responses with anatomically distinct areas of the amygdala.

The defence reaction exhibits marked cardiovascular responses which in the cat include increases in arterial pressure, heart rate, cardiac output and vasoconstriction in kidneys, intestines and skin but vasodilation in the hind limbs (Abrahams et al., 1960; 1962; Timms, 1981). Under chloralose or pentobarbitol anesthesia, the full visceral response can be elicited by stimulation of the hypothalamus and midbrain (Abrahams et al., 1960; Stock et al., 1978). However, Hilton and Zbrozyna (1963) were unable to obtain skeletal muscle vasodilation in cats under chloralose or Dial anesthesia while stimulating the amygdala. They did produce skeletal muscle vasodilation in unanesthetized cats and in anesthetized cats when

stimulating directly the defence projection pathway from the amygdala to the hypothalamus (Hilton and Zbrozyna, 1963). Other investigators atimulated the amygdala in cats and were able to block the full visceral reactions of the defence response using ketamine or pentobarbital (Stock et al., 1978; Timms, 1982). Recently, it has been demonstrated that the full visceral response elicited by stimulation of the amygdala in unanesthetized preparations, may be obtained in cats anesthetized with the steroid anesthetic althesin (Timms, 1976; 1981). It appears that anesthetics such as chloralose, barbiturates and ketamine have a selective blocking action on synapses in the amygdala mediating the defence reaction but not on the hypothalamus and brain stem.

These anesthetics also block the full visceral response to noxious stimuli (Abrahams et al., 1960; 1962; 1964) or activation of carotid chemoreceptors (Timms, 1982). However, unanesthetized preparations and those anesthetized with althesin display the full visceral response elicited by noxious stimuli or activation of carotid chemoreceptors (Abrahams et al., 1960; 1962; 1964; Hilton and Joels, 1965; Marshall, 1977; 1981). It appears that reflex activation either by noxious stimuli or activation of carotid chemoreceptors of the full visceral response of the defence or orienting reaction requires transmission through synapses to the amygdala.

5. Other behaviors

In addition to arousal and defence reactions, the amygdala is involved in many other behaviors. The results of investigations

into some of these behaviors also support a functional separation of the amygdala into dorsomedial and ventromedial components. For example, stimulation experiments indicate that anterior and medial portions of the amygdala exert an excitatory effect on alimentary reactions (Kaada, 1972) while stimulation of the basolateral part of the amygdala inhibits these responses (Fonberg and Delgado, 1961; Fonberg, 1963; Kaada, 1972). Lesions in the amygdala demonstrate a functional separation in the control of sexual activities. Lesions restricted to the basolateral region of the amygdala result in a state of hypersexuality (Eleftheriou and Zolovick, 1966; Wood, 1958) while male and female rats with lesions in the corticomedial amygdala made in the prepubertal period did not mate when observed over a period of five months (Schwartz and Kling, 1964).

These results and others have led to the concept that the amygdala has an unspecific, general modulatory influence on many functions in many classes of behaviors. In this context the dorsomedial amygdala functions as a general activator and the ventrolateral amygdala is an inhibitor of the various behaviors influenced by the amygdala (Fonberg, 1981).

B. Function of Baro- and Chemoreceptors

1. Autonomic and respiratory effects of activation of baroreceptors

The first demonstration of reflex regulation of blood pressure and heart rate was obtained in 1866 when Cyon and Ludwig stimulated the central end of a nerve parallel to the cervical vagus in the

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rabbit and observed systemic hypotension and bradycardia. The tonic nature of these nerves was demonstrated in 1885 when cutting them resulted in an increase in blood pressure (Sewell and Steiner, 1885). Koester and Tschermack (1903) showed that the nerve originated in the aortic arch and that action potentials were elicited by distention of the isolated aorta with saline.

The reflex mechanism of bradycardia resulting from a blood pressure increase was confirmed in 1925 by Heymans and Ladon. In their preparation the head of a dog was completely separated from its trunk except for intact vagi and aortic depressor nerves. Perfusion of the isolated head was maintained with blood pumped from a donor dog. An increase or decrease in the blood pressure in the trunk of the recipient dog resulted in a decrease or increase respectively in the heart rate only if the vagi were intact demonstrating the reflex nature of this mechanism.

It had been noted in 1836 that carotid occlusion elicited an increase in blood pressure, but this effect was thought to be due to cerebral ischemia (Heymans and Neil, 1958). The role of carotid baroreceptors was not demonstrated until 1923 when Hering localized the origin of nerve endings mediating a reflex in the carotid bifurcation (Downing, 1979). In 1924 he demonstrated that bradycardia and hypotension were the result of both mechanical and electrical stimulation of baroreceptors in the carotid sinus nerve in dogs. Hering also demonstrated that the heart rate and blood pressure changes were separate responses by showing that atropine injections could prevent the bradycardia but not the hypotension. It has subsequently been established that aortic baroreceptors are less sensi-

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tive than carotid baroreceptors (Downing, 1979; Pelletier et al., 1972; Levy et al., 1966; Donald and Edis, 1971).

Schneider (1931) and Bacq et al. (1934) demonstrated that baroreceptor-induced reflex changes in blood pressure are sympathetically mediated (Bacq et al., 1934; Schneider, 1931). Recordings of sympathetic nerves indicated that a rise in systemic blood pressure results in a reflex decrease in nerve activity while a decrease in blood pressure elicits a reflex increase in sympathetic nerve activity (Gernandt et al., 1946). The ganglionic sympathetic white ramus fibers responding to changes in blood pressure have been demonstrated to be located primarily in the thoracic region (Seller, 1973). Furthermore, it has been shown that sympathetic nerve activity in efferent nerves to kidney, spleen and heart can be reflexly inhibited by baroreceptors but there is little inhibition in efferent nerves to stomach and intestine (Iriki et al., 1977; Irisawa et al., 1973; Ninomiya et al., 1973).

Baroreflex control of the heart rate has been demonstrated to be vagally mediated (Heymans and Ladon, 1925; Jewett, 1964; Wang and Borison, 1947). However, it has also been demonstrated that an increase in carotid sinus pressure results in a reduction in activity in sympathetic postganglionic fibers to the heart (Bronk, 1934). The more recent results of others have supported the concept of reciprocal sympathetic and parasympathetic responses to the heart such that baroreceptor stimulation elicits inhibition of sympathetic efferents and excitation of vagal efferents (Hakumaki, 1972; Iriuchijima and Kumada, 1964; Kollai and Koizumi, 1979; 1981).

In 1836 Cooper demonstrated that carotid occlusion results in

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hyperpnea (Heymans and Neil, 1958). Originally, the increases in respiration in response to a decrease in carotid circulation were attributed to changes in blood flow to the brain (Heymans and Neil, 1958). In 1927 it was demonstrated that the hypopnea or hyperpnea elicited by an increase in carotid pressure or carotid occlusion was a reflex in response to baroreceptor input (Heymans and Neil, 1958). More recently the inhibitory effect of baroreceptor activation on respiration has been confirmed by others (Bishop, 1974; Delpierre et al., 1974; Grunstein et al., 1975; Miserocchi and Quinn, 1980). Brunner et al. (1981) with a careful study in peripherally chemodenervated, vagotomized dogs, demonstrated that a decrease in intrasinus pressure causes a large increase in respiratory frequency and a small increase in tidal volume with an overall increase in total ventilation, responses which are not secondary to changes in arterial pressure (Brunner et al., 1981). In another approach to the study of baroreceptors on respiration, it has been demonstrated that increased carotid sinus pressure elicits excitatory responses from expiratory neurons in the medulla (Gabriel and Seller, 1969).

2. Autonomic and respiratory effects of activation of chemoreceptors

Anatomically the carotid bodies were described in 1743 and the aortic in 1906 (Pick, 1959). However, it was not until 1927 that Heymans and Heymans demonstrated that reflex stimulation of breathing could be elicited by anoxemia and hypercapnia in the cardio-aortic region. As the aortic region was less accessible, Heymans et al. explored the more accessible carotid bodies which they demonstrated in 1930 to

be chemoreceptor tissue. In their experiments, perfusion of the carotid bifurcation with hypoxic or hypercapnic blood resulted in a hyperpnic response which could be abolished by section of the ipsilateral carotid sinus nerve (Heymans et al., 1930).

Studies of chemoreceptors have resulted in many discrepancies in the literature due to species differences, use of anesthetics, variability in thresholds and intensity of responses, different criteria for judging chemoreceptor responses and different doses and multiple sites of action of drugs used to stimulate chemoreceptors (Comroe, 1964). Species differences were first demonstrated by the results of Comroe (1939) in which the hyperpnic response to hypoxia in dogs was primarily mediated by the carotid chemoreceptors while in the cat the aortic chemoreceptors contributed more. Since that time it has been established in a number of species that the carotid bodies are the major chemoreceptors for ventilatory responses to hypoxia (Bisgard et al., 1976; Bouvert et al., 1973; Chalmers et al., 1967; Miller and Tenney, 1975; Morill et al., 1975; Sorenson and Mines, 1970; Wade et al., 1970). In fact, in rabbits and rats it has been demonstrated that there are few if any chemoreceptor fibers in the aortic nerve (Chalmers et al., 1967; Neil and Redwood, 1949; Sapru and Kreiger, 1977; Sapru et al., 1981).

In the cat with functional chemoreceptors in both the carotid and aortic bodies (Diamond and Howe, 1956), differences in the type of stimulus the chemoreceptors respond to have been observed (Fitzgerald and Dehghani, 1982; Lahiri et al., 1980; 1981; Pokorski and Lahiri, 1982). The aortic response to hypercapnia under hypoxic conditions is much less than that of the carotid chemoreceptors

and under normoxic and hyperoxic conditions it is non-existent (Fitzgerald and Dehghani, 1982).

It appears that the carotid and aortic chemoreceptors also differ in their reflex control of cardiovascular changes. Comroe (1939) demonstrated that a powerful vasomotor reflex in the dog could be elicited from the aortic chemoreceptors compared with a relatively ineffective reflex from the carotid. In the cat the carotid chemoreceptors were more important for the vasomotor response to anoxemia than the aortic (Comroe, 1939).

The primary vasomotor response to activation of chemoreceptors is an increase in blood pressure which is mediated by increased sympathetic discharge (Bernthal et al., 1945; Daly and Scott, 1962; Dontas, 1955; Little and Öberg, 1975). Differences in vasomotor responses are observed in spontaneously breathing and artificially ventilated animal preparations. In the artificially ventilated dog there is a generalized vasoconstriction, whereas the spontaneously breathing animal has a less pronounced vasoconstriction followed by vasodilation, suggesting that the vasodilation is due to the reflex hyperventilation (Daly and Scott, 1962).

In unanesthetized cats or those anesthetized with althesin there is skeletal muscle vasodilation not seen in other preparations (Hilton and Joels, 1965; Marshall, 1977; 1980; 1981). Marshall (1977) in althesin anesthetized cats, demonstrated an increase of up to 100% in hind limb conductance which was not secondary to muscle contractions or changes in respiration. This skeletal muscle vasodilation was demonstrated to be mediated by cholinergic dilator fibers and inhibition of sympathethic vasoconstrictor tone (Marshall,

1977). That this dilator reflex is not seen in preparations with chloralose and barbiturate anesthetics suggests that these anesthetics block synapses necessary for this response as discussed elsewhere in this review.

Heymans et al. (1931) demonstrated that the local injection of cyanide in the carotid body elicited a bradycardia which was prevented by cutting the corresponding carotid sinus nerve. This heart rate response to chemoreceptor activation was confirmed by other investigators (Bernthal, 1938; Comroe and Schmidt, 1938). However, other studies demonstrated reflex tachycardia to chemoreceptor stimulation (Alveryd and Brody, 1948; Asmussen and Chiodi, 1941; Dripps and Comroe, 1947; von Euler and Liljestrand, 1942; Whitehorn et al., 1946). Bernthal et al. (1951) provided some indication that the heart rate response was dependent on the type of preparation by demonstrating a more pronounced bradycardia in artificially ventilated dogs than in spontaneously breathing animals. Since then it has been demonstrated that under controlled ventilation conditions reflex bradycardia always occurs in response to chemoreceptor stimulation and that the tachycardia which frequently occurs during spontaneous breathing is secondary to the respiratory changes (Daly and Daly, 1957; 1959; Daly and Scott, 1958; 1962; McQueen and Ungar, 1971).

The heart rate slowing directly as a result of the chemoreflex was considerably reduced by atropine or cervical vagotomy (Daly and Scott, 1958; 1962). The remaining small response can be blocked by applying local anesthetic to the stellate ganglia or by systemic administration of hexamethonium suggesting that reflex

bradycardia resulting from activation of chemoreceptors is due to an increase in vagal activity with a reciprocal decrease in sympathetic tone (Daly and Scott, 1962).

3. Behavioral effects of baroreceptors

In 1932, Koch demonstrated that activation of baroreceptors in the unanesthetized dog causes muscle relaxation in a sleeping position and reduces muscle movements resulting from a nociceptive stimulus. Moreover, an increase in blood pressure in the carotid sinus region prevented rage or aggressive behavior of the awake dog in response to pinching of the nostrils (Koch, 1932). It appears from these experiments that a baroreceptor stimulus is capable of altering motor responses, influencing the level of wakefulness and inhibiting emotional responses.

The results of Koch (1932) on changes in muscle activity supported the findings of other investigators who demonstrated that an increase in blood pressure or stimulation of the carotid sinus or aortic depressor nerves can decrease muscle tone, and inhibit shivering and knee jerk reflexes (Johnson and Luckhardt, 1927; Schweitzer and Wright, 1937; Tournade and Malmejac, 1929). More recently, Gellhorn et al. (1942), were able to augment the effects of convulsive agents with carotid occlusion and abolish them with mechanical stimulation of the carotid sinus.

Baroreceptor input has been demonstrated to have a role in determining the level of cortical activity. In 1933, Heymans and Boukaert elicited an increase in activity in the motor cortex by sectioning the buffer nerves (Heymans and Neil, 1958). Gellhorn et al.

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(1953) demonstrated a similar increase in cortical activity by decreasing the sino-aortic pressure.

On the other hand, activation of baroreceptors elicits a decrease in high frequency cortical activity and an increase in the amplitude of slow waves, electrophysiological characteristics associated with sleep (Nakao et al., 1956; Bonvallet et al., 1953; 1954). These EEG patterns associated with sleep in response to activation of carotid sinus baroreceptors persist after high spinal section and vagotomy combined, demonstrating that these changes are mediated by activation of afferent baroreceptor fibers and are not indirectly due to changes in blood pressure or heart rate (Bonvallet et al., 1954). In addition, the development of a slow wave cortical pattern elicited by an increase in blood pressure resulting from the injection of adrenaline was prevented by sino-aortic denervation (Nakao et al., 1956).

Moreover, it has been demonstrated that there is a cortical synchronizing and sleep-inducing region in the lower brain stem where baroreceptor afferents terminate (Batini et al., 1958; 1959; Cordeau and Mancia, 1959; Magni et al., 1959).

Finally, baroreceptor activation appears to influence emotional behaviors. Bartorelli et al., (1960), elicited an increase in blood pressure and rage behavior in decorticate cats as the result of a bilateral carotid occlusion. The rage response was present in animals with spinal cord transections and selective denervation of chemorecptors, but not in decerebrate preparations (Bartorelli et al., 1960). These results suggest that there is a tonic inhibitory influence of baroreceptors on defence and rage centers rostral

to the pons. Furthermore, an increase in pressure in the carotid sinus is an effective inhibitory influence on the somatic and autonomic components of spontaneous rage (Bartorelli et al., 1960). The results of these studies were extended by Baccelli et al. (1965) using selective stimulation of aortic afferents in acute decorticate cats. Electrical stimulation of large baroreceptive fibers in the aortic nerve inhibited the somatic and visceral components of sham rage (Baccelli et al., 1965).

4. Behavioral effects of chemoreceptors

Arousal from sleep in response to hypoxia is an important protective mechanism. Hypoxia during sleep in humans at high altitudes has been reported to cause frequent awakenings (Reite et al., 1975). Moreover, sleep-apnea syndromes are characterized by repeated episodes of apnea during sleep and are terminated by behavioral arousal which is thought to be due to the progressive asphyxia (Bowes et al., 1980). Administration of oxygen to patients with sleep apnea has been shown to delay arousal and prolong the period of apnea (Motta and Guilleminault, 1978). In cats, dogs and lambs, hypoxia results in arousal from sleep and the degree of hypoxia required to elicit arousal depends on the stage of sleep (Blanco et al., 1983 a & b; Jeffery and Read, 1980; Neubauer et al., 1981; Pappenheimer, 1977; Philippson et al., 1980).

It is known that the ventilatory response to hypoxia is intact during sleep and, as previously discussed, peripheral chemoreceptors, especially those of the carotid bodies, are the primary receptors mediating the ventilatory response to hypoxia (Bowes et al., 1981;

Miller and Tenney, 1975). Early evidence in support of this hypothesis is the demonstration that electrocortical arousal can be elicited in response to peripheral chemoreceptor input (Bailey and Bremer, 1938; Bonvallet et al., 1959; Hugelin et al., 1959). Hugelin et al. (1959) demonstrated in dogs and cats that a gas mixture of low oxygen content induces a cortical arousal simultaneously with the respiratory activation which could be prevented by blocking the carotid and aortic bodies.

Other investigators have studied the effects of carotid chemoreceptors on arousal from sleep directly. Carotid-deafferented dogs and cats failed to demonstrate behavioral arousal in response to hypoxic stimulation (Bowes et al., 1981; Miller and Tenney, 1975). Prior to carotid body denervation using a rebreathing technique, dogs were aroused at an arterial O_2 saturation of 83% during slow wave sleep and 71% during REM sleep (Bowes et al., 1981). Following carotid body denervation some dogs failed to arouse at all and required active resuscitation (Bowes et al., 1981). These results show the importance of peripheral chemoreceptors as a protective mechanism that elicits arousal from sleep in response to hypoxic stimulation.

Chemoreceptors, like baroreceptors, also have an influence on emotional behaviors. In awake decorticate cats carotid body stimulation either chemically or with hypoxia consistently resulted in motor and visceral components of rage identical to those elicited by somatic peripheral stimulation or those which occur spontaneously (Bizzi et al., 1961; Hilton and Joels, 1965). In animals with spinal transections which prevent development of respiratory and pressor responses, the motor responses of rage persisted while

selective inactivation of the carotid chemoreceptors abolished all motor and visceral components of rage (Bizzi et al., 1961). Selective electrical stimulation of aortic chemoreceptor fibers in decorticate cats was also able to elicit rage behavior (Baccelli et al., 1965). Previously, evidence was presented indicating that the full expression of the visceral alerting reaction in response to activation of chemoreceptors which is the preparatory stage to the defence and rage reactions, requires synaptic transmission through the defence region of the amygdala. This is supported by the demonstration of Baccelli et al. (1965) that decerebration abolishes the rage behavior elicited by selective electrical stimulation of aortic chemoreceptor fibers in decorticate cats.

5. Influences of supramedullary structures on baro- and chemoreflexes

There is evidence that baroreceptive reflex sensitivity can be altered during different behavioral states. From a variety of investigators monitoring different behaviors it appears that an increase in arousal results in a decrease in the sensitivity of the baroreceptor reflex. Behaviors such as physical exercise, drinking and mental stimulation inhibit the baroreceptor reflex (Bristol et al., 1971; Mancia, 1978; Pickering et al., 1972; Sleight et al., 1978; Schlor et al., 1983). Arousal induced by confronting a cat with another aggressive cat depresses the baroreceptor reflex (Schlor et al., 1983). On the other hand, during a decreased state of arousal such as sleep, the baroreceptor reflex is augmented (Conway et al., 1983; Smyth et al., 1969). Possibly reflecting these

changes in the level of behavioral arousal is the evidence of a circadian rhythm to the baroreflex sensitivity (Hossman et al., 1980).

In view of the evidence that natural behaviors can alter cardiovascular reflexes, it is possible that electrical stimulation of limbic areas will also influence these reflexes. Electrical stimulation of the hypothalamus inhibits the baroreceptor reflex (Coote et al., 1979; Djojosugito et al., 1970; Gebber and Snyder, 1970; Gimpl et al., 1976; Hilton, 1963; Humphreys et al., 1971; Jordan et al., 1979; Takeuchi and Manning, 1973). There is conflicting evidence concerning whether hypothalamic stimulation inhibits or facilitates chemoreceptor reflexes. Stimulation of the posteromedial hypothalamus in cats anesthetized with chloralose has been shown to inhibit bradycardia elicited by carotid chemoreceptor stimulation (Thomas and Calaresu, 1973). On the other hand, in awake high decerebrate cats, stimulation in the hypothalamic region that integrates the defence reaction has been shown to facilitate increases in blood pressure and respiration resulting from activation of chemoreceptors (Hilton and Joels, 1965).

Two other limbic areas, the septum and amygdala, also influence baroreceptor reflexes. Apparently conflicting results have been obtained from the septum. Covian (1967) demonstrated that the reflex response of cats anesthetized with chloralose to bilateral carotid occlusion was inhibited by septal stimulation. Another investigation using the same species and anesthetic demonstrated that stimulation in the septum results in facilitation of baroreceptor-induced bradycardia (Klevans and Gebber, 1970). The dis-

crepancies in the results might be explained by differences in sites of stimulation in the septum but neither study showed the location of sites of stimulation. Stimulation in the cortical nucleus of the amygdala in anesthetized cats has been shown to facilitate baroreceptor reflexes (Gebber and Klevans, 1972) while more recently, stimulation in the central nucleus of the amygdala in awake cats reduced baroreflex sensitivity (Schlor et al., 1983).

There have been a number of reports on the interaction of baro- and chemoreceptors which, in animals anesthetized with chloralose or barbiturates, have generally indicated that baroreceptor reflexes can inhibit chemoreceptor reflexes (Heistad et al., 1974; Korner et al., 1969; Mancia, 1975; Trzebski et al., 1975; Wennergun et al., 1976). However, in cats anesthetized with althesin, which does not block transmission through the amygdala defence area, chemoreceptor stimulation markedly inhibited baroreceptor reflexes in a manner similar to the inhibition of baroreflexes by stimulation in defence areas or increased degrees of arousal (Coote et al., 1979; Marshall,1980; 1981; Schlor et al., 1983).

C. Central Nervous Control of Cardiovascular Function

1. Medullary control

The earliest investigation of central nervous system control of the circulation was done by Philip in 1818. He demonstrated that crushing the brain or pithing the spinal cord of a frog decreased the heart rate. Miller and Bowman in 1915 localized the cardio-inhibitory responses to the region of the dorsal motor nucleus of

the vagus. In addition to changes in heart rate, the lower brain stem was also shown by Owsjannikow in 1871 and Dittmar in 1873 to have a role in maintaining resting blood pressure and in mediating circulatory reflexes elicited by stimulation of the limb nerves (Bard, 1960). Bayliss (1893) suggested that there were reciprocal vasodilator and vasoconstrictor centers in the medulla.

More precise localization of medullary cardiovascular control areas was provided by the technique of electrical stimulation. Ransom and Billingsley (1916) demonstrated that there were two distinct areas in which stimulation resulted in a decrease or increase in arterial pressure. In 1923 Scott and Roberts showed that the same area from which hypotension was elicited also produced bradycardia with intact vagi. Subsequently, many points of stimulation with cardiovascular changes in the medulla were accurately localized using stereotaxic positioning of electrodes (Alexander, 1946; Bach, 1952; Monnier, 1939; Wang and Ranson, 1939). A comparison of these results by Bach (1952) led to the conclusion that pressor points are located in the dorsomedial and ventrolateral areas and depressor points are in the ventromedial medulla.

More recently, the ventrolateral medulla has been investigated for the role it plays in vasomotor regulation. A number of studies using drugs, lesions and cooling techniques have demonstrated that blocking the ventrolateral medulla results in a marked decrease in arterial pressure (Dampney and Moon, 1980; Feldberg and Guertzenstein, 1972; 1976; Guertzenstein, 1973; Guertzenstein and Silver, 1974). On the other hand, focal electrical stimulation or excitation of cell bodies by microinjection of glutamate elicits large increases in arterial pressure (Dampney and Moon, 1980; Dampney

et al., 1982). Application of kainic acid, an excitotoxic amino acid, to the ventrolateral medulla elicits an initial increase in blood pressure followed by a decrease to levels similar to those found in spinal animals (McAllen et al., 1982). After the peak in blood pressure sympathetic vasomotor activity is unresponsive to baroreceptor inhibition. These responses are likely mediated by the direct projections demonstrated from the ventrolateral medulla to spinal sympathetic centers (Amendt et al., 1979; Blessing et al., 1981; Caverson et al., 1983 a & b).

Early anatomical studies investigating the origin of vagal cardioinhibitory neurons demonstrated retrograde neuronal degeneration in the dorsal motor nucleus of the vagus following vagotomy while lesions in medullary nuclei and observation of degenerating axons in the vagus have indicated that both the dorsal motor nucleus of the vagus and the ambiguous nucleus may be sites of origin of vagal preganglionics (Calaresu et al., 1975; Ciriello and Calaresu, 1982). More recently a number of studies using the method of retrograde transport of horseradish peroxidase have also yielded conflicting evidence. In some investigations in cats injecting horseradish peroxidase into the heart labelled neurons only in the dorsal motor nucleus of the vagus (Todo, 1977; Todo et al., 1977) while others using rats and cats demonstrated labelled neurons in both the dorsal motor nucleus of the vagus and the ambiguous nucleus (Ciriello and Calaresu, 1982; Geis and Wurster, 1980; Kalia and Mesulam, 1980; Karim and Leong, 1980; Nosaka et al., 1979; Stuesse, 1982). Thus the neuroanatomical evidence appears to support the location of cardiac vagal preganglionics in both medullary nuclei.

Early neurophysiological investigators demonstrated that evoked potentials elicited by stimulation of the cervical vagus could be recorded in the ambiguous nucleus but not in the dorsal motor nucleus of the vagus (Anderson and Berry, 1956; Porter, 1963). Some support for these findings is obtained from two studies showing that stimulation of the dorsal motor nucleus of the vagus was unable to elicit bradycardia in cats (Calaresu and Pearce, 1965; Gunn et al., 1968). However, electrical stimulation of the dorsal motor nucleus of the vagus in several species has been demonstrated to elicit vagal bradycardia (Cohen et al., 1970; Gunn et al., 1968; Lee et al., 1972; Miller and Bowman, 1916; Nosaka et al., 1979; Weiss and Priola, 1972). Investigations stimulating the vagus and recording antidromically activated single units in the medulla have also yielded equivocal results. In one study in the rabbit units antidromically activated by stimulation of the vagus have been identified only in the dorsal motor nucleus of the vagus (Schwaber and Schneiderman, 1975; Schwaber and Cohen, 1978) while in another investigation both the dorsal motor nucleus of the vagus and the ambiguous nucleus in the rabbit medulla were shown to have cardioinhibitory preganglionics (Jordan et al., 1982). In the cat, units antidromically activated by stimulation of the cardiac vagal branches were identified in the ambiguous nucleus (McAllen and Spyer, 1976; 1978 a & b) while more recently using a similar technique, cardioinhibitory preganglionics were localized to both the dorsal motor nucleus of the vagus and the ambiguous nucleus (Ciriello and Calaresu, 1980; 1982). The neurophysiological evidence in general indicates that both the dorsal motor nucleus of the vagus and the ambiguous nucleus are sites

of cardiac vagal preganglionics.

The nucleus of the solitary tract is the main site of termination of baro- and chemoreceptors in the carotid sinus fibers of the IXth cranial nerve. This conclusion is based on a number of neuroanatomical and electrophysiological investigations. Patterns of degeneration as the result of sectioning the IXth and Xth cranial nerves were the first anatomical evidence to point to the intermediate area of the nucleus of the solitary tract (Cottle, 1964; Culberson and Kimmel, 1972; Kerr, 1962; Kimmel and Kimmel, 1964; Rhoton et al., 1966). This was also supported by electrophysiological evidence in which evoked potentials or single units were recorded in the medulla in response to electrical stimulation of the carotid sinus and aortic depressor nerves or selective activation of baro- and chemoreceptors (Anderson and Berry, 1956; Biscoe and Sampson, 1970 a & b; Ciriello and Calaresu, 1981; Davies and Edwards, 1973; Gabriel and Seller, 1970; Humphrey, 1967; Kumada and Nakajima, 1972; Miura, 1975; Miura and Reis, 1968; Seller and Ilhert, 1969; Weiss and Kastella, 1972). Alternatively, confirmatory results have been provided by stimulating sites in the medulla and recording antidromically activated primary afferent fibers (Crill and Reis, 1968; De Groat and Lalley, 1974; Lipski et al., 1975; Spyer, 1975). More recently the horseradish peroxidase transport technique has enabled more exact localization of the termination of aortic depressor and carotid sinus nerves. Horseradish peroxidase transport has demonstrated that the carotid sinus nerve terminates primarily ipsilateral in the medial, lateral dorsolateral and commissural subnuclei in the caudal half of the nucleus of the solitary tract (Berger, 1979;

Ciriello and Calaresu, 1981; Ciriello et al., 1981; Davies and Kalia, 1981; Nomura and Mizuno, 1982; Panneton and Loewy, 1980). There are also some projections to other medullary nuclei including the area postrema, the dorsal motor nucleus of the vagus and the ambiguous nucleus (Davies and Kalia, 1981; Panneton and Loewy, 1980). The afferent fibers in the aortic depressor nerve are reported to have a similar distribution in the nucleus of the solitary tract but with no projections to other medullary nuclei (Ciriello, 1983; Ciriello et al, 1981; Ciriello and Calaresu, 1981; Kalia and Welles, 1980; Wallach and Loewy, 1980).

2. Pontine control

Wang and Ranson (1939) first demonstrated that changes in heart rate and blood pressure could be obtained from the dorsolateral pons. Their results were confirmed by other investigators (Chai and Wang, 1962; Coote et al., 1973). These studies did not clearly localize the site of stimulation. In a number of investigations it was suggested that the locus coeruleus was the site of origin of the pontine pressor response (Fallert and Ploc, 1970; Kawamura et al., 1978; Przuntele and Philipu, 1973; Ward and Gunn, 1976 a & b). More recently it has been shown that stimulation localized to the parabrachial nucleus adjacent to the locus coeruleus elicits a powerful pressor response and vagally mediated tachycardia in the chloralose anesthetized cat (Mraovitch et al., 1982). As the cardiovascular changes obtained from the parabrachial nucleus required much less stimulus intensity than those from surrounding structures they suggested that the pressor response attributed to the locus coeruleus

may have been due to excitation of the nearby parabrachial nucleus (Mraovitch et al., 1982). In anesthetized rabbits, stimulation of the parabrachial nucleus was shown to elicit a pressor response and bradycardia (Hamilton et al., 1981).

The recent demonstrations of anatomical connections of the parabrachial nucleus with medullary and spinal cord regions involved in cardiovascular control provide the anatomical substrate for the mechanism by which the parabrachial nucleus elicits changes in the heart rate and blood pressure. The results of an anterograde autoradiographic investigation have demonstrated a large descending projection from the parabrachial nucleus to many areas of the medulla, including the nucleus of the solitary tract, nucleus ambiguous and ventrolateral medulla (Saper and Loewy, 1980). Furthermore, it has been demonstrated that the parabrachial nucleus projects to the spinal cord to the region of the intermediolateral cell column (Kuypers and Maisky, 1975; Saper and Loewy, 1980).

Retrograde transport of horseradish peroxidase has shown that the parabrachial nucleus also receives reciprocal ascending projections from cardiovascular control nuclei in the medulla such as the nucleus of the solitary tract, the dorsal motor nucleus of the vagus and the ventral lateral medulla (Kalia, 1977; Sakai et al., 1977). Other investigators have added considerably more detail to the projection from the nucleus of the solitary tract to the parabrachial nucleus (Hamilton et al., 1981; King, 1980; King and Knox, 1982; Loewy and Burton, 1978; Norgren, 1978; Ricardo and Koh, 1978). In particular, in the caudal two-thirds of the nucleus of the solitary tract, which is involved in cardiovascular and respiratory

functions, it is the medial and commissural solitary nuclei which are the primary site of origin of projections to the parabrachial nucleus (Loewy and Burton, 1978; King, 1980). On the other hand, the rostral third of the nucleus of the solitary tract which is thought to relay gustatory information projects to the caudomedial parabrachial nucleus (Bernard and Nord, 1971; Norgren and Leonard, 1971; Perrotto and Scott, 1976). In support of these neuroanatomical studies, some preliminary electrophysiological evidence demonstrated that cardiovascular afferent information projects to the parabrachial nucleus. Single units in the parabrachial nucleus which altered their frequency of firing in response to stimulation of the aortic depressor nerve were found in the parabrachial nucleus (Hamilton et al., 1981) and single units were found in the parabrachial nucleus that discharged in phase with the cardiac cycle. (Sieck and Harper, 1980).

3. Hypothalamic control

Since the early investigation of Karplus and Kreidl (1909; 1927) it has been known that stimulation of the hypothalamus can elicit an increase in arterial pressure and heart rate. These results were confirmed by other studies (Allen, 1931; Beattie et al., 1930; Hare and Geohegan, 1939; Kabat et al., 1935; Wang and Richter, 1928). Pressor sites and increases in heart rate were localized primarily to the dorsal and posterior hypothalamus (Abrahams et al., 1960; Ciriello and Calaresu, 1977; Gellman et al., 1981; Hess, 1957; McQueen et al., 1954; Thomas and Calaresu, 1972). Recently, it has been shown that stimulation of the paraventricular

nucleus in this hypothalamic region elicits a marked increase in blood pressure and heart rate as a result of reciprocal changes in parasympathetic and sympathetic activity (Ciriello and Calaresu, 1980). Neurons with activity patterns related to inferior cardiac sympathetic nerve discharge have been identified in the dorsal and posterior hypothalamus (Barman and Gebber, 1982). As previously indicated, activation of this region of the hypothalamus results in inhibition of baroreceptor reflexes.

On the other hand, Kabat et al. (1935) originally demonstrated that a decrease in arterial pressure could be obtained from the anterior hypothalamus and preoptic region. A depressor response and bradycardia from this area has been confirmed by other investigators (Enoch and Kerr, 1967; Faiers et al., 1976; Folkow et al., 1959; Gellman et al., 1981; Hess, 1957; McQueen et al., 1954). It has been shown that the decrease in arterial pressure and heart rate resulting from stimulation of the anterior hypothalamus is due to an inhibition of sympathetic vasoconstrictor tone and an excitation of vagal activity (Hilton and Spyer, 1971). Lesions restricted to this hypothalamic area reduced the response to baroreceptor stimulation (Hilton and Spyer, 1971).

Descending pathways from the hypothalamus mediating cardiovascular responses have been reviewed by Calaresu, Faiers and Mogenson (1975). The early anatomical results using fiber degeneration methods showed hypothalamic projections to a number of medullary nuclei and to the spinal cord (Beattie et al., 1980; Cheatham and Matzke, 1966). However, recent neuroanatomical data using retrograde transport of horseradish peroxidase and antero-

grade transport of labelled amino acids have indicated that the paraventricular nucleus of the hypothalamus may be particularly important in mediating descending hypothalamic cardiovascular responses. The paraventricular nucleus projects to medullary and spinal cord areas involved in sympathetic and parasympathetic output such as the dorsal motor nucleus of the vagus, the ventrolateral medulla and the intermediolateral cell column (Sawchenko and Swanson, 1982; Swanson and McKellar, 1979). In addition, neurons in the ventrolateral medulla projecting directly to the intermediolateral cell column and central autonomic area of the spinal cord alter their firing rate in response to stimulation of the paraventricular nucleus of the hypothalamus (Caverson et al., 1980; 1981).

Alternatively, the cardiovascular responses originating in the paraventricular nucleus may be mediated by the parabrachial nucleus as these two nuclei elicit similar changes in arterial pressure and heart rate (Ciriello and Calaresu, 1980; Mraovitch et al., 1982). In addition, the paraventricular nucleus of the hypothalamus also has descending connections to the parabrachial nucleus. Injections of labelled amino acids in the paraventricular nucleus of the hypothalamus result in dense terminal labelling ipsilaterally in the region of the parabrachial nucleus (Conrad and Pfaff, 1976; Saper et al., 1976). In an immunohistochemical study in the rat, fibers stained for neurophysin I, indicating the presence of oxytocin, were seen to terminate in the parabrachial nucleus (Swanson, 1977).

There is evidence that, in addition to a descending influence on cardiovascular output mechanisms, the hypothalamus also re-

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ceives baro- and chemoreceptor information. Hilton and Spyer (1968) demonstrated that, in the cat, the activity of hypothalamic units was altered by an increase in pressure in the carotid sinus. However, increases in carotid sinus pressure also elicit a decrease in systemic pressure and hypothalamic units respond to changes in systemic pressure even after baroreceptor denervation and pontine transection (Baust and Katz, 1961; Baust et al., 1962; Frazier et al., 1965). Thus, it is possible that the results of Hilton and Spyer were due to the direct effects of arterial pressure change. Furthermore, hypothalamic units respond to changes in blood gases but these may also be due to direct effects and may not be mediated by peripheral chemoreceptors (Cross and Silver, 1963). Since then it has been shown that hypothalamic units respond to single pulse electrical stimulation of the carotid sinus and aortic depressor nerves and selective activation of carotid baro- and chemoreceptors (Barker et al., 1971; Calaresu and Ciriello, 1980; Dreifuss et al., 1976; Spyer, 1972; Thomas and Calaresu, 1972; Yamashita, 1977). In a systematic exploration of the hypothalamus it was demonstrated that responsive units are located primarily in the supraoptic and paraventricular nuclei of the hypothalamus (Calaresu and Ciriello, 1980).

In support of the demonstration that the paraventricular nucleus of the hypothalamus receives baro- and chemoreceptor information, there is anatomical and electrophysiological evidence that the nucleus of the solitary tract, the primary site of termination of buffer nerve afferents, projects directly to the paraventricular

nucleus as originally demonstrated by Ricardo and Koh (1978). More detailed autoradiographic studies since then have demonstrated that the catecholaminergic A2 region of the medulla at the level of the obex projects to the parvocellular division of the paraventricular nucleus (Ciriello and Calaresu, 1980; McKellar and Loewy, 1981; Sakumoto et al., 1978; Sawchenko and Swanson, 1981; 1982) and confirmed by retrograde labelling experiments (Berk and Finkelstein, 1981; Sakumoto et al., 1978; Takagi et al., 1980; Tribollet and Dreifuss, 1981) and electrophysiology (Ciriello and Calaresu, 1980). Another catecholaminergic medullary region involved in cardiovascular control, the A1 cell group in the ventral lateral medulla, also sends a large projection to the paraventricular nucleus of the hypothalamus (Sawchenko and Swanson, 1981; 1982; Swanson and Sawchenko, 1983).

Alternatively, the neuroanatomical data suggest that cardiovascular afferent information to the hypothalamus might also be relayed through the parabrachial nucleus. The parabrachial nucleus, in addition to receiving direct projections from the site of termination of the buffer nerves in the nucleus of the solitary tract, also projects directly to the paraventricular nucleus of the hypothalamus. The results of an autoradiographic study in the rat by Saper and Loewy (1980) suggest that the projection to the paraventricular nucleus of the hypothalamus from the parabrachial nucleus originates primarily from the lateral visceral part of the parabrachial nucleus. These results can be contrasted to those of another autoradiographic study in which the injection sites were confined to the medial gustatory portion of the parabrachial nucleus in

the projection was seen to pass through the lateral hypothalamus with little labelling in the region of the paraventricular nucleus of the hypothalamus (Norgren, 1976). The results obtained by autoradiography have been confirmed by horseradish peroxidase injections in the paraventricular nucleus of the hypothalamus which resulted in retrograde labelling of many cells in the lateral parabrachial nucleus (Berk and Finkelstein, 1981; Tribollet and Dreifuss, 1981).

4. Amygdalar control

Many of the behaviors associated with the amygdala have complex cardiovascular adjustments. On this basis it would be difficult to predict the cardiovascular response from any one area of the amygdala (Kaada, 1972). Other factors such as species, anesthetics, and frequency and intensity of stimulation also appear to affect the cardiovascular response elicited from the amygdala. One of the first investigations of blood pressure changes elicited by stimulation of the amygdala in the anesthetized monkey obtained a hypotensive response (Kaada, 1951). However, some points were frequency dependent such that low frequency stimulation elicited hypertension (Kaada, 1951). These results were confirmed by other investigations. Stimulation of the amygdala in cats and monkeys elicited a decrease in blood pressure which frequently became an increase in arterial pressure when changing to a high frequency or high intensity stimulation (Anand and Dua, 1956; Andy et al., 1959; Gebber and Klevans, 1972; Koikegami et al., 1957; Torii and Kawamura, 1960; Wood et al., 1958; Yokota et al., 1963). However, in a more extensive exploration of

the amygdala in the anesthetized cat, Morin et al. (1952) demonstrated that at a low stimulus intensity an increase in arterial pressure is obtained from the dorsomedial amygdala while a hypotensive response is elicited from the lateral amygdala. These results have been confirmed in the unanesthetized cat in which low intensity stimulation elicits an increase in arterial pressure from the central nucleus of the amygdala and a decrease in pressure from the basolateral amygdala which changes to a hypertensive response with an increase in stimulus intensity (Heinemann et al., 1973; Stock et al., 1978).

Heart rate responses in cats resulting from stimulation of the amygdala have shown the same dorsomedial, ventrolateral separation with tachycardia obtained primarily from the dorsomedial amygdala and bradycardia from the ventrolateral amygdala (Bonvallet and Bobo, 1972; Heinemann et al., 1973; Stock et al., 1978). In monkeys the bradycardic response obtained primarily from the basomedial amygdala was surrounded by points yielding tachycardia (Reis and Oliphant, 1964).

In anesthetized rats and rabbits hypotension and no change in heart rate are obtained from most nuclei of the amygdala (Faiers et al., 1975; Galeno and Brody, 1982; 1983; Kapp et al., 1982; Mogenson and Calaresu, 1973; Wood et al., 1958). However, it has been shown that stimulation in the central nucleus of the amygdala in the unanesthetized rat elicits an increase in arterial pressure and tachycardia (Galeno and Brody, 1982; 1983).

Recently other cardiovascular functions of the amygdala have been investigated. It has been demonstrated that lesions and chemi-

cal blocking agents in the central nucleus of the amygdala attenuate a conditioned bradycardic response in rabbits (Gallagher, 1980; 1981; Kapp et al., 1979). This is supported by results showing that there is an increase in amygdalar unit activity with heart rate conditioning (Applegate, 1982). Finally, it has been demonstrated that lesions in the central nucleus of the amygdala inhibit the development of high blood pressure in spontaneously hypertensive rats (Folkow et al., 1982; Galeno et al., 1982).

In the cat the ventral amygdalofugal pathway has been demonstrated to mediate cardiovascular responses (Hilton and Zbrozyna, 1963). In the anesthetized rat lesions in the medial forebrain bundle block the hypotensive response to stimulation of the amygdala (Faiers et al., 1975). These results in the rat and the cat are not incompatible as it is known that fibers of the ventral amygdalofugal pathway join the medial forebrain bundle in both rat and cat (Gurdjian, 1928; Millhouse, 1969).

It is possible that the cardiovascular responses originating in the amygdala are mediated by a direct projection to the medulla as a descending projection from the central nucleus of the amygdala to the nucleus of the solitary tract and dorsal motor nucleus of the vagus can be demonstrated in species such as the rabbit, cat, rat and monkey (Hopkins, 1975; Hopkins and Holstege, 1978; Hopkins et al., 1981; Price and Amaral, 1981; Schwaber et al., 1980; Schwaber et al., 1982). These results indicate that the projection is primarily ipsilateral and originates from the medial component of the central nucleus of the amygdala. Recently, evidence has been presented demonstrating a long descending somatostatin-containing neuron system from the amygdala to the lower brain stem (Kawai et al.,

1982).

The descending cardiovascular signals from the amygdala may also relay in the parabrachial nucleus as a descending projection to the parabrachial nucleus has been demonstrated in the rat, cat and monkey using autoradiography, horseradish peroxidase and fiber degeneration methods (Hopkins and Holstege, 1978; Hopkins et al., 1981; Krettek and Price, 1978; Price and Amaral, 1981; Takeuchi et al., 1982).

The first evidence that cardiovascular afferent information might project to the amygdala was the demonstration by Dell and Olson (1951) that stimulation of the vagus nerve in the cat elicited evoked potentials in the central and lateral nuclei of the amygdala. This vagal projection has been confirmed by recording changes in single unit activity in the amygdala in response to stimulation of the vagus in the monkey (Radna and MacLean, 1976; 1981). More direct evidence for the projection of cardiovascular afferent information are the results of experiments in which evoked potentials were recorded in the amygdala in response to stimulation of the central cut end of the carotid sinus nerve (Hockman and Livingston, 1970). In addition amygdala unit activity changes related to spontaneous blood pressure increases have been observed in the lateral nucleus (Ben Ari et al., 1973).

Possible pathways for cardiovascular information from the medulla to the amygdala are suggested by neuroanatomical investigations. Ricardo and Koh (1978) using both horseradish peroxidase and autoradiographic methods, demonstrated in the rat that the nucleus of the solitary tract projects directly to the central nu-

cleus of the amygdala, a projection which has been confirmed by others (Ottersen, 1981; Pretorius et al., 1979). This projection cannot be demonstrated in other species such as the cat and monkey (Mehler, 1980; Ottersen, 1981; Russchen, 1982).

The cardiovascular afferent information from the nucleus of the solitary tract may relay in the parabrachial nucleus or the hypothalamus as both have been demonstrated to receive buffer nerve information as previously discussed and both areas project directly to the amygdala. Many neuroanatomical studies have demonstrated a direct projection from the parabrachial nucleus to the region of the central nucleus of the amygdala in the rat, cat and monkey (Mehler, 1980; Norgren, 1976; Ottersen, 1981; Russchen, 1982; Saper and Loewy, 1980; Takeuchi et al., 1982; Veening, 1978; Voshart and Van der Kooy, 1981). Injections of horseradish peroxidase in the central nucleus of the amygdala in the rat and cat have shown that the retrogradely labelled cell bodies are located primarily in the ventrolateral portion of the parabrachial nucleus (Ottersen, 1981; Russchen, 1982). The central nucleus of the amygdala also receives a projection from the paraventricular nucleus of the hypothalamus as demonstrated by the deposit of horseradish peroxidase in the central nucleus of the amygdala (Russchen, 1982), injection of ^{3}H amino acids in the paraventricular nucleus of the hypothalamus (Conrad and Pfaff, 1976) and antidromic stimulation of single units in the paraventricular nucleus of the hypothalamus by stimulation in the amygdala (Pittman et al., 1981). Swanson (1977) demonstrated that neurophysin stained fibers from the paraventricular nucleus of the hypothalamus could be followed to the amygdala suggesting that the path-

way may be oxytocinergic.

D. Objectives of Experimental Work

The objectives of this project were to study the precise location of projections of cardiovascular afferent information to the amygdala and to elucidate the central pathway(s) involved in relaying this information to the amygdala. Some background information and the experimental approach for achieving these objectives is presented.

1. Projection of cardiovascular afferent information to the amygdala

Support for the possibility that information from cardiovascular afferents may project to the amygdala is given by the demonstration that electrical stimulation of the cortical nucleus of the amygdala facilitates the cardiac vagal component of the baroreceptor reflex (Gebber and Klevans, 1972). Additional support is given by the finding that electrical stimulation of buffer nerves alters the activity of single units in the hypothalamus (Calaresu and Ciriello, 1980) in specific regions known to project to the amygdala (Mehler, 1980; Ottersen, 1981; Russchen, 1982). Furthermore, neuroanatomical studies have shown that the nucleus of the solitary tract, a known site of termination of buffer nerves, projects directly to these hypothalamic areas (Ciriello and Calaresu, 1980 a & b; Ricardo and Koh, 1978), as well as directly to the amygdala of the rat (Ottersen, 1981; Ricardo and Koh, 1978), although convincing evidence for thia direct connection has not been presented for the cat (Ottersen, 1981) nor for

the monkey (Mehler, 1980). Finally, the existence of projections from buffer nerves to the amygdala is also supported by electrophysiological recordings in the amygdala. Stimulation of the carotid sinus nerve evokes mass electrical potentials in the amygdala (Hockman, 1970) and stimulation of the central stump of the cervical vagus, including the aortic depressor nerve, elicits short latency evoked potentials in the central and lateral nuclei of the amygdala (Dell and Olson, 1951). Furthermore, activity of units in the central nucleus of the amygdala of the squirrel monkey can be altered by stimulating the cervical vagus, probably including the aortic depressor nerve (Radna and MacLean, 1981).

In view of the anatomical and physiological evidence reviewed, in the first series of experiments the possibility that the carotid sinus nerve and the aortic depressor nerve could affect the electrical activity of single units in the amygdala was investigated in the anesthetized cat by a systematic exploration of the amygdala for spontaneously firing units responding to stimulation of these nerves.

2. Selective baro- and chemoreceptor input to the amygdala

It has been demonstrated that stimulation of the dorsomedial amygdala elicits rage and defence behavior with a concomitant increase in arterial pressure and that stimulation of the lateral amygdala inhibits these responses (Fonberg, 1963; 1968; 1981; Hilton and Zbrozyna, 1963; Kaada, 1972; Morin et al., 1952). It has also been shown that diencephalic rage and defence behaviors may be elicited by chemoreceptor activation and inhibited by baroreceptor activation (Baccelli, 1965; Marshall, 1981). This latter finding suggests

that there may exist an anatomical separation of cardiovascular afferent inputs to the amygdala, with chemoreceptors projecting to the dorsomedial amygdala and baroreceptors projecting to the lateral amygdala and that these separate inputs suggest an important functional role for cardiovascular afferent information projections to the amygdala. The first series of experiments in this project demonstrated that spontaneously active single units in the central, lateral and dorsal portions of the basal nuclei of the amygdala alter their firing rate in response to electrical stimulation of the carotid sinus nerve and aortic depressor nerve in the cat, nerves which are composed of both baro- and chemoreceptor afferent fibers (Heymans and Neil, 1958; Douglas and Schaumann, 1956). In a second series of experiments the possibility of the existence of separate projections to the amygdala of baro- and chemoreceptors was tested in cats under chloralose in which the central, lateral and basal nuclei of the amygdala were explored for spontaneously firing units responding to selective activation of baro- and chemoreceptors.

3. Afferent projections to cardiovascular sites in the amygdala

This demonstrated projection of cardiovascular afferent information to the amygdala could follow at least two possible central pathways from the nucleus of the solitary tract, the primary site of termination of baro- and chemoreceptor fibers (Ciriello and Calaresu, 1981; Davies and Kalia, 1981), to the amygdala. One pathway would probably include a relay in the hypothalamus in view of the electrophysiological and neuroanatomical evidence showing direct projections from the nucleus of the solitary tract to the hypothalamus (Ciriello

and Calaresu, 1980 a; Ciriello and Calaresu, 1980 b; Ricardo and Koh, 1978), and a direct pathway from the hypothalamus to the amygdala (Conrad and Pfaff, 1976 a & b; Krieger et al., 1979; Mehler, 1980; Ottersen, 1980; Pittman et al., 1981; Renaud and Hopkins, 1977; Russchen, 1982; Saper et al., 1976; 1977; Veening, 1978). An alternate pathway could relay through the region of the parabrachial and Kolliker-Fuse nuclei as direct pathways have been demonstrated electrophysiologically and neuroanatomically from the nucleus of the solitary tract to the parabrachial and Kolliker-Fuse nuclei (Hamilton et al., 1981; Loewy and Burton, 1978; Norgren and Leonard, 1973; Norgren, 1978; Ricardo and Koh, 1978), and from the parabrachial and Kolliker-Fuse nuclei to the amygdala (Mehler, 1980; Norgren, 1976; Ottersen, 1981; Russchen, 1982; Saper and Loewy, 1980; Veening, 1978).

Although there is a wealth of neuroanatomical studies demonstrating afferent connections to the amygdala (Mehler, 1980; Ottersen, 1980 a & b; 1982; Ottersen and Ben Ari, 1978 a & b; 1979; Russchen, 1982 a & b; Veening, 1978) there has been no attempt at investigating the afferent connections of specific areas involved in cardiovascular control. Therefore, in a third series of experiments, the sensitive tetramethylbenzidine horseradish peroxidase method (Mesulam, 1978) and very discrete deposits of horseradish peroxidase were used to demonstrate retrograde neuronal labelling in brain areas which project to the central, lateral and dorsal part of the basal nuclei of the amygdala previously demonstrated to receive baro- and chemoreceptor information.

4. Projection of cardiovascular afferent information to the parabrachial and Kolliker-Fuse nuclei

The results of the third series of experiments and the results of other investigators (Ottersen, 1981; Russchen, 1982) have demonstrated that two nuclear regions, the paraventricular nucleus of the hypothalamus and the parabrachial and Kolliker-Fuse nuclei have direct projections to the amygdala. Stimulation studies have demonstrated that both these areas are involved in cardiovascular control (Ciriello and Calaresu, 1980; Hamilton et al., 1981; Mraovitch et al., 1981). In addition, a systematic exploration in the hypothalamus for spontaneously firing units responding to electrical stimulation of the carotid sinus and aortic depressor nerves has demonstrated the projection of cardiovascular afferents to the paraventricular nucleus of the hypothalamus. However, no comparable study had been done in the parabrachial and Kolliker-Fuse nuclei.

There is extensive experimental evidence, obtained with different techniques, showing that the medial parabrachial and Kolliker-Fuse nuclei are involved in the relay and integration of autonomic information to and from the forebrain (Takeuchi et al., 1982; Saper and Loewy, 1980). The parabrachial and Kolliker-Fuse nuclei have been shown to receive ascending inputs from the nucleus of the solitary tract (Loewy and Burton, 1978; Norgren, 1978), a known site of termination of baroreceptor and chemoreceptor afferent information (Ciriello et al., 1981). The parabrachial and Kolliker-Fuse nuclei in turn project to areas of the forebrain such as the hypothalamus and amygdala (Russchen, 1982; Saper and Loewy, 1980) which are known to receive inputs from buffer nerves (Calaresu and

Ciriello, 1980). There are also reciprocal descending projections to the parabrachial and Kolliker-Fuse nuclei from the forebrain, in particular from the central nucleus of the amygdala and from the paraventricular nucleus of the hypothalamus (Hopkins and Holstege, 1978; Krettek and Price, 1978; Saper et al., 1976; Takeuchi et al., 1982). Furthermore, it has been demonstrated that the parabrachial and Kolliker-Fuse nuclei project to structures in the lower brain stem and spinal cord known to be involved in autonomic function (Dampney et al., 1982; Saper and Loewy, 1980; Takeuchi et al., 1980). In addition to these neuroanatomical studies, physiological experiments have shown that electrical stimulation of the parabrachial nucleus elicits an increase in arterial pressure and heart rate in the anesthetized paralyzed cat (Mraovitch et al., 1982), and bradycardia and pressor responses in the anesthetized paralyzed rabbit (Hamilton et al., 1981).

In view of these connections, of the effects of electrical stimulation on cardiovascular variables, and of the electrophysiological evidence in the rabbit that the aortic depressor nerve projects to the parabrachial nucleus (Hamilton et al., 1981), it was reasoned that the parabrachial nucleus may play a key role in handling afferent information from the cardiovascular system in relaying this information to the forebrain sites, and in turn, in sending control signals to cardiovascular effectors. To investigate this possibility, in a fourth series of experiments the parabrachial and Kolliker-Fuse nuclei were systematically explored for spontaneously firing single units responsive to electrical stimulation of the carotid sinus and aortic depressor nerves. In addition, to demonstrate that the para-

brachial and Kolliker-Fuse nuclei relay cardiovascular afferent information to forebrain sites, single units in the parabrachial nucleus, which had been antidromically activated by electrical stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus were also tested for a response to the carotid sinus and aortic depressor nerves. Finally, since it is known that the paraventricular nucleus of the hypothalamus and the central nucleus of the amygdala project directly to the parabrachial nucleus (Hopkins and Holstege, 1978; Saper et al., 1976) the effect of electrical stimulation of these two nuclei on the rate of firing of spontaneously active parabrachial single units was investigated.

5. Role of the paraventricular nucleus of the hypothalamus and the parabrachial and Kolliker-Fuse nuclei in relaying cardiovascular afferent information to the amygdala

The previous series of experiments identified two nuclear regions, the paraventricular nucleus of the hypothalamus and the parabrachial and Kolliker-Fuse nuclei in the pons as likely candidates to relay cardiovascular afferent information from the nucleus of the solitary tract to the amygdala. In addition, it was demonstrated that the parabrachial and Kolliker-Fuse nuclei relay some buffer nerve information to the amygdala and the paraventricular nucleus of the hypothalamus. These nuclei have been demonstrated neuroanatomically to receive direct projections from the nucleus of the solitary tract (Ciriello and Calaresu, 1980; Loewy and Burton, 1978; Ricardo and Koh, 1979) and electrophysiologically to receive buffer nerve information (Calaresu and Ciriello, 1981). The paraventricular nucleus

of the hypothalamus and the parabrachial and Kolliker-Fuse nuclei in turn have been demonstrated to project directly to the amygdala (Russchen, 1982).

The possibility that both the paraventricular nucleus of the hypothalamus and the parabrachial and Kolliker-Fuse nuclei relay cardiovascular information to the amygdala was tested in cats under chloralose in which the central, lateral and basal nuclei of the amygdala were explored for spontaneously active single units responding to electrical stimulation of the paraventricular nucleus of the hypothalamus and the parabrachial and Kolliker-Fuse nuclei. Units responsive to stimulation of the paraventricular nucleus of the hypothalamus and the parabrachial and Kolliker-Fuse nuclei were then tested for responses to selective activation of baro- and chemoreceptors.

METHODS

A. Electrophysiological Studies

1. General procedures

Experiments were done in 56 adult (1.8 - 4.0 kg) cats of either sex. Anesthesia was induced with ethyl chloride and ether and maintained with α-chloralose (60 mg/kg, IV initially, supplemented with doses of 30 mg/kg every 6-8 hours). Other anesthetics including althesin were tried but were found to be unsuitable due to lack of preparation stability. The trachea was cannulated and polyethylene catheters were inserted into the femoral vein for administration of drugs. Arterial pressure, monitored with a Statham P23D transducer, and heart rate, measured by a Grass 7P44B tachograph triggered by the arterial pressure pulse, were continuously recorded on a Grass model 7 polygraph. A heating pad controlled by a Yellow Springs 73 temperature controller maintained rectal temperature at 37 ± 0.2° C.

The animals were paralyzed with decamethonium bromide (Sigma, St. Louis, MO; 0.5 mg/kg IV initially and additional doses when needed) and artificially ventilated. The level of anesthesia under these conditions was tested regularly by allowing the animal to recover from the administration of decamethonium.

2. Surgical procedures

a. Exposure of the buffer nerves for electrical stimulation

The left carotid sinus and aortic depressor nerves were

approached by a ventrolateral incision parallel to the midline in the neck extending from the tympannic bulla to about 5 cm caudal. The cranial portion of the sternomastoid muscle was reflected and the aortic depressor nerve was identified distal to the nodose ganglion, separated from the vagus and crushed distally. The carotid sinus nerve was isolated by removing the mandibular gland, reflecting the digastric muscle and removing a 2 cm segment of the hypoglossal nerve. The central ends of the isolated crushed nerves were placed on bipolar stainless steel electrodes and covered with cotton pellets soaked in warm Dow Corning 360 medical fluid (Dow Corning, Midland, MI).

b. Preparation of carotid sinus and carotid body for selective activation of baroreceptors and chemoreceptors

Both aortic depressor nerves and the right carotid sinus nerve were approached as previously described, and cut. The left common carotid artery, its bifurcation into the internal and external branches, and the medial thyroid artery were exposed. The medial thyroid artery was cannulated with a 15 cm length of PE-50 tubing and the tip of the cannula was inserted rostrally into the common carotid artery until it lay immediately caudal to the bifurcation. A thread was looped around the common carotid artery immediately caudal to the medial thyroid artery and the ends of the thread were passed through a 10 cm segment of polyethylene tubing (PE-240, Clay Adams, Parsipanny, NJ) forming a snare which could be used to temporarily occlude the common carotid artery.

c. *Exposure of brain*

The head of the animal was fixed in a Kopf stereotaxic frame and access to the parabrachial nucleus was obtained by removing portions of the parietal and occipital bones and removing the right or left cerebellum by suction. Access to the hypothalamus and amygdala was obtained through a rectangular hole (10 mm x 12 mm) in the parietal bone. Exposed cortex and brain stem were covered with warm medical fluid to prevent drying.

3. Electrical stimulation

a. *Stimulation of buffer nerves*

To elicit changes in the firing frequency of spontaneously firing single units, the carotid sinus and aortic depressor nerves were stimulated with bipolar stainless steel electrodes using 0.3 ms pulses every two seconds, at a current intensity of 1-3 times "threshold" (current necessary to elicit a decrease in heart rate of 6-10 beats per minute with a 5 second train at 30 Hz and 0.3 ms pulse duration).

b. *Stimulation of the amygdala, hypothalamus and parabrachial nucleus*

The central nucleus of the amygdala, paraventricular nucleus of the hypothalamus and parabrachial nucleus were stimulated through the central pole of bipolar stainless steel electrodes (SNEX-100, David Kopf, Tujunga, CA; 0.25 mm tip diameter, 50-100 kΩ initial DC resistance in saline); a hypodermic needle inserted into scalp muscles served as the indifferent electrode. Electrodes were positioned using stereotaxic coordinates and cardiovascular responsive

sites were selected when pressor responses from the three nuclear regions could be elicited by stimulation using 10 s trains of 0.3 ms pulses at a frequency of 80 Hz and an intensity of 50-500 μA. The stimulus was generated by a Grass S88 stimulator and was delivered to the central nucleus of the amygdala, paraventricular nucleus of the hypothalamus and parabrachial nucleus through a Grass (SIU5) stimulus isolation unit. The stimuli to elicit responses in single units were 0.3 ms pulses every 2 seconds at an intensity of 50-800 μA. For each responsive unit the minimum current required to elicit a change in the firing rate of single units was determined.

4. Selective activation of baro- and chemoreceptors

Left carotid sinus baroreceptors were activated by intravenous administration of phenylephrine (Sigma, St. Louis, MO; 1-2 μg/kg in 1 ml saline, IV). This method has been shown to selectively excite baroreceptors (Gebber and Snyder, 1970). The appearance of a transient blood pressure increase in response to the administration of phenylephrine and reflex bradycardia was taken as evidence of the activation of baroreceptors. In addition, the baroreceptor input from the left carotid sinus could be eliminated (baroreceptor unloading) by temporary occlusion (5-10 s) of the left common carotid artery below the bifurcation; this resulted in a transient reflex increase in blood pressure and heart rate followed by bradycardia when the blood flow to the left carotid sinus was restored.

Left carotid body chemoreceptors were activated by injection of sodium cyanide (Fisher, Montreal, QUE; 25-50 μg in 0.1 ml sa-

line) into the left common carotid artery via a cannula in the medial thyroid artery. This method of administration has been shown to selectively excite carotid body chemoreceptors (Fidone and Sato, 1969; Jacobs et al., 1971). The appearance of a transient increase in blood pressure and marked bradycardia after administration of sodium cyanide was taken as evidence of the activation of chemoreceptors. A control injection of saline (0.1 ml) into the left common carotid artery did not elicit any changes in heart rate or blood pressure.

5. Recording of single units during electrical stimulation of buffer nerves

a. Single units in the amygdala

Extracellular recordings from spontaneously firing units were obtained using microelectrodes made from stainless steel wire, 280 µm in diameter (Small Parts, Inc., Miami, FL) according to the method described by Green (1958). The electrodes had a tip diameter of 1-3 µm and a DC resistance in saline of 0.5 - 2.0 MΩ. The indifferent electrode was a hypodermic needle inserted into the brain. The amygdala was systematically explored using a grid with points 1 mm apart, extending 9-14 mm rostral to the interaural line, 7-14 mm lateral to the midline and from the horizontal zero to 8 mm ventral. Single unit activity was amplified through a Grass P15 preamplifier and displayed on the screen of a Tektronix R5103N storage oscilloscope from which Polaroid photographs could be obtained. The spikes were also discriminated by a Neurolog 200 Spike

trigger and peristimulus time histograms were generated by a Neurolog 750 averager and recorded on a Grass 7 polygraph. Latency and duration of single unit responses were determined from the peristimulus time histograms. The latency was calculated as the time from the stimulus artifact to a 50% change in frequency of discharge while the duration was the time during which the frequency was altered by at least 50%. There were 250 bins in each sweep. Thus, the bin width of the peristimulus time histogram was determined by the sweep duration. Typically, a sweep of 250 ms duration with a bin width of 1 ms was used. To determine a 50% change in frequency of discharge, the average firing rate before the stimulus was compared with the average of 2 sequential bins after the stimulus.

b. Single units in the parabrachial nucleus

Extracellular recordings from spontaneously firing units were obtained from stainless steel microelectrodes as described for recordings in the amygdala. The recording electrodes were inserted at an angle of 40° with respect to the frontal plane to avoid contact with the bony tentorium cerebelli. The region of the parabrachial nucleus was systematically explored using a grid with points 1 mm apart, extending from 1 mm rostral to 2 mm caudal to the caudal edge of the inferior colliculus, 2-5 mm lateral to the midline and from the surface of the brain stem to 6 mm ventral. Single unit activity was amplified through a Grass P15 and displayed as previously described. However, peristimulus time histograms were generated by a Neurograph STA-1 microprocessor (Medical Systems Corp., Great Neck, NY) and plotted on an Epson MX-80 printer. Responses of parabrachial units were identified as antidromic according to established

criteria (Lipski, 1981). These criteria included constant latency of the evoked spike, high frequency following and occurrence of a single evoked spike at threshold and suprathreshold stimulus intensities.

6. Recording of single units in the amygdala during selective activation of baro- and chemoreceptors

Extracellular recordings from spontaneously firing units were obtained using insulated stainless steel electrodes as previously described. The central, lateral and basal nuclei of the amygdala, were explored as these areas had been shown in the first series of expetiments to receive an input from the carotid sinus nerve. Single unit activity was amplified and displayed as previously described. Continuous time frequency histograms were generated by a Neurograph STA-1 microprocessor (Medical Systems Corp., Great Neck, NY) and plotted on an Epson MX-80 printer. All unit responses to baro- or chemoreceptor input were verified by a second continuous frequency histogram.

7. Histological localization of recording and stimulating sites

Sites of recording and stimulation were identified by depositing iron from the electrode tip (30 μA for 30 s). The animals were perfused with 0.9% normal saline followed by a 1% potassium ferrocyanide in 10% formalin solution to stain the marked sites by the Prussian blue reaction. The brains were removed and fixed in 10% formalin for 1 week and transverse frozen sections (50 μm) were stained with nuclear fast red. Recording and stimulation sites were mapped on drawings of transverse sections of the hypothalamus

and amygdala and of parasagittal sections of the parabrachial nucleus modified from the stereotaxic atlases of Snider and Niemer (1961) and Berman (1961).

8. Data analysis

Statistical comparisons were made using analysis of variance and Duncan's new multiple range test for significant differences between means. A modified Chi square test was used for significant differences between the percentages of units responding (Sokal and Rolf, 1973). A p value of less than 0.05 was considered to indicate significance. Latencies and durations of single unit responses are expressed as the standard error of the means (SE) to give an estimate of the population variation.

B. Horseradish Peroxidase Study of Afferent Projections to the Amygdala

1. Deposit of horseradish peroxidase

Experiments were done in 11 cats of either sex weighing 2.0-3.4 kg anesthetized with sodium pentobarbital (Nembutal, Abbott Laboratories, Montreal, QUE; 35 mg/kg i.p.). The approach to the amygdala was through a small (2 mm diameter) hole in the parietal bone. Glass micropipettes (50-120 μm tip diameter) were partly filled with concentrated (>50%) horseradish peroxidase (Sigma VI, St. Louis, MO) in distilled water and the horseradish peroxidase was allowed to dry. The micropipettes were lowered stereotaxically into the amygdala and left in place for 1-2 hours to allow the

horseradish peroxidase to diffuse out. In 3 of the cats the micropipette was lowered at an angle of 20° with respect to the midsagittal plane as a control for spillage of horseradish peroxidase in structures dorsal to the amygdala which might have occurred in the vertical penetrations. Horseradish peroxidase was deposited in the central nucleus of the amygdala in 5 cats and in the lateral nucleus in 4 cats. In two cats horseradish peroxidase was allowed to diffuse into the optic tract for comparison with diffusion sites in the amygdala. At the end of the diffusion period the micropipette was removed, the incision closed and the animal allowed to recover from anesthesia.

2. Perfusion and preparation of histological sections

After a survival period of 24-144 hours the cats were re-anesthetized with sodium pentobarbital and perfused transcardially first with 800 ml of 0.9% NaCl, then with 1.0 l of fixative consisting of 1.25% glutaraldehyde and 1% paraformaldehyde in 0.1 phosphate buffer at pH 7.4 followed by 1.0 l phosphate buffer with 10% sucrose according to the method described by Mesulam (1978). The brain was immediately removed and placed in sucrose phosphate buffer at 4° C. Transverse sections of the forebrain (from approximately 8 mm to 16 mm anterior to the interaural line) and of the brain stem (from the interaural line to 14 mm posterior) were cut on a freezing microtome at 40 µm and processed according to the tetramethylbenzidine method (Mesulam, 1978). Perfusion, cutting, processing and mounting of the brain sections were done in the same day to minimize the loss of horseradish peroxidase reaction product. The tissue sections, both

unstained or counterstained with neutral red were systematically studied using both light- and dark-field microscopy. The distribution of neurons containing horseradish peroxidase reaction product was mapped on a representative series of projection drawings of the brain for each animal. The atlases of Snider and Niemer (1961) and Bleier (1961) were used for the identification of forebrain structures, while the atlas of Berman (1961) was used for the brain stem. The nomenclature and subdivisions of the amygdaloid nuceli were derived from the studies of Hall et al. (1969), Hall (1972) and Krettek and Price (1978).

RESULTS

A. Responses of Single Units in the Amygdala to Electrical Stimulation of the Buffer Nerves

1. Number and characteristics of single units responding to buffer nerve stimulation

Single units in the amygdala responded to electrical stimulation of the carotid sinus and aortic depressor nerves in one of three ways: excitation, inhibition, or excitation followed by inhibition (Fig. 3). Of 241 spontaneously firing (0.3 - 50 spikes/s) single units tested for their response to stimulation of the carotid sinus nerve, 36% (55/150) of the units in the ipsilateral amygdala and 20% (18/91) of the units in the contralateral amygdala altered their frequency of firing.

Of 251 spontaneously firing (0.3 - 50 spikes/s) units tested for their response to stimulation of the aortic depressor nerve, 21% (31/149) of the units in the ipsilateral amygdala and 19% (19/102) of the units in the contralateral amygdala altered their frequency of firing.

These results, including latencies and durations of the responses, are shown in Table I; excitatory responses followed by inhibition are grouped with the excitatory responses. An analysis of variance showed no significant differences among the durations but some significant differences among the latencies. Using Duncan's multiple range test the latencies of units excited by ipsilateral

FIGURE 3

Photographic records of typical responses of single units in the amygdala to electrical stimulation of the carotid sinus or aortic depressor nerves. A, slowly firing unit in central nucleus of the amygdala showing excitation in response to aortic depressor nerve stimulation (3 superimposed sweeps); B, unit in lateral nucleus of the amygdala showing inhibition in response to aortic depressor nerve stimulation (100 superimposed sweeps); C, unit in central nucleus of the amygdala showing excitation followed by inhibition in response to carotid sinus nerve stimulation (25 superimposed sweeps).

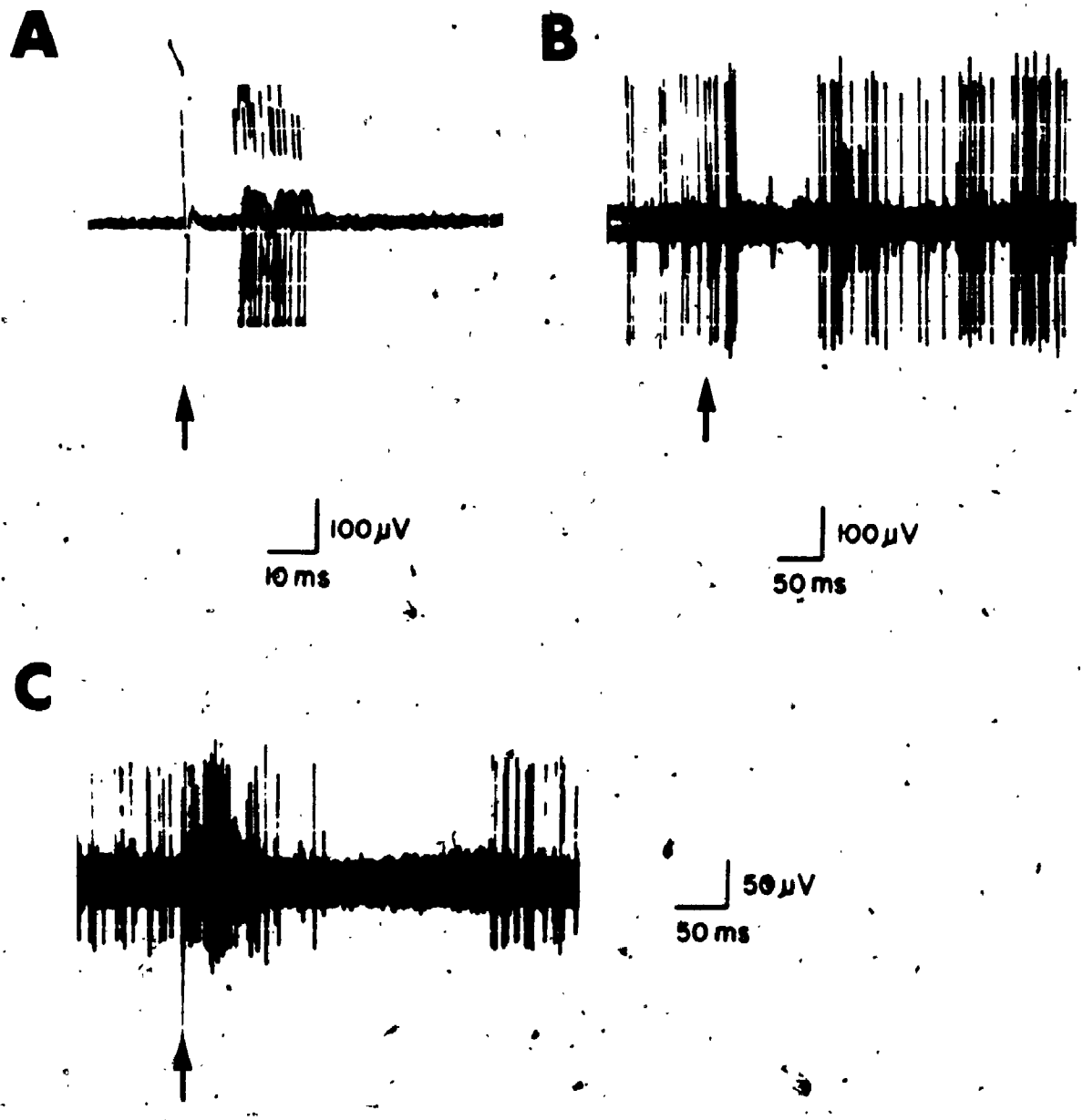

A
B
100 µV
10 ms
100 µV
50 ms
C
50 µV
50 ms

TABLE 1

Electrophysiological Characteristics of Units in the Amygdala Responding to Stimulation of the CSN and ADN

Nerve	Type of Response	Latency (ms) Ipsilateral		Latency (ms) Contralateral		Duration (ms) Ipsilateral	Duration (ms) Contralateral
CSN	Excited	35.5 ± 6.0^{a}	(23)	64.4 ± 10.2^{cd}	(11)	83.0 ± 24.7	59.2 ± 10.7
	Inhibited	58.6 ± 5.1^{bcd}	(32)	72.4 ± 17.7^{d}	(7)	99.8 ± 10.6	77.4 ± 9.6
ADN	Excited	20.5 ± 2.0^{a}	(24)	40.7 ± 5.9^{ab}	(10)	37.8 ± 13.9	44.4 ± 10.3
	Inhibited	42.4 ± 6.3^{abc}	(7)	61.4 ± 9.6^{bcd}	(9)	42.7 ± 7.1	54.2 ± 7.8

Latencies and durations are means $\pm$ SE; for the latencies, only means with different letters in superscript are significantly different ($p < 0.05$); numbers in parentheses are number of units in each group; CSN, carotid sinus nerve; ADN, aortic depressor nerve.

carotid sinus nerve stimulation were significantly shorter than the latencies of ipsilateral inhibitory responses and of contralateral excitatory responses. Frequency histograms of the latencies of single units responding to electrical stimulation of the carotid sinus and aortic depressor nerves are shown in Fig. 4.

When the same unit was tested for responses to stimulation of both carotid sinus and aortic depressor nerves, it was found that infrequently (7%, 14/188) spontaneously firing units responded to both nerves. Of these 14 units, ten exhibited responses in the same direction to stimulation of both nerves while the remaining four units showed opposite responses. Of these units responding to both, no significant difference between the average latencies to stimulation of the two nerves was found.

2. Distribution of single units responding to buffer nerve stimulation

The anatomical distribution of responsive single units was the same for ipsilateral and contralateral stimulation and is shown in Fig. 5. Responsive units were found primarily in the central nucleus, the lateral nucleus and dorsolateral portions of the basal nucleus of the amygdala. Although single units in the corticomedial amygdala were tested for their response to stimulation of the buffer nerves, none were shown to alter their frequency of firing in response to stimulation of the carotid sinus or aortic depressor nerves. In the most anterior section (A 13.5 mm) there appears to be a topographical separation of excited units from inhibited units: excited units were located in the central amygdaloid nucleus whereas inhibited units were found in the lateral amygdala.

FIGURE 4

Frequency histograms of the latencies of single units responding to electrical stimulation of the carotid sinus (CSN) and aortic depressor (ADN) nerves.

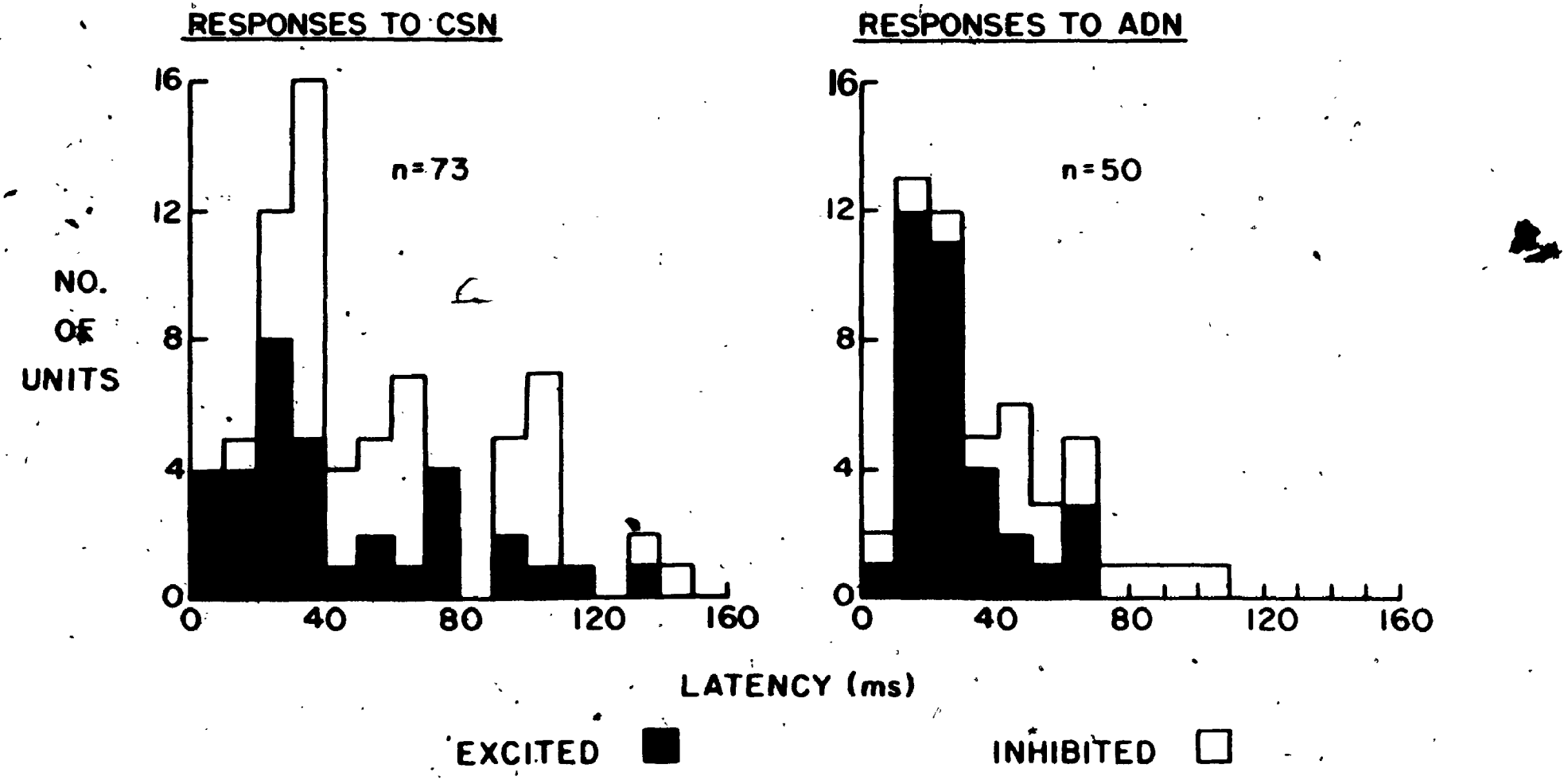
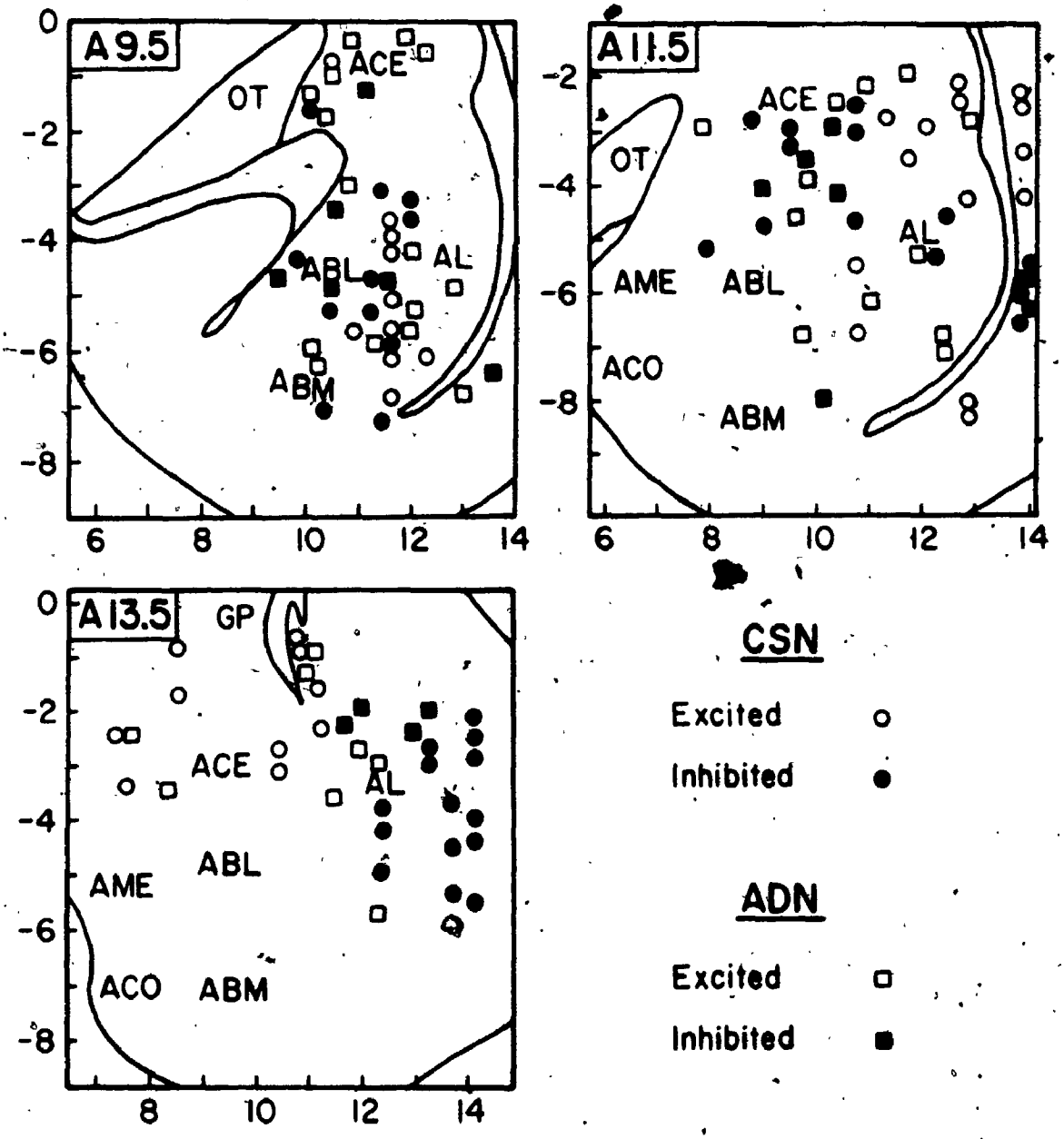

RESPONSES TO CSN
RESPONSES TO ADN
n=73
n=50
NO. OF UNITS
16
12
8
4
0
0
40
80
120
160
LATENCY (ms)
EXCITED
INHIBITED

FIGURE 5

Location of single units in the amygdala responding to stimulation of the ipsi- and contralateral carotid sinus (CSN) and aortic depressor (ADN) nerves shown in schematic transverse sections of the amygdala (from 9.5 to 13.5 mm rostral to the interaural line). Units in corticomedial amygdala were also tested but found to be unresponsive. Calibration scale in millimeters. ACE, central nucleus of the amygdala; AL, lateral nucleus; ABL, basolateral nucleus, magnocellularis; ABM, basomedial nucleus, parvocellularis; AME, medial nucleus; ACE, cortical nucleus; GP, globus pallidus; OT, optic tract.


A9.5
ACE
OT
AL
ABL
ABM
A11.5
ACE
OT
AL
AME
ABL
ACO
ABM
A13.5
GP
ACE
AL
ABL
AME
ACO
ABM
0
-2
-4
-6
-8
6
8
10
12
14
CSN
Excited
Inhibited
ADN
Excited
Inhibited

B. Response of Single Units in the Amygdala to Selective Activation of Carotid Baro- and Chemoreceptors

1. Number and characteristics of units responding to activation of baro- and chemoreceptors

One hundred and fifty-four spontaneously firing (0.3 - 30 spikes/s) single units were tested for their response to activation of carotid body chemoreceptors and carotid sinus baroreceptors. Units responded to activation of baro- and chemoreceptors in one of three ways: excitation, inhibition, or excitation followed by inhibition. In the presentation of the results excitatory responses followed by inhibition are grouped with the excitatory responses. Activation of chemoreceptors altered the firing frequency of 23% (35/154) of the units in the ipsilateral amygdala; of these units, those excited (37%) were not in significantly greater proportion than those inhibited (63%). These results are summarized in Table 2. An example of a single unit excited by activation of chemoreceptors is shown in Fig. 6A and one that was inhibited is shown in Fig. 6B.

Activation of baroreceptors altered the firing frequency of 16% (24/154) of the units in the ipsilateral amygdala; of these units, those excited (71%) were in significantly greater proportion than those inhibited (29%). Units which were excited or inhibited by activation of baroreceptors displayed the opposite response to unloading of baroreceptors. These results are summarized in Table 2. Examples of a unit excited by activation of baroreceptors (inhibited by unloading of baroreceptors) and one inhibited by activation

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TABLE 2

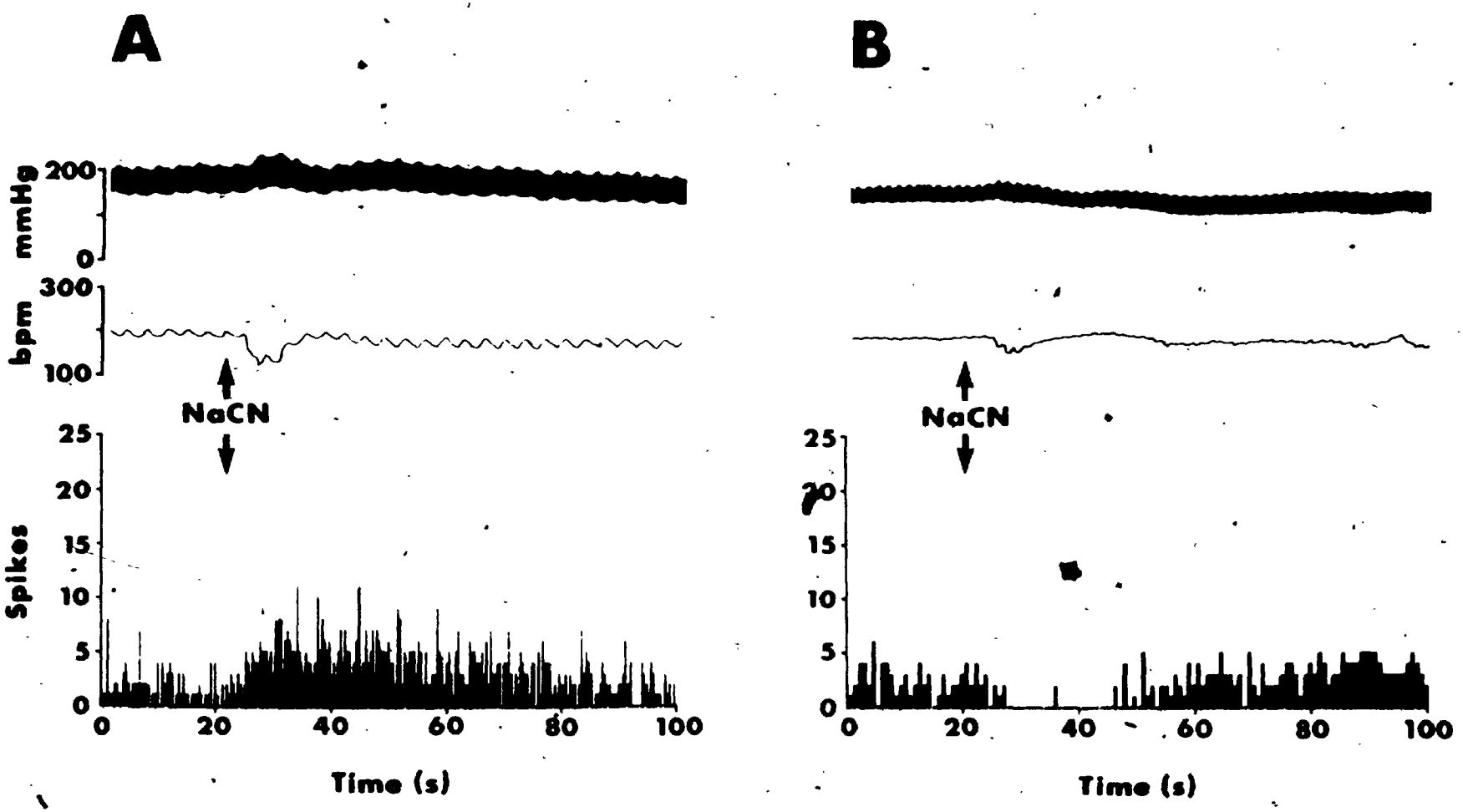
Characteristics of Units in the Amygdala Responding to Activation of Baro- and Chemoreceptors

Stimulus	No. of Units	Spontaneous Frequency (spikes/s)	Excited	Inhibited
CA	35	6.3 ± 0.91	37%(13/35)	63%(22/35)
BA	24	8.9 ± 1.49	71%(17/24)	29%*(7/24)

Spontaneous frequencies are means ± SE; asterisk indicates percentage of units inhibited was significantly different from percentage of units excited; BA, activation of left carotid sinus baroreceptors; CA, activation of left carotid body chemoreceptors.

FIGURE 6

Blood pressure and heart rate changes and continous frequency histograms of single unit activity in the central nucleus of the amygdala elicited by activation of carotid chemoreceptors by sodium cyanide. For both A and B, the upper trace is blood pressure, the middle trace is heart rate and the lower trace is the continuous frequency histogram of unit activity. A, a unit excited by activation of chemoreceptors; B, a unit inhibited by activation of chemoreceptors.


A
B
200
mmHg
0
300
bpm
100
NaCN
25
20
15
10
5
0
Spikes
0
20
40
60
80
100
Time (s)

baroreceptors (excited by unloading of baroreceptors) are shown in Fig. 7.

Of the units in the amygdala tested for a response to activation of baro- and chemoreceptors, none were found which responded to both types of stimuli.

2. Distribution of units responding to activation of baro- and chemoreceptors

Units responsive to activation of baro- and chemoreceptors were located primarily in the central, lateral and basal nuclei of the amygdala (Fig. 8). The units responsive to activation of chemoreceptors were located primarily medial and dorsal to the units responsive to activation of baroreceptors. There did not appear to be any anatomical separation between excited and inhibited units for activation of either baro- or chemoreceptors.

C. Demonstration of Afferent Connections to the Central and Lateral Nuclei of the Amygdala Using the Horseradish Peroxidase Method

1. Sites of diffusion of horseradish peroxidase in the central nucleus of the amygdala

The location of diffusion sites of horseradish peroxidase in the central nucleus of the amygdala is shown in Fig. 9. Sites in four of the cats were small (0.5 - 1.0 mm in diameter) and were contained entirely within the central nucleus while one deposit was about three times as large and extended to portions of adjacent nuclei. The central nucleus in the cat has been subdivided into lateral and

FIGURE 7

Blood pressure and heart rate changes and continuous frequency histograms of single units in the lateral amygdala elicited by activation of baroreceptors by phenylephrine (PE) or unloading of baroreceptors by occlusion of the common carotid artery (BU). A and B, from top to bottom, blood pressure, heart rate and continuous frequency histogram. A, a single unit excited by activation of baroreceptors and inhibited by unloading of baroreceptors. B, a single unit inhibited by activation of baroreceptors and excited by unloading of baroreceptors.

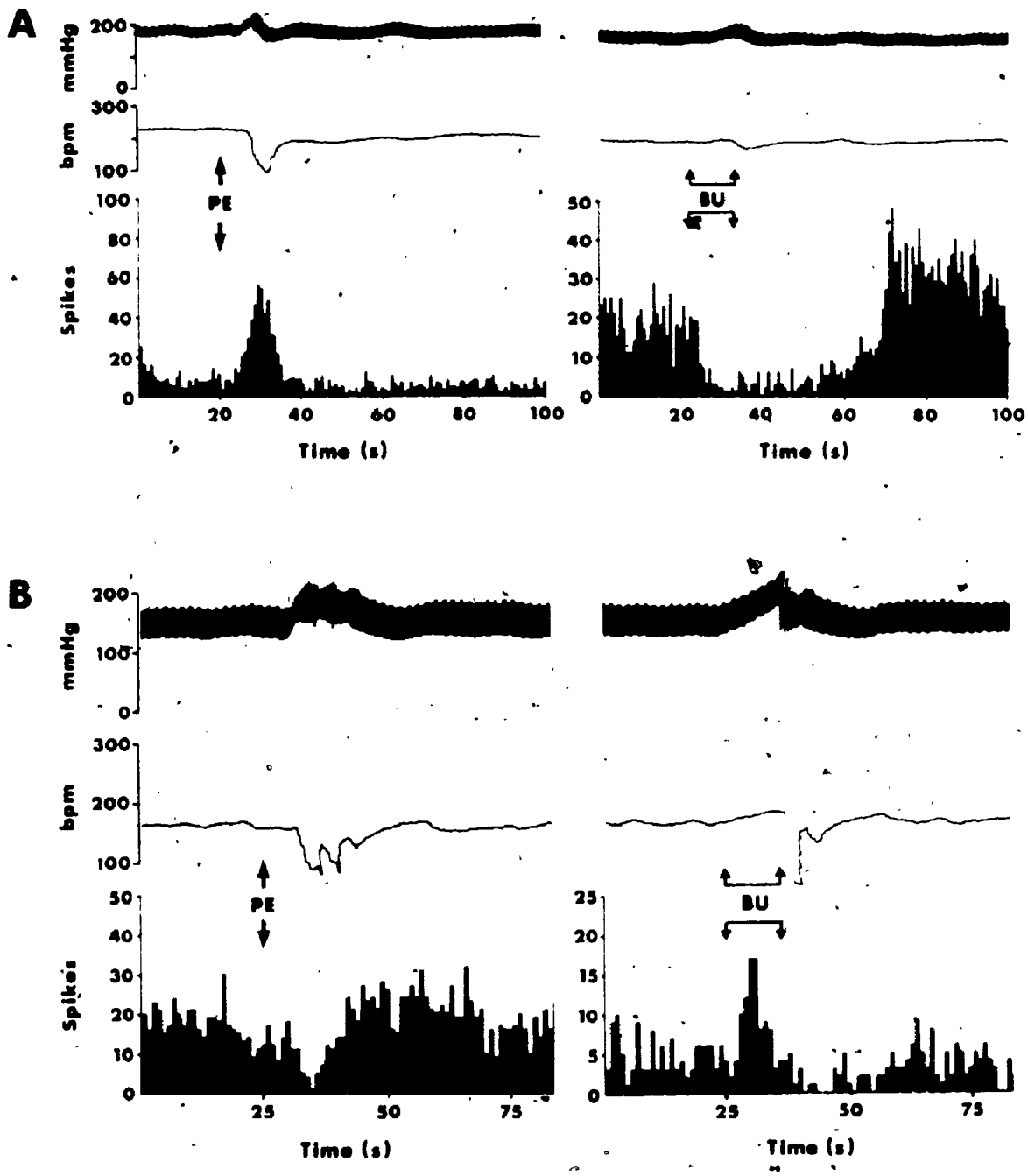

A
mmHg
200
0
bpm
300
100
PE
BU
Spikes
100
80
60
40
20
0
50
40
30
20
10
0
20
40
60
80
100
Time (s)
B
mmHg
200
100
0
bpm
300
200
100
PE
BU
Spikes
50
40
30
20
10
0
25
20
15
10
5
0
25
50
75
Time (s)

FIGURE 8

Location of units in the amygdala responding to activation of ipsilateral baro- and chemoreceptors shown in 4 transverse sections of the amygdala (from 9 to 12 mm anterior to the interaural line). Calibration scale in millimeters. △, excited by activation of chemoreceptors; ▲, inhibited by activation of chemoreceptors; □, excited by activation of baroreceptors; ■, inhibited by activation of baroreceptors; ●, unresponsive units. ABL and ABM, basolateral and basomedial nuclei of the amygdala; ACEl and ACEm, lateral and medial areas of the central nucleus of the amygdala; AL, lateral nucleus of the amygdala; AME, medial nucleus of the amygdala; EC, external capsule; IC, internal capsule; OT, optic tract.

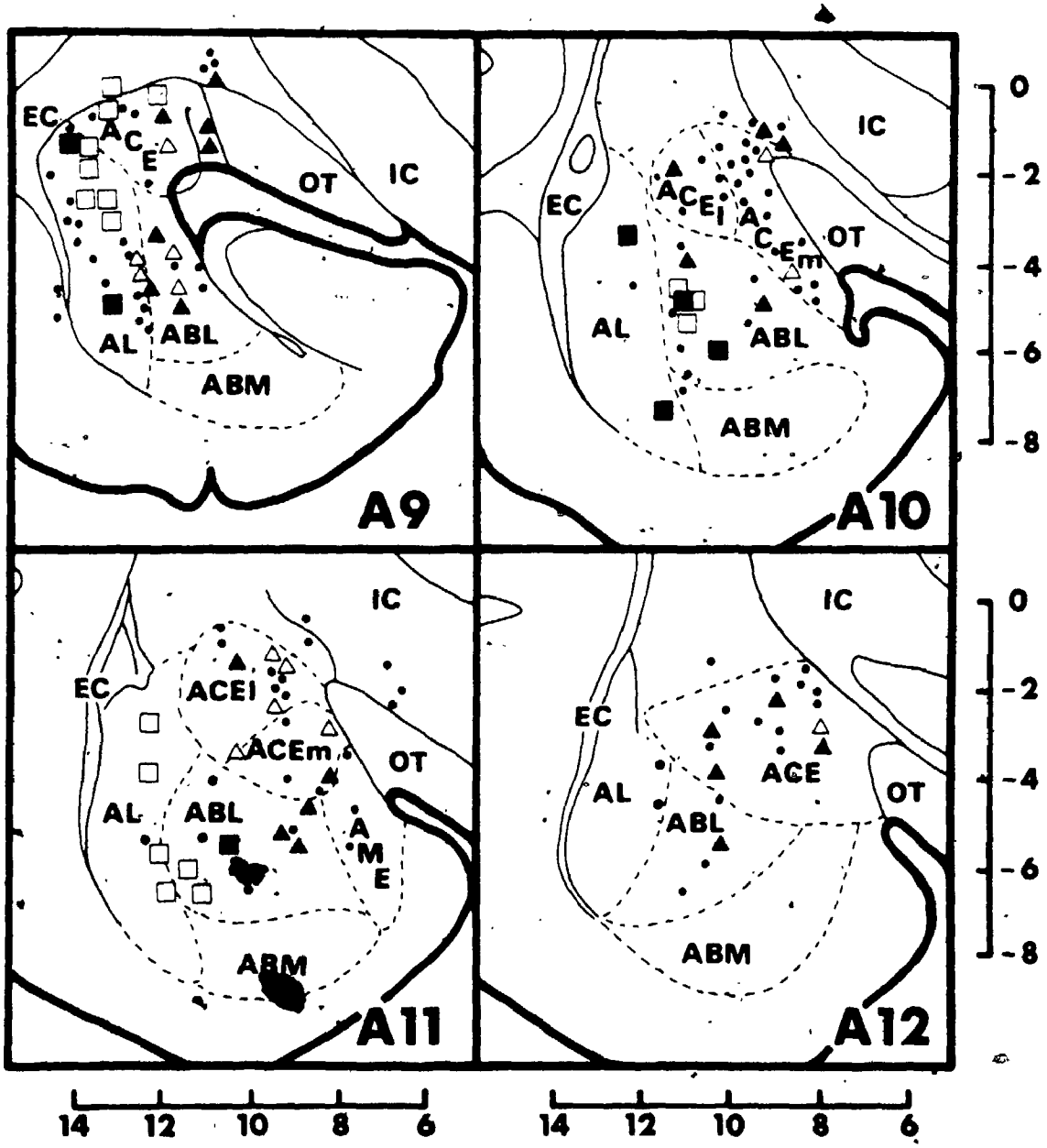
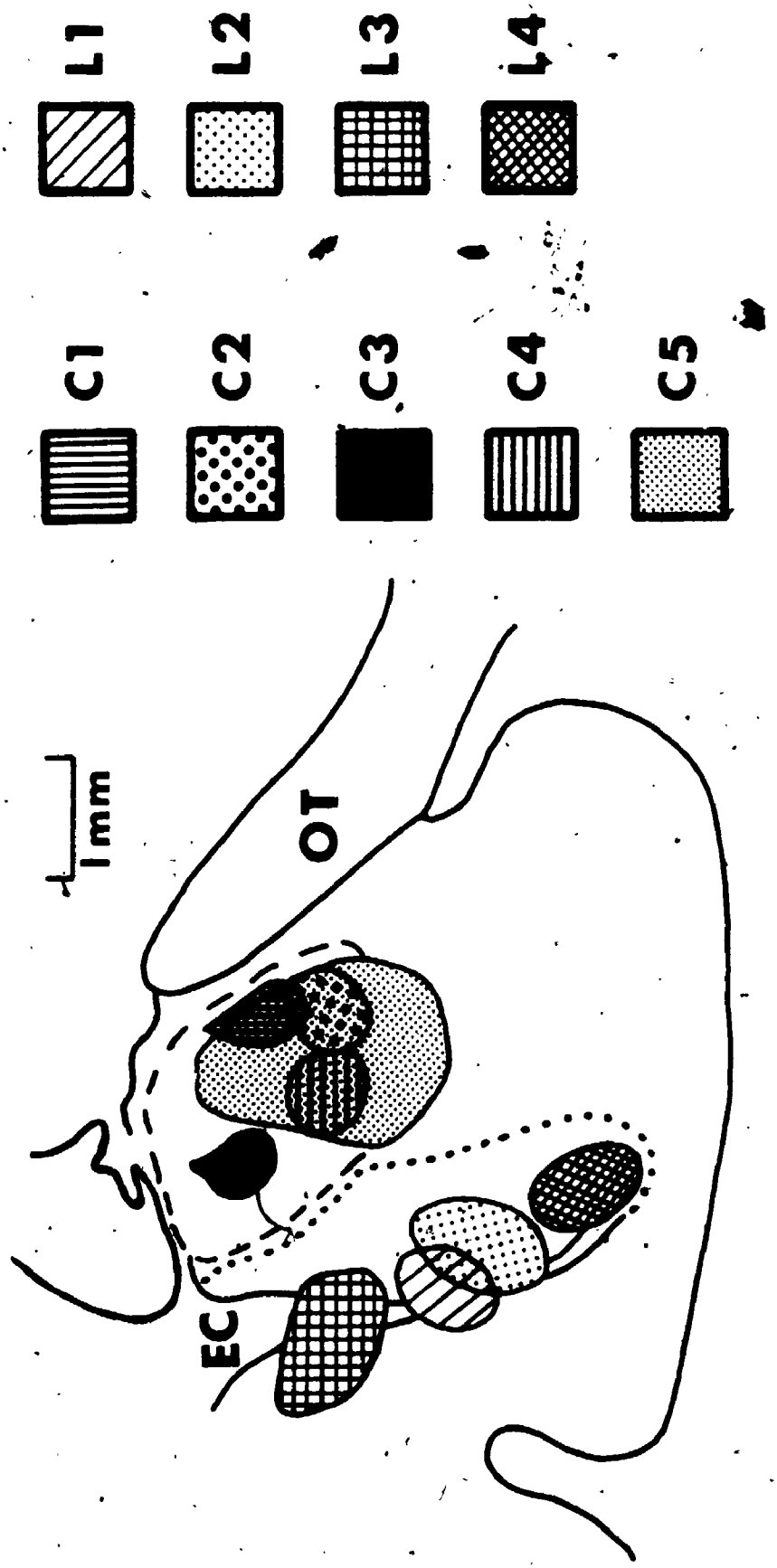

EC
ACE
OT
IC
AL
ABL
ABM
A9
IC
EC
ACEI
ACEm
OT
AL
ABL
ABM
A10
IC
EC
ACEI
ACEm
OT
AL
ABL
AME
ABM
A11
IC
EC
ACE
OT
AL
ABL
ABM
A12
0
-2
-4
-6
-8
14
12
10
8
6
14
12
10
8
6

FIGURE 9

Sites of diffusion of horseradish peroxidase in the central and lateral nuclei of the amygdala in a transverse section of the cat brain. The dashed lines show the boundary of the central nucleus of the amygdala and the dotted line the boundary of the lateral nucleus. EC, external capsule; OT, optic tract.


L1
L2
L3
L4
C1
C2
C3
C4
C5
1mm
OT
EC

medial subdivisions on the basis of cell size and shape (Hall, 1972). Two of the small diffusion sites (cats C1 and C2) were located within the medial subdivision of the central nucleus and the other two (C3 and C4) were in the lateral portion. A photomicrograph of the diffusion site in cat C1 is shown in Fig. 10A. The larger deposit (cat C5) covered the medial and some of the lateral subdivisions of the central nucleus as well as the dorsal portion of the basolateral nucleus. These deposits of horseradish peroxidase in the central nucleus and basolateral nucleus were all localized to areas receiving cardiovascular information from buffer nerves.

2. Hypothalamic projections to the central nucleus of the amygdala

Comparison of horseradish peroxidase diffusion sites located in the medial component of the central nucleus with diffusion sites in the lateral part of the central nucleus revealed striking differences in the labelling of cells in the ipsilateral hypothalamus. Discrete deposits (cats C1 and C2) of horseradish peroxidase in the medial portion of the central nucleus resulted in large numbers of labelled neurons ipsilaterally in the paraventricular, ventromedial and dorsomedial nuclei and in the anterior, lateral and posterior hypothalamic areas (solid circles, Fig. 11). The majority of labelled cells were located in the paraventricular nucleus, with a well defined group in the anterior and dorsal portions of the nucleus in the region just medial to the fornix at the level of approximately 13 mm rostral to the interaural line. A photomicrograph showing labelled neurons in the paraventricular nucleus

FIGURE 10

Dark-field microphotographs of representative horseradish peroxidase diffusion sites and of labelled neurons. A; Diffusion site in cat C1 in the medial component of the central nucleus of the amygdala. mACE, medial central nucleus of the amygdala; ST, stria terminalis. OT, optic tract. B; Diffusion site in cat L4 in the lateral nucleus. AL, lateral nucleus of amygdala; EC, external capsule; PC, pyriform cortex. C; labelled neurons (arrows) in the anterior paraventricular nucleus of the hypothalamus in cat C1. Fx, fornix; PVH, paraventricular nucleus of the hypothalamus. D; labelled neuron (arrow) in the region of the supraoptic nucleus in cat C5. HL, lateral hypothalamic area; OT, optic tract; SON, supraoptic nucleus of the hypothalamus.

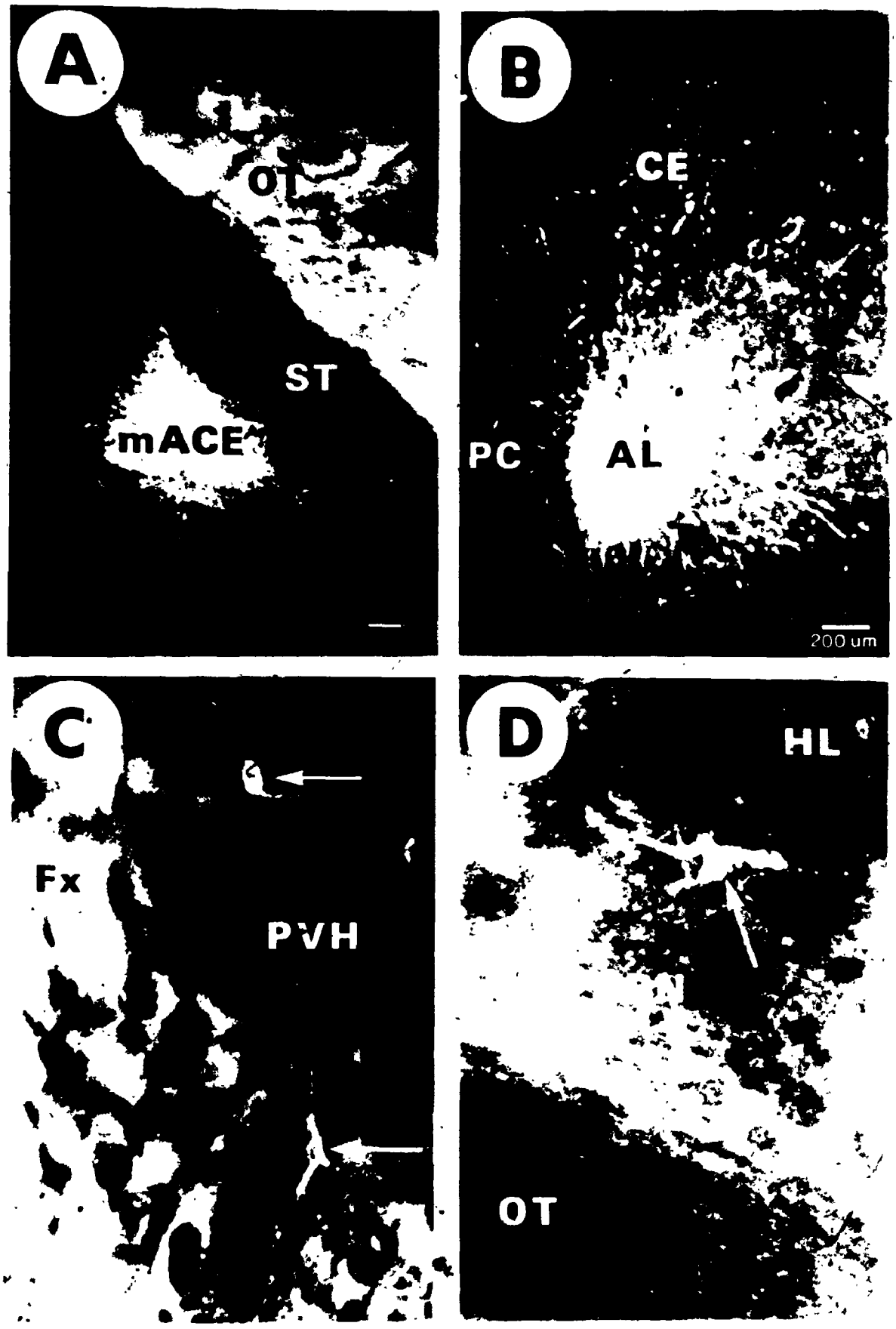
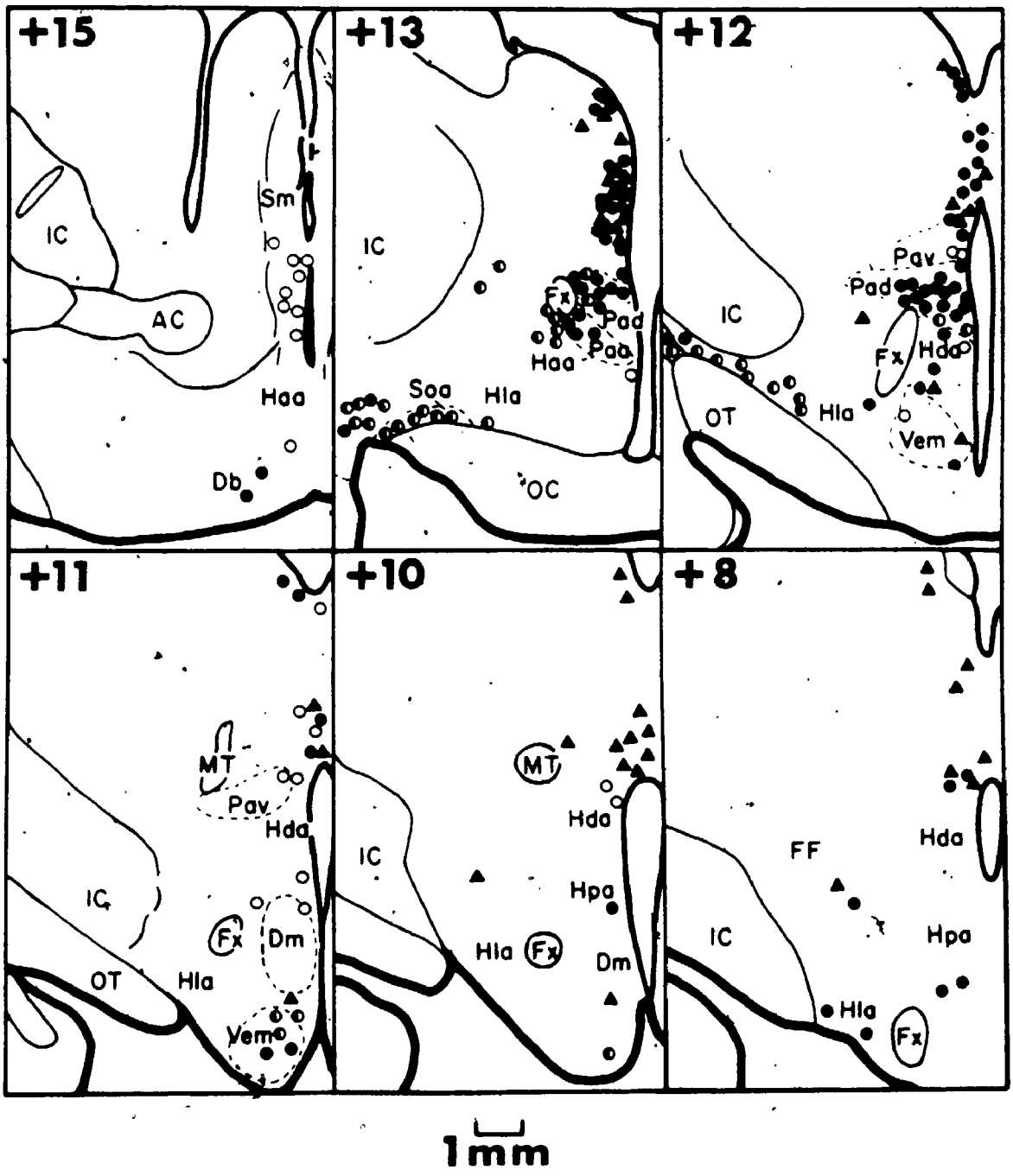

A
OT
ST
mACE
B
CE
PC
AL
200 um
C
Fx
PVH
D
HL
OT

FIGURE 11

Location of labelled neurons in the hypothalamus and thalamus after deposits of horseradish peroxidase (HRP) in the central and lateral nuclei of the amygdala plotted on representative transverse sections (8.0 - 15.0 mm anterior to the interaural line). Filled circles show neurons labelled as a result of HRP diffusion sites in the medial component of the central nucleus; open circles show neurons labelled as a result of HRP diffusion sites in the lateral component of the central nucleus; half-filled circles show neurons labelled as a result of the large HRP diffusion site in both lateral and medial components of the central nucleus; triangles show neurons labelled as a result of HRP diffusion sites in the lateral nucleus of the amygdala. AC, anterior commissure; Db, nucleus of the diagonal band of Broca; Dm, dorsomedial nucleus of the hypothalamus; Fx, fornix; FF, nucleus of the fields of Forel; Haa, Hda, Hla and Hpa, anterior, dorsal, lateral and posterior hypothalamic areas; IC, internal capsule; MT, mammillo-thalamic tract; OC, optic chiasm; OT, optic tract; Paa, Pad and Pav, anterior, dorsal and parvocellular components of the paraventricular nuclei of the hypothalamus; Soa, anterior component of the supraoptic nucleus; Sm, medial septal nucleus; Vem, ventromedial nucleus of the hypothalamus.


+15
IC
Sm
AC
Haa
Db
+13
IC
Fx
Pad
Paa
Haa
Soa
Hla
OC
+12
IC
Pav
Pad
Fx
Hda
Hla
OT
Vem
+11
MT
Pav
Hda
IC
Fx
Dm
OT
Hla
Vem
+10
MT
Hda
IC
Hpa
Hla
Fx
Dm
+8
FF
Hda
IC
Hpa
Hla
Fx
1mm

is shown in Fig. 10. Further caudally, as shown in frontal plane 12 of Fig. 11, a small group of neurons was located dorsal and medial to the fornix in the dorsal part of the paraventricular nucleus. Only a few cells were located in the parvocellular portion of the paraventricular nucleus. The larger diffusion site (cat C5) which covered the medial portion of the central nucleus as well as some of the lateral subdivision resulted in a distribution of labelled neurons in the hypothalamus (half-filled circles, Fig. 11) similar to the small deposits in the medial central nucleus. In addition, this larger horseradish peroxidase deposit resulted in the labelling of neurons in the region of the supraoptic nucleus (Fig. 10d).

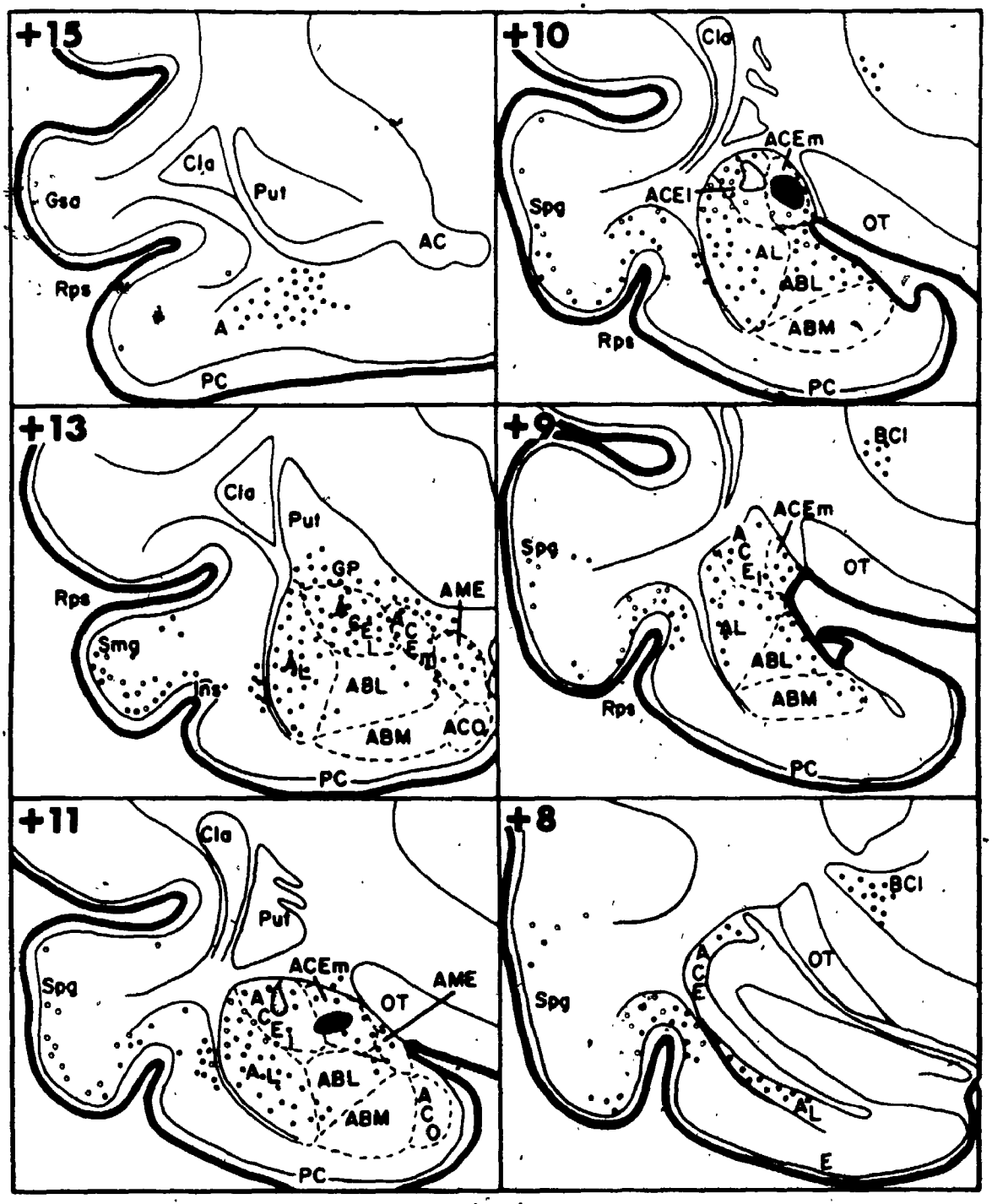
The discrete deposits (cats C3 and C4) of horseradish peroxidase in the lateral component of the central nucleus resulted in a small number of labelled neurons in the ipsilateral hypothalamus (open circles, Fig. 11). There were a few neurons found in or near the paraventricular nucleus, none in the ventromedial nucleus and only a few in the dorsal and caudal areas of the hypothalamus.

3. Other projections to the central nucleus of the amygdala

Labelled neurons were also observed in six areas of the ipsilateral thalamus. Diffusion sites restricted to only the medial component of the central nucleus resulted in many labelled neurons throughout the rostro-caudal extent of the paraventricular nucleus of the thalamus and in the nucleus of the brachium of the inferior colliculus, which is closely associated with the medial geniculate body (Figs. 11 and 12); a few neurons were also found in the reuniens,

FIGURE 12

Location of labelled neurons in the amygdala and cortex due to deposit of horseradish peroxidase (HRP) in the central nucleus of the amygdala plotted on 6 representative transverse sections (8.0 - 15.0 mm anterior to the interaural line). The lightly shaded areas and open circles show the diffusion site and labelled neurons in cat C1. The black areas and filled circles show the diffusion site and labelled neurons in cat C3. A, anterior amygdaloid area; AC, anterior commissure; ABL and ABM, basolateral and basomedial nuclei of the amygdala; BCI, nucleus of the brachium of the inferior colliculus; ACEl and ACEm, lateral and medial components of the central nucleus of the amygdala; ACO, cortical nucleus of the amygdala; Cla, claustrum; E, entorhinal cortex; GP, globus pallidus; Gsa; anterior sylvian gyrus; Ins, insular cortex; AME and AL, medial and lateral nuclei of the amygdala; OT, optic tract; Put, putamen; PC, piriform cortex; Rps, posterior rhinal sulcus; Smg, medial sylvian gyrus; Spg, posterior sylvian gyrus.


+15
Cla
Gsa
Put
AC
Rps
A
PC
+10
Cla
ACEm
Spg
ACEl
OT
AL
ABL
ABM
Rps
PC
+13
Cla
Put
GP
AME
Rps
Smg
ABL
ABM
ACO
PC
+9
BCl
ACEm
Spg
OT
ABL
ABM
Rps
PC
+11
Cla
Put
ACEm
Spg
OT
AME
ABL
ABM
PC
+8
BCl
Spg
OT
AL
E
1mm

95

rhomboid and centromedial nuclei of the thalamus. The laterally placed horseradish peroxidase deposits did not label any neurons in these nuclei of the thalamus. Both medial and lateral deposits of horseradish peroxidase in the central nucleus resulted in labelled neurons in the mediоventral nuclei of the thalamus.

Deposits of horseradish peroxidase in both the medial and lateral aspects of the central nucleus resulted in labelling in the substantia innominata and the nucleus of the diagonal band of Broca and the nucleus of the ansa lenticularis, ipsilaterally. Diffusion sites in the lateral portion of the central nucleus resulted in labelled neurons in the ipsilateral medial septum.

There were no labelled neurons in the brain stem in all four cats with smaller deposits in the central nucleus. However, in cat C5 which had a much larger deposit of horseradish peroxidase, distinctly labelled neurons were seen in the brain stem. Labelled neurons were located ipsilaterally in the locus coeruleus, the dorsal tegmental nucleus and the parabrachial nuclei. The labelled neurons in the parabrachial nucleus were located immediately ventral to the brachium conjunctivum.

Deposits of horseradish peroxidase in the central nucleus resulted in labelled neurons in the same side in adjacent cortical areas (Fig. 12), in the anterior and posterior sylvian gyrus. In one cat (C2) in which the diffusion site was restricted to the medial component of the central nucleus, the anterior ectosylvian gyrus also had extensive labelling of neurons. All deposits of horseradish peroxidase in the central nucleus of the amygdala resulted in extensive labelling in the cortical region lateral to

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the external capsule and dorsal to the rhinal sulcus. There was sparse labelling throughout the rest of the piriform cortex with the exception of cat C2 which had labelled neurons throughout the piriform cortex extending into the parahippocampal gyrus.

4. Sites of diffusion of horseradish peroxidase in the lateral nucleus of the amygdala

In four cats, small (0.5 - 1.0 mm in diameter) deposits of horseradish peroxidase were placed in the lateral nucleus of the amygdala (Figs. 9 and 10). Two of these deposits (cats L1 and L3) extended into the cortex adjacent to the lateral nucleus of the amygdala and covered the external capsule. The other two diffusion sites (cats L2 and L4) did not extend into the adjacent cortex, although L2 made contact with the external capsule. The deposit site in cat L4 was about 3 mm anterior to the deposit sites in the lateral nucleus of the amygdala in the other three cats.

5. Hypothalamic projections to the lateral nucleus of the amygdala

Few labelled neurons were found in the ipsilateral hypothalamus, in the ventromedial nucleus and the dorsal and lateral hypothalamic areas (Fig. 11). The diffusion sites in cats L1 and L3 which covered only the shell of the lateral nucleus adjacent to the external capsule resulted in few labelled cells. Almost all the labelling of hypothalamic neurons was due to the diffusion sites in cats L2 and L4 which extended into the body of the lateral nucleus.

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6. Other projections to the lateral nucleus of the amygdala

The origin of afferent projections to the lateral nucleus of the amygdala from subcortical areas other than the hypothalamus included the ipsilateral thalamus, particularly the paraventricular and medioventral subdivisions (Fig. 1[illegible]). In addition, in one cat, deposit of horseradish peroxidase in the shell of the lateral nucleus labelled neurons in the lateral habenula.

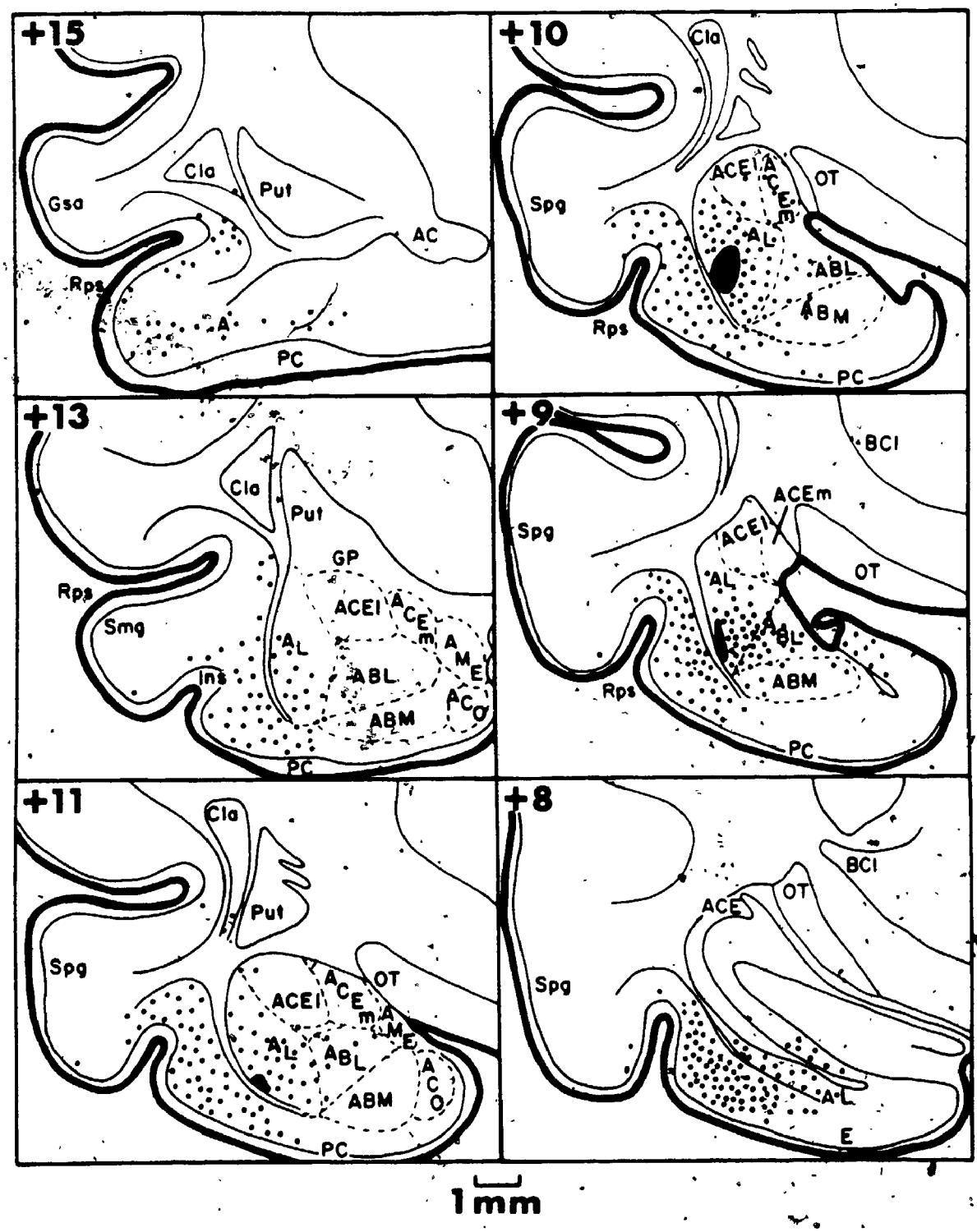
Deposits of horseradish peroxidase in the lateral nucleus resulted in extensive labelling of cortical cells in the anterior and posterior sylvian gyrus on the same side while a few labelled neurons were located in the ipsilateral ecto-sylvian gyrus. There was also some labelling of neurons in the piriform cortex, including the parahippocampal gyrus (Fig. 13).

7. Intraamygdaloid projections

The distribution of labelled neurons within the amygdala depended on the exact location of the deposit site within the central nucleus. Horseradish peroxidase in cats C1 and C2 was deposited in approximately the same location in the medial component of the central nucleus (Fig. 9). The results obtained from cat C1 are shown in Fig. 12 in which large numbers of labelled neurons are found throughout the dorso-ventral and medio-lateral extent of the lateral nucleus. The medial nucleus also had many labelled neurons and there was some labelling of neurons in the adjacent portion of the basolateral nucleus. There were virtually no labelled neurons in the cortical and basomedial nuclei. A more restricted pattern of intraamygdaloid labelling was seen in cats C3 and C4 with horse-

FIGURE 13

Location of labelled neurons (circles) in the amygdala and cortex due to the deposit of horseradish peroxidase (shaded area) in the lateral nucleus of the amygdala in cat L2 plotted on 6 representative transverse sections (8.0 - 15.0 mm anterior to the interaural line). Refer to Fig. 12 for abbreviations.


+15
Cla
Put
Gsa
AC
Rps
A
PC
+10
Cla
ACEl
ACEm
OT
Spg
AL
ABL
ABM
Rps
PC
+13
Cla
Put
GP
Rps
ACEl
ACEm
Smg
AL
AME
Ins
ABL
ACo
ABM
PC
+9
BCl
ACEm
Spg
ACEl
AL
OT
ABL
ABM
Rps
PC
+11
Cla
Put
Spg
ACEl
ACEm
OT
AME
AL
ABL
ACo
ABM
PC
+8
BCl
ACE
OT
Spg
AL
E
1mm

radish peroxidase deposits in the lateral part of the central nucleus. In these cats the labelled neurons were located primarily in the dorsal portion of the lateral nucleus as shown in cat C3 in Fig. 12. The large deposit of horseradish peroxidase in cat C5 which covered the medial and some of the lateral subdivision of the central nucleus and the dorsal area of the basolateral nucleus had the same extensive labelling of neurons in the lateral and medial nuclei seen in cats C1 and C2 but it also labelled cells in the cortical and basomedial nuclei.

Deposits of horseradish peroxidase in the lateral nucleus did not result in extensive labelling of the other nuclei of the amygdala. In two cats, L3 and L4, the labelled neurons were contained within the lateral nucleus. In the other two cats, where the deposits were located near the midpoint of the dorsoventral extent of the nucleus, labelled neurons were also seen in the basolateral and basomedial nuclei of the amygdala (Fig. 13).

D. Response of Single Units in the Parabrachial Nucleus to Electrical Stimulation of Buffer Nerves and Forebrain

Activity was recorded from 310 spontaneously firing units in the region of the parabrachial nucleus and of the anatomically and functionally related Kolliker-Fuse nucleus. These units were tested for orthodromic activation by stimulation of the carotid sinus and aortic depressor nerves and central nucleus of the amygdala and paraventricular nucleus of the hypothalamus and antidromic activation by stimulation of the central nucleus of the amygdala and the paraventricular

nucleus of the hypothalamus.

1. Parabrachial units responding to stimulation of buffer nerves

a. *Numbers and characteristics of single units responsive to buffer nerve stimulation*

Single units in the parabrachial and Kolliker-Fuse nuclei responded to electrical stimulation of the carotid sinus and aortic depressor nerves in one of three ways: excitation, inhibition, or excitation followed by inhibition. In the presentation of results, excitatory responses followed by inhibition are grouped with the excitatory responses. Two hundred and ninety-two spontaneously firing single units were tested for their response to stimulation of the carotid sinus nerve. Stimulation of the ipsilateral carotid sinus nerve altered the firing frequency of 64/189 (34%) of the units tested in the parabrachial and Kolliker-Fuse nuclei; of these, 60 were excited and 4 were inhibited. Stimulation of the contralateral carotid sinus nerve increased the firing frequency of 9/103 (9%) of the units in the parabrachial and Kolliker-Fuse nuclei; none were inhibited. Two hundred and eighty-two spontaneously firing single units were tested for their response to stimulation of the aortic depressor nerve. Stimulation of the ipsilateral aortic depressor nerve altered the firing frequency of 18/185 (10%) of the units in the parabrachial and Kolliker-Fuse nuclei, of which 16 were excited and 2 were inhibited. Stimulation of the contralateral aortic depressor nerve altered the firing frequency of 7/97 (7%) of the units in the parabrachial and Kolliker-Fuse nuclei, of which 6 were excited and one was inhibited. Two hundred and sixty-seven units were tested for

their response to stimulation of both carotid sinus and aortic depressor nerves. It was found that only 9/267 (3%) of spontaneously firing units responded to both nerves. Of these units, 8 were excited by both carotid sinus and aortic depressor nerves while one exhibited opposite responses. These results including latencies and durations of responses are shown in Table 3. Inhibitory responses could not be compared statistically because of their low number. For the units excited by buffer nerve stimulation only the mean of the latency of the responses to contralateral aortic depressor nerve stimulation was significantly different from the other groups.

b. *Distribution of single units responsive to buffer nerve stimulation*

The anatomical distribution of single units responding to buffer nerve stimulation (Fig. 14) was similar for carotid sinus and aortic depressor nerves. It can be seen that in parasagittal sections of the pons (L2.9 and 3.7) the responsive units were located primarily in the dorsal portion of the parabrachial nucleus. In the lateral sections (L4.5 and 5.2) the responsive units were further rostral and ventral and extended into the Kolliker-Fuse nucleus. Few responsive units were found in the caudal medial area of the parabrachial nucleus.

2. <u>Parabrachial units activated antidromically by stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus</u>

The central nucleus of the amygdala and the paraventricular

TABLE 3

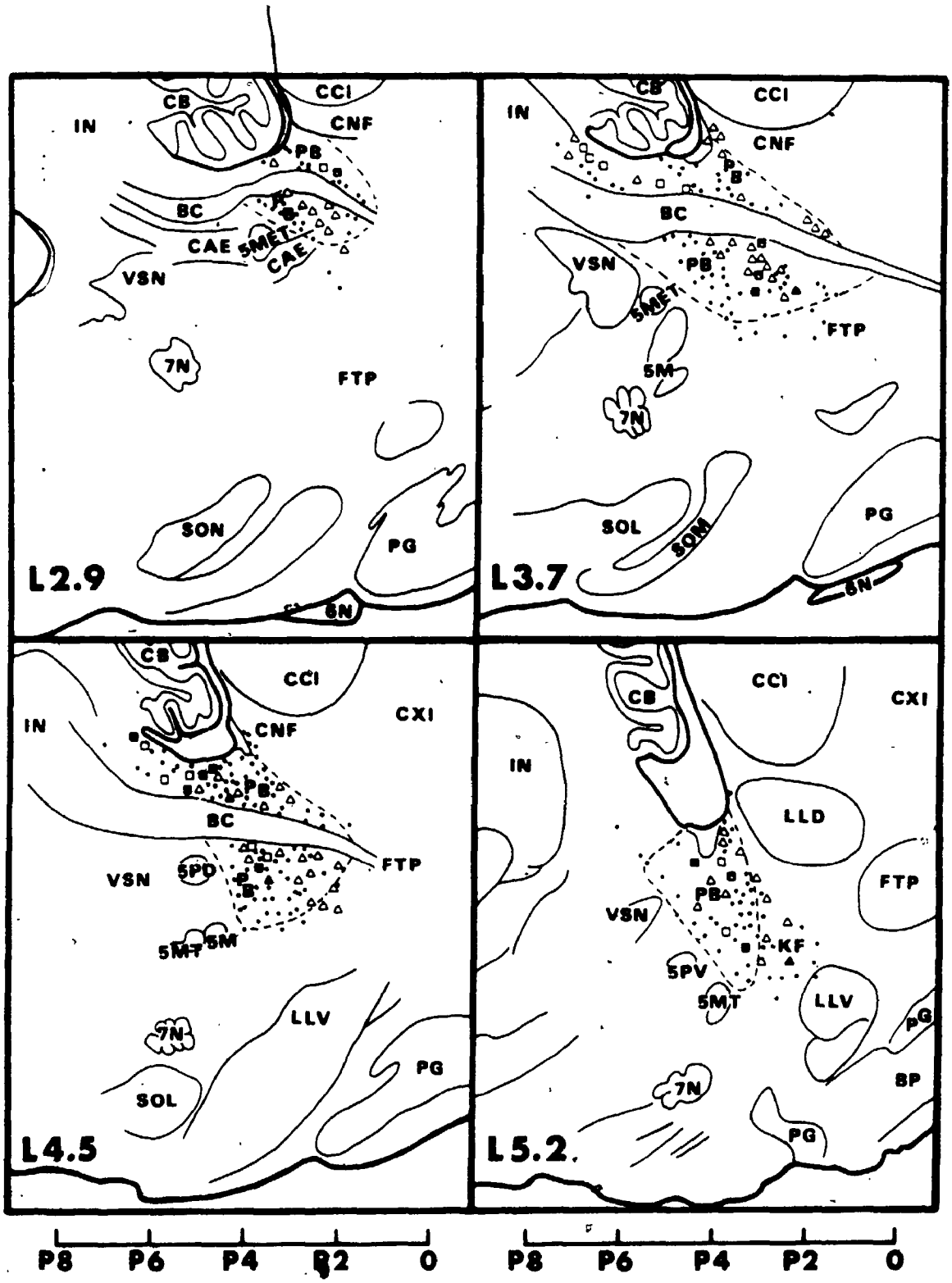
Electrophysiological Characteristics of Units in Parabrachial and Kolliker-Fuse Nuclei Responding to Stimulation of CSN and ADN

Nerve	Type of Response	Latency (ms) Ipsilateral	Contralateral	Duration (ms) Ipsilateral	Contralateral
CSN	E	14.4 ± 0.9 (60)	14.2 ± 1.8 (9)	36.1 ± 3.0	37.4 ± 7.4
	I	15.5 ± 3.5 (4)	----------	42.0 ± 7.0	----------
ADN	E	17.7 ± 3.3 (16)	26.9 ± 4.5 (6)	33.8 ± 9.3	39.8 ± 6.7
	I	29.9 ±17.0 (2)	9.6 (1)	18.0 ± 0.7	20.0
CSN/ ADN	E/E	11.6 ± 1.7/ (5) 16.3 ± 3.1	19.1 ± 1.1/ (3) 29.4 ± 8.3	31.6 ± 6.9/ 24.0 ± 7.2	39.0 ± 11.1/ 46.0 ± 7.3
	E/I	22.3/ (1) 5.2	----------	23.0/ 45.0	----------

Latencies and durations are means ± SE; numbers in parentheses are numbers of units in each group; CSN, carotid sinus nerve; ADN, aortic depressor nerve; E, excited; I, inhibited.

FIGURE 14

Location of single units in the region of the parabrachial nuclei (PB) responding to stimulation of the ipsi- and contralateral carotid sinus (CSN) and aortic depressor (ADN) nerves shown in 4 schematic parasagittal sections of the pons (from 2.9 to 5.2 mm lateral to the midline). Calibration scale in millimeters. △, excited by CSN; ▲, inhibited by CSN; ◹, excited by ADN; ■, inhibited by ADN; 5M, motor trigeminal nucleus; 5MET, mesencephalic trigeminal tract; 5MT, motor trigeminal tract; 5PD and 5PV, dorsal and ventral divisions of the principal sensory trigeminal nucleus; 6N, abducens nerve; 7N, facial nerve; BC, brachium conjunctivum; BP, brachium pontis; CAE, nucleus coeruleus; CB, cerebellum; CNF, cuneiform nucleus; FTP, paralemniscal tegmental field; CCI and CXI, central and external nuclei of the inferior colliculus; IN, nucleus interpositus; LLD and LLV, dorsal and ventral nuclei of the lateral lemniscus; PG, pontine gray; SOL and SOM, lateral and medial nuclei of the superior olive; VSN, superior vestibular nucleus.


CB
CCI
IN
CNF
PB
BC
CAE
5MET
CAE
VSN
7N
FTP
SON
PG
L2.9
5N
CB
CCI
IN
CNF
PB
BC
VSN
PB
5MET
FTP
5M
7N
SOL
5OM
PG
L3.7
5N
CB
CCI
CXI
IN
CNF
PB
BC
FTP
VSN
5PD
5MT
5M
7N
LLV
PG
SOL
L4.5
CB
CCI
CXI
IN
LLD
FTP
PB
VSN
KF
5PV
5MT
LLV
PG
8P
7N
PG
L5.2.
P8
P6
P4
P2
0
P8
P6
P4
P2
0

nucleus of the hypothalamus were stimulated in an attempt to activate parabrachial units antidromically. Sites of stimulation in the central nucleus of the amygdala (including 3 in the descending amygdalofugal pathway) and the paraventricular nucleus of the hypothalamus are shown in Fig. 15. Three hundred and ten units were tested for antidromic responses to stimulation of the central nucleus of the amygdala and 288 to stimulation of the paraventricular nucleus of the hypothalamus. Nine units were antidromically activated by stimulation of the central nucleus of the amygdala with an average latency of 8.5 ± 1.8 (SE) ms. Of the 9 units, 5 were also excited by stimulation of the carotid sinus nerve and 1 was excited by stimulation of the aortic depressor nerve. Seven units were antidromically activated by stimulation of the paraventricular nucleus of the hypothalamus with an average latency of 6.6 ± 0.7 (SE) ms. Of the 7 units, 4 were excited by stimulation of the carotid sinus nerve. Typical records of units antidromically activated by stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus and orthodromically excited by stimulation of the carotid sinus nerve are shown in Fig. 16. The location of units in the parabrachial nucleus antidromically activated by stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus is shown in Fig. 17.

3. <u>Parabrachial units activated orthodromically by stimulation of the central nucleus of the amygdala</u>

Three hundred and ten spontaneously firing single units were

FIGURE 15

Location of sites of stimu ation in the central nucleus of the amygdala and paraventricular nucleus of the hypothalamus shown in 4 schematic transverse sections of the forebrain (from 9 to 12 mm rostral to interaural line). Effective sites in the amygdalofugal pathway are also included. Calibration in millimeters. ACEl and ACEm, lateral and medial divisions of the central nucleus of the amygdala; EC, external capsule; Fx, fornix; Hda, dorsal hypothalamic area; IC, internal capsule; OT, optic tract; Pad and Pav, dorsal and ventral parvocellular divisions of the paraventricular nucleus of the hypothalamus.

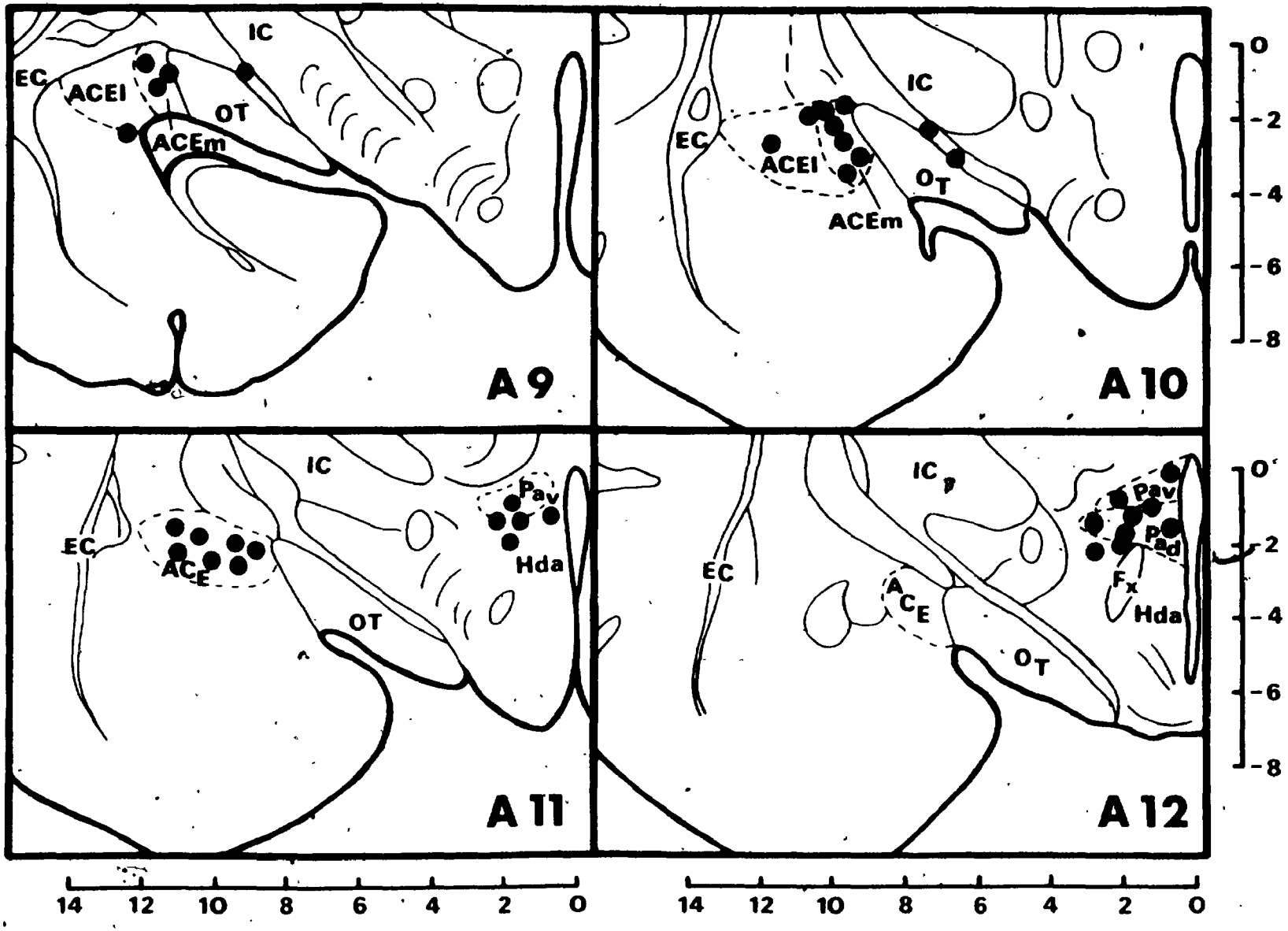

IC
EC
ACEI
OT
ACEm
A 9
IC
EC
ACEI
OT
ACEm
A 10
IC
EC
ACE
Pav
Hda
OT
A 11
IC p
EC
ACE
Pav
Pad
Fx
Hda
OT
A 12
0
-2
-4
-6
-8
14 12 10 8 6 4 2 0
14 12 10 8 6 4 2 0

FIGURE 16

Photographic records of single units in the parabrachial nucleus activated antidromically by stimulation of the central nucleus of the amygdala (panel A) and paraventricular nucleus of the hypothalamus (panel B) and responding orthodromically to stimulation of the carotid sinus nerve. For both A and B: First record shows single antidromic response to a stimulus at 0.5 Hz; second record shows antidromic responses to two stimuli at a frequency of 150 Hz; third record shows the loss of the second antidromic response when two stimuli were delivered 2 ms apart; fourth record shows an excitatory response elicited by stimulation of the carotid sinus nerve. Arrows indicate stimulus artefacts. A. Calibration of the first 3 records, 2 ms and 50 μV; fourth record, 10 ms and 100 μV. All records are 5 superimposed sweeps.

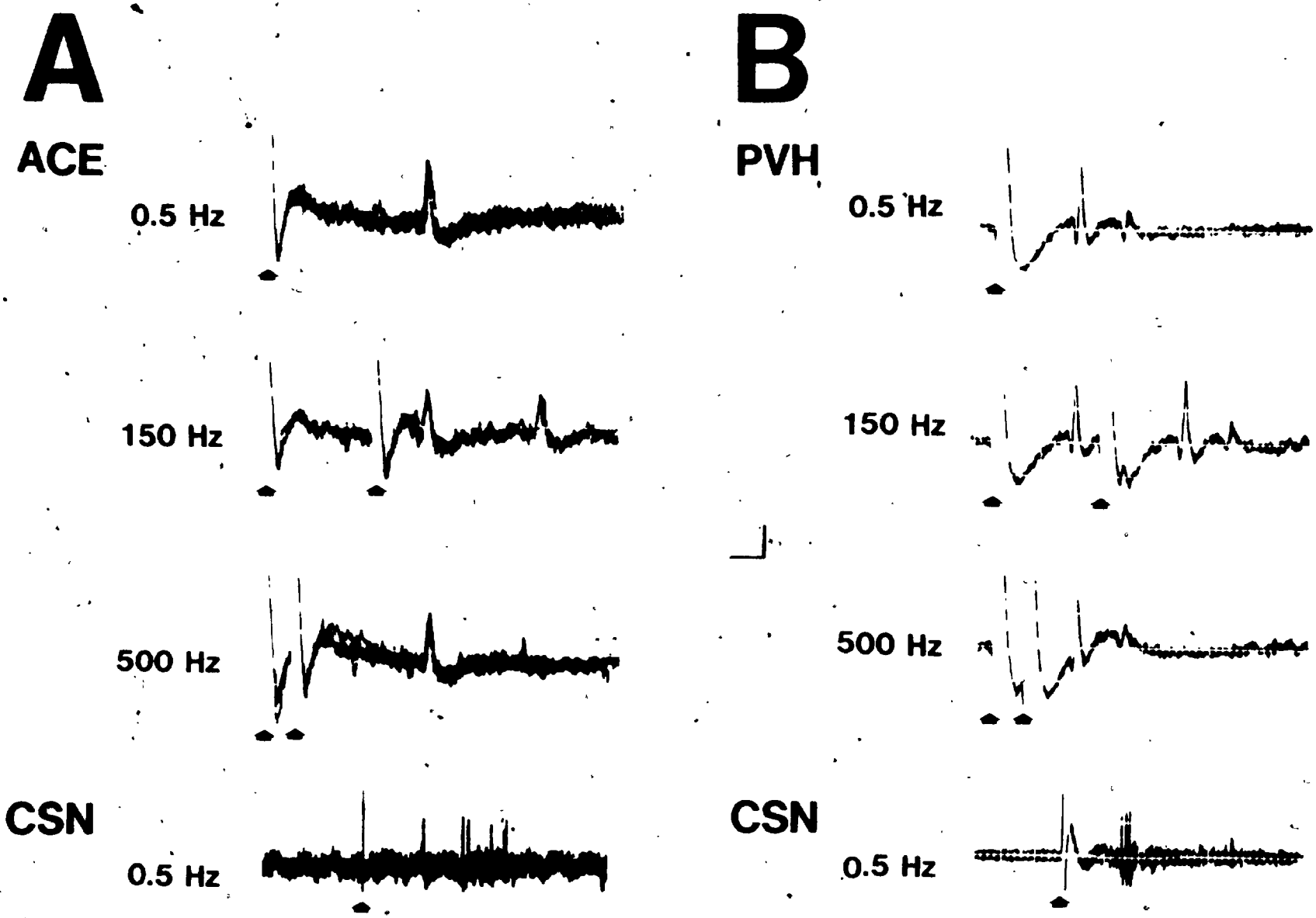
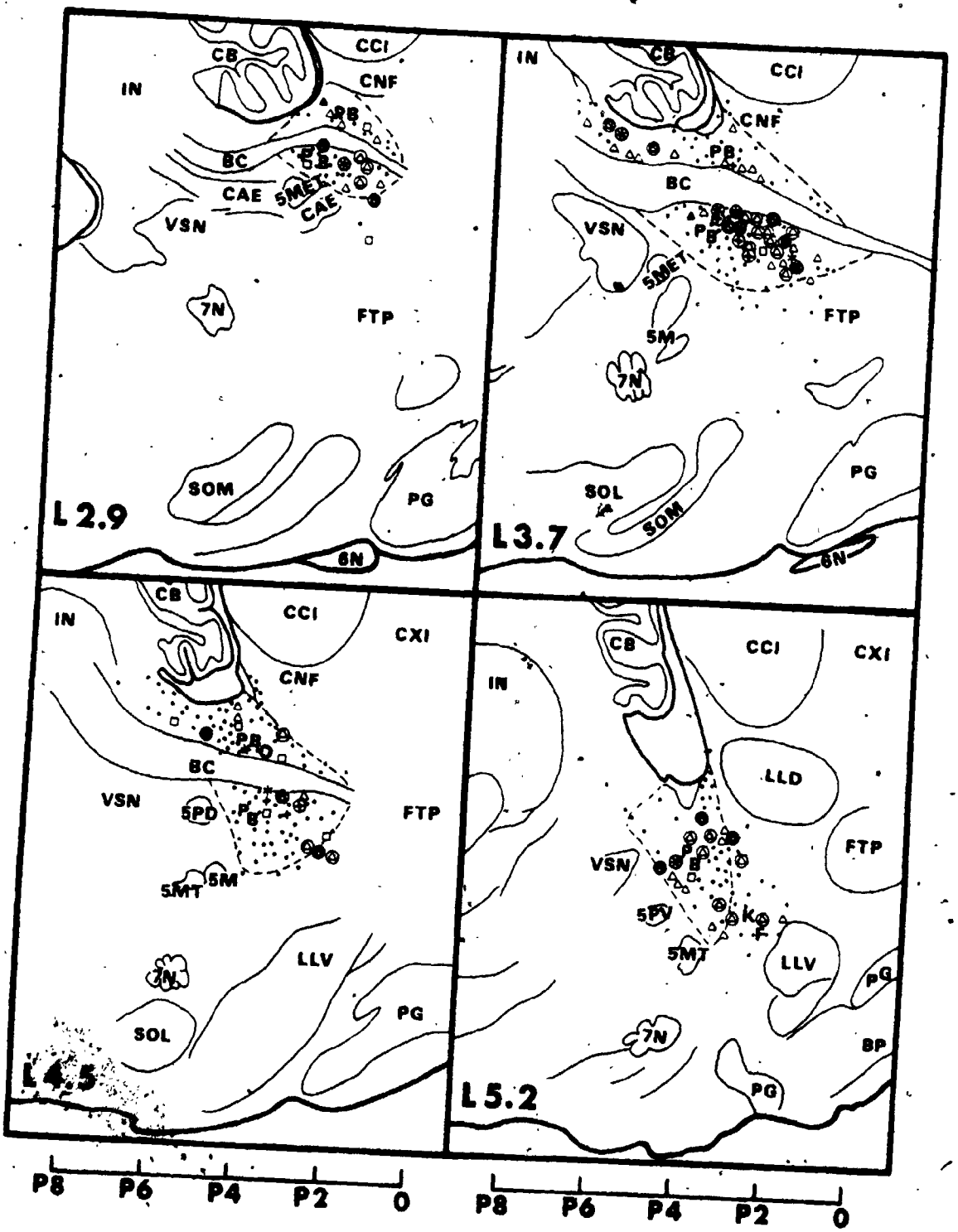

A
ACE
0.5 Hz
150 Hz
500 Hz
CSN
0.5 Hz
B
PVH
0.5 Hz
150 Hz
500 Hz
CSN
0.5 Hz

FIGURE 17

Location of single units in the region of the parabrachial nucleus responding to stimulation of the ipsi- and contralateral central nucleus of the amygdala (ACE) and paraventricular nucleus of the hypothalamus (PVH) shown in 4 parasagittal sections of the pons (from 2.9 to 5.2 mm lateral to the midline). Calibration scale in millimeters. △ , excited by ACE; ▲ , inhibited by ACE; □ , excited by PVH; ■ , inhibited by PVH; *, antidromically activated by ACE; +, antidromically activated by PVH; units circled also responded to buffer nerve stimulation. Refer to Fig. 14 for abbreviations.


CB
CCI
IN
CNF
PB
BC
5
CAE
5MET
CAE
VSN
7N
FTP
SOM
PG
L 2.9
6N
IN
CB
CCI
CNF
PB
BC
VSN
5MET
FTP
5M
7N
SOL
SOM
PG
L 3.7
6N
IN
CB
CCI
CXI
CNF
PB
BC
VSN
5PD
FTP
5MT
5M
7N
LLV
SOL
PG
L 4.5
CB
CCI
CXI
IN
LLD
FTP
VSN
5PV
5MT
LLV
PG
7N
BP
PG
L 5.2
P8
P6
P4
P2
0
P8
P6
P4
P2
0

tested for their response to stimulation of the central nucleus of the amygdala at the sites shown in Figure 15. Single units in the parabrachial nucleus responded orthodromically to electrical stimulation of the central nucleus of the amygdala with either an excitatory or inhibitory response. Stimulation of the central nucleus of the amygdala altered the firing frequency of 56/207 (27%) of the units in the ipsilateral parabrachial nucleus, of which 54 were excited and 2 were inhibited, and of 11/103 (11%) of the units in the contralateral parabrachial nucleus all of which were excited. These results, including latencies and durations, are shown in Table 4. There were no significant differences observed among the means of the latencies and durations. The anatomical distribution of the units responding to stimulation of the central nucleus of the amygdala is shown in Fig. 17. The responsive units were found primarily in the rostral ventrolateral parabrachial nucleus and the Kolliker-Fuse nucleus. Of the units excited by stimulation of the central nucleus of the amygdala, 52% (32/62) were also excited by stimulation of the carotid sinus nerve and 10% (6/59) responded to stimulation of the aortic depressor nerve; of these 5 were excited while one was inhibited. An example of a unit responding to both carotid sinus nerve stimulation and stimulation of the central nucleus of the amygdala is shown in Fig. 18. The anatomical distribution of units responding to both the central nucleus of the amygdala and buffer nerves is shown in Fig. 17.

TABLE 4

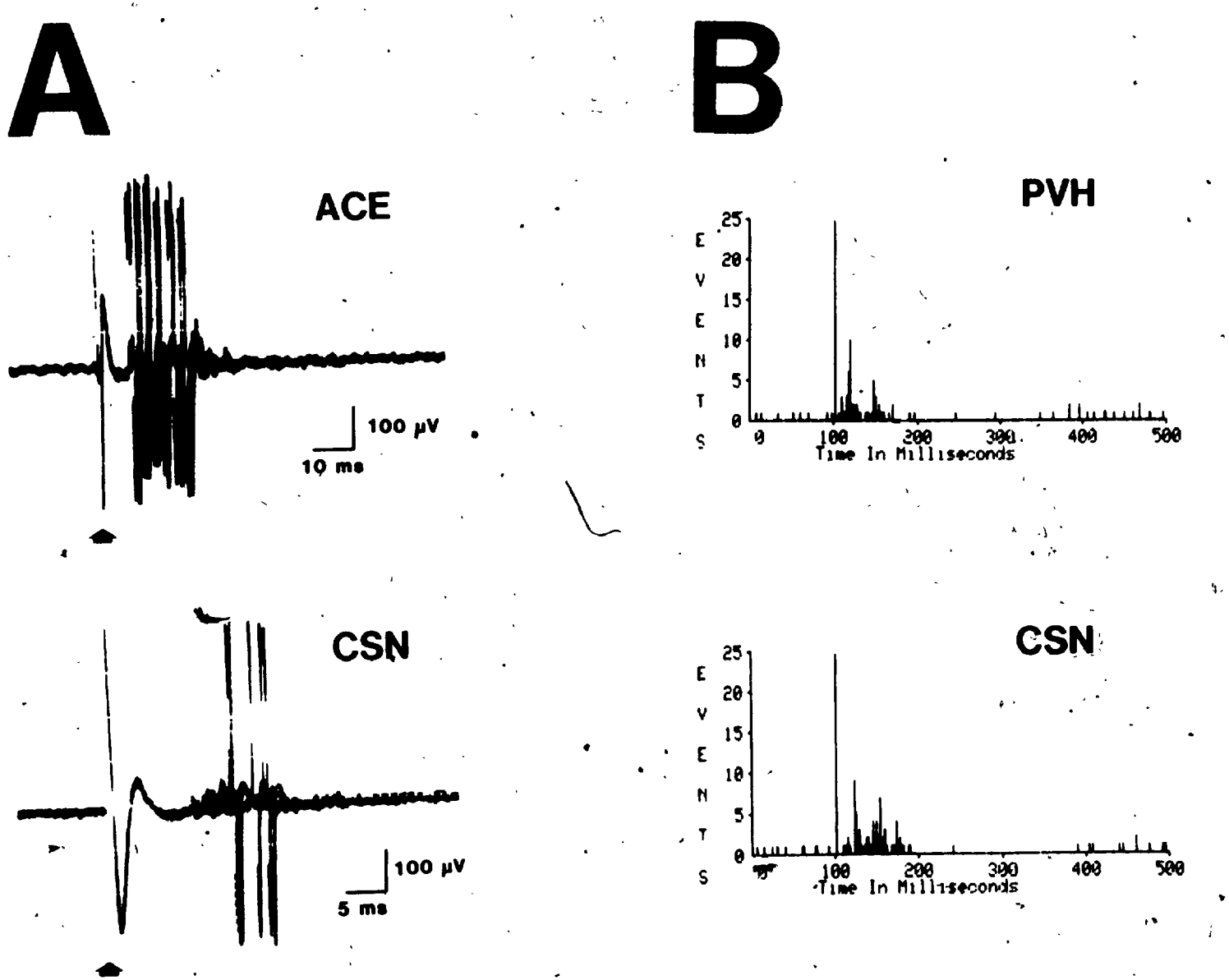
Electrophysiological Characteristics of Units in Parabrachial and Kolliker-Fuse Nuclei Responding Orthodromically to Stimulation of ACE and PVH

Site of Stimulation	Type of Response	Latency (ms)		Duration (ms)	
		Ipsilateral	Contralateral	Ipsilateral	Contralateral
ACE	E	12.5 ± 0.7 (54)	14.6 ± 1.5 (11)	18.6 ± 1.9	17.4 ± 2.7
	I	19.4 ± 1.9 (2)	---------	21.5 ± 3.2	---------
PVH	E	13.3 ± 2.0 (20)	20.0 ± 8.5 (2)	22.9 ± 3.8	24.0 ± 0.7
	I	20.6 ± 8.6 (3)	---------	34.3 ± 8.7	---------

Latencies and durations are means ± SE; numbers in parentheses are numbers of units in each group; ACE, central nucleus of the amygdala; PVH, paraventricular nucleus of the hypothalamus; E, excited; I, inhibited.

FIGURE 18

A. Photographic records of a unit in the lateral parabrachial nucleus responding orthodromically to stimulation of the central nucleus of the amygdala (ACE) and the carotid sinus nerve (CSN). Both records are 5 superimposed sweeps. Arrows indicate stimulus artefacts. B. Peristimulus time histograms of a unit in the lateral parabrachial nucleus responding orthodromically to stimulation of the paraventricular nucleus of the hypothalamus (PVH) and CSN. Both histograms are the results of 30 sweeps.


A
ACE
100 µV
10 ms
CSN
100 µV
5 ms
B
PVH
EVENTS
25
20
15
10
5
0
0
100
200
300
400
500
Time In Milliseconds
CSN
EVENTS
25
20
15
10
5
0
100
200
300
400
500
Time In Milliseconds

4. Parabrachial units activated orthodromically by stimulation of the paraventricular nucleus of the hypothalamus

Two hundred and eighty-eight spontaneously firing single units were tested for their response to stimulation of the paraventricular nucleus of the hypothalamus at the sites shown in Fig. 15. Single units in the parabrachial nucleus responded orthodromically to electrical stimulation of the paraventricular nucleus of the hypothalamus with either an excitatory or inhibitory response. Stimulation of the paraventricular nucleus of the hypothalamus altered the firing frequency of 23/177 (13%) of the units in the ipsilateral parabrachial nucleus; of these, 20 were excited and 3 were inhibited. In the contralateral parabrachial nucleus 2/103 (2%) of the units were excited; none were inhibited. These results including latencies and durations are shown in Table 4. There were no significant differences observed among the means of the latencies and durations. The anatomical distribution of units responding to stimulation of the paraventricular nucleus of the hypothalamus is similar to that of units responding to stimulation of the central nucleus of the amygdala (Fig. 17). Of the units excited by stimulation of the paraventricular nucleus of the hypothalamus, 55% (11/20) were also excited by stimulation of the carotid sinus nerve and 33% (6/18) were excited by stimulation of the aortic depressor nerve. An example of a unit responding to both the paraventricular nucleus of the hypothalamus and the carotid sinus nerve is shown in Fig. 18. All three of the units inhibited by stimulation of the ipsilateral paraventricular nucleus of the hypothalamus responded to stimulation of the carotid sinus nerve. The anatomical distribution of

units responding to both the paraventricular nucleus of the hypothalamus and buffer nerves is shown in Fig. 17.

E. Effects of Stimulation of the Paraventricular Nucleus of the Hypothalamus and of the Parabrachial Nucleus on Units in the Amygdala

1. Units in the amygdala activated orthodromically by stimulation of the paraventricular nucleus of the hypothalamus

One hundred and forty spontaneously firing (0.3 - 30 spikes/s) single units were tested for their response to stimulation of the paraventricular nucleus of the hypothalamus. An example of a cardiovascular response to stimulation of the paraventricular nucleus of the hypothalamus and the 10 sites within the paraventricular nucleus that were stimulated are shown in Fig. 19. Single units in the amygdala responded orthodromically to electrical stimulation of the paraventricular nucleus of the hypothalamus with either an excitatory or inhibitory response. Stimulation of the paraventricular nuclues of the hypothalamus altered the firing frequency of 19% (27/140) of the units tested in the ipsilateral amygdala of which 85% (23/27) were excited with an average latency of 16.0 ± 2.2 ms while 15% were inhibited with an average latency of 19.1 ± 4.8 ms. These results are summarized in Table 5. There were no significant differences between the means of the latencies and durations. The anatomical distribution of units responding to stimulation of the paraventricular nucleus of the hypothalamus is shown in Figure 20. The responsive units were found primarily in the central nucleus of the amygdala. Of the units

FIGURE 19

Heart rate and blood pressure response to stimulation (80 Hz, 100 μA) of the paraventricular nucleus of the hypothalamus and sites of stimulation shown on 3 transverse sections of the hypothalamus (from 11 mm to 13 mm rostral to the interaural line). Calibration scale in millimeters. III, third ventricle; Fx, fornix; IC, internal capsule; OC and OT, optic chiasm and tract; Paa, Pad and Pav, anterior, dorsal and parvocellular components of the paraventricular nucleus of the hypothalamus.

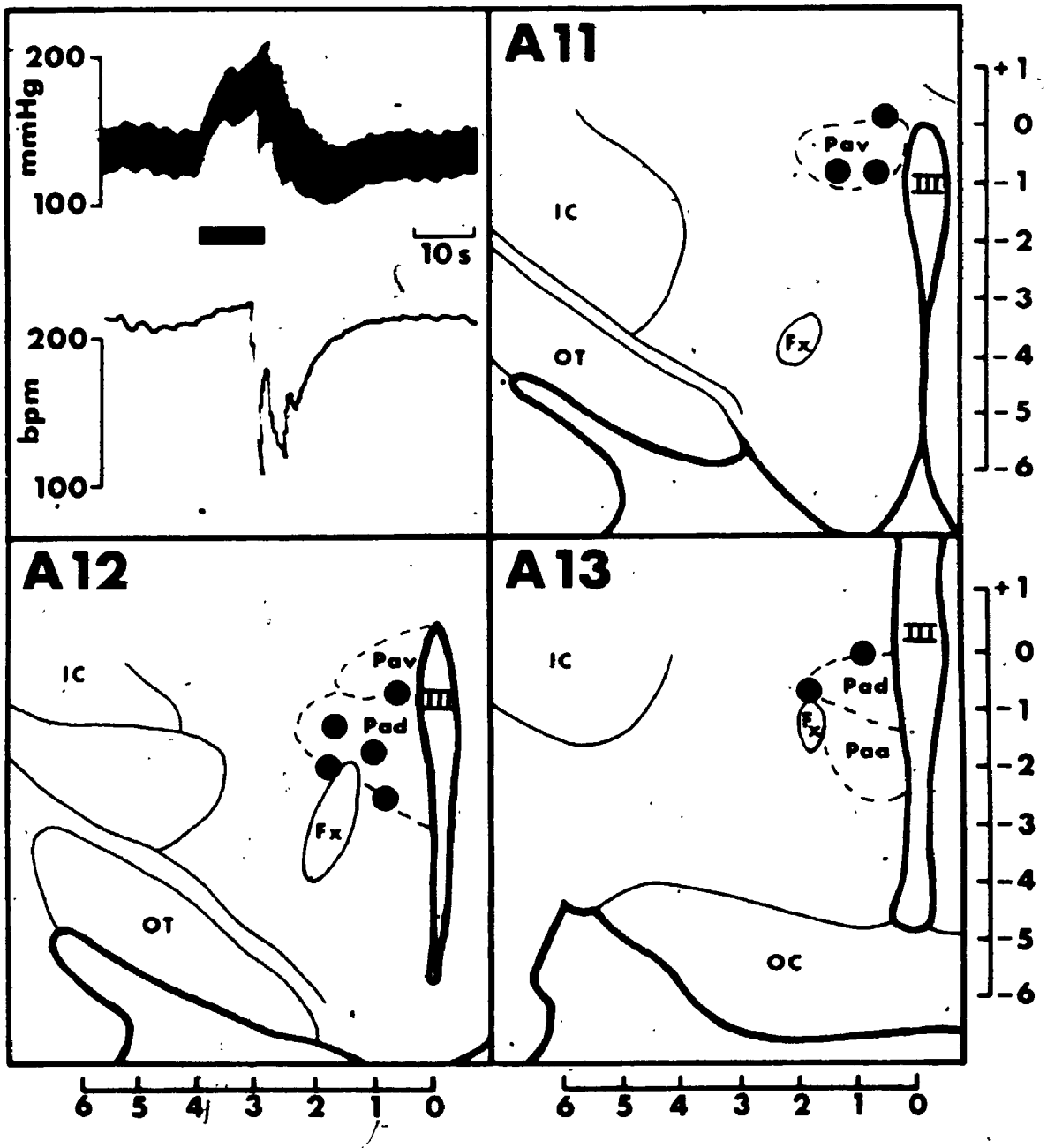

200
mmHg
100
10s
200
bpm
100
A11
IC
Pav
III
OT
Fx
+1
0
-1
-2
-3
-4
-5
-6
A12
IC
Pav
Pad
III
Fx
OT
A13
IC
III
Pad
Fx
Paa
OC
6 5 4 3 2 1 0
6 5 4 3 2 1 0

TABLE 5

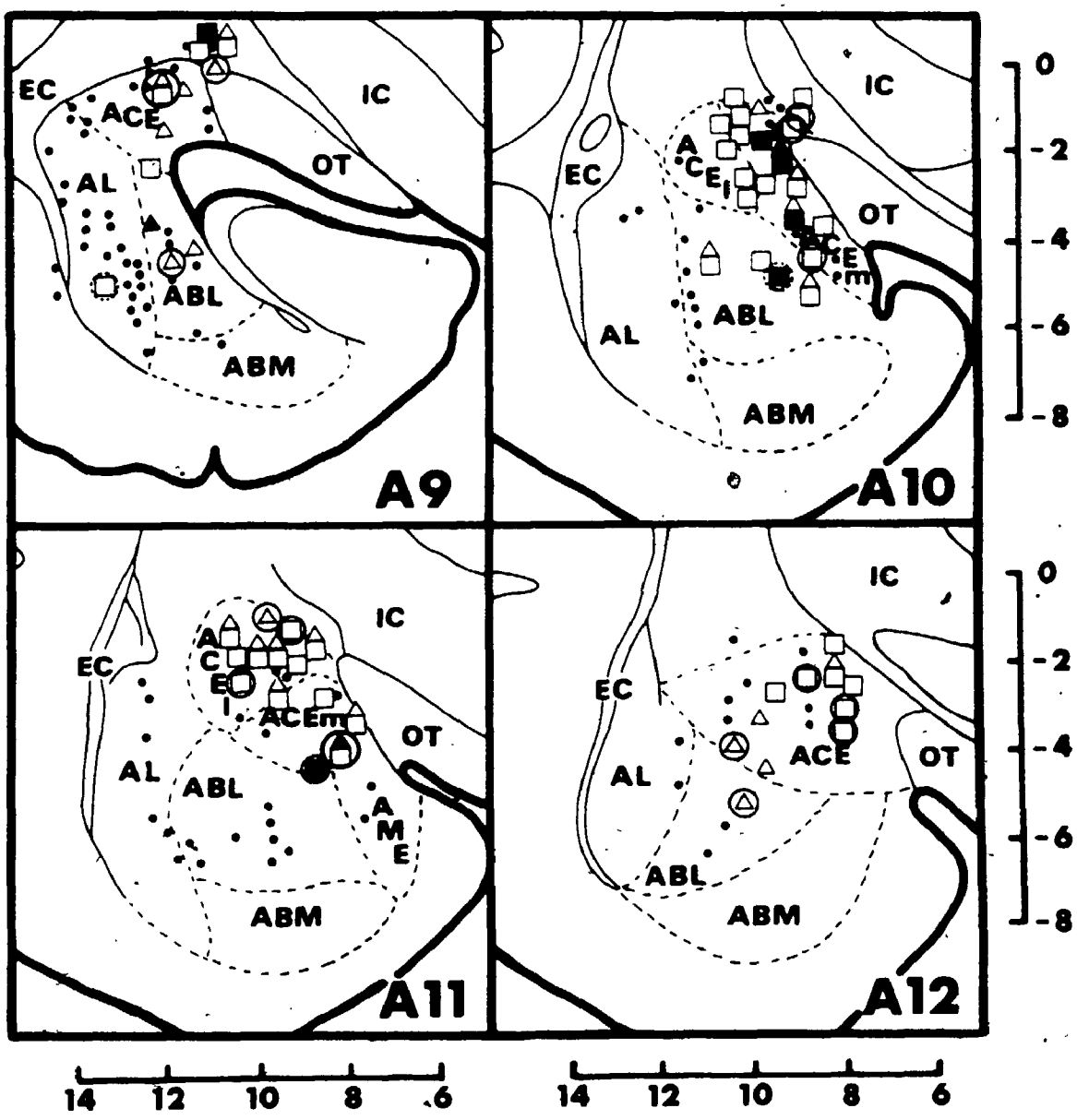
Electrophysiological Characteristics of Units in the Amygdala Responding to Stimulation of the PVH and PB

Site of Stimulation	Type of Response	No. of Units	Spontaneous Frequency (spikes/s)	Latency (ms)	Duration (ms)	CA	BA
PVH	E	23	3.8 ± 0.7	16.0 ± 2.2	42.2 ± 6.03	7	-
	I	4	5.3 ± 1.6	19.1 ± 4.8	50.8 ±17.93	2	-
PB	E	40	5.7 ± 0.9	12.2 ± 2.0*	33.7 ± 3.88+	10	1
	I	6	3.3 ± 0.5	27.6 ± 5.8	62.3 ±12.16	1	1

Values are means ± SE; * and + indicate significant differences in latency and duration of excited and inhibited units in the PB; CA, chemoreceptor activation; BA, baroreceptor activation; PVH, paraventricular nucleus of the hypothalamus; PB, parabrachial nucleus; E, excited; I, inhibited.

FIGURE 20

Location of single units in the amygdala responding to stimulation of the ipsilateral paraventricular nucleus of the hypothalamus (PVH) and parabrachial nucleus (PB) shown in 4 transverse sections of the amygdala (from 9-12 mm rostral to the interaural line). Calibration scale in millimeters. △, excited by PVH; ▲, inhibited by PVH; □, excited by PB; ■, inhibited by PB; ◯, also responsive to carotid chemoreceptors; ◌, also responsive to carotid baroreceptors; ●, unresponsive units. ABL and ABM, basolateral and basomedial nuclei of the amygdala; ACEl and ACEm, lateral and medial components of the central nucleus of the amygdala; AL and AME, lateral and medial nuclei of the amygdala; EC, external capsule; IC, internal capsule; OT, optic tract.


EC
ACE
IC
OT
AL
ABL
ABM
A9
A10
A11
A12
AMe
0
-2
-4
-6
-8
14
12
10
8
6

responding to electrical stimulation of the paraventricular nucleus of the hypothalamus, 33% (9/27) also responded to activation of chemoreceptors. None were responsive to activation of baroreceptors. An example of a unit responding to both stimulation of the paraventricular nucleus of the hypothalamus and activation of chemoreceptors is shown in Fig. 21A. The location of units responding to both stimulation of the paraventricular nucleus of the hypothalamus and activation of chemoreceptors is shown in Fig. 20.

2. Units in the amygdala activated orthodromically by stimulation of the parabrachial nucleus

One hundred and fifty spontaneously firing single units were tested for their response to electrical stimulation of the parabrachial nucleus. An example of a cardiovascular response to stimulation of the parabrachial nucleus and the 11 sites within the parabrachial nucleus that were stimulated are shown in Fig. 22. Single units in the amygdala responded orthodromically to electrical stimulation of the parabrachial nucleus with either an excitatory or inhibitory response. Stimulation of the parabrachial nucleus altered the firing frequency of 31% (46/150) of the units tested in the ipsilateral amygdala of which 87% (40/46) were excited with an average latency of 12.2 ± 2.0 ms while 13% (6/46) were inhibited with an average latency of 27.6 ± 5.8 ms. Both the latencies and durations of the excitatory responses were significantly shorter than those of the inhibitory responses. These results are summarized in Table 5. The anatomical distribution of units responding to stimulation of the parabrachial nucleus is shown in Fig. 20. The responsive units were found primarily in the central nucleus of

FIGURE 21

Response of single units in the amygdala to activation of chemoreceptors and stimulation of the paraventricular nucleus of the hypothalamus or parabrachial nucleus.

A. Traces on the left are the blood pressure and heart rate changes and continuous frequency histogram of a single unit excited by activation of chemoreceptors with sodium cyanide (NaCN). On the right is a photographic record of the same unit excited by electrical stimulation of the paraventricular nucleus of the hypothalamus (PVH).

B. Traces on the left are the blood pressure and heart rate changes and continuous frequency histogram of a single unit inhibited by activation of chemoreceptors. On the right is a peristimulus time histogram of the same unit excited by electrical stimulation of the parabrachial nucleus (PB).

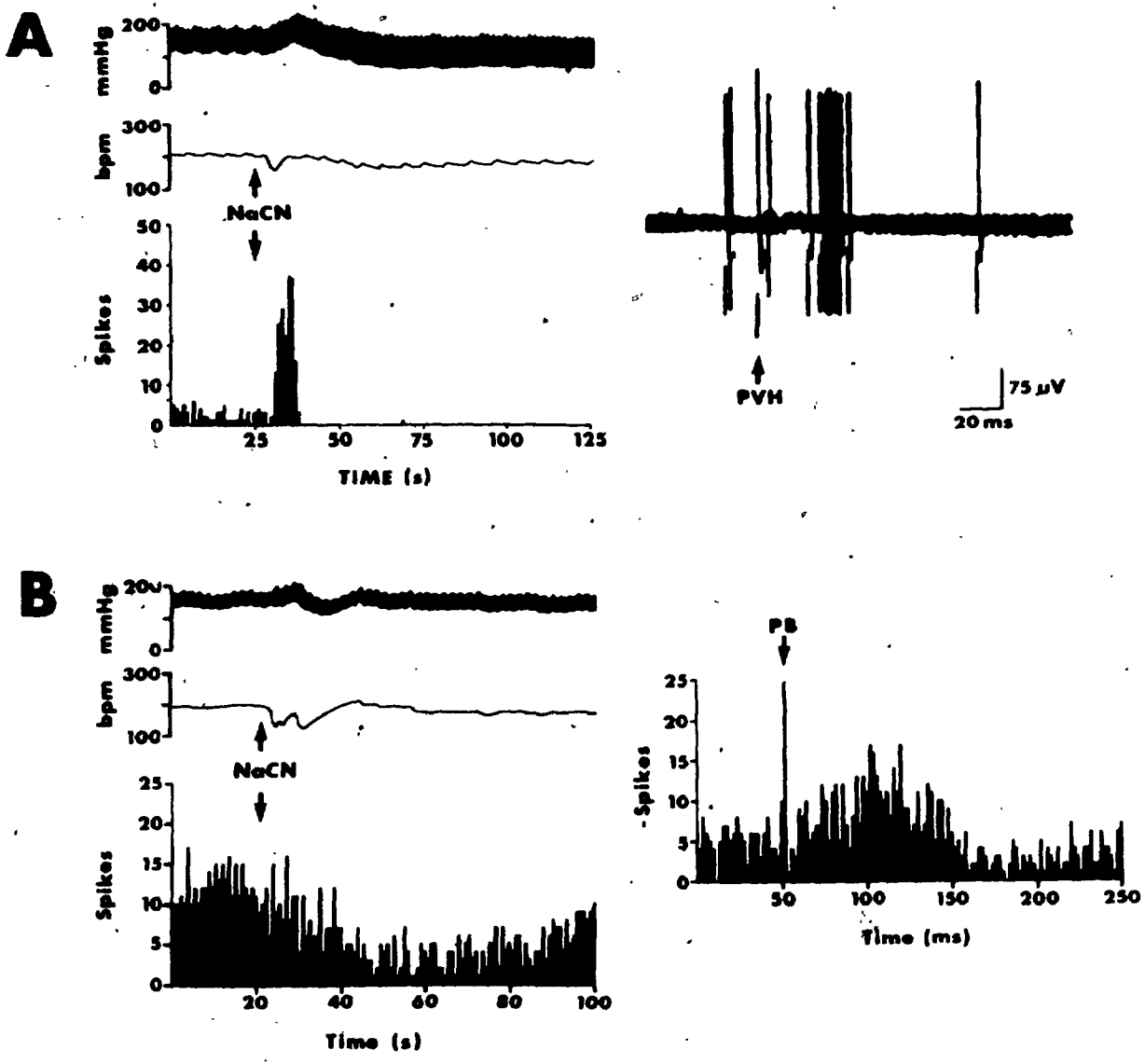
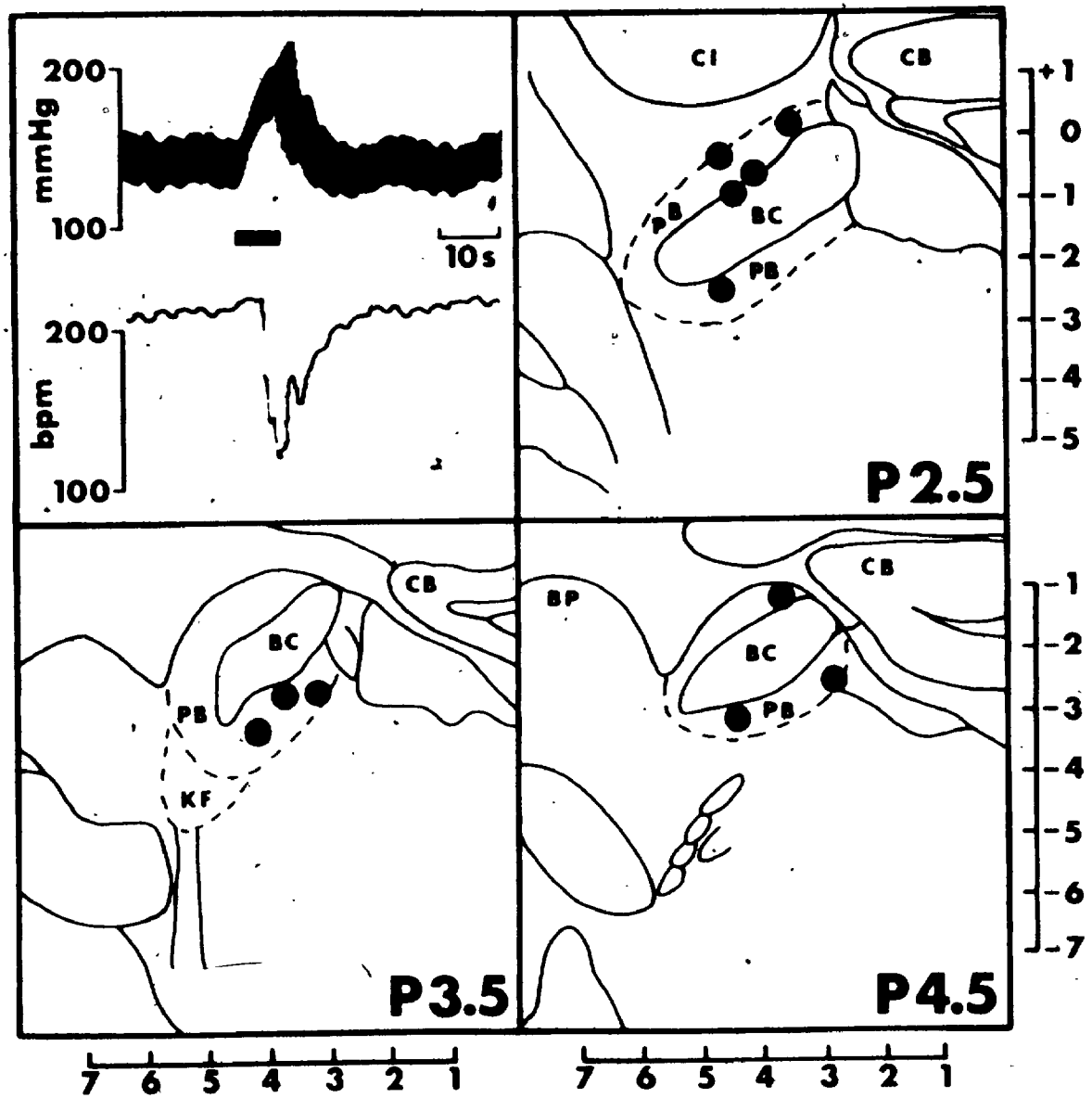

A
mmHg
200
0
bpm
300
100
NaCN
Spikes
50
40
30
20
10
0
25
50
75
100
125
TIME (s)
PVH
75 µV
20 ms
B
mmHg
200
0
bpm
300
100
NaCN
Spikes
25
20
15
10
5
0
20
40
60
80
100
Time (s)
PB
-Spikes
25
20
15
10
5
0
50
100
150
200
250
Time (ms)

FIGURE 22

Heart rate and blood pressure response to stimulation (80 Hz, 50 μA) of the parabrachial nucleus and sites of stimulation shown on 3 transverse sections of the pons (from 2.5 - 4.5 mm caudal to the interaural line). Calibration scale in millimeters. BC, brachium conjunctivum; CB, cerebellum; CI, inferior colliculus; KF, Kolliker-Fuse nucleus; PB, parabrachial nucleus.


200
mmHg
100
10s
200
bpm
100
CI
CB
PB
BC
PB
P2.5
+1
0
-1
-2
-3
-4
-5
CB
BC
PB
KF
P3.5
BP
CB
BC
PB
P4.5
-1
-2
-3
-4
-5
-6
-7
7 6 5 4 3 2 1
7 6 5 4 3 2 1

the amygdala. Of the units responding to electrical stimulation of the parabrachial nucleus, 24% (11/46) also responded to activation of chemoreceptors, while 4% (2/46) were responsive to activation of baroreceptors. An example of a unit responding to both stimulation of the parabrachial nucleus and activation of chemoreceptors is shown in Fig. 21 B. The location of units responding to stimulation of the parabrachial nucleus and activation of baro- or chemoreceptors is shown in Fig. 20. When the same unit was tested for responses to stimulation of both the paraventricular nucleus of the hypothalamus and the parabrachial nucleus, it was found that 9% (13/140) spontaneously firing units responded to both inputs. Of these 13 units, 11 exhibited responses in the same direction whereas the remaining 2 units showed opposite responses. Of these units responding to both paraventricular nucleus of the hypothalamus and parabrachial nucleus, 2 also responded to activation of chemoreceptors.

DISCUSSION

In this study electrophysiological and neuroanatomical techniques have been used to demonstrate baro- and chemoreceptor input to the amygdala, connections of these areas in the amygdala receiving buffer nerve input with nuclei in the pons and hypothalamus also involved in cardiovascular control and the central pathway by which the cardiovascular information is relayed to the amygdala. In the following sections a detailed discussion of the results of individual experiments will be presented, followed by the conclusions which can be made from the analysis of the results of this study. In the conclusions a model is presented which proposes a role for afferent baro- and chemoreceptor information in the function of the amygdala and proposes a scheme of how the pons and forebrain function in the control of cardiovascular and respiratory changes associated with the behaviors regulated by the amygdala.

A. Discussion of Experimental Results

1. Buffer nerve input to units in the amygdala

Although it has been shown unequivocally that the amygdala has a role in control of the cardiovascular system (Kaada, 1972) there is no direct demonstration that cardiovascular afferent information projects to this structure. The experiments in this study provide the first electrophysiological evidence that information from receptors in the cardiovascular system carried in the carotid sinus and

aortic depressor nerves can alter electrical activity of units located primarily in the central, lateral and dorsal portions of the basal nuclei of the amygdala, although no attempt was made to identify the function of the afferent fibers stimulated.

The demonstration that only a small proportion of neurons in the amygdala responds to stimulation of both buffer nerves in spite of the fact that the anatomical distribution of units responding to either nerve is essentially the same, has two possible explanations. First, it is possible that the distinct neuronal pool to which the two nerves project subserve separate cardiovascular control functions, although it is commonly accepted that the aortic depressor nerve in the cat contains afferent fibers that are functionally similar to those in the carotid sinus nerve. The second possibility is that the two nerves carry different functional information. In support of this possibility there is some indication that the carotid sinus nerve may monitor variables other than arterial pressure and tension of respiratory gases. For example, it has been demonstrated that animals on a high salt diet have a blunted pressor response to carotid occlusion (Rocchini et al., 1977) and that there is a change in carotid sinus baroreceptor sensitivity when the sodium concentration perfusing the sinus is altered (Kunze and Brown, 1978).

As this study has demonstrated that cardiovascular afferent pathways project primarily to the central, lateral and dorsal parts of the basal nuclei of the amygdala some discussion of the functional significance of these areas in the control of the cardiovascular system is appropriate. Stimulation of the central nucleus of the amygdala in the cat has been shown to elicit an increase in arterial

pressure (Fonberg, 1968; Hilton and Zbrozyna, 1963), whereas stimulation of the lateral nucleus of the amygala in the cat results in hypotension (Morin et al., 1952) and inhibition of the defence reaction (Fonberg, 1968). In addition, activation of chemoreceptors has been shown to elicit responses such as defence and rage similar to those obtained by stimulation of the central nucleus of the amygdala, while activation of baroreceptors inhibits these responses (Baccelli et al., 1965; Bizzi et al., 1961; Marshall, 1981). Furthermore, when a decerebrate preparation is used the chemoreceptor stimulus is no longer able to elicit the sham rage behavior, suggesting that the afferent input for this response projects to structures rostral to the midbrain (Baccelli et al., 1965). Therefore, it may be suggested that the chemoreceptor input is involved in mediating hypertension and the defence reaction in the central nucleus of the amygdala, and that the baroreceptors are involved in hypotension and inhibition of the defence reaction in the lateral nucleus.

2. Selective baro- and chemoreceptor input to units in the amygdala

The results of the second series of experiments have demonstrated that activation of both baro- and chemoreceptors results in changes in the firing frequency of single units in the central, lateral and dorsal nuclei of the amygdala. The proportion of spontaneously firing units responsive to activation of chemoreceptors was not significantly greater than that of units responding to activation of baroreceptors, indicating that both types of cardiovascular inputs are represented equally in the regions of the amygdala explored in this study. The percentage of units in the amygdala responding to activation of baro-

and chemoreceptors of the left carotid sinus and carotid body in the present study (39%) is similar to the proportion of spontaneously firing units in the amygdala (36%) demonstrated in the first study to respond to electrical stimulation of the carotid sinus nerve. The location of units in the central, lateral and basal nuclei of the amygdala responding to activation of baro- and chemoreceptors was similar to that of units responding to electrical stimulation of the carotid sinus nerve.

In this study the majority (71%) of the units in the ventrolateral amygdala altered their rate of firing to baroreceptor input with an excitatory response. In a previous study it had been shown that 2 of 28 spontaneously firing single units in the lateral nucleus of the amygdala increased their frequency of firing concomitantly with spontaneous blood pressure increases and it was suggested that this increase in unit activity was an artifact (Ben-Ari et al., 1973). We can exclude the possibility of an artifact in the units reported here because the units responding to phenylephrine injection did not respond directly to blood pressure changes. Comparison of blood pressure changes elicited by both phenylephrine and unloading of baroreceptors (Fig. 2) shows that in both cases there was an increase in blood pressure, but opposite responses in the firing frequency of the unit were observed (Fig. 2).

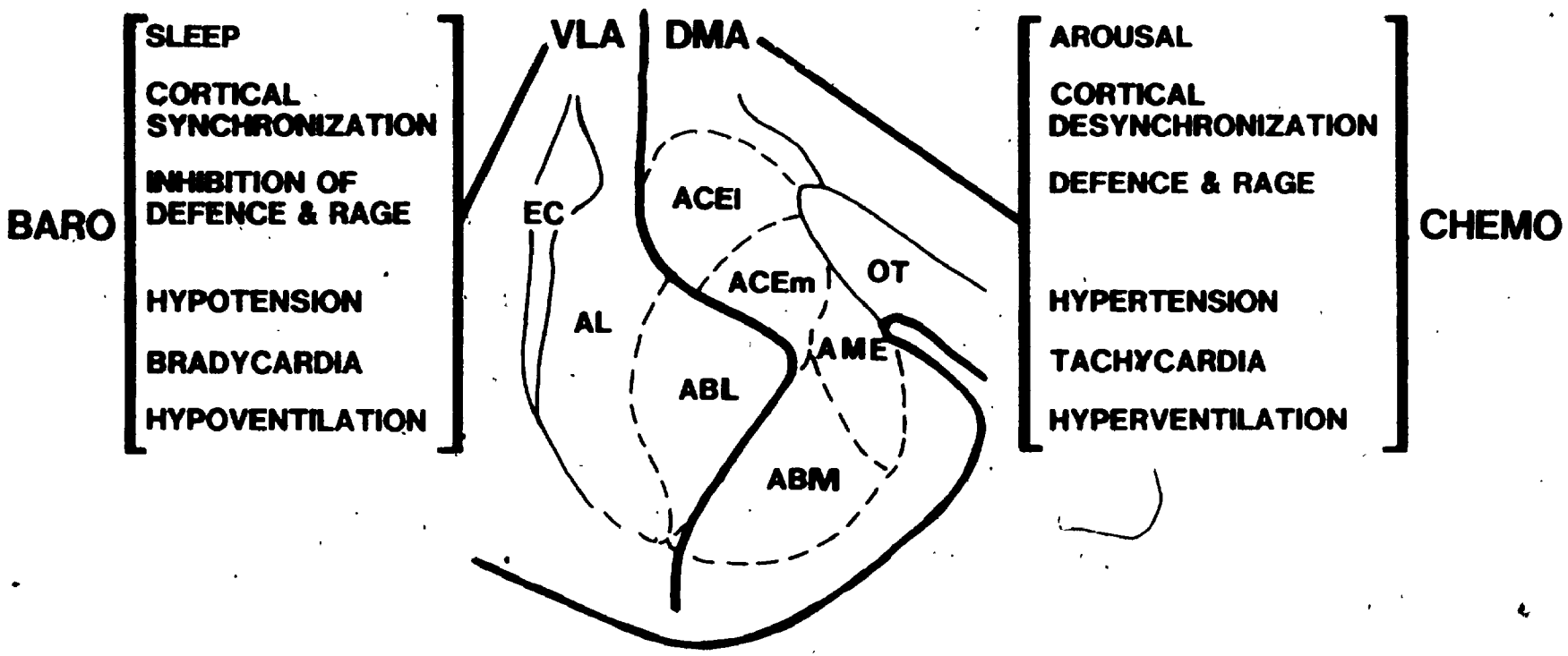
The majority of units in the lateral amygdala were excited by activation of baroreceptors. As it is well established that stimulation of baroreceptors results in a decrease in blood pressure, it is expected that stimulation of the lateral amygdala would elicit a decrease in blood pressure. In fact this has been demonstrated in both the cat

and rat (Morin et al., 1952; Wood et al., 1958).

An important contribution of these experiments is the demonstration that baro- and chemoreceptors project to separate neuronal pools in the amygdala: chemoreceptors project to the dorsal medial area while baroreceptors project primarily to the ventral and lateral areas. It is possible that this finding is functionally significant for the following reasons. Stimulation and ablation studies have demonstrated a separation of functions within the amygdala, i.e. that defence and arousal responses and an increase in blood pressure can be elicited by stimulation of the dorsomedial areas of the amygdala, while the ventral and lateral areas of the amygdala exert an inhibitory influence on defence, arousal and cardiovascular responses (Fonberg, 1968; Hilton and Zbrozyna, 1963; Kaada, 1972; Morin et al., 1952; Stock et al., 1981; Fig. 23). In addition, it has been demonstrated that activation of chemoreceptors can elicit responses such as rage, defence and arousal similar to those obtained from the dorsomedial amygdala, that activation of baroreceptors inhibits these responses (Baccelli et al., 1965; Bartorelli et al., 1960; Bizzi et al., 1961; Marshall, 1981; Fig. 23), and that these responses are dependent upon forebrain structures (Baccelli et al, 1965). Recent experiments in dogs have also demonstrated that carotid chemoreceptors are necessary for arousal from sleep in response to hypoxia (Bowes et al., 1981). These findings, taken together, prompt the suggestion that tonic chemoreceptor input to the dorsomedial amygdala represents a very important and necessary component of the central mechanism maintaining behavioral arousal while the baroreceptor input to the ventrolateral amygdala can function in deactivation of this system.

FIGURE 23

Representative transverse section of the amygdala showing the behavioral and autonomic responses elicited from the ventrolateral (VLA) and dorsomedial (DMA) amygdala similar to the responses elicited by activation of baroreceptors (BARO) and activation of chemoreceptors (CHEMO), respectively. ABL, ABM, AL and AME, basolateral, basomedial, lateral and medial nuclei of the amygdala, ACEl and ACEm, lateral and medial components of the central nucleus of the amygdala; EC, external capsule; OT, optic tract.


BARO
SLEEP
CORTICAL SYNCHRONIZATION
INHIBITION OF DEFENCE & RAGE
HYPOTENSION
BRADYCARDIA
HYPOVENTILATION
VLA
DMA
EC
AL
ACEl
ACEm
OT
AME
ABL
ABM
AROUSAL
CORTICAL DESYNCHRONIZATION
DEFENCE & RAGE
HYPERTENSION
TACHYCARDIA
HYPERVENTILATION
CHEMO

3. Afferent connections to cardiovascular sites in the amygdala

This study was done to investigate central pathways which may relay information from buffer nerves to the amygdala by depositing horseradish peroxidase at sites in the central and lateral nuclei of the amygdala where neurons that alter their rate of discharge during stimulation of the carotid sinus and aortic depressor nerves have been found. Although there are anatomical studies of the afferent inputs to the amygdala using horseradish peroxidase in the rat, cat and monkey (Mehler, 1980; Ottersen and Ben-Ari, 1978 a; b; 1979; Ottersen, 1980; 1981; 1982; Russchen, 1982a; b; Veening, 1978), this study presents evidence about afferent inputs using very discrete deposits in specific subdivisions of the central and lateral nuclei of the amygdala. The present results essentially confirm previous work but some selective projections were noted as a result of the localized nature of the deposits of horseradish peroxidase.

With regard to the projection to the central nucleus, this study has shown that the magnocellular medial component receives a large afferent input from the thalamus and hypothalamus. Previous studies in which horseradish peroxidase was placed in the amygdala of the rat, cat and monkey did not demonstrate these separate inputs to the medial and lateral subdivisions of the central nucleus (Mehler, 1980; Ottersen and Ben-Ari, 1978; 1979; Ottersen, 1980; 1981; Veening, 1978). Recently, Russchen (1982 a; b) has published results obtained by placing relatively small deposits of horseradish peroxidase in the amygdala of cats, although all her injection sites involved adjacent nuclei in contrast to the present study, where small deposits were restricted to the subdivisions of individual nuclei of the amygdala. Her results

are similar to the results of the present study demonstrating that the medial component of the central nucleus receives a large proportion of the subcortical projections from the hypothalamus, thalamus and brain stem.

The present results show that in the hypothalamus the ventromedial and paraventricular nuclei contained neurons which were almost exclusively labelled by horseradish peroxidase deposits in the medial component of the central nucleus of the amygdala. Other horseradish peroxidase studies in the rat, cat and monkey have demonstrated a projection to the amygdala from the ventromedial nucleus but they have not demonstrated labelled neurons in the paraventricular nucleus (Mehler, 1980; Ottersen, 1980; Veening, 1978). There are also some differences in hypothalamic projections when comparing the present results with those of Russchen (1982), in which a projection from the parvocellular portion of the paraventricular nucleus was demonstrated. The present results show labelled neurons throughout the paraventricular nucleus of the hypothalamus, particularly in the large-celled division. Russchen also indicated that when the medial subdivision of the central nucleus is involved in the injection site but the medial nucleus is spared, all the hypothalamic areas except the paraventricular area are involved. In contrast, in the present study with small injections contained entirely within the medial component of the central nucleus, labelled neurons were found primarily in the paraventricular nucleus.

In the present results labelled neurons in brain stem regions such as the locus coeruleus and lateral parabrachial nucleus were the result of a large deposit of horseradish peroxidase in the medial central nucleus

which overlapped into the lateral central and dorsal portion of the basolateral nucleus while discrete deposits in the medial central nucleus did not label brain stem neurons. In orthograde studies in the rat using radioactive aminoacids, projections from the parabrachial nuclei and the nucleus of the solitary tract have been shown to terminate in the entire central nucleus (Ricardo and Koh, 1978; Saper and Loewy, 1980). On the other hand, Russchen (1982) concluded from her horseradish peroxidase injections in cats that the brain stem neurons projected mainly to the medial central amygdaloid nucleus.

With regard to the lateral nucleus of the amygdala, it can be subdivided into two components based on differences in cell size: the shell of the nucleus on its lateral edge adjacent to the external capsule is composed of large cells and the body is composed of medium-sized cells (Krettek and Price, 1978). The results of the present study have shown that only deposits of horseradish peroxidase which included the body of the lateral nucleus resulted in labelled neurons in the hypothalamus. The projection from the ventromedial nucleus and the lateral and dorsal hypothalamic areas was not very extensive which is supported by other horseradish peroxidase and autoradiographic studies (Conrad and Pfaff, 1976; Krieger et al., 1979; Ottersen, 1980; Saper et al., 1978).

The present anatomical findings, as well as those of previous investigators, suggest interesting functional implications regarding the role of the amygdala in cardiovascular control. The pattern of distribution of labelled neurons in the hypothalamus after the injection of horseradish peroxidase in the medial component of the central nucleus is similar to the distribution of terminal labelling after the injec-

tion of labelled aminoacids in the region of the nucleus of the solitary tract (Ciriello and Calaresu, 1980). In particular, the anterior and dorsal paraventricular nuclei of the hypothalamus project to the central and lateral nuclei of the the amygdala. The notion that the paraventricular nuclei are likely areas for relaying cardiovascular information to the amygdala is supported by electrophysiological studies showing that single units in these nuclei alter their firing frequency in response to electrical stimulation of the buffer nerves (Calaresu and Ciriello, 1980) and that they also receive a direct projection from the region of the nucleus of the solitary tract (Ciriello and Calaresu, 1980 a; b; Ricardo and Koh, 1978). The region of the supraoptic nucleus and the ventromedial nucleus were also shown to project to the central nucleus of the amygdala. These hypothalamic nuclei have been shown to receive afferent input from the buffer nerves (Calaresu and Ciriello, 1980), but there is no evidence of a direct projection from the region of the nucleus of the solitary tract to these hypothalamic nuclei (Ciriello and Calaresu, 1980 a; Ricardo and Koh, 1978).

This study and other neuroanatomical studies have demonstrated a direct projection from the parabrachial nuclei to the region of the central nucleus of the amygdala (Mehler, 1980; Ottersen, 1981; Russchen, 1982; Saper and Loewy, 1980; Veening, 1978). These brain stem nuclei might also relay cardiovascular information from the baro- and chemoreceptors, since it has been shown that neurons in the parabrachial nuclei respond to electrical stimulation of the aortic depressor nerve (Hamilton et al., 1981), and a direct projection from the nucleus of the solitary tract to the parabrachial nuclei has been demonstrated

electrophysiologically and anatomically (Hamilton et al., 1981; Loewy and Burton, 1978; Norgren and Leonard, 1973; Norgren, 1978; Ricardo and Koh, 1978).

In summary, possible pathways for cardiovascular afferent information from buffer nerves to the amygdala were investigated using discrete deposits of horseradish peroxidase in the central and lateral nuclei of the amygdala. In the hypothalamus, the paraventricular nucleus was seen to project predominantly to the medial central nucleus of the amygdala. In the brain stem, labelled neurons were located in the parabrachial nucleus. As these two areas also receive direct projections from the nucleus of the solitary tract, it is likely that they are involved in relaying afferent projections from buffer nerves to the amygdala.

4. Buffer nerve input to units in the parabrachial and Kolliker-Fuse nuclei

The experiments reported here were prompted by recent observations demonstrating that the parabrachial nucleus in addition to its well-established role in central control of respiration (Cohen, 1979; 1981) also plays a part in the control of the circulation (Hamilton et al., 1981; Mraovitch et al., 1982). A role for the parabrachial nucleus in circulatory control is also suggested by many anatomical studies demonstrating direct connections between the parabrachial and Kolliker-Fuse nuclei and brain stem and forebrain sites involved in cardiovascular control (King, 1980; Krettek and Price, 1978; Loewy and Burton, 1978; Russchen, 1982; Saper and Loewy, 1980; Takeuchi et al., 1982). In these experiments the electrophysiological method of

single unit recording was used to demonstrate that neurons in the parabrachial and Kolliker-Fuse nuclei receive cardiovascular sensory information from buffer nerves and that these units have reciprocal connections with sites in the amygdala and hypothalamus previously shown to influence the cardiovascular system. Single unit recording with histological verification of the recording site results in the precise localization of neurons within a nucleus which send or receive information to and from specific brain nuclei or peripheral nerves as well as permitting the testing of multiple inputs to a single neuron.

The major contribution of this study is the demonstration that cardiovascular afferent information carried in the carotid sinus and aortic depressor nerves is relayed to neurons in the parabrachial and Kolliker-Fuse nuclei. The results of the present study show that only 10% of the units in the parabrachial and Kolliker-Fuse nuclei responded to stimulation of the aortic depressor nerve (Hamilton et al., 1981). A much greater proportion (27%) of units in the parabrachial and Kolliker-Fuse nuclei responded to stimulation of the carotid sinus nerve. As it is known that the carotid sinus nerve contains approximately twice as many afferent fibers as the aortic depressor nerve (Agostini, 1957; Eyzaguirre and Uchizono, 1961), this may account in part for the greater proportion of units responding to stimulation of the carotid sinus nerve.

Units responding to buffer nerve stimulation were found primarily in the ipsilateral dorsomedial parabrachial nucleus and in the ventrolateral parabrachial and Kolliker-Fuse nuclei. Few neurons in the caudomedial portion of the parabrachial nucleus received afferent buffer nerve information, which is in agreement with previous neuroanatomical studies demonstrating that the caudomedial part of the parabrachial

nucleus receives gustatory information via a dorsal pathway (King, 1980; Norgren, 1978). In contrast to this projection, the caudal nuclei of the solitary tract involved in cardiovascular and respiratory control project by a ventrolateral pathway to the dorsomedial portion of the parabrachial nucleus and the ventrolateral parabrachial and Kolliker-Fuse nuclei (King, 1980; Loewy and Burton, 1978).

The demonstration of units in the parabrachial and Kolliker-Fuse nuclei responding to stimulation of buffer nerves raises an important question concerning their function. Are these units active in cardiovascular or respiratory regulatory mechanisms? It is suggested that these units are probably involved in both respiratory and cardiovascular control. The suggestion that some of the units responding to buffer nerves may be involved in respiratory control mechanisms may be supported by two arguments. First, it has been shown that both baro- and chemoreceptors have a role in the control of respiration (Brunner et al., 1982; Lahiri and DeLaney, 1975) and that much of the area in the parabrachial nucleus where units responsive to stimulation of buffer nerves were found is the same area which has been identified as the rostral pontine pneumotaxic center (Bertrand and Hugelin, 1971; Cohen, 1979; 1981). Secondly, the present study has demonstrated that approximately 40% of the units in the ipsilateral parabrachial nucleus responded to buffer nerve stimulation and it has been shown that 80% of the units in this region have a respiratory-related pattern of discharge (Bertrand and Hugelin, 1971), suggesting that at least half of the units reported here may be involved in respiratory regulation. On the other hand, it is not likely that all the units responding to buffer nerve stimulation are involved in respiratory control mechanisms because

recent electrophysiological evidence has indicated that only a few of the neurons projecting to the parabrachial nucleus from the area of the nucleus of the solitary tract and from the medullary lateral tegmental field are involved in respiratory control (King and Knox, 1982). Furthermore, it has been demonstrated that many neurons in the medial nucleus of the solitary tract project to the parabrachial nucleus but few of these are respiratory-related units, whereas in the lateral nucleus of the solitary tract, many respiratory-related units are found, but few of these units project to the parabrachial nucleus (Cohen, 1979; King, 1980). Finally, the contention that some of the units reported here are involved in central cardiovascular control is supported by studies showing that injection of radioactive aminoacids into areas of the nucleus of the solitary tract where cardiovascular neuronal activity was recorded resulted in intense labelling of terminals in the ventrolateral parabrachial and Kolliker-Fuse nuclei (Loewy and Burton, 1978) and by the demonstration that stimulation of the parabrachial nucleus results in changes in blood pressure and heart rate independent of changes in respiration (Hamilton et al., 1981; Mraovitch et al., 1982).

5. Connections of cardiovascular neurons in the parabrachial and Kolliker-Fuse nuclei with the amygdala and hypothalamus

This study has shown that units in the parabrachial and Kolliker-Fuse nuclei antidromically activated by stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus also responded to stimulation of the carotid sinus nerve and aortic depressor nerve, suggesting that the parabrachial and Kolliker-Fuse

nuclei relay baro- and chemoreceptor information to the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus. This suggestion is supported by the finding that neurons in the central nucleus of the amygdala (results of this study) and the paraventricular nucleus of the hypothalamus respond to stimulation of buffer nerves (Calaresu and Ciriello, 1980) and by the demonstration of direct connections from the parabrachial and Kolliker-Fuse nuclei to both of these forebrain sites, shown by the results of this study and others (Russchen, 1982; Saper and Loewy, 1980). The average latencies for the antidromic response from the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus to the parabrachial and Kolliker-Fuse nuclei were 8.5 and 6.6 ms respectively. Using conduction distances of approximately 10 and 8 mm from the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus to the parabrachial and Kolliker-Fuse nuclei results in an estimated conduction velocity of 1.2 m/s characteristic of unmyelinated fibers.

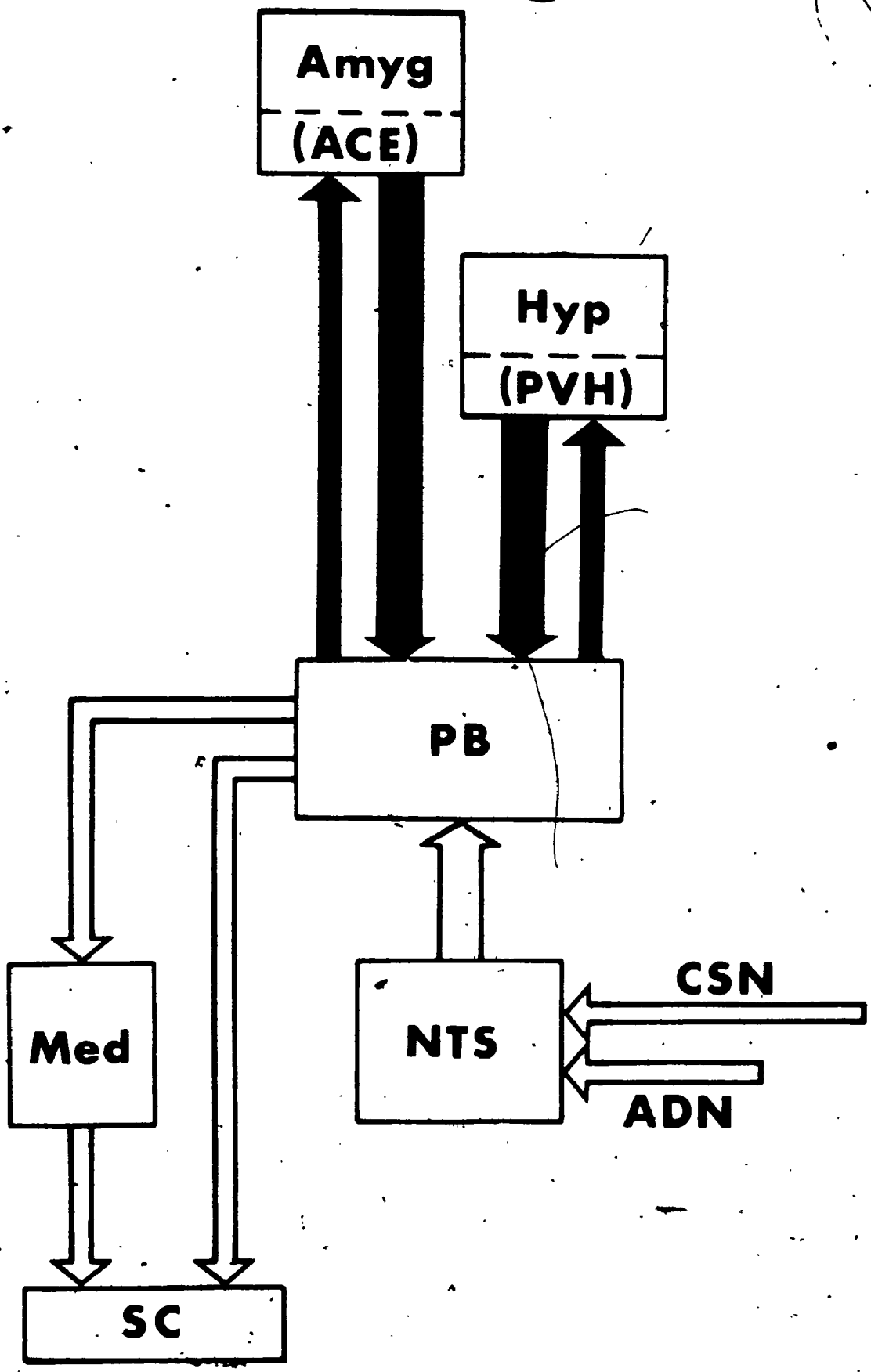
These experiments have also demonstrated that the units in the parabrachial and Kolliker-Fuse nuclei responding orthodromically to stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus were located primarily in the ventrolateral parabrachial and Kolliker-Fuse nuclei. These results are consistent with those of previous anatomical studies which have demonstrated in the rat and cat that the central nucleus of the amygdala (Hopkins and Holstege, 1978; Krettek and Price, 1978; Takeuchi *et al.*, 1982)and in the rat that the paraventricular nucleus of the hypothalamus (Saper *et al.*, 1976) project to the ventrolateral parabrachial and Kolliker-Fuse

nuclei. In addition, these results demonstrated that more than half of the units in the parabrachial and Kolliker-Fuse nuclei excited by forebrain stimulation also received incoming sensory information from the carotid sinus and aortic depressor nerves. Thus, the parabrachial and Kolliker-Fuse nuclei appear to be a brain stem area in which descending influences from the limbic system can modify incoming baro- and chemoreceptor information, suggesting that these nuclei play a key role in relaying information from the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus to sites in the medulla and spinal cord involved in cardiovascular and respiratory control. This suggestion is supported by the demonstration that in the cat stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus results in an increase in blood pressure and tachycardia similar to that elicited by stimulation of the parabrachial nucleus (Ciriello and Calaresu, 1980 b; Mraovitch et al., 1982; Stock et al., 1981), and that stimulation of the central nucleus of the amygdala results in changes in respiration similar to those elicited by stimulation of the parabrachial nucleus (Bonvallet and Bobo, 1972; Cohen, 1979; 1981). In addition, it has been shown that the parabrachial and Kolliker-Fuse nuclei have direct projections to areas of the brain stem which contain the ventral respiratory neurons and parasympathetic preganglionic neurons, the ventrolateral medulla, and to the intermediolateral cell column of the spinal cord (Dampney et al., 1982; Saper and Loewy, 1980; Takeuchi et al., 1980) which provide the neuroanatomical substrate for the efferent pathway from the parabrachial and Kolliker-Fuse nuclei mediating cardiovascular and respiratory changes.

In summary, the experiments recording from single units in the parabrachial nucleus have demonstrated the existence of spontaneously firing units in discrete regions of the parabrachial and Kolliker-Fuse nuclei which receive an input from the carotid sinus and aortic depressor nerves. Antidromic activation of some of these neurons responding to activation of buffer nerves by stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus demonstrates that the parabrachial and Kolliker-Fuse nuclei can relay this information to the forebrain. Spontaneously firing units in the parabrachial and Kolliker-Fuse nuclei which responded orthodromically to stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus have also been found and more than half of these units also responded to buffer nerve stimulation. The amygdala (Kaada, 1972) and the hypothalamus (Abrahams et al., 1960) control complex behavioral activities which include specific cardiovascular and respiratory responses. It is proposed, on the basis of the experimental findings presented here, that the cardiovascular and respiratory changes associated with these behaviors utilize neural mechanisms involving short loop and long loop reflexes as shown in Fig. 24. The amygdala and hypothalamus (Calaresu and Ciriello, 1980) receive baro- and chemoreceptor information and as demonstrated by the results of this study, the parabrachial and Kolliker-Fuse nuclei relay and presumably influence some of this afferent information. The amygdala and hypothalamus receive buffer nerve information and return an integrated signal via the central nucleus of the amygdala and paraventricular nucleus of the hypothalamus to the parabrachial and Kolliker-Fuse nuclei. The results of this study demonstrate that

FIGURE 24

Proposed long and short loop reflexes integrating baro- and chemoreceptor information to produce cardiovascular and respiratory changes during behaviors controlled by the amygdala and hypothalamus (Hyp). Solid arrows show connections demonstrated in these experiments. Amygdala and hypothalamus receive baro- and chemoreceptor information relayed through the parabrachial nucleus (PB). An integrated signal from the central nucleus of the amygdala (ACE) and paraventricular nucleus of the hypothalamus (PVH) descends primarily to the PB converging on ascending aortic depressor (ADN) and carotid sinus (CSN) nerve information relayed through the nucleus of the solitary tract (NTS). The PB then sends an integrated signal to medulla (Med) and spinal cord (SC) to produce the appropriate cardiovascular and respiratory changes.


Amyg
(ACE)
Hyp
(PVH)
PB
Med
NTS
CSN
ADN
SC

in the parabrachial and Kolliker-Fuse nuclei the descending signals from the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus converge on neurons also receiving baro- and chemoreceptor information. The integrated output from the parabrachial and Kolliker-Fuse nuclei then projects via the medulla and spinal cord to the target organs to produce the appropriate cardiovascular and respiratory responses.

6. Central pathways relaying cardiovascular afferent information to the amygdala

This study has demonstrated that stimulation of the paraventricular nucleus of the hypothalamus and the parabrachial nucleus altered the firing rate of single units in the amygdala. It is likely that this input to the amygdala from the paraventricular nucleus of the hypothalamus and the parabrachial nucleus represents afferent information relayed from the nucleus of the solitary tract as both the paraventricular nucleus of the hypothalamus and the parabrachial nucleus have been demonstrated to receive a direct projection from the region of the nucleus of the solitary tract (Berk and Finkelstein, 1979; Ciriello and Calaresu, 1980; Ricardo and Koh, 1979; McKellar and Loewy, 1981; Loewy and Burton, 1978) and both the paraventricular nucleus of the hypothalamus and the parabrachial nucleus project directly to the amygdala as demonstrated in this study and elsewhere (Russchen, 1982; Saper and Loewy, 1980). In addition, it is likely that the parabrachial nucleus is specifically involved in relaying cardiovascular afferent information for two reasons. First, the present study has shown that 24% of the units

in the amygdala responding to stimulation of the parabrachial nucleus also receive chemoreceptor information while 4% of the units responding to stimulation of the parabrachial nucleus also receive baroreceptor input. Second, it has been previously demonstrated in this study that single units in the parabrachial nucleus responding to electrical stimulation of the carotid sinus and aortic depressor nerves were also antidromically activated by stimulation of the central nucleus of the amygdala.

The possibility that the paraventricular nucleus of the hypothalamus has a role in relaying cardiovascular information from the nucleus of the solitary tract to the amygdala is supported by the finding of single units in the paraventricular nucleus of the hypothalamus responding to stimulation of the carotid sinus and aortic depressor nerves (Calaresu and Ciriello, 1980) and by the results of single unit recordings in the present study demonstrating that 33% of the units in the amygdala responding to stimulation of the paraventricular nucleus of the hypothalamus also receive chemoreceptor information.

In summary, the results of this study demonstrating that single units in the amygdala responsive to the paraventricular nucleus of the hypothalamus or the parabrachial nucleus also responded to cardiovascular afferent input suggests that both the paraventricular and parabrachial nuclei are likely candidates for relaying cardiovascular information from the medulla to the amygdala. However, none of the units in the amygdala responding to stimulation of the paraventricular nucleus of the hypothalamus and few of the units in the amygdala responding to stimulation of the parabrachial nucleus were also re-

sponsive to activation of baroreceptors. This suggests that there may be an alternate pathway conveying primarily baroreceptor information to the amygdala.

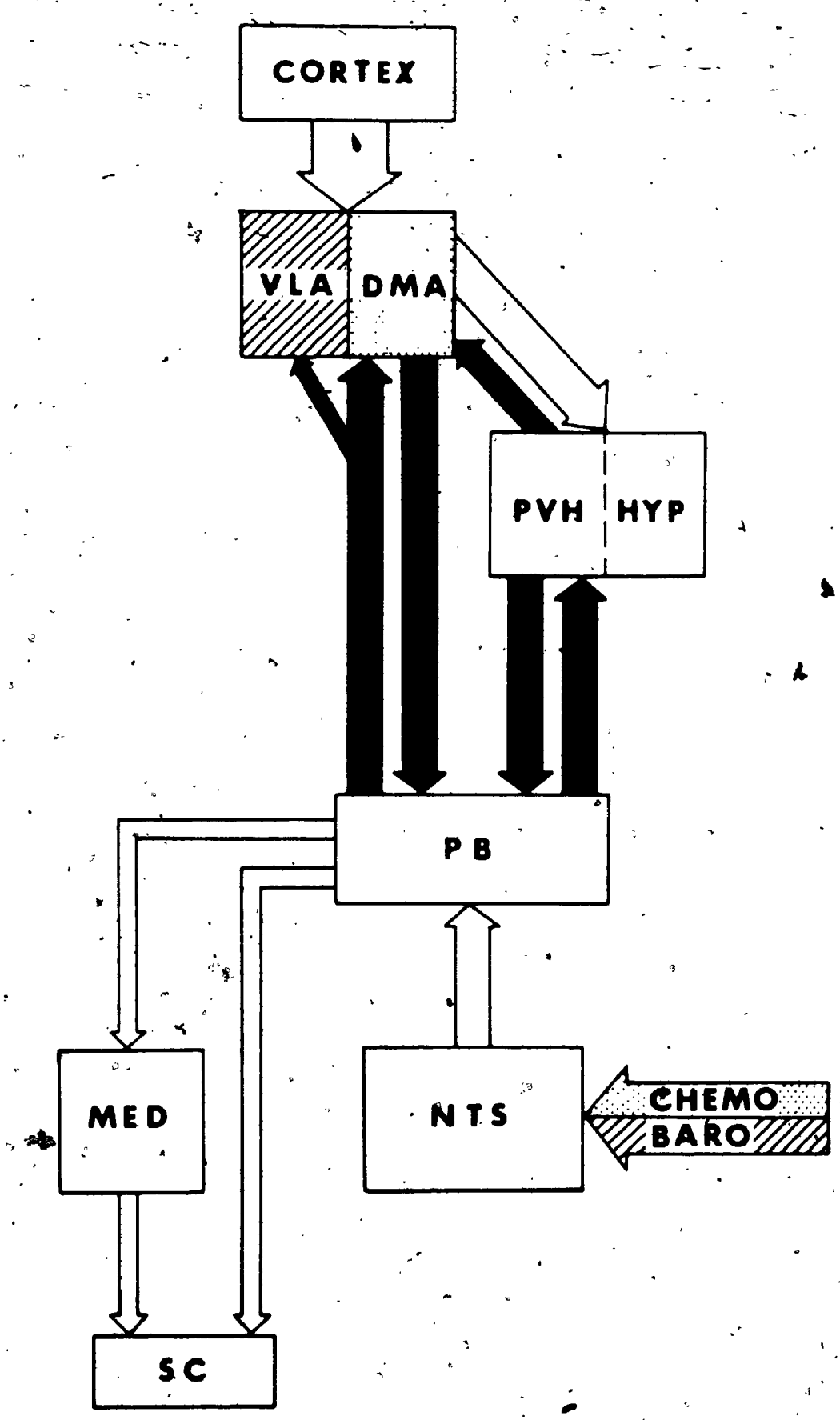
B. Conclusions

Previous investigations have attempted neuroanatomically and electrophysiologically to establish the function of the amygdala. These studies have demonstrated that this limbic structure has the unique role of relaying exteroceptive sensory information from the cortex to the hypothalamus and other subcortical structures. Highly processed auditory, visual, gustatory and somesthetic sensory information from the neocortex projects to the amygdala which in turn sends an integrated signal to alter the behavioral, autonomic and respiratory responses elicited from the hypothalamus and other brain stem nuclei (Fig. 1). However, few investigations had considered the possible role of interoceptive input to the amygdala. It is known that the behaviors controlled by the amygdala also have concomitant complex cardiovascular and respiratory changes. It is likely that baro- and chemoreceptor input to the amygdala might be important in the control of these responses during the different behavioral states. The results of this study have demonstrated a major input from baro- and chemoreceptors to the amygdala.

A proposed model for the function of the amygdala which includes a role for afferent baro- and chemoreceptor information based on evidence obtained in this study and results in the literature is shown in Fig. 25. In this proposed scheme the amygdala not only receives

FIGURE 25

Proposed neural mechanism integrating sensory information and baro- and chemoreceptor information to produce cardiovascular and respiratory changes during behaviors controlled by the amygdala. Diagonal lines indicate baroreceptor input; stippled area represents chemoreceptor input. Solid arrows show connections demonstrated in the present and previous electrophysiological investigations on the role of cardiovascular afferent input to the amygdala. The amygdala receives sensory information from the cortex and cardiovascular information from the nucleus of the solitary tract (NTS) relayed through the parabrachial nucleus (PB) and paraventricular nucleus of the hypothalamus (PVH). Some of the cardiovascular information to the PVH is relayed through the PB. The ventrolateral portion of the amygdala (VLA) receives baroreceptor information while the dorsomedial part (DMA) receives chemoreceptor information. The amygdala sends a large projection to the hypothalamus and neurons in the PVH feedback on neurons in the DMA receiving chemoreceptor input. Integrated signals from the amygdala and PVH descend primarily to the PB converging on ascending aortic depressor and carotid sinus nerve information. The PB then sends an integrated signal to the medulla (MED) and spinal cord (SC) to produce the appropriate cardiovascular and respiratory changes.


CORTEX
VLA
DMA
PVH
HYP
PB
MED
NTS
CHEMO
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highly processed exteroceptive sensory input from the cortex but also receives cardiovascular information from the aortic depressor and carotid sinus nerves. The important role of this cardiovascular information in the function of the amygdala is suggested by the following results. First, it was demonstrated that approximately one-third of all spontaneously firing neurons in the amygdala receive buffer nerve input. Secondly, these responsive neurons are widely distributed over three major nuclei of the amygdala: the central, basal and lateral. Thirdly, separate baro- and chemoreceptor input projects to regions of the amygdala in which stimulation can elicit behavioral, autonomic and respiratory responses similar to those obtained by the activation of the appropriate cardiovascular afferent (Fig. 23). For example, stimulation of both chemoreceptors and the dorsomedial amygdala elicits arousal and increases in arterial pressure and heart rate, while stimulation of baroreceptors and the ventrolateral amygdala inhibits arousal and decreases arterial pressure and respiration. It is suggested that tonic chemoreceptor input to the dorsomedial amygdala is a necessary and important component of behavioral arousal while baroreceptor input to the ventrolateral amygdala functions in deactivation of this system.

The amygdala which was previously thought to alter behavioral responses by integrating signals from the environment has now been demonstrated to be in the unique position of being able to integrate interoceptive cardiovascular information also. This visceral input to the amygdala provides a mechanism whereby the total behavioral response of the organism is seen to be dependent not only on the

environmental cues but also on facilitatory and inhibitory signals from the internal milieu, in particular baro- and chemoreceptor afferent information. In this scheme, the existing level of blood pressure and blood gases can alter the sensitivity of the two divisions of the amygdala to influence the behavioral state in response to environmental signals.

In the proposed scheme, the internal milieu in turn is altered by long loop reflexes from cardiovascular receptors to the hypothalamus and the amygdala and out to effectors via a pathway in which the parabrachial nucleus in the pons plays a pivotal role (Fig. 25). The results of this study have demonstrated that the cardiovascular afferent information to the amygdala is relayed through the paraventricular nucleus of the hypothalamus and the parabrachial nucleus from the nucleus of the solitary tract. Thus, the amygdala receives exteroceptive input from the cortex and interoceptive input from the paraventricular and parabrachial nuclei and sends a descending integrated signal to the hypothalamus. The paraventricular nucleus of the hypothalamus receives cardiovascular information some of which is relayed through the parabrachial nucleus. The paraventricular nucleus in turn projects to neurons in the dorsomedial amygdala, including those receiving chemoreceptor input. It has been demonstrated that the dorsomedial amygdala, the region of the paraventricular nucleus of the hypothalamus and chemoreceptors are inolved in control of the defence response. It is possible that the projection from the paraventricular nucleus to the dorsomedial amygdala is a feedback signal involved in the control of the defence response. Both the amygdala and hypothalamus send descending

integrated signals primarily to the pons which converge on neurons in the parabrachial nucleus also receiving cardiovascular information and possibly some neurons in the region of the nucleus of the solitary tract involved in mediating cardiovascular reflexes. The integrated output from the parabrachial nucleus projects to regions in the medulla and spinal cord which contain respiratory control neurons and sympathetic and parasympathetic preganglionic neurons. This descending pathway provides the anatomical substrate by which the behavioral responses originating in the amygdala and hypothalamus produce the appropriate cardiovascular and respiratory responses.

SUMMARY

1. (a) Stimulation of the carotid sinus nerve altered the firing frequency of 30% (73/241) of the units on both sides of the amygdala. Of these units, 47% were excited and 53% were inhibited.

   (b) Stimulation of the aortic depressor nerve elicited a change in firing frequency of 20% (50/251) of ipsilateral and contralateral units. Of these, 68% were excited and the remainder were inhibited.

   (c) The majority of the responsive units were located in the central, lateral and dorsal portions of the basal nuclei of the amygdala.

   The experiments in this study provide the first electrophysiological evidence that information from receptors in the cardiovascular system carried in the carotid sinus and aortic depressor nerves can alter the electrical activity of units located primarily in the central, lateral and dorsal portions of the basal nuclei of the amygdala.

2. (a) Chemoreceptor activation (25 µg sodium cyanide in 0.1 ml saline into the medial thyroid artery) altered the firing frequency of 23% (35/154) of spontaneously firing units in the ipsilateral amygdala, of which 37% were excited and 63% were inhibited.

   (b) Baroreceptor activation (2 µg/kg phenylephrine IV) altered the firing frequency of 16% (24/154) of spontaneously firing

units in the ipsilateral amygdala, of which 71% were excited and 29% were inhibited.

(c) The units responsive to chemoreceptor activation were located primarily in the dorsomedial amygdala while those responsive to baroreceptor activation were located in the ventrolateral amygdala.

It is known that both chemoreceptor activation and stimulation of the dorsomedial amygdala elicit arousal and an increase in blood pressure while baroreceptor activation and stimulation of the ventrolateral amygdala results in inhibition of arousal and a decrease in blood pressure. These findings and the present results, taken together, suggest that tonic chemoreceptor input to the dorsomedial amygdala represents a very important and necessary component of the central mechanisms maintaining behavioral arousal while the baroreceptor input to the ventrolateral amygdala can function in deactivation of this system.

3. (a) Horseradish peroxidase deposits localized to the medial portion of the central nucleus of the amygdala retrogradally labelled neurons in the ipsilateral hypothalamus, primarily in the paraventricular and ventromedial nuclei.

(b) In the pons the parabrachial nucleus and locus coeruleus were observed to project to the region of the central nucleus of the amygdala.

(c) Horseradish peroxidase deposits in the lateral nucleus of the amygdala labelled only a few neurons in the ipsilateral hypothalamus.

(d) Thalamic and cortical projections shown by previous investi-

gators were confirmed.

Two nuclear regions, the paraventricular nucleus of the hypothalamus and the parabrachial nucleus, were demonstrated to project directly to the amygdala. As these two areas also receive direct projections from the nucleus of the solitary tract it is possible that they are involved in relaying afferent projections from buffer nerves to the amygdala.

4. (a) Electrical stimulation of the carotid sinus and aortic depressor nerves altered the firing frequency of 25% (73/292) and 9% (25/282) respectively, of spontaneously firing units in the parabrachial and Kolliker-Fuse nuclei.

   (b) Units responsive to carotid sinus and aortic depressor nerves were located primarily in the ventrolateral region of the parabrachial and Kolliker-Fuse nuclei.

   (c) Stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus antidromically activated 9 and 7 units respectively in the parabrachial nucleus and approximately half of these also responded to buffer nerve stimulation.

   (d) Stimulation of the central nucleus of the amygdala orthodromically activated 22% (67/310) of the units in the parabrachial and Kolliker-Fuse nuclei while stimulation of the paraventricular nucleus of the hypothalamus orthodromically activated 9% (25/280) of the units in the parabrachial and Kolliker-Fuse nuclei. Of these units approximately half also responded to buffer nerve stimulation.

These experiments have demonstrated the existence of spontaneously

firing units in discrete regions of the parabrachial and Kolliker-Fuse nuclei which receive an input from the carotid sinus and aortic depressor nerves. Antidromic activation of some of these neurons responding to activation of buffer nerves by stimulation of the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus demonstrates that the parabrachial and Kolliker-Fuse nuclei can relay this information to the forebrain. In addition, descending signals from the central nucleus of the amygdala and the paraventricular nucleus of the hypothalamus converge on neurons in the parabrachial and Kolliker-Fuse nuclei also receiving buffer nerve information. It is suggested that the integrated output from the parabrachial and Kolliker-Fuse nuclei then projects via the medulla and spinal cord to the target organs to produce the appropriate cardiovascular and respiratory responses.

5. (a) Stimulation of the paraventricular nucleus of the hypothalamus altered the firing frequency of 19% (27/140) of the units tested in the ipsilateral amygdala. Of these units, 33% also responded to chemoreceptor activation while none were responsive to baroreceptor activation.

   (b) Stimulation of the parabrachial nucleus altered the firing frequency of 31% (46/150) of the units tested in the ipsilateral amygdala. Of the units responding to electrical stimulation of the parabrachial nucleus, 24% also responded to chemoreceptor activation while 4% were responsive to baroreceptor activation.

The demonstration that units in the amygdala responsive to

stimulation of the paraventricular nucleus of the hypothalamus or the parabrachial nucleus also receive cardiovascular information suggests that both these nuclear regions may relay buffer nerve information from the medulla to the amygdala.

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