ABSTRACT

ELECTROPHYSIOLOGICAL STUDIES ON THE ORGANIZATION OF CENTRAL VASOPRESSOR PATHWAYS

By

David George Taylor, Jr.

The purpose of this investigation was to study the organization of central vasopressor pathways in the cat. Emphasis was placed on defining the characteristics of spontaneously occurring and electrically evoked discharges recorded in multifiber pre- and postganglionic sympathetic nerve bundles and single preganglionic sympathetic neurons.

The slow wave of sympathetic nervous discharge (SND) locked in a 1:1 relation to the cardiac cycle ($\sim$ 3 c/sec periodicity) was studied in the anesthetized animal. Spontaneously occurring sympathetic nervous activity was recorded from the preganglionic splanchnic and postganglionic renal nerves. The data contradict the traditionally accepted view that the slow wave of SND occurs as the direct result of a waxing and waning of baroreceptor nervous discharge. Although baroreceptor denervation or hemorrhage unlocked the phase relations between SND and the cardiac cycle, the slow wave persisted and its duration was not changed.

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Early and late positive potentials were evoked when a short train of stimuli was applied to the carotid sinus nerve, aortic depressor nerve or paramedian reticular nucleus randomly with respect to the cardiac cycle. Evidence was provided to suggest that the late positive potential monitored the inhibition of the slow wave of SND. First, a single shock applied to the paramedian nucleus at appropriate points in the cardiac cycle aborted the slow wave of SND. Second, the contour of the late positive potential evoked by baroreceptor nerve or paramedian nucleus stimulation, during a time span which accounted for less than 1% of the cardiac cycle, was the mirror image of the centrally emanating slow negative wave of SND. Third, the late component of positivity was not elicited by stimulation of the paramedian nucleus during periods of asphyxia or prolonged severe hemorrhage when the 3 c/sec sympathetic oscillations were absent.

The early and late components of positivity elicited by baroreceptor nerve or paramedian nucleus stimulation persisted after midcollicular transection. Furthermore, the time course of depression of splanchnic nerve discharges evoked from descending spinal pressor tracts followed the early, but not the late positive response. This observation indicates that the early positive potential monitored sympathoinhibition of baroreceptor origin at a spinal level, while the late positivity reflected slow wave inhibition

at a brain stem locus. It was concluded that the 3 c/sec periodicity of SND is representative of a vasomotor rhythm of central origin which is entrained to the cardiac cycle by the baroreceptor reflexes at the brain stem level.

In an attempt to define the intrinsic organization of brain components transmitting the waves of SND, a study was made of the responses evoked in "vasoconstrictor" nerves. Potentials were elicited in the external carotid postganglionic sympathetic nerve by single shocks or trains of stimuli applied to pressor regions of the brain and spinal cord. The levels of the neuraxis explored included the hypothalamus, midbrain, medulla, and cervical spinal cord. Two distinct systems of vasopressor pathways were identified at each of the levels explored. Sympathetic nerve responses evoked from the more slowly conducting system of pathways were inhibited by baroreceptor reflex activation. Postganglionic potentials evoked from the more rapidly conducting system were not blocked by baroreceptor reflex activation. Potentials evoked from the baroreceptor reflex-sensitive and -insensitive system of pathways were further distinguished on the basis of their onset latency, duration, ability to follow high-frequency stimulation, and response patterns to single shocks and trains of stimuli. The baroreceptor reflex-insensitive responses could not be demonstrated in the splanchnic nerve Independent of onset latency, all splanchnic nerve responses

elicited from medullary and spinal pressor sites were inhibited by baroreceptor reflex activation.

To ascertain if the baroreceptor reflex-insensitive potentials exhibited in the external carotid nerve indeed monitored the activation of vasopressor pathways, the studies were extended to include the responses elicited in single preganglionic sympathetic neurons by stimulation of sites in the brain stem and spinal cord. Extracellular microelectrode recordings of unit discharges were made from the cat thoracic spinal cord. Preganglionic neurons were identified antidromically by stimulation of the cervical sympathetic nerve. Individual units exhibited two response patterns to stimulation of the medullary pressor region. The first unitary response type was termed the relatively fixed onset latency response pattern, while the second type was designated as the variable onset latency response pattern. The relatively fixed response type, in addition to its insensitivity to blockade by baroreceptor reflex activation, exhibited other characteristics similar to the baroreceptor reflex-insensitive responses recorded in the external carotid sympathetic nerve. The variable onset latency responses were inhibited during the pressor effect produced by norepinephrine and displayed other distinctive features resembling those of the baroreceptor reflex-sensitive postganglionic potentials. Thus, the individual preganglionic neuron of the upper thoracic

spinal cord acts as the final common pathway for those systems mediating the baroreceptor reflex-sensitive and -insensitive responses. This supports the contention that the baroreceptor reflex-insensitive pathway functions in the transmission of vasopressor information. It was concluded that vasopressor outflow from the brain to the external carotid nerve is organized into two systems of parallel pathways, each of which is related differently to the baroreceptor reflex arc. Furthermore, the central components of vasoconstrictor pathways distributed to the vascular beds innervated by the splanchnic and external carotid nerve are organized quite differently.

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Affectionately dedicated to my wife, Jacqueline,

whose presence was an inspiring force

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Central nervous elements responsible for basal and reflex-induced neurogenic discharge to the heart and vasculature are presumed to reside primarily in the caudal portions of the brain stem. Almost all of the earlier studies substantiating this idea were concerned with either changes in blood pressure evoked by afferent nerve stimulation or changes in resting blood pressure following brain transection. In 1870, Dittmar (see Bard, 1960) reported the results of experiments in which he employed both of these techniques. He found that stimulation of the central end of the sciatic nerve produced a marked rise in arterial pressure after separating the medulla from the rest of the brain. He surmised from these data that the components responsible for mediating the pressor responses were located somewhere in the bulbar region. Owsjannikow, a year later (1871; see Bard, 1960), reported results which delineated further the location of neural components in the brain stem responsible for both reflex

and tonic control of blood pressure. In cats and rabbits he found that serial frontal transections of the brain in a rostral-caudal direction had no effect on resting blood pressure until a section was made at the pontine level about 1-2 mm caudal to the inferior colliculi. Then, as transections were performed further caudally, he produced a greater and greater fall in arterial pressure. Transection at a level 4-5 mm above the obex produced the maximal decrease in pressure, which was not exceeded by section at the first cervical spinal segment. Owsjannikow also demonstrated that the reflex pressor response evoked by sciatic nerve stimulation was reduced progressively as the medulla was serially sectioned away. The sciatic reflex-induced rise in pressure was eliminated when the most caudal extent of the medulla was transected. Owsjannikow concluded that he had mapped the rostrocaudal extent of the vasomotor area and that brain stem components necessary for maintenance of tonic blood pressure as well as reflex responses were contained in this region of the brain. The classical work of Dittmar and Owsjannikow generally has been confirmed by others (Alexander, 1946; Bergmann and Korczyn, 1965; Chai *et al.*, 1963; Chai and Wang, 1968; Gutman *et al.*, 1961; Liebowitz *et al.*, 1963; Lindgren, 1961).

Implicit in these studies is the idea that the central vasotonic and vasoreflex elements are one in the same. As suggested by Porter (1918, 1915) and Porter and Turner (1915), if this is indeed the case, tonic and

reflex-induced changes in blood pressure should most likely be augmented or depressed together. Curare, the agent used in most of their experiments, did not produce this effect. In 16 experiments, curare augmented the pressor response evoked by sciatic stimulation, while resting blood pressure remained unchanged. These results lend support to the concept of two types of pressor elements; one component mediates tonic discharges responsible for maintaining resting blood pressure, while the other substrate transmits reflex vasopressor responses. However, interpretation of these data must be guarded. First, electrically evoked alterations in blood pressure should not and probably cannot be equated to changes in resting blood pressure. Second, the reflex-induced pressor responses may be due to a peripheral and not a central nervous phenomenon. That is, curare may produce changes in blood volume distribution which do not affect tonic blood pressure, but do exert substantial alterations in reflex rises in arterial pressure. In any event, these results are interesting and may warrant further investigation using newer research techniques. Until additional evidence is provided, this discussion will continue on the grounds that tonic and reflex vasomotor activity are emanating from one pressor "center."

The relative importance of spinal and medullary control of circulation deserves some additional comments.

The concept that the medullary vasomotor region is dominant over spinal components is based largely on comparisons of spinal with midcollicular decerebrate preparations. Since spinal shock or recovery from spinal shock might always be present in the spinal animal (Henneman, 1974), the contrasting properties of the cardiovascular system in these two experimental states may be interpreted incorrectly. This problem was addressed in a report by Ranson (1916). Prior to this study it was determined by Ranson and von Hess (1915) that sciatic afferent neural pathways responsible for eliciting the reflex pressor response passed through the posterior gray column which includes substantia gelatinosa and tract of Lissauer in the spinal cord. Ranson (1916) found that bilateral sectioning of this region at the first thoracic segment in chronic experiments (4-36 days) produced no detectable motor paralysis or autonomic shock. This lesion would presumably abolish all sensory input to the brain stem evoked by sciatic nerve stimulation, while not affecting most spinal reflex arcs. Since afferent inflow to the brain rostral to this lesion was left intact, the reflex rise in blood pressure produced by brachial nerve stimulation could be used as an indicator of damage to vasopressor pathways descending from supraspinal regions, as well as a control to determine brain stem responsiveness during the experiment. He found in normal cats equivalent pressor responses were produced

by electrical stimulation of either brachial or sciatic nerves. If supraspinal neural components are needed for the reflex-induced vasoconstriction, the spinal lesion should have abolished the rise in arterial pressure produced by sciatic afferent nerve stimulation, but not that produced by brachial nerve stimulation. Ranson's data demonstrated that pressor responses elicited by sciatic nerve stimulation were essentially eliminated as compared to those responses evoked from the brachial nerves. These observations support the contention that the reflex rise in arterial pressure evoked by afferent nerve stimulation results from excitation of bulbar vasomotor elements. The data portray the spinal reflex arcs as minor in the mediation of a pressor response. In addition, spinal vasoconstrictor components appear to be subservient to supraspinal influences. This may or may not be the case; since Ranson's report, other investigators have been able to elicit somatosympathetic reflex pressor responses (Brooks, 1933) and record reflex-evoked action potentials in sympathetic nerves (Koizumi and Brooks, 1972; Sato and Schmidt, 1973) in intact and spinalized animals. The reflex hypertension in most spinal animals was considerably less than that produced in intact cats (Brooks, 1933). Interestingly, the magnitude of the discharge mediated by spinal reflex pathways was much smaller than the response transmitted through supraspinal reflex arcs (Sato and Schmidt, 1973).

The intensity and the frequency of somatic afferent nerve stimulation determined whether a pressor or depressor response was elicited (for references see: Johansson, 1962; Koizumi and Brooks, 1972; Sato and Schmidt, 1973). Bayliss (1923) proposed the idea that the brain stem vasomotor region might be divided into two separate centers. One of these medullary centers mediated vasoconstriction, while the other center functioned to produce vasodilatation. Information regarding the location and nature of these bulbar centers has been obtained primarily by discrete localized electrical stimulation of vasoactive sites.

Ranson and Billingsley (1916) were the first to ascertain the location of the "so-called" medullary centers affecting blood pressure. By topical electrical stimulation of the floor of the fourth ventricle with a needle electrode they were able to locate a medial depressor area and a more lateral pressor area. With the introduction of the Horsley-Clarke stereotaxic instrument portions of the medulla could be repeatedly explored three-dimensionally with a stimulating electrode so as to locate cardiovascular reactive sites. Employing this instrument Wang and Ranson (1939a) revealed that the surface points from which Ranson and Billingsley (1916) had elicited a decrease or increase in blood pressure were not specific centers in the anatomical sense, but just the dorsal

extensions of diffusely distributed areas located within the medullary substance. Wang and Ranson (1939a) found that pressor responses were evoked most often from sites located in the periventricular gray and the dorsolateral reticular formation of the rostral third of the brain stem. As they stimulated regions more caudally vasopressor points moved centrally and dorsomedially until the most posterior medullary levels were approached; here the points shifted to the most lateral parts of the myelencephalon. Depressor responses or falls in blood pressure were elicited from sites less consistently distributed. These points were located in the central portions of the reticular substance with a tendency toward medial medullary concentration. Generally, vasoconstrictor sites occupied the rostral medullary regions, while depressor points were found in the caudal medulla. The maps provided by Wang and Ranson (1939a) have been reproduced and extended by others (Alexander, 1946; Bach, 1952; Chai and Wang, 1962; Manning, 1965; McQueen *et al.*, 1954).

Pressor responses evoked by medullary stimulation are the result of increased arterial and venous smooth muscle tone and cardiac performance. Baum and Hosko (1965) evaluated the responses exhibited by resistance and capacitance vessels to central nervous stimulation. The cat hindquarters were perfused at constant flow, and changes in the tone of pre- and postcapillary vessels were indicated

by changes in perfusion pressure and hindquarter volume, respectively. The most consistent finding was that changes in perfusion pressure were accompanied by oppositely directed changes in hindquarter volume. This was the case regardless of whether a pressor or depressor response was obtained by medullary stimulation. No central areas were found that predominantly affected perfusion pressure in preference to volume or vice versa. They concluded from these data that veins as well as arteries respond actively to stimulation of vasoactive sites in the brain stem.

Generally, the cardiac effects of stimulating pressor sites in the dorsolateral medulla are an increase in cardiac contractility and cardioacceleration (Chai *et al.*, 1963; Manning, 1965; Manning and Peiss, 1960; Peiss, 1958; Rosen, 1961). Cardiac augmentation and tachycardia remain unchanged after bilateral vagotomy or midcollicular decerebration. Contrary to a hypothesis proposed by Chai and Wang (1962), stimulation of right and left brain stem pressor sites apparently does not differentially affect cardiac performance (Chai *et al.*, 1963). In a report by Rosen (1961), muscle vascular tone could be increased in the absence of any alteration in cardiac performance, thus providing some indication of the complexity of central cardiovascular components.

On an electrophysiological basis the classical studies of Alexander (1946) probably describe best the general

functional organization of the brain stem cardiovascular centers. The cardiovascular effects produced by central and reflex stimulation, and brain transection were determined by measuring the action potentials from the inferior cardiac or the cervical sympathetic fibers, arterial pressure and heart rate. Alexander found that transections as far caudally as the lower third of the pons had no apparent effect on tonic discharges in the inferior cardiac nerve or resting blood pressure. A significant decrease in centrally emanating nervous activity and blood pressure was first seen following complete transection of the brain stem at the level of the auditory tubercle. The decrease in spontaneous discharge of fibers in the cardioaccelerator nerve produced by transection at this level is in accordance with anatomical localization of the medullary pressor region as shown by maps of Alexander (1946) and others mentioned previously (Bach, 1952; Chai and Wang, 1962; McQueen *et al.*, 1954). That is, transection at the level of the auditory tubercle eliminated a large portion of the bulbar pressor region. This transection also greatly impaired the reflex discharge in the postganglionic nerve evoked by applying single shocks to the central cut end of the sciatic nerve. Sectioning at the obex eliminated essentially all spontaneous sympathetic nervous discharge and produced a maximal fall in blood pressure. This cut also abolished sciatic-induced reflex discharges.

Subsequent transection through the first cervical spinal segment failed to produce additional hypotension, while spontaneously occurring nervous activity increased slightly. The elevated nervous discharge may have been produced either by a decreased blood flow and hypoxia at a spinal locus as suggested by earlier work of Alexander (1945) or by release of spinal preganglionic components from tonic inhibitory influences of the medullary depressor region. In regard to the latter, transection at C_1 would have eliminated the most caudal extensions of the stereotaxically mapped medullary depressor zone. Whereas the studies mentioned thus far, employing localized stimulation and transection of the brain, have been important in defining cardiovascular reactive sites, they have suggested little about the organization of central pressor pathways. That is, it cannot be determined whether high frequency electrical current applied to a small portion of the brain stem activated a group of efferent neurons, a group of internuncial neurons, or fibers which may be either afferent or efferent. It would also be difficult to decide whether pressor responses evoked by stimulation of two different brain sites involved the activation of components of the same or parallel pressor pathways.

Results of the preceding investigations would suggest that the medullary pressor center generally influences the entire cardiovascular system. Indeed, recent

electrophysiological studies have demonstrated that centrifugal pathways from the medulla are distributed to many nervous components subserving a sympathetic function. Stimulation of the bulbar pressor area has been shown to elicit action potentials in the splanchnic (Cohen and Gootman, 1969; Gootman, 1967; Gootman and Cohen, 1970, 1971; Kahn and Mills, 1967; Nathan, 1972a,b), cervical sympathetic (Kirchner *et al.*, 1970), external carotid sympathetic (Snyder and Gebber, 1973), renal (Coote and Downman, 1966), inferior cardiac (Coote and Downman, 1966), lumbar sympathetic (Weaver and Gebber, 1974), and splenic nerves (Ninomiya *et al.*, 1971).

The descending spinal vasopressor tracks transmitting excitatory impulses from the brain to spinal sympathetic neurons are located primarily in the dorsolateral white column of the spinal cord. This contention is supported on the basis of changes evoked in arterial blood pressure and sympathetic nervous activity by discrete electrical stimulation of spinal sites (Illert and Gabriel, 1970, 1972; Illert and Seller, 1969; Johnson *et al.*, 1952; Kell and Hoff, 1952; Kerr and Alexander, 1964; Snyder and Gebber, 1973). Excitatory regions in the ventrolateral columns in the spinal cord have also been reported (Chen *et al.*, 1937c; Wang and Ranson, 1939b).

The nature of the medullary depressor area remains somewhat obscure; its activity, as will be discussed later,

probably depends on afferent inhibitory influx. Vasodilatation resulting from medullary depressor region stimulation is produced by central inhibition of the prevailing tonic discharge of "vasoconstrictor" nerves. Depressor responses are produced after bilateral vagotomy, atropinization and midcollicular decerebration (Alexander, 1946; Chen *et al.*, 1937a,b; Folkow, 1955; Frumin *et al.*, 1953; Lim *et al.*, 1938; Yi, 1938). Recently it has been revealed that only sympathoinhibition or decreased spontaneous electrical activity occurs in lumbar sympathetic (Weaver and Gebber, 1974), splanchnic (Gootman and Cohen, 1971), renal (Scherrer, 1966) and external carotid nerves (Snyder and Gebber, 1973) when stimuli are applied to depressor sites in the medial medulla. The level of the neuraxis at which sympathetic inhibition occurs will be discussed in a following section.

2. Hypothalamus

Above the medulla oblongata, the brain region probably most concerned with cardiovascular control than any other is the hypothalamus. High frequency electrical stimulation of the posterior hypothalamus and adjacent parts of the brain substance produces a rise in arterial blood pressure. The vasoactive points are distributed throughout the length of the ventral subdivision of the diencephalon, except at the levels of the supraoptic and supramammilary crossings; the lateral parts are more

reactive to stimulation than the medial portions (Ranson and Magoun, 1939; Folkow, 1955). Sympathoinhibitory regions of the hypothalamus appear to reside in the most rostral portions, just caudal and ventral to the anterior commissure. Folkow and co-workers (1959) found this area to be highly localized, while Manning (1965), Peiss (1961) and Hilton and Spyer (1969, 1971) have reported a more diffuse area of sites in the anterior hypothalamus which inhibited vasoconstrictor discharge.

Stimulation of certain hypothalamic points produces the typical "defense" reaction. In terms of the cardiovascular system this response leads to sharp vasoconstriction in the skin, intestine, and kidney, but marked cholinergic vasodilatation in the skeletal muscles. Heart rate and contractility are also elevated at this time (Abrahams *et al.*, 1960, 1962; Bolme *et al.*, 1967; Feigl, 1964; Feigl *et al.*, 1962, 1964; Rosen, 1961; Uvnas, 1954, 1960a,b). Non-cardiovascular events accompanying the "defense" reaction include: piloerection, sweating, pupillary dilatation, retraction of the nictitating membrane and adrenal medullary secretion (Ranson and Magoun, 1939).

The effects of posterior hypothalamic stimulation on the blood pressure, hind limb blood flow, resistance and capacitance vessels, heart rate and cardiac performance, and distribution of cardiac output have been determined in unanesthetized animals as well (Achari *et al.*, 1973; Bolme

et al., 1967; Folkow and Rubenstein, 1966; Forsyth, 1970, 1972; Rushmer *et al.*, 1960).

The central pathways mediating pupillodilation (Loewy *et al.*, 1973), nictitating membrane contraction (Koss and Wang, 1972), vasoconstriction (Wang and Ranson, 1939b) and cholinergic vasodilatation (Lindgren and Uvnas, 1953; Lindgren *et al.*, 1956; Schramm and Bignall, 1971) have been identified.

With regard to vasopressor pathways, a number of investigators (Chai and Wang, 1968; Peiss, 1965; Smith, 1965; Wang and Ranson, 1939b) have suggested that some hypothalamic tracts bypass those medullary regions involved in the genesis of tonic vasomotor activity. Studies of Chai and Wang (1968) and Wang and Ranson (1939b) demonstrated that pressor responses could be evoked by hypothalamic stimulation after large portions of the medullary periventricular gray and dorsolateral reticular formation were destroyed. These medullary lesions significantly reduced reflex pressor responses to sciatic nerve stimulation and bilateral carotid occlusion, but not resting blood pressure (Chai and Wang, 1968). On anatomical grounds, Smith (1965) found nerve fiber degeneration at the most caudal level of the medulla and intermediolateral portions of the spinal cord after electrolytic lesioning of hypothalamic pressor sites.

There are good reasons for believing that the sympathetic effects produced by intrahypothalamic stimulation are due to activation of intrinsic neuronal components. Rioch and Brenner (1938) were able to elicit hypertensive responses by electrical excitation after complete degeneration of motor fibers from the cerebral cortex. Likewise, cholinergic vasodilatation can be evoked in chronically decorticate animals by stimuli applied to hypothalamic sites (Eliasson *et al.*, 1954). Hypothalamic components may act as relay sites for responses emanating from higher cortical sources or may constitute in themselves neurons of origin.

The hypothalamus is not recognized as an important integrative center for blood pressure homeostasis or cardiovascular reflexes, but it can have significant influence on the circulation in many circumstances. The idea that hypothalamic structures exert their effects by phasic modulation of the excitability of lower vasomotor components may not be entirely correct. Redgate and Gellhorn (1956) and others (Chai *et al.*, 1963; Manning, 1965; Yamori and Okamoto, 1969) have reported a significant reduction in resting blood pressure after transection of the hypothalamus from more caudal brain structures. Redgate and Gellhorn also found that intrahypothalamic injections of pentothal, pentobarbital or procaine produced a fall in tonic arterial pressure and heart rate in vagotomized animals. These

responses were reversible as the drug effects diminished. Consistent with the observations on blood pressure are records of tonic nervous discharge in the inferior cardiac nerve shown by Bronk and co-workers (1940). Figure 195 of their study reveals a marked reduction in basal post-ganglionic nervous activity after removal of the hypothalamus. Experiments in which there is an insignificant decrease in arterial pressure following midbrain transection might be explained on the basis of a compensatory sympathetic discharge to the heart and blood vessels due to a release of sympathoinhibition from arterial baroreceptors. In any event additional work concerning the role of hypothalamic structures in the maintenance of tonic vasoconstrictor tone is required.

Since hypothalamic excitation is able to produce both adrenergic and cholinergic sympathetic influences and drastic changes in distribution of cardiac output, then an alteration in blood pressure per se is not a reliable guide to hypothalamic effects on vasoconstrictor nerves. A few reports analyzing hypothalamic control of sympathetic nervous discharge have been made by Bronk and co-workers (1936, 1940) and others (Pitts and Bronk, 1942; Pitts *et al.*, 1941; Scherrer, 1962, 1966, 1969). A brief summary of their data will be presented here. First, high frequency hypothalamic stimulation produced an increase in discharge of whole bundle records from the inferior

cardiac, cervical sympathetic and renal nerves along with elevation in blood pressure. Discharge rate of impulses in single fibers of the cervical sympathetic nerve also increased during stimulation. Second, the hypothalamic receptive field for activation of single preganglionic neurons in the cervical sympathetic trunk was quite large, encompassing most of the pressor region in the ipsilateral and contralateral hypothalamus. Third, the maximal discharge rate exhibited by single preganglionic fibers in response to unilateral stimulation was about 10/sec. This value could be doubled if the hypothalamus was stimulated bilaterally at the same time. Lastly, single unit or multiunit responses evoked by stimuli applied to pressor sites in the hypothalamus could be inhibited during a rise in blood pressure produced by iv adrenalin.

Recording the activity in a branch of a motor nerve to the hind limb of the cat, Folkow and Gernandt (1952) observed firing in the nerve upon stimulation of the hypothalamus. Since atropine-sensitive vasodilatation occurred in the muscles innervated by this nerve, they considered the discharge to represent vasodilator activity. Horeyseck *et al.* (1972) recorded activity of single fibers in the lateral gastrocnemius muscle that could be activated exclusively by stimulation of hypothalamic sites producing cholinergic vasodilatation. These fibers exhibited no spontaneous activity or somato-sympathetic reflex activation.

3. Telencephalon

The cerebral cortical vasomotor reactive areas contain elements which upon stimulation or lesion can produce either pressor or depressor responses. The response type elicited in a given instance depends to a large extent on factors such as anesthesia and stimulation parameters. Marked pressor responses accompanied by vasoconstriction of cutaneous, renal and splanchnic vessels have been evoked during stimulation of selected sites located in the motor and premotor regions (Green and Hoff, 1937; Hoff *et al.*, 1951a,b; Hoff and Green, 1936), posterior orbital area, anterior cingulate gyrus, anterior temporal lobe (Wall and Davis, 1951) and insula (Hoff *et al.*, 1963). Similar to most hypertensive responses elicited from the posterior hypothalamus and medullary pressor regions, those elicited from cortical sites are associated with other sympathetic effects like cardiac augmentation, pilo-erection, pupillary changes, etc. (Hoff *et al.*, 1963). Vasodepressor responses are evoked from cortical sites closely associated with those loci concerned with pressor responses.

The efferent vasomotor projections from the cerebral cortex may or may not have connections in the hypothalamus. Green and Hartzell (1938) believed that some motor and premotor vasopressor pathways either make connections with or passed through portions of the hypothalamus, since

intrahypothalamic lesioning reduced the rise in blood pressure produced by cortical stimulation. In contrast, Wall and Davis (1951) and Spiegel and Hunsicker (1936) hold the view that vasopressor pathways from the motor cortex traverse with somato-motor fibers in the pyramidal tracts and essentially bypass the hypothalamus and medullary vasopressor regions. This is believed because cortical-evoked elevations in blood pressure were not abolished by bilateral destruction of the hypothalamus or dorsal portions of the medulla, but were eliminated when sections involved pyramidal and extrapyramidal tracts. The efferent vasoactive fibers are believed to decussate somewhat since unilateral stimulation produces essentially equal effects on both sides of the animal (Folkow, 1955).

Vasopressor pathways from the insula and posterior orbital cortex appear to course through and/or terminate in the hypothalamus (Wall and Davis, 1951; Spiegel and Hunsicker, 1936). On the other hand, pressor or depressor responses evoked from sites in the anterior temporal lobes were not abolished by hypothalamic lesions. Pressor responses elicited from the cingulate gyrus depend only on the existence of an intact temporal lobe, so efferent vasomotor fibers from this area probably bypass the hypothalamus as well (Wall and Davis, 1951).

Folkow and co-workers (1959) believe that most cortically-evoked sympathoinhibitory responses eliminated

by hypothalamic lesions (Wall and Davis, 1951; Spiegel and Hunsicker, 1936) are produced by fibers passing through and not terminating in the hypothalamus. They proposed this idea because depressor effects are evoked from only a localized inhibitory area (about 0.25 mm^3), just caudal and ventral to the anterior commissure and immediately rostral to the hypothalamus. They contend if synaptic relays are made in the hypothalamus that one would expect divergence and not convergence near to the relay site. Of course this view is dependent upon the size of the hypothalamic inhibitory "nucleus." Löfving (1961a) suggested that higher sympathoinhibitory influences are mediated by the medullary depressor region. This idea is supported by the observation that electrolytic destruction of the "depressor center" in the medulla abolished cerebral-evoked vasodilatation.

In the first studies of Green and Hoff (1937), they noted that pressor responses evoked from the cortical motor and premotor regions not only involved vasoconstriction of some vascular beds (viz., renal, splenic, mesenteric, etc.) but also vasodilation of skeletal muscle vascular beds. This observation was taken to indicate the existence of a specific cortical control mechanism influencing the blood supply to the muscles. Decreased vascular muscle tone was believed, and perhaps rightly so, to be produced by decreased sympathetic

vasoconstrictor activity. However, an alternative mechanism must be considered. Cortical stimulation could have evoked sympathetic cholinergic vasodilatation. This possibility was not considered since information regarding the cerebral representation of this system was unavailable at that time. Since then it has been established that atropine-sensitive vasodilatation occurs upon stimulation of motor areas closely associated to those activated by Green and Hoff (Eliasson *et al.*, 1952). Cortically-evoked cholinergic vasodilator responses are greatly diminished by bilateral lesioning of anterior portions of the hypothalamus (Uvnas, 1954), suggesting an "in series" connection with diencephalon components. Pressor responses usually were associated with striated muscular movement when curare was not employed (Hoff and Green, 1936). Therefore, the suggestion has been made by Folkow (1955) that cardiovascular events originating from somatic cortical areas may be preparatory to the initiation of muscular activity.

4. Cerebellum

Nucleus fastigius or medial cerebellar nucleus appears to be the only deep cerebellar nucleus involved in central circulatory regulation. Early studies of Moruzzi (1940) and more recent ones of Archari and Downman (1970) and Miura and Reis (1970) have demonstrated effects of electrical stimulation and lesion of the fastigial nucleus on the cardiovascular system. In addition, stimulation of

the vermal cerebellar cortex which projects onto nucleus fastigius via Purkinje cell axons (Brodal *et al.*, 1962; Eccles *et al.*, 1967) exerts an influence on cardiovascular function (Moruzzi, 1940; Dow and Moruzzi, 1958; Lisander and Martner, 1971a).

Stimulation of the nucleus fastigius is able to produce a pressor response in intact anesthetized (Sawyer *et al.*, 1961), midcollicular decerebrate (Archari and Downman, 1970; Hockman *et al.*, 1970; Miura and Reis, 1970), decorticate (Zanchetti and Zoccolini, 1954), and unanesthetized (Mitra and Snider, 1972) cats. An abrupt and sustained rise in blood pressure (80 mmHg) is evoked when the fastigial nucleus is stimulated with high frequency, short duration pulses ranging from 2-10 volts. As shown by Doba and Reis (1972a,b), the rise in pressure is paralleled by a concomitant decrease in blood flow and increase in vascular resistance in all beds measured, with the exception of carotid blood flow. Sites located in the ventromedial portions of the rostral one-third of the fastigial nucleus produce the greatest rise in arterial pressure when activated (Miura and Reis, 1970).

Miura and Reis (1971) suggested that fastigial-evoked hypertensive responses result primarily from inhibition of afferent sympathoinhibitory input from baroreceptor nerves. Although, in contrast to this view, fastigial-evoked pressor responses were elicited and even augmented

after carotid sinus, aortic depressor and vagus nerves were bilaterally sectioned (Achari and Downman, 1970). This observation would suggest that blood pressure elevation is not only due to inhibition of afferent inhibitory impulses, but also to excitation of central sympathetic vasoconstrictor elements.

Recording computer-summed evoked activity in the splanchnic nerve of the monkey, Nathan (1972a,b) elicited responses from the fastigial nucleus and from sites near to the brachium conjunctivum. Based on anatomical evidence, Cohen *et al.* (1958) and Thomas *et al.* (1956) have demonstrated that most efferent fibers from the fastigial nucleus course around the brachium conjunctivum on their way to the medulla. The median onset latency of potentials evoked ipsilaterally ranged from 98-120 msec. The median onset latency of these responses was considerably longer than those potentials evoked from vasopressor sites in the dorsolateral medulla (Nathan, 1972a), lending to the suggestion that either the cerebellar pressor pathways take a more diverse route to the medulla or spinal cord, or that fibers transmitting the efferent impulses conduct at a low velocity.

Consistently the observation has been made that activation of areas in the vermal cerebellar cortex produces a small decrease in resting blood pressure (Dow and Moruzzi, 1958; Lisander and Martner, 1971a) although, if

the vermis is stimulated during a reflex increase in pressure produced by carotid sinus occlusion or hypothalamic "defense" area stimulation, the vermal-induced depressor response is enhanced (Lisander and Martner, 1971a; Moruzzi, 1940). A pressor response elicited by excitation of the central end of the superior laryngeal nerve was completely abolished during vermal stimulation (Dow and Moruzzi, 1958). Similar responses are observed in vagotomized animals (Moruzzi, 1940). The fall in blood pressure was slow in onset, suggesting vasoconstrictor inhibition as a mechanism of action. No electrophysiological studies have been performed to confirm this contention.

Interestingly, after α-adrenergic blockade, the increase in muscle blood flow (atropine-sensitive) produced by hypothalamic "defense" area stimulation was reduced by simultaneous vermis excitation (Lisander and Martner, 1971a). Thus, there appears to be a central interaction between the vermal cerebellar area and sympathetic cholinergic mechanisms.

Fastigial nucleus stimulation elicits an increase in resting heart rate (Achari and Downman, 1970; Doba and Reis, 1972a,b; Nitra and Snider, 1972) and contractility (Doba and Reis, 1972a,b). Cardiac effects are due primarily to release of reflex parasympathetic influences and secondarily by direct sympathetic activation. Cardiac

effects are highly dependent upon the resting heart rate (Doba and Reis, 1972a,b; Lisander and Martner, 1970b; Miura and Reis, 1971).

5. Summary and conclusions

The preceding paragraphs contain some important basic ideas which should be reemphasized. First, multi-leveled "centers" responsible for the maintenance of resting blood pressure might exist. The primary center resides in the caudal brain stem; however, reasonable evidence has been cited to implicate supramedullary areas, probably the hypothalamus, as another source of tonic vasoconstrictor activity. Second, the spinal components exhibit segmental and intersegmental sympathetic reflexes, but appear to be subservient to supraspinal centers for maintaining vasopressor discharge.

Evidence was provided supporting the idea that central cardiovascular outflow from the cortical, diencephalic and medullary vasoactive loci might be organized in both a series-connected and parallel-connected manner. First, pressor pathways emanating from suprahypothalamic vasopressor sites can be closely associated with the hypothalamus (e.g., insula and posterior orbital cortex) or bypass the hypothalamus completely and descend via the pyramidal and extrapyramidal tracts or other extrahypothalamic pathways (e.g., motor and premotor cortex, anterior temporal lobes and cingulate gyrus). Second, hypothalamic

efferent pressor pathways appear to bypass medullary regions known to be intimately involved in tonic blood pressure control. Third, since pressor tracts from the cingulate gyrus are outside boundaries of hypothalamic nuclei, there is reason to postulate that sympathoinhibitory fibers are extrahypothalamic as well. In this event, it is quite possible that depressor sites or pathways found in the anterior hypothalamus reside or course in-parallel to those from the cingulate gyrus. Finally, sympathetic cholinergic vasodilator pathways are found in areas outside the borders (Lindgren and Uvnas, 1954a,b) and probably course in parallel to sympathoinhibitory tracts from the medullary depressor region.

In conclusion, the experiments in which electrical stimulation was applied to sites in the neuraxis do not firmly establish any hypothesis regarding functions of these systems in the intact animal. It is only possible to propose potential pathways and sites at which integrative functions may be accomplished. As mentioned by Peiss (1965), it merely points up to the reserve capabilities of the remaining vasomotor mechanisms. The types of nervous discharge emanating from the sympathetic center(s) is the subject of the next section.

B. Properties of Sympathetic Nervous Discharge (SND)

Some features of sympathetic discharge are introduced in this section. The patterns of background firing of

multiunit and single pre- and postganglionic sympathetic neurons are characterized. Four distinctive types of whole nerve electrical waveforms are described and the possible sources of cardiac and respiratory oscillations are discussed.

1. Centrally emanating electrical oscillations of multiunit preparations

The amplitude and frequency of formation of SND waveforms propagated in a centrifugal direction probably depend upon the patterns of spike potentials in single discharging neurons (firing rate, etc.), the number of contributing units and the phase relations between the individual spike trains (Mannard, 1970).

Just over four decades ago it was demonstrated by Adrian *et al.* (1932) that the cervical and abdominal sympathetic nerves of the decerebrate or anesthetized intact cat and rabbit transmitted a continuously fluctuating electrical discharge from the CNS to the periphery. These oscillations were considered central and not ganglionic in origin for they were not blocked by nicotine. Each waveform was believed to reflect the synchronized discharge of a number of contributing neural elements. In the majority of their experiments the waves tended to occur in groups synchronized with the respiratory cycle and/or the cardiac cycle. In the spontaneously breathing animal the amplitude of the respiratory-locked oscillation

of SND was maximal at the latter stages of the inspiratory cycle. In their opinion (Adrian *et al.*, 1932), the respiratory grouping was produced by a direct action of the respiratory center on the vasomotor center. This view was taken because oscillations of SND remained in phase with phrenic efferent discharges after cessation of artificial respiration in the curarized animal. An in-depth discussion concerning the origin of respiratory waves of SND is presented in a following section. In 3 animals SND fluctuations with the same period of oscillation as the cardiac cycle were observed. In one of these animals, SND modulation switched from cardiac to respiratory "grouping" spontaneously. It was assumed that cardiac grouping of SND was dependent on the rhythmic inhibitory discharges reaching sympathetic centers via the baroreceptor or vagus nerves. The validity of this assumption will be explored also in a later portion of this discussion.

Bronk and co-workers (1936, 1940) continued the work on centrally emanating SND waves in the cardiac nerves from the stellate ganglion of the cat. They found multiple types of grouped wavelets of SND. Oscillating periodicity of these wavelets varied between 5-20 Hz, were unrelated to any other obvious rhythm (cardiac or respiratory), and occurred only for short periods of time. Spontaneous discharge from the cardiac nerves also exhibited respiratory and cardiac modulation as well. Bronk *et al.* (1936)

also discussed the possibility that characteristics of cardiac and respiratory grouping of SND were the result of some property of the sympathetic ganglion, such as divergence of preganglionic fibers on postganglionic neurons. However, the similarity of grouped impulses observed in the preganglionic nerve and the bilateral synchrony of the cardiac and respiratory rhythmic activity led them to conclude the waves were produced by a more or less synchronous rise and fall in the level of excitation of large numbers of common sympathetic motor cells in the vasomotor centers.

Since these forerunning investigations there have been many studies devoted to the description and analysis of spontaneously occurring sympathetic nervous waveforms recorded in the cervical sympathetic nerves (Biscoe and Purves, 1967a,b,c; Biscoe and Sampson, 1968; Iggo and Vogt, 1960; Koizumi *et al.*, 1971; Polosa *et al.*, 1970), thoracic nerves (Alexander, 1945; Beacham and Perl, 1964; Downing and Siegel, 1963; Green and Heffron, 1967a,b, 1968; Koizumi *et al.*, 1971; Millar and Biscoe, 1966; Ninomiya *et al.*, 1971), abdominal nerves (Aström and Crafoord, 1968; Beck and Dontas, 1955; Cohen and Gootman, 1969, 1970; Dontas, 1955, 1957; Dontas and Nickerson, 1957; Gernandt *et al.*, 1946; Gootman and Cohen, 1970; Illert and Seller, 1969; Iwasawa *et al.*, 1969; Kedzi and Geller, 1968; Koizumi *et al.*, 1971; Millar and Biscoe, 1965,

1966, 1969; Tang *et al.*, 1957), and lumbar nerves (Koizumi *et al.*, 1971).

Especially noteworthy of the observations described in these reports are:

1. The occurrence of pre- and postganglionic SND synchronized to the cardiac cycle and/or the respiratory cycle regardless of the species or anesthesia used.

2. The observation that cardiac modulation, which was strongly exhibited in postganglionic nerves, is diminished as the recording electrode is moved closer to the white ramus. This was the case irrespective of whether recordings were obtained from cervical, thoracic, abdominal or lumbar sympathetic nerves (Koizumi *et al.*, 1971).

3. Stepwise elevations in static baroreceptor pressure were able to produce a graded decrease in the amplitude of SND bursts without inhibiting the entire train of activity (Kezdi and Geller, 1968).

4. On the other hand, all SND oscillations are inhibited by a rapid sustained rise in carotid sinus pressure (75-100 mmHg) (Koizumi *et al.*, 1971; Gootman and Cohen, 1970), or by high frequency (30-50 Hz) stimulation of a medial medullary depressor site (Gootman and Cohen, 1970) or sites in the nucleus and tractus solitarius (Scherrer, 1966).

5. In spontaneously breathing animals, respiratory and cardiac wave amplitude is usually maximal during

inspiration and minimal or absent during expiration. If artificial or positive pressure respiration is employed, then SND is minimal during inflation and maximal during deflation (Okada and Fox, 1967; Tang *et al.*, 1957).

6. In general, respiratory- and cardiac-locked waves of SND are augmented by hypercapnia and hypoxia (Downing and Siegel, 1963; Cohen and Gootman, 1970; Gernandt *et al.*, 1946; Millar and Biscoe, 1965). Whether peripheral chemoreceptor stimulation is involved in this augmentation remains debatable (Gernandt *et al.*, 1946).

7. The observation that systemic hyperoxia reduces the amplitude of SND excursions (Alexander, 1945; Gernandt *et al.*, 1946).

8. The level of overall excitability and amplitude of pulse-synchronous nervous discharge is increased by high frequency (30-50 Hz) stimulation of pressor sites in the dorsolateral reticular formation of the medulla (Gootman and Cohen, 1970) and the posterior hypothalamus (Scherrer, 1969).

9. Dontas (1955) observed that hemorrhage from 155 to 115 mmHg blood pressure enhanced the amplitude pulse-locked waves of SND. If hemorrhage was continued, reducing blood pressure to 50 mmHg, cardiac-locked SND disappeared and was replaced by randomly occurring wavelets of SND (10-30 Hz). At this time peripheral chemoreceptor activity was shown to be nearly maximal.

10. The description of a slow-wave of SND occurring at about 10 cycles per minute, usually correlated with blood pressure fluctuations (Iggo and Vogt, 1960; Polosa *et al.*, 1970).

11. Using a newer technique of computer analyzation Cohen and Gootman (1969, 1970) and Ninomiya *et al.* (1971) have elucidated the phasic relationships between SND recorded in the splanchnic, splenic, renal and inferior cardiac nerves, and the cardiac and respiratory cycle. Cohen and Gootman (1969, 1970) demonstrated two types of SND waveforms which were temporally related to the cardiac cycle. First, a relatively fast rhythm (10 c/sec) which occurred either free-running as determined by autocorrelation analysis or phase-locked to various degrees in a 3:1 fashion to the cardiac cycle. Due to the ubiquity of occurrence of the 10 c/sec wave, they suggested this rhythm represents the fundamental periodicity of vasomotor centers. Second, in 25% of their experiments, a lower frequency (3 c/sec) oscillation locked in a 1:1 relation to the pulse cycle was observed. The trough of each of the computer-summed waves occurred at the end of diastole or the start of systole and rose to a single peak near to mid-diastole. Ninomiya and co-workers (1971) showed that phasic relationships of the inferior cardiac, splenic and renal nerves to the pulse cycle are essentially the same as those observed in the splanchnic nerve by Cohen and

Gootman (1970). Ninomiya *et al.* (1971) did not report any 10 c/sec waves locked or unlocked to the cardiac cycle.

12. Cohen and Gootman (1970) revealed that respiratory modulation of SND is more intense than cardiac modulation. Also computer-summed splanchnic discharge was maximal during mid-inspiration and minimal during early expiration.

Hagbarth and Vallbo (1968) have extended some of these observations to humans. Using themselves as subjects, they recorded spontaneously occurring SND from postganglionic sympathetic nerve bundles with tungsten semi-microelectrodes. Pulse-synchronous waves of SND were found to be maximal in amplitude during later phases of inspiration and early expiration, while minimal activity occurred during late expiration and early inspiration.

Therefore, from the foregoing discussion it would appear that a defining characteristic of spontaneously occurring SND in nerve bundles is cardiac and respiratory modulation. These waves of activity must reflect the synchronized firing of many individual sympathetic neurons. The discharge properties of single preganglionic neurons would be important in understanding these modulating mechanisms.

2. Spontaneous discharges occurring in single sympathetic neurons

Analysis of tonic firing of single sympathetic preganglionic neurons (PSN) has been accomplished by recording the discharge from single axons or by positioning microelectrodes near to the neuronal extracellular electrical field.

Before discussing the electrophysiological studies, I should like to mention some of the general features of sympathetic neurons. The cell bodies of PSN lie primarily in the nucleus intermediolateralis of lamina VII (Rexed, 1952), between the most caudal cervical and upper lumbar spinal segments. There are at least three cell types which are found in this nucleus: (1) triangular or multipolar neurons, varying in size from 28 x 24 μ to 48 x 30 μ; (2) fusiform, sizes ranging from 22 x 19 μ up to as large as 58 x 18 μ; and (3) round neurons which may range in size from 18 μ to 29 μ in diameter (Petras and Cummings, 1972). Réthelyi (1972) demonstrated that the dendrites of PSN generally originate from the rostral and caudal ends of the perikaryon and immediately orient into a longitudinal direction, although transversely positioned dendrites were seen as well. Presynaptic fibers appeared to approach from the lateral funiculus in small solid bundles which quickly dispersed and coursed longitudinally so that the axons were oriented in a parallel fashion with PSN dendrites,

forming axo-dendritic and axo-somatic synapses in a "climbing type" arrangement.

Petras and Cummings (1972) have demonstrated through degeneration studies that virtually all afferent input coursing in the dorsal roots does not terminate directly on sympathetic preganglionic cell bodies. They suggest that sensory inflow is mediated by polysynaptic pathways over interneurons possibly located in the intermediomedial nucleus or other spinal relay sites. These anatomical data are in agreement with electrophysiological studies of Beacham and Perl (1964a,b). The central delay time from dorsal afferent nerves to preganglionic sympathetic rami (after subtraction of afferent and efferent nerve conduction time) was found to be at least 1.3 msec. This delay is considerably longer than that found for the monosynaptic somatic reflex arc (0.3-0.8 msec) (Eccles, 1964).

Preganglionic nerve axons are myelinated and range in the B-fiber size ($\leq$ 3 μ) (Grundfest, 1939) and conduct at velocities of 3-15 m/sec (Bishop and Heinbecker, 1932; Eccles, 1935; Janig and Schmidt, 1970).

In an extensive study of the third and fourth thoracic spinal segments, Fernandez de Molina *et al.* (1965) characterized extra- and intracellular PSN potentials that were evoked antidromically by cervical sympathetic nerve stimulation. Extracellular responses from more than one unit were commonly found, suggesting a dense packing of PSN in

a particular region. Also, cord penetrations less than 0.5 mm apart in a rostral-caudal orientation revealed several units at one location and none at another site. This observation is supported on anatomical grounds by Henry and Calaresu (1972), who reported drastic fluctuations in the number of cells in the intermediolateral nucleus from one cross-section to the next. This phenomenon was termed a "beading effect." No evidence was obtained by Fernandez de Molina *et al.* (1965) to support the possibility of antidromic initiation of inhibitory activity by axon collaterals ("Renshaw" inhibition). In support of this observation, Réthyelyi (1972) could not demonstrate any collateral branches along the entire course of the primary PSN axon. Fernandez de Molina *et al.* (1965) also showed that the contour of the extracellular and, especially, the intracellular records of PSN exhibited initial segment (IS) and soma-dendritic (SD) components of depolarization similar to those seen in α-motoneuron spikes (Brock *et al.*, 1953). Repolarization consisted of two components separated by a small inflection ("delayed depolarization" or D-D) possibly indicating active conduction of the antidromic impulse into PSN dendrites (Granit *et al.*, 1963; Nelson and Burke, 1967). Extracellular and intracellular spike durations recorded by Fernandez de Molina *et al.* (1965) were 7.2 and 7.1 msec, respectively. These values are much longer than durations reported by

other investigators. Hongo and Ryall (1966a,b) and DeGroat and Ryall (1967) have observed PSN unitary discharges of 1-2.3 msec duration; these values are similar to action potential durations of α-motoneurons (Eccles, 1964).

Spontaneous discharges of individual sympathetic neurons were first measured by examining firing rates in single fiber preparations. Bronk and co-workers (1936) found that the frequency of the sympathetic nerve impulse varied from 0.25 c/sec up to as great as 20 c/sec. More recent reports suggest the lower discharge rate to be more representative of single PSN. Seller (1973) observed a rate of 1.24 discharges/sec for thoracic white rami fibers and 1.8 discharges/sec for single fibers in lumbar white rami. Data involving nerve twigs from lumbar white rami are in good agreement with reports by Kaufman and Koizumi (1971) and Sato (1972), who observed an average discharge rate of 1.2 Hz and 2.1 Hz, respectively. Iggo and Vogt (1960) reported a discharge rate of about 1 c/sec for single fibers in the cervical sympathetic trunk. Janig and Schmidt (1970) extended the studies of fiber discharge rate in the cervical sympathetic trunk, finding a rate of 1.7 Hz for myelinated fibers and 2.9 Hz for unmyelinated fibers. Postganglionic fibers in the right inferior cardiac nerve also discharge at a slightly higher mean rate of around 6 c/sec (Green and Heffron, 1968a). Even greater discharge frequencies have been reported.

Tuttle (1963) observed frequencies of 10-25 Hz for single thoracic fibers and Koizumi and Suda (1963) reported rates up to 10 Hz for abdominal units.

Spontaneous activity exhibited by single PSN recorded by extracellular micro-electrode analysis was found to be 2.1 Hz for units activated antidromically by cervical sympathetic nerve stimulation (Wyszogrodski and Polosa, 1973), 2.3 Hz for splanchnic units (Hongo and Ryall, 1966a,b) and 2.0 Hz for neurons contributing axons to the third and fourth thoracic white rami (deGroat and Ryall, 1967).

Periodic trains of spikes synchronized with the respiratory cycle have been evidenced at the single unit level. In the "comatose" cat, Tuttle (1963) observed periodic bursts of high frequency (15-25 Hz) discharge in phase with the respiratory cycle. The number of bursts in each respiratory-synchronized train could be increased or decreased by common carotid artery occlusion or baro-receptor stimulation, respectively. In addition, hypo-thalamic pressor site stimulation resulted in a fusion of the spike trains into a repetitive pattern of discharge. Iggo and Vogt (1960) also observed respiratory modulation in single PSN. The rate of spike formation increased from 1 impulse/sec during expiratory periods to at least 7 impulses/sec during inspiration.

Correlation of the discharges of single pre- and postganglionic neurons and the cardiac cycle has remained quite ambiguous. That is, upon inspection, no set temporal relationship between most sympathetic unit discharges and the pulse cycle could be determined. Only within the last few years has significant information on this problem been revealed in reports by Green and Heffron (1968a) and Seller (1973). Green and Heffron (1968a) initially observed low frequency (2-3 spikes/sec), irregularly spaced, spontaneous spikes (usually 1 per cardiac cycle) in single inferior cardiac fibers. For individual cardiac cycles no constant time delay between the start of systole and the unitary potential was evident, but when the time interval between the onset of rise of the femoral arterial pulse and the postganglionic fiber discharge was plotted for 156 consecutive heart beats, an interesting histogram was revealed. The distribution histogram of the single fiber spikes within the pulse cycle almost took the shape of a normalized curve, which peaked at a delay time of 100 msec. If one were to superimpose a "typical" pulse wave over this histogram, it is readily observed that the fewest spikes occurred just before the upswing of systole, while the greatest number of discharges were found at mid-diastole. Green and Heffron (1968a) showed that multifiber records from this nerve displayed similar phasic relationships to each pulse cycle.

Recently, examination of this type of temporal relationship between single PSN and the cardiac cycle has been performed in an exquisite manner by Seller (1973). Using computer analysis, he constructed the post-R-wave interval histogram for 34 thoracic and 38 lumbar white ramus fibers. Of these units 23% (8 thoracic and 5 lumbar) exhibited a "normal" curve unitary response pattern correlated to the electrocardiogram (ECG). The peak of the curves for thoracic and lumbar units occurred 130-160 msec and 150-270 msec, respectively, after the R-wave. The duration of the interval histograms ranged from 140-220 msec. Other units tested exhibited random distributions showing only vague or no maximal peak in the cardiac cycle. Extending these studies further, Seller (1973) reported a number of other interesting observations. First, an early spinal reflex discharge could be evoked in only one of the 13 units exhibiting cardiac modulation upon segmental dorsal root stimulation. Second, tonic discharges of 39 PSN could be inhibited substantially by baroreceptor reflex activation; of these baroreceptor reflex-sensitive neurons none could be activated through spinal reflex pathways. Third, 90% of the ECG-correlated PSN could be discharged by ipsilateral brain stem pressor site stimulation. As discussed by Seller, the first and second observations provide strong evidence that cardiac-modulated and baroreceptor reflex-sensitive PSN constitute a population separate from

those neurons which mediate spinal somatosympathetic responses. Furthermore, characterization of "cardiovascular neurons" in the medullary substance (Preobrazhenskii, 1966; Przyhyla and Wang, 1967; Salmoiraghi, 1962) may be facilitated by analyzing patterns of unitary discharge in this manner.

Unitary correlates of slow-wave activity have been reported by Polosa *et al.* (1970). This activity cannot be attributed to baroreceptor influences, since the slow-wave discharge pattern was still present after eradication of all blood pressure oscillations by administration of tetraethylammonium. On the basis of this observation, Polosa has suggested that a central mechanism might be responsible for the low frequency trains of synchronized PSN firing. Autocorrelation analysis of thoracic PSN has also distinguished three rhythmic patterns of discharge, exhibiting periods of oscillation equal to pulse, respiration and slow-wave activity (Mannard and Polosa, 1973).

In summary, usually a small percentage (25-30%) of the total PSN isolated exhibit spontaneous activity. Those PSN which are tonically active discharge at low rates of approximately 1-2 impulses/sec. Respiratory, cardiac and slow-wave unitary discharge rhythms, similar to those observed in whole nerves, are found at the single neuron level as well. Respiratory modulation takes the form of respiratory-locked trains of higher frequency bursts,

while cardiac modulation, often masked by irregularly spaced firing, takes the form of a "normal" curve distribution phasically related to the pulse cycle. Intracellular records of Fernandez de Molina *et al.* (1965) revealed IS, SD and D-D components of action potentials of sympathetic neurons discharged by antidromic stimulation. Computer auto- and crosscorrelation analyses of tonically discharging PSN have been performed; however, computer analysis (e.g., poststimulus histograms) of discharges evoked by electrical stimulation of medullary pressor regions has been essentially neglected. Studies of this type may provide important clues concerning the organization of central vasopressor pathways.

3. Proposed origin of cardiac- and respiratory-synchronized waves of SND

a. Origin of the cardiac-locked oscillation

As was described in the preceding section, the time course of spontaneous discharge of single sympathetic neurons over many trials may be in phase with the cardiac cycle. Therefore, the component of the whole nerve waveform, phase-locked to the pulse cycle, probably represents the summation of action potentials of a population of individual PSN whose discharge is synchronized to the cardiac cycle in some manner. Sympathetic neuron oscillations locked in a 1:1 relation to the cardiac cycle

are generally considered to result from the waxing and waning of baroreceptor nervous discharge associated with the systolic and diastolic phases of the arterial pulse. That is, "continuous" SND is intermittently inhibited by baroreceptor afferents and this molds sympathetic outflow into a pulse synchronous waveform (Bronk *et al.*, 1936). This hypothesis is supported by the observation that the phase relations between SND and the cardiac cycle disappear after interruption of baroreceptor nervous discharge (Adrian *et al.*, 1932; Aström and Crafoord, 1968; Bronk *et al.*, 1936; Dontas, 1955; Downing and Siegel, 1963; Green and Heffron, 1967b, 1968b; Koizumi *et al.*, 1971; Okada and Fox, 1967; Pitts *et al.*, 1941). While some investigators (Aström and Crafoord, 1968; Bronk *et al.*, 1936; Pitts *et al.*, 1941) reported that SND appeared essentially continuous or random in character after elimination of baroreceptor activity; others (Alexander, 1945; Downing and Siegel, 1963; Green and Heffron, 1968b; Koizumi *et al.*, 1971) observed irregularly occurring oscillations of SND indicative of synchronized activity of individual fibers contained within pre- and postganglionic nerve bundles. These rhythmic oscillations, as discussed by Koizumi *et al.* (1971), were no longer in phase with the pulse cycle and were not inhibited by a large increase in blood pressure produced by the intravenous injection of adrenalin.

The records of SND presented by Downing and Siegel (1963) and Koizumi *et al.* (1971) are particularly interesting since they illustrate that the duration of the synchronous bursts of SND approach the duration of those which were locked to the cardiac cycle before section of the carotid sinus, aortic depressor and vagus nerves. The work of Kezdi and Geller (1968) and Green and Heffron (1968b) is also pertinent. Both of these groups observed the effects produced on sympathetic nervous activity by non-pulsatile pressure applied to the isolated carotid sinus region. Figure 1 of Kezdi and Geller (1968) and Figure 2 from Green and Heffron (1968b) show synchronous activity of SND when non-pulsatile pressure was applied to the carotid sinus. These results are rather striking since Green and Heffron (1968b) showed at the same time the discharge of individual baroreceptor fibers is uniform instead of rhythmical under these conditions. These observations raise the possibility that synchronous discharges of SND phase-locked in a 1:1 relation to the cardiac cycle may not be generated by the baroreceptor reflexes as traditionally believed, but may be formed by mechanisms intrinsic to the central cardiovascular centers and regulated by baroreceptor reflexes.

The observations and discussion presented by Green and Heffron (1967b) are impcrtant when analyzing the characteristics of pulse-synchronous SND. They observed predominantly

a rapid sympathetic rhythm of about 600 bursts per minute (10 Hz) in a multifiber inferior cardiac nerve preparation. Three to four synchronized bursts of 100 msec duration SND were associated with each pulse cycle (cf., Cohen and Gootman, 1970). Periods of continuous 10 Hz waves were produced by maneuvers eliminating baroreceptor reflexes, such as occlusion of the pulmonary artery, brachio-cephalic artery or inferior vena cava. There are at least two pertinent points to gain from their work. First, as discussed by them, all procedures that gave rise to an increased number of 100 msec burst packets of SND have one feature in common--diminution of baroreceptor nervous discharge. However, large vessel occlusion may not only decrease baroreceptor reflex activity but may also increase chemoreceptor activity and produce cerebral asphyxia. Therefore, two possibilities exist in the augmented production of 10 c/sec bursts of SND: (1) diminished presso-receptor discharge, or (2) enhanced chemoreceptor activity. Secondly, SND time-locked to the cardiac cycle in a 1:1 relation has been shown to consist of a smoothly-contoured waveform (Cohen and Gootman, 1970; Ninomiya *et al.*, 1971). When analyzing 1:1 cardiac-synchronized waves of SND, one must be alert to the fact that pulse-locked waves may consist of packets of 100 msec wavelets and not one continuous wave of activity.

b. Origin of the respiratory-locked oscillation

Adrian *et al.* (1932) reported that SND from cervical and abdominal nerves oscillated in phase with the respiratory cycle. According to them, sensory impulses from the vagus or carotid sinus nerves could be ruled out as the source of the respiratory related rhythmic discharges since these synchronous bursts clearly persisted after sectioning of these nerves. In artificially ventilated, vagotomized and neuromuscular blocked (curare) animals, cervical sympathetic groups of discharge phase-locked to phrenic nerve activity were observed after the respirator was stopped. Changes in magnitude or rate of formation of phrenic nervous impulses produced by asphyxia or hyperventilation were followed directly by SND. They suggested from these results that the respiratory locked synchronous bursts of SND were a consequence of the dispersion of excitation from the respiratory to the sympathetic centers.

Bronk *et al.* (1936) provide evidence that conflicts with the results of Adrian *et al.* (1932). Respiratory-locked oscillations of SND were disrupted in all but one animal in which the vagi were cut, suggesting the cardiac sympathetic center is under the inhibitory influences of afferent impulses from the lungs.

A report by Tang *et al.* (1957) employed many different procedures to alter the respiratory grouping of splanchnic nerve activity in the cat. Respiratory-synchronized bursts

of SND could be interrupted by simultaneous hyperventilation along with pneumothoracotomy. In contrast to these results, bilateral baroreceptor denervation alone or in combination with pneumothoracotomy or hyperventilation, or vagotomy alone or in combination with pneumothoracotomy or hyperventilation, failed to dissociate splanchnic SND from the respiratory cycle. Also, not surprisingly, respiratory waves of SND were present following decerebration, but abolished after C_1 transection. It was concluded from their work and reports of others (for refs., see Tang *et al.*, 1957) that respiratory-synchronized bursts of SND generally reflected respiratory center activity (as indicated by phrenic discharge) plus arterial blood pressure changes produced by excursions of the lungs.

Okada and Fox (1967) demonstrated that respiratory grouping of SND in abdominal nerves was abolished by bilateral vagotomy in the spontaneously breathing animal. In pump-respired preparations, contrary to the results of Tang *et al.* (1957), the respiratory phase-locked discharge of SND was essentially unaffected by either hyperventilation and pneumothoracotomy or hyperventilation plus baroreceptor denervation. However, the respiratory rhythm was abolished by bilateral carotid sinus plus vagus nerve sectioning. Okada and Fox concluded that respiratory-synchronized bursts of SND evolve from the reflex actions or interactions of lung stretch receptors and arterial

pressure receptors on central sympathetic centers, regardless of the rhythmic activity emanating from central respiratory structures.

In the computer-analyzed studies of splanchnic nervous discharge, Cohen and Gootman (1970) suggested that respiratory-locked sympathetic activity is probably driven by systems of phase-spanning respiratory neurons similar to those expiratory-inspiratory (E-I) type.

In conclusion, the etiology and control of respiratory rhythms in sympathetic neurons is highly complex as indicated by the conflict of results reported by many independent investigators. All reports agree on the central theme that respiratory-locked discharges of SND result from an interaction of central and peripheral mechanisms. The discrepancies arise primarily with regard to the principal mechanism generating the respiratory rhythm. Probably as suggested by Cohen and Gootman (1970), neither factor is solely responsible for forming the waves; more likely formation of the rhythm may be highly dependent on the relative strength of central and reflex mechanisms at any particular moment.

C - Baroreceptor Reflex-Induced Inhibition of Sympathetic Nervous Discharge

This section will be primarily concerned with acquainting the reader with information regarding patterns of afferent discharges transmitted in the baroreceptor

nerves, suggested central sites of baroreceptor termination and proposed brain loci of baroreceptor-sympathetic integration. Attention will be focused on inhibition of vasoconstrictor activity; however, baroreceptor excitation also causes slowing of the heart and this response mainly is dependent on the integrity of the vagus nerves. The vagal components of the baroreceptor reflex arc have been the subject of two recent reviews (Higgins *et al.*, 1973; Smith, 1974) and will not be discussed here.

Vasoconstrictor discharge, during resting conditions, is usually under continual control of afferent inhibitory impulses transmitted in the carotid sinus and aortic depressor nerves. This assumption is best demonstrated by the hypertension developed after bilateral sectioning of these baroreceptor nerves (Heymans and Neil, 1958). In addition, Bronk and Stella (1932) noted that bursts of impulses occurred in whole sinus nerve records with each systolic rise at "normal" arterial pressure. Single nerve fibers teased from the sinus nerve likewise fired with each pulse wave. The train of discharges began almost simultaneously with the initiation of each systolic rise in blood pressure and ended at mid-diastole. The impulse frequency of individual units was greatest during the rising phase of systole and tapered off as pressure diminished. The number of spikes in each pulse-locked train decreased as the mean arterial pressure was lowered.

On the whole, no fibers discharged when mean pulse pressure was reduced to approximately 40 mmHg. As static pressure was increased, different baroreceptor fibers commenced to discharge. Any single unit exhibited an elevated rate of firing as non-pulsatile pressure was raised, until a maximal pressure of about 200 mmHg was reached. Thus, individual baroreceptor fibers display different pressure thresholds of activation and the rate of discharge is not only dependent on pulsatile but mean pressure as well.

Ead *et al.* (1952) measuring impulse activity in single twigs isolated from the carotid sinus nerve demonstrated that total impulse frequency attained over a certain period of time during pulsatile flow exceeded that observed during non-pulsatile flow. In conjunction with this phenomenon, Ead and co-workers reported that systemic blood pressure would rise when flow through both intact carotid regions was converted from pulsatile to non-pulsatile flow, thus inferring that steady afferent impulse activity is less effective in controlling vasopressor discharges than pulse-induced discharges at the same mean sinus perfusion pressure. The characteristics of discharge of the aortic baroreceptors may differ from those seen in the carotid sinus region. Ninomiya and Irisawa (1967) could not demonstrate any difference in mean aortic depressor nervous activity during pulsatile and static pressure changes. Furthermore, carotid

sinus baroreceptors were more sensitive to a unit change of arterial blood pressure than the aortic baroreceptors (Angell James and Daly, 1970; Irisawa and Ninomiya, 1967). Other pressure sensitive fibers discharging in phase with the cardiac cycle have been located in the vagus nerve (Heymans and Neil, 1958), splanchnic nerve (Gammon and Bronk, 1934) and "common carotid" baroreceptor nerve (Green, 1953). The "common carotid" baroreceptor nerve innervates a pressure sensitive area about 2 cm below the carotid sinus. The nerve leaving this area courses between the common carotid artery and the vago-sympathetic trunk to join the nodose ganglion.

As was discussed in section A of this introduction, most reflex-induced and tonic sympathetic discharges require the integrity of structures or centers situated in the lower brain stem. Hence, it would be highly probable that integration of sympathetic excitatory and baroreceptor inhibitory mechanisms would occur at the medullary level also. As demonstrated by the lesion studies of Wang and Chai (1967) and others (Chai *et al.*, 1963; Chai and Wang, 1968; Katz *et al.*, 1967; Lindgren and Uvnas, 1954), this indeed may be the situation. First, decerebration did not abolish the reflex rise in blood pressure produced by bilateral carotid occlusion (Katz *et al.*, 1967) or the decrease in arterial pressure produced by electrical stimulation of the carotid sinus and the aortic depressor

nerves (Douglas and Schaumann, 1956). Second, quite large lesions of the medial and dorsolateral medulla nearly eliminated carotid occlusion-induced pressor responses, without altering the prelesion level of resting blood pressure. Third, smaller lesions confined to the dorsomedial portions of the medulla usually encompassing the nucleus tractus solitarius or the paramedian reticular area of the brain stem abolished the reflex depressor responses produced by sinus stretch, carotid sinus nerve stimulation and central vagus nerve excitation (Chai and Wang, 1968; Humphrey, 1967; Miura and Reis, 1972; Wang and Chai, 1967). These data suggest that baroreceptor reflex-induced responses are mediated at the medullary level. However, it must be emphasized that the pathways conducting sympathoinhibitory activity may not terminate at these medullary sites, but only pass through on their way to other locations.

Proof that baroreceptor fibers most likely terminate in nuclei of the medial portions of the periventricular gray and reticular formation has been provided by electrophysiological studies of several investigators. Field and unitary potentials evoked by baroreceptor nerve stimulation were recorded from sites in the nucleus of the tractus solitarius (Biscoe and Sampson, 1970a,b; Humphrey, 1967; Kumada and Nokajima, 1972; Lipski *et al.*, 1972; McAllen and Spyer, 1972; Middleton *et al.*, 1973; Miura and

Reis, 1968, 1969; Sampson and Biscoe, 1968; Seller and Illert, 1969; Spyer and Wolstencroft, 1971) and in the paramedian reticular nuclei (Homma *et al.*, 1970; Humphrey, 1967; Miura and Reis, 1968, 1969). On account of the onset and peak latencies, and following frequency of the evoked responses, it was proposed that mono- and polysynaptic baroreceptor pathways project to the paramedian reticular and solitary nuclei. Longer latency responses were also monitored from medial and lateral regions of the caudal brain stem reticular formation (Biscoe and Sampson, 1970a,b; Humphrey, 1967; Miura and Reis, 1969; Seller and Illert, 1969). These polysynaptic "late" responses (>5 msec), as termed by Miura and Reis (1969), were found in the raphé nuclei, the central tegmental area of the pons comprising the nucleus gigantocellularis, nucleus pontis caudalis and nucleus parvocellularis, and nucleus medulla oblongata centralis of the dorsolateral reticular formation.

Some of the neurons located in the solitary nucleus were spontaneously active. The temporal relation between their discharge and the pulse pressure were similar to spikes of single carotid sinus nerve fibers (Fussey *et al.*, 1967; Middleton *et al.*, 1973; Miura and Reis, 1972). Evoked unitary responses of paramedian reticular neurons consisted of 1-6 discharges lasting 5-15 msec upon application of a single supramaximal shock to the carotid sinus

nerve (Humphrey, 1967; Miura and Reis, 1970, 1972; Sampson and Biscoe, 1968).

While most investigators consider the medulla to be the primary site of baroreceptor termination, others believe that supramedullary regions may serve as integration sites too (Hilton and Spyer, 1969, 1971; Manning, 1965; Peiss, 1960; Spyer, 1972; Thomas and Calaresu, 1972). A report by Manning (1965) provides evidence that cardiovascular integration occurs exclusively in supramedullary structures, probably the hypothalamus. Massive radio-frequency lesions encompassing most of the medullary periventricular gray and dorsolateral reticular formation failed to significantly effect the reflex rise in blood pressure produced by bilateral carotid occlusion, sciatic nerve stimulation or hypothalamic excitation, although the reflex pressor response to carotid occlusion or sciatic stimulation was abolished by decerebration in animals with gross medullary lesions. Manning proposed that the integrity of afferent supramedullary pathways was needed for production of a reflex vasopressor response. Manning's data have been questioned on the basis of three points by Wang and Chai (1967). First, Manning did not vagotomize the animals, thus compounding the data interpretation. Second, sympathetic function may have been jeopardized by the 40-50 mg of gallamine administered. Third, Manning's lesions were made by a radio-frequency device, which is most likely

inferior to micropipette aspiration techniques. In my opinion these criticisms do not justify rejection of Manning's observations but point out the need for additional experiments on this problem.

Hilton and Spyer (1969, 1971) have reported in vagotomized cats that bilateral anterior hypothalamic lesions of localized sites which had elicited depressor responses during prior stimulation also reduced efficacy of the baroreceptor reflex. If the anterior hypothalamic lesions were combined with medial medullary destruction, the baroreceptor reflex arc was completely interrupted. Additional information implicating the hypothalamus in the baroreceptor reflex arc was provided by Spyer (1972). He found that 16 hypothalamic neurons exhibited an increase in discharge frequency when carotid sinus pressure was raised abruptly to 200 mmHg. Furthermore, excitation was potentiated by pulsatile in comparison to static pressure.

The preceding paragraphs appear to support the contention that excitatory connections from the carotid sinus and the aortic depressor nerves are represented in the caudal medulla and depressor area of the hypothalamus. Integration of inhibitory influences of baroreceptor origin and intrinsic excitatory components of the sympathetic nervous system has been postulated to occur at hypothalamic, medullary and spinal levels. With regard to the hypothalamus, Thomas and Calaresu (1972) observed that

the spontaneous activity of 16 medial hypothalamic units was inhibited completely by sinus nerve stimulation or a rise in arterial blood pressure produced by the intravenous injection of noradrenaline. Discrete electrical stimulation of the sites from which the extracellular potentials were recorded produced arterial hypertension of sympathetic origin. Poststimulus histograms revealed the mean onset latency and duration of inhibition evoked by sinus nerve stimulation was 68 $\pm$ 9 msec and 263 $\pm$ 23 msec, respectively.

Indirect evidence is available which suggests that integration of vasopressor excitatory components occurs at the medullary level also. Salmoiraghi (1962) and Przybyla and Wang (1967) noted that steadily firing and frequency-modulated medullary neurons exhibited a decrease in their frequency of discharge when arterial pressure was raised with norepinephrine. Biscoe and Sampson (1970a,b) reported a number of instances in which stimulation of the carotid sinus nerve or sinus distention depressed spontaneous firing of single units located primarily in the nucleus reticularis gigantocellularis, nucleus reticularis ventralis and nucleus reticularis parvocellularis of the medulla. Koizumi *et al.* (1971) observed that somatosympathetic reflex discharges in thoracic white rami transmitted over spinal segmental pathways were not inhibited during carotid sinus stretch. In contrast, reflex sympathetic discharges mediated through supraspinal

tracts were blocked during baroreceptor reflex activation. On the basis of these observations, they suggested that sympathoinhibition of baroreceptor origin occurred at a medullary locus. In view of a recent report by Seller (1973), the validity of Koizumi's interpretation might possibly be questioned. Seller demonstrated that individual spontaneous thoracic and lumbar preganglionic sympathetic units that were inhibited during baroreceptor reflex activation could not be excited segmentally by spinal afferent nerve stimulation. Seller's observations raise the possibility that baroreceptor reflex-sensitive units and neurons activated through spinal segmental pathways may constitute different populations of preganglionic sympathetic cells.

Gootman and Cohen (1971) have postulated for the following reasons that sympathoinhibition is exerted at a spinal locus via descending inhibitory pathways from the medullary depressor region. The onset latency for an evoked decrease in spontaneous sympathetic discharge (i.e., a positive potential) in the splanchnic nerve by medullary depressor site stimulation was always about 10 msec shorter than the earliest onset latency excitatory response (i.e., a negative potential) elicited from a medullary pressor site. Second, onset latencies of negative potentials elicited from descending pressor tracts in the cervical spinal cord (C_{1-3}) were longer

than positive potentials evoked from medial medullary depressor sites.

Whether the "spinal" inhibition elicited by Gootman and Cohen was baroreceptor in origin cannot be ascertained because they did not determine the temporal characteristics of sympathoinhibition evoked by stimulation of the baroreceptor nerves. With regard to this point, Coote *et al.* (1969) and Kirchner *et al.* (1971) revealed the existence of sites in the medial medullary depressor region that totally inhibit the baroreceptor reflex-insensitive spinal component of the somatosympathetic reflex. The possibility exists that the early onset latency positive potentials elicited from the medial medulla by Gootman and Cohen (1971) were reflecting the inhibition of a population of spontaneously discharging sympathetic neurons involved in spinal segmental reflexes (Janig and Schmidt, 1970). On the other hand, the alternative possibility exists that Gootman and Cohen were activating intramedullary components of the baroreceptor reflex arc resulting in the inhibition at a spinal locus of the population of spontaneously firing sympathetic neurons susceptible to baroreceptor reflex-induced inhibition (cf., Seller, 1973). Therefore, information regarding baroreceptor reflex inhibition of sympathetic nervous activity at spinal site is quite incomplete at this time.

In conclusion, the reports cited provide evidence that the central nervous areas involved in baroreceptor reflex regulation of vasoconstrictor activity may be organized longitudinally, with integrating centers represented at the hypothalamic, medullary and spinal cord levels. Electrophysiological studies have demonstrated the existence of baroreceptor excitatory and inhibitory components in the hypothalamus and medulla, while data concerning spinal cord integration are still fragmentary.

D. Statement of Problem

Spontaneous sympathetic nervous oscillations locked in a 1:1 relation to the cardiac cycle (∿ 3 c/sec periodicity) are generally considered to result from increasing and decreasing baroreceptor nervous discharge associated respectively with the systolic and diastolic phases of pulse pressure (Adrian *et al.*, 1932; Cohen and Gootman, 1970; Green and Heffron, 1968b; Heymans and Neil, 1958). However, some investigators have observed irregularly occurring oscillations of SND not synchronized to the pulse pressure following removal of baroreceptor nervous discharge (Alexander, 1945; Downing and Siegel, 1963; Koizumi *et al.*, 1971) or during uniform non-rhythmical baroreceptor activity (Kezdi and Geller, 1968). In some reports the duration of the synchronous bursts of SND appeared to approach that of those which were locked to the cardiac cycle before section of the pressoreceptor

nerves (Downing and Siegel, 1963; Koizumi *et al.*, 1971). These observations raise the possibility that synchronous discharges of SND (∿ 3 c/sec) which appear locked in a 1:1 relation to the pulse cycle are generated by central vasomotor elements rather than directly by the baroreceptor reflexes.

The purpose of the first portion of this investigation was to ascertain the origin of the slow wave (∿ 3 c/sec) of SND. More specifically, experiments were designed to answer the question of whether the cardiac-synchronized wave of spontaneously occurring SND was generated directly by pulse-induced inhibitory input from the baroreceptor nerves or generated by intrinsic mechanisms in the vasomotor centers and entrained to the pulse cycle by the baroreceptor reflexes. Synchronous bursts of SND in the splanchnic and renal nerves were recorded through a high pass amplifying circuit set at 1 Hz. Characteristics of the slow wave of SND such as duration, amplitude, rise time and phasic relations to the pulse cycle were measured accurately before and after baroreceptor denervation. In this way a decision was made concerning the origin of the 3 c/sec oscillation of SND. Furthermore, by employing this type of recording circuit, the period of decreased sympathetic nervous activity evoked by baroreceptor nerve or paramedian

reticular nucleus stimulation was displayed as a positive potential. Thus, features like onset latency, duration, amplitude, and contour of the evoked wave of inhibition were evaluated as well. Comparison of the temporal characteristics of sympathoinhibition with those of the slow wave of SND provided important knowledge about the mechanism by which baroreceptor reflexes act to control sympathetic nervous activity.

Considerable work has been performed in an attempt to determine the location and organization of regions in the brain from which vasoconstrictor discharge emanates. Most of the earlier studies were concerned with the effects of brain lesion or high frequency stimulation on arterial blood pressure (Alexander, 1946; Bach, 1952; Chai and Wang, 1962, 1968; McQueen *et al.*, 1954; Wang and Ranson, 1939a,b). Whereas these studies have been important in defining the location of cardiovascular reactive sites in the brain, they have suggested little about the organization of central vasopressor pathways. As discussed by Wang and Ranson (1939a) and Alexander (1946), a change in blood pressure produced by high frequency stimulation of the brain does not allow for a decision concerning whether the electrode activated afferent, efferent or association components of a central pathway. Also it would be difficult to decide whether pressor responses evoked by

stimulation of two different brain sites involved activation of elements of the same or parallel pressor pathways.

The second part of this study dealt with analyzing the responses evoked in the external carotid postganglionic nerve and the splanchnic preganglionic nerve by single shocks or trains of stimuli applied to the brain and spinal cord. The evoked potentials were compared in terms of their onset latencies, contours, following frequencies, and receptivity to blockade upon baroreceptor reflex activation. Analyzing the results in this manner provided important clues about the intrinsic organization of brain and spinal pressor regions as well as the relationships between central vasopressor pathways and the baroreceptor reflex arc.

The final segment of this research was extended to include the responses of single preganglionic sympathetic neurons to stimulation of cardiovascular reactive sites in the medulla and spinal cord. This was done for two reasons: (1) even though studies of Pitts and Bronk (1942) and Pitts *et al.* (1941) provided important information on the relationships between the frequency and intensity of hypothalamic stimulation and the response of single sympathetic units, they were not concerned with distinguishing the unitary response patterns elicited by electrical activation of different central pressor pathways; and (2) it was

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essential that the whole nerve responses (viz., external carotid nerve) elicited from the brain and spinal cord were in fact transmitted by preganglionic neurons subserving a vasoconstrictor function. Attention in this portion of the study was focused on: (1) the size of the medullary field for excitation of individual preganglionic units; (2) characterization of the unitary response patterns evoked from medullary pressor sites; (3) the extent to which individual preganglionic neurons are influenced by different central vasopressor pathways; and (4) the effects of baroreceptor reflex activation and medullary depressor region stimulation on the unitary responses elicted from brain stem and spinal pressor sites.

METHODS

One hundred ninety cats of either sex, weighing between 2.0 and 3.5 kg were used for this study. One hundred eighty-five of the animals were anesthetized by the intraperitoneal injection of dial-urethan solution (0.6 ml/kg), which consisted of a mixture of sodium diallylbarbiturate (70 mg/kg), urethan (280 mg/kg), and monoethylurea (280 mg/kg). The remaining experiments were performed on unanesthetized midcollicular decerebrate cats. Rectal temperature was maintained between 37-38°C by warming the cat with a heating pad or heat from a 200-watt incandescent light bulb.

Blood pressure was recorded from a femoral artery with a Statham transducer (model P23AC) and displayed on a Grass polygraph. All drugs were administered through a cannula inserted into a femoral vein.

The animals were immobilized with gallamine triethiodide (4 mg/kg, iv) and placed on artificial respiration (Harvard, model 607). The volume on the respirator was adjusted between 30-60 ml/stroke at 12-16 strokes/min depending on the weight of the cat. Bilateral pneumothoracotomy was performed to minimize movements associated

with artificial respiration. Supplemental doses (1-2 mg/kg, iv) of gallamine were administered as required during the course of the experiment to prevent somatomotor responses produced by central stimulation. The doses of gallamine employed failed to affect action potentials recorded from either pre- or postganglionic sympathetic nerve bundles, or from single PSN.

A. Experiments Characterizing Spontaneously Occurring Sympathetic Nervous Discharge

1. Sympathetic nerve recording and data analysis

The left greater splanchnic nerve was identified in the area of the costovertebral triangle. The preganglionic nerve was ligated with a saline-soaked silk thread (00, twisted silk) and cut between the tie and its entrance into the celiac ganglion. A 5 mm diameter loop was tied with the thread. The proximal portion of the splanchnic nerve bundle was positioned on one of two platinum electrodes. The saline-saturated silk loop was placed on the indifferent platinum electrode so as to record the action potentials monophasically. A small hook-ended glass rod was fastened to the loop in order to adjust the tension of the nerve on the electrode. The abdominal skin flaps were secured to a specially constructed frame in order to form a pool subsequently filled with warmed mineral oil (Fisher Scientific Co., Paraffin 0-120).

The pool of oil was sufficiently deep to cover the nerve and recording electrodes. One of the left renal nerves was traced and sectioned near to its entrance into the kidney. The renal nerve was prepared and recorded from in the same manner as the splanchnic nerve.

Nerve potentials were amplified with a capacity-coupled preamplifier (high and low pass filter settings at 1 and 1,000 Hz, respectively). Spontaneously occurring nervous activity was stored on magnetic tape and simultaneously displayed on a polygraph and oscilloscope. The phasic relationships between sympathetic activity and the cardiac cycle were analyzed by computer summation (Nicolet Inst. Corp., model 1070). The signal averaging process improves the signal to noise ratio. All responses time-locked to the trigger impulse will be summated, while randomly occurring background activity (tonic discharges and noise) will be reduced in proportion to the square root of the number of trials. Pulse pressure waves and nervous discharge were stored simultaneously on separate channels of a dual channel digitizer (Nicolet Inst. Corp., model SD72/2A). The memory control of both channels was displayed in analog form on an oscilloscope to be photographed and on an X-Y recorder. The sweep of the computer was initiated by a SYNC pulse from the stimulator. The SYNC pulse was generated by a timing pulse from a logic divider trigger circuit which monitored the R wave of the ECG. It was possible to apply stimuli to the neuraxis at

any desired point in the cardiac cycle by interfacing the logic divider trigger circuit with the delay circuit of the stimulator. The effects of non-cardiac synchronized electrical stimuli, applied to sites in the neuraxis or the baroreceptor nerves, on sympathetic nervous activity were also analyzed by computer summation techniques. Computer summed positive potentials were considered to represent periods of decreased neural activity. Control "dummy" records were obtained by triggering an equal number of computer sweeps randomly in relation to the cardiac cycle. Control sweeps were triggered at the same rate as test responses. The autocorrelation function of spontaneously occurring splanchnic and renal nervous activity was analyzed with a Nicolet Inst. Corp. auto- and cross-correlation plug-in (model SD-75A). This type of analysis was used to indicate the degree of rhythmicity of sympathetic nervous activity. The amplitude of the autocorrelogram periods is directly related to the degree of periodicity, while the period duration is an approximation of the duration of each sympathetic wave over many trials. If the occurrence of sympathetic oscillations is quite random with respect to one another, the autocorrelogram function approaches a straight line.

2. Neural stimulation

a. Peripheral nerve stimulation

The carotid sinus and aortic depressor nerves were exposed from a ventral aspect after reflection of a

portion of the trachea and esophagus into the mouth. The carotid sinus nerve was identified at its junction with the glossopharyngeal nerve. The aortic depressor nerve was located at its junction with the superior laryngeal nerve. The central ends of the baroreceptor nerves were placed on bipolar platinum electrodes and stimulated with square-wave pulses from a Grass stimulator (model S88).

b. Central nervous stimulation

(1) Brain stem. The cat was placed in a David Kopf (model 1404) stereotaxic apparatus in the standard manner and the skin, muscle, occipital bone and meninges overlying the cerebellum were removed. Stimuli were passed from a Grass S88 square-wave stimulator through an isolation unit (Grass, model SIU-5) to bipolar, concentric, stainless steel electrodes (David Kopf, model SND-100) positioned at selected sites in the medulla oblongata. The center lead of the electrode and shaft (outer contact) were exposed 0.25 mm. The distance between the two leads was approximately 0.5 mm. Stereotaxic placement in the brain stem was according to the coordinates of Berman (1968).

(2) Spinal cord. The spinal cord was held rigidly in place with a spinal investigational unit (David Kopf, model 1480). A midline incision was made from the head to the first thoracic vertebra. Skeletal muscles covering the first through fourth cervical vertebrae were taken out. The dorsal arch of the first, second and fourth vertebrae and the underlying meninges were removed. The

dorsal roots were cut at the dorsolateral sulcus Concentric stimulating electrodes (David Kopf, model SNE-100) were positioned at a right angle to the dorsal surface of the spinal cord. The dorsolateral sulcus and surface of the cord were employed as the reference points for lateral and vertical orientation. To locate descending spinal tracks, the electrodes were always positioned lateral to the dorsolateral sulcus, usually in the dorsal portions of the dorsolateral white column. Cervical skin flaps were secured to the stereotaxic apparatus to form a pool, subsequently filled with warmed mineral oil to prevent nervous tissue from drying.

Five-millisecond trains of 3 pulses (5-15 v; 0.5 msec; 600 Hz) and single shocks (5-10 v; 0.5 msec) were applied to sites in the brain stem and spinal cord. Occasionally sites were simulated continuously for 30 sec at 10-15 v, 0.5 msec and 20-50 Hz. Stimulation always was performed on the side ipsilateral to the recording electrodes. Several pressor and depressor sites were subsequently lesioned with direct current (2 ma for 10 sec) at the conclusion of the experiment.

3. Baroreceptor and vagus nerve denervation

Carotid sinus, aortic depressor and vagus nerves were approached from a ventral aspect after a portion of the trachea and esophagus was retracted into the mouth. Left and right carotid sinus and aortic depressor nerves were identified in the same manner as described above (see

Methods section A.2.a.). Both vagi were isolated from the carotid sheath in the midcervical region. A saline soaked ligature was looped loosely around each of the nerves for the purpose of identification. Baroreceptor denervation was accomplished by bilateral section of these nerves with scissors.

B. Experiments Characterizing Electrically Evoked Sympathetic Nervous Responses

1. Multiunit experiments

a. Sympathetic nerve recording

A branch of the external carotid plexus of the superior cervical ganglion (Billingsley and Ranson, 1918) was prepared for recording after removal of most connective tissue. The nerve was isolated at its exit from the ganglion to the region of the bifurcation of the common carotid artery. A saline-soaked silk ligature was tied to the external carotid nerve near to its junction with the carotid artery. The nerve was then sectioned between the tie and the artery. The proximal portion of the nerve bundle was positioned on platinum electrodes in a manner necessary for recording, monophasically, postganglionic action potentials. The recording apparatus was immersed in a pool, formed from the cervical skin flaps, filled with mineral oil.

Spontaneously occurring or electrically evoked potentials in this nerve were amplified with a capacitance-coupled preamplifier circuit (Grass, model P511) in which the band pass was set at 30 and 1,000 Hz, the output of which was displayed on an oscilloscope (Tektronix, model 502A or R564B) or processed with a Nicolet signal averaging computer (model 1070). The memory content of the computer representing the sum of 8-128 trials was displayed on an oscilloscope in either analog or digital form and photographed with an oscilloscope recording camera (Grass, model C4). In a number of instances, centrally emanating postganglionic discharges were amplified with a Grass 7P3A capacitance-coupled preamplifier and displayed on a polygraph with low and high half-amplitude filters set at 10 and 75 Hz, respectively.

Description of the preparation and recording of splanchnic preganglionic nervous activity is given in Methods section A.1.

b. Stimulating electrodes placement

(1) Brain stem. Details of preparation given in this section are concerned with experiments in which action potentials were evoked in the external carotid sympathetic nerve. With regard to evoked splanchnic nerve responses, preparation and stimulation of the brain stem and spinal cord are given in a preceding section (Methods, section A.2.b.).

The animals were positioned in a stereotaxic apparatus (David Kopf, model 1404). The frame of the stereotaxic apparatus was rotated 180° allowing for a ventral approach to the brain stem. The rostral portions of the trachea and esophagus were dissected away from surrounding tissue and then reflected into the mouth. Overlying muscle and base of the skull were removed, thereby exposing the ventral aspect of the brain stem. The dura mater was opened without damage to the vertebral and basilar arteries. Often portions of the pia mater were gently removed to reduce compression of neural tissue during initial entrance of the stimulating electrodes. The cervical skin flaps were secured to the stereotaxic frame and the exposed brain stem was covered with warmed mineral oil.

The electrodes (David Kopf, model SNE-100) were introduced into the medulla and midbrain using the ventral median fissure and ventral surface of the brain stem as reference points for lateral (Lo) and dorsoventral orientation, respectively. The anterior-posterior (A-P) and lateral (L) positioning of the electrodes was determined by the stereotaxic coordinates of Berman (1968) to ensure stimulation of certain nuclei. The stimulating electrodes were lowered from the ventral to the dorsal surface of the brain stem and then retracted toward the ventral surface in steps of 0.5-1 mm.

(2) Spinal cord and hypothalamus. The spinal cord was approached from a ventral aspect after removal of muscle layers and a portion of the base of the fourth cervical vertebra. Portions of the dura and pia mater were removed, without damage to the vascular supply, thus exposing the ventral surface of the spinal cord. Landmarks used for dorsoventral and for lateral orientation were the spinal cord surface and the ventral medial fissure, respectively. The electrodes were lowered until contact was made with the dorsal bony surface of the vertebra. The electrodes were then retracted in steps of 0.5 mm or less.

The hypothalamus was also exposed from a ventral aspect. A 5 mm diameter hole was drilled through the skull, centered at the stereotaxic coordinates of A-7, L-2. Extreme care was taken to avoid injury to the vascular supply in this region. The dura mater was usually opened, but not removed. The electrodes were lowered 8 mm, then retracted in 0.5-1 mm steps.

Single square-wave shocks (2-15 v; 0.1-0.6 msec) and 10-msec trains of 3 pulses (2-15 v; 0.1-0.6 msec; 300 Hz) were applied to sites in the neuraxis (hypothalamus, midbrain, medulla or spinal cord) at each step in the electrode track, usually once every 2 seconds. The intensity of stimulation required to evoke maximal postganglionic sympathetic nerve responses was 6-10 v. Many

sites in the brain and spinal cord were stimulated continuously for 10-60 sec at 2-15 v, 0.5 msec duration and 50 Hz. Several sites were lesioned for 10 sec at 2 ma at the end of the experiment. Stimulation, unless otherwise noted, was performed on the side ipsilateral to the recording electrode.

c. Midcollicular decerebration, baroreceptor denervation and C_1 transection

Decerebration was performed under halothane-nitrous oxide anesthesia. The skull overlying the parietal cortex was removed. A specially constructed stainless steel spatula (7 mm wide) placed in a stereotaxic electrode holder was lowered first through the right side and then through the left side of the brain stem at the midcollicular level (A-Po). After hemisection was performed, 40 ma of direct current were delivered through the spatula for 20 sec to achieve hemostasis. The anesthesia was discontinued and the classic pattern of decerebrate rigidity ensued. The completeness of decerebration was visually evaluated at the end of each experiment.

Baroreceptor denervation was accomplished from a ventral approach by bilateral section of the IXth and Xth cranial nerves at the jugular foramen. Connective tissue was cleaned away from the cranial nerves and the internal carotid artery was gently retracted. The nerves were then severed either with scissors or with low intensity electro-cauterizing.

Spinal transection at the first cervical segment was performed from the ventral side as well. Overlying connective tissue, muscle, odontoid process of the axis and ventral arch of the atlas were removed, thereby exposing the spinal cord. After removal of a portion of the dura mater, the spinal cord was quickly sectioned, usually by one cut with iris scissors.

2. Single unit experiments

a. Preganglionic unit recording

The spinal cord was exposed from the first to the fifth thoracic segments in the same manner as described in the Methods section A.2.a.(2). The left preganglionic cervical sympathetic nerve was isolated at the level of the fourth cervical vertebra. Bipolar platinum stimulating electrodes were placed on the central end of the crushed nerve for the purpose of identifying preganglionic sympathetic neurons by antidromic activation. Platinum-coated stainless steel microelectrodes (Transidyne General Corp.) with 1 μ tip diameters and exposed tip lengths of 5 μ were used for extracellular recording of unit discharges. Electrode tip resistances ranged from 5 to 10 megohms. The position of the microelectrode was controlled by a David Kopf Inst. hydraulic microdrive instrument. An indifferent platinum electrode was placed on the frontal bone. Unit discharges were

amplified with a capacitance-coupled Grass P511 preamplifier (low and high half-amplitude responses were set at 300 and 1,000 Hz) and recorded on magnetic tape (Ampex, model PR500). The data on tape were treated in three ways: (1) unit discharges were displayed on an oscilloscope and photographed; (2) poststimulus histograms (PSH) of unit discharges were processed by a Nicolet Inst. Corp. 1070 computer and plotted on an X-Y recorder (Hewlett-Packard model 7000A/7001A); (3) unit discharges were subjected to window discrimination (F. Haer and Co. model 40-75-1) and displayed in the form of a 5 v square wave on a Grass polygraph.

In some instances, compound action potentials elicited by stimulation of the thoracic ventral roots were recorded from the preganglionic cervical sympathetic trunk with bipolar platinum electrodes. The action potentials were amplified through a band pass circuit of 30 and 1000 Hz.

Preganglionic sympathetic units activated antidromically by splanchnic nerve stimulation were located in the fifth to tenth thoracic spinal segments. Unitary discharges of splanchnic PSN were amplified and recorded in the same manner as discharges of PSN whose axons compose the cervical sympathetic trunk.

b. Stimulating electrodes placement and parameters of stimulation

Stimulating electrodes were positioned in the medulla and the midcervical spinal cord from a dorsal aspect in the same manner as described in the Methods sections A.2.b.(1),(2). Responses were elicited by 5-msec trains of 3 pulses (5-15 v; 0.5 msec; 600 Hz) and single shocks (5-15 v; 0.5 msec) applied to pressor sites in the brain stem and spinal cord, usually once every 2 sec.

C. Histology

The medulla and appropriate portions of the spinal cord were removed and fixed in formalin at the end of each experiment. The formalin-fixed tissue was cut in sections of 30 μ thickness with a cryostat-microtome (Lipshaw Cryotome, model 1500). Sections were cut in the frontal plane to allow for the identification of electrode tracks and lesions. The brain sections were stained with cresyl violet for cell bodies according to a modified method of Powers and Clark (1955). Nerve fibers were stained with either luxol fast blue or Cajal's reduced silver nitrate method (Segarra, 1970). Shrinkage of 15% was taken into account before stimulation sites were plotted on maps of the brain stem or spinal cord.

D. Drugs

The following drugs were used: gallamine triethiodide, hexamethonium chloride, and norepinephrine bitartrate (NE). All doses are expressed in terms of the salts.

E. Statistical Analysis

Statistical analysis was performed with the Student's t-test for paired and unpaired data described by Snedecor (1956). P values of < 0.05 were considered to indicate statistical significance. Values presented for each series of experiments are expressed as means $\pm$ standard error.

RESULTS

I. Characteristics of Spontaneously Occurring Sympathetic Nervous Discharge (SND)

A. Central Origin of the Slow Wave of SND in Splanchnic and Renal Nerves

1. Description of spontaneous discharge

The objective of the first series of experiments was to describe the nature of centrally emanating SND. A high pass filtering circuit of 1 Hz was employed so that low and high frequency oscillations in SND would be recorded. Figure 1A shows the characteristics of a spontaneous burst of renal nerve activity recorded simultaneously with bandpass settings of 1-1000 Hz and 30-1000 Hz. With the high pass filter set at 1 Hz, SND was viewed primarily as a slow wave. The high frequency components which formed the slow wave are shown in the lower record of Figure 1A (high pass filter set at 30 Hz). Note that the duration of the slow wave accurately depicts the period of high frequency spiking. These records support the contention of Cohen and Gootman (1970) that slow waves of SND result from synchronized activity (spikes) of individual fibers contained within the nerve bundle under

Figure 1. Oscillographic traces of spontaneously occurring renal nerve discharge.

A: top trace is slow wave of SND recorded with preamplifier bandpass of 1-1000 Hz. Bottom trace shows high frequency components (high pass filter set at 30 Hz) which formed slow wave. Horizontal calibration is 100 msec. B: relationship between blood pressure in mmHg (top trace) and slow wave of SND (bottom trace). Preamplifier bandpass is 1-1000 Hz. Period of reduced SND was associated with expiratory phase of respiratory cycle (see Cohen and Gootman, 1970; Koizumi *et al.*, 1971). C: inhibition of slow wave during peak pressor action produced by norepinephrine (1 μg/kg, iv). Time base is 1 sec/division and refers to B and C. Vertical calibration is 50 μV and refers to nerve recordings in A-C. Negativity is upward in this and all subsequent figures.

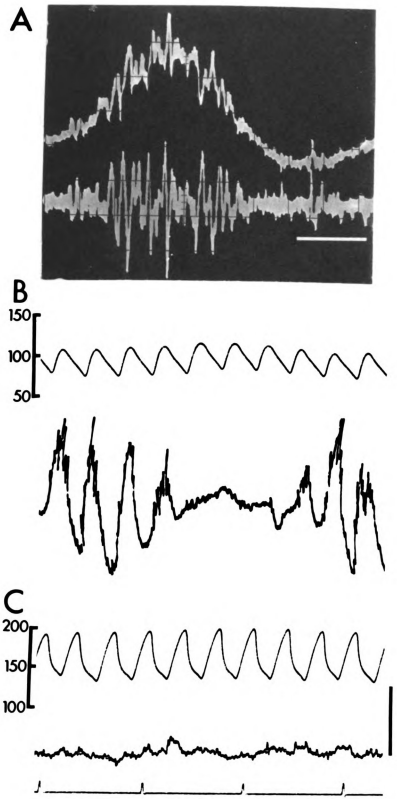


Figure 1

study. That is, the slow wave represents an envelope of nerve spikes. Figure 1B-C shows that the rise in systemic blood pressure produced by the iv injection of 1 μg/kg of norepinephrine (baroreceptor reflex activation, cf. Koizumi *et al.*, 1971) was associated with a disappearance of the slow waves. This observation further attests to the neural origin of the slow wave.

2. Origin of 3 c/sec periodicity of SND

Computer summation of 64 sweeps triggered by a timing pulse monitoring the R wave of every fourth ECG complex enabled me to analyze the phase relations between the arterial pulse and the SND exhibited in preganglionic splanchnic or postganglionic renal nerves. In this way any sympathetic nervous oscillation that was time-locked to the cardiac cycle would be summated. Periodicities not cardiac-synchronized would be averaged out. Only the slow wave (∿ 3 c/sec) was locked to the cardiac cycle. Figure 2A shows that maximum SND occurred during mid-diastole whereas minimum activity occurred close to the beginning of systole. This was observed in every cat (15 experiments) as long as mean arterial pressure was above 90 mmHg and the baroreceptor nerves were intact. The autocorrelation functions of splanchnic and renal nerve activity revealed a pronounced periodic component with a frequency of approximately 3 c/sec (Figure 2B). The supposition that the slow wave of SND monitored the

Figure 2. Relationship between cardiac cycle and SND in two cats with intact baroreceptor reflexes.

A: computer summed traces (64 sweeps) of arterial pulse (top), and splanchnic or renal SND (bottom). Computer sweep was triggered by R wave of every fourth ECG complex. Mean blood pressure was 110 mmHg (splanchnic) and 107 mmHg (renal).
B: autocorrelation functions of splanchnic and renal SND. Address bin was 4 msec. Sweep duration was 1 sec. Sample run was 4 min. Horizontal calibration is 500 msec. Vertical calibration is 133 μV and refers to records in A.

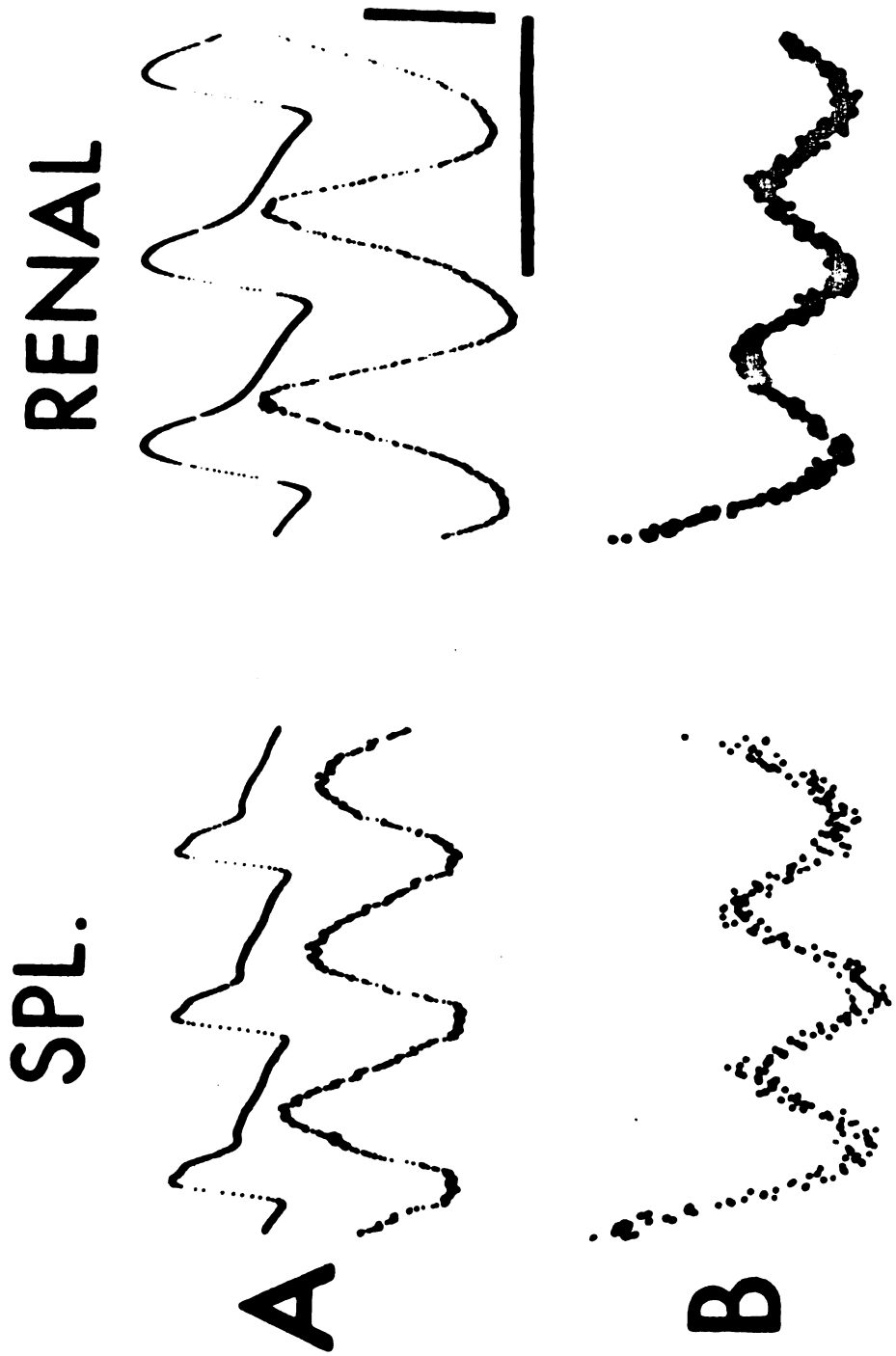


Figure 2

discharge of vasomotor fibers is warranted on the basis of the renal nerve recordings. The efferent component of the renal nerve is considered primarily if not solely vasoconstrictor in function (Coote and Downman, 1966; Coote *et al.*, 1969).

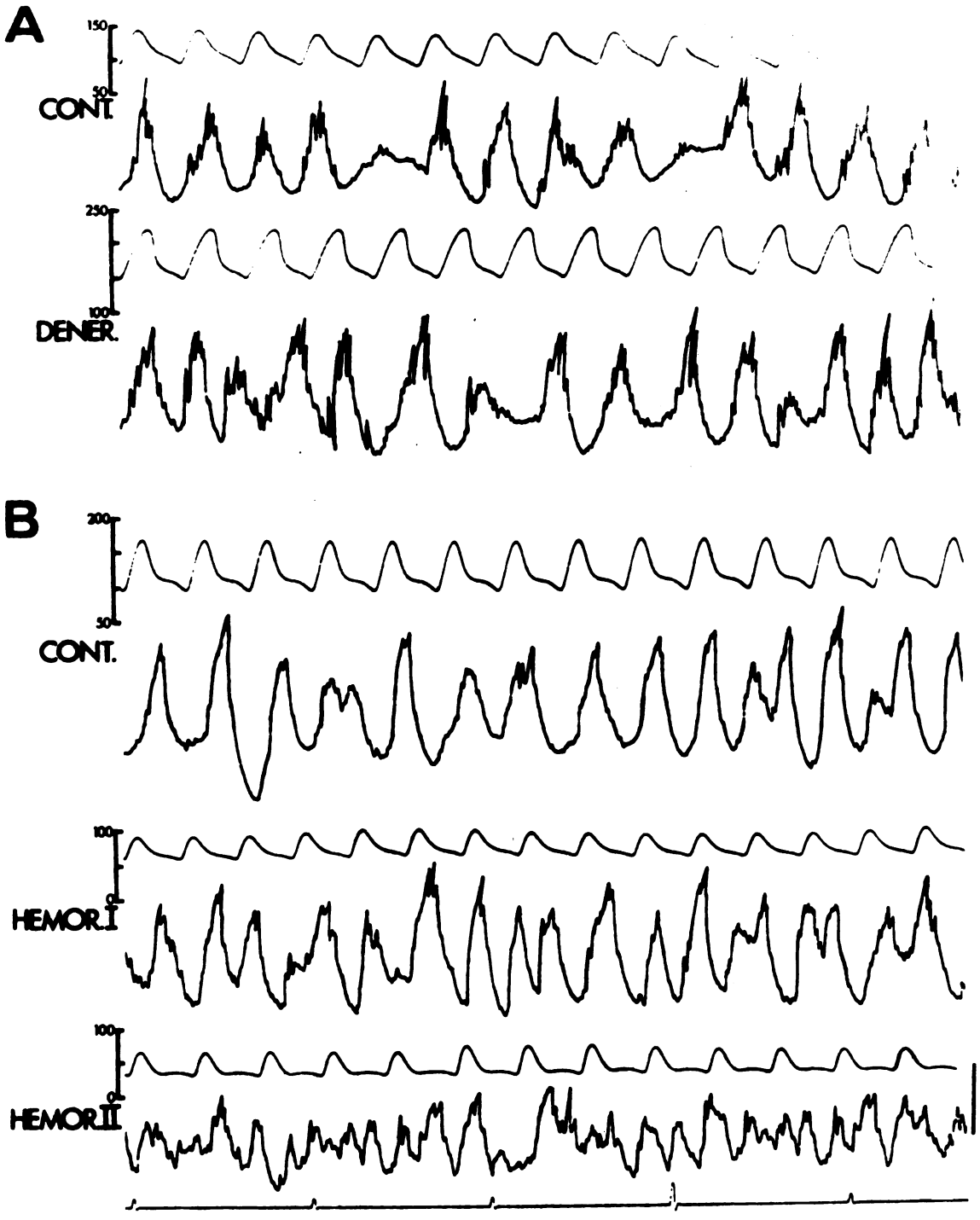
Using computer summation, Cohen and Gootman (1970) observed almost identical phase relations between the arterial pulse and splanchnic SND in approximately 25% of their experiments. Central conduction time, temporal dispersion and other factors were proposed to explain the relatively long delay between changes in pressure and SND. In the remaining cats, however, Cohen and Gootman (1970) noted a 10 c/sec periodicity of SND. These oscillations often were locked in a 3:1 relation to the cardiac cycle. Assuming that the oscillation of SND locked in a 1:1 relation to the cardiac cycle was of baroreceptor origin, Cohen and Gootman concluded that the 10 c/sec periodicity represented the fundamental rhythmicity of either brain stem or spinal vasomotor elements. Although these investigators never removed or diminished baroreceptor input to substantiate this hypothesis. In this regard, others (Downing and Siegel, 1963; Koizumi *et al.*, 1971) have shown that SND is not strictly uniform or continuous in character following removal of baroreceptor reflex influences. However, the high pass filter settings (30-80 Hz) used in these studies would have made it

difficult to measure and compare sympathetic nervous waveforms before and after baroreceptor denervation (see lower trace of Figure 1A). In contrast, I was able to measure accurately the characteristics of synchronized bursts of SND depicted as slow waves on oscillographic records when the high pass filter was set at 1 Hz.

Figure 3 demonstrates that the slow wave of SND persisted after bilateral section of the carotid sinus, aortic depressor and vagus nerves (4 experiments) or hemorrhage (6 experiments) to a mean arterial pressure between 70-80 mmHg (HEMOR I). However, the phase relations between SND and the cardiac cycle were unlocked (Figure 4). This was shown when the oscillographic records from each experiment were subjected to computer summation. The records in Figure 4 were derived, in part, from the oscillographic tracings illustrated in Figure 3A and B (HEMOR I). Computer summed records of SND triggered by the R wave after baroreceptor denervation or hemorrhage approached a straight line since signal averaging reduces those components of the electrical recording which are not time-locked to the cardiac cycle in proportion to the square root of the number of trials summed. These records were indistinguishable from those of summed traces triggered by dummy pulses applied randomly with respect to the cardiac cycle. This observation attests to the complete

Figure 3. Effects of baroreceptor denervation and hemorrhage on the slow wave of SND.

A: baroreceptor denervation. Records demonstrate occurrence of slow wave of renal SND after bilateral section of carotid sinus, aortic depressor and vagus nerves. Top traces are blood pressure (mmHg). Bottom traces are SND. B: hemorrhage. I: hemorrhage to a mean arterial pressure of 72 mmHg. II: severe hemorrhage leading to "desynchronization" of SND. Records in A and B are from two different cats. Time base is 1 sec/division. Vertical calibration is 50 μV for nerve recordings.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HEMOR.I
100
0
HEMOR.II

Figure 3

removal of baroreceptor nervous input. Bilateral section of the carotid sinus, aortic depressor and vagus nerves also eliminated inhibition of SND associated with the pressor action of iv norepinephrine. The autocorrelation functions of SND in Figure 4 show a reduced degree of periodicity after section of the baroreceptor nerves or hemorrhage. This observation indicates that the slow waves of SND were less evenly spaced following the removal of baroreceptor nervous input.

The results presented in Figures 3 and 4 suggest that the slow wave was generated by central vasomotor elements rather than by the baroreceptor reflexes as has been generally assumed (Adrian *et al.*, 1932; Cohen and Gootman, 1970; Green and Heffron, 1968b; Heymans and Neil, 1958). Table 1 further supports this contention. Most importantly, the duration ($\sim$ 200 msec) of the negative phase of the slow wave of renal nerve activity was not significantly changed by baroreceptor denervation or hemorrhage. In addition, Table 1 shows that the frequency of occurrence of the slow wave was significantly increased by baroreceptor denervation or hemorrhage. The amplitude of the slow wave was not significantly affected by either procedure. However, high frequency spiking superimposed on the slow wave often was more prominent after removal of baroreceptor nervous input (Figure 8C).

Figure 4. Unlocking of phase relations between SND and cardiac cycle.

Records are computer readouts of oscillographic tracings shown in Figure 3. A: baroreceptor denervation (bilateral section of carotid sinus, aortic depressor and vagus nerves. A1 and 2: computer summed traces (64 sweeps) of arterial pulse (1) and renal SND (2) before and after baroreceptor denervation. Computer sweep was triggered by R wave of every fourth ECG complex. Changes in mean blood pressure are not depicted in computer readouts of the arterial pulse. A3: sum of 64 computer sweeps triggered by dummy pulses applied randomly with respect to cardiac cycle. A4: autocorrelation functions of SND before and after baroreceptor denervation. Address bin was 10 msec. Sweep duration was 2.5 sec. Sample run was 5 min. B: hemorrhage to lower mean blood pressure from 112 to 72 mmHg. B1 through 4: as described for traces in A. Horizontal calibration is 500 msec for traces 1 through 3. Vertical calibration is 267 μV.

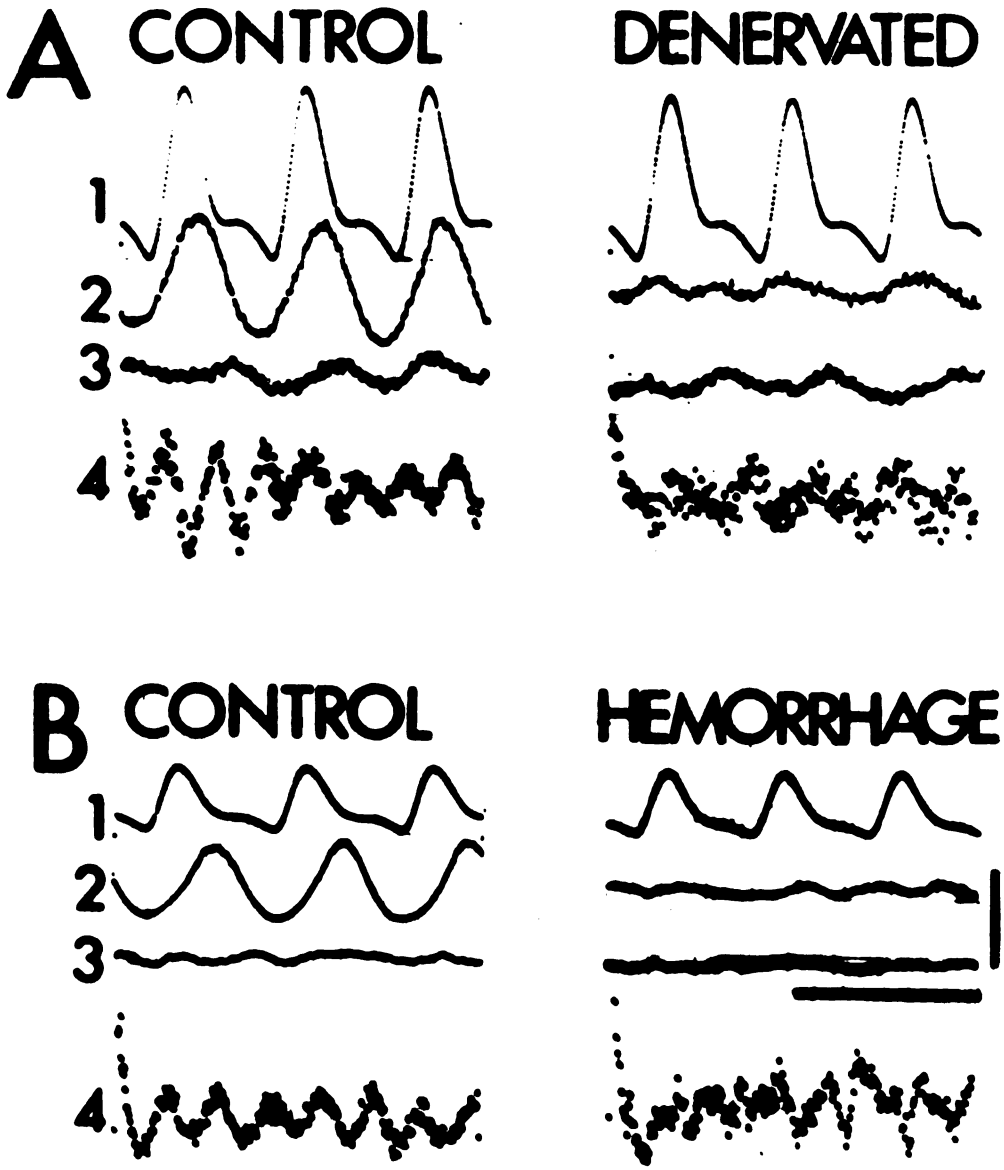


Figure 4

Table 1. Effect of baroreceptor denervation and hemorrhage on characteristics of slow wave of renal SND (3 c/sec periodicity) measured directly from oscillographic tracings

Characteristic	Control	Post-Den.	% Δ(1)
A. Baroreceptor denervation (N=4)			
Duration (msec)(2)	211± 7	203± 6	-5±7
Freq. of occurrence (c/min)	178±15	197±15	+11±1*
Amplitude (μV)	35±10	36±12	-1±9
B. Hemorrhage (3) (N=6)			
Duration (msec)(2)	191± 7	191± 6	+1±5
Freq. of occurrence	186± 7	202± 7	+12±4*
Amplitude (μV)	38± 7	52±14	+37±29

Values are mean ± S.E. calculated from 40-60 consecutively occurring slow waves. (1) is mean ± S.E. calculated from % change measured in each experiment; (2) is duration of negative phase of slow wave. The negative phase was considered that component of the slow wave which exceeded the baseline established with the preamplifier input terminals open-circuited. (3) is hemorrhage to a mean arterial pressure (70-80 mmHg) at which the phase relations between SND and the cardiac cycle were unlocked; * indicates statistical significance at the $P<0.05$ level (paired comparison).

In contrast to the results observed following baroreceptor denervation or when bleeding was carried to the point of uncoupling the phase relations between SND and the cardiac cycle, severe hemorrhage to a mean arterial pressure between 40-60 mmHg led to a marked reduction in the frequency of occurrence of the ∿ 200 msec slow wave of

SND. This is shown in the lower traces of Figure 3B (HEMOR II). The slow wave was replaced in large part by a waveform with a duration of approximately 100 msec. However, due to their irregular occurrence, I could not demonstrate 3:1 locking of these waves to the cardiac cycle with computer summation. Thus, severe hemorrhage but not baroreceptor denervation led to partial "desynchronization" of SND. That is, large amplitude slow waves were replaced by higher frequency activity.

Dontas (1955) also observed a shift from pulse-synchronous splanchnic nervous discharge to "continuous" type activity upon lowering arterial blood pressure from 115 to 50 mmHg. The "continuous" type discharge was associated with enhanced chemoreceptor activity simultaneously recorded in a carotid sinus nerve.

B. Neural Inhibition of Sympathetic Slow Wave Activity

The data presented in the previous sections support the contention that the slow wave was generated by central vasomotor elements rather than directly by the baroreceptor reflexes. Results discussed in the following sections may provide information concerning the manner in which baroreceptors act to control the 3 c/sec wave form.

1. Termination of pulse-synchronous SND by stimulation of sites located in the paramedian nucleus of the medial medullary depressor region

Single shocks of supramaximal intensity (10 v) applied to medullary depressor sites in the paramedian reticular nucleus at appropriate points in the cardiac cycle extinguished or prematurely terminated the slow wave of SND. Figure 5 is typical of the 9 experiments performed. The computer summed records in Figure 5A show locking of the slow wave of renal nerve activity to the arterial pulse. Panels B-G compare the 3 c/sec oscillation of SND shown in panel A with the computer summed waveforms following the application of a single shock to the paramedian nucleus at selected points in the cardiac cycle. Peak amplitude of the first slow wave in the triplet was reduced and delayed in time when the stimulus was applied simultaneously with the timing pulse (derived from R wave of ECG) which triggered the sweep of the computer (panel B). The original oscillographic records revealed that the first slow wave was extinguished approximately 50% of the time by the stimulus applied to the paramedian nucleus. This most likely accounted for the reduction in amplitude of the computer summed slow wave. When the single shock was applied close to the beginning of or near peak systole, the first slow wave of the triplet was extinguished or prematurely terminated (panels C and D, respectively). Application of the stimulus in early,

Figure 5. Effect of single shocks (10 v; 0.5 msec) applied to paramedian reticular nucleus on slow wave of renal SND.

A: computer summed traces (64 sweeps) of arterial pulse (top) and SND (bottom). Computer sweep was triggered by R wave of every fourth ECG complex. Mean blood pressure was 135 mmHg. B-G: comparison of computer summed trace of SND shown in A (dotted line) with those (solid line) summed following paramedian stimulation at selected points in the cardiac cycle. Single shocks applied to the paramedian nucleus were delayed as follows with respect to the R wave. B (0 msec); C (50 msec); D (120 msec); E (150 msec); F (200 msec); G (250 msec). Arrows show point of application of single shock. Horizontal calibration is 500 msec. Vertical calibration is 267 μV.

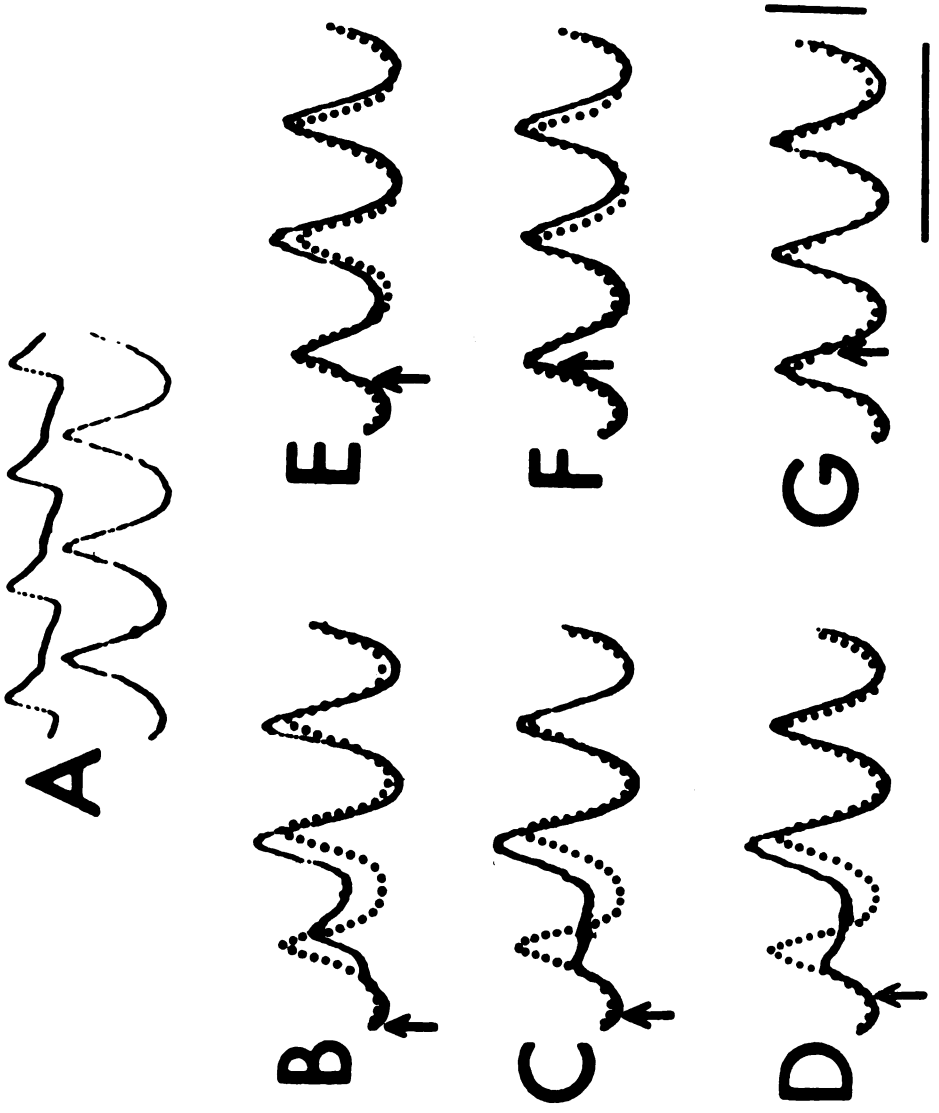


Figure 5

mid or late-diastole failed to affect the slow wave (panels E-G). The record in panel E is particularly interesting since it shows that the stimulus was ineffective when placed approximately 60 msec after the start of the slow wave. Neither a facilatory nor an occlusive interaction between naturally occurring baroreceptor nervous and electrically evoked activity was important in determining the effectiveness of paramedian stimulation. This is shown by the traces in panels C and D. In C, the single shock was applied at a time when naturally occurring baroreceptor nervous activity would have been at a minimum (presystole). In D, the stimulus was applied near peak systole, i.e., during a time when naturally occurring baroreceptor nervous activity would have been maximal. Importantly, the stimulus was effective in terminating the slow wave in both cases. It is reasonable to assume that the effects of paramedian stimulation monitored activation of intramedullary components of the baroreceptor reflex arc since the carotid sinus nerve makes primary and secondary connections with this medial medullary nucleus (Crill and Reis, 1968; Homma *et al.*, 1970; Humphrey, 1967; Miura and Reis, 1969, 1972). In addition, stimulation of the paramedian nucleus mimics the effects of baroreceptor reflex activation on pre- and postganglionic SND (Snyder and Gebber, 1973). This assumption will be substantiated in a subsequent section of the Results.

2. Temporal characteristics of sympatho-inhibition elicited by stimuli applied to paramedian reticular nucleus

The results presented in Figure 5 led to the prediction that the time course of computer summed inhibition of SND induced by paramedian stimulation would be similar to that of the spontaneously occurring slow negative wave. This was tested by summing 64 splanchnic or renal nerve responses produced by single shocks or 5 msec trains of 3 pulses (10 v) applied once every 4 sec to depressor sites in the paramedian nucleus. The stimuli were applied randomly with respect to the cardiac cycle. Inhibition of spontaneously occurring SND was displayed as a positive wave by the computer. Positive potentials result from intervals of decreased SND time-locked to the stimulus which average as periods of lesser negativity than occur spontaneously (Cohen and Gootman, 1969; Gootman and Cohen, 1970; Weaver and Gebber, 1974). Although single shocks or trains of pulses applied to the paramedian nucleus failed to change blood pressure, stimulation at 50 Hz for 15 sec decreased mean arterial pressure by 30-80 mmHg.

Figure 6 illustrates the positive potentials evoked in the splanchnic or renal sympathetic nerves of 4 different cats. Stimulation of the paramedian nucleus with a single shock evoked a wave of positivity which appeared similar in form to the spontaneously occurring slow negative wave of SND. In addition, an earlier positive

Figure 6. Computer summed traces (64 sweeps) of splanchnic and renal nerve positive potentials evoked by stimulation of paramedian reticular nucleus.

A single shock or a 5 msec train of 3 pulses was applied randomly with respect to the cardiac cycle. A1-D1: positivity evoked by single shock stimulation. Each trace is from a different cat. A2-D2: positivity evoked in same cats by trains of pulses. A3-D3: sum of 64 computer sweeps triggered in the same cats by dummy pulses. Horizontal calibration is 250 msec. Vertical calibration is 133 μV for A1-3, 267 μV for B1-3 and C1-3, and 533 μV for D1-3.

potential was elicited by trains of pulses applied to the paramedian nucleus. The early positivity was considerably shorter in duration than the late positive potential. The time course of the early and late positive potentials often overlapped (Figure 6 B_2,D_2). The duration of the late positive potential was essentially the same independent of whether elicited by a single shock or a train of pulses. The temporal characteristics of the early and late positive potentials are summarized in Table 2.

Table 2. Temporal characteristics of early and late positive potentials evoked by 5 msec trains of 3 pulses applied to paramedian nucleus

Characteristics	Splanchnic nerve		Renal nerve	
	early +	late +	early +	late +
Onset latency (msec)	28± 3(22)	99± 8(22)	47±3(23)	110±4(26)
Duration (msec)	72±11(12)*	294±22(22)	72±7(12)*	202±9(26)

Values are mean ± S.E. with (N); * measurements from experiments in which early and late positive potentials did not overlap.

Attempts to separate the early and late positive potentials by either stimulus intensity or electrode movement to another depressor site proved unsuccessful.

Figure 7 shows that the late positive potential evoked by stimulation of the paramedian nucleus indeed

Figure 7. Comparison of time course of late positive potential (renal nerve) evoked by stimulation of paramedian reticular nucleus with that of the slow wave of SND derived in the same cat by computer summation and autocorrelation analysis.

A: superimposition of traces shown in B-D; positivity (dotted line) is inverted; computer summed slow wave (solid line); one cycle of autocorrelation function (dot-dash line). B: computer summed positivity (64 sweeps) evoked by single shock (10 v; 0.5 msec) applied to the paramedian nucleus randomly with respect to the cardiac cycle. C: computer summed traces (64 sweeps) of arterial pulse (top) and SND (bottom). Computer sweep was triggered by R wave of every fourth ECG complex. D: autocorrelation function of SND. Address bin was 4 msec. Sweep duration was 1 sec. Sample run was 4 min. Horizontal calibration is 500 msec for B-D. Vertical calibration is 133 μV for B and C.

Figure 7

approximated the mirror image of the slow wave of SND derived in the same cat by computer summation or analysis of the autocorrelation function. Table 3 summarizes the results obtained in 12 cats in which renal nerve activity was recorded. The time to peak amplitude, and the total duration of the late positive potential evoked by trains of pulses were not significantly different from the corresponding values for the spontaneously occurring slow wave of SND analyzed by computer summation.

Table 3. Comparison of temporal characteristics of computer summed late positivity and spontaneously occurring slow wave of SND recorded from renal nerve in 12 cats

	Time to peak amplitude (msec)	Total duration (msec)
Late positivity	85 ± 6	202 ± 9
Slow wave of SND	94 ± 6	211 ± 11

Values are mean ± S.E.

The data in Figure 8 further attest to the association of the late positive potential with the presence of the slow wave of SND. Severe hemorrhage (3 experiments) to a mean arterial pressure below 60 mmHg led not only to the "desynchronization" of SND described in Figure 3, but also to the disappearance or marked reduction of the late

Figure 8. Relationships between character of spontaneously occurring SND and positive potentials evoked by stimulation of paramedian reticular nucleus.

Records in A, B and C are from 3 different cats. A: effect of severe hemorrhage to a mean arterial pressure of 55 mmHg on splanchnic nerve activity. 1: oscillographic tracings of SND before and after hemorrhage. 2: computer summed traces (32 sweeps) of positivity evoked by a 5 msec train of 3 pulses applied to paramedian nucleus randomly with respect to cardiac cycle before and after hemorrhage. B: effect of asphyxia (15-47 sec after artificial respiratory was turned off) on renal nerve activity. 1 and 2: as described for A. C: effect of baroreceptor denervation (bilateral section of carotid sinus, aortic depressor and vagus nerves) on renal nerve activity. 1 and 2: as described for A. Horizontal calibrations are 500 msec. Vertical calibrations are 20 μV for oscillographic tracings and 267 μV for records of positivity.

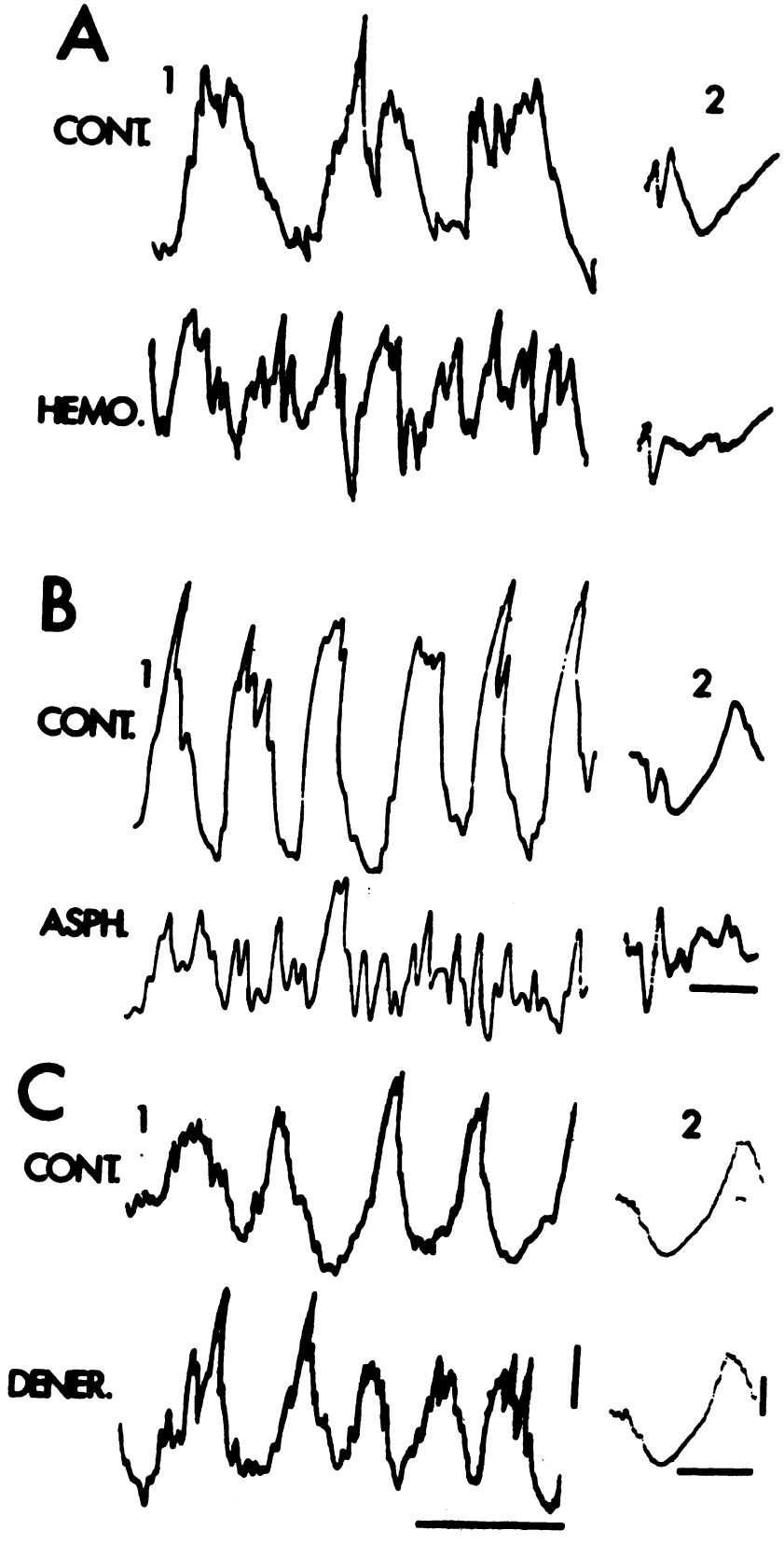


Figure 8

positive potential evoked by stimulation of depressor sites in the paramedian nucleus (Figure 8A). In contrast, the amplitude of the early positivity was increased. "Desynchronization" of SND and an increase in the ratio of early/late positivity also were observed 15-30 sec after the artificial respirator was turned off during deflation (asphyxia). One of the 2 experiments performed is shown in Figure 8B. Figure 8C illustrates that section of the baroreceptor and vagus nerves failed to affect the late positive potential evoked from the paramedian nucleus. This was expected since baroreceptor denervation did not eliminate the slow wave of SND (Figures 3 and 8C).

3. Sympathoinhibition evoked by carotid sinus and aortic depressor nerve stimulation

The splanchnic nerve responses produced by stimulation of the carotid sinus or aortic depressor nerve were studied to determine whether the early and/or late positive potentials evoked from the paramedian nucleus monitored activation of intramedullary components of the baroreceptor reflex arc. Stimuli applied to the baroreceptor nerves were in the form of a 5 msec train of 3 pulses. Sympathetic nerve responses evoked by stimuli of supramaximal intensity (10 v) most often were multiphasic in character containing negative as well as positive components. This was expected since the carotid

sinus and aortic depressor nerves contain chemoreceptor as well as baroreceptor fibers (Heymans and Neil, 1958; Lalley *et al.*, 1973; Paintal, 1973). On occasion, however, stimuli of supramaximal intensity produced sympathetic nerve responses containing only positive components. In addition, the negative potential sometimes could be deleted from the multiphasic complex by lowering the intensity of stimulation. This was accomplished most readily when the aortic depressor nerve was stimulated. In this regard, most of the A fibers of the aortic depressor nerve are baroreceptor in function (Paintal, 1973). The opposite is true for the carotid sinus nerve. Most of the myelinated fibers in the carotid sinus nerve subserve chemoreceptor function (Fidone and Sato, 1969). Representative response patterns are depicted in Figure 9. Each response pattern was observed at least two times for each of the 2 baroreceptor nerves stimulated (17 experiments). Most importantly, both early and late positive potentials could be evoked independent of preceding negativity. The temporal characteristics of the positive potentials were similar to those reported in Table 2 for positivity produced by stimulation of the paramedian nucleus. Thus, 2 distinct phases of sympathoinhibition were associated with baroreceptor nerve stimulation.

Figure 9. Computer summed splanchnic nerve response patterns evoked by carotid sinus and aortic depressor nerve stimulation.

Each representative splanchnic nerve trace represents the sum of 64 trials evoked by a 5-msec train of 3 pulses (2-10 v) applied to the carotid sinus (CSN) or aortic depressor (ADN) nerves. Trains of stimuli were applied randomly with respect to the cardiac cycle. Horizontal calibration is 500 msec for traces in A, 125 msec (CSN) and 250 msec (ADN) for traces in B. Vertical calibration is 67-533 μV depending upon the trace.

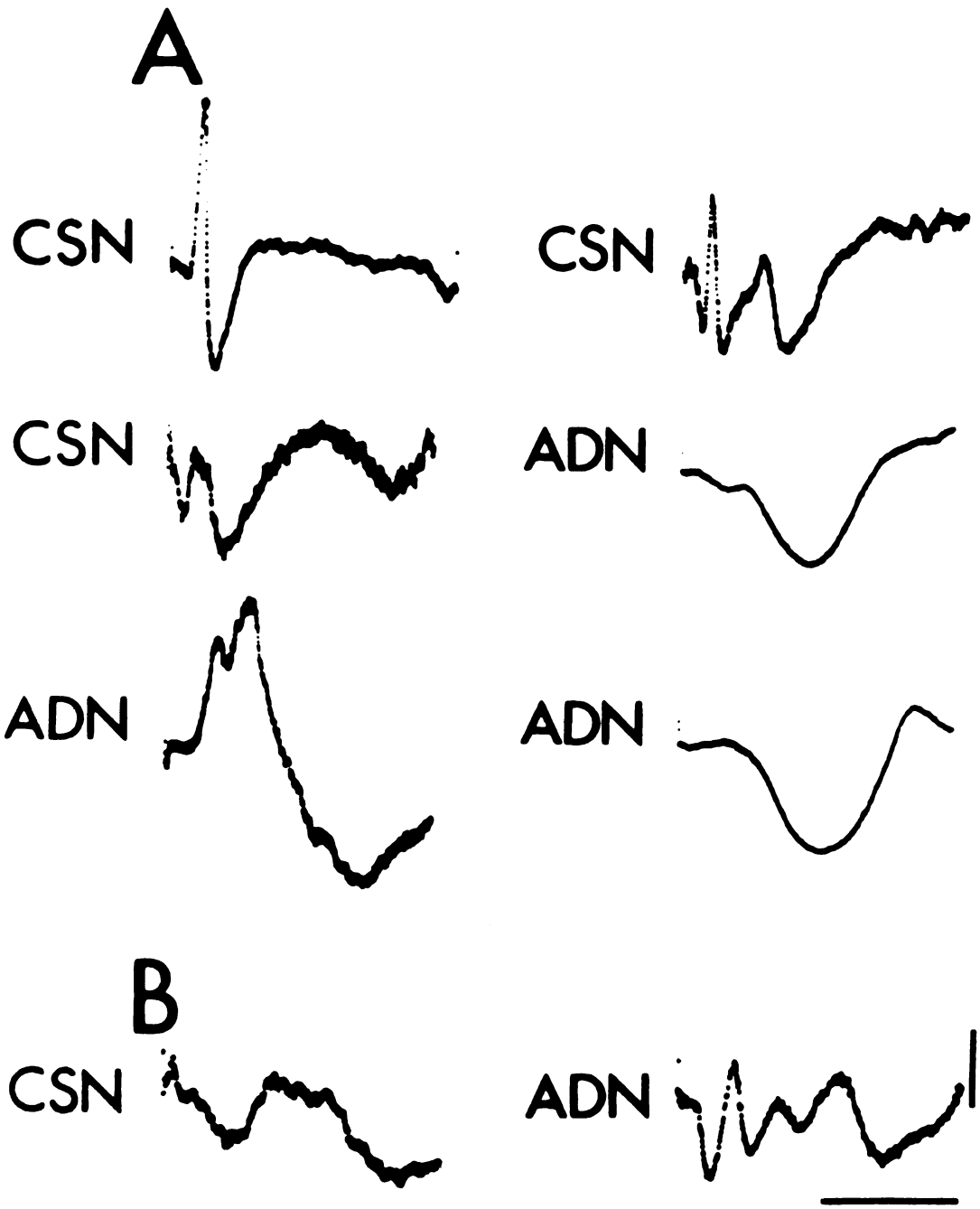


Figure 9

4. Level of neuraxis mediating entrainment of the 3 c/sec sympathetic waves

Forebrain pathways have been suggested by some (Hilton and Spyer, 1969, 1971; Manning, 1965; Spyer, 1969, 1972) to function in the baroreceptor reflex arc. Therefore, it is possible that the long latency positive potential might be monitoring the activation of recurrent inhibitory loops rostral to the brain stem. The data illustrated in Figure 10 are representative of those obtained in 4 cats in which the effect of midcollicular transection was tested on the positive potentials elicited in the splanchnic nerve by stimulation of the aortic depressor nerve (panel A) and the paramedian reticular nucleus (panel B). Decerebration performed according to the stereotaxic technique described in the Methods section had little effect on the early positive potential, but usually prolonged the duration and sometimes enhanced the amplitude of the late positive potential. The onset latency of the late positive potential was not significantly changed. These experiments suggest that sympathoinhibition evoked by stimulation of the aortic depressor nerve and paramedian nucleus occurred below the midcollicular level and did not require forebrain loops for its initiation.

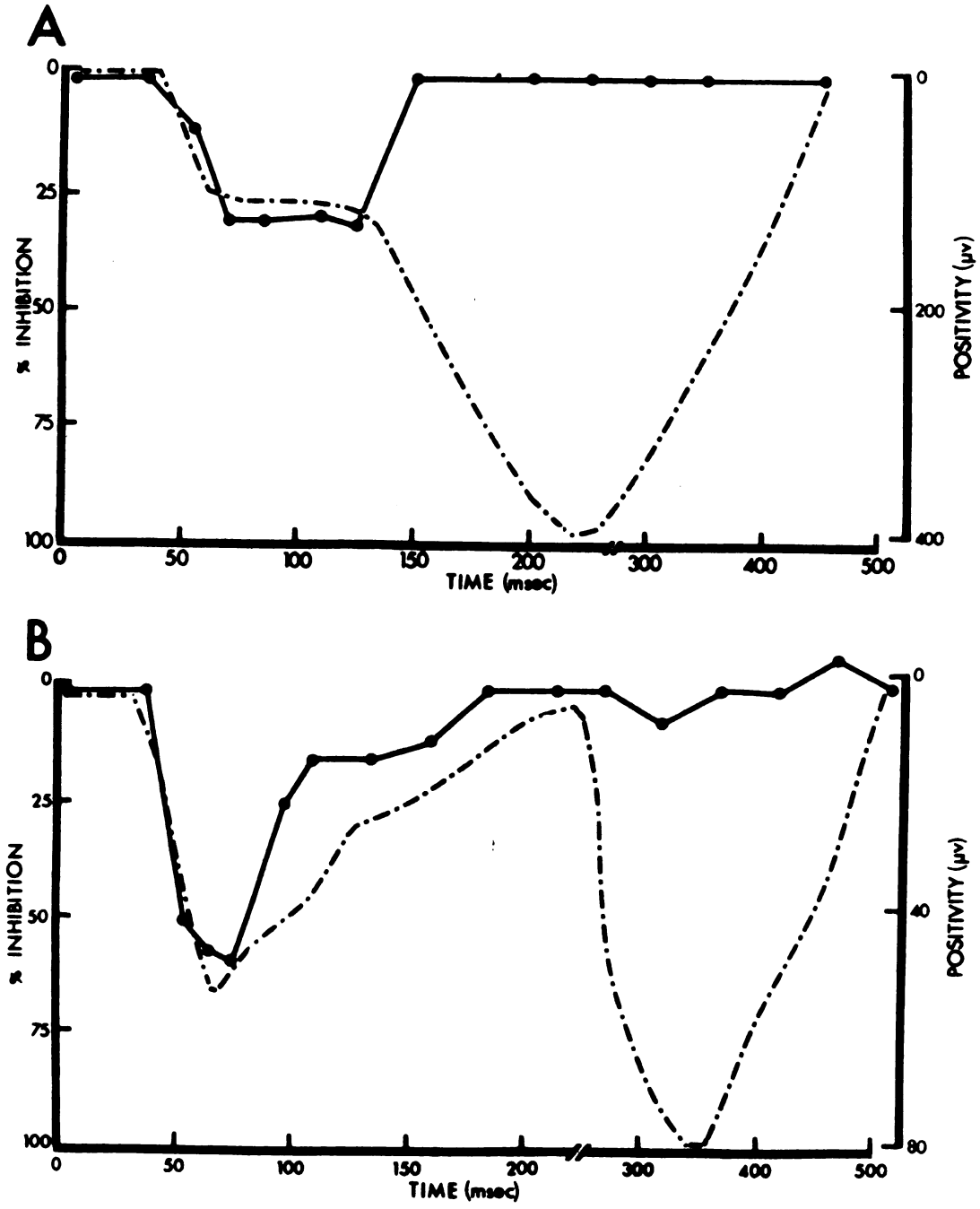
Figure 11 illustrates 2 experiments in which the time course of splanchnic nerve positivity was compared with that of spinal inhibition produced by stimulation of a

Figure 10. Effect of decerebration on positive potentials evoked in the splanchnic nerve by stimulation of aortic depressor nerve or paramedian reticular nucleus.

Records in A and B are from 2 different cats. A1: computer summed traces (64 sweeps) of positivity evoked by a 5 msec train of 3 pulses applied to aortic depressor nerve randomly with respect to the cardiac cycle. A2: same, but after midcollicular decerebration. B1: positivity (sum of 64 trials) evoked by a train of pulses applied to paramedian nucleus. B2: same, but after midcollicular decerebration. Horizontal calibrations are 250 msec. Vertical calibrations are 267 μV for A and 133 μV for B.

Figure 11. Comparison of time course of computer summed positivity evoked by stimulation (5 msec train of 3 pulses) of the paramedian nucleus with that of inhibition of computer summed splanchnic SND elicited by a 10 msec train of 3 pulses applied to descending spinal pressor tracts.

Data were obtained from two cats, A and B. Dot-dash lines: time course of positivity. Amplitude (μV) is plotted against time (msec). Train was applied to paramedian nucleus at time 0. Solid lines: time course of inhibition of SND evoked by stimulation of descending spinal pressor tract. Percent inhibition is plotted against the interval (msec) between stimulation of the paramedian nucleus and the onset latency of SND evoked by spinal stimulation. The interval was changed by delaying the stimuli applied to the descending spinal pressor tract with respect to the stimuli applied to the depressor site in the paramedian nucleus.


A
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% INHIBITION
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TIME (msec)
0
40
80
POSITIVITY (μv)

Figure 11

paramedian depressor site with a 5 msec train of 3 pulses. The time course of spinal inhibition was depicted by the excitability-recovery curve of the splanchnic nerve discharge (sum of 16 trials) elicited by a 10 msec train of 3 pulses applied to a pressor site in the dorsolateral white column of the midcervical spinal cord. The onset latencies of the computer summed splanchnic nerve discharges were 33 msec in A and 32 msec in B. These latencies were well within the range of those exhibited by potentials evoked from midcervical spinal tracts which were not abolished by C_1 transection (refer to Table 6, page 182). This indicated that the potentials were elicited from descending spinal pathways. The time course of depression of the splanchnic nerve potential evoked from the spinal cord followed only that of the early phase of positivity in both experiments. This observation suggests that the early phase of sympathoinhibition occurred in the spinal cord while the late phase was mediated at a supraspinal level. Additional evidence substantiating a spinal component of baroreceptor-induced inhibition of SND will be presented in a later section of the Results.

II. Characteristics of Electrically Evoked Sympathetic Nervous Responses

Results presented in Section I contradict the traditionally accepted view that slow waves (3 c/sec) of SND locked in a 1:1 relationship to the cardiac cycle result from periodic fluctuations in afferent inhibitory impulses

transmitted in baroreceptor nerves in response to pulse pressure. A more plausible explanation might be that the slow wave of sympathetic nervous activity is formed by "avalanche excitation" of an interconnected population of brain stem neurons. The baroreceptor reflex appears to entrain the slow waves of SND to the cardiac cycle.

As mentioned in the Introduction, the reactive areas in the hypothalamus, medulla and spinal cord affecting blood pressure have been identified primarily by the responses elicited during high frequency punctate stimulation. Whereas these studies have been informative with regard to the general location of pressor and depressor regions, they have contributed little to our understanding of the intrinsic organization of central pathways which transmit vasoconstrictor discharge (e.g., $\sim$ 3 c/sec waves of SND) from the brain centers to the end organs. By analyzing the changes in blood pressure per se produced by stimulation of supraspinal sites, one cannot discern if efferent, afferent or internuncial elements of a central pathway were excited. For this reason it was thought that a study analyzing the responses evoked in a "vasoconstrictor" nerve by low frequency stimulation at various levels of the neuraxis would contribute to our present knowledge. Clues concerning the functional organization of vasomotor centers might be revealed by analyzing and comparing the evoked potentials in terms of their onset latency, contour,

following frequency, response to single and train stimulation and receptivity to blockade by baroreceptor reflexes.

In conducting these experiments it was imperative that the nerve used for the data source contain only vasoconstrictor fibers and display a minimal amount of dispersion of impulses along the peripheral conducting pathway. Peripheral dispersion and functional qualities must be considered because the differences observed in onset latency of the responses evoked from various brain sites might be accounted for on the basis of a wide range of conduction velocities of vasoconstrictor fibers or activation of functionally dissimilar components in the peripheral pathway and not due to central vasopressor organizational properties.

Since the splanchnic and renal nerves were employed as data sources in the first part of this study, I preferred to use these nerves for determining organizational features as well. However, as shown in Figure 12, the typical splanchnic action potential evoked by stimulation of the peripheral end of a ventral root consisted of the responses of many fiber groups covering a relatively long duration. Similar results were observed in the renal nerve. Since it is well known that the splanchnic nerve subserves other non-vasomotor autonomic functions, it would be difficult to decide whether the fiber group discharged from the brain was indeed vasomotor in function.

Therefore, it was decided to record potentials from a branch of the external carotid plexus of the superior

Figure 12. Evoked activity in the left greater splanchnic nerve by ventral root stimulation.

Preganglionic nerve action potentials evoked by a single shock of supramaximal intensity (15 v; 0.1 msec) applied to the peripheral cut end of the seventh thoracic ventral root. Record represents the sum of 16 trials. Horizontal calibration is 12.5 msec. Vertical calibration is 266 μV.

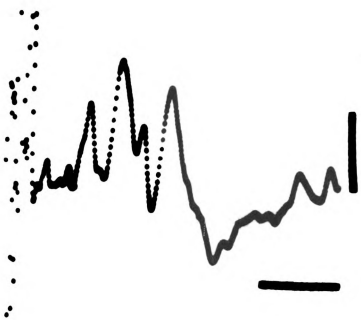

Figure 12

cervical ganglion which innervates a region of the external carotid artery (Billingsley and Ranson, 1918). This postganglionic nerve, as will be shown in the following section, exhibited properties characteristic of "vasoconstrictor" nerves and displayed less peripheral dispersion than either splanchnic or renal nerves.

A. Responses Evoked in the External Carotid Sympathetic Nerve

1. Characteristics of the peripheral conducting pathway

The external carotid postganglionic nerve exhibited spontaneously occurring or "resting" discharges which were in phase with the arterial pulse and the respiratory rhythm. The centrally emanating "resting" discharges were inhibited during the pressor response produced by iv norepinephrine (0.5-2 μg/kg). This is shown in Figure 13A. The inhibitory effect of norepinephrine was abolished by bilateral section of the IX and X cranial nerves at the jugular foramen in 6 experiments (Figure 13B). Thus, spontaneously occurring discharges in the external carotid nerve were sensitive to blockade upon baroreceptor reflex activation.

In agreement with the previous report by Volle (1962), the action potential evoked in the external carotid nerve by a supramaximal shock applied to the preganglionic cervical sympathetic trunk near its spinal origins consisted of one cell group with a mean duration of 12±1 msec. The responses elicited in one of the 23 experiments

Figure 13. Spontaneously occurring and evoked activity in the external carotid nerve.

A: reflex inhibition of centrally emanating postganglionic discharges during pressor response evoked by iv norepinephrine (1 μg/kg). Top trace is blood pressure (mmHg). Middle trace is nerve recording. Bottom trace is time base (1 sec/division). B: effect of norepinephrine after bilateral section of IXth and Xth cranial nerves. C: postganglionic potential evoked by a single shock of submaximal intensity (4 v; 0.1 msec) applied to peripheral end of sectioned preganglionic nerve. D: postganglionic response evoked by single shock of supramaximal intensity (15 v; 0.1 msec) applied to preganglionic nerve. Horizontal calibration is 20 msec in C and D. Vertical calibrations are 25 μV for nerve recordings in A and B, and 500 μV for C and D. Records in A-B and C-D are from two different cats.

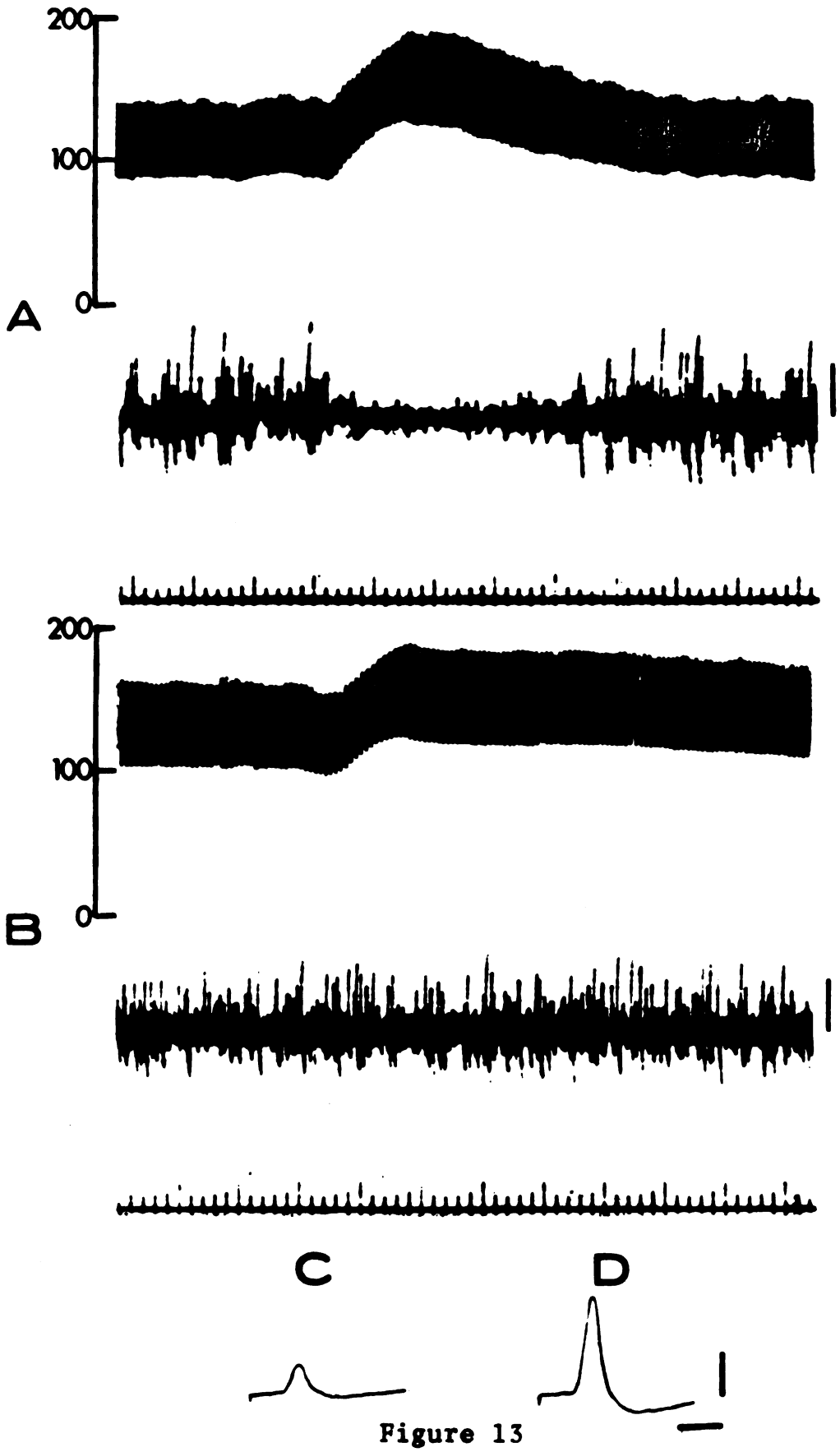

Figure 13

performed are shown in Figure 13C-D. The conduction velocity of impulses in preganglionic fibers mediating the postganglionic response was determined with the following method. The onset latencies of the postganglionic potentials produced by stimulation of the preganglionic nerve at the level of the 7th cervical vertebra and at the caudal pole of the superior cervical ganglion were ascertained. The difference in the onset latencies was divided by the distance between the two stimulating electrodes. The conduction velocity of impulses in preganglionic fibers mediating the responses in the external carotid nerve ranged from 7.5-12.2 M/sec in 9 experiments. This range was similar to that (7.7-14.5 M/sec) observed by Eccles (1935) for the S2 fiber group of the cervical sympathetic trunk. The value calculated for conduction time from the 1st thoracic vertebra to the recording electrode on the postganglionic external carotid nerve was 19±1 msec.

Simultaneous recordings were made of action potentials evoked in the external carotid and cervical sympathetic nerves by single shocks applied to the preganglionic trunk at the level of the 7th cervical vertebra in 3 experiments. The threshold intensity of activation (3-5 v) of the postganglionic action potential was found to be that for activation of the S2 fiber group of the compound action potential recorded from the cervical sympathetic trunk. This fiber group of the preganglionic cervical sympathetic trunk has been reported to innervate ganglion

cells which subserve a vasoconstrictor function (Bishop and Heinbecker, 1932).

2. Postganglionic sympathetic nerve responses evoked by medullary pressor region stimulation

a. Distribution of active sites

Sympathetic nerve responses were elicited by single shocks and trains of 3 pulses applied to 268 medullary sites in 23 cats. The distribution of 189 of these active sites which were identified upon histological examination of brain sections is presented in Figure 14. The A-P levels of stimulation were sufficiently close so that the data could be plotted on two frontal sections of the medulla. The section in Figure 14A and C is about 2 mm rostral to the obex (P-12). The section in Figure 14B and D is about 1 mm caudal to the obex (P-15). The majority of sites from which postganglionic responses were evoked were located in the periventricular gray, the adjacent dorsolateral reticular formation (primarily nucleus reticularis parvocellularis; R.pc.) and the lateral regions of nucleus reticularis ventralis (R.v.). In addition, some sympathetic nerve potentials were evoked from the vicinity of the lateral reticular nucleus (N.r.l.).

The maps presented in Figure 14 are similar to those of the medullary pressor region supplied by others

Figure 14. Distribution of 189 medullary sites in 23 cats from which responses were elicited in the ipsilateral external carotid nerve by single shocks and/or trains of 3 pulses.

A and C: represent a frontal section about 2 mm rostral to the obex. B and D: represent a section about 1 mm caudal to the obex. Abbreviations are those of Brodal (1957). cc: central canal; N.c.e.: external cuneate nucleus; N.f.c.: nucleus cuneatus; N.r.l.: lateral reticular nucleus; N.tr.sp.V: spinal nucleus of trigeminal nerve; R.pc.: nucleus reticularis parvocellularis; R.v.: nucleus reticularis ventralis; Tr.sp.V: spinal tract of trigeminal nerve; T.s.: tractus solitarius; XII: motor nucleus of hypoglossal nerve.

(Alexander, 1946; Bach, 1952; Chai and Wang, 1962; Wang and Ranson, 1939a). Indeed, high frequency (50 Hz) stimulation of sites from which sympathetic nerve potentials were evoked always elicited a rise in blood pressure. The amplitude of the pressor response elicited by high frequency stimulation appeared to be directly related to the amplitude of the nerve response evoked from the same site by a single shock or train of stimuli. Blood pressure was not changed when single shocks or trains of 3 pulses were applied to the medulla once or twice each sec.

Representative postganglionic nerve responses evoked from medullary sites rostral and caudal to the obex are illustrated in Figure 15. Although sympathetic nerve potentials were evoked from up to 4 sites in some electrode tracks, it was not uncommon to observe striking changes (10-40 msec) in the onset latency of a response upon moving the electrode 0.5-1 mm (Figure 15A, panels 2-3 and Figure 15B, panels 2-3). Small vertical movements (0.75-1 mm) of the electrode also often led to the disappearance of a response even when the intensity of stimulation was 10-15 v. These observations indicated that current spread from the electrode tips was not excessive.

b. Relationship between onset latency and site of initiation of the sympathetic nerve response

The onset latencies of potentials evoked in the external carotid nerve by stimulation of the side of

Figure 15. Representative responses evoked in the ipsilateral external carotid postganglionic nerve by stimulation of the medulla of a midcollicular decerebrate unanesthetized cat.

Ten msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) were applied to the medulla once every sec. Each potential represents the sum of 64 trials. A: frontal section about 2 mm rostral to the obex. B: section about 1 mm caudal to the obex. Horizontal calibrations for A and B are 100 msec. Vertical calibrations for A and B are 532 μV. Abbreviations are the same as those in Figure 14.

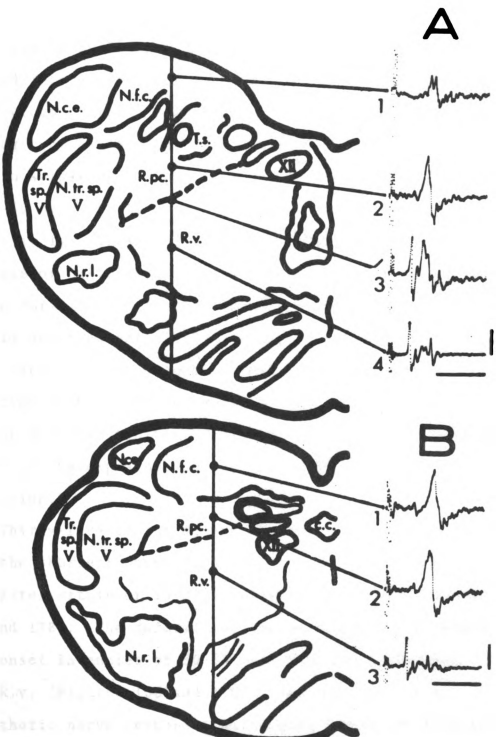
A
N.c.e.
N.f.c.
T.s.
Tr. sp. V
N. tr. sp. V
R.pc.
XII
R.v.
N.r.l.
1
2
3
4
B
N.c.e.
N.f.c.
Tr. sp. V
N. tr. sp. V
R.pc.
E.C.
XII
R.v.
N.r.l.
1
2
3

Figure 15

the medulla ipsilateral to the recording electrodes ranged from 34-104 msec in unanesthetized midcollicular decerebrate cats and from 34-100 msec in anesthetized cats with an intact neuraxis. For descriptive purposes, the potentials evoked by 10 msec trains of 3 pulses were arbitrarily divided into 5 groups on the basis of onset latency. The first group contains potentials with onset latencies ranging from 34-44 msec. The second to the fifth groups contain sympathetic nerve responses with onset latencies of 50-59 msec, 60-69 msec, 70-79 msec and 80-104 msec, respectively. These millisecond divisions were chosen for ease of distributing points and because of propinquity to the duration of the peripherally evoked external carotid nerve potential (12±1 msec). Differences in onset latency great enough to shift a postganglionic potential evoked from the medulla from one division to another probably monitor an alteration in central pathways and cannot be explained on the basis of peripheral dispersion.

Thirty-five of the 41 sympathetic nerve responses with the shortest onset latencies (34-44 msec) were evoked from sites within or in close proximity to R.v. (Figures 16B and 17B). The majority of the postganglionic responses with onset latencies of 50-59 msec also were elicited from R.v. (Figures 16C and 17C). The majority of the sympathetic nerve responses with onset latencies greater

Figure 16. Relationship between onset latency and site of initiation for responses evoked from above the obex (P-10 to P-14) by trains of 3 pulses.

Distribution of medullary sites above the obex from which sympathetic nerve responses with onset latencies of 34-44 msec in B, 50-59 msec in C, 60-69 msec in D, 70-79 msec in E and 80-104 msec in F were elicited in intact anesthetized and unanesthetized decerebrate cats by 10 msec trains of 3 pulses. Abbreviations in A are the same as those in Figure 14.

Figure 17. Relationship between onset latency and site of initiation for responses evoked from below the obex (P-14 to P-16) by trains of 3 pulses.

Distribution of medullary sites below the obex from which sympathetic nerve responses with onset latencies of 34-44 msec in B, 50-59 msec in C, 60-69 msec in D, 70-79 msec in E and 80-100 msec in F were elicited in intact anesthetized and unanesthetized decerebrate cats by 10 msec trains of 3 pulses. Abbreviations in A are the same as those in Figure 14.

than 60 msec were evoked from sites in the periventricular gray and R.pc. (Figures 16D-F and 17D-F). This is most evident for the responses with onset latencies of 70-104 msec. The distribution histograms presented in Figure 18 reveal the relationship between onset latency and site of initiation of the postganglionic nerve responses (taken from Figures 16 and 17) as a percent of total responses elicited in each group or division. As will be shown, the shortest onset latency (34-44 msec) potentials could be distinguished from all others on the basis of their receptivity to blockade upon baroreceptor reflex activation.

Gootman and Cohen (1971) attributed the short latency (5-7 msec) responses evoked in the splanchnic nerve by medullary stimulation to antidromic activation of afferent fibers. In the present study, the iv injection of 5 mg/kg of the ganglionic blocking agent hexamethonium abolished the short latency (34-44 msec) as well as the longer latency sympathetic nerve responses (4 experiments). Thus, the responses recorded from the external carotid nerve monitored only the discharge of postganglionic sympathetic neurons.

Sympathetic nerve responses were evoked by stimulation of the contralateral as well as the ipsilateral medulla in 3 cats. Only the longer latency (>55 msec) potentials were elicited from the contralateral medulla.

Figure 18. Distribution histograms depicting relationship between onset latency and site of initiation of postganglionic sympathetic nerve potentials evoked from the medulla by trains of 3 pulses.

PVG: periventricular gray; R.pc: nucleus reticularis parvocellularis of dorsolateral reticular formation; R.v.: nucleus reticularis ventralis. Postganglionic potentials evoked from the region of the lateral reticular nucleus (N.r.l.; see Figure 14) were not included in the distributions. These responses had relatively small peak amplitudes and inconsistent onset latencies.

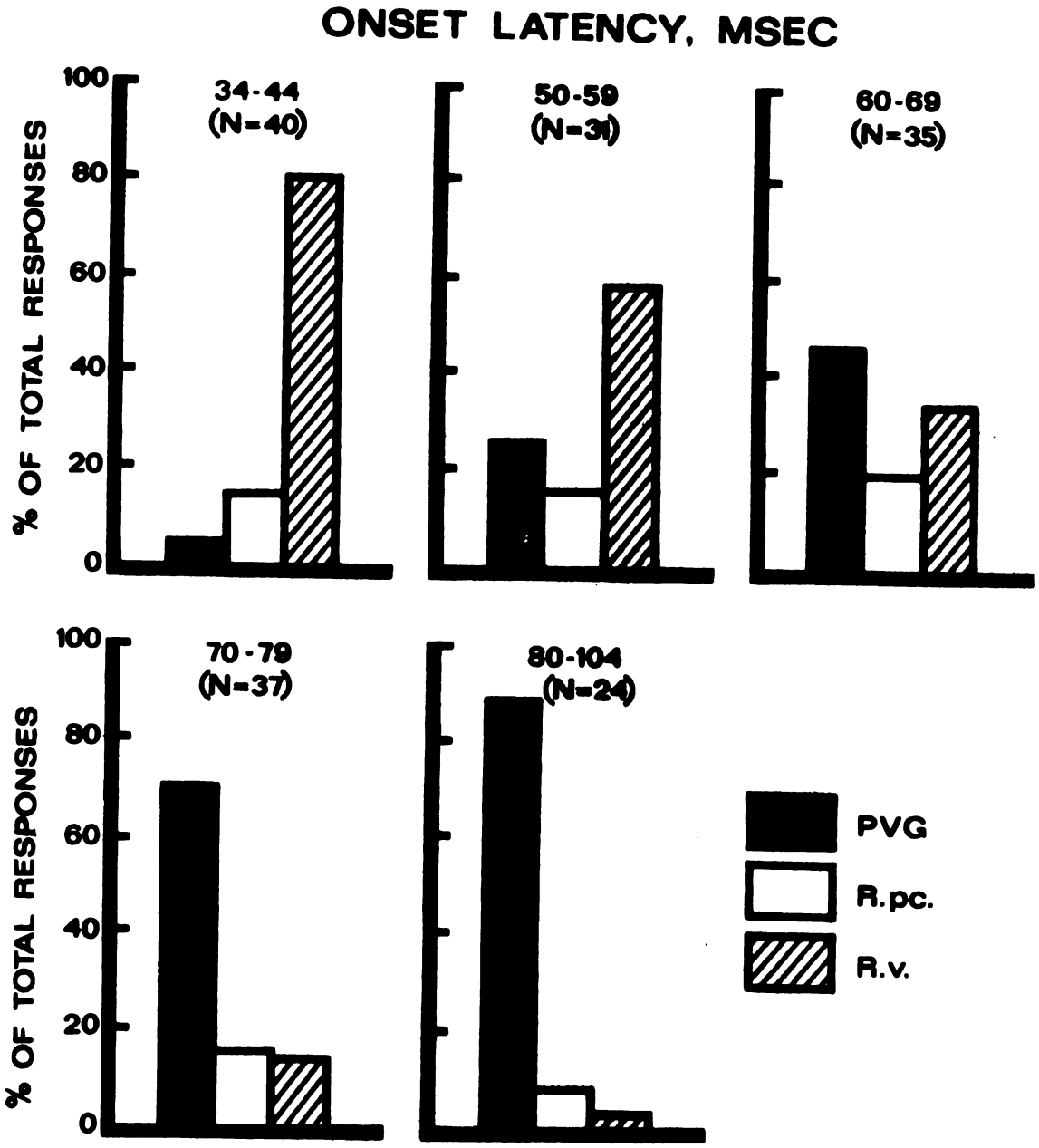
ONSET LATENCY, MSEC
% OF TOTAL RESPONSES
100
80
60
40
20
0
34-44
(N=40)
50-59
(N=31)
60-69
(N=35)
70-79
(N=37)
80-104
(N=24)
PVG
R.pc.
R.v.

Figure 18

As previously described for the cat splanchnic nerve by Gootman and Cohen (1971), the postganglionic responses evoked upon contralateral medullary stimulation were of smaller amplitude and had onset latencies 5-20 msec longer than those potentials elicited from corresponding sites in the ipsilateral medulla.

c. Effect of baroreceptor reflex activation on evoked potentials

To evaluate the relationship of the evoked potentials to the baroreceptor reflex arc, the following experiments were performed. The effect of raising mean blood pressure 60-100 mmHg was tested on the sympathetic nerve potentials evoked by stimulation of 73 medullary sites in 23 cats. Blood pressure was raised by the iv injection of 0.5-2 μg/kg of norepinephrine. The period of maximum inhibition of spontaneously occurring postganglionic discharges observed during the pressor response induced by norepinephrine was 15-20 sec (Figure 13A). During this time, 8-32 postganglionic responses elicited by stimulation of the medulla at a frequency of 1-2 trains/sec were summed. The peak amplitude of the summed potential was compared with that of control responses which were obtained in the absence of exogenously administered norepinephrine.

Sympathetic nerve responses with onset latencies greater than 50 msec always were inhibited during the

rise in blood pressure produced by norepinephrine. This can be seen in the results illustrated in Figure 19A. The inhibition was complete in the great majority of instances. The inhibitory action induced by norepinephrine on postganglionic responses with onset latencies greater than 50 msec was not observed following bilateral section of the IX and X cranial nerves. One of the 5 experiments performed is shown in Figure 19B. Thus, inhibition of the longer latency potentials observed during the rise in blood pressure produced by norepinephrine in cats in which the IX and X nerves were intact can be attributed to baroreceptor reflex activation.

Postganglionic sympathetic nerve potentials with onset latencies of 34-44 msec were not blocked during the pressor action of norepinephrine. This was the case independent of whether the response was elicited by submaximal or supramaximal intensities of stimulation. Representative examples are shown in Figure 20. Figure 20B is particularly interesting in that the postganglionic response evoked from a site in R.v. was composed of a short and a longer latency potential. The longer latency potential was inhibited during the pressor response evoked by norepinephrine while the short latency potential was unaffected.

Figure 19. Effect of hypertensive action of norepinephrine on long latency sympathetic nerve potentials evoked from the periventricular gray.

Records in A are from a cat with intact baroreceptor nerves. Records in B are from a cat in which the IX and X cranial nerves were bilaterally sectioned at the jugular foramen. Ten msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) were applied twice every sec. to a site in the periventricular gray of each cat. Each record is the sum of 32 trials. A-1, B-1: control records; A-2, B-2: responses during the peak pressor action of iv norepinephrine (1 µg/kg in A; 3 µg/kg in B). A-3, B-3: responses following dissipation of pressor action of norepinephrine. Horizontal calibration is 100 msec for records in A and B. Vertical calibration is 106 µV in A and 212 µV in B.

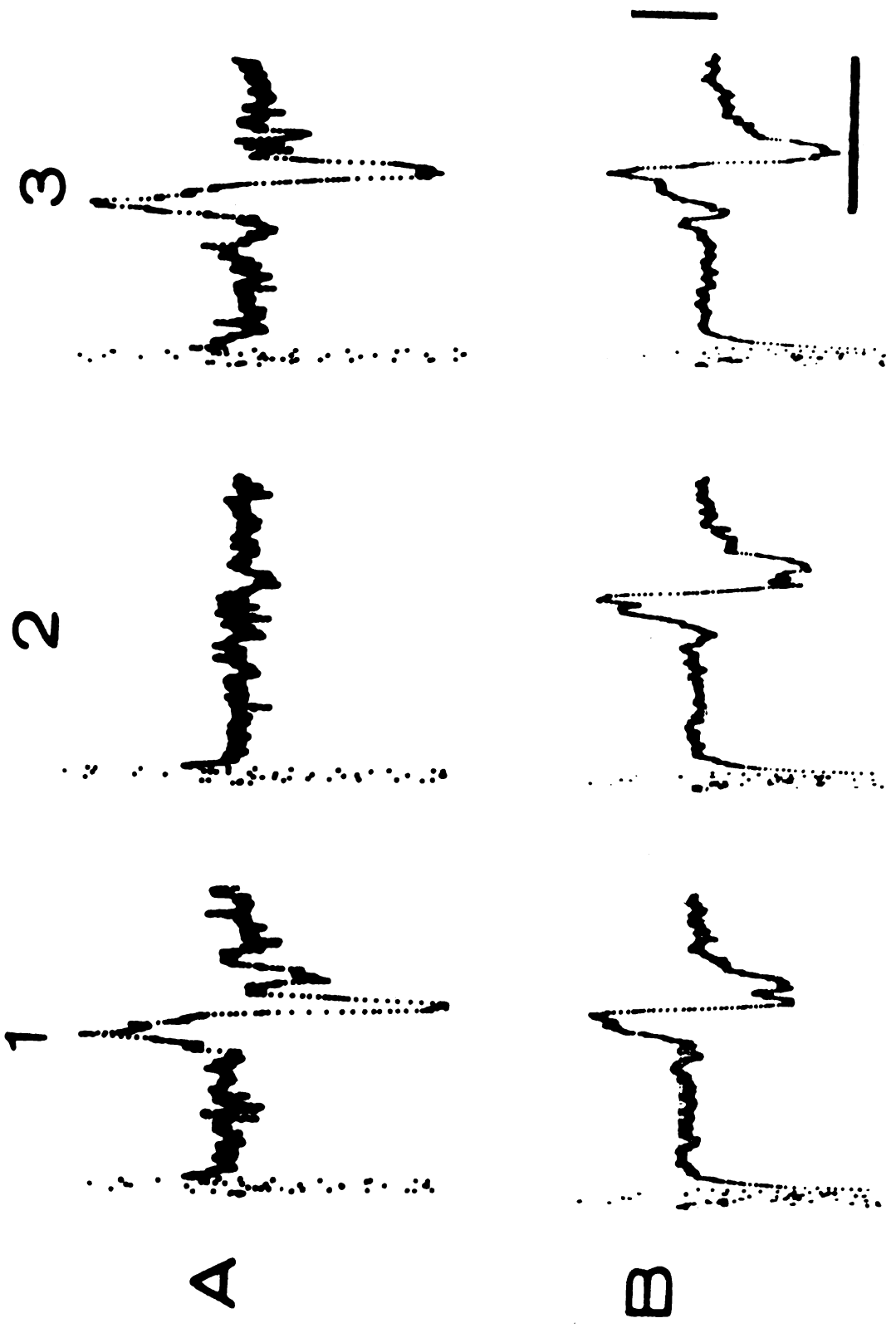

Figure 19

Figure 20. Effect of baroreceptor reflex activation on short and long latency sympathetic nerve potentials evoked by stimulation of nucleus reticularis ventralis (R.v.).

Records A and B are from two different cats. Ten msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) were applied to R.v. once each sec. Each record represents the sum of 16 trials. A-1, B-1: control responses. A-2, B-2: response during inhibition of spontaneously occurring postganglionic discharges observed when blood pressure was raised by iv norepinephrine (2 μg/kg). A-3, B-3: responses following dissipation of pressor action of norepinephrine. Horizontal calibration is 50 msec in A and 100 msec in B. Vertical calibration is 212 μV in A and 424 μV in B.

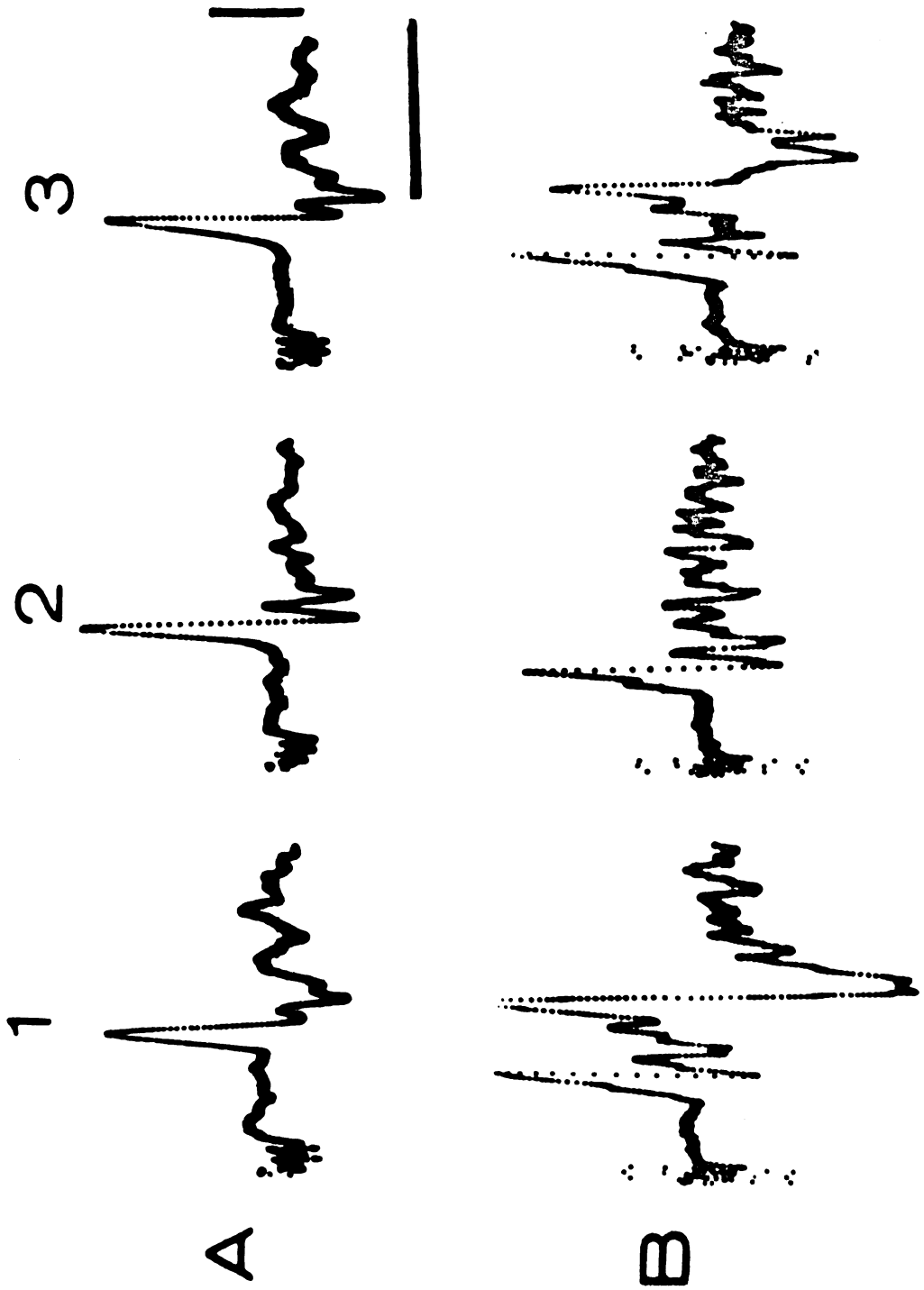

Figure 20

d. Other distinguishing characteristics of baroreceptor reflex-sensitive and -insensitive potentials

The baroreceptor reflex-sensitive and -insensitive sympathetic nerve potentials also could be distinguished on the basis of other characteristics. First, the evoked responses which were not inhibited during the pressor action of norepinephrine were elicited only by trains of pulses. As shown in Figure 21A, they were not observed following the application of a single shock to the medulla. This was the case even when the intensity of stimulation was raised to 15 v, a value in excess of that (6-10 v) needed to induce a maximum response with trains of pulses applied to the same site. These observations suggest that temporal summation was an important factor involved in the initiation of the baroreceptor reflex-insensitive postganglionic potentials. In contrast, baroreceptor reflex-sensitive responses were routinely evoked by single shocks and trains of 3 pulses applied to the same medullary site (Figure 21B). As might be expected, the amplitude of the responses evoked by trains of 3 pulses was larger than that of the potential evoked by a single shock.

Second, the frequency of stimulation at which the sympathetic nerve responses could successfully follow was studied by summing 16-64 responses elicited by repetitive 10 msec trains of 3 pulses applied to the medulla.

Figure 21. Comparison of postganglionic nerve responses evoked by single shocks and trains of 3 stimuli applied to the medulla.

A-1: sum of 16 responses evoked in the external carotid nerve by 10 msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) applied to a site in nucleus reticularis ventralis (R.v.) once each sec. A-2: sum of 16 responses evoked by single shocks (10 v; 0.5 msec) applied to same site in R.v. once each sec. B-1: sum of 32 responses evoked by 10 msec trains of 3 pulses (7 v; 0.2 msec; 300 Hz) applied to a site in nucleus reticularis parvocellularis (R.pc.) once each sec. B-2: sum of 32 responses evoked by single shocks (7 v; 0.2 msec) applied to same site in R.pc. once each sec. Horizontal calibration is 50 msec for records in A and 100 msec for records in B. Vertical calibration is 106 μV in A-1, A-2 and B-1 and is 53 μV in B-2. Records in A and B are from different experiments.

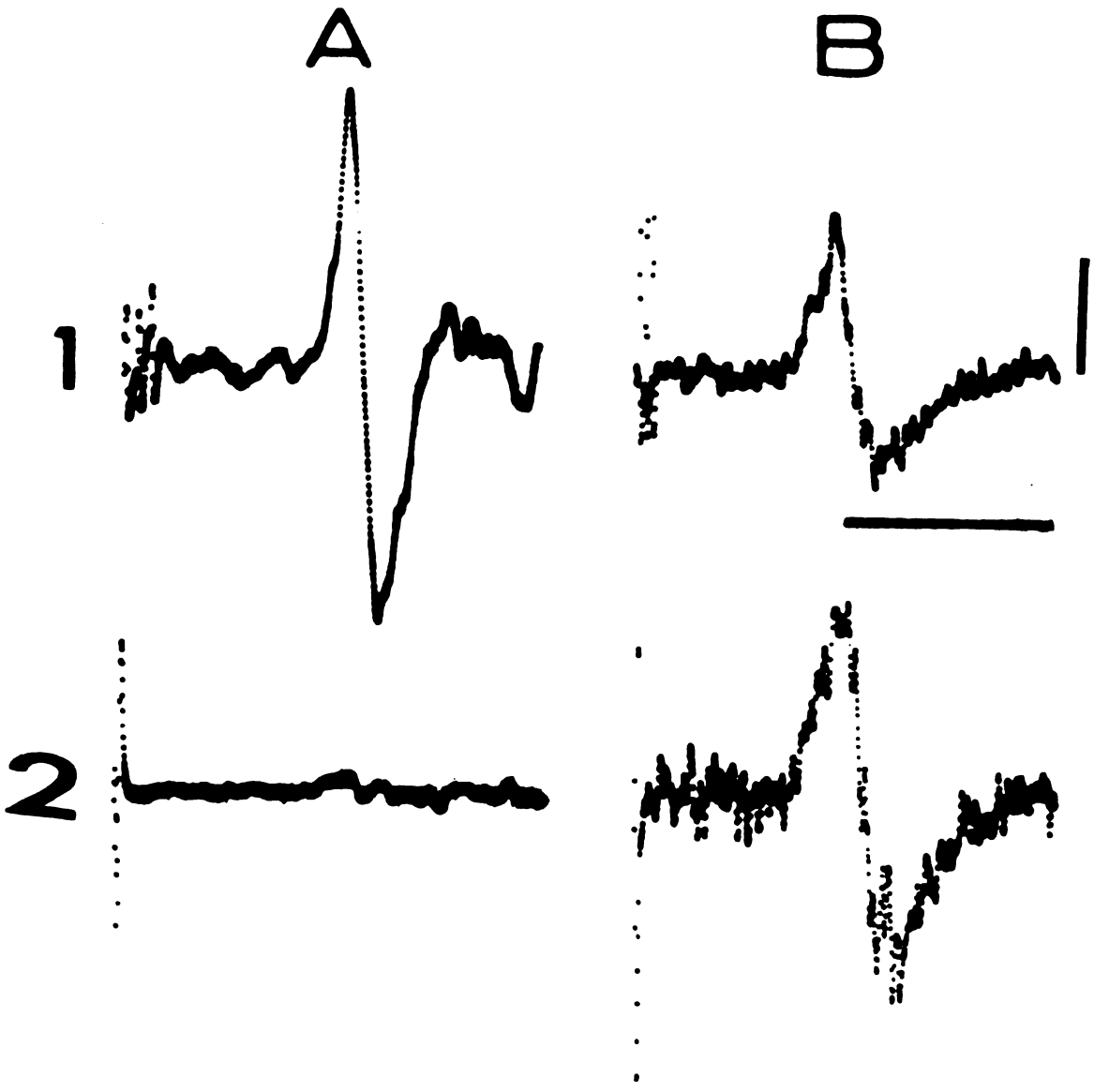

Figure 21

Postganglionic potentials with onset latencies greater than 50 msec (baroreceptor reflex-sensitive) failed to one-half of control peak amplitude when the frequency of stimulation was raised from 1 to 2-6 trains/sec. A representative example is illustrated in Figure 22A. In contrast, the peak amplitude of the shortest latency (34-44 msec) potentials (baroreceptor reflex-insensitive) faithfully followed frequencies of 8-16 trains/sec. In fact, peak amplitude often increased as the frequency of stimulation was raised from 1 to 10 trains/sec. This is shown in Figure 22B. Table 4A summarizes these data. These observations suggest that the differences in onset latency between the baroreceptor reflex-sensitive and -insensitive responses could be due to an increased number of synapses in the pathways mediating the former response (Patton, 1965).

Third, the baroreceptor reflex-insensitive sympathetic nerve potentials (34-44 msec) were sharply defined in contour, while the reflex-sensitive responses (>50 msec) were characterized by a compound action potential with one or more elevations (see Figures 19 and 20). As shown in Table 4A, the mean duration of the negative wave of the potentials which were inhibited during the pressor action of norepinephrine was significantly longer than for those responses which were not inhibited.

Figure 22. Comparison of following frequencies of long and short onset latency sympathetic nerve potentials evoked from the medulla.

A: sum of 32 responses evoked in external carotid nerve by 10 msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) applied to a site in the periventricular gray at frequencies 1, 2 and 4 trains/sec. B: sum of 16 responses evoked by 10 msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) applied to a site in nucleus reticularis ventralis (R.v.) at frequencies of 1, 5 and 10 trains/sec. Horizontal calibration is 100 msec for records in A and 50 msec for records in B. Vertical calibration is 53 μV for records in A and 106 μV for records in B. Records in A and B are from different experiments.

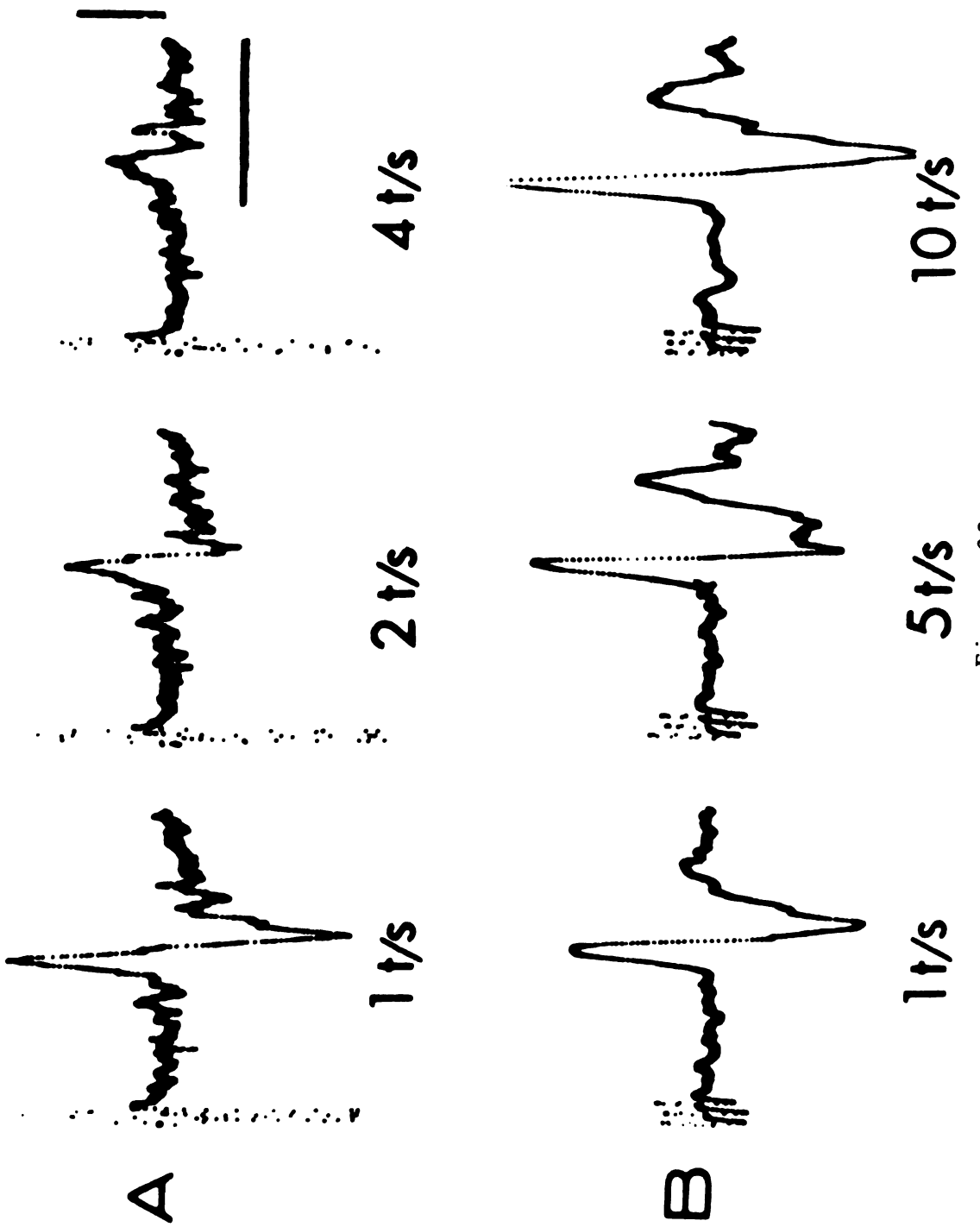

Figure 22

Table 4. Characteristics of baroreceptor reflex-sensitive and -insensitive sympathetic nerve responses evoked from medulla and descending tracts of the midcervical spinal cord

Potential type	Onset latency msec	Duration msec	f50 trains/sec
	A. Medulla		
Blockable	67.9±1.6 (50-99) N=56	24.4±1.0 (15-52) N=56	3.9±0.4 (2-6) N=14
Non-blockable	40.1±0.8 (34-44) N=17	7.6±0.7 (5-16) N=17	9.7±1.1 (8-16) N=7
	B. Spinal cord		
Partially blockable	44.9±0.8 (36-52) N=27	19.9±1.1 (9-32) N=27	3.3±0.3 (2-6) N=25
Non-blockable	34.5±1.0 (26-42) N=23	6.8±0.6 (3-14) N=23	9.5±0.3 (8-16) N=15

Values are means ± S.E. with ranges given in parentheses. Duration: total duration (msec) of negative wave of summed responses; f50: frequency of stimulation with 10 msec trains of 3 pulses at which summed response (16-64 trials) failed to one-half of control peak amplitude. Control peak amplitude was measured from the summed response elicited by a stimulation frequency of 1 train/sec.

The data presented on sympathetic nerve potentials evoked from the medulla appear to support the patterns of intrinsic organization of the brain stem reticular formation proposed on anatomical grounds by Brodal (1957) and

the Scheibels (1958, 1967). That is, sympathetic nerve responses with the longest onset latencies (>50 msec) and durations as well as the lowest following frequencies were evoked from medullary areas whose functional relationship to the reticular formation is considered chiefly sensory. With few exceptions, the shortest latency responses (34-44 msec) were evoked from nucleus reticularis ventralis (R.v.), a medial reticular structure which emits reticulospinal fibers. That these potentials might have monitored the activation of final relay sites in the system pressor pathways also was demonstrated by their synchronous contours and ability to follow the highest frequency of stimulation. It was not surprising to find that the shortest latency postganglionic responses were not blocked when blood pressure was raised with norepinephrine, in view of recent reports (Biscoe and Sampson, 1970a, 1970b; Koizumi *et al.*, 1971) which suggest that baroreceptor-induced inhibition of sympathetic nervous discharge occurs in the brain stem. These responses may have been evoked from medullary sites distal to the locus of baroreceptor-induced inhibition of sympathetic nervous discharge. The long onset latency sympathetic nerve responses evoked from the periventricular gray and dorsolateral reticular formation may have monitored activation of afferent or association components of a pressor pathway. These potentials were inhibited during the pressor action

of norepinephrine. Therefore, it is apparent that they were elicited from medullary sites central to the locus of baroreceptor-induced sympathoinhibition.

It must be emphasized that the data presented thus far fail to offer direct evidence to the effect that the shortest latency (34-44 msec) potentials monitored activation of medullary "cardiovascular" reticulospinal fibers. Indeed, a firm statement cannot be made concerning the nature of and the relationships between the neuronal elements from which the short and long latency potentials were elicited.

At least two possibilities exist regarding interpretation of these data. First, as suggested above, the short and long latency potentials may have monitored electrical activation of "in series" connected components of the same pressor pathway. Alternatively, the potentials recorded may have monitored the activation of parallel pressor pathways descending from forebrain and bulbar regions to the preganglionic sympathetic neurons of the spinal cord. To investigate these possibilities a comparison was made of postganglionic sympathetic nerve responses evoked by stimulation of descending spinal pressor tracts, and hypothalamic and midbrain pressor regions.

3. Postganglionic sympathetic nerve responses evoked by spinal cord stimulation

The spinal cord was stimulated with single shocks and 10 msec trains of 3 pulses at the level of the 4th cervical vertebra in 19 cats. The experimental protocol employed was as follows. With the neuraxis intact, the stimulating electrodes were passed from the ventral to the dorsal surface of the spinal cord. The electrodes were then retracted towards the ventral surface in steps of 0.5-1 mm. Stimulation was performed at each step in the electrode track. Two or more electrode tracks separated by at least 1 mm were explored in each experiment. The spinal cord was stimulated on the side ipsilateral to the recording electrode. Following the mapping procedure, the spinal cord was transected at the level of the 1st cervical vertebra. Mean arterial pressure was raised to about 100 mmHg by the iv infusion of dextran. Those electrode tracks previously explored before C_1 transection were reexamined with electrical stimulation.

a. Effects of baroreceptor reflex activation on evoked potentials

Potentials evoked in the ipsilateral external carotid nerve by 10 msec trains of 3 pulses (2-15 v; 0.2-0.5 msec; 300 Hz) could be divided into 3 groups on the basis of their receptivity to blockade upon baroreceptor reflex activation. The first group contained 54 responses

which were completely inhibited during the rise in blood pressure produced by the iv injection of 0.5-2 μg/kg of norepinephrine (Figure 23). These potentials had onset latencies of 60-120 msec and were elicited primarily from the dorsal funiculus and the region of the dorsolateral white column near the apex of the dorsal horn. As shown in Figure 23D, the potentials which were completely inhibited during the pressor action of norepinephrine were abolished by C_1 spinal cord transection. This observation indicated that these sympathetic nerve responses were elicited by electrical stimulation of ascending spinal tracts.

The second group contained 27 sympathetic nerve responses with onset latencies of 36-52 msec. These responses were partially blocked ($45\pm3\%$; $P<0.05$) during the pressor action of norepinephrine (Figure 24A). Transection of the spinal cord at the 1st cervical vertebra failed to affect the potentials in this group. This is shown in panel 4 of Figure 24A. Thus, it would appear that the potentials which were partially inhibited by baroreceptor reflex activation were elicited from descending spinal pathways. Although norepinephrine raised blood pressure to approximately the same level before and after C_1 transection, the potential illustrated in Figure 24A was inhibited only before the spinal cord was cut. This observation indicates that the inhibitory action of

Figure 23. Effect of baroreceptor reflex activation and C_1 transection on long latency sympathetic nerve potential evoked from dorsal funiculus of midcervical spinal cord.

Ten msec trains of 3 pulses (10 v; 0.2 msec; 300 Hz) were applied to the spinal cord once each sec. Each record is the sum of 16 trials. A: control response. B: response during inhibition of spontaneously occurring postganglionic discharge observed when blood pressure was raised by iv norepinephrine (1 µg/kg). C: response following dissipation of pressor action of norepinephrine. D: response 15 min after transection of the spinal cord at the level of the first cervical vertebra. Horizontal calibration is 100 msec. Vertical calibration is 106 µV.

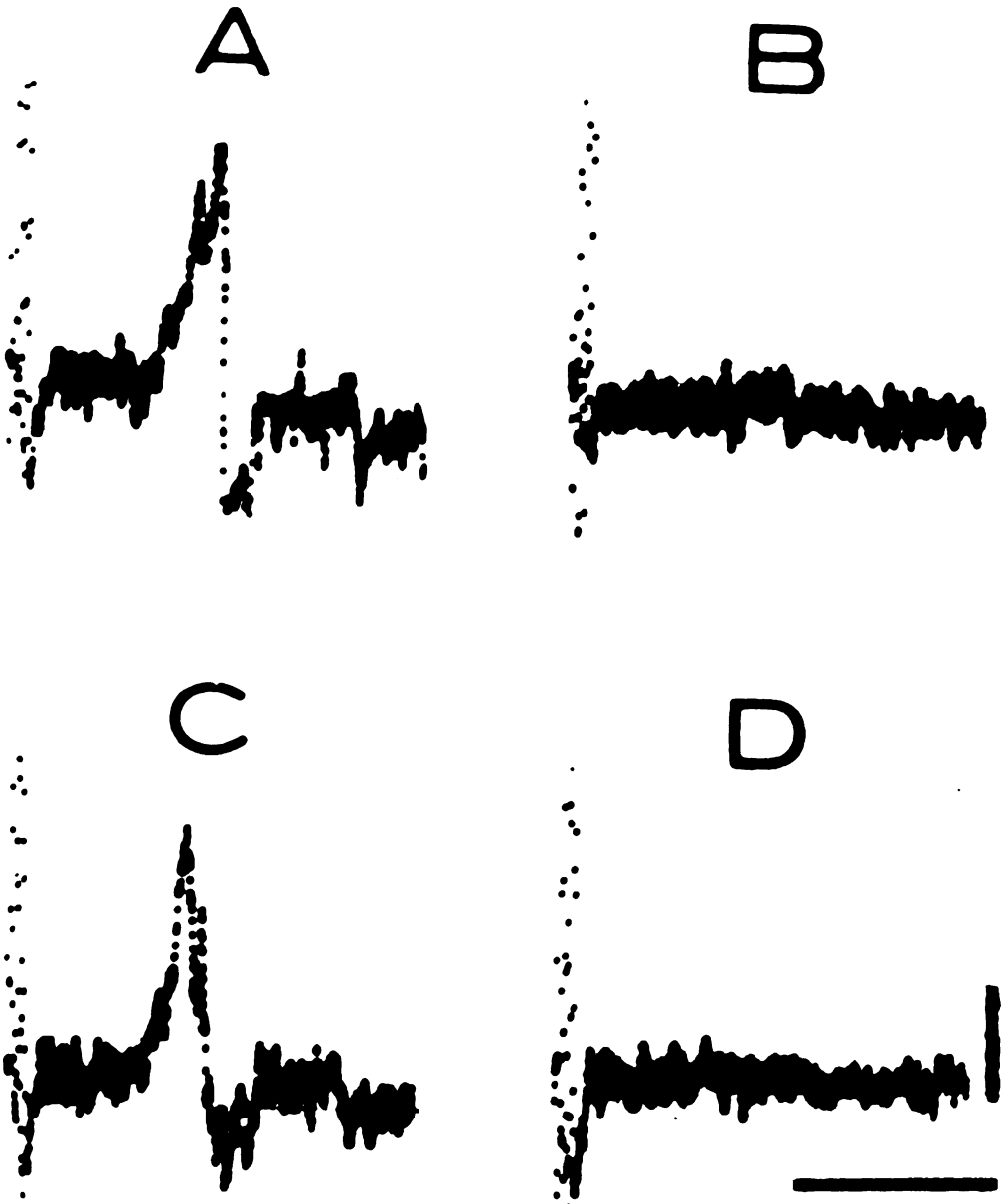

Figure 23

Figure 24. Effect of baroreceptor reflex activation and C_1 transection on short latency sympathetic nerve responses evoked from dorsolateral white column of midcervical spinal cord.

Records in A and B are from different cats. Ten msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz in A; 8 v; 0.2 msec; 300 Hz in B) were applied to the spinal cord once each sec. Each record is the sum of 8 trials. A-1, B-1: control responses. A-2, B-2: responses during inhibition of spontaneously occurring postganglionic discharge observed when blood pressure was raised by iv norepinephrine (1.5 µg/kg in A; 2 µg/kg in B). A-3, B-3: responses following dissipation of pressor action of norepinephrine. A-4, B-4: responses 20 and 10 min, respectively, after transection of the spinal cord at the level of the first cervical vertebra. A-5: response during pressor action of norepinephrine after C_1 transection. Horizontal calibration is 50 msec. Vertical calibration is 106 µV. C: spinal sites from which short latency (36-52 msec) responses were evoked which were partially inhibited upon baroreceptor reflex activation before C_1 transection. D: spinal sites from which short latency (26-42 msec) sympathetic nerve responses were evoked which were not inhibited by baroreceptor reflex activation before C_1 transection.

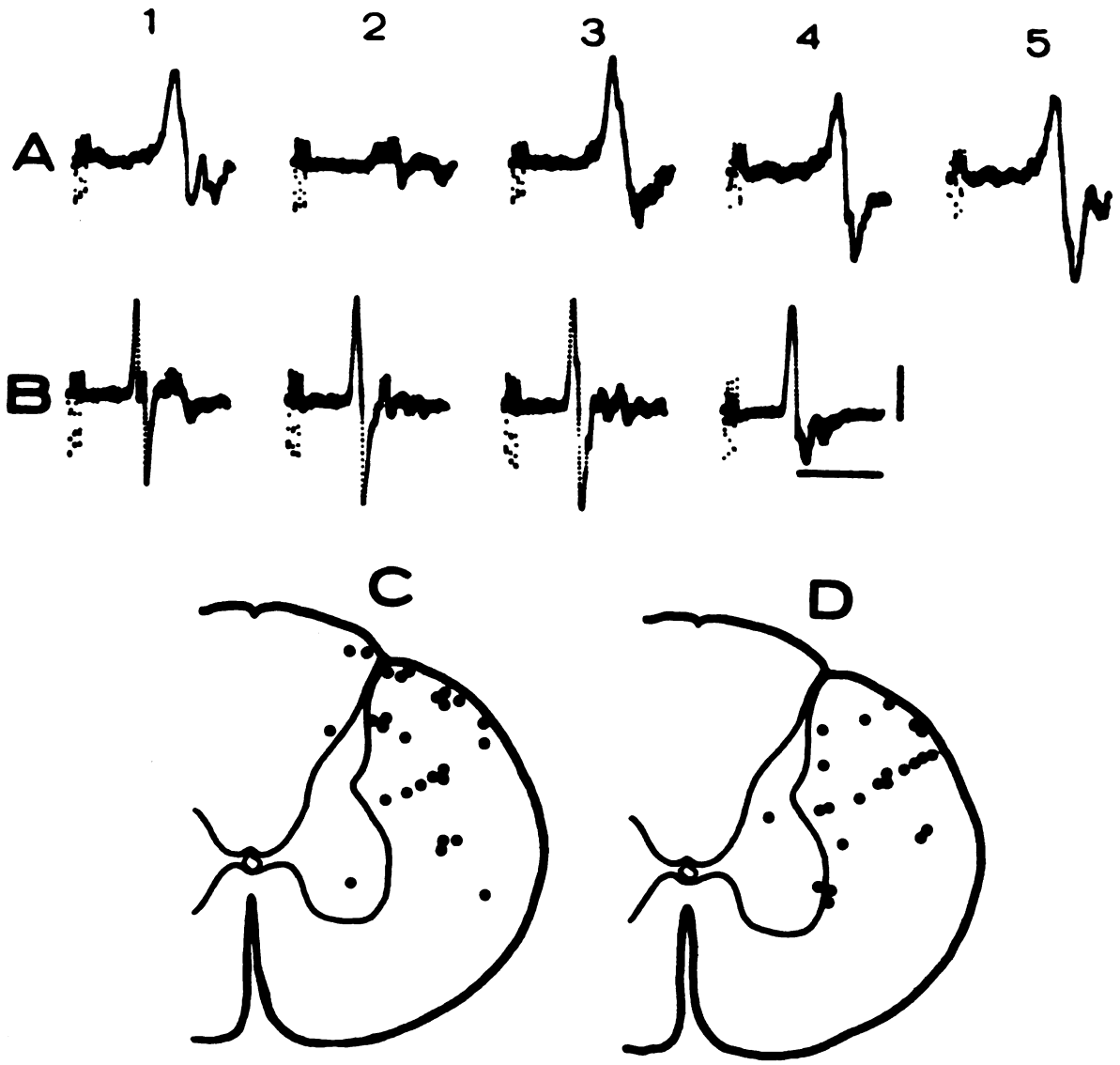

Figure 24

norepinephrine was reflexly mediated and not due to increased oxygen supply to preganglionic neurons (Alexander, 1945) or direct effects at a central (De Groat and Ryall, 1967; Ryall, 1967) or at a ganglionic locus (Marrazzi, 1939; Sakanaski, 1972). That the reflex was most likely of baroreceptor origin was indicated by earlier observation that bilateral section of the IX and X cranial nerves prevented the inhibitory action of norepinephrine on sympathetic nerve responses evoked from the dorsolateral medulla.

The third group contained 23 postganglionic responses with onset latencies of 26-42 msec. These responses were not inhibited during the rise in blood pressure produced by norepinephrine. A representative example is shown in Figure 24B. Spinal cord transection at C_1 also failed to affect significantly the potentials in this group (Figure 24B, panel 4).

Figure 24C and D show the distributions of spinal sites from which the postganglionic potentials in the second and third groups were elicited. Most of the responses were evoked from the dorsolateral white column. This is in accord with the localization of descending spinal pressor tracts reported by others (Illert and Gabriel, 1970; Illert and Seller, 1969; Johnson *et al.*, 1952; Kell and Hoff, 1952; Kerr and Alexander, 1964).

Indeed, a rise in blood pressure was produced by high frequency stimulation (50 Hz) of each of the sites plotted in Figure 24C and D.

b. Other distinguishing characteristics

In addition to the differences in receptivity o inhibition upon baroreceptor reflex activation, the wo groups of short latency descending potentials could be istinguished on the basis of their following frequencies, esponse to single shocks and trains of 3 pulses, and egative wave durations and contours. The sympathetic erve responses which were not blocked by norepinephrine ere observed only in response to stimulation of the spinal ord with trains of 3 pulses. As shown in Figure 25A nd Table 4B, they were not elicited with single shocks. his was the case for the baroreceptor reflex-insensitive otentials evoked from the medulla. In contrast, the otentials which were partially blocked during the pressor ction of norepinephrine were routinely evoked by single hocks as well as by trains of 3 pulses. As shown in igure 25B, the amplitude of the potentials evoked by rains of 3 pulses was larger than that for the response oked by a single shock.

The peak amplitude of the sympathetic nerve responses ich were not blocked during the pressor action of nor- inephrine followed frequencies of stimulation in excess 8 trains/sec. This is shown in Figure 26A. The

Figure 25. Comparison of postganglionic nerve responses evoked by single shocks and trains of 3 pulses applied to descending spinal pathways at the level of the fourth cervical vertebra.

A-1: sum of 64 responses evoked in the external carotid nerve by 10 msec trains of 3 pulses (10 v; 0.2 msec; 300 Hz) applied to a site in the dorsolateral white column once each sec. A-2: sum of 64 responses evoked by single shocks (10 v; 0.2 msec) applied to the same site once each sec. The potential shown in A-1 was not inhibited during baroreceptor reflex activation. B-1: sum of 64 responses evoked by 10 msec trains of 3 pulses (10 v; 0.2 msec; 300 Hz) applied to a site in the dorsolateral white column once each sec. B-2: sum of 64 responses evoked by single shocks (10 v; 0.2 msec) applied to same site once each sec. The response shown in B-1 was partially blocked during the rise in blood pressure produced by norepinephrine. Horizontal calibration is 50 msec for records in B. Vertical calibration is 426 μV for records in A, 106 μV for B-1 and 52 μV for B-2. Records in A and B are from different experiments.

Figure 26. Following frequencies of sympathetic nerve potentials evoked from descending spinal pathways at the level of the fourth cervical vertebra.

A: sum of 64 responses evoked in external carotid nerve by 10 msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) applied to site in dorsolateral white column at frequencies of 1, 5 and 10 trains/sec. The potential shown in A was not inhibited upon baroreceptor reflex activation. B: sum of 64 responses evoked by 10 msec trains of 3 pulses (10 v; 0.2 msec; 300 Hz) applied to dorsolateral white column at 1, 2 and 4 trains/sec. The potential shown in B was partially blocked during the rise in blood pressure produced by norepinephrine. Horizontal calibration is 50 msec for records in A and B. Vertical calibration is 426 μV for records in A and 852 μV for records in B. Records in A and B are from different experiments.

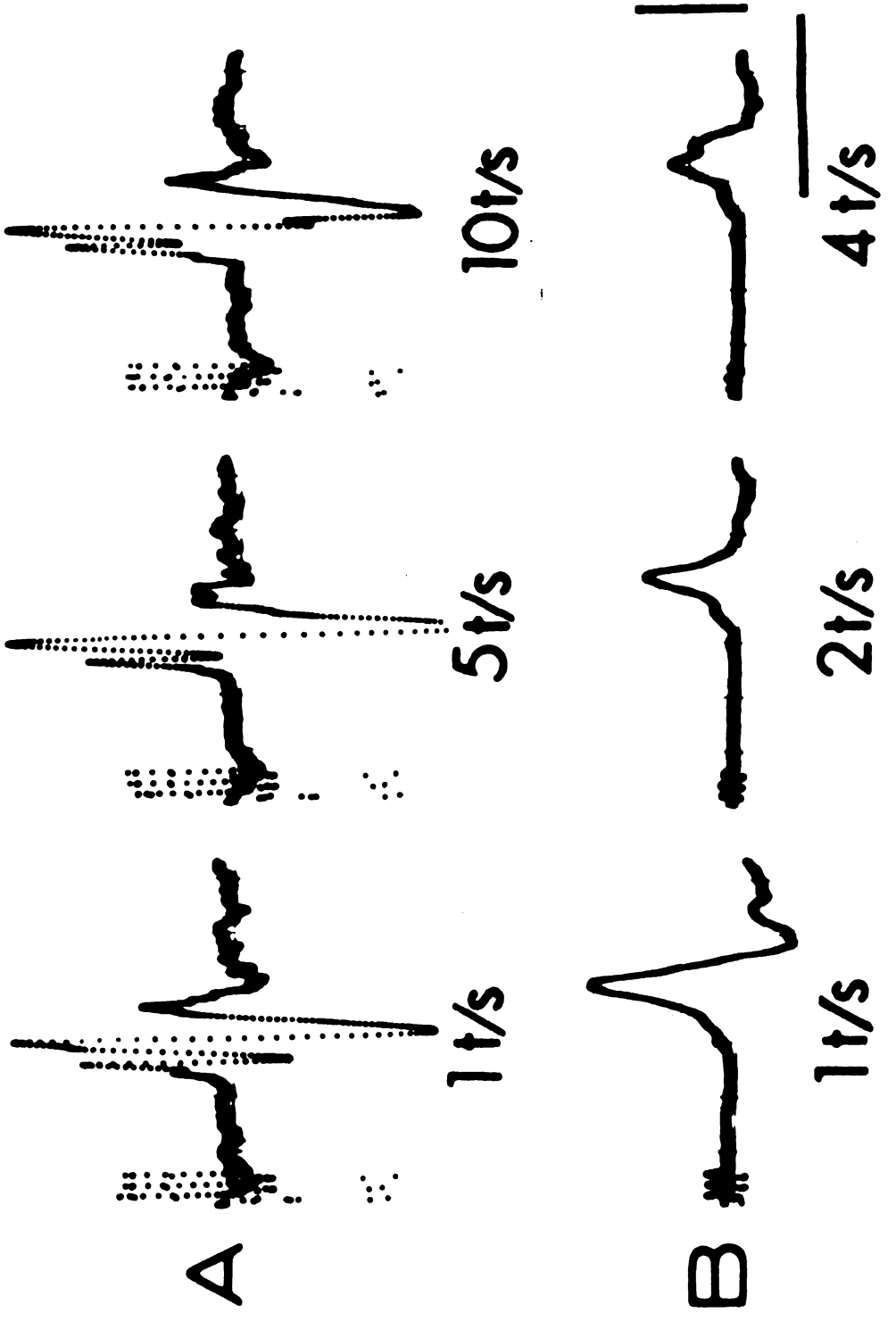

Figure 26

potentials which were partially blocked upon baroreceptor reflex activation failed to one-half of control peak amplitude when the frequency of stimulation was raised from one to 2-4 trains/sec. A representative example is shown in Figure 26B. These data are summarized in Table 4B. Also as shown in Table 4B, those potentials which were partially inhibited during the pressor action of norepinephrine had longer mean onset latencies and durations than the responses which were not blocked.

c. Comparison of central conduction velocities of responses elicited from the medulla and descending spinal pathways

Medullary reticulospinal tracts arise almost exclusively from nucleus reticularis gigantocellularis (R.g.c.) and its caudal extension, R.v. (Brodal, 1957). Since the shortest latency postganglionic sympathetic nerve responses were evoked most often from R.v., it was of interest to compare their central conduction velocities with those of the potentials evoked from descending spinal pathways. Conduction time from the 1st thoracic vertebra to the recording electrode on the postganglionic nerve was subtracted from the onset latency of the potentials evoked from R.v. and the spinal cord. The difference was divided by the distance (50-110 mm) between the stimulating electrodes in the spinal cord or brain and the 1st thoracic vertebra. Table 5 shows that the values of mean conduction

Table 5. Comparison of central conduction velocities of baroreceptor reflex-sensitive and -insensitive sympathetic nerve responses evoked from R.v. in the medulla and descending tracts of the midcervical spinal cord

Region stimulated	Non-blockable potential, m/sec†	Blockable potential, m/sec*†
R.v.	5.4±0.3†† (3.5-6.9) N=14	2.7±0.2** (2.0-3.6) N=12
Spinal cord	4.7±0.5†† (2.9-6.4) N=10	2.3±0.2 1.5-3.2 N=10

Values are means ± S.E. with ranges given in parentheses. *Potentials evoked from R.v. were completely inhibited while those elicited from spinal cord were partially blocked during hypertensive effect of norepinephrine. **Conduction velocities were calculated only for potentials with onset latencies of 50-59 msec. †No significant difference of values within columns. ††Significantly different from blockable potentials (unpaired comparison).

velocity from the site of stimulation to the 1st thoracic vertebra were comparable for the baroreceptor reflex-insensitive potentials evoked from R.v. and the cervical spinal cord. Likewise, the mean central conduction velocity of the shortest onset latency (50-59 msec) baroreceptor reflex-sensitive potentials elicited from R.v. was not significantly different from the value for the potentials evoked from the cervical spinal cord which were partially blocked during the pressor action of norepinephrine. Table 5 also shows that the mean central conduction velocities for the baroreceptor reflex-sensitive and -insensitive

potentials were significantly different from each other at each of the two levels of stimulation.

4. Postganglionic sympathetic nerve potentials evoked by stimulation of hypothalamic and midbrain pressor regions

a. Representative sympathetic nerve responses elicited from hypothalamus and midbrain

Postganglionic sympathetic nerve responses evoked by single shocks and 10 msec trains of 3 pulses applied to the hypothalamus and midbrain were studied in 17 cats. The hypothalamus was stimulated at the level of the mammillary bodies while the midbrain was explored at the midcollicular level. Action potentials were evoked in the external carotid nerve upon stimulation of sites distributed diffusely throughout the posterior and lateral hypothalamus, and the reticular formation and central gray of the midbrain. It is well established that electrical activation of these suprabulbar regions elicits pressor responses (Gebber and Snyder, 1970; Kabat *et al.*, 1935; Manning, 1965; McQueen *et al.*, 1954; Pitts *et al.*, 1941; Ranson and Magoun, 1939; Wang and Ranson, 1939b). And, as I found, a rise in blood pressure was produced by high frequency (50 Hz) stimulation of each site from which a sympathetic nerve potential was evoked.

The sympathetic nerve responses illustrated in Figure 27 are typical of those routinely elicited from the

Figure 27. Representative responses evoked in the ipsilateral external carotid nerve by stimulation of the hypothalamus and midbrain reticular formation.

Ten msec trains of 3 pulses (10 v; 0.2 msec; 300 Hz) were applied to the hypothalamus and midbrain once each sec. All records are from the same cat. Each potential represents the sum of 64 trials. A: a frontal section which includes the hypothalamus at the level of the mammillary body. B: a midbrain section about 1 mm rostral to the midcollicular level. Horizontal calibrations for A and B are 100 msec. Vertical calibrations for A and B are 212 μV. Abbreviations are those of Nauta (1958). BC: brachium conjunctivum; CM: mammillary body; H: field H of Forel; HI: nucleus lateralis habenulae; IP: nucleus interpeduncularis; LM: medial lemniscus; P: cerebral peduncle; PD: fasciculus predorsalis; PVP: nucleus periventricularis posterior hypothalami; RF: fasciculus retroflexus; RS: rubrospinal tract; VPM: nucleus ventralis posteromedialis.

hypothalamus and midbrain. Unlike the potentials evoked from the medulla and spinal cord, most of the responses elicited by a train of 3 pulses took the form of a repetitive discharge which lasted for 40-250 msec. The onset latency of the repetitive discharges evoked from the lateral and posterior hypothalamic areas ranged from 41-71 msec. The onset latency for the repetitive discharges elicited by stimulation of the midbrain tegmentum and central gray ranged from 37-60 msec. Repetitive discharges with the largest amplitude spikes and the longest durations most often were evoked from electrode tracks which were more than 1.5 mm lateral to the midline at both the midbrain and hypothalamic levels of stimulation. Longer latency (70-140 msec) sympathetic nerve responses which took the form of a smooth wave were occasionally evoked from an area just dorsolateral to the mammillary body (Figure 27A, trace 5). With the exception of these responses, a relationship between onset latency and the site of initiation of the postganglionic sympathetic nerve potentials could not be discerned. This was in contrast to the results reported for the postganglionic responses evoked by stimulation of the medulla.

b. Baroreceptor reflex-induced inhibition of evoked potentials

The effect of raising mean arterial pressure with iv norepinephrine (0.5-2 μg/kg) was tested on the

sympathetic nerve potentials evoked by trains of 3 pulses applied to the hypothalamus and midbrain in each of the 17 experiments performed. The early spikes contained within repetitive discharges with onset latencies of 37-52 msec were not inhibited during the pressor action of norepinephrine. This is shown for responses elicited from the hypothalamus (Figure 28A) and midbrain (Figure 28B). In contrast, the late components of the repetitive discharges were partially or completely blocked during the rise in blood pressure produced by norepinephrine (Figure 28A-B).

Norepinephrine inhibited all components of repetitive discharges with onset latencies in excess of 56 msec. A typical example of one such response which was evoked from the hypothalamus is shown in Figure 28C. Usually, the first few spikes contained within these longer latency repetitive discharges were not blocked as well as were the later occurring spikes.

The longest latency (70-140 msec) responses evoked from the area just dorsolateral to the mammillary body were completely inhibited during the rise in blood pressure produced by norepinephrine. A representative example is illustrated in Figure 28D.

c. Temporal characteristics

A comparison of the sympathetic nerve responses evoked by stimulation of the hypothalamus with single shocks

Figure 28. Effect of baroreceptor reflex activation on sympathetic nerve potentials evoked by stimulation of pressor sites in lateral hypothalamus (A, C-D) and midbrain tegmentum (B) in 4 experiments.

Ten msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) were applied to each site once each sec in B and D and twice each sec in A and C. Records in A and C represent the sum of 32 trials. Records in B and D represent sum of 16 trials. A-1, B-1, C-1, D-1: control responses; A-2, B-2, C-2, D-2: responses during pressor response induced by iv norepinephrine (1-2 μg/kg). A-3, B-3, C-3, D-3: responses following dissipation of pressor effect. Horizontal calibration is 100 msec in all records. Vertical calibration is 134 μV for records in A, 67 μV for records in B and D and 106 μV for records in C.

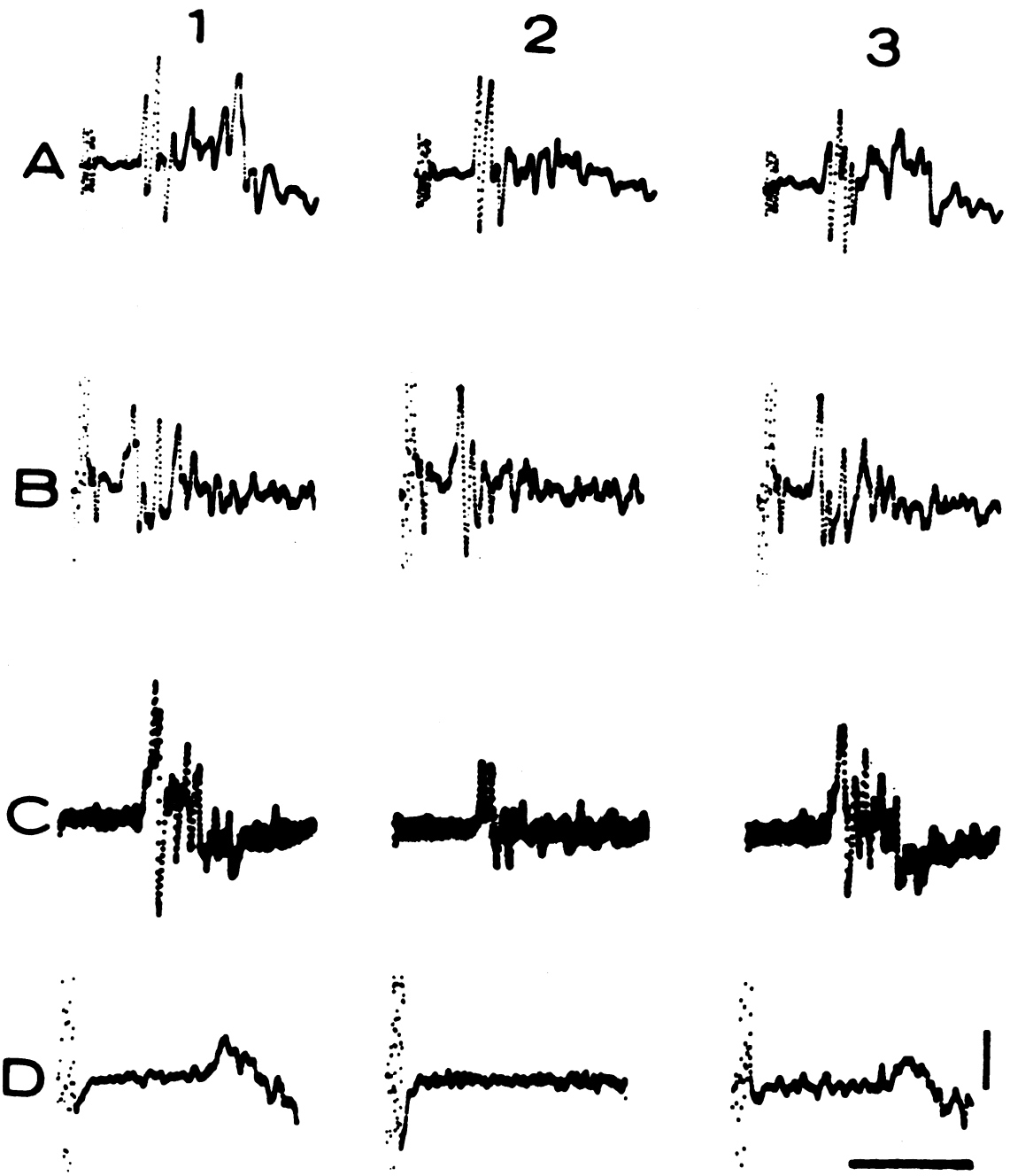

Figure 28

and trains of 3 pulses is shown in Figure 29. Repetitive discharges were routinely evoked by single shocks as well as by trains of 3 pulses (Figure 29A). As was the case for potentials evoked from medulla and spinal cord, single shocks failed to elicit the early spikes which could not be inhibited during the pressor action of norepinephrine. The longest latency responses evoked from the region near the mammillary body could be evoked either by single shocks or trains of 3 pulses (Figure 29B).

The peak amplitude of the early spikes which were not blocked during the pressor action of norepinephrine faithfully followed frequencies of stimulation up to 4 trains/sec. This is shown in Figure 30A. The early spikes usually failed to one-half of control amplitude at frequencies of stimulation between 6-8 trains/sec. This was in contrast to the higher following frequencies exhibited by those sympathetic nerve responses evoked from the medulla and spinal cord which were not blocked during the pressor action of norepinephrine. The late components of the repetitive discharges evoked from the hypothalamus and midbrain failed to one-half control amplitude at frequencies of stimulation between 2-6 trains/sec. This can be observed in Figure 30A. The longest latency (70-140 msec) potentials evoked from an area just dorsolateral to the mammillary body had the lowest following frequencies. These postganglionic

Figure 29. Comparison of postganglionic nerve responses evoked by single shocks and trains of 3 pulses applied to pressor sites in the lateral hypothalamus.

A-1: sum of 128 responses evoked in external carotid nerve by 10 msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) applied to a hypothalamic site once each sec. A-2: sum of 128 responses evoked by single shocks (10 v; 0.5 msec) applied to same site once each sec. B-1: sum of 128 responses evoked by 10 msec trains of 3 pulses (10 v; 0.5 msec; 300 Hz) applied to a hypothalamic site just dorsolateral to the mammillary body once each sec. B-2: sum of 128 responses evoked by single shocks (10 v; 0.5 msec) applied to same site once each sec. Horizontal calibration is 100 msec for records in A and B. Vertical calibration is 536 μV for records in A and 134 μV for records in B. Traces A and B were from two different cats.

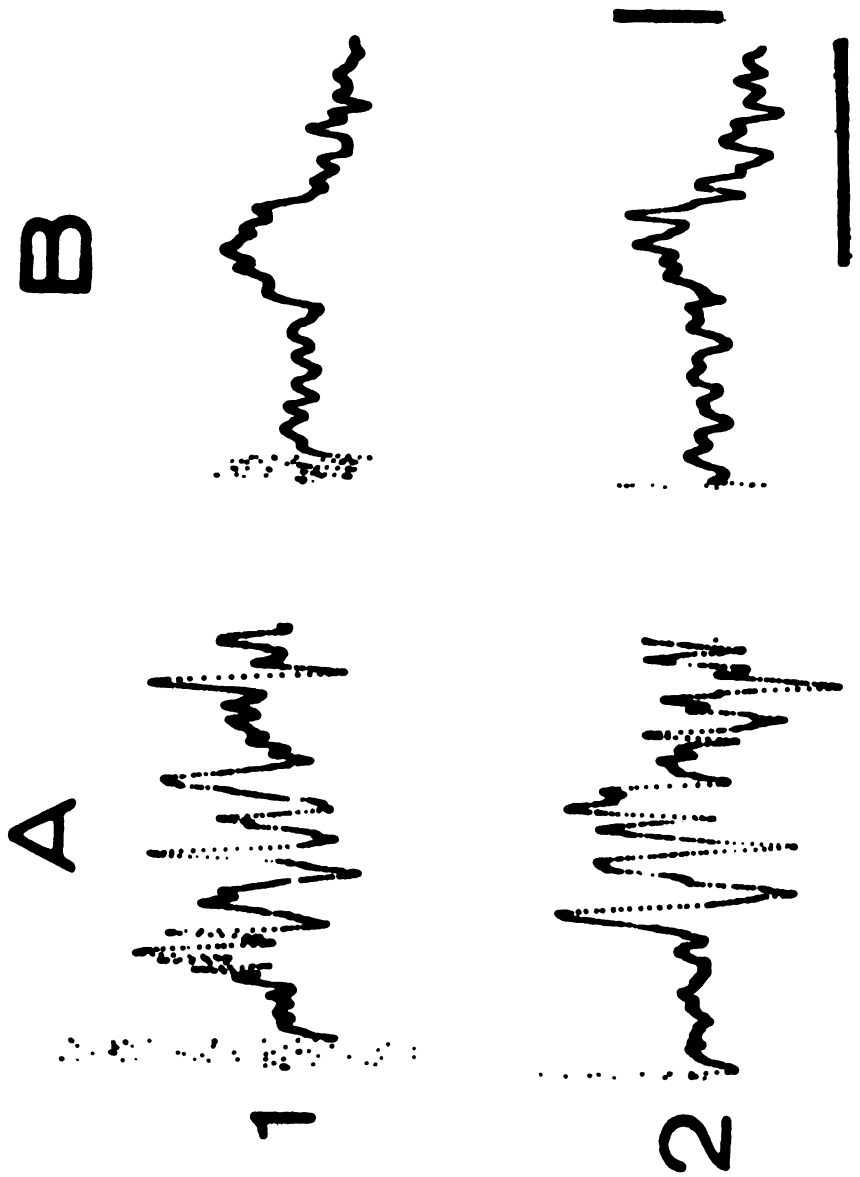

Figure 29

Figure 30. Following frequencies of sympathetic nerve potentials evoked from the hypothalamus.

A: sum of 32 responses evoked in ipsilateral external carotid nerve by 10 msec trains of 3 pulses (10 v; 0.2 msec; 300 Hz) applied to a site in the lateral hypothalamus at frequencies of 1 and 4 trains/sec. B: sum of 64 responses evoked by trains of 3 pulses (10 v; 0.5 msec; 300 Hz) applied to a hypothalamic site just dorsolateral to the mammillary body at frequencies of 1 and 2 trains/sec. Horizontal calibration is 100 msec for records in A and B. Vertical calibration is 268 μV for records in A and 134 μV for records in B. Records in A and B are from different experiments.

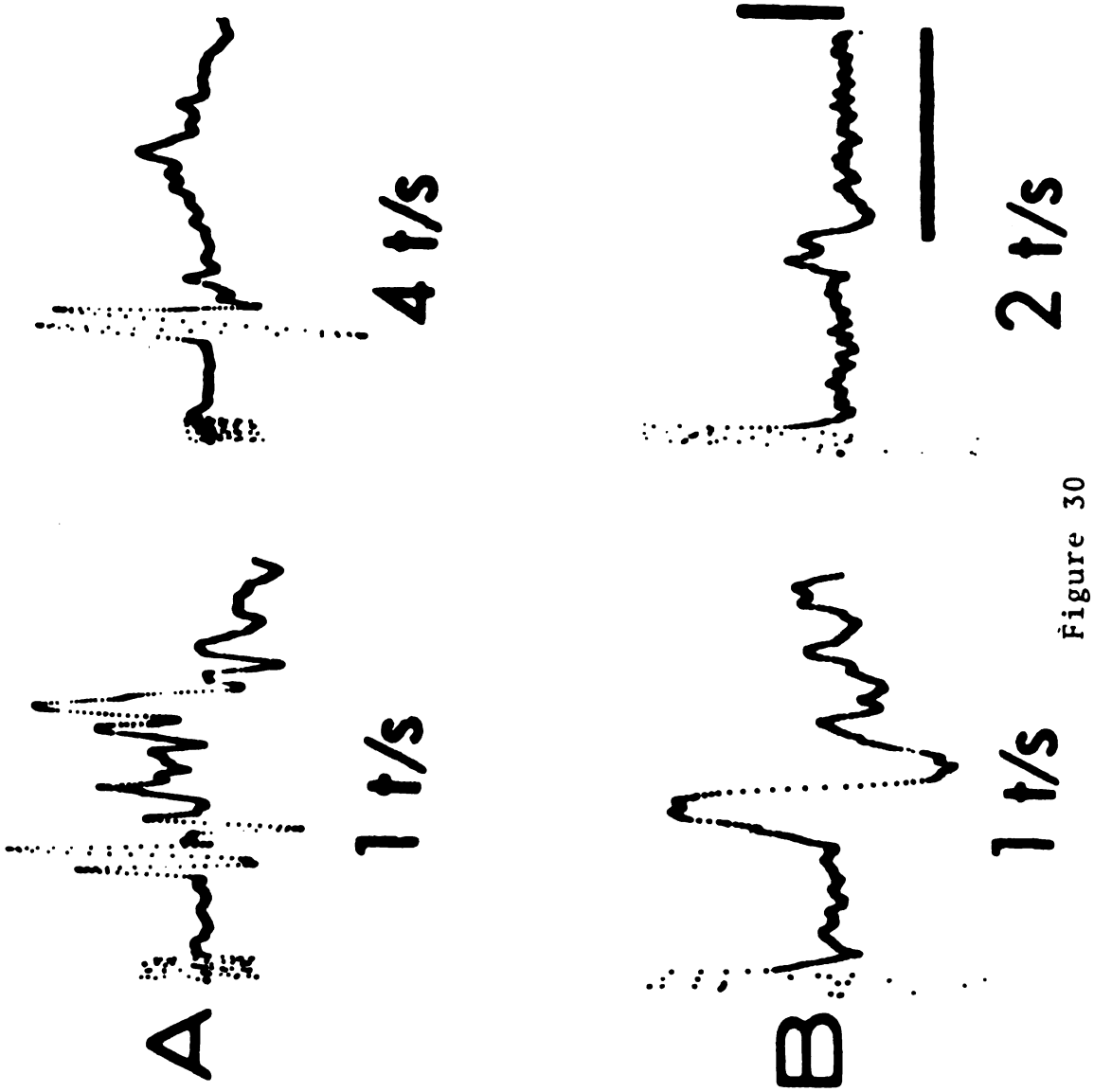

Figure 30

nerve responses failed to one-half control amplitude at frequencies of stimulation below 4 trains/sec (Figure 30B).

To briefly summarize, the results presented in Section II.A. demonstrate that potentials evoked in the external carotid postganglionic sympathetic nerve by stimulation of sites in the brain and spinal cord could be classified into two groups on the basis of their receptivity to blockade by baroreceptor reflex activation. The first group was composed of long onset latency responses which were blocked during baroreceptor reflex activation. The second group contained short onset latency potentials that were not inhibited during baroreceptor reflex activation. When evoked from hypothalamus, brain stem and spinal nerves, the baroreceptor reflex-sensitive and -insensitive potentials could be further distinguished by their contours, ability to follow high frequency stimulation, and response patterns to single shocks and trains of stimulation. These observations led to the hypothesis that vasopressor outflow from the brain to the external carotid nerve is distributed over two parallel systems of pathways. Interpretation of these results must be qualified, however, since the data were derived from a single postganglionic sympathetic nerve and, hence, may be somewhat specific to the vasculature supplied. Therefore, it was decided to examine the relationship

between the responses evoked in the splanchnic nerve by trains of stimuli applied to the neuraxis and the baroreceptor reflex arc. The splanchnic nerve and the splanchnic vascular bed have long been recognized to be important in the maintenance of blood pressure (Burton-Opitz and Edwards, 1916; Gootman and Cohen, 1970; Grayson and Mendel, 1965; Kremer and Wright, 1932).

B. Responses Evoked in the Splanchnic Preganglionic Sympathetic Nerve by Stimulation of Vasopressor Sites in the Medulla and the Spinal Cord

The effect of baroreceptor reflex activation or stimulation of depressor sites in the paramedian nucleus (10 v; 0.5 msec; 50 Hz) was compared on potentials evoked in the splanchnic nerve by stimulation of pressor sites in the dorsolateral medullary reticular formation and the dorsolateral white columns of the fourth cervical spinal segment. Sixteen preganglionic responses evoked by a 10 msec train of 3 pulses (10 v; 0.5 msec) applied to medullary or spinal pressor sites once every 2 sec were summed before and during the period of maximum inhibition of spontaneously occurring SND associated with the pressor action produced by the iv injection of 1 μg/kg of norepinephrine (i.e., baroreceptor reflex activation, see section II.A.2.c. of Results) or the depressor effect of paramedian stimulation. Although a train of pulses applied to a pressor site failed to change blood pressure,

stimulation at a frequency of 50 Hz for 15 sec raised blood pressure in excess of 40 mmHg. Independent of onset latency, each and every splanchnic nerve response evoked from medullary and spinal pressor sites was inhibited by baroreceptor reflex activation or paramedian stimulation. Representative examples are shown in Figure 31. Baroreceptor reflex-insensitive responses could not be demonstrated in the splanchnic nerve.

The summed splanchnic nerve potentials evoked from medullary pressor sites were inhibited to a significantly greater degree than those evoked from spinal pressor sites (Figure 31 and Table 6). This observation suggests that

Table 6. Effect of baroreceptor reflex activation (BRA)(1) and stimulation of paramedian nucleus on computer summed splanchnic nerve discharges evoked by 10 msec trains of 3 pulses applied to medullary and midcervical spinal pressor sites

	% Δ in responses evoked from:	
	Medulla (42-84)[2]	Spinal cord (25-45)[3]
BRA	-97±3(12)*	-72±8(18)
Paramedian stim.	-93±4(13)*	-70±8(18)
C_1 transection	---	-40±9(10)†

Values are mean ± S.E. with (N). (1) induced by raising systemic blood pressure (iv injection of 1 μg/kg of norepinephrine). Range of onset latencies for splanchnic nerve responses evoked from medulla (2) and spinal cord (3) are given in parentheses. * Significantly different from effect produced on splanchnic nerve responses evoked from spinal cord. † Significantly different from effect produced either by BRA or paramedian stimulation.

Figure 31. Effect of baroreceptor reflex activation (norepinephrine, 1 μg/kg, iv) or paramedian stimulation (10 v; 0.5 msec; 50 Hz) on splanchnic preganglionic nerve response evoked by stimulation of a medullary and a spinal pressor site in the same cat.

A1: computer summed traces (16 sweeps) of SND evoked by a 10 msec train of 3 pulses (10 v; 0.5 msec) applied once every 2 sec to a pressor site in the dorsolateral medullary reticular formation. A2: same, but during the peak pressor action of norepinephrine. A3: same, but during paramedian stimulation. B1: computer summed traces (16 sweeps) of SND evoked by stimulation of a pressor site in the dorsolateral white column of the 4th cervical spinal segment. B2,3: as described for A2,3. Post C1: response evoked from the spinal pressor site 10 min after C1 transection. Horizontal calibration is 100 msec. Vertical calibration is 133 μV.

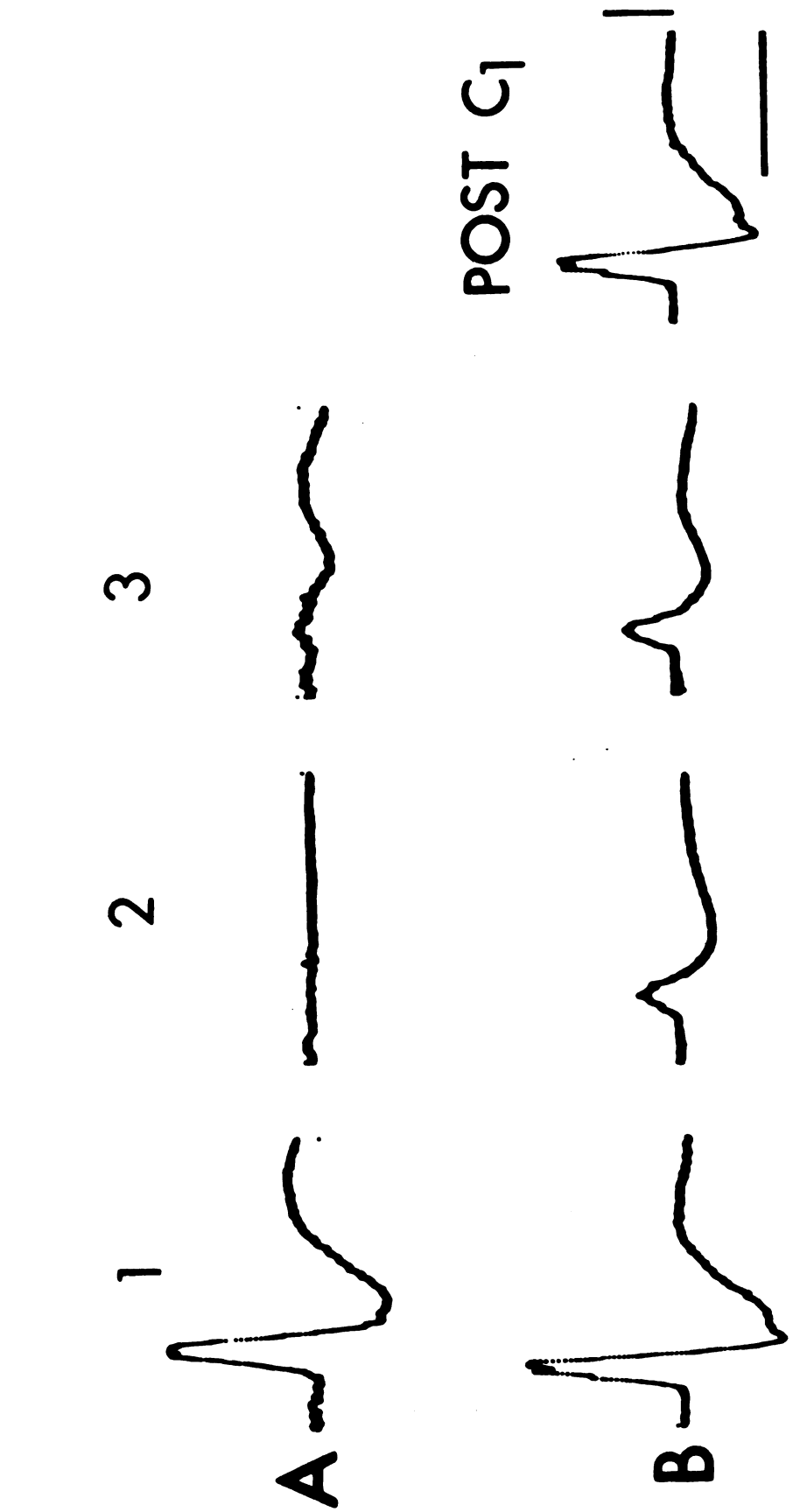

Figure 31

baroreceptor reflex-induced sympathoinhibition occurs at both spinal and brain stem levels. Two observations indicated that the splanchnic nerve potentials evoked from the dorsolateral white columns of the midcervical spinal cord monitored the activation of descending pressor tracts. First, the onset latency of the splanchnic potential elicited from spinal pressor sites was shorter than for the potential evoked from the medulla (Figure 31). Second, C_1 transection failed to abolish the splanchnic nerve responses evoked from spinal pressor sites (Figure 31 and Table 6). Baroreceptor reflex activation or paramedian stimulation reduced the splanchnic nerve responses evoked from spinal pressor sites to a significantly greater extent than did C_1 transection (Table 6). This observation indicates that the baroreceptor induced attenuation of amplitude was produced not only by a decrease in subliminal fringe of the preganglionic neurons due to removal of spontaneously occurring excitatory bombardment from medullary vasomotor centers, but also by an active spinal component of reflex-induced sympathoinhibition. Thus, the central components of "vasoconstrictor" pathways distributed to the vascular beds innervated by the splanchnic and external carotid nerves are organized quite differently.

The function of the baroreceptor reflex-insensitive potentials deserves further comment. The cat external

carotid sympathetic nerve is considered to be entirely vasoconstrictor in function by all acceptable criteria. For two reasons, it may be questioned whether the shortest latency potentials (34-44 msec) evoked in this nerve monitor activation of vasopressor pathways: (1) these potentials were not inhibited during baroreceptor reflex activation; (2) the baroreceptor reflex-insensitive responses were not elicited in the splanchnic sympathetic nerve. With regard to the external carotid nerve, Bishop and Heinbecker (1932) demonstrated that cervical sympathetic nerve fibers innervating pilomotor muscles have essentially the same thresholds of activation as pre- and postganglionic fibers subserving a vasoconstrictor function. Thus, baroreceptor reflex-insensitive potentials evoked from the neuraxis might be monitoring central pathways serving a pilomotor function. For these reasons, I decided to examine the response patterns exhibited by individual sympathetic neurons upon stimulation of pressor sites in the brain stem and spinal cord.

C. Relationships Between Medullary and Spinal Vasomotor Regions, and Single Preganglionic Sympathetic Neurons (PSN)

The data presented in this section were obtained in order to answer the following question. Do the baroreceptor reflex-sensitive and -insensitive pressor

pathways converge onto the same PSN, or do the two systems of pathways remain separated at the level of the preganglionic neuron? If the baroreceptor reflex-sensitive and -insensitive response patterns are exhibited by single "vasoconstrictor" PSN, then it is highly probable that the two central pathways mediate vasopressor responses.

1. Identification of preganglionic sympathetic units

Preganglionic sympathetic neurons (N=161) lying within the first to third thoracic spinal segments were identified antidromically upon application of single shocks (2-12 v; 0.05-0.1 msec) once every 2 sec to the cervical sympathetic nerve. The recording microelectrode was placed on or near to the dorsal sulcus and lowered in steps of 1-50 μ until a unit was located. More than 90% of the sympathetic units identified were located 1-2 mm below the dorsal surface of the cord. The amplitude of the unit discharges ranged from 50 μv-1 mv and often were recorded in the absence of potentials from other cells. The duration of the spike was 1-1.2 msec. The form of the unit discharge usually consisted of a negative-positive or positive-negative-positive wave complex. As reported by Fernandez de Molina *et al.* (1965), the negative wave of most cells appeared to contain initial

segment (IS) and soma-dendritic (SD) components. Unit discharges with amplitudes greater than 700 μv took the form of a large initial positive wave (spike component) followed by a smaller negative wave, suggesting that the electrode may have been pressing against the soma membrane (Burns, 1961). The same unitary spike could be recorded over a dorso-ventral distance of approximately 150 μ. More than 50% of the preganglionic units were held for at least 1 hr.

Potentials were considered unitary and elicited antidromically if they satisfied the following criteria: (1) the onset latency and amplitude remained essentially constant to repetitive application of single shocks to the cervical sympathetic nerve; (2) the response was all or none and exhibited a sharp threshold; and (3) the IS component of the spike followed frequencies of stimulation greater than 70 Hz.

Onset latencies of antidromically evoked unit discharges were 7-40 msec, a range which approximated the total duration of the four groups (C_1-C_4) of the compound action potential elicited in the cervical sympathetic nerve by single shocks (10 v; 0.1 msec) applied to the thoracic ventral roots (Figure 32). The range of axonal conduction velocities (1.5-11 m/sec) was similar to those reported previously for preganglionic neurons in the cervical sympathetic nerve (Polosa, 1967), splanchnic

Figure 32. Preganglionic cell groups contained within the cervical sympathetic trunk of the cat.

Records A-E are from different cats. A: compound action potential elicited in cervical sympathetic trunk by supramaximal shock (10 v; 0.1 msec) applied to third thoracic ventral root. Negativity is recorded as an upwards deflection in this and all subsequent traces. B-E: discharges of four different preganglionic neurons elicited antidromically by single shocks (4-8 v; 0.1 msec) applied to cervical sympathetic nerve. Each unitary discharge corresponds to a different component of the potential in A. Vertical calibration is 50 μV in A, B and E, 200 μV in C and 500 μV in D. Horizontal calibration is 20 msec.

nerve (Hongo and Ryall, 1966) and thoracic sympathetic rami (Fernandez de Molina *et al.*, 1965).

2. Central activation of PSN

Thirty-nine of the 161 preganglionic sympathetic units identified antidromically were activated by single shocks or 5 msec trains of 3 pulses applied to pressor sites in the medulla at a level just rostral to the obex. High frequency (50 Hz) stimulation of these sites for 10-15 sec always raised mean blood pressure. None of the 39 units could be activated by stimulation of medullary sites which failed to raise blood pressure. It was assumed that the unit discharged by central stimulation was the one identified by stimulation of the cervical sympathetic nerve if the amplitude, duration and shape of the ortho- and antidromically elicited responses were similar. In those instances where there was some doubt due to low signal/noise ratios or multiunit recordings, identification was verified by collision between the ortho- and antidromically evoked spikes. Axonal conduction velocities (Figure 33) of all but 4 of the 39 units activated by stimulation of medullary pressor sites were within the range (4.4-10 m/sec) exhibited by the second component (C_2) of the compound preganglionic action potential elicited by ventral root stimulation (Figure 32). This preganglionic fiber group is known to

Figure 33. Histogram of axonal conduction velocities of PSN activated by central stimulation.

Histogram of the axonal conduction velocities of 39 preganglionic neurons which were activated by stimulation of the medullary pressor region. Shaded portion of each bar represents the number of units which exhibited spontaneous discharges.

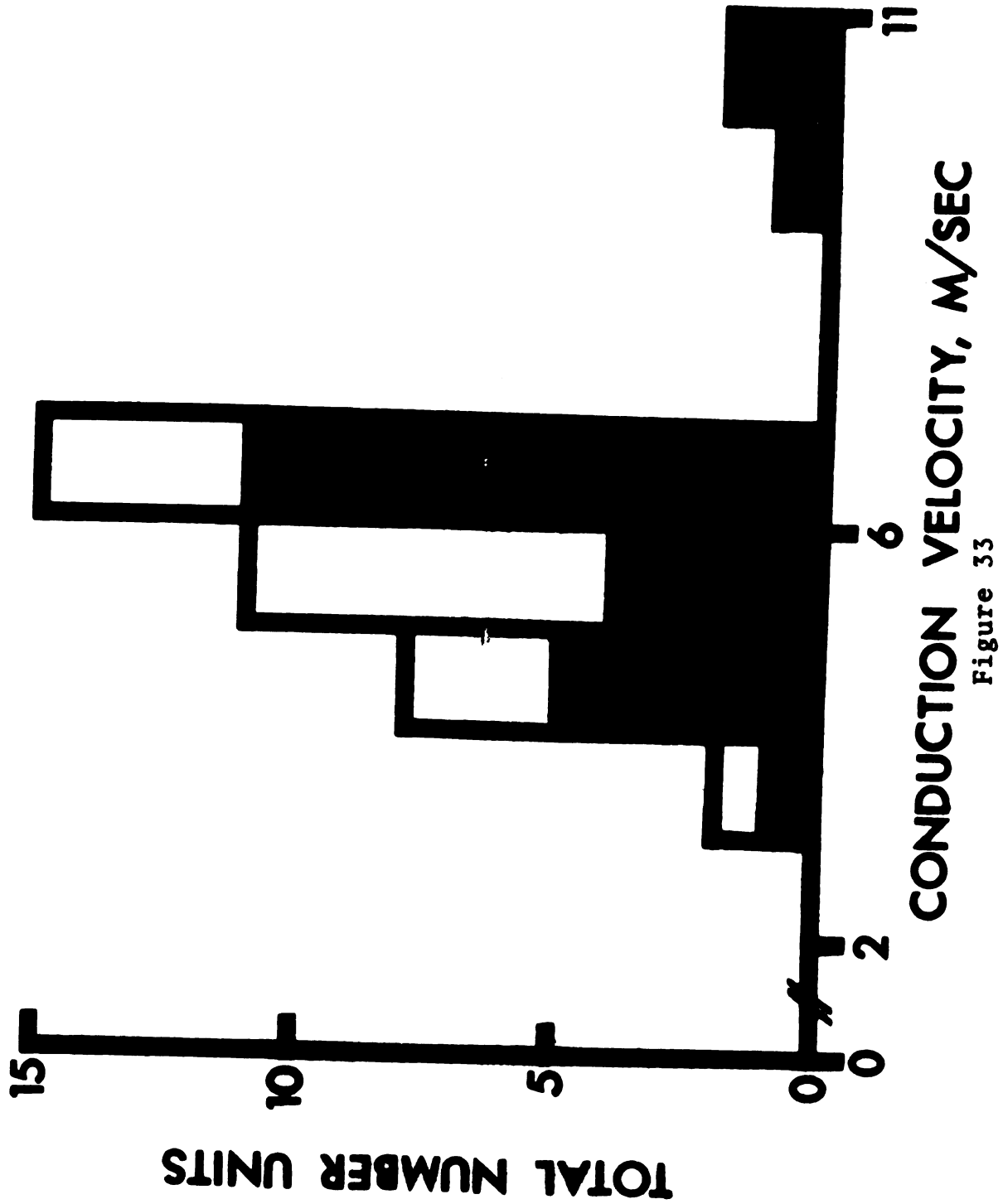

Figure 33

innervate ganglion cells which subserve vasoconstrictor function (Bishop and Heinbecker, 1932).

a. Spontaneous unitary discharge

Twenty-four of the 39 preganglionic neurons which were activated by medullary stimulation exhibited spontaneous discharges (Figure 33). The mean discharge rate of spontaneously active cells was 0.6±0.1 impulses/sec. This value is somewhat lower than that (1.7-2.9 impulses/sec) reported by Jänig and Schmidt (1970) for sympathetic fibers of the cervical nerve.

Figure 34 illustrates some of the characteristics of the spontaneous discharges of single preganglionic sympathetic units. Interspike intervals were quite variable with the greatest probability of discharge occurring during early and mid-diastole (Figure 34A). The neuron occasionally discharged during or near the peak systolic phase of the femoral pulse wave. Increases in systemic blood pressure produced by the intravenous injection of 1-2 μg/kg of norepinephrine bitartrate were accompanied by inhibition of spontaneously occurring unitary discharge (Figure 34B). As was previously reported in the Results section, NE-induced inhibition of spontaneously occurring discharges recorded from the postganglionic sympathetic external carotid nerve is eliminated by bilateral section of the baroreceptor nerves.

Figure 34. Spontaneous discharge of preganglionic sympathetic neuron.

A: continuous records of blood pressure (mmHg) in upper traces and unit discharges (displayed as 5 v pulses supplied to Grass polygraph by Window Discriminator Module) in lower traces. Horizontal calibration is 1 sec. B: inhibition of spontaneously occurring discharges of same unit during pressor action of NE (1 μg/kg, iv). NE was injected at downward deflection of time base (1 sec/division).

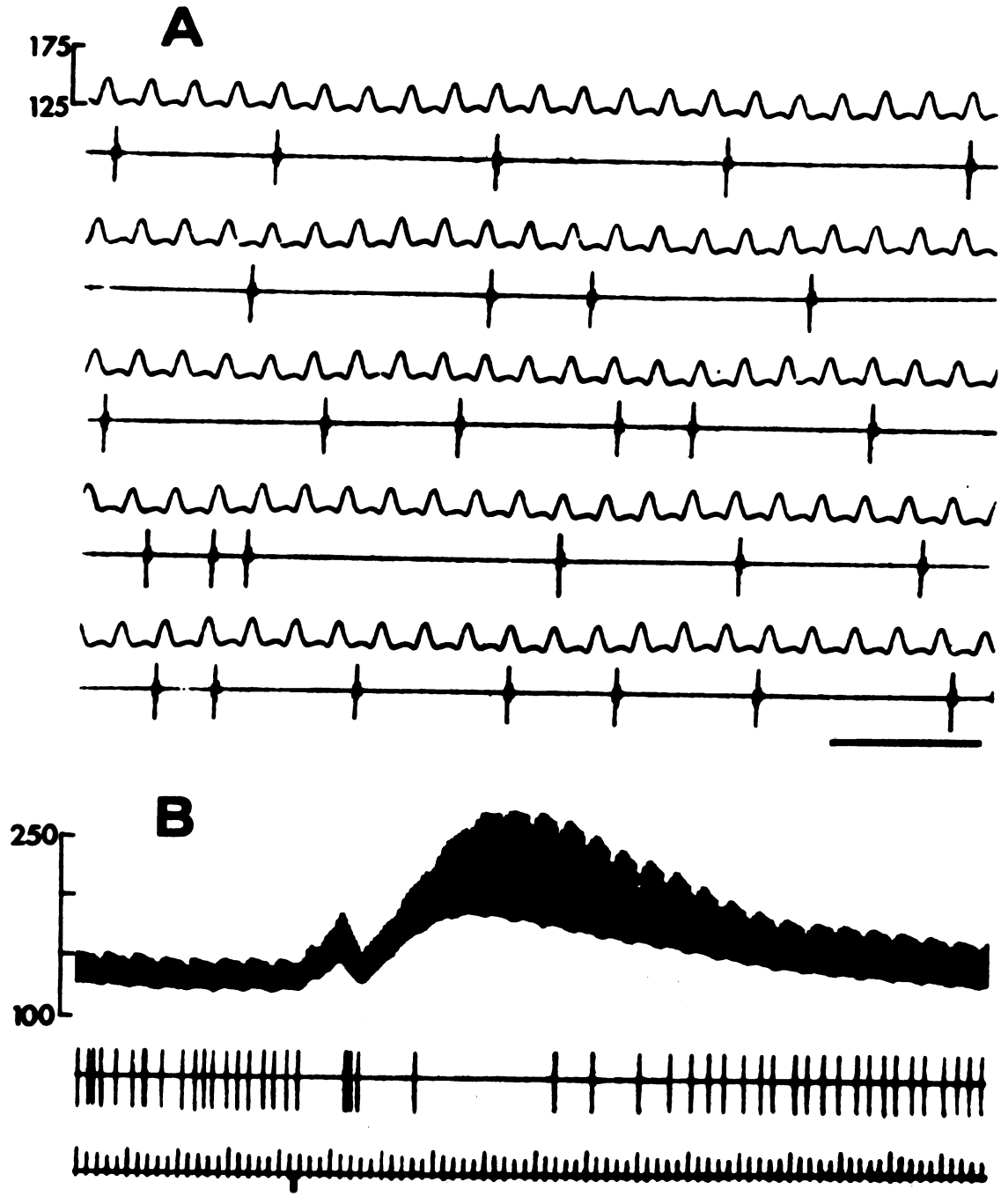

Figure 34

Thus, it can be assumed that the effect of NE on unitary discharges was of baroreceptor reflex origin.

b. Medullary receptive fields of individual PSN

The responses to stimulation of at least 5 different pressor sites were studied in 15 of the 39 preganglionic sympathetic units activated from the medulla. All of these neurons had large medullary receptive fields. A typical field is illustrated in Figure 35. The individual unit was routinely activated by stimulation of 70-80% of the pressor sites encountered. At a level just rostral to the obex, the active sites were located in the periventricular gray, underlying dorsolateral reticular formation and the lateral portions of R.v. These structures constitute the medullary pressor region as described in Figure 14. Small vertical movements (<1 mm) of the stimulating electrodes in the medulla often led to the disappearance of a unitary response even when the intensity of stimulation was 10-15 v. As will be described in subsequent sections, the response pattern of a unit often was dramatically changed when the stimulating electrodes were moved less than 1 mm in the dorsoventral orientation. These observations indicated that excessive current spread from the electrode tips could not explain the large receptive fields for excitation of individual PSN.

Figure 35. A typical medullary receptive field for the activation of a single preganglionic sympathetic neuron.

The section depicts the medulla at a level about 2 mm rostral to the obex. Five msec trains of 3 pulses (10 v; 0.5 msec) were applied to each of the medullary sites tested. Horizontal and vertical calibrations for the records of unit activity are 20 msec and 100 μV, respectively. Abbreviations are those used in Figure 14.

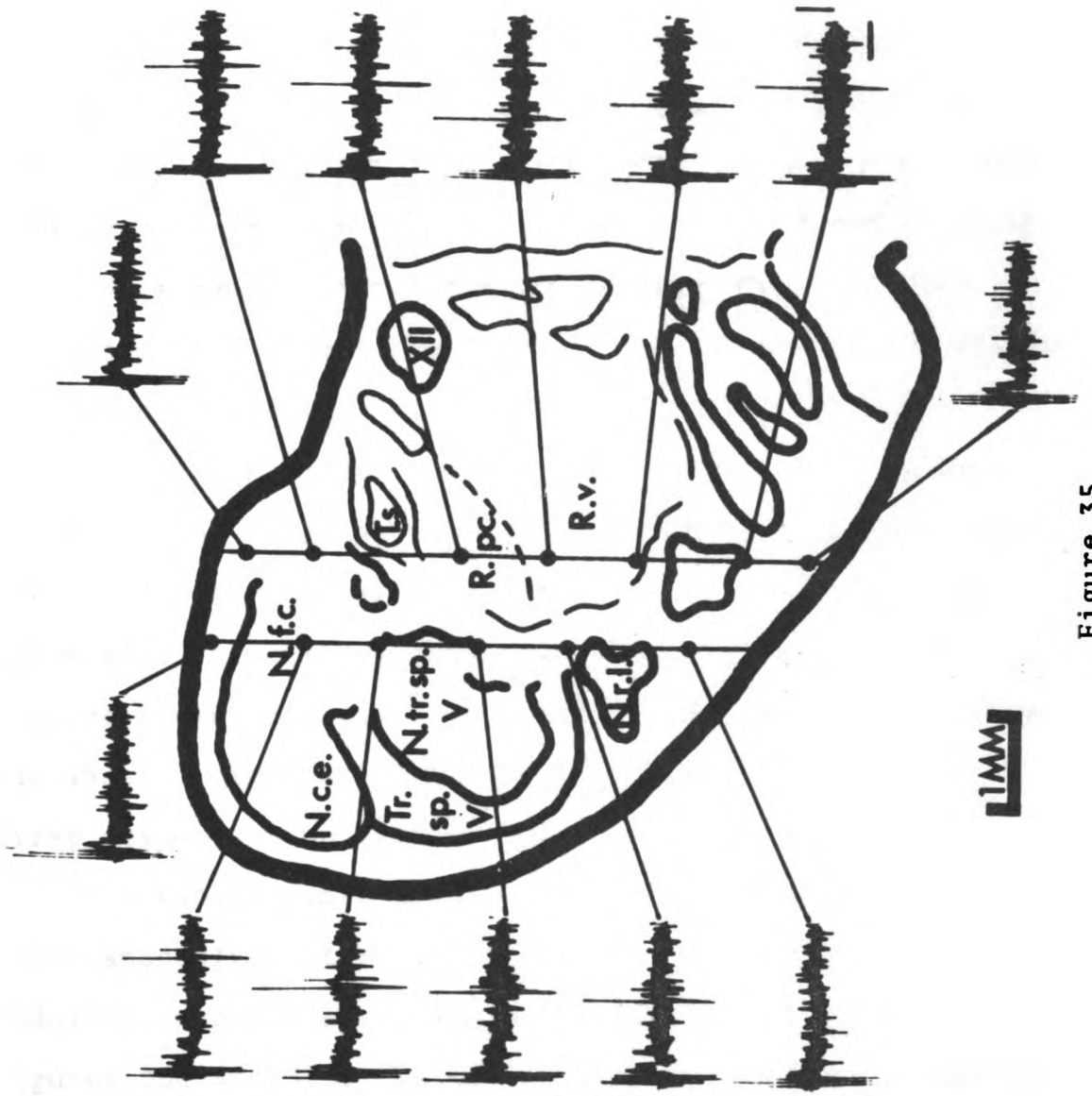

Figure 35

c. Unitary response patterns evoked by stimulation of pressor sites in the brain stem

Individual preganglionic sympathetic neurons exhibited two types of response patterns to stimulation of the medullary pressor region. The first preganglionic sympathetic unitary response pattern is illustrated in Figures 36A and 37A. The neuron responded once with a relatively fixed onset latency to either 5 msec trains of 3 pulses or single shocks of supramaximal intensity (10-15 v). The second unitary response pattern also was characterized by a single discharge to either trains of stimuli or single shocks applied to a medullary pressor site (Figures 36B and 37B). However, the modal onset latency of the second response type was significantly longer than for the first response type (Table 7). In addition, the variability of unitary discharge onset latency to successive trains of stimuli applied to the same pressor site was about 4 times as great for the second than for the first response type (Table 7).

The two response patterns were occasionally exhibited simultaneously by the same cell upon stimulation of a medullary pressor site. An example is illustrated in Figures 36C and 37C. In such instances the cell responded once or twice to each shock or train of pulses applied to the medulla. That is, discharges of each response type

Figure 36. Antidromic and orthodromic responses elicited by preganglionic sympathetic neurons.

Top tracings in A-C depict antidromic responses elicited by single shock (8 v; 0.1 msec) applied to cervical sympathetic nerve. Orthodromic responses in A represent relatively fixed onset latency response pattern evoked by 5 msec trains of 3 pulses (10 v; 0.5 msec; 600 Hz) applied to a pressor site in R.v. once every 2 sec. Orthodromic responses in B represent variable onset latency response pattern evoked from a pressor site in the dorsolateral reticular formation with the same parameters of stimulation as in A. Orthodromic responses in C are from the same unit shown in B and represent a combination of the relatively fixed and variable onset latency response patterns evoked from a pressor site in R.v. Vertical calibrations are 200 μV for the tracings in A and 100 μV for the tracings in B and C. Horizontal calibrations are 10 msec for the antidromic responses in A-C, and for the orthodromic responses in A; 20 msec for the orthodromic responses in B and C.

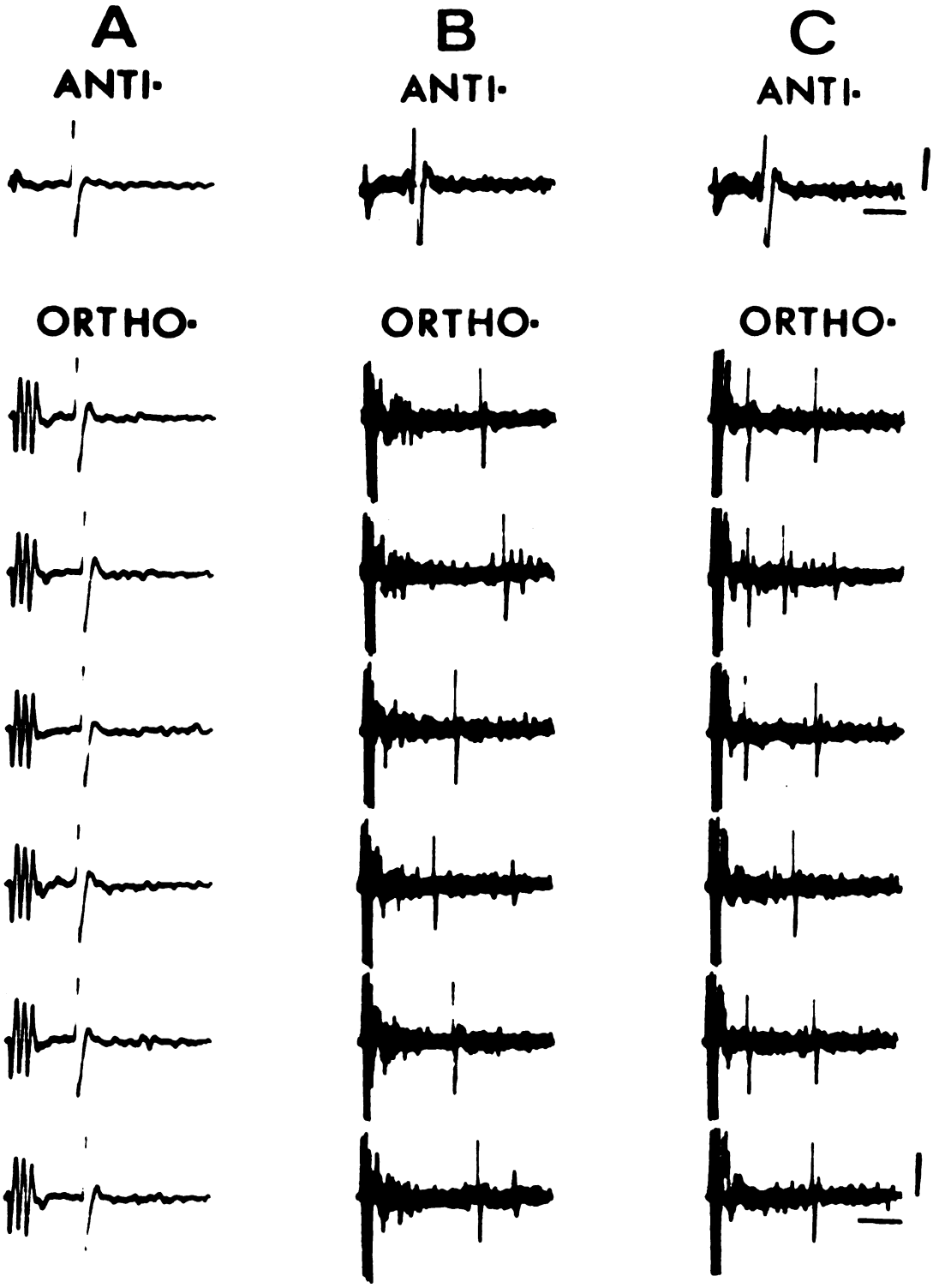

Figure 36

Figure 37. Poststimulus histograms (PSH) of cervical sympathetic preganglionic unitary responses.

PSH in A, B and C are from units shown in Figure 5 A, B and C, respectively. PSH of unitary responses evoked by antidromic stimulation of cervical sympathetic nerve are shown on the left. PSH of unitary responses elicited orthodromically by stimulation of the medullary pressor region are shown on the right. A: relatively fixed onset latency response pattern (100 trials). B: variable onset latency response pattern (200 trials). C: combination of relatively fixed and variable onset latency response patterns (100 trials).

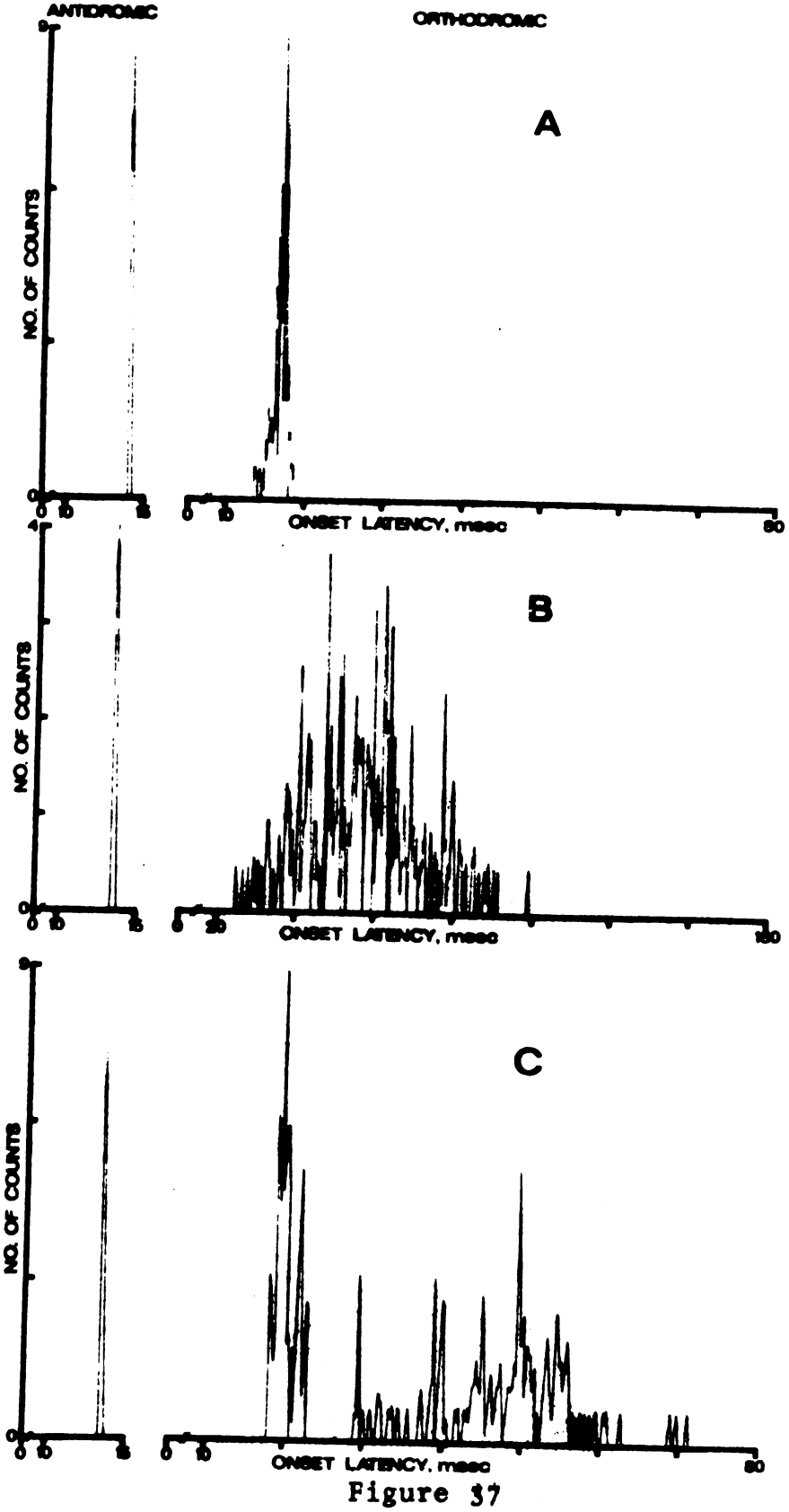
ANTIDROMIC
ORTHODROMIC
A
NO. OF COUNTS
ONSET LATENCY, msec
B
NO. OF COUNTS
ONSET LATENCY, msec
C
NO. OF COUNTS
ONSET LATENCY, msec

Figure 37

Table 7. Characteristics of the relatively fixed and the variable onset latency unitary response patterns elicited in 39 cells by stimulation of medullary pressor region with pulses of supramaximal intensity

Characteristic	Relatively fixed	Variable
Modal onset latency, msec*	21.4±1.0 (32)	55.4±3.8 (49)
Variability of onset latency, msec*	9.3±1.0 (32)	38.3±2.9 (49)
Modal conduction velocity, m/sec*	4.7±0.3 (30)	1.9±0.1 (45)
Probability of discharge, %		
a) single shocks	5.7±3.7 (10)	63.6±6.3 (16)
b) 5 msec trains of 3 pulses	85.6±4.2 (21)	77.8±4.6 (23)
f50, trains/sec	7.9±0.5 (12)	3.9±1.0 (7)

Values are means ± S.E. (N) - number of different pressor sites stimulated. Variability of onset latency is the difference (msec) between the time of occurrence of the shortest and of the longest latency responses. See text for methods used to determine probability of discharge and f50. *Values taken from PSH.

could be observed together or separately in any particular trial.

Both the relatively fixed and variable onset latency response patterns were demonstrated in 15 of the 39 neurons activated from the medullary pressor region (Table 8).

Table 8. Six combinations of the relatively fixed (R.F.R.P.) and variable (V.R.P.) onset latency response patterns exhibited in 39 preganglionic sympathetic neurons by stimulation of different medullary pressor sites

R.F.R.P.	V.R.P.	R.F.R.P.+V.R.P.	No. of cells
+	-	-	12
+	+	-	7
+	+	+	2
+	-	+	3
-	+	-	12
-	+	+	3

Plus and minus indicate presence or absence, respectively, of a response type. R.F.R.F.+V.R.P. indicates simultaneous occurrence of R.F.R.P. and V.R.P. upon stimulation of a medullary pressor site.

Vertical movements of the stimulating electrode as small as 0.5-1 mm commonly changed the response pattern elicited by a preganglionic unit. Only a few pressor sites were stimulated in those experiments in which a neuron exhibited only one of the 2 response patterns. Thus, I was left with the impression that both response patterns could be elicited by individual units if they were held long enough to allow complete exploration of the medullary pressor region.

Figure 38 shows the distributions of medullary pressor sites from which the relatively fixed and variable onset

Figure 38. Distribution of medullary sites from which preganglionic sympathetic neurons were activated by 5 msec trains of 3 pulses.

A: represents a medullary section about 2 mm rostral to the obex. Abbreviations are those used in Figure 14.
B: distribution of sites from which the relatively fixed onset latency unitary response pattern was elicited.
C: distribution of sites from which the variable onset latency unitary response pattern was elicited.

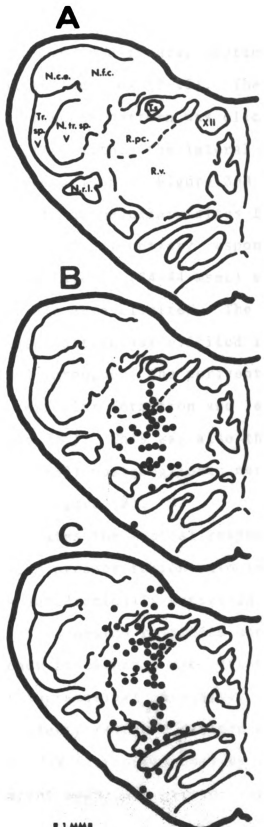

Figure 38

latency unitary response patterns were elicited. The A-P levels of stimulation were sufficiently close so that the data could be plotted on a frontal section of the medulla 2 mm rostral to the obex (P-12). The relatively fixed onset latency response pattern was elicited primarily from sites located within the lateral portions of R.v. (Figure 38B). Comparison of Figure 38B and Figure 17B reveals a similarity of medullary sites from which the relatively fixed onset latency unitary response pattern and the shortest onset latency (34-44 msec) external carotid nerve potentials were elicited. The variable onset latency response pattern was elicited from sites more evenly scattered throughout the periventricular gray, dorsolateral reticular formation and lateral portions of R.v. (Figure 38C). This was also the case for longer onset latency (>50) postganglionic nerve responses (see Figure 16C-F and Figure 18).

Figure 39 illustrates the typical response pattern elicited by brain stem pressor region stimulation in a single PSN that was antidromically activated by splanchnic nerve stimulation. This neuron responded once with a variable onset latency to either 5 msec trains of 3 pulses or single shocks of supramaximal intensity. The relatively fixed onset latency response pattern could not be evoked in splanchnic PSN (3 experiments) by stimulation of at least 5 different medullary pressor sites. The

Figure 39. Poststimulus histograms (PSH) of splanchnic preganglionic unitary response.

PSH of unitary discharges evoked by antidromic stimulation (8 v; 0.1 msec) applied to the left greater splanchnic nerve is shown on the left. On the right is the PSH of the variable onset latency response pattern evoked by 200 successive 5-msec trains of 3 pulses (10 v; 0.5 msec; 600 Hz) applied to a pressor site in the dorsolateral reticular formation once every 2 sec.

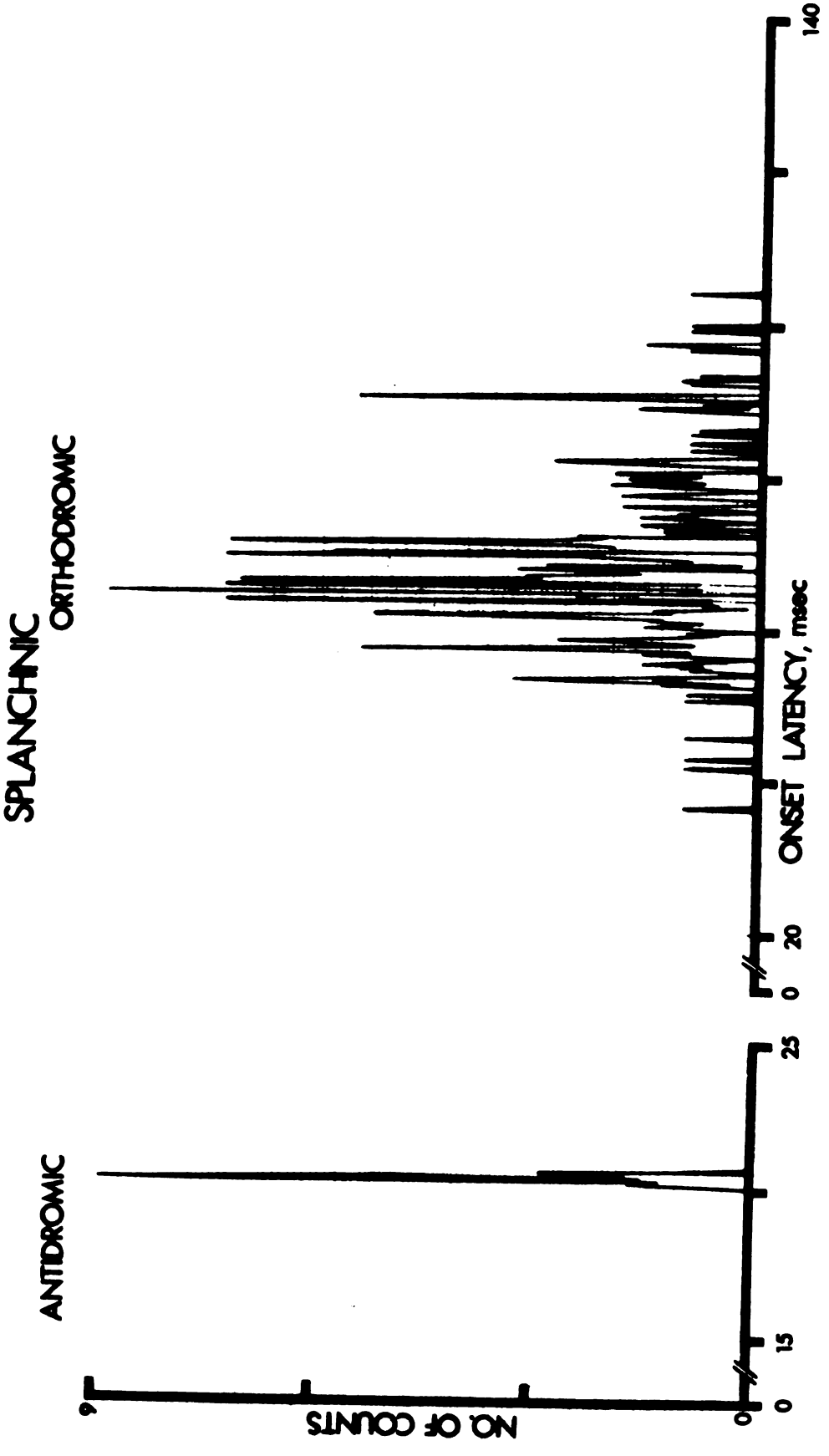
SPLANCHNIC
ORTHODROMIC
ANTIDROMIC
NO. OF COUNTS
6
0
15
0
25
0
20
ONSET LATENCY, msec
140

Figure 39

variability of onset latency exhibited by splanchnic PSN was similar to that seen in cervical sympathetic PSN (Figure 39 and Figure 37B).

Table 7 also summarizes other differences between the two response patterns exhibited by single preganglionic sympathetic neurons. First, modal conduction velocity from the stimulating to the recording electrode was significantly slower in the pathway mediating the variable onset latency unitary responses. Second, the probability of discharge (%), as determined by the number of unitary discharges elicited by 50 successive single shocks of supramaximal intensity applied to the same medullary site once every 2 sec, was significantly lower for the relatively fixed than for the variable onset latency response pattern. In contrast, the probability of discharge for the variable and for the relatively fixed onset latency unitary response patterns was not significantly different when stimulation was in the form of 5 msec trains of 3 pulses. Third, the relatively fixed onset latency unitary discharges followed higher frequencies of stimulation. These data are presented in the form of the f50 (the frequency of application of 5 msec trains of 3 pulses at which the probability of discharge fell to 50% of control value). The control value was determined with a frequency of one train every 2 sec. Comparison of the data presented in Table 7 with that described in

Tables 4 and 5 suggests that the relatively fixed and the variable onset latency preganglionic unitary response patterns monitor the activation of the medullary components of the short (34-44 msec) and longer (>50 msec) onset latency vasopressor pathways transmitting potentials recorded in the external carotid sympathetic nerve.

d. Effects of baroreceptor reflex activation and medullary depressor region stimulation on evoked unitary discharges

(1) Effects on the two unitary response patterns elicited from medullary pressor sites. The variable and relatively fixed onset latency unitary response patterns also could be distinguished by their contrasting relationships with the baroreceptor reflex arc and the medullary depressor region. The effects of baroreceptor reflex activation and depressor region stimulation on the two unitary response patterns are summarized in Table 9.

Increases in systemic blood pressure (50-100 mmHg) produced by the intravenous injection of 1-2 μg/kg of NE were accompanied by a decrease in the probability of occurrence of the variable onset latency unitary responses (Figure 40B,C). Probability of discharge (%) before and during the pressor action of NE was determined on the basis of the number of responses of the preganglionic neuron to 12 successive 5 msec trains of 3 supramaximal pulses applied once every 2 sec to a medullary pressor

Figure 40. Effect of baroreceptor reflex activation and stimulation of medullary depressor region on variable onset latency unitary response pattern evoked from a medullary pressor site.

A: PSH of unitary discharges produced by 250 successive 5 msec trains of 3 pulses (10 v; 0.5 msec; 600 Hz) applied to a site in the dorsolateral reticular formation once very 2 sec. B: representative control responses. C: inhibition of unitary discharges during pressor action of NE (1 μg/kg, iv). D: inhibition of unitary discharges during continuous stimulation (15 v; 0.5 msec; 30 Hz) of a depressor site in the medial medulla. Small deflections in records are depressor region stimulus artifacts. Vertical calibration is 100 μV. Horizontal calibration is 20 msec.

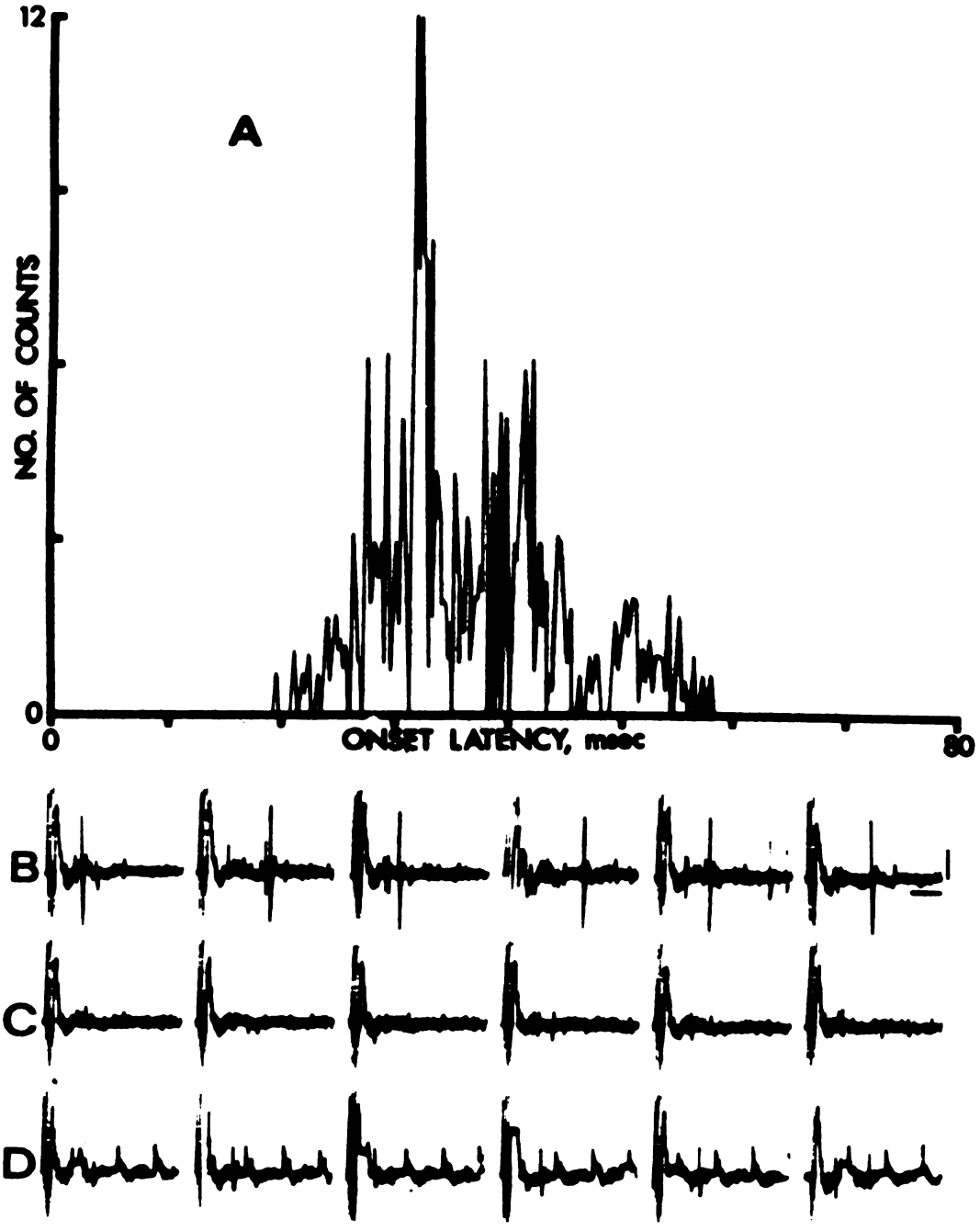

Figure 40

Table 9. Effects of baroreceptor reflex activation and depressor region stimulation on relatively fixed and variable onset latency unit responses evoked from medullary pressor sites

Response pattern	Probability of Discharge, %			
	NE		Depressor Stimulation	
	Before	During	Before	During
Variable latency	77.5 ±4.9(15)	26.9 ±4.9(15)	62.5 ±8.5(6)	17.8 ±6.6(6)
Relatively fixed latency	96.0 ±4.0(5)	88.8 ±5.0(5)	18.2 ±7.6(5)*	67.8 ±7.8(5)*

Values are means ± S.E. Numbers in parentheses are numbers of observations. See test for methods used to determine probability of discharge. Medullary pressor sites were stimulated with 5-msec trains of 3 pulses before and during (1) the pressor effect produced by the intravenous injection of 1-2 μg/kg of NE (baroreceptor reflex activation) and (2) high-frequency (20-50 Hz) stimulation of the medullary depressor region. The responses of 18 cells were studied. *Probability of discharge when pulses applied to medullary pressor sites were of submaximal (<8 v) rather than of supramaximal intensity.

site. High frequency (20-50 Hz) stimulation of depressor sites located in the medial medulla (P-12; L 0.5 to 1.5; H-6 to H-9) also inhibited the variable onset latency response pattern (Figure 40B,D). Probability of discharge in the presence and absence of depressor region stimulation was determined on the basis of the number of unitary responses elicited by 15 successive trains of 3 supramaximal pulses applied to a pressor site in the medulla.

The probability of occurrence of the relatively fixed onset latency unitary responses elicited by trains of submaximal (<8 v) pulses applied to medullary pressor sites was unchanged or slightly enhanced during the pressor action of NE and significantly increased during stimulation of the depressor region (Figure 41). Norepinephrine and depressor region stimulation failed to affect significantly the probability of occurrence of the relatively fixed onset latency unitary responses elicited by trains of supramaximal (10-15 v) pulses. Snyder and Gebber (1972, 1973) have demonstrated that high frequency stimulation of depressor sites in the medial medulla blocked the long-latency responses and enhanced the short-latency responses recorded in the external carotid sympathetic nerve. These results provide additional evidence that the relatively fixed and variable onset latency responses monitor the activation of the two systems of pressor pathways.

(2) Effects on unitary responses evoked from midcervical spinal pressor tracks. Figure 42 illustrates an experiment in which both a response type that was inhibited and a response type that was not blocked during baroreceptor reflex activation were elicited in the same PSN by stimulation of two different pressor sites in the dorsolateral white column of the fourth cervical

Figure 41. Effect of baroreceptor reflex activation and stimulation of medullary depressor region on relatively fixed onset latency unitary response pattern evoked from a medullary pressor site with pulses of submaximal intensity.

A: PSH of unitary discharges produced by 75 successive 5 msec trains of 3 pulses (6 v; 0.5 msec; 600 Hz) applied to a site in R.v. once every 2 sec. Probability of discharge was approximately 30%. B: six successive control trials. C: responses during pressor action of NE (1 µg/kg, iv). D: responses during continuous stimulation (15 v; 0.5 msec; 30 Hz) of a depressor site in medial medulla. Vertical calibration is 50 µV. Horizontal calibration is 10 msec.

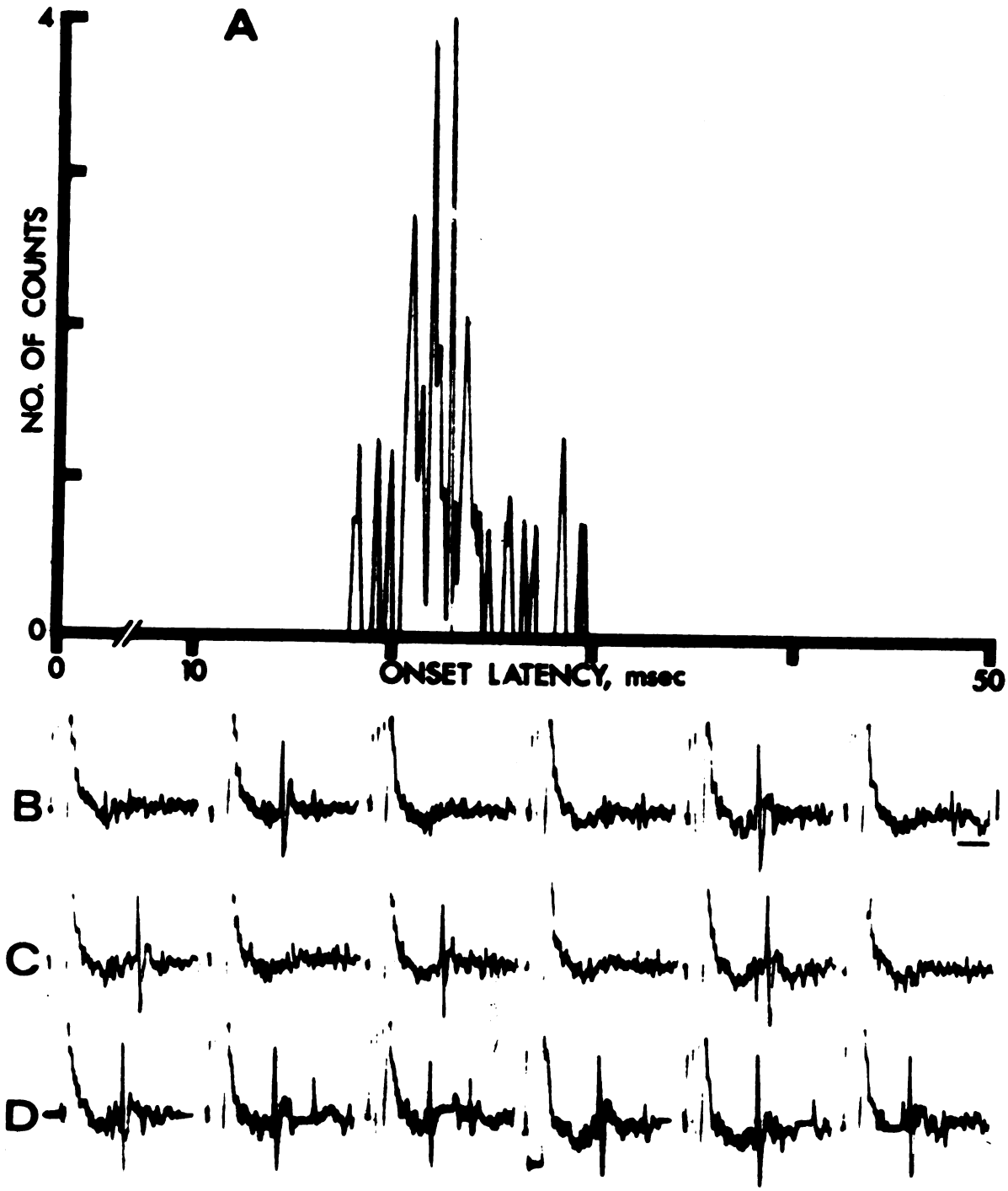

Figure 41

Figure 42. Effect of baroreceptor reflex activation on unitary discharges evoked from pressor sites in the midcervical spinal cord.

Unitary responses shown in panels A and B are from the same PSN. A and B: PSH of unitary responses produced by 100 successive 5-msec trains of 3 pulses (10 v; 0.5 msec; 600 Hz) applied to two different sites in the dorsolateral white column of the midcervical spinal cord. A1 and B1: representative control responses. A2 and B2: unitary discharges evoked during a 75-100 mmHg rise in blood pressure produced by NE (0.5 μg/kg, iv). Vertical calibration is 50 μV. Horizontal calibration is 10 msec for A and 5 msec for B.

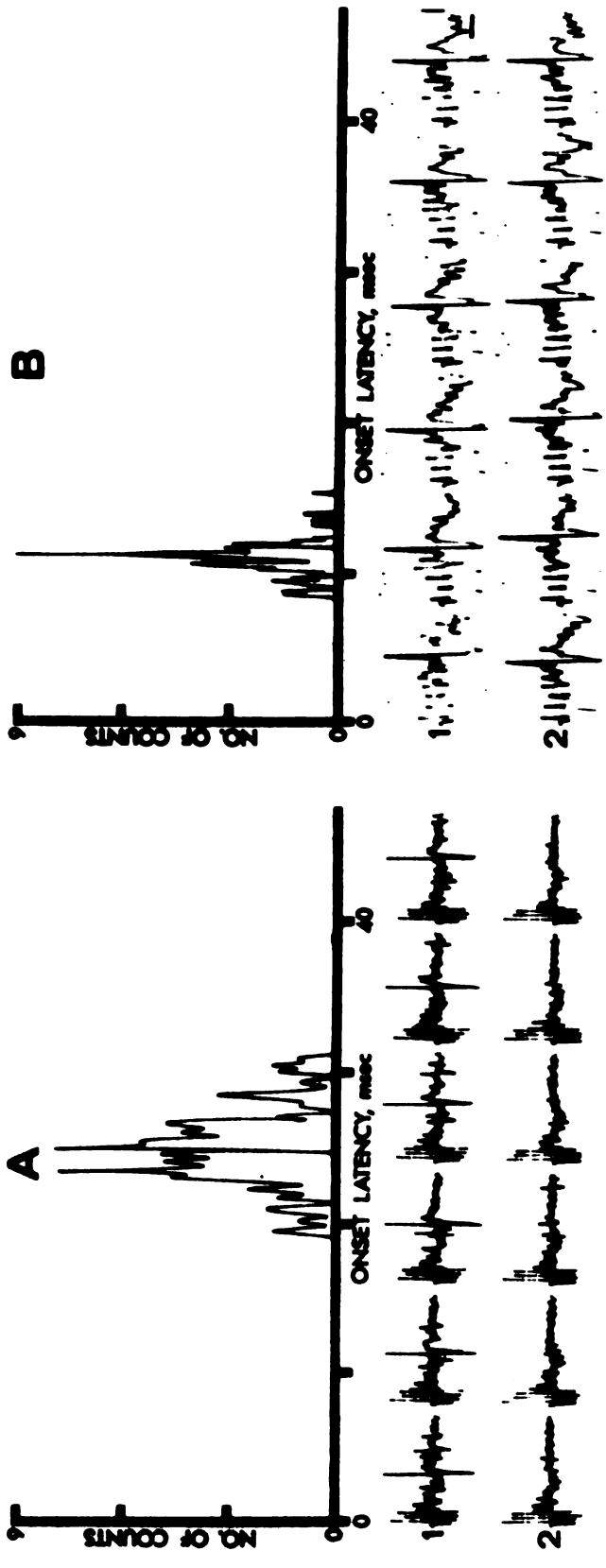

Figure 42

spinal segment. Figure 42A shows that preganglionic unitary responses evoked by trains of 3 pulses applied to one of the spinal sites were inhibited during a 75-100 mmHg rise in blood pressure produced by the intravenous injection of 1-2 μg/kg norepinephrine. In contrast, the unitary responses evoked in the same cell by stimulation of another cervical spinal site were not blocked during baroreceptor reflex activation (Figure 42B). The mode discharge onset latencies of both types of unitary responses, as shown in the poststimulus histograms (Figure 42A,B), were considerably shorter than those for the unit discharges evoked by stimulation of the brain stem. This observation strongly suggests that both response types were elicited by stimulation of two different descending spinal pressor tracks. Furthermore, in agreement with those responses evoked in the external carotid nerve, one of the systems of pressor pathways is controlled by the baroreceptor reflex arc at a spinal locus.

DISCUSSION

A. Origin and Control of Slow Wave of SND

Experiments in this portion of the study were designed with the intent of investigating the mechanisms by which baroreceptors reflexly control spontaneously occurring sympathetic nervous activity in vasoconstrictor nerves. Nervous discharge was processed through a band pass circuit set at 1-1000 Hz in order to accurately record low frequency sympathetic oscillations. Since this is a rather non-conventional method of recording SND, it was important to establish that neural activity was being recorded and not mechanical artifacts due to pulse pressure or other extraneous movement. That slow oscillations of SND measured true neural activity was indicated by the following: 1) upon processing SND through a high pass filter set at 30 Hz, nervous discharge was observed to occur throughout the duration of the slow waveform recorded at 1-1000 Hz bandpass; 2) pulse-synchronous activity could not be due to mechanical distortions resulting from pulse pressure, because the waves were inhibited during baroreceptor reflex activation at a time when pulse pressure was greater than control; 3) all wave

activity in the renal nerve was abolished following the administration of the ganglionic blocking agent hexamethonium (5 mg/kg, iv) during a period when blood pressure was maintained at control levels with iv dextran.

The data presented contradict the generally accepted view that the slow wave of SND results directly from a waxing and waning of baroreceptor nervous discharge occurring during each cardiac cycle (Adrian *et al.*, 1932; Cohen and Gootman, 1970; Green and Heffron, 1968b; Heymans and Neil, 1958). Although baroreceptor and vagus denervation or hemorrhage unlocked the phase relations between SND and the cardiac cycle, the slow wave persisted and its duration was not changed. This observation supports the contention that the slow wave was generated by central vasomotor elements rather than directly by the baroreceptor reflexes. This was further indicated by experiments in which the slow wave was aborted by stimuli delivered to the baroreceptor nerves or to the paramedian nucleus during a time span which accounted for less than 1% of the cardiac cycle. First, a single shock applied to the paramedian nucleus at appropriate points in the cardiac cycle extinguished or prematurely terminated the slow wave. The paramedian nucleus of the medial medulla functions as a relay station in the baroreceptor reflex arc (Crill and Reis, 1969; Homma *et al.*, 1970; Humphrey, 1967; Miura and Reis, 1969, 1972; Snyder and Gebber, 1973). Second,

the late positive potential produced by a single shock applied to the baroreceptor nerves or paramedian nucleus randomly with respect to the cardiac cycle approached the mirror image of the spontaneously occurring slow negative wave. This observation also is indicative of termination of the slow wave of SND by single shock stimulation.

At first glance, the conclusion that the slow wave of SND is not generated by the baroreceptor reflexes seems at odds with the results presented by Kezdi and Geller (1968). Figure 6 of their study shows that increasing the frequency at which standardized sinusoidal pressure waves were applied to the isolated carotid sinus of the dog produced a decrease in the duration of the burst of renal SND associated with each pressure cycle. This, of course, suggests that the genesis of the slow wave is directly related to the waxing and waning of baroreceptor nervous input. However, the phase relations between SND and the sinusoidal pressure wave essentially disappeared when the frequency of carotid sinus pulsation was raised above 8 c/sec. More importantly, it appears that the bursts of SND associated with lower frequencies of sinusoidal pressure wave application may have been comprised of 100 msec packets (10 c/sec periodicity). These records appear very similar to those of the 10 c/sec periodicity of SND published by Green and Heffron (1967b). Thus, the

effect of raising the frequency of sinus pulsation on the duration of the burst of SND perhaps was related to a change in the number of 100 msec packets accompanying each pressure cycle rather than to shortening of the 3 c/sec slow wave which seemed to be absent in Figure 6 of Kezdi and Geller's study.

It is well established that an inverse relationship exists between the degree of activity recorded from baroreceptor and sympathetic nerves (Dontas, 1955; Green and Heffron, 1967b; Kezdi and Geller, 1968; Ninomiya and Irisawa, 1969). The present study indicates that the baroreceptor reflexes also function to entrain the slow wave of SND to the cardiac cycle. This was made clear by the observation that baroreceptor denervation led to uncoupling of the phase relations between the slow wave and the cardiac cycle. The slow waves of SND were less evenly spaced in the absence of baroreceptor nervous discharge. This was indicated by the reduced degree of periodicity in the autocorrelograms of SND after baroreceptor nerve section or hemorrhage (Figure 4). Thus entrainment of the slow wave by the baroreceptor reflexes regularized the rhythm of central origin. The frequency of occurrence of the slow wave of SND was significantly increased after baroreceptor denervation. Thus, entrainment of the slow wave to the heart beat by the baroreceptor reflexes also is frequency limiting in effect.

The effectiveness of paramedian stimulation in terminating the slow wave was dependent upon when the single shock was applied (Figure 5). A single shock extinguished or prematurely terminated the slow wave when delivered just before or at its onset. However, a single shock applied just after the beginning of the slow wave had no effect. This could not be explained on the basis of a long central delay of inhibition for the following reason. Although the onset latency of the late positivity recorded in the experiment illustrated in Figure 5 was 85 msec, this value was considerably shorter than that time interval (150 msec) between the end of the slow negative wave and the point closest to its beginning at which the shock applied to the paramedian nucleus became ineffective (Figure 5E). These observations raise two important possibilities concerning the interactions between those central elements responsible for the generation and entrainment of the slow wave to the cardiac cycle. First, the slow wave of SND probably results as the consequence of "avalanche excitation" transmitted through an interconnected population of brain stem neurons. This would account for the similar duration of each slow wave observed either before or after baroreceptor denervation (Figure 3). Concerning this point, axon collaterals connecting large numbers of reticulospinal neurons have been described at medullary and pontine levels (Brodal, 1957; Scheibel

and Scheibel, 1958, 1967). Second, the ineffectiveness of stimuli applied to the paramedian nucleus soon after "avalanche excitation" was initiated suggests that the sympathoinhibitory effect of the baroreceptors was exerted most likely on interneuronal elements which trigger the neural network responsible for the slow wave. As a result, baroreceptor nervous discharge no longer would be effective in influencing the formation of the slow wave once the most rostral elements of the interconnected population of brain stem neurons were excited. In addition, triggering of the next wave of "avalanche excitation" would occur only after baroreceptor nervous discharge fell below some critical level. In this way, the slow wave of SND would be entrained to the cardiac cycle.

It can be assumed that the late positive potential reflects the capacity of the baroreceptor reflexes to entrain the slow wave to the cardiac cycle since 1) it approximates the mirror image of the spontaneously occurring oscillation of SND; and 2) the late phase of positivity and the slow wave of SND disappeared simultaneously during hemorrhage to approximately 50 mmHg pressure or asphyxia. On this basis, it becomes further apparent that the sympathoinhibitory effect responsible for the entrainment occurred in the brain stem. The late positive wave produced by baroreceptor nerve or paramedian

nucleus stimulation persisted after midcollicular transection. This observation indicates that a forebrain site or loop was not involved in the entrainment of the slow wave. Splanchnic nerve discharges evoked from descending spinal pressor tracts were not inhibited during the time course of the late positive potential. Thus, it is unlikely that sympathoinhibition represented by the late positivity occurred at a spinal site. By elimination, it can be concluded that sympathoinhibition of baroreceptor origin leading to the entrainment of the slow wave of SND to the cardiac cycle was mediated at a brain stem locus.

Results of this study suggest that the early positivity monitored sympathoinhibition exerted at a spinal level. This was demonstrated by the observation that the splanchnic nerve discharge evoked from descending spinal pressor tracts was depressed only during the time of the early positive potential elicited by stimuli applied to the paramedian reticular nucleus. Gootman and Cohen (1971) reached the same conclusion since the onset latency of the early positivity evoked from the medullary depressor region was less than that for the splanchnic nerve responses elicited from either the medullary or spinal pressor region of the cat. That the early phase of positivity evoked by stimulation of the paramedian nucleus in this study was of baroreceptor origin and monitored inhibition of transmission in

vasopressor pathways was indicated by the following observations. First, trains of pulses applied to the carotid sinus or aortic depressor nerve produced an early positive potential on the splanchnic nerve. Second, the early positivity could be monitored from postganglionic renal vasoconstrictor fibers.

It is necessary to relate the results reported here with those of Cohen and Gootman (1969, 1970) and Gootman and Cohen (1970, 1971). They noted a well defined 10 c/sec periodicity of SND on the cat splanchnic nerve which often was locked in a 3:1 relation to the cardiac cycle. Assuming that the oscillation of SND locked in a 1:1 relation to the cardiac cycle was of baroreceptor origin, Cohen and Gootman (1970) concluded that the 10 c/sec periodicity represented the fundamental rhythmicity of either brain stem or spinal vasomotor elements. The second of the alternative interpretations is favored. Cohen and Gootman (1969) and Gootman and Cohen (1971) noted that the computer summed early positive potential (i.e., spinal inhibition) evoked by stimulation of the medullary depressor region was followed by damped oscillations (10 c/sec) of SND. It is difficult to envision locking of the 10 c/sec periodicity to the electrical shock applied to a depressor site in the medulla unless the resultant spinal inhibition entrained a spinal rhythm. If the 10 c/sec periodicity of SND was of brain stem origin,

then the early positive potential should not have been followed by damped oscillations. On the other hand, it could be argued that stimulation of the depressor region simultaneously activated a second inhibitory system which may have entrained the 10 c/sec oscillation of SND in the brain stem. However, Gootman and Cohen (1971) failed to observe a second phase of positivity in their experiments. Thus, it is my view that the 3 c/sec periodicity of SND is representative of the fundamental oscillatory behavior of brain stem vasomotor elements while the 10 c/sec periodicity most likely is generated in the spinal cord, perhaps when brain stem outflow becomes asynchronous in nature. In this regard, it is interesting that the character of spontaneously occurring SND observed under extreme conditions in this study more closely resembled the situation described by Cohen and Gootman (1970). The 3 c/sec periodicity was virtually absent during asphyxia or following severe hemorrhage. SND occurred primarily in the form of 100 msec waves under these conditions. In addition, stimulation of the paramedian nucleus produced only an early positive potential during asphyxia or following severe hemorrhage.

B. Organization of Central Pathways Mediating Vasopressor Activity

1. Responses evoked in external carotid and splanchnic nerves

The purpose of this portion of the study was to gain some insight into the functional organization of the central vasopressor pathways transmitting SND from the brain to the sympathetic nerves. The experimental approach employed was to compare the responses evoked in a sympathetic nerve by single shocks and trains of stimuli applied to the extensive pressor regions of the hypothalamus, brain stem and spinal cord. Onset latency of discharges evoked from various sites in these pressor areas was used as one criterion to evaluate central vasomotor organization. For this reason it was imperative to consider the role played by the dispersion of impulses along the peripheral conducting pathway in accounting for the differences observed in the onset latencies of potentials evoked from different brain sites. Whereas the splanchnic and renal nerves were used to evaluate the characteristics of spontaneously occurring SND, neither was extensively employed in studies involving evoked responses. The postganglionic branch of the external carotid plexus which innervates the region of the carotid bifurcation served as the source from which data were collected because peripheral dispersion of impulses in this nerve was found to be less than that occurring in

the abdominal nerves. The action potential evoked in the external carotid nerve by supramaximal stimulation of the preganglionic cervical sympathetic trunk near to its spinal origins consisted of one synchronous cell group with a duration of 12 $\pm$ 1 msec. Thus, differences in the onset latencies of postganglionic potentials evoked from separate brain sites which were greater than 12 $\pm$ 1 msec could not be explained on the basis of peripheral dispersion.

That the evoked potentials in the external carotid nerve monitored the discharge of sympathetic fibers subserving a vasoconstrictor function was indicated by a number of observations. First, the external carotid nerve exhibited spontaneously occurring or "resting" discharges which were in phase with the arterial pulse and the respiratory rhythm. The spontaneously occurring discharges were inhibited upon baroreceptor reflex activation. Second, a rise in blood pressure always was produced by high frequency stimulation of medullary sites from which postganglionic responses were evoked. Third, action potentials elicited in the external carotid nerve were mediated by the S2 fiber group of the cervical sympathetic trunk. This preganglionic fiber group is known to innervate ganglion cells which subserve a vasoconstrictor function (Bishop and Heinbecker, 1932). This observation precluded the possibility that potentials evoked in the postganglionic nerve by brain stimulation monitored activation of the more

slowly conducting preganglionic fibers which are part of the cholinergic sympathetic vasodilator system (Folkow *et al.*, 1958). This contention is also supported by the work of Schramm and Bignall (1971). The maps provided by these workers showed that cholinergic muscle vasodilation elicited in the cat was mediated over a relatively discrete non-reticular pathway located lateral to the medullary regions stimulated in this study.

Sympathetic nerve potentials elicited from the brain and spinal cord could be classified into two major groups on the basis of their receptivity to blockade upon baroreceptor reflex activation. The first group contained potentials which were partially or completely inhibited during the pressor action of norepinephrine. The second group contained potentials which were not inhibited during the hypertensive effect of norepinephrine. At each level of the neuraxis explored, the baroreceptor reflex-sensitive and -insensitive potentials could be further distinguished by other characteristics, as follows: 1) baroreceptor reflex-sensitive responses exhibited longer onset latencies and durations than "insensitive" responses; 2) baroreceptor reflex-insensitive potentials followed higher frequencies of stimulation than reflex-sensitive responses; 3) only trains of 3 pulses evoked baroreceptor reflex-insensitive responses, while the baroreceptor reflex-sensitive potentials were elicited by

single shocks as well as trains of stimuli. These observations indicate that vasoconstrictor outflow is distributed from the brain to the postganglionic sympathetic external carotid nerve over two distinct systems of pathways.

The baroreceptor reflex-sensitive pressor system most likely functions in transmission of tonic SND. The relationships between spontaneously occurring and centrally-evoked postganglionic sympathetic nervous discharge support this idea. Snyder and Gebber (1973) demonstrated that peak amplitude of background discharges and the baroreceptor-sensitive external carotid nerve responses evoked from the medulla decreased in a parallel fashion as the intensity of depressor region stimulation was increased. Furthermore, the intensity of stimulation needed to produce threshold effects was the same for both events.

A number of investigators (Chai and Wang, 1968; Peis, 1965; Smith, 1965; Wang and Ranson, 1939b) have suggested that some hypothalamic pressor pathways bypass those medullary regions involved in the genesis of tonic sympathetic nervous discharge. The inability of baroreceptor reflex activation to inhibit the early spikes evoked from the hypothalamus supports this view. In this regard tonic sympathetic nervous discharge is generally considered to arise from the lower brain stem (Alexander, 1946; Chai and Wang, 1968) and can be inhibited by baroreceptor

reflex activation (Gebber and Snyder, 1970). Thus it is unlikely that the early spikes were elicited from hypothalamic pathways which projected to the brain stem elements responsible for spontaneously occurring sympathetic nervous discharge.

The relationships observed between onset latency and the medullary site of initiation of postganglionic sympathetic nerve responses provide clues concerning the intrinsic organization of the two systems of pressor pathways. The medullary reticulospinal neurons arise almost exclusively from the nucleus reticularis gigantocellularis (R.gc.) and its caudal extension, nucleus reticularis ventralis (R.v.) of the medial two-thirds of the reticular formation (Brodal, 1957). In the present study, the majority of the shortest onset latency (50-59 msec) postganglionic potentials elicited from the baroreceptor reflex-sensitive system of pathways were evoked from R.v. This observation raises the possibility that these potentials monitored the activation of a group of "vasopressor" reticulospinal neurons. This is supported by the similarity between the central conduction velocities of the baroreceptor reflex-sensitive potentials evoked from descending spinal pathways and those with onset latencies of 50-59 msec elicited from R.v. Activation of the axons of reticulospinal neurons coursing to the dorsolateral white column of the spinal cord may have

accounted for those short onset latency potentials evoked from more dorsal medullary sites.

It is perhaps more than coincidence that the majority of the longest latency (70-104 msec) sympathetic nerve responses evoked from the medulla were elicited from the periventricular gray and dorsolateral reticular formation. These potentials may have monitored activation of afferent and association elements of the baroreceptor reflex-sensitive system of pathways which course to reticulospinal neurons of R.v. In this regard, the functional relationship of the periventricular gray and dorsolateral reticular formation to R.v. and R.gc. of the medial medulla is considered to be chiefly sensory (Brodal, 1957; Rossi and Zanchetti, 1957). Ascending and descending tracts traversing these areas are known to supply collaterals which terminate on reticular neurons of the medial medulla (Scheibel and Scheibel, 1958, 1967).

Eighty percent of the sympathetic nerve responses elicited from the baroreceptor reflex-insensitive system at the medullary level were evoked from sites in R.v. These potentials had a limited range of onset latencies (34-44 msec). Two possibilities immediately arise concerning their origins. First, these potentials may have monitored the activation of a second group of "vasopressor" medullary reticulospinal neurons. Alternatively, they may have been initiated by stimulation of axons of neurons

which originated in midbrain and/or hypothalamic regions from which baroreceptor reflex-insensitive potentials could be evoked. Recent data of Snyder and Gebber (1973) would favor the alternative hypothesis. They demonstrated that high-frequency stimulation of some sites in the medullary depressor region blocked both the baroreceptor reflex-insensitive and -sensitive components of the sympathetic nerve discharge elicited from midbrain sites. In contrast, the short-latency postganglionic potentials evoked from medullary and spinal sites typically were not inhibited, but paradoxically enhanced, by depressor region stimulation. These results suggest the existence of at least one synapse in the baroreceptor reflex-insensitive system of pathways somewhere between the hypothalamus and medullary levels. Another observation supporting this contention was that the baroreceptor reflex-insensitive potentials evoked from the hypothalamus and midbrain failed to one-half of control peak amplitude at lower frequencies of stimulation than those evoked from R.v. or the spinal cord.

That the baroreceptor reflex-insensitive system may be somewhat specific to the external carotid nerve was indicated by the contrasting results in the splanchnic nerve. Independent of onset latency, all splanchnic nerve responses evoked from medullary and spinal sites were inhibited by baroreceptor reflex activation or medial

medullary depressor region stimulation. No evidence of paradoxical enhancement was found. Thus, the central components of vasopressor pathways distributed to the vascular beds innervated by the splanchnic and external carotid nerves are organized quite differently.

The relationships of the two systems of pressor pathways to the baroreceptor reflex arc deserve further comment. Early and late phases of positivity were evoked by stimulation of the baroreceptor nerves and the medullary depressor region. The early positive potential presumably monitored inhibition of sympathetic nervous activity at a spinal locus. Results involving centrally-evoked responses clearly demonstrate a spinal component of baroreceptor reflex-induced inhibition of sympathetic nervous discharge. This was indicated by the observation that more than one-half of the external carotid postganglionic nerve responses, and all of the splanchnic potentials, evoked from descending spinal tracts were partially inhibited during the pressor action of norepinephrine. The degree of depression of the splanchnic nerve responses was significantly greater than that produced by C_1 transection of the spinal cord. From all indications, the inhibitory effect of norepinephrine on these potentials was of baroreceptor reflex origin. First, bilateral section of the IX and X cranial nerves abolished the inhibitory action of norepinephrine on spontaneously

occurring and centrally-evoked activity in the external carotid nerve. Second, the inhibitory effect of norepinephrine was observed on the sympathetic nerve responses elicited from descending spinal pressor pathways before, but not after, C_1 transection.

It was suggested earlier that the late positive potential most likely reflects the ability of the baroreceptor reflexes to control sympathetic nervous activity by entrainment at a medullary level. Other indirect evidence is available which suggests that baroreceptor-induced inhibition of sympathetic nervous discharge occurs at a brain stem site. Salmoiraghi (1962) and Przybyla and Wang (1967) noted steadily firing and frequency modulated medullary neurons which exhibited a decrease in discharge rate when blood pressure was raised with norepinephrine. Biscoe and Sampson (1970a,b) reported a number of instances in which stimulation of the carotid sinus nerve or an increase in carotid sinus pressure depressed spontaneous discharges of single units located in R.gc. and R.v. of the medial two-thirds of the medullary reticular formation. Inhibitory postsynaptic potentials also were observed in some of these cells. Coote *et al.* (1969) and Koizumi *et al.* (1971) found that spontaneously occurring and somatosympathetic reflex-induced discharges of supraspinal origin evoked in sympathetic white rami were inhibited during carotid sinus distention. The

consistent observation in the present study that the baroreceptor reflex-sensitive potentials evoked from the medulla and ascending spinal tracts were completely blocked during the pressor action of norepinephrine, while those norepinephrine-sensitive sympathetic nerve responses evoked from descending spinal pathways were only partially blocked, indirectly supports the view that baroreceptor induced sympathoinhibition occurs at a brainstem as well as a spinal locus.

Sympathetic nerve responses which were not blocked during the pressor action of norepinephrine were routinely elicited from pressor sites in the hypothalamus and midbrain. Thus, some of the "vasoconstrictor" elements activated from suprabulbar sites are not under the influence of the medullary and spinal components of the baroreceptor reflex arc. Some investigators (Hilton and Spyer, 1971; Hockman and Livingston, 1970; Spyer, 1972) have suggested that baroreceptor control of cardiovascular function may be exerted at forebrain as well as at bulbar and spinal sites. Even though Snyder and Gebber (1973) located medial medullary sites that inhibited the baroreceptor reflex-insensitive responses elicited from midbrain sites, data in the present investigation do not preclude the possibility that a forebrain component of the baroreceptor reflex arc might affect the transmission of impulses at

a more central site in the pathways from which the norepinephrine-insensitive potentials were evoked.

2. Responses evoked in single sympathetic neurons

A number of observations indicated that the preganglionic sympathetic unitary discharges elicited by stimulation of the caudal brain stem and midcervical spinal cord monitored the activation of central pathways which subserved vasoconstrictor function. First, the sympathetic units reported upon were activated exclusively from sites located in medullary and spinal pressor regions. Second, axonal conduction velocities of all but four of the preganglionic neurons were in the range exhibited by the second component (C_2) of the compound action potential evoked in the cervical sympathetic nerve by stimulation of the thoracic ventral roots. Bishop and Heinbecker (1932) have demonstrated that this preganglionic fiber group innervates ganglion cells which are vasoconstrictor in function. Third, spontaneously occurring unitary discharges were inhibited during a 75-100 mmHg rise in systemic blood pressure produced by the intravenous injection of norepinephrine (i.e., baroreceptor reflex activation). The spontaneous preganglionic unitary discharges most often occurred during mid-diastole. These observations suggest that the occurrence of background

unitary discharge was related to the level of systemic blood pressure and phase of the cardiac cycle.

The striking similarity between the characteristics of the relatively fixed and variable onset latency responses and the baroreceptor reflex-sensitive and -insensitive potentials elicited in the external carotid postganglionic nerve suggest that the two unitary response patterns monitored the activation of the medullary components of the two systems of pressor pathways. The features of the relatively fixed onset latency unitary responses that were similar to those of the short-latency (34-44 msec) postganglionic potentials are as follows: 1) baroreceptor reflex activation failed to block these unitary responses; 2) depressor region stimulation paradoxically enhanced the probability of occurrence of the relatively fixed onset latency unitary responses and the amplitude of the short latency compound postganglionic potentials (cf. Snyder and Gebber, 1973), this effect occurred regardless of whether the PSN was firing spontaneously or silent; 3) both the relatively fixed onset latency unitary responses and the short-latency postganglionic potentials were evoked primarily from pressor sites located in R.v. of the medial reticular formation; 4) it was difficult to elicit both types of responses with single shocks applied to the medulla;

5) central conduction time and velocity in the pathways mediating the relatively fixed postganglionic potentials were approximately the same. This was also the case for the following characteristics (f_{50}) of the unitary preganglionic and compound postganglionic responses.

The characteristics of the variable onset latency unitary responses corresponded with those for the long latency potentials evoked in the external carotid nerve. These responses were blocked during depressor region stimulation and baroreceptor reflex activation. Both the variable onset latency unitary discharges and the long latency postganglionic potentials were elicited from pressor sites distributed diffusely throughout the periventricular gray, dorsolateral reticular formation and R.v. Single shocks or trains of pulses applied to the same pressor site were almost equally effective in evoking these responses. The following characteristics (f_{50}) of the unitary preganglionic and compound postganglionic responses were essentially equivalent. Finally, spinal conduction time and velocity were comparable in the pathways mediating the variable onset latency unitary discharges and the long latency potentials evoked in the external carotid nerve.

Most important was the observation that individual preganglionic units are impinged upon by both systems of

vasopressor pathways. It was common for the same cell to exhibit a response which was blocked (variable onset latency) and one which was not blocked (relatively fixed onset latency) by NE or depressor region stimulation. In some instances, a neuron simultaneously exhibited both response patterns to stimulation of a pressor site in the medulla. These data provide additional support for the contention that the baroreceptor reflex-insensitive responses evoked in the external carotid nerve monitored the activation of central components of a system of "vasoconstrictor" pathways.

This investigation uncovered some other basic relationships between the central vasomotor regions and single preganglionic units. It was found that individual preganglionic units are influenced by neuronal elements located throughout the medullary pressor region. Individual units were routinely excited by stimulation of 70-80% of the medullary pressor sites tested. The sites from which a unit could be activated were distributed throughout the periventricular gray, dorsolateral reticular formation and the lateral portions of the medial reticular formation (R.v.). Thus, the medullary receptive field for excitation of a unit was comprised of a large portion of the total pressor region as defined in earlier studies (Alexander, 1946; Bach, 1952; Chai and Wang, 1962; Wang and Ranson, 1939a).

Extensive convergence of excitatory pathways onto single preganglionic neurons also was indicated by the degree of variability of discharge onset latency observed when successive trains of stimuli or single shocks were applied to certain pressor sites in the medulla. This observation can be explained in at least two ways. First, it is possible that the variability of unitary discharge onset latency resulted from random summation of electrically evoked and spontaneously occurring excitatory postsynaptic potentials at a site of convergence of a number of descending pathways. Alternatively, stimulation of a medullary site may have activated a number of different pathways converging onto the same preganglionic unit. At this stage, the data presented in this study do not differentiate between these possibilities. In either case, the variability of the latency of preganglionic spike initiation would reflect changing patterns of discharge in the pathways converging onto the preganglionic neurons. The level of excitability in any given pathway most likely is determined by intrinsic as well as afferent sensory information processed in the vasomotor centers.

A diagram schematically illustrating the two systems of vasopressor pathways is shown in Figure 43. The short onset latency (SL) pathway was excited from hypothalamic, medullary and midcervical spinal levels of the neuraxis.

Figure 43. Diagram illustrating the distribution of the two parallel systems of pressor pathways to the cervical sympathetic and splanchnic nervous outflow.

Open circles represent excitatory synapses. Closed circles depict inhibitory relays. LL hypo, LL med, LL spinal: hypothalamic, medullary and spinal components of the long-latency (>50 msec) vasopressor pathway. SL hypo, SL med and SL spinal: hypothalamic, medullary and spinal components of the short-latency (<50 msec) system of vasopressor pathways. Pre cst and Pre spl: preganglionic sympathetic neurons whose axons are contained in the cervical sympathetic and splanchnic nerve respectively. B: baroreceptor afferent input. I_B: inhibitory system of baroreceptor origin which controls transmission in the long-latency system of pathways and tonic SND. I_{NB}: inhibitory sysatem of non-baroreceptor origin which controls transmission of impulses in the short-latency system of pathways at a medullary locus as demonstrated by Snyder and Gebber (1973).

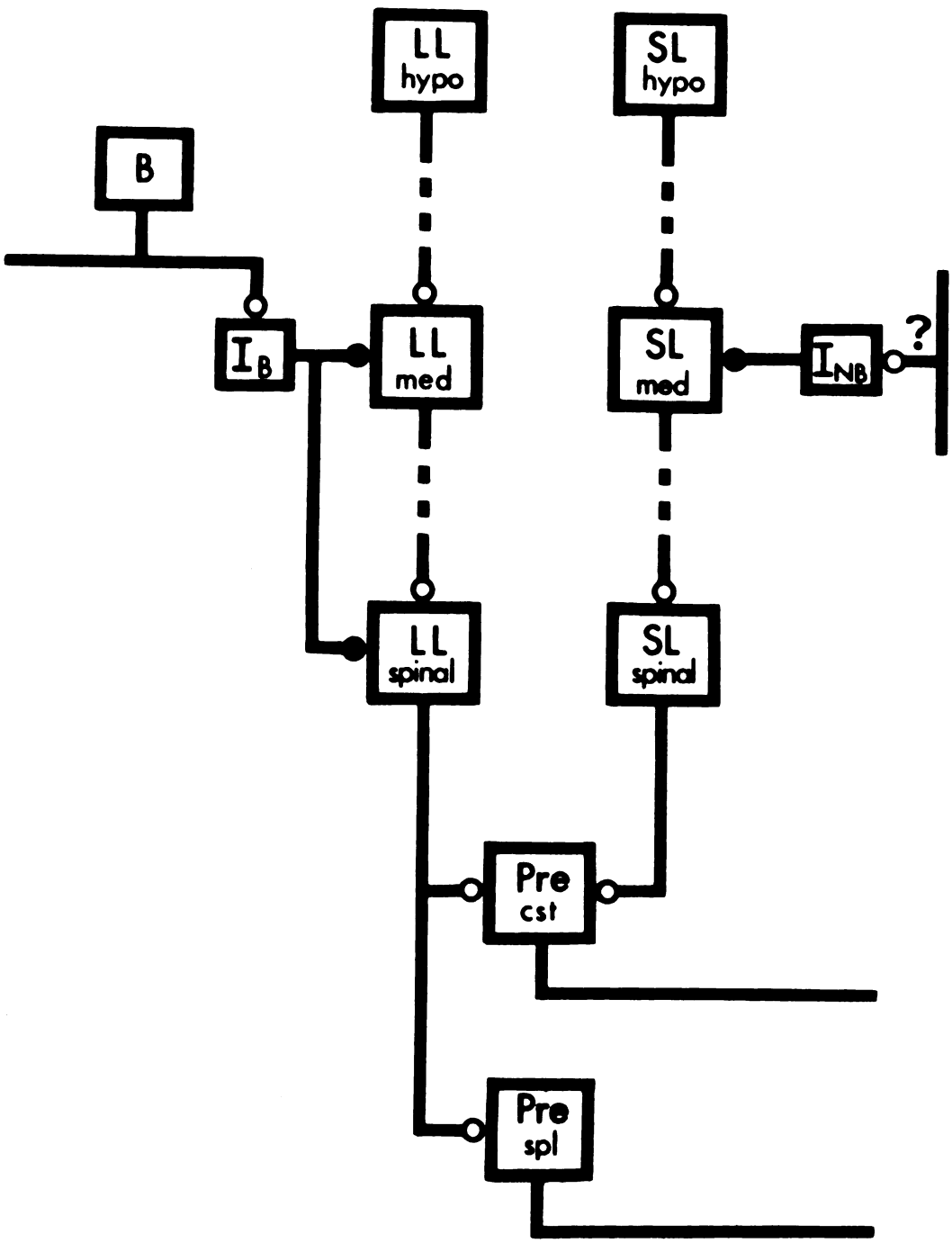
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Figure 43

Transmission of impulses in this system was not under the control of the baroreceptor reflexes. However, baroreceptor reflex-insensitive responses could be blocked at a medullary locus by high-frequency stimulation of a "non-baroreceptor" inhibitory system (I_{NB}) located in the medial medulla (Snyder and Gebber, 1973). The "question mark" indicates that the central and/or peripheral input to this inhibitory system is unknown at this time. Central elements of the baroreceptor-insensitive system do not appear to be distributed to splanchnic nerve outflow. Hypothalamic, medullary and spinal components of the long-latency (LL) baroreceptor reflex-sensitive system of pressor pathways are distributed to both cervical (Pre_{cst}) and abdominal (Pre_{spl}) sympathetic nerves. Convergence of baroreceptor-sensitive and -insensitive pathways (viz., variable and relatively fixed onset latency response patterns) onto individual PSN supplying the cervical region is indicated (Pre_{cst}).

Baroreceptor reflexes inhibit SND at a medullary and spinal locus as indicated by the lines drawn from I_B. Evidence was provided supporting the concept that the medullary component of the baroreceptor reflex arc regulates the formation and frequency of occurrence of the slow wave of SND. The amplitude of SND might be controlled by the baroreceptor reflexes at a spinal integration site.

The functional significance of the two parallel systems of pressor pathways found in the external carotid nerve is at present a matter of speculation. As suggested by Snyder and Gebber (1973), the baroreceptor reflex-sensitive system appears to mediate background vasoconstrictor discharge. The reflex-insensitive system was presumed not to be tonically active in my experimental conditions, since all spontaneously occurring activity in the external carotid nerve was reduced to noise levels during baroreceptor reflex activation. Thus, the two systems may function in the tonic and phasic control of blood pressure during certain behavioral situations.

SUMMARY

The present investigation characterized spontaneously occurring and electrically evoked discharges recorded in whole pre- and postganglionic sympathetic nerves and single sympathetic neurons. A slow wave of SND, locked in a 1:1 relation to the heart beat (∿ 3 c/sec periodicity), was recorded from splanchnic preganglionic and renal postganglionic nerves. Although baroreceptor denervation and partial hemorrhage unlocked the phase relations between SND and the cardiac cycle, the slow wave persisted and its duration was not changed. These observations contradict the generally accepted view that pulse-locked waves of SND occur as the direct result of a waxing and waning of baroreceptor nervous discharge.

Early and late positive potentials were evoked in splanchnic and renal nerves when a short train of 3 pulses was applied to the baroreceptor nerves or paramedian reticular nucleus randomly with respect to the cardiac cycle. Evidence suggesting that the late positive potential monitored the inhibition of the slow wave of SND is provided by the following observations: 1) a single shock applied to the paramedian reticular nucleus at appropriate

points in the pulse cycle inhibited the development of one entire wave of SND; 2) the contour of the late positive potential was the mirror image of the centrally emanating slow negative wave; 3) the late phase of positivity could not be evoked during asphyxia or following severe hemorrhage at a time when the 3 c/sec oscillations of SND were virtually absent. Since the late positive potential is presumed indicative of inhibition of a slow negative wave, then the 3 c/sec periodicity was aborted by stimuli delivered to the baroreceptor nerves or the paramedian nucleus during a time span which accounted for less than 1% of the cardiac cycle. It was concluded that the 3 c/sec periodicity of SND is representative of a vasomotor rhythm of central origin which is entrained to the cardiac cycle by the baroreceptor reflexes. The sympathoinhibitory effect leading to the entrainment of the slow wave is mediated at the brain stem level.

To define the functional organization of brain elements transmitting the waves of SND, a study was made of the responses evoked in vasoconstrictor nerves by single shocks or trains of stimuli applied to brain and spinal pressor regions. The data demonstrated that vasopressor outflow from the hypothalamus, midbrain, medulla and cervical spinal cord to the external carotid nerve is organized into two systems of parallel pathways. Impulse transmission in one of these systems was blocked during

baroreceptor reflex activation, while the other system was not inhibited during a rise in arterial pressure produced by iv norepinephrine. The baroreceptor reflex-sensitive and -insensitive pathways were further differentiated on the basis of their onset latencies, durations, ability to follow high-frequency stimulation, and response patterns to single shocks and trains of stimuli. The baroreceptor reflex-insensitive system could not be unveiled in the splanchnic nerve; only baroreceptor-sensitive responses were recorded. A spinal component of baroreceptor reflex-induced sympathoinhibition was demonstrated on the external carotid and the splanchnic nerve. Recently, Snyder and Gebber (1973) revealed that the baroreceptor reflex-sensitive system of pathways most likely participates in the conduction of spontaneously occurring SND.

Single sympathetic preganglionic neurons of the thoracic spinal cord, whose axons were contained in the cervical sympathetic nerve, exhibited two types of response patterns which were distinguished by their receptivity to blockade upon baroreceptor reflex activation or medullary depressor stimulation. Furthermore, it was demonstrated that the relatively fixed and variable onset latency unitary response patterns monitored the activation of the medullary components of the baroreceptor reflex-insensitive and -sensitive system of

vasopressor pathways. The individual unit functioned as the final common pathway for the two vasopressor systems descending from the medulla, thus confirming the idea that the baroreceptor reflex-insensitive system indeed functions in the transmission of vasoconstrictor information. Therefore, central components of vasopressor pathways distributed to the vascular beds supplied by the cervical sympathetic and splanchnic nerves are organized differently.

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APPENDICES

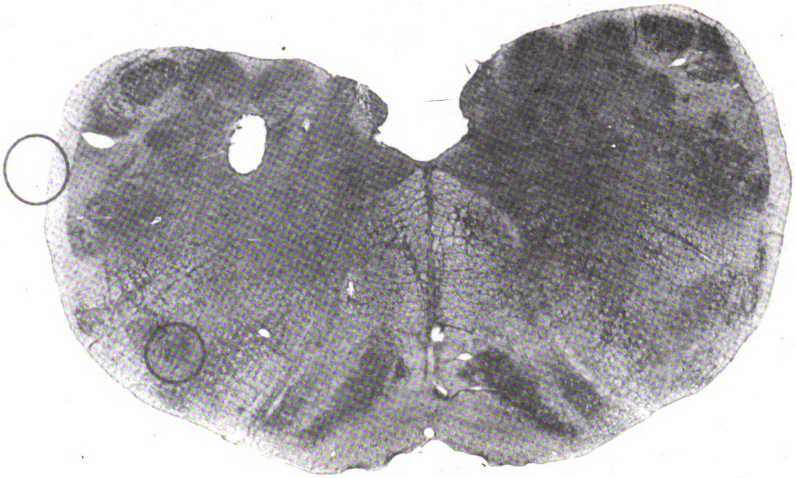
APPENDIX A. Photomicrograph revealing site in medial medulla from which early and late positive potentials were elicited.

The electrolytic lesion is located in the paramedian reticular nucleus at the stereotaxic level of P_{12}. Lesion was made with direct current of 2 ma for 10 sec through the concentric stimulating electrodes. This site was approached from the dorsal surface of the brain.

Appendix A

APPENDIX B. Photomicrograph showing location of site in medulla from which a baroreceptor reflex-sensitive response was evoked.

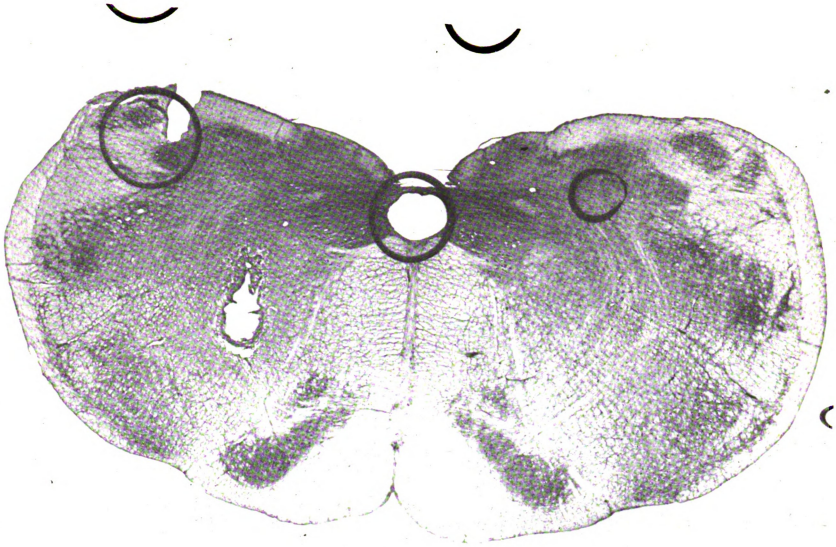
The lesion, in the dorsolateral medulla, was made with 2 ma direct current for 10 sec through the concentric stimulating electrodes. The area was approached from the ventral surface of the brain stem. This frontal section corresponds to a stereotaxic level of P_{13}.



Appendix B

APPENDIX C. Photomicrograph depicting location of site in medulla from which a baroreceptor reflex-insensitive potential was elicited.

The electrolytic lesion is in the nucleus reticularis ventralis at the stereotaxic level of P_{15}. Position of the concentric stimulating electrodes was marked with direct current of 2 ma for 10 sec. Approach to the nucleus was from a ventral aspect.



Appendix C

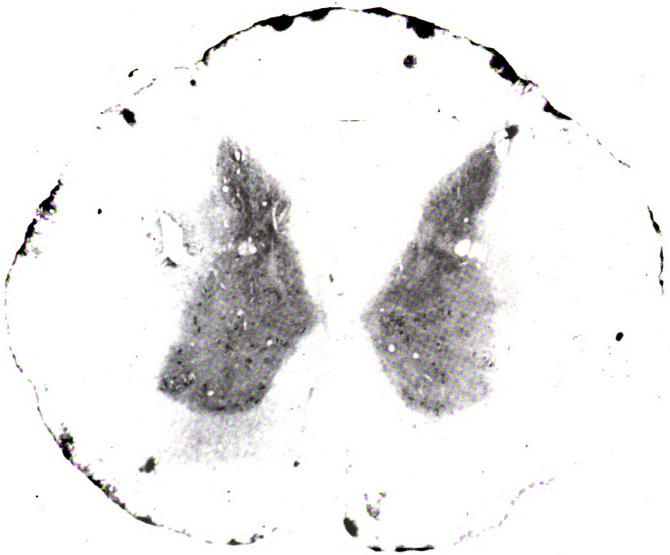
APPENDIX D. Photomicrograph revealing site in midcervical spinal cord from which descending baroreceptor reflex-sensitive potential was evoked.

Lesion was produced by direct current through the stimulating electrodes (2 ma, 10 sec). The site of lesion is in the dorsolateral white column of cervical spinal cord between C_3 and C_4. Responses elicited from this site were present after C_1 transection.

Appendix D

APPENDIX E. Photomicgrograph showing midcervical spinal site from which descending baroreceptor reflex-insensitive response was elicited.

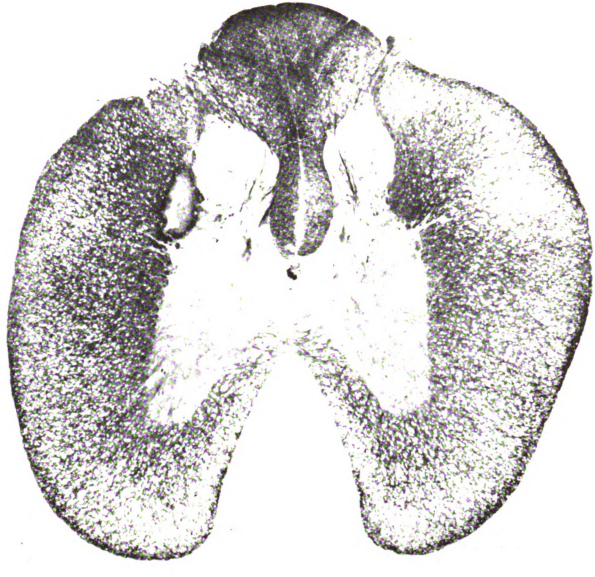
The lesion is located in the dorsolateral white column of the midcervical spinal cord (C_{3-4}). Electrolytic destruction was produced with direct current through bipolar concentric electrodes (2 ma for 10 sec). The response was not abolished by spinal transection at the first cervical level.



Appendix E

APPENDIX F. Photomicrograph depicting thoracic spinal site from which cervical sympathetic preganglionic unit was recorded.

The electrolytic lesion is located in the dorsolateral portions of the intermediolateral nucleus at the third thoracic spinal segment. Lesion was made with 0.5 ma direct current for 3 sec through the stainless steel recording microelectrode.



Appendix F