Interaction of Descending Sympathetic Pathways and Afferent Nerves in Cardiovascular Regulation

Susan Marie Barman
Loyola University Chicago

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INTERACTION OF DESCENDING SYMPATHETIC PATHWAYS AND AFFERENT NERVES IN CARDIOVASCULAR REGULATION

by

Susan Marie Barman

A Dissertation Submitted to the Faculty of the Graduate School of Loyola University of Chicago in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

February

1976
DEDICATION

I dedicate this work to my late Mother, whose hopeful expectations have been realized.
BIOGRAPHY

Susan Marie Barman was born in Joliet, Illinois, on August 28, 1949. She attended parochial grade schools and graduated from St. Francis Academy, Joliet, in 1967.

Susan attended Loyola University, Chicago, Illinois, from 1967 - 1971. During her Senior year, she was a laboratory assistant in Human Anatomy and Physiology, under the direction of Drs. M. Goldie and E. Cardona. She graduated with a Bachelors of Science Degree in Biology in June, 1971.

Susan entered graduate school in August, 1971, in the Department of Physiology at Indiana University Medical Center, Indianapolis, Indiana. In June, 1972, she transferred to Loyola University, Department of Physiology, Maywood, Illinois. In September, 1972, she began to study under the direction of Dr. Robert D. Wurster, and was supported by a Research Training Grant of the National Institute of General Medical Sciences of the National Institute of Health.

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BIOGRAPHY (continued)

Susan has accepted a two-year Research Associate position with Dr. Gerard L. Gebber, Professor of Pharmacology, Michigan State University, East Lansing, Michigan.

Susan is a student member of the Society of Neuroscience and an associate member of the American Physiological Society and Sigma Xi. She is also a member of the National Jesuit Honor Society.
ACKNOWLEDGMENT

At this time I would like to extend my sincere appreciation to my advisor, Dr. Robert D. Wurster. Throughout the past three years he has challenged me to develop patience and perseverance during a scientific investigation and, thereby, to mature as an independent researcher.

Dr. Walter C. Randall, who served as Chairman of the Department of Physiology during the major part of this investigation, will long be remembered and admired for striving to maintain a Department with free communication between faculty and students.

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I would also like to thank Mr. Jin Mo Chung and the many other students who have shared their time with me in discussing my research and offering suggestions. In addition, their friendships will long be remembered and cherished.

My sincere appreciation is extended to Ms. Helena Mauceri. The many hours she spent in helping me with the figures in this dissertation, and most especially her uncompromising friendship, will never be forgotten.

I am also grateful to Ms. Carol Birk for her long hours of patient work while typing this dissertation.
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CHAPTER I
INTRODUCTION AND STATEMENT OF PURPOSE

Neural regulation of the cardiovascular system involves the integrative action of every level of the nervous system. However, the medulla has long been recognized as the site of the major "vasomotor center." Classical experiments from Ludwig's laboratory, demonstrating the important role of the medulla in both tonic and reflex control of the circulation, have been repeatedly verified (7, 138, 142, 188). Alexander (2) localized pressor and depressor areas in the medullary reticular formation. His data indicated that the depressor areas supplies a tonic outflow to spinal cord neurons. These data suggest an important role of the spinal cord in regulating sympathetic outflow. Tonic sympathetic nerve discharges are thus determined by the balance of activity within excitatory and inhibitory pathways influencing preganglionic neurons in the thoraco-lumbar spinal cord.

Supramedullary structures involved in cardiovascular regulation may also mediate their effects by acting
on spinal cord preganglionic neurons or interneurons. Corticospinal (105), hypothalamo-spinal (12), and mesencephalo-spinal (112) pathways have been described.

In addition to central nervous system structures, afferent nerve fibers also play a role in cardiovascular regulation (97, 165). Stimulation of afferent nerve fibers elicits early and late reflex discharges in sympathetic nerve fibers. The early discharge is complete within the spinal cord. The role of this reflex in cardiovascular regulation in an intact animal is not understood, but Sato (159) has suggested that this reflex may be important for localized control of the circulation. The capability of the spinal animal to demonstrate cardiovascular reflexes following somatic nerve stimulation was shown by Sherrington (177).

These data suggest that preganglionic neurons in the thoraco-lumbar spinal cord act as the final common pathway in determining sympathetic outflow. The purpose of this study was to investigate the role of the spinal cord in regulating sympathetic outflow through integration of activity from descending spinal sympatho-excitatory (56, 59, 81, 92, 178) and sympatho-inhibitory (35, 36, 81, 82) pathways and afferent nerve fibers. Blood pressure and second thoracic (T2) preganglionic nerve discharges were monitored during stimulation of each of
these systems separately and during simultaneous stimulation of any two of these systems.
CHAPTER II
LITERATURE REVIEW

A. Cerebral Cortex and Limbic System

1. Early Literature on Cortical Regulation of the Cardiovascular System

Since 1869 many investigators have shown that several regions of the cerebral cortex are capable of regulating the autonomic nervous system. The early literature has been extensively reviewed by Hoff and co-workers (75). Hughlings Jackson (75) was one of the first investigators to suggest that the cortex can influence the sympathetic nervous system. While studying patients with epileptic seizures, he noted that convulsions occurred in association with autonomic dysfunction (shivering, facial pallor, salivation, and vomiting). Beginning in 1876, several laboratories reported experimental evidence for cerebral cortical regulation of autonomic functions. Schiff (75) noted that stimulation of the cortex in dogs resulted in cardiac acceleration. Danilewsky (75) observed a fall in arterial blood pressure and a
tachycardia during stimulation of the corpus striatum in curarized dogs. Pressor responses and bradycardia were elicited by stimulation of the suprasylvian gyrus. Bochefontaine (75) in 1876 reported that stimulation of the anterior or posterior sigmoid gyrus in curarized dogs elicited a rise in arterial pressure. Bechterew and Mislawski (75) in 1886 demonstrated that pressor responses from stimulation of the globus pallidus, internal capsule, and caudate nucleus were independent of stimulation of descending motor fibers. Animals used in this latter study had previously undergone ablation of the motor cortex, resulting in degeneration of descending motor pathways. Bechterew and Mislawski also noted pressor responses from stimulation of the posterior sigmoid gyrus and depressor responses from stimulation of the anterior sigmoid gyrus.

2. Localization of Pressor and Depressor Areas in the Motor Cortex

More definitive localization of pressor and depressor areas within the motor cortex were described by Hoff and Green (74). These investigators examined a wide area of the motor cortex in ether anesthetized cats, monkeys, and a chimpanzee. Pressor responses were most easily elicited in the cat during stimulation of the posterior and anterior sigmoid gyri and the adjacent
gyrus proreus. Depressor responses were consistently elicited from activation of the lateralis medius, suprasylvian, ectosylvian, and sylvian gyri. In the monkey, pressor responses resulted from stimulation of cortical areas adjacent to the superior precentral sulcus and the trunk and arm areas of the frontal gyri and precentral sulcus. These responses were independent of muscle movements. To verify that the responses were due to direct stimulation of cortical neurons and not due to current spread to subcortical areas, a local anesthetic was applied to a discrete area of the cortex. This procedure abolished the response to stimulation, but adjacent areas were still excitable. In a later study, Green and Hoff (65) compared the effects of ether and diallylbarbiturate (Dial) anesthesia on the responses to stimulation of the anterior sigmoid gyrus. Animals under Dial show a decrease or no change in blood pressure, a decrease in renal volume, and an increase in limb volume. Pressor responses and qualitatively similar volume changes were elicited from cortical stimulation in animals anesthetized with ether. These authors suggested that the pressor responses with ether anesthesia resulted from a predominance of splanchnic vasoconstriction; depressor responses with Dial anesthesia was due to a predominance of limb vasodilatation.
In chloralose anesthetized dogs, Hsu and co-workers (79) noted somewhat different results. Stimulation of the sigmoid gyrus in these animals evoked a decrease in blood pressure and an increase in renal volume, heart rate, and respiratory rate. Depressor responses were not affected by vagotomy. The authors concluded that vasodilatation of visceral organs was responsible for the fall in blood pressure.

Wall and Davis (189) described cardiovascular responses to cortical stimulation in monkeys and chimpanzees under Dial anesthesia. No attempt was made to distinguish pressor from depressor loci, since these authors felt that the direction of the change in blood pressure was a function of the control blood pressure, depth of anesthesia, and general condition of the animal. Maximum changes in blood pressure occurred during stimulation of the primary motor and somato-sensory areas, both posterior and anterior to the central fissure. Decamethonium was administered to insure that these responses were independent of muscle movements. Section of the pyramidal tract abolished the responses to stimulation of motor and sensory cortex.

Delgado (44) described the effects of stimulation of the motor cortex in unanesthetized cats and monkeys with implanted electrodes. The most frequent
cardiovascular response was a rise in blood pressure. However, in some instances either no change or a mild depressor response was observed.

3. Cardiovascular Responses to Frontal Lobe Stimulation

Frontal lobe areas appear to exert an inhibitory influence on the sympathetic nervous system. Kabat and co-workers (88) studied cardiovascular responses to cortical stimulation in cats under light sodium pentobarbital (Nembutal) anesthesia. Moderate depressor responses were recorded during stimulation of the rostral part of the frontal lobe. These responses were independent of muscle movement. These authors suggested that the cortex is the origin of a corticofugal inhibitory pathway which extends to the border of the diencephalon.

Livingston and co-workers (116) described cardiovascular changes during stimulation and ablation of the orbital surface of the frontal lobe in monkeys and chimpanzees. Two types of responses were elicited: an instantaneous fall in blood pressure or a slow rise in pressure. Respiratory arrest was also noted during cortical stimulations. Responses were unaffected by vagotomy or excision of the adrenal glands. Ablation of the frontal lobe resulted in hyperactivity, characterized by an increased temperature in the extremities and an enhanced reflex vasodilatation. These data indicated that
the frontal lobe exerts a tonic inhibitory influence on the sympathetic nervous system. Livingston and co-workers (117) also described the effects of frontal lobe stimulation in patients prior to undergoing frontal lobotomy. Respiratory arrest and a rise in blood pressure were the most characteristic responses to orbital surface stimulation.

4. Cardiovascular Responses from Stimulation of the Limbic System

The limbic system has also been found to exert an influence on the autonomic nervous system. Wall and Davis (189) stimulated the anterior cingulate gyrus and noted a 10 - 20 mm Hg change in arterial blood pressure. These responses were abolished by ablation of the temporal lobe. Kaada (87) made an extensive study of rhinencephalic regulation of the cardiovascular system in dogs, cats, and monkeys. Depressor responses were most easily elicited by stimulation of the corpus callosum, anterior insula, olfactory tubercle, and anterior limbic area. Vagotomy eliminated the depressor responses from the limbic area, insular region, and the temporal lobe.

Lofving (117) investigated sympatho-inhibitory regions within the anterior cingulate gyrus in cats which were curarized and chloralose anesthetized. In
order to facilitate sympathetic responses, high sympathetic tone was induced by bilateral carotid occlusion. In addition to recording blood pressure, blood flow in several vascular beds was also measured. Vasodilation was most pronounced in the skeletal muscle, moderate in the skin and intestine, and negligible in the kidney. Responses were eliminated by electrolytic lesions in sympathetic regions of the hypothalamus or medulla. Lofving suggested that the inhibitory neuron pool within the anterior cingulate gyrus may exert a steady inhibitory influence on sympathetic outflow. He also suggested that this cortical area may be responsible for the cardiovascular responses during emotional fainting in man or "playing dead" in animals.

The septal area has also been studied with regards to its role in cardiovascular regulation. Covian (41) described cardiovascular responses to stimulation of septal regions in cats and rabbits anesthetized with chloralose. Depressor responses persisted for 3 - 5 min after cessation of the stimulus. Baroreceptor reflexes (carotid occlusion) were blocked by simultaneous stimulation of the septal area.

Manning and co-workers (126) demonstrated sympatho-inhibitory responses from activation of the lateral and medial septal nuclei. Decreased heart rate,
contractility, and blood pressure persisted for 5 min after cessation of the stimulus. Cardiac responses were abolished by removal of the stellate ganglia or administration of ganglionic or beta adrenergic blocking agents. Removal of the stellate ganglia reduced the right ventricular contractile force to the same level as septal stimulation. The authors suggested that the cardiovascular responses to septal stimulation were mediated by a decrease in sympathetic tone to the blood vessels and heart.

Calaresu and Mogenson (21) reported variations in cardiovascular responses to septal stimulation, depending upon the type of anesthesia. In rats anesthetized with chloralose, stimulation of the lateral and medial septal nuclei elicited depressor and pressor responses, respectively. With identical stimulation parameters, opposite responses were noted in rats anesthetized with urethane. The authors suggested that these different responses may be due to variations in sympathetic tone, which appears to be higher in rats anesthetized with chloralose.

5. **Summary**

Activation of cortical structures leads to cardiovascular responses which are variable depending upon the type of anesthesia. In general it appears that the
motor cortex exerts a facilitatory effect on the sympathetic nervous system while the frontal lobe and limbic structures exert an inhibitory influence. Whether these responses represent activation of direct corticospinal tracts or pathways which influence medullary or hypothalamic vasomotor areas has not been determined.

B. Hypothalamus

1. Early Investigations of Cardiovascular Responses to Hypothalamic Stimulation

Karplus and Kreidl, in a series of reports between 1907 - 1927, were the first investigators to demonstrate autonomic responses to stimulation of the hypothalamus [as cited by Beattie and co-workers (12) and Kabat and co-workers (88)]. Following removal of the cerebral cortex, hypothalamic stimulation elicited pupillary dilatation, increased blood pressure, bladder contraction, increased rate and depth of respiration, alterations in gastro-intestinal peristalsis, and secretion of saliva, sweat, and tears. The cardiovascular responses were not affected by administration of curare or removal of the adrenal glands or pituitary; however, section of the splanchnic nerves greatly attenuated the rise in blood pressure. They made no attempt to define the precise localization for these autonomic responses.

Leiter and Grinker (109) were unable to confirm
Karplus and Kreidl's data. During stimulation of the hypothalamus lateral to the infundibulum, blood pressure increased. However, administration of curare abolished the responses, indicating the cardiovascular responses were secondary to somatic movements.

2. Stereotaxic Investigations of the Hypothalamus

Between 1935 - 1941 Magoun and co-workers (88, 119, 155) presented a series of papers describing the autonomic responses to stimulation of specific areas of the hypothalamus with the aid of the Horsley-Clarke investigation apparatus. Kabat, Magoun, and Ranson (88, 155) stimulated the diencephalon in 50 cats under light nembutal anesthesia and curare. Sympathetic responses, including increased blood pressure and bladder pressure and pupillary dilatation, were elicited during stimulation of the medial forebrain bundle, supra-optic commissure, lateral hypothalamus, perifornical nucleus, H1 fields of Forel, and periventricular fibers. They suggested that some of the responses were due to activation of fibers passing through these areas or to current spread. The maximal responses were between 35 and 98 mm Hg and were elicited by stimulation of the lateral hypothalamus in the region of the medial forebrain bundle. Stimulation of the region surrounding the anterior commissure and the septum resulted in bladder
contraction, decreased blood pressure, and a decreased rate and depth of breathing. The maximum decrease in blood pressure was 10 - 20 mm Hg. They suggested these were parasympathetic responses mediated by activation of corticofugal fibers. To determine the validity of this conclusion, Magoun (119) later studied the effects of stimulation of the hypothalamus before and after degeneration of the corticofugal connections from the frontal lobes. Four to six weeks after frontal lobotomy, he stimulated the preoptic area and the hypothalamus in anesthetized cats. Stimulation of the area surrounding the anterior commissure and the preoptic region still resulted in bladder contraction and a post-stimulus vasodilatation. These responses were not as pronounced as in cats with intact frontal lobes. Stimulation of regions in the anterior and posterior hypothalamus which elicited sympathetic responses were not affected by frontal lobotomy. Magoun concluded that depressor responses were due to activation of descending fibers from the cerebral cortex.

Crouch and Elliott (43) reported somewhat different patterns of changes in blood pressure, heart rate, respiration, and pupillary dilatation during stimulation of the hypothalamus. Stimulation of the anterior and lateral nuclear groups evoked the most responsive
rise in blood pressure. Stimulation of the posterior hypothalamus elicited a slight fall in blood pressure in some animals. Heart rate was never affected. Increased rate and/or depth of respiration was elicited in some animals during stimulation of the anterior, lateral, and posterior regions of the hypothalamus. Pupillary dilatation was most pronounced during stimulation of the lateral hypothalamus.

White (199) demonstrated the cardiovascular effects of electrical stimulation of the hypothalamus in patients undergoing surgery for relief of acute hydrocephalus. Stimulation in the region of the periventricular nucleus resulted in a marked increase in heart rate (from 45 to 145 beats/min in one patient) and a mild increase in systolic pressure (10 - 20 mm Hg). Stimulation of the anterior hypothalamus elicited a bradycardia which was blocked by prior administration of atropine.

McQueen and co-workers (129) noted pressor and depressor effects during hypothalamic stimulation in dogs under local anesthesia. Pressor responses were elicited from activation of the dorsal hypothalamic area, posterior hypothalamic nuclei, and perifornical nucleus. These responses were abolished by administration of an anesthetic dose of Nembutal. Mild depressor responses were occasionally evoked by stimulation of the medial
preoptic area and lateral hypothalamus. Pressor and depressor responses were both elicited at a threshold frequency of 30 Hz.

Enoch and Kerr (46, 47) described two pressor pathways in the hypothalamus using a combination of stimulation ablations, and degeneration techniques. One pathway originates in the frontal cortex, preoptic and septal nuclei, and limbic areas. Fibers then become diffuse and travel through the lateral hypothalamus and into the lateral mesencephalic tegmentum. The other pressor pathway arises from the dorsal and posterior hypothalamus near the midline (periventricular position) and then travels through the periaqueductal gray into the rostral mesencephalon. Maximal pressor responses were elicited during stimulation of an area adjacent to the dorsal surface of the optic chiasma, dorsolateral in the medial forebrain bundle, and the lateral hypothalamus. These responses were generally accompanied by tachycardia. Depressor responses were elicited during stimulation of the periventricular gray nucleus and medial hypothalamus. Depressor responses were seldom greater than a 20 mm Hg fall in systemic arterial pressure.

Folkow and co-workers (53, 54) provided a detailed description of sympatho-inhibitory mechanisms from hypothalamic stimulation in the cat. They suggested that
depressor responses may result from one of three mechanisms: (1) excitation of vasodilator fibers; (2) activation of vagal fibers; or (3) generalized or regional inhibition of tonic sympathetic nerve activity. Cats, anesthetized with chloralose, were vagotomized and atropinized to eliminate the first two mechanisms for evoking a depressor response. To induce a high sympathetic tone in the animals, the carotid arteries were bilaterally clamped. Stimulation of a restricted area in the hypothalamus below and behind the anterior commissure, 2 mm from the midline, elicited a decrease in blood pressure, decrease in heart rate, and a rise in blood flow to skeletal muscle, skin, and intestine. In addition to vasodilation of the resistance vessels, these investigators also reported decreased tonic sympathetic activity to the precapillary sphincter and venous capacitance vessels. They suggested that this area of the hypothalamus may be involved in the cardiovascular events associated with emotional fainting.

Peiss (141) studied sympatho-inhibition from hypothalamic stimulation in the dog. In contrast to the sharply delimited sympatho-inhibitory region in the cat hypothalamus, Peiss described a wide distribution of sympatho-inhibitory points in the anterior hypothalamus and limbic system. Depressor responses were also elicited
by stimulation within the posterior hypothalamus. He sug-
gested that these responses may be due to activation of
fibers from the anterior inhibitory areas. In addition to
a decrease in blood pressure, Peiss also noted a decrease
in heart rate and in ventricular contractile force.

Feigl (50) and Forsyth (58) reported effects of
stimulation of the hypothalamus on regional blood flow
distribution. While stimulating pressor regions within
the anterior and lateral hypothalamus in cats anesthe-
tized with chloralose, Feigl was unable to find points
which demonstrated differential control to kidney and
intestinal vasculature. Forsyth, while stimulating at
intensities subthreshold for a pressor response, noted a
differential response in nine vascular beds in the un-
anesthetized Rhesus monkey. Similar regional distribu-
tion of cardiac output was noted when stimulating at in-
tensities great enough to elicit an increase in blood
pressure and tachycardia.

3. Cardiac Responses to Hypothalamic Stimulation

Beattie and co-workers (11, 12) investigated the
effects of stimulation and ablation of the hypothalamus
on chloroform-induced arrhythmias. Following administra-
tion of adrenaline in cats under chloroform anesthesia,
ventricular fibrillation was often induced. This re-
sponse was abolished by decerebration. Stimulation of
the hypothalamus in chloroform anesthetized cats also resulted in ventricular fibrillation. Sciatic nerve stimulation could also elicit this arrhythmia if the hypothalamus was intact.

Wang and Ranson (197) studied heart rate responses to hypothalamic stimulation in chloralose anesthetized cats. Heart rate increased 5 - 25% above control during stimulation of pressor areas. The response was independent of the rise in pressure, since similar chronotropic responses were evoked following ligation of the abdominal vessels at the level of the diaphragm. Stimulation of the preoptic area elicited a 6 - 19% decrease in heart rate which was abolished by vagotomy. However, the associated depressor response was not blocked by vagotomy.

Korteweg and co-workers (100) studied ECG changes during stimulation of the hypothalamus in cats under ether anesthesia. Stimulation of the anterior hypothalamus elicited a slowing of the sinus rhythm and a decrease in blood pressure. Both responses were abolished by vagotomy. Posterior hypothalamic stimulation elicited an increase in blood pressure, pacemaker shift, and a change in sinus rhythm. The large rise in pressure generated arrhythmias.

Smith and co-workers (180) studied ventricular pressure, ventricular diameter, and heart rate changes
during eating, exercise, and startle both before and after hypothalamic ablation. Control responses were affected in various ways following ablation of the hypothalamus. These investigators suggested that cardiovascular changes which occur during eating, exercise, and startle are mediated by the hypothalamus.

Manning and Peiss (124) described cardiac augmentation and acceleration sites within the hypothalamus of cats anesthetized with chloralose or curare. Pure cardiac acceleration was induced by stimulation of the lateral hypothalamus 3 mm left of the midline. Only 1 mm away in the H₂ fields of Forel, stimulation resulted in increased vasomotor activity without a change in heart rate. Activation of the H₁ fields of Forel resulted in cardiac augmentation as indicated by the large rise in systolic blood pressure. No change in heart rate was elicited. Stimulation of the posterior hypothalamus, 1.5 mm to the right of the midline and dorsomedial to the fornix, resulted in activation of cardiac augmentor and vasomotor fibers, an indicated by the increase in pulse pressure associated with a large rise in diastolic pressure. Stimulation of the posterior hypothalamus, 1 mm to the right of the midline and ventromedial to the mammillothalamic tract, causes a simultaneous activation of cardiac accelerator and augmentor and vasomotor fibers.
Manning and de V. Cotten (125) also studied ECG changes during posterior hypothalamic stimulation in cats. Sinus tachycardias, ventricular premature contractions, bigheminal rhythms, A-V dissociation, or ventricular tachycardias developed immediately after onset of stimulation. These responses were abolished by cooling the vagus nerves, bilateral vagotomy, extirpation of the stellate ganglia, or administration of methylscopolamine. Stimulation of either the cut distal end of the vagus or the stellate ganglia did not elicit the arrhythmias. However, simultaneous activation of these nerves did elicit responses similar to hypothalamic stimulation.

Peiss (141) noted that stimulation of the left hypothalamus in dogs elicits a greater change in contractile force than right hypothalamic stimulation, while the opposite is true for heart rate changes. This separation of chronotropic and inotropic responses was not seen in the cat. Similar responses were noted in the dog by Fang and Wang (48).

Bruno and co-workers (19) studied the mechanism for generation of tachycardia during posterior hypothalamic stimulation. Since the response was not abolished by sympathectomy, these investigators studied the response in cats with intact vagal fibers, aortic depressor nerves, and sinus nerves. Following spinal cord
lesion at T₄⁻₅ stimulation of the hypothalamus still produced a rise in pressure and tachycardia. Removal of the stellate ganglia attenuated but did not abolish the tachycardia. Spinal cord lesion at C₇⁻₈ did abolish the cardiac response. Administration of norepinephrine to these spinal animals elicited a reflex bradycardia. Simultaneous stimulation of the hypothalamus could now elicit a tachycardia. These authors suggested that the hypothalamic-induced tachycardia was mediated by simultaneous increase in sympathetic activity and a decrease in vagal tone.

4. Electrophysiological Characteristics of Hypothalamic Stimulation

Pitts and co-workers (16, 144, 145) provided detailed descriptions of the changes in inferior cardiac nerve and cervical sympathetic nerve activity during stimulation of the lateral and posterior hypothalamus in cats. While maintaining the frequency of stimulation constant, increasing the intensity of stimulation caused an increase in nerve activity. In addition to spontaneously active units firing more frequently, fibers which were not tonically active began to discharge. Increasing the frequency of stimulation resulted in similar responses. In single fiber preparations of the cervical sympathetic trunk, they noted that fibers discharged once
to every 20 - 25 stimulations. They suggested that multiple pathways from the hypothalamus descend to influence preganglionic nerve activity in the spinal cord. More of these pathways are activated by greater intensity or greater frequency of stimulation and by changing the location of the electrode. Frequency of neuron discharge is proportional to the number of pathways activated and to the frequency of discharge within the individual pathways. The increased discharges in inferior cardiac nerve elicited by low intensity stimulation of the hypothalamus were abolished during the pressor response to nor-epinephrine. Discharges evoked from high intensity stimulation were not abolished by baroreceptor activation.

In addition to the increase in nerve activity during stimulation, these investigators also noted a decrease in tonic activity following the stimulation. This was the earliest demonstration of the silent period in sympathetic nerves. This inhibition of tonic activity lasted as long as 4 sec. Increasing the frequency or intensity of hypothalamic stimulation increased the duration of the silent period. The silent period was also prolonged if the duration of the stimulus was increased.

Scherrer (168) demonstrated changes in renal nerve activity during posterior hypothalamic stimulation in
immobilized rats anesthetized with nembutal-urethane. Spontaneous activity occurred in irregular bursts or pulse-synchronized bursts. Hypothalamic stimulation could cause these fibers to discharge continuously. The end of the stimulus is followed by an afterdischarge for 120 - 140 msec and a silent period for approximately 3 sec. The duration of the silent period was proportional to the stimulus intensity and tonic activity. In addition to the silent period following stimulation, Scherrer also noted a silent period during spontaneous bursts of discharges. During this time, renal nerves were inexcitable to hypothalamic stimulation.

Ninomiya and co-workers (136) recorded renal, splenic, and hindlimb skeletal muscle sympathetic nerve discharges during hypothalamic stimulation in nembutal anesthetized cats. Sympathetic activity in nerves to organs with differing functions was influenced simultaneously by many hypothalamic areas, but not uniquely influenced by any area. These authors presented evidence for non-uniform contribution and summation of hypothalamic stimulus effects. They suggested that these mechanisms provide for a refinement of central autonomic control.

Gebber and co-workers (59) recorded evoked discharges in external carotid sympathetic nerves during stimulation of the lateral and posterior hypothalamus
in anesthetized cats. Repetitive discharges following short trains of stimuli occurred with a latency of 41 - 71 msec and with a duration of 40 - 250 msec. Early spikes (less than 50 msec latency) were not inhibited during the pressor response to norepinephrine; however, longer latency responses were partially or completely blocked. The authors suggested that central vasopressor pathways are organized along two systems, characterized by their sensitivity to baroreceptor activation.

4. Tonic Influence from the Hypothalamus

Supramedullary structures are generally considered to have a negligible effect on tonic vasomotor activity. Bronk and co-workers (15) and Alexander (2) demonstrated that decerebration had no effect on tonic sympathetic nerve discharges. Recently evidence has accumulated that the hypothalamus may exert a tonic control on cardiovascular regulation. Redgate and Gellhorn (156) studied the cardiovascular effects of injections of pentothal or procaine into the posterior hypothalamus of cats anesthetized with chloralose. Blood pressure decreased between 10 - 80 mm Hg and heart rate was reduced following administration of these anesthetics. Gellhorn (60) later confirmed these observations in cats under local anesthesia. In addition, he injected these drugs into the anterior hypothalamus. Blood pressure then
increased approximately 20 mm Hg and heart rate increased an average of 26 beats/min. An electrolytic lesion confined to the posterior hypothalamus caused a decrease in blood pressure and heart rate, while the opposite occurred following anterior hypothalamic lesions. These data indicate that the hypothalamus is capable of exerting a tonic influence on the medullary vasomotor center or spinal cord preganglionic neurons. The posterior hypothalamus increases sympathetic activity, while the anterior hypothalamus increases parasympathetic activity.

Keller (91) noted that vasoconstrictor tone was not altered by an acute lesion above the medulla. However, in normotensive and renal-hypertensive dogs two weeks after hypothalamic ablation, blood pressure was slightly lower than in intact animals.

Smith and co-workers (180) noted a change in basal sympathetic activity following ablation of the hypothalamus in dogs. Alterations in sympathetic activity were indicated by changes in blood pressure, ventricular pressure and diameter, and blood flow measurements.

Manning (122, 123) studied the tonic and reflex changes in blood pressure, heart rate, and contractility following lesions in the medullary dorsolateral reticular formation and following decerebration in cats anesthetized with chloralose. Following the medullary lesion,
blood pressure still increased during bilateral carotid occlusion or sciatic nerve or hypothalamic stimulations. Norepinephrine injection elicited an increase in blood pressure, heart rate, and contractility. Following decerebration, blood pressure, heart rate, and contractility were reduced. Bilateral carotid occlusion, hypothalamic and sciatic nerve stimulation had no effect on blood pressure. Norepinephrine injection still resulted in an increase in blood pressure, heart rate, and contractility. Manning proposed that the hypothalamus is capable of exerting a tonic and phasic regulation of the cardiovascular system, independent of the medullary vasomotor center. Anatomical evidence to support hypothalamic regulation of the sympathetic nervous system independent of the medullary vasomotor area was obtained by Smith (179, 181). Following a lesion in the hypothalamic vasomotor area, degeneration was noted in the area around the intermedio-medial and intermediolateral cell columns. These data suggest a direct hypothalamo-spinal connection.

5. Summary

The hypothalamus is a major site for integration of autonomic and somatic function. The posterior region has an excitatory influence on the sympathetic nervous system and regulates visceral and somatic functions involved in responses to cold exposure and rage reactions. The
anterior hypothalamus exerts an inhibitory influence on the sympathetic nervous system and regulates functions related to heat exposure, water loss, and maintenance of body weight. Recent evidence suggests the hypothalamus effects both tonic and reflex activation of the cardiovascular system.

C. Mesencephalon

1. Early Literature on Cardiovascular Responses to Mesencephalic Stimulation

Early investigation of cardiovascular responses to mesencephalic stimulation have been reviewed by Lindgren (112) and Oberholzer (138). Eckhard (112, 138), in 1873, noted vasoconstriction followed by marked vasodilatation in rabbit ear arteries during mechanical stimulation of the superior colliculus. Danilewsky (112, 138), in 1875, elicited a pressor response, bradycardia, and increased pulse pressure during faradic stimulation of the deeper parts of the corpora quadrigemina in curarized animals with intact vagi. Transverse sections at pontine levels had no effect on vasomotor tone, indicating the lack of tonic input from suprapontine centers onto neurons controlling the peripheral vasculature. Prus (112, 138), in 1899, produced pressor responses from stimulation of the anterior and posterior colliculi in unanesthetized dogs. Simultaneous motor and respiratory activity,
pupillary constriction, and salivation were reported; therefore he questioned the notion of a specific pressor area in the mesencephalon. Ott (112) noted that injury to the superior colliculus caused a vasodilatation with a concomitant rise in pressure, following by a fall in pressure.

2. Stereotaxic Investigation of the Midbrain

The first use of the Horsley-Clarke stereotaxic apparatus for investigation of autonomic responses to midbrain stimulation was reported by Sachs in 1911 (157). He noted that stimulation of the superior and inferior colliculi and central gray region elicited pressor responses. Several years later, Allen (3) also demonstrated pressor responses from stimulation of the superior colliculus. In addition, he reported pronounced slowing and strengthening of the pulse, alterations in respiration, and general spasms or convulsions which persisted for some time.

Kabat and co-workers (88) stimulated 7700 points in the forebrain and midbrain in 50 cats anesthetized with Nembutal. Pressor responses from mesencephalic stimulations were localized in the central gray region, medial tegmentum, periventricular fibers, and in the midline between the interpeduncular nucleus and the posterior commissure. Moderate depressor responses
(5 - 20 mm Hg) were on occasion elicited from stimulation of the lateral tegmentum. Blood pressure responses were independent of somatic movement or respiration.

McQueen and co-workers (129) elicited pressor responses in dogs under local anesthesia during stimulation of the central gray matter, posterior commissure nucleus, and the superior border of the red nucleus. These responses were abolished by anesthetic doses of pentobarbital.

Lindgren (112) described the vascular effects during mesencephalic tectal stimulation in cats under Dial anesthesia. Blood pressure responses were variable during stimulation of this area. However, skeletal muscle blood flow increased and cutaneous and visceral blood flows decreased. The vasodilatation in the skeletal muscle was abolished by atropine, indicating activation of a sympathetic vasodilator mechanism. Lindgren suggested that the mesencephalic tegmentum may be an integrative site for skeletal muscle vasodilatation and cutaneous vasoconstriction. Lesions in this area did not affect the basal blood flow in these vascular beds, indicating the lack of tonic outflow from the mesencephalon to neurons regulating vascular resistance in skeletal muscle and skin. In addition, Lindgren noted that skeletal muscle vasodilatation and cutaneous vasoconstriction could still be elicited
after ablation of the vasomotor center in the medullary reticular formation. He concluded that the mesencephalic tectal region is the site of vasodilator and vasoconstrictor pathways which are anatomically and physiologically separate from medullary pressor and depressor areas.

Ueda and co-workers (187) described discrete activation of vasoconstrictor outflow to kidney, intestine, and hindlimb during stimulation of the mesencephalic central gray and reticular formation. Stimulation of the most dorsal areas resulted in maximum vasoconstriction in the renal vascular bed. Stimulation of more ventral regions caused maximum vasoconstriction in the skeletal muscle and intestinal vascular beds.

3. Electrophysiological Characteristics of Mesencephalic Stimulation

Gebber and co-workers (59) elicited discharges in the external carotid nerve during stimulation of the central gray and tegmentum in anesthetized cats. Short trains of stimuli evoked repetitive discharges with a latency of 37 - 60 msec and a duration of 40 - 250 msec. The early spikes contained within the repetitive discharges were not affected by the pressor response to norepinephrine injection; however, the later discharges were attenuated or completely blocked. These data suggested that sympathetic outflow is distributed along two
vasopressor pathways, a baroreceptor sensitive and a baro-
receptor insensitive pathway.

4. Descending Pathways in the Mesencephalon

Magoun and co-workers (88, 120, 121), using hypo-
thalamic stimulations and lesions within the brainstem and
spinal cord, described the distribution of descending fi-
bers from the hypothalamus to the spinal cord. They sug-
gested that fibers from pressor areas in the lateral part
of the hypothalamus divide at the level of the mammillary
bodies. Some fibers travel dorsally via the periventricu-
lar fibers to the mesencephalic central gray, while others
travel backwards from the hypothalamus to the mesencephalic
tegmentum. This latter fiber distribution was suggested
to relay information from the hypothalamus to the pregan-
glionic neurons in the spinal cord. After traversing in
the tegmentum, the fibers were diffusely spread in the
medullary lateral reticular formation and into the ven-
trolateral funiculus of the cervical spinal cord.

Thompson and Bach (186) demonstrated the effects
of lesions in the medullary reticular formation on re-
sponses to hypothalamic stimulation. The pressor re-
sponse to posterior hypothalamic stimulation was enhanced
following a lesion in the medial reticular formation (de-
pressor area). If an additional lesion was made in the
dorsolateral reticular formation (pressor area), the
response was nearly abolished. If the placement of the lesions was reversed, the pressor response to posterior hypothalamic stimulation was still greater after a lesion in the medullary depressor area. The results indicated a tonic inhibition from the medulla on descending hypothalamo-fugal fiber impulses.

5. Summary

Stimulation of several mesencephalic sites has been shown to elicit blood pressure and sympathetic nerve responses. However, further experiments are needed to determine whether these responses were mediated by activation of neurons within the mesencephalon or by stimulation of descending fibers from diencephalic or telencephalic regions.

D. Medulla

1. Early Work on Localization of Medullary Vasomotor Centers

Classical concepts of the localization of a bulbar vasomotor center originated in Carl Ludwig's laboratory in Leipzig during the later part of the 19th century (reviewed in 6, 7, 138, 142, 188). Dittmar (6, 7, 138, 142, 188) in 1870 suggested that the reflex rise in blood pressure elicited by stimulation of the sciatic afferent nerve fibers was dependent upon an intact medulla. In 1871 Owsjannikow (6, 7, 138, 142, 188) described the cardiovascular effects of serial transections of the brainstem in
the cat and rabbit. Lesioning had no effect until a cut was made 1 - 2 mm behind the caudal border of the inferior colliculi. Lesions made more caudal caused progressively greater falls in blood pressure until, upon reaching a point 4 - 5 mm above the calamus scriptorius, blood pressure fell to the same level as following complete cervical spinal cord transection. In addition, reflex changes in blood pressure were also progressively attenuated as cuts were made more caudally. In 1873 Dittmar (6, 7, 138, 142, 188) defined more precisely the cranial and caudal boundaries of the medullary vasomotor center. Using serial transections and microscopical analysis in curarized rabbits, he described a bilateral vasomotor center extending from 3 - 4 mm above the calamus scriptorius to the fovea superior and including a diffuse part of the superior olive. Local destruction of the so-called anterior nucleus (corresponding to what is now known as the ventral part of the lateral reticular formation) greatly attenuated pressor responses to sciatic nerve stimulation.

Miller and Brown (130) localized a cardio-inhibitory center in the dorsal vagal nuclei in the medulla. Bradycardia was induced by electrical stimulation of weak current strength in spinal cats.

Ranson and Billingley (152) in 1916 stimulated regions on the surface of the medulla which altered the blood
pressure in cats. The apex of the ala cinerea contained a pressor locus, while the area postrema contained a depressor locus. They suggested that since these sites are close to known vagal nuclei, the responses may be due to activation of pressor and depressor afferent fibers, respectively, in the vagus nerves. Scott (174, 175) verified the location of the depressor responses but was unable to verify the pressor locus. He also demonstrated that application of strychnine to, or cauterization of, the area postrema diminished the fall in blood pressure elicited by stimulation of the aortic depressor nerves or the medullary depressor sites. These manipulations did not affect tonic blood pressure. He concluded that the floor of the fourth ventricle contains afferent fibers from the depressor nerves. Stimulation of this region thereby initiated a depressor reflex.

Bayliss (8) suggested that these regions on the floor of the fourth ventricle are "supreme coordinating centres." Blood pressure responses elicited by stimulation of higher parts of the brain presumably were mediated through medullary vasomotor centers.

Porter (147) noted that curare was able to differentiate vasotonic and vasoreflex centers in the medulla. While curare enhanced the blood pressure response to sciatic nerve stimulation, it had no effect on the tonic
blood pressure level. Bayliss (8) did not agree with porter's theory of separate reflex and tonic centers. Instead he suggested that curare may not directly act on the medullary neurons, but may affect the synaptic mechanisms from the afferent nerve terminals. Therefore, the reflex responses may be altered without changing basal tone.

Chen and co-workers (26, 27, 114, 204) performed a series of experiments to determine the location of sympatho-excitatory and sympatho-inhibitory centers in the medulla. Using vagotomized dogs under chloralosane anesthesia, they noted that maximal pressor responses could be elicited by stimulation of the area of the inferior fovea. In addition to blood pressure responses, changes were also elicited in intestinal and renal volume, bladder contraction, splenic contraction, intestinal motility, piloerection, pupillary sphincter and nictitating membrane contractions, bronchiolar relaxation, and secretions from the liver and adrenal medulla. These data provided evidence that the pressor area described by earlier investigators was truly a "sympathetic centre." In addition, they suggested that the reflex pressor response to sciatic nerve stimulation was mediated through this sympathetic center. This was contrary to Porter's proposal (147). From the histological studies (118) the sympathetic center was localized in one of the following nuclei: nucleus
tractus solitarius, nucleus intermedialis, reticular formation nuclei, nucleus ambiguus, facial nucleus, or lateral vestibular nucleus of Deiter's. General sympatho-inhibition was produced by stimulation of the depressor points located near the obex. Since these responses were not affected by decerebration or separation of the depressor area from the pressor area, they suggested that this region represented an independent system with inhibition occurring at the spinal cord rather than merely inhibition of the sympathetic center in the medulla. This area was essential for mediating the depressor responses to stimulation of the carotid sinus nerve, vagal afferent fibers, and somatic afferent fibers. This had also been proposed by Bayliss (8) who noted that lesioning the medullary pressor area did not abolish reflex depressor responses to aortic depressor nerve stimulation.

2. Stereotaxic Investigation of the Brainstem

Precise localization of brainstem regions involved in cardiovascular regulation awaited the introduction of the Horsley-Clarke stereotaxic investigation apparatus; with this instrument the deeper structures of the brainstem could be stimulated. Monnier (131, 132, 133, 134) provided one of the first detailed descriptions of the vasomotor, respiratory, bladder and pupillary responses to stimulation of a large portion of the medulla with
fine-tipped bipolar electrodes. Following stimulation with weak faradic current, responsive sites were lesioned for histological identification. Autonomic responses were induced following curarization of the cats to eliminate any interference from somatic motor activity. Stimulation of the ventral reticular formation was associated with apneusis, a fall in blood pressure after an initial rise in pressure, an increase in intravesicular pressure and mydriasis. Stimulation of the dorsomedial structures in the medulla elicited apnea and a fall in blood pressure (40 mm Hg). Activation of the lateral reticular formation resulted in a rise in blood pressure (40 - 65 mm Hg), bilateral mydriasis, a fall in heart rate, and apneusis. Stimulation of the ventrolateral regions of the medulla was associated with an increase in blood pressure (40 - 80 mm Hg), mydriasis, increased intravesicular pressure, and either apneusis or increased respiration.

Wang and Ranson (195) also provided a detailed description of 7500 medullary and pontine sites which modulate the autonomic nervous system. Marked pressor responses were noted during stimulation of the lateral reticular formation, ventromedial inferior colliculus, periventricular gray matter, brachium conjunctivum, and medial vestibular nucleus. Depressor responses were noted during stimulation of the ventral
part of the lateral reticular formation, area postrema, and medial reticular formation. Bladder contraction was elicited by stimulation of the periventricular gray matter and the ventrolateral reticular formation. Admittedly, they were unable to determine whether the autonomic responses resulted from activation of afferent or efferent fibers or nuclei.

Alexander (2) further demonstrated the regions in the medulla which regulate the cardiovascular system by direct recordings of sympathetic nerve discharges during stimulation and serial transections of the brainstem. Stimulation studies confirmed the work of Wang and Ranson (195). Maximum pressor responses were evoked from a large area of the lateral reticular formation in the rostral two thirds of the medulla. Maximum depressor responses were elicited by stimulation of the medial reticular formation in the caudal half of the medulla. To determine the origin of the tonic activity in the inferior cardiac nerve, Alexander transected the brainstem at three locations: (I) through the auditory tubercle; (II) just rostral to the obex; and (III) at the C1 spinal cord. Section I had no effect on blood pressure or inferior cardiac nerve activity. Section II caused a maximum fall in blood pressure and abolished sympathetic nerve activity. Transection of the spinal cord was followed by a slight increase in the nerve discharges. This
was one of the first indications that the sympatho-inhibitory area in the medulla had a tonic input to the spinal preganglionic neurons. He also studied the effects of brainstem lesions on the pressor reflex to sciatic nerve stimulation. Since the response was attenuated by Section I and abolished by Section II, he suggested the reflex is mediated through the medulla. Alexander noted that the pressor area was bilateral in its outflow to the cardiac nerve, although the discharges in the cervical sympathetic trunk were increased only with ipsilateral medullary stimulation. Contralateral stimulation elicited either a decrease or no change in activity in the cervical sympathetic trunk. This provided evidence that the nervous system is capable of discrete activation of the peripheral sympathetic nerves. This is unlike Cannon's (22) view that a massive sympathetic discharge results from stimulation of autonomic centers in the brain.

Bach (5) was unable to elicit a pure cardiovascular response from activation of the lateral reticular formation. He noted simultaneous respiratory and knee jerk responses during stimulation. He concluded that the medullary reticular formation is a non-specific center and questioned the notion of a pure pressor or depressor area.

Amoroso and co-workers (4) attempted to analyze the relationship between respiratory and cardiovascular
effects to medullary stimulation in the sheep. Like Bach he noted simultaneous respiratory changes. Maximum pressor and expiratory responses were elicited by stimulation of the dorsolateral reticular formation, while maximum depressor and inspiratory responses were evoked by stimulation of the medial reticular formation. However, at many points stimulated there was no absolute relationship between the cardiovascular and respiratory effects, with either phase of respiration being associated with either a rise or fall in blood pressure. They concluded that respiratory and cardiovascular entities cannot be separated anatomically, but functionally they can act independently of each other.

The spinal trigeminal complex has recently been proposed as the site of a depressor response in the rabbit by Kumada and co-workers (103). Blood pressure and heart rate decreased as much as 80 mm Hg and 90 beats/min, respectively, during stimulation (3 - 20 Hz, 0.1 - 0.5 msec, >20 µA) of this medullary site. This response was not dependent upon activation of baroreceptor reflex pathways.

3. Investigation of Cardiac Effects of Medullary Stimulation

Peiss (139) provided one of the first descriptions of the cardiac augmentor and accelerator effects of
stimulation of the medulla in vagotomized dogs and cats under sodium pentobarbital anesthesia. Stimulation of the rostral medulla elicited a pure augmentor response, as indicated by the large change in systolic pressure (from a control of 150 mm Hg to 230 mm Hg) with little change in diastolic pressure or heart rate. Dorsal medullary stimulation elicited a change in pulse pressure (from a control of 18 mm Hg to 62 mm Hg) with a change in both diastolic and systolic pressures. Peiss suggested that stimulation of this region caused both an increase in total peripheral resistance and cardiac augmentation. However, there was no concomitant change in heart rate. In a later study, Peiss (140) characterized the responses to medullary stimulation in cats anesthetized with sodium pentobarbital or chloralose. With pentobarbital, stimulation of 1000 points in the dorsal medulla rarely changed heart rate. Ventrolateral medullary stimulation resulted in an increase in heart rate with a minimal change in blood pressure. In chloralose-anesthetized cats stimulation of the dorsal medulla elicited a large increase in heart rate. Peiss suggested that pentobarbital may depress the hypothalamus without affecting the medulla. He proposed that dorsal medullary stimulation activated afferent fibers to the hypothalamus. The reflex cardiac acceleration was mediated by hypothalamic fibers which
descended in the ventrolateral medulla. Peiss and Manning (143) later verified that pentobarbital selectively inhibits the hypothalamus without influencing medullary vasomotor responses.

Contradictory results were presented by Chai and Wang (24, 194). These investigators reported that decerebration had no effect on the chronotropic responses which they elicited from dorsal medullary stimulation. In addition, using similar procedures to those of Peiss (140) they were not able to verify his conclusions concerning pentobarbital anesthesia. The results of Wang and Chai (194) were the same under chloralose and pentobarbital anesthesia. Though midcollicular decerebration substantially altered control heart rate levels, Wang and Chai suggested that increased heart rate from medullary stimulation was not dependent upon intact supramedullary regions. On the contrary, they proposed that the medulla is the site of a major cardioaccelerator mechanism which can be influenced by supramedullary structures.

Folkow and co-workers (55) noted a profound fall in cardiac output with a decrease in blood pressure during stimulation of the medullary depressor area on the floor of the fourth ventricle. In addition, they noted a decrease in heart rate and central venous pressure. The authors suggested that these responses were similar to
those occurring with emotional fainting in man.

4. Electrophysiological Characteristics of Medullary Stimulation

Following the pioneering work of Alexander in 1946 (2), additional electrophysiological evidence for sympa-tho-excitation and sympatho-inhibition from medullary stimulation was not reported until the late 1960's. Scherrer (170) studied the effects of stimulation of the medullary inhibitory areas in rats pre-treated with phenoxybenzamine hydrochloride. This drug was given to avoid reflex alterations in sympathetic nerve activity which may result from the change in blood pressure elicited by stimulation of the central nervous system. In this way, a "pure" sympatho-inhibitory response could be evaluated. Scherrer recorded inhibition of renal nerve discharges during stimulation of two well-defined areas within the medulla: (1) the nucleus and tractus solitarius, and (2) the region of the medial longitudinal fasciculus and medial tectospinal tract. Responses from these two regions could be elicited following a lesion in the other area and could also be differentiated by latencies, stimulus frequency characteristics, and associated cardiac effects. Therefore, Scherrer proposed that the two areas represent functionally and anatomically discrete sympatho-inhibitory pathways.
Kahn and Mills (89) recorded blood pressure and splanchnic nerve activity during medullary stimulations in decerebrate, vagotomized, and paralyzed cats. They demonstrated that sympatho-excitation was distributed over two distinct pathways, separated both anatomically and functionally. The first type of response, sustained activation, was elicited by stimulation of the dorsolateral reticular formation and periventricular gray 1 - 3 mm rostral to the obex. This response was characterized by increased frequency of nerve discharges throughout the period of the rise in pressure. A post-stimulus fall in blood pressure was also noted. The second type of response, unsustained activation, was elicited by stimulation of more lateral and ventral regions. This response was characterized by an initial increase in nerve activity, followed by a fall in nerve discharges. The pressor response was identical to that in the first type of response. The secondary decrease in splanchnic nerve activity was nearly abolished by simultaneous bilateral carotid occlusion. The authors proposed that this secondary inhibition was mediated through baroreceptor activation. Kahn and Mills also demonstrated an inhibition of sympathetic nerve activity by stimulation of the ventromedial and ventrolateral reticular formation and the midline as far dorsal as the floor of the fourth ventricle. They noted a
post-stimulus rebound in nerve activity. Blood pressure responses were variable with either a rise, fall, or no change occurring simultaneously with the decrease in nerve activity. The authors suggested that splanchnic nerve activity could be altered independently of other sympathetic nerves. This observations was further supported by the change in nerve activity during bilateral carotid occlusion. The increase in splanchnic nerve activity was not proportional to the rise in pressure elicited by carotid occlusion.

Gootman and Cohen (61) also recorded splanchnic nerve discharges during stimulation of medullary pressor and depressor regions. High frequency stimulation of the dorsolateral reticular formation (nucleus reticularis parvocellularis) produced a rise in blood pressure and an increase in sympathetic nerve activity. Following the stimulus, the nerve activity decreased below control levels. High frequency stimulation of the ventromedial reticular formation produced a fall in blood pressure and an almost complete inhibition of sympathetic nerve activity. Following the stimulus, splanchnic nerve activity showed rebound activity above control levels. These responses were similar to the sustained activation and inhibition demonstrated by Kahn and Mills (89). In a later study (62), Gootman and Cohen used an average response
computer to characterize the splanchnic nerve evoked discharges from stimulation of medullary pressor and depressor sites in decerebrate or urethane anesthetized cats. Single shocks or short trains of stimuli to the same pressor sites as in their previous study elicited an evoked discharge with a latency of 37 - 49 msec and a duration of 50 - 200 msec. Stimulation of the depressor points caused an inhibition of spontaneous nerve activity after a latency of 29 - 33 msec; the inhibition lasted 20 - 30 msec. The consistently shorter delay for the sympa-tho-inhibition indicated that the response was mediated by descending pathways to the spinal preganglionic neurons or spinal interneurons.

Nathan (135) recorded computer summed splanchnic nerve discharges during stimulation of the medulla in monkeys. He characterized two types of discharges. The first response was of shorter latency and smaller magnitude than the second response. Stimulation of the nucleus reticularis ventralis evoked the shortest latency early and late discharges. Stimulation of the nucleus reticularis parvo cellularis and nucleus and tractus solitarius produced early and late discharges of longer latency. Lesions in the area of reticularis parvocellularis resulted in degeneration in the area of reticularis ventralis. Nathan suggested that responses following
stimulation of reticularis parvocellularis were mediated by activation of the reticularis ventralis.

Gebber and co-workers (59) have also recorded computer summed early and late responses in postganglionic fibers in the external carotid nerve during stimulation of the medulla in cats. These responses were distinguished both anatomically and functionally. Shortest latency early responses (34 - 44 msec) were evoked during stimulation of nucleus reticularis ventralis, in agreement with Nathan's findings. However, late responses (70 - 104 msec) were evoked primarily during stimulation of the periventricular gray. Short latency responses required short trains of stimuli, while long latency responses were elicited following single pulse stimulations. These data suggested that temporal summation was important in generation of the early discharges. Long latency responses, but not short latency responses, were inhibited during the pressor response to intravenous norepinephrine. Similar short and long latency responses were evoked from stimulation of other levels of the neuraxis. The authors proposed that central vasopressor mechanisms were distributed along two pathways, a baroreceptor sensitive and a baroreceptor insensitive pathway. Taylor and Gebber (184) later demonstrated baroreceptor insensitive (early) and baroreceptor sensitive (late) responses in single unit sympathetic
preganglionic neurons in the thoracic spinal cord. Two additional findings were also noted in this study. High frequency stimulation of the depressor area in the medial medulla or baroreceptor activation inhibited the late responses, but significantly enhanced the early responses to stimulation of medullary pressor sites. In addition, the two vasopressor pathways were able to influence the activity in the same preganglionic neurons. Thus the individual neurons function as the final common pathway for the two descending vasopressor systems.

Snyder and Gebber (82) further investigated the effects of stimulation of the medullary depressor area on the early and late discharges in preganglionic and postganglionic nerve fibers. Stimulation of many depressor points, but not baroreceptor activation, inhibited the short latency responses from medullary stimulation. Stimulation of the same depressor points did not attenuate short latency responses from spinal cord stimulation. The authors suggested that central vasodepressor mechanisms were also organized along two pathways, one inhibiting in the medulla and the other inhibiting in the spinal cord.

5. Importance of Supramedullary Areas in Eliciting Cardiovascular Responses from the Medulla

Chen and co-workers (26, 114) noted that decerebration did not affect the responses to stimulation of the
pressor area near the inferior fovea or the depressor area near the obex. Consequently, they suggested that these areas act independently of supramedullary structures. Further work on this notion was not reported until the 1960's. Lindgren (113) used chronic decerebrate cats to study true medullary effects since this lesion caused degeneration of hypothalamofugal and mesencephalofugal fibers. Electrical stimulation of the inferior fovea and sciatic afferent nerve fibers elicited responses which were the same as in intact preparations. They proposed that the medullary vasomotor center was an independent center which functions normally in the absence of hypothalamic or mesencephalic input. He also suggested that hypothalamofugal and mesencephalofugal fibers which traverse the lateral and ventral aspects of the medulla have no anatomical or functional connection with the medullary vasomotor center. This latter proposal was further investigated by Chai and co-workers (23, 25) and Manning (122). Chai and co-workers (23) agreed that diencephalic structures were not essential for reflex cardiac augmentation to carotid occlusion and medullary or sciatic nerve stimulations. Manning studied responses to bilateral carotid occlusion, sciatic nerve stimulation, and hypothalamic stimulation in cats following a lesion in the vasomotor center of the dorsolateral medulla. Vasomotor responses were still
elicited following the lesion; therefore, Manning sug-

ggested that the supramedullary structures were important in tonic and phasic blood pressure control. In addition, he agreed with Lindgren that the supramedullary structures act independently of the medullary vasomotor area. Chai and Wang (25) did a similar study with bilateral lesions to either the pressor or depressor areas. Blood pressure and heart rate responses to bilateral carotid occlusion, sciatic nerve stimulation, and stimulation of the central end of the cut vagus nerves were attenuated or abolished by lesions in the dorsal ventricular gray. Responses to hypothalamic stimulation were not affected. Bilateral lesions in the dorsal medullary depressor region abolished the response to central vagal stimulation, attenuated the responses to carotid occlusion, enhanced the pressor response to sciatic nerve stimulation, attenuated the heart rate and slightly affected the blood pressure responses to hypothalamic stimulation. They concluded that the cardiovascular reflexes elicited by baroreceptor and other afferent nerve activity were integrated at the medul-

lary level. Differences in results from Chai and Wang (25) and Manning (122) and Lindgren (113) may be attributed to the size of lesions or to general conditions of the animal.

The complexities of the anatomy of the reticular formation has been described by Brodal (15). Early neuroanatomists gave this name to an area within the brainstem which was considered to contain a rather diffuse mass of cells with fibers traveling in all directions. However, later investigators showed that the reticular formation is composed of a number of cell groups. Cells located in the medial two thirds have fiber projections to the spinal cord and to rostral brain structures. Long ascending fibers also project from this area; small fibers project medially from the lateral cells of the reticular formation. Brodal has suggested that the lateral cells are association neurons and synapse with the more medial neurons. The medial cells appear to be segregated, though incompletely, according to their fiber distribution to the spinal cord or to rostral brain regions. Fibers projecting from the cells of the reticular formation have collaterals to other neurons in the area.

These anatomical studies demonstrate the possible interconnections between neurons regulating the cardiovascular system, respiration, and motor control. In addition, these studies indicate some of the difficulties which would be involved in determining whether a particular neuron is
"cardiovascular," "respiratory," or "motor." In recent years, several laboratories have recorded from cardiovascular neurons in the medullary reticular formation. Using glass micropipettes, Salmoiraghi (158) recorded from medullary units which he considered to be cardiovascular cells based on the following criteria: (1) activity was altered during blood pressure changes to vasoconstrictor and vasodilator agents; (2) activity was synchronized with spontaneously occurring slow fluctuations in blood pressure (Mayer's Waves); and (3) activity was altered during carotid occlusion. Of the 93 neurons in 21 cats which were identified as cardiovascular units, 53 were held long enough to study their discharge patterns. These cells were located in the medial structures of the pons and medulla, mostly 3 - 6 mm from the dorsal surface of the fourth ventricle. Twelve neurons increased their firing rate with a rise in pressure and decreased activity with a fall in pressure. The other 41 cells showed the opposite characteristics. Cardiovascular medullary units showed very little change in activity which could be correlated with changes in heart rate.

Preobrazhenskii (148) recorded from 104 reticular neurons. Twenty-five cells showed reflex changes in activity following changes in sinus pressure and bladder distension. Seventy-nine units demonstrated changes in
activity following intravenous administration of epinephrine or acetylcholine, but not following reflex changes in blood pressure. He suggested this second group of neurons may be intermediate links in the central mechanisms for chemical control of vascular tone.

Pryzbala and Wang (150) recorded from 14 medullary units identified as cardiovascular neurons in 75 decerebrate cats. These cells were located in the periventricular gray and dorsolateral reticular formation. They defined a cardiovascular neuron as one which exhibits not less than 30% decrease in discharge frequency when norepinephrine was injected intravenously to raise the arterial pressure 30 mm Hg. Most cells showed greater than 60% reduction in activity with the rise in pressure. These neurons were classified into two types: (1) steadily firing (2 - 13 spikes/sec) with no apparent changes with the respiratory cycle; and (2) frequency modulated neurons which demonstrated increased activity during lung deflation. The firing pattern of these cells were related to changes in blood pressure and inferior cardiac nerve activity.

Two reports from the recent Symposia on Central Autonomic Control discussed the identification of brainstem neurons (63, 96). Koepchen and co-workers (96) criticized the techniques available for determining whether a
cell is "respiratory," "cardiovascular," or "reticular." Since many cells demonstrate similar cardiovascular and respiratory oscillations and reflex changes in activity, these criteria cannot be used to discriminate between cardiovascular, respiratory, and reticular neurons. They suggested that future research should be aimed at determining not which system a particular medullary unit belongs to but what function the neuron contributes to the physiological state of the organism.

Gootman and Cohen (63), using cross correlations and computer averaging techniques, studied a limited number of cells which showed activity patterns which were temporally related to discharge patterns in the cervical sympathetic trunk or the splanchnic nerve. They used three criteria to identify a sympathetic medullary unit: (1) respiratory modulated activity with phase spanning and tonic activity similar to peripheral sympathetic discharges; (2) cardiac cycle modulation; and/or (3) 10/sec periodicity. A cell which they considered to be close to the efferent outflow of the medullary sympathetic driving network showed maximum discharge rates during the rising phase of systole. Another neuron which they suggested to be near the afferent input to the sympathetic driver showed two discharge peaks, one in early systole and the other in early diastole. These cells apparently were
related to the rate of change of arterial pressure. No cells showed the 10/sec periodicity seen in the splanchnic nerve discharges.

7. Summary

For over 100 years the medulla has been emphasized as the main level of the nervous system involved in cardiovascular control. Tonic control, as well as reflex regulation, of cardiovascular mechanisms appear to be mediated by medullary vasomotor areas. Pressor and depressor responses are organized in cellular populations within the lateral and medial reticular formations, respectively. Medullary fibers project to the spinal cord, acting directly or via interneurons on the spinal preganglionic neurons. Since many of the medullary areas elicit simultaneous changes in blood pressure, respiration, and motor activity, the medullary reticular formation may act as a site for integration of autonomic and somatic responses.

E. Spinal Cord

1. Spinal Mediation of Cardiovascular Responses

Claude Bernard (13) in 1851, was one of the first investigators to report that an animal with an isolated spinal cord was capable of eliciting autonomic responses. Budge (20) and Waller (190) noted similar responses. A classic experiment by Sherrington (177) demonstrated the
remarkable capabilities of a chronic (300 days) spinal dog to elicit a 118 mm Hg rise in systemic arterial blood pressure during stimulation of the internal saphenous nerve.

Langley (106) noted that strychnine enhanced the reflex pressor response to sciatic nerve stimulation in spinal animals. He suggested that in pathological cases of increased spinal excitability, as mimicked by strychnine, spinal vasomotor reflexes may be very important.

Bard (6, 7), Peiss (142), and Uvnas (188) have reivewed much of the early literature on spinal mediation of cardiovascular responses.

Brooks (17) elicited reflex increases in heart rate, blood pressure, and blood sugar levels following sciatic or crural nerve stimulation in chronic (3 - 7 days) spinal cats. Denervation or extirpation of the adrenal medulla nearly abolished the changes in blood sugar and greatly attenuated the rise in blood pressure and heart rate. In a later study, Brooks (18) demonstrated the ability of spinal animals to compensate for hemorrhage of 10 - 25% of their blood volume. This response was not affected by cutting the dorsal roots; however, cutting the ventral roots or removal of the sympathetic trunk and adrenal medulla abolished the response. These data indicate that the origin of the compensatory
mechanism was within the spinal cord.

Heymans and co-workers (73), using anesthetized spinal dogs, showed that reflexes elicited by changes in blood pressure arise from baroreceptors in visceral organs supplied by the coeliac and superior mesenteric arteries. He suggested that these reflexes may play a role in blood distribution to deep abdominal vessels.

Kuntz (104) elicited a reflex vasodilatation and vasoconstriction by cutaneous heating and cooling, respectively, in cervical spinal rats. He concluded that these responses were mediated by segmental and intersegmental reflex arcs, with the afferent limb being the sympathetic nervous system.

Walther and co-workers (192) showed that central thermal stimulation in spinal cats and rabbits can elicit differential outflow to cutaneous and visceral sympathetic fibers. Heating the spinal cord caused an increased discharge in visceral fibers and attenuated the activity in cutaneous nerves.

Cardiovascular regulation in human spinal patients has been the subject of a number of studies. Corbett and co-workers (38, 39, 40) investigated the effects of muscle spasms, cutaneous and visceral stimuli, and head tilting in non-bedridden patients with complete cervical spinal cord transections. Muscle spasms, pinprick and
cold stimuli below the level of the lesion, bladder per-
cussion, and squeezing the chest caused a spinally medi-
ated reflex rise in blood pressure. Head tilt elicited a fall in pressure. Changes in pulse pressure, heart rate, hand and calf blood flows, and occluded vein pressure were also noted in these patients.

Guttman and Whitteridge (67) studied the effects of bladder distension on blood pressure and toe and finger blood flows in spinal patterns. In those patients with a lesion above T5 a marked pressor response, decreased heart rate, and vasoconstriction in both vascular beds followed bladder distension. Pressor responses were of lesser magnitude in patients with lesions below T5. In addition, vasodilatation was noted in the fingers. Wurster and Randall (202) have recently made similar observations in blood pressure responses to bladder distension. However, only three out of seven patients with a transection above T5 showed a decreased heart rate with the marked elevations in blood pressure and pulse pressure. They suggested that inotropic changes in the heart, in addition to changes in total peripheral resistance, were responsible for the large increase in pulse pressure in these patients.

Several investigators have provided electrophysi-
ological evidence for increased sympathetic nervous
discharge in spinal animals during afferent nerve stimulation. These experiments are discussed in another section of this Chapter (see Afferent Nerves).

2. Spontaneous Activity in Spinal Animals

The importance of the spinal cord in maintaining vasomotor tone in spinal animals was evidenced by several investigators. Provided blood loss was minimal, Leriche and Fontaine (111) noted that trauma to the medulla did not cause a profound fall in blood pressure. If the spinal cord was slowly (over a period of two hours) separated from the medulla, Hermann and co-workers (72) and Peiss (142) showed that the usual "spinal" blood pressure level was not reached. Peiss suggested that these data demonstrate the inherent capabilities of the spinal cord, independent of inflow from higher centers, to mediate cardiovascular reflexes and to maintain vasomotor tone. Brooks (17) noted that 3 to 7 days following spinal cord lesion, animals had a nearly normal blood pressure.

These studies indicate that the sympathetic preganglionic neurons may exhibit activity in the absence of supraspinal control. Alexander (1, 2) observed spontaneous inferior cardiac nerve discharges in decentralized, deafferented spinal cord preparations. He concluded that spontaneous activity resulted from direct
anoxic stimulation of a spinal vasomotor center following changes in blood flow in the cord. He suggested that oxygen tension may contribute to the excitatory state of the preganglionic neurons in a normal animal, reinforcing the buffer reflexes that are integrated supraspinally.

Beacham and Perl (9, 10) recorded spontaneous discharges in upper thoracic and lumbar white rami 5 - 18 hr after C₁ spinal cord transection. Some fibers discharged at regular interval from less than 1 to 50 impulses/sec. Most neurons fired in irregular bursts of activity, with no relationship to the cardiac or respiratory cycles. Fernandez de Molina and Perl (51) noted spontaneous changed in preganglionic and postganglionic nerve activity which corresponded to cyclic changes in blood pressure. Increasing systemic blood pressure (circulatory volume expansion or adrenalin) decreased the activity in some neurons and increased the activity in others. Likewise, a fall in blood pressure was followed by an increased discharge rate in some fibers. These results clearly demonstrate a spinal component to vasomotor regulation.

Polosa (146) reported spontaneous firing rate of 0.3 impulses/sec in decentralized, deafferented spinal cord preparations. This discharge rate was much lower than in an intact preparation (0.1 - 5.6 impulses/sec).
However, these residual discharges indicate that some mechanism other than afferent input to preganglionic neurons is responsible for maintaining activity in a spinal animal. Polosa suggested several possible mechanisms which may account for spontaneous discharges in sympathetic neurons: (1) direct or indirect activation of preganglionic neurons by chemical or physical factors (e.g., respiratory gases, metabolites, pH); (2) spontaneous leakage of excitatory transmitter from presynaptic terminals; or (3) true pacemaker activity of preganglionic neurons. Since in an intact preparation interpolation of antidromic impulses caused a resetting of the discharge pattern, Polosa concluded that the rhythm is endogenous to the sympathetic neuron itself; and he suggested that the sympathetic neuron is an integrating neuron.

3. Role of the Spinal Cord in CNS-Intact Preparations

The spinal cord is generally considered to have only a minor role in cardiovascular regulation. However, evidence presented in the previous section indicates the spinal cord may be more than a mere relay station for input from higher centers and afferent nerves. Sato (159) suggested that the spinal component of the somato-sympathetic reflex provides for a localized outflow from the sympathetic nervous system, while the supraspinal component generates a massive sympathetic discharge. Simon and
co-workers (83, 84, 191, 192) have presented substantial evidence that central thermal stimulation, asphyxia, and changes in blood gas composition in CNS-intact preparations can cause a differential outflow from the sympathetic nervous system. These investigators suggested that single preganglionic neurons or groups of neurons can be influenced separately by a variety of supraspinal or segmental inputs. Ninomiya and co-workers (137) demonstrated nonuniform discharges in splenic, renal, and cardiac nerves during baroreceptor activation. Though they suggested the discrete activation of sympathetic fibers resulted from activation of specific supraspinal neuronal pools, the possibility of the nonuniform response being of spinal origin cannot be ruled out.

4. Spinal Component to Baroreceptor-Induced Sympatho-Inhibition

Recently, several laboratories have described a spinal component to inhibition of sympathetic nerve discharges during baroreceptor activation. Kirchner and co-workers (94) and Coote and Macleod (36) have described an inhibition of the spinal component of the somato-sympathetic reflex during carotid sinus distension or intravenous administration of pressor doses of norepinephrine. These data will be discussed later. In addition, Taylor and Gebber (185) reported early and late positive
potentials in the splanchnic and renal nerve fibers during stimulation of the aortic depressor nerve and paramedian reticular nucleus. By studying the effect of baroreceptor activation on evoked discharges from medullary and spinal pressor points, they were able to distinguish the early and late potentials as spinal and medullary components, respectively, of baroreceptor-induced sympatho-inhibition.

5. Spinal Pathways Mediating Cardiovascular Responses

Peiss (142) described the spinal sympathetic preganglionic neurons as the final common pathway in the cardiovascular regulatory system. He suggested that these cells integrate the activity from all descending projections. The output of these neurons is determined by the spatial and temporal summation of excitatory and inhibitory input from supraspinal centers, spinal interneurons and afferent nerve fibers.

a. Descending spinal sympatheo-excitatory pathways

One of the earliest descriptions of the location of the spinal component of the efferent pathway mediating cardiovascular reflexes was presented in 1916 by Ranson and Billingsley (153). Following bilateral lesions in the upper thoracic cord in an area around the dorsal horns, the vasomotor response to brachial nerve stimulation was not affected. They indirectly concluded that the efferent limb of this reflex was in the lateral or
ventral funiculus of the spinal cord.

A direct hypothalamo-spinal pathway was described anatomically and physiologically by Beattie and co-workers (12). This pathway was localized near the fasciculus proprius anterior and the lateral part of the ventral funiculus.

In patients with therapeutic partial cordotomies, Foerster [as cited by Kerr and Alexander (92)] described vasomotor fibers reaching from the dentate ligament in a transverse plane to the lateral aspect of the ventral horn. Lesioning this area in the lower cervical spinal cord abolished vasoconstrictor reflexes.

Chen and co-workers (28, 29) described a region in the ventrolateral funiculus which was responsible for mediating the responses to ipsilateral stimulation of the ventromedial vestibular nuclei or dorsolateral medullary reticular formation. In dogs with the ventrolateral pathway lesioned bilaterally, exposure to cold produced a profound drop in body temperature. Piloerection was absent in these animals during shivering. Histological studies (118) following lesions in the medullary sympathetic centers indicated degeneration in the vestibulospinal tract. Chen suggested these may be the fibers which transmit sympatho-excitatory activity.

Wang and Ranson (196) studied blood pressure and
bladder responses to stimulation of the hypothalamus before and after lesioning areas within the spinal cord. They concluded that the vasomotor fibers traverse in the ventrolateral funiculus. However, examination of their figures indicates that in six out of seven cats the area immediately dorsal to the dentate ligament may also be involved in the cardiovascular responses to hypothalamic stimulation. This descending pathway appears to be uncrossed, supporting the earlier work of Harrison and co-workers (69).

Johnson and co-workers (86) studied human patients with unilateral and bilateral cordotomies. A major portion of autonomic fibers were located in the ventrolateral funiculus. Verification of the extent of the lesions was impossible in their studies.

Autonomic responses elicited by stimulation of the corticospinal tracts were investigated by Landau (105). He reported a variety of blood pressure changes, including pressor, depressor and biphasic responses, to stimulation of the medullary pyramids. To verify that these responses were not related to muscle movements, he also recorded increased nerve discharges in the cervical and abdominal sympathetic trunks.

Stimulation of the anterior sigmoid gyrus results in a pressor response which can be abolished by
contralateral spinal cord hemisection (90). Following both acute and chronic lower cervical cord lesions in cats, Kell and Hoff have localized the pressor pathway at the junction of the dorsolateral and ventrolateral funiculi.

Kerr and Alexander (92) studied blood pressure, bladder pressure, and piloerection responses in cats and monkeys during electrical stimulation of the surface of the spinal cord from the dorsolateral sulcus to midway between the dentate ligaments and the ventrolateral sulcus. They localized a vasoconstrictor pathway about 2 mm ventrolateral to the dorsolateral sulcus in the thoracic spinal cord. During stimulation of the surface of the cervical spinal cord, blood pressure responses were the same from the dorsolateral sulcus to the dentate ligament. Superficial lesions of the dorsolateral funiculus resulted in a fall in blood pressure similar to that following complete cervical cord transection, indicating the major portion of descending tonic impulses travel in this position of the cord.

Since 1972 several laboratories have verified and extended the conclusions of Kerr and Alexander. Smirnov and Potekhina (178) recorded blood pressure responses during spinal cord stimulations. They suggested the dorsolateral surface of the spinal cord contains a major
descending sympatho-excitatory pathway. Illert and Gabriel (81) recorded renal nerve discharges and blood pressure responses in C2 spinal cats during stimulation of the spinal cord. Sympatho-excitatory fibers were located in the dorsolateral funiculus of the cervical spinal cord. The maximum increase in blood pressure and sympathetic nerve activity was elicited by stimulation just dorsal to the dentate ligament. Their stimulations were not superficial but required penetration of the spinal cord.

Gebber and co-workers (59) recorded blood pressure and evoked discharges in the postganglionic external carotid nerve during stimulation of the dorsolateral white columns in anesthetized cats. The majority of the effective stimulation sites were near the surface of the cord ventral to the dorsolateral sulcus. Early discharges (latency: 26 - 42 msec) and late discharges (latency: 36 - 52 msec) were noted. They were able to separate areas which are sensitive (late discharges) and insensitive (early discharges) to baroreceptor reflex activation. They concluded that vasomotor outflow from the central nervous system to the external carotid nerve is organized into two systems, distinguished by their sensitivity to the baroreceptor reflex arc.

Foreman and Wurster (56) did an extensive
electrophysiological and functional study of the descending spinal sympato-excitatory pathway in anesthetized cats. They demonstrated that maximal pressor responses and maximal T<sub>2</sub> preganglionic nerve evoked discharges were elicited by stimulation of the surface of the dorsolateral funiculus, 1.5 - 2 mm ventrolateral to the dorsolateral sulcus. Discrete lesions on the surface of the dorsolateral funiculus decreased the blood pressure to the level of a spinal animal, indicating that the majority of fibers responsible for maintaining vasomotor tone are located in this area. In addition, blood pressure responses to carotid occlusion were attenuated following bilateral lesions of this region. Conduction velocity in this uncrossed pathway was determined to be 6 m/sec.

In a later study (57) these investigators showed that the responses to afferent nerve stimulation are dependent upon an intact dorsolateral funiculus, indicating that this pathway is involved in reflex activation of the cardiovascular system.

Fibers from cardioacceleratory neurons within the medulla were found to descend along the dorsolateral funiculus by Henry and Calaresu (70). Stimulation of fiber terminals in the intermediolateral nucleus of the thoracic spinal cord elicited field potentials in the
medullary neurons. These evoked potentials were abolished following surgical or electrolytic lesions within the dorsolateral funiculus.

b. Descending spinal sympato-inhibitory pathways

Literature dealing with the localization of descending sympato-inhibitory pathways is not as extensive as that on sympato-excitatory pathways. Eh and Haun-Ji (45) demonstrated a pathway in the ventrolateral funiculus which is essential for mediating the depressor responses to medullary stimulation. Lim and co-workers (114) described a sympato-inhibitory pathway in the dorsolateral funiculus. They suggested this area carried efferent fibers from the bilateral medullary depressor regions near the area postrema. Lesioning this pathway did not affect vasomotor tone, indicating the absence of tonic input to the spinal cord.

Illert and Seller (82) noted that stimulation of the ventral part of the spinal cord in anesthetized cats elicited decreases in blood pressure and renal nerve activity. Responses to carotid sinus distension were not affected by lesions in the ventrolateral funiculus; therefore, the authors concluded that this area is not involved in baroreceptor-induced sympatho-inhibition. In a later study by Illert and Gabriel (81) several inhibitory regions were located in the cord: ventral
funiculus, ventrolateral funiculus, and lateral to the apex and head of the dorsal horn. Maximal inhibition of sympathetic discharges resulted from stimulation of the surface of the cord in the ventrolateral funiculus near the ventrolateral sulcus.

Henry and Calaresu (70, 71) localized pathways in the dorsolateral funiculus and the ventral horn which transmits impulses from the cardioinhibitory regions of the medulla.

Using histochemical and electrical stimulation techniques, Coote and Macleod (35, 36) localized two descending sympatho-inhibitory pathways in the spinal cord: dorsolateral funiculus in the area of the dorsolateral sulcus and the ventrolateral funiculus. These areas correspond to catecholamine-containing fibers from the ventrolateral medulla and 5-hydroxytryptamine-containing fibers from the raphe nuclei, respectively. They suggested that the pathway in the dorsolateral funiculus was responsible for the spinal component of baroreceptor-induced sympatho-inhibition. They noted that following a lesion in the dorsolateral funiculus, the spinal component of the somato-sympathetic reflex was no longer inhibited during baroreceptor activation. However, in these two experiments the control reflex was recorded during bilateral carotid occlusion. Since the
Efferent limb of the carotid occlusion reflex is mediated through sympatho-excitatory pathways in the dorsolateral funiculus (56), one must be cautious in interpreting the results from these experiments. The lack of inhibition following a lesion in the dorsolateral funiculus may, in part, be due to the removal of excitatory input to the preganglionic neurons.

Kirschner and co-workers (95) have also studied the effects of stimulation of the sympatho-inhibitory pathway in the dorsolateral funiculus. While recording extracellular potentials in T1 preganglionic neurons, identified by antidromic activation of the cervical sympathetic nerve, these investigators stimulated the ipsilateral spinal cord. Of 12 sympathetic units investigated, only six showed a pure inhibition of activity. Three units showed excitation followed by inhibition; the others showed a sequence of inhibition - excitation - inhibition. These investigators also studied the effects of stimulation of the sympatho-inhibitory pathway on the somato-sympathetic reflex in spinal cats. In acute spinal cats, a conditioning stimulus to the spinal cord evoked an excitation followed by inhibition of renal nerve or lumbar white rami activity. The test stimulus to the T11 dorsal root or L2 spinal nerve was inhibited with a condition - test latency of 50 msec. In chronic spinal
cats, the threshold for inhibition of sympathetic activity from spinal cord stimulation was less than the threshold for excitation. The latency for inhibition of the reflex discharge was a condition - test interval of 2.4 - 12.0 msec for the renal nerve and 5 - 12 msec in the L₂ white rami. These authors concluded that the sympatho-inhibitory pathway in the dorsolateral funiculus does not originate in supraspinal structures. In chronic animals, descending fibers from supraspinal structures should have degenerated. They offer two possible alternatives: (1) a propriospinal system composed of short axon neurons with cell bodies located along the cord, or (2) an ascending fiber system with collateral branches at the segmental level, antidromically activated by spinal cord stimulation.

6. Summary

The importance of the spinal cord in regulating sympathetic outflow has recently received attention from many investigators. Spontaneous and reflex discharges have been recorded in spinal animals. Also, evidence has been presented suggesting that both excitatory and inhibitory input from medullary and supramedullary structures act on spinal preganglionic neurons or interneurons. These reports suggest the possibility that the spinal cord is a major regulator of sympathetic outflow.
Afferent Nerves

1. Mechanisms for Pressor and Depressor Responses to Afferent Nerve Stimulation

For over a century now it has been well-documented that afferent nerve stimulation can elicit a change in arterial blood pressure. Mc Dowall (127) has reviewed a large volume of early literature beginning with von Bezold in 1863 demonstrating vasoconstrictor and vasodilator responses to sensory nerve stimulation. The factors responsible for the mediation of pressor and depressor reflexes have been debated since the late 19th century. In 1895 Hunt (80) suggested that activation of different afferent fiber types determined the pressure change induced by peripheral nerve stimulation. The depressor afferent nerves would respond to low intensity stimuli, while the pressor afferent nerves would be activated by high intensity stimuli. In 1916 Ranson and Billingsley reported a series of investigations dealing with this topic. The first two reports (151,153) were in agreement with Hunt. Transection of lateral dorsal root fibers (small diameter afferent nerves) abolished the rise in blood pressure evoked by painful stimuli. However, transection of medial dorsal root fibers (large diameter afferent nerves) did not affect the response. The ventrolateral funiculus and the area around the tract of Lissauer were
suggested to be the spinal ascending pathways for the depressor and pressor reflexes, respectively. In their later work, Ranson and Billingsley (154) concluded that it was unlikely that different fiber types were responsible for variations in blood pressure responses, thus negating their earlier work. Instead they suggested that increased stimulus intensity activated a greater number of fibers of the same type. The depressor ascending spinal pathway, composed of long fibers with only a few synapses, was most easily excited by weak stimuli. The ascending spinal pressor pathway, composed of short fibers with many synapses, required multiple stimuli to be activated. Consequently, low frequency stimuli to a sensory nerve activated the depressor pathway. High frequency stimuli to the same fibers activated the pressor pathway which is capable of overriding the effects of depressor pathway activation. Thus, central summation of impulses may determine reflex effects of afferent nerve stimulation.

In 1917 Gruber (66) reported that variation in stimulus frequency, while maintaining constant intensity, resulted in a reversal of the blood pressure response to afferent nerve stimulation. This was in general support to Ranson and Billingley's later suggestion (154).

In 1943 Gordan (64) provided evidence supporting both Hunt (80) and Ranson and Billingsley (154).
Cocainization and asphyxia of sciatic nerve fibers selectively blocked the pressor and depressor reflexes, respectively. He suggested that small diameter, unmyelinated fibers, which are more susceptible to cocaine block, are responsible for the pressor reflex; while larger diameter, myelinated fibers, which are more susceptible to asphyxia, were responsible for the depressor reflex. In addition, increasing the frequency of stimulation without altering the intensity reversed the depressor to a pressor response. Consequently, he concluded that both variations in afferent fiber types and central nervous system mechanisms determined the cardiovascular responses to afferent nerve stimulation.

2. Cardiovascular Responses to Stimulation of Specific Fiber Groups

More recent studies by Laporte and co-workers (107, 108) demonstrated the specific fiber types in cutaneous and muscle afferent nerves which are responsible for eliciting a particular blood pressure response. Low frequency stimulation of cutaneous and muscle Group I - III fibers elicited a depressor response, while high frequency stimulation of the same fibers resulted in a pressor reflex. Activation of cutaneous and muscle Group IV fibers, regardless of stimulus frequency, elicited a rise in blood pressure. Stimulation of Group I muscle afferent
fibers did not cause a change in blood pressure.

Johansson (85) made an extensive study of the cardiovascular system effects to somatic afferent nerve stimulation. He recorded arterial blood pressure and regional blood flows to the kidney, skeletal muscle, intestine and skin. He demonstrated a marked depressor response and vasodilatation in all vascular beds during activation of Group III muscle afferent fibers. This was particularly evident in cats with high spontaneous vasoconstrictor tone. Though this response was most noticeable at low stimulus frequencies, it was also noted at higher frequencies (100 - 500 Hz). When the intensity of stimulation was increased to activate unmyelinated Group IV fibers, high frequency stimulation resulted in a pressor reflex, while low frequency stimulation produced a depressor response. Stimulation of myelinated cutaneous fibers caused a decrease in blood pressure at low stimulus frequencies, but an increase in pressure was elicited by high intensity stimulation of unmyelinated cutaneous afferent fibers. Adequate stimuli for eliciting a depressor reflex was a pinch to the muscle, while nociceptive stimuli resulted in a pressor reflex.

Coote and co-workers (34) investigated the mechanism for the rise in arterial pressure during hindlimb
exercise in the cat. Stimulation of ventral roots caused contraction of hindlimb muscles and a rise in blood pressure. This response was abolished by an injection of gallamine, indicating its reflex nature. Occlusion of the arterial inflow to the hindlimb enhanced the pressor reflex. They suggested that, since tetanic contraction decreased arterial inflow, the rise in arterial pressure following ventral root stimulation or hindlimb exercise was due to the release of a chemical substance produced by the contracting muscle. This substance then activates "metabolic receptors" innervated by free nerve endings of Group III and IV afferent fibers surrounding blood vessels.

3. Effects of Anesthesia and Brainstem Transections on Cardiovascular Responses to Afferent Nerve Stimulation

In addition to the effects of variations in stimulus parameters, anesthesia and brainstem transections have also been shown to influence the cardiovascular responses to afferent nerve stimulation. Laporte and co-workers (107) reported that low frequency stimulation of Group III afferent fibers elicited a depressor response in unanesthetized, decerebrate cats; however, a depressor response resulted from the same stimulus following urethane administration. McLennan (128) further demonstrated
the effects of anesthetics and curare on blood pressure and renal nerve discharges during afferent nerve stimulation. In pentobarbital anesthetized rabbits, a single stimulus to the auricular nerve resulted in a fall in arterial pressure and an inhibition of nerve discharges. Administration of curare reversed this response to a rise in pressure and an increased sympathetic discharge. In unanesthetized rabbits only pressor responses were noted. Administration of nonanesthetic doses of pentobarbital reversed this response. McLennan suggested that the physiological stimulus to afferent fiber activation would be a pressor response. He proposed that anesthetics inhibit the vasomotor center while curare excites this area. Khayutin and co-workers (49, 93) noted similar responses in the cat following tibial nerve stimulation. However, decerebration also led to a reversal from a pressor to a depressor response. These authors proposed that decerebration or anesthetics cause activation of an inhibitory mechanism in the bulbar reticular formation. In addition, they suggested that anesthesia interrupted transmission in ascending spinal tracts which mediate impulses from slow conducting Group III and Group IV fibers.

Leibowitz and co-workers (110) investigated the effects of various brainstem transections on the
cardiovascular responses to sciatic nerve stimulation in unanesthetized rabbits. A series of lesions from the level of the caudate nucleus to the lower medulla resulted in a conversion of pressor to depressor responses. Following suprapontine lesions, low frequency stimulation of afferent nerves elicited a fall in arterial pressure. Following a lesion at the lower pons, stimulation of the sciatic nerve resulted in a decreased blood pressure, regardless of stimulus frequency.

4. Somato-Sympathetic Reflexes

Though measurements of cardiovascular parameters provided indirect evidence that stimulation of sensory nerves activated the sympathetic nervous system, it was not until 1946 that Alexander (2) directly demonstrated the somato-sympathetic reflex. He was able to elicit reflex discharges in the inferior cardiac nerve by stimulating the sciatic nerve. After lesioning areas within the medulla, both spontaneous and reflex discharges were abolished. Therefore, he concluded that the same areas which were essential for spontaneous sympathetic tone were responsible for the mediation of the somato-sympathetic reflex. This was in opposition to Porter's (147) suggestion that there were separate "vasotonic" and "vaso-reflex" centers in the medulla.

Nearly 20 years later, Schaefer (167) provided the
next major study of the somato-sympathetic reflex. He noted that the latency for reflex discharges in cardiac and renal nerves was independent of the segmental level of the afferent nerve being stimulated. He concluded that the latency was dependent upon the distance between the recording site and a supraspinal reflex center. In addition, the medulla was considered essential for any circulatory effects from sensory nerve stimulation.

Though much evidence had accumulated that spinal animals were capable of eliciting autonomic responses (see previous section on Spinal Cord), the studies by Alexander and Schaefer suggested that supraspinal structures were necessary for mediating sympathetic nerve discharges following afferent nerve stimulation. However, Beachman and Perl (9, 10) provided definitive evidence for reflex preganglionic nerve activity in spinal (C₁) cats. Multisegmental, reflex discharges in upper thoracic and lumbar white rami were elicited by nociceptive and thermal stimuli to the limbs and electrical stimulation of dorsal roots, spinal nerves, and limb nerves. On the basis of latency (3 - 15 msec) the reflex was described as polysynaptic.

Fernandez de Molina and Perl (51) recorded spontaneous and reflex discharges in thoracic and lumbar postganglionic fibers in C₁ spinal cats. Horeyseck and Jänig
(78) also noted reflex discharges in postganglionic fibers to the skin and skeletal muscle in chronic (7 - 95 days) spinal (T7 - 8) cats.

The spinal component of the somato-sympathetic reflex has also been recorded in CNS-intact preparations by Sato and co-workers (164,166) and Coote and Downman (31). These investigators have noted that the spinal reflex is most easily elicited by stimulation of adjacent dorsal roots or spinal nerves. This indicates the segmental nature of this reflex. Sato (59) suggested that the spinal reflex may be important for localized or segmental reflex control in CNS-intact animals.

5. Activation of Specific Fiber Groups

Since blood pressure responses were shown to be affected by the afferent fiber type being stimulated, studies were initiated to relate sympathetic discharges with specific afferent nerve volleys. While recording from the renal nerve, Fedina and co-workers (49) noted that activation of fast conducting Group III fibers from the tibial and mesenteric nerves caused a reflex discharge. Increasing the intensity of stimulation to include the slow conducting Group III fibers resulted in an excitation followed by an inhibition (silent period). Activation of Group IV fibers mediated an additional later reflex.

Sato and co-workers (162,163) reported that only
cutaneous Group I and II fibers and muscle Group II and III fibers were involved in the supraspinal component of the somato-sympathetic reflex in the cervical sympathetic trunk. Activation of cutaneous Group IV fibers and muscle Groups I and IV fibers did not affect the reflex sympathetic discharges. The spinal component had a higher threshold for activation, requiring stimulation of cutaneous and muscle Group III afferent fibers.

Using a computer for averaging transients, reflex responses in the cervical sympathetic trunk were recorded by Schmidt and Schönfuss (171). Their data verified and extended the observations of Sato and co-workers (162, 163). They noted three reflex discharges (latencies: 40, 70, and 110 msec) following single shocks to an afferent nerve. Activation of low threshold cutaneous Group II fibers was the most effective stimulus. The reflex was enhanced by including Group III fibers in the afferent volley. Repetitive stimulation increased the amplitude but not the time course of the reflex discharge. Muscle afferents required greater intensity of stimulation (Group III) before eliciting a response. Muscle afferent nerve volleys produced smaller reflexes of longer latency than those following activation of skin afferent fibers. They concluded that cutaneous nerves had a greater excitatory influence on sympathetic reflex centers. In
addition, using a condition-test paradigm they noted that as the interval between stimuli was between 100-1200 msec the test response was attenuated, with complete suppression occurring with an interval of 100-300 msec. This inhibition was due to the silent period from the previous response.

Coote and Perez-Gonzalez (37) described variations in reflex sympathetic discharges following cutaneous and muscle afferent nerve stimulation. They concluded that low threshold Group III fibers mediate only an inhibitory response, while activation of higher threshold Group III fibers are necessary to elicit an excitatory reflex. In contrast to Sato and co-workers (162,163) Group IV afferent fibers were capable of eliciting a sympathetic discharge of long latency (350-400 msec) if the myelinated afferent fibers were previously blocked by anodal current. With repetitive stimulation to an afferent nerve, a Group IV reflex was also mediated and it was not affected by the previous silent period of the Group III reflex.

Wysogrodski and Polosa (203) have also described a pure inhibitory response in single unit sympathetic preganglionic neurons following somatic afferent nerve stimulation. The inhibitory response following single pulse stimulation had a latency of 96 msec and a duration of
1100 msec. Ulnar nerve stimulation caused an inhibition of sympathetic discharges after a latency of 48 msec and with a duration of 720 msec. In C2 spinal cats, the latency and duration were reduced to 65 msec and 250 msec, respectively, for sciatic nerve stimulation and to 40 msec and 266 msec, respectively, for ulnar nerve stimulation. Since glutamate-induced activity was also inhibited the authors suggested that the inhibition occurred by a post-synaptic effect on the preganglionic neuron.

Schmidt and Weller (172) provided a detailed description of the stimulus conditions which are most effective in producing a reflex discharge in the cervical and lumbar sympathetic trunks following activation of unmyelinated fibers. Stimulation of Group I - IV fibers, using paired pulses with an interval of 50 msec, elicited a late reflex discharge (latency: 250 - 500 msec). Following anodal block of myelinated fibers, afferent nerve stimulation still elicited the late reflex discharge. The Group IV reflex was determined to be completely independent of the excitation and inhibition following myelinated fiber activation. Consequently, they suggested that unmyelinated fibers activate a different population of sympathetic neurons than the myelinated afferent nerves. The most effective stimuli for eliciting the Group IV reflex were pairs or short trains of stimuli at
low frequency (10 - 30 Hz) or repeating single volleys at intervals of less than 8 sec. Thus, they concluded that unmyelinated fibers require temporal facilitation of afferent volleys to evoke a sympathetic discharge. Koizumi and co-workers (98) also demonstrated a Group IV reflex in lumbar white rami after anodal current block of the myelinated afferents. In addition, they correlated sympathetic nerve activity with the blood pressure responses. Low frequency stimulation of cutaneous Group I - IV fibers or myelinated fibers alone resulted in a depressor response. Nerve activity showed a prolonged silent period during which spontaneous and reflex activity was attenuated. Low frequency stimulation of unmyelinated fibers alone induced a pressor response. Simultaneous nerve recordings showed no silent period. They concluded that myelinated fibers have synaptic input to both excitatory and inhibitory reflex centers, while unmyelinated fibers influence only excitatory areas.

These studies indicated that unmyelinated fibers appear to have only a supraspinal component to the somato-sympathetic reflex. Sato (161) re-investigated responses to unmyelinated afferent stimulation in spinal cats. He noted that stimulation of hindlimb Group IV fibers in acute spinal cats did not elicit a discharge in the lumbar white rami. However, the reflex discharge reappeared
Group IV fibers from adjacent spinal nerves can elicit a discharge in the lumbar white rami. This spinal component of the Group IV reflex is not abolished in acute spinal cats.

Horeyseck and Jänig (76, 77) used natural stimulation to the skin to evoke discharges in skin and muscle postganglionic nerves. Non-noxious stimuli (air jets over hair cells, constant force to foot pads, and sinusoidal stimulation of Pacinian corpuscles in fat pads) elicited decreased activity in muscle sympathetic fibers and increased activity in skin postganglionic fibers. These data suggested that non-noxious stimuli to the skin activated Group II and III afferent fibers which resulted in a redistribution of blood flow from the skin to the muscle. Noxious stimuli (mechanical damage or thermal stress) caused the opposite response; that is, attenuation of skin sympathetic discharges and activation of muscle sympathetic discharges. They suggested that these reflexes were initiated by Group III and IV afferent nerve volleys. These data suggest that the central nervous system has a "mirror image" organization of the somato-sympathetic reflex to skin and muscle sympathetic nerve, possibly important in the opposite regulation of blood flow through the skin and muscle.
6. Supramedullary Component to Somato-Sympathetic Reflexes

In addition to the well-documented spinal and medullary components of the somato-sympathetic reflex, Sato (160) described a very late reflex (latency: 300 - 350 msec) following myelinated afferent nerve stimulation 8 - 10 hr after chloralose anesthesia was initiated. Additional doses of chloralose abolished this reflex, suggesting the response was directly related to the level of anesthesia. The response was also abolished by decerebration, indicating it is mediated by a suprapontine pathway.

7. Supraspinal Control of Somato-Sympathetic Reflexes

Experiments described above indicate that supraspinal structures are involved in mediating the late reflex responses to afferent nerve stimulation. Afferent fibers apparently activate medullary sympatho-excitatory neurons which project to spinal preganglionic neurons or interneurons. Coote and co-workers (32, 33, 35, 36) and Kirschner and co-workers (94) have shown that stimulation of medullary sympato-inhibitory regions may inhibit sympathetic reflex discharges. Coote and co-workers (33) demonstrated that discharges in thoracic white rami, elicited by splanchnic nerve,
dorsal root, or intercostal nerve stimulation, could be inhibited by high frequency stimulation of the ventro-medial reticular formation. Reflex responses in this study were mediated within the spinal cord, since the responses were not abolished following C2 transection. Consequently, the inhibition of the reflex discharges must have occurred at the spinal level. Baroreceptor activation (carotid sinus distension) did not affect the reflex discharges. Coote and Downman (32) also showed that supraspinally mediated reflexes were inhibited by medullary stimulation. Complete inhibition of the ninth intercostal to renal nerve reflex was noted during high frequency stimulation of the medullary depressor area. These authors suggested that this inhibition occurred at the spinal level, since intercostal - intercostal nerve reflexes were inhibited by activation of the same sites. Renal nerve reflex discharges were also inhibited by carotid sinus distension. However, intercostal - intercostal reflex discharges were not effected by baroreceptor activation. These data, together with the data described previously (33), suggested that baroreceptor inhibition did not occur at the spinal level.

In two later reports, Coote and Macleod extended these studies by stimulating several bulbospinal
monoaminergic pathways (35) and re-evaluating the responses to baroreceptor activation (36). Activation of three pathways from the medulla were effective in abolishing both spontaneous activity and reflex discharges in the renal nerve and thoracic preganglionic nerve. These three pathways are: a noradrenergic system originating in the ventrolateral medulla, a 5-hydroxytryptaminergic system from the raphe nucleus, and the reticulospinal system within the ventromedial reticular formation. Stimulation of descending tracts in the spinal cord (near the dorsolateral sulcus and in the ventrolateral funiculus) was also effective in abolishing reflex responses in sympathetic nerves. The time course of baroreceptor-induced sympatho-inhibition was also examined (36). Cardiac and renal nerve discharges following intercostal nerve stimulation could be inhibited by carotid sinus distension. Maximum inhibition of reflex discharges occurred after a latency of 125 - 330 msec in the cardiac nerve and 138 - 342 msec in the renal nerve. In addition to inhibition of supraspinally mediated reflexes, these authors demonstrated that baroreceptor activation can inhibit the spinal sympathetic reflex in T11 white rami. However, unlike the late reflex which could be completely abolished, the spinal reflex was inhibited by 30 - 75%.
Kirschner and co-workers (94) noted similar responses while recording discharges in the renal nerve evoked by stimulation of thoracic dorsal roots. Both early and late reflexes were inhibited by stimulation of the medial reticular formation. Intravenous injection of norepinephrine (3 - 5 µg/kg) abolished the late reflex, but only slightly affected the early reflex. Higher doses of the pressor agent (8 - 15 µg/kg) resulted in an inhibition of the early reflex.

8. Summary

Activation of afferent nerves can elicit an increase or a decrease in sympathetic nerve discharges, depending upon the type of nerves stimulated and the frequency of stimulation. The physiological role of the somato-sympathetic reflex is still unclear. Coote (30) has suggested that small myelinated Group III and unmyelinated Group IV fibers may be involved in initiating cardiovascular and respiratory responses accompanying exercise. Sato (159) has suggested that the spinal and supraspinal components of the somato-sympathetic reflex may be important for regional and general regulation, respectively, of the sympathetic nervous system.
CHAPTER III
MATERIALS AND METHODS

A. General Animal Preparation

Experiments were performed on adult cats of either sex. Animals were preanesthetized with ketamine hydrochloride (Ketaset$^R$ or Vetalar$^R$, 10 - 20 mg/kg, iv) followed by alpha-chloralose (40 - 60 mg/kg, iv).

The femoral artery and vein were cannulated for blood pressure recordings and drug administration, respectively. Catheters were made from polyethylene tubing (I.D. 0.045" - O.D. 0.062") fitted over an 18 gauge needle. A tracheotomy was performed, but animals were allowed to breathe spontaneously throughout the surgical procedures. Common carotid arteries and vagus nerves were isolated and loose ligatures were placed around them. Rectal temperatures were maintained at $37 \pm 1^\circ C$ by a heating pad on the animal table.

Prior to any experimental procedure, animals were bilaterally vagotomized and maintained on positive pressure respiration (Bird Mark 7 Respirator) with an air-$O_2$ mixture.
Respiration rate and depth were adjusted to approximate spontaneous breathing patterns. Animals were immobilized with gallamine triethiodide (Flaxedil®, 4 mg/kg, iv). Additional doses of the neuromuscular blocking agent were administered as needed during the experiments.

B. Spinal Cord Preparation

Following removal of the overlying musculature, a laminectomy was performed in the mid to low cervical level (C₃ - C₈). Animals were then placed in a stereotaxic apparatus (Trent H. Wells, Jr.). The vertebral column was stabilized with a spinal clamp attached to the T₄ spinous process. With the aid of a dissecting microscope (Zeiss) at magnification 16X, the dura mater was carefully resected using micro-dissecting scissors. In some animals the dorsal roots and dentate ligament were cut. Small pins were carefully placed into the resected dura mater, which was then attached to the surrounding muscle. These manipulations permitted clear exposure of the lateral funiculus.

C. Afferent Nerve Preparation

Either the tibial nerve, cervical dorsal roots, or dorsolateral sulcus region of the spinal cord were prepared for stimulation of afferent nerve fibers. Cut central ends of the peripheral nerve or dorsal root were placed on bipolar stainless steel electrodes.
The T₂ preganglionic nerve was exposed retropleurally following removal of the musculature overlying the upper three ribs and the head of the second rib near its articulation with the vertebral column. With the aid of a microscope (16X) and a pair of fine forceps, the nerve was carefully traced to its junction with the sympathetic trunk ganglion. In many experiments it was necessary to ligate small blood vessels lying lateral and dorsal to the sympathetic chain. The T₂ preganglionic nerve was cut and the central end was placed on a pair of bipolar stainless steel electrodes.

Skin flaps were tied to the side bars of the stereotaxic apparatus to form a pool for warm mineral oil to protect the exposed spinal cord, dorsal roots, and preganglionic nerve.

E. Stimulation Techniques

Figure 1 illustrates the sites of spinal cord stimulation and preganglionic nerve recordings. Output from square wave stimulators (Grass S48 and S88) was passed through stimulus isolation units (Grass SIU 5 and SIU 4658). Coaxial electrodes (David Kopf SNE-100 or NE-100) were used for spinal cord stimulations. Electrodes were carefully filed so that both leads were able to contact the surface of the spinal cord without penetration. Electrodes
A schematic diagram depicting stimulation and recording techniques. DLF: dorsolateral funiculus; VLF: ventrolateral funiculus. The insert on the bottom shows examples of spontaneous activity (left), a single evoked response (middle), and a computer summed tracing of the evoked response (right) in the T2 preganglionic nerve. The horizontal calibrations are 10 msec and the vertical calibrations are 25 µV.
were positioned on the surfaces of the dorsolateral and ventrolateral funiculi and the dorsolateral sulcus area by means of a stereotaxic electrode carrier (Trent H. Wells, Jr.) or a micromanipulator (Sobotka Model C-3). Afferent nerve fibers in the tibial nerve or dorsal roots were stimulated with a pair of bipolar stainless steel electrodes made from insect pins size 00. Electrodes were insulated except at the tips. Stimuli were applied to the right spinal cord and afferent nerve fibers.

Stimulus parameters were monitored using a differential amplifier and an oscilloscope (Tektronix 565).

F. Recording Techniques

1. Blood Pressure and Heart Rate

Blood pressure was recorded on a polygraph (Grass Model 79C) via a catheter placed in the right femoral artery and connected to a pressure transducer (Statham P23Dc). Both mean and pulsatile pressures were continuously monitored. Heart rate was determined from the pulsatile pressure recordings.

2. T2 Preganglionic Nerve Recordings

Monophasic nerve recordings were made from a multifiber T2 preganglionic nerve preparation by crushing the nerve ending over one electrode. Electrodes were connected to a preamplifier (Grass P-9AC) with bandpass filters set at 2 and 2 kHz. Activity was monitored on an oscilloscope.
The output of the preamplifier was also connected to a computer (PDP-12) terminal. With the use of the Signal Averager Program, the evoked discharges were digitized at a rate of 8 kHz, displayed on an oscilloscope (Tektronix 602), and summated. One thousand points were collected during each evoked response. Responses to 10 - 100 stimulations were sampled and the computer summed responses were stored on LINC-tape for later analysis using Waveform: Evoked Potential Analysis Program (200). This program computes amplitude, latency, rise and fall times, and area of the evoked discharge. The area of the evoked discharge refers to the area under the curve produced by the summation of the responses to the stimuli. A curve which rises above the baseline indicates an increase in sympathetic nerve activity time-locked to a stimulus. A curve which falls below the baseline indicates a decrease in sympathetic nerve activity time-locked to a stimulus.

Polaroid prints were obtained from the computer display scope using an oscilloscope camera (Polaroid C-5).

The insert in Figure 1 shows examples of spontaneous activity in the T2 preganglionic nerve (left), a single evoked discharge (middle), and a computer summed tracing of the evoked response following 50 single pulse stimulations of the descending spinal excitatory pathway (right).
In a few preparations the spontaneous activity occurred in bursts related to the cardiac and/or respiratory cycles. However, in most preparations the spontaneous discharges occurred randomly.

G. Experimental Protocols

1. Cardiovascular and Electrophysiological Responses to Variations in Stimulus Parameters of Descending Sympatho-Excitatory Pathways

Computer summed traces of sympathetic nerve activity following stimulation of descending spinal sympatho-excita-
tory pathways show a period of reduced activity following the evoked discharge (56, 59, 182, 185). This is similar to the "silent period" which has been described by sev-
eral investigators during stimulation of afferent nerve fibers and supraspinal structures (see Literature Review).

The purpose of this series of experiments was to determine how the silent period following sympatho-excitative stim-
ulation affects subsequent stimuli to the same pathway. Discharges in the T₂ preganglionic nerve were recorded during twin pulse stimulations with various intervals be-
tween pulses (1.0 - 2500 msec, corresponding to 0.4 - 1000 Hz). Responses to twin pulse stimulations were used as an indication of sympathetic nerve activity during stimulation of the excitatory pathway at varying frequencies. Blood pressure responses were also investigated during
stimulations of the sympatho-excitatory pathways at various frequencies (0.5 - 750 Hz). The cardiovascular and electrophysiological responses were then compared to determine the relationship between the sympathetic nerve discharges and the magnitude and direction of changes in blood pressure during stimulation of descending sympatho-excitatory pathways in the cervical (C₃ - C₆) spinal cord.

Evoked discharges in T₂ preganglionic nerves were recorded in seven animals. Fifty responses were summed during twin pulse stimulations with the interval between stimuli varying from 1 - 2500 msec corresponding to frequencies of 0.4 - 100 Hz. In any given experiment, voltage and duration were maintained constant at 3 - 10 volts and 0.1 second pulse of twin pulse stimuli was compared to the area of the response following single pulse stimulations.

In eight animals blood pressure was monitored while stimulus frequencies were varied between 0.5 - 750 Hz. In any given experiment, voltage and duration were maintained constant at 5 - 10 V and 0.1 - 1 msec, respectively. In three experiments, frequency was maintained constant at 50, 5, or 2 Hz and intensity was varied from 1 - 15 V.

To describe the relationship between changes in blood pressure and sympathetic nerve activity during variations in stimulus parameters, all data was expressed as
per cent of control. Control blood pressure refers to the prestimulatory mean pressure level; control nerve responses refer to the area of the evoked discharge following single pulse stimulations.

2. Cardiovascular and Electrophysiological Responses to Stimulation of Descending Spinal Sympatho-Inhibitory Pathways

The purpose of this study was to determine the cardiovascular and sympathetic nerve responses to stimulation of the sympatho-inhibitory pathway located on the surface of the ventrolateral funiculus of the cervical (C5 - C7) spinal cord. Optimum stimulation parameters for eliciting depressor responses could then be determined. Blood pressure responses were recorded in nine animals while varying the stimulus frequency from 0.5 - 200 Hz. In any given experiment, voltage and duration were maintained constant at 6 - 15 V and 1 msec, respectively. Stimuli were maintained for 20 - 60 sec.

In six animals frequency and duration of stimulation were maintained constant (25 - 100 Hz and 1 msec, respectively) while the intensity of stimuli was varied from 3 - 20 V.

Inhibition of sympathetic nerve discharges were successfully recorded in eight animals. Responses to 50 - 100 single pulse (0.5 Hz, 0.1 - 1 msec, and 6 - 15 V) or short
trains (10 - 20 msec) of high frequency (100 - 300 Hz) stimuli were summed. Stimulations were applied to the surface of the ventrolateral funiculus in an area which elicited a depressor response when activated at high frequency for 20 - 60 sec.

3. Cardiovascular and Electrophysiological Responses to Afferent Nerve Stimulation

Cardiovascular and sympathetic nerve responses to afferent nerve stimulation have been described in detail (97, 165). The purpose of this series of experiments was to verify these earlier results and to compare the responses to peripheral afferent nerve, dorsal root, and dorsolateral sulcus stimulations.

Blood pressure responses were recorded during variations in stimulus frequencies (0.1 - 200 Hz) to tibial nerve afferent fibers (n = 4), dorsal root (n = 2), and dorsolateral sulcus (n = 3). In any given experiment, voltage and duration were maintained constant at 9 - 18 V and 0.5 - 1 msec, respectively.

Cardiovascular responses to variations in stimulus intensity was investigated in seven animals. While maintaining frequency and duration constant at 25 - 100 Hz and 1 msec, respectively, intensity of stimulation was varied from 0.1 - 18 V.

Preganglionic nerve discharges were summed during
10 - 25 single pulse stimulations (0.4 - 0.5 Hz, 0.1 - 1 msec, 8 - 15 V) of the tibial nerve (n = 2), dorsal root (n = 4), and dorsolateral sulcus (n = 10).

4. Interactions of Descending Sympatho-Excitatory and Sympatho-Inhibitory Pathways

The purpose of this series of experiments was to determine the ability of descending spinal excitatory and inhibitory pathways to interact with each other in regulation of sympathetic outflow. Blood pressure and T2 preganglionic nerve discharges were recorded during stimulation of the descending sympatho-excitatory and sympatho-inhibitory pathways located on the surfaces of the dorsolateral and ventrolateral funiculi of the cervical spinal cord, respectively.

The interaction of these pathways on blood pressure responses was examined in 14 cats. The cardiovascular responses to stimulation of each of these pathways alone was first determined. Following separate stimulations, the interaction of these pathways was studied under four conditions:

a. sympatho-inhibitory stimulation beginning 13 - 30 sec after onset of sympatho-excitatory stimulation (n = 14);

b. sympatho-inhibitory stimulation during various levels of sympatho-excitatory activity (n = 3);
c. sympatho-excitatory stimulation beginning 9 - 45 sec after onset of sympatho-inhibitory stimulation (n = 7); and
d. simultaneous activation of the two pathways (n = 4).

The interaction of sympatho-excitatory and sympatho-inhibitory pathways on evoked discharges in the T2 preganglionic nerve was noted in eleven animals. The time course of inhibition of sympathetic discharges was determined using the condition-test paradigm in six cats. A subthreshold or threshold stimulus (condition) to the sympatho-inhibitory pathway preceded a stimulus (test) to the sympatho-excitatory pathway by 0 - 300 msec. The area of the evoked discharge to 25 - 50 test stimuli was expressed as per cent of the area of the unconditioned evoked discharge.

T2 preganglionic nerve discharges evoked by 10 - 25 stimulations of the sympatho-excitatory pathway were summed. These responses were then evaluated during simultaneous high frequency stimulation (50 - 100 Hz, 0.5 - 1 msec, 8 - 15 V) of the sympatho-inhibitory pathway in eight animals. The area of the evoked discharge during simultaneous inhibitory stimulation was compared to the area of the response to excitatory stimulation alone.
5. Baroreceptor Interaction with Descending Spinal Sympatho-Excitatory Pathways and Afferent Nerves

The purpose of this study was to evaluate the influence of baroreceptor activity on spinal evoked sympathetic discharges. Changes in baroreceptor activity were induced by a pressor dose of norepinephrine (Levophed, 1 - 3 μg/kg, iv) or by bilateral occlusion of the common carotid arteries. The rise in blood pressure elicited by norepinephrine causes an increase in baroreceptor nerve discharges and a reflex decrease in spontaneous sympathetic nerve activity. The rise in pressure during bilateral carotid occlusion results from a decrease in carotid sinus baroreceptor nerve discharges and a reflex increase in spontaneous sympathetic nerve activity.

The effects of baroreceptor activation on spinal evoked discharges from descending sympatho-excitatory pathway and afferent nerve stimulation were evaluated in 12 animals. Preganglionic nerve discharges following 10 - 25 stimulations were summed. Control responses, before and after the pressor response to norepinephrine, were compared to those evoked with identical stimulation during baroreceptor activation.

The effects of inhibition of baroreceptor activity on sympathetic discharges elicited from stimulation of descending spinal sympatho-excitatory pathways were
studied in five animals. \( T_2 \) preganglionic nerve discharges during 25 stimulations were recorded before, during, and after bilateral carotid occlusion.

6. Interaction of Descending Sympatho-Excitatory Pathways and Afferent Nerves

The purpose of this series of experiments was to describe the role of the spinal cord in cardiovascular regulation through integration of impulses from afferent nerve fibers and descending spinal sympatho-excitatory pathways. Blood pressure and \( T_2 \) preganglionic nerve responses were monitored during stimulation of these two systems.

Blood pressure responses were recorded during stimulation of the descending sympathetic pathway on the surface of the dorsolateral funiculus of the cervical spinal cord and afferent nerve fibers in the tibial nerve \((n = 5)\), and dorsal root \((n = 2)\), or dorsolateral sulcus \((n = 2)\). Cardiovascular responses to stimulation of each of these systems alone was first determined. Following separate stimulation, the interaction of these fibers was investigated under four conditions:

a. afferent nerve stimulation beginning 16 - 35 sec after onset of sympatho-excitatory stimulation \((n = 6)\);
b. sympatho-excitatory stimulation beginning 17 - 40 sec after onset of afferent nerve stimulation \((n = 6)\);
c. simultaneous activation of both systems (n = 4);
and,
d. afferent nerve stimulation at various intensities during subthreshold or just threshold stimulation of the sympato-excitatory pathway (n = 5). (A "just threshold" stimulus was arbitrarily defined as a stimulus which elicits a 5 mm Hg rise in pressure.)

Preganglionic nerve discharges were summed during 25 - 50 single pulse stimulations of the sympato-excitatory pathway in the C₅ - C₇ spinal cord and afferent nerve fibers in the tibial nerve (n = 1), C₇ - C₈ dorsal root (n = 2), and C₇ - C₈ dorsolateral sulcus (n = 4). The interaction of descending pathway and afferent nerves was determined using the condition - test paradigm. Subthreshold stimuli (condition) to the sympato-excitatory pathway preceded stimuli (test) to the afferent nerves by 0 - 1000 msec. The area of the evoked discharge following the conditioned stimuli was compared to the evoked response following unconditioned afferent nerve stimuli. The time course of facilitation and inhibition of both the spinal and supraspinal components of the somato-sympathetic reflex was described.

7. Interaction of Descending Sympatho-Inhibitory Pathways and Afferent Nerves

The purpose of this study was to describe the role
of the spinal cord in cardiovascular regulation by integrating impulses from afferent nerve fibers and descending spinal sympatho-inhibitory pathways. Blood pressure and $T_2$ preganglionic nerve responses were monitored during stimulation of these two systems.

Blood pressure responses were recorded during stimulation of the sympatho-inhibitory pathway and afferent nerve fibers in the $C_7 - C_9$ dorsal root ($n = 2$) or the $C_7 - C_8$ dorsolateral sulcus ($n = 3$). Cardiovascular responses to stimulation of each of these systems alone were first determined. Following separate stimulation, the interaction of these fibers was investigated under four conditions:

a. afferent nerve stimulation beginning 15 - 26 sec after onset of sympatho-inhibitory stimulation ($n = 5$);
b. sympatho-inhibitory stimulation beginning 14 - 25 sec after onset of afferent nerve stimulation ($n = 5$);
c. simultaneous activation of both systems ($n = 4$);
and
d. afferent nerve stimulation during just threshold stimulation of the sympatho-inhibitory pathway ($n = 3$).

(A "just threshold" stimulus was arbitrarily defined as a stimulus which elicits a 5 mm Hg fall in arterial pressure.)

$T_2$ preganglionic nerve discharges were summed
during stimulation of the sympatho-inhibitory pathway and afferent nerve fibers. The time course of inhibition of the somato-sympathetic reflex discharges was successfully determined in two animals using the condition - test paradigm. The stimulus intensity applied to the sympatho-inhibitory pathway was determined by recording blood pressure responses during high frequency stimulation. A stimulus intensity which elicits a depressor response was used to investigate the inhibition of evoked discharges. A single pulse stimulus (condition) to the sympatho-inhibitory pathway was followed after 0 - 500 msec by a single pulse stimulus (test) to the afferent nerve fibers. The area of the evoked discharge to 25 conditioned stimulations of the afferent nerve was compared to the area of the response to 25 unconditioned stimuli.

In six animals, the inhibition of $T_2$ preganglionic nerve responses following 10 - 25 stimulations of afferent nerve fibers was determined during high frequency (50 - 100 Hz) stimulation of the sympatho-inhibitory pathway. The area of the $T_2$ preganglionic nerve evoked discharge to afferent nerve stimulation alone was compared to the response following identical afferent nerve stimulation during simultaneous activation of the sympatho-inhibitory pathway.
H. Statistical Analysis

Statistical analysis was performed with the Student t-test for paired and unpaired data. Linear relationships were determined using the Pearson product-moment coefficient of correlation. P values of <0.05 were considered to indicate statistical significance (176).
CHAPTER IV
RESULTS AND DISCUSSION

A. Cardiovascular and Electrophysiological Responses to Variations in Stimulus Parameters of Descending Sympatho-Excitatory Pathways

Stimulation of descending spinal sympato-excitatory pathways elicits a sympathetic nerve evoked response with two components: an increased nervous discharge followed by a silent period. The effects of these two phases on subsequeint stimuli to the same pathway were evaluated. Evoked discharges in the T\textsubscript{2} preganglionic nerve were summed following twin pulse stimuli to the descending sympato-excitatory pathway on the surface of the dorsolateral funiculus of the cervical (C\textsubscript{3} - C\textsubscript{6}) spinal cord. The interval between stimuli was varied from 1 - 2500 msec. In addition, blood pressure was recorded during stimulation of the pathway at various frequencies (0.5 - 750 Hz). The relationship between blood pressure and sympathetic nerve responses could then be determined.
Figure 2 illustrates the relationship between changes in blood pressure and sympathetic nerve discharges in one animal. The control response in the T2 preganglionic nerve is the computer summed tracing during 50 single pulse stimulations (0.5 Hz, 0.1 msec, 6 V) of the sympathetic pathways. This stimulus elicited a submaximal response. All other preganglionic nerve responses represent the computer summed tracings following the second pulse of 50 twin pulse stimulations. As the interval between stimuli was varied from 1000 to 100 msec (corresponding to 1 - 10 Hz), the evoked response following the second stimulus was attenuated. Maximum attenuation of the evoked response occurred at an interpulse interval of 200 msec (corresponding to 5 Hz). The evoked discharge was 10% of the control discharge. As the interpulse interval was decreased to 20 - 1.5 msec (corresponding to 50 to approximately 650 Hz), the evoked potential was enhanced. Maximum facilitation of the responses occurred with a twin pulse interval of 3.5 msec (corresponding to approximately 300 Hz). The evoked discharge increased to 232% of control. With an interval of 1.5 msec, the evoked response was only 117% of control.

In the same animal changes in blood pressure were also recorded while stimulating the descending sympathetic excitatory pathway. Stimulation parameters were
FIGURE 2

STIMULATION OF DESCENDING SYMPATHO-EXCITATORY PATHWAYS
Blood pressure and sympathetic nerve activity during stimulation of descending spinal sympatho-excitatory pathways. Changes in blood pressure were recorded during stimulation at 0.5 - 300 Hz (1 msec, 6 V). Computer summed tracings were obtained from 50 twin pulse stimulations with the interval between pulses of 1000 - 1.5 msec (0.5 Hz, 0.1 msec, 6 V). The computer sweep was triggered with the second pulse of the twin pulse stimuli, except in recordings from interpulse intervals of 20 msec. Control nerve activity represents 50 responses to single pulse stimulations (0.5 Hz, 0.1 msec, 6 V). Scales to the left of the blood pressure tracings are the calibration for blood pressure (mm Hg). The white line below nerve recordings and the dark line below blood pressure tracings indicate the time scales of 10 msec and 10 sec, respectively. The dark line above the blood pressure tracings indicates the period of stimulation.
0.5 - 300 Hz, 1 msec, and 6 V. As noted in Figure 2, stimulation at 0.5 Hz did not elicit a change in blood pressure. As the frequency of stimulation was varied from 1 - 10 Hz, a depressor response was observed. Maximum decreases in blood pressure resulted from stimulation at 2 Hz, with the mean blood pressure falling 50 mm Hg (to 63% of control). Stimulation at 50 - 300 Hz elicited a pressor response. Maximum increases in blood pressure resulted from stimulation at 200 Hz, with the mean blood pressure increasing 95 mm Hg (to 186% of control). In addition, the time to peak pressure was decreased as the frequency of stimulation was increased. Peak responses were attained 22, 13, 8, and 6 sec following the onset of stimulation at 50, 100, 200, and 300 Hz, respectively.

Heart rate did not change during stimulation of the sympatho-excitatory pathway in this experiment.

The relationship between changes in mean arterial blood pressure and preganglionic nerve activity for 12 cats is summarized in Figure 3. Blood pressure responses were recorded in eight animals and nerve activity was monitored in seven animals. In four of these cats, both responses were recorded. Data represented in this figure indicate the mean ± S.E. of the changes in mean blood pressure or preganglionic nerve activity (ordinate) while varying the frequency or interval between stimuli (abscissa).
FIGURE 3

RELATIONSHIP BETWEEN BLOOD PRESSURE AND SYMPATHETIC NERVE ACTIVITY
Summary of relationship between blood pressure and $T_2$ preganglionic nerve discharges during stimulation of descending spinal sympatho-excitatory pathways. The abscissa indicates the frequency of stimulation or the interval between twin pulse stimuli. The ordinate indicates the change in blood pressure (dotted line) and preganglionic discharges (solid line) expressed as percent of control. Values represent mean $\pm$ S.E. for seven cats (nerve responses) and eight cats (blood pressure responses).
Data were expressed as per cent of control.

As the frequency of stimulation was varied from 1 - 10 Hz, a depressor response could be elicited. The maximum decrease in blood pressure resulted from stimulation at 3 - 4 Hz (range: 1 - 8 Hz). Optimum responses decreased mean blood pressure 5 - 30 mm Hg (to 58 - 87% of control). Stimulation of 1 - 4 Hz consistently resulted in a depressor response; however, stimulation at 5 - 10 Hz elicited either a pressor or depressor response. Stimulation at all frequencies greater than 10 Hz resulted in a pressor response. Maximum increases in blood pressure occurred during stimulation at 200 Hz (range: 75 - 400 Hz). Maximum rises in mean arterial pressure were 80 - 145 mm Hg (to 171 - 276% of control). In five out of eight experiments, the time to reach peak pressure decreased as the frequency of stimulation was increased.

Changes in preganglionic nerve evoked potentials followed a similar pattern. With an interpulse interval of 1000 - 100 msec (corresponding to 1 - 10 Hz), the response following the second stimulus was attenuated. Maximum inhibition of evoked discharges occurred with an interpulse interval of 200 msec (range: 200 - 700 msec, corresponding to 1.5 - 5 Hz). Optimum inhibition decreased evoked discharges to 0 - 65% of control. When the interval between stimuli was less than 50 msec, the
response following the second stimulus was enhanced. Optimum facilitation of the evoked activity occurred at an interpulse interval of 7 - 8 msec (range: 2 - 15 msec, corresponding to 65 - 500 Hz). Evoked responses were increased to a maximum of 128 - 232% of control. Varying the interval between stimuli had no effect on the latency of the evoked discharge or the time to reach peak activity.

Control heart rates varied from 130 - 225 beats per minute in these animals. Heart rate never increased to more than 133% of control at any stimulus frequency. Optimum chronotropic responses increased heart rate 10 - 55 beats/minute (107 - 133%). Low frequency stimulation (<10 Hz) did not elicit a change in heart rate.

As noted in Figure 2 and 3 if the interval between stimuli was between 1000 - 100 msec (corresponding to 1 - 10 Hz), the response following the second stimulus was attenuated. These data suggest that if the second stimulus arrives during the silent period of the previous response, the stimulus is ineffective in eliciting an additional discharge. However, if the interval between stimuli was between 50 - 1 msec (corresponding to 20 - 1000 Hz), the response following the second stimulus was enhanced. These data suggest that if the second stimulus arrives prior to or during the response to the first
stimulus, additional fibers may be activated. The initial stimulus, while causing some preganglionic neurons to discharge, may bring other cells closer to their threshold for firing. Additional stimuli close in time may then cause these cells to discharge (temporal summation). Similar facilitation and inhibition of sympathetic nerve discharges were described by several investigators during twin pulse stimulations to afferent nerve fibers (10, 99) and the hypothalamus (99).

Blood pressure responses followed a similar pattern. During low frequency stimulation (1 - 10 Hz) a depressor response could be elicited. High frequency stimulation (25 - 750 Hz) elicited a pressor response. This reversal from a pressor to a depressor response has been described by many investigators since 1917 following stimulation of afferent nerve fibers (64, 66, 85, 107, 108, 127, 128), hypothalamus (14, 68, 145), medulla (14, 201), and rhinencephalon (87).

The data described here indicate a relationship between changes in blood pressure and sympathetic nerve activity during variations in stimulus parameters to the descending sympatho-excitatory pathway. The depressor response to low frequency stimulation may be explained by impulses occurring during the silent period of the previous response. During this time the preganglionic neuron
may be inexcitable and spontaneous activity would be abolished; therefore, blood pressure would fall. High frequency stimulation may result in a pressor response by increasing the number of preganglionic neurons which are activated through a process of temporal summation. This suggests an electrophysiological mechanism for the reversal from a pressor to a depressor response during descending sympathetic pathway stimulation.

Several explanations for the reversal response following afferent nerve stimulation have been discussed in the Literature Review. Variations in fiber types (64, 80, 85, 107, 108, 151) and central nervous system mechanisms (64, 154) have been suggested to play a role in determining the cardiovascular response to afferent nerve stimulation. Pitts and co-workers (145) suggested that the reversal response recorded during stimulation of the hypothalamus may be due to the activation of two different fiber systems: a sympato-inhibitory pathway which is most easily excited by low frequency stimulation and a sympato-excitatory pathway with a high frequency threshold. However, these must be distinct from the known sympato-inhibitory pathways which respond to high frequency stimulation of the cortex (41, 117, 126), hypothalamus (53, 54, 129, 141), mesencephalon (112), medulla (1, 62, 89, 170, 182), and spinal cord (81, 82). The basis for
their conclusions was the inhibition of spontaneous activity in the inferior cardiac nerve during low frequency stimulation of the hypothalamus.

Berry and co-workers (14) reported a depressor response associated with a decrease in inferior cardiac nerve activity during low frequency (<5 Hz) stimulation of the hypothalamus and medulla. Stimulation at frequencies >5 Hz elicited pressor responses and increased nerve activity. In addition, the effects of twin pulse stimulations of these areas on inferior cardiac nerve activity were described. They noted that the magnitude of the response to the second stimulus varied with the time separation between the stimuli. Immediately following the initial spike the activity in the nerve was inhibited. Beginning at intervals of 70 msec, the magnitude of the second response recovered at a logarithmically decreasing rate. They suggested that the initial spike in some way disrupts the tonic activity, as well as the ability of the nerve to respond to external stimuli. They suggested that this may account for the depressor response during low frequency stimulation. Berry did not report the effects of twin pulse stimulations with short intervals between stimuli.

Koizumi and co-workers (99) described the relationship between blood pressure responses and sympathetic
nerve activity during stimulation of afferent nerve fibers and the hypothalamus. Action potentials in lumbar white rami were reduced or abolished during low frequency (<10 Hz) stimulation of the sciatic nerve. Simultaneous blood pressure recordings showed a fall in blood pressure. The magnitude of the depressor response was related to the degree of inhibition of spontaneous discharges. Similar responses were noted during low frequency stimulation (<5 Hz) of the hypothalamus. Stimulation of afferent nerve fibers or the hypothalamus elicited an increased sympathetic discharge and a pressor response. In addition, the effects of twin pulse stimulations of the sciatic nerve on sympathetic discharges were reported. If the interval between stimuli was <50 msec, the evoked discharge was enhanced. If the interpulse interval was between 100 and 700 msec, no discharge could be evoked. Furthermore, they noted that the silent period was prolonged even when the second pulse came 100 - 700 msec after the first. Similar responses were recorded during hypothalamic stimulation. These authors suggested that this prolongation of the silent period, associated with inhibition of spontaneous and reflex sympathetic discharges, resulted in the depressor response. During high frequency stimulation, the excitatory processes dominated and increased sympathetic discharges resulted in a pressor
The present data support the conclusions of Berry and co-workers (14) and Koizumi and co-workers (99). Though the concept of activation of two fiber systems, as described by Pitts and co-workers, may be the explanation for the reversal response in some regions, the present study suggests that it is not necessary to propose a close anatomical association of sympatho-inhibitory and sympatho-excitatory pathways. If the sympatho-excitatory pathway has a high frequency threshold for activation, one would expect a total absence of evoked discharges following the second pulse of a twin pulse stimulus at intervals of >100 msec. However, as indicated in Figures 2 and 3, evoked discharges are attenuated (and only occasionally abolished) during twin pulse stimulations with interpulse intervals between 100 - 1000 msec.

These data do not rule out the possibility of simultaneous activation of sympatho-excitatory and sympatho-inhibitory pathways. This is particularly interesting in view of the prolongation of the silent period, as described by Koizumi and co-workers (99). Possibly this period of reduced spontaneous and reflex discharges is mediated by activation of a sympatho-inhibitory pathway. Though each of these pathways may respond at any frequency, perhaps the sympatho-inhibitory pathway has an
optimum frequency for activation in the low range, while the sympatho-excitatory pathway has a high frequency optimum. Assuming these separate pathways would have distinct neurotransmitters, perhaps a combination of pharmacological and electrophysiological experiments would provide insight into the mechanism for the reversal response. Pharmacological blockade of the sympatho-excitatory pathway should cause activation of the silent period at all interpulse intervals. Pharmacological blockade of the sympatho-inhibitory pathway should cause evoked discharges of similar magnitude at all interpulse intervals >100 msec.

The experiments described in this study involved measurement of activity in multifiber preparations. Electrophysiological data would be quite different if a single unit preparation had been used. A single pulse stimulus would cause an all-or-none discharge. Subsequent stimuli arriving during the silent period of the first discharge would not elicit a response. Folkow (52) reported the maximum physiological discharge frequency of sympathetic fibers was 8 impulses/sec; however, Pitts and co-workers (145) were able to drive the single units in the inferior cardiac nerves or cervical sympathetic trunk to a maximum of 10 - 50 impulses/sec. High intensity stimuli at frequencies >150 - 200 Hz were
required to elicit these discharges. Each pulse does not elicit a response; there is a 25 or 15 to 1 step down in the discharge rate from the hypothalamus to the peripheral nerve (16, 144). If at least a portion of this step down in discharge rate occurs at the preganglionic neuron, it is unlikely that twin pulses with any interval between stimuli could elicit an additional spike in a single unit. While recording from single unit thoracic preganglionic neurons, Taylor and Gebber (184) elicited only single spike discharges following short trains of high frequency stimuli (600 Hz) to medullary pressor sites in the cat. Consequently, if identical stimulation techniques as used in the present study were repeated in a single unit preparation, either one or no spikes would be expected to follow stimulation of the descending sympatho-excitatory pathway. If the first pulse failed to activate the neuron (e.g., occurring during the refractory period of a spontaneous discharge), the second pulse may activate the cell. Thus, computer summed tracings may show an unexpected response. The relationship between blood pressure responses and sympathetic nerve activity would be difficult to evaluate.

Green and Hoff (65) suggested that the variations in intensity of stimulation may reverse the blood pressure response. Maintaining the frequency of stimulation...
at 60 Hz, low intensity stimulation of the cerebral cortex resulted in a depressor response while higher intensity stimulation produced a pressor response. In the present study, spinal cord stimulation did not elicit similar responses. In three experiments the descending sympatho-excitatory pathway was stimulated at constant frequencies of 100, 50, 5, and 2 Hz with intensities varying from 1 - 15 V. Stimulation at high frequencies and low intensity (1 - 2 V) did not elicit a change in blood pressure. As the intensity of stimulation was increased, the magnitude of the pressor responses increased. Optimum responses occurred with a stimulus intensity of 13 - 15 V. Stimulation at low frequencies and low intensity did not elicit a change in pressure. As intensity was increased, a depressor response was elicited. However, in one experiment, stimulation at 5 Hz with an intensity greater than 11 V converted the depressor response to a small pressor response.

Strom (183) proposed that the response to low frequency stimulation was dependent upon the pre-existing vascular tone. Thus, if the spontaneous vasoconstrictor tone is high, low frequency stimulation may elicit a vasodilatation. If spontaneous vasomotor tone is low, low frequency stimulation is more likely to result in a mild vasoconstriction. Data presented in the present study do
not support this conclusion. In all experiments stimulation at 1 - 4 Hz resulted in a depressor response. While stimulating between 5 - 10 Hz, the response was variable. However, the variability was not related to the control blood pressure level. The range of control mean pressures in this series of experiments was between 90 - 150 mm Hg. Strom's conclusion might be supported at very low or very high levels of control blood pressure.

To verify that the responses described in the present experiments resulted from stimulation of a descending pathway, in three experiments a lesion was made approximately 1 - 1.5 mm in depth on the surface of the dorsolateral funiculus. Stimulation distal to the lesion evoked responses similar to those in an intact preparation.

In summary, these data provide evidence for a relationship between sympathetic nerve discharges and cardiovascular responses during varying stimulations of the descending spinal sympato-excitatory pathways. A possible electrophysiological mechanism for the reversal response in blood pressure is described.

During low frequency stimulation the interval between stimuli is such that impulses are arriving during the silent period of the previous response and therefore do not evoke additional discharges. In addition, the
spontaneous activity is abolished during the silent period. Consequently, the blood pressure decreases. At high frequency stimulation, the initial impulse excites some fibers and brings other fibers closer to their threshold for firing. Additional stimuli at close intervals then excites these fibers. Consequently, the blood pressure rises.

B. Cardiovascular and Electrophysiological Responses to Stimulation of Descending Spinal Sympatho-Inhibitory Pathways

Several investigators have localized descending sympatho-inhibitory pathways in the ventrolateral funiculus. Illert and Seller (82) and Illert and Gabriel (81) described depressor responses associated with decreased renal nerve discharges during activation of this area. Coote and Macleod (35) also reported that 5-hydroxytryptamine-containing fibers from the raphe nuclei travel through the ventrolateral funiculus.

In the present study, the cardiovascular and electrophysiological characteristics to stimulation of descending spinal sympatho-inhibitory pathways were described. Optimum stimulation parameters for eliciting depressor responses were determined.

Decreases in blood pressure were successfully recorded in 37 animals during stimulation of the descending
sympatho-inhibitory pathways on the surface of the ventrolateral funiculus of the cervical spinal cord between the dentate ligament and the ventrolateral sulcus. The most responsive sites were in the region near the ventrolateral sulcus. This was also the site of the maximum depressor response reported by Illert and Gabriel (81). Responses varied from 10 - 50 mm Hg fall in mean arterial pressure. The minimum pressure reached by sympatho-inhibitory stimulation was 55 mm Hg. In nine animals the responses to variations in stimulus frequencies were evaluated. Data from one animal is shown in Figure 4A. Intensity of stimulation was maintained constant at 15 V and 1 msec. Mean blood pressure decreased 10, 7, 19, 29, 31, and 31 mm Hg during stimulation at 1, 10, 25, 40, 50, and 100 Hz, respectively. Stimulation at 200 Hz elicited a rise in mean arterial pressure of 15 mm Hg. Heart rate did not change during stimulation of the sympatho-inhibitory pathway.

Figure 5 summarizes the data from nine cats in which frequency of stimulation (abscissa) was varied while recording changes in mean blood pressure (ordinate). Data represent the mean ± S.E. of change in mean pressure (mm Hg). Maximum decreases in blood pressure were elicited during stimulation of the sympatho-inhibitory pathway at 25 - 100 Hz. Stimulation at frequencies <10 Hz
FIGURE 4
STIMULATION OF DESCENDING SYMPATHO-INHIBITORY PATHWAYS

A

\[ \text{mm Hg} \]

\[
\begin{array}{ccc}
1 \text{Hz} & 10 \text{Hz} & 25 \text{Hz} \\
\hline
\end{array}
\]

B

Control Caudal Rostral
Blood pressure responses to sympatho-inhibitory stimulation. A. Changes in blood pressure were recorded during stimulation at 1 - 100 Hz (1 msec, 15 V). B. Changes in blood pressure were recorded during stimulation (75 Hz, 1 msec, 15 V) rostral and caudal to a lesion in the ventrolateral funiculus. Data is from the same animal as in A. Scales to the left of the tracings are the calibration for blood pressure in millimeters of Hg. The dark lines below the time scale indicate the period of stimulation. Each mark of the time scale is 1 sec.
FIGURE 5

DEPRESSOR RESPONSES AT VARIOUS STIMULUS FREQUENCIES
FIGURE 5

LEGEND

Summary of depressor responses elicited during stimulation of the descending sympatho-inhibitory pathway. Changes in mean blood pressure (ordinate) are plotted against frequency of stimulation (abscissa). Data are expressed as mean ± S.E. for nine cats.
did not consistently elicit a change in blood pressure. Stimulation at frequencies >100 Hz elicited only moderate changes in pressure, often of short duration and followed by a rise in pressure during the period of stimulation. On many occasions the depressor responses elicited by stimulation of the sympatho-inhibitory pathway were followed by a post-stimulatory rise in blood pressure.

In five animals blood pressure was recorded during stimulation of the descending sympatho-inhibitory pathway at constant frequency and duration but varying the intensity of stimuli from 3 - 20 V. Optimum depressor responses were elicited by stimulation at 10 - 15 V.

To verify that these responses represented stimulation of descending fibers, the ventrolateral funiculus was lesioned and stimulations rostral and caudal to the lesion were compared in three animals. Figure 4B demonstrates this response in one animal. Prior to lesioning the pathway, stimulation (75 Hz, 1 msec, 15 V) elicited a 38 mm Hg fall in pressure. Stimulation caudal to the lesion resulted in a 25 mm Hg fall in pressure, while stimulation rostral to the lesion elicited either a rise or no change in pressure. Similar responses were noted in the other two experiments.

In three animals atropine (0.5 - 1 mg/kg, iv) was administered to test for the possible activation of
sympathetic cholinergic vasodilators. This drug did not affect the responses to stimulation of the spinal sympatho-inhibitory pathway.

Heart rate did not change during stimulation of the sympatho-inhibitory pathway in any of the 37 animals in which stimulation resulted in a fall in arterial pressure.

Stimulus frequencies eliciting maximum depressor responses during stimulation of the descending sympatho-inhibitory pathway are similar to those described for stimulation of depressor areas in the septum (41, 126), rhinencephalon (87), hypothalamus (53, 141), mesencephalon (112), and medulla (129). However, Lofving (117) and Kumada (103) have described optimum depressor responses from lower frequency stimulation of the anterior cingulate gyrus and spinal trigeminal complex, respectively. Lofving reported depressor responses while stimulating the cingulate gyrus at 5 - 30 Hz. Higher frequency stimulation often elicited an initial fall, followed by a rise, in pressure. Kumada reported depressor responses while stimulating the trigeminal area at 3 - 20 Hz. Stimulation at higher frequencies elicited a pressor response. In view of the data presented in the previous section, one must be cautious in defining a region as a "depressor area." Sympatho-excitatory pathways appear to be depressor pathways with low frequency
stimulation because of the silent period.

Folkow and co-workers (53, 54) and Lofving (117) found it necessary to induce a high level of vasomotor tone (bilateral carotid occlusion) to elicit effectively depressor responses. Other investigators (101, 169, 180) have reported that the magnitude of depressor responses is directly related to the level of the control blood pressure. Data from the present study do not support these results. Control blood pressure varied between 75 and 195 mm Hg in these 37 experiments. There was no correlation between the fall in pressure and the level of vasomotor tone. In fact, in a number of animals in which control blood pressure was high (175 - 200 mm Hg), depressor responses were not elicited. However, in some animals with low blood pressure (75 - 90 mm Hg), depressor responses of 10 - 20 mm Hg were recorded. Kaada (87) reported that depressor responses to rhinencephalic stimulation were most easily elicited in animals with low blood pressure. The relationship between pre-stimulus blood pressure levels and magnitude of depressor responses will be discussed in more detail in a later section of this Chapter.

The post-stimulatory rise in blood pressure noted in some experiments was also described by Illert and Seller (82) and Illert and Gabriel (81). Since the
carotid baroreceptors were not denervated in the present study, this rise in pressure may be due to a reflex symp-patho-excitatory response by inhibition of baroreceptor afferent fibers. However, Illert and Gabriel (81) used spinal animals. Consequently, the carotid sinus baroreceptors could not affect their recordings. The possible involvement of visceral baroreceptors in spinal prepa-rations (73) has not been tested.

In some animals stimulation of the ventrolateral funiculus did not elicit a depressor response. Either no change or a moderate rise in pressure was noted. The pressor responses were of smaller magnitude and slower onset than those resulting from stimulation of descending excitatory pathways in the dorsolateral funiculus. A possible explanation for the pressor response is a spread of current to sympatho-excitatory pathways. Since ventrolateral funiculus, the spread of current is particularly a problem in animals in which the flow of cerebrospinal fluid was difficult to control.

Illert and Seller (82) and Illert and Gabriel (81) recorded inhibition of sympathetic discharges in the renal and splanchnic nerves during high frequency stimulation of the sympatho-inhibitory pathway in the ventrolateral funiculus. An attempt to describe the electrophysiologi-cal characteristics of this pathway was made in the present
study. Spontaneous activity in the $T_2$ preganglionic nerve was inhibited in eight cats by single pulse or short trains of stimuli to the descending sympatho-inhibitory pathway on the ventrolateral funiculus of the cervical spinal cord. This inhibition was demonstrated by computer summed responses to 25 - 100 stimulations. In six animals inhibition of sympathetic discharges appeared after a latency of 12 - 25 msec. Peak inhibition occurred after a latency of 20 - 49 msec. The duration of sympatho-inhibition was 34 - 77 msec. In two animals sympathetic activity was not inhibited until 49 and 119 msec after the onset of stimulation. In addition, in one of the animals in which an early onset inhibition was noted, two subsequent inhibitions were also recorded following latencies of 98 and 134 msec. In three animals in which single pulse stimulation was not effective in producing an inhibition of sympathetic discharges, short trains of stimuli (10 - 20 msec, 200 - 300 Hz) were capable of eliciting an inhibition of sympathetic activity. Figure 6 illustrates the computer summed tracings from the $T_2$ preganglionic nerve in two animals during single pulse (left) and short trains of high frequency (right) stimulation. Inhibition occurred after a latency of 14 and 11 msec and peak inhibition followed a delay of 49 and 20 msec. The inhibition lasted 77 and 36 msec. The
FIGURE 6

$T_2$ PREGANGLIONIC NERVE RESPONSES TO
SYMPATHO-INHIBITORY STIMULATION

Single Pulses

3-Pulse Trains
Inhibition of spontaneous discharges in the T2 preganglionic nerve in two animals. The recording on the left shows the summed response following 50 single pulse stimulations (0.5 Hz, 1 msec, 9 V) of the descending sympato-inhibitory pathway. The recordings on the right shows the summed response following 50 short trains of high frequency (300 Hz) stimulation (0.5 Hz, 1 msec, 7 V). The horizontal calibration is 10 msec for the left tracing and 20 msec for the right tracing. The vertical calibration is 5 µV for both.
post-inhibitory increase in sympathetic activity noted on the left was also seen in three other preparations.

Several investigators have used the signal-averaging method to demonstrate sympatho-inhibition from stimulation of medullary sites (62, 185, 198). When the responses to a number of stimulation are summed, an interval of decreased spontaneous discharges, time locked to the stimulus, appears as a fall in the tracing below the initial baseline. Gootman and Cohen (62) reported evoked decreases of activity in the splanchnic nerve during stimulation of depressor points in the medial reticular formation. The onset latency and durations were 29 - 33 msec and 20 - 30 msec, respectively. Taylor and Gebber (185) reported two waves of sympatho-inhibition following stimulation of the paramedian nucleus. The onset latencies were 28 ± 3 and 99 ± 8 msec in the splanchnic nerves and 47 ± 3 and 110 ± 4 msec in the renal nerve. The durations of inhibition were 72 ± 11 and 294 ± 22 msec in the splanchnic nerve and 72 ± 7 and 202 ± 9 in the renal nerve. The responses recorded by Gootman and Cohen and the early potentials described by Taylor and Gebber were determined to be due to inhibition within the spinal cord.

The responses with early latencies of 12 - 25 msec and durations of 34 - 77 msec reported in the present
study may result from activation of fibers from depressor sites similar to those described above. Since conduction velocities for the sympatho-inhibitory pathway have not been determined, it is impossible to estimate the expected difference in onset latency between medullary and cervical spinal cord stimulations. In addition, the responses from medullary stimulation were recorded in the splanchnic nerve, while the T2 preganglionic nerve was used in the present study. The duration of inhibition of spontaneous discharges during spinal cord stimulation was similar to that described by Taylor and Gebber for the spinal inhibition. To determine whether the inhibition of spontaneous discharges reported by these investigators results from activation of the pathway in the ventrolateral funiculus, medullary stimulations should be repeated following lesions in the spinal cord.

Taylor and Gebber proposed that the longer latency inhibitory responses resulted from inhibition of brain-stem neurons. The longer latency responses (49 - 134 msec) reported in three animals in this study may have resulted from activation of afferent fibers which cause inhibition in supraspinal vasomotor neurons.

A post-inhibition increase in activity, noted in three out of eight animals in the present study, has also been described by Gootman and Cohen (62) and Weaver and
Gebber (198). Gootman and Cohen proposed the existence of mutually inhibitory pressor and depressor systems, possibly occurring at the spinal level. They suggested this explanation based on the observation that post-stimulus variations in nerve activity occur at the same frequency as spontaneous discharges (usually 10/sec).

In a number of animals in which high frequency stimulation elicited a decrease in arterial blood pressure, neither single pulse or short trains of stimuli were effective in inhibiting the spontaneous discharges in the T2 preganglionic nerve. Several explanations can be suggested. Possibly the majority of spontaneously active units are cardiac or non-vasomotor. There is no change in heart rate during sympatho-inhibitory stimulation; therefore, preganglionic neurons which synapse with neurons innervating cardiac fibers would not decrease their firing rate during stimulation. Non-vasomotor functions which may be affected by the T2 preganglionic fibers (e.g., pupillary constriction and nictitating membrane contraction) were not investigated in this study. Another possible explanation may be in the type of vascular beds which are involved in mediating the fall in pressure. Perhaps the renal and splanchnic vasculatures are primarily dilated, causing a fall in pressure. The depressor responses to septal (42), motor
cortex (79), and sigmoid gyrus (117) stimulation were suggested to be the result of vasodilatation in visceral organs. The majority of studies in which sympatho-inhibition has been described have used renal and splanchnic nerve recordings. Evoked responses in renal or splanchnic nerves should be investigated during stimulation of the descending sympatho-inhibitory pathway on the surface of the ventrolateral funiculus.

The physiological role of this pathway has not been determined. Illert and Seller (82) reported that lesions in the ventrolateral funiculus did not affect the depressor response to carotid sinus distension. However, the major fall in pressure during baroreceptor activation may be mediated by inhibition of medullary vasomotor neurons. The depressor response to baroreceptor activation would then appear to be unaffected by a lesion in the ventrolateral funiculus. The experiments by Illert and Seller do not rule out a possible role of this pathway in mediating a spinal component of baroreceptor-induced sympatho-inhibition.

In summary, high frequency activation of the surface of the ventrolateral funiculus elicits a depressor response of 10 - 50 mm Hg. Stimulation of this sympatho-inhibitory pathway with single pulses or short trains of high frequency in some preparations can inhibit
spontaneous discharges in the $T_2$ preganglionic neuron.

C. Cardiovascular and Electrophysiological Responses to Afferent Nerve Stimulation

Afferent nerve stimulation has been shown to elicit changes in sympathetic nervous system activity (97, 165). The purpose of this series of experiments was to certify these observations and compare the responses to activation of afferent fibers in peripheral nerves, dorsal roots, and the dorsolateral sulcus.

Blood pressure responses were monitored during stimulation of the tibial nerve ($n = 4$), dorsal root ($n = 2$), or dorsolateral sulcus ($n = 3$) at frequencies of 0.1 - 200 Hz. Stimulation at 1 Hz elicited the maximum depressor responses (16 to 27 mm Hg) in all animals. Maximum pressor responses were elicited during stimulation of the tibial nerve, dorsal root, and dorsolateral sulcus at 50 - 100 Hz, 25 - 100 Hz, and 25 - 50 Hz, respectively.

Figure 7 illustrates the change in mean blood pressure (ordinate) during stimulation of afferent nerve fibers at various frequencies (abscissa). Data points represent the mean change in mean blood pressure during stimulation of the tibial nerve ($n = 4$), dorsal root ($n = 2$), and dorsolateral sulcus ($n = 3$). Blood pressure responses followed a similar pattern, regardless of the
FIGURE 7

STIMULATION OF AFFECTENT NERVE FIBERS

![Graph](image-url)

- Tibial Nerve
- Dorsolateral Sulcus
- Dorsal Root

Δ Blood Pressure (mmHg)

Frequency (Hz)
FIGURE 7

LEGEND

Blood pressure responses during stimulation of afferent nerve fibers. Changes in mean blood pressure (ordinate) are plotted against frequency of stimulation (abscissa) of the tibial nerve (n = 4), dorsal roots (n = 2), and dorsolateral sulcus (n = 3). Values represent the mean change in mean blood pressure.
location of the stimulation. Though the quantitative changes are different depending upon the site of afferent nerve stimulation, the qualitative changes are the same. Maximum pressor responses ranged from 25 - 41 mm Hg, 54 - 83 mm Hg, and 35 - 60 mm Hg during activation of the afferent fibers in the tibial nerve, dorsal root, and dorsolateral sulcus.

While maintaining frequency constant at 25 - 100 Hz, maximum increases in mean arterial pressure were elicited in 13 animals when stimulating afferent fibers at 10 - 18 V. In three out of four animals in which stimulus intensity was reduced to <2 V, high frequency stimulation elicited a depressor response. The threshold intensity for eliciting a pressor response varied from 0.1 - 9 V.

The type of afferent fibers (Group I - IV) stimulated in these experiments was not determined. However, since several investigators (64, 85, 98, 107, 108) have proposed that pressor responses require activation of small fibers (small myelinated Group III and unmyelinated Group IV), one can indirectly conclude that these fibers are being activated in this study. In addition, the intensity of stimuli used (0.5 - 1 msec, 9 - 18 V) was within the range described by several investigators for activation of Group IV fibers (85, 98).
In three out of four experiments in which intensity was reduced to <2 V, a depressor response was elicited during high frequency stimulation as well. These data suggest that only large myelinated fibers were activated at this intensity. Similar high frequency depressor responses have been described by Johansson (85) and Coote and Perez-Gonzales (37). La Porte and co-workers (107, 108) were unable to elicit a depressor response during high frequency stimulation of Group I - III fibers. Possibly their stimulation activated some small Group III fibers as well. This may then result in a pressor response. In one animal in the present study, high frequency stimulation at 0.1 V elicited a pressor response, suggesting the activation of small myelinated or unmyelinated fibers. In general, pressor responses were not noted until stimulus intensities of 3 - 9 V and 0.5 - 1 msec.

The depressor responses during low frequency (0.5 - 5 Hz) and high intensity (9 - 18 V) stimulation may result from mechanisms similar to those described in the previous section for the depressor responses during sympatho-excitatory stimulation. Coote and Perez-Gonzales (37) and Koizumi and co-workers (99) also suggested that during low frequency stimulation, the impulses arriving during the silent period of the previous response are
unable to elicit a discharge. Since both spontaneous and reflex activity are attenuated, the blood pressure falls. Group IV afferent fibers do not elicit a silent period (98); therefore, it transmission in myelinated fibers was blocked, low frequency stimulation should elicit a pressor response. Koizumi and co-workers (98) demonstrated this response following anodal block of myelinated afferent fibers.

Thus cardiovascular responses to afferent nerve stimulation is dependent upon both the types of fibers stimulated and the frequency of activation of these fibers. Pressor responses apparently require activation of small diameter myelinated and unmyelinated fibers. Low or high frequency stimulation of these fibers alone produces a pressor response. Depressor responses result from activation of Group II and III afferent fibers at any frequency. In addition, low frequency stimulation of both large and small diameter fibers may elicit a fall in blood pressure because of the silent period.

In addition to the cardiovascular responses to afferent nerve stimulation, computer summed discharges in the T2 preganglionic nerve were recorded during stimulation of the tibial nerve (n = 2), dorsal root (n = 4), and dorsolateral sulcus (n = 10).

Stimulation of the tibial nerve elicited both an
early (latency: 21 - 35 msec) and a late (latency: 69 - 91) reflex. Dorsal root (C7 - C8) stimulation evoked an early (latency: 11 - 15 msec), a late (latency: 49 - 59 msec), and an intermediate (latency: 35 msec) reflex. The intermediate reflex was seen in only one of three animals. Dorsal root (C5) stimulation elicited only a late (latency: 87 msec) reflex (one animal). Dorsolateral sulcus (C6 - C8) stimulation elicited an early (latency: 9 - 16 msec), a late (latency: 44 - 88 msec), and an intermediate (latency: 26 - 61 msec) reflex. The intermediate reflex was seen in 5 out of 10 animals, and the early reflex was seen in 9 out of 10 animals.

Computer summed tracings in Figure 8 depict pre-ganglionic nerve discharges following stimulation of the tibial nerve, C8 dorsal root, and C8 dorsolateral sulcus. Fifty stimulations (0.5 Hz, 0.1 msec, 15 V) of the tibial nerve evoked a small, early reflex after a latency of approximately 35 msec. A larger, late reflex occurred after a latency of 91 msec. Twenty-five stimulations (0.5 Hz, 1 msec, 12 V) of the C8 dorsal root elicited an early (latency: 10 msec) and a late reflex (latency: 47 msec). Three reflex discharges (latencies: 9, 26, and 49 msec) resulted from 25 stimulations (0.5 Hz, 0.5 msec, and 7 V) of the C8 dorsolateral sulcus.

Early (spinal) and late (supraspinal) reflexes in
FIGURE 8
SOMATO-SYMPATHETIC REFLEXES

TN

DLS

DR
FIGURE 8

LEGEND

Reflex discharges in T2 preganglionic nerve following afferent nerve stimulation. Computer summed responses represent 50 single pulse stimulations of the tibial nerve (TN) and 25 stimulations of the dorsal root (DR) and dorsolateral sulcus (DLS). Horizontal calibration indicates 25 msec. Vertical calibration indicates 20 µV for TN and 10 µV for DR and DLS.
sympathetic nerves have been reported by numerous investigators during stimulation of dorsal roots, spinal nerves, or peripheral nerves (97, 165). The early reflex is most easily elicited by stimulation of afferent fibers entering the same or adjacent segmental levels from which sympathetic responses are being recorded. Though the spinal reflex was recorded in both experiments in which the tibial nerve was stimulated, the discharge was smaller than that recorded during stimulation of the dorsal root or dorsolateral sulcus (see Figure 8). The intermediate reflex has been described by Foreman and Wurster (57) during stimulation of the dorsolateral sulcus. Their data suggest that this reflex may be, at least in part, of spinal origin.

Reflex discharges noted in the present study apparently result from activation of Group II and III fibers, since Group IV reflexes have a much longer latency (37, 172). The intensity of stimulation (8 - 15 V) was probably high enough to activate Group IV fibers. However, the sweep times used in these studies (125 - 250 msec) was not long enough to record the later reflex. In addition, Group IV reflexes are most easily elicited by repetitive stimulation (37, 98, 161, 172).

In summary, these data indicate that cardiovascular and electrophysiological responses to afferent nerve
stimulation are similar, regardless of whether peripheral nerves, dorsal roots, or dorsolateral sulcus fibers were activated. Stimulation at 25 - 100 Hz, 9 - 18 V, 0.5 - 1 msec elicited a pressor response. With the same intensity of stimulation, but at frequencies of <10 Hz, a depressor response could be recorded. Stimulation at 1 Hz elicited the maximum depressor response in all animals. Single pulse stimulation of afferent nerve fibers could elicit early, intermediate, and late reflexes.

D. Interaction of Descending Spinal Sympatho-Excitatory and Sympatho-Inhibitory Pathways

The purpose of this series of experiments was to describe the role of the spinal cord in integrating the activity of descending excitatory and inhibitory pathways. Blood pressure and $T_2$ preganglionic nerve activity were recorded during simultaneous stimulation of these pathways.

Blood pressure responses to stimulation of the descending sympatho-excitatory and sympatho-inhibitory pathways were examined in fourteen cats. Figure 9 shows the response in one animal in which the pathways were first stimulated separately. The pathways were then together, with a delay between the onset of the two stimulations. Mean blood pressure increased 60 mm Hg
FIGURE 9

INTERACTION OF EXCITATORY AND INHIBITORY PATHWAYS
Blood pressure responses to stimulation of descending sympathetic pathways. The tracings on the left show the changes in mean and pulsatile arterial pressure during separate stimulation of the sympatho-excitatory and sympatho-inhibitory pathways. The top tracing on the right shows the response to an initial stimulus to the excitatory pathway followed by an inhibitory stimulus; the bottom tracing shows the response to an initial stimulus to the inhibitory pathway followed by an excitatory stimulus. Scales to the left are the calibrations for blood pressure (mm Hg). The dark line below the tracings indicate the period of stimulation.
and decreased 30 mm Hg during stimulation of the sympato-excitative and sympato-inhibitory pathways, respectively. Sympatho-excitative stimulation, followed after 26 sec by sympatho-inhibitory stimulation, resulted in a 60 mm Hg rise in mean pressure followed by a 25 mm Hg fall in pressure. When the stimulus to the inhibitory pathway was terminated, blood pressure again rose to the level attained by excitative stimulation alone. When the order of stimulations were reversed, inhibitory stimulation alone resulted in a 30 mm Hg fall in mean arterial pressure. Activation of the excitative pathway 45 seconds later resulted in an 80 mm Hg rise in mean pressure. Cessation of the excitative stimulation returned the blood pressure to the control level; however, the pressure did not return to the level attained by inhibitory stimulation alone.

Several investigators have reported that the pre-stimulus blood pressure level influences the magnitude of depressor responses to stimulation of supraspinal sympato-inhibitory areas (53, 101, 117, 169, 183). Folkow and co-workers (53, 54) and Lofving (117) induced high sympathetic tone by occluding the carotid arteries to enhance the depressor responses to stimulation of the hypothalamus and anterior cingulate gyrus, respectively. In the present study, the effects of an initial
sympatho-excitatory stimulus on the depressor responses to activation of the descending sympatho-inhibitory pathway were examined in 14 animals. The upper right-hand tracing in Figure 9 shows an example of this response. Figure 10 illustrates these results from 23 stimulations in fourteen animals. The magnitude of the depressor response to sympatho-inhibitory stimulation alone (abscissa) is compared with the magnitude of the depressor response when an excitatory stimulus preceded the inhibitory stimulus (ordinate). Points lying on the diagonal line indicate depressor responses which were not affected by the excitatory stimulation. If the fall in blood pressure was greater due to higher background sympathetic activity, the data points would be above the line. Points below the line depict depressor responses which were attenuated during increased vasomotor tone. As indicated in this figure, depressor responses were increased in magnitude in only two out of 25 cases. Though the inhibitory stimulus was still effective in eliciting a fall in pressure, except in one animal, prior activation of the sympathetic nervous system caused a significant (p < 0.001, paired t-test) attenuation of the depressor response. The magnitude of the depressor response to stimulation of the descending sympatho-inhibitory pathway changed from $21 \pm 1$ to $14 \pm 2$ mm Hg.
FIGURE 10

EFFECTS OF EXCITATORY STIMULATION ON DEPRESSOR RESPONSES
Changes in blood pressure during stimulation of descending sympato-inhibitory pathways. Changes in mean blood pressure during stimulation of the inhibitory pathway alone (abscissa) are plotted against the responses to inhibitory stimulation preceded by activation of the excitatory pathway. Data points indicate the results of 23 stimulations in 14 animals. The diagonal line passes through points of equal responses.
These data suggest that the magnitude of the symp-
patho-inhibitory response is not directly related to the
level of vasomotor activity prior to stimulation. This
was also suggested from the results of stimulation of
the sympato-inhibitory pathway alone, as described in
an earlier section of this Chapter. Further indication
that the magnitude of the depressor response is not di-
rectly related to the pre-stimulus blood pressure level
was obtained in three cats. Identical sympato-inhibi-
tory stimulations were applied at various pre-stimula-
tory blood pressure levels. Figure 11 demonstrates this
response in one animal. This figure shows the relation-
ship between the magnitude of the depressor response to
sympatho-inhibitory stimulation (75 Hz, 1 msec, 11 V)
(ordinate) and the pre-stimulus blood pressure level
(abscissa). The variations in blood pressure resulted
from stimulation of the sympato-excitatory pathway at
various intensities or from spontaneous changes in con-
trol blood pressure. As noted in this figure, maximum
depressor responses (20 to 28 mm Hg) occurred when the
blood pressure was 100 - 125 mm Hg. However, as blood
pressure varied from 75 to 175 mm Hg, the depressor re-
sponses ranged from 5 to 28 mm Hg. In another animal,
although pre-stimulus blood pressure varied from 88 - 205
mm Hg, the depressor responses had a much smaller range
FIGURE 11

EFFECTS OF VASOMOTOR TONE ON DEPRESSOR RESPONSES
FIGURE 11

LEGEND

Blood pressure responses to stimulation of descending sympatho-inhibitory pathways at various levels of vasomotor tone. Changes in mean blood pressure (ordinate) are plotted against pre-stimulus blood pressure levels (abscissa). Variations in vasomotor tone were produced by stimulation of the descending sympatho-excitatory pathways at various intensities and spontaneous changes in blood pressure. Stimulus parameters for sympatho-inhibitory stimulation were 75 Hz, 1 msec, 12 V.
The data in Figure 10 and 11 describe the effects of excitatory stimulation on an inhibitory response. The reverse responses were also investigated in seven animals. That is, the effects of prior activation of the inhibitory pathway on the pressor response to sympatho-excitatory stimulation were determined. The lower right-hand tracing in Figure 9 shows an example of this response. Figure 12 summarizes the data from 24 stimulations in seven cats. The peak level of mean blood pressure attained during activation of the descending sympatho-excitatory pathway alone (abscissa) is compared with the peak level of mean blood pressure attained with identical excitatory stimulation when superimposed on an inhibitory stimulus (ordinate). Points lying on the line indicate pressor responses which were not affected by prior activation of the sympatho-inhibitory pathway. Points lying above or below the line indicate responses which were facilitated or attenuated, respectively, by the inhibitory stimulus. The peak pressure attained by excitatory stimulation was attenuated 14 out of 24 times. However, the peak pressure during simultaneous stimulation (166 ± 7 mm Hg) was not significantly different (p > 0.10, paired t-test) from the peak pressure during excitatory stimulation alone (170 ± 7 mm Hg).
FIGURE 12

EFFECTS OF INHIBITORY STIMULATION ON PRESSOR RESPONSES
Blood pressure responses to stimulation of descending sympathetic pathways. The peak level of mean blood pressure reached during stimulation of the sympatho-excitatory pathway (abscissa) is compared with the peak level of mean blood pressure reached during excitatory stimulations preceded by activation of sympatho-inhibitory pathways (ordinate). Data points represent the result of 24 stimulations in seven cats. The diagonal line passes through the points of equal responses.
In a number of animals it was noted that depressor responses do not persist beyond 40 sec of sympatho-inhibitory stimulation. Since the excitatory stimulation was not applied until 9 - 45 sec after the onset of the inhibitory stimulus, this may account for the lack of significant attenuation of the pressor response. To test this possibility, the following experiments were performed. After determining the cardiovascular effects of excitatory and inhibitory stimulations alone, the response to simultaneous activation of these pathways was tested. Figure 13 illustrates the responses during 14 stimulations in four cats. The abscissa in Figure 13A represent the peak mean blood pressure attained during sympatho-excitatory stimulation alone.

The ordinate represents the peak level of mean blood pressure attained during simultaneous stimulation of the descending sympatho-excitatory and sympatho-inhibitory pathways. Points lying on the diagonal line represent pressor responses which were not affected by the inhibitory stimulus. Points lying above or below the line represent pressor responses which were facilitated or attenuated, respectively, during simultaneous stimulation of the sympatho-excitatory and sympatho-inhibitory pathways. Peak blood pressure responses to excitatory stimulation alone (154 ± 9 mm Hg) were
FIGURE 13

SIMULTANEOUS STIMULATION OF EXCITATORY AND INHIBITORY PATHWAYS

A

Peak BP Excit. and Inhib. (mmHg)

B

Actual ΔBP Excit. and Inhib. (mm Hg)

Summation ΔBP Excit. and Inhib. Alone (mm Hg)
FIGURE 13

LEGEND

Changes in mean blood pressure during simultaneous stimulation of descending excitatory and inhibitory pathways. A. The peak mean blood pressure level reached during excitatory stimulation alone (abscissa) is plotted against responses to simultaneous stimulation of the excitatory and inhibitory pathways (ordinate). B. The sum of the change in mean blood pressure during separate stimulation of the inhibitory and excitatory pathways (abscissa) is plotted against the responses during simultaneous activation of the two pathways (ordinate). Data points represent the results from 14 stimulations in four animals. The diagonal lines pass through the points of equal responses.
significantly (p < 0.01, paired t-test) attenuated during simultaneous activation of the inhibitory pathways (138 ± 13 mm Hg).

Figure 13B illustrates the same data as Figure 13A. However, this figure shows the relationship between the magnitude of the cardiovascular responses during separate and simultaneous stimulation of the two pathways. The abscissa indicates the arithmetic sum of the change in blood pressure obtained during separate stimulations to the sympatho-excitatory and sympatho-inhibitory pathways. That is, the magnitude of the fall in mean pressure noted during inhibitory stimulation alone is added to the magnitude of the rise in mean pressure noted during excitatory stimulation alone. A negative value indicates that the fall in pressure during the inhibitory stimulus was greater than the rise in pressure during the excitatory stimulus. The reverse is indicated by positive values. The ordinate illustrates the actual change in mean arterial pressure noted during simultaneous stimulation of the two pathways. Points lying on the diagonal line indicate responses in which the pressor and depressor responses summated during simultaneous stimulation. Points lying above or below the line indicate responses in which the excitatory or inhibitory pathways, respectively, overcame some of the effects of
activation of the other pathway. The arithmetic sum of the responses to separate stimulation (23 ± 6 mm Hg) was not significantly different (p > 0.10, paired t-test) from the actual change in mean blood pressure during simultaneous stimulation (24 ± 9 mm Hg). This suggests that the responses during simultaneous stimulation were equivalent to the arithmetic sum of the pressor and depressor responses during separate stimulations. Examination of the data in this figure, however, suggests an alternative description of the interaction of these pathways. When the sum of the responses to separate stimulations is less than 20 mm Hg (indicating a depressor response of greater or nearly as great a magnitude as the pressor response), the actual change in pressure can be less than the sum of the separate responses. When the sum of the responses to separate stimulation is greater than 35 mm Hg, the actual change in pressure is greater than the sum of the separate responses. These observations indicate that either pathway can overcome some of the influences from the other pathway. During intense activation of the excitatory pathway, the inhibitory pathway becomes less effective in eliciting a depressor response. This is similar to the earlier results describing the relationships between the magnitude of the depressor response and the level of vasomotor activity. During intense activation of the
inhibitory pathway, the excitatory pathway becomes less effective in eliciting a pressor response.

The data described in Figures 9 - 13 illustrate the potential role of the spinal cord in regulating the cardiovascular system through integration of excitatory and inhibitory input to preganglionic neurons or interneurons. The interaction of these pathways on T2 preganglionic nerve discharges was also tested.

In six cats the time course of inhibition of sympathetic discharges evoked from stimulation of the excitatory pathway was investigated using a condition - test paradigm. A single stimulus to the sympatho-inhibitory pathway (condition) preceded a stimulus to the sympatho-excitatory pathway (test) by 0 - 300 msec. Evoked discharges following 25 - 50 stimulations were summed. The area of conditioned evoked discharges was compared to the area of the unconditioned response. Responses were quite variable in the six cats. Figure 14 shows the time course of inhibition in two cats. In both animals high frequency stimulation of the sympatho-inhibitory pathway elicited a depressor response of 20 - 30 mm Hg. Using the same intensity of stimulation, but single pulses at a frequency of 0.5 Hz, the time course of inhibition of evoked discharges was determined. The results from these two animals were considerably different. One animal
FIGURE 14
INTERACTION OF EXCITATORY AND INHIBITORY PATHWAYS

[Graph depicting the interaction of excitatory and inhibitory pathways over time.]
FIGURE 14

LEGEND

The effects of a conditioning stimulus to the sym-patho-inhibitory pathway on evoked discharges to symp-patho-excitatory stimulation. The abscissa indicates the in-terval between stimuli to the two pathways (inhibitory preceeding excitatory). The ordinate represents the area of the computer summed evoked discharges to a conditioned stimuli expressed as percent of the area of unconditioned responses. The two lines represent data from two animals.
(solid line) showed three phases of inhibition at 10, 70, and 150 msec intervals between inhibitory and excitatory stimuli. Stimulation of the inhibitory pathway alone elicited three phases of inhibition of spontaneous discharges with latencies of 25, 98, and 134 msec. The other animal (dashed line) showed an early inhibition (20 msec) of small magnitude followed by a period of enhanced discharges. Stimulation of the inhibitory pathway alone had no apparent effects on spontaneous discharges.

There were no consistent characteristics to the time course of inhibition in the six cats. There was an early (10 - 25 msec) onset inhibition in four cats and a late (75 - 200 msec) facilitation in four cats. Both responses were seen in only two animals.

T2 preganglionic nerve discharges in response to stimulation of the sympatho-excitatory pathway were also recorded during simultaneous high frequency stimulation of the sympatho-inhibitory pathway in eight animals. Figure 15 shows this response in one animal. The area of the evoked discharge following 25 single pulse stimulations of the sympatho-excitatory pathway (0.5 Hz, 1 msec, 13 V) was decreased to 72% of control during sympatho-inhibitory stimulation (75 Hz, 1 msec, 10 V). This
FIGURE 15
INHIBITION OF EVOKED DISCHARGES IN
\(T_2\) PRE-GANGLIONIC NERVE

Control

Sympatho-Inhibitory Stimulation
FIGURE 15

LEGEND

Effects of sympatho-inhibitory stimulation on discharges in the T2 preganglionic nerve. The descending sympatho-excitatory pathway was stimulated (0.5 Hz, 1 msec, 13 V) before and during stimulation (75 Hz, 1 msec, 10 V) of the sympatho-inhibitory pathway. Evoked discharges represent the computer summed responses to 25 stimulations. Vertical calibration is 10 µV and horizontal calibration is 10 msec.
response was examined during 33 stimulations in eight ani-
mals. Evoked discharges were attenuated to 57 - 97% of
total in 21 cases, enhanced to 103 - 117% of control in
four cases, and remained unchanged in eight cases. These
data suggest that the cardiovascular system can be regu-
lated by integration of excitatory and inhibitory input
in the spinal cord. Thus the concept of a "supreme coor-
dinating center" (8) in the medulla is questionable.

Alexander (2) reported that the medullary depres-
sor area supplies tonic input to the spinal cord. This
conclusion was based on the reappearance of sympathetic
nervous discharges after lesioning the medullary de-
pressor area. The activity had initially been abolished
by a lesion in the pressor area. Coote and co-workers
(33) also demonstrated a tonic inhibitory input to the
spinal cord from supraspinal structures. They noted
that the spinal component of the somato-sympathetic re-
flex was enhanced following spinal cord transection.
These data, together with the localization of descending
sympatho-inhibitory pathways in the spinal cord (see
section B of this Chapter), suggest that some degree of
regulation of the sympathetic nervous system occurs at
the level of the spinal cord.

Though sympatho-excitatory and sympatho-inhibitory
areas have been reported to exist at every level of the
nervous system (see Literature Review), few investigators have described the interaction of these systems. Thompson and Bach (186) studied the cardiovascular effects to stimulation of hypothalamic pressor and medullary depressor areas. Stimulation of the pressor area increased blood pressure; an additional stimulus to the depressor area caused a fall in pressure. Termination of the inhibitory stimulus returned the pressure to the level attained by the excitatory stimulus alone. Similar to the results described in the present study, the magnitude of the depressor response noted during the pressor response to hypothalamic stimulation was never greater than the magnitude of the depressor response to medullary stimulation alone. The pressor response to hypothalamic stimulation was enhanced by a lesion in the medullary depressor area. The level of interaction of these systems was not determined. However, since some hypothalamic-induced pressor responses were still attained after lesions in the medullary reticular formation, the spinal cord may be the site of interaction. Perhaps hypothalamic-spinal excitatory pathways are tonically inhibited by reticulo-spinal inhibitory pathways.

Schramm and co-workers (173) described the circulatory effects of the interaction of a hypothalamic sympathetic vasodilator system and a mesencephalic
vasoconstrictor system. Vasodilatation in the femoral vascular bed, elicited by supramaximal hypothalamic stimulation, was only slightly blocked by mesencephalic stimulation which, by itself, elicited intense vasoconstriction. Vasodilatation resulting from submaximal stimulation of the hypothalamus was attenuated by mesencephalic stimulation. The degree of inhibition of the vasodilatation was directly related to the magnitude of the vasoconstriction. The interaction of the vasodilator pathway with norepinephrine-induced vasoconstriction followed a similar pattern. Therefore, they concluded that the interaction of the hypothalamic and mesencephalic systems must occur at the neuroeffector site, rather than within the central nervous system.

The interaction of central pressor and depressor areas on sympathetic nerve activity has been described by Snyder and Gebber (182). Sympathetic discharges elicited during stimulation of brainstem and spinal cord pressor sites were recorded during simultaneous high frequency stimulation of the medullary depressor area. These investigators described two distinct sympatho-inhibitory systems. One pathway acts at the spinal level, inhibiting transmission in the pressor pathways which mediate long-latency sympathetic discharges. The second pathway acts at a supraspinal level, inhibiting
transmission in the pressor pathway which mediates short-latency sympathetic discharges. These investigators reported a 79 ± 9\% reduction in the spinal evoked discharges. This is much greater than that noted in the present series of experiments. The evoked discharges were reduced to only 57 - 97\% of control, or a reduction of only 3 - 43\%. Synder and Gebber also reported an enhancement of short-latency sympathetic discharges during activation of several sites within the medullary depressor area. They suggested that this may not represent actual facilitation of pathways mediating the short latency response. Instead, these authors proposed that transmission in the short-latency pathway may be affected by the level of spontaneous discharges in the long-latency pathway. During depressor area stimulation, spontaneous discharges in the long-latency pathway are inhibited. This releases an inhibitory mechanism acting on the short-latency pathway, causing an enhancement in sympathetic discharges elicited by this system. The authors suggested that this interaction occurred at the level of the spinal cord.

In the present study, the evoked discharges in the T2 preganglionic nerve were enhanced during high frequency stimulation of the descending inhibitory pathway 4 out of 33 times. The magnitude of the enhancement
(3 - 17%) was much less than that described by Snyder and Gebber (72 ± 13%). While evaluating the time course of interaction of descending spinal sympato-excitatory and sympato-inhibitory pathways, a facilitation of evoked discharges was also noted in four cats with an interval between stimuli of 75 - 200 msec (Figure 14). Possibly the facilitation noted in the present study is due to simultaneous activation of a sympato-excitatory mechanism in the ventrolateral funiculus. Such pathways have been described (28, 86, 196). Because of the longer delay (75 - 200 msec), this may result from stimulation of an afferent system. However, one would then expect a late evoked discharge to be recorded during stimulation of the ventrolateral funiculus. This was not seen in any of these experiments.

In summary, these data indicate that the spinal cord is capable of regulating the cardiovascular system by integrating activity from excitatory and inhibitory pathways. Pressor responses to stimulation of the descending spinal sympato-excitatory pathways are attenuated during simultaneous stimulation of descending spinal sympato-inhibitory pathways. In addition, sympathetic nerve discharges, evoked by stimulation of excitatory pathways, can be attenuated during stimulation of the inhibitory pathway.
In the past few years, several investigators (36, 59, 94, 182, 185) have reported a spinal component in baroreceptor-induced sympatho-inhibition. The purpose of this series of experiments was to determine the influence of baroreceptor activity on spinally mediated sympathetic discharges. Increased and decreased baroreceptor nerve discharges were induced by administration of pressor doses of norepinephrine (1 - 3 µg/kg, iv) and bilateral carotid occlusion, respectively. Evoked responses to stimulation of descending spinal sympatho-excitatory pathways and afferent nerves were evaluated during changes in baroreceptor activity. Both spinal and supraspinal components of the somato-sympathetic reflex were investigated.

The effects of baroreceptor activation on sympathetic discharges elicited by stimulation of descending sympathetic pathways were studied in eight animals. An example of this interaction is shown in Figure 16. Evoked discharges following ten single pulse stimulations (0.5 Hz, 0.5 msec, 6 V) of the sympatho-excitatory pathway at the C6 spinal cord level were compared before, during, and after an injection of norepinephrine (2 µg/kg, iv). Blood pressure increased to 205 mm Hg during the
FIGURE 16
EVOKED DISCHARGES DURING BARORECEPTOR ACTIVATION

Control

During NE

Recovery
Effect of baroreceptor activation on discharges in the T2 preganglionic nerve. The descending sympathoexcitatory pathway was stimulated (0.5 Hz, 0.5 msec, 6 V) before, during, and after pressor response to norepinephrine (2 μg/kg, iv). Each discharge represents the computer summed responses to ten stimulations. NE: Norepinephrine.
administration of the adrenergic agent. The evoked responses were attenuated to 31% of control during the pressor response to norepinephrine.

Responses to submaximal stimulation of the sympatho-excitatory pathway in six animals were attenuated to 19 - 90% of control during baroreceptor activation. Baroreceptor-induced inhibition of the sympathetic discharges was related to the peak pressure attained during the administration of norepinephrine. This relationship is indicated in Figure 17. The abscissa represents the peak pressure recorded during the pressor response to norepinephrine and the ordinate indicates the area of the evoked discharge expressed as per cent of control. The data points represent 13 responses in six animals. The correlation coefficient is $r = 0.81$ and is significant at $p < 0.001$. If maximal stimuli were applied to the descending spinal sympatho-excitatory pathway, baroreceptor activation was less effective in inhibiting the evoked discharges. Baroreceptor interaction with maximal stimuli were examined six times in four animals. Regardless of the change in pressure (205 - 225 mm Hg), maximal evoked discharges in the T$_2$ preganglionic nerve never fell to less than 59% of control (range: 59 - 101%).

The effects of baroreceptor activation on the somato-sympathetic reflex were also evaluated. Figure 18
FIGURE 17
BARORECEPTOR-INDUCED SYMPATHO-INHIBITION

[Graph showing the relationship between percent of control and peak BP during NE (mm Hg)]
Relationship between the peak blood pressure and inhibition of evoked discharges. The abscissa indicates the peak level of mean blood pressure following an injection of norepinephrine. The ordinate indicates the area of the computer summed evoked discharge during baroreceptor activation expressed as percent of the area of control responses. The evoked discharges resulted from stimulation of descending sympato-excitatory pathways. The line represents a correlation coefficient of $r = 0.81$. The various symbols represent responses in individual animals. NE: Norepinephrine.
FIGURE 18

SOMATO-SYMPATHETIC REFLEXES DURING BARORECEPTOR ACTIVATION

Control

During NE

Recovery
FIGURE 18
LEGEND

Effects of baroreceptor activation on reflex discharges in the T2 preganglionic nerve. The C8 dorsolateral sulcus was stimulated (0.4 Hz, 0.1 msec, 7 V) before, during, and after a pressor response to norepinephrine (1.5 µg/kg, iv). Each discharge represents the computer summed responses to 25 stimulations. Vertical calibration is 5 µV and horizontal calibration is 25 msec. NE: Norepinephrine.
shows the preganglionic discharges to 25 single pulse stimulations (0.4 Hz, 0.1 msec, 7 V) of the C8 dorsolateral sulcus before, during, and after an injection of norepinephrine (1.5 µg/kg, iv). Blood pressure rose to 210 mm Hg during the administration of norepinephrine. The early (spinal) reflex was reduced to 78% of control. A separation between the intermediate and late reflexes was not evident during the pressor response to norepinephrine. Therefore, the sum of the areas of the intermediate and late reflexes were compared to the second reflex during the pressor response. This response fell to 16% of control.

The effects of baroreceptor activation on the spinal component of sympathetic discharges to afferent nerve stimulation were studied in seven animals. During the pressor response to norepinephrine, these responses were reduced to 27 - 100% of control. The relationship between the inhibition of sympathetic discharges and the magnitude of the pressor response is illustrated in Figure 19 (dashed line). The abscissa indicates the peak level of mean blood pressure resulting from norepinephrine injection. The ordinate represents the area of the evoked discharge expressed as per cent of control. The data points represent 15 responses in seven animals. The correlation coefficient is \( r = 0.54 \) which is
FIGURE 19
BARORECEPTOR-INDUCED INHIBITION OF
SOMATO-SYMPATHETIC REFLEXES

![Graph showing baroreceptor-induced inhibition of somato-sympathetic reflexes.]
Relationship between peak blood pressure and inhibition of the somato-sympathetic reflex. The abscissa indicates the peak level of mean blood pressure following an injection of norepinephrine. The ordinate indicates the area of the spinal (dashed line) and supraspinal (solid line) reflexes during baroreceptor activation expressed as percent of the area of control responses. The lines represent correlation coefficients of $r = 0.54$ (dashed line) and $r = 0.51$ (solid line). NE: Norepinephrine.
significant at \( p < 0.05 \).

The supraspinal component of the somato-sympathetic reflex was also examined in six cats. Supraspinally mediated responses were attenuated to \( 0 - 53\% \) of control during baroreceptor activation. The relationship between the inhibition of sympathetic discharges and the magnitude of the pressor response is shown in Figure 19 (solid line). Data points represent 13 stimulations in six animals. The correlation coefficient is \( r = 0.51 \) which is not significant. Supraspinal components of the somato-sympathetic reflex are also under the influence of a supraspinal component of baroreceptor-induced inhibition. This may account for the inhibition of reflex activity at lower pressure levels.

The interaction of baroreceptors and sympathetic nerve evoked discharges was also examined during bilateral carotid occlusion in five animals. Figure 20 illustrates this response in one animal. Preganglionic nerve evoked responses following 25 stimulations (0.5 Hz, 0.5 msec, 4 V) of the sympato-excitatory pathway at the C7 spinal cord level were enhanced to 173% of control during bilateral carotid occlusion (BCO). Blood pressure rose to 200 mm Hg during this maneuver. Preganglionic nerve discharges were enhanced to 110 - 173% of control during eight observations.
FIGURE 20
PREGANGLIONIC NERVE DISCHARGES DURING CAROTID OCCLUSION
Effects of bilateral carotid occlusion on T2 pre-ganglionic nerve evoked discharges. Stimulation (0.5 Hz, 0.5 msec, 4 V) of the descending sympa-tho-excitatory pathway was repeated before, during, and after bilateral carotid occlusion (BCO). Each discharge represents the computer summed response to 25 stimulations. Vertical calibration is 5 µV and horizontal calibration is 10 msec.
These data suggest that alterations in baroreceptor afferent nerve activity, induced by pressor doses of norepinephrine or bilateral carotid occlusion, can influence sympathetic activity by a mechanism occurring at the spinal level.

Coote and co-workers (32, 33) were unsuccessful in demonstrating a spinal component to baroreceptor-induced sympatho-inhibition. Distension of the carotid sinus, increasing the intrasinus pressure to 200 mm Hg, had no effect on the spinal reflex recorded in the T10 white ramus. However, the supraspinal reflexes recorded in the renal nerve could be inhibited by identical procedures. The authors concluded that inhibition of sympathetic activity during baroreceptor activation was mediated within supraspinal structures only.

Kirschner and co-workers (94) reported that increased activity in baroreceptor afferent nerves, resulting from administration of a pressor dose of norepinephrine (0.5 - 1 µg/kg, iv), inhibited only the supraspinal component of the somato-sympathetic reflex. Baroreceptor denervation prevented this inhibition. Much greater doses (8 - 15 µg/kg, iv) were required to cause an attenuation in the spinal reflex. Following denervation of the carotid sinus and aortic arch, the inhibitory effect was still noted with this high dose
of norepinephrine. Therefore, these authors suggested that the inhibition may result from a direct inhibitory effect of the drug on preganglionic neurons in the spinal cord. These authors do not clearly show a spinal component to baroreceptor-induced sympatho-inhibition.

Coote and Macleod (36) later re-evaluated the effects of baroreceptor activation on the spinal component of a somato-sympathetic reflex. They stimulated the carotid sinus nerve and noted that the computer summed early reflex in the T₁₀ or T₁₁ white ramus could be reduced by 30 - 75%. The late component was completely inhibited. They suggested that the spinal component of baroreceptor-induced sympatho-inhibition was mediated over a slow conducting pathway from the raphe nuclei or ventrolateral medulla.

Gebber and co-workers (59, 182, 185) have also described a spinal component to inhibition of sympathetic discharges during baroreceptor activation. During the pressor response to norepinephrine, the long latency discharges in the external carotid nerve elicited by stimulation of spinal pressor sites were inhibited. The early discharges were either unaffected or enhanced (59, 182). However, only baroreceptor sensitive discharges were recorded in the splanchnic and renal nerves during stimulation of central vasomotor sites (185).
The authors suggested that this variation in sympathetic discharges may represent differences in the organization of central components of vasoconstrictor pathways distributed to the vascular beds innervated by these sympathetic nerves. The early discharge is mediated by a pathway with a conduction velocity of about 5 m/sec (59). This is similar to the conduction velocity of the pathway stimulated in the present series of experiments (56). These data suggest that the same pathways may be activated. However, in the present study the discharge in the T2 preganglionic nerve were attenuated during baroreceptor activation. A possible explanation for the discrepancy between these results and those of Gebber and co-workers is that the discharges may represent activation of different pathways. This explanation is supported by the stimulus conditions which elicit these responses. While single pulse stimulations are adequate for evoking a discharge in the present study, Gebber and co-workers have reported that trains of stimuli are necessary to elicit the early discharge in sympathetic nerves.

In addition, Taylor and Gebber (185) also reported that stimulation of the aortic depressor nerve or paramedian reticular nucleus caused an early and a late inhibition of spontaneous discharges in the renal and
and splanchnic nerves. The splanchnic nerve discharges evoked from stimulation of descending spinal sympatho-excitatory pathways were depressed during the time course of the early inhibition elicited by activation of the paramedian nucleus. These data suggest that the early phase of inhibition was mediated at the spinal level.

The present study verifies the presence of a baroreceptor-induced sympatho-inhibitory mechanism within the spinal cord. Figures 17 and 19 show that the degree of spinal inhibition is related to the peak level of blood pressure. The greater inhibition noted in the late component of the somato-sympathetic reflex may reflect inhibition of these discharges at a supraspinal level.

Several explanation may be offered for the earlier reports suggesting the lack of a spinal component to baroreceptor-induced sympatho-inhibition (32, 33). These studies monitored only single responses to afferent nerve stimulation. Computer summation of sympathetic responses, as used in the present study and in the earlier studies in which spinal inhibition was reported (36, 59, 182, 185), may reveal this inhibition. Since evoked discharges were only partially inhibited, single sweeps may not provide an accurate index of sympatho-inhibition. By comparing summed discharges before and during baroreceptor activation, one is more likely to observe this inhibition.
Another possible explanation for the apparent lack of spinal inhibition may be the intensity of stimuli used to evoked a discharge. As reported in this study, maximal evoked discharges were less frequently inhibited. Even at high pressures (205 - 225 mm Hg), the response to a supramaximal stimulus to the descending sympatho-excitatory pathway was inhibited to an average of 85% of control (range: 59 - 101%). During identical pressor responses, evoked discharges to submaximal stimuli are attenuated to an average of 44% of control (range: 19 - 67%). Even at lower blood pressure levels (115 - 195 mm Hg), the responses to submaximal stimuli are attenuated to an average of 74% of control (range: 48 - 90).

In addition to the effects of baroreceptor activation, the present study also evaluated the effects of inhibition of baroreceptor activity upon evoked discharges from spinal cord stimulation. The baroreceptors were inhibited by occluding both common carotid arteries. This results in a reflex increase in spontaneous nerve discharges. Evoked discharges were enhanced during carotid occlusion. These data suggest that baroreceptor inhibition facilitates the response to stimulation of descending spinal sympatho-excitatory pathways. This may result from a mechanism similar to that described for the facilitation noted during twin pulse stimulations.
of the descending pathway. Possibly the reflex induced sympatho-excitation during carotid occlusion brings some neurons closer to their firing threshold. Stimulation of the descending pathway then excites these cells, resulting in an enhanced discharge. The efferent limb of the carotid occlusion reflex is mediated by the sympatho-excitatory pathway located on the surface of the dorsolateral funiculus (56). Thus the same descending fibers are being activated during carotid occlusion and electrical stimulation.

In summary, these data indicate that spinal preganglionic neurons are under the influence of baroreceptor activity. This is indicated by inhibition of the spinal component of the somato-sympathetic reflex and evoked discharges from the descending spinal sympatho-excitatory pathway during the pressor response to norepinephrine. Additional evidence was the facilitation of evoked discharges noted during bilateral carotid occlusion.

F. Interaction of Descending Sympatho-Excitatory Pathways and Afferent Nerves

Though many investigators have discussed the important role of medullary pressor areas in mediating reflex sympathetic discharges and circulatory responses to afferent nerve stimulation [reviewed by Koizumi and Brooks...
(97) and Sato and Schmidt (165), few reports have described the interaction of central pressor sites and afferent nerves (16, 145).

The purpose of this series of experiments was to describe the regulation of sympathetic outflow through the interaction of impulses from afferent nerve fibers and descending sympatho-excitatory pathways. Since the descending pathway activates neurons within the spinal cord, the interaction of these systems is occurring at the spinal level. Blood pressure and T2 preganglionic nerve discharges were recorded during stimulation of afferent nerve fibers and descending sympatho-excitatory pathways on the surface of the dorsolateral funiculus of the cervical (C5 - C8) spinal cord. Tibial nerve fibers, dorsal roots, or the C7 - C8 dorsolateral sulcus area were stimulated for activation of afferent nerve fibers.

The cardiovascular interaction of these two systems was evaluated by first determining the effects of separate stimulation and then activating these systems together with a delay between the stimuli. Figure 21A summarizes the responses from six animals. The abscissa represents the sum of the changes in mean blood pressure during separate stimulation of afferent nerve fibers (tibial nerve, n = 4; dorsolateral sulcus, n = 2) and the descending sympatho-excitatory pathway. That is,
FIGURE 21
INTERACTION OF EXCITATORY PATHWAYS
AND AFFERENT NERVES

A

*Aff. During Excit.
* Excit. During Aff.

B

ΔBP Simultaneous

ΔBP Aff. + Excit. (mm Hg)

Summation ΔBP Aff. + Excit. (mm Hg)
Blood pressure responses to stimulation of descending sympatho-excitatory pathways and afferent nerves. A. The sum of the changes in mean blood pressure during separate stimulations of these two systems (abscissa) is plotted against the total change in mean blood pressure when the two systems are activated together with a delay between the onset of the two stimuli. Data are from six animals. Stars represent 13 responses in which afferent stimulation began after the onset of the excitatory pathway stimulus. Dots represent 18 responses in which excitatory pathway stimulation began after the onset of the afferent stimulus. B. The sum of the changes in mean pressure during separate stimulations of these two systems (abscissa) is plotted against the change in mean pressure during simultaneous stimulation. Data are from four animals. Diagonal lines pass through the points of equal responses.
the magnitude of the pressor response to afferent nerve stimulation was added to the magnitude of the pressor response to sympatho-excitatory stimulation. The ordinate indicates the total change in mean blood pressure when one stimulus was superimposed on the other. Stars represent 13 responses in which the afferent fibers were activated 16 - 35 sec after onset of sympatho-excitatory stimulation. Dots represent 18 responses in which the sympatho-excitatory pathway was activated 17 - 40 sec after onset of afferent nerve stimulation. Points falling on the diagonal line represent responses in which the total change in blood pressure when both systems were activated was equal to the arithmetic sum of responses to separate stimulations. Points lying above or below the line represent responses in which the total change in mean blood pressure was greater or lesser, respectively, than the arithmetic sum of the separate responses. The total change in mean blood pressure resulting from activation of both systems (60 ± 4 mm Hg) was significantly (p < 0.001, paired t-test) less than the arithmetic sum of the responses during separate stimulations (70 ± 5 mm Hg).

These data suggest that activation of one of these systems has an inhibitory effect on the other system. An alternative explanation may be that the first stimulus
became less effective as it continued. To test this possibility, the excitatory pathway and afferent nerve fibers were stimulated simultaneously in four animals. Figure 21B summarizes this data. The abscissa represents the arithmetic sum of the changes in mean blood pressure during separate stimulations. The ordinate indicates the actual change in mean blood pressure during simultaneous stimulation. The responses during simultaneous stimulation \((33 \pm 9 \text{ mm Hg})\) were not significantly different \((p > 0.10, \text{ paired t-test})\) from the arithmetic sum of the responses to separate stimulation \((33 \pm 11 \text{ mm Hg})\).

To further test for the possibility of a facilitatory influence of one of these systems on the other, the effects of a subthreshold or just threshold stimulus to the descending sympatho-excitatory pathway on the blood pressure responses to afferent nerve stimulation at various intensities was also investigated in five animals. Stimulation of the sympatho-excitatory pathway did not affect the threshold of the pressor response to afferent nerve stimulation. The magnitude of the pressor response to afferent nerve stimulation was only slightly enhanced.

These data suggest that cardiovascular regulation can occur at the spinal level through integration of afferent and descending excitatory impulses. The electrophysiological characteristics of this interaction were
also investigated. Descending sympato-excitatory pathways and afferent nerve fibers were stimulated while recording sympathetic nerve discharges in six animals. Evoked discharges in the T₂ preganglionic nerve were recorded during 25 single pulse stimulations of the dorsal root (n = 2) or dorsolateral sulcus (n = 4). The time course of facilitation of afferent nerve evoked sympathetic discharges was investigated using the condition - test paradigm. A subthreshold stimulus (condition) to the descending sympato-excitatory pathway in the cervical (C₆ - C₇) spinal cord preceded a submaximal stimulus (test) to afferent nerve fibers by 0 - 1000 msec. The computer summed tracings showed no discharges during activation of the descending pathway, however occasionally a stimulus did elicit a response. Figure 22 shows the time course of facilitation and inhibition of the spinal component (solid line) of the somato-sympathetic reflex in six animals. The abscissa shows the interval between stimuli and the ordinate represents the area of responses following the conditioned stimulus, expressed as per cent of the unconditioned responses. Data are expressed as mean ± S.E. The peak facilitatory effect occurred with a 1 msec interval between stimuli (range: 0.5 - 10 msec). The facilitatory effects lasted 10 - 20 msec. This phase was followed by a period of inhibition of the evoked discharges
FIGURE 22
FACILITATION OF SOMATO-SYMPATHETIC REFLEXES

Facilitation of Somato-Sympathetic Reflexes

Spinal
Supraspinal

Interval Between Stimuli (msec)
The time course of interaction of impulses from descending sympato-excitatory pathways and afferent nerves. The abscissa indicates the interval between stimuli to the descending pathway (condition) and the afferent nerve (test). The condition stimulus was sub-threshold for eliciting a discharge in the T2 preganglionic nerve. The change in the area of the conditioned spinal (solid line) and supraspinal (dashed line) responses is expressed as percent of the unconditioned responses (ordinate). Values represent mean ± S.E. for 6 cats (spinal) and 5 cats (supraspinal).
which lasted approximately 75 msec. The peak inhibitory effect occurred with a 30 - 35 msec interval between stimuli (range: 25 - 75 msec). The evoked discharges were facilitated to a maximum of 118 - 197% of control (average maximum facilitation: 156%). The maximum inhibition decreased the evoked discharges to 47 - 93% of control (average maximum inhibition: 70%).

The effects of subthreshold stimuli (condition) to the sympatho-excitative pathway on the supraspinal component of the somato-sympathetic reflex was also evaluated in five cats. The area of the conditioned response was compared to the area of the unconditioned discharge. As indicated in Figure 22 (dashed line) a prior stimulus to the sympatho-excitative pathway did not facilitate the supraspinally mediated reflex discharge in the T2 preganglionic nerve. During the time in which the early discharge was facilitated, the late reflex was attenuated.

The excitatory inputs to spinal cord neurons from descending pathway stimulation and from the late component of afferent nerve stimulation occur at different times. Stimulation of the C6 - C7 descending sympathetic pathway elicits a discharge in the T2 preganglionic nerve after a delay of 9 - 25 msec. Activation of afferent fibers elicits a late reflex after a delay of 48 - 91 msec. In order to facilitate the supraspinal reflex
discharge, the stimulus to the descending sympa­toly pathway must occur close in time to the onset of the late reflex. Therefore, in one animal the order of stimu­lations were reversed. A subthreshold stimulus (condi­tion) to the sympa­excitatory pathway was applied after the onset of stimulation to the tibial nerve, but before and during the activation of the late reflex. 

Figure 23 depicts this response. The abscissa indicates the interval between stimuli to the afferent nerves and descending sympathetic pathway, while the ordinate repre­sents the area of the conditioned evoked discharge ex­pressed as per cent of the unconditioned reflex. If the afferent nerve was stimulated 100 - 150 msec prior to stimulation of the descending pathway, the late reflex was enhanced. Maximum facilitation occurred with an in­terval of 100 msec, with the area of the evoked discharge increasing to 167% of control.

The data described in this study indicate that the spinal cord is capable of regulating sympathetic dis­charges through integration of impulses within afferent nerve fibers and descending sympa­excitatory pathways.

Blood pressure responses to simultaneous stimula­tion of afferent nerve fibers and a sympa­excitatory area in the hypothalamus have been described by Pitts and co-workers (16, 145). If stimulus intensities were
FIGURE 23

FACILITATION OF LATE REFLEX
The time course of interaction of impulses from descending sympatho-excitatory pathways and afferent nerves. The abscissa indicates the interval between stimuli to the descending pathway (condition) and the afferent nerve (test). The afferent nerve stimulus preceded the pathway stimulus. The condition stimulus was subthreshold for eliciting a discharge in the T2 preganglionic nerve. The change in the area of the conditioned reflex is expressed as percent of the unconditioned response (ordinate).
adjusted to produce comparable responses from hypothalamic and afferent nerve stimulation, simultaneous activation elicited a rise in blood pressure equivalent to the arithmetic sum of the separate responses.

Similar summation of blood pressure and sympathetic nerve responses have been reported during activation of two pressor areas in the hypothalamus (136, 144, 145). Ninomiya and co-workers (136) suggested that the summation may result from a combination of activation of a greater number of preganglionic neurons and convergence of impulses onto identical neurons. In the present study, the blood pressure response to simultaneous stimulation of afferent nerves and descending sympatho-excitatory pathways is not necessarily the arithmetic sum of the separate responses. As indicated in Figure 21B, the responses can be greater than or less than the sum of the separate responses.

In the present study, subthreshold or just threshold stimuli to the excitatory pathway only slightly enhanced the blood pressure responses to afferent nerve stimulation. More pronounced facilitation of cardiovascular responses has been reported during stimulation of vasoconstrictor systems in the mesencephalic central gray and hypothalamus (173). Stimulation of each of these areas produced renal vasoconstriction. If the central
gray is stimulated at an intensity which produces only minimal vasoconstriction, the response to hypothalamic vasoconstriction was enhanced. The central site of interaction of the mesencephalic and hypothalamic systems was not determined.

In the present study, the spinal component of the somato-sympathetic reflex was facilitated by subthreshold stimuli to the excitatory pathway (Figure 22). Similar facilitation of the spinal reflex has been described by Beacham and Perl (10) following a conditioning volley in afferent fibers from an adjacent level. The facilitation period described by these authors lasted 20 msec. The period of facilitation (10 - 20 msec) noted in the present experiments is similar to the duration (19 - 20 msec) of an evoked discharge following threshold stimulation of the sympatho-excitatory pathway. Apparently, a subthreshold stimulus (condition) to the excitatory pathway brings some cells closer to their firing threshold. This may increase the excitability of a population of preganglionic neurons. A threshold stimulus (test) to an afferent nerve may now discharge a greater number of neurons. Thus the evoked response is enhanced. This is similar to the mechanism described for the facilitation of evoked discharges following twin pulse stimulations to the sympatho-excitatory pathway (section A of
this Chapter). However, in the previous study the facilitation was noted with twin pulse stimulations, with interpulse intervals of <50 msec. This longer period of facilitation may result from a greater number of cells being depolarized by a conditioning stimulus of threshold intensity, as used in that study.

As indicated in Figure 22, the phase of facilitation is followed by a phase of inhibition of the spinal reflex. This period of inhibition suggests that stimulation of the descending sympatho-excitatory pathway may have elicited a silent period. Since the stimulus was subthreshold for evoking an increased discharge in sympathetic activity, this would indicate that the silent period is not necessarily a post-excitatory depression. In addition, this would suggest that the threshold for activation of fibers mediating inhibition may be lower than that for excitation. Kirschner and co-workers (95) have reported that inhibition following stimulation of the spinal cord in the area of the dorsolateral sulcus has a lower threshold than excitation in spinal animals. Alternatively, inadvertent subthreshold stimulation of fibers mediating the inhibitory response may lower the excitability of some cells. Consequently, stimulation of the afferent nerve fibers would not activate as many preganglionic neurons and the evoked response would be
attenuated.

In addition to the inhibition of early discharges, subthreshold stimulation of the sympa-tho-excitatory pathway also caused an inhibition of the late reflex (Figure 22). This may result from several mechanisms. First, descending pathway stimulation may elicit a silent period as just described. While the spinal reflex is under the facilitatory phase of sympa-tho-excitatory stimulation, the supraspinal reflex may be under the influence of the inhibitory phase. If this was the explanation, one would expect the duration of the inhibitory phases for both reflexes to be about the same. The precise durations are difficult to determine; however, examination of Figure 22 indicates that the early discharge was inhibited for approximately 80 msec (between interpulse intervals of 20 - 100 msec), while the late reflex is inhibited for 50 msec (between interpulse intervals of 0.1 - 50 msec). In general, the early discharge had a longer phase of inhibition than the late discharge.

The inhibition of the supraspinal reflexes may also result from generation of a silent period following the early reflex. In spinal animals, Beacham and Perl (10) reported that the spinal reflex is followed by a silent period of 20 - 25 msec. Sato [as cited by Koizumi and Brooks (97)] has reported that the duration
of the silent period from the spinal reflex is greatest when recorded from the white ramus of the same segmental level as the afferent input. No relationship between the magnitude of the evoked discharge and the magnitude of the silent period have been described. If the magnitude of the silent period is proportional to the magnitude of the evoked response, one would expect a relationship between the facilitation of the early reflex and the inhibition of the late reflex. It is interesting to note that in four out of five animals, the peak facilitation of the spinal reflex and the peak inhibition of the supraspinal reflex occur at the same interval between stimuli. However, no direct relationship can be established between the degree of facilitation and inhibition.

A third possibility for this apparent inhibition may be "collision" of antidromic and orthodromic impulses. The efferent limb of the supraspinal reflex is mediated through the descending pathway on the surface of the dorsolateral funiculus (57). Antidromic impulses occurring during electrical stimulation of this pathway may collide with orthodromic impulses occurring during stimulation of afferent nerve fibers. This would cause a decrease in the number of impulses activating preganglionic neurons or interneurons.

One of these mechanisms described for the inhibition
of the late reflex may also account for the general inability to elicit cardiovascular responses which summate during simultaneous activation of the two systems (Figure 21). Supraspinally mediated reflexes are considered to be essential for eliciting cardiovascular responses in an intact animal (2, 110, 167). The attenuation of late discharges noted in this study (Figure 22) during sympatho-excitatory stimulation may affect blood pressure responses during simultaneous stimulation of these two systems. However, one must be cautious in making a comparison between the interaction of these two systems on evoked discharges and their interaction on the cardiovascular system. The reflex components evaluated in this study presumably result from activation of Group I - III fibers, since Group IV fibers elicit a later reflex (see section C of this Chapter). However, pressor responses are mediated by activation of Group IV fibers. One cannot presume from this study that the efferent limb of the reflex which mediates the pressor response is also attenuated during simultaneous activation of the excitatory pathway.

The facilitation of the spinal reflex (Figure 22) with subthreshold stimulation of the sympatho-excitatory pathway is evidence for regulation of sympathetic discharges at the spinal level. Perhaps a more feasible
method to study the interaction of these systems on blood pressure regulation would be in a chronic spinal animal. Afferent nerve stimulation in a chronic spinal animal elicits a marked rise in blood pressure (17, 177). Blood pressure responses during simultaneous stimulation of afferent fibers and the descending excitatory pathway may more clearly reveal the capabilities of the spinal cord in integrating impulses in afferent nerves and descending sympathetic pathways.

In summary, these data indicate that the spinal cord may regulate the sympathetic nervous system through integration of impulses from afferent nerve fibers and descending sympato-excitatory pathways. Submaximal stimulation of the descending pathway slightly facilitates the blood pressure response to afferent nerve stimulation. The spinal and supraspinal component of the somato sympathetic reflex can be facilitated, as well as inhibited, by submaximal stimulation of the descending pathway.

G. Interaction of Descending Sympatho-Inhibitory Pathways and Afferent Nerves

Recently, several investigators (32, 33, 35, 36, 94, 95) have suggested that the somato-sympathetic reflexes may be modified by activity within bulbar depressor areas. The purpose of the present study was to
describe the role of the spinal cord in cardiovascular regulation through integration of activity within afferent nerve fibers and descending sympatho-inhibitory pathways. Blood pressure and T₂ preganglionic nerve discharges were recorded during stimulation of the descending sympatho-inhibitory pathway on the surface of the ventrolateral funiculus and afferent nerve fibers (C₅ - C₈ dorsal roots or C₅ - C₈ dorsolateral sulcus area).

The cardiovascular interaction of these two systems was evaluated by first determining the effects of separate stimulation and then activation of both systems with a delay between the onset of the two stimuli. The effects of a prior stimulus to afferent nerve fibers on the depressor response to sympatho-inhibitory stimulation was evaluated in five animals. The afferent nerve stimulus caused a pressor response of 21 - 58 mm Hg. Figure 24 summarizes the results from ten stimulations in five animals. The abscissa indicates the magnitude of the depressor response to sympatho-inhibitory stimulation alone. The ordinate indicates the magnitude of the depressor response to identical sympatho-inhibitory stimulation when preceded by afferent nerve stimulation. Points lying on the diagonal line indicate depressor responses which were unaffected by the pressor response to afferent nerve stimulation. If the fall in pressure was greater due to higher
FIGURE 24
EFFECTS OF AFFERENT STIMULATION ON DEPRESSOR RESPONSES
Changes in blood pressure during stimulation of descending sympatho-inhibitory pathways. Changes in mean blood pressure during stimulation of the inhibitory pathway alone (abscissa) are plotted against the responses to inhibitory stimulation preceded by activation of the afferent nerve fibers (ordinate). Data points indicate the results of ten stimulations in five cats. The diagonal line passes through points of equal responses.
background sympathetic activity, the data points would be above the line. Points below the line depict depressor responses which were attenuated during increased vaso-motor tone. As indicated in this figure, depressor responses preceded by afferent nerve stimulation could be greater or less than the responses during inhibitory stimulation alone. The depressor responses to sympathetic inhibition alone (25 ± 3 mm Hg) were not significantly different (p > 0.10, paired t-test) from the response to identical inhibitory stimulation during the pressor response to afferent nerve stimulation (24 ± 5 mm Hg). This finding indicates that the depressor response was not related to the level of excitation. This was also noted during stimulation of the inhibitory pathway and descending excitatory pathway (section D of this Chapter). However, in the earlier study, the depressor responses were attenuated during the excitatory stimulus.

These data describe the effects of an afferent excitatory stimulus on the responses to an efferent inhibitory stimulus. The reverse responses were also examined in five cats. Figure 25 describes the effects of an initial stimulus to the descending inhibitory pathway on the pressor responses to afferent nerve stimulation. The abscissa indicates the peak level of mean blood pressure attained during stimulation of afferent
FIGURE 25
EFFECTS OF INHIBITORY STIMULATION ON PRESSOR RESPONSES

![Graph showing the effects of inhibitory stimulation on pressor responses. The x-axis represents peak BP Aff. Alone (mmHg), and the y-axis represents peak BP Aff. During Inhib. mmHg. The data points are plotted on a linear scale, showing a positive correlation.]
Blood pressure responses to stimulation of afferent nerve fibers. The peak level of mean blood pressure reached during stimulation of afferent nerve fibers alone (abscissa) is compared with the peak level of mean blood pressure reached during identical stimulations preceded by activation of sympato-inhibitory pathways (ordinate). Data points represent the result of eight stimulations in five animals. The diagonal line passes through the points of equal responses.
nerve fibers alone. The ordinate represents the peak level of mean pressure attained during identical afferent nerve stimulation when preceded by an inhibitory stimulus which decreased blood pressure 10 – 25 mm Hg. Points lying on the diagonal line represent responses which were unaffected by the inhibitory stimulus. Points lying above or below the line represent responses which were facilitated or attenuated, respectively, by prior stimulation of the inhibitory pathway. The peak pressure attained during afferent stimulation preceded by an inhibitory stimulus was attenuated five out of eight times. However, the peak pressure during simultaneous stimulation (167 ± 7 mm Hg) was not significantly different (p > 0.10, paired t-test) from the response during afferent nerve stimulation alone (173 ± 6 mm Hg).

On several occasions it was noted that the inhibitory stimulus was no longer effective after 40 sec of stimulation. Since the afferent nerve stimulus was not applied until 15 – 26 sec after onset of the inhibitory stimulus, this may account for the inability to inhibit the pressor response. Therefore, the blood pressure responses to simultaneous stimulation of these systems were evaluated in four animals. After determining the effects of stimulation of each of these systems alone, the blood pressure responses to simultaneous stimulation was
investigated. Figure 26A illustrates the results of eight stimulations in four animals. This figure compares the peak level of mean pressure during afferent stimulation alone (abscissa) to the peak pressure during simultaneous stimulation of afferent nerves and descending sympato-inhibitory pathway (ordinate). Points lying on the diagonal line indicate responses which were unaffected by the inhibitory stimulus. Points above or below the line depict responses which were facilitated or inhibited, respectively, by the depressor stimulus. The peak pressure during simultaneous stimulation (153 ± 8 mm Hg) was significantly less (p < 0.05, paired t-test) than the response to afferent stimulation alone (165 ± 8 mm Hg). These data suggest that the inhibitory pathway interacted with afferent nerve fibers in regulation of the cardiovascular system.

Figure 26B illustrates the same data as in Figure 26A. However, this figure shows the relationship between the magnitude of cardiovascular responses during separate and simultaneous stimulation of the afferent fibers and descending inhibitory pathway. The abscissa depicts the arithmetic sum of the responses to separate stimulation. That is, the magnitude of the depressor response to inhibitory stimulation alone was added to the magnitude of the pressor response to afferent nerve stimulation.
FIGURE 26
SIMULTANEOUS STIMULATION OF INHIBITORY PATHWAYS
AND AFFERENT NERVES

A

Peak BP Aff. + Inhib. (mm Hg)

B

Actual ΔBP Inhib. + Aff. (mm Hg)

Summation ΔBP Inhib. + Aff. Alone (mm Hg)
FIGURE 26

LEGEND

Changes in mean blood pressure during simultaneous stimulation of descending inhibitory pathways and afferent nerves. A. The peak mean blood pressure level reached during afferent nerve stimulation alone (abscissa) is plotted against responses to simultaneous stimulation of afferent nerves and inhibitory pathways (ordinate). B. The sum of the change in mean blood pressure during separate stimulation of the inhibitory pathway and afferent nerves (abscissa) is plotted against the responses during simultaneous activation of the two systems (ordinate). Data points represent the results from eight stimulations in four cats. The diagonal lines pass through the points of equal responses.
The ordinate represents the change in mean pressure during simultaneous stimulation of the inhibitory pathway and afferent nerves. Points lying on the diagonal line represent responses in which the actual change in pressure during simultaneous stimulation is equal to the arithmetic sum of the responses to separate stimulation. Points lying above or below the line indicate responses in which the afferent nerves or inhibitory pathway, respectively, overcame some of the effects of activation of the other system. The arithmetic sum of the responses to separate stimulation ($18 \pm 6 \text{ mm Hg}$) were not significantly different ($p > 0.05$, paired t-test) from the responses to simultaneous stimulation ($21 \pm 6 \text{ mm Hg}$).

The effects of an inhibitory stimulus on the pressor response to afferent nerve stimulation at various intensities were evaluated in three animals. A subthreshold or threshold stimulus was applied to the sympatho-inhibitory pathway. This stimulus had variable effects on the magnitude of the pressor responses to afferent nerve stimulation. The change in pressure was slightly increased, slightly decreased or unaffected by the inhibitory stimulus. In general, unless the inhibitory stimulus caused a $10 \text{ mm Hg}$ drop in pressure, the pressor response to afferent nerve stimulation was not attenuated. The threshold intensity of stimulation was also
unaffected unless the blood pressure was first decreased by 10 mm Hg.

The data described in Figures 24 - 26 indicate that the spinal cord is capable of regulating the cardiovascular system through integration of impulses from afferent nerve fibers and descending sympatho-inhibitory pathways. Preganglionic nerve responses were also investigated to describe the role of the spinal cord in regulation of the sympathetic nervous system. Discharges elicited during single pulse stimulation of afferent nerves (dorsal roots or dorsolateral sulcus) were evaluated during high frequency stimulation of the descending sympa­
patho-inhibitory pathway in five animals. The influence of the inhibitory stimulation on the early and late discharges was remarkably different. Figure 27 demonstrates this response in one animal. Discharges in the T₂ pre-
ganglionic nerve were elicited by 25 single pulse stimu-
lations (0.5 Hz, 1 msec, 8 V) to the C₈ dorsolateral sul-
cus. The early discharge was attenuated to 53% of control during simultaneous stimulation (75 Hz, 1 msec, 10 V) of the sympatho-inhibitory pathway. The late discharge was facilitated to 124% of control. Blood pressure decreased 15 mm Hg during the inhibitory stimulus. Similar responses were noted in the other animals. The early reflex was consistently attenuated during sympatho-inhibitory
FIGURE 27

EFFECTS OF INHIBITORY STIMULATION ON
REFLEX DISCHARGES.
FIGURE 27

LEGEND

Effects of sympa-tho-inhibitory stimulation on reflex discharges in the T2 preganglionic nerve. The C8 dorsolateral sulcus was stimulated (0.5 Hz, 1 msec, 8 V) before, during, and after stimulation of the sympa-tho-inhibitory pathway (75 Hz, 1 msec, 10 V). Evoked dis-charges represent the computer summed responses to 25 stimulations. Vertical calibration is 5 µV and horizon-tal calibration is 25 msec.
stimulation. The response was decreased to an average of 56% of control (range: 0 - 88%) during 12 stimulations in five animals. The late reflex was either increased or decreased during sympatho-inhibitory stimulation. The responses were changed to an average of 114% of control (range: 56 - 154%). In one animal, only the late reflex was recorded. High frequency stimulation of the sympatho-inhibitory pathway reduced the discharge to 89% of control.

In two animals, a conditioning stimulus (single pulse) to the sympatho-inhibitory pathway was applied at various intervals before afferent nerve stimulation (condition - test paradigm). The early reflex was inhibited at interpulse intervals of <100 msec. Peak inhibition occurred at an interpulse interval of 75 msec with the reflex falling to 65% of control. The late reflex was enhanced at all interpulse intervals (0.5 - 500 msec). Peak facilitation occurred at an interpulse interval of 10 msec, with the reflex being increased to 175% of control.

These data describe the modulation of the somato-sympathetic reflex at the level of the spinal cord during activation of the descending sympatho-inhibitory pathway on the surface of the ventrolateral funiculus. Several investigators have proposed that the
medullary depressor areas are capable of mediating their sympatho-inhibitory effects at the level of the spinal cord. Alexander (2) was one of the first to propose that bulbar depressor areas supply a tonic inhibitory influence on sympathetic nerve discharges. Lim and co-workers (114) and Yi (204) have reported that the medullary depressor area acts independently of the medullary pressor area, causing sympatho-inhibition at the level of the spinal cord. Gootman and Cohen (62) also proposed that sympatho-inhibition of ventromedial medullary origin is mediated within the spinal cord.

The interaction of these medullary depressor sites with autonomic reflexes has also been described by several investigators (32, 33, 35, 36, 94, 95, 149, 193).

Wang and Brown (193) described the inhibition of the galvanic skin reflex during stimulation of several supraspinal areas. The greatest inhibition of this autonomic reflex resulted from stimulation of the ventromedial medullary reticular formation.

Prout and co-workers (149) reported that stimulation of the ventromedial medulla could attenuate the localized vasoconstrictor reflex in the pads of the hindfoot. The vasoconstrictor reflex was mediated by single pulse or short trains of stimuli to the radial nerve. The threshold for inhibition was less than the
threshold for eliciting a change in blood pressure or paw volume. In the present study, blood pressure responses to afferent nerve stimulation were not reduced until the inhibitory stimulus alone produced at least a 10 mm Hg drop in pressure.

Electrophysiological evidence for the interaction of central depressor areas and somatic afferent nerves was first reported by Coote and co-workers (33). They proposed that the medullary depressor area supplies a tonic inhibition to preganglionic neurons involved in the spinal component of the somato-sympathetic reflex. They noted that the amplitude of the reflex in thoracic preganglionic neurons was enhanced following C₂ spinal cord transection. In addition, high frequency stimulation of the ventromedial medullary reticular formation could cause complete inhibition of the reflex elicited by stimulation of the ninth intercostal nerve. Coote and Downman (32) also reported that activation of the ventromedial medulla could completely inhibit the late supraspinal discharge in renal nerve. These investigators also recorded a somato-somatic reflex in the tenth intercostal nerve. Since the same medullary sites could inhibit this spinal reflex, the authors concluded that the ventromedial medulla inhibits at the spinal level.

Kirschner and co-workers (94) reported that the
late discharge in the renal nerve was completely inhibited and the early discharge was partially or completely inhibited during stimulation of the medullary depressor area at the level of the obex.

Coote and Macleod (35, 36) reported three regions within the medulla which inhibit spontaneous and reflex discharges in the renal nerve. These sympatho-inhibitory areas were localized in the ventromedial and ventrolateral medulla and the raphe nucleus. Both spinal and supraspinal reflexes were inhibited during stimulation of these areas. In addition, these investigators reported an inhibition of the spinal reflex during stimulation of sympatho-inhibitory regions in the ventrolateral funiculus and dorsolateral sulcus area of the cervical spinal cord. This study was performed in the spinal animal; therefore, the effects of this stimulation on the late reflex were not reported.

Kirschner and co-workers (95) described the time course of inhibition of the spinal reflex in lumbar white rami and renal nerves in spinal animals. A conditioning stimulus to the sympatho-inhibitory area in the dorsolateral sulcus region depressed the reflex discharge beginning with a 50 msec interval between stimuli. The inhibition lasted 500 - 1600 msec. Peak inhibition attenuated the reflex to 24 - 65% of control. The inhibitory
phase was preceded by a phase of slight facilitation. The conditioning stimulus alone elicited an increased nervous discharge followed by an inhibition of spontaneous activity (or silent period). Thus, the stimulus may not represent activation of a sympatho-inhibitory pathway. Stimulation of sympatho-inhibitory areas in the medulla or ventrolateral funiculus does not elicit an excitation prior to an inhibition of sympathetic activity (35, 62, 81, 185). Possibly Kirschner and co-workers (95) have activated a sympatho-excitatory pathway. The two phases of interaction (facilitation and inhibition) with the spinal reflex may be similar to those described earlier (section F of this Chapter) for the effects of stimulation of an excitatory pathway on the somato-sympathetic reflex.

In the present study, the spinal reflex was attenuated or abolished, while the late reflex was usually facilitated (Figure 27). If the same neurons that are activated by the spinal reflex are also activated by the supraspinal reflex, both discharges should be affected in the same direction if stimulation of the inhibitory pathway exerts its effects at the level of the preganglionic neuron. Apparently, each of these reflexes is mediated through a different population of interneurons. The inhibitory pathway may differentially affect the
interneurons involved in eliciting the sympathetic discharges, exciting the interneurons involved in the late discharge while inhibiting those involved in the early reflex. An alternative suggestion is that there may be no direct effect on the interneurons involved in the late reflex. Instead, the late discharge may be influenced by the silent period of the early discharge. Depression of the spinal reflex may release the inhibitory influence on the supraspinal reflex, resulting in an enhanced discharge.

These data suggest that stimulation of the sympato-inhibitory pathway in the spinal cord does not represent activation of descending fibers from the same medullary structures which have been shown to inhibit both early and late discharges.

A physiological role for the differential effect on the spinal and supraspinal reflexes is an important question. However, the physiological role of the reflexes themselves are not known. Sato (159) has proposed that the spinal reflex may be important for local cardiovascular control while the supraspinal reflex may be important for generalized cardiovascular control. This suggests that inhibition of the early reflex eliminates a local control mechanism.

As mentioned in the previous section of this
Chapter, one must be cautious in comparing electrophysiological results with cardiovascular results during afferent nerve stimulation. Pressor responses are mediated through activation of Group IV fibers (85, 107). The reflex components evaluated in the present study presumably result from activation of Group I - III fibers (see section C of this Chapter). A comparison of the interactions between afferent fibers and descending inhibitory fibers on cardiovascular and preganglionic nerve responses must be limited. These studies demonstrate that the spinal cord plays a role in regulation of sympathetic outflow to the cardiovascular system through integration of afferent nerve and descending inhibitory impulses. A more specific relationship between the blood pressure and electrophysiological responses reported in this study awaits the understanding of the role of the spinal and supraspinal reflexes in regulating the cardiovascular system.

In summary, these data indicate that the regulation of the sympathetic nervous system may occur at the spinal level through integration of afferent nerve and descending inhibitory impulses. Pressor responses to afferent nerve stimulation were attenuated during simultaneous stimulation of the sympa-tho-inhibitory pathway. Spinal reflexes from afferent nerve stimulation were
attenuated and supraspinal reflexes were facilitated during simultaneous stimulation of the sympatho-inhibitory pathway.
CHAPTER V
GENERAL DISCUSSION

The role of the spinal cord in autonomic regulation has received little attention until recently. The spinal cord has been considered to have only a subordinate role in determining sympathetic outflow, with the medulla being considered as the main center for integration of activity from supramedullary structures and afferent nerves.

However, several investigators have shown that supramedullary structures and afferent nerve fibers make direct connections with spinal cord neurons mediating sympathetic nervous discharges. Direct corticospinal (105), hypothalamo-spinal (12, 179, 181), and tectospinal (112) pathways have been reported to mediate cardiovascular responses, independent of the vasomotor center in the medulla. These reports have dealt primarily with sympatho-excitatory fibers. However, Lindgren (112) proposed that vasodilatation resulting from activation of tectofugal fibers is independent of
medullary depressor areas. Folkow and co-workers (53) also suggested that sympatho-inhibition of hypothalamic origin may occur at the level of the spinal cord.

Stimulation of somatic afferent nerves can elicit dramatic pressor responses in chronic spinal animals (177). In addition, activation of dorsal roots can elicit a reflex discharge in sympathetic nerve fibers which is complete within the spinal cord (reviewed in 97, 165).

These data lead to some scepticism regarding the unique role of the medulla in cardiovascular control. The purpose of the present study was to demonstrate the regulation of the sympathetic nerve discharges at the level of the spinal cord.

Single pulse stimulation of descending sympatho-excitatory pathways in the spinal cord elicit a sympathetic discharge followed by a silent period. The cardiovascular responses noted during repetitive stimulation of this pathway result from the balance between these two phases of activity (Figure 3). Low frequency stimulation elicits a depressor response because of the silent period. Additional stimuli are unable to activate the preganglionic neuron. During this time the spontaneous activity is depressed and the blood pressure falls. High frequency stimulation elicits a pressor response through a temporal and spatial
summation. An initial stimulus activates some cells and brings other cells closer to their firing threshold. Additional stimuli, close in time, excite these neurons. Consequently the blood pressure rises. Thus the final overall sympathetic discharge is determined at the level of the spinal cord.

The mechanism described for the reversal response is similar to that described by others for activation of afferent nerves and the hypothalamus (37, 99). The silent period remains a "mystery" with regards to its mechanism of activation and the cell population (pre-ganglionic neuron or interneuron) in which it arises. Much of the understanding of how an "excitatory" fiber can activate, as well as depress, the sympathetic outflow awaits a detailed description of the silent period.

The inhibitory effects of stimulation of the sympatho-excitatory pathway are quite distinct from those arising from stimulation of a sympatho-inhibitory pathway on the surface of the ventrolateral funiculus (Figures 3 and 5). Though the range of the magnitude of the depressor responses were similar (5 - 30 mm Hg and 10 - 50 mm Hg for excitatory and inhibitory pathway stimulations, respectively), the frequency eliciting these responses is quite different. Maximum depressor responses were elicited during stimulation of the excitatory and
inhibitory pathway at 1 - 8 Hz and 25 - 100 Hz, respectively. The electrophysiological correlates are also different during activation of these two pathways. High frequency stimulation of the sympatho-inhibitory pathway has been shown to depress spontaneous activity in renal and splanchnic nerves (51, 81, 82). Low frequency stimulation of the excitatory pathway elicits a discharge followed by a silent period, rather than a pure inhibition of spontaneous discharges. In the present study, inhibition of spontaneous activity in the T2 preganglionic nerve following single pulse or short trains of high frequency stimuli was noted in a limited number of animals (Figure 6). Perhaps the choice of the nerve is a major factor in this matter. The splanchnic or renal nerves have been used for recording sympatho-inhibition from the spinal cord (35, 81, 82) and medulla (62, 182, 198). In addition, vasodilatation of visceral organs has been implemented in depressor responses from supraspinal structures (42, 79, 117).

Thus, the spinal cord has at least two mechanisms for generating a depression of sympathetic outflow: activation of the silent period and pure inhibition; which system is more important physiologically is difficult to determine. Scherrer (168) noted that spontaneous discharges which occur in bursts is followed by a silent
period. Hypothalamic stimulation was ineffective in eliciting a response during this time. Perhaps these "spontaneous" silent periods act as a mechanism to prevent "over-excitation" of the sympathetic nervous system. Alexander (2) reported that medullary depressor areas supply a tonic inhibitory influence on sympathetic discharges. Stimulation of these areas result in an inhibition of sympathetic discharges without prior excitation (62, 89, 170, 182, 198). Thus both mechanisms of inhibition may operate in limiting sympathetic outflow.

Afferent nerve fiber stimulation can elicit either a pressor or depressor response, depending upon the type of nerve fibers stimulated and the frequency of stimulation (Figure 7). It has been suggested that Group II and III fibers activate both excitatory and inhibitory centers, while Group IV fibers have input to only excitatory neurons (98, 172). The inhibitory neurons presumably mediate the silent period through activation of medullary depressor areas (reviewed in 97, 165). The level of the nervous system in which the inhibitory effect is exerted has not been determined. Presumably, inhibitory fibers descend to the spinal cord and inhibit preganglionic neurons or interneurons. Activation of Group IV fibers may by-pass the inhibitory neurons and activate excitatory cells only.
In addition to the variations in fiber types, stimulus frequency also determines the type of cardiovascular response to afferent nerve stimulation. Coote and Perez-Gonzales (37) and Koizumi and co-workers (99) have suggested that the silent period is responsible for the depressor response during low frequency stimulation. Koizumi and co-workers (96) also suggested that during high frequency stimulation excitatory processes dominated, and increased sympathetic discharges elicited a pressor response.

Apparently, depressor responses from afferent nerve stimulation are dependent upon the silent period. If Group II and III fibers mediate the silent period through activation of medullary depressor areas (97, 165), the silent period may not be different from other inhibitory mechanisms. That is, the silent period may not be dependent upon previous excitation. Supportive evidence comes from Wysogrodski and Polosa (203) and Coote and Perez-Gonzales (37). They recorded pure inhibition from low intensity stimulation of afferent nerves. This would suggest that the excitation-inhibition pattern of the somato-sympathetic discharges may represent activation of two descending pathways: sympatho-excitatory and sympatho-inhibitory pathways. Thus, sympathetic outflow may be determined by the overall activity within these
pathways terminating on spinal preganglionic neurons or interneurons.

Since descending sympatho-excitatory and sympatho-inhibitory pathways and afferent nerves mediate cardiovascular responses due to activation of spinal cord neurons, presumably sympathetic outflow is regulated through integration of activity within these various systems at any instant in time. To describe this interaction, cardiovascular and preganglionic nerve responses have been recorded during simultaneous activation of these systems.

Pressor responses from activation of descending sympatho-excitatory pathways and afferent nerves are attenuated during simultaneous stimulation of the sympatho-inhibitory pathway (Figures 13 and 26). In addition, stimulation of the sympatho-inhibitory pathway attenuated evoked discharges from activation of sympatho-excitatory pathway and the spinal reflex from activation of afferent nerves (Figures 14, 15, and 27). Interestingly, the late (supraspinal) reflex was generally enhanced during sympatho-inhibitory stimulation. Whether or not this represents differential activation of the neuron pools involved in mediating the two reflexes is unknown. Perhaps the facilitation results from the absence of an inhibitory influence from the spinal reflex. This would, however, presume that the
silent period was also attenuated during the stimulation of the inhibitory pathway.

Several investigators have described a depression of spinal evoked discharges following stimulation of medullary depressor sites (32, 33, 35, 36, 94, 182, 184, 185).

In addition to stimulation of the inhibitory pathway located on the surface of the ventrolateral funiculus, sympatho-inhibition was also induced by injecting apressor dose of norepinephrine. The role of baroreceptor activation in inhibition of evoked discharges was also evaluated. Responses to stimulation of descending sympatho-excitatory pathways and afferent nerves were attenuated during baroreceptor activation (Figures 16 - 19). The magnitude of the depression of the spinal reflex and the evoked discharge from sympatoh-excitatory stimulation was related to the peak level of mean pressure attained during norepinephrine administration. Since these responses were of spinal origin, the baroreceptor-induced sympatho-inhibition must have occurred at the segmental level. Several investigators have proposed that baroreceptor activation can affect sympathetic discharges at the level of the spinal cord (36, 59, 95, 182, 184, 185).

The present study describes the interaction of excitatory and inhibitory systems at the level of the spinal
cord. The interaction of two excitatory systems were also evaluated in this study.

Pressor responses to simultaneous stimulation of descending sympatho-excitatory pathways and afferent nerve were greater than the response to stimulation of either of these systems alone. However, the responses could be either greater or less than the arithmetic sum of the responses to separate stimulations (Figure 21).

The interaction of sympatho-excitatory pathways and afferent nerve fibers was also demonstrated with facilitation of the somato-sympathetic reflex during subthreshold stimulation of the sympatho-excitatory pathway (Figures 22 and 23). If impulses from these two systems arrive coincidentally at the preganglionic neurons or spinal interneurons, the reflex discharge can be enhanced. This phase of facilitation is followed by a phase of inhibition, possibly resulting from activation of the silent period. Coote and Macleod (35) were unable to demonstrate a facilitation of reflex discharges during stimulation of medullary or spinal pressor sites. However, the evoked discharges were already maximal in their study. In the present study, submaximal reflex discharges were facilitated. No attempt was made to evaluate the effects of stimulation of the sympatho-excitatory pathway on maximal reflex discharges.
Facilitation of evoked discharges from sympathoexcitatory stimulation were also described in this study. During inhibition of baroreceptor activity (bilateral carotid occlusion) the evoked discharges from stimulation of the descending sympatho-excitatory pathway were enhanced (Figure 20). Thus temporal or spatial summation of excitatory input must be occurring at the level of the spinal cord.

These data demonstrate that the spinal cord is capable of integrating activity from descending excitatory and inhibitory pathways and afferent nerves. The final sympathetic outflow is thus determined at the level of the spinal cord. Precisely which neurons are involved in the integration is not known. This study has used a multifiber preparation. Consequently it is difficult to determine whether the same preganglionic neurons are being activated by the various systems. Ideally, the interaction must be studied on a single fiber preparation. If subthreshold activation of two excitatory systems elicited a response, one could conclude that both systems activate the same preganglionic neuron. However, more important information may be gained from recording activity from cells within the spinal cord. Recording from single units, both preganglionic neurons and interneurons, may reveal the mechanism of the interaction of
these systems. Do each of these systems activate the same population of interneurons? Do each of these systems activate the same population of preganglionic neurons? Are all preganglionic neurons influenced by both excitatory and inhibitory impulses? Is the silent period generated at the level of the preganglionic neuron or interneuron? Is sympatho-inhibition generated at the level of the preganglionic neuron or interneurons? The techniques used in the present study are inadequate to answer these questions. The data described here demonstrate that regulation of sympathetic discharges can occur at the spinal level. Excitatory and inhibitory impulses from supraspinal structures and afferent nerves impinge upon the spinal cord. The sympathetic outflow can be regulated through processes of temporal and spatial summation.
CHAPTER VI
CONCLUSIONS

The following observations and conclusions can be obtained from the results of these experiments:

1. Activation of sympatho-excitatory pathways located on the surface of the dorsolateral funiculus can elicit pressor or depressor responses, depending upon the frequency of stimulation. An electrophysiological mechanism for this reversal response was described.
   a. Low frequency stimulation elicits a depressor response because of the silent period in the preganglionic nerve.
   b. High frequency stimulation elicits a pressor response as a result of temporal or spatial summation of impulses to preganglionic neurons.

2. Activation of the descending sympatho-inhibitory pathway elicits depressor responses when stimulated between 1 - 100 Hz. Maximal responses resulted from stimulation at 25 - 100 Hz, 10 - 13 V, 1 msec.

3. The magnitude of the depressor response was not
related to the level of vasomotor tone.

4. Computer summed responses in the $T_2$ preganglionic nerve demonstrate an inhibition of spontaneous discharges following single pulse or short trains of high frequency stimulation of the inhibitory pathway.

   a. Early phases of inhibition have an onset latency of $12 - 25$ msec and duration of $34 - 77$ msec.

   b. Later phases of inhibition have an onset latency of $49 - 134$ msec.

5. Stimulation of afferent nerve fibers in the tibial nerve, dorsal roots, or dorsolateral sulcus elicited pressor responses at high frequency (>5 Hz) stimulation and depressor responses at low frequency stimulation. Though the magnitude of the responses varied, the qualitative changes were similar regardless of the source of afferent stimulation.

6. Single pulse stimulation of afferent nerve fibers could elicit an early, intermediate, and late discharge in the $T_2$ preganglionic nerve.

   a. Tibial nerve stimulation evoked early (latency: $21 - 35$ msec) and late (latency: $69 - 91$ msec) discharges.

   b. Dorsal root stimulation elicited early (latency: $11 - 15$ msec), intermediate (latency: $35$ msec), and late discharge (latency: $49 - 59$ msec) discharges.
c. Dorsolateral sulcus stimulation elicited early (latency: 8 - 16 msec), intermediate (latency: 26 - 61 msec), and late (latency: 44 - 88 msec) discharges.

7. The cardiovascular interaction of the descending sympatho-excitatory and sympatho-inhibitory pathways was described. Since these pathways are located in the spinal cord, the interaction must be mediated at the segmental level.
   a. Depressor responses to sympatho-inhibitory stimulation were reduced during activation of the sympatho-excitatory pathway.
   b. Pressor responses to sympatho-excitatory stimulation were attenuated during simultaneous stimulation of the sympatho-inhibitory pathway.

8. The electrophysiological interaction of descending sympatho-excitatory and sympatho-inhibitory pathways was also evaluated.
   a. The time course of interaction was determined using the condition - test paradigm. Preganglionic nerve evoked discharges could be attenuated with various intervals between stimuli.
   b. Preganglionic nerve discharges were also depressed during high frequency stimulation of the sympatho-inhibitory pathway.

9. Baroreceptor activation (norepinephrine injection)
inhibited discharges in the T2 preganglionic nerve which were evoked from stimulation of the descending sympatho-excitatory pathway and afferent nerves. The degree of inhibition of the spinal component of the somato-sympathetic reflex and the evoked discharges from spinal cord stimulation was related to the peak blood pressure during norepinephrine injection.

10. Inhibition of baroreceptor activity (bilateral carotid occlusion) facilitated the evoked discharge from stimulation of the descending sympatho-excitatory pathway.

11. The cardiovascular interaction of the descending sympatho-excitatory pathway and afferent nerve fibers was determined. The blood pressure responses to simultaneous stimulation of these systems was always greater than the response to stimulation of either of these systems separately.

12. The electrophysiological interaction of the descending sympatho-excitatory pathway and afferent nerve fibers was also determined.

a. A conditioning stimulus to the sympatho-excitatory pathway facilitated the spinal reflex elicited by stimulation of afferent nerve fibers. The phase of facilitation (interval between stimuli: 0.1 - 20 msec)
was followed by a phase of inhibition (interval between stimuli: 25 - 100 msec). During the phase of facilitation, the late reflex was attenuated.

b. The late reflex elicited by afferent nerve stimulation could be facilitated by a conditioning stimulus to the excitatory pathway applied 100 - 150 msec after onset of afferent nerve stimulation.

13. The cardiovascular interaction of the descending sympatho-inhibitory pathway and afferent nerve fibers was determined.

a. The depressor response to sympatho-inhibitory stimulation was not changed by stimulation of the afferent nerve fibers.

b. The pressor response to afferent nerve stimulation was attenuated during simultaneous stimulation of the sympatho-inhibitory pathway.

14. The electrophysiological interaction of the sympatho-inhibitory pathway and afferent nerve fibers was also described.

a. High frequency stimulation of the sympatho-inhibitory pathway attenuated the spinal component of the somato-sympathetic reflex, while enhancing the late reflex.

b. A conditioning stimulus to the sympatho-inhibitory pathway attenuated a test spinal reflex discharge
with an interval between stimuli of <100 msec. The late reflex was facilitated at all interpulse intervals <500 msec.


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The dissertation is therefore accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Jan 9, 1976

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