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The Effect of Electrical Stimulation of the Nervous System at Three Levels on Hypertensive Response in the Cat

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THE EFFECT OF ELECTRICAL STIMULATION OF THE
NERVOUS SYSTEM AT THREE LEVELS ON
HYPERTENSIVE RESPONSE IN THE CAT

by

KEE SOON KIM



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

Kee Soon Kim was born in Sizuoka-Gen, Japan on October 19, 1934. In 1939 he moved with his parents to Taegu, Korea and lived there until he came to the United States in 1964.

In 1953 he entered the College of Liberal Arts and Sciences of Kyungpook National University, Taegu, Korea. In the above college he majored in Biology and received the Bachelor of Science degree in 1957. The same year he was accepted by the Graduate School of the same University. He received the Master of Science degree in Zoology in 1959.

In 1959 Kee Soon Kim was appointed a full-time teaching assistant in Physiology in the School of Medicine at Kyungpook National University. In 1961 he was promoted to an Instructor in Animal Physiology and transferred to the Department of Biology, the College of Liberal Arts and Sciences of the same University. He also taught English, physiology and biology at Nursing School as a part-time Instructor from 1958 to 1962. In 1963 he was promoted to an Assistant Professor in Animal Physiology.

Kee Soon Kim married Hyo Kyung Myung in March, 1964.

In August, 1964 Kee Soon arrived in the United States in order to begin a graduate study program toward a degree of Doctor of Philosophy in Physiology at Loyola University. He is also a Fulbright Travel Grantee.

On January 21, 1965, a girl, Nam Yong, was born to Hyo Kyung and Kee Soon. After a heart-breaking separation of one year and a half, he was joined by his wife, Hyo Kyung, through warm and most thoughtful arrangements by Dr. and Mrs. Walter C. Randall and Mr. and Mrs. Edward Kennedy in February, 1966. A second daughter, Nam Hye, was born on July 28, 1967.

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CHAPTER I

INTRODUCTION AND REVIEW OF LITERATURE

A. Cardiovascular Responses to Electrical Stimulation of the Nervous System

In the study of nervous control of the cardiovascular system, introduction of electrical current into certain nervous structures with simultaneous response recording has been one of the most productive procedures.

From the beginning of this century, intensive electrical explorations have been made at various levels of the neuroaxis by means of various current supplying instruments such as condenser discharge, inductorium, thyratron tube, and the modern square wave voltage generator.

In addition to peripheral autonomic outflows, central nervous structures known to be concerned with the control of cardiovascular system include the brain stem, diencephalon, cerebral cortex and spinal cord.

There is evidence indicating that even the cerebellum may influence the hypothalamic and bulbopontine vasoconstrictor control (131).

1. Bulbar or medullary level

In 1946 Ranson and Billingsley (151) electrically stimulated the floor of the fourth ventricle finding both pressor and depressor points.

This study and others (3, 7, 130, 181) as well as the classical transection studies of Dittmar (50, 51) and Owsjannikow (134) have established the concept of a vasomotor center in the medulla oblongata. Recently, however, depressions of blood pressure resulting from medullary transection are considered to be more comparable to conditions of spinal shock (88).

Studying changes in blood pressure, heart rate and other autonomic responses, Chen and his associates (35, 36) repeated the stimulation experiment of Ranson and Billingsley. They concluded that Ranson's medullary pressor and depressor areas seemed more like general sympatho-excitatory and sympatho-inhibitory regions respectively.

During stimulation of the pontobulbar region of the brain stem in decerebrate cats, Alexander (3) recorded action potentials from the fibers of the inferior cardiac and cervical sympathetic nerves as well as blood pressure and heart rate.

Alexander's work and other similar explorations (7, 130, 181) located rather diffuse medullary pressor and depressor areas which are now generally known as the diffuse medullary vasomotor area.

This pressor area occupies a more rostral and lateral part of the medullary reticular formation and surrounds a medial depressor area. In the caudal part of medulla, the depressor area widens displacing the pressor area laterally.

During stimulation of the medullary reticular formation, Peiss (135) observed cardiac augmentor response. In further work in the cat, Peiss (136) could not support the concept that the medulla is the only integrative center for sympathetic cardioacceleration.

Peiss and Manning reported that the electrical excitability of the medullary vasomotor areas was depressed following injection of d-tubocurarine (137) while in the hypothalamus excitability was depressed by sodium pentobarbital (138).

In both anesthetized and conscious cats, Abrahams et al (1, 2) explored regions in the hypothalamus and brain stem which caused active muscle vasodilation with electrical stimulation and suggested that muscle vasodilation should be considered as a component of the defense reactions.

During electrical stimulation of caudal and ventral portions of the medulla, non-cholinergic vasodilation was reported by Aoki and Brody (5).

Recently Prout et al (144) observed that a vasoconstrictor reflex produced by the excitation of afferent nerves was abolished by stimulation in the ventromedial medullary reticular formation at the level of the obex.

In the exquisite book published recently, Randall (146) reviewed the past concept of the cardiac control of central nervous system and introduced the current concept of it. Also, past and present concepts of

cardiovascular regulation were described and a new concept was proposed by Peiss (139). He suggested that in classical views of central nervous control of the cardiovascular system, the role of the medulla has been over-emphasized.

Now it is clear that the medulla is one of the most important, but not the only integration center for cardiovascular control.

2. Diencephalic level

Karplus and Kreidl (101, 102, 103, 104) pioneered early work on the effect of hypothalamic stimulation of blood pressure and various other autonomic functions. In decorticated animals, Cannon and coworkers (30, 31) found that an increased adrenal medullary secretion during the sham rage response was related to diencephalic excitation. They ascribed an important integrative role to the diencephalic structures during "emergency reactions".

Bard and associates (9) held that these responses were primarily mediated by the mesencephalon but that an intact hypothalamus was necessary for the normal intensity and coordination of these responses.

Ranson and Magoun and their collaborators (99, 152, 153) stereotaxically explored in great detail the hypothalamus and adjacent areas of the brain with small stimulating electrodes. They observed many autonomic

responses, e. g., changes in blood pressure, dilatation of pupil, contraction of nictitating membrane, piloerection and sweating which were similar to those reported by Karplus and Kreidl.

They also noticed a profound influence of hypothalamic stimulation on the augmentation of the adrenal medullary secretion and the elaboration of sham rage responses.

Rioch and Brenner (157) demonstrated that many of the autonomic responses elicited by posterior hypothalamic stimulation are due to activation of intrinsic mechanisms, i. e., responses independent of descending pathways from the cerebral cortex.

In 1941, Hare and Geohegan (83) studied the effects of stimulation frequency on the cardiovascular and respiratory responses from the hypothalamus.

Recording discharges of impulse in peripheral sympathetic nerves as well as blood pressure, Bronk and his associates (23, 142) concluded that the medulla alone is adequate for tonic maintenance and reflex regulation of cardiovascular functions. They held that sympathetic responses to hypothalamic stimulation are mediated through medullary sympathetic centers, not via direct pathway from hypothalamus to spinal sympathetic motor neurones.

They felt that the frequency of firing of a sympathetic motor neuron in response to hypothalamic stimulation is determined by the level of excitation maintained by the hypothalamic volleys, the time course of the recovery cycle, and the degree of activity of inhibitory afferents at some critical point between the hypothalamus and motor neurone.

Hess and Brügger (85) were the first to stimulate the hypothalamus and to observe defense reaction in chronic conscious animals. They also supported the concept that the sympathetic system is represented in the posterior hypothalamus while the parasympathetic is in the anterior hypothalamus.

Earlier Beattie et al (14, 15, 16) claimed that the parasympathetic system had a definite representation in the hypothalamus.

In 1951 Eliasson, Folkow, Lindgren and Uvnäs (55) demonstrated the activation of the sympathetic cholinergic vasodilator nerves to skeletal muscle during stimulation of the hypothalamus. Later Lindgren and his associates (119) showed that these muscle vasodilator fibers originate in the anterior sigmoid gyrus and pass to the spinal cord via the hypothalamus, mid-brain tegmentum and medulla.

Folkow and von Euler (62) reported that stimulation in the hypothalamus not only increased secretion of adrenal medulla, but also influenced the ratio of epinephrine to norepinephrine released.

Gellhorn and collaborators (72, 154) suggested that the hypothalamus plays an important role in tonic and phasic control of cardiovascular function.

They observed that injection of pentothal and procaine into the caudal hypothalamus of anesthetized cats lead to a fall in arterial blood pressure and heart rate. Furthermore, Gellhorn (74) suggested that a reciprocal inhibitory innervation exists between the anterior and the posterior hypothalamus.

In 1959 Folkow and his associates (63) found a region in the hypothalamus from which a distinct inhibition of sympathetic activity can be elicited and suggested that this structure constitutes a hypothalamic relay station for cortical inhibitory pathways to subordinated sympathetic structures, mainly affecting the discharge of the medullary vasomotor center.

In resting unanesthetized dogs, Rushmer, Smith and their colleagues (159, 160) found that electrical stimulation of the H1 and H2 fields of Forel and the periventricular gray of the third ventricle resulted in

cardiovascular responses very similar to those which result from exercise. This was the first demonstration that the hypothalamus may influence cardiac contractility.

At almost the same time, Manning and Peiss (125) also made an extensive exploration of hypothalamus and brain stem mapping many spots which elicited various cardiovascular responses. They emphasized that in many animals the major component of a pressor response is often the result of increased force of myocardial contraction rather than vasoconstriction. Furthermore, they indicated that the lateral and posterior hypothalamus and part of subthalamus are included in the most reactive areas for eliciting these inotropic responses.

In further studies, Manning (126) stimulated the hypothalamus in dogs with extensive lesions in medullary vasomotor center and found additional evidence supporting the concept of existence of hypothalamic tonic activity and direct nervous pathways to the spinal cord.

However, it seems now that further direct functional evidence is necessary to prove this concept.

Cardiac arrhythmia has been noted often during or after electrical stimulation of central nervous structures (4, 17).

Manning and Cotten (127) studied the mechanism of cardiac arrhythmias induced by diencephalic stimulation and indicated that such arrhythmia resulted from an interplay of both sympathetic and parasympathetic influence on the heart.

In 1960 Abrahams et al (1) found that in anesthetized animals the hypothalamic skeletal muscle vasodilatory region was very similar to the defense reaction regions found by Hess and Brügger in conscious cat. Abrahams et al concluded that muscle vasodilation produced by stimulation of the hypothalamic area was really part of the whole defense reaction. They also suggested that the defense reaction must be considered as a reflex phenomenon which has its center in the hypothalamus and brain stem regions with the efferent limb of this reflex arc by-passing the so-called vasomotor center in the medulla.

There seems to be relatively little work done regarding hypothalamic control of specific vascular beds.

Feigl (59) stimulated diencephalic and rostral mesencephalic structures of the cat finding a region which gives vasoconstriction in the kidney and vasodilation in skeletal muscle.

During stimulation of the hypothalamic defense area, Cobbold et al (38) observed a pronounced vasoconstriction of both resistance and capacitance vessels of the intestinal wall.

Folkow et al (68) reported that electrical stimulation of the sympatho-inhibitory area in the anterior parts of the hypothalamus (cat) elicited an inhibition of the tonic sympathetic activity not only to the heart and resistance vessels, but also to precapillary sphincters and venous capacitance vessels as well.

Baum and Hesko (11) observed that veins as well as arteries respond actively to stimulation of the central nervous structures.

On the other hand, Juhás-Nagy et al (96) claimed the existence of an extensive representation of adrenergic coronary constrictor system in the medial and posterior hypothalamus of the dog.

The stimulation of the hypothalamic area by an optimal intensity of current demonstrated the presence of the compensatory role of the depressor mechanisms while superstrong stimulus produced a marked inhibition of the compensatory depressor reactions (19).

During and after stimulation of certain parts of the anterior hypothalamus, Teplov (171) observed prolonged periods of elevated blood pressure which were abolished by adrenalectomy.

Tsybenko (174) studied hypothalamic regulation of pulmonary circulation observing a marked decrease in systemic and, concurrently, an increase in pulmonary arterial pressure while Bartorelli and Gerola (10) demonstrated a rapid hypertensive response in the right ventricular pressure. This was occasionally accompanied by elevated systemic arterial pressure, depending upon the area stimulated.

In the conscious dog, Tsybenko (175) stimulated the hypothalamus observing, as in the anesthetized animal, pressor and cardioaccelerator responses from the posterior hypothalamus and depressor and cardiac slowing from anterior part of the hypothalamus. Comparing to anesthetized group, only the magnitude of response was a little reduced in the conscious group.

Recently several workers (64, 176) studied the effect of chronic stimulation of the hypothalamus on cardiovascular responses probably suggested by the idea that some dysfunction in central nervous system might be a cause of hypertension.

Ueda and his associates (176) chronically stimulated the diencephalon of rabbits with and without unilateral renal artery constriction.

They observed significant blood pressure elevation in 2 of 9 intact rabbits with the stimulation alone and in 9 of the 12 animals in which unilateral renal artery clamping and stimulation were also performed. They concluded that sympathetic stimuli and renal pressor might act synergically in producing hypertension.

Very recently Folkow and Rubenstein (64) stimulated hypothalamic defense area of rats for about four months and concluded from statistical analysis of their data that average mean blood pressure of the stimulated group was significantly higher than that of the control group.

The general current opinion on hypothalamic function regarding the cardiovascular system appears to be that the hypothalamus might not be the most prominent but is surely an important integrating area which controls and regulates cardiovascular function.

3. Cerebral cortex

The cortical areas generally known to influence cardiovascular functions include the motor and premotor cortex, the hidden motor areas, the orbital surface of frontal lobe, the anterior part of temporal lobe, the cingulate gyrus and the insula.

a. Motor, premotor and hidden motor cortex. As early as 1876, Rochefontaine (22) and others (18, 58) claimed to have observed cardiovascular responses (mostly depressor) to electrical stimulation in the sigmoid gyrus and other motor areas. However, in many of these experiments, they could not completely rule out the possibility of current spread to subcortical regions.

One of the best works which demonstrated cardiovascular responses to the direct activation of the cortical neurons was that by Hoff and Green (91). They obtained pressor and cardioaccelerator responses mostly from the motor cortex while depressor response was obtained from more caudal regions. In a further study they (78) observed a simultaneous decrease in renal volume and increase in limb volume during electrical stimulation of motor cortex of cat and monkey. Later, the influence of motor and premotor cortex on the cardiovascular functions was reported by many other workers in man and animals (42, 56, 94, 141).

In 1956 Lindgren et al (119) reported that muscle vasodilator pathways originate in the motor cortex.

In the hidden motor cortex of the cat Delgado et al (44, 45) demonstrated the existence of cardiovascular representation.

b. Orbital surface of frontal lobe. In cat, dog and monkey Bailey and Sweet (8) and others (46, 92, 180) described the influence of the orbital surface of the frontal lobe on cardiovascular functions.

Kaada et al (97) found that direction of blood pressure change was related to the frequency of stimulation.

Mainly from stimulation in the posterior part of the orbital cortex, vasomotor responses have also been observed in man (120).

c. Temporal lobe. By the electrical stimulation of the temporal lobe, Poirer and Schulman (143) elicited a depressor response whereas a pronounced elevation of blood pressure was obtained by Wall and Davis (180).

In man, Chapman et al (33) observed a significant elevation of systolic and diastolic arterial blood pressure.

d. Cingulate gyrus. During electrical stimulation of the cingulate gyrus, Smith (164) observed three different responses: an elevation of blood pressure without cardiac rate response, a depression of blood pressure and heart rate, and a temporary cardiac arrest with marked depression of blood pressure. Later Kremer (110) also reported similar findings.

In Pool and Ransohoff's study (145) the elevation of both systolic and diastolic blood pressures was obtained by electrical stimulation of the cingulate gyrus in eight of twelve men studied.

e. Insula. Hoffman et al (92) and others (180) studied the effect of insular stimulation on the cardiovascular responses finding mostly depression of blood pressure.

In his review of cortical influences on cardiovascular functions, Delgado (47) indicated that cardiovascular representation in the cerebral cortex is discontinuous and not systematized. These cardiovascular responses elicited by electrical stimulation of the cortex, he felt, are characterized by variabilities in direction, magnitude and latency and by fatigue. He further stated that conflicting results reported by earlier works could be explained as the result of uncontrolled experimental variables such as homeostatic mechanisms, anesthesia and stimulation parameters.

4. Spinal cord

Though there are many works (61, 95, 107, 113, 182) in which descending spinal sympathetic cardiovascular pathways have been traced, their exact topography in the spinal cord has not been definitively established. In early studies the pathways of descending sympathetic fibers have been traced by section and degeneration techniques.

Gellhorn and Murphy (73) studied autonomic responses to electrical stimulation of the dorsal surface of the spinal cord, as well as medulla

and hypothalamus, in order to find out if the whole sympathetic system is involved during maximal sympathetic responses. They concluded that the excitation of autonomic centers under physiological and pathological conditions may lead to a partial discharge of the sympathetic system.

Using cats and monkeys Kerr and Alexander (108) electrically explored the low cervical and high thoracic segments of the spinal cord with monopolar stimulating electrodes finding that the descending vasomotor and vesicomotor pathways are located in the most superficial aspect of the anterolateral column. In order to prove that the stimulated nerve fibers were descending pathways, they made spinal transection above the stimulation levels.

It has long been known that spinal transection at any cervical level results in an immediate and profound depression of arterial blood pressure and the pressor reflex.

On the other hand, it has also been observed by many workers (13, 76, 162) that an isolated spinal cord is capable of developing tonic discharges to the heart and blood vessels and is capable of mediating pressor reflexes after recovering from spinal shock (26, 80, 86, 162).

Additional evidence for such independent spinal mediation of autonomic reflexes was provided by Randall et al (147) who observed in

paraplegic patients profound elevations in blood pressure with cutaneous vasoconstriction during distension of the urinary bladder.

There are also some recent reports (84, 139) which indicate that spinal transection does not necessarily cause an acute and long lasting depression of vasomotor and other reflexes.

There are few studies on the effect of electrical stimulation of the spinal cord, especially in high cervical segments, on cardiovascular functions. Studies of stimulation parameter characteristics of this spinal structure are particularly scarce.

The prevailing opinion on the role of the spinal cord in the control of cardiovascular functions seems to be that under normal conditions the spinal cord has minor integrative functions. However, if the higher centers are isolated, spinal centers become active and mediate tonic and phasic cardiovascular discharges.

5. Peripheral sympathetic outflows

It is traditionally taught that sympathetic preganglionic cell bodies are located in the lateral and medial parts of spinal gray matter. They are generally thought to arise exclusively from the thoracic and lumbar segments of the spinal cord. However, there is good evidence to indicate

that the sympathetic outflows are not confined to the thoracolumbar levels of the spinal cord.

In the anesthetized dog Wiesman, Jones and Randall (133) electrically stimulated the intact or cut distal end of the ventral root of the lower cervical nerves. They often obtained cardiac acceleration and augmentation, pressor response and vasoconstriction in the frontal footpad. They concluded that in some dogs there are sympathetic preganglionic fibers leaving the cervical spinal cord through the ventral roots of the lower cervical nerves.

It also has been reported that in the vagus nerve there are some sympathetic cardiac accelerator fibers which probably arise from the medulla oblongata (100).

During the middle part of the 19th century first Brown-Sequard and later Claude Bernard separately demonstrated the existence of vasoconstrictor nerves. They independently observed that electrical stimulation of the cephalic end of the cervical sympathetic trunk reversed the changes induced by its section. However, it was Brown-Sequard who first suggested that cervical sympathetic nerve fibers are motor as related to the blood vessels of the head.

On the other hand, the Cyon brothers (43) were among the first to prove the existence of sympathetic cardiac accelerators, stimulation of which generally resulted in increased heart rate and elevation of blood pressure.

From these early works the sympathetic cardiac nerve was called the cardiac accelerator nerve because recording manometers were rather insensitive to cardiac inotropic effects. However, in later works other investigators observed additional effects of electrical stimulation of the cardiac sympathetic nerve on conduction velocity, pacemaker activity, coronary blood flow and cardiac contractility.

Recently Randall and Rhose (148) studied the differential influence of the left and right cardiac sympathetic nerves on the cardiac functions concluding that electrical stimulation of the right cardiac nerve generally caused both cardiac acceleration and augmentation while stimulation of the left resulted primarily in augmentation.

Arnoud and Lavarenne (6) also reported that chronotropic tonus is exclusively exerted via the right pathways whereas phasic activities are achieved via the left pathway.

After prolonged electrical stimulation of the stellate ganglion, marked endocardial hemorrhages in the left ventricle, particularly along

the axis of the papillary muscles, were observed by Kaye, McDonald and Randall (106).

Recording pressure pulses directly from the four chambers of the canine heart, Randall and Priola (149, 150) found that excitation of cardiac sympathetic nerves caused more synchronous contractions of the left and right ventricles, of auricle and ventricle and of the individual segments of muscle within the outflow tract of the left ventricle.

In many of these studies it has been found that the degree of elicited vasoconstriction or cardiac activity is a function of stimulation frequency.

The curves correlating the rate of impulse discharge and the vasoconstrictor and heart rate responses have been found to be hyperbolic (32, 69). It has been also reported that the hyperbolic frequency-response curve of the capacitance vessels is steeper and displaced to the left as related to that of the resistance vessels (65).

6. Sympathetic vasodilator system

In 1880 Dastre and Morat electrically stimulated the cervical sympathetic trunk, first observing flushing in the mouth and lips. However, the first direct evidence for the existence of the sympathetic muscle

vasodilator system was provided by Burn (29). During electrical stimulation of the lumbar sympathetic chain, Burn observed a profound vasodilation in the leg muscle of the dog.

Later Uvnäs (177, 178) and Folkow et al (55, 66, 119) described central representation of this sympathetic cholinergic vasodilator system and its pathways in the central nervous system.

Though it has been claimed by some early workers (77, 173) that tonic discharge was also detected in the decentralized peripheral sympathetic nerve (isolated sympathetic ganglion), it seems safe to consider that sympathetic outflow fibers are the final common pathway which connects central control center to effectors.

B. The Electrical Parameters of Stimulating Pulses and the Optimal Stimulation Parameters for Cardiovascular Responses from the Various Levels of the Neuroaxis

In acute stimulation experiments the electrical parameters to be considered are pulse frequency, intensity and duration. The type of electrode and the effect of polarization must also be considered in chronic stimulation where tissue injury is a critical problem.

It is generally known that different nervous structures are characterized by different stimulation parameters.

It has been reported also that evoked cardiovascular responses are dependent upon the stimulation parameters.

Although it is not clear to what extent the variables of a parametric set are interdependent, it is probable that each variable affects elicited cardiovascular responses in magnitude, as well as in maintenance.

1. The effect of electrical parameters of stimulation pulses on cardiovascular responses

a. Wave form. In early studies currents with various waveforms produced by the inductorium, thyratron tube and condensor discharge were used. In modern studies, however, stimulation pulses with rectangular or sine waveforms are most commonly used. Waveforms may be more important in chronic stimulations where a long period of continuous excitation of certain nervous structures without injury is desired (117, 118).

Hoff et al (93) have indicated that the inductorium (a faradic current) causes less injury to tissues than square wave pulses.

Major advantages of bidirectional pulses are minimum tissue injury and minimal polarization effects.

However, Delgado et al (48) could find no significant difference in the effectiveness between unidirectional and bidirectional pulses.

Hoffman and Ramussen (92) found that rectangular, sine and rectified sine waves are equally effective in evoking autonomic responses.

b. Pulse duration. In the strength-duration curve for a single unit of peripheral nerve fibers, a reciprocal relationship has been demonstrated between stimulation intensity and duration showing that within certain ranges (above rheobase) the effect of intensity and duration of stimulating pulses are equivalent.

During electrical stimulation of central nervous structures, Wilkus and Peiss (184) and Lilly (117) obtained an exponential strength-duration curve similar to that for peripheral nerves.

In many studies on the effect of electrical stimulation of central nervous structures on autonomic responses, pulses with 1-2 msec duration have been used. Longer durations of 10-20 msec have also been used by some investigators (34, 75, 98, 143). On the other hand, pulse durations of 3-10 msec, most frequently of 5 msec, have been generally used for the stimulation of peripheral sympathetic outflows (67, 148, 156).

It appears that too little attention has been paid to the duration of stimulating pulses, partly because its effect on the responses is not remarkable and partly because this variable has been neglected in early works

because of the inadequacy of the stimulator used. Even in the exquisite works by Bronk et al (23, 142), the effect of pulse duration on responses was not described.

It seems now to be generally accepted that within certain ranges, longer pulse duration is more effective in evoking cardiovascular responses than short pulse duration. However, it also should be noted that both extremely short and long pulse durations are detrimental to the tissues.

c. Intensity. It is now clear that statement of voltage alone is not an adequate expression of stimulation intensity since tissue impedance may change significantly during stimulation.

A common choice of stimulation intensity has been less than 7 volts. However, it is worth noting that determination of the physiological range of voltage levels has not been based upon experimentally demonstrated facts.

Therefore, it seems more reasonable to assume that tissue injury is not only related to voltage (or current) levels, but also to other factors such as duration of pulse, frequency, and total stimulation time.

At a constant duration and frequency of pulses, intensity, within a certain range, influences the magnitude of responses evoked by stimulation. In theory, an intensity which activates all of the fibers within the

sphere of influence of the electrodes, but does not injure them, is considered optimal.

Though a measurement of frequency of action potential alone might not be a perfect criterion of cardiovascular responses, Pitts et al (142) obtained an excellent sigmoid curve relating frequency of action potentials and stimulus intensity. At constant frequency and pulse duration, Pitts et al electrically stimulated the hypothalamus with various intensities measuring frequency of impulse discharge in a single fiber of cervical sympathetic nerves. They also studied, at different hypothalamic stimulation frequencies, the effect of stimulus intensity on the frequency of impulses detected at the peripheral sympathetic nerve finding that stimulation frequency and intensity are synergistic.

Kaada (98) and Delgado (47) indicated that changes in blood pressure may be induced at threshold levels below those required to elicit skeletal muscle motor responses.

Wilkus and Peiss (184) obtained excellent strength-duration curves while recording changes in heart rate elicited by intracranial stimulation.

d. Frequency. It is well known that cardiovascular responses to electrical stimulation of central nervous structures are significantly

influenced by stimulation pulse frequency and that different responses may be produced by different stimulation frequencies (20, 46, 79).

In the hypothalamus, Hare and Geohegan (83) first studied the effect of stimulation frequency on the cardiovascular responses observing the maximum pressor responses at 200/sec and depressor responses at 30/sec.

During stimulation of central nervous structures, pressor and cardioaccelerator responses have been reported frequently with high stimulation frequency (usually around 100/sec) while depressor and cardiac slowing are induced by low frequencies (10-20/sec).

On the other hand, Folkow et al (63) reported that maximum tonic sympathetic inhibitory effects were observed at frequencies of about 60/sec which is considered to be rather high.

Abrahams et al (1) also observed maximum muscle vasodilator responses during electrical stimulation of the brain stem at 70/sec whereas maximum response was produced by stimulation of muscle vasodilator nerve at 12/sec by Folkow (67).

During electrical stimulation of the hypothalamus, Pitts et al (142) found a linear relationship between the stimulation frequency and the

frequency of postganglionic action potentials. Though the intensities of the stimulation current were not specified, these also exercised a remarkable influence upon the frequency conversion rates.

In the stimulation of the peripheral sympathetic outflows, a definite range of stimulation frequency is required to produce a vasomotor effect.

Van Bobben-Broekema et al (179) reported that effective frequency range is 3-150/sec with optimum at 15-20/sec whereas Girling (75) demonstrated it to be 0.5-60/sec with optimum at 0.5-25/sec.

Rosenblueth (158) indicated that in most cases visceroeffectors showed maximum responses at stimulation rates around 20/sec.

There is good evidence (24, 67) to suggest that the autonomic system normally fires at rates below 10/sec and that tonic vasomotor discharge is around 1-3/sec.

In studies on the relationship between efferent impulse discharge rate and the peripheral resistance of blood vessels in dog's leg muscle and skin, a hyperbolic curve was obtained showing that almost full responses are obtainable at discharge rates around 10/sec (32). This type of hyperbolic frequency-response curve was also observed in our recent study in

which stimulation frequency and local cardiac effector response (contractile force) was correlated.

2. The optimal stimulation parameters for cardiovascular responses

It is generally agreed that in acute experiments, optimal stimulation parameters are those parametric variables within physiological ranges which evoke nearly maximum responses. However, in many of the studies cited, it is noted that often not all the variables were taken into consideration. In fact, it has not been known in any detail, to what extent each variable is responsible for the elicitation of the responses.

It seems more reasonable to assume that with a stimulation current of a certain waveform, each of the three variables, e. g., intensity, pulse duration and frequency, could be a limiting factor for the elicitation of responses and that tissue injury would be more related to total energy dissipated into tissues in unit time (current density).

To induce pressor and cardioacceleration responses from stimulation in the brain stem, hypothalamus and cerebral cortex, the most frequently used stimulation parameters fall in the range of 50-70/sec, 2 msec, 2-7 volts (59, 136, 137) to 100/sec, 1 msec, 2-7 volts (10, 11). Less frequently currents with low frequency (10-20/sec) and high intensity or longer duration have been used (34, 98, 143).

In 1963 Wilkus and Peiss (184) found that optimal stimulation parameters for the cardiovascular responses from the medulla and hypothalamus of the cat are 100/sec, 1-2 msec duration.

Kerr and Alexander (103) used a parametric set of 60/sec, 1 msec and 1.5-10 volts in their study in which the spinal cord was electrically stimulated for precise tracing of descending sympathetic fibers mediating vesico and vasomotor activities.

In 1957 Rhose, Kaye and Randall (156) reported that stimulation of the stellate ganglion of the open chest dog at high frequency (up to 80/sec) elicited a rapid increase in systolic and pulse pressure which was not sustained whereas with frequencies as low as 3/sec, responses could be sustained for as long as 5 to 11 hours with continued stimulation. They found that for cardiovascular responses derived from stellate ganglion stimulation, 1-3/sec, 5-10 msec, 0.5-4.5 volts are optimal parameters as related to both magnitude and maintenance of responses.

In cardiovascular studies on the effect of chronic stimulation of central nervous structures, almost the same range of stimulation parameters as for acute experiments have been used except that stimulation was applied intermittently with various frequencies and train durations.

In general it appears that optimal stimulation parameters may be different depending upon the area and the type of responses under study and therefore may not be identical for acute and chronic experiments.

C. Decay of Cardiovascular Responses

It has been reported that during prolonged electrical stimulation of certain nervous structures, ensuing cardiovascular responses are rarely prolonged despite continuous application of the stimulus.

1. Cerebral cortex

Hoff and Green (91) were among the first to observe such decay in cardiovascular responses elicited by cortical stimulation. They observed that during 40 seconds of cortical stimulation the systemic blood pressure reached a peak and began to decline about 16 seconds after the beginning of stimulation. They interpreted the decay to be a result of fatigue. On the other hand, Pool and Ransohoff (145) found that the pressor response in man lasted up to 5 minutes after stimulation of rostral part of cingulate gyrus was terminated.

In 1959 Delgado (49) studied the effects of repeated stimulation of different cerebral structures in unanesthetized monkey. He observed

many somatic, autonomic, behavioral and EEG responses and also found varying rates of fatigability of different areas of the brain. He observed prompt fatigue (generally beginning in seconds) with stimulation in the motor cortex while delayed or slow fatigue (generally beginning in minutes) was observed in the putamen and hypothalamus. Upon stimulation of inferior part of lateral hypothalamus, a prolonged pupillary contraction without fatigue persisted as long as 72 hours with continuous stimulation. Later Delgado (47) recorded additional evidence that cardiovascular responses elicited by cerebral stimulation could not be prolonged beyond seconds (or, at most, minutes), suggesting that neuronal fatigue or alterations in compensatory mechanism were responsible for response decay.

2. Hypothalamus

Ström (169) reported that fatigue phenomenon usually appeared if hypothalamic stimulation was continued for more than 30 seconds or if stimulations were repeated at short intervals (10-15 seconds). Belyaeva (19) ascribed this decay phenomenon to the compensatory role of the depressor mechanism which represents the central homeostatic regulation of the blood pressure.

During stimulation of the posterior hypothalamus of awake cats, using relatively large stimulating currents (0.5-2.0 mA), Tsybenko (175) also noticed that elevated blood pressures tend to recover slowly.

While stimulating the hypothalamic defense area in cats, Cobbold et al (38) observed that blood pressure initially elevated some 50% above control values, but then dropped to half the initial magnitude in 3 minutes or so. They indicated that such decay phenomenon may have been due partially to fatigue or damage to hypothalamic neuron, since after a period of rest, responses were still obtainable. They also noticed that responses to repeated stimulation tended to be smaller than previous responses while full responses were obtained again when the electrode was moved horizontally for a short distance.

On the other hand, Abrahams et al (1) reported that stimulation in the same hypothalamic defense area induced up to 13 successive skeletal muscle vasodilator responses without noticeable diminution in magnitude.

Cobbold et al further concluded that gradual failure of hypothalamic stimulation could hardly be solely responsible for declining pressures since constriction of capacitance vessels persisted throughout the entire period of stimulation.

Finally, Teplov (171) reported that anterior hypothalamic stimulation elicited prolonged pressor responses which lasted up to 3 hours even after stimulation ceased, and the response was abolished by adrenalectomy.

3. Spinal cord

There seems to be little or no information on the decay of cardiovascular responses elicited by electrical stimulation in the spinal cord.

4. Peripheral sympathetic nerve

Studying the effect of supramaximal stimulation rates (above 20/sec) on the vasoconstrictor response and the nictitating membrane contraction, Folkow (67) observed that evoked responses gradually declined when rates of 15-20/sec, or higher, were applied for more than 2-3 minutes.

He concluded that an exhaustion of the transmitter release mechanism was the probable explanation for the response decay phenomenon.

During prolonged stimulation of the canine stellate ganglion, Rhose, Kaye and Randall (156) observed decay of systolic and pulse pressure responses. They indicated that with the increase of stimulation frequency, rate of response decay also increased whereas with low frequency (1-3/sec), systolic and pulse pressure responses could be maintained for as long as 11 hours with continuous stimulation. They also suggested the

response decay is probably related to exhaustion of transmitter substances at the sympathetic synapse.

Thus it seems that decay of cardiovascular response has been more frequently reported during cerebral cortex and peripheral sympathetic nerve stimulation and less frequently during hypothalamic and medullary stimulation. Spinal cord excitation appears to have been completely neglected.

Suggested explanations for response decay include: (1) damage of stimulated neuronal elements, (2) refractoriness of excited neuronal elements, (3) exhaustion of transmitter release mechanism in the synapses, as well as in neuroeffector junctions, and (4) inhibition.

D. Electrical Excitation of Neuronal Elements

In the electrical stimulation of specific nervous structures, the magnitude of elicited cardiovascular responses will theoretically be determined by the amount of transmitter released at the postganglionic nerve endings. In turn, the amount of transmitter liberated at the neuroeffector junction is determined by the number of excited preganglionic nerve fibers and the frequency of impulses conveyed by these fibers.

Assuming that tissue damage, reflex inhibition and failure in responsiveness of effectors are negligible, the magnitude of cardiovascular responses elicited by such electrical stimulation therefore should depend primarily upon the continuous excitation of a constant number of neurons, upon prolonged unfailling impulse transmission across the synapses, and upon an inexhaustible supply of neurotransmitter.

By choosing areas in the central nervous system and positioning electrodes properly, it should be possible to stimulate neuronal fibers selectively or in small aggregates of neurons, depending upon the size of the electrodes and current intensity. Unfortunately, it is difficult to know which part of the neurons are mainly in the effective field of implied stimulating current.

It should be anticipated that both afferent and efferent fibers, as well as cell bodies, may be excited.

Hagiwara et al (81) found that the somas of the large cells of the lobster cardiac ganglion are virtually devoid of electrical excitability.

It has been also postulated by Freygang and Frank (70) that the spinal motoneuron cell body in cats was not invaded actively by impulses. However, while recording extracellular and intracellular potentials

simultaneously from a motoneuron, Terzuolo and Araki (172) proved that the soma membrane is actively involved in producing soma-dendrite spikes.

Tauc (170) also concluded that the cell body of giant neuron of *Aplysia* is electrically excitable, but has the highest threshold of all parts of the neuron.

It is generally accepted that both dendrites and soma of most neurons are less readily excitable (electrically) than axon, and that conduction velocity in dendrites and possibly over the soma is very slow, being usually much less than 1 m/sec for dendrites.

It is well known that ionic distribution in a neuron is affected by stimulation and consequently a change in neuronal excitability may result. After 5 minutes stimulation at frequency of 40-140/sec, Cowan (40) observed a measurable amount of K^+ leakage in crab nerve. Using radioactive isotopes Keynes and Lewis (109) proved that intracellular Na^+ concentration increases after repetitive stimulation. Furthermore, Keynes and Lewis measured the net leakage of potassium and net gain of sodium in the axon of *Sepia*. After repetitive stimulation of giant axon of *Sepia*, potassium loss was found to be $3-4 \times 10^{-12}$ meq/cm²/impulse, while sodium gain amounted to $3.5-3.8 \times 10^{-12}$ meq/cm²/impulse.

On the other hand, Kato (105) and Erlanger and Blair (57) observed that excitability of nerve was abolished when the sodium concentration of external medium was reduced. Hodgkin and Katz (39) also observed that when sodium concentration in external medium was decreased below 20% of normal value by addition of an increasing proportion of isotonic dextrose solution, the height of action potentials decreased and were finally abolished while resting potential was affected minimally.

Ionic distribution is disturbed by stimulation, and excitability is restored very quickly by the sodium-potassium pump mechanism unless stimulation at high frequency is prolonged. Hodgkin and Keynes (90) indicated that when the neuron of Sepia is stimulated at over 100/sec, the sodium pump cannot keep pace with sodium influx.

It is obvious that the refractory period may limit frequency at which a neuron discharges or conducts impulses; the absolute refractory period being not more than 2 msec in mammalian peripheral nerve (C-fiber).

It is generally accepted that the absolute refractory period is due to persisting inactivation of the Na^+ permeability system, associated with persistence of elevated permeability of K^+ . The same mechanism is responsible for accommodation phenomenon; the increase in threshold being associated with passage of a constant current.

In A- and C- fibers of vertebrate nerves, it is believed that after excitation, normal excitability of nerve is recovered following hyper- and hypo-excitability periods which are usually associated with negative and positive after potentials, respectively. Excitability changes for A- and C-fibers are similar except for differences in magnitude and duration, whereas no hyper-excitability stage exists for B-fibers.

Shanes (161) suggested that the negative after potential, which is 50-80 msec in mammalian C-fiber, is due to the accumulation of K^+ on the outside of the nerve membrane. The positive after potential, which is probably associated with activity of sodium pump has a long duration, being 300-1000 msec for C-fibers.

Following a prolonged stimulation of frog nerve at high frequency, Connelly (39) observed a long lasting hyperpolarization finding that effects of successive impulses are cumulative.

It has been postulated that duration of the hyperpolarization of sympathetic neurons and spinal motoneurons which are reported to be significantly correlated with the conduction velocity along their axons (52, 112, 132) is responsible for determining the frequency at which it discharges when subjected to a sustained depolarization (52, 53, 112, 132).

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According to Nishi and Koketsu (132) there are two different types of neurons in the sympathetic ganglion of the toad, sB and sC neurons of which axons are the B- and C-fibers, respectively. They state that recovery cycles of both neurons followed similar time course after a single response. The excitability of axon and soma of sB neuron recovered gradually along an exponential time course following an absolute refractory period not longer than 10 msec. The recovery was almost complete (90%) within 40 msec but became slow thereafter reaching normal excitability in 150-200 msec. The recovery time was longer in sC neuron requiring 500-600 msec for complete recovery of excitability.

During repetitive firing of neurons of *Limulus* evoked by stimulation with trains of shocks, Fuortes and Mantegazzini (71) found that firing was evoked by a portion of the shocks and the interval between successive impulses increased with time. Therefore, they concluded that prolonged current flows depress the process leading to excitation and that repetitive firing is controlled both by after-effect of firing (refractoriness) and by the depressant effects of stimuli (accommodation).

There is not much information on the electrophysiological activities of neurons in central nervous system of vertebrates during prolonged electrical stimulation.

E. Neural Pathways of Cardiovascular System and Synaptic Transmission

When supramedullary cardiovascular areas are electrically stimulated, it seems reasonable to assume that neurons in the effective zone discharge impulses at the frequency at which they are stimulated. Subliminal summation is also possible for those neurons adjacent to effective zones either through the activities of interneurons or through successive stimuli.

1. Neuronal pathways of cardiovascular system

Impulses generated in the central nervous system reach the cardiac and vasomotor effectors through more than one synapse. Therefore, magnitude and maintenance of response which are primarily determined by the number of activated nerve fibers and impulse frequency, are largely influenced by the morphological and physiological properties of synapses or synaptic transmission.

Synaptic sites in the neuronal linkage of sympathetic cardiovascular pathways include sympathetic ganglia, spinal cord, medullary vasomotor center, mesencephalon, and hypothalamus. The cerebral cortex can also influence cardiovascular reactions either through the hypothalamus or independent of it (113). Landau (113) concluded that cerebral cortex can

effectively influence most autonomic functions by direct impingement in the spinal cord separately from the hypothalamus and its descending pathways.

Uvnäs and co-workers (119) suggested that cholinergic muscle vasodilator pathways have relay stations at least in the hypothalamus and midbrain but not in the medullary vasomotor center.

There are several descending hypothalamic paths which have been known to convey cardiovascular impulses to the brain stem and spinal cord:

- (1) Mamillotegmental tract arises from medial mammillary nuclei and descends into lateral and medial reticular formation of the brain stem to terminate in the dorsal and ventral tegmental nuclei.
- (2) Periventricular system arises mainly from dorso-medial, ventromedial and posterior hypothalamic nuclei and descends in periventricular and central gray, forming a longitudinal bundle (dorsal longitudinal fasciculus of Schütz) (37). Beattie et al (17) suggested that the majority of these fibers run in the medial longitudinal fasciculus while some of them merge in midbrain tegmentum.
- (3) The diffuse fiber system arises from the lateral hypothalamic area and connects with the reticular formation of mesencephalon by means of

polysynapses. From physiological evidence, this system which actually looks like a caudal extension of median forebrain bundle is emphasized as the most important descending projection (122, 123).

From an anatomical study of the central neural pathways mediating cardiovascular functions, Smith (165, 166) claimed some support for almost all the previous findings, even though he found some unexpected additional fiber projections from the supramedullary area to the inferior olive.

The possible existence of a direct hypothalamo-spinal pathway which does not make synapse with bulbar vasomotor center in series was first suggested by Peiss and Manning (137, 139). They observed that following d-tubocurarine administration excitability of the vasomotor center in medulla (to electrical stimulation) was remarkably depressed, whereas that of hypothalamus was not affected much. Smith provided anatomical evidence which supported the concept.

Regarding supramedullary regulation of cardiovascular function, Peiss (140) further postulated three possible fiber projections:

- (1) Neurons which descend from supramedullary levels and synapse by series connections at successively lower levels, including the vasomotor area.
- (2) Neurones which descend with one or more synapses at successively lower levels but do not make connection with the dorsal reticular formations in the medulla.
- (3) Neurons which descend through the entire brain stem, sending off numerous collaterals, eventually terminating in the spinal cord.

It is generally believed that sympathetic fibers mediating cardiovascular functions descend in the ventrolateral column of the spinal cord (61, 107, 182). However, Kerr and Alexander (108) recently emphasized that more important pathways run in the most peripheral part of lateral funiculus.

The final relay station of sympathetic fibers which mediate cardiovascular function are located in either lateral or collateral sympathetic ganglia.

Studying the stellate ganglion of cat, Larrabee and Bronk (115) found an average sympathetic preganglionic neuron is synaptically related

through its many terminal branches with 15 to 30 cells scattered through several adjacent lateral ganglia. They suggested that this divergent relation forms the anatomical basis for the diffuse nature of activity in this system.

Langley (114) found that the preganglionic fibers forming any one white ramus pass to a series of lateral ganglia, never to a single segmental ganglion. He also indicated that any one preganglionic fiber may send collaterals to make synaptic connections with postganglionic neurons in several ganglia.

2. Synaptic transmission

Though physiological discharge rate for the cardiovascular system is generally believed to be below 10/sec, Bronk et al (25) demonstrated that peripheral sympathetic nerves can carry impulses at rates up to 100/sec.

There is good evidence to show that during prolonged rapid repetitive stimulation of presynaptic fibers, synaptic transmission progressively fails.

Finding a fatigue phenomenon during high frequency stimulation of sympathetic ganglia, Orias (133) stated that it is associated with the preganglionic fibers, as well as the long refractory phase of the ganglia.

Well sustained responses were obtained at high stimulation rates when postganglionic fibers (to nictitating membrane) were stimulated.

Stimulating sympathetic preganglionic nerves in the cat, Bronk et al (25) observed well synchronized postganglionic discharges at low frequency, whereas rate and height of postganglionic action potentials decreased progressively at above 30-40/sec and were completely abolished at 60/sec. However, they also observed a prolonged cardiac acceleration during stimulation of preganglionic fibers at frequencies as high as 120/sec and that electrical records of postganglionic activity during such high frequency stimulation showed a negative displacement of base line throughout the entire stimulation period. Therefore, they felt that there were continued activities in the postganglionic fibers despite the absence of usual spike potential. They explained this failure in the postganglionic response was due to asynchronous discharge of individual ganglion cells, probably due to an increased refractory period and to differences in conduction time for the various postganglionic fibers.

In a study of the effects of high stimulation frequency on vasoconstrictor response in the hind limb of the cat, Folkow (67) observed that if stimulation rates of 15-20/sec or higher were applied for more than 2-3

minutes, vasoconstrictor effect declined. In order to test whether this fatigue phenomenon is primarily localized to preganglionic or to postganglionic endings, Folkow stimulated both preganglionic and postganglionic fibers to the nictitating membrane finding that both nerve endings were involved. He concluded that fatigue phenomenon is due, most probably to exhaustion of the transmitter release mechanism at either or both preganglionic and postganglionic fiber endings.

The work of Birks and McIntosh (21) has given the first precise and comprehensive picture of the cellular mechanism involved in the manufacture of a transmitter substance. They analyzed the metabolic handling of acetylcholine in the superior cervical ganglion of cat, both by the use of hemicholinium-3 (HC-3), which inhibits acetylcholine synthesis and by the suppression of AchE by anticholinesterase such as eserine. They estimated maximum capacity of Ach liberation and that of synthesis equally as 28 $\mu\text{g}/\text{min}$ under optimal condition of ganglion perfusion (plasma equilibrated with O_2 and CO_2). Further they reported that accurate measurement of depot-Ach in superior cervical ganglion of cat perfused by plasma or blood did not show any depletion, even during 2 hours of stimulation at 20/sec, while it depleted exponentially when Ach synthesis was blocked by hemicholinium-3.

Feldberg et al (60) reported that the quantity of Ach appearing in venous effluents from sympathetic ganglia in response to a single maximal preganglionic volley was from 6×10^{-5} to 1×10^{-4} γ or of the order of 10^{-9} γ (10^{-15} g) per synapse.

In the isolated rat diaphragm preparation Straughan (168) obtained an output of 3.5×10^{-16} g/impulse at a synapse when stimulated at 6/sec, while Krnjevic and Mitchell (111) found output up to five times greater still when stimulated at 2/sec.

By chemical extraction and chromatographic separation, Brown et al (27, 28) have demonstrated that output of NEpi in the venous effluent from spleen shows a good quantitative relation of transmitter release to frequency of stimulation. When splanchnic nerves were stimulated at 10/sec, average NEpi output per stimulus was 160 pg with a maximum average output (980 pg/impulse) at 30/sec. Above 30/sec the output fell progressively until at 300/sec NEpi was just detectable. Further they found that adrenergic blocking agents such as dibenamine, dibenzylamine or phentolamine alter the NEpi output : stimulation frequency relationship. After administration of either of these drugs, the output of NEpi at stimulation frequencies below 30/sec was increased showing that the output per stimulus

at all frequencies in the range of 1-30/sec were equal. Since at higher frequency the interval between successive impulses were insufficient for the complete destruction of transmitter, NEpi accumulated in the tissue and spilled into the blood stream.

Brown et al further indicated that at stimulation above 50/sec, the decline in NEpi output per stimulation is due, not to destruction of transmitter, but to a failure of liberation. After a brief repetitive conditioning stimulation, changes follow which facilitate subsequent excitation of the ganglion cell by impulses in presynaptic fibers (synaptic potentiation). However, it seems that frequency and duration of conditioning pulses for synaptic potentiation has not been well established.

The effect of epinephrine on synaptic transmission has long been known. Recording postganglionic action potentials before and after splanchnic nerve stimulation (for 2 minutes at 15/sec), Marrazzi (128) found that increased adrenal secretion inhibits synaptic transmission in the superior cervical ganglion.

In the sympathetic ganglion of the cat, Lundberg (121) observed that even 1 μ g epinephrine intravenously administered caused noticeable inhibition of synaptic transmission and also that epinephrine was about

four times more potent than norepinephrine as an inhibitor of transmission. He suggested that if there could be a situation where adrenal epinephrine secretion is exclusively increased, peripheral sympathetic transmission will be blocked and consequently the overall vasodilator effect of epinephrine will dominate.

On the other hand, Malmejac (124) reported that in the dog small doses of epinephrine (0.5-4.0 $\mu\text{g}/\text{kg}/\text{min}$) increased synaptic transmission, whereas higher doses (12-15 $\mu\text{g}/\text{kg}/\text{min}$) reduced transmission.

External recording from the curarized superior cervical ganglion of turtles and rabbits revealed a complex series of potential changes which are characterized by an initial negative potential followed by a long lasting positive wave and, in many cases, a prolonged late negative phase. With the aid of a number of specific blocking agents, R. E. Eccles and Libet (54) further investigated and interpreted this complex synaptic potential. Later Libet (116) suggested that positive and late negative potentials appear to form part of the response of normal (uncurarized) ganglia and significantly affect excitability. He further suggested possible existence of a slow inhibitory and definitely of a slow excitatory postganglionic response in sympathetic ganglia.

In giant synapse of the squid Hagiwara and Tasaki (82) reported that during prolonged high frequency presynaptic stimulation, synaptic transmission progressively failed while synaptic delay time was not altered.

In frogs, Bazanova et al (12) studied morphological and electrical changes in interneuronal synapses during 2 min stimulation of preganglionic fibers at various frequencies. With stimulation at 20/sec, synaptic conduction was blocked in 100 sec, while at 50/sec and 100/sec the blockade developed in 6.6 sec and 2.4 sec, respectively. They suggested that failure in synaptic transmission is due to inhibition rather than to fatigue since after stimulation at higher frequency, recovery of conduction is faster than after stimulation at low frequency. They also found that changes in structure of the synaptic apparatus associated with stimulation were quite definite, distinct and persisted for minutes or even hours after stimulation. Synaptic transmission was restored within a few seconds after 2 min stimulation. Finally, the maximum height of postganglionic action potentials were obtained by stimulation at 20/sec, while frequencies 5/sec to 10/sec were best for prolonged transmission of nerve impulses.

F. Purpose

From the literature reviewed it seems generally established that in acute experiments, stimulation parameters which can elicit maximum cardiovascular responses are dependent upon types of response and areas of nervous system to be stimulated. For the elicitation of cardiovascular responses from higher levels of the neuroaxis, higher stimulation frequency is required. There is little information on the optimal stimulation parameters for elicitation of cardiovascular responses from spinal cord.

Although there is evidence to show that evoked cardiovascular response never fails in prolongation as long as stimulation parameters are optimal, it has been more frequently reported that cardiovascular responses were rarely prolonged in spite of continuous stimulation. Failure in maintenance of responses, often alluded to as fatigue phenomenon, is rather well known during cerebral cortex and peripheral sympathetic ganglia, but not as clear during hypothalamic, brain stem and spinal cord stimulation. There are many suggested causes for the response decay, but little agreement among workers. There is very little information on the rate of cardiovascular response decay. Furthermore, it is not known whether optimal stimulation parameters for elicitation of maximum responses are also best for maintenance of responses.

Therefore, the first purpose of this dissertation is to find stimulation parameters which elicit maximum cardiovascular responses and those which best maintain responses from three different nervous structures: posterior hypothalamus, high cervical segments of spinal cord and stellate ganglion of cats. Special interest is directed toward finding whether high stimulation frequency is better for the stimulation of the higher central nervous system, and to determining optimal stimulation parameters for stimulation of descending sympathetic pathways in spinal cord.

The second object is to quantitate the rate of cardiovascular response failure in terms of 50% response decay time and to compare response decay rates of the aforementioned areas to each other and with those of cerebral cortex and peripheral sympathetic ganglia.

Thirdly, it is also hoped by comparison of cardiovascular responses to stimulation of the three areas, to obtain evidence on the possible mechanisms of response decay.

CHAPTER II
MATERIAL AND METHODS

A. Stimulation of the Posterior Hypothalamus

Experiments were carried out on 30 cats of either sex weighing 2-3.5 kg. After premedication with 1 mg/kg of phencyclidine hydrochloride (Sernylan), all animals were anesthetized with alpha chloralose at dosage of 30 mg/kg. Positive pressure respiration was maintained by means of a Harvard respirator.

Two points in the left posterior hypothalamus (A:8.0, L:1.5, H:-2.0 and A:8.0, L:1.0, H:-5.0) were stimulated with bipolar needle electrodes which were positioned stereotaxically. These two reactive points were selected by preliminary stimulation tests. The stimulating electrodes were of the concentric bipolar type which consisted of 22 gauge hypodermic needle tubing as a reference electrode with teflon insulated nichrome wire snugly fitted into it as an active electrode. Integrity of insulation was routinely tested.

Stimulation parameters employed included rectangular pulses of 1, 3, 5 msec duration, frequencies of 10, 20, 100 cps and intensity of 2-5 volts (0.3 - 0.8 mA). Duration of stimulation was from 5 to 30 minutes.

Square wave stimulation pulses were delivered from a Grass Model S5 stimulator. Actual stimulating voltage was read from a Hewlett Packard Model 120B oscilloscope. Similarly the instantaneous current of stimulation was ascertained by measuring the IR drop across a 100 ohm resistor with an identical oscilloscope. Mean arterial blood pressure and pulse pressure were recorded from the carotid artery with Statham P23Db transducer and heart rate was registered continuously with an integrating cardiometer (129). All recordings were made on a Grass Model 7 polygraph. Heparin was used to prevent coagulation in the carotid artery catheter. In some cases the vagi were cut in order to test their effect upon the cardiovascular responses.

B. Stimulation of the Spinal Cord before and after Transection

In 10 animals of the hypothalamic stimulation group and in another 36 cats, the cervical spinal cord between C1 and C2 was stimulated with the same type of needle electrodes used in hypothalamic stimulation.

Since heart rate response was rather irregular in the vagi-intact animal, all animals were given 0.8 mg/kg of atropine every two hours for vagal blockade. In order to prevent electrode dislocation due to movement, 0.05 mg/kg of decamethonium bromide (Syncurine) was given to animals every 30 to 60 minutes.

By means of stereotaxic apparatus, the stimulating electrode was positioned over the cervical segments of the spinal cord. Careful attention was paid to keep the longitudinal axis of spinal cord so that the electrode might penetrate the spinal cord perpendicularly. This was achieved by fixing animals to a self-made animal board adjusted to the stereotaxic apparatus.

In 16 of these animals the spinal cord was stimulated before and after complete transection in order to identify descending sympathetic pathways. Transection was made between the medulla oblongata and C1 segment of spinal cord by means of a razor blade clamped into a curved mosquito hemostat. In 10-20 minutes after rapid hemisection, the remaining half of the cord was slowly cut over a period of 10-20 minutes. Throughout the whole transection period sympathetic tonus was increased by the continuous stimulation of cervical segments of the spinal cord. In order to prevent

bleeding the cut area was tamponed with a thin piece of gelform, and, of course, heparin was not used for flushing of the carotid artery catheter until transection was completed.

The same stimulation parameters used in the hypothalamic stimulation were employed. Mean arterial blood pressure, pulse pressure and heart rate were recorded on the same recording system by the same techniques used in hypothalamic stimulation.

At the end of experiments electrolytic lesions were made in the stimulated area by means of a Grass Model LM3 lesion maker. After fixing this segment of the spinal cord with 10% formalin, serial sections were made and stained by the hematoxylin-eosin methods in order to identify position of electrode tip.

C. Stimulation of Stellate Ganglion

In 20 cats the stellate ganglion was stimulated bilaterally with fine wire electrodes. After the chest of the animal was opened in the third intercostal space, both stellate ganglia were freed of connective tissue.

The hooked terminal part of an electrode was placed under the stellate ganglia and the upper part of the electrode was suspended in air

giving a slight tension on the nerve trunk. In order to prevent nervous tissue from drying and to minimize spread of current, the stellate ganglia were embedded in mineral oil. Since the stellate ganglion of cat is so small, it was difficult to maintain the electrode in good contact with nervous tissue.

Every two hours all animals were given 0.8 mg/kg of atropine for vagal blockade. Stellate ganglia were stimulated with rectangular pulses of 1, 5, 10 msec duration at frequencies of 5, 10, 20, 100 cps. Stimulation intensity was in the range of 2 - 5 volts (0.3 - 0.8 mA). Mean arterial pressure, pulse pressure and heart rate were recorded by the same technique used in the stimulation of the hypothalamus and spinal cord.

D. Data Analysis

The magnitude of responses was represented first by maximum peak in initial phase of responses. In order to compare maintenance or decay rate of response, 50% response decay time was calculated as the time required for response to fall to 50% of the maximum elevation. To eliminate the effect of previous stimulation, succeeding stimulations were delayed for at least half of the previous stimulation period.

CHAPTER III

EXPERIMENTAL RESULTS

A. Stimulation of Posterior Hypothalamus

The two areas stimulated (A: 8.0, L: 1.5, H: -1.0 to -3.0; A: 8.0, L: 1.0, H: -4.0 to -6.0) in this experiment are not the only, but are the most reactive, points in the posterior hypothalamus for the elicitation of pressor and cardioaccelerator responses. Stereotaxic coordinates of these two spots extend horizontally from -1.0 to -3.0 mm and from -4.0 to -6.0, respectively. This does not imply that every point within these ranges are equipotent in eliciting responses, but rather that active points are scattered throughout.

For convenience of description one spot (H: -1.0 through -3.0) will be called the dorsal spot and the other (H: -4.0 through -6.0) the ventral spot. According to the atlas of Snider and Niemer (167) the ventral area coincides with the location of the medial mammillary nucleus.

Three different stimulation frequencies (10, 20 and 100 cps) were selected for the following reasons. The stimulation frequency of 10 cps is

known to be in the upper range of physiological discharge rate in which synaptic transmission rarely fails in peripheral sympathetic ganglia. The frequency of 100 cps is generally considered to be optimal frequency for stimulation of the hypothalamus and medulla oblongata. A frequency of 20 cps is between and ultimately proved to be optimal for the stimulation of spinal cord.

Typical pressor and cardioaccelerator responses to stimulation with various parameter sets are shown in figure 1 and 2. Table I is a summary of data from the two test areas in the posterior hypothalamus.

The intensity of current at which responses reach plateau was not determined, but it was clear that magnitude of responses generally increased with increments in current intensity, whereas maintenance of responses was not affected within ranges employed in this experiment. The largest pressor response was obtained with 100 cps -- 1 msec, and 20 cps -- 3 msec from both the ventral and the dorsal spots in the hypothalamus. While employing parameters of 20 cps -- 1 msec and 10 cps -- 5 msec, pressor responses were approximately half those elicited with 100 cps -- 1 msec and 20 cps -- 3 msec. However, even with 20 cps -- 1 msec, large responses were obtained and well maintained if intensity of stimulating

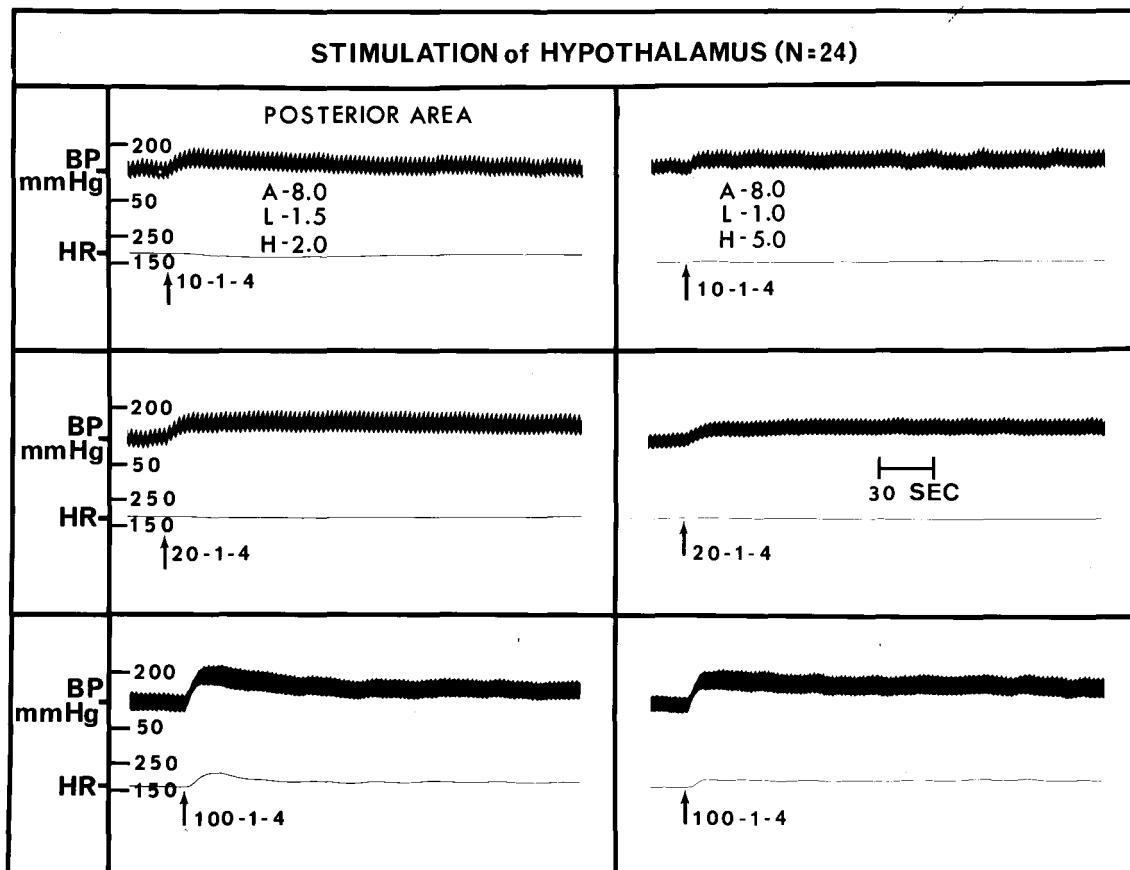


Figure 1

Pressor and cardiac rate responses to stimulation of two spots in the posterior hypothalamus (A: 8.0, L: 1.5, H: -2.0 and A: 8.0, L: 1.0, H: -5.0) with 10 cps, 1 msec, 4 volts (c. 0.6 mA); 20 cps, 1 msec, 4 volts (c. 0.6 mA) and 100 cps, 1 msec, 4 volts (c. 0.6 mA).

STIMULATION of HYPOTHALAMUS

A:8.0, L:1.5, H:-2.0

A:8.0, L:1.0, H:-5.0

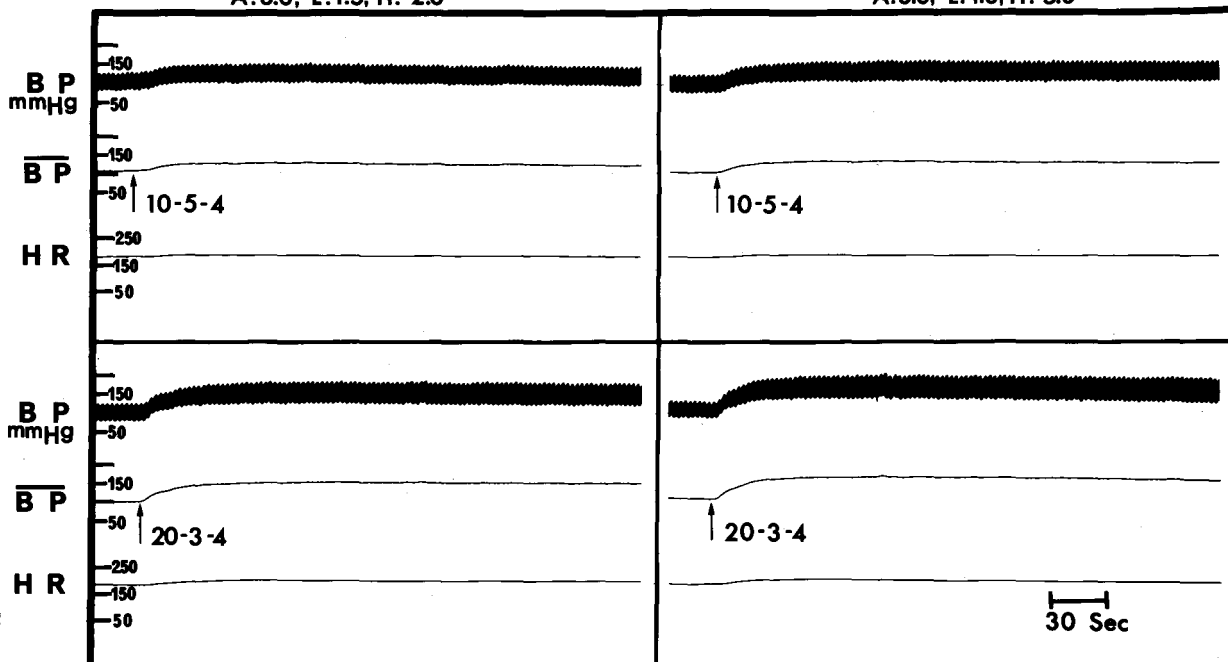


Figure 2

Pulse pressure, mean arterial pressure and cardiac rate changes elicited by the stimulation of two spots in the posterior hypothalamus with 10 cps, 5 msec, 4 volts (c. 0.6 mA) and 20 cps, 3 msec, 4 volts (c. 0.6 mA).

TABLE I

CHANGES IN MEAN ARTERIAL PRESSURE, HEART RATE, AND 50% RESPONSE DECAY TIMES DURING
STIMULATION OF TWO POINTS IN THE POSTERIOR HYPOTHALAMUS
WITH VARIOUS STIMULATION PARAMETERS

LOCATION	PARAMETER cps-msec-volt (mA)	ΔBP_{+++} (MEAN \pm SE) ⁺⁺ mm Hg	50% RESP. DECAY (MEAN \pm SE) sec	ΔHR_{+++} (MEAN \pm SE) Beat/min	50% RESP. DECAY (MEAN \pm SE) sec	NO. OF ANIMALS	NO. OF STIM.
Left Posterior A:8.0 L:1.5 H:-1.0 to -3.0	100-1-3.6 (c.0.55)	52 \pm 2.8	280 \pm 29	33 \pm 3.6	350 \pm 67	25	66
	20-3-4.2 (c.0.6)	46 \pm 3.0	720 \pm 77	25 \pm 3.3	920 \pm 120	9	35
	20-1-4.1 (c.0.6)	28 \pm 6.9	700 \pm 148	-----	-----	6	10
	10-5-4.5 (c.0.65)	27 \pm 2.3	630 \pm 90	23 \pm 8.0	790 \pm 150	5	10
	10-1-4.1 (c.0.6)	16 \pm 5.8	-----	-----	-----	2	5
A:8.0 L:1.0 H:-4.0 to -6.0	100-1-3.8 (c.0.6)	50 \pm 2.2	280 \pm 38	30 \pm 2.9	380 \pm 74	18	50
	20-3-4.6 (c.0.65)	55 \pm 5.3	600 \pm 58	32 \pm 3.6	1420 \pm 163	4	19
	20-1-4.7 (c.0.65)	25 \pm 8.2	670 \pm 108	-----	-----	7	14
	10-5-4.5 (c.0.65)	32 \pm 8.2	550 \pm 150	28 \pm 4.8	1290 \pm 400	3	5

†c = approximate
 ††SE = standard error
 ††† ΔBP = change in the mean arterial pressure
 †††† ΔHR = change in the heart rate

current was greatly increased (to 8 v; 1.2 mA). The smallest response was elicited by stimulation with 10 cps -- 1 msec. Sometimes, responses were undetectable and rarely even slightly negative responses were obtained.

While using constant stimulation frequency and intensity, response generally increased with increased duration of pulses. However, response reached plateau with a pulse duration of 5 msec at stimulation frequency of 10 cps and with duration of 3 msec and 1 msec at 20 cps and 100 cps, respectively.

The pressor response was maintained for the shortest period while employing parameters of 100 cps -- 1 msec, the 50% response decay time (50% RDT) being around 300 seconds. In other words, blood pressure fell linearly or sometimes exponentially to half of the maximum response in approximately 5 minutes. Of course, this does not mean that by the stimulation of the posterior hypothalamus with 100 cps -- 1 msec pressor response can never be prolonged beyond 5 to 10 minutes.

With the remainder of the parameter sets (20 cps -- 3 msec; 20 cps -- 1 msec; 10 cps -- 5 msec), pressor responses fell more slowly and at almost the same decay rate with 50% RDT of 600 - 700 seconds.

Pressor responses were so small with 10 cps -- 1 msec, that it seemed impractical to calculate 50% RDT. There was no difference between responses from the ventral and dorsal spots of the posterior hypothalamus.

In a majority of instances, pressor responses were accompanied by heart rate changes. The cardioaccelerator responses were generally comparable while employing parameters of 100 cps -- 1 msec; 20 cps -- 3 msec; 10 cps -- 5 msec. With 10 cps -- 1 msec cardiac rate responses were so small that calculation was impractical. The 50% response decay time of accelerator responses were also longer with 20 cps -- 3 msec and 10 cps -- 5 msec and shortest with 100 cps -- 1 msec. Generally the cardiac accelerator response was better maintained than was the pressor response and those from the ventral spot sustained a little longer than those from the dorsal spot. Heart rate changes were more prominent during stimulation in the right hypothalamus.

The pressor response was not different when the vagi were transected, whereas the heart rate response was frequently irregular when the vagi remained intact.

In several experiments the hypothalamus was stimulated in conscious cats by means of chronically implanted electrodes, in acutely

adrenalectomized cats and in animals whose carotid sinus nerve was bilaterally ablated in addition to vagotomy. However, pressor and cardiac accelerator responses of these animals did not appear to be significantly different from those of intact animals.

Generally the pressor responses reached their maximum peak more rapidly during higher frequency stimulation. With repeated stimulation, the magnitude of successive responses tended to fall progressively unless enough time for recovery was allowed between stimulation. In many instances the first response was larger than successive ones even when enough time was given for successive stimulation after blood pressure and heart rate returned to prestimulation levels. In many cases negative rebound in blood pressure and cardiac rate occurred after cessation of stimulation (successive autonomic induction), and the negative rebound in heart rate usually returned to base line more promptly than did the pressor response.

After termination of stimulation, blood pressure returned to base line showing two different patterns. The first was rather rapid (less than 1 minute) and looked like the reverse time course of rising pressure at the beginning of stimulation showing that there was little or no after discharge from the hypothalamus or vasomotor center. In a second pattern, blood

pressure returned to base line in 2 to 5 minutes or more suggesting that either sympathetic inhibitory system or the vagal inhibitory system were activated.

It has also been often observed that whenever the posterior hypothalamus was stimulated with high intensity currents, cardiac arrhythmias appeared which were not completely abolished by vagotomy or atropinization.

Occasionally when stimulation with 100 cps -- 1 msec was prolonged (more than 10 minutes), initially elevated blood pressure fell below the prestimulation level suggesting either that the depressor system was involved or that tonic sympathetic activity was decreased. This kind of depressor response was also observed when the same spots, which previously had showed pressor responses, were stimulated repeatedly for long periods without adequate time for recovery.

It was also a common observation in both anesthetized and conscious animals that when pressor response returned to prestimulation level during a prolonged stimulation of the posterior hypothalamus (with 100 cps -- 1 msec), comparable responses were again producible by an increase in stimulation intensity. It appeared that recovery of response to base line is not a complete indication of recovery of excitability of stimulated nervous

tissues and its conducting system. When one spot did not respond to stimuli after a prolonged stimulation, full fresh responses were obtainable if the stimulating electrode was moved either horizontally or laterally for only a short distance. Further, it was observed that when the stimulating electrode was not in the most reactive area or when stimulating current was very weak, responses tended to show a small peak response which persisted for only a few seconds.

B. Stimulation of the Spinal Cord

In cats weighing from 2 to 3.5 kg, the long and short diameters of high cervical segments of spinal cord rarely exceeded 12 mm and 10 mm, respectively.

Before spinal transection cardiovascular responses were elicited by electrical stimulation of numerous points in both the white and the grey matter of the C1-C2 segments of the cord. However, after total transection between the medulla oblongata and the first cervical segment of the spinal cord, there were only two points which consistently showed good pressor and cardioaccelerator responses to electrical stimulation (figures 3 and 4). Therefore, these two points were considered to be sites of

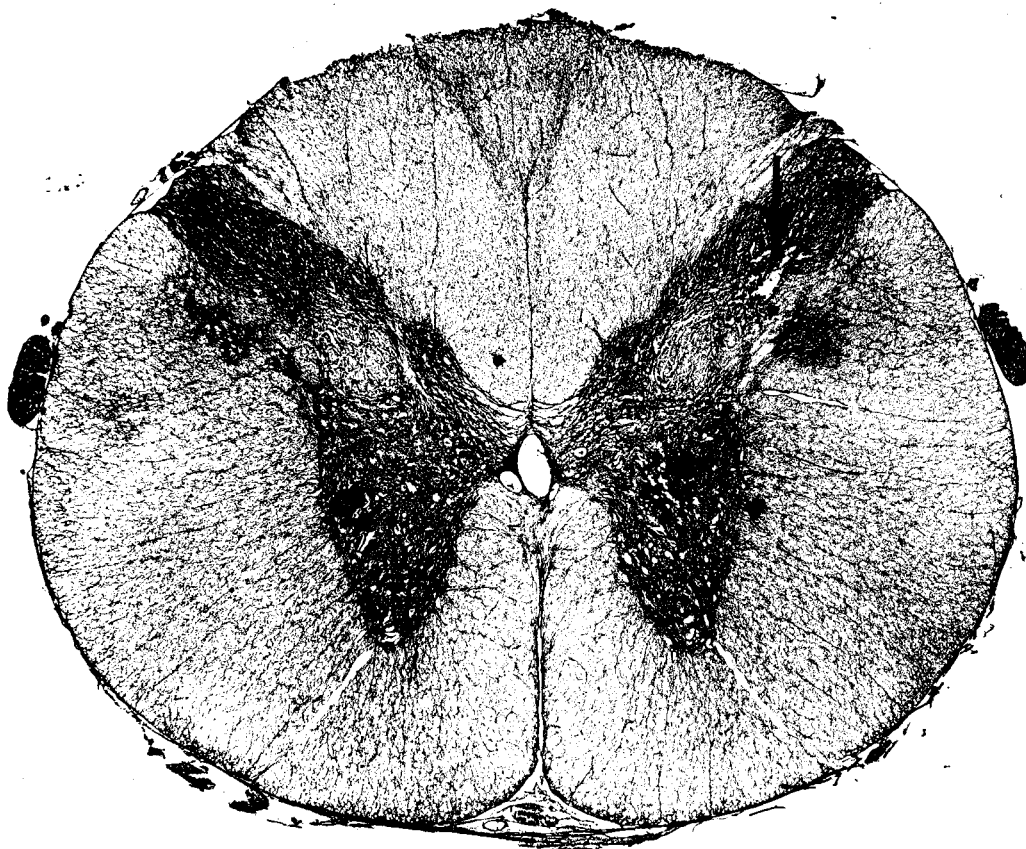


Figure 3

A 17 X photographic enlargement of cross-section of cervical spinal cord between C1 and C2. The position of an electrode track is shown at the dorsal point which is 2-3 mm left of the medial line and at a depth of 0.3 - 1.0 mm from the dorsal surface.

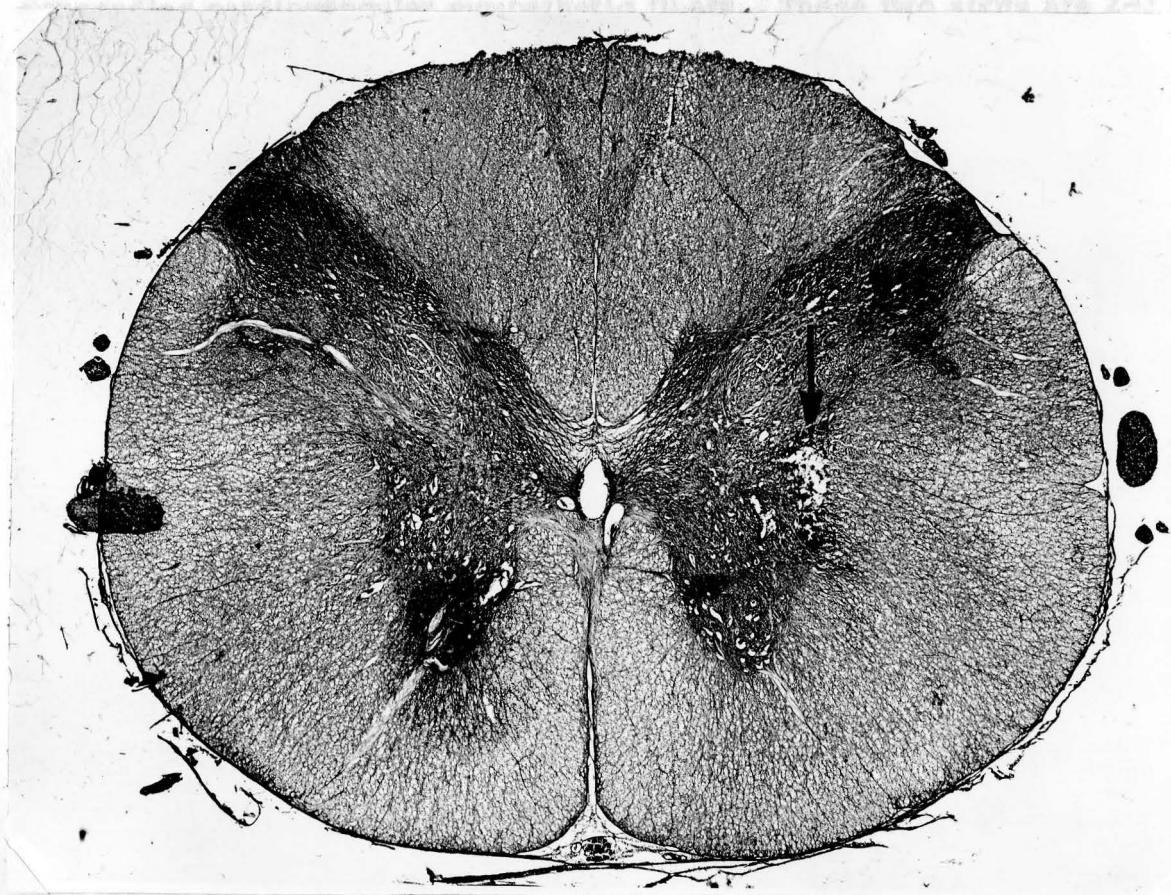


Figure 4

A 17 X photographic enlargement of cross-section of cervical spinal cord between C1 and C2. The position of an electrode track is shown at the ventral point which is 2-3 mm left of the medial line and at a depth of 2.5 - 3.5 mm from the dorsal surface.

descending cardiovascular sympathetic fibers. These two spots are 2-3 mm left from medial line and at a depth of 0.3 - 1.0 mm and 2.5 - 3.5 mm, respectively from the dorsal surface of the spinal cord.

For the convenience of description one (depth 0.3 - 1.0 mm) will be called the dorsal spot and the other (depth 2.5 - 3.5 mm) the ventral spot. Typical responses to stimulation at each different frequency are shown in figure 5. Results of stimulation in the dorsal and the ventral spots before and after transection are tabulated in Tables II and III.

Generally, responses from the spinal cord were larger than those from the hypothalamus probably because neuronal units are more densely packed in the spinal cord or because the intensity threshold of nerve fibers is lower. Before spinal transection, pressor responses from both dorsal and ventral spots were larger with stimulation parameters of 100 cps -- 1 msec; 20 cps -- 5 msec and 20 cps -- 3 msec than with 20 cps -- 1 msec; 10 cps -- 5 msec and 10 cps -- 1 msec. Differing from the hypothalamus, even 10 cps -- 1 msec and 10 cps -- 5 msec were also very effective in the elicitation of pressor responses. After transection, however, responses were remarkably decreased especially with 20 cps -- 1 msec, 10 cps -- 5 msec and 10 cps -- 1 msec despite increase in stimulation

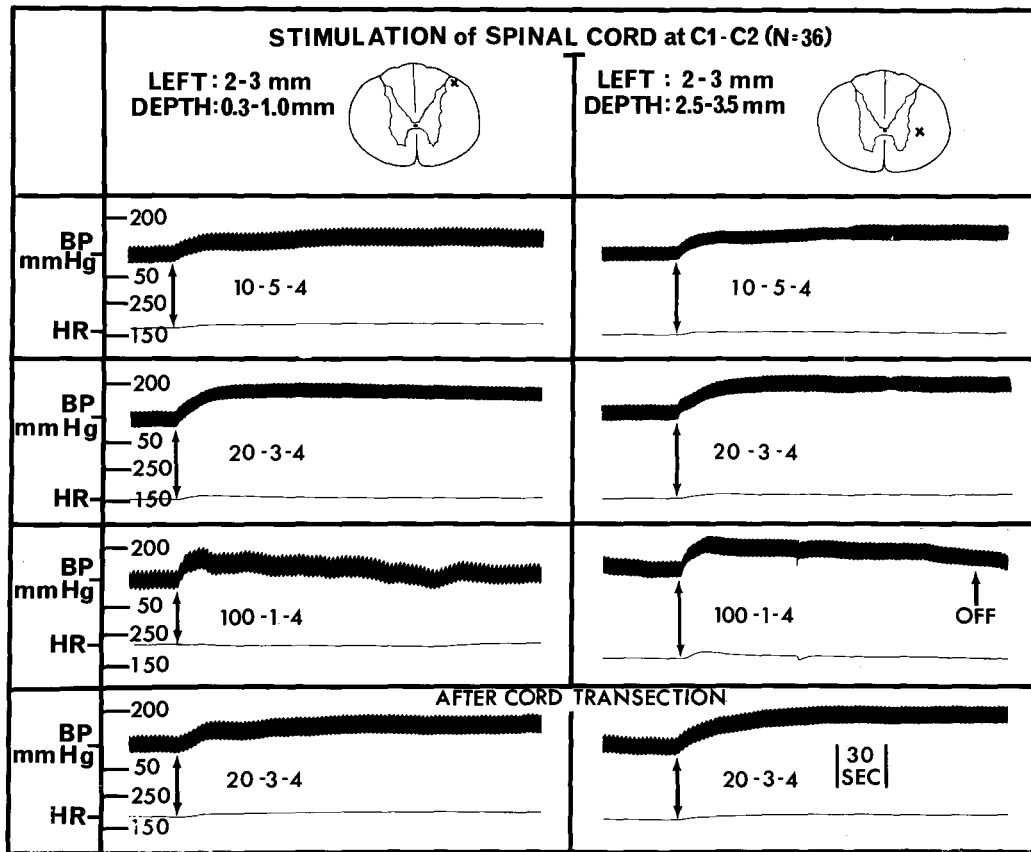


Figure 5

Pressor and cardiac rate responses to stimulation of two spots in the cervical segments of spinal cord (C1-C2, Left 2-3 mm, Depth 0.3-1.0 mm and C1-C2, Left 2-3 mm, Depth 2.5-3.5 mm) with 10 cps, 5 msec, 4 volts (c. 0.6 mA), 20 cps, 3 msec, 4 volts (c. 0.6 mA) and 100 cps, 1 msec, 4 volts (c. 0.6 mA) and responses from two spots during stimulation with 20 cps, 3 msec, 4 volts (c. 0.6 mA) after transection between medulla and the first cervical segment of spinal cord.

TABLE II

CHANGES IN MEAN ARTERIAL PRESSURE, HEART RATE, 50% RESPONSE DECAY TIMES DURING STIMULATION OF THE DORSAL SPOT IN THE CERVICAL SPINAL CORD (DEPTH 0.3-1.0mm) OF THE ATROPINIZED CATS WITH VARIOUS STIMULATION PARAMETERS

LOCATION Left: 2-3mm Depth: 0.3-1.0mm	PARAMETER cps-msec-volt(mA)	ΔBP_{+++} (MEAN \pm SE) $_{++}$ mm Hg	50% RESP. DECAY (MEAN \pm SE) sec	ΔHR_{++++} (MEAN \pm SE) Beat/min	NO. OF ANIMALS	NO. OF STIM.
BEFORE TRANSECTION	100-1-2.0 (c.0.3)	74 \pm 4.4	290 \pm 38	20 \pm 2.5	15	27
	20-5-2.3 (c.0.3)	70 \pm 10.0	900 \pm 359	19 \pm 2.2	5	7
	20-3-2.5 (c.0.3)	88 \pm 12.0	860 \pm 174	18 \pm 2.6	8	10
	20-1-2.1 (c.0.3)	60 \pm 4.8	800 \pm 203	19 \pm 4.0	13	18
	10-5-2.5 (c.0.3)	65 \pm 8.1	810 \pm 127	13 \pm 1.0	8	9
	10-1-2.2 (c.0.3)	58 \pm 7.1	960 \pm 223	17 \pm 3.2	9	13
AFTER TRANSECTION	100-1-4.2 (c.0.6)	58 \pm 8.8	150 \pm 26	22 \pm 5.3	8	10
	20-5-4.3 (c.0.6)	66 \pm 5.0	530 \pm 104	17 \pm 1.8	10	18
	20-3-4.4 (c.0.6)	58 \pm 6.1	620 \pm 110	19 \pm 2.5	7	14
	20-1-4.7 (c.0.65)	36 \pm 4.3	680 \pm 104	17 \pm 1.6	6	6
	10-5-4.2 (c.0.6)	38 \pm 10.0	440 \pm 102	10 \pm 1.0	6	7
	10-1-5.0 (c.0.65)	47 \pm 27.0	500 \pm 16	-----	3	3

$\dagger c$ = approximate
 $\dagger\dagger SE$ = standard error
 $\dagger\dagger\dagger \Delta BP$ = change in mean arterial pressure
 $\dagger\dagger\dagger\dagger \Delta HR$ = change in the heart rate

TABLE III

CHANGES IN MEAN ARTERIAL PRESSURE, HEART RATE, AND 50% RESPONSE DECAY TIMES DURING STIMULATION OF THE VENTRAL SPOT IN THE CERVICAL SPINAL CORD (DEPTH 2.5-3.5mm) OF THE ATROPINIZED CATS WITH VARIOUS STIMULATION PARAMETERS

LOCATION Left: 2-3mm Depth: 2.5-3.5mm	PARAMETER cps-msec-volt(mA)	ΔBP_{+++} (MEAN \pm SE) $_{++}$ mm Hg	50% RESP. DECAY (MEAN \pm SE) sec	ΔHR_{++++} (MEAN \pm SE) Beat/min	NO. OF ANIMALS	NO. OF STIM.
BEFORE TRANSECTION	100-1-2.6 (c \dagger 0.35)	81 \pm 4.3	310 \pm 33	23 \pm 2.4	25	41
	20-5-2.6 (c.0.35)	73 \pm 10.0	1120 \pm 219	-----	4	6
	20-3-2.9 (c.0.35)	85 \pm 7.5	2240 \pm 316	23 \pm 5.0	10	12
	20-1-2.6 (c.0.35)	71 \pm 4.1	1110 \pm 90	22 \pm 3.9	20	40
	10-5-2.8 (c.0.35)	65 \pm 6.5	1150 \pm 170	15 \pm 3.3	9	15
	10-1-2.9 (c.0.35)	64 \pm 4.4	1300 \pm 149	14 \pm 2.4	15	27
AFTER TRANSECTION	100-1-4.4 (c.0.6)	63 \pm 11.0	140 \pm 44	26 \pm 5.5	5	9
	20-5-4.5 (c.0.6)	81 \pm 6.5	560 \pm 96	25 \pm 2.9	5	16
	20-3-4.6 (c.0.6)	80 \pm 6.5	730 \pm 134	25 \pm 2.0	6	22
	20-1-5.0 (c.0.65)	49 \pm 5.5	550 \pm 139	18 \pm 2.7	6	12
	10-5-5.0 (c.0.65)	41 \pm 5.8	480 \pm 114	20 \pm 1.9	5	11
	10-1-5.0 (c.0.65)	38 \pm 6.9	560 \pm 133	19 \pm 2.9	4	7

$\dagger c$ = approximate
 $_{++}SE$ = standard error
 $_{+++}\Delta BP$ = change in mean arterial pressure
 $_{++++}\Delta HR$ = change in the heart rate

intensity. On the other hand, control blood pressure dropped, on an average, from 110 mm Hg to 80 mm Hg.

There was no difference in magnitude between responses from the dorsal spot and from the ventral spot. With 100 cps -- 1 msec 50% RDT of both dorsal and ventral spots was the shortest, being around 300 sec which is similar to that obtained from the hypothalamus. However, with the other parameter sets, 50% RDT ranged approximately from 800 sec to 1000 sec in the dorsal spots and from 1100 sec to 2200 sec in the ventral spots.

In two cases the ventral spot was stimulated with 20 cps -- 3 msec for more than one hour resulting in several hours for the 50% RDT. In spinal animals responses were less well maintained, 50% RDT being reduced to almost half of those obtained before transection.

Generally responses were far better maintained and excitability recovered faster following stimulation of the spinal cord than from hypothalamic stimulation. As in hypothalamic stimulations, when the spinal cord was stimulated at frequencies above 30 cps, responses fell almost as rapidly as those elicited by frequency of 100 cps. With other parameters held constant, responses generally increased with stimulation

intensity and with pulse duration. At constant intensity, however, responses seemed to reach a maximum plateau during cord stimulation with a pulse duration of 5 msec at 10 cps and with a pulse duration of 3 msec at 20 cps.

The 50% response decay time was not affected by activation of the vagal system, whereas heart rate responses generally were affected. However, bradycardia did not seem to be solely due to vagal influences since sometimes it remained even after vagal blockade by atropine and since there was little correspondence between the degree of increased blood pressure and cardiac slowing.

Heart rate responses were observed in approximately 75% of cases while in 25% there was no detectable change. Heart rate responses were also generally larger with higher stimulation frequency and with longer pulse durations, both before and after transection. It was also a common observation that more prominent heart rate responses were elicited by the stimulation of the right half of the spinal cord.

After termination of stimulation, blood pressure returned to pre-stimulation level rather rapidly in 66% of the cases and slowly in the rest. In approximately 40% of the experiments, blood pressure and heart rate fell

below control levels before recovery, but not as profoundly as during hypothalamic stimulation. Cardiac arrhythmia was not observed as commonly as during hypothalamic stimulation.

C. Stimulation of the Stellate Ganglia

During stellate ganglion stimulation it is clear that both pre-ganglionic and postganglionic fibers are excited, even though the percentage of preganglionic and postganglionic fibers is not known precisely. Typical responses to bilateral stimulation of the stellate ganglia at each different frequency are shown in figure 6, and all the results are tabulated and compared in Table IV.

The largest pressor response was observed during the stimulation of both stellate ganglia at 20 cps. Up to stimulation frequency of 20 cps, the magnitude of pressor response generally increased with frequency, whereas at 100 cps, a characteristic response was not much larger than that obtained during stimulation at 5 cps.

Within the stimulation frequency range from 5 cps to 20 cps, both pressor and cardiac rate responses reached a plateau with pulse duration of 5 msec. Within the stimulation intensity range employed in these experiments (2-5 volts), responses also increased with stimulation intensity.

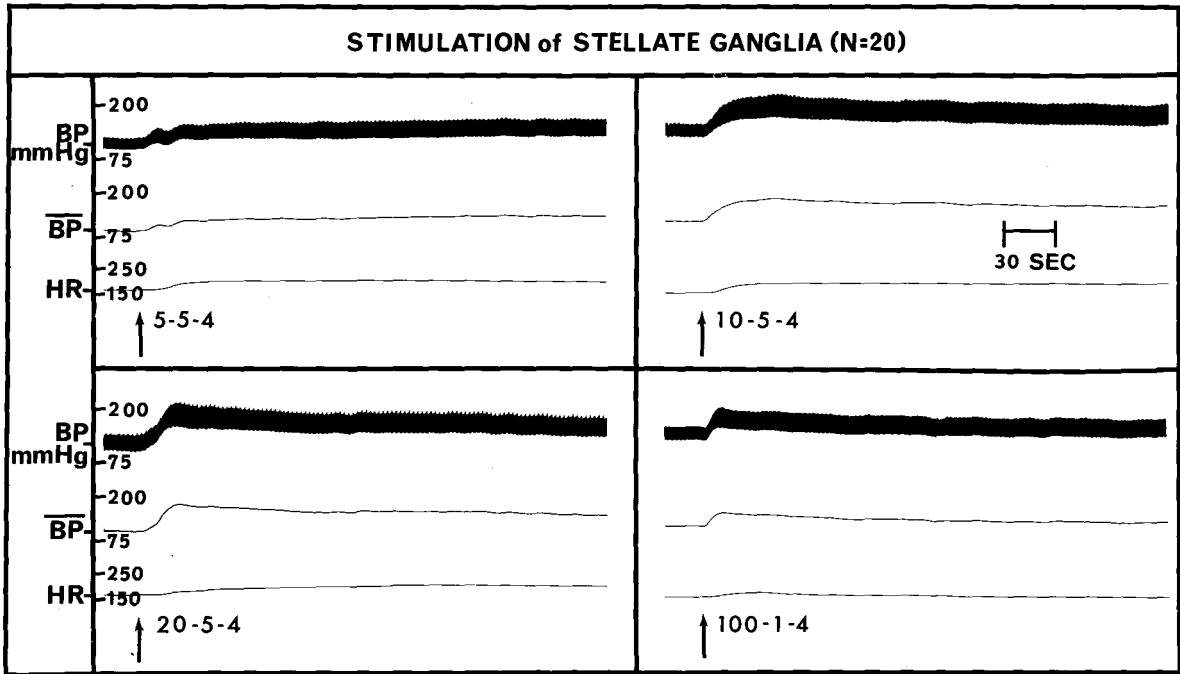


Figure 6

Pulse pressure, mean arterial pressure and cardiac rate changes elicited by bilateral stimulation of the stellate ganglia with 5 cps, 5 msec, 4 volts (c. 0.6 mA), 10 cps, 5 msec, 4 volts (c. 0.6 mA), 20 cps, 5 msec, 4 volts (c. 0.6 mA) and 100 cps, 1 msec, 4 volts (c. 0.6 mA).

TABLE IV

CHANGES IN MEAN ARTERIAL PRESSURE, HEART RATE, AND 50% RESPONSE DECAY TIMES DURING BILATERAL STIMULATION OF THE STELLATE GANGLIA OF THE ATROPINIZED CATS WITH VARIOUS STIMULATION PARAMETERS

PARAMETER cps-msec-volt(mA)	ΔBP_{+++} (MEAN \pm SE) $_{++}$ mm Hg	50% RESP. DECAY (MEAN \pm SE) sec	ΔHR_{++++} (MEAN \pm SE) Beat/min	50% RESP. DECAY (MEAN \pm SE) sec	NO. OF ANIMALS	NO. OF STIM.
100-1-3.6 (c. [†] 0.6)	36 \pm 4.2	240 \pm 38	29 \pm 5.7	460 \pm 220	7	10
20-10-4.8 (c.0.7)	58 \pm 4.5	200 \pm 98	45 \pm 16.0	330 \pm 180	2	3
20-5-4.3 (c.0.65)	60 \pm 4.4	200 \pm 20	48 \pm 4.4	870 \pm 91	7	14
10-10-4.3 (c.0.65)	47 \pm 2.1	580 \pm 61	52 \pm 3.6	1540 \pm 195	10	30
10-5-3.8 (c.0.6)	49 \pm 2.3	710 \pm 73	43 \pm 3.7	1850 \pm 140	11	30
10-1-3.4 (c.0.6)	43 \pm 5.4	210 \pm 35	25 \pm 9.6	650 \pm 250	2	4
5-10-4.3 (c.0.65)	37 \pm 2.8	630 \pm 93	46 \pm 6.0	1830 \pm 310	9	14
5-5-4.0 (c.0.65)	36 \pm 3.3	620 \pm 99	40 \pm 7.1	1590 \pm 240	8	10

†c = approximate
 ++SE = standard error
 +++ ΔBP = change in the mean arterial pressure
 ++++ ΔHR = change in the heart rate

Remarkably similar heart rate responses were obtained during stimulation of both stellate ganglia at 5 cps, 10 cps or 20 cps. Heart rate response often reached a consistent plateau at stimulation frequency as low as 5 cps. On the other hand, with 100 cps -- 1 msec, heart rate response was extremely small, thus indicating that high frequencies are relatively ineffective.

The pressor response was better sustained with stimulation frequency of 10 cps and 5 cps (except with 10 cps -- 1 msec), the 50% response decay time being approximately 600-700 sec. During stellate ganglion stimulation, pressor responses to stimulation at 20 cps declined as rapidly as those at 100 cps, whereas in spinal cord and hypothalamic stimulation, comparable responses declined rapidly only at frequencies above 30 cps. The 50% response decay time of pressor responses to stimulation of the stellate ganglion at 20 cps and 100 cps was approximately 200 sec which is actually shorter than that obtained from the spinal cord and hypothalamus.

It was also observed that during stimulation of the stellate ganglia, pressor responses elicited by frequencies between 20 cps and 100 cps fell almost as fast as those induced by 100 cps and 20 cps

stimulation. However, even during stimulation at frequency as low as 10 cps, blood pressure fell as fast as that at 100 cps when pulse duration was 1 msec. Thus it appears that if pulse duration is in the order of 1 msec, responses are small and decay is rapid.

Regardless of stimulation parameters, cardiac rate response generally was maintained better than pressor response. With stimulation frequency of 5 cps and 10 cps, the 50% response decay times for heart rate were approximately 1500 - 1800 sec, whereas they varied from 300 to 900 sec with stimulation frequencies of 20 cps and 100 cps. On the other hand, the 50% response decay time for heart rate to stimulation of stellate ganglia with 10 cps -- 1 msec -- 4 volts was in the range of 600 - 700 seconds.

In the animals whose vagus nerves were not blocked by atropine, heart rate responses were very irregular, sometimes biphasic, and pressor responses fell faster than in vagal blocked animals. After termination of stimulation blood pressure returned to prestimulation level rather rapidly in a majority of cases although this was not invariable and sometimes it recovered quite slowly. Occasionally blood pressure dropped slightly below control level before complete recovery, but this rarely compared

with those changes observed during hypothalamic and spinal cord stimulation. Cardiac arrhythmia was also observed during stimulation of stellate ganglia both before and after atropinization.

Figure 7 illustrates typical responses to stimulation of the nervous system at each of three levels by the optimal stimulation parameters from the respect of both magnitude and maintenance of response.

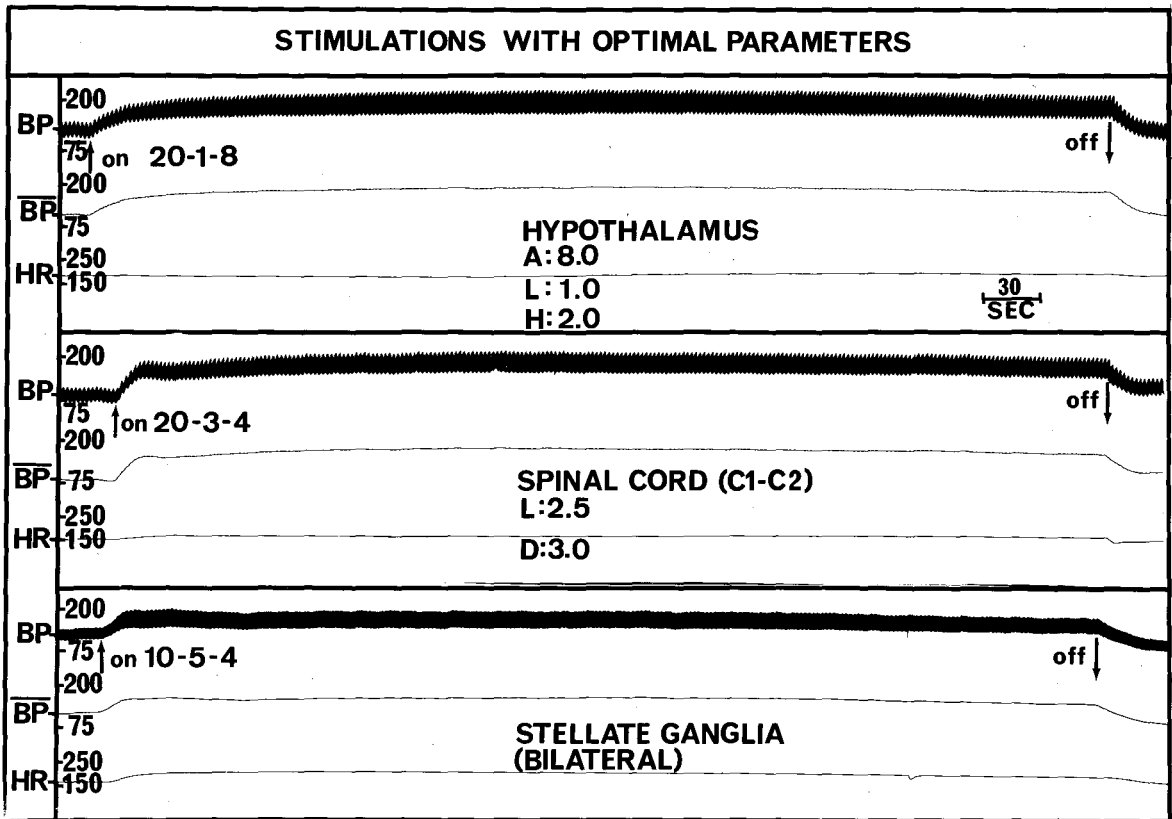


Figure 7

Ten-minute stimulation of the nervous system at three levels.

- Upper Panel: Pulse pressure, mean arterial pressure and cardiac rate changes elicited by stimulation of the posterior hypothalamus -- 20 cps, 1 msec, 8 volts (c. 1.2 mA)
- Middle Panel: Responses to stimulation of the cervical spinal cord with 20 cps, 3 msec, 4 volts (c. 0.6 mA)
- Lower Panel: Responses to bilateral stimulation of the stellate ganglia with 10 cps, 5 msec, 4 volts (c. 0.6 mA)

CHAPTER IV

DISCUSSION AND CONCLUSIONS

A. Stimulation Parameters and Magnitude of Cardiovascular Responses from Three Levels of the Nervous System

From both ventral and dorsal spots in the posterior hypothalamus, the largest pressor responses were induced by stimulation, at constant intensity, with either 100 cps -- 1 msec or 20 cps -- 3 msec. Also, 20 cps -- 1 msec was very effective, but only when stimulation intensity was considerably raised.

Two spots in the cervical spinal cord which showed cardiovascular responses to stimulation after complete cord transection are believed to mark descending autonomic fibers. The ventral spot appears to coincide with tracts which Foerster found in man while the dorsal spot seems to be that which Kerr and Alexander described in low cervical and high thoracic segments in animals.

Large pressor responses were obtained from both dorsal and ventral spots of the spinal cord, using all parameter sets described. However,

parameter sets of 20 cps -- 3 msec; 20 cps -- 5 msec and 100 cps -- 1 msec seemed more effective than others. Moreover, after spinal transection, strikingly greater responses were elicited with these parameter sets than with other parameter sets. During stimulation of the stellate ganglia, pressor responses reached a consistent plateau with 10 cps -- 5 msec, while the largest response was obtained with 20 cps -- 5 msec. Though no attempt was made to determine voltage (or current) levels at which the pressor response reached a plateau, it was generally increased as stimulation intensity was raised, probably due to an increase in the number of excited neuronal units. In order to elicit a given magnitude of pressor response by spinal cord stimulation, an intensity of less than half that required for hypothalamic and stellate ganglion stimulation was required. However, following spinal cord transection, a much higher stimulating voltage was necessary, comparable to the voltage required to stimulate the hypothalamus and stellate ganglion.

The larger pressor responses from spinal cord stimulation appear to be due to greater density of neuronal units in descending sympathetic pathways and perhaps to lower excitation thresholds for these fibers. The marked depression in neuronal excitability in spinal animals might be

explained by varying degrees of anoxia, or decreased metabolism resulting from transection since conduction of impulses along nerve fibers and across synapses are known to be greatly affected by anoxia. Removal of facilitatory effects from higher levels of the central nervous system might also be responsible, considering that control systemic blood pressure was also decreased by an average of 30 mm Hg.

With constant stimulation intensity, pressor responses from the hypothalamus and spinal cord attained a plateau with pulse durations of 1 msec at stimulation frequency of 100 cps, and with 3 msec, and 5 msec durations at frequencies of 20 cps and 10 cps, respectively. Furthermore, in additional unreported experiments employing frequencies between 50 and 70 cps, I have observed that a maximum response may be elicited by pulses having a duration of 2 msec. On the other hand, pressor responses from the stellate ganglion did not increase further when pulse duration was raised above 5 msec with stimulation frequencies below 20 cps.

Theoretically it is possible that an increase in excited neuronal units within the hypothalamus and spinal cord can alter impulse frequencies in postganglionic fibers by spatial summation at synapses.

One response characteristic of stellate ganglion excitation is that pressor responses obtained by high frequency stimulation are smaller

than those elicited with low frequency stimulation. The pressor responses generally reached plateau levels at frequencies of around 20 cps and started to decline at frequencies between 50 and 80 cps. A comparable frequency-response relationship has been reported in vasoconstrictions (32).

It also has been shown that the amount of transmitter released at nerve endings, and the height of postganglionic action potentials, are decreased during high frequency stimulations (27, 25, 12). However, it is not clear whether this diminution in transmitter results from decreased quantal size or from decreased number of preganglionic fibers.

During acute stimulation, parameters of 100 cps -- 1 msec are one of the most effective for elicitation of cardiovascular responses from excitation of the hypothalamus and spinal cord. This might be explained by the assumption that impulse frequency is reduced at synapses in the intermediolateral column of the spinal cord.

The present experiment suggests the possibility that impulse frequency is reduced to approximately one half across the synapses in the spinal cord. Responses were best maintained with frequencies up to 20 cps in hypothalamic and spinal cord stimulation, whereas frequencies up to 10 cps were best for prolonged responses from the stellate ganglion.

In all three levels of the nervous system, heart rate responses were generally more prominent during stimulation of the right side. There was no marked difference in cardiac rate response to different stimulation parameter sets suggesting that excitation threshold for heart rate response may be rather low. The low threshold for cardiac rate response might be explained by an unusually dense sympathetic innervation to the SA node.

Results of the present experiment indicate that the magnitude of pressor and heart rate responses are affected, within certain ranges, by stimulation frequency, intensity and pulse duration. From studies of the influence of stimulation frequency on responses elicited by stimulation of the hypothalamus, Hare and Geohegan (83) concluded that a frequency of 200 cps was optimal for the largest response. However, it should be noted that in their study pulse duration was not varied. Studying vasomotor effects of electrical stimulation of the cervical sympathetic nerve in the rabbit, Girling (75) reported that stimulation frequencies below 0.5 cps or above 60 cps were ineffective.

These data quoted in a textbook are apt to give an impression that nerves to blood vessels can never be excited by stimulation frequencies above 60 cps. Girling employed pulse duration of 12 msec with intensity

of 0.5 volts. It is probable that if he had employed higher intensity of stimulation with shorter pulse duration (5 msec), he would have obtained responses at much higher frequencies.

The problem of determination of optimal stimulation parameters may lie in the selection of one which causes little tissue injury. Since tissue injury caused by stimulation appears to be related also to total energy dissipated in unit time, it is important to choose a parametric set which involves a minimum total energy. Therefore, it may be concluded that for an acute stimulation experiment 100 cps -- 1 msec; 20 cps -- 3 msec and probably 50-70 cps -- 2 msec with moderate intensity are optimal stimulation parameters for hypothalamic and spinal cord stimulations while those for the stellate ganglion are 20 cps -- 5 msec.

The present study not only confirms effectiveness of 100 cps -- 1 msec and 50-70 cps -- 2 msec found by earlier workers (10, 11, 59, 136, 137), but also shows that frequency as low as 20 cps with 3 msec duration is also very effective for elicitation of cardiovascular responses from the central nervous system. The concept that higher levels of central nervous structures require higher stimulation frequency for elicitation of cardiovascular responses appears to be valid only when short pulse durations less than 2 msec are employed.

B. Stimulation Parameters and Maintenance of Cardiovascular Responses from Three Levels of the Nervous System

It should be noted that 50% response decay time is not equal to half of the total response time when the rate of decay is not linear.

Generally pressor responses were well maintained at stimulation frequencies below 20 cps in the hypothalamus and spinal cord and at a frequency below 10 cps in the stellate ganglion.

The 50% response decay time of pressor responses to stimulation of two areas of the posterior hypothalamus at frequency below 20 cps was approximately 600-700 sec, while those from the dorsal and the ventral spots of high cervical spinal cord were 800-1000 and 1100-2200 sec, respectively. On the other hand, the 50% response decay time of pressor responses from the stellate ganglia was also approximately 600-700 sec at stimulation frequency below 10 cps.

During stimulation of the stellate ganglion of the dog, Rhose, Kaye, and Randall (156) reported that a pressor response could be prolonged for as much as 11 hours with stimulation parameters of 1-3 cps -- 10 msec -- 3.2 volts. In this experiment, however, it proved difficult to maintain good contact between electrode and nervous tissue (STG) because the size of the ganglion is so small that wire electrodes cannot be satisfactorily applied.

Such technical problems may account for differences in maintenance of responses. In the present study, stimulation at 1-3 cps was not tried because with stimulation intensity and pulse durations employed, response was rather small.

However, with stimulation parameters of 100 cps -- 1 msec, maintenance of pressor responses from the three levels of the nervous system were similar, 50% RDT being approximately 200-300 sec. Thus it appears that critical frequency for pressor responses from the hypothalamus and spinal cord is 20 cps while that for stellate ganglia is 10 cps.

Before spinal transection responses were better maintained in spinal cord stimulation than during hypothalamic and stellate ganglia stimulations. However, after transection the 50% RDT of pressor responses to stimulation of both dorsal and ventral spots of the spinal cord at a frequency below 20 cps ranged from 500 sec to 700 sec, whereas the 50% RDT with 100 cps -- 1 msec was less than 200 sec.

Generally heart rate responses were maintained longer than pressor responses with all stimulation parameters employed. It may be assumed that better maintenance of cardiac rate is probably due to a dense innervation of sympathetic fibers to the SA node.

Finding a prolonged heart rate response even when there were no detectable postganglionic action potentials during high frequency stimulation of preganglionic fibers, Bronk et al (25) concluded that there was continued activity in the postganglionic fibers. From the result of this experiment, it is quite obvious that maintenance of response is predominantly frequency-dependent although intensity and pulse duration can also affect impulse frequency to some degree presumably by spatial summation at the synapses.

Therefore, considering both magnitude and maintenance, it may be concluded that optimal stimulation parameters for prolonged stimulation of the posterior hypothalamus and descending autonomic fibers in the spinal cord are 20 cps -- 3 msec; while for the stimulation of stellate ganglia, 10 cps -- 5 msec is most adequate.

It is interesting to note that the same low frequency of 20 cps is optimal for hypothalamic and spinal cord stimulation suggesting that there is probably no frequency conversion at the level of the brain stem. This can be explained if all nerve fibers from the hypothalamus are assumed to travel directly down to spinal motor neurons without making any synapse at brain stem levels. However, even though the existence of some direct

pathways has been claimed (137, 139), there is not enough evidence to support the above concept. As Peiss (140) suggested earlier, this can be better explained by assuming that nerve fibers originating from the posterior hypothalamus do not make series synapses with neurons in vasomotor center in the medulla oblongata, but connect rather by collateral branches. Of course, there is no compelling reason to believe that impulse frequency must necessarily be converted at synaptic junctions. The frequency conversion rate will be dependent not only upon stimulation intensity, as Bronk et al reported, but also upon pulse duration. However, the present experiments can be interpreted to indicate that impulse frequency is reduced to approximately one-half at spinal synapses since responses from spinal cord were best maintained at 20 cps while 10 cps was best for maintenance of responses at the stellate ganglia.

Another fact which supports the effectiveness of low frequencies in stimulation of the hypothalamus and spinal cord is that resting discharge rates of hypothalamic neurons are under 10 cps, and, even when excited, such rates rarely exceed 50 cps (41). Therefore, it is suggested from these experiments that the physiological conduction rate of nerve fibers in central nervous system which mediate cardiovascular function may rarely exceed 20-30 cps.

During hypothalamic stimulation, baroreceptor reflex did not seem to affect maintenance of pressor response while occasionally heart rate response was somewhat irregular. The 50% RDT (response decay time) of pressor and heart rate responses to specific stimulation parameters were similar before and after denervation of the carotid sinus and vagotomy. There have been several studies which examined baroreceptor activity during hypothalamic stimulation.

Reis (155) reported that baroreceptor reflex responsiveness is under tonic and phasic control of supramedullary structures and that pressor and depressor limbs of reflex arc are independent of each other. Finding that when the hypothalamus (defense area) was stimulated for 10 seconds before application of stimulus to the carotid sinus, the reflex response was completely suppressed, Hilton (87) suggested that during hypothalamic stimulation baroreceptor reflexes are inhibited.

C. Response Decay during Stimulation of the Nervous System at High Frequency

In early studies on electrical stimulation of central nervous structures, failure in maintenance of response despite continuous application of stimuli has been attributed to fatigue because after certain periods

of rest, the response was again producible. Such fatigue phenomena are relatively well known as a result of stimulation of the cerebral cortex.

It is noticeable that in many early stimulation studies in which response decay was observed, stimulation frequencies higher than 20 cps were used. While investigating vascular responses in the intestinal wall to stimulation of hypothalamic defense areas (with 100 cps -- 1 msec), Cobbold et al (38) described systemic blood pressure elevations of 50% above control but within 2-3 minutes they declined to 25% above control values. These authors further stated that such a decline in blood pressure could not be explained on the basis of gradual failure in hypothalamic stimulation due to fatigue or damage of tissue and indicated that constriction of capacitance vessels lasted throughout the entire stimulation period whereas resistance vessels failed to do so. It is rather clear from these experiments that the blood pressure fall observed by Cobbold et al was due to high frequency stimulation since 50% RDT is very close to that observed in this experiment.

At low frequencies such as 20 cps, gradual failure in synaptic transmission seems to be due more to desensitization of receptors than to failure in transmitter release. At higher frequencies such as 100 cps, the latter may be more responsible.

Results of the present experiments support the proposed explanation for synaptic transmission failure or response decay. At frequencies above 20 cps to approximately 50 cps, response reached a maximum before starting to decay, whereas at frequencies above 50 cps, the initial responses were smaller than those obtained with low frequencies. As Folkow indicated, a failure in transmitter synthesis is less likely since a brief interruption of stimulation restored responses immediately. Further, if high frequency stimulation were suddenly switched to low, responses immediately began to increase and were consistently maintained at a higher level.

As to possible sites where synaptic transmission failure may occur, Orias (133) held that fatigue phenomenon is predominantly localized to preganglionic nerve endings. However, Folkow (67) felt that both preganglionic and postganglionic nerve endings are involved. However, there is good evidence to suggest that, at least, with low frequencies (in the range of 15-30 cps), transmitter release mechanisms are not exhausted.

Birks et al (21) could not find any decrease in depot-acetylcholine in the superior cervical ganglion of cat after 2 hours of stimulation at 20 cps. Studying the transmitter-stimulation frequency relationship before and after

administration of adrenergic blocking agents, Brown et al (27) concluded that the amount of norepinephrine liberated at adrenergic nerve endings by each nerve impulse is equal, at least, up to a frequency of 30 cps. At frequencies above 50 cps the decline in output per stimulation is due, not to destruction of transmitter, but to a failure in liberation.

Bronk et al (25) reported good 1:1 correspondence between pre-ganglionic impulse traffic and postganglionic action potentials up to a frequency of 40 cps. Therefore, it appears that there are at least two different causes for failure in synaptic transmission.

There are many factors which can affect maintenance of responses; tissue damage, defects in stimulating electrodes, changes in neuronal excitability, failure in synaptic transmission (transmitter release mechanism and desensitization of receptors), inhibition and exhaustion of effectors.

In prolonged electrical stimulation of nervous tissues, some degree of tissue damage cannot be completely ruled out. However, tissue damage alone can hardly be a significant cause for response decay since responses are reproducible after a certain period of rest.

At present, there exists much evidence to assume that failure in synaptic transmission and changes in neuronal excitability are the most

probable cause for response decay. Though there is some discrepancy as to the critical frequency among different investigators, it is well known that in peripheral sympathetic ganglia synaptic transmission fails when stimulation rates of 15-20 cps or higher are applied to presynaptic fibers. In an excellent discussion on the mechanism of synaptic transmission failure, Folkow (67) concluded that exhaustion of transmitter release mechanisms seemed to be a more probable explanation. It seems reasonable to assume that during hypothalamic stimulation synaptic transmission failure is not limited to synapses in peripheral sympathetic ganglia but rather at all central synapses located between the hypothalamus and the effector units since impulse transmission mechanisms across synapses are believed to be the same. Of course, transmission failure presumably will be most severe at the site of the first synapse.

In an unpublished study conducted in our laboratory, the stellate ganglion and ventrolateral cervical cardiac nerve stimulations resulted in increased blood pressure and myocardial contractile force. After response from the stellate ganglion had shown complete decay, good responses were induced by electrical stimulation of the ventrolateral cervical cardiac nerve. The latter response then showed decay, particularly during high frequency stimulation.

Although not as significant as synaptic transmission failure, changes in excitability of neuronal tissue may also be responsible for response decay.

It has been reported that during prolonged high frequency nerve stimulation, noticeable alterations in intracellular potassium and sodium levels occurred. Potassium ions "leaked" out of the cell while intracellular sodium concentrations increased (40, 109). Thus, several observations suggest that excitability of neuronal elements are changed during high frequency stimulation.

The first of a series of pressor responses was usually the largest, although a similar magnitude of response was sometimes observed after a long period of rest. Increased stimulation intensity also frequently resulted in reproduction of the initial magnitude of response. It is conceivable that such restored responses could be due to recruitment of additional neurons by the increased current, but the magnitude of restored response was larger than that which could be obtained by separate stimulation involving increased intensities. According to Nishi and Koketsu (132), time for recovery of excitability of sympathetic neurons in the toad is very long; complete recovery time of sympathetic B neurons and sympathetic C neurons being 150-200 msec and 500-600 msec, respectively.

The question of why responses are not sustained as long as stimulation with optimal parameters remains essentially unsolved. It appears reasonably certain that alterations in neuronal excitability play a role.

Although it is reported in the neuron of *Sepia* that a sodium pump can keep pace with sodium influx during stimulation frequencies up to 100 cps, there is little information on other neurons (90).

It has been observed that the hypo-excitabile period, which is usually associated with a positive after-potential and probably with activity of the sodium pump, was increased during prolonged stimulation of nerve at high frequencies (39). On the other hand, the duration of hyperpolarization was claimed to be correlated with conduction velocity and to be responsible for determining the frequency at which neurons discharge impulses when subjected to sustained depolarization.

Studying repetitive firing of neurons of *Limulus* evoked by stimulation with trains of stimuli, Fuortes et al (71) concluded that prolonged current flow depressed the process leading to excitation and that repetitive firing is controlled both by after-effect of firing (refractoriness) and by the depressant effect of sustained stimulation (accommodation). Bronk et al (25)

also indicated that postganglionic action potential base lines were shifted negatively when there was no detectable action potential during prolonged high frequency stimulations.

In many early works in which response decay was observed from the central nervous system, fatigue of neuronal elements, tissue damage and defects in stimulating electrodes have been emphasized as participating causes. Relatively little attention has been paid to failure in synaptic transmission.

By comparison of responses from hypothalamic and spinal cord stimulations, it may be concluded that rapid response decay observed during stimulation of the former is not due to tissue damage or defects in electrodes. During a prolonged high frequency stimulation in the hypothalamus and spinal cord, responses decreased slightly below control pressures but returned to prestimulation levels upon termination of stimulation. This would imply that sympathetic tonic firing was also blocked, probably at synaptic sites where conduction was impeded by high frequency stimulation.

In a study on the effect of vasoconstrictor fiber stimulation on resistance and capacitance vessels, Folkow et al (65) observed that autoregulatory escape (decline in resistance following peak response) was more

pronounced at higher stimulation frequencies. They also noted that sometimes at higher frequencies, steady-state resistance responses were less than control.

CHAPTER V

SUMMARY

While recording pressor and cardiac rate responses, two points in the posterior hypothalamus, both stellate ganglia and two areas in high cervical spinal cord before and after cord transection between caudal medulla and C1 spinal segment were electrically stimulated with a range of selected stimulation parameters.

The results obtained from the present study may be summarized as follows:

(1) In acute experiments upon cats, optimal stimulation parameters were determined for induction of cardiovascular responses from the posterior hypothalamus and spinal cord. Moderate intensity (voltage or current) stimulation employing frequency-duration parametric sets of 100 cps -- 1 msec; or 20 cps -- 3 msec were found to provide consistent reproducible results. The parameter set of 20 cps -- 5 msec proved to be most appropriate for stellate ganglion stimulation.

(2) The maintenance of cardiovascular responses during prolonged stimulation was quantitated by calculating the 50% response decay time as the time in which responses progressively decreased to one half the maximum response. The 50% RDT of pressor and heart rate responses from hypothalamic and spinal cord stimulation were approximately the same when stimulation frequencies up to 20 cps were employed, whereas those from the stellate ganglia were comparable to each other during excitation with frequencies up to 10 cps.

(3) Considering both magnitude and maintenance of response, however, the optimal stimulation parameters for prolonged cardiovascular responses from the hypothalamus and spinal cord are, with moderate intensities, 20 cps -- 3 msec while 10 cps -- 5 msec is best for stellate ganglion stimulation.

(4) The magnitude of response seems to be determined primarily by stimulation intensity, pulse duration and frequency while maintenance of response is predominantly frequency-dependent.

(5) The 50% response decay time of cardiac rate responses are longer than pressor responses during stimulation at all three levels of the nervous system. However, other response characteristics to different stimulation parameters are similar to those concerned with pressor responses.

(6) Since there is little or no difference in optimal stimulation parameters for the posterior hypothalamus and spinal cord, it may be speculated that no frequency conversion occurs at the brain stem level. However, impulse frequency appears to be reduced to approximately one half in the intermediolateral columns of the spinal cord.

(7) Two locations from which responses could be elicited after high cervical cord transection (C1) are believed to identify descending autonomic fibers mediating cardiovascular functions. Before transection, the spinal cord is the most reactive of all three test levels of the nervous system. After transection, its responses, at the same voltage, are relatively weak and can be maintained for only brief period of time.

(8) From the present experimental results, together with available literature, it is suggested that the physiological impulse rate of descending central autonomic fibers mediating cardiovascular function rarely exceed 20-30 cps.

(9) At the higher frequencies, exhaustion of a transmitter release mechanism seems the more probable cause of response decay, while desensitization of transmitter receptors may account for failure in maintenance of responses at frequency ranges of 20-30 cps. It also seems reasonable to assume that failure in synaptic transmission is not localized to one particular synapse but rather that it occurs in many, perhaps all, synapses between the hypothalamus and the effector organs. Neuronal excitability changes may also be responsible for response decay observed during stimulation with optimal stimulation parameters.

(10) The most probable cause of response decay phenomenon which have been observed in earlier studies resides in the use of inordinately high frequency stimulations. The present study does not support the concept that higher frequency is necessary for the stimulation of higher central nervous structures.

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APPROVAL SHEET

The dissertation submitted by Kee Soon Kim has been read and approved by five members of the faculty of the Graduate School.

The final copies have been examined by the director of the dissertation and the signature which appears below verifies the fact that any necessary changes have been incorporated, and that the dissertation is now given final approval with reference to content, form, and mechanical accuracy.

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

1-22-68

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Signature of Advisor