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THE ELECTRODERMAL RESPONSE: NEUROPHYSIOLOGICAL AND NEUROPHARMACOLOGICAL CHARACTERISTICS

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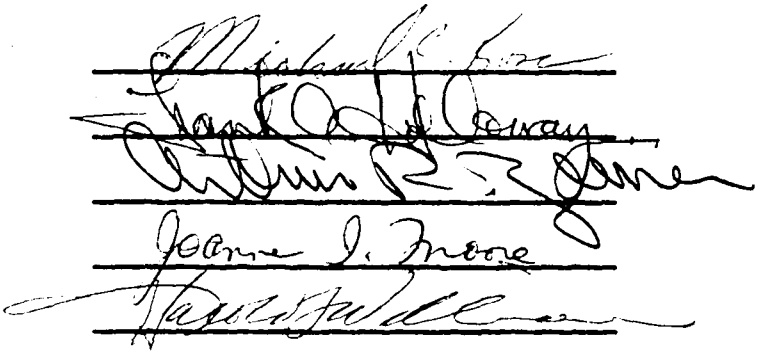

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CHAPTER I

INTRODUCTION

Electrical activity of the skin (variously called galvanic skin responses, skin potentials, electrodermal responses, etc.) can be measured as either potential or resistance changes. The records of the electrical activity of the skin, obtained by either of these methods, have many similarities (Wang, 1964). However, the precise relationship between skin potential and skin resistance has not been definitely established (Wilcott, 1965). For reasons of simplicity and consistency with other investigators, all research done by this author was performed with the potential method. The term electrodermal response (EDR) is used in this dissertation to signify all changes in sudomotor activity which can be measured as an action potential by means of surface skin electrodes.

The action potentials generated by the sweat glands were first measured by Hermann and Luchsinger in 1878. They found that when the footpads of an anesthesized cat were kept in close contact with two non-polarized electrodes the galvanometer showed no flow of current. However, when one sciatic nerve was severed, current flowed from the denervated footpad to the footpad with the intact innervation. Although this was an

interesting discovery, further progress in recording fast and small electrical changes in animal tissues was prevented for several years by a lack of suitable instrumentation.

Investigation of this electrical activity of the skin continued in 1888 when Féré observed a decrease in electrical resistance in the footpads of the cat following sensory or emotional stimulation. Two years later Tarchanoff noted similar skin potential changes in man. Almost a decade passed before the first systematic study of these electrical changes in the skin was published by Veraguth (1909) in a monograph entitled Das Psychogalvanische Reflexphenomen. This name for the skin reflex excited much interest on the part of psychiatrists who were eager to find a physical indicator of mental events. At about this same time Peterson and Jung (1907) were beginning to utilize the galvanic skin reflex in their psychological studies. This reflex was brought to the attention of the American scientific community in 1925 when Wechsler claimed that the psychogalvanic reflex could be used for the measurement of emotional state. Since that time the electrical activity of the sweat glands has been utilized extensively by psychologists and psychiatrists as a tool with which to determine the physiological correlates of mental events even though much of the basic physiological mechanism underlying the reflex remains to be elucidated.

In the first three decades of this century Gildemeister and his associates were active in investigating the electrical activity of the sweat glands and did many of the preliminary studies attempting to describe the physical basis and peripheral mechanism of the EDR in the cat (Gildemeister, 1928). They established that the effector organs involved

in the production of the EDR are the sweat glands, each gland consisting of secretory tubules and a sweat duct surrounded by muscular fibers which are capable of contraction.

Sweat glands are currently subdivided histologically into two basic types, eccrine and apocrine. In man both types are found, with the former distributed over most of the body and being involved primarily in temperature regulation and the latter being located in only a few body areas and appearing to respond mainly to emotional changes. It is well established that the cat has sweat glands in the footpads, and although these are slightly different histologically from those of man, they are generally considered to be functionally analagous to the human apocrine system.

Kuno (1956) was the first to demonstrate that man sweats from the palm and sole during mental distress but not during an increase in ambient temperature. Since the sweat glands in the footpads of the cat do not appear to be primarily involved in temperature regulation it has been assumed that they react in a similar manner to those in the human palm and sole, i.e., sweating to emotional stimuli. The fact that the cat does have the EDR on the footpads, as does man on his plantar and palmar surfaces, strengthens this assumption. In both man and cat the sweat glands secrete after injection of pilocarpine and this response is completely blocked by small doses of atropine.

In his early studies of the EDR in the cat, Waller (1901; 1904) observed that these responses could be recorded only at the footpads and that they were abolished by atropine. Furthermore, he observed that the waveform of the EDR evoked by post-ganglionic nerve stimulation could be

either uniphasic (negative) or biphasic (negative followed by positive). Waller's observations and conclusions have been generally supported by other researchers (Wilcott, 1965) except that it is now widely agreed that the EDR evoked by stimulation in the cat is primarily a uniphasic negative wave (Deckert, 1970) and that the positive potentials observed are most likely artifacts of the recording techniques.

Knowledge concerning the peripheral mechanism of sudomotor activity is incomplete. One of the oldest and most obvious explanations for the EDR is that sweat changes the conductivity of the skin. Several factors seem inconsistent with this hypothesis such as the observation that the EDR can be elicited from skin immersed in saline (Edelberg, 1972). However, Adams (1966; Adams and Vaughan, 1965) in a series of experiments on the cat has shown results which are consistent with a model in which electrical changes are a function of changes in hydration due to sweat production. Briefly, he visualizes sweat rising through a duct with permeable walls which permits hydration of the corneum. Some of the characteristics which Adams attributes to the corneum are hypothetical although not unreasonable.

Darrow (1964; Darrow and Gullickson, 1970) proposed a model which implicates other structures as well as the sweat glands as the source of the EDR. He began with two assumptions: 1) that the intraluminal portion of the sweat gland is positive in respect to the exterior and 2) that neural impulses may cause increases in the permeability of the epidermis and/or corneum as well as the sweat gland itself. With either of these assumptions the occurrence of positive potentials caused by the rise of sweat in the duct would be expected. It is difficult to reconcile

this model with the fact that increasing activity is ordinarily associated with increasing negativity rather than positivity and that positive responses are extremely rare in the cat (Leiderman and Shapiro, 1964).

Other investigators of the EDR have given serious consideration to a vascular hypothesis to explain the sudomotor response. However, the experiments of Lader and Montagu (1962) essentially eliminated this vascular theory as an explanation for the genesis of the EDR. They found that the EDR was unaffected by decreases in local blood flow, and similarly, that drug induced vasodilation produced no electrodermal changes. In addition, independent central controls for vasomotor and sudomotor responses have been demonstrated in the cat (Prout, Coote, and Downman, 1965).

Several other hypotheses for the basis of the EDR have been proposed but exactly how the various characteristics of the sweat gland actually function to produce the observed electrical changes remains to be explicated. Edelberg (1972) has recently reviewed the various theories and the status of their support. He concludes that the EDR is most likely produced as a result of a combination of events, including membrane changes in both the skin and the sweat gland, as well as the production and elaboration of sweat itself.

In spite of the lack of consensus concerning its origin, the appropriateness of using the EDR as an indicator of sweat gland activity, as opposed to directly measuring sweat output, can be argued for several reasons. First, the EDR is a more direct measure of sweat gland activity than output of sweat itself (Lloyd, 1968b). Sweat output is distinct from sweat formation since it is the product of two opposing actions, sweat

formation and reabsorption. Thus the EDR is probably a more sensitive indicator of sweat gland activity than sweat production. Gross collection of sweat is also more subject to error than is measurement of an electrical potential. A major requirement for any method of measuring sudomotor activity is to maintain a steady state response prior to experimental manipulation.

The peripheral innervation of the sweat glands has been studied extensively and consequently is better defined than other aspects of the EDR. However, little information is known concerning the ascending pathways from the periphery to the central nervous system. Since sweating occurs in response to pain and thermal sensation as well as to emotional and unexpected stimuli, it is obvious that this afferent stimulation comes from a variety of systems.

On the efferent side of the central control of sweating our information is more factual. Both the sympathetic and parasympathetic divisions of the autonomic nervous system have been implicated as mediators of the EDR although it is now the general consensus that the control is sympathetic but with many characteristics of the parasympathetic system (especially the involvement of acetylcholine as the mediator at the neuro-effector junction). The sympathetic nature of the EDR has been deduced primarily from anatomical data. Langley (1891; 1894-95) and Patton (1948) found the preganglionic sudomotor fibers, controlling secretion of sweat in the forepaws of the cat, exit from spinal segments T_4 to T_9 and those controlling sweat secretion in the hindpaws from T_{12} to L_4. These nerve fibers supplying the sweat glands come from the ganglia of the sympathetic chain, each of which functions as a multiplier since each pre-ganglionic

fiber comes into contact with as many as twenty post-ganglionic neurons in the ganglia (Wang, 1964).

In their investigation of the central control of autonomic activity, Karplus and Kreidl (1910) noted that stimulation of the hypothalamus induced sweating in the footpads of an anesthetized cat. Wang and Richter repeated this experiment in 1928 and observed that hypothalamic stimulation could also elicit potential changes in the cat's footpad. Subsequent to this work G. H. Wang and his associates undertook an investigation of the central neural control of reflex activation of the EDR. To briefly summarize their extensive work, the sensorimotor cortex, the anterior hypothalamus, and the facilitory reticular system in the interbrain and the midbrain were found to be involved in the suprasegmental excitatory pathways of the reflex EDR. The frontal lobe, the caudate nucleus, the anterior lobe of the cerebellum and the ventromedial reticular formation of the hindbrain were found to exert an inhibitory influence on the electrodermal reflex (Wang, 1964). Wang concluded that the reflex response is the algebraic summation of the excitatory and inhibitory influences and that the most important role in the regulation of the reflex is exerted by the brain stem reticular formation.

Wang became convinced after many years of studying the electrodermal reflex that autonomic reflexes differed only in minor details from somatic reflexes. Accordingly, he believed that both followed one general group of principles which govern all reflexes. In particular, Wang (1957; 1958a and b) stressed the similarities between the electrodermal and the flexor reflexes. For example, both are elicited by nociceptive stimulation and each is present in chronic preparations after severance of the

spinal cord (Wang and Brown, 1956a and b). Wang also reported that intercollicular decerebration inhibits the electrodermal reflex as it depresses the flexor reflex. Therefore, from Wang's observations, it appears likely that autonomic reflexes may follow the same general principles of central regulation as do somatic reflexes.

Wang's studies (Wang, Pan, and Lu, 1929; Wang, Stein, and Brown, 1956) suggest that the electrodermal reflex is mediated not only through the hypothalamus as was traditionally assumed, but also through structures underlying the superior colliculi. For example, Wang found that the reflex capability of the EDR to peripheral afferent nerve stimulation remained at a level of more than 50% of control level after section above the superior colliculi. In contrast, he reported that reflex responses were totally abolished after section at the midcollicular level. Only a few cats were examined by Wang in this way but the results of these experiments suggest that this region may be necessary for the integration of the electrodermal reflex. No further determinations of the central loci for integration of this reflex have been reported by other investigators.

Virtually all of the research on the electrodermal response and reflex by Wang and his associates employed the techniques of ablation and peripheral afferent nerve stimulation. Except for observing the EDR in response to stimulation of several brain regions, Wang undertook no systematic mapping of the brain. Langworthy and Richter (1930) were the first to show that stimulation of the sensorimotor cortex in the cat could produce an EDR. Subsequent investigators (Rhines and Magoun, 1946; Shimamura and Fujimori, 1961; Isamat, 1961; Wilcott, 1969) confirmed this finding and demonstrated that activation of the sweat glands

can also be obtained by stimulation of the limbic cortex and lateral reticular formation. Celesia and Wang (1964), using single shock stimulation, localized an excitatory region for the elicitation of the EDR in the anterior portion of the hypothalamus caudal to the optic chiasm and within the tuber cinerium. These scattered attempts to delineate the reactive loci for elicitation of the EDR have essentially confirmed the existence of the excitatory regions which the ablation studies of Wang suggested.

Cholinergic mediation of the sudomotor response has long been suspected since the EDR is extremely sensitive to atropine. In the cat atropine has been consistently shown to abolish sudomotor activity (Ott and Wood Field, 1878; Wang and Lee, 1930; Patton, 1949). In humans the effect of atropine on the EDR was disputed until Montagu (1958) introduced a reliable technique for application of this agent locally by iontophoresis. It is now clear that atropine (Lader and Montagu, 1962; Wilcott, 1964) and other cholinergic blocking agents (Martin and Venables, 1964; Edelberg, 1972) block neurodermal activity in both man and cats.

The apparent discrepancy between the anatomical innervation and the pharmacodynamics of the sweating mechanism puzzled both physiologists and pharmacologists for many years. It was not until 1934 that Dale and Feldberg presented what has come to be the classical indentification of acetylcholine in the mediation of impulses to the sweat glands. The fibers supplying the sweat glands were thus identified as cholinergic even though anatomically they pass to the periphery via sympathetic pathways. According to our current understanding, the chemical mediator liberated at the sudomotor ending is acetylcholine and it acts directly on the sweat gland. The subsequent events leading to the EDR remain unknown.

Numerous investigators have attempted to demonstrate an adrenergic step in the cholinergic innervation of the sweat glands. Lloyd reported in 1959 that systemic injection of norepinephrine increased sweat gland secretion. However, Gooch and Edelberg (1972) observed a reduction of the EDR after norepinephrine. Lloyd (1968a and b) has also presented evidence that phenoxybenzamine, guanethidine, and bretylium, in extremely large doses, all reduce the EDR magnitude. The disagreement in this research may be due to the fact that all of the agents used have multiple effects on both the sympathetic and parasympathetic nervous system. Also, the doses of the drugs used were frequently much greater than could be considered either physiological or pharmacological.

A possible site of action for adrenergic agents on sudomotor activity is the myoepithelial cells which surround the sweat duct. These cells are very similar to smooth muscle cells but are of ectodermal origin. They are spindle shaped and arranged in a spiral fashion around the axis of the duct. Several investigators have considered these cells to be contractile. It is possible that some of the effects of adrenergic drugs may be due to their action on these myoepithelial cells (Hurley and Shelley, 1954). There is currently no firm evidence to implicate a noradrenergic process in the genesis of the EDR but the controlled studies to conclusively answer this question have not been performed. The best evidence, however, supports the viewpoint that the innervation of the sweat glands is entirely cholinergic and that only large doses of adrenergic drugs can affect the EDR.

The occurrence of acetylcholine as the transmitter substance at the neuroeffector junction would seem to make the sweat glands a unique

system for pharmacological investigation. However, in their review of the pharmacology of sweating, Randall and Kimura (1955) note:

> Although structural and functional information concerning the sweat glands has been accumulating for many years, there remains a deficit of organized knowledge concerning the pharmacology of sweat forming and secreting apparatus. Even though the important relationships of acetylcholine, epinephrine, and other naturally occurring substances with the process of sweating have been studied by many investigators, it is surprising indeed that very few firmly established principles may be clearly stated concerning these relationships [p.365].

Very little research on the pharmacology of sweating has been done in the two decades which have passed since this review was written.

Pharmacological studies concerning centrally evoked sympathetic responses have been undertaken utilizing many effectors such as blood pressure, heart rate, nictitating membrane and pupillary dilation (Harrison and Goth, 1956; Wang, Kanai, Markee, and Wang, 1964; Koss and Wang, 1972). Analysis of the central actions of adrenergic drugs on these systems is difficult in that the CNS effects are masked, at least in part, by the actions of these agents on peripheral mechanisms. For example, in their study of the effects of reserpine and chlorpromazine on the cardiovascular system, Wang et al (1964) had to use a complicated cross-circulation experiment in order to segregate the central and peripheral actions of these agents. The sudomotor system appears to be particularly well suited for the study of those adrenergic drugs thought to have a central action as well as a known peripheral effect since the neurotransmitter at the peripheral receptor of the sweat glands is acetylcholine.

Electrical potentials of the sudomotor system have been used extensively in behavioral research, primarily as an indicator of

sympathetic autonomic activity. The EDR appears to be related to level of sympathetic activity. For example, Burch and Greiner (1958) have shown that spontaneous electrodermal activity is positively related to pharmacologically manipulated arousal levels. However, investigators in psychophysiological experiments have frequently gone further and equated electrodermal activity with either baseline arousal level or emotional activity (Edelberg, 1972). This simplistic interpretation of the EDR is dangerous for several reasons. It overlooks the fact that the EDR is the product of numerous influences, both excitatory and inhibitory. Both behavioral and neurophysiological evidence point to the complexities of what is referred to as arousal. Activation or arousal as evidenced by one autonomic parameter may not always be accompanied by concommitant arousal in another autonomic system. For example, it is known that there is heightened electrodermal activity during Stage 4 of sleep while other autonomic indices (i.e., respiration and heart rate) are depressed. It is also generally accepted that emotion can not be thought of as a non-specific dimension (Lang, Rice, and Sternbach, 1972). Several studies have reported that different patterns of autonomic arousal accompany various emotions (Ax, 1953; Schachter, 1957;Schachter and Singer, 1962; Lang, Rice, and Sternbach, 1972). The problem with the use of the EDR as a physiological indicator in psychological experiments has been due to over-generalization of the meaning of the isolated EDR and a lack of appreciation of the complexity of this response. It is the overall aim of this dissertation to supply additional information regarding the electrodermal response which might make it a better tool in the investigation of behavioral mechanisms.

In summary, the EDR has been used extensively for many years in behavioral studies as a tool with which to determine physiological correlates of mental events. The physiological mechanism underlying the electrical response of the sudomotor system is poorly understood. It is known that the sweat glands, in both man and cats, are entirely under neural control, that they receive their nerve supply from the sympathetic nervous system, and that they are totally excitatory in function. It has also been established that, paradoxically, acetylcholine rather than norepinephrine is the transmitter substance at the neuroeffector junction. Other than a description of several areas in the central nervous system which enhance or inhibit the reflexly evoked EDR, there is little knowledge of the central control mechanisms for the sudomotor system.

The specific aims of this dissertation research were:

1) to determine those brain stem loci, stimulation of which will activate the EDR. Although a few central nervous system areas from which the EDR can be elicited are known, no systematic mapping of the brain stem has been undertaken. Therefore, the first task of this investigation was to methodically map the brain stem from the preoptic region of the anterior hypothalamus to the cervical cord so as to locate the central pathway(s) for evoking the EDR in the cat.

2) to investigate the site for primary integration of the electrodermal reflex. The early studies of Wang hint that a center for the integration of the reflexly evoked EDR may be located in the region of the superior colliculi. By use of ablation techniques, the area of the brain stem necessary for primary mediation of the reflex was investigated.

3) to test the effects of various adrenergic stimulants and

blockers on the centrally and peripherally evoked EDR. There is much confusion in the literature over a possible adrenergic step in the cholinergic innervation of the sweat glands.

4) to test the feasibility of using the sudomotor system as a model with which to segregate the peripheral and central actions of adrenergic drugs. Since acetylcholine is the transmitter at the neuro-effector junction, the peripherally and centrally evoked EDR would appear to be a suitable system with which to study the central nervous system actions of adrenergic drugs. Reserpine and chlorpromazine were chosen as prototype agents in order to determine whether or not this system would be a useful model for pharmacological investigations of centrally acting agents.

CHAPTER II

METHODS AND PROCEDURES

One hundred and fifty-nine cats of either sex weighing 2.5-4.0 kg were anesthetized with alpha chloralose (50-80 mg/kg, i.p.). Pentobarbital was avoided as the primary anesthetic since it has been shown to have a more depressant action of the rostral brain stem and must be replenished more frequently. However, pentobarbital (36 mg/kg) was used in a few animals (8) as a control procedure to ensure that any observed effects were not due to an interaction with the anesthetic.

Skin potentials were measured from the footpads by means of Beckman miniature size biopotential skin electrodes (11 mm; 0.42" dia.) using Beckman electrode paste. These potentials were recorded in reference to another electrode placed on an inactive region of the same paw which had been shaved and washed with water. Femoral arterial blood pressure was recorded by means of a Statham P23AC pressure transducer and heart rate by a Grass Tachograph (model 7P1B). All measures were recorded on a Grass model 7B polygraph. Stimulation to both the central and peripheral sites was derived from a Grass S48 stimulator coupled with a Grass photoelectric stimulus isolation unit with constant current output (model PSIU6B). Body temperature was maintained at 38°C by an electric heating pad which was controlled by a thermosensitive rectal probe. All drugs were administered intravenously (femoral vein). In the cats that

were decerebrated (12), the external carotid arteries were occluded and a hematostatic clip applied to the exposed basilar artery. When decerebration was performed under ether anesthetic, adequate time for its effects to dissipate (90-150 minutes) was allowed before the experiment was begun. In order to reduce artifacts due to activation of skeletal muscles, many of the animals were immobilized by intravenous administration of gallamine triethiodide (2-4 mg/kg) and artificially ventilated.

In mapping the central reactive sites for eliciting the EDR, the hypothalamus and mesencephalon were approached dorsally at a 90° angle after removing part of the parietal bone; the lower brain stem was approached following removal of the occiput. In this latter instance, the electrode was inserted at a 60° angle in relationship to the horizontal plane. For central stimulation small coaxial electrodes (Rhodes, model NE-100, center contact diameter 0.50 mm) were mounted in an electrode carrier and introduced into the desired brain stem region with the aid of a David Kopf stereotaxic instrument. The atlas used to determine the initial stereotaxic coordinates was that of Snider and Niemer (1961). Stimulation was applied only as the electrode was withdrawn dorsally from the brain in 0.5 or 1.0 millimeter steps. The minimal stimulus parameters for a near maximal response to central stimulation are in the range of 200-600 μa, 5-25 H_Z, 1-3 msec rectangular pulses, and a total duration of 0.5-2.0 seconds. In all mapping experiments the EDR was recorded from two or more footpads, usually the left and right forepaws.

For direct peripheral stimulation of the EDR, the distal (efferent) portion of a crushed nerve (either median or ulnar) was stimulated with a bipolar electrode. Electrodermal reflexes were elicited

by stimulation of the proximal (afferent) portion of a sectioned peripheral nerve (median, ulnar, or peroneal) while the electrodermal reflex was recorded from anotner limb. Typical stimulation parameters for peripheral elicitation of the EDR were 100-500 μa, 1-3 msec rectangular pulses, 10-50 H_z for a total duration of 0.50-0.75 seconds. For reflex elicitation of the EDR stimulus parameters were approximately 0.50-5 ma, 10-20 H_z, 1-3 msec rectangular pulses for 0.50-1.50 seconds. In most cases maximal stimulation was used. Dissected nerves were kept moist by being covered with a cotton pad saturated with warm mineral oil.

Seventy-eight cats were used in the experiments to determine those reactive brain stem areas from which the EDR could be elicited. These animals were anesthetized, mounted in the stereotaxic apparatus, and surgically prepared so as to allow stimulation of the brain regions. The area of the brain stem extending from the preoptic area of the hypothalamus to the spinal cord was systematically explored for reactive loci. Midline regions as well as points up to 5 mm lateral on both sides of the brain were stimulated. Once the minimal stimulation parameters necessary to evoke a maximal response were determined in an individual animal, these parameters were not varied for the duration of the experiment, thus assuring that all stimulation at varying sites within one animal were equivalant. At the conclusion of each experiment, the brain was perfused with physiological saline followed by a solution of 10% buffered formalin phosphate. After fixation the brain stem was removed, sectioned serially by the frozen technique, and stained with cresyl violet acetate.

In those experiments focusing upon localization of the area necessary for integration of the electrodermal reflex, a control period

of reflexly elicited EDR's was first obtained. The cats were then decerebrated at the midcollicular level. The response was continuously elicited at the rate of once or twice per minute, thus allowing for the comparison of the reflex before, during, and after decerebration. In these preparations, decerebration was followed by section between the pons and the medulla or of the spinal cord at C_2.

Sixty-nine cats were used to investigate the effect of drugs on the EDR. The general procedure for testing the feasibility of using the evoked EDR as a model system for the study of centrally acting adrenergic agents is illustrated in Figure 1. On one side the peripheral nerve was crushed centrally and stimulated distal to the cut to serve as a control peripheral response. The EDR was also evoked by direct stimulation of the efferent pathway in one of several brain stem regions (hypothalamic, mesencephalic, pontine, and medullary) and recorded on another footpad. With this preparation one can observe the central effects of drugs separately from any possible peripheral action and also maintain a peripheral control in each experiment. This preparation also allows for the effects of drugs on the reflexly evoked EDR to be observed since the reflex can be evoked by stimulation of an afferent nerve and recorded from a footpad with intact central innervation.

Drugs used in this study included the adrenergic stimulants, epinephrine (EPI), norepinephrine (NE), and isoproterenol (ISO), as well as the alpha adrenergic blocker phenoxybenzamine (PBZ) and beta adrenergic blocker propranolol (PRO). Other agents also employed in this investigation included: chlorpromazine, a major tranquilizing drug which appears to affect adrenergic brain systems; reserpine whose primary mechanism of

action is to deplete the tissue stores of catecholamines; atropine which blocks the receptor sites at parasympathetic post-ganglionic neurons (muscarinic); hexamethonium (C_6), a classical agent used to block ganglionic receptors. Dosage levels utilized were as follows: norepinephrine bitartrate, 1 - 100 µg/kg (Winthrop), epinephrine hydrochloride, 1 - 100 µg/kg (Parke-Davis), isoproterenol hydrochloride, 1 - 100 µg/kg (Winthrop), propranolol hydrochloride 0.5 - 2 mg/kg (Ayerst), phenoxybenazmine hydrochloride, 2 - 10 mg/kg (Smith, Kline, and French), chlorpromazine hydrochloride, 0.02 - 7.5 mg/kg (Smith, Kline, and French), reserpine, 1 - 5 mg/kg (Ciba), atropine sulfate, 0.03 - 1 mg/kg (Nutritional Biochemical), and hexamethonium chloride, 2 - 10 mg/kg (Nutritional Biochemical).

CHAPTER III

RESULTS

The electrodermal response (EDR) can be evoked by stimulating an apparently continuous pathway extending from the rostral border of the hypothalamus throughout the ventrolateral extent of the brain stem to the cervical cord. The responses evoked by stimulation of this pathway were found to be highly reactive (requiring only minimal stimulus parameters), consistently yielding maximal responses in the footpads of 10-30 mV in amplitude. All centrally evoked EDR's were bilateral suggesting that the pathway is entirely crossed, probably at the spinal level. The EDR evoked by central stimulation was reproducible from animal to animal and very stable in nature. Changes in blood pressure in excess of 75 mm Hg did not alter the magnitude of this response. Similarly, no consistent alterations in either blood pressure or heart rate occurred concommitant with the evoked EDR. As the stimulation parameters were used to elicit the EDR were brief trains of low intensity, large cardiovascular responses were not generally observed. All evoked responses were uniphasic (negative) with a small artifactual positive inflection due to capacitance in the recording system.

One characteristic of the EDR which was observed in responses elicited by means of central, peripheral, and reflex stimulation was that the initial response gradually increased in amplitude until a stable level

was reached (usually in about 10 minutes). However, if the stimulation was interrupted for more than 10 or 15 minutes, this build-up occurred again when stimulation was resumed. Figure 2 is an example of this response build-up. The mechanism underlying this potentiation of response magnitude is unknown although it has been noted by other investigators (Wang and Brown, 1956a). Since it occurs in responses elicited by either central, peripheral, or reflex stimulation, it appears to be mediated by a peripheral mechanism, perhaps sweat rising in the duct or gradual membrane depolarization. This characteristic of the EDR made it necessary to always be certain that the observed EDR was maximal, especially in the comparison of the EDR evoked from different brain areas. If stimulation was continued at a rate of once or twice per minute without pause, no diminution or increase in response magnitude was found following the initial period of response build-up. In most experiments, responses evoked by central or peripheral stimulation at this rate deviated less than 10% in amplitude over many hours. In some cases the control period was extended up to eight hours with little diminution in response magnitude.

Central Reactive Loci

Reactive loci for the elicitation of the EDR are schematically represented in the nine serial cross sections of the brain stem shown in Figures 3 and 4. These cross sections, taken at 3 mm intervals, represent sections perpendicular to the horizontal plane (Figure 3) or at an angle of 60° from the horizontal plane (Figure 4). All points are plotted on the left side of the brain although the right side was also explored. No differences were found between the right and left sides of the brain stem. Each solid circle represents a point of maximal reactivity. For the sake

of clarity, all individual reactive sites are not represented as there was considerable overlap.

The first cross section (Figure 3a) is at the level of the posterior hypothalamus. This is the rostral border of the pathway from which maximal EDR's could be elicited. The pathway was located 2.5-3.5 mm lateral from the midline and at approximately 1-4 mm ventral from stereotaxic zero. Reactive sites in the posterior hypothalamus were found in a fairly large area but within each individual experiment they were more discrete. Figure 5 is an example of a typical EDR evoked from the posterior hypothalamus. The most reactive site (Figure 5e) is located 2.0 mm ventral from zero and 2.5 mm lateral from the midline. Responses could be evoked from loci directly surrounding this most reactive point but they were consistently smaller and most likely due to current spread.

In all investigations of the hypothalamus, both the posterior and anterior portions were carefully investigated with identical stimulation parameters so as to make a comparison of the reactivity of these two areas possible. The most reactive loci were consistently found in the posterior rather than the anterior hypothalamus. In some animals the EDR could be evoked by stimulation of the anterior hypothalamus but these responses were invariably of less magnitude than those evoked from the posterior hypothalamus or from more caudal sites.

The pathway from which the EDR could be evoked continued caudally through the ventrolateral extent of the reticular formation (Figures 3, b, c and d). With one exception, the central gray was unresponsive to stimulation.

The cross sections in Figure 4 show the reactive loci for eliciting the EDR which were found caudal to the colliculi. At the level of the

inferior colliculi, reactive sites were found to occupy a somewhat more ventrolateral position (Figure 4e). Throughout the lower brain stem, sites which elicited maximal EDR's were found in a more circumscribed area (Figure 4, f-i). At the pontine (Figure 4, f and g) and medullary (Figure 4, h and i) levels reactive loci were consistently found to be located at 2-3 mm lateral from the midline and 1-3 mm from the ventral surface. Stimulation of these lower brain stem reactive areas yielded bilateral EDR's of the same magnitude as those elicited from the hypothalamic and mesencephalic regions. No responses could be elicited from either the classical dorsal medullary cardiovascular areas or from the midline region where nictitating membrane and pupillary responses have been previously reported.

The EDR could also be elicited by stimulation of the medullary sites in cats which had been decerebrated at the level of the inferior colliculi. These responses were similar in all aspects to those elicited in the intact animal. They were stable over time and were invariably evoked from the same loci. However, in several decerebrate preparations the evoked EDR was greater than those obtained in the same animal before decerebration. Figure 6 is a record of the EDR elicited by stimulation of the ventrolateral medulla in the decerebrate cat.

Electrodermal Reflexes

The classical electrodermal reflex can be elicited by a variety of stimuli. In most of these experiments the peroneal nerve was stimulated with the reflex being recorded from the footpads of the forepaws. The reflexly elicited EDR was more difficult to maintain over time, compared to the centrally and peripherally elicited responses. However, a stable

response could be maintained for 30-60 minutes, and in some experiments, several hours. The reflex was generally smaller in magnitude (5-15 mV) than the centrally evoked EDR.

Decerebration at the midcollicular level did not abolish the electrodermal reflex and in five of six experiments, the response either remained at the same level or increased following decerebration. Decerebration also caused a marked increase in spontaneous electrodermal activity. However following subsequent section of the brain stem between the pons and the medulla, no further reflexes could be elicited during the acute phase (one hour). In addition, no reflexes could be elicited in any preparation following transection of the spinal cord (C_2). Figure 7 is an example of one experiment in which the pons and medulla were sectioned following decerebration. These findings suggest that, at least during the acute phase, the primary area for the integration of the electrodermal reflex is located in the lower mesencephalic and/or pontine region.

Pharmacological Characteristics of the EDR

Administration of hexamethonium (C_6) totally abolished the EDR elicited by central stimulation while having no effect on the peripheral response elicited by post-ganglionic nerve stimulation. The finding that the EDR is abolished by muscarinic anti-cholinergic agents was also confirmed. All evoked responses were sensitive to atropine in that intravenous administration of 100 µg/kg was generally found to abolish the response. The basic pharmacological characteristics of the EDR evoked by both central and peripheral stimulation are illustrated in Figure 8.

The effect of adrenergic stimulants on the EDR were also investigated. Moderate doses (3 µg/kg) of epinephrine, norepinephrine, and

isoproterenol were all found to cause a rapid decrease in the magnitude of the EDR elicited by both peripheral and central stimulation (Figure 9). These decreases were of short duration; recovery to control levels always occurred in 5-10 minutes. The effect of isoproterenol could be readily abolished by propranolol. However, neither propranolol nor phenoxybenzamine was able to block the action of epinephrine and norepinephrine. It is possible that this failure to abolish the effect of epineprhine and norepinephrine may be due to incomplete blockade of alpha-adrenergic receptors or due to a more nonspecific action of these catecholamines. Nevertheless, the results clearly indicate that adrenergic stimulants do cause a rapid, brief decline in EDR magnitude. Since the effect of these drugs was observed on both the centrally and peripherally evoked response, it is likely that this effect occurs at the peripheral sudomotor mechanism. Table 1 summarizes the data on the effects of adrenergic agents on the EDR.

The preparation illustrated in Figure 1 was utilized in all experiments investigating the effects of drugs on the EDR. Centrally evoked EDR's were elicited by means of stimulation of one of four brain stem areas: hypothalamus, mesencephalon, pons, medulla. Peripherally evoked responses were elicited by stimulation of the distal portion of either the ulnar or median nerve after it had been crushed centrally. These peripheral responses were invariably stable in nature and provided a control response with which to compare the central effects of drugs on the EDR. An example of both centrally and peripherally evoked EDR's are shown in Figure 9. In all experiments a stable control period of at least 10-20 minutes was established before any drugs were given.

Reserpine

In 17 experiments reserpine (2-5 mg/kg) was administered to cats and its acute effect on both the peripherally and centrally evoked EDR was observed. Centrally evoked EDR's were elicited by stimulation of four brain stem regions: hypothalamus, mesencephalon, pons, and medulla. In all of these experiments reserpine had no effect on the EDR elicited by either peripheral or central stimulation despite a significant decline in blood pressure. The dose of reserpine chosen for use in these experiments was one that has been shown to be large enough to cause an acute depression of other sympathetic effector organs, i.e., pupil, nictitating membrane, arterioles, myocardial tissue, etc. One of the experiments in which the effects of reserpine on the centrally and peripherally evoked EDR were investigated is shown in Figure 10.

The effect of reserpine on the electrodermal reflex was also studied. Contrary to the findings on the baroreceptor reflex, it was found that reserpine did not depress this reflex.

Chlorpromazine

The same basic preparation was used to investigate the effects of chlorpromazine with both centrally and peripherally evoked EDR's being recorded. Chlorpromazine (0.02, 0.10, 0.50, and 2.50 mg/kg) was administered to each animal beginning with the lowest dose and increasing in a stepwise fashion. The total amount of drug each cat received was 2.50 mg/kg. A stable control period of at least 20 minutes was established and after each dose of drug another period of time was allowed for the EDR to plateau.

Chlorpromazine consistently depressed the centrally evoked

responses with little if any peripheral effects. In this study, the EDR was again evoked from four distinct areas of the ventrolateral brain stem pathway: hypothalamus, mesencephalon, pons, medulla. Chlorpromazine was shown to have a differential effect on the EDR evoked by stimulation of these brain stem areas. Using the binomial test, chlorpromazine was shown to significantly reduce the EDR evoked by stimulation of the mesencephalon ($p = 0.001$) and the pons ($p = 0.05$) at a dosage level of 0.10 mg/kg. A larger dose of chlorpromazine (0.50 mg/kg) was required before the EDR evoked by stimulating either the hypothalamus ($p = 0.03$) or the medulla ($p = 0.002$) was significantly reduced. The reflexly evoked EDR was significantly reduced ($p = 0.05$) at the same dose (0.10 mg/kg) required to reduce the response evoked from the mesencephalon or the pons.

As is shown in Figure 11, chlorpromazine was relatively ineffective in depressing the EDR evoked by hypothalamic stimulation even at a dose of 2.50 mg/kg. In several experiments, 7.50 mg/kg was also found to be ineffective in decreasing the magnitude of the EDR. In marked contrast to the effects of chlorpromazine on the EDR evoked by hypothalamic stimulation, the EDR elicited by stimulation of the mesencephalon was greatly reduced. Figure 12 is a typical experiment where the EDR evoked from this region was decreased 85% from control following 2.50 mg/kg of chlorpromazine. The effect of chlorpromazine on the EDR elicited by stimulating the pons was similar to that evoked by mesencephalic stimulation. As seen in Figure 13, the EDR elicited by pontine stimulation was greatly reduced after 0.50 mg/kg chlorpromazine.

In many cases an attempt was made to reestablish the EDR after it had been reduced by chlorpromazine by increasing the current. For example,

in Figure 13 the current was doubled at the large arrow. This attempt to reestablish the EDR was not successful if the stimulating electrode was located in either the pons or the mesencephalon. However, afer an EDR evoked in these regions had been reduced by chlorpromazine, it was still possible to stimulate either the hypothalamus or medulla and readily elicit large responses (Figure 13b). Like the hypothalamic loci, the EDR evoked by stimulation of the medulla was relatively refractory to the depressant actions of chlorpromazine. The EDR evoked by stimulation of the ventrolateral pathway in the medulla shown in Figure 14 was reduced only 10% following the largest dose of chlorpromazine (2.50 mg/kg). Similar results demonstrating chlorpromazine's lack of effectiveness in depressing the EDR evoked from medullary sites were also observed in the decerebrate preparations (Figure 15).

Chlorpromazine was found to have its greatest effect on the EDR evoked reflexly. In five of six experiments the reflex response was totally abolished at the largest dose (2.5 mg/kg). The results of the experiments locating the area of integration of the electrodermal reflex in the lower mesencephalic and/or pontine region are supported by the finding that the reflex is greatly reduced by chlorpromazine as are centrally evoked EDR's elicited by mesencephalic and pontine stimulation. In a typical experiment, a moderate dose of chlorpromazine (0.5 mg/kg) totally abolished the electrodermal reflex (Figure 16).

A graph of the average percentage of control amplitude of the EDR evoked from varying brain regions at a single dose of chlorpromazine (0.50 mg/kg) is illustrated in Figure 17.

The Mann-Whitney test was used to examine the differences in the

inhibitory effect of chlorpromazine (0.50 mg/kg) on the EDR evoked from various brain stem areas. The EDR elicited by hypothalamic stimulation was found to decline significantly less than the EDR evoked by either mesencephalic ($U = 20$, $p < 0.05$), pontine ($U = 23$, $p < 0.01$), or reflex stimulation ($U = 10.5$, $p < 0.05$). Chlorpromazine also caused a significantly greater decline in response amplitude to both pontine ($U = 26.5$, $p < 0.05$) and mesencephalic ($U = 18$, $p < 0.05$) stimulation when compared to the decline observed in the EDR elicited by medullary stimulation. All other paired comparisons were found to be non-significant. Table 2 summarizes these statistical tests.

The differential effect of chlorpromazine on the EDR elicited by stimulation of various levels of the brain stem could be shown both between and within animals. Usually chlorpromazine was given while one brain stem locus and a control peripherally evoked EDR were both being activated. However, in eight experiments two brain stem areas (i.e., hypothalamus and pons) were stimulated alternately in the same cat. The same differential effect of chlorpromazine was observed using this method of dual stimulation.

The dose response effect of chlorpromazine is represented graphically in Figure 18. The magnitude of depression of the EDR increases as the dose of chlorpromazine is increased from 0.02-2.50 mg/kg. The pontine and the mesencephalic region appear to be more sensitive to chlorpromazine than either the hypothalamic or the medullary regions, especially at the larger doses (0.5 and 2.5 mg/kg). The specificity of chlorpromazine's action on the mesencephalic/pontine region is apparent in the slope of the dose response curve. The means and standard errors for each dose level and brain stem site of stimulation is presented in Table 3.

CHAPTER IV

DISCUSSION

One aim of this research was to systematically localize, by means of direct stimulation, those brain stem regions from which the EDR could be elicited. These reactive loci were found to extend from the rostral border of the posterior hypothalamus through the ventrolateral extent of the brain stem to the cervical cord. No responses could be elicited from either the classical dorsal medullary cardiovascular areas or from the midline regions. In previous studies, Wang and his associates proposed that the anterior hypothalamus and the lateral reticular formation were the primary excitatory brain stem regions. Wang's work was partially confirmed by Shimamura and Fujimori (1961) who reported that stimulation of the lateral medulla and midbrain enhanced the magnitude of the electrodermal reflex. Using direct stimulation techniques, Celesia and Wang (1964) delimited an excitatory region in the anterior hypothalamus (caudal to the optic chiasm and within the tuber cinereum) from which the EDR could be successfully elicited. The results of the present study are in conflict with these findings in that it was found that the posterior hypothalamus was the more reactive area. In some experiments the EDR could be evoked by stimulation of the anterior hypothalamus. However, in these same preparations, responses elicited from the posterior hypothalamus were consistently of greater magnitude. It is unclear whether Celesia and Wang investigated the more

caudal regions of the hypothalamus as no cross sections were included in their report. From the paramedial sagittal section presented, it appears that many of their reactive sites were indeed in the posterior hypothalamus.

Most of Wang's work utilized the electrodermal reflex rather than the EDR. An excitatory region was defined as one which resulted in an enhancement of the reflex when stimulated. Many of the brain stem areas which Wang designated as either excitatory or inhibitory were determined by ablation techniques. For example, all of the cats used in the study of Celesia and Wang to determine the hypothalamic loci for eliciting the EDR were acute thalamic preparations. In contrast, the mapping studies reported in this dissertation were obtained by directly stimulating the brain stem of intact cats and recording the evoked potential response. The discrepancies between the present investigation and the studies of Wang may be due to differences in terminology as well as experimental technique.

Another primary aim of this dissertation was to investigate the site for primary integration of the electrodermal reflex. Early investigations by Wang had hinted that a center for the integration of the reflexly elicited EDR might be located in the region of the superior colliculus. By use of ablation techniques this investigator found the electrodermal reflex to be present after removal of the forebrain rostral to the inferior colliculi. All electrodermal activity was abolished following section of the brain stem either at C_2 or between the pons and the medulla.

An early investigation by Foà and Peserico (1923) had suggested, on the basis of a few experiments, that the electrodermal reflex was still present in the acute phase after intercollicular decerebration but not

after spinal section. The present studies have confirmed and expanded on these findings. In conflict with the results of Foà and Peserico, Wang reported (Wang et al., 1929; Wang and Brown, 1956a) that midcollicular decerebration led to abolishment of the electrodermal reflex as well as to suppression of all spontaneous activity. On the basis of further investigations he (Wang and Brown, 1956b) concluded this loss of reflex response to be the result of inhibitory effects of the bulbar ventromedial reticular system. In the present investigation the reflex was suppressed only momentarily following midcollicular decerebration. Within minutes the reflex returned to its control amplitude and spontaneous activity was increased.

Once again methodological differences between these investigations may be responsible for the conflicting results. In Wang's study the animals were decerebrated following two other surgical sections, removal of the forebrain and the thalamus. All of the preparations used in this study were intact animals prior to midcollicular decerebration. It is possible that the amount of trauma sustained by Wang's cats may explain his inability to observe an electrodermal reflex following midcollicular decerebration.

Another finding in the present study was that the electrodermal reflex was totally abolished in the acute phase after section at either the pons/medulla junction or C_2. These results suggest that the primary area responsible for integration of the electrodermal response is in the lower mesencephalic/pontine region. In contrast, Wang had suggested that mediation of the electrodermal reflex might occur in the area beneath the superior colliculi (Wang and Brown, 1956a; Wang, 1964). The present finding of no persistent reduction in reflex magnitude following removal of the

forebrain rostral to the inferior colliculi makes this hypothesis unlikely. One reason for the disagreement between Wang's work and the present investigation might be his use of chronic rather than acute preparations. It is possible that secondary areas such as those in the spinal cord may become capable of mediating this reflex response in the chronic phase.

The basic pharmacological characteristics of electrodermal activity were also examined in this research. As expected C_6 totally abolished the centrally evoked EDR while atropine abolished all electrodermal activity, centrally and peripherally. In addition, adrenergic stimulants, such as epinephrine, norepinephrine and isoproterenol, consistently caused a brief, rapid depression of the EDR evoked by either central or peripheral stimulation. Propranolol blocked the effect of isoproterenol but neither propranolol nor phenoxybenzamine abolished the effects of epinephrine or norepinephrine.

A possible site of action for this depressive effect of adrenergic stimulants on sudomotor activity is the myoepithelial cells which surround the sweat duct. The fact that phenoxybenzamine did not block the effects of epinephrine and norepinephrine on the EDR suggests that these catecholamines may be having a nonspecific effect rather than acting on alpha receptors. However, alpha receptors are known to be difficult to completely block. This depressive action of adrenergic stimulants on the EDR stresses the need for using a peripherally evoked EDR as a control in experiments investigating the central effects of adrenergic drugs.

Earlier attempts to demonstrate the effects of adrenergic substances on electrodermal activity have been inconsistent. Lloyd (1959) reported that norepinephrine increased sweat gland secretion and in 1968 he

presented evidence that large doses of adrenergic blockers, phenoxybenzamine, guanethidine, and bretylium, caused a reduction in EDR magnitude (Lloyd, 1968 a and b). Other studies have suggested just the opposite, that adrenergic stimulants either have no effect on sweating (Patton, 1949) or cause a depression in both sweat secretion (Langley and Uyene, 1922) and the EDR (Gooch and Edelberg, 1972). The effects which Lloyd reports may be due to the extremely large doses used as all of these agents have other actions unrelated to receptor blockade.

Following definition of reactive areas for eliciting the EDR this sudomotor system was used as a model with which to investigate the effects of drugs on sympathetic efferent activity. As detailed previously, reserpine or chlorpromazine were administered intravenously and their effects on both centrally and peripherally evoked EDR's were observed.

The finding that reserpine did not depress either centrally or peripherally evoked responses during the acute phase is in agreement with other studies. Schneider (1955) and Harrison and Goth (1956) both reported that reserpine did not inhibit pressor responses elicited from hypothalamic stimulation. In addition, Wang et al. (1964) observed a similar lack of effect on the pressor response evoked from the medullary vasomotor centers in the dog. Bein (1955) found no reduction by reserpine of the pressor responses elicited from stimulation of the cortex, nor were cortically induced nictitating membrane responses reduced 50 minutes after administration of reserpine. Koss and Wang (1972) presented evidence that reserpine did not significantly depress the evoked activity along the cervical sympa- nerve. Previously, Iggo and Vogt (1960) had observed no diminution of spontaneous activity along the preganglionic cervical ganglia in reserpinized cats. The present investigation confirms these previous results that

sympathetic efferent activity is not depressed by reserpine in the acute phase. Thus, sudomotor activity appears to react to reserpine in a manner similar to that of other sympathetic systems.

However, it should be noted that reserpine also had no effect on the electrodermal reflex whereas other investigators have reported that the cardiovascular reflex is reduced by reserpine (Bein, 1955; Wang et al., 1964). The reason for this lack of responsiveness of the electrodermal reflex to the depressive action of reserpine is not known. One possible explanation is that cardiovascular and electrodermal responses are integrated in separate brain stem regions. It is well established that cardiovascular reflexes are mediated in the dorsal medulla while the evidence obtained in this investigation suggests that the electrodermal reflex is mediated in the mesencephalic/pontine area.

Chlorpromazine markedly depressed the EDR evoked by stimulation of the mesencephalic/pontine region while having only a minor effect on the EDR elicited by stimulation of the hypothalamus and medulla. While there were no effects on the EDR evoked by peripheral stimulation, the reflexly elicited EDR was greatly depressed by chlorpromazine. Results reported earlier in this dissertation indicate that the mesencephalic/pontine region is the most likely site for the integration of the reflex response. This finding, coupled with the seemingly selective action of chlorpromazine on the mesencephalic/pontine loci for eliciting the EDR, may explain chlorpromazine's selectivity of action. A system of chlorpromazine-sensitive neurons which mediate the electrodermal reflex would appear to be located in this region. Direct stimulation of either the midbrain or the pons could activate these neurons as well as the efferent pathway.

Thus, responses following stimulation of this area might be expected to be reduced by chlorpromazine.

The results of this investigation are in general agreement with other studies concerning the site of action of chlorpromazine in the brain. Many investigations have suggested that the mesencephalic reticular formation is a primary target of the central action of chlorpromazine (Dureman, 1959; Himwich, 1958; Rutledge and Doty, 1957; Killam, 1967). It has also been suggested that chlorpromazine interferes with motor activity primarily by its depressant action on the brain stem reticular formation (Dasgupta and Werner, 1955). In contrast to the actions of reserpine, Wang et al. (1964) demonstrated that the hypotensive effect of chlorpromazine was at least in part centrally mediated. The results of the present investigation confirm this finding for another sympathetic system, the sudomotor.

The observation that both reserpine and chlorpromazine differentially affect the EDR as they do cardiovascular responses lends support to using the electrodermal system as a model for studying the effects of adrenergic drugs on central sympathetic outflow. The sudomotor system has many characteristics which appear to make it suitable for such investigations. Responses are easily measured, reliably elicited and extremely stable. With acetylcholine rather than norepinephrine as the peripheral neurotransmitter the central action of adrenergic agents can be more readily segregated from their peripheral effects. The fact that the EDR can be elicited from numerous anatomical loci within the brain stem (as well as from other parts of the central nervous system) allows for the site of action of a drug to be investigated. In addition, the readily elicited, reflexly evoked EDR can be utilized in investigating other aspects of central drug action. Since the behavioral concommitants of the EDR have been

extensively investigated it should be possible to use this model system in combination with behavioral measures to analyze the complex pharmacological and psychological effects of psychotropic substances. In conclusion, the results of this dissertation research suggest that the sympathetic-cholinergic sudomotor system may provide a unique model for selectively and quantitatively analyzing the effects of drugs on the central nervous system.

CHAPTER V

SUMMARY

A ventrolateral brain stem pathway from which maximal electrodermal responses could be elicited was systematically explored in the cat by direct stimulation techniques. Reactive loci in this pathway were found to extend from the rostral border of the posterior hypothalamus to the cervical cord. Sites stimulated were highly reactive (10-30 mV), reproducible between animals, and extremely stable in nature.

In addition, it was found that stimulation of the ventrolateral extent of the medulla evoked similar, if not somewhat greater responses in the decerebrate preparation. By use of ablation techniques it was determined that the primary area for integration of the electrodermal reflex is located in the lower mesencephalic/pontine region.

Moderate doses of adrenergic stimulants were found to cause a brief decline in the magnitude of the electrodermal response elicited by either central or peripheral stimulation. Propranolol blocked the depressive effect of isoproterenol but neither propranolol nor phenoxybenzamine abolished the effects of epinephrine and norepinephrine.

Once the brain stem pathway was determined and the basic characteristics of the electrodermal response were defined, direct (central and peripheral) and reflex activation of this sudomotor system were utilized as a model with which to study drug effects on the CNS. Reserpine and

chlorpromazine were chosen as the prototype agents with which to test the feasibility of this model. Reserpine was found to have no effects on either the peripherally or centrally elicited electrodermal response, nor did it affect the reflexly evoked response. In contrast, chlorpromazine depressed the electrodermal response elicited from the mesencephalic or pontine region while having less effect on the electrodermal response elicited by hypothalamic or medullary stimulation. In addition, chlorpromazine greatly depressed the magnitude of the reflexly evoked electrodermal response. This data suggests that chlorpromazine may be having a more selective effect on the mesencephalic/pontine region in the same area where the electrodermal reflex appears to be primarily mediated. As the peripheral neurotransmitter to the sweat glands is acetylcholine, this system appears to be particularly well suited to the study of those adrenergic drugs thought to have a central action as well as their known peripheral effects.

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TABLE 1

EFFECTS OF ADRENERGIC AGENTS ON THE EDR EVOKED BY CENTRAL AND PERIPHERAL STIMULATION

			% Decline from Control EDR After Adrenergic Stimulant		
Stimulated	DRUG	DOSE	Control	Phenoxybenzamine (5-10 mg/kg)	Propranolol (2 mg/kg)
hyp.	EPI	1 µg/kg	37		
	EPI	2 µg/kg	42		
peripheral nerve	EPI	10 µg/kg	25		
	NE	10 µg/kg	10		
	ISO	10 µg/kg	10		
pons	EPI	100 µg/kg	66		
	NE	100 µg/kg	25		
	ISO	100 µg/kg	30		
medulla	EPI	3 µg/kg	27	27	
	NE	3 µg/kg	35	27	
	ISO	3 µg/kg	28	40	
midbrain	EPI	20 µg/kg	66		
	NE	20 µg/kg	50	55	
	ISO	20 µg/kg	30		
hyp.	EPI	3 µg/kg	35		35
	NE	3 µg/kg	5		2
	ISO	3 µg/kg	20		0
peripheral nerve	EPI	3 µg/kg	35		35
	NE	3 µg/kg	5		1
	ISO	3 µg/kg	25		0
peripheral nerve	EPI	3 µg/kg	38		21
	NE	3 µg/kg	46		34
	ISO	3 µg/kg	38		0
hyp.	EPI	2 µg/kg	36	36	36
hyp.	EPI	2 µg/kg	15	35	45
	NE	2 µg/kg	0	5	8
	ISO	2 µg/kg	20	19	0
hyp.	EPI	2 µg/kg	14	17	25
	NE	2 µg/kg	5	0	8
	ISO	2 µg/kg	20	15	0

TABLE 2

PAIRED COMPARISONS OF THE EFFECTS OF CHLORPROMAZINE ON THE EDR ELICITED FROM BRAIN STEM SITES

	Hypothalamus	Mesencephalon	Pons	Medulla	Reflex
Hypothalamus	--	U = 20 p 0.05*	U = 23 p 0.01**	U = 38 NS	U = 10.5 p 0.05*
Mesencephalon	--	--	U = 56 NS	U = 18 p 0.05*	U = 15.5 NS
Pons	--	--	--	U = 26.5 p 0.05*	U = 30 NS
Medulla	--	--	--	--	U = 115 NS

MANN-WHITNEY U TEST

TABLE 3

EFFECTS OF CHLORPROMAZINE ON THE EDR ELICITED FROM BRAIN STEM SITES

Site of Brain Stem Stimulation		Dose of Chlorpromazine (mg/kg)			
		0.02	0.10	0.50	2.50
Hypothalamus	N	11	11	14	14
	$\bar{X}$	6.3	6.3	22.6	36.4
	SE	5.9	3.7	6.9	9.0
Mesencephalon	N	8	9	10	10
	$\bar{X}$	10.9	32.7	56.4	71.0
	SE	7.1	12.8	8.2	7.2
Pons	N	7	10	13	13
	$\bar{X}$	21.0	37.3	57.4	69.6
	SE	10.0	12.0	9.5	9.1
Medulla	N	5	7	9	9
	$\bar{X}$	1.6	12.7	32.0	42.0
	SE	1.6	5.6	9.7	9.9
Reflex	N	--	3	6	6
	$\bar{X}$	--	37.3	63.5	66.8
	SE	--	12.6	14.6	14.4

N = Number of raw scores

$\bar{X}$ = Mean percentage decrease of control response

SE = Standard error of the mean

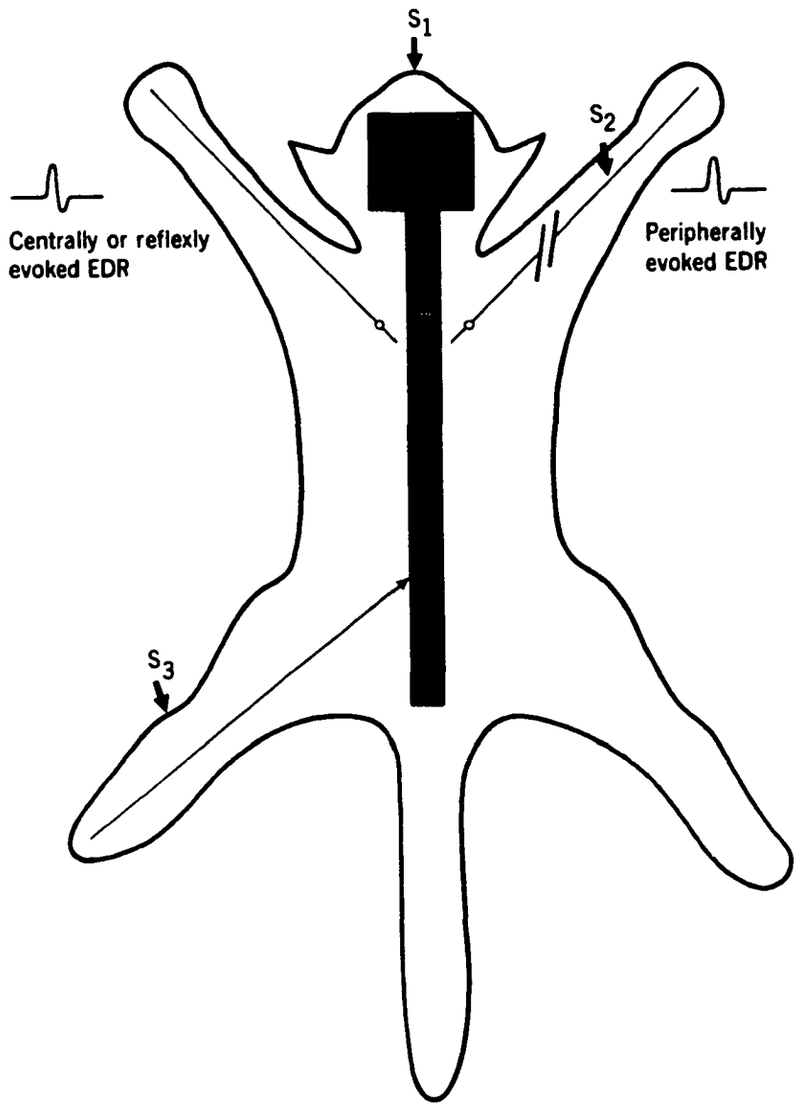

Figure 1 - Schematic diagram of preparation used to study the effects of drugs on the EDR. The centrally evoked EDR is elicited by stimulation of the central nervous system (S_1) and recorded from a footpad with intact innervation. To elicit the peripherally evoked EDR the distal portion of a severed peripheral nerve is stimulated (S_2). The electrodermal reflex is elicited by stimulating an afferent nerve (S_3) and recording the reflex from another limb.

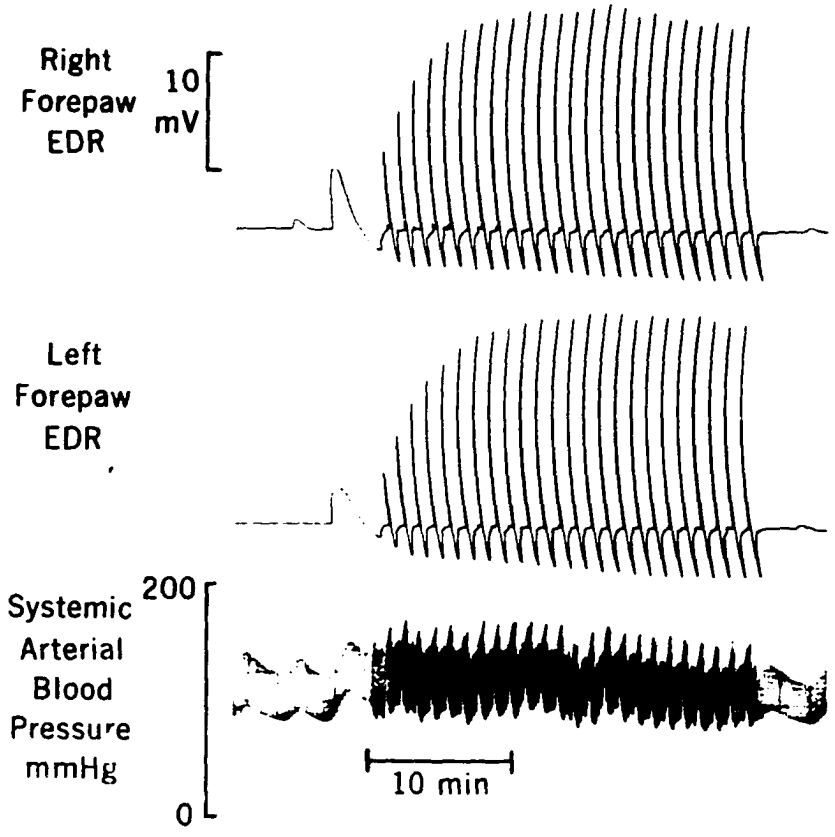

Figure 2 - Example of initial increase in the magnitude of the EDR. Right forepaw EDR elicited by stimulation of hypothalamus. Left forepaw EDR evoked by stimulation of efferent nerve (ulnar). Note that the rate of build-up is similar for both centrally and reflexly evoked EDR's. In all records an upward deflection is negative.

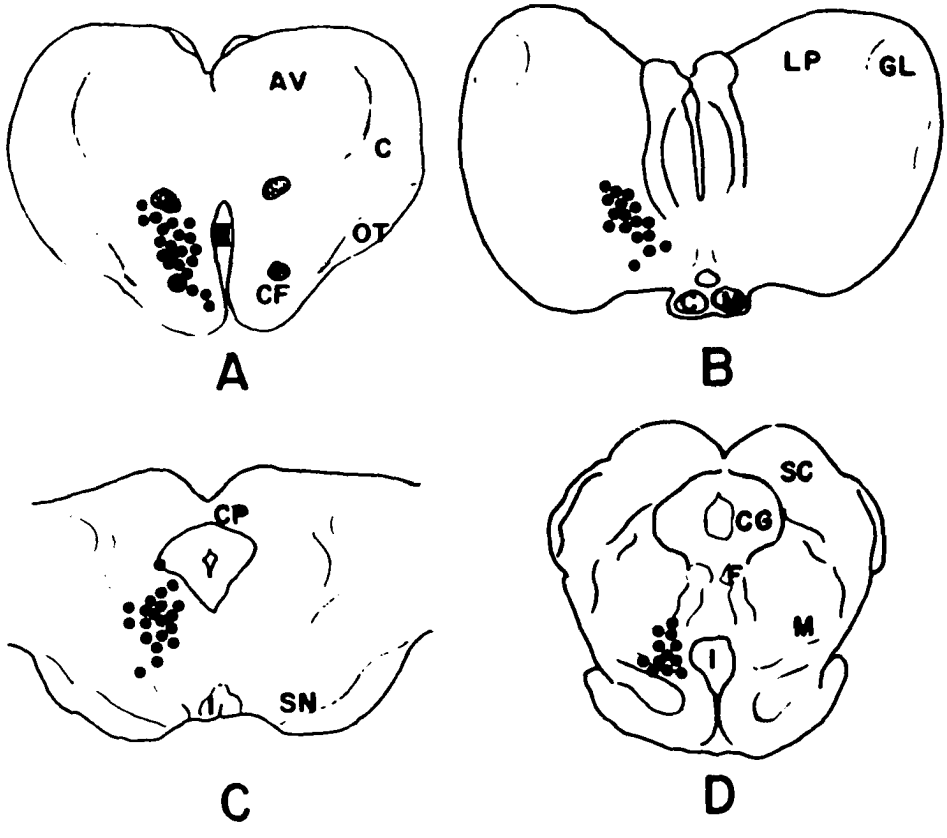

Figure 3 - Maximally reactive loci for eliciting the EDR in the upper brain stem. AV - ventral anterior nucleus, CF - column of formix, C - internal capsule, CG - central gray, CM - mammillary bodies, CP - posterior commissure, F - medial longitudinal fasciculus, GL - lateral geniculate body, I - interpeduncular nucleus, LP - lateral posterior nucleus, M - medial lemniscus, OT - optic tract, SC - superior colliculus, SN - substantia nigra

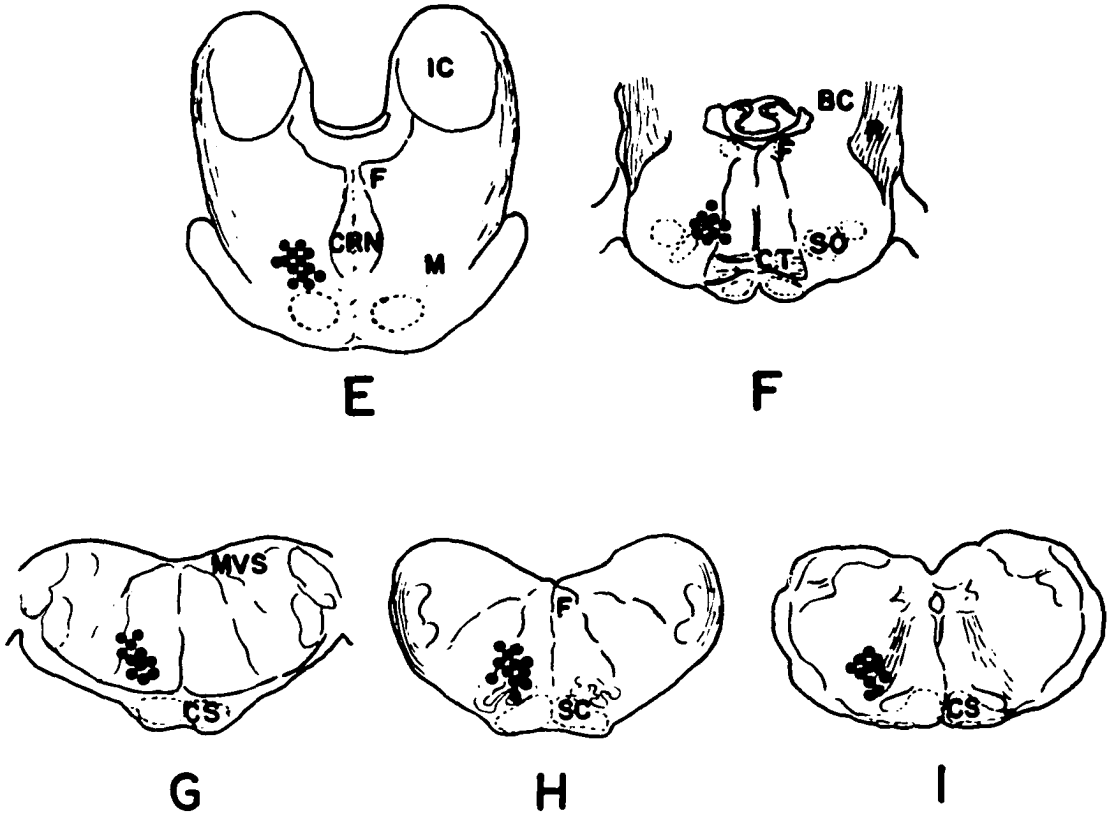

Figure 4 - Maximally reactive loci for eliciting the EDR in the lower brain stem. BC - brachium conjunctimum, CRN - raphe nucleus, CT - trapazoid body, CS - corticospinal tract, F - medial longitudinal fasciculus, IC - inferior colliculus, M - medial lemniscus, MVS - medial vestibular nucleus

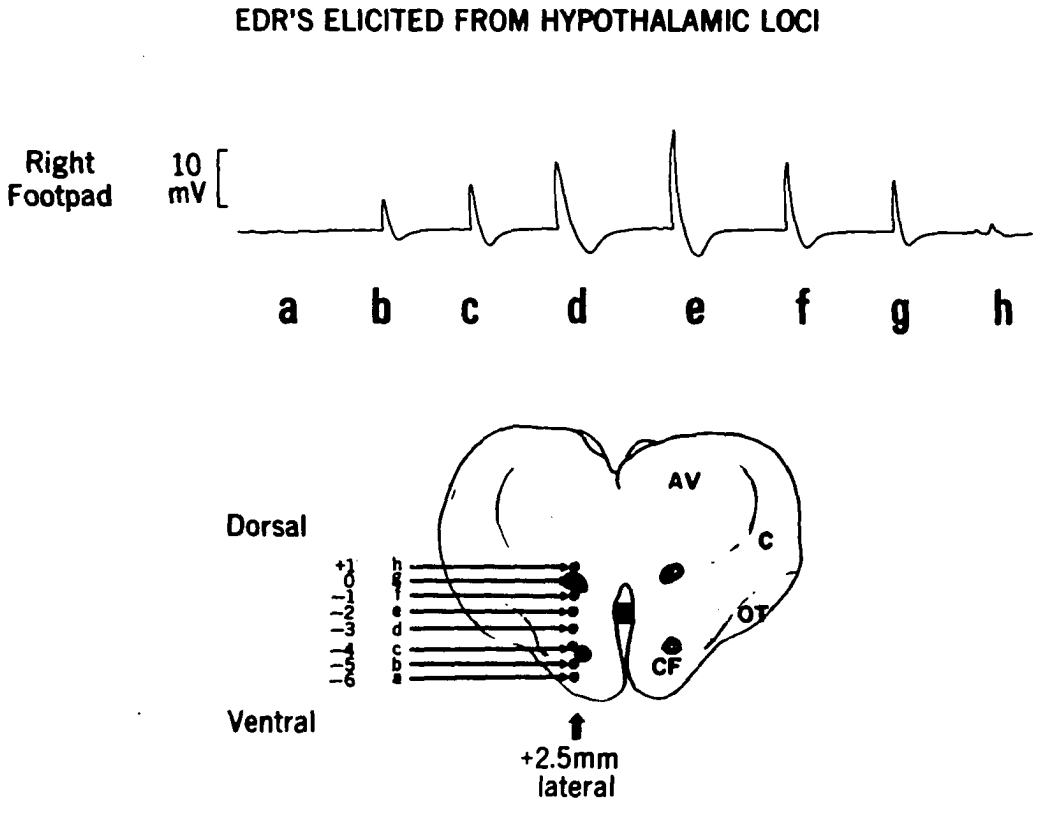

Figure 5 - EDR's elicited from posterior hypothalamic loci. Upper tracing represents responses evoked by stimulation of the hypothalamic sites (a - h) as shown in cross section. Stimulus parameters were identical for all responses: 600 μa, 1.5 msec pulses, 20 H_Z for a total duration of 1.5 sec. Note maximal response at e and gradual dimunition in response magnitude from sites surrounding this point.

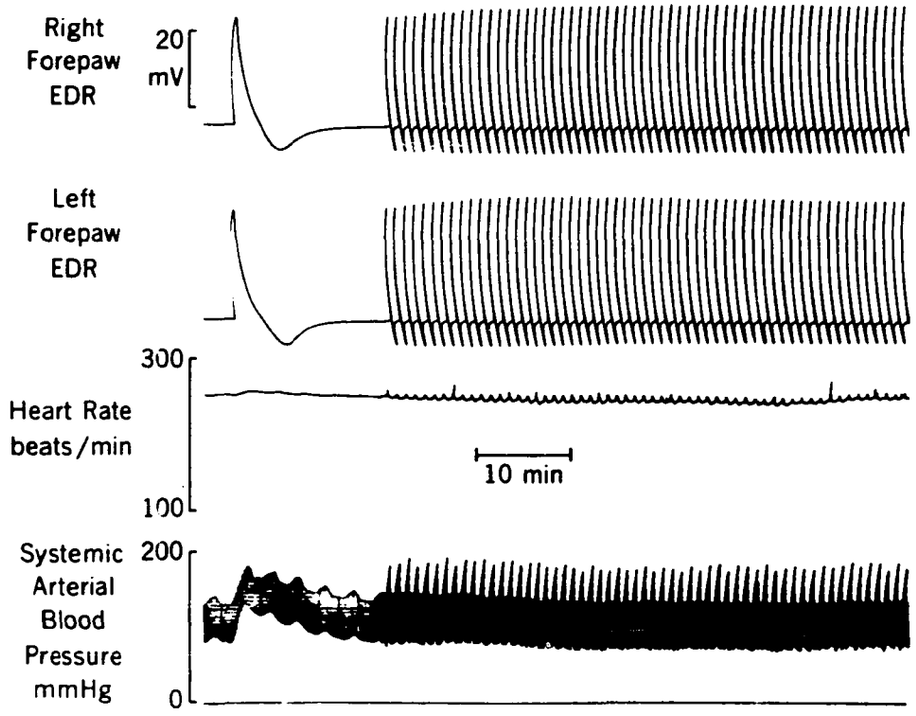

Figure 6 - EDR elicited from stimulation of ventrolateral medulla in decerebrate cat. Note stability and magnitude of responses.

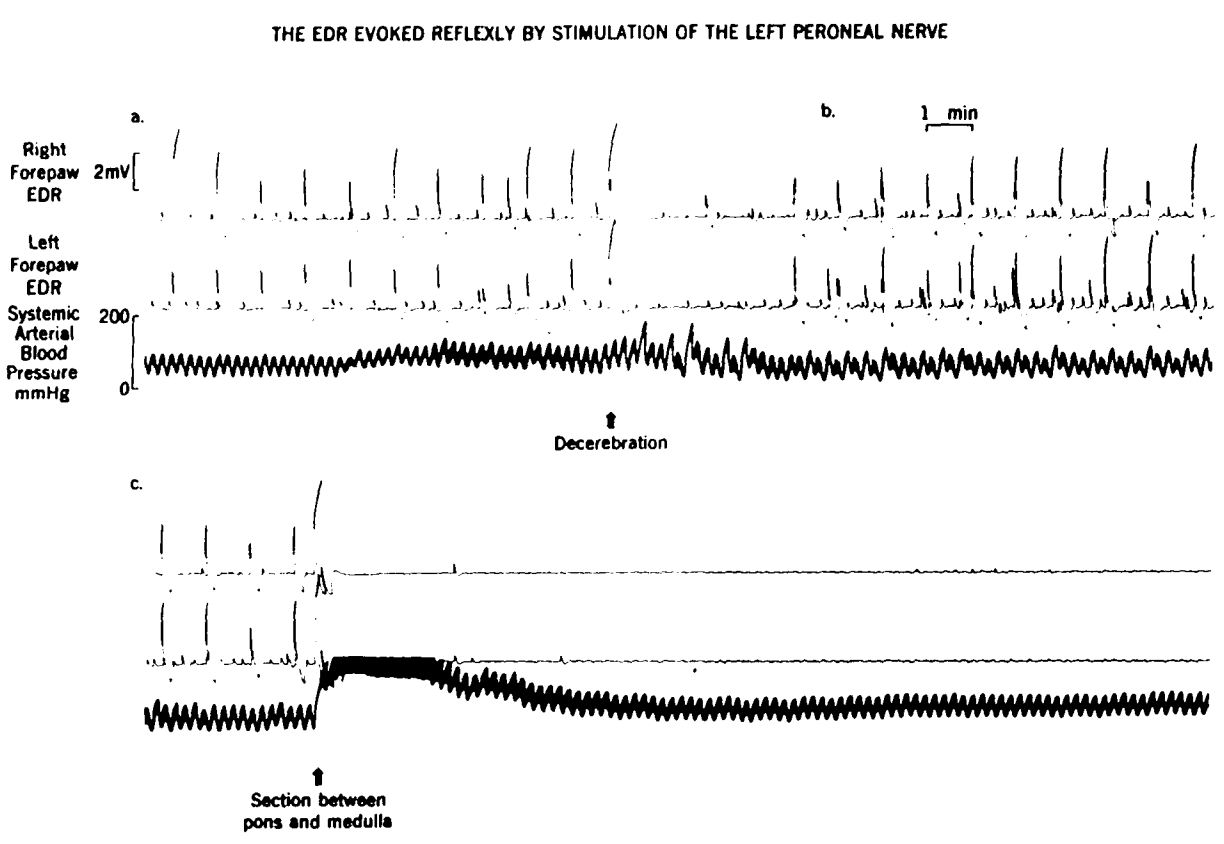

Figure 7 - The reflexly evoked EDR in response to stimulation of the left peroneal nerve at a rate of once per minute. Top two tracings represent reflex response in the right and left forepaws respectively. Lower tracing represents systemic arterial blood pressure. Part a is the control reflex response in the intact animal. Part b is the response following midcollicular decerebration. Note that following section between the pons and medulla (c) no further reflex activity could be evoked and that only desynchronized, low voltage activity was observed.

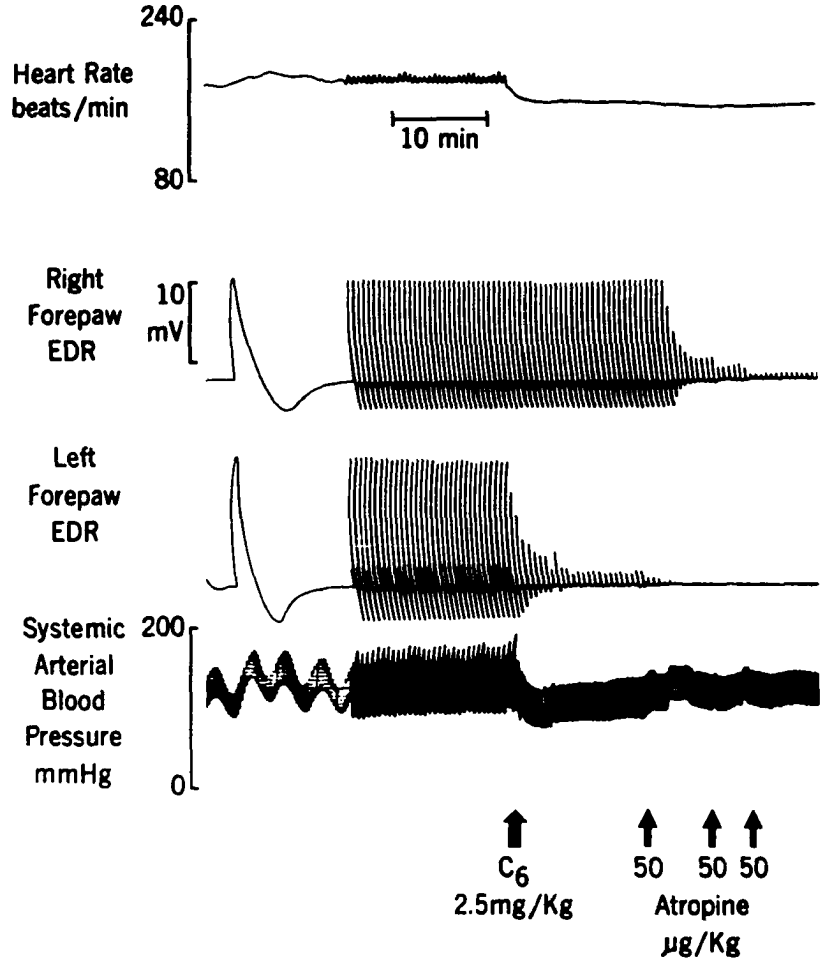

Figure 8 - Pharmacological characteristics of the EDR. Right forepaw EDR is evoked by stimulation of the distal portion of the severed ulnar nerve. Left forepaw EDR is elicited by stimulation of a ventrolateral medullary site. Note that hexamethonium (C_6) caused a rapid decline in the centrally evoked EDR and that all responses were quickly abolished by atropine.

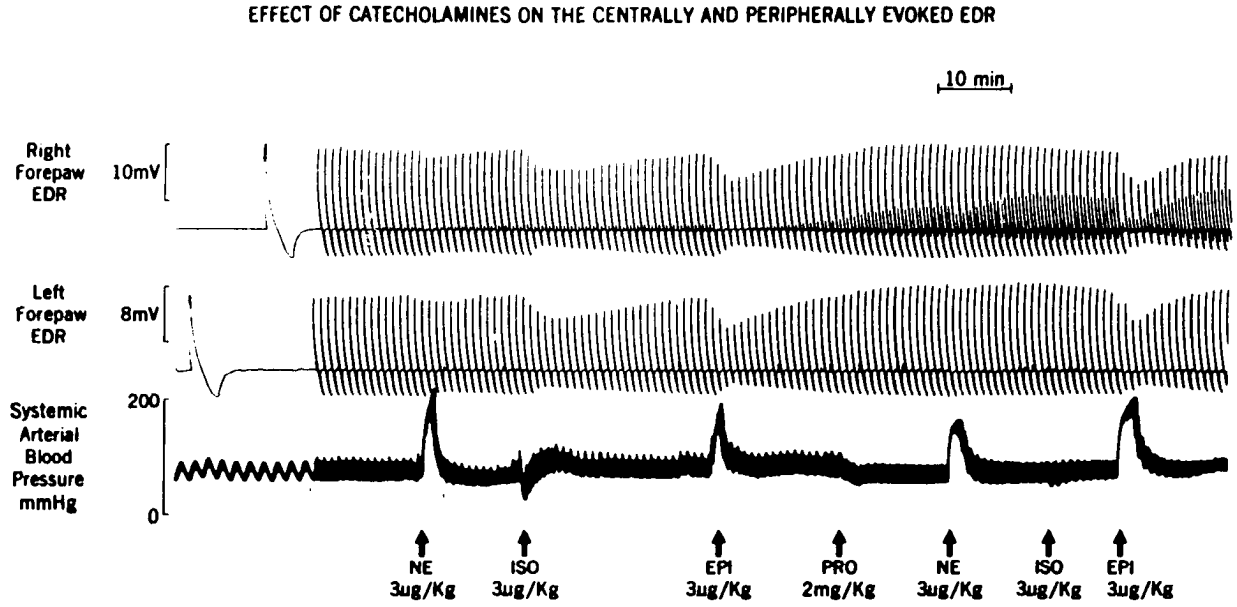

Figure 9 - Effect of catecholamines on centrally and peripherally evoked EDR. EDR recorded from right forepaw is evoked by hypothalamic stimulation and left forepaw EDR is evoked by stimulation of the distal portion of the severed median nerve. Note that propranolol abolished the effect of isoproterenol on both the blood pressure and the EDR. NE - norepinephrine, ISO - isoproterenol, EPI - epinephrine, PRO - propranolol

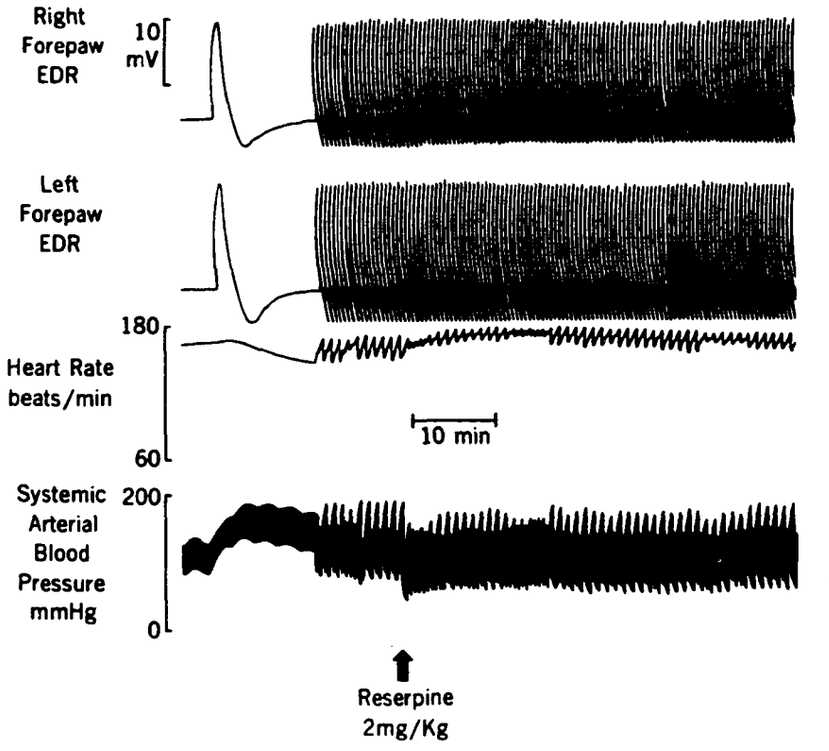

Figure 10 - Effect of reserpine on the EDR. Right forepaw EDR is the response to stimulation of the efferent peripheral nerve (ulnar). Left forepaw EDR is the response to stimulation of a ventrolateral pontine loci. Other tracings are heart rate and systemic arterial blood pressure. The stimulus was applied at 30 second intervals. Reserpine (2 mg/kg) was given i.v. at the arrow.

EFFECT OF CHLORPROMAZINE ON EDR EVOKED BY HYPOTHALAMIC STIMULATION

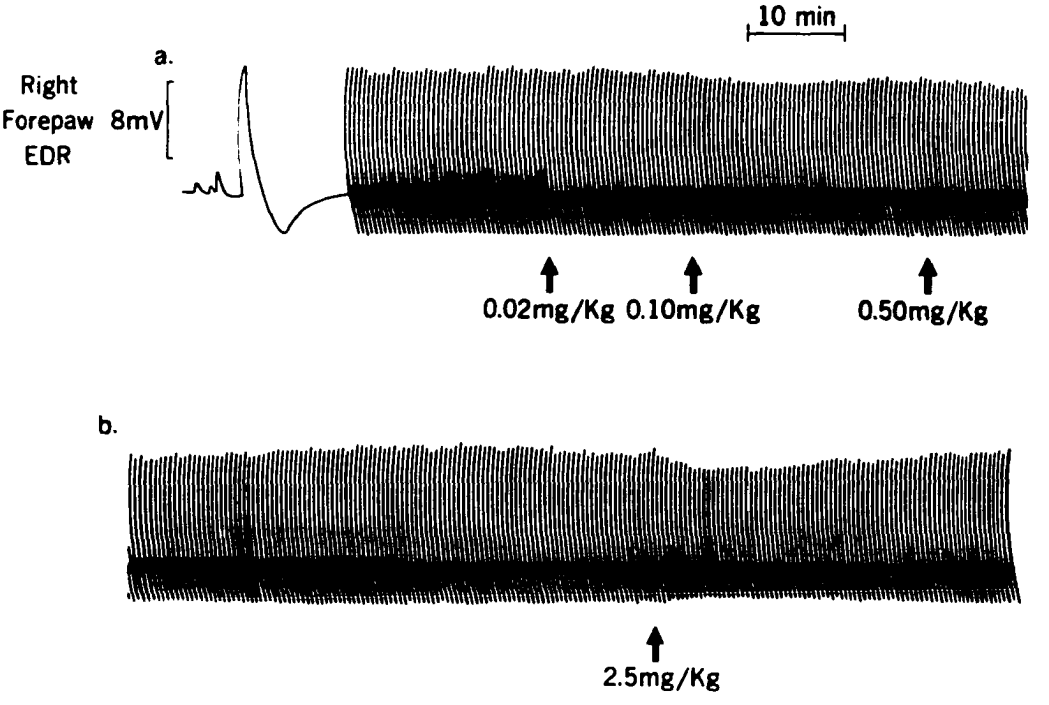

Figure 11 - Effect of chlorpromazine on EDR evoked by hypothalamic stimulation. The stimulus was applied at 30 second intervals. Panel b is a continuation of Panel a. Note the recovery of the EDR to control level following 2.5 mg/kg of chlorpromazine.

EFFECT OF CHLORPROMAZINE ON THE EDR EVOKED BY MESENCEPHALIC STIMULATION

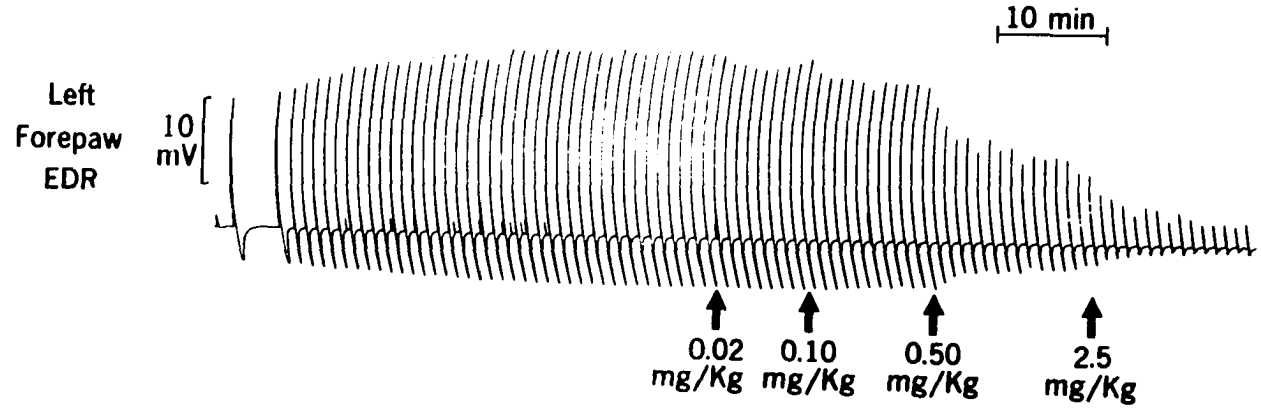

Figure 12 - Effect of chlorpromazine on EDR evoked by mesencephalic stimulation. The stimulus was applied at one minute intervals. Note the reduction in response magnitude after the larger doses of chlorpromazine (0.50 and 2.50 mg/kg).

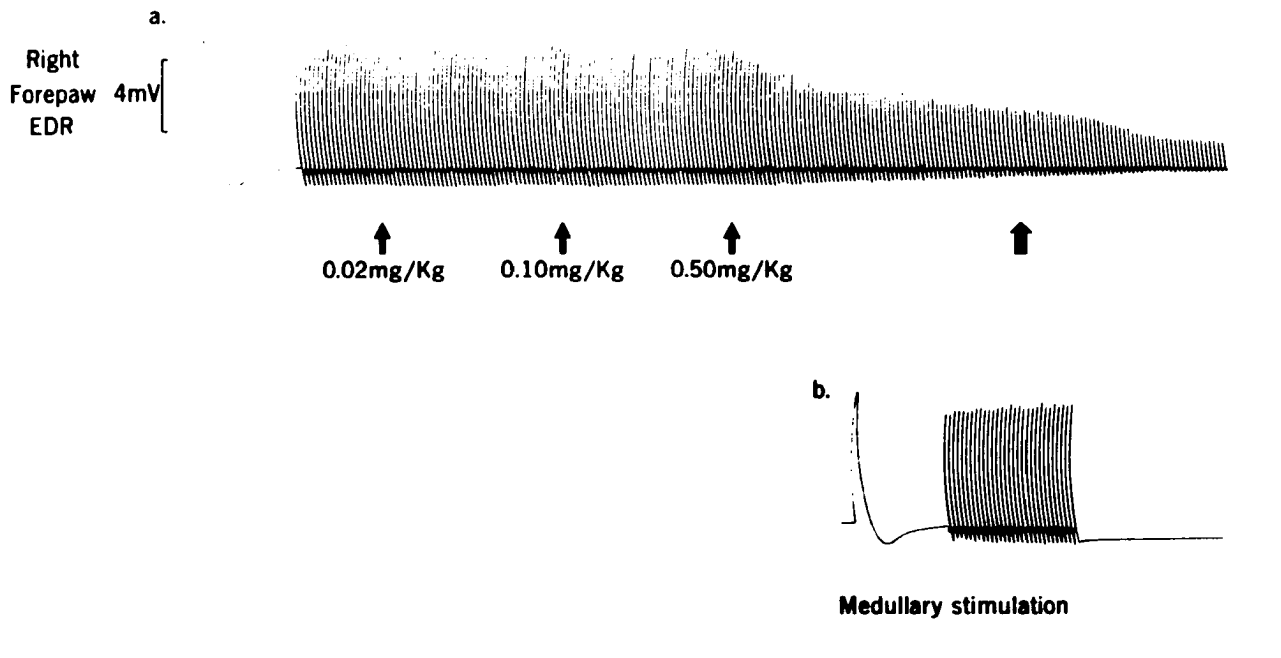

Figure 13 - Effect of chlorpromazine on EDR evoked by pontine stimulation. The stimulus was applied at 30 second intervals. Total time for panel a is 110 minutes. The largest dose of chlorpromazine (2.50 mg/kg) was not given since the response continued to decline. In an attempt to reestablish the EDR the current was doubled at the large arrow. Panel b shows the EDR which could be elicited from the ventrolateral medulla after the EDR evoked by pontine stimulation had been abolished by chlorpromazine.

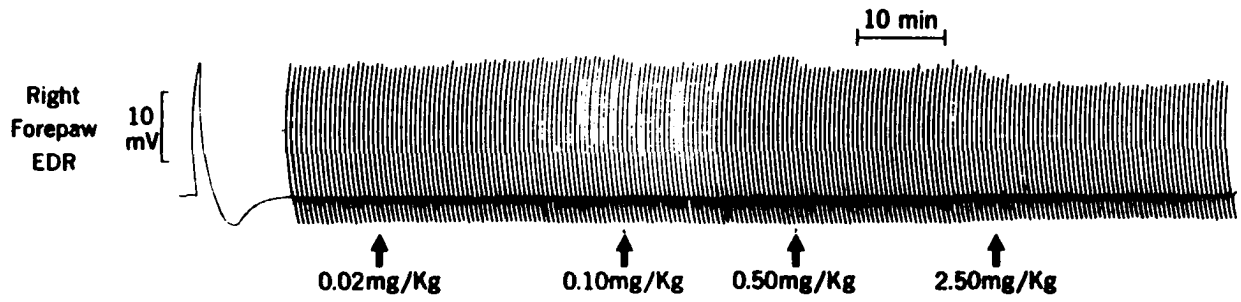

Figure 14 - Effect of chlorpromazine on EDR evoked by medullary stimulation. The stimulus was applied at 30 second intervals. Note that even the largest dose of chlorpromazine (2.50 mg/kg) caused only a small decline in the magnitude of the EDR.

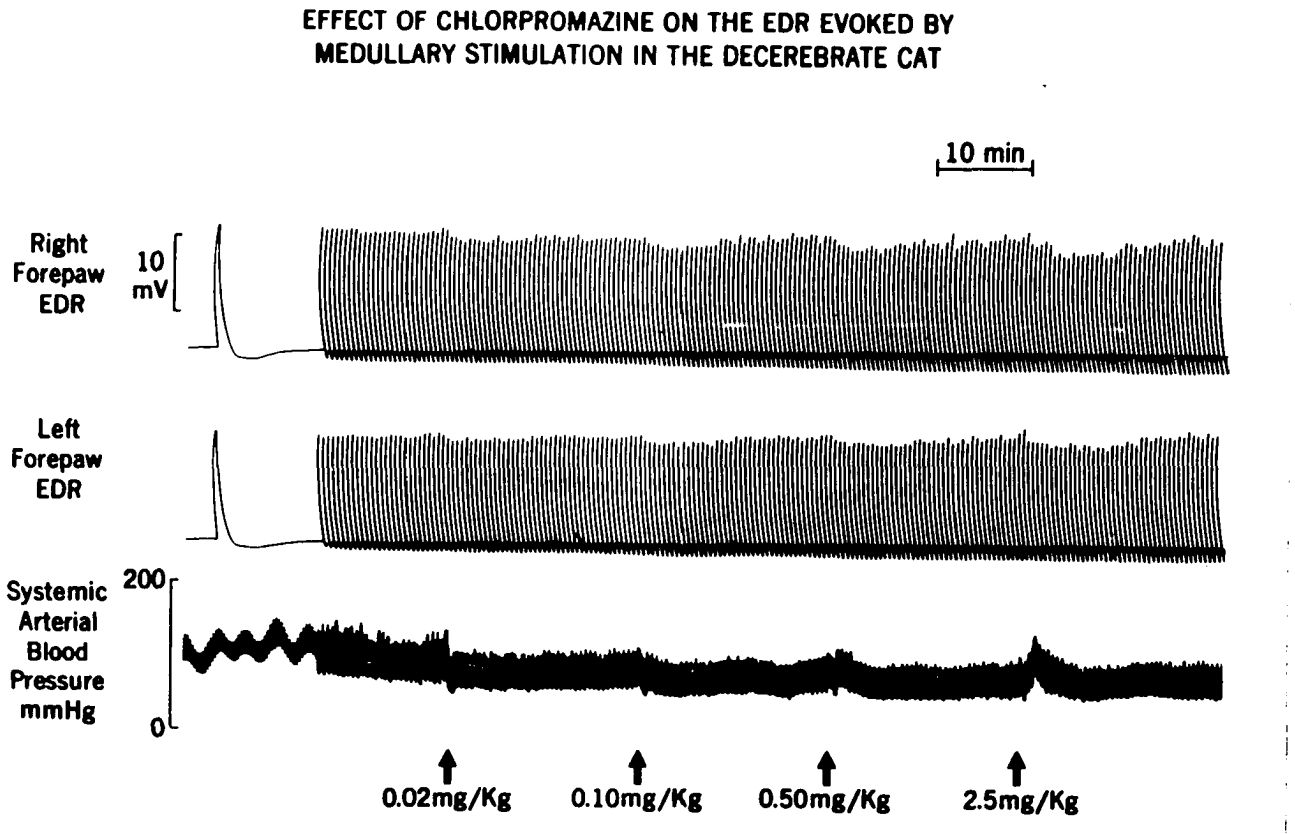

Figure 15 - Fffect of chlorpromazine on EDR evoked by medullary stimulation in the decerebrate cat. The stimulus was applied at 30 second intervals. Top two tracings are both EDR elicited by stimulation of ventrolateral medulla. Note the similarity to Figure 14.

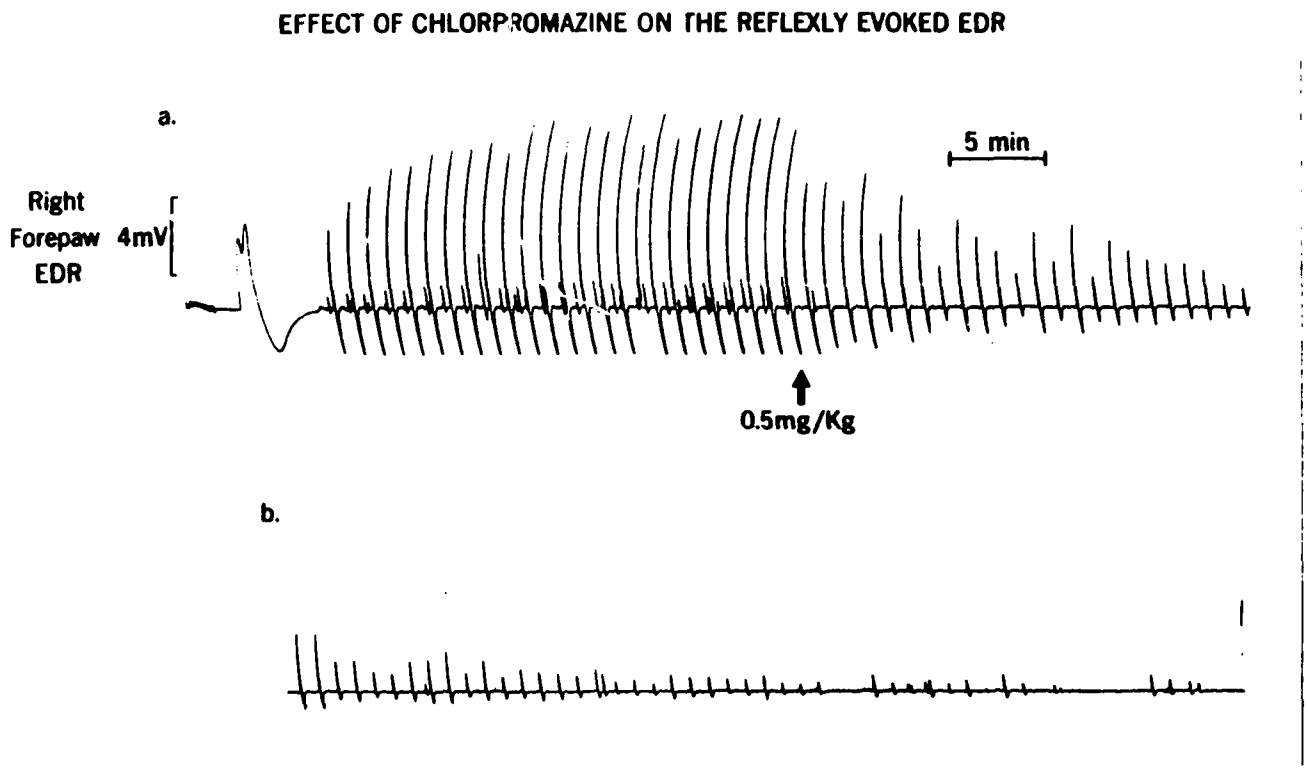

Figure 16 - Effect of chlorpromazine on reflexly evoked EDR. The electrodermal reflex is being elicited by stimulation of the peroneal nerve. Panel b is a continuation of panel a. The stimulus was applied at 50 second intervals. Note that the reflex is totally abolished by chlorpromazine (0.50 mg/kg).

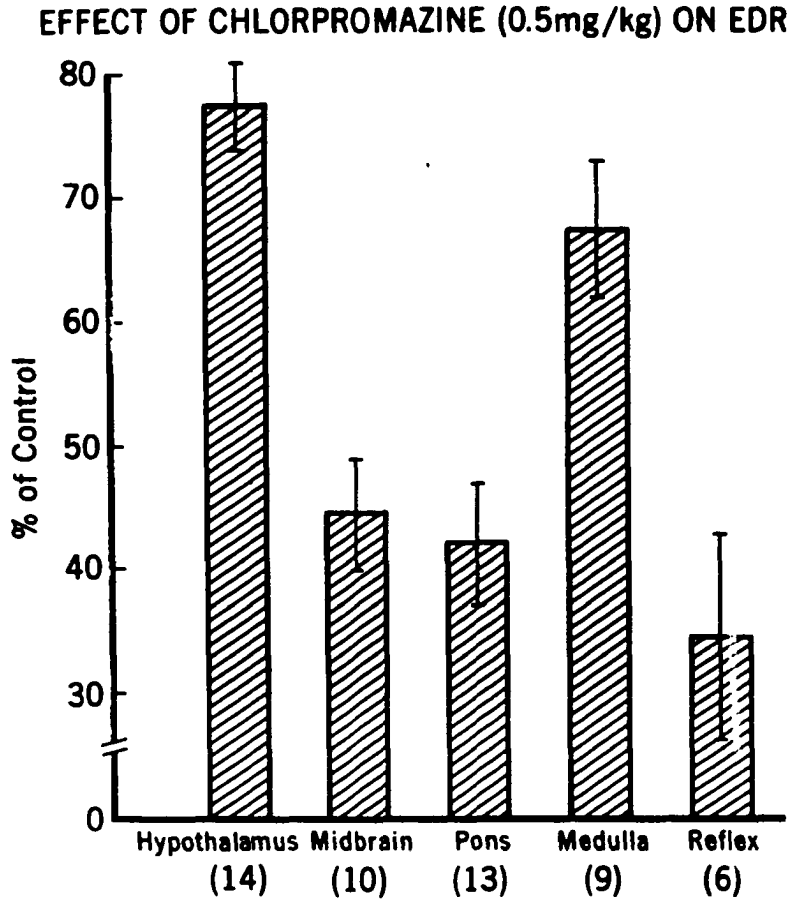

Figure 17 - Comparison of the effect of chlorpromazine on the EDR evoked from different brain stem sites. The mean percentage of control magnitude of the EDR following administration of chlorpromazine (0.50 mg/kg) is shown on the graph. Standard error of the mean is also illustrated for each group. Numbers below the brain stem sites indicate the number of animals in each group.

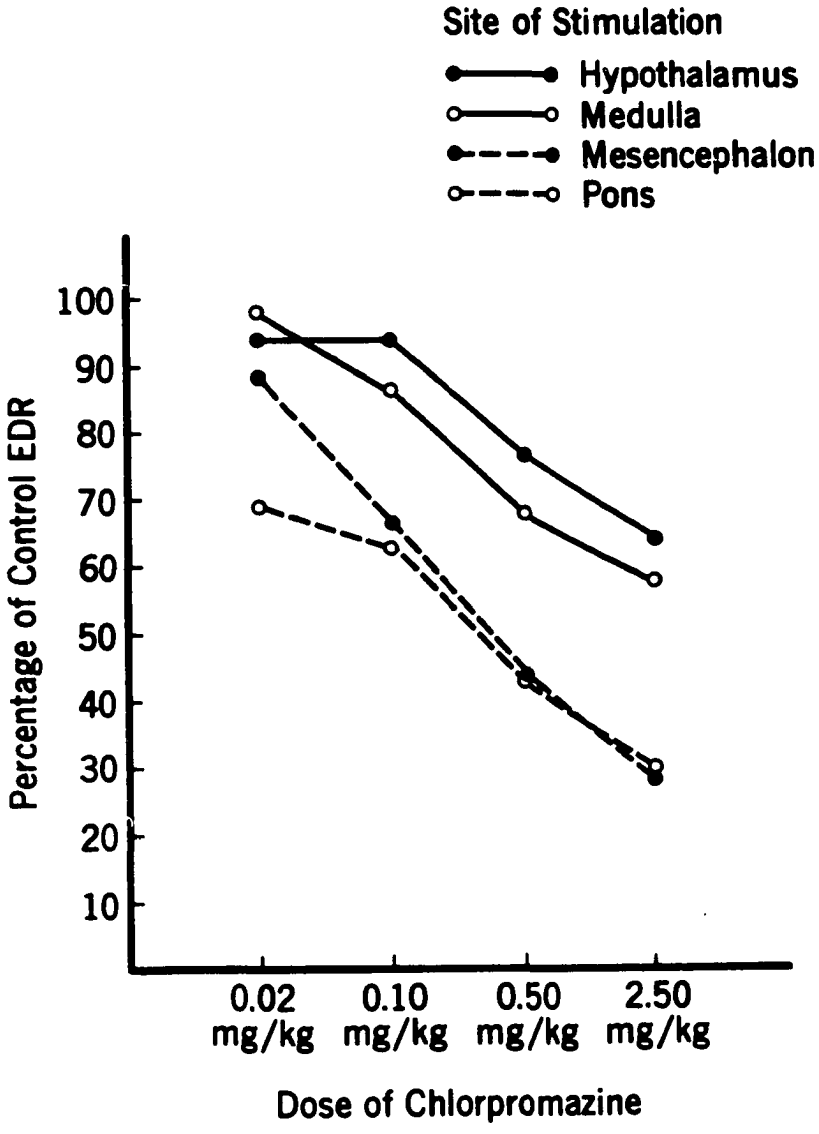

Figure 18 - Dose response effect of chlorpromazine. The mean percentage of the control EDR following increasing doses of chlorpromazine is shown for the EDR elicited from different brain stem loci. The N for each group is shown in Table 1.