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Motor-evoked potentials elicited from pyramidal system stimulation in the rat

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MOTOR EVOKED POTENTIALS

ELICITED FROM PYRAMIDAL SYSTEM

STIMULATON IN THE RAT

BY

JOHN RYDER

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, City University of New York.

1989

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Abstract

MOTOR EVOKED POTENTIALS
ELICITED FROM PYRAMIDAL SYSTEM
STIMULATON IN THE RAT

by

John Ryder

Adviser: Professor Rosario Zappulla

This study examines the generators and pathways mediating spinal motor evoked potentials to transcortical stimulation in the rat. A series of experiments were performed to define the electrophysiologic activity that is elicited during focal, low intensity stimulation restricted to the motor cortex under various conditions. The results demonstrate a long latency response originating in the cortex and recordable from the thoracic spinal cord which is different from the short latency responses previously reported. The conduction velocity of this later response is that reported for the pyramidal tract in the rat. Further experiments confirm that the

longer latency response depends upon activation of the pyramidal system in the motor cortex and travels through the pyramidal tract. The utility of the rat model and the implications of these results with respect to the motor system are discussed.

ACKNOWLEDGEMENT

There is purpose to everything. The purpose of science is to offer the most accurate explanations for the cause of certain things or events. Unfortunately, this path is often laborious, tedious and its fruits are sometimes difficult to appreciate. Those who boldly chose to explore science accept to bare its many burdens. Few are successful at this task, many even go unrecognized, plagiarized, ostracized, but those who can really call themselves scientists remain true to the ultimate objectives: truth, purpose and cause.

I have learned to appreciate science and admire those who know how to promote its forceful presence in our world. My mentor, friend and scientist Professor Rosario Zappulla has through his passionate pursuit of truth and meaning demonstrated to me what scholarship, research and science really can do. His wealth of interests and ever expanding knowledge is something for anyone to marvel at, as is his inexhaustable energy. He has earned the most

profound respect and admiration from this humble student. With respect to the completion of this dissertation I wish express my deepest gratitude to Professors Louis Gerstman and Bernard Karmel and doctors Richard Radna and James Adamson. These gentlemen embody the essence of humanity, wisdom, and scholarship. They have motivated me and supported me with great patience throughout this trying experience. I thank Victoria White and Julia Nieves whose laughs, smiles and technical assistance made this burden bareable.

I also have to thank my parents whose dream I am fulfilling, and most of my beloved Lidia, with whom I share many dreams, whose love, energy, enthusiasm, and great help made it possible for me to complete this work. Then, there are all of my wonderful friends who filled my days with hopes and joys. I thank them all for helping me achieve this goal.

J.R.

New York

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INTRODUCTION

Electrophysiology has been an effective tool in exploring the functional connectivity of the nervous system. Evoked responses have been used to assess the activation of specific areas of the nervous system to sensory and motor stimulation. Much of the work has been carried out in a clinical population where the effects of pathological lesions on selected components of the response have assisted in the elucidation of CNS generators of these responses. These studies have been supplemented by the use experimental animal models. This study examines the configuration of spinal evoked responses to electrical stimulation of the motor cortex in the rat. The special attributes of the rat model will be discussed and compared to other higher mammals with respect to the study of the motor system.

Recently, it has become possible to stimulate, with brief electrical or magnetic currents, the motor cortex through the intact scalp and to record evoked electrical responses from efferent pathways (Levy et al, 1984; Amassian and Cracco, 1987). Evoked responses to motor

cortex stimulation have been recorded from the spinal cord, peripheral nerves, muscle and the cortex contralateral to stimulation (Cracco, 1987). The evoked responses recorded either from the skin surface or by electrodes placed in proximity to neural structures have been referred to as motor evoked potential (MEP) to indicate their dependence on stimulation and activation of the motor system.

The MEP has been advocated as an experimental and clinical tool to investigate the integrity of the motor system, which was previously evaluated by behavioral measures of motor activity or invasive neurophysiological techniques. Previous studies have focused on the configuration of the MEP; neural generators of specific components of the MEP; the effects of stimulus parameters on the MEP and the effects of localized lesions on the MEP. In addition, animal models have been used in an attempt to expand our understanding of MEP generators. The MEP has also been used to evaluate the integrity of the motor system during experimental manipulation of the motor system.

Electrical stimulation of the motor system has been delivered through the intact cranium (transcranial

stimulation) (Merton and Morton, 1980) or directly on the cortical surface (transcortical stimulation) (Patton and Amassian, 1954). The spatial configuration of the stimulating electrodes has also varied among reports. Some studies have limited stimulus spread by employing closely spaced stimulating electrodes (bipolar stimulation) over the motor cortex area (Patil et al, 1985). Other studies have maximized current spread by using one electrode over the motor area referenced to an electrode a significant distance from the motor area (Levy et al, 1984). While MEPs have been elicited with either stimulus configuration, the stimulus threshold and shape of the MEP has varied depending on the technique used (Zappulla et al, 1988).

Activation of the motor cortex and subsequent activation of motor efferent pathways have been suggested as the mechanism for the generation of the MEP in man and in higher mammals (Amassian et al, 1987; Levy et al, 1986; Patton and Amassian, 1954). This is supported by the proximity of the stimulating electrode to the motor cortex. In addition, the conduction velocity reported for the MEP in higher mammals has been in the range established for pyramidal fibers (Rossini et al, 1985;

Merton et al, 1982; Lance, 1953; Patton and Amassian, 1954). Selective lesioning of the pyramidal system with reduction in the amplitude of the MEP has been offered as additional evidence that the MEP recorded from spinal cord, peripheral nerve and muscle is dependent on pyramidal activity (Levy et al, 1984; Adamson et al, 1988).

While the MEP in higher mammals may be completely or partially dependent on pyramidal activation, and, therefore, an appropriate measure of pyramidal activity in experimental models, this is not the case in lower mammals such as the rat. Several publications (Fehlings et al, 1987; Patil et al, 1985; Simpson and Baskin, 1987) have reported MEPs from the spinal cord, sciatic nerve and muscle to stimulation of the motor cortex in the rat. The configuration of the spinal MEP resembles that obtained in higher mammals, and, therefore, the response obtained in the rat has been attributed to activation of the pyramidal system as in higher mammals. However, recent reports by Zappulla et al (1988) and Adamson et al (in press) have demonstrated that the MEP in rats persists despite ablation of the motor cortex and the spinal pyramidal tract. In addition, the conduction

velocity of the rat spinal MEP was significantly faster than that reported for the rat pyramidal tract. These authors concluded that the rat MEP represents efferent activity propagated from stimulation of intracranial structures outside the motor cortex due to stimulus dispersion, and they cautioned against the use of the MEP as a measure of pyramidal system activity without further investigation into the generators of the MEP in the rat.

Because the rat has been used as an experimental model for studies of the motor system and the MEP has recently been advocated as a monitor of pyramidal activity in these models, it is essential to determine the neural generators of this response. Numerous studies have suggested that motor system in the rat may differ in fundamental ways from higher mammals, thereby making comparisons between MEPs in rats and higher mammals open to error.

The present study was designed to attempt to elicit an MEP from selective stimulation of the motor cortex in the rat. This was accomplished by minimizing stimulus dispersion by the use of closely spaced bipolar stimulating electrodes applied to the motor cortex. The configuration of the response and its conduction velocity

is described as well as the MEP changes to alterations in stimulus parameters. The MEP to motor cortex stimulation is compared to the MEP obtained with extrapyramidal stimulation. A series of experiments are reported which conclusively demonstrate that the MEP obtained with motor cortex stimulation represents activation of the pyramidal system alone.

BEHAVIORAL RESPONSES TO MOTOR TRACT STIMULATION

In 1870 Fritsch and Hitzig demonstrated that a galvanic current applied through bipolar electrodes to the anterior cortex of the dog produced movements contralaterally. Sixty-seven years later Penfield and Boldrey (1937) mapped the cortex of 126 patients by applying a small current to the exposed cortex while these individuals were under local anesthesia. The movements that were elicited by either a unipolar or bipolar electrical stimulus were brief, primitive, focal flexion or extension of the contralateral musculature. The sensations produced most often were tingling,

numbness or a sense of movement even in the absence of any visible movement.

These studies presented a detailed account of the sensory and motor events that followed localized stimulation of the cortical surface. It was primarily from this work that the human homonculus was conceived. Stimulation of any discrete cortical area often produced both sensation and movement in the same body part but never sensation of one part and movement in another. Consequently, the area surrounding the Rolandic fissure is referred to as the sensori-motor cortex.

Electrical stimulation of the motor cortex through the intact scalp (transcranial) has been demonstrated. Merton and Morton (1980) first described a non-invasive method to electrically stimulate the human motor cortex transcranially. They were able to consistently elicit flick movements of the opposite index and middle fingers to transcranial motor cortex stimulation through electrodes placed on the scalp.

In another study of transcranial motor cortex stimulation of anesthetized patients undergoing spinal surgery, Boyd et al (1986), using high voltage bipolar stimuli, consistently observed muscle activity. Rossini

et al (1986) introduced an alternative low voltage method of motor cortex stimulation (monopolar) by delivering electrical pulses between a large anodal electrode over the motor area and a flexible steel band around the head. They report eliciting motor responses at one-tenth the voltage required for bipolar stimulation. Unlike bipolar stimulation, this technique did not cause contractions of scalp and facial muscles or cause as much discomfort to the subject.

Transcranial monopolar stimulation was also used by Levy et al (1984) to elicit contralateral movements in anesthetized patients. Stimulus intensities ranged between 20 to 40 mA were used (Levy et al, 1986).

The location, polarity and configuration of the surface stimulating electrodes have been shown to be important in obtaining motor responses. When a sufficiently strong stimulus is applied at the scalp over the hand or leg sensori-motor cortex, movements in the respective contralateral muscles have been reported (Merton et al, 1982; Boyd et al, 1986; Rossini et al, 1986; Cowan et al, 1983; Rothwell et al, 1987; Levy et al, 1986). However, if the electrodes are placed on the scalp away from the motor strip, movement decreases or is

eliminated (Rossini et al, 1986).

A stimulus intensity that may fail to produce visible muscle movement may be adequate to excite small muscle groups. Consequently, investigators have used electromyographic (EMG) recordings following transcranial stimulation to identify muscle activity that might not result in visible motor activity. Merton and Morton (1980) successfully measured EMG latencies in muscle groups of the arms and legs at 16 and 34 msec respectively following contralateral transcranial motor cortex stimulation. These latencies were replicated on a larger sample of patients (Merton et al, 1982). The stimulus current needed to obtain EMG activity is lower than that required to elicit visible movement (Levy et al, 1984). Rothwell et al, (1987) recorded EMGs to magnetic and electrical stimuli and found a short but consistent latency difference between the magnetic and electrical stimulation, the latter being 2 msec faster.

Similar responses to transcranial and transcortical stimulation of the motor cortex have been described in other mammals. Gualtierotti and Paterson (1954) were the first to observe contractions of contralateral muscles following transcranial stimulation through the intact

scalp in the baboon. Hern et al (1961) also conducted a study of the baboon using direct cortical stimulation, and observed movements of the hand from stimulation over the central fissure. They reported that the polarity of the stimulus had an effect on the threshold of the motor response. The authors showed that anodal stimulation of the motor cortex had a lower threshold than cathodal stimulation. These studies corroborated the notion of a somatotopically organized motor cortex.

Motor activity in the cat has been investigated by Levy et al (1984) using a wide range of stimulus parameters. They reported eliciting contralateral movement in the fore- and hindlimbs to monopolar stimulation of the motor cortex (transcranial: scalp - anodal, palate - cathodal). The position of the stimulating electrode influenced which limb responded. With the stimulating electrode placed on the scalp (relative to midline) over the medial motor cortex, movement was elicited in the lower extremity, while placing the electrode more laterally produced motor activity in the forelimb.

Cortical mapping studies in lower mammals such as the rat have established accurate cortical areas where

electrical stimulation results in movement of the extremities (Hall and Lindholm, 1974; Donogue and Wise, 1982; Collins et al, 1986). The motor cortex is somatotopically organized. Using a monopolar microelectrode, Hall and Lindholm (1979) were able to define the motor cortex by observing movement in the contralateral limbs to cortical stimulation. The motor area was anatomically defined as that area from 1 to 3mm lateral to the midline with the anterior margin at the coronal suture extending 2mm posteriorly. The motor cortex was functionally divided into an anterior and posterior region, which on stimulation, produced short duration movements of the fore- and hindlimbs respectively. They found that thresholds to long duration (250 msec) 300 Hz stimuli were consistently lower than a 25 msec 1 kHz stimulus, and the mean difference between these two was 25 uA. The stimulus threshold at the surface of the cortex was 9 to 10 times greater than at cortical depths of 1.5 to 2 mm.

Patil et al (1985), using bipolar transcortical motor cortex stimulation in rats, observed EMG responses in the contralateral lower extremity. The distance between the stimulating electrodes was 6mm, with one

electrode placed over the motor cortex extradurally and 2mm posterior to the coronal suture just lateral to the midline while the other electrode was placed under the scalp. They report recording a polyphasic EMG responses with a latency of 6 to 7 msec after a brief 325 mV stimulus. Complete transection of the cord above the recording site resulted in total loss of the response.

Simpson and Baskin (1987) also reported EMG activity to motor cortex stimulation in the rat. Cortical stimulation was produced using a 2mm ball electrode epidurally on the motor cortex referenced to the hard palate with a cathodal square pulse ranging between 3 and 5 mA. EMG activity was measured through electrodes placed in the hindlimb muscles. Following cortical stimulation, six identifiable and replicable EMG peaks were recorded. The earlier peaks arrived 6 to 7 msec following cortical stimulation. The authors also reported hindlimb movement associated with the EMG activity.

THE CONFIGURATION OF THE MOTOR EVOKED POTENTIAL:

The electrophysiologic responses to transcranial or transcortical stimulation have been recorded from the spinal cord, peripheral motor nerves and muscle. The motor response occurs within milliseconds of stimulation and the latency increases the more peripheral the recording electrode. The response has been purported to arise from activity of efferent pathways of the motor cortex. Although some reports have suggested that the electrical responses arise from pyramidal tract activation, other studies suggest that the response may arise from extrapyramidal systems. The following is a summary of experimental and clinical findings in human and animal models.

Lance (1953) successfully recorded evoked responses from the spinal cord of the cat during stimulation of the pyramidal tract. He reported that the response recorded over the spinal cord consisted of two peaks. The conduction velocity of the earliest peak was calculated at 50 m/sec and for the slower wave at 8 to 70 m/sec. Lance concluded that the difference in conduction velocity was related to conduction down large and small

pyramidal fibers that have been identified in the corticospinal tract.

Based on findings in the cat and monkey, Patton and Amassian (1954) concluded that transcortical stimulation of the motor area resulted in evoked electrophysiological responses in the bulbar pyramids and lateral columns (corticospinal tract) in the cervical cord. They consistently recorded an initial positive peak which they labeled the "direct or D wave". This response was followed by a series of later waves which recurred at intervals of 2 to 2.5 msec and were labeled "indirect or I waves". The latency of the D wave at the pyramids in the cat was between 0.4 and 0.7 msec and was between 0.5 and 0.8 msec in the monkey. The D wave could also be recorded from the cervical cord where the latencies ranged from 0.75 to 1.0 msec in the cat and 0.75 to 1.2 msec in the monkey. They concluded that the D wave was a result of direct activation of pyramidal cells in the cortex since a synaptic delay would add at least 0.5 msec to the latency of the D wave. They estimated the conduction velocities of the D wave to range from 50 to 65 m/sec.

Patton and Amassian (1954) differentiated the D and

I waves on the basis of their behavior under a variety of physiologic conditions. The configuration of the D was resistant to high frequency stimulation, whereas the I waves were abolished at high stimulus rates. The D wave was also shown to be more resistant to cortical injury or asphyxia than the I waves. In addition, stimulus polarity was found to differentially effect the D and I waves. Anodal stimulation of the motor cortex was found to enhance the D wave while cathodal current favored the emergence of I waves. They concluded that the D wave arose from direct activation of pyramidal cells or axons while the I waves resulted from activation of pyramidal cells through an interneuronal network. The latencies of the I waves represent the synaptic delays that occur in the interneuronal network.

MEPs following motor cortex bipolar stimulation have also been elicited in dogs (Konrad et al, 1987). These investigators recorded responses simultaneously from the spinal cord and bilateral sciatic nerves. A 30 mA stimulus was necessary to elicit bilateral sciatic responses, whereas a stimulus of 10 to 15 mA was sufficient to elicit a MEP from the spinal cord. The conduction velocity of the MEPs calculated from the

sciatic nerve was 56 m/sec and from the spinal cord 63 m/sec (Konrad et al, 1987).

Spinal and sciatic nerve MEPs in the cat have been investigated by Levy et al. (1984). MEPs were recorded from epidural electrodes in the lower thoracic cord to bipolar monopolar stimulation. With monopolar stimulation, a complex response was recorded from the spinal cord. Conduction velocity of the first peak of the spinal response was 81 m/sec. The response became more complex as the stimulus intensity was increased. At the same stimulus intensity, bipolar stimulation failed to produce a response. Levy accounted for this difference by suggesting that the monopolar stimulus was more effective in exciting neuronal populations due to the spread and direction of the stimulus.

Merton et al (1982) estimated the conduction velocity of human spinal MEPs at 50 m/sec by measuring the MEP latencies from epidural electrodes in the spinal cord of patients undergoing surgery. They used a 0.1 uF condenser charged to about 2kV, discharged by a relay through electrodes with a 100 ohm impedance for a brief duration (50us); the positive electrode was placed over the motor cortex for the arm area while the other

electrode was placed 4cm anterior to the motor cortex (a bipolar montage). Their estimated conduction velocity was based on the difference between cortical stimulation and direct spinal stimulation above the recording electrodes. This estimate was corroborated by Boyd et al (1984) who conducted a similar study using the same high voltage bipolar stimuli as Merton and Morton (1982). The conduction velocities they obtained ranged between 50 and 70 m/sec.

In a more recent report, Boyd et al (1986) used high voltage bipolar transcranial stimulation in humans and reported producing MEPs from the spinal cord using epidural recording electrodes. Besides calculating conduction velocities from within the cord (ranging from 50 to 74 m/sec), they observed that the MEP latency decreased slightly with increasing stimulus intensity above threshold. They suggested that this effect could be caused by either the recruitment of faster conducting axons or by the spread of stimulation current to more distal parts of the cortical axon. Since activation depends on placement of the stimulating electrode over the appropriate contralateral motor area, they suggested that these MEPs arise from activation of the

corticospinal tract since it is the principle decussating pathway. Another observation in support of this conclusion is that the responses in the lower thoracic level were smaller than those at the cervical level. In addition to the effects of dispersion on the signal, it is known that the density of the corticospinal tract decreases in the lower cord which may account for this decrease in amplitude.

Rossini et al (1985) measured conduction velocity for MEPs in a human population during monopolar transcranial stimulation. The conduction velocity between the scalp and thoracic spine was calculated at 38.7 m/sec while the intraspinal MEPs were slightly faster at 55.4 m/sec. They also reported a significant relationship between the subject's height and peak latencies. Based on the fast conduction times, Rossini suggested that the MEPs are mediated by the fast pyramidal tract fibers that synapse monosynaptically on motor neurons and which are more susceptible than other fibers to trigger an impulse from electrical stimulation of the motor cortex.

Levy et al (1984) in the cat compared transcranial and transcortical stimulation using an anodal plate

electrode on the scalp (or cortex) and a cathodal electrode against the palate. The MEP was recorded from epidural electrodes on the spinal cord. Their results indicate that although both methods produce morphologically similar waveforms and latencies, direct cortical stimulation gave better resolution of the latter smaller peaks. However, when recording MEPs from the ulnar nerves bilaterally by transcranial stimulation, only a contralateral MEP was obtained whereas direct cortical stimulation produced an ipsilateral response as well. Levy et al (1984) estimated that current strength at the cortex is one thirtieth of that at the scalp, i.e., a 0.5 mA stimulus is effective at the cortex while a 15 mA current is required at the scalp.

Stimulation of the motor cortex, in addition to activation of spinal and peripheral efferent fibers, also excites contralateral cerebral structures. This has been demonstrated in humans by Amassian and Cracco, (1987) who were able to elicit an evoked response over the contralateral hemisphere to motor cortex stimulation. The response was purported to reach contralateral cortex through collosal fibers. The latency of the transcallosal response was measured to be between 9 and

11 msec. The conduction velocity was calculated at 13 to 17 m/sec based on the estimated distance across callosal fibers. These findings substantiate the role of the corpus callosum in mediating interhemispheric activity. This contention is also supported in a report by Levy et al, (1984) who demonstrated an increase in the amplitude of the MEP to motor cortex stimulation in a patient with a tumor of the contralateral motor cortex.

THE EFFECT OF STIMULUS PARAMETERS ON THE MEP

The previous discussion and review of the literature reveals that MEPs from the spinal cord, peripheral nerves and muscles have been elicited in several animal models using various stimulus configurations. Alteration of the stimulus parameters can result in enhancement or depression of various components of the MEP. This has been interpreted as a reflection of the changes in the excitatory levels or activation of additional neural structures. Consequently, any association between the peaks of the MEP and neural structures responsible for

their generation must take into account the stimulus parameters used to generate the MEP. The MEP does not appear to be an all-or-nothing phenomenon, since increases in stimulus intensity result in increases in peak amplitude and decreases in peak latency. Therefore, any classification of the MEP based on latency and amplitude must take into consideration stimulus parameters used to elicit the response.

Stimulation of the descending pathways through the intact scalp and skull in humans requires an adequate current. The resistance of the scalp and skull ranges between 6,000 to 16,000 ohms. Therefore, only 5 to 10 % of the stimulus current reaches the cortical surface (Geddes, 1987).

Current intensity, using closely placed bipolar stimulating electrodes, has been reported to be in the range of 340 to 2000 volts with a duration of 0.01 to 0.05 msec (Rossini et al, 1985; Mills et al, 1987; Merton et al, 1982). Rossini et al (1986) modified the stimulation technique of Merton and Morton (1980) by using a conductive band around the head as one stimulating electrode and one disk electrode over the motor cortex as the other. This configuration has the

effect of dispersing the stimulating current. Using this technique, they reported that only about one-tenth of the voltage was needed to elicit an MEP as compared to the technique used by Merton et al, (1982). Another variation of this was described by Levy et al (1984) who used a 3-5cm plate electrode over the motor strip and a second curved electrode placed up against the hard palate in the mouth. They found that a stimulus intensity of 20 - 40 mA with a duration of 1 msec and a frequency of 5 to 25 Hz was effective in producing movements of the extremities. However, the techniques of Rossini and Levy result in more dispersion of the stimulating current, therefore, increasing the possibility of exciting a greater number of intracranial neural structures.

As described earlier, MEPs can be elicited at much lower stimulus intensities with transcortical stimulation than with transcranial. Furthermore, stimulation at a depth of 2 to 3mm beneath the surface of the motor cortex enhances the response further (Levy et al, 1986). Direct stimulation of the cortex can be accomplished with any of the above stimulus configurations with adjustment of the stimulus intensity.

The effects of stimulus duration and frequency on

MEPs recorded from the spinal cord using a monopolar configuration have been reported by Levy et al (1984) in the cat. He reported that increasing the stimulus pulse duration from 0.05 to 1.0 msec resulted in a lowering of the MEPs stimulus threshold. The initial peak of the spinal MEP could be elicited up to a stimulus frequency of 300 Hz while the amplitudes of the later peaks decreased at rates above 100 Hz.

The physiologic mechanism enabling electrical or magnetic stimuli to initiate an action potential down specific nerve fibers has been addressed by Ranck (1975), Patton (1954), Marks (1975), Mills et al (1987), and Amassian et al (1987). Ranck reviewed various properties of neurons and discussed the proportionate size and type of stimuli that would excite them. He pointed out that when the electrode orientation is perpendicular to axons so that current flows longitudinally down the axon, the threshold is 4 to 5 times lower than if the electrodes are parallel and current flows transversely across the axon. This fact coincides with Levy's (1984) findings that monopolar stimulation was more effective in exciting neuronal populations.

Mills et al (1987) more recently reported that it is

uncertain which neural elements - dendrites, presynaptic terminals, cell bodies, efferent axons or some combination of these - are excited by scalp stimulation. The fact that MEPs are generated by brief currents necessitates a plausible theory of neural activation. Amassian et al (1987) proposed that for a given electric field intensity, the activation of a neuron is a function of (1) the orientation of the excitable portion of the neuron with respect to the electrical field, (2) the size of the neuron and (3) membrane excitability (the ratio of densities of voltage-dependent Na vs K ion channels).

In summary, stimulation intensity, polarity and orientation will determine the number and degree to which the surrounding neurons will be depolarized as a consequence of changes in the electrical field. Under the proper conditions, such an event will propagate a signal down the axons.

The preceeding review of the literature and discussion have presented conclusive evidence that stimulation of the motor cortex in man and in higher mammals can elicit motor activity and associated electrical responses (MEPs) in the spinal cord,

peripheral motor nerves and muscles. It has also been demonstrated that an adequate stimulus for eliciting motor activity and MEP can be produced under a variety of stimulus conditions. This motor and electrical activity is presumed to arise from activation of efferent pathways from the motor cortex (pyramidal system). Direct and indirect evidence that this is the case has been derived from recordings from intracranial and intraspinal efferent pathways as well as changes in the motor and electrical responses following experimental and clincial ablation of various components of the pyramidal system.

Recent evidence indicates that MEPs can be elicited from lower animals such as the rat following motor cortex stimulation (Fehlings et al 1987, Fehlings et al 1988, Zappulla et al 1988). Based upon the similarity of the configuration between the spinal MEP in the rat and in higher mammals, Fehlings et al (1987) have proposed that the response in the rat arises from activation of the pyramidal system. He and others have advocated the use of the MEP in experimental models of spinal cord injury to assess pyramidal system integrity. Zappulla et al (1988), however, have presented evidence that is in conflict with the conclusion that the spinal MEP in the

rat arises from pyramidal system activation. They present findings that demonstrate that the MEP elicited by monopolar stimulation arises from extrapyramidal efferent pathways. The following is a review of the literature on the findings and controversies regarding the MEP of the rat.

THE MEP IN THE RAT MODEL

Recently, several studies reported eliciting MEPs from the sciatic nerve, muscle and spinal cord to transcranial motor cortex stimulation. One group has reported that the configuration of the rat MEP was similar to that obtained from higher mammals (Fehlings et al 1987). These authors assumed that the MEP in the rat arose from pyramidal system activation as demonstrated in higher mammals. The spinal MEP consisted of a series of five peaks that occurred during the first seven milliseconds following stimulation. Fehlings et al (1987) and Fehlings et al (1988), labeled the initial peak of the rat MEP as the D wave and later peaks as I

waves, using the nomenclature for MEPs in man and higher mammals. They reported that the D wave had a conduction velocity of 67 m/second. This value is comparable to that obtained for the D wave in higher mammals. He demonstrated that the MEP represented activity in efferent spinal cord pathways by abolishing the MEP after spinal cord injury above the spinal cord recording electrode.

Simpson and Baskin (1987) and Patil et al (1985) reported eliciting muscle MEPs in the rat using the same stimulus parameters as Fehlings et al (1987). These authors demonstrated that lesions of the spinal cord abolished or significantly reduced the muscle MEP. Simpson and Baskin (1987) also reported an association between changes in the MEP and motor activity following spinal cord injury. They reported that complete loss of the MEP following spinal cord injury resulted in the complete loss of motor activity, while animals with reduced MEP amplitude had varying degrees of motor loss.

Zappulla et al (1988) challenged the pyramidal origins of the spinal MEP in the rat on several points. First, the conduction velocity reported by Fehlings et al (1987) for the initial peak of the spinal MEP was much

faster than that reported in the literature for conduction velocity of pyramidal fibers in the rat. Bannister and Porter (1967) reported that over ninety percent of the pyramidal fibers are between 1.0 and 2.5 microns in diameter with conduction velocities ranging from 8 to 18 m/sec. This value is significantly slower than that reported by Fehlings et al (1987) for the D wave which they purport arises from the pyramidal tract. Zappulla et al (1988) proposed that the response reported by Fehlings et al (1987) may represent activity in the extrapyramidal efferent pathways such as the rubrospinal tract, where the conduction velocity has been measured at 40 to 55 m/second (Kuypers, 1981), a value that is close to that reported for the initial peak of the rat spinal MEP.

Zappulla et al (1988) also challenged the pyramidal origin of the rat spinal MEP on the grounds that threshold anodal stimulation resulted in the initial emergence of the I waves. This is opposite to previously published studies by Patton and Amassian (1954) who demonstrated in higher mammals that anodal stimulation favors the emergence of the D wave through direct activation of pyramidal cells, while cathodal stimulation

favors the production of I waves through recurrent activation of pyramidal cells through neural networks.

Zappulla et al (1988) suggest that the above discrepancies may be explained by the spread of stimulus current within the compact intracranial compartment of the rat. Therefore, the rat spinal MEP, previously described, may arise from stimulation of neural generators outside the motor cortex.

This hypothesis was tested by Zappulla et al (1988) in a study where spinal MEPs were elicited using the same stimulus configuration as Fehlings et al (1987). The spinal MEPs obtained were identical to those reported by Fehlings et al (1987). MEPs collected to anodal and cathodal motor cortex stimulation produced enhancement of the initial peak (D wave) and the later peaks (I waves), respectively. These findings were in conflict with reports Patton and Amassian 1954. Zappulla et al (1988) reported that when the stimulus current was directed across the brain (motor cortex to palate) the amplitude of the initial peak of the MEP increased. In contrast, when stimulating current was restricted to the motor cortex, the response decreased. This is contrary to the assumption that activation of the motor cortex is

responsible for the rat MEP. More definitive evidence that the spinal MEP arises outside of the motor cortex was the persistence of the MEP following complete ablation of the motor cortex.

Zappulla et al (1988) concluded that the spinal MEP in rats to monopolar motor cortex stimulation arises from efferent pathways outside the motor cortex. Consequently, the labeling of the rat MEP as D and I waves is incorrect in light of the accepted use of this nomenclature for activity arising from motor cortex activation.

More recent evidence demonstrating the extrapyramidal origins of the rat MEP have been presented by Adamson et al (in press). These authors demonstrated that the rat MEP persists despite localized lesions of the spinal pyramidal tracts. The previous discussion demonstrates that the MEP generated by monopolar stimulation of the rat motor cortex arises from extrapyramidal systems. No conclusive evidence has been presented that an MEP can be elicited from pyramidal system activation in the rat. Evidence from previously published reports suggest that the localization of stimulus current to the motor cortex is essential to

activate the pyramidal system and prevent the activation of extrapyramidal pathways. In addition, previous studies have mitigated against recording a pyramidal MEP by using a short sweep duration. With a conduction velocity for pyramidal fibers between 8 to 18 m/second, then the pyramidal MEP in the thoracic cord would begin at 8 to 12 msec following stimulation. The short sweep duration used in previous studies most probably prevented recording the pyramidal response. Based upon the above, then the MEP arising from pyramidal activation should be elicited if the stimulus current is localized to the motor cortex and the recording epoch is lengthened.

STATEMENT OF THE AIMS

The preceding discussion has demonstrated that electrical stimulation of the rat brain results in activation of efferent pathways that results in an evoked response recorded from the surface of the spinal cord. The evidence suggests that this response arises from

activation of extrapyramidal pathways. As of yet no evidence has been presented that demonstrates an evoked spinal response following activation of the motor cortex and the efferent pyramidal pathway.

The present study will address the question of whether electrical stimulation of the rat's motor cortex results in an evoked spinal response that reflects activation of the pyramidal system. Stimulation of the motor cortex will be performed using the monopolar stimulus configuration previously described and also restricted motor cortex stimulation using closely placed bi-polar electrodes. The response will be monitored beyond the period of time required to obtain an extrapyramidal response. The configuration of the response will be described and the spinal origin of the response will be determined by the use of various reference electrodes.

The bipolar and monopolar stimulus response will be compared for waveform configuration and response latency. To prove that the response is physiological and not artifactual the effect of the spinal cord cooling on the response will be studied.

This study will test the hypothesis that the MEP

from pyramidal activation has a response latency longer than that reported in the literature for the rat extrapyramidal MEP and that the response latency of the MEP arising from pyramidal activation will be in the range predicted by published values for the conduction velocity of the pyramidal system in rat. Conduction velocity of the pyramidal MEP will be measured and compared to these published values and the similarity of these values will present indirect evidence that the response obtained arises from pyramidal activation. More direct evidence for a pyramidal origin for the response will be provided by the results of direct recording from the pyramidal tract and the effects of spinal cord pyramidal tract lesioning on the MEP.

A series of intensity studies will be performed to determine the response threshold of the pyramidal MEP.

The role of the motor cortex in the generation of the pyramidal MEP will be investigated in a separated series of studies. Bipolar stimulation outside the motor cortex will be performed in order to demonstrate that the pyramidal MEP is elicitable only from the motor cortex. The effects of permanent and temporary ablation of the motor cortex on the pyramidal MEP will be tested by

surgical ablation and spreading depression, respectively.

The implications of the pyramidal and extrapyramidal MEPs will be discussed with respect to the respective neuroanatomy of the rat motor system.

EXPERIMENT I

INTRODUCTION

The following experiments report on the ability to evoke a spinal pyramidal MEP following focal bipolar stimulation of the rat's motor cortex. In an attempt to determine the origin of the spinal MEP stimulus and recording parameters were varied. The effects of stimulus intensity and the depth of bipolar stimulation on the MEP configuration are reported. The conduction velocity of the spinal MEP are calculated. Recordings directly from within the spinal cord to focal bipolar stimulation are also reported. These experiments attempt to determine the configuration of a pyramidal MEP recorded from the spinal cord during bipolar stimulation of the rat's motor cortex.

METHODS

Surgery

Thirty-three Sprague-Dawley rats weighing between 250-300gm each were anesthetized with Ketalar (ketamine, 13 mg/kg intraperitoneally) and Rompum (xylazine, 35

mg/kg intramuscularly). The animals were tracheostomized, intubated, paralyzed (Tubo-curare) and respiration was maintained with a small-animal respirator (Model 683, Harvard Apparatus, South Natick, Massachusetts). A femoral venous line was used to administer fluids, and blood pressure was monitored through a femoral arterial line. Rectal temperature was maintained at 36 C with a heating pad. Arterial pressure and heart rate were monitored continuously. Blood gases were obtained periodically throughout the experiments and maintained within normal range. The animals were placed in a sterotaxic holder. Laminectomies and craniotomies were performed on the animals with the aid of a surgical microscope under 16 X and 25 X magnification (OPMI-1 microscope, Carl Zeiss Inc., 444 Fifth Ave., New York, New York).

The craniectomy was performed over the right hemisphere using a dental drill with a carbide tip under constant saline irrigation. The full anterior - posterior extent of the right hemisphere was exposed. The craniectomy extended medially to the sagittal sinus and laterally to the temporal lobe. The dura was opened with a 24 guage needle under 16 X magnification.

A laminectomy was performed in the lower thoracic spine (T9 - T10 levels) using a dental drill. The midline of the spinal cord was identified by the presence of vessels running on the midline of the posterior surface of the spinal cord. For some experiments, an additional laminectomy was performed in the upper thoracic region (T4 - T5 levels).

Stimulation

Monopolar and/or bipolar transcortical stimulation of the motor cortex was performed in thirty-three animals. The motor cortex extends approximately 2mm posterior to the coronal suture and lies between 1 and 3mm from the sagital suture (Hall and Lindholm, 1974). Bipolar stimulation was performed using two stainless steel electrodes 0.5mm in diameter fixed in a stereotaxic manipulator with which they were lowered onto the pial surface of the motor cortex; the interelectrode distance was 2 to 3mm. The electrodes were insulated except for the last 0.5mm at the tip. Monopolar stimulation was carried out with one 0.5mm electrode on the pial surface of the motor cortex and the second needle electrode, which was made of platinum, was placed submucosally in

the hard palate (Fehlings et al, 1988; Zappulla et al 1988).

Constant current stimulation was delivered through a Grass Constant Current Stimulator (model S44, Grass Instrument Co., Quincy, Massachusetts). For bipolar stimulation, the current was delivered between the two electrodes on the pial surface. Monopolar stimulation was delivered between the electrode on the cortical surface (anode) and the electrode in the hard palate (cathode). Constant current square wave pulses of 0.05 msec were delivered to the brain through a Grass stimulus isolation unit (model CCU-1) at 10.1 Hz. During the course of the experiment, the stimulus intensity was increased in steps until threshold was determined by the emergence of an MEP. In a separate experiment, stimulus intensity was increased above threshold in order to determine the effects of supra-threshold stimulus intensity on the MEP.

Recording

MEPs were recorded from the spinal cord with an insulated stainless steel (0.5 mm diameter) electrode. The electrode was uninsulated at the tip for

approximately 0.5mm. The electrode was inserted epidurally under the lamina above the laminectomy for a distance of 2 to 4mm and was referenced to a needle electrode placed in the adjacent paraspinal muscles. The animal was grounded by a subcutaneous copper band placed around the neck. The analog signals were amplified (400K X), filtered (bandpass 50 - 3000 Hz), artifacted and averaged on a QSI System 9000 (Quantified Signal Imaging Inc., Toronto, Ontario, Canada). Each MEP was the average of 200 to 500 stimuli. A sweep time of 12 msec was used to resolve short latency responses while long latency responses were collected with sweep durations of up to 200 msec. Data was stored on magnetic media for subsequent analysis. Each record was averaged and printed on a dot matrix printer.

PYRAMIDAL TRACT RECORDINGS AND LESIONING

In five animals, pyramidal tract recordings from the upper thoracic spinal cord were collected from a tungsten microelectrode with a resistance of 100 kilohm, positioned in the pyramidal tract and referenced to the adjacent paraspinal muscle. MEPs were collected from the lower thoracic electrode simultaneously. The location of

the pyramidal tract was determined from prior autopsy examination and measurement of the rat spinal cord.

MEPs were recorded from the upper and lower thoracic cord to monopolar and bipolar motor cortex stimulation at 10 mA. After obtaining baseline recordings, electrolytic lesions were made in the pyramidal tracts (upper electrode) by passing constant D.C. current (10 mA for 10 seconds) through the microelectrode using the same Grass S44 stimulator and constant current unit. During lesioning, the animal respirator was briefly turned off to eliminate small excursions of the electrode within the spinal cord caused by respiratory movement. On completion of the lesion, MEPs were recorded again.

The animals were sacrificed by an overdose of ketamine. The spinal cord was removed at the level of the upper thoracic lesion in order to determine the location and extent of the spinal lesion. These cord sections were frozen and then cut at a thickness of 40 microns and mounted on glass slides. The sections were stained by the hematoxylin and eosin method or by the Wiegert method. Alternate slides from the tissue block were processed by each method for comparison in determining the extent of the lesion.

CONDUCTION VELOCITY

In six animals the conduction velocity (CV) was calculated by measuring the distance from the site of motor cortex stimulation to the spinal cord recording electrode and dividing it by the latency of the first peak of the MEP. This distance was obtained by removing the spinal cord and brain enbloc and running a suture between the two sites. In five animals, where simultaneous recordings were obtained from the upper and lower spinal cord, intraspinal CV was calculated by measuring the distance between upper and lower recording electrodes and dividing the latency difference between the first peak of the MEP recorded from the upper and lower thoracic electrodes.

RESULTS

In nine animals, transcortical stimulation resulted in a complex waveform that could be classified into an early and late response depending upon the stimulus configuration used. Figure 1 depicts MEPs in one animal to a 10 mA monopolar and bipolar motor stimulus. The early response following monopolar stimulation consisted of a series of peaks occurring within the first 6 msec following stimulation (figure 1A). The waveform morphology of the early response obtained in all nine animals in this study corroborated previously published articles using monopolar stimulation (Fehlings et al 1987, Fehlings et al 1988, Zappulla et al 1988). When the acquisition time was increased to 90 msec, a longer latency response was observed following the early latency response (figure 1B). The longer latency response began at approximately 8 msec with two prominent peaks, followed by a series of oscillating waves decreasing in amplitude over time.

Figure 1 C illustrates the MEP response of one animal to a 10 mA bipolar stimulus of the motor cortex. The response has the same configuration as that of the late response to monopolar stimulation recorded during the same epoch duration. The major difference between the monopolar MEP and the bipolar MEP was the absence of the early latency activity during bipolar stimulation. The configuration of the bipolar response consisted of two initial prominent peaks with a mean latency of 8.8 (s.d. 0.73) and 17.1 (s.d. 1.83) msec respectively, at a 10 mA stimulation, were followed by a series of oscillating waves that progressively decrease in amplitude with increasing time from stimulation. With the sweep time extended to 200 msec, the resulting waveform configurations to monopolar and bipolar stimulation maintain their similarity and demonstrate the dampening effect on the amplitude of the later peaks (figures 1 D & E).

The rate of decay in the amplitude of the later peaks of the MEP were quantified by calculating the percent decrease in amplitude of each of the later peaks relative to peak 2. Figure 2 is a graph of these percentages for all peaks recorded subsequent to peak 2

for each of the nine animals to a 5 mA bipolar stimulus. As is evident in the graph, the decrease in amplitude of each subsequent later peak followed a linear trend.

In order to verify that the activity recorded from the spinal cord represented spinal activity and not electromyographic activity from the reference electrode, MEPs were collected in six animals with both the active and reference electrodes placed alternately on the spinal cord or muscle. Bipolar stimulation of the motor cortex resulted in a typical MEP response when both the active and reference electrodes were on the surface of the cord (figure 3A). When both recording electrodes were placed in the left and right paraspinal muscles, no MEP response could be recorded (figure 3B). The presence of the MEP with the spinal electrode but not the muscle electrode demonstrates the origin of the MEP to be in the spinal cord.

To further demonstrate that the long latency spinal MEP represents physiological activity and not electrical artifact, in three animals changes in the MEP were monitored during physiologic manipulation of the spinal cord. This was performed by collecting spinal MEPs to bipolar stimulation while the spinal cord was

progressively cooled with iced saline. Figure 4 A presents the MEPs of one animal to spinal cord cooling and rewarming. After two minutes of cooling, there is an increase in latency of all the peaks of the MEP. Following five minutes of spinal cooling there is a further decrease in amplitude and an increase in latencies of all the peaks. After twenty-five minutes of cooling, the MEP response was nearly abolished. In figure 4 B the spinal MEP is shown to slowly return when warm saline is used to reverse the cooling effects. Within five minutes the amplitudes of the MEP increase. After fifteen minutes the amplitudes and latencies of the peaks approach baseline values.

The stimulus threshold of these long latency MEPs was determined by progressively increasing bipolar stimulus intensity applied to the mid-motor area in six animals. The MEP responses were elicited at stimulus intensities as low as 1 mA in two of the six animals. Figure 5 A shows the MEP from one animal following a no stimulus condition and stimulation at 1, 2, 3, 5, and 10 mA to bipolar stimulation of the motor cortex. In all animals no response was obtained during the no stimulus condition. At 1 to 2 mA stimulation, the early peak of

the MEP emerged in all animals. With an increase in stimulus intensity, the later components of the MEP emerged. Figure 5 B illustrates a second animal's MEP with bipolar stimuli ranging from a 1 mA up to a 25 mA. These waveforms demonstrate that the long latency response does not change significantly beyond threshold stimulation (3 mA in figure A and 5 mA in figure B). With increasing stimulus intensity the amplitude of the first two peaks increased and the latency decreased. Tables 1 and 2 list the means and standard deviations for the latencies and amplitudes for the MEP peaks studied at various intensities in the six animals.

The effect of current spread during bipolar stimulation was assessed by increasing the stimulus intensity while recording the MEP in six animals during a 20 msec epoch. In figure 6 A, the MEP from one animal to a 2, 5, and 10 mA bipolar stimulus demonstrates that with increasing stimulus intensity, an early MEP response emerges which is almost identical to the monopolar response. These results were similar in the other animals studied. In another series of four animals, MEPs were collected during bipolar stimulation at varying depths into the cortex in 2mm increments. In figure 6 B,

the MEP recorded during a 20 msec epoch from one animal demonstrates the changes that occur with consecutively deeper bipolar stimulation. At the surface, the bipolar longer latency MEP is seen. Two millimeters below the surface, the bipolar MEP longer latency response increases minimally in amplitude. At a depth of 4mm, the longer latency bipolar MEP decreases and an early MEP response can be seen to arise. At 6mm the surface the early response increases in amplitude and the longer latency response disappears.

The mean CV for the first peak of the long latency MEP was 6 m/second calculated from the site of stimulation to the lower thoracic electrode for six rats during 10 mA bipolar stimulation. This value approximates the intraspinal CV of 4 m/second calculated using the distance between the upper and lower thoracic recording electrodes in five animals (figure 7).

To determine whether the MEP reflected activity in the pyramidal tract of the spinal cord, direct recording and lesioning of the spinal pyramidal tract was performed in five animals. A microelectrode was placed in the pyramidal tract at T4. Bipolar stimulation of the motor cortex was carried out as the electrode was lowered

through the cord. Table 3 lists the mean latencies and amplitudes for peaks 1 and 2 at four different electrode positions. While MEPs were recorded at each depth, the initial peak of the MEP was largest when the electrode was positioned in the pyramidal tract (2 and 3mm from the posterior surface of the cord) (figure 8).

In the same five animals, following positioning of the microelectrode in the pyramidal tract of the upper thoracic cord, lesions were made in the pyramidal tract following baseline MEP recordings. MEPs to bipolar and monopolar motor cortex stimulation were recorded from an electrode positioned in the lower thoracic epidural space. The pyramidal tract was lesioned and recordings from the lower thoracic cord were obtained. Figures 9, 10 and 11 demonstrate the effects of pyramidal tract lesions on the MEP for three of the animals. The early latency monopolar response does not change after lesioning of the pyramidal system (figure 10 D and figure 11 C). However, the long latency bipolar response is abolished following the pyramidal tract lesions (figure 10 C and figure 11 D). In figure 9 C, the response from the upper microelectrode post-lesioning represents the end response.

Figure 12 is a diagram of a cross section of the thoracic spinal cord in a rat indicating a lesion of the pyramidal tract.

DISCUSSION

The results of these experiments demonstrate that stimulation of the motor cortex results in an early and late spinal evoked potential. With monopolar stimulation, an early response occuring within the first seven milliseconds was observed, a longer latency response beginning at eight milliseconds and extending out to 100 milliseconds also was recorded. In contrast, stimulation restricted to the motor cortex using bipolar electrodes elicits only the later response which is identical to the late response obtained with monopolar stimulation and represents activity of the pyramidal efferent system. This later response was notable in that there was a dampening of the amplitude of the later waves with increasing time from stimulation. This dampening of the amplitude with the later peaks had a linear trend.

The persistence of the pyramidal MEP with recording electrodes placed on the cord and the absence of any evoked response when recording electrodes are confined to the muscle demonstrates the pyramidal MEP is generated within the cord. Similarly, the loss of the MEP with spinal cord cooling and its return during rewarming substantiates that this response is physiological as cooling would not be expected to produce changes in the response if it were an electrical artifact.

Both monopolar and bipolar stimulation resulted in similar thresholds for eliciting the pyramidal MEP. At super threshold levels of stimulation, there was minor enhancement of the amplitude of the response which remained unchanged with further increases in stimulus intensity. The only exception was the emergence of an early response with high intensity bipolar stimulation. The configuration of this response was similar to the early response of monopolar stimulation. The emergence of this early response during high intensity, bipolar stimulation most likely represents stimulus spread to efferent pathways outside the motor cortex, and the similarity in configuration between the bipolar early response and the monopolar early response suggests that

the same pathways are activated.

The CV calculated for the initial peak of the later component of the MEP was four to six meters per second. This value approximates published reports for the CV of pyramidal fibers in the rat (Bannister, 1967). These findings support the conclusion that the later response of the MEP originates in the cortex and travels down the pyramidal system because the latency to the spinal cord from the brain matches the CV for the pyramidal tract. This is corroborated by the presence of the pyramidal response recorded directly from the spinal pyramidal tract and from the results of pyramidal lesions which eliminate the response below the cord lesion.

EXPERIMENT II

INTRODUCTION

The results of the previous experiments provide substantial evidence that the longer latency MEP is generated by stimulation of the motor cortex. In order to test the hypothesis that the spinal MEP following bipolar stimulation of the motor cortex arises solely from pyramidal activation, the subsequent study investigated whether stimulation of non motor cortex results in a recordable spinal MEP. Low intensity bipolar stimulation was applied to the motor and non motor cortex in order to minimize stimulus spread. MEPs recorded from the thoracic spinal cord during cortical stimulation established a functional map of motor activity.

METHODS

Seven animals were prepared as described in experiment I. Recordings were obtained from lower thoracic cord as described in experiment I. The cortical

surface of the right hemisphere was stimulated using bipolar stimulation at currents just above threshold. The surface of the hemisphere was mapped at five positions in the anterior - posterior direction. The points of cortical stimulation are represented as millimeters anterior to or posterior to the coronal suture (0 mm), which delineates the anterior aspect of the motor cortex (figure 13).

RESULTS

Figure 13 presents the bipolar MEP recorded during a 100 msec epoch to a 3 mA stimulus applied to the pial surface of the cortex at 2mm intervals from the extreme anterior to far posterior of the right hemisphere. The 0 mm location was defined as the mid-motor area immediately lateral to the coronal suture which was labled "C". Occasionally, the stimulating electrodes had to be moved slightly forward or backward to avoid injury to a cortex vessel. A 3 mA stimulus was used because it was greater than the threshold response in all animals. The mapping revealed the largest MEP response to bipolar stimulation over the mid-motor cortex and a similar

response with lower amplitudes 2mm posterior to the coronal suture. The MEP response was absent when stimulating anterior to the mid-motor area or in the far (4mm) posterior area.

A second animal's response is presented in figure 14 which illustrates the spinal MEP in response to bipolar stimulation of the cortex. The MEP was successfully generated only with the stimulating electrodes over the motor area as in the previous example.

These mapping studies corroborate the findings of Hall and Lindholm (1979) and represent the topographic distribution of motor fibers at 0mm (mid-motor) and 2mm posterior for the forelimbs and hindlimbs respectively. The mean latencies and amplitudes for the mid-motor MEP response can be seen in tables 1 and 2 under the 3 mA column.

DISCUSSION

This experiment demonstrates that when focal electrical current is used to stimulate the cortex, only a restricted area of the cortex is capable of generating

a long latency MEP. This area corresponds to the cortical area reported by Hall and Lindholm (1979) to be responsible for contralateral motor activity during electrical stimulation. Therefore, the MEP may represent a neurophysiological correlate of motor cortex stimulation. In contrast, the short latency monopolar MEP elicited spinal responses from any position from far anterior to far posterior (Zappulla et al 1988).

EXPERIMENT III

INTRODUCTION

This research has demonstrated that focal stimulation of the rat motor cortex with bipolar stimulation can reliably elicit a spinal MEP. To determine that the only origin of the longer latency MEP is within the motor cortex, the following experiment was performed. The present experiment was performed to determine the effect of permanent and temporary ablation of the motor cortex on the generation of the spinal

pyramidal MEP. The question as to whether a pyramidal MEP persists in the absence of a functioning motor cortex is addressed.

METHODS

Surgical, stimulation and recording procedures for this experiment are described in experiment I. After bilateral craniotomies in six animals, baseline MEPs were collected following bipolar and monopolar stimulation of the left and right motor cortex. The electrodes were lifted off the cortex and the motor cortex and surrounding areas were ablated using suction and bipolar coagulation. On completion of ablation, the stimulating electrodes were placed in the same position on the brain as before ablation and bipolar and monopolar stimulation were performed.

To determine if reversable cortical depression is reflected in changes in the MEP, cortical depression was induced in the cerebral hemispheres of the rat by the application of potassium chloride (KCL) to the cortex. In six rats a saturated solution of KCL was placed onto

the exposed motor cortex. The KCL was applied to the cortex for two minutes. Bipolar and monopolar stimulation were performed prior to and following the application of KCL.

RESULTS

The results of cortical ablation on the MEP are presented for three of the six animals in figures 15, 16 and 17. The long latency response to bipolar stimulation is depicted in the top trace of each figure. In figures 15 and 17 both hemispheres were studied; first the right side was ablated and tested then the left side was ablated. Figure 15 A demonstrates baseline response in each hemisphere to monopolar stimulation of the motor cortex, 15 B represents the baseline response for both left and right hemispheres to bipolar stimulation. Figure 15 C demonstrates that the long latency response to bipolar stimulation was abolished after cortical ablation. The same finding can be observed in figures 16 B and 17 B. Despite cortical ablation both the early and a diminished late MEP persisted following monopolar

stimulation (figures 15D and 17C).

In figure 18, the effects on the MEP of spreading cortical depression on the right hemisphere can be seen during bipolar stimulation of the right motor cortex. After two minutes of KCL on the cortex, the bipolar response is diminished (figure 18 B) when compared to baseline recording (figure 18 A). Two minutes after rinsing with normal saline, the response is still depressed (figure 18 C). At five minutes post rinsing, the response returned to baseline levels (figure 18 D). In another animal, KCL was alternately applied to each hemisphere. Figure 19 presents MEPs following bipolar stimulation prior to and following KCL application to the right hemisphere. Following KCL application, there was complete loss of the bipolar response (figure 19 B). Five minutes after rinsing the brain with normal saline, the MEP is beginning to emerge (figure 19 C). Figure 20 presents the MEPs prior to and following KCL application to left hemisphere of the same animal. This figure shows the same loss and return of the MEP following KCL application.

DISCUSSION

The results of this experiment corroborate the findings in experiment 2 that the late latency MEP arises from stimulation of the motor cortex. Surgical ablation of the motor cortex resulted in the complete loss of the MEP. In contrast, the early response to monopolar stimulation persisted following motor cortex ablation substantiating previous claims that the early response arises from extrapyramidal stimulation. The partial persistence of the late response to monopolar stimulation may be explained by the fact that pyramidal efferent fibers are being stimulated subcortically.

MEP changes following the application of KCL demonstrate that physiologic ablation of the motor cortex has the same effect as surgical ablation. The fact that the MEP returned to baseline values at the end of the cortical depression suggests that the MEP can be used as a monitor of motor cortex integrity.

GENERAL DISCUSSION

This study provides experimental evidence that transcortical stimulation of the rat's brain can generate the early MEP and a longer latency MEP recorded from the spinal cord that has not been reported before. The results of these experiments support the conclusion that the early MEP, evoked by monopolar stimulation, is extrapyramidal, and not cortical, in origin. The longer latency MEP, when evoked by bipolar stimulation of the motor cortex, originates in the cortex in the pyramidal system and is mediated by the pyramidal tract within the spinal cord. It is important that the difference between the rat's cortical and non-cortical MEP be clearly defined so that it may serve as an effective and accurate model of motor activity and spinal cord integrity.

The short latency spinal MEP elicited by monopolar stimulation produced a polyphasic response as previously described (Fehlings et al, 1987; Zappulla et al, 1988). This early response is followed by a longer latency MEP during monopolar stimulation when the recording epoch

length was increased. When focal bipolar stimulation was restricted to the motor cortex the early response disappeared while the later response remained. This means that a low intensity stimulus localized within the motor cortex in the rat will generate only the long latency response which must be mediated by a different path from the early MEP response.

This distinction of an early and late MEP enables researchers to monitor the neurophysiologic activity of the cortex and deeper structures simultaneously. This may enhance the rat's clinical utility to model experimental manipulations of brain and spinal cord function.

In rats like higher mammals the motor cortex projects to spinal motor neurons via the pyramidal tract. In the rat the spinal pyramidal tract is located at the base of the dorsal columns in the posterior white matter, unlike higher mammals where it is located in the lateral white matter (Kuypers 1981; Ranson 1913). Localized electrical stimulation of the rat's motor cortex results in specific body movements that can be projected as a topographic map on the surface of the motor cortex (Hall and Lindholm 1974). The present study demonstrates for

the first time the ability to evoke a pyramidal response (pyramidal MEP) from the spinal cord to single pulse electrical stimulation restricted to the motor cortex in rat. Evidence has been presented to substantiate the pyramidal origin of the evoked response.

Previous studies have described an evoked spinal response occurring within the first 5 msec following brain stimulation (Fehlings et al, 1987; Fehlings et al 1988; Elgers et al, 1977). These studies concluded that the response arose from pyramidal activity based upon the similarity between the configuration of the rat evoked response and the pyramidal response described for higher mammals including man. These authors further substantiated their conclusion based upon the fact that one of the stimulating electrodes was directly over the motor cortex and that the conduction velocity for the evoked response was 60 m/sec, a value that has been calculated for pyramidal tract conduction in higher mammals. However, recently published findings suggest that this response arises from extrapyramidal efferent pathways (Zappulla et al, 1988; Adamson et al, 1989). Indirect evidence for an extrapyramidal origin for this early response is based upon the fact that a conduction

velocity of 60 m/sec is well above the value reported for the conduction velocity of the rat pyramidal tract, approximately 5-19 m/sec (Bannister and Porter 1967; McComas and Wilson 1967; Mediratta and Nicoll 1983). This value (60 m/sec) is in the range of that reported for the rat reticulospinal tract and indeed other studies have demonstrated a similar evoked spinal response in the rat elicited by stimulation of the reticular system (Shapovalov and Gurevitch 1970). More direct evidence for an extrapyramidal origin for this early response is the persistence of the response following motor cortex ablation (Zappulla et al, 1988) and spinal pyramidal lesions (Adamson et al). The extrapyramidal origin of the early latency response to monopolar stimulation was substantiated in the present study by the finding that lesions of the spinal pyramidal tract resulted in loss of the pyramidal response, but persistence of the early extrapyramidal evoked response.

Zappulla et al (1988) suggested that the early evoked response most likely arises from activation of extrapyramidal pathways due to stimulus spread. This conclusion is supported by the finding in the present study that with increasing stimulus current, during

bipolar stimulation, there is an emergence of the early latency evoked response. This can be explained by the spread of the stimulus current beyond the motor cortex to extrapyramidal structures. That these structures are most probably subcortical in location is supported by the finding in this study that the early extrapyramidal response was also elicited at low stimulus intensities when the bipolar electrodes are positioned subcortically in the white matter. This would explain the low threshold response of the extrapyramidal MEP using the monopolar stimulus configuration, where the stimulus is directed from the cortical surface to subcortical and brainstem structures.

When the stimulus is restricted to the motor cortex using closely placed bipolar electrodes and low stimulus current the spinal evoked response is limited to the longer latency pyramidal response. The dependence of the pyramidal response on the motor cortex is demonstrated by the inability to evoke a response when the stimulus is delivered outside the motor cortex. This was further demonstrated by the absence of an evoked response following permanent and temporary motor cortex ablation. The reemergence of the pyramidal response with increasing

stimulus intensity following motor cortex ablation may be accounted for by the excitation of the efferent pyramidal axons in the subcortical white matter. The higher stimulus intensity required to elicit the pyramidal response from axons, may reflect a higher stimulus threshold in the pyramidal axons as compared to pyramidal cell bodies and dendrites.

The configuration of the rat pyramidal response approximates that described by Patton & Amassian (1954) in higher mammals. The response consists of an initial sharp peak followed by a successive number of slower peaks that decrease in amplitude with increasing time from stimulus onset. The initial peak (D wave) of the response was attributed to direct activation of pyramidal cells, while that later peaks (I waves) were purported to arise from recurrent activation of pyramidal cells through cortical interneuronal loops. Certain findings in this study suggest that the origin of the rat pyramidal response differs from that described by Patton and Amassian (1954) for higher mammals. The ability to evoked short (D wave) and long (I waves) latency components of the pyramidal MEP in this study following cortical ablation argues against an interneuronal loop as

the generator for the I waves in rat.

Two alternative possibilities exist to explain the origins of these later waves of the pyramidal MEP in rat. First, previous studies of the rat pyramidal tract have demonstrated a non-uniformity in the diameter of the pyramidal axons and their myelin coverings. This indicates a range of conduction velocities for the axons that constitute the pyramidal tract. This would result in the type of complex waveform reported in this study with pyramidal tract activation. Each peak of the pyramidal MEP could represent a population of pyramidal fibers with different conduction velocities. However, while the differing conduction velocities for fibers within the pyramidal tract may explain the number and latencies of the peaks of the pyramidal MEP, it is difficult to explain the amplitude modulation of the later peaks of the pyramidal MEP by this mechanism. Although peak amplitude modulation could be accounted for by a linear decrease in the number of neurons with increasing conduction velocity, there is no experimental evidence to suggest that this is the case. The decrease in amplitude with increasing time from stimulus onset has been explained for higher mammals as a progressive decrease in

the level of recurrent excitation of pyramidal cells by cortical interneuronal loops.

As discussed above this is not the case for the rat pyramidal MEP, since ablation of the motor cortex does not preclude eliciting these later peaks with subcortical white matter stimulation. An alternative hypothesis is that the peaks of the spinal MEP reflect not only activity in pyramidal efferent fibers, but also postsynaptic activity of the cells that these fibers project to. Recurrent interneuronal loops within the spinal grey matter, which function similarly to those described in the motor cortex, have been described. These recurrent spinal interneuronal loops activated by efferent fiber activity may result in the recurrent excitation of motorneurons which is reflected in the occurrence and amplitude modulation of the later peaks of the pyramidal MEP. This hypothesis has recently been supported by preliminary data that shows that strychnine, a blocker of glycine a inhibitory transmitter in the spinal cord, applied to the surface of the spinal cord results in enhancement of the later peaks of the extrapyramidal MEP (unpublished data).

The rat's pyramidal MEP offers an important measure

to evaluate motor activity. Hall and Lindhlom (1974) demonstrated that trains of electrical pulses were required to produce movement during bipolar stimulation of the motor cortex. These authors failed to demonstrate any motor activity to a single electrical stimulus delivered to the motor cortex. This finding appears contrary to the finding in this study that single pulses to the motor cortex result in activation of the pyramidal efferent system at the spinal level. This would suggest that the evoked response at the spinal level may be present at stimulus levels less than that required to produce muscle activation and movement. Alternatively, the lack of movement with activation of the pyramidal system suggests that the pyramidal system may play an insignificant role in the generation of movement in the rat. This is supported by the findings of Castro et al, who demonstrated that incomplete transection of the pyramidal tracts in rats resulted in mild or no motor abnormalities. Even with complete transections of the pyramidal tracts in rat these authors reported that although there was a significant decrease in their motor performance they retained a considerable amount of motor function. Similar findings have been reported for higher

mammals including man (Lawrence and Kuypers, 1968; Bucy et al, 1963). It may be the case that the pyramidal system rather than initiating movement may play a modulating role over other efferent systems that initiate and maintain movement. These latter efferent systems may be responsible for the extrapyramidal MEP reported in this and previous studies.

The pyramidal MEP described in this study presents a unique tool for investigating experimental and clinical questions concerning the pyramidal system. As has been demonstrated this response depends upon an intact motor cortex and the descending pyramidal tract. Any manipulation of these structures may be monitored by means of the pyramidal MEP. For example, chemical manipulation of the motor cortex and alteration of its excitability with epileptic and antiepileptic agents may result in altering the stimulus threshold for the pyramidal MEP. These changes in excitability give a quantitative estimate of motor cortex excitability, which previously could only be accomplished by a qualitative analysis of motor performance. Similarly, experimental manipulation of spinal excitability by agents that effect spinal neurons may be assessed by the pyramidal MEP.

Perhaps the most significant application of the pyramidal MEP are in those experimental and clinical conditions that require continuous monitoring of spinal cord integrity. Indeed much of the impetus for development of a model of an electrophysiologic measure of efferent spinal activity arose in the area of spinal cord compression. Recent studies have urged the use of the MEP as an adjunct to other electrophysiologic measures in assessing spinal cord integrity following various experimental spinal cord injury models. The magnitude and direction of the changes in the MEP have been correlated with the extent of the spinal lesion as well as the amount of recovery following therapeutic experimental manipulations.

The clinical utility of MEPs have been described in other animals. Furlow et al, (1986) described the differential sensitivity of various components of the MEP to the effects of cerebral ischemia in the dog. Konrad et al, (1987) also studied the effects of cerebral ischemia on the spinal MEP in the dog to bipolar stimulation. They report that the MEP signals from peripheral nerves were eliminated after just one minute of ischemia (by cardiac arrest) after an initial increase

in amplitude. While the amplitudes of the spinal MEP decreased gradually and disappeared over several minutes. Zappulla et al, (1988) reported that anoxia had a similar effect in the short latency rat MEP.

The spinal MEP of the rat is also comparable to those of the cat. Levy et al. (1986); Levy et al. (1984) report that the MEP was more sensitive to cord injury than the SEP. Bennett (1983) comparing spinal MEPs and SEPs in the cat report that compressing the spinal cord resulted in complete elimination of descending activity at a point where there was only a 30 % decrease in the amplitude of the SEP. This again supports the potential value of monitoring spinal cord function with MEPs. Zappulla et al, (1988), also studied spinal cord compression and found the MEP a sensitive measure of cord function. Fehlings et al, (1988) conclude that the MEP and SEP are complimentary tests that together are a powerful monitor of spinal cord integrity.

SEPs have been an effective method of detecting focal lesions or pathological processes that affect the ascending sensory tracts through the brainstem to the cortex (Celesia, 1982; Owen et al, 1979; Cant and Shaw, 1986; Yamada et al, 1986). However, there are many

limitations regarding the reliability of SEPs during neurosurgical procedures (Bunch et al, 1983). The technical difficulties associated with recording SEPs and the lack of direct correlations between a given pathology and changes in SEPs creates a distinct need for a complementary neurophysiologic monitor. Consequently, a method to monitor the descending pathways, as in the MEPs, has been advocated by Boyd et al (1986; Owen et al (1980); Rossini et al (1986); Cracco (1986); Levy and York (1983) and Levy (1987).

MEPs have been used to monitor patients during surgery which entails a risk to their motor function. Levy (1987); Levy and York (1983); Levy et al. (1984); Amassian and Cracco, (1987) have all published reports of MEPs recorded from humans either in the laboratory or the operating room where spinal function was being monitored. Levy (1987) explains that as a new technique for monitoring neurological function during surgery, the MEP may soon become a routine practice.

The rat spinal MEP offers a method to quantitatively assess the functional integrity of the spinal cord as well as the cortical and subcortical functioning of the brain. The present study refines this measure in that it

describes for the first time in the rat model that the efferent pathways activated depend upon the type of stimulation and recording techniques. This finding has important implications for the application of the MEP to experimental spinal cord injury research. The effect on motor activity of lesions of each of each of these efferent systems is as yet undetermined. Consequently, an independent MEP measure of extrapyramidal and pyramidal integrity is important in evaluating the individual and combined effects of lesions of each system on eventual motor performance.

TABLE 1

THE MEAN LATENCIES FOR BIPOLAR STIMULATION (N=6)

		PEAK 1	PEAK 2	PEAK 3	PEAK 4
1 mA	Latencies:	8.04	18.79	35.67	
	(s.d.)	.98	2.55		
2 mA	Latencies:	7.05	17.34	30.71	42.23
	(s.d.)	.32	1.00	.67	2.33
3 mA	Latencies:	8.64	17.29	30.55	42.35
	(s.d.)	2.29	1.13	.81	2.11
5 mA	Latencies:	7.65	17.29	30.32	43.11
	(s.d.)	1.25	1.17	1.66	1.19
10 mA	Latencies:	8.28	16.05	28.66	40.99
	(s.d.)	.74	1.83	2.70	3.66

TABLE 2

MEAN AMPLITUDES FOR BIPOLAR STIMULATION (N=6)

		PEAK 1	PEAK 2	PEAK 3	PEAK 4
1 mA	Amplitude	4.66	2.09	2.31	
	(s.d.)	3.26	.95		
2 mA	Amplitude	8.42	14.30	1.66	4.30
	(s.d.)	4.19	6.46	.99	1.24
3 mA	Amplitude	9.98	11.94	2.34	4.44
	(s.d.)	4.95	7.76	1.89	3.19
5 mA	Amplitude	18.6	24.60	3.20	11.39
	(s.d.)	17.9	27.59	2.43	11.63
10 mA	Amplitude	25.65	26.86	1.68	11.10
	(s.d.)	18.91	26.20	1.21	9.2

TABLE 3

MEAN LATENCIES AND AMPLITUDES FROM DEPTH RECORDING WITHIN THE SPINAL CORD (N=4)

DEPTH	PEAK 1		PEAK 2	
	LATENCY:	AMPLITUDE:	LATENCY:	AMPLITUDE:
1 mm	7.04	36	17.60	50
2 mm	8.80	80	19.00	18
3 mm	9.15	70	19.00	12
4 mm	8.80	73	21.50	10

FIGURES LEGENDS

FIGURE 1. Spinal MEPs from a 10 mA mid-motor stimulus. Positivity is upwards in this figure and all subsequent ones. A: The MEP to monopolar stimulation recorded during a 12 msec epoch. B: The MEP to monopolar stimulation recorded during a 90 msec epoch. C: The MEP to bipolar stimulation recorded during a 90 msec epoch. D: The MEP to monopolar stimulation recorded during a 200 msec epoch. E: The MEP to bipolar stimulation recorded during a 200 msec epoch.

FIGURE 2. Graph of the percent of decrease in amplitude for each oscilating peak from the second peak of the long latency spinal MEP to a 3 mA bipolar stimulus in nine animals.

FIGURE 3. A: The spinal MEP from a 5 mA bipolar stimulus, recorded from the left epidural electrode referenced to the right epidural electrode. B: The activity recorded during the same epoch from the left paraspinal muscle referenced to the right paraspinal muscle.

FIGURE 4. A: A series of spinal MEPs recorded from a 10 mA bipolar stimulus. The first wave represents a baseline and each subsequent waveform indicates the number of minutes after irrigation began with iced saline. B: A

series of spinal MEPs recorded the number of minutes indicated after warm saline irrigation replaced the cold one.

FIGURE 5. A: The spinal MEPs recorded from one animal at different bipolar stimulus intensities starting at 0 mA up to 10 mA with a 100 msec epoch. B: Spinal MEP's recorded from another animal to a bipolar stimulus ranging from 1 mA to 25 mA with a 100 msec epoch.

FIGURE 6. A: The spinal MEP in one animal to a bipolar stimulus at increasing intensities recorded during a 20 msec epoch. B: The spinal MEP to a 10 mA bipolar stimulus at the cortical surface and at 2 mm increments below the surface in one animal.

FIGURE 7. A: The spinal MEP to a 5 mA bipolar stimulus recorded from the upper thoracic cord during a 90 msec epoch. B: The same MEP response recorded from the lower thoracic cord. The time difference between peaks in the upper waveform and lower one represent conduction latencies from the upper to lower spinal cord for the MEP.

FIGURE 8. This series of MEPs were recorded from the upper thoracic cord with a micro-electrode lowered through the cord in 1 mm increments. The epoch length was 100 msec, responses were evoked by a 10 mA bipolar stimulus.

FIGURE 9. The spinal MEP responses to 10 mA bipolar and monopolar stimuli during a 100 msec epoch; before and after placing stereotaxic lesions in the pyramidal tracts. A: The MEP response to monopolar stimulation pre and post lesioning. B: The MEP response to bipolar stimultion pre and post lesioning. C: The MEP response recorded from the micro-electrode in the upper thoracic cord pre and post lesioning. After lesioning the end response can still be identified in the recording.

FIGURE 10. The spinal MEP responses to 10 mA bipolar and monopolar stimuli during a 100 msec epoch; before and after placing streotaxic lesions in the pyramidal tracts. A and B: The baseline MEP response to bipolar and monopolar stimulation respectively. C and D: The MEP response after pyramidal tract lesioning in the upper thoracic cord to bipolar and monopolar stimultion respectively.

FIGURE 11. A and B: The baseline MEP response to monopolar and bipolar stimulation respectively. C and D: The MEP response to monopolar and bipolar stimulation after lesioning the pyramidal tract. The long latency MEP response is eliminated after lesioning.

FIGURE 12. A drawing of the upper thoracic cord section after lesioning (black area) the pyramidal tract (shaded area).

FIGURE 13. Bipolar MEP recorded during a 100 msec epoch to a 3 mA stimulus applied to the pial surface of the cortex at 2 mm intervals from the extreme anterior to far posterior of the right hemisphere. The 0 mm location was defined as the mid-motor area immediately lateral to the coronal suture which was labled "C".

FIGURE 14. The spinal MEP to a 3 mA bipolar stimulus, configured as in figure 13, showing the area of the cortes from where a MEP was elicited.

FIGURE 15. The spinal MEP elicited with a 10 mA monopolar and bipolar stimulus on the left and right hemispheres before ablation rows: A and B respectively. The same animal after cortical ablation to monopolar and bipolar stimulation rows: C and D.

FIGURE 16. A: The long latency spinal MEP response to a 10 mA bipolar stimulus. B: The long latency spinal MEP to a 10 mA stimulus after cortical ablation. C: The short latency monopolar response after cortical ablation.

FIGURE 17. A: Long latency spinal MEP responses from the left and right hemispheres to bipolar stimulation. B: Long latency spinal MEP responses from the left and right hemispheres to bipolar stimulation after cortical ablation. C: Long latency spinal MEP responses from the left and right hemispheres to monopolar stimulation after cortical ablation.

FIGURE 18. A: The long latency response to a bipolar stimulus. B: The latency response after application of KCL to the cortex. C: the long latency response two minutes after rinsing KCL with saline. D: The long latency response five minutes after rinsing KCL with saline.

FIGURE 19. The long latency response from the left hemisphere to a 10 mA bipolar stimulus at baseline (A), after KCL application (B), and five minutes after rinsing KCL with saline (C).

FIGURE 20. The long latency response of the same animal on the right hemisphere to a 10 mA bipolar stimulus at baseline (A), after KCL application (B), two minutes after rinsing KCL with saline (C), and five minutes after rinsing the KCL with saline (D).

FIGURE 1

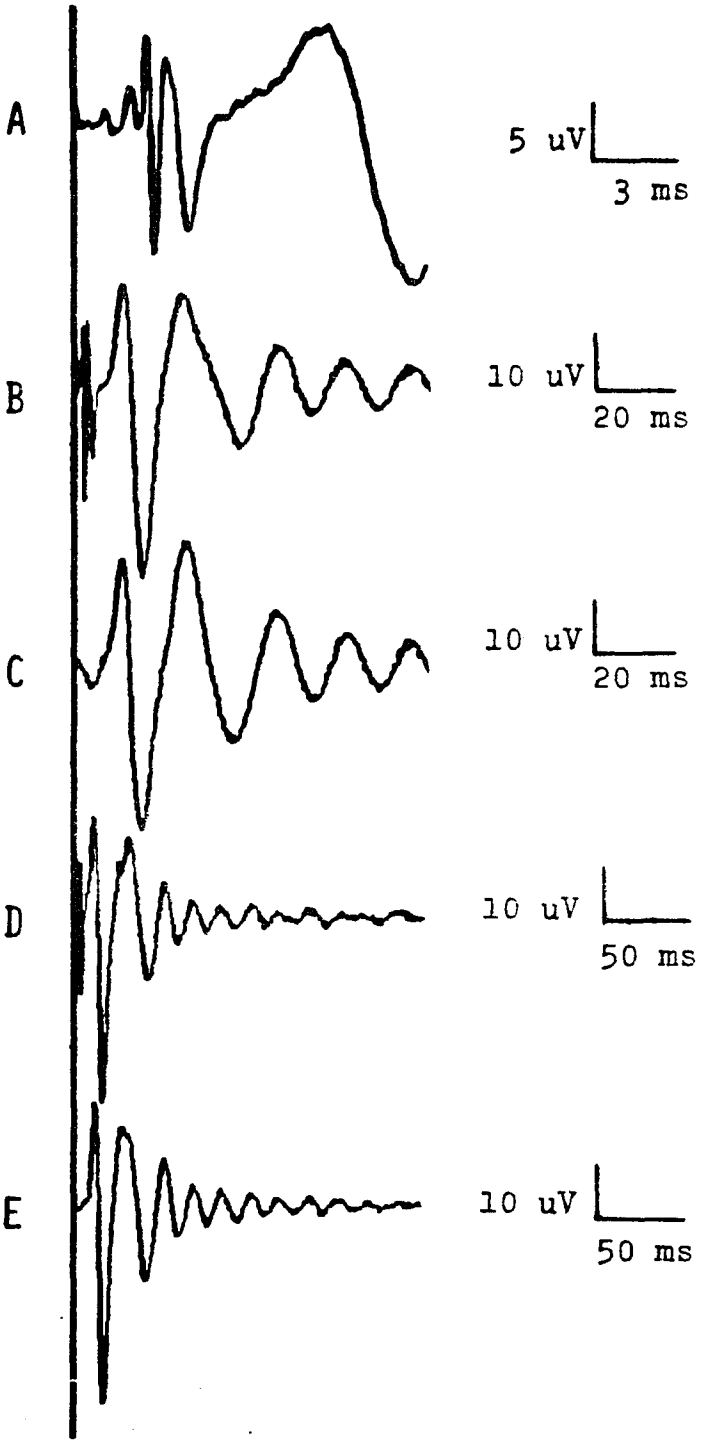
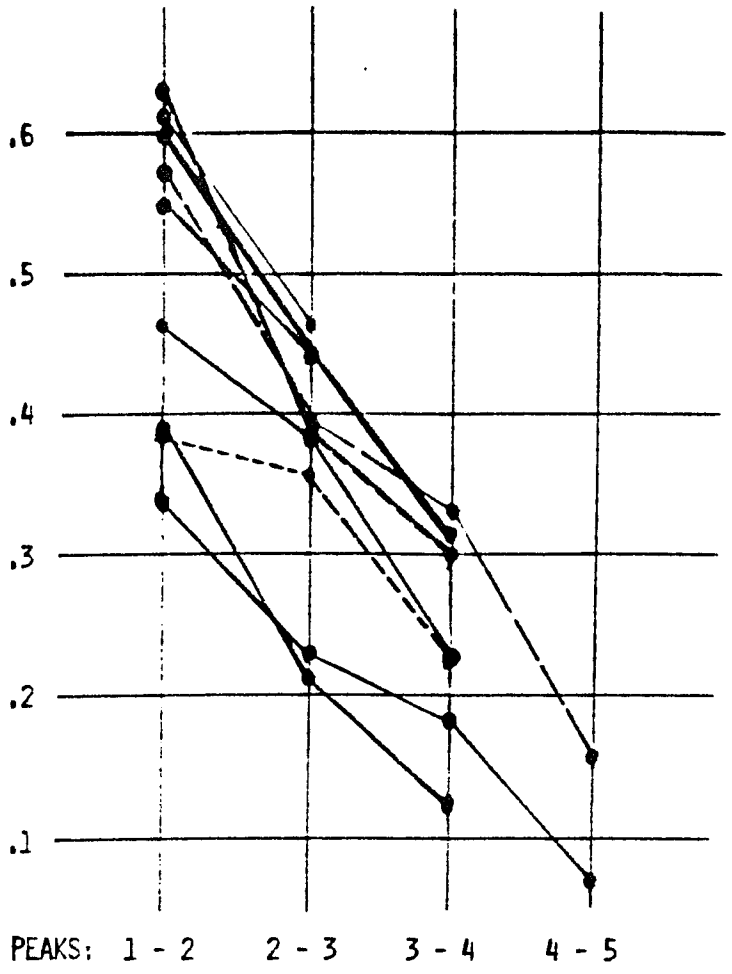


FIGURE 2



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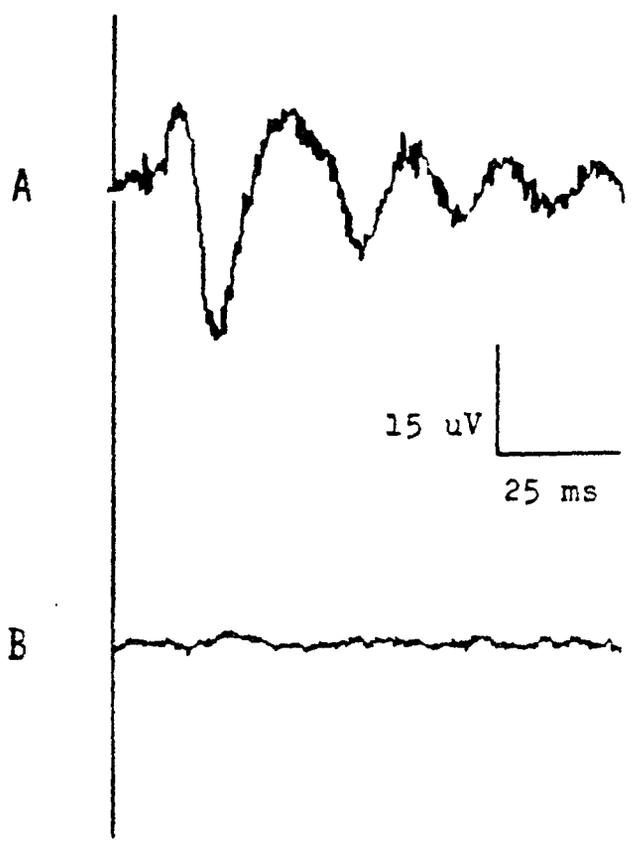


FIGURE 4

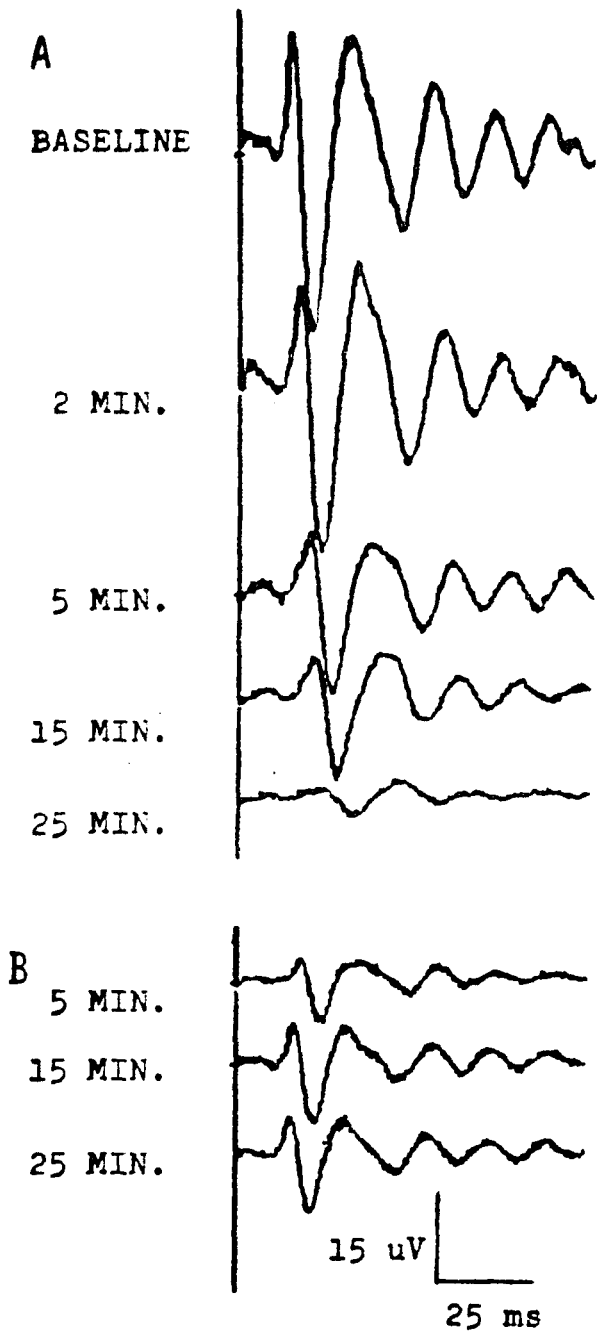

A
BASELINE
2 MIN.
5 MIN.
15 MIN.
25 MIN.
B
5 MIN.
15 MIN.
25 MIN.
15 uV
25 ms

FIGURE 5

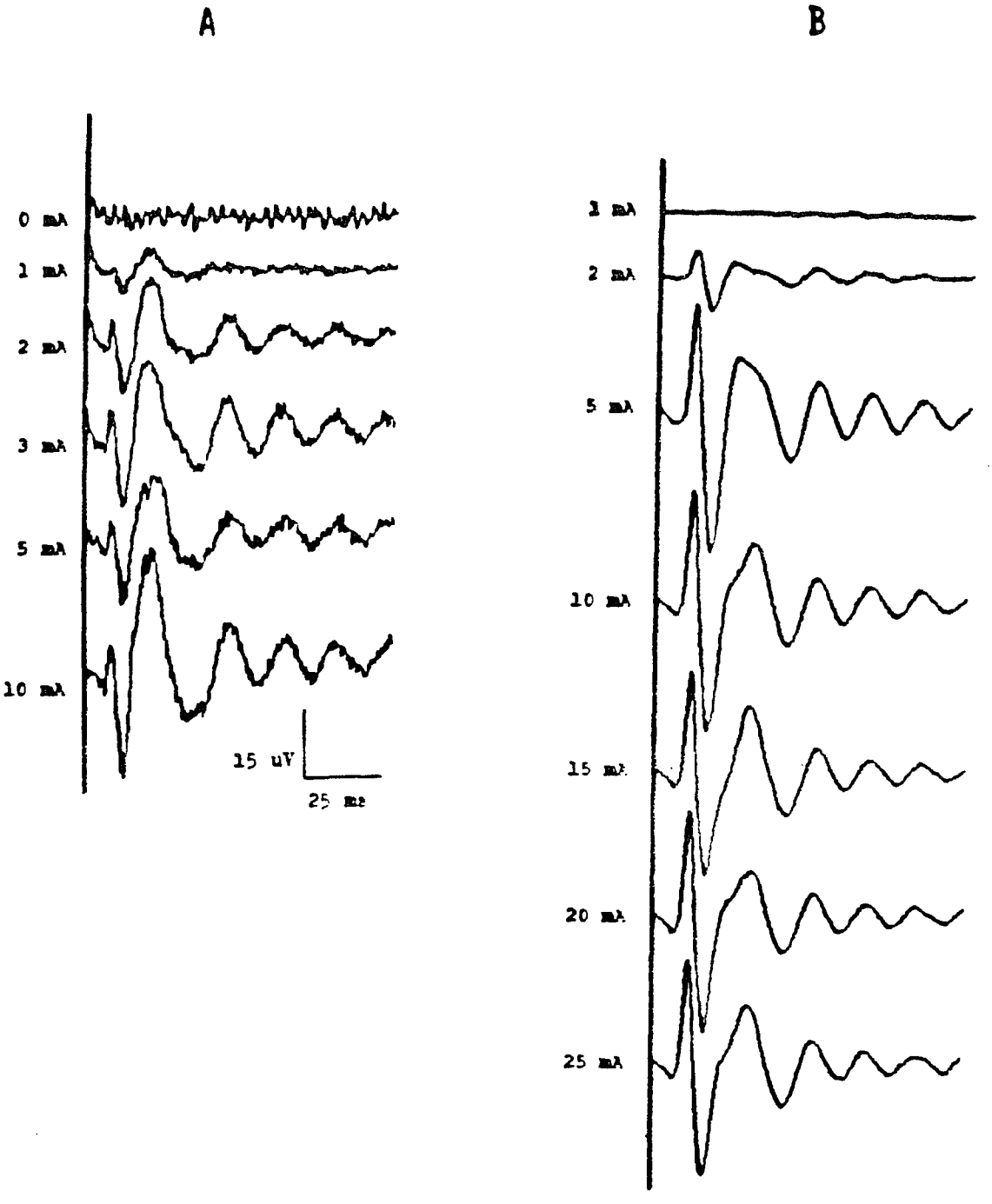

A
B
0 mA
1 mA
2 mA
3 mA
5 mA
10 mA
15 uV
25 ms
1 mA
2 mA
5 mA
10 mA
15 mA
20 mA
25 mA

FIGURE 6

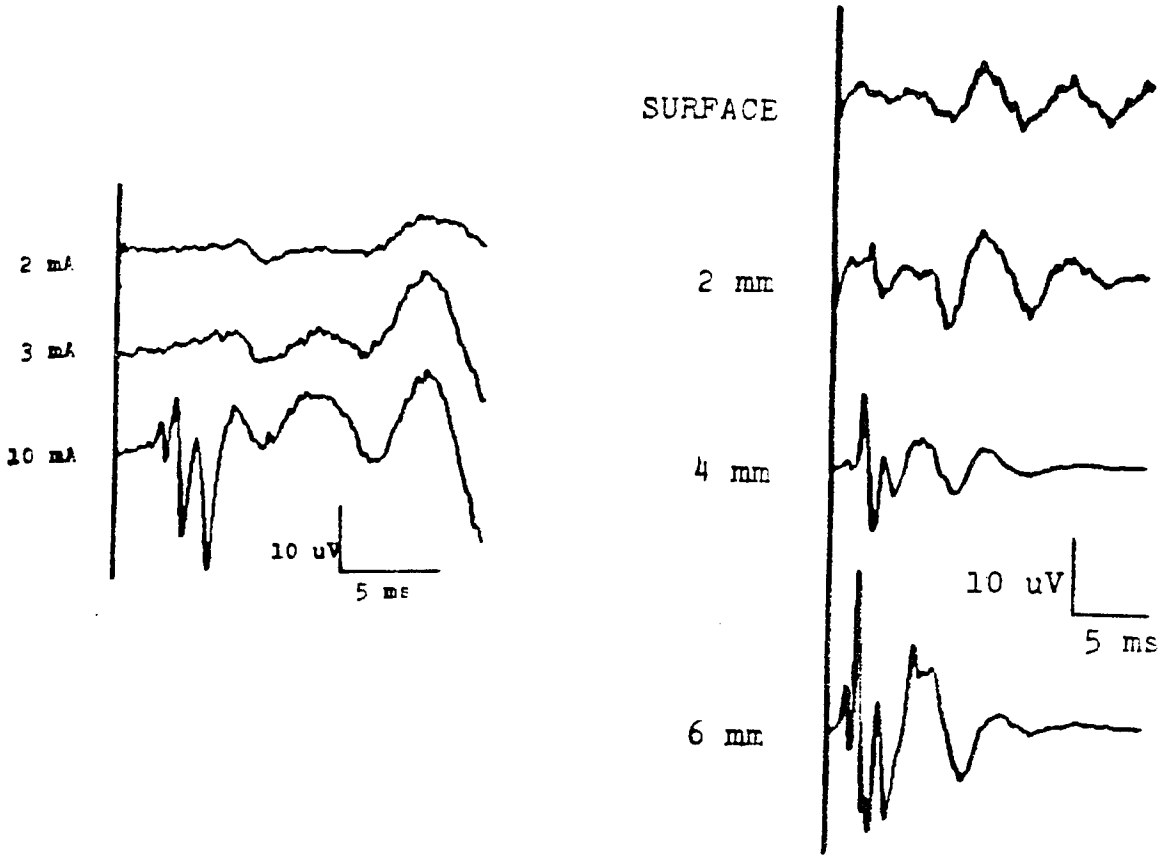


FIGURE 7

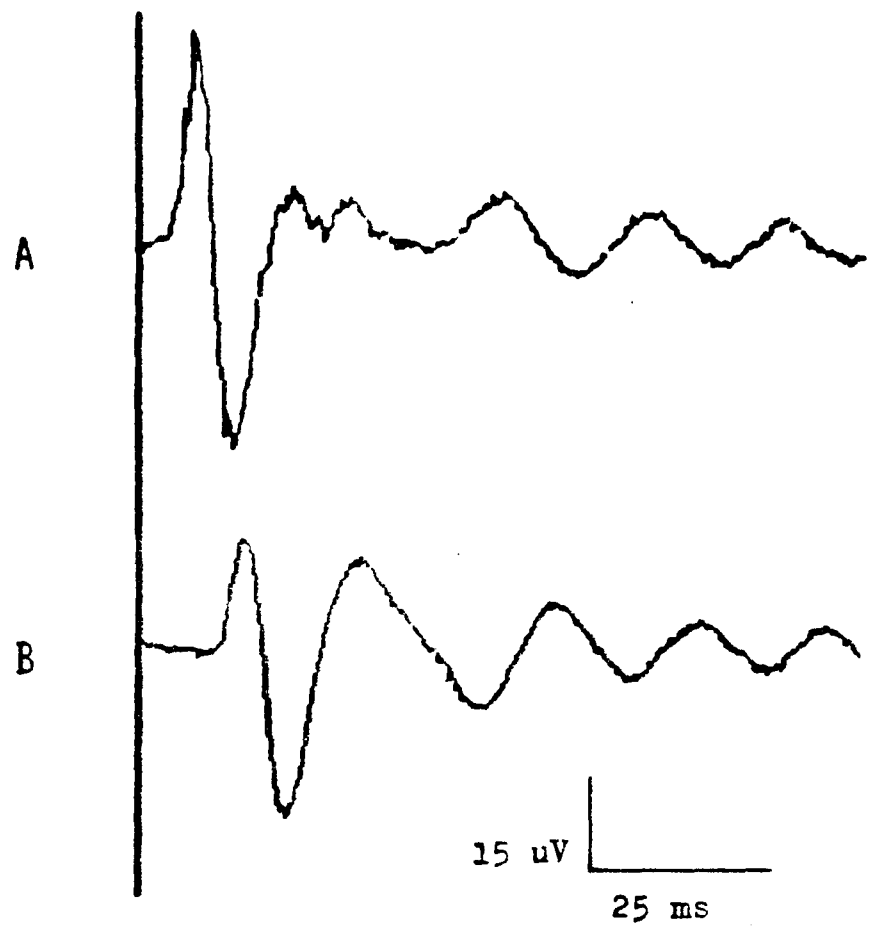


FIGURE 8

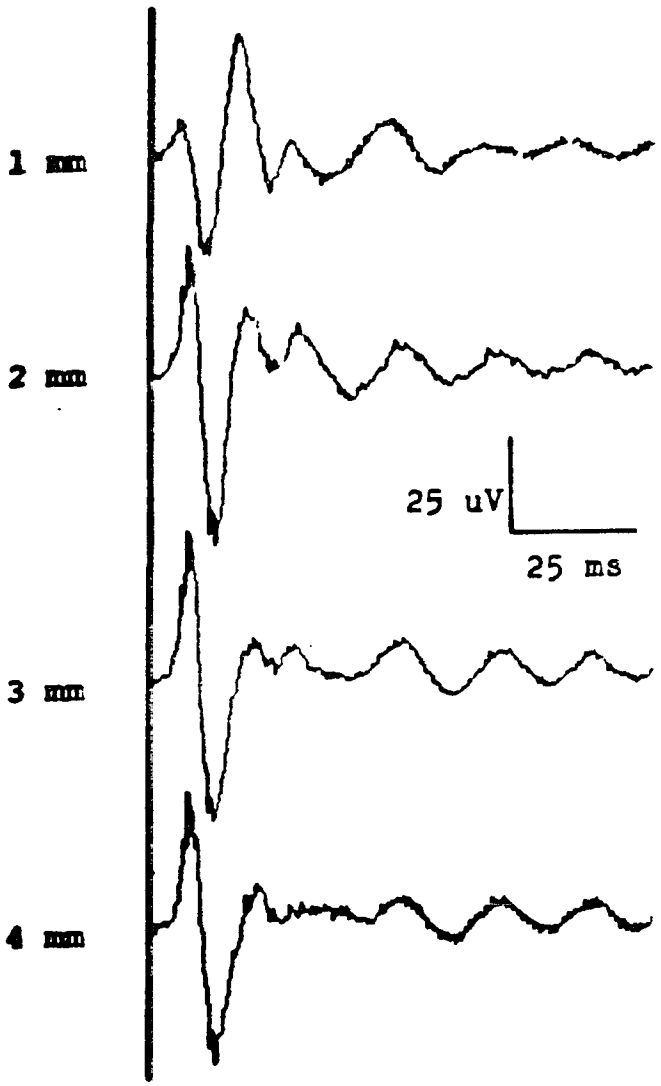


FIGURE 9

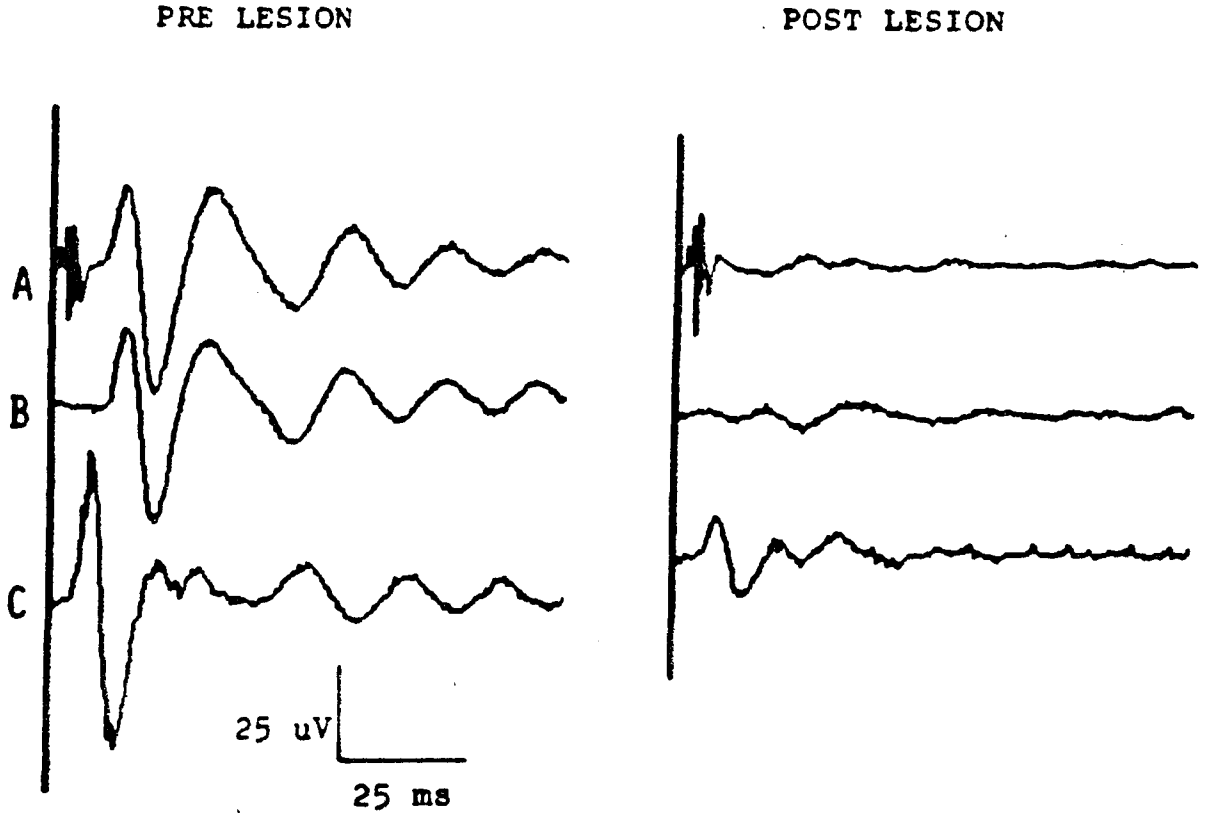
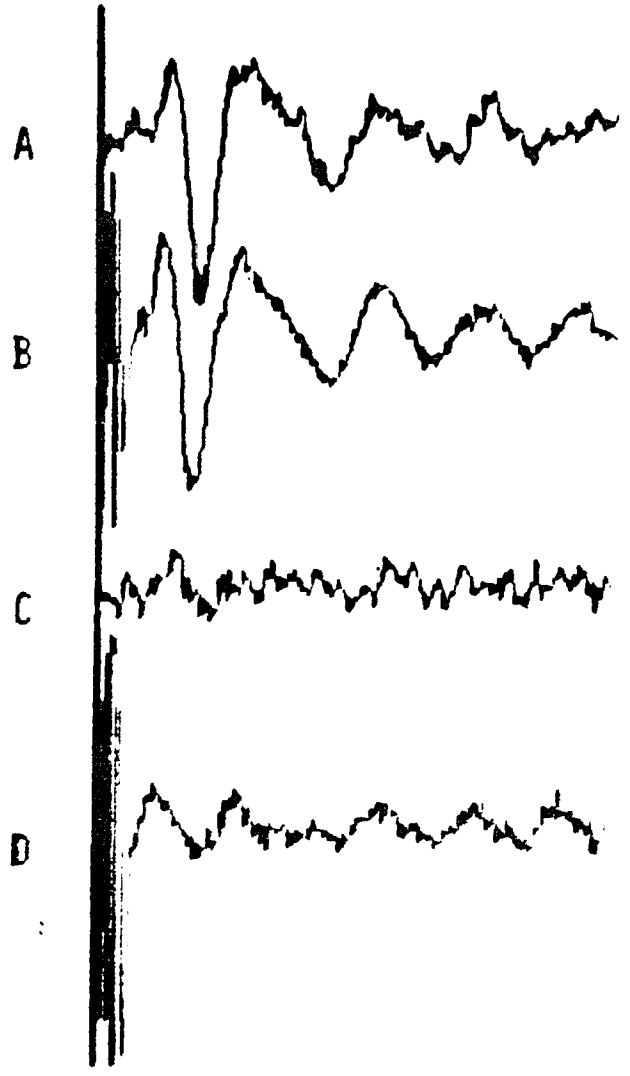


FIGURE 10



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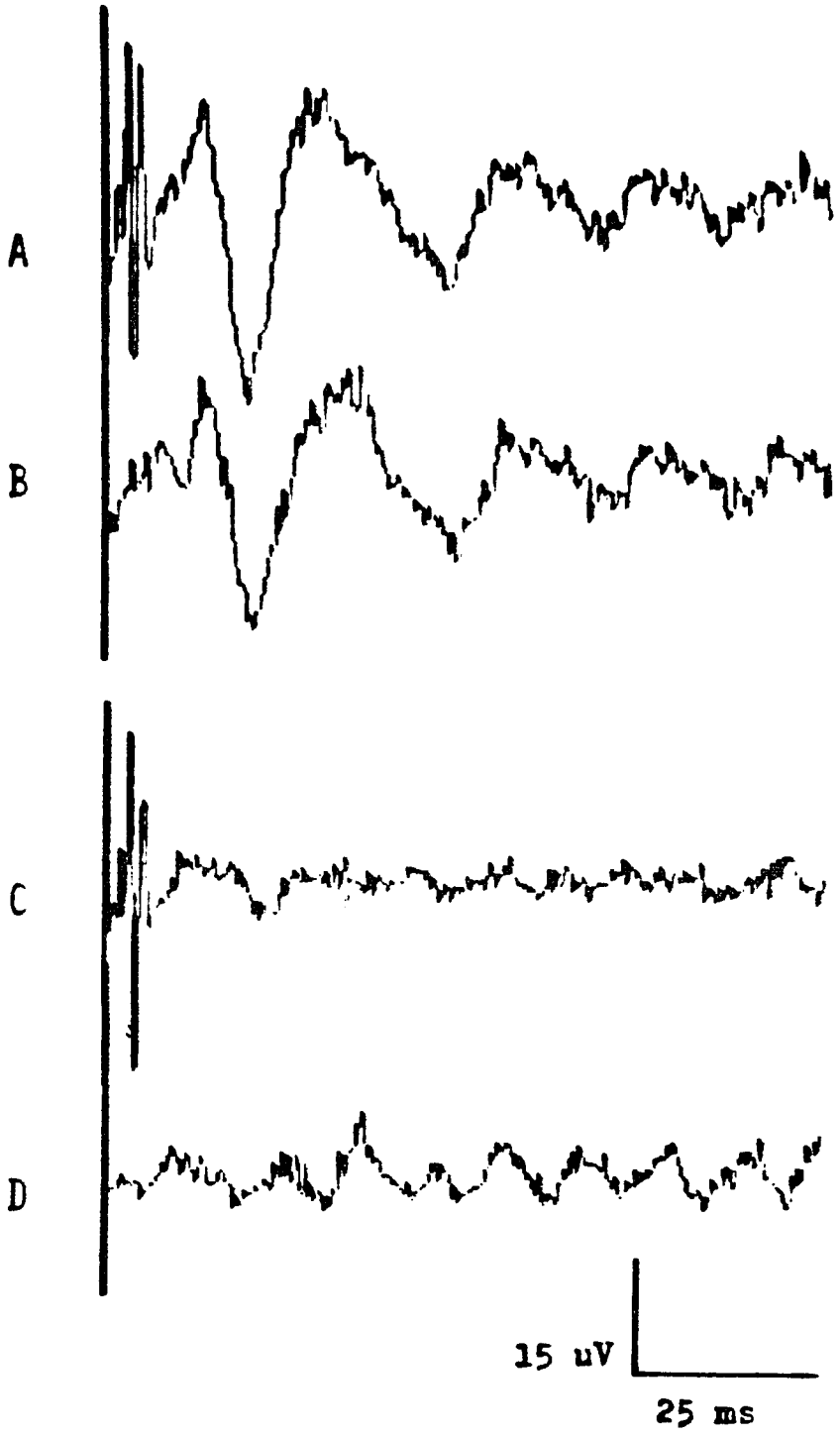

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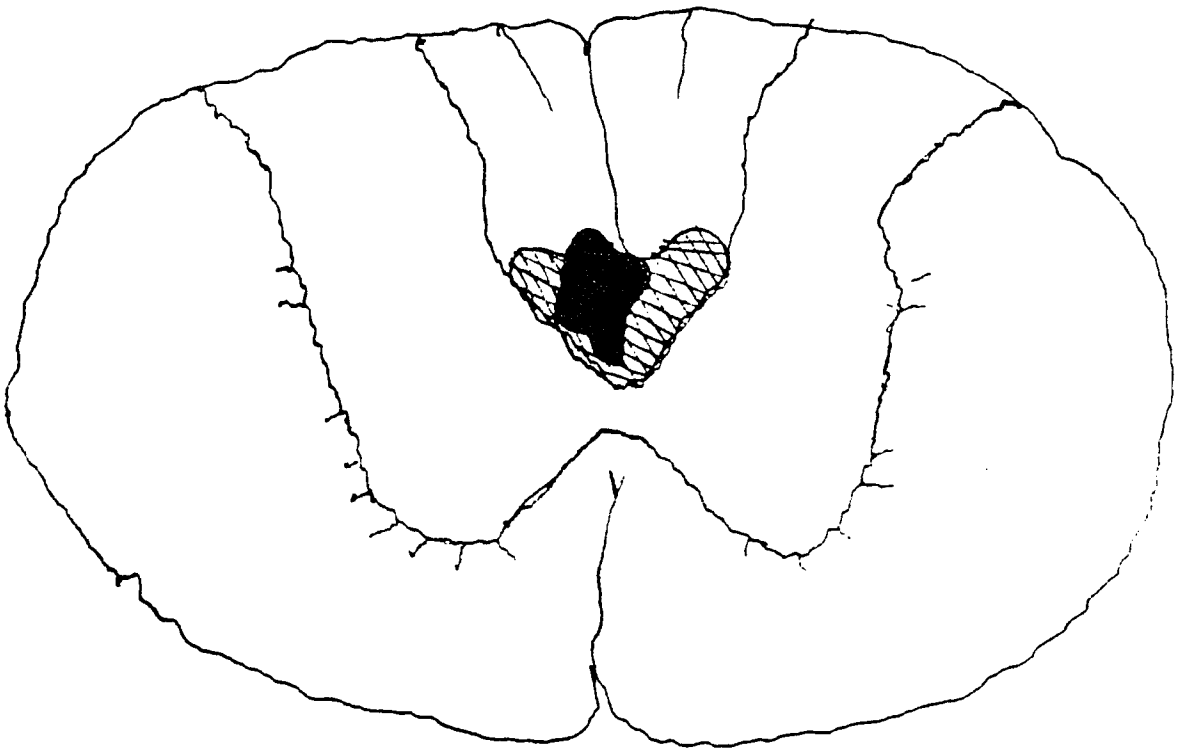


FIGURE 13

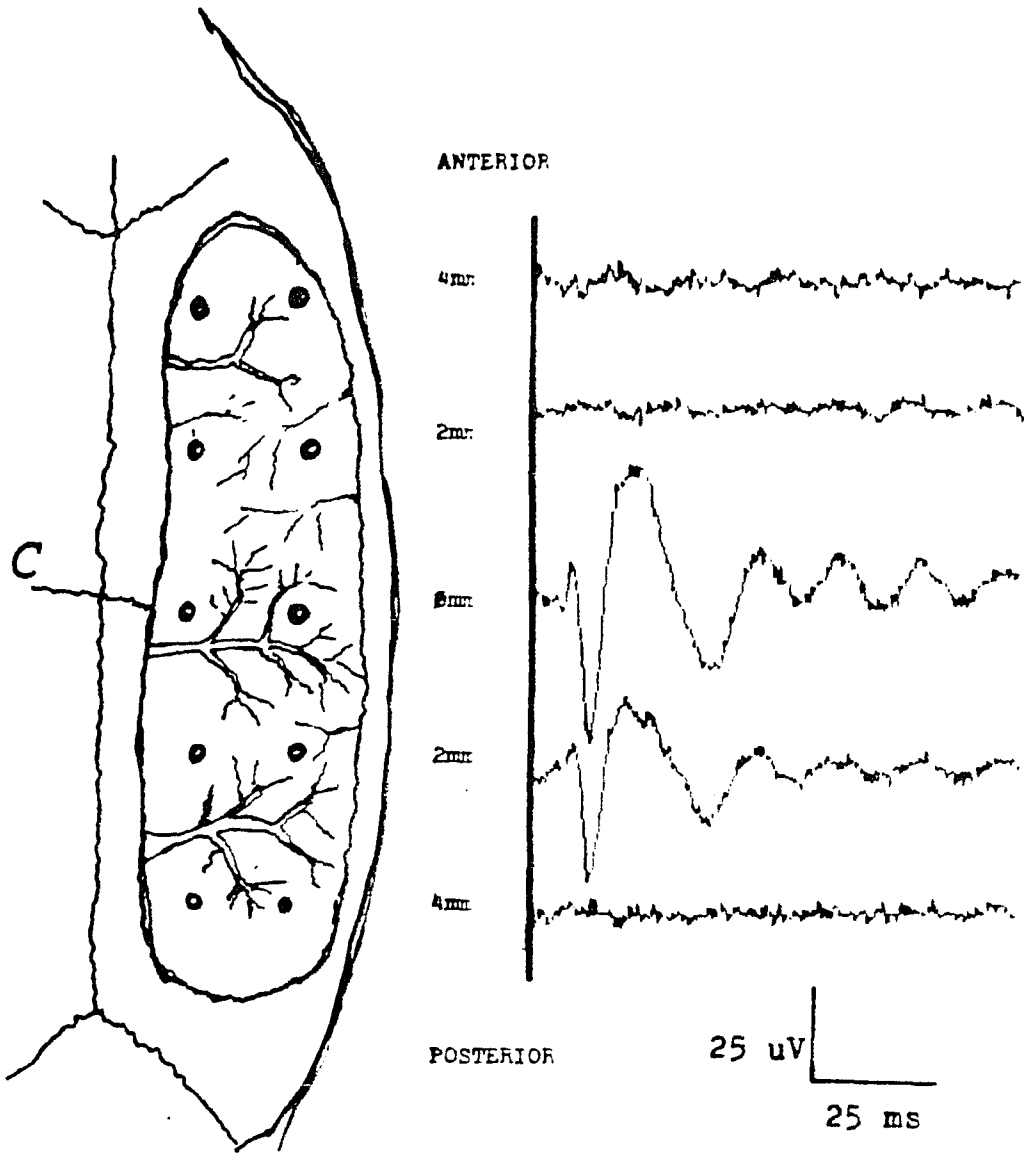


FIGURE 14

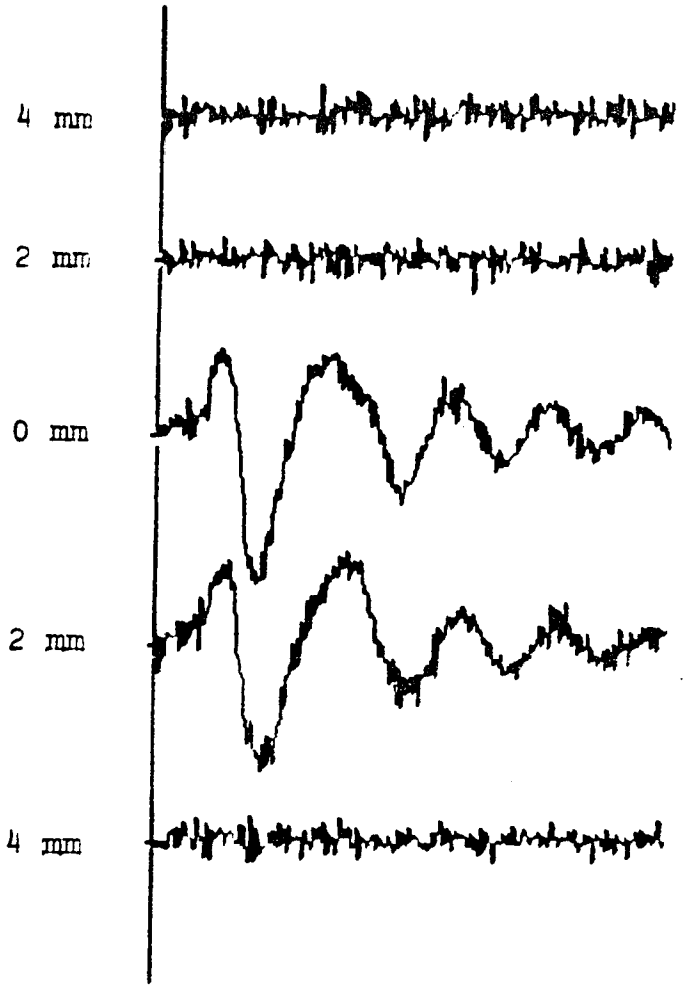


FIGURE 15

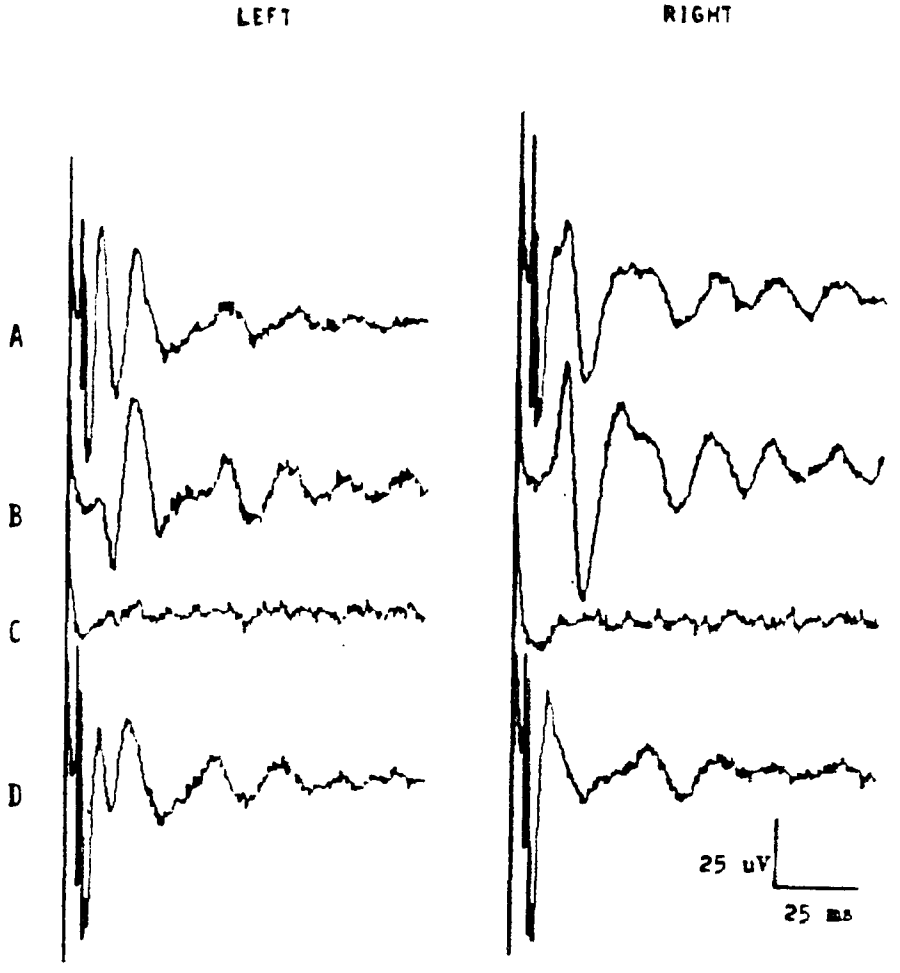


FIGURE 16

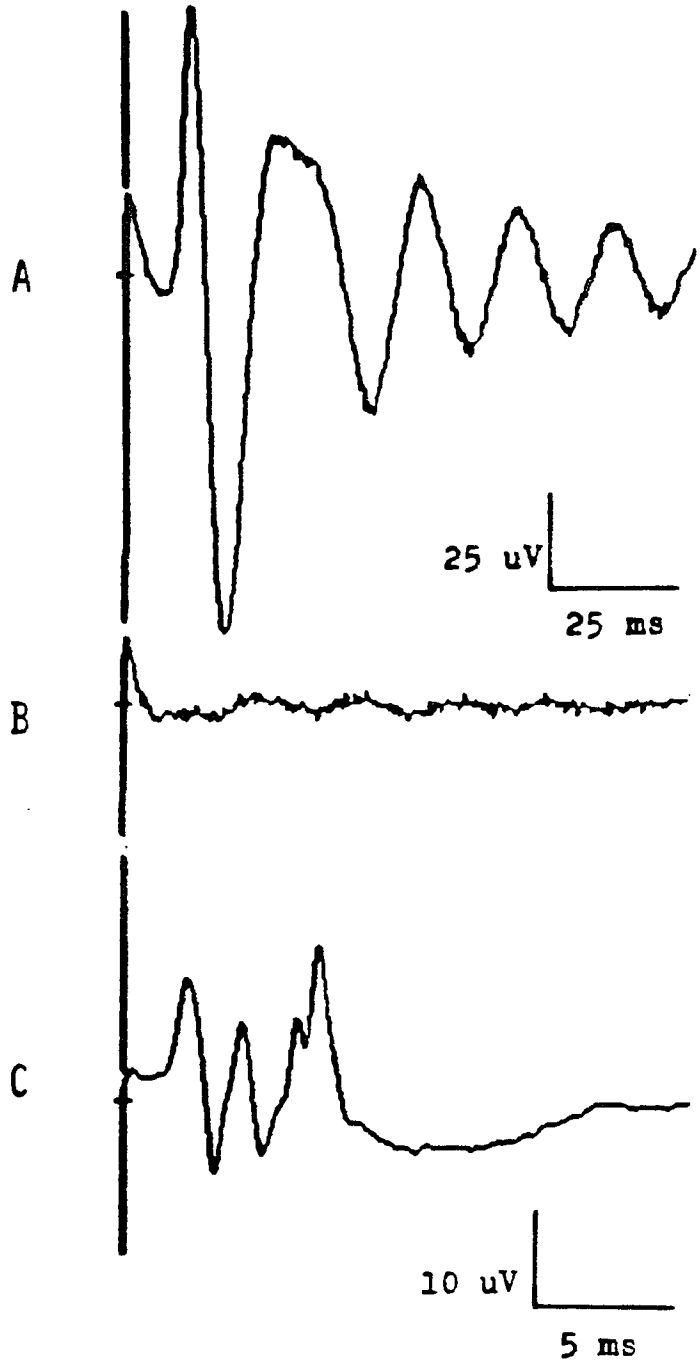


FIGURE 17

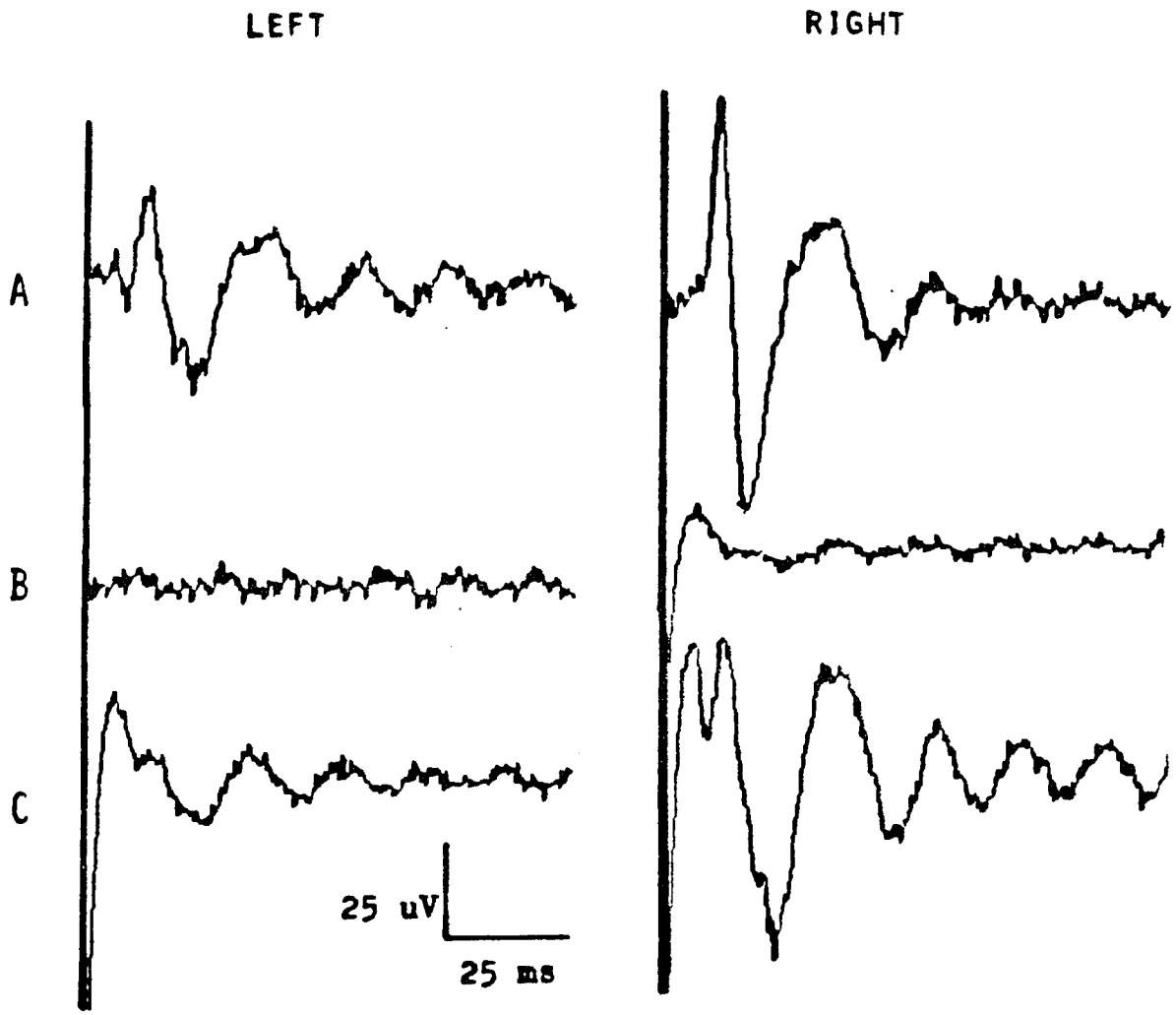


FIGURE 18

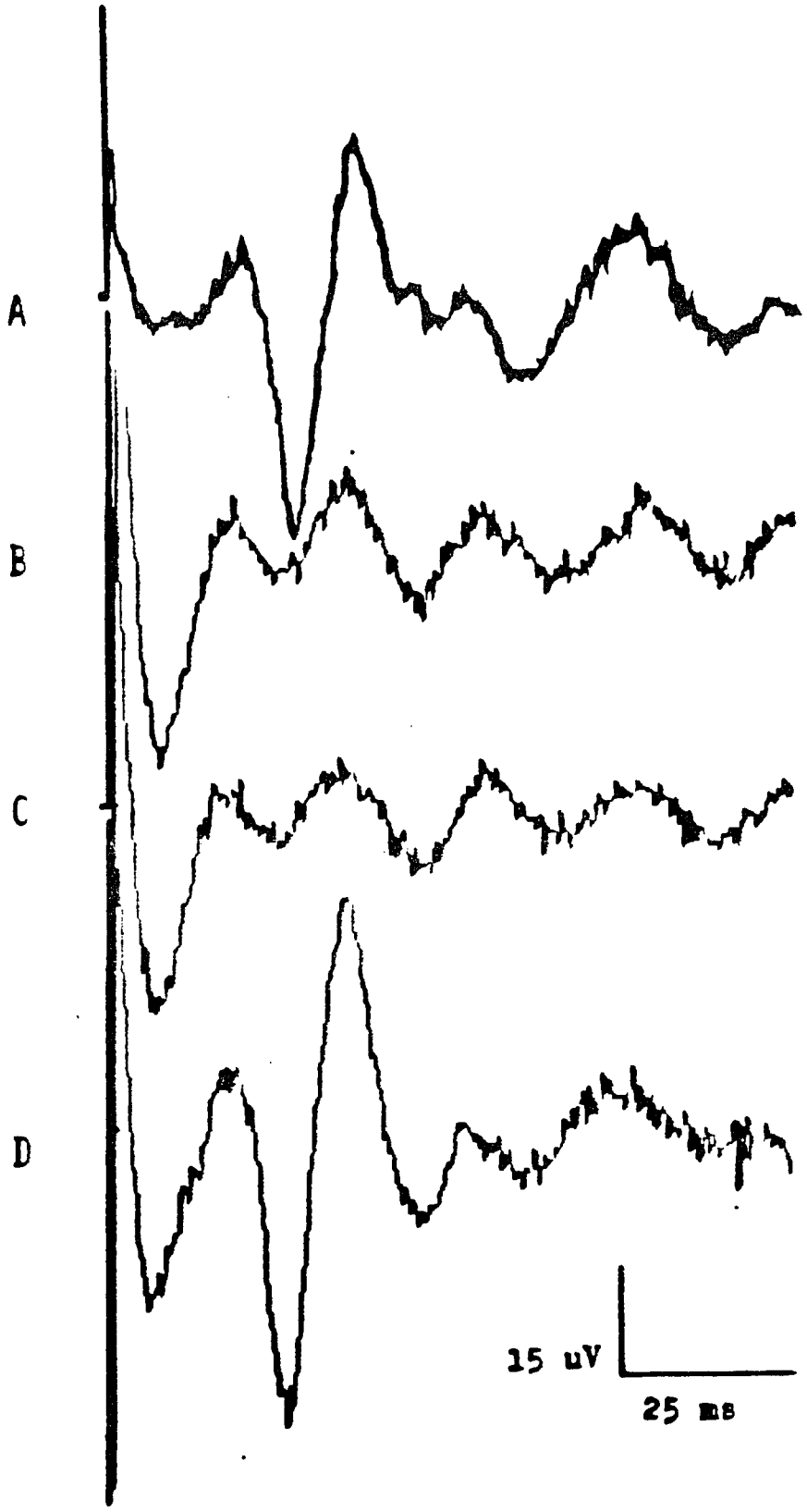


FIGURE 19

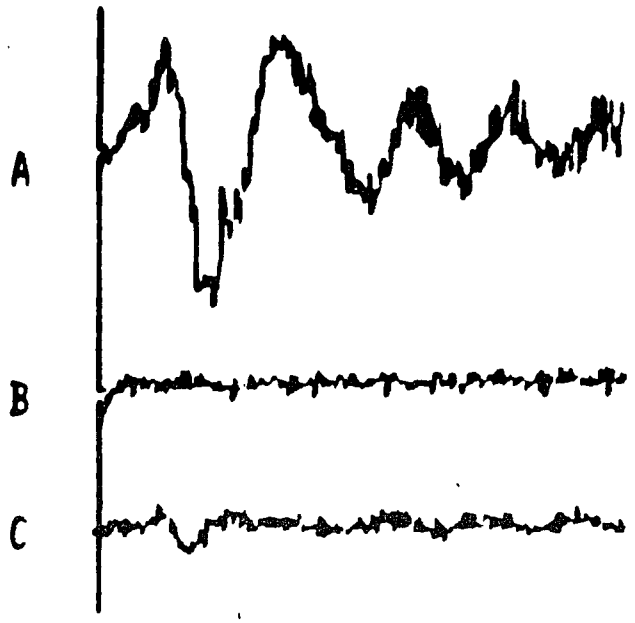
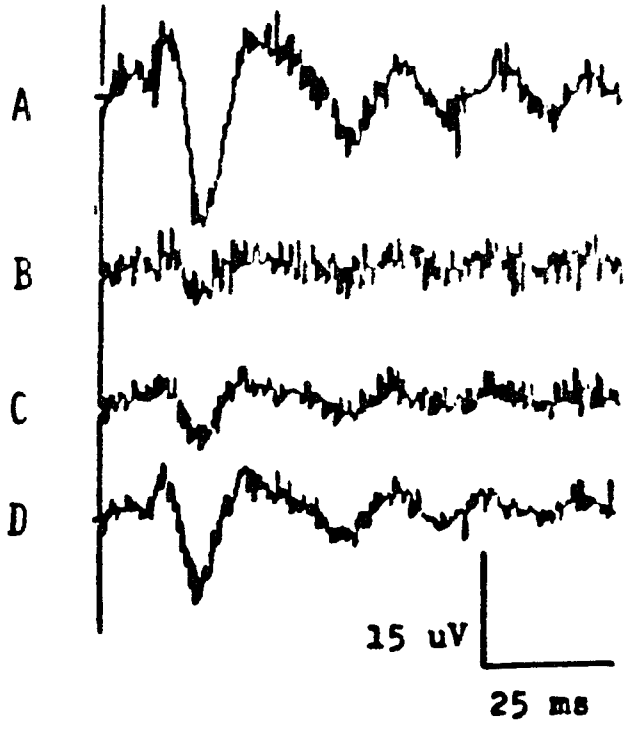


FIGURE 20



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