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THE PHARMACOLOGICAL PROPERTIES OF AN EVOKED POTENTIAL IN THE MIDBRAIN RETICULAR FORMATION

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Directorate of Medical Research
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DIGEST

This study was undertaken to determine if brain stem evoked potentials could be altered by a variety of pharmacological agents.

Evoked potentials in the midbrain reticular formation and in the posterior lateral ventral nucleus of the thalamus (VPL) were studied in 31 cats.

The results show that there was no consistent alteration in the evoked potentials following the administration of any drug except pentobarbital.

The following conclusions were reached:

1. Pentobarbital depresses the evoked potential in the midbrain reticular formation of the cat.

2. The locus of action of lysergic acid diethylamide (LSD) chlorpromazine, physostigmine, atropine, adrenaline, gamma aminobutyric acid (GABA), succinylcholine, mecholyl, and reserpine either is not at the recording sites investigated in this study (midbrain reticular formation and posterior lateral ventral nucleus of the thalamus), or the alterations in electrical activity produced by the drugs are too subtle to be detected by the methods used.

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THE PHARMACOLOGICAL PROPERTIES OF AN EVOKED POTENTIAL IN THE MIDBRAIN RETICULAR FORMATION

I. INTRODUCTION.

One of the methods of studying the pharmacology of the central nervous system is to determine if a compound alters the electrical properties of physiologically defined pathways in the brain and spinal cord. Since the advent of the cathode ray oscilloscope as a tool of neurophysiology, many of the pathways described by neuroanatomists have been confirmed by the neurophysiologist. This has been especially true of the primary sensory systems, so that there is now a comprehensive literature on the propagation of electrical impulses from the periphery of the body to the cortex. With appropriate placement of electrodes, evoked potentials may be recorded along these pathways and the effect of a drug on the electrical properties of the system may be determined by measuring changes in amplitude, configuration, or latency of the evoked potentials.

The central nervous system properties of a variety of drugs have been studied with this technique, but interpretation of results has frequently been difficult for several reasons. First, it is necessary to examine the criteria used to determine a change in evoked potentials. As previously noted, amplitude, latency, and configuration can be accurately measured, but in many preparations these are quite variable; therefore, the spontaneous variability must be determined before it can be proved that the change which occurrs following the administration of a drug could not have happened on the basis of chance. It is apparent that statistical evaluation is not necessary in some instances. For example, if the amplitude of a consistently reproducible evoked potential, such as is seen in the sensory cortex with deep barbiturate anesthesia, is reduced by half, it can be said with certainty that this is a drug effect. If an evoked potential that varies consistently in amplitude is abolished and subsequently recovers, this can also be attributed to the drug. A second factor is the effect of the drug on the vital signs of the preparation. Alterations in the rate and rhythm of the heart, peripheral vascular tone, and respiratory pattern can lead to neuronal changes, which may be interpreted as primary drug effects. Another problem in interpretation, and perhaps the most difficult of all, is determining a locus of drug action. If there is reduction in the amplitude of an evoked potential, this indicates a reduction in the number of units firing at the recording point. If there is a selective change in the evoked potential and it can be proved that the particular deflection, which is altered by the drug, represents the activity of synaptically activated dendrites or soma, and that this is the only synapse between the

stimulating and recording points, then this is evidence that the locus of drug action is at the recording point. This is, however, probably true only if the pathway under study can be treated as isolated from impulses impinging on the recording point from other neurons.

There have been many reports in the past few years that have demonstrated that sensory relay nuclei and primary sensory cortex are influenced by afferent impulses from a variety of different sources. Some of these afferent volleys produce synaptic excitation; whereas, others produce hyperpolarization of the postsynaptic membrane and are, therefore, inhibitory. If it is assumed that a drug may exert its effect not only at the recording point but also on neurons that send impulses into the area of recording, a complex structure evolves. Thus, if point A is stimulated and B is the recording point, reduction in the evoked potential at B could be due to reduction in the number of neurons activated from point A; however, if E represents an area that normally exerts a tonic excitatory effect on B, and if the activity of the neurons at E is inhibited by the drug, the result would be the same, but this would be unknown to the investigator unless he also recorded at E. If the result of the drug were an increase in amplitude of the evoked potential at B, and if it is assumed that area I has a tonic inhibitory effect on B, a similar situation exists; that is, if the drug acted at I to reduce the inhibitory impulses to point B, the evoked potential at B would be increased in amplitude.

In previous experiments,[1,2] the effect of lysergic acid diethylamide (LSD) on five different cortical evoked potentials was studied. Blood pressure, respiratory rate, and electrocardiogram were recorded in most experiments. It was found that LSD did not alter the amplitude, latency, or configuration of these evoked potentials except in those preparations in which there was a marked change in the vital signs. In reporting those experiments, it was noted that this did not necessarily mean that LSD failed to act on cortical neurons, but that perhaps present neurophysiological techniques were inadequate to record such an effect.

The present experiments were undertaken in an attempt to examine the pharmacological properties of responses in the brain stem and thalamus. The inhibitory effect of LSD on visual evoked potentials in the lateral geniculate nucleus has been reported,[3,4] but other areas of the brain stem and diencephalon have not been investigated. The posterior lateral ventral nucleus of the thalamus (VPL) was selected for investigation because, like the lateral geniculate nucleus, it is a relay station in a primary sensory system. Also, a long-lasting response in the rostral medial midbrain was studied because, anatomically, this is in the midbrain reticular formation. Unlike the previous experiments in which numerous different cortical areas were studied with a single drug, several drugs were investigated in these preparations.

II. MATERIALS AND METHODS.

A total of 31 cats were used in this study. All of the animals were anesthetized with ether and then paralyzed with succinylcholine after the surgical procedures. Skin edges and pressure points were infiltrated with 0.5% procaine hydrochloride. Electrical recording was begun no less than 2 hr following cessation of ether anesthesia. The initial paralyzing dose was 20 mg, followed by 20-mg supplements as required to prevent spontaneous movement. The animals were ventilated with a Marshall respirator.

Tactile, auditory, and electrical stimuli were used. Tactile stimulation was produced by a Goodman Industries vibrator mounted over one of the footpads or the nose. Clicks from a loudspeaker mounted near the animal's head were used for auditory stimulation. Bipolar electrodes for electrical stimulation were made from no. 28 stainless steel plain enameled wire with an interelectrode distance of approximately 1 mm. Insl-X was used to cement the wires together and also served as additional insulation.

A bank of 10 electrodes was used for recording from the cortex. The electrodes were spring-mounted, cylindrical, silver electrodes with a tip diameter of approximately 1 mm. The deep recording electrodes were the same as those used for stimulation and were either monopolar or bipolar. All of the evoked potentials in the illustrations (figures 1 through 5) are monopolar recordings with the indifferent electrode on the head holder or on bone surrounding the area of the craniectomy. The output was led differentially into Tektronix preamplifiers, displayed on a Dumont dual-beam oscilloscope, and photographed with a Grass camera.

All deep electrodes, except those in the medulla, were placed stereotactically. The latter were inserted under direct vision. Serial coronal sections at 30μ, were made of five cat brains, and every ninth section was stained by the Weil method for myelin. In some preparations, it was necessary to search for a maximum electrical response and to change the position of the electrodes several times during the course of the experiment. Therefore, multiple punctures were made, and it has been difficult to be certain of the precise anatomical localization of the evoked potential in these sections.

III. RESULTS.

The response studied most frequently in these experiments was obtained in the midbrain from stimulation of the contralateral forepaw. This is a monophasic positive evoked potential with a latency that varied between 12.5 and 27.5 msec. On occasion, there were two distinct positive waves, as

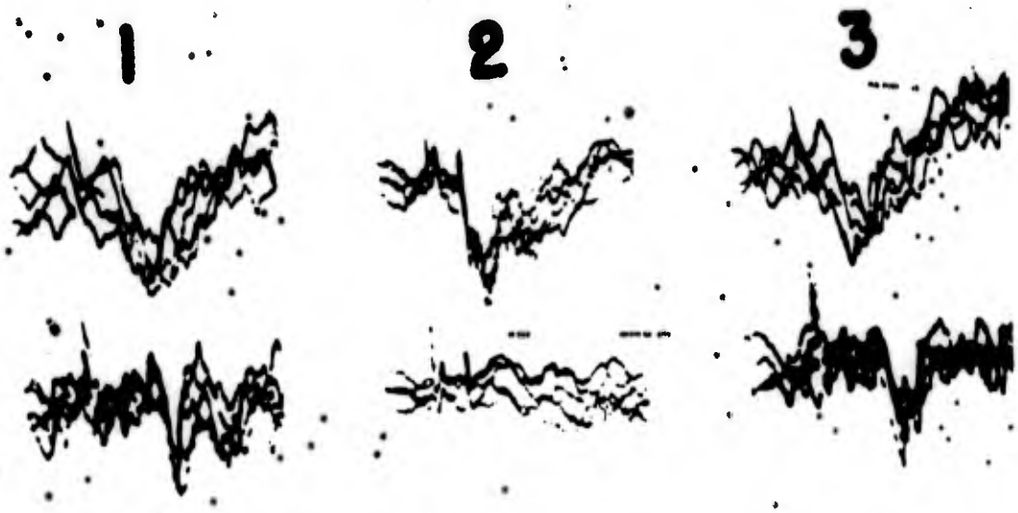

FIGURE 1

ABOLITION AND SUBSEQUENT RECOVERY OF THE MIDBRAIN RESPONSE FOLLOWING INTRAVENOUS INJECTION OF PENTOBARBITAL, 10 mg/kg.

The upper line shows the posterior lateral ventral nucleus (VPL) of the thalamus evoked potential; the lower line, the midbrain evoked potential. Recordings are 5 single-sweep superimposed continuously recording oscilloscope (CRO) traces.

FIGURE 2

THE EFFECT ON TWO EVOKED POTENTIALS OF REPETITIVE STIMULI

Tactile stimulation of contralateral forepaw at a repetitive rate:

1 shows 1 per second
2 shows 5 per second
3 shows .10 per second

The upper line shows the VPL evoked potential; the lower line, the midbrain evoked potential. Note almost complete disappearance of midbrain response, with only slight change in VPL response in 2. Recordings are 5 single-sweep superimposed CRO traces.

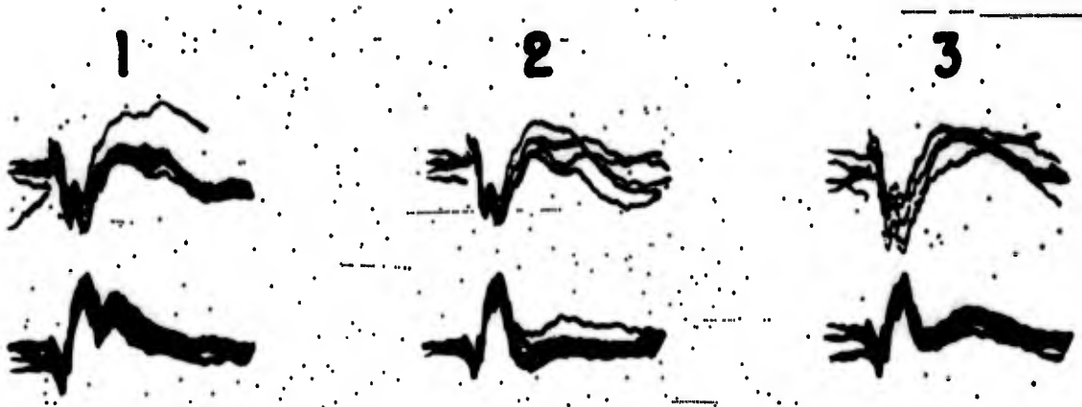

FIGURE 3

THE EFFECT OF PENTOBARBITAL (10 mg/kg)
ON TWO EVOKED POTENTIALS

The upper line shows VPL evoked potential; the lower line, the midbrain evoked potential. Recordings are 5 single-sweep superimposed CRO traces.

Tactile stimulation of contralateral snout shows very little difference in latency of the VPL and midbrain responses. The second negative wave in the midbrain potential is abolished in 2 by pentobarbital (10 mg/kg); with partial recovery in 3. There is no apparent change in the VPL potential.

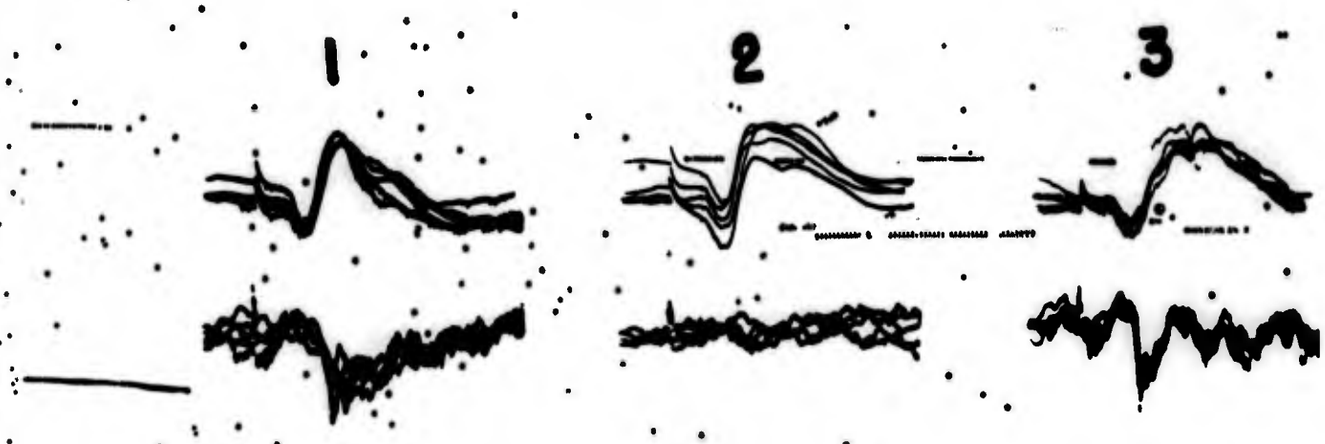

FIGURE 4

THE EFFECT OF LSD (0.5 mg/kg) ON TWO EVOKED POTENTIALS

The upper line shows cortical somatic evoked potentials, the lower line responses from the midbrain electrode. LSD (0.5 mg/kg) caused marked reduction in the amplitude of the midbrain evoked potential, with recovery, and no change in the cortical evoked potential except for increase in background activity manifested by less precise superimposition of traces. Recordings are 5 single-sweep superimposed CRO traces.

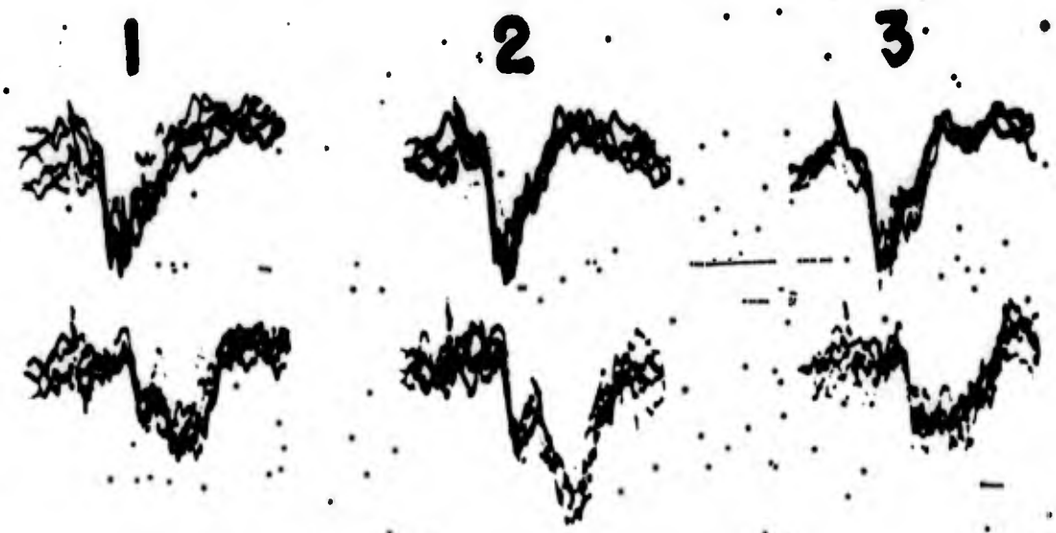

FIGURE 5

THE EFFECT OF CHLORPROMAZINE (2 mg/kg)
ON TWO EVOKED POTENTIALS

The upper line shows the VPL evoked potential; the lower line the midbrain evoked potential. Recordings are 5 single-sweep superimposed CRO traces.

Chlorpromazine (2 mg/kg) increased the amplitude of an infrequently recorded second negative wave in the midbrain response with subsequent recovery. There is no change at the VPL electrode.

illustrated in figure 5, and frequently the evoked potential was preceded by a small positive-negative potential. On lowering the electrode into the region of the evoked potential, there was often an increase in the frequency and amplitude of the background activity preaging the appearance of the evoked potential. The evoked potential was usually encountered 20 to 22 mm below the cortical surface. In a few experiments, further manipulation of the electrode was not required, and the potential maintained its form and amplitude for many hours. In most preparations, however, it was difficult to keep a steady potential for more than 2 hr, and some preparations, despite large amplitude initial recordings, were unsuitable for study because the potential deteriorated in a few minutes.

The evoked potentials recorded in VPL had a latency between 8.0 and 8.7 msec. They were essentially positive-negative potentials, but there was considerable variation in configuration among preparations. In general, they were more stable than those recorded in the midbrain.

In one experiment in which stimulation of the contralateral forepaw produced a midbrain response with a latency of 16.7 msec, latencies from stimulation of other parts of the body were: ipsilateral forefoot, 19.4 and 18.5 msec in two series of stimuli; ipsilateral hindfoot, 23.5 msec; and the ipsilateral side of the snout, 3.8 msec.

In addition to the anatomical location and latency of the midbrain potential, there is additional evidence that this evoked potential represents the activity of neurons quite dissimilar to those in VPL.

Figure 1 shows the comparative response of evoked potentials recorded in VPL and the midbrain following the intravenous injection of pentobarbital (10 mg/kg). There is elimination of the mibrain response with complete recovery in 1 hr. In other experiments, pentobarbital (5 mg/kg) produced a marked reduction in the midbrain response with recovery in 15 min.

Figure 2 shows the effect of repetitive stimuli on the two evoked potentials, and it is evident that the midbrain response is eliminated at repetitive rates of 5 per second. At 10 per second, the negative component of the VPL response is almost eliminated but the initial deflections are unchanged.

Figure 3 shows the effect of pentobarbital (10 mg/kg) on evoked potentials in the posterior ventral thalamus and in the midbrain in response to stimulation of the contralateral snout. There is evidence that primary

trigeminal afferents to the thalamus occupy a medial position in the brain stem, and the little difference in the latency of responses at the thalamic and midbrain recording electrodes indicates that these afferent pathways pass near the midbrain recording point. The abolition of the second negative wave in the midbrain by pentobarbital suggests that this represents the activity of neurons in the reticular formation adjacent to the primary sensory pathways.

In one experiment, systematic stimulation of the sigmoid, lateral, and suprasylvian gyri of the cortex of both hemispheres with a wide variety of parameters did not produce a detectable evoked response at the midbrain electrode.

In two experiments, evoked potentials were obtained in the midbrain with bipolar electrodes in response to tactile stimulation of the contralateral forepaw; then electrical stimuli were applied to the bipolar electrode. In one preparation, 10 to 30 pulses at 2 msec intervals, and at an intensity of 4 to 5 volts, produced inhibition of cortical somatic evoked potentials. It appeared that the intensity, number of pulses, and interval of time between stimuli were factors affecting the inhibitory process. In the second preparation, electrical stimulation of the midbrain recording point did not alter the amplitude of somatic evoked potentials recorded in VPL or somatic cortex, or evoked potentials in auditory cortex produced by clicks; also, there was no change in the amplitude of the second of paired tactile and auditory responses in the cortex, indicating no apparent lengthening in the recovery time of the cortical neurons involved. The electrical trains were delivered 0 to 100 msec prior to the sensory stimuli.

In one experiment, stimulation of the rostral ventral pons produced an evoked potential in the medial midbrain but none in VPL; also, stimulation of this point did not change the amplitude of tactile responses in VPL.

The table lists the drugs that were studied in these experiments. All solutions were given intravenously except for GABA (gamma amino-butyric acid), which was also injected into the carotid artery ipsilateral to the recording electrode. In all preparations in which these compounds were investigated, the evoked potentials studied were those previously described in VPL and the midbrain in response to tactile stimulation of the contralateral forepaw.

Following 1 of 10 injections of LSD, there was marked reduction in the amplitude of the midbrain evoked potential with complete recovery, as illustrated in figure 4. Figure 5 shows an increase in the amplitude of the

TABLE

COMPOUNDS STUDIED

Drug	No. of injections	Dose range
		mg/kg
LSD	10	0.25-0.5
Chlorpromazine	10	1.0 - 5.0
Physostigmine	7	0.2 - 0.4
Atropine	4	0.5 - 2.0
Adrenaline	4	0.05-0.1
GABA	4	1.0 - 8.0
Succinyl choline	2	7.0
Mecholyl	2	2.0 - 10.0
Reserpine	1	1.0

midbrain response following 2 mg/kg of chlorpromazine; but following 9 other injections of chlorpromazine in doses of 1 to 5 mg/kg there was no change. None of the other drugs listed in the table affected the amplitude of the evoked potential, and in no instance was there a change in latency. Finally, the evoked potential in VPL remained unchanged.

IV. DISCUSSION.

The midbrain evoked potential, which was studied in these experiments, has many of the characteristics of the response obtained by Collins and O'Leary.[5] Although there is not accurate histological localization of the electrode tips, the coordinates are approximately the same as those described by these authors. They noted the high voltage, fast background activity observed prior to detection of the evoked potential as the electrode was lowered through the midbrain and stated that the evoked potential was frequently hidden in this activity. Stimulation of the contralateral superficial radial nerve in their experiments gave a latency of 8.5 to 11.0 msec for the midbrain response as compared to 12.5 to 27.5 msec in our experiments. There was a similar discrepancy, however, in VPL latencies (4.0 to 5.5 msec as opposed to 8.0 to 8.7 msec). It is likely that the different methods of stimulation, i.e., electrical stimulation of the radial nerve and tactile stimulation of a footpad, could account for some of this difference.

The longer latency of the midbrain potential as compared to VPL indicates that it is conducted along smaller, slower velocity axons and/or there is one or more additional synapse between the periphery and the recording point. Collins and O'Leary demonstrated that much of the latency difference between the two responses can be explained on the basis of axon conduction; the initial deflection in the VPL response appears at slightly above A axon threshold; whereas, the midbrain potential appears to be activated from peripheral axons of the gamma-delta group. It has not been proved, however, that additional synapses are present in the pathway of the midbrain response.

Our observation that the midbrain response is diminished in amplitude with repetitive stimuli of 5 per second, or more, indicates a recovery time of more than 200 msec for the neurons involved in contrast to a recovery time of slightly more than 100 msec in VPL. These findings agree with those of Marshall,[6] who found recovery times up to 100 msec in VPL, but differ somewhat from those of Collins and O'Leary, who found a similar recovery time of the midbrain potentials.

The isolated changes in the amplitude of the midbrain potential following LSD and chlorpromazine are not significant because they occurred in only 1 of 10 injections. The other compounds produced no detectable change in amplitude of either the VPL or midbrain evoked potentials.

Bradley and Elkes[7] investigated the effect of many of the drugs used in these experiments on the behavior and electroencephalogram (EEG) pattern of unanesthetized encephale isole preparations. They noted that LSD produced activation of the EEG and behavioral alertness in contrast to physostigmine, which caused EEG activation without behavioral alerting, and atropine, which produced a cortical sleep rhythm but the animal remained awake. On the basis of their LSD studies, they postulated that its site of action might be in the medial mesencephalon and diencephalon related to the collaterals of the afferent pathways. Killam and Killam[8] found that chlorpromazine facilitated evoked potentials recorded in the anterior reticular formation from stimulation of the sciatic nerve. Rinaldi and Himwich[9] found evidence for cholinergic synaptic transmission in the reticular formation in contrast to Dell,[10] who offers evidence of adrenergic mechanisms in the production and maintenance of reticular activity.

The present results neither confirm nor contradict these previous reports, although it does seem unlikely that LSD acts on medial collateral afferents at the midbrain level as Bradley suggested. The number of collaterals entering the reticular formation at this level is probably very small,[11,12] but the midbrain potential studied in our experiments is a large, long latency response from stimulation of a somatic nerve, and this conforms to what was originally interpreted as collateral activation of reticular neurons. The midbrain evoked potential in our experiments does not have the configuration of the one illustrated by Killam and Killam, and their coordinates indicate a slightly more anterior location; therefore, our results may not be comparable.

In regard to adrenergic versus cholinergic activation of the reticular formation, it is difficult to relate such diverse physiological observations as the effect of a drug on cortical arousal and behavior and its effect on midbrain evoked potentials, albeit the latter may represent the activity of reticular neurons. An adrenaline, mecholyl, or atropine effect in these experiments, however, would have indicated possible interference in synaptic transmission and suggested further studies.

There are disadvantages of the recording technique used in these experiments and in the other reports cited above. The activity of a large number of neurons is recorded because of the size of the electrode. If the neuron pool is relatively homogeneous, as it is in the posterior ventral thalamus, this is of less importance than in the medial midbrain where a variety of neurons with diverse functions may be activated by a single afferent volley. There is anatomical evidence of a definite organization of the reticular formation,[13] but this has been difficult to confirm in physiological experiments. A different approach to the pharmacology of the reticular formation is the study

of single units with microelectrodes; however, since adjacent neurons in the reticular formation may be influenced by stimuli from diverse origins, these neurons may have different pharmacological properties. The electrical response of the neuronal pool is then the net result of positive and negative impulses entering the pool. The macroelectrode records the net electrical response but does not provide information on the activity of single units or small groups of cells.

In the past 2 yr, the effect of LSD on several electrophysiological properties of the brain has been investigated in the cat. This included the electrocorticogram, evoked potentials in primary visual, auditory and somatic cortex, the direct response of the cortex, the transcallosal evoked potential, and somatic evoked responses in the thalamus and midbrain reticular formation. LSD failed to alter the evoked potentials in any of these areas, even in massive doses. The lateral geniculate nucleus is the only area in which LSD appears to exert a definite effect on electrical activity, and this has been proved with gross electrodes and in single unit experiments. The dose required to inhibit the postsynaptic potential in the lateral geniculate, however, is probably 100 times the quantity needed to produce visual hallucinations in man.

The difficulties involved in attempting to define the neurophysiological correlates of behavior are legion, and this is exemplified by the LSD problem. LSD is of interest primarily because it produces signs and symptoms that mimic some of the abnormal mental states encountered in clinical psychiatry. If one could prove that the pathological process leading to visual hallucinations is in some manner associated with the lateral geniculate nucleus, this might be evidence that the physiological effects of LSD on the lateral geniculate are of clinical significance. This, however, would ultimately require human investigations because the act of hallucinating is a subjective phenomenon that can be known to the investigator only through the medium of language. By the same token, such terms as paranoia and depersonalization, which are so frequently seen in the LSD literature, are not applicable to the behavior of subhuman species. In the large number of clinical studies reported, LSD has never produced a definite neurological deficit and in only a few reports has it been related to the organic toxic psychoses. This is of importance in interpreting the lateral geniculate effects of the drug, since the most logical clinical manifestation of this effect would be decreased visual acuity, which has not been observed in man. As noted, however, the dose required to alter the electrical properties of the lateral geniculate in cats and monkeys is 100 times the hallucinating dose in man, and, in fact, somewhat larger doses in monkeys appear to produce blindness. Therefore, decreased vision must be considered a toxic effect of the drug that is unrelated to its hallucinatory properties.

It is evident that knowledge of the mechanism of LSD action involves the same difficulties encountered in attempting to bridge the mind-brain barrier. The neuropharmacological properties of the drug in animal preparations will be important part of the investigation of its mode of action, but ultimate interpretation must rely on similar data in man.

V. CONCLUSIONS:

The following conclusions were reached:

1. Pentobarbital depresses the evoked potential in the midbrain reticular formation of the cat.

2. The locus of action of lysergic acid diethylamide (LSD), chlorpromazine, physostigmine, atropine, adrenaline, gamma aminobutyric acid (GABA), succinylcholine, mecholyl, and reserpine either is not at the recording sites investigated in this stydy (midbrain reticular formation and posterior lateral ventral nucleus of the thalamus), or the alterations in electrical activity produced by the drugs are too subtle to be detected by the methods used.

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3. LSD, effect of
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