

AN ELECTROGRAPHIC STUDY OF PSILOCIN AND
4-METHYL- α -METHYL TRYPTAMINE (MP-809)^{1, 2}

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Much work has been done to delineate the actions of the indole amines. One of the important indole amines, serotonin (5-hydroxytryptamine), is a natural constituent of the brain (Costa and Aprison, 1958) and is considered by some investigators to be a neurotransmitter (Brodie *et al.*, 1959). This study is concerned with an electroencephalographic (EEG) analysis of a group of indole amines substituted in the fourth position instead of the fifth, namely psilocybin and its congeners, in an effort to determine their sites of action (see fig. 1). Psilocybin has been shown to have psychotomimetic properties (Isbell *et al.*, 1961).

METHODS. Fifty-nine albino rabbits ranging in weight from 2.3 to 2.8 kilograms were used in these experiments. All animals were tracheotomized under ether and local pontocaine anesthesia, curarized and artificially respired. Sufficient time was allowed for the animals to eliminate the ether before tracings were made. A polyethylene cannula was inserted in the animal's femoral vein through which the drugs could be administered without causing tactile stimulation. In the experiments involving blood pressure, another cannula was placed in the femoral artery and connected to a mercury manometer. Brain wave recordings were made on an S-channel, Grass Model III D electroencephalograph (EEG). Coaxial electrodes were implanted according to the maps of Sawyer *et al.* (1954) for the rabbit. The coordinates were as follows: Anterior cortex (motor), anterior 3, lateral 3½, vertical plus 8; posterior cortex (limbic), posterior 4, lateral 4,

vertical plus 8½; caudate nucleus, anterior 3, lateral 3½, vertical plus 4; amygdaloid complex, anterior 2, lateral 5½, vertical minus 6; hippocampus, posterior 4, lateral 4, vertical plus 5½; thalamus (VPL), posterior 4, lateral 4, vertical minus 1. A limited number of histological determinations was made to check on the adequacy of these coordinates but since no attempt was to be made to treat recordings as representing specific nuclear sites in such structures as the thalamus and amygdala, a complete histological confirmation on every animal brain was not undertaken.

Four different types of preparations were used: one with the intact brain, two others with transections of the brain at two different levels and a fourth with cervical cord as well as brain transections. The first group of experiments was done on intact brains where preparation for EEG readings simply involved placing monopolar coaxial electrodes into the brain at predetermined locations in accordance with methods previously described (Van Meter *et al.*, 1958). Five drugs were used in these experiments (structures shown in fig. 1). All drugs were dissolved in distilled water and injected through the femoral vein cannula at intervals of 3 to 7 minutes. Total dosages used in the production of alerting were as follows: O-phosphoryl-4-hydroxy-N-dimethyl tryptamine (psilocybin) 4.5 to 7.5 mg/kg; 4-hydroxy-N-dimethyl tryptamine (psilocin) 1.2 to 5.0 mg/kg; 4-methyl- α -methyl tryptamine (MP-809) 1.0 to 3.0 mg/kg; 4-hydroxy- α -methyl tryptamine (MP-14) 2.5 to 12.0 mg/kg; and 1-methyl psilocybin 6.8 to 12.6 mg/kg. Single injections ranged between 0.5 and 2.0 mg/kg with the exception of psilocin which were 0.1 to 0.5 mg/kg.

The second preparation involved the complete transection of the brain in the prepontine, precollicular plane in accordance with Steiner and Himwich (1962) and was therefore rostral to the midbrain (see fig. 2, transection 1). Animals so transected were pretreated with 3.0 grams of urea dissolved in 7.0 cc of distilled water 30 minutes before the operation was begun. Numerous control observations revealed that urea given in this dosage, *i.e.*, 1 g/kg, did not affect normal EEG patterns. In this preparation no curare was given after the initial injection. The procedure for mak-

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¹MP-809 is the code number of Sandoz Pharmaceuticals for 4-methyl- α -methyl tryptamine. Both names will be used interchangeably throughout the paper.

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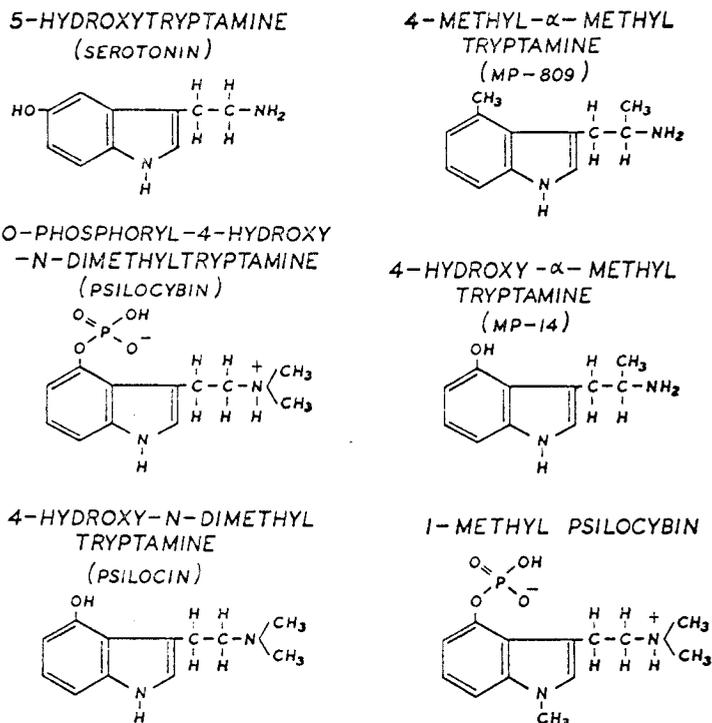


FIG. 1. Chemical structures of serotonin and of compounds investigated in the present study.

ing the transection involved drilling 3 to 4 holes on each side of the sagittal suture in a line parallel to the coronal suture 11 mm posterior to it. The tilt of the head brings the actual plane of transection to a position 8 mm posterior to the coronal suture with respect to the brain. No holes were drilled directly over the sagittal suture. A Wappler cold cautery scalp with a needle-like fitting was then inserted into each hole several millimeters at a time with intermittent use of current (1 to 2 seconds at a time). This cauterization was done on each side, working towards the center. The holes in the scalp were then connected with a rongeur, leaving a section about 2 to 3 mm long on both sides of the sagittal suture. Next the cautery was used to burn a shallow V under the intact center piece in order to eliminate excess bleeding from the central sinus. The remaining center section of bone was then removed and the central section of brain cauterized. Then the needle was replaced with a flat spatula-like fitting which was passed along the entire extent of the open area in an effort to sever any remaining connections. To be certain that all fibers were severed, the footpads of these animals were stimulated peripherally and in successful preparations, EEG cortical alerting failed to occur. As an additional precaution, the brains were removed at the end of each experi-

ment to ascertain if the transection was complete and in the prescribed plane. Five of the animals prepared in this manner were injected with MP-809 to a total dosage of from 5.0 to 12.0 mg/kg in each experiment. Three other animals were given 3.0 mg/kg of *d*-amphetamine (in 1-mg/kg doses at 3-minute intervals) and then 0.1 mg/kg of eserine after being pretreated with 8.5 mg/kg of MP-809. Two others were injected with psilocin for total dosages of 1.0 to 1.2 mg/kg.

The third preparation involved a postcollicular, postpontine transection resulting in a cut caudad to the midbrain (see fig. 2, transection 3). The procedure used for this transection was the same as that for the more anterior cut, except that only two holes could be made on each side of the sagittal suture, these being on a line 22 mm posterior and parallel to the coronal suture. This transection was much less critical than the one more anterior because fewer of the main sources of blood supply pass through this area. Each of three animals prepared in this manner was given 5.0 to 12.0 mg/kg of MP-809. Two others received first 2.9 to 4.0 mg/kg of psilocin and then 3.0 mg/kg of *d*-amphetamine. In addition, two intact animals were injected with psilocin until an alert pattern was evoked (1.0 to 1.1 mg/kg) and then they were tran-

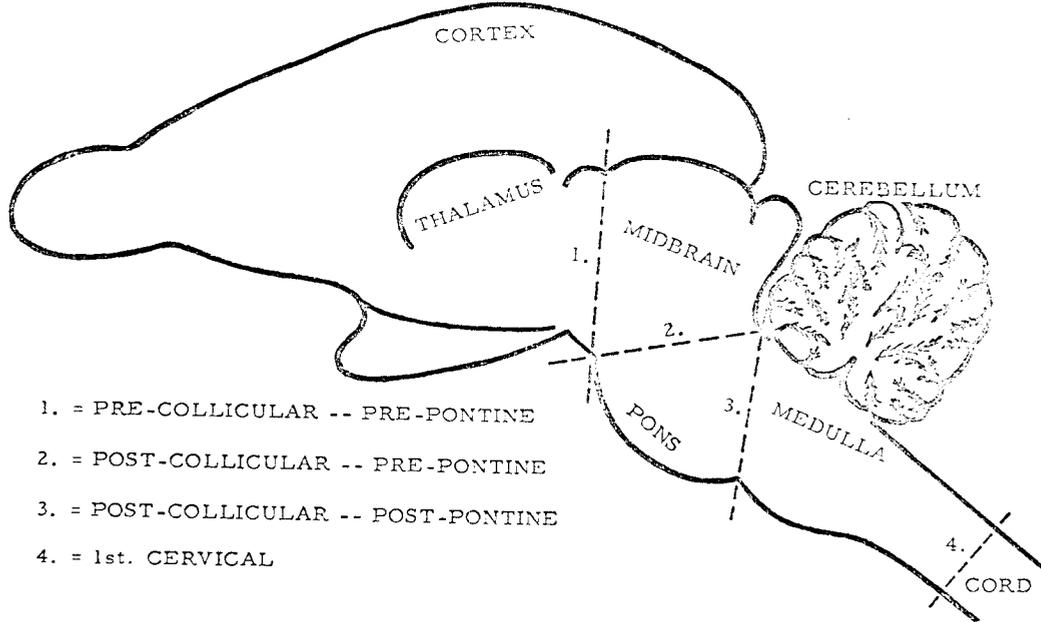


Fig. 2. Schematic representation of the rabbit brain showing planes of transections; in our experiments transections 1, 3 and 4 were employed.

sected cephalad to the midbrain (fig. 2, transection 1).

The fourth type of preparation involved a transection of the spinal cord at the level of the first cervical vertebra (fig. 2, transection 4). The animals were prepared in standard manner for EEG recording, the posterior neck muscles were then retracted and a portion of the atlanto-occipital membrane was removed, thus exposing the spinal cord to direct view. The upper part of the first cervical vertebra was rongeuared away permitting transection at a point 4 to 5 millimeters caudal to the obex. The actual transection was accomplished by passing a dental excavator under the spinal cord and drawing it upward across the entire horizontal extent of the cord under direct vision. After each experiment, the completeness of the transection was reconfirmed by postmortem examination.

In an effort to localize a site of action of psilocin, in one group of four animals, the atlanto-occipital membrane was removed prior to the injection of psilocin but the actual transection was not made until a sustained arousal pattern had been obtained in the EEG by multiple injections of psilocin at the rate of 0.25 mg/kg every 5 minutes. Sustained alerting occurred at values between 0.5 and 2.0 mg/kg. In two of these animals, a second transection was made at the postcollicular level (fig. 2, transection 3) to differentiate the action of psilocin from that of *d*-amphetamine.

We also undertook to determine whether or not an increase in the content of total brain serotonin accompanied the changes in the EEG pattern in four controls and four drug-injected animals. The drug-injected animals received either MP-809 (1.0 mg/kg in 1.0 cc of distilled water) or psilocin (0.7 mg/kg in 2.6 cc of distilled water) while the controls were given either 1.0 cc or 2.6 cc of distilled water. Injections were made into a marginal ear vein at intervals of 7 minutes; three injections were given for each trial. Because alerting was usually seen 7 minutes after the last of a series of three such drug injections, the animals were sacrificed at that time and their brains were removed. Each of the hemispheres and the brain stems were then separated and preserved by freezing with solid carbon dioxide. Serotonin and norepinephrine were determined by the method of Shore and Olin (1958).

RESULTS. As shown in figure 3, a normal resting EEG pattern consisted of high amplitude slow waves interrupted by relatively rapid spindles (14/sec). Noise produced by hand clapping or pain stimulation changed the resting pattern markedly. All leads showed a sharp reduction in amplitude and an increase in frequency in addition to the elimination of spindles. Under these conditions the control alert pattern lasted for 10 to 20 seconds.

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RABBIT EEG RESTING PATTERN

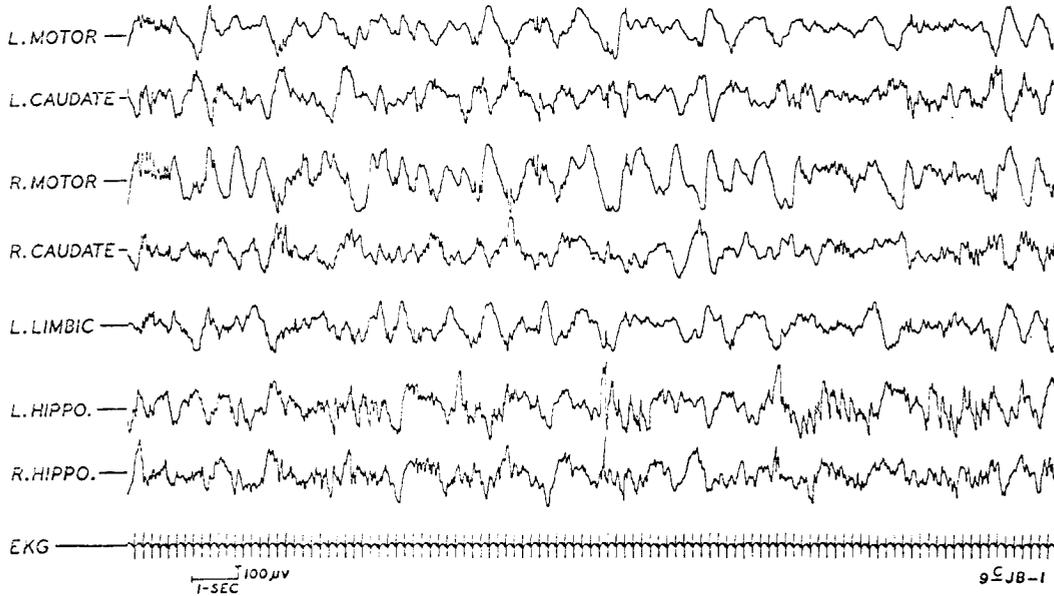


FIG. 3. Cerebral electrical activity of a curarized unanesthetized rabbit showing typical synchronous patterns of high voltage waves and 14/sec spindles.

The leads are (reading downward) (1) right motor cortex, (2) left caudate nucleus, (3) right amygdala, (4) left limbic cortex, (5) right limbic cortex, (6) left hippocampus, (7) right thalamus and (8) EKG.

EEG ALERT PATTERN OF INTACT RABBIT AFTER INJECTION OF MP 809 -1.5 mg/kg I.V.

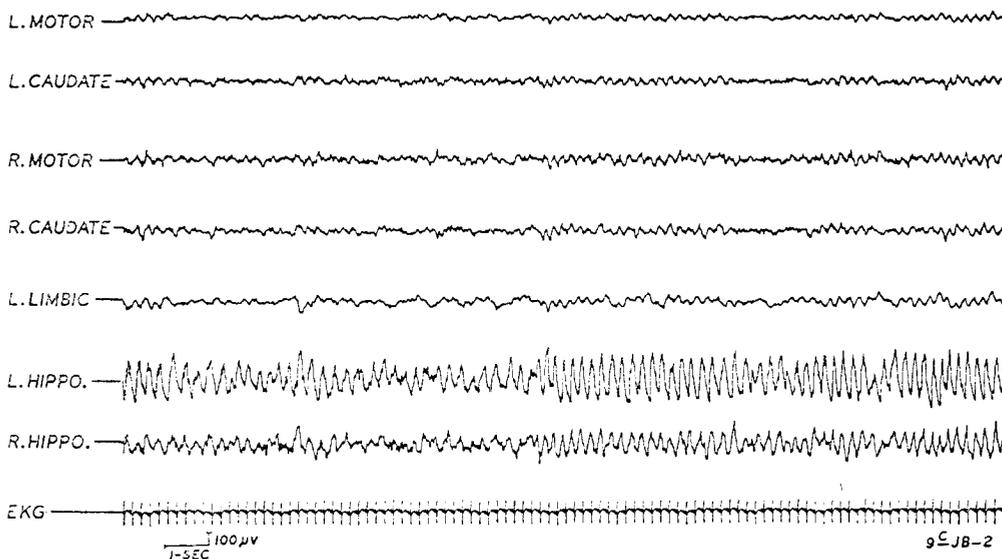


FIG. 4. Cerebral electrical activity of rabbit with intact brain after administration of 1.5 mg/kg of MP-809.

Notice the desynchronization characterized by low amplitude and absence of sleep spindles and slow waves.

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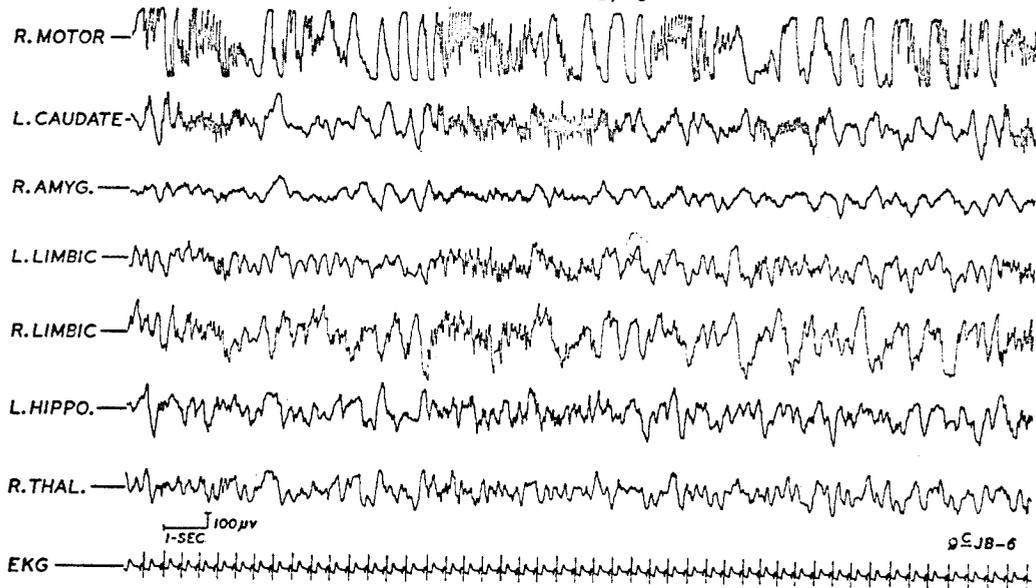


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A EEG PATTERN OF RABBIT, WITH PRE-COLLICULAR PRE-PONTINE TRANSECTION,
BEFORE MP 809-8.5 mg/kg I.V.



B EEG PATTERN OF RABBIT, WITH PRE-COLLICULAR PRE-PONTINE TRANSECTION,
AFTER MP 809-8.5 mg/kg I.V.

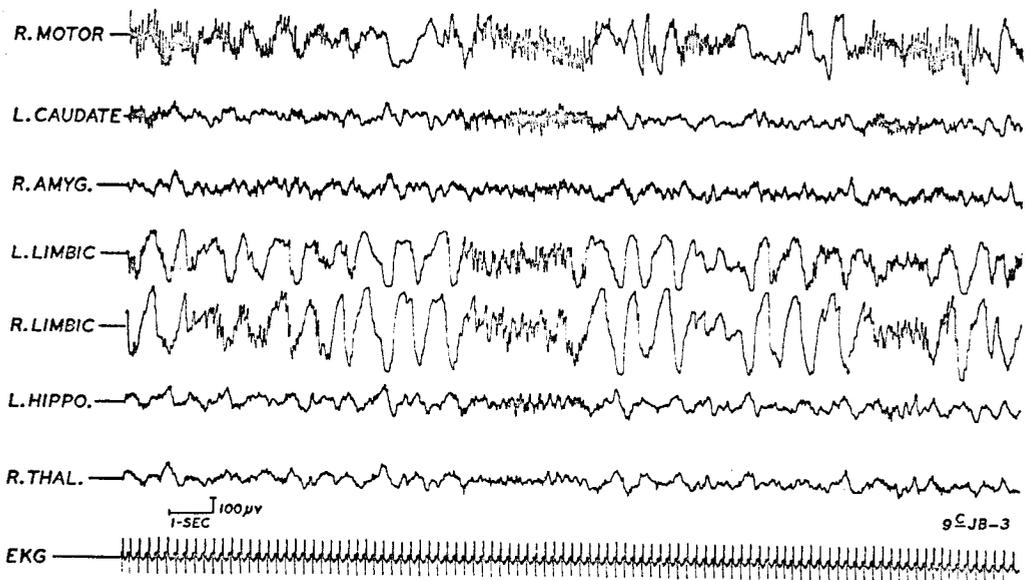


FIG. 5. Cerebral electrical activity of a rabbit transected in a precollicular prepontine plane and administered 8.5 mg/kg MP-809. Notice the persistence of high voltage waves and sleep spindles and the lowering in amplitude from the caudate nucleus, amygdala, hippocampus and thalamus after MP-809.

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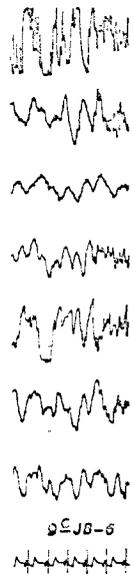
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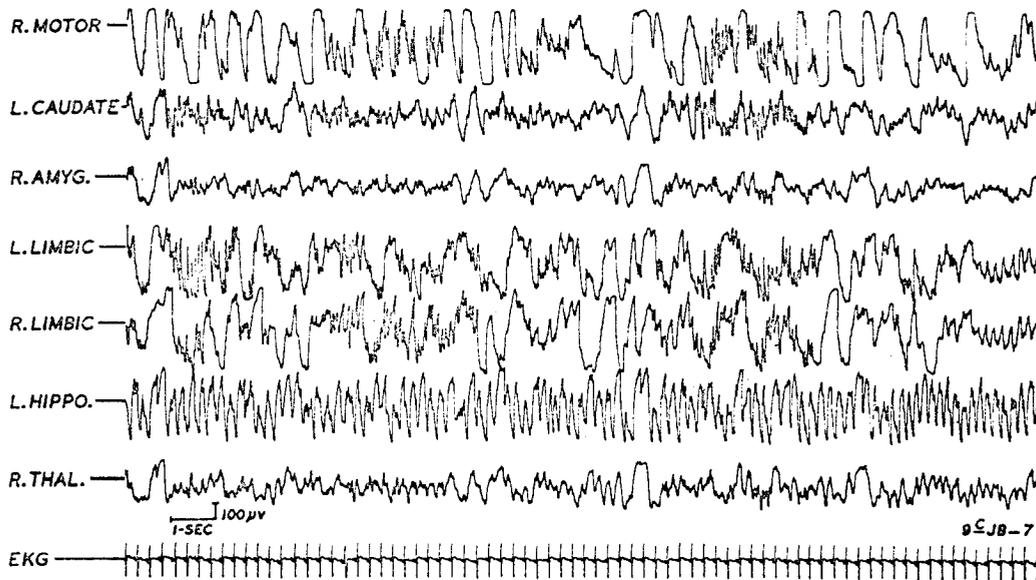
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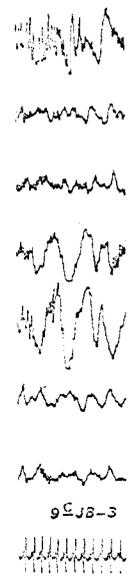
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A EEG PATTERN OF RABBIT, WITH POST-COLLICULAR POST-PONTINE TRANSECTION, BEFORE MP 809-7.0 mg/kg I.V.



SECTION,



B EEG PATTERN OF RABBIT, WITH POST-COLLICULAR POST-PONTINE TRANSECTION, AFTER MP 809-7.0 mg/kg I.V.

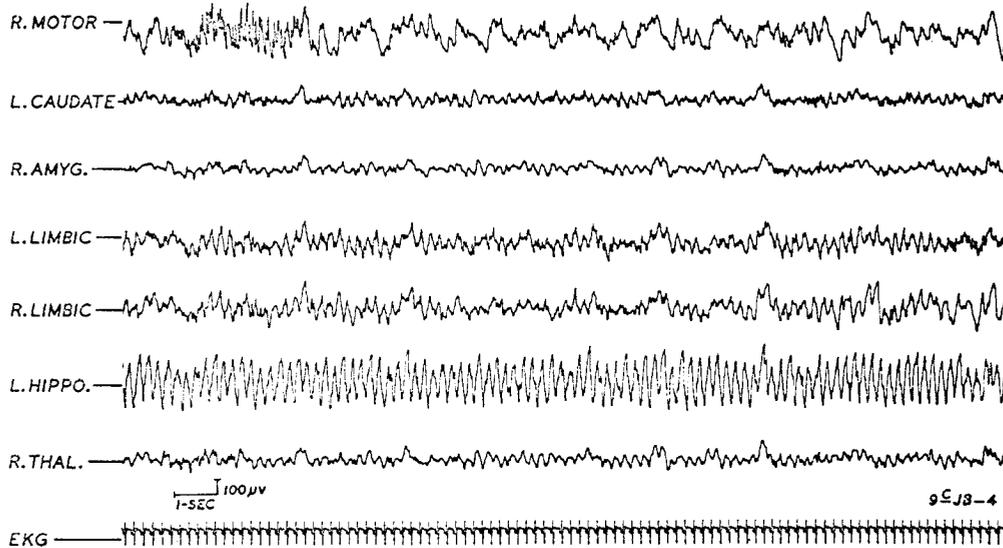


FIG. 6. Cerebral electrical activity of rabbit transected in a postcollicular postpontine plane and administered 7.0 mg/kg of MP-809.

The pattern observed in B resembles the desynchronization presented in figure 3 differing only in the somewhat higher amplitude of the cortical brain waves.

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Experiments performed on groups of 6 intact animals using each of the five compounds—psilocybin, psilocin, MP-809, MP-14 and 1-methyl psilocybin showed that patterns identical to the control alerting were obtained after sufficient drug was administered (see fig. 4). The amount of drug required to produce a pattern similar to control alerting varied from one experiment to another. However, once established, the alert pattern held for 45 minutes or longer with each agent and thus was of significantly longer duration than the arousal evoked on control. The quantity of each agent needed to produce sustained activation was psilocybin 4.0 to 6.0 mg/kg; psilocin 0.5 to 2.0 mg/kg; MP-809 1.0 to 2.0 mg/kg; MP-14 5.0 to 7.0 mg/kg; and 1-methyl psilocybin 6.8 to 12.6 mg/kg.

The two most potent drugs on a weight basis, psilocin and MP-809, produced activation in a more sustained manner than the other congeners. For these two drugs there was a specific dosage level at which the drug evoked EEG activation. Furthermore, this level was practically the same for all trials. The above cannot be said for the

other three; MP-14, psilocybin and 1-methyl psilocybin. Although the final result with these three drugs was an alert pattern like that described for pain or hand clapping, there was greater variation in the dosage required for arousal. The point at which the final alert pattern appeared varied to a greater extent and the pattern preceding it often fluctuated between alert and rest.

Experiments on animals successfully transected at the precollicular, prepontine plane indicated only a slight lowering of amplitude in the subcortical leads after 8.5 mg/kg of MP-809 had been administered (see figs. 5A and 5B). Sleep spindles and high amplitude in the cortical regions (motor and limbic) remained unchanged. The amount of drug used in these trials was in excess of five times that needed to cause alerting in nontransected animals. Rabbits given a total of 3.0 mg/kg of *d*-amphetamine after the usual total dose of 8.5 mg/kg of MP-809 showed no change in the resting pattern. However, a subsequent injection of 0.1 mg/kg of eserine salicylate, only one-third the dose usually required for sustained arousal, evoked characteristic

SYNCHRONIZED EEG PATTERN OF RABBIT, WITH POST-COLLICULAR POST-PONTINE
TRANSECTION, DESPITE PSILOCIN-3.2 mg/kg I.V.

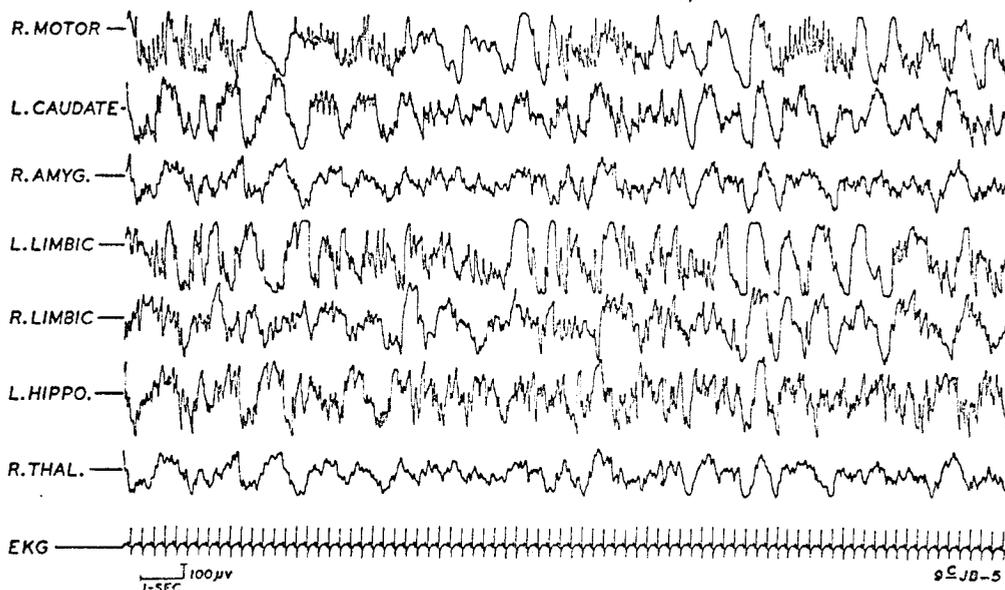


FIG. 7. In this rabbit an alerted EEG pattern had been previously produced by the administration of 1.2 mg/kg psilocin.

Subsequent postcollicular postpontine transection changed the pattern to one of synchronization which was maintained despite an additional dose of 2.0 mg/kg of psilocin.

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EEG alerting. Some animals displayed a tendency to alert at a dose of 0.1 mg/kg of eserine but to obtain the maximal degree of alerting in all animals, the dose of 0.3 mg/kg is usually required (Steiner and Himwich, 1962).

When the animals were transected in a post-collicular, postpontine plane, a total dosage of 7.0 mg/kg of MP-S09 induced a marked arousal in the EEG pattern (see figs. 6A and 6B). The comparison of the brain waves before and after administration of the drug revealed a marked reduction in amplitude in all leads together with an elimination of slow waves and all but an

occasional sleep spindle. A comparison of these waves with the sensory-stimulated and drug-induced alert pattern in animals with intact brains showed that the waves in the transected animals were not desynchronized to the same degree as the nontransected animals because the amplitude was slightly higher in the cortical leads and because an occasional spindle was seen in the motor area.

Animals transected rostral to the midbrain (transection 1) and given a total of 1.0 to 1.2 mg/kg of psilocin alone, showed no apparent change in the EEG pattern. Similarly psilocin

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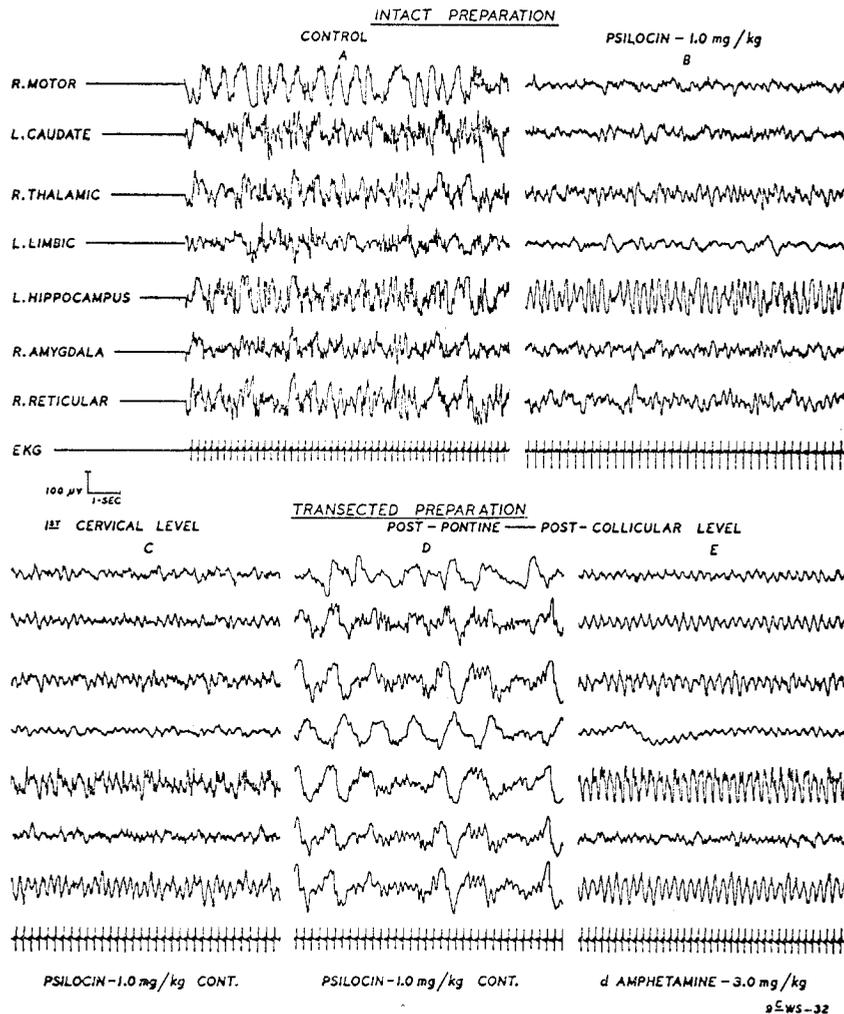


FIG. 8. Limits of site of action of psilocin.

(A) Predrug resting rhythm, (B) psilocin alerting, (C) continued maintenance of psilocin alerting after transection of spinal cord at first cervical vertebra, (D) loss of EEG arousal after second transection caudad to midbrain, and (E) arousal restored by *d*-amphetamine.

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failed to cause an EEG alerting when administered to animals transected caudad to the mid-brain (transection 3) in total doses of 2.0 to 3.0 mg/kg. When, however, these animals were then given additional drug in the form of 3.0 mg/kg of *d*-amphetamine, a fully alert EEG pattern was induced. In other animals transected after an alert pattern had been evoked with psilocin, the transection eliminated all signs of the alerting and prevented its return in spite of further administration of psilocin (see fig. 7).

A total of 4 animals was transected at the level of the first cervical vertebra (transection 4) in experiments with psilocin. Cervical transection did not abolish previously induced psilocin activation in each of the rabbits studied. The pattern was abolished, however, when two of these animals were transected a second time at the postcollicular level. EEG alerting was re-established in these two animals with 3.0 mg/kg of *d*-amphetamine after the psilocin induced arousal had been abolished by postcollicular transection. EEG tracings from this sequence of events are presented in figure 8.

It is known that drugs which act by inhibiting the monoamine oxidase may produce increases of brain biogenic amines by 50% or more in a period of 2 hours. In order to ascertain whether psilocin and MP-809 possess such powers, some pilot experiments were done under the experimental conditions previously stated including dosages used and the time intervals for injections and total duration of experimental periods. Under these conditions, the differences between controls on 4 rabbits and two each of psilocin and MP-809 were not significant, thus suggesting that no appreciable changes were produced by these two drugs in our experimental conditions. In the animals given MP-809, the average contents of serotonin changed as follows: brain stem 0.82 $\mu\text{g/g}$ to 0.86 $\mu\text{g/g}$ and for the hemispheres 0.37 $\mu\text{g/g}$ to 0.48 $\mu\text{g/g}$. The averages for epinephrine contents were as follows: brain stem 0.58 $\mu\text{g/g}$ to 0.57 $\mu\text{g/g}$ and for the hemispheres, 0.38 $\mu\text{g/g}$ to 0.37 $\mu\text{g/g}$. In animals injected with psilocin, the average contents of serotonin changed as follows: brain stem 0.82 $\mu\text{g/g}$ to 1.01 $\mu\text{g/g}$ and for the hemispheres 0.37 $\mu\text{g/g}$ to 0.44 $\mu\text{g/g}$. The averages for epinephrine contents were as follows: brain stem 0.58 $\mu\text{g/g}$ to 0.51 $\mu\text{g/g}$ and for the hemispheres 0.38 $\mu\text{g/g}$ to 0.35 $\mu\text{g/g}$.

Changes in blood pressure were studied in

each of the four animal preparations for the two more important drugs, MP-809 and psilocin, which yielded information from 14 animals. MP-809 induced a slight fall in mean arterial pressure while psilocin induced a slight elevation of a similar magnitude with the degree of changes being about equal for the two drugs (10 to 20 mm/Hg). Alterations in blood pressure occurred normally after the first dose of either drug and continued throughout the experiment with random fluctuations of 5 to 10 mm/Hg.

DISCUSSION. Our results show that psilocybin and its congeners O-phosphoryl-4-hydroxy-N-dimethyl tryptamine (psilocybin), 4-hydroxy-N-dimethyl tryptamine (psilocin), 4-methyl- α -methyl tryptamine (MP-809), 4-hydroxy- α -methyl tryptamine (MP-14) and 1-methyl psilocybin all evoked alert EEG patterns in rabbits with intact brain. In addition it was found that MP-809 acts effectively at the midbrain level while psilocin does not.

In contrast to MP-809, the inability of psilocin to produce EEG alerting in animals transected caudad to the midbrain presents evidence that psilocin does not possess a site of action in the midbrain region. LSD-25, another psychotomimetic drug, also evokes EEG alerting (Rinaldi and Himwich, 1955; Himwich *et al.*, 1959), an action which also fails in animals transected caudad to the midbrain (Bradley, 1958). According to Bradley (1958), LSD-25 has a selective action on the afferent collaterals leading from the lemnisci to the reticular formation and our evidence indicates a similar action for psilocin. The nature of the present experiments with psilocin does not permit a precise assignment of effects to the afferent collaterals specifically, but the data from the cervical and postcollicular transection experiments indicate a site of action consistent with this view.

Both psilocybin and psilocin are psychotomimetic substances. Probably psilocybin is dephosphorylated in the body to form the active compound, psilocin (Horita and Weber, 1961; Kalberer *et al.*, 1962; Hofmann and Troxler, 1959). Psilocybin given to human beings (Isbell *et al.*, 1961) causes feelings of strangeness, difficulty in thinking, anxiety, altered sensual perception, elementary and true visual hallucinations and an alteration of body image. In addition, elevation in body temperature, pulse, respiratory rate and systolic blood pressure

have been noted. Isbell has shown that there is a cross tolerance between psilocybin and LSD-25, and concludes that these two drugs cause psychic disturbances by acting on some common mechanism or on mechanisms acting through a common pathway. Our experiments disclose that one common site of action for these two psychotomimetics may reside in the collaterals to the reticular formation. These drugs evidently pass through the blood-brain barrier readily (Kalberer *et al.*, 1962) and probably possess additional central sites of action to account for their psychotomimetic effect upon behavior (Isbell *et al.*, 1961).

The necessity of a synergistic action of eserine to evoke an alerting pattern with MP-809 in rabbits transected rostrally to the midbrain indicates a limited degree of activity anterior to the midbrain, an area which contains a cholinergic element (Himwich, 1962; Steiner and Himwich, 1962). In addition, the ability of MP-809 to elicit EEG alerting in animals transected caudad to the midbrain disclosed a potent site of action in the midbrain region, an area possessing a strong adrenergic component (Himwich, 1962; Bradley, 1958). The present work does not decide whether MP-809 penetrates the blood-brain barrier and acts directly upon the reticular formation like amphetamine or on the contrary exerts indirect effects like those of epinephrine and norepinephrine which pass through the blood-brain barrier very slowly and cause alerting chiefly by stimulation of peripheral receptors (Bradley, 1958).

Our data on animals with intact brains show that all five drugs studied produce EEG alerting in rabbits. The distinct differences in the amounts of drugs needed to elicit these changes may be related to the small differences in the chemical structures of these compounds. It is of interest that though psilocin and MP-809 are congeners there is little agreement in their central sites of action. In further support of this conclusion are the differences of their behavioral effects, psilocybin and psilocin being psychotomimetic agents while MP-809 is a candidate drug for use as a stimulant in depressed patients. Perhaps *N,N*-dimethyl substitution is instrumental in conferring the psychotomimetic properties. A similar substitution in serotonin transforms it to bufotenin, also a psychotomimetic drug. It is evident that small but strategic differences in

chemical structure may induce fundamental changes and in this instance affect not only sites of action but also behavior.

Our chemical determinations indicate only insignificant rises in total brain serotonin with MP-809 and psilocin. Freedman (1963), however, showed that psilocybin produces an 11% rise in serotonin and a 20% fall in norepinephrine. It remains to be proved, however, that changes of these small magnitudes are of functional significance. It is also improbable that the comparatively small alterations in blood pressure associated with the administration of MP-809 and psilocin, could account for the observed EEG effects.

SUMMARY

In this study 59 rabbits were used for an EEG analysis of five compounds: O-phosphoryl-4-hydroxy-*N*-dimethyl tryptamine (psilocybin), 4-hydroxy-*N*-dimethyl tryptamine (psilocin), 4-methyl- α -methyl tryptamine (MP-809), 4-hydroxy- α -methyl tryptamine (MP-14) and 1-methyl psilocybin. Four different preparations were employed, two involving transection of the brain and one of the cervical cord. In experiments on the intact brain groups of 6 rabbits were used and each of the five compounds was tested. The precollicular, prepontine preparation was employed in ten rabbits to localize sites of action of MP-809 and psilocin. In other experiments involving the postcollicular, postpontine transection 15 animals were studied for additional information on the same two drugs. In addition, 4 animals having a transection at the level of the first cervical vertebra were used in a further study of psilocin.

In rabbits with intact brain all five drugs produced EEG alert patterns. When MP-809 was administered to animals transected in a prepontine, precollicular plane only a slight lowering of amplitude was seen in the EEG pattern. But when one-third the dose of eserine needed to evoke sustained activation in an animal so transected was administered to animals pretreated with MP-809 a fully alert pattern was obtained indicating a site of minor action rostral to the midbrain and probably cholinergic in nature. When, however, MP-809 was administered to animals transected in a postcollicular, postpontine plane the EEG pattern duplicated, with minor variations, the EEG arousal seen in

intact animals. Thus a potent site of action for MP-809 was found in the midbrain, a region possessing a strong adrenergic component. Psilocin failed to evoke alert patterns in animals transected either rostral or caudal to the midbrain, thus excluding the midbrain and structures more rostrally situated as possible sites of action. On the other hand, animals injected with psilocin and subsequently transected at the level of the first cervical vertebra continued to display EEG alerting thus indicating a site of action below the midbrain but excluding the spinal cord. It is not likely that small changes in brain serotonin or in systemic blood pressure could account for the alterations in EEG produced by these two drugs.

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