9. EFFECTS OF VARIOUS PSYCHOTROPIC DRUGS ON ELECTRICAL ACTIVITY OF THE BRAIN AND BEHAVIOR OF THE CAT

(CHLORPROMAZINE, IMIPRAMINE, PHENOBARBITURATE, LSD-25, LAE, JB-336, ATROPINE, DMAE, JB-516)

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The drugs examined in this study are variously called, according to their actions, tranquillizer, thymolepticum, relaxant, narcotic, hallucinogen, stimulant, anti-depressant etc. It is the purpose of this paper to characterize the alterations produced by these drugs in the behavior and the electrical activity, especially of the cerebral cortex, rhinencephalon and meso-diencephalic reticular system.

The following drugs were examined: chlorpromazine (chloro-3-[dimethylamino-3-propyl]-10-phenothiazine), imipramine (N-[γ-dimethylamino-propyl]-iminodibenzyl hydrochloride), phenobarbital sodium, LSD-25 (d-lysergic acid dimethylamide), LAE (d-lysergic acid monoethylamide), JB-336 (N-methyl-3-piperidylbenzylate), atropine, DMAE (2-dimethylamino-ethanol) and JB-516 (β-phenylisopropyl hydrazine hydrochloride).

Methods

Seventy cats were used in this study. All the experiments except some cases with JB-516 were performed on unrestrained cats with cortical and subcortical electrodes implanted more than a week before hand, with a stereotaxic apparatus of the Nöken type and by the aid of the map of Jasper and Ajmone-Marsan5). The cortical electrodes were made of silver balls, 0.5 mm in diameter. The subcortical electrodes consisted of pairs of stainless steel wires, 250 µm in diameter, insulated except at the tips, the distance between the tips being within 2 mm. The drugs were injected into the peritoneal cavity.

In some cases of the study with JB-516, the experiments were performed on paralysed cats with succinyl-choline chloride and on encéphale isolé cats under artificial respiration, and JB-516 was injected intravenously.

In all the experiments EEG and ECG were recorded simultaneously. The drug effects were observed with respect to the following points: (a) behavior of the animal, (b) spontaneous electrical activities of the cortical and subcortical...
regions, (c) cortical desynchronizing response to electrical high frequency stimulation (1 msec 100 c/s square wave 5 sec) of the brain stem reticular formation at the mesencephalic level\(^4\), (d) recruiting response to low frequency stimulation (0.5-1 msec 6-10 c/s square wave) of the thalamic diffuse activating system\(^1\text{-}^3\), and (e) seizure afterdischarge following high frequency stimulation (1 msec 100 c/s square wave 5 sec) of the limbic system (hippocampus and amygdaloid nucleus)\(^2\). Concerning (c), (d) and (e), the threshold voltage of electrical stimulation for provoking the response was chiefly examined. Direct electrical stimulation of the limbic system was performed at intervals of more than 5 min. When a seizure afterdischarge was provoked, the following test stimulation was performed, it being observed that the electrical activity in the EEG recovered to the previous state after a period of more than 20 min..

At the end of the experiments, the animals were killed and the brain was perfused with 10% formaline and the positions of the tips of the electrodes were determined.

**Results**

Phenobarbiturate (2-10 mg/kg) and chlorpromazine (10-25 mg/kg): Some minutes after the injection of the drugs, their sedative action appeared, the effect being more marked with phenobarbiturate at the same doses. At higher doses the animal became quite unresponsive to the stimuli; touch, tone, pinch etc. Cortical EEG showed a predominantly synchronous high voltage slow wave pattern, with recurrent appearance of spindle activity. The threshold voltage of electrical stimulation at the mesencephalic reticular formation to obtain the cortical desynchronizing response was remarkably elevated and, when the desynchronizing response was provoked, a marked decrease in its duration was observed. The threshold voltage for provoking the recruiting response was kept at a lower level as compared with the control value. The minimal voltage necessary for provoking the hippocampal seizure afterdischarge was remarkably elevated in the cases with phenobarbiturate, but a definite change was not observed with chlorpromazine.

Imipramine (8-15 mg/kg, mainly 15 mg/kg): Sedative action of this agent was observed some minutes after its administration and lasted more than 2 hours, but the action was not so prominent as that of chlorpromazine. In pararell with the behavioral changes, a marked generalized slowing of the EEG activity and frequent spike-like discharges in the amygdaloid nucleus and the hippocampus were observed. The threshold voltage of the cortical desynchronizing response in the EEG to electrical stimulation of the brain stem reticular system was markedly elevated and a decreased duration of the response was observed. The threshold voltage of the recruiting response was lowered slightly and its amplitude was increased definitely by the stimulation of the same voltage. The threshold of the
seizure afterdischarge following the stimulation of the rhinencephalon was lowered slightly in the hippocampus and markedly in the amygdaloid nucleus.

LSD-25 (30-40 \( \gamma \)/kg) and LAE (30-40 \( \gamma \)/kg): After the administration of these drugs, the animal was kept in an alert state and highly responsive to external and harmful stimuli, showing prompt attention reactions or orientation reflexes. No definite difference was found between the behavioral effects of LSD-25 and LAE. The two drugs also had the same effect upon the electrical activity of the brain. In parallel with the behavioral effect, the electrical activity showed a low amplitude fast wave pattern in the cerebral cortex, amygdaloid nucleus and the brain stem reticular formation. Meanwhile in the hippocampus and some regions in the thalamus, 5-6 c/s sinusoidal rhythmic electrical activities were observed. This state in the EEG lasted about 2 to 3 quarters of an hour, and gradually the regular 5-6 c/s activity in the hippocampus and other subcortical regions disappeared and the low voltage fast wave pattern in the cortex was replaced by a 5-6 c/s relatively rhythmic activity like what had been observed in the hippocampus. In this state, with high frequency electrical stimulation at a suitable voltage of the brain stem reticular formation, the cortical 5-6 c/s rhythmic activity was replaced by a low voltage fast wave pattern (Fig. 1.). This indicates a relatively lowered activity of the reticular formation as compared with that in the preceding state. As compared with the control value, a fall in the threshold of cortical desynchronizing response by direct electrical stimulation of the brain.

![Fig. 1.](image)

**Fig. 1.** F (L): Frontal (Left side), P (R): Parietal (Right side), O: Occipital, Hipp: Hippocampus, downward arrows below the time signal indicate the onset of electrical stimulation of the reticular activating system at the mesencephalic level. EEG on the left: control, in the middle: 5 min. after administration of LSD-25 (30\( \gamma \)/kg), on the right: 20 min. later, appearance of slow wave burst on the cortical EEG like what was observed in the hippocampus in the previous state (in the middle record), and these slow waves were blocked by stimulation of the reticular formation.

— 104 —
stem reticular formation and a slight rise in the threshold of the recruiting response by low frequency stimulation of the diffuse thalamic activating system were observed. No remarkable change was observed in the threshold of the hippocampal seizure afterdischarge by direct stimulation of the hippocampus.

JB-336 (0.3 mg/kg) and atropine (1-1.2 mg/kg): JB-336 is a hallucinogenic agent described by L. G. Abood et al. (1958) and its chemical structure is closely related to atropine. About 10-15 minutes after the administration of JB 336, the animal was excited, and tachycardia and mydriasis were observed. On the EEG; high voltage irregular slow waves appeared in the cortex, thalamus, lower brain stem and hippocampus. This pattern was similar to what is observed in the drowsy or sleeping state. In this experiment, although high voltage slow waves were dominant in the recording of the electrical activity, sleeping or drowsy states of the animals were never observed and the animals remained fully awake and excited. A rise in the threshold of the cortical desynchronizing response by direct stimulation of the brain stem reticular formation or by the afferent sensory stimuli was observed. This dissociation of EEG from behavior and a rise in the threshold of the cortical desynchronizing response were similarly observed in the cases of atropine. A slight rise in the threshold of the hippocampal seizure afterdischarge was observed in the cases of JB-336, but it was not observed in the cases of atropine. In some cases, 30 to 40 minutes after the administrations of JB-336 and atropine, after their effects on the EEG were observed, eserine (1 mg/kg) was injected into the peritoneal cavity. The electrical activity showed low voltage fast wave pattern in the cortex and 5-6 c/s regular slow wave pattern (hippocampal arousal) appeared in the hippocampus, and the recruiting response in the cortex decreased in its amplitude without any change in the behavioral alertness produced by atropine or JB-336.

DMAE (50-100 mg/kg): After intraperitoneal injection of this drug, the animals remained highly aroused. Electroencephalographically, a decrease in voltage and an increase in frequency of the cortex were observed. The threshold of the recruiting response was elevated as Königsmark (1958) showed in the encéphale isolé animals. The thresholds of the hippocampal and amygdaloid seizure afterdischarges were little altered.

JB-516 (3-15 mg/kg, mainly 15 mg/kg): This drug caused behavioral arousal, bradycardia and mydriasis. EEG of the cortex showed very low voltage, high frequency activity even in encéphale isolé animals, suggesting a very low threshold for arousal responses to the stimulation of the mid-brain reticular formation. The threshold of recruiting response was elevated and that of hippocampal and amygdaloid seizure afterdischarges remained the same.

Comment

The data presented above are summarized in the Table 1. After administration of barbiturate, slow waves in the cortical EEG became

— 105 —
dominant and the threshold voltage required for evoking cortical desynchronizing response by direct electrical stimulation of the reticular activating system showed marked increase, this indicating a lowered excitability of this system\textsuperscript{6-12). The recruiting response was enhanced\textsuperscript{14,15) and the threshold voltage required for evoking the hippocampal seizure afterdischarge was elevated remarkably, this indicating an inhibitory action of barbiturate upon this system\textsuperscript{13,15).}

It is generally accepted that chlorpromazine has a sedative action. Electroencephalographically, it produced slow activity and increase in the threshold voltage required for inducing the cortical arousal response by electrical stimulation of the midbrain reticular formation\textsuperscript{15-22). The same results were obtained in the present study. Preston (1956)\textsuperscript{18) observed spontaneous seizure afterdischarges in the amygdaloid nucleus after administration of chlorpromazine. On the other hand, Monnier (1957)\textsuperscript{15,19) observed an increase in the threshold voltage of electrical stimulation required for evoking the hippocampal seizure afterdischarge. The authors observed that chlorpromazine had had no effect upon the threshold voltage for provoking the seizure afterdischarge by electrical stimulation of the hippocampus.

Imipramine (antidepressant) showed sedative action. Many authors observed high voltage slow wave pattern on the EEG and an increase in the threshold voltage of electrical stimulation of the brain stem reticular formation required for evoking the cortical arousal response and a decrease in the threshold of the recruiting response\textsuperscript{10,23). The authors confirmed these data in the present study. Concerning the effect of imipramine upon the rhinencephalic electrical activities,
Himwich (1959)\textsuperscript{23} observed spike-like discharges and a seizure afterdischarge with large doses (45-50 mg/kg). Monnier et al. (1959)\textsuperscript{19} observed no effect with smaller doses (9 mg/kg). In the experiment of these authors, with medium doses (15 mg/kg) of imipramine, a decrease in the threshold voltage required for evoking the hippocampal and amygdaloid seizure afterdischarges were observed.

LSD-25 had arousal effects on behavior and EEG, and suppressed the recruiting response. These results are in accordance with that reported by Monnier and other authors\textsuperscript{15,26,27} but an inhibitory effect upon the hippocampal seizure afterdischarge reported by Monnier\textsuperscript{15} was not observed in the present study. After a period of 2 to 3 quarters of an hour following the administration of LSD-25, 5-6 c/s rhythmic slow wave burst appeared in the cortical EEG\textsuperscript{22,25}). These cortical slow waves were blocked and replaced by a low voltage fast wave pattern, during and after electrical stimulation of the reticular formation. This indicates a relatively lowered activity of the reticular formation as compared with its activity during the previous period when the EEG showed a low voltage fast wave pattern in the cortex and a 5-6 c/s rhythmic slow wave pattern in the hippocampus. LAE had the same effects as LSD-25 on the behavior and the EEG of the animal.

It is reported that intoxication with atropine induces excitation of the central nervous system (restlessness and excitation in animal experiments, and also hallucination in man) but no sedation or sleep. Meanwhile the EEG showed a sleep-like pattern (dissociation of EEG from behavior)\textsuperscript{28-31}, and this effect upon EEG was antagonised by eserine\textsuperscript{30}). The arousal response on the cortical EEG by stimulation of the reticular formation was suppressed by atropine. As to the threshold of the hippocampal seizure afterdischarge, this drug had no effect on it\textsuperscript{32}). These data were confirmed by the present study. Except a slight inhibitory effect upon the hippocampal seizure activity, JB-336 had the same effects as atropine. Based on the data that the arousal action of the reticular formation upon the cortical EEG was facilitated by acetylcholine and suppressed by atropine, it was suggested that cholinergic mechanism should take parts in the arousal function\textsuperscript{34,33}). The authors suppose that JB-336 may produce its effects by acting upon this cholinergic mechanism.

DMAE (deanol) is a stimulant of the central nervous system\textsuperscript{35,36,37,38,40}). During preparation of this report, the authors received a report of Goldstein (1960)\textsuperscript{39}, who observed a EEG pattern with frequent appearance of a high voltage low frequency wave burst or spindle and an arousal effect on the behavior of unrestrained rabbits, after administration of DMAE (5-10 mg/kg). The authors of the present report observed an EEG pattern of low voltage fast wave, an increase in the threshold for inducing the recruiting response and an arousal effect on the behavior of unrestrained cats. Konigsmark (1958)\textsuperscript{35} reported the same effects on the electrical activities of encephale isolé cats.

JB-516 has been reported as a potent and long acting monoamine oxidase inhibitor\textsuperscript{41}) and has been applied to the depressive patients as a therapeutic agent\textsuperscript{42}).
The authors observed an EEG pattern of low voltage fast waves on the cortex, an elevation of the threshold of the recruiting response and a decrease in the amplitude of this response after administration of the drug, in unrestrained and encéphale isolé cats. The authors also observed that the arousal effect on the EEG was markedly diminished or blocked after transection of the brain stem at the meso-diencephalic level (these data are to be reported as a separate paper). Therefore it is suggested that JB 516 has an excitatory effect upon the lower reticular activating system. It is reported by many workers that serotonine and catechol amine in the brain increase remarkably after administration of JB 51643-45), and that noradrenaline is localized in especially high concentration in the brain stem reticular formation and the hypothalamus46-47), and that noradrenaline and adrenaline have excitatory effects upon the reticular formation and cause the cortical arousal on the EEG48-50). The present observation seems to have some relation to these data. Serotonine is reported to be localized in the limbic system44) and it increases remarkably after administration of JB-51644). But no change in the threshold voltage required for evoking the hippocampal and amygdaloid seizure afterdischarges were observed in the present study. Thus the authors suppose that the excitation in the central nervous system produced by JB-516 may be related to the increase of noradrenaline content rather than that of serotonine content in the brain.

References