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Behavioral and Electroencephalographic Effects of Hallucinogenic Drugs

nges in Cats on Intraventricular Injection

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Feldberg and Sherwood's* previous studies of the behavior of cats after the intraventricular injection of various drugs opened up a new method of investigation. By this technique they showed that drugs injected into this area of high pharmacologic sensitivity could evoke various complex behavioral responses and conditions resembling sleep, anesthesia, profound muscular weakness, catatonia, and convulsions. Their classification of the effects characterized by certain common features of reaction suggested further experiments in which, in addition to the effects of the drug alone, antagonisms of various chemicals within the central nervous system might be studied. Of particular interest to experimental psychiatry is the possible antagonism of lysergic acid diethylamide and serotonin. Previously, Gaddum [3] had shown the effect of such antagonism on smooth muscle. Woolley and Shaw [4] hypothesized that, if such an antagonism exists, it might be an important factor in schizophrenia. Other drugs of interest behaviorally are mescaline, adrenochrome, adrenolutin (1-methyl-3,5,6-indolestriol), and ergotamine.

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* References 1 and 2.

METHOD

Three cats anesthetized with pentobarbital sodium were operated on. Their heads were fixed in a cat Horsley-Clark stereotactic instrument. Midline incisions were made, and the fascia and temporalis muscles were laterally deflected. A trephination was made 15 mm. anterior to the line of the external auditory meatus and 7 mm. to the right of the midline. After a tiny incision had been made in the dura mater, a polyethylene catheter with a No. 22 stainless-steel stylet was introduced perpendicular to the cortex, but on a 15-degree angle with the midline. As the catheter was being inserted, the stylet was frequently withdrawn until clear cerebrospinal fluid, which freely pulsated with respiration, was evident. At this point a Lucite ring 8 mm. in diameter and approximately 4 mm. in height was cemented with Acralite plastic. The cap was securely fastened to the skull by pouring liquid Acralite around the catheter and allowing it to harden. The catheter was then cut off approximately 1 cm. above the cortex and was connected to a solid stainless-steel stylet. The catheter and stylet were then covered under a Lucite cone screwed into the skull receptacle (Fig. 1). Postmortem examination demonstrated the patent catheters (Fig. 2*a* and *b*) in the right lateral ventricle in two cats; in the third cat the tip of the catheter was located in the third ventricle.

Fig. 1.—Cat with intraventricular catheter and electrodes in position.

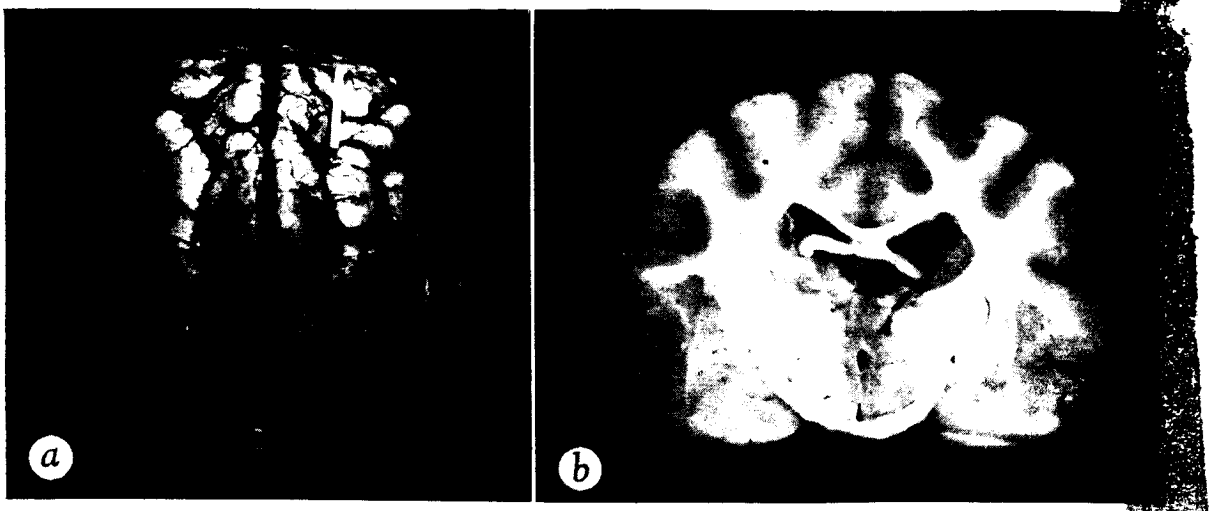
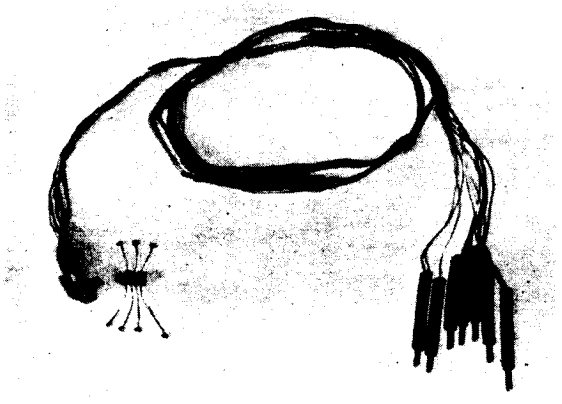


Fig. 2.—(*a*) Dorsal view of brain of cat, with catheter in place; (*b*) coronal section of brain of cat, showing position of catheter in right lateral ventricle.

As indicated in the electroencephalograms, six burr holes were made in the frontal, temporal, and occipital regions bilaterally. Electrodes (Fig. 3) connected to the central plug were placed extradurally in these locations and were permanently fixed with Acralite. Their location was confirmed by anteroposterior and lateral roentgenograms of the head. The fascia and muscles were then approximated in the midline with nonabsorbable surgical (silk) sutures, and the remaining area was smoothly covered with Acralite. Postoperatively, 0.5 cc. of a solution of procaine penicillin G was given for three days. The cats were fully alert and conscious when receiving the injections of the various drugs (Fig. 4). An intraventricular injection of 0.2 to 0.4 ml. of Tyrode's solution or isotonic solution of sodium chloride was given as a control measure to each cat before any of the drugs were administered. Electroencephalograms were made with a six-channel Offner Type-A crystographic ink writer. The animals were free and unrestrained during the recording, connections to the electroencephalographic recorder being maintained by means of a light-weight cable and plug. The latter was introduced into the implanted socket on the head of the cat. The pH of all drugs tested was within the range of the diluent Tyrode solution, and the quantity injected at one time was never more than 0.2 cc. The cats were allowed to recover completely before new compounds were administered, unless specific antagonism experiments were in progress. The pH values of the cerebrospinal fluid and blood in an anesthetized cat (thiopental [Pentothal] sodium) were found to be 7.[illegible] and 7.23, respectively.

Fig. 3.—Electrodes and plug.



RESULTS

Serotonin.—Doses of 75γ to 500γ (pH 7.[illegible] were used on three different occasions, and they produced fairly consistent results. Within a few minutes after injection of serotonin, the pupils of the cat became moo[illegible]

Fig. 4.—Simulated injection into intraventricular catheter.

erately dilated transiently. The cat lay down quietly in a corner of the screened cage, alert and with the eyes open. Several times licking, and occasionally retching, was noticed. The cats cried when they were picked up. On two occasions a previously docile cat snarled and struck out at the observer. There was a tendency to maintain a fixed position, with the least spontaneous exploring or darting about. The animals walked in an unsteady manner and had muscular weakness. Although no classic catalepsy was seen, there was a tendency for the hindlegs to be stiff. Occasionally, there was a fine twitching of the head, with the mouth open. At times rhinorrhea appeared. Usually, the animals preferred the dark corner. There was no striking or consistent change in the respiratory rate. The electroencephalogram showed fast, low-voltage activity, consistent with an alert state.

Serotonin Followed by d-Lysergic Acid Diethylamide (LSD-25).—On three occasions, 24, 40, and 45 minutes after the intraventricular injection of serotonin, 15γ of LSD-25 (pH 7.4) was administered in the same manner. There were no striking changes in behavior or in the electroencephalogram. The reaction resembled the unopposed effect of serotonin, as noted in the controls.

LSD-25 Alone.—Restlessness and retching, which persisted intermittently throughout the period of observation, were early effects produced by the intraventricular injection of 15γ of LSD-25. Later, the cats became drowsy, and were less playful and less responsive to patting. There was no motor impairment in gait or jumping. The electroencephalogram revealed low-voltage, fast activity with occasional slow waves consistent with a relaxed state. There was no difference in the responses to hand clapping, kissing noises, or pinching, as compared with the control pattern.

LSD-25 Followed by Serotonin.—At various intervals within one hour after the administration of LSD-25, serotonin was injected intraventricularly in amounts of 250γ to 500γ without any evidence of a blocking effect of LSD-25. The effects of serotonin were the same as those described when serotonin was given alone.

Mescaline Alone.—Definite effects were observed after the intraventricular injection of mescaline in doses ranging from 0.3 to 15 mg. (pH 7.7). After the higher doses the cat started to cry and howl. There was a copious liquid bowel movement. The pupils were maximally dilated, and the animal had frequent paroxysms of scratching at the face and ears, sometimes using the two forelegs simultaneously. There were episodes of shaking the head and twitching of the right cheek, followed by passage of another loose stool. The cat was totally preoccupied with itching and became difficult to handle. With the onset of the howling and scratching, the electroencephalogram revealed 3 to 4 cps, sharp waves from all positions, maximal in the right temporal region. Without any clinical evidence of a motor seizure, there developed an 80-second paroxysm of 10 cps spikes, beginning in the right frontotemporal area and spreading to the occipital area, and finally to the whole left hemisphere. In the interparoxysmal period the electroencephalogram was characterized by a low-voltage, fast background and random 1 to 3 cps, sharp waves, maximal in the right hemisphere. This was followed by two other electroencephalographic paroxysms, lasting 70 and 50 seconds, respectively, and finally terminating in generalized, diffuse, high-voltage, slow waves and death. Necropsy revealed acute pulmonary edema, which probably was the cause of death.

Within five minutes after the injection of 1 mg. of mescaline into one cat, there occurred, every five seconds, complex paroxysms of sharp, positive deflection with many superimposed spikes, followed by a large, slow, negative phase in the right frontal area, with spread to the right temporal and occipital areas and the homologous areas on the left, except the left frontal area. Within 11 minutes these complex paroxysms became more frequent, and a 40-second episode of 14 cps spikes occurred in the right hemi-

phere, with spread to the left occipital and emporal areas (Fig. 5). Over the 40-second nterval this increased in voltage and slowed o 10 cps, and then finally ended abruptly, vith restoration to the low-voltage, fast, ontrol type of background. Additional com-lex paroxysms, leading to prolonged, diffuse pike activity, occurred. During neither of hese episodes was there evidence of any iotor convulsion. The cat could not be ıfluenced by clapping, kissing noises, or /histling. The animal sat crouched and tared into space. When called or visually istracted, it would turn its head toward ıe source of stimulation. No behavioral

such as increased licking, muscle relaxation, and retching, were observed. For several minutes there seemed to be an accentuation of muscular weakness. The electroencephalogram showed no essential changes other than the mescaline effects, which continued.

Adrenochrome.†—In doses ranging from 0.125 to 1 mg., a freshly prepared solution of pure adrenochrome (pH 7.7) administered intraventricularly produced states of drowsiness of various degrees. Within a few minutes the cats blinked, yawned, or retched. They then either sat or lay down and went to sleep. However, they were easily and readily aroused. They would sometimes sud-

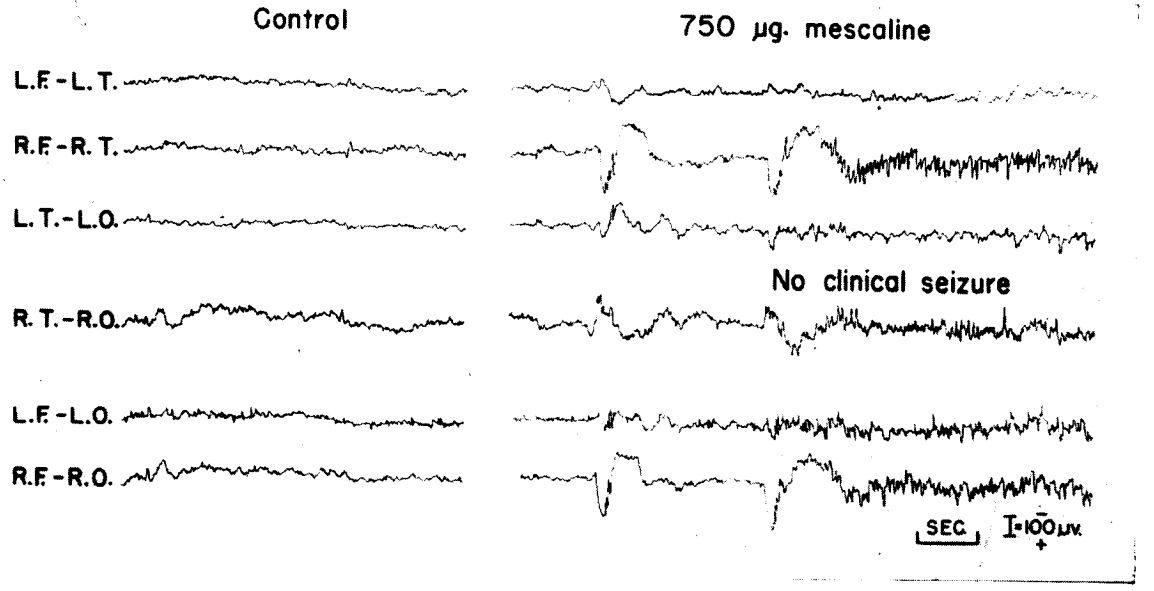


Fig. 5.—Electroencephalographic effect of intraventricular injection of 750γ of mescaline into a cat.

fference was noted either preceding or mediately following this spike episode. ven when the smaller doses were employed, e cats did not respond normally until six ıurs after the injection.

Mescaline Followed by Serotonin.—Seven, teen, and twenty-five minutes, respectively, ter the injection of 1.0, 0.3, and 0.7 mg. mescaline, each cat was given intra-ntricularly 500γ of serotonin (pH 7.6). no instance was the progress of the effect the mescaline halted. In the two instances which the reaction was permitted to con-ıue, the presumed effects of serotonin,

denly look up toward the ceiling or around them and then remain motionless, staring into space. The gait was intact. After about 20 minutes the cats became moderately insensitive to painful stimulation. There was no prompt withdrawal or voicing of pain when the paw was squeezed or the ear was pinched. When cotton was hung over an eye, no attempt was made to shake it off. The cat generally withdrew on inhaling tincture

† The authors are indebted to A. Hoffer, M.D., Ph.D., Director of Psychiatric Research, Psychiatric Services Branch, Department of Public Health, Regina, Sask., Canada, for his generosity in supplying pure adrenochrome and adrenolutin.

of valerian, and miauled. Yet the cats had a clear sensorium, insofar as they were affectionate and responded to petting with purring. They readily responded to a bowl of warm milk and shared it without quarreling. Their memory apparently was intact, because when they were left completely alone they would seek out one of their favorite resting places upon an instrument tray or bench. The cats could be placed on a chair and would remain sitting there for long periods, without jumping off and running away. After a short while the male cat mounted the small female cat and made frequent attempts to copulate. Although the observations are too few and the effects seemed to be a poorly balanced position. After the injection of 1 mg. of adrenochrome the cats were drowsy for 24 hours. The electroencephalographic changes accompanying these drowsy, trance-like states were occipital 4 cps. slow waves with low-voltage spike components, spreading to the frontal regions and then diffusely over the brain. There was inconstant electroencephalographic arousal when painful stimulation was employed. One cat with electrodes implanted over the auditory cortex showed a spike response to stimuli, such as hand claps, kissing sounds, and the sound of the metronome, similar to that observed in the control period. These single-response spikes were

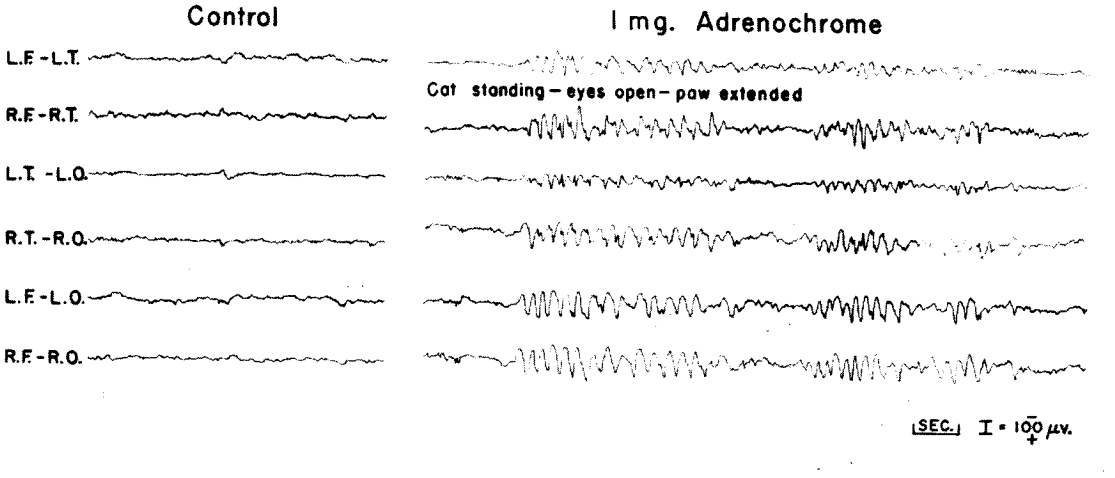


Fig. 6.—Electroencephalographic effect of intraventricular injection of 1 mg. of adrenochrome into a cat.

too inconstant to permit any conclusions, it must be noted that this behavior was not seen when any of the other drugs were used (except adrenolutin), nor did it appear spontaneously during the control periods. Although the female cat frequently would complain or cry out loudly when the nape of her neck was bitten too hard, she would always return to the male cat. Once a male cat attempted to copulate with a comatose dog, which was also in the laboratory. The cat frequently could hold its forelegs in a position behind its ears with minimal restraint before attempting to put them down. The male cat frequently rested his paw on top of the smaller female cat's head in what not related to the background electroencephalogram, which was unaltered unless the cat was clinically aroused. An arousal pattern appeared when the animal was drinking milk and when inhaling tincture of valerian. Many times the diffuse slow waves and spindles were noticeable when the cat was sitting up with the eyes open and expressionless (Fig. 6). During copulation the electroencephalogram described a background of low-voltage, fast activity. With cessation of the thrusts, there was a speedy reversion to the trance pattern.

Adrenochrome Followed by Serotonin and Nicotinic Acid.—In two instances, at 20 and 30 minutes after the administration of 200γ

and 500γ of adrenochrome, 250γ and 500γ of serotonin (pH 7.6) were injected. Aside from some initial retching and licking, the animals manifested no essential changes, either behaviorally or in the electroencephalogram, which continued to show the trance pattern unless the animal was aroused. After a few hours, however, both cats had copious, loose bowel movements. The intraventricular (1.25 mg. at a pH of 8.1) or intramuscular (25 mg.) administration of nicotinic acid did not have any influence on the effects of 1 mg. of adrenochrome.

Adrenolutin.‡—Four doses of a freshly prepared solution of adrenolutin (pH 7.6), ranging from 300γ to 650γ, were injected intraventricularly. The effects were similar to those produced by adrenochrome, except that they were more nearly immediate and pronounced. The cats became very drowsy and assumed unusual positions. Yet they were easily aroused. At times the cats suddenly made searching movements of the head, and then would lapse into a blank, staring expression. Although partially anesthetic, they would frequently lick and cry. The predominant frequency seen was in the theta range, with the occasional appearance of rhythmic, 3 cps discharges, resembling those produced when adrenochrome was used (Fig. 7). During copulation the electroencephalogram pattern was low-voltage, fast waves. In the doses used, the agent allowed the sensorium to remain clear, and the cats returned to their control status 24 hours later.

Ergotamine Tartrate.—On four separate occasions 20γ (pH 7.5) of ergotamine tartrate was injected intraventricularly. Within a few minutes frequent bouts of retching were noted. One of the cats vomited. Licking and hiccuping occurred. Both cats made feeble cries. They were still affectionate and playful. Although they seemed not to be so curious as before the experiment, they walked and jumped well. Despite the retching and miauling, the cats apparently were not in acute distress. They appeared to be relaxed and contented. The electroencephalogram showed a pattern characteristic of an alert state for most of the time, with infrequent episodes of high-voltage, 5 to 6 cps waves associated with apparent drowsiness. The cats could be alerted readily.

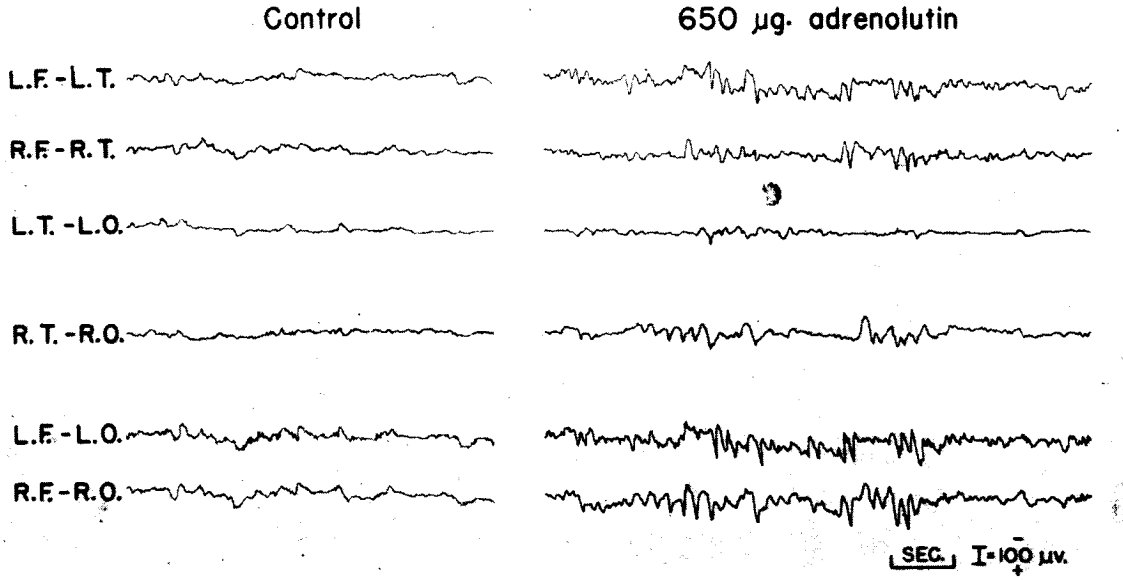


Fig. 7.—Electroencephalographic effect of intraventricular injection of 650γ of adrenolutin into a cat.

‡ Supplied by Dr. A. Hoffer, of Regina, Sask., Canada.

Ergotamine Tartrate Followed by Serotonin.—In all instances the behavioral reactions to the administration of ergotamine tartrate followed by serotonin resembled the response to serotonin alone, as described previously.

COMMENT

In general agreement with Feldberg and Marwood's § experience with other drugs, the hallucinogenic drugs, when tested on the basis of behavior and electroencephalographic changes after direct intraventricular injection, show more similarities than differences. That the effects are truly central, and not peripherally mediated, is indicated by Feldberg's review of the literature and his own experiments with curarine and dimethonium. He found that convulsions and spastic paresis, respectively, were produced after intraventricular injection of the agents, instead of the flaccid motor paralysis that follows intravenous injection.

The behavioral changes ranged from slight and relative immobility (caused by serotonin) to stupor and anesthesia (caused by adrenochrome and adrenolutin) to the violent paroxysms of scratching that resulted from mescaline. Both LSD-25 and ergotamine tartrate produced similar effects in respect to pronounced retching followed by slight drowsiness. No antagonism was observed among any of the drugs used; namely, serotonin, LSD-25, mescaline, adrenochrome, adrenolutin, and ergotamine tartrate. The second compound injected seemed to exert the usual behavioral and electroencephalographic effect, and there was no suggestion of any protection conferred by the drug first injected. Stupor and catatonia, as described by de Jong,[5] were observed after the administration of adrenochrome and adrenolutin. After an initial gradual reduction in motor activity, the cats would finally sit in odd positions with their eyes wide open for long periods and howl. Although, for various reasons, the term "waxy flexibility" cannot be used as it would be used in referring to human beings, the cats permitted their limbs to be placed passively in unnatural positions without immediately correcting them, or even resisting such positions. In the presence of a clear sensorium, other bizarre forms of behavior were noted to follow the injection of adrenochrome and adrenolutin. Frequently, the cats were in a deep trance, with concomitant electroencephalographic changes; but they could always be alerted readily. The similarity of the effects of adrenochrome and adrenolutin to the reported actions of epinephrine and arterenol (norepinephrine) is striking.[1] The suggested relationship of an increased content of epinephrine and arterenol in the cerebrospinal fluid to the "exhaustion and fatigue" that follow strong emotional upheavals should hold equally well in the case of adrenochrome. Similar questions in reference to normal sleep and pathologic stupor also can be raised. Hoffer and associates [6] were the first to recognize the effects of adrenochrome on the central nervous system. The effects in question are (1) production of a model psychosis without insight in normal volunteer subjects, and (2) an increase in dysrhythmias in the electroencephalogram.[7] They speculated as to whether schizophrenia could be in part a disease of abnormal metabolism. Additional studies might reveal what areas of the ventricular system of the cat are susceptible, and what enzyme systems might be affected. Anatomically, the injected drugs could gain access to the autonomic areas that border the third ventricle or to many of the vital centers in the vicinity of the fourth ventricle.

The remarkable feature of LSD-25, when it is given intraventricularly, is the minimal effect which it exerts on the behavior of the cat. The dose used in the cat would be sufficient, if it were administered orally to some human beings, to cause a model psychosis. Presumably, comparable minimal doses of mescaline, on the other hand, caused a reaction of intense scratching and paroxysms of diffuse spike discharges in the electroencephalogram. Descriptively similar phenomena have followed the intraventricular injection of physostigmine, acetylcholine,

§ References 1 and 2.

and isoflurophate (diisopropyl fluorophosphate; DFP).‖

SUMMARY

Although the effects of some of the hallucinogenic drugs, when such drugs are administered by way of the blood stream of animals, are well recognized, the present study was particularly concerned with the intraventricular injection of some of these compounds. It should be noted that the effects of these agents may differ, according to which route of administration is employed.

By use of a polyethylene catheter permanently placed in the ventricles of the brain and six electrodes placed symmetrically in the frontal, temporal, and occipital regions, the behavioral and electroencephalographic changes in the trained cat were studied after the intraventricular injection of some hallucinogenic drugs and related compounds.

1. Serotonin produced muscular weakness, relative motor immobilization, and salivation, without any significant changes in the electroencephalogram.

2. LSD-25, or *d*-lysergic acid diethylamide, produced initially a restless state, with frequent bouts of retching. Later there was a tendency toward drowsiness, associated with occasional slow waves in the electroencephalogram.

3. No central nervous system, behavioral, or electroencephalographic antagonism was observed between serotonin and LSD-25 when these drugs were administered by the intraventricular route in the described doses.

4. Mescaline caused paroxysms of violent scratching. Later, but not necessarily associated with this scratching, electroencephalographic evidence of paroxysms of 10 cps spikes, occurring asymmetrically in the brain and spreading to homologous areas, was noted.

5. No antagonism between mescaline and serotonin was demonstrated when the intraventricular route of administration was employed.

6. Adrenochrome brought about a stuporous state, associated with electroencephalographic changes of 4 cps, slow waves, occu ring in the occipital regions.

7. Adrenolutin (1-methyl-3,5,6-indol triol), in smaller doses than adrenochro caused essentially similar behavioral chan associated with rhythmic theta activity in electroencephalogram.

8. Neither adrenochrome nor adrenolu produced any evident antagonism w either was employed with serotonin via intraventricular route.

9. Ergotamine tartrate when administe intraventricularly produced a condition diminished spontaneous motor activity episodes of vomiting and retching. The el troencephalographic changes were mini and resembled those recorded when LSD was administered.

10. No antagonism between ergotam tartrate and serotonin was noted when th were administered intraventricularly.

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