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Some Effects of Bufotenine and Lysergic Acid Diethylamide on the Monkey

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INTRODUCTION

Bufotenine (5-hydroxy-3-[2-dimethylaminoethyl]-indole) is the N-dimethyl derivative of the vasoconstrictor substance serotonin (5-hydroxytryptamine). It was first synthesized by Wieland in 1934. Raymond-Hamet found that intravenous injection of bufotenine caused transient elevation of blood pressure and apnea, followed by tachypnea, in anesthetized dogs.* To date, however, there is little published material concerning the effects of bufotenine on unanesthetized animals. Our interest in such effects was based on the fact that bufotenine was recently isolated from the bean of Piptadenia peregrina,[5] a bean long known to be the source of cohoba, a narcotic snuff. This snuff has been used by inhabitants of the West Indies to induce hallucinations and mystical states,[6] states which seem similar to those produced by mescaline, harmine, and lysergic acid diethylamide. It was felt, in view of the reported psychological effects of bufotenine-containing snuff, that it would be worth while to investigate the effects of bufotenine on unanesthetized monkeys.

The effects of lysergic acid diethylamide (LSD-25) on unanesthetized monkeys were studied for similar reasons. As is well known, LSD-25 in minute doses produces marked alterations of mood and perception in man. Extensive clinical investigations of the effects of LSD-25 have been reported.† As little as 0.001 mg/kg. of LSD-25 has produced psychological alterations that have been compared to schizophrenia. The present study was carried out to gain knowledge of the effects of LSD-25 in doses higher than may safely be administered to man.

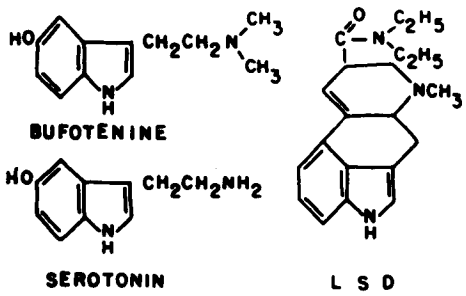

Fig. 1.—Structures of lysergic acid diethylamide (LSD), bufotenine, and serotonin.

The structures of bufotenine, LSD-25, and serotonin are shown in Figure 1.

MATERIALS AND METHODS

Eight immature monkeys (Macaca mulatta), weighing from 3 to 4.5 kg., were used as subjects. Bufotenine,‡ as the free base, was dissolved in creatinine sulfate solution, 1 part of bufotenine to 1.6 parts of creatinine sulfate by weight. Doses of bufotenine refer to the free base. Aqueous solutions of LSD-25 were freshly prepared from crystalline material. Solutions were prepared immediately before injection and were administered via the saphenous vein.

The accompanying Table lists observations which were carried out. In addition, attempts were made

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National Institute of Mental Health, National Institutes of Health, U. S. Public Health Service, Department of Health, Education, and Welfare.

* References 2 to 4.

† References 7 to 9.

‡ The bufotenine used in these experiments was extracted from the bean of Piptadenia peregrina by Dr. V. Stromberg, of the National Heart Institute, and was supplied to the author by Dr. Evan Horning, of the National Heart Institute.

Effects of Lysergic Acid Diethylamide (LSD-25) and Bufotenine on the Monkey *

Observation	LSD-25 1.0 Mg./Kg. Effect	LSD-25 1.0 Mg./Kg. Duration, Min.	Bufotenine 5.0 Mg./Kg. Effect	Bufotenine 5.0 Mg./Kg. Duration, Min.
Muscle power	Grossly normal	.....	Grossly normal	.....
Deep tendon reflexes	Grossly normal	.....	Hyperactive	15
Vestibular eye movements	Grossly normal	.....	Grossly normal	.....
Reaction to auditory stimuli	Grossly normal	.....	Grossly normal	.....
Pupillary light reflex	Present	.....	Present	.....
Locomotion	Ataxic	55 (20-85)	Ataxic	50 (20-90)
Reaction to painful stimuli	Absent	65 (30-95)	Absent	67 (35-110)
Reaction to visual stimuli	Absent	77 (35-103)	Absent	69 (45-110)
Reaction to handling	Marked tameness	110 (85-130)	Marked tameness	105 (70-120)

* This Table lists certain of the effects of LSD-25 and bufotenine and gives the mean and range of duration of these effects following injection.

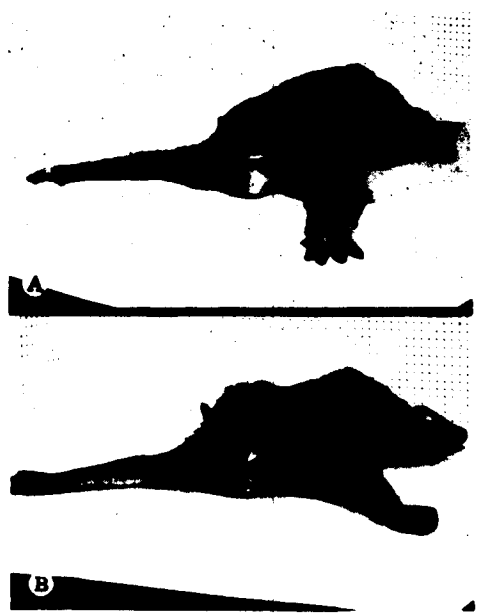
to estimate changes in general behavior of the monkey when handled by the examiner. Observations were carried out with the subject either in his cage or free in an examining room in which he could run about unimpeded. Subjects were deprived of food for 24 hours preceding experiments. Monkeys were used repeatedly, but never more than once a week.

RESULTS

The Table lists the effects of 1.0 mg/kg. of LSD-25 and 5.0 mg/kg. of bufotenine.§ The similarity of effect of the two substances is apparent. The drug effects indicated in the Table were generally maximal within one minute following injection.

During approximately the first 20 minutes following drug administration, subjects did not walk or climb. During this period they maintained a constant prone position (Fig. 2), which they vigorously maintained in spite of attempts to place them in any other position. In their attempts to regain the prone position, when displaced, they demonstrated good muscular power. Another demonstration of preserved muscular power is indicated in Figure 3. This Figure shows monkeys, within five minutes following injections of LSD-25 and bufotenine, holding onto the experimenter's finger; subjects were able to maintain this hold for long periods, despite attempts by the experimenter to shake them loose. The prone position was maintained for approximately 20 minutes, after which monkeys assumed a sitting posture and began to make attempts to move about. Their movements generally consisted of ataxic circling. Within an average of 55 minutes following injection, ataxia had become slight to absent. There remained, however, lack of response to visual stimuli and absence of reaction to noxious stimuli. After reaction to painful stimuli returned, usually at about 65 minutes following drug injection, only blindness and unu-

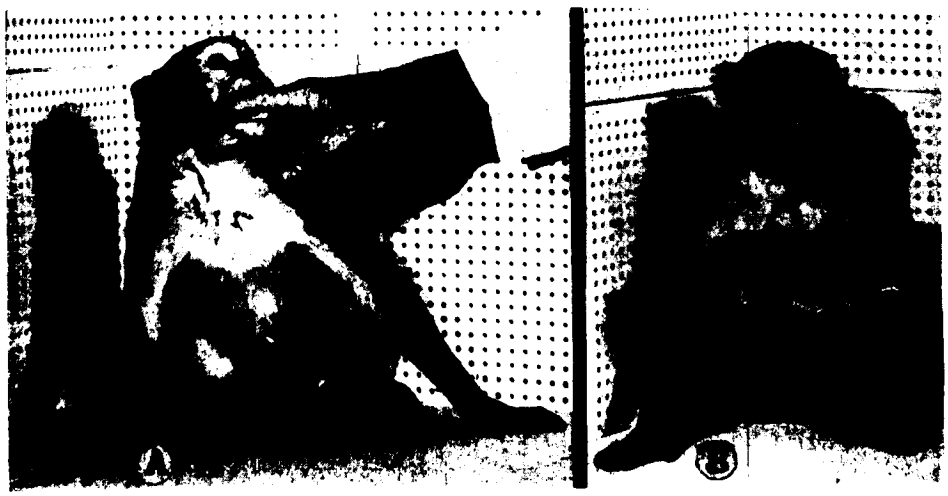
Fig. 2.—Effects of LSD-25 and bufotenine on position. This Figure shows the position assumed immediately following injection of LSD-25 (*A*) and bufotenine (*B*).



§ Though the effects of a wide range of doses were studied, only the effects of the highest doses used are presented. The reason for this is the fact that the observations reported were most clearly present at these high doses and may be most simply and concisely described for these dosage levels.

Fig. 3.—Effects of LSD-25 and bufotenine on motor power. This Figure demonstrates the ability of subjects to support their own weight immediately after LSD-25 (*A*) and bufotenine (*B*).

Fig. 4.—Taming effects of LSD-25 and bufotenine. This Figure shows striking tameness of subjects one hour following LSD-25 (*A*) and bufotenine (*B*).



sual tameness remained of the original symptoms. At this stage the monkey would run about the examining room without ataxia, but would bump headlong into any objects interposed in its path. No reactions to moving objects or lights could be discovered. After visual reactions had returned, an unusual degree of tameness persisted. It was possible to place one's finger in the monkey's mouth with impunity (Fig. 4). Within one and a half to two hours of drug injection, the monkeys had usually become grossly normal, the only residual effect being a decreased tendency to climb and jump about the cage.

COMMENT

The most prominent feature of the effects of LSD-25 and bufotenine in monkeys is the occurrence of a marked impairment of function in certain sense modalities in the absence of a clear defect of muscular power. The predominance of sensory disorder is well demonstrated (during the period between 55 and 75 minutes following injection of LSD-25) by the presence of impaired visual responsiveness in an animal that can, at the same time, run about the room with agility. The disturbance of locomotion and the unusual posture assumed by subjects during the early stage of drug effect might also be looked upon as sensory in origin. Lassek [10] has shown that posterior rhizotomy leads to "inactivation of motor function." Goody [11] has pointed out that purposive movement is dependent upon a continuous input of proprioceptive impulses. One may take the data of these authors as supporting the notion that the disorder of movement seen in monkeys following LSD-25 and bufotenine might well be related to a disorder of proprioceptive sensation, rather than to a primary disorder of the efferent motor system.

In addition to the dissociation of defects within the motor and sensory fields, there was dissociation of defects within various sense modalities. Auditory and vestibular reactions were not clearly disturbed at any time. Moreover, function returned at differential rates in those modalities that were affected. Proprioceptive sensation, disturbed initially, returned gradually and was not grossly deficient at a point when responses to visual and noxious stimuli were still absent. Reactions to pain generally returned before visual reactions, though in some animals this was not the case. Tameness, apparent through the period of gross sensory disorder, remained even after responsiveness to gross visual and tactile stimuli had returned.

The nature of this drug-induced syndrome suggests the speculation that these drugs may alter transmission of sensory impulses. Experiments at this Institute have shown that this is the case. In studies of the effects of LSD and bufotenine on neural transmission in the visual system of the cat,[12] we have found that LSD-25 and bufotenine block transmission in the lateral geniculate nucleus.

The experiments reported here may cast some light on the pharmacological mechanism of the action of LSD-25 and bufotenine, which, however, must remain a matter of speculation. Page,[13] in a recent review devoted to 5-hydroxytryptamine (serotonin), suggested that LSD-25 might act by antagonizing some presently unknown function of serotonin in the central nervous system. He based this speculation on Gaddum's [14] discovery that LSD-25 is a highly potent serotonin antagonist, inhibiting serotonin action on rat uterus in concentrations as low as 10^{-6}. Wooley [15] has put forward the idea that the central effects of LSD-25 are due to serotonin antagonism, basing this notion on his finding that harmine, as well as LSD-25, is a serotonin antagonist. Harmine has long been known to produce LSD-25-like effects.[16] Our observation that bufotenine has effects in monkeys which are similar to those of LSD-25, both behaviorally and electrophysiologically, adds weight to the idea that LSD-25 and bufotenine may owe their neuropsychological effects to the fact that they are serotonin analogues. Such an idea must be clearly labeled as speculation at the present time, however, since no direct evidence has

yet been developed to prove the point. Studies of the function of serotonin in the central nervous system, it may be hoped, will elucidate this matter.

SUMMARY

Lysergic acid diethylamide (LSD-25) and bufotenine, in doses of 1.0 and 5.0 mg/kg. injected intravenously, produce a syndrome characterized by gross sensory disorder in the absence of a clear defect in muscle power, and by a marked degree of tameness.

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