Lysergic Acid Diethylamide (LSD 25): II. Psychobiological Effects on the Siamese Fighting Fish

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The striking effects following the oral administration of LSD 25 in man were first noted by Hofmann and described in detail by Stoll (*1*). These phenomena, which included both vegetative and psychotic responses, are described in detail elsewhere (*2*). Briefly, LSD 25 produces in man a schizophrenialike state lasting about 8 hr with doses of 50 to 100 μg by mouth. Because of the essentially psychic nature of the response that distinguishes LSD 25 from other ergot derivatives in the dosages employed, man has thus far been the best test animal.

It is the purpose of this paper (*3*) to show that the Siamese fighting fish exhibits vegetative, motor, and behavioral responses when administered solutions of LSD 25 in concentrations as low as 1 μg/ml dissolved in spring water. There is a quantitative difference between the responses of adult and juvenile fish. The juvenile *Betta* has thus far been the more sensitive of the two.

With fish approximately 1 in. in body length (snout to base of caudal fin rays) responses occur within minutes. The data in Table 1 were obtained by exposing groups of four fish each in glass vessels of uniform size containing 100 ml of the concentrations given in Table 1.

At the end of 6 hr, each group of fishes was dipped with a fish net five times in 100 ml of fresh spring water and then studied in glass jars containing 1 lit of spring water. The water was collected from a natural spring and permitted to stand 48 hr at room temperature before being used. Six hours after removal from the drug, the following observations were noted. The controls were normal. The remaining four groups exhibited the characteristic response of the juvenile fish, which may be listed as follows:

Table 1. Effect of concentration on the development and intensity of reaction to LSD 25 during 6 hr of immersion and subsequent recovery up to 53 hr. All of the 16 fish treated recovered completely from the effects of the drug within 150 hr; x's indicate a rough estimate of the intensity of response. With exposure in water containing LSD 25 for several hr, 0.1 μg/ml may be determined by this technique. This is not illustrated in the table.

Immersion	1	2	3	4	5	6	7	8	9
Untreated									
¼ hr }								x*	
½ hr }								x*	
¾ hr } in spring water								x*	
6 hr }								x*	
21 hr }								x*	
53 hr }								x*	
1 μg/ml									
¼ hr }					x	x		x	
½ hr } in LSD 25			x		x	x		x	x
¾ hr }	x	x	x	x	x	x	x	x	x
6 hr }	x	x	xx	xx	xx	xx	xx	xx	xxx
21 hr } in spring water		x	x	x	x	x	x	xxx*	
53 hr }								xx*	
5 μg/ml									
¼ hr }		x			x			x	x
½ hr } in LSD 25		x	x		x	x	x	xx	xx
¾ hr }	x	x	x	x	xx	xx	x	xx	xx
6 hr }	xx	xxx	xxx	xx	xx	xx	xx	xx	xxx
21 hr } in spring water	x	x	x	x	x			xx*	xx
53 hr }			x					xxx*	
25 μg/ml									
¼ hr }	x	x						x	xx
½ hr } in LSD 25	xx	xx	x	x	x	x	x	xx	xxx
¾ hr }	xxx	xxx	xx	xx	xx	xxx	xxx	xx	xxx
6 hr }	xxx	xxx	xxx	xxx	xxx	xxxx	xxx	xxx	xxxx
21 hr } in spring water	xxx	xx	xx	xxx	xx	xx	x	xxxx*	xx
53 hr }	x	x	x	x	x	x	x	xxxx*	x
50 μg/ml									
¼ hr }	x	xx			x	x	xx	x	xx
½ hr } in LSD 25	xx	xx	xx	x	xx	xx	xx	xx	xxx
¾ hr }	xxx	xxx	xxx	xxx	xxx	xxx	xxx	xx	xxx
6 hr }	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxx	xxxx
21 hr } in spring water	xxx	xx	xxx	xxx	xxx	xxx	xx	xxx*	xx
53 hr }	x	xx	x	x	xx	xx	x	xxxx*	x

* Display toward a rival with aspects of fighting.

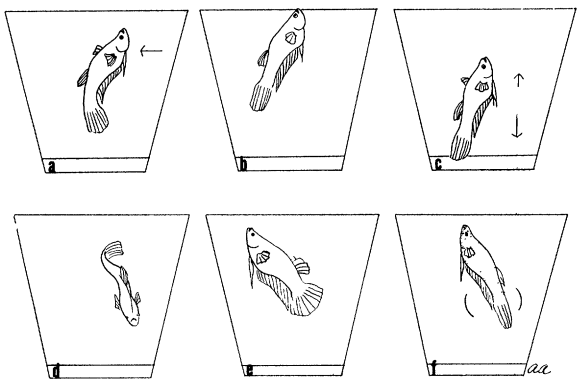

Fig. 1. The six diagrams illustrate the nine criterions or effects of LSD 25 upon the fighting fish, *Betta splendens*. Such effects are essentially exaggerated postures or caricatures of the normal fish.

1) Backward movements; accomplished almost entirely by pectoral fin movements (Fig. 1*a*).

2) Head up, body usually suspended in the vertical plane or some angle from the vertical. In maximum stage of narcosis the snout is kept at the surface. As effects begin to wear off, the fish sinks slowly below the surface until after 6 hr it might take a position 2 in. below the surface (Fig. 1*b*).

3) "Cartesian diver" effect. Treated fish sinks or rises very slowly in near-vertical plane without visible body movement except by means of pectoral fins (Fig. 1*c*).

4) "Barrel-roll" effect, change of position or location is by a peculiar rolling of the fish upon its long axis in the vertical plane (Fig. 1*a, f*).

5) "Trancelike" effect, motionless position maintained for minutes at a time at the peak of the narcosis. The "trance" is broken by a very brief change of position by means of a very slight stimulus. Succeeding "trances" become gradually shorter after cessation of treatment (Fig. 1*e*).

6) All movements of treated fish are slow and deliberate as compared with the typical swift and sudden movements of normal fish (Fig. 1*a, c, d, f*).

7) Treated fish exhibits a typical "kinking" in its body conformation, easily observed from above (Fig. 1*d*).

8) Lateral display, most commonly involving the ventral and dorsal fins, less usually the tail as well. This posture persists while fish is in trancelike state (Fig. 1*e*).

9) Pigmentation effects, best exhibited in juveniles. Immediate effect is darkening of basic body color. This fades slowly as recovery occurs (Fig. 1*f*).

Table 1 shows the manner in which the foregoing criterions may be used to follow the reactions of the fish to the drug. Note in the table a reaction of recovery that we have consistently observed. This reaction is a slow return to normal from the stuporlike state induced by the drug with coemplete recovery in the low dose range within a day and with the high dose range within a week. Although recovery usually occurs within a week, exposure to the drug has, in many cases, actually altered the social behavior. This will be described in a future paper. However, we should call attention to some of these aspects of behavior. For example, the lysergized fish can be aroused from a stupor by an attacking male and even counterattack. But after a brief battle, there is an immediate relapse into the stuporous state, showing many of the afore-mentioned nine criterions. Lysergized fish will respond rheotropically but not as effectively as untreated fish. All the effects have been observed in both sexes and in unsexed juveniles. Quantitative data are not yet available on the way weight, age, and dosage are related. The qualitative data hold for the species ranging in body length from 1 in. to full adult size, as studied at Cold Spring Harbor in the summer of 1954. Fish were obtained from various dealers and, consequently, were of heterogeneous genetic make-up.

In conclusion, we would like to point out that our technique provides a new bioassay method for LSD 25 and possibly other ergot drugs. For example, LSD 25 in urine and other body fluids is difficult to determine by chemical means. Preliminary experiments on urine show that *Betta* has essentially normal activity in spring water containing as much as 25 percent of urine for at least as long as 44 hr. This opens up the possibility not only of detecting LSD 25 in urine, but also of studying the urines of clinically schizophrenic patients for chemical agents occurring naturally, which might be the cause of clinical schizophrenia in man. It should be emphasized that not a single fish has been lost owing to the action of the drug, regardless of dosage used, even after the injection of 50 μg in the caudal musculature.

References and Notes

1. W. A. Stoll, *Schweiz. Arch. Neurol. Psychiat.* **60** (1947).
2. H. J. DeShon, M. Rinkel, and H. C. Solomon, *Psychiat. Quart.* **26**, 33 (1952); M. Rinkel *et al., Am. J. Psychiat.* **108**, 572 (1952); H. A. Abramson *et al., J. Psychol.* **39**, 3 (1955).

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Inhibition of Growth of Excised Tomato Roots by Desoxypyridoxin and Its Reversal by Pyridoxin

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Using microorganisms or animals as test material (*1, 2*) a number of analogs of pyridoxin have been found to act as antimetabolites. Similar results using test material from higher plants are scanty. Robbins (*3*) studied the specificity of pyridoxin in the nutrition of excised tomato roots and found that it could be replaced by either one of two acetoxy analogs. Two other analogs inhibited growth, but it was not shown that pyridoxin could prevent the inhibition. It has, however, been shown (*4*) that 4-desoxypyridoxin (DOP) inhibited the increase in nicotinic acid and ascorbic acid found in certain germinating pulse seeds