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**Effect of Pretreatment with Tryptamine,
Tryptophan and DOPA on LSD Reaction in Tropical Fish**

By

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In studying the reaction of eleven species of tropical fish to LSD (lysergic acid diethylamide) (CHESICK 1963) we found that serotonin (1 mg/ml), reserpine (10 μ g/ml), and norepinephrine (50 μ g/ml) did not affect the LSD reaction of the fish when they were placed in water containing both one of these drugs and LSD (1 μ g/ml), and compared with fish placed in water containing only LSD (1 μ g/ml). The present study was then designed to investigate the possibility of modifying the LSD reaction by pretreatment of the fish with metabolic precursors of norepinephrine and of serotonin or other indoles.

The species used for this study were the Siamese Fighting Fish (*Betta splendens*), the White Cloud (*Tanichthys albonubes*), and the Guppy (*Lebistes reticulatus*). The classical LSD reaction of the Siamese Fighting Fish has been described by other investigators (ABRAMSON and EVANS 1954). The White Cloud reacts to LSD (1 μ g/ml) by swimming at the surface within the top centimeter of water and with an increase in backward swimming (CHESICK 1963). The reaction of the Guppy to LSD (4 μ g/ml) before and after pretreatment with tryptamine has also been described (KELLER and UMBREIT 1956), as "a characteristic vibrating behavior" to LSD consisting of "a rapid swimming until the wall of the container was reached, at which point the fish continued to swim apparently unaware that they were not making any progress." Pretreatment with indole or tryptamine tended to markedly prolong this effect.

Methods

The fish were always observed by two independent observers and placed in 400 cc beakers, containing 300 cc of solution at pH 7.5, and suspended in a glass water bath kept at 30°C. These were approximately

the same conditions as used by KELLER and UMBREIT. Six fish of each species were used as test fish and six of each species were used as controls for each drug. The drugs used were tryptophan, tryptamine, and DOPA (DL-3-[3,4-Dihydroxyphenyl]Alanine). Tryptophan and tryptamine, as precursors of serotonin, might be expected to antagonize the LSD effect. DOPA, as precursor to norepinephrine, might be expected to synergize the LSD effect. Only one of these drugs was used at a time for pretreatment. Two pretreatment periods of 1 h, chosen because of use by previous authors (KELLER and UMBREIT 1956) and of 48 h, chosen as a reasonable period for allowing internal metabolic conversion of substances, were employed for each drug, at each concentration.

Two concentrations were used for each drug. 1. Based on previous work (KELLER and UMBREIT 1956) we chose 0.02 mg/ml for each drug. This produces approximately 10^{-4} M concentration of tryptamine used by them. 2. The second concentration was just sufficient to insure that no fish would die after 48 h of exposure. This was determined for each drug by trial and error. It was found that some fish would die if one exposed ten fish to more than 0.50 mg/ml of tryptamine or DOPA for 48 h, or to more than 1.00 mg/ml of tryptophan for 48 h. Therefore, for the pretreatment experiment we used 0.20 mg/ml of tryptamine and DOPA, and 0.75 mg/ml of tryptophan as the maximum doses.

At the end of each pretreatment period with each concentration of drug, six fish were transferred to LSD (1 μ g/ml for the Siamese Fighting Fish and the White Cloud, and 4 μ g/ml for the Guppies) and observed alongside of a group of six control fish in the same concentration of LSD for 1 h. All fish were then transferred to ordinary tank water and observed carefully for 24 h, under the same conditions.

Results

There was no observable behavioral change in any fish during pretreatment with any of the drugs at the low concentration. At the higher concentration there was a general decrease of activity and less interest in food, seen with all three drugs.

There was no difference between the control and pretreated fish in regard to the response to LSD or persistence of the response after transfer to tank water, regardless of length of pretreatment, drug used in either concentration, or species. This was in such contrast to the previous work (KELLER and UMBREIT 1956) that we repeated the entire procedure using 10 pretreated Guppies and 10 control Guppies at both concentrations and pretreatment periods for tryptophan and tryptamine, but again there was no difference between controls and pretreated fish in LSD or afterwards.

Responses to LSD observed in all 3 species, whether pretreated or not, were darkening of color, surface swimming, decrease of flight response from a probe, decreased spontaneous activity, slower fin movements that resulted in a rocking, side-to-side swim that could be especially seen when the fish approached the observer, and backward swimming using the pectoral fins for the main locomotion. The Siamese Fighting Fish showed the additional characteristic LSD reaction previously described (ABRAMSON and EVANS 1954).

These responses, whether the fish were pretreated or not, disappeared within an hour after removal from LSD, except for a tendency to swim at the surface, which persisted for several hours.

In our judgement, most of the effects common to all the species in LSD represent signs of non-specific distress. We believe this includes the "characteristic vibrating behavior" and "swimming against the glass" (we saw the latter only rarely for any of the species) previously described (KELLER and UMBREIT 1956). This has been known as the "shakes" or the "shimmies" (INNES 1956) and is probably due to a non-specific toxic effect, which may be produced by a number of agents such as drugs, sudden temperature changes, foul water, disease, etc.

Summary

Neither pretreatment with DOPA, tryptamine or tryptophan affects in any way the reactions of Siamese Fighting Fish (*Betta splendens*), White Clouds (*Tanichthys albonubes*), or Guppies (*Lebistes reticulatus*) to LSD, or the persistence of these reactions after removal from LSD.

References

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