Discussion of the Pharmacologic Studies on the Structure-Activity Relationship of Indolealkylamines

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In comparing 4- and 5-substituted tryptamines and *N*-dimethyltryptamines on conditioned behavior in rats, we have found the order of their potency to agree closely with the pharmacologic data presented by Doctors Cerletti, Taeschler, and Weidmann.

Figure 1 presents data obtained from rats trained to press a lever for food in two separate test conditions. In the first assay (left panel) responding was reinforced on a variable interval 120-second (VI 120) schedule and a control record reveals a steady rate

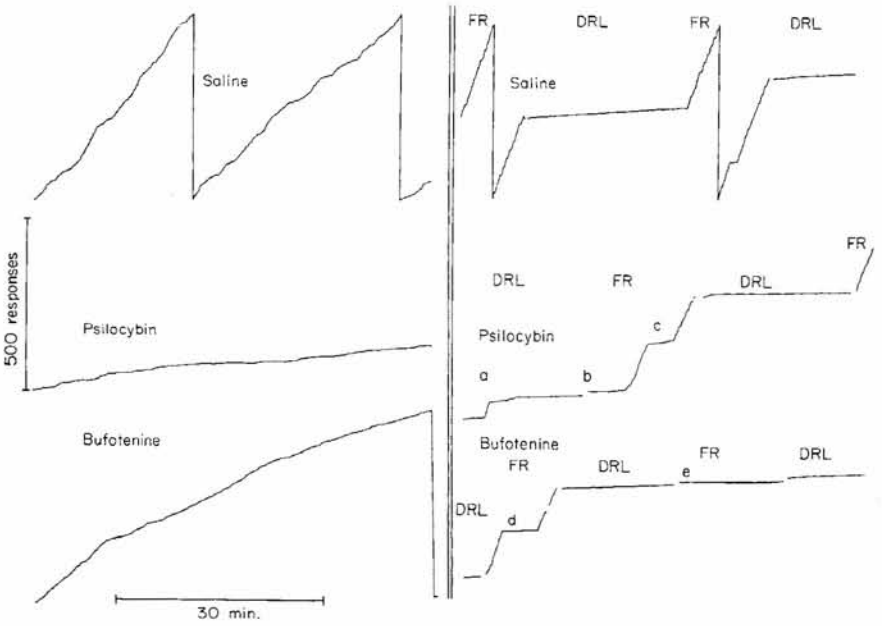

FIG. 1. Effect of 4- and 5-hydroxylated tryptamines on responding under VI (left panel) and MS FR DRL (right panel) schedules. Breaks in the multiple schedule record indicate changes in reinforcement contingencies and associated stimulus.

of responding for the entire 1-hour experimental session. A 2 mg/kg dose of psilocybin (i.p.) produced a considerably greater suppression of responding during an hour session than did a similar dose of bufotenine.

In the second test (right panel), responding was reinforced on a multiple schedule comprised of two components: fixed ratio 50 (FR 50) in which every fiftieth response is reinforced by a food pellet and differential reinforcement of low rate of 20 seconds (DRL 20) in which only responses spaced a minimum of 20 seconds apart are reinforced.

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Each component schedule is alternated in random sequence and each is associated with an external signal: a moderate tone for FR reinforcement and a panel light for DRL. A control record reveals that the rat pressed the lever at a rapid rate during the FR-reinforced intervals and at a paced, slow rate during DRL. Psilocybin (0.3 mg/kg) produced a disruption in performance at (a) where the rate broke from an appropriate DRL rate into a brief FR burst, at (b) where it did not change from a DRL to a FR rate when the FR signal was reinstated and at (c), where it responded at a DRL pace during an FR period.

Bufotenine at a dose level of 2 mg/kg produced only a suppression in responding during FR periods (d) and (e), but the rat still reacted to the two signals in a differential manner, as can be seen by the coincidence of changes in responding with changes in the stimulus conditions.

These data would appear to demonstrate that not only does 4-hydroxylation increase the potency of *N*-dimethyltryptamines, but it also induces a qualitative change in their action on behavior. Could this loss of stimulus control of behavior noted in the multiple schedule be likened to an hallucinogenic reaction in man? Some evidence to support such a possibility is provided by the finding that of the many drugs we have screened on this schedule, LSD is the only other compound which produces a disruption in performance similar to that shown with psilocybin.

In interpreting the pharmacologic and behavioral effects of the indolealkylamines, their mode of metabolism should not be overlooked. For example, 5-HT (Udenfriend *et al.*, 1956; McIsaac and Page, 1959) 5-methoxytryptamine (Kveder and McIsaac, 1961), and 5-methoxy-*N*-methyltryptamine (Taborsky and McIsaac, 1964a) are all rapidly metabolized by MAO. *N*-dimethylation confers relative immunity from degradation by MAO (Gessner *et al.*, 1960). We have found that 5-methoxy-*N*-dimethyltryptamine has a longer duration of activity than 5-methoxytryptamine.

Evidence has been presented for the enhancement of some pharmacologic activities by α-alkylation. Since, for example, the antireserpine assay is performed *in vivo*, the observation of Eberts and Daniels (reported by Heinzelman and Szmuszkovicz, 1963) that a metabolite of α-methyltryptamine occasionally formed in large quantity was the corresponding tetrahydro-β-carboline becomes pertinent. Using an *in vitro* assay for MAO with tryptamine-^{14}C as substrate, we have found that this β-carboline is 3 times more potent as an inhibitor than the α-methyltryptamine from which it is derived. In general, we have found that the β-carbolines are very potent 5-HT antagonists, (Taborsky and McIsaac, 1964b), MAO inhibitors (McIsaac and Estevez, 1966), and cause elevations of brain amines and readily disrupt conditioned behavior. Whether some of the actions of indolealkylamines result from β-carboline formation *in vivo* is an intriguing but so far unproven possibility.

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