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INDOLAMINE HALLUCINOGENS AS MAO INHIBITOR AGENTS—THEORETICAL APPROACH

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A new theoretical hypothesis on the mode of action of LSD and other hallucinogens of the indolamine family is proposed. In view of the suggestions that LSD acts both on the 5-HT system as an antagonist and on the DA system as an agonist, we suggest that in addition to 5-HT blocking capacity, LSD and the other indolamine hallucinogens act as MAO inhibitors.

The mechanism of the hallucinogenic action of LSD and other LSD-like drugs is still obscure. The structural resemblance of LSD, and other hallucinogens of the indol family, to the neurotransmitter serotonin (5-HT) has led investigators to attribute their hallucinogenic effects to alterations in the functioning of that neurotransmitter. In fact, the earliest hypothesis postulated an antagonistic action of LSD at the 5-HT receptors in the brain (Gaddum & Hameed, 1954; Wooley & Shaw, 1954). The hypothesis that postulated interaction of LSD with the serotonergic system has been supported by experimental data. Freedman (1961) found that LSD raised brain 5-HT level and decreased the level of 5-HIAA (the main metabolite of 5-HT). These data led Freeman to the conclusion that LSD causes accumulation of 5-HT in the nerve cells. Aghajanian, Foote and Sheard (1968) proved that LSD blocks the brain 5-HT functions almost completely.

However, the hallucinogenic effects of LSD (and LSD-like drugs) are not similar to the effects of 5-HT agonists or blockers and it was quite obvious from the early stages of research that interaction of LSD with the 5-HT system cannot, by itself, explain the overall behavioral effects of this potent hallucinogen. This conclusion can be supported by the studies of Trulson, Heym and Jacobs (1981) who found several important dissociations between raphe unit activity and behavioral effects of LSD, and by the study of Rogawski and Aghajanian (1979) who showed that lisuride (an ergot derivative structurally related to LSD) is 5–10 times as potent as LSD in depressing raphe neuronal activity, but has never been reported to produce hallucinations after acture administration to humans. Obviously another, or rather an additional, mechanism is involved in the action of LSD.

The marked attentuation of LSD induced symptoms of chlorpromazine, haloperidol and other antipsychotic drugs (Jacobs & Trulson, 1979; Moskovitz, 1971) suggests that interaction of LSD with dopaminergic transmission may be involved. Pieri, Pieri and Haefel (1974) used a rotational model to test the effects of LSD on rats after a unilateral lesion of the nigrostriatal dopamine system. They concluded that LSD acted as a potent agonist of dopamine receptors in the striatum. The involvement of

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DA in the action of LSD was also indicated lately in the eports of Kelly and Iversen (1975) and Nichols (1976). Recently, it was postulated that strong hallucinogens are those drugs that possess both 5-HT antagonistic and DA agonistic properties (Kier & Glennon, 1978; Jacobs & Trulson, 1979). One such drug is the strong hallucinogen DOM which, although it does not have an indol structure, does act both as DA-mimetic and 5-HT-blocking agent (ibid.).

The above data indicate that the effects of LSD and similar hallucinogens are imposed through their action on at least two neurotransmitters: 5-HT and DA, or as Trulson *et al.*, have stated: "It is interesting to note that all three neurotransmitters (serotonin, dopamine, and norepinephrine) investigated in any detail for their involvement in drug-induced hallucinogenesis seem to play an important role in this process" (Trulson *et al.*, 1981).

The question still remains concerning the mechanism by which LSD and similar hallucinogens impose their effect on both DA and 5-HT neural systems. Since both transmitters are decomposed by a common enzyme, namely MAO, we suggest the hypothesis that an important part of the hallucinogen effects is due to MAO inhibition. This hypothesis finds support in several experimental findings which will now be described.

First, it is well established by now that LSD inhibits the action of raphe neurons (e.g., Aghajanian *et al.*, 1968; Trulson, Ross, & Jacobs, 1977). The inhibition can be accomplished either by blocking of postsynaptic or presynaptic 5-HT receptors (Baumann & Waldmeier, 1981; Freedman, 1968a). In both cases the result should be an increase in 5-HT level in the synaptic gap resulting in the inhibition of the nerve function via a negative feedback mechanism (Aghajanian *et al.*, 1970a, b; Squires, 1978). Since the feedback mechanism of 5-HT seems to allow high levels of the neurotransmitter, up to 300% (Squires, 1978), one would expect accumulation of 5-HT in the nerve axon, as was actually found by Freedman (1961). However, the accumulation of 5-HT should in turn result in an increase of 5-HIAA level, contrary to what was found by Freedman (ibid.). In fact, the above findings have led Freedman (1968b) to assume that LSD caused some kind of "inaccessibility" of 5-HT to MAO. We suggest that these results can be explained by assuming that LSD acts as a MAO inhibitor.

Further support to the hypothesis that LSD acts as a MAO inhibitor can be derived from the fact that symptoms similar to those of LSD can be obtained by the combination of MAO inhibitors and drugs which cause an increase in 5-HT level, but which by themselves are not hallucinogens, such as: reserpine (a 5-HT release inhibitor) and tryptamine (a 5-HT blocker) (Squires, 1978).

Final support to the hypothesis that LSD and other indol hallucinogens possess MAO inhibiting properties can be found in a structural analysis of the hallucinogens and traditional MAO inhibitors. As can be seen in Figure 1, all the indol-type hallucinogens as well as the traditional MAO inhibitors share common structural features: They all have an aromatic moiety to which a three-bonds chain is attached, at the end of which is a trivalent nitrogen atom. This structure fits the active sites of MAO which are composed of one hydrophobic and one hydrophilic moiety. In fact, this is exactly the structure expected of all MAO inhibitors as described by Maxwell and White (1978).

The hypothesis that MAO inhibiting capability is necessary for hallucinogenic action can explain, and find support, in the confusing findings, that minor structural changes in hallucinogens can cancel their effect. For instance, Br-LSD has no hallucinogenic effect. Although it inhibits 5-HT neurons *in vitro*, it does not increase

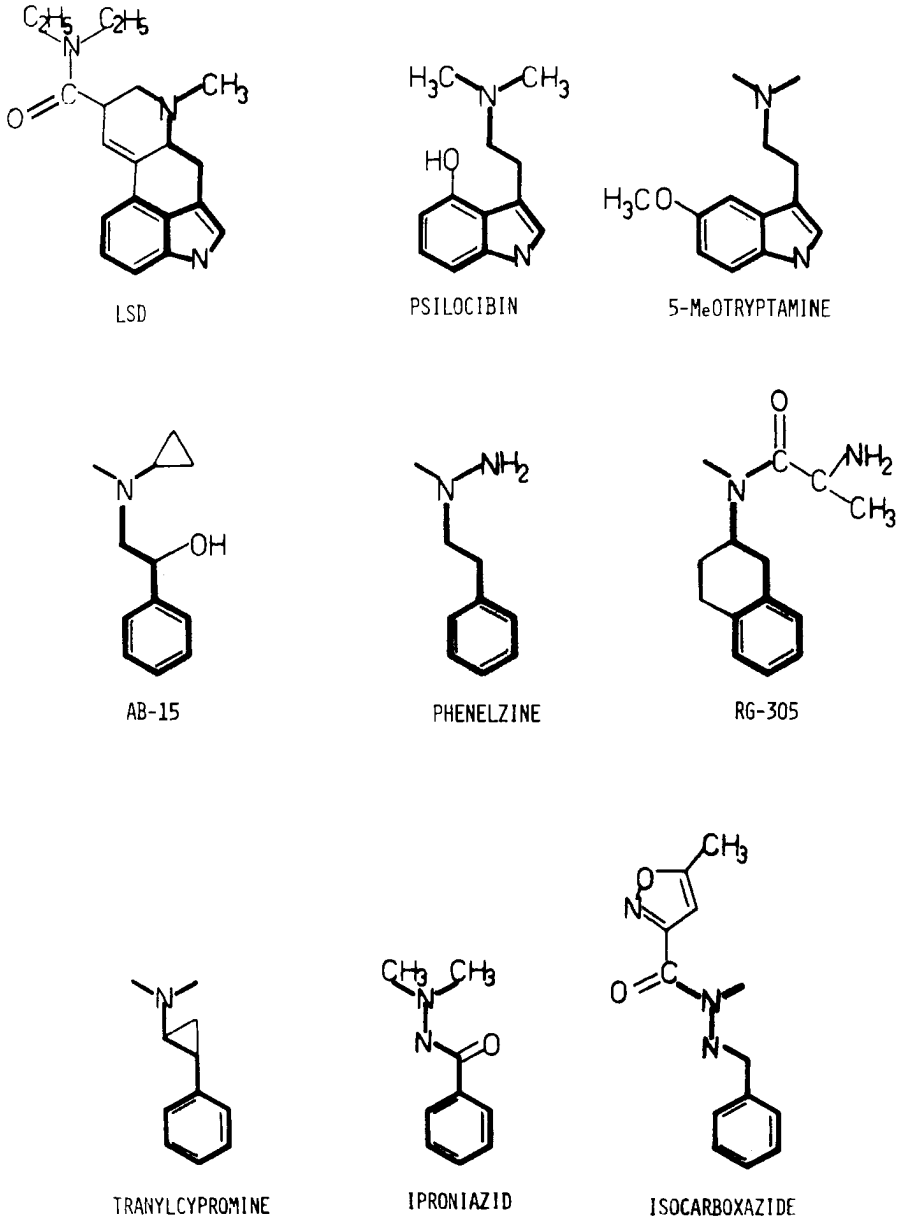

FIGURE 1 Structures of some indolamine hallucinogens and MAO inhibitors. Common features are emphasized by bold lines.

the level of brain 5-HT *in vivo*, contrary to LSD (Aghajanian *et al.*, 1970a, b; Freedman 1961). This can be explained by assuming that the bulky Br atom prevents the inhibition of MAO by sterically hindering the approach of Br-LSD to the enzyme. The same explanation can be used to explain the crucial role of the β position in both the phenylethylamine and indolamine drugs for psychotomimetic activity (Gentile, Friedman, & Vogel, 1982).

Another example is Lisurid Hydro Maleate (LHM) which has no hallucinogenic effect although it does block 5-HT receptors (White & Appel, 1982). The absence of hallucination effect can again be explained by lack of MAO inhibition capability due to the steric interference caused by the bulkiness of the substituent. Since LHM is as potent as LSD as 5-HT receptors and much more potent than LSD as a DA agonist (ibid.), this example further demonstrates that "something" more is necessary for hallucination. We suggest that this "something" is the inhibition of MAO (contrary to the conclusion of the authors).

In conclusion, all hallucinogens of the indolamine group share two structural features: 1. A structure expected to have 5-HT antagonistic effects, and 2. A structure expected to have MAO inhibition effect. The combination of 5-HT disinhibition in the limbic and visual system and simultaneous increased DA activity explains the many pharmacological and behavioral effects of this class of drugs.

This hypothesis that LSD acts both on 5-HT system (as blocker) and on the DA system (as MAOI—i.e., stimulator) could explain several other pharmacological properties of LSD activity, such as "tolerance," "cross-tolerance" and "flashback effect." However, several studies should be done before going into further speculations. It seems that this hypothesis opens a new direction for research, mainly on the role of LSD and other hallucinogens as MAO inhibitors.

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