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A New View of the Structural Relationship Between LSD and Mescaline

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NICHOLS, D. E., W. R. PFISTER, G. K. W. YIM AND R. J. COSGROVE. *A new view of the structural relationship between LSD and mescaline.* BRAIN RES. BULL. **2**(3) 169–171, 1977. – An examination of the effects of S-(–) and R-(+) 2-amino-1,2,3,4-tetrahydronaphthalene (2-AT) on mouse spontaneous activity and rabbit EEG has shown that the S-(–) enantiomer shows selective central effects similar to those of hallucinogens like mescaline. A stereochemical analysis of these results indicates that the structural relationship between mescaline, or other phenethylamine type hallucinogens, may involve correspondence between the aromatic ring of the phenethylamines and the pyrrole portion of the indole nucleus in LSD.

2-Amino-1,2,3,4-tetrahydronaphthalene Mescaline Hallucinogens

SINCE THE discovery of the mind-altering properties of LSD, much effort has been directed toward relating its structure to that of other hallucinogens such as mescaline [2, 8, 13, 15]. A major component of an hallucinogen's action is believed to be the stimulation of serotonin (5-HT) receptors in the brain. It is of great significance, therefore, to identify the critical molecular features that are responsible for this effect. For LSD and hallucinogenic tryptamines, the similarity to serotonin is obvious. Yet, it is still not clear how phenethylamine hallucinogens are related.

A most promising approach is the evaluation of rigid phenethylamine derivatives. For example, 2-amino-1, 2, 3, 4-tetrahydronaphthalene (2-AT) or its 7-hydroxy derivative, in animal models, both produce effects typical of an hallucinogen. In the rat, on a discriminated Sidman avoidance schedule, 2-AT generates a profile characteristic of hallucinogens [1]. In addition, 2-AT has a depressant effect on motor activity in mice, and its 7-hydroxy-derivative shows cross tolerance to the EEG effects of mescaline [4].

Our initial interest was to determine whether one of the enantiomers of 2-AT would show selective activity. It is known that only the R-(–) isomer of hallucinogenic amphetamine derivatives produces hallucinatory effects [14]. The absolute configuration of 2-AT has been unequivocally established by asymmetric synthesis to be R-(+) and S-(–) [18]. By examination of the pharmacological activity of (+) and (–) 2-AT we now have evidence which supports a new and improved way of relating the structure of LSD (Fig. 1a) to that of hallucinogenic phenethylamine derivatives such as 2,5-dimethoxy-4-methylphenylisopropylamine (DOM, STP) (Fig. 1c) and mescaline (Fig. 1d).

Adult male Swiss Webster mice, weighing 24–36 g were housed 10 to a cage and supplied with food and water ad lib for one week prior to use. The drugs, (±) 2-AT·HCl, (+) 2-AT·HCl and (–) 2-AT·HCl, were administered intraperitoneally in a volume of sterile saline equal to 0.1 ml per 10 g of body weight. Spontaneous motor activity of each group was measured using circular photocell activity cages (Woodard Research Corp., Herndon, VA) Mice were divided into groups of three per cage, and remained in the activity cage for the duration of the experiment. The data for each time were analyzed by an analysis of variance and Newman-Keuls comparison of means.

The results are shown in Table 1. Values represent the percent increase (+) or decrease (–) in activity, relative to the saline-injected control animals. It is clear that the depression of spontaneous activity previously reported for racemic 2-AT is due entirely to the effect of the (–) enantiomer. At times past 40 min, both (+) and (±) 2-AT activity levels remain at about the 30 min values, with activity for saline treated controls gradually decreasing.

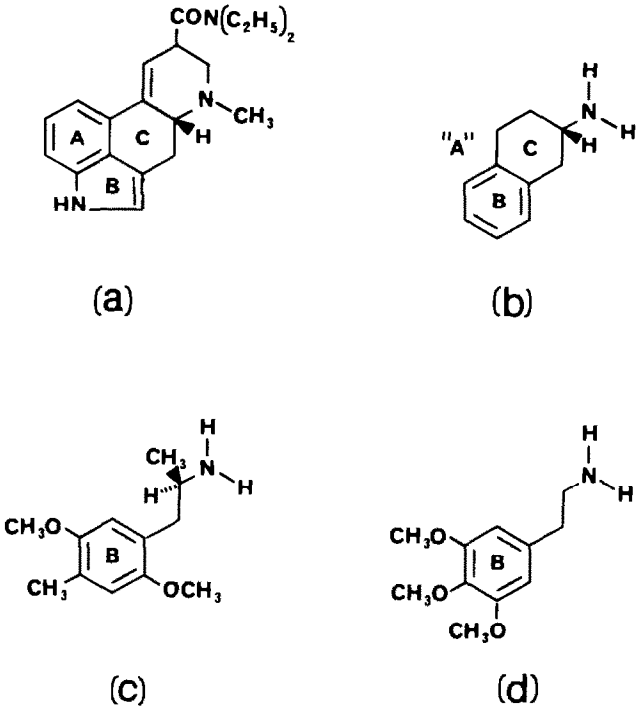

FIG. 1. Proposed structural relationship between (a) LSD, (b) S-(−)-2-amino-1,2,3,4-tetrahydronaphthalene (S-(−) 2-AT), (c) the staggered conformation of 2,5-dimethoxy-4-methylphenylisopropylamine (DOM, STP) with the aromatic ring approximately anti to the amino group, and (d) mescaline, illustrating how the aromatic rings of phenethylamine derivatives correlate with the pyrrole portion (ring B) of LSD. Rings A and B in LSD represent the indole nucleus and are the portions which, along with the aliphatic nitrogen, correspond to the structure of the neurotransmitter serotonin.

Agents which selectively deplete brain 5-HT produce an increase in spontaneous activity [5, 6, 7]. Conversely, drugs which stimulate 5-HT receptors, such as hallucinogens, could be expected to reduce the activity of an animal. Indeed, Lopatka et al. [10] have found that the hallucinogens DOM, para-methoxyamphetamine (PMA) and 3,4-methylenedioxyamphetamine (MDA) all produce a marked decrease in spontaneous activity in mice.

Examination of the quantitative EEG parameters total power, P, and median frequency in the power spectrum, f_{50}, has shown that, of the isomers of 2-AT, only the (−) enantiomer (4 mg/kg, IV) produces effects in the rabbit EEG similar to mescaline (20 mg/kg, IV). These results support the view that the hallucinogenic effects reported [1] for racemic 2-AT can be attributed to the selective central action of the S-(−) enantiomer.

A comparison between the structure of LSD and S-(−) 2-AT (Fig. 1b) is inconsistent with currently accepted views [1, 2, 4, 8, 13, 14, 15] which suggest that the aromatic ring of the phenethylamine type hallucinogens corresponds to ring A in LSD. Rather, the evidence shows that the aromatic ring of the phenethylamines corresponds to the pyrrole portion (Ring B) of the indole nucleus in LSD, as depicted in Fig. 1. From a chemical point of view this is a more appealing analogy, since one need not consider the sp^2 nature of C-10 in LSD as being incorporated into a phenethylamine moiety, an idea required by earlier concepts. Using results of theoretical calculations it was first

TABLE 1

EACH VALUE REPRESENTS THE PERCENT INCREASE (+) OR DECREASE (−) IN SPONTANEOUS ACTIVITY RELATIVE TO SALINE CONTROLS, FOLLOWING THE INTRAPERITONEAL ADMINISTRATION OF RACEMIC 2-AMINO-1,2,3,4-TETRAHYDRONAPHTHALENE HYDROCHLORIDE (2-AT) OR ONE OF ITS ENANTIOMERS

	Time After Injection (min)				
	5	10	20	30	40
(+) 2-AT (4 mg/kg)	−4.7	+6.8	+5.4	+27.2	+23.3
(±) 2-AT (8 mg/kg)	−35.9†	−11.6†	−5.8	+11.4	+11.7
(−) 2-AT (4 mg/kg)	−54.1†	−64.6†	−59.7†	−47.1*	−21.8*

*$p<0.05$.
†$p<0.01$.

suggested by Kang and Green [8] that receptor binding occurs from the underside, or alpha face, of LSD [8]. X-ray, solution, and theoretical studies by several other workers have supported the suggestion. This indicates that the R-(−) isomer of hallucinogenic phenylisopropylamines is active because the alpha methyl is allowed to project away from the receptor surface, and does not interfere with binding. This is quite obvious if one examines the ability of space filling molecular models of the two enantiomers to interact with a planar surface. Only the staggered conformer of the R isomer, where the aromatic ring is anti to the amino group (Fig. 1c), is able to fulfill this requirement.

There is apparently no published evidence which is inconsistent with this new approach. It is clear, from the work of Cooper and Walters [3] with the cis and trans cyclopropyl analogues of mescaline (2-(3,4,5-trimethoxyphenyl) cyclopropylamine) that the receptor accommodates a transoid side chain conformation for the hallucinogenic phenethylamines. However, these workers did not resolve the more active trans isomer into its enantiomers. Until this is accomplished, it is impossible to determine whether their data support this new proposal, or whether it is consistent with the earlier ideas. If our revised view is correct, only the 1R,2S isomer should possess activity. On the other hand, if the earlier ideas are correct the 1S,2R isomer should be active.

Molecular orbital calculations have also been used to support earlier analogies [8]. However, these describe the electronic character of the aromatic system, and would equally well support congruence of the aromatic ring of phenethylamines with either Ring A or Ring B of LSD.

A serious deficiency in the earlier ideas [4,8] is the inability of the R-(−) isomer of the phenylisopropylamines to adopt the coplanar aminotetralin-like conformation required by the A-C ring analogy. This is primarily due to steric interaction between the alpha methyl and the hydrogens on the ortho positions of the aromatic ring. On the other hand, the staggered conformation which we propose for DOM (Fig. 1c) has been calculated to be the low energy solution conformer [17].

This concept shows explicitly how phenethylamines can relate to serotonin and other tryptamines by simply considering them all to be arylethylamines. Consideration of a recent hypothesis put forth regarding the structural

relationship between LSD and certain dopaminergic agonists [12], which can relate the stereochemistry of LSD to that of other classes of rigid agents such as benzomorphans, suggests that there may well be a great deal of similarity between dopamine and serotonin receptors.

We emphasize, however, that this approach applies specifically to the 5-HT agonist properties of hallucinogens. Suggestions [9, 11, 16] that 2-AT derivatives represent an oxytocic A-C ring fragment of lysergic acid may still be justified when considering the ability of ergot alkaloids to interact with alpha adrenergic receptors.

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