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Structural Correlation between Apomorphine and LSD: Involvement of Dopamine as Well as Serotonin in the Actions of Hallucinogens

DAVID E. NICHOLS

Department of Medicinal Chemistry and Pharmacognosy,
School of Pharmacy and Pharmacal Sciences,
Purdue University,
West Lafayette, Indiana 47907, *U.S.A.*

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It is suggested that the action of LSD and other hallucinogens depends, not only on stimulation of serotonin receptors, but also on stimulation of central dopamine receptors. Both pharmacological and structural-chemical evidence is presented to support the latter hypothesis. A structural correlation is also demonstrated between LSD and apomorphine, and the probable dopaminergic element in LSD is discussed.

1. Introduction

Despite over 20 years of research into the action of LSD, the hallucinogenic tryptamines, mescaline and the phenylisopropylamines (amphetamines), the exact mechanism still remains obscure. Numerous *in vivo* and *in vitro* pharmacology studies have failed to bring into focus a definite pattern of events which might result in the unique action observed for hallucinogenic agents.

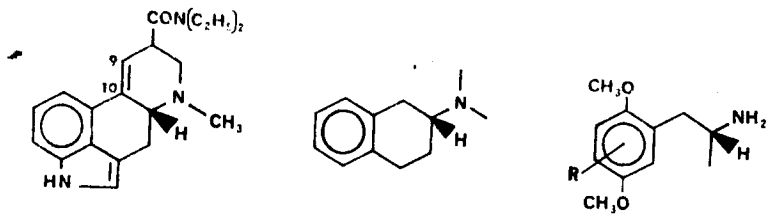
In the discussion that follows evidence will be presented which supports the following hypothesis; that hallucinogens (LSD, mescaline, methoxylated amphetamines) in addition to their ability to stimulate central serotonin (5-HT) receptors, also stimulate dopamine receptors and that this dopamine receptor stimulation is an essential feature of their action. Their ability to exert powerful effects in two different monoamine systems and the resulting changes can explain the diversity of action which is observed for the various agents.

Demonstration of cross tolerance between LSD and other psychotomimetics and the similar subjective effects reported for the various hallucinogens have prompted attempts to develop correlations which interrelate the

structures of LSD, mescaline, tryptamines, and the methoxylated amphetamines to some common structural element. Within this context LSD has been used as the model hallucinogen, and attempted correlations have usually emphasized the relationship of the more flexible phenethylamine and tryptamine derivatives back to the more rigid structure of LSD.

The actions of hallucinogens are complex and both similarities and important differences exist between the various classes (Brawley & Duffield, 1972). The single most important finding to emerge is that psychotomimetics all have the ability to diminish serotonin (5-HT) turnover in the brain. Even though the original hypothesis of Woolley & Shaw (1954) regarding antagonism of serotonin receptors by LSD is no longer accepted, the involvement of 5-HT receptors in the actions of hallucinogens is well recognized today, and there seems no doubt that LSD has postsynaptic stimulatory actions on 5-HT receptors (Andén, Corrodi, Fuxe & Hökfelt, 1968; Tonge & Leonard, 1969; Aghajanian, Haigler & Bloom, 1972). Phenethylamine and amphetamine type psychotomimetics have a similar effect on 5-HT receptors (Andén, Corrodi, Fuxe & Meek, 1974; Dyer & Gant, 1973; Dyer, Nichols, Rusterholz & Barfknecht, 1973).

A relatively large amount is known about the conformation and stereochemistry of LSD [Fig. 1(a)] and about the tryptamines and amphetamines.



(a) (b) (c)

FIG. 1. Relationship between LSD (a), aminotetralins (b), and substituted amphetamines (c), illustrating the similar stereochemistry at the asymmetric carbon atoms. These structural similarities are believed to be associated with 5-HT receptor stimulation.

Solution studies on lysergic and isolysergic acid amides by Bailey & Grey (1972), and theoretical and solid state studies (Kang, Johnson & Green, 1973; Chothia & Pauling, 1969; Baker, Chothia & Pauling, 1973; Pullman, Courriere & Berthod, 1974) imply that binding probably occurs between the underside, or alpha face of LSD and the receptor if N-6 of LSD is a site of binding.

Based on numerous studies of simplified lysergic acid analogs, a general theory regarding conformational and structural relationships has evolved

which relates the 5-HT receptor stimulating conformer of mescaline and the amphetamines to the aminotetralin fragment [Fig. 1(b)] in the hallucinogen LSD. The first clear formulation of this concept as applied to the hallucinogens was presented by Kang & Green (1970*a*) with some further considerations regarding stereochemistry and absolute configuration later published by Nichols, Barfknecht, Rusterholz, Benington & Morin (1973). The proposal by Barfknecht & Nichols (1972) that the R-(−) isomers of the amphetamines [Fig. 1(c)] would possess activity was based on stereochemical considerations and has been largely borne out by subsequent studies (Shulgin, 1973; Benington, Morin, Beaton, Smythies & Bradley, 1973; Snyder, Unger, Blatchley & Barfknecht, 1974; Dyer *et al.*, 1973). This should be contrasted with unsubstituted amphetamine where stimulant activity resides primarily in the S-(+) isomer.

2. Involvement of Dopamine Receptors

Several early papers describe actions for psychotomimetics which indicate that dopamine or dopamine receptors may be involved. Fog (1969) has suggested that the stereotypic behavior characteristic of LSD, amphetamine and other stimulant drugs in rodents may be a result of interactions with dopaminergic systems. Recent studies suggest that LSD may have a direct postsynaptic dopamine receptor stimulating effect, while with the methoxylated amphetamines, it appears more likely that these agents cause release of dopamine, and thus are indirectly acting at dopamine receptors.

Cheng, Long, Nichols & Barfknecht (1974) reported that there appear to be three classes of psychotomimetic amphetamines; (1) those which directly stimulate serotonin receptors (principally 2,5-disubstituted compounds such as 2,5-dimethoxy-4-methylamphetamine (DOM) and 2,5-dimethoxy-4-bromoamphetamine (DOB), (2) compounds which directly stimulate α-adrenergic receptors, and (3) indirectly-acting compounds which induce release of stored catecholamine. This latter class contained the bulk of methoxylated amphetamines which were examined. A potent compound, *para*-methoxyamphetamine (PMA) (Shulgin, Sargent & Naranjo, 1969) was found to be of the latter type, has little ability to stimulate 5-HT receptors (Dyer *et al.*, 1973), and has toxicity and other effects similar to amphetamine itself (Nichols, Ilhan & Long, 1975).

Low doses of DOM have been shown to produce amphetamine-like effects on schedule-controlled behavior in rats (Beaton, Smythies, Benington & Morin, 1969; Marquis, Tilson & Rech, 1973). Vrbanac, Tilson, Moore & Rech (1975) have recently shown that the effect of both d-amphetamine and

DOM on *in vivo* release and/or blocking reuptake of catecholamine from brain periventricular nerve terminals in rats is qualitatively similar. Pijnenburg, Honig & Van Rossum (1975) summarized the evidence regarding involvement of dopamine both in stereotypic behavior and in locomotor activity changes following administration of amphetamine to rats. Their results with dopaminergic, alpha-adrenergic, and beta-adrenergic blocking agents confirm the significance of dopaminergic mechanisms in the effects of amphetamine. Dill (1972) reported that mescaline, on intrastriatal injection into rats, produces a dyskinesia which is significantly reduced by administration of haloperidol, a potent dopamine receptor blocker. It also has been shown that certain ergot alkaloids can produce long lasting effects similar to other dopamine receptor stimulants such as apomorphine (Corrodi, Fuxe, Hökfelt, Lidbrink & Ungerstedt, 1973; Johnson, Vigouret & Loew, 1973).

Johnson, Ary, Teiger & Kassel (1973) studied emetic activity for a series of 9,10-dihydrolysergamides. Several of the compounds possessed greater emetic potency than apomorphine, an agent believed to stimulate dopamine receptors (Ernst, 1965; Cotzias, Papavasiliou, Fehling, Kaufman & Mena, 1970; Vernier, 1971). Von Hungen, Roberts & Hill (1974) found that cell-free adenyl cyclase fractions from rat corpus striatum were reproducibly activated by low concentrations of LSD. Adenyl cyclase activity from other regions of rat brain was not affected by LSD. The response of striatal adenyl cyclase to either dopamine or to LSD was almost completely blocked by either haloperidol or chlorpromazine. Pieri, Pieri & Haefely (1974) have shown that in rats with unilateral lesions in the nigrostriatum (rotating rats), LSD had a potent ability to stimulate dopamine receptors, and had effects similar to apomorphine. The inability of α-methyltyrosine pretreatment to alter the response and the antagonism of the rotational effect by haloperidol led these workers to propose that this action of LSD was purely dopaminergic and postsynaptic. 2-BromoLSD (BOL) was inactive in inducing rotation. No tolerance was found to develop to the rotational effects after five days of repeated treatment with LSD. Although it is known that tolerance to the hallucinogens rapidly develops, Bridger, Mandel & Stoff (1973) have also reported that in rats tolerant to the behavior disruptive effects of mescaline, no tolerance to the excitatory effects was observed. Grabowska, Antkiewicz & Michaluk (1974) studied the effect of LSD in reserpinized mice. LSD was found to stimulate locomotor activity and to antagonize reserpine-induced ptosis. Neither cyproheptadine nor methysergide influenced LSD-induced locomotor stimulation in reserpinized mice. Significant inhibition was obtained, however, following treatment with haloperidol or spiroperidol. These workers concluded that dopamine receptor stimulation may be involved in LSD-induced reactions.

3. Structural Requirements for Dopamine Receptor Stimulation by LSD

The indication of dopamine receptor involvement in the actions of LSD and other hallucinogens prompted this examination of the lysergic acid structure in search of a possible structural element which could be responsible for such activity. For comparison purposes consider apomorphine to be a prototype dopamine agonist (Ernst, 1967; Ungerstedt, Avemo, Avemo, Ljungberg & Ranje, 1973) [see Fig. 2(a)]. Apomorphine has a rigid structure

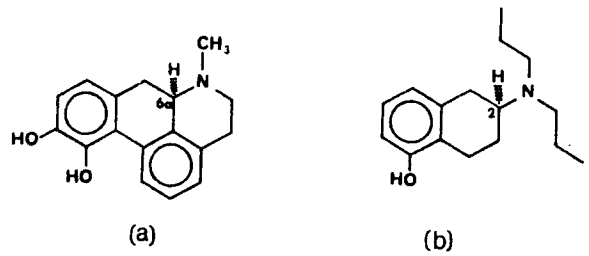


FIG. 2. Comparison between 6aR-(−)-apomorphine (a) and 2S-(−)-5-hydroxy-2-*N*,*N*-dipropylamino-1,2,3,4-tetrahydronaphthalene, illustrating the similar stereochemistry at the chiral center. An aminotetralin fragment is believed responsible for the dopaminergic activity of apomorphine.

of known stereochemistry and the absolute configuration at the chiral center (C-6a) has been shown to be R (Corrodi & Hardegger, 1955; Cymerman-Craig & Roy, 1965; Shamma, 1967). The recent synthesis and testing of 6aS-(+)-10,11-dihydroxyaporphine, the enantiomer of apomorphine (Saari, King & Lotti, 1973) has demonstrated that only the 6aR-(−) isomer, which is derived from natural morphine, possesses dopaminergic activity. A related structure, 5-hydroxy-2-*N*,*N*-dipropylamino-1,2,3,4-tetrahydronaphthalene [Fig. 2(b)] has been resolved by McDermed, McKenzie & Freeman (1975) and it was shown that only the (−) isomer was active, the (+) enantiomer being devoid of apomorphine-like activity. The stereochemistry was reported to be similar to that for apomorphine, and would be predicted, from its sign of rotation, to possess the S absolute configuration (Zymalkowski & Dornhege, 1969; Nichols *et al.*, 1973). Upon examination the S configuration of this aminotetralin is seen to correlate with the R configuration of apomorphine. In a related series of aminotetralins, McDermed, McKenzie & Phillips (1975) have reported that two free catechol hydroxyls are not required for activity, although maximum potency was obtained when both were present.

If one attempts to correlate the aminotetralin portions of apomorphine or 5-hydroxy-2-*N*,*N*-dipropylaminotetralin and LSD, one finds that the stereochemistry at the asymmetric centers is reversed. It is known that only the 5R8R isomer of LSD is active (Hofmann, 1968). Since only one isomer of apomorphine or the related aminotetralin possesses activity, it seems highly unlikely that such opposite stereochemistry at the chiral centers in the two types of compounds would give rise to the same type of activity, if indeed the aminotetralin portions correspond. Assuming that the same receptor systems are involved, it may be tentatively concluded that this approach is invalid.

If instead, one places priority on correspondence at the asymmetric carbons and the aliphatic nitrogens, a striking structural similarity becomes apparent, as illustrated in Fig. 3. In addition to the defined correspondence between the

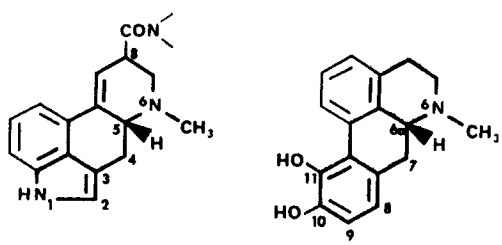


FIG. 3. Proposed structural correlation between lysergic acid derivatives and apomorphine, with the 2,3,4,5,6 positions of the lysergic structure corresponding to the 8,7a,7,6a,6 positions of apomorphine to account for the dopaminergic activity of ergot derivatives.

asymmetric carbons and the aliphatic nitrogens, several other observations can be made. The highly activated catechol portion of apomorphine corresponds to the pyrrole portion of the indole nucleus in LSD, with the 10 hydroxy of apomorphine being in about the same spatial position as the indole NH. The 2 position in LSD corresponds to the 8 position of apomorphine or the aminotetralins. Using the analogies of Cannon, Kim, Aleem & Long (1972) and Cannon *et al.* (1972) this position would correlate with the 6 position of dopamine. The ability of 3-substituted indole compounds to undergo facile electrophilic substitution or oxidative reactions at the 2 position and the ease of electrophilic substitution into the 6 position of 3,4-dioxygenated alkyl benzene derivatives is both predictable and well documented in the literature. Although the oxidation of apomorphine gives rise to complex products, the facile oxidation of the catecholamines at the 6 position has been well known for many years. This type of reactivity depends on localization of charge density at these positions.

Although these are the most outstanding similarities, the non-catechol aromatic ring of apomorphine might also correspond to the pi electrons in the 9,10,11,12 region of LSD. However, some 9,10-dihydrolysergamides retain dopamine-like activity, and in the simpler aminotetralin analogs of Cannon *et al.* (1972) or McDermed *et al.* (1975) there is no area of electron density in this region. It may be reasonable to conclude that there is a general chemical correspondence between the pyrrole portion of the indole nucleus and the catechol nucleus, and especially between the 2 indole position and the 6 catecholamine position.

Biological implications for high reactivity at the 2 position in LSD (based on molecular orbital calculations) were initially proposed by Karreman, Isenberg & Szent-Györgyi (1959). It was suggested that high electronic energy might be consistent with pi-complex formation or electron donation at the receptor level. Later calculations by Snyder & Merril (1965) included other psychotomimetics and underscored this possibility. Similar work by Kang & Green (1970*b*) demonstrated a correlation between activity and electronic energy for the methoxylated amphetamines. It should be noted that both BOL and 2-oxoLSD (Axelrod, Bradley, Witkop & Evarts, 1957) are inactive as hallucinogens. BOL caused no excitation characteristic of LSD but produced instead sedation in mice, and sedation, fatigue and some nausea in humans (Cerletti & Rothlin, 1955). *In vitro* LSD is rapidly and almost quantitatively metabolized by liver microsomes to 2-oxoLSD. This oxidation is inhibited by chlorpromazine or SKF 525 and in mice chlorpromazine was found to approximately double the half-life of unmetabolized LSD (Axelrod *et al.*, 1957).

Another important point which should be defined is the relative importance of the substituent at the C-8 position of LSD. It has been demonstrated that small changes in substitution on the amide nitrogen produce, in every instance, a molecule with decreased hallucinogenic activity when compared with the diethylamide (Hofmann, 1968). Speculation concerning the role of the amide function of LSD as a result of this finding continues. However, Bach, Hall & Kornfeld (1974) have shown that 8-descarboxylysergic acid, completely lacking an 8 substituent, still retains a profile of activity in mice similar to LSD. Activity of this compound on rabbit aortic strips was demonstrated to be comparable to ergonovine, and on rat stomach strips was about one-third the potency of methysergide as a serotonin antagonist. Thus the importance of C-8 substitution may lie in metabolic, distribution, or conformational factors, rather than to some receptor requirement for binding at this site.

Whether or not a strict structural analogy needs to be applied in the case of the flexible amphetamine psychotomimetics is not clear. Such an analogy

would imply that the 2, or *ortho*, position of the amphetamines correlates with the 2 position of LSD. However, since an *ortho* methoxy gives compounds with highest activity (Shulgin *et al.*, 1969) it seems more likely that the suggestions of Chothia & Pauling (1969) apply and that the n-electrons of the *ortho*-methoxy are correlated with the region of electron density at the 9,10 double bond in LSD (see Fig. 1). However, a dopaminergic effect may still be invoked since it appears that the amphetamines can exert an indirect effect caused by release of catecholamine from nerve terminals (Cheng *et al.*, 1974; Vrbanac *et al.*, 1975). It is important to point out that the only active isomeric amphetamine psychotomimetics which have been tested in humans, namely DOM and DOEt (2,5-dimethoxy-4-ethylamphetamine) (Shulgin, 1973; Snyder *et al.*, 1974) are compounds which are very potent in stimulation of 5-HT receptors (Dyer *et al.*, 1973). Human activity for isomers of indirectly-acting amphetamine derivatives, for example PMA, has not been reported. Ota (1948) has indicated that for the isomers of 3,4-methylenedioxyamphetamine (MDA), a compound which is psychotomimetic in humans, the (+) isomer possessed analeptic activity in animals whereas the (−) isomer did not. Although the mechanism of action for MDA has not been well studied, its pharmacological similarity to PMA (Nichols *et al.*, 1975) suggests that it is an indirectly acting agent. These differences in mechanism of action could easily explain the spectrum of effects which is known for the various psychotomimetics.

Another observation which may support this hypothesis is the finding by Smythies, Beaton, Benington & Morin (1970) that 1-methyl-1,2,5,6-tetrahydropyridine *N,N*-diethylcarboxamide (THPC) was able to potentiate the effects of mescaline but showed antagonism to the effects of LSD. These workers offered the explanation that there might be a receptor shaped to accommodate LSD and that mescaline filled one portion of it while THPC occupied another to essentially give a more completely filled LSD receptor. Since lysergic acid derivatives are not endogenous in mammals the existence of an LSD shaped receptor is questionable. On the other hand, the interaction with two different monoamine systems could better explain this finding.

Cheng & Long (1974) reported that DOM antagonized apomorphine-induced pecking in pigeons and that DOB was a potent emetic, indicating possible involvement in dopaminergic pathways. Neither of these compounds has been reported to cause vomiting in humans. McDermed *et al.* (1975) found that certain methyl ethers of aminotetralins related to apomorphine were inactive in dogs when injected but were potent emetics when given orally. It was speculated that the *O*-methyl ethers might be cleaved in the gut prior to absorption to yield active emetic compounds. These findings

are similar to those reported by Cannon *et al.* (1972) for a possible O-demethylation by pigeons. A similar demethylation of mescaline or methoxylated amphetamines in humans might account for production of metabolites possessing higher activity at dopamine receptors. Although 4-O-demethyl mescaline is inactive as an hallucinogen, it is possible that an oxidative transformation could take place at or near the receptor level, and might be intrinsically involved in the actual receptor interaction. Belleau & Morgan (1974) recently proposed such an oxidative transformation to be involved in the action of opiate analgesics.

Admittedly, there are certain difficulties in testing this hypothesis. Although it has so far not been possible to develop a good animal model for hallucinogens, human studies are at present out of the question. However, certain aspects of this proposal can be tested. Specifically, the isomers of methoxylated amphetamine type hallucinogens need further examination for their potential ability to interact with different monoamine systems before final conclusions can be drawn about stereoselective activity. A directed search for areas of dopamine involvement in the action of hallucinogens is definitely needed to decide the validity of this hypothesis. As an example, the isomers of PMA or MDA could be examined within this context for possible effects on dopaminergic systems.

The correlation between apomorphine and LSD has far-reaching implications. If the analogy can be proved to be valid, it provides valuable information about the structural and stereochemical requirements of central dopamine receptors. It should aid in receptor mapping and could lead to insights which will allow more efficient design of drugs to interact at dopamine receptors. Applications of this approach to other classes of drugs which interact at dopamine receptors may allow recognition of structural similarities not previously apparent. It may also suggest certain similarities between the chemical and pharmacological actions of dopamine and serotonin in the CNS.

Finally, if it can be shown without doubt that interaction with dopamine receptors is fundamentally involved in the action of hallucinogens, the study of psychotomimetics in relation to mental illness will become much more relevant. The possible involvement of dopaminergic systems in relation to certain types of psychosis and in paranoid schizophrenia, and the relationship between paranoid schizophrenia and amphetamine psychosis has been discussed (Snyder, 1972; Connell, 1958; Faurbye, 1968; Angrist & Gershon, 1971; Angrist, Shopsin & Gershon, 1971).

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