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Stereoselective pharmacological effects of lysergic acid amides possessing chirality in the amide substituent

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Abstract

Studies of the affinities for serotonin 5-HT_{2A} and 5-HT_{1A} receptor subtypes of lysergic acid amides prepared from chiral 2-aminoalkanes showed a stereoselective preference at both receptor types for the amides with alkyl groups containing the *R* configuration. The 5-HT_{2A} receptor was less tolerant of long alkyl groups than was the 5-HT_{1A} subtype. In vivo assays in rats trained to discriminate LSD from saline also showed that amides with alkyl groups having the *R* configuration were most potent.

Keywords: Pharmacological effect; Lysergic acid; Serotonin receptor; Stereoselective; Lysergamide; LSD; 5-HT_{2A} receptor; 5-HT_{1A} receptor

Among the hallucinogenic agents, (+)-lysergic acid *N*,*N*-diethylamide (LSD) and certain closely related ergoline structures remain the most potent [5]. The hallucinogenic potency of LSD is also exquisitely sensitive to the nature of the substituents attached to the amide nitrogen; the *N*,*N*-diethyl substitution gives *optimal* potency [8]. Substituents that might intuitively be expected to have activity similar to LSD, such as the pyrrolidide, fail to live up to expectations, being an order of magnitude less potent [1]. Very minor changes, such as replacement of the diethyls with isomeric *N*-methyl-*N*-propyl substituents also lead to compounds with activity about one order of magnitude lower than that of LSD [3]. The human potencies of some structurally related lysergamides are presented in Table 1 to illustrate this point.

What accounts for this unique effect of the diethylamide? It seems doubtful that it can be related to hydrophobicity, since the pyrrolidide, or *N*-methyl-*N*-propylamide will have hydrophobic characteristics very similar to the diethyl. One might speculate that the diethyl somehow confers unique pharmacokinetic properties onto the molecule, or is somehow more resistant to metabolism than other dialkyl groups, but these also seem to be unlikely answers.

Table 1
Human potencies of representative lysergic acid amides

Amide N,N-dialkyl groups		Human potency as a percent of LSD
R	*R'*	
H	H	<10
Ethyl	H	10
Ethyl	Methyl	<10
Ethyl	Ethyl (LSD)	100
Ethyl	n-Propyl	30
Methyl	n-Propyl	<10
n-Propyl	n-Propyl	10
Pyrrolidyl		10
Morpholinyl		30

Data are taken from Refs.[1,2,3] and [8].

The most reasonable explanations seem to arise from the possibility that the diethyl has optimal complementarity with the target receptor(s). Assuming that the amide binds in a portion of the receptor defined by a three-dimensional array of amino acids, the simple change of a glycine to an alanine in this region, for example, might be expected to have a dramatic effect on binding. We have speculated that the amide carbonyl oxygen of LSD may serve as a hydrogen bond acceptor [6]. It thus seems possible that the amide substituents may also serve, through interaction with the receptor, to force the carbonyl oxygen to adopt an optimal

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conformation for interaction with a hydrogen bond donor on the receptor. At the present time, however, little data exist upon which to develop a firm conclusion.

We decided to gain additional information regarding the structure–activity relationships of the amide substituents of lysergamides. Unfortunately, we are not able to test these compounds in man, so the data to be used for the structure–activity relationships bear a degree of uncertainty with respect to how well they will actually reflect the effects of these compounds in humans. We have primarily relied upon the two-lever drug discrimination assay, in rats trained to discriminate between saline and LSD tartrate (0.08 mg/kg) [6].

Several years ago, we attempted to constrain the diethyl groups of LSD by incorporating them into a 2,3-dimethylaziridine moiety (Fig. 1). However, the lysergoyl aziridines proved extremely labile to acid, and in the presence of protons and chloride ion the acylated *cis*- and *trans*-dimethylaziridine rings were cleaved to afford 4 isomeric 2-chlorobutyllysergamides [7]. Although we never firmly established the absolute configurations of these 4 isomers, the ED_{50} values for substitution in the drug discrimination assay are shown in Fig. 1, and they varied widely. Thus, these data showed, for the first time, that the introduction of chirality into the amide groups would lead to differing biological activities. We therefore undertook to study the effects of chiral alkyl groups on LSD-like biological activity.

The second study involved an examination of the lysergic acid amides of commercially available (*R*)- and (*S*)-2-aminobutanes [6]. Table 2 presents the biological assay data for these compounds. More recently, we have extended the *N*-alkyl groups to higher homologs [4]. Fig. 2 shows these isomeric compounds, and Table 3 summarizes the receptor affinities and the drug discrimination data, compared to LSD.

These data reinforce the idea that the amide substituent can be a powerful determinant of biological activity in the lysergamides. The most potent LSD-like compound, with greatest similarity to LSD itself in all the bioassays was the lysergamide prepared from (*R*)-2-aminobutane (see Table 2). In vivo activity in the drug discrimination assay rapidly drops off when the alkyl group is extended to the next higher homolog, the (*R*)-2-aminopentane derivative, even though affinity for the ketanserin-labeled 5-HT_{2A} receptor is comparable to that of LSD, and affinity for the 5-HT_{1A} receptor is increased about 7- or 8-fold.

Whereas affinity for the ketanserin-labeled 5-HT_{2A} receptor decreases with increasing alkyl chain length,

Table 2
Biological data for lysergic acid amides of *R*- and *S*-2-aminobutanes

Drug	k_i values (nM)					ED_{50} (nM/kg)
	5-$HT_{2A}H$	5-$HT_{2A}L$	5-HT_{1A}	D_1	D_2	
LSD	6.3	5	4.4	45	13	48
R-2-butyl	2.6	9	2	41	13	33
S-2-butyl	7.8	34	4.6	47	28	124

5-$HT_{2A}H$ refers to the receptor labeled with [^{125}I]DOI and 5-$HT_{2A}L$ refers to the receptor labeled with [^{3}H]ketanserin. Data are taken from Refs. [6] and [9]. The D_1 receptor in rat striatum was labeled with [^{3}H]SCH 23390. The D_2 receptor was labeled with [^{3}H]spiperone in the presence of ketanserin to mask 5-HT_{2A} receptors. See Ref. [9] for details.

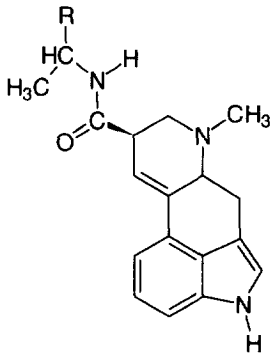

Fig. 2. Structures of lysergic acid amides with chiral substituents attached to the amide nitrogen. The CH attached directly to the amide nitrogen is chiral and is assigned either as the *R* or *S* absolute configuration.

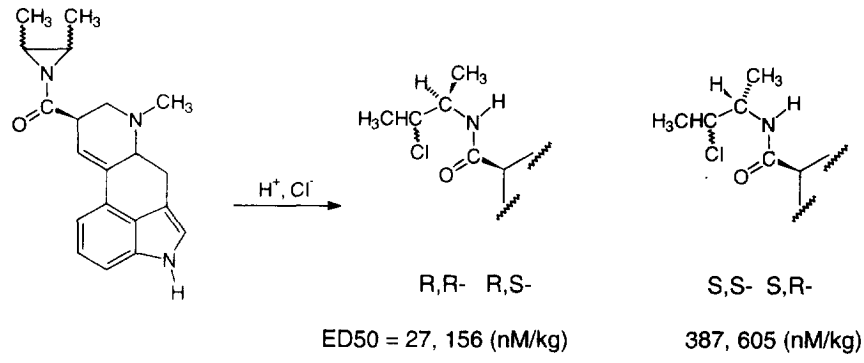

Fig. 1. HCl-catalyzed cleavage of lysergoyl *cis*- and *trans*-dimethylaziridines gave 4 isomeric chlorobutylamides with differing LSD-like in vivo activity in the drug discrimination assay [7].

Table 3
Biological data for lysergic amides of *R*- and *S*-2-aminoalkanes

R Group[a]	Enantiomer	5-HT_{2A}*L* k_i (nM)	5-HT_{1A} k_i (nM)	ED_{50} (nM/kg)
LSD	*NA*	4.8	4.4	48 (32–73)
$-C_3H_7$	*R*	4.5	0.6	102 (61–169)
$-C_3H_7$	*S*	105	7.6	NS[b]
$-C_4H_9$	*R*	16	0.32	PS[c]
$-C_4H_9$	*S*	55	4.9	NS
$-C_5H_{11}$	*R*	80	3.3	ND
$-C_5H_{11}$	*S*	357	14	ND
$-CH(CH_3)C_6H_5$	*R*	21	ND	ND
$-CH(CH_3)C_6H_5$	*S*	368	ND	ND

ND indicates that the compound was not tested in the behavioral assay. 5-HT_{2A}*L* refers to the receptor labeled with [^{3}H]ketanserin. The 5-HT_{1A} receptor was labeled with [^{3}H]8-OH-DPAT. Data are taken from Ref. [4] except for the last two entries.
[a]The first 3 sets of isomers all contain n-alkyl groups.
[b]No substitution, that is, less than 60% of the animals selected the LSD-appropriate lever.
[c]Partial substitution occurred, that is, 60–79% of the animals selected the LSD-appropriate lever.

affinity for the 5-HT_{1A} receptor is optimal when the alkyl group is 2-hexyl, being more than an order of magnitude higher than for LSD itself. We have not yet had an opportunity to examine affinities at other receptors such as the dopamine D_1 or D_2 subtypes, where LSD and several other of its analogs have relatively high affinity [9]. One would anticipate, however, based on the structural similarities between G-protein-coupled monoamine receptors, that stereochemical preferences would exist at all monoamine receptors for lysergamides with isomeric alkyl groups in the amide moiety.

We are continuing these studies with lysergamides prepared from a variety of isomeric amines. Based on these early studies, it is anticipated that it may be possible to identify molecules that may serve as selective pharmacological probes for the various receptors that interact with LSD. Such selectivity might allow an assessment of the relative contribution of each receptor to the overall mechanism of action of LSD.

A continuing study of the lysergamides still presents a major difficulty, however, in that we have no human correlates for the in vitro and rat behavioral data. Because LSD is such a potent psychopharmacological agent, what would be the effect in man, for example, of the lysergamide of (*R*)-2-aminobutane? All of the assays obtained thus far seem to suggest that it would rival LSD in potency. Yet, based on the observed attenuation of human activity reported for compounds with only minor modifications of the amide moiety, one intuitively feels that the in vitro and animal behavioral data may be misleading. Therefore, for the present, these structure–activity studies will have most direct application to understanding the functional topography of the receptors to which the lysergamides bind.

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