THE IDENTIFICATION OF LSD-LIKE HALLUCINOGENS USING THE CHRONIC SPINAL DOG

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Summary

The effects of several indoleamines and phenethylamines were studied in the chronic spinal dog and compared with two standard drugs, LSD and amphetamine. In the nontolerant chronic spinal dog, their effects on a variety of physiologic and behavioral functions were measured in untreated dogs, as well as dogs treated with certain antagonists. The effects of the antagonists phenoxybenzamine and cyproheptadine on the various physiologic effects were studied for all drugs. For some indoleamines and phenethylamines, the effects of chlorpromazine and pimozide were also studied. Indoleamines and phenethylamines in the LSD-tolerant chronic spinal dog and their anorexigenic effects in the intact dog were also studied. The results of these studies indicate that psilocin, mescaline, dimethyltryptamine and tryptamine are LSD-like drugs. DOM, DOB, DMA, and TMA are predominantly LSD-like drugs but do have some amphetamine-like actions. PMA and PEA are predominantly amphetamine-like drugs with some LSD-like activity. MMDA and MDA have a more complicated pharmacology showing properties that resemble LSD and amphetamine, but they have other actions which are not shared by either LSD or amphetamine, which suggests they have yet other modes of action.

Introduction

The prediction of the abuse potentiality of chemicals is a difficult and uncertain endeavor. As we proceed in this operation, our goals in themselves are obscure, and our logic is frequently less than rigorous. One of the methods for minimizing the abuse of chemicals has been to decrease their availability by regulating their manufacture, sale and distribution. It is difficult to know how sucessful this type of endeavor is, but it has fallen far short of expectations. However, there is quite another value that stems from the regulation of drugs. It alerts physicians to their dangers and perhaps makes them prescribe

in a more constrained and responsible manner. This is one of the more effective preventive health measures in limiting certain types of drug abuse, as well as preventing the abuse of new drugs and chemotherapeutic agents.

The drugs with which this paper deals have at this time, for the most part, no well-established role in medicine; however, they have been abused on the street. Several of the substituted amphetamines were placed in Schedule I under the Comprehensive Drug Abuse Prevention and Control Act of 1970, partly because of the assumption that they were hallucinogens or represented a risk to public health, in addition to their history of abuse. Few well-controlled and validated studies have been done which assist in their pharmacologic classifications.

One method that has served in good stead in identifying morphine-like drugs has been the demonstration of pharmacologic equivalence. Several years ago our interests turned to the LSD-like hallucinogens and in the course of identifying their modes of action we began to use a variety of techniques employing the chronic spinal dog for their study. These techniques have evolved and now include: (1) a comparison of effects of the experimental drug on reflex activity, autonomic responsivity and behavior, (2) the interaction of the drug with certain prototypic antagonists, and (3) the existence of cross-tolerance in the LSD-tolerant dog as well as the ability of the drug to induce tolerance and confer cross-tolerance to LSD [1 - 3].

The purpose of this paper will be to summarize studies of a variety of LSD-like hallucinogens and substituted β-phenethylamines (Fig. 1) using these techniques.

Methods

Methods employed in this study have been previously described [1 - 3]. Female beagle-type chronic spinal dogs were used in all experiments. The spinal cord was transected at the T-10 or T-11 level. The hindlimb reflex of the chronic spinal dog was evoked by electrical stimulation and was recorded isotonically on an ink-writing kymograph. The occurrence of stepping movements was also recorded, as well as pupillary diameter and nictitating membrane width measured photographically, pulse rate, respiratory rate, rectal temperature, and the latency of the skin twitch reflex using a radiant heat method.

Dose-ranging studies were conducted for all drugs. Doses of drugs that were judged to be equieffective in facilitating the flexor reflex and producing the stepping reflex were selected. Subsequently, relative potencies were calculated for facilitation of the flexor reflex. These results are presented in Table 2. Drugs were infused to allow the rapid and economic generation of dose response curves. As can be seen, the doses actually employed were not disparate from the calculated potencies. The potency of amphetamine was determined twice using 2.0 and 3.2 mg/kg. Based on relative potencies (0.0055 and 0.0038), the two equivalent doses were 2.7 and 3.9 mg/kg, respectively.

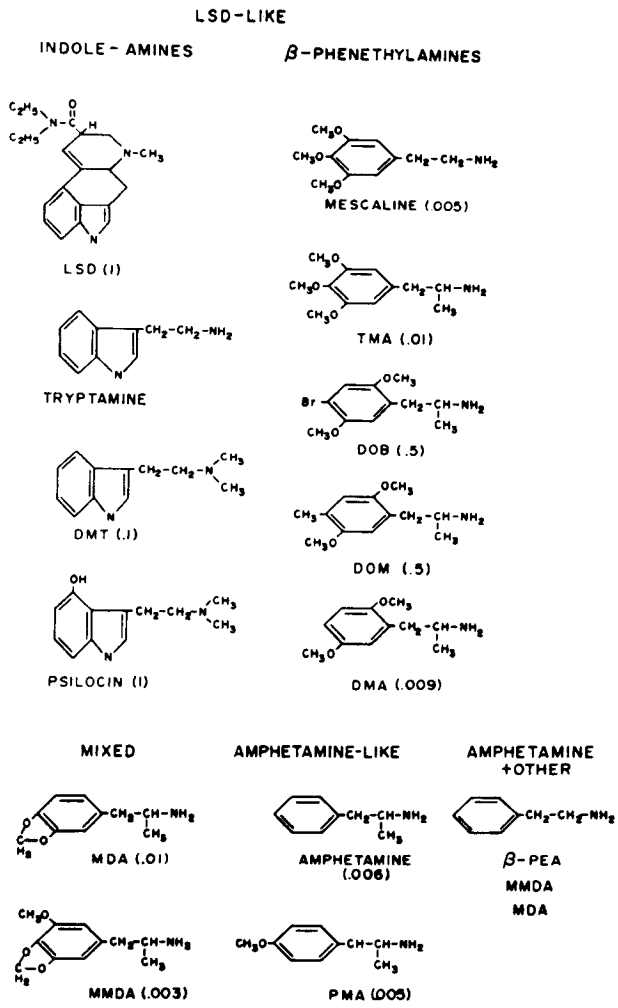

Fig. 1. Chemical structures. Figures in parentheses are the relative potencies of the agents facilitating the flexor reflex of the chronic spinal dog.

In addition, a check list was devised for recording a variety of types of behavior including unresponsiveness, sleeping, quietness, restlessness, struggling, vocalization of various sorts, and various patterns of head and eye movements. The stereotypic head movements included head raising, head tossing, head rotation, head rocking, tongue extrusion, nose licking, and gnawing. Eye movements were categorized as being darting, staring or tracking.

In an attempt to dissociate the various types of drugs, several antagonists were used: cyproheptadine (a selective tryptamine antagonist), phenoxybenzamine (a selective α-adrenergic antagonist), chlorpromazine and, in some studies, pimozide (a dopaminergic antagonist). The administration of the antagonists was completed 30 min before the beginning of the infusion of the

test compound, except for pimozide which was administered 60 min before the infusion.

Chronic spinal dogs were made tolerant to LSD which was administered by programmed injection through a chronic indwelling silastic catheter implanted in the jugular vein. Animals were made tolerant to 30 μg/kg per day of LSD over a 6-day period and were stabilized on this dose throughout the experiment. At weekly intervals, the LSD-tolerant dogs were challenged with the test doses.

In addition, the effects of a variety of drugs on food intake were studied in female and male beagle-type dogs. In general, several doses of amphetamine and the test drugs were administered and relative potencies of the appetite suppressant effects of the drugs were calculated [4].

In general, statistical calculations were done on areas under time–action curves for the various physiologic and behavioral parameters, and statistical significance was determined using independent or paired t tests. Many studies were designed as Latin squares and were analyzed as such.

Results

Table 1 compares the pharmacologic activities of two prototypic drugs, LSD and amphetamine, in the chronic spinal dog. Both LSD and amphetamine facilitate the flexor reflex; however, LSD produces a greater effect. LSD consistently evokes the stepping reflex in the chronic spinal dog while amphetamine does so only rarely and, for the most part, stepping movements seen in the presence of amphetamine are fragmentary. Both LSD and amphetamine dilate pupils; however, amphetamine produces a greater degree of mydriasis. Both drugs stimulate respiration. LSD most commonly produces tachycardia, while amphetamine usually produces bradycardia which is reflex in nature, secondary to its marked vasopressor effect. LSD has little effect on the nictitating membrane, while amphetamine consistently retracts it. Both drugs increase the latency of the skin twitch reflex; however, the effects of amphetamine are more reproducible. Both LSD and amphetamine increase body temperature. LSD over the dose levels studied has only a very modest effect on appetite, while amphetamine produces a dose-related decrease.

As can be seen from Table 2, LSD, psilocin, mescaline, tryptamine, DOB, DOM, DMA, and TMA produce patterns of effects similar to LSD. DOB and DOM have approximately the same potency as psilocin and are only a little less potent than LSD. Mescaline, DMA, TMA, MMDA, and MDA are approximately 1/100 as potent as LSD. Relative to their ability to facilitate spinal cord reflex activity, DOB, DOM, DMA, TMA, MMDA, MDA, and PMA are less effective than amphetamine in suppressing appetite. MMDA, MDA, and PEA produce a pharmacologic profile that shares features in common with LSD and amphetamine, whereas PMA has a pharmacologic profile almost identical with that of amphetamine.

Table 3 summarizes the ability of phenoxybenzamine (PBZ), cyproheptadine (CY), and chlorpromazine (CPZ) to antagonize certain effects of LSD-

TABLE 1

Comparison of effects of LSD and *d*-amphetamine in the chronic spinal dog

	LSD	Amphetamine
Flexor reflex	↑↑	↑
Stepping reflex	↑↑	FR
Pupils	↑	↑↑
Respiration	↑	↑
Pulse rate	↑	↓
Nictitating membrane	0	↓
Skin twitch latency	↑	↑↑
Temperature	↑	↑
Appetite	0	↓

FR, fragmentary stepping; ↑, increase; ↓, decrease; 0, no effect.

like hallucinogens. As can be seen, cyproheptadine and chlorpromazine are more effective in antagonizing the effects of LSD-like hallucinogens than phenoxybenzamine. Cyproheptadine antagonizes the effects of LSD on the flexor reflex, stepping reflex, pupils, and skin twitch reflex. The effects of LSD on respiration and pulse rate may be antagonized to a degree by cyproheptadine. Phenoxybenzamine antagonizes only the effects of LSD on pupils and possibly respiration and the skin twitch reflex. Chlorpromazine antagonizes the effects of LSD on spinal cord reflexes, pupils, and the skin twitch reflex. The effects of LSD on temperature in the chronic spinal dog are not antagonized by either cyproheptadine, phenoxybenzamine or chlorpromazine.

Table 4 summarizes the effects of the antagonists on amphetamine and congeners that have predominantly amphetamine-like effects. As can be seen, phenoxybenzamine and chlorpromazine antagonize many of the effects of amphetamine, while cyproheptadine is ineffective. Phenoxybenzamine antagonizes the effects of amphetamine on the flexor reflex (partially), pupils, nictitating membrane, and temperature, whereas cyproheptadine does not. Chlorpromazine antagonizes the effects of amphetamine on the flexor reflex, pupils, nictitating membrane, and temperature. Pimozide antagonized the effects of amphetamine on pupils. Phenoxybenzamine, chlorpromazine and pimozide, but not cyproheptadine, produce some antagonism ($p < 0.1$) of the analgesic effects of amphetamine on the skin twitch reflex. As can be seen, PMA has a profile very similar to amphetamine, except that both phenoxybenzamine and cyproheptadine did antagonize its respiratory effects and phenoxybenzamine did not antagonize its analgesic effects. MDA's effects on pupils and temperature were antagonized by phenoxybenzamine, whereas its effects on spinal cord reflex activity, the nictitating membrane, and the skin twitch reflex were not. Cyproheptadine was ineffective in antagonizing the effects of MDA. In contrast to phenoxybenzamine and cyproheptadine, chlorpromazine was an effective antagonist of the effects of MDA. The effects

TABLE 2

The effects of single doses of several LSD-like hallucinogens and substituted β-phenethylamines on somatomotor reflexes, autonomic function and appetite in the chronic spinal and intact dog

	LSD	PSI	MES	DMT	T	DOM	DOB	DMA	TMA	MMDA	MDA	PEA	PMA	A
Flexor reflex	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Stepping reflex	+	+	+	+	+	+	+	+	+	+-FR	+	+	FR	FR
Pupils	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑↑	↑↑	↑↑	↑↑	↑↑
Respiration	↑	↑	↑	↑	↑	0	↑	↑	↑	↑	↑	↑	↑	↑
Pulse rate	↑	↑	↑	↑	↑	↑	↑	↑	0	0	0	↓	↓	↓
Nictitating membrane	0	0	0	↓		0	0	0	0	↓	↓	↓	0	↓
Skin twitch (latency)	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Temperature	↑	↑	↑	↑		↑	↑	↑	↑	↑	↑	↑	↑	↑
Appetite	0**	0**	0**			↓	↓	↓	↓	↓	↓		↓	↓
Doses (mg/kg - dog)	0.01-0.015	0.025-0.050	3.0-4.0	0.3 mg/kg/min	0.5 mg/kg/min	0.1	0.05	2.4	2.0	5.0	2.0-2.2	0.8 mg/kg/min	2.0	2.0-3.2
Dose equal to LSD (0.015 mg/kg)	0.015	0.015	3.3	0.15		0.03	0.03	1.7	1.4	4.7	1.4		2.8	2.7
Potency (dog)*	1	1.0 (0.6-1.7)	0.004 (0.0004-0.017)	0.1 (0.002-0.33)		0.5 (0.2-0.7)	0.5 (0.3-0.7)	0.009 (0.001-0.03)	0.01 (0.001-0.4)	0.003 (0.0006-0.01)	0.01 (0.001-0.4)		0.005 (0.000-0.033)	0.006 (0.0001-0.027)
Potency (man)	1	0.014	0.0003	0.003										

FR, fragmentary stepping; ↑, increase; ↓, decrease; ↑↑, marked increase; +, induces stepping reflex; 0, no effect; open spaces, no relevant data.

*Potencies are expressed in mg of LSD equivalent to 1 mg of drug. Relative potencies with 95% confidence limits were calculated using facilitation of the flexor reflex.

**Higher doses produce some anorexia.

LSD, lysergic acid diethylamide; PSI, psilocin; MES, mescaline; DMT, *N,N*-dimethyltryptamine; T, tryptamine; DOM, 4-methyl-2,5-dimethoxyamphetamine; DOB, 2,5-dimethoxy-4-bromo-amphetamine; TMA, 3,4,5-trimethoxyamphetamine; MMDA, 5-methoxy-3,4-methylenedioxyamphetamine; MDA, 3,4-methylenedioxyamphetamine; PEA, β-phenethylamine; PMA, *p*-methoxyamphetamine; A, amphetamine.

TABLE 3

The effects of antagonists on the actions of LSD-like hallucinogens in the chronic spinal dog

	PBZ	CY	CPZ	PBZ	CY	CPZ	PBZ	CY	CPZ	PBZ	CY
	LSD (10 and 15 mg/kg)			Psilocin (25 mg/kg)			Mescaline (3 mg/kg)			DMT (0.3 mg/kg/min)	
Flexor reflex	0	↓	↓	0	↓	↓	0	↓	↓	0	↓
Stepping reflex	0	↓	↓	0	↓	↓	0	↓	↓	0	↓
Pupils	↓	↓	↓	↓	↓	↓	↓	↓	↓	0	0
Respiration	↓-0	↓-0	↓-0	0	0	0	0	↓	0	0	↓
Pulse rate	0	↓-0	0	0	0	0				0	↓
Nictitating membrane										↓	0
Skin twitch	0-↓	↓	↓							0	↓
Temperature	0	0	0								

PBZ, phenoxybenzamine 1 and 4 mg/kg; CY, cyproheptadine 0.2 mg/kg; CPZ, chlorpromazine 5 mg/kg; ↓, decrease; 0, no effect; ↑, increase.

TABLE 4

The effects of antagonists on the actions of amphetamines and some of its congeners

	PBZ	CY	CPZ	PIM	PBZ	CY	PBZ	CY	CPZ	PBZ	CY	CPZ
	Amphetamine (2 mg/kg)				PMA (2.0 mg/kg)		MDA (2.2 mg/kg)			MMDA (5.0 mg/kg)		
Flexor reflex	↓	0	↓	0	↓	0	0	0	↓	0	↓	↓
Stepping reflex							0	0	↓			
Pupils	↓	0	↓	↓	↓	0	↓	0	↓	↓	0	↓
Respiration	0	0	↓	↓	↓	↓	↓	0	↓	↓	0	↓
Pulse rate	0	0	0	0	0	0						↑
Nictitating membrane	↓	0	↓	0	↓	0	0	0	0	0	0	↑
Skin twitch	↓-?	0	↓-?	↓-?	0	0	0	0	↓	↓	0	↓
Temperature	↓	0	↓	↓	↓	0	↓	0	↓	↓	0	↓

Abbreviations are the same as in Tables 2 and 3.

TABLE 6

Behavioral effects in the chronic spinal dog

	LSD	PSI	MES	DMT	T	DOM	DOB	DMA	TMA	MMDA	MDA	PEA	PMA	A
Arousal	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Restlessness	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Whining	+	+	+	+		+	+	0	+	+	+	0	+	0
Tracking or staring	+	+	+	+		+	+	+	+	+	+	0	+	0
Stereotypy	0	0	0	0		0	0	+	0	0	+	+	0	+
Eye movements	0	0	0	0		0	0	0	0	0	+	+	0	+

+, behavior commonly observed. 0, behavior rarely observed. Blanks, observations have not been made.
Abbreviations are the same as in Table 2.

TABLE 7

Tolerance and cross-tolerance in LSD-tolerant spinal dog

	LSD	PSI	MES	DMT	T	DOM	DOB	DMA	TMA	MMDA	MDA	PEA	PMA	A
Flexor reflex	+	+	+	0	+	+	+	+	+	+	+	0	0	0
Stepping reflex	+	+	+	+	+	+	+	+	+		+	+		
Pupils	+	+	+	0	+	+	+	+	0	0	0	0	0	0
Respiration	+	+	+	+	+	+NS	+	+	+	0	0	0	0	0
Pulse rate	+	+	+	+	+NS	+	+	+	0			0	?	0
Temperature	+	+	0	0		+	+	+	+	0	+	0	0	0
Skin twitch	+	+	+	+		+	+	0	0	+	+	0	0	0
Behavior	+	+	+	+		+	+	+	+	0	+	0	0	0

+, tolerance or cross-tolerance in LSD-tolerant spinal dog. 0, no tolerance or cross-tolerance. Blanks, no observations.
NS, not statistically significant.
Abbreviations are the same as in Table 2.

of antagonists on the actions of MMDA were similar to MDA, except that cyproheptadine partially antagonized the facilitatory effect of MMDA on the flexor reflex. The effects of drugs presented in Table 5 most nearly resembled LSD in that cyproheptadine antagonized some, but not all, effects. Further, phenoxybenzamine antagonized some effects.

TABLE 5

The effects of antagonists on the actions of substituted amphetamines in the chronic spinal dog

	PBZ	CY	PBZ	CY	PBZ	CY	PBZ	CY
	DOM (0.1 mg/kg)		DOB (50 μg/kg)		DMA (2.4 mg/kg)		TMA (2.0 mg/kg)	
Flexor reflex	0	↓	0	↓	0	0	0	↓
Stepping reflex	0	↓	0	↓	0	↓	0	↓
Pupils			0	0	0	↓	↓	0
Respiration			↓	0	↓	↓	↓	↓
Pulse rate			0	0	0	↓	↓	0
Nictitating membrane			↑	0	0	0	0	0
Skin twitch			0	↓			0	0
Temperature			0	0	0	0	↓	0

Abbreviations are the same as in Tables 2 and 3.

Table 6 summarizes some of the behavioral effects of LSD, amphetamine, and other drugs. As can be seen, both LSD and amphetamine produce some arousal and restlessness. LSD produces whining, tracking and staring, while amphetamine produces stereotypic head movements and rapid eye movements. As can be seen, psilocin, mescaline, DMT, DOB, DOM, DMA, TMA, MMDA, and PMA produce a behavioral profile similar to LSD. MDA produces behavioral effects that share features of both the LSD and amphetamine profile, while PEA is amphetamine-like.

Table 7 summarizes the experiments that have been conducted in LSD-tolerant dogs. Tolerance develops to all of the effects of LSD that we have measured. Insofar as tryptamine has been studied, LSD-tolerant animals are cross-tolerant to its effects. Extensive cross-tolerance develops to the effects of psilocin, mescaline, DOM, DOB, and DMA. No cross-tolerance was seen to the effects of amphetamine or PMA. The degree of cross-tolerance to DMT, TMA, MMDA, MDA, and PEA is less than that seen with LSD.

Discussion

Table 8 summarizes the data that have been obtained from the four different types of experiments. LSD, psilocin, mescaline, and tryptamine seem to be quite similar to each other by all measures that have been made. DMT, DOM, DOB, DMA and TMA also appear to be predominantly LSD-like agents; however, all except DMT have some effects that resemble amphetamine.

Figure 1 categorizes the structures of the compounds studied. The actions of LSD are similar to those of tryptamine which can be regarded as the simplest and prototypic agonist. The aliphatic substitution on nitrogen increases the duration of action of tryptamine, probably by decreasing the rate degradation. The substitution of the hydroxyl group on the 4 position increases the potency but may decrease the agonistic action of tryptamine (possibly making it a partial agonist) or confer on it other pharmacologic properties. The substitution on the α-methyl group on mescaline increases its potency. The TMA pharmacologic profile is similar to mescaline except that it is a more effective anorexigenic. The substitution of the methoxy group in the para position of amphetamine may confer a liminal degree of LSD-like activity but does not otherwise alter its potency or pharmacologic profile. The presence of a methoxy group in the ortho position is not necessary for LSD-like activity. The presence of a meta-methoxy substitution may be necessary for LSD-like activity in the dog; however, it is not known yet whether it is sufficient. It appears to enhance the LSD-like activity of the 3 - 4 methylenedioxy congeners.

The methylenedioxy congeners have LSD- and amphetamine-like activity as well as other properties sharing some characteristics of β-PEA. Evidence has been obtained in the chronic spinal dog of a possible distinct phenethylaminergic receptor [7].

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TABLE 8

Summary of the effects of LSD-like hallucinogens and substituted β-phenethylamines

	Pharmacologic profile	Antagonist (flexor reflex)	Behavioral	Cross-tolerance	Predominant type of effects
LSD	LSD	LSD	LSD	LSD	LSD
PSI	LSD	LSD	LSD	LSD	LSD
MES	LSD	LSD	LSD	LSD	LSD
DMT	LSD	LSD	LSD	Partial	LSD
T	LSD	LSD	LSD	LSD	LSD
DOM	LSD + A	LSD	LSD	LSD	LSD + a
DOB	LSD + A	LSD	LSD	LSD	LSD + a
DMA	LSD + A	LSD	LSD + A	LSD	LSD + a
TMA	LSD + A	LSD	LSD	LSD	LSD + a
MMDA	LSD + A	0 + lsd	LSD	Partial	LSD + A + 0
MDA	LSD + A	0	LSD + A	Partial	A + LSD + 0
PEA	A	0	A	Partial	A + 0 + lsd
PMA	lsd + A	A	LSD	0	A + lsd
A	A	A	A	0	A

LSD, LSD-like. A, amphetamine-like. lsd, some LSD-like activity.
a, some amphetamine-like activity. 0, other modes of action or no cross-tolerance to LSD.

As can be seen from Table 2, the dose of DMT employed may have been excessively large. Further, the use of infusion data may underestimate the potency of a short-acting agent such as DMT. Thus, the failure to demonstrate a high degree of cross-tolerance in the LSD-tolerant dog may be because an overly large dose of DMT was employed. MMDA, MDA, and PMA also appear to have some LSD-like activity, but the case is not a clear-cut one, and they have other activities as well. Some of the actions of MDA appear to be amphetamine-like. PEA appears most like amphetamine; however, it may well have other types of activity including some LSD-like effects. PMA also appears to have predominantly amphetamine-like activity, but it too may have some LSD-like activity.

It is not at all certain that the terms "LSD-like" and "amphetamine-like" have sharp pharmacologic meanings in the sense that they have a single mode of action. LSD has at least three relevant clearly demonstrated pharmacologic modes of action. It is a tryptaminergic and serotonergic agonist as well as being a serotonin antagonist. Amphetamine also has several modes of action. It is a dopamine, norepinephrine and epinephrine releaser and has agonistic properties similar to β-phenethylamine, and perhaps other types of action. These pharmacologic classifications may have some relevance, at least as far as identifying potential for abuse.

Although MDA has a "street" reputation for being an hallucinogen [5], Griffiths *et al.* [6] found that it was strongly reinforcing and suppressed appetite in the baboon. These findings also suggest that MDA has amphetamine-like properties.