3681

Psychopharmacology of Hallucinogens

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THE MODE OF ACTION OF LSD-LIKE HALLUCINOGENS AND THEIR IDENTIFICATION

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This paper will describe a series of experiments that have been done to demonstrate that tryptamine is a neurotransmitter in the brain and that one of the primary modes of action of the LSD-like hallucinogens is their ability to function as tryptaminergic agonists. The second purpose of this paper will be to show how some of the methods developed in demonstrating that LSD and similar hallucinogens are tryptaminergic agonists have been applied in the identification of the mode of action of substituted amphetamines. Our interest in the LSD-like hallucinogens was stimulated by observations that in the chronic spinal dog LSD facilitated the hindlimb flexor reflex and evoked the stepping reflex, dilated pupils, increased respiratory and pulse rate, and elevated body temperature, a syndrome not unlike that seen in man with LSD-like hallucinogens, and that these effects were also produced by psilocin, mescaline and DOM. It was further observed that tryptamine produced a similar constellation of signs in the chronic spinal dog (Martin and Eades, 1970). It was also shown that the effects of LSD, mescaline, psilocin, DOM and tryptamine were selectively antagonized by cyproheptadine but not by phenoxybenzamine. Studies by Vaupel and Martin (1976) demonstrated that tryptamine facilitated the mono- and polysynaptic segmental reflexes of the acute spinal cat and this facilitatory action was antagonized by cyproheptadine but not by phenoxybenzamine. Isbell *et al.* (1956) used the facilitation of the patellar reflex in man as one of the indicators of LSD-like activity and showed that tolerance and cross tolerance developed to this effect. These data, as well as other data, strongly suggested that the LSD-like hallucinogens were mimicking the actions of tryptamine and that the actions of tryptamine did not involve noradrenergic processes. It was not until the series of experiments undertaken by Bell and Martin (1974) in which the effects of LSD and tryptamine were studied on the C-fiber reflex of the acute spinal cat that it was shown that the LSD-like hallucinogens were operating through a tryptaminergic and not a serotonergic mechanism. Bell and Martin (1974) first showed that LSD facilitated the C-fiber reflex as did tryptamine, and this facilitatory action was selectively antagonized by cyproheptadine. Bell *et al.* (1976) further showed that *l*-tryptophan facilitated the flexor reflex in the acute spinal cat and that the facilitatory effect was antagonized by cyproheptadine and alpha methyldopa which inhibits the decarboxylation of *l*-tryptophan to tryptamine but not by *p*-chlorophenylalanine which inhibited the conversion of *l*-tryptophan to 5-hydroxytryptophan.

One of the thrusts of the research endeavor was to determine if tryptamine was present in the brain. It was found that tryptamine was present in the brain of man, steer, dog, cat, guinea pig and rat (Martin *et al.*, 1972; Sloan *et al.*, 1975). Other investigators including Saavedra and Axelrod (1972), Snodgrass and Horn (1973) and Philips *et al.* (1974) have also demonstrated the presence of tryptamine in the brain of several species. Evidence has been obtained indicating that the brain releases tryptamine (Martin *et al.*, 1974).

The functional role of tryptamine in brain function has by no means been completely elucidated. On the basis of degeneration studies, it has been concluded that there are both ascending and descending tryptaminergic pathways in the spinal cord and that the descending pathway is undoubtedly involved in the facilitation of spinal cord reflexes, including the flexor reflex, the C-fiber reflex and in all probability, the patellar reflex. In the chronic spinal dog, concentrations of tryptamine above the level of transection are elevated, particularly in the spinal cord, medulla, cerebellum and mesencephalon, but unchanged below the level of transection.

The role of tryptaminergic processes in the modulation of the flexor reflex in the dog and the C-fiber reflex in the cat seems to have been unequivocally established. Mention has already been made of the fact that in the acute spinal cat, ℓ-tryptophan facilitates the C-fiber reflex through its conversion to tryptamine and that there are ascending and descending tryptaminergic spinal cord pathways. It has now been shown that ℓ-tryptophan facilitates the flexor and C-fiber reflexes in the acute but not the chronic spinal dog and cat (Martin *et al.*, 1976; J. A. Bell, unpublished observations) indicating that the descending tryptaminergic pathways degenerate following transection of the spinal cord. Data would also suggest that tryptaminergic processes may also be involved in the modulation of respiration, pupillary diameter, body temperature and probably pulse rate and blood pressure.

Of course, the most interesting of the effects of tryptamine are on mood and perceptual processes. It has been shown that tryptamine produces perceptual distortions as does LSD (Martin and Sloan, 1970). In addition, LSD produces feelings of well-being in small to moderate doses and hallucinations and anxiety reactions in higher doses. It is thus highly probable that there may be tryptaminergic processes that are responsible for feelings of well-being. Although much of the early work with LSD-like hallucinogens was conducted with the end of understanding distortions of perceptual processes, it may be that these drugs are equally important tools in understanding mood and feeling states, processes that are of great relevance to the antisocial personality.

The work thus far described was conducted primarily to elucidate one of the modes of action of LSD. The following describes studies conducted to understand the mode of action of substituted amphetamines.

METHODS

Some of the techniques that have been used to elucidate the modes of action of LSD and tryptamine in the dog have also been used to compare a variety of hallucinogens and abused substituted amphetamine derivatives. In

general, these methods employ female beagle type dogs whose spinal cords have been transected at the T-10 or T-11 level. A variety of observations are made systematically on these animals throughout the course of the experiment including recording of the flexor reflex, measurement of pupillary diameter, pulse and respiratory rate, the width of the nictitating membrane and body temperature. The flexor reflex is evoked either pneumatically with a toe squeezer or electrically using a stimulating electrode placed on the fourth toe. The skin twitch reflex is evoked using a radiant heat source. In addition to these physiologic observations, measurements of certain types of behavior are recorded using a check list. Particular behavioral changes seen with LSD and amphetamine in the chronic spinal dog include arousal, restlessness, whining, tracking or staring, and stereotypic head movements.

In addition, the effects of the antagonists cyproheptadine and phenoxybenzamine on these autonomic, somatomotor and behavioral measures are determined; the results of these types of experiments will not be included in this report.

Another experiment that is done involves making spinal dogs tolerant to LSD by administering it every 4 hours intravenously with a programmed 2 minute infusion. The dose level is gradually accelerated over a 6 day period from 3 μg/kg/day to 30 μg/kg/day. Prior to the chronic administration of LSD, standard doses of LSD and the test drugs are administered, usually using a latin square design with one week intervening between experiments. These same drugs are administered again when the animal is tolerant to LSD, and in one experiment with LSD and DMA, again 6 weeks after the termination of chronic LSD administration to show loss of tolerance. Tolerance was lost at this interval.

In addition, studies of the effects of drugs on the appetite of food deprived male and female beagle type dogs were also conducted. In these studies, graded doses of the drugs as well as a saline placebo are administered subcutaneously usually at weekly intervals and the relative potencies of the drugs in depressing appetite are calculated using standard bioassay techniques. Usually six or more chronic spinal dogs are used for each treatment condition and standard statistical procedures are employed to compare treatments.

RESULTS

Table 1 summarizes the pharmacologic changes that two prototypic drugs, LSD and amphetamine, as well as tryptamine, β-phenethylamine and several substituted amphetamines, produce in the chronic spinal dog. LSD facilitates the flexor reflex, evokes the stepping reflex, dilates pupils, increases respiratory and pulse rate, increases the latency of the skin twitch reflex, and rectal temperature. In the intact dog, small doses of LSD (1.25 - 2.5 μg/kg) produce a modest increase in appetite, while larger doses have no effect (5-20 μg/kg). Amphetamine also facilitates the flexor reflex but does not evoke continuous stepping. On occasions, fragmentary stepping is seen usually after the evocation of the flexor reflex. Amphetamine produces a greater degree of mydriasis than LSD and increases respiratory rate. Pulse rate is usually reduced, a consequence of a reflex bradycardia. Amphetamine causes a retraction of the nictitating membrane and an increase in latency

TABLE 1

Single Dose Studies

Somatomotor, Autonomic and Appetite

	LSD	T	DOB	DMA	TMA	MMDA	MDA	PEA	PMA	A
Flexor reflex	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Stepping reflex	+*	+	+	+	+	+FR	+	+	0	FR*
Pupils	↑*	↑	↑	↑	↑	↑↑	↑↑	↑↑	↑↑	↑↑*
Respiration	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Pulse rate	↑*	↑	↑	↑	0	0	0	↓	↓	↓*
Nictitating membrane	0*		0	0	0	↓	↓	↓	0	↓*
Skin twitch (latency)	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Temperature	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑
Appetite	0*		↓	↓	↓	↓	↓		↓	↓*

LSD	Lysergic acid diethylamide (10-15 μg/kg)
T	Tryptamine (0.5 mg/kg/min)
DOB	2,5-Dimethoxy-4-bromoamphetamine (0.05 mg/kg)
DMA	2,5-Dimethoxyamphetamine (2.4 mg/kg)
TMA	3,4,5-Trimethoxyamphetamine (2.0 mg/kg)
MMDA	5-Methoxy-3,4-methylenedioxyamphetamine (5.0 mg/kg)
MDA	3,4-Methylenedioxyamphetamine (2.0-2.2 mg/kg)
PEA	β-Phenethylamine (0.8 mg/kg/min)
PMA	p-Methoxy amphetamine (2.0 mg/kg)
A	*d*-Amphetamine (2.0-3.2 mg/kg)
FR	Fragmentary stepping

of the skin twitch reflex. It also increases body temperature and reduces appetite. Although LSD and amphetamine produce many similar effects there are several ways of qualitatively differentiating them that are indicated with an asterisk (*) in Table 1: (1) LSD evokes the stepping reflex while amphetamine does not, (2) LSD increases pulse rate while amphetamine decreases it, (3) amphetamine retracts the nictitating membrane while LSD does not, and (4) amphetamine suppresses appetite while LSD does not.

The effects of tryptamine are, aside from its short duration of action, virtually identical to LSD while the effects of PMA are very similar to amphetamine. PEA also resembles amphetamine except that it evokes the stepping reflex. Chlorpromazine, but neither cyproheptadine nor phenoxybenzamine, antagonizes this effect of PEA. In contrast, phenoxybenzamine antagonizes stepping evoked by methoxamine, an alpha adrenergic agonist, while cyproheptadine antagonizes tryptamine-evoked stepping. The stepping reflex appears to be modulated or evoked by three distinguishable receptor systems: noradrenergic, tryptaminergic and phenethylaminergic. Some of the effects of amphetamine may be mediated through phenethylaminergic systems. As can be seen from Table 1, the effects of DOB, DMA, TMA, MMDA, and MDA represent a mixture of LSD and amphetamine effects. DOB, DMA and TMA seem to have predominantly LSD-like effects, while MMDA and MDA are predominantly amphetamine-like. The former (DOB, etc.) clearly evoke the stepping reflex, produce modest mydriasis and do not cause retraction of the nictitating membrane; however, they do reduce appetite. MMDA and MDA, on the other hand, produce a marked mydriasis, retraction of the nictitating membrane and suppression of appetite. MMDA did not consistently evoke the stepping reflex.

Table 2 summarizes some of the behavioral changes produced by those drugs. Both LSD and amphetamine produce arousal and restlessness in the dog. Vocalization such as whining and occasionally barking as well as tracking or staring are seen in LSD- but not amphetamine-treated spinal dogs. Amphetamine produces stereotypic head raising and dropping movements; whereas, LSD does not. DOB, TMA, MMDA and PMA produce behavioral changes that resemble LSD while PEA's effects resemble amphetamine. DMA and MDA produce changes resembling both LSD and amphetamine.

TABLE 2

Single Doses-- Behavioral Effects

	LSD	T	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	+

Table 3 presents the results of studies conducted in the LSD tolerant dog. Tryptamine, on the basis of the variables investigated, appears to resemble LSD. Cross tolerance was also seen with DOB on all variables. Cross tolerance to all of the effects of DMA except prolongation of the latency of the skin twitch reflex was seen. The LSD tolerant spinal dog did not exhibit cross tolerance to amphetamine or PMA. Some cross tolerance was seen to the effects of PEA on the stepping reflex and pulse rate but not with regard to the other variables studied. Cross tolerance was seen to some but not all effects of TMA, MMDA and MDA but no systematic pattern was evident.

TABLE 3

Tolerance to LSD and Cross Tolerance

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

Data acquired using the antagonists cyproheptadine, phenoxybenzamine, and chlorpromazine have not been completely analyzed.

DISCUSSION

The modes of action of both LSD-like hallucinogens and amphetamine-related drugs are complex. LSD has been shown to have both tryptaminergic and serotonergic actions, and the relative selectivity of these neurotransmitters seems to vary between functional systems in the brain and among species. The fact that amphetamine acts through noradrenergic, adrenergic and dopaminergic mechanisms is well-established, and there is increasing evidence that phenethylaminergic mechanisms may play a role in some of its actions. It is for this reason that the terms LSD-like and amphetamine-like may not be appropriate and useful terms from the standpoint of pharmacologic classification or with regard to mode or site of action. However, they do have a rough meaning with regard to scheduling of compounds under the Comprehensive Drug Abuse Prevention and Control Act, and it is for this reason as well as convenience that these terms will be employed in this discussion.

It is quite clear that LSD and amphetamine can be distinguished in the chronic spinal dog on the basis of their effects on autonomic and somatomotor

systems and reflexes, appetite and behavior as well as using direct and cross tolerance studies. The salient features of the actions of LSD that make significant contributions to its abuse potentiality are its euphorigenic and hallucinatory activity neither of which can be measured directly in animals. It is possible that tracking and staring may be related to the hallucinatory actions of LSD. All of the agents studied except amphetamine and PEA produced tracking and/or staring. However, on the basis of studies in man n (Isbell *et al.*, 1956) tolerance develops *pari passu* to the subjective, psychotomimetic and autonomic effects as well as facilitation of the patellar reflex of LSD-like hallucinogens, suggesting that these effects are the consequence of a common mode of action. Further, most of the effects of small and hallucinogenic doses of LSD can be mimicked by tryptamine. Other facts that extend the analogous relationship between LSD and tryptamine are the demonstration of hyperresponsivity of the flexor reflex of the chronic spinal dog and rat to both LSD and tryptamine (Nozaki *et al.*, in prep., Martin *et al*, 1976) and the demonstration that the actions of LSD and tryptamine are also antagonized selectively by cyproheptadine in the spinal rat and dog.

For these reasons, the methods employed in these studies probably do measure the actions of LSD-like hallucinogens. The three substituted amphetamines that most closely resemble LSD are DOB, TMA and DMA. TMA and DMA in addition to their LSD-like actions have properties in common with amphetamine. Although PMA produces some behavioral changes which resemble LSD, other aspects of its pharmacologic profile are most similar to amphetamine. Further, LSD tolerant chronic spinal dogs were not cross tolerant to PMA. PEA is clearly not LSD-like; however, it shares many pharmacologic actions in common with amphetamine. It is also known to release catecholamines. Since it is possible that PEA may be a neurotransmitter as well as being an amphetamine-like drug, it is possible that the pharmacologic and physiologic actions of PEA may be different. MMDA and MDA, although having some actions of both LSD and amphetamine, do not particularly favor either of the prototypic drugs. It is possible that most of their pharmacologic actions can be explained by assuming that they are strong agonists of both LSD and amphetamine type. Whether they have other modes of actions cannot be decided at this time.

In conclusion, data obtained in the chronic spinal dog would indicate that DMA, DOB, TMA, MDA and MMDA have LSD-like activity. It is not clear, however, that PMA is an LSD-like agonist for its actions are most similar to amphetamine.

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