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The Action of Tryptamine on the Dog Spinal Cord and its Relationship to the Agonistic Actions of LSD-Like Psychotogens*

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Abstract. In chronic spinal dogs, LSD, mescaline, psilocin, 2,5-dimethoxy-4-methylamphetamine, methysergide and tryptamine facilitate the flexor reflex evoked by tetanic electrical stimulation of the toe and induce the stepping reflex. These effects are antagonized by chlorpromazine and cyproheptadine, but not by phenoxybenzamine. 5-Hydroxytryptophan and serotonin also facilitate the flexor reflex and evoke the stepping reflex, but these effects are not antagonized by cyproheptadine. These findings suggest that the mode of action of several LSD-like psychotogens is similar to that of tryptamine and is different from that of serotonin or 5-hydroxytryptophan.

Key-Words: Tryptamine — LSD — Psychotogens — Chlorpromazine — Spinal Cord.

Introduction

A previous study has shown that methoxamine, amphetamine and physostigmine enhance the flexor reflex and evoke the stepping reflex (Martin and Eades, 1967), which are signs of the morphine abstinence syndrome (Wikler, 1948). It was concluded that there were both adrenergic and cholinergic facilitatory influences that modulated the flexor reflex and were in part responsible for evoking the stepping reflex. Further, adrenergic processes were not involved in spinal cord signs of abstinence, and although there was a cholinergic component, its role was of only minor importance. Finally, there were unidentified changes responsible for the facilitatory influences of the morphine abstinence syndrome.

The present studies were concerned with the effect of several serotonin precursors, as well as serotonin antagonists and related psychotogens, on the flexor and stepping reflexes, pulse rate, respiratory rate and pupillary

* A preliminary report of these data was presented at the fall meeting of the American Society for Pharmacology and Experimental Therapeutics, 1968, and was published in The Pharmacologist 10, 196 (1968).

diameter of the chronic spinal dog. The initial purposes of the studies were (1) to further investigate the role of indoles on the flexor reflex and its modulation, and (2) to determine their relationship to spinal cord signs of abstinence in morphine dependent spinal dogs. However, the unexpected finding that the hallucinogenic serotonin antagonists LSD and methysergide facilitated the flexor reflex and evoked the stepping reflex changed the aim of the study to determining their mode of action on the spinal cord.

Methods

All of the studies herein reported were conducted in the chronic spinal dog (four of which were transected at the T-5 level and one at the T-10 level), using methods previously described (Martin and Eades, 1967). Briefly, the flexor reflex was evoked by stimulating electrically the second toe of the ipsilateral leg, and the reflex was recorded isotonically on an ink-writing kymograph. The intensity of the stimulus, which was a 1 sec train of 20 cps square waves with a pulse width of 1 msec, was adjusted so that the flexor reflex amplitude was approximately 50 mm at the beginning of the experiment. A series of 10 trains of stimuli, each evoking a flexor response, was administered at 10 sec intervals, and the polarity of the square wave was reversed between the 5th and 6th trains. These series of stimuli were repeated at 5 min intervals throughout the experiment. Respiratory rate, pulse rate, pupillary diameter determined photographically, and relaxation of the nicitating membrane were measured periodically throughout the course of the experiment. Rectal temperature was measured at the beginning and end of the experiment.

Experiment 1. In this series of experiments, an antagonist (drug 1), either phenoxybenzamine (4 mg/kg), chlorpromazine (5 mg/kg) or cyproheptadine (0.2 mg/kg), was infused over a 20 min period. Thirty minutes after the infusion of the antagonist, a period sufficient to allow the blocking effects of the antagonist to become well established, several psychotogens (drug 2) were infused over a 40 min period: LSD, 15 mcg/kg; psilocin, 25 mcg/kg; mescaline, 3 mg/kg; and 2.5-dimethoxy-4-methylamphetamine (DOM), 100 mcg/kg. Observations were continued for at least 90 min after the infusion of drug 2. In these experiments, the mean amplitude of the last four groups of stimuli prior to the administration of drug 1 was determined in each experiment, and subsequent reflex amplitudes were expressed as percentages of this mean. Because the amplitude of the flexor reflex decreases across time (Martin and Eades, 1967), a saline control condition was included for both drug 1 and drug 2 to assess and correct for this decay. A cross-over design was used in which each animal received all treatment conditions. Animals were tested at intervals of 1 week or longer; the most frequent interval was 2 to 3

weeks. The effects of various antagonists on the actions of LSD, mescaline and psilocin were conducted as three independent blocks in which the treatment conditions were randomized for each animal. There was no evidence of change in the effectiveness of antagonists across blocks or across treatment conditions. A paired replicate analysis was used for all statistical comparisons (Snedecor, 1956). Preliminary dose ranging studies were conducted with the LSD-like agents and the antagonists. The criterion for the infusion rates of the psychotogens was to produce a time course for facilitation and a latency for onset of the stepping reflex that was similar to that obtained with methoxamine in previous studies (Martin and Eades, 1967). The doses of chlorpromazine and phenoxybenzamine were those previously employed in studies characterizing their antagonism to methoxamine and amphetamine (Martin and Eades, 1967, 1968). Dose ranging studies were done to obtain a dose of cyproheptadine that antagonized the facilitatory effect of LSD to a degree comparable to that of chlorpromazine (5 mg/kg).

Experiment 2. The procedures employed in the tryptamine experiments were somewhat different than those employed with the other agonists because of its short duration of action. A tryptamine infusion was started immediately after the last predrug control group of stimuli and was continued for 12 min through 2 groups of stimuli and terminated approximately 2 min before the next group of stimuli was to be administered. Three infusions of tryptamine were administered at 40 min intervals prior to giving antagonists. Antagonists (phenoxybenzamine, 4 mg/kg; chlorpromazine, 5 mg/kg; cyproheptadine, 0.2 mg/kg) were given 40 min after the last of these tryptamine infusions. The antagonist was infused over a 20 min period. Thirty minutes after the antagonist was administered, tryptamine again was infused, and the infusion was repeated at 40 min intervals.

In addition, a variety of other experiments were done. To assess the central adrenergic blocking properties of cyproheptadine (0.2 mg/kg), it was infused over a 20 min period 30 min prior to the administration of methoxamine or amphetamine. Methoxamine was infused at a rate of 11 mcg/kg/min for 80 min. Amphetamine was infused at the rate of 0.1 mg/kg/min for 20 min. To assess the effect of cyproheptadine on methysergide facilitation of the flexor reflex, methysergide infusion (12.5 mcg/kg/min) was begun 30 min after administration of cyproheptadine and was continued for 20 min.

The following salts of the drugs were used: LSD tartrate, psilocin ascorbate, mescaline hydrochloride, 2.5-dimethoxy-4-methylamphetamine hydrochloride (DOM), tryptamine hydrochloride, chlorpromazine hydrochloride, cyproheptadine hydrochloride, phenoxybenzamine hydrochloride, methysergide bimaleate, tryptophan hydrochloride, methox-

amine, amphetamine, 5-hydroxytryptophane monohydrate, and 5-hydroxytryptamine creatine sulfate.

Table 1. *Effects of the antagonists phenoxybenzamine, chlorpromazine and cyproheptadine on the flexor reflex of the chronic spinal dog (n = 5)*

Comparison	Mean Difference
Saline-phenoxybenzamine	2
Saline-chlorpromazine	7
Saline-cyproheptadine	$10^{.05}$

Each value is the mean of the differences between the saline treatment condition and the antagonist treatment condition for 5 dogs. Superscript indicates the level of significance of the difference.

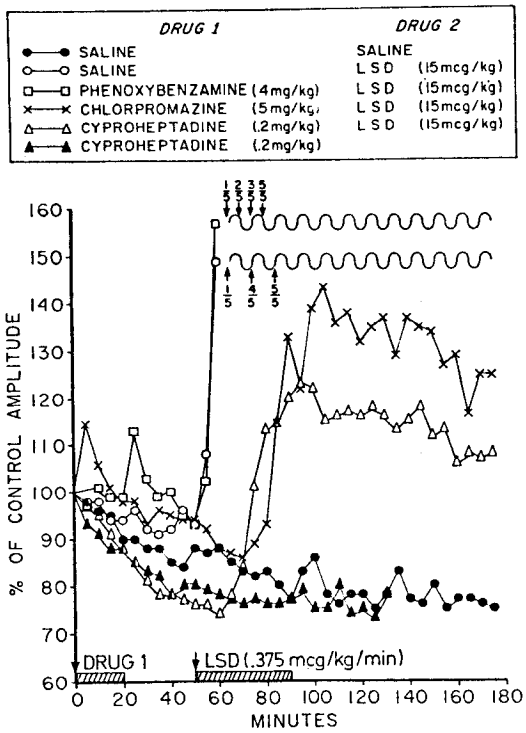

Fig. 1. The effects of phenoxybenzamine, chlorpromazine and cyproheptadine on the flexor reflex and its facilitation and production of stepping movements by LSD in the chronic spinal dog. The wavy lines indicate the emergence of spontaneous stepping movements, which in most instances precluded accurately determining the amplitude of the flexor reflex. The fractions above the wavy lines indicate the proportion of the dogs that exhibited the stepping reflex at these times. Each value represents the mean determinations made in 5 dogs

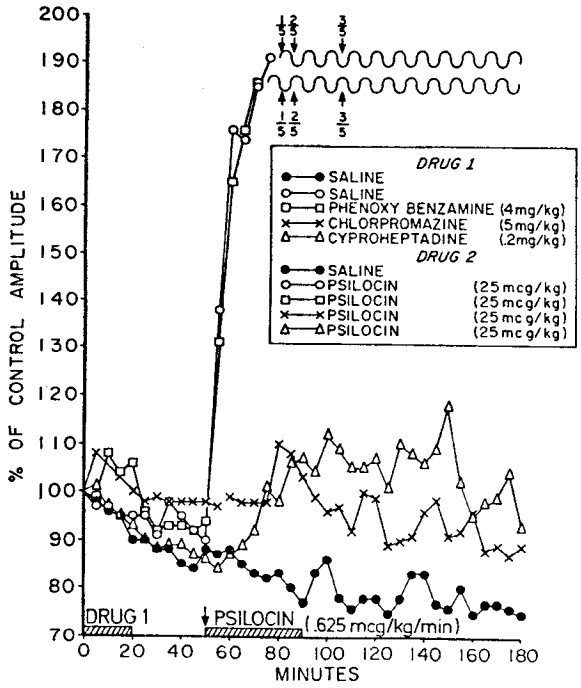

Fig. 2. The effects of phenoxybenzamine, chlorpromazine and cyproheptadine on the flexor reflex and its facilitation and evocation of the stepping reflex by psilocin in the chronic spinal dog. Symbols are the same as in Fig. 1. Each point represents the mean of determinations made in 5 dogs

Results

Effects of Phenoxybenzamine, Chlorpromazine and Cyproheptadine on the Flexor Reflex. Figs. 1, 2 and 3, as well as Table 1, summarize the effects of phenoxybenzamine, chlorpromazine and cyproheptadine on the flexor reflex. Both phenoxybenzamine and chlorpromazine produced a small initial transient enhancement of the flexor reflex; however, at the time the hallucinogens (drug 2) were administered, the reflex amplitude was not different from the amplitude seen under the saline control conditions at comparable times. Cyproheptadine produced a small but statistically significant depression of the flexor reflex.

Effects of LSD-Like Hallucinogens and Tryptamine on the Flexor Reflex. LSD was initially studied because of its serotonin antagonistic properties; however, unlike chlorpromazine and cyproheptadine which are also serotonin antagonists, it increased the amplitude of the flexor reflex and evoked the stepping reflex. These changes are illustrated in the upper

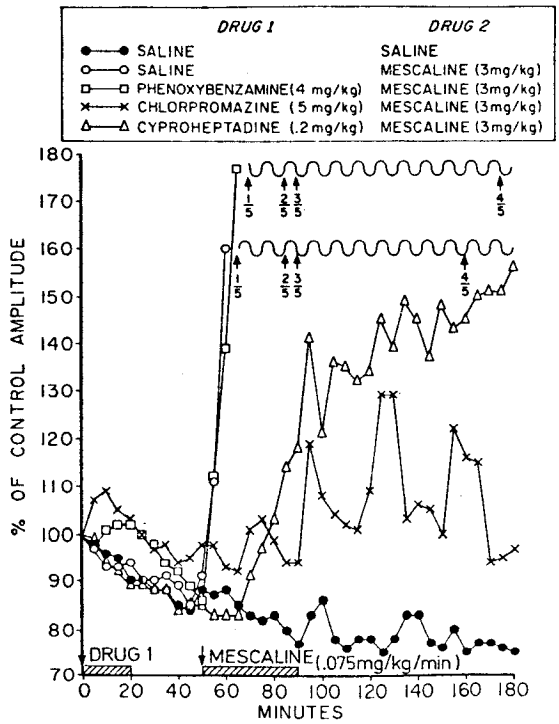

Fig. 3. The effects of phenoxybenzamine, chlorpromazine and cyproheptadine on the flexor reflex and its facilitation and evocation of the stepping reflex by mescaline. Symbols are the same as in Fig. 1. Each point represents the mean of determinations made in 5 dogs

row of Fig. 5 and summarized in Fig. 1. The effects of several other LSD-like hallucinogens, psilocin, mescaline and DOM, were also studied. These agents were found to also facilitate the flexor reflex and evoke the stepping reflex (Figs. 2, 3 and 4). The effect of tryptamine infusion on the flexor reflex is illustrated in Fig. 6 and summarized in Fig. 7. Tryptamine also facilitated the flexor reflex and evoked the stepping reflex. It differed from LSD, psilocin, mescaline and DOM in that its duration of action was much shorter. As can be seen from Figs. 6 and 7, the stepping reflex, when once established, persisted as long as tryptamine was infused but subsided within 1 min after the infusion was terminated. The amplitude of the flexor reflex returned to preinfusion level within 10 min after the end of the infusion.

Interaction Studies. As can be seen from Figs. 1, 2, 3 and 6, phenoxybenzamine, which will antagonize facilitation of the flexor reflex and the

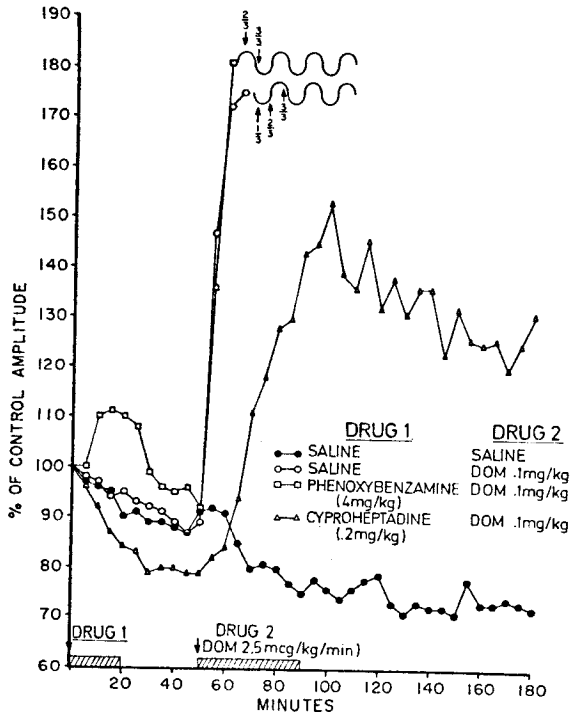

Fig. 4. The effects of phenoxybenzamine and cyproheptadine on the flexor reflex and its facilitation and evocation of the stepping reflex by DOM. Symbols are the same as in Fig. 1. Each point represents the mean of determinations made in 3 dogs

evocation of the stepping reflex by methoxamine and amphetamine (Martin and Eades, 1967), did not alter the reflex changes produced by LSD (Fig. 1), psilocin (Fig. 2), mescaline (Fig. 3), DOM (Fig. 4) or tryptamine (Fig. 7). On the other hand, chlorpromazine, which also antagonizes the effects of methoxamine and amphetamine on the flexor reflex (Martin and Eades, 1968), did antagonize the effects of LSD (Fig. 1), psilocin (Fig. 2), mescaline (Fig. 3), tryptamine (Fig. 6) and DOM by delaying the onset and decreasing the degree of facilitation and by preventing the emergence of the stepping reflex.

Cyproheptadine also antagonized the effects of LSD (Fig. 1), psilocin (Fig. 2), mescaline (Fig. 3), DOM (Fig. 4) and tryptamine (Fig. 7), also by delaying and decreasing the facilitatory effects and by preventing the emergence of the stepping reflex.

Table 2 presents the statistical analysis of the data from the interaction studies between LSD, psilocin and mescaline with phenoxybenz-

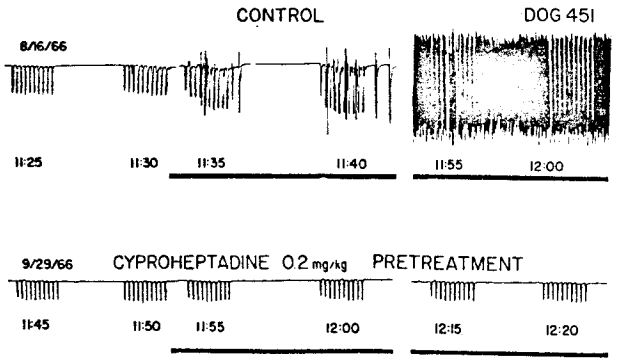

Fig. 5. The effects of LSD on the flexor reflex of the chronic spinal dog and its modification by cyproheptadine. The solid bar indicates the infusion of LSD (0.375 mcg/kg/min) which was administered continuously over a 40 min period. The figures below the tracing indicate the times at which the first of a train of toe stimuli were administered. The flexor reflex is recorded as a downward deflection. As can be seen in the upper panel, the amplitude of the flexor reflex was enhanced and spontaneous extension and flexion of the leg as well as fragmentary stepping movements became manifest after only a few min of infusion of LSD. After 20 min of infusion, the stepping reflex had become well developed and continuous, as can be seen in the right hand panel. Further, application of a stimulus to the toe inhibited the stepping reflex and evoked a greatly enhanced flexor reflex

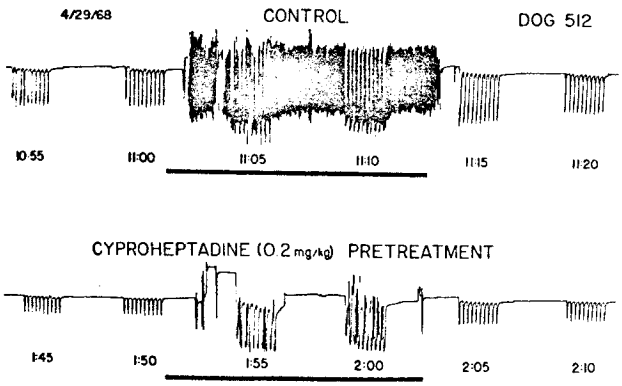

Fig. 6. The effects of tryptamine (0.5 mg/kg/min) on the flexor reflex of the chronic spinal dog and the antagonism of its effects by cyproheptadine. The solid bar indicates the period of tryptamine infusion. The flexor reflex is recorded as a downward deflection. The figures beneath the tracing indicate the time at which the first of a train of toe stimuli were administered. The stepping reflex became manifest after only a minute or two of tryptamine infusion, and subsided within a minute after the termination of the infusion. The flexor reflex was clearly facilitated at the time of the first stimulus train after the infusion was terminated

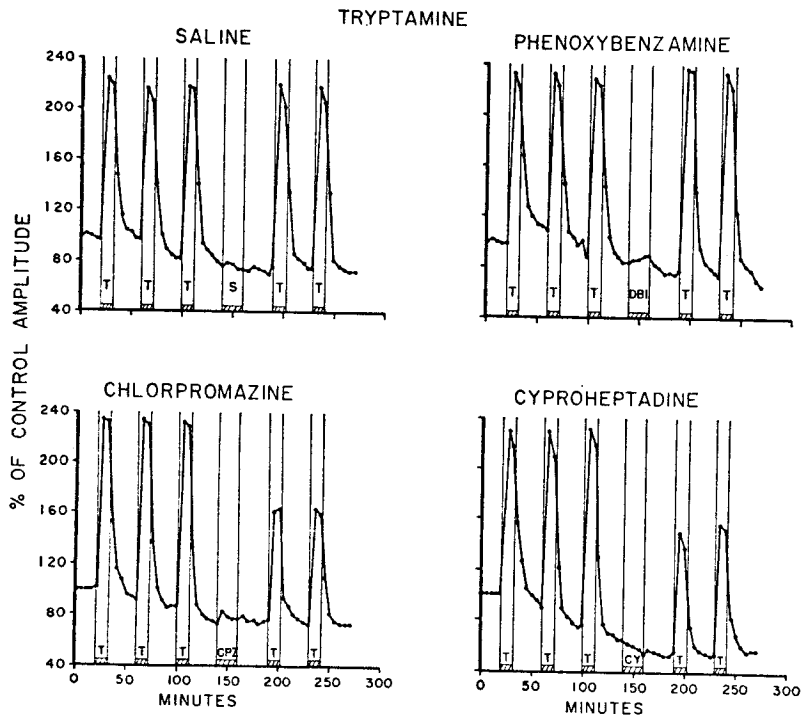

Fig. 7. The effects of saline, phenoxybenzamine, chlorpromazine and cyproheptadine on facilitation of the flexor reflex of the chronic spinal dog produced by tryptamine infusion. After three tryptamine infusions (*T*) administered at 40 min intervals, either saline (*S*), phenoxybenzamine (*DBI*), chlorpromazine (*CPZ*) or cyproheptadine (*Cy*) was administered over a period of 20 min. Thirty minutes after the antagonist was administered, 2 tryptamine infusions were repeated at 40 min intervals. Each point on each graph represents the mean of observations made in 5 dogs

amine, chlorpromazine and cyproheptadine. These data show that LSD, psilocin and mescaline significantly enhanced the reflex and that this facilitation is significantly diminished by chlorpromazine and cyproheptadine but not by phenoxybenzamine. The statistical analysis of the effects of these antagonists on tryptamine-induced facilitation is presented in Table 3. As can be seen, chlorpromazine and cyproheptadine also produced a significant antagonism of tryptamine facilitation; whereas, phenoxybenzamine was not significantly different from saline.

Several compounds related to tryptamine were studied. 5-OH-tryptophan was studied in 3 animals and infused at a rate of 0.085 mg/kg/min for 40 min (total dose 3.4 mg/kg). It produced facilitation of the flexor reflex and evoked the stepping reflex to a degree that was comparable

les:

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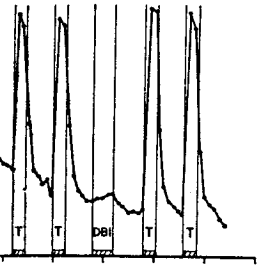

YPROHEPTADINE

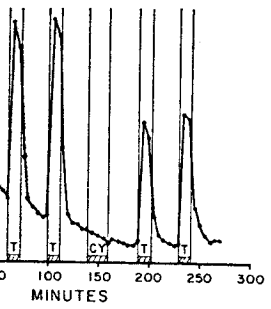

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Table 2. *The effects of phenoxybenzamine, chlorpromazine and cyproheptadine on the facilitatory action of LSD, psilocin and mescaline on the flexor reflex of the chronic spinal dog (n = 5)*

Comparison	Drug (D)		
	LSD	Psilocin	Mescaline
D-saline	$60^{.01}$	$104^{.01}$	$72^{.01}$
Phenoxybenzamine (Pa)			
(D + Pa)-saline	$69^{.01}$	$104^{.01}$	$52^{.05}$
D − (D + Pa)	5	− 3	20
Chlorpromazine (CPZ)			
(D + CPZ)-saline	0	$15^{.05}$	6
D − (D + CPZ)	$61^{.01}$	$88^{.05}$	$67^{.05}$
Cyproheptadine (Cy)			
(D + Cy)-saline	14	10	5
D − (D + Cy)	$74^{.01}$	$94^{.01}$	$77^{.01}$

Superscripts indicate the level of significance of the differences.

Table 3. *The effect of phenoxybenzamine, chlorpromazine and cyproheptadine on tryptamine facilitation of the flexor reflex of the chronic spinal dog (n = 5)*

Comparison	Mean
Saline	32
Phenoxybenzamine	28
Chlorpromazine	$-49^{.02}$
Cyproheptadine	$-40^{.05}$

Each value is the mean of the differences between the mean effect of tryptamine before and after treatment with saline or an antagonist. Superscript indicates level of significance of the difference.

to that seen with LSD (15 mcg/kg) except that the duration of action was shorter. A cross-over study showed that the facilitation was not antagonized by cyproheptadine (0.2 mg/kg) or chlorpromazine sulfoxide (5 mg/kg) and was enhanced by atropine (0.2 mg/kg). Dose ranging studies showed that serotonin infused at a rate of 0.3 mg/kg/min produced a facilitation of the flexor reflex and evoked the stepping reflex to a degree comparable to that produced by 0.5 mg/kg/min of tryptamine. The effects of cyproheptadine (0.2 mg/kg) on serotonin facilitation was investigated in 3 dogs using a cross-over design. Cyproheptadine produced a modest enhancement of the facilitatory effect of serotonin; however, this change was not statistically significant. L-Tryptophan in dose levels up to 1000 mg/kg infused over a 60 min period did not enhance the flexor reflex. Further, tetrabenazine (20 mg/kg) was administered after L-trypto-

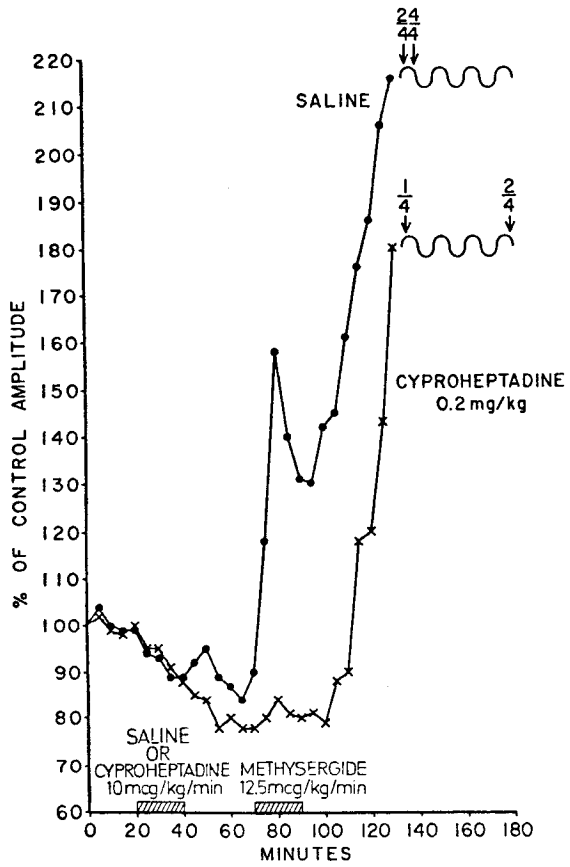

Fig. 8. The effects of methysergide on the flexor reflex and its antagonism by cyproheptadine. Symbols are the same as in Fig. 1. Each point represents the mean of determinations made in 4 animals

phan infusion, and the effect on the flexor reflex was not different from tetrabenazine alone.

Fig. 8 shows the facilitation of the flexor reflex and induction of the stepping reflex produced by methysergide (0.250 mg/kg). As can be seen, cyproheptadine does partially antagonize methysergide facilitation; however, the degree of antagonism is less than that seen against LSD, psilocin, mescaline or DOM.

In order to assess the central adrenergic blocking properties of cyproheptadine in comparison to chlorpromazine and phenoxybenzamine, the effects of cyproheptadine on facilitation of the flexor reflex and evocation of the stepping reflex by methoxamine and amphetamine were

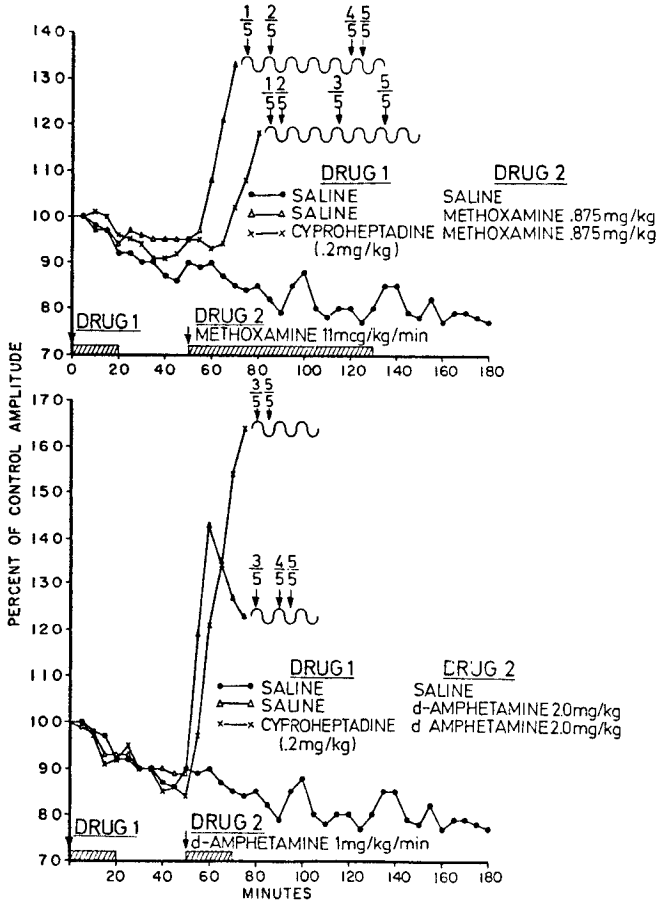

Fig. 9. The effects of cyproheptadine on facilitation of the flexor reflex and evocation of the stepping reflex by methoxamine and D-amphetamine. Symbols are the same as in Fig. 1. Each value represents the mean of determinations made in 5 animals

studied. Cyproheptadine, which was as effective as chlorpromazine in antagonizing the facilitatory actions of LSD, psilocin, mescaline and DOM, was much less effective in antagonizing methoxamine-induced facilitation than chlorpromazine (Fig. 9) and not only failed to antagonize the facilitatory effects of amphetamine but enhanced them (Fig. 9).

Table 4 summarizes the effects of tryptamine, LSD, psilocin and mescaline on respiratory rate, pulse rate and pupillary diameter. As can be seen, all agents increased respiratory rate, but the increase was statistically significant for only tryptamine. They also increased pulse rate

Table 4. *The effects of tryptamine, LSD, psilocin and mescaline on respiration, pulse rate and pupillary diameter*

	Respiratory rate (breaths/min)	Pulse rate (beats/min)	Pupillary Diameter (mm)
Tryptamine (0.5 mg/kg/min)	51 ± 8[a]	32 ± 5[a]	2.2 ± 0.2[a]
LSD (15 mcg/kg)	53 ± 22	42 ± 9[a]	1.5 ± 0.1[a]
Psilocin (25 mcg/kg)	43 ± 33	23 ± 7[a]	1.5 ± 0.3[a]
Mescaline (3 mg/kg)	37 ± 25	14 ± 6[a]	1.6 ± 0.3[a]

All values represent the mean difference between the treatment condition and the appropriate saline control and its standard error [a] ($p < 0.05$; $n = 5$).

Table 5. *The effects of the antagonists phenoxybenzamine (4 mg/kg), chlorpromazine (5 mg/kg) and cyproheptadine (0.2 mg/kg) on the autonomic actions of tryptamine, LSD, psilocin and mescaline*

	Respiratory rate (breaths/min)	Pulse rate (beats/min)	Pupillary Diameter (mm)
Tryptamine (0.5 mg/kg/min)			
DBI	17 ± 10	− 12 ± 7	0.1 ± 0.1
CPZ	36 ± 9[a]	3 ± 15	1.0 ± 0.2[a]
Cy	24 ± 11[a]	36 ± 45	1.0 ± 0.2[a]
LSD (15 mcg/kg)			
DBI	50 ± 22	10 ± 15	1.6 ± 0.6[a]
CPZ	55 ± 22	24 ± 12	3.0 ± 0.2[a]
Cy	40 ± 16	− 9 ± 14	0.8 ± 0.7
Psilocin (25 mcg/kg)			
DBI	23 ± 17	3 ± 6	1.0 ± 0.3[a]
CPZ	49 ± 38	16 ± 13	3.6 ± 0.9[a]
Cy	38 ± 33	8 ± 4	2.4 ± 1.0[a]
Mescaline (3 mg/kg)			
DBI	33 ± 24	3 ± 6	1.4 ± 0.3[a]
CPZ	31 ± 27	7 ± 5	3.6 ± 0.2[a]
Cy	12 ± 3[a]	5 ± 10	1.6 ± 0.4[a]

All values represent the mean difference between agonist treatment condition and the agonist + antagonist treatment condition and its standard error [a] ($p < 0.5$; $n = 5$).

and dilated pupils, and these changes were all statistically significant except for the effect of mescaline on pulse rate. Table 5 summarizes the effects of the antagonists phenoxybenzamine, chlorpromazine and cyproheptadine on the stimulatory actions of the psychotogens on these autonomic responses. In general, all of the agents produced some antagonism,

but this was statistically significant only for certain conditions, and no pattern emerged which facilitated the analysis of the mode of action of the antagonists.

Discussion

A variety of LSD-like hallucinogens including LSD, mescaline, psilocin and DOM have been found to facilitate the flexor reflex and evoke the stepping reflex in the chronic spinal dog. In addition the serotonin antagonist methysergide, which has been reported to produce hallucinations and feelings of unreality as side effects, also facilitates the flexor reflex and evokes stepping movements.

The facilitation of the flexor reflex by LSD and psilocin has been previously reported. Thus, Slater *et al.* (1955) found that LSD (0.1 mg) initially enhanced the facilitatory action of serotonin on the flexor reflex of the acute spinal cat. Subsequently, or after a second dose, LSD antagonized the effects of serotonin. Weidmann and Cerletti (1957, 1960) showed that LSD increased the flexor and crossed extensor reflexes and that psilocin and psilocybin enhanced the patellar reflex in the acute spinal cat. The mechanisms whereby these changes are produced have not been clarified by electrophysiological studies of segmental pathways. Geiger and Cervoni (1958) found that LSD in doses up to 1000 mcg/kg produced a relatively short-lasting enhancement of the monosynaptic reflex in the cat and depression of polysynaptic potentials. Krivoy (1961) found that LSD in dose levels of 5 and 10 mcg/kg enhanced the dorsal root IV potential in the decerebrate and spinal cat. Banna and Anderson (1968) found that LSD (300 mcg/kg) enhanced the monosynpatic spike and produced a slight depression of polysynaptic activity in the spinal cat. In contrast, methysergide (0.2 to 10 mg/kg) produced a depression of the monosynaptic reflex. Thus, there is not a good correlation between the facilitatory actions of these agents on the flexor and patellar reflexes and their effects on either the mono- or polysynaptic reflex; however, there is an excellent correlation between the facilitatory actions of these agents on the flexor and stepping reflexes and their hallucinogenic actions.

The observations of the effects of tryptamine and norepinephrine (Martin and Eades, 1967) on the flexor reflex of the chronic spinal dog are in partial agreement with the findings of Marley and Vane (1967) in the acute spinal cat, who reported that tryptamine but not norepinephrine facilitated the flexor reflex and that the facilitatory action of tryptamine was not antagonized by phenoxybenzamine. However, there must be differences between reflex responsiveness in the acute spinal cat and the chronic spinal dog since methysergide in a dose level of 0.42 mg/kg did not affect the flexor reflex amplitude in the acute spinal cat and antagonized the facilitatory action of tryptamine (Marley and Vane, 1967),

while it facilitated the flexor reflex in dose levels as low as 0.06 mg/kg, and in a dose level of 0.25 mg/kg evoked the stepping reflex in the chronic spinal dog. The facilitatory effect of methysergide, like that of LSD and tryptamine, was antagonized by cyproheptadine.

In attempting to characterize the mode of action of LSD, psilocin, mescaline and DOM, it is felt that the facilitatory action should be considered an agonistic action. The principical reason is that chlorpromazine which does not affect the flexor reflex in the chronic spinal dog (Martin and Eades, 1968) does antagonize the facilitatory actions of LSD, mescaline, psilocin, DOM and methysergide. The agonistic actions of these agents can be clearly distinguished from those of methoxamine and amphetamine which also facilitated the flexor reflex and evoked the stepping reflex in two ways: (1) Phenoxybenzamine was ineffective in antagonizing the effects of these agents; whereas, it was quite effective in antagonizing the facilitatory effects of methoxamine and amphetamine. (2) Cyproheptadine effectively antagonized the actions of these LSD-like hallucinogens, but produced only a liminal antagonism of methoxamine facilitation and actually enhanced facilitation produced by amphetamine. Tryptamine resembles the LSD-like psychotogens in three respects: (1) It too facilitates the flexor reflex and evokes the stepping reflex. (2) It produces a similar pattern of autonomic effects. (3) Its effects are antagonized by cyproheptadine and chlorpromazine but not by phenoxybenzamine. Tryptamine can be distinguished from 5-OH-tryptophan which also facilitates the flexor reflex and evokes the stepping reflex since its actions are not antagonized by cyproheptadine. Shibuya and Anderson (1968) found that 5-OH-tryptophan facilitated the monosynaptic reflex in the chronic spinal cat and that this facilitation could be antagonized by 1 or 2 mg/kg of methysergide. However, they could not facilitate the monosynaptic reflex with l-tryptophane in the chronic spinal cat, which is similar to observations on the flexor reflex made in the chronic spinal dog. Serotonin when infused at a rate of 0.3 mg/kg/min will also facilitate the flexor reflex and evoke the stepping reflex. The effects are not antagonized by cyproheptadine.

These findings are consistent with the hypothesis that LSD, psilocin, mescaline, DOM and methysergide have a similar type of agonistic activity and mode of action and that this agonistic activity in turn is similar to that of tryptamine. Further the facilitatory effect of tryptamine can be differentiated from that of serotonin and 5-OH-tryptophan by cyproheptadine. The action of tryptamine on spinal cord reflex activity is distinguishable from the LSD type of hallucinogen in that its duration of action is much shorter. This is to be expected since tryptamine probably has ready access to intracellular monoamine oxidases and is therefore rapidly metabolized (Handschumacher and Vane, 1967). It is therefore

proposed that the LSD-like hallucinogens owe at least some of their agonistic activity in the spinal cord to their agonistic activity at tryptamine receptors.

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