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STUDIES OF TRYPTAMINE AND LYSERGIC ACID DIETHYLAMIDE (LSD) ON CUTANEOUS C-FIBER AND POLYSYNAPTIC REFLEXES IN THE CAT

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ABSTRACT

BELL, J. A. AND W. R. MARTIN: Studies of tryptamine and lysergic acid diethylamide (LSD) on cutaneous C-fiber and polysynaptic reflexes in the cat. J. Pharmacol. Exp. Ther. **190:** 492–500, 1974.

The superficial peroneal nerve of the acute decerebrate spinal (L_1) cat was stimulated with a voltage and duration maximal for C-fiber activation. Short latency polysynaptic reflexes (PSR) and long latency C-fiber reflexes (CFR) were recorded from an ipsilateral S_1 ventral root. Both the PSR and the integral of the CFR were recorded on tape and averaged using a PDP-12 computer. Infusions of tryptamine at a rate of 0.5 mg/kg/min for 10 minutes increased the CFR to a mean of 308% (S.E.M. ± 37.3%) of control and the PSR to a mean of 125% (S.E.M. ± 5.7%) of control. The facilitation by tryptamine was antagonized by cyproheptadine 0.5 mg/kg. Lysergic acid diethylamide (LSD) infused at a rate of 0.375 μg/kg/min for 40 minutes produced facilitation of the CFR which reached a maximum of 297% of control (S.E.M. ± 43.7%) 60 minutes postinfusion. Facilitation of the PSR by LSD was significant only immediately postinfusion (110% control). The facilitation of the CFR by LSD was partially antagonized by cyproheptadine, 0.5 mg/kg. Methysergide, 0.4 mg/kg, had a biphasic action on the CFR, producing an initial depression followed by facilitation. Tryptamine infusion produced a significant depression of the CFR after methysergide pretreatment. LSD produced no further increase in the CFR after facilitation produced by methysergide. These studies demonstrated that tryptamine and LSD have a similar mode of action on spinal cord CFR, and that tryptamine and LSD produce a greater facilitation of the CFR than the short-latency PSR.

The mechanism of the hallucinogenic action of lysergic acid diethylamide (LSD) is unknown; however, two general hypotheses have been advanced. One hypothesis is that LSD produces its hallucinogenic action by being a competitive antagonist of 5-hydroxytryptamine at central serotonergic synapses (Gaddum, 1957; Woolley and Shaw, 1957). Another hypothesis is that LSD acts as an agonist at central nervous system serotonergic receptors to produce its hallucinogenic effects (Andén *et al.*, 1968; Aghajanian and Freedman, 1968). Martin and Eades (1970) demonstrated that LSD acts as an agonist in facilitating the flexor reflex in the chronic spinal dog and that the facilitatory actions of LSD, mescaline, psilocin, 2,5-dimethoxy-4-methylamphetamine and methysergide were similar to the actions of tryptamine. It was postu-

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lated that LSD and other hallucinogens exerted their actions by acting as agonists at tryptamine receptors. These findings take on added significance since it has been shown that tryptamine is present in the central nervous system of several species including man (Martin *et al.*, 1971, 1972; Saavedra and Axelrod, 1972, 1973; Snodgrass and Horn, 1973) and that it is released into perfusates of the brain (Sloan and Martin, 1973; Martin *et al.*, 1974). Therefore, it seems possible that tryptamine could be involved in the etiology of psychopathological states which can be mimicked in part by LSD.

There are several apparent discrepancies between the effects of LSD on somatomotor reflex activity and its effects on the segmental reflex of the acute spinal cat as well as differences between the effects of LSD and tryptamine on spinal reflex activity. Thus, large doses of LSD (100–300 μg/kg) inhibit the flexor and polysynaptic reflexes (Weidmann and Cerletti, 1957; Banna and Anderson, 1968), whereas, low doses of LSD (10–15 pg/kg) facilitate the flexor reflex (Weidmann and Cerletti, 1957; Little *et al.*, 1957; DiStefano and Leary, 1958). Tryptamine has been shown to facilitate the cat mono- and polysynaptic segmental reflex (Marley and Vane, 1967; Vaupel and Martin, 1971) and the flexor reflex of the cat (Marley and Vane, 1967) and dog (Martin and Eades, 1970). Insofar as a comparison can be made, the effects of low doses of LSD and tryptamine on spinal cord reflexes are similar. However, the difference between the inhibitory effect of large doses of LSD on the polysynaptic segmental reflex and the facilitatory effects of small doses of LSD and tryptamine on the flexor reflex needs resolution.

To help resolve this apparent paradox, the effect of low doses of LSD and tryptamine were studied on the C-fiber reflex (CFR). The flexor reflex differs from the polysynaptic segmental reflex (PSR) in that it is usually evoked by a persisting or tetanic stimulus and has a long-lasting afterdischarge. The CFR, which was described by Koll *et al.* (1961, 1963), exhibits the phenomena of persistence and afterdischarge and may be a better electrophysiologic counterpart of the flexor reflex than the polysynaptic segmental reflex. The purpose of this investigation was to determine and characterize the effects of tryptamine and LSD on long-latency, long-persisting potentials evoked by C-fiber stimulation. In addition the effects of LSD and tryptamine on short-latency polysynaptic potentials were also examined. To further investigate the possibility that methysergide may act both as a tryptaminergic agonist and a serotonergic antagonist and to gain additional insight into its hallucinogenic side effects (Hale and Reed, 1962), its actions on the CFR were also studied. Low doses of LSD are hallucinogens and enhance the patellar reflex in man (Isbell *et al.*, 1956) but have not been reported to affect segmental mono- or polysynaptic reflexes. LSD (5–10 μg/kg) does enhance the dorsal root potential in the decerebrate spinal cat (Krivoy, 1961). The demonstration of activity of low doses of LSD on spinal cord electrophysiologic phenomena may facilitate the neuropharmacologic analysis of its hallucinogenic activity.

Methods

Cats of either sex weighing between 1.6 and 4.0 kg were used in this study. The cats were initially anesthetized with ether. The trachea was cannulated, a polyethylene cannula connected to a Statham blood pressure transducer was placed in the common carotid artery and arterial blood pressure was registered on a Grass polygraph. The vagus nerve was sectioned bilaterally. Cats were kept under ether anesthesia until after they were mounted in a stereotaxic frame. Ether was then discontinued and the cats were decerebrated by intercollicular electrocoagulation (Martin and Eades, 1960). They were artifically respired with air throughout the remainder of the experiment. End-tidal CO_2 was measured with a Beckman medical gas analyzer (model LB-1) and was maintained between 3.5 and 4.5%. A polyethylene cannula was placed in the antecubital vein, and a slow continuous infusion of succinylcholine (0.5% solution) was given in order to provide better control of respiration as well as to prevent reflex movements during surgery and electrical recording. The spinal cord was then transected at the L_1 level. A laminectomy was performed, and the spinal cord was exposed from the L_6 to the S_2 segments. Skin flaps were elevated and the spinal cord was covered with warm mineral oil. The superficial peroneal nerve was exposed and carefully dissected free at the level of the ankle. Skin flaps were elevated, and the superficial peroneal nerve was covered with warm mineral oil. The L_7, S_1 and S_2 ventral roots were sectioned at the point where they exited the dura. The S_1 ventral root was dissected free to its origin from the ventral

spinal cord and placed on a bright silver bipolar hook electrode. Body temperature and mineral oil pool temperatures were maintained at 36.5°C by two Yellow Springs Instruments model 71A Thermistemp temperature controllers with appropriate rectal and mineral oil probes.

A single stimulus applied to the superficial peroneal nerve at intensities of 15 to 30 V and 2-msec duration (Grass S88 stimulator with stimulus isolation unit) was sufficient to elicit a reflex in the S_1 ventral root (see fig. 1) of a latency (200 msec) which corresponded to the distance of the stimulus point from the S_1 ventral root (approximately 200 mm) and the conduction velocity of C-fibers (approximately 1 m/sec). Koll *et al.* (1961, 1963) found that a characteristic property of the C-fiber reflex was that its discharge was markedly increased by the summation of several (3–10) afferent impulse volleys. The optimal interval between these volleys was 15° to 300 msec. In our studies it was found that a series of four stimuli (15 V, 2-msec duration) applied to the superficial peroneal nerve with an interpulse interval of 150 msec was sufficient to elicit a large C-fiber reflex. This stimulus was applied once every 10 seconds (fig. 1).

In initial experiments the sural nerve was stimulated at the level of the ankle. We found that although sural nerve stimulation produced a brisk short-latency polysynaptic potential, we were unable to evoke a long-latency C-fiber reflex, even when a series of stimuli were used. Our inability to evoke a C-fiber reflex recorded from a ventral root by sural nerve stimulation agrees with a similar finding by Mendell and Wall (1964).

The action potentials from the ventral root (short-latency polysynaptic potentials and long-latency C-fiber potentials) were amplified with a Grass P 511 AC preamplifier with high impedance probe and recorded on magnetic tape (Bell and Howell CPR-4010) for further analysis. The amplified action potentials were integrated (time constant 0.02 msec) with a Grass wide band a.c. preamplifier and integrator model 7P3B. The integral was also recorded on tape for analysis (see fig. 1). The area of the polysynaptic potentials (the first one in the series of four) was measured using a PDP-12 computer with the Digital Equipment Corporation Sigavg I program and in later experiments by the Culver Sigsys program. The area of the averaged polysynaptic reflex was determined with the Catacal (Digital Equipment Corporation, Maynard, Mass.) or Sigsys program. The C-fiber reflex was quantified by averaging with the PDP-12 (Sigavg I program or Culver program) 10 of the integrals of the long-latency action potentials. The area of values was expressed as a percentage of the predrug control.

All drugs were dissolved in physiologic saline and infused into the antecubital vein.

The statistical significance of drug-induced changes in reflexes was determined by utilizing group comparison analysis of variance and *t* tests. In cases where heterogenous variances were encountered, the nonparametric Wilcoxon and Mann-Whitney two sample test (Walpole and Myers, 1972) was utilized.

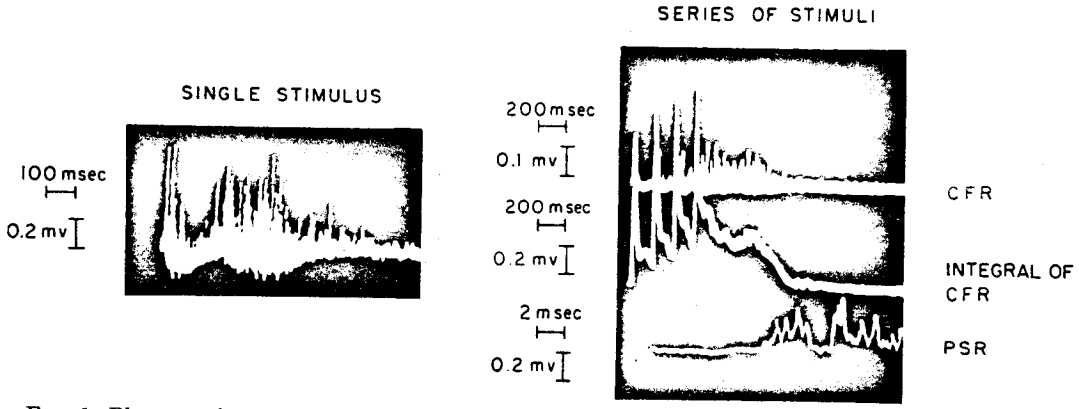

FIG. 1. Photographs of oscilloscope tracings of the CFR. In the left frame a single stimulus of 15 V, 2 msec duration was applied to the superficial peroneal nerve (SP), and the action potentials pictured were recorded from the first sacral ventral root. The long-latency firing which begins approximately 200 msec after the stimulus represents the CFR. In the right frame a series of 4 stimuli of 15 V, 2 msec duration, 150 msec apart were applied to the superficial peroneal nerve and the series of asynchronous discharges following the last high-amplitude deflection were designated as the CFR. The integral of the action potentials is shown on the second oscilloscope trace. The lower tracing shows the short-latency polysynaptic reflex following the first stimulus.

Results

Tryptamine when administered parenterally has a short duration of action probably because of its rapid degradation by monoamine oxidase. Therefore, in these experiments tryptamine was infused at a rate and dose which produced a stable pharmacologic effect. Tryptamine infused at a rate of 0.5 mg/kg/min in 14 cats caused a large facilitation of the C-fiber reflex (308% of control ± 37 S.E.M.) and a smaller facilitation of the polysynaptic reflex (125% ± 6) (fig. 2). The effect of the tryptamine infusion reached a peak 3 minutes after the beginning of the infusion and stayed at this level throughout the 10-minute infusion. After the infusion was ended, evoked responses returned to control levels within 10 minutes. Subsequent tryptamine infusions produced a facilitation equivalent to the first infusion (fig. 2). Also, the magnitude of the evoked responses when tryptamine was not being infused did not change significantly across time when compared to animals which received control saline infusions.

The effects of norepinephrine (13 μg/kg) infused intravenously on the CFR and PSR were studied in five cats. This dose of norepinephrine produced a vasopressor effect comparable to that produced by tryptamine (Vaupel and Martin, 1971). Norepinephrine infusion (13 μg/kg) for 5 minutes increased the CFR to 114% of control (± 8.4%) and decreased the PSR to 96% of control (± 11.6%). Neither of these effects was statistically significant when compared to a control saline infusion (group t test). In two experiments, three infusions of tryptamine were given intra-arterially directly to the spinal cord through the abdominal aorta (Holmstedt and Skoglund, 1953) in order to prevent tryptamine from stimulating peripheral sensory receptors (Armstrong *et al.*, 1953). Significant increases in the CFR were obtained with an infusion of 40 μg/kg/min of tryptamine for 2 minutes indicating that tryptamine did have a significant central effect. This method of intra-arterial infusion of tryptamine was found to be unsatisfactory for long-lasting experiments. Temporary occlusion of the ipsilateral arterial supply during tryptamine infusion by

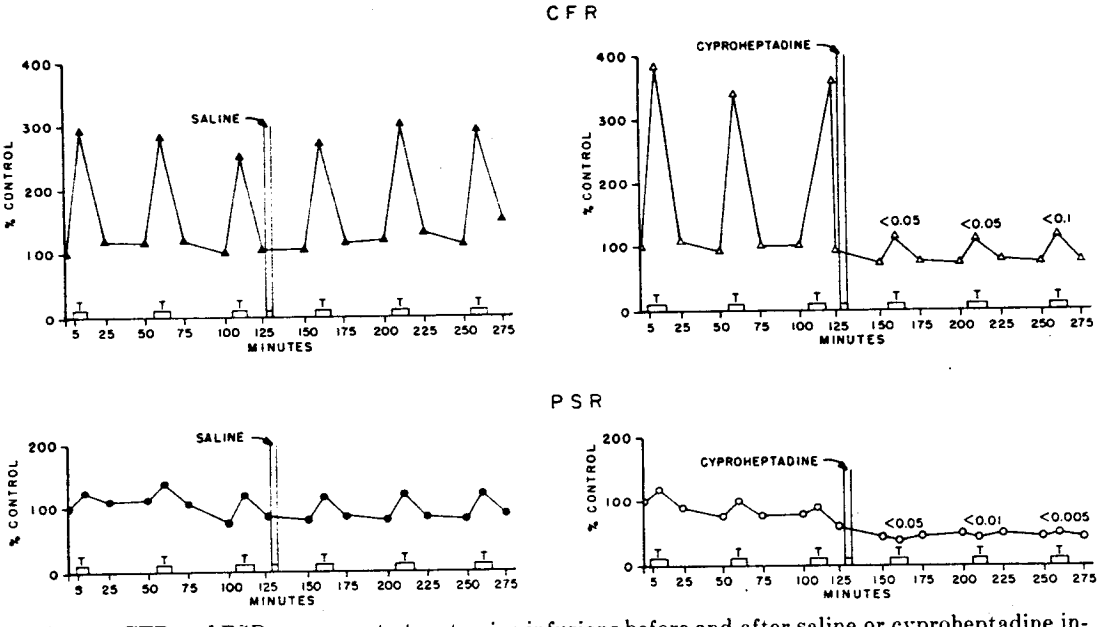

FIG. 2. CFR and PSR responses to tryptamine infusions before and after saline or cyproheptadine infusions. The saline groups represent the averages of four cats and the cyproheptadine groups represent the averages of six cats. The post-saline responses of the CFR and PSR to tryptamine were compared with the post-cyproheptadine responses to tryptamine. In the case of the CFR, the nonparametric group comparison of Wilcoxon and Mann-Whitney (Walpole and Myers, 1972) was used. The PSR saline and cyproheptadine groups were compared by a group t test (probability values are indicated on graph). T represents tryptamine infusion.

lifting a ligature on the internal and external iliac arteries caused a spastic vasoconstriction and permanent occlusion of these arteries with a consequent ischemic functional impairment of the peroneal nerve.

Cyproheptadine antagonism. Because the effect of tryptamine on the C-fiber reflex was variable (first infusion range was 158% of control to 572% of control) and because cyproheptadine antagonism was not complete, the design of the cyproheptadine experiment was such that each cat was given control infusions of tryptamine before cyproheptadine was administered. Thus, each animal served in part as its own control. Experiments were also done in other cats in which saline was substituted for cyproheptadine to control for possible changes in tryptamine's effect across time.

Figure 2 illustrates the effect of cyproheptadine and saline on the response of the C-fiber and polysynaptic reflexes to tryptamine infusions. Cyproheptadine produced a significant antagonism of the facilitatory actions of tryptamine on the C-fiber reflex when compared to the animals which received saline (Wilcoxon test). Cyproheptadine also antagonized the facilitatory effects of tryptamine on the polysynaptic reflex. Cyproheptadine (0.5 mg/kg) did not significantly depress the CFR or PSR 30 minutes after its administration when compared to the appropriate saline control (group t test).

Methysergide effect. The effects of methysergide (0.4 mg/kg) on the CFR were variable and consisted of an initial depression followed by facilitation. As can be seen in figure 3 (O——O), a 20-minute infusion of methysergide produced a significant depression of the CFR which was followed by a modest nonsignificant facilitation in this study ($n = 7$). When methysergide was administered more rapidly over a 5-minute period, the initial depression of the CFR was marked and significant in one experimental

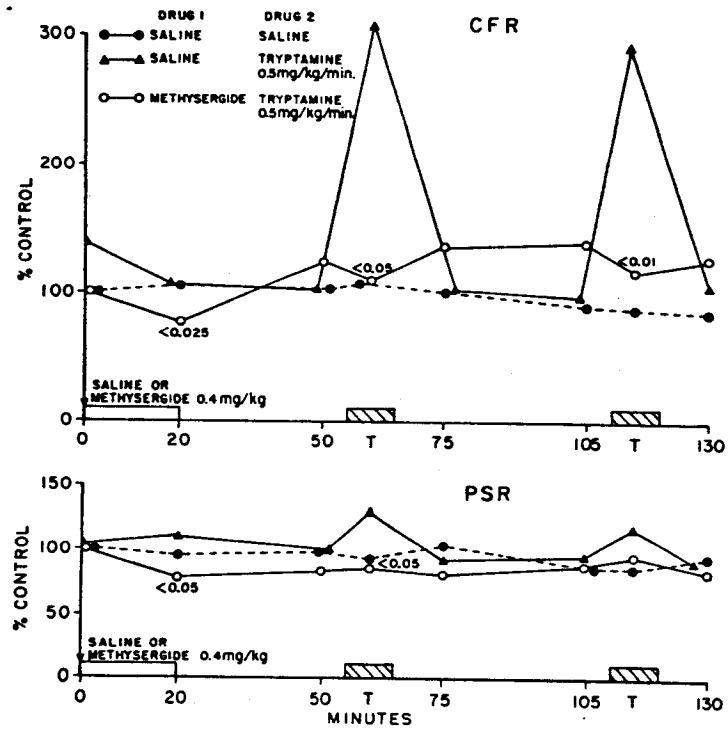

FIG. 3. The effect of methysergide on the responses of the CFR (upper graph) and the PSR (lower graph) to tryptamine infusions (T). Each point represents the average of seven experiments. On the CFR graph, the probability value immediately after the methysergide infusion indicates the significance of the suppression of the C-fiber reflex as compared to a saline control. The P values during tryptamine infusion indicate that a significant suppression of the CFR has occurred when compared to a control saline infusion. On the PSR graph, the first P value indicates significant suppression of the PSR by methysergide. The second P value during tryptamine infusion indicates significant antagonism of tryptamine facilitation. There was no significant reduction of the PSR during tryptamine infusion.

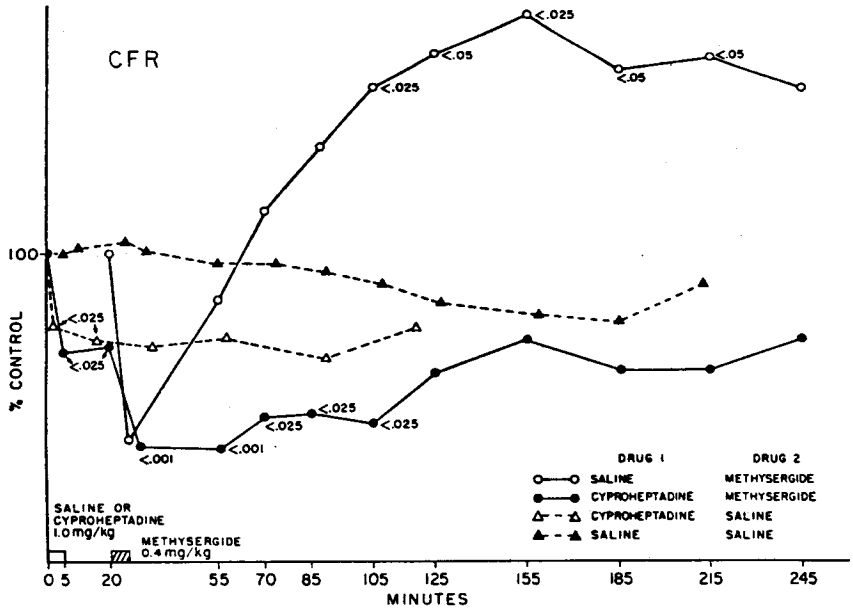

FIG. 4. The effect of cyproheptadine pretreatment on the facilitatory and inhibitory actions of methysergide. Cyproheptadine (1.0 mg/kg) in 10 cats (△- - -△ and ●——●) produced an initial significant ($P < 0.025$) depression of the C-fiber reflex. Administration of methysergide (0.4 mg/kg) after cyproheptadine (●——●) and in nonpretreated cats (○——○), also produced significant depression of the C-fiber reflex. Facilitation of the C-fiber reflex by methysergide (○——○) was blocked by cyproheptadine (●——●).

situation (fig. 4, ○——○) and slight and nonsignificant in another (fig. 6, ■——■). In both of these experiments, the facilitation produced by methysergide was marked and highly significant and appeared after 30 minutes (fig. 6, ■——■) and 90 minutes (fig. 6, ○——○). When the results of the three separate methysergide studies were pooled ($n = 17$), the initial depression was statistically significant.

In an attempt to determine the mode of the biphasic action of methysergide, five cats were pretreated with cyproheptadine (1.0 mg/kg) before methysergide (0.4 mg/kg) was administered. The results of these experiments are illustrated in figure 4. Cyproheptadine (●——●) caused an initial depression of the CFR. Subsequent methysergide administration caused a further depression of the CFR which was no greater than that produced by methysergide alone; however, cyproheptadine pretreatment completely antagonized methysergide's facilitation of the CFR. It is possible, however, that this antagonism was nonspecific because cyproheptadine (1 mg/kg) depressed the CFR.

In cats treated with methysergide, tryptamine infusion produced a significant decrease of the CFR (fig. 3). Tryptamine facilitation of the polysynaptic reflex was abolished 30 minutes after methysergide; however, unlike the C-fiber reflex, the polysynaptic reflex was not significantly suppressed by tryptamine. The second tryptamine infusion after methysergide facilitated the polysynaptic reflex, and this facilitation was not significantly different from the facilitation produced by tryptamine in cats which had not been pretreated with methysergide.

LSD. LSD was infused intravenously at a rate of 0.375 μg/kg/min over a 40-minute period (total dose 15 μg/kg). Midway through the LSD infusion, when a total dose of 7.5 μg/kg had been administered, the C-fiber reflex was significantly elevated to 180% of control value (fig. 5, ×——×). At the end of the infusion, the C-fiber reflex was further increased to 266% of control, and the polysynaptic reflex was significantly enhanced to 110% of control. For 2 hours after the LSD infusion, the C-fiber reflex remained significantly facilitated while the polysynatic reflex was not significantly different from control.

Cyproheptadine. Figure 5 illustrates the ef-

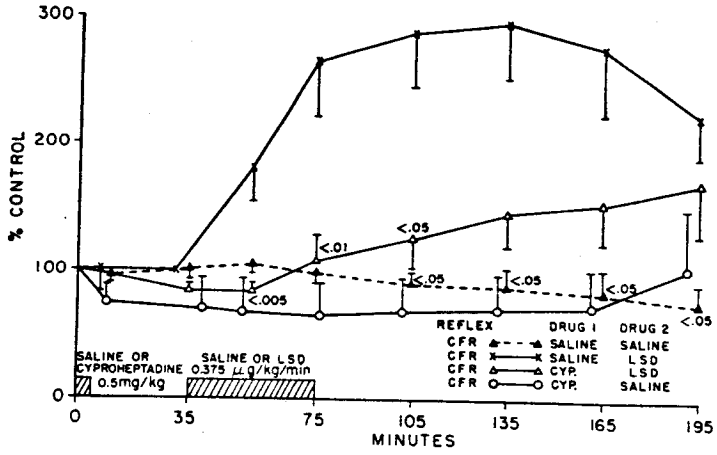

FIG. 5. The effect of cyproheptadine pretreatment on LSD-induced facilitation of the CFR. Each point is the average of five experiments. The P values on cyproheptadine-LSD points indicate the level of significance of antagonism of LSD's facilitatory effects. The P values on saline-saline points indicate the significance of the facilitatory action of LSD in cyprophetadine-pretreated cats.

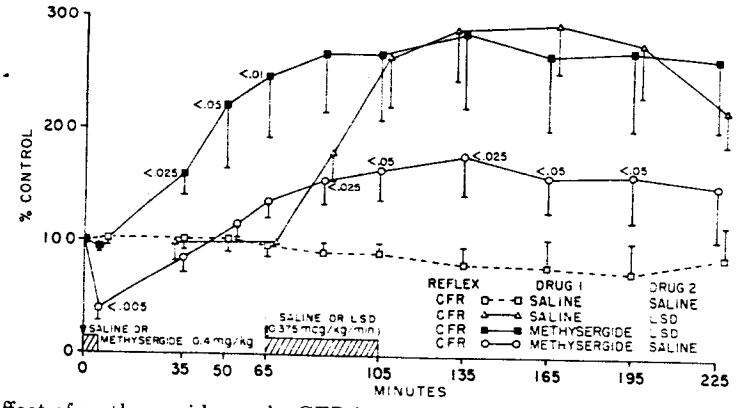

FIG. 6. The effect of methysergide on the CFR in a series of five experiments and the response of the CFR to the facilitatory effects of LSD after methysergide in another set of five experiments. The P values indicate the level of significance of methysergide's inhibitory and facilitatory effects as compared to saline control.

fect of cyproheptadine pretreatment (0.5 mg/kg) on LSD facilitation of the C-fiber reflex. Cyproheptadine completely suppressed LSD's facilitatory effect midway through and immediately following the LSD infusion; thereafter, LSD's facilitatory effect was decreased. Although cyproheptadine decreased the facilitatory effect of LSD, the facilitation was statistically significant from the 105th through the 195th minutes. Cyproheptadine tended to depress the CFR, but this depression was not statistically significant. Cyproheptadine pretreatment had no effect on the small and transient facilitation of the polysynaptic reflex produced by LSD.

Methysergide. The study of the effects of methysergide on LSD-induced facilitation of the C-fiber reflex was confounded by the fact that methysergide produced a marked facilitation of the C-fiber reflex as previously discussed (fig. 6). As seen in figure 6, LSD did not produce a significant increase in the C-fiber reflex after methysergide. Thus, either methysergide was blocking the LSD effect or the C-fiber reflex was already close to maximum facilitation by methysergide, and further facilitation by LSD was not possible.

Methysergide significantly antagonized the LSD facilitation of the PSR. Immediately after the methysergide infusion, the PSR was significantly suppressed and a significant suppres-

sion compared to the saline control group was also seen at 195 minutes.

Discussion

These findings demonstrated that both tryptamine and LSD facilitated the C-fiber reflex and the polysynaptic reflex, and that these effects are antagonized by cyproheptadine. These experiments show the similarity of the effects of tryptamine and LSD on the C-fiber reflex of the decerebrate low spinal cat and the flexor reflex of the chronic spinal dog (Martin and Eades, 1970). The short-latency polysynaptic potential was not markedly facilitated by tryptamine, and the effect of LSD on this potential was quite small and transient. The doses of LSD (7.5–15 μg/kg) which produce marked facilitation of the flexor reflex in the chronic spinal dog (Martin and Eades, 1970) and the C-fiber reflex in the acute decerebrate low spinal cat are much smaller than those used in previous studies of spinal segmental-pathways (Geiger and Cervoni, 1958; Banna and Anderson, 1968) and indicate that the C-fiber and flexor reflexes are responsive to the agonistic actions of tryptamine and LSD. Further, the fact that LSD and tryptamine have a similar potency in the acute spinal cat and the chronic spinal dog argues against the possibility that facilitation produced by tryptamine and LSD in the chronic spinal dog is due to denervation sensitivity. These data also suggest that the C-fiber reflex is more closely related pharmacologically to the flexor reflex of the chronic spinal animal than is the short-latency polysynaptic potential.

The site of the facilitatory actions of tryptamine and LSD was not conclusively demonstrated in this study; however, the preponderance of evidence indicates that the action of these drugs is directly on the central nervous system. Close arterial injection of small doses of tryptamine, which limited tryptamine's access to the spinal cord and the vertebral musculature, facilitated the C-fiber reflex, confirming the observation of Marley and Vane (1967) who showed that small doses of tryptamine administered intra-arterially to the spinal cord facilitated reflexly evoked muscle twitches.

It has been shown that tryptamine is 1/10 as potent as serotonin in activating pain receptors in the exposed base of a cantharidin blister (Armstrong *et al.*, 1953). Thus, tryptamine, although not a potent agent, can activate sensory afferents. It has beeen demonstrated that activation of sensory afferents can have both excitatory and inhibitory effects on spinal cord neurons (Hagbarth, 1953). Thus, the role of peripheral effects in tryptamine's excitatory action on the C-fiber reflex cannot be completely excluded. The action of LSD on cutaneous sensory receptors and visceral enteroreceptors is not clear, since to our knowledge no definitive study has been done on the action of LSD on these receptors.

Methysergide showed a biphasic action on the C-fiber reflex in our experiments. The reflex was initially depressed and then showed a gradual but marked increase over a 2- to 3-hour time course. Pretreatment of the cats with cyproheptadine did not affect the depressant effects of methysergide but did block its facilitatory effects. This finding suggests that methysergide, tryptamine and LSD may have a similar mode of action in facilitating the CFR. The polysynaptic reflex was initially significantly depressed by methysergide and remained depressed throughout the course of the experiment, although the later depression was not statistically significant. These findings show both differences and similarities to the experiments with methysergide on spinal reflexes by Martin and Eades (1970) and Banna and Anderson (1968). Martin and Eades (1970) saw no suppression of the flexor reflex in the chronic spinal dog with methysergide but an immediate and marked facilitation. Banna and Anderson (1968) demonstrated suppression but no facilitation of the segmental monosynaptic and polysynaptic reflexes with methysergide.

Methysergide could not be assessed as a tryptamine antagonist in the chronic spinal dog because of its agonistic properties, which produced continuous stepping movements (Martin and Eades, 1970). In our experiments, methysergide reversed tryptamine's action, changing its facilitatory effects to inhibitory. This suggests the possibility that tryptamine could be acting on two different types of receptors in the central nervous system.

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