Psychopharmacologia (Berl.) 27, 93—98 (1972)

Original Investigations

Cross Tolerance to Tryptamine in the LSD Tolerant Dog

W. R. Martin and C. G. Eades

National Institute of Mental Health, Addiction Research Center, Lexington, Kentucky, U.S.A.

Received May 8, 1972

Abstract. Infusions of LSD or tryptamine increase heart rate, respiratory rate and pupillary diameter, facilitate the flexor reflex and evoke the stepping reflex in the chronic spinal dog. When LSD is administered twice daily in a dose of 15 mcg/kg subcutaneously, tolerance develops to these effects of LSD and cross tolerance to these effects of tryptamine. These observations support the concept that tryptamine and LSD have a common mode of action and the hypothesis that LSD exerts some of its pharmacologic effects by acting as an agonist at tryptamine receptors.

Key words: Tryptamine—LSD—Tolerance—Cross Tolerance—Schizophrenia—Hallucinations.

Tryptamine has been shown to share many pharmacologic properties in common with LSD and LSD-like hallucinogens in the spinal dog (Martin and Eades, 1970) and in man (Martin and Sloan, 1970), and it has been suggested that LSD exerts its pharmacologic effects by acting as an agonist at tryptamine receptors. It has been further demonstrated that tryptamine is present in the brain of the steer, dog and man (Martin, Sloan and Christian, 1971; Martin, Sloan, Christian and Clements, 1972), and it has been suggested that certain disorders in perception and thinking may be a consequence of pathologic utilization of tryptamine (Martin *et al.*, 1972). The present experiments were conducted to provide further evidence that tryptamine and LSD do share a common mode of action, using the phenomena of tolerance and cross tolerance.

Methods

These experiments were conducted in six chronic spinal dogs whose spinal cords were transected at the T-5 or T-10 level. The experimental procedures have for the most part been previously described (Martin and Eades, 1967; Martin and Eades, 1970). The flexor reflex was evoked by electrically stimulating the second toe of the ipsilateral leg, using a 1 sec train of 20 Hz square waves with a pulse width of 1 msec and an intensity sufficient to evoke a reflex with an amplitude of 50 mm at the beginning of the experiment. Ten trains of stimuli, each evoking a flexor reflex, were administered at 10 sec intervals, and the polarity of the square wave was reversed between the fifth and sixth trains. These series of stimuli were administered at 5 min intervals throughout

the experiment. The reflex was recorded isotonically on an ink writing kymograph. Respiratory rate, pulse rate, relaxation of the nictitating membrane and pupillary diameter, determined photographically, were measured at 10 min intervals throughout the course of the experiment.

Each dog received tryptamine. Tryptamine HCl was infused at a rate of 0.5 mg/kg/min for 12 min. Three infusions were administered at 40 min intervals. One week later the same dog received a 40 min intravenous infusion of LSD tartrate (0.375 mcg/kg/min), and observations were continued for 160 min after the beginning of the infusion. The dose of LSD employed was the same that had been employed in previous experiments (Martin and Eades, 1970) and produced facilitatory effects that were comparable in magnitude to those studies. Following the control assessment of the actions of LSD and tryptamine, LSD was administered twice daily at 0700 and 1600 in a dose level of 15 mcg/kg subcutaneously. On the seventh and fourteenth days of chronic administration of LSD, the morning dose of LSD was infused, and observations made to assess the presence and degree of direct tolerance to LSD. One week later the effects of tryptamine were studied and the administration of LSD was discontinued. Approximately 3 weeks later tryptamine was again infused.

To assess the development of tolerance to LSD, the areas under the time action curves for the different parameters for each animal were calculated, and the statistical significance of the differences between the control observations and the observations made when the dogs had been receiving LSD chronically for 1 and 2 weeks was determined, using a paired replicate analysis. The area of the time action curve for facilitation of the flexor reflex was determined for the first 15 min of infusion of LSD, since the stepping reflex became manifest shortly thereafter. For the other parameters, the area was calculated for the entire 160 min infusion and post-infusion period. Two types of statistical analyses of the tryptamine data were done. The differences between the means of the observations made prior to the beginning of the tryptamine infusion and the observations made during each tryptamine infusion or immediately after termination of the infusion were calculated for each infusion in each dog for the three treatment conditions. Observations made immediately after the termination of the infusion were used for the measurement of tryptamine's effect on respiratory rate, pulse rate and pupillary diameter. The means of the two trains of ten flexor reflexes evoked during the tryptamine infusion were used as the measure of tryptamine's effect on the flexor reflex. The significance of the differences between the control observations and the observations obtained during and after chronic intoxication with LSD for the means of the three replicate infusions was assessed using a paired replicate analysis. In addition, an analysis of variance was done in which the

variance due to treatm
actions was calculated a
mined.

Table 1 summarizes t
it is administered chron
seen, a high and signi
cardioaccelerator effects
cantly increased respirat
was administered chroni
dose of LSD, this differ
did tolerance develop to
pupillary constriction in
observation and in all d
observation has not bee
of LSD, the miotic effec
of evidence indicated th
effect upon the spinal co
reflex was significantly l
degree of facilitation wa
administered. Secondly, a
LSD evoked the stepping
of LSD when the animals

Table 2 summarizes s
to tryptamine. Although
tor action in the dogs r
significant using a pair
treatment effect using a
decrement in the respira
amine was seen in the d

Table 1. Direct tolerance to

Pulse (Beats—min)	
Respiration (Breaths—min)	
Pupils (mm—min)	
Flexor reflex (mm—min)	

The values for pulse rat
the group mean of the areas
tion period after the beginni
of significance of differences
the dogs had received LSD
a paired "t" test.

variance due to treatment, replication and subjects and their interactions was calculated and the significance of appropriate F ratios determined.

Results

Table 1 summarizes the changes seen in responsivity to LSD when it is administered chronically in the chronic spinal dog. As can be seen, a high and significant degree of tolerance developed to the cardioaccelerator effects of LSD. Although LSD markedly and significantly increased respiratory rate and the mean changes seen when LSD was administered chronically were less than were seen with the first dose of LSD, this difference was not statistically significant. Not only did tolerance develop to the mydriatic effect of LSD, LSD produced pupillary constriction in four of the six tolerant dogs at the first test observation and in all dogs at the 2 week test. To our knowledge, this observation has not been previously reported. At the second test dose of LSD, the miotic effect was highly significant ($p < 0.01$). Two lines of evidence indicated that tolerance developed to LSD's facilitatory effect upon the spinal cord. First, the degree of facilitation of the flexor reflex was significantly less in dogs receiving LSD chronically and the degree of facilitation was increasingly attenuated the longer LSD was administered. Secondly, as can be seen from Fig. 1, the initial infusion of LSD evoked the stepping reflex in all dogs; whereas, subsequent infusion of LSD when the animals were tolerant failed to evoke stepping in any dog.

Table 2 summarizes some of the results concerning cross tolerance to tryptamine. Although the attenuation of tryptamine's cardioaccelerator action in the dogs receiving LSD chronically was not statistically significant using a paired replicate analysis, there was a significant treatment effect using an analysis of variance ($p < 0.05$). A significant decrement in the respiratory stimulant and mydriatic effects of tryptamine was seen in the dogs when they were tolerant to LSD. As can

Table 1. Direct tolerance to LSD in dogs receiving LSD (15 mcg/kg) twice daily subcutaneously

	Control	1st week	2nd week
Pulse (Beats—min)	5012	$294^{\cdot 025}$	$783^{\cdot 025}$
Respiration (Breaths—min)	4589	$1874^{\cdot 2}$	$1078^{\cdot 2}$
Pupils (mm—min)	231	$-155^{\cdot 025}$	$-229^{\cdot 001}$
Flexor reflex (mm—min)	411	$365^{\cdot 10}$	$339^{\cdot 05}$

The values for pulse rate, respiratory rate and pupillary diameter represent the group mean of the areas under the time action curve for the 160 min observation period after the beginning of the LSD infusion. Superscripts indicate the level of significance of differences between the control response and the responses when the dogs had received LSD chronically (15 mcg/kg b.i.d.) for 1 and 2 weeks, using a paired "t" test.

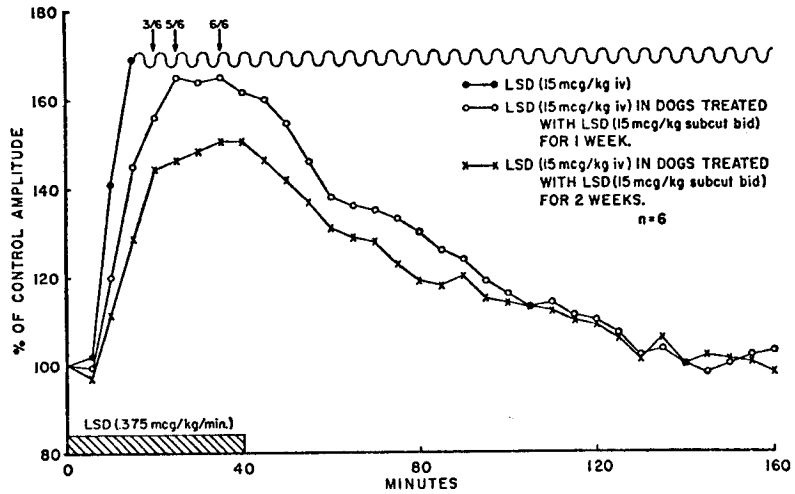

Fig. 1. The effect of an infusion of LSD on the flexor reflex of the chronic spinal dog prior to and during the chronic administration of LSD. Each point represents the mean of determinations made in six dogs. The wavy line shows the presence of the stepping reflex, and the fractions above this line are the proportion of the dogs showing the stepping reflex at the indicated time

be seen from Table 2 and Figs. 2 and 3, chronic treatment with LSD attenuated the facilitatory action of tryptamine on the flexor and stepping reflexes. Partial recovery of the pupillary and respiratory effects of tryptamine was seen 3 weeks after the discontinuation of the daily administration of LSD, and complete or near complete recovery was seen for its cardioaccelerator and spinal cord facilitatory effects.

One of the reasons for designing the tryptamine experiment as we did and for performing the analysis of variance was to obtain data which would bear on the hypothesis that the phenomenon of tryptamine tachyphylaxis could be related to LSD tolerance. There was a trend for all parameters for the response to successive infusions to decrease; however, this trend was only statistically significant for pupils, and there were no significant treatment × replication interactions.

Table 2. Cross tolerance to tryptamine (0.5 mg/kg/min) in dogs receiving LSD 15 mcg/kg twice daily subcutaneously ($N = 6$)

Pulse (beats/min)	47.0 ± 32.0
Respiration (breaths/min)	$87.0 \pm 31.0^{.05}$
Pupils (mm)	$4.6 \pm 1.4^{.025}$
Flexor reflex (mm)	$73.0 \pm 26.0^{.05}$

Each value represents the mean difference ± S.E. between the control response to tryptamine and the response when the dogs had received LSD chronically (15 mcg/kg b.i.d.) for approximately 3 weeks. The superscripts indicate the level of significance, using a paired "t" test.

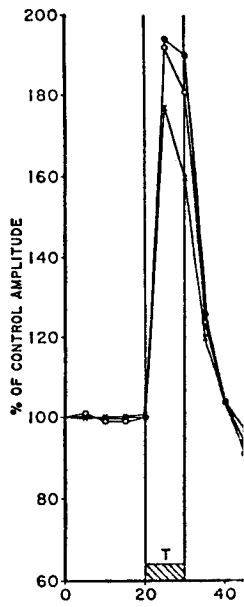

Fig. 2. The effects of infusio
chronic spinal dog before, d
LSD. Each point is

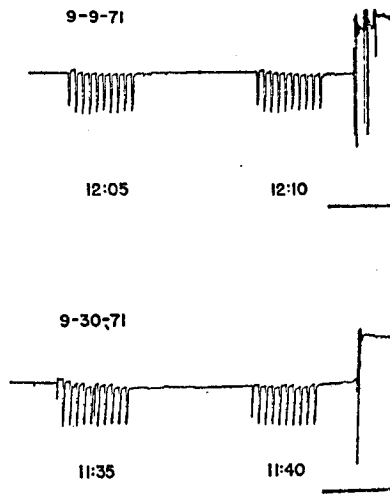

Fig. 3. Kymographic tracin
prior to (upper tracing) an
LSD (15 mcg/kg/b.i.d.). Th
electrical stim

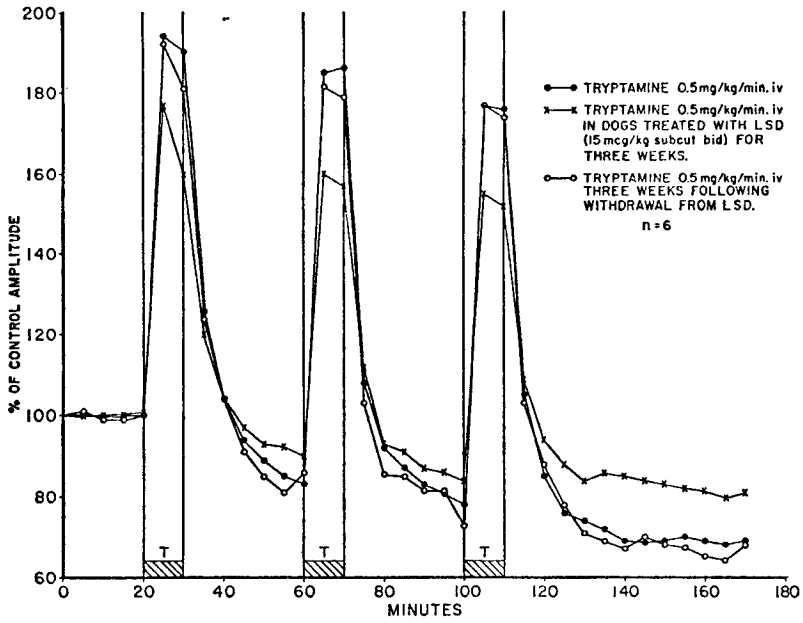

Fig. 2. The effects of infusions of tryptamine on the flexor reflex amplitude of the chronic spinal dog before, during and 3 weeks after the chronic administration of LSD. Each point is the mean of determinations made in six dogs

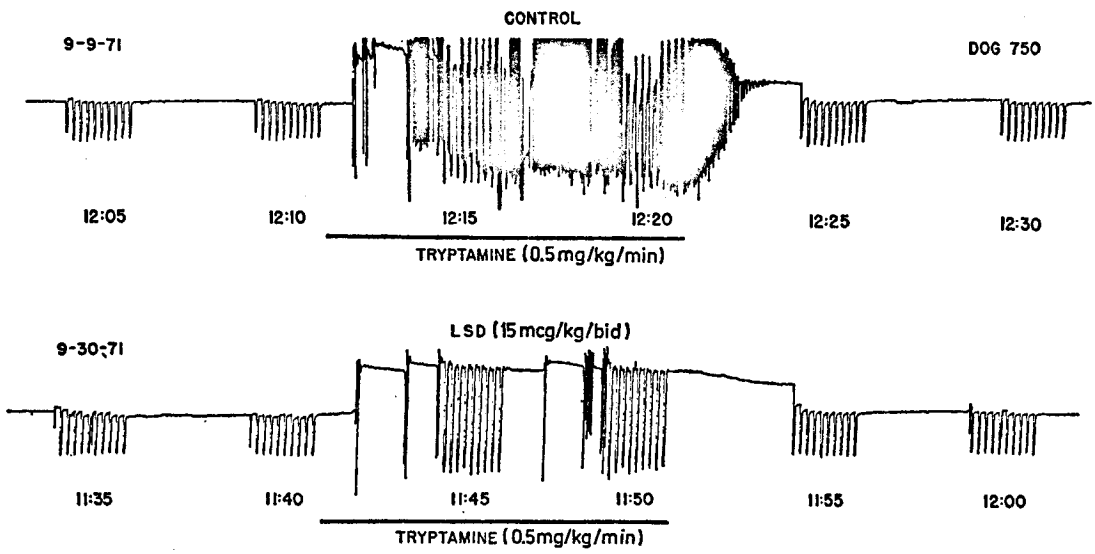

Fig. 3. Kymographic tracings of the flexor reflex during a tryptamine infusion prior to (upper tracing) and during (lower tracing) the chronic administration of LSD (15 mcg/kg/b.i.d.). The dates of the experiments as well as the time the electrical stimulus was applied to the toe are indicated

Discussion

These studies have confirmed previous observations that both LSD and tryptamine increase pulse rate, respiratory rate and pupillary diameter, facilitate the flexor reflex, and evoke the stepping reflex in the chronic spinal dog (Martin and Eades, 1970). Chronic administration of LSD produces tolerance to these effects which are mediated at spinal and supraspinal levels of the central nervous system. The only parameter studied for which direct tolerance to LSD was not statistically significant was the increase in respiratory rate, an effect of LSD in the dog which has previously been shown to be highly variable (Martin and Eades, 1970).

The presence of cross tolerance to the effects of tryptamine in the LSD tolerant chronic spinal dog provides further evidence that tryptamine and LSD have a similar mode of action. The phenomenon of cross tolerance between hallucinogens that are thought to be of the LSD type has been used by a number of investigators in animals (Freedman and Aghajanian, 1959) and in man (Isbell, Miner and Logan, 1959) with the underlying concept that agents which exhibit cross tolerance may do so because of a similar mode of action and through a common mechanism. There are thus three lines of evidence that tryptamine and LSD have a similar mode of action: 1. They produce a similar spectra of pharmacological actions in the dog and in man (Martin and Eades, 1970; Martin and Sloan, 1970). 2. They exhibit a similar susceptibility to antagonists (Martin and Eades, 1970). 3. When tolerance to LSD has been produced in the dog, cross tolerance to tryptamine is present.

References

Freedman, D. X., Aghajanian, G. K.: Time parameters in acute tolerance, cross tolerance, and antagonism to psychotogens. Fed. Proc. **18**, 390 (1959).

Isbell, H., Miner, E. J., Logan, C. R.: Cross tolerance between D-2-bromlysergic acid diethylamide (BOL-148) and the D-diethylamide of lysergic acid (LSD-25). Psychopharmacologia (Berl.) **1**, 109–116 (1959).

Martin, W. R., Eades, C. G.: Pharmacological studies of spinal cord adrenergic and cholinergic mechanisms and their relation to physical dependence on morphine. Psychopharmacologia (Berl.) **11**, 195–223 (1967).

Martin, W. R., Eades, C. G.: The action of tryptamine on the dog spinal cord and its relationship to the agonistic actions of LSD-like psychotogens. Psychopharmacologia (Berl.) **17**, 242–257 (1970).

Martin, W. R., Sloan, J. W.: Effects of infused tryptamine in man. Psychopharmacologia (Berl.) **18**, 231–237 (1970).

Martin, W. R., Sloan, J. W., Christian, S. T.: Brain tryptamine. Fed. Proc. **30**, 271 (1971).

Martin, W. R., Sloan, J. W., Christian, S. T., Clements, T. H.: Brain levels of tryptamine. Psychopharmacologia (Berl.) **24**, 331–346 (1972).

Dr. W. R. Martin
NIMH Addiction Research Center
P. O. Box 2000
Lexington, Kentucky 40507, U.S.A.

Psychopharmacologia (B

Enhance
of Res
after 6-

Barrett R. Co

Departments of Psychiatr
Child Devel
C

Received Ma

Abstract. The effects
ance in an operant, shuttle
depletions of brain cate
significant reductions in
of 1 mg/kg of reserpine
severe disruption of bar
treated rats. Similarly,
control rats produced a se
but also responding in th
sympathectomized subject
catecholamines are import
possible mechanisms invol
discussed.

Key words: 6-Hydroxy
Box Avoidance — T-ma
nephrine — Dopamine.

Since the discovery
reported that this drug
of behavioral tasks (C
Smith and Dews, 19
(α-MPT), which was f
that the production of b
catecholamine depletio
Rech, Carr, and Moore
tered intracisternally
of brain catecholamine
processes (Bloom, Alge
and Traylor, 1970, 1971
ment with 6-hydroxy