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THE EFFECT OF D-LYSERGIC ACID DIETHYLAMIDE (LSD) UPON SHOCK ELICITED FIGHTING IN RATS

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Summary

The action of different doses of LSD on shock elicited fighting was tested in rats. A biphasic dose response was found with low doses facilitating fighting whereas a high dose had no effect. The results are discussed in terms of the effects of LSD on single units of the serotonin neuronal system.

There is increasing support for the notion that brain serotonin (5-hydroxytryptamine - 5-HT) plays an important role in the neural control of aggressive behavior. For example, shock elicited fighting in rats is increased by lesions of specific raphe nuclei containing 5-HT (1), or by the drug p-chlorophenylalanine - PCPA (2,3), which reduces brain 5-HT by an inhibition of tryptophan hydroxylase (4). These results indicate that a reduction of brain 5-HT is associated with enhanced aggressive behavior and suggest that release of 5-HT would be associated with inhibition of aggressive behavior. In fact, the drug p-chloroamphetamine (PCA), which shortly after administration releases 5-HT (5) does markedly inhibit shock-elicited aggression (6,7).

Another drugs which affects the 5-HT neuronal systems in brain is d-lysergic acid diethylamide (LSD). Single cell studies have shown that low doses of LSD specifically inhibit the spontaneous firing rate of presynaptic neurons in the midbrain raphe region (8) and decrease the release of 5-HT (9). On the other hand high doses of LSD can also inhibit cells which are postsynaptic to the midbrain raphe (10) and thus mimic the action of 5-HT on postsynaptic sites. These effects of LSD on single cells suggest, therefore, that LSD should have a biphasic dose-response effect on behaviors which are modulated by the raphe-5-HT system. In fact, non-monotonic dose-response effects of LSD have been reported on several behavioral measures (11,12,13). The purpose of the present study was to evaluate whether LSD would also have a non-monotonic dose response effect on shock-elicited fighting, since this form of aggression does seem to be modulated by the raphe-5-HT system.

Methods

Shock elicited aggression was tested using a 30 x 28 x 24 cm Plexiglas cage housed in a Lehigh Valley sound attenuated chamber. The chamber was dimly lighted

by a lamp mounted 5 cm above the test cage and animals were viewed through a window from a darkened room. A Lehigh Valley shock generator and scrambler delivered shocks to the 0.5 mm parallel bar grid floor. The intershock intervals as well as the duration and intensity of the shocks were controlled automatically via conventional electromechanical switching and timing circuits. The background noise level was 55 db throughout.

A total of 120 male albino rats of the Sprague-Dawley strain (300-350 g) were used. Rats were weighed and then paired on the basis of similar weights. Subjects were housed 4 to a cage in a colony room on a 12-12 light-dark schedule. Food and water were available ad lib. Paired animals were not housed together. Prior to drug treatment, all 60 pairs were pretested for initial levels of shock elicited aggression. During pretesting twenty, 1 sec, 2 mA shocks were delivered at a 15 sec interstimulus interval (ISI). Fights were defined as a directed movement toward the opponent resulting in contact puls one of the following: biting, sparring, upright attack posturing or supine submissive posturing adopted by the attacked rat. Based on the total number of fights for each pair during the pretest, the 60 paris were matched into 5 groups of 12 pairs each which had similar mean levels of shock elicited fighting.

Following the pretest (2-3 days later) half the pairs within each matched group were injected with either 20, 40, 80 160 or 640 µg/kg LSD (using a different matched group for each dose) and half with deionized water, the LSD vehicle. Both LSD and water were injected intraperitoneally (i.p.) in a volume of 1 ml. Each pair of rats was placed in the test chamber 10 min following injection. Five min later a series of 40 shocks were delivered, 10 at each of 4 intensities (1, 1.5, 2 and 2.5 mA). The shocks were increased throughout the session and were not random. All shocks were of a 1 sec duration with a 15 sec ISI and 1 min between intensity. Seventy-two hrs later all groups were tested again in reverse conditions. Rats which received LSD initially now received water and vice versa.

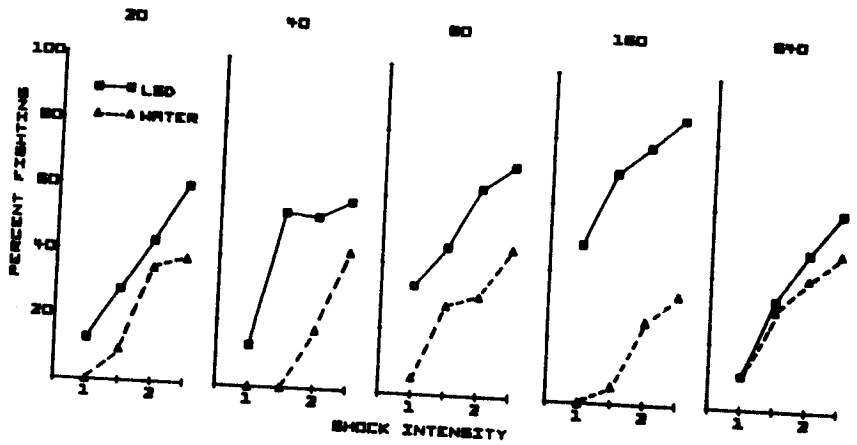

FIG. 1

The effect of LSD versus water in doses of 20, 40, 80, 160 and 640 µg/kg upon shock elicited fighting in rats at various shock intensities in mA.

Results

The results are shown in Fig. 1. LSD had a nonmonotonic dose-response effect on shock elicited aggression. Thus at the low doses (20-160 µg/kg) treated animals fought more than controls at each shock intensity, whereas at the highest dose (640 µg/kg) LSD no longer increased fighting. These observations were confirmed by an analysis of variance which revealed a significant drug effect ($F = 116.31$, $df = 1/30$, $p < .001$), a significant intensity effect ($F = 179.1$, $df = 3/90$, $p < .001$) and a significant dose X Drug Interaction ($F = 10.51$, $df = 4/30$, $p < .001$).

Discussion

The results show that LSD enhances shock elicited fighting in rats when given in doses from 20-160 µg/kg. Since the effect of low doses in single cell studies is to specifically inhibit the presynaptic 5-HT neuron, and thereby decrease impulse mediated release of 5-HT, the results are consistent with those experiments which show increased shock elicited fighting when brain 5-HT is lowered either by raphe lesions or PCA. The fact that the high dose of LSD acted differently than the low doses may have occurred because the high dose of LSD also directly inhibited postsynaptic 5-HT neurons in addition to the presynaptic 5-HT neurons. In this case the postsynaptic agonistic effect may have effectively cancelled the excitatory effect resulting from inhibition of the presynaptic neurons. Such a mechanism would account for the biphasic dose response effects seen in this and perhaps other behavioral studies and would be consistent with the effects of LSD on single neuronal firing. For example the behavioral effects are in agreement with other studies which have shown an increase in performance in food reward and shock avoidance situations following small doses of LSD but an impairment with higher doses (12).

Another possible explanation is that LSD might cause a hyperalgesia. Preliminary experiments in our laboratory however reveal that while low doses of LSD do produce an increased sensitivity to pain as tested by the flinch-jump method doses over 40 µg do not. A hyperalgesia therefore cannot be the explanation for an increase in aggressive behavior which is seen up to doses of 160 µg LSD. It should also be pointed out, however, that high doses of LSD also appear to have dopamine agonist properties (14,15,16). In fact in the present study enhanced motor activity of many different kinds was observed at the 640 µg/kg dose. This included increased escape behavior jumping and frenzied running activity which occurred both spontaneously and during the shocks. In addition the spontaneous fighting between shocks also occurred at this dose similar to that reported with the dopamine agonist, apomorphine. It is possible, therefore, that the enhanced motor activity actually interfered with well directed shock elicited fighting and this, rather than a direct stimulation of postsynaptic 5-HT neurons actually produced the nonmonotonic LSD dose-response effect. Further studies in which high doses of LSD were given after pretreatment with dopamine receptor blockers might resolve this question.

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