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Short communication

LSD AND 5-HTP: TOLERANCE AND CROSS-TOLERANCE RELATIONSHIPS

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Tolerance and cross-tolerance relationships between lysergic acid diethylamide (LSD) and 5-hydroxytryptophan (5-HTP) were studied in rats trained on an operant task. The results demonstrated that behavioral tolerance to both compounds occur in the rat and that asymmetrical cross-tolerance relationships exist; that is, animals tolerant to 5-HTP were cross-tolerant to LSD, but animals tolerant to LSD were not cross-tolerant to 5-HTP.

LSD 5-HTP Serotonin (5-HT) Tolerance Cross-tolerance

1. Introduction

The results of several recent studies suggest that some of the behavioral effects of lysergic acid diethylamide (LSD) and 5-hydroxytryptophan (5-HTP) may be related to the similar actions of these compounds on central serotonergic neuronal systems. Systemic (i.p.) injections of both LSD (Aghajanian et al., 1970) and 5-HTP (Gallager and Aghajanian, 1976) have been shown to inhibit the firing of serotonergic raphe neurons while not altering the activity of other adjacent neuronal systems. Moreover, simultaneous subthreshold doses of LSD and serotonin (the neurotransmitter metabolite of 5-HTP responsible for its effects) when applied to the raphe microiontophoretically, produce combined inhibitory effects that are additive (Aghajanian and Haigler, 1974). It has further been noted that certain behavioral changes induced by LSD and 5-HTP are not only similar (Freedman and Giarman, 1963), but seem to parallel the time course of drug-induced increases of serotonin in brain (Aprison et al., 1962; Freedman and Boggan, 1974).

If the similarity of the effects of LSD and 5-HTP on behavior is related to the similarity of their effects on central serotonergic systems, we might expect that cross-tolerance between these compounds would occur (Appel and Freedman, 1968). The present study was designed to answer this question.

2. Materials and methods

The tolerance/cross-tolerance procedure used in the present experiment has been evaluated and described elsewhere (Appel and Freedman, 1968). In short, water deprived rats (n = 18) were placed in a standard operant chamber and required to learn a lever-pressing response (FR-32) to obtain 0.1 ml of tap water. After responding had stabilized (±5% change in responding) over daily 30 min sessions, intraperitoneal (i.p.) injections of 1 ml/kg isotonic saline solution (NaCl) were begun.

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Two days after the start of NaCl injections, animals were divided into four groups; (1) LSD challenge, 5-HTP test, n = 7; (2) 5-HTP challenge, LSD test, n = 7; (3) LSD challenge, 5-HTP vehicle test, n = 2; and (4) 5-HTP challenge, LSD vehicle test, n = 2.

The cross-tolerance procedure consists of: (1) giving the challenge drug, (2) giving five days of control injections (NaCl), (3) giving the test drug for nine days (tolerance regimen) and (4) giving the challenge drug on the day following the last tolerance day. 5-HTP vehicle control injections were given on the day following the second challenge to control for pH and NaCl was administered on the day following vehicle injections.

All injections were given i.p. in volumes of 1 ml/kg, 15 min prior to the start of the experimental session. LSD tartrate (0.13 mg/kg), obtained from the National Institute on Drug Abuse, was dissolved in NaCl. d,l-5-HTP (50 mg/kg) was dissolved in water adjusted with dilute HCl and NaOH to a pH of 2.0. Dosage and time parameters were selected on the basis of similar amounts of initial disruption of FR responding.

Results are presented in terms of group mean percent control response rates. This score for each animal is obtained by dividing the total number of responses on a given day by the average number of responses during the two NaCl control days preceding the start of the experiment and multiplying by 100.

3. Results

The effects of giving LSD as the challenge drug and 5-HTP as the test drug are presented in fig. 1. On day 1 of the tolerance regimen, 5-HTP, but not the 5-HTP vehicle caused a marked decrement in bar pressing behavior (21% of control as opposed to 94% of control). This 5-HTP-induced decrement gradually diminished as a function of repeated daily doses such that, by day 9, responding had returned to 82% of control. The difference between day 1 and day 9 is significant (t =

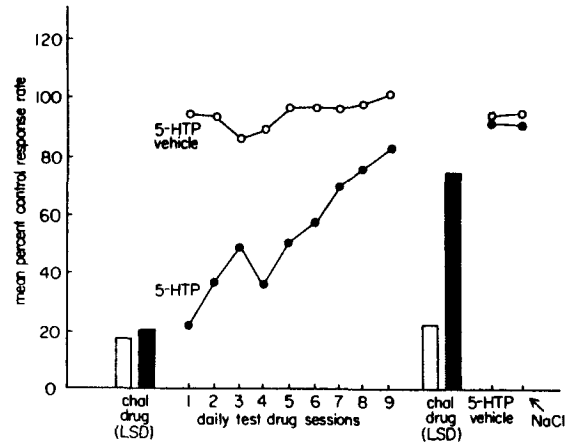

Fig. 1. Average effects of 5-HTP (50 mg/kg) and 5-HTP vehicle on mean percent control response rates. Bar graphs indicate effects of LSD (0.13 mg/kg) before and after test drugs: Open bars are from animals which received 5-HTP vehicle, dark bars are from animals which received 5-HTP as the test drug. Mean percent control response rates for the two days of NaCl injections prior to (baseline) and five days following (recovery to baseline) the first challenge drug day have been omitted for clarity (see text).

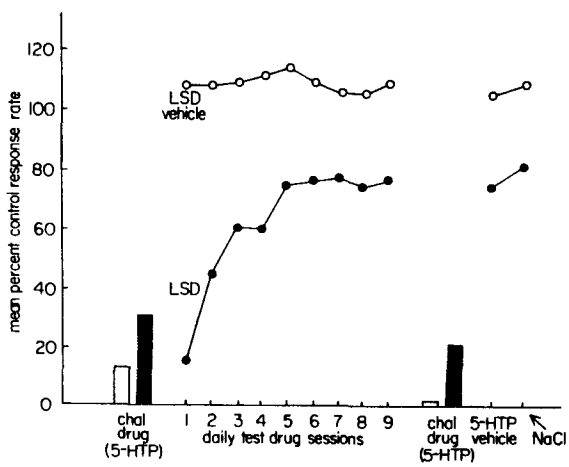

Fig. 2. Average effects of LSD (0.13 mg/kg) and LSD vehicle on mean percent control response rates. Bar graphs indicate effects of 5-HTP (50 mg/kg) before and after test drugs: Open bars are from animals which received LSD vehicle, dark bars are from animals which received LSD as the test drug. Mean percent control response rates for the two days of NaCl injections prior to (baseline) and five days following (recovery to baseline) the first challenge drug day have been omitted for clarity (see text).

6.34, df = 6, $P < 0.001$). When the effect of LSD challenge given before the tolerance regiment is compared with that given afterwards, a significant difference is observed in those animals which received chronic 5-HTP ($t = 6.82$, df = 6, $P < 0.001$), but not in those animals which received 5-HTP vehicle.

The results of administering 5-HTP as the challenge drug and LSD as the test drug are presented in fig. 2. On day 1 of the tolerance regimen, LSD, but not LSD vehicle, produced a large decrement in responding (15% of control as opposed to 108% of control). By day 9 this decrement has diminished and responding was at 76% of control. The difference between day 1 and day 9 on LSD was significant ($t = 5.83$, df = 6, $P < 0.001$). There were, however, no significant differences between levels of responding on the first and second 5-HTP challenge days in those animals which received either LSD or LSD vehicle during the tolerance regimen.

4. Discussion

The results of this experiment confirm the well-documented finding that tolerance to the behaviorally disruptive effects of LSD occurs in the rat (Appel and Freedman, 1964; Appel and Freedman, 1968) and that tolerance to the same behavioral effect of 5-HTP (disruption of bar-pressing maintained by a FR schedule of reinforcement) also occurs. Qualitatively, tolerance to 5-HTP was observed to develop in much the same manner as it does to numerous other psychoactive compounds when given to animals whose behavior is maintained on an FR schedule of reinforcement, i.e., the decrement of effect is primarily due to a shortening of the single period of nonresponding (Appel and Freedman, 1968). Following the period of nonresponding, animals showed complete recovery of response rate and patterns within several fixed-ratio performances.

The most interesting result of this experiment was the occurrence of asymmetrical cross-tolerance between LSD and 5-HTP, i.e., animals made tolerant to 5-HTP were cross-tolerant to LSD, but animals made tolerant to LSD were not cross-tolerant to 5-HTP. This result might be explained on the basis of recent data which suggests that the rate-decreasing effects of 5-HTP on operant responding are due largely to effect of serotonin outside the blood-brain barrier (Carter and Appel, 1976). In contrast, LSD appears to exert 5-HT agonist-like effects only at central neuronal systems (Aghajanian and Haigler, 1974). Thus, daily administration of LSD might produce tolerance to central serotonergic neurons, but not at peripherally located serotonergic neurons. Thus, animals which received chronic treatment with LSD would not be protected against any disruptive effects that might be exerted by 5-HTP peripherally.

Thus, our data demonstrate that tolerance to the behaviorally disruptive effects of both LSD and 5-HTP occur in the rat. The fact that the cross-tolerance observed between these compounds was asymmetrical indicates that similar (e.g., serotonergic), but not identical, mechanisms might mediate some of the behavioral effects of these agents.

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References

Aghajanian, G.K., W.E. Foote and M.H. Sheard, 1970, Action of psychotogenic drugs on single midbrain raphe neurons, J. Pharmacol. Exptl. Therap. 171, 178.

Aghajanian, G.K. and H.J. Haigler, 1974, Mode of action of LSD on serotonergic neurons, in: Advances in Biochemical Pharmacology, Vol. 10, eds. E. Costa, G.L. Gessa and M. Sandler (Raven Press, New York) p. 167.

Appel, J.B. and D.X. Freedman, 1964, Chemically induced alterations in the behavioral effects of LSD-25, Biochem. Pharmacol. 13, 861.

Appel, J.B. and D.X. Freedman, 1968, Tolerance and cross-tolerance among psychotomimetic drugs, Psychopharmacologia 13, 267.

Aprison, M.H., M.A. Wolf, G.L. Poulos and T.L. Folkberth, 1962, Neurochemical correlates of behavior. III. Variation of serotonin content in several brain areas and peripheral tissues of the pigeon following 5-hydroxytryptophan administration, J. Neurochem. 9, 575.

Carter, R.B. and J.B. Appel, 1976, Blockade of the behavioral effects of 5-HTP by the decarboxylase inhibitor Ro4-4602, Pharmacol. Biochem. Behav. 4, 407.

Freedman, D.X. and W.O. Boggan, 1974, Brain serotonin metabolism after tolerance dosage of LSD, in: Advances in Biochemical Pharmacology, Vol. 10, eds. E. Costa, G.L. Gessa and M. Sandler (Raven Press, New York) p. 151.

Freedman, D.X. and N.J. Giarman, 1963, Brain amines, electrical activity, and behavior, in: EEG and Behavior, ed. G.H. Glaser (Basic Books, New York) p. 198.

Gallager, D.W. and G.K. Aghajanian, 1976, Inhibition of firing of raphe neurons by tryptophan and 5-hydroxytryptophan: blockade by inhibiting serotonin synthesis with Ro4-4602, Neuropharmacology 15, 149.