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Antagonism of a Behavioral Effect of LSD and Lisuride in the Cat

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Abstract. These experiments investigated the role of serotonin (5-HT) and dopamine (DA) receptors in the limb-flick (LF) response elicited by the hallucinogenic ergot LSD and its nonhallucinogenic structural congener lisuride. Pretreatment with either the 5-HT antagonist pizotifen (BC-105) or the DA antagonist haloperidol significantly attenuated LF elicited by either LSD or lisuride. Thus, the LF model failed to differentiate the neuropharmacological actions of LSD and lisuride. Cocaine also prevented LSD- and lisuride-elicited LF simply by reducing the activity of cats (response competition) suggesting the need for caution in interpreting 'antagonism' of the LF response.

Key words: LSD – Lisuride – Limb flicks – Hallucinogens

Lysergic acid diethylamide (LSD) elicits a variety of unconditioned behaviors in the cat, two of which, limb flicking (LF) and abortive grooming (AG), have been proposed as an animal behavior model of hallucinogenic drug action (Jacobs et al. 1977). However, recent evidence demonstrates that this model is not specific for hallucinogenic drugs; that is, a variety of nonhallucinogens have been found to induce both LF and AG (Marini 1982; Marini and Sheard 1981; White et al. 1981). Therefore, the utility of the LF model as a probe for specific hallucinogenic drug actions has been compromised.

The utility of the LF model would be enhanced if the underlying neuropharmacological mechanisms responsible for hallucinogen-induced LF were shown to differ from those that mediate nonhallucinogen-induced LF. The most stringent test of this possibility would involve a comparison between LSD and its nonhallucinogenic congener lisuride hydrogen maleate (LHM) because LHM exerts many LSD-like pharmacological effects at central serotonin (5-HT) and dopamine (DA) receptors (Freedman and Boggan 1981 for review) and is the only drug that is as potent as LSD in eliciting LF (White et al. 1981).

Despite these similar effects of LSD and LHM, recent evidence has shown that the neuropharmacological actions of these ergots can be differentiated (White and Appel 1982a). Thus, the discriminative stimulus effect of LSD (the LSD cue) is antagonized only by 5-HT antagonists (White and Appel 1982c), whereas the LHM cue is antagonized only by DA antagonists (White and Appel 1982b). The present experiments were designed to ascertain whether similar differences exist between the neuropharmacological mechanisms responsible for LSD-induced and LHM-induced LF. Therefore, we have tested the ability of the 5-HT antagonist pizotifen (BC-105) and the DA antagonist haloperidol to antagonize LF elicited by these two ergolines. In addition, since it has been previously reported that drug-induced reduction in activity levels may be an important variable in assessing antagonism data (Haigler and Spring 1979), cocaine, which has been found to depress activity in caged cats (White et al. 1981), was also tested for its effects on LSD- and LHM-induced LF.

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Materials and Methods

Six adult mongrel female cats (2.2–3.9 kg) were used. They were housed individually in stainless steel cages in a colony maintained at constant temperature (21°–23° C), humidity 40%–50%), and lighting conditions (12-h light-dark cycle).

All behavioral observations were made with the cats in their home cages by observers who were blind to experimental treatments. Observation periods continued for 60 min and at least 6 days intervened between consecutive test sessions for each cat.

Before initiating antagonism testing, the reliability of LF response elicited by LSD (0.08 mg/kg) and LHM (0.02 mg/kg) was determined by test-retest correlations obtained during consecutive weekly administrations of each compound. The doses of LSD and LHM were chosen on the basis of earlier findings that LHM was approximately four-times as potent as LSD in eliciting LF (White et al. 1981). For half of the subjects, the order of administration was LSD – LSD – saline – LHM – LHM and for the other half, the order was LHM – LHM – saline – LSD – LSD.

For antagonism testing, cats were pretreated with haloperidol (0.1 or 0.5 mg/kg), pizotifen (5.0 mg/kg), or cocaine (5.0 mg/kg), 30 min prior to the injection of LSD (0.08 mg/kg), LHM (0.02 mg/kg), or 0.9% saline. All injections were given IP in a volume of 0.5 ml/kg. Observation periods began immediately following the second injection. The order of antagonist-drug administration for each cat was random.

D-Lysergic acid diethylamide bitartrate (NIDA, Rockville, MD, USA), lisuride hydrogen maleate (Schering AG, Berlin, FRG) cocaine HCl (Merck Sharp and Dohme, Rahway, NJ, USA), and pizotifen maleate (Sandoz, East Hanover, NJ, USA) were dissolved in 0.9% saline. Doses of these drugs refer to their respective salts. Haloperidol (McNeil, Fort Washington, PA, USA) was diluted with saline from ampule solutions provided by the supplier.

Table 1. Antagonims of the limb-flick (LF) response elicited by LSD (0.08 mg/kg) or LHM (0.02 mg/kg)

Antagonist	Dose (mg/kg)	Saline	LSD	LHM
No antagonist 1[c]	–	1.0 ± 0.5	39.8 ± 13.2[a]	51.7 ± 20.3[a]
No antagonist 2[c]	–	–	57.7 ± 13.5[a]	48.3 ± 13.9[a]
No antagonist (mean)	–	1.0 ± 0.5	49.0 ± 12.2[a]	50.2 ± 16.8[a]
Pizotifen	5.0	0.3 ± 0.3	0.5 ± 0.3[b]	6.2 ± 2.3[b]
Haloperidol	0.1	1.0 ± 0.8	22.5 ± 7.2[a]	28.4 ± 11.7[a]
Haloperidol	0.5	0.6 ± 0.3	6.0 ± 3.4[b]	1.0 ± 0.4[b]
Cocaine	5.0	1.0 ± 0.5	21.7 ± 18.5[a]	14.7 ± 4.1[a,b]

[a] Significantly different from saline, $P < 0.05$
[b] Significantly different from LSD or LHM alone, $P < 0.05$
[c] 1 and 2 refer to the first and second administration of LSD and LHM

Test-retest reliability was evaluated with the Pearson product-moment correlation. All statistical comparisons were made using Student's *t*-test for correlated measures.

Results

The results are summarized in Table 1. Both LSD and LHM elicited the LF response. Since the test-retest correlations for LSD (0.83) and LHM (0.93) were reliable ($P < 0.05$), statistical comparisons were made between antagonist-LSD or antagonist-LHM combinations and the mean values of the two administrations of LSD or LHM, respectively.

Pizotifen significantly attenuated LF elicited by LSD (99% reduction) or by LHM (88% reduction). Pizotifen (alone or in combination with LSD or LHM) caused infrequent episodes of unsteady gait and wavering balance in some cats. Haloperidol (0.1 mg/kg) reduced both LSD- and LHM-elicited LF but, at this dose, the reductions were not significant. At 0.5 mg/kg, haloperidol significantly attenuated LF elicited by LSD (88% reduction) or by LHM (98% reduction). During most antagonism tests with pizotifen or haloperidol, the activity levels of the cats (observed, but not quantitatively measured) did not differ from LSD or LHM sessions. Cocaine (5 mg/kg) significantly reduced LHM-elicited (71% reduction), but not LSD-elicited (52% reduction) LF. However, this compound completely prevented LSD-elicited LF in five of the six cats. The sixth cat emitted 114 LF, accounting for the large mean value and 82% of the variance: a second test with this cat resulted in 104 LF and, during both test sessions with cocaine plus LSD, this cat was highly active. This was an unusual response because, following cocaine (in combination with saline or other drugs), the animals were typically immobile, primarily sitting in one corner of the cage, as described by White et al. (1981). During cocaine antagonism sessions, LF occurred whenever the cats were active.

Discussion

These results have demonstrated that both 5-HT and DA antagonists can attenuate LF induced by either LSD or LHM. It should be noted that, at the doses employed, neither pizotifen or haloperidol severely diminished locomotor activity. In fact, on many occasions, the cats were extremely active following administration of these antagonists, though LF was not observed. Therefore, the attenuation of LF was not merely the result of inactivity.

Although pizotifen caused infrequent periods of ataxia, the attenuation of LF cannot be ascribed to ataxia because some drugs (e.g., clonazepam) can induce severe ataxia in cats while potentiating LSD-induced LF, and other drugs (e.g., ketamine) can simultaneously induce ataxia and LF (White et al., unpublished observations). Therefore, the attenuations of LF by pizotifen and haloperidol were probably the result of pharmacological antagonism rather than nonspecific interference with the LF response. Although the present findings support the hypothesis that both 5-HT and DA receptors are involved in LF induced by hallucinogenic drugs (Jacobs et al. 1977), they also indicate that the same neuronal mechanisms are involved in LF induced by at least one nonhallucinogen (LHM). Therefore, these findings cast further doubt on the utility of this behavioral model as a probe for specific hallucinogenic drug actions.

The fact that cocaine completely blocked LSD-elicited LF in five of six cats and significantly reduced LHM-elicited LF recommends a cautious approach to interpreting 'antagonism' of the LF response, because this 'antagonistic' effect was probably due to response competition, i.e., the reluctance of the cats to move following cocaine. Therefore, our results amplify the warning issued by Haigler and Spring (1979) that future investigations regarding antagonism of the LF response should report changes in the overall activity of the subjects. Without such information, reductions in LF behavior cannot be interpreted unequivocally.

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