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BRIEF COMMUNICATION

Verapamil Does Not Antagonize LSD-Induced Stimulus Control

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WINTER, J. C. *Verapamil does not antagonize LSD-induced stimulus control.* PHARMACOL BIOCHEM BEHAV **25**(1) 227–228, 1986.—Discriminative stimulus control was established in rats (N=6) with LSD (100 microg/kg) and saline using a 2-lever response choice task and an FR10 schedule of food reinforcement. Subjects were then tested once per week with either pizotyline (BC-105) or verapamil alone or in combination with LSD. In agreement with previous reports, pizotyline antagonized LSD and, when tested alone, exhibited modest agonistic effects (18% LSD-appropriate). In contrast, verapamil failed to block LSD at any dose tested. Verapamil alone appeared to have somewhat greater agonistic activity (35% LSD-appropriate) than did pizotyline but neither drug substituted completely for LSD. These data suggest that calcium channel antagonism by pizotyline is not essential to its anti-LSD effects.

LSD Stimulus control Verapamil Pizotyline

IT has long been recognized that lysergic acid diethylamide (LSD) can function as a discriminative stimulus [4] and that its stimulus properties are diminished by a variety of serotonergic (5-HT) antagonists [3]. Peroutka *et al.* [5] reported that one such antagonist, pizotyline (BC-105, pizotifen), blocks 5-HT-induced contractions of the canine basilar artery by an action on calcium channels. Furthermore, verapamil, a classical calcium antagonist, blocks the effects of 5-HT on human blood platelets and competes with [H^3]spiperone and [^{3}H]ketanserin for 5-HT_2 receptors in rat cerebral cortex [1,6].

The present experiments compared the ability of pizotyline and verapamil to antagonize the discriminative stimulus properties of LSD in rats.

METHOD

Animals

All subjects were male Fischer 344 rats obtained from Charles River Breeding Laboratories, Inc., Wilmington, MA. They were housed in pairs under a natural light-dark cycle and had free access to tap water in the home cage. Subjects were maintained at 75–80% of their expected free-feeding weight by limiting access to dry food to 2 hours per day.

Procedure

Six rats were trained with LSD (100 microg/kg) and saline in a two-lever response choice task [4] using a fixed-ratio 10 (FR10) schedule of reinforcement. The reinforcer was sweetened condensed milk diluted with tap water. During discrimination training, either LSD or saline was injected 15 minutes before each session. Each week began with the saline treatment. LSD and saline were then alternated on a daily basis. During each training session, the lever on which 10 responses were first emitted was designated the selected lever. In addition, the percentage of responses on the LSD-appropriate lever prior to emission of 10 responses on either lever was recorded. To determine whether pizotyline or verapamil have agonist properties in LSD-trained rats, cross tests were conducted in which one of the antagonists was given by itself. Pretreatment times were 60 minutes (pizotyline) and 30 minutes (verapamil). During cross tests, no responses were reinforced and the session was terminated after lever selection was made. Tests of antagonism of LSD by pizotyline and verapamil were similar to cross tests except that administration of the antagonists was followed by the training dose of LSD.

Drugs

d-LSD tartrate (NIDA, Washington, DC), pizotyline maleate (Sandoz Pharmaceuticals, East Hanover, NJ), and verapamil HCl (G.D. Searle & Co., Skokie, IL) were dissolved in 0.9% NaCl and injected IP. All doses are in terms of the respective salts.

RESULTS

When tested alone both pizotyline and verapamil exhib-

TABLE 1

EFFECTS OF PIZOTYLINE AND VERAPAMIL ON LSD-INDUCED STIMULUS CONTROL

Dose of antagonist (mg/kg)	N	Response distribution†	Lever selection†
0	6	99	100
Pizotyline 3	6	50	50
Pizotyline 10	6	26	17
Verapamil 10	6	98	100
Verapamil 20	6	87	100
Verapamil 30	1	100	100

*Six animals were tested at each dose; N designates the number of animals who completed the test session.

†Percentage of responses on the LSD-appropriate lever.

‡Percentage of animals choosing the LSD-appropriate lever.

ited limited evidence of LSD-like activity. Maximum values occurred at 10 mg/kg pizotyline (18% of responses were LSD-appropriate and 1 of 6 rats chose the LSD-appropriate lever) and at 10 mg/kg of verapamil (35%; 2/6). When injected with saline under identical conditions, the group emitted only 2% of its responses on the LSD-lever and none selected the LSD-lever.

The results of tests of antagonism are seen in Table 1. In agreement with many previous reports (e.g. [7]), pizotyline clearly antagonized LSD. In contrast, verapamil was completely ineffective as an antagonist of the stimulus properties of LSD. At a dose of 30 mg/kg, only 1 of 6 animals completed the test.

DISCUSSION

The finding that pizotyline can function as a calcium channel blocker [5] raises the possibility that this property might be a factor in its well known ability to antagonize LSD-induced stimulus control. In addition, because LSD's stimulus properties are believed to be mediated primarily by 5-HT_2 receptors, the affinity of verapamil for these receptors [1,6] suggests that verapamil might likewise be an antagonist of LSD. Indeed, Altura and Altura [2] observed relaxation by verapamil of LSD-induced spasms of isolated cerebral arteries of the dog.

Under the conditions of the present study, the inability of verapamil to antagonize the stimulus properties of LSD suggests that pizotyline's activity as a blocker of calcium channels is not essential to its antagonism of LSD. Furthermore, the present data provide no evidence that antagonism by verapamil of LSD's contractile effects on smooth muscle of isolated cerebral arteries is relevant to antagonism of LSD-induced stimulus control in the intact rat.

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