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RAPID COMMUNICATION

Generalization of the Discriminative Stimulus Properties of 8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and Ipsapirone to Yohimbine[1]

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WINTER, J. C. *Generalization of the discriminative stimulus properties of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and ipsapirone to yohimbine.* PHARMACOL BIOCHEM BEHAV **29**(1) 193–195, 1988.—Rats were trained with either 8-OH-DPAT (0.2 mg/kg) or ipsapirone (10 mg/kg) versus saline in a 2-lever discrimination task. Tests of generalization were then conducted with yohimbine. All drugs were administered IP 15 min before testing. In 8-OH-DPAT-trained subjects, 85% of the responses following yohimbine (3 mg/kg) were on the drug-appropriate lever. Likewise, yohimbine (6 mg/kg) yielded 86% drug-appropriate responses in ipsapirone-trained rats. Previous studies have provided evidence that both 8-OH-DPAT and ipsapirone have high affinity for 5-HT_{1A} receptors and the anxiolytic-like activity of the latter drug has been attributed to its activity at those receptors. In contrast, yohimbine is an $alpha_2$ adrenergic antagonist, has negligible affinity for the 5-HT_{1A} receptor, and is generally regarded as being anxiogenic. The present data, which indicate a high degree of similarity between the stimuli induced by yohimbine, 8-OH-DPAT, and ipsapirone, suggest that a re-evaluation of the presumed mechanisms of actions of these drugs is in order.

Drug discrimination 8-OH-DPAT Ipsapirone Yohimbine

YOHIMBINE [13], 8-OH-DPAT [4,11], and ipsapirone [9] have previously been trained as discriminative stimuli and evidence has been presented that the stimulus properties of 8-OH-DPAT and ipsapirone are similar [9,11]. In the present investigation, groups of rats were trained with 8-OH-DPAT and ipsapirone, respectively, versus saline and tests of generalization were conducted with yohimbine. The decision to test yohimbine was based on the observation (Winter, unpublished) that rats trained with 8-OH-DPAT are more irritable than expected.

METHOD

Animals

Eighteen male Fischer 344 rats were obtained from Charles River Breeding Laboratories, Inc., Wilmington, MA. They were housed in pairs under a natural light-dark cycle and allowed free access to water in the home cage. Subjects were maintained at 75–80% of their expected free-feeding weight by limiting access to food to 1 hour per day.

Apparatus

Two small-animal test chambers (Coulbourn Instruments model E10-10) housed in larger light-proof sound-insulated boxes were used for all experiments. Boxes contained a house light and exhaust fan. Chambers contained two levers mounted at opposite ends of one wall. Centered between the levers was a dipper which delivered 0.1 ml of sweetened condensed milk diluted 2:1 with tap water.

Procedure

Training. Subjects were assigned either to Group I (N=10) or to Group II (N=8). After learning to drink from the dipper, subjects were trained to depress first one and then the other of the two levers. The number of responses for each reinforcement was gradually increased from one to ten and all subsequent training and testing employed a fixed ratio ten (FR10) schedule of reinforcement. Discrimination training was then begun. Fifteen minutes before each ten-minute session, subjects were injected (IP) with either saline or drug. Following the administration of drug, every tenth response on the drug-appropriate lever was reinforced. Similarly, responses on the saline-appropriate lever were reinforced following the injection of saline. For half of the subjects, the left lever was designated as the drug-appropriate lever. During discrimination training, drug and saline were

[1]A preliminary report of these data was made at the 31st Annual Meeting of the Behavioral Pharmacology Society, Rockville, MD, May 30, 1987.

TABLE 1
CROSS TESTS WITH YOHIMBINE

Train (mg/kg)	Drug Control	Saline Control	Yohimbine (mg/kg)	Yohimbine Test	N
	Percentage of responses appropriate to the training drug (SE)				
8-OH-DPAT (0.2)	91 (6)	1 (1)	1	33 (13)	10/10
			3	85 (8)	10/10
			6	81 (5)	10/10
ipsapirone (10)	99 (1)	1 (1)	1	23 (10)	8/8
			3	71 (13)	8/8
			6	86 (5)	8/8

N: Number of animals completing the test/number tested.

alternated on a daily basis. Drug-induced stimulus control was assumed to be present when, in five consecutive sessions, 83% or more of all responses prior to delivery of the first reinforcer were on the appropriate lever. For Group I, the drug was 8-OH-DPAT (0.2 mg/kg); for Group II, the drug was ipsapirone (10 mg/kg).

Tests of generalization. After drug-induced stimulus control was well established, cross tests were conducted with yohimbine (IP) in Groups I and II. In both groups, the order of testing was 3, 1, and 6 mg/kg. Cross tests were conducted once per week in each animal so long as performance during the preceding sessions of the week did not fall below a criterion of 83% correct responding. In general, tests were equally divided between Thursday and Friday sessions. During cross tests, no responses were reinforced and the session was terminated after the emission of ten responses on either lever. The distribution of responses between the two levers was expressed as the percentage of total responses emitted on the drug-appropriate lever. Prior to and following the yohimbine tests, both training conditions were tested in exactly the same fashion. Following the second test of training conditions, the 6 mg/kg dose of yohimbine was repeated. All injections were made 15 minutes before testing.

Drugs

Racemic 8-hydroxy-2-(di-*n*-propylamino)tetralin HBr (8-OH-DPAT) was purchased from Research Biochemicals Inc., Wayland, MA. Yohimbine HCl was purchased from Aldrich Chemical Co., Milwaukee, WI. Ipsapirone (2-(4-(2-pyrimidinyl)-l-piperazinyl)butyl)-1,2-benzisothiazol-3-(2H) one 1,1-dioxide HCl) was generously provided by Dr. Jorg Traber, Troponwerke GMBH & Co., Cologne, FRG, and, more recently, by Dr. Alexander Scriabine, Institute for Preclinical Pharmacology, Miles Laboratories, Inc., New Haven, CT. All doses refer to the respective salts.

Statistics

Wilcoxon's signed ranks test was used to determine the statistical significance of differences in response distribution following yohimbine and either 8-OH-DPAT or ipsapirone.

RESULTS

In the table are shown the results of the tests of generalization of 8-OH-DPAT and ipsapirone to yohimbine. At a dose of 3 mg/kg, yohimbine was followed by a degree of 8-OH-DPAT-appropriate responding (85%) which was not significantly different from that of the training drug (91%). In ipsapirone-trained subjects, yohimbine (6 mg/kg) yielded 86% drug-appropriate responses. This value differed significantly ($p<0.05$) from that following the training dose of ipsapirone (99%).

DISCUSSION

The present data clearly indicate that 8-OH-DPAT, ipsapirone, and yohimbine share similar stimulus properties in the rat. The fact that the maximum degree of ipsapirone-appropriate responding following yohimbine (86% at a dose of 6 mg/kg) was significantly different from tests of the training dose of ipsapirone ($p<0.05$) is possibly an artifact due to the unusually small degree of variation in the latter tests (99%±1). Although there are no fixed criteria for complete generalization of one drug to another, the data shown are compatible with a high degree of similarity between yohimbine and the drugs which were trained.

These findings are surprising for two reasons. First, the behavioral effects of ipsapirone and yohimbine in animals are decidedly different: yohimbine is widely regarded as anxiogenic [2] while ipsapirone is anxiolytic-like [10]. Second, studies of receptor binding indicate a high degree of specificity on the part of ipsapirone and 8-OH-DPAT for the 5-HT_{1A} binding site [3,7] while yohimbine has high affinity for the clonidine-labeled alpha$_2$ adrenergic site [12] and low affinity for the 5-HT_{1A} site ([5]; Rabin and Winter, unpublished). An action of yohimbine on serotonin receptors was postulated by Colpaert [1] on the basis of his observation of the generalization of the yohimbine cue to LSD and vice versa. However, an earlier report [13] failed to observe either complete generalization of yohimbine to LSD or antagonism of the yohimbine cue by pizotyline.

Previous studies have found a high degree of correlation between stimulus generalization and the pharmacological properties of drugs [8]. Thus, opiates tend to mimic other opiates, hallucinogens other hallucinogens, and so on. The present results suggest that either 8-OH-DPAT, ipsapirone, and yohimbine are less specific in their stimulus effects than previously thought or there are behaviorally significant interactions between adrenergic and serotonergic systems in the brain. With respect to the latter, there is evidence for the presence of alpha$_2$ adrenergic receptors on serotonergic nerve terminals [6].

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NOTE ADDED IN PROOF

Dr. James Howard has observed that yohimbine has anti-conflict activity in rats tested with a modified Geller-Seifter procedure (personal communication).

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