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Failure of SCH 23390 to Function as a Discriminative Stimulus in Rats[1]

JONATHAN B. KAMIEN[2] AND WILLIAM L. WOOLVERTON[3]

The Drug Abuse Research Center, Pritzker School of Medicine
The University of Chicago, Chicago, IL 60637

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KAMIEN, J. B. AND W. L. WOOLVERTON. *Failure of SCH 23390 to function as a discriminative stimulus in rats.* PHARMACOL BIOCHEM BEHAV **34**(2) 337–340, 1989.—Four rats were studied in a two-lever, food-reinforced drug discrimination paradigm using the D1 dopamine antagonist SCH 23390 (0.03 mg/kg, IP, 30 minutes prior to the session) and saline as the training stimuli. After at least 100 training sessions there was no evidence of stimulus control over responding by SCH 23390 in 3 of the 4 rats, and only briefly in the fourth. On the other hand, food delivery exerted control over behavior indicating that SCH 23390 did not disrupt control of behavior by the reinforcing stimulus. An increase in training dose to 0.06 mg/kg for an additional 12 sessions did not improve discriminative accuracy although this dose reduced rate of responding to an extent that made further training using 0.06 mg/kg untenable. The results provide no evidence of stimulus control of behavior by SCH 23390 and suggest that SCH 23390 does not function as a discriminative stimulus in rats.

Drug discrimination SCH 23390 Behavior Rats D1 receptors Dopamine

SCH 23390 (SCH), a selective D1 dopamine (DA) antagonist (14,15), has proven an important tool for the study of the function of multiple DA receptors. Although SCH has proven quite selective for D1 receptors (7, 9, 15), SCH has many behavioral effects, such as blockade of conditioned avoidance responding (15) and induction of catalepsy (19), that are commonly associated with D2 antagonists. Furthermore, catalepsy induced by SCH can be blocked by pretreatment with D2 agonists (17,22). Therefore, the behavioral effects of SCH as demonstrated by the conventional tests of CNS DA activity appear to overlap with those of D2 antagonists.

Drug discrimination paradigms have proven highly selective for separating behaviorally active drugs according to their pharmacological actions in the CNS (2, 12, 16). Therefore, the discriminative stimulus (DS) properties of SCH may provide a behavioral correlate that separates the effects of D1 receptor blockade from the effects of D2 receptor blockade. However, there has been ambiguity in the literature concerning the ability of antipsychotic compounds (primarily D2 antagonists) to function as discriminative stimuli. Chlorpromazine was trained as a DS first by Stewart (24). Unfortunately, Stewart did not include the stimulus control criterion used nor the number of training sessions necessary to achieve that criterion so the degree of discriminative control displayed by chlorpromazine in that study is not known. Since then, several authors have reported inability (11,20) or difficulty (3, 5, 10) demonstrating stimulus control over responding using a classical neuroleptic as the DS. In addition, there is at least one report (8) in which a D2 antagonist (haloperidol) was trained as a DS with relative ease. Thus, the appropriate conditions for studying the DS effects of DA antagonists are not known.

The present experiment was designed to investigate whether SCH can serve as a DS. Because of the selectivity of drug discrimination procedures, the DS properties of SCH may reflect behavioral effects of SCH which do not overlap with those of D2 antagonists. Moreover, the DS properties of SCH may provide an opportunity to investigate the suggestion that D1 blockade may enhance the effects of D2 receptor stimulation (23,25).

METHOD

Animals and Apparatus

Four male Sprague-Dawley (Holtzman Co., Madison, WI) rats served as subjects. They were maintained at 280–300 g (80 ± 5% of their initial free-feeding body weights) by restricting food intake. They were individually housed in stainless steel cages in a room maintained at 24°C and on a 12-hour (7 a.m.–7 p.m.) light-dark cycle. In addition to the 45 mg food pellets (P. J. Noyes Co., Lancaster, NH) delivered during the experimental sessions, diet was supplemented with Teklad 4% Mouse and Rat Diet (Winfield, IA). Water was continuously available except during experimental sessions.

Four identical operant chambers for rats (R. Gerbrands Co.,

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[2]Requests for reprints should be addressed to J. B. Kamien at his present address: Harvard Medical School, McLean Hospital, 115 Mill St., Belmont, MA 02178.

[3]Departments of Pharmacological and Physiological Sciences and Psychiatry.

Arlington, MA) were used. In each chamber, two response levers were mounted on one wall and a food receptacle was located between them. Each chamber was illuminated at the onset of experimental sessions by a single six-watt light located on the wall opposite the levers. Extraneous noise was diminished by enclosing each chamber in an insulated picnic chest and by operating ventilation fans mounted on the outside of each chest. An AIM-65 microcomputer (Dynatem Corp., Irvine, CA), connected to a custom designed input/output interface (ERH Electronics, Delton, MI) located in an adjacent room, controlled stimulus events and recorded lever presses.

Procedure

The rats were assigned randomly to one of the four experimental chambers. In two chambers, the right lever was designated as the saline-appropriate lever and the left lever the SCH-appropriate lever. In the other two chambers, the reverse assignments were made. Thirty minutes after rats received an intraperitoneal injection of 0.03 mg/kg SCH or saline, the house light was illuminated and food was available for every response on the injection-appropriate lever. This training dose and pretreatment time was chosen based on the finding that 0.03 mg/kg SCH given 30 minutes prior to a test session blocks the DS effects of the D1 agonist SKF 38393 (16). Half of the rats in each group were shaped initially by successive approximation to press the SCH-appropriate lever after SCH injections and half were shaped initially to press the saline-appropriate lever after saline injections. Fifteen-minute training sessions were conducted once a day, 6 days a week, following a double alternation sequence in which two sessions of SCH pretreatments alternated with two sessions of saline pretreatments. This double alternation sequence was in effect from the first day of lever press shaping. Gradually the response requirement was increased from 1 to 30 (fixed-ratio 30: FR30) on each of the two levers. The FR value was increased for each lever when response patterns were similar under both conditions. Responses on the inappropriate lever were counted and reset the response requirement on the correct lever. The double alternation training sequence continued until a rat met a two-part criterion for stimulus control over responding: at least 80% of the responses before the delivery of the first food pellet and 90% of the total responses in the 15-minute session had to occur on the appropriate lever for at least seven of eight consecutive sessions. If an animal did not meet and maintain this criterion after 100 sessions, the training dose was increased to 0.06 mg/kg SCH for an additional 12 sessions.

Testing

If an animal met the criterion for stimulus control over responding, a test session was conducted in which food was available under a FR30 schedule on either lever. Nonconsecutive responding (i.e., responding on one lever and then the other) did not reset the response requirement on either lever. Otherwise test sessions were identical to training sessions.

Data Analysis

The percentage of responses that occurred on the SCH-appropriate lever before the first reinforcer was calculated for each session as a measure of stimulus control of responding by the injection. The percentage of responses occurring on the SCH-appropriate lever throughout the session was calculated as a measure of stimulus control afforded by the drug and the delivery of the reinforcer. The rate of responding throughout the session (total number of responses/600 sec) was calculated as an additional measure of drug effects on behavior. If a rat failed to receive a food pellet in any session, the data for that session were not included in the percent drug-appropriate responses calculation but were included in the response rate determination.

Drugs

SCH (R-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepine-7-ol) was a gift of Schering-Plough Corporation, Bloomfield, NJ. SCH was dissolved in physiological saline at a concentration of 0.03 or 0.06 mg/ml, expressed in terms of the salt. Injections were always intraperitoneal, at a volume of 1.0 ml/kg, 30 minutes before the session.

RESULTS

The percentage of responses that occurred on the correct lever did not reach criterion levels within 100 training sessions in 3 of the 4 rats (Table 1, rats 1, 2 and 3). The performance of rat 4 met the criterion for stimulus control over responding after 87 sessions. However, when the training dose of 0.03 mg/kg SCH was subsequently administered before a test session, responding occurred exclusively on the saline-appropriate lever. Increasing the training dose to 0.06 mg/kg SCH did not improve discriminative accuracy before the first reinforcer in 3 of the 4 rats. The apparent exception was rat 4, although this increase is based on only the 2 of 6 possible sessions in which the rat earned a reinforcer (Table 1 and below). On the other hand, by about the 60th session, the percentage of SCH-appropriate responses measured over the entire session was almost always greater than 80% on days when SCH was injected and less than 20% when saline was injected.

Two rats (1 and 3) developed strong preferences for the saline-appropriate lever during training. Rat 1 met the criterion for stimulus control 4 times as often on saline training days as on drug training days. Even more striking was the saline lever preference developed by rat 3. This rat met the criterion for stimulus control more than six times more often following saline injections than following drug injections.

Response rates following 0.03 SCH were clearly lower than those following saline in rat 2 but not in any of the other 3 rats (Table 1). An increase in training dose to 0.06 mg/kg SCH substantially reduced or eliminated responding in all rats (Table 1).

DISCUSSION

SCH (0.03 mg/kg) did not acquire stimulus control over responding following at least 100 training sessions, except briefly in one rat. An increase in training dose to 0.06 mg/kg did not improve discriminative accuracy and reduced rate of responding to an extent that made further training using 0.06 mg/kg untenable. The single test session that was conducted used the training dose as a test stimulus and resulted in 0% SCH-appropriate responding. Thus, the evidence suggests that SCH exerted no, or at best weak, stimulus control over responding under these conditions.

Although it is possible that pretreatment parameters for SCH were inappropriate, it seems unlikely. The training dose (0.03 mg/kg) and pretreatment time (30 min) of SCH were chosen based on the finding that 0.03 mg/kg SCH blocks the DS effects of the D1 agonist SKF 38393 under these conditions (16). Similar doses and pretreatment times have also been shown to have effects on unconditioned behavior. A dose of 0.01 mg/kg reduces rearing in rats (13) and 0.05 mg/kg antagonizes apomorphine- and amphetamine-induced stereotypy (17). Catalepsy is observed following administration of about 0.1 mg/kg SCH (4,18). In all of these studies, the peak effects of SCH were reported to occur between 30 and 60 min. Thus, the training dose and pretreatment time

TABLE 1

AVERAGE PERFORMANCE OF FOUR RATS OVER THE LAST SIXTEEN SESSIONS OF TRAINING WITH SCH 23390

Condition	Number of Sessions	% Correct Over Session*	% Correct Before First Reinforcer*	Rate* (resp/sec)
Rat 1				
Saline	3	100 ± 0	100 ± 0	0.68 ± 0.2
0.03	7	93.6 ± 3.4	53.4 ± 21.0	0.56 ± 0.14
0.06	6(5)†	90.0 ± 5.6	58.5 ± 19.5	0.37 ± 0.32
Rat 2				
Saline	3	85.9 ± 20.7	76.3 ± 41.0	0.52 ± 0.08
0.03	7(6)	96.0 ± 6.1	71.8 ± 42.4	0.24 ± 0.22
0.06	6(4)	84.8 ± 12.8	44.1 ± 26.5	0.26 ± 0.25
Rat 3				
Saline	4	92.8 ± 44.4	68.6 ± 36.2	0.97 ± 0.04
0.03	6	87.3 ± 8.3	35.6 ± 7.1	0.83 ± 0.14
0.06	6(3)	63.4 ± 33.1	76.8 ± 20.1	0.35 ± 0.40
Rat 4				
Saline	5	100 ± 0	100 ± 0	1.01 ± 0.14
0.03	5	95.6 ± 4.2	58.3 ± 38.2	1.15 ± 0.15
0.06	6(2)	71.8 ± 28.6	100 ± 0	0.17 ± 0.27

*These numbers represent the mean ± the standard deviation. If a rat failed to receive a food pellet in any session, the data for that session were not included in the percent correct responses calculation but were included in the response rate determination.

†The numbers in parentheses are the number of sessions in which a reinforcer was actually delivered. In cases where there are no parentheses, reinforcers were delivered in all sessions.

chosen have been shown to be active in other behavioral preparations. Moreover, when the training dose was increased to 0.06 mg/kg response rates were reduced to a point where training with this dose and the FR30 schedule of food presentation was not practical. It is also possible that SCH would function as a DS if more training sessions were conducted. However, stimulus control of responding generally develops with other drugs in substantially less than 100 sessions (1,21). In fact, Colpaert *et al.* (6) reported that haloperidol could function as a DS in rats after approximately 80 training sessions. Thus, even if the SCH discrimination were to be acquired in additional training sessions the drug could at best be termed a weak DS.

A final possibility is that SCH interfered with the process of discrimination generally rather than lacking DS effects. Such a possibility has been raised previously as an account for the blockade of the DS effects of cocaine and amphetamine by neuroleptics (6). This interpretation of the results of the current study is unlikely. The percentage of SCH-appropriate responding over the entire session indicates that the delivery of the reinforcer acquired stimulus control over responding by about the 60th session in all rats trained. It should also be noted that SCH has been found not to interfere with already established discriminations based on the D2 agonist piribedil (PIR) and saline (16).

In short, SCH 23390 failed to function as a DS in rats under conditions where other compounds readily function as DS, and it is unclear why this is the case. Compounds that are primarily D2 or mixed D1/D2 antagonists have proven to be difficult to train as DS as well. Although some investigators have reported stimulus control of responding by DA antagonists in rats (5, 8, 24), most have reported inability (11,20) or difficulty (3, 5, 10) establishing the discrimination. It seems, therefore, that DA antagonists are not efficacious DS regardless of their receptor actions. One might postulate that blockade of stimulation of DA receptors by endogenous DA may not create the kind of salient change in interoceptive stimuli that is readily discriminable by rats. This is in contrast to the "supraphysiological" state that may be produced by DA agonists in this procedure that is clearly distinguished from the physiological state that is present on saline training days. Only additional research can clarify this issue.

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