Pharmacology Biochemistry and Behavior, Vol. 57, No. 4, pp. 829–833, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(96)00400-5

Conditioned Grooming Induced by the Dopamine D1-like Receptor Agonist SKF 38393 in Rats

SARAH J. PAGE AND PHILIP TERRY[1]

School of Psychology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK

Received 25 April 1996; Revised 2 August 1996; Accepted 2 August 1996

PAGE, S. AND P. TERRY. *Conditioned grooming induced by the dopamine D1-like receptor agonist SKF 38393 in rats.* PHARMACOL BIOCHEM BEHAV **57**(4) 829–833, 1997.—Stimulation of dopamine D1-like receptors reliably increases grooming in rats and mice. The study examined whether the grooming response elicited by the prototypical D1-like agonist SKF 38393 (8 mg/kg SC) could be conditioned to the specific environment in which it occurred. Rats in one group (Paired) received SKF 38393 and rats in another group (Unpaired) received saline in observation boxes outside of their housing room; the rats were then scored for duration and frequency of grooming bouts over 25 min. The ordering of injections was reversed the next day in the rats, housing room. The procedure was repeated twice, with at least one intervening drug-free day, to give three conditioning trials. The D1-like agonist significantly increased grooming on each of the three conditioning trials, without obvious tolerance or sensitization, and the effect tended to persist for the duration of each trial. On the test trial for conditioned grooming, mean grooming duration was significantly greater in the Paired than the Unpaired group, suggesting that SKF 38393-induced grooming had been conditioned to the test environment. This is the first time that drug-elicited grooming has been conditioned to environmental cues. © 1997 Elsevier Science Inc.

D1-like receptors Grooming Conditioned drug effects SKF 38393 D1 agonists

DIFFERENT behavioural effects have been attributed to drugs having different selectivities among the various dopamine receptor subtypes. Adopting the view that dopamine receptor subtypes may be categorized into two families, the so-called "D1-like" and "D2-like" receptor families (11,29), the characteristic rodent behaviour associated with selective stimulation of D1-like receptors is increased grooming. Indeed, the first behavioural studies of the prototypical agonist SKF 38393 identified grooming as the predominant effect in rats (20). The increase in grooming that follows administration of SKF 38393 to rats has since been confirmed many times [e.g., (21,40)]; the drug has also been shown to provoke increased grooming in mice (32,33). As regards other D1-like agonists, grooming has been reported following administration of other benzazepines of different intrinsic efficacies (23), as well as the isochroman A-68930 (7), the benzophenanthredine dihydrexidine (8), and the indolphenanthredine CY 208-243 (24). However, as is the case for other behaviours associated with the actions of D1-like agonists [e.g., (35)], there is no clear relationship between grooming and the efficacies of D1-like agonists to stimulate adenylyl cyclase (41). Despite this, the specific involvement of D1-like receptors has been supported by findings that the effect can be attenuated by pretreatment with the D1-like antagonist SCH 23390 [e.g., (20,40)]. The antagonist also attenuates grooming behaviour induced either by novelty or by various neuropeptides, perhaps suggesting a general regulatory role for D1-like receptors in grooming behaviour (38).

Although many studies have looked at grooming induced by D1-like agonists administered acutely, few studies have explored the consequences of chronic agonist treatment on grooming, and none have examined whether the grooming response might come under environmnental control with repeated drug–environment pairings (i.e., whether the response can be classically conditioned to environmental cues). This omission is surprising, because the chronic and conditioned effects of dopaminergic drugs have long been a focus of intense research interest. Indirect dopamine agonists, such as cocaine and *d*-amphetamine, reliably produce classically conditioned locomotor activity [e.g., (1,16,26)], as does apomorphine, a dopamine agonist that is not selective between receptor subtypes [e.g., (19,27)]. Classically conditioned locomotor

[1]To whom requests for reprints should be addressed. E-mail: p.terry@bham.ac.uk

behaviours have also been produced by pairing injections of D2-like receptor agonists with specific environments [e.g., (14,17)]. Indeed, there have been many conditioning studies looking at the effects of either nonselective or D2-like dopaminergic agonists, probably in part because of the recognition that dopamine release, uptake inhibition, or D2-like receptor stimulation are important to the effects of stimulant drugs of abuse, and because of the importance attributed to conditioning processes in the aetiology of drug abuse and addiction. However, recent work has begun to place greater emphasis on the role of D1-like receptors in the actions of abused drugs [e.g., (5,6,28)], thus demonstrating a need for better characterization of the chronic effects of drugs that interact with D1-like receptors. To date, however, only one study has explicitly examined whether certain behaviours produced by a D1-like agonist (SKF 38393) can be conditioned to a particular environment by repeated drug–environment pairings (18). In that study, the authors reported a weak (but significant) conditioning of horizontal locomotor activity to a specific test chamber; however, the drug's primary behavioural effect—grooming—was not measured. In the present study we report, for the first time, that grooming induced by SKF 38393 can be conditioned to a particular environment. To our knowledge, this is also the first report of conditioned grooming induced by any class of drug, even though it has long been known that many classes of drug elicit grooming, for example, some peptides and hormones [e.g., (12,31,34,37,39)]. The method adopted was based on that of Mazurski and Beninger (18).

METHOD

Subjects

Subjects were 16 male Sprague–Dawley rats (Charles River UK Ltd., Kent, UK) housed in groups of four per cage and weighing 225–280 g at testing. The rats were maintained on a 12 L:12 D cycle (lights on at 0700 h) at 21 ± 2°C and had free access to food and water at all times, except during exposure to the test apparatus. In each cage, two rats were assigned (randomly) to the Paired group, and two to the Unpaired group; thus, there were eight rats in each group. Rats were tested 2 weeks after delivery to the housing room.

Apparatus and Test Environment

The test apparatus consisted of two identical transparent Perspex boxes (50 × 50 × 35 cm high), each open at the top and bottom, placed on a bench in the test room. The boxes were equidistant from the observer (who was seated approximately 2.5 m away) and were separated by 1.7 m with an opaque screen between them. The test room was dimmer than the housing room, being illuminated by two 60-W desk lamps angled toward the ceiling and away from the test boxes.

Procedure

First, each rat was exposed for 30 min to one of the test boxes to reduce novelty-induced grooming and exploratory behaviours on subsequent observation days. Rats were tested in pairs, balanced for treatment within a pair and for test box between pairs; the observer was present throughout. Three days later, the first conditioning trial was given. Two rats were taken from their home cage to the test room. One rat was injected with either 8 mg/kg SKF 38393 (Paired group) or saline (Unpaired group) and placed directly into the first test box. The dose used has been shown to induce grooming reliably (40). Five minutes later, the second rat was injected with the converse treatment and placed into the second test box. The first rat was then observed for 5 min, during which the following behaviours were recorded: incidence of grooming bouts and duration of each grooming bout (timed by stopwatch). For the next 5-min period, the second rat was observed, and grooming scores were recorded as before. This cycle of observation was repeated twice more, thus yielding (for each rat) three 5-min measurement periods separated by 5-min intervals. Grooming included washing of the forelegs and head; cleaning of the hindlegs, body trunk, tail, or genitals; shaking of the whole body; and/or scratching. These components were not differentiated during measurement, nor was any distinction drawn between "intense" or "stereotyped" grooming and other forms. After the observation session, the rats were returned to the housing room, the number of fecal boli in each test box was counted, and the boxes and bench surfaces were thoroughly cleaned with mild detergent. Fecal boli were counted to provide a simple supplementary measure: both grooming and defecation have been used as indices of stress reactivity in rodents; it was of interest to see if the two measures followed similar conditioning profiles. The whole process was then repeated until all 16 rats were tested. All testing was conducted between 1000 and 1630 h. The second conditioning trial was performed in an identical manner 3 days later, and the third conditioning trial was conducted 4 days after the second. The observer did not administer injections and was blind to the treatments given; however, to compensate for the possibility that the observer might learn to attribute rats

TABLE 1

DURATION OF GROOMING (s; MEAN ± SEM) AND FREQUENCY OF GROOMING BOUTS (MEAN ± SEM) FOR PAIRED AND UNPAIRED GROUPS OVER CONDITIONING TRIALS AND TIME PERIODS (WITHIN TRIALS)

	Trial 1		Trial 2		Trial 3	
	Duration	Frequency	Duration	Frequency	Duration	Frequency
Paired group						
Time period 1	102.8 ± 23.6	4.0 ± 0.6	124.5 ± 9.1	3.4 ± 0.7	118.5 ± 22.3	3.3 ± 0.6
Time period 2	95.0 ± 22.7	4.3 ± 0.8	88.3 ± 17.9	3.1 ± 0.6	92.9 ± 24.2	2.8 ± 0.4
Time period 3	91.9 ± 15.6	4.8 ± 1.2	72.1 ± 15.7	2.5 ± 0.6	65.7 ± 12.0	2.1 ± 0.3
Unpaired group						
Time period 1	28.6 ± 10.6	1.4 ± 0.5	23.3 ± 20.9	1.6 ± 1.1	27.2 ± 15.5	2.1 ± 1.0
Time period 2	31.7 ± 15.0	2.5 ± 0.9	2.4 ± 2.4	0.3 ± 0.3	26.7 ±1 4.8	1.6 ± 0.8
Time period 3	18.9 ± 9.7	1.8 ± 0.9	15.5 ± 14.7	0.8 ± 0.6	10.1 ± 6.9	0.5 ± 0.4

For statistical analyses, see the text.

TABLE 2
NUMBERS OF FECAL BOLI (MEAN ± SEM) FOR PAIRED AND UNPAIRED GROUPS OVER TRIALS

	Trial 1	Trial 2	Trial 3	Test
Paired group	2.6 ± 0.7	3.4 ± 0.4	2.8 ± 0.4	1.6 ± 0.5
Unpaired group	1.6 ± 0.7	0.6 ± 0.5	0.5 ± 0.3	1.9 ± 0.7

For statistical analyses, see the text.

to treatment groups over trials (enhanced grooming might indicate SKF 38393-treated rats), the test order of pairs of rats within a cage was randomized over trials. On the final conditioning trial, a second person, located outside the test room and observing through a window, also provided behavioural measurements on one pair of rats. These data were used to assess interobserver reliability.

The day after each conditioning trial the rats were injected again, this time in their home cages (housing room): rats in the Paired group received saline, and rats in the Unpaired group received SKF 38393. The conditioning test occurred 3 days after the last conditioning trial and was identical to the conditioning trials with the exception that all rats were injected with saline.

Drugs

(±)-SKF 38393 HCl [(±)-1-phenyl-2,3,4,5-tetrahydro-(1H)-3-benzazepine-7,8-diol hydrochloride] was obtained from Research Biochemical Ltd. [Semat Technical (UK) Ltd., St. Albans, Herts., UK]. The drug was dissolved in physiological saline and injected subcutaneously in a volume of 1 ml/kg.

Analysis

The three successive observation periods for each rat constituted the factor Time Period, the three conditioning trials constituted the factor Trials, and the drug–environment association (Paired vs. Unpaired) constituted the factor Group. Separate analyses of variance were conducted on the various measures, first for the conditioning trial data, then for the test data (factors Group and Time Period only).

RESULTS

Conditioning Trials

In all three conditioning trials, SKF 38393 increased the duration and frequency of grooming at all three time periods (Table 1). For duration, there was a significant main effect of Group [$F(1, 56) = 27.80$, $p < 0.001$], but no main effect of Time Period [$F(2, 56) = 2.87$, $p > 0.05$] or Trials [$F(2, 56) = 0.6$, $p > 0.05$] and no significant interactions between any of these factors [all $p > 0.05$]. Thus, drug-treated rats groomed for longer than saline-treated rats throughout the conditioning phase, but there was no significant change in the measure within test sessions or across conditioning trials. For frequency of grooming bouts, there was again a significant main effect of Group [$F(1, 56) = 19.35$, $p < 0.001$] and no effect of Time Period [$F(2, 56) = 0.64$, $p > 0.05$]; however, there was now a significant effect of Trials [$(2, 56) = 8.42$, $p < 0.01$] but again no interactions between factors (all $p > 0.05$).

There was a main effect of Group on the number of fecal boli counted (see Table 2), with a significantly greater number counted in the Paired condition [$F(1, 28) = 12.84$, $p < 0.01$], but there was no effect of Trials and no interaction between the two factors [$p > 0.05$].

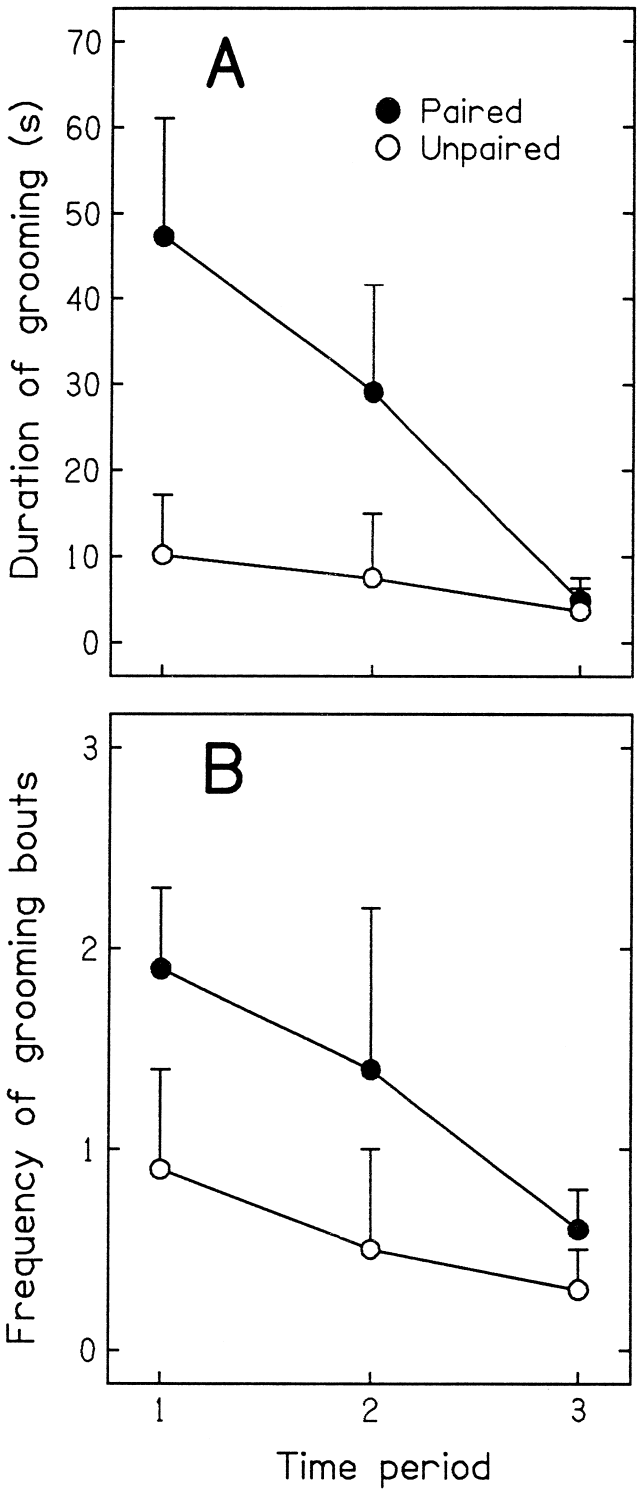

FIG. 1. Test trial: mean grooming time (A) and mean grooming frequency (B) for Paired and Unpaired groups over three time sampling intervals; both groups were injected with saline. The total observation period was 15 min; $n = 8$ at each point.

Test Trial

The mean durations and frequencies of grooming behaviour in the test session are presented in Fig. 1. There was a significant effect of Group on duration of grooming [$F(1, 28) =$

6.48, $p < 0.05$; Fig. 1A] but not on frequency of grooming bouts [$F(1, 28) = 2.66$, $p > 0.05$; Fig. 1B]. Duration, but not frequency, also declined significantly over the session [Time Period: $F(2, 28) = 4.33$, $p < 0.05$; $F(2, 28) = 1.99$, $p > 0.05$, respectively]. There was no interaction between the two factors for either measure [$p > 0.05$]. Thus, the duration measure provided strong support for the induction of conditioned grooming.

Finally, unlike for the conditioning trials, in the test trial there was no effect of Group on number of fecal boli [$F(1,14) = 0.08$, $p > 0.05$; Table 2].

Interobserver Reliability

The post hoc test for interobserver reliability in the final conditioning trial revealed very strong agreement between the two independent observers (frequency scores identical; for duration, $n = 6$, $r > 0.99$, $p < 0.001$).

DISCUSSION

The D1-like receptor agonist SKF 38393 reliably increased grooming behaviour over the three conditioning trials, and the effect tended to persist for the duration of each trial. The results indicated that there was no tolerance or sensitization to the effect of the drug, although the frequency measure suggested a modest decline in responsiveness over trials (Table 1; but see below regarding the relative importance of the two measures). Duration of grooming tended to decline over the time sampling periods within trials, although not significantly. The finding of maximal levels of grooming from the outset of recording (5 min postinjection) corresponds with the results of others (40) and is perhaps surprising, given that the drug has poor brain penetrability and its other effects can have slow onset and long duration (36). The absence of clear tolerance over trials contrasts with previous reports that repeated administration of SKF 38393 leads to a marked decline in drug-elicited grooming (15,42). However, the interdrug interval adopted in the present study was long compared with intervals used in previous studies of chronic drug exposure on grooming (most commonly two injections per day for more than 2 weeks). The scheduling of drug exposures plays an important role in changing behavioural responsiveness to drugs, with short interdrug intervals promoting tolerance (25).

In the test trial, rats in the Paired group groomed significantly longer than rats in the Unpaired group, indicating that drug-induced grooming had been conditioned to the test environment. The general level of grooming in the Paired group was, however, much reduced in comparison with the levels of grooming recorded in the conditioning trials, demonstrating that the conditioned effect was not as strong as the drug-elicited effect. On the other hand, the frequency measure did not reveal a significant effect between groups in the test trial (although it approached significance; see also Fig. 1). Rather than take this dissociation as suggesting (perhaps) a change in the profile of grooming in the test trial compared with the conditioning trials, it should be noted that grooming frequency has previously been described as a less reliable and more variable measure than grooming duration (40); many researchers use the latter measure exclusively.

Because grooming has been interpreted as a stress-related behaviour (9,22,31), and SKF 38393 has been reported to produce anxiogenic-like or aversive effects (13,30), it was considered potentially useful to record another common measure of stress reactivity: the number of fecal boli produced during trials. This secondary measure yielded some interesting results: the drug was associated with significantly higher defecation rates in the observation boxes, congruent with the possibility that SKF 38393-induced grooming might be associated with a stresslike syndrome. A previous study found that SKF 38393 had the opposite effect, namely, it reduced defecation (4), but measures were not taken before 30 min after drug administration, thus raising the possibility that increased early defecation (unrecorded) might have been responsible for the reduced score later. Unlike grooming, in the present experiment, the drug-increased incidence of defecation did not condition to the test environment. Such a dissociation between these two effects of the drug suggests that if both phenomena are attributable to a common action of the drug (e.g., on stress or arousal), then only one component of this common action can be classically conditioned. In fact, the independence of the two measures as indices of stress reactivity has been reported (10).

The possibility that different behavioural effects of a drug might exhibit different conditioning profiles has not been well examined previously. Most studies have recorded only single behaviours, usually variants of locomotor activity or stereotypic actions. To our knowledge, this is the first report of a qualitatively different type of behaviour, elicited by a dopaminergic agonist, being conditioned to a specific environment. However, grooming is itself a complex sequence of behavioural components amenable to detailed analysis [e.g., (2,3,38)] and thus would lend itself well to future studies addressing the similarities between drug-elicited and conditioned behaviour. In fact, the structure of the unconditioned grooming associated with SKF 38393 has not yet been characterized in precise detail. The drug has been reported to increase the frequencies of head washing, paw licking, and (to a lesser extent) anogenital grooming, but not scratching, thus eliciting a behavioural profile quite different from that of most neuropeptides (38,39). Further comparisons with grooming induced by other drugs, and further comparisons with normal grooming, would be welcome.

In conclusion, it has previously been established that locomotor activity produced by SKF 38393 can be conditioned to a particular environment (18); we found that the drug's most prominent behavioural effect, grooming, can also be conditioned to the environment in which it was produced.

ACKNOWLEDGEMENTS

We thank Mr. Dave Barber for expert technical assistance.

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