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A Role for D_2, but not D_1, Dopamine Receptors in the Response-Reinstating Effects of Food Reinforcement

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CHAUSMER, A. L. AND A. ETTENBERG. *A role for D_2, but not D_1, dopamine receptors in the response-reinstating effects of food reinforcement.* PHARMCOL BIOCHEM BEHAV **57**(4) 681–685, 1997.—Although the reinforcing properties of food are reduced in the presence of dopamine antagonist drugs, controversy exists about the relative roles of D_1 vs D_2 receptor subtypes in the actions of these drugs. The current experiment compared the effects of raclopride (a selective D_2 receptor antagonist) and SCH 39166 (a selective D_1 receptor antagonist) in the response-reinstating effects of food reinforcement. Hungry rats were trained to run a straight-alley for food reinforcement during single daily trials. The operant was then extinguished during consecutive daily non-reinforced trials. Subjects were then injected with one of four doses of raclopride (0.0, 1.0, 0.5, and 0.25 mg/kg, IP) or SCH 39166 (0.0, 1.0, 0.5, and 0.1 mg/kg IP) 30 min prior to a single reinforced treatment trial. Twenty-four h later, a test trial was conducted in an unbaited runway. The single reinforced trial in the midst of extinction was observed to reinstate operant runway performance. Raclopride, but not SCH 39166, dose-dependently attenuated this reinstatement. Motor control groups ruled out the possibility that these results were due to differential residual motor effects of the drugs. Results suggest that D_2, but not D_1, dopamine receptors, are involved in the response-reinstating properties of food reinforcement. © 1997 Elsevier Science Inc.

Raclopride SCH 39166 Runway Operant behavior Dopamine receptor antagonists

CONSIDERABLE evidence points to an involvement of central dopaminergic pathways in the reinforcing properties of naturally occurring incentives such as food and water (e.g., for reviews see 2,12,29). Such evidence has often taken the form of demonstrations that operant response rates in food- or water-reinforced tasks are diminished during dopamine receptor antagonist drug challenge—even at doses that do not appear to produce obvious sedative or motor-incapacitating effects (3,9,25,35). It remains the case, however, that decreases in operant behavior can be attributed to a wide variety of factors independent of reward attenuation (1,29).

Our laboratory has addressed this concern by employing behavioral test procedures that examine putative drug-induced reductions in reinforcer efficacy at a time when the test animals are no longer drugged (and hence not subject to motoric, sedative, or attentional deficits that might otherwise account for changes in the drugged response) (13,14,15,16,22). In one such study, Horvitz and Ettenberg (22) trained hungry animals to traverse a straight alley and enter a goal box where food reinforcement was delivered. The subjects were tested on but one trial a day. Once the operant was established, an extinction phase was instituted during which daily single trials were continued but no food was delivered upon goal box entry. Once runway behavior slowed, a single treatment trial was conducted, the effects of which were examined the next day. Animals that continued to experience an empty goal box on treatment day, continued to run slowly on Test Day (24 h later). However, animals that found food in the goal box on Treatment Day reinstated their operant running on the next trial. This response-reinstating effect of food reinforcement was dose-dependently attenuated in animals pretreated on Treatment Day with the dopamine receptor antagonist drug, haloperidol. Note again, that the critical test day data were collected 24 h post-injection. The authors suggested that operant performance on test day reflected the quality of the reinforcer experienced in the goal box on the previous day.

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Therefore, since animals that experienced food+haloperidol on treatment day subsequently behaved in a manner comparable to those who had experienced no reinforcer at all during treatment day, it was concluded that normal dopamine function was necessary for demonstrating the response-reinstating properties of food reinforcement (22).

The Horvitz and Ettenberg (22) study described above employed the drug haloperidol. However, given the current controversy on the relative importance of different receptor subtypes in reinforced and motivated behaviors (2,10,30, 37,40), it was of interest to extend our investigation to dopamine antagonist compounds thought to have a more selective site of action. Although haloperidol has a far greater affinity for the D_2 than D_1 dopamine receptor (8,24,27), conclusions about the relative importance of these two receptor subtypes must necessarily await a direct comparison of selective antagonist activity at each site. Toward that end, the present study was devised to build upon the results of Horvitz and Ettenberg (22) by comparing the effectiveness of the putative D_2 receptor antagonist, raclopride, with the putative D_1 receptor antagonist, SCH 39166, in preventing the response-reinstating properties of food reinforcement.

METHOD

Subjects

The subjects were 111 six-month old male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) maintained at 85% of free-feeding weight throughout the experiment (mean 290 g at start of training). Water was available on an ad lib basis. The rats were individually housed in the Psychology Vivarium which was maintained on a 12L:12D cycle (lights on at 0700) at an ambient temperature of 22°C.

Apparatus

The apparatus consisted of a straight wooden runway, measuring 156 cm long × 10.5 cm wide × 20 cm high. Sliding doors separated the identically-sized (20 × 24 × 20 cm) start and goal boxes from the runway. Food reinforcement (ten 45 mg Noyes pellets) was delivered into a metal feeder cup located on the far wall of the goal box (facing the alley). Infrared Photocell emitter-detector pairs were located in the alley just outside the start box door, and in the goal box (just inside the goal box door). Once the animal broke the first (start box) photobeam, a timer (Synesthesia Reaction-Choice Display Instrument model S-2) was activated, the timing of which stopped when the animal interrupted the goal box photobeam. This served as a measure of the time required for the rat to traverse the runway and enter the goal box (i.e., Run Time). Breaking the goal box infrared photobeam also served as the signal for a goal box door to close thereby restricting the animal to the goal box (to prevent retracing).

Drugs

Raclopride tartate (Astra Arcus, Sodertalje, Sweden) was prepared in a vehicle solution of 0.9% physiological saline and injected intraperitoneally 30 min prior to testing in a volume of 2.0 ml per kilogram of body weight. SCH 39166 (Schering-Plough Research Institute, Kenilworth, New Jersey) was prepared in a vehicle solution of sterile water and injected intraperitoneally 30 min prior to testing in a volume of 1.0 ml per kilogram of body weight.

Procedure

Throughout the experiment, animals experienced a single runway trial each day. The experiment was performed in four successive phases: acquisition (12 trials), extinction (variable number of trials), Treatment Day, and Test Day. Animals were fed in their home cages 20–30 min after daily testing.

Acquisition

Each rat was individually placed into the start box, the start box door was opened, and the Run Time was recorded. Animals remained in the goal box until the food reinforcement (10 pellets) was consumed (i.e., this rarely took more than 30 s by the end of acquisition). The animal was then removed from the apparatus and returned to its home cage. Testing continued in this manner for 12 consecutive days/trials.

Extinction

Beginning on Day 13, food reinforcement was no longer provided to the animals upon goal box entry. Single daily extinction trials continued until each rat had met an extinction criterion arbitrarily defined as an increase in Run Time (a slowing in operant running) to a level five times that of the fastest acquisition trial/day. A subject completed the extinction phase of the experiment when it performed at this "extinction criterion" on four of five consecutive days (mean time to extinction ± SEM was 33.4 ± 4.0 trials).

Treatment Day

Following extinction, a single treatment trial was conducted during which subjects ran to either an empty or food-baited goal box and were pretreated with either raclopride (0.0, 0.25, 0.5 or 1.0 mg/kg) or SCH 39166 (0.0, 0.1, 0.5 or 1.0 mg/kg). This procedure resulted in five groups for each drug: a Vehicle-Food group and a Vehicle-No Food group in which Ss were pretreated with vehicle 30 min prior to testing with either a baited (food) or unbaited (no food) goal box. Three additional groups received one of the doses of raclopride and three more groups received one of the doses of SCH 39166 prior to a single food reinforced trial (i.e., Raclopride-Food or SCH 39166-Food groups). Finally, two groups were administered either the high dose of SCH 39166 or raclopride 30 min after a food reinforced trial (i.e. Motor Control groups) to assess any residual motor impairments on Test Day 24 h later.

Test Day

The effects of finding food (or no food) on Treatment Day were observed during a final trial (Test Day) which was conducted 24 h later in undrugged, untreated animals using an unbaited runway. This trial assessed the influence of the previous day's unbaited or baited goal box experience on running behavior. On the basis of previous work (22) it was hypothesized that a single food-reinforced trial in the midst of extinction would be sufficient to reinstate operant running 24 h later. The present experiment tested raclopride's and SCH 39166's ability to attenuate this response-reinstating action of food reinforcement.

RESULTS

One-way Analyses of Variance (ANOVA) were computed on the mean group Run Times for each drug on both Treatment and Test days. The ANOVAs confirmed that there were no reliable differences in runway performance among raclo-

pride groups ($F(5, 50) = 1.114, p > .05$) or SCH 39166 groups ($F(5, 49) = 2.2056, p > .05$) on Treatment day. Thus, by restricting daily performance to a single trial, all groups were able to traverse the runway unimpaired during either raclopride or SCH 39166 challenge.

Test Day performance was, however, altered by the previous day's treatment protocol. Figure 1 depicts the mean (+SEM) Run Times for each raclopride group on Test Day. The ANOVA on these data revealed a highly reliable difference between groups ($F(5, 50) = 3.983, p = 0.0041$). Post-Hoc analyses (Fisher's Protected Least Significant Differences Test) were computed to assess which treatment groups yielded results different from one another. Six significant differences ($p < 0.05$) were identified in this manner. The Vehicle-No Food group ran more slowly on Test Day than either the Vehicle-Food or the Motor Control groups. Thus, finding no-food on Treatment Day, led to slow running on Test Day, while finding food in the goal box on Treatment Day reinstated operant behavior on the next trial. This response-reinstating property of food-reinforcement was dose-dependently prevented by pretreatment with the dopamine D_2 receptor antagonist, raclopride. Thus, the low dose group (0.25 mg/kg raclopride-food group) ran reliably faster than the Vehicle-No Food group, while the animals that experienced the high dose of raclopride (1.0 mg/kg Raclopride-Food Group) were reliably slower than either the Vehicle-Food, low dose-food, or Motor Control groups. The performance of the Motor Control group is particularly important here since these animals exhibited response-reinstatement on Test Day (see Fig. 1) and hence were able to perform unimpaired one day after raclopride administration.

Figure 2 shows the mean (±SEM) Run Times for each SCH 39166 group on Test Day. The animals in these groups were all tested subsequent to those of the raclopride groups and their baseline Run Times were reliably shorter. Nevertheless, the pattern of responding seen in the Vehicle-No-Food and Vehicle-Food groups were highly comparable to those of the raclopride condition. As with raclopride, the ANOVA on the SCH 39166 data revealed a highly reliable difference between groups ($F(5, 49) = 3.758, p = 0.006$). Post-Hoc analyses (Fisher's Protected Least Significant Differences Test) indicated that the Vehicle-No Food group ran significantly slower than all other groups. There were no differences between any of the food groups. Thus, SCH 39166 administration had no effect on the response-reinstating properties of food reinforcement.

DISCUSSION

One of the properties of positive reinforcers is their ability to reinstate responding following a period of nonreinforced trials (18,21,41). In the present study, we were able to demonstrate the response-reinstating properties of food reward in a runway paradigm where a single reinforced trial reinstated operant running 24 h later. The present results, therefore, confirm previous results from our laboratory using the same procedure (22). In that earlier work, Horvitz & Ettenberg (22) found that pretreatment with the moderately selective D_2 antagonist, haloperidol, prevented the subsequent reinstatement of behavior. Our work extends this finding by demonstrating that highly selective antagonism of D_2 dopamine receptors with raclopride, but not D_1 receptors with SCH 39166, was sufficient to block the response-reinstating effects of food reinforcement. This work is consistent with reports that D_2 antagonists such as raclopride decrease food-reinforced operant behaviors (20,30) and also attenuate the reinforcing properties of intracranial stimulation (4,17,31, but see 23). Studies of drug reinforcement have produced less impressive dissocia-

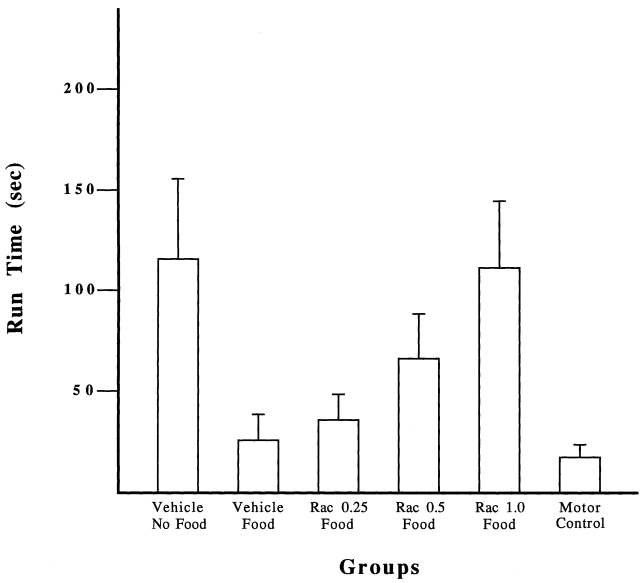

FIG. 1. Mean Run Times (± SEM) for each raclopride group on Test Day. Groups are designated by their Treatment Day conditions. Rac 0.25, Rac 0.5 and Rac 1.0 represent raclopride pretreatments in mg/kg. The Motor Control group received a 1.0 mg/kg dose of raclopride 30 min after a reinforced Treatment Trial. Test Day scores were derived from a single Trial 24 h after Treatment Day in undrugged animals running an unbaited runway.

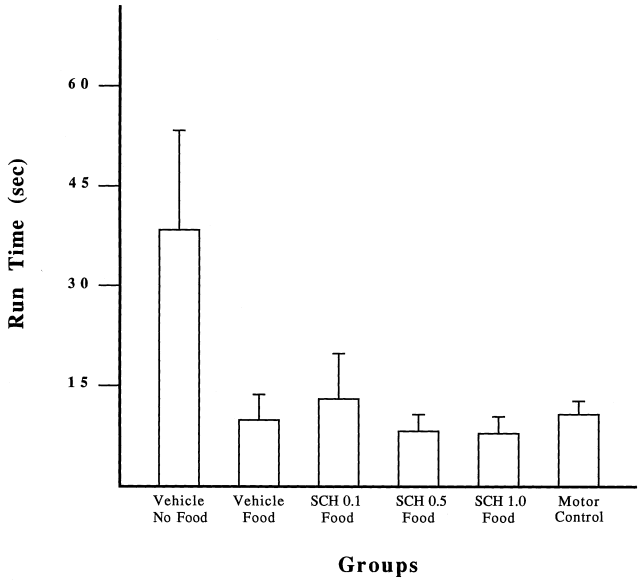

FIG. 2. Mean Run Times (± SEM) for each SCH 39166 group on Test Day. Groups are designated by their Treatment Day conditions. SCH 0.1, 0.5, 1.0 represent SCH 39166 pretreatments in mg/kg. The Motor Control group received a 1.0 mg/kg dose of SCH 39166 30 min after a reinforced Treatment Trial. Test Day scores were derived from a single trial 24 h after Treatment Day in undrugged animals running an unbaited runway.

tions of D_1 and D_2 receptor function (6) although in a recent study (39) D_2 but not D_1 dopamine receptor agonists reinstated the operant responding of rats previously trained to work for cocaine reinforcement. The uniqueness of the current study is that the response-reinstating actions of food reinforcement, and the effects of the D_1/ D_2 receptor antagonism of these actions, were observed in undrugged animals tested 24 hrs post-treatment. Hence the current results are not likely the result of nonspecific actions of drug administration.

Of course it remains possible that the slowing of Run Times in the raclopride-treated animals could be related to the presence of some residual sedative or motor impairments on Test Day (24 h post-injection). Raclopride is known to cause motor depression, and has been reported to antagonize drug-induced hyperlocomotion (22,26,33,34,43). In this view, the lack of significant group differences in Run Times on Treatment Day could be accounted for by a form of "ceiling effect": i.e., the animals were already running slowly due to the extinction procedure, and hence further motor impairment produced by the drug may not have been identifiable. On Test Day, a residual drug-induced impairment could conceivably slow the running of Ss who received drug on the previous trial and hence account for the group differences reported here. If this were true, then the Motor Control subjects (who received drug 30 min after the treatment trial) should have exhibited slow Run Times on Test Day. This was not the case. Whereas the pre-treated 1.0 mg/kg raclopride animals ran slowly, the post-treated Motor Control animals did not. Thus, slow Run Times on Test Day required not just the presence of the raclopride, but rather the combination of drug and food reinforcement on Treatment Day.

Another possible explanation for the reduced running of the food + raclopride animals on Test Day involves the presence of some form of drug-induced learning or memory impairment. This explanation could conceivably take either one of two forms: the development of State Dependent Learning, or an interference with the animals' ability to encode new information. State Dependent Learning has been used to describe a phenomenon on where animals who learn new information under one "state" are most likely to retrieve that information if they are in the same "state" during subsequent testing (11,19, 32,35,36,42). For example, if an animal is drugged during acquisition/training, it may need to be drugged again during testing in order to produce the most efficient retrieval of the original learned response. In the current context, one might argue that the raclopride-treated subjects ran slowly on Test Day because they were being tested in a "state" (undrugged) different from that which was present during the original reinforced trial (when they were drugged)—hence memory retrieval was impaired. While this certainly remains a possibility, the authors are aware of no demonstration of State Dependent Learning using dopamine antagonist drugs in general, nor raclopride in particular. In fact, Horvitz & Ettenberg (22) were able to directly test and rule out a State Dependent Learning hypothesis as an explanation for haloperidol's effects in this same food-reinstatement paradigm.

A second memory-type explanation for the current results presumes that the presence of raclopride on Treatment Day interfered with the animals' ability to encode new associations. In this view, the reduced running of the food + raclopride groups on Test Day stemmed not from some action of the drug on reinforcement processes, but rather an inability of the animals to recall that reinforcement was presented on the previous trial. Once again, although this hypothesis is a viable one, the available data regarding raclopride's effects on learning and memory do not support it as an explanation for the current data. Thus, while raclopride has been shown to enhance the memory impairing effects of other drugs (28), it has not been demonstrated to produce memory deficits when administered on its own (5,7,28,38).

The paradigm incorporated in this study essentially examines the efficacy of drugs used to alter reinforcement processes in animals undrugged at the time of testing. The utility of such a procedure for the investigation of drugs with suspected or documented sedative or motor incapacitating properties is obvious. The present results serve to provide strong support for the view that D_2, but not D_1, receptor subtypes are critical for the response-reinstating properties of food reinforcement.

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