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Intraaccumbens Raclopride Attenuates Amphetamine-Induced Locomotion, But Fails to Prevent the Response-Reinstating Properties of Food Reinforcement

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CHAUSMER, A. L. AND A. ETTENBERG. *Intraaccumbens raclopride attenuates amphetamine-induced locomotion, but fails to prevent the response-reinstating properties of food reinforcement.* PHARMCOL BIOCHEM BEHAV **62**(2) 299–305, 1999.—It has been well established that the presentation of a single reinforced trial in the midst of extinction results in a reinstatement of the previously reinforced operant response. In previous experiments, we have shown that systemically applied raclopride (a selective dopamine D_2 receptor antagonist) dose dependently blocked the response-reinstating properties of food reinforcement, while SCH39166 (a selective dopamine D_1 receptor antagonist) did not (11). The current experiments investigated the possible role of the nucleus accumbens in these actions of raclopride. In the first of two experiments, hungry rats were trained to traverse a straight runway for food reinforcement, a response that was then weakened through a series of extinction trials. On a single treatment trial, subjects were infused with one of three doses of intraaccumbens raclopride (0.0, 2.5, or 5.0 μg/0.5 μl/side) just prior to a reinforced trial. Twenty-four hours later, a single test trial was run in an unbaited runway. The results demonstrate that the prior day's reinforced trial produced a reinstatement of operant runway performance that was unaltered by intraaccumbens applications of raclopride. Two days later, the same animals were tested in a second experiment investigating the effects of intraaccumbens raclopride on amphetamine-induced locomotion. Subjects were pretreated with 1.0 mg/kg SC amphetamine prior to a 90-min locomotor activity session. The following day, subjects were again pretreated with amphetamine, but this time with a challenge dose of raclopride. Results demonstrate that the same raclopride doses that produced no effect in the response-reinstating experiment produced, in the same rats, a dose-dependent attenuation in amphetamine-induced locomotion. These data suggest that dopamine D_2 receptors in the nucleus accumbens may not, in and of themselves, be necessary for the response-reinstating effects of food reinforcement. © 1999 Elsevier Science Inc.

Raclopride Runway Operant behavior Dopamine receptor antagonist Nucleus accumbens Amphetamine Locomotion

THE role of dopamine pathways in the behavioral actions of reinforcers has been extensively investigated [e.g., for reviews, see (3,16,22,38,39)]. However, the precise relative roles of D_1 vs. D_2 dopamine receptor subtypes in the reinforcing properties of such stimuli remain unclear [e.g., for review, see (43)]. For example, while the administration of selective D_1 or D_2 dopamine receptor agonists resulted in decreased reinforced responding in some studies [e.g., (25,49)], others have reported increases in operant responding (D_2 agonist), or no change in responding (D_1 agonist) [e.g., (29)]. This lack of consistency across experiments is also seen in studies that administer selective antagonists. Once again, in some cases, selectively blocking D_1 or D_2 receptors appears to decrease reinforcement [e.g., (44,53,60)], while other results indicate an enhancement of reinforcement (23). As a means of resolving these inconsistencies, some authors have suggested joint involvement of D_1 and D_2 receptors [e.g., (1,6)]; others suggest an uneven contribution. For example, some propose that D_2

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receptors play a greater role in reinforcement than D_1 receptors [e.g., (12)], while others suggest the opposite [e.g., (11,20)]. In addition to the problems inherent in understanding such diverse findings, it is sometimes difficult to interpret results in this field because subjects are tested while they are drugged. After dopamine manipulation, changes in presumed reinforcement may, therefore, be confounded by effects on performance. In attempting to address such interpretive difficulties, our laboratory has employed an operant runway procedure that has successfully examined the effects of dopamine antagonist drugs in animals undrugged at the time of testing [e.g., (12,17,18,19,26,36)]. Animals are first trained to traverse a straight alley for reinforcement delivered upon subjects' entry into the goal box. Following response-acquisition, a series of daily extinction trials is provided during which the operant running response gradually slows. In the midst of extinction, a single reinforced trial results in reinstatement of the runway response on the very next trial (24 h later). With this procedure, animals can be treated prior to the reinforced trial with selective receptor antagonists, whose putative attenuation of reinforcement can be assessed 24 h later (when the drug is no longer active) by the degree of response-reinstatement observed in the undrugged animals.

This procedure has been successfully used to dissociate the relative roles of D_1 and D_2 dopamine receptors in food reinforcement (12). In that study, the dopamine D_2 receptor antagonist attenuated the response-reinstating properties of food reinforcement. Because (a) numerous studies have indicated a relationship between the nucleus accumbens and reinforcement [e.g., see (7,8,21,31,50,51)]; and (b) the site is a terminal region of the mesolimbic dopamine system and, hence, a likely site of action of DA antagonist drugs, it seemed reasonable to examine this structure as the putative site of raclopride's action in our previous work. The current experiment was devised to test this possibility.

METHOD

Subjects

The subjects were 41 male Sprague–Dawley rats (Charles River Laboratories, Wilmington, MA) maintained at 85% of free-feeding weight (mean 360 g at start of experiment). Water was available on an ad lib basis. The rats were individually housed in metal hanging wire cages located within an animal vivarium that was maintained on a 12 L:12 D cycle (lights on at 0800 h) and at an ambient temperature of 22°C.

Apparatus

The runway apparatus consisted of a straight wooden alley 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 wall of the goal box opposite the opening to 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 infused (0.5 μl/45 s) bilaterally in a volume of 0.5 μl/side just prior to testing. The concentration of solution was 0.0, 2.5, or 5.0 μg/0.5 μl.

Surgery

Bilateral cannulae were aimed at the nucleus accumbens shell. Subjects were administered intramuscular atropine (0.3 mg/kg) to help dry up respiratory secretions. Anesthesia was produced with Nembutal (55 mg/kg IP) supplemented by chloral hydrate (160 mg/ml) and halothane as needed. The incisor bar was set so that bregma and lambda had the same D/V coordinates. The target coordinates were as follows: A/P +1.2 mm, M/L ± 0.7 mm, D/V −6.0 mm. The subjects were allowed at least 5 days to recover from surgery before the start of behavioral testing.

Response-Reinstatement Test

The experiment was performed in four successive phases: acquisition (four trials a day for 5 days), extinction (four trials a day for 5 days, followed by single daily trials), treatment day, and test day. Subjects were fed their daily rations in their home cages 30–60 min after the completion of their daily testing.

Acquisition. Each rat was individually placed into the start box. After 3 s, the start box door was opened, and the time required for the subject to traverse the alley (once it had left the start box) was recorded (i.e., run time). Subjects were restricted to the goal box until the food reinforcement (ten 45 mg Noyes pellets) was consumed (i.e., this rarely took more than 30 s). The animal was then removed from the apparatus and returned to its home cage. Testing continued in this manner for 5 consecutive days with four trials/day and an intertrial interval of 30–45 min.

Extinction. Beginning on day 6, food reinforcement was no longer provided to the subjects upon goal box entry. Subjects were run four trials/day for 5 days, and then 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 recorded for the fastest acquisition trial/day. A subject completed the extinction phase of the experiment when it performed at this "extinction criterion" on 3 of 4 consecutive days (mean number of trials to extinction ± SEM was 32.6 ± 1.6).

Treatment day. Once an animal had met extinction criterion performance, a single treatment trial was conducted, during which subjects ran to either an empty or a food-baited goal box. Immediately prior to behavioral testing, each animal was infused with a bilateral application of raclopride (0.0, 2.5, or 5.0 μg/side). This procedure resulted in four groups of subjects: a vehicle-food group and a vehicle-no food group, in which subjects were infused with vehicle just prior to testing with either a baited (food) or unbaited (no food) goal box, respectively. Two additional groups received bilateral intraaccumbens applications of raclopride (either 2.5 or 5.0 μg/0.5 μl/side) just prior to a single food-reinforced trial (i.e., Raclopride-Food Groups).

Test day. The consequences of finding food (or no food) on treatment day were observed during a final trial (test day)

that was conducted in an unbaited runway 24 h later when the effects of the prior day's drug treatments had dissipated (i.e., subjects were tested undrugged). 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 (12,26) 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 whether intraaccumbens applications of raclopride would attenuate this response-reinstating action of food reinforcement.

Amphetamine-Induced Locomotor Activity Test

To ensure that the doses of raclopride employed in the response-reinstatement test were behaviorally active, a second experiment was conducted (using the same subjects) in which the drug's ability to prevent amphetamine's locomotor activating properties was examined [e.g., (54)]. Upon completion of test day in the response-reinstatement experiment, subjects were returned to their home cages and provided with ad lib access to food. Two days later the amphetamine experiment was initiated.

Testing consisted of two 90-min locomotor sessions. For the first session, subjects were pretreated with D-amphetamine (1.0 mg/kg SC) just prior to being placed in the locomotor chambers. The drug was prepared in a vehicle of 0.9% physiological saline and injected SC in a volume of 1.0 mg/ml. The locomotor activity apparatus consisted of 16 hanging wire cages (37 × 26 × 20.5 cm) equipped with two pairs of photocell emitter-detector units, one placed approximately 4 cm from the front, and the other at equal distance from the back of the cage. The number of beam crossings made during each session was recorded via a laboratory-built I/O interface controlled by an IMB-PC 386 desktop computer. Twenty-four hours later, a second session was run. Subjects were again pretreated with D-amphetamine (1.0 mg/kg SC); however, each rat also received the same dose of raclopride (0.0, 2.5, or 5.0 μg/side) that it had received on treatment day of the previous response-reinstatement experiment. Immediately after drug infusions, subjects were placed in the locomotor chambers for 90 min.

Histology

Upon completion of the locomotor activity study, animals were perfused with 10% formalin. The brain tissues were frozen, and cannulae placements were verified from 40-micron sections stained with cresyl violet. Figure 1 illustrates the range of placements within the shell region of the nucleus accumbens.

RESULTS

Response-Reinstatement Test

The mean (+SEM) run times of each group of animals on test day are depicted in Fig. 2. Animals that experienced no food in the goal box on treatment day (the vehicle-no food group) continued to exhibit slow extinction-like responding. In contrast to this, animals that found food on treatment day subsequently reinstated their operant running 24 h later on test day (the vehicle-food group). These animals ran down the alley over six times faster than the nonreinforced vehicle-no food animals. Of particular relevance are the results of the two raclopride-treated groups, both of whom reinstated normally on test day. Hence, D_2 receptor antagonism in the nucleus accumbens on treatment day did not attenuate the response-reinstating properties of food reinforcement. An independent group one-way analysis of variance (ANOVA) computed on the data from Fig. 2 confirmed the presence of a reliable main effect for group, $F(3, 37) = 4.313$, $p = 0.01$. Tukey HSD post hoc analyses revealed that the vehicle-no food group ran reliably slower on test day than each of the other three food-reinforced groups ($p < 0.05$).

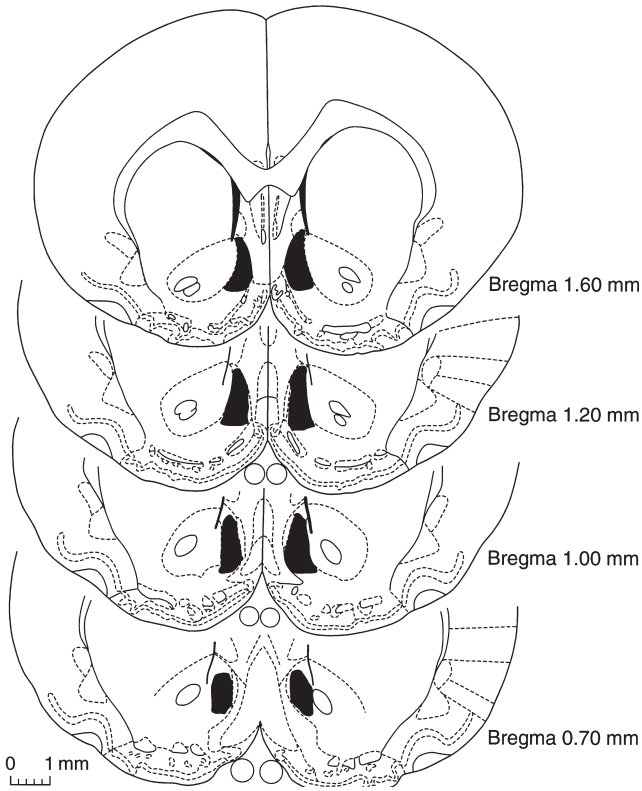

FIG. 1. Histographical verification of cannulae placements within the nucleus accumbens shell region. Sections were redrawn from Paxinos and Watson (45). Shaded areas represent the regions within which all cannulae placements were located.

Amphetamine-Induced Locomotor Activity Test

Figure 3 depicts the locomotor counts of each of the three groups of subjects (corresponding to the different bilateral doses of IC raclopride: 0.0, 2.5, and 5.0 μg/side) on the initial amphetamine baseline (open bars) and the amphetamine + raclopride-treatment trial (dark bars). A group × trial two-factor ANOVA (with repeated measures on one factor) computed on the data from Fig. 3 revealed that while there was no overall main effect for group, $F(2, 32) = 1.131$, $p = 0.335$, there was a highly reliable effect of trial, $F(2, 32) = 10.051$, $p = 0.003$, and a group × trial interaction, $F(2, 32) = 3.24$, $p = 0.05$. Thus, the same intracranial doses that had no effect on the response-reinstating effects of food reinforcement, dose dependently reduced amphetamine's locomotor activating effects in the same animals.

DISCUSSION

Results of this experiment confirm that a single reinforced trial in the midst of extinction is sufficient to produce a rein-

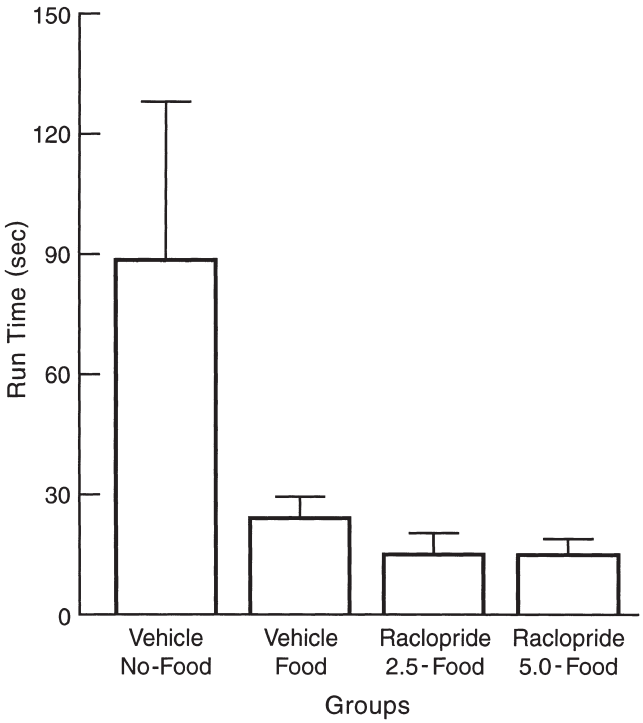

FIG. 2. Mean run times (+SEM) for each group on test day 24 h after a single treatment trial in the midst of extinction. Animals that continued to find an empty goal box (vehicle–no-food group) continued to run slowly, while subjects that found food on treatment trial (vehicle–food) reinstated their running on test day. Pretreating animals with either of two doses of raclopride delivered directly into the nucleus accumbens (the raclopride 2.5-food and raclopride 5.0-food groups, respectively) did not alter subjects' positive response to food, i.e., both groups still demonstrated response-reinstatement when tested again 24 h later.

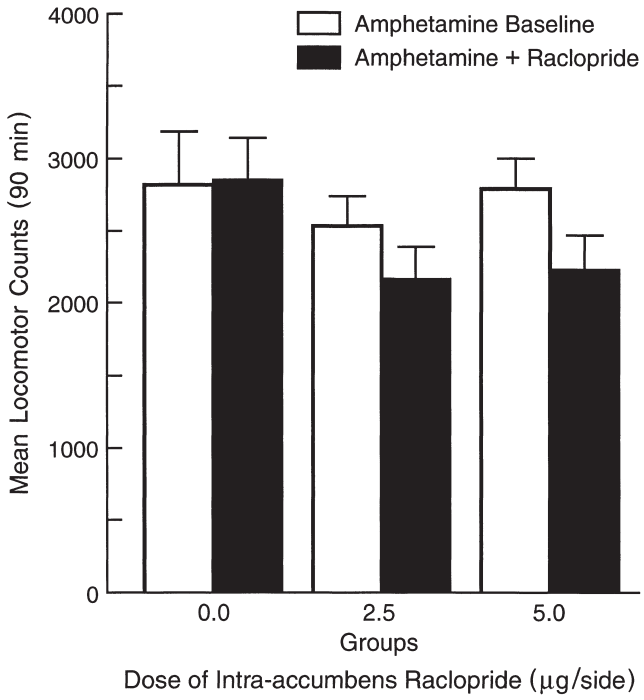

FIG. 3. Mean number of locomotor counts (+SEM) during two 90-min sessions each following an IP administration ot 1.0 mg/kg *d*-amphetamine. The open bars represent a baseline session and the dark bars indicate a challenge test with one of three doses of intraaccumbens raclopride (0.0, 2.5, or 5.0 μg/0.5 μl/side) administered just prior to testing. Raclopride dose dependently attenuated the locomotor repsonse to amphetamine.

statement in operant runway responding on the very next trial, even if that trial occurs 24 h later. This replicates previous work in our laboratory using a variety of different positive reinforcers [e.g., (12,17,18,19,26,36)].

In previous studies, haloperidol was shown to prevent the response-reinstating effects of food reinforcement (26) thereby adding support to the view that brain dopamine systems are involved in the neurobiology of food reinforcement, as many others have proposed [e.g., for reviews, see (30,42,58)]. Despite this consensus, the relative roles of D_1 vs. D_2 dopamine receptor subtypes mediating the putative anhedonic effects of DA antagonist drugs has remained unresolved. Although haloperidol has been used as a preferential D_2 receptor antagonist (2,29,33), it also shows weak affinity for D_1 receptors (14,34). Indeed, both D_1 and D_2 antagonists have been reported to decrease operant responding for food (15,44,52,60), and reduce oral intake of sucrose (41,53).

In previous work using the same runway procedures as described here, Chausmer and Ettenberg (12) compared the effects of systemically administered raclopride, a selective D_2 antagonist (32), with those of SCH 39166, a selective D_1 antagonist (55). In that study, blocking D_2, but not D_1, receptors, attenuated the response-reinstating properties of food reinforcement (12). The current study extends this work by examining the role of the nucleus accumbens in mediating the behavioral effects of raclopride that had been observed in the prior response-reinstatement study.

Although the nucleus accumbens may be involved in food reinforcement [e.g., (35,40)], our findings indicate that intraaccumbens raclopride did not attenuate response reinstatement. This lack of an effect was not likely due to the use of insufficient doses of raclopride. In point of fact, others have found significant behavioral effects using similar or lower doses (24,52,54,59). Additionally, we have demonstrated that the same doses that failed to alter the response-reinstating properties of food reinforcement reliably decreased amphetamine-induced locomotion in the same animals. This represents a dissociation in the role of the nucleus accumbens in the neurobiology of food reinforcement and locomotor processes. There are many examples of locomotor activity changes being predictive of reinforcement effects. That is, drugs that increase locomotor activity also tend to be reinforcing (i.e., self-administered), while drugs that decrease locomotor activity tend to attenuate the reinforcing properties of various stimuli [e.g., for reviews, see (3,57)]. The present study, however, suggests that at least within the nucleus accumbens, these two processes can be independently manipulated [see also (48)].

Others have examined the effects of administering intraaccumbens dopamine antagonists on food reinforcement. For example, Hodge et al. (24) trained rats to lever press for sucrose, and found that intraaccumbens administration of raclopride (0.05–2.5 μg/0.5 μl/side) produced dose-dependent decreases in operant responding. The pattern of responding suggested that the decrease in lever press activity was not due

to motoric incapacitation, because, at the low dose (0.05 μg/side), responding was initially high and only decreased as the session continued (i.e., a pattern of responding thought to reflect an anhedonic response to the sucrose during raclopride challenge). At higher doses (2.5 μg/side), the latency to start responding was increased and responding quickly tapered off. Beninger and Ranaldi (4) similarly reported gradual declines in food-reinforced responding following systemic flupenthixol (a nonspecific DA antagonist). However, these investigators saw no such declines when the DA receptor antagonist was applied directly to the nucleus accumbens. They concluded that nucleus accumbens dopamine may not be critical for food reinforcement. Clearly, the current data are consistent with those of Beninger and Ranaldi (4).

Functional differences between the shell and core regions of the nucleus accumbens have been documented [e.g., (56)], and could have contributed to the negative results obtained with raclopride in the current study. Perhaps the "critical" dopamine receptor antagonism must occur in the core region. Although many experiments fail to distinguish between the core and shell regions, examination of the histological data from experiments that explore the relationship between the nucleus accumbens and various reinforcing stimuli often appear to have targeted the core more often than the shell [e.g., (24,59)]. However, when specifically investigating differential involvement of the shell and core regions in reinforcement, several studies suggest that the shell region is of primary importance. For example, animals will self-administer D_1 and D_2 dopamine agonists and nomifensine (a dopamine reuptake inhibitor) into the shell, but not core, region (9,27). Additionally, systemic cocaine, morphine, and amphetamine produce greater increases in extracellular dopamine in the shell region compared to the core region (46). These results served as the rationale for the decision to target the nucleus accumbens shell region in the current study. Clearly, additional work will be needed to more fully assess the relative roles of core and shell regions in the neurobiology of reinforcement.

Performance on test day requires that the animal remember what happened on the previous trial (treatment day). Therefore, if raclopride altered the capacity of the animals to register that memory, they would not be able to demonstrate the behavior the next day. This may explain why direct application of raclopride did not result in slower, extinction-like running behavior. Perhaps reinforcement processes were not affected by the raclopride and the effects seen with systemic administration were due to memory impairments. If this were true, then brain regions involved in different types of memory [e.g., the terminals of ventral tegmental area projections into the hippocampus (28)], might be reasonable sites to investigate. Although this certainly represents a viable approach, the question of memory involvement is a complicated one. For example, a drug-induced deficit in reinforcement might be expected to produce a secondary impairment in learning or memory, i.e., animals would be less likely to acquire a new operant response if the quality of the reinforcer was compromised. Indeed, animals treated with a dopamine receptor antagonist failed to acquire cocaine-induced conditioned place preferences when the antagonist was given during acquisition, but were unaffected by the drug if the place preference was already learned (5). This suggests a role for dopamine in reinforcement but not memory. In the current study, no impairment was observed for "acquisition" or "recall" of the runway response. Hence, animals were able to both encode the fact that food was again present on treatment day and to retrieve that fact in producing reinstatement on test day. It is possible that dopamine antagonism in areas thought to be more directly associated with memory processes (e.g., the hippocampus) would have produced deficits in the subjects' runway performance. However, although dopamine antagonists have been observed to augment the memory deficits produced by other drugs [e.g., (37)], they have not been particularly effective in producing such deficits on their own [see (7,13)].

Perhaps blocking the dopamine receptor population in the nucleus accumbens is not, in and of itself, sufficient to produce an attenuation in food reinforcement. Extracellular dopamine has been reported to increase in the medial frontal cortex with eating (10), as does dopamine in the nucleus accumbens (47). Indeed, interactions between several areas of the mesolimbic dopamine system have been suggested for the neurobiology of food reinforcement [e.g., for review, see (50)]. It may, therefore, be that the effectiveness of systemically applied raclopride (12) but not the intraaccumbens raclopride (current study) to attenuate the response-reinstating properties of food reinforcement, requires antagonism of dopamine function at multiple sites.

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