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D1 or D2 antagonism in nucleus accumbens core or dorsomedial shell suppresses lever pressing for food but leads to compensatory increases in chow consumption

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In memory of Phillippe Faulkenberg.

Abstract

Although interference with dopamine (DA) systems can suppress lever pressing for food reinforcement, it is not clear whether this effect occurs because of a general disruption of food motivation. One way of assessing this has been a choice procedure in which a rat responds on an fixed ratio 5 (FR5) schedule for preferred Bioserve pellets while a less preferred lab chow is concurrently available in the operant chamber. Untreated rats consume little of the chow, preferring to respond for the Bioserve pellets. Previous studies have shown that depleting DA in the accumbens substantially decreased lever pressing while increasing chow consumption. In the present study, low doses (0.0625–1.0 μg) of the D1 antagonist SCH 23390 or the D2 antagonist raclopride were injected into the either the core or shell subregions of nucleus accumbens, and rats were tested on the concurrent lever pressing/feeding task. Analysis of the dose response curves showed that injections of SCH 23390 into the core were more potent than injections into the shell for suppressing lever pressing (i.e., the ED_{50} was lower in the core). Nevertheless, injections of either drug into either site suppressed lever pressing and increased intake of the concurrently available chow. Across both drugs and at both sites, the amount of chow consumed was negatively correlated with the total number of responses. Neither drug significantly increased response duration, suggesting that accumbens DA antagonism did not produce the type of motor impairment that leads to severe alterations in the form of lever pressing. In summary, the blockade of D1 or D2 receptors in nucleus accumbens core or shell decreased lever pressing for food reinforcers, but rats remained directed toward the acquisition and consumption of food. These results indicate that accumbens D1 antagonism does not decrease lever pressing because of a general reduction in food motivation. Nevertheless, interference with accumbens DA does appear to set constraints upon which responses are selected for obtaining food, and may impair the ability of animals to overcome work-related response costs in order to obtain food.

Keywords: Operant; Instrumental; Behavior; Reinforcement; Motivation; Dopamine; Behavioral economics; Reward

1. Introduction

For many years, it has been suggested that dopamine (DA) in nucleus accumbens mediates the positive reinforcing effects of drugs of abuse (e.g., Caine and Koob, 1994; Wise, 1982) and the primary reinforcing characteristics of natural reinforcers such as food (Cheeta et al., 1995; Hernandez and Hoebel, 1988; Smith, 1995; Wise, 1982; Wise et al., 1978). Although this view has been predominant and popular for many years, a substantial body of evidence now indicates that accumbens DA does not mediate primary food reinforcement or motivation. Accumbens DA depletions that severely disrupted cocaine self-administration had little effect on some schedules of food-reinforced behavior (Caine and Koob, 1994; Roberts et al., 1977). In fact, responding on several schedules for food reinforcement is relatively unaffected by accumbens DA depletions. Accumbens DA depletions had little or no effect on the performance of schedules with relatively low baseline rates, such as variable- or fixed-interval 30-s schedules (Cousins et al., 1999; Sokolowski and Salamone, 1998). Despite the fact that performance on the continuous reinforcement schedule is highly dependent upon primary reinforcement and food motivation (Aber-

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man and Salamone, 1999; Salamone et al., 1991), overall response rates on this schedule are relatively unaffected by accumbens DA depletions (Aberman and Salamone, 1999; McCullough et al., 1993; Salamone et al., 1995). Responding on some schedules, including progressive ratio (Aberman et al., 1998; Hamill et al., 1999), and fixed ratio (FR) schedules that generate high rates, such as FR5, FR16, or FR64 (Aberman and Salamone, 1999; Salamone et al., 1993a; Sokolowski and Salamone, 1998), are sensitive to the effects of accumbens DA depletions. Many factors, such as dependence upon conditioned stimuli, the baseline rate of responding, or the work requirement of the schedule, may contribute to make some schedules more sensitive to the effects of accumbens DA depletions (Aberman and Salamone, 1999; Salamone et al., 1997, 1999). Nevertheless, there is little evidence to indicate that performance on some schedules can be affected by accumbens DA depletions because of impairment in primary food reinforcement or motivation. In fact, the effects of accumbens DA depletions on lever pressing do not resemble the effects of extinction (McCullough et al., 1993; Salamone et al., 1995; see Salamone et al., 1997 for review), nor do they resemble the effects of prefeeding to reduce food motivation (Aberman and Salamone, 1999; Salamone et al., 1991).

Accumbens DA depletions also affect the relative allocation of instrumental responses between various alternatives (for review, see Salamone et al., 1997). Procedures that provide choices between responses with different reinforced outcomes and different response requirements are highly sensitive to the effects of accumbens DA depletions. In a T-maze task, rats with accumbens DA depletions were less likely to climb a barrier to receive a higher density of food, but were more likely to choose the arm with the lower reinforcement density because it had a lower response requirement (Cousins et al., 1996; Salamone et al., 1994). Considerable research in this area has focused on concurrent lever-pressing/chow-feeding procedures. With this type of procedure, rats can lever press for a preferred food (Bioserve pellets) or can approach and consume a less preferred food that was available in the chamber (Cousins and Salamone, 1994; Cousins et al., 1993, 1994; Salamone et al., 1991, 1997). If the lever-pressing component of the task is a FR1 or FR5 schedule, rats typically eat little of the chow and get most of their food by lever pressing (Cousins and Salamone, 1994; Cousins et al., 1993, 1994; Salamone et al., 1991, 1997). This choice behavior is sensitive to the schedule requirement, and increasing the ratio requirement up to FR20 causes rats to shift away from lever pressing and towards chow consumption (Salamone et al., 1997). Using the FR5/chow-feeding task, a number of studies have shown that DA antagonists, or depletions of accumbens DA, decrease lever pressing but actually increase consumption of the concurrently available chow (Cousins and Salamone, 1994; Cousins et al., 1993, 1994; Koch et al., 2000; Salamone et al., 1991, 1997). This effect is neither produced by prefeeding to reduce food motivation, nor is it produced by appetite suppressants such as amphetamine or fenfluramine (Cousins et al., 1993; Salamone et al., 1991; unpublished data). In addition, ventrolateral striatal DA depletions, which cause severe feeding deficits, impair skilled movements, and increase lever press duration (Cousins and Salamone, 1996; Cousins et al., 1993, 1999; Salamone et al., 1993a,b), do not produce the shift from lever pressing to chow consumption, but instead decrease both types of behavior (Cousins et al., 1993). Thus, considerable evidence indicates that nucleus accumbens is the critical locus at which DA depletions cause the shift from lever pressing to chow consumption on the concurrent FR5/chow-feeding tasks.

Although the accumbens has been identified as the critical site for this effect, the involvement of specific subtypes of receptors or specific subregions of accumbens remains uncertain. Thus, in the present study, the D1 antagonist SCH 23390 and the D2 antagonist raclopride were injected into either the core or dorsomedial shell subregions of accumbens. Previous work with systemic administration of DA antagonists has shown that haloperidol, SCH 23390, and *cis*-flupenthixol all decrease lever pressing and increase chow consumption, but a highly selective D2 antagonist with good central penetrability, such as raclopride, has not been studied. It was hypothesized that both the D1 antagonist and the D2 antagonist should decrease lever pressing and increase chow consumption when injected into the nucleus accumbens. The present studies also were undertaken to determine if either subregion (Maldonado-Irizarry et al., 1995; Parkinson et al., 1999; Pecina and Berridge, 2000; Smith-Roe et al., 1999; Sokolowski and Salamone, 1998; Zahm, 2000, 1999) is more critical for producing the behavioral effects observed after interference with accumbens DA. Previous work with 6-hydroxydopamine (6-OHDA) injected into the core or dorsomedial shell demonstrated that the core was the most effective site at which 6-OHDA could decrease lever pressing and increase chow consumption (Sokolowski and Salamone, 1998). However, in that study, the DA depletions were not regionally selective, and a mild behavioral effect was also produced after shell 6-OHDA injections. Based upon the previous work, it was hypothesized that, at some dose, lever pressing could be suppressed by local injections into either subregion. Nevertheless, it was thought that core injections would be more potent than injections into the dorsomedial shell. In addition, it was hypothesized that increases in chow consumption should accompany the decreases in lever pressing, and that these two effects should be correlated across animals (Cousins et al., 1993). In addition to using total number of lever presses as a measure of operant responding, the present studies also report data on average duration of lever pressing. This measure has been used previously as an index of catalepsy or slowness of movement transition in rats treated with various drugs, or in rats that have received striatal DA depletions (Carriero et al., 1997, 1998; Cousins and Sala-

mone, 1996; Faustman and Fowler, 1981). Previous studies of sucrose consumption have employed very high doses of SCH 23390 or raclopride injected into the nucleus accumbens that are comparable to systemic doses (e.g., Smith, 1995; 12 μg SCH 23390 or 40 μg raclopride). In contrast, the present studies have employed a low injection volume (0.5 μl) and very low doses of drug (i.e., 1.0 μg per side or lower). Finally, in order to minimize the effects of brain damage from repeated injections, and to employ a large number of doses to obtain useful pharmacological information, the present studies used each rat for only one injection of vehicle or drug. A total of six treatment groups (vehicle controls plus five doses) were used for each study, and each of the two experiments was therefore a between-groups factorial design, with 2 placement sites (core and shell) × 6 injection treatments. Coordinates for placement of cannulae into core and dorsomedial shell were based upon those used in previous studies (Maldonado-Irizarry et al., 1995; Sokolowski and Salamone, 1998).

2. Methods

2.1. Subjects

A total of 168 adult male Sprague–Dawley rats (Harlan Sprague–Dawley, Indianapolis, IN) were used in this experiment. Rats were housed in a colony maintained at a constant temperature (23°C) with a 12-h light/dark cycle (lights on at 06:00, 07:00, or 08:00 hours depending on the colony room). All rats weighed between 290 and 330 g at the beginning of the study. Animals were food-deprived to 85% of their free feeding body weight, but were allowed a modest growth (up to 95% of original body weight) over the course of the study. Water was available ad libitum in the home cages at all times. All procedures were approved by the institutional animal care and use committee.

2.2. Behavioral procedures

Testing sessions of lever pressing and chow consumption were conducted in operant chambers (28 × 23 × 23 cm; Med Associates), and all tests were conducted during the light part of the light/dark cycle (2–8 h after light onset). Animals were trained to lever press beginning with 1 day of magazine training and were then switched to a continuous reinforcement schedule for an additional 4 days (30-min sessions; reinforcement pellets were 45 mg, Bioserve, Frenchtown, NJ). Rats were then moved to a FR5 schedule (30-min sessions, 5 days/week), and were trained on the FR5 schedule alone for four weeks. During the fifth week, animals were trained on a concurrent FR5/choice procedure, which consisted of having 15–20 g of lab chow available on the floor of the operant chamber during the 30-min FR5 sessions. This procedure required the animals to make a choice between lever pressing for the more preferred food (Bioserve pellets) or consuming the readily available lab chow. In some rats, lever pressing was reduced slightly for the first few days after the introduction of chow, but, generally, FR5 responding was stable during this period, was maintained at relatively high levels (i.e., >1200 responses per 30 min). On operant test days, rats received supplemental feeding in their home cages, with the amount varying depending upon the weight of the rat and the amount of lever pressing on that day.

2.3. Cannulae implantation

Following 1 week of training on the FR5/choice procedure, animals received bilateral cannulations under sodium pentobarbital anesthesia (50 mg/kg, ip). Stereotaxic surgical procedures were followed to obtain precise placement of the cannulae at the following sites (using the bregma as the landmark): core AP +2.8 mm, ML +1.8 mm, DV −6.8 mm; shell AP +2.8 mm, ML +1.0 mm, DV −6.8 mm; incisor bar 5.0 mm above the interaural line. The cannulae (23-gauge stainless steel) were anchored to the skull with cranioplastic cement and machine screws. Rats were allowed between 5 and 7 weeks to recover baseline lever pressing on the FR5/choice procedure before drug testing. Rats were considered stable if they pressed over 1200 times per 30 min for at least a week.

2.4. Pharmacological agents

SCH 23390 and raclopride were obtained from Research Biochemicals International (RBI, Natick, MA). For intracranial injection, both drugs were dissolved in a 0.9% saline vehicle. These experiments used six drug treatment conditions (saline vehicle, 0.0625, 0.125, 0.25, 0.5, and 1.0 μg/μl) in each of the two sites.

2.5. Experimental procedure

Rats were randomly assigned to different drug and dosage groups, and there were no differences in predrug responding between groups. Bilateral injections of SCH 23390 or raclopride were made through the guide cannulae using 30-gauge injectors set to extend 1.0 mm beyond the tips of the cannulae. Each injector was attached to a 10.0-μl Hamilton syringe via PE_{10} tubing, with the injections driven by a Harvard syringe pump. All injections were at a volume of 0.5 μl per side, at a flow rate of 0.5 μl/min, and the injector was left in place for 1 min after injection. Each animal received an injection of only one drug treatment condition. Directly following injection procedure, the animals were placed in the operant chamber for a 30-min FR5/choice procedure session. A BASIC program designed to run this schedule recorded such data as total number of lever presses, number of rodent pellets delivered, time to first response from onset of session, and average lever press duration. In addition, chow was

weighed out before and after the session, accounting for spillage, to determine how much was consumed by the animal during the operant session.

2.6. Histological procedures

Several days after the testing session, each animal was anesthetized with CO_2 and perfused with physiological saline followed by a 3.7% formaldehyde solution. The brains were removed and stored in formaldehyde and were then sliced and mounted on slides. Following slicing, slides were stained with Cresyl violet, and cannulae placements were determined using a microscope. All 168 animals used for statistical analyses in the present experiments had verified cannula placements (approximately 33% of the initial group were dropped due to bad placements, asymmetry, or lesions).

2.7. Statistical analyses

As each animal received only one treatment condition, the two drug experiments were both between subjects designs. The total number of lever presses, the amount of chow consumed, and the average duration all lever presses under each condition were analyzed using a 2 (Site) $\times$ 6 (Drug treatment) factorial analysis of variance (ANOVA; Sigmastat). In addition, correlational analyses were used to measure the relation between lever pressing and chow consumption for each drug and placement site, with the data collapsed across injection treatments. Determination of ED_{50} values and 95% confidence intervals was performed using a curve-fitting procedure in GraphPad Prism v3.00. The dose response curves were fit with a single exponential decay function, and the curve was constrained with a minimum of zero and a maximum of the control mean. The ED_{50} was estimated from the curve as the dose value that yielded a response that was 50% of the control mean. The 95% confidence intervals were determined in the program by multiplying the standard error by the appropriate t value for the degrees of freedom that was appropriate for each analysis. The confidence intervals are symmetrical on a logarithmic scale, but are asymmetrical on an arithmetic scale. The ED_{50} values and confidence intervals are reported as arithmetic doses (in μg/side).

3. Results

Fig. 1 shows cannulae placements from four representative rats. The rats represented here all received 1.0 μg/μl of either SCH 23390 or raclopride, into either core or dorsomedial shell. The placements for these particular rats are displayed because these animals showed suppression of

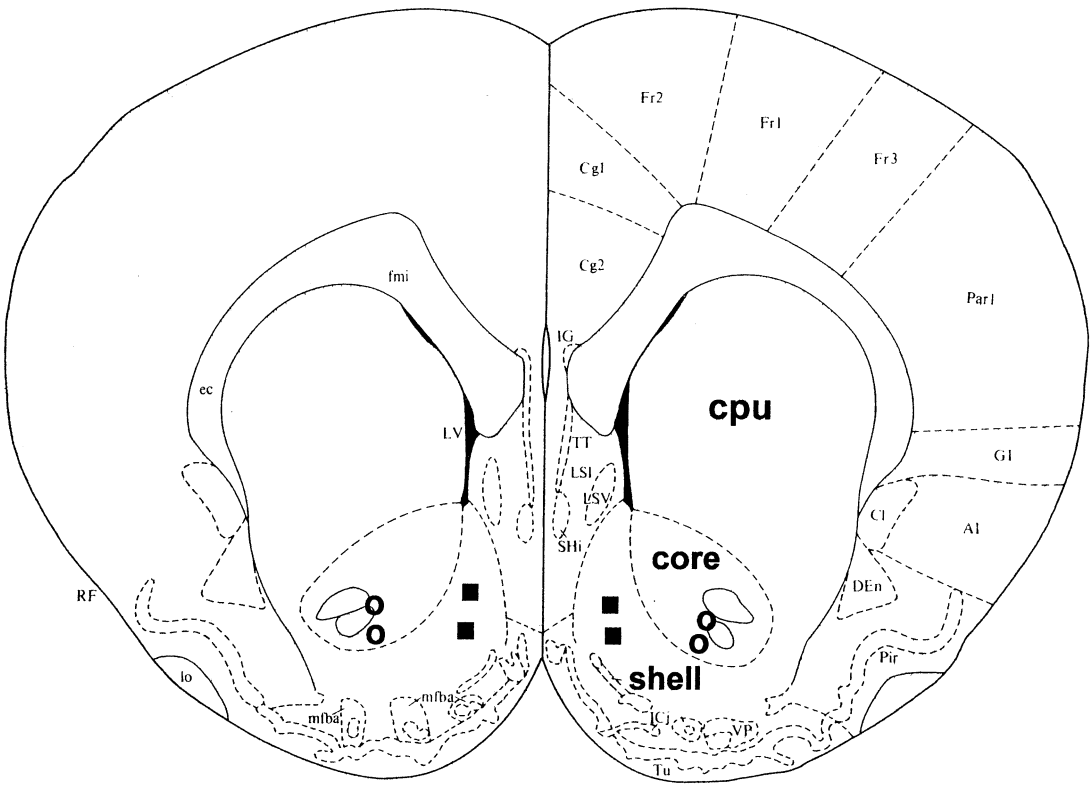

Fig. 1. This figure, which is modified from Paxinos and Watson (1986), shows cannulae placements from four representative rats. The rats represented here all received 1.0 μg/μl of either SCH 23390 or raclopride into either the core or dorsomedial shell. The four rats whose placement are show in this figure had reductions in lever pressing that were at the median level for each drug and placement group.

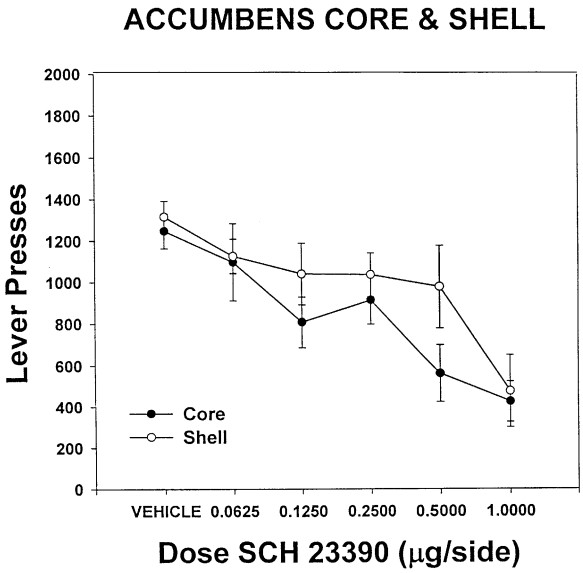

Fig. 2. Dose–response curve of the effects of SCH 23390 injected into the core and shell on lever pressing (mean ± S.E.M. number of responses). Collapsed across both placement groups, the 0.5- and 1.0-μg doses are significantly different from vehicle (Tukey's test, $P < .05$).

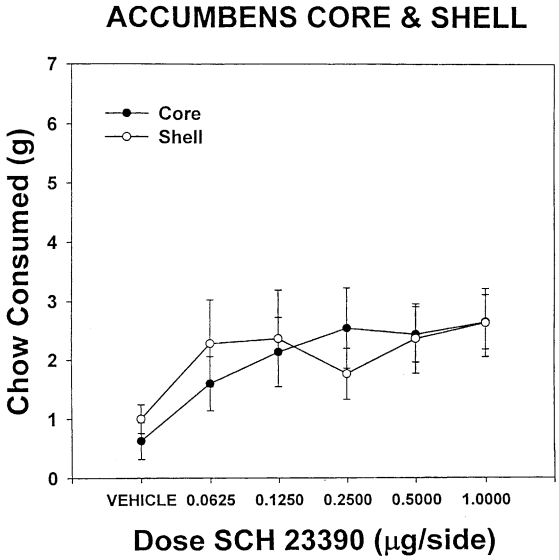

Fig. 3. Dose–response curve of SCH 23390 injected into the core and shell on chow consumption (mean ± S.E.M. weight of chow intake in grams) during the operant session. Collapsed across both placement groups, the 0.5- and 1.0-μg doses are significantly different from vehicle (Tukey's test, $P < .05$).

lever pressing that was at the median level for each drug and placement group.

3.1. Effects of SCH 23390

The effects of local core and shell injections of SCH 23390 on lever pressing on the FR5/chow-feeding procedure are illustrated in Fig. 2. Factorial ANOVA revealed a significant effect of dose [$F(5,72) = 9.2$, $P < .001$], and in Fig. 2, it can be seen that SCH 23390 suppressed lever pressing. There also was a difference between placement groups that approached statistical significance [$F(1,72) = 3.9$, $P = .051$], which reflects the slightly lower overall performance in the core group. There was no dose by group interaction [$F(5,72) = 0.38$, ns]. Table 1 shows the results of the curve-fitting analyses to determine the potency (i.e., ED_{50}) of the drug effect in each site. The ED_{50} value for the core was significantly lower than the value for the shell (i.e., the core value was outside the 95% confidence interval for the shell). Fig. 3 shows the effects of SCH 23390 injections on chow consumption. SCH 23390 produced a dose-related increase in chow consumption [$F(5,72) = 2.7$, $P < .05$], but there were no differences between placement groups [$F(1,72) = 0.53$, ns] and no Dose × Site interaction [$F(5,72) = 0.4$, ns]. In Fig. 4, the effects of SCH 23390 on lever press duration are shown. There was no significant effect of SCH 23390 dose on average duration of lever presses [$F(5,72) = 0.6$, ns], no significant difference between placement sites [$F(1,72) = 0.4$, ns], and no interaction effect [$F(5,72) = 0.6$, ns]. With data collapsed across all six injection treatment groups, correlational analyses revealed that there were significant inverse correlations between lever pressing and chow consumption in both the core-injected ani-

Table 1
ED_{50}s for suppressive effects of DA antagonists injected into core or shell on lever pressing

	ED_{50} (μg/side)	95% Confidence interval
SCH 23390		
Core	0.48	0.35–0.75
Shell	0.76	0.54–1.29
Raclopride		
Core	0.58	0.43–0.91
Shell	0.66	0.47–1.07

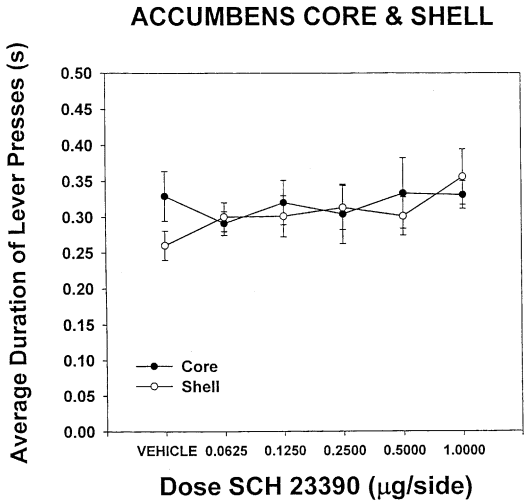

Fig. 4. The effects of SCH 23390 injected into the core and shell on the average duration of lever presses (means ± S.E.M., expressed in seconds) during the operant test session.

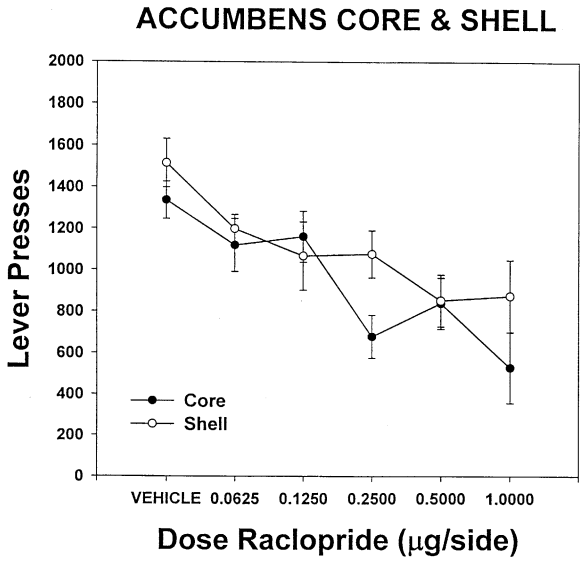

Fig. 5. Dose–response curve of the effects of raclopride injected into core and shell on lever pressing (mean ± S.E.M. number of responses). Collapsed across both placement groups, the 0.25-, 0.5- and 1.0-μg doses are significantly different from vehicle (Tukey's test, $P < .05$).

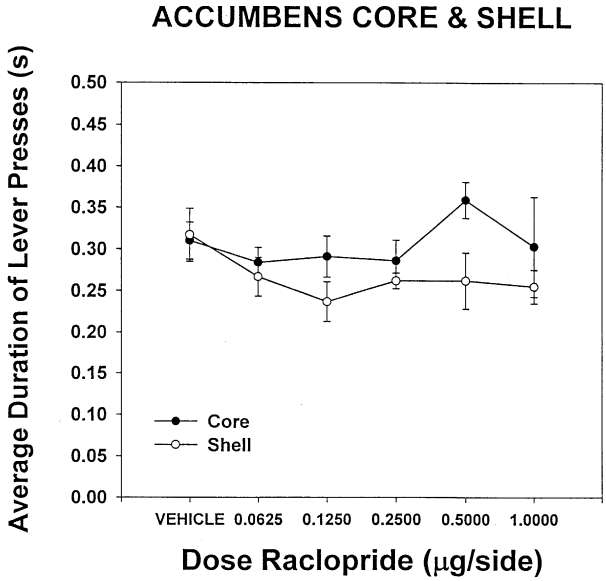

Fig. 7. The effects of raclopride injected into the core and shell on the average duration of lever presses (means ± S.E.M., expressed in seconds) during the operant test session.

mals ($r = -.723$, $P < .001$) and the shell-injected animals ($r = -.613$, $P < .001$).

3.2. Effects of raclopride

Fig. 5 depicts the effects of local core and shell injections of the D2 antagonist raclopride on lever pressing on the FR5/chow-feeding procedure. Factorial ANOVA revealed a significant effect of dose [$F(5,68) = 8.2$, $P < .001$], which reflects the suppression of lever pressing produced by raclopride. There also was a significant overall difference between placement groups [$F(1,68) = 4.3$, $P = .04$], which is related to the slightly lower overall performance in the core group. There was no dose by group interaction [$F(5,68) = 1.1$, ns]. Table 1 shows the results of the curve-fitting analyses to determine the ED_{50} of the drug effect in each site. The ED_{50} value for raclopride injected into the core was slightly lower than the value for the shell, but it was not outside the 95% confidence interval. Fig. 6 shows the effects of raclopride injections on chow consumption. Intraaccumbens injections of raclopride resulted in a dose-related increase in chow consumption [$F(5,68) = 3.4$, $P < .01$], but there were no differences between placement groups [$F(1,68) = 0.05$, ns] and no Dose × Site interaction [$F(5,68) = 0.4$, ns]. In Fig. 7, the effects of raclopride on the average duration of lever pressing are shown. There was no significant effect of raclopride dose on average duration of lever presses [$F(5,68) = 1.2$, ns], there was a significant difference between placement sites [$F(1,68) = 5.7$, $P < .05$], and no interaction effect [$F(5,68) = 0.73$, ns]. Correlational analyses revealed that with raclopride, there were significant inverse correlations between lever pressing and chow consumption in both the core-injected animals ($r = -.68$, $P < .001$) and the shell-injected animals ($r = -.72$, $P < .001$).

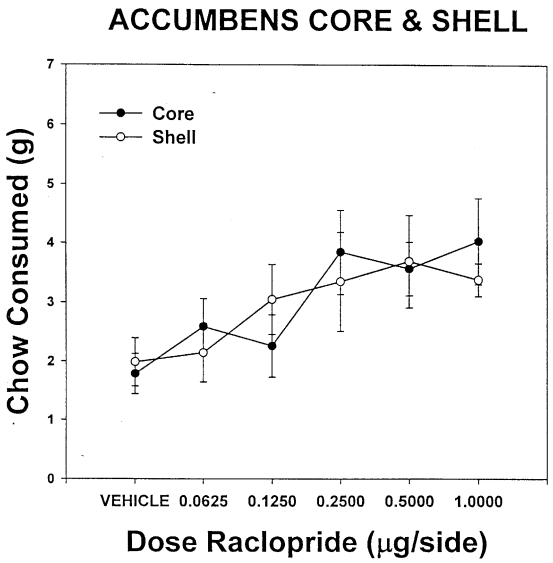

Fig. 6. Dose–response curve of raclopride injected into the core and shell on chow consumption (mean ± S.E.M. weight of chow intake in grams) during the operant session. Collapsed across both placement groups, the 0.25-, 0.5- and 1.0-μg doses are significantly different from vehicle (Tukey test, $P < .05$).

4. Discussion

The results of these experiments demonstrate that injections of SCH 23390 or raclopride, into either the core or the dorsomedial shell subregion of nucleus accumbens,

decreased lever pressing but led to a concomitant increase in chow consumption. Correlational analyses demonstrated that there was a strong inverse relation between lever pressing and chow consumption across treatment groups. Injections of SCH 23390 into the core produced effects on lever pressing that were more potent than in the shell. There were no significant effects of either drug on average duration of lever presses. These results demonstrate that low to moderate doses of DA antagonists, which are capable of suppressing lever pressing, still leave the animals directed towards the acquisition and consumption of food. The shift from lever pressing to chow consumption that occurs after injections of low doses of DA antagonists is apparently a robust phenomenon, which occurs regardless of which family of DA receptor is blocked, and independently of the particular subregion of accumbens into which the drug is injected. Consistent with other data, the present results suggest that low doses of DA antagonists injected into nucleus accumbens are not reducing lever pressing simply because of a general reduction in food motivation, or due to a loss of appetite.

The primary effects observed in these experiments were the dose-related decreases in lever pressing and increases in chow consumption in rats treated with DA antagonists. FR5 lever-pressing rate was suppressed by both the D1 antagonist SCH 23390 and the D2 antagonist raclopride. In the concurrent FR5/chow-feeding task, lab chow is concurrently available in the chamber, and drug-treated rats that showed suppressed lever pressing also showed a concomitant increase in consumption of the available chow. Both effects, i.e., the decrease in lever pressing and the increase in chow consumption, were shown for SCH 23390 and raclopride. It is possible that these effects occurred because of independent actions of SCH 23390 and raclopride on D1 and D2 receptors, respectively, or because both drugs interfere with some of the synergistic effects of D1 and D2 stimulation (Ikemoto et al., 1997). Moreover, these drug-induced decreases in lever pressing and increases in chow consumption were shown after injections into either core or shell. Thus, the shift from lever pressing to chow consumption, which is the effect typically seen with low doses of systemic DA antagonists, as well as with accumbens DA depletions, occurs with either D1 or D2 antagonists injected into either the core or the dorsomedial shell.

The present results, along with other previous findings, make it difficult to argue that interference with accumbens DA transmission suppresses lever pressing because of a fundamental reduction in food motivation or a loss of appetite for food (e.g., Salamone et al., 1998; Timberlake and Allison, 1974; Wise et al., 1978). Previous studies have shown that interference with accumbens DA did not produce a broad or fundamental reduction in food motivation. Depletions of DA in nucleus accumbens do not suppress food intake (Koob et al., 1978), and did not affect several parameters of feeding behavior, including food intake, time spent feeding, feeding rate, or food handling (Salamone et al., 1993b). Injections of high doses of the D2 antagonist haloperidol directly into the accumbens did not suppress food intake, although similar doses injected into ventrolateral striatum did impair feeding (Bakshi and Kelley, 1991). Using the concurrent FR5/chow-feeding paradigm (Salamone et al., 1991), accumbens DA depletions suppressed lever pressing for food but increased free feeding upon chow. Subsequent research replicated the finding that accumbens DA depletions shifted behavior away from lever pressing and towards feeding, and also demonstrated that anterior striatal DA depletions had little effect, while ventrolateral striatal DA depletions produced severe motor impairments that suppressed both lever pressing and chow consumption (Cousins et al., 1993). In that study, correlational analyses were employed to provide a further characterization of the behavioral effects of DA depletions. It was reported that there was a significant positive correlation between lever pressing and chow consumption in animals that received injections of 6-OHDA into the ventrolateral striatum. In contrast, there was a significant negative correlation between lever pressing and chow consumption in rats that received accumbens DA depletions. Consistent with the Cousins et al. (1993) study, the present experiments demonstrated that there were robust inverse correlations between lever pressing and chow consumption across treatment groups for both the core and shell sites, with both SCH 23390 and raclopride. This inverse correlation between lever pressing and chow consumption provides another statistical marker of the shift from lever pressing to chow consumption resulting from interference with accumbens DA transmission. Despite the fact that the shell is an important site for the modulation of feeding by opiates and glutamate (Maldonado-Irizarry et al., 1995; Pecina and Berridge, 2000), the present results demonstrate that DA antagonism in the shell, as in the core, produces reductions in lever pressing that are accompanied by increases in chow consumption. Thus, even with shell DA antagonism, it does not appear that lever pressing is decreased because of a general lack of food motivation. In the present studies, as well as in previous work using the concurrent lever-pressing/chow-feeding procedure (Cousins et al., 1993, 1994; Salamone et al., 1991), interference with accumbens DA did result in a decrease in the total amount of food consumed. However, this is merely an artifact of the shift from Bioserve pellets to chow consumption, and the different baseline rates of consumption from each food source. In free-feeding FR1 or FR5 procedures, rats typically consume about 13 or more grams of the 45-mg Bioserve pellets in 30 min, while the large chow pellets are consumed much more slowly (i.e., 5–6 g per 30 min, see Salamone et al., 1993b). Thus, anything that shifts the rat from Bioserve pellets to lab chow will invariably reduce total food intake because the animal's consumption

is simply regressing towards the mean chow intake that would occur if only chow were available. Additional research has shown that the shift from lever pressing to chow consumption does not occur after prefeeding to reduce food motivation (Salamone et al., 1991), nor does it occur after administration of appetite suppressants such as amphetamine (Cousins et al., 1994) or fenfluramine (Arizzi and Sandoval, unpublished data). Taken together, the present set of results indicates that rats with compromised DA transmission in nucleus accumbens still retain a fundamental aspect of food motivation, in that they remain directed towards the acquisition and consumption of food. As lever pressing is decreased by injections of DA antagonists, the rats shift to an alternative food source, i.e., the lab chow that is available in the chamber. In view of the fact that primary food motivation is seen by many researchers as a fundamental aspect of food reinforcement (Berridge and Robinson, 1998; Salamone, 1992; Salamone et al., 1997, 1999; Staddon, 1983; Thorndike, 1911; Timberlake, 1993), the present results provide further evidence that important aspects of food reinforcement are left intact after interference with accumbens DA transmission.

Several previous lesion and drug studies have reported functional differences between accumbens core and shell (Maldonado-Irizarry et al., 1995; Parkinson et al., 1999; Pecina and Berridge, 2000; Smith-Roe et al., 1999; Sokolowski and Salamone, 1998; Zahm, 2000, 1999). In contrast, the present study did not uncover any Dose × Placement site interactions, which would tend to indicate that the effects of SCH 23390 and raclopride did not differ between the core and the shell. Nevertheless, there was an overall tendency for animals with core injections to show lower levels of responding, and there was an overall site difference that approached significance in one study and reached significance in another. Moreover, curve-fitting analyses to determine the potency (i.e., ED_{50}) of the suppression of lever pressing demonstrated that the core was the most potent site for the effect of SCH 23390. With raclopride, the ED_{50} value was lower in the core, but it was not outside the 95% confidence interval for the shell. Thus, the hypothesis that the core would be the more potent site was not supported by some types of statistical evidence, yet, was supported by the potency data from the SCH 23390 experiment. Regression analyses of dose response curves is very powerful, because it relies upon the quantitative nature of the *x* axis variable (i.e., dose), and also because it makes assumptions about the specific mathematical relations between the variables that are not made in the ANOVA. In considering the sensitivity of the regression analysis to small differences between two dose response curves, it is reasonable to conclude that the core is slightly more sensitive than the shell to the suppressive effects of SCH 23390 upon lever pressing. Nevertheless, the differences in potency between these two sites were relatively small, and there was not a significant difference in potency with raclopride. This relative lack of a difference between the core and shell injection sites in the present study may seem surprising in view of the report by Sokolowski and Salamone (1998), that injections of 6-OHDA into the core, but not the shell, produced a significant shift from lever pressing to chow consumption in the FR5/chow-feeding task. It is possible that the spread of 6-OHDA from the injection site in the previous study (Sokolowski and Salamone, 1998) was restricted by the DA uptake mechanism, while SCH 23390 and raclopride may spread away from the injection site more easily, which would make it more difficult to obtain site differences. Nevertheless, it should also be emphasized that, in the previous DA depletion study, there was still a strong tendency for rats with the shell 6-OHDA injections to show a decrease in lever pressing and an increase in chow consumption (see Sokolowski and Salamone, 1998; Figs. 5–7). In addition, correlational analyses in the previous study did show that DA levels in the shell were positively correlated with lever pressing and negatively correlated with chow consumption (Sokolowski and Salamone, 1998). Thus, taking together both this previous report and the present findings, it is clear that interference with core DA transmission decreases lever pressing for food and increases chow consumption when both are concurrently available. It is possible that the core is in fact the primary active site for this effect (Sokolowski and Salamone, 1998), and that the present study was not able to differentiate fully the core from the shell because of spread of SCH 23390 or raclopride from the injection site. Alternatively, it also appears possible that this phenomenon (i.e., decreased lever pressing and increased chow intake) is not completely restricted to interference with DA at the core site, and that the shell also may be involved.

The behavioral processes that lead to the suppression of lever pressing after interference with accumbens DA transmission remain uncertain (Berridge and Robinson, 1998; Salamone, 1991, 1992; Salamone et al., 1997, 1999). It is evident that DA in accumbens mediates functions that are different from other striatal regions, such as ventrolateral neostriatum. As noted above, ventrolateral striatal DA depletions severely impair both lever pressing and feeding (Cousins and Salamone, 1996; Cousins et al., 1993, 1999; Salamone et al., 1993b), and these impairments have been interpreted as representing a Parkinsonian type of motor deficit in these rats (Salamone et al., 1998). Ventrolateral striatal DA depletions produce tremulous jaw movements that have the frequency characteristics of Parkinsonian tremor (Salamone et al., 1998). Depletions of DA in ventrolateral striatum impair feeding by severely disrupting feeding rate, food handling with the forepaws, and oral motor activity (Salamone et al., 1993b). In addition, the lever pressing deficits seen after ventrolateral striatal DA depletions are characterized by substantial increases in response duration (Cousins and Salamone, 1996). Increases in response duration have been interpreted as representing

aspects of motor dysfunction, including catalepsy, bradykinesia, and slowness in transition between movements (i.e., Carriero et al., 1997, 1998, ; Cousins and Salamone, 1996). In the present studies, injections of SCH 23390 or raclopride did not significantly increase response duration, although there was a slight tendency to do so at one dose of raclopride. Although the absence of a response duration effect does not preclude the presence of all types of motor deficits, the present data do suggest that intraaccumbens injections of SCH 23390 or raclopride in the doses used did not produce the type of severe motor deficit that is marked by increases in response duration. Various alternative hypotheses have been put forth to explain the effects of interference with accumbens DA upon lever pressing. These suggestions include the presence of subtle motor deficits, a lack of sensitivity to the activating effects of conditioned stimuli that normally induce responding, a general tendency towards response slowing, or a reduction in the tendency to overcome work-related response costs attached to instrumental contingencies (Aberman and Salamone, 1999; Salamone, 1991, 1992; Salamone et al., 1997, 1999). Indeed, instrumental behavior is a complex phenomenon, and many factors influence response output, including associative factors, motivational processes, and work requirements of the schedule (Aberman and Salamone, 1999; Aberman et al., 1998; Berridge and Robinson, 1998; Hursh et al., 1988; Kaufman, 1980; Koob et al., 1978; Salamone, 1987, 1991, 1992; Salamone et al., 1997, 1999; Sokolowski and Salamone, 1998; Staddon, 1979, 1983; Timberlake, 1993; Timberlake and Allison, 1974). Further research must be conducted to identify more precisely the behavioral effects of interference with accumbens DA transmission.

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