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Pimozide, like extinction, devalues stimuli associated with sucrose taking

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Abstract

Conditioned stimuli (CS) can be devalued by exposure to those stimuli in the absence of primary reward. We tested the hypothesis that dopamine (DA) mediates the control of behavior by conditioned appetitive stimuli. Long–Evans rats were trained to respond for sucrose under a heterogeneous chain schedule in which seeking responses (lever press) turned on a houselight [variable interval (VI)-120 s]; taking responses (wheel turn or chain pull) in the presence of the houselight were reinforced [fixed ratio (FR)-1] by a sucrose pellet. When responding on this schedule was stable, the levers were retracted and subjects had access to the sucrose-taking manipulandum only. Sucrose-taking responses were either extinguished or reinforced under the influence of the DA antagonist, pimozide. Control groups were also reinforced for sucrose-taking responses but received no injection or a vehicle injection prior to each session. Responses of extinction and pimozide-treated groups declined over sessions. Sucrose-seeking responses were measured in a later test when subjects had no access to the sucrose-taking manipulandum or to the reinforcer. Both extinction and pimozide manipulations reduced seeking responses, relative to the respective control groups. Pimozide injections in the home cage had no effect. These data support the idea that DA mediates the conditioned reinforcing properties provided by access to the taking link of the chain.

Keywords: Dopamine; Reward; Operant responding; Conditioned reinforcement; Devaluation

1. Introduction

Instrumental responding for primary rewards is controlled by associations that are formed between environmental stimuli, the operant response, and the reinforcer (Colwill and Rescorla, 1986; Dickinson, 1994). Instrumental responding may also be acquired, maintained, and facilitated by a conditioned stimulus (CS) that predicts a primary reinforcer (Mackintosh, 1974). The mesolimbic and nigrostriatal dopamine (DA) systems are clearly involved in instrumental responding for both primary and conditioned rewards (Beninger and Olmstead, 2000; Cador et al., 1991; Koob and Swerdlow, 1989; Salamone et al., 1997; Schultz et al., 1997; Wise and Rompre, 1989), however, the mechanism by which DA influences these behaviors is unclear. It is unlikely that mesolimbic DA mediates the incentive value of primary rewards because dopaminergic manipulations or excitotoxin lesions of the nucleus accumbens do not affect hedonic reactions (Pecina et al., 1997) or the reassignment of incentive value to a food reward (Balleine and Killcross, 1994; Dickinson et al., 2000). Moreover, in many cases, operant responding is not disrupted by systemic or intra-accumbens DA antagonism or by DA lesions (Amalric and Koob, 1987; Beninger and Ranaldi, 1993; Dworkin et al., 1988; Phillips et al., 1987; Roberts et al., 1977). Dopaminergic manipulations disrupt operant responding under some schedules of reinforcement, but these effects are quite distinct from the effects of extinction or prefeeding (Salamone et al., 1997, 1999). Taken together, these data suggest that DA blockade does not impair the impact of primary rewards. On the other hand, DA may interact with the conditioned associations that are acquired during instrumental learning.

Recently, we examined the learned associations that control operant responding for either a sucrose reward or a cocaine infusion (Olmstead et al., 2001). Animals were trained to respond under a two-link heterogeneous chain schedule in which responding in the initial, seeking link gave access to the opportunity to perform a different, taking response that produced the reinforcer. Seeking responses under this schedule appear to reflect the motivation to obtain

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the reinforcer in that the rate of responding increases with reward magnitude (i.e., sucrose concentration; Olmstead et al., 2000). Seeking responses per cocaine infusion also increase with dose, as long as the satiety producing effects of the drug have dissipated. On the other hand, seeking and taking responses (at least for cocaine) are dissociable because they are differentially affected by changes in dose and the introduction of a time-out period. Following training on the seeking-taking chain schedule, the taking response was extinguished in the absence of the opportunity to perform the seeking response (Olmstead et al., 2001). This extinction treatment effectively devalues the reinforcing properties of the taking link without devaluing the reinforcer itself. In a subsequent extinction test, seeking responses were reduced in the extinction group relative to a control group that had not undergone the devaluation procedure. These results show that there is an associative link between the neurons controlling the taking response and those controlling the seeking response, such that weakening the control of behavior by the former reduces the control of behavior by the latter.

The present experiment used the same behavioral paradigm to test the hypothesis that decreased DA neurotransmission during performance of the taking response will lead to a decrease in seeking responses in a subsequent extinction test. Subjects were trained to respond for sucrose pellets under a heterogeneous chain schedule using a lever press as the seeking response and a wheel turn or a chain pull as the taking response. When responding on the chain schedule had stabilized, the sucrose-taking response was devalued in one of two ways. One group experienced the taking manipulandum in extinction; the second group was reinforced for taking responses under the influence of the DA receptor blocker, pimozide. The effectiveness of the devaluation treatment was subsequently evaluated by measuring seeking responses, which no longer provided access to the taking link or to the reinforcer. If pimozide, like the extinction manipulation, results in reduced performance of the seeking response, it would indicate that DA mediates the conditioned reinforcing properties provided by access to the taking link of the chain.

2. Method

2.1. Subjects

Seventy male Long–Evans rats (Charles River, Canada) weighing 300–350 g at the beginning of the experiment were housed in pairs on a 12-h light/dark cycle with lights on at 19:00 h. Behavioral testing was conducted during the dark cycle. Animals were given 1 h/day of free access to regular chow in their home cage, maintaining body weight at 85–90% of their free-feeding weight. Water was freely available in the home cage. All experiments were conducted in accordance with the Canadian Council on Animal Care and Queen's University Animal Care Committee regulations.

2.2. Apparatus

Training and testing took place in eight sound-attenuated operant chambers (26.5 × 22 × 20 cm) that were fitted with two retractable levers (3.5 cm wide), each 4 cm from the outer wall. A retractable response wheel and chain were located on opposite sides of the chamber. All manipulanda were 9 cm from the grid floor. Sucrose pellets (45 mg; Bioserve) could be delivered to a recessed magazine (3.8 cm wide and 5.5 cm from the grid floor) which was situated between the two levers. The illumination of the houselight in each chamber acted as the discriminative stimulus. External noise was masked by ventilating fans mounted on the side of each chamber. The manipulanda and stimuli were controlled by an IBM-compatible 486 computer with software written in house.

2.3. Drugs

Pimozide (Janssen, Pharmaceutica; Beerse, Belgium) was dissolved in a vehicle solution containing 6-mg tartaric acid/1-ml distilled water. The solution was prepared daily and injected 90 min before behavioral testing (1.0 mg/kg ip). The dose and route of administration were based on previous research (Beninger and Hahn, 1983; Beninger et al., 1987; Wise et al., 1978a).

2.4. Behavioral procedures

2.4.1. Training

Thirty-nine animals were trained to respond for sucrose under a heterogeneous chain schedule. Responding on one lever in the first link of the chain (sucrose-seeking) turned on a discriminative stimulus (houselight), indicating that responses on either the chain or wheel (sucrose-taking) would produce a sucrose pellet. The choice of right vs. left lever as the sucrose-seeking manipulandum and wheel or chain as the sucrose-taking manipulandum was counterbalanced within groups.

In the first stage of training, the sucrose-seeking lever was retracted and responses on the sucrose-taking manipulandum were reinforced on a fixed-ratio (FR-1) schedule of reinforcement, only in the presence of the discriminative stimulus. Over seven sessions, the latency to turn on the discriminative stimulus following the presentation of the reinforcer was increased from 0, 2, 5, 15, 30, 60 to 120 s. Animals could receive a maximum of 20 pellets per 2-h session. Animals were tested at the 120-s latency until responding was stable (20 pellets received in less than 50 min).

Once sucrose-taking responses were stable (three to four sessions at the 120-s latency), the chain schedule was introduced. Both sucrose-seeking and sucrose-taking

manipulanda remained in the chamber throughout the chain schedule sessions. The first response on the sucrose-seeking lever initiated a variable interval (VI) schedule and the first response meeting the VI contingency turned on the houselight. In the presence of the discriminative stimulus, food-taking responses were reinforced on an FR-1 schedule. After the sucrose pellet was delivered, the houselight turned off and the cycle began with the next sucrose-seeking response. The VI contingency was increased across sessions through 2, 5, 15, 30, 60 to 120 s. Five baseline sessions on the chain schedule were conducted at the 120-s VI. Animals could receive a maximum of 20 rewards per 2-h session.

2.4.2. Devaluation

2.4.2.1. Extinction. Sixteen animals were randomly assigned to extinction and reinforcement groups ($N=8$ each). For half of the animals in each group, the wheel was the sucrose-taking manipulandum. The sucrose-seeking lever was retracted and the sucrose-taking manipulandum remained in the chamber throughout the devaluation sessions. During each session, the discriminative stimulus was turned on at random intervals averaging 120 s. For the reinforcement group, the first response in the presence of the discriminative stimulus produced a sucrose pellet and turned off the houselight. For the extinction group, the discriminative stimulus stayed on for 20 s, but sucrose-taking responses did not produce a sucrose pellet. Sessions continued until rats in the extinction group were making fewer than five responses on the sucrose-taking manipulandum per 2-h session. Using this criterion, rats in both the extinction and reward groups completed 10 devaluation sessions.

2.4.2.2. Pimozide. A second set of rats ($N=19$) was split into pimozide ($N=11$) and vehicle ($N=8$) groups. Again, the sucrose-taking manipulandum was counterbalanced within groups. Animals were injected with pimozide (1.0 mg/kg ip) or vehicle 90 min before each devaluation session. All rats were returned to their home cages during the 90-min interval. During the session, only the sucrose-taking manipulandum was in the chamber and the discriminative stimulus was presented at random intervals of 120 s. Both pimozide and vehicle groups were reinforced (FR-1) for sucrose-taking responses in the presence of the discriminative stimulus. Rats could receive a maximum of 20 pellets per 2-h session. Sessions continued until pimozide-treated rats were making fewer than five responses per session (five sessions in total).

2.4.2.3. Home cage. The remaining four animals served as controls for the effect of repeated pimozide injections on operant responding. These animals were trained on the chain schedule but did not undergo any devaluation training. They received one pimozide injection per day and were returned to their home cage for 5 days.

2.4.3. Testing

Twenty-four hours after the last devaluation sessions, sucrose-seeking responses were assessed in an extinction test during which the sucrose-taking manipulandum was retracted. The session started with the insertion of the sucrose-seeking lever and ended with its retraction after 30 min. No sucrose pellets were presented and the discriminative stimulus was not turned on during this test session.

3. Results

3.1. Training

In order to determine that responses of all groups were comparable prior to devaluation sessions, data from the last five sessions on the chain schedule (VI-120 s) were analyzed using a repeated-measures analysis of variance (ANOVA) with devaluation treatment as a between-subjects factor and session as a within-subjects factor. Fig. 1 shows that the number of drug-seeking responses per reward did not vary significantly across these five baseline sessions [$F(4,132)=1.18$, $P=.32$]. There were no group differences in the rate of seeking responses per reward [$F(4,33)=0.37$, $P=.86$] and no significant group × session interaction [$F(16,132)=1.51$, $P=.1$]. The latencies to sucrose-seek following the presentation of a sucrose pellet are shown in Fig. 2. There were no significant group differences in this measure [$F(4,33)=0.74$, $P=.58$], no significant changes across session [$F(4,132)=0.63$, $P=.46$], and no significant group × session interaction [$F(16,132)=0.63$, $P=.85$].

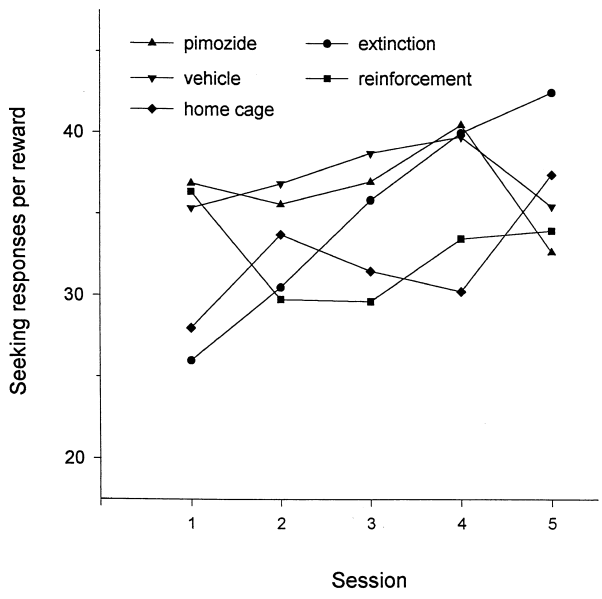

Fig. 1. Baseline sucrose-seeking responses: Data points represent the mean number of seeking responses per reward presentation over the last five training sessions of the chain schedule (VI-120 s). The five groups (extinction, reinforcement, pimozide, vehicle, and home cage) were distinguished by the treatment they received during devaluation sessions.

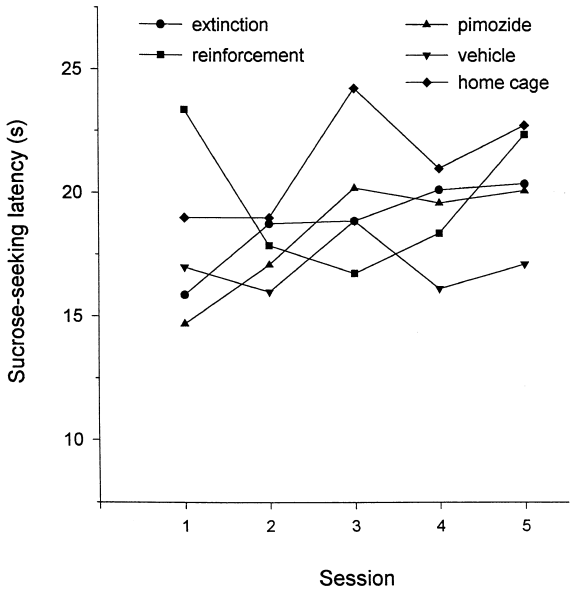

Fig. 2. Baseline latency to sucrose-seek: Data points represent the mean latency(s) to the first sucrose-seeking response following the presentation of a sucrose pellet (bottom) over the last five training sessions of the chain schedule (VI-120 s). The five groups (extinction, reinforcement, pimozide, vehicle, and home cage) were distinguished by the treatment they received during devaluation sessions.

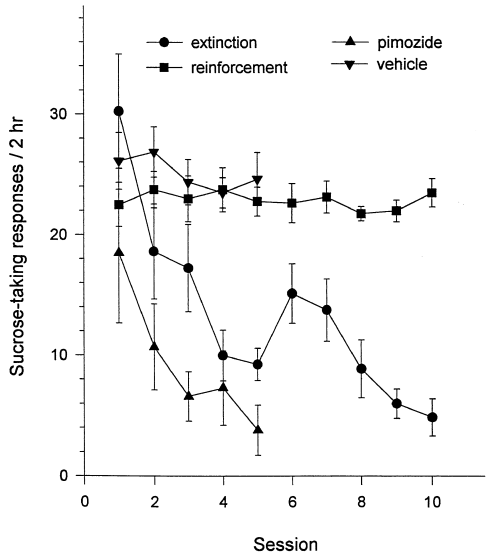

Fig. 3. Devaluation of sucrose-taking: Data points represent the mean number of sucrose-taking responses during extinction and pimozide devaluation sessions when the discriminative stimulus was on. The extinction group did not receive any sucrose pellets during the devaluation sessions, whereas the reinforcement, pimozide, and vehicle groups were reinforced for responding (FR-1) in the presence of the discriminative stimulus.

These data verify that there were no group differences in the rate of responding or latency to sucrose-seek prior to the devaluation manipulations.

3.2. Devaluation

The extinction and pimozide groups required a different number of devaluation sessions to reach criterion levels of responding (10 and 5 sessions, respectively). Thus, the data from these two manipulations were analyzed separately using a repeated-measures ANOVA with group (reinforcement vs. extinction or vehicle vs. pimozide) as a between-subjects factor and session as a within-subjects factor. It can be seen in Fig. 3 that sucrose-taking responses declined across devaluation sessions in the extinction group but remained stable for the reinforced group. This effect was verified statistically by a group × session interaction [$F(9,126)=7.31$, $P<.001$] and main effects of group [$F(1,14)=62.48$, $P<.001$] and session [$F(9,126)=7.43$, $P<.001$]. Post-hoc tests (Scheffé) revealed that responses of the extinction group were significantly lower than the reinforced group from the fourth session onwards. There were no differences in sucrose-taking responses (either between groups or across sessions) when the discriminative stimulus was off (data not shown; all F's <1).

Fig. 3 also shows that responses of pimozide-treated animals were reduced compared to the vehicle-treated animals over the five devaluation sessions [$F(1,16)=50.47$, $P<.001$] although neither the main effect of session [$F(4,64)=2.12$, $P=.08$] nor the group × session interaction [$F(4,64)=1.01$, $P=.41$] were statistically significant. Responses of pimozide-treated animals were significantly lower than vehicle-treated animals during the last four sessions (post-hoc tests). Responses when the discriminative stimulus was off did not differ between groups or across sessions (Scheffé's post-hoc test, all $P>.05$).

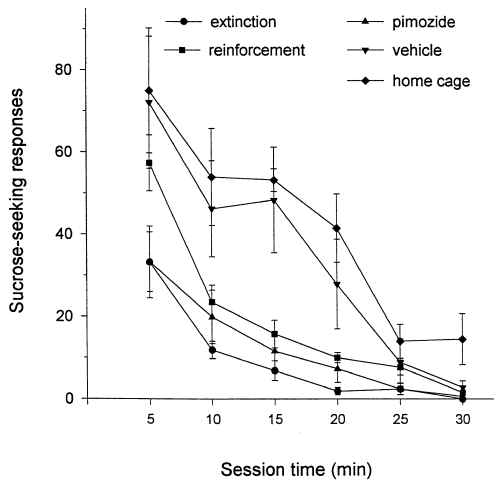

Fig. 4. Effects of devaluation on sucrose-seeking: Data points represent the mean number of sucrose-seeking responses per 5-min bin across a 30-min extinction test. The top graph shows the responses of the extinction devaluation group and their control (reinforcement). The bottom graph shows the responses of the pimozide devaluation group and the two control groups (vehicle and home cage). Neither sucrose pellets nor the discriminative stimulus were presented during the test session.

Sucrose-taking responses in the two control groups (reinforced and vehicle) were slightly higher than 20 responses per session despite the fact that animals were responding on an FR-1 schedule and the session ended after 20 presentations of the reinforcer. This apparent discrepancy is probably due to the calibration of the response wheel; a single response (turn) of this sucrose-taking manipulandum sometimes recorded more than one response while only producing one sucrose pellet.

3.3. Testing

Fig. 4 shows the food-seeking responses of the five different treatment groups during a 30-min extinction test. The significant group × time interaction [$F(20,165) = 3.56$, $P < .05$] and main effect of group [$F(4,33) = 15.46$, $P < .001$] were due to the fact that both extinction and pimozide treatments during devaluation sessions reduced subsequent sucrose-seeking responses, relative to their respective control groups. Responses of all groups declined across the session [$F(5,165) = 76.57$, $P < .001$]. Post-hoc tests (Scheffé) confirmed that responses of the extinction group were lower than that of the reinforcement group and responses of the pimozide group were lower than those of the vehicle group. Moreover, repeated pimozide injections in the home cage group did not reduce sucrose-seeking responses compared to vehicle-treated animals. There was no significant difference between response rates of the two experimental groups (extinction and pimozide). In contrast, responses of the reinforcement group were significantly lower than the other two control groups (vehicle and home cage) which did not differ significantly from each other.

The latency to the first sucrose-seeking response during the final test is shown in Fig. 5. A one-way ANOVA revealed a significant group effect [$F(4,33) = 21.03$, $P < .01$] and post-hoc tests (Scheffé) showed that the extinction group was significantly slower to respond than the reinforcement group but there were no significant differences between the pimozide, vehicle, and home cage groups.

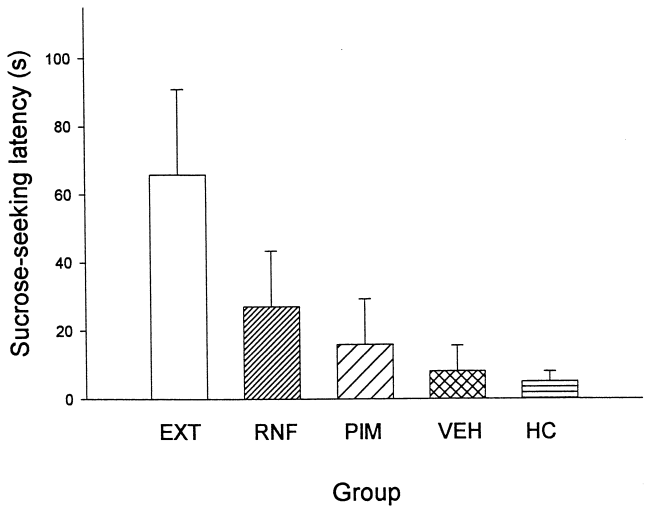

Fig 5. Effects of devaluation on the latency to sucrose-seek: Bars represent the mean latency(s) to the first sucrose-seeking response in the extinction test. The five groups were distinguished by the treatment they received during devaluation sessions. EXT= extinction; RNF= reinforcement; PIM= pimozide; VEH= vehicle; HC= home cage.

4. Discussion

When animals are responding under a heterogeneous chain schedule for a sucrose reward, extinction of the taking response increases the latency to the first seeking response and reduces the overall rate of responding in a later test. This result confirms our recent finding (Olmstead et al., 2001) using a between, rather than a within, subjects design. The present experiments also replicate the numerous reports that DA antagonists produce extinction like responding for a food reward (Willner et al., 1988; Wise et al., 1978a,b). Most importantly, the decline in sucrose-taking responses under the influence of pimozide was associated with a reduction in sucrose-seeking responses in a later test. It is unlikely that the reduced responding in the pimozide-treated animals was due to the motor inhibiting effects of the drug because the animals were drug-free during testing and repeated pimozide injections in the home cage had no effect on seeking responses during the final test. Nor can the drug-induced effect be explained by a disruption in stimulus discrimination as pimozide does not block this ability in rats (Beninger, 1982; McFarland and Ettenberg, 1999; Tombaugh et al., 1980). Although the pimozide-treated group exhibited longer latencies to sucrose-seek than either of the two control groups (vehicle and home cage), the effect was not statistically significant. This may reflect a floor effect as all three groups initiated responding in less than 18 s. The extinction and pimozide manipulations produced almost identical rates of responding during the final seeking test, whereas response rates of one control group (reinforcement) were much lower than those of the other two control groups (vehicle and home cage; see Fig. 4). The only obvious difference between the control groups was the amount of exposure to the taking link following training on the chain schedule (10, 5, and 0 sessions), but it is not clear why this would lead to lower response rates and more rapid extinction in the reinforcement group. Regardless, the critical finding in our study is that responding of each experimental group was significantly different from the respective control group.

We favour the interpretation that both extinction and pimozide decrease sucrose-seeking by reducing the conditioned reinforcing properties of the sucrose-taking link. This interpretation is consistent with evidence that post-training devaluation of a positive reinforcer reduces performance in a subsequent extinction test (Colwill and Rescorla, 1986; Dickinson, 1989) and that DA antagonists block the reinstatement of responding for a food reward following extinction (Chausmer and Ettenberg, 1997). It is interesting to

note that the acquisition of conditioned reinforcing properties to previously neutral stimuli is disrupted by DA antagonists (Beninger and Phillips, 1981; Ettenberg and Camp, 1986a,b; Killcross et al., 1987; Nader and van der Kooy, 1994; Spyraki et al., 1982), but once these are established, DA is not essential for the expression of behaviors elicited by the conditioned stimuli (Beninger and Hahn, 1983; Beninger and Herz, 1986; Franklin and McCoy, 1979; Horvitz and Ettenberg, 1991; McFarland and Ettenberg, 1999). Disruption of DA transmission, therefore, is only effective in altering responses when animals have repeated exposure to the conditioned stimuli. Experience-dependent changes in responding under the influence of DA antagonists are also observed when animals are running for a sucrose reward (Ikemoto and Panksepp, 1996). Taken together, these data indicate that DA is essential for the establishment of associative links between stimuli, responses, and reinforcers and for acquiring new associations when the relationship between the three is changed.

An alternative explanation of our results is that the devaluation treatments simply produced a general reduction in instrumental performance. This is particularly pertinent to the pimozide group because DA antagonists (Dickinson et al., 2000) or nucleus accumbens lesions (Balleine and Killcross, 1994) decrease the general excitatory effect of contextual stimuli on instrumental responding. However, the seeking and taking responses in our paradigm are distinct (lever press and wheel turn or chain pull, respectively), making it less likely that the animals generalized between the two. Moreover, when animals are trained simultaneously on two different chain schedules, extinction of one taking link selectively reduces seeking responses associated with that link (Olmstead et al., 2001). Thus, although DA may influence general arousal associated with appetitive stimuli, the present results are more likely due to a reduction in the conditioned association between the seeking and taking links in the chain.

Although we cannot rule out the possibility entirely, it is unlikely that our results can be explained by a change in the incentive value of the reinforcer. The extinction manipulation could not be acting through this mechanism because animals had no access to the reinforcer during the devaluation sessions. Thus, it was the association between the sucrose-taking response and the sucrose that was devalued, not the sucrose itself. In the pimozide manipulation, reinforced sucrose-taking responses declined across devaluation sessions, but animals consumed all of the pellets that were presented during these sessions, suggesting that the incentive value of the reinforcer was still intact. Indeed, lesions of the mesolimbic DA system do not attenuate consumption of primary rewards (Kelley and Stinus, 1985; Koob et al., 1978), DA antagonists do not reduce sucrose intake (Ikemoto and Panksepp, 1996), and neither lesions nor DA antagonism alter hedonic reactions to a food reward (Pecina et al., 1997). Some reports indicate that blockage of DA mechanisms does not reduce operant responding for a food reward (Amalric and Koob, 1987; Beninger and Ranaldi, 1993; Dworkin et al., 1988; Phillips et al., 1987; Roberts et al., 1977), although a more thorough analysis of the phenomenon indicates that performance under high ratio schedules is disrupted by these manipulations (Salamone et al., 1999). The selective effect on reinforcement schedules, which require a high response output, has been interpreted as evidence that DA lesions or antagonism decrease the ability of conditioned stimuli to instigate and sustain operant responding (Salamone et al., 1997). Finally, when animals are trained to respond for a sucrose reward, reexposure to the reinforcer under the influence of pimozide or following nucleus accumbens lesions does not reduce subsequent responding for the sucrose (Balleine and Killcross, 1994; Dickinson et al., 2000). Again, this suggests that DA does not mediate the hedonic pleasures of reinforcers but may be necessary for the control of behavior by stimuli associated with the reinforcer (Beninger and Olmstead, 2000; Berridge and Robinson, 1998).

A critical feature of our paradigm is that animals were restricted to 20 reinforcers per session. With limited exposure to the instrumental contingency, responding is controlled by an association between the instrumental action and its consequences (Adams and Dickinson, 1981; Balleine and Dickinson, 1991; Colwill and Rescorla, 1985; Rescorla, 1992). With extended training, control of responding is shifted to a strengthened association between environmental stimuli and the operant response. Under these conditions, responses that are elicited somewhat automatically by the environmental stimuli are insensitive to devaluation (Dickinson, 1985). In line with this interpretation, preliminary work showed that devaluation of the sucrose-taking link through extinction was ineffective if animals could receive 100 rewards per session (Olmstead, Everitt and Dickinson, unpublished observation). The reduction of seeking responses following extinction of the taking response confirms that sucrose-seeking is driven by an association between the seeking response and its outcome (access to the taking link): the finding strengthens our argument that DA mediates the control of behavior by stimuli associated with a primary reward. Our results do not address the role of DA in stimulus–response associations but, given that extensive training attenuates responses of DA neurons to conditioned stimuli (Ljungberg et al., 1992), the maintenance of overlearned responses may be independent of dopaminergic mechanisms. If DA is critical for behaviors that are driven by stimulus–response associations, the effect is more likely mediated in the dorsal, rather than the ventral, striatum (McDonald and White, 1993).

In summary, our results support previous evidence that DA transmission is critically involved in processes whereby stimuli associated with primary rewards acquire the ability to control behavior. This proposal is in agreement with recent formulations of the role of DA in reward-related behaviors (Beninger and Olmstead, 2000; Berridge and Robinson, 1998) and the idea that "DA antagonists could

be altering arousal functions that are related to aspects of associative processes'' (Salamone et al., 1997). At a neuronal level, DA alters responses of other neurons to excitatory or inhibitory stimuli (Surmeir, 2000), suggesting that a primary function of DA is to modify other connections or associative links.

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