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The D_1 Agonist SKF 38393 Attenuates Amphetamine-Produced Enhancement of Responding for Conditioned Reward in Rats

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RANALDI, R., D. PANTALONY AND R. J. BENINGER. *The D_1 agonist SKF 38393 attenuates amphetamine-produced enhancement of responding for conditioned reward in rats.* PHARMACOL BIOCHEM BEHAV **52**(1) 131–137, 1995. – The present study investigated the hypothesis that the D_1 subtype of DA receptors is critically involved in reward-related learning. The effects of SKF 38393, a D_1-specific agonist, on amphetamine-produced enhancement of responding for conditioned reward were tested. We exposed 69 male Wistar rats to an experimental design consisting of three phases. The preexposure phase consisted of five sessions during which the rats were exposed to an operant chamber containing two levers. One lever produced a lights-off stimulus (3 s) and the other a tone stimulus (3 s). This was followed by four conditioning sessions during which the levers were removed and the rats were exposed to pairings of the lights-off stimulus with food. This phase was followed by two test sessions during which the levers were present and the number of responses made on each lever was calculated as a ratio of the number of responses made during the preexposure phase. A group receiving saline during the test sessions showed a higher ratio of responding for the lights-off stimulus than the tone stimulus, demonstrating that the lights-off stimulus had become a conditioned reward. Amphetamine [2.0 mg/kg, intraperitoneally (IP), 5 min before the test] enhanced responding specifically on the lever producing the conditioned reward. Groups receiving SKF 38393 (5.0, 10.0, and 20.0 mg/kg, IP, 5 min before the test) failed to show significantly greater responding for the lights-off stimulus than the tone, indicating a reduction or elimination of the conditioned reward effect. Moreover, SKF 38393 dose dependently reduced the amphetamine-produced enhancement of responding for conditioned reward. The possible role for D_1 receptors in reward-related learning is discussed.

Amphetamine Conditioned reinforcement Conditioned reward Dopamine D_1 agonist D_1 receptors Reinforcement Reward SKF 38393

THERE exists strong evidence that dopamine (DA) plays a critical role in reward-related learning (3,61). For instance, rats will self-administer compounds that facilitate DA neurotransmission (41,43,44,52). Such compounds also have been shown to enhance the rewarding value of electrical stimulation of the brain (17–20) and to produce preferences for environments with which they had been paired (2,24,25,27). These findings suggest that the ability of stimuli to control instrumental responding depends, at least in part, on dopaminergic neurotransmission.

Neutral stimuli can acquire incentive motivational properties through pairings with unconditioned rewarding stimuli such as food or water (10). The acquisition of incentive properties by neutral stimuli has been demonstrated experimentally when animals increased responding on a lever that produced a stimulus that was paired previously with reward (55,56). When a stimulus acquires incentive properties through pairings with a reward it is referred to as a conditioned reward.

Dopamine appears to play a role in the control of responding by conditioned reward. When animals were administered compounds that increase the neurotransmission of DA, they showed an enhancement of responding for conditioned reward (6,7,9,12,23,28,29,35,47,48,50,51,57,58). However, the administration of apomorphine, a direct DA agonist, resulted in an impairment of responding for conditioned reward (9,35,51). DA also is important for the acquisition by neutral stimuli of the ability to act as conditioned rewards. Accordingly, administration of compounds that block the neurotransmission of

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DA resulted in an impairment of responding for conditioned reward (8,26).

The effects of DA receptor-selective compounds on reward-related learning were evaluated. In the conditioned reward paradigm the D_2 agonists, bromocriptine and quinpirole, enhanced responding for conditioned reward whereas SKF 38393, a D_1 partial agonist, impaired it (9).

The conflicting effects on responding for conditioned reward of indirect vs. direct and D_1 vs. D_2 agonists may suggest that the role of DA in reward-related learning is to act as a signal for the rewarding stimulus. Increased release of DA has been observed when animals are presented with rewarding stimuli (11,22,38,42,45). If rewarding stimuli are associated with a signal at DA receptors, then amphetamine, which acts presynaptically, might be expected to leave the signal intact and allow the conditioned reward to control responding. In contrast, apomorphine, which acts postsynaptically, might be expected to mask the signal and disrupt the ability of the conditioned stimulus to control responding. The differential D_1 vs. D_2 agonist effects may suggest that the putative reward signal occurs at D_1 receptors (5,9,37).

Some data may appear to contradict this hypothesis. Thus, it was observed that injections of SKF 38393 into the nucleus accumbens enhanced responding for conditioned reward (62), suggesting that tonic stimulation of D_1 receptors, at least in this region, did not mask a putative D_1 reward signal. It is possible, however, that the reward signal is distributed across the nucleus accumbens and other DA terminal regions such as the caudate-putamen, and thus failed to be masked by such highly localized injections. Several findings support the notion of a distributed reward signal: a) a small increase in responding for conditioned reward was observed with intracaudate-putamen injections of amphetamine (28,57); b) in studies examining potentiated responding for conditioned reward produced by accumbens amphetamine, 6-hydroxydopamine (6-OHDA) lesions of this region eliminated the amphetamine effect but, surprisingly, not the conditioned reward effect itself (58); and finally c) in a study performed to evaluate the contributions of both accumbens and caudate-putamen dopamine to avoidance responding, a behavior that can be understood in terms of reward processes (3–5), it was shown that disruption occurred only when both sites were destroyed with 6-OHDA (34).

The present experiment was designed to investigate further the role of D_1 receptors in responding for conditioned reward. Because the conditioned reward effect is relatively weak we enhanced the effect with systemic injections of amphetamine and challenged the psychostimulant-enhanced responding for conditioned reward with the D_1 agonist, SKF 38393. If responding for conditioned reward is at least partly dependent on a signal at D_1 receptors, then direct stimulation of these receptors during the learning of the lever press response should lead to a masking of the signal and a loss of responding for conditioned reward. The present experiment tested this prediction.

METHOD

In the present study, the rats were treated in accordance with the Animals for Research Act, the Guidelines of the Canadian Council on Animal Care, and relevant University policy; the study was approved by the Queen's University Animal Care Committee.

Subjects

Sixty-nine experimentally naive male Wistar rats (Charles River, Canada) initially weighing between 225 and 275 g (free-feeding) were individually housed in a temperature-controlled environment (21 °C) on a 12L : 12D cycle (lights on at 0700 h). Rats were habituated to the housing environment for approximately 1 week and their weights increased by 25–40 g. Weights were then reduced to 80% of these values for the 11-day duration of the experiment through daily feedings with measured rations.

Apparatus

The experimental environments consisted of four similarly constructed operant chambers measuring 29 × 23 × 19 cm. The chambers were constructed of aluminum sides and transparent plastic tops and doors. The floors consisted of aluminum grids. Each chamber was placed in a ventilated sound-attenuating box. Each 29-cm wall of each chamber contained a removable lever measuring 7.5 × 3.5 cm. A force of approximately 0.09 N was required to depress each lever. At the center of the 23-cm wall was positioned a 2.0 × 4.0 cm feeder cup at a height of 2.5 cm from the floor. An illuminated 2-W lightbulb was positioned on each side (8.5 cm apart) of the feeder cup at a height of 10 cm from the floor. Each chamber also contained a 4.9-kHz tone generator positioned at 14 cm from the floor between the two lightbulbs and at the center of the 23-cm wall. The tone generator was adjusted to deliver a tone 10 dB above the background noise level.

Procedure

Each group was exposed to an experimental design that consisted of three distinct phases referred to as preexposure, conditioning, and test. The procedure employed for the group receiving saline was as follows. All groups followed exactly the same procedure except that drugs were injected before each test session, as described subsequently.

The preexposure phase consisted of five 40-min sessions held once per day on 5 consecutive days. The two levers were present. Pressing one lever produced the tone stimulus and pressing the other produced the lights-off stimulus. The duration of each stimulus was 3 s. Two of the chambers had the tone-producing lever on the right wall and the lights-off-producing lever on the left wall; the relationship between lever side and stimulus was reversed for the other two chambers. The number of responses on each lever was measured for each preexposure session.

The conditioning phase consisted of four 60-min sessions held once per day for the 4 consecutive days following the last day of the preexposure phase. During conditioning both levers were removed from the operant chamber and the rats were exposed to 80 presentations of the 3-s lights-off stimulus according to a random time 45-s schedule—that is, the average time between lights-off stimulus presentations was 45 s (range 5–90 s). During the first conditioning session each lights-off stimulus presentation was terminated with the delivery of one 45-mg food pellet (Bioserv). During the remaining three conditioning sessions food delivery occurred following a random 33% of the lights-off stimulus presentations. This procedure was employed because Knott and Clayton (33) observed that partial pairing resulted in a greater magnitude of conditioned reward than continuous pairing.

The test phase consisted of two 40-min sessions held on the 2 consecutive days following the last day of conditioning. The levers were again present in the operant chambers and the number of responses on each lever was measured. Conditioned reward was observed as a relative increase in the number of responses on the lever producing the lights-off stimulus in the test phase compared to the preexposure phase.

A total of eight groups were tested. One group (n = 16) received 0.9% saline. Another group (n = 16) received a 2.0-mg/kg dose of amphetamine. Three groups received the D_1 agonist, SKF 38393, in doses of 5.0 (n = 7), 10.0 (n = 7), and 20.0 (n = 12) mg/kg, and three other groups received these same SKF 38393 doses (n 7, 7, and 6, respectively) and a dose of 2.0 mg/kg amphetamine. All doses were administered intraperitoneally (IP) 5 min before each test session.

Drug Preparation

(+)-Amphetamine sulphate (Smith, Kline, and French Canada, Inc.) was dissolved in saline and injected in a volume of 1 ml/kg body wt. SKF 38393 (Research Biochemicals, Inc.) was dissolved in distilled water. Because of low solubility, the doses of 5.0, 10.0, and 20.0 mg/kg were injected in volumes of 2.0, 3.0, and 4.0 ml/kg, respectively.

Data Analyses

The data within the last 30 min provided the most stable estimate of preconditioning rates. In previous studies (26) the number of responses in each 10-min segment of preexposure sessions was analyzed; rates were found to be higher in the first 10 min but did not differ significantly for the remaining 10-min periods. Therefore, only data from the last 30 min were used for preexposure sessions in the analyses of the present results. The number of responses made on each lever during the last 30 min of the five sessions in the preexposure phase was averaged for each rat. The number of responses made on each lever during the last 30 min of each session in the test phase was averaged for each rat. Finally, the number of responses on each lever in the test phase was divided by the number of responses on that lever in the preexposure phase [adding 1.0 to each value entering into the ratio to reduce the influence of numerically small numbers (60)]. These ratios were square-root transformed to normalize their distribution for the purposes of analyses (31). Thus, the data consisted of two numbers for each rat.

To evaluate the conditioned reward effect in the saline group, a one-way analysis of variance (ANOVA) compared the ratios for each lever. A significantly higher ratio of responding on the lights-off lever than on the tone lever was taken as evidence that the procedure produced a conditioned reward effect. The data for the saline and amphetamine-alone groups were subjected to a two-way ANOVA with repeated measures on the lever factor. When the ratio for the lights-off lever was greater than that for the tone lever for the amphetamine group and there was a significant interaction of lever and group in the comparison with saline, it was concluded that the dose of amphetamine enhanced responding for conditioned reward. The data for the groups receiving SKF 38393 were subjected to a two-way ANOVA with repeated measures on the lever factor. If these groups showed a lever effect, then the analysis was repeated with the inclusion of the saline data to determine whether the lever effect was different from that seen in the saline group. The data for the groups receiving combined SKF 38393 and amphetamine and amphetamine-alone were subjected to a two-way ANOVA with repeated measures on the lever factor. If a lever × dose interaction was observed, then interaction comparisons, using the error term from the overall ANOVA, were carried out. Geisser-Greenhouse adjusted degrees of freedom were used whenever repeated measures were involved.

RESULTS

Table 1 contains the mean (± SEM) responses emitted on the tone- and lights-off-producing levers during the preexposure and test phases for all groups. These values indicate that the saline group showed a greater increase during the test phase of responding on the lever that produced the lights-off stimulus than on the lever that produced the tone stimulus, suggesting a conditioned reward effect. This description of the saline data was supported by the statistical analysis of the ratios; a one-way ANOVA revealed a significant lever effect [$F(1, 15) = 7.6, p < 0.02$].

Figure 1 illustrates the mean (± SEM) square root of ratios of responding on each lever in the test phase for the groups receiving saline or increasing doses of SKF 38393. When these groups were analysed together in a mixed design ANOVA, a significant overall lever effect was found [$F(1, 38) = 4.19, p < 0.05$]. However, groups receiving SKF 38393 showed patterns of responding that appeared to differ from that seen in the saline group. The group receiving 5.0 mg/kg SKF 38393 showed a smaller preference for the lights-off stimulus than was apparent in the saline group. The group receiving the 10.0-mg/kg dose did not show a preference for the lights-off lever. The group receiving the 20.0-mg/kg dose showed re-

TABLE 1

MEAN RESPONDING (SEM) ON THE LIGHTS-OFF (LO) AND TONE (T) LEVERS IN THE PREEXPOSURE AND TEST PHASES FOR THE GROUPS RECEIVING SALINE, ONE OF INCREASING DOSES OF SKF 38393 AND A COMBINATION OF 2.0 MG/KG AMPHETAMINE (AMPH), AND ONE OF INCREASING DOSES OF SKF 38393

	Preexposure		Test		Square root of ratio	
Group	Tone	Lights off	Tone	Lights off	Tone	Lights off
Saline	7.73 (1.28)	9.24 (2.01)	9.22 (1.26)	21.00 (2.75)	1.16 (0.13)	1.72 (0.23)
SKF 38393						
5.0 mg/kg	2.23 (0.66)	4.60 (1.15)	9.00 (1.94)	24.50 (4.59)	1.87 (0.26)	2.22 (0.14)
10.0 mg/kg	4.86 (2.18)	8.14 (3.14)	13.86 (5.21)	23.79 (99.68)	1.58 (0.24)	1.44 (0.19)
20.0 mg/kg	9.08 (2.06)	9.83 (2.44)	16.08 (3.06)	30.42 (8.11)	1.48 (0.18)	2.06 (0.42)
SKF 38393 plus Amph						
Saline	8.29 (1.12)	10.30 (2.48)	43.50 (14.00)	607.00 (126.00)	1.92 (0.48)	8.38 (1.84)
5.0 mg/kg	5.51 (1.37)	7.46 (2.05)	27.36 (8.25)	694.70 (231.70)	2.06 (0.27)	9.73 (2.24)
10.0 mg/kg	6.09 (1.67)	5.63 (0.77)	17.64 (3.86)	159.60 (49.26)	1.67 (0.23)	4.49 (1.06)
20.0 mg/kg	6.60 (1.72)	10.13 (2.45)	18.17 (7.06)	87.58 (20.25)	1.57 (0.29)	2.91 (0.27)

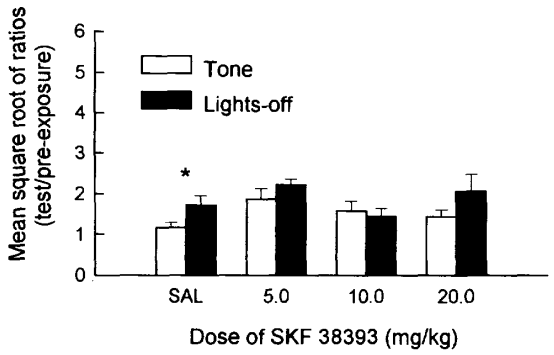

FIG. 1. Mean square roots of ratios of test phase responding relative to preexposure responding on each lever for groups receiving saline or one of three doses of SKF 38393. Vertical bars represent the SEM. Lights-off was the conditioned stimulus; tone was the neutral stimulus. Saline and SKF 38393 were administered IP, 5 min before testing. *Significant ($p < 0.05$) conditioned reward effect in the saline group.

sponding that was similar to saline, although with slightly greater variability for the lights-off lever. It is noteworthy that for the 20.0-mg/kg group, there was one rat that made almost no responses on the lights-off lever in the preexposure phase but averaged close to 50 responses in the test, yielding a ratio of 41.25. The square root of this ratio (6.42) was almost double the ratio values for either lever for all rats in all groups. This value contributed greatly to the mean and SE for the lights-off ratio for the 20-mg/kg group; without this rat, the values of the mean (± SEM) square-root ratios for the tone and lights-off lever would have been 1.46 (± 0.19) and 1.66 (± 0.16), respectively. Thus, the data suggest that SKF 38393 may have reduced the preference in responding for conditioned reward. These observations were supported by the statistical analyses of the data. A two-way ANOVA with repeated measures on the lever factor for the three SKF 38393 groups failed to reveal a significant lever or group effect, suggesting that the D_1 agonist led to a failure of the lights-off stimulus to act as a conditioned reward.

Figure 2 illustrates the mean (± SEM) square root of ratios of responding on each lever in the test phase for groups receiving amphetamine alone or in combination with increasing doses of SKF 38393. Inspection of the figure reveals a large enhancement in responding specifically for the lights-off stimulus in the group receiving 2.0 mg/kg of amphetamine-alone compared to the saline group (shown in Fig. 1). This observation was supported by the two-way ANOVA performed on the data from the saline and amphetamine-alone groups, revealing a significant interaction between lever and group [$F(1, 21) = 21.60$, $p < 0.001$]. A test of simple main effect of group for each lever revealed a significant group effect for responding on the lights-off lever but not on the tone lever. Hence, the interaction was a result of an enhancement in responding specifically on the lights-off lever in the group receiving amphetamine.

Responding for groups receiving combined amphetamine and SKF 38393 appeared to show a dose-dependent attenuation in the selective enhancement on the lights-off lever produced by amphetamine (Fig. 2). Statistical analyses supported this observation. A two-way ANOVA performed on the data from groups receiving amphetamine alone or in combination with SKF 38393 revealed a significant lever × group interaction [$F(3, 23) = 3.20$, $p < 0.05$]. This analysis suggested that the amphetamine-produced enhancement of responding for conditioned reward was different among these groups. Interaction comparisons identified the source of the interaction in the group receiving 20.0 mg/kg SKF 38393, suggesting that the conditioned reward effect in this group was significantly lower than in the amphetamine-alone group.

DISCUSSION

The results from the saline group showed that the lights-off stimulus, which had been paired with food, became a conditioned reward. Previous studies have shown that this conditioned reward effect failed to occur unless there existed a positive contingency between the food pellets and the conditioned stimulus during the pairing phase (8,9,26). The present results are consistent with those obtained previously in this laboratory (9,26,35) and elsewhere (16,23,28,29,49,50).

The present results showed that rats given SKF 38393 failed to show a reliable increase in responding for the lights-off stimulus. These results suggest that SKF 38393 reduced or elim-

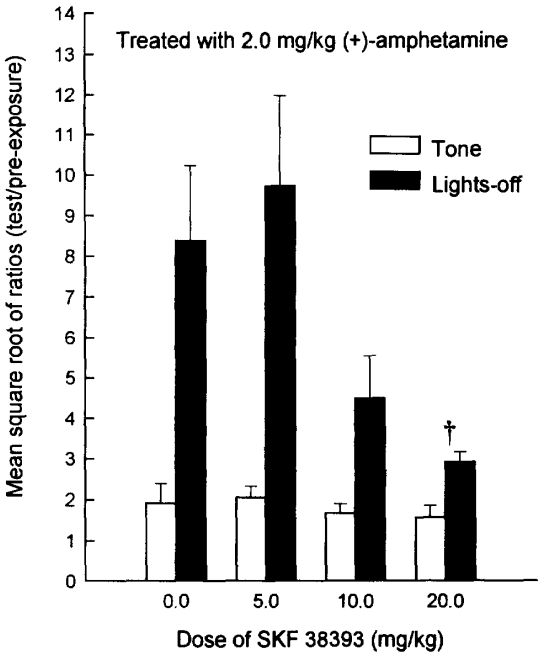

FIG. 2. Mean square roots of ratios of test phase responding relative to preexposure responding on each lever for groups receiving amphetamine or amphetamine combined with one of three doses of SKF 38393. Vertical bars represent the SEM. Lights-off was the conditioned stimulus; tone was the neutral stimulus. Amphetamine and SKF 38393 were administered IP, 5 min before testing. *Significant attenuation ($p < 0.05$) of conditioned reward effect when compared to amphetamine alone.

inated the conditioned reward effect and are in agreement with those found previously in this laboratory (9).

Rats given amphetamine showed an enhancement of responding specifically for the conditioned reward, a finding that is in accordance with previous reports (9,14,15,35,51). Because amphetamine enhanced responding selectively on the lever that produced the conditioned reward, it is unlikely that this occurred simply through a general stimulant effect, which might be expected to have increased responding on both levers. Moreover, Beninger and Ranaldi (9) demonstrated that amphetamine significantly increased responding for the tone when this stimulus was previously paired with food, and failed to significantly increase responding for either stimulus when neither was paired with food. This further supports the conclusion that amphetamine enhanced responding for conditioned reward.

Animals treated with amphetamine and increasing doses of SKF 38393 showed a dose-dependent decrease in the amphetamine-produced enhancement of responding for conditioned reward. It is possible that SKF 38393 enhanced the stimulant action of amphetamine and shifted the amphetamine dose-response curve to the left. This would be consistent with previous findings that higher doses of amphetamine (i.e., 5.0 mg/kg) failed to enhance responding for conditioned reward (46). It is also possible that SKF 38393 led to an impairment in the ability of conditioned reward to control responding, an effect consistent with the present finding that SKF 38393 impaired responding for conditioned reward in animals not treated with amphetamine. Because the decrease in responding was specific to the conditioned stimulus it is unlikely that SKF 38393 reduced the amphetamine effect through a simple impairment of motor capacity. SKF 38393 also has been shown to have disruptive effects on responding for brain stimulation reward (39).

SKF 38393 has been shown to act as a partial agonist at D_1 receptors (1,40). This reduced intrinsic efficacy may lead this compound to behave as a weak D_1 antagonist and thus attenuate the postsynaptic effects of DA transmission. It is possible, then, that SKF 38393 attenuated the reward-enhancing effects of amphetamine by partially blocking the synaptic action of DA.

The differential effects on responding for conditioned reward produced by SKF 38393 and amphetamine may be understood with reference to their different mechanisms of action. Amphetamine acts presynaptically by increasing the release of DA (53,59), whereas SKF 38393 acts postsynaptically by directly stimulating D_1 receptors (54). The fact that amphetamine (2.0 mg/kg) did not impair responding for conditioned reward suggests that presynaptic facilitation of DA release does not disrupt the putative reward signal. This interpretation is consistent with the view that reward is associated with a DA signal (5,9,21,37,51), a view for which there now exists considerable neurochemical evidence [11,22,32,38,42, 45; but see (36)]. That amphetamine actually enhanced responding for conditioned reward may suggest that it increased the DA signal associated with reward. SKF 38393, on the other hand, impaired responding for conditioned reward. This may suggest that direct stimulation of D_1 receptors masks the DA reward signal. This interpretation is further supported by the present finding that SKF 38393 dose dependently reduced the amphetamine-produced enhancement of responding for conditioned reward. This would lead to the interpretation that a critical element of the amphetamine effect may be an increase in a reward signal at D_1 receptors, an effect which apparently may be masked by tonic D_1 stimulation. Perhaps animals treated with high doses (5.0 mg/kg) of amphetamine (46) similarly fail to show enhanced responding for conditioned reward because the high levels of synaptic DA produced by these doses lead to a masking of the putative endogenous DA reward signal.

As mentioned earlier, the D_1-signal hypothesis is contradicted by studies showing that injections of SKF 38393 or DA itself into the nucleus accumbens enhanced responding for conditioned reward (57,62). However, Chu and Kelley (13) failed to observe an enhancement of responding for conditioned reward with microinjections of CY 208-243, a different D_1-selective agonist, into the nucleus accumbens. Furthermore, it has been reported that microinjections of SKF 38393 into the nucleus accumbens cause neurotoxicity (30). These findings raise the possibility that enhanced responding for conditioned reward observed with SKF 38393 (62) may have been related to this action of the compound.

That intra-accumbens DA enhanced responding for conditioned reward (57) might still be expected if a DA signal at the D_1 receptor in some other DA terminal region, such as the caudate-putamen, may be sufficient for reward. There is evidence of increased responding for conditioned reward when amphetamine is injected directly into the caudate-putamen of rats (28,57). However, 6-OHDA lesions of the caudate-putamen failed to disrupt responding for conditioned reward enhanced by microinjections of amphetamine into the nucleus accumbens, except perhaps at the highest amphetamine dose. Moreover, 6-OHDA lesions of the nucleus accumbens did eliminate the enhancement of responding for conditioned reward produced with intra-accumbens injections of amphetamine but, surprisingly, not the conditioned reward effect itself (58). This latter observation might suggest that the signal exists in both the nucleus accumbens and the caudate-putamen, and that either one is sufficient to support responding for conditioned reward. From this point of view it would be predicted that a disruption of the putative DA signal in both structures might be required to impair the enhanced responding for conditioned reward produced by systemic amphetamine and the conditioned reward effect itself. This speculation is supported by a study showing that avoidance responding, a behavior that can be understood in terms of reward processes (3–5), was disrupted only when DA terminals in both the nucleus accumbens and the caudate-putamen were destroyed with 6-OHDA (34). Thus, the data of Everitt and co-workers do not necessitate rejection of the hypothesis that there may be a signal at the D_1 receptor that is critical for reward-related learning.

The present results provide further support for the role of DA in reward-related learning. The findings that amphetamine enhanced responding specifically for the conditioned reward is in accordance with the view that reward-related learning may involve a DA signal associated with rewarding stimuli. Finally, the present findings that SKF 38393 eliminated the conditioned reward effect and dose dependently attenuated the amphetamine-enhanced conditioned reward effect suggest that reward-related learning may involve a DA signal at D_1 receptors.

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