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Receptor Subtype-Specific Dopaminergic Agents and Conditioned Behavior

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BENINGER, R. J., D. C. HOFFMAN AND E. J. MAZURSKI. *Receptor subtype-specific dopaminergic agents and conditioned behavior*. NEUROSCI BIOBEHAV REV **13**(2/3) 113–122, 1989.—Dopaminergic neurotransmission has been implicated in reward-related learning. With the advent of pharmacological agents that are relatively specific for D1 and D2 dopamine receptors, it has become possible to assess the role of these receptor subtypes in this form of learning. Antagonist studies have shown that either D1 or D2 receptor blockers produced extinction-like effects on operant responding for food, water or brain stimulation reward and in drug self-administration paradigms. They also blocked place preference learning based on amphetamine. Agonist studies showed that D2, but not D1 agonists were self-administered, produced place preferences and enhanced responding for conditioned reward. It may be that the dopaminergic signal at the D1 receptor is important for the establishment and maintenance of reward-related learning. From this point of view the effects of D1 antagonists can be understood. D2 antagonists may produce extinction-like effects because they lead to increased dopamine release and, therefore, indirectly mask the dopamine signal at the D1 receptor. D1 agonists may fail to produce reward effects because they, unlike D2 agonists, directly mask the dopaminergic signal at the D1 receptor.

Dopamine D1 receptors D2 receptors Avoidance learning Operant responding Conditioned reward Drug self-administration Place conditioning Conditioned activity

THE discovery by Olds and Milner (61) that electrical stimulation of the brain acts as a rewarding stimulus started behavioral neuroscientists on a journey of discovery that continues today. The quest to identify the neuronal mechanisms underlying reward-related learning began with identification of the anatomical sites that supported brain stimulation reward (BSR). It continues today at the electrophysiological level with efforts to identify the characteristics of BSR-relevant neurons and at the neurochemical level with efforts to identify the neurotransmitters involved. Dopamine (DA) has become a prime candidate for one of the neurotransmitters playing an important role in mediating reward-related learning.

DA has a widespread distribution within the mammalian central nervous system [see Bjorklund and Lindvall (12)]. There are at least two subtypes of receptors for this transmitter and Kebabian and Calne (43) have categorized them as D1 and D2; the D1 receptor stimulates the enzyme adenylate cyclase, whereas the D2 receptor is either unrelated to, or in some areas of the brain inhibits, this enzyme.

Currently, DA neurotransmission is implicated in at least two behavioral functions: unconditioned motor activity and reward-related learning (1). Numerous studies have demonstrated that enhanced dopminergic transmission results in a general increase in locomotor activity and stereotypy while a decrease results in hypomotility and catalepsy [see Costall and Naylor (17)]. The integrity of DA neurotransmission also appears necessary for the acquisition and maintenance of learning that is governed by rewarding stimuli [see Beninger (1) and Wise (77)]. Over the past several years the introduction of pharmacological compounds that are relatively specific for DA receptor subtypes has led to the evaluation of the possible contribution of D1 and D2 receptors to behavioral phenomena previously found to involve DA neurotransmission [see reviews by Clark and White (16); Joyce (41); Kebabian *et al.* (42); O'Boyle *et al.* (60); Waddington and O'Boyle (74)]. In this paper, studies which examined the effects of D1 and D2 receptor subtype-specific pharmacological agents on conditioned behaviors will be reviewed. Results provide new insights into the role of DA in reward-related learning.

Reward is defined as a biologically important stimulus that elicits approach and/or consummatory responses. For example, the consumption of food by a food-deprived animal or the finding of safety by an animal in danger would be considered as rewarding events. For almost a century, behavioral scientists have been studying the effects of reward on behavior and a sophisticated technology of behavior including classical and operant conditioning is now available [cf., Mackintosh (50,51)].

One of the consequences of reward is learning. Thus, once certain environmental stimuli become signals for reward, the behavior of animals in the presence of those stimuli changes in predictable ways. For example, if a rat is placed in a chamber, it will move about the environment for a time, apparently exploring. If the rat is then fed (rewarded) in one side of the chamber and not in the other, later, in the absence of food, the rat will be more active and spend more time on the side (in the presence of the stimuli) previously associated with reward. This change in behavior from before to after finding the reward is defined as learning.

Although this type of learning has been and continues to be studied extensively, there is no agreed-upon theoretical basis for understanding what is learned. Historically, learning theory has gone through a number of changes as various ideas have been proposed, tested and modified. A relatively recent and influential position is termed incentive motivational theory [cf., Bindra (11)].

According to this point of view, when reward-related learning takes place, an association is formed between the stimuli that signal reward and the reward itself. As reward has the unconditioned ability to elicit approach and consummatory responses (i.e., rewarding stimuli are unconditioned incentive motivational stimuli), environmental stimuli associated with reward acquire this ability, and, therefore, become conditioned incentive motivational stimuli or, more simply, conditioned incentive stimuli. Thus, once a previously neutral stimulus becomes associated with reward, it will acquire similar motivational properties as the actual reward. That is, the conditioned incentive stimuli, for example, the side of the chamber where the rat was fed in the example given above, will attract the animal in future tests.

An exciting development in the study of reward-related learning was the discovery that the neurotransmitter, DA, played an important role. Wise *et al.* (77) reported that rats treated with the DA receptor blocker, pimozide showed an *extinction-like decline* in lever-pressing for food as if the food was no longer rewarding. Thus, animals treated with DA receptor blockers demonstrated a gradual decrease in rates over time that was similar to the within-session decline observed in nondrugged rats that no longer received the rewarding stimulus. As DA is clearly involved in the control of unconditioned behavior, the results of Wise *et al.* (77) might, at first glance, simply be seen as another example of the motor consequences of DA receptor blockade. However, this hypothesis has been extensively tested in recent years and has been shown to be inadequate to account for the data [see reviews by Beninger (1,2) and Wise (75)]. Some recent excellent studies by Ettenberg and his associates provide further support for the hypothesis that DA mediates reward effects (21,22). Thus, it appears that DA does play an important role in the learning associated with reward.

Interestingly, although DA receptor antagonists blocked the usual effects of reward on behavior, they failed to block the learning of associations between environmental stimuli signalling reward and reward itself. For example, it was observed that animals receiving pairings of a tone with food while under the influence of pimozide failed to show reward-related learning in subsequent tests of the ability of the tone to act as a conditioned reward (8). However, the animals did show evidence of learning the association between the tone and food in transfer tests where the tone was used as a discriminative stimulus (9). Similarly, for pimozide-treated animals undergoing avoidance training, the safety-related stimuli failed to acquire the ability to attract (i.e., failed to become conditioned incentive stimuli); however, trial by trial analyses showed that the animals did learn the location of safety (7).

These data are important for the following reason: they show that when DA receptors are blocked animals can learn the association between environmental stimuli that signal reward and reward itself; however, these environmental stimuli signalling reward fail to acquire the ability to act as conditioned incentive stimuli. This suggests that when normal reward-related learning occurs, at least two processes are involved: 1) the learning of the association between environmental stimuli signalling reward and reward itself and 2) the acquisition by the environmental stimuli of the ability to attract the animal in the future. It would appear that DA is involved in the latter, but not the former process. This suggests a refinement to the previous theory of incentive conditioning as outlined above. Possibly, there are stimulus-stimulus associative learning processes that function independent of DA neurotransmission and there are incentive learning processes that involve DA. Further discussion of the differential role of DA in these two types of learning can be found in Beninger (1,2).

The remainder of this chapter will review the relatively small number of studies concerned with the possible contribution of D1 and D2 receptors to incentive learning. The data have been organized into sections according to the paradigms used to study incentive learning. In each case a brief theoretical account of incentive learning will be presented followed by a review of the relevant studies.

D1 AND D2 ANTAGONISTS AND CONDITIONED AVOIDANCE RESPONDING

In the conditioned one-way avoidance paradigm, animals may learn the association between the stimuli that signal shock (e.g., tone, shock side of the chamber) and shock itself, and they also may learn the association between safety-related stimuli and safety itself. In addition, incentive learning may take place; the environmental stimuli associated with safety may acquire the ability to elicit approach responses. DA receptor antagonists block the latter type of learning, but not the former types [see Beninger *et al.* (7) and Beninger (3)].

The classical behavioral profile of nonselective DA receptor blockers in this paradigm is a decrease in one-way avoidance responding of pretrained animals at doses that minimally affect escape responding. However, the fact that the animals continued to escape may not preclude a motor impairment produced by the drug. Possibly, the drugged animals were less able to move than when nondrugged, but were still able to overcome this impairment when receiving shock. Recent experiments have shown that this may not be the case. By averaging the number of avoidance responses from trial to trial, it was seen that pretrained animals treated with nonselective DA receptor blockers initially showed a high level of performance, but with repeated testing their performance declined, revealing an extinction curve (10). Thus, the animals were capable of responding initially, thereby ruling out a simple motor deficit interpretation. The gradual decline in avoidance responding over time suggests that the conditioned incentive stimuli (i.e., the safety-related stimuli) were losing their ability to elicit and sustain the avoidance response.

Recently, Sanger (65,66) used this approach to assess the effects of SCH 23390 and metoclopramide on avoidance responding in pretrained rats. He found that the D2 antagonist (as well as the nonselective DA receptor blocker, haloperidol) produced a gradual decline in avoidance responding within the drug session, whereas the D1 antagonist produced neither a within- nor a between-session decline. These results suggest that the effects of D2 antagonists on conditioned avoidance responding might be to block incentive learning, whereas the effects of D1 blockers may be attributable to their deleterious action on unconditioned motor responses.

Some additional studies employing either a Sidman or a signalled avoidance schedule showed that lever-press responding for shock avoidance or escape was affected by D1 or D2 antagonists. Decreased responding in rats or monkeys was observed after SCH 23390 (27,40) or the D2 antagonists, metoclopramide, sulpiride or YM 09151-2 (39, 48, 73). Two-way avoidance was similarly impaired by metoclopramide or sulpiride (59) and the extinction of pole jumping avoidance was enhanced by sulpiride (68). Unfortunately, in these paradigms, it is not possible to dissociate the well-documented motor effects of these compounds from possible effects on incentive learning.

In summary, the evidence to date implicates the D2 receptor in incentive learning as manifested in the avoidance conditioning paradigm. However, given the limited number of studies which have successfully separated motor versus incentive learning effects associated with subtype-specific antagonists, it is difficult to draw any conclusions.

RECEPTOR SUBTYPE-SPECIFIC DA COMPOUNDS AND OPERANT RESPONDING FOR REWARD

Antagonists

When animals learn to press a lever for reward, incentive learning theory would predict an enhanced ability of the lever-related stimuli to elicit approach responses in the future. Treatment with nonselective DA receptor blockers led to a gradual decrease of responding for reward as if the incentive learning effect was gradually lost [e.g., Wise *et al.* (77)]. This is comparable to the case of avoidance responding where within-session or between-session declines were observed in animals treated with DA receptor antagonists (7).

Results from operant conditioning studies employing food as the reinforcing stimulus have implicated both receptor subtypes in this learning. For example, it was found that either SCH 23390 or metoclopramide produced a gradual decline in operant responding for food (4). Sanger (65,66), on the other hand, failed to show a role for the D1 receptor. Metoclopramide produced a dose-dependent reduction in lever-pressing in rats and at higher doses a within-session decline in responding was observed (65). Although SCH 23390 also decreased lever-pressing, the drug failed to produce a within-session decline (66). The reason for the discrepancy between this finding and that of Beninger *et al.* (4) is unknown.

Other studies have also demonstrated a role for either the D1 or D2 receptor. Nakajima (57) reported that SCH 23390, but not sulpiride, decreased responding for food, water or saccharin solutions. However, the lack of effect with sulpiride may have been due to the insufficient time interval between injection and test. A recent study by Ljungberg (49) noted significant behavioral effects with sulpiride only when a 5-hr delay between time of injection and test was imposed. Interestingly, in this latter study, treatment with either metoclopramide or sulpiride reduced responding for water at doses that failed to affect drinking. This suggests that the D2 antagonists may have differentially affected the incentive learning component of the task.

Studying operant responding maintained by brain stimulation reward (BSR) has also implicated either the D1 or the D2 receptor. Thus, Ferrer *et al.* (24) found that responding for BSR of the prefrontal cortex was unaffected by sulpiride, but decreased by nonselective receptor blockers; the additional finding that BSR was unaffected by bromocriptine, but decreased by the nonselective agonist, apomorphine, suggested to the authors that reward in this site may be mediated by D1 receptors. A role for the D1 receptor was also suggested by the results of Nakajima and McKenzie (58) who demonstrated that SCH 23390 produced a within-session decline in responding for BSR in rats. Sulpiride had no significant effect; however, as pointed out earlier, a longer time interval between injection and test may have been necessary.

A number of studies have suggested an important role for the D2 receptor. For example, Fenton and Liebman (23) found a within-session decline in BSR responding in animals treated with metoclopramide. An important role for the D2 receptor was further suggested in another study (26). Testing the effects of nine DA receptor blockers on the responding of rats for BSR in the medial forebrain bundle, it was found that their affinity for the D2 receptor predicted their effectiveness in blocking responding for reward. Furthermore, the effects of DA antagonists were environment-specific; i.e., once a decline in responding was seen in one operant chamber, placement of the rats into a different chamber temporarily reinstated responding, followed by another decline. The resumption of responding in the second chamber can be understood as an example of conditioned incentive stimuli exerting their ability to elicit approach responses. In addition, a motor deficit interpretation can be ruled out because the drug-treated animals that had ceased responding in the first chamber were capable of responding at least initially in the second.

A significant correlation between the dose of neuroleptic required to disrupt self-stimulation and the affinity of the drug for the D1 receptor was not found (26). The interpretation of this latter finding should be made with caution, however. The majority of neuroleptics employed in the study were potent in blocking the D2 receptor, but an adequate range of values representing D1 receptor affinity may not have been sampled. Because the reliability of a correlation coefficient decreases as the range of measures of one or both variables decreases (20), it may not be surprising that a significant correlation was not obtained.

Recently, Kurumiya and Nakajima (46) investigated the possible role of D1 and D2 receptors in mediating responding for BSR of the ventral tegmental area (VTA). In a well-controlled study they found that SCH 23390, but not sulpiride microinjections into the nucleus accumbens ipsilateral to the electrode produced a decline in responding. Comparable injections into the contralateral side or into the striatum ipsilateral to the electrode were without effect. They concluded that D1 receptors in the nucleus accumbens may be involved in mediating the rewarding effects of VTA stimulation.

In summary, it appears that conditioned operant responding for food, water or BSR can be shown to undergo an extinction-like decline following treatment with either D1 or D2 antagonists. To date, only D1 antagonism has been shown to produce this effect on responding for saccharin. Although some inconsistencies exist regarding the relative importance of each receptor subtype, the data together suggest that blockade of either receptor subtype may lead to a loss of this type of learning.

Agonists

If the effects of reward on behavior are in some way mediated by the release of DA at a particular subset of DA synapses, it might be expected that treatment with appropriate doses of an indirect-acting DA agonist like amphetamine would enhance responding by increasing the DA signal at the relevant synapses, whereas direct-acting agonists like apomorphine might reduce responding for reward because they would lead to a masking of the DA signal. It has been found that amphetamine and apomorphine produced this profile of effects in animals responding for BSR (18,34).

We have recently investigated the effects of amphetamine, apomorphine and specific D1 or D2 agonists on responding in a similar paradigm using food reward. Unlike results with BSR, treatment with either amphetamine or apomorphine produced a dose-dependent decrease in responding. Similar dose-dependent decreases were observed with SKF 38393 or quinpirole; however, these latter compounds also produced intrasession declines in responding. The within-session decline with SKF 38393 may have been due to slow absorption of the drug because a group given the drug 30 min prior to the test showed uniformly reduced response rates throughout the session. This did not appear to be the case with quinpirole as the drug was no longer effective in reducing lever-pressing if administered 30 min prior to test (37). Possibly, then, the within-session decrease in responding with quinpirole was a result of effects on incentive learning rather than pharmacodynamic properties.

The rate-reducing effect of amphetamine, although inconsistent with the BSR studies, may not be surprising given that amphetamine's effects on operant responding are rate-dependent, enhancing low rates of responding while decreasing high rates (63). Variable interval schedules of reinforcement tend to produce high

rates of responding and although exceptions do exist, recent studies using this schedule have demonstrated predominantly dose-dependent decreases in response rates in amphetamine-treated animals (55,56). The possibility that amphetamine and other DA agonists have anorexic or emetic properties that may contribute to their effects on operant responding also cannot be ruled out (14).

In summary, treatment with either a D1 or D2 agonist produced a dose-dependent decrease in food-rewarded lever-pressing which was generally similar to the reductions observed with the receptor-nonselective DA agonists, apomorphine and amphetamine. The additional finding that the D2 agonist produced a within-session decline in responding similar to the profile observed with DA receptor antagonists suggests that the disruptive effects of this drug may be related to an impairment in incentive motivational learning.

D1 AND D2 AGONISTS AND ACQUISITION OF RESPONDING FOR CONDITIONED REWARD

A number of studies have examined the role of DA in the establishment and expression of conditioned reward. In this paradigm, animals receive several sessions during which a neutral stimulus (e.g., tone) is paired with reward (e.g., food). Later, tests which assess the ability of that stimulus to act as a conditioned reward are conducted. In these tests, animals are exposed to a chamber outfitted with two levers and presentation of the reward-related stimulus (i.e., the tone) is contingent upon pressing one lever; unconditioned reward is never presented during the test sessions. If animals press the lever producing the reward-related stimulus more than the other one, that stimulus is said to be a conditioned reward; theoretically, it would be said to have conditioned incentive motivational properties, increasing the ability of the lever-associated stimuli to elicit approach responses

In this paradigm, apomorphine and amphetamine have been shown to have a differential effect analogous to that seen in studies of lever pressing for BSR. Thus, when these drugs were administered during the test, amphetamine dose-dependently enhanced responding on the lever producing conditioned reward, whereas apomorphine led to a dose-dependent enhancement on both levers [Fig. 1; also see Mazurski and Beninger (53)]. Groups treated with higher doses of SKF 38393 failed to respond significantly more on the lever producing the stimulus previously associated with food. The D2 agonists, bromocriptine or quinpirole, on the other hand, produced a dose-dependent enhancement of responding only on the conditioned reward lever (Fig. 2).

How might these results be understood? Firstly, it may be useful to identify two, possibly separate, aspects of the data. The first is the effects of the compounds on overall responding and the second is their effects on differential responding on the two levers. With regard to overall responding, amphetamine, apomorphine and the D2 agonists produced dose-dependent enhancements of responding, whereas the D1 agonist, SKF 38393 did not. This is entirely consistent with findings from studies of the effects of the compounds on unconditioned behavior; nonspecific DA agonists and D2 agonists were found to be potent stimulants of activity, whereas SKF 38393 was relatively weak (16, 60, 74).

With regard to differential responding on the two levers, the results may provide a clue to the relative contribution of D1 and D2 receptor stimulation to incentive learning. According to the hypothesis that DA is involved in incentive learning, DA release may occur when a rewarding stimulus is presented (13, 30–34, 44) and this, in some way, may lead to an enhanced ability of the reward-related stimulus to elicit approach responses in the future [cf., Beninger (1,2)]. In the present paradigm, DA release may occur upon presentation of the conditioned reward [see Schiff (67)] leading to the increased ability of lever-associated stimuli to elicit responses as indicated by the significant increase in responding on the lever producing the conditioned reward. From this point of view, the differential effects of amphetamine and apomorphine can be understood, as already discussed briefly in the preceding section. Thus, at appropriate doses, amphetamine may enhance the reward signal by increasing the release of DA from the subset of synapses normally activated by presentation of reward; apomorphine, on the other hand, may mask the reward signal by directly stimulating DA receptors at all synapses. Both compounds increased responding but, under the influence of amphetamine, the conditioned reward continued to control responding whereas, under the influence of apomorphine, control was lost.

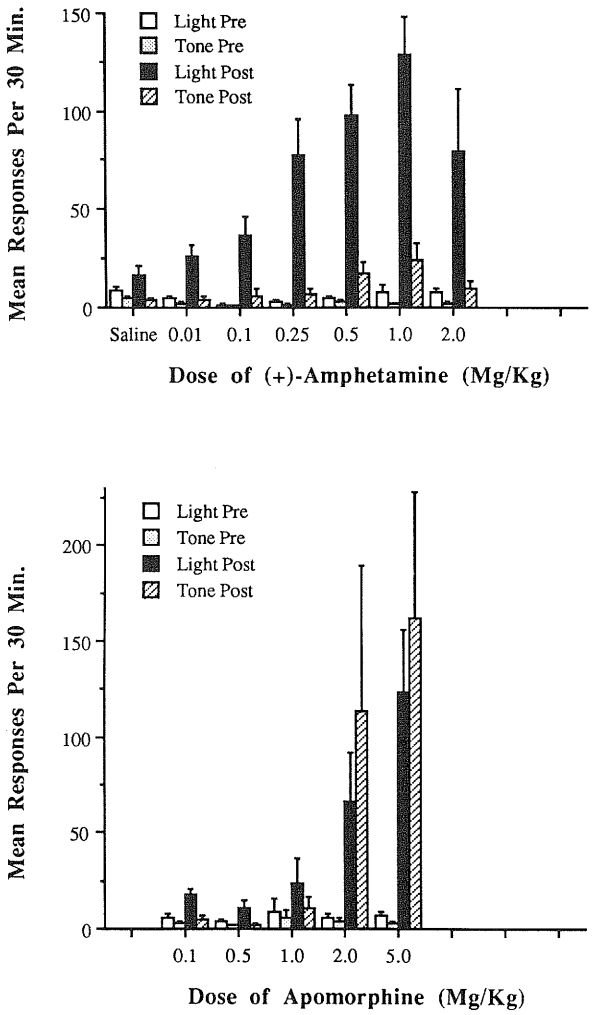

FIG. 1. Differential effects of amphetamine and apomorphine on the acquisition of responding for conditioned reward. Rats received three phases of training in a two-lever box. The preexposure phase measured the rates of pressing the levers; one produced a 3-sec tone and the other turned the lights off for 3 sec. In the conditioning phase, with the levers absent, the light-off stimulus was paired with food for four sessions. The test phase again measured the rate of pressing the levers. Conditioned reward was shown by a relative increase in responding on the light-off lever during the test. Separate groups of male Wistar rats were treated (IP) with amphetamine or apomorphine prior to the test session. The mean (±SEM) number of responses on each lever during the preexposure and test phases are presented.

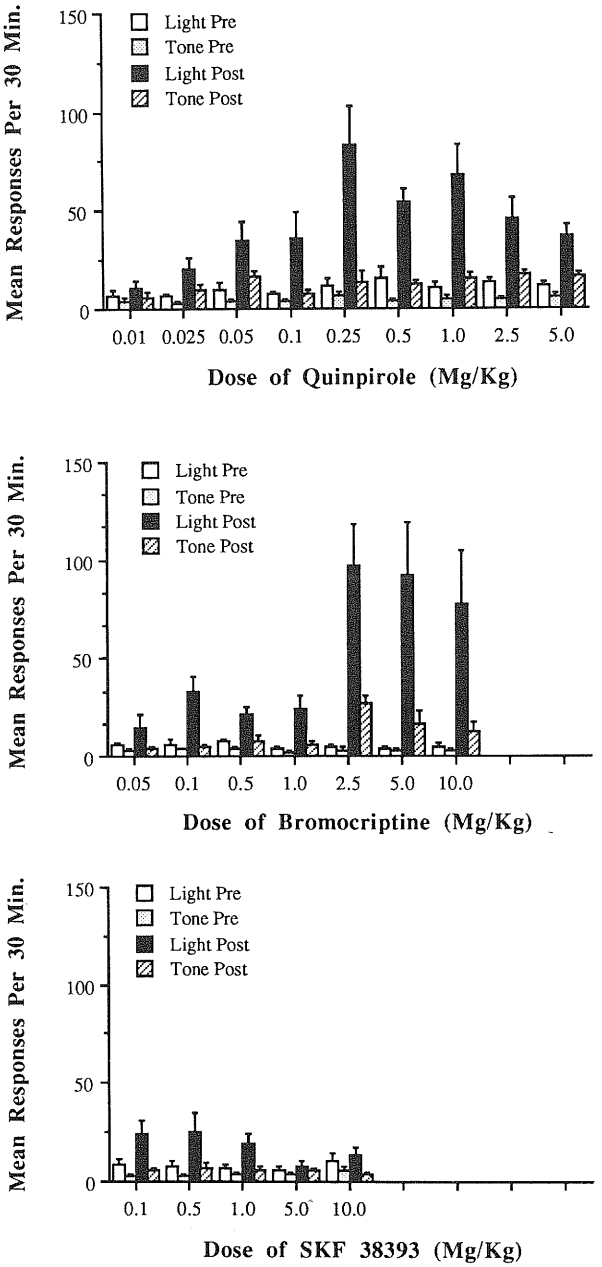

FIG. 2. Effects of bromocriptine, quinpirole and SKF 38393 on the acquisition of responding for conditioned reward. The mean (±SEM) number of presses on the tone and light-off lever during the preexposure and test phases are presented. For a description of the procedure see caption of Fig. 1.

This scheme for understanding the differential effects of amphetamine and apomorphine on responding for conditioned reward can be applied to the data from the groups receiving DA receptor subtype-specific compounds. It would follow that treatment with the D1 agonist masked the reward signal, whereas the D2 agonist did not. Although DA receptor subtype-specific agonists are direct acting, like apomorphine, apparently the stimulation of all D2 receptors by quinpirole or bromocriptine failed to mask the reward signal. This might suggest that the putative release of DA at a subset of DA synapses associated with reward leads to stimulation of D1 receptors in that subset of synapses to produce incentive learning. Treatment with a D1 agonist and its subsequent action at all DA synapses might mask this signal and the control of behavior by the conditioned reward might be lost.

In summary, amphetamine, apomorphine or D2 agonists led to an enhancement of overall responding, whereas the D1 agonist did not. In animals treated with amphetamine or D2 agonists, the conditioned reward controlled responding, but this control was lost in animals treated with apomorphine or SKF 38393. These results may indicate that the stimulation of a subset of D1 receptors in association with reward is critical for incentive learning.

RECEPTOR SUBTYPE-SPECIFIC DA COMPOUNDS AND DRUG SELF-ADMINISTRATION

Animals can learn to perform an operant response to produce the direct intravenous (IV) or intracranial injection of certain compounds. This is another example of incentive learning and there is good evidence that DA mediates this learning [see Wise and Bozarth (76)]. It is well documented that decreases in the concentration of the self-administered compound lead to *increases* in responding. If DA receptor blockers lead to a decrease in the effectiveness of the self-administered compound, an increase in responding should be seen, an effect that is difficult to attribute to performance impairments. Thus, the self-administration paradigm is particularly well suited to resolving the conflict between reward versus performance explanations of the effects of DA receptor blockers on operant responding. Several studies have now demonstrated that receptor-nonselective DA antagonists produced an increase in cocaine or amphetamine self-administration rates [see Wise and Bozarth (76)].

Some studies have investigated whether animals will self-administer drugs that preferentially stimulate either D1 or D2 receptors. These reports indicated that monkeys self-administer the D2 agonists, piribedil or bromocriptine, but not the D1 agonist, SKF 38393 (78, 79, 82). Other studies have examined the effects of selective D1 or D2 antagonists on cocaine or amphetamine self-administration rates. In rats or monkeys, it has been found that metoclopramide or sulpiride increased rates of cocaine self-administration suggesting an antagonism of the reward effect (64,78). In contrast, the effects of the D1 antagonist, SCH 23390, remain equivocal; Koob *et al.* (45) reported that this compound increased cocaine self-administration rates in rats, whereas Woolverton (78) found that it was without effect in monkeys. Finally, it was reported that rats would self-administer cocaine directly into the frontal cortex; local coadministration of SCH 23390 was without effect whereas sulpiride reduced rates (29).

How might these data from self-administration studies be understood? Only speculation is possible at present. One explanation requires the assumption that a subset of DA synapses may be active in association with the performance of a particular operant response such as pressing a lever. This hypothesis is directly supported by the observation of increased levels of DA metabolites in various brain regions following the performance of motor tasks (15, 25, 35, 62, 70, 80, 81) and indirectly by the observation that, under certain circumstances the opportunity to perform operant responses is rewarding in its own right [see Dunham (19)]. Theoretically, the consequences of reward would be to enhance the incentive properties of stimuli associated with reward. If the intravenous injection of a D2 agonist is made contingent upon performing an operant response, the following might ensure. First, note the recent results of Martin-Iverson *et al.* (52) who reported an apparent tolerance in rats to the stimulant effects of a chronically administered D2 agonist during the daytime. They suggested that the stimulation of autoreceptors led to a decrease in the release

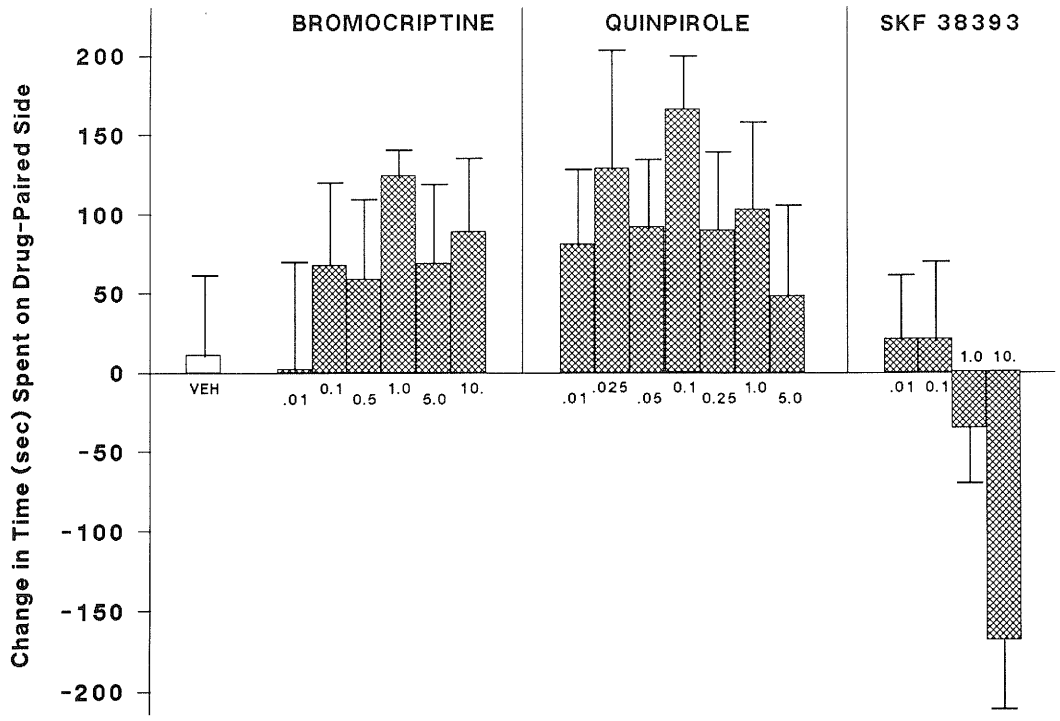

FIG. 3. Place conditioning with bromocriptine, quinpirole and SKF 38393. The experiment consisted of three phases. During the preexposure phase, male Wistar rats explored two distinctive compartments ($38 \times 27 \times 36$ cm) joined by a small tunnel for 15 min on each of 3 days. The compartments differed in brightness, pattern and floor texture and the amount of time spent in each compartment was recorded. During the 8-day conditioning phase, separate groups of rats were treated (IP) with one dose of either bromocriptine, quinpirole or SKF 38393 and confined to one compartment for 30 min. On alternate days, rats received saline and were placed in the opposite compartment. The postconditioning test occurred on the following day during which drug-free animals explored both compartments for 15 min and the time spent on each side was recorded. The mean ($\pm$ SEM) difference scores for each dose of bromocriptine, quinpirole and SKF 38393 are presented. The difference scores were calculated by subtracting the time spent on the drug-paired side during the preexposure session (averaged over the three days) from the test day. Thus, a positive score suggests a preference, whereas a negative score suggests an aversion for the drug-paired environment. Doses are indicated in mg/kg under each bar and VEH denotes a group that received vehicle injections on drug-pairing days.

of endogenous DA and, therefore, a loss of stimulation of D1 receptors. As stimulation of both D1 and D2 receptors appears to be necessary in the normosensitive rat for the observation of locomotor effects, the stimulant effects of the D2 agonist during the daytime may have been lost because of reduced levels of endogenous DA release. They cited evidence showing that the ability of a D2 agonist to shut down endogenous DA release was greatest when endogenous DA release was low. As endogenous DA release is lower during the daytime than during the nighttime, apparent tolerance to the stimulant effects of the D2 agonist was seen only during the day.

It may be possible to combine the assumption that a subset of DA synapses is active during the performance of an operant response with the explanation of Martin-Iverson *et al.* (52) for the daytime tolerance to the stimulant properties of a D2 agonist to understand the self-administration of D2 agonists. Thus, the injection of a D2 agonist following an operant response might lead to a reduction of endogenous DA release; this effect would be greatest at DA synapses where endogenous release is lowest, i.e., those not activated during performance of the response. There might, therefore, be a relatively greater stimulation of D1 receptors at the subset of DA synapses activated during performance of the response, possibly leading to incentive learning. As a result of this learning, stimuli associated with, for example, the lever would have an enhanced ability to elicit operant responses. This explanation places the emphasis on stimulation of D1 receptors for producing reward-related learning. The explanation is consistent with the idea (see previous section) that it is the DA signal, and specifically the stimulation of D1 receptors, that is important for incentive learning. The failure of SKF 38393 to be self-administered might thus be understood as resulting from a masking of the reward-related signal. Even though the administration of SKF 38393 would be contingent on a response in the self-administration paradigm, its effect presumably would be indiscriminate, stimulating all D1 receptors, not just those in the synapses carrying the response-produced signal. The ability of the D1 antagonist SCH 23390 to block the self-administration of cocaine, at least in rats, is consistent with the suggestion that stimulation of D1 receptors may be necessary for reward-related learning. Finally, the effective antagonism of self-administration of DA agonists by D2 blockers needs to be explained. Possibly the large increase in the release of endogenous DA following blockade of presynaptic D2 receptors (16) leads to a masking of the putative D1 signal associated with performance of the response. As a result, the ability of lever-associated stimuli to control responding may be lost. The observed effects of D1 and D2 antagonists on operant responding for other rewards, reviewed above, can also be understood from this point of view.

In summary, D2 but not D1 agonists are self-administered. D2 and possibly D1 blockers antagonize the self-administration of DA

agonists. These data can be understood as consistent with the idea that stimulation of D1 receptors in association with reward may be critical for incentive learning.

RECEPTOR SUBTYPE-SPECIFIC DA COMPOUNDS AND PLACE CONDITIONING

If animals are fed in one side of a chamber and not the other, they will subsequently show a preference for the side associated with food. Theoretically, stimuli associated with food have acquired incentive properties that increase their ability to elicit approach responses. Many data suggest that DA is necessary for this type of learning [e.g., Spyraki *et al.* (71)].

Some studies have investigated the ability of D1 or D2 agonists to produce place conditioning. It has been found that the D2 agonists, N-0437, quinpirole or bromocriptine produced a place preference (28, 36, 38), whereas the D1 agonist, SKF 38393, produced a place aversion (3). Some of these results are shown in Fig. 3.

We have found that SCH 23390 or metoclopramide were effective in blocking amphetamine-induced place preference or SKF 38393-induced place aversion. Similar results for amphetamine and SCH 23390 were reported by Leone and Di Chiara (47) and Shippenberg and Herz (69) have reported that SCH 23390 blocked place preference conditioning based on morphine and place aversion conditioning based on a kappa opiate receptor agonist. The establishment of the quinpirole place preference, on the other hand, was blocked by the two lower doses of SCH 23390, but not the highest dose (a dose that was without effect on place learning when given alone). Metoclopramide also blocked the quinpirole place preference at a low dose, but not at a higher dose; however, the higher dose of metoclopramide produced a place preference on its own that almost reached significance (Fig. 4). The interpretation of these latter effects of the antagonists versus quinpirole awaits further study.

In summary, the results were consistent with findings from self-administration studies and their explanation may be similar (see above). SKF 38393 was not self-administered and did not produce a place preference; in fact, this drug produced a significant place aversion. On the other hand, D2 agonists were self-administered and produced place preference conditioning. Interestingly, the D1 or D2 antagonists produced similar effects in the place preference paradigm. SCH 23390 and metoclopramide blocked place preference learning induced by amphetamine and place aversion induced by SKF 38393. They also blocked quinpirole-produced place preference, but only at some doses. Thus, an asymmetry in the function of DA receptor subtypes appears evident when the effects of selective agonists and antagonists in the self-administration and place preference paradigms are considered. The effects of preferentially stimulating either the D1 or D2 receptor were in a sense opposite; one supported incentive learning while the other did not. However, treatment with either a D1 or D2 antagonist produced similar effects; each drug impaired the estab-

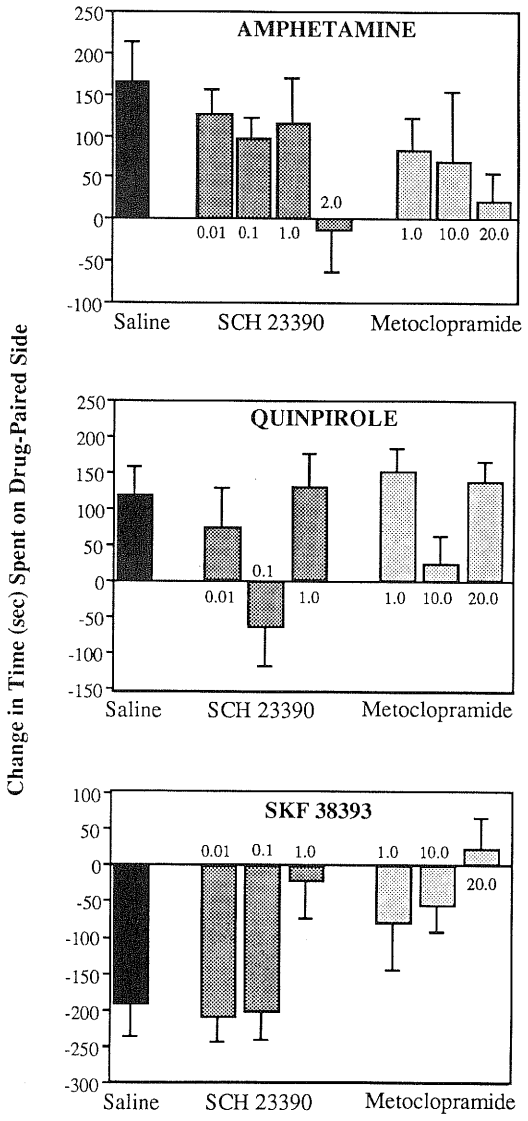

FIG. 4. The effects of SCH 23390 or metoclopramide on place conditioning produced by either (+)-amphetamine, quinpirole or SKF 38393. The details of the place conditioning experiment are described in the caption for Fig. 3. In addition, on drug days of the conditioning phase, separate groups of rats were pretreated with either saline, SCH 23390 (0.01, 0.1, 1.0 or 2.0 mg/kg IP) or metoclopramide (1.0, 10.0 or 20.0 mg/kg IP). One hour later, rats were injected with either 2.0 mg/kg (+)-amphetamine, 1.0 mg/kg quinpirole or 10.0 mg/kg SKF 38393 and then placed in the drug-paired environment for 30 min. The mean (±SEM) difference scores for each drug combination are presented. The calculation of these scores is described in the caption for Fig. 3.

was blocked by SCH 23390, but not metoclopramide. However, metoclopramide is short acting (59) and the conditioning sessions were two hours in duration; perhaps the failure of metoclopramide to block conditioning was related to this variable. Contrary to this argument was the observation that metoclopramide did block the establishment of incentive learning based on quinpirole, whereas SCH 23390 did not. Finally, SCH 23390 blocked and metoclopramide failed to antagonize the establishment of conditioned activity based on SKF 38393.

In summary, both D1 and D2 agonists were seen to produce conditioned activity. Contrary to reported effects of antagonists on the unconditioned behavioral effects of agonists, a selective D1 antagonist failed to block conditioning based on a D2 agonist although blocking the D1 agonist-induced effect, and a D2 antagonist failed to block conditioning based on a D1 agonist although blocking the D2 agonist-induced effect. This profile of results is reminiscent of those seen in denervated animals where the usual interdependence of the two DA receptor subtypes is lost. Perhaps in conditioned activity studies where animals are repeatedly drugged and tested, the interdependence of the two receptor subtypes also is lost.

CONCLUSIONS

Although there are not many studies which have addressed the possible role of DA receptor subtypes in conditioned behavior, a somewhat consistent pattern of results appears to be emerging. Treatment with subtype-specific agonists often produced qualitatively different effects. Thus, D2 but not D1 agonists supported incentive motivational learning. For example, animals would self-administer compounds that preferentially stimulated the D2 receptor and treatment with D2 agonists produced place preferences and facilitated the acquisition of responding for conditioned reward. None of these effects were observed when D1 receptors were preferentially stimulated.

The general lack of conditioning effects with D1 agonists does not preclude a functional role for this receptor in incentive learning. Thus, many of the effects of D2 receptor agonists on conditioned behavior were attenuated by D1 antagonists, suggesting that normal functioning of D1 receptors is critical for the acquisition of this type of learning. For example, place preference conditioning induced by either a nonselective or D2 receptor agonist was blocked by a D1 antagonist. It also appears that selective D1 or D2 receptor antagonists produced similar effects on conditioned behaviors; in the majority of experiments in which animals were trained to lever-press for rewarding stimuli (e.g., food, water or BSR) either a D1 or D2 antagonist produced a within-session decline in responding.

In conclusion, DA receptor subtypes appear to be differentially involved in reward-related learning. Although many data show that stimulation of D1 receptors may not be rewarding, these results may not preclude a functional role for this receptor subtype in reward-related incentive learning.

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