19. Dopamine D_1-like receptors and molecular m echanisms of incentive learning

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Introduction

Rewarding stimuli, such as food or water to an appropriately deprived animal, alter behaviour. For example, when a rat learns to press a lever for food, the effects of food on behaviour are to increase the rat's future likelihood of approaching the lever and lever-related stimuli and of manipulating (pressing) the lever. The rewarding stimulus is said to have increased the ability of reward-related stimuli to elicit approach and other responses. This type of learning is defined as incentive motivational learning or, more simply, incentive learning (Bindra, 1974). Many data show that the neurotransmitter dopamine (DA) plays a critical role in incentive learning (Beninger, 1983, 1993; Beninger *et al.*, 1989; Miller *et al.*, 1990).

DA receptors have been found to exist in at least five different subtypes, termed D_1 through D_5. Based on their ability to stimulate and inhibit the enzyme adenylate cyclase, these receptors have been classified into two groups, D_1-like and D_2-like, respectively (Civelli *et al.*, 1993; Niznik and Van Tol, 1992; Sibley *et al.*, 1993; see also Sokoloff and Schwartz, Chapter 10 of this volume).

Many data show that antagonists acting at either D_1- or D_2-like receptors impair incentive learning but some data suggest that the effects of reward on behaviour may be more strongly influenced by D_1-like receptor antagonists. Similarly, many data show that either D_1- or D_2-like agonists influence incentive learning but some data show that the two types of agonists have differential effects on behaviour suggesting that it may be the action of DA at D_1-like receptors that is particularly important for incentive learning. These findings suggest the hypothesis that the second messenger pathway activated by stimulation of D_1-like receptors leads to putative long term changes in synaptic effectiveness underlying incentive learning.

The present chapter will review data from five paradigms that are commonly used to study the neurotransmitters and neuronal mechanisms involved in incentive learning. The paradigms include: operant responding for food or water; operant responding for electrical stimulation of the brain; operant responding to self-administer drugs; operant responding for conditioned rewards; and place

conditioning. The effects of antagonists affecting D_1- or D_2-like receptors will be reviewed for each paradigm, and then the effects of agonists will be reviewed for each paradigm, paying particular attention to reports of differential effects of agents acting at a specific DA receptor category. This will be followed by a brief review of convergent findings from diverse experiments that point to stimulation of D_1-like receptors and resultant activation of second messengers as critical events in incentive learning.

D_1- and D_2-like receptor antagonists

Operant responding for food or water: The simple observation that responding for a reward is reduced by a DA antagonist is not sufficient to allow the conclusion that the treatment reduced the effectiveness of reward. For example, motor abilities or motivation to attain the reinforcing stimulus may have been affected by the treatment. However, researchers have used many experimental approaches to circumvent the possible confounding effects of treatments on performance versus the effectiveness of reward.

In one study, rats treated with the D_1-like receptor antagonist SCH 23390 or the D_2-like antagonists metocolpramide or pimozide showed a pattern of within- and across-session decreases in responding for food somewhat like that seen during the extinction of responding when food no longer was given (Beninger *et al.*, 1987). The dorsal striatum was implicated in this effect of D_2-like antagonists by the finding that local injections of sulpiride into the dorsal striatum, but not the nucleus accumbens or amygdala, produced a within-session decline in responding (Phillips *et al.*, 1991). In another study, an across-session decrease was seen over several days of testing with SCH 23390 but not with the D_2 antagonist raclopride. This latter study included an extensive and sophisticated behavioural analysis that led to the conclusion that the D_2-like receptor antagonist produced a greater effect on motor function than the D_1-like antagonist, results consistent with the differential effects of these agents on schedule-controlled responding (Fowler and Liou, 1994). A simple motor effect of the drugs would have been expected to produce an uniform decrease in responding within or across sessions. Although results implicated both D_1- and D_2-like receptors in the control of behaviour by food reward, some findings suggested a greater role for D_1-like receptors in reward and a greater role for D_2-like receptors in motor function.

In other studies, rats treated with low doses of SCH 23390 showed a greater decrease in responding on schedules of intermittent reinforcement for food than the decrease seen in responding for continuous reinforcement; raclopride, on the other hand, similarly affected responding on both schedules (Nakajima, 1986; Nakajima and Baker, 1989). The differential results with SCH 23390 could not be attributed to a motor effect whereas the effects of raclopride were consistent with a motor

effect. Results suggest a greater involvement of D_1-like receptors in the control of behaviour by reward.

Some researchers have shown that SCH 23390 or D_2-like antagonists including haloperidol, metoclopramide or sulpiride decreased operant responding for food or water at doses that failed to affect drinking and, in fact, increased eating when free food was available in the test cage (Cousins *et al.*, 1994; Ljungberg, 1987, 1989, 1990). Although these results do not show any differential effects of D_1- versus D_2-like antagonists on responding for reward, they show that the response-decreasing effects of these agents are not related to a decrease in motivation to eat or drink, another possible confound in behavioural studies seeking to evaluate the role in reward of DA receptor subtypes.

Two studies used 11- or 17-day old rat pups in an instrumental conditioning paradigm requiring a running response for nipple attachment reinforcement. In both, SCH 23390, but not sulpiride, produced an extinction-like decrease in running speed, although sulpiride augmented the effects of SCH 23390 when they were given together (McDougall *et al.*, 1991, 1992). Results show that both D_1- and D_2-like receptors are involved in reward-related learning but the differential effects of antagonists acting at the two receptor classes, when given alone, suggest that D_1-like receptors may be more importantly involved.

To summarize so far, data from a number of studies show that antagonists acting at either D_1- or D_2-like receptors seem to produce a decrease in the ability of rewarding stimuli to control operant responding. Furthermore, some results show differential effects with antagonists relatively specific for either DA receptor subclass that suggest a more important role for the D_1-like receptor in the mechanisms by which rewarding stimuli control behaviour.

Operant responding for brain stimulation reward (BSR): With electrodes located in a number of regions including the central gray, ventral tegmental area or lateral hypothalamus, researchers have found that systemic injections of either the D_1-like antagonist SCH 23390 or the D_2-like antagonist raclopride shifted the response rate-frequency or running speed-frequency function to the right (Hunt *et al.*, 1994; Nakajima and Baker, 1989; Nakajima and McKenzie, 1986; Nakajima and O'Regan, 1991; Rompré and Bauco, 1990). One study reported similar findings following intra-accumbens injections of SCH 23390 and showed further that this effect occurred with injections ipsi- but not contralateral to the stimulating electrode (Kurumiya and Nakajima, 1987).

The use of response-frequency functions is a sophisticated behavioural technique implemented to dissociate effects of pharmacological treatments on reward versus performance. If a DA antagonist reduces reward but not motor capacity, responding for BSR should be observed with higher frequencies that overcome the effects of receptor blockade. If performance is not affected, response rates should be seen to rise to the same asymptote with increasing frequency. This

pattern was observed in all of the studies cited above. One study (Hunt *et al.*, 1994) reported a failure to dissociate reward from performance effects with the D_2-like antagonist spiperone but did see this dissociation with SCH 23390. These studies implicate both D_1- and D_2-like receptors in reward from brain stimulation and the results of one study might suggest a more important role for D_1-like receptors.

Operant responding to self-administer drugs: The self-administration paradigm is particularly well suited to a dissociation of reward versus motor effects of DA antagonists because DA antagonists can produce increases in responding like those seen following decreases in the concentration of the rewarding drug. Thus, an effect on reward produces a change in responding in a direction opposite to the decrease in responding that would be expected if motor ability was being affected. Another variable also seems to be important in these experiments, however. Thus, many researchers use a time out period, during which responding has no programmed consequences, following delivery of a self-administered drug. With a long time out (*e.g.*, 2 min), increases in responding are not seen following any doses of DA antagonists (Caine and Koob, 1994).

Many studies using a long time out have shown that antagonists acting at D_1-like receptors, including SCH 23390, SCH 39166 and A69024, or antagonists acting at D_2-like receptors, including pimozide, eticlopride and spiperone decrease responding for self-administration of cocaine (Caine and Koob, 1994; Winger, 1994; Woolverton and Virus, 1989); in these studies, effects of antagonists on performance cannot be ruled out. However, many additional studies using a short time out have reported an increase in responding for cocaine following these drugs (Bergman *et al.*, 1990; Britton *et al.*, 1991; Caine and Koob, 1994; Corrigall and Coen, 1991; Hubner and Moreton, 1991; Koob *et al.*, 1987; Woolverton, 1986). These results implicate both D_1- and D_2-like receptors in reward.

Differential effects of D_1- versus D_2-like antagonists on responding to self-administer drugs have been reported. Thus, SCH 23390 was found to produce a dose-dependent increase in responding for cocaine (followed by a short time out) whereas spiperone was effective at only one dose (Koob *et al.*, 1987). In other studies, D_1-like antagonists were found to decrease responding for cocaine on a multiple schedule (with long time outs) at doses that were less effective at decreasing responding for food (Caine and Koob, 1994; Kleven and Woolverton, 1990); no similar dissociation was found for D_2-like antagonists (Caine and Koob, 1994).

D_1-like receptors in the nucleus accumbens, amygdala and frontal cortex have been implicated in the rewarding effects of intravenous cocaine self-administration by the observation that response rates were increased by injections of SCH 23390 into these structures (Caine *et al.*, 1995; Maldonado *et al.*, 1993; McGregor and Roberts, 1993; Phillips *et al.*, 1994a). The D_2-like antagonist sulpiride similarly increased responding when it was injected into the accumbens (Phillips *et al.*,

1994a). Dorsal (Caine *et al.*, 1995; McGregor and Roberts, 1995), but not posterior striatal (Maldonado *et al.*, 1993) injections of SCH 23390 were reported to increase cocaine self-administration; however, careful studies of the time of onset of the effect of dorsal striatal injections suggested that this effect resulted from diffusion of the drug to the accumbens (Caine *et al.*, 1995).

Interestingly, analyses of responding on progressive ratio schedules for intravenous cocaine self-administration revealed that SCH 23390 injections into the accumbens or frontal cortex, but not the amygdala, decreased breaking points, defined as the leanest ratio that will maintain responding (McGregor and Roberts, 1993, 1995). The finding that intra-amygdaloid injections of SCH 23390 increased rates of self-administration of cocaine suggests that the amygdala plays an important role in reward-related learning; however, the dissociation of effects on self-administration rates versus breaking points further suggests that the role of the amygdala is different from that of the accumbens or frontal cortex where increases in rate of self-administration and decreases in breaking points are seen.

Some researchers have found that animals will self-administer the indirect catecholamine agonist amphetamine directly into the nucleus accumbens; these studies found that co-injections of amphetamine plus either SCH 23390 or sulpiride increased rates of self-administration (Phillips *et al.*, 1994b, c). These results are consistent with a role for D_1- and D_2-like receptors in reward.

Taken together, evidence from self-administration studies using systemic administration of DA antagonists suggests that both D_1- and D_2-like receptors play a role. Central injection studies implicate DA in the nucleus accumbens, amygdala and frontal cortex. Like studies of operant responding for food, water or BSR, data revealing differential effects of D_1- and D_2-like antagonists further suggest that the action of DA at the D_1-like receptor may play a particularly important role in reward-related learning.

Operant responding for conditioned rewards: Animals will learn an operant response when rewarded with a stimulus that has acquired its rewarding properties as a result of a prior history of association with a primary rewarding stimulus such as food or water; such a stimulus is termed a conditioned reward. Previous studies have shown that treatment with amphetamine specifically enhances the acquisition of responding for conditioned rewards, as reviewed by Beninger and Ranaldi (1994). Treatment with SCH 23390 was found to shift the amphetamine dose-response curve in this paradigm to the right; the D_2-like antagonist pimozide also shifted the curve to the right but the maximum level of responding seen following treatment with SCH 23390 was never seen with pimozide. The D_2 antagonist metoclopramide, on the other hand, decreased the amphetamine enhancement of responding in a dose-dependent manner but failed to shift the amphetamine dose-response curve to the right (Ranaldi and Beninger, 1993). In a related study, intra-accumbens injections of amphetamine enhanced responding for conditioned reward

and systemic injections of SCH 23390 or raclopride decreased this effect (Chu a Kelley, 1992). These latter findings were consistent with those seen followi systemic amphetamine plus DA receptor subtype-specific antagonists.

Results from studies of the effects of DA antagonists on amphetamine-enhanc responding for conditioned reward implicate both D_1- and D_2-like receptors incentive learning produced by conditioned rewards. Although limited data a available from this paradigm, the results also suggest that D_1-like antagonists ma produce effects somewhat specific to reward whereas D_2-like antagonists affe reward and motor responding, as also suggested by data reviewed above fro studies of operant responding for food, water, BSR and stimulant self administration.

Place conditioning: Given a choice between two familiar chambers, one of whic previously has been paired with reward, rats show a preference for the place associate with reward. For example, preferences have been reported for places associated wit food, water, psychostimulants or morphine. Guyon *et al.* (1993) showed that place conditioning based on food was augmented by low doses of D_2-like antagonists that would augment DA release by blocking presynaptic receptors; higher doses decreased place preferences. Furthermore, they showed that SCH 23390 reversed the augmentation of place conditioning produced by amisulpiride. This finding shows that place conditioning requires stimulation of D_1-like receptors.

Place preference conditioning with water was blocked by SCH 23390, raclopride or pimozide (Ågmo *et al.*, 1993). Similar conditioning with amphetamine was blocked by SCH 23390, metoclopramide or sulpiride (Hiroi and White, 1991; Hoffman and Beninger, 1989b; Leone and Di Chiara, 1987) and conditioning with pipradrol was blocked with SCH 23390 (White and Hiroi, 1992). Place conditioning with morphine was blocked by acute SCH 23390 or SCH 39166 (Acquas and Di Chiara, 1994; Leone and Di Chiara, 1987) and by chronic systemic SCH 23390 or intra-accumbens injections of SCH 23390 but not by chronic systemic spiperone or intra-accumbens sulpiride (Shippenberg and Hertz, 1987, 1988; Shippenberg *et al.*, 1993). Similarly, place conditioning based on cocaine was blocked by SCH 23390 but not by sulpiride (Cervo and Samanin, 1995). These latter finding suggest that, at least in the case of place conditioning with morphine or cocaine, D_1-like receptors may play a more critical role than D_2-like receptors.

In the above studies reporting that SCH 23390 blocked place conditioning, control experiments showed that the same doses of SCH 23390 given alone did not produce a place aversion. However, a number of studies have found that SCH 23390 or the D_1-like antagonist A69024, at some doses, can produce a place aversion when given systemically (Acquas and Di Chiara, 1994; Shippenberg and Herz, 1988; Shippenberg *et al.*, 1991) and two studies reported an aversion when SCH 23390 was given alone into the nucleus accumbens (Shippenberg *et al.*, 1991; Shippenberg *et al.*, 1993). In contrast, metoclopramide or sulpiride, given alone,

failed to produce a place aversion (Shippenberg and Herz, 1988; Shippenberg *et al.*, 1991). Perhaps these results too indicate a more important role for D_1- than D_2-like receptors in reward.

D_1- and D_2-like receptor agonists

Operant responding for food: Both the D_1-like agonists SKF 38393 and SKF 75760 and the D_2-like agonist N-0437 and RU 24213 decreased responding on a fixed ratio schedule for food (Katz and Witkin, 1992; Rusk and Cooper, 1988, 1989); similarly, SKF 38393 and quinpirole decreased variable interval responding for food (Hoffman and Beninger, 1989a). However, with the use of a multiple schedule including fixed interval and fixed ratio components, differential effects of D_1- versus D_2-like agonists have been found. Thus, SKF 38393 decreased both fixed interval and fixed ratio responding of monkeys whereas quinpirole increased fixed interval responding at doses that decreased fixed ratio responding (Katz and Witkin, 1993; Witkin *et al.*, 1991). In independent groups of monkeys trained on either a fixed interval schedule of shock avoidance or a fixed ratio for food, D_1-like agonists similarly decreased responding on both schedules whereas D_2-like agonists similarly increased fixed interval responding at doses that decreased fixed ratio responding (Bergman *et al.*, 1995). In a related study, mice were seen to decrease responding for food presented according to a multiple schedule following SKF 38393 at doses that failed to affect unconditioned social and motor responses; quinpirole, on the other hand, showed no similar dissociation, decreasing operant and unconditioned responding at each effective dose (Tidey and Miczek, 1992). Finally, a number of D_1-like agonists were found to decrease fixed interval responding for shock whereas amphetamine produced an increase at some doses (Katz *et al.*, 1995).

The effects of D_1- versus D_2-like agonists on operant responding for food can be summarized as follows. Regardless of the schedule of reinforcement, D_1-like agonists are seen to produce decreases in responding. Thus, D_1-like agonists decrease responding on variable interval, fixed interval and fixed ratio schedules. D_2-like agonists, on the other hand, are seen to increase responding at some doses on fixed interval schedules although they consistently decrease responding on fixed ratio schedules. Results suggest that D_1- and D_2-like receptors play different roles in the control of responding by reward. Stimulation of D_1-like receptors more strongly interferes with operant responding.

Operant responding for BSR: In a number of studies using stimulation of the lateral hypothalamus or ventral tegmental area as the rewarding stimulus for each lever press, D_2-like agonists including quinpirole, CV 205-502 or bromocriptine produced leftward shifts in the rate-frequency function, indicative of enhanced reward (Carey, 1983; Knapp and Kornetsky, 1994; Nakajima and O'Regan, 1991;

Nakajima *et al.*, 1993; Ranaldi and Beninger, 1994). The effects of D_1-like agonists have been less consistent. Thus, A77636 produced a leftward shift (Ranaldi and Beninger, 1994) but SKF 38393 had no effect in one study (Nakajima and O'Regan, 1991) and produced a rightward shift, suggesting decreased reward, in another (Hunt *et al.*, 1994). It is noteworthy that in the latter study BSR was presented according to a fixed interval schedule making the observation of decreased responding consistent with the effects of D_1 agonists on operant responding for food, as reviewed above.

One study investigated the effects of central injections of DA receptor subtype-specific agents on operant responding for BSR. Ranaldi and Beninger (1994) found that A77636 injected into the nucleus accumbens, but not the caudate nucleus or overlying cortex, shifted the rate-frequency function to the left, like the effect seen with systemic injections. On the other hand, quinpirole injected into any of these structures shifted the rate-frequency function to the right, in contrast to its effects when administered systemically. Further studies are needed to identify the central site of action mediating the leftward shift in the rate-frequency function produced by systemic quinpirole.

Operant responding to self-administer drugs: Both D_1- and D_2-like agonists are self-administered by animals. It was reported that SKF 38393 was not self-administered by monkeys (Woolverton *et al.*, 1984) but subsequent studies found that low concentrations of the D_1-like agonist SKF 81297 were self-administered by monkeys (Weed *et al.*, 1993) and SKF 82958 or SKF 77434 were self-administered by rats (Self and Stein, 1992; Self *et al.*, 1993); higher concentrations did not maintain responding. The D_2-like agonists bromocriptine and piribedil were self-administered by monkeys and rats (Woolverton, *et al.*, 1984; Woolverton, 1986; Wise *et al.*, 1990). Results suggest a role for both D_1- and D_2-like receptors in reward.

One study evaluated the effects of systemic SKF 38393 on operant responding to self-administer cocaine and found a decrease, the dose-response curve being shifted to the right (Katz and Witkin, 1992). These results are consistent with the findings reviewed above showing that operant responding for food or BSR is decreased by D_1-like agonists and the finding that self-administration of D_1-like agonists is seen only at low concentrations. Finally, two recent studies reported that the D_3 receptor-selective agonist 7-OH-DPAT, when co-infused with cocaine, decreased cocaine self-administration, an effect consistent with an increase in reward (Caine and Koob, 1993, 1995). This finding implicates the D_3 receptor in reward (see Koob *et al.*, this volume).

Operant responding for conditioned reward: Like their effects on operant responding for food, BSR or self-administered cocaine, systemic injections of D_1-like agonists decrease responding for conditioned reward in a dose-dependent manner (Beninger and Rolfe, 1995; Ranaldi *et al.*, 1995; Ranaldi and Beninger,

1995). D_2-like agonists, on the other hand, increase responding at some doses (Beninger and Ranaldi, 1992; Ranaldi and Beninger, 1995). We have argued that there is a DA signal associated with the presentation of a rewarding stimulus that acts critically at D_1-like receptors to produce incentive learning. Thus, treatment with D_1-like agonists impairs the control of responding by conditioned incentive stimuli because it masks the reward signal; such an impairment is not seen following treatment with D_2-like agonists at moderate doses because the putative reward signal at the D_1-like receptor remains intact (Beninger and Ranaldi, 1992, 1994; Beninger and Rolfe, 1995).

In contrast to the D_1-like receptor signal hypothesis, some studies have reported that intra-accumbens injections of SKF 38393, like amphetamine or D_2-like agonists, increased responding for conditioned reward (Phillips *et al.*, 1994c; Wolterink *et al.*, 1993). In a related study, however, intra-accumbens injections of the D_1-like agonist CY 208-243 failed to affect responding for conditioned reward although co-injection with a D_2-like agonist produced an enhancement (Chu and Kelley, 1992). If the DA signal at D_1-like receptors in the nucleus accumbens was critical for reward-related learning, it might be expected that direct stimulation of D_1-like receptors would mask the signal. We have argued elsewhere that perhaps the DA signal is distributed to the accumbens and other structures leading to the observation of impaired responding following systemic injections of D_1-like agonists but not following intra-accumbens injections (Beninger and Ranaldi, 1994; Beninger and Rolfe, 1995).

Place conditioning: SKF 38393 was reported to produce a place aversion, not a preference (Hoffman and Beninger, 1988, 1989b). A subsequent study reported that intra-accumbens, but not systemic, injections of SKF 38393 produced a place preference (White *et al.*, 1991). This finding suggested that some action of SKF 38393 other than its effects on accumbens D_1-like receptors was responsible for its aversive properties, a suggestion consistent with the finding that the appetite suppressing effects of SKF 38393 were not blocked by SCH 23390 although those of other D_1-like agonists were (Terry and Katz, 1992). In a recent study we confirmed that the aversive properties of SKF 38393 may be unrelated to its action at D_1-like receptors. Thus, systemic injections of the D_1-like agonist SKF 82958 produced a place preference in a dose-dependent manner (see Figure 1). In several studies, D_2-like agonists have been found to produce a place preference (Hoffman and Beninger, 1988, 1989b; Hoffman *et al.*, 1988; Morency and Beninger, 1986; White *et al.*, 1991). Recent results have shown that 7-OH-DPAT produced a place preference (Chaperon and Thiébot, 1996; Mallet and Beninger, 1994); this compound has a weak selectivity for D_3 versus D_2 receptors but the doses that produced place conditioning were high and may have affected D_2 receptors. Thus, place preferences are produced by D_1- or D_2-like agonists.

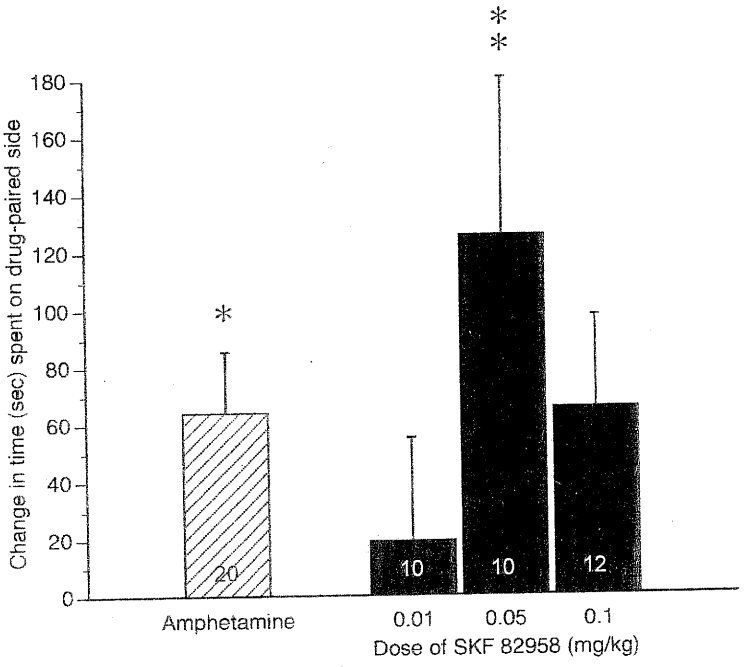

Figure 1. Place conditioning with amphetamine or the high efficacy D_1-like agonist SKF 82958. Rats (number per group is indicated on each bar) received three 15-min sessions of exposure to an apparatus consisting of two chambers connected by a tunnel. Over the eight subsequent days, with the tunnel blocked, one chamber was paired with injections of amphetamine (2.0 mg/kg) or SKF 82958 (0.01, 0.05, 0.1 mg/kg) for 30 min on days 1, 3, 5 and 7 and the other chamber was paired with injections of saline on days 2, 4, 6 and 8. Over one 15-min test session, the tunnel again was open. For each group, the change in time spent on the drug-paired side from pre-exposure to the test session is shown. Amphetamine and 0.05 mg/kg of SKF 82958 produced significant increases in time spent on the drug-paired side (* $p<0.05$; ** $p<0.01$). Unpublished data from Jeff Rutherford, Paul E. Mallet and Richard J. Beninger.

D_1- and D_2-like receptor interactions

A few studies have investigated the effects of D_1-like antagonists on the behavioural effects of D_2-like agonists or vice versa. Generally, results support a role for both receptor categories in incentive learning but some data suggest a more critical role for the D_1-like receptor. In one study, monkeys trained on a multiple fixed interval fixed ratio schedule for food showed an increase in fixed interval responding and a decrease in fixed ratio responding following quinpirole but a decrease in both components following SKF 38393, as reviewed above; both D_1- and D_2-like antagonists shifted the quinpirole dose-response curve to the right

implicating both receptor subtypes in the behavioural effects of quinpirole (Katz and Witkin, 1993). However, SCH 23390 or spiperone failed to shift the SKF 38393 dose-response curve leading the authors to suggest that the behavioural effects of SKF 38393 were not related to its action at D_1-like receptors. This important finding underscores the need to evaluate other D_1-like agonists in a variety of behavioural paradigms.

In a study of the effects of quinpirole on responding for BSR, the D_1-like antagonist SCH 23390 reversed the leftward shift in the dose-response curve (Nakajima *et al.*, 1993). This finding, like those of Katz and Witkin (1993), discussed in the previous paragraph, suggests that the apparent enhancement of reward produced by the D_2-like agonist requires stimulation of D_1-like receptors.

Self *et al.* (1993) evaluated the effects of SCH 23390 or raclopride on responding to self-administer the D_1-like agonist SKF 82958. They observed a dose-dependent increase in responding, indicative of a decrease in reward following SCH 23390 but not following raclopride. They concluded that SKF 82958 produces rewarding effects by its action at the D_1-like receptor. Their data suggest further that stimulation of the D_1-like receptor can produce reward even when D_2-like receptors are blocked.

The dose-response curve for the enhancement of responding for conditioned reward produced by bromocriptine was shifted to the right by either the D_2-like antagonist pimozide or the D_1-like antagonist SCH 23390 (Ranaldi and Beninger, 1995). This result is consistent with those from studies of responding for food or BSR in showing that the reward-enhancing effects of a D_2-like agonist require stimulation of D_1-like receptors.

Summary

Data from a number of paradigms including operant responding for food, water, BSR, drug self-administration or conditioned reward or place conditioning show that DA antagonists acting at either D_1- or D_2-like receptors produce a decrease in the ability of rewarding stimuli to control responding. Furthermore, some results show differential effects with antagonists relatively specific for either DA receptor subclass that suggest a more important role for the D_1-like receptor in the mechanisms by which rewarding stimuli control behaviour.

This conclusion is further supported by the results of studies with D_1- and D_2-like agonists. Thus, operant responding in a variety of paradigms was seen to be augmented by D_2-like agonists but impaired by D_1-like agonists. These results suggest that a reward-related DA signal at the D_1-like receptor may be critical for incentive learning. Results from studies of interactions of DA receptor subtypes in behavioural paradigms further support a critical role for D_1-like receptors in reward.

D_1-like receptors and the mechanisms of learning

The defining characteristic of D_1-like receptors is their ability to activate adenylate cyclase and the resultant second messenger pathway including cyclic adenosine 3'5'-monophosphate (cAMP) formation and activation of cAMP-dependent protein kinase (PKA). There is now a wealth of data from a number of different species and paradigms that provide converging evidence that activation of this pathway is critical for learning (Nestler *et al.*, 1993; Nestler, 1994). Some of that evidence will be reviewed briefly in this section.

Recent reviews have focused on the role of the cAMP cascade in learning and memory. After briefly discussing some of the evidence from studies of *Drosophila*, *Aplysia*, and mice, Kandel and Abel (1995) noted "... the interesting possibility that reinforcing stimuli may activate monoaminergic... modulatory systems and that these may produce functional changes in the pathway of the conditioned stimulus by activating the cAMP cascade" (p. 826). In the context of the present discussion, reinforcing stimuli may produce incentive learning by leading to the activation of DA neurons that stimulate D_1-like receptors and activate the cAMP pathway.

There have been a number of review and theoretical papers in the past ten years that propose that DA produces reward-related incentive learning by altering the effectiveness of glutamatergic synapses in the striatum (including the caudate, putamen, nucleus accumbens and olfactory tubercle). Following on the proposal, by Greengard and his co-workers (Hemmings *et al.*, 1987), of a DA-glutamate interaction mediated by the second messenger cAMP, Wickens, Miller and Beninger, in a series of papers, have proposed a mechanism by which DA acting at D_1-like receptors can produce incentive learning by altering the effectiveness of recently activated glutamatergic synapses in the striatum (Beninger, 1993; Miller *et al.*, 1990; Wickens, 1990, 1993). The interaction leads to a putative activity dependent modification of glutamatergic synapses presumably activated by environmental stimuli that precede the rewarding stimulus; the rewarding stimulus itself would have activated striatopetal DA neurons. Recently, Wickens and Kötter (1995) and Kötter (1994) have elaborated further the details of the proposed mechanism of interaction of DA and glutamate, including the second messenger cAMP, in the striatum and have tested some predictions of the model in computer simulations.

D_1-like receptors and working memory: The recent studies of Goldman-Rakic and her co-workers may be relevant to a consideration of the mechanisms by which DA produces learning. Arnsten *et al.* (1994) trained monkeys in a delayed matching to position task; correct responding required working memory -- the recall of which food well had been baited -- and has been shown to require intact prefrontal cortical function. Results revealed that D_1-like agonists augmented

performance in aged or DA-depleted monkeys; SCH 23390 reversed this effect and impaired performance in young monkeys. Similar results were reported in a related study from the same laboratory (Sawaguchi and Goldman-Rakic, 1991). Electrophysiological studies showed that D_1-like antagonists increased the "memory fields" of prefrontal cortical neurons during the delay interval of the matching task (Williams and Goldman-Rakic, 1995); as the normal function of DA acting at D_1-like receptors is to constrain neuronal activation during the delay interval, these results are consistent with the observation of impaired performance following systemic treatment with D_1-like antagonists. The molecular mechanisms of this D_1-like receptor-mediated memory phenomenon are not known but Goldman-Rakic (1995) has suggested that DA modulates the excitatory (glutamatergic) inputs to dendritic spines of pyramidal cells in the frontal cortex. This interaction is remarkably similar to that proposed for the striatum by Wickens (1990) and others as discussed above. Although the cAMP cascade has not yet been investigated in tests of working memory, the dependence of working memory on D_1-like receptors suggests the involvement of this second messenger.

A cellular analogue of reward-related learning: In a novel paradigm, Stein *et al.* (1993, 1994), recording from single pyramidal cells in hippocampal slices, applied pharmacological agents contingent upon a bursting pattern of electrical activity. They found that DA itself or D_1- or D_2-like agonists were effective reinforcers, increasing burst firing when applied contingently but not noncontingently. These results provide further evidence implicating DA receptor subtypes in reward-related learning. Receptor subtype interaction studies are needed to evaluate the relative importance of stimulation of D_1- versus D_2-like receptors in this paradigm.

PKA and glutamate receptor effectiveness: Some studies have used cultured hippocampal cells and investigated the effects of agents influencing various stages of the cAMP cascade on the effectiveness of glutamatergic synapses using non-NMDA receptors. Wang *et al.* (1991) and Greengard *et al.* (1991) found that agents that activated adenylate cyclase or PKA, or an inhibitor of cellular phosphatases, led to a potentiation of currents induced by activation of non-NMDA receptors through an increase in the open time and opening frequency of non-NMDA receptor channels. Further studies revealed that the modification of glutamate receptor effectiveness influenced by activation of the cAMP cascade involved phosphorylation of the receptor (Blackstone *et al.*, 1994; Wang *et al.*, 1993). The authors suggested that the dynamic regulation of glutamate receptors may be associated with learning and memory. These studies may be identifying one of the processes through which activation of D_1-like receptors produces incentive learning.

PKA and learning: In *Drosophila*, researchers using molecular techniques developed a fly that could be heat shocked as an adult to activate genes that led to

the production of a protein that inhibited PKA. Such flies were found to be deficient in an olfactory discrimination learning paradigm implicating the second messenger cAMP in learning (Drain *et al.*, 1991). Interestingly, transgenic flies engineered to over-produce PKA also were deficient in learning. This led the authors to suggest that PKA must be regulated at a physiologically appropriate level for proper learning to occur.

In psychopharmacological experiments, sensitization is defined as an increased response to a particular dose of a drug with repeated intermittent exposure to that drug. Indirect acting DA agonists such as amphetamine produce sensitization. Detailed studies have shown that conditioning to environmental stimuli associated with the drug plays a role in sensitization but does not account for the entire effect (Stewart, 1992; Stewart and Vezina, 1988). The observation that the development of sensitization to systemic treatments with amphetamine is blocked by systemic SCH 23390 but not by D_2-like antagonists implicates D_1-like receptors in this effect (Vezina and Stewart, 1989); however, localization studies showed that injections of the D_1-like antagonist into the mesencephalic regions containing DA cell bodies were effective at blocking sensitization (Stewart and Vezina, 1989), suggesting plasticity in those regions. In spite of this finding, Miserendino and Nestler (1995), following on the observation that repeated injections of cocaine lead to increased levels of adenylate cyclase and PKA in the nucleus accumbens, evaluated the effects of intra-accumbens injections of a PKA activator or inhibitor on the development of cocaine sensitization. Results revealed that treatment with the PKA activator led to a significant enhancement of the sensitization effect; treatment with the inhibitor had no significant effect on the development of sensitization. No specific tests for conditioned drug effects were carried out in this study so it is not possible to determine the role of learning. However, insofar as conditioning is involved in sensitization, results with the PKA activator are consistent with a role for the cAMP second messenger cascade in learning.

In a recent study, we evaluated the effects of the PKA inhibitor Rp-cAMPS on incentive learning produced by intra-accumbens injections of amphetamine (20 µg/0.5 µl/side) in the place conditioning paradigm. We found that doses of 25.0 or 250, but not 2.5 ng/0.5 µl/side, co-injected with amphetamine during conditioning sessions, blocked the establishment of place preference conditioning (Figure 2). In control studies, animals treated with 2.5, 25.0 or 250 ng/0.5 µl/side of Rp-cAMPS alone during conditioning sessions did not show a significant place conditioning effect. Results are consistent with the hypothesis that incentive learning involves the action of DA at D_1-like receptors and the subsequent activation of the cAMP cascade.

In summary, studies from different species using a wide range of neuroscience techniques provide convergent evidence suggesting that some forms of learning are mediated by the activation of adenylate cyclase, the formation of cAMP and the

Figure 2. Place conditioning with intra-accumbens injections of amphetamine, amphetamine plus the cyclic adenosine-3',5-monophosphate dependent protein kinase inhibitor Rp-cAMPS or Rp-cAMPS alone. Rats (number per group is indicated on each bar) received three 15-min sessions of exposure to an apparatus consisting of two chambers connected by a tunnel. Over the eight subsequent days, with the tunnel blocked, one chamber was paired with intra-accumbens injections of amphetamine (20 µg in 0.5 µl/side), amphetamine plus Rp-cAMPS (2.5, 25.0 or 250.0 µg in 0.5 µl/side) or Rp-cAMPS alone (2.5, 25.0 or 250.0 µg in 0.5 µl/side) for 30 min on days 1, 3, 5 and 7 and the other chamber was paired with injections of saline on days 2, 4, 6 and 8. Over one 15-min test session, the tunnel again was open. For each group, the change in time spent on the drug-paired side from pre-exposure to the test session is shown. Intra-accumbens amphetamine and amphetamine plus 2.5 µg Rp-cAMPS produced significant increases in time spent on the drug-paired side (* $p<0.05$). The effect of amphetamine was blocked by Rp-cAMPS doses of 25.0 or 250.0 µg/0.5 µl/side. Rp-cAMPS on its own failed to produce significant changes in place preference. Unpublished data from Patricia L. Nakonechny and Richard J. Beninger.

activation of PKA (see also Izquierdo and Chaves, Chapter 18 of this volume). Preliminary data implicate PKA in amphetamine-produced place conditioning, in agreement with the results of many studies pointing to a critical role for D_1-like receptors in reward-related incentive learning.

Protein synthesis and learning: There is an extensive old literature showing that many forms of learning are impaired in animals treated with various protein synthesis inhibitors during training, as reviewed by Davis and Squire (1984). They conclude that the data make a compelling case for the hypothesis that protein synthesis during or shortly after training is an essential step in long term memory formation. In recent studies of the sea slug *Aplysia* it has been found that PKA is responsible for the phosphorylation of nuclear proteins, termed cAMP response element binding proteins (CREBs), that modulate transcription (Kaang *et al.*, 1993). Other studies have shown that the resultant newly synthesized proteins target regulatory subunits of PKA, prolonging the activity of this enzyme, and, therefore, prolonging its influence on synaptic plasticity (Hegde *et al.*, 1993). Similar findings have come from studies of the molecular mechanisms of learning and memory in *Drosophila* (DeZazzo and Tully, 1995; Skoulakis *et al.*, 1993; Spatz, 1995). In rats, it was shown that amphetamine acts via D_1-like receptors to induce phosphorylation of CREB providing a mechanism for some of the long term effects of amphetamines (Konradi *et al.*, 1994). Here again, the cAMP cascade is implicated in learning.

Long term potentiation (LTP) of connections in the hippocampus has been used extensively as a model of potential synaptic changes underlying learning and memory (Kuba and Kumamoto, 1990). Recently, LTP has been found to have two distinct components, a transient component that requires the influx of calcium through NMDA receptor channels and activation of several kinases, and a more persistent component that requires protein synthesis. This later component is mediated at least partially by the cAMP cascade. Thus, the persistent form of LTP is induced by D_1-like agonists and this effect is blocked by D_1like antagonists (Huang and Kandel, 1995). It also is induced by PKA (Frey *et al.*, 1993). Furthermore, the D_1-like agonist or PKA effect on LTP is blocked by protein synthesis inhibition (Frey *et al.*, 1993; Huang and Kandel, 1995). This provides yet another example of the involvement of D_1-like receptors and the second messenger cAMP cascade in synaptic plasticity thought to underlie learning.

Conclusions

In recent years there has been intense research activity directed towards identifying the molecular mechanisms underlying changes in synaptic effectiveness associated with learning. Some of the most influential work has been done on the marine mollusk *Aplysia*. Results have led to the identification of a second messenger

pathway involving activation of adenylate cyclase, cAMP and PKA. Phosphorylation events stimulated by PKA include both relatively short term changes in ion channels and long term changes requiring protein synthesis, both types of changes underlying altered responsiveness to environmental stimuli (Kandel, 1991). As reviewed in this chapter, similar mechanisms involving activation of the cAMP pathway have been found in studies of learning in *Drosophila* (DeZazzo and Tully, 1995) and LTP (Kuba and Kumamoto, 1990).

Perhaps it is time for DA-mediated incentive learning in the striatum to take its place along with these other paradigms as a mechanism of synaptic plasticity. As reviewed here, many findings point to stimulation of D_1-like receptors as a critical event for incentive learning. Recent studies are beginning to show that incentive learning involves steps along the pathway from activation of adenylate cyclase to protein synthesis. Future studies may identify the specific genes involved in the synaptic plasticity underlying incentive learning. All of these findings will lead to a new understanding of incentive learning and to new approaches to its regulation.

The hypothesis that DA, in some way, may hyperfunction in the brains of schizophrenic patients continues to be influential especially as DA receptor antagonists continue to be the pharmacotherapy of choice for treating schizophrenia. This observation and the involvement of DA in incentive learning implies that schizophrenia may occur, in part, as a result of an abnormality (excess) of incentive learning. The identification of a critical role for D_1-like receptors in incentive learning suggests the involvement of D_1-like receptors in schizophrenia (Lynch, 1992; Miller *et al.*, 1990). As the molecular mechanisms of synaptic plasticity underlying learning in general, and incentive learning in particular, come into better focus with continued research, new possibilities for the treatment of schizophrenia will emerge, as has already been suggested by some authors (Grebb, 1991).

Acknowledgements

This chapter is dedicated to Mariah. Funded by a grant from the Natural Sciences and Engineering Research Council of Canada.

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