
CHAPTER 5

ROLE OF D₁ AND D₂ RECEPTORS IN LEARNING

(C8)

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The neurotransmitter dopamine (DA) appears to play a role in the control of locomotor activity and reward-related incentive learning. Rewarding stimuli include, for example, food for a food-deprived animal, sexual stimuli, safety from aversive stimuli, and water for a water-deprived animal. Reward is the presentation of a rewarding stimulus and may affect behaviour by increasing the ability of stimuli immediately preceding reward to elicit approach and other responses in the future. Stimuli that acquire this ability are termed conditioned incentive motivational stimuli or, more simply, conditioned incentive stimuli, and the process is referred to as incentive motivational learning or, more simply, incentive learning (Bindra, 1974; Bolles, 1972). There is now extensive evidence implicating DA in reward-related incentive learning (Beninger, 1983; Le Moal and Simon, 1991; Lieberman and Cooper, 1989; Wise and Rompré, 1989).

The neuronal mechanisms underlying incentive learning have not been identified. However, in recent years there has been extensive research effort directed towards understanding the mechanisms of plasticity in the nervous system (e.g. Alkon, 1987; Byrne and Berry, 1989; Martinez and Kesner, 1991). A common finding is that the intracellular second messengers, activated through synaptic inputs to the cell, play a role in altering future responsiveness of the cell (e.g. Schwartz and Greenberg, 1987). It is possible that DA-mediated changes in responsiveness to stimuli signalling reward involve second messengers activated by stimulation of DA receptors. This possibility is supported by the finding that some DA receptors are linked in an excitatory manner to intracellular enzyme systems that influence second messengers.

One of the earliest and most influential classifications of DA receptors was made by Keabian and Calne (1979). D₁ receptors were defined as those linked in an excitatory manner to the enzyme adenylyl cyclase. Stimulation of adenylyl cyclase leads to the formation of cAMP, a second messenger. D₂ receptors were defined as those not linked to adenylyl cyclase. Subsequent studies found that stimulation of some receptors may lead to the inhibition of cAMP formation (Stoof and Keabian, 1981); these receptors also were classified as D₂. Recently, the use of molecular biological techniques has led to the identification of a number of distinct DA receptor proteins, designated D₁ to D₅ (Bunzow *et al.*, 1988; Dearth *et al.*, 1990; Monsma *et al.*, 1990; Sokoloff *et al.*, 1990; Sunahara *et al.*, 1990, 1991; Van Tol *et al.*, 1991; Zhou *et al.*, 1990). Although these receptors differ with respect to absolute protein sequence and some aspects of neuroanatomical distribution, their pharmacological profiles suggest that they fall into two categories. Waddington (1992) has suggested that they be classified as D₁-like (D₁ and D₅) and D₂-like (D₂, D₃, D₄). As few pharmacological agents are available that are specific for subclasses of D₁-like or D₂-like receptors, the remainder of this chapter will refer to DA receptor subtypes as 'D₁' or 'D₂'.

There is now an extensive selection of pharmacological agents that have relatively specific dopaminergic or antagonistic action at D₁ and D₂ receptors (Waddington and O'Boyle, 1989). These agents have permitted an evaluation

of the possible differential roles of DA receptor subtypes in incentive learning (reviews: Beninger, 1991, 1992; Beninger *et al.*, 1989; Miller *et al.*, 1990). Incentive learning can be assessed with the use of a wide range of behavioural paradigms and many of these have been used in tests of the role of DA receptor subtypes. Section 5.1 will be organized around specific paradigms and the effects of agonists or antagonists with relative selectivity for D₁ or D₂ receptors will be compared. Section 5.2 will propose a possible mechanism for DA-mediated reward-related incentive learning. Results of the reviewed studies will then be considered in Section 5.3 in the light of this proposed mechanism.

5.1 Role of D₁ and D₂ receptors in incentive learning

Many paradigms use rewarding stimuli to alter the behaviour of animals. By definition, these paradigms involve incentive learning. Paradigms include: lever pressing for food, water, electrical stimulation of the brain and drug self-administration; the acquisition of lever pressing for a conditioned reward, a previously neutral stimulus that has acquired rewarding properties by having been associated with a rewarding stimulus such as food; place conditioning; the establishment of certain environments as conditioned stimuli for stimulant drug effects; and avoidance learning paradigms, where reward is provided by the presentation of safety-related stimuli. Some studies evaluate the effects of post-training treatments with agents that affect DA neurotransmission on subsequent performance of tasks possibly involving incentive learning. The effects of pharmacological agents relatively specific for D₁ or D₂ receptors on performance in paradigms using reward to alter behaviour, and therefore involving incentive learning, will be reviewed in this section. Note that many paradigms have been used to evaluate the effects of agents such as pimozide or haloperidol, DA antagonists relatively specific for D₂ receptors; only paradigms where data are also available for the effects of antagonists relatively specific for D₁ receptors will be reviewed here.

5.1.1 Lever pressing for food

Some of the earliest studies implicating DA in reward-related learning evaluated the effects of systemic pimozide, a DA antagonist relatively specific for D₂ receptors (e.g. Seeman, 1981), on responding according to a schedule of continuous food reward. Results revealed that drugged animals showed an intra- and/or intersession pattern of decline in responding similar to that seen in animals undergoing extinction, i.e. no longer receiving food reward following lever press responses (Faustmann and Fowler, 1982; Mason *et al.*, 1980; Tombaugh *et al.*, 1979, 1982; Wise *et al.*, 1978a, b). Similarly, Nakajima and Baker (1989) reported gradually decreased intrasession responding for food with the D₂ antagonist raclopride. Pimozide also produced intersession declines in

responding for sucrose (Gramling *et al.*, 1987). These results suggest that DA acting at D₂ receptors plays a role in incentive learning. Recently, Hammond *et al.* (1991) used a sophisticated version of this procedure in conjunction with pharmacological compounds affecting either DA or, by other mechanisms, motor capacity, to confirm that the effects of pimozide are to block the rewarding effects of food.

Others have found that responding rewarded with food presented according to a number of different schedules of intermittent reward similarly underwent intra- and/or intersession declines when animals were treated with D₂ antagonists, including pimozide, haloperidol, metoclopramide and raclopride. These effects were observed in animals trained on fixed interval (Greenshaw *et al.*, 1981; Tombaugh *et al.*, 1980), variable interval (Beninger *et al.*, 1987; Gray and Wise, 1980; Nakajima and Baker, 1989; Phillips and Fibiger, 1979; Tombaugh *et al.*, 1980; Willner *et al.*, 1988) and fixed ratio schedules (Salamone, 1986; Sanger, 1986; Tombaugh *et al.*, 1980). Faustman and Fowler (1981) reported that responding for food on a fixed ratio schedule did not show a session-to-session decline following haloperidol but their dose (0.5 mg/kg) was higher than that (0.1 mg/kg) used by Salamone (1986) or those (0.03, 0.1, 0.3 mg/kg) used by Sanger (1986). Perhaps, with the high dose, responding may have decreased rapidly to a low level in the first drug session leading to little further decrease in subsequent drug sessions. One study trained pigeons to respond to a variable ratio schedule of food reward. Using chlorpromazine, a drug that blocks D₂ receptors, Dearing and Branch (1981) reported intrasession declines in pecking responses. It would appear from the results of these studies that antagonists acting at D₂ receptors block the usual effects of reward on behaviour.

Fewer studies have evaluated the effects of antagonists relatively specific for D₁ receptors. Beninger *et al.* (1987) reported that the D₁ antagonist SCH 23390 produced both inter- and intrasession declines in responding rewarded with food according to a variable interval schedule. In contrast, Sanger (1987) found no significant intrasession decline in SCH 23390-treated rats responding for food according to a fixed ratio schedule. It is possible that the latter finding reflects the prior experience of the rats. Sanger (1987) reported that his rats treated with SCH 23390 had received previous injections of several other drugs while participating in an earlier study. As reviewed above, repeated injections with DA antagonists in the context of behavioural testing lead to a progressively greater drug effect. It is possible that the earlier drug history of these animals may have influenced the results of the SCH 23390 test. This might be expected to be the case only if the drug history had been with DA antagonists in the context of lever pressing for food. Unfortunately, this type of information is not available in the paper.

One other study reported the effects of SCH 23390 on lever pressing for food. Nakajima (1986) trained groups of rats on schedules of continuous reward or variable interval schedules. He reported neither intra- nor intersession data, making the assessment of patterns of responding produced by SCH 23390

impossible. However, he found that responding on the schedule of continuous reward was more resistant to the effects of SCH 23390 than responding on the variable interval schedules; for example, a dose of 40 µg/kg almost completely abolished variable interval responding while reducing continuously rewarded responding by less than 50%. This makes it difficult to attribute the effects of SCH 23390 to purely motoric consequences of the drug. There is a need for further studies of the effects of D₁ antagonists on lever pressing according to classical schedules of food presentation. Studies to date seem to suggest that treatments with either a D₁ or D₂ receptor antagonist block the usual effects of reward on behaviour.

This conclusion is supported by another small set of studies using Herrnstein's (1970) matching law to separate the effects of drugs on reward versus performance in operant responding tasks. Herrnstein used an equation to describe the relationship between the rate of responding on interval schedules and the frequency of reward. By fitting the equation to response rate data it is possible to derive two constants, one reflecting the theoretical maximum response rate (k) and the other reflecting the reward frequency needed to maintain a half-maximal rate (R_e). Verification studies showed that these two constants were indeed affected in the predicted manner by experimenter-induced changes. For example, reductions in reward magnitude affected R_e whereas changes in response parameters such as force requirements for a lever press affected k (Heyman *et al.*, 1986). Thus, if DA receptor antagonists produce their effects on responding for food reward primarily by affecting ability to perform the response, k should be altered; if the effects of DA antagonists are to reduce the amount of reward, R_e should be altered.

Results of experiments using the matching law analysis to assess the effects of D₁ and D₂ antagonists on reward versus performance generally have revealed changes in both parameters. This was found with the D₂ antagonists pimozide and sulpiride and with the D₁ antagonist SCH 23390 (Heyman, 1983; Heymann *et al.*, 1986; Porter and Villanueva, 1989; Willner *et al.*, 1990). Morley *et al.* (1984) found that pimozide affected k but failed to find an effect on R_e , suggesting that the effects were attributable to performance decrements. However, Willner *et al.* (1990), by varying the number of variable interval components in the multiple schedule used to derive values of k and R_e , were able to show that results were more reliable with a larger number of components. They suggested that Morley *et al.* (1984) may have used too few components in their multiple schedule, leading to unreliable results. Willner *et al.* (1990) further suggested that the unequal session lengths for the two schedules may have complicated interpretation of the results of Morley *et al.* (1984). This latter point was supported by reports from Willner *et al.* (1989, 1990) of significant time-dependent effects of both D₁ and D₂ antagonists on R_e with relatively constant effects on k . The gradual effect of DA antagonists on responding points up the importance of session length in any analysis of their effects. These observations, suggesting that the effects of DA antagonist on reward may be

gradual (producing an extinction-like pattern), are in excellent agreement with studies reviewed above. The observation of an effect of D_1 and D_2 antagonists on motor performance in the matching law analysis is consistent with an extensive literature demonstrating that antagonists selective for either receptor subtype decrease locomotor activity (reviews: Beninger *et al.*, 1991; Clark and White, 1987; Daly and Waddington, 1992; Joyce, 1983; Keabian *et al.*, 1986; O'Boyle *et al.*, 1986; Waddington, 1989; Waddington and O'Boyle, 1987, 1989). Finally, the observation of an effect of D_1 and D_2 antagonists on R_e , the parameter reflecting amount of reward in the matching law analysis, supports the hypothesis that both receptor subtypes play an important role in mediating the effects of reward on behaviour.

Some studies have evaluated the effects of DA agonists acting preferentially at the D_1 or D_2 receptor on operant responding for food. The D_1 agonist SK & F 38393 and the D_2 agonists N-0437 or quinpirole reduced responding on variable interval (Hoffman and Beninger, 1989b) or fixed ratio schedules (Rusk and Cooper, 1988, 1989b). Hoffman and Beninger (1989b) found that quinpirole but not SK & F 38393 produced a gradual decrease in intrasession response rates; Rusk and Cooper (1988, 1989b) found no intrasession effects with either SK & F 38393 or N-0437. These results make it difficult to attribute the effects of D_1 and D_2 agonists to an action on reward in this paradigm. Furthermore, both D_1 and D_2 agonists have been found to decrease food consumption (Clifton *et al.*, 1989; Cooper *et al.*, 1990; Rusk and Cooper, 1989a, b; Timmerman *et al.*, 1989), raising the possibility that the effects of D_1 and D_2 agonists on operant responding for food may be secondary to their anorectic effect.

In conclusion, studies evaluating the role of DA receptor subtypes in lever pressing for food reveal that antagonists acting at either the D_1 or D_2 receptor produce extinction-like declines in responding. Studies using the matching law to assess drug effects similarly reveal a role for both DA receptor subtypes in reward. It is difficult to interpret the results of studies of the effects of DA receptor subtype-specific agonists on lever pressing for food since these agents produce anorexia. In general, results with antagonists implicate both D_1 and D_2 receptors in food reward-related incentive learning.

5.1.2 Lever pressing for water

Water-deprived animals have been trained to lever press for water reward and the effects of D_1 and D_2 antagonists evaluated. The D_2 antagonists pimozide, haloperidol, metoclopramide and sulpiride produced inter- and/or intrasession declines in responding for water presented according to a schedule of continuous reward (Gerber *et al.*, 1981; Ljungberg, 1987, 1990). Intrasession responding for water on a fixed ratio schedule was affected similarly by haloperidol (Ljungberg, 1987). Only one study has reported the effects of a D_1 antagonist on patterns of operant responding for water. Ljungberg (1990) found that continuously rewarded lever pressing for water decreased on the first day of

treatment with SCH 23390 but recovered over the next 3 days. In two studies, it was reported that SCH 23390 dose-dependently decreased water-rewarded lever pressing but patterns of responding were not presented (Ljungberg, 1989; Nakajima, 1986). As patterns of lever press responding for water have been evaluated with only one dose of SCH 23390 in only one study, there is a clear need for further studies in this area.

In conclusion, there is good evidence that treatments with antagonists specific for the D₂ receptor produce patterns of responding consistent with a block of the usual effects of water reward on behaviour. At present there is no evidence that treatments with a D₁ antagonist block the effects of water reward; results from the one relevant study suggest that the effects of SCH 23390 get weaker with repeated administration and testing, an effect opposite to that expected when a block of reward occurs.

5.1.3 Lever pressing for electrical stimulation of the brain (ESB)

The results of numerous studies support the conclusion that DA neurones play an important role in mediating the rewarding effects of ESB (reviews: Le Moal and Simon, 1991; Milner, 1991; Phillips and Fibiger, 1989; Stellar and Rice, 1989; Wise, 1982, 1991; Wise and Rompré, 1989). Some studies have reported the pattern of responding after treatment with pharmacological agents relatively specific for D₂ receptors making it possible to assess the contribution of this receptor subtype to reward-related incentive learning. Thus, it has been found that responding continuously rewarded with ESB delivered to various target regions (e.g. lateral hypothalamus, ventral tegmental area, medial forebrain bundle in posterior hypothalamus) shows an extinction-like intrasession decline following treatment with a number of D₂ antagonists, including haloperidol, pimozide, metoclopramide, raclopride, sulpiride and sultopride (Fenton and Liebman, 1982; Fouriez and Wise, 1976; Fouriez *et al.*, 1978; Franklin and McCoy, 1979; Gallistel *et al.*, 1982; Hori *et al.*, 1983; Nakajima and Baker, 1989). Although not reporting response patterns, Gallistel and Davis (1983) demonstrated that the effects of pimozide on responding for ESB were task specific, making it difficult to attribute the results to a drug-induced motor deficit. Zarevics and Setler (1979) used a sophisticated two-lever titration technique to show similarly that pimozide decreased the usual amount of ESB reward.

Animals are capable of responding for ESB presented on schedules of intermittent reward (Beninger *et al.*, 1977, 1978) but few studies have investigated the effects of DA antagonists in this paradigm. Phillips and Fibiger (1979) and Greenshaw *et al.* (1981) trained rats to respond for ESB on a variable interval or fixed interval schedule, respectively. In both studies, treatment with a D₂ antagonist led to a gradual extinction-like decrease in responding. To my knowledge, no studies have reported the effects of systemically delivered D₁ antagonists on patterns of lever pressing for ESB delivered according to schedules of continuous or intermittent reward. However, the effects of SCH 23390 and

haloperidol on ESB-produced continuous reward using spout contact as the required operant have been reported. Nakajima and McKenzie (1986) found that these compounds produced gradual extinction-like decreases in intrasession responding. The results from studies using schedules of continuous or intermittent reward seem to show a role for D_1 and D_2 receptors in mediating the effects of reward on behaviour.

Another paradigm that has been used extensively is the reward summation function. Variations in the number or frequency of pulses per train of ESB produce systematic changes in rates of lever press responding or running down an alley for ESB. Once frequency is increased to a threshold value, response rates show a rapid rise with each additional increase in frequency until an asymptote is reached (Gallistel, 1986; Stellar *et al.*, 1988). Validation studies have shown that manipulations that increase performance demands on the animals reduce the asymptote of the reward summation function without affecting the locus of rise (defined as the frequency needed to produce half-maximal levels of responding) whereas manipulations that reduce reward (e.g. a decrease in current level) shift the locus of rise to the right without affecting the asymptote (Gallistel, 1986; but see Fouriez *et al.*, 1990). Some studies have evaluated the effects of DA antagonists on lever pressing for ESB using the reward summation function. Both D_1 and D_2 antagonists have been reported to shift the locus of rise to the right (Gallistel, 1986; Nakajima and O'Regan, 1991; Rompré and Bauco, 1990). Similar effects of D_1 and D_2 antagonists have been reported when running was the ESB-rewarded response (Franklin, 1978; Nakajima and McKenzie, 1986; Stellar *et al.*, 1983).

One study has evaluated the effects of D_1 - and D_2 -specific *agonists* using the reward summation function. Previous studies have shown that the indirect-acting DA agent amphetamine shifts the locus of rise to the left (Gallistel and Karras, 1984). Nakajima and O'Regan (1991) similarly found that the D_2 agonists quinpirole and CV 205-502 shifted the locus of rise to the left. In contrast, the D_1 agonist SK & F 38393 was without significant effect at low doses and led to a cessation of responding at high doses. Results of these studies, contrary to the many studies using antagonists, might suggest that D_1 and D_2 receptors may be differentially involved in mediating the effects of reward on behaviour.

Some investigators have used central microinjection techniques in conjunction with tests of ESB reward to evaluate the possible contribution of DA in specific terminal regions. One approach has been to place electrodes into the ventral tegmental region, an area containing DA cell bodies, and cannulae into the nucleus accumbens, an important target structure for the DA cells of the ventral tegmental region. DA antagonists could then be injected into the nucleus accumbens and their effect on ESB reward evaluated. Using this approach, the D_1 antagonist SCH 23390 and the D_2 antagonist spiperone were shown to reduce ESB reward (Kurumiya and Nakajima, 1988; Mogenson *et al.*, 1979). N.L. Freedman and I have recently replicated this finding with SCH 23390 (Figure 1). Pure motor effects of the injections were ruled out by injecting some rats

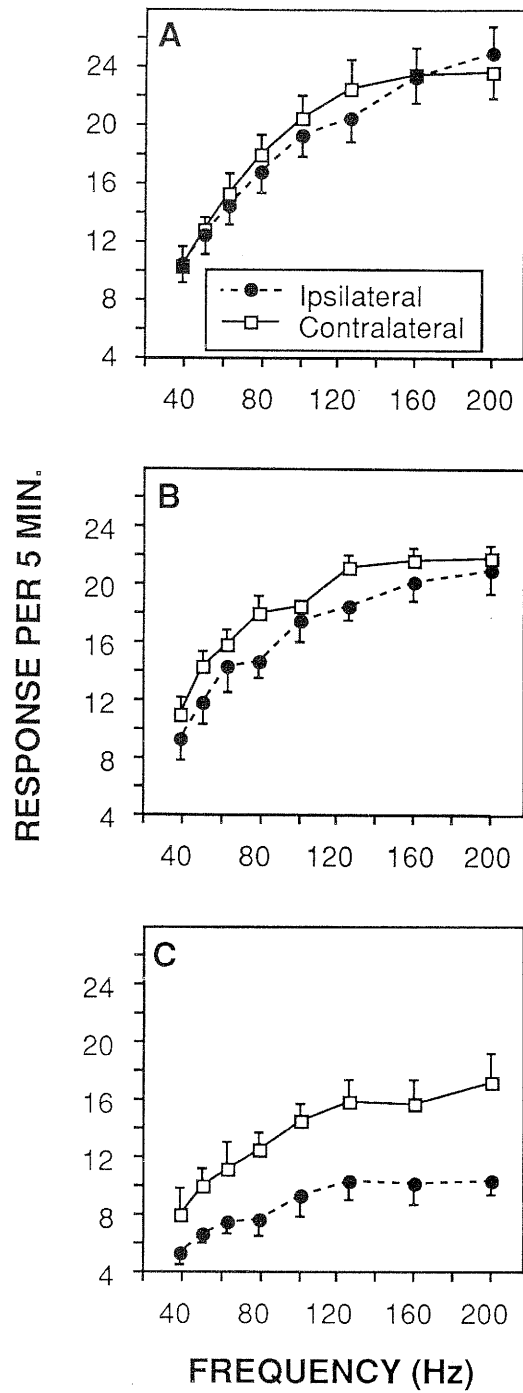
with the antagonists into the nucleus accumbens contralateral to the electrode; these injections had little influence on responding for ESB. Using a similar approach, Ferrer *et al.* (1983) placed both electrode and cannula into the DA terminal region of the medial frontal cortex. They found that the D₂ antagonist pimozide, when injected ipsilateral to the electrode, blocked ESB reward while contralateral injections had little effect. These studies further implicate both D₁ and D₂ receptors in mediating the effects of reward on behaviour.

In conclusion, experimenters studying animals responding for ESB reward have used many ingenious approaches to evaluate the possible contribution of D₁ and D₂ receptors. There is broad agreement in the results with antagonists relatively specific for D₁ or D₂ receptors; both block the usual effects of ESB reward on behaviour. There are few studies evaluating the effects of agonists. In the one study reported by Nakajima and O'Regan (1991), a differential effect of a D₁ versus D₂ agonist was found in the reward summation function. This result raises the intriguing possibility that studies using agonists in other paradigms may begin to reveal differential roles for D₁ and D₂ receptors in reward-related incentive learning.

5.1.4 Stimulant self-administration

Animals have been surgically prepared with chronic intravenous cannulae allowing them to self-inject stimulant drugs when placed into an operant test cubicle. They were attached by tubing to a syringe that was filled with the stimulant drug and mounted on an infusion pump. Animals could activate the pump by pressing a lever. With the use of this procedure rats and monkeys have been found to self-administer a number of dopaminergic agents, including apomorphine, amphetamine and cocaine (reviews: Koob and Goeders, 1989; Le Moal and Simon, 1991; Wise and Rompré, 1989). Results from studies using the self-administration procedure provide strong support for the hypothesis that DA is involved in reward-related incentive learning.

There is one aspect of this procedure that makes it especially attractive to experimenters trying to sort out the possible motoric versus reward-reducing effects of DA antagonist. That is that rates of stimulant self-administration *increase* with reductions in the concentration of injected drug. If a low dose of a DA antagonist produced an increase in rate, it would not be possible to attribute the effect of the DA antagonist to a motor impairment. Rather, it would be concluded that the rewarding effects of the stimulant were reduced. Precisely this effect has been seen when rats or dogs were self-administering cocaine or amphetamine and then treated with low doses of either the D₁ antagonist SCH 23390 or the D₂ antagonists spiperone, haloperidol, pimozide, sulpiride or metoclopramide (Corrigall and Coen, 1991; de Wit and Wise, 1977; Koob *et al.*, 1987; Risner and Jones, 1976; Roberts and Vickers, 1984, 1987; Yokel and Wise, 1975, 1976). These results suggest that stimulation of both D₁ and D₂ receptors may be necessary for reward to occur.



Two studies with monkeys self-administering cocaine have failed to find results in full agreement with those reported above. Woolverton and Virus (1989) found that both SCH 23390 and pimozide caused a decrease in self-administration and Woolverton (1986) reported that pimozide led to an increase whereas SCH 23390 produced a decrease. The discrepancy in the results with pimozide from these two studies may be related to details of the procedure, as suggested by Corrigan and Coen (1991). Thus, Woolverton and Virus (1989) used a time-out following cocaine infusions, possibly limiting the ability of monkeys to increase the dose by pressing the lever more. Woolverton (1986) did not use a time-out and observed increases in self-administration rates with low doses of pimozide, an effect frequently observed by others, as reviewed above.

This explanation also would account for the self-administration rate-decreasing effects of SCH 23390 reported in the study of Woolverton and Virus (1989) but not the apparent differential effects of SCH 23390 and pimozide in the study of Woolverton (1986). However, inspection of Woolverton's (1986) figure 1 reveals that in four of four monkeys receiving SCH 23390, there was a small increase in responding following a low dose of SCH 23390; in two cases, the magnitude of this increase was as great as or greater than that produced by pimozide. This observation and the findings of several investigators who have now reported that low doses of SCH 23390, like D₂ antagonists, have rate-increasing effects in animals responding to self-administered cocaine (Corrigan and Coen, 1991; Koob *et al.*, 1987), suggest that the negative results of Woolverton (1986) should be viewed with caution. It is noteworthy that a recent paper from the laboratory of Woolverton reports that SCH 23390 differentially affected cocaine- and food-maintained behaviour. This observation ruled out a purely motoric interpretation of the effects of SCH 23390. It was concluded that D₁ antagonists may decrease the rewarding properties of cocaine (Kleven and Woolverton, 1990).

A related paper reported effects of DA antagonists on self-administration in a complex paradigm. Bergman *et al.* (1990) trained monkeys to respond for cocaine self-administration on a second order schedule. According to this

Figure 1 Mean ($\pm$ SEM) responses per 5 min, rewarded with electrical stimulation of the brain (ESB) delivered to the ventral tegmental area, at frequencies ranging from 40 to 200 Hz, for groups ($n = 6$) implanted with cannulae in the ipsilateral (filled symbols) or contralateral (open symbols) nucleus accumbens. Each frequency was available for 5 min in ascending order during 40-min test sessions. There were three treatments: (A) no injections preceded the test session; (B) both groups were injected with drug vehicle (2.0 μ l) into the nucleus accumbens prior to the test session; (C) both groups were injected with the D₁ antagonist SCH 23390 (5.0 μ g in 2.0 μ l) into the nucleus accumbens immediately prior to the session. Analysis of variance revealed a significant group by treatment interaction; the interaction was due to the significantly greater effect of SCH 23390 in the nucleus accumbens on the side ipsilateral to the electrode (N.L. Freedman and R.J. Beninger, unpublished).

schedule, responding was rewarded with a conditioned stimulus previously associated with cocaine injection on a fixed ratio 10 or 30, depending on the monkey, until 10 min had elapsed. Completion of the first ratio after 10 min was rewarded with the conditioned stimulus and an intravenous injection of cocaine. After establishing dose-response curves for cocaine, the effects of SCH 23390 and the D₂ antagonist eliclopride were tested. Both drugs shifted the cocaine dose-response curves to the right, suggesting a blunting of the effects of cocaine reward. It was concluded that antagonism at either D₁ or D₂ receptors reduced the usual effects of reward on behaviour.

In some studies rats have been trained to self-administer extremely low doses of cocaine directly into DA-innervated regions of the brain. It was found that injections into the medial prefrontal cortex would support this behaviour (Goeders and Smith, 1983, 1986; Goeders *et al.*, 1986). Furthermore, the rewarding effects of these injections seemed to be mediated by D₂ receptors. Thus, the addition of the D₂ antagonist sulpiride, but not the D₁ antagonist SCH 23390, to the cocaine solution significantly reduced self-administration (Goeders and Smith 1983, 1986; Goeders *et al.*, 1986). Although few studies have been carried out, from these results it would appear that cocaine reward in the medial prefrontal cortex is mediated by D₂, not D₁, receptors.

Another approach has been to evaluate the ability of D₁ and D₂ receptor-specific agonists to support self-administration. In two studies it has been reported that the D₂ agonist bromocriptine, but not the D₁ agonist SK & F 38393, were self-administered by rats (Wise *et al.*, 1990; Woolverton *et al.*, 1984). SK & F 38393 was tested only in the Woolverton *et al.* (1984) study and further studies are needed to confirm these findings. One possible explanation is that systemic SK & F 38393 has an aversive effect in some brain region other than the nucleus accumbens (Section 5.1.1), leading to its failure to support self-administration. On the basis of the data available, it would appear that agonists acting at the D₂ but not the D₁ receptor are rewarding.

In conclusion, the self-administration paradigm provides a powerful tool for assessing the role of DA receptor subtypes in reward-related incentive learning. Results with antagonists were generally in good agreement with those from studies of lever pressing for food, water or ESB. Both D₁ and D₂ antagonists blunted the usual effects of stimulant reward on behaviour. In the case of agonists, few studies have been carried out. Based on the two studies available, it appears that D₂ but not D₁ agonists are capable of supporting self-administration behaviour.

5.1.5 Lever pressing for conditioned reward

When a neutral stimulus (e.g. tone or light) is repeatedly paired with a rewarding stimulus such as food, that stimulus, now termed a conditioned reward, can be shown to have acquired the properties of reward. Thus, animals will learn an operant response such as lever pressing when the only reward for that response

is the presentation of the conditioned reward. Of course, with each presentation of the conditioned reward in the absence of primary reward, the rewarding properties of the conditioned reward will weaken. Thus, the acquired response will quickly undergo an extinction-like decline with repeated testing (Mackintosh, 1974, pp. 233–237).

This paradigm has been used to assess the effects of DA agonists on responding for reward. One advantage over the use of lever pressing for food, for example, is that possible anorexic properties of DA agonists may be less of a problem when the rewarding stimulus is not food but a conditioned stimulus based on food. The procedure frequently used involves first pairing a neutral stimulus with food during several sessions. Then animals are given access to a chamber with two levers, presses on one of which produce the stimulus previously paired with food. If the lever producing that stimulus is pressed more, the food-associated stimulus can be said to be a conditioned reward. Numerous experiments have demonstrated this effect; additionally, treatments with a number of agents that augment DA neurotransmission have been found to produce a relatively specific enhancement of responding on the lever producing conditioned reward. This effect has been seen with amphetamine, pipradrol and several similarly acting drugs (Beninger *et al.*, 1980a, 1981; Hill, 1970; Mazurski and Beninger, 1986; Robbins, 1975, 1976, 1978; Robbins and Koob, 1978; Robbins *et al.*, 1983). Several recent studies have shown this effect with direct injections of amphetamine or DA into the nucleus accumbens (Cador *et al.*, 1991; Kelley and Delfs, 1991a, b; Taylor and Robbins, 1984, 1986). The relatively selective effect on responding on the lever producing conditioned reward suggests that DA may participate in mediating the effects of conditioned rewarding stimuli on behaviour.

An interesting dissociation has been noted between the effects of amphetamine, a DA agent with the action of enhancing the release and blocking the uptake of DA, and apomorphine, a dopamimetic acting at both D₁ and D₂ receptors (Cooper *et al.*, 1982). As reviewed above, amphetamine enhances responding for conditioned reward. Apomorphine, on the other hand, produces an indiscriminate increase in responding on both levers so that a conditioned reward effect is not seen (Mazurski and Beninger, 1986; Robbins *et al.*, 1983). This differential effect might be related to the different mechanisms of action of the two drugs (e.g. Stellar and Rice, 1989). However, it is noteworthy that DA itself, which, like apomorphine, would directly stimulate DA receptors, produced a specific enhancement of responding for conditioned reward when it was applied directly to the nucleus accumbens (Cador *et al.*, 1991). The reconciliation of these findings awaits further study.

In a series of studies, the effects of the D₁ agonist SK & F 38393 and the D₂ agonists quinpirole and bromocriptine on responding of rats for conditioned reward were assessed (Beninger and Rinaldi, 1992). Results revealed that the D₂ agonists, like amphetamine, enhanced responding for conditioned reward. SK & F 38393, on the other hand, appeared to impair responding for conditioned reward. The finding that systemically administered direct-acting D₂ agonists

produced amphetamine-like effects was surprising since systemic apomorphine, also direct acting, led to a loss of specific responding for conditioned reward. This finding and the observation that SK & F 38393 appeared to lead to a loss of responding for conditioned reward might suggest that apomorphine produced an impairment of the conditioned reward effect through its action at D₁ receptors. This possibility will be discussed in further detail in Section 5.3.

5.1.6 Place conditioning

One of the simplest paradigms for assessing reward-related incentive learning is place conditioning. The test apparatus often consists of a rectangular box with two distinct sides attached by a tunnel that can be closed with guillotine doors. After several sessions of pairing one side with a rewarding stimulus such as food or a stimulant drug, animals are given access to both sides by removing the guillotine doors. Incentive learning is said to have taken place if animals are observed to spend significantly more time on the side previously associated with the rewarding stimulus. There is now a large body of data showing that DA plays an important role in reward-related incentive learning assessed with the use of place conditioning procedures (reviews: Carr *et al.*, 1989; Hoffman, 1989).

Conditioned place preferences based on systemic injections of amphetamine have been found to be blocked by both D₁ and D₂ antagonists, including SCH 23390, and haloperidol, pimozide, sulpiride and metoclopramide (Hiroi and White, 1991; Hoffman and Beninger, 1989a; Mackey and van der Kooy, 1985; Mithani *et al.*, 1986; Spyraiki *et al.*, 1982b). The rewarding effects, in a place conditioning paradigm, of some non-dopaminergic compounds also have been shown to be affected by receptor subtype-specific DA antagonists. The μ -opioid agonist morphine produced a place preference that was blocked by SCH 23390 but not sulpiride, spiperone or haloperidol (Mackey and van der Kooy, 1985; Shippenberg and Herz, 1987, 1988). Rewarding effects of the 5-hydroxytryptamine (5-HT_{1A}) receptor agonist 8-hydroxy-2-(di-*n*-propylamine) tetralin were similarly blocked by SCH 23390 but not sulpiride (Shippenberg, 1991). On the other hand, the rewarding effects of the benzodiazepine diazepam were blocked by the D₂ antagonist haloperidol; a D₁ antagonist was not studied (Spyraiki and Fibiger, 1988). These results suggest that D₁ and D₂ receptors may play a role in mediating reward produced by amphetamine and strongly implicate each receptor subtype in mediating the rewarding effects of some non-dopaminergic agents.

Some studies have reported that animals show an aversion to an environment associated with the pharmacological effects of the D₁ antagonists SCH 23390 and A-69024 (Shippenberg and Herz, 1988; Shippenberg *et al.*, 1991) although this effect of SCH 23390 was not seen in another study (Hoffman and Beninger, 1989a). The D₂ antagonists sulpiride, haloperidol, pimozide and spiperone have been reported to be neutral in place conditioning tests (Bozarth and Wise, 1981; Martin-Iverson *et al.*, 1985; Shippenberg and Herz, 1988; Shippenberg *et al.*,

1991; Spyraiki and Fibiger, 1988; Spyraiki *et al.*, 1982a, b) but one study found a place preference with the D₂ antagonist metoclopramide (Hoffman and Beninger, 1989a). Shippenberg *et al.* (1991) used intracranial microinjection techniques to show that injections of SCH 23390 into the nucleus accumbens but not the caudate-putamen, ventral tegmental area or medial prefrontal cortex produced a place aversion. Overall, it appears that D₁ and D₂ antagonists may differ with respect to their ability to produce place aversions, D₁ antagonists being effective and D₂ antagonists generally having little effect. The localization of these effects to the nucleus accumbens is in good agreement with related studies with agonists (see below).

The ability of agonists with relative specificity for D₁ or D₂ receptors to produce place conditioning has also been evaluated. It has been found that the D₂ agonists bromocriptine and quinpirole produced a place preference (Hoffman and Beninger, 1988, 1989a; Hoffman *et al.*, 1988; Morency and Beninger, 1986; White *et al.*, 1991). The D₁ agonist SK & F 38393, on the other hand, was found to produce an aversion (Hoffman and Beninger, 1988, 1989a; White *et al.*, 1991). These results seemed to indicate a differential role for D₁ and D₂ receptors in place conditioning; however, recent studies using central injection techniques have challenged this conclusion.

Carr and White (1983, 1986) were the first to show that amphetamine place conditioning could be produced by microinjections into the nucleus accumbens but not a number of other DA-innervated structures, including the dorsolateral, anteromedial or lateroventral caudate, medial prefrontal cortex, amygdala and region of the area postrema. Recently, researchers in White's laboratory have shown that place conditioning can be produced by either the D₁ agonist SK & F 38393 or the D₂ agonist quinpirole injected directly into the nucleus accumbens (White *et al.*, 1991). The discrepant results with systemic versus intra-accumbens SK & F 38393 might suggest that the aversive effects of this drug are related to an action in the periphery or an action in some other part of the central nervous system. The first of these alternatives was tested by Hoffman and Beninger (1988), who evaluated the effects of systemic SK & F 82526 (fenoldopam), a D₁ agonist that does not readily cross the blood-brain barrier, in a place conditioning experiment. Results revealed no effect. This suggests that the aversive effects of peripherally administered SK & F 38393 may result from its action in some region of the central nervous system other than the nucleus accumbens. It would appear that direct stimulation of either D₁ or D₂ receptors in the nucleus accumbens leads to reward-related learning in place conditioning studies.

Finally, in one study the effects of DA receptor subtype-specific antagonists on receptor subtype-specific agonist-produced place conditioning have been evaluated. Hoffman and Beninger (1989a) found that at least one dose of either SCH 23390 or metoclopramide was effective in antagonizing the place preference or aversion produced by systemic quinpirole or SK & F 38393, respectively.

In the previous study, antagonists and agonists were given during conditioning sessions. In a recent paper, Hiroi and White (1991) compared the effects of DA

antagonists giving during conditioning to their effect when given during the test phase on the establishment and expression, respectively, of place preference conditioning produced by intra-accumbens amphetamine. Results revealed that systemic injections of the D₁ antagonist SCH 23390 and the D₂ antagonists sulpiride and metoclopramide dose-dependently blocked both the establishment and expression of place preference conditioning. For the D₂ antagonists, effective doses for blocking the expression were higher than those needed to block establishment. Although the differential effects were weaker, the D₁ antagonist seemed to produce a similar profile; at one dose (120 µg/kg) SCH 23390 blocked establishment but not expression of conditioning. Hiroi and White (1991) also showed that intra-accumbens injections of DA receptor subtype-specific antagonists were effective in blocking the expression of place preference conditioning. These results show that both D₁ and D₂ antagonists are effective in blocking place conditioning and replicate previous studies showing that the expression of incentive conditioning is more resistant to the effects of DA antagonists than its establishment (Beninger and Hahn, 1983; Horvitz and Ettenberg, 1991).

In summary, place conditioning produced by amphetamine was blocked by either D₁ or D₂ antagonists. Both D₁ and D₂ agonists produced place preferences but the D₁ agonist had to be given directly into the nucleus accumbens to produce this effect. Place conditioning produced by agonists at either DA receptor type appears to be blocked by antagonists at either receptor type.

5.1.7 Conditioned activity

When animals receive treatments with stimulant drugs repeatedly in a particular environment, stimuli in that environment apparently acquire the ability to elicit responses like those produced by the drug itself (e.g. increased locomotor activity). This can be seen in two ways: (1) as an enhanced response to the drug upon repeated administrations in the test environment (i.e. sensitization); or (2) when animals are returned to the drug-associated environment in a drug-free state, as a drug-like response (conditioned activity). Control animals with a similar drug history but never having received the drug in the test environment do not show these effects. Thus, the observed response in the animals previously receiving the drug–environment pairings is a genuine conditioned effect rather than an unconditioned effect related to previous treatments with the drug. This section will be concerned with sensitization and conditioned activity, phenomena that can be understood as further examples of incentive learning (Stewart, 1992; Stewart and Vezina, 1988).

The establishment of sensitization with the DA agents amphetamine or methamphetamine has been reported to be blocked by co-administration with the D₁ antagonist SCH 23390 or the D₂ antagonist YM 09151-2 (Hammamura *et al.*, 1991; Ujike *et al.*, 1989). In contrast, others have found that the establishment of conditioned activity or sensitization following repeated injections

of amphetamine was blocked by co-administration of SCH 23390 but not the D₂ antagonists metoclopramide, pimozide and Ro 22-2586 (Drew and Glick, 1990; Mazurski and Beninger, 1991; Vezina and Stewart, 1989). In agreement with these findings with D₁ antagonists, one study showed that the direct microinjection of SCH 23390 into the ventral tegmental area blocked the establishment of sensitization to the stimulant effects of amphetamine (Stewart and Vezina, 1989). The experiments that reported that D₂ antagonists failed to block the establishment of conditioned activity or sensitization found that D₂ antagonists were effective in decreasing the unconditioned effects of amphetamine. From this it would appear that a manifestation of the unconditional stimulant effect of amphetamine is not necessary for it to produce conditioned effects.

One recent study has reported that neither a D₁ nor a D₂ antagonist was effective in blocking the establishment of conditioned activity based on amphetamine (Martin-Iverson and McManus, 1990). The findings with SCH 23390 are inconsistent with those from a number of other studies. Perhaps the 20 µg/kg dose of racemic SCH 23390 used by Martin-Iverson and McManus (1990) was lower than that used in other studies. Thus, with one exception, the papers reporting that SCH 23390 blocked the establishment of conditioned activity or sensitization used doses of the racemate ranging from 40 to 500 µg/kg. The one exception is the paper by Drew and Glick (1990). They found effects with SCH 23390 doses of 1.0 and 10 µg/kg but used many fewer conditioning sessions than Martin-Iverson and McManus (1990). If drug dose interacts with amount of conditioning, this would provide a possible explanation for these inconsistent data. In general, results seem to suggest that intact D₁ receptors but possibly not D₂ receptors are necessary for the establishment of conditioned activity or sensitization to amphetamine.

It has been found that either the D₁ agonist SK & F 38393 or the D₂ agonists quinpirole or (+)-4-propyl-9-hydroxynaphthoxazine (PHNO) can produce conditioned activity (Martin-Iverson and McManus, 1990; Mazurski and Beninger, 1991). The effect of SK & F 38393 was blocked by SCH 23390 but not metoclopramide; the effects of quinpirole were blocked by metoclopramide but, surprisingly, not by SCH 23390 (Mazurski and Beninger, 1991). The effects of PHNO were blocked by neither SCH 23390 nor haloperidol (Martin-Iverson and McManus, 1990). The failure of SCH 23390 to block the effects of PHNO may be related to the dose as discussed above; alternatively, D₁ antagonists may not block D₂ agonist-produced conditioned activity, as reported by Mazurski and Beninger (1991). The failure of haloperidol to block conditioning based on PHNO was surprising, as these two compounds should compete for the same receptors. Perhaps the dose of haloperidol was also too low. In the study of Martin-Iverson and McManus (1990), animals treated with haloperidol and PHNO during conditioning were more active than vehicle-treated controls, providing some support for this speculation. It is difficult to draw conclusions from the current small number of studies in this area.

Some researchers have found that conditioned activity based on stimulant drugs like amphetamine is more resistant to the effects of DA antagonist than the unconditioned activity produced by the drug itself. Thus, it has been found that SCH 23390 or haloperidol blocked the unconditioned effects of apomorphine but not the conditioned effects (Carey, 1990). Others have reported that the D₂ antagonists pimozide or haloperidol produced this effect in animals conditioned with apomorphine or amphetamine (Beninger and Hahn, 1983; Welsh-Kunze *et al.*, 1988). These results might suggest that during conditioning DA receptors mediate a plastic change in the brain that is non-dopaminergic.

In summary, both D₁ and D₂ agonists produce conditioned activity. In most cases, co-treatment with D₁ but not D₂ antagonists during conditioning sessions seems to block the establishment of conditioned activity or sensitization responses.

5.1.8 Conditioned avoidance responding

Animals quickly learn to avoid noxious stimuli. Acquisition of this ability may involve different types of learning. Thus, animals may learn the association between stimuli signalling the noxious event and the noxious event itself and they may learn the location of safety. Safety is rewarding and safety-related stimuli may acquire the ability to elicit approach and other responses that lead to successful avoidance. It appears that DA plays an important role in this latter incentive learning component of avoidance responding but not the learning of associations among stimuli (Beninger, 1983, 1989a, b, 1991).

Just as was the case in evaluating the effects of DA antagonists on responding for food, water or ESB, the pattern of avoidance responding seen in animals treated with DA antagonists provides insight into effects that may not be simply motor. Thus, trained animals have been observed to show significant intra- and/or intersession declines in avoidance responding following treatment with D₂ antagonists, including pimozide, haloperidol, metoclopramide and spiperone (Anisman *et al.*, 1982; Beninger *et al.*, 1980b, c, 1983; Blackburn and Phillips, 1989, 1990; Carey, 1987; Carey and Kenney, 1987a, b; Fibiger *et al.*, 1975; Hillegaart *et al.*, 1987; Ranje and Ungerstedt, 1977; Sanger, 1986, 1987). Similar effects have been seen in animals trained to lever press to avoid shock and then treated with haloperidol, metoclopramide, sulpiride or sultopride (Hori *et al.*, 1983). This extinction-like pattern of responding is consistent with a block of the usual effects of reward on behaviour.

There is ample evidence that D₁ antagonists also block avoidance responding. Thus, a dose-dependent decrease in avoidance responding of rats or monkeys has been seen following treatments with the D₁ antagonists SCH 23390, SCH 39166 and SCH 12697 (Breese *et al.*, 1990; Chipkin *et al.*, 1988; Iorio *et al.*, 1983, 1991; McQuade *et al.*, 1991). The authors of these studies emphasized that the D₁ antagonists produced effects on avoidance responding at doses that neither affected escape responses nor produced catalepsy, making it difficult to attribute

avoidance deficits to an action of the drugs on motor capacity. Unfortunately, in none of these studies were changes over time reported. In one study, Sanger (1987) evaluated the effects of SCH 23390 and haloperidol on avoidance responding of trained rats and separated the first ten-trial session into two five-trial blocks. He found that the D₂ antagonist produced a significant decrease in responding from the first block to the second; SCH 23390, on the other hand, although producing an overall decrease in avoidance responding and a small intrasession decline at one dose, did not produce a significant intrasession decline. Sanger (1987) also evaluated the effects of SCH 23390 and haloperidol over 4 days of avoidance testing and found that the D₂ antagonist but not the D₁ antagonist produced an intersession decline. These results led Sanger (1987) to conclude that antagonists relatively selective for the two receptor subtypes acted in a dissimilar manner.

From these studies it is clear that D₂ antagonists produce extinction-like decreases in avoidance responding consistent with an effect of the drug on reward-related incentive learning. It is equally clear that D₁ antagonists produce decreases in avoidance responding but there is currently no strong evidence to tie this effect to an action of the drugs on incentive learning. More studies with D₁ antagonists in avoidance paradigms are eagerly awaited.

5.1.9 Post-training treatments

There is one final paradigm in which DA receptor subtype-specific agonists have been evaluated that will be covered in this section. The post-training treatment literature is extensive and only a few recent studies will be the focus of this section. It may not be immediately clear how these studies relate to those reviewed above. However, an attempt to link these studies to those reviewed above and to show how their results can be understood in relation to possible molecular mechanisms involved in DA-mediated reward-related incentive learning will be made in the final section of this chapter.

The presentation of rewarding stimuli a short time *after* a brief period of training in some tasks repeatedly has been found to lead to improved recall of that task when retesting was carried out a day or more later. This has been found whether the task involved classical or operant conditioning and whether it involved appetitive or aversive stimuli (review: Huston *et al.*, 1977). For example, post-training memory-improving effects have been seen with a number of rewarding stimuli, including ESB (Coulombe and White, 1980, 1982; Huston and Mueller, 1978) and glucose (Messier and White, 1984). Further studies implicated DA in these effects. Thus, memory improvement was found with ESB when electrodes were placed into the substantia nigra (Staubli and Huston, 1978) or into the nigrostriatal dopaminergic pathway (Major and White, 1978). Further studies showed that post-training injections of the DA-releasing agent amphetamine could produce memory enhancement and that the effect was

abolished by lesions of the nigrostriatal pathway (Carr and White, 1984; White, 1988). It appeared that the post-training stimulation of DA neurones led to enhanced memory.

Subsequent studies assessed the role of DA receptor subtypes. White and Major (1978) found that the D₂ antagonist pimozide blocked the memory-improving effects of ESB. Packard and White (1989) reported that post-training systemic treatments with the D₂ agonist quinpirole but not the D₁ agonist SK & F 38393 improved memory on two different radial maze tasks. White and Viaud (1991) reported similar differential effects of the two agonists injected directly into the caudate nucleus. However, in a recent study, Packard and White (1991) found memory-improving effects of both D₁ and D₂ agonists injected into either the caudate or the hippocampus. This latter study used higher doses of SK & F 38393 than those used in the earlier studies, possibly accounting for the significant effects in the recent study. These studies seem to be leading to the conclusion that post-training stimulation of either D₁ or D₂ receptors may lead to memory enhancement.

One final study may be relevant to this section. Weldon *et al.* (1991) trained rat pups in an odour conditioning task by pairing odours with a rewarding tactile stimulus. They observed that post-pairing injections with the D₁ antagonist ($\pm$) SK & F 83566 but not the D₂ antagonist spiperone impaired conditioning assessed 1 day later. This interesting finding strongly implicates D₁ receptors as playing a role in the formation of memories.

Post-training treatment experiments have progressed over the last 20 years from implicating rewarding stimuli in memory improvement to beginning to identify a role for DA in this effect and the possible contribution of DA receptor subtypes. Studies to date have not ruled out either subtype. There is at least some evidence in favour of both D₁ and D₂ receptors being involved in the process of establishing memories.

5.1.10 Summary

D₁ antagonists have been found to block the usual effects of reward in animals lever pressing for food, ESB and stimulant self-administration. They block place conditioning and conditioned activity produced by stimulant drugs. Their effects in conditioned avoidance paradigms have not been studied extensively; the one available study does not provide evidence that a block of D₁ receptors leads to an extinction-like effect. On the other hand, the one study of post-training treatments with a D₁ antagonist implicates D₁ receptors in memory.

D₂ antagonists block the usual effects of reward in animals lever pressing for food, ESB and stimulant self-administration. They block place conditioning and conditioned activity produced by stimulant drugs. They produce an extinction-like decrease in avoidance responding and block the memory improving effects of post-training reward.

D₁ agonists have little effect or block responding for ESB in the reward

summation paradigm and may impair responding for conditioned reward. In the one available study, they failed to support self-administration. They have been reported to support place conditioning and conditioned activity. When given immediately following a brief training trial, they improve memory assessed a day or more later.

D₂ agonists, like amphetamine, shift the reward summation function to the left and enhance responding for conditioned reward. They support self-administration, place conditioning and conditioned activity. They have been found to produce memory-improving effects when given after the training of a number of tasks.

5.2 Possible mechanism for dopamine-mediated incentive learning

Throughout the twentieth century, learning theorists have proposed various schemes for understanding the influence that reinforcing or rewarding stimuli have on behaviour (Mackintosh, 1974). There has never been a generally agreed upon scheme, perhaps partly because previous theories were not constrained by knowledge of the anatomical organization and neurochemical systems of the brain. Research over the past 20 years providing strong evidence that the neurotransmitter dopamine forms a critical link in the neurocircuitry mediating the effects of reward on behaviour, in the context of extensive refinements in knowledge about the anatomical organization and neurochemistry of the brain, provide new possibilities for understanding mechanisms underlying the effects of reward on behaviour. One such mechanism will be proposed in this section. In Section 5.3, the results reviewed in Section 5.1 will be considered in the context of this mechanism.

5.2.1 Reward and dopamine

As reviewed above, many data support the conclusion that DA is involved in reward-related incentive learning. It might be possible, therefore, to measure elevated levels of DA or its metabolites in various DA terminal regions of the brain in association with the presentation of rewarding stimuli. This approach has been taken by a number of researchers and results provide strong evidence that DA is released in association with the presentation of unconditioned or conditioned rewarding stimuli (reviews: Phillips *et al.*, 1989, 1991). In subsequent sections, this reward-related DA release will be referred to as the DA signal.

The earliest results were provided by neurochemical studies using postmortem tissue. Levels of DA metabolites and/or content of DA were measured in a number of brain regions of rats that had eaten food just prior to being killed. Results revealed increased levels of DA metabolites and/or decreased content of

DA, both indicative of increased DA neurotransmission, in the nucleus accumbens, caudate-putamen and/or amygdala (Blackburn *et al.*, 1986; Church *et al.*, 1986; Heffner *et al.*, 1980; Holmes *et al.*, 1989). Similar results were seen in animals lever pressing on various schedules for food, water or ESB reward just prior to being killed (Church *et al.*, 1986; Heffner and Seiden, 1980; Heffner *et al.*, 1981; Phillips *et al.*, 1987). Some studies reported that neurochemical indices of DA release in the nucleus accumbens or caudate-putamen were increased in rats exposed to conditioned stimuli signalling food, i.e. conditioned rewarding stimuli, without presentation of food itself, just prior to death (Blackburn *et al.*, 1989; Holmes *et al.*, 1989). A similar effect was seen in rats exposed to a conditioned stimulus for the DA agonists amphetamine or apomorphine prior to being killed (Schiff, 1982). These data strongly suggest that unconditioned and conditioned rewarding stimuli can lead to DA release, i.e. can produce a DA signal, in some regions of the brain.

A number of electrophysiological studies have recorded from DA cells in the ventral tegmental area of monkeys or rats during the performance of behavioural tasks rewarded with food. Results have generally shown that these cells often increase their firing rate in response to stimuli signalling reward (Fabre *et al.*, 1983; Miller *et al.*, 1981; Nishino *et al.*, 1987). For further discussion of these studies see Grace (1991).

Recently developed *in vivo* electrochemical and microdialysis techniques have made it possible to monitor intracerebral levels of DA and DA metabolites in active animals. Results have shown an elevation of DA and/or DA metabolites in the caudate-putamen or nucleus accumbens for food- or water-deprived rats eating or drinking (Keller *et al.*, 1983; Phillips *et al.*, 1991). Phillips *et al.* (1991) also found that DA levels increased during a conditioned stimulus signalling food, prior to food consumption. Others showed that caudate or accumbens levels of DA or DA metabolites increased in rats lever pressing for food or ESB (Joseph and Hodges, 1990; Joseph *et al.*, 1989; Nakahara *et al.*, 1989; Phillips *et al.*, 1989). A number of recent studies have evaluated brain DA in association with male sexual behaviour. Results have revealed increases in nucleus accumbens DA during a period of exposure to stimuli associated with a sexually receptive female or during sexual reward (Louilot *et al.*, 1986, 1991; Mas *et al.*, 1990; Pfaus *et al.*, 1990; Pleim *et al.*, 1990). Results from studies using *ex vivo* and *in vivo* techniques provide strong evidence that DA neurones are activated in association with the presentation of unconditioned or conditioned rewarding stimuli, producing a reward-related DA signal.

5.2.2 Dopamine in the brain

The anatomical organization of the brain's dopaminergic systems has been worked out in great detail (e.g. Lindvall, 1979). Although DA is to be found in many areas, projections from ventral mesencephalic nuclei to basal forebrain structures collectively termed the striatum have received much attention with

respect to reward-related learning. Another DA-innervated area that has been found to play a role in reward is the medial prefrontal cortex (e.g. Ferrer *et al.*, 1983; Goeders and Smith, 1983, 1986; Goeders *et al.*, 1986). This area will not be considered further in the following; this is not intended to suggest that DA in the medial prefrontal cortex is any less important in reward-related learning. The focus for this section will be DA in the striatum.

The striatum consists of the caudate-putamen, nucleus accumbens and olfactory tubercle. These areas receive massive neo- and allocortical input and project to dorsal and ventral pallidum, respectively. They are also major targets of the dopaminergic cells of the substantia nigra and the ventral tegmental area (Heimer and Wilson, 1975; Heimer *et al.*, 1982; Nauta and Domesick, 1984). As DA has been found to play an important role in reward-related incentive learning and many studies have implicated dopaminergic projections to the striatum, it may be there that DA produces changes in connectivity that constitute the substrate of incentive learning.

In recent years, many details of the synaptic, neurochemical and ultrastructural organization of the striatum have become known (e.g. Bolam, 1984; Graybiel, 1990; Smith and Bolam, 1990). For present purposes, the focus will be on a subset of afferents of the most common neurones of the striatum, the medium spiny cells. These striatal efferent cells receive glutamatergic inputs from the cortex and dopaminergic inputs from the ventral mesencephalon (Figure 2). The dopaminergic inputs are noteworthy in that they come from a relatively small number of cells that have been found to arborize extensively; it has been estimated that a single DA neurone may form as many as 500 000 to 1 000 000 synaptic connections in the striatum (Andén *et al.*, 1966; Doucet *et al.*, 1986). The ultrastructural studies of Bolam and his co-workers have revealed that glutamatergic terminals are found on dendritic spines of the medium spiny cells; furthermore, dopaminergic terminals have been found on the same spines (Smith and Bolam, 1990). This arrangement may provide a locus where DA can modify the effectiveness of cortical afferents to the striatum.

5.2.3 Dopamine and glutamate

In recent years, *in vitro* electrophysiological studies have shown that DA may modify the effectiveness of glutamate synapses. Using fish retinal cells, Knapp and Dowling (1987) found that DA enhanced ionic conductances gated by L-glutamate or the glutamate receptor subtype agonist kainic acid. Furthermore, they found that this effect was produced by application of a membrane-permeable form of cAMP. It is known that DA receptors in the fish retina can stimulate the formation of cAMP, making them, by definition, of the D₁ subtype. Thus, DA, acting via D₁ receptors, stimulated second messenger formation that led to modification of a glutamate synapse. The authors concluded that their data '... provide the first direct evidence for dopaminergic regulation of excitatory amino-acid neurotransmission in the vertebrate nervous system.' Two subsequent

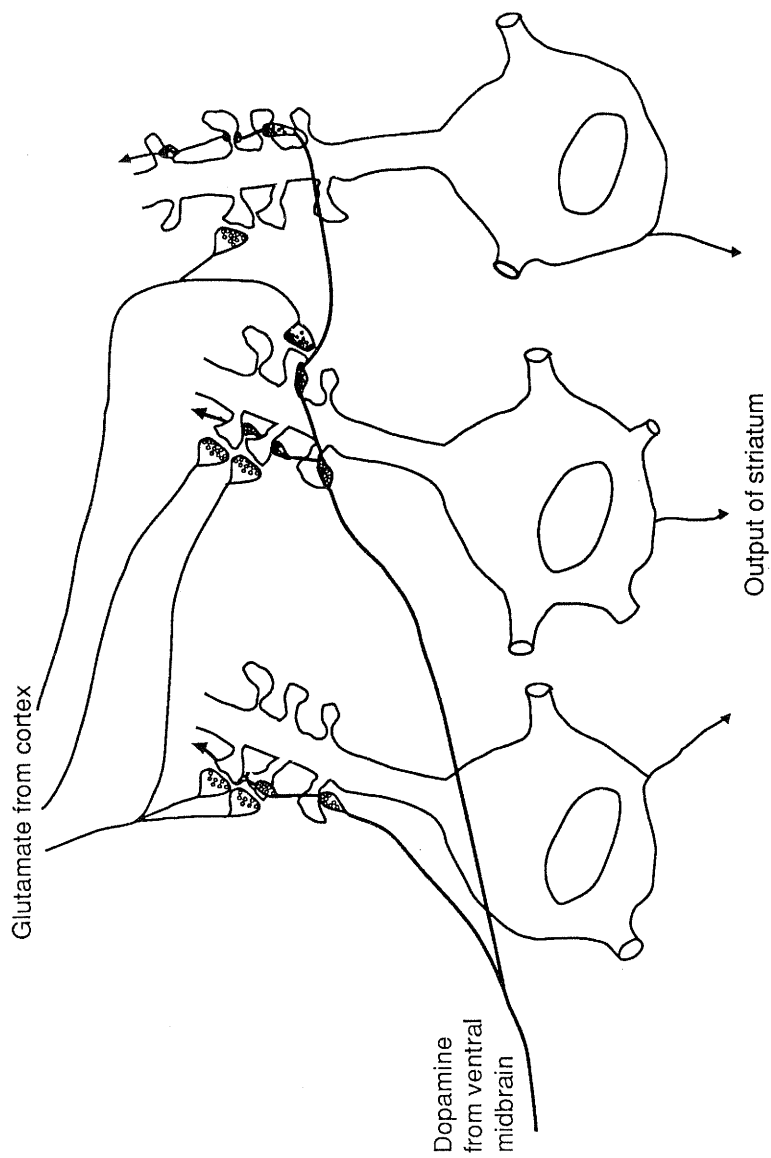


Figure 2 Three striatal medium spiny neurones and some of their afferents. These include glutamatergic inputs from the cortex making axospinous contact with dendritic spines that also receive dopaminergic synapses from the ventral midbrain. There are additional inputs that are not shown (see Smith and Bolam, 1990).

papers elaborated on this basic finding. In one, it was shown that intracellular application of a cAMP-dependent protein kinase similarly modified the response of the cell to kainate. This suggested that DA may modify kainate-type glutamate receptor-gated channels by a phosphorylation event (Linman *et al.*, 1989). In the other, the authors sought to identify the mechanism by which DA enhanced channels activated by kainate. Results revealed that DA led to a change in the kinetics of the ion channel to favour the open state (Knapp *et al.*, 1990).

Two recent studies used cultured hippocampal cells to show a similar DA-produced modification of a glutamate synapse. In one, the response to kainate was shown to be enhanced by stimulation of cAMP-dependent protein kinase or by intracellular injection of the catalytic subunit of protein kinase. An inhibitor of protein phosphatase also enhanced the response to kainate (Wang *et al.*, 1991). In the other, forskolin, an activator of adenylyl cyclase, modified responses to kainate. Cyclic AMP-dependent protein kinase similarly modified kainate responses and the mechanism was identified as an increased opening frequency and open time of kainate channels, similar to the effect reported above for retinal cells (Greengard *et al.*, 1991). The authors concluded that glutamatergic neurotransmission could be modulated by a variety of receptors that are coupled to adenylyl cyclase and the activation of protein kinases. An obvious candidate is the D₁ receptor.

5.2.4 A possible mechanism

Making the leap from structure to function is always difficult. In the present enterprise, making this leap will require oversimplifications and generalizations; however, these will provide a general framework allowing for a focus on the striatum and the possible molecular mechanisms that may take place there in association with reward-related incentive learning.

Sensory stimuli are processed by the central nervous system from receptor organs often through several sensory nuclei, sometimes with parallel pathways concerned with different aspects of the sensory input, ultimately to the cortex where there may be many additional levels of processing as there is in the case of vision and audition (e.g. Imig and Morel, 1983; Maunsell and Newsome, 1987). As mentioned in Section 5.2.2 above, one of the major projection areas of the cortex is the striatum. Therefore, it is suggested that much of the input to the striatum from the cortex be viewed as sensory in nature, bringing to the striatum representations of events in the environment that are encountered by an animal. It is further suggested that striatal output be viewed as motor, influencing locomotion in part through a series of brainstem nuclei (Garcia-Rill, 1986). There is a long tradition in anatomy of viewing the striatum as part of the extrapyramidal motor system and many pathologies of the striatum produce neurological disorders with a motor component (e.g. Garcia-Rill, 1986). These considerations would make it possible to view the striatum as a sensory-motor interface in the brain.

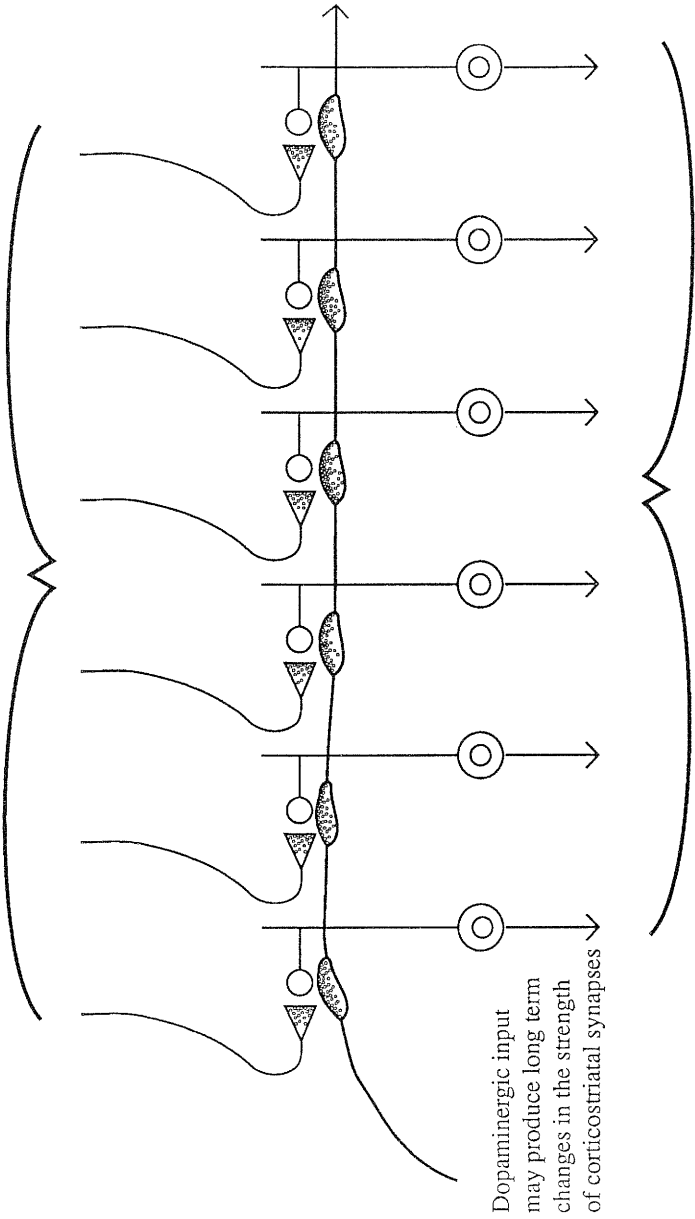
Dopaminergic neurones project heavily to the striatum. They are well positioned to modulate the influence that striatal inputs have on striatal outputs. From the present point of view, DA may modify the influence that sensory events have on motor behaviour of an animal. Numerous investigators have drawn similar conclusions concerning the modulating influence of DA in the striatum (e.g. Divac *et al.*, 1987; Lidsky *et al.*, 1985; Mogenson, 1984; West *et al.*, 1987). Figure 3 is a schematic representation of the connections of glutamatergic corticostriatal projections with the dendritic spines of striatal medium spiny cells and the common dopaminergic connection with each spine, as was illustrated in Figure 2. When reward-related incentive learning occurs, a reward-related DA signal may lead to a modification of these glutamatergic synapses.

As an animal encounters various different stimuli in its environment, different sets of cortical cells would be expected to be activated. Since the cortex projects heavily to the striatum, an associated set of corticostriatal glutamatergic synapses would be expected to be active. When reward occurs producing the DA signal, DA would be expected to be released widely in the striatum because of the extensive arborization of DA axons there. This event could modify the strength of the *most recently active* corticostriatal glutamatergic synapses forming the structural basis of incentive learning. One requirement for this scheme is that there be a means for selection of the most recently active synapses, which are the only ones to be modified.

Previous authors have suggested that activity in corticostriatal synapses may produce a state of readiness during which these synapses may be modifiable (Miller, 1981; Miller *et al.*, 1990; Wickens, 1990). Wickens (1990) proposed that the state of readiness might be mediated by the concentration of calcium ($[Ca^{2+}]$) in the spines of striatal medium spiny neurones. In an earlier paper, Wickens (1988) argued that spine $[Ca^{2+}]$ may be brought to the critical level for permitting synaptic modification by a conjunction of activity at the glutamate input to the spine and dendritic depolarization, fulfilling the elements of the rule for synaptic modification proposed by Hebb (1949). Wickens (1990) proposed that spine $[Ca^{2+}]$ might decrease to a level ineffective for synaptic modification within a short time following synaptic activation (e.g. 1.0 s).

Reward-related incentive learning might take place as follows. When reward occurs producing a DA signal in the striatum, glutamatergic axospinous synapses activated by the most recently encountered environmental stimuli would be in a state of readiness. The action of DA at D_1 receptors would lead to the stimulation of cAMP formation which, in turn, would activate cAMP-dependent protein kinase. This would lead to the phosphorylation of proteins that may participate in modifying the effectiveness of the glutamate synapse. Wickens (1990) suggested that one candidate for phosphorylation by the action of cAMP-dependent protein kinases is the DA- and cAMP-regulated phosphoprotein DARPP-32 (Hemmings *et al.*, 1987). This protein, when in the phosphorylated state, inhibits protein phosphatase I. Wickens (1990) suggested that when protein phosphatase I is inhibited, calcium- and calmodulin-dependent protein kinase II may be able to

Sensory events may be represented by activity in subsets of glutamatergic corticostriatal projections



Responses may be controlled by striatal output

Figure 3 Highly schematized drawing of a possible locus of putative DA-mediated changes in the strength of corticostriatal glutamatergic synapses onto striatal output cells that may influence approach and other behaviours of an animal.

bring about long-term effects that lead to the enhanced efficacy of the glutamate synapse. By this mechanism, DA could lead to changes in glutamate synaptic effectiveness, like those that have now been shown to take place (Section 5.2.3), but only when the synapse is in a state of readiness defined as an increase in intracellular $[Ca^{2+}]$ (Figure 4).

An interesting aspect of the model proposed by Wickens (1990) is that each time a glutamate synapse is active and participates in activating the postsynaptic cell, an increase in $[Ca^{2+}]$ in the dendritic spine would occur. This increase

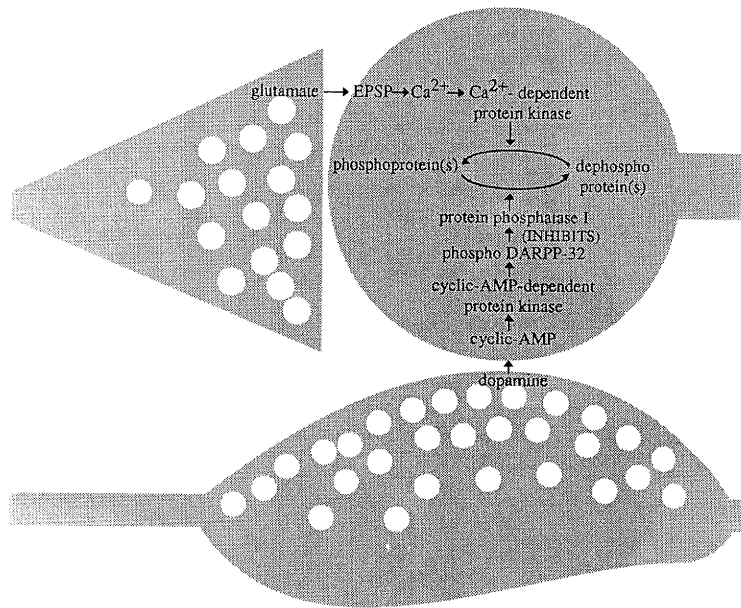


Figure 4 Possible mechanism for reward-related incentive learning. The release of dopamine in association with reward (the dopamine signal) may lead to the production of cAMP that activates a cAMP-dependent protein kinase, leading to the phosphorylation of proteins. One candidate for phosphorylation is DARPP-32; the phosphorylated form of this protein inhibits protein phosphatase I. If there had been a glutamatergic input to this dendritic spine just prior to the dopaminergic input, the increase in $[Ca^{2+}]$ resulting from the excitatory postsynaptic potential (EPSP) may have activated a calcium-dependent protein kinase that may be able to bring about long-term changes in efficacy of the glutamatergic synapse. In the absence of a dopaminergic signal, the consequences of activation of the calcium-dependent protein kinase may have been reversed by protein phosphatase I. If there was a dopaminergic input, the inhibition of protein phosphatase I by DARPP-32 may permit a long-term change (mediated by phosphoproteins) to take place. In this way, activation of D_1 receptors may lead to long-term changes in glutamatergic synapses. For further details see Hemmings *et al.* (1987) and Wickens (1990).

would lead to the activation of calcium- and calmodulin-dependent protein kinase that could potentially produce a long-term change in glutamate synaptic effectiveness. However, in the absence of reward and a DA signal leading to stimulation of D₁ receptors, protein phosphatase I may reverse the effects of the kinase. When there is reward and a DA signal, the stimulation of cAMP formation, activation of cAMP-dependent protein kinase and phosphorylation of DARPP-32 may lead to inhibition of protein phosphatase I, removing the normal inhibition of the effects of calcium- and calmodulin-dependent protein kinase. This may permit the changes that lead to increased effectiveness of the glutamate synapse. The postulated interactions are shown in Figure 4. Although some aspects of this model remain speculative, there is strong evidence to support many of its details, as reviewed above.

How permanent might the changes in glutamate synaptic effectiveness be? If this is the structural basis of reward-related learning, it should be relatively permanent without use but gradually should weaken if the modified glutamate synapses are used in the absence of reward, showing a normal extinction effect. Studies of the regulatory effects of cAMP-dependent protein kinase on the kainic acid glutamate receptor subtype provide some relevant data. Thus, Wang *et al.* (1991) found that the enhanced effectiveness of kainate receptors produced by cAMP-dependent protein kinase (PKA) was gradually lost when an inhibitor of the kinase was given (Section 5.2.3). They concluded that '... kainate receptors may be directly phosphorylated and dephosphorylated by PKA and phosphatases, respectively'. They also acknowledged that these effects could be mediated by an intermediate regulatory protein. This would provide a basis for understanding the gradual loss of incentive learning when reward is no longer given.

5.3 Consideration of the results of psychopharmacological studies of the role of D₁ and D₂ receptors in incentive learning from the point of view of the mechanism

The mechanism proposed in Section 5.2 makes stimulation of D₁ receptors crucial for DA-mediated reward-related incentive learning to take place. It would follow that treatments with D₁ antagonists in reward paradigms would lead to a block of the usual effects of reward on behaviour. D₁ agonists might be expected to affect incentive learning but the direction of their effect may depend on the paradigm under consideration and the relative importance of the timing of the DA signal. D₂ antagonists, by influencing the release of DA, may also affect the DA signal and therefore incentive learning. D₂ agonists may stimulate locomotor activity, leading to an enhancement of activity in DA neurones and increased stimulation of D₁ receptors, thereby influencing incentive learning in an indirect manner. These points will be considered in greater detail below. For related

discussions, see Beninger (1991, 1992), Beninger *et al.* (1989) and Miller *et al.* (1990).

5.3.1 D₁ antagonists

The proposed mechanism for DA-mediated reward-related incentive learning requires the stimulation of D₁ receptors. Therefore, any paradigm involving reward should be affected by D₁ antagonists. They might be expected to block the establishment of incentive learning. In general, results support this prediction. Thus, D₁ antagonists impaired the establishment of incentive learning in place conditioning or conditioned activity tasks using amphetamine as the unconditioned rewarding stimulus (Drew and Glick, 1990; Hiroi and White, 1991; Hoffman and Beninger, 1989a; Mazurski and Beninger, 1991; Stewart and Vezina, 1989; Vezina and Stewart, 1989).

D₁ antagonists also might be expected to produce a gradual loss of incentive learning in animals trained prior to drug tests. Here, too, many data support this conclusion. D₁ antagonists have been found to produce declines, consistent with a block of the usual effects of reward, in animals responding for food (Beninger *et al.*, 1987; Nakajima, 1986; Willner *et al.*, 1990), ESB (Kurumiya and Nakajima, 1988; Nakajima and McKenzie, 1986; Nakajima and O'Regan, 1991; Rompré and Bauco, 1990) and stimulant self-administration (Bergman *et al.*, 1990; Corrigall and Coen, 1991; Kleven and Woolverton, 1990; Koob *et al.*, 1987).

Results to date provide strong evidence that D₁ receptor antagonists block the usual effects of reward on behaviour. These data are in good agreement with the mechanism described in Section 5.2 proposing that it is the action of DA at D₁ receptors that leads to reward-related incentive learning.

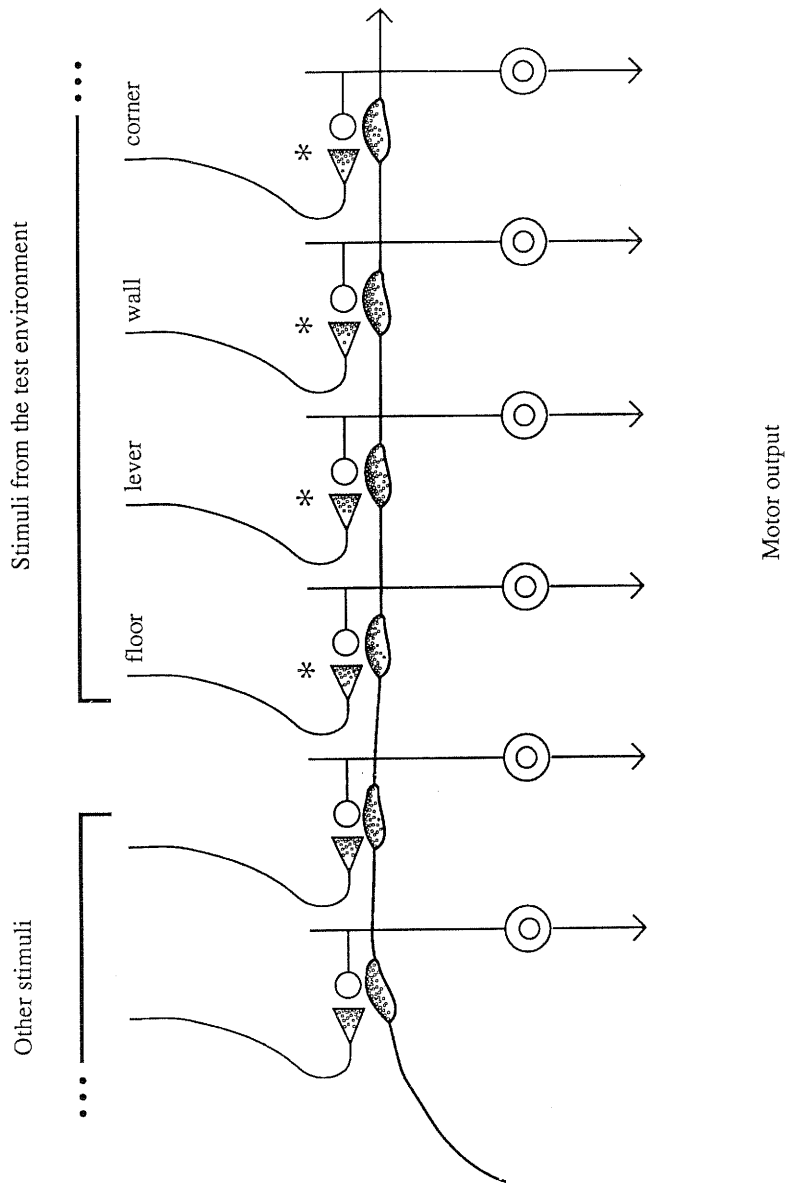
5.3.2 D₁ agonists

Some incentive learning paradigms require that animals learn to respond to a specific stimulus in the test environment (e.g. a lever). Others only evaluate the time that animals spend in a particular place (place conditioning) or their level of activity in a particular place (conditioned activity). Incentive learning involves the acquisition by certain stimuli of an enhanced ability to elicit approach and other responses. It was proposed that those glutamate synapses activated by stimuli encountered just prior to the reward-related DA signal may undergo the DA-mediated change in effectiveness. From this it follows that treatment with D₁ agonists might mask the reward-related DA signal in paradigms where incentive learning of particular cues in the test environment is required to perform the task. On the other hand, where there is no need to select a particular cue in the test environment to control responding, D₁ agonists might be effective at producing incentive learning. These possibilities are discussed in further detail below.

Paradigms where a particular environmental stimulus must come to control responding include lever-pressing tasks. Animals responding for food show a decrease in lever pressing following treatment with a D₁ agonist but this may reflect drug-produced anorexia (Hoffman and Beninger, 1989b; Rusk and Cooper, 1989b). Anorexia may not be a problem when animals are responding for ESB, stimulant self-administration or conditioned reward. In two of these paradigms, a D₁ agonist has been found to lead to an impairment in the ability of the lever and lever-related stimuli to control responding (Beninger and Ranaldi, 1992; Nakajima and O'Regan, 1991). The D₁ agonist produced effects similar to those seen following treatment with the direct-acting DA agonist apomorphine. A consideration of the effects of apomorphine and amphetamine may provide some insight into the effects of D₁ agonists.

A number of authors have suggested that the differential effects of amphetamine and apomorphine on responding for ESB or conditioned reward may be related to their different mechanisms of action (Beninger and Ranaldi, 1992; Herberg *et al.*, 1976; Mazurski and Beninger, 1986; Robbins *et al.*, 1983; Stellar *et al.*, 1988). Amphetamine enhances responding for ESB or conditioned reward whereas apomorphine leads to a loss of control of responding by the reward-related stimuli. Amphetamine enhances neurogenic release of DA and blocks uptake whereas apomorphine mimics the action of DA at DA receptors (Cooper *et al.*, 1982). It has been proposed that amphetamine may enhance the DA signal, leading to increased responding for reward, whereas apomorphine may mask the DA signal associated with reward, leading to the observed loss of control of responding by reward-related stimuli. The mechanism proposed in section 5.2 might lead to a complementary explanation but with different emphases.

When animals press a lever and receive reward, there is a putative DA signal. Presumably the subset of glutamatergic synapses in a state of readiness are those activated by environmental stimuli associated with the lever. The release of DA might lead to a modification in the strength of those synapses; therefore, lever-related stimuli might become incentive stimuli controlling responding in the test environment. Treatment with amphetamine, at least at moderate doses, might preserve the temporal relationship between the lever-related stimuli and the DA signal, but the DA signal might be larger, possibly leading to greater incentive learning and more vigorous lever pressing. Treatment with apomorphine, on the other hand, might lead to an indiscriminate stimulation of DA receptors, uncoupling the usual relationship between the lever-related stimuli and the reward-produced DA signal. Control of responding by the lever-related stimuli in this latter case may be lost. As the crucial DA receptor for incentive learning has been proposed to be the D₁ subtype, agonists acting at the D₁ receptor might be expected to produce apomorphine-like effects. This is exactly what has been found (Figure 5). The possible importance of the D₁ receptor in the reward-masking action of apomorphine is suggested further by the observation that D₂ agonists produce amphetamine-like effects in animals



lever pressing for ESB or conditioned reward. Apparently, with D₂ agonists the putative reward signal is not lost.

D₁ agonists have been found to produce a place preference (White *et al.*, 1991) and conditioned activity (Mazurski and Beninger, 1991), both examples of incentive learning. This may be understood in the present context when task demands are taken into consideration. Thus, in both of these tasks, a particular environment is paired with injections of a D₁ agonist. The D₁ agonist would be expected to stimulate D₁ receptors tonically. This should lead to an increase in the effectiveness of glutamatergic synapses brought into a state of readiness while the drug is active. The stimuli encountered while the animals are drugged are those associated with the test environments. Thus, those stimuli would acquire increased ability to elicit approach and other responses. This conditioning would be manifested as more time spent approaching the drug-paired side in the place conditioning task and increased activity in the conditioned activity task (Figure 5).

In summary, D₁ agonists impair responding for ESB or conditioned reward but produce place conditioning and conditioned activity. These results can be understood when the different nature of the tasks is taken into consideration. Lever pressing tasks require that *specific* stimuli in the test environment control responding. Place and activity conditioning tasks require simply that animals approach *any* stimuli in the test environment. In both cases, treatment with a D₁ agonist may lead to many stimuli in the test environment acquiring the ability to control responding. In the former case, this learning impairs control of responding by lever-related stimuli. In the latter, it produces the effect.

Figure 5 Schematized diagram of synaptic interactions in the striatum that may provide a basis for understanding the reported effects of D₁ agonists in different incentive learning tasks. According to the mechanism described in Section 5.2.4 and Figure 4, glutamatergic terminals (see Figure 3) brought into a state of readiness while D₁ receptors are being stimulated in a relatively tonic manner by a D₁ agonist might be expected to be strengthened (*). Various stimuli from the test environment (e.g. floor, lever, wall, corner) might undergo this modification while stimuli from elsewhere (other stimuli), not being encountered in association with stimulation of D₁ receptors, might not. This learning can be seen to have different consequences depending on the task. If an animal was lever pressing for conditioned reward, for example, the ability of the lever to control responding might be lost due to the increase in the ability of other stimuli in the test environment to control responding. This could explain the detrimental effects of apomorphine or SK & F 38393 on selective responding for conditioned reward. If an animal was simply placed into an environment while drugged and then later tested for approach to that environment (place conditioning) or level of activity in that environment (conditioned activity), both effects should be seen. This would indicate that stimuli from the test environment had acquired an enhanced ability to elicit approach and other responses. As no specific response is required in these tasks, D₁ agonists are effective in producing conditioning.

5.3.3 D₂ antagonists

If D₁ receptors are critical for reward-related incentive learning to take place, why are D₂ antagonists so effective at blocking the effects of reward on behaviour? There are two aspects of the effects of D₂ antagonists that may be relevant to answering this question. D₂ antagonists are well known to produce decreases in motor activity (e.g. Beninger, 1983; Beninger *et al.*, 1991). As motor activity has been shown to lead to activation of DA neurones (Freed and Yamamoto, 1985; Heyes *et al.*, 1988; Speciale *et al.*, 1986; Szostak *et al.*, 1986, 1988, 1989; Yamamoto and Freed, 1984; Yamamoto *et al.*, 1982), it is possible that treatment with D₂ antagonists leads to a reduction in the drive on DA neurones. This may have the effect of reducing the strength of the reward signal and, therefore, reducing the stimulation of D₁ receptors in association with reward. The second aspect of D₂ antagonist effects that may influence stimulation of D₁ receptors in association with the reward-related DA signal is that D₂ antagonists have been shown to produce an increase in DA release, probably as a result of blocking presynaptic receptors (Blaha and Lane, 1984; Di Chiara and Imperato, 1985, 1988; Imperato and Di Chiara, 1985; Louilot *et al.*, 1985; Nielson and Moore, 1982; O'Neill and Fillenz, 1985). These elevated levels of synaptic DA may mask the DA signal associated with reward in a similar manner to D₁ agonists, as discussed in the previous section.

By decreasing the drive on DA neurones, thereby weakening the DA signal associated with reward, and/or by increasing the level of DA release, thereby masking to some degree the DA signal associated with reward, D₂ antagonists may critically reduce the ability of rewarding stimuli to control responding. Both of these effects would influence the ability of DA released during the reward-related DA signal to produce a temporally discrete stimulation of D₁ receptors. Thus, D₂ antagonists, although acting primarily at the D₂ receptor, may have an important effect on events at the D₁ receptor that are critical for incentive learning.

Either the putative weakening of the reward signal or the masking of the reward signal at the D₁ receptor would be expected to produce the observed reward-blocking effects of D₂ antagonists in a number of paradigms. Thus, D₂ antagonists reduce the effects of reward in animals lever pressing for food, water, ESB and stimulant self-administration (Section 5.1). The action of D₂ antagonists on avoidance responding can similarly be understood as resulting from either of the above effects on the reward signal.

In considering the effects of D₂ antagonists in place conditioning and conditioned activity paradigms, both of the above-mentioned actions of D₂ antagonists cannot account for the observations. Recall that tonic stimulation of D₁ receptors with a D₁ agonist resulted in place preference conditioning and conditioned activity (Section 5.3.2). If the action of D₂ antagonists was to lead to enhanced concentrations of synaptic DA (as shown by the data, see above) and tonic stimulation of D₁ receptors, D₂ antagonists might be expected to produce

place preferences and conditioned activity. In general, they do not. This might suggest that the reward-attenuating effects of D₂ antagonists are more importantly related to their reducing the drive on DA neurones and thereby weakening the DA signal than to their increasing striatal synaptic DA concentrations and putatively masking the reward signal. It is interesting to note, however, that there are reports of a D₂ antagonist producing place preference conditioning (Hoffman and Beninger, 1989a) and conditioned activity (Mazurski and Beninger, 1991). I am currently evaluating the possibility that the place conditioning effect is related to the stimulation of D₁ receptors by increased synaptic DA concentrations following blockade of D₂ receptors.

In summary, the ability of D₂ antagonists to mitigate the usual effects of reward on behaviour does not require rejection of the D₁-based mechanism of reward-related incentive learning proposed in Section 5.2. D₂ antagonists have been shown to have effects on the level of activation of DA neurones and on the concentrations of synaptic DA in the striatum. Either of these actions could influence the DA signal associated with reward and its action at D₁ receptors.

5.3.4 D₂ agonists

D₂ agonists have been reported to have amphetamine-like reward-enhancing effects on responding for ESB and conditioned reward and are self-administered (Section 5.1). As described in Section 5.3.3, increases in activity appear to lead to increases in the level of drive on DA neurones. As D₂ agonists have potent stimulant effects, they may increase the drive on DA neurones and thereby increase the magnitude of the reward signal. It is noteworthy that D₂ agonists, although directly and tonically stimulating D₂ receptors, produce effects like the DA release enhancer amphetamine, and do not produce effects like the direct-acting DA (D₁ and D₂) agonist apomorphine. These observations would suggest that tonic stimulation of D₂ receptors does not mask the reward signal; rather, D₂ agonists seem to increase motor output and enhance the ability of rewarding stimuli to control responding.

D₂ agonists also produce place preferences and conditioned activity. These effects can similarly be understood as resulting from an enhancement of drive on DA neurones leading to increased stimulation of D₁ receptors and incentive learning, as proposed in Section 5.2.

There is a clear prediction from these considerations. D₁ antagonists should block the reward-enhancing effects of D₂ agonists. Very few studies have addressed this question. Ranaldi and Beninger (unpublished) have investigated the effects of the D₁ antagonist SCH 23390 on the stimulation of responding for conditioned reward produced by the D₂ agonist bromocriptine. We found that SCH 23390 reduced the magnitude of this effect. Hoffman and Beninger (1989a) found that some doses of SCH 23390 were effective at blocking place preference conditioning based on the D₂ agonist quinpirole. Mazurski and Beninger (1991), on the other hand, found that SCH 23390 failed to block the establishment of

conditioned activity based on quinpirole. There is an urgent need for more studies of this type.

There is at least some direct evidence that the apparent rewarding effects of D_2 agonists are mediated through the D_1 receptor. Although there is a need for further studies, results to date can be seen as consistent with the mechanisms proposed in Section 5.2.

5.3.5 Post-training treatments

Experiments involving the injection of DA receptor-subtype-specific agonists immediately following training are more difficult to understand from the point of view of the proposed mechanism. Only speculation is possible. It would appear that once the mechanism of reward-related learning has been initiated, post-training stimulation of either D_1 or D_2 receptors enhances the strength of learning. In only one study, a D_1 antagonist was injected immediately after pairing an odour with reward and it was found to impair memory for the incentive conditioning task (Weldon *et al.*, 1991). Interestingly, a D_2 antagonist was without effect. Further studies using this paradigm may provide valuable insights into the mechanism involved in incentive learning. An experiment that would be of great interest would be to evaluate the effects of D_1 antagonists on the memory-enhancing effects of D_1 and D_2 agonists. The present mechanism would lead to the prediction that the effects of agonists at either receptor subtype would be blocked.

5.4 Conclusions

In recent years there has been a rapid increase in the number of published papers evaluating the role of D_1 and D_2 receptors in learning. Results of these studies, in conjunction with findings from anatomical and neurochemical experiments, have led to the development of a possible mechanism for how DA may change the ability of reward-related stimuli to elicit approach and other responses. The results of most experiments can be understood from the point of view of this mechanism. However, there is a continuing need for further studies of the interactions of agonists and antagonists specific for DA receptor subtypes in paradigms evaluating incentive learning. The time is also right to begin a more thorough investigation of possible DA–glutamate interactions in studies of reward-related incentive learning.

Acknowledgements

This chapter is dedicated to L.O. Hanson. Thanks go to Robert Ranaldi for helpful comments on an earlier draft of this manuscript. The author wishes to

acknowledge support from the Natural Sciences and Engineering Research Council of Canada.

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