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Receptor Subtype-Specific Dopamine Agonists and Antagonists and Conditioned Behaviour

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INTRODUCTION

There is good evidence that dopamine (DA) may play a critical role in reward-related incentive learning (Beninger, 1983). This type of learning involves the acquisition of the ability to elicit approach and other responses by reward-associated stimuli. For example, when a rat receives a food reward for pressing a lever, an increase in lever pressing is observed. This can be understood as a consequence of the effects of food reward on the lever-associated stimuli, increasing their ability to elicit responses. Such conditioned stimuli are defined as incentive stimuli. Many data implicate DA in this learning process.

In recent years, the availability of pharmacological compounds that are relatively specific for subtypes of the DA receptor has progressively increased to the point where there are several agonists and antagonists to choose from for both the D1 and the D2 receptor (Clark and White, 1987; Waddington and O'Boyle, 1989). This has made possible the evaluation of the role of receptor subtypes in functions previously found to be mediated by DA, including reward-related learning (Beninger, 1983; Wise, 1982, 1989a).

Interpretation of the results of behavioural studies of the possible involvement of DA in reward has been widely debated (Ettenberg, 1989; Liebman and Cooper, 1989; Willner et al., Chapter 10, this volume). This

The Mesolimbic Dopamine System: From Motivation to Action.
Edited by P. Willner and J. Scheel-Krüger

debate reflects the historical problem of distinguishing between performance versus learning effects in physiological psychology (Beninger, 1989a), and the fact that DA is clearly involved in the control of unconditioned locomotor activity (Beninger, 1983). However, there have been numerous convincing demonstrations that DA is involved in the rewarding effects of brain stimulation reward (Phillips and Fibiger, 1989; Schizgal and Murray, 1989; Steller and Rice, 1989), drugs (Carr et al., 1989; Hoffman, 1989; Katz, 1989; Koob and Goeders, 1989) and natural reinforcers such as food (Ettenberg, 1989; Bradshaw and Szabadi, 1989; Willner et al., Chapter 10, this volume). The following review will include studies of behavioural paradigms previously shown to allow a dissociation of reward from performance effects.

This chapter will be concerned with a review of the results of behavioural studies that report the effects of D1 or D2 receptor-specific compounds in paradigms assessing reward-related learning. This will be followed by a review of a range of data from the neurosciences which suggest the hypothesis that the D1 receptor may be critically involved in this type of learning (Miller et al., 1990). The hypothesis will then be evaluated in the light of the behavioural data.

D1 ANTAGONISTS AND REWARD-RELATED LEARNING

It has been shown the the D1 antagonist SCH 23390 blocks the rewarding effects of self-administered cocaine in rats; rates were elevated in a dose-related manner similar to the elevations in rate seen following decreases in the concentration of cocaine (Koob et al., 1987). Woolverton (1986) failed to see a similar elevation of rate of self-administration following treatment with SCH 23390 in three of four monkeys tested. However, only three of five monkeys given the D2 receptor blocker pimozide showed the typical pattern of dose-dependent increases in responding. The reasons for the discrepancies between the results of these two studies are not clear and further studies are needed. It has been reported that rats will self-administer cocaine or amphetamine directly into the frontal cortex (Phillips et al., 1981; Goeders et al., 1986) and Goeders et al. (1986) have reported that this effect was not blocked by co-administration of SCH 23390 although it was blocked by a D2 antagonist. This result may reflect a differential involvement of D1 receptors in the frontal cortex versus elsewhere in mediating the effects of reward on behaviour. However, additional studies are clearly needed.

In place-preference studies it has recently been shown that SCH 23390 dose-dependently blocked learning produced by amphetamine (Figure 1) (Leone and DiChiara, 1987; Hoffman and Beninger, 1989a). Hoffman and Beninger (1989a) reported that SCH 23390 produced no place-preference or aversion when administered on its own; others, however, have reported

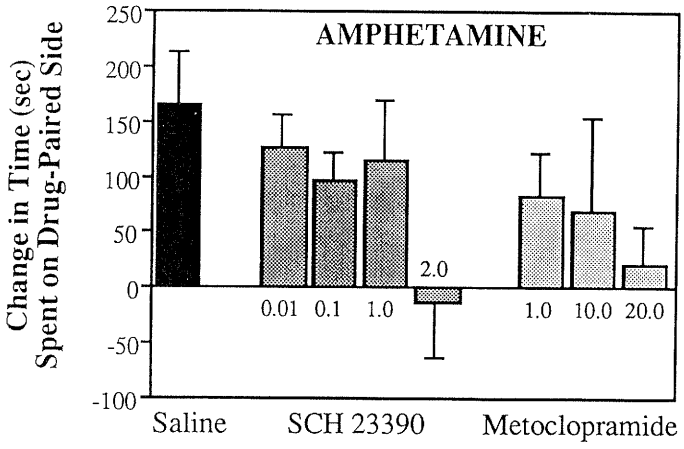

Figure 1. The effects of SCH 23390 or metoclopramide on place conditioning produced by (+)-amphetamine. The experiments consisted of three phases. During the pre-exposure phase, male Wistar rats explored two distinctive compartments (38 × 27 × 36 cm) joined by a small tunnel for 15 minutes on each of 3 days. The compartments differed in brightness, pattern and floor texture, and the amount of time spent in each compartment was recorded. During the 8-day conditioning phase, separate groups of rats were treated (i.p.) with amphetamine (2.0 mg/kg) preceded 1 hour earlier with saline, SCH 23390 (0.01, 0.1, 1.0, or 2.0 mg/kg) or metoclopramide (1.0, 10.0 or 20.0 mg/kg), and were confined to one compartment for 30 minutes. On alternate days rats received saline and were placed in the opposite compartment. The postconditioning test occurred on the following day during which drug-free animals explored both compartments for 15 minutes and the time spent on each side was recorded. The mean (±SEM) difference score for each group is presented. The difference scores were calculated by subtracting the time spent on the drug-paired side during the pre-exposure session (averaged over the 3 days) from the test-day. Thus, a positive score suggests a preference, whereas a negative score suggests an aversion for the drug-paired environment. Doses are indicated in mg/kg under each bar. From Hoffman and Beninger (1989a)

place aversions with SCH 23390 alone (Shippenberg and Herz, 1987). In studies of opiate receptor subtypes in place conditioning, SCH 23390 blocked the reward effects of the μ-opiate agonist morphine (Leone and DiChiara, 1987; Shippenberg and Herz, 1987), and, furthermore, also blocked place aversions produced by a κ-opiate agonist (Shippenberg and Herz, 1987). As opiate-mediated incentive learning has been shown to involve DA in the brain (Bozarth, 1986; Wise, 1989a, b; Wise and Rompre, 1989; Cooper, Chapter 13, this volume), these data suggest that DA may produce its learning effects, at least in part, via the D1 receptor.

Treatments with SCH 23390 of animals performing operant responses for various rewards (Nakajima, 1989) have quite consistently produced results

supporting a role for the D1 receptor in incentive learning. Animals responding for food showed effects consistent with a reduction of reward following SCH 23390 in the studies of Beninger et al. (1987) (Figure 2), Willner et al. (Chapter 10, this volume) and Nakajima (1986), but this effect was not seen by Sanger (1987). In related studies, SCH 23390 significantly reduced the rewarding effects of saccharin (Nakajima, 1986), water (Nakajima, 1986) or brain stimulation (Nakajima and McKenzie, 1986). In a well-controlled study, Kurumiya and Nakajima (1988) recently reported that brain stimulation reward from the region of the dopaminergic cell bodies in the ventral tegmentum was reduced by intra-accumbens injections of SCH 23390 ipsilateral to the electrode.

Conditioned avoidance learning is a classic paradigm for studying negative reinforcement or reward (Mackintosh, 1974; Hineline, 1977). This is another paradigm that involves incentive learning and that is impaired by DA receptor blocking drugs (Beninger, 1989b). In one study, where the intra- or inter-session effects of SCH 23390 on the maintenance of a pretrained avoidance response were investigated, no evidence of a reduction in reward

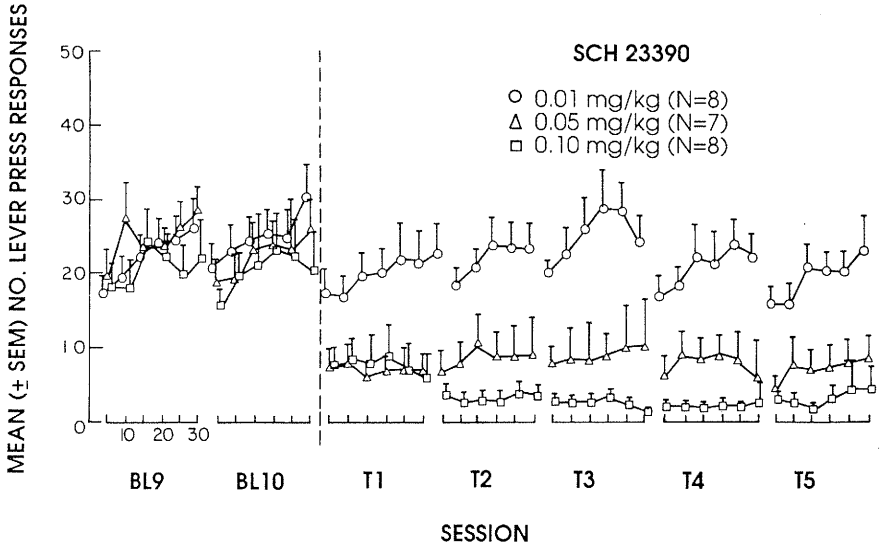

Figure 2. Effects of SCH 23390 on lever pressing for food reward. Data show the mean (±SEM) responses per minute for 5-minute segments of the last two of ten 30-minute baseline training sessions (BL9 and BL10) on a variable interval 30-second schedule, and five test sessions (T1–T5). Two hours before each test-session groups received injections of SCH 23390 in doses of 0.01, 0.05 or 0.1 mg/kg s.c. SCH 23390 produced a significant dose-dependent decrease in responding, and the high doses produced a significant within session effect on responding. From Beninger et al. (1987)

was observed although response reductions consistent with a motor effect of the drug were seen (Sanger, 1987). This was the only study to have specifically investigated possible reward-reducing effects of a D1 antagonist in an avoidance paradigm. Others have reported that SCH 23390 or the D1 antagonist SCH 39166 impaired pretrained avoidance in rats or monkeys (Iorio et al., 1983; Gerhardt et al., 1985; Chipkin et al., 1988). In these studies it was reported that avoidance responding was reduced at some doses that minimally affected escape responding, suggesting that the effects of the drugs may not have been simply motor. However, further studies are needed before any conclusions can be drawn about the effects of D1 antagonists on negative reward in avoidance paradigms.

It has been argued previously that conditioned activity effects seen in animals injected with saline and placed in an environment previously associated with injections of a stimulant drug, e.g. amphetamine, can be understood as an example of incentive learning (Beninger, 1983; Beninger et al., 1989). The establishment of these effects has been shown to depend on DA (Beninger and Hahn, 1983; Beninger and Herz, 1986); it has also been found that the establishment of amphetamine-produced conditioned activity is blocked by co-treatment with SCH 23390 during conditioning sessions (Mazurski and Beninger, in preparation). When sensitization to a stimulant effect can be shown to follow repeated injections in a particular environment (Stewart and Vezina, 1988; Post et al., Chapter 17, this volume), this phenomenon, like conditioned activity, can also be understood as an example of incentive learning. Thus, stimuli associated with the test environment become conditioned incentive stimuli which acquire an enhanced ability to elicit approach and other responses, and this effect adds to the unconditioned effects of the drug producing the sensitized response. Note that the sensitized response to the drug is only seen in the test environment, supporting this analysis. Recently, Vezina and Stewart (1989) reported that sensitization produced by amphetamine was blocked by co-administration of SCH 23390. This result, and the finding that the D1 antagonist blocked the establishment of conditioned activity, suggest that D1 receptors may participate in the establishment of incentive learning.

An additional finding that may be relevant to the current discussion is the recent report by Koechling et al. (1988) that SCH 23390 increased latencies to initiate feeding. Food was periodically presented on a small automated platter. Latencies increased progressively over testing with the drug but there were still instances when latencies of the drugged rats were as fast as those seen in undrugged animals. The authors argued from this that the drug was not simply reducing performance capacity. From an incentive learning point of view, during training of this task, stimuli associated with the food presentation (e.g. the platter, click of the automated equipment, etcetera) would become conditioned incentive stimuli, acquiring

an enhanced ability to elicit approach responses in the (undrugged) animals. During testing with the D1 antagonist, if the usual reward effects of the food were blocked, these incentive stimuli would gradually lose their ability to elicit approach responses, and latencies would lengthen progressively. The elegant approach of the authors, allowing the observation of some peak latencies in the drugged rats and the progressive nature of the drug effect, makes simple motor interpretations of the data difficult to support.

In summary, the effects of D1 receptor antagonists have been assessed in a number of paradigms that may involve reward-related DA-mediated incentive learning. These include stimulant self-administration, place-preference conditioning, operant conditioning rewarded with food, water, saccharin or brain stimulation, conditioned activity or sensitization, avoidance conditioning and conditioned approach to a feeder. In every case, perhaps with the exception of avoidance conditioning where more studies are needed, good evidence that a D1 antagonist could block reward-related learning was found.

D1 AGONISTS AND REWARD-RELATED LEARNING

It is perhaps worth noting here that all studies reviewed in this section use the partial D1 agonist, SKF 38393. Although a full D1-specific agonist is now available (Waddington and O'Boyle, 1989), no studies evaluating its effects in conditioning paradigms have yet appeared. However, preliminary studies of the effects of this new compound on unconditioned behaviours reveal results similar to those of SKF 38393 (Waddington et al., 1988). It will be especially interesting to compare the results of studies with full D1 agonists eventually to those reviewed here.

In self-administration studies it has been reported that the D1 agonist SKF 38393 was not self-administered by monkeys (Woolverton et al., 1984). This can be contrasted with agonists such as cocaine or D2-specific agonists that were self-administered (Woolverton et al., 1984; Woolverton 1986). The D2 agonists are discussed below.

In place conditioning studies it has been reported that SKF 38393 did not produce place-preferences in experiments where significant effects were seen with non-specific or D2 agonists (Gilbert et al., 1986; Hoffman and Beninger, 1988). In fact, Hoffman and Beninger (1988) found that SKF 38393 produced a significant place aversion (Figure 3)!

Animals trained in an operant learning situation for food reward showed a disruption of responding when injected with SKF 38393 (Hoffman and Beninger, 1989b). However, in the same study, animals treated with amphetamine or a D2 agonist showed a similar disruption. It is unclear how to interpret these data in the present context.

Using a different approach, Beninger (in preparation) investigated the

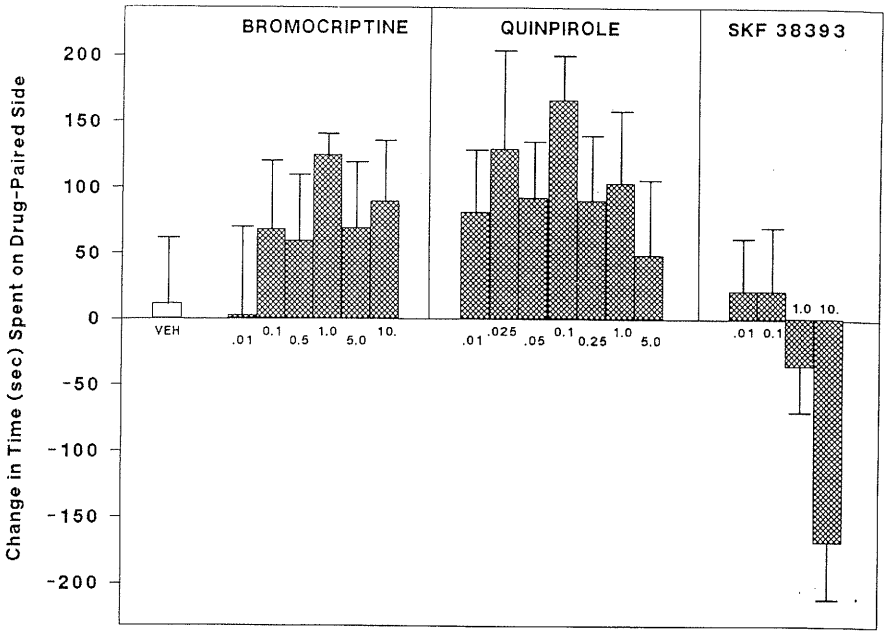

Figure 3. Place conditioning with bromocriptine, quinpirole and SKF 38393. The details of the place conditioning experiment are described in the caption for Figure 1. On conditioning days, individual groups of rats received injections (i.p.) of saline (VEH) or drug in the doses (mg/kg) indicated below or above each bar. The mean difference score for each group is presented. The calculation of these scores is described in the caption for Figure 1. Adapted from Hoffman and Beninger (1988) and Hoffman et al. (1988)

effects of D1- or D2-specific DA agonists on the acquisition of responding for conditioned reward. A lights-off stimulus was repeatedly paired with food when the animals were drug-free, and was then subsequently used to reward acquisition of pressing one of two levers in conditioned reward tests carried out when the animals were drugged. Whereas amphetamine or D2 agonists differentially enhanced responding on the lever producing conditioned reward, SKF 38393 did not enhance responding and impaired, in a dose-related fashion, differential responding on the lever producing conditioned reward. Apomorphine, although producing an overall enhancement in responding, also led to an impairment in differential responding for conditioned reward (Figures 4 and 5) (for further discussion see Beninger et al., 1989).

One recent result might be seen to be inconsistent with these data. Mazurski and Beninger (in preparation) observed conditioned activity in rats having received a number of pairings of SKF 38393 with a particular

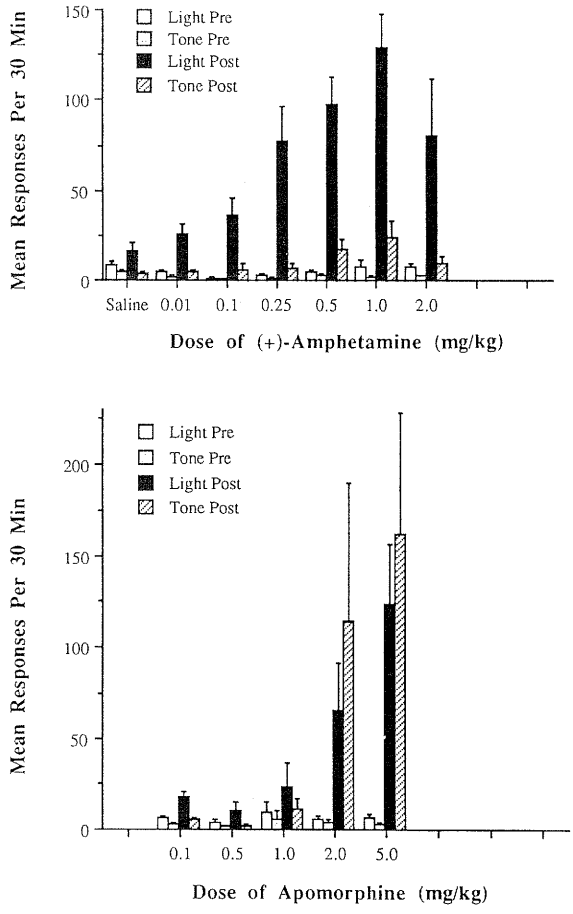

Figure 4. Differential effects of amphetamine and apomorphine on the acquisition of responding for conditioned reward. Rats received three phases of training in a two-lever chamber. The pre-exposure phase measured the rates of pressing the levers; one produced a 3-second tone and the other turned the lights off for 3 seconds. In the conditioning phase, with the levers absent, the light-off stimulus was paired with food for four sessions. The test phase again measured the rate of pressing the levers. Conditioned reward was shown by a relative increase in responding on the light-off lever during the test. Separate groups of male Wistar rats were treated (i.p.) with amphetamine or apomorphine before the test-session. The mean (±SEM) number of responses on each lever during the pre-exposure and test-phases are presented

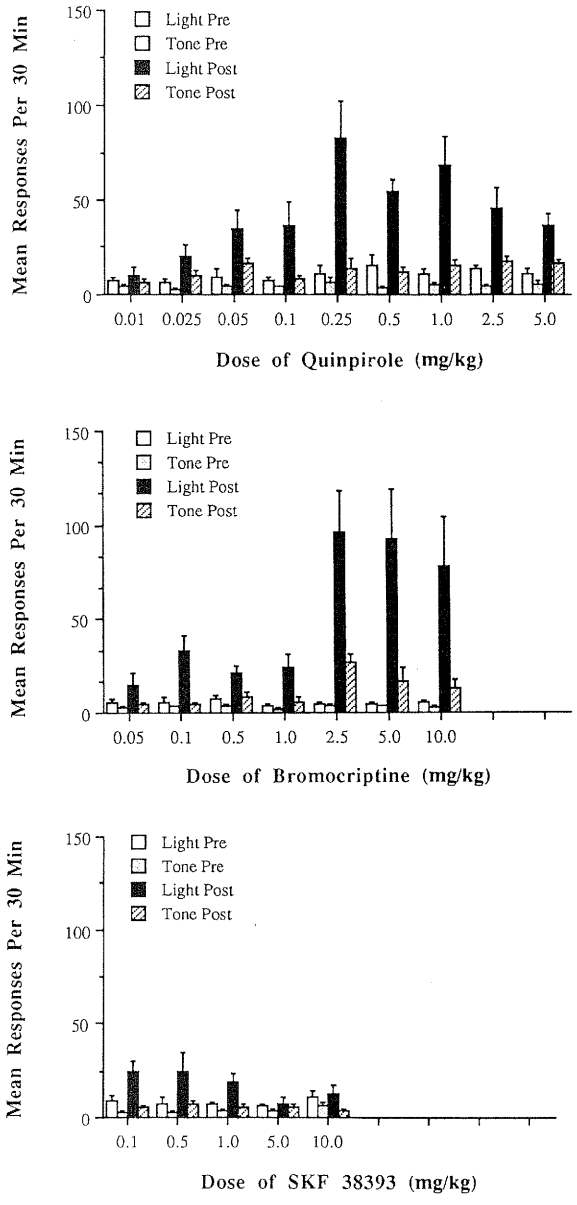

Figure 5. Effects of quinpirole, bromocriptine and SKF 38393 on the acquisition of responding for conditioned reward. The mean (±SEM) number of presses on the tone and light-off lever during the pre-exposure and test-phases are presented. For a description of the procedure, see the caption of Figure 4

test environment. Control animals that received the same number of exposures to the test environment and the same number of injections of drug did not show conditioned activity. This effect was replicated several times. It awaits explanation (Miller et al., 1990).

In summary, studies of the abilities of D1 agonists to support self-administration or place-preferences were consistent in finding that these compounds were not effective. These findings are in agreement with the observation that SKF 38393 impaired responding for conditioned reward. On the other hand, a D1 agonist did produce conditioned activity.

D2 AGONISTS AND ANTAGONISTS AND REWARD-RELATED LEARNING

The basis for the claim that SCH 23390 is a selective D1 antagonist is the observation, reported by Iorio et al. (1983), that this compound was in the order of 1000 times more potent in inhibiting by 50 per cent the ability of DA to stimulate adenylate cyclase than in inhibiting by 50 per cent the binding of [^{3}H]spiperone to striatal membranes. Many of the DA receptor blockers extensively used in studies of the role of DA in reward, e.g. pimozide, spiroperidol and haloperidol, over the past 20 years have the opposite potencies in the two assays of DA receptors (Seeman, 1981). Thus, if SCH 23390 is accepted as a selective D1 antagonist it would seem appropriate to identify pimozide, spiroperidol and haloperidol as selective D2 antagonists. In recent papers, this has become common practice (Woolverton, 1986; Koechling et al., 1988).

Accepting pimozide, spiroperidol and haloperidol as selective D2 antagonists makes an undertaking of a review of the effects of D2 antagonists on reward-related learning unnecessary as it has been done many times in recent years (Wise, 1982; Beninger, 1983; Ettenberg, 1989; Liebman and Cooper, 1989; Wise and Rompre, 1989; Willner et al., Chapter 10, this volume). There have also been a number of studies of the effects of the selective D2 antagonist substituted benzamide compounds (Jenner and Marsden, 1981) on reward-related learning (Beninger et al., 1989). The conclusion from these reviews is clearly that D2 antagonists block the usual effects of reward on behaviour (see Figure 1).

Some studies have investigated the possibility that D2 agonists may have rewarding effects. In general, results have shown that they do. Thus, the D2 agonists piribedil and bromocriptine were self-administered by monkeys (Woolverton et al., 1984; Woolverton, 1986). Place-preference conditioning has been reported following pairings of the D2 agonists bromocriptine, quinpirole or N-0437 with a specific environment (see Figure 3) (Gilbert et al., 1986; Hoffman and Beninger, 1988, 1989a; Hoffman et al., 1988), and Morency and Beninger (1986) reported this effect following intracerebroven-

tricular injections of bromocriptine in rats. Quinpirole decreased operant responding (Hoffman and Beninger, 1989b); however, as already discussed, the same effect was seen with amphetamine or SKF 38393, making interpretation of these results in the present context difficult. When the effects of quinpirole or bromocriptine on the acquisition of operant responding for conditioned reward were assessed, a dose-dependent enhancement was seen (Figure 5) (Beninger, in preparation). Finally, quinpirole produced conditioned activity (Mazurski and Beninger, in preparation). In general, these effects are suggestive of a role for D2 receptors in reward.

D1 RECEPTOR AS A POSSIBLE MEDIATOR OF INCENTIVE LEARNING

There may be good reason for suspecting that the D1 receptor subtype is specifically involved in reward-related learning (Miller et al., 1990). D1 receptors activate the enzyme adenylate cyclase that, in turn, stimulates the formation of the cyclic nucleotide, cyclic 3′, 5′ adenosine monophosphate (AMP) (Kebabian et al., 1972). There has been considerable interest in the possibility that second messengers, including cyclic AMP, may be involved in the storage of information that underlies learning and memory (Greengard and Kuo, 1970: for a recent review see Matthies, 1989).

In recent years, huge advances in our understanding of the possible molecular mechanisms underlying memory have been made. In a recent review, for example, Schwartz and Greenberg (1987) discussed three protein kinases that may participate in memory formation. The cascade of events that follows the binding of DA to the D1 receptor leads to the activation of cyclic AMP-dependent protein kinase; this kinase, in turn, leads to protein modifications that may participate in the molecular mechanisms underlying the consolidation of memory (Schwartz and Greenberg, 1987). The actual proteins involved in the formation of memory remain to be specified. However, there is intense research activity directed at identifying changes in proteins associated with stimulation of D1 receptors, and steady advances are being made. For example, the studies of Greengard and his associates (Walaas et al., 1983; Hemmings et al., 1984, 1987) have revealed a DA- and cAMP-regulated phosphoprotein in the brain. Researchers studying long-term potentiation of the hippocampus have similarly identified a protein kinase and membrane protein associated with memory in this model (Akers et al., 1986; Lovinger et al., 1986). Results to date strongly suggest that activation of D1 receptors may lead to a cascade of molecular events which eventually produce the structural basis of memory.

There is a related line of study that also points to the D1 receptor as the possible mediator of learning produced by DA. In a now classic paper, Libet et al. (1975) demonstrated that DA could produce lóng-term

enhancement of the muscarinic cholinergic response in the rabbit superior cervical ganglion. They suggested that this constituted a form of memory (for further discussion see Libet, 1984). In more recent studies, Libet and his co-workers have shown that this DA-mediated memory effect required the stimulation of D1 receptors; thus the effect was blocked by the D1 antagonist SCH 23390, but not by the D2 antagonists sulpiride or domperidone (Mochida et al., 1987). Using a hippocampal slice preparation, Gribkoff and Ashe (1984) and Stein and Belluzzi (1989) have shown a similar DA-mediated modulation of the excitability of CA1 cells. Although the substrate proteins mediating the changes in these models remain to be identified, the results combine with those of molecular studies to point to the D1 receptor as a good candidate for mediating DA-related learning.

Some theorists have recognized the potential of the results of Libet et al. (1975) in the understanding of the neuronal organization that may underlie the action of DA in memory consolidation. As early as 1978, Routtenberg and Kim proposed that nigroneostriatal dopaminergic projections may modulate muscarinic synaptic effectiveness via DA receptors linked to adenylate cyclase. Beninger (1983) similarly drew on the findings of Libet et al. (1975) to suggest that, when reward-related learning occurs, it might be the action of DA at D1 receptors in the striatum (i.e. the caudate, putamen, nucleus accumbens and olfactory tubercle; Heimer and Wilson, 1975) that may mediate changes in cholinergic synaptic effectiveness that form the substrate of the memory. D1 receptor stimulation would presumably lead to the formation of cyclic AMP, the activation of protein kinases, and the eventual phosphorylation of proteins leading to changes in synaptic effectiveness.

One aspect of the model developed by Beninger (1983) involved the assumption that DA would act to modify only muscarinic synapses that were most recently active. According to the model, specific stimuli, for example from the environment, would lead to the activation of specific subsets of cortical cells and therefore specific subsets of corticostriatal fibres (see Grofova (1979) for a review of the extrinsic connections of the striatum and Viaud and White (1989) for a related discussion; see also Groenewegen et al., Chapter 2, this volume). These fibres would, in turn, activate specific subsets of cholinergic neurons intrinsic to the striatum. When reward occurs and the dopaminergic neurons are activated (Keller et al., 1983; Phillips et al., 1989), there would be a fairly diffuse release of DA (the DA signal) in the striatum (McGeer et al., 1978). However, only the synapses of the most recently active neurons, representing the most recently encountered stimuli, would undergo the DA-mediated modification in synaptic effectiveness. Thus, a diffuse DA signal would effectively select the most recently active synapses to modify.

The results of recent highly sophisticated studies using *in vivo* voltammetry to assess the effects of reward on DA levels in the striatum (including the

nucleus accumbens) bear importantly on the model under development (Phillips et al., Chapter 8, this volume). Perhaps the most crucial finding is that DA levels have not been observed to rise immediately after unsignalled food reward but only after a considerable delay. In fact, in one of the experiments reported by Phillips et al. (this volume), the first presentation of a palatable liquid diet was not followed by increases in DA levels at all, even after a delay! Do these results indicate that there is not a DA signal associated with reward?

Such a conclusion may not be necessary for the following reasons. There is a wealth of data, some of which is reviewed here, showing that the establishment of reward-related incentive learning fails to occur in animals undergoing conditioning trials while dopaminergic neurotransmission is blocked; this has been seen, for example, in lever pressing for food (Tombaugh et al., 1979; Wise and Schwartz, 1981), avoidance learning (Beninger et al., 1980), place conditioning based on food (Spyraki et al., 1982), establishment of conditioned reward based on food (Beninger and Phillips, 1980; Hoffman and Beninger, 1985), and establishment of conditioned activity (Beninger and Hahn, 1983; Beninger and Herz, 1986), all examples of incentive learning (Beninger, 1983). Thus, DA seems to play an important role in the establishment of incentive learning.

A reconciliation of these findings with the *in vivo* voltammetric data reported by Phillips et al. (Chapter 8, this volume), showing a delayed onset of action of feeding on DA levels, may be possible. In this regard it may be useful to note the differential rate of acquisition in some tasks involving incentive learning. Thus, responding for brain stimulation reward (BSR) is acquired extremely rapidly, especially with electrodes in the ventral tegmental area (VTA). Similarly, responding in one-way conditioned avoidance paradigms is acquired extremely rapidly, usually in less than five trials (Levis, 1989). By comparison, acquisition of lever pressing for food is slow; usually a session of magazine training precedes one or two sessions of response shaping. Results of *in vivo* voltammetric experiments have shown that the increases in DA levels following VTA BSR are very rapid (Phillips et al., 1989), and electric shock has been shown to produce rapid onset of increased DA levels (D'Angio et al., 1988; Keller et al., 1983), but, as already mentioned, the onset of effects of unsignalled food on DA levels is slow (Phillips et al., Chapter 8, this volume). Perhaps this apparent relationship between the rate of acquisition of tasks involving incentive learning, and the immediacy of the effects of different types of reward on increases in DA levels, may provide a basis for reconciling the observation that, while DA appears to play an important role in the establishment of incentive learning, food reward has a delayed effect on DA release (Phillips et al., Chapter 8, this volume). The data reported here by Phillips et al. clearly show that delayed increases in DA levels follow unsignalled food,

and that immediate increases occur during conditioned stimuli that signal food. As the acquisition of responding for food is relatively slow, perhaps during the period of acquisition, the peak increase in DA levels slowly shifts from some time during the postingestive period of the meal towards the onset of the meal, and is finally elicited by the stimuli that signal food. Such a pattern was seen in some experiments described by Phillips et al. (Phillips, personal communication).

Why was no DA increase seen on the first day of eating the palatable liquid diet? Only speculation is possible. Perhaps, on the first occasion of a novel food, no reward mechanism is engaged until the postprandial effects of the meal are assessed, assuring that the food is not toxic. The well-documented observation of taste aversion learning following a substantial delay between ingestion and illness is consistent with this suggestion. If no toxic effects ensue, the next ingestion of the food may lead to a delayed increase in DA levels that may act to produce incentive learning to taste cues, for example, and, as acquisition continues, other preingestion cues may become conditioned incentive stimuli. (The results of Koechling et al. (1988), discussed above, may reflect the gradual loss of this conditioning with repeated exposure to food while DA receptors are blocked.)

Whether or not the mechanisms being proposed here eventually prove correct, it is important to note that the acquisition by neutral stimuli of conditioned incentive properties, and of the ability to stimulate increases in DA levels (Phillips et al., Chapter 8, this volume), involves a plastic change in the brain. The mechanism proposed here provides a means by which this learning might take place. Thus, a diffuse DA signal associated with the presentation of rewarding stimuli might alter synapses most recently activated by environmental stimuli signalling reward.

The notion of selective modification by a diffuse signal has been suggested by others. For example, in a recent paper, Miller (1988) suggested that the most recently active synapses go into a 'state of readiness' whereby they are primed for modification if the appropriate signal arrives. He credited Hebb (1949) with the origin of this basic idea. From a somewhat different orientation, researchers interested in computational models of learning have developed the concept of a diffusely projecting reward system that would only strengthen connections that happen to be active at that moment (Donahoe and Palmer, 1989).

The hypothesis that a diffuse DA signal might modify only the most recently active synapses has, at least, heuristic value for understanding some of the behavioural effects of D1 agonists, as reviewed below. How might the most recently active synapses be selected for modification? A number of investigators have reported that electrically- or K^+-evoked DA release is modulated by presynaptic muscarinic (de Belleroche and Gardiner, 1982; Lehmann and Langer, 1982; Raiteri et al., 1982) or perhaps nicotinic

cholinergic receptors (Giorguieff-Chesselet et al., 1979). Such a modulation could have the effect of producing a relatively greater increase in the local concentrations of DA when diffuse dopaminergic activity putatively increases as a result of a rewarding stimulus being encountered. This might enhance the local stimulation of cyclic AMP formation and thus produce the largest modification in cholinergic synaptic effectiveness at the cholinergic synapses that have been most recently active.

The model for DA-mediated learning proposed by Beninger (1983) hypothesized that the locus of synaptic modifications was muscarinic cholinergic synapses in the striatum. This was a direct application of the elements of the Libet et al. (1975) finding in the peripheral nervous system to the central nervous system. It was appealing because the main elements of the Libet et al. (1975) model, namely, efferent cells receiving both cholinergic and dopaminergic afferents, and having both muscarinic and D1 receptors, could be found in the striatum. However, cholinergic cells in the striatum are relatively rare (Bolam, 1984). Although I know of no current data supporting this suggestion, another possible locus for the DA-mediated synaptic change in the striatum is the glutamatergic corticostriatal synapses themselves (Wickens, 1990). They, like cholinergic synapses, are found on striatal efferent cells along with dopaminergic afferents, and the activity of cortical glutamatergic cells would change with changing environmental stimuli. Previous studies have shown that glutamate, like acetylcholine, can modulate striatal DA release (Chéramy et al., 1986; Romo et al., 1986). Furthermore, a DA- and cyclic AMP-regulated striatal phosphoprotein may influence glutamate neurotransmission (Hemmings et al., 1987).

Clearly, more work is needed before the mechanisms underlying the structural changes associated with DA-mediated learning can be specified. However, from this brief review it can be seen that results from a number of areas of neuroscience converge on the possibility that DA-mediated reward-related learning could involve the D1 receptor.

CONSIDERATION OF THE BEHAVIOURAL DATA FROM THE POINT OF VIEW OF THE D1 HYPOTHESIS

If D1 receptors are critical for DA-mediated reward-related learning to occur, D1 antagonists should block the usual response acquisition and maintenance effects of rewarding stimuli. Many data support this hypothesis. As reviewed above, D1 antagonists have been reported to produce effects consistent with a block of reward in self-administration, place-preference, operant responding for various rewards, avoidance responding, conditioned activity, sensitization and conditioned approach to a feeder. These results provide strong support for the hypothesis that the D1 receptor may be involved in mediating learning produced by reward.

As discussed in the previous section, there is theoretically a diffuse DA signal associated with reward, and the effect of this putative signal may be to modify the strength of the striatal synapses most recently activated by the particular environmental stimuli encountered by the organism. One mechanism suggested for this selective action of DA at only a subset of synapses was the possible local enhancement of DA release by adjacent synapses activated by the most recently encountered stimuli (see above). From this point of view, the administration of D1 agonists would not be expected to produce a reward effect because they would act not only at the synapses activated in association with the pre-reward stimuli but, rather, indiscriminately at many synapses in DA terminal regions; i.e. they would create noise that would interfere with the usual selective action of the DA signal. As a consequence, environmental stimuli associated with reward might not uniquely undergo a change in their ability to elicit approach and other responses in the future. Therefore, little or no stimulus control of responding would be seen.

In general, the few results that are available provide some support for this point of view. Thus the partial D1 agonist SKF 38393 was not self-administered, perhaps because the D1 noise created by the postsynaptic action of the self-administered D1 agonist did not lead to the specific enhancement of the ability of lever-associated stimuli to control responding. The failure of SKF 38393 to support place-preference conditioning or to enhance responding for conditioned reward can be similarly understood. SKF 38393 also produced a place aversion. It is not clear how this result can be understood from the present point of view. However, this result and the failure of a D1 agonist to be self-administered might suggest that the putative state of indiscriminate incentive learning may be undesirable (Miller et al., 1990).

If D1 receptors mediate learning associated with reward, as the data suggest, how might the apparent reward effects of D2 agonists and reward-blocking effects of D2 antagonists be understood? It should be pointed out that the results with D2-specific compounds do not negate the hypothesis being developed in this chapter; the observation of reward effects related to manipulations of the D2 receptor does not in itself lead to the conclusion that the D1 receptor is not involved. The D2 effects require explanation, however, but only speculation is possible at this time. The following is an attempt to understand the data within a single explanatory framework.

It now appears clear that the activation of dopaminergic neurons leading to the release of DA at their terminal regions (the DA signal) may form an essential link in the neurocircuitry mediating the effects of reward on behaviour. As discussed in the previous section, there are many data that show that DA is released when animals encounter unconditioned (Heffner et al., 1980; Keller et al., 1983; Blackburn et al., 1986; Damsma et al.,

1989; Phillips et al., 1989, Chapter 8, this volume) or conditioned rewarding stimuli (Schiff, 1982; Blackburn et al., 1989; Phillips et al., Chapter 8, this volume). Additionally, there are many data that suggest that DA is released simply as a consequence of the performance of motor acts, presumably by the influence of striatal efferent systems on mesencephalic DA neurons (Heffner and Seiden, 1980; Heffner et al., 1981, 1984; Yamamoto et al., 1982; Yamamoto and Freed, 1984; Freed and Yamamoto, 1985; Church et al., 1986; Szostak et al., 1986; Speciale et al., 1986; Heyes et al., 1988). It is therefore suggested that, under normal circumstances, reward-related learning may occur as a consequence of the DA signal generated by the combined influence from these two sources on the dopaminergic neurons. The main effect of blocking D2 receptors might be to decrease the motor output of the animal (Clark and White, 1987) or, at least, to decrease the amount of drive on the DA neurons; this would have the effect of reducing the usual stimulation of the DA neurons provided from this source and, therefore, reducing the strength of the DA signal normally associated with reward. As a result, the stimulation of D1 receptors that may mediate reward-related learning may be proportionally reduced. Shifts to the right in the function relating response output to reward magnitude (Willner et al., Chapter 10, this volume) or extinction-like decreases in responding for reward may, therefore, be seen following D2 receptor blockade, perhaps depending on dose. It is noteworthy that such a combined influence may provide a basis for understanding the apparent synergistic action of D1 and D2 receptors on behaviour. See Miller et al. (1990) for further discussion of this point.

Another mechanism may also be involved. It is well known that one of the effects of D2 receptor blockers is to produce an acute increase in *in vivo* DA release in the terminal regions, probably as a consequence of blocking autoreceptors (Nielsen and Moore, 1982; Blaha and Lane, 1984; DiChiara and Imperato, 1985, 1988; Imperato and DiChiara, 1985; Louilot et al., 1985; O'Neill and Fillenz, 1985). Thus, following treatment with D2 antagonists, the level of DA would be high and D1 receptor stimulation would be possible. However, this tonic stimulation of D1 receptors would constitute noise and the DA signal may be lost or, at least, critically attenuated. As a result, the usual D1 receptor stimulation may not occur at a discrete time associated with the presentation of reward (as discussed above), but rather in a more sustained fashion masking any reward-related signal. In this way the noise effects at the D1 receptor produced by D2 antagonists and D1 agonists might be expected to be similar.

Either of these two consequences of D2 receptor blockade, reduced stimulation of the dopaminergic neurons in association with striatal output and the performance of motor acts or increased dopaminergic noise in the terminal regions, could reduce the effectiveness of reward. The two might

also sum to lead to the observed reductions in reward-related learning following D2 blockade. Further studies are needed to sort out the possible contribution of these two mechanisms.

From the point of view of the first mechanism, some of the effects of D2 agonists can be understood. In the self-administration paradigm, the performance of the required operant response would lead to an intravenous injection. The resultant pulse of stimulation of D2 receptors might lead to increased stimulation of DA neurons and a strong DA signal that might mediate incentive learning via an action at the D1 receptor; the lever-related stimuli might therefore maintain their ability to control responding. In the case of responding for conditioned reward, increased activity produced by the D2 agonist combined with the presentation of conditioned reward might provide an enhanced DA signal, possibly leading to greater responding for the conditioned reward. Here the putative DA signal at the D1 receptor associated with reward would be intact, only larger than normal, producing the selective enhancement of responding for the conditioned reward. In place conditioning with a D2 agonist, the DA signal at the D1 receptor associated with the performance of motor acts would be intact, only larger as a result of increased stimulation of dopaminergic neurons. This may allow for selective incentive conditioning of stimuli in the drug-associated environment.

The second mechanism suggested that D2 antagonists might produce acute increases in DA release that may have the effect of masking the DA signal at the D1 receptor, leading to a failure of incentive conditioning. If D2 agonists had the complementary effect of decreasing DA release, they might be expected also to lead to a loss of incentive conditioning because the DA signal might be lost. However, D2 agonists produce reward effects, not a block of the reward signal. This apparent contradiction may be resolved by reference to a recent paper by Martin-Iverson et al. (1988). They cited evidence suggesting that the ability of D2 agonists to shut down release in DA neurons was inversely proportional to the level of activity of those neurons. Thus, from the present perspective, the activation of DA neurons in association with the performance of a motor act might release sufficient DA to produce learning effects even in the presence of a D2 agonist. Although this account is clearly speculative, it is supported by the data.

There is a clear prediction from the hypothesis that the D1 receptor may mediate the incentive learning effects of DA. The reward effects of D2 agonists should be blocked by D1 antagonists. There are very few relevant data available at this time and there is a great need for more studies on this specific topic. The available data certainly do not provide a strong case for the model being developed here. Woolverton (1986) reported that only one of four monkeys self-administering the D2 agonist piribedil showed an extinction-like elevation in rate following SCH 23390; five of five monkeys

showed this effect with the D2 antagonist pimozide. However, Hoffman and Beninger (1989a) found that some doses of SCH 23390 antagonized the development of place conditioning based on quinpirole. Finally, Mazurski and Beninger (in preparation) found that SCH 23390 failed to antagonize the establishment of conditioned activity based on quinpirole although the same dose was effective in blocking conditioning produced by amphetamine or SKF 38393. The final resolution of this question must await further studies.

SUMMARY AND CONCLUSIONS

There is evidence that DA may play a critical role in reward-related incentive learning. This type of learning involves the acquisition of the ability to elicit approach and other responses by reward-associated stimuli. Learning may involve structural changes in the brain and these changes may be effected through the activation of receptor-linked enzymes that lead to a cascade of intracellular biochemical events. One receptor that is a candidate for producing learning via these mechanisms is the D1 receptor, the one linked in an excitatory fashion to the enzyme adenylate cyclase.

Neuronal organization and events underlying DA-mediated incentive learning might be as follows. Specific subsets of cortical cells may be activated by specific environmental stimuli; as these cells project heavily into the striatum (including the nucleus accumbens), their terminals there may be correspondingly activated. Whenever a corticostriatal terminal is activated, its synapses may be brought into a transient 'state of readiness' during which an appropriate signal may lead to a relatively permanent change in the effectiveness of these synapses. The signal in this case would be the activation of dopaminergic neurons that project into the same target region as the corticostriatal fibres. The DA signal might effect the change in synaptic strength via D1 receptors. A possible mechanism for the 'state of readiness' might be a transient local enhancement of DA release produced by the corticostriatal projections. The usual influence of corticostriatal projections on striatal output cells may be to alter their firing rate, leading to increases in locomotor activity. The consequence of the change in synaptic strength might be to augment the ability of corticostriatal projections to increase locomotor activity, specifically, approach responses, in the future. This would be the basis of DA-mediated incentive learning.

A critical feature of this model is that the reward-related activation of dopaminergic neurons (the DA signal), and the subsequent stimulation of D1 receptors, be a discrete event associated with the most recently encountered environmental stimuli. Treatment either with a D1 agonist leading directly to indiscriminate stimulation of D1 receptors, or with a D2 antagonist leading to increased release of DA, and indirectly to indiscriminate

stimulation of D1 receptors, might mask the usual reward signal. Decreases in motor activity produced by D2 antagonists might also reduce the strength of the reward signal by reducing the level of stimulation of dopaminergic neurons provided from this source. D1 antagonists would block the reward signal directly. Finally, D2 agonists might lead to an enhancement of the reward signal by increasing the stimulation of the dopaminergic cell bodies that normally accompanies motor output.

In general, the data fit this scheme. Thus, either D1 or D2 antagonists produce a block of the usual effects of reward on behaviour. D1 agonists do not apparently produce reward effects. D2 agonists appear to produce reward effects in their own right and to augment the acquisition of responding for conditioned rewards. D1 antagonists would also be expected to block reward effects produced by D2 agonists according to this scheme. Additional data are eagerly awaited for a definitive evaluation of this possibility.

ACKNOWLEDGEMENTS

This chapter is dedicated to Lynne and Max. The author was supported by grants from the Natural Sciences and Engineering Research Council of Canada, and the Ontario Ministry of Health.

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