Beninger, R.J. (1999) Dopamine-second messenger interactions in reward-related learning. In: Strategies for Studying Brain Disorders, Vol. 4: Interactive Monoaminergic Disorders (Eds T Palomo, RJ Beninger and T Archer), pp. 499-514, Editorial Sintesis, Madrid.

(C17)

Dopamine-second messenger interactions in reward-related learning

30

Richard J Beninger

30.1. Introduction

One question that drove many studies of the anatomical substrates of rewarding electrical stimulation of the brain (Olds and Milner, 1954) during the 1970s concerned the contribution of the neurotransmitters dopamine and norepinephrine. As results began to point to a critical role for dopamine in this type of reward-related learning (Milner, 1991; Wise, 1978), related experiments began to identify dopamine as playing a critical role in learning produced by other rewards including psychomotor stimulants and opiates (Wise and Bozarth, 1981) and conventional rewards such as water, food (Wise, 1991; Wise and Rompré, 1989) and sexual stimulation (Everitt, 1990; Melis and Argiolas, 1995). Today, there is broad agreement that dopamine plays an important role in reward-related learning (Beninger, 1983; Koob, 1992; LeMoal and Simon, 1991; Phillips *et al.,* 1989; Robinson and Berridge, 1993; Salamone, 1994; Schultz *et al.,* 1997; White and Milner, 1992; Wickens, 1993; also see Schmidt and Tzchentke, this volume). However, the mechanisms underlying the role of dopamine in this phenomenon remain to be specified.

A wide range of studies from many areas of neuroscience has shown that second messenger pathways, including the cascade of events that follows activation of adenylyl cyclase and cyclic adenosine monophosphate (cAMP) formation, play a key role in modifying synaptic function when learning occurs. For example, long term potentiation of connections in the hippocampus, a widely studied model of learning in rats (Kuba and Kumamoto, 1990), recently has been shown to have two distinct components with the cAMP cascade being critical to the more persistent late component (Huang and Kandel, 1995). In the invertebrate mollusc Aplysia, Kandel and his co-workers have shown that the cAMP cascade is critical to several forms of learning (Kandel, 1991). Similarly, in the insect Drosophila, genetic manipulations led to an inducible mutation of the cAMP cascade; once the muta-

tion was induced, the flies were shown to be deficient in learning an olfactory discrimination (Drain *et al.*, 1991). Results point to a critical role for signal transduction by the second messenger cAMP in learning in a variety of paradigms and species.

The observation that second messengers in general and the cAMP cascade in particular are involved in learning in a number of paradigms and in a number of species may be relevant to identifying the underlying mechanisms by which dopamine mediates reward-related learning. This is so because the five known dopamine receptor subtypes have been found to belong to two different families defined originally by the action of these receptors on the second messenger adenylyl cyclase (Kebabian and Calne, 1979): the D_1 and D_5 dopamine receptor subtypes stimulate the enzyme adenylyl cyclase and are classified as members of the D_1-like dopamine receptor family; D_2, D_3 and D_4 dopamine receptors inhibit adenylyl cyclase and are classified as members of the D_2-like dopamine receptor family (Civelli *et al.*, 1993; Niznik and van Tol, 1992; Sibley *et al.*, 1993). These considerations suggest the following hypothesis: *dopamine-mediated reward- related learning might be brought about by the action of dopamine at D_1-like dopamine receptors.*

The results of a number of psychopharmacological experiments have implicated D_1-like dopamine receptors in reward-related learning (Beninger and Miller, 1998). In particular, studies with dopamine receptor agonists have produced results supporting the above hypothesis. In this chapter, I will review studies of the effects of dopamine receptor agonists on behaviour in a number of paradigms; I will argue that the results can be understood from the point of view of the above hypothesis. This will be followed by a brief consideration of some recent studies of the role of second messenger pathways in dopamine-mediated reward-related learning.

30.2. Dopamine D_1-Like Receptor Agonists and Reward-Related Learning

The ability of dopamine receptor family-specific agonists to produce place conditioning or conditioned activity has been evaluated in a number of studies. Other studies have evaluated the ability of these agents to support self-administration behaviour. A large number of related studies have involved an evaluation of the effects of dopamine receptor family-specific agonists on lever press responding maintained by other rewarding stimuli such as food, shock termination, conditioned reward or cocaine self-administration. As the following review will show, either D_1- or D_2-like dopamine receptor agonists produce place conditioning or conditioned activity and either are self-administered. On the other hand, lever press responding maintained by a variety of rewards generally is impaired by D_1-like dopamine receptor agonists but augmented by at least some doses of D_2-like dopamine receptor agonists.

30.2.1. Place conditioning, conditioned activity and self-administration

Beginning with place conditioning, it recently was shown that the D_1-like dopamine receptor agonist SKF82958 produced a place preference in rats. The effect was repli-

cated and both times was seen at only one dose following systemic administration. In the same study, the D_1-like dopamine receptor agonists SKF81297 or SKF77434 were without significant effect (Abrahams *et al.,* 1998). Previous studies had shown that the prototypical D_1-like dopamine receptor agonist SKF38393 failed to produce a place preference; in fact, it produced an aversion (Hoffman and Beninger, 1988, 1989; White *et al.,* 1991). One exception was the finding that intra- accumbens injections of SKF38393 produced a place preference (White *et al.,* 1991). Thus, different place conditioning effects were seen with different D_1-like dopamine receptor agonists.

A somewhat similar story came out of studies of the ability of D_1-like dopamine receptor agonists to support self-administration. SKF38393 and SKF77434 were found to be ineffective in monkeys (Grech *et al.,* 1996; Weed and Woolverton, 1995; Woolverton *et al.,* 1984). Other reports appeared of self-administration of SKF77434 or SKF82958 in rats (Self *et al.,* 1996b; Self and Stein, 1992) and self-administration of SKF81297 or SKF82958 in monkeys (Grech *et al.,* 1996; Weed *et al.,* 1993; Weed and Woolverton, 1995). Like the place preference studies, it appeared that different self-administration results were seen with different D_1-like dopamine receptor agonists.

TABLE 30.1

Effects of dopamine D_1-like receptor agonists in place preference learning and self- administration paradigms and their ability to stimulate adenylyl cyclase activity as a per cent of the level stimulated by dopamine (DA).

D_1-like Agonist	Place Preference	Self Administration	Stimulation of Adrenylyl Cyclase Compared to DA
SKF82958	Yes [1]	Yes [10,11] Yes(m) [5,13]	149% [9] 86%(m) [8] 78% [8]
SKF81297	No [1]	Yes(m) [5,12,13]	88% [3] 81% [8] 68% [4] 27%(m) [8]
SKF77434	No [1]	Yes [11] No(m) [5,13]	55% [3] 48% [9]
SKF38393	No [6,7,14] Yes(NAc) [14]	No(m) [13,15]	69% [4] 59% [8] 46% [9] 45% [2,3] 36%(m) [8]

Abbreviations: DA: dopamine; NAc: nucleus accumbens.

Note: All results are for rats except where followed by an "m" indicating monkeys.

References: 1. Abrahams *et al.,* (1998); 2. Andersen *et al.,* (1985); 3. Andersen and Jansen (1990); 4. Arnt *et al.,* (1992); 5. Grech *et al.,* (1996); 6. Hoffman and Beninger (1988); 7. Hoffman and Beninger (1989); 8. Izenwasser and Katz (1993); 9. O'Boyle *et al.,* (1989); 10. Self *et al.,* (1996b); 11. Self and Stein (1992); 12. Weed *et al.,* (1993); 13. Weed and Woolverton (1995); 14. White *et al.,* (1991); 15. Woolverton *et al.,* (1984).

To some extent, the variable effects of D_1-like dopamine receptor agonists in place conditioning and self-administration paradigms may be attributable to the differential ability of these agents to stimulate the enzyme adenylyl cyclase (Table 30.1). Compared to dopamine itself, the reported range of values for stimulating the enzyme by SKF38393 is 36-69% whereas the corresponding range for SKF82958 is 78-149% (Andersen *et al.*, 1985; Andersen and Jansen, 1990; Arnt *et al.*, 1992; Izenwasser and Katz, 1993; O'Boyle *et al.*, 1989); on the basis of these observations, these agents are referred to as partial and full dopamine D_1-like receptor agonists, respectively. In studies using rat striatal tissue, the corresponding ranges for SKF81297 and SKF77434 are 68-88% and 48-55%, respectively (Andersen and Jansen, 1990; Arnt *et al.*, 1992; Izenwasser and Katz, 1993; O'Boyle *et al.*, 1989). In one study using monkey striatal tissue, SKF81297 was found to produce activation of adenylyl cyclase that was only 27% of the value produced by dopamine (Izenwasser and Katz, 1993). With this exception, these four D_1-like dopamine receptor agonists can be ranked in potency from highest to lowest in ability to activate adenylyl cyclase as follows: SKF82958>SKF81297>SKF77434>SKF38393. As can be seen in Table 30.1, the most potent agent produced both a place preference and supported self-administration whereas the least potent agent did neither.

In conditioned activity studies, SKF38393 was found to produce a small unconditioned locomotor effect over three sessions in previously habituated animals and a small conditioned locomotor effect in a drug-free test session that followed (Mazurski and Beninger, 1991). A more recent study failed to see conditioned activity following one conditioning day with SKF38393 or SKF82958 in non-habituated rats that were treated with cocaine on the test day (Fontana *et al.*, 1993). Because of the methodological differences between these two studies it is difficult to compare them and Fontana *et al.*, (1993) acknowledged that their results should not be taken as evidence that D_1-like dopamine receptor agonists are incapable of producing conditioning under other circumstances.

From the results reviewed above, it is concluded that D_1-like dopamine receptor agonists can produce a place preference and can support self-administration although these effects appear to depend on the efficacy of the agent at stimulating adenylyl cyclase. D_1-like dopamine receptor agonists also produce conditioned activity following a number of pairings with a test environment. As has been reviewed elsewhere, D_2-like dopamine receptor agonists similarly produce a place preference, conditioned activity and support self-administration (Beninger, 1991, 1993; Beninger and Miller, 1998; Beninger and Nakonechny, 1996; Miller *et al.*, 1990).

30.2.2. Lever press responding for a variety of rewards

Unlike the studies reviewed above, where the ability of D_1-like dopamine receptor agonists themselves to produce reward was evaluated, the studies to be considered here involve an evaluation of the effects of these agents on lever press responding maintained by other rewarding stimuli such as food. Also unlike the

studies reviewed above, where D_1- and D_2-like dopamine receptor agonists produced similar effects, in the studies reviewed here, the effects are different for dopamine receptor agonists with relative specificity for the D_1- versus the D_2-like dopamine receptor family. Thus, two dissociations will become clear: 1) D_1- and D_2-like dopamine receptor agonists produce different effects in tests of their action on responding for other rewards; 2) D_1- and D_2-like dopamine receptor agonists produce similar effects in tests of their ability to act as rewarding stimuli but different effects in tests of their action on responding for other rewards.

TABLE 30.2

Effects of systemic treatments with D_1-like or D_2-like dopamine receptor agonists on lever press responding in several paradigms.

Paradigm	D_1-like Agonist	D_2-like Agonist
Lever pressing for:		
Food: FI	decrease [6,11]	increase [6,11]
Stimulus-shock termination: FI	decrease [3]	increase [3]
Shock: FI	decrease [4]	
Conditioned reward*	decrease [1,2,8]	increase [1,7]
Cocaine self-administration	decrease [5]	increase [9] decrease [9]
Cocaine seeking	no effect [9]	increase [9]
Cocaine-induced cocaine seeking	decrease [9]	increase [9,10] decrease [10]

Abbreviations: FI: fixed interval schedule of reinforcement; *relative to responding on a control lever. References: 1. Beninger and Ranaldi (1992); 2. Beninger and Rolfe (1995); 3. Bergman *et al.*, (1995); 4. Katz *et al.* (1995); 5. Katz and Witkin (1992); 6. Katz and Witkin (1993); 7. Ranaldi and Beninger (1995); 8. Ranaldi *et al.* (1995); 9. Self *et al.* (1996a); 10. Weissenborn *et al.* (1996); 11. Witkin *et al.* (1991).

Some studies have evaluated the effects of D_1-like dopamine receptor agonists on responding rewarded with food according to a fixed interval (FI) schedule of reinforcement (see Table 30.2). The schedule is important as previous studies have shown that the indirect acting dopamine receptor agonist methamphetamine increases FI responding at some doses but decreases fixed ratio (FR) responding at all effective doses (Dews, 1958). Similarly, both D_1- and D_2-like dopamine receptor agonists decrease FR responding in monkeys (Katz and Witkin, 1993; Witkin *et al.*, 1991). However, the effects of agents acting at the two dopamine receptor families on FI responding differ. Thus, the D_2-like dopamine receptor agonist quinpirole increased FI responding of monkeys at some doses whereas the D_1-like dopamine receptor agonist SKF38393 decreased FI responding at all effective doses (Katz and Witkin, 1993; Witkin *et al.*, 1991).

One study evaluated the effects of D_1- and D_2-like dopamine receptor agonists on FI responding of monkeys for stimulus-shock termination. Bergman *et al.* (1995) tested a number of D_1-like dopamine receptor agonists and found that they decreased responding at all effective doses; several D_2-like dopamine receptor agonists were tested and found to increase FI responding at some doses. One interesting finding is that, in contrast to the possible relationship between efficacy at stimulating adenylyl cyclase and ability to support a place preference or self-administration (see above and Table 30.1), D_1-like dopamine receptor agonists with differing efficacies similarly affected FI responding. The results of Bergman *et al.*, (1995) from studies of monkeys responding to avoid or escape shock and shock-associated cues are in good agreement with those from studies evaluating the effects of D_1- and D_2-like dopamine receptor agonists on FI responding for food. In both cases, D_1-like dopamine receptor agonists decreased responding at all effective doses whereas D_2-like dopamine receptor agonists increased responding at some doses.

Katz *et al.*, (1995) trained monkeys to respond on a FI schedule for electric shock presentation. The D_1-like dopamine receptor agonists SKF75670, SKF82958, SKF81297, SKF77434, and SKF38393 decreased responding in a dose-dependent manner. There appeared to be no clear relationship between the efficacy of these agents at stimulating adenylyl cyclase and their ability to decrease FI responding. These results are consistent with those reviewed above showing that D_1-like dopamine receptor agonists decrease FI responding.

A number of studies have evaluated the effects of D_1- and D_2-like dopamine receptor agonists on responding for conditioned reward. In these studies, rats can respond on either of two levers, one of which produces a stimulus paired previously with food reward. Control animals press the conditioned reward lever significantly more than the non-conditioned reward lever. Animals treated with the D_2-like dopamine receptor agonists bromocriptine or quinpirole selectively pressed more often on the conditioned reward lever; those treated with SKF82958, SKF81297, SKF77434, SKF38393 or CY 208-243 showed a dose-dependent decrease in selective responding on the conditioned reward lever (Beninger and Ranaldi, 1992; Beninger and Rolfe, 1995; Ranaldi and Beninger, 1995; Ranaldi *et al.*, 1995). These results are consistent with those from studies evaluating the effects of these agents on responding for food, shock or stimulus-shock termination (Table 30.2).

The effects of D_1- and D_2-like dopamine receptor agonists on cocaine self-administration have been reported. Consistent with the effects in other lever pressing paradigms, SKF38393 decreased and the D_2-like dopamine receptor agonist SDZ 208-911 increased cocaine self- administration (Katz and Witkin, 1992; Weissenborn *et al.*, 1996). However, another D_2-like dopamine receptor agonist bromocriptine produced a decrease instead of an increase in cocaine self-administration (Weissenborn *et al.*, 1996). At present it is unclear why the two D_2-like dopamine receptor agonists produced different effects in the study of Weissenborn *et al.* (1996). In the studies reviewed above, bromocriptine was effective at increasing responding for conditioned reward. Further studies are needed with this agent

to resolve these apparently contradictory data. With the exception of this result with bromocriptine, however, results from studies of the effects of D_1- and D_2-like dopamine receptor agonists on cocaine self-administration are consistent with those from studies using other rewards to maintain lever pressing (Table 30.2).

In self-administration studies, it has been found that animals that have ceased to respond for cocaine will begin to respond if given a priming injection of a low dose of cocaine. In these priming studies, lever press responses are rewarded by the response-contingent presentation of stimuli previously associated with cocaine injections; in this regard, these studies resemble the conditioned reward studies described above. Self *et al.* (1996a) evaluated the priming effects of SKF82958 or the D_2-like dopamine receptor agonists quinpirole or 7-hydroxy-N,N-di-n-propyl-2- aminotetralin (7-OH-DPAT). They found that treatment with quinpirole or 7-OH-DPAT produced a dose-related increase in cocaine seeking, defined as responding on the cocaine lever. On the other hand, SKF82958 was without effect. These results are consistent with those from the conditioned reward studies reviewed above; D_2- but not D_1-like dopamine receptor agonists increase responding for stimuli associated with reward.

As mentioned in the previous paragraph, cocaine seeking behaviour can be induced by injections of low doses of cocaine. Some researchers have evaluated the effects of D_1- and D_2-like dopamine receptor agonists on cocaine-induced cocaine seeking. The ability of cocaine to induce responding on the lever that produced cocaine previously was decreased by SKF82958 or SKF81297 and increased by 7-OH-DPAT or SDZ 208-911 (Self *et al.*, 1996a; Weissenborn *et al.*, 1996). As was the case with its effects on cocaine self-administration, bromocriptine, unlike the other D_2-like dopamine receptor agonists, decreased, rather than increased, cocaine-induced cocaine seeking (Weissenborn *et al.*, 1996). With the exception of this one finding, results are consistent with those from many related paradigms (Table 30.2) in showing that D_1- and D_2-like dopamine receptor agonists produce different effects on lever press responding for various rewarding stimuli.

30.2.3. Summary

From the studies reviewed here, it can be concluded that D_1-like dopamine receptor agonists can produce a place preference and can support self-administration although these effects appear to depend on the efficacy of the agent at stimulating adenylyl cyclase. D_1-like dopamine receptor agonists also produce conditioned activity following a number of pairings with a test environment. Previous studies have shown that D_2-like dopamine receptor agonists similarly support place conditioning, conditioned activity and self-administration. When the effects of dopamine receptor family-specific agents are evaluated in tasks where lever pressing is being maintained by some other rewarding stimulus, the effects of agents acting at the two families of receptors are different. Thus, D_1-like dopamine receptor agonists produce a decrease and D_2-like dopamine receptor agonists generally produce an increase in FI responding for food, stimulus-shock termination, shock,

conditioned reward, cocaine self-administration, cocaine seeking and cocaine-induced cocaine seeking. From these results, two dissociations can be identified: 1) D_1- and D_2-like dopamine receptor agonists produce different effects in tests of their action on responding for other rewards; 2) D_1- and D_2-like dopamine receptor agonists produce similar effects in tests of their ability to act as rewarding stimuli but different effects in tests of their action on responding for other rewards.

30.3. Dopamine-Mediated Reward-Related Learning Might be Brought About by the Action of Dopamine at D_1-like Dopamine Receptors

Studies of the effects of dopamine D_1-like receptor agonists on reward have yielded fairly consistent results within paradigms. On the other hand, across paradigms, the results may appear to be less consistent. For example, the D_1-like dopamine receptor agonist SKF82958 has been found to support self-administration behaviour (Self and Stein, 1992) but to impair responding for conditioned reward (Beninger and Rolfe, 1995). However, the apparent differential effects of D_1- like dopamine receptor agonists in different paradigms can be reconciled when the elements of learning in those paradigms are identified.

Under natural conditions, there is a burst of activity in dopaminergic neurons when reward occurs (Schultz *et al.,* 1997). This will be termed the "dopamine signal". As I and others have argued elsewhere, the effect of the dopamine signal is to increase the ability of recently encountered environmental stimuli to elicit approach and other responses in the future (see references in Beninger and Miller, 1998). These altered stimuli are termed conditioned incentive stimuli and this process is termed incentive learning (Bindra, 1974; Bolles, 1972). In different paradigms, the need for specifying precisely which stimuli are to become conditioned incentive stimuli differs and the importance of precise timing in the occurrence of those stimuli and the dopamine signal differs. By identifying these differences, the varying effects of D_1-like dopamine receptor agonists in a number of paradigms can be seen to be consistent with one another.

In lever press tasks, the lever and lever-related stimuli that signal reward must come to control responding. Therefore, the timing of the presentation of reward and the animal's encounter with those stimuli would need to be precise. However, in other paradigms like place conditioning or conditioned activity, where any one or several features of the environment associated with reward can come to control responding, there is not the same need for precise timing in the presentation of the environmental stimuli and the reward signal. From this point of view, pharmacological agents that alter the timing of the dopamine signal might impair lever press responding where the timing is critical but might not impair place conditioning or conditioned activity where that timing is less critical.

If the effects of D_1-like dopamine receptor agonists on lever pressing for a variety of rewards are considered from this point of view, they can be understood as revealing that, for reward-related learning, the dopamine signal associated with reward is critical at the D_1-like dopamine receptor. As reviewed above (Table 30.2),

in a variety of lever pressing tasks, injections of D_1-like dopamine receptor agonists lead to a decrease in responding. If these agonists tonically activated the receptors that were critical for incentive learning, then when the dopamine signal occurred it would be masked by tonic activation produced by the receptor agonist. This could provide an explanation for the response decreasing effects of D_1-like dopamine receptor agonists in lever pressing tasks for a variety of rewards. D_2-like dopamine receptor agonists also tonically activate dopamine receptors but they lead to an increase in responding. These results can be seen as suggesting that D_2-like dopamine receptors are not critical for reward-related learning. When they are stimulated, animals are more active but their behaviour still is controlled by incentive learning. Thus, the differential effect of D_1- versus D_2-like dopamine receptor agonists on lever pressing for a number of different rewarding stimuli can be understood as supporting the hypothesis that D_1-like receptors are critical for reward-related learning.

Turning to the paradigms in which the ability of D_1- or D_2-like dopamine receptor agonists themselves to produce reward is assessed, stimulation of either receptor subtype family has been shown to support place conditioning, conditioned activity and self-administration. In place conditioning and conditioned activity, there is not a strong need for precise timing in the presentation of specific environmental cues and dopamine receptor stimulation. Therefore, systemic treatment with a D_1-like dopamine receptor agonist in a particular experimental test chamber is sufficient to lead to incentive learning for some aspects of that environment that subsequently can control behaviour in the test. Thus, D_1-like dopamine receptor agonists produce a place preference (Table 30.1) and conditioned activity.

In self-administration studies, there is a need for precise timing in the presentation of the reward signal and environmental stimuli (*e.g.*, the lever and lever-related stimuli) so that those stimuli can come to control responding. However, when a D_1-like dopamine receptor agonist is being self-administered, it is being injected in conjunction with the lever press response. It may have a delayed onset of action following intravenous injection but there are almost always secondary cues like a light and the sound of the pump that occur immediately following execution of the rewarded response; these cues could preserve the timing of the reward signal in self-administration studies. The finding reviewed above that cocaine self-administration is impaired by systemic treatment with a D_1-like dopamine receptor agonist emphasizes the critical role played by D_1-like dopamine receptors in self-administration.

D_2-like dopamine receptor agonists also support place preference learning, conditioned activity and self-administration. These results show that D_2-like dopamine receptors also play a role in reward-related learning. However, although stimulation of either dopamine receptor family produces reward in these paradigms, only stimulation of D_1-like dopamine receptors but not stimulation of D_2-like dopamine receptors impairs responding in lever pressing tasks. This dissociation can be understood if stimulation of D_1-like dopamine receptors is viewed as being critical for reward-related incentive learning. I and my colleagues have argued elsewhere that the rewarding actions of D_2-like dopamine receptor agonists are

mediated indirectly by D_1-like dopamine receptors (Josselyn *et al.*, 1997; Miller *et al.*, 1990).

30.4. The Role of Second Messengers in Dopamine-Mediated Reward-Related Learning

The observation that D_1-like dopamine receptors are critical for reward-related learning might suggest a role for the second messenger pathway activated by these receptors in this form of learning. I and my colleagues have tested this hypothesis in several experiments in rats. D_1-like dopamine receptors stimulate adenylyl cyclase leading to the formation of cAMP which, in turn, activates cAMP-dependent protein kinase (PKA). Recently, we examined the effects of the PKA inhibitor Rp-cAMPS on place preference conditioning produced by intra-accumbens injections of amphetamine. During conditioning sessions, co-injection of Rp-cAMPS and amphetamine led to an increase in locomotor activity. In spite of this apparent activating effect of a mixture of the two compounds, results revealed a dose-dependent blockade of the place preference effect. Control studies showed no effect of the inhibitor when it was injected alone into the nucleus accumbens and tested for possible effects on place conditioning (Beninger *et al.*, 1996; for further details see also Beninger and Nakonechny, 1996). Thus, by blocking the second messenger pathway normally activated by stimulation of D_1-like dopamine receptors, we were able to block reward- related learning.

In a related study, Savina *et al.* (1997) evaluated the ability of intra-accumbens injections of the PKA activator Sp-cAMPS to produce place preference conditioning. Although a wide range of doses was tried, no significant effect was seen. In more recent studies (J Savina, unpublished), a dose-response curve for intra-accumbens amphetamine-produced place conditioning was established. A subthreshold dose of amphetamine then was injected in combination with a range of doses of Sp-cAMPS in different groups of rats and the ability of this drug combination to produce place conditioning evaluated. However, these experiments also failed to yield significant place conditioning effects. The general failure of studies using the PKA activator to test place conditioning might be related to intracellular second messenger "noise" created by the Sp-cAMPS. Thus, receptors for other neurotransmitters including, for example, norepinephrine and serotonin also activate the cAMP cascade. Perhaps by injecting the PKA activator we are stimulating the cAMP cascade normally produced by these other receptors in addition to that activated by dopamine. This might create signals that interfere with the putative reward-related learning-relevant dopamine signal.

A further study evaluated the ability of the PKA inhibitor Rp-cAMPS to affect conditioned activity produced by three intra-accumbens injections of amphetamine. Although co-injection of Rp-cAMPS and amphetamine did not produce a significant reduction in locomotor activity during conditioning (in fact, some doses produced increased locomotor activity like that seen in the place conditioning studies with this compound reported above), a dose-dependent decrease in con-

ditioned activity was seen on the saline test day (Sutton *et al.*, 1997). This result and the finding that Rp-cAMPS blocked place conditioning produced by intra-accumbens amphetamine provides strong support for the hypothesis that reward-related learning depends critically on D_1- like dopamine receptors and that this type of learning involves activation of the cAMP cascade.

30.5. Conclusions

The focus of this chapter has been the dopamine D_1-like receptor and its possible role in reward- related or incentive learning. I have argued that the variety of findings including rewarding effects of D_1-like dopamine receptor agonists in some paradigms and their apparent disruption of reward in others can be understood as providing consistent support for the hypothesis that D_1-like dopamine receptors play a critical role in reward-related learning. Recent studies showing the ability of inhibition of PKA, an enzymatic step in the cAMP cascade initiated by D_1-like dopamine receptors, to block incentive learning in two different paradigms provides further support for this hypothesis.

A number of recent findings show the critical role played by second messengers in a variety of species and paradigms. For example, the systematic and thorough studies of Izquierdo and his colleagues investigating the role of second messenger cascades in inhibitory avoidance learning in rats clearly show a role for the cAMP cascade in the late post-training memory processing in this task (Bernabeu *et al.*, 1996; Izquierdo *et al.*, this volume). Recently, Guzowski and McGaugh (1997) have shown that disruption in the hippocampus of the cAMP response element binding protein, a transcription factor that is activated along the cAMP cascade, during training in a water maze task impairs rats' memory when tested two days following training but not when tested immediately or four hours following training. Romano *et al.*, (1996) showed that inhibition of PKA impaired habituation learning in crabs. In the invertebrate mollusc Aplysia, Kandel and his co-workers have shown that the cAMP cascade is critical to several forms of learning (Kandel, 1991). Similarly, in the insect Drosophila, genetic manipulations led to an inducible mutation of the cAMP cascade; once the mutation was induced, the flies were shown to be deficient in learning an olfactory discrimination (Drain *et al.*, 1991). All of these findings combine with the studies reviewed here to indicate a critical role for second messengers in learning and memory. Many of these results point to a central role for the D_1-like dopamine receptor, an activator of the cAMP second messenger pathway, in reward-related learning.

For many years the efficacy of antipsychotic drugs in the treatment of schizophrenia has suggested the hypothesis that dopamine is overactive in the brains of people with this disorder (Snyder, 1976, 1981). This hypothesis has been expanded by Weinberger and his associates who have argued that insults early in development might lead to hyper functioning of the dopamine system and schizophrenia later in life (Lipska and Weinberger, 1993). I have suggested that schizophrenia might be understood as an impairment of incentive learning (Beninger, 1983). From

the hypothesis discussed in the present paper, it follows that schizophrenia might result from over stimulation of D_1-like dopamine receptors.

A case for the D_1-like dopamine receptor as a primary site of therapeutic action of neuroleptic drugs was presented by Miller *et al.* (1990). More recently, Josselyn *et al.* (1997) argued that the therapeutic effects of clozapine may be mediated through the blockade of D_1-like dopamine receptors. If it is the case that the symptoms of schizophrenia are associated with over stimulation of the D_1-like dopamine receptor, it may be possible to develop therapeutic agents that work by affecting the second messenger cascade to reduce incentive learning. Some work with Parkinson's disease already has begun to explore this possibility (see Chase and Oh, this volume).

One of the apparent problems with the suggestion to target the cAMP second messenger cascade in treatment is the fact that a large number of hormonal, neurotransmitter and other signalling substances have their signals converged at one sole second messenger, cAMP. However, recent molecular studies have shown that there are a number of PKA isozymes, consisting of homo- and heterodimers of regulatory subunits with a number of associated catalytic subunits. Taskén *et al.*, (1997) show that the various isozymes of PKA display distinct biochemical properties, show cell-specific expression, differential regulation at the transcription level and distinct subcellular localization. These results suggest that in the future it may be possible to isolate specific second messenger pathways that are activated by D_1-like dopamine receptors. Thus, there is much work yet to be done as we move towards the next generation of treatments for schizophrenia and other monoaminergically based disease states.

Acknowledgment

This chapter is dedicated to Julie Strifler. Supported by a grant from the Natural Sciences and Engineering Research Council of Canada.

References

Abrahams BS, Rutherford JD, Mallet PE and Beninger RJ (1998) Place conditioning with the dopamine D_1-like agonist SKF 82958 but not SKF 81297 or SKF 77434. *European Journal of Pharmacology*, **343**, 111-118.

Andersen PH and Jansen JA (1990) Dopamine receptor agonists: selectivity and dopamine D_1 receptor efficacy. *European Journal of Pharmacology*, **188**, 335-347.

Andersen PH, Grønvald FC and Jansen JA (1985) A comparison between dopamine-stimulated adenylate cyclase and ^{3}H-SCH 23390 binding in rat striatum. *Life Sciences*, **37**, 1971-1983.

Arnt J, Hyttel J and Sanchez C (1992) Partial and full dopamine D_1-receptor agonists in mice and rats - relation between behavioural effects and stimulation of adenylate cyclase activity in vitro. *European Journal of Pharmacology*, **213**, 259-267.

Beninger RJ (1983) The role of dopaminwe in locomotor activity and learning. *Brain Research Reviews*, **6**, 173-196.

Beninger RJ (1991) Receptor subtype-specific dopamine agonists and antagonists and conditioned behaviour. In: *The mesolimbic dopamine system: From motivation to action* (Eds P Willner and J Scheel-Krüger), pp. 273-299. John Wiley & Sons: Chichester.

Beninger RJ (1993) Role of D_1 and D_2 receptors in learning. In: *D_1:D_2 Dopamine Receptor Interactions: Neuroscience and Pharmacology* (Ed J Waddington), pp. 115-157. Academic Press, London.

Beninger RJ and Miller R (1998) Dopamine D_1-like receptors and reward-related incentive learning. *Neuroscience and Biobehavioral Reviews*, **22**, 335-345.

Beninger RJ and Nakonechny PL (1996) Dopamine D_1-like receptors and molecular mechanisms of incentive learning. In: *Dopamine Disease States* (Eds RJ Beninger, T Palomo and T Archer), pp. 407-431. CYM Press, Madrid.

Beninger RJ and Ranaldi R (1992) The effects of amphetamine, apomorphine, SKF 38393, quinpirole and bromocriptine on responding for conditioned reward in rats. *Behavioural Pharmacology*, **3**, 155-163.

Beninger RJ and Rolfe NG (1995) Dopamine D_1-like receptor agonists impair responding for conditioned reward in rats. *Behavioural Pharmacology*, **6**, 785-793.

Beninger RJ, Nakonechny PL and Todd MJ (1996) Inhibition of protein kinase A in the nucleus accumbens blocks amphetamine-produced conditioned place preference in rats. *Society for Neuroscience Abstracts*, **22**, 1127.

Bergman J, Rosenzweig-Lipson S and Spealman RD (1995) Differential effects of dopamine D-1 and D-2 receptor agonists on schedule-controlled behavior of squirrel monkeys. *Journal of Pharmacology and Experimental Therapeutics*, **273**, 40-48.

Bernabeu R, Schmitz P, Faillace MP, Izquierdo I and Medina JH (1996) Hippocampal cGMP and cAMP are differentially involved in memory processing of inhibitory avoidance learning. *NeuroReport*, **7**, 585-588.

Bindra D (1974) A motivational view of learning, performance and behavior modification. *Psychological Review*, **81**, 199-213.

Bolles RC (1972) Reinforcement, expectancy, and learning. *Psychological Review*, **79**, 394-407.

Civelli O, Bunzow JR and Grandy DK (1993) Molecular diversity of the dopamine receptors. *Annual Reviews of Pharmacology and Toxicology*, **32**, 281-307.

Dews PB (1958) Analysis of the effects of psychopharmacological agents in behavioral terms. *Federation Proceedings*, **17**, 1024-1030.

Drain P, Folkers E and Quinn WG (1991) cAMP-dependent protein kinase and the disruption of learning in transgenic flies. *Neuron*, **6**, 71-82.

Everitt BJ (1990) Sexual motivation: A neural and behavioural analysis of the mechanisms underlying appetitive and copulatory responses of male rats. *Neuroscience and Biobehavioral Reviews*, **14**, 217-232.

Fontana D, Post RM, Weiss SRB and Pert A (1993) The role of D_1 and D_2 dopamine receptors in the acquisition and expression of cocaine-induced conditioned increases in locomotor behavior. *Behavioural Pharmacology*, **4**, 375-388.

Grech DM, Spealman RD and Bergman J (1996) Self-administration of D_1 receptor agonists in squirrel monkeys. *Psychopharmacology*, **125**, 97-104.

Guzowski JF and McGaugh JL (1997) Antisense oligodeosynucleotide-mediated disruption of hippocampal cAMP response element binding protein levels impairs consolidation of memory for water maze training. *Proceedings of the National Academy of Sciences, USA*, **94**, 2693-2698.

Hoffman DC and Beninger RJ (1988) Selective D_1 and D_2 dopamine agonists produce opposing effects in place conditioning but not in conditioned taste aversion learning. *Pharmacology Biochemistry and Behavior*, **31**, 1-8.

Hoffman DC and Beninger RJ (1989) The effects of selective dopamine D_1 and D_2 receptor antagonists on the establishment of agonist-induced place conditioning in rats. *Pharmacology Biochemistry and Behavior*, **33**, 273-279.

Huang YY and Kandel ER (1995) D_1/D_5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. *Proceedings of the National Academy of Sciences, USA*, **92**, 2446-2450.

Izenwasser S and Katz JL (1993) Differential efficacies of dopamine D_1 receptor agonists for stimulating adenylyl cyclase in squirrel monkey and rat. *European Journal of Pharmacology*, **246**, 39-44.

Josselyn SA, Miller RJ and Beninger RJ (1997) Behavioral effects of clozapine and dopamine receptor subtypes. *Neuroscience and Biobehavioral Reviews*, **21**, 531-558.

Kandel ER (1991) Cellular mechanisms of learning and the biological basis of individuality. In: *Principles of Neural Science* (Eds ER Kandel, JH Schwartz and TM Jessell), pp. 1009-1031. Appleton & Lange, Norwalk, CT.

Katz JL, Alling K, Shores E and Witkin JM (1995) Effects of D_1 dopamine agonists on schedule- controlled behavior in the squirrel monkey. *Behavioural Pharmacology*, **6**, 143-148.

Katz JL and Witkin JM (1992) Selective effects of the D_1 dopamine receptor agonist, SKF 38393, on behavior maintained by cocaine injection in squirrel monkeys. *Psychopharmacology*, **109**, 241- 244.

Katz JL and Witkin JM (1993) Behavioral effects of dopaminergic agonists and antagonists alone and in combination in the squirrel monkey. *Psychopharmacology*, **113**, 19-25.

Kebabian JW and Calne DB (1979) Multiple receptors for dopamine. *Nature*, **277**, 93-96.

Koob GF (1992) Drugs of abuse: Anatomy, pharmacology and function of reward pathways. *Trends in Pharmacological Science*, **13**, 177-184.

Kuba K and Kumamoto E (1990) Long-term potentiations in vertebrate synapses: A variety of cascades with common subprocesses. *Progress in Neurobiology*, **34**, 197-269.

LeMoal M and Simon H (1991) Mesocortical dopaminergic network: Functional and regulatory roles. *Physiological Reviews*, **71**, 155-234.

Lipska BK and Weinberger DR (1993) Cortical regulation of the mesolimbic dopamine system: Implications for schizophrenia. In: *Limbic Motor Circuits and Neuropsychiatry* (Eds PW Kalivas and CD Barnes), pp. 329-349. CRC Press, Boca Raton, FL.

Mazurski EJ and Beninger RJ (1991) Effects of selective drugs for dopaminergic D_1 and D_2 receptors on conditioned locomotion in rats. *Psychopharmacology*, **105**, 107-112.

Melis MR and Argiolas A (1995) Dopamine and sexual behavior. *Neuroscience and Biobehavioral Reviews*, **19**, 19-38.

Miller R, Wickens JR and Beninger RJ (1990) Dopamine D-1 and D-2 receptors in relation to reward and performance: A case for the D-1 receptor as a primary site of therapeutic action of neuroleptic drugs. *Progress in Neurobiology*, **34**, 143-183.

Milner PM (1991) Brain-stimulation reward: A review. *Canadian Journal of Psychology*, **45**, 1- 36.

Niznik HB and van Tol HHM (1992) Dopamine receptor genes: New tools for molecular psychiatry. *Journal of Psychiatry and Neuroscience*, **17**, 158-180.

O'Boyle KM, Gaitanopoulos DE, Brenner M and Waddington JL (1989) Agonist and antagonist properties of benzazepine and thienopyridine derivatives at the D_1 dopamine receptor. *Neuropharmacology*, **28**, 401-404.

Olds J and Milner P (1954) Positive reinforcement produced by electrical stimulation of septal area and other regions of the rat brain. *Journal of Comparative and Physiological Psychology*, **47**, 419-427.

Phillips AG, Blaha CD and Fibiger HC (1989) Neurochemical correlates of brain-stimulation reward measured by ex vivo and in vivo analyses. *Neuroscience and Biobehavioral Reviews*, **13**, 99-104.

Ranaldi R and Beninger RJ (1995) Bromocriptine enhancement of responding for conditioned reward depends on intact D_1 receptor function. *Psychopharmacology*, **118**, 437-443.

Ranaldi R, Pantalony D and Beninger RJ (1995) The D_1 agonist SKF 38393 attenuates amphetamine-produced enhancement of responding for conditioned reward in rats. *Pharmacology Biochemistry and Behavior*, **52**, 131-137.

Robinson TE and Berridge KC (1993) The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Research Reviews*, **18**, 247-291.

Romano A, Locatelli F, Delorenzi A, Pedreira ME and Maldonado H (1996) Effects of activation and inhibition of cAMP-dependent protein kinase on long-term habituation in the crab Chasmagnathus. *Brain Research*, **735**, 131-140.

Salamone JD (1994) The involvement of nucleus accumbens dopamine in appetitive and aversive motivation. *Behavioural Brain Research*, **61**, 117-133.

Savina I, Nakonechny PL, Abrahams BS and Beninger RJ (1997) Place conditioning with intra-accumbens amphetamine: The role of cyclic-AMP-dependent protein kinase (PKA). *Journal of Psychopharmacology*, **11[Suppl.]**, A18.

Schultz W, Dayan P and Montague PR (1997) A neural substrate of prediction and reward. *Science*, **275**, 1593-1599.

Self DW and Stein L (1992) The D_1 agonists SKF-82958 and SKF-77434 are self-administered by rats. *Brain Research*, **582**, 349-352.

Self DW, Barnhart WJ, Lehman DA and Nestler EJ (1996a) Opposite modulation of cocaine-seeking behavior by D_1- and D_2-like dopamine receptor agonists. *Science*, **271**, 1586-1589.

Self DW, Belluzzi JD, Kossuth S and Stein L (1996b) Self-administration of the D_1 agonist SKF 82958 is mediated by D_1, not D_2, receptors. *Psychopharmacology*, **123**, 303-306.

Sibley DR, Monsma FJ Jr and Shen Y (1993) Molecular neurobiology of D_1 and D_2 dopamine receptors. In: *D_1: D_2 Dopamine Receptor Interactions* (Ed J Waddington), pp. 1-17. Academic Press Limited, London.

Snyder SH (1976) The DA hypothesis of schizophrenia: Focus on the DA receptor. *American Journal of Psychiatry*, **133**, 197-202.

Snyder SH (1981) DA receptors, neuroleptics and schizophrenia. *American Journal of Psychiatry*, **138**, 460-464.

Sutton MA, McGibney K and Beninger RJ (1997) Inhibition of protein kinase A in the nucleus accumbens blocks conditioned, but not unconditioned, locomotor stimulation by amphetamine. *Society for Neuroscience Abstracts*, **23**, 1315.

Taskén K, Skålhegg BJ, Taskén KA, Solberg R, Knutsen HK, Levy FO, Sandberg M, Ørstavid S, Larsen T, Johansen AK, Vang T, Schrader HP, Reinton NTK, Torgersen KM, Hansson V and Jahnsen T (1997) Structure, function, and regulation of human cAMP-dependent protein kinases. In: *Signal Transduction in Health and Disease: Advances in Second Messenger and Phosphoprotein Research Vol. 13* (Eds J Corbin and S Francis), pp. 191-204. Lippencott-Raven Publishers, Philadelphia.

Weed MR and Woolverton WL (1995) The reinforcing effects of dopamine D_1 receptor agonists in rhesus monkeys. *Journal of Pharmacology and Experimental Therapeutics*, **275**, 1367-1374.

Weed MR, Vanover KE and Woolverton WL (1993) Reinforcing effect of the D_1 dopamine agonist SKF 81297 in rhesus monkeys. *Psychopharmacology*, **113**, 51-52.

Weissenborn R, Deroche V, Koob GF and Weiss F (1996) Effects of dopamine agonists and antagonists on cocaine induced responding for a cocaine-associated stimulus. *Psychopharmacology*, **126**, 311-322.

White NM and Milner PM (1992) The psychobiology of reinforcers. *Annual Review of Psychology*, **43**, 443-440.

White NM, Packard MG and Hiroi N (1991) Place conditioning with dopamine - D_1 and D_2 agonists induced peripherally or into nucleus accumbens. *Psychopharmacology*, **103**, 271-276.

Wickens J (1993) *A Theory of the Striatum*, Oxford: Pergamon Press.

Wise RA (1978) Catecholamine theories of reward: A critical review. *Brain Research*, **152**, 215- 247.

Wise RA (1991) Neuroleptic-induced anhedonia - Recent studies. In: *Advances in Neuropsychiatry and Psychopharmacology, Vol.1: Schizophrenia research* (Eds CA Tamminga and SC Schulz), pp. 323-331. Raven Press, New York.

Wise RA and Bozarth MA (1981) Brain substrates for reinforcement and drug self-administration. *Progress in Neuropsychopharmacology*, **5**, 467-474.

Wise RA and Rompré P-R (1989) Brain dopamine and reward. *Annual Review of Psychology*, **40**, 191-227.

Witkin JM, Schindler CW, Tella SR and Goldberg SR (1991) Interaction of haloperidol and SCH-23390 with cocaine and dopamine receptor subtype-selective agonists on schedule-controlled behavior of squirrel monkeys. *Psychopharmacology*, **104**, 425-420.

Woolverton WL, Goldberg LI and Ginos JZ (1984) Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. *Journal of Pharmacology and Experimental Therapeutics*, **230**, 678-683.