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Dopamine D1-like Receptors and Reward-related Incentive Learning

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BENINGER, R. J., R. MILLER. *Dopamine D1-like receptors and reward-related incentive learning*. NEUROSCI BIOBEHAV REV **22**(2), 335–345, 1998.—There now is general agreement that dopaminergic neurons projecting from ventral mesencephalic nuclei to forebrain targets play a critical role in reward-related incentive learning. Many recent experiments evaluate the role of dopamine (DA) receptor subtypes in various paradigms involving this type of learning. The first part of this paper reviews evidence from these studies that use antagonists or agonists relatively specific for D1- or D2-like receptors in operant paradigms with food, brain stimulation, self-administered stimulant or conditioned rewards or place conditioning. The focus is on studies that directly compare agents acting at the two DA receptor families, especially those studies where the agents produce differential actions. Results support the conclusion that D1-like receptors play a more critical role in reward-related learning than D2-like receptors. D1-like receptors initiate a cascade of intracellular events including cyclic adenosine monophosphate (cAMP) formation and activation of cAMP-dependent protein kinase (PKA). The final section of this paper reviews evidence from a wide range of neuroscience experiments that implicates the cAMP/PKA pathway in learning in general and in reward-related incentive learning in particular. We conclude that the molecular mechanism underlying DA-mediated incentive learning may involve DA release in association with reward, stimulation of D1-like receptors, activation of the cAMP/PKA cascade and additional intracellular events leading to modification of cortico-striatal glutamatergic synapses activated by stimuli encountered in close temporal contiguity with reward. Thus, when reward-related incentive learning takes place, it may be the action of DA acting at D1-like receptors that leads to plastic changes in the striatum that form the substrate of that learning. © 1998 Elsevier Science Ltd. All rights reserved.

cAMP D1 D2 Dopamine Incentive Learning Plasticity Protein kinase Reward Striatum

INTRODUCTION

INVESTIGATIONS OVER many years have shown a relationship between dopamine (DA) and psychoses. The observations that most pharmacological agents used in the treatment of schizophrenia are DA receptor blockers, and that stimulant drugs such as cocaine and amphetamine are psychotogenic, originally contributed to the hypothesis that brain DA is hyperfunctional in schizophrenia. (For a recent update of the DA hypothesis see (47).) In parallel, the animal literature has shown a strong relationship between DA and reward-related incentive learning. Incentive learning is defined as the acquisition by previously neutral stimuli of the ability to elicit approach and other responses and occurs in association with the presentation of rewarding stimuli to animals (11,12,14). Thus, DA receptor antagonists block the usual effects of reward on behaviour, and agonists support incentive learning in a number of paradigms (3,123). As an attempt to join together these two bodies of information, we have suggested previously that much of the symptomatology observed in psychoses can be viewed as an exaggeration or distortion of reward-related learning (3,66–68,70).

Recently, DA receptors have been found to exist in at least five different subtypes, termed D1 through D5. Based on their ability either to stimulate or inhibit the enzyme adenylate cyalase, these receptors have been classified into two groups, D1-like, including D1 and D5 and D2-like, including D2, D3 and D4 (21,80,99).

For many years it was believed that the D2-like receptors mediated the actions of antipsychotic drugs (108). However, recently it has been found that this mechanism of action cannot account for the antipsychotic properties of the drug clozapine. Thus: (i) clozapine does not fall on the line describing the relationship between clinical potency and D2-like receptor affinity (108); (ii) clozapine does not cause extrapyramidal side effects, normally attributed to blockade of D2-like receptors (18); and (iii) in studies of receptor occupancy, effective antipsychotic doses of clozapine produce a much lower level of D2 receptor occupancy than classical neuroleptic drugs (108). Because clozapine has affinity for a wide variety of receptors, a number of hypotheses are compatible with the observation that it is an effective antipsychotic medication. For example, any of 5-HT2 plus D2 combined receptor antagonism, or D4 DA

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receptor antagonism, or D1-like receptor antagonism could be responsible (45,70). Seeman and coworkers (108) have pointed out that clozapine falls on the line relating clinical potency to D4 receptor affinity, supporting the hypothesis that clozapine produces antipsychotic effects by acting at the D4 receptor.

Part of our own arguments in favour of reduced activation of the D1-like receptor as mediating the antipsychotic actions of clozapine depend on identifying the D1-like receptor as critical to reward-related learning. However, the arguments for this idea are not straightforward, but involve a number of other subsidiary assumptions (70). Because of the need for these assumptions, our interpretation of the evidence may appear complex, and other interpretations may appear more straightforward and equally plausible. One of the difficulties is that in many paradigms the effects of drugs acting at D1- and D2-like receptors are similar. This has been discussed in previous publications (45,69,70) in which we have argued that the effects of drugs acting upon reward-related learning are achieved indirectly, being mediated via effects on motor performance and the firing rate of midbrain DA neurons.

In the present paper, we review recent studies concerning the role of D1-like receptors in reward-related incentive learning. The focus is on those aspects of the psychopharmacological evidence where drugs acting on D1- or D2-like receptors have different actions, or where there are other interesting dissociations. We argue that, despite some complications, the hypothesis that D1-like receptors play a critical role in incentive learning provides a good account of the evidence. D1-like receptors activate the enzyme adenylate cyclase, leading to stimulation of cyclic adenosine monophosphate formation, and a cascade of intracellular events that has been implicated in various forms of learning and memory in diverse experimental paradigms. In the final section, we review some of these findings and suggest that similar mechanisms may operate in incentive learning.

D1- AND D2-LIKE ANTAGONISTS

In 1993, after reviewing a large number of studies of the effects of DA receptor family subtype-specific antagonists in a variety of behavioural tasks involving reward, Beninger (4) came to the following conclusion. Both D1- and D2-like antagonists block the usual effects of reward in animals performing tasks such as lever pressing for food, electrical stimulation of the brain and stimulant self-administration. They also block place conditioning and conditioned activity produced by stimulant drugs. In tests of avoidance responding, D2-like antagonists produce an extinction-like decline in responding, suggestive of a block of the rewarding effects of safety; in the one available study, a D1-like antagonist failed to produce a gradual decline in avoidance responding. Both types of antagonists blocked the memory improving effects of post-training treatments with rewarding stimuli. Overall, the data suggested that both D1- and D2-like receptors were involved in mediating the usual effects of reward on behaviour.

Since writing that review, a number of additional studies have been published that allow a more direct comparison of D1- and D2-like antagonists in a number of paradigms involving reward-related learning. These data have been reviewed more recently, in 1996, by Beninger and Nakonechny (6). As in the previous review, it was concluded that data from a number of paradigms (including operant responding for food, water, brain stimulation reward, or drug self-administration, or conditioned reward or place conditioning) show that DA antagonists acting at either D1- or D2-like receptors produce a decrease in the ability of rewarding stimuli to control responding. However, the observation that some results show differential effects with antagonists relatively specific for either DA receptor subclass allowed the further conclusion that the D1-like receptor played a more important role in the mechanisms by which rewarding stimuli control behaviour. Following is a review of the studies showing differential effects of D1- vs D2-like antagonists in paradigms involving reward-related learning.

In a recent study by Fowler and Liou (27) of the effects of DA antagonists on operant responding for food, an across-session decrease was seen over several days of testing with SCH 23390, but not with the D2 antagonist raclopride. This study included an extensive and sophisticated behavioural analysis that led to the conclusion that the D2-like receptor antagonist produced a greater effect on motor function than the D1-like antagonist, results consistent with the differential effects of these agents on schedule-controlled responding. A simple motor effect of the drugs would have been expected to produce a uniform decrease in responding within or across sessions. These findings suggested a greater role for D1-like receptors in reward and a greater role for D2-like receptors in motor function.

In related but older studies by Nakajima and coworkers (74,75), rats treated with low doses of the D1-like receptor antagonist SCH 23390 showed a greater decrease in responding on schedules of intermittent reinforcement for food than the decrease seen in responding for continuous reinforcement; the D2-like antagonist raclopride, on the other hand, similarly affected responding on both schedules. The differential results with SCH 23390 could not be attributed to a motor effect, whereas the effects of raclopride were consistent with a motor effect. Results suggest a greater involvement of D1-like receptors in the control of behaviour by reward.

Two studies by McDougall and coworkers (63,64) used 11- or 17-day old rat pups in an instrumental conditioning paradigm requiring a running response for nipple attachment reward. In both studies, SCH 23390, but not the D2-like antagonist sulpiride, produced an extinction-like decrease in running speed, although sulpiride augmented the effects of SCH 23390 when they were given together. Results show that both D1- and D2-like receptors are involved in reward-related learning, but the differential effects of antagonists acting at the two receptor classes, when given alone, suggest that D1-like receptors may be more importantly involved.

A recent study by Hunt et al. (43), using brain stimulation as the rewarding stimulus, reported a failure to dissociate reward from performance effects with the D2-like antagonist spiperone, but did observe this dissociation with SCH 23390. This study, like that of Fowler and Liou (27) using food reward, might suggest a more important role for D1-like receptors in reward-related learning.

The self-administration paradigm is particularly well suited to a dissociation of reward versus motor effects of DA antagonists because DA antagonists can produce increases

in responding like those seen following decreases in the concentration of the rewarding drug; an effect on reward produces a change in responding in a direction opposite to the decrease in responding that would be expected if motor ability was being affected. Another variable also seems to be important in these experiments, however. Thus, many researchers use a time out period, during which responding has no programmed consequences, following delivery of a self-administered drug. With a long time out (e.g., 2 min), increases in responding are not seen following any doses of DA antagonists; only no effect or decreases are seen depending on dose (15).

Some studies have found differential effects of D1- vs D2-like antagonists on responding to self-administer drugs. Thus, in a study by Koob et al. (57), SCH 23390 was found to produce a dose-dependent increase in responding for cocaine (followed by a short time out) whereas spiperone was effective at only one dose. In other studies from the laboratories of Koob or Woolverton (15,54), D1-like antagonists were found to decrease responding for cocaine on a multiple schedule (with long time outs) at doses that were less effective at decreasing responding for food; no similar dissociation was found for D2-like antagonists (15). Like studies of operant responding for food or brain stimulation reward, these data, revealing differential effects of D1- vs D2-like antagonists, further suggest that the action of DA at the D1-like receptor may be particularly involved in reward-related learning.

Animals will learn an operant response when rewarded with a stimulus that has acquired its rewarding properties as a result of a prior history of association with a primary rewarding stimulus such as food or water; such a stimulus is termed a conditioned reward. Previous studies have shown that treatment with amphetamine specifically enhances the acquisition of responding for conditioned rewards, as reviewed by Beninger and Ranaldi (8). Treatment with SCH 23390 was found to shift the amphetamine dose-response curve in this paradigm to the right; the D2-like antagonist pimozide also shifted the curve to the right but the maximum level of responding seen following treatment with SCH 23390 was never seen with pimozide. The D2 antagonist metoclopramide, on the other hand, decreased the amphetamine enhancement of responding in a dose-dependent manner but failed to shift the amphetamine dose-response curve to the right (82). These results implicate both D1- and D2-like receptors in incentive learning produced by conditioned rewards. Although limited data are available from this paradigm, the results also suggest that D1-like antagonists may produce effects somewhat specific to reward whereas D2-like antagonists affect reward and motor responding, as also suggested by data reviewed above from studies of operant responding for food, brain stimulation reward and stimulant self-administration.

Given a choice between two familiar chambers, one of which previously has been paired with reward, rats show a preference for the place associated with reward. For example, preferences have been reported for places associated with food, water, psychostimulants or morphine. Place preference conditioning with water was blocked by SCH 23390, raclopride or pimozide (2). In studies from the laboratories of Beninger and others, place conditioning with amphetamine was blocked by SCH 23390, and by the D2-like antagonists metoclopramide or sulpiride (37,40,60) and conditioning with pipradrol (another stimulant drug) was blocked with SCH 23390 (116). Di Chiara and coworkers showed that place conditioning with morphine was blocked by acute SCH 23390 or SCH 39166 (1,60). These results show that both DA receptor families seem to be involved in incentive learning in this task, but some studies further show differential effects. Thus, the work of Shippenberg and coworkers showed that morphine place conditioning was blocked by chronic systemic SCH 23390 or intra-accumbens injections of SCH 23390 but not by chronic systemic spiperone or intra-accumbens sulpiride (95,97,98). Similarly, place conditioning based on cocaine was blocked by SCH 23390 but not by sulpiride (19). These latter findings suggest that, at least in the case of place conditioning with morphine or cocaine, D1-like receptors may play a more critical role than D2-like receptors.

In the above studies, reporting that SCH 23390 blocked place conditioning, control experiments showed that the same doses of SCH 23390 given alone did not produce a place aversion. However, a number of studies have found that SCH 23390 or the D1-like antagonist A69024, at some doses, can produce a place aversion when given systemically (1,96,98), and two studies reported an aversion when SCH 23390 was given alone into the nucleus accumbens (95,96). In contrast, metoclopramide or sulpiride, given alone, failed to produce a place aversion (96,98). Perhaps these results also indicate a more important role for D1- than for D2-like receptors in reward.

In psychopharmacological experiments, sensitization is defined as an increased response to a particular dose of a drug with repeated intermittent exposure to that drug. Indirect acting DA agonists such as amphetamine produce sensitization. Detailed studies have shown that conditioning to environmental stimuli associated with the drug plays a significant role in sensitization although it does not account for the entire effect (105,106). The relative role of D1- and D2-like receptors in the different components of stimulant sensitization is at present controversial. It has been observed that the development of sensitization to systemic treatments with amphetamine is blocked by systemic SCH 23390 but not by D2-like antagonists, implicating D1-like receptors in this effect (111). However, localization studies showed that injections of the D1-like antagonist into the mesencephalic regions containing DA cell bodies were effective at blocking sensitization (107), implicating D1-like receptors in those regions. To the extent that sensitization to the effects of amphetamine includes conditioned responses to environmental stimuli associated with the drug (105,106), this result further supports the conclusion that D1-like receptors may be more important in DA mediated learning, though more studies of the conditions in which each receptor subtype is involved, and the site of their actions, need to be carried out.

In summary, results from a large number of studies show that the capacity of a number of different types of rewards to alter the ability of stimuli associated with reward to control responding is reduced by agents that block either D1- or D2-like receptors. Additionally, a number of more recent studies present results suggestive of a more critical role for D1-like receptors in the rewarding effects of food, brain stimulation, self-administered drugs, conditioned rewards and agents used in place conditioning paradigms.

D1- AND D2-LIKE AGONISTS

In place conditioning or self-administration experiments, where D1- or D2-like agonists are used as the potentially rewarding agents, results show that stimulation of either receptor family is rewarding. However, as will be reviewed in this section, only low doses of D1-like agonists will maintain self-administration. Furthermore, in operant lever pressing tasks rewarded with food, brain stimulation reward or conditioned reward, there is a convergence of results from a number of recent papers suggesting that D1-, but not D2-like agonists impair responding. In the following section, we will argue that these results are consistent with a role for D1-like receptors in reward-related incentive learning.

Place conditioning studies from Beninger's laboratory showed that the D1-like agonist SKF 38393 produced a place aversion, not a preference (38,40). A subsequent study from White's laboratory reported that intra-accumbens, but not systemic, injections of SKF 38393 produced a place preference (117). This finding suggested that some action of SKF 38393 other than its effects on accumbens D1-like receptors was responsible for its aversive properties, a suggestion consistent with the finding of Terry and Katz (109) that the appetite suppressing effects of SKF 38393 were not blocked by SCH 23390 although those of other D1-like agonists were. In a recent unpublished study, Beninger and coworkers confirmed that the aversive properties of SKF 38393 may be unrelated to its action at D1-like receptors. They found that systemic injections of the D1-like agonist SKF 82958 produced a place preference in a dose-dependent manner. In several studies, D2-like agonists have been found to produce a place preference (38,40,41,73,117). Recent results have shown that 7-OH-DPAT produced a place preference (20,62); this compound has a weak selectivity for D3 vs D2 receptors, but the doses that produced place conditioning were high and may have affected D2 receptors. Thus, place preferences are produced by either D1- or D2-like agonists.

As stated above, both D1- and D2-like agonists are self-administered by animals. Woolverton et al. (126) reported originally that SKF 38393 was not self-administered by monkeys, a finding consistent with the aversive properties observed for this agent in place conditioning. Subsequent studies from Woolverton's lab found that low concentrations of the D1-like agonist SKF 81297 were self-administered by monkeys (114), and Self and Stein and coworkers found that SKF 82958 or SKF 77434 were self-administered by rats (93,94). Higher concentrations did not maintain responding; this observation may be consistent with the finding that D1-like agonists impair responding for other types of reward as reviewed below. The D2-like agonists bromocriptine and piribedil were self-administered by monkeys and rats (122,125,126). Results suggest a role for both D1- and D2-like receptors in reward.

Both the D1-like agonists SKF 38393 and SKF 75760 and the D2-like agonists N-0437 and RU 24213 decreased responding on a fixed ratio schedule for food (51,88,89); similarly, SKF 38393 and the D2-like agonist quinpirole decreased variable interval responding for food (39). However, with the use of a multiple schedule including fixed interval and fixed ratio components, differential effects of D1- versus D2-like agonists have been found. Thus, SKF 38393 decreased both fixed interval and fixed ratio responding of monkeys whereas quinpirole increased fixed interval responding at doses that decreased fixed ratio responding (52,124). Bergman et al. (10), in independent groups of monkeys trained on either a fixed interval schedule of shock avoidance or a fixed ratio for food, found that D1-like agonists similarly decreased responding on both schedules whereas D2-like agonists similarly increased fixed interval responding at doses that decreased fixed ratio responding. In a related study by Tidey and Miczek (110), mice were seen to decrease responding for food presented according to a multiple schedule following SKF 38393 at doses that failed to affect unconditioned social and motor responses; quinpirole, on the other hand, showed no similar dissociation, decreasing operant and unconditioned responding at each effective dose. Finally, Katz et al. (50) reported that a number of D1-like agonists decreased fixed interval responding for shock whereas amphetamine produced an increase at some doses.

The effects of D1- vs D2-like agonists on operant responding for food can be summarized as follows. Regardless of the schedule of reinforcement, D1-like agonists are seen to produce decreases in responding. Thus, D1-like agonists decrease responding on fixed interval, variable ratio and fixed ratio schedules. D2-like agonists, on the other hand, are seen to increase responding at some doses on fixed interval schedules although they consistently decrease responding on fixed ratio schedules. Results suggest that D1- and D2-like receptors play different roles in the control of responding by reward. Stimulation of D1-like receptors more strongly interferes with operant responding.

Katz and Witkin (51) evaluated the effects of systemic SKF 38393 on operant responding to self-administer cocaine and found a decrease, the dose-response curve being shifted to the right. This result is consistent with the findings reviewed above showing that D1-like agonists impair operant responding for food reward.

In a number of studies using stimulation of the lateral hypothalamus or ventral tegmental area as the rewarding stimulus for each lever press, D2-like agonists including quinpirole, CV 205-502 or bromocriptine produced leftward shifts in the rate-frequency function, indicative of enhanced reward (17,55,76,77,83). The effects of D1-like agonists have been less consistent. Thus, A77636 produced a leftward shift (83) but SKF 38393 had no effect in one study (77) and produced a rightward shift, suggesting decreased reward, in another (43). It is noteworthy that in the latter study brain stimulation reward was presented according to a fixed interval schedule, making the observation of decreased responding consistent with the effects of D1-like agonists on operant responding for food, as reviewed above.

In studies of rats responding for conditioned reward, Beninger and coworkers showed that, similar to their effects on operant responding for food, brain stimulation reward or self-administered cocaine, systemic injections of D1-like agonists decrease responding for conditioned reward in a dose-dependent manner (9,84,85). D2-like agonists, on the other hand, increase responding at some doses (7,84).

In summary, comparisons of the actions of D1- vs D2-like agonists in a number of incentive learning paradigms have yielded a complex picture showing a similar effect of agonists acting at the two receptor families in some paradigms but differential effects in others. On the one hand, in place

conditioning and self-administration studies, where agonists are used as the rewarding stimuli themselves, both D1- and D2-like agonists have rewarding effects although only low doses of D1-like agonists are effective in self-administration. On the other hand, in lever pressing tasks rewarded with food, brain stimulation, cocaine or conditioned reward, D1-like, but not D2-like agonists impair responding.

DISCUSSION: THE PRINCIPLES OF ACTION OF D1-LIKE AGENTS

The preceding review yields three important dissociations:

1. Although both D1- and D2-like antagonists impair responding for a number of rewarding stimuli, the effects of D1-like antagonists seem to be more strongly associated with reduced reward whereas those of D2-like antagonists seem to be more strongly linked to impaired performance.
2. D1-like agonists have a rewarding effect in some paradigms, but impair responding in others
3. D1- and D2-like agonists produce similar effects in some paradigms but different effects in others.

How can these dissociations be understood? To answer this question, we will discuss the theory of action of DA agonist drugs in relation to the release of endogenous DA.

When DA is released under natural circumstances in association with the presentation of a rewarding stimulus, release is controlled by a brief burst of impulses lasting only a few hundred milliseconds (71,90–92). Correspondingly, the concentration of DA in the synaptic cleft shows an intense but short-lived peak (29,53). This we refer to as the 'DA signal'.

When a direct-acting DA agonist drug is administered, it will interact with DA receptors but will not mimic the precise time course of the natural DA signal. Indeed, since such an agonist will bind to the receptors continuously, it may prevent DA receptors from detecting and responding to the natural DA signal associated with the presentation of a rewarding stimulus. Thus, in some circumstances, a DA agonist may have an action similar to a DA antagonist. This argument from theory is borne out in practice by evidence obtained using direct acting agonists such as apomorphine (3,5,7,23,36,86,87).

In contrast to the above, indirect acting DA agonists such as amphetamine and pipradrol enhance reward effects when given in small doses, as reviewed by Beninger and Ranaldi (8). With larger doses, indirect acting DA agonists, like direct acting agonists, attenuate or abolish reward effects (82,87). These facts can be explained in terms of the mechanism of action of the indirectly acting drugs. While amphetamine releases DA from nerve terminals by an impulse-independent mechanism (16,81,115), as shown for instance by microdialysis, it is also true that it increases impulse-associated DA release (30,44); this latter effect is only seen with the use of voltammetric methods which have far higher temporal resolution than microdialysis. Thus, for low doses of indirectly acting drugs, the DA signal may remain intact and even be potentiated. However, with larger doses, the flood of DA released may obscure the natural DA signal associated with the presentation of reward.

The DA signal associated with reward will be more critical in some reward paradigms than others. In typical instrumental conditioning (e.g., lever pressing for food), a specific stimulus or set of stimuli from within the environment must come to control responding. In this case, the dopaminergic signal associated with the presentation of reward must occur in close temporal contiguity with the lever press response if the lever and related stimuli are to come to control responding. In other paradigms (e.g., place conditioning), there is no specific stimulus or stimuli in the environment that must come to control responding. In this case, there is no requirement for accurate timing of the DA signal other than the need to associate enhanced DA activity with the test environment as a whole. This means that the action of DA agonist drugs on the former class of paradigm depends critically on whether the DA signal is preserved or obscured by the drug; on the other hand, in the latter class of paradigm, drugs with either mode of action will have similar effects on reward.

Based on the above, we suggest the following classification: Paradigms in which the DA signal must occur in close temporal contiguity with the response would include lever pressing for food, water, brain stimulation reward, conditioned reward and stimulant self-administration. Paradigms in which there is no requirement for accurate timing of the DA signal other than the need to associate enhanced DA activity with the test environment as a whole would include place conditioning and conditioned activity.

Given this classification and the previous theory, we can identify the receptor type underlying the reward effect by the convergence of two lines of evidence. Agonists acting by direct means at the critical receptor subtype should: (a) mimic the effects of natural rewards in the second class of paradigm; and (b) obscure or mask the effects of reward in the first class of paradigm.

From the review above, it is clear the D1-like agonists fit the above criteria. Thus, D1-like agonists generally impair responding in paradigms requiring a specific DA signal, but produce rewarding effects in paradigms where the signal is not required. Admittedly, in drug self-administration experiments, D1-like agonists can be self administered, but only when the dose is low. At higher doses, self-administration does not occur, as predicted by the argument that such doses would mask any precisely timed signal. D2-like agonists, on the other hand, do not fit these criteria. These compounds enhance reward in both classes of paradigm, in accord with our previous suggestions (45,69,70) that the rewarding effects of such drugs are achieved indirectly, mediated by changes in motor performance capability.

The results reviewed above for the effects of DA receptor family subtype-specific antagonists on reward-related learning in a variety of paradigms led to the general conclusion that D1-like receptors play a more critical role in the rewarding effects of food, brain stimulation, self-administered drugs, conditioned rewards and agents used in place conditioning paradigms. This conclusion is in good agreement with the outcome of the analysis of the actions of D1-like agonists in a number of paradigms involving reward-related learning.

D1-LIKE RECEPTORS AND MECHANISMS OF LEARNING

In this section we bring together results from a variety of neuroscience experiments that provide clues to how DA may produce learning. We begin with the widely accepted

idea that learning involves synaptic change. We then report results suggesting that DA can produce synaptic change and that synaptic change in the striatum may be produced by DA released as a result of encountering a rewarding stimulus. From the studies reviewed in this paper, we suggest a critical role for D1-like receptors in the mechanism of synaptic change mediated by DA. D1-like receptors stimulate a second messenger pathway and we review evidence implicating this pathway in learning in general and in reward-related learning in particular. Taken together, findings suggest that the mechanism of synaptic change produced by DA released in association with reward may involve similar mechanisms to those discovered for learning in a variety of species and learning models.

DA and synaptic change

Learning generally is thought to be mediated by changes in selected synapses (33). We have proposed previously that reward-related learning in mammals involves synaptic change taking place in the striatum (including the caudate, putamen, nucleus accumbens and olfactory tubercle), with DA as an essential 'catalyst' (3,65). Wickens (118) has made the specific suggestion that DA may produce reward-related incentive learning by altering the effectiveness of glutamatergic synapses in the striatum. Greengard and coworkers (35) have also proposed a DA-glutamate interaction. A variety of empirical evidence supports hypotheses of this type and some of the evidence specifically applies to the striatum and/or to reward-related learning.

One line of evidence implicating DA in the production of altered synaptic strength comes from the studies of Stein and Belluzzi (102). They have developed a cellular analogue of reward-related learning. In this novel paradigm, these researchers and their coworkers recorded from single pyramidal cells in hippocampal slices and then applied pharmacological agents contingent upon a bursting pattern of electrical activity. They found that DA itself (or D1- or D2-like agonists) was an effective reinforcer, increasing burst firing when applied contingently but not noncontingently (103,104). These results support the idea that DA acting via one or more of its receptor subtypes can be involved in reward-related learning at the cellular level.

More direct evidence was reported recently by Wickens et al. (121). Electrophysiological results showed that pulsatile application of DA to striatal slices in conjunction with cortical stimulation produced an enduring change in the effectiveness of synapses of corticostriatal axons. In related studies, Levine et al. (61) have shown recently in striatal slices that DA can increase excitatory responses to the glutamate agonist N-methyl-D-aspartate (NMDA) delivered iontophoretically. These results provide further support for the hypothesis that DA produces learning by modifying the effectiveness of corticostriatal glutamatergic projections.

Assuming that DA produces synaptic changes when it is released in association with reward, it follows from the psychopharmacological evidence reviewed in this paper that D1-like receptors should be involved in producing synaptic change. Wickens and ourselves, in a series of papers, have proposed a mechanism by which DA acting at D1-like receptors can produce incentive learning by altering the effectiveness of recently activated glutamatergic synapses in the striatum (4,70,118,119). (Such interaction is envisaged to lead to modification of glutamatergic synapses presumably activated by environmental stimuli that precede a rewarding stimulus; the rewarding stimulus itself would have activated striatopetal DA neurons, as discussed in the previous section.) In fact, Levine et al. (61) have provided empirical evidence for this conjecture: In slice preparations, the enhancement of excitatory responses of striatal cells to NMDA produced by DA is mimicked by D1-like agonists, and is deficient in slices from mutant mice with abnormal D1 receptors.

DA-dependent synaptic change and second messengers

There are a number of indications, in widely different animal species, that synaptic modification in which monoamine transmitters play a part involves intracellular second messenger systems including cyclic adenosine 3′5′-monophosphate (cAMP) formation and activation of cAMP-dependent protein kinase (PKA). In invertebrates, the comments of Kandel and Abel (49) are particularly interesting in this context. After briefly discussing some of the evidence from studies of Drosophila, Aplysia, and mice, these authors noted ''...the interesting possibility that reinforcing stimuli may activate monoaminergic...modulatory systems and that these may produce functional changes in the pathway of the conditioned stimulus by activating the cAMP cascade'' (p. 826).

Further evidence for a general role of the cAMP/PKA pathway in learning at a behavioural level comes from work on Drosophila. Using molecular techniques a Drosophila mutant was developed that could be heat-shocked as an adult to activate genes that led to the production of a protein that inhibited PKA. After heat-shock, these flies were found to be deficient in an olfactory discrimination learning paradigm (26). These results implicated the second messenger cAMP in learning. Interestingly, transgenic flies engineered to over-produce PKA also were deficient in learning. This led the authors to suggest that PKA must be regulated at a physiologically appropriate level for proper learning to occur.

Other evidence relating the cAMP/PKA system to learning draws on an extensive older literature showing that many forms of learning are impaired in animals treated with various protein synthesis inhibitors during training, as reviewed by Davis and Squire (24). They conclude that the data make a compelling case for the hypothesis that protein synthesis during or shortly after training is an essential step in long term memory formation. In recent studies of the sea slug Aplysia it has been found that PKA is responsible for the phosphorylation of nuclear proteins, termed cAMP response element binding proteins (CREBs), that modulate transcription (46). Other studies have shown that the resultant newly synthesized proteins help target regulatory subunits of PKA, prolonging the activity of this enzyme, and, therefore, prolonging its influence on synaptic plasticity (34). Similar findings have come from studies of the molecular mechanisms of learning and memory in Drosophila (25,100,101).

In mammalian systems, the suggestion of Greengard and coworkers (35) of a DA/glutamate interaction was also envisaged to be mediated by the second messenger cAMP. This is now supported by data using a number of different preparations providing converging evidence that activation

of this pathway is critical for learning (78,79). Two studies have investigated the effects of agents influencing various stages of the cAMP cascade on the effectiveness of glutamatergic synapses using non-NMDA receptors on cultured hippocampal cells: Wang et al. (112) and Greengard et al. (32) found that agents that activated adenylate cyclase or PKA, or an inhibitor of cellular phosphatases, led to a potentiation of currents induced by activation of non-NMDA receptors through an increase in the open time and opening frequency of non-NMDA receptor channels. Further studies revealed that the modification of glutamate receptor effectiveness influenced by activation of the cAMP cascade involved phosphorylation of the receptor (13,113). The authors suggested that the dynamic regulation of glutamate receptors may be associated with learning and memory.

With regard to the DA-rich mammalian striatum, Wickens and Kötter (120) and Kötter (59) have elaborated further the details of the proposed mechanism of interaction of DA and glutamate, which also includes the second messenger cAMP in the striatum, and these authors have tested some predictions of the model in computer simulations. Such an involvement of the cAMP/PKA pathway would be important for the present discussion because biochemical studies indicate that activation of this pathway in the striatum is achieved by D1- but not D2-like receptors (in fact, this activation being the basis for the distinction between the two receptor families (21,80,99)). Hence any evidence linking reward-related learning or striatal synaptic modification to activation of the cAMP/PKA pathway constitutes additional important evidence for a role of D1-like receptors in such learning or the synaptic changes which mediate it. From the point of view of the present discussion, such evidence would also suggest that rewarding stimuli may produce incentive learning by leading to the activation of DA neurons that stimulate D1-like receptors and activate the cAMP/PKA pathway.

Three recent sets of experiments provide evidence of such a link between reward-related learning or striatal synaptic modification and activation of the cAMP/PKA pathway. The first experiment is electrophysiological. Recording intracellularly in striatal slices, Colwell and Levine (22) showed that activation of adenylate cyclase increased the size of excitatory post-synaptic potentials (EPSPs) evoked by local electrical stimulation. Inhibition of PKA attenuated this effect, while activation of PKA enhanced the effect on EPSP size.

The remaining two experiments provide direct links between the second messenger system and behaviour. One of them refers to behavioural sensitization to stimulant drugs, discussed briefly in the above section on D1- and D2-like antagonists. As mentioned, the relative role of different DA receptor subtypes, and their site of action is not resolved, though conditioning appears to play a significant part in stimulant sensitization. Despite the fact that amphetamine-mediated sensitization has been found to be blocked by D1-like antagonist injections into the mesencephalic regions containing DA cell bodies (107), Miserendino and Nestler (72) implicated second messenger effects within the striatal complex for cocaine sensitization: Repeated injections of cocaine led to increased activities of adenylate cyclase and PKA in the nucleus accumbens. Following this, these authors evaluated the effects of injections of a PKA activator or inhibitor into the nucleus accumbens, on the development of cocaine sensitization. The results revealed that treatment with the PKA activator led to a significant enhancement of the sensitization effect; treatment with the inhibitor had no significant effect on the development of sensitization. No specific tests for conditioned drug effects were carried out in this study, so it is not possible to determine the role of learning. However, insofar as conditioning is involved in sensitization (105,106), results with the PKA activator are consistent with a role for the cAMP second messenger cascade in DA-related learning.

The third set of experiments has been carried out recently by P.L. Nakonechny, working in the laboratory of Beninger (77a). These experiments evaluated the effects of the PKA inhibitor Rp-cAMPS on incentive learning produced by intra-accumbens injections of amphetamine (20 μg/0.5 μl/side) in the place conditioning paradigm. She found that doses of 25.0 or 250, but not 2.5 ng/0.5 μl/side, co-injected with amphetamine during conditioning sessions, blocked the establishment of place preference conditioning. In a control study, animals treated with the 2.5, 25.0 or 250 ng dose of Rp-cAMPS alone during conditioning sessions did not show a significant place conditioning effect. The results from this preliminary study are consistent with the hypothesis that incentive learning involves the action of DA at D1-like receptors and the subsequent activation of the cAMP cascade.

A fourth experiment, related to the effects of PKA on proteins described above, is also worth a brief mention. In rats, it was shown that amphetamine acts via D1-like receptors to induce phosphorylation of CREB, providing a mechanism for some of the long term effects of amphetamines (56). Here again, the cAMP cascade is implicated in DA-related learning processes.

In summary, studies from different species using a wide range of neuroscience techniques provide convergent evidence suggesting that some forms of learning are mediated by the activation of adenylate cyclase, the formation of cAMP and the activation of PKA. Preliminary data implicate the cAMP/PKA second messenger system in striatal synaptic enhancement, in cocaine sensitization, and in amphetamine-produced place conditioning. These results are in agreement with the results of many studies pointing to a critical role for D1-like receptors in reward-related incentive learning.

The role of D1-like receptors and the cAMP/PKA cascade is probably not limited to the striatum. Long term potentiation (LTP) of connections in the hippocampus has been used extensively as a model of potential synaptic changes underlying learning and memory (58). Recent work by Huang and Kandel (42) shows that LTP has two distinct components, a transient component that requires the influx of calcium through NMDA receptor channels and activation of several kinases, and a more persistent component that requires protein synthesis. This later component is mediated at least partially by the cAMP cascade. Thus, the persistent form of LTP is induced by D1-like agonists and this effect is blocked by D1-like antagonists. It also is induced by PKA (28). Furthermore, the D1-like agonist or PKA effect on LTP is blocked by protein synthesis inhibition (28,42). This provides yet another example of the involvement of D1-like receptors and the second messenger cAMP cascade in synaptic plasticity thought to underlie

learning. However, in the hippocampal system the role of DA-mediated synaptic change on large-scale information processing in vivo may not be the same as in the striatum. This depends on the mechanisms of control of firing of the DA neurons innervating each structure, in the freely-moving animal.

CONCLUSIONS

Some of the most influential work aimed at identifying the molecular mechanisms underlying changes in synaptic effectiveness associated with learning has been done on the marine mollusk Aplysia, and the second messenger pathway involving activation of adenylate cyclase, cAMP and PKA has been implicated strongly. Phosphorylation events stimulated by PKA include both relatively short term changes in ion channels and long term changes requiring protein synthesis, both types of changes underlying altered responsiveness to environmental stimuli (48). As reviewed in this chapter, similar mechanisms involving activation of the cAMP pathway have been found in studies of learning in Drosophila (25) and on LTP (58).

DA-mediated incentive learning in the striatum may soon join these other paradigms as a mechanism of synaptic plasticity. As reviewed here, many findings point to stimulation of D1-like receptors as a critical event for incentive learning. Recent studies have begun to show that incentive learning involves steps along the pathway from activation of adenylate cyclase to protein synthesis. Future studies may identify the specific genes involved in the synaptic plasticity underlying incentive learning. All of these findings will lead to a new understanding of incentive learning and to new approaches to its regulation.

DA may hyperfunction in the brains of schizophrenic patients. This hypothesis is supported by the observation that DA receptor antagonists continue to be the pharmacotherapy of choice for treating schizophrenia. This observation and the involvement of DA in incentive learning implies that schizophrenia may occur, in part, as a result of an abnormality (excess) of incentive learning. The identification of a critical role for D1-like receptors in incentive learning suggests the involvement of D1-like receptors in schizophrenia (70), as does a comparison of the behavioural effects of the atypical neuroleptic clozapine to those of D1- and D2-like antagonists (45). Continued study of the molecular mechanisms of synaptic plasticity underlying incentive learning should reveal further details that may suggest new possibilities for the treatment of schizophrenia (31).

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REFERENCES

1. Acquas, E. and DiChiara, G., D1 receptor blockade stereospecifically impairs the acquisition of drug-conditioned place preference and place aversion. *Behav. Pharmacol.*, 1994, **5**, 555–569.
2. Agmo, A., Federman, I., Navarro, V., Padua, M. and Velazquez, G., Reward and reinforcement produced by drinking water: Role of opioids and dopamine receptor subtypes. *Pharmacol. Biochem. Behav.*, 1993, **46**, 183–194.
3. Beninger, R.J., The role of dopamine in locomotor activity and learning. *Brain Res. Rev.*, 1983, **6**, 173–196.
4. Beninger, R.J. Role of D1 and D2 receptors in learning. In: Waddington, J., ed. D1, D2 Dopamine receptor interactions: Neuroscience and pharmacology. London: Academic Press; 1993: 115-157.
5. Beninger, R.J., Hoffman, D.C. and Mazurski, E.J., Receptor subtype-specific dopaminergic agents and conditioned behavior. *Neurosci. Biobehav. Rev.*, 1989, **13**, 113–122.
6. Beninger, R.J.; Nakonechny, P.L. Dopamine D1-like receptors and molecular mechanisms of incentive learning. In: Beninger, R.J.; Palomo, T.; Archer, T., eds. Dopamine disease states. Madrid: CYM Press; 1996:407–431.
7. Beninger, R.J. and Ranaldi, R., The effects of amphetamine, apomorphine, SKF 38393, quinpirole and bromocriptine on responding for conditioned reward in rats. *Behav. Pharmacol.*, 1992, **3**, 155–163.
8. Beninger, R.J.; Ranaldi, R. Dopaminergic agents with different mechanisms of action differentially affect responding for conditioned reward. In: Palomo, T.; Archer, T., eds. Strategies for studying brain disorders: Vol 1. Depressive, anxiety and drug abuse disorders. London: Farrand Press; 1994: 411–428.
9. Beninger, R.J. and Rolfe, N.G., Dopamine D1-like receptor agonists impair responding for conditioned reward in rats. *Behav. Pharmacol.*, 1995, **6**, 785–793.
10. Bergman, J., Rosenzweig-Lipson, S. and Spealman, R.D., Differential effects of dopamine D-1 and D-2 receptor agonists on schedule-controlled behavior of squirrel monkeys. *J. Pharmacol. Exp. Therap.*, 1995, **273**, 40–48.
11. Bindra, D., A motivational view of learning, performance and behavior modification. *Psychol. Rev.*, 1974, **81**, 199–213.
12. Bindra, D., How adaptive behavior is produced: A perceptual-motivational alternative to response-reinforcement. *Behav. Brain Sci.* , 1978, **1**, 41–91.
13. Blackstone, C., Murphy, T.H., Moss, S.J., Baraban, J.M. and Huganir, R.L., Cyclic AMP and synaptic activity-dependent phosphorylation of AMPA-preferring glutamate receptors. *J. Neurosci.*, 1994, **14**, 7585–7593.
14. Bolles, R.C., Reinforcement, expectancy, and learning. *Psychol. Rev.*, 1972, **79**, 394–407.
15. Caine, S.B. and Koob, G.F., Effects of dopamine D-1 and D-2 antagonists on cocaine self-administration under different schedules of reinforcemet in the rat. *J. Pharmacol. Exp. Therap.*, 1994, **270**, 209–218.
16. Carboni, E., Imperto, A., Perezzani, L. and DiChiara, G., Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus accumbens of freely moving rats. *Neurosci.*, 1989, **28**, 653–663.
17. Carey, R.J., Bromocriptine promotes recovery of self-stimulation in 6-hydroxydopamine-lesioned rats. *Pharmacol. Biochem. Behav.*, 1983, **18**, 273–276.
18. Casey, D.E., Neuroleptic-induced EPS and tardive dyskinesia. *Psychopharmacol.*, 1989, **99 (Suppl)**, S47–S53.
19. Cervo, L. and Samanin, R., Effects of dopaminergic and glutamatergic receptor antagonists on the acquisition of cocaine conditioning place preference. *Brain Res.*, 1995, **673**, 242–250.
20. Chaperon, F. and Thiébot, M.-H., Effects of dopaminergic D3-receptor-preferring ligands on the acquisition of place conditioning in rats. *Behav. Pharmacol.*, 1996, **7**, 105–109.
21. Civelli, O., Bunzow, J.R. and Grandy, D.K., Molecular diversity of the dopamine receptors. *Ann. Rev. Pharmacol. Toxicol.*, 1993, **32**, 281–307.
22. Colwell, C.S. and Levine, M.S., Excitatory synaptic transmission in neostriatal neurons: Regulation by cyclic AMP-dependent mechanisms. *J. Neurosci.*, 1995, **15**, 1704–1713.
23. Davies, J.A., Jackson, B. and Redfern, P.H., The effect of amantadine, L-DOPA, (+)-amphetamine and apomorphine on the acquisition of the conditioned avoidance response. *Neuropharmacol.*, 1974, **13**, 199–204.

24. Davis, H.P. and Squire, L.R., Protein synthesis and memory: A review. *Psychol. Bull.*, 1984, **96**, 518–559.
25. DeZazzo, J. and Tully, T., Dissection of memory formation: From behavioral pharmacology to molecular genetics. *Trends Neurosci.*, 1995, **18**, 212–217.
26. Drain, P., Folkers, E. and Quinn, W.G., cAMP-dependent protein kinase and the disruption of learning in transgenic flies. *Neuron*, 1991, **6**, 71–82.
27. Fowler, S.C. and Liou, J.-R., Microcatalepsy and disruption of forelimb usage during operant behavior: Differences between dopamine D1 (SCH-23390) and D2 (raclopride) antagonists. *Psychopharmacol.*, 1994, **115**, 24–30.
28. Frey, U., Huang, Y.-Y. and Kandel, E.R., Effects of cAMP simulate a late stage of LTP in hippocampal CA1 neurons. *Science*, 1993, **260**, 1661–1664.
29. Garris, P.A., Ciolkowski, E.L., Pastore, P. and Wightman, R.M., Efflux of dopamine from the synaptic cleft in the nucleus accumbens of the rat brain. *J. Neurosci.*, 1994, **14**, 6084–6093.
30. Gonon, F.G. and Buda, M.J., Regulation of dopamine release by impulse flow and by autoreceptors as studied by *in vivo* voltammetry in the rat striatum. *Neurosci.*, 1985, **14**, 765–774.
31. Grebb, J.A. Protein phosphorylation in the nervous system: Possible relevance to schizophrenia research. In: Nakazawa, T., ed. The biological basis of schizophrenic disorders. Tokyo: Japanese Scientific Societies Press; 1991:77–89.
32. Greengard, P., Jen, J., Nairn, A.C. and Stevens, C.F., Enhancement of the glutamate response by c-AMP-dependent protein kinase in hippocampal neurons. *Science*, 1991, **253**, 1135–1138.
33. Hebb, D.O. The organization of behavior: A neurophysiological theory. New York: John Wiley; 1949.
34. Hegde, A.N., Goldberg, A.L. and Schwartz, J.H., Regulatory subunits of cAMP-dependent protein kinases are degraded after conjugation to ubiquitin: A molecular mechanism underlying long-term plasticity. *Proc. Natl Acad. Sci. USA*, 1993, **90**, 7436–7440.
35. Hemmings, H.C. Jr., Walaas, S.I., Ouimet, C.C. and Greengard, P., Dopaminergic regulation of protein phosphorylation in the striatum: DARPP-32. *Trends Neurosci.*, 1987, **10**, 377–383.
36. Herberg, L.J., Stephens, D.N. and Franklin, K.B.J., Catecholamines and self-stimulation: Evidence suggesting a reinforcing role for noradrenaline and a motivating role for dopamine. *Pharmacol. Biochem. Behav.*, 1976, **4**, 575–582.
37. Hiroi, N. and White, N.M., The amphetamine conditioned place preference—Differential involvement of dopamine receptor subtypes and two dopaminergic terminal areas. *Brain Res.*, 1991, **552**, 141–152.
38. Hoffman, D.C. and Beninger, R.J., Selective D1 and D2 dopamine agonists produce opposing effects in place conditioning but not in conditioned taste aversion learning. *Pharmacol. Biochem. Behav.*, 1988, **31**, 1–8.
39. Hoffman, D.C. and Beninger, R.J., Preferential stimulation of D1 or D2 receptors disrupts food-rewarded operant responding in rats. *Pharmacol. Biochem. Behav.*, 1989, **34**, 923–925.
40. Hoffman, D.C. and Beninger, R.J., The effects of selective dopamine D1 and D2 receptor antagonists on the establishment of agonist-induced place conditioning in rats. *Pharmacol. Biochem. Behav.*, 1989, **33**, 273–279.
41. Hoffman, D.C., Dickson, P.R. and Beninger, R.J., The dopamine D2 receptor agonists, quinpirole and bromocriptine produce conditioned place preferences. *Prog. Neuropsychopharmacol. Biol. Psychiatry*, 1988, **12**, 315–322.
42. Huang, Y.Y. and Kandel, E.R., D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. *Proc. Natl Acad. Sci. USA*, 1995, **92**, 2446–2493.
43. Hunt, G.E., Atrens, D.M. and Jackson, D.M., Reward summation and the effects of dopamine D-1 and D-2 agonists and antagonists on fixed-interval responding for brain stimulation. *Pharmacol. Biochem. Behav.*, 1994, **48**, 853–862.
44. Hurd, Y.L. and Ungerstedt, U., Ca2 + -dependence of the amphetamine, nomifensine, and Lu-19-005 effect on *in vivo* dopamine transmission. *Eur. J. Pharmacol.*, 1989, **166**, 261–269.
45. Josselyn, S.A., Miller, R.J. and Beninger, R.J., Behavioral effects of clozapine and dopamine receptor subtypes. *Neurosci. Biobehav. Rev.*, 1997, **21**, 531–558.
46. Kaang, B.-K., Kandel, E.R. and Grant, S.G.N., Activation of cAMP-responsive genes by stimuli that produce long-term facilitation in aplysia sensory neurons. *Neuron*, 1993, **10**, 427–435.
47. Kahn, R.S.; Davis, K.L. New developments in dopamine and schizophrenia. In: Bloom, F.E.; Kupfer, D.J., eds. Psychopharmacology: The fourth generation of progress. New York: Raven Press; 1995: 1193–1203.
48. Kandel, E.R. Cellular mechanisms of learning and the biological basis of individuality. In: Kandel, E.R.; Schwartz, J.H.; Jessell, T.M., eds. Principles of neural science. Norwalk: Appleton and Lange; 1991: 1009–1031.
49. Kandel, E.R. and Abel, T., Neuropeptides, adenylyl cyclase, and memory storage. *Science*, 1995, **268**, 825–826.
50. Katz, J.L., Alling, K., Shores, E. and Witkin, J.M., Effects of D1 dopamine agonists on schedule-controlled behavior in the squirrel monkey. *Behav. Pharmacol.*, 1995, **6**, 143–148.
51. Katz, J.L. and Witkin, J.M., Selective effects of the D1 dopamine receptor agonist, SKF 38393, on behavior maintained by cocaine injection in squirrel monkeys. *Psychopharmacol.*, 1992, **109**, 241–244.
52. Katz, J.L. and Witkin, J.M., Behavioral effects of dopaminergic agonists and antagonists alone and in combination in the squirrel monkey. *Psychopharmacol.*, 1993, **113**, 19–25.
53. Kawagoe, K.T., Garris, P.A., Weidemann, D.J. and Wightman, R.M., Regulation of transient dopamine cocentration gradients in the microenvironment surrounding nerve terminals in the rat striatum. *Neurosci.*, 1992, **51**, 55–64.
54. Kleven, D.S. and Woolverton, W.L., Effects of continuous infusions of SCH 23390 on cocaine- or food-maintained behavior in rhesus monkeys. *Behav. Pharmacol.*, 1990, **1**, 365–374.
55. Knapp, C.M. and Kornetsky, C., Bromocriptine, a D-2 receptor agonist, lowers the threshold for rewarding brain stimulation. *Pharmacol. Biochem. Behav.*, 1994, **49**, 901–904.
56. Konradi, C., Cole, R.L., Heckers, S. and Hyman, S.E., Amphetamine regulates gene expression in rat striatum via transcription factor CREB. *J. Neurosci.*, 1994, **14**, 5623–5634.
57. Koob, G.F., Le, H.T. and Creese, I., The D1 dopamine receptor antagonist SCH 23390 increases cocaine self-administration in the rat. *Neurosci. Lett.*, 1987, **79**, 315–320.
58. Kuba, K. and Kumamoto, E., Long-term potentiations in vertebrate synapses: A variety of cascades with common subprocesses. *Prog. Neurobiol.*, 1990, **34**, 197–269.
59. Kötter, R., Postsynaptic integration of glutamatergic and dopaminergic signals in the striatum. *Prog. Neurobiol.*, 1994, **44**, 163–196.
60. Leone, P. and Di Chiara, G., Blockade of D-1 receptors by SCH 23390 antagonizes morphine- and amphetamine-induced place preference conditioning. *Eur. J. Pharmacol.*, 1987, **135**, 251–254.
61. Levine, M.S., Altemus, K.L., Cepeda, C., Cromwell, H.C., Crawford, C., Ariano, M.A., Drago, J., Sibley, D.R. and Westphal, H., Modulatory action of dopamine on NMDA receptor mediated responses are reduced in D1a-deficient mutant mice. *J. Neurosci.*, 1996, **15**, 5870–5882.
62. Mallet, P.E. and Beninger, R.J., 7-OH-DPAT produces place conditioning in rats. *Eur. J. Pharmacol.*, 1994, **261**, 5–6.
63. McDougall, S.A., Crawford, C.A. and Nonneman, A.J., Reinforced responding of the 11-day-old rat pup—Synergistic interaction of D1 and D2 receptors. *Pharmacol. Biochem. Behav.*, 1992, **42**, 163–168.
64. McDougall, S.A., Nonneman, A.J. and Crawford, C.A., Effects of SCH-23390 and sulpiride on the reinforced responding of the young rat. *Behav. Neurosci.*, 1991, **105**, 740–744.
65. Miller, R. Meaning and purpose in the intact brain. Oxford: Clarendon Press; 1981.
66. Miller, R., Major psychosis and dopamine: Controversial features and some suggestions. *Psychol. Med.*, 1984, **14**, 779–789.
67. Miller, R., The time course of neuroleptic therapy for psychosis: Role of learning processes amd implications for concepts of psychotic illness. *Psychopharmacol.*, 1987, **92**, 405–415.
68. Miller, R., Striatal dopamine in reward and attention: A system for understanding the symptomatology of acute schizophrenia and mania. *Internat. Rev. Neurobiol.*, 1993, **35**, 161–278.
69. Miller, R. and Chouinard, G., Loss of striatal cholinergic neurons as a basis for tardive and L-dopa-induced dyskinesias, neuroleptic-induced supersensitivity psychosis and refectory schizophrenia. *Biol. Psychiat.*, 1993, **34**, 713–738.
70. Miller, R., Wickens, J.R. and Beninger, R.J., 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. *Prog. Neurobiol.*, 1990, **34**, 143–183.

71. Mirenowicz, J. and Schultz, W., Preferential activation of midbrain dopamine neurons by appetitive rather than aversive stimuli. *Nature*, 1996, **369**, 449–450.
72. Miserendino, M.J.D. and Nestler, E.J., Behavioral sensitization to cocaine: Modulation by the cyclic AMP system in the nucleus accumbens. *Brain Res.*, 1995, **674**, 299–306.
73. Morency, M.A. and Beninger, R.J., Dopaminergic substrates of cocaine-induced place conditioning. *Brain Res.*, 1986, **399**, 33–41.
74. Nakajima, S., Suppression of operant responding in the rat by dopamine D1 receptor blockade with SCH 23390. *Physiol. Psychol.*, 1986, **14**, 111–114.
75. Nakajima, S. and Baker, J.D., Effects of D2 dopamine receptor blockade with raclopride on intracranial self-stimulation and food-reinforced operant behavior. *Psychopharmacol.*, 1989, **98**, 330–333.
76. Nakajima, S., Liu, X. and Lau, C.L., Synergistic interaction of D1 and D2 dopamine receptors in the modulation of the reinforcing effect of brain stimulation. *Behav. Neurosci.*, 1993, **107**, 161–165.
77. Nakajima, S. and O'Regan, N.B., The effects of dopaminergic agonists and antagonists on the frequency-response function for hypothalamic self-stimulation in the rat. *Pharmacol. Biochem. Behav.*, 1991, **39**, 465–468.

77a. Nakonechny, P.L. The effects of microinjections of the protein kinase inhibitor Rp-cAMPS into the nucleus accumbens of rats: A conditioned place preference study. M.A. Thesis, Queen's Univ., 1996.

78. Nestler, E.J., Molecular neurobiology of drug addiction. *Neuropsychopharmacol.*, 1994, **11**, 77–87.
79. Nestler, E.J., Hope, B.T. and Widnell, K.L., Drug addiction: A model for the molecular basis of neural plasticity. *Neuron*, 1993, **11**, 995–1006.
80. Niznik, H.B. and Van Tol, H.H.M., Dopamine receptor genes: New tools for molecular psychiatry. *J. Psychiat. Neurosci.*, 1992, **17**, 158–180.
81. Olivier, V., Guibert, B. and Leviel, V., Direct *in vivo* comparison of two mechanisms releasing dopamine in the rat striatum. *Brain Res.*, 1995, **695**, 109–115.
82. Ranaldi, R. and Beninger, R.J., Dopamine D1 and D2 antagonists attenuate amphetamine-produced enhancement of responding for conditioned reward in rats. *Psychopharmacol.*, 1993, **113**, 110–118.
83. Ranaldi, R. and Beninger, R.J., The effects of systemic and intracerebral injections of D1 and D2 agonists on brain stimulation reward. *Brain Res.*, 1994, **651**, 283–292.
84. Ranaldi, R. and Beninger, R.J., Bromocriptine enhancement of responding for conditioned reward depends on intact D1 receptor function. *Psychopharmacol.*, 1995, **118**, 437–443.
85. Ranaldi, R., Pantalony, D. and Beninger, R.J., The D1 agonist SKF 38393 attenuates amphetamine-produced enhancement of responding for conditioned reward in rats. *Pharmacol. Biochem. Behav.*, 1995, **52**, 131–137.
86. Robbins, T.W. and Everitt, B.J., Functional studies of the central catechlolamines. *Internat. Rev. Neurobiol.*, 1982, **23**, 303–365.
87. Robbins, T.W., Watson, B.A., Gaskin, M. and Ennis, C., Contrasting interactions of pipradol, d-amphetamine, cocaine, cocaine analogues, apomorphine and other drugs with conditioned reinforcement. *Psychopharmacol.*, 1983, **80**, 113–119.
88. Rusk, I.N. and Cooper, S.J., Profile of the selective dopamine D-2 receptor agonist N-0437: Its effects on palatability- and deprivation-induced feeding, and operant responding for food. *Physiol. Behav.*, 1988, **44**, 545–553.
89. Rusk, I.N. and Cooper, S.J., The selective dopamine D1 receptor agonist SK and F 38393: Its effects on palatability- and deprivation-induced feeding, and operant responding for food. *Pharmacol. Biochem. Behav.*, 1989, **34**, 43–49.
90. Schultz, W., Activity of dopamine neurons in the behaving primate. *Semin. Neurosci.*, 1992, **4**, 129–138.
91. Schultz, W., Apicella, P. and Ljungberg, T., Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J. Neurosci.*, 1993, **13**, 900–913.
92. Schultz, W., Apicella, P., Scarnati, E. and Ljungberg, T., Neuronal activity in monkey ventral striatum related to the expectation of reward. *J. Neurosci.*, 1992, **12**, 4594–4610.
93. Self, D.W.; Lam, D.M.; Kossuth, S.R.; Stein, L. Effects of D1 and D2-selective antagonists on self-administration of the D1 agonist SKF 82958. In: Harris, L., ed. NIDA research monograph 132, College on the problems of drug dependence. Washington: NIDA; 1993: 230.
94. Self, D.W. and Stein, L., The D1 agonists SKF-82958 and SKF-77434 are self-administered by rats. *Brain Res.*, 1992, **582**, 349–352.
95. Shippenberg, T.S., Bals-Kubik, R. and Herz, A., Examination of the neurochemical substrates mediating the motivational effects of opioids: Role of the mesolimbc dopamine system and D-1 vs. D-2 dopamine receptors. *J. Pharmacol. Exp. Therap.*, 1993, **265**, 53–59.
96. Shippenberg, T.S., Balskubik, R., Huber, A. and Herz, A., Neuroanatomical substrates mediating the aversive effects of D-1 dopamine receptor antagonists. *Psychopharmacol.*, 1991, **103**, 200–209.
97. Shippenberg, T.S. and Hertz, A., Place preference conditioning reveals the involvement of D1-dopamine receptors in the motivational properties of mu- and k-opioid agonists. *Brain Res.*, 1987, **436**, 169–172.
98. Shippenberg, T.S. and Herz, A., Motivational effects of opioids: Influence of D-1 versus D-2 receptor antagonists. *Eur. J. Pharmacol.*, 1988, **151**, 233–243.
99. Sibley, D.R.; Monsma, F.J.,Jr.; Shen, Y. Molecular neurobiology of D1 and D2 dopamine receptors. In: Waddington, J., ed. D1: D2 Dopamine Receptor Interactions. London: Academic Press; 1993: 1–17.
100. Skoulakis, E.M.C., Kalderon, D. and Davis, R.L., Preferential expression in mushroom bodies of the catalytic subunit of protein kinase A and its role in learning and memory. *Neuron*, 1993, **11**, 197–208.
101. Spatz, H.C., Postranslational modification of protein kinase A. The link between short-term and long-term memory. *Behav. Brain Res.*, 1995, **66**, 79–84.
102. Stein, L. and Belluzzi, J.D., Cellular investigations of behavioral reinforcement. *Neurosci. Biobehav. Rev.*, 1989, **13**, 69–80.
103. Stein, L., Xue, B.G. and Belluzzi, J.D., A cellular analog of operant conditioning. *J. Exp. Anal. Behav.*, 1993, **60**, 41–53.
104. Stein, L., Xue, B.G. and Belluzzi, J.D., *In vitro* reinforcement of hippocampal bursting: A search for Skinner's atoms of behavior. *J. Exp. Anal. Behav.*, 1994, **61**, 155–168.
105. Stewart, J. Conditioned stimulus control of expression of sensitization of the behavioral activating effects of opiate and stimulant drugs. In: Gormezano, I.; Wasserman, E.A., eds. Learning and memory: Behavioral and biological substrates. Hillsdale: Lawrence Erlbaum Publishers; 1992: 129–151.
106. Stewart, J.; Vezina, P. Conditioning and behavioral sensitization. In: Kalivas, P.W.; Barnes, C.D., eds. Sensitization in the nervous system. Caldwell: Telford Press; 1988: 207–224.
107. Stewart, J. and Vezina, P., Microinjections of SCH-23390 into the ventral tegmental area and substantia nigra pars reticulata attenuate the development of sensitization to the locomotor activating effects of systemic amphetamine. *Brain Res.*, 1989, **495**, 401–406.
108. Sunahara, R.K., Seeman, P., Van Tol, H.H.M. and Niznik, H.B., Dopamine receptors and antipsychotic drug response. *Br. J. Psychiatr.*, 1993, **163**, 31–38.
109. Terry, P. and Katz, J.L., Differential antagonism of the effects of dopamine D1-receptor agonists on feeding behavior in the rat. *Psychopharmacol.*, 1992, **109**, 403–409.
110. Tidey, J.W. and Miczek, K.A., Effects of SKF 38393 and quinpirole on aggressive, motor and schedule-controlled behaviors in mice. *Behav. Pharmacol.*, 1992, **3**, 553–566.
111. Vezina, P. and Stewart, J., The effect of dopamine receptor blockade on the development of sensitization to the locomotor activating effects of amphetamine and morphine. *Brain Res.*, 1989, **499**, 108–121.
112. Wang, L.Y., Salter, M.W. and MacDonald, J.F., Regulation of kainate receptors by cAMP-dependent protein kinase and phosphatases. *Science*, 1991, **1132**, 1132–1135.
113. Wang, L.Y., Taverna, F.A., Huang, X.-P., MacDonald, J.F. and Hampson, D.R., Phosphorylation and modulation of a kainate receptor (GLuR6) by cAMP-dependent protein kianse. *Science*, 1993, **259**, 1173–1175.
114. Weed, M.R., Vanover, K.E. and Woolverton, W.L., Reinforcing effect of the D1 dopamine agonist SKF 81297 in rhesus monkeys. *Psychopharmacol.*, 1993, **113**, 51–52.
115. Westerink, B.H.C., Tuntler, J., Damsma, G., Rollema, H. and De Vries, J.B., The use of tetrodotoxin for the characterizartion of drug-induced dopamine release in conscious rats studied by brain dialysis. *Nauny. Schmied. Arch. Pharmacol.*, 1987, **336**, 502–507.
116. White, N.M. and Hiroi, N., Pipradrol conditioned place preference is blocked by SCH23390. *Pharmacol. Biochem. Behav.*, 1992, **43**, 377–380.

117. White, N.M., Packard, M.G. and Hiroi, N., Place conditioning with dopamine—D1 and D2 agonists induced peripherally or into nucleus accumbens. *Psychopharmacol.*, 1991, **103**, 271–276.
118. Wickens, J., Striatal dopamine in motor activation and reward-mediated learning: Steps towards a unifying model. *J. Neural Transm.*, 1990, **80**, 9–31.
119. Wickens, J. A theory of the striatum. Oxford: Pergamon Press; 1993.
120. Wickens, J.; Kötter, R. Cellular models of reinforcement. In: Houk, J.C.; Davis, J; Beiser, D.G., eds. Models of information processing in the basal ganglia. Cambridge: MIT Press; 1995: 187–214.
121. Wickens, J.R., Begg, A.J. and Arbuthnott, G.W., Dopamine reverses the depression of rat corticostriatal synapses which normally follows high-frequency stimulation of cortex *in vitro*. *Neurosci.*, 1996, **70**, 1–6.
122. Wise, R.A., Murray, A. and Bozarth, M.A., Bromocriptine self-administration and bromocriptine-reinstatement of cocaine-trained and heroin-trained lever pressing in rats. *Psychopharmacol.*, 1990, **100**, 355–361.
123. Wise, R.A. and Rompré, P.-R., Brain dopamine and reward. *Ann. Rev. Psychol.*, 1989, **40**, 191–227.
124. Witkin, J.M., Schindler, C.W., Tella, S.R. and Goldberg, S.R., Interaction of haloperidol and SCH-23390 with cocaine and dopamine receptor subtype-selective agonists on schedule-controlled behavior of squirrel monkeys. *Psychopharmacol.*, 1991, **104**, 425–431.
125. Woolverton, W.L., Effects of a D1 and a D2 dopamine antagonist on the self-administration of cocaine and piribedil by rhesus monkeys. *Pharmacol. Biochem. Behav.*, 1986, **24**, 531–536g.
126. Woolverton, W.L., Goldberg, L.I. and Ginos, J.Z., Intravenous self-administration of dopamine receptor agonists by rhesus monkeys. *J. Pharmacol. Exp. Therap.*, 1984, **230**, 678–683.