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D-1 receptor involvement in reward-related learning

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A comparison of the effects of apomorphine, amphetamine and dopamine (DA) receptor subtype-specific agonists in responding for conditioned reward, self-administration and place conditioning paradigms provides insights into the possible involvement of D-1 and D-2 receptors in reward-related learning. Amphetamine and the D-2 agonists bromocriptine and quinpirole enhanced responding for conditioned reward, were self-administered and produced place preferences. Apomorphine impaired responding for conditioned reward by enhancing responding on two levers, was self-administered and produced a place preference. The D-1 agonist SKF 38393 impaired responding for condition reward, did not support self-administration and produced a place preference. The failure of SKF 38393 to support self-administration may have been related to effects of this drug, for example, peripheral aversive effects or a slow onset of action, unrelated to its action at the D-1 receptor. It was suggested that a D-1 agonist might be expected to be self-administered from the point of view of the hypothesis that it is the action at D-1 receptors of DA released in association with reward that produces reward-related learning. This hypothesis was supported by the remaining data. Thus, apomorphine and SKF 38393 may have masked the DA signal associated with reward in the conditioned reward paradigm leading to a loss of control of responding by the conditioned rewarding stimulus. In self-administration, apomorphine would have its onset of action after the performance of the response which is followed immediately by a conditioned reward. The conditioned reward may effectively maintain control of behaviour by the lever and related stimuli while the drug may maintain the effectiveness of the conditioned reward. In place conditioning, there is no specific environmental stimulus that must come to control responding; therefore, apomorphine and SKF 38393 may have been seen to produce place preferences in spite of their relatively tonic action at D-1 receptors. Finally, the finding that the D-1 antagonists SCH 23390 or SCH 39166 blocked the effects of reward in these paradigms was taken as further evidence that the D-1 receptor may be critically involved in the learning produced by rewarding stimuli.

Key words: D-1 dopamine receptor; reward-related learning; conditioned reward; self-administration; place conditioning

Introduction

Dopaminergic pathways originating in the ventral mesencephalon and projecting to subcortical and cortical target structures appear to form a critical link in the neurocircuitry mediating the effects of rewarding stimuli on behaviour (Beninger, 1983; Wise, 1982). An examination of the effects on reward-related learning of pharmacological agents with relative specificity for dopamine (DA) receptor subtypes (Waddington and O'Boyle, 1989) suggests that D-1 and D-2 receptors may be differentially involved. Results have led to the hypothesis that stimulation of the D-1 receptor may be critical for reward-related learning to occur (Beninger, 1991; Beninger, Hoffman and Mazurski, 1989; Miller Wickens and Beninger, 1990).

The present paper will review the effects of amphetamine, apomorphine and D-1 and D-2 receptor-specific dopaminergic agonists on responding for conditioned reward. This will be followed by a description of the possible elements of reward-related learning in the conditioned reward paradigm, the possible neuronal substrates of these elements and a consideration of the agonist effects from this point of view. The effects of DA agonists in self-administration and place conditioning paradigms will then be reviewed and similarly followed by a description of the possible elements of learning, neuronal substrates and a consideration of the drug effects from this point of view. A comparison of the possible elements and substrates of learning in the conditioned reward, drug self-administration and place conditioning paradigms will reveal differences that may

account for apparent inconsistencies in the effects of dopaminergic agents across these paradigms.

DA agonists and responding for conditioned reward

A neutral stimulus such as a tone or light that has repeatedly been paired with an unconditioned rewarding stimulus such as food can be shown to acquire rewarding properties like those of the unconditioned rewarding stimulus. For example, animals will press a lever more often in extinction if that response produces a click previously paired with food; similarly, animals will learn new responses when the only rewarding stimulus for performing those responses is the presentation of a stimulus previously associated with an unconditioned rewarding stimulus such as food (MacKintosh, 1974). Stimuli that have acquired rewarding properties in this manner are termed conditioned rewarding stimuli.

One paradigm for studying conditioned reward involves the use of an operant chamber outfitted with two levers. Pressing one lever results in the presentation of a tone (3 s) and the other in offset of the lights (i.e. darkness) for a brief period (3 s). Following a conditioning phase consisting of classical pairings of the lights-off stimulus with food in the absence of the levers, food-deprived rats in a test phase pressed the lever producing the lights-off stimulus significantly more often than the other lever. This effect was not seen when food and lights-off were negatively correlated during the conditioning phase. Thus, the lights-off stimulus became a conditioned reward by virtue of its association with food (Hoffman and Beninger, 1985).

Responding for conditioned reward in the test phase of this and related paradigms has been shown to be affected differently by different DA agonists. (+)-Amphetamine, a drug that potentiates DA release and blocks re-uptake, led to significantly greater dose-dependent enhancement of responding on the lever producing the conditioned reward than on the other lever. On the other hand, apomorphine, a direct-acting DA agonist, dose-dependently stimulated responding on both levers about equally (Beninger, Hoffman and Mazurski, 1989; Mazurski and Beninger, 1986; Robbins *et al.*, 1983). Perhaps surprisingly, quinpirole or bromocriptine, both relatively selective D-2 agonists, produced an effect like amphetamine, dose-dependently and selectively enhancing responding on the lever producing conditioned reward (Beninger, Hoffman and Mazurski, 1989). The D-1 agonist, SKF 38393 did not stimulate responding on either lever; however, at higher doses it led to a loss of selective responding for the conditioned reward (Beninger, Hoffman and Mazurski, 1989).

These results can be understood with reference to the possible elements of learning in the conditioned reward paradigm and their possible neuronal substrates. The reward, a conditioned reward, is the presentation of the lights-off stimulus. It has been argued that the effects of reward are to increase the ability of stimuli signalling reward to elicit approach and other responses in the future. This has been defined as incentive learning (Beninger, 1983). In the case of the test phase of the conditioned reward paradigm, the stimuli regularly preceding the presentation of reward would be those associated with the lever. The putative effect of reward would be to increase the ability of those lever-related stimuli to elicit approach and other responses in the future; this would lead to the relative increase in approaching and pressing of that lever rather than the other one.

It has been argued that DA forms a critical link in the neuronal circuitry mediating the effects of reward on behaviour (Beninger, 1983; Wise, 1982). It follows from the above that DA mediates incentive learning, increasing the ability of stimuli associated with reward to elicit responses in the future. What neuronal mechanisms might underlie this effect?

Many data show that the presentation of unconditioned or conditioned rewarding stimuli leads to a phasic increase in the release of DA in the striatum [i.e. caudate, putamen, nucleus accumbens and olfactory tubercle (Heimer and Wilson, 1976)] (Blackburn *et al.*, 1986, 1989; Heffner, Hartman and Seiden, 1980; Keller, Stricker and Zigmond, 1983; Phillips *et al.*, 1989, 1991). The striatum receives extensive projections from the cortex (Grofová, 1979; Heimer and Wilson, 1975) and it has been suggested that when a particular stimulus is present in the environment a specific subset of cortical cells, and therefore striatal afferents, is active (Beninger, 1983, 1991). These corticostriatal afferents synapse on the dendritic spines of medium spiny striatal cells that also receive dopaminergic input (Bolam, 1984; Smith and Bolam, 1990). It has been hypothesized that activity of corticostriatal afferents leads to a transient state of readiness in the synapses of those neurons whereby they are primed for modification if the appropriate signal arrives (Miller, 1988). In summary, the elements of learning in the conditioned reward paradigm, namely reward and stimuli signalling reward, can be seen as neuronally represented in the striatum.

Incentive learning might take place as follows. As various environmental stimuli are encountered, specific subsets of cortical cells and therefore corticostriatal afferents may be activated. The synapses of these cells on medium spiny neurons in the striatum may be activated and may go into a transient state of readiness during which they are primed for modification. When reward occurs and DA is released (the DA signal; cf. Grace, 1991) throughout the striatum, whichever corticostriatal synapses were most recently active may undergo a DA-mediated change leading to an increase in

their subsequent ability to activate striatal output. This may produce an increase in approach and other responses to stimuli signalling reward (for further details see Beninger, 1991; Miller, Wickens and Beninger, 1990).

Returning to the effects of DA agonists in the conditioned reward paradigm, the results may be understood as follows. Amphetamine may have been seen to specifically increase responding on the lever producing conditioned reward as it increased the amount of DA release (the DA signal) associated with the presentation of reward; this, in turn, may have led to stronger incentive learning enhancing the ability of stimuli associated with the conditioned reward lever to elicit approach and other responses. Apomorphine, on the other hand, by occupying the DA receptors (both D-1 and D-2) directly, may have masked the DA signal associated with the presentation of reward. Although it stimulated motor activity, the ability of the rewarding stimulus to control responding was lost.

The results with quinpirole and bromocriptine are interesting from this perspective. These D-2 agonists might have been expected to produce apomorphine-like effects as they are direct-acting agonists. However, they enhanced responding specifically on the conditioned reward lever leading to the conclusion that the DA signal associated with reward must have been intact as it continued to control responding. This suggests that the relevant receptors for the effects of reward on behaviour are of the D-1 subtype. In support of this conclusion, it was found that the D-1 agonist, SKF 38393 led to a loss of specific responding on the conditioned reward lever. Apparently, direct stimulation of the D-1 receptor masked the DA signal produced by presentation of the conditioned reward following depression of the appropriate lever.

In recent studies from my laboratory we have evaluated the effects of the D-1 receptor antagonist SCH 23390 on the bromocriptine-produced enhancement of responding for conditioned reward (Ranaldi and Beninger, unpublished). SCH 23390 dose-dependently decreased the bromocriptine effect. These data were taken as further evidence that it is the stimulation of D-1 receptors by DA during the DA signal associated with reward that leads to incentive learning. In animals treated with the D-2 agonist bromocriptine the transient increase in DA associated with reward apparently requires intact D-1 receptors for incentive learning to occur.

In conclusion, an evaluation of the effects of DA agonists on responding for conditioned reward has revealed that the indirect-acting DA agent amphetamine enhanced responding specifically on the lever producng reward; the direct-acting agonist apomorphine enhanced responding on both levers. The D-2 agonists quinpirole and bromocriptine, like amphetamine, enhanced responding on the reward lever. SKF 38393 failed to enhance responding and led to a loss of specific responding on the reward lever. These results are consistent with the hypothesis that it is the action at the D-1 receptor of DA released in association with reward that leads to incentive learning.

DA agonists and drug self-administration

It has been found that animals will regularly press a lever when the only programmed consequence is an intravenous injection of a small quantity of certain drugs with the injection being signalled by a stimulus (e.g. a cue light). Drugs maintaining this behaviour would, by definition, be rewarding and this drug self-administration paradigm has been used to assess the rewarding properties of various compounds (for a review, see Koob and Goeders, 1989).

It has been widely reported that amphetamine is an effective reward and apomorphine has been found to maintain self-administration behaviour (see Katz, 1989). Recently, it has been found that the D-2 agonists bromocriptine, quinpirole and piribedil were self-administered whereas the D-1 agonist SK 38393 was not (Wise, Murray and Bozarth, 1990; Woolverton, 1986; Woolverton, Goldberg and Ginos, 1984). These data might be taken to suggest that stimulation of the D-2 and not the D-1 receptor is rewarding, but see below.

The elements of learning in the self-administration paradigm are not entirely clear. The unconditioned rewarding stimulus is the drug but there are conditioned rewarding stimuli (e.g. a cue light) that are presented immediately when the lever press response is made. According to incentive theory, these unconditioned and conditioned rewarding stimuli would increase the ability of the lever and stimuli associated with it to elicit approach and other responses in the future. In reward-related learning, it is well known that the insertion of a delay between the operant response and an unconditioned reward reduces the effectiveness of the reward and that this effect can be mitigated by the presentation of a conditioned reward during the delay (MacKintosh, 1974). Delay of reward may be an important element in self-administration experiments as the drugs employed have variable onsets of action. Indeed, it has been shown that varying the onset of action of cocaine in a self-administration study by presenting equal doses over variable infusion times resulted in a systematic decrease in response rate with increase in infusion time (see Katz, 1989). Thus, it may be that the elements of self-administration include two rewarding stimuli, a conditioned reward presented immediately upon pressing the lever and an unconditioned reward occurring some time later, and lever-associated stimuli signalling reward.

As discussed above, there is a wealth of data showing that the presentation of either unconditioned or conditioned rewarding stimuli leads to a phasic increase in the release of striatal DA (Blackburn *et al.*, 1986, 1989; Heffner, Hartman and Seiden, 1980; Keller, Stricker and Zigmond 1983; Phillips *et al.*, 1989, 1991). If the conditioned reward in self-administration paradigms led to DA release in the striatum it might be expected to alter the effectiveness of corticostriatal synapses activated just prior to this event by environmental stimuli signalling the conditioned reward, as outlined in the above model. The most recently encountered stimuli would have been the lever itself and lever-related stimuli. Through this mechanism, those stimuli would become conditioned incentive stimuli with an enhanced ability to elicit approach and other responses in the future. The unconditioned rewarding stimulus, onset of action of the injected drug, presumably would occur some time later depending on the pharmacokinetics of that drug. The enhanced DA neurotransmission produced by the drug would be expected to increase the incentive value of those stimuli encountered in close temporal contiguity with this event; one such stimulus might be the stimulus signalling the injection, the conditioned reward. By this mechanism, the unconditioned reward would maintain the rewarding effectiveness of the conditioned reward but it would be the DA signal associated with the conditioned reward that actually maintained the ability of the lever and associated stimuli to elicit the drug self-administering lever press response.

It may be that the DA signal associated with the presentation of the conditioned rewarding stimulus signalling onset of the infusion, like the DA signal associated with the presentation of conditioned reward discussed in the previous section, is susceptible to masking effects by apomorphine or SKF 38393. However, as the onset of effects of self-injected drugs is delayed in self-administration, the putative masking effects of direct-acting agonists at the D-1 receptor should not interfere with the ability of the conditioned reward to control incentive learning associated with the lever. Once the self-injected drug becomes active at D-1 receptors, it should produce learning resulting in an enhanced incentive value of any recently encountered stimuli that have led to a state of readiness in synapses in the striatum (see above). Although a variety of stimuli from the test apparatus may have been encountered prior to this self-injected drug-induced DA signal, the specific signal associated with the infusion (the conditioned reward) will reliably be present in close temporal contiguity with the DA signal. Thus, over trials, the infusion signal will become a conditioned reward even though the drug may be a direct-acting DA agonist. This explanation accounts for the observation that apomorphine is self administered. It may be worth pointing out, however, that apomorphine self-administration is difficult to train, with only 30% of animals showing the effect and response rates are usually low (D. C. S. Roberts, personal communication). Perhaps this reflects the pharmacokinetics of apomorphine since onset of action is an important variable influencing rate of self-administration (Katz, 1989).

The results of experiments examining the effects of drugs injected following a learning task on the subsequent strength of that learning may be relevant to drug self-administration learning. Thus, it has been reported that post-training injections of amphetamine or other treatments that increase the release of DA following a learning task can strengthen the learning (Carr and White, 1984; McGaugh, 1989); furthermore, it has been shown that these effects of amphetamine are eliminated by neurotoxic destruction of mesencephalic DA cell bodies (White, 1988). Examining the effects of DA receptor subtype-specific agonists, it has been reported that the D-2 agonist quinpirole enhanced learning in appetitive and aversive tasks (Packard and White, 1989, 1991; White and Viaud, 1991). In two of these papers the D-1 agonist SKF 38393 was found to be without significant effect but Packard and White (1991) reported that they did find enhanced learning with post-training injections of SKF 38393 at higher doses than those used in the other two studies. They speculated that the slow onset of action of SKF 38393 may have led to the failures to observe significant effects (White and Viaud, 1991); the use of higher doses may have overcome this problem.

Besides influencing the incentive value of the infusion signal, self-administered drugs may work retroactively on the incentive learning associated with acquisition by the lever and related stimuli of the ability to elicit approach and other responses. In this way the self-administration paradigm can be seen to have features in common with the post-training drug injection paradigm. The mechanisms for this possible influence are not known but it would appear that there is a period of consolidation of recent learning during which enhanced DA neurotransmission can strengthen the learning (Packard and White, 1989, 1991; White, 1988; White and Viaud, 1991). This effect apparently can be brought about even with direct-acting agonists.

The failure of SKF 38393 to support self-administration (Woolverton, Goldberg and Ginos, 1984) is not consistent with this analysis. As SKF 38393 was seen to enhance learning when injected post-training, it might have been expected to be self-administered. Furthermore, since apomorphine was self-administered, the putative DA reward signal masking effect of direct-acting agonists at the D-1 receptor apparently is not relevant in the self-administration paradigm, again suggesting that SKF 38393 should be rewarding in this paradigm. There are several possible explanations for the failure of SKF 38393 to support self-administration. One is related to the

pharmacokinetics; perhaps the onset of action of SKF 38393 is slow leading to a long delay between the infusion signal and the DA signal and, therefore, no apparent learning (see Katz, 1989). One way to reduce this possibility might be to inject higher doses. When Packard and White (1991) followed this strategy in their post-training injection studies, they found that SKF 38393 enhanced learning. Another possibility is that systemic SKF 38393 may have peripheral side effects that are aversive. Thus, peripheral SKF 38393 produced a place aversion whereas central injections of the same compound were rewarding (Hoffman and Beninger, 1988, 1989; White, Packard and Hiroi, 1991). This is discussed further in the next section. These possibilities may account for the apparent failure of SKF 38393 to support self-administration.

If it is the action of DA at the D-1 receptor subtype that is necessary for reward-related incentive learning, as being hypothesized here, by what mechanism do D-2 agonists support self-administration? One possibility, suggested by Miller, Wickens and Beninger, (1990), is that D-2 agonists have a general motor-enhancing action and that this leads to an increase in DA release. Many data show that motor activity leads to increases in the release of striatal DA (Church *et al.*, 1986; Freed and Yamamoto, 1985; Heffner and Seiden, 1980; Heffner *et al.*, 1981, 1984; Heyes, Garnett and Coates, 1988; Speciale *et al.*, 1986; Szostak *et al.*, 1986; Yamamoto and Freed, 1984; Yamamoto, Lane and Freed, 1982). Reward might then occur by an action of DA at D-1 receptors. Indirect support for the suggestion that D-2 agonists produce rewarding effects via an action at the D-1 receptor has recently been reported; it was found that the rewarding effects of self-administered cocaine, an indirect-acting DA agonist, in rats and monkeys was significantly reduced by treatment with the D-1 receptor-specific antagonists SCH 23390 or SCH 39166 (Bergman, Kamien and Spealman, 1990; Kleven and Woolverton, 1990; Koob, Le and Creese, 1987). To my knowledge, no comparable experiments have been done examining the effects of D-1 antagonists on self-administration of D-2-specific compounds. Clearly, there is a need for such studies.

In summary, amphetamine, apomorphine and D-2 but not D-1 agonists have been found to be self-administered. The self-administration paradigm may involve both conditioned reward occurring immediately following the lever-press response and delayed unconditioned reward occurring when the drug infusion has its onset of action. The DA signal produced by the conditioned reward may enhance the incentive value of the lever and related stimuli. The DA signal produced by the drug may have two effects: it may maintain the rewarding properties of the conditioned reward and it may act retroactively to strengthen incentive learning produced by the conditioned reward. The finding that drugs that maintained self-administration also produced post-training enhancement of learning supports this view. The finding that SKF 38393 was not self-administered, although self-administration of this compound would be predicted by the hypothesis that D-1 receptors mediate reward, may be related to peripheral or pharmacokinetic properties of this drug. In general, results are consistent with the hypothesis that it is the action at the D-1 receptor of DA released in association with reward that leads to incentive learning.

DA agonists and place conditioning

Place conditioning apparatus usually consist of two main chambers connected either by a tunnel or an anteroom. Conditioning consists of restricting the animal repeatedly to one of the chambers while it is under the influence of a potentially rewarding drug; placement into the other chamber is consistently associated with injections of the drug's vehicle. Testing is carried out with access to both chambers available and the amount of time spent in each is measured. If the animals are seen to spend significantly more time in the chamber associated with injections of the drug that drug is said to be rewarding (for reviews, see Carr, Fibiger and Phillips, 1989; Hoffman, 1989).

Studies have shown that amphetamine, apomorphine and the D-2 agonists, bromocriptine and quinpirole, produce preferences for the place associated with the drug (Hoffman and Beninger, 1988, 1989; Hoffman, Dickson and Beninger, 1988; Morency and Beninger, 1986; Spyraki, Fibiger and Phillips, 1982; White, Packard and Hiroi, 1991). Systemic injections of the D-1 agonist SKF 38393 have been reported to produce a place aversion (Hoffman and Beninger, 1988, 1989; White, Packard and Hiroi, 1991). However, the results of recent studies suggest that this aversive effect may have been due to peripheral actions of the drug as administration directly into the nucleus accumbens was seen to produce a place preference (White, Packard and Hiroi, 1991). Thus, both D-1 and D-2 agonists were rewarding.

In place conditioning there does not appear to be a discrete reward signal like there is in studies where reward is presented periodically in association with responding in a particular stimulus situation. Rather, there is the general enhancement of DA neurotransmission either by increasing neurogenic release, as in the case of amphetamine, or by directly stimulating DA receptors, as in the case of direct-acting agonists such as apomorphine or the receptor subtype-specific agonists. The incentive learning effects of reward would then be hypothesized to occur with respect to all of those stimuli that are encountered in association with the reward. Thus, stimuli from the side of the apparatus associated with

reward should aquire an enhanced ability to elicit approach and other responses. From this point of view, the elements of conditioning in place preference studies would be a somewhat protracted reward signal and perhaps many apparatus stimuli associated with reward.

If a drug tested in the place conditioning paradigm increases stimulation of post-synaptic DA receptors, it would be expected to modify the strength of any corticostriatal projections brought into a state of readiness during the action of that drug. It has been suggested above that different subsets of corticostriatal fibers are activated by different environmental stimuli. Thus, those stimuli that are encountered while the animal is in the drug state would become incentive stimuli, acquiring an enhanced ability to elicit approach and other responses. As this learning effect would take place on the drug-paired side and not on the vehicle-paired side, in the test when both sides are available, animals would be expected to approach the stimuli on the drug-paired side more of the time and therefore spend more time on that side. The observation that a wide range of DA agonists produces place preference conditioning is consistent with this analysis.

Even though apomorphine and SKF 38393 are direct-acting DA agonists that might mask any ongoing reward signals produced by phasic stimulation of D-1 receptors, this would not impair place conditioning since there is no specific reward signal in association with any specific environmental stimuli. It may be the whole of the drug-paired side that is the incentive stimulus acquiring the ability to elicit approach and other responses. Thus, the observation that apomorphine and SKF 38393 produce place conditioning is consistent with the hypothesis that D-1 receptors mediate the effects of reward on behaviour.

The rewarding effects of D-2 agonists in place conditioning might depend on intact D-1 receptors that are stimulated as a result of the enhanced DA release associated with the locomotor-stimulating effects of these compounds, as was argued in the case of self-administration of D-2 agonists. In support of this hypothesis it has been found that place conditioning based on quinpirole was blocked by the D-1 antagonist SCH 23390 (Hoffman and Beninger, 1989). SCH 23390 also blocked the place preference produced by amphetamine further implicating the D-1 receptor in this type of learning (Hoffman and Beninger, 1989; Leone and Di Chiara, 1987). Thus, place conditioning based on D-2 agonists may require intact D-1 receptor function.

In summary, amphetamine, apomorphine and D-1 and D-2 agonists produce place preferences. The place conditioning paradigm may involve a relatively long-term reward signal and environmental stimuli from the drug side of the apparatus. The effects of DA agonists might be to produce incentive learning, enhancing the ability of many stimuli from the drug side to elicit approach and other responses. When the animals are given free access to both sides of the apparatus, incentive learning may result in their spending significantly more time on the side associated with the drug than on the other side, thereby demonstrating a preference for the place associated with the drug. A consideration of the effects of agonists and the D-1 antagonist SCH 23390 suggests that it is the action at the D-1 receptor of DA released by rewarding drugs that leads to incentive learning.

Conclusions

The observation that D-1 and D-2 agonists have different effects in some paradigms but similar effects in others challenges the psychopharmacologist to unravel the sources of these apparent contradictions. Often this task can be difficult, especially in the absence of a generally agreed upon language for describing the effects of rewarding stimuli on behaviour. However, it may be possible to develop such a language by tying psychological concepts to neuronal mechanisms, a possibility that is becoming more real with the flood of new data showing localized neurochemical changes in unrestrained, behaving animals. A consideration of the elements of learning in various conditioning paradigms, their possible neuronal bases and the effects of pharmacological compounds with known mechanisms of action provides a starting point for understanding the possible neuronal mechanisms of reward-related incentive learning.

The effects of the indirect-acting DA agonist amphetamine, the direct D-1 and D-2 agonist apomorphine and the respective D-1- and D-2-specific compounds SKF 38393 and quinpirole or bromocriptine have been assessed in responding for conditioned reward, drug self-administration and place conditioning paradigms. Amphetamine enhanced responding for conditioned reward, was self-administered and produced a place preference. Apomorphine enhanced responding non-specifically in the conditioned reward paradigm impairing the conditioned reward effect, was self-administered and produced a place preference. SKF 38393 impaired the conditioned reward effect, failed to support self-administration and produced a place preference. Finally, quinpirole and bromocriptine enhanced responding for conditioned reward, were self-administered and produced place conditioning. Can these results be understood with reference to a single hypothesis?

The attempt in the present paper has been to show that all of the above findings are consistent with the hypothesis that it is the action at the D-1 receptor of DA released by rewarding drugs that leads to incentive learning. In reaching this conclusion it was necessary to speculate that the failure of SKF 38393 to support self-administration

was a result related to some aspect of this drug, perhaps a peripheral aversive effect or slow onset of action, other than its stimulation of D-1 receptors. According to the hypothesis developed in this paper, a D-1 agonist would be expected to support self-administration.

The results with amphetamine and D-2 agonists in the three paradigms were consistent. Given the above caveat, the important differences were that apomorphine and SKF 38393 produced similar effects to amphetamine and quinpirole or bromocriptine in self-administration and place conditioning but not in responding for conditioned reward. It is in the explanation of these differences that the hypothesis that D-1 receptors mediate the effects of reward on behaviour begins to take shape.

Reward is defined as the presentation of a biologically important stimulus and has the effect of increasing the likelihood that an animal will approach and interact with stimuli that immediately precede reward. Extensive research has now shown that mesencephalic DA neurons are activated when a rewarding stimulus is encountered and that these neurons release more DA in striatal terminal areas as a result. It was suggested that specific environmental stimuli activate specific subsets of cortical neurons and therefore specific subsets of corticostriatal synapses. It was further suggested that this activation leads to a transient state of readiness in those synapses during which their susceptibility to modification may be increased. A reward-produced DA signal at the time of readiness of a particular set of synapses might lead to a strengthening of those synapses. As a result the particular environmental stimulus represented by those synapses may have an enhanced ability to elicit approach and other responses in the future.

If a conditioning paradigm demands that a specific environmental stimulus comes to control responding, then a pharmacological manipulation that leads to direct and relatively tonic stimulation of DA receptors may mask the usual effects of reward on the ability of stimuli to control responding. As a result, learning may not be seen. Two of the paradigms reviewed in this paper, namely, conditioned reward and self-administration, required that specific stimuli come to control responding. However, only in the conditioned reward paradigm were drugs given systemically in a single large dose. In that paradigm, direct stimulation of DA receptors by apomorphine had the predicted effect of impairing the ability of the lever producing the conditioned reward to control responding. In self-administration, drugs were given in small doses contingent on responding. Furthermore, a conditioned reward was used to bridge the delay between the response on the lever and the onset of action of the infused drug. In this case, apomorphine may not have masked the DA signal produced by the conditioned reward. However, temporal contiguity between the infusion signal and onset of the drug may have had the effect of maintaining the reward strength of the conditioned reward. In this way the apparent different effects of apomorphine in the two paradigms can be understood.

The conditioned reward paradigm revealed more information. Only SKF 38393, and not the D-2 agonists, acted like apomorphine. This result suggested that it was the action of apomorphine at the D-1 receptor that led to the apparent masking of the reward signal and the failure of stimuli associated with the lever producing conditioned reward to control responding. This result directly supports the hypothesis that it is the action of DA at D-1 receptors, when reward occurs, that leads to incentive learning. Finally, studies showing that the ability of D-2 agonists to enhance responding for conditioned reward and to produce place preferences was blocked by a D-1 receptor-specific antagonist further suggest a role for D-1 receptors in reward.

Some experiments not yet done, to my knowledge, would further test the hypothesis that D-1 receptors are importantly involved in reward-related incentive learning. One important experiment is to examine the effects of a D-1 antagonist on self-administration of a D-2 agonist. The D-1 antagonist would be expected to block the rewarding effect of the D-2 agonist. Further studies of the possibility that a D-1 agonist will be self-administered also are needed. Finally, studies using other paradigms, e.g. brain stimulation reward, requiring that a specific set of environmental stimuli come to control responding and evaluating the effects of D-1 and D-2 agonists, would provide good tests of the hypothesis that it is the action at the D-1 receptor of DA released by rewarding stimuli that leads to incentive learning.

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