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REVIEW

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Psychopharmacology of conditioned reward: evidence for a rewarding signal at D_1-like dopamine receptors

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Abstract A neutral stimulus can acquire conditioned rewarding properties through association with an intrinsically rewarding stimulus. The acquisition of responding for conditioned rewards requires that environmental stimuli and reward processes interact in a highly specific manner; analyses of this phenomenon may provide valuable insight into the processes that underlie reward-related learning. The effects of dopaminergic agents with different mechanisms of action in this paradigm have revealed several interesting dissociations suggesting that a rewarding signal at dopamine D_1-like receptors may mediate both the acquisition of rewarding properties by neutral stimuli and their ability to control behavior. Dopamine-induced changes in responding for conditioned reward are susceptible to modulation by other neurotransmitter systems. In many cases, the molecular and cellular bases of these interactions support the notion that signaling through D_1-like receptors is critical for a conditioned reward to direct responding. The model outlined in this paper reflects a comprehensive integration of the existing literature in the field, and has several implications that are readily testable by future research. Moreover, given the known biochemical coupling of D_1-like receptors, this model may help in characterizing the sequence of intracellular events, from signal transduction to possible transcriptional and/or translational regulation, that give rise to the acquisition of rewarding properties by neutral stimuli.

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Introduction

Rewarding or reinforcing stimuli can be potent determinants of future behavior. For example, stimuli associated with food or water rewards presented to an appropriately deprived animal can come to elicit approach or other responses like those elicited by the food or water themselves, a phenomenon termed incentive-motivational learning, or simply incentive learning (Bolles 1972; Bindra 1974; Beninger 1983). Furthermore, reward-related or conditioned incentive motivational stimuli have the ability to act as rewards themselves and thus are referred to as conditioned rewards. Investigations of responding for conditioned reward allow an examination of the effects of various pharmacological agents on reward-related learning, somewhat independent of their action on primary motivation. For example, potential anorexic properties of dopamine (DA) agonists may confound response procedures when the rewarding stimulus is food, but not when the reward is a conditioned stimulus based on food.

We have chosen to use the term "conditioned reward" throughout this paper; however, we view "conditioned reinforcer" as a synonymous term. Our choice reflects the extensive use of "conditioned reward" in the literature reviewed here. Historically, reinforcement theory has been contrasted with incentive theory as alternative explanatory systems for the type of learning produced by reinforcers or rewards (e.g. Bindra 1974). Because we favor incentive theory, we also use the term "conditioned reward" to avoid the conceptualizations of reinforcement theory. From an incentive learning point of view, a conditioned reward is also a conditioned incentive stimulus. As will be evident in the latter portion of this paper, our version of incentive theory goes well beyond traditional formulations, incorporating anatomical structures and molecular aspects of synaptic plasticity underlying learning.

The effects of conditioned rewards on behavior have been studied using several methods, classified by Mackintosh (1974). The first involves the maintenance of responding during extinction. For example, during extinction of responding for food, animals that received response-contingent presentation of the click of the feeding apparatus (which previously signaled food) emitted more responses than animals that did not (Bugelski 1938). The click might have become a conditioned reward. This procedure, however, is confounded by differential generalization decrement during extinction (Mackintosh 1974). A better approach examines the ability of the conditioned reward to support a novel operant. Rats given response-independent presentations of food paired with the feeder click (magazine training) later learned to press a lever for the click alone (Skinner 1938). The acquisition of a new response with a conditioned stimulus as the only reinforcement demonstrates the rewarding properties of that stimulus and has become an accepted criterion for identifying stimuli as conditioned rewards (Mackintosh 1974).

The third procedure utilizes second-order schedules, wherein animals complete one schedule as a component of another. For example, five separate fixed-interval (FI) 1-min schedules may have to be completed to attain primary reinforcement [an FR5 (FI 1-min) schedule]. The completion of each FI is signaled by a stimulus that has been associated with primary reward. This procedure has the advantage that responding for the conditioned stimulus is not confined to extinction as it is in the established and new response procedures; thus the control of responding by conditioned rewards will not be lost gradually by repeated presentations of the stimulus in the absence of primary reward (Kelleher 1966). Some studies have used second-order schedules to evaluate the conditioned rewarding properties of stimuli associated with primary reward. For example, second-order schedules have identified the powerful influence of conditioned rewards on behavior predictive of substance abuse. Ranaldi and Roberts (1996) demonstrated that the presentation of stimuli associated with self-administered cocaine conferred greater resistance to extinction when cocaine was withdrawn. Thus, second order schedules provide another tool for studying the control of behavior by conditioned rewards.

Due partly to the potential influence of pharmacological agents on primary reward in second-order schedules, current analyses of drug effects on responding for conditioned reward tend to utilize the new response procedure. Animals undergo a Pavlovian conditioning phase – a neutral stimulus (e.g. a light) is paired with a primary reward (e.g. food) for several sessions. During the test phase, the animals are exposed to a chamber with two levers, one producing the stimulus associated with primary reward (CR lever) and the other either no consequence or a neutral stimulus (NCR lever). A selective increase of responding on the CR lever is evidence that the stimulus serves as a conditioned reward. The acquisition of rewarding properties by neutral stimuli (learned during conditioning) is determined empirically by the subsequent acquisition of responding for that stimulus in the test – this would be the conditioned reward effect.

The new response procedure avoids a number of confounds. First, a change in activity may affect responding similarly on the CR and NCR levers but should not influence the magnitude of the conditioned reward effect. In addition, by making a neutral stimulus contingent on NCR lever responses, responding for stimulus change can not explain an apparent conditioned reward effect. Moreover, the conditioned reward effect is not specific for either the type of conditioned stimulus or primary reward. Indeed, turning the chamber lights on or off, a tone or a compound visual/auditory stimulus can be effective conditioned rewards when paired with primary rewards such as food, water or brain stimulation (Stein 1958; Knott and Clayton 1966; Hill 1970; Beninger and Phillips 1980; Robbins et al. 1983; Beninger and Ranaldi 1992).

The inclusion of control groups in previous research has established that conditioned reward reflects associational learning between the unconditioned and conditioned stimuli. If the conditioned stimulus is correlated negatively with food or food alone is presented during conditioning, greater responding on the CR lever is not seen (Robbins 1976, 1978; Beninger and Phillips 1980; Taylor and Robbins 1984; Hoffman and Beninger 1985; Cador et al. 1991).

DA appears to play a key role in acquisition and expression of conditioned reward. The presentation of a primary or conditioned reward is accompanied by increased DA release in striatal regions such as the nucleus accumbens (NAc) and caudate-putamen (for reviews, see Salamone 1994; Kiyatkin 1995; Westerink 1995; Schultz et al. 1997), suggesting a possible role for DA in both the acquisition of incentive properties by neutral stimuli and the ability of those stimuli then to act as conditioned rewards. Moreover, DA agents with different mechanisms of action have distinct effects on responding for conditioned reward, which appear to be localized to certain areas of the brain (see Beninger and Ranaldi 1994). This paper will first review the psychopharmacology of conditioned reward. This information will then be integrated into a theoretical framework that describes potential processes that underlie reward-related learning.

Dopaminergic agents administered systemically

Systemic indirect DA agonists

The DA releaser pipradrol (Scheel-Krüger 1971) increases responding for conditioned reward. Hill (1970) and Robbins (1975) found that it dose-dependently potentiated responding in extinction when a reward-paired stimulus was contingent on responding and decreased rates in the absence of this stimulus. Studies using the new response procedure confirmed that pipradrol augments responding for conditioned reward (Robbins 1976, 1978;

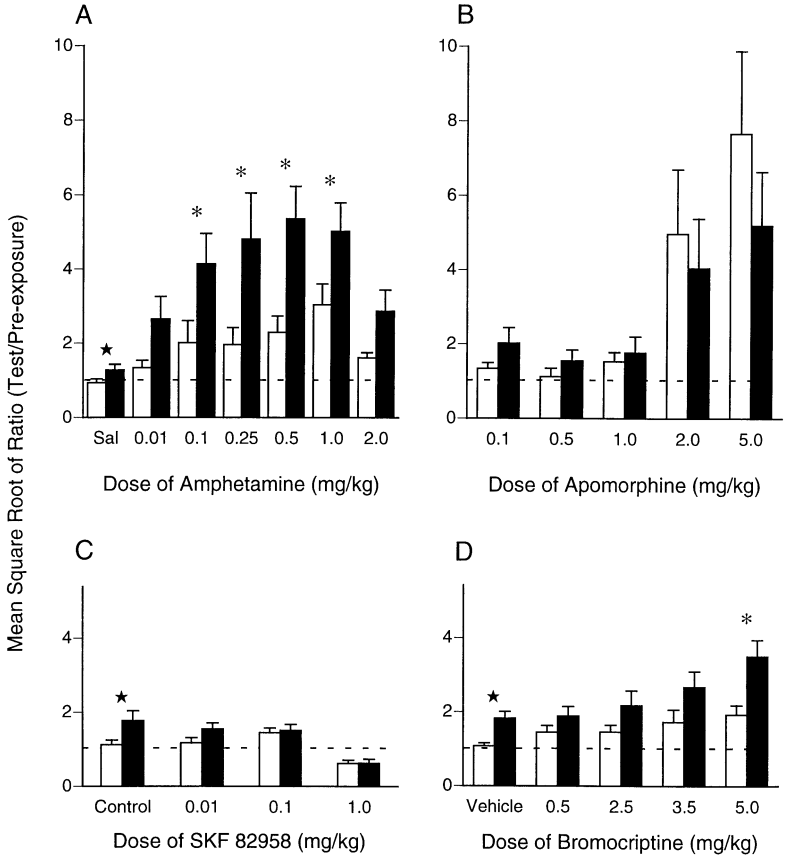

Fig. 1A–D Effects of dopaminergic drugs on responding for conditioned reward. *Open bars* indicate responding on the lever that produced a tone stimulus and *solid bars* indicate responding on the lever that produced a lights-off stimulus that had been paired with food during conditioning. The *broken lines* at 1 indicate no change in responding from pre-exposure to test; values greater than 1 indicate an increase in responding from pre-exposure to test. *Stars* indicate a significant conditioned reward effect (i.e. a greater increase in responding on the lights-off lever than on the tone lever from pre-exposure to test) in saline (*Sal*), control or vehicle groups; *asterisks* indicate a significant enhancement of the conditioned reward effect compared to Sal (**A**) or vehicle (**D**). **A**, **B** And **C** have been modified from Beninger and Ranaldi (1992) and Beninger and Rolfe (1995)

Robbins and Koob 1978; Beninger et al. 1980, 1981; Robbins et al. 1983; Chu and Kelley 1992; Kelley et al. 1997).

Amphetamine increases the neurogenic release of DA and blocks its re-uptake (Scheel-Krüger 1971; Westerink 1979). It enhances the conditioned reward effect in a dose-dependent manner, as shown in Fig. 1A (Robbins et al. 1983; Mazurski and Beninger 1986; Beninger and Ranaldi 1992; Ranaldi and Beninger 1993; Ranaldi et al. 1995). Earlier investigations reported no significant effect (Robbins 1978; Beninger et al. 1981) but the range of doses lacked those found later to be effective. Amphetamine also enhances responding for conditioned reward in second-order schedules (Cohen 1991; Cohen and Branch 1991). Thus, amphetamine, like pipradrol, potentiates the conditioned reward effect. Amphetamine also enhances the effects of a conditioned aversive stimulus by depressing responding on a lever producing that stimulus (Killcross et al. 1997). Therefore, it appears that amphetamine can enhance the control over behavior by conditioned stimuli, regardless of whether they are associated with reward or aversion.

Methylphenidate, a stimulator of DA release (Scheel-Krüger 1971), produced a differential increase on the CR lever that approached significance (Robbins 1978). The indirect DA agonist nomifensine (Braestrup and Scheel-Krüger 1976) almost eliminated responding on both levers (Robbins 1978). Cocaine, another indirect agonist (Moore et al. 1977), increased responding on both levers, although no differential enhancement on the CR lever was observed (Beninger et al. 1981; Robbins et al. 1983). The two cocaine analogues WIN 35,428 and WIN 35,065-2 dose-dependently enhance responding for conditioned reward over a wide range of doses (Robbins et al. 1983). As the analogues demonstrate slower dissociation kinetics at the DA transporter (Madras et al. 1989), the negative results with cocaine may relate to its relatively transient action. Under other conditions, however, systemic treatment with cocaine can enhance the control of behavior by conditioned rewards. Kelley and Holahan (1997) report that cocaine had this effect in animals that received infusions of cholera toxin (an agent that up-regulates the cyclic AMP second messenger system) into the dorsal striatum. Taylor and Horger (1999) demonstrate that systemic cocaine treatment over 5 consecutive days augments the conditioned reward effect and further enhances responding for conditioned reward after amphetamine infusion into the NAc.

In summary, the indirect DA agonists pipradrol, amphetamine and two cocaine analogues and under some conditions cocaine itself, enhance responding for conditioned reward. The effects of methylphenidate are marginal and nomifensine decreases responding.

Systemic direct DA agonists

In contrast to amphetamine and pipradrol, apomorphine (which directly stimulates DA receptors; Colpaert et al. 1976) inhibits the conditioned reward effect (Fig. 1B). It has a biphasic action on responding for conditioned reward, reducing it at low doses (Taylor and Robbins 1986) and increasing it at higher doses (Robbins et al. 1983; Beninger and Ranaldi 1992). However, increased responding is not selective for the CR lever (Robbins et al. 1983; Mazurski and Beninger 1986; Beninger and Ranaldi 1992). Therefore, apomorphine augments lever-press responding, but unlike indirect DA agonists, this is independent of the CR contingency.

The effects of apomorphine might relate to its actions at specific DA receptor subtypes. DA can bind to at least five distinct receptors that are dichotomized into D_1-like (D_1, D_5) and D_2-like (D_2, D_3, D_4), depending on whether binding leads to stimulation or inhibition, respectively, of adenylate cyclase (Niznick and Van Tol 1992; Civelli et al. 1993; Sibley et al. 1993).

Systemic D_1-like agonists disrupt the acquisition of responding for conditioned reward. The partial agonist SKF 38393 (Setler et al. 1978) impairs responding for conditioned reward (Beninger and Ranaldi 1992; Ranaldi et al. 1995) and disrupts amphetamine-induced potentiation of the effect (Ranaldi et al. 1995). In addition, the partial agonists SKF 81297, SKF 77434, and CY 208-243 (Markstein et al. 1988) and the full agonist SKF 82958 (O'Boyle et al. 1989) disrupt responding for conditioned reward (Beninger and Rolfe 1995). The effect of SKF 82958 discounts the idea that the actions of partial agonists are due to partial stimulation of adenylate cyclase that otherwise would be activated fully by endogenous DA. Therefore, systemic D_1-like agonists impair the acquisition of responding for conditioned reward (Fig. 1C).

In marked contrast, systemic administration of D_2-like agonists enhances the acquisition of responding for conditioned reward; this was seen with the D_2-like agonists bromocriptine (Fig. 1D) and quinpirole (Beninger and Ranaldi 1992; Ranaldi and Beninger 1995). Systemic treatment with the D_2-like agonist 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) failed to enhance responding for conditioned reward, but neither did it impair the effect (unpublished results). Therefore, D_2-like agonists appear to preserve or potentiate the conditioned reward effect, while D_1-like agonists impair it.

Apomorphine stimulates both D_1- and D_2-like receptors (Neve and Neve 1997). Studies with agonists relatively specific for D_1- versus D_2-like receptors revealed that stimulation of D_1-like receptors, like apomorphine, led to a loss of the conditioned reward effect. Conversely, stimulation of D_2-like receptors, like indirect DA agonists, led to a specific enhancement of responding on the CR lever. From these observations, it is concluded that loss of the ability of conditioned rewarding stimuli to control responding after systemic injection of apomorphine is due to this drug's action at D_1-like DA receptors.

Systemic DA antagonists

Studies using DA antagonists suggest that intact DA neurotransmission is necessary for the acquisition of rewarding properties by neutral stimuli and their subsequent ability to control behavior. The DA antagonist α-flupenthixol (Nielson et al. 1973) given during the test phase dose-dependently blocked responding on the CR lever (Robbins et al. 1983; Fletcher and Higgins 1997; Killcross et al. 1997). It also attenuated the enhancement of conditioned reward seen after intra-NAc DA or amphetamine (Cador et al. 1991; Fletcher and Higgins 1997).

The effects of receptor subtype-specific DA antagonists administered in the test phase further suggest that intact DA activity is necessary for the conditioned rewarding stimulus to control responding. Ranaldi and Beninger (1993) examined the effects of D_1- and D_2-like antagonists on amphetamine-induced enhancement of responding for conditioned reward. The D_1-like antagonist SCH 23390 (Iorio et al. 1983) shifted the amphetamine dose-response function to the right, but did not alter maximal responding. In contrast, the D_2-like antagonists pimozide or metoclopramide attenuated maximal responding. Pimozide shifted the amphetamine dose-response curve to the right, but to a lesser extent than SCH 23390. Interestingly, SCH 23390 also shifted the dose-response function for the D_2-like agonist bromocriptine to the right, as did pimozide (Ranaldi and Beninger 1995). These results suggest that D_1- and D_2-like receptors may play different roles in responding for conditioned reward, although intact transmission at both receptor types appears necessary for amphetamine or bromocriptine enhancement of conditioned reward.

The role of DA in the acquisition of rewarding properties by neutral stimuli has been assessed by pharmacological manipulations during the conditioning phase. Beninger and Phillips (1980) treated animals with pimozide during the pairing of a tone with food. Even though these rats ate the food, they failed to respond more on the lever producing the tone in a subsequent test, a finding that has been replicated with α-flupenthixol (Fletcher and Higgins 1997). Beninger and Phillips (1980) ruled out state-dependent learning as an explanation by demonstrating that pimozide treatment before test sessions did not reinstate the conditioned reward effect. Hoffman and Beninger (1985) later discounted the possibility of a conditioned taste aversion. They further demonstrated that the pimozide effect is dose-dependent and reducing the number of conditioning sessions from four to two shifted the dose-response function to the left. These findings demonstrate a role for DA in mediating the acquisition of rewarding properties by neutral stimuli.

In summary, DA receptor antagonists block the acquisition of responding for conditioned reward. When given during pairing sessions, DA antagonists block the subsequent ability of the food-associated stimulus to control responding.

Systemic administration of other drugs

The effects of non-dopaminergic agents on responding for conditioned reward have also been examined. The opiate morphine generally decreased responding, but selective responding on the CR lever was preserved. Chlordiazepoxide, a benzodiazepine, had a biphasic effect, increasing responding at lower doses and reducing it at higher doses, but similarly did not impair the conditioned reward effect (Robbins et al. 1983). The benzodiazepine midazolam also failed to affect the acquisition of responding for conditioned reward (Killcross et al. 1997).

Fletcher and his colleagues have investigated the role of 5-hydroxytryptamine (5-HT). Alone, 5-HT agents do not affect the acquisition of responding for conditioned reward, although (as discussed later) studies implicate 5-HT in regulating DA-dependent potentiation of responding for conditioned reward. The indirect 5-HT agonist fenfluramine reduced responding but selectivity on the lever producing conditioned reward was maintained (Fletcher 1995). The 5-HT antagonist metergoline was without effect on responding for conditioned reward (Fletcher 1995). Fletcher and Higgins (1997) found that the 5-HT_3 antagonist ondansetron during conditioning failed to affect subsequent responding for conditioned reward, contrasting with the blocking effects of DA antagonists. Ondansetron in the test phase similarly had little effect. These negative results with non-DA drugs provide indirect evidence that the effects of putative DA agents on responding for conditioned reward are due to their DA action.

DA agents administered directly into striatal regions

Both dorsal (caudate and putamen) and ventral (NAc) aspects of the striatum likely contribute to the acquisition of responding for conditioned reward. The NAc is sensitive to DA agents in many behavioral paradigms (e.g. Carr and White 1986) and is a critical substrate for many forms of reward-related learning (see Beninger 1993). Studies using central administration have suggested that DA transmission in the NAc and other striatal sub-regions is critical for conditioned rewarding stimuli to control behavior.

Indirect DA agonists

Like systemic administration, pipradrol administered into the NAc dose-dependently and selectively elevates responding on a lever producing conditioned reward (Chu and Kelley 1992). Systemic pretreatment with either SCH 23390 or the D_2-like antagonist raclopride (Köhler et al. 1985) blocks this effect. Therefore, the pipradrol-induced augmentation of conditioned reward appears to require intact transmission at both D_1- and D_2-like receptors.

Intra-NAc amphetamine produces a dose-dependent potentiation of responding for conditioned reward (Taylor and Robbins 1984, 1986; Cador et al. 1989, 1991; Jones et al. 1990; Kelley and Delfs 1991a,b; Chu and Kelley 1992; Cunningham and Kelley 1992a,b; Burns et al. 1993; Wolterink et al. 1993; Inglis et al. 1994; Fletcher 1995, 1996; Fletcher et al. 1996; Fletcher and Higgins 1997). In control studies, responding for stimuli that are either randomly or negatively associated with reward is unaffected by intra-NAc amphetamine (Taylor and Robbins 1984); thus, the amphetamine effect is dependent on a prior positive stimulus-reward contingency.

There is a difference in the effects of excitotoxic lesions of core versus shell NAc subregions on the enhancement of responding for conditioned reward by amphetamine (Parkinson et al. 1999). Following lesions of either region and then pairings of a stimulus with reward, rats responded more on a lever producing conditioned reward. However, the shell but not the core lesion blocked the potentiation of responding for conditioned reward by intra-NAc amphetamine. Rats with lesions of the core appeared to be deficient in learning the association between the stimulus and primary reward during pairings in spite of showing a conditioned reward effect. The authors concluded that the core is implicated in learning associations between stimuli, whereas the shell appears critical for the enhancing effects of amphetamine on responding for conditioned reward.

Unlike the results of Beninger et al. (1981) and Robbins et al. (1983) with systemic cocaine (see above), intra-NAc cocaine dose-dependently and selectively augments responding for conditioned reward (Chu and Kelley 1992). Therefore, administration of indirect DA agonists into the NAc enhances responding for conditioned reward and there may be a critical role for the shell region in this effect.

Direct DA agonists

Bilateral NAc infusions of DA produce a dose-dependent enhancement of responding for a stimulus previously paired with water; this effect was not observed when the presentations of the stimulus and water were random (Cador et al. 1991). Pretreatment with α–flupenthixol blocked this effect. Furthermore, DA infusions into the posterior region of the caudate-putamen did not produce an enhancement, nor did 6-hydroxydopamine (6-OHDA) lesions of the dorsal noradrenergic bundle (depleting norepinephrine in the NAc) reduce the enhancement of conditioned reward with intra-NAc DA. Thus, DA in the NAc is critical for enhanced responding for conditioned reward.

The effects of NAc administration of D_1-like agonists markedly contrast with those of systemic administration. Chu and Kelley (1992) observed no effects of NAc administration of the D_1-like agonist CY 208-243 (Murray and Waddington 1990) or the D_2-like agonist quinpirole;

the two agents in combination, however, enhanced responding for conditioned reward, suggesting an additive (and possibly synergistic) effect of D_1- and D_2-like receptor co-stimulation. In contrast, NAc administration of the D_1-like agonist SKF 38393 or quinpirole alone *has* been reported to enhance responding for conditioned reward (Wolterink et al. 1993; Phillips et al. 1994). Perhaps the discrepant effects are related to the doses studied. Regardless, Wolterink et al. (1993) replicated the finding of Chu and Kelley (1992) that co-administration of D_1- and D_2-like agonists produces a cooperative effect. It appears that stimulation of either D_1- or D_2-like receptors in the NAc enhances responding for conditioned reward.

In the continuing effort to delineate the physiological processes underlying reward-related behavioral plasticity, greater attention is being allocated to the intracellular events downstream from the receptor. Kelley and Holahan (1997) examined the effects of manipulating the intracellular cyclic adenosine monophosphate (cAMP)-dependent second-messenger pathway on responding for conditioned reward. cAMP synthesis is activated and inhibited, respectively, by D_1- and D_2-like postsynaptic receptor types through their coupling to adenylate cyclase. Intra-NAc infusion of cholera toxin, which produces a sustained upregulation of cAMP through persistent activation of a stimulatory G protein, enhances both previously established responding as well as acquisition of responding for conditioned reward. Moreover, Westly et al. (1998) found that intra-NAc injections of the cAMP-dependent protein kinase inhibitor Rp-cAMPS blocked the enhancement of responding for conditioned reward produced by intra-NAc amphetamine. Therefore, the cAMP-dependent second messenger system in the NAc appears to play an important role in the control of responding by conditioned rewards. This possibility is discussed further in a later section.

Interaction of other brain regions with the NAc

Some attempts have been made to further delineate the neural circuitry mediating the acquisition of responding for conditioned reward and studies have implicated additional substrates, including the ventral pallidum (VP), pedunculopontine tegmental nucleus (PPN), basolateral (BLA) and central nuclei of the amygdala, and basal forebrain.

Fletcher et al. (1996) have suggested that DA transmission in output structures of the NAc such as the VP may contribute to the control of responding by conditioned rewards. Thus, intra-VP infusions of amphetamine enhanced responding for conditioned reward, although the effect was smaller than that seen following NAc injections. If this effect was due to spread of the drug from the VP to the NAc, higher doses of amphetamine injected into the VP might be expected to lead to larger concentrations in the NAc, and therefore a larger effect. This shift in the dose-response curve was not seen, implicating DA in the VP in conditioned reward. Moreover, blockade of GABAergic neurotransmission in the VP with picrotoxin abolished selective responding on a lever producing conditioned reward (Fletcher et al. 1998), while quinolinic acid lesions of this area impaired enhanced responding for conditioned reward following NAc amphetamine (Olmstead et al. 1997). These results support a role for the VP in reward-related learning.

The PPN, a structure receiving innervation from the NAc directly and by way of the VP, appears to be important for the control of responding by conditioned rewards. Excitotoxic lesions of this structure abolish the acquisition of responding for conditioned reward, as well as the augmentation of the effect by intra-NAc amphetamine (Inglis et al. 1994). These results are similar to those from other reward paradigms (Bechara and van der Kooy 1989; Olmstead and Franklin 1994), and implicate the PPN as a necessary downstream target of the NAc for the control of responding by conditioned rewards.

Olmstead et al. (1997) investigated the role of the cholinergic nucleus basalis magnocellularis of the basal forebrain, a projection target of the NAc. Excitotoxic lesions exaggerated the enhancing effects of NAc amphetamine on responding for conditioned reward. The authors related their findings to a lesion-induced attentional deficit.

Specific afferents to the NAc contribute differentially to reward processing. Cador et al. (1989) first demonstrated that excitotoxic lesions of the amygdala (particularly the BLA) impair responding for conditioned reward, although differential responding on the CR lever was not eliminated entirely. Moreover, these lesions did not affect the ability of intra-NAc amphetamine to enhance this responding. Later, Burns et al. (1993) investigated these effects with lesions of different sources of NAc innervation: the medial prefrontal cortex (MPC), BLA and ventral subiculum (SUB). Lesions of the BLA or SUB, but not the MPC, reduced the conditioned reward effect but it still was potentiated by NAc amphetamine. Similarly, BLA lesions impaired the acquisition of responding for IV cocaine under a second-order, but not first-order schedule (Whitelaw et al. 1996). Thus, BLA lesions disrupt the acquisition of responding for conditioned reward, but not the ability of primary reward to control behavior. Lesions of the central amygdaloid nucleus, in contrast, do not impair the conditioned reward effect, but block the enhancement after intra-NAc amphetamine (Robledo et al. 1996). It appears that amygdala subregions differentially modulate the acquisition of responding for conditioned reward.

Collectively, these results show that effects on responding for conditioned reward mediated by the NAc are dependent on several other afferent and efferent structures; the nature of this dependence, however, is poorly understood.

Neurochemical interactions with DA

The interaction of other neurotransmitter systems with DA-mediated effects on responding for conditioned reward may prove to be useful in understanding the physiological mechanisms that underlie reward-related learning. Since an interaction may be receptor subtype- and/or site-specific, identifying its biochemical locus could give powerful insight into the processes whereby a conditioned reward is both acquired and used to direct behavior.

Glutamate (GLU)

The striatum receives GLU projections from the cortex (McGeorge and Faull 1989) and some of these synapse on the same dendritic spines as DA afferents (Bouyer et al. 1984; Freund et al. 1984). The interaction between GLU and DA in the striatum may be responsible for processes of sensorimotor integration. Systemic GLU agonists or antagonists similarly disrupt enhanced responding for conditioned reward after intra-NAc amphetamine (Kelley and Throne 1992; Burns et al. 1994). This effect is seen following the agonists NMDA, AMPA or quisqualate, as well as the NMDA receptor antagonist APV or the AMPA antagonist CNQX. These findings are consistent with theoretical perspectives discussed later. In contrast, Kelley et al. (1997) have reported that a dose of APV into the NAc core region (that disrupted responding for food) during conditioning did not significantly affect subsequent responding for conditioned reward.

Opiates

Kelley and Delfs (1991b) first described the effects of central opiate agonist infusions on responding for conditioned reward. Microinjections of the mixed μ/δ-agonists DALA or morphine into the ventral tegmental area (VTA), which increase DA cell firing (Ostrowski et al. 1982) and synaptic levels of DA in the NAc, were *ineffective* in altering the conditioned reward effect. Similarly, intra-NAc administration of the κ-agonist U50,488H, δ-agonist DPEN, μ-agonist DAMGO, or DALA or morphine did not significantly affect responding for conditioned reward, although morphine tended to increase overall responding (Cunningham and Kelley 1992a,b). On the other hand, Phillips et al. (1994) have reported that intra-NAc DALA, DAMGO or DPEN enhance responding for conditioned reward. The apparent discrepancy might relate to the use of a lower dose range by Phillips et al. (1994). The data suggest that acute infusions of opiates into the NAc, but not the VTA, enhance responding for conditioned reward.

The effects of chronic opiate treatment provide a clearer dissociation of the NAc and VTA. Infusions of DALA into the VTA over 10 days attenuated the augmented conditioned reward effect found after NAc amphetamine, quinpirole or DALA itself, but had a negligible effect on enhanced responding for conditioned reward induced by NAc injections of the D_1-like agonist SKF 38393 (Phillips et al. 1994). Conversely, 4-day NAc pretreatment with DAMGO or morphine further enhanced the effect of NAc amphetamine on responding for conditioned reward; similar pretreatment with DPEN had no effect (Cunningham and Kelley 1992b). Therefore, opiate/DA interactions appear to be site-specific and selective for individual opiate and DA receptor subtypes.

5-Hydroxytryptamine (5-HT)

5-HT and DA inputs converge in the NAc (Phelix and Broderick 1995), suggesting possible interactions between these transmitters. In support of this notion, Fletcher (1995, 1996) has found that either systemic administration of the indirect 5-HT agonist fenfluramine, or intra-NAc 5-HT itself dose-dependently attenuates the augmentation of conditioned reward induced by intra-NAc amphetamine. Fenfluramine did not shift the amphetamine dose-response function suggesting that the effects of these drugs arise via independent mechanisms. The effects of fenfluramine or 5-HT were completely reversed by the antagonist metergoline, suggesting that 5-HT receptor binding is necessary to bring about the inhibition of amphetamine's effects.

The 5-HT_{1b} agonists 5-CT (non-selective 5-HT_1), RU 24969 (5-$HT_{1a/1b}$) or CP 93,129 (5-HT_{1b}), but not the 5-HT_{1a} agonist 8-OH-DPAT or the 5-HT_2 agonist DOI, attenuated the enhancement of responding produced by intra-NAc amphetamine when co-injected with it (Fletcher and Korth 1997). Thus, the 5-HT_{1b} receptor may play a critical role in regulating the action of DA in the NAc. Results suggest that 5-HT in the NAc and possibly elsewhere acts to reduce the DA-dependent augmentation of responding for conditioned reward. On the other hand, systemic administration of the 5-HT_3 receptor antagonist ondansetron produced a small reduction in the enhancement of responding for conditioned reward by NAc amphetamine (Fletcher and Higgins 1997). This result suggests that 5-HT_3 receptors may have a facilitatory effect on DA neurotransmission in the NAc. However, it remains unclear as to how different 5-HT receptors and DA interact on a biochemical and/or cellular level to produce these effects.

Cholecystokinin (CCK)

CCK is co-localized with DA within portions of the NAc (Hökfelt et al. 1980). It induces a dose-dependent enhancement of amphetamine's effect on conditioned reward when co-infused into the posteromedial aspect of the NAc; this effect was reversed by systemic treatment with the CCK_a antagonist devazepide (Phillips et al. 1993). Moreover, CCK receptors appear to differentially

regulate DA function in the NAc. Systemic L-365,260 or intra-NAc PD-135158, both CCK_b antagonists, further potentiate the enhancement of responding for conditioned reward after intra-NAc amphetamine (Josselyn and Vaccarino 1995; Josselyn et al. 1996a). In contrast, the CCK_a antagonists devazepide or PD-140548, when administered systemically or intra-NAc, respectively, block the ability of the conditioned stimulus to act as a conditioned reward (Josselyn and Vaccarino 1996; Josselyn et al. 1996b). Therefore, it appears that activity at CCK_a receptors enhances DA function in the NAc, while that at CCK_b receptors inhibits it.

Neurotrophins

Horger et al. (1997) reported that the acquisition of responding for conditioned reward is modulated by neurotrophic factors. Chronic bilateral infusions of brain-derived neurotrophic factor (BDNF) were made into the NAc with osmotic minipumps following the conditioning phase. This regimen enhanced the conditioned reward effect, an action that was further potentiated by systemic cocaine (at a dose that did not alter responding in control rats). Moreover, both the enhancement produced by BDNF on its own and the greater sensitivity to cocaine persisted for weeks after neurotrophin administration was terminated, suggesting that stable BDNF-induced neuroadaptations underlie these effects. The means by which BDNF produces the above effects and whether they can be mimicked by other neurotrophins are issues that await further research.

Summary

Systemic indirect DA agonists enhance the acquisition of responding for conditioned reward, while the direct acting DA agonist apomorphine blocks the conditioned reward effect by producing indiscriminate responding on the CR and NCR levers. A similar dissociation is found with systemic receptor-subtype specific agents: D_1-like agonists impair, whereas D_2-like agonists enhance responding for conditioned reward. Thus, the disruptive effects of apomorphine may result from its action at D_1-like receptors. Studies utilizing DA antagonists have demonstrated that blockade of either D_1- or D_2-like receptors can disrupt responding for conditioned reward. This finding does not preclude the possibility that each receptor type plays a unique role (see below).

The dissociations observed after systemic DA agonists are conspicuously absent in studies employing central administration. There are no apparent differential effects of indirect- and direct-acting DA agonists when these drugs are infused into the NAc; both augment the conditioned reward effect. Likewise, intra-NAc D_1- or D_2-like agonists enhance the conditioned reward effect. Finally, a number of different neurotransmitters including GLU, opiates, 5-HT and CCK, as well as the neurotrophic factor BDNF can modulate DA-dependent effects on responding for conditioned reward. The biochemical locus of these interactions may suggest possible mechanisms by which conditioned reward is both acquired and used to control behavior.

Reward-related learning mediated through a DA signal at D_1-like receptors?

GLU afferents from the cortex, amygdala, and hippocampus converge with DA projections from the midbrain in the NAc and caudate-putamen: this architecture is ideally suited for mediating various forms of sensorimotor integration. Since the GLU input is so widespread, the breadth of perceptual information to the striatum is extensive. As striatal output appears to be related to voluntary motor control, behavioral responses to a given stimulus may relate to the ability of specific GLU inputs (coding that stimulus) to drive particular efferents. Moreover, modifications of synaptic efficacy could underlie changes in the ability of particular stimuli to evoke specific behaviors.

Environmentally significant stimuli, including rewards (e.g. food, water), induce DA release in the striatum (for reviews, see Salamone 1994; Kiyatkin 1995; Westerink 1995; Schultz et al. 1997). Similarly, conditioned rewarding stimuli increase striatal DA release (for reviews, see Beninger 1993; Schultz et al. 1997). DA selects GLU inputs to neostriatal neurons (Flores-Hernández et al. 1997) and alters the responses of striatal cells to GLU agonist application (Chiodo and Berger 1986; Cepeda et al. 1993; Calabresi et al. 1996; Levine et al. 1996; Wickens et al. 1996). Thus, DA release in the striatum might be a mechanism by which specific synapses are modified after significant environmental events.

This scheme can explain the acquisition of rewarding properties by neutral stimuli paired with primary reward (see Fig. 2). Thus, it has been proposed that environmental stimuli associated with primary reward activate synaptic connections between GLU inputs and response-controlling efferents in the striatum and that the release of DA that accompanies reward might act to strengthen those synapses that were recently active (Beninger 1983, 1991, 1993; Wickens 1990; Miller et al. 1992; Wickens and Kötter 1995; Beninger and Miller 1998). Following these synaptic modifications, environmental stimuli associated with reward themselves acquire the ability to stimulate DA release, possibly through striatal efferents to the VTA or zona reticulata of the substantia nigra. These conditioned rewarding stimuli themselves then can modify response-controlling corticostriatal synaptic connections activated by stimuli associated with their presentation. In this way, stimuli associated with conditioned reward can come to control responding.

The effects of GLU agents on the NAc DA-mediated enhancement of responding for conditioned reward demonstrate that GLU indeed may play a role like that outlined above. The finding that systemic GLU agonists or

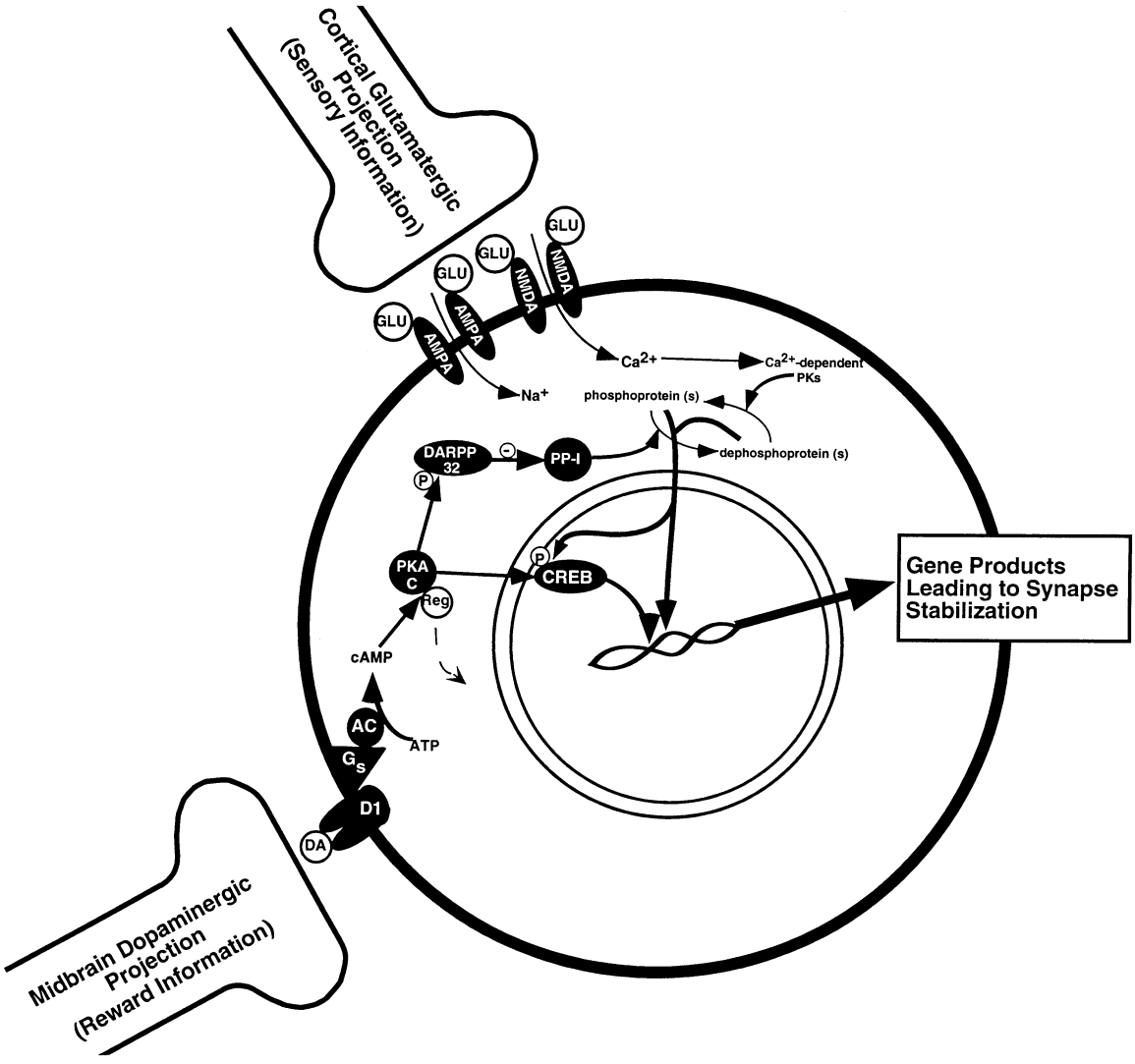

Fig. 2 Potential intracellular events that may underlie the acquisition of rewarding properties by neutral stimuli. Shown are dopaminergic and glutamatergic projections converging on a common striatal medium spiny neuron. Dopamine (DA)-mediated signaling through D_1-like receptors stimulates the production of cAMP, which displaces the regulatory subunit (*Reg*) from protein kinase A freeing the catalytic subunit (*PKA-C*). One important target of PKA phosphorylation may be cAMP-response element binding protein (*CREB*), which may stimulate transcription of specific genes when it is phosphorylated at a specific serine amino acid residue. Another substrate of PKA is DARPP-32; this phosphorylated enzyme inhibits the activity of protein phosphatase I (*PP-I*), thus increasing intracellular levels of phosphoproteins. Voltage-dependent calcium (Ca^{2+})-mediated signaling through NMDA receptors can interact with both of these pathways. In the case of DARPP-32, Ca^{2+}-dependent protein kinases (PKs) may cooperatively enhance intracellular levels of phosphoproteins, producing many possible biochemical effects. Likewise, DA-stimulated CREB phosphorylation depends critically on intact transmission at NMDA receptors (Konradi et al. 1996), suggesting that the D_1-like receptor signaling stimulates nuclear events (including those required for long-term changes in synaptic efficacy) only during periods of postsynaptic activation

antagonists reduce amphetamine's effect on conditioned reward (Kelley and Throne 1992; Burns et al. 1994) can be understood if GLU synapses become modified as a result of the association between environmental stimuli and reward. GLU antagonists might attenuate incoming sensory information pertaining to environmental stimuli or might inhibit the output pathway activated by that stimulus. If, on the other hand, GLU synapses were activated indiscriminately by a GLU agonist, synapses corresponding to irrelevant stimuli would be activated and control of responding by the conditioned stimulus would be lost. The finding of Kelley et al. (1997) that NAc core infusion of an NMDA antagonist during stimulus-reward pairings did not block subsequent responding for conditioned reward may appear to conflict with this interpretation. However, this negative finding is based on a single dose of APV; other doses need to be tested. Furthermore, region-specific NMDA receptor antagonism may not block a process that is distributed in nature (see below).

Psychopharmacological studies of conditioned reward have led to an emerging consensus that the release of DA serves as a signal, coding rewarding properties of specific environmental stimuli (Robbins et al. 1983; Beninger

et al. 1989; Beninger and Ranaldi 1992; Schultz et al. 1997). With few exceptions, indirect agonists that induce the release of DA reliably enhance responding for conditioned reward. Conversely, the direct agonist apomorphine increases responding indiscriminately on CR and NCR levers, reflecting an impairment in the ability of the conditioned stimulus to direct responding. These results suggest that the control of responding by a conditioned reward depends on an intact DA signal (cf. Beninger and Miller 1998).

There is evidence that synaptic expression of the DA reward signal exists at D_1-like receptors. D_1- and D_2-like receptors are differentiated by stimulation and inhibition, respectively, of adenylate cyclase activity and cAMP formation (Niznick and Van Tol 1992; Civelli et al. 1993; Sibley et al. 1993). The formation of cAMP leads to the activation of cAMP-dependent protein kinase, phosphorylation of cAMP-response element binding protein (CREB) and transcription of immediate early genes. It has been proposed that these intracellular messengers modify the effectiveness of synapses through the phosphorylation of other proteins (e.g. DARRP-32) and/or transcriptional regulation of genes that induce long-term structural change (e.g. stabilization) at the synapse. Recently activated synapses, identifiable by transiently increased levels of postsynaptic Ca^{2+}, may be the sole target of this modification (see Wickens 1990; Wickens and Kötter 1995). In support of this idea, amphetamine or D_1-like agonist-induced expression of immediate early genes in the striatum depends on functional transmission at NMDA receptors (Konradi et al. 1996), GLU-gated Ca^{2+}-channels that conduct ions only when the cell is depolarized sufficiently. Therefore, at least some D_1-like receptor mediated events are dependent on the active state of the postsynaptic cell (cf. Hernández-López et al. 1997).

The effects of systemically administered receptor subtype-specific agonists also point to D_1-like receptors as a locus for the DA reward signal. The D_2-like agonists bromocriptine and quinpirole dose-dependently enhance responding for conditioned reward (Beninger and Ranaldi 1992; Ranaldi and Beninger 1995); in contrast, D_1-like agonists attenuate the effect (Beninger and Ranaldi 1992; Beninger and Rolfe 1995). These results imply that tonic stimulation of D_1-like receptors may mask the DA reward signal. It is interesting that SKF 38393 also disrupts the potentiated responding for conditioned reward by amphetamine (Ranaldi et al. 1995), suggesting that masking the DA reward signal with tonic D_1-like receptor stimulation renders increased DA release ineffective in enhancing the signal.

The effects of subtype-specific antagonists on amphetamine-induced enhancement of conditioned reward (Ranaldi and Beninger 1993) again suggest that D_1- and D_2-like receptors play different roles. A D_1-like antagonist, without altering maximal responding, shifted the amphetamine dose-response function to the right. D_2-like antagonists either were less effective or failed to shift the amphetamine effect to the right, and also attenuated maximal responding. These results suggest that an intact signal at D_1-like receptors is critical for the acquisition of responding for conditioned reward. D_2-like antagonists, on the other hand, failed to dissociate alterations in the selectivity of responding on the CR lever from reductions in overall response rate.

Preliminary investigations into the role of second-messenger mediated events also have highlighted the possible importance of D_1-like receptor signal transduction in the acquisition of responding for conditioned reward. Chronic up-regulation of cAMP in the NAc with cholera toxin enhances both the acquisition of rewarding properties by neutral stimuli, as well as the ability of those conditioned rewards to control behavior (Kelley and Holahan 1997) and inhibition of NAc cAMP-dependent protein kinase blocks the ability of amphetamine to enhance responding for conditioned reward and the conditioned reward effect itself (Westley et al. 1998). These findings implicate D_1-like receptor-mediated second messenger events in reward related learning.

The interaction of other neurochemicals with DA-dependent effects on conditioned reward further supports the D_1-like receptor as a target for the DA reward signal. For example, the potentiating effect of CCK in the posterior regions of the NAc on the DA-dependent augmentation of the conditioned reward effect (Phillips et al. 1993) may correspond with its effect on adenylate cyclase. CCK, despite having no effect on the activity of adenylate cyclase by itself, potentiates DA-induced activation of this enzyme in the posterior aspect of the NAc (Studler et al. 1986). Thus, CCK augments the response of D_1-like receptors in this area, with a corresponding potentiation of the conditioned reward effect. This effect differs from that of D_1-like agonists, in that it affects only those cells that are already active. The facilitatory effect of CCK on DA also appears to be selective for the CCK_a receptor, as it can be reversed by the antagonist devazepide (Phillips et al. 1993). The CCK/DA interaction is site-specific within the NAc, as CCK inhibits DA-stimulated adenylate cyclase activity in anterior regions (Studler et al. 1986), where CCK_b receptors likely predominate (see Crawley 1992; Vaccarino 1994). Therefore, the interaction of CCK receptor subtypes with DA-dependent potentiated responding for conditioned reward parallels their effects on adenylate cyclase activity. Based on these findings, selective CCK_a agonists would be predicted to mimic the potentiating effect of CCK infusion into the posterior NAc. In contrast, CCK infused into the anterior NAc should attenuate enhanced responding for conditioned reward by amphetamine, an effect that should be reproduced by CCK_b agonists.

Although it is not yet clear what form of interaction between opiate and DA neurotransmission gives rise to the effects reviewed above, the site-dependence of these effects raises some interesting possibilities. Chronic systemic administration of the μ/δ-agonist morphine has been shown to have different effects on DA neurons arising in the VTA, the axon terminals of those cells in the NAc, and postsynaptic DA receptors in the NAc. In-

creased levels of tyrosine hydroxylase (TH), the enzyme responsible for DA synthesis, have been observed in the VTA, yet reduced TH activity is observed in the NAc (Beitner-Johnson and Nestler 1991). An explanation for these effects derives from the finding that chronic morphine impairs axonal transport (Beitner-Johnson and Nestler 1993), which accounts both for the buildup of TH in the VTA, and reduced DA synthesis in the NAc. Thus, chronic intra-VTA infusions of the μ/δ-agonist DALA may reduce the enhancement of conditioned reward observed after amphetamine, quinpirole, and DALA (Phillips et al. 1994) by decreasing the DA available for release in the NAc.

Chronic intra-VTA infusions of DALA had a negligible effect on the potentiation of conditioned reward after NAc infusion of a D_1-like agonist (Phillips et al. 1994; the theoretical implications of the effects of NAc D_1-like agonists are discussed below). This observation is important for two reasons. First, this dissociation provides further evidence that D_1- and D_2-like receptors augment responding for conditioned reward through different processes. Second, the means by which D_2-like receptor activation (as well as amphetamine and DALA) augments the conditioned reward effect may depend on DA release in the NAc, while that of D_1-like receptors may not. It would follow that D_1-like receptor stimulation in the NAc directly amplifies the DA reward signal, as the augmentation of the conditioned reward effect persists, despite reductions in endogenous DA input.

While the above interpretation is in need of further testing (see below for examples), it is consistent with the biochemical effects in the NAc and the corresponding outcome on responding for conditioned reward of chronic μ/δ-agonist infusion into the NAc. Repeated systemic administration of morphine produces a long-term supersensitivity of D_1-like receptor-mediated responses in the NAc (Tjon et al. 1994), an effect that would amplify the DA reward signal if it is localized to D_1-like receptors. Assuming that this supersensitivity is mediated by a local action of morphine in the NAc, the further enhancement of the amphetamine potentiated conditioned reward effect with chronic intra-NAc μ/δ-agonist treatment (Phillips et al. 1994) may result from D_1-like receptor supersensitivity. In other words, chronic intra-NAc μ/δ-agonist treatment may amplify the DA reward signal directly through amplification of D_1-like receptor mediated responses.

Several testable implications follow from the above ideas. First, of the effects of chronic systemic opiate administration, the amplification of the DA reward signal through D_1-like receptor supersensitivity should dominate with respect to responding for conditioned reward. Therefore, chronic systemic treatment with morphine should produce a leftward shift in the dose-response curve for D_1-like agonists infused into the NAc. Moreover, since opiate-induced D_1-like receptor supersensitivity is long-lasting, one would also predict that prior chronic treatment with systemic morphine itself would enhance the acquisition of responding for conditioned reward. In this regard, a recent study has demonstrated that chronic administration of cocaine in a sensitizing regimen does enhance the conditioned reward effect (Taylor and Horger 1999). Studies such as the ones proposed above may prove useful in elucidating the locus of opiate/DA interactions that give rise to differential effects on DA-dependent potentiation of responding for conditioned reward.

The effects of systemically delivered DA agents on responding for conditioned reward correspond quite well with a DA signal expressed at D_1-like receptors but findings from central administration are not as clear. Like systemic treatments, indirect DA agonists administered into the NAc increase the conditioned reward effect, presumably by augmenting the DA reward signal through enhanced DA release. However, a D_1-like agonist (Wolterink et al. 1993; Phillips et al. 1994) or DA itself (Cador et al. 1991) infused into the NAc increased responding for conditioned reward. Furthermore, rats having undergone DA denervation of the NAc show enhanced responding for conditioned reward when treated with a low dose of apomorphine (Taylor and Robbins 1986). In these studies direct stimulation of D_1-like receptors in the NAc failed to mask the putative DA reward signal, findings that are in apparent contradiction with the D_1-like receptor-mediated signal hypothesis.

One possibility is that systemic D_1-like agonists attenuate the conditioned reward effect by acting peripherally. However, several lines of evidence show that they have a central action. Thus: 1) they induce immediate early gene expression in the NAc (Robertson and Jian 1995); 2) their behavioral effects are blocked by irreversible inactivation of D_1-like receptors in the striatum (Neisewander et al. 1995) or ICV administration of antisense oligonucleotides to D_1 receptor mRNA (Zhang et al. 1994). These results show that systemic D_1-like agonists have sufficient penetrance into the striatum and NAc to induce biochemical and behavioral effects; however, they do not rule out the possibility that the effects of systemic treatment are the result of peripheral D_1-like receptor activation. Other evidence suggests that this scenario is unlikely, given that: 1) the full D_1-like agonist SKF 82958, in similar doses, produces "rewarding" effects as measured by other behavioral paradigms including stimulant self-administration (e.g. Self et al. 1996) and place conditioning (Abrahams et al. 1998); 2) SKF 82526 (fenoldopam), a D_1-like agonist that does not readily cross the blood-brain barrier, is without effect in place conditioning (Hoffman and Beninger 1988), demonstrating that peripheral stimulation of D_1-like receptors is behaviorally neutral in another reward paradigm. A similar finding that fenoldopam failed to affect responding for conditioned reward would provide evidence for the central action of systemically administered D_1-like agonists in attenuating this effect.

Systemic administration also leads to a more diffuse pharmacological action within the brain than does local infusion. Therefore, the differential effects on conditioned reward stemming from systemic versus NAc ad-

ministration may relate to actions in brain sites other than the NAc, possibly more dorsal regions of the striatum. Local infusion of amphetamine into the caudate nucleus has been shown to enhance responding for conditioned reward, albeit in a less robust manner than similar infusion into the NAc (Taylor and Robbins 1984). Moreover, infusion of amphetamine into the anterodorsal and ventromedial regions of the striatum also potentiated the conditioned reward effect, although similar infusion into striatal regions located more distally from the NAc had no effect (Kelley and Delfs 1991a). These results identify the caudate-putamen as another potential neuroanatomical substrate for the enhanced control of responding by conditioned rewards after systemic treatment with indirect DA agonists. In fact, several lines of evidence suggest that dorsal regions of the striatum contribute significantly to many types of reward (see Beninger and Ranaldi 1993; Beninger et al. 1993; Wickens and Kötter 1995).

Additional support for this idea derives from the effects of 6-OHDA on responding for conditioned reward. 6-OHDA lesions of the NAc, but not the caudate-putamen, attenuate the enhancement of responding for conditioned reward induced by intra-NAc amphetamine (Taylor and Robbins 1986). However, 6-OHDA lesions of the NAc do not eliminate the conditioned reward effect itself. Taken together with the finding that diffuse blockade of DA receptors with systemically administered α-flupenthixol does abolish the conditioned reward effect (Robbins et al. 1983; Fletcher and Higgins 1997; Killcross et al. 1997), the expression of the DA signal may be distributed throughout the striatum (and possibly elsewhere). In support of this notion, 6-OHDA lesions of the posterior caudate-putamen reduced the enhanced responding for conditioned reward after systemic pipradrol (Robbins and Everitt 1982). The prediction follows that DA in both the caudate-putamen and NAc must be compromised to eliminate the conditioned reward effect. Although this hypothesis has yet to be tested, concurrent elimination of DA in the NAc and the caudate-putamen is necessary to abolish avoidance responding (Koob et al. 1984), a behavior that can be understood in terms of reward-related learning (Beninger 1983, 1989, 1991). A role for D_1-like receptors, specifically, in the dorsal striatum is implied by the finding that a reportedly ineffective (Robbins et al. 1983) dose of cocaine can enhance responding for conditioned reward following up-regulation of the cAMP second messenger system in this region (Kelley and Holahan 1997). These findings support the view that the DA signal is distributed throughout the striatum, including regions dorsal to the NAc.

Concluding comments

The idea of a rewarding signal at D_1-like receptors that is distributed throughout the striatum can accommodate all the available findings based on responding for conditioned reward. Indirect agonists increase DA neurotransmission, but leave the DA reward signal intact, hence they increase the ability of the conditioned reward to direct responding. Similarly, D_2-like receptor agonists may enhance responding for conditioned reward because they stimulate motor activity but do not mask the DA signal at D_1-like receptors. Systemic administration of the direct-acting DA agonist apomorphine or D_1-like selective agonists reduces the ability of conditioned reward to control responding, an effect that is consistent with masking the DA reward signal. The results of selective DA antagonists also support the notion that the ability of a conditioned reward to control behavior appears to correspond directly to the action of DA at D_1-like receptors. The modulation of DA-dependent effects on responding for conditioned reward by other neurotransmitters also suggests that D_1-like receptor-mediated signal transduction represents the molecular basis for the DA reward signal (see Fig. 2). Central to the above idea is that intra-NAc infusions of DA or D_1-like agonists do not produce enough tonic D_1-like receptor activation to mask sufficiently the DA reward signal; only with tonic stimulation of D_1-like receptors throughout the striatum may the control of responding by conditioned rewards be lost.

It is now clear that stimulation of either D_1- or D_2-like receptors can produce "rewarding" effects (e.g. Self and Nestler 1995). We stress that this idea is compatible with the theory outlined in this paper and elsewhere (Miller et al. 1990; Beninger 1993; Beninger and Ranaldi 1994). Indeed, D_2-like receptors may play even a larger role in the processes that initiate primary reward; however, the ability of specific stimuli associated with that primary reward to control later behavior appears to depend predominantly on D_1-like receptor-mediated events. Although this hypothesis has been outlined in this paper specifically to address responding for conditioned reward, its basis also derives from effects in several other behavioral paradigms that assess reward-related responding (see Miller et al. 1990; Beninger 1991; Beninger and Miller 1998). Empirical data from each of these paradigms have accumulated to such a degree that both their shared and unique characteristics may be exploited to elucidate the mechanisms that underlie specific forms of reward processing in the brain. For example, the acquisition of responding for conditioned reward is a form of reward-related learning in which the DA reward signal is based on a specific stimulus within a larger environment. When compared to other paradigms, such as place conditioning, this feature can be highly instructive. In place conditioning, neutral stimuli from the reward-paired environment come to acquire rewarding properties through their association with primary rewards. However, unlike responding for conditioned rewards where specific lever-associated stimuli must come to control behavior, many stimuli within that environment may be conditioned, hence less stringent specificity is required for the DA reward signal to control behavior (cf. Beninger and Miller 1998). From this point of view, tonic D_1-like receptor stimulation associated with a specific environment

should enhance the reward properties of stimuli from that environment. In support of this view, systemic treatment with the full D_1-like agonists SKF 82958 (Abrahams et al. 1998) or dihydrexidine (unpublished results) has been shown to induce a conditioned place preference. An exhaustive set of such comparisons across behavioral paradigms is beyond the scope of this paper; however, that approach may prove useful in more accurately specifying the molecular correlates of reward-related learning.

The acquisition of responding for conditioned reward is a useful assay of reward-related learning, as specific processing of stimuli in the animal's environment is a necessary prerequisite for the behavioral pattern to emerge. This type of information processing, detection of an environmental stimulus (signal) among several other non-associated stimuli (noise) for the purpose of directing responding, is affected differentially by DA agents with known mechanisms of action. Several recent studies have implicated specific DA-coupled second-messenger-mediated events that may underlie the transformation of environmental cues from irrelevant noise elements to biologically-significant signals. With continued advances in biotechnology, the control of behavior by conditioned rewards may soon be understood at the molecular level.

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