

The dopamine hypothesis of reward: past and current status

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Mesolimbic dopaminergic neurons are thought to serve as a final common neural pathway for mediating reinforcement processes. However, several recent findings have challenged the view that mesolimbic dopamine has a crucial role in the maintenance of reinforcement processes, or the subjective rewarding actions of natural rewards and drugs of abuse. Instead, there is growing evidence that dopamine is involved in the formation of associations between salient contextual stimuli and internal rewarding or aversive events. This evidence suggests that dopaminergic-neuron activation aids the organism in learning to recognize stimuli associated with such events. Thus, mesolimbic dopaminergic neurons have an important function in the acquisition of behavior reinforced by natural reward and drug stimuli. Furthermore, long-lasting neuroadaptive changes in mesolimbic dopamine-mediated transmission that develop during chronic drug use might contribute to compulsive drug-seeking behavior and relapse.

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EXTERNAL AND INTERNAL STIMULI have signaling and reinforcing functions. In its reinforcing capacity, a stimulus increases or decreases the frequency of preceding responses, and accordingly is called a reinforcer or, respectively, a punisher. In 1954 experiments by Olds and Milner¹ revealed that the brain has specialized 'centers' for reward functions. In these studies, electrical stimulation of specific brain sites was found to be highly rewarding in the sense that rats responded operantly to electrical stimulation of these brain sites, often to the exclusion of any other activity. A neurotransmitter system that is particularly sensitive to electrical self-stimulation is the midbrain dopaminergic projection that originates in the ventral tegmental area (VTA) and projects to structures closely associated with the limbic system, most prominently the nucleus accumbens (NAC) shell region and the prefrontal cortex (Fig. 1). Because of its ubiquitous involvement in the regulation of reward-related behavior, this system has been characterized as a neurochemical substrate of reward². Synaptic dopamine-mediated transmission in the NAC shell region is increased preferentially not only by natural rewards such as food, water and sex, but also by a variety of drugs abused by humans^{3,4}. Furthermore, it has been hypothesized that long-term adaptive changes within midbrain dopaminergic neurons take place following repeated drug administration and lead to a disruption or desensitization of neural mechanisms that mediate reward^{5,6}, while rendering these neurons more sensitive to other behavioral actions of drug stimuli⁷.

Do all natural rewards and drugs of abuse interact with midbrain dopamine?

Natural rewards, including food, liquids and sex, as well as electrical brain stimulation and many drugs of abuse, increase extracellular dopamine levels in the NAC following acute administration²⁻⁴. However, many agents, such as inhalants, barbiturates or benzodiazepines, do not activate midbrain dopamine-mediated

transmission consistently, despite the fact that these drugs have rewarding properties and are heavily abused⁸⁻¹⁰.

The responses to conditioned reinforcers – that is, those stimuli that gain their reinforcing efficacy by means of their association with unconditioned rewarding natural or drug stimuli – have also been linked to midbrain dopamine-mediated transmission. However, conditional changes in dopamine release in the NAC are found only after stimuli that are predictive of strong aversive events such as footshock¹¹ or, in the case of appetitive stimuli, under food-deprivation conditions but not under *ad libitum* conditions^{12,13}. In addition, preferential activation of midbrain dopaminergic neurons by appetitive rather than aversive stimuli has been reported in monkeys¹⁴, suggesting that conditioned stimuli can enhance mesolimbic dopamine release, but that this effect depends on the type of the unconditioned stimuli used and on the deprivation state.

Natural rewards and midbrain dopamine

Numerous studies have shown that dopamine release in the NAC is increased by ingestion of food and water. The observation that microinfusion of the μ -opioid-receptor antagonist, naloxonazine, into the VTA impairs food-induced stimulation of dopamine release in the NAC shell region¹⁵, indicates that food acts via a specific neuronal mechanism in this brain region that leads to an activation of dopaminergic neurons (Fig. 2). However, consistent stimulation of dopamine release by food or liquids can be demonstrated only under deprivation conditions and not in nondeprived rats^{12,13}, suggesting a role for incentive rather than consummatory factors in dopamine-mediated activation by natural rewards. Another major determinant of the responsiveness of midbrain dopamine to natural rewards appears to be novelty. Thus, in rats fed *ad libitum* with standard food, feeding of a novel, palatable food elicits an immediate increase in extracellular dopamine release in the NAC,

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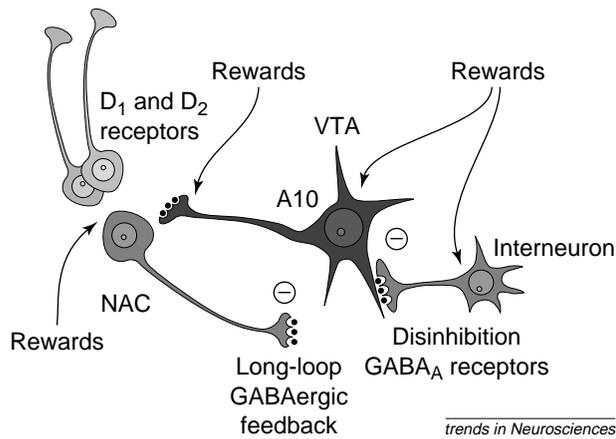


Fig. 1. The mesolimbic dopamine system. A10 dopaminergic neurons originate in the ventral tegmental area (VTA) and project mainly to the nucleus accumbens shell region (NAC). GABAergic interneurons within the VTA and a long-loop GABAergic feedback projection provides tonic inhibition (-) of A10 neurons. Different dopamine receptors (D₁ and D₂) are involved in mediating the action of rewards.

but this effect is blunted by a previous meal of the palatable food¹³. These results indicate that novelty is important for activation of mesolimbic dopamine by food stimuli in a nondeprived condition, and that the dopamine signal adapts to the repeated presentation of the same natural reward. Electrophysiological studies in monkeys further illustrate the role of midbrain dopaminergic neurons in the processing of information related to natural rewards, and suggest that these neurons have an important role in the learning of stimulus–reward associations by coding the temporal contiguity

between conditioned and unconditioned stimuli, and detecting the occurrence versus omission of an expected reward¹⁶ (see Box 1).

Psychostimulants and midbrain dopamine

Both amphetamine and cocaine elevate extracellular dopamine concentrations in the terminal region of mid-brain dopaminergic neurons, especially in the NAC (Refs 3,4,8). Extracellular dopamine levels are also reliably increased during self-administration of these drugs^{17,18}. However, psychostimulant-induced increases in synaptic dopamine in self-administering animals might involve factors other than only the direct pharmacological actions of these drugs. Rats that received non-response-contingent injections of cocaine administered by an animal self-administering cocaine, by means of a ‘yoking’ procedure, showed substantially smaller increases in extracellular dopamine concentrations than self-administering rats¹⁹. Thus, as suggested by the differences in the effects of food in deprived versus nondeprived animals on dopamine release, the ‘incentive salience’ of the stimulus (incentive salience refers to the magnitude of a reinforcing stimulus) appears to have an important role in the response of midbrain dopaminergic neurons to rewarding stimuli. Experiments that examined the dopaminergic response to cocaine in self-administering rats with high time resolution suggest that the cocaine response is regulated by changes in extracellular dopamine levels in the NAC (Refs 20–22). Self-injections of cocaine produce a transient rise in dopamine levels; when synaptic dopamine concentrations decrease to preinjection levels, the next lever press is initiated. Thus, phasic changes in

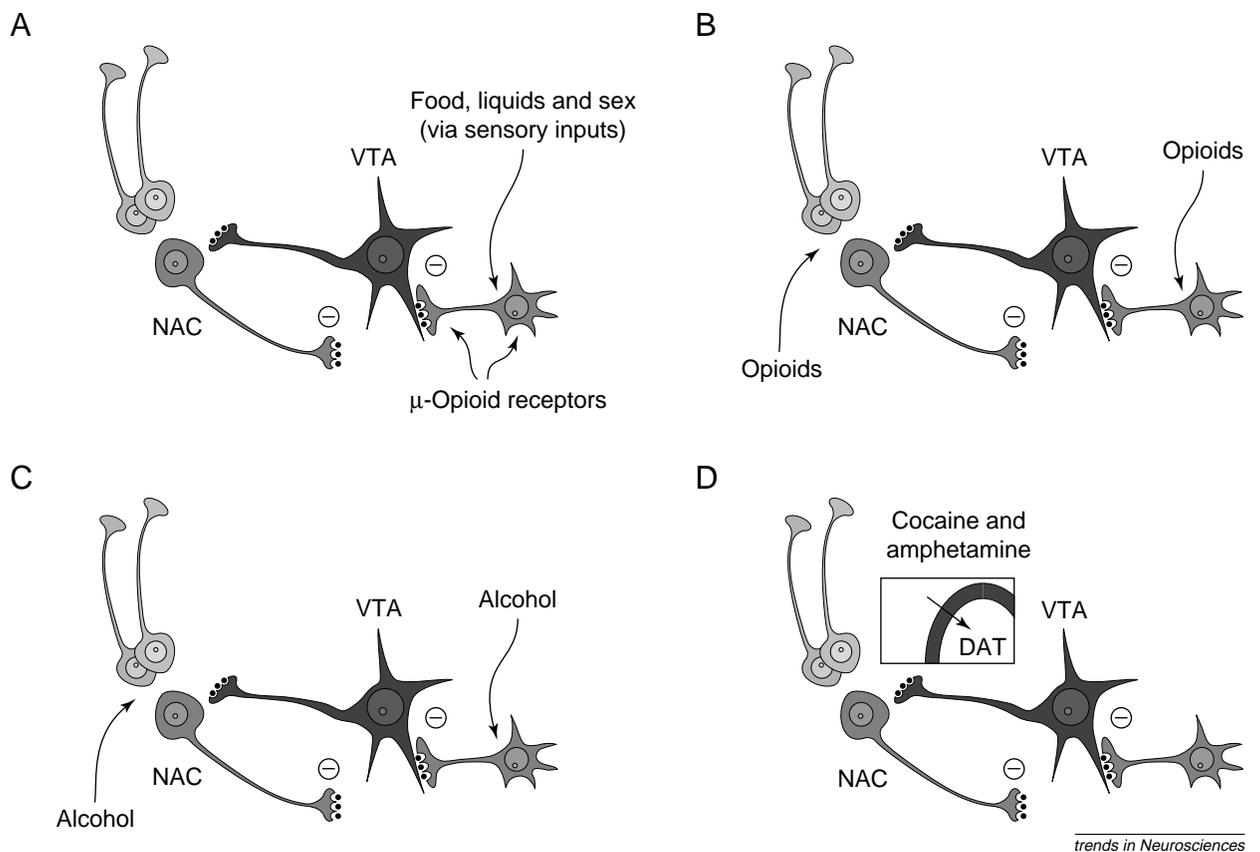


Fig. 2. The mechanisms of action of natural and drug rewards on mesolimbic dopaminergic neurons. Natural rewards (food, liquids and sex) act in an indirect manner to activate A10 neurons (A). Opioids and alcohol also increase dopamine-mediated neuronal activity in an indirect manner (B) and (C), whereas psychostimulants (cocaine and amphetamine) activate dopamine release by stimulating the release or inhibiting the dopamine transporter (DAT) (D). Abbreviations: NAC, nucleus accumbens shell region; VTA, ventral tegmental area.

Box 1. Past and current opinions: what is the role of dopamine within the mesolimbic system?

The hypothesis that mesolimbic dopaminergic neurons are the final common pathway for positive reinforcement by natural rewards or drugs of abuse has guided the field for more than two decades. Except in the case of psychostimulant reinforcement, however, this hypothesis remains to be confirmed unequivocally, and alternative views on the role of mesolimbic dopamine-mediated transmission have emerged. Recent work by Schultz and co-workers indicates that, whereas midbrain dopaminergic neurons respond to natural rewards such as food and liquid, the activation of these neurons depends on the predictability of reward presentation^a. An unexpected reward elicits a strong positive dopamine signal, which declines with repeated presentation and learning, such that the presentation of a predicted reward eventually no longer elicits dopamine-mediated neuronal responses. By contrast, omission of a predicted reward leads to suppression of the dopamine signal. These findings suggest that the response of midbrain dopaminergic neurons represents a learning signal that codes for prediction errors of reward^b. An alternative interpretation of these data has been offered, which proposes that the dopamine signal facilitates the reallocation of limited behavioral and cognitive processing capacity towards any unexpected event of behavioral significance, including reward. This behavioral-switching hypothesis^c stipulates that the dopamine signal has a more-general role in associative learning. Indeed, it has been demonstrated that associative learning is linked to enhanced dopamine release in the nucleus accumbens (NAC)^d. Thus, a selective increase in dopamine release in the NAC, but not in the dorsal striatum, is seen when an association is formed between two stimuli, of which neither is a biological reinforcer nor affects dopamine levels prior to formation of the association^d. These new findings suggest a role for mesolimbic dopamine in the modulation of associative learning in general, not only that involving reinforcement (see Fig. 1).

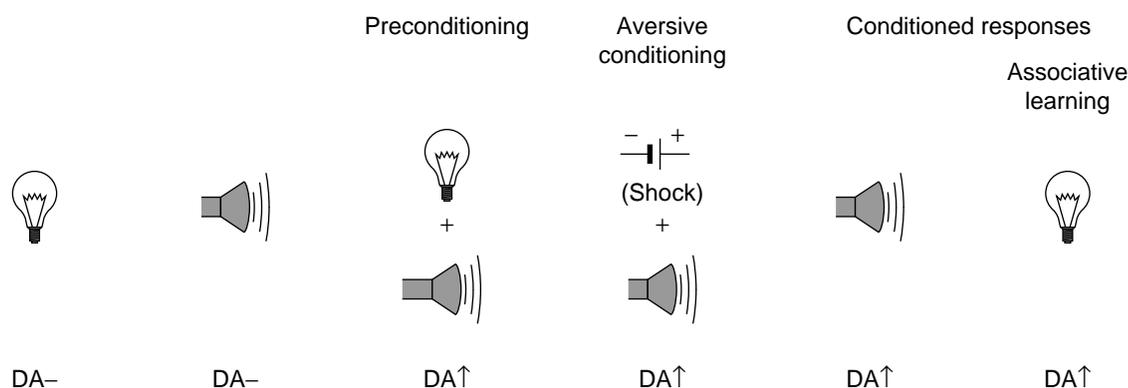
With respect to chronic drug use, neuroadaptive processes within the dopaminergic system have been identified. Sensitization has been implicated in the development of compulsive drug use^e, and involves a dramatic augmentation of behavioral and neurochemical responses that are

associated predominantly with mesolimbic dopamine-mediated transmission, which often develops with intermittent exposure to drugs of abuse. However, chronic drug use can also result in dysfunction or desensitization of neuronal mechanisms that mediate reward, including dopamine neurotransmission^{f,g}. As a result of this compromised condition of the reward system, affective states emerge that are opposite to the initial mood-elevating effects of drugs, such as dysphoria, depression and anxiety. This view of dependence identifies a single motivational consequence of withdrawal, negative affect, rather than physical withdrawal symptoms in compulsive and escalating drug-seeking behavior, and suggests a common basis for withdrawal from many, if not all, classes of drugs of abuse^g.

Another hypothesis, proposed by Di Chiara^h, attributes an important role to mesolimbic dopamine-mediated transmission in reward-related learning processes, and suggests that drug addiction is a dopamine-dependent associative-learning disorder. This view distinguishes between associative learning and dopaminergic-neuron activation induced by natural rewards, and 'abnormal' associative learning and dopamine activity stimulated by drugs of abuse. According to this hypothesis, activation of dopamine in the NAC shell region by natural rewards underlies habituation. In contrast, drugs of abuse have nonhabituating effects, resulting in nonadaptive or even sensitized dopamine release after repeated drug use^h. These neurochemical consequences of drugs of abuse are thought to strengthen drug stimulus-reward associations, which constitute the basis of addictive behavior.

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Fig. 1. The role of dopamine in associative learning processes. Brain microdialysis was used to study changes in dopamine (DA) in the nucleus accumbens during associative learning between two neutral stimuli (flashing light and tone)^d. Separately, the flashing light or tone did not affect dopamine release (DA-). However, when presented on a paired schedule during preconditioning, dopamine release was increased (DA↑). The tone was subsequently paired with mild footshock (aversive conditioning), and the formation of a conditioned association between the flashing light and the tone was assessed by measuring the ability of the flashing light to elicit the same conditioned response as the tone when presented during the test.

Box 2. The human midbrain dopamine system and the action of drugs of abuse

Cocaine euphoria and reward are linked to dopamine transporter (DAT) occupancy

The reinforcing and subjective, pleasurable effects of cocaine are thought to depend on blockade of the DAT by cocaine, which results in increased synaptic availability of dopamine. A direct relationship between DAT blockade and self-report measures of 'high' was recently demonstrated in humans^a. The degree and timecourse of DAT block by cocaine (as measured by PET) was correlated significantly with the temporal profile of cocaine euphoria and the binding kinetics of cocaine in the striatum of cocaine abusers. Although these measures were made in the dorsal striatum rather than the nucleus accumbens (NAC; the structure that is commonly associated with cocaine reinforcement in animals), DAT occupancy by cocaine is sufficiently similar in these brain regions that these results provide evidence for DAT blockade as a crucial mechanism in mediating the reinforcing and subjective effects of cocaine in humans.

Both cocaine euphoria and cocaine craving are associated with functional MRI (fMRI) activation in the nucleus accumbens

Breiter *et al.*^b used fMRI in conjunction with behavioral ratings to investigate brain circuitries mediating cocaine-induced euphoria and craving in cocaine-dependent subjects. Following an infusion of cocaine, several brain regions, including the ventral tegmentum and basal forebrain, showed an immediate but transient activation that was correlated with reinforcement-related ratings of 'rush'. Other regions, including the NAC and amygdala, showed sustained activation that was closely associated with incentive-related measures of craving. Although some rush-associated early activation was observed in the NAC, the temporal pattern of activation in this struc-

ture suggests that it is involved in both reinforcement and incentive functions. The stronger association of signal changes in the NAC with 'craving' rather than 'rush' ratings (see Fig. 1) challenges the view that dopamine transmission in the region of the NAC has a central and selective role in the mediation of reward and subjective euphoria.

Cocaine addicts show reduced euphoria and striatal dopamine response to dopamine reuptake inhibitor

Volkow *et al.* compared the responses of cocaine addicts and normal controls to intravenous methylphenidate^c, a drug that, like cocaine, increases synaptic dopamine levels. The effects of methylphenidate on both striatal dopamine release (as determined by PET measures of [¹¹C]raclopride displacement by endogenous dopamine) and subjective feelings of 'high' were significantly reduced in cocaine-dependent subjects. These findings are compatible with a decrease or desensitization in striatal dopamine function and a decrease in the reinforcing efficacy of psychostimulants, but contrast with the view that sensitization (that is, enhanced dopamine transmission or the reinforcing effects, or both) is a mechanism in human cocaine addiction.

High doses of a dopamine-receptor antagonist do not block amphetamine-induced euphoria in humans

The dopamine hypothesis of reward rests, in part, on evidence that dopamine antagonists reliably attenuate the reinforcing actions of psychostimulants in animals. However, in studies designed to examine whether the role of dopamine in psychostimulant reward in animals extends to psychostimulant-induced euphoria in humans, the dopamine antagonist, pimozone, failed to antagonize consistently the euphorogenic effects of amphetamine^d. By failing to demonstrate a role for dopamine in the mood-elevating effects of amphetamine, these data call into question the assumption that dopamine-dependent reinforcing effects of psychostimulants in animal models are directly related to drug-induced euphoria in humans.

Neuroadaptations in the dopamine system in drug addicts

In humans, cocaine withdrawal is associated with persistent hyperprolactinemia^e, a condition that might reflect reduced dopaminergic-neuron function because prolactin secretion is inhibited tonically by hypothalamic dopamine. More-direct evidence for an enduring dopaminergic-neuron hypofunction comes from brain-imaging studies showing that striatal dopamine synthesis decreases with increasing duration of abstinence^f. A hypofunctioning of the dopaminergic system has also been reported following long-term alcohol abuse. Alcohol-abuse patients show impairments in the function of central dopamine receptors that depend on the amount of long-term alcohol consumption, and retardation in the recovery of dopamine function is associated with early relapse in alcoholics^g.

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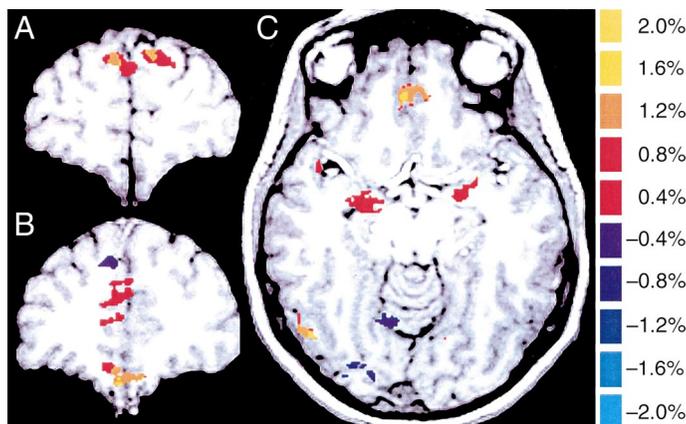


Fig. 1. Functional MRI (fMRI) during cocaine craving. Brain regions demonstrate significant activation in response to viewing a film depicting explicit cocaine use in a group ($n=14$) of experienced cocaine users. A self-report questionnaire revealed high scores of craving in most of the cocaine users compared with controls. Colors represent percentage change of fMRI signal averaged over 7 mm of activated cortex. Depicted regions include the bilateral superior frontal gyrus (A), cingulate gyrus and gyrus rectus (B), and the bilateral amygdala (C). Data courtesy of E. Stein.

dopamine levels might be a mechanism that transduces declining brain cocaine levels into drug-seeking behavior²². These observations extend earlier findings showing that selective destruction of midbrain dopamine neurons by 6-hydroxydopamine (6-OHDA) abolish cocaine self-administration²³, and support the hypothesis that the mesolimbic dopaminergic system is crucial for psychostimulant reward.

As cocaine-induced increases in extracellular dopamine concentrations are due to the block of presynaptic dopamine transporters (DAT), disruption of the DAT should attenuate the reinforcing effects of cocaine. In order to test this hypothesis, Rocha *et al.*²⁴ trained DAT

knockout and wild-type mice to self-administer cocaine intravenously. Contrary to expectations, DAT-knockout mice acquired self-administration of cocaine. Thus, the reinforcing actions of cocaine did not depend on cocaine-induced increases in synaptic dopamine in these mutants, because cocaine injections markedly increased extracellular dopamine levels in wild-type mice but did not alter the already high synaptic dopamine levels in the DAT knockouts²⁴. The observation of specific binding of a cocaine analog and enhanced *Fos* expression in response to cocaine in serotonergic brain regions of the DAT-deficient mutants²⁴ led to speculation that the 5-HT transporter might provide a mechanism for

the reinforcing actions of cocaine in these animals. However, while occupancy of 5-HT transporters might be sufficient to initiate self-administration of cocaine in DAT knockouts, this hypothesis was not supported by a recent study in which conditioned place preference was established in DAT as well as in 5-HT-transporter knockout mice²⁵. Thus, neither the DAT nor the 5-HT transporters alone, seems essential for conditioned reinforcement associated with cocaine. Although these new findings challenge the dopamine hypothesis of cocaine reward, it is possible that developmental adaptations in these mutants might supervene and allow another transporter to substitute for function of the deficient transporter. One candidate might be the nor-adrenaline transporter. A recent study suggests that cocaine, as well as amphetamine, increases extracellular dopamine levels largely through inhibition of the nor-adrenaline transporter, although these results were obtained in the prefrontal cortex²⁶. In addition, compensatory adaptations in these mutants could result in upregulation of as yet unknown pharmacological targets of cocaine that might not have a significant role in wild-type animals. These issues might soon be resolved by the use of inducible monoamine-transporter knockouts. The involvement of monoamine transporters and dopamine in cocaine reinforcement has been also studied using various noninvasive neuroimaging approaches in humans (see Box 2). However, although these experiments confirm a role for the DAT transporter and activation of dopamine-rich brain regions in the subjective effects of cocaine, the view that mesolimbic dopamine-mediated transmission has a central and selective role in the mediation of psychostimulant euphoria has not remained unchallenged in human experimental studies (see Box 2).

Opioids and midbrain dopamine

Opiate drugs and opioid peptides can modulate mesolimbic dopamine activity (Table 1). *In vivo* microdialysis data demonstrate that acute systemic or intracerebroventricular administration of μ - or δ -opioid-receptor agonists increase dopamine release in the NAC, whereas κ -opioid-receptor agonists decrease dopamine release³¹. Opioid-receptor agonists increase extracellular dopamine levels within the NAC by disinhibiting GABA interneurons in the VTA (Ref. 32). Activation of μ -opioid receptors on GABAergic interneurons hyperpolarizes these interneurons and concomitantly disinhibits dopamine-cell firing³². These disinhibitory actions of opiate agonists are restricted to the VTA as direct application of μ -opioid-receptor agonists into the midbrain increases mesolimbic dopamine-mediated activity, whereas intranuclear infusions do not alter extracellular dopamine levels in this structure³³. In contrast to these effects of non-contingent opioid-receptor agonist treatments, heroin self-administration failed to elevate extracellular dopamine levels in the NAC (Ref. 34). This finding is consistent with several pharmacological studies showing that administration of dopamine antagonists, either systemically^{35,36} or directly into the NAC (Ref. 37), does not alter the responses maintained by intravenous heroin. Furthermore, selective destruction of presynaptic dopaminergic nerve terminals in the NAC, using the neurotoxin 6-OHDA, does not attenuate intravenous opiate self-administration^{37,38}. In contrast to the prediction of the classical dopamine hypothesis of reward, these data suggest that the maintenance of

TABLE 1. Dopamine release in the nucleus accumbens in response to natural and drug rewards

Reward	Acute	Repeated (sensitization)	Withdrawal
Natural reward	↑	—	—
Opioids	↑↑	↑↑ ^a	↓
Psychostimulants	↑	↑↑	↓
Alcohol	↑	↑ ^b	↓

Abbreviations: ↑↑, augmented increase; ↑, increase; ↓, decrease; —, no change.

^aMixed results^{27,28}.

^bNo augmented increase and no tolerance^{29,30}.

heroin self-administration is mediated by dopamine-independent mechanisms, presumably opiate receptors localized postsynaptically in the NAC (Ref. 8).

In contrast to self-administration, opiate reward, as measured by the conditioned place-preference method, seems to depend on midbrain dopamine-related mechanisms. Microinjections of μ -opioid-receptor agonists into the VTA, but not NAC, induced conditioned place preference^{39,40}. This effect could be blocked by injection of 6-OHDA or the dopamine antagonist SCH23390 into the NAC (Ref. 41). However, D₁ receptors are not the only receptors that are crucial for morphine-induced conditioned place preference. In mice that lack D₂ receptors, suppression of morphine-induced place preference was observed⁴². These data suggest that the acquisition and expression of the secondary reinforcing effect of opioids, as measured by conditioned place preference, depend on the functional integrity of mesolimbic dopaminergic neurons, whereas dopamine-independent mechanisms have to be postulated for mediating primary reinforcing effects of opioids during self-administration.

Alcohol and midbrain dopamine

Several lines of evidence indicate that ethanol activates the mesolimbic dopaminergic system. Alcohol injected intravenously increased firing of dopamine neurons in the VTA (Ref. 43), and acute administration of alcohol resulted in preferential release of dopamine from the NAC shell region^{3,44}. Similar to opioid-induced stimulation of dopamine release, alcohol is thought to decrease the activity of GABAergic neurons in the VTA, which leads to a disinhibition of mesolimbic dopaminergic neurons⁴⁵; however, alcohol might also have some local effects in the NAC (Ref. 45). Indeed, the activation of dopaminergic neurons by ethanol might involve an interaction with endogenous opioids in the VTA, as the suppression of alcohol intake by nonselective opiate-receptor antagonists has been linked to interference of these agents with the dopamine-stimulatory actions of ethanol⁴⁶.

Numerous pharmacological studies have investigated the role of midbrain dopaminergic neurons in alcohol reinforcement, but the results have been inconsistent²⁹. Lesioning of dopaminergic neurons by 6-OHDA does not affect the maintenance of alcohol self-administration^{47,48}, whereas acquisition of alcohol drinking is substantially reduced by this manipulation⁴⁸. These findings illustrate that different neuronal mechanisms mediate acquisition and maintenance of alcohol drinking and that functional integrity of midbrain dopaminergic neurons is not required to maintain alcohol self-administration.

However, rats will self-administer ethanol directly into the ventral tegmental cell-body region of mesolimbic dopaminergic neurons⁴⁹, and both D₁- and D₂-receptor antagonists administered either systemically or locally into the NAC decrease home-cage drinking and operant responses to alcohol^{50,51}.

Measurements of ethanol-induced dopamine release in genetically selected alcohol-preferring rat strains have also produced conflicting results²⁹. Many alcohol-preferring strains show deficiencies in forebrain dopaminergic function compared with their nonpreferring counterparts, and it has been proposed that these abnormalities could be a factor in genetically determined ethanol preference. However, in alcohol-naïve high-alcohol-drinking (HAD) and low-alcohol-drinking (LAD) strains of rat, dose–response curves for alcohol-induced dopamine release show no difference in sensitivity to alcohol between the lines⁵². A similar lack of line differences has been reported in alcohol-preferring and alcohol-avoiding rats^{53,54}. Furthermore, in alcohol-preferring rats with a history of alcohol self-administration, dopamine release after alcohol injections was completely attenuated⁵⁴. In contrast, operant responses to alcohol were associated with a considerably greater relative stimulation of dopamine release within the NAC in alcohol-preferring P-rats than in control Wistar rats⁵⁵. These data suggest that ethanol preference is not related to the amount of dopamine released by noncontingent alcohol treatment; however, concomitant measures of ethanol-maintained reinforcement and dopamine release have revealed a possible link between genetic ethanol preference and ethanol-induced dopaminergic-neuron activation⁵⁵.

Long-term changes in mesolimbic dopamine release following chronic drug administration

Repeated administration of psychoactive drugs can have neuroadaptive consequences that lead to either a decrease (tolerance or desensitization) or an increase (sensitization) of their behavioral effects. In the case of psychostimulants and opioids, *in vivo* measurements of extracellular dopamine levels have provided direct evidence that these drugs, when administered under an intermittent injection schedule, can lead to a more-pronounced increase in dopamine levels than the increase seen after acute administration of these drugs^{27,28}; however, rats that received repeated intermittent injections of alcohol did not show sensitization of alcohol-induced dopamine release in the NAC (Ref. 30). Whether sensitization of mesolimbic dopamine neurons is linked to enhanced rewarding efficacy remains unclear. Indeed, current conceptualizations of the significance of sensitization in compulsive drug-seeking behavior hold that, rather than enhancing 'reward', repeated drug use leads to a progressive and persistent hypersensitivity of neural systems that mediate 'incentive salience', resulting in excessive craving^{6,56} (see Box 1). Craving elicited by drug stimuli that share stimulus properties of the abused drug (that is, 'priming effects') and drug-related conditioned cues is one factor, among others (for example stress), that can induce relapse^{57,58}.

There is evidence to suggest that dopamine-related mechanisms have a role in relapse, as measured by reinstatement of cocaine and heroin self-administration after extinction. Selective dopamine-receptor antagonists attenuated reinstatement of heroin self-administration induced by heroin priming injections⁵⁷ but failed to

attenuate stress-induced reinstatement of heroin self-administration⁵⁷, a finding that argues against a role for dopamine in stress-associated heroin-seeking behavior, in spite of the fact that stress stimuli typically produce robust increases in accumbal dopamine release. Another study has demonstrated an opposite modulation of cocaine reinstatement by D₁- and D₂-receptor agonists⁵⁹, whereby these agonists were able to induce reinstatement of cocaine-seeking behavior. Moreover, D₁-receptor agonists prevented reinstatement behavior induced by cocaine priming, whereas D₂-receptor agonists even enhanced this behavior⁵⁹. As inhibition of cAMP-dependent protein kinase in the NAC also reinstated cocaine-seeking behavior⁶⁰, a role for dopamine in the D₁-linked cAMP system in the NAC has been proposed as a potential mechanism in relapse to cocaine-seeking behavior. Examination of dopaminergic-neuron function in the NAC associated with the alcohol-deprivation effect, which has been proposed as a model for relapse and craving⁵⁸, revealed that heightened alcohol-seeking behavior was accompanied by enhanced dopamine release⁶¹. In agreement with this finding, craving induced by alcohol priming in detoxified alcoholics could be prevented by haloperidol pretreatment⁶². Conversely, administration of dopamine-receptor antagonists did not influence or even enhance relapse in human alcoholics²⁹. These findings suggest that dopamine-related mechanisms might have a role in ethanol-priming effects, but not in the resumption of drinking elicited by other stimuli.

While repeated administration of many drugs of abuse can induce sensitized dopaminergic-neuron responses, chronic drug administration can also lead to dopaminergic-neuron dysfunction that becomes unmasked during withdrawal. Thus, marked inhibition of mesolimbic dopamine release seems to be a common feature of drug withdrawal in rats⁶³. It is suggested that long-term exposure to a drug suppresses basal dopamine-mediated activity in order to 'balance' chronic stimulation by this drug. Such dopaminergic-neuron dysfunction following chronic drug use is not restricted to the acute withdrawal phase as reduced activity of dopamine neurons is still present long after termination of chronic alcohol treatment (>3 days), although behavioral manifestations of the alcohol-withdrawal syndrome recede within several hours^{64,65}. A similar long-lasting decrease in mesolimbic dopaminergic-neuron activity has been observed following cocaine withdrawal⁶⁶.

Experimental studies of the behavioral significance of dopaminergic-neuron dysfunction are, however, sparse. Withdrawal from many drugs of abuse attenuates the rewarding effects of electrical brain stimulation, a phenomenon that has been linked to the negative emotional changes in withdrawal states⁵. As brain-stimulation reward is sensitive to disruption of mesolimbic dopamine transmission, withdrawal-associated reward deficits might be linked to impairments in mesolimbic dopamine-mediated transmission⁵.

Concluding remarks

There is now little doubt that midbrain dopamine has an essential role in the acquisition of natural reward and drug-seeking behavior. However, except in the case of psychostimulants (see also Box 2), mesolimbic dopamine neurotransmission does not seem to have a crucial role in reinforcement maintained by drugs of abuse and natural rewards. Rather, it seems likely that

dopaminergic-neuron activation highlights important stimuli and functions as a learning signal. This function would also account for the growing evidence of dopaminergic-neuron activation during reward expectation, and increased dopamine release associated with natural reinforcers under conditions of deprivation and novelty. These conclusions are in agreement with a recent report demonstrating that, although activation of mesolimbic dopaminergic neurons is a necessary condition for intracranial self-stimulation, elicited dopamine release is actually diminished during self-stimulation of the mesolimbic system⁶⁷. With regard to a role in the development of compulsive drug-seeking behavior and dependence, neuroadaptive changes in midbrain dopaminergic neurons might be involved in the generation of deficit states that enhance vulnerability to drug craving and relapse.

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