

Addiction, Dopamine, and the Molecular Mechanisms of Memory

Review

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The central feature of drug addiction is compulsive drug use—loss of control over apparently voluntary acts of drug seeking and drug taking (Goldstein, 1994). Addiction is a chronic disorder, since even after treatment and extended periods of drug abstinence, the risk of relapse to active drug use remains high. In this review, we consider some molecular mechanisms and neural circuits that may be involved in persistent, compulsive drug abuse. We do not attempt to provide a comprehensive account of the numerous effects of addictive drugs on the brain. Rather, we focus principally on the consequences of drug-enhanced release of dopamine in the striatum, with particular reference to psychomotor stimulants (such as cocaine and amphetamine). We contrast two different types of brain responses to addictive drugs—*neuronal adaptations*, which are mostly homeostatic responses to excessive stimulation, and *synaptic plasticity*, which allows for the association of drug-related stimuli with specific learned behaviors. Most recent investigations into the molecular neurobiology of addiction have emphasized homeostatic adaptations to drug administration (for representative reviews, see Koob and Le Moal, 1997; Koob et al., 1998). However, while homeostatic adaptations may underlie important aspects of drug dependence and withdrawal symptoms, it is unlikely that they can account either for the compulsive nature of drug abuse or for the persistent tendency to relapse. In contrast, we describe how addictive drugs can engage a set of molecular mechanisms normally involved in associative learning—stimulation of dopamine D1 receptors, the activation of the cAMP/PKA/CREB signal transduction pathway, a transient burst of altered gene expression, and synaptic rearrangements. The persistence of drug addiction may thus reflect the persistence of specific altered patterns of synaptic connectivity, as is thought to occur for normal memory formation. Finally, we describe how plasticity in multiple neuronal systems may contribute to distinct phases of drug taking, and argue that dorsal striatal circuits involved in normal habit learning may be of particular importance in the shift from controlled drug use to compulsive drug abuse.

Tolerance, Dependence, and Sensitization

Psychostimulants have both acute and long-lasting effects on behavior. In humans, they acutely increase

alertness and produce a sense of well-being. In animal studies, low doses of psychostimulants reduce the time spent sleeping or quiescent, while causing increased locomotor activity. Psychostimulants also tend to increase the rate at which previously learned actions are performed, such as pressing a bar for a reward (Lyon and Robbins, 1975). As the dose increases, the range of observed behavior decreases, until at high doses “stereotypies” are observed—perseverative repetitions of a motor activity, such as sniffing or biting (Randrup and Munkvad, 1967). If cocaine or amphetamine is used repeatedly, some acute drug effects may diminish (“tolerance”), while others are enhanced (“sensitization”). Whether tolerance or sensitization occurs depends in part on the pattern of drug administration. Animals given several drug injections spaced out at intervals of a day or more tend to show sensitized locomotor activity and stereotypy, progressively increasing with each injection. Animals given the drug continuously through an osmotic pump, or by closely spaced injections, show a diminished locomotor response to a subsequent challenge dose (Post, 1980; Kuribara, 1996a).

Neural changes responsible for tolerance and sensitization can coexist. For example, Dalia et al. (1998) gave intermittent injections of cocaine (40 mg/kg, given at 3-day intervals) and observed a sensitized response to a challenge dose of cocaine (7.5 mg/kg). They then implanted the same animals with an osmotic pump that delivered cocaine continuously (80 mg/kg/day) for 7 days. One day after the pump was removed, the animals displayed tolerance to the challenge dose. However, by 10 days after pump removal, they once again displayed a sensitized response to the challenge. Thus, neural mechanisms of tolerance can mask the expression of sensitization, but may fade more rapidly (e.g., Kalivas and Duffy, 1993). Sensitized locomotor activity can persist in rats for over a year after the end of drug administration (Paulson et al., 1991).

A drug user who abruptly stops active drug use may display withdrawal symptoms. Some drugs give rise to clear “physical” symptoms of withdrawal, such as hypertension or abdominal cramps after stopping opiate use, or seizures after ceasing heavy alcohol use (Goldstein, 1994). All addictive drugs, including psychostimulants, can produce emotional withdrawal symptoms such as dysphoria and anhedonia, a diminished capacity for experiencing pleasure (e.g., Gawin and Ellinwood, 1989; Markou and Koob, 1991), although such symptoms are not always observed, even in individuals who use drugs compulsively. The behavioral phenomena of tolerance and withdrawal symptoms both appear to result, at least in part, from compensatory adaptations that occur during drug administration. In response to potent stimulation by drugs, such adaptations act to maintain equilibrium by reducing drug effects (tolerance). In the absence of the drug, these adaptations are unmasked, and a subset of these may produce symptoms generally opposite to those of the drug (withdrawal). A role for such neuroadaptations has been most

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convincingly documented for the opiate physical withdrawal syndrome (Nestler and Aghajanian, 1997). It should be noted, however, that for some forms of tolerance, e.g., in opiate analgesia, there is increasing evidence for involvement of associative learning mechanisms (Cepeda-Benito et al., 1999).

Tolerance and withdrawal are the defining aspects of drug "dependence." In contrast, human addiction is defined by uncontrolled, compulsive drug use despite negative consequences. Dependence narrowly defined can occur without addiction (for example, in patients requiring morphine for cancer pain, or benzodiazepines for panic disorder; Petursson, 1994; Vgontzas et al., 1995). In addition to being insufficient for addiction, dependence is also not necessary. Both withdrawal symptoms and drug tolerance tend to disappear within a few days or weeks (Gawin, 1991; Paulson et al., 1991) and are therefore unlikely to account for the persistence of drug addiction. As has been pointed out before, it is therefore essential to distinguish between neural alterations that account for dependence and those that responsible for compulsive drug use (Wise and Bozarth, 1987) and late relapse.

Associative Learning in Relapse and Sensitization

Humans and other animals can readily learn to take addictive drugs; this process requires the specific recognition of drug-associated cues and the performance of specific, often complex, actions. Self-administration of psychostimulants may involve several distinct forms of learning (Robbins et al., 1989; White, 1989; White, 1996). An action that is followed by administration of psychostimulants, such as pressing a lever for intravenous injection, tends to be repeated ("reinforced"; e.g., Woolverton, 1992). In addition, cues associated with drug administration acquire motivational significance; for example, rats will choose to spend more time in a location in which they have passively received an injection of psychostimulants than in another location paired with saline injection ("conditioned place preference"; Tzschentke, 1998). Psychostimulants act to enhance memory consolidation in general, even facilitating learning of specific behaviors unrelated to drug intake. For example, systemic injections of amphetamine after training can enhance learning of discrimination or avoidance tasks (Krivanek and McGaugh, 1969; White, 1988, and references therein).

There is evidence that relapses among drug-addicted humans also involve associative learning. Relapse often occurs when addicts encounter people, places, or other cues associated with their prior drug use (e.g., Childress et al., 1986; Shiffman et al., 1996). In contrast, the great majority of US soldiers who became addicted to heroin in Vietnam were able to stop drug use upon returning to the distinct context of the United States (Robins et al., 1975). In laboratory studies, drug users display conditioned emotional responses to drug-associated cues, including increased expressed desire for drugs (e.g., Ehrman et al., 1992). Conditioned responses to drug-associated cues persist far longer than withdrawal symptoms (O'Brien et al., 1992) and can occur despite years of abstinence from drugs.

As behavioral sensitization to drugs can also be persistent, it has been considered a model for some aspects

of addiction. Sensitization can be operationally defined as a leftward shift in the drug's dose-response curve (Altman et al., 1996). Mechanistically, this could arise in at least two different ways. The drug could have an increased pharmacological effect, for example as a result of increasing the number of drug receptors or strengthening their coupling to effector proteins. Alternatively, an increased behavioral effect could result from the drug acting on neural circuits in which there are altered patterns of stored information, resulting from prior associative learning. While both forms of sensitization probably occur under certain circumstances, many experiments have demonstrated a role for associative learning in psychostimulant sensitization. If, for example, a rat is taken from its home cage to a novel "test" cage for intermittent amphetamine injections, the sensitized locomotor response to a challenge dose is much greater if the challenge is also given in that test cage than if given in a different environment (e.g., Hinson and Poulos, 1981; Badiani et al., 1995). Several groups have demonstrated that this "context dependence" can be complete—i.e., substantial sensitization expressed in the drug-associated location, no sensitization at all in a different environment (for reviews, see Pert et al., 1990, and Anagnostaras and Robinson, 1996; for recent examples, see Tirelli and Terry, 1998). Even without an acute drug injection, an animal placed back in the drug-associated environment will often show a conditioned response, repeating in part the behavior previously performed there (such as locomotor activity or stereotypy). Discrete stimuli such as tones or lights that are paired with drug administration can also come to control both sensitization and conditioned locomotion (Pickens and Dougherty, 1971; Bridger et al., 1982; Panlilio and Schindler, 1997). At least some aspects of sensitization also involve performance of learned responses to specific stimuli and contexts, rather than enhancement of an unlearned locomotor response to drug. A sensitized stereotypy response to amphetamine appears to consist largely of behavioral elements performed during the prior exposure to drug (Ellinwood and Kilbey, 1975), and the expression of this response is diminished in a novel environment (Robbins et al., 1990). Also, mice prevented from moving around freely during initial exposure to psychostimulants do not exhibit locomotor sensitization to a subsequent dose (Kuribara, 1996b, 1997).

Context-dependent sensitization and cue-conditioned human relapse suggest that the brain stores *specific* patterns of drug-related information. In contrast, other mechanisms appear to regulate the *overall* responsiveness of an organism. Such mechanisms can produce either context-independent sensitization (see below; Stewart, 1992) or, as in the state of psychostimulant withdrawal, a general reduction in responsiveness to a broad range of information, resembling mild depression (Gawin and Ellinwood, 1989). In the remainder of this review, we examine neurobiological evidence supporting this distinction (see Table 1), and consider how neural mechanisms involved in normal memory formation might also be responsible for compulsive drug use.

Architecture of Striatal Information Processing and Its Modulation by Dopamine

Psychostimulants act at axonal terminals of neurons that release monoamines (dopamine, serotonin, and

Table 1. Psychostimulant-Induced Behavioral Change: One Possible Classification

General Changes in Behavioral Responsiveness		versus	Associative Learning
(e.g., altered presynaptic release of dopamine, altered postsynaptic dopamine signaling pathways)			(e.g., structural plasticity of specific glutamatergic synapses)
compensatory adaptations can cause tolerance and withdrawal symptoms (dependence)	context-independent sensitization; stress-induced sensitization		conditioned responses to drug-related stimuli; context-dependent sensitization; persistent relapse liability; compulsive drug use

norepinephrine). Psychostimulants increase the extracellular concentrations of these neuromodulators: cocaine by blocking transporter-mediated reuptake and amphetamine by promoting efflux from synaptic terminals (for review, see Seiden, 1993). Many brain regions receive monoamine inputs, including striatum, neocortex, amygdala, and hippocampus (Fallon and Loughlin, 1995), and following psychostimulant administration, markers of brain activity are altered in many structures (e.g., Stein and Fuller, 1993; Lyons et al., 1996; Breiter et al., 1997). While the full diversity of drug effects is mediated by multiple neurotransmitters acting in multiple brain regions, most addictive drugs share the common property of increasing dopamine release in the striatum (e.g., Di Chiara and Imperato, 1988; Kuczenski et al., 1991). The dopamine input to the striatum is provided by a very dense network of axon terminals arising from cell bodies in the midbrain—substantia nigra pars compacta and ventral tegmental area (see Fallon and Loughlin, 1995). The increased locomotor activity and stereotypy caused by psychostimulants seem especially to involve dopamine release in ventral and dorsal parts of striatum, respectively (Kelly et al., 1975). The ventral striatum includes the “core” and “shell” of the nucleus accumbens (see Heimer et al., 1991); blockade of dopamine neurotransmission in this region attenuates most rewarding effects of addictive drugs, such as conditioned place preference (see Wise 1996 and references therein). The dopaminergic projection to ventral striatum has therefore been intensely investigated for its potential involvement in addiction (for review, see Self and Nestler, 1995).

The dorsal and ventral striatum are components of large-scale neural circuits, encompassing the cerebral cortex, basal ganglia, and thalamus (Figure 1; for reviews, see Alexander et al., 1990, and Gerfen and Wilson, 1996). The striatum receives glutamatergic inputs from all cortical areas. Neocortical areas project mainly to more dorsal parts of striatum, while other regions such as hippocampus and amygdala project mainly to ventral parts of striatum (e.g., McGeorge and Faull, 1989). Ninety to ninety-five percent of striatal neurons are medium-sized GABAergic cells, with dendrites that have a dense population of spines. These spines receive synaptic contacts from glutamatergic afferents; each spiny cell receives synapses from thousands of distinct cortical neurons (Kincaid et al., 1998). This anatomical organization is consistent with the idea that spiny cells integrate information from many sources and contrasts with the point-to-point transmission of information that characterizes, for example, primary sensory cortical areas. Medium spiny neurons are silent most of the time, until simultaneous activity in many glutamatergic afferents

pushes them into an active mode (the “up” state); once in this mode, small changes in input can then trigger action potentials, and the cells fire in bursts (Stern et al., 1998). This activity of striatal neurons is frequently observed to be context dependent. A striatal neuron, for example, may fire in conjunction with a particular movement made as part of a specific behavioral task, but not with the same movement in a different behavioral situation (e.g., Kimura et al., 1992).

Striatal spiny neurons themselves project out of the striatum; half of these projections form the “direct” pathway to the internal part of the globus pallidus (GPi; SNr in rodents), while the other half project indirectly to GPi via the external part of the globus pallidus (GPe) and the subthalamic nucleus. From GPi there are projections to the mediodorsal thalamus. This part of the thalamus in turn has (reciprocal) connections with frontal neocortical areas, including prefrontal cortex. Overall, many investigators have suggested that neural circuits through the striatum are involved in response selection and the performance of actions (e.g., Robbins et al., 1990; Passingham, 1993; Wise et al., 1996; Brown and Marsden, 1998).

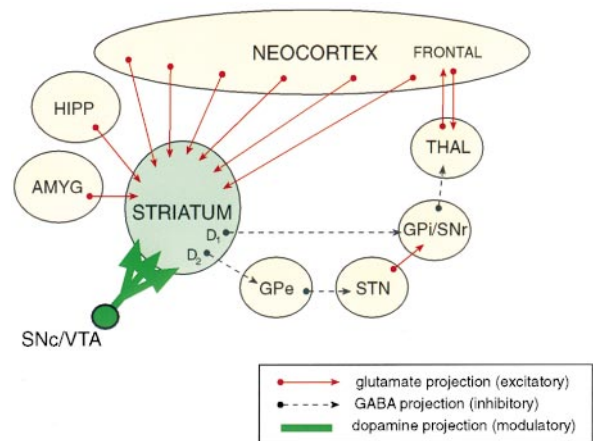


Figure 1. Simplified Anatomy of Cortex-Basal Ganglia Circuits
Multiple circuits project from a wide range of cortical regions through the basal ganglia and back to cortex. The processing of discrete patterns of information in these circuits can be modulated by the diffuse dopamine input from the midbrain. D1-type dopamine receptors are located principally on striatal neurons projecting to GPi/SNr, while D2-type dopamine receptors are principally on striatal neurons projecting to GPe. Additional important connections, such as the direct cortical projection to STN and dopamine inputs to other forebrain areas, are omitted for simplicity. Abbreviations: GPe, globus pallidus—external; GPi, globus pallidus—internal; STN, subthalamic nucleus; SNr, substantia nigra pars reticulata; SNc/VTA, substantia nigra pars compacta/ventral tegmental area; THAL, thalamus; HIPP, hippocampus; AMYG, amygdala.

Superimposed on this cortex–basal ganglia–thalamus–frontal lobe circuitry are the modulatory dopamine projections. The architecture of dopaminergic and other monoaminergic systems in the brain differs markedly from that of neuronal projections involved in communication of detailed information. Dopamine is released by a restricted number of neurons that project widely to a large number of targets. The striatum is so heavily innervated by dopamine terminals that the average distance between release sites is only 4 μm , and the dynamics of dopamine reuptake allow rapid diffusion to nonsynaptic receptors (Gonon, 1997). Dopamine receptors are commonly found at nonsynaptic sites; they do not seem to be clustered at synapses (Caille et al., 1996). In addition, they are G protein coupled; Hille has pointed out that the characteristics of G protein signaling, such as high affinity for agonists and spare receptors, encourage extrasynaptic transmission (Hille, 1992). When dopaminergic axons or cell bodies are briefly stimulated with a burst of current pulses, the resulting increase in striatal dopamine is transient, lasting less than a second (Gonon, 1997; Garris et al., 1999). Thus, dopamine neurotransmission in striatum may have some temporal specificity (see below), but it is thought that it represents a “global” signal rather than conveying spatially detailed patterns of information (e.g., Schultz, 1998a, 1998b). Neural changes that alter dopamine neurotransmission are therefore unlikely, by themselves, to account for behavioral changes that are specific to particular patterns of information.

Striatal Dopamine Sets Thresholds for Action

Striatal dopamine levels modulate the “behavioral reactivity” of the organism (Salamone, 1996; see also Blackburn et al., 1992; Robbins et al., 1998). Loss of the dopamine input to striatum results in Parkinson’s disease, characterized by slowness in initiating actions. Similarly, mice genetically modified to lack dopamine are hypoactive and stop eating a few weeks after birth; they starve unless given dopaminergic drugs such as L-DOPA, in which case they grow at near normal rates (Zhou and Palmiter, 1995). Adult animals whose dopamine cells are completely destroyed by neurotoxins such as 6-hydroxydopamine (6-OHDA) or MPTP are also akinetic and aphagic (Ungerstedt, 1971; Langston et al., 1984), as are animals given large doses of dopamine-blocking drugs, such as the antipsychotic drug haloperidol. Rats given 6-OHDA lesions or haloperidol may not respond to normal food, but will often eat highly palatable food. Near-normal behavior can also be induced by arousing stimuli such as pinching the tail (Schwab and Zieper, 1965; Marshall et al., 1974, 1976), and such lesioned animals will swim effectively if placed in a tank of water (Keefe et al., 1989). Thus, rather than preventing the capacity for action, removal of dopamine leads to a “psychomotor” deficit, in many ways opposite to the effects of psychostimulants (for review, see Wise and Bozarth, 1987). Conversely, increases in striatal dopamine levels are observed in response to a wide array of naturally occurring events that are arousing. These include rewarding, novel, and stressful stimuli (for reviews, see Blackburn et al., 1992, and Salamone et al., 1997).

Consistent with the broad set of inputs to striatum, increasing striatal dopamine can enhance behavioral responsiveness to a broad range of information. For example, the ventral striatum receives inputs from nuclei of the amygdala that are thought to process information about the emotional and motivational significance of environmental stimuli (Everitt et al., 1991; McDonald, 1991; Hatfield et al., 1996). Animals will normally work for presentation of a cue that has been previously presented in conjunction with reward. The amount of responding for such “conditioned reinforcers” is increased by injections of amphetamine either systemically or into ventral striatum (Cador et al., 1989; Kelley and Delfs, 1991). Dopamine blockade or destruction of dopamine terminals in ventral striatum block this effect of amphetamine, without preventing responding for “primary” rewards such as food (Robbins et al., 1989; Ranaldi and Beninger, 1993; Wolterink et al., 1993). Hence, the ventral striatum has been described as an interface between motivational and motor systems in the brain (Mogenson et al., 1980), with dopamine regulating the extent to which previously obtained information about the motivational significance of cues affects ongoing behavior.

Striatal Dopamine Also Assists Consolidation of New Behaviors

In addition to a short-term effect facilitating action, dopamine also regulates learning in striatal circuits. Parkinsonian patients have specific deficits in “habit” or “skill” learning (e.g., Flowers, 1975; Saint-Cyr et al., 1988; Knowlton et al., 1996). This form of associative learning is believed to involve the dorsal striatum, and is characterized by the progressively smoother execution of a particular action or behavioral sequence, generally in response to specific stimuli (for reviews, see Mishkin et al., 1984; White, 1997; Graybiel, 1998). During the initial learning of a task, one must pay attention, but with many repetitions the process becomes increasingly automatic. This habit learning is a form of “procedural” or “implicit” memory—it is preserved in patients with amnesia who cannot consciously recall the training episodes (Milner et al., 1998). Habit learning includes not just overt motor actions but also other tasks involving the gradual, incremental learning of implicit associations (e.g., Knowlton et al., 1996). Once established, some learned habits can be hard to extinguish, as they tend to persist even when the outcome becomes less desirable (i.e., they are resistant to devaluation; Altman et al., 1996; Balleine and Dickinson, 1998).

Removal of dopamine interferes with striatally based learning processes; conversely, intrastriatal injections of psychostimulants can enhance learning of striatum-dependent tasks. For example, if rats that are learning to move to a marked target in a water maze are given intrastriatal amphetamine immediately after training, they show enhanced performance the next day (Packard et al., 1994). This facilitatory action of psychostimulants on learning appears to respect the topography of cortical afferents to striatum. Amphetamine injections in parts of striatum receiving inputs from visual cortex selectively improve learning of a conditioned response to a visual cue, while injections into regions of striatum receiving inputs from olfactory cortex selectively improve learning of a conditioned response to an olfactory

cue (Viaud and White, 1989). Systemic injections of amphetamine can also facilitate learning of such tasks, provided the dopamine input to striatum is intact (White, 1988).

This memory-enhancing effect of striatal dopamine does not require high temporal precision, since it is observed even with psychostimulant injections administered just *after* the training episodes. However, temporally precise changes in striatal dopamine may play other important roles in learning. Midbrain dopamine cells continuously supply dopamine to the striatum by firing tonically. Schultz and colleagues have found that certain external events, especially unexpected rewards, cause a transient increase in their rate of firing (for review, see Schultz, 1998b). This decrease disappears if the rewarding event comes to be reliably predicted by a prior cue (such as a tone) and instead occurs in response to the predictive cue. Rewards presented without prior cues still elicit an increased response, and if a reward is "expected" from prior cues but omitted, there is a suppression of cell firing at the expected time of reward (Schultz et al., 1993). Recent results using high-speed voltammetry to measure brief changes in dopamine in the rat ventral striatum have also found an important role for prediction (Garris et al., 1999). In animals learning to press a lever to cause brief stimulation of dopamine cell bodies (intracranial self-stimulation), the first few lever presses resulted in increased dopamine release, and this dopamine release was necessary for the animals to learn to consistently perform the lever-pressing behavior. However, this dopamine response faded after the first few presses, even though the animals kept pressing the lever to receive stimulation. Unpredictable stimulation of dopamine cell bodies still caused a brief increase in dopamine release. Given these properties, it has been suggested that such transient changes in dopamine release may be evoked when the animal's predictions of rewarding events turn out to be inaccurate and that dopamine is involved in adjusting those predictions (Schultz et al., 1995b; Schultz et al., 1997). Transient changes in dopamine levels may correspond to the "error signal" found in certain neural network models of reinforcement learning (Barto, 1995; Sutton and Barto, 1998; but see Redgrave et al., 1999).

Dopamine release in striatum can thus both potentiate performance of previously established behaviors (psychostimulation) and assist in the learning of new patterns of behavior (reinforcement/consolidation). We next turn to some of the molecular mechanisms underlying these effects, which are both likely to be important in the long-term effects of addictive drugs.

Molecular Actions of Dopamine in Striatum

There are at least five types of dopamine receptors in the vertebrate CNS, and these fall into two classes: D1-type (D1, D5) and D2-type (D2, D3, D4) (for reviews, see Neve and Neve, 1997; Robinson, 1997). The striatum has a very high density of D1 and D2 dopamine receptors, localized concentrations of D3 receptors in regions of the ventral striatum, and lower levels of D4 and D5 receptors (Mansour and Watson, 1995; Bordet et al., 1997). In view of their high striatal density, we focus here on D1 and D2 receptors. D1 receptors are localized primarily on striatal spiny neurons that project to the internal

part of the globus pallidus/substantia nigra pars reticulata, while D2 receptors are found on spiny neurons projecting to the external part of the globus pallidus (see Figure 1). There are also D2 autoreceptors on the dopaminergic terminals themselves (Le Moine and Bloch, 1995; Khan et al., 1998). (As shorthand, we shall refer to D1 receptor-bearing striatal medium spiny neurons as "D1 cells" and D2 receptor-bearing striatal spiny neurons as "D2 cells"). D1 receptors are coupled to G_s/G_{olf} and thus stimulate adenylate cyclase to produce the intracellular second messenger cAMP. cAMP in turn activates cAMP-dependent protein kinase (PKA), which phosphorylates numerous substrates, including L-type calcium channels, transcription factors such as CREB, and other intracellular signaling components (see Figure 2). D2 receptors are coupled to G_i/G_o and thus inhibit adenylate cyclase and also activate an inwardly rectifying potassium channel.

Striatal D2 receptors are tonically (continuously) stimulated by basal levels of dopamine, and this tonic activity is important for normal motor behavior. Mice lacking D2 receptors show parkinsonian symptoms (Baik et al., 1995), as do normal animals given D2 antagonists. Dopaminergic drugs effective in the treatment of Parkinson's disease vary in their efficacy at D1 receptors, but they all cause stimulation of D2 receptors (Cummings, 1991). Administration of D2 antagonists, or dopamine depletion with reserpine, causes disinhibition of the cAMP/PKA/CREB pathway and induction of immediate-early genes (IEGs) in D2 cells (Dragunow et al., 1990; Robertson et al., 1992; Konradi and Heckers, 1995; Adams et al., 1997). This is blocked by coadministered D2 agonists but not D1 agonists (Dragunow et al., 1990; Cole and Di Figlia, 1994).

D1 receptor stimulation leads to phosphorylation of striatal ion channels (including calcium, sodium, and potassium channels and NMDA receptors), with complex effects on cell firing that depend, in part, on the activation state of the neuron (Surmeier and Kitai, 1993; Hernandez-Lopez et al., 1997; Cepeda et al., 1998; Cantrell et al., 1999). Mice lacking D1 receptors do not show parkinsonian symptoms or other gross motor abnormalities (Drago et al., 1994; Xu et al., 1994), suggesting that D2 receptor stimulation may be more essential for the enabling role of striatal dopamine on behavior. D1 receptors may have a greater role in the effects of dopamine on learning (see below; Beninger and Miller, 1998). However, activation of both D1 and D2 receptors can have synergistic effects on acute neural activity, gene expression, and behavior (Paul et al., 1992; LaHoste et al., 1993; Gerfen et al., 1995; Hu and White, 1997). The activating effect of increased striatal dopamine release on behavior may result in part from coordinated actions of D1 and D2 receptor stimulation on "direct" and "indirect" basal ganglia pathways, respectively (Wise et al., 1996), although the exact nature of the information processing achieved through these circuits remains unclear.

Prolonged Dopamine Stimulation Causes Compensatory Cellular Adaptations

Intracellular signaling produced by D1 receptor stimulation can cause a variety of cellular responses, with varying time courses. Some of these changes cause altered

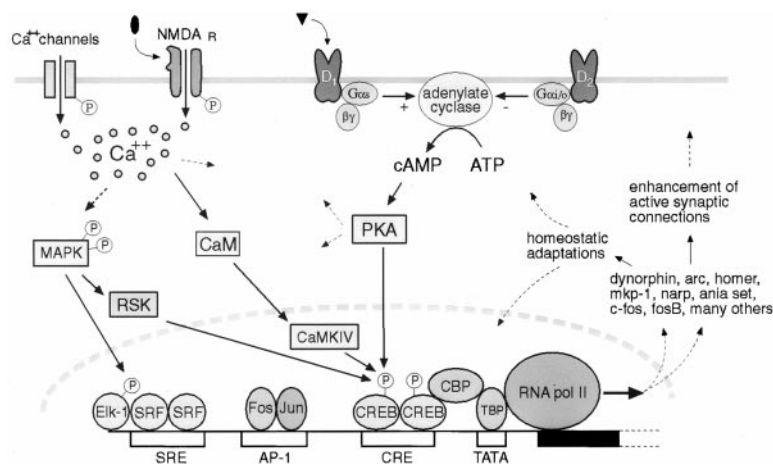


Figure 2. Neurotransmitter Control of Striatal IEG Expression

Induction of IEG expression is under the joint control of calcium- and cAMP-dependent signal transduction pathways. In striatum these pathways appear to be mutually inhibitory at many stages (not shown), but their effects inside the nucleus can be cooperative. Both PKA and CaMKIV can phosphorylate CREB at serine 133. Calcium-dependent CREB phosphorylation may also occur as a result of activation of the ERK MAPKs in striatal cells. ERK MAPKs also increase transcription of striatal IEGs through phosphorylation of the transcription factor Elk-1. A complex set of genes can be induced in striatal neurons. Some genes appear to be part of a homeostatic response, reducing sensitivity to subsequent stimulation; others may be involved in consolidating changes in the

strength of specific synaptic connections. Abbreviations: D1, dopamine D1 receptor; D2, dopamine D2 receptor; PKA, cAMP-dependent protein kinase; CaM, calmodulin; CaMKIV, calcium/calmodulin-dependent protein kinase IV; MEK, MAP and ERK kinase; MAPK, mitogen-activated protein kinase; SRF, serum response factor; AP-1, activator protein-1; CRE, cAMP response element; CREB, CRE binding protein; TBP, TATA binding protein; RNA pol II, RNA polymerase II.

sensitivity to neurotransmitters and may therefore be involved in altered behavioral responses to drugs. For example, phosphorylation and internalization of striatal D1 receptors can occur within minutes of exposure to amphetamine or D1 agonists and are associated with a diminished cAMP response to subsequent D1 stimulation (e.g., Roseboom and Gnegy, 1989; Tiberi et al., 1996; Dumartin et al., 1998). This type of rapid adaptation may be responsible for the first cocaine administration in a "binge" having the largest subjective and physiological D1 effects ("acute tolerance"). Longer-lasting changes in dopamine neurotransmission can be achieved through altered gene expression. For example, prolonged activation of D1 receptors can lead to increased expression of the neuropeptide dynorphin in striatal D1 cells (Gerfen et al., 1990; Cole et al., 1995). Increased dynorphin precursor mRNA is also seen in the striata of human cocaine abusers postmortem (Hurd and Herkenham, 1993). Dynorphin activates κ opioid receptors on presynaptic dopamine terminals, causing decreased dopamine release (Spanagel et al., 1992). Thus, some effects of psychostimulants on gene expression appear to be compensatory adaptations to excessive stimulation of neurotransmitter receptors. Following an extended period of cocaine self-administration, extracellular levels of dopamine are depressed below normal baseline levels (Weiss et al., 1992). Increases in dynorphin expression may be one of the mechanisms involved in this blunting of normal dopamine neurotransmission (Steiner and Gerfen, 1996). κ receptor agonists are aversive in both humans and rats (Shippenberg et al., 1993), so an increase in dynorphin expression due to psychostimulant administration may contribute to the dysphoria seen during withdrawal (Shippenberg and Rea, 1997). Dopamine-induced increases in dynorphin expression require prolonged stimulation of D1 receptors (J. D. B. and S. E. H., unpublished data) and increased phosphorylation of CREB (Cole et al., 1995). Prolonged overexpression of phospho-CREB in the ventral striatum via a viral vector also increases dynorphin expression and reduces the rewarding effects of cocaine (Carlezon et

al., 1998). The increase in striatal dynorphin mRNA levels is one of the longest-lasting of the dozens of mRNA changes induced by cocaine or D1 agonists (Spangler et al., 1996; Berke et al., 1998), yet even this increase fades within days if no further drugs are administered. Thus, the upregulation of striatal dynorphin by psychostimulants is an example of a reversible homeostatic adaptation that may contribute to withdrawal symptoms. The set of withdrawal symptoms produced by a given addictive drug result from multiple such homeostatic responses, in multiple brain regions (Rasmussen et al., 1990; Hyman, 1996; Koob et al., 1998b; Zhang et al., 1998). When drug administration ceases, these neural systems gradually return to their normal sensitivity. This can take anywhere from minutes to weeks depending on the particular homeostatic response, but so far none appears sufficiently long-lasting to be involved in the persistent tendency of addicted individuals to relapse.

Nonassociative Mechanisms Contributing to Sensitization

The idea that changes in behavioral responses to psychostimulants reflect altered dopamine neurotransmission is attractively straightforward and has been extensively investigated. Psychostimulants can evoke a wide range of changes in both midbrain dopamine neurons and their forebrain targets (Self and Nestler, 1995); a subset of these likely contribute to some forms of sensitization. For example, after a period of psychostimulant administration, the ability of a subsequent dose to evoke dopamine release in the striatum can be increased (for reviews, see Kalivas and Stewart, 1991, and Robinson and Becker, 1986). This effect can persist for at least several weeks (e.g., Robinson et al., 1982; Kalivas and Duffy, 1993; Hooks et al., 1994). Injections of amphetamine or D1 agonists directly into the vicinity of midbrain dopamine cells can also lead to an enhanced ability of subsequent doses of psychostimulants to cause dopamine release from terminals in the striatum (Kalivas and Weber, 1988; Vezina, 1993, 1996; Pierce et al., 1996).

Enhanced dopamine release can be observed even in dissociated striatal slices and may involve alterations to signal transduction pathways in dopamine terminals (e.g., Kantor et al., 1999).

Other behavioral manipulations, notably stress or social isolation, can also enhance the locomotor effects of subsequent doses of psychostimulants (Sahakian et al., 1975; Piazza and Le Moal, 1996). Stress-induced sensitization occurs most readily when the stressor is unpredictable and/or uncontrollable (MacLennan and Maier, 1983; Goeders and Guerin, 1994). Components of stress pathways may also be important in the development of some forms of psychostimulant sensitization (Deroche et al., 1995; Rouge-Pont et al., 1998). Psychostimulant injections cause increased levels of stress hormones such as glucocorticoids, which may produce adaptations in midbrain dopamine neurons, leading to enhanced subsequent release of dopamine (Piazza and Le Moal, 1996).

However, behavioral sensitization to psychostimulants can occur without increased striatal dopamine release (e.g., Segal and Kuczenski, 1992a, 1992b; Kalivas and Duffy, 1993; Heidbreder et al., 1996; Kuczenski et al., 1997). In addition, behavioral sensitization to direct dopamine agonists occurs even when the dopamine projection to forebrain is absent. In 6-OHDA-lesioned rodents, repeated administration of L-DOPA or dopamine agonists causes a progressively enhanced locomotor response to these drugs ("priming"; e.g., Jenner and Marsden, 1987; Morelli and Di Chiara, 1987; Carey, 1991). This effect may contribute to the dyskinesias, response fluctuations, and psychotic symptoms experienced by most human patients receiving long-term L-DOPA therapy for Parkinson's disease (Cummings, 1991; Olanow and Koller, 1998). Like psychostimulant sensitization, priming can persist for many months in the absence of drugs (e.g., Criswell et al., 1989).

Alterations in postsynaptic responsiveness to dopamine may be involved in some forms of sensitization (for review, see Nestler et al., 1996). Although psychostimulant sensitization is not consistently correlated with lasting changes in dopamine receptor mRNA or protein levels (e.g., Meador-Woodruff et al., 1993), psychostimulants can cause changes in levels of G proteins and other components of intracellular signaling pathways (Terwilliger et al., 1991; Striplin and Kalivas, 1993). For example, multiple components of the cyclic AMP signaling pathway are upregulated by psychostimulants (Terwilliger et al., 1991; Nestler et al., 1996). Such observations may explain reports of increased coupling of D1 receptors to adenylate cyclase (e.g., Sala et al., 1995). At the electrophysiological level, it is also known that the ability of cocaine or D1 agonists to inhibit glutamate-evoked firing of striatal neurons in anesthetized rats can be enhanced by prior cocaine treatment (Henry and White, 1991; Henry and White, 1995), and this change can be observed for 1 month after the last cocaine injection.

Just as increased dynorphin expression is thought to contribute to behavioral tolerance and withdrawal, physiological changes underlying persistent sensitization and addiction might be due to persistent changes in gene expression. Psychostimulants can cause the induction of a large number of genes in striatal D1 cells

(Cole et al., 1992; Douglass et al., 1995; Berke et al., 1998). However, this induction seems to be transient, with most mRNAs returning to baseline expression within a few hours to a day (Wang et al., 1995; Berke et al., 1998). Certain protein products of psychostimulant-induced genes can persist longer in striatum (Cha et al., 1997). To date the longest-lived known are posttranslationally modified products of the *fosB* gene, referred to as "chronic Fos-related antigens" (chronic FRAs; Hope et al., 1994). These have been shown to exhibit increased levels for up to 4 weeks and may alter the ability of subsequent stimuli to induce genes regulated by AP-1 transcription factors; thus, they could alter subsequent patterns of psychostimulant-induced gene expression. Overexpression of Δ FosB in the striatum of transgenic mice is correlated with altered behavioral sensitivity to cocaine (Kelz et al., 1999). Overall, however, there is no evidence to date for up- or downregulated mRNA or protein levels in the brain that last long enough to account for the persistence of some forms of sensitization—and in humans, addiction.

If long-term changes in gene expression are important, it is not as a result of altering dopamine release or postsynaptic dopamine sensitivity alone. Enhancing dopamine neurotransmission in striatum, which appears to lack spatial specificity, would be expected to enhance the behavioral response to psychostimulants irrespective of any specific behavioral situation. It is not therefore obvious how such mechanisms could account for the observations that both sensitization and drug taking can come under the control of specific cues (for a thorough experimental analysis of context-dependent sensitization, see Anagnostaras and Robinson, 1996).

When the acute behavioral effects of psychostimulants occur in association with specific (especially novel) cues, there is an opportunity for the animal to learn this association. Most reports cited above of neurochemical or neurophysiological changes with repeated psychostimulant injections used drug administration paradigms (such as injections in the home cage) that avoid pairing drug infusions with distinct contexts. Such unpredictable drug injections may preferentially evoke nonassociative forms of sensitization.

Dopamine D1 Receptors Are Coupled to Mechanisms of Synaptic Plasticity

For context-dependent sensitization and for addiction, a state in which cues can initiate complex foraging and drug-taking behaviors, additional or alternative associative learning processes must be involved. It is striking that striatal D1 receptors are coupled to the cAMP/PKA/CREB intracellular cascade (Konradi et al., 1994; Hyman, 1996), a pathway implicated in memory formation and synaptic change in species as diverse as fruit flies, mollusks, and mice (for review, see Silva et al., 1998). D1 receptors have been shown to have an important role in hippocampal long-term potentiation (LTP), the most influential current model of synaptic plasticity. In the CA1 hippocampal region, simultaneous depolarization of pre- and postsynaptic neurons leads to opening of NMDA receptors, calcium entry into the cell, and enhancement of the strength of specific synaptic connections (Malenka and Nicoll, 1993; Milner et al., 1998). For

LTP to persist for more than 2–3 hr (“late-phase” LTP or L-LTP) requires increases in postsynaptic cAMP, phosphorylation of CREB, gene transcription, and protein synthesis (Bourtchuladze et al., 1994; Nguyen et al., 1994; Frey et al., 1996; Nguyen and Kandel, 1996). The requirement for activation of gene expression seems to be transient, since hippocampal L-LTP is disrupted by blockers of transcription or translation if they are given within a few hours of the LTP-inducing stimulus but not if given later (Frey and Morris, 1997). Activators of the cAMP cascade, including D1 agonists, can induce L-LTP (Frey et al., 1993; Huang and Kandel, 1995), and D1 agonists can prevent depotentiation of potentiated synapses (Otmakhova and Lisman, 1998). D1 blockade blocks hippocampal L-LTP (Frey et al., 1990, 1991; Huang and Kandel, 1995), and D1 knockout mice do not show L-LTP (Matthies et al., 1997). In the hippocampus, therefore, D1 receptor activation may act to gate synaptic plasticity, helping to determine whether changes in synaptic strength are long lasting or merely transient. A role for dopamine receptors in the modification of synaptic strength fits well with the idea that increases in extracellular dopamine can act as a reinforcement learning signal in striatum (Wickens and Kotter, 1995). LTP (and also LTD, long-term depression) is found at corticostriatal synapses in vivo (Charpier and Deniau, 1997) and in vitro (e.g., Kombian and Malenka, 1994; Calabresi et al., 1997). Some groups have found that striatal LTP can be modified by dopamine receptor stimulation (Wickens et al., 1996; Calabresi et al., 1997; but see Pennartz et al., 1993). To our knowledge, however, existing studies of the effects of dopamine on striatal synaptic plasticity have only examined effects at early time points after LTP induction rather than L-LTP.

Changes in gene expression resulting from CREB phosphorylation can affect the whole neuron (Casadio et al., 1999), but hippocampal LTP involves change at specific synapses. To account for this, one current theory suggests that appropriate activation of a synapse sets up a “tag” that marks the synapse as eligible for long-lasting modification by a subsequent signal from the nucleus (Frey and Morris, 1997, 1998; Martin et al., 1997b). Theories of striatal reinforcement learning suggest that following an action, there is a period during which an “eligibility trace” allows the representation of that action to be modified if the reinforcement signal is received (e.g., Houk et al., 1995; Schultz, 1998a). While there may well be multiple mechanisms acting at different time scales, one candidate mechanism for an eligibility trace is the establishment of synaptic tags, with dopamine effects on gene expression acting as the reinforcement signal.

Addictive Drugs and Synaptic Change

Just as dopamine and glutamate receptors are jointly involved in hippocampal synaptic plasticity, dopamine and glutamate inputs to striatum cooperate in the induction of gene expression and behavioral change. In normal animals, selective stimulation of striatal D1 receptors alone causes only a modest induction of IEG expression (Robertson et al., 1992). However, D1 receptor activation can increase the striatal IEG expression caused by cortical stimulation. For example, Arnault et

al. (1996) found that a modest dose of systemic D1 agonists increased the striatal IEG response to auditory stimuli, or to direct stimulation of auditory cortex. This response was specific to areas of striatum receiving inputs from auditory cortex. Conversely, if cortical projections to striatum are severed, the striatal IEG response to amphetamine is reduced (Cenci and Bjorklund, 1993). Increased activity of cortical areas may also account for observations that giving an amphetamine injection in a novel environment greatly enhances the degree of both striatal IEG induction and behavioral sensitization, without affecting the extent of striatal dopamine release (Badiani et al., 1998).

Cocaine, amphetamine, nicotine, and morphine all cause induction of IEG expression in striatum; for each of these drugs IEG induction is blocked by either D1 antagonists or NMDA receptor antagonists (Young et al., 1991; Kiba and Jayaraman, 1994; Liu et al., 1994). Mutant mice lacking D1 receptors do not show this IEG response (Moratalla et al., 1996); in such mice locomotor sensitization to amphetamine is diminished and does not progressively increase with repeated injections (Crawford et al., 1997). Similarly, the development of psychostimulant sensitization is blocked by NMDA receptor antagonists (Karler et al., 1989; Wolf and Khansa, 1991). NMDA receptor blockade also prevents development of a conditioned locomotor response to a psychostimulant-associated environment (Wolf and Khansa, 1991). Infusions of NMDA antagonists into the nucleus accumbens interfere with acquisition of an operant task, in which a rat has to learn to press a lever to receive food (Kelley et al., 1997). In that experiment, NMDA antagonism did not interfere with performance of a previously learned task. Similarly, doses of NMDA antagonists that prevent development of sensitization do not prevent expression of previously established psychostimulant sensitization (Karler et al., 1991; for review, see Wolf, 1998).

As in the hippocampus, combined increases in the second messengers cAMP and calcium appear to be critical in altering striatal gene expression. In cultured striatal cells, D1 agonists cause phosphorylation of CREB and IEG expression, but this is blocked by NMDA receptor antagonists or calcium removal (Konradi et al., 1996; Das et al., 1997). Increased intracellular calcium can contribute to CREB phosphorylation by multiple signal transduction mechanisms (Figure 2). Phosphorylation via mitogen-activated protein kinase (MAPK) pathways (Xing et al., 1996) is thought to be important for synaptic plasticity and certain forms of learning (Kornhauser and Greenberg, 1997; Martin et al., 1997a; Impey et al., 1998). Stimulation of cortex causes activation of the ERK MAPKs in striatal cells (Sgambato et al., 1998a), and this is dependent on NMDA receptor stimulation and calcium entry (Vincent et al., 1998). ERK activation can also contribute to striatal IEG induction through phosphorylation of Elk-1 (Sgambato et al., 1998b).

Psychostimulants cause the rapid, transient induction of a large number of distinct genes in striatal D1 cells (Berretta et al., 1992; Cole et al., 1992; Berke et al., 1998). Although the function of most of these genes is not yet clear, there is substantial overlap with the set of genes induced in hippocampal LTP. This includes genes such as *homer-1a*, *narp*, and *arc* that are potentially involved

in regulation of synaptic function (e.g., Cole et al., 1989; Yamagata et al., 1994; Fosnaugh et al., 1995; Lyford et al., 1995; Brakeman et al., 1997; O'Brien et al., 1999). In some systems, persistent alterations in behavior are associated with structural changes to synaptic connections (Bailey and Kandel, 1993). Similarly, the late phase of hippocampal LTP may also involve localized formation of new synaptic contacts (Engert and Bonhoeffer, 1999). Such structural modifications may also be involved in the long-lasting effects of psychostimulants. Chronic amphetamine administration causes increased dendritic spine density in the nucleus accumbens (and also in prefrontal cortex), as well as an increased number of branched spines (Robinson and Kolb, 1997). Conversely, dopamine denervation causes a reduction in striatal dendritic spine density (Ingham et al., 1989, 1993; Meredith et al., 1995) and in the number of asymmetric synapses in the striatum (Ingham et al., 1998). Dopamine can stimulate neurite extension and growth cone formation in embryonic striatal cultured neurons; this action of dopamine involves D1 receptors, the cAMP/PKA pathway, and protein synthesis (Schmidt et al., 1996, 1998).

Learning Mechanisms in Addiction and Sensitization

Addictive drugs cause dopamine release in the striatum, stimulation of D1 receptors, and induction of gene expression. D1 stimulation of gene expression is associated with long-lasting changes in synaptic efficacy and structural synaptic change. Many aspects of persistent drug-induced behavioral change may thus result from altered synaptic connectivity, without requiring persistent changes in overall neurotransmitter release, post-synaptic sensitivity, or gene expression. Despite much research on addiction and associative learning at the behavioral level, homeostatic mechanisms have been a more significant focus at the molecular and cellular level (Koob et al., 1998b).

The ability of addictive drugs to engage molecular mechanisms of synaptic plasticity, and thus to alter the functioning of specific circuits, is likely to be central to their ability to reinforce and thereby establish addictive behaviors. Striatal neurons are components of brain circuits involved in the control of behavioral responses, particularly in specific contexts (Schultz et al., 1995a; Wise et al., 1996). By preferentially facilitating change at active glutamatergic striatal synapses, dopamine can reinforce an association between a particular set of stimuli and a particular behavioral response. The engagement of these striatal "habit"-learning mechanisms by addictive drugs could similarly promote a tendency for drug-related cues and contexts to provoke specific behaviors, such as drug self-administration (White, 1996; Robbins and Everitt, 1999). The development of stimulus-response habits has been attributed particularly to learning processes involving dorsal parts of striatum. Facilitation of synaptic plasticity in ventral striatum may also contribute to drug use through enhanced learning about the motivational significance of drug-related cues (Carr and White, 1983).

The exact nature of the relationship between associative learning and sensitization is controversial (Pert et al., 1990; Stewart, 1992; Jodogne et al., 1994; Anagnostaras

and Robinson, 1996; Carey and Gui, 1998). One possibility is that context-dependent sensitization may arise from the acute drug enhancement of previously conditioned behavioral responses to drug-associated stimuli. Psychostimulants, nonselective dopamine agonists such as apomorphine, and specific D1 receptor agonists can all produce increases in locomotor activity that become persistently conditioned to specific contexts (Silverman and Ho, 1981; Schiff, 1982; Moller et al., 1987; Silverman, 1991; Page and Terry, 1997). Once established, the expression of conditioned locomotor responses does not require acute dopamine release (Beninger and Hahn, 1983; Brown and Fibiger, 1992; Carey, 1992; Burechailo and Martin-Iverson, 1996). However, the acute effect of a psychostimulant challenge dose will be to facilitate expression of previously established, cue-conditioned behaviors—increasing the observed locomotor effects of the drug (this effect may also be involved in the ability of low doses of addictive drugs or D2 agonists to cause reinstatement of drug self-administration; Stewart et al., 1984; Self et al., 1996).

While stimulation of striatal D1 receptors may be necessary for the acquisition of conditioned responses to psychostimulant-paired environments, it may not be sufficient. Direct amphetamine injections into striatum appear to produce neither conditioned responses nor context-dependent sensitization (Dougherty and Ellinwood, 1981; Kalivas and Weber, 1988; Vezina and Stewart, 1990). An additional drug action on midbrain dopamine cells may be involved, though how this interacts with associative learning mechanisms remains unclear.

Although molecular events are crucial, the present view of sensitization and relapse is an attempt at a systems-level explanation, involving storage of specific information in neuronal circuits. This stands in contrast to most conceptions of sensitization, in which the functioning of a brain pathway shows a general change irrespective of particular patterns of information (e.g., Pierce and Kalivas, 1997). Both types of mechanism may have important roles in addiction. For example, nonassociative changes in dopamine neurotransmission may set thresholds for the effects of drugs on associative learning. Animals that have high general behavioral reactivity (indicated by a large locomotor response to a novel environment) appear to release larger amounts of dopamine into the striatum in response to stress or psychostimulants (Rouge-Pont et al., 1993). Such animals are more likely to acquire psychostimulant self-administration (Piazza et al., 1989) and are also more likely to acquire a conditioned locomotor response to an amphetamine-associated environment (Jodogne et al., 1994). Once drug addiction is established, nonassociative sensitization might also serve to exacerbate the action of stressful circumstances to increase the probability of drug use (Shaham and Stewart, 1995). Nonassociative sensitization of dopamine neurotransmission in ventral areas of striatum may be responsible for enhanced learning about the incentive/motivational properties of stimuli (e.g., Shippenberg and Heidbreder, 1995), and such mechanisms have been suggested to underlie addiction (Robinson and Berridge, 1993). However it is not clear how nonassociative forms of sensitization could account for the specificity of drug self-administration—why do addictive drugs become such a focus

Table 2. Hypothetical Scheme of the Changing Neural Substrates for Addictive Drug Use

Phase of Drug Use	Cumulative Reasons for Drug Use	Possible Neural Systems
Initial	Experimentation, self-medication, peer group behavior	?
Early/medium	PLUS: Explicit memories of pleasure, increased incentive value of drug-related stimuli	Synaptic plasticity in hippocampus, amygdala, and their projections to ventral striatum
	Relief or avoidance of withdrawal symptoms	Compensatory adaptations in many brain regions, including striatum (and locus ceruleus for opiates)
Late/relapse	PLUS: Automatized stimulus-response habits	Synaptic plasticity of neocortical projections to dorsal striatum

of behavior (as opposed to, for example, food or sex)? Nonassociative sensitization mechanisms also cannot account for the specific ability of drug-associated cues to provoke drug relapse.

Abnormal Associative Learning and Compulsive Behavior

Associative learning is necessary for the establishment of drug-taking behavior. But is it sufficient for addiction? After all, most psychostimulant users do not become addicted (Gawin, 1991). It is therefore important to separate the question “why do people take drugs?” from the question “why do people take drugs compulsively?” For this reason, simple drug self-administration in animals may not necessarily be a particularly good model for human addiction, though there have been recent efforts to find improved models (e.g., Ahmed and Koob, 1998).

One key factor may be the unusual way in which drugs can engage synaptic plasticity. In current models of the role of dopamine in normal reinforcement learning, reinforcing events that are fully predicted do not evoke dopamine release and hence do not provoke further learning (Schultz, 1998b). However, the direct pharmacological actions of psychostimulants and other addictive drugs may override such normal constraints on learning (Di Chiara, 1998). This could lead to excessive strengthening of synaptic patterns representing drug-taking behavior, relative to other behaviors performed by the animal. To put this another way, compulsive drug use could be the result of an increasingly biased competition between behavioral options (for related ideas, see Rolls, 1996; Bigelow et al., 1998). Drug-addicted humans display an overall narrowing of behavioral repertoire (Koob et al., 1998a), with progressively more of the addict’s time spent in drug-related activities.

In addition, the manner of drug intake becomes progressively more fixed—particular sequences of actions become “ritualized” and automatic (Tiffany, 1990), consistent with the involvement of the dorsal striatal “habit”-learning system. Among all brain regions, it is dorsal parts of striatum that show the most robust and consistent induction of IEGs following a wide range of addictive drugs (for review, see Harlan and Garcia, 1998). Loss of control over drug taking may therefore arise from excessive synaptic plasticity in a neural system used to

perform actions without the need for deliberate, attentive control. In normal learning, behavioral flexibility can be achieved by overriding automatic responses that have become inappropriate; this executive process is thought to involve prefrontal cortex (e.g., Goldman-Rakic, 1987). The abnormal strengthening of drug-taking behaviors may make this progressively more difficult.

The activation of synaptic plasticity is tightly regulated by numerous intracellular mechanisms. Simulations of associative learning in neural networks indicate that if synaptic plasticity occurs too readily, new learning can interfere with previously stored representations (e.g., McClelland et al., 1995; Hasselmo, 1997). Such mechanisms have been proposed to be involved in the pathogenesis of schizophrenia (Greenstein-Messica and Ruppel, 1998). Psychostimulants can cause abnormally strong and prolonged release of neurotransmitters. The diminished specificity of synaptic plasticity induced by psychostimulants may be another factor contributing to the narrowing of behavioral repertoire.

Multiple Memory Systems and the Development of Addiction

Modern conceptions of learning and memory recognize the importance of multiple, semi-independent brain circuits (e.g., McDonald and White, 1993; Milner et al., 1998). Though interconnected, these different circuits contribute to distinct aspects of behavior. We have focused on the role of brain circuits involving the striatum, for the many reasons discussed above. However, addictive drugs likely engage learning mechanisms in many brain regions. These include other targets of dopamine innervation such as hippocampus, amygdala, and prefrontal cortex (Goldman-Rakic, 1995). The contributions of multiple memory circuits to addiction has been the subject of an extensive recent review (White, 1996).

An unexpected “rewarding” event provokes multiple forms of learning, each of which contributes to the overall “reinforcing” effects of that event (White and Milner, 1992; Robbins and Everitt, 1996). These include stimulus-response learning, assignment of emotional significance to cues and contexts associated with the rewarding event, and an enhanced explicit memory for the episode in which the event occurred. As a given task is repeatedly performed, the neural circuits most

important for performing the task may change, reflecting a shift in behavioral strategy (McDonald and White, 1993). For example, rats may initially move toward a target using hippocampal-dependent knowledge of spatial cues but eventually shift to a more automatic, dorsal striatum-based strategy of performing a fixed sequence of movements (Packard and McGaugh, 1996). Extended training can also cause performance of a task to no longer be contingent on a desirable outcome (devaluation insensitivity; Balleine and Dickinson, 1998), consistent with a shift from evaluative decision making to an automatized stimulus-response habit. Similarly, many different factors, including learning about the motivational significance of drug cues, explicit memories of euphoria, and social pressures, may be responsible for early phases of human drug use. Different drugs may differentially activate these multiple learning processes—for example, nicotine does not provoke substantial euphoria yet is highly addictive, with very high relapse rates (O'Brien and McLellan, 1996). Just as in normal learning, with prolonged drug use the relative roles of distinct neural memory circuits may change (White, 1996), with the increasing automatization of drug-taking behavior being critical for addiction (Tiffany, 1990). One hypothetical scheme is shown in Table 2.

Future Directions for Research

We have argued that the most intractable aspects of addiction may result from the inappropriate engagement of molecular mechanisms of long-term memory. In this view, addiction is very different to a brain lesion or a neurodegenerative disease, in that it involves learning specific patterns of information. Through a drug-induced excess of structural synaptic plasticity, certain behavioral "rules" have become strengthened to an unusual degree. Brain circuits involving both dorsal and ventral parts of striatum are likely to be involved in drug self-administration. The likely importance of the ventral striatum in the acquisition of drug-taking behavior should not deter investigations into the role of the dorsal striatum in the transition to addiction.

Drug-associated cues and contexts activate a narrow repertoire of drug-taking behaviors in the fully addicted person. These behaviors can often be suppressed, at least for a time, by "top-down" control mechanisms that are likely to require the prefrontal cortex. Given the deeply ingrained nature of the drug-related behaviors, however, it is not surprising that without effort and vigilance, relapses occur. Clinically, a delicate balance has to be reached. While encouraging addicts to play an active, responsible role in regaining control of their drug intake, at the same time a relapse must not be allowed to signify a catastrophic failure of the treatment (O'Brien and McLellan, 1996).

Most molecular biological accounts of addiction have not emphasized associative learning mechanisms, instead attempting to find a molecular signature of addiction in persistent neurochemical changes (Koob and Le Moal, 1997; Koob et al., 1998b). We suggest that the role of transient changes in gene expression, leading to behavioral changes through persistent synaptic rearrangements, deserves greater attention. The current intense investigation of the molecular mechanisms of

memory is yielding results that can usefully be applied to the understanding of addiction.

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References

- Adams, M.R., Brandon, E.P., Chartoff, E.H., Idzerda, R.L., Dorsa, D.M., and McKnight, G.S. (1997). Loss of haloperidol-induced gene expression and catalepsy in protein kinase A-deficient mice. *Proc. Natl. Acad. Sci. USA* *94*, 12157–12161.
- Ahmed, S.H., and Koob, G.F. (1998). Transition from moderate to excessive drug intake: change in hedonic set point. *Science* *282*, 298–300.
- Alexander, G.E., Crutcher, M.D., and DeLong, M.R. (1990). Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. *Prog. Brain Res.* *85*, 119–146.
- Altman, J., Everitt, B.J., Glautier, S., Markou, A., Nutt, D., Oretti, R., Phillips, G.D., and Robbins, T.W. (1996). The biological, social and clinical bases of drug addiction: commentary and debate. *Psychopharmacology (Berl.)* *125*, 285–345.
- Anagnostaras, S.G., and Robinson, T.E. (1996). Sensitization to the psychomotor stimulant effects of amphetamine: modulation by associative learning. *Behav. Neurosci.* *110*, 1397–1414.
- Arnauld, E., Jeantet, Y., Arsaut, J., and Demotes-Mainard, J. (1996). Involvement of the caudal striatum in auditory processing: c-fos response to cortical application of picrotoxin and to auditory stimulation. *Brain Res. Mol. Brain Res.* *41*, 27–35.
- Badiani, A., Anagnostaras, S.G., and Robinson, T.E. (1995). The development of sensitization to the psychomotor stimulant effects of amphetamine is enhanced in a novel environment. *Psychopharmacology (Berl.)* *117*, 443–452.
- Badiani, A., Oates, M.M., Day, H.E., Watson, S.J., Akil, H., and Robinson, T.E. (1998). Amphetamine-induced behavior, dopamine release, and c-fos mRNA expression: modulation by environmental novelty. *J. Neurosci.* *18*, 10579–10593.
- Baik, J.H., Picetti, R., Saiardi, A., Thiriet, G., Dierich, A., Depaulis, A., Le Meur, M., and Borrelli, E. (1995). Parkinsonian-like locomotor impairment in mice lacking dopamine D2 receptors. *Nature* *377*, 424–428.
- Bailey, C.H., and Kandel, E.R. (1993). Structural changes accompanying memory storage. *Annu. Rev. Physiol.* *55*, 397–426.
- Balleine, B.W., and Dickinson, A. (1998). Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology* *37*, 407–419.
- Barto, A.G. (1995). Adaptive critics and the basal ganglia. In *Models of Information Processing in the Basal Ganglia*, J.C. Houk, J.L. Davis, and D.G. Beiser, eds. (Cambridge, MA: MIT Press), pp. 214–232.
- Beninger, R.J., and Hahn, B.L. (1983). Pimozide blocks establishment but not expression of amphetamine-produced environment-specific conditioning. *Science* *220*, 1304–1306.
- Beninger, R.J., and Miller, R. (1998). Dopamine D1-like receptors and reward-related incentive learning. *Neurosci. Biobehav. Rev.* *22*, 335–345.
- Berke, J.D., Paletzki, R.F., Aronson, G.J., Hyman, S.E., and Gerfen, C.R. (1998). A complex program of striatal gene expression induced by dopaminergic stimulation. *J. Neurosci.* *18*, 5301–5310.
- Berretta, S., Robertson, H.A., and Graybiel, A.M. (1992). Dopamine and glutamate agonists stimulate neuron-specific expression of Fos-like protein in the striatum. *J. Neurophysiol.* *68*, 767–777.
- Bigelow, G.E., Brooner, R.K., and Silverman, K. (1998). Competing motivations: drug reinforcement vs non-drug reinforcement. *J. Psychopharmacol.* *12*, 8–14.
- Blackburn, J.R., Pfau, J.G., and Phillips, A.G. (1992). Dopamine

- functions in appetitive and defensive behaviours. *Prog. Neurobiol.* **39**, 247–279.
- Bordet, R., Ridray, S., Carboni, S., Diaz, J., Sokoloff, P., and Schwartz, J.C. (1997). Induction of dopamine D3 receptor expression as a mechanism of behavioral sensitization to levodopa. *Proc. Natl. Acad. Sci. USA* **94**, 3363–3367.
- Bourtchuladze, R., Frenguelli, B., Blendy, J., Cioffi, D., Schutz, G., and Silva, A.J. (1994). Deficient long-term memory in mice with a targeted mutation of the cAMP-responsive element-binding protein. *Cell* **79**, 59–68.
- Brakeman, P.R., Lanahan, A.A., O'Brien, R., Roche, K., Barnes, C.A., Haganir, R.L., and Worley, P.F. (1997). Homer: a protein that selectively binds metabotropic glutamate receptors. *Nature* **386**, 284–288.
- Breiter, H.C., Gollub, R.L., Weisskoff, R.M., Kennedy, D.N., Makris, N., Berke, J.D., Goodman, J.M., Kantor, H.L., Gastfriend, D.R., Riorden, J.P., et al. (1997). Acute effects of cocaine on human brain activity and emotion. *Neuron* **19**, 591–611.
- Bridger, W.H., Schiff, S.R., Cooper, S.S., Paredes, W., and Barr, G.A. (1982). Classical conditioning of cocaine's stimulatory effects. *Psychopharmacol. Bull.* **18**, 210–214.
- Brown, E.E., and Fibiger, H.C. (1992). Cocaine-induced conditioned locomotion: absence of associated increases in dopamine release. *Neuroscience* **48**, 621–629.
- Brown, P., and Marsden, C.D. (1998). What do the basal ganglia do? *Lancet* **351**, 1801–1804.
- Burechailo, L., and Martin-Iverson, M.T. (1996). Behavioral sensitization to cocaine, but not cocaine-conditioned behavior, is associated with increased dopamine occupation of its receptors in the nucleus accumbens. *Behav. Neurosci.* **110**, 1388–1396.
- Cador, M., Robbins, T.W., and Everitt, B.J. (1989). Involvement of the amygdala in stimulus-reward associations: interaction with the ventral striatum. *Neuroscience* **30**, 77–86.
- Caille, I., Dumartin, B., and Bloch, B. (1996). Ultrastructural localization of D1 dopamine receptor immunoreactivity in rat striatonigral neurons and its relation with dopaminergic innervation. *Brain Res.* **730**, 17–31.
- Calabresi, P., Saiardi, A., Pisani, A., Baik, J.H., Centonze, D., Mercuri, N.B., Bernardi, G., and Borrelli, E. (1997). Abnormal synaptic plasticity in the striatum of mice lacking dopamine D2 receptors. *J. Neurosci.* **17**, 4536–4544.
- Cantrell, A.R., Scheuer, T., and Catterall, W.A. (1999). Voltage-dependent neuromodulation of Na⁺ channels by D1-like dopamine receptors in rat hippocampal neurons. *J. Neurosci.* **19**, 5301–5310.
- Carey, R.J. (1991). Chronic L-dopa treatment in the unilateral 6-OHDA rat: evidence for behavioral sensitization and biochemical tolerance. *Brain Res.* **568**, 205–214.
- Carey, R.J. (1992). Pavlovian conditioning of L-dopa induced movement. *Psychopharmacology (Berl.)* **107**, 203–210.
- Carey, R.J., and Gui, J. (1998). Cocaine conditioning and cocaine sensitization: what is the relationship? *Behav. Brain Res.* **92**, 67–76.
- Carlezon, W.A., Jr., Thome, J., Olson, V.G., Lane-Ladd, S.B., Brodtkin, E.S., Hiroi, N., Duman, R.S., Neve, R.L., and Nestler, E.J. (1998). Regulation of cocaine reward by CREB. *Science* **282**, 2272–2275.
- Carr, G.D., and White, N.M. (1983). Conditioned place preference from intra-accumbens but not intra-caudate amphetamine injections. *Life Sci.* **33**, 2551–2557.
- Casadio, A., Martin, K.C., Giustetto, M., Zhu, H., Chen, M., Bartsch, D., Bailey, C.H., and Kandel, E.R. (1999). A transient, neuron-wide form of CREB-mediated long-term facilitation can be stabilized at specific synapses by local protein synthesis. *Cell* **99**, 221–237.
- Cenci, M.A., and Bjorklund, A. (1993). Transection of corticostriatal afferents reduces amphetamine- and apomorphine-induced striatal Fos expression and turning behaviour in unilaterally 6-hydroxydopamine-lesioned rats. *Eur. J. Neurosci.* **5**, 1062–1070.
- Cepeda, C., Colwell, C.S., Itri, J.N., Chandler, S.H., and Levine, M.S. (1998). Dopaminergic modulation of NMDA-induced whole cell currents in neostriatal neurons in slices: contribution of calcium conductances. *J. Neurophysiol.* **79**, 82–94.
- Cepeda-Benito, A., Tiffany, S.T., and Cox, L.S. (1999). Context-specific morphine tolerance on the paw-pressure and tail-shock vocalization tests: evidence of associative tolerance without conditioned compensatory responding. *Psychopharmacology (Berl.)* **145**, 426–432.
- Cha, X.Y., Pierce, R.C., Kalivas, P.W., and Mackler, S.A. (1997). NAC-1, a rat brain mRNA, is increased in the nucleus accumbens three weeks after chronic cocaine self-administration. *J. Neurosci.* **17**, 6864–6871.
- Charpier, S., and Deniau, J.M. (1997). In vivo activity-dependent plasticity at cortico-striatal connections: evidence for physiological long-term potentiation. *Proc. Natl. Acad. Sci. USA* **94**, 7036–7040.
- Childress, A.R., McLellan, A.T., and O'Brien, C.P. (1986). Role of conditioning factors in the development of drug dependence. *Psychiatr. Clin. North Am.* **9**, 413–425.
- Cole, D.G., and Di Figlia, M. (1994). Reserpine increases Fos activity in the rat basal ganglia via a quinpirole-sensitive mechanism. *Neuroscience* **60**, 115–123.
- Cole, A.J., Saffen, D.W., Baraban, J.M., and Worley, P.F. (1989). Rapid increase of an immediate early gene messenger RNA in hippocampal neurons by synaptic NMDA receptor activation. *Nature* **340**, 474–476.
- Cole, A.J., Bhat, R.V., Patt, C., Worley, P.F., and Baraban, J.M. (1992). D1 dopamine receptor activation of multiple transcription factor genes in rat striatum. *J. Neurochem.* **58**, 1420–1426.
- Cole, R.L., Konradi, C., Douglass, J., and Hyman, S.E. (1995). Neuronal adaptation to amphetamine and dopamine: molecular mechanisms of prodynorphin gene regulation in rat striatum. *Neuron* **14**, 813–823.
- Crawford, C.A., Drago, J., Watson, J.B., and Levine, M.S. (1997). Effects of repeated amphetamine treatment on the locomotor activity of the dopamine D1A-deficient mouse. *Neuroreport* **8**, 2523–2527.
- Criswell, H., Mueller, R.A., and Breese, G.R. (1989). Priming of D1-dopamine receptor responses: long-lasting behavioral supersensitivity to a D1-dopamine agonist following repeated administration to neonatal 6-OHDA-lesioned rats. *J. Neurosci.* **9**, 125–133.
- Cummings, J.L. (1991). Behavioral complications of drug treatment of Parkinson's disease. *J. Am. Geriatr. Soc.* **39**, 708–716.
- Dalia, A.D., Norman, M.K., Tabet, M.R., Schlueter, K.T., Tsubulsky, V.L., and Norman, A.B. (1998). Transient amelioration of the sensitization of cocaine-induced behaviors in rats by the induction of tolerance. *Brain Res.* **797**, 29–34.
- Das, S., Grunert, M., Williams, L., and Vincent, S.R. (1997). NMDA and D1 receptors regulate the phosphorylation of CREB and the induction of c-fos in striatal neurons in primary culture. *Synapse* **25**, 227–233.
- Deroche, V., Marinelli, M., Maccari, S., Le Moal, M., Simon, H., and Piazza, P.V. (1995). Stress-induced sensitization and glucocorticoids. I. Sensitization of dopamine-dependent locomotor effects of amphetamine and morphine depends on stress-induced corticosterone secretion. *J. Neurosci.* **15**, 7181–7188.
- Di Chiara, G. (1998). A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. *J. Psychopharmacol.* **12**, 54–67.
- Di Chiara, G., and Imperato, A. (1988). Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. *Proc. Natl. Acad. Sci. USA* **85**, 5274–5278.
- Dougherty, G.G., Jr., and Ellinwood, E.H., Jr. (1981). Chronic D-amphetamine in nucleus accumbens: lack of tolerance or reverse tolerance of locomotor activity. *Life Sci.* **28**, 2295–2298.
- Douglass, J., McKinzie, A.A., and Couceyro, P. (1995). PCR differential display identifies a rat brain mRNA that is transcriptionally regulated by cocaine and amphetamine. *J. Neurosci.* **15**, 2471–2481.
- Drago, J., Gerfen, C.R., Lachowicz, J.E., Steiner, H., Hollon, T.R., Love, P.E., Ooi, G.T., Grinberg, A., Lee, E.J., Huang, S.P., et al. (1994). Altered striatal function in a mutant mouse lacking D1A dopamine receptors. *Proc. Natl. Acad. Sci. USA* **91**, 12564–12568.
- Dragunow, M., Robertson, G.S., Faull, R.L., Robertson, H.A., and Jansen, K. (1990). D2 dopamine receptor antagonists induce fos and related proteins in rat striatal neurons. *Neuroscience* **37**, 287–294.

- Dumartin, B., Caille, I., Gonon, F., and Bloch, B. (1998). Internalization of D1 dopamine receptor in striatal neurons in vivo as evidence of activation by dopamine agonists. *J. Neurosci.* *18*, 1650–1661.
- Ehrman, R.N., Robbins, S.J., Childress, A.R., and O'Brien, C.P. (1992). Conditioned responses to cocaine-related stimuli in cocaine abuse patients. *Psychopharmacology (Berl.)* *107*, 523–529.
- Ellinwood, E.H., Jr., and Kilbey, M.M. (1975). Amphetamine stereotypy: the influence of environmental factors and prepotent behavioral patterns on its topography and development. *Biol. Psychiatry* *10*, 3–16.
- Engert, F., and Bonhoeffer, T. (1999). Dendritic spine changes associated with hippocampal long-term synaptic plasticity. *Nature* *399*, 66–70.
- Everitt, B.J., Morris, K.A., O'Brien, A., and Robbins, T.W. (1991). The basolateral amygdala-ventral striatal system and conditioned place preference: further evidence of limbic-striatal interactions underlying reward-related processes. *Neuroscience* *42*, 1–18.
- Fallon, J.H., and Loughlin, S.E. (1995). Substantia nigra. In *The Rat Nervous System*, G. Paxinos, ed. (New York: Academic Press), pp. 215–238.
- Flowers, K. (1975). Ballistic and corrective movements on an aiming task. Intention tremor and parkinsonian movement disorders compared. *Neurology* *25*, 413–421.
- Fosnaugh, J.S., Bhat, R.V., Yamagata, K., Worley, P.F., and Baraban, J.M. (1995). Activation of arc, a putative "effector" immediate early gene, by cocaine in rat brain. *J. Neurochem.* *64*, 2377–2380.
- Frey, U., and Morris, R.G. (1997). Synaptic tagging and long-term potentiation. *Nature* *385*, 533–536.
- Frey, U., and Morris, R.G. (1998). Synaptic tagging: implications for late maintenance of hippocampal long-term potentiation. *Trends Neurosci.* *21*, 181–188.
- Frey, U., Schroeder, H., and Matthies, H. (1990). Dopaminergic antagonists prevent long-term maintenance of posttetanic LTP in the CA1 region of rat hippocampal slices. *Brain Res.* *522*, 69–75.
- Frey, U., Matthies, H., Reymann, K.G., and Matthies, H. (1991). The effect of dopaminergic D1 receptor blockade during tetanization on the expression of long-term potentiation in the rat CA1 region in vitro. *Neurosci. Lett.* *129*, 111–114.
- Frey, U., Huang, Y.Y., and Kandel, E.R. (1993). Effects of cAMP simulate a late stage of LTP in hippocampal CA1 neurons. *Science* *260*, 1661–1664.
- Frey, U., Frey, S., Schollmeier, F., and Krug, M. (1996). Influence of actinomycin D, an RNA synthesis inhibitor, on long-term potentiation in rat hippocampal neurons in vivo and in vitro. *J. Physiol.* *490*, 703–711.
- Garris, P.A., Kilpatrick, M., Bunin, M.A., Michael, D., Walker, Q.D., and Wightman, R.M. (1999). Dissociation of dopamine release in the nucleus accumbens from intracranial self-stimulation. *Nature* *398*, 67–69.
- Gawin, F.H. (1991). Cocaine addiction: psychology and neurophysiology. *Science* *251*, 1580–1586.
- Gawin, F.H., and Ellinwood, E.H., Jr. (1989). Cocaine dependence. *Annu. Rev. Med.* *40*, 149–161.
- Gerfen, C.R., and Wilson, C.J. (1996). The basal ganglia. In *Handbook of Chemical Neuroanatomy*, L.R. Swanson, A. Bjorklund, and T. Hokfelt, eds. (New York: Elsevier), pp. 371–468.
- Gerfen, C.R., Engber, T.M., Mahan, L.C., Susel, Z., Chase, T.N., Monsma, F.J., Jr., and Sibley, D.R. (1990). D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* *250*, 1429–1432.
- Gerfen, C.R., Keefe, K.A., and Gauda, E.B. (1995). D1 and D2 dopamine receptor function in the striatum: coactivation of D1- and D2-dopamine receptors on separate populations of neurons results in potentiated immediate early gene response in D1-containing neurons. *J. Neurosci.* *15*, 8167–8176.
- Goeders, N.E., and Guerin, G.F. (1994). Non-contingent electric footshock facilitates the acquisition of intravenous cocaine self-administration in rats. *Psychopharmacology* *114*, 63–70.
- Goldman-Rakic, P.S. (1987). Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In *Handbook of Physiology*, F. Plum, ed. (Bethesda, MD: American Physiological Society), pp. 373–417.
- Goldman-Rakic, P.S. (1995). Cellular basis of working memory. *Neuron* *14*, 477–485.
- Goldstein, A. (1994). *Addiction: From Biology to Drug Policy* (New York: W. H. Freeman and Company).
- Gonon, F. (1997). Prolonged and extrasynaptic excitatory action of dopamine mediated by D1 receptors in the rat striatum in vivo. *J. Neurosci.* *17*, 5972–5978.
- Graybiel, A.M. (1998). The basal ganglia and chunking of action repertoires. *Neurobiol. Learn. Mem.* *70*, 119–136.
- Greenstein-Messica, A., and Ruppin, E. (1998). Synaptic runaway in associative networks and the pathogenesis of schizophrenia. *Neural Comput.* *10*, 451–465.
- Harlan, R.E., and Garcia, M.M. (1998). Drugs of abuse and immediate-early genes in the forebrain. *Mol. Neurobiol.* *16*, 221–267.
- Hasselmeier, M.E. (1997). A computational model of the progression of Alzheimer's disease. *MD Comput.* *14*, 181–191.
- Hatfield, T., Han, J.S., Conley, M., Gallagher, M., and Holland, P. (1996). Neurotoxic lesions of basolateral, but not central, amygdala interfere with Pavlovian second-order conditioning and reinforcer devaluation effects. *J. Neurosci.* *16*, 5256–5265.
- Heidbreder, C.A., Thompson, A.C., and Shippenberg, T.S. (1996). Role of extracellular dopamine in the initiation and long-term expression of behavioral sensitization to cocaine. *J. Pharmacol. Exp. Ther.* *278*, 490–502.
- Heimer, L., Zahm, D.S., Churchill, L., Kalivas, P.W., and Wohltmann, C. (1991). Specificity in the projection patterns of accumbal core and shell in the rat. *Neuroscience* *41*, 89–125.
- Henry, D.J., and White, F.J. (1991). Repeated cocaine administration causes persistent enhancement of D1 dopamine receptor sensitivity within the rat nucleus accumbens. *J. Pharmacol. Exp. Ther.* *258*, 882–890.
- Henry, D.J., and White, F.J. (1995). The persistence of behavioral sensitization to cocaine parallels enhanced inhibition of nucleus accumbens neurons. *J. Neurosci.* *15*, 6287–6299.
- Hernandez-Lopez, S., Bargas, J., Surmeier, D.J., Reyes, A., and Galarraga, E. (1997). D1 receptor activation enhances evoked discharge in neostriatal medium spiny neurons by modulating an L-type Ca²⁺ conductance. *J. Neurosci.* *17*, 3334–3342.
- Hille, B. (1992). G protein-coupled mechanisms and nervous signaling. *Neuron* *9*, 187–195.
- Hinson, R.E., and Poulos, C.X. (1981). Sensitization to the behavioral effects of cocaine: modification by Pavlovian conditioning. *Pharmacol. Biochem. Behav.* *15*, 559–562.
- Hooks, M.S., Duffy, P., Striplin, C., and Kalivas, P.W. (1994). Behavioral and neurochemical sensitization following cocaine self-administration. *Psychopharmacology (Berl.)* *115*, 265–272.
- Hope, B.T., Nye, H.E., Kelz, M.B., Self, D.W., Iadarola, M.J., Nakabeppu, Y., Duman, R.S., and Nestler, E.J. (1994). Induction of a long-lasting AP-1 complex composed of altered Fos-like proteins in brain by chronic cocaine and other chronic treatments. *Neuron* *13*, 1235–1244.
- Houk, J.C., Adams, J.L., and Barto, A.G. (1995). A model of how the basal ganglia generate and use neural signals that predict reinforcement. In *Models of Information Processing in the Basal Ganglia*, J.C. Houk, J.L. Davis, and D.G. Beiser, eds. (Cambridge, MA: MIT Press), pp. 249–270.
- Hu, X.T., and White, F.J. (1997). Dopamine enhances glutamate-induced excitation of rat striatal neurons by cooperative activation of D1 and D2 class receptors. *Neurosci. Lett.* *224*, 61–65.
- Huang, Y.Y., and Kandel, E.R. (1995). D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. *Proc. Natl. Acad. Sci. USA* *92*, 2446–2450.
- Hurd, Y.L., and Herkenham, M. (1993). Molecular alterations in the neostriatum of human cocaine addicts. *Synapse* *13*, 357–369.
- Hyman, S.E. (1996). Addiction to cocaine and amphetamine. *Neuron* *16*, 901–904.

- Impey, S., Obrietan, K., Wong, S.T., Poser, S., Yano, S., Wayman, G., Deloulme, J.C., Chan, G., and Storm, D.R. (1998). Cross talk between ERK and PKA is required for Ca^{2+} stimulation of CREB-dependent transcription and ERK nuclear translocation. *Neuron* 21, 869–883.
- Ingham, C.A., Hood, S.H., and Arbuthnott, G.W. (1989). Spine density on neostriatal neurones changes with 6-hydroxydopamine lesions and with age. *Brain Res.* 503, 334–338.
- Ingham, C.A., Hood, S.H., van Maldegem, B., Weenink, A., and Arbuthnott, G.W. (1993). Morphological changes in the rat neostriatum after unilateral 6-hydroxydopamine injections into the nigrostriatal pathway. *Exp. Brain Res.* 93, 17–27.
- Ingham, C.A., Hood, S.H., Taggart, P., and Arbuthnott, G.W. (1998). Plasticity of synapses in the rat neostriatum after unilateral lesion of the nigrostriatal dopaminergic pathway. *J. Neurosci.* 18, 4732–4743.
- Jenner, P., and Marsden, C.D. (1987). Chronic pharmacological manipulation of dopamine receptors in brain. *Neuropharmacology* 26, 931–940.
- Jodogne, C., Marinelli, M., Le Moal, M., and Piazza, P.V. (1994). Animals predisposed to develop amphetamine self-administration show higher susceptibility to develop contextual conditioning of both amphetamine-induced hyperlocomotion and sensitization. *Brain Res.* 657, 236–244.
- Kalivas, P.W., and Duffy, P. (1993). Time course of extracellular dopamine and behavioral sensitization to cocaine. I. Dopamine axon terminals. *J. Neurosci.* 13, 266–275.
- Kalivas, P.W., and Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. *Brain Res. Brain Res. Rev.* 16, 223–244.
- Kalivas, P.W., and Weber, B. (1988). Amphetamine injection into the ventral mesencephalon sensitizes rats to peripheral amphetamine and cocaine. *J. Pharmacol. Exp. Ther.* 245, 1095–1102.
- Kantor, L., Hewlett, G.H., and Gnegy, M.E. (1999). Enhanced amphetamine- and K^{+} -mediated dopamine release in rat striatum after repeated amphetamine: differential requirements for Ca^{2+} - and calmodulin-dependent phosphorylation and synaptic vesicles. *J. Neurosci.* 19, 3801–3808.
- Karler, R., Calder, L.D., Chaudhry, I.A., and Turkanis, S.A. (1989). Blockade of “reverse tolerance” to cocaine and amphetamine by MK-801. *Life Sci.* 45, 599–606.
- Karler, R., Calder, L.D., and Turkanis, S.A. (1991). DNQX blockade of amphetamine behavioral sensitization. *Brain Res.* 552, 295–300.
- Keefe, K.A., Salamone, J.D., Zigmond, M.J., and Stricker, E.M. (1989). Paradoxical kinesia in parkinsonism is not caused by dopamine release. *Studies in an animal model. Arch. Neurol.* 46, 1070–1075.
- Kelley, A.E., and Delfs, J.M. (1991). Dopamine and conditioned reinforcement. I. Differential effects of amphetamine microinjections into striatal subregions. *Psychopharmacology (Berl.)* 103, 187–196.
- Kelley, A.E., Smith-Roe, S.L., and Holahan, M.R. (1997). Response-reinforcement learning is dependent on N-methyl-D-aspartate receptor activation in the nucleus accumbens core. *Proc. Natl. Acad. Sci. USA* 94, 12174–12179.
- Kelly, P.H., Seviour, P.W., and Iversen, S.D. (1975). Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res.* 94, 507–522.
- Kelz, M.B., Chen, J., Carlezon, W.A., Jr., Whisler, K., Gilden, L., Beckmann, A.M., Steffen, C., Zhang, Y.J., Marotti, L., Self, D.W., et al. (1999). Expression of the transcription factor Δ FosB in the brain controls sensitivity to cocaine. *Nature* 401, 272–276.
- Khan, Z.U., Mrzljak, L., Gutierrez, A., de la Calle, A., and Goldman-Rakic, P.S. (1998). Prominence of the dopamine D2 short isoform in dopaminergic pathways. *Proc. Natl. Acad. Sci. USA* 95, 7731–7736.
- Kiba, H., and Jayaraman, A. (1994). Nicotine induced c-fos expression in the striatum is mediated mostly by dopamine D1 receptor and is dependent on NMDA stimulation. *Brain Res. Mol. Brain Res.* 23, 1–13.
- Kimura, M., Aosaki, T., Hu, Y., Ishida, A., and Watanabe, K. (1992). Activity of primate putamen neurons is selective to the mode of voluntary movement: visually guided, self-initiated or memory-guided. *Exp. Brain Res.* 89, 473–477.
- Kincaid, A.E., Zheng, T., and Wilson, C.J. (1998). Connectivity and convergence of single corticostriatal axons. *J. Neurosci.* 18, 4722–4731.
- Knowlton, B.J., Mangels, J.A., and Squire, L.R. (1996). A neostriatal habit learning system in humans. *Science* 273, 1399–1402.
- Kombian, S.B., and Malenka, R.C. (1994). Simultaneous LTP of non-NMDA- and LTD of NMDA-receptor-mediated responses in the nucleus accumbens. *Nature* 368, 242–246.
- Konradi, C., and Heckers, S. (1995). Haloperidol-induced Fos expression in striatum is dependent upon transcription factor cyclic AMP response element binding protein. *Neuroscience* 65, 1051–1061.
- Konradi, C., Cole, R.L., Heckers, S., and Hyman, S.E. (1994). Amphetamine regulates gene expression in rat striatum via transcription factor CREB. *J. Neurosci.* 14, 5623–5634.
- Konradi, C., Leveque, J.C., and Hyman, S.E. (1996). Amphetamine- and dopamine-induced immediate early gene expression in striatal neurons depends on postsynaptic NMDA receptors and calcium. *J. Neurosci.* 16, 4231–4239.
- Koob, G.F., and Le Moal, M. (1997). Drug abuse: hedonic homeostatic dysregulation. *Science* 278, 52–58.
- Koob, G.F., Rocio, M., Carrera, A., Gold, L.H., Heyser, C.J., Maldonado-Irizarry, C., Markou, A., Parsons, L.H., Roberts, A.J., Schulteis, G., et al. (1998a). Substance dependence as a compulsive behavior. *J. Psychopharmacol.* 12, 39–48.
- Koob, G.F., Sanna, P.P., and Bloom, F.E. (1998b). Neuroscience of addiction. *Neuron* 21, 467–476.
- Kornhauser, J.M., and Greenberg, M.E. (1997). A kinase to remember: dual roles for MAP kinase in long-term memory. *Neuron* 18, 839–842.
- Krivanek, J.A., and McGaugh, J.L. (1969). Facilitating effects of pre- and posttrial amphetamine administration on discrimination learning in mice. *Agents Actions* 1, 36–42.
- Kuczenski, R., Segal, D.S., and Aizenstein, M.L. (1991). Amphetamine, cocaine, and fencamfamine: relationship between locomotor and stereotypy response profiles and caudate and accumbens dopamine dynamics. *J. Neurosci.* 11, 2703–2712.
- Kuczenski, R., Segal, D.S., and Todd, P.K. (1997). Behavioral sensitization and extracellular dopamine responses to amphetamine after various treatments. *Psychopharmacology (Berl.)* 134, 221–229.
- Kuribara, H. (1996a). Effects of interdose interval on ambulatory sensitization to methamphetamine, cocaine and morphine in mice. *Eur. J. Pharmacol.* 316, 1–5.
- Kuribara, H. (1996b). Inhibitory effect of restraint on induction of behavioral sensitization to methamphetamine and cocaine in mice. *Pharmacol. Biochem. Behav.* 54, 327–331.
- Kuribara, H. (1997). Effects of postmethamphetamine treatment with restraint on ambulatory sensitization to methamphetamine in mice. *Brain Res. Bull.* 43, 97–100.
- LaHoste, G.J., Yu, J., and Marshall, J.F. (1993). Striatal Fos expression is indicative of dopamine D1/D2 synergism and receptor super-sensitivity. *Proc. Natl. Acad. Sci. USA* 90, 7451–7455.
- Langston, J.W., Forno, L.S., Rebert, C.S., and Irwin, I. (1984). Selective nigral toxicity after systemic administration of 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) in the squirrel monkey. *Brain Res.* 292, 390–394.
- Le Moine, C., and Bloch, B. (1995). D1 and D2 dopamine receptor gene expression in the rat striatum: sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum. *J. Comp. Neurol.* 355, 418–426.
- Liu, J., Nickolenko, J., and Sharp, F.R. (1994). Morphine induces c-fos and junB in striatum and nucleus accumbens via D1 and N-methyl-D-aspartate receptors. *Proc. Natl. Acad. Sci. USA* 91, 8537–8541.
- Lyford, G.L., Yamagata, K., Kaufmann, W.E., Barnes, C.A., Sanders, L.K., Copeland, N.G., Gilbert, D.J., Jenkins, N.A., Lanahan, A.A., and

- Worley, P.F. (1995). Arc, a growth factor and activity-regulated gene, encodes a novel cytoskeleton-associated protein that is enriched in neuronal dendrites. *Neuron* 14, 433–445.
- Lyon, M., and Robbins, T. (1975). The action of central nervous system drugs: a general theory concerning amphetamine effects. *Curr. Dev. Psychopharmacol.* 2, 80–163.
- Lyons, D., Friedman, D.P., Nader, M.A., and Porrino, L.J. (1996). Cocaine alters cerebral metabolism within the ventral striatum and limbic cortex of monkeys. *J. Neurosci.* 16, 1230–1238.
- MacLennan, A.J., and Maier, S.F. (1983). Coping and the stress-induced potentiation of stimulant stereotypy in the rat. *Science* 219, 1091–1093.
- Malenka, R.C., and Nicoll, R.A. (1993). NMDA-receptor-dependent synaptic plasticity: multiple forms and mechanisms. *Trends Neurosci.* 16, 521–527.
- Mansour, A., and Watson, S.J. (1995). Dopamine receptor expression in the central nervous system. In *Psychopharmacology: The Fourth Generation of Progress*, F.E. Bloom and D.J. Kupfer, eds. (New York: Raven Press), pp. 207–219.
- Markou, A., and Koob, G.F. (1991). Postcocaine anhedonia. An animal model of cocaine withdrawal. *Neuropsychopharmacology* 4, 17–26.
- Marshall, J.F., Richardson, J.S., and Teitelbaum, P. (1974). Nigrostriatal bundle damage and the lateral hypothalamic syndrome. *J. Comp. Physiol. Psychol.* 87, 808–830.
- Marshall, J.F., Levitan, D., and Stricker, E.M. (1976). Activation-induced restoration of sensorimotor functions in rats with dopamine-depleting brain lesions. *J. Comp. Physiol. Psychol.* 90, 536–546.
- Martin, K.C., Michael, D., Rose, J.C., Barad, M., Casadio, A., Zhu, H., and Kandel, E.R. (1997a). MAP kinase translocates into the nucleus of the presynaptic cell and is required for long-term facilitation in *Aplysia*. *Neuron* 18, 899–912.
- Martin, K.C., Casadio, A., Zhu, H.E.Y., Rose, J.C., Chen, M., Bailey, C.H., and Kandel, E.R. (1997b). Synapse-specific, long-term facilitation of *Aplysia* sensory to motor synapses: a function for local protein synthesis in memory storage. *Cell* 91, 927–938.
- Matthies, H., Becker, A., Schroeder, H., Kraus, J., Hollt, V., and Krug, M. (1997). Dopamine D1-deficient mutant mice do not express the late phase of hippocampal long-term potentiation. *Neuroreport* 8, 3533–3535.
- McClelland, J.L., McNaughton, B.L., and O'Reilly, R.C. (1995). Why there are complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. *Psychol. Rev.* 102, 419–457.
- McDonald, A.J. (1991). Topographical organization of amygdaloid projections to the caudatoputamen, nucleus accumbens, and related striatal-like areas of the rat brain. *Neuroscience* 44, 15–33.
- McDonald, R.J., and White, N.M. (1993). A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. *Behav. Neurosci.* 107, 3–22.
- McGeorge, A.J., and Faull, R.L. (1989). The organization of the projection from the cerebral cortex to the striatum in the rat. *Neuroscience* 29, 503–537.
- Meador-Woodruff, J.H., Little, K.Y., Damask, S.P., Mansour, A., and Watson, S.J. (1993). Effects of cocaine on dopamine receptor gene expression: a study in the postmortem human brain. *Biol. Psychiatry* 34, 348–355.
- Meredith, G.E., Ypma, P., and Zahm, D.S. (1995). Effects of dopamine depletion on the morphology of medium spiny neurons in the shell and core of the rat nucleus accumbens. *J. Neurosci.* 15, 3808–3820.
- Milner, B., Squire, L.R., and Kandel, E.R. (1998). Cognitive neuroscience and the study of memory. *Neuron* 20, 445–468.
- Mishkin, M., Malamut, B., and Bachevalier, J. (1984). Memories and habits: two neural systems. In *Neurobiology of Learning and Memory*, G. Lynch, J.L. McGaugh, and N.M. Weinberger, eds. (New York: Guilford Press), pp. 65–77.
- Mogenson, G.J., Jones, D.L., and Yim, C.Y. (1980). From motivation to action: functional interface between the limbic system and the motor system. *Prog. Neurobiol.* 14, 69–97.
- Moller, H.G., Nowak, K., and Kuschinsky, K. (1987). Conditioning of pre- and post-synaptic behavioural responses to the dopamine receptor agonist apomorphine in rats. *Psychopharmacology (Berl.)* 91, 50–55.
- Moratalla, R., Xu, M., Tonegawa, S., and Graybiel, A.M. (1996). Cellular responses to psychomotor stimulant and neuroleptic drugs are abnormal in mice lacking the D1 dopamine receptor. *Proc. Natl. Acad. Sci. USA* 93, 14928–14933.
- Morelli, M., and Di Chiara, G. (1987). Agonist-induced homologous and heterologous sensitization to D-1- and D-2-dependent contraversive turning. *Eur. J. Pharmacol.* 141, 101–107.
- Nestler, E.J., and Aghajanian, G.K. (1997). Molecular and cellular basis of addiction. *Science* 278, 58–63.
- Nestler, E.J., Berhow, M.T., and Brodtkin, E.S. (1996). Molecular mechanisms of drug addiction: adaptations in signal transduction pathways. *Mol. Psychiatry* 1, 190–199.
- Neve, K.A., and Neve, R.L. (1997). Molecular biology of dopamine receptors. In *The Dopamine Receptors*, K.A. Neve and R.L. Neve, eds. (Totowa, NJ: Humana Press), pp. 27–76.
- Nguyen, P.V., and Kandel, E.R. (1996). A macromolecular synthesis-dependent late phase of long-term potentiation requiring cAMP in the medial perforant pathway of rat hippocampal slices. *J. Neurosci.* 16, 3189–3198.
- Nguyen, P.V., Abel, T., and Kandel, E.R. (1994). Requirement of a critical period of transcription for induction of a late phase of LTP. *Science* 265, 1104–1107.
- O'Brien, C.P., and McLellan, A.T. (1996). Myths about the treatment of addiction. *Lancet* 347, 237–240.
- O'Brien, C.P., Childress, A.R., McLellan, A.T., and Ehrman, R. (1992). Classical conditioning in drug-dependent humans. *Ann. NY Acad. Sci.* 654, 400–415.
- O'Brien, R.J., Xu, D., Petralia, R.S., Steward, O., Haganir, R.L., and Worley, P. (1999). Synaptic clustering of AMPA receptors by the extracellular immediate-early gene product *Narp*. *Neuron* 23, 309–323.
- Olanow, C.W., and Koller, W.C. (1998). An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines. *American Academy of Neurology. Neurology* 50, S1–S57.
- Otmakhova, N.A., and Lisman, J.E. (1998). D1/D5 dopamine receptors inhibit depotentiation at CA1 synapses via cAMP-dependent mechanism. *J. Neurosci.* 18, 1270–1279.
- Packard, M.G., and McGaugh, J.L. (1996). Inactivation of hippocampus or caudate nucleus with lidocaine differentially affects expression of place and response learning. *Neurobiol. Learn. Mem.* 65, 65–72.
- Packard, M.G., Cahill, L., and McGaugh, J.L. (1994). Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proc. Natl. Acad. Sci. USA* 91, 8477–8481.
- Page, S.J., and Terry, P. (1997). Conditioned grooming induced by the dopamine D1-like receptor agonist SKF 38393 in rats. *Pharmacol. Biochem. Behav.* 57, 829–833.
- Panlilio, L.V., and Schindler, C.W. (1997). Conditioned locomotor-activating and reinforcing effects of discrete stimuli paired with intraperitoneal cocaine. *Behav. Pharmacol.* 8, 691–698.
- Passingham, R. (1993). *The Frontal Lobes and Voluntary Action* (Oxford: Oxford University Press).
- Paul, M.L., Graybiel, A.M., David, J.C., and Robertson, H.A. (1992). D1-like and D2-like dopamine receptors synergistically activate rotation and c-fos expression in the dopamine-depleted striatum in a rat model of Parkinson's disease. *J. Neurosci.* 12, 3729–3742.
- Paulson, P.E., Camp, D.M., and Robinson, T.E. (1991). Time course of transient behavioral depression and persistent behavioral sensitization in relation to regional brain monoamine concentrations during amphetamine withdrawal in rats. *Psychopharmacology (Berl.)* 103, 480–492.
- Pennartz, C.M., Ameerun, R.F., Groenewegen, H.J., and Lopes da Silva, F.H. (1993). Synaptic plasticity in an in vitro slice preparation of the rat nucleus accumbens. *Eur. J. Neurosci.* 5, 107–117.
- Pert, A., Post, R., and Weiss, S.R. (1990). Conditioning as a critical

- determinant of sensitization induced by psychomotor stimulants. *NIDA Res. Monogr.* 97, 208–241.
- Petursson, H. (1994). The benzodiazepine withdrawal syndrome. *Addiction* 89, 1455–1459.
- Piazza, P.V., and Le Moal, M.L. (1996). Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. *Annu. Rev. Pharmacol. Toxicol.* 36, 359–378.
- Piazza, P.V., Deminiere, J.M., Le Moal, M., and Simon, H. (1989). Factors that predict individual vulnerability to amphetamine self-administration. *Science* 245, 1511–1513.
- Pickens, R., and Dougherty, J.A. (1971). Conditioning of the activity effects of drugs. In *Stimulus Properties of Drugs*, T. Thompson and R. Pickens, eds. (New York: Appleton-Century-Crofts, pp. 39–50).
- Pierce, R.C., and Kalivas, P.W. (1997). A circuitry model of the expression of behavioral sensitization to amphetamine-like psychostimulants. *Brain Res. Brain Res. Rev.* 25, 192–216.
- Pierce, R.C., Born, B., Adams, M., and Kalivas, P.W. (1996). Repeated intra-ventral tegmental area administration of SKF-38393 induces behavioral and neurochemical sensitization to a subsequent cocaine challenge. *J. Pharmacol. Exp. Ther.* 278, 384–392.
- Post, R.M. (1980). Intermittent versus continuous stimulation: effect of time interval on the development of sensitization or tolerance. *Life Sci.* 26, 1275–1282.
- Ranaldi, R., and Beninger, R.J. (1993). Dopamine D1 and D2 antagonists attenuate amphetamine-produced enhancement of responding for conditioned reward in rats. *Psychopharmacology (Berl.)* 113, 110–118.
- Randrup, A., and Munkvad, I. (1967). Stereotyped activities produced by amphetamine in several animal species and man. *Psychopharmacologia* 11, 300–310.
- Rasmussen, K., Beitner-Johnson, D.B., Krystal, J.H., Aghajanian, G.K., and Nestler, E.J. (1990). Opiate withdrawal and the rat locus coeruleus: behavioral, electrophysiological, and biochemical correlates. *J. Neurosci.* 10, 2308–2317.
- Redgrave, P., Prescott, T.J., and Gurney, K. (1999). Is the short-latency dopamine response too short to signal reward error? *Trends Neurosci.* 22, 146–151.
- Robbins, T.W., Cador, M., Taylor, J.R., and Everitt, B.J. (1989). Limbic-striatal interactions in reward-related processes. *Neurosci. Biobehav. Rev.* 13, 155–162.
- Robbins, T.W., and Everitt, B.J. (1996). Neurobehavioural mechanisms of reward and motivation. *Curr. Opin. Neurobiol.* 6, 228–236.
- Robbins, T.W., and Everitt, B.J. (1999). Drug addiction: bad habits add up. *Nature* 398, 567–570.
- Robbins, T.W., Mittleman, G., O'Brien, J., and Winn, P. (1990). The neuropsychological significance of stereotypy induced by stimulant drugs. In *Neurobiology of Stereotyped Behaviour*, S.J. Cooper and C.T. Dourish, eds. (Oxford: Clarendon Press), pp. 25–63.
- Robbins, T.W., Granon, S., Muir, J.L., Duranrou, F., Harrison, A., and Everitt, B.J. (1998). Neural systems underlying arousal and attention. Implications for drug abuse. *Ann. NY Acad. Sci.* 846, 222–237.
- Robertson, G.S., Vincent, S.R., and Fibiger, H.C. (1992). D1 and D2 dopamine receptors differentially regulate c-fos expression in striatonigral and striatopallidal neurons. *Neuroscience* 49, 285–296.
- Robins, L.N., Helzer, J.E., and Davis, D.H. (1975). Narcotic use in southeast Asia and afterward. An interview study of 898 Vietnam returnees. *Arch. Gen. Psychol.* 32, 955–961.
- Robinson, S.W. (1997). Interactions of dopamine receptors with G-proteins. In *The Dopamine Receptors*, K.A. Neve and R.L. Neve, eds. (Totowa, NJ: Humana Press), pp. 137–164.
- Robinson, T.E., and Becker, J.B. (1986). Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res.* 396, 157–198.
- Robinson, T.E., and Berridge, K.C. (1993). The neural basis of drug craving: an incentive-sensitization theory of addiction. *Brain Res. Brain Res. Rev.* 18, 247–291.
- Robinson, T.E., and Kolb, B. (1997). Persistent structural modifications in nucleus accumbens and prefrontal cortex neurons produced by previous experience with amphetamine. *J. Neurosci.* 17, 8491–8497.
- Robinson, T.E., Becker, J.B., and Presty, S.K. (1982). Long-term facilitation of amphetamine-induced rotational behavior and striatal dopamine release produced by a single exposure to amphetamine: sex differences. *Brain Res.* 253, 231–241.
- Rolls, E.T. (1996). The orbitofrontal cortex. *Philos. Trans. R. Soc. Lond. B Biol. Sci.* 351, 1433–1444.
- Roseboom, P.H., and Gnegy, M.E. (1989). Acute in vivo amphetamine produces a homologous desensitization of dopamine receptor-coupled adenylate cyclase activities and decreases agonist binding to the D1 site. *Mol. Pharmacol.* 35, 139–147.
- Rouge-Pont, F., Piazza, P.V., Kharouby, M., Le Moal, M., and Simon, H. (1993). Higher and longer stress-induced increase in dopamine concentrations in the nucleus accumbens of animals predisposed to amphetamine self-administration. A microdialysis study. *Brain Res.* 602, 169–174.
- Rouge-Pont, F., Deroche, V., Le Moal, M., and Piazza, P.V. (1998). Individual differences in stress-induced dopamine release in the nucleus accumbens are influenced by corticosterone. *Eur. J. Neurosci.* 10, 3903–3907.
- Sahakian, B.J., Robbins, T.W., Morgan, M.J., and Iversen, S.D. (1975). The effects of psychomotor stimulants on stereotypy and locomotor activity in socially-deprived and control rats. *Brain Res.* 84, 195–205.
- Saint-Cyr, J.A., Taylor, A.E., and Lang, A.E. (1988). Procedural learning and neostriatal dysfunction in man. *Brain* 111, 941–959.
- Sala, M., Braidà, D., Colombo, M., Groppetti, A., Sacco, S., Gori, E., and Parenti, M. (1995). Behavioral and biochemical evidence of opioidergic involvement in cocaine sensitization. *J. Pharmacol. Exp. Ther.* 274, 450–457.
- Salamone, J.D. (1996). The behavioral neurochemistry of motivation: methodological and conceptual issues in studies of the dynamic activity of nucleus accumbens dopamine. *J. Neurosci. Methods* 64, 137–149.
- Salamone, J.D., Cousins, M.S., and Snyder, B.J. (1997). Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. *Neurosci. Biobehav. Rev.* 21, 341–359.
- Schiff, S.R. (1982). Conditioned dopaminergic activity. *Biol. Psychiatry* 17, 135–154.
- Schmidt, U., Beyer, C., Oestreicher, A.B., Reiser, I., Schilling, K., and Pilgrim, C. (1996). Activation of dopaminergic D1 receptors promotes morphogenesis of developing striatal neurons. *Neuroscience* 74, 453–460.
- Schmidt, U., Pilgrim, C., and Beyer, C. (1998). Differentiative effects of dopamine on striatal neurons involve stimulation of the cAMP/PKA pathway. *Mol. Cell. Neurosci.* 11, 9–18.
- Schultz, W. (1998a). The phasic reward signal of primate dopamine neurons. *Adv. Pharmacol.* 42, 686–690.
- Schultz, W. (1998b). Predictive reward signal of dopamine neurons. *J. Neurophysiol.* 80, 1–27.
- Schultz, W., Apicella, P., and Ljungberg, T. (1993). Responses of monkey dopamine neurons to reward and conditioned stimuli during successive steps of learning a delayed response task. *J. Neurosci.* 13, 900–913.
- Schultz, W., Apicella, P., Romo, R., and Scarnati, E. (1995a). Context-dependent activity in primate striatum reflecting past and future behavioral events. In *Models of Information Processing in the Basal Ganglia*, J.C. Houk, J.L. Davis, and D.G. Beiser, eds. (Cambridge, MA: MIT Press), pp. 11–27.
- Schultz, W., Romo, R., Ljungberg, T., Mirenovic, J., Hollerman, J.R., and Dickinson, A. (1995b). Reward-related signals carried by dopamine neurons. In *Models of Information Processing in the Basal Ganglia*, J.C. Houk, J.L. Davis, and D.G. Beiser, eds. (Cambridge, MA: MIT Press), pp. 232–248.
- Schultz, W., Dayan, P., and Montague, P.R. (1997). A neural substrate of prediction and reward. *Science* 275, 1593–1599.
- Schwab, R.S., and Zieper, I. (1965). Effects of mood, motivation,

- stress and alertness on the performance in Parkinson's disease. *Psychiatr. Neurol.* 150, 345–357.
- Segal, D.S., and Kuczenski, R. (1992a). In vivo microdialysis reveals a diminished amphetamine-induced DA response corresponding to behavioral sensitization produced by repeated amphetamine pretreatment. *Brain Res.* 571, 330–337.
- Segal, D.S., and Kuczenski, R. (1992b). Repeated cocaine administration induces behavioral sensitization and corresponding decreased extracellular dopamine responses in caudate and accumbens. *Brain Res.* 577, 351–355.
- Self, D.W., and Nestler, E.J. (1995). Molecular mechanisms of drug reinforcement and addiction. *Annu. Rev. Neurosci.* 18, 463–495.
- Self, D.W., Barnhart, W.J., Lehman, D.A., and Nestler, E.J. (1996). Opposite modulation of cocaine-seeking behavior by D1- and D2-like dopamine receptor agonists. *Science* 271, 1586–1589.
- Sgambato, V., Pages, C., Rogard, M., Besson, M.J., and Caboche, J. (1998a). Extracellular signal-regulated kinase (ERK) controls immediate early gene induction on corticostriatal stimulation. *J. Neurosci.* 18, 8814–8825.
- Sgambato, V., Vanhoutte, P., Pages, C., Rogard, M., Hipskind, R., Besson, M.J., and Caboche, J. (1998b). In vivo expression and regulation of Elk-1, a target of the extracellular-regulated kinase signaling pathway, in the adult rat brain. *J. Neurosci.* 18, 214–226.
- Shaham, Y., and Stewart, J. (1995). Stress reinstates heroin-seeking in drug-free animals: an effect mimicking heroin, not withdrawal. *Psychopharmacology (Berl.)* 119, 334–341.
- Shiffman, S., Paty, J.A., Gnys, M., Kassel, J.A., and Hickcox, M. (1996). First lapses to smoking: within-subjects analysis of real-time reports. *J. Consult. Clin. Psychol.* 64, 366–379.
- Shippenberg, T.S., and Heidbreder, C. (1995). Sensitization to the conditioned rewarding effects of cocaine: pharmacological and temporal characteristics. *J. Pharmacol. Exp. Ther.* 273, 808–815.
- Shippenberg, T.S., and Rea, W. (1997). Sensitization to the behavioral effects of cocaine: modulation by dynorphin and kappa-opioid receptor agonists. *Pharmacol. Biochem. Behav.* 57, 449–455.
- Shippenberg, T.S., Bals-Kubik, R., and Herz, A. (1993). Examination of the neurochemical substrates mediating the motivational effects of opioids: role of the mesolimbic dopamine system and D-1 vs. D-2 dopamine receptors. *J. Pharmacol. Exp. Ther.* 265, 53–59.
- Silva, A.J., Kogan, J.H., Frankland, P.W., and Kida, S. (1998). CREB and memory. *Annu. Rev. Neurosci.* 21, 127–148.
- Silverman, P.B. (1991). Sensitization and conditioned rotation: apomorphine, quinpirole and SKF-38393 compared. *Neuroreport* 2, 669–672. Erratum: *Neuroreport* 3(3), 1992.
- Silverman, P.B., and Ho, B.T. (1981). Persistent behavioural effect in apomorphine in 6-hydroxydopamine-lesioned rats. *Nature* 294, 475–477.
- Spanagel, R., Herz, A., and Shippenberg, T.S. (1992). Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. *Proc. Natl. Acad. Sci. USA* 89, 2046–2050.
- Spangler, R., Ho, A., Zhou, Y., Maggos, C.E., Yuferov, V., and Kreek, M.J. (1996). Regulation of kappa opioid receptor mRNA in the rat brain by "binge" pattern cocaine administration and correlation with preprodynorphin mRNA. *Brain Res. Mol. Brain Res.* 38, 71–76.
- Stein, E.A., and Fuller, S.A. (1993). Cocaine's time action profile on regional cerebral blood flow in the rat. *Brain Res.* 626, 117–126.
- Steiner, H., and Gerfen, C.R. (1996). Dynorphin regulates D1 dopamine receptor-mediated responses in the striatum: relative contributions of pre- and postsynaptic mechanisms in dorsal and ventral striatum demonstrated by altered immediate-early gene induction. *J. Comp. Neurol.* 376, 530–541.
- Stern, E.A., Jaeger, D., and Wilson, C.J. (1998). Membrane potential synchrony of simultaneously recorded striatal spiny neurons in vivo. *Nature* 394, 475–478.
- Stewart, J. (1992). Neurobiology of conditioning to drugs of abuse. *Ann. NY Acad. Sci.* 654, 335–346.
- Stewart, J., de Wit, H., and Eikelboom, R. (1984). Role of unconditioned and conditioned drug effects in the self-administration of opiates and stimulants. *Psychol. Rev.* 91, 251–268.
- Striplin, C.D., and Kalivas, P.W. (1993). Robustness of G protein changes in cocaine sensitization shown with immunoblotting. *Synapse* 14, 10–15.
- Surmeier, D.J., and Kitai, S.T. (1993). D1 and D2 dopamine receptor modulation of sodium and potassium currents in rat neostriatal neurons. *Prog. Brain Res.* 99, 309–324.
- Sutton, R.S., and Barto, A.G. (1998). *Reinforcement Learning* (Cambridge, MA: MIT Press).
- Terwilliger, R.Z., Beitner-Johnson, D., Sevarino, K.A., Crain, S.M., and Nestler, E.J. (1991). A general role for adaptations in G-proteins and the cyclic AMP system in mediating the chronic actions of morphine and cocaine on neuronal function. *Brain Res.* 548, 100–110.
- Tiberi, M., Nash, S.R., Bertrand, L., Lefkowitz, R.J., and Caron, M.G. (1996). Differential regulation of dopamine D1A receptor responsiveness by various G protein-coupled receptor kinases. *J. Biol. Chem.* 271, 3771–3778.
- Tiffany, S.T. (1990). A cognitive model of drug urges and drug-use behavior: role of automatic and nonautomatic processes. *Psychol. Rev.* 97, 147–168.
- Tirelli, E., and Terry, P. (1998). Amphetamine-induced conditioned activity and sensitization: the role of habituation to the test context and the involvement of Pavlovian processes. *Behav. Pharmacol.* 9, 409–419.
- Tzschenke, T.M. (1998). Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. *Prog. Neurobiol.* 56, 613–672.
- Ungerstedt, U. (1971). Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta Physiol. Scand. Suppl.* 367, 95–122.
- Vezina, P. (1993). Amphetamine injected into the ventral tegmental area sensitizes the nucleus accumbens dopaminergic response to systemic amphetamine: an in vivo microdialysis study in the rat. *Brain Res.* 605, 332–337.
- Vezina, P. (1996). D1 dopamine receptor activation is necessary for the induction of sensitization by amphetamine in the ventral tegmental area. *J. Neurosci.* 16, 2411–2420.
- Vezina, P., and Stewart, J. (1990). Amphetamine administered to the ventral tegmental area but not to the nucleus accumbens sensitizes rats to systemic morphine: lack of conditioned effects. *Brain Res.* 516, 99–106.
- Vgontzas, A.N., Kales, A., and Bixler, E.O. (1995). Benzodiazepine side effects: role of pharmacokinetics and pharmacodynamics. *Pharmacology* 51, 205–223.
- Viaud, M.D., and White, N.M. (1989). Dissociation of visual and olfactory conditioning in the neostriatum of rats. *Behav. Brain Res.* 32, 31–42.
- Vincent, S.R., Sebben, M., Dumuis, A., and Bockaert, J. (1998). Neurotransmitter regulation of MAP kinase signaling in striatal neurons in primary culture. *Synapse* 29, 29–36.
- Wang, J.Q., Smith, A.J., and McGinty, J.F. (1995). A single injection of amphetamine or methamphetamine induces dynamic alterations in c-fos, zif/268 and preprodynorphin messenger RNA expression in rat forebrain. *Neuroscience* 68, 83–95.
- Weiss, F., Markou, A., Lorang, M.T., and Koob, G.F. (1992). Basal extracellular dopamine levels in the nucleus accumbens are decreased during cocaine withdrawal after unlimited-access self-administration. *Brain Res.* 593, 314–318.
- White, N.M. (1988). Effect of nigrostriatal dopamine depletion on the post-training, memory-improving action of amphetamine. *Life Sci.* 43, 7–12.
- White, N.M. (1989). Reward or reinforcement: what's the difference? *Neurosci. Biobehav. Rev.* 13, 181–186.
- White, N.M. (1996). Addictive drugs as reinforcers: multiple partial actions on memory systems. *Addiction* 91, 921–965.
- White, N.M. (1997). Mnemonic functions of the basal ganglia. *Curr. Opin. Neurobiol.* 7, 164–169.
- White, N.M., and Milner, P.M. (1992). The psychobiology of reinforcers. *Annu. Rev. Psychol.* 43, 443–471.

- Wickens, J., and Kotter, R. (1995). Cellular models of reinforcement. In *Models of Information Processing in the Basal Ganglia*, J.C. Houk, J.L. Davis, and D.G. Beiser, eds. (Cambridge, MA: MIT Press), pp. 187–204.
- Wickens, J.R., Begg, A.J., and Arbuthnott, G.W. (1996). Dopamine reverses the depression of rat corticostriatal synapses which normally follows high-frequency stimulation of cortex in vitro. *Neuroscience* 70, 1–5.
- Wise, R.A. (1996). Addictive drugs and brain stimulation reward. *Annu. Rev. Neurosci.* 19, 319–340.
- Wise, R.A., and Bozarth, M.A. (1987). A psychomotor stimulant theory of addiction. *Psychol. Rev.* 94, 469–492.
- Wise, S.P., Murray, E.A., and Gerfen, C.R. (1996). The frontal cortex-basal ganglia system in primates. *Crit. Rev. Neurobiol.* 10, 317–356.
- Wolf, M.E. (1998). The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. *Prog. Neurobiol.* 54, 679–720.
- Wolf, M.E., and Khansa, M.R. (1991). Repeated administration of MK-801 produces sensitization to its own locomotor stimulant effects but blocks sensitization to amphetamine. *Brain Res.* 562, 164–168.
- Wolterink, G., Phillips, G., Cador, M., Donselaar-Wolterink, I., Robbins, T.W., and Everitt, B.J. (1993). Relative roles of ventral striatal D1 and D2 dopamine receptors in responding with conditioned reinforcement. *Psychopharmacology (Berl.)* 110, 355–64.
- Woolverton, W.L. (1992). Cocaine self-administration: pharmacology and behavior. *NIDA Res. Monogr.* 124, 189–202.
- Xing, J., Ginty, D.D., and Greenberg, M.E. (1996). Coupling of the RAS-MAPK pathway to gene activation by RSK2, a growth factor-regulated CREB kinase. *Science* 273, 959–963.
- Xu, M., Hu, X.T., Cooper, D.C., Moratalla, R., Graybiel, A.M., White, F.J., and Tonegawa, S. (1994). Elimination of cocaine-induced hyperactivity and dopamine-mediated neurophysiological effects in dopamine D1 receptor mutant mice. *Cell* 79, 945–955.
- Yamagata, K., Kaufmann, W.E., Lanahan, A., Papapavlou, M., Barnes, C.A., Andreasson, K.I., and Worley, P.F. (1994). Egr3/Pilot, a zinc finger transcription factor, is rapidly regulated by activity in brain neurons and colocalizes with egr1/zif268. *Learn. Mem.* 1, 140–152.
- Young, S.T., Porrino, L.J., and Iadarola, M.J. (1991). Cocaine induces striatal c-fos-immunoreactive proteins via dopaminergic D1 receptors. *Proc. Natl. Acad. Sci. USA* 88, 1291–1295.
- Zhang, X.F., Hu, X.T., and White, F.J. (1998). Whole-cell plasticity in cocaine withdrawal: reduced sodium currents in nucleus accumbens neurons. *J. Neurosci.* 18, 488–498.
- Zhou, Q.Y., and Palmiter, R.D. (1995). Dopamine-deficient mice are severely hypoactive, adipsic, and aphagic. *Cell* 83, 1197–1209.