Neuron, Vol. 44, 161–179, September 30, 2004, Copyright ©2004 by Cell Press

Memory and Addiction: Shared Neural Circuitry and Molecular Mechanisms

Review

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An important conceptual advance in the past decade has been the understanding that the process of drug addiction shares striking commonalities with neural plasticity associated with natural reward learning and memory. Basic mechanisms involving dopamine, glutamate, and their intracellular and genomic targets have been the focus of attention in this research area. These two neurotransmitter systems, widely distributed in many regions of cortex, limbic system, and basal ganglia, appear to play a key integrative role in motivation, learning, and memory, thus modulating adaptive behavior. However, many drugs of abuse exert their primary effects precisely on these pathways and are able to induce enduring cellular alterations in motivational networks, thus leading to maladaptive behaviors. Current theories and research on this topic are reviewed from an integrative systems perspective, with special emphasis on cellular, molecular, and behavioral aspects of dopamine D-1 and glutamate NMDA signaling, instrumental learning, and drug cue conditioning.

Introduction

At some point in our evolutionary history, humans began to use psychoactive drugs. The use of the coca plant can be traced back at least 7000 years, and there is archeological evidence that the betal nut (containing arecoline, a muscarinic agonist) was chewed 11,000 years ago in Thailand and 13,000 years ago in Timor (Sullivan and Hagen, 2002). Indeed, there is a close evolutionary relationship between plant alkaloids and brain neurotransmitters; nervous systems of both vertebrates and invertebrates contain chemical transmitters and receptors that bear remarkable resemblance to the structure of plant-derived drug substances. Cannabinoids, nicotine, cocaine, and opiates act on brain protein substrates that specifically bind these compounds; alcohol also indirectly affects these substrates. In humans, these and other drugs of abuse are able to induce feelings of positive emotion or pleasure and to relieve negative emotional states such as anxiety and depression (Nesse and Berridge, 1997). However, in vulnerable individuals, repeated use of psychoactive drugs carries the risk of dependence and addiction, characterized by loss of control over drug-seeking behavior and serious adverse consequences (Koob et al., 2004; Volkow and Fowler, 2000). The puzzle of addiction has captured the attention of clinicians, psychologists, and pharmacologists for many decades—but it is only in recent years that great advances in molecular, cognitive, and behavioral neuroscience have provided an integrative framework for approaching this problem.

Perhaps the most significant conceptual advance constitutes the growing understanding that the process of addiction shares striking similarities with neural plasticity associated with natural reward learning and memory. Specifically, basic cellular mechanisms involving dopamine, glutamate, and their intracellular and genomic targets have been the focus of intense research in both the areas of reward-related learning and addiction. These two neurotransmitter systems, widely distributed in many regions of cortex, limbic system, and basal ganglia, appear to play a key integrative role in motivation, learning, and memory. It is currently believed that coordinated molecular signaling of dopaminergic and glutamatergic systems, particularly through dopamine D-1 and glutamate *N*-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, is a critical event in the induction of intracellular transcriptional and translational cascades, leading to adaptive changes in gene expression and synaptic plasticity, the reconfiguring of neural networks, and ultimately behavior. Normally, the brain uses these mechanisms to optimize responses in organisms that ultimately enhance survival; it is clearly highly adaptive to learn where or under what circumstances food is found or danger encountered and to alter behavioral actions accordingly. Many drugs of abuse exert their primary effects precisely on these pathways and are apparently able to induce very long-term, perhaps even permanent, alterations in motivational networks, thus leading to maladaptive behaviors (Berke and Hyman, 2000; Hyman and Malenka, 2001; Kelley and Berridge, 2002; Koob and Le Moal, 1997).

In this review, I aim to focus primarily on dopaminergic and glutamatergic neuronal networks and their interactions. I first consider the problem of biological motivation and its neural underpinnings in an evolutionary context, emphasizing the early phylogenetic development of molecular systems suited to plasticity. Current research on dopamine and glutamate-coded systems in relation to synaptic plasticity and adaptive motor learning is then reviewed. Finally, I attempt to link these findings with related work on drugs of abuse, drawing parallels with regard to shared mechanisms between memory and addiction. In addition to illuminating basic mechanisms, work on plasticity in appetitive motivation systems has important implications for human health. Maladaptive use of drugs (addiction) and of our most vital natural reward, food (obesity), while not obviously linked in terms of etiology, nevertheless together constitute the most significant public health problems facing developed human societies in the 21st century.

An Evolutionary Framework for Plasticity in Motivational Systems

In order to understand the relationship between memory and addiction, it is first useful to consider drug use

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and the systems upon which they act from a broad evolutionary perspective. As noted above, sometime in the evolutionary development of *Homo sapiens*, individuals and cultures began to incorporate drug and alcohol use in daily life. These behaviors likely evolved from incidental exposure to compounds in wild plants while foraging. For example, archeological evidence suggests that aborigines throughout Australia made use of indigenous nicotine-containing plants for tens of thousands of years before the arrival of colonists (Sullivan and Hagen, 2002), and it is well established that native peoples in the Andean region of South America exploited the coca plant well before its cultivation over 7000 years ago (Schultes, 1987). Fructivore vertebrates have consumed low levels of alcohol for millions of years, in ripe fruit eaten by birds and mammals, and fermenting alcohol has been cultivated by human societies for over 6000 years (Dudley, 2002). Clearly, whether encountered by foraging or purposefully cultivated, psychoactive drugs are by definition reinforcing, in that behaviors will be repeated in order to obtain these substances. Drugs serving as reinforcers are not a uniquely human phenomenon. Many species, such as rats, mice, and nonhuman primates, will directly self-administer most drugs that are used or abused by humans—such as alcohol, heroin, and other opiates, cannabinoids, nicotine, cocaine, amphetamine, and caffeine. Animals will perform an operant response—for example, pressing a lever—in order to obtain an intravenous infusion of these compounds, and in some cases (such as cocaine) will self-administer the drug to the point of death, ignoring other essential rewards such as food and water (Aigner and Balster, 1978; Bozarth and Wise, 1985). It is remarkable that 5-day-old rat pups learn to prefer odors that have been associated with morphine (Kehoe and Blass, 1986); even crayfish show positive place conditioning to psychostimulants (Panksepp and Huber, 2004). Note that in all these examples, *learning* has occurred—the organism shows an adaptation in behavior that presumably reflects some level of reward value of the drug, or more precisely, the value of the state that it induces. These behavioral findings suggest not only that there are common chemical and molecular substrates that rewarding drugs access across phyla but also that a critical feature of drug-organism interaction is plasticity. Why is this so?

Before thinking about how rewarding events or drugs alter plasticity in the brain, it is useful to begin with two important premises. First, specific and phylogenetically ancient motivational systems exist in the brain and have evolved over the course of millions of years of evolution to ensure adaptation and survival. The primordial roots of motivation can be observed even in bacteria, the earliest form of life on earth. For example, *E. coli* bacteria have complex genetic machinery that spurs them toward nutrients such as sugar and away from irritants and toxins (Adler, 1966; Qi and Adler, 1989). Second, these systems are engaged by perception of environmental stimuli, that is, information, and when so engaged generate specific affective states (positive or negative emotions) that are temporary, powerful drivers and/or sustainers of behavior. Positive emotions generally serve to bring the organism into contact with potentially beneficial resources—food, water, territory, mating, or other social opportunities. Negative emotions serve to protect the organism from danger—mainly to ensure fight-or-flight responses or other appropriate defensive strategies, such as submissive behavior or withdrawal, protection of territory or kin, and avoidance of pain. Brain systems monitor the external and internal (bodily) world for signals and control the ebb and flow of these emotions. Moreover, the chemical and molecular signature for the generation of motivational states and initiation of plasticity (e.g., monoamines, G protein-coupled receptors, protein kinases, CREB) is for the most part highly conserved throughout evolution (Kelley, 2004a).

Special Purpose Motivational Systems

With regard to the first premise, the vertebrate brain contains multiple selective systems that are adapted for specific purposes, such as mating, social communication, and ingestion. Corresponding systems exist in the invertebrate brain. A neuroanatomical framework for the organization of motivational systems has recently been extensively developed, with focus on what is termed "behavioral control columns" (Swanson, 2000). Swanson proposes that very well defined and highly interconnected sets of nuclei in the hypothalamus and its brainstem extensions are devoted to the elaboration and control of specific behaviors necessary for survival: spontaneous locomotor behavior and exploration, and ingestive, defensive, and reproductive behaviors. Animals with chronic transections in which the hypothalamus is spared can more or less eat, drink, reproduce, and show defensive behaviors—whereas, if the brain is transected below the hypothalamus, the animal displays only fragments of these behaviors, enabled by motor pattern generators in the brainstem. Many complex neurochemically, anatomically, and hormonally coded systems exist to optimize survival of the individual and the species, ranging from opioids signaling distress calls in rat pups separated from their mother to sex steroids directing sexual differentiation and reproductive behavior. Thus, hunger, thirst, sex, aggression, and the need for air, water, and shelter or territory are specific motivational states that exist to goad the organism to seek the stimuli that will address its basic survival.

Motivational Systems Are Activated by Salient Stimuli, Resulting in Affective States

However, these states are not activated at all times (with the exception of breathing); only in response to particular conditions, situations, or needs will motivational circuits be utilized, leading to the second premise—that these pathways are activated by specific environmental (internal or external) stimuli or sensory conditions and are amplified and energized by *affect* or *emotion*. It has been postulated that motivation is the "*potential*" for behavior that is built into a system of behavioral control (Buck, 1999). Emotions or affective states are the *readout* of these special purpose systems when activated, that is, the *manifestation* of the potential. For example, all organisms have instinctive, built-in mechanisms for defensive behavior in the face of threat or danger; when threat is present, the systems are activated and species-species defensive behavior ensues. Thus, neural and chemical systems exist for

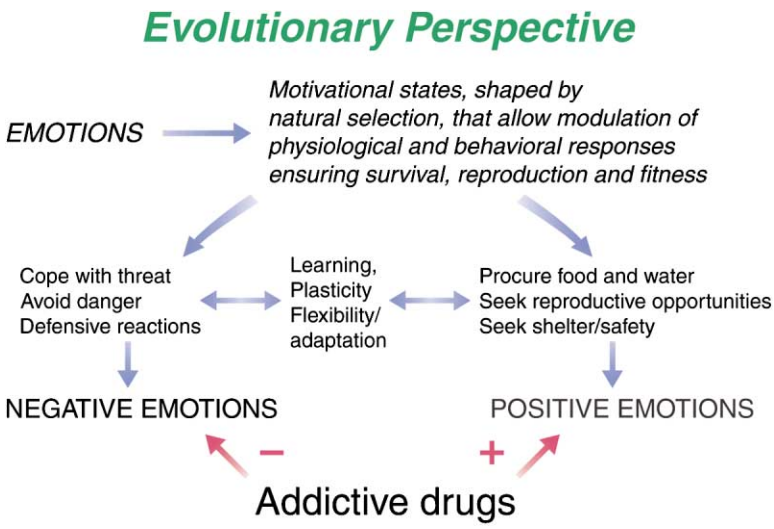

Figure 1. An Evolutionary Framework for Understanding the Function of Motivational-Emotional Systems, as Discussed in the Text

Drugs with addictive potential can act on positive and negative emotional states and induce acute subjective emotional effects as well as long-term neuroadaptations in core motivational systems. (Based on ideas discussed in Nesse and Berridge, 1997, with permission.)

ingestion, aggression, and self-defense, but these are normally only manifested, or "moved out" (the Latin root of the word emotion), under appropriate conditions. This premise is important for understanding addiction, because drugs of abuse exert short-lived effects on emotion (e.g., heroin or cocaine inducing euphoria, alcohol or benzodiazepines relieving anxiety, nicotine improving attention) but additionally appear to have profound long-term neuroadaptive effects on the resting state of core motivational systems and their sensitivity to perturbation. A schematic view of these ideas, also discussed by Nesse and Berridge (1997) is shown in Figure 1.

Brain Circuitry Involved in Memory and Addiction

The foregoing account suggests that there are specific brain networks that subserve motivation and emotions and that both function and adaptation (plasticity) within these networks are enabled by extracellular and intracellular molecular signaling. In recent decades, knowledge concerning these networks has advanced at a rapid pace in terms of the detailed understanding of their functional organization, connectivity, neurochemical and neurohumoral integration, molecular biology, and role in cognition and behavior. The purpose of this section is to provide a very condensed overview of the key elements and basic organization of these networks, with particular focus on brain regions and pathways that are commonly implicated in appetitive learning and drug addiction. A number of more in-depth excellent reviews of anatomy related to motivated behavior exist, to which the reader is referred for more detailed information as well as theoretical implications of brain neuroarchitecture (Risold et al., 1997; Swanson, 2000). The underlying theme is that, through evolution, progressively increasing anatomical and molecular complexity of corticothalamostriatal circuitry enabled greater control and more complex interactions with hard-wired hypothalamic-brainstem circuits (the "behavioral control columns," or special purpose systems). Because of the rich plasticity of cortex and associated areas such as striatum, mammals are capable of extraordinarily flexible motivated behavior and, as an evolutionary side effect as it were, are tuned to be highly sensitive to drugs that activate these systems. Figure 2 provides a diagram of these relevant neural systems.

Reciprocal Communication between Subcortical Special Purpose Systems and the Expanded Neocortex

Central to this basic model of motivated behavior is appreciation of the main inputs to these hypothalamic systems, the features of its organization with regard to other major brain regions, and its targets (see Figure 2). As elaborated above, motivational-emotional systems are triggered into action by specific signals—energy deficits, osmotic imbalance, olfactory cues, threatening stimuli—that impinge on the system and initiate (as well as terminate) activity in specific brain pathways, thereby effecting responses. In higher mammals, neural and chemical signals from sensory systems reach the behavioral control column in multiple ways, through both anatomical and neuroendocrine routes. However, a second critically important input to the behavioral control column is from the cerebral cortex, including massive direct and indirect afferents from such areas as hippocampus, amygdala, prefrontal cortex, striatum, and pallidum. Via these inputs, the motivational core has access to the highly complex computational, cognitive, and associative abilities of the cerebral cortex. For example, the hippocampus is a brain structure that plays a key role in associative memory networks, the encoding and consolidation of novel environmental information, and in the learning of relational information between environmental stimuli (Morris et al., 2003). Hippocampal inputs from subiculum innervate the caudal aspect of the column involved in foraging and provide key spatial information to control navigational strategies; place cells are found in regions of the mammillary bodies as well as hippocampus, anterior thalamus, and striatum (Blair et al., 1998; Ragozzino et al., 2001). The amygdala's role in reward valuation and learning (Cardinal et al., 2002; Schoenbaum et al., 2000), particularly in its lateral and basolateral aspects (that are intimately connected with the frontotemporal association cortex) can influence the

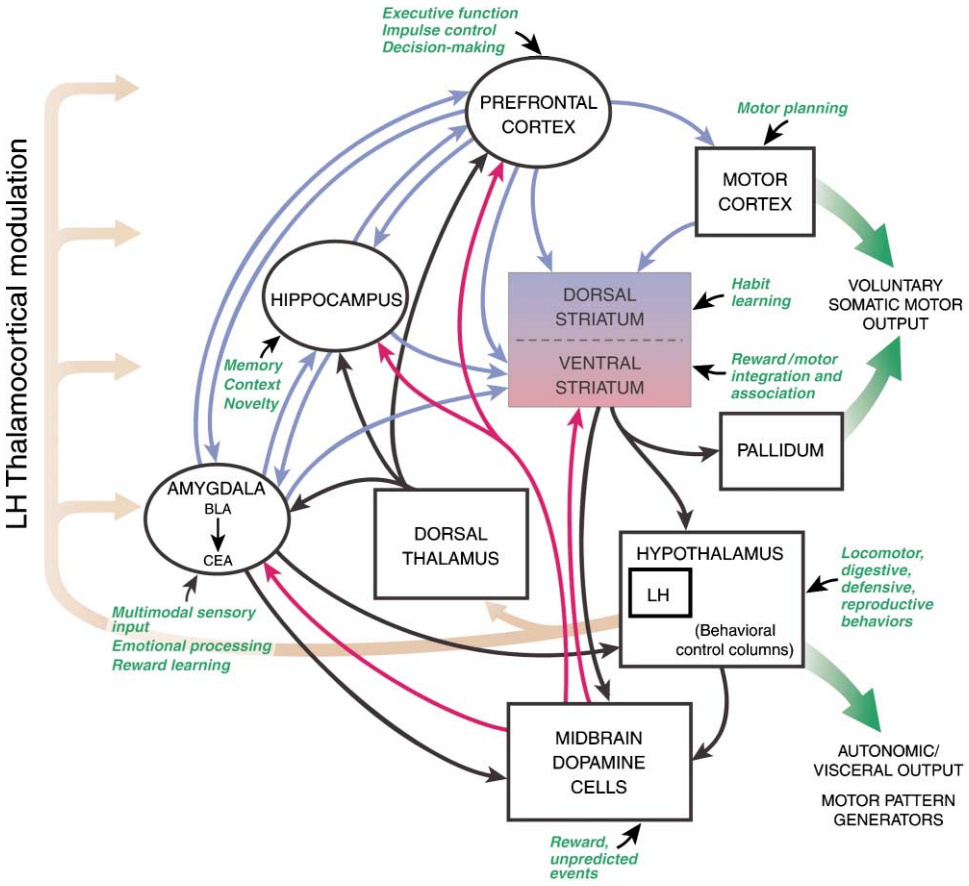

Figure 2. A Schematic View of Brain Circuitry Involved in Learning, Memory, and Addiction

Pathways coded by glutamate as the main neurotransmitter are shown in blue, while dopamine pathways are shown in red. Tan lines arising from the lateral hypothalamus (LH) indicate widespread direct and indirect projections from hypothalamus to neocortex and forebrain limbic structures, as discussed in Swanson (2000).

lateral hypothalamus, a key reward and arousal integrative node within the hypothalamus. Indeed, recent studies have supported this notion; disconnection of the amygdalo-lateral hypothalamic pathway does not abolish food intake per se, but alters subtle assessment of the comparative value of the food based on learning or sensory cues (Petrovich et al., 2002). In some of our recent work, inactivation of the amygdala prevents expression of ingestive behavior mediated by striatal-hypothalamic circuitry (Will et al., 2004). The prefrontal cortex is also a critical part of the motivational network, mediating executive functions, working memory, and response guidance; in addition to massive reciprocal connections with many other cortical regions, it too projects widely to the hypothalamus (Floyd et al., 2001). In addition to influencing hypothalamo-brainstem pathways, all of these key cortical regions—hippocampus, amygdala, and prefrontal cortex—project extensively to the striatum, using glutamate as the primary neurotransmitter (refer to Figure 2). The thalamus also sends dense glutamate-coded projections to all of neocortex and striatum. All of these regions possess high levels of the main subtypes of glutamate receptors—NMDA, AMPA/kainate, and metabotropic receptors. Since activity-dependent, glutamate-coded synaptic modification is the main model for long-term plasticity in the nervous system (Malenka and Nicoll, 1999), it is not surprising that glutamatergic activity in these complex networks can fundamentally alter the behavior of the network and of the organism, as will be elaborated below.

An additional key component to the plasticity inherent in these circuits is dopamine (DA). Dopaminergic neurons are located in the midbrain, within the ventral tegmental area and substantia nigra. They send their axons through the medial forebrain bundle and innervate wide regions within the systems elaborated above—primarily striatum, prefrontal cortex, amygdala, and hippocampus. Dopaminergic reception and the intracellular influence of DA signaling are mediated through the two major subtypes of G protein-coupled DA receptors, the D-1 family (D-1 and D-5) and D-2 family (D-2/3 and D-4). Other amines, such as serotonin and norepinephrine, that innervate these forebrain regions also clearly have an important role in synaptic plasticity; however, since the development of major theories of addiction and motivation have been based on the role of dopamine, the present discussion will be limited to this system's interaction with glutamate. An additional critical structural feature pertinent to the present argument is colocalization of dopaminergic and glutamatergic terminals in close proximity on the same dendritic spines (Sesack and Pickel, 1990; Smith and Bolam, 1990; Totterdell and

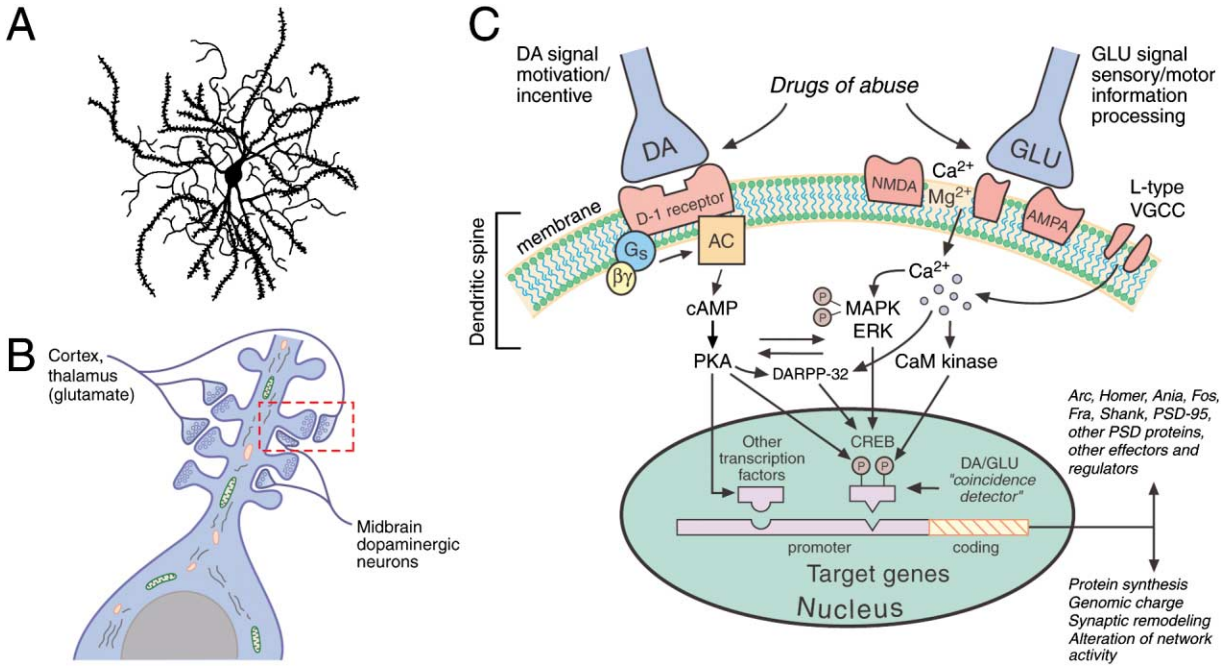

Figure 3. Axons Containing Glutamate and Dopamine Converge onto Dendritic Spines within Striatal and other Corticolimbic Regions

(A) An example of a striatal medium-sized spiny neuron from the striatum. A typical cell has extensive dendritic and axonal arborizations, and the dendrites are characterized by numerous protrusions (spines).

(B) Close-up schematic view of a dendrite that receives dopaminergic input from the midbrain and glutamatergic input from cortex or thalamic regions synapsing in close apposition on the same dendritic spine. This arrangement has been shown for medium spiny neurons but is thought to exist for neurons in other key regions (such as the pyramidal cells of prefrontal cortex and magnocellualar neurons of basolateral amygdala). (Adapted from Smith and Bolam, 1990, with permission.)

(C) Cellular convergence of dopamine (DA) and glutamate (GLU) signals in medium spiny neurons. This convergence leads to activation of intracellular transduction mechanisms, induction of regulatory transcription factors, and, ultimately, long-term changes in cellular plasticity involving a myriad of postsynaptic density proteins, as discussed in the text. (Adapted from Berke and Hyman, 2000, with permission.)

Smith, 1989). An example of this arrangement in a striatal medium spiny neuron is shown in Figure 3.

The potential for cellular plasticity in cortical and striatal regions is greatly expanded compared to brainstem and hypothalamic systems. Indeed, gene expression patterns can reveal this expansion in evolutionary development. Plasticity-related genes, such as those encoding protein kinases, CREB, immediately early genes, and postsynaptic density proteins, are enriched in corticostriatal circuits. An example from our material, shown in Figure 4, shows that the cortex and striatum, compared with diencephalic structures, are rich in the pro-

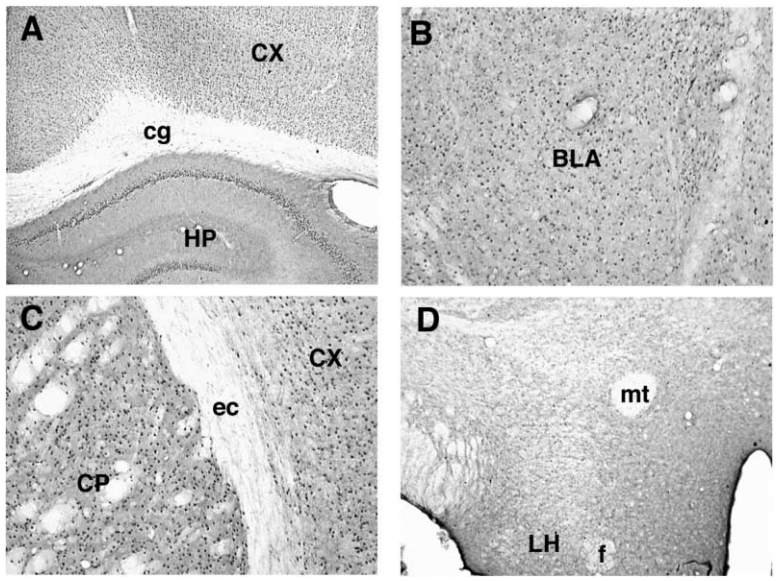

Figure 4. Expression of the Immediate Early Gene *zif268* Is High in Corticostriatal Regions

Immunostained sections of rat brain showing expression of the immediate early gene *zif268* (also known as NGFI-A), which has been implicated in cellular plasticity. *Zif268* is regulated by dopamine and glutamate and may mediate long-term alterations underlying learning and memory. Each black dot represents nuclear staining in a cell. Note strong expression in cortical, hippocampal, striatal, and amygdala areas (A–C) and much weaker expression in diencephalic areas (D). This gene and others like it may be preferentially expressed in corticolimbic and striatal circuits, which participate in behavioral plasticity. (From unpublished material.)

tein product of the gene *zif268* (also known as *NGFI-A*), a transcription factor that may be involved in glutamate- and dopamine-mediated plasticity (Keefe and Gerfen, 1996; Wang and McGinty, 1996). Thus, the phylogenetically most recently developed and expanded brain region (neocortex) is intricately wired to communicate with and influence the ancestral behavioral control columns and is capable of complex cellular plasticity based on experience.

As the origin of the term would suggest, motivation must ultimately result in behavioral actions. Actions occur when the motor outputs of these systems are signaled—whether via autonomic output (heart rate, blood pressure), visceroendocrine output (cortisol, adrenaline, release of sex hormones), or somatomotor output (e.g., locomotion, instrumental behavior, facial/oral responses, defensive or mating postures). During coordinated expression of context-dependent motivated behaviors, various combinations of these effector systems are utilized. Indeed, all the behavioral control columns project directly to these motor effector routes (see Figure 2). However, in mammals, conscious, voluntary control of actions is further enabled by superimposition of cortical systems on the basic sensory-reflexive networks. Moreover, there is extensive reciprocal communication between the cerebral hemispheres and motor effector networks. An additional major principle for organization of the behavioral control columns is that they project massively *back* to the cerebral cortex/voluntary control system directly or indirectly via the dorsal thalamus, as shown in Figure 2 (Risold et al., 1997; Swanson, 2000). For example, nearly the entire hypothalamus projects to the dorsal thalamus, which in turn projects to widespread regions of neocortex. Moreover, recently characterized neuropeptide-coded systems have revealed that orexin/hypocretin- and melanin concentrating hormone-containing cells within the lateral hypothalamus (which itself has intimate access to endocrine, energy balance, and autonomic regions) project directly to widespread regions within neocortex, amygdala, hippocampus, and ventral striatum and may be very important for behavioral state regulation and arousal (Baldo et al., 2003; Espana et al., 2001; Peyron et al., 1998). Figure 5 shows examples of hypothalamically innervated forebrain regions from our work (Baldo et al., 2003). This feedforward hypothalamic projection to the cerebral hemispheres is an extremely important anatomical fact for grasping the notions elaborated above, that intimate access of associative and cognitive cortical areas to basic motivational networks enables the generation of emotions or the manifestation of "motivational potential." Thus, in the primate brain, this substantial reciprocal interaction between phylogenetically old behavioral control columns and the more recently developed cortex subserving higher order processes such as language and cognition has enabled a two-way street for the control of motivational states. Not only can circuits controlling voluntary motor actions, decision making, and executive function influence and modulate basic drives, but activity within the core motivational networks can impart emotional coloring to conscious processes and bias them in ways not readily accessible to the conscious mind. This idea, instantiated in certain theories of addiction that emphasize habit and automatic mechanisms

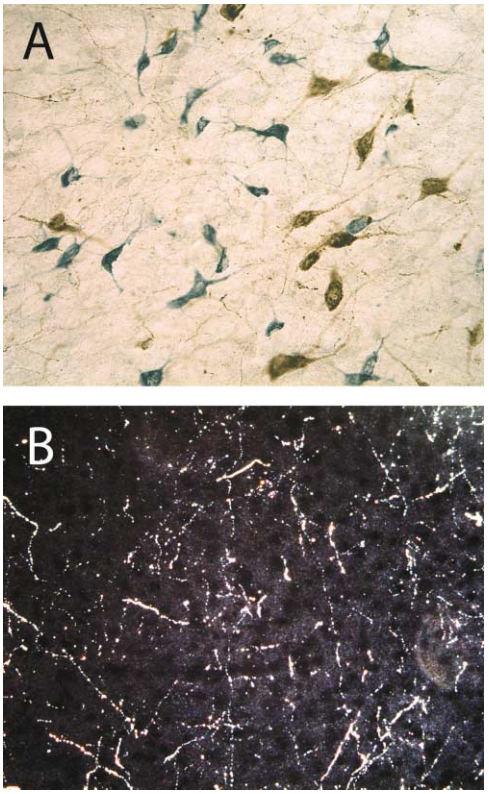

Figure 5. Example of Communication between Diencephalic Structures and Neocortex

(A) Staining for two neuropeptides, orexin/hypocretin (brown) and melanin concentrating hormone (blue), reveals many clusters of immunopositive cells within the lateral hypothalamus of the rat. Many of these cells project to widespread forebrain regions involved in plasticity, such as the medial prefrontal cortex shown in (B). The dark-field view shows numerous fibers in the medial wall of the cortex. (From Baldo et al., 2003).

(e.g., Everitt et al., 2001; Tiffany and Conklin, 2000), may be key for understanding human motivational drives, including those associated with addiction.

Dopamine- and Glutamate-Initiated Plasticity: From Cell to Behavior

There is now much evidence that integration of dopamine and glutamate-coded signals at the cellular and molecular level is a fundamental event underlying long-term plasticity and reward-related learning in corticostriatal networks. Indeed, the major current model suggests that cells upon which dopaminergic and glutamatergic signals impinge (e.g., medium-sized spiny neurons within striatum, or pyramidal cells within cortex) act as coincidence detectors in associative learning processes (Berke and Hyman, 2000; Horvitz, 2002; Kelley et al., 2003; Reynolds and Wickens, 2002; Sutton and Beninger, 1999). Thus, glutamate encodes relatively specific sensory, motor, and mnemonic information in cortico-cortical, corticostriatal, and thalamocortical systems, while dopamine neurons are thought to respond in a global sense to unpredicted, rewarding, or salient events in the environment (Horvitz, 2000; Schultz, 2002). The coordinated signaling of both of these systems plays an essential

role in shaping synaptic configurations and in altering the activity of neural ensembles.

Cellular Evidence

In the model systems studied, primarily the dorsal and ventral striatum and prefrontal cortex, there is convergent evidence that dopamine input, particularly stimulation of D-1 receptors, significantly alters neuronal excitability, membrane potential oscillations, and the bias of incoming excitatory signals. Pyramidal and medium spiny neurons exhibit unusual, nonlinear state transitions; normally held nearly silent by a very negative resting membrane potential mainly driven by K^+ currents ("down state"), they periodically shift state to a more depolarized "up state" where they can generate action potentials (Wilson and Kawaguchi, 1996). These up states, necessary for cell firing and transmission of coherent signals to motor output regions, are dependent on input from cerebral cortex and thalamus (O'Donnell and Grace, 1995; Wilson, 1995). These transitions are probably critical both for system stability and gating of information flow; the massive excitatory input from cortex would be toxic without the powerful inwardly rectifying potassium currents; yet summation of specific, salient excitatory signals allows selection of particular inputs that are currently most relevant. By differentially interacting with excitatory AMPA- and NMDA-mediated currents, dopamine modulates this selection process, and its postsynaptic effects largely depend on the current membrane potential. For example, D-1 receptor activation seems to have two main postsynaptic effects and also appears to be necessary for cellular plasticity and ultimately for the strengthening of the selected corticostriatal ensemble and promotion of new adaptive behavior. How does this occur?

First, D-1 receptor activation has important interactions with both K^+ channels and L-type Ca^{2+} channels. D-1 activation enhances K^+ currents near the resting potential, promoting the suppression of excitability (Pacheco-Cano et al., 1996). However, near more depolarized states, D-1 stimulation has the opposite effect; it *increases* excitability by enhancement of L-type Ca^{2+} currents (Hernandez-Lopez et al., 1997). A number of studies in striatum and cortex show that dopamine D-1 receptor activation enhances NMDA-evoked excitations (Cepeda et al., 1993, 1998; Harvey and Lacey, 1997; Wang and O'Donnell, 2001). In a study in the prefrontal cortex (PFC), Seamans and colleagues showed that D-1 agonists selectively enhance sustained (NMDA-mediated) components of the excitatory postsynaptic current; they propose that this neuromodulatory mechanism could be key in maintaining activity patterns that are essential for working memory (Seamans et al., 2001). There is additional evidence that DA signals play an influential role in enabling and maintaining up states. For example, transitions to up states in prefrontal neurons are blocked by application of a D-1 antagonist (Lewis and O'Donnell, 2000); a similar outcome was observed in striatal neurons (West and Grace, 2002).

Integration of a systems approach with electrophysiological methodologies, in both slice work and in vivo models, has revealed much about network plasticity in pathways subserving motivation and reward learning. There is considerable evidence from the past decade that stimulation of cortical inputs to striatal cells can induce LTP or LTD, depending on stimulation parameters, striatal region, and various synaptic conditions (Pennartz et al., 1993; Centonze et al., 2003; Lovinger et al., 2003; Nicola et al., 2000; Reynolds and Wickens, 2002). For example, LTP in striatal slices is dependent on the temporal coincidence of excitatory input with dopamine D-1 activation (Kerr and Wickens, 2001; Wickens et al., 1996). Stimulation of hippocampal or amygdala afferents to ventral striatum induces long-term plasticity (Mulder et al., 1997), and there is evidence of important interactions or gating between these inputs (Mulder et al., 1998). Floresco and colleagues showed that D-1 and NMDA receptors participate in this process (Floresco et al., 2001a, 2001b). The work of Jay and colleagues further underscores the role of D-1 and NMDA-dependent signaling and associated intracellular events in systems plasticity; for example, long-term potentiation in hippocampal-prefrontal synapses depends on coactivation of DA D-1 and NMDA receptors as well as intracellular cascades involving PKA (Gurden et al., 1999, 2000; Jay et al., 1995, 1998). Indeed, the hippocampus may be a crucial region for determining synaptic integration within the ventral striatum, since it seems essential for maintaining up states (and therefore spike firing) in ventral striatal neurons. Goto and O'Donnell reported that synchronous activity is observed between the ventral hippocampus and ventral striatum (Goto and O'Donnell, 2001) and that analysis of the temporal organization of synaptic convergence between prefrontal and other limbic (e.g., amygdala, hippocampus, paraventricular thalamus) inputs provides evidence for input selection and coincidence detection (Goto and O'Donnell, 2002). Taken together, this impressive array of neurophysiological data provides strong support for the notion that synaptic integration of DA- and glutamate-mediated signals, at multiple nodes in corticothalamic striatal networks, participates in shaping neural activation patterns that may reflect new learning.

Molecular and Genomic Approaches

If extracellular temporal coordination of DA and glutamate signaling allows the reconfiguration of neural networks, this signaling must be reflected in the activity of intracellular signal transduction molecules, such as cyclic AMP and protein kinases, in regulation of certain genes and in new protein synthesis at the synapse. Such activity is of course well known to be the basis for learning and memory, and in recent years, many excellent summaries have been provided (e.g., Abel and Lattal, 2001; Kandel, 2001; Morris et al., 2003). Here, I would like to focus specifically on examples of DA- and glutamate-mediated alterations in transcription and translation that may have special relevance to adaptations in corticostriatal networks. The dendritic spines of pyramidal cells in cortex and spiny neurons in ventral and dorsal striatum are thought to be the main site of synaptic modification (refer to Figure 3). As noted earlier, dopaminergic and glutamatergic axons converge on the same dendritic spines, in close proximity to each other (Sesack and Pickel, 1990; Smith and Bolam, 1990; Totterdell and Smith, 1989). The major intracellular biochemical cas-

cades underlying responses to stimulation that result in long-term plasticity are well worked out. Activity at the glutamate synapse involves activation of AMPA receptors and voltage-dependent NMDA receptors, which results in major influx of calcium through NMDA channels. Dopamine regulates expression of cAMP via interactions with D-1 and D-2 (G protein coupled) receptors. These various second messengers activate multiple kinase pathways, including PKA, PKC, CaMK, and ERK/MAP/RSK kinases, that interact with each other, control the flow of calcium, and converge on key transcriptional elements such as CREB. Phosphorylation of CREB results in CREB binding to numerous response elements in many genes, thus resulting in the induction of gene expression and synthesis of many synaptic proteins, some of which are discussed below. CREB is an interesting candidate for a coincidence detector involved in associative learning, as it is regulated by both calcium and PKA, which transduce the glutamate and dopamine signals, respectively (Silva et al., 1998). The intracellular protein DARPP-32 and one of its major targets, protein phosphatase-1 (PP-1), is also a significant regulator of the phosphorylation state of many intracellular effectors (Greengard et al., 1998). An early event in synaptic plasticity is induction of an array of immediate early genes and transcription factors, which are distributed in a widespread manner but particularly enriched in corticostriatal structures, such as c-*fos*, c-*jun*, *NGFI-B*, *homer1A*, *ania 3*, *arc*, and *zif268* (NGFI-A, *krox-24*). Induction of many of these genes has been shown to be NMDA and/or DA D-1 dependent. For example, phosphorylation of CREB and induction of early response genes is blocked by NMDA and/or D-1 antagonists (Das et al., 1997; Konradi et al., 1996; Liste et al., 1997; Steiner and Kitai, 2000; Steward and Worley, 2001b; Wang et al., 1994). Thus, many details of dopaminergic and glutamate-regulated biochemical pathways have been elucidated (as summarized in Figure 3), although how these mechanisms translate into stable synaptic change and alterations in behavior remains unknown.

Exciting recent findings provide new directions for research in bridging these challenging gaps. Some of these focus on novel interactions between glutamate and D-1 receptors. For example, in addition to convergent signals within the neuron, there appear to be direct physical interactions between D-1 and NMDA receptors. Very recent investigations in hippocampal tissue show distinct protein-protein interactions that regulate the function of NMDA receptors, with specific regions in the carboxyl tail of the D-1 receptor interacting with NR1-1a and NR2A subunits of the NMDA receptor (Lee et al., 2002; Pei et al., 2004). This interaction allows increased plasma membrane insertion of D-1 receptors, providing a potential basis for increased plasticity with DA release. In accordance with this idea, it is reported that, in cultured striatal neurons, activation of the NMDA receptor causes a redistribution of D-1 (but not D-2) receptors from the interior of the cell to the plasma membrane of dendritic spines, also resulting in a functional increase in adenylate cyclase activity (Scott et al., 2002). Remarkably, the converse may be true, at least for AMPA receptors; stimulation of D1 receptors in cultured nucleus accumbens neurons enhances surface AMPA (gluR1) receptor expression (Chao et al., 2002), a process dependent on PKA (Mangiavacchi and Wolf, 2004).

Further insight into translational changes induced by NMDA-D-1 interactions may be provided by work on protein synthesis at dendritic synaptic sites and organization of postsynaptic density proteins. Much exciting work has been carried out on dendritically targeted mRNAs such as *arc* (activity-regulated cytoskeletal protein) and CaMKII (Steward and Schuman, 2001). *Arc* is an early response gene whose mRNA is selectively targeted to recently activated synaptic sites, where it is translated and incorporated into the postsynaptic density complex (Steward and Worley, 2001a). This selective activation and targeting is blocked by local infusion of NMDA receptors antagonists (Steward and Worley, 2001b). Arc therefore appears to be one of many proteins (e.g., PSD-95, Shank, Homer, to name just a few) that are physically linked to the NMDA receptor and contribute to both function and scaffolding of newly modified synapses through control of dendritic spine formation (Sheng and Lee, 2000).

Adaptive Behavior, Learning, and Reward: From Dendrites to Decision Making

The next question focuses on how such cellular and molecular phenomena underlying glutamate-dopamine interactions could result in the adaptations in behavioral actions that reflect learning. Although there is a large literature on the cellular basis of different types of learning and memory, for the purposes of this discussion, I will focus on goal-directed instrumental learning. Instrumental learning, in which an organism learns a new motor response in order to procure a positive outcome (procurement of food when hungry, avoidance of danger or pain), is one of the most elementary forms of behavioral adaptation (Dickinson and Balleine, 1994; Rescorla, 1991). Indeed, even *Aplysia* can be trained to engage in a learned instrumental response; remarkably, dopamine is involved in the formation of this response (Brembs et al., 2002). Response learning is mediated by the development of knowledge (or a cognitive representation) of a contingency between the action and the outcome or goal (the "reward"). Much empirical work supports the idea that animals do develop knowledge of contingencies and are sensitive to changes in contingencies, motivational states, current and past value of the reinforcer, and so on (Colwill and Rescorla, 1990; Dickinson and Balleine, 1994). Pavlovian cues, stimuli, or contexts that have come to be associated with reward also have a strong impact on instrumental learning (Cardinal et al., 2002; Rescorla, 1991). Rescorla proposes that the three main elements present during instrumental learning, the response or action, the outcome or reward, and the stimulus, or context that becomes associated with the reward, all share binary associations with each other. Binary associations may become elaborated into more complex hierarchical representations in which the stimulus is associated with the response-outcome relationship (see Figure 6).

Such learning would require a system that selectively amplifies behaviors that are initially generated by stochastic processes; the adaptive value of actions must be instantiated by synaptic changes in circuits relevant

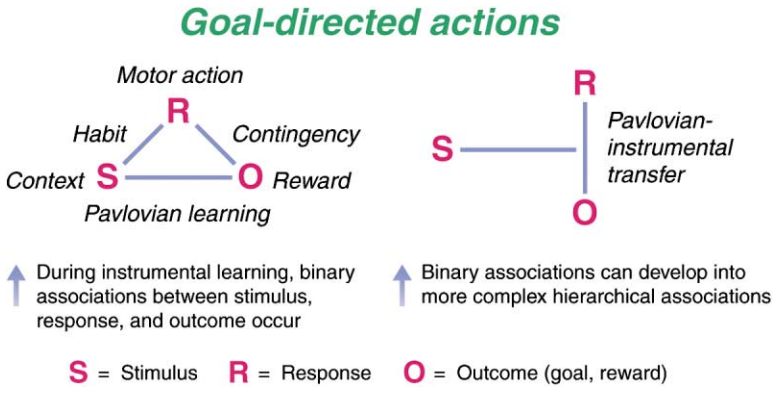

Figure 6. Instrumental Learning Involves Multiple Relationships between Stimuli, Motor Responses, and Rewards

(A) Binary associations are learned during instrumental training, between stimulus (S) and response (R), between response and outcome (O), and between stimulus and outcome. (B) It is postulated that binary associations may become elaborated into more complex hierarchical representations in which the stimulus is associated with the response-outcome relationship. (Based on ideas discussed in Rescorla, 1991.)

to those behaviors (neural "value systems" [Friston et al., 1994]). Neural network theory and computational modeling have addressed this problem of reinforcement learning. Artificial reinforcement learning (RL) systems adjust their behavior with the goal of maximizing the occurrence of reinforcing events over time (Barto, 1995; Sutton and Barto, 1981). RL models employ response-dependent feedback that evaluates outcomes and enables the learner to adjust performance to maximize "goodness" of behavior. Barto notes that such a system would need to evaluate delayed as well as immediate consequences and "deal with complex tangles of action and their consequences occurring through time." This is called the "temporal credit assignment problem." In what is termed "actor-critic" architecture within the neural network, the "critic" (which has access to context and motivational state) supplies the "actor" with feedback on behavioral output and assigns weights to the actor's *immediately preceding actions*. Closely related to this notion are mathematical models employing the temporal-difference algorithm of reinforcement learning (Sutton and Barto, 1998). In this model, which is proposed to account for the behavior of the dopaminergic neurons during animal learning (Schultz, 2002; Schultz et al., 1997), learning is dependent on the degree of unpredictability of primary reinforcers. Networks encode a "prediction error" in real time, which is based on the difference between the actual occurrence of a reinforcer and its prediction; no more learning occurs when the event is entirely predicted and the error term is zero. The model is applied to both Pavlovian and instrumental or behavioral learning (Schultz and Dickinson, 2000). In the latter case, behavioral actions are evaluated in relation to unpredicted events (for example, a random lever-press and an unexpected food pellet), and the prediction error is computed which then modifies subsequent predictions and performance. A network suited to reinforcement learning would also need to be able to modify synapses in enduring ways, utilizing a Hebbian learning mechanism, in which pre- and postsynaptic activity combine to influence long-term changes in cellular functions. Several computational models have incorporated glutamatergic presynaptic input to striatal medium spiny neurons, postsynaptic rise in calcium, and the precise timing of the dopamine signal as a basis for modifiable synapses embedded within a corticostriatal network (Kotter, 1994; Pennartz, 1997; Wickens and Kötter, 1995).

Corticostriatal networks are beautifully designed to handle the requirements of adaptive motor learning elaborated above, both in terms of their anatomical and molecular architecture. Indeed, there is much experimental evidence that systems involving prefrontal cortex, striatum, amygdala, and dorsal and ventral striatum participate in instrumental learning. We have shown that glutamate and dopamine-mediated signaling in many of these regions is critical for the adaptations necessary for new motor learning. In the model we use, hungry animals must learn a simple lever-press task in order to obtain sucrose pellets (Andrzejewski et al., 2004; Pratt and Kelley, 2004). We are particularly interested in the early learning period, when the animal is engaged in intense exploration in an operant chamber (in our currently employed version of this task, it has already experienced a certain degree of experience in this chamber with random, unexpected sucrose pellets being presented). During this period, the rat is motivationally and motorically activated (sniffs, rears, ambulates, nosepokes, in effect, "forages") because of its deprivation state and the activating effects of the occasional reward. A random lever-press results in reward presentation; following several of these random pairings, rats begin to repeat the lever-press. Although for an individual rat the contingency representation develops fairly quickly (while this may take several days of training), the speed and efficacy of the behavior is acquired relatively slowly; over many days, the animal improves its performance and presses at a very high rate (see Figure 7).

We have found that infusion of the selective NMDA antagonist AP-5 into certain corticolimbic sites (including the nucleus accumbens core, basolateral amygdala, and medial prefrontal cortex) during this early learning period disrupts or abolishes the ability of rats to learn response-outcome contingencies (Kelley, 2004b; Kelley et al., 2003). Remarkably, such infusions in the same rats, once they have learned the task (which they all do when trained without drug treatment), have no effect on behavior (in most sites). Spatial behavior and aversive learning also involve glutamate receptor activation within nucleus accumbens (De Leonibus et al., 2003; Roullet et al., 2001; Smith-Roe et al., 1999). Acquisition of instrumental behavior is also dependent on DA D-1 receptor activation, and further data suggest that coincident detection of D-1 and NMDA receptor activation, in the accumbens core, prefrontal cortex, and perhaps

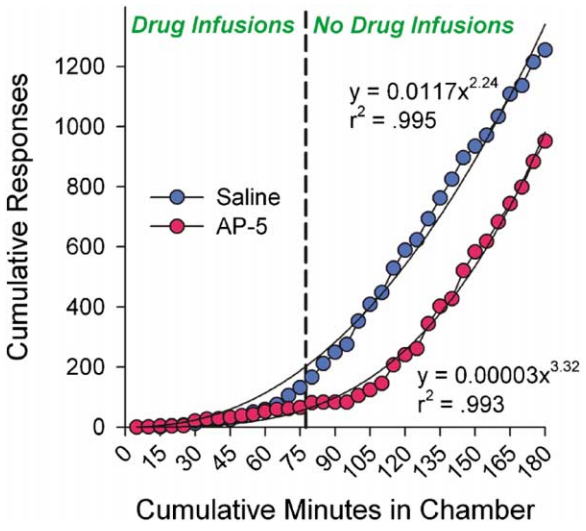

Figure 7. Effect of NMDA Receptor Blockade on Acquisition of Instrumental Responses

Acquisition of instrumental learning (lever pressing for food in hungry rats) follows an orderly pattern that is well described by a power function. The NMDA antagonist AP-5 infused into the nucleus accumbens core shifts the learning function to the right. The graph shows cumulative responses across cumulative minutes for two rats (saline treated, blue circles; AP-5 treated, red circles). Power functions were fit to both rats' data (using the general form $y = ax^b$). Best-fit functions are drawn in with solid lines and are shown next to each curve with the respective variance accounted for. Other functions, like exponential growth, hyperbolic, and quadratic, were also fit to the data, but accounted for less of the variance. (From M. Andrzejewski, personal communication.)

other regions, is necessary for learning (Baldwin et al., 2002b; Smith-Roe and Kelley, 2000). Drugs interfering with AMPA and muscarinic receptor function also disrupt learning, suggesting that multiple complex signals interact to control plasticity (P.J. Hernandez et al., submitted; Pratt and Kelley, 2004a). With regard to intracellular signaling, recent data also suggest a role for PKA and de novo protein synthesis in the nucleus accumbens (Baldwin et al., 2002a; Hernandez et al., 2002). It is of interest to note that blockade of protein synthesis in the motor cortex has no effect on contingency learning, but does impair the improvement of instrumental motor skill over sessions (Luft et al., 2004). While coordinated action of dopamine and glutamate systems may play differential roles in these various forebrain regions (e.g., the amygdala is likely processing different types of information than the hippocampus or accumbens core), intriguing insights have been suggested in recent investigations. For example, the Pavlovian contextual cues that come to be associated with reward have a powerful influence in activating and regulating ongoing behavior (Corbit et al., 2001; Dayan and Balleine, 2002; Dickinson and Balleine, 1994). NMDA receptor blockade in the nucleus accumbens core prevents acquisition of Pavlovian approach behavior (Di Ciano et al., 2001), suggesting that NMDA receptor activation in this region is necessary for salient cues to gain control over approach responses. Interestingly, in that study, a DA antagonist also strongly disrupted approach learning, and an AMPA antagonist affected performance of the learned response. Lesions and dopamine depletions within the accumbens also abolish learned approach behavior (Parkinson et al., 1999, 2002). This work suggests that early stimulus-stimulus (Pavlovian) associations influence the production of instrumental responses that may lead to future positive outcomes and that this influence requires DA and glutamate activity in the amygdalo-accumbens pathway (Cardinal et al., 2002).

Our own analysis of the microstructure of behavior in the operant chamber also provides insights into the behavioral mechanisms underlying disruptions in learning induced by glutamate or dopamine antagonists (P.J. Hernandez et al., submitted; P.J. Hernandez et al., 2003, Soc. Neurosci., abstract, Volume *29*). In addition to measuring lever-pressing during instrumental learning, we also record nose-pokes into the food tray—an unconditioned response necessary to actually obtain the food but also greatly increased under high-arousal or "occasional reward" conditions. We analyzed these responses in the first few sessions of the task and used a computer program that time stamps the order and temporal relation of events (nose-poke, lever pressing, reward deliveries). Since (in more recent experiments, e.g., Pratt and Kelley, 2004) we design the task such that all animals get "free," randomly delivered pellets during these first 2 days and since most animals have not yet learned to lever-press, these sessions provide an opportunity to measure the temporal organization of behavior surrounding reward delivery, before or during early instrumental learning. As can be observed in Figure 8, animals under the influence of AP-5 showed drastically lowered levels of nose-pokes, even when reinforcer density is equated between drug and control groups. Moreover, if the latency between reinforcer delivery and nose-poke is measured, as well as the probability of a nose-poke occurring given that reinforcer was just delivered, we find marked differences in the behavior of animals with accumbens NMDA receptor blockade. These rats had nearly tripled latencies to retrieve pellets and lowered probability that a nose-poke would occur following a reinforcer delivery. Yet, our other studies show no effect on general motor activity in nonlearning contexts, nor on food intake or any aspect of eating behavior (Kelley et al., 1997; Smith-Roe et al., 1999), and the drug-treated rats always consume the pellet once they find it. Thus, general motivational or motor impairments cannot account for this profile. The DA D-1 antagonist also reduced nose-pokes, but to much less of a degree, and had no influence on latencies or probabilities (data not shown). This profile suggests that glutamate signals acting on NMDA receptors in the accumbens may be critical for increasing the output and speed of foraging responses *under certain motivational and contextual conditions*. When the output of these responses is high over a restricted time window, the probability that random lever presses resulting in reward will occur is higher. Under the influence of AP-5, rats appear to make fewer attempts at lever-pressing or nose-poking, despite presentation of arousal-inducing food pellets. Although the precise mechanisms are not yet clear, somehow AP-5 prevents the occurrence of associative processes between reward delivery and the animal's actions. It may be that striatal spiny neurons must shift into the NMDA-mediated up state for production of a

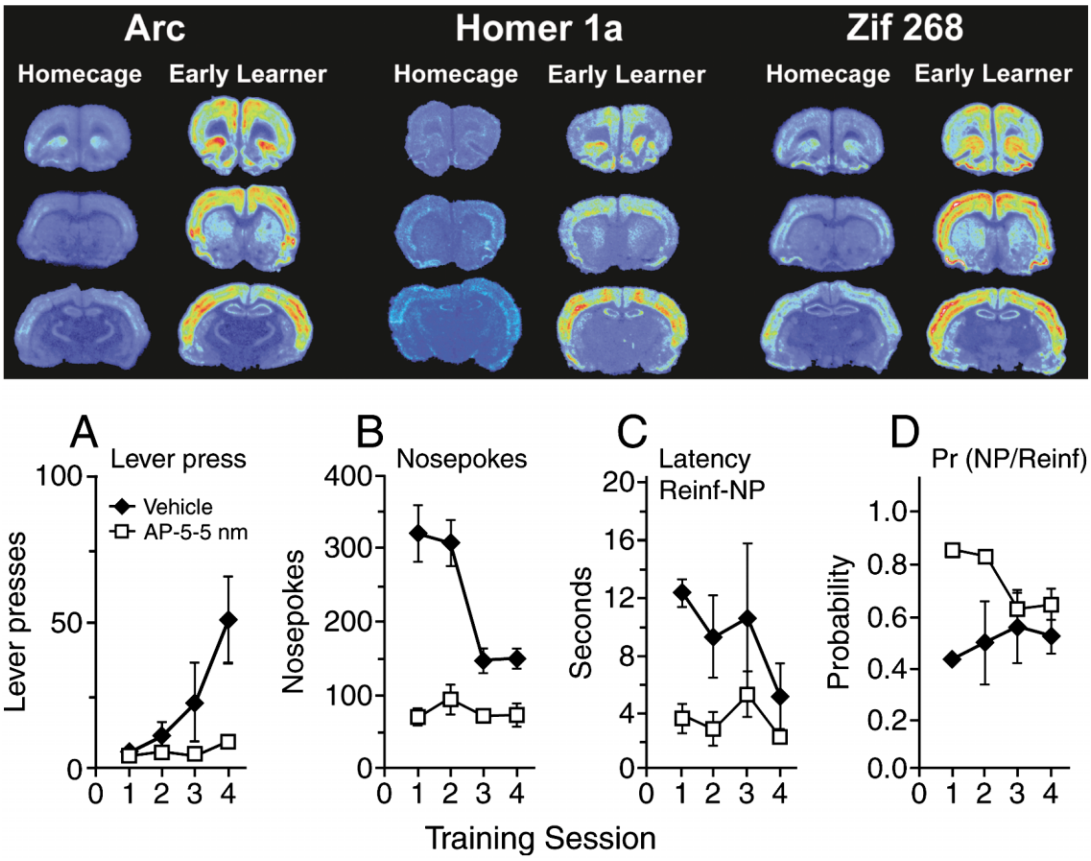

Figure 8. Instrumental Learning Processes Depend on NMDA Receptor Activation within the Nucleus Accumbens Core

Shown are the first 4 days of instrumental training in a typical experiment. Intra-accumbens treatment with the selective NMDA antagonist AP-5 (5 nmol bilaterally) prevents instrumental learning (A) and greatly reduces the number of exploratory nose-pokes in these early sessions (B). During sessions 1 and 2, "free" randomly delivered food pellets are available to all rats. (C) represents the latency in seconds between delivery of a reinforcer and a nose-poke, and (D) represents the probability that a nose-poke will occur given that the last recorded event was delivery of a reinforcer. Drug-treated animals show impaired food-seeking responses, although they always eat the pellet once they find it (P.J. Hernandez et al., 2003, Soc. Neurosci., abstract, Volume *29*). (Above) Brain sections from an in situ hybridization experiment in which brains from animals were processed for early response gene expression during early learning (average of 50–100 lever presses) or food-deprived home cage control animals. Note the high expression in widespread corticolimbic regions of *arc*, *homer1A*, and *zif268*, as discussed in the text (P.J. Hernandez et al., 2004, Soc. Neurosci., abstract, Volume *30*).

critical level of foraging responses and, therefore, reward-response pairings. DA (which gets phasically released with each unexpected reward) also is undoubtedly involved in this early acquisition period; in addition to our data, Wickens and colleagues have found that acquisition of a lever-press response for electrical brain stimulation correlates closely with DA stimulation-induced potentiation of cortiocostriatal synapses, and they propose that such a mechanism is key for the integration of reward with context-dependent response probabilities and bias of behavioral actions (Reynolds et al., 2001; Wickens et al., 2003).

We and others have recently begun exploring what early response genes or postsynaptic density proteins may be involved in early stages of reward learning. For example, Kelly and Deadwyler have shown that *arc* is strongly upregulated in corticolimbic networks during the acquisition of an instrumental task similar to ours (Kelly and Deadwyler, 2002, 2003), and we too find that *arc*, *homer1A*, and *zif26* (*NGFI-A*) are upregulated in cortical and striatal sites in the early phase of instrumental learning (P.J. Hernandez et al., 2004, Soc. Neurosci., abstract, Volume *30*) (examples of data shown in Figure 8). Supportive evidence for closely related types of learning is provided by the work of Everitt and colleagues, who demonstrate induction of *zif268* in corticolimbic-striatal networks in motivationally relevant contexts (Hall et al., 2001; Thomas et al., 2002, 2003). In accordance with the computational notion that surprise, novelty, or unpredicted events set the stage for new learning, *arc* and *homer1A* are found to be strongly upregulated in hippocampus and cortical networks following exploration of a novel environment (Vazdarjanova et al., 2002), which might explain why we find these genes to by upregulated even in animals that have not yet learned to lever-press but are experiencing random food pellet presentation and are engaged in strong exploratory responses. Since activity-induced expression of most of these genes has been shown to be dependent on NMDA activation (Sato et al., 2001; Steward and Worley, 2001b; Wang et al., 1994), these findings suggest that, like other types of learning, the formation of

instrumental memory requires activity-dependent immediately early gene expression in multiple brain regions, which may then in turn contribute to synaptic and network modifications.

Dopamine- and Glutamate-Initiated Plasticity: Drugs and Addiction

The above account suggests that glutamate-dopamine interactions within corticolimbic-striatal networks and the intracellular and molecular consequences of these interactions play a critical role in appetitive instrumental learning. Much evidence has accrued over the past decade to support this hypothesis. An extension of this hypothesis with regard to addiction is that drugs with addictive potential exert their effects through these very same pathways and mechanisms that are important in normal reinforcement learning and that this property is central to their ability to establish addictive behaviors. These two areas of inquiry, the neurobiology of learning and memory and the neurobiology of addiction, have greatly benefited from advances within each field informing the other. In recent years, there have been a number of excellent reviews on addiction with this focus (e.g., Berke and Hyman, 2000; Cardinal and Everitt, 2004; Di Chiara, 1998; Hyman and Malenka, 2001; White, 1996). For the purposes of the present review, I wish to focus on examples of relatively recent discoveries and to link these with some of the ideas proposed earlier in the paper.

Cellular and Molecular Approaches

There is convincing evidence that drugs of abuse have profound effects on glutamate and dopamine signaling. Most of this focus has been on nucleus accumbens, prefrontal cortex, and ventral tegmental area, the main regions implicated in the neural changes associated with addiction, although other areas are being investigated as well, such as amygdala and hippocampus (Everitt et al., 1999; Vorel et al., 2001). There are a large number of studies showing that chronic or repeated exposure to drugs of abuse significantly alters synaptic proteins associated with dopaminergic and glutamatergic synapses; only a few examples will be given here. It is well established that drugs of abuse exert marked effects on G protein-mediated signaling and in this way can alter the neuron's response to many extracellular stimuli (Hyman, 1996). A recent study by Bowers et al. demonstrates that an activator of G protein signaling, AGS3, is persistently upregulated in the prefrontal cortex and nucleus accumbens after cessation of chronic cocaine treatment (Bowers et al., 2004). Remarkably, these changes lasted up to 2 months in the prefrontal cortex following cessation of cocaine treatment. They also found that antisense to AGS3 infused into the PFC blocked cocaine priming-induced reinstatement of cocaine-seeking behavior. Alterations in an additional family of G protein regulators, RGS, have also been shown for cocaine (Bishop et al., 2002; Rahman et al., 2003). These studies suggest that drugs of abuse alter molecules at very early stages of intracellular signaling or "gatekeepers" of downstream biochemical cascades. Other long-lasting effects of chronic drug treatment include changes in deltaFosB and its downstream target CdK5 (Bibb et al., 2001; Nestler et al., 1999). It has further been shown that Homer1 proteins, mentioned earlier as being important for the postsynaptic density complex in plasticity, are also modified by cocaine (Ghasemzadeh et al., 2003). An intriguing idea is that Homer proteins are proposed to "tune" the intensity of calcium signaling to G protein-coupled receptors and to regulate the frequency of Ca^{2+} oscillations through RGS proteins (Shin et al., 2003). A further elegant study showed that sustained decreases in PSD-95, a critical synaptic scaffolding protein, was found in mice treated chronically with cocaine—even as late as 2 months following the cessation of treatment (Yao et al., 2004). In these mice, synaptic plasticity (LTP) at prefrontal-accumbens glutamatergic synapses is enhanced, suggesting that the persistent downregulation of PSD-95 may contribute to long-lasting adaptations observed in addiction. It is extraordinary that even a single exposure to drugs can have a lasting impact; a single exposure to cocaine, amphetamine, nicotine, morphine, or ethanol (as well as a single exposure to stress) induced long-term potentiation of AMPA currents in dopamine cells (Saal et al., 2003; Ungless et al., 2001), while long-term depression was observed at GABAergic synapses in the VTA, following one exposure to ethanol (Melis et al., 2002). Accumbens and hippocampal synaptic plasticity were altered by a single exposure to THC (Mato et al., 2004). Taken together, this group of studies (representing a small selection) suggests that many signaling proteins within the postsynaptic density in regions that are important for motivation and learning are fundamentally altered, in a long-term manner, with chronic (or even acute) exposure to drugs. Many of these proteins have been established to be important in both synaptic and systems models of memory, as noted earlier.

Adaptations in brain areas that are important for learning and motivation would suggest that that a fundamental feature of addiction is altered or new learning in response to repeated self-administration of a substance in particular circumstances or contexts (both emotional and environmental). Indeed, major theoretical accounts of addiction posit that learning and memory systems are "pathologically subverted" and that this alteration results in compulsive habits that are difficult to control (Everitt et al., 2001) or that such systems are abnormally sensitized, resulting in excessively attributed salience or motivational importance to various drug-related cues or emotional states (Robinson and Berridge, 2001). Although the cause or explanation of addiction will undoubtedly prove very complex and multifactorial, an array of recent data utilizing drug-seeking or drug-conditioning paradigms strongly supports these general notions. An important advance in this regard has been the use of reinstatement drug-seeking models, in which drug-associated cues, stress, or the drug itself is used to "reinitiate" responding in animals in which responding had been extinguished due to removal of the reinforcer (Shaham et al., 2003). This paradigm is proposed to model relapse following a period of drug abstinence. Glutamate (and dopamine) release within nucleus accumbens increases during drug-seeking behavior, and glutamate antagonists infused into this region block cocaine priming-induced reinstatement of drug seeking

(Cornish and Kalivas, 2000). At least one source of increase in accumbens extracellular glutamate during drug seeking is likely to be the prefrontal cortex (McFarland et al., 2003). Moreover, repeated cocaine causes elevated levels of glutamate in the accumbens core in association with behavioral sensitization (Pierce et al., 1996). Wolf and colleagues have found that discrete stimuli paired with cocaine (but not unpaired stimuli) elicit increased glutamate levels in the nucleus accumbens (Hotsenpiller et al., 2001). A role for dopamine and in particular D-1 receptors has also been suggested. For example, presentation of drug-associated cues can elicit reinstatement of responding (drug seeking) in animals that have extinguished responding; this reinstatement is dependent on D-1 receptor activation (Alleweireldt et al., 2002; Ciccocioppo et al., 2001; Khroyan et al., 2003). Infusions of antagonists into the accumbens shell or basolateral amygdala also reduce or abolish cocaine seeking (Anderson et al., 2003; See et al., 2001), and a very recent study elegantly shows that simultaneous activation of DA receptors within the basolateral amygdala and of AMPA receptors with the accumbens core is required for cocaine seeking under control of drug-associated stimulus (Di Ciano and Everitt, 2004). Some recent exciting data using a novel fast-scan cyclic voltammetry technique that can sample DA release at 100 ms intervals shows direct evidence for increased dopamine release during cocaine seeking. Cocaine-related cues also caused rapid rises in extracellular DA in animals where the cues had been paired with cocaine delivery, but not in animals where the cues were unpaired (Phillips et al., 2003). This group has also shown a very similar profile of subsecond dopamine release in relation to natural reward (sucrose) seeking; sucrose-associated cues also provoked rapid release (Roitman et al., 2004). These studies suggest further commonalities between plastic changes underlying natural and drug rewards. Finally, work with sensitization models shows that prior chronic exposure to stimulants increases rats' willingness to work for drug self-injection (Vezina et al., 2002), suggesting that long-term molecular and cellular alterations indeed change motivation for the drug and (in some cases) motivation for natural rewards (Fiorino and Phillips, 1999).

While the above discussion focus on examples mostly with stimulants, it is important to keep in mind that other drugs of abuse, such as alcohol, nicotine, and opioids, also exert clear cellular effects on DA and glutamatergic systems. There is evidence that both glutamate and dopamine systems participate in both the acute and longer-term effects of nicotine (Dani et al., 2001; Kenny et al., 2003; Mansvelder and McGehee, 2000; Pontieri et al., 1996) and alcohol (Brancucci et al., 2004; Koob et al., 1998; Lovinger et al., 2003; Maldve et al., 2002).

Contextual Conditioning, Drug Memory, and Reward

In the past decade, much attention has been focused on drug-conditioning models and analysis of the neural basis of the Pavlovian conditioning processes that govern drug conditioning. This field has grown from early clinical observations that recovering addicts seemed to respond abnormally to drug-associated contextual cues (O'Brien et al., 1992; Wikler, 1973). Environmental cues that have been previously associated with the drug state can be powerful determinants in relapse (Stewart et al., 1984). Indeed, research with recovering opioid and cocaine addicts suggests that an altered emotional state with physiological concomitants can be elicited by drug-related cues. For example, it has been found that drug-associated cues (videos of heroin paraphernalia, "cook up" rituals, buying and selling) can induce autonomic responses such as increased heart rate and blood pressure as well as subjective feelings of craving (Childress et al., 1986; Sideroff and Jarvik, 1980). Conditioned autonomic responses have also been documented in nicotine and alcohol dependence (Kaplan et al., 1985; Ludwig et al., 1974; Droungas et al., 1995). In more recent years, neuroimaging studies have revealed significant brain activation patterns when addicts are exposed to drug-related cues; most of the studies suggest a critical role for prefrontal cortex and associated circuitry such as the amygdala (for reviews, see Goldstein and Volkow, 2002; Jentsch and Taylor, 1999; London et al., 2000). For example, functional MRI investigations report that exposure to cocaine cues in cocaine abusers elicited craving and activation of amygdala and prefrontal cortical regions (Bonson et al., 2002) and a similar study using regional cerebral blood flow showed activation in amygdala and cingulate cortex (Childress et al., 1999; Kilts et al., 2001). Such studies reveal that, in humans, associative processes and stimulus-induced activation of specific motivational states reflecting drug craving or wanting are key components of the addictive process.

Recent work using animal models has also addressed the question of how repeated associative pairings of drugs and environment alter brain circuits that are important for motivation and learning. Robinson and colleagues have shown modulatory powerful effects of environmental novelty and context on behavioral and molecular indices of drug sensitization (Anagnostaras and Robinson, 1996; Badiani et al., 1997; Badiani et al., 1998). This group has recently shown that amphetamine induces *arc* expression in the striatum and prefrontal cortex to a greater degree in a relatively novel environment compared with the home cage (Klebaur et al., 2002). This gene, discussed earlier in relation to plasticity and alterations in the postsynaptic density, may potentially be involved in drug-induced changes in spine formation in prefrontal cortex and striatum, which last over 3 months after discontinuation of drug treatment (Li et al., 2003).

Our own work has focused on context-associated changes in early response- and plasticity-related genes in corticolimbic circuits. We and others have shown that exposure of rats to drug-paired environments induces c-*fos* expression in these brain regions. For example, morphine-paired cues (which also cause conditioned locomotor activation) induce Fos protein expression most strongly in the medial prefrontal, ventrolateral orbital and cingulate cortex; this induction is context specific in that animals given similar prior morphine treatment and exposed to an unpaired context do not show increased fos expression (Schroeder et al., 2000; Schroeder and Kelley, 2002). Context-specific c-*fos* induction in prefrontal regions has been shown for cocaine, amphetamine, nicotine, beer, and palatable food

(Franklin and Druhan, 2000a; Hotsenpiller et al., 2002; Neisewander et al., 2000; Schroeder et al., 2001; Topple et al., 1998). Recently, we have begun to investigate this phenomenon in more detail with nicotine administration in rats, examining the response of genes such as *arc* (C.A. Schiltz et al., submitted; C.A. Schiltz et al., 2003, Soc. Neurosci., abstract, Volume *29*). All rats were given nicotine and saline in distinct environments. However on the test day, half of the animals went into their nicotine-paired environment and half into their saline-paired environment. Nicotine-related cues induced strongly enhanced *arc* expression not only in prefrontal cortex but also in widespread sensorimotor cortical regions (see Figure 9). In accordance with the idea that the PFC is critical for the influence of drug-related cues on behavior, local inactivation of the medial PFC completely blocks cocaine cue-induced conditioned behavioral activation (Franklin and Druhan, 2000b).

This profile of early response gene induction suggests that that cortical networks that are normally important for plasticity and consolidation processes are altered by repeated drug-context pairings. It is not clear what the gene induction represents in animals, but the neural activation in human experimental paradigms is often associated with craving or drug-related thoughts. Perhaps this gene activation represents a "mismatch," an unexpected event in which cues predicting reward (drug, food) are present, yet the primary reward does not follow. Relapse can occur months or even years after cessation of drug taking and long periods of abstinence, suggesting that very stable, perhaps even permanent changes occur in the brain that may contribute to this vulnerability. Since the prefrontal cortex is critical for many cognitive functions involving inhibitory control, decision making, and emotional regulation, many have speculated that neuromolecular changes in this brain region may be central to the loss of control that accompanies advanced states of addiction (Jentsch and Taylor, 1999; London et al., 2000; Volkow and Fowler, 2000). In relapse, individuals fail to make a rational choice, despite their former resolve and apparent knowledge of future adverse outcomes. Confronted by external cues that serve as "drug reminders," such individuals may experience conditioned autonomic responses and powerful cravings. If prefrontal cortical function is compromised by global cellular and molecular signaling abnormalities, the degree of voluntary control that the subject has over these feelings may be greatly impaired. Indeed, an important cognitive model of addiction posits that thoughts and behaviors associated with drug taking become so automatized and habit-like that their generation and performance are under little voluntary control (Tiffany and Conklin, 2000).

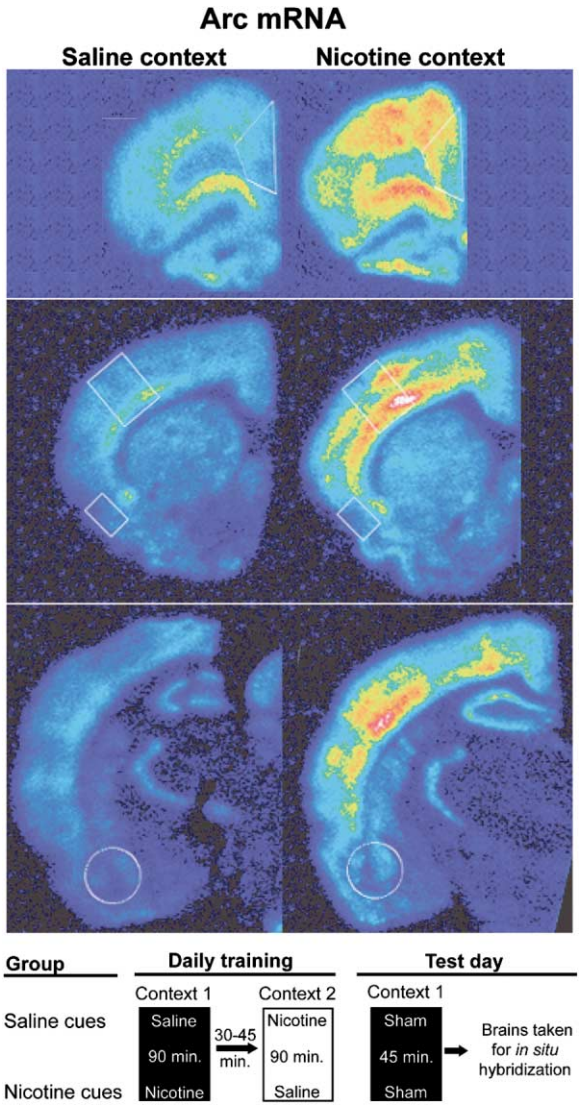

Figure 9. The Dendritically Targeted mRNA *arc* Is Upregulated by Nicotine-Related Cues

Arc mRNA, which is thought to be targeted to activated synapses, is induced in numerous forebrain regions, including prefrontal cortex, following exposure of rats to a nicotine-associated environment and in situ hybridization. Below the brain sections is shown the behavioral conditioning protocol. All animals receive the same nicotine treatment (see text), but on the test day, half are placed in the saline (control) context and half in the nicotine context. (From C.A. Schiltz et al., submitted; C.A. Schiltz et al., 2003, Soc. Neurosci., abstract, Volume *29*.)

Synthesis and Conclusions

In this review, the basic mechanisms that are shared by natural reward learning processes and drugs of abuse have been considered within an evolutionary and integrative neural systems framework. Neurochemically coded brain circuits have evolved to serve as critical substrates in guiding adaptive behavior and in maximizing fitness and survival. The development of motivational-emotional systems in mammals has its molecular roots in behaviors of organisms millions and even billions of years ago. These systems enable animals to seek stimuli that enhance the availability of resources (food, mating opportunities, safety, shelter) and to avoid danger or defend against predators. A major feature of this circuitry, at least in mammalian brains, is reciprocal and feedforward links between core motivational systems within the hypothalamus and brainstem and higher-order corticostriatal and limbic structures. This cross-talk between cortical and subcortical networks enables intimate communication between phylogenetically newer brain regions, subserving complex cog-

nition, learning, and plasticity, with basic motivational systems that exist to promote survival behaviors. Neurochemical and intracellular molecular coding impart an extraordinary amount of specificity, flexibility, and plasticity within these networks. Plasticity within these circuits is mediated, at least in part, by the coincident detection of glutamate- and dopamine-mediated signaling and its intracellular and genomic consequences. While motivational-emotional systems generally serve a highly functional and adaptive role in behavior and learning, they can be affected in maladaptive ways in the case of addiction. Future research will undoubtedly generate deeper insight into the chemical, genetic, and organizational nature of brain reward circuitry and its alteration in addiction.

Acknowledgments

I would like to acknowledge support from grants DA09311 and DA04788 from the National Institute on Drug Abuse and Carol Dizack for her artwork.

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