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MOLECULAR NEUROBIOLOGY OF DRUG ADDICTION

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■ **Abstract** Addiction can be viewed as a form of drug-induced neural plasticity. One of the best-established molecular mechanisms of addiction is upregulation of the cAMP second messenger pathway, which occurs in many neuronal cell types in response to chronic administration of opiates or other drugs of abuse. This upregulation and the resulting activation of the transcription factor CREB appear to mediate aspects of tolerance and dependence. In contrast, induction of another transcription factor, termed ΔFosB, exerts the opposite effect and may contribute to sensitized responses to drug exposure. Knowledge of these mechanisms could lead to more effective treatments for addictive disorders.

INTRODUCTION

The *Diagnostic and Statistical Manual of Mental Disorders* refers to drug addiction as "substance dependence," the essential characteristic of which is a compulsive pattern of drug-seeking and drug-taking behavior that continues despite adverse consequences. "Addiction," however, is by far the preferable term, since "dependence"—a pharmacological term—describes only one of the many types of adaptations to drug exposure that comprise addiction. "Dependence" refers to drug-induced adaptations that compensate for drug exposure and lead to an array of withdrawal symptoms when drug use ceases. Withdrawal symptoms vary with the substance but usually involve a significant negative affective state (dysphoria) and in some cases profound somatic abnormalities. "Tolerance" refers to drug-induced adaptations that lead to diminishing effects of a constant drug dose. "Sensitization," or reverse tolerance, refers to drug-induced adaptations that enhance drug responsiveness with repeated drug exposure. Many drugs cause both tolerance and sensitization, with some drug effects decreasing over time while others increase. The term drug abuse is often used, though confusing, since it can refer to widely varying levels of drug intake.

The key questions in the study of addiction are why some individuals make the transition from casual drug use to compulsive use (addiction) whereas others do not, and why relapse is so common, independent of the time elapsed since last drug use. Theories proposed to explain the compulsive element of addiction include hedonic or opponent-process, incentive-sensitization, and learning-based theories (for review, see 1).

As the name implies, the hedonic theory characterizes the transition to addiction in terms of affective states, either positive or negative, experienced by the individual. The basic tenet of this theory draws from the traditional view of addiction, in which initial drug-taking results in a positive affective state (e.g., euphoria or pleasure) but, upon cessation of the drug, a withdrawal reaction of anhedonia or dysphoria occurs. The need to alleviate this negative affective state by continued drug use would underlie the compulsive element of addiction. The dueling processes of euphoria and dysphoria, measured on a hedonic scale, make up the components of the opponent-process theory (2, 3). As the hedonic set point is raised, the same amount of drug results in weaker hedonic effects and stronger negative after-effects when the drug is withdrawn. The transition from the initial positive hedonic state to an increasing negative hedonic state draws the individual into a spiral of homeostatic dysregulation of brain reward pathways, resulting in the development of addiction and vulnerability to relapse.

The theory of incentive sensitization draws a distinction between drug "liking" (an affective response, as described above) and drug "wanting." This theory proposes that the excessive wanting of drug and the excessive incentive salience attached to drug-associated stimuli drives compulsive drug seeking, drug taking, and relapse (4, 5).

Learning-based theories of addiction propose that repeated drug exposure is associated with particularly strong memories, mediated by drug-induced changes in brain reward regions. Accordingly, drug taking is a learned response to conditioned stimuli, such as drug-associated cues (6–8).

It is likely that a combination of factors proposed in each of these theories contributes to the neural and behavioral pathology that underlies addiction. A major challenge in drug-abuse research is to identify the molecular and cellular changes that drugs cause in the brain to produce the complex behavioral syndrome called addiction. Before discussing these molecular and cellular mechanisms of addiction, we briefly summarize the brain's reward circuitry.

It is generally believed that drugs of abuse usurp neural circuitry in the brain that normally controls responses to natural rewards, such as food, sex, and social interactions (Figure 1). Perhaps the most important mediator of drug reward per se is the mesolimbic dopamine system, comprised of dopamine neurons with cell bodies in the ventral tegmental area (VTA) of the midbrain and the projection areas of these neurons in the limbic forebrain, in particular, the nucleus accumbens (NAc). This VTA-NAc circuit is a key detector of a rewarding stimulus; drug-induced changes in these regions could increase or decrease an individual's sensitivity to the rewarding effects of drug exposure. The amygdala is particularly

important for conditioned aspects of drug exposure, for example, establishing associations between environmental cues and both the rewarding actions of acute drug exposure and the aversive symptoms during drug withdrawal. The hippocampus, a traditional memory circuit, is no doubt crucial for memories of the context of drug exposure and withdrawal. The hypothalamus is important in mediating many effects of drugs on the body's physiological state. Probably most important, but least understood, is the role of the frontal regions of the cerebral cortex, such as the medial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex. These regions provide executive control over drug use, which is severely impaired in many addicts. Of course, these brain regions, and many more, do not function separately but are parts of a complex and highly integrated circuit that is profoundly altered by drug exposure.

MOLECULAR MECHANISMS OF ADDICTION

Not surprisingly, drugs of abuse have been reported to change literally hundreds of proteins in the various reward-related brain regions mentioned above. Rather than attempting a comprehensive review of these drug-induced changes, we focus on a small number of well-characterized changes that have been shown to contribute to certain features of the behavioral syndrome of addiction. Moreover, we focus on drug-induced changes in transcription factors, which are nuclear proteins that bind to the regulatory regions of certain genes and thereby regulate their transcription into mRNA. This focus on transcription factors is based on the notion that drug-induced changes at the level of gene expression could explain the longevity of the behavioral abnormalities associated with addiction.

cAMP and CREB

CREB (cAMP response element binding protein) is a member of the bZIP superfamily of transcription factors. It is composed of a C-terminal basic domain that is responsible for binding to DNA and a leucine zipper domain that mediates dimerzation with itself or other members of the CREB family of transcription factors, including CREM (cAMP response element modulator) and ATF-1 (activating transcription factor 1). The CRE (consensus cAMP response element) to which CREB dimers bind consists of the palindromic sequence TGACGTCA. Many genes have CRE sites in their promoters, including neuropeptides, neurotransmitter synthesizing enzymes, neurotransmitter receptors, signaling proteins, and other transcription factors (9, 10). CRE-mediated transcription requires CREB activation via phosphorylation at Ser-133. Phosphorylation and subsequent activation of CREB is a site of convergence for several signal transduction cascades, including the cAMP pathway via protein kinase A (PKA), intracellular Ca^{2+} via Ca^{2+}-calmodulin-dependent kinases (CaMK), the Ras/extracellular signal regulated kinase (ERK) protein kinase pathway, the phosphotidylinositol-3-kinase (PI3K)/Akt

kinase pathway, and stress-induced signaling cascades (10). CREB binding protein (CBP) subsequently binds to the phosphorylated CREB dimer and serves as an adaptor to the transcription initiation complex. The histone acetyltransferase (HAT) activity endogenous to CBP unravels chromatin and facilitates transcription (9, 11).

CREB is of particular interest in drug addiction because its activation is downstream of the cAMP signaling pathway, whose upregulation has been extensively characterized as an adaptation to chronic exposure to drugs of abuse (12). Beginning with cultured neuronal cell lines and extending to several brain regions involved in addiction, chronic opiate exposure has been shown to upregulate the cAMP signaling cascade (13, 14). This upregulation is viewed as a homeostatic compensatory response to the acute inhibitory actions of opiates, which bind to Gi-coupled receptors and inhibit adenylyl cyclase production of cAMP. Upregulation of the cAMP pathway mediates several aspects of addiction, depending on the specific region of the brain involved (15). Effects on the locus coeruleus (LC) and NAc are discussed here.

The response to repeated exposure to morphine has been studied extensively in the LC, which has served as a useful model system (Figure 2). The LC, located at the base of the fourth ventricle, is the major noradrenergic nucleus in the brain, mediating the control of attention, vigilance, and the sympathetic nervous system (16, 17). Upregulation of the cAMP pathway and CREB in the LC is implicated in mediating some of the symptoms underlying physical opiate dependence and withdrawal (14, 18). Acute exposure to opiates inhibits the cAMP signaling cascade; however, upon chronic opiate administration, CREB expression is increased in the LC (12, 19), implying a homeostatic or compensatory regulatory mechanism. This increased CREB activity appears to play an important role in physical opiate dependence and withdrawal (18). Among the genes involved are adenylyl cyclase type VIII and tyrosine hydroxylase, whose expression is upregulated by chronic morphine administration via a CREB-dependent mechanism (18, 20). Consistent with these data, mice containing targeted mutations of the α and Δ isoforms of the CREB gene show attenuated physical symptoms of morphine withdrawal (21). Interestingly, these mice also exhibit a strong aversion to opiate withdrawal in a conditioned-aversion paradigm despite their attenuated physical withdrawal symptoms, indicating that the mechanisms or circuitry of physical dependence may be distinct from those mediating the negative motivational aspects of morphine withdrawal (22).

Chronic exposure to opiates, cocaine, and alcohol also upregulates the cAMP pathway in the NAc (14, 23, 24). As would be expected from this upregulation, activation of CREB and CRE-mediated transcription have also been observed in response to chronic morphine and amphetamine treatments in this brain region (25–27). Understanding of the functional role of CREB activity in addiction was facilitated by a series of studies examining the behavioral manifestations of a localized increase in CREB activity in the NAc. First, bilateral intra-NAc infusions of a PKA activator, which would be expected to activate CREB, decreased cocaine reward in rats as demonstrated by reduced baseline cocaine self-administration,

whereas infusion of PKA inhibitors increased cocaine reward (28). Studies overexpressing CREB in the rat NAc via viral-mediated gene transfer provided more direct evidence of the effects of CREB activity on reward. Increased CREB expression decreases the rewarding effects of cocaine, opiates, and sucrose, a natural reward (25, 29), whereas expression of the dominant-negative mutant form of CREB resulted in the opposite effects. Finally, inducible transgenic mice overexpressing CREB in the NAc and dorsal striatum (30) demonstrate decreased preference for cocaine in the conditioned-place-preference paradigm (CA McClung, EJ Nestler, unpublished observations). Together, these data indicate that upregulation of the cAMP pathway and CREB in the NAc as a result of chronic drug administration decreases the rewarding effects of cocaine and morphine. CREB α/Δ mutant mice showed partially consistent results, demonstrating increased rewarding responses to cocaine as assayed by conditioned-place-preference assays while showing no increase in response to morphine (22). The anatomically unrestricted nature of the CREB mutation in these mice makes it unclear whether these responses are due to lack of CREB in the NAc or perhaps elsewhere in the brain; however, these interesting results highlight the importance of generating inducible, region-specific knockout mice to further elucidate these mechanisms.

Beyond attenuating the rewarding effects of drugs of abuse, upregulation of the cAMP pathway and CREB in the NAc may also contribute to states of dysphoria seen early in withdrawal (15, 32). Thus, CREB overexpression in the NAc, achieved with viral vectors or in inducible transgenic mice, produces depression-like responses in the forced-swim and learned-helplessness tests, whereas mutant CREB expression causes antidepressant-like responses (33, 33a). Recent data more precisely define the depression-like state mediated by CREB, namely, a general state of emotional numbness and anhedonia (25).

Efforts are under way to identify target genes for CREB in the NAc. One apparent target is dynorphin, an opioid peptide expressed in a subset of medium spiny neurons in the NAc, which is induced in this region after chronic drug exposure (29, 34–36) (Figure 3). Dynorphin release from the NAc contributes to dysphoria during withdrawal through what amounts to a negative-feedback loop to VTA dopamine neurons (32, 37). Dynorphin binds to κ opioid receptors on VTA dopamine neuron cell bodies and terminals to inhibit their activity and decrease dopamine release in the NAc (38). The cocaine aversion caused by CREB overexpression in the NAc can be attenuated with a κ opioid antagonist (29), as can depression-like responses seen under these conditions (33).

The search for additional CREB target genes in the NAc has been extended to the use of DNA microarrays on bitransgenic mice (33a; CA McClung, EJ Nestler, unpublished observations) expressing CREB or a dominant negative CREB (mCREB) in an inducible, region-specific manner. These studies have shown that the vast majority of the genes upregulated by CREB in the NAc are downregulated by mCREB, attesting to both the functional implications of increased expression of these genes and the reliability of the microarray detection technique. In addition, some of these CREB-regulated genes comprise a small subset of the genes regulated in this brain

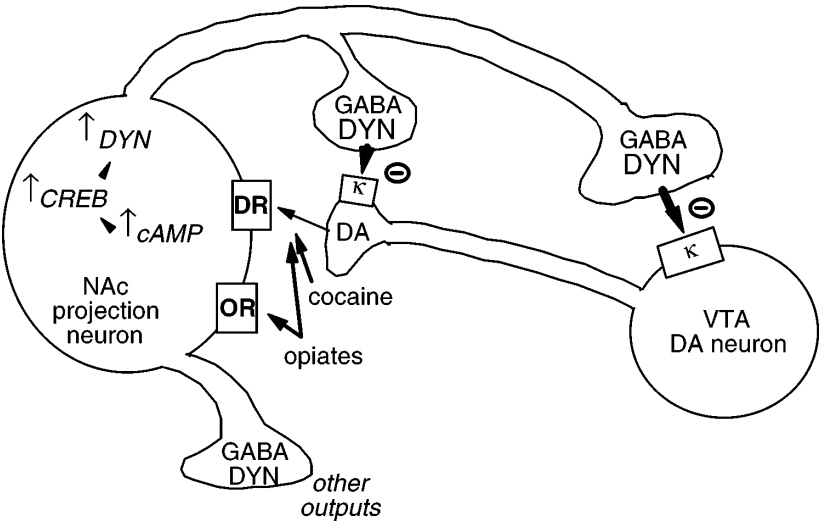

Figure 3 Regulation of CREB by drugs of abuse. The figure shows a ventral tegmental area (VTA) dopamine (DA) neuron innervating a class of nucleus accumbens (Nac) GABAergic projection neurons that expressed dynorphin (dyn). Dynorphin serves as a negative-feedback mechanism in this circuit: Dynorphin, released from terminals of the NAc neurons, acts on κ opioid receptors located on nerve terminals and cell bodies of the DA neurons to inhibit their functioning. Chronic exposure to cocaine or opiates upregulates the activity of this negative-feedback loop by upregulating the cAMP pathway, activation of CREB, and induction of dynorphin. (From Reference 113 with permission.)

region by cocaine administration. These potential target genes provide possible mechanisms of drug-induced plasticity and deserve further study.

ΔFosB

Immediate early genes are a class of genes whose expression is induced within minutes of exposure to a stimulus. Of particular interest in the study of addiction are the Fos and Jun families of immediate early genes, which encode transcription factors. The Fos family of transcription factors includes c-Fos, FosB, Fos-related antigens 1 and 2 (Fra-1 and -2), and ΔFosB. ΔFosB is a truncated splice variant of full-length FosB, and lacks a portion of the C-terminal transactivation domain present in other Fos proteins (39). Fos family members heterodimerize with Jun family transcription factors (c-Jun, JunB, JunD) to form the activator protein–1 (AP-1) complex. The AP-1 complex binds to specific DNA sequences in the promoters of various target genes, with the consensus sequence TGAC/GTCA. AP-1 complexes can act as either a transcriptional inducer or repressor, depending on the specific AP-1 binding site and promoter in question.

Acute exposure to drugs of abuse rapidly (in 1–4 h) induces all Fos family members in the NAc and dorsal striatum (40, 41) (Figure 4). Even with continued drug exposure, levels of these proteins decline rapidly toward basal levels within 8–12 h. However, biochemically modified isoforms of ΔFosB exhibit a very different expression pattern. Acutely, ΔFosB expression is only modestly induced, but it persists long after the other Fos family members have returned to basal levels. In fact, several lines of evidence point toward ΔFosB being a unique target of chronic exposure to drugs of abuse. First, as noted above, whereas other Fos family proteins respond to drugs of abuse with a characteristic sharp upregulation followed by a quick decline to basal levels within hours (42–44), ΔFosB isoforms are very stable and demonstrate in vivo half-lives of weeks (45). They therefore persist for weeks after the drug is withdrawn (46). As a result, ΔFosB levels gradually accumulate with repeated drug exposure, suggesting that its dynamics allow it to play a longer-term role in subsequent regulation of gene expression. Second, ΔFosB expression is significantly induced in response to chronic exposure to several drugs of abuse, including cocaine, amphetamine, opiates, nicotine, ethanol, and phencyclidine (40, 47–51). Importantly, these substances induce ΔFosB most prominently in the NAc and dorsal striatum, but to a lesser extent in other brain regions known to be important in addiction, including the NAc amygdala and prefrontal cortex (51).

Because of its unique temporal properties and its induction by virtually all drugs of abuse, the functional significance of ΔFosB in drug-related behaviors has been studied extensively. In response to chronic exposure to drugs of abuse, ΔFosB is selectively upregulated within a subpopulation of medium spiny neurons containing the neuropeptides substance P and dynorphin in the NAc and dorsal striatum (41, 51). Exposure to antipsychotic drugs also induces ΔFosB expression in these same regions, but this induction occurs in the other major subpopulation of medium spiny neurons in the NAc, namely those neurons containing the neuropeptide enkephalin (52, 53). Further, ΔFosB accumulates in dynorphin-containing neurons of the NAc after excessive running behavior, suggesting that the induction of ΔFosB in this specific subset of neurons in the NAc may be triggered by many types of compulsive behaviors (54).

Transgenic mice were generated that exhibit inducible expression of ΔFosB primarily in the NAc and dorsal striatum (55). When ΔFosB is expressed specifically within the dynorphin-positive neurons in these regions of adult mice, the mice exhibit sensitized behavioral responses to drugs of abuse (56). Inducible expression of ΔFosB increases sensitivity to the locomotor activating properties of cocaine (56). The mice also demonstrate enhanced sensitivity to the rewarding effects of cocaine and morphine in place-conditioning assays (51, 56). In addition, they self-administer cocaine at lower doses than their littermate controls that do not overexpress ΔFosB, and they maintain self-administration at even lower doses (57). These mice also work harder to self-administer cocaine in progressive ratio self-administration assays, indicating that ΔFosB may be involved in sensitizing mice to the motivational effects of cocaine as well, leading to a greater likelihood

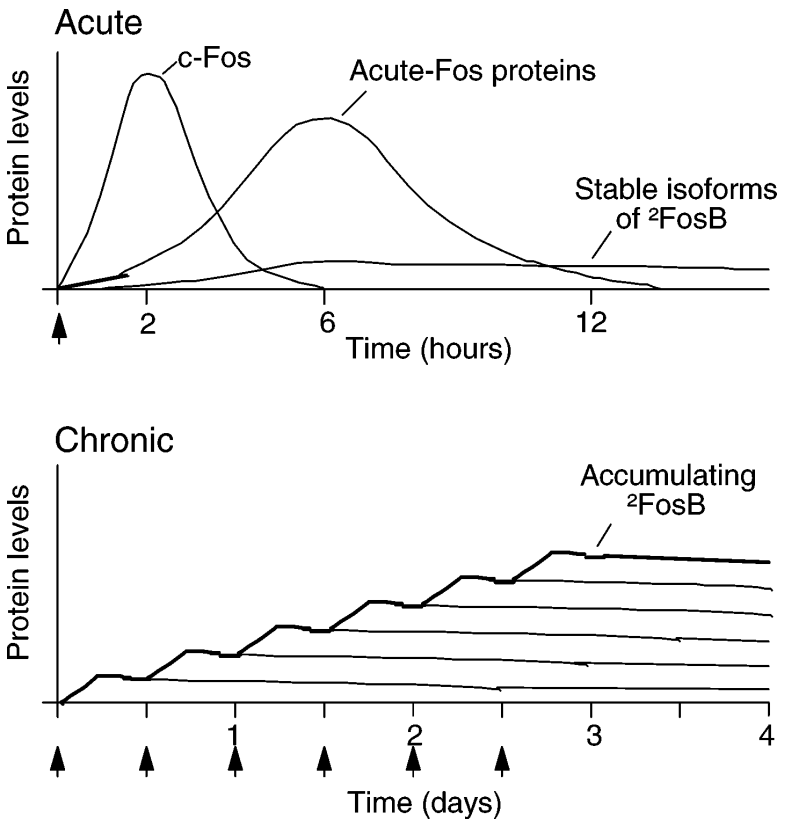

Figure 4 Gradual accumulation of ΔFosB versus the rapid and transient induction of acute Fos family proteins in brain. *Top*: Several waves of Fos-like proteins are induced in neurons by acute stimuli (e.g., single drug administration). c-Fos is induced rapidly and degraded within several hours of the acute stimulus, whereas other "acute Fos proteins" [e.g., FosB, ΔFosB, and Fos-related antigen (Fra)-1 and -2] are induced somewhat later and persist somewhat longer than c-Fos. Stable isoforms of ΔFosB are also induced at low levels following a single acute simulus but persist in brain for long periods. In a complex with Jun-like proteins, these waves of Fos proteins form AP-1 binding complexes with shifting composition over time. *Bottom*: With repeated (e.g., twice daily) stimulation, for example by repeated drug administration, each acute stimulus induces low levels of stable ΔFosB isoforms. This is indicated by the lower set of overlapping lines, which indicate ΔFosB induced by each acute stimulus. The result is a gradual increase, indicated by the stepped line in the graph, in the total levels of ΔFosB with repeated stimuli during a course of chronic treatment. The increasing levels of ΔFosB with repeated stimulation would result in the gradual induction of significant levels of a long-lasting AP-1 complex, which is hypothesized to underlie persisting forms of neural plasticity in the brain. (From Reference 113 with permission.)

of relapse when the drug is withheld (57, 58). ΔFosB expression also increases running activity, demonstrating a similar effect on natural rewards (54).

If an increase in ΔFosB activity heightens sensitivity to the behavioral effects of cocaine and morphine, then manipulations that decrease ΔFosB activity should block these effects. Indeed, mice that inducibly express a dominant negative antagonist of ΔFosB, Δc-Jun, in the NAc and dorsal striatum show a decrease in cocaine place conditioning, suggesting reduced sensitivity to the rewarding effects of cocaine as expected (59).

Together these data indicate that accumulation of ΔFosB both enhances drug sensitivity and increases the incentive properties of cocaine. Thus, ΔFosB accumulation could amount to a "molecular switch," whose uniquely stable expression bridges the gap between acute responses to drug exposure and long-term adaptations in the neural and behavioral plasticity of addiction (15).

Some of the findings of earlier studies using *fosB* knockout mice were similar to those of the ΔFosB inducible transgenic studies described above (60). For example, the knockout mice do not sensitize to repeated cocaine administration. However, their initial exposure to cocaine results in enhanced behavioral responses, discrepant with findings from the transgenic studies. Interpretation of data from the *fosB* knockout is complicated by the inability to ascribe these effects specifically to ΔFosB, given that the mice lack both gene products, ΔFosB and FosB. It is interesting that the results of chronic cocaine administration in the knockout mice, where ΔFosB would be expected to have a greater effect, are consistent with those of the ΔFosB transgenic studies. In contrast, the discrepant behavioral responses after acute drug administration support the possibility that the immediate and transient induction of FosB expression may play the more dominant role in short-term behavioral responses. Also, in the *fosB* knockout mice, the *fosB* gene is ubiquitously absent from the earliest stages of development, so the results from these mice are more complicated to interpret than those from the inducible, region-specific expression of the ΔFosB and ΔcJun transgenic mice.

A major goal of current research is to identify ΔFosB target genes. Using the candidate-gene approach, two target genes have been identified. Transgenic mice that overexpress ΔFosB show increased expression of the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid) glutamate receptor subunit GluR2 (56), whereas ΔcJun expression blocks the ability of chronic cocaine exposure to induce this protein (59). In addition, the promoter region of this gene contains an AP-1 site that binds ΔFosB, and overexpression of GluR2 in the NAc via viral-mediated gene transfer increases rewarding responses to cocaine, comparable to the result of ΔFosB overexpression (56). Another potential target gene of ΔFosB is the neuropeptide dynorphin. In contrast to the actions of CREB on dynorphin expression, ΔFosB decreases expression of the neuropeptide, which could further contribute to the enhancement of reward sensitivity seen with ΔFosB induction (58, 61).

Another approach to identifying potential ΔFosB target genes has been through the use of DNA microarrays (62, 63; CA McClung, EJ Nestler, unpublished observations). Inducible overexpression of ΔFosB regulates the expression of

several genes in the NAc and other regions (62, 63). The transcriptional regulation of these genes by ΔFosB requires additional confirmation, and their significance to drug-related plasticity has yet to be elucidated. However, one putative ΔFosB target gene identified by DNA microarray analysis is cyclin-dependent kinase 5 (Cdk5) (62, 64). Subsequently found to be induced in the NAc and dorsal striatum by chronic cocaine administration (64), Cdk5 has an AP-1 site in its promoter region, and ΔFosB increases promoter activity via this site (62). A possible function of Cdk5 in addiction plasticity is discussed below.

Another recent study using DNA microarrays indicates that the expression profile of genes induced by ΔFosB in the NAc can account for close to 30% of all the genes regulated by chronic cocaine (CA McClung, EJ Nestler, unpublished observations). Interestingly, short-term ΔFosB expression results in gene-expression effects opposite to those seen with long-term ΔFosB expression. These differences are reflected in opposing effects on cocaine reward, which is reduced by short-term ΔFosB expression and increased by long-term ΔFosB expression. This dynamic regulation of gene expression profiles by ΔFosB in either a time-dependent or, because of its stability, concentration-dependent manner is unusual, and the relationship of its putative target genes to drug-induced gene expression and addiction behavior warrants further investigation.

Other Transcription Factors

Although this review emphasizes CREB and ΔFosB, other transcription factors related to addiction have also been studied. For example, NAC-1 is a transcription factor whose mRNA expression is increased in the NAc of rats after chronic cocaine self-administration (65), and it is believed to play a role in some of the behavioral responses to cocaine, including sensitization (66, 67). Levels of the transcription factor NURR1, shown to activate transcription of the dopamine transporter in vitro, are markedly low in midbrain dopamine neurons of human cocaine abusers, which implies that the cocaine-induced decrease in NURR1 mRNA levels may mediate decreased dopamine transporter gene transcription in these neurons after repeated drug exposure (68). Immunoreactivity of another transcription factor, nuclear factor-κB, is induced in the NAc of mice with repeated cocaine exposure, and nuclear factor-κB has been identified as a target gene of ΔFosB by use of DNA microarrays (63). As more microarray studies elucidate transcriptional changes in animal models of addiction, it is expected that additional transcription factors, their target genes, and their roles in addiction plasticity will be identified and studied (62, 69; CA McClung, EJ Nestler, unpublished observations).

NEUROTROPHIC MECHANISMS OF ADDICTION

Neuronal Morphology

As the relationship between a cell's chemistry and structure becomes increasingly apparent, it is not surprising that chronic exposure to drugs of abuse has been

shown to alter the morphology of neurons in reward circuits of the brain. Chronic morphine administration decreases the size and caliber of VTA dopamine neurons (70), and changes in cytoskeletal proteins and impairment in axoplasmic transport have been observed specific to these neurons (71, 72). It is possible that these morphological alterations reflect a decrease in dopaminergic transmission to the NAc, which may in turn contribute to dysphoria during withdrawal. In addition, chronic morphine has been shown to decrease the complexity of dendritic branching and the number of spines on medium spiny neurons in the NAc and prefrontal cortex in rats (73). In contrast, chronic cocaine or amphetamine increases dendritic branching and spine density in the NAc and prefrontal cortex in rats (73, 74). It is hypothesized that these alterations in limbocortical circuitry may contribute to incentive-motivational effects as well as impaired decision making and judgment (75). Results of studies in which rats self-administered heroin or cocaine were similar to results from rats receiving experimenter-administered drugs (75, 76), indicating that alterations of neuronal morphology occur in both settings. Significantly, these dendritic changes persist for up to one month, leading some to surmise that the structural modifications are important in mediating long-term behavioral changes after chronic drug exposure.

Neurotrophic Factors

Although the relationship between drug-induced alterations in dendritic morphology and behavior remains conjectural, studies have implicated neurotrophic factors, which can control neuronal morphology, in aspects of drug addiction. Evidence accumulated during the past decade suggests that neurotrophic factors, whose role in the development of the nervous system is well-characterized, also mediate plasticity in the adult nervous system via their ability to regulate synaptic transmission as well as maintain growth, survival, and differentiation of neurons (77–80).

Dopaminergic neurons of the VTA express brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT3) mRNA, as well as their receptors, the tropomyosin-related kinase (Trk) receptors TrkB and TrkC, respectively. Medium spiny neurons of the NAc express TrkB and TrkC receptors as well as low levels of BDNF (81). An early study showed that BDNF infusion could reverse certain morphological and biochemical changes seen in VTA dopaminergic neurons following repeated morphine exposure (70, 82). More recent experiments have shown that BDNF and NT3 potently influence behavioral sensitization to cocaine and the regulation of dopaminergic transmission to the NAc (83–85). Further, BDNF has been implicated in mediating cue-induced cocaine craving even after 90 days of withdrawal, possibly through sustained increases in BDNF but not nerve growth factor (NGF) levels within the VTA, NAc, and amygdala (86). Knockout mouse studies show that BDNF is responsible for inducing normal expression of D3 dopamine receptors in the NAc shell and plays an important role in behavioral sensitization (87). This may be relevant to addictive behaviors; infusion of D3 receptor partial agonists has been shown to achieve selective inhibition of cocaine-seeking

behavior (88), and D3 receptor blockade attenuates both the rewarding effects of cocaine (as assayed by conditioned place preference) and cocaine-induced drug-seeking behavior (89). Thus, BDNF-dependent induction of D3 receptor gene expression in the NAc may be one mechanism by which the neurotrophic factor can modulate drug-associated behaviors. Finally, conditional BDNF knockout mice also have an attenuated opiate withdrawal syndrome, which implies their involvement in opiate-induced behaviors as well (90).

Other neurotrophic factors, such as NT3, ciliary neurotrophic factor, basic fibroblast growth factor, and glial-cell–derived neurotrophic factor (GDNF) also influence psychostimulant-induced behavioral sensitization (see 81 for review). GDNF infusion into the VTA decreases the usual cocaine-induced upregulation of intracellular proteins, and GDNF knockout mice show increased behavioral sensitization to cocaine (91). BDNF and NT3 have each been shown to modulate opiate withdrawal and noradrenergic signaling (90, 92). These and other findings suggest that neurotrophic factors play an important role in regulating psychostimulant- or opiate-induced behaviors. Given the function of neurotrophic factors in influencing neuronal morphology, it is tempting to speculate that they may mediate the cocaine- and morphine-induced structural changes described above, but there is as yet no direct evidence that they are responsible for such long-term changes.

Studies show that repeated exposure to drugs of abuse alters neurotrophic-factor signaling cascades in neurons of the mesolimbic dopamine system (85, 93–97). Neurotrophic factor binding to the Trk family of receptor tyrosine kinases activates several signal-transduction cascades, including the Ras/ERK protein kinase pathway, the PI3K/Akt kinase pathway, and an isoform of phospholipase C, phospholipase Cγ1 (PLCγ1) (98). For example, repeated exposure to morphine increases the expression of PLCγ1, an activator of the phosphatidylinositol pathway, in the VTA (97). When PLCγ1 is expressed by viral-mediated gene transfer at levels similar to the upregulation in response to chronic morphine in the VTA, the behavioral response to the rewarding effects of morphine is altered (96). These and other studies in the MAPK cascade and the JAK-STAT pathway indicate that neurotrophic-factor signaling pathways are altered by chronic drug exposure and provide possible mechanisms whereby changes in neurotrophic-factor signaling affect behavioral plasticity.

Recent studies identify a molecular substrate that may link chronic drug abuse with dendritic changes in neurons in response to cocaine. Cyclin-dependent kinase 5 (Cdk5), part of a family of serine/threonine cyclin-dependent kinases, is best characterized for regulation of neuronal cytoarchitecture (99). It is known to play a role in neuronal migration, actin dynamics, microtubule stability, synaptic structure, and plasticity. Unlike other Cdk family members, which are regulators of eukaryotic cell-cycle transitions, Cdk5 functions in neurons, which are postmitotic cells. Cdk5 activity is regulated by its interaction with the noncyclin coactivators p35 and p39, and by transcriptional regulation and post-translational events such as phosphorylation. Interestingly, it has been shown that Cdk5 is transcriptionally

regulated by ΔFosB (62). cDNA-array analysis of brain regions overexpressing ΔFosB in inducible transgenic mice reveals that Cdk5 is consistently upregulated, and promoter analysis identified an AP-1 binding site whereby ΔFosB activates Cdk5 transcription in vitro. In addition, either chronic cocaine administration or overexpression of ΔFosB increases Cdk5 and p35 expression in the striatum (64). Further, inhibition of Cdk5 activity in the striatum both potentiates the behavioral effects of chronic cocaine and attenuates the cocaine-induced dendritic spine outgrowth in the NAc core and shell (64, 100). Together, these data point toward a scheme whereby chronic cocaine upregulates the uniquely long-lasting transcription factor ΔFosB, which increases Cdk5 transcription and activity, which then contributes to the structural modification of dendritic spines in the NAc, which may in turn play a role in the development of behavioral sensitization to cocaine (Figure 5). Neurotrophic factors may also be involved in this pathway, since NGF has been shown to induce p35 expression in PC12 cells via the ERK cascade (101), and BDNF induces Cdk5 kinase activity in primary neuronal cultures (102). This pathway represents at least one potential mechanism whereby drug-induced upregulation of a transcription factor can lead to structural and behavioral changes that are strongly implicated in addiction plasticity. The significance of these schemes

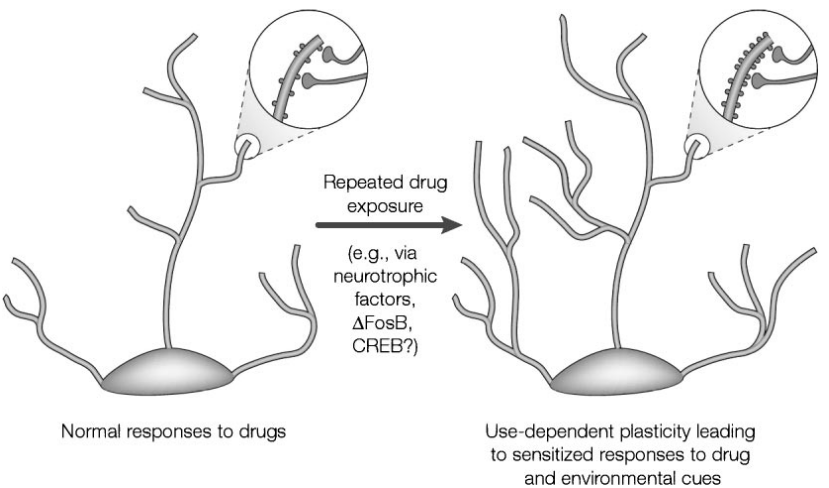

Figure 5 Regulation of dendritic structure by drugs of abuse. The figure shows the expansion of a neuron's dendritic tree after chronic exposure to a drug of abuse, as has been observed in the NAc and prefrontal cortex for cocaine and related psychostimulants. The areas of magnification show an increase in number of dendritic spines, which is postulated to coincide with activated nerve terminals. Such alterations in dendritic structure, which are similar to those observed in some learning models (e.g., long-term potentiation), could mediate long-lived sensitized responses to drugs of abuse or environmental cues. (From Reference 15 with permission.)

requires further study, but it is tantalizing to view synaptic, and therefore neural-circuit, reorganization as a potential mechanism of the long-term effects of drugs on reward, learning, and relapse seen in addiction.

Neurogenesis

Traditionally, the hippocampus is viewed as a critical mediator of declarative memory, but increasing evidence points to its role in the acquisition and maintenance of drug-taking behavior (103–105). Still, the details of its involvement in addiction remain poorly understood. Chronic exposure to drugs of abuse has been shown to decrease the birth of new neurons in the subgranular zone of the adult hippocampus. Both chronic morphine treatment and self-administration of opiates decrease neurogenesis in this region (106). In addition, studies have shown that ethanol inhibits neural progenitor-cell differentiation and survival in the adult rat subgranular zone (107), and self-administration of nicotine decreases neurogenesis in the dentate gyrus in a dose-dependent manner (108). Although acute exposure to psychostimulants has yielded partially contradictory results, studies involving chronic cocaine or amphetamine administration have yet to be done (see 109 for review). A recent study shows that a cannabinoid receptor antagonist given in vivo increases adult neurogenesis in the hippocampus (110). The functional significance of these findings remains unclear, given the current controversy in the field regarding the physiologic importance of adult neurogenesis. Growing evidence supports a correlation between increased neurogenesis and learning and memory (111, 112); further studies are needed to clarify the role of adult neurogenesis in addiction plasticity.

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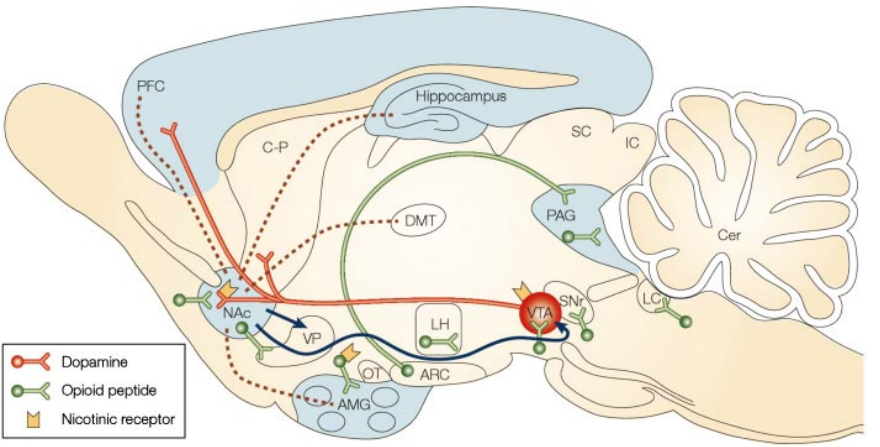

Figure 1 Key neural circuits of addiction as visualized in a mid-sagittal diagrammatic representation of the rat brain. Dotted lines indicate limbic afferents to the nucleus accumbens (NAc). Arrows represent efferents from the NAc thought to be involved in drug reward. Dopamine pathways indicate projections of the mesolimbic dopamine system thought to be a critical substrate for drug reward. This system originates in the ventral tegmental area (VTA) and projects to the NAc and other limbic structures, including olfactory tubercle (OT), ventral domains of the caudate-putamen (C-P), amygdala (AMG), and prefrontal cortex (PFC). Opioid peptide pathways indicate opioid peptide-containing neurons, which are involved in opiate, ethanol, and possibly nicotine reward. These opioid peptide systems include the local enkephalinergic circuits (short segments) and the hypothalamic midbrain beta-endorphin circuit (long segment). Blue areas indicate the hypothesized distribution of $GABA_A$ receptor complexes, which may contribute to ethanol reward. Nicotinic acetylcholine receptors are hypothesized to be located on dopaminergic and opioid peptidergic systems. ARC, arcuate nucleus; Cer, cerebellum; DMT, dorsomedial thalamus; IC, inferior colliculus; LC, locus coeruleus; LH, lateral hypothalamus; PAG, periaqueductal gray; SC, superior colliculus; SNr, substantia nigra pars reticulata; VP, ventral pallidum. (From Reference 15 with permission.)

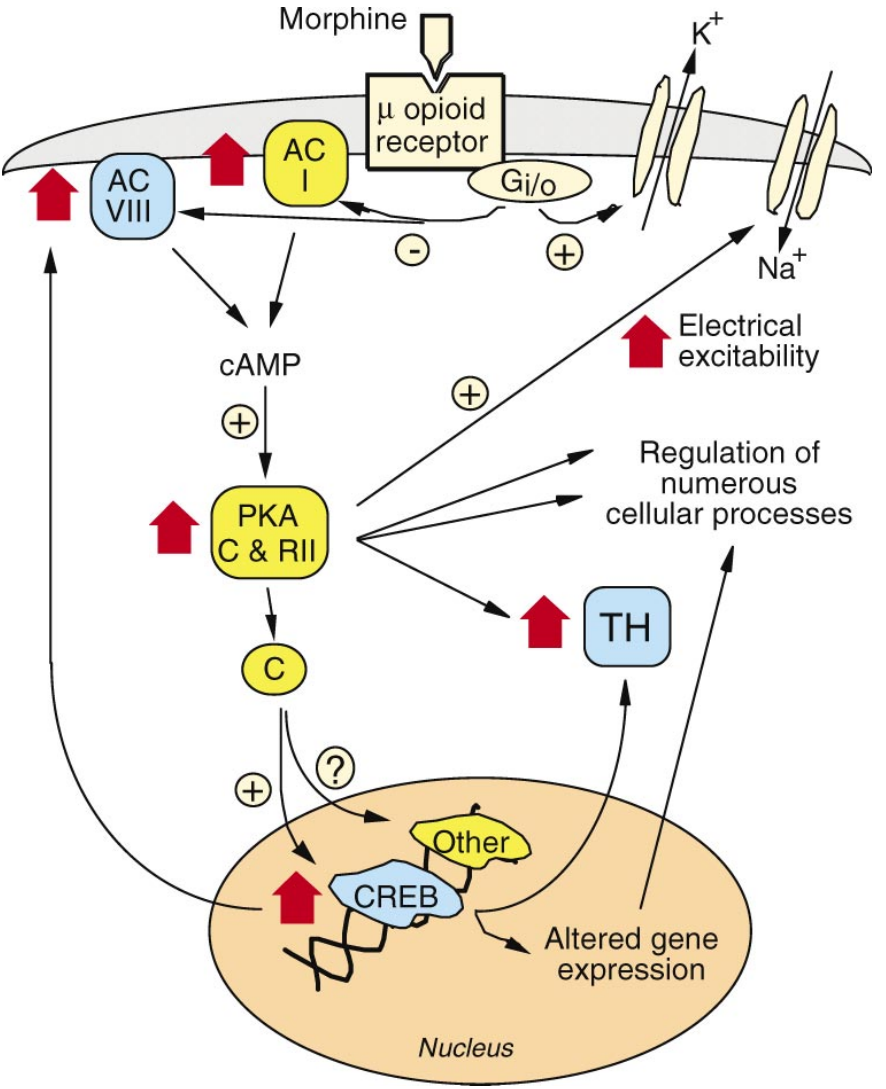

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Figure 2 Opiates acutely inhibit neurons in the locus coeruleus (LC) by increasing the conductance of an inwardly rectifying K^+ channel via coupling with subtypes of Gi/o and by decreasing a Na^+-dependent inward current via coupling with Gi/o and the consequent inhibition of adenylyl cyclase. Reduced levels of cAMP decrease protein kinase A (PKA) activity and the phosphorylation of the responsible channel or pump. Inhibition of the cAMP pathway also decreases phosphorylation of numerous other proteins and thereby affects many additional processes in the neuron. For example, it reduces the phosphorylation state of CREB, which may initiate some of the longer-term changes in LC function. Red arrows summarize effects of chronic morphine in the LC. Chronic morphine increases levels of types I (ACI) and VIII (ACVIII) adenylyl cyclase, PKA catalytic (C) and regulatory type II (RII) subunits, and several phosphoproteins, including CREB and tyrosine hydroxylase (TH), the rate-limiting enzyme in norepinephrine biosynthesis. These changes contribute to the altered phenotype of the drug-addicted state. For example, the intrinsic excitability of LC neurons is increased via enhanced activity of the cAMP pathway and Na^+-dependent inward current, which contributes to the tolerance, dependence, and withdrawal exhibited by these neurons. Upregulation of ACVIII and TH is mediated via CREB, whereas upregulation of ACI and the PKA subunits appears to occur via a CREB-independent mechanism not yet identified. (From Reference 113 with permission.)

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