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Molecular Mechanisms of Psychostimulant-induced Structural Plasticity

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Abstract

Drug addiction is characterized by persistent behavioral and cellular plasticity throughout the brain's reward regions. Among the many neuroadaptations that occur following repeated drug administration are alterations in cell morphology including changes in dendritic spines. While this phenomenon has been well documented, the underlying molecular mechanisms are poorly understood. Here, within the context of drug abuse, we review and integrate several of the established pathways known to regulate synaptic remodeling, and discuss the contributions of neurotrophic and dopamine signaling in mediating this structural plasticity. Finally, we discuss how such upstream mechanisms could regulate actin dynamics, the common endpoint involved in structural remodeling in neurons.

Introduction

Drug addiction is characterized by persistent behavioral and cellular plasticity throughout the brain's reward regions. During the transition from initial drug use to addiction, people experience tolerance and sensitization to varying aspects of drug action, reward dysfunction, escalation of drug intake, and, finally, compulsive use in the face of severely adverse physical or psychosocial consequences [24,43,46,67,82]. Although the neurobiological mechanisms driving addiction are not known with certainty, it is hypothesized that molecular and cellular changes occur during initial drug exposure, which then accumulate over time and, in vulnerable individuals, drive compulsive drug use. Several long-term molecular and cellular changes induced by drugs of abuse have already been shown throughout diverse neuronal populations within the brain reward circuit (● Fig. 1). Despite these advances, only a few studies have definitively linked a specific molecular change with structural and behavioral plasticity. A more detailed understanding of this relationship could lead to the development of more effective treatments that target specific behavioral features of addiction by reversing the drug-induced restructuring of neurons.

Several molecular and cellular changes induced by drugs of abuse have been implicated in regulating drug-induced structural plasticity and behavioral responses to cocaine [67,68,84]. These include changes in protein kinase A (PKA), cyclin-dependent kinase 5 (Cdk5), and protein kinase B (also known as Akt) as well as downstream transcription factors such as Δ FosB, nuclear factor kappa B (NF κ B), and myocyte enhancing factor 2 (MEF2). Through the use of pharmacological antagonists and agonists, genetic mutant mice, and viral gene transfer, each of these molecules has been shown to mediate structural plasticity in several brain regions, including the reward circuitry. However, the direct relationship between synaptic alterations and addictive behaviors remains much more complex.

In this review, we discuss new advances in our understanding of the molecular mechanisms of structural plasticity in psychostimulant addiction. Additionally, recent work indicates the need to reevaluate the hypothesis that psychostimulant-induced increases in dendritic spines on brain reward neurons are necessary for behavioral sensitization after repeated exposure to drugs of abuse. Based on these published studies, we will propose new areas of research that warrant further investigation.

Psychostimulants and structural plasticity of brain reward circuitry

The brain's reward circuit evolved to direct one's resources to obtain natural reward, such as food, sex, and social interaction, but this system can be corrupted or hijacked by drugs of abuse. Within this circuit, drug-induced plasticity has been shown to involve altered dendrite branching or arborization as well as changes in the density or morphology of dendritic spines. A large literature, over the past decade, has characterized the effects of long-term psychostimulant administration on structural plasticity of brain reward regions. Most of these studies are correlative, and associate structural changes in specific brain regions with a behavioral phenotype (for review see [82]) As depicted in Table 1, psychostimulants such as amphetamine and cocaine have been shown to increase dendritic spines and neurite complexity in NAc (nucleus accumbens) medium spiny neurons, VTA (ventral tegmental area) dopaminergic neurons, and PFC (prefrontal cortex) pyramidal neurons [51,71,79-81,88].

Neurotrophic factor signaling and psychostimulant-induced structural plasticity

Changes in levels of BDNF (brain derived neurotrophic factor) protein and mRNA have been examined in multiple brain regions following administration of many classes of addictive substances. Psychostimulants produce a widespread, but transient, induction of BDNF protein in the NAc, PFC, VTA, and central (CeA) and basolateral [111] nuclei of the amygdala [31, 32,50]. Both contingent and non-contingent (i.e., animals yoked to self-administering animals) cocaine administration causes transient yet significant elevation of BDNF protein in the NAc [31,53,117]. While the increase in BDNF during cocaine administration appears to be dynamic in nature, there is a more stable and long-term induction of BDNF protein in the NAc, VTA, and amygdala [32,75] following prolonged withdrawal from cocaine, and there is evidence that epigenetic regulation at the *bdnf* gene may be involved in mediating this persistent induction [49]. Interestingly, BDNF application has been shown to increase spine density and induce plasticity through some of the same signaling pathways that are activated by drug exposure, providing a possible mechanism for both induction and maintenance of structural and functional changes described with psychostimulants [2,12,42,107].

Several proteins in neurotrophin signaling cascades are regulated within the mesolimbic dopamine system by drugs of abuse; these include drug effects on IRS (insulin receptor substrate) 1 & 2, PI3K (phosphatidylinositol-3-kinase), Akt, PLC γ (phospholipase C γ), the Ras-ERK (extracellular signal regulated kinase) pathway, and NF κ B signaling (Fig. 2). Psychostimulants dramatically increase ERK phosphorylation in numerous brain regions, including the NAc, VTA, and PFC, following acute or chronic drug administration [41,63, 73,91,92,96,108,109]. These findings are consistent with stimulant-induced increases in neuronal branching and spine number, given Ras-ERK's established role in neurite outgrowth (discussed in more detail below). The effects of psychostimulants on the IRS-PI3K-Akt pathway are more complex, and inconsistencies in the literature are often accounted for by differences in the interval after drug administration and heterogeneity of the tissue sampled. For example, chronic cocaine increases PI3 K activity in the NAc shell, with decreases observed in the NAc core [118]. These data are in line with a previous report showing that chronic cocaine selectively increased BDNF mRNA levels in the NAc shell and decreased TrkB (tyrosine

receptor kinase B) receptor mRNA in the NAc core [26]. Thus, shell and core differences in PI3 K activity could be explained by differential upstream regulation of BDNF and TrkB by cocaine. Interestingly, when a more general dissection of striatum is used (including NAc and CPu [caudate putamen]), it has been shown that amphetamine decreases Akt activity in synaptosome preparations [110,111], and we have observed similar effects of chronic cocaine in the NAc without distinguishing between core and shell [76]. Although the antibodies used here were not selective, it should be noted that given the predominance of the Akt1 versus Akt2 isoform in brain, these changes are likely to be specific to Akt1. Additionally, comparison among these studies is complicated by the time-course used to study Akt signaling changes, as recent work by McGinty and colleagues suggests that chronic amphetamine causes a transient and nuclear-specific change in Akt phosphorylation in striatum [59]. At early timepoints after amphetamine administration there is a nucleus-specific increase in Akt phosphorylation, however, after two hours Akt phosphorylation is decreased, suggesting a compensatory mechanism to turn off this activity. Although it is unclear whether adaptations in NAc Akt signaling are driving drug-induced structural plasticity, as we have shown in the case for the VTA⁷⁷, understanding the patterns of psychostimulant induction of Akt signaling in distinct subregions of NAc, in combination with functional studies using viral vectors to manipulate Akt signaling directly, we can define with greater precision, the distinct molecular networks driving structural plasticity in NAc.

Alterations in the PLC γ and NF κ B signaling pathways in drug abuse are not as well studied as ERK and Akt; however, recent work shows that both pathways are regulated by cocaine. Graham and colleagues [31] observed increased phosphorylation of PLC γ in the NAc following acute, chronic yoked, or chronic self-administered cocaine, an effect that was dependent on BDNF. Additionally, it is unknown whether this cocaine-induced regulation of PLC γ results in activation of NF κ B; however, based on in vitro studies, there may be significant crosstalk between these pathways [52,74]. An earlier study from our group showed that the NF κ B subunits p105, p65, and I κ B are increased in the NAc in response to chronic cocaine administration [4]. This is consistent with findings from Cadet and colleagues [5], who demonstrated that methamphetamine induces NF κ B binding activity in striatal regions. We have more recently shown that chronic cocaine induces NF κ B-dependent transcription in the nucleus accumbens of NF κ B-LacZ transgenic mice. This induction of NF κ B activity is accompanied by increased expression of several NF κ B genes (p105, p65, and I κ B β), the promoters of which show chromatin modifications after chronic cocaine exposure consistent with their transcriptional activation [85]. In addition, functional studies show that viral-mediated overexpression of a dominant negative form of I Kappa kinase, that serves as an antagonist of the NF κ B pathway in the NAc, prevents the ability of chronic cocaine to increase the density of dendritic spines on NAc medium spiny neurons. Such inhibition of NF κ B signaling also blunts sensitization to the rewarding effects of cocaine [85]. These data support a link between increased spine density and behavioral sensitization to cocaine. However, such a link is not supported by studies of other signaling molecules (e.g., Cdk5, see below), emphasizing the complexity of these phenomena and the need for further study.

Dopamine signaling and psychostimulant-induced structural plasticity

The release of dopamine and the subsequent activation of dopamine receptors lead to a cascade of intracellular events, which may play an important role in structural plasticity during exposure to psychostimulants. Dopamine receptors are generally classified into a D1-like or D2-like receptor family based on whether they are positively or negatively coupled to adenylyl cyclase activity [reviewed in 62] and are thought to be localized to largely distinct populations of neurons within the NAc and CPu [1,29,30,99]. Receptors in the D1-like family (D1 and D5) are positively coupled to adenylyl cyclase through G_{s/olf} proteins and, upon stimulation, increase cytosolic levels of cyclic AMP (cAMP) and downstream activation of PKA [98]. Once

active, PKA can influence numerous intracellular targets, including activation of dopamine- and cAMP-dependent phosphoprotein of 32 kDa (DARPP-32) [100], altered function and trafficking of glutamate receptors [34,93], and activation of the transcription factor cAMP-responsive element binding protein (CREB) [68]. Dopamine D2-like receptors (D2, D3, and D4 receptors) are coupled to $G_{i/o}$ proteins, which inhibit adenylyl cyclase [34,95]. In contrast to D1-like receptors, activation of the D2 family of dopamine receptors can lead to activation of PLC generating diacylglycerol (DAG) and protein kinase C (PKC) activation, and subsequent IP_3 activation and the mobilization of intracellular calcium stores [98]. D2 receptor activation also results in enhancement of potassium conductance [62] and, like D1 activation, can lead to changes in calcium channel properties, glutamatergic signaling, and regulation of the Ras-ERK cascade [33,39].

In the NAc, intracellular signaling stimulated by D1 receptor activation has been implicated in behavioral and biochemical responses to drugs of abuse in part mediated through activation of CREB [13,14,70,90,106]. Given the large amount of data to suggest that CREB activity in the NAc regulates an individual's sensitivity to a broad range of emotional stimuli including the rewarding properties of drugs of abuse [6,7,15], one can imagine a role of CREB in mediating drug-induced structural plasticity. In one such study, Murphy and Segal [64] report that spine density changes are mediated through cAMP-PKA-CREB activation in cultured rat hippocampal neurons and, based on data showing that antisense knockdown of CREB regulated spines only at long-term time points, they suggest that the lasting effects may occur through repression of a CREB target. Evidence such as this implicates CREB and certain of its target genes in the structural plasticity that occurs in brain reward regions after drug administration. However, despite the wealth of information demonstrating CREB's role in learning and memory as well as in drug addiction, two fields in which changes in dendritic spine number and shape have been well documented, few studies have directly examined the role of CREB in synaptic remodeling.

The Ras-ERK pathway may also contribute to structural plasticity induced by psychostimulants in brain reward regions [19,61]. As stated earlier, these drugs induce a transient but dramatic activation of ERK in numerous reward-associated brain regions after acute or chronic administration, with effects seen in the NAc, VTA, and PFC, [108,109]. Studies performed in vitro suggest that ERK activation is critical for the formation, but not the stability, of new spine protrusions induced by temporally spaced K^+ -induced depolarizations [112], while blockade of ERK activation via inhibition of Ras signaling leads to a significant suppression of hippocampal spine number and length [86]. In line with the notion that ERK regulates the proliferation or induction of new spines, but not the stability of dendritic outgrowths, pharmacological inhibition of ERK in CA1 hippocampal neurons prevents BDNF-induced spine proliferation without causing a reduction in spine number. These observations suggest that ERK activation may be necessary for neurotrophic factors such as BDNF, or dopamine receptor activation, to induce plastic changes [2], although this remains to be demonstrated directly.

Additional signaling molecules, known to interact with dopamine receptors, may also be involved. D2-class dopamine receptors can function through an Akt-GSK-3 (glycogen synthase kinase 3) signaling cascade that has previously been implicated in morphological alterations such as changes in the size of VTA dopamine cell bodies following chronic exposure to opiate drugs of abuse [8,83]. Beaulieu and colleagues (2005) have demonstrated that amphetamine alters the formation of signaling complexes containing the scaffolding protein β -arrestin2, and the negative regulator of Akt, PP2A (protein phosphatase 2A), ultimately leading to dephosphorylation and deactivation of Akt and subsequent activation of GSK-3. These molecular events then regulate dopamine activity and have been implicated in psychiatric diseases such as schizophrenia, bipolar disorder, and drug addiction [3,9].

Consistent with the involvement of dopamine in these cellular and behavioral processes associated with addiction, it is not surprising that induction of dendritic spines after repeated treatment with psychostimulants occurs in both D1- and D2-expressing MSNs (medium spiny neurons) [49]. Interestingly, however, the long-term stability of new spines appears to be greater in D1 + compared to D2 + neurons. The persistence of increased dendritic spines in D1-containing MSNs correlates with the stable induction of Δ FosB [61], through the D1/DARPP-32/PP1 signaling pathway [51,116]. A member of the Fos family of genes, Δ FosB is a highly stable transcription factor that accumulates following drug administration in brain areas associated with rewarding aspects of drugs of abuse, including the NAc [40,69]. Overexpression of Δ FosB increases the rewarding properties of several classes of drugs of abuse, including psychostimulants, while blockade of Δ FosB causes a reduction in drug reward [66,68]. Given the considerable evidence for an obligatory role of Δ FosB in behavioral and molecular adaptations to drugs of abuse, investigation of how Δ FosB directly mediates dendritic plasticity is a high priority. Preliminary data from our laboratory has indeed found that overexpression of Δ FosB increases dendritic spine density in medium spiny neurons of the NAc.

Furthermore, several studies have elucidated some interesting candidates downstream of Δ FosB that may mediate the synaptic remodeling which occurs in response to psychostimulant exposure. Using genome wide analysis, our group has shown that Δ FosB overexpression leads to changes in several genes known to mediate spinogenesis [58]. One such target induced by Δ FosB is NFkB [3], which as noted above increases spine density on NAc neurons. Another target induced by Δ FosB is Cdk5. Inhibition of Cdk5 prevents the cocaine-induced spine proliferation in the NAc [71] while also paradoxically potentiating the behavioral responses to cocaine [10,103]. Additionally, Pulipparacharuvil et al. [76] have recently demonstrated that a direct downstream target of Cdk5, MEF2, appears to directly regulate cellular adaptations that are involved in cocaine-induced increases in dendritic spine density. Viral-mediated overexpression of MEF2 inhibits, while knockdown of MEF2 potentiates, the cocaine-induced increases in MSN spine density. Reduction of MEF2 activity in response to cocaine, achieved via phosphorylation by Cdk5, may allow for transcription of cytoskeleton associated genes such as the neural Wiskott-Aldrich syndrome proteins (N-WASP) and WASP-family verprolin homologue (WAVE) proteins which were identified as having putative MEF binding sites in their proximal promoter regions [76]. There is also considerable evidence to suggest that one particular WAVE protein, WAVE1, regulates spine morphogenesis in a Cdk5-dependent manner [45,97]. In this way, Cdk5 activation, induced by chronic cocaine administration via Δ FosB, could result in regulation of WAVE activity, while MEF2 may regulate its expression level to mediate longer-term changes involved in drug addiction.

Interestingly, as in the case of Cdk5 inhibition, overexpression of a constitutively active form of MEF2 reduced the density of dendritic spines on MSNs while paradoxically increasing sensitivity to cocaine's behavioral effects. Given the large amount of prior correlative data suggesting a link between sensitized behavioral responses to psychostimulants and an increase in spine number, these data on Cdk5 and MEF2 suggest a functional uncoupling between the two phenomena and argue that this dogma needs much further investigation. In addition, these data underscore the importance of studying complex molecular systems and moving beyond the analysis of single components. As suggested by Pulipparacharuvil and co-workers [76], cocaine-induced spine density changes may not lead to increased sensitivity per se, but may be a result of "homeostatic adaptations" to compensate for other changes caused by chronic psychostimulant exposure, such as a reduction in glutamatergic stimulation of medium spiny neurons by prefrontal cortical afferents. Understanding the dynamic changes in molecular systems in the context of structural plasticity of the brain's reward circuitry, will help us to better identify specific forms of maladaptive plasticity important in addictive behaviors.

Actin binding proteins and stimulant-induced structural plasticity

While changes in the density of dendritic spines following exposure to drugs of abuse has been well characterized, very little investigation into alterations in the morphology of these spines has been carried out to date. Spine morphology is an important factor in considering functional connectivity within neuronal circuitry, as it is highly correlated with synaptic function. Dendritic spines come in various shapes and sizes, which can be divided into general categories such as stubby, thin, and mushroom-like that are thought to reflect differences in functional properties [38]. Along these lines, it has been shown that the size of the spine head is proportional to the size of the postsynaptic receptor density and presynaptic active zone [37, 77,89,102], suggesting that larger spines are indicative of stronger connections, and that changes in the structure of dendritic spines can result in an alteration of synaptic function [18,22,87,115]. In addition, the long-term potentiation (LTP) of synaptic responses in hippocampus is facilitated by the amplified membrane potentials that occur in the spine head as a result of the constricted neck of the mushroom-shaped dendritic spine [36]. In this same model of learning and memory, the induction of synaptic potentiation alters the morphology of dendritic spines, by enlarging the spine head or creating new structures [17,35,55,105]. An alteration in the shape of dendritic spines, therefore, can have strong functional consequences and is something that should be investigated more thoroughly in brain reward regions after exposure to drugs of abuse.

Dendritic spines are highly enriched with actin, which is thought to enable these types of structural changes [25,57]. The polymerization and arrangement of filamentous actin is critical for regulation of spine growth and morphological plasticity [20,23,27,54,56,78,119]. This process is continuous, and even stable spines contain a dynamic architecture of actin [94], which results in “twitching” of the spine head that is observed over a timescale of seconds [27]. The dynamic architecture is maintained by the polymerization and depolymerization of actin within the spine head. In general, profilin, an actin monomer sequestering protein, regulates the polymerization of actin, and the Arp2/3 complex is responsible for nucleating actin branches on pre-existing filaments, whereas the depolymerization of actin filaments is regulated mainly by the actin filament severing proteins, ADF/cofilin and gelsolin [16,78].

Recent work by Toda and colleagues [104] demonstrate changes in some of the actin cytoskeleton regulators in response to drugs of abuse. Their findings show that chronic cocaine exposure increases the amount of polymerized actin (f-actin) in dendritic spines of medium spiny neurons in the NAc. These effects can be long-term, as increases in f-actin can be observed after 3 weeks of withdrawal from repeated cocaine exposure. The long-term changes were also observed in areas of the prefrontal cortex, but not CPu. These changes in actin polymerization occurred in concert with a reduction in the inactive form of cofilin, which may be the result of reduced levels of LIM kinase, known to phosphorylate, and thereby inhibit, cofilin activity [113]. Levels of several other actin-binding proteins were altered in response to psychostimulant withdrawal. These data suggest that while initial exposure to drugs such as cocaine increases the amount of polymerized actin, repeated exposure results in changes to the baseline cycling of actin. Indeed, pharmacological manipulation of actin cycling to mimic these effects promoted cocaine-induced reinstatement of drug-taking behavior. While this study is the first to examine changes in direct regulators of actin assembly within the context of drug abuse models, it implicates another class of molecular pathways that have yet to be examined following exposure to drugs of abuse. The activity of many of these actin cytoskeleton regulators are known to be governed, at least in part, by the Rho family of small GTPases, namely RhoA, Cdc42, and Rac. The activation of these GTPases leads to the subsequent activation of several protein kinases and protein phosphatases that ultimately control the polymerization and assembly of actin filaments [for review, see 54,65]. Therefore, further

investigation into how these molecules are affected after drug use is greatly needed to understand the mechanism of drug-induced structural plasticity.

Insight into how these pathways may function in drug addiction comes from studies of synaptic plasticity in hippocampus [reviewed in 115]. Induction of LTP causes a similar increase in f-actin [7,44,47], and this polymerization of actin is required for LTP, as inhibition of actin dynamics blocks the development of LTP [28,48]. It has been hypothesized that the “treadmilling” of actin that occurs via the ongoing directional polymerization and depolymerization of actin filaments serves as a route for the trafficking of actin-binding and synaptic proteins to and from the postsynaptic density [11,56]. Further evidence suggests that it is this regulation of actin assembly in response to changes in synaptic activity that provides a foundation for synaptic plasticity [72]. This mechanism may be universal for induction of plastic changes regardless of the source of activity, whether from artificial electrical stimulation, learning in response to environmental challenges, or exposure to chemical agents such as drugs of abuse.

The arrangement of actin filaments within the spine head is such that there is a bundle of parallel actin filaments in the neck, and a meshwork of cross-linked actin filaments in the spine head. The meshwork of actin filaments provides a scaffold for postsynaptic proteins such as PSD-95 (postsynaptic density protein of 95 kDa), scaffolding proteins, and glutamate receptors. A major component of the postsynaptic structure, it is interesting that levels of PSD-95 are reduced after repeated exposure to cocaine [114]. Reduced levels of this synaptic protein can be correlated with an enhanced predisposition for the induction of synaptic potentiation, as knockdown of PSD-95 has been shown to result in enhanced LTP [60]. In fact, reduced levels of PSD-95 were also shown to increase dendritic spine instability, reminiscent of the higher rate of turnover that is characteristic during development [21]. This would suggest that the changes observed in response to psychostimulant exposure may in fact indicate a shift in the overall plasticity of the neurons themselves. However, in vitro studies have demonstrated that, while PSD-95 overexpression results in a maturation and stabilization of synapses, it can also increase dendritic spine density [22], which is counter to the reduced expression but increased spine density seen with psychostimulants. These findings suggest that the reduced PSD-95 is perhaps only one of many changes occurring in structural proteins of the dendritic spine of MSNs in the context of drug exposure. Other components of the postsynaptic density, such as members of the homer family of scaffolding proteins that are involved with the maturation of dendritic spines [87], may also play a role in the plasticity associated with exposure to drugs of abuse. Recent studies have shown that the expression of homer genes is altered, albeit in a complex manner, with several drugs of abuse [reviewed in 101]. Further exploration into alterations of these scaffolding proteins after psychostimulant exposure may help to provide a clearer understanding of the mechanisms responsible for long-term changes in the drug-mediated structural plasticity.

Conclusion

The data presented in this review demonstrate that we have made considerable progress in understanding how drugs of abuse mediate changes in postsynaptic complexity. Nevertheless, much remains unanswered. With the exception of a few works cited above, most of the information currently available about drug-induced alterations in dendritic spine number and morphology has been largely phenomenological in nature. We have presented here numerous pathways that appear to be important in regulating dendritic spines, however, many of these pathways are overlapping and involved in a complex mosaic within the cell. Due to the complex nature of these molecular networks, future research is needed to more completely understand how psychostimulants change intracellular signaling pathways to alter actin structure and ultimately influence addictive-like behavior. Indeed, we have only a rudimentary

understanding of how drugs of abuse regulate basic actin dynamics that have been so richly studied in other models of plasticity such as hippocampal LTP. Given the progress that has been made in understanding basic spine regulation in these other models, we now need to move beyond correlative assessments to fully understand the molecular mechanisms of drug-induced structural plasticity.

Finally, although this review has focused on plastic changes within the NAc that occur following psychostimulant administration, we should emphasize the importance of investigating morphological changes known to occur in other limbic brain regions, such as VTA and prefrontal cortex, to name just two (● Fig. 1). Additionally, by focusing on the identification of single molecular adaptations in these individual brain regions and ignoring the many dynamic changes, such as the kinetics of protein-protein or protein-DNA interactions that occur in response to drug administration across numerous brain regions and circuits, it is likely that the field has not captured all of the molecular, cellular, and systems level changes that are important in the expression of addictive behaviors. Therefore, a major goal of future research is to understand addictive behavior at the level of the neural and molecular circuit, which requires temporally and spatially localized manipulations of complex molecular networks in vivo integrated over the many brain regions that are known to influence drug reward and motivation. A more complete understanding of how drugs of abuse alter dendritic spines and other features of structural plasticity in these brain regions and across different cell types will give us a greater appreciation on a systems level of how drugs of abuse mediate such powerful and long-lasting behavioral effects (● Fig. 3).

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Fig. 1.

Neuronal subtypes in the neural circuitry underlying addiction. Projections of VTA dopamine neurons (shown in solid red lines) innervate directly NAc and mPFC neurons, as well as amygdala and hippocampal neurons (the latter projections are not shown in the figure). The solid purple line represents GABAergic afferents (some direct, some indirect) from the NAc to the VTA, which provide feedback to VTA dopamine neurons. The dotted purple lines represent glutamatergic afferents to the NAc from mPFC, amygdala, and hippocampus. Each structure contains specialized neuronal cell types thought to play an integral role in the complex behavioral phenotypes associated with drug reward and addiction. These cell types, color-coded in the key, include amygdala (green) and NAc (purple) spiny neurons, PFC (black) and hippocampal CA3 (blue) pyramidal neurons, and VTA dopamine neurons adapted from [84].

Fig. 2.

Molecular pathways implicated in the structural changes that occur as a result of exposure to drugs of abuse. Transcription factors, such as NFκB, ΔFosB, CREB, and MEF2 play a role in regulating changes in dendritic spines, and can be activated by a variety of signaling pathways. Neurotrophins can signal via receptor tyrosine kinases to activate the PI3K-Akt and Ras-ERK pathways, which ultimately regulate transcriptional activity, and possibly control actin cytoskeletal dynamics through regulation of the Rho family of small GTPases. Dopaminergic stimulation of D1 and D2 receptors can in turn act on some of these same pathways by activation of PKA and PKC. Structural plasticity induced by psychostimulants can therefore result from manipulation of several signaling pathways that impinge on actin assembly processes as well as gene expression.

Fig. 3.

Actin arrangement in the cytoskeleton. **Top panel:** Many proteins help regulate the polymerization and arrangement of actin filaments within the cytoskeletal network. Actin sequestering proteins provide a ready pool of actin monomers (globular actin, or g-actin) for the polymerization into filamentous actin (f-actin), while severing proteins cut the filaments and aid in depolymerization. A variety of capping, branching and bundling proteins provide the organization of these filaments in the cytoskeletal network. **Bottom panel:** Within each filament, there is a steady state of continuous polymerization and depolymerization such that ATP bound g-actin is favored for addition to the filament at one end, and dissociation of the hydrolyzed ADP bound g-actin at the other. This directionality of addition and subtraction of g-actin monomers to a filament results in a treadmilling effect, where an individual monomer be added at one end, and travel towards the opposite end before dissociating from the filament.

Table 1

This table describes the morphological changes, which occur in a number of different neuronal cell types in the brain's reward circuitry following chronic exposure to psychostimulants.⁷

Neuron Type	Neuron Function	Morphology Change
Amygdala spiny neuron	Emotional memory processing and encoding	?
NAc medium spiny neuron	Integration of positive and negative stimuli	↑ Dendrite complexity and spine density/morphometry
VTA dopamine neuron	Arousal and parsing of relevant emotional stimuli	↑ Spine density/morphometry
CA3 pyramidal neuron	Encoding contextual association memory	?
PFC pyramidal neuron	Executive functioning	↑ Dendrite complexity and spine density/morphometry

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