Addiction to Cocaine and Amphetamine

Minireview

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Addiction to the psychostimulant drugs, of which cocaine and the amphetamine derivatives are the most important, is one of the foremost public health problems in the United States. Cocaine and amphetamine share two critical properties with other addictive drugs: they are reinforcing when administered acutely (i.e., drug use entails repeated drug use) and produce compulsive use if administered chronically with adequate dose and frequency.

The mesoaccumbens dopamine (DA) pathway, extending from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens (NAc; the major component of the ventral striatum), has been identified as the critical shared substrate of the reinforcing effects of cocaine, amphetamine, and all other addictive drugs (Koob, 1996 [this issue of *Neuron*]). Drugs such as cocaine and amphetamine are thought to be addictive because they produce significant molecular adaptations both within and outside the mesoaccumbens circuitry that alter the function of neurons that regulate motivated behavior and emotion. Progress has been made in identifying both the properties of drugs that make them reinforcing and the potentially relevant adaptations within the VTA and in dopaminergically innervated brain regions including both the NAc and dorsal striatum.

Acute Actions of Cocaine and Amphetamine

The critical mechanism by which cocaine and amphetamine produce reinforcement is their ability to increase synaptic DA levels in the mesoaccumbens circuit. Cocaine blocks the DA reuptake transporter (DAT), a member of the Na^+/Cl^--dependent twelve transmembrane domain transporter family that also includes the norepinephrine and serotonin transporters. Amphetamine has more complex actions, but its most significant effect is to cause reverse transport of DA via the DAT. In mice lacking a DAT, as a result of targeted gene disruption, amphetamine does not increase synaptic DA levels (Giros et al., 1996).

There are significant homologies within the Na^+/Cl^--dependent transporter family; thus, cocaine and amphetamine also increase synaptic levels of norepinephrine and serotonin. While these other monoamine neurotransmitters may contribute to the reinforcing or addictive (i.e., plasticity-inducing) effects of cocaine and amphetamine, it is the increase in synaptic DA that is necessary for and central to reinforcement. Antidepressant drugs that block norepinephrine and/or serotonin, but not DA reuptake, produce neither significant reinforcement in animal models nor euphoria in humans. Moreover, antidepressants do not produce dependence in humans even with very long-term use. In addition, lesioning of DA terminals within the NAc or full pharmacological blockade of DA receptors inhibits cocaine or amphetamine self-administration (reviewed by Self and Nestler, 1995). It is also significant that mice lacking the DAT are entirely insensitive to the locomotor stimulant effects of cocaine or amphetamine (Giros et al., 1996).

The precise contributions of different postsynaptic DA receptors to reinforcement have yet to be fully established because of the lack of adequately selective antagonists directed against the five known DA receptors. Studies of drug self-administration in mice with disruptions in the genes encoding each of the different DA receptors as well as the DAT may also prove informative; however, the difficulty of establishing drug self-administration in the mouse strains currently used for homologous recombination and the problem of developmental compensation has slowed this type of analysis. Based on pharmacological data available to date, both D1 family and D2 family DA receptors contribute to cocaine and amphetamine reinforcement (reviewed by Self and Nestler, 1995), although it is the D1 receptor that has been implicated in cocaine- and amphetamine-induced plasticity to date.

Addiction to Cocaine and Amphetamine

The acute reinforcing effects of cocaine and amphetamine lead to patterns of drug use that, in epigenetically vulnerable individuals, result eventually in addiction, a state hypothesized to be the result of plastic changes in multiple neural circuits. The types of plasticity that underlie addiction can be divided conceptually into three groups: compensatory adaptations in neural systems that regulate autonomic and other somatic functions leading to physical dependence and withdrawal; adaptations in the mesoaccumbens brain reward circuitry itself resulting in the emotional and motivational aspects of dependence and withdrawal; plasticity involving both the mesoaccumbens circuitry and other limbic circuits yielding sensitization and cue-dependent, positively biased emotional memories of drug use that may predispose to relapse. Unlike the opiates and ethanol, cocaine and amphetamine do not produce physical dependence; they are nonetheless among the most reinforcing and addictive drugs known, underscoring the importance of plasticity in emotional circuits.

With cocaine and amphetamine, tolerance to the reinforcing effects may be marked, leading to administration of very high drug doses. Compared with amphetamine, cocaine has a very short duration of action that leads to a typical pattern of administration: rats or humans given access to adequate supplies of cocaine often binge, i.e., self-administer multiple closely spaced doses over long periods of time. Abstinence following such a binge may dramatically unmask neural adaptations that have occurred, as evidenced by a withdrawal

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syndrome in humans of dysphoria, anhedonia, and drug craving with eventual reinstatement of drug use. Anhedonia in humans may be modeled in rats by transient decreases in DA neurotransmission and elevations in electrical brain self-stimulation reward thresholds observed after cocaine administration (Markou and Koob, 1991).

Pharmacological attempts to inhibit the reinstatement of cocaine or amphetamine self-administration after discontinuation have utilized both DA receptor antagonists, aimed at blocking subsequent reinforcement, or DA receptor agonists, aimed either at supplementing transient decreases in dopaminergic neurotransmission during withdrawal, or decreasing the likelihood of subsequent cue-dependent drug craving. Current DA receptor antagonists are unacceptable treatments because they exacerbate anhedonia and dysphoria and because D2 receptor antagonists cause serious motor side effects. Selective D2 agonists such as bromocriptine have been used to treat craving in humans without great success. Strikingly, in a rat model in which cocaine self-administration was extinguished by replacement of cocaine with saline, D2 agonists caused reinstatement of self-administration, possibly as an interoceptive cue, whereas a D1 agonist did not. In addition, a D1 agonist prevented reinstatement of self-administration caused by a priming dose of cocaine itself (Self et al., 1996).

While a subset of adaptations to cocaine and amphetamine produce tolerance and dependence (and therefore upon drug cessation, withdrawal), other drug-induced adaptations produce sensitization, i.e., a subset of drug effects increase with repeated use. In humans, some aspects of sensitization may increase craving for drugs even if, as a result of tolerance, the actual enjoyment of drugs is diminished (Robinson and Berridge, 1993). Another form of sensitization observed in humans is a syndrome of cocaine- or amphetamine-induced paranoia, which, once initiated, may be reinstated even with relatively low drug doses after prolonged abstinence.

In animal models, behavioral sensitization is generally studied by observing an increase in the locomotor stimulatory effects or stereotyped behaviors produced by cocaine and amphetamine. Tolerance, dependence, or sensitization is differentially most strongly elicited with different drug administration paradigms and different timepoints after the final dose. Differences in these parameters likely explain many inconsistencies in behavioral and physiological findings of different labs. Tolerance, dependence (with subsequent withdrawal), and sensitization are likely all experienced by drug addicted humans and contribute to compulsive drug use.

Adaptations Correlated with Sensitization

The VTA appears to be required for initiation of locomotor sensitization; however, the NAc is required for its expression (see references in Self and Nestler, 1995). Changes in the mesoaccumbens circuitry that would increase the effects of DA and might therefore contribute to sensitization include augmentation of the ability of cocaine or amphetamine to increase extracellular DA concentrations in the NAc, decreased sensitivity of DA autoreceptors (presynaptic D2 receptors), and supersensitivity of postsynaptic D1 receptors. Locomotor sensitization to cocaine has been reported to persist for a month after withdrawal and is correlated with an enhancement of D1 DA receptor responses in the NAc (Henry and White, 1995). D1 receptors are expressed in the NAc and in the dorsal striatum, predominantly on striatonigral neurons, which are GABAergic and also synthesize the neuropeptide precursors prodynorphin and preprotachykinin. Since no consistent changes have been observed in D1 receptor number or affinity after chronic cocaine administration, supersensitive D1 responses likely reflect changes in postreceptor signal transduction. Since D1 receptors are positively linked to the adenylyl cyclase via G_s and G_{olf}, it is significant that chronic cocaine administration increases levels of adenylyl cyclase and cAMP-dependent protein kinase in the NAc, while decreasing levels of $G_{i\alpha}$ (reviewed by Self and Nestler, 1995).

Cocaine- and Amphetamine-Regulated Gene Expression

Cocaine and amphetamine have potent effects on protein phosphorylation and gene regulation in dopaminoceptive neurons in the dorsal striatum and the NAc. An ongoing challenge is to relate these effects to electrophysiological and behavioral observations. Acute administration of amphetamine and cocaine induce cAMP response element–binding protein (CREB) phosphorylation (Konradi et al., 1994) and expression of both AP-1 (e.g., *c-fos*, *fras*, and *junB*) and non-AP-1 family immediate early genes (IEGs) in both the dorsal and ventral striatum (Self and Nestler, 1995). In addition, both amphetamine and cocaine have been shown to induce AP-1 binding activity in striatal cell extracts (Nguyen et al., 1992; Hope et al., 1992).

As described, D1 DA receptor signaling has been implicated in sensitization; it appears to play an obligate role in cocaine- and amphetamine-induced gene expression. Psychostimulant-induced CREB phosphorylation and IEG expression are both blocked by D1 receptor antagonists (Konradi et al., 1994, and references therein). Consistent with this pharmacological finding, double label in situ hybridization studies demonstrate that cocaine (Kosofsky et al., 1995) and amphetamine (Jaber et al., 1995) induce IEG expression primarily in striatonigral neurons.

Induction of CREB phosphorylation and expression of IEG transcription factors by acute cocaine and amphetamine have been hypothesized to initiate downstream molecular events, which in the longer term could exert significant behavioral consequences. Potential targets of cocaine- and amphetamine-induced transcriptional activators include the neuropeptide genes expressed within D1 receptor expressing neurons. Indeed, cocaine and amphetamine have been shown to induce expression of preprotachykinin mRNA and of prodynorphin mRNA and peptides in striatonigral neurons (Jaber et al., 1995, and references therein). Prodynorphin gene expression has also been shown to be induced in other states of putative DA excess, either due to the loss of functional DAT in knockout mice (Giros et al., 1996) or following administration of D1 receptor agonists in rats with a 6-hydroxydopamine lesion substantia nigra (Steiner and Gerfen, 1995, and references therein). In contrast, mice lacking D1 receptors as a

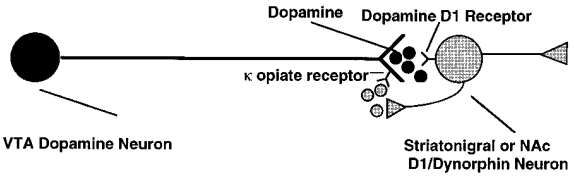

Figure 1. Potential Role for Prodynorphin Induction as a Compensatory Adaptation to Cocaine and Amphetamine

Projection neurons in the NAc and dorsal striatum also have recurrent collateral axons. A subset of these neurons express D1 DA receptors and the prodynorphin gene, expression of which is induced by excess DA stimulation produced by cocaine and amphetamine. The release of dynorphin, via recurrent collaterals, on the presynaptic terminals of DA neurons acts via inhibitory κ opioid receptors to decrease DA release, thus acting as a compensatory "brake" on further DA release.

result of targeted gene disruption exhibit decreased prodynorphin gene expression (Xu et al., 1994).

The regulation of the prodynorphin gene by cocaine and amphetamine could be a biologically significant adaptive mechanism contributing to the motivational aspects of withdrawal. Dynorphin peptides can signal back on presynaptic DA terminals within the striatum via recurrent axon collaterals (Figure 1). Acting via κ opiate receptors on DA terminals, dynorphin peptides appear to decrease DA release (Steiner and Gerfen, 1995). κ receptor agonists produce an aversive dysphoric syndrome in drug naive humans and rats. Thus, an increase in dynorphin peptides following chronic psychostimulant administration may be a compensatory adaptation to excess DA stimulation that, by inhibiting the release of DA, may contribute to the dysphoric state that occurs with drug cessation and therefore to withdrawal.

The prodynorphin gene contains three cAMP response elements (CREs) in its 5′ flanking region. In primary striatal cultures, induction of prodynorphin gene expression by DA has been shown to be dependent on D1 receptor stimulation and to correlate with Ser-133 phosphorylation of CREB (Cole et al., 1995). CREB has been shown to be phosphorylated on its critical Ser-133 in vivo in response to amphetamine (Konradi et al., 1994); with chronic amphetamine administration, the time course of CREB phosphorylation is markedly prolonged (Cole et al., 1995), consistent with up-regulation of other components of the cAMP system (described above) by chronic cocaine (Self and Nestler, 1995). The D1 receptor–cAMP–CREB pathway (Figure 2) may serve as an important mechanism of adaptation, contributing not only to prodynorphin gene regulation, but also to regulation of many additional target genes that contain CREs. The posited role for CREB in plasticity produced by drugs of abuse has a parallel in recent work implicating CREB in some forms of long-term synaptic plasticity, including a role in the maintenance phase of long-term potentiation (LTP) and in models of learning in Aplysia, Drosophila, and mice (reviewed by Carew, 1996). Both LTP and LTD have been demonstrated in the NAc (Kombian and Malenka, 1994), although the molecular correlates in the NAc have not yet been identified. While there is a long way to go in dissecting the role of CREB in different types of long-term behavioral change, it appears to be a critical molecular switch in both cocaine-

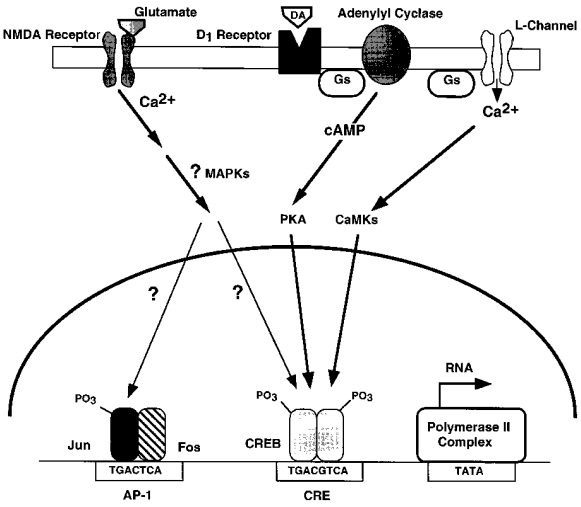

Figure 2. Schematic Representation of Transcriptional Regulation Mediated via the D1 DA Receptor and NMDA Glutamate Receptor Pathways

Cocaine- and amphetamine-regulated gene expression in the dorsal and ventral striatum is inhibited by D1 or NMDA receptor antagonists. Shown in the lower half of the figure is a composite promoter with a consensus AP-1 site and CRE. D1 receptor stimulation of the cAMP pathway leads to CREB phosphorylation that has been linked to induction of both the c-*fos* and prodynorphin genes in striatal neurons. Activation of calmodulin-dependent protein kinases also leads to CREB phosphorylation, although this has not been investigated directly in striatal neurons. The downstream actions of NMDA receptor stimulation in these dopaminoceptive neurons on both AP-1 and CREB-mediated transcription, including the role, if any of MAP kinase cascades, remains unsettled.

and amphetamine-induced plasticity (subserving a type of implicit memory), as well as in other types of memory functions.

Cocaine- and amphetamine-induced gene regulation is more complex, however, with increasing evidence that the D1 DA receptor pathway interacts significantly with N-methyl-D-aspartic acid (NMDA) glutamate receptor pathways (Figure 2). It has been demonstrated by several groups that cocaine- and amphetamine-induced IEG expression is inhibited by NMDA receptor antagonists in vivo. Moreover, behavioral sensitization and D1 receptor supersensitivity are also prevented if MK-801 is coadministered with amphetamine (Wolf et al., 1994). Explanations for the effects of MK-801 have largely focused on neural circuit interactions. NMDA receptor blockade has been hypothesized to inhibit the release of DA within the striatum or to inhibit DA D1 receptor function. However, NMDA receptor–activated intracellular Ca^{2+} pathways may also play a critical role in D1 receptor–mediated gene expression and deserve further investigation. CREB has been shown to be a substrate not only for the cAMP-dependent protein kinase, but also for several Ca^{2+}/calmodulin protein kinases; in addition, NMDA receptors may activate additional signaling pathways within neurons such as MAP kinases.

Potential Functional Roles of AP-1 Proteins in Adaptations to Psychostimulants

Unlike CREB, which is constitutively synthesized and regulated largely by protein phosphorylation, proteins

of the Fos family are induced from very low levels of expression by acute cocaine or amphetamine administration. With repeated stimulation, induction of c-*fos*, c-*jun*, *junB*, and *zif/268* is markedly down-regulated (Hope et al., 1992). In contrast, certain Fos-related antigens accumulate with chronic cocaine treatment or other chronic stimuli ("chronic Fras") and are expressed persistently (Hope et al., 1994). Alterations in the composition of AP-1 complexes over time might permit cells to activate specific programs of adaptation appropriate to the strength and time course of the stimulus. However, an unsolved problem with respect to downstream effects of AP-1 proteins in the dorsal and ventral striatum is that increased expression of AP-1 proteins, per se, or increased binding of AP-1 proteins to DNA as measured by gel shift assays does not necessarily indicate increases in transcriptional activation. Thus, in transformed cell lines, phosphorylation of Ser-63 or Ser-73 within the c-Jun activation domain by Jun N-terminal kinases (JNKs) has been shown to increase its ability to activate transcription markedly without affecting its ability to heterodimerize or bind DNA. The degree to which cocaine- and amphetamine-induced Fos and Jun family members are active as transcription factors in DA receptive neurons has not yet been established (Figure 2). Additional challenges include the identification of targets of both the CREB and AP-1 pathways that might lead to significant neural plasticity and behavioral change.

Several other alterations in cellular proteins caused by chronic cocaine administration are of particular interest because they also occur with chronic morphine administration. Thus, for example, both cocaine and morphine increase levels of tyrosine hydroxylase and decrease levels of three neurofilament proteins in the VTA (reviewed by Self and Nestler, 1995). Understanding the relationship of potential cytoskeletal changes to physiology or behavior remains an important goal.

In addition to adaptations within the brain reward circuitry itself, drugs of abuse produce long-lived, positively biased, emotional memories that may be activated by environmental or interoceptive cues. The mesoaccumbens DA circuitry appears to be involved in producing memories associated with reinforcement. It is an open question whether cue-dependent drug craving activates the mesoaccumbens DA pathway or whether DA is involved in the production of such memories but not in their subsequent recall. Evidence exists on both sides of the issue (Brown and Fibiger, 1992, and references therein). The resolution is important since development of pharmacological blockers of cue-dependent craving, which has been hypothesized (but not shown) to predispose to relapse in humans, will obviously differ depending on the receptors and circuits involved.

In summary, progress is being made in understanding the molecular and cellular basis of addiction to cocaine and amphetamine. While the identification of significant molecular alterations and their relationship to behavior are in their early days, the field is progressing rapidly and should lead to the development of treatments for cocaine and amphetamine addiction.

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