Molecular and Cellular Basis of Addiction

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Drug addiction results from adaptations in specific brain neurons caused by repeated exposure to a drug of abuse. These adaptations combine to produce the complex behaviors that define an addicted state. Progress is being made in identifying such time-dependent, drug-induced adaptations and relating them to specific behavioral features of addiction. Current research needs to understand the types of adaptations that underlie the particularly long-lived aspects of addiction, such as drug craving and relapse, and to identify specific genes that contribute to individual differences in vulnerability to addiction. Understanding the molecular and cellular basis of addictive states will lead to major changes in how addiction is viewed and ultimately treated.

Addiction is a complex phenomenon with important psychological and social causes and consequences. However, at its core, it involves a biological process: the effects of repeated exposure to a biological agent (drug) on a biological substrate (brain) over time. Ultimately, adaptations that drug exposure elicits in individual neurons alter the functioning of those neurons, which in turn alters the functioning of the neural circuits in which those neurons operate. This leads eventually to the complex behaviors (for example, dependence, tolerance, sensitization, and craving) that characterize an addicted state (1, 2).

A critical challenge in understanding the biological basis of addiction is to account for the array of temporal processes involved (Fig. 1). Thus, the initial event leading to addiction involves the acute action of a drug on its target protein and on neurons that express that protein. These actions are now well understood and will not be reviewed here (1, 2). Rather, this review focuses on the molecular and cellular adaptations that occur gradually in specific neuronal cell types in response to chronic drug exposure, particularly those adaptations that have been related to behavioral changes associated with addiction. We focus on opiates and cocaine, not only because they are among the most prominent illicit drugs of abuse, but also because considerable insight has been gained into the adaptations that underlie their chronic actions. As will be seen, the relatively short-lived adaptations that contribute to relatively transient features of addiction (for example, somatic and motivational withdrawal symptoms and changes in drug sensitivity) are becoming increasingly understood. In contrast, a major need for future research is to identify and characterize more long-lived adaptations that underlie aspects of addiction (for example, craving and relapse) and can persist for a lifetime.

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Up-Regulation of the cAMP Pathway

The best established molecular adaptation to chronic drug exposure is up-regulation of the adenosine 3′,5′-monophosphate (cAMP) pathway, a phenomenon first discovered in cultured neuroblastoma × glioma cells (3) and later demonstrated in neurons (4) in response to repeated opiate administration. Acute opiate exposure inhibits the cAMP pathway in many types of neurons in the brain (5), whereas chronic opiate exposure leads to a compensatory up-regulation of the cAMP pathway in at least a subset of these neurons. This up-regulation involves increased concentrations of adenylyl cyclase, cAMP-dependent protein kinase A (PKA), and perhaps other components of this signaling pathway. Up-regulation of the cAMP pathway would oppose acute opiate inhibition of the pathway and thereby would represent a form of physiological tolerance; upon removal of the opiate, the up-regulated cAMP pathway would become fully functional and contribute to features of dependence and withdrawal (3, 4).

There is now direct evidence to support this model in neurons of the locus coeruleus, the major noradrenergic nucleus in the brain. These neurons normally regulate attentional states and activity of the auto-
nomic nervous system and have been implicated in somatic opiate withdrawal (6). Up-regulation of the cAMP pathway in the locus coeruleus (4, 7, 8) (Fig. 2) appears to increase the intrinsic firing rate of the neurons through the activation of a nonselective cation channel (9). This increased firing has been related to specific opiate withdrawal behaviors (6–8). Increased locus coeruleus activity during withdrawal is also caused by increased glutamatergic activation of the neurons (10). This may be mediated in part by an up-regulated cAMP pathway in primary sensory neurons (11, 12), which would contribute to the activation of ascending excitatory inputs to the locus coeruleus. Although there has been some debate about the degree to which the locus coeruleus contributes to the overall opiate withdrawal syndrome (13), its cellular and neurochemical homogeneity makes it a useful model system to delineate the precise molecular and cellular mechanisms underlying neuronal adaptations to chronic drug exposure.

Detailed knowledge of the molecular steps by which up-regulation of the cAMP pathway occurs in the locus coeruleus is becoming available (Fig. 2). Chronic opiate administration selectively up-regulates two forms of adenylyl cyclase (types I and VIII) in these neurons (14, 15). Up-regulation of the type VIII enzyme appears to be mediated by cAMP response element–binding protein (CREB), one of the major cAMP-regulated transcription factors in the brain. A reduction in CREB concentration (achieved by infusion of antisense oligonucleotides to CREB directly into this region) blocks the morphine-induced increase in this enzyme (15). In contrast, up-regulation of type I adenylyl cyclase and of PKA subunits is not affected by this treatment and, thus, would appear to be mediated by distinct mechanisms. Accordingly, antisense oligonucleotide treatment partially attenuates the activation of locus coeruleus neurons seen during withdrawal, as well as the severity of certain opiate withdrawal behaviors (15). Consistent with these observations in the locus coeruleus is the more general observation that mutant mice deficient in CREB, a deficiency expressed ubiquitously, show attenuated opiate withdrawal (16).

Up-regulation of the cAMP pathway also occurs in neurons of the nucleus accumbens in response to chronic administration of opiates, cocaine, or alcohol (12, 17). However, it remains unclear which of several cell types within this region expresses this adaptation. The nucleus accum-

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**Fig. 1.** Scheme illustrating the life cycle of addiction—the complex, time-dependent effects of drug exposure. The upper boxes show the prominent processes associated with each stage of drug action [see (1, 2) for definitions]; the lower boxes show the underlying molecular and cellular mechanisms involved (↑, increase; ↓, decrease). The dashed arrow indicates that the changes in neurotransmission associated with short-term abstinence (withdrawal) are thought to be mediated by the molecular and cellular adaptations associated with the chronic drug state (dependence).

**Fig. 2.** Scheme illustrating opiate actions in the locus coeruleus. Opiates acutely inhibit locus coeruleus neurons by increasing the conductance of an inwardly rectifying K+ channel through coupling with subtypes of G<sub>GluR</sub> as well as by decreasing a Na<sup>+</sup>-dependent inward current through coupling with G<sub>GABA</sub> and the consequent inhibition of adenylyl cyclase. Reduced concentrations of cAMP decrease 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 locus coeruleus function. Upward bold arrows summarize effects of chronic morphine administration in the locus coeruleus. Chronic morphine increases concentrations of types I and VIII adenylyl cyclase (AC I and VIII), PKA catalytic (C) and regulatory type II (RII) subunits, and several phosphoproteins, including CREB. These changes contribute to the altered phenotype of the drug-addicted state. For example, the intrinsic excitability of locus coeruleus neurons is increased by enhanced activity of the cAMP pathway and Na<sup>+</sup>-dependent inward current, which contributes to the tolerance, dependence, and withdrawal exhibited by these neurons. Up-regulation of type VIII adenylyl cyclase is mediated by CREB, whereas up-regulation of type I adenylyl cyclase and of the PKA subunits appears to occur by means of a CREB-independent mechanism not yet identified.
bens, one target of the mesolimbic dopamine system, is believed to play a role in motivational states and is implicated in the reinforcing actions of most drugs of abuse (1, 2). Because D₁ dopamine receptors are known to act through stimulatory heterotrimeric guanosine triphosphate–binding (Gₛ) proteins and activation of the cAMP pathway, up-regulation of this pathway in the nucleus accumbens could account for the functional supersensitivity of D₁ receptors observed in these neurons—which occurs in the absence of detectable changes in the receptors themselves—after chronic cocaine (or other stimulant) exposure (18). There is evidence that the up-regulated cAMP pathway may produce this effect through PKA-mediated phosphorylation of voltage-gated Na⁺ channels (19).

Recent work has directly related up-regulation of the cAMP pathway in the nucleus accumbens to behavioral aspects of drug action. One hypothesis is that the up-regulated cAMP pathway opposes drug reinforcement mechanisms as well as the actions of natural reinforcers and thereby contributes to a negative motivational (aversive) state during withdrawal (20). However, there is evidence supporting the opposite view (21). There is also evidence that an up-regulated cAMP pathway could simultaneously contribute to sensitization to the locomotor-activating effects of stimulants (22).

The mechanisms by which chronic drug exposure elicits up-regulation of the cAMP pathway in the nucleus accumbens remain poorly understood. Chronic administration of opiates or stimulants is reported to alter CREB phosphorylation (23) or expression (24) in this and related striatal regions. Genes for opioid peptides, which contain CRE sites (the specific sequences of DNA on which CREB acts) and are known to be regulated by chronic drug administration, represent potential targets for CREB in these regions (25). However, such molecular adaptations have not yet been related directly to drug-regulated behaviors. Consistent with the involvement of CREB in addiction is the role hypothesized for CREB in mediating several other forms of long-term neural and behavioral plasticity (26).

Preliminary evidence has implicated the cAMP pathway in other brain regions, including the ventral tegmental area (the site of mesolimbic dopamine cell bodies implicated in drug reinforcement) (27) and the periaqueductal gray (a brainstem region that contains a major serotonergic nucleus and has been implicated in opiate withdrawal states) (8, 28). Biochemical and electrophysiological evidence suggests that chronic opiate exposure leads to an up-regulated cAMP pathway in these brain regions, specifically within γ-aminobutyric acid–containing (GABAergic) neurons that innervate the dopaminergic and serotonergic cells (27, 28). According to this model, up-regulation of the cAMP pathway would lead to increased GABA release during withdrawal and thereby to a reduction in the firing of the dopaminergic and serotonergic neurons. The former could account for the reduction in dopaminergic neurotransmission from the ventral tegmental area to the nucleus accumbens that occurs during early phases of drug withdrawal and is thought to contribute to the associated aversive state (1, 29). The latter could contribute to both somatic and motivational aspects of withdrawal through the inhibition of the diffuse serotonergic innervation of the neocortex (1, 2, 28).

Work in these various discrete brain regions raises the possibility that up-regulation of the cAMP pathway may occur in response to chronic opiate or other drug exposure in other brain regions as well. For example, up-regulation may occur in specific cell types within the cerebral cortex and hippocampus—brain regions that would appear to be critical for the more long-lasting, particularly cognitive, aspects of drug addiction (see below). Such adaptations have not in general been detected in these regions by biochemical methods, probably because of their greater cellular heterogeneity.

**Adaptations in Receptor–G Protein Coupling**

Opioid and dopamine receptors, which belong to the G protein–coupled receptor superfamily, are critical mediators of the acute reinforcing actions of opiates and cocaine (1, 2). These and other G protein–coupled receptors are known to undergo complex processes of desensitization and down-regulation after short-term exposure to a receptor agonist. A major unanswered question is whether adaptations in such processes contribute to long-term changes in receptor sensitivity (for example, tolerance or sensitization) that occur after repeated exposure to a drug of abuse (Fig. 3). A related challenge is to show that such adaptations underlie specific forms of behavioral plasticity to drug exposure.

One putative mechanism for short-term desensitization of opioid and dopamine receptors is receptor phosphorylation. This model presumes that these receptors function similarly to the β-adrenergic receptor, whose phosphorylation by several types of protein kinases can promote receptor inter-

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**Fig. 3.** Scheme illustrating possible mechanisms of drug-induced changes in opioid or D₂-like dopamine receptor sensitivity. Drug-induced adaptations in the efficacy of receptor–Gₚₖ₆ coupling could contribute to aspects of drug tolerance or sensitization. One possible mechanism is adaptations in processes that mediate acute desensitization of receptor function, such as receptor phosphorylation by GRKs (1). Other possible mechanisms include alterations in the abundance of G protein α (2) or βγ (3) subunits or of other proteins [for example, phosducin (4), RGS proteins (5)] that modulate G protein function. Phosphorylation of the receptor by PKA cannot mediate acute receptor desensitization because receptor activation leads to inhibition of the kinase; however, up-regulation of the kinase (6) after chronic drug administration (see Fig. 2) could phosphorylate and regulate receptor function during withdrawal states. Also shown is agonist-induced receptor internalization, which may be mediated by receptor phosphorylation.
nalization and perhaps reduce coupling to G proteins (30). One such mechanism involves G protein kinase (GRKs), which phosphorylate only the agonist-bound form of the receptor, and associated proteins, termed arrestins, that bind and apparently sequester the phosphorylated receptor. Opioid and dopamine receptors are reported to be phosphorylated by GRKs and other protein kinases, and in some cases they have been shown to be desensitized as a result (31). Similarly, opioid receptors have been shown to undergo internalization in vitro and in vivo after acute agonist exposure (32). However, whether such phosphorylation and internalization mechanisms are altered in vivo in the chronic drug-treated state remains unclear. One suggestive finding is that concentrations of certain GRKs and arrestins are up-regulated in specific brain regions after chronic opiate administration (33).

Another putative mechanism for adaptations in opioid and dopamine receptor functioning after chronic drug exposure involves altered receptor–G protein coupling (34). This could be mediated by adaptations in receptor phosphorylation mechanisms, as outlined above. Alternatively, adaptations in the abundance of G protein subunits themselves (or of several proteins known to modulate G protein function) could be involved. Indeed, chronic opiate or cocaine exposure has been shown to decrease the extent of expression of the Gαs family of G protein α subunit, which provides the primary coupling mechanism for opioid and D1-like dopamine receptors, in specific brain regions (12, 35). Adaptations have been observed in other types of G protein α subunit as well (36). It would also be interesting to assess whether chronic drug exposure leads to changes in receptor–G protein coupling by regulating other proteins known to modulate α subunit function. These proteins may include G protein βγ subunits (37), phosducin (which modulates the ability of βγ subunits to bind their α subunit) (38), or RGS (regulators of G protein signaling) proteins, which regulate subunit function by activating the guanosine triphosphatase (GTPase) activity intrinsic to the α subunits (39). The recent discovery of more than 18 RGS isoforms that modulate Gαi/o function and exhibit highly specific patterns of expression in the brain makes these proteins attractive targets for drug adaptation (39, 40). In addition, tolerance or sensitization could conceivably be mediated by drug-induced alterations (41) in ion channels (for example, the G protein–gated inwardly rectifying K+ channel and presynaptic Ca2+ channels) that mediate some of the acute actions of opioid and D1-like receptors.

Longer-Lasting Molecular and Cellular Adaptations

Most of the molecular and cellular adaptations to repeated drug administration that have been observed to date are relatively short-lived after the cessation of drug exposure, in contrast to some longer-lasting consequences of drug exposure seen in animals and humans. A major goal of current research is to gain insight into the molecular and cellular basis of these more long-lived adaptations. One possibility, by analogy with other models of long-term memory (26), is that such long-lived adaptations involve relatively stable changes in gene expression, which lead to changes in neurotransmission and even in the structure and number of synaptic connections formed by individual neurons.

Transcription factors are clearly one potential mechanism for persistent drug-induced plasticity. A role for CREB has already been discussed. The Fos and Jun families of transcription factors have also been studied extensively within the context of addiction. Several of these are induced rapidly but transiently in the nucleus accumbens and related striatal regions by acute administration of stimulants, opiates, or nicotine. In contrast, chronic drug exposure desensitizes the ability of these proteins to be induced and results instead in the gradual accumulation of novel Fos-like proteins, termed chronic FRAs (Fos-related antigens) (42). The chronic FRAs have been identified as isoforms of ΔFosB, a truncated splice variant of the fosB gene (43–45). Because of their extraordinary stability, the ΔFosB isoforms accumulate in the brain after repeated drug treatment (43) and thereby are candidates to serve as molecular switches for long-lived adaptations to drug exposure. Although specific target genes for the ΔFosB isoforms remain unknown, evidence for the importance of these isoforms in behavioral plasticity to drugs of abuse has been obtained recently: Mice lacking the fosB gene show enhanced locomotor and reinforcing responses to cocaine (44). These findings support a scheme wherein induction of these proteins would represent a relatively stable compensatory adaptation that opposes acute drug action.

Adaptation in glutamatergic transmission represents a potential mediator of long-term drug effects, given its proposed role in neural plasticity in general (46). Dopaminergic neurons of the ventral tegmental area show enhanced responsiveness to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor stimulation after chronic stimulant exposure (47), which could in turn be mediated by increased expression of specific AMPA receptor subunits in these neurons observed in response to chronic opiate, cocaine, or alcohol administration (48). This adaptation could contribute to heightened activity of the mesolimbic dopamine system, a proposed mechanism for drug sensitization (1, 2, 29, 49). Direct support for this possibility comes from a recent study in which overexpression of specific AMPA receptor subunits selectively within ventral tegmental area neurons, achieved by viral-mediated gene transfer, sensitizes animals to the locomotor-activating and reinforcing effects of morphine (50). Neurons of the nucleus accumbens also show altered responsiveness to glutamate as well as altered extents of expression of specific glutamate receptor subunits (47, 51).

A role for glutamatergic transmission in drug addiction is further supported by numerous reports that chronic coadministration of glutamate receptor antagonists—particularly N-methyl-D-aspartate (NMDA) receptor antagonists—can attenuate the development of tolerance to the analgesic effects of opiates, as well as the development of locomotor sensitization to several drugs of abuse (49, 52). Pharmacological inhibitors or antisense oligonucleotide-induced reductions of nitric oxide synthase have been shown to produce similar effects (53). This enzyme is known to generate a nitric oxide signal in response to NMDA receptor activation, which has been proposed to mediate some of the physiological effects of the receptor. However, interactions between NMDA receptor antagonists and drugs of abuse would appear to be more complex than the former simply blocking the latter. Like opiates, cocaine, and other drugs of abuse, NMDA antagonists [including phencyclidine (PCP) and MK-801] have powerful stimulant and reinforcing actions of their own, and can potentiate the activating and reinforcing effects of drugs of abuse [see (54)]. These findings suggest that chronic coadministration of NMDA receptor antagonists could conceivably make certain drugs more addictive, regardless of their effects on analgesic tolerance and locomotor sensitization. Clearly, more work is needed to characterize the molecular and cellular basis of the complex interactions between these agents.

It is conceivable that some long-lasting aspects of addiction could involve neurotrophic factors, which were first studied for their role in the growth and differentiation of neurons during development, but are now known to play an important role in the survival, maintenance, and signal transduction of adult neurons. While this possibility remains hypothetical, neurotrophic factor infusions directly into specific brain regions have been shown to prevent and reverse specific molecular adaptations to chronic
opiate or cocaine administration (55). In addition, chronic drug exposure has been shown to alter concentrations of specific proteins in neurotrophic factor signaling cascades (56).

An important consideration in searching for particularly persistent adaptations associated with addiction is that they may well occur in part outside of the mesolimbic dopamine system. The likely involvement of other brain regions such as the cerebral cortex, hippocampus, and other limbic structures (for example, amygdala and septum) is based on the complex cognitive, affective, and motivational components of addiction. Yet very little is known about the effects of chronic drug exposure on the physiological and biochemical properties of neurons in these regions. Similarly, there is a need for animal models that move beyond measures of acute drug reinforcement and assess the role of these regions in more complex aspects of addiction.

**Future Directions**

A biological understanding of addiction requires knowledge of how acute effects of drugs of abuse on the brain are transformed into progressively longer-lasting adaptations in specific brain regions (see Fig. 1). The identification of long-lived adaptations has proved the most difficult, and this is where our greatest gap in knowledge exists. Thus, while molecular and cellular models of dependence, tolerance, sensitization, and withdrawal have been developed, very little is known about longer-lived forms of sensitization as well as the drug craving and high risk for relapse seen after months and even years of abstinence. In this way, challenges in the addiction field are analogous to those in other fields involving adaptations in higher brain function. For example, although good molecular and cellular models of memory exist, our understanding of the specific mechanisms that underlie behavioral memory remains rudimentary.

Simply giving a drug to an animal, or even permitting an animal to self-administer a drug to itself, does not capture the complete picture of an addicted state (1, 2). Animal models of relapse—in which "drug-seeking behavior" can be stimulated, even after relatively long periods of abstinence, by exposure to the drug itself, by conditioned environmental cues associated with drug exposure, and perhaps most potently by certain forms of stress (57)—represent a promising area for future research. Stress-induced relapse, which may be particularly relevant to human addiction, could potentially be mediated by any of the many neural and hormonal systems known to be stress-responsive. Most attention has focused on the hypothalamic-pituitary-adrenal axis (for example, corticotropin-releasing factor and glucocorticoids (1, 57)), although a role for monoamines, opioid peptides, and cytokines, to name a few, is also worthy of future investigation. As more is learned at the systems level, it will be possible to identify the precise molecular and cellular adaptations in specific neurons that are responsible for stress-induced and other forms of relapse.

Transgenic and knockout methodologies represent powerful tools with which to establish causal relations between molecular and behavioral aspects of drug addiction (for example, (16, 44, 58, 59)). Many such studies to date have confirmed the role played by particular proteins (for example, dopamine and opioid receptors and the dopamine transporter) in mediating the acute actions of drugs of abuse on the brain. In one recent study, mice lacking the D$_2$ dopamine receptor were found to lack reinforcing responses to opiates but still developed physical opiate dependence (59). These findings are consistent with earlier evidence for an important role for dopaminergic mechanisms in opiate reinforcement and for primarily nondopaminergic mechanisms in physical dependence (2, 6).

In addition to lacking acute drug responses, however, some of the mutant mice show interesting adaptations in neural systems and behavior, and thereby could perhaps serve as models of the ways in which the brain compensates for drug-induced adaptations. Moreover, some of the studies have provided insight into the role of particular gene products not previously directly implicated in the addiction process. The ability to relate alterations in specific proteins to mechanisms of drug addiction will be greatly facilitated by recently developed transgenic (60) and viral vector (50, 61) methodologies, which have made it possible to alter the expression of specific genes in specific neuronal populations at different stages of the life cycle of an animal.

The ability of drugs of abuse to alter the brain depends in part on genetic factors: Acute drug responses as well as adaptations to repeated drug exposure can vary markedly, depending on the genetic composition of the individual (62). Genetic factors can also influence the brain’s responses to stress and are thus also likely to contribute to stress-induced relapse. Although it has been difficult to identify specific genes that contribute to individual differences in drug and stress vulnerability in laboratory animals and in humans, this work remains of the highest priority because it will greatly inform our understanding and treatment of addictive disorders. In addition, the genetic basis of individual differences in drug and stress responses represents a powerful model of the ways in which genetic and environmental factors combine to control brain function in general. Knowledge derived from these investigations could have an important impact on psychiatry and neurology overall, as we seek to understand the genetic and environmental causes not only of behavioral abnormalities, but also of normal variants in behavioral traits.

Ultimately, a detailed understanding of the molecular and cellular mechanisms of addiction will transform the way society views and treats this illness. Vague notions of addiction, stress, and relapse will be replaced by specific knowledge, which will serve as the basis of new medical treatments of addictive disorders. The possibilities include treatments that reverse some of the deleterious effects of drug exposure on vulnerable neurons, as well as treatments that prevent the ability of specific environmental stimuli (for example, stress and conditioned cues) to precipitate relapse. It may one day be possible to identify individuals who are particularly vulnerable to addiction and stress and thereby target them with specific psychosocial interventions. In this way, addiction will eventually be seen as analogous to other medical illnesses—as complex constructs of genetic, environmental, and psychosocial factors that require multiple levels of intervention for their treatment and prevention.

**REFERENCES AND NOTES**

Psychoactive Drug Use in Evolutionary Perspective

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Pure psychoactive drugs and direct routes of administration are evolutionarily novel features of our environment. They are inherently pathogenic because they bypass adaptive information processing systems and act directly on ancient brain mechanisms that control emotion and behavior. Drugs that induce positive emotions give a false signal of a fitness benefit. This signal hijacks incentive mechanisms of “liking” and “wanting,” and can result in continued use of drugs that no longer bring pleasure. Drugs that block negative emotions can impair useful defenses, although there are several reasons why their use is often negative. Nevertheless, a deeper understanding of the evolutionary origins and functions of the emotions and their neural mechanisms is needed as a basis for decisions about the use of psychoactive drugs.

The neural mechanisms that regulate emotion and behavior were shaped by natural selection to maximize Darwinian fitness, so psychoactive drugs that disrupt those mechanisms should impair adaptation. As the toll of substance abuse tragically demonstrates, they can. But psychoactive drugs can also improve adaptation in some circumstances (what would many scientists do without caffeine?), relieve the symptoms of mental disorders, and induce pleasurable states that can sometimes be safe. Here, we consider substance use and abuse from the perspective of Darwinian medicine, the enterprise that explains substance use and abuse from the perspective of the operation of natural selection characteristics that make organisms sign characteristics that make organisms .

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