PERSPECTIVE

nature neuroscience

Is there a common molecular pathway for addiction?

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Drugs of abuse have very different acute mechanisms of action but converge on the brain's reward pathways by producing a series of common functional effects after both acute and chronic administration. Some similar actions occur for natural rewards as well. Researchers are making progress in understanding the molecular and cellular basis of these common effects. A major goal for future research is to determine whether such common underpinnings of addiction can be exploited for the development of more effective treatments for a wide range of addictive disorders.

Drugs of abuse are highly diverse chemical substances. Accordingly, each drug binds to its distinct initial protein target in the brain and periphery and elicits a distinct combination of behavioral and physiological effects upon acute administration. However, despite these disparate mechanisms of action and pharmacological effects, all drugs of abuse cause certain common effects after both acute and chronic exposure. The drugs are all acutely rewarding, which promotes repeated drug intake and leads eventually, in vulnerable individuals, to addiction—a loss of control over drug use. All drugs also produce similar negative emotional symptoms upon drug withdrawal, a prolonged period of sensitization, and associative learning toward drug-related environmental cues. These adaptations are thought to contribute to the intense drug craving and relapse that can persist even after long periods of abstinence, although the relative contribution of each mechanism remains a subject of considerable controversy. The question addressed by this Perspective is whether there are common neural and molecular pathways underlying these shared rewarding and addicting actions of drugs of abuse.

Common actions on brain reward circuits

There is now considerable evidence, from animal models and more recently from humans, that all drugs of abuse converge on a common circuitry in the brain's limbic system[1–5]. Most attention has been given to the mesolimbic dopamine pathway, which includes dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain and their targets in the limbic forebrain, especially the nucleus accumbens (NAc). This VTA-NAc pathway is one of the most important substrates for the acute rewarding effects of all drug of abuse, and research over the past several decades has delineated how each drug, regardless of its distinct mechanism of action, converges on the VTA and NAc with common acute functional effects (**Fig. 1**). Each drug activates dopaminergic transmission in the NAc and many produce dopamine-like, yet dopamine-independent effects on the same NAc neurons, in many cases via indirect, circuit-level actions[1–8]. In addition, several drugs (see **Fig. 1** legend) seem to activate the brain's endogenous opioid and cannabinoid systems within the VTA-NAc pathway, as exemplified by reduced drug effects in cannabinoid and opioid receptor knockout mice, which further underscores shared acute mechanisms of drug action[1,8].

On the basis of these common acute actions, one would expect that chronic exposure to drugs of abuse would also cause common chronic functional changes in the VTA-NAc pathway. Indeed, numerous common chronic adaptations have been described, examples of which are discussed in the next sections. Consistent with common mechanisms of addiction are the observations that certain drugs of abuse, under particular experimental conditions, can induce cross-tolerance and cross-sensitization to one another with respect to their locomotor activating and rewarding effects[9,10].

More recent work has established that several additional brain areas that interact with the VTA and NAc are also essential for acute drug reward and chronic changes in reward associated with addiction. These regions include the amygdala (and related structures of the so-called 'extended amygdala'), hippocampus, hypothalamus and several regions of frontal cortex, among others[1,2,4,10–13]. Some of these areas are part of the brain's traditional memory systems; this has led to the notion, now supported by increasing evidence, that important aspects of addiction involve powerful emotional memories[2,4,5,11–13].

Growing evidence indicates that the VTA-NAc pathway and the other limbic regions cited above similarly mediate, at least in part, the acute positive emotional effects of natural rewards, such as food, sex and social interactions[14,15]. These same regions have also been implicated in the so-called 'natural addictions' (that is, compulsive consumption of natural rewards) such as pathological overeating, pathological gambling and sexual addictions. Preliminary findings suggest that shared pathways may be involved: two examples are cross-sensitization that occurs between natural rewards and drugs of abuse[16] and similar abnormalities found in brain imaging scans in drug and natural addictions[4]. However, it must be emphasized that the mechanisms underlying natural addictions are much less well understood than those underlying drug addictions because the animal models are far less straightforward, and the clinical syndromes of the natural addictions are likely to be much more heterogeneous. Nevertheless, early findings in the field raise the possibility that the similar behavioral pathology that characterizes drug addictions and certain natural addictions may be mediated, at least in part, by common neural and molecular mechanisms.

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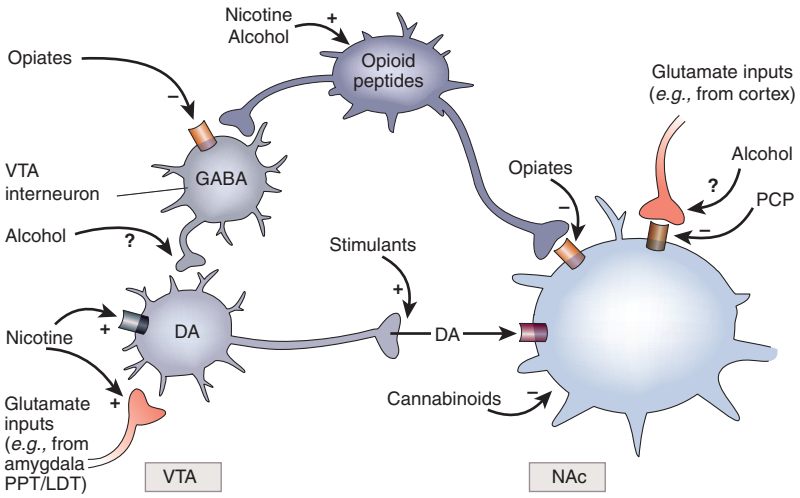
Published online 26 October 2005; doi:10.1038/nn1578



Ann Thomson

Figure 1 Highly simplified scheme of converging acute actions of drugs of abuse on the VTA-NAc. Drugs of abuse, despite diverse initial actions, produce some common effects on the VTA and NAc[1–8]. Stimulants directly increase dopaminergic transmission in the NAc. Opiates do the same indirectly: they inhibit GABAergic interneurons in the VTA, which disinhibits VTA dopamine neurons. Opiates also directly act on opioid receptors on NAc neurons, and opioid receptors, like D_2 dopamine (DA) receptors, signal via G_i; hence, the two mechanisms converge within some NAc neurons. The actions of the other drugs remain more conjectural. Nicotine seems to activate VTA dopamine neurons directly via stimulation of nicotinic cholinergic receptors on those neurons and indirectly via stimulation of its receptors on glutamatergic nerve terminals that innervate the dopamine cells. Alcohol, by promoting $GABA_A$ receptor function, may inhibit GABAergic terminals in VTA and hence disinhibit VTA dopamine neurons. It may similarly inhibit glutamatergic terminals that innervate NAc neurons. Many additional mechanisms (not shown) are proposed for alcohol. Cannabinoid mechanisms seem complex, and they involve activation of CB1 receptors (which, like D2 and opioid receptors, are Gi linked) on glutamatergic and GABAergic nerve terminals in the NAc, and on NAc neurons themselves. Phencyclidine (PCP) may act by inhibiting postsynaptic NMDA glutamate receptors in the NAc. Finally, there is some evidence that nicotine and alcohol may activate endogenous opioid pathways and that these and other drugs of abuse (such as opiates) may activate endogenous cannabinoid pathways (not shown). PPT/LDT, peduncular pontine tegmentum/lateral dorsal tegmentum.

Common circuit-level adaptations

Just as all drugs of abuse increase dopaminergic transmission to the NAc after acute administration, they also produce common adaptations in dopamine function after chronic exposure. These adaptations seem to be complex in that different effects have been reported by numerous laboratories even for the same drug, partly because of differing drug doses, routes of administration and dosing regimens. Nevertheless, it is possible to piece together the following scheme[1,3,5]. Chronic exposure to any of several drugs of abuse causes an impaired dopamine system, which can be viewed as a homeostatic response to repeated drug activation of the system (in other words, tolerance; **Fig. 2**). After chronic drug use, baseline levels of dopamine function are reduced, and normal rewarding stimuli may be less effective at eliciting typical increases in dopaminergic transmission. These changes may contribute to the negative emotional symptoms observed between drug exposures or upon drug withdrawal. At the same time, chronic drug exposure seems to sensitize the dopamine system, with greater increases in dopaminergic transmission occurring in response to the drug in question and to drug-associated cues[5,9,10,13]. This sensitization can last long after drug-taking ceases and may relate to drug craving and relapse.

Chronic drug states are also associated with common changes in central corticotropin releasing factor (CRF) systems. Abrupt withdrawal from virtually any drug of abuse leads to activation of CRF-containing neurons in the amygdala[17]. These neurons, classically characterized for their involvement in fear and other aversive states, innervate many forebrain and brainstem regions. We now know that activation of these neurons during drug withdrawal partly mediates the negative emotional symptoms as well as many of the somatic symptoms that occur upon drug withdrawal, and may contribute to drug craving and relapse as well. CRF can therefore be viewed as an example of 'opponent process'–like changes that drugs induce in the brain that serve to counteract drug effects and drive withdrawal symptoms when the drug is discontinued[1]. Current work is focusing on the molecular basis of this hyperfunctional CRF system, which presumably involves adaptations within amygdala neurons or their inputs (see below).

Another common adaptation to chronic drug use is cortical 'hypofrontality': namely, reduced baseline activity of several regions of frontal cortex, as inferred from brain imaging studies[4]. These regions (for example, prefrontal cortex, anterior cingulate cortex and orbitofrontal cortex) control executive function, including working memory, attention and behavioral inhibition and are important in controlling an individual's response to environmental stimuli, in part via glutamatergic projections from these regions to the NAc and VTA. Impressive evidence from rodent models and from human brain imaging studies demonstrates that chronic exposure to any of several drugs of abuse causes complex changes in these frontal cortical regions and their glutamatergic outputs, which are implicated in the profound impulsivity (acting on sudden urges to take a drug) and compulsivity (being driven by irresistible inner forces to take a drug) that characterizes a state of addiction[4,9,11,18]. The chronic drug-treated state is associated with reduced basal activity of cortical pyramidal neurons and a reduced sensitivity of the neurons to activation by natural rewards. This presumably underlies the hypofrontality noted in human brain scans. In contrast, these neurons are hypersensitive to activation by drugs of abuse as well as drug-associated stimuli. These drug-induced changes in glutamatergic transmission to the NAc parallel the changes reported in dopaminergic transmission to the NAc discussed earlier (**Fig. 2**).

Common cellular and molecular adaptations

Chronic exposure to drugs of abuse causes numerous common adaptations at the cellular and molecular level in the VTA-NAc and other brain reward regions. There are too many adaptations to describe here comprehensively; only a few illustrative examples are included (**Fig. 2**). However, whereas the occurrence of such shared adaptations is indisputable, the behavioral consequences of each of these adaptations remain uncertain, along with the extent to which they mediate common behavioral abnormalities associated with drug and natural addictions.

Numerous types of drugs of abuse, including cocaine, amphetamine, opiates, alcohol or nicotine, induce a long-term potentiation (LTP)-like state in VTA dopamine neurons[19–22]. This sensitized state is mediated via increases in AMPA glutamate receptor responsiveness, which may occur via induction of the GluR1 AMPA glutamate receptor subunit and altered intracellular trafficking of AMPA receptors in these neurons[21,23]. These adaptations in glutamatergic transmission have been related directly to sensitized behavioral responses to drugs of abuse, although aspects of this model remain controversial[23]. Alterations in GABAergic regulation of VTA

dopamine neurons have also been implicated for opiates[24], but whether similar changes occur with other drugs of abuse is not yet known.

Chronic administration of any of several drugs of abuse, including cocaine, amphetamine, opiates, alcohol and nicotine, also increases levels of tyrosine hydroxylase (TH), the rate-limiting enzyme in dopamine biosynthesis, in the VTA[25,26]. Concomitantly, decreased TH levels or activity in VTA nerve terminals in the NAc are reported under certain experimental conditions. This latter adaptation could mediate the reduction in dopaminergic signaling seen after chronic drug exposure (see above). Recent evidence implicates the transcription factor CREB (cAMP response element binding protein), which is also activated in VTA by several drugs of abuse after chronic administration, in mediating drug induction of GluR1 and TH in this region[27] as well as in some of the behavioral plasticity associated with addiction[27–29].

Reduced amounts of neurofilament proteins seen within the VTA after chronic opiate, cocaine or alcohol exposure may be a biochemical marker of common morphological changes to VTA neurons induced by these drugs[25,30]. To date, such changes have been documented only for opiates, which, after chronic exposure, reduce the size of cell bodies and the caliber of proximal processes of VTA dopamine neurons. Reduced neurofilament levels could also account for the impaired axonal transport from the VTA to the NAc observed after chronic opiates. This latter finding could, in turn, explain the disparity between the higher levels of TH seen in VTA and the lower levels seen in NAc. Although the functional consequences of these changes are not known, one can speculate that they reflect a fundamental impairment of the dopamine cells. Interestingly, infusion of any of several neurotrophic factors into the VTA prevents these morphological changes and also produces sensitized behavioral responses to several drugs of abuse, whereas blockade of endogenous neurotrophic factors exerts the opposite effects[30–33].

Most evidence for common chronic effects of drugs of abuse in the NAc is biochemical. One of the most dramatic examples is induction of the transcription factor ΔFosB, a Fos family protein, which accumulates in the NAc after chronic exposure to all drugs of abuse, including cocaine, amphetamine, opiates, alcohol, nicotine, cannabinoids and phencyclidine[34,35]. It is also induced in this same region by chronic consumption of natural rewards, such as high levels of wheel running and sucrose drinking. In contrast to ΔFosB, cFos and other Fos family members are induced in NAc after acute exposure to drugs or natural rewards, whereas ΔFosB accumulates in this region uniquely after chronic exposure, when induction of the other family members shows desensitization. ΔFosB accumulates during chronic exposure owing to its unique stability at the protein level. There is now considerable evidence that ΔFosB accumulation within NAc neurons contributes to a state of sensitization[34,35]. Overexpression of ΔFosB in NAc increases behavioral responses to cocaine and opiates as well as to sucrose and wheel-running, including increased incentive drive for these rewards. Conversely, blockade of ΔFosB function in the NAc by overexpression of a dominant negative antagonist causes the opposite effects. Our hypothesis is that induction of ΔFosB mediates many shared aspects of drug and natural addictions by regulating a set of common target genes[34–36].

Activation of CREB is another common adaptation in the NAc, although it is not as universal as induction of ΔFosB. Repeated exposure to cocaine, amphetamine or opiates induces CREB activity in this region[37–39], whereas alcohol and nicotine reduce CREB phosphorylation (an indirect marker of CREB activity) in the NAc (although they induce CREB activity elsewhere)[40–42]. Despite this opposite regulation of CREB in the NAc by different drugs, activation of CREB seems to produce similar behavioral effects: in numerous experimental systems, increased CREB activity in the NAc decreases behavioral responses to cocaine, opiates and alcohol, whereas decreased CREB activity increases such responses[28,36,39,41,43,44]. CREB is also induced in the NAc by natural rewards (such as sucrose) and similarly reduces an animal's sensitivity to sucrose's rewarding effects[39]. The molecular mechanisms governing drug regulation of CREB in NAc remain

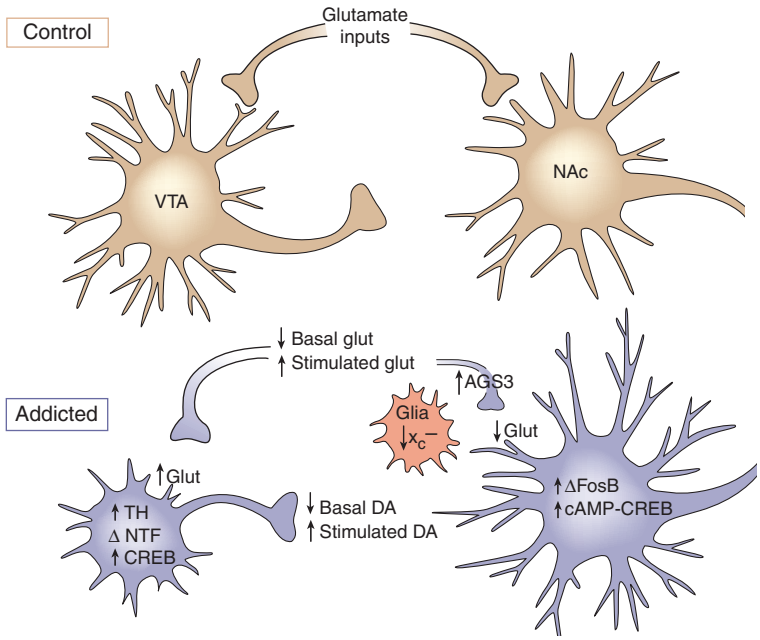


Figure 2 Highly simplified scheme of some common, chronic actions of drugs of abuse on the VTA-NAc. The top panel (Control) shows a VTA neuron innervating an NAc neuron and glutamatergic inputs to the VTA and NAc neurons, under normal conditions. After chronic drug administration (lower panel), several adaptations occur. In VTA, drug exposure induces TH and increases AMPA glutamatergic responses (Glut) via regulation of glutamate receptors. There is also evidence that VTA dopamine neurons decrease in size. Induction of CREB activity and alterations in neurotrophic factor (NTF) signaling may partly mediate these effects. In NAc, all drugs of abuse induce the transcription factor ΔFosB, which may then mediate some of the shared aspects of addiction by regulation of numerous target genes. Several, but not all, drugs of abuse induce CREB activity in this region, which may be mediated by upregulation of the cAMP pathway. Several additional changes have been found for stimulant exposure; it is not yet known whether they generalize to other drugs. Stimulants decrease AMPA glutamatergic responses in NAc neurons, possibly by regulation of glutamate receptors or postsynaptic density proteins (such as PSD95 and Homer-1). These changes in postsynaptic glutamate responses are associated with complex changes in glutamatergic innervation of the NAc, effects mediated in part by upregulation of AGS3 in cortical neurons and downregulation of the cystine-glutamate transporter (system x_c^-) in glia. Stimulants and nicotine also induce dendritic outgrowth of NAc neurons, although opiates produce the opposite action. The net effect of these adaptations on glutamatergic transmission remains uncertain.

unknown but could involve upregulation of the cAMP pathway observed in this region after repeated exposure to any of several drugs of abuse, including cocaine, amphetamine, opiates and alcohol[2,45,46]. Consistent with this view is that in most behavioral assays, cAMP pathway activation also causes reduced behavioral responses to drugs of abuse, whereas inhibition of the pathway facilitates drug responses. One target gene in the NAc through which CREB may exert these effects on drug and natural rewards is the opioid peptide dynorphin, which decreases dopaminergic tone and opposes reward via activation of κ opioid receptors on VTA dopamine neurons and their nerve terminals[44,46].

A major gap in our knowledge is whether chronic exposure to drugs or natural rewards also elicits common changes in the electrophysiological properties of NAc neurons or of their synaptic inputs. This type of information is available for stimulants like cocaine and amphetamine but has not been examined sufficiently for the other drugs or natural rewards. Stimulants cause a long-term depression (LTD)-like state in NAc neurons and also reduce postsynaptic responses to glutamate[21]. This could occur in part via ΔFosB-mediated induction of GluR2 (which reduces AMPA receptor conductance and Ca^{2+} permeability) in the NAc[34,35]. Changes in postsynaptic responses could also be mediated by altered AMPA receptor trafficking or by adaptations in the neurons' postsynaptic densities (PSDs), including reduced levels of PSD95 and Homer or increased levels of F-actin[18,47]. These findings, along with the evidence of abnormal glutamatergic innervation of the NAc from frontal cortical regions (discussed in the next section) would suggest a profound dysfunction in cortical control over the NAc[18], which could in turn relate to the impulsive and compulsive features of stimulant addiction. A major need for future investigations is to determine whether similar changes occur with other drugs of abuse or natural rewards.

Fewer studies have searched for common drug-induced molecular changes in other brain areas (outside the VTA and NAc) associated with addiction. This is unfortunate, as these other regions are also key to the addiction process. For example, one can presume that the hyperactivity of central CRF pathways upon precipitation of drug withdrawal[17] reflects underlying molecular adaptations in amygdala neurons. An interesting candidate is CREB, because it is induced in amygdala by stimulants, opiates and alcohol, and the CRF gene is regulated by CREB[37,38,41].

As another example, one can presume that the hypofrontality demonstrated in rodents and humans after chronic exposure to several drugs of abuse is mediated via common molecular and cellular adaptations in these cortical regions (**Fig. 2**). To date, such adaptations have been characterized only for stimulants and suggest an interesting pathophysiology[13,18]. According to this scheme, which requires further analysis, dopamine has a profound effect on activity of prefrontal cortical neurons, with D_1 and D_2 dopamine receptors exerting opposite effects: D_2 receptor activation tends to promote the neurons' responsiveness to diverse environmental stimuli, whereas D_1 receptor activation favors activation by the strongest stimuli only. Chronic stimulant administration seems to cause a shift toward the D_1 state in part by induction of AGS3 (activator of G protein signaling-3), which is a negative regulator of G_i and hence of D_2 signaling. This could explain the functional observations cited above that baseline activity of these neurons and their responses to natural rewards is dampened, whereas responses to cocaine and cocaine-associated stimuli are enhanced. Induction of AGS3 is accompanied by decreased levels of the cystine-glutamate transporter in glial cells in the NAc; this transporter promotes release of glutamate from prefrontal cortical glutamatergic nerve terminals, perhaps further exaggerating glutamatergic transmission to the NAc when the cell bodies fire in response to cocaine and associated cues[13,18]. Clearly, these changes are complex and interact with postsynaptic adaptations in glutamate receptor function in NAc neurons in ways that remain incompletely understood. Nevertheless, these important findings now highlight the need to characterize the effects of other drugs of abuse, as well as natural rewards, on these same endpoints.

We know that several drugs of abuse, after chronic administration, converge to reduce neurogenesis—birth of new neurons—in the dentate gyrus of adult hippocampus, an effect reported to date for cocaine, opiates, alcohol, nicotine and cannibinoids[48]. The function of adult hippocampal neurogenesis is a subject of great debate: the new nerve cells may be critical for the formation of new memories, although this remains unproven. In any event, the finding that reduced neurogenesis is a common consequence of chronic drug administration raises interesting questions. For example, might this effect contribute to common abnormalities in memory or other cognitive functions seen in many addicts?

Drug-specific actions in brain reward circuits

The argument that acute and chronic drug effects are mediated by common mechanisms is inconsistent with the knowledge that drugs of abuse can readily be distinguished from one another. This is probably due in large part to the very different effects the drugs elicit outside the brain's reward circuitry. For example, opiates are analgesics and sedatives owing to their actions on opioid receptors, which are located in brainstem and spinal cord, whereas cocaine activates the cardiovascular system because of its actions on monoamine transporters, which are located in heart and vascular tissue. Nevertheless, there are likely to be very important differences in the effects of each drug of abuse on reward circuitry as well, and such differences may help explain why most addicts have their preferred drug of abuse.

The most striking example of different chronic cellular actions of drugs of abuse comes from morphological changes observed in NAc and prefrontal cortical pyramidal neurons. Chronic exposure to cocaine, amphetamine or nicotine causes long-lasting increases in dendritic arborization and in the density of dendritic spines of these neurons[49]. These morphological changes, which may be partly mediated via ΔFosB and some of its target genes[35], could contribute to the state of sensitization seen after stimulant exposure, although this has not yet been demonstrated with certainty. In contrast, chronic opiate administration causes opposite changes in the dendritic arbor of NAc and prefrontal cortical neurons[49]. This opposite action of opiates is surprising, given that chronic opiate administration, like chronic stimulant administration, causes very similar sensitization to the behavioral effects of the drugs, and even cross-sensitization, as mentioned earlier. More work is needed to better understand this paradox. One possibility is that the different morphological effects may still lead to a common behavioral endpoint owing to the more specific changes in synaptic transmission associated with the altered morphology. Hence, much more detailed examination is needed of pre- and postsynaptic elements as a function of chronic drug administration.

There are also large numbers of molecular adaptations reported for one drug of abuse that are not seen with the others[2,13,46]. One general principle is that such drug-specific adaptations may increase in likelihood with increasing proximity of a protein to the immediate drug target, whereas more common adaptations may be expected more distally. For example, chronic administration of cocaine, opiates, alcohol or nicotine is specifically associated with changes in dopamine transporters, opioid receptors, $GABA_A$ receptors and nicotinic cholinergic receptors, respectively, in numerous brain regions[4,6,7,9,46], even though all of the drugs alter dopaminergic transmission[3] and induce ΔFosB[34,35] in the NAc.

Implications for treatment of drug and natural addictions

Because common mechanisms seem to contribute to at least some aspects of all drug addictions, and possibly to natural addictions as well, it might be possible to develop treatments that would be effective for a wide range of addictive disorders. Drugs that target the brain's dopamine, glutamate,

CRF, opioid or cannabinoid systems might well be expected to exert common palliative effects in individuals addicted to a wide range of drugs or natural rewards. Studies are underway in each of these areas. In the more distant future, it might be possible to exploit our increasing knowledge of common molecular adaptations to drugs and natural rewards, for example, in the cAMP-CREB pathway, ΔFosB, or any of their numerous target genes, or in the complex molecular constituents of the glutamatergic synapse, although this approach remains highly speculative.

At the same time, however, our knowledge of shared mechanisms of action of drugs of abuse and natural rewards raises serious red flags about the ultimate safety and effectiveness of such treatments. Is it possible to dampen common mechanisms of impulsive and compulsive consumption of drug or natural rewards without affecting the normal functioning of the individual (that is, healthy responses to natural rewards)? Thus far, all established treatments for addiction are drug-specific and are aimed at the acute protein target of the drugs[46]. For example, methadone, buprenorphine and naltrexone, which are, respectively, an agonist, partial agonist and antagonist at the μ opioid receptor, are effective for opiate addiction, whereas nicotine patches and chewing gum are effective for nicotine addiction. Naltrexone can also be of some use in the treatment of alcohol and nicotine addictions, but the magnitude of its effect is modest in most individuals. Acamprosate, which may act by reducing NMDA glutamatergic receptor function (although this remains speculative), is reported to be effective for some alcohol addicts[50].

Thus, no treatment aimed at common drug mechanisms has yet been fully validated across of range of addictions to multiple drugs of abuse and to natural rewards. A high priority for current research should be to focus on bringing some of the most promising common anti-addiction mechanisms into the clinic for broad trials across several addictive disorders. Such trials, while clearly difficult, are critically important to help us understand whether addictions can be treated, at least in part, as a unitary disorder.

ACKNOWLEDGMENTS

Preparation of this review was supported by the National Institute on Drug Abuse.

COMPETING INTERESTS STATEMENT

The author declares that he has no competing financial interests.

Published online at http://www.nature.com/natureneuroscience/

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