

The Addicted

Drug abuse produces long-term changes in the reward circuitry of the brain. Knowledge of the cellular and molecular details of these adaptations could lead to new treatments for the compulsive behaviors that underlie addiction

BRAIN

By Eric J. Nestler and Robert C. Malenka

White lines on a mirror. A needle and spoon. For many users, the sight of a drug or its associated paraphernalia can elicit shudders of anticipatory pleasure. Then, with the fix, comes the real rush: the warmth, the clarity, the vision, the relief, the sensation of being at the center of the universe. For a brief period, everything feels right. But something happens after repeated exposure to drugs of abuse—whether heroin or cocaine, whiskey or speed.

The amount that once produced euphoria doesn't work as well, and users come to need a shot or a snort just to feel normal; without it, they become depressed and, often, physically ill. Then they begin to use the drug compulsively. At this point, they are addicted, losing control over their use and suffering powerful cravings even after the thrill is gone and their habit begins to harm their health, finances and personal relationships.

Neurobiologists have long known that the euphoria induced by drugs of abuse arises because all these chemicals ultimately boost the activity of the brain's reward system:

ILLUSTRATION BY JANA BRENNING (photograph used for illustration purposes only)



ADDICTION ARISES in part because habit-forming drugs cause the brain's circuit for assessing reward to deem the drugs more desirable than anything else in life.

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a complex circuit of nerve cells, or neurons, that evolved to make us feel flush after eating or sex—things we need to do to survive and pass along our genes. At least initially, goosing this system makes us feel good and encourages us to repeat whatever activity brought us such pleasure.

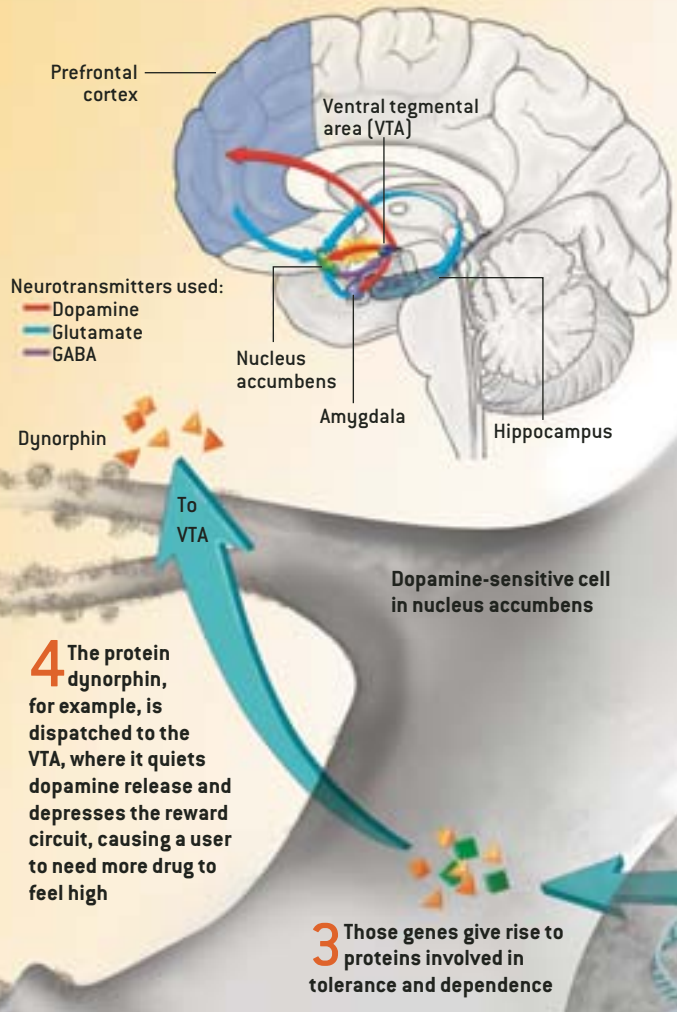
But new research indicates that chronic drug use induces changes in the structure and function of the system's neurons that last for weeks, months or years after the last fix. These adaptations, perversely, dampen the pleasurable effects of a chronically abused substance yet also increase the cravings that trap the addict in a destructive spiral of escalating use and increased fallout at work and at home. Improved understanding of these neural alterations should help provide better interventions for addiction, so that people who have fallen prey to habit-forming drugs can reclaim their brains and their lives.

Drugs to Die For

THE REALIZATION that various drugs of abuse ultimately lead to addiction through a common pathway emerged largely from studies of laboratory animals that began about 40 years ago. Given the opportunity, rats, mice and nonhuman primates will self-administer the same substances that humans abuse. In these experiments, the animals are connected to an intravenous line. They are then taught to press one lever to receive an infusion of drug through the IV, another lever to get a relatively uninteresting saline solution, and a third lever to request a food pellet. Within a few days, the animals are hooked: they readily self-administer cocaine, heroin, amphetamine and

THE BRAIN UNDER THE INFLUENCE

CHRONIC USE of addictive substances can change the behavior of a key part of the brain's reward circuit: the pathway extending from the dopamine-producing nerve cells (neurons) of the ventral tegmental area (VTA) to dopamine-sensitive cells in the nucleus accumbens. Those changes, induced in part by the molecular actions depicted at the right and in the graph, contribute significantly to the tolerance, dependence and craving that fuel repeated drug use and lead to relapses even after long periods of abstinence. The colored arrows on the brain indicate some of the pathways linking the nucleus accumbens and VTA with other regions that can help to make drug users highly sensitive to reminders of past highs, vulnerable to relapses when stressed, and unable to control their urges to seek drugs.



many other common habit-forming drugs.

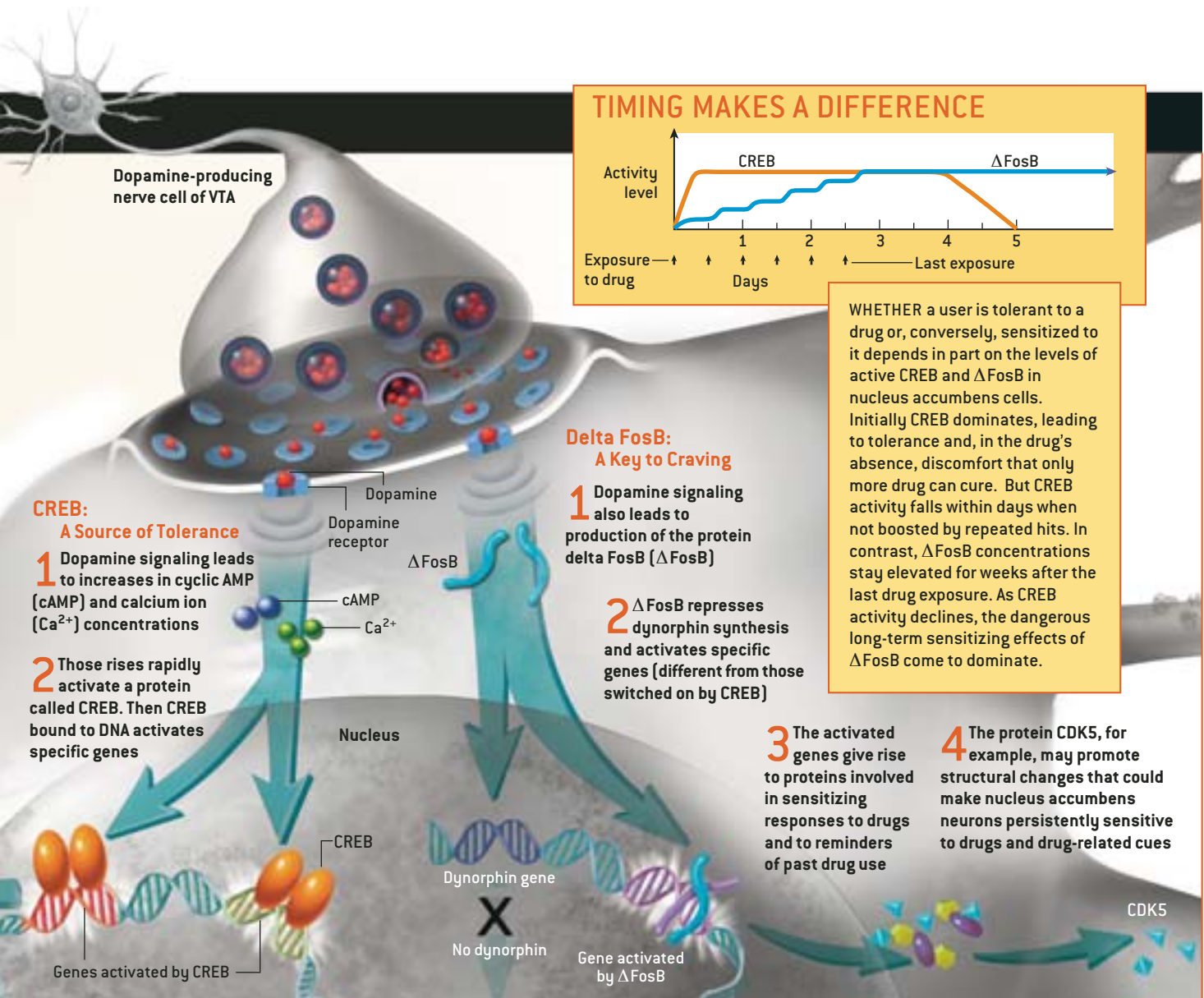
What is more, they eventually display assorted behaviors of addiction. Individual animals will take drugs at the expense of normal activities such as eating and sleeping—some even to the point that they die of exhaustion or malnutrition. For the

most addictive substances, such as cocaine, animals will spend most of their waking hours working to obtain more, even if it means pressing a lever hundreds of times for a single hit. And just as human addicts experience intense cravings when they encounter drug paraphernalia or places where they have scored, the animals, too, come to prefer an environment that they associate with the drug—an area in the cage in which lever pressing always provides chemical compensation.

When the substance is taken away, the animals soon cease to labor for chemical satisfaction. But the pleasure is not forgotten. A rat that has remained clean—even for months—will immediately return to its bar-pressing behavior when given just a taste of cocaine or placed in a cage it associates with a drug high. And certain

Overview/*The Evolution of Addiction*

- Drugs of abuse—cocaine, alcohol, opiates, amphetamine—all commandeer the brain's natural reward circuitry. Stimulation of this pathway reinforces behaviors, ensuring that whatever you just did, you'll want to do again.
- Repeated exposure to these drugs induces long-lasting adaptations in the brain's chemistry and architecture, altering how individual neurons in the brain's reward pathways process information and interact with one another.
- Understanding how chronic exposure to drugs of abuse reshapes an addict's brain could lead to novel, more broadly effective ways to correct the cellular and molecular aberrations that lie at the heart of all addiction.



psychological stresses, such as a periodic, unexpected foot shock, will send rats scurrying back to drugs. These same types of stimuli—exposure to low doses of drug, drug-associated cues or stress—trigger craving and relapse in human addicts.

Using this self-administration setup and related techniques, researchers mapped the regions of the brain that mediate addictive behaviors and discovered the central role of the brain's reward circuit. Drugs commandeer this circuit, stimulating its activity with a force and persistence greater than any natural reward.

A key component of the reward circuitry is the mesolimbic dopamine system: a set of nerve cells that originate in the ventral tegmental area (VTA), near the base of the brain, and send projections to target regions in the front of the brain—

most notably to a structure deep beneath the frontal cortex called the nucleus accumbens. Those VTA neurons communicate by dispatching the chemical messenger (neurotransmitter) dopamine from the terminals, or tips, of their long projections to receptors on nucleus accumbens neurons. The dopamine pathway from the VTA to the nucleus accumbens is critical for addiction: animals with lesions in these brain regions no longer show interest in substances of abuse.

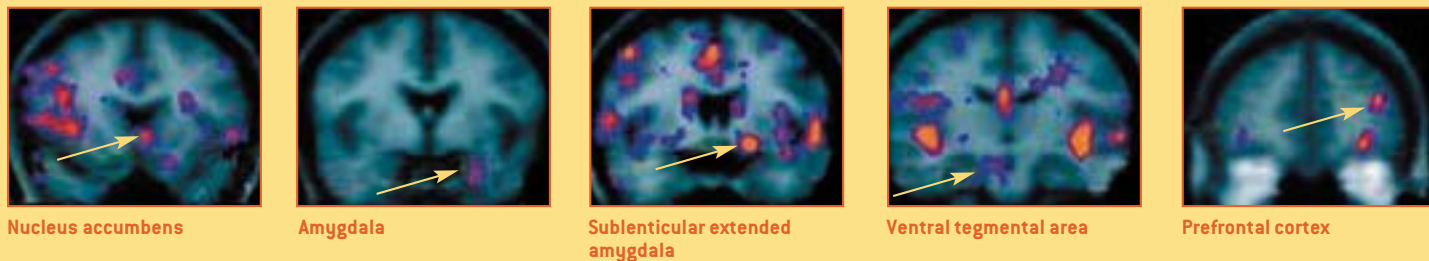
Rheostat of Reward

REWARD PATHWAYS are evolutionarily ancient. Even the simple, soil-dwelling worm *Caenorhabditis elegans* possesses a rudimentary version. In these worms, inactivation of four to eight key dopamine-containing neurons causes an ani-

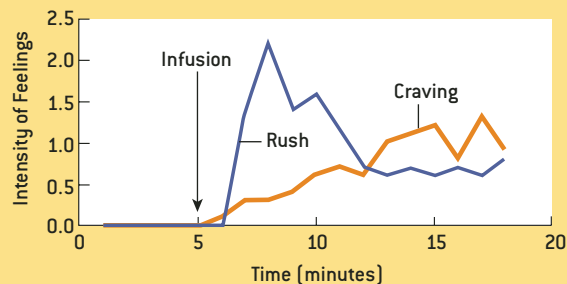
mal to plow straight past a heap of bacteria, its favorite meal.

In mammals, the reward circuit is more complex, and it is integrated with several other brain regions that serve to color an experience with emotion and direct the individual's response to rewarding stimuli, including food, sex and social interaction. The amygdala, for instance, helps to assess whether an experience is pleasurable or aversive—and whether it should be repeated or avoided—and helps to forge connections between an experience and other cues; the hippocampus participates in recording the memories of an experience, including where and when and with whom it occurred; and the frontal regions of the cerebral cortex coordinate and process all this information and determine the ultimate behavior of the

INSIGHTS FROM IMAGING



SPOTS OF COLOR in brain scans of cocaine addicts (above) confirm animal studies indicating that drug intake can induce profound immediate activity changes in many brain regions, including those shown; brightest spots show the most significant change. While being scanned, the subjects rated their feelings of rush and craving on a scale of zero to three—revealing that the VTA and the sublenticular extended amygdala are important to the cocaine-induced rush and that the amygdala and the nucleus accumbens influence both the rush and the craving for more drug, which becomes stronger as the euphoria wears off (graph).



individual. The VTA-accumbens pathway, meanwhile, acts as a rheostat of reward: it “tells” the other brain centers how rewarding an activity is. The more rewarding an activity is deemed, the more likely the organism is to remember it well and repeat it.

Although most knowledge of the brain’s reward circuitry has been derived from animals, brain-imaging studies conducted over the past 10 years have revealed that equivalent pathways control natural and drug rewards in humans. Using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) scans (techniques that measure changes in blood flow associated with neuronal activity), researchers have watched the nucleus accumbens in cocaine addicts light up when they are offered a snort. When the same addicts are shown a video of someone using cocaine or a photograph of white lines on a mirror, the accumbens responds similarly, along with the amygdala and some areas of the cortex. And the same regions react in compulsive gamblers who are shown images of slot machines, suggesting that the VTA-accumbens pathway has a similarly critical role even in nondrug addictions.

Dopamine, Please

HOW IS IT POSSIBLE that diverse addictive substances—which have no common structural features and exert a vari-

ety of effects on the body—all elicit similar responses in the brain’s reward circuitry? How can cocaine, a stimulant that causes the heart to race, and heroin, a pain-relieving sedative, be so opposite in some ways and yet alike in targeting the reward system? The answer is that all drugs of abuse, in addition to any other effects, cause the nucleus accumbens to receive a flood of dopamine and sometimes also dopamine-mimicking signals.

When a nerve cell in the VTA is excited, it sends an electrical message racing along its axon—the signal-carrying “highway” that extends into the nucleus accumbens. The signal causes dopamine to be released from the axon tip into the tiny space—the synaptic cleft—that separates the axon terminal from a neuron in the nucleus accumbens. From there, the dopamine latches onto its receptor on the accumbens neuron and transmits its signal into the cell. To later shut down the signal, the VTA neuron removes the dopamine from the synaptic cleft and repackages it to be used again as needed.

Cocaine and other stimulants temporarily disable the transporter protein that returns the neurotransmitter to the VTA neuron terminals, thereby leaving excess dopamine to act on the nucleus accumbens. Heroin and other opiates, on the other hand, bind to neurons in the VTA that normally shut down the dopamine-producing VTA neurons. The opi-

ates release this cellular clamp, thus freeing the dopamine-secreting cells to pour extra dopamine into the nucleus accumbens. Opiates can also generate a strong “reward” message by acting directly on the nucleus accumbens.

But drugs do more than provide the dopamine jolt that induces euphoria and mediates the initial reward and reinforcement. Over time and with repeated exposure, they initiate the gradual adaptations in the reward circuitry that give rise to addiction.

An Addiction Is Born

THE EARLY STAGES of addiction are characterized by tolerance and dependence. After a drug binge, an addict needs more of the substance to get the same effect on mood or concentration and so on. This tolerance then provokes an escalation of drug use that engenders dependence—a need that manifests itself as painful emotional and, at times, physical reactions if access to a drug is cut off. Both tolerance and dependence occur because frequent drug use can, ironically, suppress parts of the brain’s reward circuit.

At the heart of this cruel suppression lies a molecule known as CREB (cAMP response element-binding protein). CREB is a transcription factor, a protein that regulates the expression, or activity, of genes and thus the overall behavior of



MICROGRAPHS of nucleus accumbens neurons in animals exposed to nonaddictive drugs display dendritic branches with normal numbers of signal-receiving projections called spines (*left and center*). But those who become addicted to cocaine sprout additional spines on the branches, which consequently look bushier (*right*). Presumably, such remodeling makes neurons more sensitive to signals from the VTA and elsewhere and thus contributes to drug sensitivity. Recent findings suggest that delta FosB plays a part in spine growth.

nerve cells. When drugs of abuse are administered, dopamine concentrations in the nucleus accumbens rise, inducing dopamine-responsive cells to increase production of a small signaling molecule, cyclic AMP (cAMP), which in turn activates CREB. After CREB is switched on, it binds to a specific set of genes, triggering production of the proteins those genes encode.

Chronic drug use causes sustained activation of CREB, which enhances expression of its target genes, some of which code for proteins that then dampen the reward circuitry. For example, CREB controls the production of dynorphin, a natural molecule with opiumlike effects. Dynorphin is synthesized by a subset of neurons in the nucleus accumbens that loop back and inhibit neurons in the VTA. Induction of dynorphin by CREB thereby stifles the brain's reward circuitry, inducing tolerance by making the same-old dose of drug less rewarding. The increase in dynorphin also contributes to dependence, as its inhibition of the reward pathway leaves the individual, in the drug's absence, depressed and unable to take pleasure in previously enjoyable activities.

But CREB is only a piece of the story. This transcription factor is switched off within days after drug use stops. So CREB cannot account for the longer-lasting grip that abused substances have on

the brain—for the brain alterations that cause addicts to return to a substance even after years or decades of abstinence. Such relapse is driven to a large extent by sensitization, a phenomenon whereby the effects of a drug are augmented.

Although it might sound counterintuitive, the same drug can evoke both tolerance and sensitization. Shortly after a hit, CREB activity is high and tolerance rules: for several days, the user would need increasing amounts of drug to goose the reward circuit. But if the addict abstains, CREB activity declines. At that point, tolerance wanes and sensitization sets in, kicking off the intense craving that underlies the compulsive drug-seeking behavior of addiction. A mere taste or a memory can draw the addict back. This relentless yearning persists even after long periods of abstinence. To understand the roots of sensitization, we have to look for molecular changes that last longer than a few days. One candidate culprit is another transcription factor: delta FosB.

Road to Relapse

DELTA FOSB APPEARS to function very differently in addiction than CREB does. Studies of mice and rats indicate that in response to chronic drug abuse, delta FosB concentrations rise gradually and progressively in the nucleus accumbens and other brain regions. Moreover, because the protein is extraordinarily stable, it remains active in these nerve cells for weeks to months after drug administration, a persistence that would enable it to maintain changes in gene expression long after drug taking ceased.

Studies of mutant mice that produce excessive amounts of delta FosB in the nucleus accumbens show that prolonged induction of this molecule causes animals to become hypersensitive to drugs. These mice were highly prone to relapse after the drugs were withdrawn and later made available—a finding implying that delta FosB concentrations could well contribute to long-term increases in sensitivity in the reward pathways of humans. Interestingly, delta FosB is also produced in the nucleus accumbens in mice in response to repetitious nondrug rewards, such as excessive wheel running and sugar consumption. Hence, it might have a more general role in the development of compulsive behavior toward a wide range of rewarding stimuli.

Recent evidence hints at a mechanism for how sensitization could persist even after delta FosB concentrations return to normal. Chronic exposure to cocaine and other drugs of abuse is known to induce the signal-receiving branches of nucleus accumbens neurons to sprout additional buds, termed dendritic spines, that bolster the cells' connections to other neurons. In rodents, this sprouting can continue for some months after drug taking ceases. This discovery suggests that delta FosB may be responsible for the added

THE AUTHORS

ERIC J. NESTLER and ROBERT C. MALENKA study the molecular basis of drug addiction. Nestler, professor in and chair of the department of psychiatry at the University of Texas Southwestern Medical Center at Dallas, was elected to the Institute of Medicine in 1998. Malenka, professor of psychiatry and behavioral sciences at the Stanford University School of Medicine, joined the faculty there after serving as director of the Center for the Neurobiology of Addiction at the University of California, San Francisco. With Steven E. Hyman, now at Harvard University, Nestler and Malenka wrote the textbook *Molecular Basis of Neuropharmacology* (McGraw-Hill, 2001).

DIFFERENT DRUGS, SAME ULTIMATE EFFECT

DRUGS OF ABUSE hit various targets in the brain, but all directly or indirectly enhance the amount of dopamine signaling in the nucleus accumbens, thereby promoting addiction. Knowledge of the targets raises ideas for therapy (see box on opposite page).

Projection from cortex, amygdala or hippocampus

Glutamate

Glutamate receptor

MANY DRUGS, including cocaine, amphetamine (speed), morphine and alcohol, can alter the responses of nucleus accumbens and VTA cells to glutamate in long-lasting ways. Those changes contribute to drug cravings by heightening memories of past drug experiences even after the substance is no longer used

COCAINE AND RELATED STIMULANTS block dopamine uptake or increase dopamine release by the terminals of VTA cells and thus increase dopamine signaling in the nucleus accumbens

NICOTINE induces VTA cells to release dopamine into the nucleus accumbens

Dopamine-releasing VTA neuron

Inhibitory neuron in VTA

ALCOHOL AND OPIATES (opium, heroin and their relatives) enhance dopamine release by quieting neurons that would otherwise inhibit dopamine-secreting neurons

Dopamine

Dopamine transporter

Cocaine

CREB

Dopamine receptor

Opiate receptor

Δ FosB

OPIATE DRUGS mimic some of dopamine's actions in nucleus accumbens cells

Opiumlike neurotransmitter made by neurons

Nucleus accumbens neuron

spines. Highly speculative extrapolation from these results raises the possibility that the extra connections generated by delta FosB activity amplify signaling between the linked cells for years and that such heightened signaling might cause the brain to overreact to drug-related cues. The dendritic changes may, in the end, be the key adaptation that accounts for the intransigence of addiction.

Learning Addiction


THUS FAR WE HAVE focused on drug-induced changes that relate to dopamine in the brain's reward system. Recall, however, that other brain regions—namely, the amygdala, hippocampus and frontal cortex—are involved in addiction and communicate back and forth with the

VTA and the nucleus accumbens. All those regions talk to the reward pathway by releasing the neurotransmitter glutamate. When drugs of abuse increase dopamine release from the VTA into the nucleus accumbens, they also alter the responsiveness of the VTA and nucleus accumbens to glutamate for days. Animal experiments indicate that changes in sensitivity to glutamate in the reward pathway enhance both the release of dopamine from the VTA and responsiveness to dopamine in the nucleus accumbens, thereby promoting CREB and delta FosB activity and the unhappy effects of these molecules. Furthermore, it seems that this altered glutamate sensitivity strengthens the neuronal pathways that link memories of drug-taking experiences with high reward,


thereby feeding the desire to seek the drug.

The mechanism by which drugs alter sensitivity to glutamate in neurons of the reward pathway is not yet known with certainty, but a working hypothesis can be formulated based on how glutamate affects neurons in the hippocampus. There certain types of short-term stimuli can enhance a cell's response to glutamate over many hours. The phenomenon, dubbed long-term potentiation, helps memories to form and appears to be mediated by the shuttling of certain glutamate-binding receptor proteins from intracellular stores, where they are not functional, to the nerve cell membrane, where they can respond to glutamate released into a synapse. Drugs of abuse influence the shuttling of glutamate receptors in the


TREATMENT POSSIBILITIES




Hypothetical anticompetitive agent might reduce dopamine signaling in the nucleus accumbens by interfering with cocaine's ability to block dopamine uptake by VTA neuron terminals.



Hypothetical broad-spectrum agent would mute dopamine's effects by preventing CREB or Δ FosB from accumulating or from activating the target genes of these molecules.



Hypothetical broad-spectrum agent might interfere with the unhelpful changes in glutamate signaling that occur in nucleus accumbens cells with chronic drug use.



Opiate antagonists (such as naltrexone), already on the market, block opiate receptors. They are used against alcoholism and cigarette smoking because alcohol and nicotine trigger release of the brain's own opiumlike molecules.

reward pathway. Some findings suggest that they can also influence the synthesis of certain glutamate receptors.

Taken together, all the drug-induced changes in the reward circuit that we have discussed ultimately promote tolerance, dependence, craving, relapse and the complicated behaviors that accompany addiction. Many details remain mysterious, but we can say some things with assurance. During prolonged drug use, and shortly after use ceases, changes in the concentrations of cyclic AMP and the activity of CREB in neurons in the reward pathway predominate. These alterations cause tolerance and dependence, reducing sensitivity to the drug and rendering the addict depressed and lacking motivation. With more prolonged abstinence, changes

in delta FosB activity and glutamate signaling predominate. These actions seem to be the ones that draw an addict back for more—by increasing sensitivity to the drug's effects if it is used again after a lapse and by eliciting powerful responses to memories of past highs and to cues that bring those memories to mind.

The revisions in CREB, delta FosB and glutamate signaling are central to addiction, but they certainly are not the whole story. As research progresses, neuroscientists will surely uncover other important molecular and cellular adaptations in the reward circuit and in related brain areas that will illuminate the true nature of addiction.

A Common Cure?

BEYOND IMPROVING understanding of the biological basis of drug addiction, the discovery of these molecular alterations provides novel targets for the biochemical treatment of this disorder. And the need for fresh therapies is enormous. In addition to addiction's obvious physical and psychological damage, the condition is a leading cause of medical illness. Alcoholics are prone to cirrhosis of the liver, smokers are susceptible to lung cancer, and heroin addicts spread HIV when they share needles. Addiction's toll on health and productivity in the U.S. has been estimated at more than \$300 billion a year, making it one of the most serious problems facing society. If the definition of addiction is broadened to encompass other forms of compulsive pathological behavior, such as overeating and gambling, the costs are far higher. Therapies that could correct aberrant, addictive reactions to rewarding stimuli—whether cocaine or cheesecake or the thrill of winning at blackjack—would provide an enormous benefit to society.

Today's treatments fail to cure most addicts. Some medications prevent the

drug from getting to its target. These measures leave users with an "addicted brain" and intense drug craving. Other medical interventions mimic a drug's effects and thereby dampen craving long enough for an addict to kick the habit. These chemical substitutes, however, may merely replace one habit with another. And although nonmedical, rehabilitative treatments—such as the popular 12-step programs—help many people grapple with their addictions, participants still relapse at a high rate.

Armed with insight into the biology of addiction, researchers may one day be able to design medicines that counter or compensate for the long-term effects of drugs of abuse on reward regions in the brain. Compounds that interact specifically with the receptors that bind to glutamate or dopamine in the nucleus accumbens, or chemicals that prevent CREB or delta FosB from acting on their target genes in that area, could potentially loosen a drug's grip on an addict.

Furthermore, we need to learn to recognize those individuals who are most prone to addiction. Although psychological, social and environmental factors certainly are important, studies in susceptible families suggest that in humans about 50 percent of the risk for drug addiction is genetic. The particular genes involved have not yet been identified, but if susceptible individuals could be recognized early on, interventions could be targeted to this vulnerable population.

Because emotional and social factors operate in addiction, we cannot expect medications to fully treat the syndrome of addiction. But we can hope that future therapies will dampen the intense biological forces—the dependence, the cravings—that drive addiction and will thereby make psychosocial interventions more effective in helping to rebuild an addict's body and mind. SA

MORE TO EXPLORE

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