

Neuroplasticity in addictive disorders

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Compulsive drug-taking behavior develops in vulnerable individuals who ingest substances that activate the reward system. This intense activation produces learned associations to cues that predict drug availability. With repetition the reward system becomes reflexively activated by cues alone, leading to a drive toward drug-taking. The central nervous system changes underlying this conditioned behavior are just beginning to be understood. New treatments aimed at this neuroplasticity are being tested in animal models. The clinical significance of these brain changes is that addiction, once established, becomes a chronic illness with relapses and remissions. It therefore requires chronic treatment with medications and behavioral therapies based on an understanding of the fundamental nature of these changes in the brain.

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Addiction is a disease of neuroplasticity. In the past, clinicians considered detoxification to be the treatment for addiction. However, detoxification is simply removal of the drug from the body and treatment of withdrawal symptoms. Now we know that the essence of addiction continues long after the last dose of the drug, often lasting for years. This was first demonstrated in animal models, and later shown in human addicts more than 30 years ago.¹ Addiction is fundamentally a memory trace that manifests itself by reflex activation of brain circuits, especially the reward system, resulting in motivation to resume drug-taking behavior when drug-related cues are encountered.

Drugs that activate the reward system carry liability for the development of addiction, but vulnerability to this disorder is influenced by complex genetic and environmental variables. A characteristic of all drugs that are abused by humans is that they activate dopamine circuits in brain reward systems by a variety of mechanisms. This has been demonstrated directly in animal models and indirectly in human brain imaging studies. Other neurotransmitters are also involved, but dopamine has received the greatest attention.

While a given drug of abuse will tend to have very similar immediate effects in all users, only a minority of users progress to the stage of compulsive use or addiction. Two general forms of neuroplasticity can be demonstrated. The first, and most common, is tolerance accompanied by physical dependence. Tolerance is manifested by reduced effects from a given dose that is given repeatedly, and "physical" dependence (not addiction) is manifested by withdrawal symptoms when the drug is stopped abruptly. This form of plasticity occurs in all individuals when cer-

tain drugs are taken repeatedly. Examples include prescribed medications such as β -blockers, antidepressants, sedatives, and opioids for pain, as well as commonly abused drugs such as alcohol, cocaine, and nicotine.

The second form of neuroplasticity is manifested by compulsive drug-seeking behavior. The reward system, which developed early in evolution, reinforces adaptive behavior such as that leading to the acquisition of water, food, and sex. Drugs that directly activate the reward system may produce learning that diverts the individual to those behaviors that repeat the drug-induced feelings of reward. An important feature of this form of neuroplasticity is that it is stable and perhaps permanent. The dopamine release caused by a drug of abuse tends to be greater than that of natural rewards, and to continue with repeated exposure rather than diminish, as is the case with natural, expected rewards.² Thus, the drug experience becomes associated with environmental cues and acquires increasing salience. Individuals who develop this neuroplasticity tend to suffer from a chronic illness with potential for relapse, even years after the last dose of the drug. Drug-taking then acquires more salience than natural or adaptive behaviors.

Evidence of the plasticity that has occurred with the development of addiction can be demonstrated by brain imaging studies that show rapid activation (increased blood flow to reward pathways) when drug-related cues are shown to addicts who have been free of drugs for at least a month.³ Even cues so brief that they do not reach consciousness (33 msec) can produce rapid activation.⁴ During brain reward system activation, the addict reports drug craving. The strength of the craving is related directly to the amount of endogenous dopamine released in reward structures, as measured by displacement of labeled raclopride in positron emission tomography (PET) studies.⁵

More direct studies of the plasticity induced by drugs of addiction can be seen in animal models. Shaham and colleagues have studied the relapse or reinstatement of drug-taking in rats trained to self-administer intravenous cocaine.⁶ Availability of cocaine is signaled by a light that the animal then associates with cocaine. After the behavior is well trained, the cocaine can be turned off; thus, pushing the lever no longer provides cocaine. After the extinction process is complete, the animal can be tested for reinstatement by returning it to the drug-taking environment and giving the light cue. This is considered to be a model of "relapse" in human addicts. The intensity

of relapse can be measured by the number of times the light causes the rat to press the bar despite not receiving any cocaine. Eventually, the unrewarded bar pressing stops. It was found that reinstatement occurred when rats were tested 1 week after extinguishing cocaine-seeking, but the reinstatement was significantly greater at 4 weeks, and progressively increased further if the rats were allowed to rest in their cages for up to 6 months before relapse testing. The strengthening of relapse tendency over time has been called "incubation" and is associated with increases in the levels of the growth factor brain-derived neurotrophic factor (BDNF) in the ventral tegmental area and in the nucleus accumbens. The authors also found that exposure to cocaine cues increased extracellular signal-related kinase (ERK) in central amygdala after 30 days of rest, but not after 1 day. This shows that there is an active neuroplastic process in the brain that increases over time and is manifested by increased cocaine-seeking behavior.

Transcription factors have been observed to be changed by addictive drugs. Delta Fos B accumulates in dopamine terminals in the cortex and striatum.⁷ All drugs of abuse tested produce an increase in delta Fos B, which appears to be involved in the development of motivated behaviors. Disruption of this process blocks the development of drug-associated plasticity such as behavioral sensitization. The latter is the increase in motor behavior in response to repeated, fixed doses of a stimulant.⁸ Genes directly regulated by delta Fos B appear to have different effects and may limit as well as promote drug reinforcement. The delta Fos B changes are temporary, with return to prior levels when the drug is no longer present. Thus, these transcription factor changes do not seem to underlie long-term neuroplasticity.

Changes in neuronal morphology have also been noted in animals exposed to drugs that are abused. In the nucleus accumbens, an increase in dendritic spine density has been reported in medium spiny neurons from rats self-administering cocaine. These changes persisted during abstinence, and may be involved in long-term changes associated with drug-seeking behavior.⁹

Changes in neuronal morphology have also been found in individuals chronically exposed to opioids. Chronic morphine given to rats, for example, has been found to reduce dendritic spines (whereas stimulants increased spines) on ventral tegmental area neurons. Chronic morphine also reduces neurogenesis in the hippocampus.¹⁰ These changes may be the basis for the cognitive losses

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seen in some patients receiving chronic opioids for pain. Since the learned addictive behavior is thought to result from neuroplasticity such as that described above, it seems logical to consider reversal of these changes as a target for the treatment of addictive behaviors. A very interesting animal model of this approach has been illustrated by a series of experiments by Kalivas et al. Using rats trained to self-administer cocaine, they reported a reduction in glutamate in the brains of animals exposed to long-term cocaine and a disruption of glutamate homeostasis. Following withdrawal from chronic cocaine there is a marked imbalance in glutamate homeostasis, with both cystine-glutamate exchange and glutamate uptake being reduced in the nucleus accumbens.¹¹ The imbalance in glutamate homeostasis is associated with a reduction in basal extracellular glutamate levels and a potentiated release of synaptic glutamate during drug-seeking.¹² In addition, there is a basal increase in the α -amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) to N-methyl-D-aspartic acid (NMDA) current ratio and a loss of both long-term potentiation (LTP) and long-term depression (LTD).¹³

There are therapeutic implications in these observations on glutamate homeostasis. Cystine can be administered to animals withdrawn from chronic cocaine using N-acetylcysteine as a carrier, or glutamate uptake can be increased by the antibiotic ceftriaxone. By restoring the glutamate homeostasis in this manner, reinstatement of cocaine seeking is prevented. The treated animals also show a restored ability to induce LTP and LTD, as well as a normalization of the AMPA:NMDA ratio. The treatment also prevents changes in spine head diameter induced during cocaine-seeking.¹³

Taken together, the data above suggest the possibility that normalization of glutamate homeostasis in addicts might restore the ability to induce synaptic plasticity in the nucleus accumbens, which in turn could facilitate establishing behaviors that might compete with drug-seeking.

Exogenous N-acetyl cysteine is used for the treatment of hepatic failure in acetaminophen overdose. Thus, it was available to be administered to cocaine addicts presented with cocaine-related cues in an attempt to translate findings in the animal model to human addicts. Those treated with N-acetyl cysteine reported reduced desire for cocaine compared with the control group.¹⁴ In another human study, N-acetyl cysteine was found to reduce pathological gambling¹⁵ and cigarette smoking.¹⁶ Further clinical trials are in progress.

Another attempt to reverse the learned behaviors seen in addiction involves a new technology of real-time functional magnetic resonance imaging biofeedback of brain activity.¹⁷ Addicts have been shown to have poor ability to inhibit impulses, and this correlates with decreased frontal lobe activity. Normal subjects can activate frontal control mechanisms when attempting to inhibit sexual arousal, but cocaine-dependent patients are unable to inhibit craving when shown drug-related stimuli. By providing feedback of frontal activation, the patients will attempt to learn to activate inhibitory structures and inhibit drug craving. This represents a therapeutic attempt to introduce new learning to control addictive behavior. The continued study of the underlying mechanisms of plasticity will undoubtedly produce other novel pharmacological and behavioral treatments. □

Neuroplasticidad en los trastornos adictivos

La conducta compulsiva de consumir drogas se desarrolla en individuos vulnerables que ingieren sustancias que activan el sistema de recompensa. Esta intensa activación produce asociaciones aprendidas frente a señales que predicen la disponibilidad de droga. Con la repetición, el sistema de recompensa se activa en forma refleja sólo por las señales, favoreciendo el camino hacia el consumo de drogas. Recién se están comenzando a comprender los cambios del sistema nervioso central que subyacen a esta conducta condicionada. En modelos animales se están evaluando nuevos tratamientos orientados a esta neuroplasticidad. El significado clínico de estos cambios cerebrales es que la adicción, una vez establecida, llega a ser una enfermedad crónica con recaídas y remisiones. Esta patología requiere por lo tanto de un tratamiento crónico con medicamentos y terapias conductuales basadas en una comprensión de la naturaleza fundamental de estos cambios en el cerebro.

Neuroplasticité et troubles addictifs

Les comportements compulsifs de prise de substance se développent chez des individus vulnérables qui ingèrent des substances activant le système de récompense. Cette activation intense entraîne des associations à des signaux qui indiquent la disponibilité de la drogue par un phénomène d'apprentissage. Avec les répétitions du processus, le système de récompense s'active de façon réflexe par les seuls signaux, provoquant une pulsion de prise de drogue. Les modifications du système nerveux central qui sous-tendent ce comportement conditionné commencent seulement à être comprises. De nouveaux traitements ciblant cette neuroplasticité sont en train d'être testés dans des modèles animaux. Ces modifications cérébrales signifient cliniquement que l'addiction, une fois installée, se comporte comme une maladie chronique avec rechutes et rémissions. Ceci nécessite donc un traitement chronique avec des médicaments et des thérapies comportementales basées sur la compréhension de la nature fondamentale de ces modifications cérébrales.

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