What links addiction and the learning process?

Memory Sickness?

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Processes associated with the appearance of addiction are remarkably similar to learning and memory processes. Addictive substances induce false memory traces in reward system structures

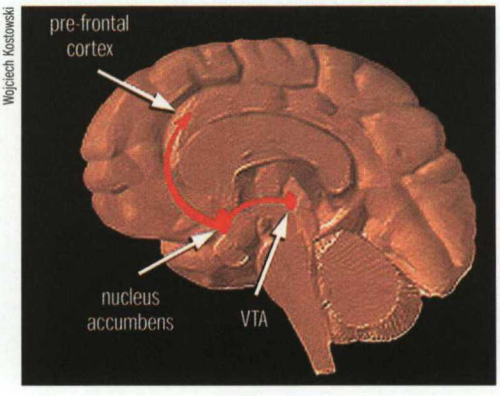
Addiction is first and foremost understood as chemical dependence (addiction to medication, drug addiction, alcoholism), but the term is obviously of broader application and also covers a variety of behavioral addictions, for instance to gambling, computers, shopping or attractive foods. All in all, it seems that the mechanism and neurobiological bases of all addictions are very closely related.

Addiction is a complex condition of the central nervous system which is characterized by a loss of control over behaviors. The behavior of the addict is compulsive, limited to constant or periodic seeking out and taking of the addictive substance (or other source of reward) in order to experience the psychological effects of its action or avoid the unpleasant symptoms related to its absence. Addiction is a chronic disorder with relapses occurring even after a very long period of abstinence. Although many people have contact with a variety of addictive substances, only some of them fall into addiction. This happens when contact with the substances is renewed and may especially affect particularly susceptible, genetically predisposed individuals.

The reward system

The essential features of addiction, such as its durability, tendency to relapse, and a mental state which enforces renewed contact with the narcotic (craving), are the subject of intense clinical and laboratory research. The currently dominant view maintains that the basis of addiction lies in complex neuroadaptive changes leading to alterations in the function of the central nervous system, particularly in the motivational and emotional spheres, as well as learning and memory processes. The fundamental mechanism of addiction is associated with a disturbance in the function of the reward system, in which an essential role is played by neurotransmitters such as dopamine, glutamate and endogenous opioid peptides. It is believed that the dysfunction of the reward system and the body's attempt to compensate for it may be an important cause of the development of addiction. In addiction, however, it is not the reward itself – the stimulus causing the subjective positive feeling – that is crucial, but rather gradual growth in the desire for such reward and efforts to obtain it (wanting). And so the point is that addiction is a motivation disorder. Narcotics affect the natural motivation and reinforcement mechanisms associated with the obtaining of rewards necessary for life functions such as food and sexual stimuli.

One particularly interesting idea about the mechanism of addiction, which has been put forward in the last decade, is that the cellular and molecular phenomena which underlie addiction are closely linked to the cellular mechanisms characterizing the learning process. It has been discovered that the



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The fundamental mechanism of addiction is associated with a disturbance in the function of the reward system. This diagram shows the reward system in the brain with the pre-frontal cortex, the nucleus accumbens of the basal ganglia and the ventral tegmental area (VTA)

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The term "addiction" applies to more than just dependence on medicines, narcotics, and alcohol. Many people also fall victim to dangerous behavioral dependences such as gambling, computer games, shopping, or attractive foods

cellular and molecular processes associated with learning, which occur in the cells of the hippocampus (the main brain structure responsible for the process) also appear in the mesolimbic reward system (particularly in the ventral tegmental area - VTA) under the influence of addictive substances.

An error in stimulus evaluation

Most known addictive substances intensify the release of dopamine from the dopaminergic neuron endings whose nerve cell bodies are located in the VTA, while the axons extend to the nucleus accumbens septi and the prefrontal cortex. The VTA neurons are activated by various types of reward (both natural and psychoactive substances) and by conditional signals promising reward, but also by new hitherto unknown stimuli. Conditional signals associated with rewards themselves become dopamine releasing signals, and the subsequent reward itself loses these properties. However, if the promised reward is not forthcoming, the bioelectric activity of the VTA drops dramatically. Changes in the activity of dopaminergic neurons then signal an error in the evaluation of the stimulus.

The recognition of this phenomenon has been crucial for our understanding of the action of addictive substances and the role of dopaminergic neurons. Tonic activation of VTA neurons or direct dopamine release from neurons is marked as a presage to reward ("the situation is better than expected"). The phenomena which underpin this excessive and extensive activation of dopaminergic transmission in the reward system are strikingly similar to cellular learning processes - chiefly long term potentiation (LTP), a long-term enhancement in transmission between neurons that is seen as responsible for the fixing of memory traces in the processes of learning and memory.

Memory fixation

Memory occurs in two basic states: temporary (labile, short-term memory) and permanent (stable, long-term memory). Directly after the learning phase, the memory trace is in an unstable phase as short-term memory, susceptible to destruction and erasure. Later the memory undergoes consolidation and moves on to the stable phase, more resistant to destructive factors.

There are several hypotheses concerning the consolidation process. The newest of these theories concentrates on the cellular and molecular processes which transform the traces from the labile to the stable stage. It seems that a crucial role is played here by the processes of neuronal protein synthesis. In our laboratory, we have investigated the role of the protein synthesis process in the creation of a drug-associated memory trace. We have confirmed that blocking such synthesis using cycloheximide stops the acquisition of an instrumental self-administration reaction to cocaine - it abolishes the creation of a memory trace strengthened by this strong narcotic.

Long-term synaptic strengthening

LTP triggers changes in the structure of a synapse on both the pre- and post-synapse sides. The formation of concentrations of neuronal proteins on the membranes is one of the key elements of this process.

In *in vitro* breeding of hippocampal cells, LTP can be registered in the form of a long-

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The cellular and molecular phenomena which underlie addiction are now known to be closely linked to the cellular mechanisms characterizing the learning process

term (up to 10 hours) increase in the half potential. An important role in the creation of LTP is played by calcium ions and NMDA ionotropic glutamate receptors. These are membrane receptors which strongly bind N-methyl-D-aspartate. The activation of NMDA receptors is a condition for the development of LTP. This leads to the activation of calcium conduction through these channels. Conduction grows as a measure of the depolarization and summation of the temporary currents in the post-synaptic neuron as an effect of the action of a series of stimuli. As a result of the increased concentration of calcium ions inside the dendritic spines on which the aroused synapses are located, a cascade of biochemical processes is set in motion which maintains the increased synaptic transmission for an extended period.

LTP induction depends on the presence in synapses of another type of glutamate receptor called an AMPA receptor; in particular on the expression of the GluR1 subunit of that receptor. For the induction of LTP, it is the increase in the AMPA/NMDA ratio that is important.

VTA akin to hippocampus

The hypothesis associating the development of addiction with plastic processes in VTA neurons, depending among other things on the expression of the AMPA receptor's GluR1 subunit and the increase in the AMPA/NMDA receptors, is being intensively analyzed by researchers. It assumes that addictive substances induce "pathological" LTP in the dopaminergic synapses of the mesolimbic system.

Just as with the hippocampus, the crucial role in this process is played by the AMPA and NMDA receptors. Administration of cocaine almost doubles the AMPA/NMDA receptor ratio in dopaminergic VTA neurons in rats. This effect does not occur if an NMDA receptor antagonist is administered first. In GABAergic neurons (those which excrete gamma-aminobutyric-acid, GABA), in turn, morphine can prevent the occurrence of LTP. GABAergic neurons have a suppressing influence on other types of neurons, including glutamatergic and dopaminergic neurons. Halting these therefore leads to the unblocking of dopaminergic neurons and the induction of LTP within them. The induction of LTP and the sensitization of VTA dopaminergic neurons associated with it may be the main mechanism for the action of addictive substances and may be of crucial importance for the development of dependence. Another mechanism under investigation is the blocking of the long-term depression (LTD) process, which is the

opposite of LTP. The LTD process is blocked by amphetamine, for example. Blocking LTD may cause the strengthening of LTP, an increase in the AMPA/NMDA receptor ratio, and the development of sensitization.

Erasing the trace

It seems that addictive substances with different activity profiles (psychostimulants, opioids, nicotine, and alcohol) have the same ability to cause plastic changes in VTA neurons. Similar plastic changes in VTA are induced by stress stimuli. This explains the ability of stress to trigger craving and relapses.

A better understanding of the labile and stable forms of memory may make it possible for drug-associated memories to be evoked and removed while still in labile form. We can imagine several methods of erasing the memory trace associated with addiction, such as the use of a protein synthesis inhibitor or electroshock. Both of these methods are burdened, however, with the risk of undesirable effects which are difficult to predict, and also bring with them many medical and ethical reservations. Pharmacological methods would be a great deal better. The memory trace creation process involves a complex cascade of intra-cellular signals, with an important role played by protein kinase activation. Blocking the cascade could stop or destroy reconsolidation of a drug-associated memory, although it is difficult to predict the side effects of such treatment.

Fighting addiction

One exciting prospect is the possibility of blocking extracellular signal-regulated kinase (ERK). This enzyme participates in the creation of new inter-neuronal connections associated with the creation of permanent memory traces. Research on rats has shown that stopping ERK activity in the nucleus accumbens septi stops the reward action of cocaine. ERK blocking may have properties which prevent the reconsolidation of memory traces and the appearance of craving.

A crucial aspect of LTP induction in the hippocampus is the modulation by adrenergic neurons in cooperation with cholinergic neurons, which leads the activation of MAPK (mitogen-activated protein kinase). A better understanding of this process also opens up new therapeutic possibilities. In the late LTP phase (L-LTP), which is a process dependent on protein synthesis, a crucial role is played by β-adrenergic receptors. It has been shown that an antagonist for these receptors, propranolol, stops the growth of L-LTP in rat hippocampi induced by new stimuli. Therefore, it is theoretically possible that the consolidation and reconsolidation of the pathological memory traces associated with addictive substances may be suppressed using certain β-adrenolytic substances (which pass through the blood/brain barrier). That would make it possible to link the effects of β-adrenolytic medicines with NMDA receptor antagonists. Administering glutamate antagonists and L calcium channel and dopaminergic D-1 receptor antagonists is now known to decrease the symptoms of sensitization. Unfortunately, most known NMDA receptor antagonists have psychotropic effects.

Do plastic changes in dopaminergic neurons in the reward system explain the basic mechanism by which addictive substances work? Further research at the cellular and molecular level on the appearance of LTP may unravel this fascinating problem and help in devising a new effective addiction therapy. ■

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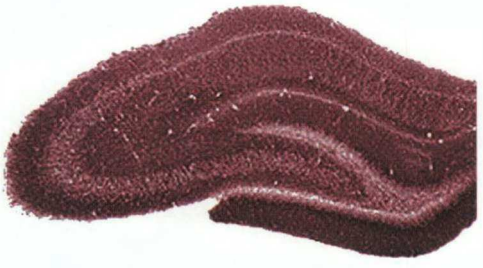

The hippocampus is the brain structure responsible for learning and memory processes

Further reading:

Kauer J.A. (2004). Learning mechanisms in addiction: Synaptic plasticity in the ventral tegmental area as a result of exposure to drugs of abuse. *Annual Review of Physiology, 66*, 447-475.

Nugent F.S., Penick E., Kauer J. (2007). Opioids block long-term potentiation of inhibitory synapses. *Nature, 446*, 1086-1090.

Mierzejewski P., Siemiątkowski M., Radwańska K., Szyndler M., Bieńkowski P., Stefański R., Kaczmarek L., Kostowski W. (2006). Cycloheximide impairs acquisition but not extinction of cocaine self-administration. *Neuropharmacology, 51*, 367-373.