

The Physiological Basis Of Drug Addiction

Researchers have conducted numerous investigations using animal models and functional brain imaging on humans in order to define the mechanisms underlying drug addiction in the brain. This intriguing topic incorporates several areas of the brain and synaptic changes, or neuroplasticity, which occurs in these areas.

Acute effects

Acute (or recreational) drug use causes the release and prolonged action of dopamine and serotonin within the reward circuit. Different types of drugs produce these effects by different methods. Dopamine (DA) appears to harbor the largest effect and its action is characterized. DA binds to the D1 receptor, triggering a signaling cascade within the cell. cAMP-dependent protein kinase (PKA) phosphorylates cAMP response element binding protein (CREB), a transcription factor, which induces the synthesis of certain genes including C-Fos.^[4]

Reward circuit

When examining the biological basis of drug addiction, one must first understand the pathways in which drugs act and how drugs can alter those pathways. The reward circuit, also referred to as the mesolimbic system, is characterized by the interaction of several areas of the brain.

- The ventral tegmental area (VTA) consists of dopaminergic neurons which respond to glutamate. These cells respond when stimuli indicative of a reward are present. The VTA supports learning and sensitization development and releases dopamine (DA) into the forebrain.^[5] These neurons also project and release DA into the nucleus accumbens^[6], through the mesolimbic pathway. Virtually all drugs causing drug addiction increase the dopamine release in the mesolimbic pathway,^[7] in addition to their specific effects.
- The nucleus accumbens (NAcc) consists mainly of medium-spiny projection neurons (MSNs), which are GABA neurons.^[8] The NAcc is associated with acquiring and eliciting conditioned behaviors and involved in the increased sensitivity to drugs as addiction progresses.^[5]
- The prefrontal cortex, more specifically the anterior cingulate and orbitofrontal cortices,^[4] is important for the integration of information which contributes to whether a behavior will be elicited. It appears to be the area in which motivation originates and the salience of stimuli are determined.^[9]
- The basolateral amygdala projects into the NAcc and is thought to be important for motivation as well.^[9]
- More evidence is pointing towards the role of the hippocampus in drug addiction because of its importance in learning and memory. Much of this evidence stems from investigations manipulating cells in the hippocampus alters dopamine levels in NAcc and firing rates of VTA dopaminergic cells.^[6]

Stress response

In addition to the reward circuit, it is hypothesized that stress mechanisms also play a role in addiction. Koob and Kreek have hypothesized that during drug use corticotropin-releasing factor (CRF) activates the hypothalamic-pituitary-adrenal axis (HPA) and other stress systems in the extended amygdala. This activation influences the dysregulated emotional state associated with drug addiction. They have found that as drug use escalates, so does the presence of CRF in human cerebrospinal fluid (CSF). In rat models, the separate use of CRF antagonists and CRF receptor antagonists both decreased self-administration of the drug of study. Other studies in this review showed a dysregulation in other hormones associated with the HPA axis, including enkephalin which is an endogenous opioid peptides that regulates pain. It also appears that the μ-opioid receptor system, which enkephalin acts on, is influential in the reward system and can regulate the expression of stress hormones.^[2]

Behavior

Understanding how learning and behavior work in the reward circuit can help understand the action of addictive drugs. Drug addiction is characterized by strong, drug seeking behaviors in which the addict persistently craves and seeks out drugs, despite the knowledge of harmful consequences.^{[4][2]} Addictive drugs produce a reward, which is the euphoric feeling resulting from sustained DA concentrations in the synaptic cleft of neurons in the brain. Operant conditioning is exhibited in drug addicts as well as laboratory mice, rats, and primates; they are able to associate an action or behavior, in this case seeking out the drug, with a reward, which is the effect of the drug.^[5] Evidence shows that this behavior is most likely a result of the synaptic changes which have occurred due to repeated drug exposure.^{[4][2][5]} The drug seeking behavior is induced by glutamatergic projections from the prefrontal cortex to the NAc. This idea is supported with data from experiments showing the drug seeking behavior can be prevented following the inhibition of AMPA glutamate receptors and glutamate release in the NAc.^[4]

Allostasis

Allostasis is the process of achieving stability through changes in behavior as well as physiological features. As a person progresses into drug addiction, he or she appears to enter a new allostatic state, defined as divergence from normal levels of change which persist in a chronic state. Addiction to drugs can cause damage to your brain and body as you enter the pathological state; the cost stemming from damage is known as allostatic load. The dysregulation of allostasis gradually occurs as the reward from the drug decreases and the ability to overcome the depressed state following drug use begins to decrease as well. The resulting allostatic load creates a constant state of depression relative to normal allostatic changes. What pushes this decrease is the propensity of drug users to take the drug before the brain and body have returned to original allostatic levels, producing a constant state of stress. Therefore, the presence of environmental stressors may induce stronger drug seeking behaviors.^[2]

[edit] Neuroplasticity

Neuroplasticity is the putative mechanism behind learning and memory. It involves physical changes in the synapses between two communicating neurons, characterized by increased gene expression, altered cell signaling, and the formation of new synapses between the communicating neurons. When addictive drugs are present in the system, they appear to hijack this mechanism in the reward system so that

motivation is geared towards procuring the drug rather than natural rewards.^[5] Depending on the history of drug use, excitatory synapses in the nucleus accumbens(NAc) experience two types of neuroplasticity: long-term potentiation (LTP) and long-term depression (LTD). Using mice as a model, Kourrich *et al.* showed that chronic exposure to cocaine increases the strength of synapses in NAc after a 10-14 day withdrawal period, while strengthened synapses did not appear within a 24 hour withdrawal period after repeated cocaine exposure. A single dose of cocaine did not elicit any attributes of a strengthened synapse. When drug-experienced mice were challenged with one dose of cocaine, synaptic depression occurred. Therefore, it seems the history of cocaine exposure along with withdrawal times affects the direction of glutamatergic plasticity in the NAc.^[8]

Once a person has transitioned from drug use to addiction, behavior becomes completely geared towards seeking the drug, even though addicts report the euphoria is not as intense as it once was. Despite the differing actions of drugs during acute use, the final pathway of addiction is the same. Another aspect of drug addiction is a decreased response to normal biological stimuli, such as food, sex, and social interaction. Through functional brain imaging of patients addicted to cocaine, scientists have been able to visualize increased metabolic activity in the anterior cingulate and orbitofrontal cortex (areas of the prefrontal cortex) in the brain of these subjects. The hyperactivity of these areas of the brain in addicted subjects is involved in the more intense motivation to find the drug rather than seeking natural rewards, as well as an addict's decreased ability to overcome this urge. Brain imaging has also shown cocaine-addicted subjects to have decreased activity, as compared to non-addicts, in their prefrontal cortex when presented with stimuli associated with natural rewards. The transition from recreational drug use to addiction occurs in gradual stages and is produced by the effect of the drug of choice on the neuroplasticity of the neurons found in the reward circuit. During events preceding addiction, cravings are produced by the release of DA in the prefrontal cortex. As a person transitions from drug use to addiction, the release of dopamine (DA) in the NAc becomes unnecessary to produce cravings; rather, DA transmission decreases while increased metabolic activity in the orbitofrontal cortex contributes to cravings. At this time a person may experience the signs of depression if cocaine is not used.^[10] Before a person becomes addicted and exhibits drug-seeking behavior, there is a time period in which the neuroplasticity is reversible. Addiction occurs when drug-seeking behavior is exhibited and the vulnerability to relapse persists, despite prolonged withdrawal; these behavioral attributes are the result of neuroplastic changes which are brought about by repeated exposure to drugs and are relatively permanent.^[4]

The exact mechanism behind a drug molecule's effect on synaptic plasticity is still unclear. However, neuroplasticity in glutamatergic projections seems to be a major result of repeated drug exposure. There are several ways in which glutamate transmission is altered. One way is by increasing presynaptic release of glutamate and the other is increased response to glutamate.^{[4][5]} The two main glutamate receptors involved are NMDAR and AMPA. The expression of these receptors on the cell surface increases with repeated drug use. This type of synaptic plasticity results in LTP, which strengthens connections between two neurons; onset of this occurs quickly and the result is constant. In addition to glutamatergic neurons, dopaminergic neurons present in the VTA respond to glutamate and may be recruited earliest during neural adaptations caused by repeated drug exposure. As shown by Kourrich, et al, history of drug exposure and the time of withdrawal from last exposure appear to play an important role in the direction of plasticity in the neurons of the reward system.^[5]

An aspect of neuron development that may also play a part in drug-induced neuroplasticity is the presence of axon guidance molecules such as semaphorins and ephrins. After repeated cocaine treatment, altered expression (increase or decrease dependent on the type of molecule) of mRNA coding

for axon guidance molecules occurred in rats. This may contribute to the alterations in the reward circuit characteristic of drug addiction.^[11]

Neurogenesis

Drug addiction also raises the issue of potential harmful effects on the development of new neurons in adults. Eisch and Harburg raise three new concepts they have extrapolated from the numerous recent studies on drug addiction. First, neurogenesis decreases as a result of repeated exposure to addictive drugs. A list of studies show that chronic use of opiates, psychostimulants, nicotine, and alcohol decrease neurogenesis in mice and rats. Second, this apparent decrease in neurogenesis seems to be independent of HPA axis activation. Other environmental factors other than drug exposure such as age, stress and exercise, can also have an effect of neurogenesis by regulating the hypothalamic-pituitary-adrenal (HPA) axis. Mounting evidence suggests this for 3 reasons: small doses of opiates and psychostimulants increase corticosterone concentration in serum but with no effect of neurogenesis; although decreased neurogenesis is similar between self-administered and forced drug intake, activation of HPA axis is greater in self-administration subjects; and even after the inhibition of opiate induced increase of corticosterone, a decrease in neurogenesis occurred. These, of course, need to be investigated further. Last, addictive drugs appear to only affect proliferation in the subgranular zone (SGZ), rather than other areas associated with neurogenesis. The studies of drug use and neurogenesis may have implications on stem cell biology.^[6]

Psychological drug tolerance

The reward system is partly responsible for the psychological part of drug tolerance; The CREB protein, a transcription factor activated by cyclic adenosine monophosphate (cAMP) immediately after a high, triggers genes that produce proteins such as dynorphin, which cuts off dopamine release and temporarily inhibits the reward circuit. In chronic drug users, a sustained activation of CREB thus forces a larger dose to be taken to reach the same effect. In addition it leaves the user feeling generally depressed and dissatisfied, and unable to find pleasure in previously enjoyable activities, often leading to a return to the drug for an additional "fix".^[12]

Sensitization

Sensitization is the increase in sensitivity to a drug after prolonged use. The proteins delta FosB and regulator of G-protein Signaling 9-2 (RGS 9-2) are thought to be involved: A transcription factor, known as delta FosB, is thought to activate genes that, counter to the effects of CREB, actually increase the user's sensitivity to the effects of the substance. Delta FosB slowly builds up with each exposure to the drug and remains activated for weeks after the last exposure—long after the effects of CREB have faded. The hypersensitivity that it causes is thought to be responsible for the intense cravings associated with drug addiction, and is often extended to even the peripheral cues of drug use, such as related behaviors or the sight of drug paraphernalia. There is some evidence that delta FosB even causes structural changes within the nucleus accumbens, which presumably helps to perpetuate the cravings, and may be responsible for the high incidence of relapse that occur in treated drug addicts.

Regulator of G-protein Signaling 9-2 (RGS 9-2) has recently been the subject of several animal knockout studies. Animals lacking RGS 9-2 appear to have increased sensitivity to dopamine receptor

agonists such as cocaine and amphetamines; over-expression of RGS 9-2 causes a lack of responsiveness to these same agonists. RGS 9-2 is believed to catalyze inactivation of the G-protein coupled D2 receptor by enhancing the rate of GTP hydrolysis of the G alpha subunit which transmits signals into the interior of the cell.

Individual mechanisms of effect

The basic mechanisms by which different substances activate the reward system are as described above, but vary slightly among drug classes.^[13]

Depressants

Depressants such as alcohol and benzodiazepines work by increasing the affinity of the GABA receptor for its ligand; GABA. Narcotics such as morphine and methadone, work by mimicking endorphins—chemicals produced naturally by the body which have effects similar to dopamine—or by disabling the neurons that normally inhibit the release of dopamine in the reward system. These substances (sometimes called "downers") typically facilitate relaxation and pain-relief.

Stimulants

Stimulants such as amphetamines, nicotine, and cocaine, increase dopamine signaling in the reward system either by directly stimulating its release, or by blocking its absorption (see "reuptake"). These substances (sometimes called "uppers") typically cause heightened alertness and energy. They cause a pleasant feeling in the body, and euphoria, known as a high. This high wears off leaving the user feeling depressed. This sometimes makes them want more of the drug, and can worsen the addiction

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