Mechanisms of Addiction

**What is addiction?** Although the term addiction is controversial because it can be stigmatizing and divisive, we use it here as a useful shorthand for the processes by which people become dependent on the use of drugs, or activities such as gambling, to the point where it distorts and even takes over their lives. The key feature of addiction is the inability to stop using the drug despite clear evidence of harm; the drug becomes progressively more important, dominating the expense of family, friends and work. Not all those who use drugs become addicted and factors that predispose to addiction include the class of drug, family history of addiction and propensity to withdrawal reactions and craving. Using drugs to deal with psychiatric problems is particularly likely to lead to addiction.

**Brain Circuits Associated with Addiction**

The brain circuits involved in addiction have been characterized in preclinical and now human imaging studies. The figure above shows four of the interacting circuits that can be involved, to varying extents, in different addictions and different persons. The gray areas in green are the dopamine pathways from the ventral tegmental area to the nucleus accumbens (NAcc, also called ventral striatum), which then outflow through the ventral pallidum (VP). This pathway has a role in responding to rewards and directing behavior towards them. The red areas regulate the encoding and reactivation of memories of drug use. The hippocampus (HP) is responsible for place memories of drug use and the amygdala (Amyg) for the emotional aspects of these. Drug memories are some of the most powerful known and are very hard to disable or overwrite. The purple areas of the prefrontal cortex (PFC) and anterior cingulate gyrus (ACG) are responsible for cognitive control and rely on an appropriate balance of GABA and glutamate interactions, so that this region can exert “top-down” control on the motivation and pleasure areas. The orbito-frontal cortex (OFC) assesses the salience or value of rewards and the decision to use. Normally these are in balance, with the OFC having the final “say” in behavioral control, i.e. “NO-GO” for drug use. In addiction the balance is disrupted, the drives to use drugs become more powerful, drug memories more dominant and the “NO-GO” mechanisms become weaker such that use can’t be restrained, a “GO” takes drug states result.

**Classes of Addictive Drugs**

**Stimulants**
- Drugs that act by releasing dopamine and, in some cases, blocking its reuptake. This class includes cocaine (and crack), amphetamines, and some cannabinoids, such as methamphetamine (crystal meth) and methylenedioxymethamphetamine (MDMA, “Ecstasy”). Stimulants include cocaine (and crack), amphetamines, methylenedioxymethamphetamine (MDMA), and some opioids such as methadone, codeine and fentanyl. They vary in terms of affinity and efficacy at the opioid receptor, which is their site of action in reward. They are powerful analesgics but can cause lethal respiratory depression. Partial agonists, such as buprenorphine, are safer. Antagonists such as naltrexone, nalmefene and nalmefene block these actions.

**Opioids**
- Drugs that mimic the actions of the endogenous opioid endorphin peptides. They include heroin, morphine, codeine and fentanyl. They vary in terms of efficacy and affinity at the opioid receptor, which is their site of action in reward. They are powerful analesgics but can cause lethal respiratory depression. Partial agonists, such as buprenorphine, are safer. Antagonists such as naltrexone, nalmefene and nalmefene block these actions.

**Alcohol**
- Alcohol and other sedatives act largely through the GABA receptor. Alcohol seems to enhance the actions of both GABA, and GABAA receptors and at higher doses also affects dopamine release, stimulates 5-HT, and blocks NMDA glutamate receptors. Benzodiazepines are selective positive allosteric modulators (PAMs) of GABA receptors. Barbiturates are GABAergic agents that have actions that in some ways oppose those of benzodiazepines. Barbiturates are GABAergic agents that have actions that in some ways oppose those of benzodiazepines. Benzodiazepines are selective PAMs, which at anesthetic doses also open the GABA chloride ionophore.

**Psychoactive cannabinoids, particularly Δ9-THC (the “siting” element of herbal cannabis), mimic the effects of endogenous cannabinoids, such as anandamide and 2-arachidonoyl glyceryl alcohol, which are produced by breakdown of phospholipids in cell membranes. The brain effects of cannabinoids are mediated via CB1 receptors, which are found at high density in the brain, particularly in the striatum and prefrontal cortex. They include THC and other active cannabinoids such as tetrahydrocannabinol (THC) and cannabidiol (CBD). Cannabinoids bind to two G-protein-coupled receptors, CB1 and CB2, which are expressed in the brain and in peripheral tissues. CB1 receptors are present in the brain, particularly in the prefrontal cortex and the limbic system, where they modulate reward, memory and motor functions. CB2 receptors are present in the peripheral nervous system, where they modulate pain and immune function. The endocannabinoid system plays a role in the regulation of appetite, mood, pain and immune function. The endocannabinoid system is involved in the regulation of appetite, mood, pain and immune function. The endocannabinoid system is involved in the regulation of appetite, mood, pain and immune function.

**NMDA glutamate receptors**
- NMDA glutamate receptors are located in the prefrontal cortex, hippocampus and striatum. They are activated by glutamate and are involved in the regulation of learning and memory. The activation of NMDA receptors leads to a decrease in inhibitory GABAergic transmission, which is important for the expression of declarative memories. The activation of NMDA receptors also leads to an increase in excitatory glutamatergic transmission, which is important for the expression of procedural memories. The activation of NMDA receptors is involved in the expression of declarative memories. The activation of NMDA receptors is involved in the expression of procedural memories. The activation of NMDA receptors is involved in the expression of declarative memories. The activation of NMDA receptors is involved in the expression of procedural memories.

**Dopamine D1 receptors**
- Dopamine D1 receptors are involved in the expression of associative memories. They are located in the prefrontal cortex and the striatum. The activation of D1 receptors leads to an increase in cAMP and PKA activity, which is important for the expression of associative memories. The activation of D1 receptors also leads to an increase in the expression of CREB, which is involved in the expression of associative memories.

**Dopamine D2 receptors**
- Dopamine D2 receptors are involved in the expression of working memory. They are located in the prefrontal cortex and the striatum. The activation of D2 receptors leads to a decrease in cAMP and PKA activity, which is important for the expression of working memory. The activation of D2 receptors also leads to a decrease in the expression of CREB, which is involved in the expression of working memory.

**Dopamine D1 receptors**
- Dopamine D1 receptors are involved in the expression of declarative memories. They are located in the prefrontal cortex and the striatum. The activation of D1 receptors leads to an increase in cAMP and PKA activity, which is important for the expression of declarative memories. The activation of D1 receptors also leads to an increase in the expression of CREB, which is involved in the expression of declarative memories.

**Dopamine D2 receptors**
- Dopamine D2 receptors are involved in the expression of procedural memories. They are located in the prefrontal cortex and the striatum. The activation of D2 receptors leads to a decrease in cAMP and PKA activity, which is important for the expression of procedural memories. The activation of D2 receptors also leads to a decrease in the expression of CREB, which is involved in the expression of procedural memories.