Mechanisms of Addiction

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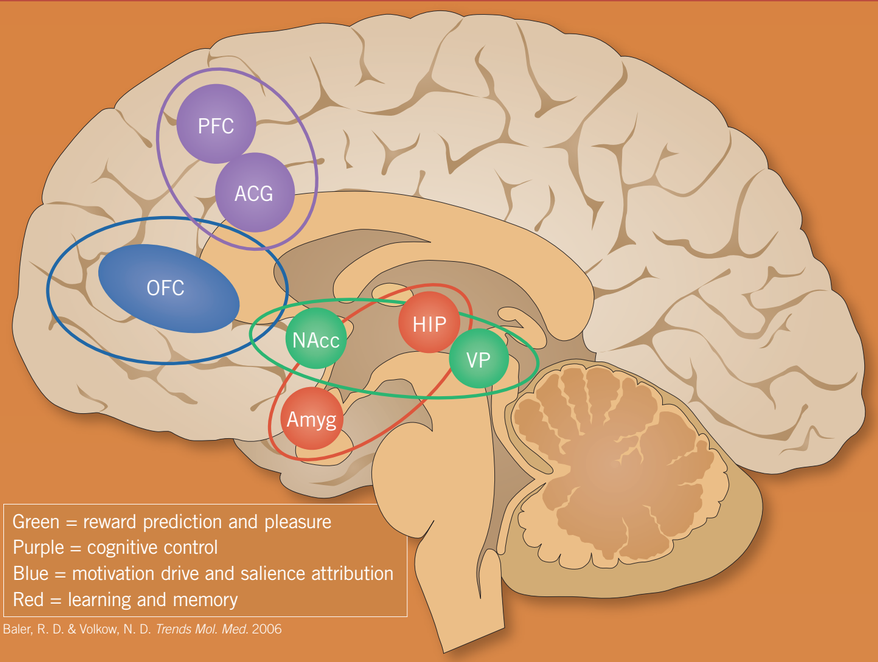
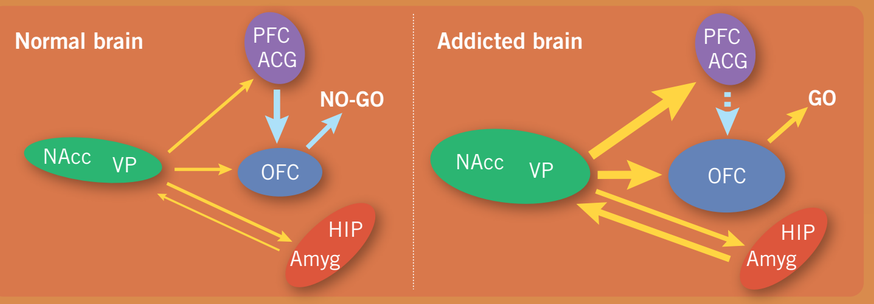
What is addiction? **Although the term addiction is controversial because it can be stigmatizing and divisive, we use it here as a useful shorthand for the processes by which people become dependent on the use of drugs, or activities such as gambling, to the point where it distorts and even takes over their lives. The key feature of drug addiction is the inability to stop using the drug despite clear evidence of harm; the drug becomes progressively more important, dominating life at 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



Baler, R. D. & Volkow, N. D. *Trends Mol. Med.* 2006

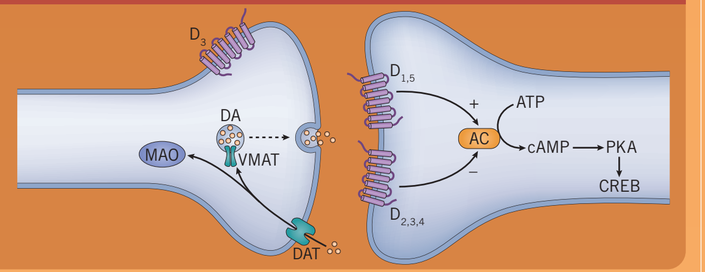
The brain circuits involved in addiction have been characterized in preclinical and now human imaging studies. The figure above shows the four interacting circuits that can be involved, to varying extents, in different addictions and different persons. The reward circuit (green) is the dopamine pathway from the ventral tegmental area to the nucleus accumbens (NAcc, also called ventral striatum), which then outflows 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 (HIP) 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 dislodge 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 "top-down" mechanisms become weaker such that use can't be restrained; a "GO" take drugs state results.

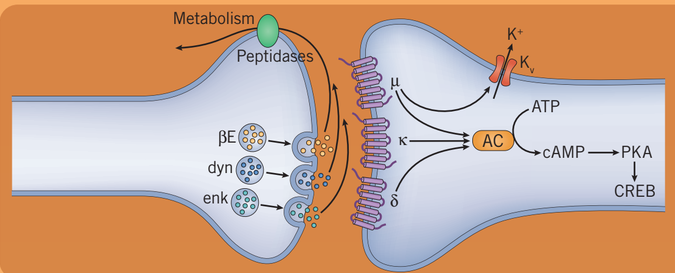


Since not all people who use drugs become addicted, something must be different in the addict's brain. This is thought to be due to either the reason for drug use in the first place or some adaptive changes that the drugs induce. However recreational use of drugs also leads to adaptive changes, such as tolerance, that predispose to continued drug use, as the withdrawal that emerges when drugs are stopped is so aversive it drives relapse. In the case of alcohol the κ-receptor-acting opioid peptide dynorphin is thought to be responsible for withdrawal symptoms. Stimulants, ketamine and potentially opioids appear to reduce the function of the PFC/OFC so they are less able to exert "top-down" control over impulses and urges.

Classes of Addictive Drugs

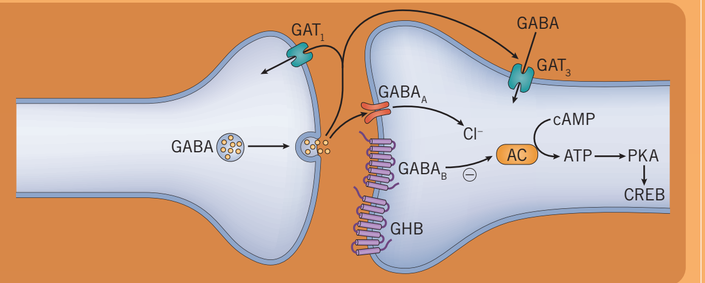
Stimulants are drugs that act by releasing dopamine and, in some cases, blocking its reuptake. This class includes cocaine (and crack), amphetamine and its derivatives such as metamphetamine (crystal meth) and methylphenidate, and some cathinones, such as mephedrone. Their actions are dependent on speed of brain penetration, with smoking and iv injection the most addictive routes, but are largely unaffected by dopamine receptor antagonists. Other neurotransmitter effects, such as endorphin release, could therefore explain their addictive properties.

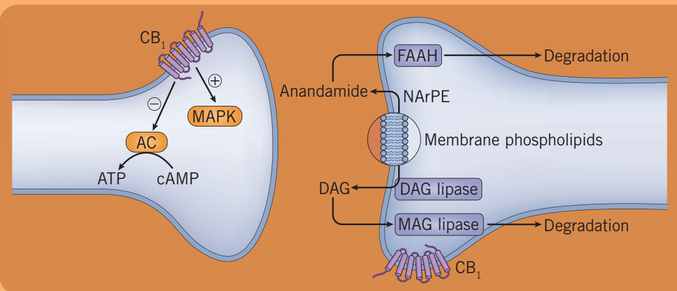




Opioids are drugs that mimic the actions of the endogenous opioid endorphin peptides. They include heroin, morphine, methadone, codeine and fentanyl. They vary in terms of affinity and efficacy at the μ opioid receptor, which is their site of action in reward. They are powerful analgesics but can cause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

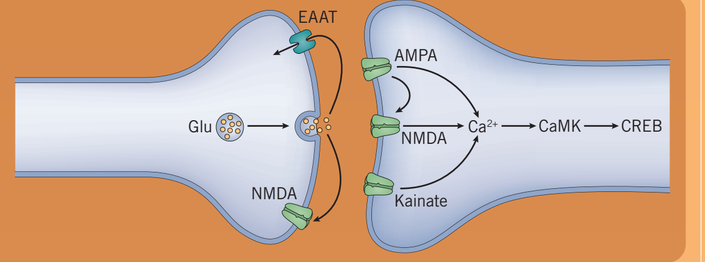
Alcohol and other sedatives act largely through the GABA receptor. Alcohol seems to enhance the actions of both $GABA_A$ and $GABA_B$ receptors and at higher doses also affects dopamine release, stimulates $5\text{-}HT_3$ and blocks NMDA glutamate receptors. Benzodiazepines are selective positive allosteric modulators (PAMs) of the α1, 2, 3, and 5 subunits of the $GABA_A$ receptor. GHB is a $GABA_B$ agonist, but also acts on GHB receptors. Barbiturates are $GABA_A$ PAMs, which at anesthetic doses also directly open the $GABA_A$ chloride ionophore.





Psychoactive cannabinoids, particularly Δ^9 THC (the "stoning" element of herbal cannabis), mimic the effects of endogenous cannabinoids, such as anandamide and diacylglycerol that are produced by breakdown of phospholipids in cell membranes. The brain effects of cannabinoids are mediated via CB_1 receptors, which are found at high concentrations in brain areas associated with motivation and reward. They also act on CB_2 receptors that are largely found in the immune system. Cannabidiol is another cannabinoid that has actions that in some ways oppose those of THC through as yet-to-be-understood mechanisms.

Ketamine, and previously PCP, are dissociative respiratory-sparing anesthetics that also treat depression (acutely) and chronic pain. However, they can cause psychosis and are addictive. They act as glutamate NMDA receptor antagonists but, because there are many of these receptors present presynaptically on glutamate neurons and on GABA interneurons, the ketamine blockade leads to an increase in glutamate, which stimulates AMPA receptors. This, in turn, can increase dopamine, which may be reinforcing.



Abbreviations: 5-HT, 5-hydroxytryptamine; **AC**, adenylyl cyclase; **AMPA**, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; **ATP**, adenosine triphosphate; **CaMK**, Ca^{2+}/calmodulin-dependent protein kinase; **cAMP**, cyclic adenosine monophosphate; **CREB**, cAMP response element-binding protein; **D**, dopamine receptor; **DA** dopamine; **DAG**, diacylglycerol; **DAT**, dopamine transporter; **dyn**, dynorphin; **βE**, β-endorphin; **EAAT**, excitatory amino acid transporter; **enk**, enkephalin; **FAAH**, fatty acid amide hydrolase; **GABA**, γ-aminobutyric acid; **GAT**, $GABA_A$ Transporter; **GHB**, γ-hydroxy butyrate; **Glu**, glutamate; **MAG**, monoacylglycerol; **MAO**, monoamine oxidase; **MAPK**, mitogen-activated protein kinase; **NArPE**, N–arachidonoyl phosphatidylethanolamine; **NMDA**, N-methyl-D-aspartate; **PKA**, protein kinase A; **THC**, tetrahydrocannabinol; **VMAT**, vesicular monoamine transporter

Products available from Tocris

Stimulants
Cocaine, (D)-Amphetamine sulfate, Morphine, Mephedrone, Threo-methylphenidate
MAO
(*R*)-(-)-Deprenyl, Moclobemide
DAT
GBR 12909, Tetrabenazine, Reserpine, (±)-MDMA
Dopamine D_1 and D_5
SKF 38393, SKF 81297, Dopamine, SCH 23390, SCH 39166
Dopamine D_2
Sumanirole, L-741,626, Olanzapine, PAOPA
Dopamine D_3
(+)-PD 128907, Pramipexole, Eticlopride, SB 277011A
Dopamine D_4
PD 168077, A 412997, L-745,870
μ Opioid
Endomorphin-1, DAMGO, β-Funaltrexamine, Cyprodime
κ Opioid
(±)-U-50488, Dynorphin A, nor-Binaltorphimine
δ Opioid
SNC 80, SB 205607, Naltrindole
Miscellaneous Opioid
[Leu^5]-Enkephalin, Naloxone, Naltrexone
$GABA_A$
Muscimol, SR 95531, L-655,708, Midazolam, Ganaxolone, Acamprosate calcium
$GABA_B$
(*R*)-Baclofen, CGP 55845, CGP 7930, Gabapentin, Pentobarbital
GAT
Riluzole, (*S*)-SNAP 5114, NNC 711
Cannabinoids
AM 251, CP 55,940, WIN 55,212-2, Anandamide, (-)-Cannabidiol
FAAH
PF 3845, URB 597, JZL 195
DAG Lipase
RHC 80267
MAG Lipase
JZL 184, JZL 195, KML 29, JJKK 048
NMDA
Ibotenic acid, D-AP5, Memantine, (+)-MK 801, Phencyclidine, Ketamine
AMPA/Kainate
NBQX disodium salt, CNQX disodium salt, GYKI 52466, GYKI 53655, PEPA, S 18986, LY 404187
Nicotinic α4β2 Receptors
(-)-Nicotine, Varenicline, Dihydro-β-erythroidine
mGlu Group I
(*RS*)-3,5-DHPG, MPEP, JNJ 16259685, MTEP, CDPPB, ADX 10059
mGlu Group II
LY 379268, LY 354740, LY 341495, LY 487379, BINA
mGlu Group III
(*S*)-3,4-DCPG, AMN 082, MMPIP, AZ 12216052

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