

# Neurobiology and principles of addiction and tolerance

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## Abstract

Substances of abuse dysregulate key brain systems involved in motivation, reward, decision-making and memory. As drug use evolves into a compulsive addiction, there are adaptations in these systems, mediated by a number of different neurotransmitters. The mesolimbic dopaminergic pathway plays a central role in the pleasurable and positive reinforcing effects of drugs. As an individual becomes addicted, there is a shift away from this positive reinforcement to the compulsive, habitual drug-seeking behaviours driven, for example, by cravings or withdrawal symptoms. Although the potential for addiction is common with all drugs of abuse, the underlying mechanisms, neurotransmission systems and adaptations vary between drugs. This review focuses on the neurobiology of addiction and tolerance for alcohol, benzodiazepines, opioids and stimulants.

**Keywords** Addiction; alcohol; benzodiazepine; dependence; neurobiology; opioid; stimulant; tolerance

## Introduction

Substances of abuse dysregulate key brain systems involved in motivation, reward, decision-making and memory. The dopaminergic mesocorticolimbic 'reward' pathway plays a key role in the reward of classical natural hedonic activities such as food and sex, and the motivation to pursue these behaviours. The neurotransmitter dopamine has long been regarded as playing a central role as the neurotransmitter of reward and addiction to substances of abuse. However, the degree of its central role may vary depending on the substance of abuse. For example, it has been harder to demonstrate robust increases in dopamine with opiates and cannabis in humans, and medications that block the

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## Key points

- Initial drug use is driven by reward and pleasure through the mesolimbic dopaminergic pathway. Dopamine and endogenous opioids play a key role in positive reinforcement
- As addiction develops, there is a shift from the ventral to the dorsal striatum. Negative reinforcement through withdrawal symptoms, craving and anxiety motivates continued drug use. Excitatory neurotransmitters, glutamate and noradrenaline (norepinephrine) have increasing importance
- Tolerance is caused by adaptations leading to reduced sensitivity of neurotransmission systems targeted by particular drugs of abuse to maintain a homeostatic balance. Withdrawal symptoms are associated with these neuroadaptations
- Pharmacotherapy for addiction includes substitution medication such as methadone, and medications that target neurotransmission systems involved in reward, such as naltrexone and nalmefene

dopamine system have generally proved ineffective at treating addiction.<sup>1</sup> Other neurotransmitters, for example the endogenous opioid system, are likely to be equally important in pleasure and reward as in drug use and addiction.<sup>2</sup>

As the associative pairing between drug-related cues and a rewarding response develops, this reinforces further drug use, leading to adaptive neuronal and behavioural changes. With continued repeated use, there is a shift in neuronal control of drug use behaviour from the ventral striatum to the dorsal striatum. Drug use becomes compulsive and habitual, driven by the negative reinforcement of withdrawal and associated negative affect. Finally, there is the development of anticipation and craving, which play a key role in relapse and the reinstatement of drug use.<sup>3,4</sup>

## Tolerance and withdrawal

For many drugs of abuse, continual drug use results in tolerance. This is particularly evident for alcohol and opiates, although less so for stimulants. Such tolerance is driven by neuroadaptive changes in which receptors activated by the drug are down-regulated or exhibit reduced sensitivity to return brain function to a homeostatic balance. Abrupt cessation of the drug results in the process of withdrawal because there is no longer the input needed to maintain the homeostatic balance, and opponent processes are initiated. The exact underpinning neurobiology of tolerance and withdrawal varies because of the range of neurotransmitter systems involved in the pharmacology of many substances of abuse (Table 1).

## Vulnerability to addiction

Although many people try drugs experimentally, only a small proportion progress to addiction. Genetic predisposition may play a contributory factor in the development of addiction. Dopamine receptors have been implicated in predisposition to

### Main neurotransmitter changes in the different stages of drug use

#### Risk factors and vulnerability for addiction

- Liking: low dopamine receptor D<sub>2</sub> availability
- Liking: high mu opioid receptor availability
- Anxiety: low  $\gamma$ -aminobutyric acid (GABA) function (particularly for alcohol)

#### Maintenance and neuroadaptation

- Reduced dopaminergic tone
- Reduced GABA (mainly for alcohol)
- Dysregulated mu to kappa opioidergic tone
- Increased glutamatergic activity

Table 1

addiction, with higher dopamine receptor D2 (DRD2) receptor levels reported in a study of non-addicted individuals with a family history of alcoholism. Reduced dopamine receptor levels were reported in individuals who found the effects of methylphenidate 'pleasurable'. Preclinical literature suggests that additional factors such as social hierarchy and impulsivity may determine DRD2 receptor levels and subsequent cocaine consumption. Associations have also been shown between variations in  $\gamma$ -aminobutyric acid (GABA) A-subtype receptor genes (*GABRA2*, *GABRG2*) and an increased risk of alcohol and heroin dependence.

These studies illustrate that vulnerability to addiction is likely to be complex and influenced by multifactorial environmental and genetic factors. Large longitudinal cohort studies such as the Avon Longitudinal Study of Parents and Children (ALSPAC) and IMAGEN are collecting data to better understand the genetic and developmental factors that predispose to alcohol and drug addiction.

### Neurobiology of addiction

Mesolimbic dopaminergic neurones in the ventral tegmental area project to brain regions including the nucleus accumbens and amygdala. GABA-ergic interneurons have a key inhibitory or 'braking' effect on these dopaminergic neurones. A range of inhibitory receptors, including mu opioid, cannabinoid CB1 and nicotinic, regulate GABA-ergic activity, in turn modulating the mesolimbic reward dopaminergic neurones. Therefore, when these inhibitory receptors are activated (e.g. by release of endogenous endorphins by alcohol or stimulants, or by consumption of opioids or cannabis), the GABA-ergic neuronal inhibition of the dopaminergic neurone is reduced. The resulting phasic firing of the dopaminergic mesolimbic results in increased dopamine concentrations in the nucleus accumbens or ventral striatum. Given the central role of the mesolimbic dopaminergic system, it is not perhaps surprising that similarities in these other modulators have been found in a variety of addictions.

As mentioned above, recent research has highlighted the importance of other neurotransmitters, such as endogenous opioids, in reward and addiction. Endogenous opioid receptors consist of three subtypes: mu, kappa and delta. The endogenous agonist at the mu opioid receptor is  $\beta$ -endorphin, which has euphoric and analgesic effects. Changes in the availability of mu

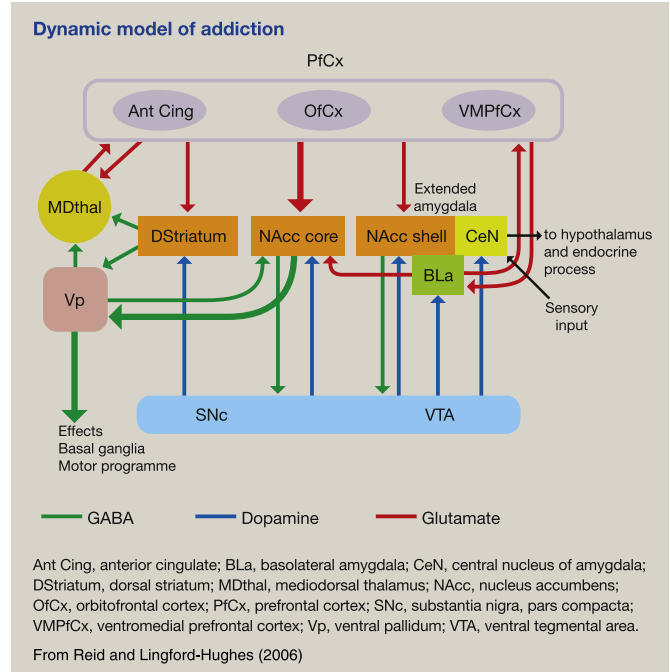


Figure 1

opioid receptors have been demonstrated in alcohol and cocaine addiction. Kappa opioid receptors are associated with dysphoria, and dynorphin is the endogenous agonist. Thus, mu and kappa have opposite effects, with stimulation of kappa receptors reducing the pleasurable effects associated with mu stimulation. Delta opioid receptors are important in analgesia and have enkephalins as the endogenous agonist. There is evidence that delta receptors may modulate the rewarding effects of drugs, but their role in addiction is poorly understood.

As addiction develops, the modulation of the dopaminergic pathways by excitatory neurotransmitter pathways increases. There are several well-defined theories regarding neurobiological changes as drug use develops from compulsive to impulsive use. In general, glutamatergic projections from the prefrontal cortex and other limbic areas to the nucleus accumbens are strengthened, and cellular adaptations can be observed in the anterior cingulate cortex, both key regions in addiction (Figure 1). Noradrenergic (norepinephrine) neurotransmission in the amygdala may also play an increasing role in stress and anxiety behaviours associated with addiction.

### Neurobiology associated with specific drugs of abuse

#### Alcohol

Alcohol impacts on a broad range of neurotransmitter systems, and different effects can be attributed to the activation of different receptors. Alcohol is a positive allosteric modulator of the GABA-A receptor, enhancing receptor function in response to endogenous GABA, an inhibitory neurotransmitter. Ataxia, sedation and anxiolysis are mediated primarily through this GABA-A activity. Additionally, alcohol acts acutely as an antagonist at *N*-methyl-D-aspartate (NMDA) glutamate receptors, thereby reducing excitatory glutamatergic neurotransmission.

Dysregulation of the NMDA receptor system is thought to underpin alcohol-related memory impairments.

Alcohol increases  $\beta$ -endorphin release in the ventral tegmental area and nucleus accumbens, although the mechanism by which this occurs is not understood. In the ventral tegmental area,  $\beta$ -endorphin stimulation of the mu opiate receptors reduces the GABA 'brake' on the mesolimbic dopaminergic neurones, increasing their activity.  $\beta$ -Endorphin release in the nucleus accumbens also modulates dopaminergic activity. Opioid receptor antagonist medications such as nalmefene and naltrexone block the mu opiate receptor to reduce the pleasurable and rewarding effects of alcohol.

Over time, neuroadaptations occur to counteract the continual depression of the system. Chronic activation of the GABA-ergic system by alcohol results in a reduction in GABA-A receptor function. This probably contributes primarily to tolerance to alcohol. Conversely, chronic consumption of alcohol results in an upregulation of NMDA receptors to compensate for the continued reduction in NMDA receptor function (Table 2).

### Benzodiazepines

Benzodiazepine-binding sites are part of the GABA-A receptor complex and act to boost opening of the chloride channel by GABA and thus inhibition, resulting in anxiolysis and sedation.

## Drugs of abuse: their pharmacology and that of their pharmacotherapy<sup>5</sup>

Drug	Primary target	Main effects/transmitters	Other actions	Clinical pharmacotherapy <sup>5</sup>
<b>Opiates</b>				
Morphine, heroin, codeine, etc.	Mu opioid receptors	? Dopamine	Kappa and delta opioid receptors Noradrenaline	Methadone – full agonist Buprenorphine – partial agonist and antagonist Naltrexone – full antagonist Lofexidine and clonidine – $\alpha_2$ -adrenergic receptor agonists
<b>Stimulants</b>				
Cocaine	DAT	↑ Dopamine	Local anaesthetic effects by disrupting voltage-gated sodium channels	Lorcaserin 5HT <sub>2C</sub> receptor agonist (preclinical)
Amphetamine		↑ Dopamine	Glutamate, ↑ $\beta$ -Endorphin	(DRD3)
Methamphetamine		↑ Dopamine	↑ NA/5HT	
Nicotine	Nicotinic ACh receptor	↑ Dopamine		Nicotine – replacement Varenicline – partial nicotinic agonist
<b>Sedatives</b>				
Alcohol	GABA Glutamate	↑ GABA-A function, ↓ Glutamate	↑ $\beta$ -Endorphin Many other systems	Benzodiazepines – GABA-A positive allosteric modulator Baclofen – GABA-B agonist Acamprosate – reduced NMDA and glutamate activity Naltrexone, nalmefene – opioid receptor antagonists
Benzodiazepines	GABA-A	↑ GABA-A function	↑ Dopamine	Flumazenil – GABA-A antagonist
GHB	GABA-B GHB receptor	↑ GABA function		Baclofen
Cannabis	CB <sub>1</sub> receptors	? Dopamine ? Opioids		
<b>Others</b>				
MDMA/ecstasy	5HT transporter (SERT)	↑ 5HT Weak 5HT <sub>1</sub> and 5HT <sub>2</sub> agonist	↑ Dopamine	
Ketamine/PCP	NMDA	↓ Glutamate		
LSD	5HT <sub>2</sub> receptor	5HT <sub>2</sub> agonist	D <sub>2</sub> receptor agonist	

5HT, 5-hydroxytryptamine; ACh, acetylcholine; DAT, dopamine transporter; DRD3, dopamine D<sub>3</sub> receptor; GABA,  $\gamma$ -aminobutyric acid; GHB,  $\gamma$ -hydroxybutyrate; NA, noradrenaline; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine.

Table 2

There are six different subtypes of the GABA-A receptor, specific functions being associated with particular subtypes (e.g. anxiety with  $\alpha 2$  and  $\alpha 3$ ). Finding which subtype is involved in abuse potential has been a clinical goal, and research suggests possible involvement of the  $\alpha 1$  and  $\alpha 5$  subtypes. Of all the drugs of abuse, an increase in mesolimbic dopaminergic activity has been less easy to demonstrate with benzodiazepines.

### Opioids

The pleasurable and rewarding effects of morphine and heroin are primarily caused by their agonism of the mu opioid receptor. This receptor is also responsible for analgesia and respiratory depression. Chronic opioid consumption is associated with development of tolerance to its wide range of effects. Tolerance develops at different rates; for example, tolerance to the euphoriant effects occurs rapidly, driving further opioid use. However, tolerance to opioid effects on respiration or constipation appears more slowly and is incomplete. Understanding the differential rates of tolerance is important, given the risk of respiratory depression and death from opiate overdose in individuals following withdrawal, but the mechanism is currently poorly understood.

In addition to using opioid substitute treatment, opioid withdrawal symptoms can be treated with non-opioid medication. Excessive arousal and insomnia symptoms are caused by increased noradrenergic function, and can be ameliorated with  $\alpha_2$ -adrenergic agonists, such as lofexidine and clonidine, which reduce noradrenergic activity.

### Stimulants

Stimulants, such as cocaine, amphetamine and methamphetamine are the only drugs of abuse to directly target the dopamine system by blocking dopamine transporters, therefore preventing dopamine reuptake into the nerve terminal. Amphetamines also increase dopamine release. Chronic stimulant use is associated with a reduction in dopaminergic function. Although much focus has been placed on dopamine as a key neurotransmitter in stimulant addiction, other systems, including endogenous opioids as described above, are also likely to be important. Mice that lack dopamine transporters still self-administer cocaine, supporting a compensatory role for alternative transmitters such as serotonin and noradrenaline.

Some drugs of abuse have both stimulant and hallucinogenic properties. For instance, ecstasy (methylenedioxyamphetamine) increases the release of serotonin and blocks the serotonin reuptake transporter. Users of ecstasy may experience visual hallucinations but maintain a sense of reality, which is different from that caused by drugs with greater hallucinogenic activity such as lysergic acid diethylamide (LSD), which induces states of altered perception. ◆

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### Definitions — derived using the World Health Organization International Classification of Diseases (ICD-10)

**Dependence:** When use of a substance becomes a higher priority than other behaviours that once had greater value. Descriptive characteristics include: a strong desire or craving to use the substance, difficulties in controlling substance-taking behaviour, a withdrawal, tolerance (see below), neglect of alternative pleasures or interests and substance use despite clear evidence of harmful consequences. For more details see [www.who.int/substance\\_abuse/terminology/ICD10ClinicalDiagnosis.pdf](http://www.who.int/substance_abuse/terminology/ICD10ClinicalDiagnosis.pdf).

**Tolerance:** the process by which chronic drug use results in a need to increase the drug dose to maintain the original pharmacological effect.