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

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 cause 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

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

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.[3,4]

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

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Main neurotransmitter changes in the different stages of drug use

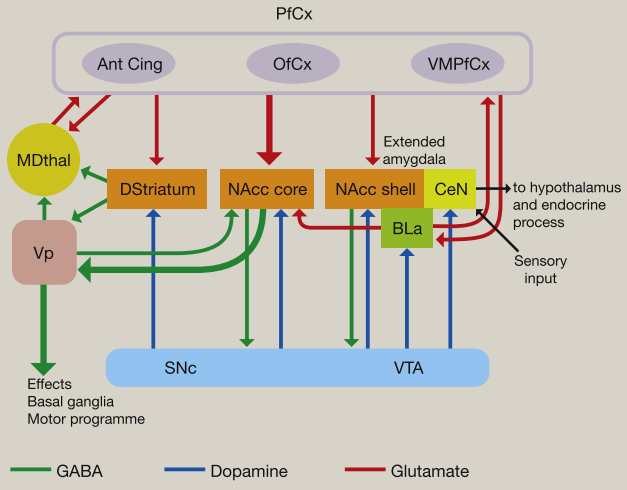
Risk factors and vulnerability for addiction

- Liking: low dopamine receptor D_2 availability
- Liking: high mu opioid receptor availability
- Anxiety: low γ-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



Ant Cing, anterior cingulate; BLa, basolateral amygdala; CeN, central nucleus of amygdala; DStriatum, dorsal striatum; MDthal, mediodorsal thalamus; NAcc, nucleus accumbens; OfCx, orbitofrontal cortex; PfCx, prefrontal cortex; SNc, substantia nigra, pars compacta; VMPfCx, ventromedial prefrontal cortex; Vp, ventral pallidum; VTA, ventral tegmental area.

From Reid and Lingford-Hughes (2006)

Figure 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 γ-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 interneurones 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 β-endorphin, which has euphoric and analgesic effects. Changes in the availability of mu 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 (norepinephrinic) 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.

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