Neuropharmacology of addiction

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Abstract

Until recently, much of our knowledge of the neuropharmacology of addiction was derived from animal studies, but we are now able to study the human brain directly and there is a growing body of knowledge on the underlying neuropharmacology of addiction. Addiction is increasingly viewed as a disorder of motivated behaviour and the following brain structures are thought to be crucial in the circuitry of reward and motivation: the orbitofrontal cortex (for stimulus evaluation); the nucleus accumbens (predicting rewards); and the amygdala (response to primary stimuli). Nearly all substances of abuse cause an increase in synaptic dopamine, although through different mechanisms, and dopamine is implicated in the development of addiction, with an important role particularly in the pairing of drug-related cues with responses. In end-stage addiction, however, changes in the synaptic strengths of glutamate fibres from prefrontal cortex to nucleus accumbens have a major effect. These changes may underlie the switch from impulsive substance use to compulsive substance use that seems to occur in addiction. A reduction in post-synaptic dopamine D_2 receptor levels following alcohol or stimulant dependence may be involved in the sensation of craving. In general, dysfunction of the neural circuitry of reward and motivated behaviour may be the neural substrate for the development and maintenance of addiction. The neuropharmacology of specific substances such as alcohol, stimulants, opioids, cannabis, ecstasy (MDMA) and nicotine are varied, but different substances disrupt different parts of this circuitry to give the same net effect – namely addiction.

Keywords accumbens; addiction; alcohol; amygdala; cocaine; dopamine; ecstasy; glutamate; neuropharmacology; nicotine; opioid; orbitofrontal; withdrawal

Although psychological theories of addiction predominate and generally form the basis for treatment, within the past decade neurobiological theories have become much better defined and more evidence-based, and their impact on treatment is likely to increase.[1,2] Much of our knowledge is derived from animal models, and it should be recognized that such models struggle to recreate the complexities of drug and alcohol misuse in humans and have to rely on behavioural measures to assess psychological phenomena such as craving. Nevertheless, as preclinical models develop to represent human experiences more closely, and as neuroimaging techniques become more widely used, many hypotheses are now directly testable in humans and we are better able to understand the neuroscience of addiction.[3]

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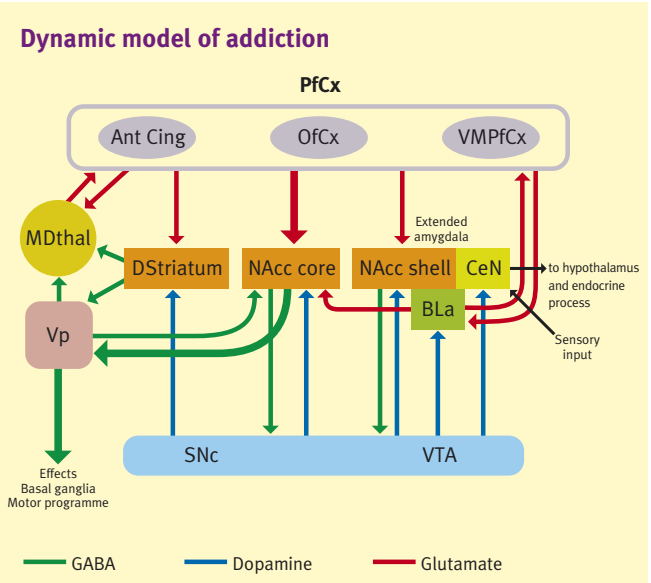
Neurophysiological pathways in addiction

We now know that there are complex interactions between different parts of the brain in the addicted individual.[4] Figure 1 illustrates some of the neural circuitry that is involved in the process of addiction. Much of this circuitry is involved in motivation, the processing of rewards, and making decisions about how to deal with rewards. Addiction can be seen as a dysfunction in these processes. What starts off as a system in homeostatic balance may undergo an allostatic shift so that equilibrium can be maintained only by the continuing consumption of drugs.[5]

Important structures in the circuitry of reward and motivated behaviour are:

- the orbitofrontal cortex (OfCx), which is involved in stimulus evaluation – telling us 'what we want'
- the nucleus accumbens (NAcc), which is implicated in learning to predict rewards and to express adaptive behaviours
- the amygdala, which responds to the intensity of rewarding and aversive stimuli and also links motivationally relevant



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

Figure 1

events with neutral stimuli and the autonomic and endocrine systems.

Three stages of addiction

Kalivas and Volkow outline three stages of addiction and relate these to different brain regions and neurotransmitters:

- acute drug effects
- transition to addiction
- end-stage addiction.[6]

The dopamine system has an important role to play in generating acute drug effects, and in the pairing of drug-related cues with responses. The amount of dopamine release required for these processes is unclear, however, since different substances of addiction have differing effects on the dopamine system. The transition to addiction, however, may occur due to additional changes in the glutamatergic system which then predominate in end-stage addiction. This highlights the idea that in the genesis of addiction there is a switch from *impulsive* episodes of drug use with recovery within normal homeostatic limits, to a *compulsive* overriding need to seek out and use drugs in the face of physical, psychological and social deterioration.

At the neurophysiological level there is a gradual change from ventral to dorsal activation in the NAcc with an accompanying shift in activity from ventral tegmental area (VTA) to substantia nigra (SNc) dopaminergic projections. There is also a reduction in OfCx and ventromedial prefrontal cortex (VMPfCx) activity at rest in addicts, which reflects a switch from prefrontal control, with reflective decision-making, to more compulsive striatal control.[7] This switch from drug use, with associated pleasure and liking, to drug dependence, with compulsive drug wanting, is marked by changes in synaptic plasticity and neurotransmitter function. Kalivas and Volkow suggest that there is a final common pathway consisting of PfCx–NAcc–ventral pallidum in drug-craving and drug-seeking behaviour (connections in bold in Figure 1).[6] Changes in the strengths of synaptic connections in this pathway can account for the rapid reinstatement of drug use during a relapse from abstinence. Such reinstatement can be triggered by stress, a drug-specific cue, or a single dose of the drug. These changes in synaptic connections depend upon glutamatergic fibres from the PfCx which converge on NAcc dendritic spines with dopaminergic afferents from the VTA. Repeated use of drugs may lead to plastic reorganization of these synaptic connections, which then cements changes in neural activity, and so behaviour. Molecular changes that affect synaptic connection strengths may occur both pre-synpatically and post-synaptically in the NAcc, and also in the PfCx itself, as reflected by changes in activity seen there in neuroimaging studies.

Dysfunction in the neural circuitry outlined here may underlie the development and maintenance of addiction in a general sense; however, individual substances disrupt this circuitry in specific ways which will be discussed below. This means that different perturbations of the circuitry can give rise to the same net effect, namely addiction.

The dopaminergic mesolimbic system

The dopaminergic mesolimbic system arises in the VTA in the brainstem and projects to the NAcc in the ventral striatum and PfCx. Preclinical studies have shown that increased levels of dopamine in the NAcc are critical in mediating rewarding effects or positive reinforcement for all drugs of misuse, except possibly for benzodiazepines.[5] This increase in dopamine may occur directly as a result of:

- dopamine reuptake blockade in the NAcc (e.g. cocaine)
- blockade combined with dopamine release from the terminals (e.g. amphetamine)
- increasing dopaminergic neuronal firing through disinhibition in the VTA (e.g. alcohol, opiates).

More recently, neuroimaging techniques such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) have shown that such an increase in dopamine occurs in humans. The pleasurable or euphoric effects of stimulants, amphetamine and methylphenidate relate directly to increased dopamine release in the ventral striatum. Volkow *et al.* have also shown that lower striatal dopamine D_2 receptor levels are associated with finding methylphenidate pleasurable.[8]

Withdrawal

While increasing dopamine levels are crucial in mediating pleasure, neuroadaptations occur in chronic use, resulting in a hypodopaminergic state. Reduced dopamine D_2 receptor levels in humans have been shown for drugs including alcohol, stimulants and opiates, and while there may be some functional recovery, reduced receptor levels can persist for months.[8] These changes, occurring in withdrawal and early abstinence, probably underlie symptoms such as dysphoria, anhedonia and irritability, and may lead to craving and drug-seeking behaviour. Presumably the release of dopamine produced by the individual's drug of choice provides relief, though this has not been shown.

Anticipation

It is now recognized that dopamine plays a critical role in anticipation. Schultz found that after a period of training primates to associate a particular cue with a reward, dopamine was released not after consuming the reward, as initially, but rather in the presence of the cue.[9] Importantly, if the reward was not available, dopaminergic activity was reduced. Therefore, in humans, the occurrence of a cue without the drug being taken may result in a hypodopaminergic state, with the associations described above.

Dopamine and pharmacotherapy

Drugs that block the dopamine transporter or dopamine receptors (D_1-like and D_2-like) or increase dopamine have not been consistently shown to improve outcome for a number of addictions. Bupropion, which is used to treat nicotine dependence, is a dopamine and noradrenaline reuptake inhibitor, but the exact mechanism underlying its therapeutic effect has yet to be determined. The development of dopaminergic partial agonists at the D_3 receptor (BP-897) holds some promise in the treatment of cocaine addiction. In animal models, this compound inhibits cocaine-seeking behaviour in response to cues.[10] Since it is a partial agonist, BP-897 stimulates the D_3 receptor sufficiently to avoid hypofunction, but without causing a 'high' or being reinforcing (see Table 1).