

Neurobiology of addiction and implications for treatment

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Drug and alcohol misuse result in immense harm at both individual and societal level. Our understanding of the neuropharmacology of these disorders is increasing through the use of approaches such as neuroimaging and gene targeting and the availability of specific receptor agonists and antagonists. Our aim here is to describe some interesting new findings that are likely to inform advances in treatment.

THE DOPAMINERGIC PATHWAY

Reward

Over the past 20 years there has been immense interest in the mesolimbic dopaminergic system; most drugs of misuse (except benzodiazepines) increase dopamine here. It is widely accepted that increased levels of dopamine in the nucleus accumbens are key in mediating the rewarding effects or positive reinforcement of drugs of misuse (Koob & Le Moal, 2001). Evidence is still accruing to support this. For instance, alcohol and morphine are no longer rewarding in mice lacking the D₂ receptor (D₂ knockout mice; Maldonado *et al.*, 1997; Risinger *et al.*, 2000). In humans, Volkow *et al.* (1999) showed in a series of neuroimaging studies using cocaine or methylphenidate that increased dopamine levels in the brain were associated with euphoria and pleasure. Interestingly, low levels of dopamine D₂ receptors were associated with pleasure after methylphenidate in drug-naïve individuals, whereas high receptor levels were associated with unpleasant feelings. This study gives us an insight into the role of neurobiology in explaining why drug use for some people is pleasurable and likely to be repeated and for others is unpleasant and not repeated.

Anticipation

The role of dopamine in addiction is now recognised as critical in anticipation and

withdrawal as well. In an elegant series of experiments, Schultz (2001) found that in primates trained to associate a cue with a pleasurable experience (food), increased dopaminergic activity was seen in response to the cue and not to the food. If the food was not then presented, dopaminergic function dropped. Reduced dopaminergic function is thought to be associated with negative affect (e.g. dysphoria). Thus, an individual with an addiction may see a 'cue' (e.g. a public house, mirror or needle) and if their drug of choice is not available may feel dysphoric, which is likely to increase the drive to obtain the drug.

Withdrawal

Reduced dopaminergic function has been seen in withdrawal and early abstinence from many drugs of misuse. Neuroimaging studies in cocaine, opiate and alcohol addictions have revealed reduced levels of dopamine D₂ receptors, which may recover to some extent during abstinence, but have been shown to persist for months (Volkow *et al.*, 1999). Early stages of abstinence are associated with elevated levels of craving, drug-seeking and risk of relapse, and it is likely that hypodopaminergic function plays a mediating role. Presumably the release of dopamine produced by the drug of choice provides relief from withdrawal, although this has not yet been studied.

Pharmacotherapy (Table 1)

Because of the pre-eminence of the dopaminergic reward system in addiction, this has been a target for pharmacotherapy, but with mixed results. One strategy, for instance, has been to block the binding of cocaine to the dopamine transporter site (Nutt, 1993). In cocaine addiction, the development of dopaminergic partial agonists at the D₃ receptor, such as BP-897, currently holds some promise. In rats, BP-897 inhibits cocaine-seeking behaviour in response to cues (Pilla *et al.*, 1999). As a

partial agonist, this drug stimulates the D₃ receptor enough to keep withdrawal at bay, but not enough to cause a 'high' or to be rewarding. It is currently in phase 1 trials.

One drug that affects the dopaminergic system and has proven efficacy in the treatment of nicotine addiction is bupropion (Jorenby *et al.*, 1999). The exact mechanism underlying this effect still has to be fully characterised; however, it has been shown that bupropion increases dopamine and noradrenaline levels by acting as an uptake inhibitor (Ascher *et al.*, 1995).

Related systems involved in reward

Our understanding of other neurotransmitter systems that are involved in reward and that may modulate dopaminergic activity provides further targets for pharmacotherapy.

Opioids

The opioid system has three receptor subtypes: mu, kappa and delta. The mu subtype appears to be key in opiate addiction: for mice lacking this receptor, morphine is no longer rewarding or reinforcing (Kieffer, 1999). In addition, a morphine withdrawal syndrome is not seen in these animals. Neuroimaging studies suggest that alterations in mu opiate receptor levels may be fundamental to addiction. Using [¹¹C]-carfentanil positron emission tomography (PET) to label mu opiate receptors in the brain, Zubieta *et al.* (2000) found increased receptor levels in the anterior cingulate in recently abstinent humans addicted to cocaine or opiates. This may reflect elevated mu opiate receptor levels or decreased endogenous opioid levels. In either case, craving may result.

Roles for kappa and delta opiate receptors in addiction are also evident. Unlike mu receptors, kappa receptor stimulation reduces dopamine function in the nucleus accumbens. This may possibly result in dysphoria. In animal models, delta antagonists can reduce self-administration of alcohol, suggesting that this receptor also plays a key role in reinforcement.

Naltrexone is a long-acting opiate antagonist. Its use in opiate addiction is based on its ability to antagonise any effects of opiates. However, in alcoholism the efficacy of naltrexone is thought to be a consequence of its ability to block the actions of endorphins that are released by alcohol and that mediate pleasure (Herz, 1997).

Glutamate

Glutamate is the brain's principal excitatory neurotransmitter for which there are three receptors – the ion channels *N*-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) and kainate – and also another receptor family which is coupled to G-proteins and the second (metabotropic) messenger system. Glutamatergic neurons from the prefrontal cortex and amygdala project onto the mesolimbic reward pathway, from which reciprocal dopaminergic projections arise (Louk *et al*, 2000). There is evidence that the glutamatergic projection from the prefrontal cortex to the nucleus accumbens plays a role in the reinstatement of stimulant-seeking behaviour.

The NMDA receptor has been implicated in nicotine, ethanol, benzodiazepine and cannabinoid addiction (Wolf, 1998). For example, NMDA antagonists inhibit sensitisation (i.e. enhanced responses) to stimulants such as cocaine and amphetamine and the development of opioid dependence. Not all NMDA antagonists are clinically

useful, owing to their psychomimetic properties (cf. ketamine, phencyclidine). Nevertheless, memantine is a non-competitive NMDA receptor antagonist, used to treat neurological disorders, which has recently been shown to attenuate naloxone-precipitated withdrawal in humans addicted to opiates (Bisaga *et al*, 2001).

There is recent evidence to suggest an important role for other glutamate receptors, such as the metabotropic receptor, that may be independent of the dopaminergic system. In mice lacking the mGlu5 subtype of the metabotropic glutamatergic receptor, cocaine still increases dopamine in the nucleus accumbens; but the mice do not self-administer cocaine or show increased locomotor activity (Chiamulera *et al*, 2001).

Cannabinoids

Opioids and cannabinoids share some pharmacological properties producing effects such as sedation, hypothermia and anti-nociception. In addition, there is increasing recognition that opiate-cannabinoid interactions are important in

drug addiction, although their precise nature remains to be characterised. The most potent cannabinoid in cannabis is Δ^9 -tetrahydrocannabinol (Δ^9 -THC) (Ashton, 2001). Cannabinoids have been shown to increase opioid synthesis and/or release (Manzanas *et al*, 1999). This may explain why opiate antagonists block some effects of cannabis and induce withdrawal in Δ^9 -THC-dependent rats or, conversely, why marijuana may reduce opiate withdrawal.

There are two cannabinoid receptors: CB₁ in the brain, for which the endogenous compound is anandamide, and CB₂ on immune cells. CB₁ receptors are widely distributed throughout the brain, but particularly in the cerebral cortex, hippocampus, cerebellum, thalamus and basal ganglia (Ameri, 1999). In mice lacking the CB₁ receptor, rewarding and withdrawal responses to morphine and cannabinoids but not to cocaine are reduced (Ledent *et al*, 1999; Martin *et al*, 2000). This suggests that the CB₁ receptor is involved in dependence on not only cannabinoids but also opiates. As a result, CB₁ agonists may have clinical utility in treating opiate addiction.

Table I Molecular targets of drugs of misuse and pharmacological approaches (current and theoretical) directed at these

Drug	Primary target	Main effects/transmitters	Other actions	Substitution therapy	Partial agonists	Antagonists/blockers
Opiates	Mu opiate receptors	? Inc. dopamine	Kappa and delta opiate receptors	Methadone Buprenorphine	Buprenorphine	Naltrexone Naloxone Nalmefene ³
Stimulants						
Cocaine	DAT	Inc. dopamine	Local anaesthetic Inc. 5-HT	Bupropion ¹	D ₃ ligands (BP-897) ¹	GR12909 ¹
Amphetamines	DAT	Inc. dopamine	?NA/5-HT release	Bupropion ¹	D ₃ ligands (BP-897) ¹	D ₃ receptor drugs ¹
Nicotine	Nicotinic ACH receptor	Inc. dopamine		Nicotine (patches etc.)		Mecamylamine ¹
Sedatives						
Alcohol	GABA/glutamate	Inc. GABA Dec. glutamate	Many other systems	BDZs ²	BDZ partial agonists ¹	Acamprosate ⁴ Naltrexone ⁴
BDZs	GABA	Inc. GABA		Long t _{1/2} BDZs	BDZ partial agonists ¹	Flumazenil
GHB	GABA	?Inc. GABA	Inc. dopamine	BDZs ¹	BDZ partial agonists ¹	None
Solvents	Not known	?Dec. glutamate	? membrane changes	None	None	None
Cannabis	CB ₁ receptors	? dopamine ? opiates		None	None	SRI141716A ¹
Ecstasy	5-HT transporter	Inc. 5-HT	Some DA release also	SSRIs ¹	5-HT drugs ¹	SSRIs ¹
LSD	5-HT ₂ receptors	Inc. 5-HT		None	5-HT drugs ¹	5-HT ₂ antagonists

BDZs, benzodiazepines; GHB, gamma-hydroxybutyrate; LSD, lysergic acid diethylamide; DAT, dopamine transporter; ACH, acetylcholine; GABA, gamma-aminobutyric acid; 5-HT, 5-hydroxytryptamine; Inc., increase in levels or function; Dec., decrease in levels or function; NA, noradrenaline; DA, dopamine; SSRIs, selective serotonin reuptake inhibitors.

1. Theoretically effective but no clinical trial data.

2. Controversial, risk of dependency.

3. Not available in UK.

4. Used to maintain abstinence.

The development of a CB₁ receptor antagonist, SR141716A (Rinaldi-Carmona *et al*, 1995), not only accelerated research into cannabinoids but also provided a possible treatment. This antagonist blocks both the physiological and psychological effects of smoked marijuana and therefore could be to cannabis what naltrexone is to heroin.

ALCOHOL WITHDRAWAL: THE ROLE OF GLUTAMATE

The neurobiology of alcoholism involves many different neurotransmitters, but key are the gamma-aminobutyric acid (GABA)-ergic system and the glutamatergic system (Nutt, 1999). In alcohol withdrawal, increased glutamatergic NMDA function is present and is thought to be involved in seizures and cell death, by means of increased Ca²⁺ influx through its channel and low Mg²⁺. The hippocampus appears to be a critical site for such glutamatergic hyperactivity. Acamprosate, a taurine derivative, is increasingly used to maintain abstinence from alcohol as it has been shown to double abstinence rates. How acamprosate achieves its therapeutic effect has not yet been fully characterised; it antagonises the NMDA receptor (possibly through the polyamine site). Acamprosate also reduces glutamate levels and may be neuroprotective (Dahchour & De Witte, 2000). If such neuroprotection occurs in humans, this would have important implications for the treatment of alcoholism; currently some workers advocate starting acamprosate with detoxification.

OPIOID DEPENDENCE: WHAT OTHER NEUROTRANSMITTER SYSTEMS ARE INVOLVED?

As described above, the mu opiate receptor plays a key role in opiate reward, but many of the mechanisms underlying opiate tolerance, dependence and withdrawal remain elusive. As the opiate receptor may not change with chronic opiate exposure, changes 'downstream' of the receptor may be more critical. For example, noradrenergic overactivity is seen in opiate withdrawal and can be treated with α_2 agonists such as lofexidine or clonidine (Strang *et al*, 1999).

In the treatment of opiate addiction, methadone is the most commonly prescribed drug, although the use of buprenorphine is increasing. Methadone (like

heroin) is a full agonist at the mu receptor, whereas buprenorphine is a mu partial agonist. Partial agonists give lower levels of response at maximal receptor occupancy. Also, when a partial agonist occupies receptors, fewer are available for a full agonist (e.g. heroin). The partial agonist is therefore acting as an antagonist. Consequently, buprenorphine will stimulate the mu opioid receptor, but not maximally (hence, there is less risk of respiratory depression in overdose), and will also prevent the effects of heroin taken 'on top'. In addition, its longer half-life allows less than daily dosing, an advantage in supervised consumption.

ECSTASY: THE 5-HT SYSTEM AND NEUROTOXICITY

Ecstasy (3,4-methylenedioxymethamphetamine or MDMA) and its derivatives MDA (Adam) and MDEA (Eve) have both stimulant and hallucinogenic properties. Acutely, MDMA increases 5-hydroxytryptamine (5-HT or serotonin) levels, and, to a lesser extent, dopamine levels, by stimulating release and inhibiting uptake.

Animal studies have revealed ecstasy and its derivatives to be neurotoxic to serotonergic neurons (MDA > MDMA > MDEA), but it is controversial whether and to what extent the same occurs in man (Boot *et al*, 2000). Neuroimaging studies using PET and single photon emission tomography (SPET) to measure 5-HT transporter levels in persons who are regular heavy ecstasy users report reduced levels. However, methodological questions about the tracer, contribution of blood flow and choice of subjects necessarily limit these conclusions (Semple *et al*, 1999; Reneman *et al*, 2001). There is some evidence for cognitive impairments in individuals using ecstasy which may persist after a period of chronic use, and it is not clear how reversible these are with time. In animal models, fluoxetine has been shown to be neuroprotective, apparently by blocking ecstasy uptake into 5-HT neurons, but it is unknown whether this protective effect occurs in humans.

THE GABAERGIC SYSTEM: TARGET FOR SEDATIVES

The most widely misused group of drugs acting on this system are the benzodiazepines. These modulate the GABA-benzodiazepine receptor, increasing

the action of GABA, and so result in greater inhibitory activity in the brain (Nutt & Malizia, 2001). In contrast to other drugs of misuse, benzodiazepines do not increase dopamine release in the mesolimbic system. Misuse of these drugs is probably driven by the development of tolerance leading to withdrawal if these drugs are not taken. Benzodiazepine dependence in the context of drug addiction, where large doses of benzodiazepines are taken, is distinct from dependence in the context of long-term use of a prescribed benzodiazepine for anxiety.

Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid which, among other effects, enhances GABAergic function. GHB inhibits central nervous system activity and is a sedative but is also euphoric, presumably being linked to an increase in dopamine (Nicholson & Balster, 2001). It is increasingly used as a 'recreational club drug' and there is growing concern about its safety, particularly when combined with alcohol to render women vulnerable to sexual assault.

CONCLUSION

This is an exciting time in addiction as the neurobiology of addiction disorders becomes clearer. Such characterisation not only provides a greater understanding of why people become addicted and what happens to the brain after a period of substance misuse, but also allows better understanding of current pharmacotherapies and, we hope, the development of new treatments.

DECLARATION OF INTEREST

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REFERENCES

- Ameri, A. (1999) The effects of cannabinoids on the brain. *Progress in Neurobiology*, **58**, 315–348.
- Ascher, J. A., Cole, J. O., Colin, J. N., *et al* (1995) Bupropion: a review of its mechanism of antidepressant activity. *Journal of Clinical Psychiatry*, **56**, 395–401.

Ashton, C. H. (2001) Pharmacology and effects of cannabis: a brief review. *British Journal of Psychiatry*, **178**, 101–106.

Bisaga, A., Comer, S. D., Ward, A. S., et al (2001) The NMDA antagonist memantine attenuates the expression of opioid physical dependence in humans. *Psychopharmacology (Berl)*, **157**, 1–10.

Boot, B. P., McGregor, I. S. & Hall, W. (2000) MDMA (Ecstasy) neurotoxicity: assessing and communicating the risks. *Lancet*, **355**, 1818–1821.

Chiamulera, C., Epping-Jordan, M. P., Zocchi, A., et al (2001) Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nature Neuroscience*, **4**, 873–874.

Dahchour, A. & De Witte, P. (2000) Ethanol and amino acids in the central nervous system: assessment of the pharmacological actions of acamprosate. *Progress in Neurobiology*, **60**, 343–362.

Herz, A. (1997) Endogenous opioid systems and alcohol addiction. *Psychopharmacology*, **129**, 99–111.

Jorenby, D. E., Leischow, S. J., Nides, M. A., et al (1999) A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. *New England Journal of Medicine*, **340**, 685–691.

Kieffer, B. L. (1999) Opioids: first lessons from knockout mice. *Trends in Pharmacological Sciences*, **20**, 19–26.

Koob, G. F. & Le Moal, M. (2001) Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, **24**, 97–129.

Ledent, C., Valverde, O., Cossu, G., et al (1999) Unresponsiveness to cannabinoids and reduced addictive effects of opiates in CBR1 receptor knockout mice. *Science*, **283**, 401–404.

Louk, J. M. J., Vanderschuren, L. J. & Kalivas, P. W. (2000) Alterations in dopaminergic and glutamatergic transmission in the induction and expression of behavioral sensitization: a critical review of preclinical studies. *Psychopharmacology (Berl)*, **151**, 99–120.

Maldonado, R., Saiardi, A., Valverde, O., et al (1997) Absence of opiate rewarding effects in mice lacking dopamine D2 receptors. *Nature*, **388**, 586–589.

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Manzanas, J., Corchero, J., Romero, J., et al (1999) Pharmacological and biochemical interactions between opioids and cannabinoids. *Trends in Pharmacological Sciences*, **20**, 287–294.

Martin, M., Ledent, C., Parmentier, M., et al (2000) Cocaine, but not morphine, induces conditioned place preference and sensitization to locomotor responses in CBR1 knockout mice. *European Journal of Neuroscience*, **12**, 4038–4046.

Nicholson, K. L. & Balster, R. L. (2001) GHB: a new and novel drug of abuse. *Drug and Alcohol Dependence*, **63**, 1–22.

Nutt, D. (1993) Neurochemistry of drugs other than alcohol. *Current Opinion in Psychiatry*, **6**, 395–402.

— (1999) Alcohol and the brain. Pharmacological insights for psychiatrists. *British Journal of Psychiatry*, **175**, 114–119.

— & Malizia, A. L. (2001) New insights into the role of the GABA_A-benzodiazepine receptor in psychiatric disorder. *British Journal of Psychiatry*, **179**, 390–396.

Pilla, M., Perachon, S., Sautel, F., et al (1999) Selective inhibition of cocaine-seeking behaviour by a partial dopamine D3 receptor agonist. *Nature*, **400**, 371–375.

Reneman, L., Lavalaye, J., Schmand, B., et al (2001) Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. *Archives of General Psychiatry*, **58**, 901–906.

Rinaldi-Carmona, M., Barth, F., Heaulme, M., et al (1995) Biochemical and pharmacological characterisation of SR141716A, the first potent and selective brain cannabinoid receptor antagonist. *Life Sciences*, **56**, 1941–1947.

Risinger, F. O., Freeman, P. A., Rubinstein, M., et al (2000) Lack of operant ethanol self-administration in dopamine D2 receptor knockout mice. *Psychopharmacology (Berl)*, **152**, 343–350.

Schultz, W. (2001) Reward signaling by dopamine neurons. *Neuroscientist*, **7**, 293–302.

Semple, D. M., Ebmeier, K. P., Glabus, M. F., et al (1999) Reduced *in vivo* binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *British Journal of Psychiatry*, **175**, 63–69.

Strang, J., Bearn, J. & Gossop, M. (1999) Lofexidine for opiate detoxification: review of recent randomised and open controlled trials. *American Journal on Addictions*, **8**, 337–348.

Volkow, N. D., Fowler, J. S. & Wang, G. J. (1999) Imaging studies on the role of dopamine in cocaine reinforcement and addiction in humans. *Journal of Psychopharmacology*, **13**, 337–345.

Wolf, M. E. (1998) The role of excitatory amino acids in behavioral sensitization to psychomotor stimulants. *Progress in Neurobiology*, **54**, 679–720.

Zubieta, J., Greenwald, M. K., Lombardi, U., et al (2000) Buprenorphine-induced changes in mu-opioid receptor availability in male heroin-dependent volunteers: a preliminary study. *Neuropsychopharmacology*, **23**, 326–334.