Addiction: brain mechanisms and their treatment implications

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Drug addiction, or as it is also called, drug dependence, is a serious health problem; in addition to the huge direct health costs (psychiatric and physical), there are massive costs in terms of crime, loss of earnings and productivity, and social damage. The drugs of primary concern are the opioids, stimulants (amphetamines, cocaine), and alcohol, although nicotine addiction (smoking) is also an important health issue. Reducing the extent of drug dependence is one of the major goals of medicine.

The processes of addiction involve alterations in brain function because misused drugs are neuroactive substances that alter brain transmitter function. There is an impressive and rapidly growing research base that is giving important insights into the neurochemical and molecular actions of drugs of misuse—the processes that are likely to determine such misuse in human beings. Exciting new developments in neuroimaging with both PET (positron emission tomography) and SPECT (single photon emission computed tomography) provide, for the first time, the possibility of testing in human beings theories of drug addiction derived from preclinical studies. Key concepts of addiction are shown in the panel.

Pharmacological aspects

Drugs of misuse were traditionally classified into groups according to their physiological or psychological actions (eg, stimulants, sedatives). This classification is unsatisfactory because a single drug may have several actions; alcohol often acts as a stimulant in the early (rising) phase of intoxication, but as brain concentrations increase sedation ensues. The molecular sites of action of most drugs of misuse have been well characterised in recent years (see table) so it is preferable to classify drugs according to their pharmacodynamic actions.

Generally, the more efficacious the drug is at producing its pharmacological effect, the greater is the addiction potential and street value (figure 1). Drugs with lower efficacy are called partial agonists (eg, buprenorphine for opioid receptors,[1] bretazenil for benzodiazepine receptors[2]). The pharmacological profile of partial agonists is such that they are useful in maintenance treatment since they provide some reinforcement; thus, buprenorphine will keep opioid addicts in treatment. Nonetheless, because partial agonists attenuate the actions of full agonists, buprenorphine should diminish intravenous street heroin use. Moreover, the lower efficacy means that it is much safer in overdose.

Antagonists have zero efficacy (eg, naltrexone for opioid receptors,[3] flumazenil for benzodiazepine receptors[4]). They are very effective blockers of agonists. Their limitations are that they can precipitate withdrawal in physically dependent addicts and, because they do not provide any reinforcement, there is little incentive for addicts to stay on them. Naltrexone is useful in highly motivated individuals in whom relapse to opioid use could portend the end of their career (eg, doctors and pharmacists). This antagonist is also used in some countries under probation orders where non-compliance with treatment will then lead to prison.

For most drugs of misuse, the molecular sites of action are receptors or transporter sites; many of these have been cloned and sequenced, discoveries which in themselves are important advances for molecular biology. The dopamine transporter was cloned to expedite the understanding of cocaine's action;[5] all three of the opioid receptors and the multiple subunits of the γ-aminobutyric acid agonist A-type (GABA-A) receptor have also been cloned. Such discoveries help direct research towards a more rational design of treatment, and help develop theories of the brain mechanisms underlying addiction. There is a large research effort being directed towards finding a drug that will bind to the dopamine transporter and prevent the binding, and hence the actions, of cocaine without interfering with dopamine uptake.[6]

New μ opioid receptor drugs with potential treatment use such as antagonists (clocinnamox)[7] or partial agonists (buprenorphine) have been designed. The knowledge that alcohol acts through GABA and excitatory aminoacid receptors is leading to the study of drugs acting at these receptors (eg, acamprosate[8]) as treatments.

Pharmacokinetic factors are also important in determining the misuse potential of drugs; in general the faster the drug enters the brain the more reinforcing it is. Many of the developments in drug misuse reflect efforts

Mechanism	Transmitter	Potential treatment
Mimicking (substituting for) natural transmitters		
Opioids	Endorphin/encephalin	Partial ags (buprenorphine), antags (naltrexone)
Alcohol	GABA-A/endorphins	Partial ags (bretazenil), opioid antags*
Benzodiazepines	GABA-A	Partial ags, antags (flumazenil)
Nicotine	Acetylcholine	Antags (mecamylamine)
Cannabis	? anandamide	Antags (SR 141716A)
LSD	5-HT (1,2 receptors)	Antags (ritanserin)
Increasing endogenous transmitter release		
Cocaine	Dopamine	Substitute, ? antag/ uptake site blocker
Amphetamine	Dopamine	Substitute, ? antag/ uptake site blocker
Ecstasy	5-HT/dopamine	? antag, uptake blocker
Solvents	? noradrenaline	? antags
Blocking natural transmitters		
Alcohol	Glutamate	NMDA antags
Barbiturates	Glutamate	AMPA antags

ags=agonists, antags=antagonists, GABA-A=γ-aminobutyric acid A-type receptor 5-HT=serotonin, NMDA=N-methyl-D-aspartate, AMPA=aminomethylisoxazole propionic acid. *Eg, Naltrexone

Table: **Drugs of misuse: how they work and potential for new treatments**

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Panel: **Key concepts**

Drug dependence Because addiction is an imprecise and potentially pejorative term, the WHO recommended in 1969 that it should be replaced by the term drug dependence. Dependence is a continuous variable; for any individual its extent is determined by a range of factors such as amount and frequency of drug use, development of tolerance and withdrawal, inability to abstain, and degree of physical, personal, and social damage. The dependence spectrum thus ranges from simple physical dependence, as for example in some long-term therapeutic-dose benzodiazepine users, to the complete disintegration of personal and social functioning found in end-stage alcoholics and "hard drug" users. Physical dependence is caused by alterations in brain function that lead to the experiences of withdrawal. Psychological dependence describes repeated drug seeking and taking in the absence of withdrawal. Both can occur independently and contribute differing amounts to dependence on different drugs.

Tolerance This is the state in which drug actions diminish on repeated administration. Tolerance means that the addict needs more drug per dose; this increase in cost drives criminal activities. Tolerance often develops at a different rate for different actions of the drug. The respiratory depression caused by opioids reduces faster than the euphoric actions; this explains why addicts can use doses of heroin that would be lethal to non-addicts (several grams a day). A person becomes tolerant to the euphoric actions of cocaine faster than to its cardiostimulant actions, so on binge use, cardiotoxic concentrations are frequently reached.

Withdrawal Withdrawal is signified by signs and symptoms that occur when a drug is stopped or an antagonist (eg, naloxone for opioids) is given. Both physiological and psychological (conditioning) processes contribute. Because withdrawal is almost invariably unpleasant (eg, morning shakes with alcohol) it is a common reason for reuse of a drug. Moreover, withdrawal may also cause secondary problems. Examples are excitotoxic brain damage in the case of alcohol, and depression and anxiety in the case of cocaine. Withdrawal from some drugs (eg, methadone) may be long lived, and can be associated with continued craving.

Sensitisation This is the opposite of tolerance—ie, an increase in some actions of a drug on repeated administration—and tends to be seen with the stimulating actions of drug states. One example is the increased locomotor activating effects of cocaine and amphetamine; a clinical corollary of this may be the psychotic state seen during stimulant binges. Both probably reflect dopamine receptor supersensitivity. Sensitisation to the excitatory changes found in withdrawal also occurs and this explains the long-established clinical observations that alcohol withdrawal progressively worsens. Sensitisation may also be the process of reinstatement, in which as an addiction "career" progresses, relapses escalate much more rapidly to a state of decompensation.

Craving Craving, the desire to get (more of) the drug, is difficult to define because it has several subcomponents, which differ between drug and between individuals. For instance, with stimulants and alcohol, the first dose of drug can lead to a euphoric priming that drives repeated consumption. In many opioid addicts and alcoholics, craving is associated with withdrawal symptoms that seem to be conditioned to significant aspects of previous drug use—eg, needles and syringes or bars. Craving often leads to the addict's behaviour becoming highly focused on getting the drug with a narrowing of the normal behavioural repertoire. For example, an alcoholic will spend more and more time thinking about and engaging in drinking, and this leads to a progressive reduction in participation in work and family activities.

Euphoria Known by many synonyms (eg, rush, high, buzz) euphoria is the state of pleasure produced by a drug. This state is closely linked to the reinforcing effects of the drug (ie, how likely it is to lead to continued use). Euphoria is thought to relate to endogenous dopamine and or endogenous opioid release and is determined by both pharmacodynamic and pharmacokinetic factors. Euphoria is *not* the sole reason for the use of drugs. Many addicts start drug use to deal with psychiatric difficulties, especially anxiety, which sedatives, opioids, and even stimulants can reduce.

Maintenance therapy In this therapeutic approach, the need for illicit drug use is removed because the addict is prescribed a drug whose actions substitute for the drug of misuse. Maintenance therapy is an important component of harm reduction programmes, which seek to reduce the personal and social cost of drug addiction when abstinence is not an option. The best example is with opioid addiction, in which methadone reduces HIV infection and crime as well as engages the addict in treatment. Methadone has the disadvantage of the need for daily prescription and a high diversion potential into street (black market) use. Longer acting alternatives under investigation are buprenorphine and LAAM (l-α-acetylmethadol); these can be given every 2–3 days, have lower street value, and are safer in overdose. Nicotine gums and patches are a safer route for nicotine self-administration than is smoking. It is likely that maintenance therapy can be used for most drugs of dependence although clinical trials would be needed. Examples would be use of methylphenidate for cocaine or amphetamine dependence and long-acting benzodiazepines for intravenous temazepam users.

by addicts to speed up the rate of drug delivery. Perhaps the best example is cocaine; when chewed in the form of coca leaves it has little misuse potential. Progressively it has been refined so that entry to the brain is accelerated, from paste to powder and finally the lipophilic free-base (crack). In parallel, the route of administration has changed from oral through nasal to intravenous or smoking; the latter two result in brain concentrations that peak within minutes of drug taking.[9] Addicts prefer heroin to morphine because it is more lipophilic and so enters the brain faster. The quest for immediate reinforcement fuelled the epidemic of intravenous drug use that is now the major cause of HIV and hepatitis C virus spread. Reducing this behaviour is one of the most important goals in addiction treatment programmes.

Brain transmitters involved in addiction

Drugs are used because they produce alterations in brain function that result in positive changes in mood; this can be an elevation in mood from normal (euphoria) or the reduction of a negative dysphoric mood as in withdrawal. These changes are effected by interactions with neurochemical processes, usually by mimicking or increasing the action of endogenous transmitters.

Dopamine

Most drugs that produce elevations of mood or euphoria, including nicotine and alcohol, release dopamine in either the nucleus accumbens or the prefrontal cortex in animals, as demonstrated by brain dialysis.[10] Dopamine release can be either direct (for example, the stimulants

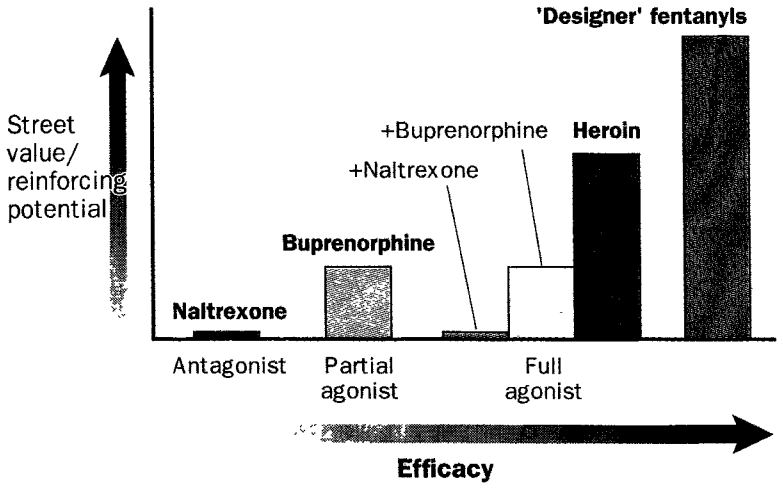

Figure 1: **Efficacy predicts street value**
+=reinforcing effect of heroin in presence of either buprenorphine or naltrexone

cocaine and amphetamines release dopamine), or indirect (opioids switch off the firing of GABA neurons that tonically inhibit dopamine cell firing). Several studies have shown that blockade of either D1 or D2 dopamine receptors attenuates the reinforcing actions of both these classes of drugs, which argues for a central mediating role of dopamine receptor activation in the initiation of addiction.[11] Of clinical relevance is the suggestion that a genetic polymorphism of the D2 receptor is strongly linked to drug misuse but this is still controversial.[12]

Homoeostatic adaptation occurs to the dopamine-increasing actions of drugs so that when the drug is stopped dopamine release is decreased below normal; this explains the "crash" after stimulant discontinuation[9] and some aspects of nicotine, opioid, and alcohol withdrawal. Drugs that block dopamine reuptake (eg, desipramine and mazindol, which are used to treat cocaine withdrawal) presumably work by increasing dopamine concentrations.[9] Dopamine overactivity probably underlies alcoholic delirium tremens and the need to treat with dopamine-D2-receptor blocking agents such as haloperidol.[13] Chronic dysregulation of dopamine function in detoxified alcoholics as revealed by a decreased number of uptake sites in SPECT studies with ^{123}I-βCIT[14] may explain the new finding that the low potency neuroleptic tiapride reduces relapse.[15]

It is now possible to measure both D1 and D2 dopamine receptors and the dopamine uptake site in human beings with neuroimaging techniques (figure 2). Cocaine has been shown with PET to bind predominantly to the dopamine-rich areas of the basal ganglia;[16] ^{11}C-RTI, an isopropyl derivative of cocaine, is a newer and better marker of these dopamine uptake sites. Now that D2 receptors (with ^{11}C-raclopride) and D1 receptors (with ^{11}C-SCH-23390) can be visualised, alterations in function in addicts could be studied.[16] Dopamine metabolism can also be monitored in vivo with ^{18}F-dopa. Similarly, the local metabolic effects of cocaine can be studied with ^{18}F-deoxyglucose uptake. These studies have shown that cocaine globally decreases brain metabolic activity.[17] An exciting potential development of PET/SPECT technology is to measure endogenous dopamine release; if cocaine and amphetamine do act by releasing dopamine this should be seen as a displacement of radiolabelled receptor ligand.

Endogenous agonist opioids

The brain makes a complex mixture of peptides that act as endogenous transmitters at opioid receptors—the β-endorphins and encephalins; these are involved in appetite, pain, and response to stress.[17] Misused opioids such as heroin act at the same receptors as the natural opioid system. However, because they have much higher efficacy than the endogenous transmitter they "high jack" the natural system by producing a much exaggerated response. Endogenous opioids are thought to be involved in the actions of other misused drugs such as alcohol and stimulants. For example, alcohol may cause dependence because it releases endogenous opioids; this could explain the therapeutic benefit of opioid antagonists such as naltrexone.[18]

There are three types of opioid receptors (μ, κ, and δ) that are distinguished by selective agonists and in some cases antagonists. μ and/or δ receptors mediate the euphoric actions of opioids,[19] with δ being possibly more important for alcohol.[20] Activation of κ receptors is aversive and could explain some aspects of opioid actions including the dysphoria of withdrawal.[21] Many misused opioids have activity at all three receptor types so adaptive changes in each may be important in the process of addiction.

Brain opioid receptors can be imaged in PET with ^{11}C-labelled diprenorphine (non-selective antagonist) (figure 3) or carfentanyl (μ agonist).[16] Diprenorphine has been used to show the release of endogenous opioids in some forms of seizures[22] and so could potentially be used to reveal whether non-opioid drugs cause their release also. Diprenorphine could also be used to determine the degree of receptor occupation required for optimum therapy with the various maintenance treatments such as methadone and naltrexone. Neuroimaging techniques not only offer the opportunity to test directly theories of drug dependence developed from animal studies in human beings; they can also be used to understand and optimise current treatments and develop new ones. For instance, the proportion of brain opioid receptors occupied during maintenance therapy with methadone could be determined and related to degree of dependence, craving, and treatment outcome. The linking of the clinical effects of partial agonists and their brain binding should lead to

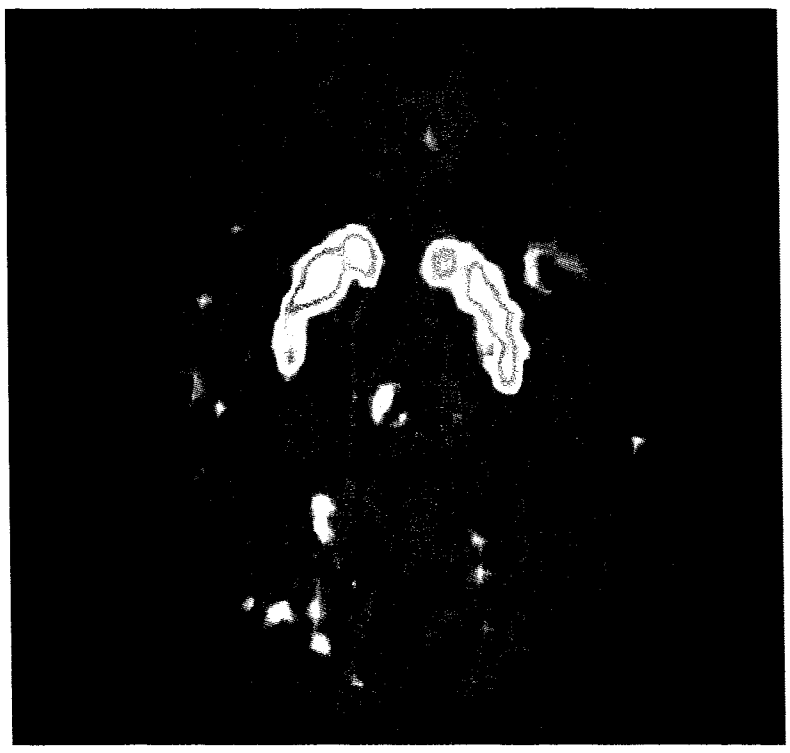

Figure 2: **PET scan showing dopamine-uptake sites labelled with the cocaine derivative ^{11}C-RTI$_{121}$**
Highest (white) to lowest (blue) density of binding sites. Courtesy of the Cyclotron Unit, MRC Clinical Sciences Centre

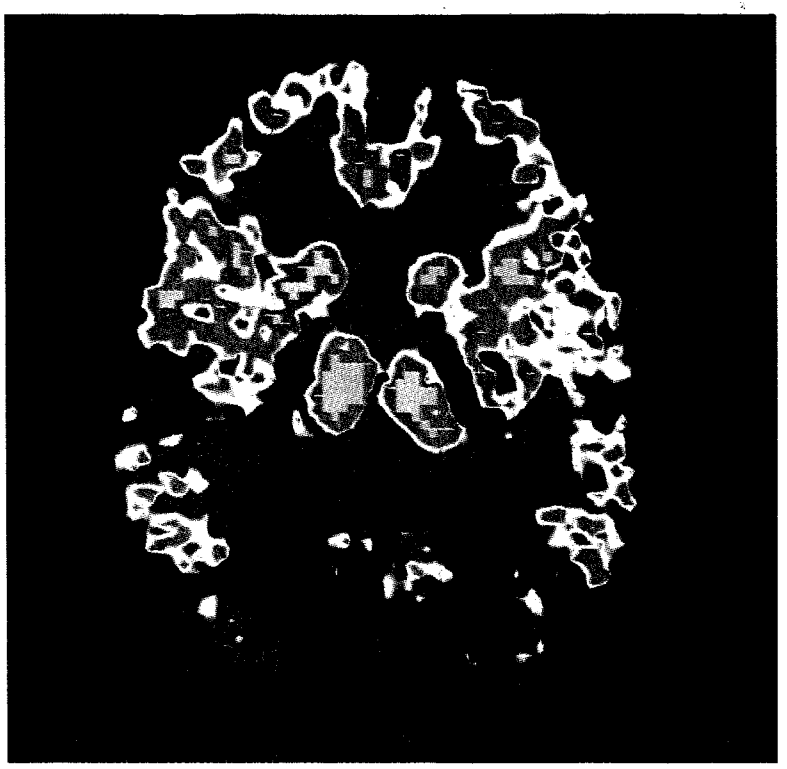

Figure 3: **Distribution of opioid receptors in human brain labelled with ^{11}C-diprenorphine (PET scan)**
Highest (white) to lowest (blue) density of binding sites. Courtesy of the Cyclotron Unit, MRC Clinical Sciences Centre

the more rational design of new compounds.

Another interesting possibility would be to explore the role of endogenous opioids in craving once reliable methods of inducing this state have been developed. One major future need for opioid receptor neuroimaging is the development of subtype-selective antagonist ligands to unravel the role of μ, δ, and κ receptors in the actions of the various drugs of misuse.

Noradrenaline

The activity of noradrenergic neurons is decreased by opioids, and withdrawal is thought to be due in part to the unopposed expression of compensatory processes. This explains why clonidine[23] or lofexidine,[24] α2-adrenoceptor agonists that inhibit noradrenergic neuronal activity, are effective treatments of opioid withdrawal. A similar hyperadrenergic state accounts for many features of alcohol withdrawal, especially anxiety, tremor, sweating, and hypertension,[25] although clonidine is not a recommended treatment for this condition because it does not protect against seizures. Some clinical data suggest that longer-term reduction in noradrenaline activity may predispose alcoholics to relapse and that drugs that selectively reverse this process may have clinical use.[26] Complex time-dependent alteration in noradrenaline function has recently been reported in patients withdrawing from stimulants[27] which may open new therapeutic avenues.

Recent animal data suggest that noradrenaline/dopamine interactions in the nucleus accumbens and frontal cortex may be important in the actions of stimulant drugs, contributing to features such as sensitisation.[28] As yet neuroimaging of brain noradrenaline systems is not possible, although a potential α2-adrenoceptor ligand has been identified.[29]

Serotonin (5-HT)

5-HT is an amine transmitter secreted by cells whose bodies are found in the raphe nuclei of the brain stem and whose axons arborise and diffusely innervate higher brain structures, as is the case for noradrenaline. 5-HT has many roles in brain function, but in relation to addiction the main ones relate to appetite, impulsivity, and craving. Early-onset (type II) alcoholics with a history of violent crime have low brain 5-HT turnover,[30] perhaps due to a polymorphism in their gene for the synthetic enzyme tryptophan hydroxylase. This subgroup of alcoholics also shows altered 5-HT receptor sensitivity in that administration of the 5-HT$_2$ receptor agonist mCPP produced craving rather than anxiety.[31] In this context it is intriguing that in rodents trained to self-administer alcohol, 5-HT receptor antagonists such as ritanserin and amperozide reduce intake.[32] Clinical trials of these drugs are now continuing. Increasing brain 5-HT function by blocking its reuptake with selective serotonin reuptake inhibitors (SSRIs) reduces voluntary alcohol consumption in heavy social drinkers.[33] The 5-HT receptor agonist buspirone reduces relapse in detoxified alcoholics with comorbid anxiety disorders.[34]

Neuroimaging of 5-HT is in its infancy but one of the newer PET dopamine uptake site tracers RTI$_{55}$ also labels the 5-HT transporter. Considerable progress is also being made towards producing an ^{18}F-labelled precursor for turnover studies. 5-HT$_2$ receptors have been imaged with ^{11}C-ritanserin,[16] although not yet in addicts, and a PET ligand for 5-HT$_{1A}$ receptors (^{11}C-WAY 100635) is under development.[35]

Aminoacid receptors

The major excitatory and inhibitory transmitters in the brain are the closely related aminoacids GABA (inhibitory) and glutamate (excitatory). The GABA receptor complex contains a binding site for the benzodiazepines, which is their sole site of action. Alcohol(s) and the barbiturates also enhance GABA function but in addition block some glutamate receptors.[37] This dual action probably explains their added toxicity and dependence liability. Children at high risk of becoming alcoholics seem to have altered benzodiazepine receptor sensitivity.[36]

On repeated use of the alcohol(s) and barbiturates, there is a compensatory increase in the number of brain glutamate receptors which contributes to the hyperexcitable state found in withdrawal. Since excessive glutamate activity can be neurotoxic, one suggestion is that repeated withdrawal, as seen nightly in alcoholics, may explain the brain damage in heavy drinkers.[37] Brain excitatory aminoacid receptors are involved in dependence on other drugs; thus, tolerance to opioids can be attenuated by co-treatment with dizocilpine, a blocker of the N-methyl-D-aspartate (NMDA) class of glutamate receptor.[38] Because NMDA receptors are very important in processes such as learning and memory, this suggests that drugs of this class could be used to treat some aspects of addiction, especially conditioned responses. Acamprosate has been suggested to act in this way in alcoholics.

The benzodiazepine site on the GABA-A receptor can be well visualised by PET with ^{11}C-flumazenil[39] or SPECT with ^{123}I-iomazenil,[40] which are both antagonists. Recent studies have revealed that intoxicating doses of benzodiazepine agonists occupy only about 30% of brain receptors (figure 4).[41] It would be of interest to determine whether this fraction is altered after chronic use, especially high-dose intravenous use as found with many addicts. The brain circuits involved in benzodiazepine withdrawal in animals are parts of the limbic system and

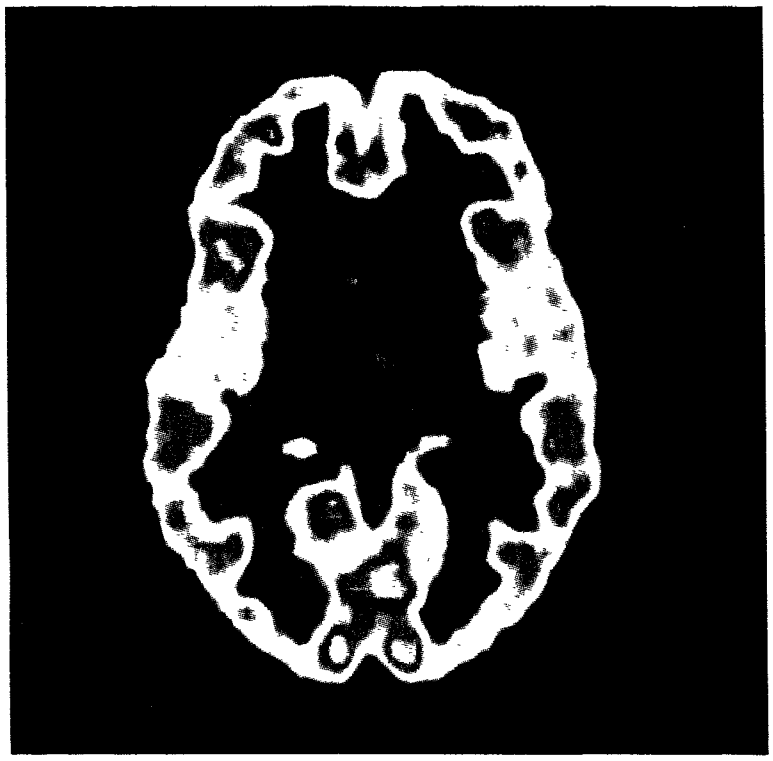

Figure 4: **PET scan showing distribution of benzodiazepine receptors in human brain labelled with ^{11}C-flumazenil**
Highest (white) to lowest (blue) density of binding sites. Courtesy of the Cyclotron Unit, MRC Clinical Sciences Centre

thalamus;[42] these studies used the deoxyglucose technique which is applicable to PET.

As yet there are no satisfactory neuroimaging ligands for excitatory receptors, although ketamine can be used to block NMDA receptor function in patients and could be used in imaging studies of brain metabolism.

Other transmitters

There are at least 80 other brain neurotransmitters, some of which are likely to be involved in addiction. One good candidate is CCK (cholecystokinin), which is found in larger amounts in the brain than in the gut. There are two subtypes of brain CCK receptors (A and B), and selective antagonists for each are now available. CCKB-receptor activation seems to be involved in withdrawal from a range of drugs including benzodiazepines, alcohol, and cocaine since antagonists (such as PD 134308) block several aspects of this syndrome.[43] CCK antagonists also moderate tolerance development to opioid analgesia so might have some use in opioid addiction.

Recently, receptors for cannabis have been discovered; one is found predominantly in the brain and the other in peripheral tissues, especially spleen. Both are members of the family of receptors that are coupled to G-proteins which includes the receptors for dopamine, noradrenaline, and many 5-HT receptors. Intriguingly the cannabis receptor in the brain is by far the most abundant of these which suggests an important role in brain function.[44] Several possible endogenous transmitters for these receptors have been suggested, with anadamide being the best candidate at present.[45] The role of endogenous cannabinoids in addiction can now be tested since a selective antagonist to this receptor has been synthesised.[46]

Calcium channels

The regulation of intracellular calcium homoeostasis is critical to all cells and several different calcium channels control the passage of this ion across cell membranes. One of these, the L-type channel, is substantially altered by alcohol and some other misused drugs. Alcohol administration reduces calcium entry through these channels; this results in an adaptive increase in their number so that in withdrawal calcium flux is excessive. Calcium-channel antagonists of the dihydropyridine type (eg, nitrendipine) block some aspects of alcohol withdrawal and when given with the alcohol prevent the increase in channel number.[47] The clinical implications of such findings are potentially very important and should be investigated especially since increased calcium flux could also contribute to neuronal death.

Brain circuits of addiction

Such brain circuits are beginning to be understood in animals, though there are little supporting data from human beings. The primary circuit seems to be the dopamine pathway that runs from the ventral tegmental area (VTA) through the nucleus accumbens to the prefrontal cortex (figure 5).[19] Dopamine release in either the nucleus accumbens, prefrontal cortex, or both is produced by all misused drugs apart from the benzodiazepines.[10] Some (eg, cocaine) act on the dopamine terminals, whereas others (eg, opioids) increase cell firing at the level of the cell bodies. Direct injection of drugs into these brain regions is reinforcing since animals will self-administer opioids and cocaine directly into them. Moreover drug withdrawal is associated with reduced dopamine transmission in these regions and aversive drugs (eg, κ agonists) inhibit dopamine release there.[10,21] Paradoxically some other aversive experiences such as pain cause dopamine release, and some argue that changes in this transmitter reflect not simply the reinforcing actions of drugs but their salience as a conditioned cue. The feasiblity of measuring dopamine release in human brain by displacement of radioligands has already been mentioned and requires exploration.

Other brain regions important in addiction are the globus pallidus and the amygdala (both of which receive projections from the nucleus accumbens), and the monoaminergic nuclei of locus coeruleus and raphe.[19] Significant changes in transmitter function in these regions have been found with opioids and stimulants in

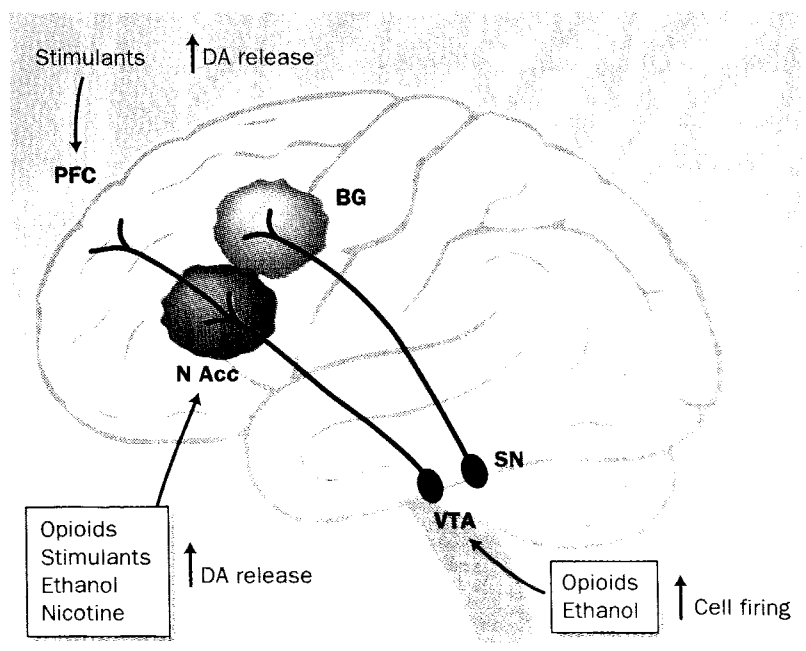

Figure 5: **Brain circuits of addiction**

rodents. The pathways have been mapped with markers for altered metabolism (deoxyglucose) and expression of gene products after neuronal activation (eg, cFOS, cJUN). Although many of these brain areas are small in human beings, it is possible to detect alterations in brain metabolism by measuring changes in regional blood flow in some areas (eg, frontal cortex) using PET (^{15}O-water or ^{18}F-deoxyglucose) or SPECT (^{99m}Tc HMPAO). These procedures can also be applied to explore the brain regions that are activated or shut off during other drug-related states such as craving and withdrawal. New techniques of image analysis (correlation and spectral analysis) and improved PET camera technology should allow regions such as the nucleus accumbens, and even brainstem structures such as the VTA and the locus coeruleus, to be imaged in future.

Conclusions

Major advances in the science of addiction have been made in the past two decades. We now have a good understanding of the molecular pharmacology of most drugs of misuse, the only exception being inhaled solvents. The neurobiology of addiction in animals is becoming clearer with the use of new techniques such as drug self-administration. The growth of neuroimaging techniques offers the exciting possibility that the hypotheses developed from the preclinical studies could, and hopefully will, be tested in human beings.

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