

# EUROBRAIN

## *Addiction*

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Drug addiction is an increasing problem in our affluent societies and carries great social and economic costs through its impact on crime and health. Our policy for the past fifty years has been to treat addicts as criminals and to punish them, but this has manifestly failed to prevent the increase in drug abuse. Nor have campaigns to educate people about the dangers of drugs, tobacco and alcohol had anything other than relatively minor effect. From the neuroscientist's point of view addiction is increasingly seen as an organic disorder of brain function; if this could be better understood we might hope to be able to offer more effective treatments to addicts.

The definition of "addiction" has changed in recent years. The term was previously applied only to such "hard" drugs as

heroin, where there are obvious signs of tolerance and physical dependence in regular users and a painful or even life-threatening physical withdrawal syndrome when drug use is stopped. Psychiatrists now use the term "substance dependence" to include both psychological dependence (where there may be no obvious withdrawal syndrome or tolerance) and physical dependence. The cigarette smoker who cannot stop smoking or the cannabis smoker whose drug habit has come to dominate their life is no less addicted than the chronic heroin user, even though they may suffer only mild withdrawal signs when drug use is stopped.

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# *Brain mechanisms in addiction*

## **HOW DO DRUGS ACT IN THE BRAIN?**

Great progress has been made in understanding the mechanisms by which the various classes of addictive substances act in the brain. These include the “psychostimulants” – a large group of drugs encompassing cocaine and various amphetamines. These drugs all act in the brain to stimulate receptors that recognise the neurotransmitter dopamine. Cocaine works by blocking the inactivation of dopamine after its release from nerve terminals in the brain – a process that involves recapture of the released

chemical into the nerve endings. Blocking this process makes more dopamine available to stimulate brain receptors. The amphetamines work by displacing dopamine from nerve terminals. The “rave dance” drug ecstasy is an amphetamine derivative that combines psychostimulant (dopamine) properties with a mild hallucinogenic effect – thought to be due to stimulation of receptors for another brain chemical messenger – serotonin. The opiates (for example heroin), cannabis and nicotine all act on specific receptors that are present in the brain that recognise these different drugs. When the drug binds to the receptor it triggers activity in nerve cells. One might wonder why the brain should contain such receptors, since the drugs themselves are plant products that do not exist naturally in the brain. The answer is that in each case there are naturally occurring brain chemicals, which activate these receptors, and the drug molecules hijack these normal brain mechanisms. Precisely how alcohol works remains unclear, but it is increasingly thought to act by modifying the responsiveness of the brain to the principal “on” and “off” chemical signals (glutamic acid and GABA) thus lowering excitability.

## **THE PROBLEM OF RELAPSE**

In addition to chronic drug use altering the brain and changing an individual’s behaviour, environmental and behavioural factors may alter brain function and influence a drug’s effects. These environmental or conditioned cues, such as people, places, and things, that have been associated with the drug use, can become an integral part of the addiction process. Even in the absence of the drugs themselves, these cues can trigger tremendous drug craving. This craving, or the intense and overwhelming desire to use a drug, can drive an ex-addict into relapse even after years of successful abstinence.

Total abstinence for the rest of one’s life is a relatively rare outcome; having relapses is more the norm. Thus, addiction must be approached more like other chronic illnesses – diabetes, chronic hypertension – than like an acute illness, such as a bacterial infection or a broken bone. Recognising craving and relapse as an integral part of addiction has tremendous importance for developing treatment strategies. In particular, strategies must encompass mechanisms to enable the patient to deal with continued exposure to drug-related cues long after formal treatment is completed.

Alan Leshner, Ph.D.

## **THE ROLE OF THE “PLEASURE CIRCUIT”**

Knowing how these drugs act, however, does not explain why they are addictive. Furthermore, there seem to be a bewildering number of different brain mechanisms activated by the different classes of drugs. Consequently great excitement has been generated in recent years by the first glimmers of some common themes of

understanding in this area. One important series of research findings points to a common brain mechanism that is activated by all known drugs of addiction – namely the activation of dopamine mechanisms in a region of the forebrain known as the nucleus accumbens (see fig. 1). This is a small dopamine-rich brain region underlying the larger dopamine-rich movement control centres, the caudate nucleus and putamen. The nucleus accumbens is part of the limbic forebrain circuitry, known to be important in emotional behaviour and in pain and pleasure. By direct measurements of dopamine release from animal brain, using tiny probes inserted into the nucleus accumbens, it has been found that cocaine, amphetamines, alcohol, nicotine and cannabis all share the ability to cause increased levels of dopamine. When low doses of the drugs are used, the nucleus accumbens is the only brain region showing such increased levels of dopamine. Furthermore, rats in which the dopamine-containing nerve terminals in the nucleus accumbens are selectively destroyed (by means of the selective chemical neurotoxin 6-hydroxydopamine) no longer self-administer amphetamines or cocaine. Could it be that dopamine release in the nucleus accumbens is the common mechanism underlying the pleasurable actions of these drugs, and the drugs simply hijack a normal brain mechanism in which pleasurable or “reinforcing” stimuli assist the animal in learning to repeat the behaviour? Addiction can be viewed as an “aberrant form of learning” – the drugs recruit brain mechanisms that have a normal place in cognitive and

emotional behaviour and cause these to malfunction, so the addict “learns” to continue using the drug.

### THE PROCESS OF ADDICTION

Understanding the actions of addictive drugs on chemical messenger systems in

standing how repeated exposure to drugs may cause changes in the pattern of genes expressed in brain cells, leading in turn to changes in the proteins which they make, thus causing long term changes in neural function. Although progress has been made in identifying changes in the

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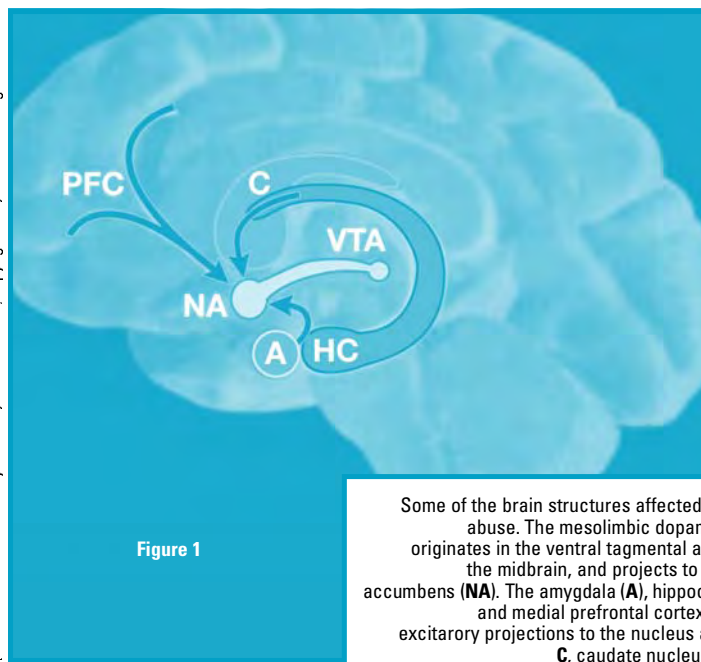


Figure 1

Some of the brain structures affected by drugs of abuse. The mesolimbic dopamine system originates in the ventral tegmental area (VTA) of the midbrain, and projects to the nucleus accumbens (NA). The amygdala (A), hippocampus (HC) and medial prefrontal cortex (PFC) send excitatory projections to the nucleus accumbens. C, caudate nucleus (striatum).

the brain certainly helps to provide a unifying theme, but it still fails to explain the process of addiction – which by its nature must represent a slow adaptation of normal brain mechanisms. Consequently much attention is now focused on under-

expression of certain genes, notably those or the “CREB” family of transcription factors there is as yet no common theme that links together such actions for the various different classes of addictive drugs.

Other links between addictive drugs with apparently quite different mechanisms of action have been found, however. For example, like the other drugs of addiction cannabis can activate dopamine release in the nucleus accumbens, but it does so apparently by indirect brain pathways that involve activation of an opiate mechanism. The ability of cannabis to cause dopamine release is prevented if animals are treated with the drug naloxone, which selectively blocks brain receptors for opiates. Animals that have been treated repeatedly with large doses of cannabis also show some physical signs of withdrawal when challenged with naloxone. Chronic alcoholics have also been successfully treated with another opiate receptor antagonist drug naltrexone to help them from relapsing – suggesting that alcohol too may activate opiate mechanisms in the brain.

#### **FUTURE DIRECTIONS FOR TREATMENT**

Despite the importance of this area of research for improving future treatment strategies there is lamentably little effort or resource devoted to it at the moment. In thinking of treatments that might help to wean addicts from their drug habit we need to think of different goals, aiming to reduce craving for the drug, assisting in overcoming the withdrawal signs both psychological and physical, and helping the reformed addict from relapsing. We are not very close to achieving any of these at the moment. The most effective strategy we have currently is to treat addicts with a safer form of the drug itself – the heroin addict with methadone, the

#### **WHAT THE RESEARCH SHOWS**

We now know more about abused drugs and the brain than is known about almost any other aspect of brain function. This is due to dramatic advances in the past two decades in both the neurosciences and the behavioural sciences. For example, scientists have identified molecules in the brain associated with every major drug of abuse. They have identified the cellular sites – called receptors – where drugs such as cocaine, marijuana, and opiates bind to the brain. In the case of cocaine, they have recognised the dopamine reuptake transporter in specific nerve cells as one major site of cocaine's action.

Researchers have discovered not only specific brain circuits involved in drug experiences, such as euphoria, but the processes of addiction occurs as a result of the prolonged effects of abusable drugs on the brain – and that addiction actually results in a changed brain.

We have also done a lot over the years to dispel the myths about addiction (though we still have a lengthy journey ahead). Contrary to popular belief, research shows that addiction is not just a lot of drug use. It is actually a different state of being, a state where one's mind is overtaken by drugs. It is literally a disease of the brain. Once a person becomes addicted, the sole focus in life becomes seeking and using drugs. A person addicted no longer cares about any consequences that may result from taking drugs.

This is very different from a person who is a drug abuser. A drug abuser can choose whether or not to use a drug. This is why we often say drug abuse is a voluntary activity, but drug addiction is a disease characterised by compulsive, often uncontrollable drug seeking and use, even in the face of appalling negative consequences.

We also know why people take drugs. They take drugs for a variety of reasons: to modify their mood, their perception, their emotional state, or to self-medicate in an effort to cope with their problems. Basically people take drugs because drugs make them feel better immediately – which happens because drugs change brain function. Thus, we often say people like drugs because they like what they do to their brains.

**Alan Leshner, Ph.D.**

cigarette smoker with nicotine patches or gum. We must learn approaches that are both more sophisticated and more effective if we are to make any real impact on the problem.

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Michel Le Moal,  
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# *Individual vulnerability to addiction*



According to Michel Le Moal, Professor of Experimental Psychopathology at the University of Bordeaux 2, France, the problems raised by addiction in the West have been considered too exclusively from a classical epidemiological point of view, i. e. the eradication of the agents responsible. In this “drug-centred” approach, the central theme of the “anti-drugs war” is to limit the availability of illegal substances in the belief that this will result in fewer addicts. Police training and educational campaigns continue to absorb considerable resources. Despite this, at the turn of the century, drug addiction is as insidious as ever. For their part, physicians, psychiatrists and social workers are faced with a very different logic. They see that, although the number of people using drugs in a recreational or social context is high, very few move on to more serious abuse of harmful substances and only a small percentage become dependent, i. e. addicts. Why

some succumb and others do not is a fundamental biomedical question which leads to another approach, the “individual-centered” approach, as emphasised by Le Moal. Understanding why certain people are biologically vulnerable to drugs is more of a medical problem. “These two philosophies must be combined”, says Le Moal, “but institutions that take into account the reasons for these differences, whether inherent or acquired, are still few and far between.”

The greatly increased understanding, over the past decade, of drug action on specific chemical messengers in the brain, neurotransmitter systems at the cellular and molecular levels, and especially long-term neuroadaptive changes has to be placed in this context. According to Prof. Le Moal, it cannot be denied that certain individuals have a “specific brain state”, and this medical vulnerability deserves further investigation with a view to discovering reliable predictive biological pa-

rameters that result in certain individuals becoming dependent. Such an approach is fundamental to modern medicine and psychiatry.

Over the past fifteen years, Prof. Le Moal and his group, including P. V. Piazza, have developed working hypotheses and animal models to investigate the pathophysiological chain of events leading to this differential vulnerability.

They have demonstrated that stress and stress hormones, mainly adrenal glucocorticoids, act on brain dopamine neurons (the central common pathway on which all drugs act) and modify them, making them more sensitive to drugs. Put another way, these individuals have dysregulation of stress mechanisms as a result of life events (even prenatal) or inherent predispositions; they also show long-lasting dopamine changes in specific regions specialised in reward integration. Interestingly, Le Moal’s group has clearly shown that, however much drug is available,



Michel Le Moal

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“resistant” animals are less prone to self-administer the drugs than vulnerable ones. The animals also differ in terms of the dopamine system and in their response to stress.

#### ADAPTIVE PROCESSES AND ADDICTION

In recent theoretical papers published together with G. F. Koob, San Diego (Koob, G. F. & Le Moal, M., *Science*, 278, p. 52-58, 1997), Prof. Le Moal stresses the fact that the biological basis of dependence, while of considerable interest, is only one part of the complex process of human addiction. Animal models cannot explain all aspects of the problem. For scientists like Le Moal, how the brain regulates the way we seek pleasure and reward in normal circumstances provides clues to the alterations in these mechanisms that result in a biological downward spiral towards drug dependence.

The neuronal structures that regulate reward and punishment, the “reward

system”, are influenced by education and social environment. The role of training is to enlarge and increase the number of connections. “We are taught how to control our behaviour and inhibit our natural propensity for pleasure in early life”, says Le Moal, “at a time when the plasticity of our neuronal systems is optimal. Lack of such control is at the centre of the medical definition of addiction and dependence.” If we believe, as does Pr. Le Moal, that a biological relationship exists between environment, training, education, psychology and brain structure and function, it will be important to invest in research in these areas in order to clarify the neurobiological meaning of the terms “inhibition”, “control of our behaviour” and “loss of control”.

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