AMPHETAMINE AND COCAINE – MECHANISMS AND HAZARDS

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Stimulant drugs, such as cocaine and amphetamine, interact directly with dopamine systems in the brain (as well as with noradrenaline and serotonin neurons), and there is widespread agreement that large increases in dopamine in the nucleus accumbens underlie the reinforcing, as well as psychomotor stimulant effects of these drugs. There is also evidence that some of the effects of cocaine and amphetamine show sensitization on repeated drug use, that is, the behavioural response to these drugs increases with drug exposure and this may contribute to the development of addiction. Although there is no physical withdrawal syndrome associated with abstinence from stimulants, there is a 'psychological' withdrawal syndrome that is characterised by dysphoria or anhedonia – depression-like symptoms. Another prevalent view of stimulant addiction is that it is driven by attempts to alleviate the unpleasant effects of withdrawal.

Of special importance is the clinical and experimental observation that otherwise neutral environmental stimuli can become associated with the effects of self-administered cocaine or amphetamine through Pavlovian conditioning. Just as Pavlov demonstrated that a bell associated with food could subsequently, when presented alone, elicit salivation, so cocaine-associated stimuli can have powerful motivational effects. Thus, these stimuli can elicit strong drug cravings, support drug-seeking behaviour and precipitate relapse into a drug-taking habit even in long-abstinent individuals. The behavioural effects of cocaine-associated cues have also been replicated in animal models of addiction, and there are significant similarities between rats and humans in terms of the neural mechanisms that underlie the aberrant learning which contributes to the persistence of addictive behaviour. Reducing the impact of drug cues on craving and relapse is a major novel target of treatments for addiction, and potential pharmacological leads arising from our own experimental work are undergoing clinical evaluation.

Finally, there is some evidence that chronic abuse of cocaine and other drugs, including alcohol, leads to long-term changes in brain function, especially to a decreased activity of the prefrontal cortex. This decreased activity may also contribute to the persistence of addictive habits. Thus, reduced functioning of the prefrontal lobes can disrupt higher brain functions, such as the inhibitory processes that normally hold potentially maladaptive behaviour in check. Some of the behavioural and cognitive characteristics of drug-abusers – including impulsivity, risk-taking and apparently poor decision-making abilities – resemble effects of damage to the frontal lobes. We have shown that chronic amphetamine-abusers show deficits in their decision-making abilities that closely resemble those seen in subjects with orbital frontal lobe lesions. Therefore, chronic abuse of cocaine, amphetamine and perhaps other addictive drugs may impair brain function in a way that contributes to the persistence of addictive behaviour.

SUMMARY

- Cocaine and amphetamine predominantly block re-uptake of dopamine in the nucleus accumbens, hence more dopamine is available in the synaptic cleft .

- Environmental stimuli become associated with the effects of self-administered cocaine or amphetamine through Pavlovian conditioning. These environmental stimuli subsequently elicit craving, drug-seeking and relapse. Treatment may be able to target drug cravings by reducing these secondary cue motivations.

- Aberrant learning contributes to the persistence and gravity of addictive behaviour, and may be a significant cause of relapse in addicts.

- Addicts show impairment of executive functions, for example: impulsivity, poor decision-making, decreased capacity to inhibit inappropriate behaviour and thus reduced self-control.

- Adaptive consequences of chronic drug usage may reduce the decision-making abilities of users by inducing changes in the prefrontal cortex, which are likely to impact on cognitive processes. On a behavioural level, these changes can cause the persistence of maladaptive drug-taking.

- Alternatively, addicts may begin to abuse drugs in the first place due to their pre-existing poor decision-making abilities, which could result from damage to the prefrontal cortex. In other words, damage to the prefrontal cortex may predispose individuals to addiction.

- Novel treatments may be able to act prophylactically to prevent drug cues eliciting relapse and drug-seeking behaviour.

CONCLUSION

- More research is needed into the neurophysiological changes which accompany addiction, in order to provide a greater understanding of addictive behaviour and the predisposition to it.

- Pharmacological and behavioural approaches need to be developed that aid the extinction of reinforcing cues.

QUESTIONS AND ANSWERS

How can we relate scientific findings to more socially-orientated studies?

We may be able to identify mechanisms of drug-taking persistence, and on the basis of these develop treatments. If the underlying mechanisms can be identified, suitable interventions can more readily be developed. People will always experiment with drugs, and we need to understand the mechanisms that can turn use into abuse, and that may finally lead to addiction. It is also important to remember that some abusers die, so any findings with potential applications must be investigated, as they could potentially save lives.

Are certain people more vulnerable to addiction and can they be identified?

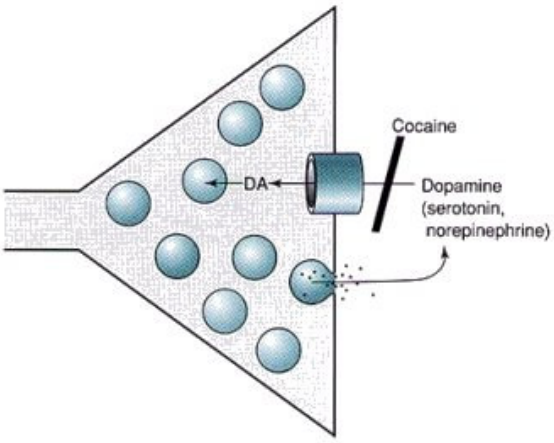
There is no single picture of an addictive individual. There are many people who use cocaine for years without becoming addicted. Some people become addicted and some do not. The finding of low density of dopamine receptors in drug-users could be interpreted as these people having *congenitally* low levels of dopamine receptors, which tends to make them seek a way to self-medicate by taking drugs. Primate studies show subordinate animals have low levels of dopamine receptors, and this predicts their drug-taking behaviour. This is an area that we need to explore in much greater detail.

What are the effects of stopping drug use?

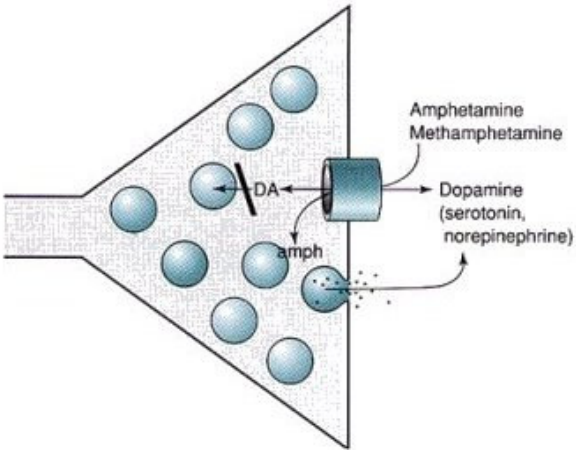
After stopping drug use, there is a reduced availability of dopamine receptors in the striatum and decreased dopamine in the nucleus accumbens, leading to symptoms similar to depression. Studies on glucose metabolism, (which is an indirect way of looking at brain activity) show that 100 days after stopping chronic cocaine use, frontal cortex activity is still reduced, executive functions are impaired and there is a reduced ability to control bad habits. Tests of cognitive functions in amphetamine users have shown poor results. Damage to the pre-frontal cortex can predispose animals to take drugs.

Why are treatments for dependence so ineffective?

Pharmacological treatments have tended not to be developed because there has been some stigma attached to treating addicts. Additionally such drugs may not be considered economically viable by pharmaceutical companies. Methadone and nicotine patches are drug substitutes, keeping addicts off more harmful drugs during a slow withdrawal process. Pharmaceutical companies are only just beginning to be interested in drugs that act as abstinence aids rather than as substitutes. Many treatments have serious side-effects. Treatment and harm reduction must be used conjointly.



(A) Cocaine inhibits dopamine re-uptake (also re-uptake of noradrenaline and serotonin)



(B) Amphetamine enhances dopamine release (also release of noradrenaline and serotonin)

Conditioning and Psychomotor Stimulant Addiction

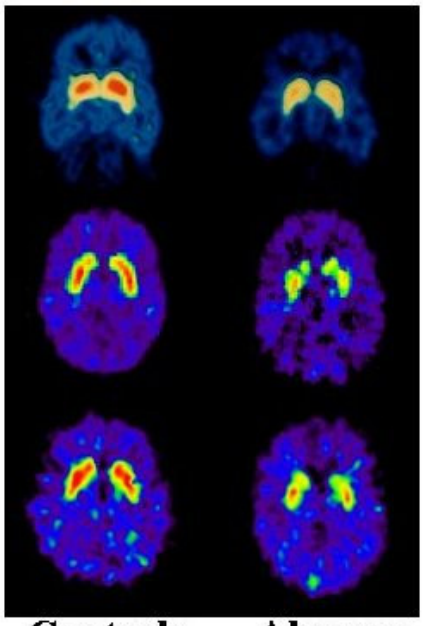
Environmental stimuli become associated with the effects of cocaine and amphetamine through Pavlovian conditioning

Dopamine D2 Receptors are persistently decreased in the brains of addicts

COCAINE

METH

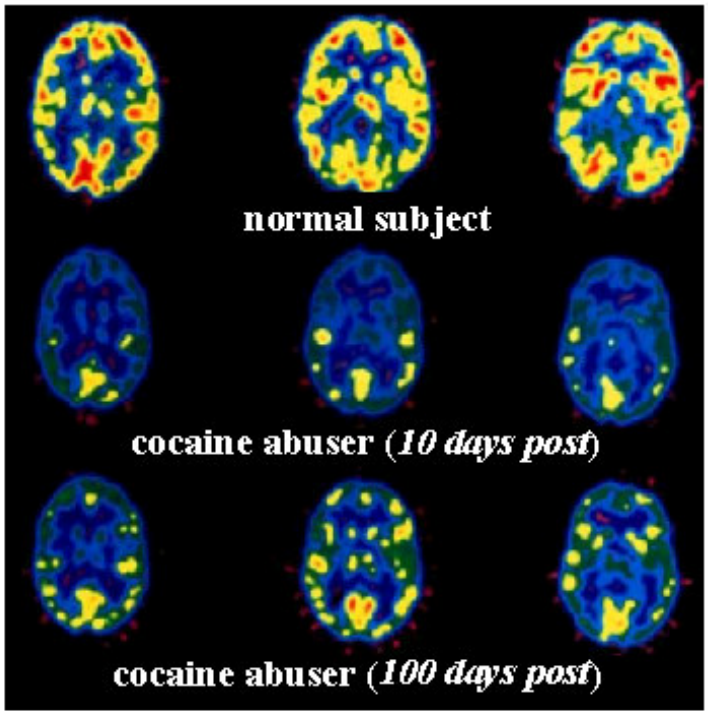
ALCOHOL

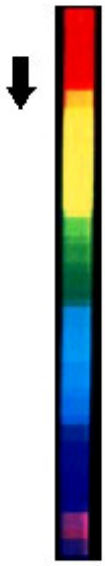


Controls Abusers

Volkow et al., 1999

Cocaine Abuse and Brain Glucose Metabolism





Volkow et al., 1998