Loosening addiction's deadly grip

Recent research paints a picture of addiction as a progressive, chronic neurological disease that wreaks havoc with brain chemistry

What started as a curious observation led to an intriguing discovery. M. Leann Dodd, a psychiatrist at the Mayo Clinic (Rochester, MN, USA), found several cases of unusual side effects in a handful of Parkinson's patients treated with pramipexole (Mirapex®; Boehringer Ingelheim, Ingelheim am Rhein, Germany). Eleven patients with no previous history of gambling developed dramatic, sudden-onset compulsive gambling habits, and suffered catastrophic loss of family and finances (Dodd *et al*, 2005). Patients who reduced their drug dosage found that their desire to gamble subsided, whereas those who stopped taking pramipexole saw their desire to gamble disappear overnight.

"Since the article was published, I've literally been flooded with hundreds of emails from patients taking Mirapex for Parkinson's, or at a much lower dose for restless-leg syndrome," said Dodd. "They came forward to say that they had also suddenly developed problems with uncontrollable gambling, overeating, or hypersexuality." What the patients had in common was that none had these addictive traits before using pramipexole—an agonist for the D3 dopamine receptor subtype.

According to Nora Volkow, Director of the US National Institute on Drug Abuse (NIDA; Rockville, MD, USA), it is not surprising that a dopamine agonist could loosen inhibitions against gambling, eating and sex. "We know that stimulants such as cocaine and methamphetamine, which directly increase dopamine levels in the brain, and even more specific dopamine D3 receptor agonists like Mirapex, can have these effects," she said. Although these side effects occur in only a small fraction of patients, they can be devastating. "It is crucial to determine who is most vulnerable to the addictive effects of excess dopamine," Dodd said.

The report of these side effects, widely covered by the US media, points to a central issue in addiction research: who is most at risk and why? And once susceptibility is identified in individuals, how can risk be mediated or managed? In the case of Mirapex and gambling, Dodd's next step will be to determine whether her patients share a common polymorphism of the D3 receptor gene that might explain their particular vulnerability. Such genetic studies, along with live brain imaging, the development of rodent models and research with large animals, are shedding new light on the neurobiology of addiction, and pointing to new targets for intervention.

Addiction is a widespread social and public health problem. In 2004, 22.5% of Americans over the age of 12 were substance dependent or substance abusers—9.4% of the population, according to the US Department of Health and Human Services' Substance Abuse and Mental Health Services Administration (www.samhsa.gov). Of that subset of the population, 3.4 million were dependent on or abused both alcohol and illicit drugs, and 15.2 million were addicted to alcohol alone. At the same time, 70.3 million Americans were smokers—nearly 30% of those older than 12 years. According to a report issued in July 2005 by the National Center on Addiction and Substance Abuse (CASA) at Columbia University (New York, NY, USA), the number of Americans who abuse controlled prescription drugs—opioids, depressants and stimulants—has almost doubled from 7.8 million to 15.1 million between 1992 and 2003 (CASA, 2005).

Long considered the result of a lack of willpower, addiction is now understood to be a chronic, progressive and relapsing brain disease. Repeated administration of drugs—including alcohol and nicotine—in vulnerable individuals wreaks havoc with brain chemistry and structure, so on a brain scan one can clearly distinguish an addict's brain from a non-abuser's brain. Addiction can also extend to compulsive behaviours such as kleptomania and overeating, which are accompanied by similar changes in the brain. At the cellular level, synapse structure, cell shape and the way nerve cells communicate with each other also change regardless of the substance being abused (Kalivas & Volkow, 2005), although each drug has its own devastating effects—alcohol, cocaine and amphetamines, for instance, kill cells outright in certain areas of the brain.

Chronic substance abuse hijacks the normal dopamine reward and stress pathways, thus flooding the brain with far more dopamine than is secreted normally. Eventually, the drug crowds out all other pleasures and becomes the object of compulsive desire. Obtaining the drug compromises all other life activities, and even derails free will. Scientists now understand why: some drugs commandeer the brain circuits involved in motivation and control in the prefrontal cortex, where judgement and inhibition are controlled. This process occurs gradually over time, and may be compared with the activation of a dimmer switch, rather than turning a light switch on. As the first step of the Alcoholics

Anonymous credo states, the addict becomes truly 'powerless' against alcohol or any other addictive substance.

As addiction develops, the chronic flooding of dopamine eventually results in the depletion and deregulation of dopamine and other neurotransmitters involved in stress and reward. Consequently, by the time an addiction is established, the drug brings little pleasure and only helps the user to feel temporarily 'normal'. Addiction researcher George Koob of the Scripps Research Institute (La Jolla, CA, USA) refers to the eventual disruption in the brain's reward and reinforcement system as 'allostasis'—a persistent alteration in the set point of reward, which results in a 'new normal' state—as opposed to homeostasis of the non-addicted brain (Koob & Le Moal, 2001). The addicted brain maintains allostasis by continued overactivity in brain stress circuits and compulsive drug-seeking behaviour, according to Koob.

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Although dopamine is key to the early stages of addiction, recent research indicates that glutamate, a main excitatory neurotransmitter, is crucial to the development of end-stage addiction (McFarland *et al*, 2003; Holden, 2003). GABA (γ-aminobutyric acid), a principal inhibitory neurotransmitter, also has an important role, according to Frank Vocci, Director of NIDA's Division of Pharmacotherapies and Medical Consequences of Drug Abuse. Other neurotransmitters—including corticoreleasing factor (CRF) and neuropeptide Y (NPY), certain signalling molecules, hormones, endocannabinoids, endogenous opioids and their receptors, and transcription factors such as cAMP-responsive element binding protein (CREB)—may also be involved in the descent to addiction.

But dopamine, long known as the 'pleasure' or 'reward' chemical, is still the main factor in the early steps of addiction development. As well as controlling movement, dopamine is released in the brain in response to, and in anticipation of, reward—be it sex, food, drugs or a shopping binge. The release is especially powerful

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when the outcome is uncertain or unexpected. According to the newer, 'salience' model of addiction developed over the past 15 years (Robinson & Berridge, 1993), dopamine is released not only when we anticipate or receive a reward, but also when we come across salient information or situations that require us to pay attention in order to survive—food, sex or danger.

Using live imaging, researchers discovered that brain cells experience a significant loss of dopamine D2 receptors as a result of chronic drug use (Volkow *et al*, 2001). "In human non-abusers, we see significantly higher levels of D2 receptors in the striated areas of the brain as compared to abusers. Users with the lowest density of D2 receptors in the ventral striatum experience more drug craving, are more responsive to drug cues, and more prone to relapse than those with more D2 receptors," said Volkow. Experiments with primates showed that animals with more D2 receptors are protected against addiction (Nader & Czoty, 2005); however, "if they are exposed to cocaine, the number of receptors drop as they begin to self-administer the drug," Volkow added.

This finding provides clues as to why some people may be more vulnerable to becoming hooked on drugs. Scientists measured the number of D2 receptors in normal individuals (non-abusers) and then gave them methylphenidate, a stimulant used to treat attention deficit hyperactivity disorder (ADHD; Volkow & Swanson, 2003). Those with more D2 receptors reported that they found the drug's effects unpleasant, whereas those with fewer receptors found it pleasurable. Participants with more receptors, and hence higher levels of endogenous dopamine, were less likely to experience the drug rush as enjoyable.

In another study focusing on D2 receptor density and alcohol consumption, Peter Thanos of Brookhaven National Laboratory (Upton, NY, USA) compared normal rats with rats bred to prefer alcohol (P), and increased the number of D2 receptors in both groups (Thanos *et al*, 2004). P rats, with additional D2 receptors, decreased their alcohol intake by 37% and cut their total alcohol consumption by half. Normal rats also reduced their drinking preference and intake, but not as dramatically. "These findings further support our hypothesis that high levels of [D2] are causally associated with a reduction in alcohol consumption and may serve as a protective factor against alcoholism," the authors wrote. Interestingly, similar results have been reported for obese patients: they had fewer dopamine receptors than those with normal weight (Wang *et al*, 2001). Animal studies showed that exercise not only elevates dopamine levels and mood, but also increases the number of D2 receptors (Hattori *et al*, 1994; Wilson & Marsden, 1995).

Other research points to the role of anxiety in alcohol abuse. Subhash Pandey, Associate Professor and Director of Neuroscience Alcoholism Research at the University of Illinois (Chicago, IL, USA), found that P rats displayed more anxiety-related behaviour and drank more alcohol than normally bred rats, and that their levels of CREB and NPY were lower in the amygdala, the brain region that is central to reward, reinforcement and motivation (Pandey *et al*, 2005). Alcohol intake reduced anxiety-like behaviour in P rats, an effect associated with increased CREB function and NPY production; administering a drug that promoted CREB function and NPY production in the central amygdala reduced anxiety and alcohol intake in these rats. "Turning off CREB function in normal rats made them look like P rats—more anxious and more likely to drink," said Pandey. These results implicate the CREB pathway in the genetic predisposition to high anxiety and alcohol consumption of P rats, according to Pandey.

Genetics also affects novelty-seeking behaviour: several studies reveal polymorphisms in humans and animals that correlate with novelty-seeking and risk-taking behaviour. Recent studies have found a strong association between smoking and novelty-seeking and polymorphisms of the serotonin transporter gene and the D4 dopamine receptor gene (Kremer *et al*, 2005; Kotler *et al*, 1997). Vulnerability to addiction

> Social order is a powerful factor in who decides to take the first drink or drug and who continues to partake

may therefore have two stages: the desire for new experiences when first taking a drug and a subsequent accumulation of neural adaptations to repeated drug-taking that moves the user down the road to addiction, Volkow hypothesized. Adolescents, whose brains are still developing and who normally seek out new experiences as a part of their developmental process, may therefore be at particular risk for substance abuse.

> …like other chronic, relapsing diseases, addiction must be treated on a long-term basis, with the realistic goal of increasing the length of time between relapse

However, genetics alone cannot completely explain vulnerability to addiction. "After all, many people with naturally low [D2] levels do not become addicts, and some who have protective genetic factors do go on to become addicted," Volkow observed. Environmental and social influences have significant roles in the impetus to try drugs and in relapse. Social order is a powerful factor in who decides to take the first drink or drug and who continues to partake. In one study, researchers used positron emission tomography to scan the brains of rhesus monkeys living in individual quarters, then put them into communal housing and repeated the scans (Morgan *et al*, 2002). "Whereas the monkeys did not differ during individual housing, social housing increased the amount or availability of dopamine D2 receptors in dominant monkeys and produced no change in subordinate monkeys," the study reported. Subordinate monkeys self-administered cocaine more often than dominant ones.

Developing drugs to treat addiction was, until a few years ago, a low priority for large pharmaceutical companies and was pursued mostly by a handful of smaller biotech companies. But industry is now getting involved, partly because it has realized that a large market exists for effective treatments, and partly because addiction is less stigmatized and considered more as a disease, commented Volkow and Vocci. The overlap between addiction and other psychiatric disorders, and the economics of using one drug for multiple indications, are also motivating companies to develop addiction treatments. Aripiprazole (Abilify®; Bristol-Myers Squibb, New York, NY, USA), a dopamine stabilizer approved for schizophrenia and bipolar disorder, is now being tested in cocaine users, and modafinil (Provigil®; Cephalon, Frazer, PA, USA), approved for narcolepsy, is in trials for cocaine addiction and ADHD.

In 1989, NIDA's Medication Development Program (MDP) started developing medications for opiate and cocaine dependence and more recently widened its focus to include methamphetamine and marijuana dependence. There are 21 medications now in development by 11 companies, 18 of which are sponsored by NIDA. In a 'top–down' approach, the MDP tests existing medications for treatment of cocaine and alcohol addiction. "Overlapping pathways and potential common mechanisms of addiction are of great interest to us," said Vocci. So far, naltrexone, originally developed to treat opiate addiction, also appears to be effective in treating alcoholism (O'Brien, 2005). MDP also pursues rational drug discovery based on neuroscience findings. For example, it is testing a glutamate antagonist, talampanel (Ivax Corporation, Miami, FL, USA), as a potential anti-relapse medication for cocaine addiction in phase II trials; the compound was initially developed to treat epilepsy and Parkinson's-associated dyskinesia.

But, like other chronic, relapsing diseases, addiction must be treated on a long-term basis, with the realistic goal of increasing the length of time between relapses. With preliminary evidence that abstinence, and certain compounds, can restore normal brain activity in addicts, and imaging studies showing that cognitive behavioural therapy may have similar effects in certain psychiatric conditions, many experts believe that a combination of psychosocial support and pharmaceutical treatment may have the best chance of helping people shake off the deadly grip of addiction.

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doi:10.1038/sj.embor.7400635