nature neuroscience

Neurobiology of addiction

The pleasant sensation of sipping a drink after a hard day's work is familiar to many people, but for some, recreational use easily slips into dependence and tolerance. Some users then progress to addiction. Even in the face of harmful consequences to self and others, addicts cannot resist the urge to engage in the addictive activity. Moreover, if they do stop taking drugs, even after years of abstinence, addicts may relapse into drug use under stress or when faced with otherwise benign cues that remind them of the addicting drug.

Drug use and addiction are pervasive. The 2005 World Drug Report from the United Nations estimates that 200 million people, or 5% of the global population, consumed illicit drugs at least once in the last 12 months. The US Department of Health estimates that in 2004, 22.5 million Americans aged 12 or older (9.4% of the population) experienced substance dependence or abuse. During this period, about 21.1 million people needed but did not get treatment for their addiction in the US alone.

Although drug abuse cuts across all societal strata and age groups, the young and poor are affected most. Addiction has very high overall health costs, once related factors such as heart disease, cancer and accidents are considered. The National Institute on Drug Abuse estimated the cost of drug and alcohol abuse at about $246 billion in 1992 (without considering nicotine addiction). This figure includes health consequences from drug abuse and their effects on the health care system, criminal behavior, negligent driving, job loss and the effects of impaired productivity on these individuals and their employers.

The progression from initial drug use to addiction is influenced by the drug, the user's personality, peer influences and environmental stressors. These complex interactions determine why some individuals are more easily addicted than others. In this focus, we highlight the biology of the most commonly abused substances, explore the genetics of predisposition to addiction, and examine the components of addictive behavior itself.

Drug addiction can clearly vary with the drug. Cocaine, marijuana, LSD or amphetamine can create psychological dependence, in which the individual feels satisfaction and euphoria and is driven by a need to repeat the experience. Heroin or alcohol can produce physical dependence. Drugs also act on specific receptors and brain areas. Given this complexity, can addiction be treated as a unitary disorder? Are there common brain targets for all addictive substances that could be exploited to provide a 'magic bullet' for addiction treatment? A perspective by Eric Nestler addresses this issue.

Exposure to drugs causes plasticity in neural circuits related to reward and motivation, supporting the idea that addiction is a biological disorder. Plasticity (of synapses and circuits) results from drug use and drug abuse. How do we make sense of the multitude of observations in so many different areas under different circumstances? What animal models are likely to have the most validity for studying addiction, and what specific changes should we examine? In three separate commentaries, George Koob and Michel LeMoal, Peter Kalivas, and Yavin Shaham and Bruce Hope discuss which changes are likely to be critical to addiction.

Taking drugs may begin as a voluntary choice to seek a pleasant stimulus, but for addicts, that choice is no longer volitional, even in the face of terrible personal consequences. Barry Everitt and Trevor Robbins review the cortical and subcortical circuits that mediate reinforcing effects of drugs, presenting a framework for how occasional behaviors become habits and then compulsions through pavlovian and instrumental learning. Antoine Bechara proposes that volitional decisions involve a balance between neural systems signaling the immediate and delayed consequences of actions. He discusses how drugs may tip this balance, leading to an inability to weigh future consequences and the urge to make impulsive decisions.

What makes certain individuals more vulnerable to drug use and abuse? Mary Jeanne Kreek and colleagues discuss the genetic influences on complex personality traits such as impulsivity, risk taking and stress responsiveness, and their relationship to addiction vulnerability. They also discuss the difficulty in teasing out genetic vulnerability factors, in light of the strong comorbidity between addiction and other mental disorders.

Alcohol and nicotine are legal drugs that are prone to abuse. Nicotine is one of the most widely abused substances, and tobacco addiction kills more than 430,000 Americans each year. John Dani and Adron Harris review progress in understanding nicotine addiction and its comorbidity with alcoholism. John Crabbe and David Lovinger discuss the neurobiology of alcohol abuse and genetic influences that may predispose animals (and humans) to alcoholism.

Despite the enormous social and economic cost of addiction, long-term treatments are few and far between. Only a handful of pharmaceutical therapies exist. In a commentary, Charles Dackis and Charles O'Brien discuss social issues that may be hampering development and access to treatment, pointing out that loss of control, the hallmark of addiction, is the source of its societal stigma. A naive public is likely to conceptualize addiction as a character flaw rather than a *bona fide* brain disorder. Dackis and O'Brien argue that to effectively develop treatments for addiction, we must change this perception.

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