Review

Drug addiction: a general review of new concepts and future challenges

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SUMMARY Relevant papers published in peer reviewed journals in the past 2 decades were identified and screened to abstract pertinent information. Substance dependence/addiction, involving both a common brain reward mechanism and longer-lasting molecular and cellular changes, is a preventable chronic, relapsing brain disease and as such a public health problem. Physical and psychological dependence, characterized by withdrawal syndrome, are now given less weight compared with compulsive behaviour and uncontrolled use of drugs in the comprehension of addiction. The challenging components of drug addictions, including counteradaptation, sensitization, abstinence, craving and relapse need further neurobiological and non-neurobiological exploration and understanding, which may be possible through the use of advanced imaging and genetic techniques and animal models of drug addiction together with relevant human studies.

Introduction

Over the past 2 decades, dramatic advances in behavioural neuroscience have greatly enhanced our understanding of substance abuse and dependence. Recently, the following three-stage conceptualization of drug-taking behaviour applying to all psychoactive drugs has been proposed [*1*].

- Drug use: refers to the taking of drugs, in the narrow sense, to distinguish it from a more intensified pattern of abuse.
- Drug abuse: refers to any harmful use, regardless of whether the behaviour constitutes a disorder in DSM-IV of the American Psychiatric Association [*2*].
- Dependence: refers to substance dependence as defined by DSM-IV [*2*] or addiction as defined by ICD 10 [*3*].

Diagnostic criteria of substance dependence (Box 1) have also been further refined [*2*]. Although it is a challenging task to define drug addiction, Heather best defined it as repeated failures to refrain from drug use despite prior resolutions to do so [*4*]. He further characterized the behaviour and experience of the drug addict by three central features: conflict, ambivalence and decision-making. Based on these features, he proposed a three-level conceptual framework for explaining addiction, which consists of the level of neuroadaptation, the level of desire for drugs and the level of

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akrasia, or failure of resolve. However, Bigelow and associates view drug abuse as a learned operant behaviour that is reinforced by the positive effects produced by drugs of abuse [*5*]. Accordingly, they characterized drug abuse as involving attraction rather than compulsion [*5*]. Other researchers have expressed similar views, but with compulsion as an integral part of the phenomenon of addiction [*6*]. Tiffany and Carter characterized compulsive drug-taking as an automatized behaviour that tends to be stimulus-bound, stereotyped, effortless, difficult to control and regulated largely outside of awareness [*7*]. Koob and associates defined substance dependence as a compulsive behaviour and presented evidence through separate animal models that explained most of the diagnostic criteria for substance dependence [*8*]. Some researchers consider the concept of compulsive drug use no longer useful in the explanation of addiction [*4*]. Likewise, the physical and psychological dependence also may not matter, nor the physiological component [*2,4*]. Despite considerable drug abuse research, there is still no international consensus on the definition of substance abuse and dependence/addiction.

At the biological level, mesocorticolimbic dopamine is recognized as the underlying neurochemical substrate of compulsive drug use [*9*]. Moreover, researchers have identified and cloned the receptors and natural ligands of most substances of abuse. For example, researchers have identified and cloned a tetrahydrocannabinol (THC) receptor in the rat brain [*10*]. Phylogenetically, it is expected that the human brain may have similar THC receptors that are affected by cannabis use. Additionally, biochemical, cellular and molecular cascades within the cell that follow receptor activation by drugs of abuse have been partly revealed. Researchers have further revealed subtle damage to the developing brain as a result of fetal cocaine exposure [*11*] and frontal lobe injury as evidenced by decreased N-acetyl compounds and increased myoinositol [*12*].

Thus, based on these precepts, drug addiction can be defined as a chronic, relapsing brain disease. Broadly speaking, drug addiction also affects other body systems including the heart, lungs, liver and immune system, and therefore may be referred to as a multisystem disorder.

Box 1 DSM-IV diagnostic criteria for drug dependence [*2*]

A maladaptive pattern of substance use, leading to clinically significant impairment or distress as occurring at any time in the same 12-month period:

- Need for markedly increased amounts of substance to achieve intoxication or desired effect; or markedly diminished effect with continued use of the same amount of substance
- Characteristic withdrawal syndrome for substance occurs; or substance (or a closely related substance) is taken to relieve or avoid withdrawal symptoms.
- Persistent desire or one or more unsuccessful efforts to cut down or control substance use.
- Substance used in larger amounts or over a longer period than the person intended.
- Important social, occupational or recreational activities given up or reduced because of substance use.
- A great deal of time spent in activities necessary to obtain substance to use substance or recover from its effect.
- Continued substance use despite knowledge of having a persistent problem that is likely to be caused or exacerbated by substance use.

From an evolutionary perspective, the use of psychoactive drugs to induce positive emotions is inherently pathogenic because the drugs bypass adaptive information processing systems and act directly on brain mechanisms that control emotion and behaviour. This false signal of well-being overrides incentive mechanisms of "liking" and "wanting" and can result in continued use of drugs that no longer bring pleasure but instead produce different, negative, emotions, such as dysphoria, depression, irritability and anxiety [*2,13*]. Treatment of negative emotions by pschoactive drugs and psychosocial and behavioural therapies can impair useful defences, although their use is often safe and effective nonetheless. From this perspective, the neural mechanisms underlying positive and negative emotions and behaviour should be understood separately before making decisions about the therapeutic use of psychoactive drugs [*13*] and other methods including psychotropic medications.

Addiction as a chronic, relapsing brain disease

The conceptualization of addiction as a chronic, relapsing brain disease is the most important step towards understanding its different perspectives. Unfortunately, drug dependence is still viewed as a social problem, i.e. moral failure, which should be tackled by the criminal justice system [*14*]. However, concerned scientific experts now consider addiction as both a health and social problem. The integration of a medical component to the social dimension of drug abuse and addiction has revolutionized the management of patients with addiction. This sociomedical model highlights several important facets of drug addiction that require well defined epidemiological data, classification and diagnostic criteria (Box 1), biological and psychosocial etiologies [*15*] along with neurophysiological maladaptations, distinctive phenomenology, a profile of adverse effects on society and, finally, pharmacological, psychosocial and relapse prevention therapies supplemented by appropriate rehabilitation measures. Moreover, the previously identified information gap [*16*] should be eliminated with intensive dissemination of the latest knowledge to patients and the general public. Educating people about the neurological component of drug dependence would help to lessen the social stigma attached to patients with addictions and addictive disorders. Patients with substance dependence should no longer be isolated and stigmatized but should have easy access to appropriate treatment. This new concept of addiction/dependence would also aid in removing other obstacles (political, economic and cultural) in the application of scientific knowledge to the prevention, treatment and rehabilitation of addicted patients.

Patients with multiple addictions require comprehensive assessment and acute treatment in the form of detoxification by appropriate medications in proper settings followed by long-term maintenance treatment for preventing relapses. It has been reported that when maintenance treatment is discontinued, addiction, like other chronic illnesses, worsens [*17*]. In addition to drug therapy, psychosocial support services are also required to reduce the cost of overall management of addiction, as illustrated in heroin addicts on methadone maintenance therapy [*18*]. More often than not, these patients have co-morbid axis-I disorders [*19,20*] and axis-II personality disorders [*21*], which should be addressed appropriately while considering the overall management of such patients.

Drug dependence and the social perspective

Substance dependence cannot be understood without describing the social settings in which it develops. It adversely affects the physical, psychological and social health of both the individual and the general public. It is a disease of socially disadvantaged people, and stressful conditions are potential risk factors in the development of substance dependence and abuse. This has been amply illustrated by studies related to post-traumatic stress disorder and drug dependence identified among Vietnam War veterans, and survivors of earthquakes, car accidents, rape, kidnappings, hijackings and shootings. In addition to causing other health and social problems, substance dependence is an important vehicle in the spread of major infectious diseases such as acquired immunodeficiency syndrome (AIDS), hepatitis and tuberculosis. There is a large body of literature that strongly attests to the relationship between these diseases and substance abuse and dependence, in particular cocaine abuse. Drug addiction is also a major cause of homicides.

Addiction is a major public health problem; hence, its treatment should include basic public health approaches, such as health promotion and education through national and international campaigns, primary prevention, treatment, rehabilitation, relapse prevention and social services. It is evident that society and the relevant authorities are moving in right direction in order to achieve these goals. The legalization of substances of abuse, an extremely challenging task in some cultures, has both advantages and limitations. It has been reported that commercial access is associated with growth in the drug-using population [*22*].

Biological considerations

Drug dependence is viewed as a chronic brain disease because it is reported to produce changes in the dynamic functioning of the brain. It is now well known that the drug exposure episode activates specific structures, neurotransmitters and other related chemicals within the neurons and associated receptors [*23*]. It also leaves behind a memory trace that persists long after the drug has disappeared from the body. Such drug exposures are usually paired with environmental and social cues that through conditioning acquire the ability to activate the same or complementary brain circuits, even in the absence of drug exposure. Such long-term persistent effects have been studied directly from behavioural [*24*], structural and molecular perspectives [*25*], using a variety of advanced imaging techniques in human studies and animal models of drug addiction.

Furthermore, it has been revealed that the changes in brain metabolic activity and hormones, genetic expression, receptor density, and responsiveness to environmental cues differentiate the brains of addicted people from those of non-addicted individuals. In two recent studies, genotype associated with midbrain serotonin transporter binding sites and mRNA levels [*26*] and A9 allelic variations associated with dependence dopamine transporter protein [*27*] were linked to patients with chronic alcohol dependence and cocaine-induced paranoia respectively. Unlike in ethanol users, serotonin transporter binding in the dorsal raphe was found to be low in chronic cocaine users [*26*]. No such changes were reported in non-addicted control subjects. These findings have potential clinical implications in identifying individuals at risk of developing drug addiction. The functional and structural changes seen in the brains of addicted in-

dividuals are fundamental evidence of addiction as a chronic brain disease. Notably, in some individuals, there appears to be a metaphorical switch, the mechanism of which is unknown, which governs the initial voluntary drug-taking behaviour changing into an involuntary habit [*16*]. Each drug of abuse has some idiosyncratic effects on brain functions; however, the underlying mechanisms of drug addiction appear to be common to all drugs, as they induce more or less similar neuroadaptations in the brain.

Determining whether genetic factors influence addiction requires two steps: defining an appropriate phenotype with a neurobiological foundation [*28,29*] and identifying appropriate candidate genes. Recent studies have focused on alcohol withdrawal behaviour, the presence of which might identify a clinically relevant phenotype with genetic/neurobiological determinants [*30*]. However, not all alcohol-dependent patients develop withdrawal symptoms, and there may be different phenotypes as well as genotypes. In a study of cocaine abusers, no difference between patients was observed with regard to withdrawal [*31*], which could be due to the lower severity of cocaine withdrawal compared with alcohol withdrawal. However, alcohol withdrawal as a relevant phenotype is suggested by a recent study of the serotonin transporter in an alcohol-dependent population [*32*].

In related developments, genetic factors appear to determine cannabis use, abuse and dependence [*33*] as well as the behavioural response to ethanol in rodents. In addition, a few specific genes increasing and decreasing the action of cannabis have been identified. The behavioural effects of alcohol are mediated by N-methyl-D-aspartate (NMDA) and α-aminobutyric acid A (GABAA) receptor, which are phosphorylated and electrophysiologically modulated by tyrosine kinases. Mice lacking fyn (homozygous fyn-deficient), a non-receptor tyrosine kinase, were significantly more sensitive to the hypnotic effect of alcohol than control mice (heterozygous fyn-deficient) [*34*]. It was demonstrated that the administration of alcohol up-regulated tyrosine phosphorylation of the NMDA receptor (NMDAR) in the hippocampus of the control mice but not the homozygous fyn-deficient mice. Furthermore, an acute tolerance to ethanol inhibition of NMDAR-mediated excitatory postsynaptic potentials in hippocampal slices developed in control mice but not in the homozygous fyn-deficient mice. The findings indicated that fyn affects behavioural, biochemical and physiological responses to ethanol. The findings also supported the development of acute tolerance to ethanol mediated by enhanced tyrosine phosphorylation of NMDARε2, a tyrosine-phosphorylated protein band of molecular mass 180 kD in the postsynaptic density fraction. This acute tolerance could be eliminated when ethanol was applied together with ifenprodil, an agent considered to be a selective antagonist of NMDAR containing NMDARε2. In addition to using knockout mice, the genetic vulnerability of animals to alcohol and other drugs can be studied using transgenic mice and quantitative trait loci analysis. Although extrapolations from animal studies are fraught with difficulties, they provide important insights into the problems of drug addiction in humans.

A 1987 study supported the idea of the heritability of a novelty-seeking behavioural trait and its dopamine link, i.e. the D4 dopamine receptor gene (DRD4) in the ventral midbrain [35]. However, a recent study does not substantiate this concept [*36*], and the authors concluded that DRD4 did not appear to be a plausible candidate gene for novelty-seeking behaviour. How-

ever, the dopamine transporter system may be involved in conditions that predispose an individual to alcoholism and other disorders [*37*]. A recent study found that, rather than directly producing pleasure, dopamine released in the brain heightens significant stimuli that predict reward [*38*].

Platelet and postmortem brain studies have revealed that serotonin transporter functions are altered in patients who abuse alcohol. It has been suggested that brain serotonin transporter function is altered in chronic alcohol and cocaine abusers and may be related to a common serotonin promoter polymorphism [*26*]. The authors showed that serotonin transporter binding sites were regulated in a region- and substance-specific pattern, which was not simply a local response to functional blockade. It was also found that a reciprocal relationship appeared to exist between cocaine and ethanol effects in the dorsal raphe, which may have interesting clinical implications for dual-diagnosis patients. They concluded that the serotonin transporter promoter genotype may play a complex role in chronic ethanol dependence. In a study of nonhuman primates, increased availability of the serotonin transporter was significantly correlated with less intoxication upon initial exposure to alcohol and greater aggressiveness, two variables implicated in the pathogenesis of alcoholism [*39*].

In addition to serotonin, both dopamine and glutamate play a critical role in substance abuse and dependence. Glutamate neurons originate in the cerebral cortex, hippocampus and amygdala and release glutamate onto neurons in the nucleus accumbens. Direct evidence of glutamate involvement in addiction stems from the fact that MK 801, a selective NMDA receptor antagonist, prevents rats and mice from becoming sensitized to cocaine and amphetamine. Animals sensitized to cocaine experienced 50%–100% increases in glutamate levels. Another glutamate receptor is α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), which affects the firing rates of the dopamine ventral tegmental area in the brain. Craving in addicts parallels the intensity of neuronal activity in the frontal cortex and the amygdala, which are regions of the brain that release glutamate into the nucleus accumbens and serve learning and memory functions. Another antagonist of the glutamate receptor is LY274614, which reverses tolerance to morphine in rats [*40*]. Glutamate also creates lasting memories by changing the plasticity of neurons, which is also the basis of everyday learning, i.e. long-term potentiation and spatial memory [*23,41*].

Psychological and physiological dependence

Recently, it has been emphasized that psychological and physical dependence on addictive drugs is not as important as the compulsive seeking of drugs and their uncontrolled use [*1,2,16*]. This is because drugs of abuse do not produce these features with equal intensity, although they all affect the same mesolimbic reward system, which extends from the ventral tegmentum to the nucleus accumbens with projections to the limbic system and the orbitofrontal cortex. The predicted common mechanisms of reinforcement by various drugs of abuse are also supported by several studies [*4,42,43*]. Furthermore, these substances affect the brain at all levels. However, DSM-IV criteria (Box 1) still include the physiological component, as defined by tolerance and withdrawal, in the diagnosis of drug dependence.

Schuckit et al., in a study of alcohol-dependent patients with and without withdrawal or tolerance, reported that patients with withdrawal symptoms showed more severe alcohol dependence [*30*]. This was indicated by: higher number of drinks consumed in 24 hours; more binges reported; more alcohol-related life problems; more relevant DSM-IIIR criteria endorsed; more physiological complications; and more alcohol-related emotional/psychiatric symptoms such as depression and anxiety. They also found that the most severe clinical course of alcoholism was predicted by the presence of withdrawal, which defines the physiological component of dependence. These important indicators of drug dependence severity were independent of gender and antisocial personality disorder. Other researchers have substantiated these findings [*44*]. However, the data are insufficient to draw any conclusion between physiological components and drug abuse severity [*31,45*], in particular cocaine abuse. Furthermore, 13.1% of the subjects denied meeting the criteria for physiological dependence and 48.7% gave no history of withdrawal symptoms [*30*]. Nonetheless, it has been suggested that a clinical distinction based on physiological symptoms would have broad clinical applications.

Several researchers have advocated the significance of the physiological component, i.e. tolerance and withdrawal [*43,46, 47*]. However, this component is now considered to have less diagnostic value. Although tolerance and physical dependence have become part of the spectrum of substance use disorders, they are not considered required elements for the diagnosis of addiction. This is because devastating problems can develop from the use of some drugs, even without tolerance or withdrawal, and because there are insufficient data to support a greater significance of physiological conditions compared to other aspects of dependence [*31,45,48*].

On the other hand, other researchers have argued that there are not sufficient data to justify this lessened emphasis on tolerance and withdrawal [*47,49,50*]. There are several advantages to retaining the physiological component in the formulation of addiction. Doing so may help to: avoid classifying mild cases as dependent; enhance the distinction between drugs with higher and lower abuse liabilities; identify individuals most in need of immediate medical treatment; help justify the cost of more intensive care [*31*]; recognize the potential reinforcing role of continued substance use to relieve withdrawal symptoms; emphasize the importance of physiological symptoms as markers of a greater probability of relapse [*31,51,52*]; build the framework for the concept that dependence might relate to biological mechanisms; and highlight the important implications for genetic research [*46,53*].

The results of several other related studies are mixed [*31,45,54*]. It has been found that the physiological components of tolerance and withdrawal differ markedly among different drugs and treatment settings. Furthermore, determinants of individual vulnerability to alcohol withdrawal are unknown; however, it has been reported that the A9 allele of the dopamine transporter 1 (DAT1) gene is associated with more severe effects of alcohol withdrawal, possibly because of modification of the brain's capacity to compensate for long-term effects of ethanol on cerebral function [*55*]. DAT1 is also involved in neuroadaptation. Support for the dopamine transporter system also comes from an earlier study, which showed a greater frequency of the A7 allele

of the DAT1 gene in alcoholics with an inactive aldehyde dehydrogenase 2 gene [*56*].

Vulnerability to alcohol withdrawal is also determined by other gene polymorphism-regulating neurotransmitter systems, such as the dopamine D2 receptor [*57*], α-aminobutyric acid [*58*], noradrenaline [*59*] and glutamate.

Conclusions and future research implications

Substance dependence is a major public health problem. It adversely influences the physical, mental and social health of the drug abusers and the public at large. Therefore, the principles of the community health paradigm should be applied in dealing with this modern epidemic. At the same time, it is a social problem, so the sociology of drug abuse should focus on several important social dimensions, including stress, poverty, domestic and societal violence and various diseases that are spread by drug abuse and addiction. Most importantly, appropriate cultural and religious prescriptions should be encouraged in the control of this disease.

The conceptualization of addiction as a chronic, relapsing brain disease also has multiple implications and offers many opportunities, such as access to treatment facilities for patients with substance use disorders. There should be continuing mass media campaigns highlighting the most devastating consequences of drug addiction and at the same time disseminating current information and attempting to change attitudes towards addicted patients. Self-help groups and related organizations worldwide can be of tremendous help in achieving this objective. This would help in bridging the existing information gap between clinicians and the public.

Furthermore, neuroscience and social research should continue to explore the neural substrates and psychosocial determinants underlying different aspects of drug addiction, including tolerance, sensitization, abstinence, craving and relapses. Moreover, genetic research on drug addiction should target its phenotypes and related genetic markers in order to develop genetic therapies for the treatment of patients who may be predisposed to addiction. The cascade of acute changes in the neuronal network following drug exposure, i.e. neurobiology, is being researched and further studies should focus on revealing the long-term neuronal changes linked to drug addiction.

It is now known that relapses in drug abuse patients are usual, and therefore relapse prevention strategies should be explored further. The individual and environmental mechanisms underlying relapse should be addressed on a continuing basis, and appropriate drugs and psychosocial therapies should be used to prevent relapse. Substance-addicted patients, whether living in prison or in the community, are essentially suffering from a chronic brain disease in the form of substance abuse and dependence. They require acute and long-term maintenance treatment and relapse prevention, complemented by suitable rehabilitation. These are some of the challenges posed by drug abuse and addiction that should be addressed appropriately by the scientific community in collaboration with society.

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