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Review

Etiological theories of addiction: A comprehensive update on neurobiological, genetic and behavioural vulnerability

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ABSTRACT

Currently, about 246 million people around the world have used an illicit drug. The reasons for this use are multiple: e.g. to augment the sensation of pleasure or to reduce the withdrawal and other aversive effects of a given substance. This raises the problem of addiction, which remains a disease of modern society. This review offers a comprehensive update of the different theories about the etiology of addictive behaviors with emphasis on the neurobiological, environmental, psychopathological, behavioural and genetic aspects of addictions, discussed from an evolutionary perspective. The main conclusion of this review is that vulnerability to drug addiction suggests an interaction between many brain systems (including the reward, decision-making, serotonergic, oxytocin, interoceptive insula, CRF, norepinephrine, dynorphin/KOR, orexin and vasopressin systems), genetic predisposition, sociocultural context, impulsivity and drugs types. Further advances in biological and psychological science are needed to address the problems of addiction at its roots.

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1. Introduction

Historically, psychoactive substances have been largely used for medicine purposes and in rituals and ceremonies (Lang, 2004). It has been reported that Australian aborigines and North and South Americans used nicotine from two different indigenous sources 40,000 years

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ago (Saah, 2005). In addition, the earliest reference to marijuana use was found in China 12,000 years ago (Abel, 1980), while archaeological evidence of human use of coca dates back to at least 3000 BCE (Antonil, 1978). According to evolutionary biologists, many plants have evolved the ability to synthesize secondary metabolites, such as nicotine, morphine and cocaine which are potent neurotoxins that can prevent their consumption by herbivores (Karban and Baldwin, 1997; Roberts and Wink, 1998). After the advent of agriculture, these substances have become potentially available in larger quantities. This bioavailability facilitated drug use and people can ingest frequently highly concentrated drugs. By contrast, this type of access to drugs did not exist during our evolutionary history (Lende, 2008). The most recent data available from the United Nations Office against Drugs and Crime reported that 246 million people have used psychoactive drug in 2013 (UNODC, 2015). Drug addiction has a detrimental effect not only on the health and behavior of the individual, but on the social cohesion and social development. Repeated use of drugs usually leads to tolerance, a phenomenon in which a larger and progressive dose of the drug is needed to maintain initial drug responsiveness. This in turn leads to dependence, as a result of recurrent compulsive drug seeking and drug-taking behaviors and in which cessation of substance use produces withdrawal symptoms (APA, 2000; Wise and Koob, 2014).

It has been suggested from observations of wild, domesticated and captive animals that ingest intuitively psychoactive plants, that the use of psychoactive drug may be simply a common behavioural trait in the mammals (Siegel, 2005). Importantly, the animal laboratory studies in addiction have reported that other mammals exhibit, as humans, signs of compulsive drug-seeking and drug-taking behaviors (Campbell and Carroll, 2000), which add another argument in favor of the hypothesis that drugs of abuse must act on evolutionarily conserved brain specific areas (Wise, 1998). As a result, a number of insights in the role of the mesolimbic/mesocortical dopaminergic pathway or brain reward system (one of the evolutionary oldest parts of the brain) in the development of drug dependence and in reward behavior emerged (Wise, 2002). All mammalian species appear to share the anatomical, chemical and emotional/motivational properties of this neural system (Panksepp et al., 2002; Panksepp and Panksepp, 2000). Studies have shown that different types of natural activities (e.g. humour, sexual activity, food, positive social interaction, play, aesthetic works, and photos of loved ones) can activate the reward system (Dome et al., 2010).

Some studies have shed light on the importance of biology, psychology, and social influences on drug use, and suggest that evolutionary approaches have implications for substance abuse research, treatment, and social policy (Nesse, 1994; Gerald and Higley, 2001; Lende and Smith, 2002; Hill and Newlin, 2002; Saah, 2005; Lende, 2008; Durrant et al., 2009). Most recently, and in order to give a new evolutionary view to addiction, Hill (2013) proposes three main evolutionary approaches to addiction. The first considers addiction to be a disease of modern civilization. The second asserts that our exposure to psychoactive substances is not a recent development and finds evidence for plant–animal co-evolution. The third proposes a life-history approach to understand individual differences in vulnerability to addiction. The author concluded that addiction is not adaptive, but considered susceptibility to addiction as apparent effects of natural selection for other traits. In this way, over time, accidental ingestion by humans and other animals of psychoactive plants to survive has led to tolerance and dependence when high doses are becoming widely available (Hill, 2013).

The objective of this review is to provide a comprehensive update and share evolutionary insight into drug addiction. An overview of the role of the brain's reward and others systems implicated in addiction are discussed in the context of evolutionary and genetic predisposition to addiction. Furthermore, a brief review of studies highlighting the importance of socio-cultural factors, psychopathology and impulsivity in the initiation, development and maintenance of drug addiction.

2. Brain systems and drug addiction

Parsimonious theories have attempted to explain how and why addiction occurs. One of the major theories asserts that overall enjoyment of life and pleasure-seeking behaviors push drug abusers to use higher doses of drugs to improve mood and to cope with physical and/or emotional pain. However, the wise way to explain addiction is to consider its biological component as hypothesized by the incentive-sensitization theory. Research in humans and animals demonstrates that repeated drug use changes the brain of addicts in progressive, persistent and complex ways (Robinson and Berridge, 2008). The incentive-sensitization theory asserts that the motivational properties of drugs are related directly to their subjective pleasurable effects which create adaptations in the brain (Robinson and Berridge, 1993, 2000).

In an evolutionary biology perspective, early study suggested that pleasure was associated with an event that contributed to ensure the survival of species called beneception (Troland, 1928). Thus, it is well known that the brain reward system evolved to ensure activities essential to species survival, such as sexual activity and feeding behaviors and that dopamine regulates pleasure and reward in this system. Unfortunately, the evolutionary processes that attached pleasure and reward to advantageous behaviors also reinforced negative ones.

2.1. Dopamine system

Addiction to all major classes of abused drugs has been linked to increased dopamine (DA) transmission in the same parts of the brain associated with normal reward processing. Drugs of abuse often induce high levels of neural dopamine release in an extremely convenient way, causing the reward system to become flooded with it and reinforcing the addictive cycle (Bressan and Crippa, 2005; Kelley and Berridge, 2002). All addictive drugs elicit the excitation of the dopaminergic neurons in the ventral tegmental area (VTA) of the midbrain and in the shell of the nucleus accumbens (NAcc) (Nestler, 2005). New research shows that the mechanisms underlying addiction predisposition occur in a reward pathway of the brain (Casey et al., 2014). In fact, there is emerging evidence that having a reduced dopamine response to drugs is a high risk factor for developing addiction in humans (Casey et al., 2014).

Importantly, repetitive substance abuse produces the activation of the reward pathways in the brain in unusual way causing neurophysiological and neuroplastic changes (Ross & Peselow, 2009). This unnaturally high levels release of dopamine in reward system is associated with the generation of the Brain Derived Neurotrophic Factor (BDNF) as a compensatory mechanism to deal with oxidative stress in dopaminergic neurons (Vargas-Perez et al., 2014).

This suppressive effect of BDNF on dopamine unnatural release causes the pain, distress and withdrawal symptoms (Vargas-Perez et al., 2014). It's interesting to mention that the way BDNF regulates addiction depends greatly on the drug type, the brain region and the phase of addiction (Koo et al., 2012; Lin and Wolfn, 2015). At the receptor level, D2/D3 receptors stimulation in the striatum and other areas is linked to sensitization, drug addiction and relapse (Wise and Koob, 2014; Lee et al., 2009), with a significant decrease in D2 receptor availability in dorsal and ventral striatum induced by the drug that persist months after protracted detoxification (Volkow et al., 2011). In a most recent study examining 40 years of dopamine addiction research, substantial evidence has established that stimulants and alcohol increase striatal dopamine levels, while little evidence are available for cannabis and opiates (Nutt et al., 2015). Within the striatal dopamine receptors, accumulating evidence suggests that their availability diminished in individuals with stimulant or alcohol dependence but not in individuals with opiate, nicotine or cannabis dependence (Nutt et al., 2015).

By contrast, there is no unanimity on the classic DA hypothesis of reward. Considerable evidence indicated that addictive behavior may persist after subsequent lesions of DA neurons as well as after inhibition of DA synthesis or DA receptors blockade (Pettit et al., 1984; Rassnick et al.,