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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.

Contents

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.,

1993). In addition, the premorbid Parkinsonian personality syndrome and the occurrence of addiction in Parkinson Disease when they are overdosed with dopaminergic medication, directly falsified this hypothesis (Dagher and Robbins, 2009; Salamone and Correa, 2012). These observations suggest that dopamine's role in addiction is more complicated and support the involvement of other neurotransmitters and probably neuropeptides and hormonal systems in addictive behavior.

2.2. Decision-making system

Several researchers consider addiction as a disease of decision making, learning and motivation, and that dopamine acting on corticostriatal neurons is directly involved in the estimating the value of different outcomes, in planning actions and in the process of motivation (Salamone and Correa, 2012; Dagher and Robbins, 2009; Hyman, 2005; Berke and Hyman, 2000). In fact, many addicts choose to use drugs, despite that their choice can be dangerous, and they continue to use those drugs mainly because of brain change and adaptation that alter the process of motivation (Foddy and Savulescu, 2010). In his review, Duncan (2012) reported the ability of the prefrontal cortex to regulate neuronal activity of reward system (e.g. the NAcc and VTA) and its implication in inhibitory control processes that govern executive functions such as planning and decision-making.

From preclinical and clinical studies, there is clear evidence that drug exposure alters neuronal activity in orbitofrontal cortex (OFC) and impairs orbitofrontal-dependent learning tasks. However, these studies do not allow us to clarify whether functional changes in the OFC are induced by exposure to drugs or represent a pre-existing vulnerability condition that that make someone more likely to develop addiction (Schoenbaum and Shaham, 2008). Recently, Scientists found that self-control in addiction results from a suppression of reward signals in the medial orbitofrontal cortex (mPFC), an area known to be central to evaluating and pursuing goals by the dorsolateral prefrontal cortex (DLPFC), an area known to be involved in planning actions to reach a goal (Hayashi et al., 2013). Additionally, a recent research report proposed that drug seeking and extinction are differentially controlled by dorsal and ventral mPFC respectively (Moorman et al., 2005). Taken together, the results suggests that abnormal decision-making brain regions interactions may contribute to the vulnerability to addiction, and then may be a useful target for drugs of abuse modulation.

2.3. Interoceptive insula system

Insular cortex has considerable morphologic variability among mammals. These differences could be related to its multiple cognitive, affective-chemosensory and sensorimotor functions, associated with dorsoanterior, ventroanterior, and posterior regions of the insula respectively (Butti and Hof, 2010; Yates, 2012; Chang et al., 2013). Recently, human brain lesions and neuroimaging studies (both structural and functional) as well as animal literature highlighted the key role that insula plays in addiction (Droutman et al., 2015; Naqvi et al., 2014).

Substantial evidence proposed the anterior insula, a substrate for the capacity of self-awareness and the processing of interoception (Gschwind and Picard, 2014), to be the neural basis for intense urges and decision-making processes that involve certain risks and rewards in smokers (Naqvi et al., 2007; Brody et al., 2007; Zhang et al., 2011; Engelmann et al., 2012; Sutherland et al., 2013a, 2013b; Maria et al., 2014; Morales et al., 2014; Carroll et al., 2014; Stoeckel et al., in press; Bi et al., in press). In cocaine-dependent subjects, numerous studies have reported a gray matter volume reduction in the insula (Franklin et al., 2002; Mackey and Paulus, 2013). Animal modeling studies are also consistent with human studies (Contreras et al., 2007, 2012; Forget et al., 2010; Pushparaj et al., 2013; Li et al., 2013). It has been suggested that the representation of interoceptive aspects of drug use relevant to goal-directed reward seeking is the insula main function in addiction (Naqvi and Bechara, 2010). By contrast to the automatic drug seeking role played by the central amygdala–dorsal striatal system, insula plays a specific role in goal-directed drug seeking like avoiding actions that have negative consequences and reinforcing of alternative rewards, which is a representation of relative reward value (Naqvi et al., 2014). To improve the treatment of people with drug addiction, it is thus crucial to advance research on the interoceptive effects of drug use. It should be pointed out, however, that in Polish population, Bienkowski et al. (2010) reported that patients with insular strokes were not more likely to quit smoking than patients without insula strokes. This discrepancy can be explained partly by the fact that nearly half of Polish smokers do not perceive the link between the health problems and smoking (Sieminska et al., 2008) as well as the fact that any change in the insula by lesion or damage affects also its networking which in turn alters its function.

2.4. Serotonin system

The serotonin (5-HT) system is one of the oldest neurotransmitter/hormone systems in evolution, probably as old as 800 million years (Mengod et al., 2010). There is considerable evidence that this system is implicated in the vulnerability and establishment of drug use-associated behaviors as well as the transition and maintenance of addiction (Müller and Homberg, 2015; Kirby et al., 2011; Müller et al., 2010). Analysis of animal and human studies have shown that drugs of addiction profoundly change the extracellular 5-HT activity and 5-HT receptor function as well as the organization of brain circuitry by direct and indirect interaction depending on the type of drugs (Müller et al., 2010). It has been suggested that a genetic predisposition may anticipate these serotonergic adaptations and then increasing vulnerability to drug use-associated behaviors. In fact, it has been reported that polymorphisms in the gene encoding the 5-HT transporter is associated with alcoholism in non-human and human primates (Todkar et al., 2013) as well as with sociopathy in alcoholics (Herman et al., 2011).

2.5. Oxytocin system

Poor development of the oxytocin system during early childhood has been directly implicated in addictive behavior such as drug and alcohol abuse (Buisman-Pijlman et al., 2014). It has been demonstrated in young animals that oxytocin inhibits the development of tolerance to opioids (Kovács et al., 1998; Sarnyai and Kovacs, 1994), which suggests that oxytocin plays a significant evolutionary role in sustaining the efficacy of opioid reward (Panksepp et al., 2002). Additionally, long-term changes in markers of oxytocin function caused by many drugs of abuse (e.g. alcohol, cannabis, cocaine and opiates) have been associated with enduring deficits in social behavior that are commonly observed in animal models and human which highlights oxytocin as a potential therapeutic target for addiction (McGregor and Bowen, 2012).

2.6. Stress system

In line with the view that stress contributes to the maintenance of addiction, researchers highlight the role of stress system in vulnerability to drug addiction and relapse through five major components: corticotrophin-releasing factor (CRF), norepinephrine and dynorphin/KOR, orexin and vasopressin systems (Volkow and Morales, 2015; Koob et al., 2014; Shalev et al., 2002; Shaham et al., 2000). In humans and animal brains, CRF receptors are widely distributed, and the major illicit drugs can enhance the release of CRF in the central nucleus of the amygdala (Edwards and Koob, 2010; Wise and Koob, 2014). It has been proposed that exposure to stressors induces the stimulation of the reward system through the enhancement of CRF activity which is involved in relapse behavior (Bruchas et al., 2010). In addition, the CRF system is suggested to control the hypothalamic-pituitary adrenal response to stressors, which contributes impulsivity associated with adolescent drug taking

and the vulnerability to addiction (Koob, 2007, 2008, 2015; Sinha, 2008).

Numerous studies established a significant relationship between drug use and norepinephrine stress-responsive system (Erb et al., 2000; Xu et al., 2000; Dunn et al., 2004; Sulzer et al., 2005). All major drugs of abuse act by blocking norepinephrine reuptake and increasing norepinephrine release into the synaptic cleft, or both, which leads to increasing their availability to act upon post-synaptic receptors (Rothman et al., 2001; Sulzer et al., 2005; Weinshenker and Schroeder, 2007). Interestingly, a direct interaction between CRF and norepinephrine systems in mediating the negative affect associated with stress and increasing the rewarding effects of abused drugs has been suggested. In fact, it has been shown that CRF and norepinephrine systems coexist closely in the amygdala (Dunn et al., 2004; Smith and Aston-Jones, 2008) with direct synaptic interactions (Kravets et al., 2015), and regulate each other's expression levels and synaptic release thought direct synaptic interactions (Koob, 1999; Reyes et al., 2011; Kravets et al., 2015).

In addition, the dynorphin/kappa opioid system is well known to contribute to the effects of stress on drug consumption. Results from different studies indicated that the release of dynorphin induced by stress exposure, activate preferentially kappa opioid receptors (kOR) and subsequently increased the rewarding values of drugs (Ehrich et al., 2014; Redila and Chavkin, 2008; Valdez et al., 2007; McLaughlin et al., 2003). Anatomical evidence indicates that CRF and dynorphin colocalize to a large extent in the central nucleus of the amygdala (Van Bockstaele et al., 1998, 2010; Marchant et al., 2007; Reyes et al., 2008) and reciprocally activate one another (Land et al., 2008; McLaughlin et al., 2003; Nikolarakis et al., 1986; Buckingham and Cooper, 1986).

Importantly, a recent study reported that in response to stress, norepinephrine modulation may influence significantly the dynorphin and CRF circuitry, and in turn, the activation of CRF and dynorphin neurons in the amygdala by noradrenergic afferents may regulate the release of norepinephrine via projections to the locus coeruleus (Kravets et al., 2015).

In addition, accumulating evidence highlights the importance of orexin system in drug-seeking behavior, especially cue-induced relapse and stress through the activation of stress pathways in the brain but not by drug itself (Ebrahimian et al., 2016; Sakurai, 2014; Mahler et al., 2012; Aston-Jones et al., 2009; Boutrel et al., 2005; Sakamoto et al., 2004). A reciprocal activation was previously suggested between CRF and orexin systems (Winsky-Sommerer et al., 2004; Sakamoto et al., 2004). This interaction is pharmacologically significant as reported recently by Navarro et al. (2015) and may explain stress-induced relapse in former cocaine users. In addition, orexin receptors have been identified as potentially important targets for anti-relapse treatment (Zhou et al., 2011a). There is in fact considerable evidence that orexin receptor antagonists might be effective at blocking addiction-related behaviors (Yeoh et al., 2014).

Over the last few decades, the potential role of vasopressin system as a mediator of the drug's effects has been suggested (Zhou and Leri, 2016; Buisman-Pijlman et al., 2014; Bisagno and Cadet, 2014; Koob, 2008). Vasopressin is genetically and structurally related to oxytocin (Goodson et al., 2012), and functionally proposed to play an important role in drug addiction; from drug seeking and drug taking behaviors to withdrawal (Zhou et al., 2005, 2008, 2011b; Rodríguez-Borrero et al., 2010). Zhou et al. (2008) indicated that stress-induced hypothalamic–pituitary–adrenal (HPA) axis activation is coordinated by vasopressin that involves processing and release of HPA related peptides (e.g. ACTH and POMC).

Moreover, administration of a vasopressin receptor antagonist in animals was shown to partially alter the drug seeking behavior, as well as prevent reinstatement of drug seeking behavior after abstinence (Subiah et al., 2012; Zhou et al., 2008). Hence, it may be important to explore the value of vasopressin receptor antagonists in implementing treatment and management strategies for drugs abuse and prevention of relapse (Zhou and Leri, 2016).

It's important to note that all the stress systems compounds cited here are interconnected with several reward-related macro-systems including mesocorticolimbic dopamine and extended amygdala, which confer them an ideal position for the modulation of addiction-related behaviors and reward processing.

3. Genetic vulnerability to drug addiction

Several anatomical, functional, cellular and molecular neuroadaptations as well as changes in gene in a number of brain systems have been related to drugs of abuse (Hyman and Malenka, 2001). The genetic mechanisms involved in the complex physiological and behavioural processes underlying drug addiction have been investigated for several decades using specific molecular genetic approaches (i.e. genetic animal models, genome-wide association analysis, genome-wide linkage analysis, candidate gene screening) and human chromosomes 4, 5, 9–11, 15 and 17 have been suggested to be more likely to harbour susceptibility genes for the development of multiple substances addiction (Li and Burmeister, 2009).

In order to study the intergenerational transmission process, the Collaborative Study on the Genetics of Alcoholism (COGA) has accumulated substantial information and genotypes from more than 10,000 individuals from hundreds of multigenerational families, but failed to detect one specific gene increasing risk for alcoholism (Foroud et al., 2000; Schuckit et al., 2001). However, the best way to identify the loci/genes that affect the risk for addiction to substances is the genome linkage and genome association studies (Epps and Wright, 2012). In fact, variants in several genes, including aldehyde dehydrogenases, gamma-aminobutyric acid A receptor subunit 2 (GABRA2), nicotinic acetylcholine receptor (nAChR) subunits, ankyrin repeat and kinase domain containing 1 (ANKK1), and neurexins 1 and 3, have been related to multiple substances abuse (Duncan, 2012; Li and Burmeister, 2009; Kreek et al., 2005).

More interestingly, several new studies have explored the genetic background of addiction using the most abundant genetic variants in mammalian genomes called Single nucleotide polymorphisms (SNPs) and provided evidence for a significant contribution of common SNPs in the prediction of vulnerability to alcohol, tobacco, cocaine, cannabis and other illicit substance dependence (Palmer et al., 2015; Levran et al., 2012). In fact, polymorphisms of alcohol metabolizing-enzyme genes [e.g. aldehyde dehydrogenase (ALDH2)], in the CHRNA5-A3-B4 cholinergic gene cluster and in the dopamine receptor 2 (DRD2) and ANKK1 genes, have to date, consistently demonstrated a significant relationship with alcohol and nicotine susceptibility (Berrettini and Doyle, 2012; Bühler et al., 2015).

A cannabinoid receptor 1 (CNR1) gene SNP has been repeatedly associated with cocaine dependence and cannabis use (Bühler et al., 2015). In an evolutionary conserved region, SNP was associated with significant alterations in the CNR1 mRNA expression and lead to increase the risk of cocaine dependence (Clarke et al., 2013).

In addition, polymorphisms in the opioidergic receptor genes; μ-Opioid Receptor (OPRM1), κ-Opioid Receptor (OPRK1) and δ-opioid receptor (OPRD1) have been associated with alterations of the individual's vulnerability to drug addiction, and have been proposed to be potential targets for addiction treatment. The OPRD1 gene encoding delta opioid receptors and one OPRD1 polymorphism (rs1042114) which changes the evolutionarily conserved phenylalanine to cysteine in the N-terminus of the receptor has been linked to alcohol, cocaine, and opioid dependence (Zhang et al., 2008) and variants of the OPRM1 gene appear to be strong predictors of the degree of vulnerability to drug addiction (Li and Zhang, 2013). An association between OPRK1 and opiate addiction was also shown (Yuferov et al., 2004). In a detailed systematic review, Bauer et al. (2015), reported that the genetic variability of the opioidergic system (OPRM1, OPRD1

and OPRK1) plays a crucial role in the modulation of the opioid antagonist treatments efficacy such as methadone and naltrexone, as well as the cocaine vaccine. Interestingly, the use of knockout models (knockout mice) to study molecular mechanisms of opioid dependence has revealed a role for several gene products that were not expected from previous studies, including CB1, the substance P receptor (NK1), the GluR-A subunit of AMPA-type glutamate receptor (GluR-A), ORL1 receptors, the dopamine transporter (DAT), and the neuropeptide αCGRP. However, specific neuronal pathways in which these proteins modulate morphine withdrawal are unknown (Kieffer and Simonin, 2003).

Moreover, CREB (cAMP Response Element Binding protein) is expressed in almost all mammalian cells and is a transcription factor with important functions in many tissues, including high levels expression throughout the brain (Walters et al., 2003). CREB, with a remarkable degree of conservation in different brain regions in humans and others animals, is known to be essential in neuronal plasticity, learning and memory (Kandel, 2012). Specific roles of CREB in drug addiction have been reported (Pandey et al., 2005; Nestler, 2001). In the nucleus accumbens, CREB activation has been associated with the motivational symptoms of drug withdrawal, such as dysphoria, while in the dorsal striatum it has been related to sensitivity to substance of abuse (Madsen et al., 2012; Huang et al., 2008; Dong et al., 2006; Carlezon et al., 1998).

As previously mentioned, the CRF system is another interesting system with a specific role in the etiology and development of drug-seeking behavior as well as the motivational aspects of drug withdrawal and dependence which is highly conserved among mammals (Zorrilla et al., 2014; Boorse et al., 2005; Sarnyai et al., 2001). In this system, polymorphisms in the genes that encode CRF receptors (CRF1 and CRF2) have been associated with exacerbated stress responses and the propensity to develop drug addiction (Logrip et al., 2011).

Clearly, it is tempting to consider addiction as a highly polygenic disorder. However, to date there is little evidence for genes with major effects on addiction. In fact, more animals and human studies can be of increasing interest to capture interesting genes which confer vulnerability to addiction and thus present an ideal target for developing treatments.

4. Impulsivity and drug addiction

Several studies suggest that impulsivity might be more likely to contribute to drug abuse and addiction (De Wit, 2009; Jentsch et al., 2014). According to Moallem and Ray (2012) impulsivity is a multidimensional construct significantly involved in the initiation, maintenance of drug-seeking behavior as well as relapse after abstinence. This personality trait as well as risk taking and novelty seeking are considered as hallmark behavioural features that predict compulsive drug seeking inn human and animals (Galvan et al., 2011; Belin et al., 2008; Field et al., 2007; Kreek et al., 2005; Gerald and Higley, 2001). A neurodevelopmental perspective has been proposed by Chambers et al. (2003), who reviewed data from animal and human studies suggesting that adolescence is a vulnerable period for initiating substance abuse, because of changes occurring during this period in brain organization and function with relative increases in promotivational dopamine function and relative reduction in inhibitory serotonin systems. In addition, increased substance use has been linked to rebelliousness, disobedience and the desire to transgress social and conventional norms (Hawkins et al., 1992). The result tips the balance toward impulsivity and risk taking and suggests that impulsive individuals tend to underestimate the risk associated with health behaviors such as drug use.

Interestingly, it has been reported that polymorphism in the dopamine D4 receptor exon 3 is significantly associated with impulsive behaviors in humans, nonhuman primates, and dogs (Jentsch et al., 2014), supporting the fact that allele associated with higher tendency for impulsivity may be highly conserved in mammals. Indeed, the connection between dopamine and risk-associated behaviors is already known and conserved across animals from worms to mammals (Calhoun et al., 2015; Schultz, 2002).

Several studies in rodent models highlighted the role of impulsivity as a marker for drug addiction and provided considerable insight into neurobiological, genetic and environmental mechanisms underlying this behavioural endophenotype (Jupp et al., 2013).

In non-human primates, Gerald and Higley (2001), show that impulsive and aggressive behaviors contribute indirectly to the maintenance of traits involved in alcoholism and excessive alcohol intake. Research in humans has shown that in several specific neuropsychiatric disorders, impulsivity is also a risk-factor associated with substance use (Ouzir, 2013; Duva et al., 2011).

By contrast, evidence supports the notion of comorbidity of impulsivity and drug use and that impulsivity both pre-dates and is exacerbated by drug exposure, suggesting their relationship is reciprocal. In other word, drug consumption is mediated by the hypervaluation of the drug as the outcome of goal-directed drug-seeking, which may lead to an exacerbation of impulsive behavioural problems by the formation of automatic drug-seeking/taking behavior (Hogarth, 2011). In addition, impulsivity has been shown to predict and increase susceptibility to relapse after abstinence major substance of abuse (Everitt and Robbins, 2013; Economidou et al., 2009) may be potential therapeutic target for the pharmacological prevention or control of drug addiction.

More recently, a study done in young occasional users of amphetamine and ecstasy (MDMA) provided the evidence showing that individual differences in fronto-stiato-limbic regions underlying impulsivity and decision making are responsible for mediating the individuals transition from occasional drug users to addicted drug users (Becker et al., 2015).

5. Psychiatric disorders and drug addiction

Another important source of vulnerability to develop drug addiction is psychiatric disorders. Epidemiological studies found the prevalence of substance use disorder, a common key feature of several serious psychiatric illnesses such as bipolar disorder, schizophrenia, major depressive disorder, and attention deficit hyperactivity disorder, to be high compared to the general population (Lieb, 2015; Drake et al., 2007). According to Berg et al. (2014), psychiatric diseases make the brain more susceptible to addiction. This observation is supported by studies in animal models suggesting that psychiatric disorders potentiate behavioural and reinforcing effects of drug of abuse (Le Foll et al., 2015). However, further research will be necessary to advance our understanding of the potential link between psychosis and vulnerability to addiction. It important to note that Piazza and Deroche-Gamonet (2013) in their multistep general theory of transition to addiction (strongly criticized by Badiani, 2014; George et al., 2014; Ahmed, 2014) argue that transition from voluntary drug use to compulsive drug use should be considered as a true psychiatric disease caused by an interaction between vulnerable individuals and the amount of drug exposure. To explain why only a minority of individuals who regularly use psychoactive drugs develop the most severe form of the disease, Piazza and Deroche-Gamonet (2013) proposed that the plausible scenario is that two independent vulnerable phenotypes are needed; the first one initiates the drug taking and maintain it and the second phenotype exacerbates the loss of control associated with compulsive drug use and facilitate the progression to drug addiction.

It's important to note that antipsychotics, though not typically considered drugs of abuse, induced supersensitivity within the brain's dopamine systems and then are used to enhance the effects of other drugs (alcohol, opioids, cocaine, cannabis…) or as a way to counter the adverse effects of illicit substances (Malekshahi et al., 2015; Samaha, 2014). Moreover, legally prescribed anti-depressants such as selective serotonin reuptake inhibitors (SSRIs) and anxiolytics such as

benzodiazepines are categorized as addictive drugs (Fava et al., 2015; Evans and Sullivan, 2014; Nielsen et al., 2012, 2013).

6. Sociocultural context and drug addiction

As human evolution is biocultural at its core (Saniotis and Henneberg, 2013), it has been suggested that the evolution of the rituals of drugs preparation and use over time highlights this interaction between biology and culture in addiction (Lende, 2008). In addition, modern environments and sociocultural beliefs play an important role in the development of drug seeking/taking behavior, in forming the expectations of individuals about potential problems they may face with drugs use and in the reasons individuals return to drug use (Heath, 2001). In most culturally distinct groups, the lifestyle and the social relationships can help establish initial drug taking and provided drug availability. Social isolation during adolescence has been well documented to have negative effects in increasing addiction vulnerability (Whitaker et al., 2013; Karkhanis et al., 2014). In animal models, social isolation during a critical period of adolescence has been reported to result in altered responding to addictive drugs (Whitaker et al., 2013). However, a discordant view on the role of adolescent social isolation as a valuable model to study vulnerability to addiction emerged recently by Butler et al. (2014). Further researches are needed to clarify this issue.

On the other hand, the pleasurable and rewarding effects produced by drugs lead the addicted users to admit that drug use confers valuable mental states and blocks negative emotional states preventing the brain from providing precise information on the decrease of substance abuse desired outcomes (Nesse and Berridge, 1997). It has been reported that light to moderate alcohol consumption confers psychological benefits including positive mood, stress reduction, improved social integration, reduced social anxiety and reductions in depression (El-Guebaly, 2007; Peele and Brodsky, 2000). However, because several drugs produce a variety of unpleasant effects, it has been suggested that drugs of abuse provided false health outcomes by usurping the normal motivational process (Panksepp et al., 2002; Nesse and Berridge, 1997).

Moreover, in the past decade, synthetic or designer drug (Bath salts, synthetic cannabinoids, and synthetic hallucinogens) use has expanded especially among young adults. Also known as "legal highs", they are designed experimentally to mimic the natural mode of action of drugs like marijuana, cocaine, methamphetamine, and ecstasy, without causing the same side effects (Weaver et al., 2015). However, the consequences of using those designer drugs can be severe (e.g., intoxication, anxiety, psychosis and death) (Gunderson et al., 2013; Hill and Thomas, 2011; Hill et al., 2013).

Similarly, in modern societies, pleasurable behaviors that can generate syndromes that are behaviorally and biological similar to addictions but do not involve the ingestion of a drug have increased dramatically and sex addictions, pathological gambling, and shopping addiction become new fields of research and interest (Anselme, 2013; Griffiths, 2005).

Interestingly, with the extraordinary development in technological tools in the modern civilization, Internet addiction has emerged as a serious menace to mental health with the excessive and uncontrollable Internet use (Andreassen and Pallesen, 2014; Griffiths, 2013; Alavi et al., 2012; Kuss and Griffiths, 2011). Several studies have demonstrated that young people addicted to internet display a number of drug addiction-like symptoms (Echeburúa and de Corral, 2010; Zhu et al., 2015) and share some neural features with substance and gambling addiction (Turel et al., 2014; Kuss and Griffiths, 2012; Potenza, 2008).

Taken together, It seem plausible to recognize that the human ability to constantly develop new drugs and technological tools that are more effectively policed than others to satiate psychological and recreational needs may be an evolutionary indicator that will ensure our ever increasing dependence on them.

7. Creativity and drug addiction

In many cultures, one of the motivational factors for substance use is that people often think that using drugs will enhance their creativity and authenticity (Tart, 1970; Kamali and Steer, 1976; Green et al., 2003; Novacek et al., 2005). One study reported that the use of marijuana by students has been associated with increased creativity and novelty-seeking (Eisenman et al., 1980). In a test of associative processes, marijuana administration has also been reported to increase the number of original responses (Block et al., 1992). Furthermore, higher prevalence of substance use was detected in creative people, especially writers, composer-musicians and fine artists (Smith, 2015; Post, 1994). Because creative people have to produce original and novel works, it has been suggested that their high rate of substance use is specifically linked to novelty seeking (Heilman et al., 2003). However, accumulating evidence does not suggest that creativity is generated or enhanced by the use of marijuana or alcohol (Holm-Hadulla and Bertolino, 2014; Vizi, 2007; Bourassa and Vaugeois, 2001; Lapp et al., 1994; Lang et al., 1984; Tinklenberg et al., 1978). More recently, it has been shown that low doses of cannabis do not have any impact on creativity, while high doses of cannabis actually impair the ability to think creatively (Kowal et al., 2015). Further scientific investigation may clarify this ambiguous relationship between drugs of abuse and creativity.

8. Conclusion

Drug addiction is an undesirable aspect of modern society characterized by a compulsive drug taking, with goal-directed drug seeking and a loss of control in limiting intake. Drug addiction is now believed to be a brain disease that affects the physiology of certain brain regions and causes severe alterations in behavior, memory and neural cell life and may even cause neuronal cell death (Mewes et al., 2010; Koob and Volkow, 2010; Gold et al., 2009; Fowler et al., 2007). Examination of the previous and recent findings raises the need for a novel integrative etiological theory in which there is an interaction between many brain systems involved in addiction (reward system, decision-making system, serotonergic system, oxytocin system, interoceptive insula system, stress system…), genetic predisposition, environmental influences (e.g. sociocultural context), personality traits (e.g. impulsivity) and drug types. Such a comprehensive theory of addiction would tell us how and why the human seems to be more susceptible to addiction, how to distinguish psychoactive drug users who become addicts from those who use psychoactive drugs without becoming addicted, and why some addicts unintentionally relapse.

In many of the studies reviewed, neurobiological systems and genetic factors that contribute to the development and maintenance of addiction are conserved across species. Furthermore, a highly conserved behavioural trait like impulsivity emerged as a risk factor in drug addiction. Elucidating the molecular mechanisms underlying the initiation of drug use and compulsive drug use as well as the progress in the identification of specific new genes with major role in predisposing to addiction or protecting against it is a helpful way to understand why some people who experiment with substances become addicted while others do not and to prevent and treat addiction with adequate psychological and pharmacological treatment approaches. Finally, it appears that the human ability to constantly innovate and develop new drugs and addictive behavioural tools may be considered as an evolutionary indicator that will ensure our ever increasing dependence on those drugs and tools and that advances in biological and psychological science are required to tackle the issue of addiction from multiple perspectives.

Conflict of interest

None.

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