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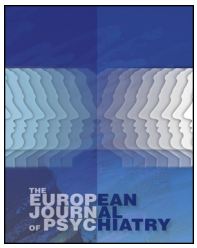

REVIEW ARTICLE

The neurobiology of addiction. A vulnerability/resilience perspective

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Abstract
Aim: The objective of this review is to provide a synthesis of current knowledge of the neurobiological mechanisms underlying vulnerability and resilience in substance use disorders (SUD).
Methods: PubMed and PsycINFO database search was conducted from May 1997 until April 2017, for relevant articles outlining the outcomes of case files, control studies and observational studies regarding neurochemical aberrations secondary to drug abuse as well as allostatic processes affecting the course and severity of SUD.
Results: The relation between drugs of abuse and the neurobiological milieu seems to be a mutual process; drugs of abuse affect the expression of neurobiological systems, and neurobiological systems affect the manifestation of addiction. The review of current literature outlines the roles of early life experience, allostatic processes and genetic polymorphism, which confer the vulnerable or resilient phenotype in SUD. Human and animal studies have revealed dysregulation and adaptive responses of specific neurochemical mechanisms in the brain reward systems (dopamine, opioid peptides, substance P, GABA, estrogen), the brain stress systems (CRH, cortisol, norepinephrine), the brain anti-stress system (serotonin, DHEA, NYP, endocannabinoids, galanin, oxytocin), as well as glutamate implicated in impulse control and BDNF associated with neuroprotection. Genetic studies suggest roles for the genes encoding the neurochemical elements involved in these neurobiological systems, predisposing to vulnerability and resilience in hedonic biochemical use.
Conclusion: Major neurobiological changes in substance abuse disorder common to human and animal studies include a compromised reward system, over activated brain stress systems, compromised anti-stress system as well as compromised impulse control and response inhibition system. Existing data indicate that allostatic processes and genetic polymorphism exert a significant influence on the course and severity of SUD, conferring the vulnerable or resilient phenotype.

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Introduction

While it is beyond the scope of this article to provide a comprehensive socio-neurogenetic portrayal of the multidimensionality of vulnerability and resilience in SUD in its entirety, the general purpose is to provide a neurobiological framework by which the reader can contextualize those influences, the biochemical milieu comprised of neuropeptides, neurosteroids, systemic and gonadal hormones, endogenous excitatory amino acids and neurotrophic factors, in context of allostasis and genetic polymorphism, which confer vulnerability and resilience in SUD.

The reward system

Drug addiction is a chronic disorder that builds up from initial recreational drug use and progresses toward compulsive drug seeking and intake. The reinforcing properties of abused drugs are thought to be responsible, in interaction with various genetic and environmental factors, for the initiation of drug use. Once repeated drug use is established, complex neuroadaptative mechanisms develop that lead to dependence, craving and relapse and contribute to the maintenance of repeated drug intoxication. A current hypothesis in the field of drug addiction is that drugs of abuse abnormally recruit neuronal pathways and transmitter systems responding to reinforcement and progressively alter their function. The mesolimbic dopamine (DA) system has received most attention in this regard.[1] Most types of rewards increase the level of DA in the brain, and many addictive drugs increase DA neuronal activity. Dopaminergic neuron distribution in the central nervous system consists of the midbrain, Ventral Tegmental Area (VTA), cerebral cortex and hypothalamus, affecting movement, attention, memory, pleasure and reward. Mesolimbic dopamine signaling is central to the onset of addiction, as well as to the transition to dependence in interaction with other neurotransmitter systems.[2] Cocaine, methamphetamine, amphetamine and virtually all drugs of abuse directly or indirectly augment dopamine in the reward pathway. Findings from animal studies suggest that early-life stress can lead to long-lasting changes in gene expression in the mesolimbic DA pathway (Table 1), ultimately increasing vulnerability to addictive disorders.[3] Conversely, findings from several studies suggest that higher dopamine D2 receptor availability in the striatum might promote resilience to alcohol use disorders. In a study of unaffected members of alcoholic families, higher striatal dopamine D2 receptor availability was associated with higher positive emotionality (Table 2), considered as a protective factor against alcohol use disorders.[2]

Opioid receptors are expressed primarily in the cortex, limbic system, and brain stem. Binding sites for the three opioid receptors overlap in most structures, but some structures exhibit higher expression of one receptor over the others. Their stimulation via opioid peptides affect locomotor activity, food intake, sexual behavior, anxiety-like behavior, and drug intake 1. Recent studies have demonstrated an essential role of μ-receptors in mediating natural rewards. The μ-receptor agonist endomorphin induced a conditioned place preference (CPP) when injected into the VTA or nucleus accumbens (NAc). In another study, endomorphin induced a CPP when infused into the posterior VTA, but not the anterior VTA or the NAc. Moreover, rats self-administered endomorphin into the VTA. These results indicate that mu-receptors in the VTA are critically involved in reinforcement and that the VTA is not functionally homogeneous. Genetic studies have addressed the role of μ-receptors in drug reinforcement and dependence in mutant mice. Mu-opioid receptor knockout mice are insensitive to morphine, demonstrating that μ-receptors are the primary molecular target for the prototypical opiate in vivo.[4] The opiate reward was tested in several studies. Morphine and heroin CPP, as well as morphine self-administration, were abolished in the μ-mutant. Furthermore, the reinforcing properties of non-opioid drugs of abuse are generally diminished in μ-receptor knockout mice. In these animals, nicotine and THC induced CPP were undetectable, alcohol self-administration was abolished, ethanol consumption was decreased and cocaine self-administration was reduced, suggesting that μ-receptors also contribute to non-opioid drugs reward.[1] The data reveal that μ-receptors mediate the rewarding properties of most drugs of abuse and therefore represent a key molecular switch conferring vulnerability to addictive behaviors and contribute to long-term neuroadaptations to non-opioid drugs of abuse. Pharmacological studies have long shown that κ-receptor activation is aversive in animal models. Kappa receptors have been proposed to oppose μ-receptors in the regulation of hedonic homeostasis. The notion that κ-receptor activity is aversive and negatively modulates reward was strengthened by a number of studies using κ-receptor knockout mice. Deletion of the κ-receptor gene did not modify a morphine CPP and enhanced a THC CPP. In contrast, κ-receptor knockout mutants showed reduced ethanol CPP. Finally, κ-receptor knockout mice showed potentiated cocaine CPP induced by stress, consistent with the notion that κ-receptors also counteract reward processes under stressful conditions. The analysis of δ-receptor knockout animals appeared highly interesting, in that behavioral phenotypes often differ or even oppose phenotypes of μ-receptor knockout animals. Delta receptor mutants showed increased anxiety levels and a depressive-like behavior. Directly relevant to drug abuse, δ-receptor knockout mice showed increased ethanol self-administration, and ethanol intake reduced the innate high-anxiety levels in these animals. There was no detectable change in a tetrahydrocannabinol (THC) CPP. Morphine CPP was reduced. Finally, δ-receptor knockout mice showed increased motor impulsivity, suggesting a facilitatory role of delta receptor activity on inhibitory controls. Altogether, the data suggest that δ-receptors regulate emotional behaviors, drug reinforcement, and impulsivity in a unique way that influences the development of addictive behaviors differently from μ-receptors. At present, and in contrast to μ-receptors, the direct implication of δ-receptors in hedonic control has not been demonstrated. Relevant to drug intake, genetic data demonstrate that μ-receptors contribute to the reinforcing properties of most drugs of abuse, whereas κ receptors induce dysphoria and counteract μ-receptors in regulating hedonic homeostasis. With regard to other aspects of addictive behaviors, the data show a role for μ-receptors in drug dependence, for κ-receptors in stress-induced drug intake, and for δ-receptors in emotional control.[1]

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