Eur. J. Psychiat. 2018;**32(3)**:139–148

THE EUROPEAN JOURNAL OF PSYCHIATRY

www.elsevier.es/ejpsy

REVIEW ARTICLE

The neurobiology of addiction. A vulnerability/resilience perspective

R. Miela[a], **W.J. Cubała**[a], **D. Wojciech Mazurkiewicz**[b], **K. Jakuszkowiak-Wojten**[a,*]

[a] *Department of Psychiatry, Medical University of Gdańsk, Poland*
[b] *St. Mark's Place Institute for Mental Health, New York, United States*

Received 28 May 2017; accepted 23 January 2018
Available online 19 February 2018

KEYWORDS
Addiction;
Allostasis;
Genetic polymorphism;
Vulnerability;
Resilience

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.

* Corresponding author.
E-mail address: k.jakuszkowiak@gumed.edu.pl (K. Jakuszkowiak-Wojten).

https://doi.org/10.1016/j.ejpsy.2018.01.002

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]

Table 1 The vulnerable phenotype.

Reward system	Stress system	Anti-stress system	Impulse control	Neuroprotection
Early life stress can lead to long-lasting changes in gene expression in the mesolimbic dopamine pathway	Amygdalar CRF increase stimulates compulsive drug seeking	Reduced activity 5-HT system might contribute to depression during withdrawal and increase relapse rate	VGLUT3 inactivation associated with anxiety related behaviors, enhanced stimulant effects of cocaine and increased vulnerability to cocaine use and relapse	BDNF Val (66) Met genotype, may promote drug seeking phenotypes in methamphetamine and heroin-dependent individuals
μ-Opioid receptor stimulation increases reinforcement and reward	Elevated CRF levels increase negative emotional states during abstinence and increase risk for relapse	Pronounced elevation in 5-HT in NAc, VTA, amygdala, and hippocampus in alcohol dependence	VGLUT3 polymorphism associated with ten-fold increase in prevalence in the severely dependent population	Corticosteroids play a key role in adaptive plasticity in the brain
δ-Opioid receptor inactivation associated with increase in anxiety, impulsivity, depression, and alcohol self-administration	Increased amygdalar CRF & NE stimulates consolidation of emotional memories associated with drug use	Association between increased VS $5HT_{1\beta}$ receptor density and alcohol dependence		
SP neurotransmission implicated in the behavioral response to stress and in the process of drug sensitization and relapse	Increased adrenal sensitivity (increased CORT:CRF) decreases time to relapse	LS serotonin transporter genotype associated with higher levels of ethanol preference and increased consumption		
NK1 receptor required for opioids to produce their rewarding and motivational effects	Lower plasma levels of ACTH but not cortisol might predate the onset of alcoholism	Early life stress is associated with decreased 5HT receptor density and anxiety		
Reduced cortical and subcortical GABA receptor binding in patients with PTSD and panic disorder	Increased brain NE enhances vulnerability to stressors during abstinence	5HT inactivation associated with anxiety		
Enhanced levels of estrogen evidence an increase in overall cocaine administration, motivation to administer cocaine, and an increase in the length of initial cocaine binge	α2 receptor antagonism increases self-administration of alcohol and induces reinstatement of alcohol seeking	NPY attenuation may relate to anxiety and depression associated with cocaine withdrawal		
Estradiol increases amphetamine-induced DA release in the striatum via attenuated GABA release	α2c receptor polymorphism (Del322-325) reduces feedback inhibition of sympathetic NE release	Upregulation of CB1 receptor signaling might contribute to increased alcohol consumption in chronic alcohol dependence		
		Certain CB2 receptor polymorphisms may be associated with depression		
		GalR3 polymorphism is associated alcohol dependence		

Table 2 The resilient phenotype.

Reward system	Stress system	Anti-stress system	Impulse control	Neuroprotection
Increased DA receptor density in striatum association with higher positive emotionality considered as a protective factor against alcohol use disorders	Regulation of NE system responsive-ness via $\alpha 2$ receptors	DHEA level and DHEA: CORT ratio are biomarkers of resilience	Regulation of DA release in the NAc prevents up-regulation of the system and entry into addiction	Enhanced BDNF levels in hippocampus and plasma of methamphetamine users
μ-Opioid receptor inactivation reduces reinforcement and reward		Exogenous DHEA associated with attenuation of cocaine self-administration, reduction of cocaine seeking behavior, reduced response to acute priming with cocaine and relapse prevention		
κ-Opioid receptor stimulation reduces reinforcement and reward		Enhanced activity of $5HT_{1\alpha}$ receptor may facilitate recovery		
NK-1 receptor antagonism attenuates hedonic response to opioids		Reduced activity of $5HT_{1\beta}$ receptor facilitates resilient stress response		
NK-1 receptor inactivation renders opioids non-rewarding		Increased NPY levels In the amygdala associated with decreased feelings of anxiety and enhanced performance under stressful conditions		
Reduction in self-administration of cocaine following ovariectomy		NPY associated with decreases in rate and level of NE secretion		
		Overexpression of NPY associated with decreased consumption of alcohol		
		Early life stress and certain NPY gene polymorphisms associated with differential susceptibility to alcohol and cocaine dependence		
		Galanin agonists have been shown to decrease opiate reinforcement and withdrawal		
		Oxytocin facilitates extinction of meth-induced CPP, reduces cocaine-induced hyperactivity, locomotor sensitization, stereotyped behaviors, and methamphetamine induced FOS expression in NAc, antagonizes cocaine-induced increases in dopamine utilization in NAc, prevents stress-induced reinstatement of methamphetamine taking, development of tolerance to ethanol and opiates, induction of stereotyped, hyperactive behavior by stimulants, and withdrawal symptoms associated with sudden abstinence from drugs and alcohol		

Accumulating evidence suggests that the neuropeptide substance P (SP), and its principal receptor neurokinin 1 (NK1), play a specific role in the behavioral response to opioids and stress that may help to initiate and maintain addictive behavior.[5] SP belongs to a group of neurokinins (NKs), small peptides that are broadly distributed in the central nervous system (CNS) and peripheral nervous system (PNS).[6] The biological effects of SP in the CNS have been associated with the regulation of mood disorders, anxiety, stress and reinforcement. In animal models, the NK1 receptor is required for opioids to produce their rewarding and motivational effects. SP neurotransmission is also implicated in the behavioral response to stress and in the process of drug sensitization, potentially contributing to vulnerability to addiction or relapse. The importance of NK1 signaling to addiction-related behaviors was emphasized by studies using mice lacking functional NK1 receptors.[5] That is, opioids no longer appear rewarding in NK1-knockout mice, at least as indicated in two behavioral paradigms, CPP and drug self-administration behavior. The effects of SP on major neurotransmitter systems involved in addiction-related behaviors including dopamine, serotonin, norepinephrine and acetylcholine had also been known. Furthermore, more recent studies have shown that lesion of cells bearing NK1 receptors in the amygdala mimics the results in the NK1 knockout mice and administration of NK1 receptor antagonists to normal mice attenuates their response to opioids on CPP. Thus a variety of approaches has converged to support a role for NK1 signaling in opioid addiction-related behaviors. Considering these observations, the most likely interpretation of the effect of the NK1 knockout on opioid-related behaviors is that the administration of opioids elicits an endogenous SP release that activates NK1 receptors. NK1 signaling may then play a permissive role, or possibly enhance the effects of opioids. Supporting this notion there has been a report showing that administration of morphine increases extracellular SP, at least in the periaqueductal gray. Relevant NK1 signaling may occur within several brain areas associated with reward.[5]

Gamma-aminobutyric acid (GABA) is the most widely distributed inhibitory neurotransmitter in the central nervous system (CNS). As such, GABA limits the excitability of neuronal activity in all areas of the brain.[7] Excessive GABAergic signaling results in sedation, amnesia, and ataxia, whereas the mildest attenuation of GABAergic signaling results in arousal, anxiety, restlessness, insomnia, and exaggerated reactivity.[8] Exposure to inescapable stressors, produce decreases in GABA receptor binding in the cortex, with some studies showing a decrease in the hippocampus. Exposure to stress has no effects on GABA receptor binding in the pons, striatum, thalamus, cerebellum, midbrain, or occipital cortex. These data support a role for alterations in GABA binding in anxiety, with a specific decrease in the frontal cortex and, although not as consistently, a decrease in the hippocampus. Neuroimaging studies reveal reduced cortical and subcortical GABA receptor binding in patients with PTSD and panic disorder.[9] The findings could be related to a down-regulation of GABA receptor binding after exposure to stress. Other possible explanations are that stress results in changes in receptor affinity, changes in an endogenous benzodiazepine ligand (the existence of which is controversial), and stress-related alterations in GABAergic transmission or neurosteroids that affect benzodiazepine receptor binding. A preexisting low level of GABA receptor density may be a genetic risk factor for the development of stress-related anxiety disorders.[7] Individuals exposed to chronic stress exhibit a greater vulnerability to SUD. For example, abuse rates in combat veterans suffering from PTSD are significantly higher than those veterans without PTSD. Stress-induced relapse is also higher in PTSD patients. In general, there is a higher prevalence of addiction in patients diagnosed with anxiety disorders and depression. Additionally, childhood trauma is associated with increased vulnerability to addiction.[10]

The direct effect of gonadal hormones on motivation and reward has also become an area significant development, largely because of an increasing literature documenting gender differences in expression, course, and outcomes of substance use disorders. These differences are, in part, mediated by direct effects of gonadal hormones on reward value, but are also likely interacting with the HPA axis to moderate these effects. For example, females evidence an enhanced HPA axis response to cocaine contributing to the increased escalation of cocaine use observed among women. Estradiol has also been linked to cocaine use. Ovariectomized rats demonstrate a reduction in self-administration of cocaine, whereas rats with enhanced levels of estrogen evidence an increase in overall cocaine administration, motivation to administer cocaine, and an increase in the length of their initial cocaine binge. Electrophysiological research indicates that estradiol increases amphetamine-induced DA release in the striatum of females via attenuated GABA release. More specifically, estradiol binds to the alpha estrogen receptor, which activates the glutamate receptor (mGluR), and attenuates depolarization – triggered GABA release in the striatum. This results in an attenuated release of GABA and subsequently an increase in DA release. This relationship between estradiol and DA release is likely to be U-shaped, and suggestive of different mechanisms by which estradiol affects behavioral responses to drugs of abuse. For instance, the time course effects of estradiol on GABA release in the striatum indicate changes that occur too quickly for classic genomic receptor effects, suggesting a specific role for non-classical estrogen receptor effects on acute modulation of DA release.[11]

The stress system

Chronic abuse of addictive substances results in hallmark symptoms of dependence, namely, compulsive drug use, tolerance, and withdrawal. States of tolerance and withdrawal are associated with alterations in brain stress circuits, namely the CRH-HPA and noradrenergic systems.[12] The HPA axis is a system regulated by a complex negative-feedback system. Corticotrophin-releasing hormone (CRH) released by the hypothalamus in response to stress, triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. This process leads to the synthesis and release of cortisol by the adrenal cortex. In the brain, corticosteroids play a key role in adaptive plasticity, as well as in the damage resulting from allostatic overload, and there are modulators that work synergistically to promote

adaptation over damage, including the mineralocorticoid and glucocorticoid receptors.[13] Cortisol secretion acutely facilitates cognitive, metabolic, immunologic, and behavioral adaptations to stress. Resilience is maintained when the stress response is both activated and terminated efficiently.[2] Studies showing lower plasma levels of ACTH but not cortisol in men with a family history of alcoholism suggest that hypothalamic-pituitary-adrenal (HPA) axis dysfunction might predate the onset of alcoholism. Long-term alcohol abuse is associated with increased extrahypothalamic CRH signaling and dampened HPA axis responsivity. Increases in extrahypothalamic CRH contribute to negative emotional states during abstinence, increasing the risk for relapse.[14] In a recent study, researchers asked alcoholics who had been abstinent for 1 month to imagine a relaxing situation of their choice while listening to a previously recorded audio tape of this situation. A greater cortisol-to-corticotrophin ratio (i.e., higher adrenal sensitivity) during this relaxed state was found to predict a shorter time to alcohol relapse, thus suggesting that new treatments aimed a decreasing adrenal sensitivity could reduce relapse rates.[2] Amygdalar CRH levels are also increased in rats during withdrawal from all major drugs of abuse, an effect that has been suggested to drive compulsive drug seeking. During active drug use, alcoholics, chronic smokers and cocaine addicts show hypercortisolism, whereas opiate addicts show reduced plasma levels of ACTH and cortisol.[15] Acute withdrawal states are associated with increases in CRH levels in CSF, plasma ACTH, cortisol, norepinephrine and epinephrine levels. Early abstinence states are associated with a blunted ACTH response to CRH in alcoholics, while hyper-responsivity of HPA hormones in response to metyrapone have been reported in opiate and cocaine addicts. An abnormal noradrenergic response to yohimbine challenge in early abstinence from cocaine has also been observed. Furthermore, neurochemical tolerance in the HPA response to cocaine, alcohol, nicotine and opiates with chronic abuse has been reported.[12]

During the acute stress response, the hormone norepinephrine (NE) is released through direct projections from the brain site where NE is synthesized (i.e., locus coeruleus) and other brain stem nuclei (i.e., structures that act as transit points for brain signals) into the amygdala, hippocampus, NAc, prefrontal cortex (PFC), as well as other brain areas mediating emotional responses. Norepinephrine's main CNS functions are sensory processing, movement, mood, memory, anxiety and control of the rest cycle. Several studies have linked abnormal regulation of brain NE systems to stress disorders.[2] As drug dependence develops, levels DA decrease and the NE stress system in the brain is activated, contributing to ''stress-like states'' and increased vulnerability to stressors during periods of abstinence. In combination with CRH, NE also might contribute to the consolidation of emotional memories associated with drug use in the amygdala. Resilience may be enhanced through the regulation of NE system responsiveness, which is mediated through effects on the NE transporter on catecholamine receptors (i.e., α2 adrenoreceptors), as well as interactions between the NE and other neurobiological systems, such as the dopamine and serotonin systems. For example, animal studies have shown that PFC NE nerve cell projections (i.e., axons) have a latent capacity to enhance synthesis and recovery of the transmitter, which might underlie the capacity to adapt to stress. Other targets include the α2a and α2c receptors, which have complementary roles in the regulation of stress responses. Yohimbine, a drug that blocks the α2 receptors (i.e., a receptor antagonist) increases alcohol self-administration and induces reinstatement of alcohol seeking. The recent finding that a α2c receptor polymorphism (Del322-325) reduces feedback inhibition of sympathetic NE release as well as evidence from studies in mice bred to have an inactivated α2c receptor suggest that interventions targeting this receptor might modulate stress and anxiety responses.[2]

The anti stress system

Serotonin has been implicated in practically every type of behavior, such as appetitive, emotional, motor, cognitive, autonomic, circadian rhythmicity and neuroendocrine function.[16] The central serotonin (5-HT) system consists primarily of neurons from the dorsal raphe nuclei that project widely throughout the brain, including the amygdala, ventral striatum (VS), and PFC, is involved in the regulation of stress and anxiety.[2] Serotonergic stimulation of 5-HT_{2A} receptors is anxiogenic, while stimulation of 5-HT_{1A} receptors is anxiolytic. Alcohol dependence in humans, like in rodent models, is associated with increased levels of ventral striatal 5-HT_{1B} receptors.[17] Serotonin has an important role in promoting neuroplasticity in the central nervous system, both during development and in adulthood. Serotonin also regulates the neurochemical effects of drugs of abuse, including alcohol, and is involved in modulating impulsivity, known to increase the risk for alcohol and drug abuse. The 5-HTsystem is itself modulated by drugs of abuse. For example, alcohol administration elevates 5-HT levels in the NAc, VTA, amygdala, and hippocampus, an effect that is more pronounced in alcohol-preferring rats.[2] Reduced activity of the 5-HT system might contribute to depression during withdrawal and increase vulnerability to relapse. In studies of macaques, differential function of the 5-HT system in interaction with early life stress was found to affect alcohol consumption: peer-reared female macaques with a specific variant (i.e., the l/s genotype) of the serotonin transporter polymorphism showed higher levels of ethanol preference and increased consumption over time. The behavioral phenotype of 5-HT_{1A} knockout mice includes increases in anxiety-like behaviors. In fact, ongoing research suggests a scenario in which early-life stress increases CRH and cortisol levels, which, in turn, down-regulate 5-HT_{1A} receptors, resulting in a lower threshold for anxiogenic stressful life events.[7] High activity of postsynaptic 5-HT_{1A} receptors may facilitate recovery. Restrained function of another 5-HT receptor, $5HT_{1B}$, might be central to resilient stress responses by enhancing the synaptic availability of 5-HT in the amygdala and other cortical regions as well as promoting DA release in the VS.[2]

The natural neurosteroid DHEA and cortisol are both adrenal steroids released in response to stress. Individuals exposed to chronic stress exhibit a higher propensity toward addiction. For example, SUD rates in combat veterans suffering from PTSD are significantly higher than those veterans without PTSD. Stress-induced relapse is also higher

in PTSD patients. In general, there is a higher prevalence of addiction in patients diagnosed with anxiety disorders and depression. Additionally, childhood trauma is associated with increased vulnerability to addiction.[10] Both DHEA levels and DHEA/cortisol ratios have been suggested as biological markers of resilience. Morgan et al.[18] reported positive correlations between DHEA levels (and DHEA/cortisol ratios) and the performance of military recruits under stressful conditions. Rasmusson et al.[19] found a negative correlation between DHEA reactivity to stress and PTSD symptom severity, which may suggest that high levels of DHEA protect against the adverse effects of stress and trauma.[20] A study by Doron at al.,[21] tested the effect of DHEA on cocaine-seeking behavior using a controlled self-administration paradigm in rats. Several days of chronic exposure to exogenous DHEA (2 mg/kg) attenuated cocaine self-administration. A longer period (19 days) of daily DHEA treatment decreased the cocaine-seeking behavior of the rats to 20% of their maintenance levels. Rats receiving DHEA (2 mg/kg) daily showed a minimal response to acute priming with cocaine, which suggests that DHEA can protect against relapse to cocaine usage following re-exposure to the drug.[21]

One of the leading candidates in resilience research is known as neuropeptide Y or NPY. NPY is a 36 amino acid peptide which is found throughout the mammalian brain. Receptors for NPY are associated with key locations in the brain that deal with stress: the amygdala, the hippocampus, and the locus coeruleus (LC). In the amygdala, increased NPY levels may be associated with decreased feelings of anxiety. In addition, NPY levels may also decrease the rate of LC firing, resulting in lower levels of NE in the brain, which can lead to decreased chances of the brain sustaining prolonged damage due to constant stress.[22] Probably the most important function of NPY comes in its interaction with CRH. CRH receptors are found throughout the brain, in areas specifically associated with stress reactions, such as the amygdala and the LC. On both of these brain structures, NPY and CRH have counterbalancing functional effects. In the amygdala, CRH can promote activation, resulting in stimulation and increased feelings of anxiety, while NPY results in decreased amygdala arousal, and anti-anxiety feelings. In the locus coeruleus, CRH causes an increase in firing rate, increasing NE levels, while NPY has a counter effect, resulting in decreases in rate and level. Findings in combat veterans also support the idea that high levels of NPY serve as a biological marker for resilience.[20] Patients with PTSD show reduced baseline levels of NPY and, conversely, individuals with high levels of NPY show enhanced performance under stressful conditions. Evidence from animal and human studies suggests that NPY has a key role in regulating alcohol intake, dependence, and withdrawal. Mice genetically modified to overexpress NPY consume less alcohol, and administration of NPY into the cerebral ventricles of the brain (i.e., intracerebroventricular infusion) reduces alcohol consumption in alcohol-preferring rats. Infusion of NPY into the central nucleus of the amygdala has been shown to normalize both anxiety behaviors and alcohol intake, suggesting that NPY might work by modulating anxiety responses. In rhesus macaques exposed to early-life stress, and in human studies, certain NPY gene polymorphisms are associated with differential susceptibility to alcohol or cocaine dependence.[2] NPY may be a sensitive marker for chronic cocaine use. Its decrease may relate to the anxiety and depression associated with cocaine withdrawal in humans.[21]

Multiple human and animal studies support that endocannabinoids (ECBs) play a key role in memory, mood, brain reward systems and drug addiction. The endocannabinoid system regulates the release of stress-induced neurotransmitters including the systemic release of norepinephrine and cortisol. CB1-R receptors are abundant in the brain, specifically the mesocorticolimbic system, the spinal cord, and the peripheral neurons.[22] Evidence derived from animal studies suggests a role of the ECS in alcohol-related behaviors. Such research suggests that upregulation of CB1receptor-mediated G-protein signaling in a brain circuit that mediates AD susceptibility (involving the amygdala, hippocampus, ventromedial prefrontal cortex, insula, and ventral striatum) might contribute to the increased alcohol consumption in patients with chronic AD.[2] CB2 receptors are located peripherally, with a high density on immune-modulating cells, including microglia in the brain. CB2-R may have some relationship to depression based on animal studies and the finding of a high incidence of CB2-R polymorphisms in a depressed Japanese population.[22] In a study by Sihvola et al.,[23] adolescents presenting with depressive symptoms might be at increased risk for developing substance use disorder.

Galanin is a neuropeptide synthesized in many neuronal types including brainstem norepinephrine-producing cells of the locus coeruleus and the serotonin-producing neurons of the dorsal raphe nucleus. Galanin inhibits the firing of rodent norepinephrine, serotonin and dopamine neurons and reduces the release of these neurotransmitters in forebrain target regions.[24] Like a number of neuropeptides, galanin can alter neural activity in brain areas that are important for both stress-related behaviors and responses to drugs of abuse. Accordingly, drugs that target galanin receptors can alter behavioral responses to drugs of abuse and can modulate stress-related behaviors. Stress and drug-related behaviors are interrelated: stress can promote drug-seeking, and the behavioral signs of drug withdrawal result from increased activity in brain circuits involved in the stress response.[25] The distribution of galanin and its receptors and its actions on monoamine signaling have fostered interest in this neuropeptide in the field of behavioral pharmacology and the potential role of galanin in the pathophysiology of psychiatric disorders such as anxiety, depression, and drug addiction, particularly withdrawal. In rodent models, expression of galanin in the brain is altered by various stressors, while administration of galanin can modulate anxiety-like responses to stress. Emerging evidence further supports a role for galanin in the mediation of depression-related behaviors in rodents. Recently, galanin agonists have been shown to decrease behavioral signs of opiate withdrawal, which are thought to result from hyperactivation of brain stress pathways. Studies using genetically modified mice suggest that galanin normally plays a protective role against opiate reinforcement and withdrawal.[24] Both human genetic and behavioral animal data have suggested that galanin action in the amygdala and elsewhere, is involved in addictive behavior such as repeated alcohol intake. Indeed, GalR3 showed a significant association with alcoholism that was driven by one single nucleotide polymorphism, and there was no effect of GalR1 or GalR2 haplotypes on

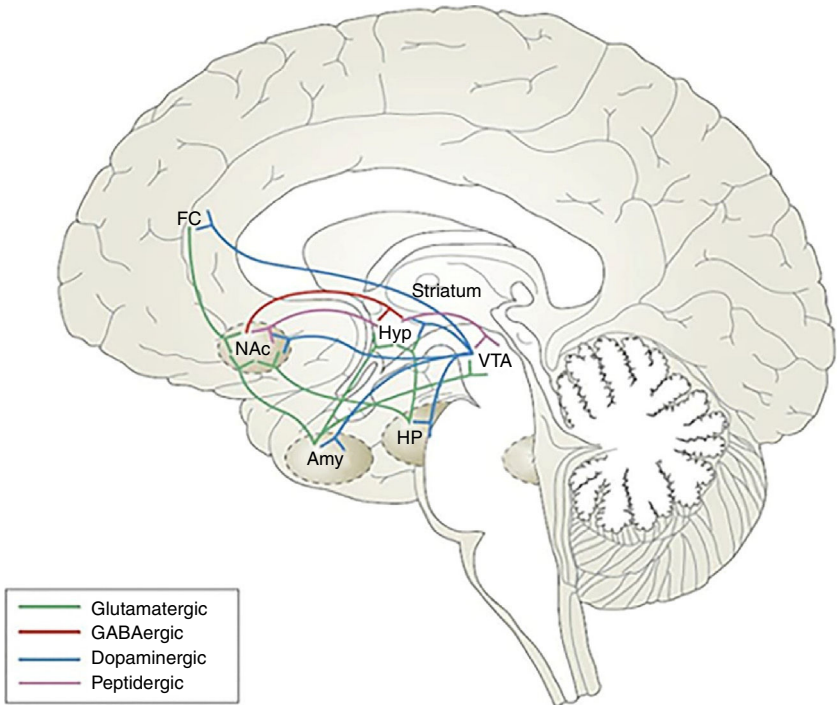

Figure 1 Neural circuitry of addiction.

alcoholism risk. This finding is of particular interest since mood disorders are often comorbid with alcoholism in humans. Therefore, development of galanin receptor antagonists, in particular, GalR3 antagonists, might be a breakthrough in the addiction relevant field.[26] The ability of galanin to alter norepinephrine, serotonin, acetylcholine, and glutamate release may indirectly alter the activity of dopamine neurons, leading to modulation of drug-related behaviors. Taken together, a large, convergent body of evidence suggests that endogenous galanin exerts a tonic inhibition on multiple neurotransmitter systems that may mediate drug self-administration and withdrawal symptoms (Fig. 1).[25]

Drug use typically occurs within a social context, and social factors play an important role in the initiation, maintenance, and recovery from addictions.[27] There is now accumulating evidence of an interaction between the neural substrates of affiliative behavior and those of drug reward, with a role for brain oxytocin systems in modulating acute and long-term drug effects. There is a consensus that oxytocin modulates fear and anxiety. The neural architecture of the oxytocinergic system is evolutionarily conserved and targets brain areas critical for emotion regulation (e.g., amygdala, lateral septum, and brainstem.[28] Oxytocin has been shown to alter central dopaminergic responses associated with non-social behaviors, including addictive behaviors and stress. Of direct relevance to the issue of addiction, oxytocin has been shown to influence the biochemical and behavioral effects of various drugs of abuse.[10] Exogenously administered oxytocin decreased cocaine-induced hyperactivity, locomotor sensitization, and stereotyped behaviors in rodents, and antagonized cocaine-induced increases in dopamine utilization in the NAc. Conversely, cocaine administration decreased hippocampal, preoptic and hypothalamic oxytocin levels. Methamphetamine might also influence the function of CNS oxytocin pathways. For example, methamphetamine-induced FOS expression in the NAc core, but not shell, was significantly reduced by oxytocin. More recently, intracerebroventricular oxytocin was shown to inhibit methamphetamine-induced place preference, to facilitate the extinction of meth-induced CPP, and to prevent the stress-induced reinstatement of methamphetamine taking in mice. The effects of oxytocin on meth-induced behavioral activation and FOS expression might be due to an oxytocin-mediated reduction of methamphetamine-induced dopamine efflux in the NAc. Additionally, oxytocin is known to inhibit prefrontal glutamate release during stress-induced reinstatement of methamphetamine place preference. It is also of interest that oxytocin can also block intravenous methamphetamine self-administration in rats. In rats, systemic administration of oxytocin, or microinjections of oxytocin directly into the NAc, or subthalamic nucleus, can also reduce meth-induced CPP. Overall, these findings suggest that addiction to various psychostimulants might trigger substantial neuroadaptations in oxytocin systems in the mammalian brain.[10] Early research in this field indicated that exogenous oxytocin administration can prevent the development of tolerance to ethanol and opiates, the induction of stereotyped, hyperactive behavior by stimulants, and the withdrawal symptoms associated with sudden abstinence from drugs and alcohol. Oxytocin is a therapeutic candidate for acute drug withdrawal and detoxification. The preclinical results offer hope for the objective of using oxytocin to cause lasting reductions in drug craving and drug abuse. Other intriguing evidence also speaks to the ability of oxytocin to ameliorate physical and behavioral effects associated

with acute drug withdrawal. In seminal preclinical studies, oxytocin was shown to reduce the severity of withdrawal after chronic high dose administration of opiates and ethanol.[27]

Impulse control

Glutamate is the major excitatory neurotransmitter in the mammalian brain and accounts for approximately 70% of synaptic transmission in the central nervous system.[29] Glutamate contributes to regulating DA release in the NAc. More precisely, it is its subtle balance with another neurotransmitter, acetylcholine that prevents up-regulation of the system and entry into addiction. Dopamine levels rise in the cerebral structures that form the reward system. The intensity and rapidity of DA release provide a basis for the processes that will lead to the development of addiction. The cholinergic neurons in the NAc, one of the centers of reward, are known to regulate this DA release. These acetylcholine-using neurons are also able to utilize glutamate. These neurons, which are to some extent ''bilingual'', can thus both activate (via acetylcholine) and inhibit (via glutamate) DA secretion. Inhibiting a gene essential to this signaling by glutamate (VGLUT3) in mice renders them more vulnerable to cocaine. The mice experience enhanced stimulant effects of the drug, developing addiction more easily and being more likely to relapse after a period of abstinence. Amilhon et al.[30] found that deletion of VGLUT3 increased several anxiety-related behaviors. The glutamate from these acetylcholine neurons, therefore, plays an important regulatory role in limiting cocaine addiction. A mutation of this gene was ten times more common among severely dependent patients than in individuals without psychiatric symptoms. This mutation may explain the greater vulnerability to addiction of these patients. These observations appear to confirm the role of glutamate in the addictive mechanism and help to clarify the neuronal mechanisms that underlie the search for hedonic sensations. Contrary to what scientists thought until now, these findings show that it is not acetylcholine alone that regulates DA release, but a balance between acetylcholine and glutamate. Thus, it appears that an unsuspected target for the treatment of drug addiction has been identified. Indeed, although acetylcholine has numerous other functions in the brain and muscles, this glutamate signaling is more specific. The next step is to identify the receptor involved so that pharmacological therapies can be developed.[31]

Neuroprotection

The role of neurotrophic factors (NTFs) is well-recognized for their actions on neuronal survival, differentiation, proliferation, and migration, of cells in the nervous system. Besides their role in regeneration, NTFs also have neuroprotective functions.[32] Likewise, NTFs have been shown to be involved in synaptic plasticity in the brain. Synaptic plasticity is considered the basis for most models of learning, memory, and development in neural circuits. Drug abuse can elicit neural maladaptation leading to drug addiction. Currently, the role of synaptic plasticity in addiction has begun to yield vitally important insights into mechanisms that underlie the addiction. Drugs of abuse alter (either increasing or decreasing) the strength of excitatory synapses by tapping into traditional mechanisms of plasticity, including long-term potentiation (LTP) and long-term depression (LTD).[32] Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF) are the most studied NTFs. BDNF is proved to be a promoter of methylation in association with drug addiction. In fact, how GDNF or BDNF affect the drug-seeking behavior depends on the drug type, addiction phase, and the timing of GDNF/BDNF treatment in relation to drug administration. In support of this notion, addictive substances have been revealed to increase the BDNF protein levels in multiple brain regions. Enhanced BDNF levels are found in the hippocampus of methamphetamine self-administering rats and the plasma of human methamphetamine users. Remarkably, primary results suggest that the BDNF Val (66) Met genotype, which has been associated with neurobehavioral deficits, may promote drug-seeking phenotypes in methamphetamine and heroin-dependent individuals.[32]

Conclusion

A greater understanding of the neurobiology of vulnerability and resilience is crucial to the prevention of SUD and to the development of evidence-based treatment strategies. The development of such interventions will benefit from an understanding of the specific circuitry or functional processes being targeted, rather than using abstinence as the only beneficial outcome in addiction treatment. From treatment perspective, future research should focus on which changes in neurotransmission can be most safely and effectively targeted by pharmacological or genetic interventions that either counteract the adaptive changes in the brain produced by prolonged intake of drugs of abuse, or promote new synaptic plasticity that can help the individual regain volitional control over drug intake and extinguish drug-associated memories and cravings. Interventions designed to counteract dysphoria or strengthen executive control, even if not resulting in complete abstinence, may improve long-term success and recovery from addiction. In parallel, these neurobiological advances have begun to reveal the molecular, neuronal and genetic bases underlying the heterogeneity of the clinical presentation and the outcomes of SUD. These advances might enable the development of tailored therapeutic interventions on the basis of the specific molecular targets and/or circuits disrupted in a given individual. In conclusion, uncovering the neurobiology underlying SUD has led to the recognition of addiction as a chronic disease of the CNS. At the same time, these advances have revealed potential targets for interventions, reducing vulnerability and enhancing resilience that could herald a new era of more effective and personalized addiction treatments.

Authors contribution

All authors contributed to and have approved the final manuscript.

Funding

There was no funding for this work.

Conflict of interest

The authors have no conflict of interest to declare.

References

1. Le Merrer J, Becker AJ, Befort K, Keiffer B. Reward processing by the opioid system in the brain. Physiol Rev. 2009;89:1379–412.
2. Alim TN, Lawson WB, Feder A, Iacoviello BM, Saxena S, Bailey CR, et al. Resilience to meet the challenge of addiction psychobiology and clinical considerations. Alcohol Res. 2012;4:506–15.
3. Adinoff B. Neurobiologic processes in drug reward and addiction. Harv Rev Psychiatry. 2004;12:305–20.
4. Lutz P-E, Kieffer BL. Opioid receptors: distinct roles in mood disorders. Trends Neurosci. 2013;36:195–206.
5. Commons KG. Neuronal pathways linking substance P to drug addiction and stress. Brain Res. 2010;1314:175–82.
6. Mantyh PW. Neurobiology of substance P and the NK1 receptor. J Clin Psychiatry. 2002;63:6–10.
7. Charney DS. Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. Am J Psychiatry. 2004;161:195–216.
8. Nutt D. GABBA receptors: subtypes, regional distribution and function. J Clin Sleep Med. 2006;2:7–11.
9. Geuze E, van Berckel BNM, Lammertsma AA, Boellaard R, de Kloet CS, Vermetten E, et al. Reduced GABAA benzodiazepine receptor binding in veterans with post-traumatic stress disorder. Mol Psychiatry. 2008;13:74–83.
10. Bisagno V, Cadet JL. Stress, gender, and addiction: potential roles of CRF, oxytocin and arginine vasopressin. Behav Pharmacol. 2014;25:445–57.
11. Hildebrandt T, Greif R. Stress and addiction. Psychoneuroendocrinology. 2013;9:1923–7.
12. Sinha R. How does stress increase risk of drug abuse and relapse? Psychopharmacology. 2001;158:343–59.
13. Herman JP, McKlveen JM, Ghosal S, Kopp B, Wulsin A, Makinson R, et al. Regulation of the hypothalamic-pituitary-adrenocortical stress response. Compr Physiol. 2016;6:603–21.
14. Koob GF, Le Moal M. Addiction and the brain antireward system. Annu Rev Psychol. 2008;59:29–53.
15. Logrip ML, Koob GF, Zorrilla EP. Role of corticotropin-releasing factor in drug addiction: potential for pharmacological intervention. CNS Drugs. 2011;25:271–87.
16. Siegel GJ, Agranoff BW, Albers RW, Fisher SK, Uhler MD. Basic neurochemistry: molecular, cellular and medical aspects. 6th ed. Philadelphia: American Society for Neurochemistry/Lippincott-Raven; 1999.
17. Hu J, Henry S, Gallezot JD, Ropchan J, Neumaier JF, Potenza MN, et al. Serotonin 1B receptor imaging in alcohol dependence. Biol Psychiatry. 2010;67:800–3.
18. Morgan CA 3rd, Southwick S, Hazlett G, Rasmusson A, Hoyt G, Zimolo Z, et al. Relationships among plasma dehydroepiandrosterone sulfate and cortisol levels, symptoms of dissociation, and objective performance in humans exposed to acute stress. Arch Gen Psychiatry. 2004;61:819–25.
19. Rasmusson AM, Vythilingam M, Morgan CA 3rd. The neuroendocrinology of posttraumatic stress disorder: new directions. CNS Spectr. 2003;8:651–6, 665–7.
20. Elliott R, Sahakian BJ, Charney DS. The neural basis of resilience. The Government Office for Science. Mental Capital and Wellbeing Project; 2008.
21. Doron R, Fridman L, Gispan-Herman I, Maayan R, Weizman A, Yadid G. DHEA, a neurosteroid, decreases cocaine self-administration and reinstatement of cocaine-seeking behavior in rats. Neuropsychopharmacology. 2006;31:2231–6.
22. Nulk M, Schuh W, Burrell LM, Matthews MD. Effects of neuropeptide Y on resilience to PTSD. Department of Behavioral Sciences and Leadership. West Point Resilience Project (WPRP). Research Report PL488E3; 2011.
23. Sihvola E, Rose RJ, Dick DM, Pulkkinen L, Marttunen M, Kaprio J. Early-onset depressive disorders predict the use of addictive substances in adolescence: a prospective study of adolescent Finish twins: early-onset depressive disorders and substance use. Addiction. 2008;103:2045–53.
24. Holmes A, Picciotto MR. Galanin: a novel therapeutic target for depression, anxiety disorders and drug addiction? CNS Neurol Dis Drug Targets. 2006;5:225–32.
25. Picciotto MR, Brabant C, Einstein EB, Kamens HM, Neugebauer NM. Effects of galanin on monoaminergic systems and HPA axis: potential mechanisms underlying the effects of galanin on addiction- and stress-related behaviors. Brain Res. 2010;1314:2006–18.
26. Mitsukawa K, Lu X, Bartfai T. Galanin, galanin receptors, and drug targets. EXS. 2010;102:7–23.
27. McGregor IS, Bowen MT. Breaking the loop: oxytocin as a potential treatment for drug addiction. Horm Behav. 2012;61:331–9.
28. Tost H, Kolachana B, Hakimi S, Lemaitre H, Verchinski BA, Mattay VS, et al. A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. Proc Natl Acad Sci. 2010;107:13936–41.
29. Gass JT, Olive MF. Glutamatergic substrates of drug addiction and alcoholism. Biochem Pharmacol. 2008;75:218–65.
30. Amilhon B, Lepicard E, Renoir T, Mongeau R, Popa D, Poirel O, et al. VGLUT3 (vesicular glutamate transporter type 3) contribution to the regulation of serotonergic transmission and anxiety. J Neurosci. 2010;30:2198–210.
31. Sakae DY, Marti F, Lecca S, Vorspan F, Martín-García E, Morel LJ, et al. The absence of VGLUT3 predisposes to cocaine abuse by increasing dopamine and glutamate signaling in the nucleus accumbens. Mol Psychiatry. 2015;20:1448–59.
32. Nafea OE. Update in the neurobiology of addiction. Int J Sci Rep. 2016;2:212–4.