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Review

The role of stress in drug addiction. An integrative review

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ABSTRACT

Background: The high prevalence and burden to society of drug abuse and addiction is undisputed. However, its conceptualisation as a brain disease is controversial, and available interventions insufficient. Research on the role of stress in drug addiction may bridge positions and develop more effective interventions.

Aim: The aim of this paper is to integrate the most influential literature to date on the role of stress in drug addiction.

Methods: A literature search was conducted of the core collections of Web of Science and Semantic Scholar on the topic of stress and addiction from a neurobiological perspective in humans. The most frequently cited articles and related references published in the last decade were finally redrafted into a narrative review based on 130 full-text articles.

Results and discussion: First, a brief overview of the neurobiology of stress and drug addiction is provided. Then, the role of stress in drug addiction is described. Stress is conceptualised as a major source of allostatic load, which result in progressive long-term changes in the brain, leading to a drug-prone state characterized by craving and increased risk of relapse. The effects of stress on drug addiction are mainly mediated by the action of corticotropin-releasing factor and other stress hormones, which weaken the hippocampus and prefrontal cortex and strengthen the amygdala, leading to a negative emotional state, craving and lack of executive control, increasing the risk of relapse. Both, drugs and stress result in an allostatic overload responsible for neuroadaptations involved in most of the key features of addiction: reward anticipation/craving, negative affect, and impaired executive functions, involved in three stages of addiction and relapse.

Conclusion: This review elucidates the crucial role of stress in drug addiction and highlights the need to incorporate the social context where brain-behaviour relationships unfold into the current model of addition.

1. Introduction

In the last two decades, drug addiction has been considered a chronic and relapsing brain disease characterized by compulsive drug seeking and taking. This view rest on the existence of dysfunctions in specific brain systems as proposed by Leshner in a landmark study, in which he states "that addiction is tied to changes in brain structure and function is what makes it, fundamentally, a brain disease" [89] and further developed by Volkow and others [140,141]. An alternative view considers that addiction is caused and sustained by psychosocial factors and learning processes that translate them into addiction, and therefore, not as a brain disease [1,58,88,90,91,123]. Nowadays, there is still an open debate on whether the brain or the context is the most important level of analysis for understanding and approaching addiction.

In any event, regardless of the conceptualisation of drug addiction, the prevalence and burden to society of drug abuse and addiction is accepted. Only the harmful use of alcohol causes more than 3 million deaths per year, 6 every minute [149].

Drug addiction has drawn much attention from research in neuroscience. However, the budget has been relatively scarce in comparison with other chronic conditions. Research in drug addiction has focused heavily on uncovering the neurobiological basis of drug addiction as a brain disease from animal models, which cannot fully emulate the human condition, and neuroimaging studies in humans. For instance, the initiative HEAL (Helping to End Addiction Long-term) was launched in April 2018 as part of the Brain Research Advancing Innovative Neurotechnologies (BRAIN), which has increased by 50% its 2017 budget, leading the research of the brain to prevent and treat brain disorders. Unfortunately, this approach has overlooked the limited contribution that genetic and psychopharmacology research has so far made to the understanding and treatment of drug addiction, especially in preventing relapse [18,59,67,70,79].

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Interestingly, psychological stress (hereafter stress) has proven to be an excellent model to take into account how complex social factors are involved in health and might contribute to the development of more effective explanations and interventions and public policies in drug addictions ([1,28,29,113,123]. However, the neurobiological mechanisms involved in the role of stress on drug addiction remain unclear.

The aim of this paper is to provide an integrative review of the most influential literature to date on the role of stress in drug addiction from a neurobiological perspective in humans.

2. Literature review

A literature search was conducted of the core collections of Web of Science on the topics of "stress and addiction". The search was limited to articles published in English in the last decade (2008–2018) under the category of "Neuroscience and Drug Abuse". A total of 1.710 records were found, including a selection of the 100 most influential articles in the field (according to Semantic Scholar), and supplementary articles (40) located in the reference section of identified articles or by hand search of the most influential authors in the field of stress and addiction: George F. Koob, director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA), Eric J. Nestler, researcher of the National Institute on Drug Abuse (NIDA) and the National Institute of Mental Health (NIMH), Nora D. Volkow, director of the National Institute on Drug Abuse (NIDA), pioneer in the study of drug addiction using neuroimaging, and Rajita Sinha, director of Yale Interdisciplinary Stress Center, pioneer in the study of the neurobiology of chronic stress and drug addiction. The website of the National Institute on Drug Abuse (NIDA) was also consulted to reduce the risk of publication bias. Most articles were excluded because the terms "stress" and "addiction" were missing from the title or keywords, they were duplicated, focused on animal models of drug addiction, or dealt with non-drug/behavioral addictions, considered outside of the scope of this review. Finally, a total of 130 full-text core papers focused on neuropharmacology and neuroimaging were finally selected for a state -of-the-art narrative synthesis.

3. Neurobiology of the stress response

Stress occurs "when an individual perceives that environmental demands tax or exceed his or her adaptive capacity" [29], so the brain plays a central role in the perception of threat and the trigger of the stress response. The stress response is mediated by three main stress-hormones: corticotropin-releasing factor (CRF) and cortisol (corticosterone in rodents) released by the hypothalamic–pituitary–adrenal (HPA) axis and adrenal cortex; and catecholamines, and norepinephrine or noradrenaline) released by the adrenal medulla and sympathetic nerves [99,100]. Stress hormones also provide feedback to the brain, regulating the activity of the HPA axis. This negative feedback loop depends on the activation of two types of glucocorticoid receptors in the brain: high-affinity mineralocorticoid receptors, activated by lower doses of cortisol, preventing further release of CRF; and low-affinity glucocorticoid receptors, activated by higher doses of cortisol, and resulting in the opposite effect, an increase in the release of CRF [99,100].

Classical research has described the detrimental effects of stress-hormones on the hippocampus and amygdala of the limbic system: In the hippocampus, acute stress enhances memory formation, while chronic and/or severe stress disrupts memory formation, leading to fragmented declarative memories or missing contextual details [38,61,120]. In contrast, acute and even mild stressors enhance amygdala function, attaching emotional significance to memories, which may activate the locus coeruleus to initiate the classical fear/anxiety response [45,116,120]. As expected, stress reductions result in structural changes in the amygdala [63]. New research suggests that emotional memories, involved in long-term aversive stress responses, may be stored in the bed nucleus of the stria terminals (BNST), located in the central part of the amygdala [27,116,126].

In recent years, research has increasingly focused on the effects of stress on the prefrontal cortex (PFC). Stress hormones significantly impair executive functions in the PFC that should play a key role in turning off the stress response once the threat is over [4,20,62,99,100]. Executive functions include control inhibition (self-control, resisting acting impulsively), interference control (selective attention and cognitive inhibition), working memory, and cognitive flexibility [35].

In sum, the effects of stress on the limbic system strikingly reflect differences between the hippocampus and the amygdala, highlighting the dominance of the amygdala over the hippocampus to enhance implicit emotional learning and memory, in particular fear conditioning, while disrupting of explicit learning and memory; the effects on the PFC further aggravate the situation, impairing the executive functions required for a slow-rational decision-making based on good inhibitory control, working memory and cognitive flexibility, leading instead to fast-emotional behaviour.

4. Neurobiology of drug addiction

Drug addiction is defined as a brain disease, characterized by a compulsion to seek and take the drug, loss of control in limiting intake despite harmful consequences, and the emergence of a negative emotional state when access to the drug is prevented [41,51,80,82]. For most people, it is a chronic, relapsing disorder, similar to other chronic conditions such as diabetes or hypertension, so the standard for treatment success would be the management of drug use over long periods of abstinence with occasional relapses. However, whether chronicity is a feature of drug addiction or a reflection of the lack of effective treatments remains a question [17].

A three-stage model has been proposed to explain the transition from drug abuse to addiction (for a complete review, see [82]).

4.1. Binge/intoxication stage

The initial positive reinforcing effect of drugs (liking) has long been associated with the dopamine reward system. Most psychostimulant drugs of abuse activate D1 receptors of dopamine in the mesolimbic pathway in the nucleus accumbens, and the inhibit D2 receptors of the striatocortical pathway in the PFC [36,107,108,141]. As a consequence, a higher incentive value (reward) and salience is attributed to drugs and drug-related cues (wanting) or craving, increasing the risk of binge and intoxication ([115,119]. Consistently, D2-agonist, like psychostimulants, induce positive reinforcing effects [141].

However, this incentive-salience theory of addiction does not fully explain why some positive rewarding effects of drugs seem to be independent of dopamine [119,142]. First, the positive reinforcement effects of opioids such as heroin, morphine, and endogenous endorphins (β-endorphin) are directly mediated by their action on μ receptors [31,145,152]. In fact, μ opioid antagonists such as naloxone and naltrexone prevent the rewarding effects of opioid drugs [31,145]. Second, the positive reinforcement effects of cannabis are mediated by the endocannabinoid system, also involved in the reinforcing effects of natural rewards [94,102,110,125].

4.2. Withdrawal/negative affect stage

Drug abuse leads to neuroadaptations, long-term changes in the brain, resulting in the emergence of a negative emotional state or withdrawal symptoms. According to the allostatic theory of addiction, these neuroadaptations involve dynamic readjustments towards a new set point, achieving stability through change, instead of just going back to homeostasis [14]. Accumulated in the long-term, this leads to an increased risk of addiction and relapse [43,81,82,100].

An early neuroadaptation involves the down-regulation of the dopamine reward system (also referred to as within-brain reward system

neuroadaptation), reducing the availability and responsivity of the D2 receptors in the nucleus accumbens and modifying the reward threshold ([39,139], leading to a failure to experiment pleasure with natural reinforcers (anhedonia) and increasing the risk of escalation of drug intake [81,82]. Furthermore, changes in the cortico-striatal glutamate pathway reduce sensitivity to non-drug rewards and increase reactivity to drug-related cues and negative emotional states [66,121,141].

A later neuroadaptation involves the recruitment of brain anti-reward systems (also referred to as between-system neuroadaptation) induced, basically, by CRF, dynorphin and hypocretin (orexin) hormones. First, CRF would be responsible of an early dysregulation of the HPA axis and later, the dysregulation of the extra-hypothalamic system in the extended amygdala, which induce an aversive negative emotional state [55,72,73,75,76]. Complementarily, CRF antagonists block negative emotional states induced by drug absence [43,73]. On another hand, activation of receptors from the dynorphin-κ aversive opioid system receptors are also responsible for inducing a negative emotional state in the extended amygdala by decreasing dopamine activity in the reward system and impairing executive functions in the PFC [26,133,144]. Second, antagonists of dynorphin-k receptors such as naltrexone are used as anti-craving medication [6]. Third, hypocretin (orexin), involved in the regulation of arousal and appetite, may also be involved in inducing a negative emotional state and reward-seeking, by modulating the activity of the HPA axis and the extended amygdala [11,16]. However, this negative emotional state associated with withdrawal may be modulated (buffered) by the action of, at least, four components: μ-agonist opioids [31,144], endocannabinoids [94,102,110,125], neuropeptide Y [47] and, finally, oxitocin, involved in reward, social affiliation and bonding [151].

4.3. The preoccupation/anticipation stage

One of the key findings from neuroimaging studies in recent years has been the dysregulation of the PFC induced by drug abuse. Interestingly, PFC is heavily involved in decision-making and self-regulation, necessary to prevent loss of control, compulsive drug-taking and to prevent relapse [9,64,140]. Furthermore, disruption of the dorsolateral PFC seems to be involved in decision-making, overestimating drug-related rewards and underestimating drug-related aversive consequences [97], while changes in the ventromedial PFC cortex seem to be more involved in inhibitory control or emotional regulation of craving induced by drugs/drug-related cues or by negative emotional states [62,111,115,146]. Interestingly, recent research suggests that the insular cortex, responsible for awareness of all subjective feelings, may also be involved in craving and decision-making [106,115].

In sum, drugs “hijack” the brain reward, anti-reward and prefrontal systems resulting in neuroadaptations involved in the pervasive transition from drug abuse to addiction, which worsens over time.

5. The role of stress on addiction

A growing body of evidence emphasises the central role of stress in the transition from drug abuse to addiction ([2,37,57,60,76,78,80,82,127,143]. The progression towards drug addiction is currently best described as the result of an accumulation of allostatic changes, similar to other chronic conditions such as hypertension, diabetes or obesity. This is worth noting because allostatic changes involve gaining stability through change, beyond a simple return to the initial homeostatic state [100]. Stress (chronic stress) is one of the major sources of allostatic (over)load, resulting in brain changes that lead to a progressive imbalance between states of opposite hedonic valence (positive and negative), increasing the risk of addiction [14,78,80,100].

Interestingly, brain changes induced by chronic stress mediate and overlap the brain changes induced by drug abuse, providing a better understanding of the three stages involved in the transition from drug use to addiction.

First, chronic exposure to stress and drug abuse both lead to down-regulation or deficit of the brain reward system. In the case of drug abuse, as a direct result of the over-activation of the brain reward system, driven by the positive reinforcement that characterises the binge/intoxication stage. This down-regulation is involved in the experience of reward-craving induced by the exposure to drugs or drug-related cues during the binge/intoxication stage [57,80,86,147]. However, most importantly, stress exposure and drug abuse result in the progressive up-regulation or excess of the brain stress system (till now referred to as the “anti-reward” brain system), which is the key to understanding the stress-like state of the negative emotion/withdrawal stage, driving drug-seeking and taking through negative reinforcement. This up-regulation results from the increase in the reactivity of the HPA axis and amygdala, also increasing hypersensitivity to stress [10,74,75,77,78,87,143]. It is, therefore, involved in the relief-craving [115,127,143]. Furthermore, repeated exposure to drugs and withdrawal from drugs can be considered, in themselves, as stressors, inducing the same brain changes, increasing the risk of relapse, a hallmark of addiction ([44,78].

Second, both stress and drug abuse lead to, on the one side down-regulation of the hippocampus, disrupting learning and emotion regulation, including the brain ability to inhibit the reactivity of the HPA axis [10,84]; on the other side, disruption of PFC, impairing the executive functions required not only for self-regulation of negative emotional states, but also involved effort-related decision-making, necessary to suppress amygdala activation during the preoccupation/anticipation stage ([20,100,126,129]. Stress floods the PFC with dopamine and norepinephrine, resulting in a progressive reduction of functional connectivity within the PFC, disrupting the ability to inhibit relapse in the presence of craving and facilitating the transition to compulsive drug-taking, the hallmark feature of drug addiction [25,97]. In fact, stress has been regarded as the single most powerful and reliable trigger of craving and relapse [10,71–76,84,115,127,143], being associated with higher severity of drug addiction and worse treatment outcomes [65].

Consistently, brain-imaging studies, mostly using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), indicate that classic drug-prone state of drug addiction would be mediated by the action of pro-stress hormones in hypothalamic, extra hypothalamic regions and the PFC, involved in the appraisal or regulation of the stress response and addiction. CRF mediates the activity of the HPA axis and amygdala and is responsible for inducing a stress-like negative emotional state [34,55,72,73,93,127,130,153]. The dynorphin-κ aversive opioid system is responsible not for only inducing a stress-like negative emotional state by increasing stress sensitivity, but also for impairing the dopamine reward system and executive function, facilitating the transition to addiction [26,44,147]. Finally, the hypocretins (orexin) would also be involved in the modulation of the stress and reward pathways [46]. In contrast, some other hormones work as stress relievers or anti-stress hormones, such as neuropeptide Y [47,50,132]. As expected, κ-antagonists (naltrexone) are considered anti-craving medication, reducing stress induced by craving and preventing relapse [77,115].

In brief, stress contributes to set up and aggravate drug addition, respectively, by promoting incentive salience of drugs and drug-related stimuli, inducing a negative emotional state and impairing executive functions. Not surprisingly, drug addiction has been conceptualised as a learning disorder, a reward deficit disorder or anti-reward excess disorder, an executive function disorder, and more recently, as an allostatic disorder.

5.1. Implications of early life stress and drug addiction in humans

Despite the strong evidence of genetic contributions to addiction vulnerability (around 50% heritable), specific genes have not been identified yet [124]. Stress provides a conceptual framework to understand how non-genetic factors, such as social environment and life experiences throughout the life span, induce epigenetic changes, regulating the expression of genetic information, either by inhibiting gene expression by methylation or facilitating gene expression by acetylation ([83,92,95,98,154]). For example, genetic polymorphisms of the serotonin transporter and receptor genes associated with adverse life events are thought to increase susceptibility to drug addiction, although research in this area continues [32,59].

Stress has been involved in the dysregulation of the synthesis of Nur transcription factors [24], responsible for increasing the HPA reactivity in response to exposure to stress-related hormones during the life span, making individuals more vulnerable to addiction and more susceptible to their pervasive effects ([21,101,109,155,156]). Stress has also been involved in the disruption of the synthesis of the brain-derived neurotrophic factor (BDNF), responsible for promoting the growth of new neurons and preventing existing ones from dying, especially in the hippocampus, mediating memory consolidation [5,69,118].

In particular, exposure to early life stress is a well-known risk factor for the development of addiction and vulnerability to relapse [14,37,96,105,127]. Developing brains are more vulnerable to the toxic effects of exposure to stress hormones associated with virtually every form of abuse (psychological or physical), neglect, poverty or major sources of the "allostatic load" that leads to long-term brain changes through long-term potentiation or depression, strengthening synapses in the amygdala, and weakening them in the hippocampus, HPA axis and PFC (synaptic plasticity)([13,22,56,93,105,128].

5.2. Implications for translating animal research in drug addiction to humans

Most studies in drug addiction use animal models of rodents. However, although brain stress and reward systems are largely shared by humans and animals, there has been little translation of these findings to humans [137]. One of the reasons may be that animal studies tend to underestimate, limit or simply fail to incorporate psychosocial stressors that play a critical role in human drug addiction [59]. Yoshimasu [150] highlights three psychosocial stressors: legal regulations and social norms, which can induce guilt or stigma; lower socioeconomic status, unemployment or job stress, characterized by low job control and high job demand, which lead to a loss or lack of access to financial resources; and loneliness or conflictive personal relationships, with opposite effects to supportive social interactions. In this line, a very recent study using rodents that are offered a choice between drugs and social interaction found that social reward prevented drug self-administration and craving regardless of sex, drug class, drug dose, training conditions, abstinence duration, and even addiction score [135].

Based on the role of stress in human drug addiction, future research in this field should explore, first, such psychosocial factors to guarantee ecological validity [131]; second, individual differences in susceptibility versus resilience to stress (Al'Absi, 2018; [21,23,130]), including sex differences in the brain response or neuroadaptations to exposure to stress and drugs that might affect the risk of addiction ([7,8,103]. For example, women seem to engage more often in drug abuse to regulate stress and negative emotional states than men [136]. Third, future research should also explore similarities between the role of stress in drug-addiction and non-drug/behavioral addictions, which resemble some of the neurobiological mechanisms described in drug addiction [52,85].

5.3. Implications for interventions in drug addiction in humans

A better understanding of the key role of stress in drug addiction provides an opportunity for more effective interventions and social policies that include a comprehensive psychosocial assessment and a stress-reduction approach within the larger social context [2,23,137,148].

The brain-disease model of addiction has dominated funding and direction in research but has led to poor policies focused on removing drugs from society (war on drugs) or pharmacologically treating the "addicted" brain, with limited success, contributing to over-medicalization [124,134]. Furthermore, most of these drugs were developed prior to the establishment of the brain-disease model and consist of drugs of substitution (e.g., methadone), drugs to reduce withdrawal symptoms or cravings (e.g., clonidine in opioid addiction) or drug-antagonists to prevent relapse (e.g., naltrexone; [54,77,137]). Overall, most available pharmacological treatments target the reward dopaminergic system instead of stress brain systems, which remain a major challenge in drug addictions [79]. Drugs to treat addiction to psychostimulants such as cocaine or amphetamines, or to prevent relapse remain a challenge.

Interestingly, stress can induce similar long-term brain changes to those induced by drugs. Therefore, stress control or negative emotion reduction may be key elements for successful individual drug addiction treatments in humans, ranging from social support, physical exercise to contingency management, offering non-drug alternative reinforcers for pleasure-seeking or stress-relief, decreasing the risk of engaging in problematic drug-taking [112] and, more recently, mindfulness treatments [104,138]. Furthermore, evidence from randomised controlled trials is growing in favour of stress-reduction based intervention centred on mindfulness ([42,63,122]. According to the Web of Science, the most cited paper in the field of "stress and addiction" is a review of mindfulness interventions by Creswell [30]. Furthermore, the inability to tolerate or cope with stress predicts poor adhesion to treatments in human drug addiction [33,49]. In a recent study conducted of Kaye, Bradford, Magruder, and Curtin [68], unpredictable stress played a central role in the transition from drug abuse to addiction, but the importance of targeting stress in addiction treatments is underscored. Furthermore, stress-based interventions may work differently from drug-based treatments, benefiting PFC function instead of targeting amygdala function [3].

Based on the impact of stress on addiction, our brains seem to have evolved to be vulnerable to addiction if exposed to intense or chronic stress [40,48]. Therefore, it is time to bring the social context into human drug addiction, both for prevention and intervention, designing stress-reduction-based social policies that foster resources and opportunities to cope with life demands and guarantee a nurturing environment ([53,58,131]. Access to fewer resources are associated with increased susceptibility to the harmful impact of a stressful life events and adverse consequences of drug abuse [114]. Future research needs to rely not only on the brain, but on the prominent role of psychosocial factors and stress in how brain-behavior relationships unfold in the social context.

Unfortunately, to date, most social policies fail to address stressful or adverse social conditions in which drug addiction occurs, is maintained, or aggravated [19], and focus almost exclusively on individual pharmacological treatments after drug addiction is established [18].

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