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Review

Substance use modulates stress reactivity: Behavioral and physiological outcomes

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HIGHLIGHTS

- Drugs of abuse and alcohol alter behavioral & physiological responses to stress
- Drug use leads to altered CRF response to stress
- CRF antagonists have not been effective in treating SUD
- Therapies targeting both central & peripheral stress responses may be more effective

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ABSTRACT

Drug addiction is a major public health concern in the United States costing taxpayers billions in health care costs, lost productivity and law enforcement. However, the availability of effective treatment options remains limited. The development of novel therapeutics will not be possible without a better understanding of the addicted brain. Studies in both clinical and preclinical models indicate that chronic drug use leads to alterations in the body and brain's response to stress. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis may shed light on the ability of stress to increase vulnerability to relapse. Further, within both the HPA axis and limbic brain regions, corticotropin-releasing factor (CRF) is critically involved in the brain's response to stress. Alterations in both central and peripheral CRF activity seen following chronic drug use provide a mechanism by which substance use can alter stress reactivity, thus mediating addictive phenotypes. While many reviews have focused on how stress alters drug-mediated changes in physiology and behavior, the goal of this review is to focus on how substance use alters responses to stress.

Contents

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1. Introduction

Recreational drug use has existed in nearly every society throughout history. However, this recreational use can spiral into addiction for a subset of vulnerable individuals. One of the factors mitigating this vulnerability is stress. Clinical research demonstrates that chronic stress is a risk factor in the development of addiction [1,2], and as many as 70% of addicts have experienced trauma within their lifetime [3]. Furthermore, life stress is a critical factor mediating treatment outcomes and relapse rates [4–6]. In light of this, treatments aimed at reducing stress could increase addiction treatment success [7].

To promote the identification of therapies to reduce stress in addicts, we must first determine the neurobiological mechanisms underlying the interactions between drugs of abuse and stress. Many studies have examined the ability of stress exposure to potentiate addictive phenotypes [8–11]. However, it is just as important to examine how addicts respond to stress and how drugs of abuse can alter stress responsivity. This review will focus on how chronic drug administration in both preclinical and clinical models can lead to alterations in behavioral and physiological responses to stress. Furthermore, we will discuss the neurobiological alterations underlying the ability of chronic drug use to affect responses to stress and the implications of these alterations in designing new treatment options.

2. Stress-related psychiatric disorders and substance abuse comorbidity

Preclinical research has clearly demonstrated that drugs and stressful stimuli exhibit cross-sensitization, whereby experience with drugs leads to an enhanced response to stress and vice versa [12–15]. This cross-sensitization between drugs and stress is likely mediated by the overlap in neural circuitry. Both preclinical and clinical studies have demonstrated that acute stress and drug exposure lead to the activation of similar brain regions [5,16,17].

As there is such a clear relationship between the neurobiological circuits underlying stress and addiction, it is not surprising that there is a high comorbidity between substance use disorders (SUD) and post-traumatic stress disorder (PTSD). While overall estimates of SUD prevalence are 3–7% nationally [18], within individuals with PTSD, the lifetime prevalence increases to 19–35% for SUD and 36–52% for alcohol use disorder (AUD) [19–21]. Likewise, PTSD is more common in individuals with SUD, with an estimated lifetime PTSD prevalence of 26–52% (compared to 8% in the total population) [3,22,23].

Individuals with both PTSD and SUD have more severe symptomology and exhibit poorer treatment outcomes than those with PTSD or SUD alone [24,25], suggesting a magnifying effect of substance use on stress responsivity. Poorer treatment outcomes for these disorders, are compounded by additional physical and psychiatric health problems, including higher incidence of depression and anxiety disorders [22,25–27], as well as cardiovascular and neurological problems [28]. Furthermore, these individuals are more likely to be unemployed and are more prone to violence [24,29,30]. Taken together, this suggests that gaining a better understanding of the neurobiological mechanisms underlying this relationship could help reveal unique treatment options for this population.

While much research has focused on patients with PTSD using alcohol and drugs to "self-medicate", there is evidence that SUD can predate PTSD. Individuals with SUD have a heightened likelihood of trauma exposure, which in turn, leads to a heightened risk of PTSD [31,32]. Furthermore, SUD, as well as nicotine dependence, can increase PTSD vulnerability after trauma exposure [26,33,34]. Regardless of the temporal order of SUD and PTSD, it is clear that SUD can sustain, prolong, or worsen PTSD symptoms [35].

For example, within a population of PTSD patients, those with lifetime substance use, specifically cocaine and marijuana use, exhibited significantly higher PTSD symptomology than those without drug use [36]. Furthermore, PTSD patients that smoke exhibit more severe withdrawal from nicotine and this withdrawal leads to exacerbated PTSD symptomology [37,38]. Additionally, PTSD patients that successfully quit smoking exhibit improved negative affect compared to those who are unsuccessful [39]. Moreover, alcohol withdrawal and craving can increase response to trauma cues in alcoholics with comorbid PTSD [40]. Consistent with this, a study of individuals with comorbid SUD and PTSD reported intensified trauma symptoms following relapse [41].

Although the effects of drugs of abuse on stress reactivity may be most prominently seen in individuals with PTSD, they are not the only individuals affected. Drug abuse is often comorbid with other stress-related psychiatric disorders. For example, approximately 20% of individuals with mood disorders and 15% with anxiety disorders report at least one concurrent SUD. Major depression is strongly associated with SUD as individuals with major depression are 7 times more likely to exhibit drug abuse or dependence [42]. When examining lifetime SUD prevalence, 50% of individuals with generalized anxiety disorder (GAD) report problems with substance abuse. The rates of SUD increase in individuals with concurrent anxiety disorders, as 46% of individuals with concurrent panic disorder, social phobia, and generalized anxiety disorders report comorbid SUD [43]. As with PTSD, substance use can exacerbate symptoms of anxiety and initiate additional anxiety disorders [44].

Chronic drug use leads to an increased response to stress, even in individuals who do not exhibit comorbid psychiatric conditions. Unfortunately, clinical studies are limited by extreme environmental and genetic variability, which can obscure the data and misinform scientific interpretations. Therefore, this review will focus on the way individuals

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