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Mini-review

Connecting the pathology of posttraumatic stress and substance use disorders: Monoamines and neuropeptides

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ABSTRACT

Posttraumatic stress disorder (PTSD) co-occurs highly with substance use disorders (SUDs), yet the neurobiological basis for this comorbid relationship remains unclear. PTSD and SUDs result in similar pathological states including impulsive behavior, reward deficiency, and heightened stress sensitivity. Hence, PTSD and SUD may depend on overlapping dysfunctional neurocircuitry. Here we provide a short overview of the relationship between comorbid PTSD and SUD, as well as the potential role of select neurotransmitter systems that may underlie enhanced vulnerability to drug abuse in the context of PTSD.

Contents

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1. Introduction

1.1. Epidemiological data on the incidence of co-occurring PTSD and substance abuse disorders

Psychological trauma is a risk factor for the development of both posttraumatic stress disorder (PTSD) and substance use disorder (SUD). Many persons with PTSD go on to develop secondary psychiatric disorders, and substance use disorders are highly prevalent in the PTSD-afflicted population. In 1995, the National Comorbidity Survey reported that the lifetime prevalence of alcohol use disorder was approximately 52% in men and 28% in women, whereas prevalence of drug use disorder was 35% in men and 27% in women with a history of PTSD (Kessler et al., 1995). Recently, NESARC (National Epidemiological Survey on Alcohol and Related Conditions) reported similar results, indicating the prevalence of alcohol and drug use disorders in individuals with PTSD to be about 42% and 22%, respectively (Pietrzak et al., 2011). NESARC reported the lifetime prevalence of alcohol use disorders at rate of 21–26.7% in men and 9.9–12.5% in women in the general population (Goldstein et al., 2012). Lifetime prevalence of drug use disorders was 4.4–13.9% and 2.5–6.7% in men and women, respectively (Goldstein et al., 2012). Higher rates of comorbidity are reported in populations at high risk for traumatic stress exposure such as military personnel. For example, a recent study documented that 63–76% of veterans meeting the criteria for substance use disorders had co-occurring PTSD (Seal et al., 2011). A positive PTSD diagnosis increased the odds of having an alcohol or drug use disorder or both, 3- to 4-fold (Seal et al., 2011). These epidemiological studies suggest that PTSD and SUD are strongly linked.

1.2. Theories on the causative relationship between substance abuse and PTSD

Concurrent PTSD–SUD is a significant public health concern. Treatment of comorbid PTSD and SUD is costly (Brown et al., 1999). Individuals who are dually diagnosed exhibit poorer psychosocial functioning and treatment outcomes than those with PTSD or SUD alone (Drapkin et al., 2011; Read et al., 2004). Understanding the causal nature of comorbid PTSD–SUD may lead to more efficient treatment strategies for dually-diagnosed individuals and better preventative interventions to reduce substance abuse in persons with PTSD.

There are several hypotheses regarding the causal relationship of co-occurring PTSD and SUD. One hypothesis suggests that PTSD temporally precedes the development of a substance use disorder. Under this notion, it is hypothesized that individuals self-medicate their PTSD symptoms with drugs and alcohol or use drugs as an avoidant coping strategy (Khantzian, 2013). Alternatively, emotional dysregulation evident in persons with PTSD may lead to impulsive behavior, which may manifest in response to emotional distress and result in drug use as a maladaptive coping mechanism (Weiss et al., 2012). Drug consumption may result in negative reinforcement of drug-taking behavior, motivating escalating use due to the expectation of symptom relief and culminating in a SUD. A second hypothesis suggests that substance abuse precedes and enhances vulnerability to PTSD. In this scenario, drug abusers may engage in risky behaviors that increase the likelihood of a traumatic experience, subsequently increasing the risk for PTSD (Kilpatrick et al., 1997; Kaysen et al., 2006). Alternatively, persons with SUD may be at risk for PTSD following a trauma due to pathological arousal and stress states resulting from repeated drug use or withdrawal (Stewart and Conrod, 2003). A third hypothesis indicates that predispositions shared by PTSD and SUD may influence development of both disorders due to shared risk (Xian et al., 2000; McLeod et al., 2001; Sartor et al., 2011). Regardless of temporal occurrence of PTSD and SUD, it is possible that once comorbidity has been established the two disorders interact and lead to a cyclical relationship. PTSD may maintain, prolong, or exacerbate SUD symptoms through self-medication, while the same relationship could be hypothesized for the maintenance of PTSD symptoms by substance abuse or dependence (Stewart and Conrod, 2003).

Although evidence exists in support of each of the aforementioned hypotheses, this review will focus on potential mechanisms by which PTSD may enhance the vulnerability to SUDs. Many studies demonstrate that PTSD temporally precedes and increases the risk for subsequent development of a SUD (Bremner et al., 1996; Chilcoat and Menard, 2003). Persons with PTSD perceive their co-occurring PTSD–SUD as functionally related (Brown et al., 1998), and report self-medicating their untreated symptoms with drugs and alcohol (Leeies et al., 2010). CNS depressants such as alcohol, benzodiazepines, marijuana, and heroin ease hyperarousal and intrusion symptoms in patients with PTSD, while symptoms of emotional numbing and avoidance are highly prevalent in patients with comorbid cocaine dependence (Bremner et al., 1996; Najavits et al., 2003). Studies demonstrate that PTSD symptom severity is positively related to the level of substance use (Bremner et al., 1996; Back et al., 2006a; Hien et al., 2010), and PTSD severity predicts drug craving in response to trauma- and drug-related cues (Saladin et al., 2003). Improved PTSD symptomology predicts improvement of SUD symptoms (Hien et al., 2010; Back et al., 2006b; Burns et al., 2010). Taken together, these studies suggest that PTSD enhances the susceptibility to substance abuse. Given the wealth of literature in support of this hypothesis, this review largely focuses on the neurobiological underpinnings that may contribute to this casual relationship. Examples of neurobiological alterations observed in clinical studies of PTSD and SUD, as well as preclinical rodent models, are presented in Table 1.

2. Common neuropathological states in PTSD and SUD

PTSD and SUD share common psychopathological states which may provide mechanistic insights regarding the increased incidence of substance abuse in individuals with PTSD. Herein we discuss impulsivity and negative emotional states associated with these disorders including anhedonia and heightened states of anxiety and stress sensitivity, each of which putatively serves as a risk factor for susceptibility to drug abuse in PTSD.

2.1. Impulsivity

Many functional imaging studies demonstrate differences in the activation of the prefrontal cortex in brains of PTSD patients (Hughes and Shin, 2011). Hypothetical framework based on these studies suggests that hypoactivity of the ventral medial prefrontal cortex may convey a lack of inhibitory control over networks mediating emotion and arousal in PTSD, while hyperactivity of the dorsal anterior cingulate and insular cortices may contribute to enhanced expression of fear- and anxiety-like states (Pitman et al., 2012). Altered functional capacities of the prefrontal cortices may also lead to altered executive functioning and cognition in the form of impulsivity or altered decision making behaviors, which could ultimately introduce or perpetuate substance use. Impulsivity measures include impulsive motor action and choice, both of which have putative relationships with drug abuse (reviewed in Kirby et al., 2011). Motor impulsivity in humans predicts the severity of psychostimulant abuse (Moeller et al., 2001). Likewise, rodents with high motor impulsivity escalate their cocaine intake more quickly (Dalley et al., 2007). Animal studies show that impulsive choice contributes to the severity of substance use. Rats with high impulsive choice in delayed discounting acquire self-administration of psychostimulants at a faster rate and are more likely to reinstate to drug-seeking behavior than low impulsive rats (Perry et al., 2005, 2008). Additionally, high-alcohol preferring mice are more impulsive than those that prefer alcohol less (Oberlin and Grahame, 2009).

Individuals with PTSD demonstrate greater motor impulsivity in the form of more inhibition-related errors in the Go/No-Go task which measures prepotent motor response inhibition (Swick et al., 2012). This