Neuropharmacology 62 (2012) 552–564

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Stress modulation of drug self-administration: Implications for addiction comorbidity with post-traumatic stress disorder

Marian L. Logrip*, Eric P. Zorrilla, George F. Koob

Committee on the Neurobiology of Addictive Disorders, The Scripps Research Institute, 10550 North Torrey Pines Road, SP30-2400, La Jolla, CA 92037, USA

ARTICLE INFO

Article history:
Received 19 April 2011
Received in revised form
11 June 2011
Accepted 6 July 2011

Keywords:
Maternal separation or isolation
Shock or trauma
Social defeat or resident-intruder
Ethanol or alcohol
Cocaine or amphetamine or psychostimulant
Opiate
Post-traumatic stress disorder
Alcoholism

ABSTRACT

Drug abuse and dependence present significant health burdens for our society, affecting roughly 10% of the population. Stress likely contributes to the development and persistence of drug use; for example, rates of substance dependence are elevated among individuals diagnosed with post-traumatic stress disorder (PTSD). Thus, understanding the interaction between stress and drug use, and associated neuroadaptations, is key for developing therapies to combat substance use disorders. For this purpose, many rodent models of the effects of stress exposure on substance use have been developed; the models can be classified according to three categories of stress exposure: developmental, adult nonsocial, and adult social. The present review addresses preclinical findings on the effect of each type of trauma on responses to and self-administration of drugs of abuse by focusing on a key exemplar for each category. In addition, the potential efficacy of targeting neuropeptide systems that have been implicated in stress responses and stress system neuroadaptation in order to treat comorbid PTSD and substance abuse will be discussed.

This article is part of a Special Issue entitled 'Post-Traumatic Stress Disorder'.

1. Introduction

Substance abuse and addiction cause significant health care burdens on society, with current estimates suggesting 10% of the population suffers from some form of substance use disorder (Hall et al., 1999; Ross, 1995; Stinson et al., 2005). The progression of drug abuse has been depicted as a downward spiral comprised of three stages: binge/intoxication, preoccupation/anticipation, and withdrawal/negative affect (Koob and Le Moal, 1997). During the acquisition phase, characterized by episodes of intoxication, drug taking produces positive reinforcement. With the development of drug dependence, withdrawal leads to a negative emotional state; as a result, drugs are taken to alleviate or avoid withdrawal symptoms (i.e., negative reinforcement). Periods of abstinence are characterized by pervasive thoughts about the addictive drug, yielding a high rate of relapse (Koob et al., 2004). Brain stress systems are thought to play a significant role in generating the negative emotional state characteristic of drug dependence, with dysregulation of stress systems also underlying the persistence of drug-seeking and relapse (Koob, 2008). The recruitment of brain stress systems during the progression to drug dependence suggests that anxiety disorders, characterized by heightened stress responses, may predispose individuals to develop addictive disorders and/or perpetuate and worsen addictive disorders once established.

One anxiety-related disorder receiving increased attention as a possible contributing factor to the development of addictive disorders in humans is post-traumatic stress disorder (PTSD). Triggered by exposure to a traumatic experience, PTSD is characterized by persistent maladaptive symptoms related to the trauma, including blunted emotional responses, hyperarousal, and flashbacks. Among individuals diagnosed with PTSD, the incidence of drug abuse and addiction is markedly elevated, with the highest comorbidity observed for alcohol dependence, followed by other depressants, such as opioids and cannabinoids, although stimulants like cocaine are also abused by some, possibly dependent on the sequelae of symptoms experienced by the individual (Jacobsen et al., 2001). Multiple studies have shown three- to five-fold increases in the development of substance abuse among PTSD patients, yielding substance abuse comorbidity in nearly half of all PTSD patients (Breslau et al., 2003; Mills et al., 2006; Perkonigg et al., 2000). Conversely, upwards of 25% of the substance abusing population may suffer from some form of PTSD (Driessen et al., 2008). Even in the absence of PTSD, traumatic experiences can precipitate relapse in recovering addicts (Dewart et al., 2006; Zywiak et al., 2003). Individuals with substance abuse disorders

* Corresponding author. Tel.: +1 858 784 8026; fax: +1 858 784 7405.
E-mail address: mlogrip@scripps.edu (M.L. Logrip).

0028-3908/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neuropharm.2011.07.007

with comorbid PTSD face worse treatment outcomes (Brown et al., 1995; Brown and Wolfe, 1994), indicating a need for improved therapies to address the dual diagnosis. Thus, understanding the neural mechanisms that may jointly subserve PTSD and substance abuse presents an important target for therapeutic development.

Several animal models have been established that resemble key phenotypes of PTSD, such as long-term persistence of conditioned fear responses and heightened sensitivity to novel stressful stimuli. Such paradigms include delivery of electric shocks to tail or paws, social stress from exposure to predators or aggressive conspecifics, or multiple stressors experienced one after the other, termed single prolonged stress (Stam, 2007). Lack of predictability and controllability of the stressors are central features of paradigms that generate persistent post-traumatic effects (Foa et al., 1992; Koolhaas et al., 2011). While not fully validated as rodent models of PTSD, early life traumas, such as maternal separation, can have long-lasting effects on adult stress responsiveness, including heightened startle and novelty responses, hypothesized to be key elements of rodent PTSD models (Kalinichev et al., 2002a,b). Exposure to social and nonsocial stressors in adulthood has been used to model how adult traumatic stress alters behavior, both acutely and following extended post-stress intervals. Social stressors, such as isolated housing and defeat by a dominant animal, rely on the innate sociability and social structures of the animals in question. Numerous paradigms exist to generate nonsocial stress, including restraint, forced swimming, tail pinch, and electric shock. Chronic variable stress may utilize both varieties of adult stressors, as it involves sequential exposure to multiple stressors over time. Although published studies have not explicitly investigated the interaction between a PTSD-like state and drug self-administration, many have utilized stress delivery paradigms in the context of drug self-administration that have otherwise been verified to generate PTSD-like symptoms in rodents.

This review focuses on rodent models designed to test the effects of stressors on motivational properties of alcohol and drugs of abuse. The interaction between stressful life events and drug addiction will be analyzed by focusing on one prototypical stressor from each category – maternal separation, footshock and social defeat as models of early life, adult nonsocial and adult social stress – and their ability to modulate rodent behavioral responses to and self-administration of drugs of abuse. The studies discussed below highlight the dual temporal impact of stressors, which can both acutely precipitate behavioral changes and exert effects following an extended post-stress interval, as is characteristic of PTSD (Fig. 1). It should be noted, however, that none of the studies has directly addressed the generation of a PTSD-like state in the rodent on drug self-administration, and thus the intention is not to validate the existing paradigms as rodent models of comorbid PTSD and drug abuse. Instead, synthesis of the current knowledge regarding stress modulation of rodent drug self-administration, as well as pharmacological targets showing promise for decreasing drug self-administration in these models, may provide a foundation for the future development of behavioral paradigms that more directly address the role of trauma in modulating drug use, as well as the efficacy of new pharmacotherapies to treat comorbid PTSD and drug abuse.

2. Effects of early life trauma: maternal separation

Stress experienced early in life can profoundly affect adult behavior, with childhood trauma associated with the severity of drug dependence (Enoch et al., 2010; Triffleman et al., 1995). One common model of early life traumatic stress in rodents is maternal separation, a paradigm involving repeated separation of pre-weaning pups from their mothers (Lehmann and Feldon, 2000; Plotsky and Meaney, 1993). The effects of maternal separation depend on the length of separation, as brief (15-min) separation may be protective from, and extended (>180 min) separation predisposing to, heightened stress responses (Plotsky and Meaney, 1993). Extended maternal separation results in increased anxiety-like behavior in adult rats (Huot et al., 2001; Kalinichev et al., 2002b; Romeo et al., 2003), as well as elevated startle responses (Caldji et al., 2000), indicative of the face validity of maternal separation as a model for early life trauma yielding PTSD-like symptoms in adulthood. In humans, newborns that required isolation from their mothers during the first few months of life for medical reasons had increased risk of developing drug dependence (Veijola et al., 2008). Thus maternal separation provides a plausible model for studying the protracted effects of childhood trauma on drug self-administration in rodents.

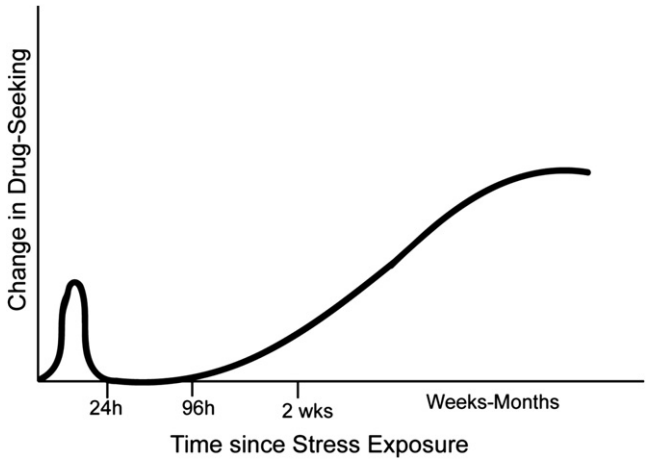

Fig. 1. Temporal modulation of stress effects on drug-seeking in rodents. Stress exposure acutely elevates behavioral responses to drugs of abuse and drug-seeking at all phases of drug self-administration. Post-stress increases in drug-seeking are usually short-lived, dissipating within 24 h after cessation of the stressor. The effects of traumatic stress history on drug-seeking begin to emerge again after an interval, postulated to be on the order of days to several weeks depending on the nature and severity of the stressor. These distal stress history-dependent elevations in drug-seeking behavior may persist for weeks or even months, akin to the effects of post-traumatic stress on human drug-seeking.

2.1. Alcohol

A history of maternal separation dose-dependently alters alcohol self-administration in adulthood; that is, the duration of the maternal separation directly impacts its modulation of alcohol drinking. Brief, 15-min daily separations of the litter from the dam, often referred to as "handling," reduced two-bottle choice alcohol intake, as compared with non-handled controls, in male rats from multiple strains (Hilakivi-Clarke et al., 1991; Jaworski et al., 2005; Ploj et al., 2003), including the alcohol-preferring Alko alcohol (AA) rats (Roman et al., 2003). Handling also reduced the acquisition rate of two-bottle drinking in AA rats, suggesting that brief intervals of maternal separation may protect against the development of high alcohol intake in rats otherwise prone to excessive alcohol consumption.

Unlike brief exposure, extended maternal separation increased alcohol intake in adulthood. Moderate, 3-hour neonatal separation elevated sweetened 10% alcohol intake in adult mice (Cruz et al., 2008). Rats with similar extended separation histories also drank significantly more sweetened alcohol in adulthood than handled rats, although results varied in comparison to control rats, with maternally separated rats showing either significant increases (Huot et al., 2001) or no significant difference (Jaworski et al., 2005) in alcohol intake. Increasing the duration of separation to 6 h yielded elevated