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Invited review

Neurobiological mechanisms that contribute to stress-related cocaine use

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ABSTRACT

The ability of stressful life events to trigger drug use is particularly problematic for the management of cocaine addiction due to the unpredictable and often uncontrollable nature of stress. For this reason, understanding the neurobiological processes that contribute to stress-related drug use is important for the development of new and more effective treatment strategies aimed at minimizing the role of stress in the addiction cycle. In this review we discuss the neurocircuitry that has been implicated in stress-induced drug use with an emphasis on corticotropin releasing factor actions in the ventral tegmental area (VTA) and an important pathway from the bed nucleus of the stria terminalis to the VTA that is regulated by norepinephrine via actions at beta adrenergic receptors. In addition to the neurobiological mechanisms that underlie stress-induced cocaine seeking, we review findings suggesting that the ability of stressful stimuli to trigger cocaine use emerges and intensifies in an intake-dependent manner with repeated cocaine self-administration. Further, we discuss evidence that the drug-induced neuroadaptations that are necessary for heightened susceptibility to stress-induced drug use are reliant on elevated levels of glucocorticoid hormones at the time of cocaine use. Finally, the potential ability of stress to function as a "stage setter" for drug use – increasing sensitivity to cocaine and drug-associated cues – under conditions where it does not directly trigger cocaine seeking is discussed. As our understanding of the mechanisms through which stress promotes drug use advances, the hope is that so too will the available tools for effectively managing addiction, particularly in cocaine addicts whose drug use is stress-driven.

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1. Stress-related cocaine use: evidence from human addicts

An accumulating body of evidence suggests that there is a strong relationship between stress and drug use by cocaine addicts. Anecdotal reports suggesting that stressful life events can precipitate relapse are paralleled by laboratory findings that the presentation of pre-recorded individualized stress-related scripts can induce craving in cocaine-dependent individuals (Sinha et al., 1999, 2000) and by epidemiological studies demonstrating high rates of co-morbidity between cocaine dependence and a number of stress-related disorders, including depression, anxiety, and post-traumatic stress disorder (PTSD; Rounsaville et al., 1991; Chen et al., 2011). In fact, it is likely that most incidents of relapse in cocaine addicts are in some way stress-related. In the case of PTSD, morbidity is not only higher in cocaine-dependent individuals (Cottler et al., 1992), but in many cases traumatic events predate cocaine use (Brady et al., 1998) and imagery based on the traumatic episode can elicit drug craving (Coffey et al., 2002). Indeed, one study noted that 95% of individuals with co-morbid PTSD and cocaine dependence reported a functional relationship between PTSD-related symptoms and drug use, with 86% reporting that a worsening of symptoms resulted in increased cocaine use (Back et al., 2006). While it is clear that a relationship exists between stress and cocaine use, the precise contribution of stress to the addiction process remains unclear and in many cases likely involves a complex interaction between stressful stimuli, cocaine-related cues, and the effects of the drug itself and may vary across different subpopulations of addicts (Preston and Epstein, 2011). These effects of stress on cocaine use are particularly problematic due to their unavoidable nature, making stress a key target for interventions aimed at relapse prevention. Thus, understanding the neurobiological processes that mediate the influence of stress on cocaine use is important for devising new and more effective therapeutic approaches for the management of addiction.

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2. Rodent models for studying stress-induced relapse

The contribution of stress to drug relapse can be studied preclinically using reinstatement-based designs in which the ability of various stressful stimuli to re-establish extinguished cocaine seeking is assessed in rats or mice. Despite some concerns about their construct validity (e.g., extinction of behavior in rodents is not the same as abstinence in human addicts) and their predictive validity (it is not clear that these approaches can be used to reliably identify effective relapse interventions), these approaches have been critical in shaping our understanding of the neurobiological pathways that contribute to stress-related drug use. Brief overviews of the two primary variations of these approaches, as applied in our laboratory, are provided below. Representative graphs depicting stress-induced cocaine seeking as measures using these approaches are shown in Fig. 1.

2.1. Self-administration/reinstatement approaches in rats

In rats, the study of relapse typically involves testing for the reinstatement of extinguished responding following intravenous cocaine self-administration (SA). Although a variety of stressors have been demonstrated to reinstate cocaine seeking following SA in rats, including food restriction (Shalev et al., 2003) and forced swim (Conrad et al., 2010), the most common method involves the use of uncontrollable intermittent electric footshock delivered through the grid floors of the SA chambers (Ahmed and Koob, 1997; Erb et al., 1996). Notably, while a number of laboratories have demonstrated footshock-induced reinstatement of cocaine seeking following SA in rats, the conditions under which reliable reinstatement has been observed are very specific (see e.g., Shelton and Beardsley, 2005) and, in our hands, depend on a history of SA under conditions of prolonged daily access (Mantsch et al., 2008a,b).

2.2. Conditioned place preference/reinstatement approaches in mice

Methodological considerations limit the utility of SA-based approaches in mice. Instead, relapse is commonly studied in mice by examining the ability of stressors to re-establish preference for a cocaine-paired environment following the extinction of cocaine-induced conditioned place preference (CPP). As is the case with the SA approach in rats, a number of stressors, including social stress (Ribeiro Do Couto et al., 2006) and uncontrollable electric footshock (Redila and Chavkin, 2008), have been demonstrated to reinstate extinguished drug-induced CPP in mice. However, the most frequently applied approach, and the one used in our laboratory, involves a brief (6-min) forced swim at 22 °C prior to transfer to the conditioning apparatus (Kreibich and Blendy, 2004; Mantsch et al., 2008a,b).

3. Anatomy of stress-induced relapse

3.1. Overview of the neurocircuitry implicated in stress-induced reinstatement

Using the reinstatement approach in rodents, we and others have begun to define the neurocircuitry involved in stress-induced

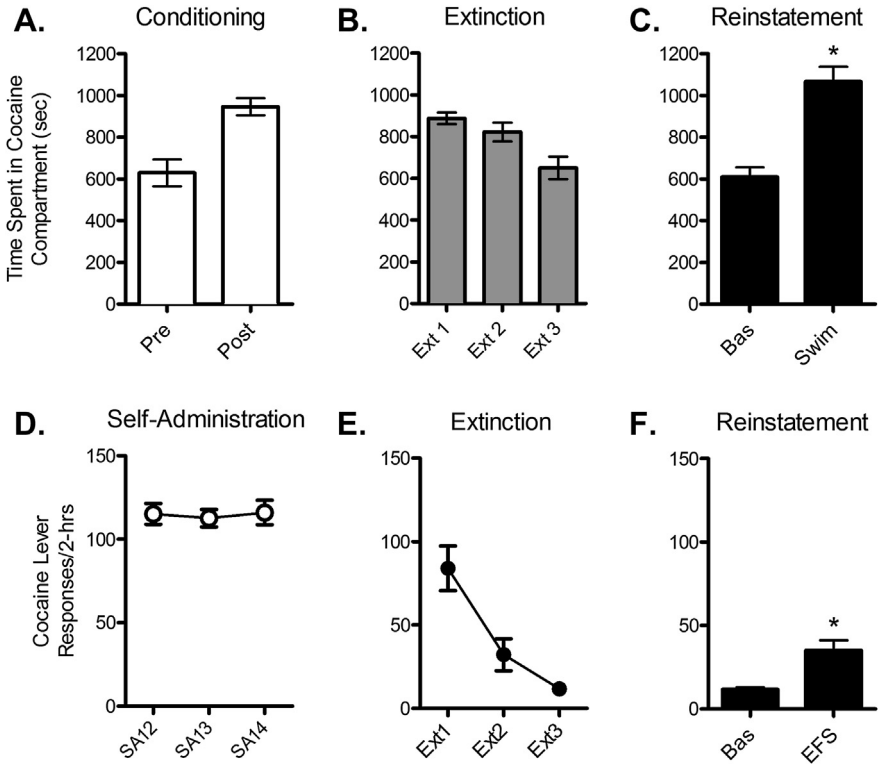

Fig. 1. Stress-induced cocaine seeking in mouse (A–C) and rat (D–F) models. Stress-induced reinstatement of extinguished cocaine-induced CPP is shown in Figs. A–C. Preference for a cocaine-paired compartment (4 × 15 mg/kg, ip) was established (A; increase in time spent post-conditioning vs. pre-conditioning) and extinguished (B) in C57BL/6 mice ($n = 4$) prior to reinstatement of preference by pre-exposure to a forced swim session (C; 6-min swim in 22 °C water; $^*P < 0.05$ vs. Bas). Stress-induced reinstatement in rats following cocaine self-administration and extinction is shown in Figs. D–F. Following training, rats ($n = 5$) self-administered cocaine (1.0 mg/kg/inf) by pressing a lever during daily 6-h sessions for 14 days (D) prior to undergoing extinction over a 10-day period during daily 2-h sessions (E) and reinstatement testing (F). Stress-induced reinstatement was observed as the ability of footshock stress (0.5 mA; 0.5″ duration delivered an ave. of 40-s apart over a 15-min session) to increase responding on the cocaine lever ($^*P < 0.05$ vs. Bas).