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`Up-regulation of histone acetylation induced by social defeat mediates the conditioned rewarding effects of cocaine

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ABSTRACT

Social defeat (SD) induces a long-lasting increase in the rewarding effects of psychostimulants measured using the self-administration and conditioned place procedures (CPP). However, little is known about the epigenetic changes induced by social stress and about their role in the increased response to the rewarding effects of psychostimulants. Considering that histone acetylation regulates transcriptional activity and contributes to drug-induced behavioral changes, we addressed the hypothesis that SD induces transcriptional changes by histone modifications associated with the acquisition of place conditioning. After a fourth defeat, H3(K9) acetylation was decreased in the hippocampus, while there was an increase of HAT and a decrease of HDAC levels in the cortex. Three weeks after the last defeat, mice displayed an increase in histone H4(*K*12) acetylation and an upregulation of histone acetyl transferase (HAT) activity in the hippocampus. In addition, H3(K4)me3, which is closely associated with transcriptional initiation, was also augmented in the hippocampus three weeks after the last defeat. Inhibition of HAT by curcumin (100 mg/kg) before each SD blocked the increase in the conditioned reinforcing effects of 1 mg/kg of cocaine, while inhibition of HDAC by valproic acid (500 mg/kg) before social stress potentiated cocaine-induced CPP. Preference was reinstated when animals received a priming dose of 0.5 mg/kg of cocaine, an effect that was absent in untreated defeated mice. These results suggest that the experience of SD induces chromatin remodeling, alters histone acetylation and methylation, and modifies the effects of cocaine on place conditioning. They also point to epigenetic mechanisms as potential avenues leading to new treatments for the long-term effects of social stress on drug addiction.

1. Introduction

Stressful experiences in life cause physiological and behavioral impairments, including depression and anxiety-like behaviors, as well as memory deficits (Basta et al., 2007; Kessler, 1997; Post, 1992). Nowadays, social influences on the development of drug dependence and relapse is a topic of increasing interest among neuroscience fieldworkers. Since the nineties, several studies have highlighted stress as an important trigger of drug consumption, maintenance and relapse after detoxification periods (Miczek and Mutschler, 1996; Tidey and Miczek, 1997; for a revision see Miczek et al., 2008 or Burke and Miczek, 2015).

Among the different types of stressors, SD stress is a naturalistic paradigm consisting of an agonistic encounter between conspecifics (Tornatzky and Miczek, 1993) that generates emotional stress. In these circumstances, social animals develop dominance-based social hierarchies based on agonistic interactions (Huntingford and Turner, 1987). Experimentally, the effect of social stress is often studied using agonistic encounters through which a dominant rat or mouse (the resident or an aggressive individual) is confronted with a subordinate animal (intruder) in its home cage. The resident-intruder model has several advantages, including ecological and ethological validity, as well as avoiding habituation to stress through repeated exposure (Tidey and Miczek, 1997; Miczek et al., 2008). After a brief encounter with an aggressive individual, the defeated animal exhibits elevated glucocorticoid activity (increased corticosterone and ACTH levels) (Martí-Carbonell et al., 1992; García-Pardo et al., 2014, 2015; Montagud-Romero et al., 2015; Rodríguez-Arias et al., in press), tachycardia and hyperthermia for several hours (Schurman, 1980; Tornatzky and Miczek, 1993). Long-term changes, such as decreased aggression and sexual behaviors (Meerlo et al., 1996; García-Pardo et al., 2015), locomotor activity (Koolhaas et al., 1997; Meerlo et al., 1996), anhedonia (Rygula et al., 2005), heightened defensive/submissive behaviors, anxiety and impaired learning (Ruis et al., 1999; García-Pardo et al., 2015) have also been described. SD during adolescence also impairs the structure and permeability of the BBB (Rodríguez-Arias et al., in press). An increase of dopamine (DA) release in the nucleus accumbens (N Acc) and the prefrontal cortex (PFC) has been observed in defeated

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animals (Tidey and Miczek, 1996; Anstrom et al., 2009; Watt et al., 2014). An increase in the rewarding effects of psychostimulants has also been reported in defeated rodents using self-administration and the conditioned place preference (CPP) procedures (Boyson et al., 2011, 2014; Cruz et al., 2011; Han et al., 2015; Miczek et al., 2008, 2011; Quadros and Miczek, 2009; Yap et al., 2015; Rodríguez-Arias et al., in press; Montagud-Romero et al., 2015).

The heritability of characteristics that make a particular human more susceptible to drug addiction cannot be explained simply by genetic factors (Schuckit et al., 1972; Cloninger et al., 1981). Environment plays an important role in the development of addiction, and both genetics and environment contribute to the individual's vulnerability to addiction (Bierut, 2011). Epigenetic factors may provide the missing link between environmental stimuli and genetic heritability. However, while long-term behavioral responses following SD have been studied in depth, little attention has been focused on epigenetic changes induced by this kind of stress. Epigenetic changes remodel chromatin, modifying DNA, histones and/ or non-histone proteins. One of the most important of these modifications is the acetylation of histones (Peixoto and Abel, 2013), an alteration of lysine residues on the histone amino terminal tails (Levenson and Sweatt, 2005; Sananbenesi and Fischer, 2009; Morris et al., 2010). This modification is closely related with a rise in levels of gene transcription (Chuang et al., 2009; Sananbenesi and Fischer, 2009; Morris et al., 2010; Lubin et al., 2011; Trollope et al., 2012), while hypoacetylation has the opposite effect (Forsberg and Bresnick, 2001; Ito and Adcock, 2002). Histone acetylation is controlled by the enzyme histone acetyl trasferase (HAT), which facilitates transcriptional activation (Bannister and Kouzarides, 1996; Ogryzko et al., 1996; for review see Roth et al., 2001). On the other hand, the histone deacetylase (HDAC) increases the net positive charge and the affinity of histones for the negatively charged DNA through a reverse action (Tsankova et al., 2006).

Epigenetic mechanisms are a relevant underlying cause of numerous psychiatric disease states, and may mediate the impact of stress on the function of neural circuits (Tsankova et al., 2006; Sananbenesi and Fischer, 2009; Nelson and Monteggia, 2011). Epigenetic modification induced by chronic SD has been addressed in several studies, with increases in histone H3 acetylation constituting the most frequent finding. For instance, after 30 min, 24 h or 10 days of exposure to chronic SD stress, increases in H3/K14 acetylation have been described in the N Acc, medial prefrontal cortex (mPFC), dorsal raphe or hippocampus (Covington et al., 2009; Hinwood et al., 2011; Hollis et al., 2010, 2011; Kenworthy et al., 2014). These changes seem to be mediated by inter-individual variances in the response to novelty, since an increase in H3 acetylation after SD is only observed in low-responding rats (Hollis et al., 2011). Rats that are less resilient to SD stress also display higher levels of histone H3 acetylation (Kenworthy et al., 2014). However, the results with respect to H4 are controversial; although most studies have observed no changes after SD, others have found increased acetylation in H4(K12) of less resilient rats (Tsankova et al., 2006; Hollis et al., 2010, 2011; Kenworthy et al., 2014). Other epigenetic changes have been described after chronic SD; for example, decreases in global levels of H3K9 dimetylation (H3K9me2) in the NAc were observed only in susceptible mice (Covington et al., 2011). However, H3(K27)me2 was increased in BDNF promoters in the hippocampus one month after cessation of chronic SD stress (Tsankova et al., 2006).

The different enzymes that control epigenetic processes are altered after SD. A decrease in HDAC 2 levels in the N Acc has been observed 24 h after the last defeat, and continuous infusion of either MS-275 (100 μM) or SAHA (100 μM) (both HDAC inhibitors) into the NAc was found to reverse stress-induced social avoidance in defeated mice and to restore the amount of time the animals spent interacting socially (Covington et al., 2009). Whereas HDAC inhibitors in the hippocampus reverse sucrose preference deficits, they reverse social avoidance only when administered to the amygdala and prefrontal cortex (Covington et al., 2011, 2015). Furthermore, a downregulation of HDAC6 (in raphe neurons) and HDAC5 (in the NAcc) has been reported 10 days after the last SD, and the HDAC inhibitor imipramine has been found to reverse HDAC5 levels (Espallergues et al., 2012; Renthal et al., 2007). Considered together, these results suggest that epigenetic changes are associated with the behavioral response to stress of socially defeated rodents.

Based on the aforementioned studies, which show that social stress produces histone acetylation in some brain structures and that these histone variations may be a mechanism underlying the long-lasting effects of SD, the aim of the present study was to characterize the effects of SD on histone acetylation and levels of HAT and HDAC enzymes. We studied alterations in histone acethylation and thrimethylation in the cortex and hippocampus, important brain regions for the regulation of behavioral and cognitive responses to stress, and which have been implicated in aggressive behavior (for review see Takahashi and Miczek, 2014). The importance of the PFC in the inhibitory control of aggression has been reported in primates, including humans (Nelson and Trainor, 2007). The hippocampus is essential for memory consolidation and storage, and plays important roles in neurogenesis and emotional mechanisms. In addition, it has been associated with escalated aggression (Takahashi and Miczek, 2014).

Since the aim of this study was to demonstrate that the long-term effects of social defeat on the conditioned rewarding effects of cocaine are mediated by histone modifications, we evaluated the effect of different chemical and social interventions 3 weeks later, as this is considered a time lapse in which the acute effects of such interventions (e.g. alcohol levels or corticosterone increases) completely disappear (Rodríguez-Arias et al., 2015, in press, 2016; Montesinos et al., 2015).

Since we found that changes in both histone and HAT/ HDAC enzyme levels were associated with SD, in a second study we assessed the effects of HAT (curcumin) and HDAC (valproic acid) inhibitors on the increase in the conditioned rewarding effects of cocaine induced by this social stress. HAT and HADAC inhibitors were administered prior to each defeat and the development of cocaine-induced conditioned place preference was evaluated three weeks later.

2. Material and methods

2.1. Animals

A total of 165 OF1 male mice (Charles River, Barcelona, Spain) of 42 days of age on arrival at our laboratory were employed as experimental subjects. All mice (except those used as aggressive opponents) were housed in groups of four in plastic cages (25 × 25 × 14.5 cm) for 8 days before the experiments began. Adult mice used as resident aggressive opponents ($n = 15$) were housed individually in plastic cages (21 × 32 × 20 cm) for a month prior to experiments in order to induce heightened aggression (Rodríguez-Arias et al., 1998). All mice were housed under the following conditions: constant temperature, a reversed light schedule (white lights on 19:30–07:30 h), and food and water available ad libitum, except during behavioral tests. Procedures involving mice and their care were conducted according to national, regional and local laws and regulations, which are in compliance with the Directive 2010/63/EU. Details of the number of animals and procedures are described in the supplementary material. Two different sets of mice were used in this study: the first ($n = 24$) was employed for the biochemical analyses (Western blot and Elisa tests); and the second ($n = 120$) was employed for the CPP procedure. Brain samples of the first set of mice were obtained after the 1st social defeat o exploration; after the 4th social defeat; and 3 weeks after the last defeat. All the mice belonging to the second set experienced four social defeats or explorations (controls). HAT or HDAC inhibitors were administered 30 min prior to each social defeat or exploration. Three weeks later, 1 mg/kg of cocaine-induced CPP was performed.