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Histone deacetylase 5 modulates the effects of social adversity in early life on cocaine-induced behavior

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HIGHLIGHTS

- Heterozygous null mutation in HDAC5 moderated the effects of exposure to stress in early life on cocaine-mediated behavior.
- Heterozygous null mutation in HDAC5 moderates the effect of exposure to isolation but not to social threat in early age.
- Dorsal striatum mediates the interaction between heterozygous null mutation in HDAC5 and early isolation on cocaine-seeking.

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ABSTRACT

Psychostimulants induce stable changes in neural plasticity and behavior in a transcription-dependent manner. Further, stable cellular changes require transcription that is regulated by epigenetic mechanisms that alter chromatin structure, such as histone acetylation. This mechanism is typically catalyzed by enzymes with histone acetyltransferase or histone deacetylase (HDAC) activity. Class IIa HDACs are notable for their high expression in important regions of the brain reward circuitry and their neural activity-dependent shuttling in and out of the cell nucleus. In particular, HDAC5 has an important modulatory function in cocaine-induced behaviors and social defeat stress-induced effects. Although a mutation in HDAC5 has been shown to cause hypersensitive responses to chronic cocaine use whether this response worsens during chronic early life stress has not been examined yet. In this study, we exposed mouse pups to two different early life stress paradigms (social isolation, ESI, and social threat, EST) to determine whether the heterozygous null mutation in HDAC5 (HDAC5 +/−) moderated the effects of exposure to stress in early life on adult cocaine-induced conditioned place preference (CPP). Notably, HDAC5 +/− mice that had been exposed to ESI were more susceptible to developing cocaine-induced CPP and more resistant to extinguishing this behavior. The same effect was not observed for HDAC5 +/− mice experiencing EST, suggesting that only ESI induces behavioral changes by acting precisely through HDAC5-related biological pathways.
Finally, an analysis of c-Fos expression performed to discover the neurobiological substrates that mediated this phenotype, identified the dorsolateral striatum as an important structure that mediates the interaction between HDAC5 mutation and ESI. Our data demonstrate that decreased HDAC5 function is able to exacerbate the long-term behavioral effects of adverse rearing environment in mouse.

1. Introduction

Psychostimulants generally refer to drugs that have a wide range of physiological and subjective effects in humans, including increased blood pressure, heart rate, and respiration and better performance on motor tasks [1–4]. In rodents, acute psychostimulant administration enhances locomotor activity and exploratory behavior [5], and chronic application of amphetamine and cocaine can induce behavioral sensitization [6–10]. It has been repeatedly suggested that posttranslational modifications of histones mediate long-lasting transcriptional and behavioral changes in the response to psychostimulants [11]. A function for histone acetylation in cocaine-induced responses was first suggested in behavioral and pharmacological studies that treated cocaine-treated animals with histone deacetylase (HDAC) inhibitors—usually valproic acid and sodium butyrate. By intraperitoneal injection and intra-cerebral [12–14] microinjection, nonspecific HDAC inhibitors regulate the cocaine-induced molecular effects in the brain.

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Nevertheless, it appears that the various HDAC isoforms have distinct functions in the development and maintenance of cocaine-induced plasticity. Class IIa HDACs (e.g., HDAC4, 5, 9) are notable for their high expression in important regions of the brain reward circuitry and their neural activity-dependent shuttling in and out of the cell nucleus [15]. In particular, HDAC5 is an essential regulator of the effects of chronic cocaine administration on reward [12,16,17]. Cocaine dynamically regulates the subcellular localization and function of HDAC5.

Renthal and colleagues [16] and Taniguchi et al. [18] showed that viral overexpression of HDAC5 in the nucleus accumbens (NAc) of mice attenuated the rewarding effects of cocaine in the conditioned place preference (CPP) paradigm. Specifically, the latter group reported that the dephosphorylation of HDAC5 increases its nuclear accumulation (HDAC5 deacetylates histones only in the nucleus) and suppresses the development but not expression of cocaine-induced CPP. Conversely, HDAC5 knockout mice have a hypersensitive response to chronic cocaine in a CPP protocol in which preference was assessed after prior sensitization to cocaine [16].

Notably, HDAC5 has been proposed to also mediate the development of depression-like behavior after chronic social defeat [16,19]. Chronic stress downregulates HDAC5 mRNA in the NAc, and HDAC5 knockout mice experience increased sensitivity to the deleterious effects of chronic social defeat stress [16]. Thus, chronic stress, like chronic cocaine administration, attenuates HDAC5 function, suggesting that these stimuli share biological substrates [16,19]. Although a mutation in HDAC5 has been shown to cause hypersensitive responses to chronic cocaine use [16], whether this response worsens during chronic social stress has not been examined. This would suggest the existence of an interaction between such a mutation and the environmental conditions in the development of cocaine-induced CPP.

Here we hypothesize that the heterozygous null mutation in HDAC5 (HDAC5 +/−) - which in presence of normal environmental conditions does affect cocaine-induced CPP [16] - could instead modulate this behavior in case of adverse social postnatal environment. Recently we have shown that the application of social stress, either social isolation (ESI) or social threat (EST), during the mouse third postnatal week is able to modulate adult cocaine-induced CPP [20,21]. In detail, we demonstrated that the exposure to social threat (EST) promotes both cocaine-induced CPP and reinstatement (after withdrawal), while the exposure to ESI slightly increases cocaine-induced CPP, but the same is not sufficient to promote reinstatement [20,21]. The ability of the ESI and EST procedures to induce a stress response in the pups, was previously evaluated and characterized by means of ultrasonic vocalization, plasmatic corticosterone levels and body weight loss as physiological response to the stress [20]. In the current study, we exposed HDAC5 +/− mice to both ESI and EST and observed that the HDAC5 +/− moderates only the effect of ESI on cocaine-induced CPP. Moreover, biochemical analysis of these mice allowed us to identify in the striatum the neurobiological substrate of the interaction between HDAC5 and stress induced by social isolation environment (ESI).

2. Materials and methods

2.1. Animals and early life stress procedure

To obtain wild type and HDAC5 +/− offspring, the breeding was performed mating HDAC5 +/− male mice (>10 generation backcross to C57BL/6J) with wild-type (+/+) females at 12 weeks of age. Mouse pup litters were randomly assigned to unhandled control (UN; N = 44 pups), Early Social Isolation (ESI; N = 37) or Early Social Threat (EST; N = 33) group at postnatal day (PD) 14. Pups were stressed as previously described [20] (Fig. 1a). Briefly, in the UN group mothers and offspring were left undisturbed until weaning (PD22). In the ESI group each pup was singly-housed in a novel clean bedding cage for 30 min per day from PD14 to 21. In the EST group, each pup was housed in a cage with a resident adult CD1 male mouse (different every day) for 30 min per day from PDs 14 to 21 (Fig. 1a). To avoid killing of the pups, CD1 males were gonadectomized and singly-housed one month before the manipulation protocol. All pups were weaned and housed three to five per cage at postnatal day 22. The ability of these stress procedures (ESI and EST) to induce a physiological and emotional activation in the pups has been previously demonstrated [20]. Genotyping for the HDAC5 null allele was performed by polymerase chain reaction of tail biopsies as previously described [22]. Only male mice (N = 54) were tested for behavioral phenotype at 12–14 weeks of age. All experiments were carried out in accordance with Italian national law (DL 26/2014) on the use of animals for research based on the European Communities Council Directive (2010/63/UE), and approved by the ethics committee of the Italian Ministry of Health (license/approval ID #: 42/2015-PR).

2.2. Drugs

Cocaine hydrochloride was purchased from Sigma (Sigma Aldrich, Milan, Italy) and dissolved in saline (0.9% NaCl) and injected intraperitoneally (i.p.) in a volume of 10 ml/kg. A 5 mg/kg dose of cocaine was used to condition the mice [20,21]. We used "sub-threshold" dose, that fails to induce CPP in control mice, in order to be able to discriminate mice that, due their adverse early experience, would be more susceptible to the effects of cocaine [20,21]. To measure the c-Fos activation induced by cocaine, mice were injected with a cocaine dose of 1.25 mg/kg the day after extinction test.

2.3. Conditioned place preference test (CPP)

2.3.1. Apparatus

CPP apparatus was composed by two gray lateral polyvinyl chloride (PVC) chambers (15 × 15 × 20 cm) connected by a central corridor (15 × 5 × 20 cm). Two sliding doors (4 × 4 cm) connected the alley to the chambers. In each chamber, two parallelepipeds with triangular bases (5 × 5 × 20 cm) made of black PVC and arranged to form different patterns (always covering the same surface of the chamber) were used as conditioned stimuli (Fig. 1b). Behavioral data were collected and analyzed by "Etho Vision" (Noldus Information Technology, Wageningen, The Netherlands), a fully automated video tracking system. The acquired digital signal was then processed by the software to extract the "time spent" (in seconds) in the three compartments of the apparatus

2.3.2. Behavioral procedures

Mice were tested for cocaine-induced CPP as previously described [20,21] (Fig. 1c). Briefly, on day 1 (pretest), mice were free to explore the entire apparatus for 20 min. On the following 8 days (conditioning phase), mice were injected and confined daily for 40 min alternatively in one of the two chambers. For each animal, during the conditioning phase, one of the patterns was consistently paired with a saline injection and the other one with a drug injection. Pairings were balanced so that for half of the animals in each experimental group, the drug was paired with one of the patterns and half of them with the other one. On days 2, 4, 6, and 8, all animals received injections of cocaine immediately before starting the conditioning session and on the other days received saline injections immediately before starting the conditioning session. Testing was conducted on day 10 in drug-free state and lasted 20 min similar to the pretest.

After conditioning and the initial CPP test, mice were given extinction training in which saline was paired four times with each of the two compartments, once per day, over 8 days. After extinction training all mice were left undisturbed for 10 days (withdrawal) and then retested to evaluate extinction learning on day 30. The day after mice were injected with either saline or cocaine (1.25 mg/kg), exposed to the CPP apparatus for 20 min, and sacrificed 1 h after the injection.