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Nonmuscle myosin II inhibition disrupts methamphetamine-associated memory in females and adolescents

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ABSTRACT

Memories associated with drug use can trigger strong motivation for the drug, which increases relapse vulnerability in substance use disorder (SUD). Currently there are no treatments for relapse to abuse of psychostimulants, such as methamphetamine (METH). We previously reported that storage of memories associated with METH, but not those for fear or food reward, and the concomitant spine density increase are disrupted in a retrieval-independent manner by depolymerizing actin in the basolateral amygdala complex (BLC) of adult male rats and mice. Similar results are achieved in males through intra-BLC or systemic inhibition of nonmuscle myosin II (NMII), a molecular motor that directly drives actin polymerization. Given the substantial differences in physiology between genders, we sought to determine if this immediate and selective disruption of METH-associated memory extends to adult females. A single intra-BLC infusion of the NMII inhibitor Blebbistatin (Blebb) produced a long-lasting disruption of context-induced drug seeking for at least 30 days in female rats that mirrored our prior results in males. Furthermore, a single systemic injection of Blebb prior to testing disrupted METH-associated memory and the concomitant increase in BLC spine density in females. Importantly, as in males, the same manipulation had no effect on an auditory fear memory or associated BLC spine density. In addition, we established that the NMII-based disruption of METH-associated memory extends to both male and female adolescents. These findings provide further support that small molecular inhibitors of NMII have strong therapeutic potential for the prevention of relapse to METH abuse triggered by associative memories.
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1. Introduction

Recurring bouts of relapse are one of the main defining characteristics of substance use disorder (SUD). At the time of drug use, strong associative memories are formed between surrounding environmental cues and the drug experience, which can later exert motivation for the drug and promote drug seeking (Childress et al., 1999). These deeply engrained memories are numerous, highly specific to the individual and often abstract in nature (Childress et al., 1993). Currently, there are no available pharmacotherapies for psychostimulant abuse or the prevention of relapse to their use.

Dendritic spines are small, highly dynamic postsynaptic structures that contribute to the physical storage of memory (Kasai et al., 2010). By enabling input-specific biochemical and electrical isolation of synapses, dendritic spines facilitate signal transduction and information storage during memory formation. Furthermore, dendritic spines undergo volumetric and functional changes at the time of learning that are thought to be critical for stabilizing synapses and long-term memories (Lai, Franke, & Gan, 2012; Yang, Pan, & Gan, 2009). The ability of dendritic spines to undergo rapid changes in response to stimulation is governed by dynamic changes to the local actin cytoskeleton (Kasai et al., 2003; Smart & Halpain, 2000). Indeed, the dendritic spine enlargement that occurs during learning is driven by actin polymerization, the process of adding actin monomers (G-actin) to actin filaments (F-actin). Evidence from synaptic plasticity and fear memory studies indicate that actin becomes highly dynamic within minutes, and perhaps seconds, of stimulation, but also rapidly stabilizes, such that long-term potentiation (LTP) and memory quickly become invulnerable to actin depolymerizing agents, such as Latrunculin A (LatA) (Fischer et al., 2004; Gavin et al., 2012; Rex et al., 2010; Star, Kwiatkowski, & Murthy, 2002).

Evidence from our group suggests that, unlike LTP and memories associated with fear and food reward, the F-actin supporting METH-associated memories remains dynamic long after learning within the BLC, a subregion of the brain's emotional memory center (Gavin et al., 2012; Rex et al., 2010; Young et al., 2014, 2016).

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This renders METH-associated memories selectively vulnerable to disruption by actin depolymerization days to weeks after learning. Indeed, a single intra-BLC infusion of LatA is capable of producing an immediate and long-lasting disruption of METH-associated memories in adult male rats and mice without the need for retrieval. This memory loss is accompanied by a reversal of BLC spine density to pre-METH control levels (Young et al., 2014).

While promising, this discovery has limited therapeutic potential because of actin's many roles in the periphery. Indeed, systemic delivery of an actin depolymerizer would likely be fatal because β-actin participates in numerous cellular processes, such as cell polarity, adhesion, and migration (Pollard, 2003). Therefore, we shifted focus upstream of actin polymerization to the molecular motor nonmuscle myosin II (NMII), which we have previously demonstrated to have a critical and temporally restricted role in synaptic actin polymerization and fear memory (Gavin et al., 2012; Rex et al., 2010). As with targeting actin polymerization directly, inhibiting NMII with a single infusion of Blebb, the small molecular inhibitor of NMII, in the BLC immediately disrupted METH-associated memories in adult males, without the need for retrieval and continued to prevent drug seeking behavior for at least one month (Young et al., 2016). Importantly, we have found that systemic injections of Blebb are tolerated by rodents. Furthering this, we found that Blebb is highly brain penetrant, enabling systemic injections to disrupt METH-associated memories and reverse the associated changes in BLC spine density (Young et al., 2016).

All of our work on NMII to date has been performed in adult male rodents. Men account for more than half of the illicit substance use in the United States (SAMHSA, 2014). However, men and women have an equal likelihood to develop SUD and women are approximately twice as likely to use METH as their primary substance of abuse (Kim & Fedrich, 2002; Rawson, Obert, McCann, & Brethen, 2005). In addition to rates of use, gender differences are also apparent in the different phases of substance use, motivation to use and biological effects of abused drugs. For instance, women tend escalate to addiction faster, and be more susceptible to feelings of craving and relapse, relative to men (Becker & Hu, 2008; Fox, Morgan, & Sinha, 2014; Hitschfeld et al., 2015; Kippin et al., 2005; Robbins et al., 1999; Rubonis et al., 1994). Moreover, greater bioavailability of psychostimulants has been shown in female animals, as compared to males, and consistent with this, females tend to self-administer lower drug doses (Milesi-Halle et al., 2015). Adolescents are another population that is under-studied and at significant risk for SUD. Many individuals experiment with substance use and develop SUD during adolescence. These factors combine to make adolescence through mid-twenties the age range associated with the highest amount of substance use (NIDA, 2013). Therefore, it is crucial that the efficacy of a potential pharmacotherapy for relapse to METH use be determined in females and adolescents.

2. Materials and methods

2.1. Animals

All procedures were performed in accordance with the Scripps Research Institute Animal Care and Use Committee and national regulations and policies. All animals were handled at least 3 days prior to the start of training. Heterozygous Thy1-GFPm adult female mice (2–3 months old) were bred on site. This line was used because of the Golgi-like GFP expression in a sparse subset of neurons (the Thy1 lineage), enabling dendritic spine density analysis. Adult Sprague-Dawley female rats were obtained from Charles River (300 g). To ensure sufficient numbers of mice for adolescent experiments, E16 pregnant C57BL6J females were obtained from Jackson Laboratory. Mice were weaned at postnatal day (PND) 23 and training began on PND 28.

2.2. Drugs

Several different doses of methamphetamine hydrochloride (Sigma-Aldrich) were used, depending on age, species and behavioral task. Adult rats undergoing self-administration received METH IV at 0.02 mg in a 0.05 ml infusion. For conditioned place preference (CPP), adult female mice received 2 mg/kg of METH IP and adolescent mice received one of three METH doses IP (1, 1.5 or 2 mg/kg). Racemic Blebb (Tocris) was diluted to 1 mg/ml in a vehicle of 0.9% saline and 6.7%DMSO/25% Hydroxypropyl β-Cyclodextrin (HPβCD) and delivered to mice at 10 mg/kg (IP). For intracranial infusions, both enantiomers of Blebb (− = active Blebb, + = inactive Blebb [Vehicle control]; Calbiochem) were infused into the BLC at a concentration of 90 ng/μl in 10% DMSO and 0.9% saline (Total DMSO = 20%). The delivery rate of intra-BLC infusions was 0.25 μl/min over 2 min for rats. Injectors were left in place for 1 min following infusion to allow for sufficient diffusion of drug away from the needle tip.

2.3. Surgery

Anesthesia, BLC cannulation, intra-jugular catheterization and post-operative care were performed as previously described (Young et al., 2014, 2016). Briefly, rats were implanted bilaterally with 26G guide cannulae (Plastics One) 2 mm above the BLC (lateral and basolateral nuclei; AP −2.9 mm, ML +5 mm relative to bregma; DV −6.7 mm from skull, (Paxino & Watson)). Cannula and needle tip placement was verified, following completion of behavior, by checking 40 μm Cresyl Violet-stained sections. Animals were excluded from the study if the needle tip was located outside the BLC.

2.4. Behavior

2.4.1. Self-administration

Self-administration training procedures and animal care were conducted as previously described (Young et al., 2014, 2016). Rats underwent 20 h of FR1 food training prior to jugular catheterization and BLC cannulation. All self-administration phases were conducted in Coulbourn Rat Test Cages, which had different contextual and olfactory cues, as previously described (Young et al., 2014). One week after surgery, animals underwent 14 days of FR1 METH training with a 30 s time-out between infusions in Context A for 2 h each day. Five females failed to achieve the training criteria of an average of 10 active lever presses per day over the course of training and were excluded from the experiment. The females that successfully completed training were pseudorandomly assigned to either vehicle or Blebb groups, while ensuring equivalent means between the groups, and went on to extinction in Context B. Animals underwent 6–14 days of extinction, depending on when animals met their extinction criteria. Extinction criteria was 3 consecutive days of lever pressing less than 25% of their average lever pressing on the last 3 days of training. Twenty-four hours after meeting their extinction criteria, animals underwent a 1 h reinstatement session in the training context (Context A).

2.4.2. Conditioned place preference

CPP was conducted in mice as previously described (Young et al., 2016). CPP consisted of three different phases: pretesting, training and testing. For the 2 days of pretesting, animals were injected with saline and allowed free access to all three chambers for 30 min. The final 15 min of the second 30 min session was used

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