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Research Report

Intracranial self-stimulation reward thresholds during morphine withdrawal in rats bred for high (HiS) and low (LoS) saccharin intake

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ABSTRACT

Rationale: Sweet preference is a marker of vulnerability to substance use disorders, and rats selectively bred for high (HiS) vs. low saccharin (LoS) intake display potentiated drug-seeking behaviors. Recent work indicated that LoS rats were more responsive to the negative effects of drugs in several assays.
Objective: The current study used the intracranial self-stimulation (ICSS) procedure to investigate the anhedonic component of morphine withdrawal in male HiS and LoS rats.
Methods: Rats were administered morphine (10 mg/kg) or saline for 8 days. To evaluate withdrawal effects, reward thresholds were measured 24 and 28 h following the 8th morphine injection (spontaneous withdrawal) and again for 4 days following daily acute morphine and naloxone (1 mg/kg) administration (precipitated withdrawal).
Results: 24 h following the final morphine injection, reward thresholds in LoS rats were significantly elevated compared to reward thresholds in LoS controls, indicating spontaneous withdrawal. This effect was not observed in HiS rats. LoS rats also showed greater elevations of reward thresholds on several days during naloxone-precipitated withdrawal compared to their HiS counterparts.
Conclusions: LoS rats were more sensitive to morphine withdrawal-mediated elevations in ICSS thresholds than HiS rats. While these differences were generally modest, our data suggest that severity of the negative affective component of opiate withdrawal may be influenced by genotypes related to addiction vulnerability.

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1. Introduction

High sweet preference is an indicator of drug abuse liability (Carroll and Holtz, 2014; Holtz and Carroll, 2015). In humans, drug-dependent individuals showed greater preference for sweetened dietary substances than nondependent individuals (Kampov-Polevoy et al., 2001; Pepino and Mennella, 2007), and a history of drug abuse was associated with avidity for higher concentration of sweet substances (Janowsky et al., 2003; Pomerleau et al., 1991). Animal research has also demonstrated that sweet preference is a genetically mediated marker for addiction susceptibility. For instance, rats selectively bred for high saccharin consumption (HiS) drink more ethanol (Dess et al., 1998), demonstrate greater locomotor response to cocaine (Carroll et al., 2007), higher rates of reinstatement of cocaine seeking and greater cocaine intake (Holtz and Carroll, 2011, 2013; Perry et al., 2006) than rats bred for low saccharin consumption (LoS).

In addition to positive rewarding effects, negative drug effects contribute to the development of addiction (Koob and Volkow, 2010). These effects include heightened stress reactivity, anxiety, and anhedonia elicited during drug withdrawal (Schulteis et al., 1994). HiS and LoS animals show differential responses when withdrawn from ethanol and morphine (Dess et al., 2005; Radke et al., 2013), as well as non-drug reinforcers like glucose (Yakovenko et al., 2011), with most of these studies demonstrating heightened vulnerability in LoS animals. Furthermore, we have shown that LoS (vs. HiS) rats are more sensitive to the effects of i.v. histamine punishment on cocaine self-administration (Holtz et al., 2013), suggesting a more general link between phenotypic sensitivity to aversive events and addiction vulnerability.

In the present study, the negative, anhedonic effects of spontaneous and naloxone-precipitated morphine withdrawal were assessed using an intracranial self-stimulation (ICSS) threshold procedure. Cessation of drug exposure elevates the minimal (threshold) electrical stimulation intensity that maintains ICSS, a putative measure of the diminished sensitivity to rewarding stimuli (anhedonia) associated with withdrawal (Schulteis et al., 1994). Given the differential vulnerability of HiS and LoS rats to the negative effects of drugs in other assays, it was hypothesized that LoS compared to HiS rats would demonstrate increased threshold elevations during spontaneous and naloxone-precipitated morphine withdrawal.

2. Results

2.1. Baseline measures (phase 1)

No differences were found in baseline threshold measures between groups (see Table 3). There was a main effect of phenotype for baseline latency measures [$F(1,27)=4.33$, $p<.05$]. Overall, HiS animals had shorter average baseline latencies (2.7 s ± .2 SEM) compared to LoS animals (3.1 s ± .1 SEM).

2.2. Spontaneous withdrawal (phase 3)

2.2.1. ICSS thresholds

Analysis of changes in thresholds in HiS and LoS rats 24 and 28 h after their last morphine or saline injection revealed a main effect of treatment (Fig. 1) [$F(1,22)=27.2$, $p<.0001$]. Post-hoc analysis showed that LoS rats treated with MOR+SAL had a greater increase in thresholds 24 h after their last morphine injection compared to LoS control animals treated with SAL+SAL ($p<.05$), indicating a significant withdrawal effect. This effect was not observed in HiS rats, nor were there differences between HiS and LoS rats treated with MOR+SAL. In contrast, both LoS and HiS rats treated with MOR+SAL showed increases in thresholds 28 h following their last morphine injection compared to their respective control groups ($p<.05$).

2.2.2. Latency

There were no differences in ICSS latencies in either HiS or LoS rats during the spontaneous withdrawal phase (data not shown).

2.3. Precipitated withdrawal (phase 4)

2.3.1. ICSS thresholds

No differences were found in baseline thresholds between groups for this phase (see Table 3). Analysis of changes in thresholds across the entire session during the precipitated withdrawal phase indicated only a main effect of treatment (Fig. 2) [$F(1,27)=96.7$, $p<.0001$]. Post-hoc comparisons showed that MOR+NAL animals had greater increases in thresholds compared to their SAL+NAL controls for each of the 4 days regardless of phenotype ($p<.01$).

Data from the first and second halves of session during this phase were also analyzed separately (see Section 4.7). There were main effects for treatment [$F(1,27)=77.1$, $p<.0001$] and day [$F(3,81)=2.8$, $p<.05$] following the analysis of threshold changes during the first half of session (Fig. 3A). Post-hoc comparisons showed that all MOR+NAL groups had greater threshold increases than their SAL+NAL treated control groups for each day ($p<.01$). There were main effects for treatment [$F(1,27)=47.7$, $p<.0001$] and day [$F(3,81)=3.7$, $p<.05$],

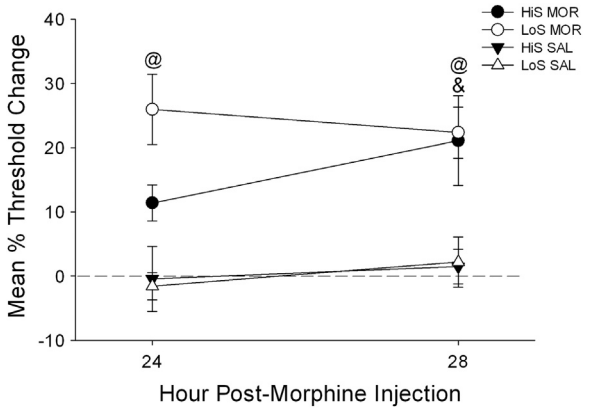

Fig. 1 – Mean (±SEM) percent changes in intracranial self-stimulation reward thresholds compared to baseline in HiS and LoS rats 24- and 28-h following the last of 8 daily injections of morphine+saline (MOR) or saline+saline (SAL). @ indicates that LoS MOR rats had a greater percent increase in reward threshold compared to LoS rats treated with SAL. & indicates that HiS MOR rats had a greater percent increase in reward thresholds compared to HiS rats treated with SAL.