Heroin addiction engages negative emotional learning brain circuits in rats

Stephanie A. Carmack,[1] Robin J. Keeley,[2] Janaina C. M. Vendruscolo,[1] Emily G. Lowery-Gionta,[1] Hanbing Lu,[2] George F. Koob,[1] Elliot A. Stein,[2] and Leandro F. Vendruscolo[1]

[1]Integrative Neuroscience Research Branch and [2]Neuroimaging Research Branch, National Institute on Drug Abuse (NIDA), Intramural Research Program, NIH, Baltimore, Maryland, USA.

Opioid use disorder is associated with the emergence of persistent negative emotional states during drug abstinence that drive compulsive drug taking and seeking. Functional magnetic resonance imaging (fMRI) in rats identified neurocircuits that were activated by stimuli that were previously paired with heroin withdrawal. The activation of amygdala and hypothalamic circuits was related to the degree of heroin dependence, supporting the significance of conditioned negative affect in sustaining compulsive-like heroin seeking and taking and providing neurobiological insights into the drivers of the current opioid crisis.

Introduction

The United States is experiencing an opioid dependence and overdose crisis (1). New conceptual frameworks and therapeutic targets are needed to more effectively treat opioid use disorder (OUD) and curb opioid overdose deaths. Individuals with OUD are hypothesized as compulsively using opioid drugs to avoid the severe negative emotional states (e.g., dysphoria, pain, anxiety, and depression) that are experienced during abstinence (2). In both clinical and preclinical models, environmental stimuli conditioned to these negative emotional states can induce opioid use on their own (3–5). Individuals with OUD report withdrawal symptoms and drug craving when encountering drug-related stimuli (6).

Stimuli that are conditioned to opioid withdrawal may perpetuate and reinstate drug seeking by generating negative emotional states that are relieved by drug taking via negative reinforcement (2, 4, 7). Identifying the brain circuits that support motivational aspects of conditioned withdrawal may provide insights into the long-term neuroplasticity-based consequences that frustrate therapeutic interventions in OUD (2, 8). Thus, we hypothesized that conditioned withdrawal would engage brain circuitry that is involved in negative emotional learning. In the present study, we found that cue-induced conditioned withdrawal engaged brain emotional systems in a rat model of heroin dependence.

Results and Discussion

To test our hypothesis, we utilized a behavioral model in which cues were paired with heroin withdrawal–induced negative emotional-like states (4). Rats were first trained to self-administer heroin (60 μg/kg/i.v. infusion) in short-access (ShA; 1 h/d) or long-access (LgA; 12 h/d) sessions that were designed to model nondependent, controlled use versus dependent, compulsive heroin use (9). LgA rats rapidly escalated their heroin intake, whereas ShA rats exhibited stable drug intake (Figure 1A).

In the conditioning phase, rats were treated with saline or naloxone (120 μg/kg, s.c.) 30 minutes into each heroin self-administration session. Naloxone competes with heroin at μ-opioid receptors and, in this dose range, precipitates motivational signs of withdrawal (e.g., place aversion, increased intracranial self-stimulation thresholds), but not somatic signs of withdrawal (e.g. "wet dog" shakes) in opioid-dependent rats (4, 9–11). The treatments were paired with distinct olfactory cues (lemon- or vanilla-scented bedding) in the self-administration chamber. The cue pairings lasted 30 minutes to coincide with the short-acting pharmacological effect of naloxone. After the cue pairing, ShA rats were returned to their home cages and LgA rats completed their 12-hour session without olfactory cues (i.e., with unscented bedding).

Naloxone treatment increased heroin intake relative to saline treatment in both self-administration groups (Figure 1B). Heroin intake remained stable across cue pairings (Supplemental Figure 1; supplemental material available online with this article; https://doi.org/10.1172/JCI125534DS1). As naloxone has a greater affinity for the μ-opioid receptor than heroin, naloxone likely immediately produced opioid withdrawal in LgA rats. This withdrawal effect might have been relieved by the elimination of naloxone concomitantly with increases in heroin self-administration. An alternative explanation for the increase in heroin intake during naloxone treatment may be that the maintenance of a hedonic tone is disrupted by naloxone and that rats that self-administer more heroin have increased tolerance to heroin.

Earlier work demonstrated that presentation of a compound auditory and visual cue previously paired with naloxone treatment increased intracranial self-stimulation thresholds and motivated heroin intake during heroin self-administration in LgA rats, suggesting that the cue became conditioned to naloxone-precipitated withdrawal (4). Here we confirmed that an olfactory cue previously paired with naloxone similarly increased heroin intake in LgA rats, but not ShA rats, when presented in the absence of naloxone during heroin self-administration (Supplemental Figure 2). Additionally, presentation of an olfactory cue previously paired with naloxone

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