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Preventing and Treating Dependence to Help Break the Addiction Cycle

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Abstract

Opioid use disorder (OUD) is defined as a compulsion to seek and take opioids, loss of control over intake and the development of a negative emotional state when access to opioids is denied.

Keywords: Prostate Cancer; DNA repair; estrogen; ATM; p53; BRCA1

Introduction

In 2019, 2.2% of the US population reported any lifetime use of heroin [1], with ~50,000 people dying from respiratory depression induced by opioid overdose [2]. Heroin is a prodrug for metabolites that bind to the mu-opioid receptor [3]. Heroin use generally begins with drug taking induced intoxication, followed by the rapid development of tolerance and subsequent escalation of intake [4]. Abstinence from heroin results in somatic and affective signs of withdrawal and craving, manifest as dysphoria, physical discomfort, and preoccupation with obtaining more drug. Consequently, opioid use disorder (OUD) is defined as a compulsion to seek and take opioids, loss of control over intake and the development of a negative emotional state when access to opioids is denied. Each stage of OUD is characterized by distinct behaviors and is hypothesized to be driven by changes to discrete brain regions and circuits [5]. For example, the initial binge/intoxication stage is characterized by habit behaviors and involves changes in the basal ganglia [6], whereas the withdrawal/negative affect stage is thought to be characterized by a negative emotional state with changes in, among other regions, the extended amygdala and its interconnections [4,[5], [7]]. Finally, the preoccupation/anticipation stage is often characterized by deficits in executive function, increased drug cravings and ruminations and involves changes in prefrontal cortical circuits [5].

Previous research from our group has identified the extended amygdala and the hypothalamus as responsive to odor cues previously associated with conditioned heroin withdrawal in heroin dependent rats [8]. In that study [8], we used the long (LgA) and short access (ShA) model of heroin self-administration (SA), in which rats are given access to heroin for either 1 h (ShA) or 12 h per SA session (LgA). Rodents exposed to LgA opioid SA exhibit multiple signs of opioid dependence that reflect those that are observed in humans with OUD. These signs include both somatic signs (e.g., wet-dog shakes, diarrhea) and motivational signs (e.g., compulsive-like opioid seeking and taking). However, rodents exposed to ShA opioid SA exhibit significantly less of these signs, and as such, LgA rats are considered opioid dependent, whereas ShA rats are considered nondependent. In this study, using the behavioral data that we have already published [8], we measured the degree to which a rat increased its heroin intake as compared to its initial intake under ShA or LgA conditions, which was considered a measure of escalation. Next, we measured the SA of heroin following administration of a low dose of naloxone, which competes with opioid agonists at opioid receptors [8]. The amount of heroin taken under this condition was considered a measure of activity of opioid-sensitive neurons. Using this pre-published behavior dataset [8], we now sought to define how intrinsic brain circuits, determined from correlated spontaneous brain activity in the absence of outside stimulation, are altered by heroin dependence and how these circuits relate to these discrete aspects of heroin dependence behavior.

To measure individual differences in intrinsic circuits related to the behavioral characteristics of heroin dependence, rats with a history of heroin SA and naloxone administration under ShA or LgA conditions [8] underwent functional magnetic resonance imaging (fMRI) twenty-four hours after the last SA session. We hypothesized that distinct brain circuits would reflect individual differences in heroin SA escalation trajectory and naloxone-induced increases in SA. In follow up exploratory analyses, we examined alterations in regional coordinated activity using the amplitude of low frequency fluctuations (ALFF) analyses to determine within-region changes in spontaneous brain activity in addition to any functional connectivity changes between regions.

Methods

Animals and heroin self-managing

Details about the experimental animals and heroin SA procedures have been previously described by Carmack et al. [8]. After a recovery period, the rats were trained to self-administer heroin (60 µg/kg/infusion) in 1-h sessions under a fixed-ratio 1 (FR1) schedule of reinforcement. Rats were randomly split into ShA (1 h/day) or LgA (12 h/day) SA groups and self-administered heroin over 10 sessions. The two groups were then injected with saline or naloxone (120 µg/kg, s.c.) while being exposed to cues during 8 alternating SA sessions. The rats underwent fMRI scanning 24 h after the last SA session. Behavioral data are published in [8].

Behavioral scoring

From the behavior reported in [8], two behavioral metrics were created. An escalation score was defined as the average number of heroin infusions during the last three sessions of SA under LgA or ShA conditions only subtracted by the average number of infusions during the first three sessions of SA under LgA or ShA conditions only (sessions 13, 14, 15; i.e., baseline intake). For the naloxone-induced increases in the SA metric, we used the average number of self-administered heroin infusions following naloxone injections during the first 30 min of each of the naloxone injection sessions.

Magnetic resonance

Twenty-four hours following the last odor cue conditioning session, rats underwent fMRI scanning under light anesthesia using a combination of dexmedetomidine (Domitor®; Webster Veterinary) and isoflurane (Henry Schein), which has minimal interference on spontaneous brain oscillations.

The amplitude of low frequency fluctuations (ALFF), measuring regional baseline spontaneous brain activity fluctuations, was computed by voxel-wise Fourier transformation. Then, the square root of the power

spectrum across 0.01–0.1 Hz was defined as the ALFF index. Compensating for global variations, normalized ALFF was defined as the output subtracted by mean intensity in the whole brain mask divided by the standard deviation. Following results demonstrating the Cg's role in dependence behavior, we investigated innate activity differences within the Cg that could be affecting connectivity with brain regions seen in the above rsFC analyses. Therefore, ALFF values were extracted from within the anatomically defined cingulate (Cg) region for each rat. The Cg seed was made up of cingulate area 1 (Cg1) and cingulate area 2 (Cg2) based on a stereotaxic atlas.

Results

Escalation of drug intake and naloxone-induced increases in SA reflect independent measures

On average, LgA rats had significantly higher escalation scores and self-administered more heroin following a low dose injection of naloxone than ShA rats. The dose of naloxone was chosen to induce motivational effects of withdrawal (e.g., opioid taking, place-aversion and increased intracranial self-stimulation thresholds) but induce few somatic effects (e.g., shakes and abdominal constrictions) in opioid dependent rats.

Finally, given the distinct functions and anatomy of the CPu/GP and the BNST in drug dependence (for review, [5]), we conducted an exploratory analysis to determine whether the effects observed between the CPu/BNST-Cg circuit were driven primarily by one of the two identified cluster regions. We anatomically separated the CPu/BNST cluster into the BNST and the dorsal striatum (CPu and GP) seeds based on a stereotaxis atlas . Although no significant circuits were observed using the anatomically separated BNST as a seed,suggesting that in the originally combined cluster that demonstrated a change in rsFC, the alterations to the connectivity relationship were driven primarily by a dorsal striatal-cingulate circuit. There were no significant effects found as a result of heroin access group (LgA versus ShA) or due to an interaction between heroin access group and escalation score in any of the escalation-related findings.

Discussion

Using resting state BOLD signal to infer changes in functional connectivity along the trajectory of heroin dependence, we observed that two dependence associated behaviors (heroin escalation and naloxone-induced increases in heroin SA) were associated with distinct cingulate cortex based neural circuits. To do this, we used a priori regions of interest from our previous findings of activity changes in the hypothalamus and extended amygdala that demonstrated differential responses to conditioned opioid withdrawal cues [8]. Independent of heroin access group (i.e., ShA or LgA), we found a strong positive relationship between the number of self-administered infusions following a low, motivation-inducing injection of naloxone and functional circuits to the cingulate cortex from both the a priori amygdala and hypothalamic seeds. It is critical to note that no circuit directionality is implied here and elsewhere when discussing functional connectivity circuits, the circuit is simply denoted from the location of the seed ROI. Given that both withdrawal cue-induced activity-based seeds identified circuits with the cingulate, we next interrogated this region, exploring its connectivity with other regions by using the newly identified cingulate as a seed.

Although our data suggest that the distinct circuits, identified here, drive different behavioral facets of opioid dependence, they both converge on the Cg. We propose that as dependence develops, reward-associated Cg-dorsal striatal circuitry contributes to escalating drug taking behaviors. However, following increased opioid receptor sensitivity, Cg-limbic circuits, which are associated with negative emotional learning [7,8], strengthen and are associated with increased heroin use following injection of a low-dose opioid antagonist.

Conclusion

Using a LgA and ShA model of heroin SA, we demonstrate that escalation of SA and naloxone-induced increases in heroin infusions are associated with several neural circuits that center on the Cg, demonstrating its key role in heroin dependence. These results support the hypothesis that pivoting away from the current non-specific, pharmacologic therapeutic approach, and towards circuit-based targeted approaches may be useful in treating addiction. Specifically, this work calls for mechanistic investigations into the Cg-dorsal striatal and the Cg-limbic circuits (and potentially their network interactions), and their role in preventing and/or treating dependence to help break the addiction cycle.

Competing Interest

The authors, declare that we have no known competing interests.

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