Fos Expression in Lateral Hypothalamus/Perifornical Area is Correlated with Psychosocial Stress-Induced Cocaine-Seeking Behavior in a Sex-Specific Manner

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Fos expression in lateral hypothalamus/perifornical area is correlated with psychosocial stress-induced cocaine-seeking behavior in a sex-specific manner

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Introduction

Cocaine Use Disorder persists as a significant public health concern in the United States, with recent epidemiological data indicating that rates of cocaine-involved overdose deaths are rising. Stress can precipitate cocaine craving and trigger relapse in cocaine users, but the underlying neural circuitry by which stressors drive cocaine seeking is not completely understood. Our laboratory has recently discovered that Fos expression within the rostral taenia subregion of the periaqueductal gray (rPAG) is correlated with psychosocial stress-induced cocaine-seeking behavior in rats. Neuroanatomical evidence has revealed dense reciprocal connectivity between the rPAG and the lateral hypothalamus (LH) and neighboring perifornical area (PfA), two brain regions previously implicated in drug-seeking behaviors. However, whether activity within the LH/PfA is associated specifically with psychosocial stress-induced cocaine seeking has not been previously explored. In the present study, we used Fos immunohistochemistry to examine whether neural activation in the LH/PfA of male and female rats was associated with psychosocial stress-induced cocaine-seeking behavioral output and/or concomitant neural activity in other brain regions of interest during a cocaine-seeking episode.

Results: Self-Administration, Reinstatement, and LH/PfA Fos Expression

Re-exposure to the “cue” box reinstates cocaine-seeking in SDS and EC rats. (A) Active and inactive lever presses and (B) reinstated earned in sessions 1-20 and final 3 days of extinction (E1-E3). (C) Active-lever presses during sessions 8-10 of cocaine self-administration (Main), final 3 days of extinction (Ex), and reinstatement (Reinst). Data are mean ± SEM values. Gray bars in (A) and (B) indicate sessions in which stress/no-stress events immediately followed the self-administration session. ***p<0.001, main effect of “Main” or “Reinst” compared to extinction. n=12-16 per group.

No group differences in Fos expression during cocaine-seeking

Figure 1. Cocaine self-administration and reinstatement of cocaine-seeking in SDS and EC rats. (A) Active and inactive lever presses and (B) reinstatement rates in sessions 1-20 and final 3 days of extinction (E1-E3). (C) Active-lever presses during sessions 8-10 of cocaine self-administration (Main), final 3 days of extinction (Ex), and reinstatement (Reinst). Data are mean ± SEM values. Gray bars in (A) and (B) indicate sessions in which stress/no-stress events immediately followed the self-administration session. ***p<0.001, main effect of “Main” or “Reinst” compared to extinction. n=12-16 per group.

Methods

Experimental Groups

Social Defeat Stress (SDS). Immediately after sessions 11, 14, 17, and 20, rats were removed from the self-administration (SA) box and placed into the home cage of a conspecific, aversive-aggressive Long-Evans male rat, and after 1:2 it was removed from the home cage and placed back into the ‘cue’ box and returned to the resident-aggressor’s home cage for 5 additional minutes of isolation. All-anxiety group control (AGC). Rats underwent the same procedure as the SDS group with the exception that they were placed into an unfamiliar resident-aggressor home cage.

Extraction & Reinstatement

Extraction sessions began on session 21 and lasted 2 hr for 5-6 weeks, during which lever presses had no scheduled consequence. Extraction criteria is 15 active lever presses in 3 of 4 consecutive sessions. The day after criteria were met, animals were re-exposed to the “cue” box that agoed their assigned reinstatement post-reinforcement event and were allowed to be press for 2 further extinction sessions. Animals were sacrificed immediately after the session.

Results: Correlation Analyses

Fos expression in LH/PfA non-orexinergic cells correlates with cocaine-seeking behavior and Fos expression in rPAG and piPFC, but only in SDS male rats

Figure 3. Correlation analyses for LH/PfA Fos expression with cocaine-seeking magnitude and Fos expression in rPAG and piPFC. (A-B) Correlations in EC or SDS rats between cocaine-seeking and Fos expression in (A) orexin+ cells or (B) orexin- cells of LH/PfA (n=12-16/group). (C-D) Correlations in SDS males or females between cocaine-seeking and Fos expression in (C) orexin+ cells or (D) orexin- cells in LH/PfA (n=8/group). (E-F) Correlations in SDS males or females between Fos expression in LH/PfA orexin+ cells and Fos expression in (E) rPAG or (F) piPFC (n=8/group).

Summary

- No robust group or sex differences in LH/PfA activity when cocaine-seeking is elicited via a stress-predictive vs. cocaine-predictive cue.
- Psychosocial stress-induced cocaine-seeking behavior is correlated with activation of non-orexin LH/PfA cells in males.
- Activity of non-orexin LH/PfA cells during psychosocial stress-induced cocaine seeking is correlated with neural activity in rPAG and piPFC in males.
- These findings indicate the potential engagement of a neural circuit involving piPFC, LH/PfA, and rPAG during stress-induced cocaine-seeking behavior in males.

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