Title

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Authors

Birnie, Matthew
Short, Annabel K
Pham, Aidan L
et al.

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281-282 **P387. Aberrant Functional Maturation of a Novel Cell-Type-Specific Brain Pathway Impacts Reward-Seeking Behaviors After Early-Life Stress**

Matthew Birnie*, Annabel K. Short, Aidan L. Pham, Ashima Kundu, Christy A. Itoga, Xiangmin Xu, Stephen V. Mahler, Yuncai Chen, Tallie Z. Baram

University of California-Irvine, Irvine, California, United States

Background: The seeking of pleasure is a fundamental human behavior, executed by coordinated activity of the brain's reward circuitry. Disrupted operation of this circuit is thought to underlie major emotional disorders including depression and drug-abuse, disorders commonly arising after early-life stresses. Yet, how early-life adversities (ELA) impact the functional maturation of reward circuitries to promote disease remains unclear. The nucleus accumbens (NAc) is a major component of the reward circuit and key structure mediating pleasure, motivation, and emotional processes. Multiple inputs converge onto the NAc to modulate reward-seeking behaviors, including the basolateral amygdala (BLA). The BLA mediates associate learning for both aversive and appetitive stimuli, and stimulation of glutamatergic projections from the BLA to NAc promotes appetitive behaviors. In this study, we employ viral-genetic technologies to identify a novel GABAergic projection that co-expresses the stress-related neuropeptide corticotropin-releasing hormone (CRH) and connects the basolateral amygdala (BLA) and nucleus accumbens (NAc). In the NAc, CRH + axon terminals modulate reward and motivational behaviors. Here, we identify the role of this CRH + BLA-NAc projection during reward in naïve and stress-experiencing mice.

Methods: To identify CRH + projections to the NAc, we utilized viral-genetic approaches to map these pathways using Cre-dependent viruses injected into CRH-IRES-Cre mice. To determine the function of the novel CRH + BLA-NAc projection we employ chemogenetic and optogenetic strategies in both control and early-life adversity experiencing mice. In these mice, we injected excitatory or inhibitory Cre-dependent DREADD (hM3Dq and hM4Di) and optogenetic (ChR2) carrying viruses into BLA, followed by medial NAc shell targeted microinjections of CNO or light activation. We tested the function of this pathway using three reward (sucrose preference, sex-cue approach, and palatable food tasks), and non-reward tasks (object location memory and open field).

Results: Viral genetic tracing paired with fluorescence in situ hybridization and immunostaining identified a novel GABAergic projection that co-expresses the stress-reactive neuropeptide CRH + projection from the BLA to the medial NAc shell. Excitation of this projection using chemo- and optogenetic tools reduced preference for sucrose, palatable food consumption, and sex-cue approach, but did not alter non-reward specific tasks (object location memory and open field). Compared with control mice, male mice that experienced ELA had reduced preference for sucrose, palatable food consumption and sex-cue approach. In adult ELA mice, chemogenetic inhibition of the CRH + BLA-NAc projection rescued all three reward behaviors.

Conclusions: We identify a novel GABAergic CRH + BLA-NAc projection and establish its role in mediating the effects of ELA on reward behaviors. These discoveries provide potential selective targets for prevention and intervention in the disruption of such behavior that accompanies several psychopathologies.

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Keywords: CRH, Reward, Adversity, Nucleus Accumbens, Amygdala

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