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Background: Disrupted operation of reward circuits is thought to underlie several emotional disorders including depression and drug abuse, disorders commonly arising after early-life stress. 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 behaviors, including the basolateral amygdala (BLA). The BLA mediates associative learning for aversive and appetitive stimuli, and stimulation of glutamatergic projections from the BLA to NAc promotes appetitive behaviors. Here, we identified a novel projection that expresses the stress neuropeptide corticotropin-releasing hormone (CRH) to connect 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 ELA mice.

Methods: Pairing viral-genetic approaches with CRH-IRES-Cre mice and Cre-dependent viruses, we identified CRH + BLA projections to the NAc. To determine the function of this novel CRH + BLA-NAc projection we used chemo-, optogenetic and electrophysiology strategies in control (CTL) and ELA mice. In these mice, excitatory or inhibitory Cre-dependent DREADDs and optogenetic viruses were injected into BLA, followed by medial NAc shell targeted microinjections of CNO or light activation. In behavior, we tested the function of this pathway using reward, and non-reward tasks.

Results: Male ELA mice have reduced preference for sucrose, palatable food, and a sex-cue, compared with CTLs. Viral-genetic tracing combined with electrophysiology identified a novel GABAergic projection that co-expresses the stress neuropeptide CRH from the BLA to the medial NAc shell. In freely behaving mice, exciting this projection using chemo- and optogenetic techniques reduced preference for sucrose, palatable food, and a sex-cue, but did not alter non-reward-mediating tasks. In adult ELA mice, chemogenetic inhibition of the GABAergic CRH + BLA-NAc projection rescued these reward behaviors.

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

Keywords: Basolateral Amygdala, Nucleus Accumbens, CRH, Early Life Stress, GABA

Disclosure: Nothing to disclose.