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Endocannabinoid regulation of innate fear responding

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Anxiety disorders, including generalized anxiety disorder (GAD) and post-traumatic stress disorder (PTSD), are the most common mental illness in the United States. Symptoms characteristic of these diseases have been suggested to rely on maladaptive fear learning processes. For example, an oversensitivity to unpredictable aversive events, persistence of fear memory, and excessive fear in the absence of true danger all present as symptoms in anxiety disorders, and also relate to dysfunctional fear expression, consolidation, and extinction. The endocannabinoid (eCB) system includes crucial components of the processes involving fear learning and has recently been identified as an emerging therapeutic target to treat stress-related disorders. Here, we assess the neural mechanism through which eCBs may modulate fear learning by focusing on an understudied input from the ventral hippocampus (vHIPP) to the nucleus accumbens (NAc). Using slice electrophysiology and fiber photometry, we assess how eCBs modulate vHIPP-NAc activity ex vivo and in vivo. Furthermore, using a viral-mediated INTERSECT approach, we selectively delete components of the eCB system in the vHIPP-NAc circuit to assess how eCB signaling at these synapses mediates contextual fear expression and fear generalization. These data ultimately provide insight into the specific neural mechanisms by which eCB signaling modulates fear learning.