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CNIH3 expression in female mice modulates hippocampal synapse stability and AMPAR-dependent memory and learning

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A 2016 genome-wide association study comparing non-dependent and dependent opioid misusers found the strongest genetic association with opioid dependence risk involved single nucleotide polymorphisms in *CNIH3*, a gene encoding for cornichon family AMPA receptor (AMPAR) auxiliary protein homolog-3 (CNIH3). AMPAR activity in the hippocampus is critical for opioid-associated memory and learning, but evidence for CNIH3 modulation of AMPAR-dependent mechanisms in the brain is scarce. This study aims to characterize the role of CNIH3 in the mammalian brain to build the foundational knowledge necessary for future study of the link between CNIH3 and opioid dependence. We hypothesize that CNIH3 regulates hippocampal AMPAR-dependent memory and learning behavior through maintenance of AMPAR-dependent biochemical mechanisms and synaptic activity mediating synaptic morphology. To study the role of CNIH3 in these processes, we bred *CNIH3* knockdown (KD) mice and developed a *CNIH3* viral construct for targeted hippocampal *CNIH3* overexpression (OE). Western blots of *CNIH3* KD hippocampal post-synaptic density (PSD) fractionations demonstrate a significant reduction in the excitatory scaffolding protein PSD-95 in female mice. Preliminary experiments analyzing dendritic spine morphology in CA1 pyramidal neurons suggest a decrease in stable mushroom spines in *CNIH3* KD females. Behavioral data in the Barnes Maze reveal significant improvement in short-term memory and learning in female mice with hippocampal *CNIH3* OE. These findings provide evidence for sex-dependent modulation of hippocampal synaptic structure and memory and learning by the AMPAR auxiliary protein CNIH3. Future studies will build upon this data to investigate CNIH3 modulation of AMPAR-dependent opioid associated memory and learning.