Fatty Acid Binding Protein 5 Modulates Brain Endocannabinoid Tone and Retrograde Signaling in the Striatum and Hippocampus

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Background: The endocannabinoids (eCB) anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are lipid neurotransmitters that regulate an array of physiological functions including pain, stress homeostasis, and reward. Fatty acid binding protein 5 (FABP5) is a key modulator of intracellular eCB transport and inactivation. Recent evidence suggests that FABP5 controls synaptic 2-AG signaling at excitatory synapses in the dorsal raphe nucleus. However, it is currently not known whether this function extends to other brain areas, has a cell specific role, or aids in synaptic transport.

Methods: Striatal and hippocampal FABP5 in the mouse brain were visualized using immunohistochemistry with antibody specific labeling for neurons, astrocytes, and FABP5 from microtome brain sections. hSynapsin and GFAP driven AAVs were injected into the hippocampus in FABP5 KO mice, via stereotaxic surgery. Brain regions were micro dissected from wild-type and FABP5 KO mice for qPCR and mass spectrophotometry analysis of various proteins and lipids in the eCB pathway. Lastly, electrophysiology was performed to examine the effects of FABP5 inhibition and re-expression upon eCB signaling.

Results: FABP5 deletion elevates AEA levels in the striatum, PFC, midbrain, & thalamus, as well as midbrain 2-AG levels. The expression of eCB biosynthetic and catabolic enzymes was largely unaltered in these regions, although minor sex and region-specific changes in the expression of 2-AG catabolic enzymes were observed in female FABP5 KO mice. Robust FABP5 expression was observed in the striatum. Re-expression of FABP5 in astrocytes rescues eCB signaling better in FABP5 KO mice, as compared to re-expression in neurons. Deletion of FABP5 impaired tonic 2-AG and AEA signaling at striatal GABA synapses of MSNs and blunted phasic 2-AG mediated short-term synaptic plasticity without altering CB1R expression or function.

Conclusion: Collectively, these results support the role of FABP5 as a key regulator of eCB signaling at excitatory and inhibitory synapses in the brain.

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Model of synaptic eCB transport by FABP5 with role specificity to brain regions and cell types. FABP5 is secreted into synapses by glial cells. Activation of postsynaptic neurons leads to the biosynthesis of the eCB 2-AG, which is transported across the synapse by FABP5 and subsequently activates presynaptic CB1 receptors. This regulates release of neurotransmitters. Alternatively, 2-AG gets catabolized by MAGL in the pre-synaptic neuron (Kaczocha and Haj-Dahmane, 2021).