Endocannabinoid (EC)

The inhibition of monoacylglycerol lipase (MAGL), the key enzyme that metabolizes the endocannabinoid 2-arachidonoylglycerol (2-AG) in the brain, significantly reduced chronic traumatic encephalopathy (CTE)-like neuropathologic changes in a mouse model of repetitive mild head injury (MHI). Inhibition of 2-AG metabolism promoted neurologic recovery following MHI and reduced proinflammatory cytokines, astroglial reactivity, expression of amyloid precursor protein and the enzymes that make Aβ, as well as formation of Aβ. Importantly, neurodegeneration, TDP-43 protein aggregation, and tau phosphorylation, which are the neuropathologic hallmarks of CTE, were significantly suppressed by MAGL inactivation. Furthermore, alterations in expression of glutamate receptor subunits and impairments in basal synaptic transmission, long-term synaptic plasticity, and spatial learning and memory were recovered by inhibition of 2-AG metabolism in animals exposed to (CHI). The results suggest that MAGL inhibition, which boosts 2-AG and reduces 2-AG metabolites prostaglandins in the brain, may lead to a new therapy for CTE [1)].

Katz et al. suggest that EC degradation inhibition post-TBI exerts neuroprotective effects. Whether repeated dosing would achieve greater protection remains to be examined [2)].

1)
Zhang J, Teng Z, Song Y, Hu M, Chen C. Inhibition of monoacylglycerol lipase prevents chronic traumatic encephalopathy-like neuropathology in a mouse model of repetitive mild closed head injury. J Cereb Blood Flow Metab. 2014 Dec 10. doi: 10.1038/jcbfm.2014.216. [Epub ahead of print] PubMed PMID: 25492114.

2)
Katz PS, Sulzer JK, Impastato RA, Teng SX, Rogers EK, Molina PE. Endocannabinoid Degradation Inhibition Improves Neurobehavioral Function, Blood-Brain Barrier Integrity, and Neuroinflammation following Mild Traumatic Brain Injury. J Neurotrauma. 2015 Mar 1;32(5):297-306. doi: 10.1089/neu.2014.3508. Epub 2014 Dec 19. PubMed PMID: 25166905.