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Modulation of the endocannabinoid system in traumatic brain injury

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Modulation of the endocannabinoid system has emerged as an attractive strategy for the treatment of many neurological diseases but its role in the management of traumatic brain injury is still in its infancy. The endocannabinoids 2-arachidonoyl glycerol (2-AG) and N-arachidonoyl ethanolamine (anandamide, AEA) are elevated after brain injury and believed to be protective. However, the compensatory effect of the endocannabinoids is transient due to their rapid degradation by hydrolytic enzymes. In a mouse model of traumatic brain injury (TBI), we found that post-injury chronic treatment with WWL70 and PF3845, the respective and selective inhibitors of the 2-AG and AEA hydrolytic enzymes alpha/beta hydrolase domain 6 (ABHD6) and fatty acid amide hydrolase (FAAH), improved locomotor function, working memory and anxiolytic behavior. The treatment reduced lesion volume in the cortex and neuronal death in the hippocampal dendate gyrus. It also suppressed the expression of inducible nitric oxide synthase and cyclooxygenase-2 and enhanced the expression of arginase-1 in the ipsilateral cortex at 3, 7 and 14 days post-TBI, suggesting microglia/macrophages are shifted from a proinflammatory (M1) to an anti-inflammatory (M2) phenotype. Treatment with PF3845 also suppressed the increased production of amyloid precursor protein, prevented dendritic loss and restored the levels of synaptophysin in the ipsilateral dentate gyrus. The beneficial effects of WWL70 and PF3845 were mediated by activation of cannabinoid type 1 and type 2 receptors and might be attributable to the phosphorylation of the extracellular signal regulated kinase (ERK1/2) and the serine/threonine protein kinase (AKT). These results suggest that fine-tuning of 2-AG and AEA signaling by regulating ABHD6 and FAAH activity can afford anti-inflammatory and neuroprotective effects in TBI.

Biography

Yumin Zhang is an Associate Professor in the Department of Anatomy, Physiology and Genetics and the Department of Neuroscience at the Uniformed Services University of the Health Sciences in Bethesda, USA. He has obtained his MD in Binzhou Medical School, China, PhD in Hebrew University of Jerusalem, Israel and Post doctorate study in the Children's Hospital, Harvard Medical School.

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