N-Palmitoylethanolamine and Neuroinflammation: a Novel Therapeutic Strategy of Resolution.

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Abstract

Inflammation is fundamentally a protective cellular response aimed at removing injurious stimuli and initiating the healing process. However, when prolonged, it can override the bounds of physiological control and becomes destructive. Inflammation is a key element in the pathobiology of chronic pain, neurodegenerative diseases, stroke, spinal cord injury, and neuropsychiatric disorders. Glia, key players in such nervous system disorders, are not only capable of expressing a pro-inflammatory phenotype but respond also to inflammatory signals released from cells of immune origin such as mast cells. Chronic inflammatory processes may be counteracted by a program of resolution that includes the production of lipid mediators endowed with the capacity to switch off inflammation. These naturally occurring lipid signaling molecules include the N-acylethanolamines, N-arachidonoylethanolamine (an endocannabinoid), and its congener N-palmitoylethanolamine (palmitoylethanolamide or PEA). PEA may play a role in maintaining cellular homeostasis when faced with external stressors provoking, for example, inflammation. PEA is efficacious in mast cell-mediated models of neurogenic inflammation and neuropathic pain and is neuroprotective in models of stroke, spinal cord injury, traumatic brain injury, and Parkinson disease. PEA in micronized/ultramicronized form shows superior oral efficacy in inflammatory pain models when compared to naïve PEA. Intriguingly, while PEA has no antioxidant effects per se, its co-ultramicronization with the flavonoid luteolin is more efficacious than either molecule alone. Inhibiting or modulating the enzymatic breakdown of PEA represents a complementary therapeutic approach to treat neuroinflammation. This review is intended to discuss the role of mast cells and glia in neuroinflammation and strategies to modulate their activation based on leveraging natural mechanisms with the capacity for self-defense against inflammation.

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