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Stearoylethanolamide interferes with retrograde endocannabinoid signalling and supports the blood-brain barrier integrity under acute systemic inflammation

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Abstract

Neuroinflammation plays a prominent role in the onset of demyelinating diseases, major depressive disorder and delayed neurodegeneration. An open question remains whether pharmacological suppression of inflammation can effectively reduce the progression of these states. Bioactive lipid mediators such as N-acylethanolamines (NAEs) have an anti-inflammatory activity and are of pharmacological interest due to their endogenous on-demand production and the existence of distinct biological targets in humans and animals. Here we demonstrate for the first time, that treatment with stearoylethanolamide (SEA), a prevailing endogenously formed NAE, is neuroprotective against LPS-induced neuroinflammation in C57BL/6 male mice. SEA restricted the spreading of peripheral inflammation to the brain, and averted the activation of resident microglia and leukocyte trafficking to the brain parenchyma. Treatment with SEA per se increased the neuronal expression of cannabinoid receptors $CB_{1/2}$ and brain levels of the most potent endogenous $CB_{1/2}$ agonist 2-arachidonoylglycerol in vivo. SEA enhanced the amplitude of synaptic vesicle release, supported the balanced signal-to-noise ratio in glutamate- and GABAergic neurotransmission and decreased the excitotoxic risk associated with higher extracellular glutamate levels under neuroinflammation. The interference of SEA with the endocannabinoid system and presynaptic neurotransmitter release may represent an intrinsic neuroprotective mechanism that is triggered by inflammation and glutamate excitotoxicity. Thus, our data allows to consider SEA for the preventive therapy of acute and late-onset neuroinflammation-associated synaptic dysfunction and neurodegeneration.

Keywords: 2-Arachidonoylglycerol; Cannabinoid receptors CB(1/2); Glutamate/GABA release; Leukocyte migration across the blood-brain barrier; Neuroinflammation; Stearoylethanolamide.

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