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PEA and luteolin synergistically reduce mast cell-mediated toxicity and elicit neuroprotection in cell-based models of brain ischemia.

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Abstract

The combination of palmitoylethanolamide (PEA), an endogenous fatty acid amide belonging to the family of the N-acylethanolamines, and the flavonoid luteolin has been found to exert neuroprotective activities in a variety of mouse models of neurological disorders, including brain ischemia. Indirect findings suggest that the two molecules can reduce the activation of mastocytes in brain ischemia, thus modulating crucial cells that trigger the inflammatory cascade. Though, no evidence exists about a direct effect of PEA and luteolin on mast cells in experimental models of brain ischemia, either used separately or in combination. In order to fill this gap, we developed a novel cell-based model of severe brain ischemia consisting of primary mouse cortical neurons and cloned mast cells derived from mouse fetal liver (MC/9 cells) subjected to oxygen and glucose deprivation (OGD). OGD exposure promoted both mast cell degranulation and the release of lactate dehydrogenase (LDH) in a time-dependent fashion. MC/9 cells exacerbated neuronal damage in neuron-mast cells co-cultures exposed to OGD. Likewise, the conditioned medium derived from OGD-exposed MC/9 cells induced significant neurotoxicity in control primary neurons. PEA and luteolin pre-treatment synergistically prevented the OGD-induced degranulation of mast cells and reduced the neurotoxic potential of MC/9 cells conditioned medium. Finally, the association of the two drugs promoted a direct synergistic neuroprotection even in pure cortical neurons exposed to OGD. In summary, our results indicate that mast cells release neurotoxic factors upon OGD-induced activation. The association PEA-luteolin actively reduces mast cell-mediated neurotoxicity as well as pure neurons susceptibility to OGD.

KEYWORDS: Brain ischemia; Luteolin; Mast cells; Neuroinflammation; Neurons; PEA

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