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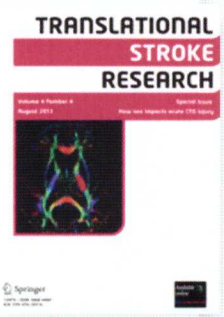
ORIGINAL ARTICLE

Co-ultramicronized Palmitoylethanolamide/Luteolin in the Treatment of Cerebral Ischemia: from Rodent to Man



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Abstract Acute ischemic stroke, the most frequent cause of permanent disability in adults worldwide, results from transient or permanent reduction in regional cerebral blood flow and involves oxidative stress and inflammation. Despite the success of experimental animal models of stroke in identifying anti-inflammatory/neuroprotective compounds, translation of these putative neuroprotectants to human clinical trials has failed to produce a positive outcome. Tissue injury and stress activate endogenous mechanisms which function to restore homeostatic balance and prevent further damage by upregulating the synthesis of lipid signaling molecules, including *N*-palmitoylethanolamine (PEA or palmitoylethanolamide). PEA exerts neuroprotection and reduces inflammatory secondary events associated with brain ischemia reperfusion injury (middle cerebral artery occlusion (MCAo)). Here, we examined the neuroprotective potential of a co-ultramicronized composite containing PEA and the antioxidant flavonoid luteolin (10:1 by mass), nominated co-ultraPEALut. The study consisted of two arms. In the first, rats subjected to MCAo and treated with co-ultraPEALut post-ischemia showed reduced edema and brain infract volume, improved neurobehavioral functions, and reduced expression of pro-inflammatory markers and astrocyte markers. In the second arm, a cohort of 250 stroke patients undergoing neurorehabilitation on either an inpatient or outpatient basis were treated for 60 days with a pharmaceutical preparation of co-ultraPEALut (Glialia®). At baseline and after 30 days of treatment, all patients underwent a battery of evaluations to assess neurological status, impairment of cognitive abilities, the degree of spasticity, pain, and independence in daily living activities. All indices showed statistically significant gains at study end. Despite its observational nature, this represents the first description of co-ultraPEALut administration to human stroke patients and clinical improvement not otherwise expected from spontaneous recovery. Further, controlled trials are warranted to confirm the utility of co-ultraPEALut to improve clinical outcome in human stroke.

Keywords Palmitoylethanolamide · Luteolin · Co-ultramicronization · Neuroinflammation · Neuroprotection · Brain ischemia reperfusion injury

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