

Neuroprotective effects of PMC, a potent alpha-tocopherol derivative, in brain ischemia-reperfusion: reduced neutrophil activation and anti-oxidant actions

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摘要

Abstract

2,2,5,7,8-Pentamethyl-6-hydroxychromane (PMC) is the most potent analogue of α -tocopherol for anti-oxidation. It is more hydrophilic than other α -tocopherol derivatives and has potent free radical-scavenging activity. In the present study, PMC significantly attenuated middle cerebral artery occlusion (MCAO)-induced focal cerebral ischemia in rats. Administration of PMC at 20 mg/kg, showed marked reductions in infarct size compared with that of control rats. MCAO-induced focal cerebral ischemia was associated with increases in HIF-1 α , active caspase-3, iNOS, and nitrotyrosine expressions in ischemic regions. These expressions were markedly inhibited by treatment with PMC (20 mg/kg). In addition, PMC (4 – 12 μ M) inhibited respiratory bursts in human neutrophils stimulated by fMLP (800 nM) and PMA (320 nM). Furthermore, PMC (6, 12, and 60 μ M) also significantly inhibited neutrophil migration stimulated by leukotriene B₄ (160 nM). An electron spin resonance (ESR) method was conducted on the scavenging activity of PMC on the free radicals formed. PMC (12 μ M) greatly reduced the ESR signal intensities of superoxide anion, hydroxyl radical, and methyl radical formation. In conclusion, we demonstrate a potent neuroprotective effect of PMC on MCAO-induced focal cerebral ischemia in vivo. This effect may be mediated, at least in part, by inhibition of free radical formation, followed by inhibition of HIF-1 α activation, apoptosis formation (active caspase-3), neutrophil activation, and inflammatory responses (i.e., iNOS and nitrotyrosine expressions), resulting in a reduction in the infarct volume in

ischemia-reperfusion brain injury. Thus, PMC treatment may represent a novel approach to lowering the risk or improving function in ischemia-reperfusion brain injury-related disorders.