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

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Abstract

2,2,5,7,8-Pentamethyl-6-hydroxychromane (PMC) is the most potent analogue of alpha-tocopherol for anti-oxidation. It is more hydrophilic than other alpha-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 20mg/kg, showed marked reductions in infarct size compared with that of control rats. MCAO-induced focal cerebral ischemia was associated with increases in HIF-1alpha, active caspase-3, iNOS, and nitrotyrosine expressions in ischemic regions. These expressions were markedly inhibited by treatment with PMC (20mg/kg). In addition, PMC (4-12 microM) inhibited respiratory bursts in human neutrophils stimulated by fMLP (800 nM) and PMA (320 nM). Furthermore, PMC (6, 12, and 60 microM) also significantly inhibited neutrophil migration stimulated by leukotriene B(4) (160 nM). An electron spin resonance (ESR) method was conducted on the scavenging activity of PMC on the free radicals formed. PMC (12 microM) 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-1alpha 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.