Therapeutic window for cinnamophilin following oxygen–glucose deprivation and transient focal cerebral ischemia

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Cinnamophilin (CINN, (8R, 8'S)-4, 4'-dihydroxy-3, 3'-dimethoxy-7-oxo-8, 8'-neolignan) protects against ischemic stroke in mice. While some anti-oxidative effects of CINN have been characterized, its therapeutic window and molecular basis for neuroprotection remain unclear. We evaluated antioxidant and anti-inflammatory properties and therapeutic window of CINN against brain ischemia using a panel of in vitro and in vivo assays. Data from lipid peroxidation and radical scavenging assays showed that CINN was a robust antioxidant and radical scavenger. CINN effectively inhibited the production of tumor necrosis factor alpha (TNF-α), nitrite/nitrate, interleukin-6 (IL-6) in lipopolysaccharide (LPS)-stimulated RAW 264.7 and BV2 cells ($P<0.05$, respectively). Relative to controls, CINN, administrated at 80 mg/kg, 2, 4, or 6 h postinsult, but not 12 h, significantly reduced brain infarction by 34–43% ($P<0.05$) and improved neurobehavioral outcome ($P<0.05$) following transient focal cerebral ischemia in rats. CINN (10–30 μM) also significantly reduced oxygen–glucose deprivation-induced neuronal damage ($P<0.05$) in rat organotypic hippocampal slices, even when it was administrated 2, 4, or 6 h postinsult. Together, CINN protects against ischemic brain damage with a therapeutic window up to 6 h in vivo and in vitro, which may, at least in part, be attributed by its direct antioxidant and anti-inflammatory effects.