4-Hydroxynonenal

Ischemia reperfusion injury produce reactive oxygen species that promote the Lipid peroxidation process resulting in the production of an endogenic lipid peroxide, 4-hydroxy-trans-2-nonenal (4-HNE), a highly cytotoxic aldehyde that induces cell death.

4-Hydroxynonenal, or 4-hydroxy-2-nonenal or 4-HNE or HNE, (C9H16O2), is an α,β-unsaturated hydroxyalkenal that is produced by lipid peroxidation in cells. 4-HNE is the primary alpha,beta-unsaturated hydroxyalkenal formed in this process.

Noguchi et al. from Fukuoka, synthesized a novel 4-HNE scavenger - a carnosine-hydrazide derivative, l-carnosine hydrazide (CNN) - and examined its neuroprotection effect in a model of transient ischemia. PC12 cells were pre-incubated with various doses (0-50 mmol/L) of CNN for 30 min, followed by incubation with 4-HNE (250 μM). An MTT assay was performed 24 h later to examine cell survival. Transient ischemia was induced by bilateral common carotid artery occlusion (BCCO) in the Mongolian gerbil. Animals were assigned to sham-operated (n = 6), placebo-treated (n = 12), CNN pre-treated (20 mg/kg; n = 12), CNN post-treated (100 mg/kg; n = 11), and histidyl hydrazide (a previously known 4-HNE scavenger) post-treated (100 mg/kg; n = 7) groups. Heat shock protein 70 immunoreactivity in the hippocampal CA1 region was evaluated 24 h later, while delayed neuronal death using 4-HNE staining was evaluated 7 days later. Pre-incubation with 30 mmol/L CNN completely inhibited 4-HNE-induced cell toxicity. CNN prevented delayed neuronal death by >60% in the pre-treated group ($p < 0.001$) and by >40% in the post-treated group ($p < 0.01$). Histidyl hydrazide post-treatment elicited no protective effect. CNN pre-treatment resulted in high heat shock protein 70 and low 4-HNE immunoreactivity in CA1 pyramidal neurons. Higher 4-HNE immunoreactivity was also found in the placebo-treated animals than in the CNN pre-treated animals. Our novel compound, CNN, elicited highly effective 4-HNE scavenging activity in vitro. Furthermore, CNN administration both pre- and post-BCCO remarkably reduced delayed neuronal death in the hippocampal CA1 region via its induction of heat shock protein 70 and scavenging of 4-HNE [1)].

1)
Noguchi K, Ali TFS, Miyoshi J, Orito K, Negoto T, Biswas T, Taira N, Koga R, Okamoto Y, Fujita M, Otsuka M, Morioka M. Neuroprotective effects of a novel carnosine-hydrazide derivative on hippocampal CA1 damage after transient cerebral ischemia. Eur J Med Chem. 2018 Nov 28;163:207-214. doi: 10.1016/j.ejmech.2018.11.060. [Epub ahead of print] PubMed PMID: 30522055.