Neuroprotective effect of low-molecular weight compounds derived from fetal tissue

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Excitatory amino acids, including glutamate, induce both acute membrane depolarization and latent cellular toxicity, which often leads to apoptosis in ischemic brain injury and a wide range of neurodegenerative disorders. Accordingly, substances that can prevent glutamate neurotoxicity are expected to be potential tools in the therapy of various neurological and neurodegenerative disorders. We previously reported that a novel neuroprotective substance, serofendic acid, was found in fetal calf serum. Serofendic acid is a low-molecular-weight substance of atisane-type diterpenoids. The chemical structure is 15-hydroxy-17-methylsulfinylatisan-19-oic acid, a sulfur-containing atisane-type diterpenoid. The compound exhibited potent protective action against neurotoxicity induced by glutamate, nitric oxide and oxidative stress without inhibiting glutamate receptors in cultured neurons. The molecular mechanisms of neuroprotection of serofendic acid remains to be determined, but it was demonstrated that serofendic acid inhibited the generation of a hydroxyl radical, a presumed executor radical in the neurotoxic cascade and exhibits neuroprotective effects by preventing mitochondrial membrane depolarization and the sequential activation of caspase-3 mediated by glutamate receptors, including NMDA receptors. Thus, we propose that serofendic acid may play a crucial role in the CNS by attenuating cytotoxic consequences induced by necrotic and apoptotic signals mediated by neuronal glutamate receptors. Our results raise the possibility that the survival of certain types of cells including CNS neurons is supported by new types of low-molecular weight bioactive factors.