Department of Pharmacology

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Research Projects:

The trouble with a higher brain dysfunction due to neurodegenerative disease such as the Alzheimer's diseases and Parkinson's diseases and cerebral ischemia has features in the neuronal death of the neuron group of a specific area of brain by the process of apoptosis and necrosis. Glutamate is known as one of risk factors of the neuronal death according to the neurodegenerative disease and cerebral ischemia. We investigate the mechanisms of the neuronal death and the exploratory research of low-molecular compounds that control the neuronal death accompanied by the neurodegenerative disease and cerebral ischemia using the techniques of in vivo experiment system that used the brain disease model animal and in vitro system including the primary neuronal cultures. Our current research projects are listed below.

1) Analysis of physiological and pharmacological action of serofendic acid

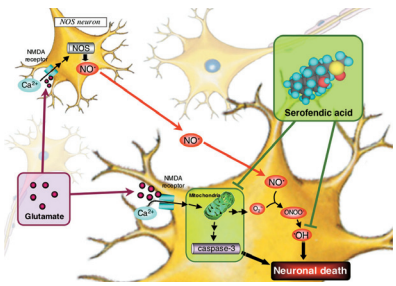
Serofendic acid is a cyclic diterpenoid with a unique structure of low molecular weight discovered from the fetal calf serum in our laboratory. We previously reported that neuronal death caused by glutamate, reactive oxygen species (ROS) and nitric oxide (NO) has been controlled by the research that uses the primary neuronal culture system so far. Moreover, serofendic acid was clarified to the possession of the hydroxy radical deletion action without giving the directly influence on glutamate receptor function and NO, and the control of the depolarization of the mitochondrial membrane caused with the glutamate (Refer to the figure below). However, a direct target molecule of serofendic acid is not determined. Then, to clarify the physiological and pharmacological action of serofendic acid, the search for the target molecule of serofendic acid is advanced in addition to the clarification of the mechanism that controls the mitochondrial damage.

2) Research on nicotinic acetylcholine receptor

We previously reported that long-term exposure to nicotine of cerebral cortical neurons prevented neuronal death induced by glutamate and amyloid β protein. Furthermore, we also reported that central-type acetylcholinesterase inhibitors including donepezil protected cortical neurons against glutamate neurotoxicity via the stimulation of nicotinic acetylcholine receptors. Then, we examine detailed mechanisms of the neuroprotective effect of acetylcholinesterase by the nicotinic receptor stimulation. Especially, the examination of a control of the intracellular calcium concentration, which is important to elicit glutamate neurotoxicity, and the expression and the function of the nicotinic receptor in the glial cells is advanced.

3) Research on neuroprotective compounds derived from food

Neurodegenerative diseases have the features in the neuronal death of neuron group of a specific area of brian as mentioned above. As the cause of neuronal death in neurodegenerative diseases, various endogenous substances are proposed. Thus, the development of neuroprotective drugs that control the neuronal death by these factors is advanced. However, it stays in the use of the drug to aim at symptomatic treatment under the present situation, and the drugs that inhibit the neuronal death is not developed yet. In addition, it is very difficult to overcome these neurodegenerative diseases only by the drug treatment because the symptoms gradually progress for a long period of several years or more. From such a background it is considered that the importance of the management from the point of view of preventive medicine comes to be recognized. Attempting the prevention of the diseases and the slowing of the progress by using food with the neuroprotective effect as manegement of the aging risk becomes important. We currently explore that the compounds derived from foods with neuroprotective action. We now pay attention that isothiocyanate compounds that are pungent conponents including broccolis and wasabi.



Schematic representation of putative neuroprotective mechanism of serofendic acid.
Glutamate induces Ca^{2+} influx via the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor channels. The evaluation of intracellular Ca^{2+} triggers the formation of nitric oxide (NO) in NO synthase (NOS)-containing neurons. The impairment of mitochondria is caused by the rise of the intracellular calcium concentration. As a result, free radicals are release into the cytoplasm. Radical chain reaction elicited by these radicals finally generates hydroxy radical and induces neuronal death. Moreover, the activation of the apoptotic pathway through the caspase driven from the mitochondrial damage is comparatively suggested as for the toxicity caused by the glutamate of the relatively low concentration. As for the serofendic acid, the neuroprotective action is thought to be appearance by controlling hydroxy radical□s production, and protecting the mitochondrial dysfunction.

Recent publications

- Izumi *et al.* Isolation, identification, and biological evaluation of Nrf2-ARE activator from the leaves of green perilla (Perilla frutescens var. crispa f. viridis), *Free Radic Biol Med*, in press
- Osakada *et al.* Toward the generation of rod and cone photoreceptors from mouse, monkey and human embryonic stem cells. Nature *Biotechnol.* **26**, 215, 2008
- Fujimoto *et al.* Plasminogen potentiates thrombin cytotoxicity and contributes to pathology of intracerebral hemorrhage in rats. *J. Cereb. Blood Flow Metab.* **28**, 506, 2008