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 or 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. 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 and 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) Elucidation of pathogenesis and exploratory study of preventive and therapeutic agents of neurodegenerative diseases

“Amyloid hypothesis,” which amyloid β protein (Aβ) that plays an important role in the development of Alzheimer’s disease, has been recognized; but the toxic mechanisms of Aβ have still unsolved. We previously identified the toxic conformer of Aβ42 with a turn at positions 22 and 23 (“toxic turn”). Our recent study suggested that oxidative stress is a key factor of the oligomerization and cognitive impairment induced by Aβ overproduction in vivo. However, the involvement of the toxic conformer in Aβ42-induced oxidative damage remains unclear. To investigate this mechanism, we examined the levels of intracellular reactive oxygen species (ROS) and neurotoxicity in rat primary neurons using E22P-Aβ42, a mutant that induces a turn at positions 22 and 23. E22P-Aβ42 induced greater ROS production than Wt-Aβ42 in addition to potent neurotoxicity. Trolox (a radical scavenger) and Congo red (an aggregation inhibitor) significantly prevented the neurotoxicity and intracellular ROS induced by E22P-Aβ42 and Wt-Aβ42, respectively. These results suggest that Aβ42-mediated toxicity is caused by the turn that favors toxic oligomers, which increase generation of ROS. We currently investigate the in vivo effect of toxic conformer of Aβ42.

2) Study on function of nicotinic acetylcholine system in CNS

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 are currently examining detailed mechanisms of the neuroprotective effect of acetylcholinesterase by the nicotinic receptor stimulation.

3) Study on neuroprotective compounds derived from food

For overcoming these neurodegenerative diseases, it is necessary to manage them from the point of view of preventive medicine because neuronal death has already occurred at the onset. In addition, it is important to slow the progress not only by the drug treatment but also by the auxiliary use of food with the neuroprotective effect because the symptoms gradually progress for a long period of several years or more. Our aim is to explore and analyze the neuroprotective or neuroregenerative compounds derived from food for the management of aging risk, such as dementia. We previously identified DDC from green perilla as a novel functional component and clarified that DDC induced upregulation of intracellular antioxidant enzymes. We are currently investigating the neuroprotective actions of several components derived from foods including green perilla.

4) Study on survival and regeneration of dopaminergic neurons

With respect to Parkinson disease characterized by selective loss of dopaminergic neurons in the substantia nigra, we reported that dopaminergic neurons were particularly vulnerable to cellular stress because they are rich in dopamine, which can easily undergo autoxidation, as a neurotransmitter. Therefore, we are exploring the compounds which regulate the abnormal autoxidation of dopamine as candidates for dopaminergic neuroprotective drugs. In addition, dysfunction of protein quality control is implicated in Parkinson disease. We are examining the novel neuroprotective mechanisms by clarifying the role of proteasome and autophagy in dopaminergic neuronal death. Furthermore, the study aimed at regeneration of the nigrostriatal dopaminergic projection is in progress. By the use of original methods, the mechanism by which dopaminergic axons innervate striatal neurons is investigated. Findings which will be obtained from this study might be applicable to stem cell-derived cell transplantation therapy.

Recent publications

Izumi et al. Endogenous dopamine is involved in the herbicide praquat-induced dopaminergic cell death. Toxical Sci. 139, 466, 2014


Izuo et al. Toxicity in rat primary neurons through the cellular oxidative stress induced by the turn formation at positions 22 and 23 of Aβ42. ACS Chem Neurosci, 3, 674, 2012


Schematic representation of cytoprotective mechanism of DDC.

DDC was extracted and isolated from the leaves of green perilla. DDC activated Nrf2-ARE pathway, a cellular defense system against oxidative stress. Nrf2, a transcriptional factor, is translocated to the nucleus and bound to antioxidant response element (ARE), resulting in the transcriptional activation of a number of antioxidant enzymes. Cells treated with DDC acquired resistance to oxidative damage.