S61-5 Regulation of dopaminergic neuronal death by endogenous dopamine and proteasome activity

◯Yasuhiko IZUMI[1], Toshiaki KUME[1], Akinori AKAIKE[1]

[1]Kyoto Univ. Grad. Sch. of Pharm. Sci.

Parkinson disease is one of the most common neurodegenerative disorders and characterized by a selective loss of dopaminergic neurons in the substantia nigra pars compacta. The exact cause of the neuronal loss remains unclear, although endogenous dopamine could serve as a vulnerability factor for dopaminergic neurons because dopamine itself exhibits cytotoxicity. Therefore, our aim is to clarify the mechanisms by which endogenous dopamine contributes to dopaminergic neuronal death. Treatment with the herbicide paraquat, a potential risk factor for the development of Parkinson disease, induced an increase in intracellular dopamine, and depletion of intracellular dopamine suppressed paraquat-induced cytotoxicity. In addition, we demonstrated that dopamine-oxidized intermediates played a pivotal role in dopamine-induced toxicity. Interestingly, treatment with paraquat induced a decrease in proteasome activity, and inhibition of proteasome activity suppressed dopamine-mediated cytotoxicity. Since a decrease in proteasome activity was found in patients with sporadic Parkinson disease, the relationship between ubiquitin-proteasome system and dopaminergic neuronal death has been focused, but remains controversial. In this symposium, on the basis of our findings, we introduce the mechanisms for endogenous dopamine-mediated cytotoxicity and discuss the effect of proteasome activity on dopaminergic neuronal death.