No. 1631

Study for Intracellular Mg^{2+} Mobilization in Perkinson's Like Cell Death by Using New Fluorescent Imaging Techniques

Kotaro Oka

Faculty of Science and Technology, Keio University

Summary

Mg^{2+} is an essential cation to maintain cellular functions, and intracellular Mg^{2+} concentration ($[Mg^{2+}]_i$) is regulated by Mg^{2+} channels and transporters. Our previous study demonstrated that MPP^+ elicits Mg^{2+} influx across the cell membrane and Mg^{2+} mobilization from mitochondria, and the resulting $[Mg^{2+}]_i$ is an important determinants of the cell viability in MPP^+ model of Parkinson's disease (PD) of PC12 cells. In this study, we also investigate this model in neurons induced form human iPS cells. By using the bio-imaging techniques for visualizing the $[Mg^{2+}]_i$, inner mitochondrial Mg^{2+} concentration ($[Mg^{2+}]_{mito}$), and mitochondrial inner membrane potential, we found that MPP^+ depolarizes mitochondrial inner membrane potential and induces Mg^{2+} releases from mitochondria to the cytosol. This mechanism is almost same to the MPP^+ model of Parkinson's disease previously reported. Furthermore, we also estimated the mRNA expression levels of Mg^{2+} transport proteins upon the exposure to MPP^+ in PC12 cells. In thirteen Mg^{2+} transport proteins examined, mRNA expression level of SLC41A2 was increased and that of ACDP2, NIPA1 and MMgT2 were decreased. Knockdown of SLC41A2, ACDP2 or NIPA1 accelerated the MPP^+-induced cell degeneration, and overexpression attenuated it. The decrease in the mRNA expression levels of NIPA1 and MMgT2 were also elicited by rotenone, H_2O_2 and FCCP, indicating that mitochondrial dysfunction related to this down-regulation. The increase in that of SLC41A2 was induced by an uncoupler, FCCP, as well as MPP^+, suggesting that it is an intrinsic protection mechanism against depolarized mitochondrial membrane potential and/or cellular ATP depletion. We also interested in the function of Mg^{2+} transporter Mrs2 that is localized in mitochondria. The knockdown of Mrs2 reduces the cytosolic level of ATP and also induces fission of mitochondria. Furthermore, comprehensive metabolome analysis reveals that some of the metabolites of TCA cycle decreased. Our results shown here indicate that alteration of Mg^{2+} transport proteins is implicated in the MPP^+ model of PD, and it affects cell degeneration *via* alternation of energy metabolism.