【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy)

Title of Project : Pathophysiological calcium signaling in the central nervous system network

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Research Area : Pharmacology
Keyword : Receptor, Channel/Transporter, Signal Transduction

【Purpose and Background of the Research】

In the central nervous system (CNS), numerous neurons and glial cells form a complex network that underlies the performance of brain functions. Among the signaling mechanisms within the CNS network, Ca^{2+} signal is involved in a multitude of important cellular functions. We have shown that Ca^{2+} signaling mechanisms play important roles in the cellular responses to brain injury. In this project we plan to extend our previous work and clarify the pathophysiological mechanisms in response to brain injury, aiming at identifying therapeutic targets for the pathological states.

【Research Methods】

For this project, we have generated three lines o f genetically engineered mice. Using these lines of mice and cutting-edge fluorescence imaging methods, we will clarify the molecular and cellular mechanisms of Ca^{2+}-mediated pathophysiological states in the CNS. In particular, we should like to clarify the relationship between Ca^{2+} release due to pathological generation of NO (NO-induced Ca^{2+} release, NICR) and neuronal cell death (Fig. 1), as well as the neuroprotective role of Ca^{2+} signal-dependent reactive astrogliosis (Fig. 2). We should also like to clarify the mitochondrial Ca^{2+} dynamics in conjunction with neuronal cell death, using newly developed intraorganellar Ca^{2+} indicators.

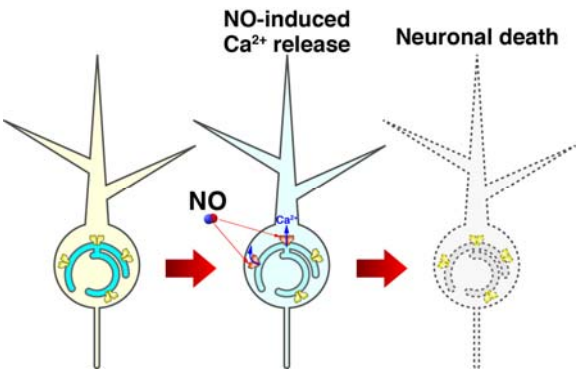

Fig. 1 NICR mechanism and neuronal death

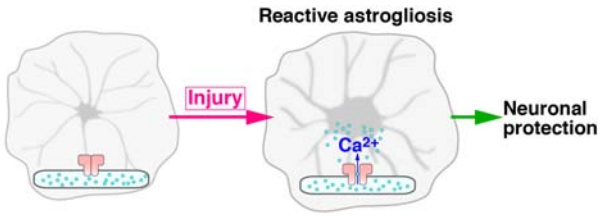

Fig. 2 Ca^{2+} signaling and reactive astrogliosis

【Expected Research Achievements and Scientific Significance】

If our results establish the relationship between neuronal cell death and NICR in disease models, NICR can be a potential therapeutic targeted for the management of neuronal cell death in pathological conditions including ischemic brain injury. Analyses of reactive astrogliosis are expected to establish a basis for the development of therapeutics for preventing neuronal cell death in response to traumatic brain injury. Furthermore, we can clarify the relationship between the mitochondrial Ca^{2+} dynamics and neuronal death. This would provide a basis for identification of new therapeutic targets for the control of neuronal cell death.

【Publications Relevant to the Project】

- Kakizawa, S., Yamazawa, T., Chen, Y., Ito, A., Murayama, T., Oyamada, H., Kurebayashi, N., Sato, O., Watanabe, M., Mori, N., Oguchi, K., Sakurai, T., Takeshima, H., Saito, N. and Iino, M. Nitric oxide-induced calcium release via ryanodine receptors regulates neuronal function. **EMBO J.** 31, 417-428, 2012.
- Okubo, Y., Sekiya, H., Namiki, S., Sakamoto, H., Iinuma, S., Yamasaki, M., Watanabe, M., Hirose, K. and Iino, M. Imaging extrasynaptic glutamate dynamics in the brain. **Proc. Natl. Acad. Sci. U.S.A.** 107, 6526-6531, 2010.

【Term of Project】 FY2013-2017

【Budget Allocation】 178,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://calcium.cmp.m.u-tokyo.ac.jp/