【Grant-in-Aid for Scientific Research(S)】

Biological Sciences (Biological Sciences)

Title of Project : Role of IP3 receptor in the Regulation of Synaptic Plasticity, neuronal Function and neuronal Development

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Research Area : Developmental Neurobiology
Keyword : Ca^{2+}signaling, IP_3 receptor, Synaptic Plasticity, Endoplasmic reticulum (ER) stress

【Purpose and Background of the Research】

The 2nd messenger IP_3 increases cytosolic Ca^{2+}. There was uncertainty as to the source of the Ca^{2+} and as to the nature of the IP_3-binding protein and its relationship to the putative Ca^{2+} channel. Mikoshiba discovered the IP_3 receptor (IP_3R) and IP_3R is an IP_3-binding protein and a Ca^{2+} channel, which was located on the ER where Ca^{2+} is stored. He determined the entire primary sequence (313kDa) (***Nature*** 1989). He solved the X-ray crystallographic structure of the IP_3-binding core (***Nature*** 2002) and the regulatory domain (***Mol Cell*** 2005). He solved the 3-dimensional structure of the IP_3R by cryo-EM (***J Mol Biol.*** 2004). He revealed the gating mechanism of the IP_3R channel pore to release Ca^{2+}. His discovery started from the work on the P400 protein missing in ataxic mutant mice and identified P400 as the IP_3R. He has established that this IP_3R has many different cellular functions. It is involved in fertilization in both the egg (***Science*** 1992) and the sperm (***Science*** 2001) and is essential for dorsoventral axis formation (***Science*** 1997) and cell cleavage (***J Cell Biol*** 1996). In the nervous system it functions in neurite extension (***Science*** 1998; ***Science Signaling*** 2009) and is important for neuronal plasticity in the cerebellum (***J Neurosci.*** 1998) and hippocampus (***Nature*** 2000; ***Neurosci.*** 2010) and in secretion (***Science*** 2005). He discovered a pseudo-ligand of the IP_3R (IRBIT) released upon IP_3 binding to the IP_3R (Mol ***Cell*** 2006). IRBIT regulates acid-base balance. (***PNAS*** 2006; ***J Clinical Invest.*** 2009). These functions became abnormal when the IP_3R is blocked. He found that neurodegeneration (***Neuron*** 2010) and redox damage (***Cell*** 2005) was protected by chaperons (GRP78, ERp44) that bind to the IP_3R. He found numerous signaling molecules that associate with the IP_3R suggesting links with many other signaling pathways with implications for various diseases and he also found mutations in the human IP_3R. He contributed to the Ca^{2+} signaling field by developing an inhibitor for the IP_3R called 2-APB.

【Research Methods】

1) Study of the role of spine in neural plasticity, brain development and differentiation
2) Single molecule analysis of functional molecules in the brain by FRET, TIRF and quantum dot analysis
3) Analysis of micro-RNA (miRNA) in neuronal plasticity and development in IP_3R1 KO mice.
4) Electrophysiological analysis of the cerebellum, hippocampus and cerebral cortex
5) Screening the IP_3R associated molecules which works in dorso-ventral axis formation, neural development and their pathogenesis
6) Development of efficient indicator of IP_3.
7) Analysis of the mechanism of neuronal circuit formation by macropinocytosis
8)Study of disturbance of the neuronal function accompanied with IP_3 receptor dysfunction
a) Dysfunction of IP_3R1 and its pathogenesis
b) Production of region specific conditional KO of IP_3R1 and the study of its neuronal activity
9) Development of inhibitors of IP_3Rs
10) Synthesis inhibitors of Ca^{2+} signaling

【Expected Research Achievements and Scientific Significance】

Studying the role of each type of IP_3R in neurons and glial cells for neural plasticity, neural function and neural development makes it possible to understand the mechanism how normal brain functions, and many brain diseases occur. These gives us an opportunity to prevent and rescue the diseases.
The IRBIT works as a 3rd messenger released in the presence of IP_3 regulates acid-base balance. The KO mice of IRBIT show severe psychiatric disorder, it would be possible to open a new field in neuroscience and its disorders.

【Publications Relevant to the Project】

- Furuichi T, Yoshikawa S, Miyawaki A, Wada K, Maeda N, Mikoshiba K. Primary structure and functional expression of the inositol 1,4,5-trisphosphate-binding protein P400. ***Nature*** 342(6245): 32-8. (1989)
- Higo T, Hattori M, Nakamura T, Natsume T, Michikawa T, Mikoshiba K. Subtype-specific and ER lumenal environment-dependent regulation of inositol 1,4,5-trisphosphate receptor type 1 by ERp44. ***Cell*** 120(1): 85-98. (2005)

【Term of Project】FY2013-2017
【Budget Allocation】166,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.brain.riken.jp/en/faculty/details/29