Form 2-4-2

Japan-U.S. Brain Research Cooperation Program
Group Joint Study Project Report

Field: (4)

1. Principal Researcher
   Name: Masato Hirata
   Title: Professor
   Affiliation: Faculty of Dental Science, Kyushu University

2. Project Title:
   Roles of a novel molecule, PRIP in neurotrophine secretion

3. Japanese Group
   Names, Titles and Affiliations of Principal Researcher and Collaborating Research Members
   Chief: Masato Hirata, Professor of Faculty of Dental Science, Kyushu University
   Collaborator: Hiroshi Takeuchi, Associate Professor of Faculty of Dental Science, Kyushu University

4. U.S. Group
   Names, Titles and Affiliations of Principal Researcher and Collaborating Research Members
   Chief: Thomas F.J. Martin, Professor of The Department of Biochemistry, University of Wisconsin-Madison
   Collaborator: Declan James, Post-Doctoral Fellow in the same lab as described above.

5. Research Period, from/to (mm/dd/yyyy) and total number of years.
   From 04/01/2008 to 03/31/2011 (3 years)

6. Abstract, Results, and Research Significance (300 words):

The present groups joint-research was performed as a part of our project to study the molecular mechanisms by which PRIP (phospholipase C-related catalytically inactive protein), which we isolated as a novel IP_3 binding protein, is involved in vesicular secretion including nerve growth factors.

By analyzing PRIP-DKO mice (PRIP, type 1 and 2-double deficient mice), we found that Langerhans islets from the mutant mice secrete more insulin upon high-glucose stimulation with no difference in the Ca^{2+} concentration. Serum level of luteinizing hormone was also higher in the mutant mice, indicating that PRIP negatively regulates secretion, probably by interfering with molecules involved in mechanisms common to dense-core vesicle secretion. This collaborative research was started to clarify the molecular mechanisms underlying the negative roles of PRIP on vesicular secretion, with special reference to the function of CAPS (calcium activated protein for secretion). CAPS was first identified by Professor Martin in University of Wisconsin-Madison as a protein enhancing the dense-core vesicle secretion. The Japanese investigator, Takeuchi tested the series of deletion mutants and site-directed point mutants of PRIP on, (1) Fusion Assay, (2) Rotating Disc Electrode (RDE) Voltammetric Measuerment, (3) TIRFM (Total Internal Reflection Fluorescent Microscopy), all of which were well designed to analyze the final steps of exocytosis, membrane fusion, in Prof. Martin's Laboratory. We clarified the inhibitory roles of PRIP on dense core vesicle exocytosis by competing with CAPS, which facilitates the fusion processes by helping SNARE complex formation following the priming process on the target membranes, for binding to PIP_2.

The results of the current study would provide the molecular basis for treatment of neuronal disorders including autism, as it has been reported that CAPS deficiency in mice caused the impairment of neurotrophic factors secretion, and the mutant mice exhibited the behavioral phenotypes like autism.

7. Other (Research-related concerns, particular points of note):
   Not particular.