Studies on a novel signaling molecule, PRIP involved in GABAA receptor function

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【 Outline of survey 】

GABAA receptor is the predominant transducer of fast synaptic inhibitory neurotransmission in the brain, and therefore is involved in multiple brain functions such as vigilance, anxiety, muscle tension, epileptogenic activity, memory etc. These receptors are heteropentamers that can be assembled from 7 subunit classes with multiple members: a1-6, b1-3, g1-3, d, e, p and q. The majority of GABAA receptor subtypes in the brain are however believed to be composed of a, b, and g_subunits. Changes in GABAA receptors are relevant in a number of disease states including epilepsy, depression and chronic substance abuse. On the other hand, PRIP was originally identified as a novel inositol 1,4,5-trisphosphate binding protein, homologous to PLC-d1, but is catalytically inactive. PRIP has a number of binding partners including catalytic subunit of protein phosphatase 1a and GABAA receptor associated protein, which is believed to facilitate GABAA receptor membrane trafficking and/or clustering. A role for PRIP in regulating GABAA receptor function is further suggested by the pheno-type of PRIP knockout (PRIP-/-) mice, which have altered GABAA receptor pharmacology and behavior. On the basis of these findings, the present studies aim to unveil the molecular mechanisms underlying that PRIP is involved in the assembly of the functional pentameric GABAA receptors and in the phospho-dependent modulation of GABAA receptors. Furthermore, the relationship between the proper mastication and expression of PRIP in the brain, with special reference to the function of GABAA receptors are also examined.

【 Expected results 】

Expected outcome from these studies could be summarized as follows: (1) Elucidation of the molecular mechanisms by which PRIP plays an important roles in the functional assemble of heteropentameric GABAA receptors, especially those including g-subunit. (2) Contribution to the social prevalence of the importance of oral health by which the general health is led.

【 References by the principal researcher 】

(1) Role of the PLC-related, catalytically inactive protein p130 in GABAA receptor function. Kanematsu, T. and Hirata, M. et al., EMBO J. 21, 1004-1011, 2002
(2) InsP4 facilitates store-operated calcium influx by inhibition of InsP3 5-phosphatase. Hermosura, M.C. and Hirata, M. et al., Nature 408, 735-740, 2000.

【 Term of project 】 FY 2004 — 2008

【 Budget allocation 】 87,300,000 yen

【 Homepage address 】 http://www.dent.kyushu-u.ac.jp/sosiki/a04/index.html