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

Integrated Science and Innovative Science (Comprehensive fields)

Title of Project： Study of brain mechanisms controlling body-fluid homeostasis

Masaharu Noda
(National Institute for Basic Biology, Division of Molecular Neurobiology, Professor)

Research Area：Neuroscience (general)
Keyword：Molecular and cellular neurobiology

【Purpose and Background of the Research】

It is essential to life for mammals including humans to maintain electrolyte (especially Na^+) levels in body fluids, including blood and CSF: so-called body-fluid/Na homeostasis. For this purpose, our brain constantly monitors the levels of Na^+ and osmolarity in body fluids and controls the intake of salt/water and excretion by the kidney. We have identified the Na_x channel as a sensor of Na^+-level increase in the brain, and elucidated a battery of sensing mechanisms. Recently, we also showed that TRPV1 is sensitive to an osmotic increase exclusively at around the body temperature. Based on these findings, the present study attempts to elucidate the whole picture of brain mechanisms controlling body-fluid homeostasis.

【Research Methods】

To elucidate brain mechanisms for body-fluid homeostasis, we promote the following projects. First, identification and characterization of cell species which constitute the sensory circumventricular organs (CVOs), the sensing center of body-fluid conditions, with specific marker proteins. Second, elucidation of projection neurons among them by Fos expression and retrograde axonal labeling. Third, clarification of the inter-relationship between Na_x signaling and peptide hormones, such as endothelins and neurokinin B. Fourth, demonstration of the postulated functional role of Na_x signaling in salt-intake suppression using light-activated channels. Fifth, identification of TRPV1-positive cells in the CVOs and the characterization of defects in water-intake behavior and VP expression in *TRPV1*-KO mice.

【Expected Research Achievements and Scientific Significance】

Brain mechanisms for body-fluid homeostasis are essential to life, and they have evolved and developed in animals for terrestrial life. Although this theme has long been studied, the details have not been clarified. The main reason is that the molecular entities of the sensors of body-fluid conditions have not been identified. Because we identified two sensors which recognize an increase of Na^+ or osmolarity, respectively, it has become possible to start studies to clarify the brain mechanisms from the molecular to organismal level as a system. The present projects are composed of many steps, including the identification of cell species in the CVOs and relevant circuits, significance of information transmission from Na^+-positive glial cells to neurons, relation between hormones related to blood pressure and sensing mechanisms of the brain, and elucidation of neural networks which control salt/water intake and its regulation mechanisms. From this perspective, this study is highly original and comprehensive. Studies on body-fluid control mechanisms by peripheral organs like the kidney have markedly advanced; however, those involving the brain have been delayed. The present study will contribute to basic physiology worldwide and shed light on the direction of brain science in the future, because of the integration of neurobiology and endocrinology.

【Publications Relevant to the Project】

- Hiyama TY, Matsuda S, Fujikawa A, Matsumoto M, Watanabe E, Kajiwara H, Niimura F and Noda M. (2010). Autoimmunity to the sodium-level sensor in the brain causes essential hypernatremia. ***Neuron*** 66, 508-522.
- Shimizu H, Watanabe E, Hiyama TY, Nagakura A, Fujikawa A, Okada H, Yanagawa Y, Obata K and Noda M. (2007). Glial Na_x channels control lactate signaling to neurons for brain $[Na^+]$ sensing. ***Neuron*** 54, 59-72.
- Noda M. (2006). The subfornical organ, a specialized sodium channel, and the sensing of sodium levels in the brain. ***The Neuroscientist*** 12, 80-91.

【Term of Project】FY2012-2016

【Budget Allocation】172,000 Thousand Yen

【Homepage Address】

http://niwww3.nibb.ac.jp/