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

Broad Section I

Title of Project： Integrative study of brain mechanisms to induce hypertension

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Keyword：hypertension, leptin, angiotensin II, aldosterone, Na_x channel

【Purpose and Background of the Research】

It is well-known that excess salt intake (HS) induces hypertension; however, the mechanism has not been elucidated until recently. We, for the first time, revealed brain mechanisms for salt-induced elevations of blood pressure (BP) (Fig. 1). Briefly, increases of $[Na^+]$ in body fluids activate Na_x channels in the organum vasculosum lamina terminalis (OVLT). The Na_x signal in glial cells in transferred to the central nuclei [paraventricular nucleus (PVN) and rostral ventrolateral medulla (RVLM)] controlling sympathetic nerve activity (SNA). The increase in SNA leads to BP elevations.

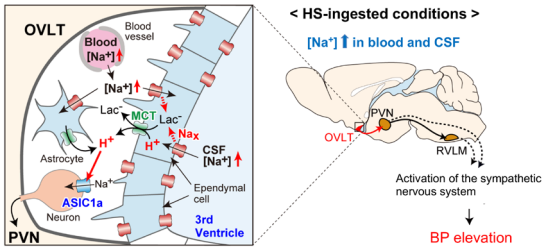

Figure 1　Central mechanisms of salt-induced BP elevations

On the other hand, it is known the obesity and psychological stress elevate BP through activation of SNA. The present study is aimed to elucidate the overall picture of brain mechanisms controlling BP.

【Research Methods】

Under obesity or stress conditions, the level of leptin, angiotensin II, or aldosterone increase in blood. After these factors are received by specific brain loci, the signals are eventually transferred to the central nuclei controlling SNA. We hypothesized that sensing receptive loci of these factors are circumventricular organs (CVOs) that lack blood-brain barrier in the brain.

In the present study, we will promote the following projects: Elucidation of; 1) receptive loci for respective factors, 2) signaling pathways to the PVN or RVLM and, 3) integration mechanism of these signals in some central nuclei. For this purpose, we employ modern research techniques, such as tracing methods by using multiple viral vectors, optogenetics to reveal the function of a specific neural pathway, and Ca^{++} imaging of a nucleus at the single neuronal level.

【Expected Research Achievements and Scientific Significance】

Although the mechanism of salt-induced hypertension has long been studied, the details have not been clarified until recently. The main reasons were that the sensor to detect increases in $[Na^+]$ of body fluids was an enigma, and the mechanisms for sensing and transmitting signal to the center controlling SNA were unknown.

We do not know the sensing loci of leptin, angiotensin II, or aldosterone in the brain, nor the cellular mechanisms of signal transmission. The present study will integratively elucidate brain mechanisms of BP elevations caused by these endogenous pressor factors. This study is of marked academic value and will contribute to the development of a novel strategy to treat hypertension.

【Publications Relevant to the Project】

・Nomura K, Hiyama TY, (他 8 名) and Noda M. $[Na^+]$ increases in body fluids sensed by central Na_x induce sympathetically mediated blood pressure elevations via H^+-dependent activation of ASISC1a. **Neuron** *101*, 60-75 (2019).
・Matsuda T, Hiyama TY, (他 5 名) and Noda M. Distinct neural mechanisms for the control of thirst and salt appetite in the subfornical organ. **Nature Neurosci.** *20*, 230-241 (2017).
・Noda M, and Sakuta H. Central regulation of body-fluid homeostasis. **Trends Neurosci.** *36*, 661-673 (2013).

【Term of Project】FY2019-2023

【Budget Allocation】140,500 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.rcb.iir.titech.ac.jp/index.html