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Central Mechanisms for the Integration of Na^+ and Ang II Signals in Blood Pressure Elevation by High-Salt Ingestion

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Summary

In terrestrial animals including humans, the concentrations of sodium ions (Na^+) in body fluids are maintained at a constant level, and this "sodium homeostasis" is essential for maintaining the life. The brain senses changes in Na^+ levels in body fluids and receives signals encoding the internal environment via circulating hormones such as angiotensin II (Ang II), and the integral control of salt- and water-intakes and blood pressure is accomplished. In the brain, sensory circumventricular organs (sCVOs) such as the organum vasculosum lamina terminalis (OVLT) and subfornical organs (SFO) are known as brain regions sensing peripheral signals, because they lack a blood-brain barrier. Recently, our laboratory revealed mechanisms responsible for salt-dependent hypertension: Glial cells expressing Na_x, a sodium level sensor, in the OVLT detect an increase in Na^+ levels in body fluids caused by excessive salt intake, which results in elevation of blood pressure through activation of sympathetic nerve activities. On the other hand, elevation of Ang II levels in body fluids induced by the increase of Na^+ levels also elevates blood pressure like Na^+ signals; however the Ang II-mediated central mechanism for the blood-pressure elevation has not been adequately understood. Also, integration mechanisms of these two signals in the brain have not been well clarified.

In the present study, we first analyzed the mechanism of Ang II-induced blood-pressure elevation in the brain. Intracerebroventricular infusion of Ang II activated neuronal activities in the SFO and OVLT, and an increase of ~12 mmHg in blood pressure was observed. Moreover, we identified Ang II receptor (AT1a)-positive neurons in the SFO, projecting to the hypothalamus. When these neurons were activated by using an optogenetic technique, an increase of ~10 mmHg in blood pressure was observed. At present, we are analyzing the inter-relationship between Na^+ and Ang II signaling.

The central mechanism of Ang II-mediated blood pressure elevation may lead to the understanding of the relationship between Ang II signals and salt-dependent hypertension, which reveal the pathogenesis of neurogenic hypertension and finally contributes to improvement of the treatment.