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Central Mechanisms for the Inhibitory Controls of Salt and Water Intakes.

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Summary

In terrestrial animals including humans, sodium ions (Na^+) in body fluids play an important role in maintaining the life. To keep a physiological Na^+ concentration in body fluids, the brain senses changes of Na^+ concentration, osmolality, and circulating honnones in body fluids, and translates these information into neural activity to control various physiological functions. When the Na^+ concentration in body fluids begins to deviate from the physiological levels, the brain attempts to return the Na^+ concentration to the normal range by controlling salt appetite, thirst, blood pressure, and urination. If the Na^+ concentration remains abnormal level for a long time, various systemic disorders such as hyponatremia and hypernatremia can occur.

We previously identified two populations of neurons that induce salt appetite (salt neurons) and thirst (water neurons) in the subfornical organ (SFO), one of the sensory circumventricular organs (sCVOs) that lacks a blood-brain barrier in the brain. We also identified inhibitory systems in the SFO for salt neurons and water neurons in response to body fluid conditions. Moreover, our recent findings suggest the existence of a distinct inhibitory mechanism for salt appetite and thirst.

In the present study, we revealed CCK neurons in the hindbrain that control salt appetite. We monitored activities of CCK neurons during salt intake (0.3 M NaCl) using *in vivo* calcium imaging. These neurons were activated immediately after salt intake, before the changes in the body fluid level. We found that a subset of CCK neurons projects to the ventral part of the bed nucleus of the stria tenninalis (vBNST), which is downstream of salt neurons in the SFO. Furthermore, optogenetic activation of this population of CCK neurons suppressed salt appetite. Finally, combined analyses of calcium imaging and optogenetics suggested that CCK neurons in the hindbrain activate GABAergic neurons in the vBNST to inhibit salt intake behaviour.

These results indicate that the subpopulation of CCK neurons in the hindbrain have a function to prevent excessive salt intake prior to the changes in body fluid level by transiently suppressing salt intake behavior. In the animals, the body fluid salt balance is thus maintained by combinational control mechanisms based on prediction of changes in body fluid condition (feed-forward control) and actual body fluid condition (feed-back control).