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Analyses of Neural Mechanism Underlying Salt-Intake Control Based on Appetite

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Summary

Body fluid conditions are continuously monitored in the brain to regulate thirst and salt-appetite. Angiotensin II drives both thirst and salt appetite; however, the neural mechanisms underlying the generation of thirst and salt-appetite, and selective controls of thirst and salt-appetite remain unknown. We previously identified Na_x channels as a brain [Na^+] sensor that detects [Na^+] elevations in body fluids within the physiological range. Na_x channels are specifically expressed in the glial cells (ependymal cells and astrocytes) of the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT), brain regions that lack a blood–brain barrier but harbor neuronal cell bodies. In this study, we investigated neural mechanisms underlying thirst and salt appetite. We visualized Ang II receptor type 1a (AT1a)-positive neurons in sCVOs using AT1a$^{lacZ/+}$ mice and characterized their functions using optogenetic and electrophysiological techniques. We identified neurons driving thirst and salt appetite in the SFO and named them water neurons and salt neurons, respectively. Our results show that they are distinct groups of angiotensin II receptor type 1a-positive excitatory neurons. Water neurons were suppressed by cholecystokinin via GABAergic inhibitory neurons. On the other hand, salt neurons were suppressed by another population of GABAergic neurons, downstream of Na_x. In addition, Na_x is also involved in thirst control: The Na^+ signals generated in Na_x-positive glial cells lead to the activation of TRPV4-positive neurons by using epoxyeicosatrienoic acids as gliotransmitters, and stimulated water intake. Finally, our data indicate that the generation of antoantibodies targeting to the subfornical organ elicit adipsic hypernatremia without causing any structural anomaly in the hypothalamus.