Pass the salt: Mapping the neurons that drive salt cravings

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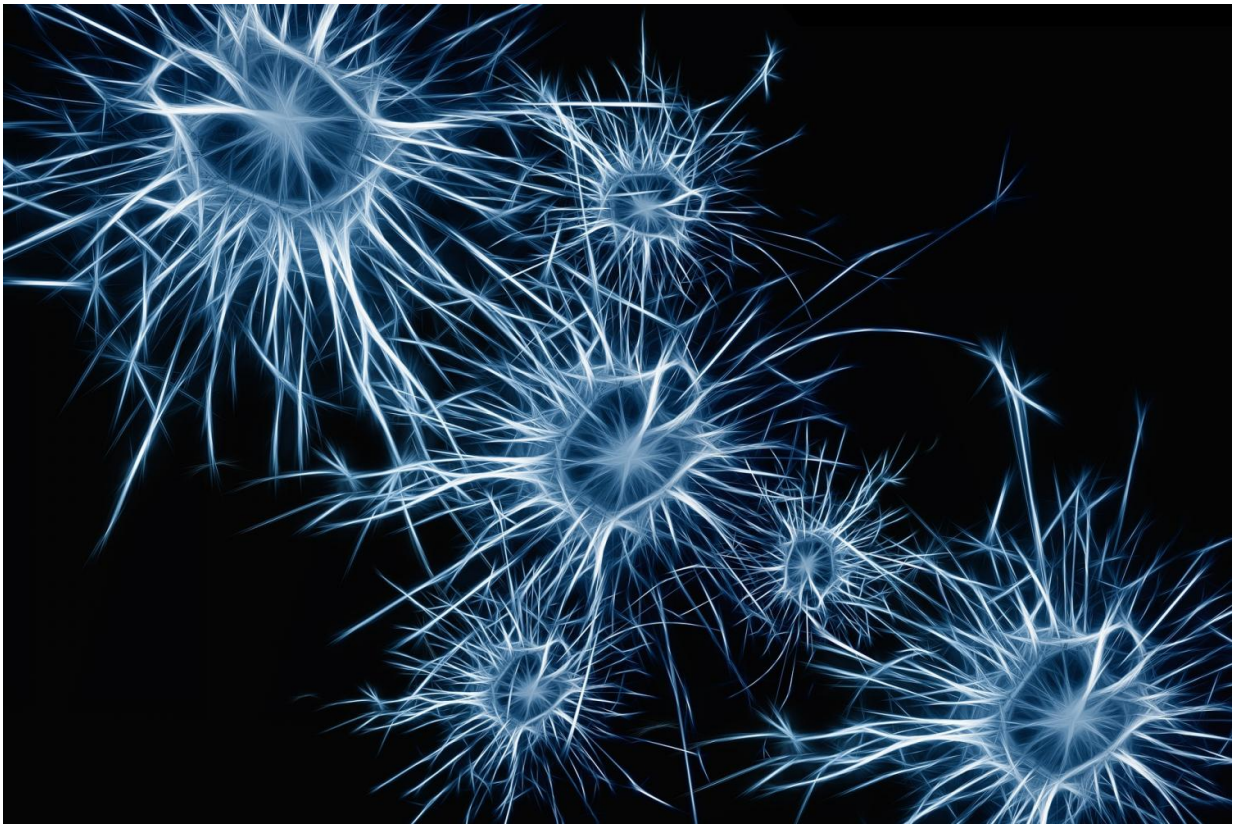

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While the average American's high-salt diet has been linked to high blood pressure and cardiovascular disease, the truth is we couldn't live without this once scarce mineral. Salt helps the body balance its water

content and plays a critical role in regulating blood pressure and cellular function throughout the body. As salt is lost through excretion and other metabolic processes, hormones are released in response to sodium deficiency. But exactly how these hormones work on the brain to trigger salt-seeking and salt-consuming behavior has remained a mystery.

Now, a team of scientists in the Division of Endocrinology, Diabetes and Metabolism at Beth Israel Deaconess Medical Center (BIDMC), have shed new light on the process. In research published today in the journal *Neuron*, a team of scientists working in the lab of Bradford Lowell, MD, PhD, identified the sub-population of neurons that respond to the body's sodium deficiency and mapped the brain circuitry underlying the drive to consume salt.

"We identified a specific circuit in the brain that detects sodium deficiency and drives an appetite specific for sodium to correct the deficiency," said co-first author Jon M. Resch, PhD, a post-doctoral fellow in Lowell's lab. "In addition, this work establishes that sodium ingestion is tightly regulated by the brain, and dysfunction in these neurons could lead to over- or under consumption of sodium, which could lead to stress on the cardiovascular system over time."

The team focused on a subset of neurons—known as NTSHSD2—discovered a decade ago by co-corresponding author, Joel Geerling, MD, PhD, formerly of BIDMC and now assistant professor in the Department of Neurology at Carver College of Medicine at the University of Iowa. In a series of experiments in sodium-deficient mice, the researchers demonstrate that sodium deficiency activates these neurons. They also showed that the presence of the hormone aldosterone, which the body releases during sodium deficiency, increases the neurons' response.

"These neurons appear to be highly influenced by these hormones and

less so by inputs from other neurons—though further study is warranted," said Resch. "This is a unique and very unexpected feature of these NTSHSD2 neurons."

The researchers also revealed that NTSHSD2 neurons - located in a part of the brain called the nucleus of the solitary tract—are not solely responsible for driving the sodium appetite. In experiments using mice not deficient in sodium, artificial activation of NTSHSD2 neurons triggered sodium consumption only when there was also concurrent signaling by angiotensin II, a hormone also released by the body during sodium deficiency. From this, Resch and colleagues concluded that another set of neurons sensitive to angiotensin II likely plays a role in driving sodium appetite.

These neurons have yet to be identified.

The findings demonstrated that only a synergistic relationship between the two distinct sub-populations of neurons that respond to aldosterone and angiotensin II can cause the rapid and robust onset of the sodium appetite seen in the experimentally deficient mice. Resch notes the sodium-appetite circuity he and colleagues have revealed provides a physiological framework for a hypothesis put forth in the early 1980s.

"Several questions remain with regard to how sodium appetite works, but a major one is where ATII is acting in the brain and how the signal works in concert with NTSHSD2 neurons that respond to aldosterone," he said. "We have already begun work to help us close these gaps in our knowledge."

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