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New Ion Channel Detects Salt Balance in Vertebrates

Researchers have identified a protein in vertebrates that detects a cell's total salt concentration and appears to play a role in regulating the balance of salt and water. The discovery may lead to better treatment of kidney disorders, high blood pressure and ear diseases.

In an article in the October 27, 2000, issue of *Cell*, a research team that included Howard Hughes Medical Institute investigators A. James Hudspeth and Jeffrey M. Friedman at The Rockefeller University reported identifying a novel gene, vanilloid receptor related osmotically activated channel (*VR-OAC*), in the cells of rats, mice, chickens and humans. The gene produces an ion channel receptor protein found in brain, kidney and inner ear cells.

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— Jeffrey M. Friedman

The researchers' experiments indicate that the receptor sits in the cell membrane and is capable of sensing a buildup of osmotic pressure from reduced salt concentrations outside the cell. As the membrane stretches, the VR-OAC receptor opens to allow calcium to flow into the cell. This inflow of calcium, in turn, triggers key intracellular reactions which lead to adaptive changes.

"Osmotic pressure is one of the most aggressively defended setpoint values in the vertebrate animal," said Friedman. "In order for cells to maintain their proper size and shape, the concentration of salt outside the cell has to equal the concentration inside the cell, or else there will be dramatic, and possibly life-threatening changes in cell function."

"Osmotic receptors have been found in bacteria and other lower organisms using genetic approaches, but it has been extremely difficult to find them in higher animals where there are a far greater number of genes to sort through," said Friedman.

The trail that ended with the discovery of VR-OAC actually began as a search for temperature-sensing receptors by the paper's lead author, Wolfgang Liedtke, a postdoctoral fellow in Friedman's laboratory. Liedtke was looking for proteins that sense and respond to changes in temperature as part of Friedman's laboratory's efforts to understand weight-regulation and energy balance. "I began by looking at candidate genes, one of which produces VR1, a receptor that is responsive to painful heat as well as to capsaicin, the pungent ingredient in hot chili peppers," said Liedtke.

Liedtke's experiments to isolate additional genes from the vanilloid receptor family, however, led him to gene libraries of mouse brain hypothalamus cells (because these cells are known to harbor genes involved in temperature regulation) and to rat kidney cells. From those gene libraries, Liedtke discovered a novel gene for a protein that was later called VR-OAC, for vanilloid receptor-related osmotically activated ion channel.

Although VR-OAC was found in the hypothalamus, it was not active in the temperature-regulating region. It was active in the region that regulates salt balance. Liedtke then collaborated with postdoctoral fellow Stefan Heller in Hudspeth's laboratory, who had isolated VR-OAC from a chick gene library, to show that VR-OAC was also present in hair cells of the inner ear. VR-OAC may help to regulate salt concentration to "tune" these hair cells to respond to a spectrum of mechanical stimuli in detecting sound.

These observations suggested that the researchers had found a protein involved in osmotic regulation. To better understand the role of VR-OAC, the scientists inserted the *VR-OAC* gene into cells that normally lacked the gene. Co-author Yong Choe in Hudspeth's laboratory tested the responsiveness of these cells to changes in salt concentrations, revealing that the genetically altered cells were not sensitive to temperature, but were exquisitely sensitive to changes in salt balance.

"Our laboratories then began to characterize the properties of what we now know to be an osmotically-gated channel," said Friedman. "These studies showed that, indeed, the channel opens in response to decreased salt concentration, or osmolarity. This opening admits a small amount of calcium, which in turn triggers the release of a burst of calcium from storage depots inside the cell. When this happens in nerve cells in the brain's osmotic regulatory centers in the hypothalamus, we suspect that these receptors would fire and elicit a number of responses that affect thirst, salt intake, and salt excretion by the kidney."

According to Friedman, VR-OAC's presence in kidney cells is not a surprise since sensing salt concentration is an important function of the kidney. Also, he said, the gene was expressed in other cells that surround fluids such as brain and ear cavities in which sensing salt concentration is crucial.

Furthermore, the gene is expressed in skin cells that are responsive to touch, hinting that the VR-OAC protein might be involved in mechanical sensing in general, said Friedman.

"VR-OAC seems to respond to decreasing osmolarity, but not as well to increasing osmolarity," he said. "So, there could be other channels that sense increasing osmolarity." Although the medical implications of the discovery are not yet clear, Friedman says, "many anti-hypertensive medications change salt flow through the kidney, so it's possible that this ion channel could be a target for drugs that affect water balance in the kidney. Such drugs could be used to treat high blood pressure."