

# Starving for GABA

A SMALL CHEMICAL IN THE BRAIN IS THE DIFFERENCE BETWEEN EATING AND WASTING AWAY.

Control of feeding behavior and body weight is a complicated business. The field has been dominated by studies investigating the role of hormones and neuropeptides for the last 15 years. Yet the roles of glutamate and GABA, two major neurotransmitters in the brain, have been largely ignored. But now, HHMI investigator Richard Palmiter has shown that GABA plays a critical role in maintenance of feeding behavior.

A group of neurons in the arcuate nucleus, a part of the brain's hypothalamus, has long drawn the attention of scientists looking for the neural circuits that control eating. These neurons synthesize protein messengers that promote eating, called agouti-related peptide (AgRP) and neuropeptide Y (NPY). Though these peptides were strong candidates for eating regulators, there was a hitch: animals without them eat normally. Yet killing the neurons that make them induces starvation; mice won't even consume food put directly into their mouths. "So the neurons must be making something that's critical, and it's probably not AgRP or NPY," says Palmiter, at the University of Washington.

In a series of experiments published in *Cell* on June 26, 2009, the authors fingered GABA, a neurotransmitter that inhibits neuronal activity throughout the brain, as the missing ingredient. After selec-

tively killing the AgRP/NPY neurons, Palmiter and colleagues observed that the activity of many postsynaptic neurons, in an area of the brain called the parabrachial nucleus, was greatly elevated. They postulated that the sudden loss of GABA from AgRP/NPY neurons was responsible and showed that they could prevent starvation

by supplementing mice with a drug that activates GABA receptors. Conversely, blocking GABA receptors there led normal mice to starve.

Although it's unclear how hyperactivity in the parabrachial nucleus halts eating, the results reveal a pathway critical for food consumption, one that Palmiter will further delineate by identifying the transmitters involved in activating the nucleus and the targets of the parabrachial nucleus. Judging by how quickly appetites can be suppressed, he may not have to look far. "I think this is a pretty short circuit," he says. "But that would just be my gut feeling." ■ —MICHELE SOLIS



Whether or not a mouse eats food placed in front of it depends on a complex circuit in the brain.

## IN BRIEF

### IMMUNE SYSTEM OVERDRIVE

Natural killer cells find and destroy abnormal cells in the body, playing an important role in preventing cancers. The pathway of molecules that allows them to do this, however, has not been fully elucidated. Now, HHMI international research scholar André Veillette has put one piece of the puzzle into place, by identifying a molecular switch that tells natural killer cells to attack.

The results explain how a healthy immune system works and give a better understanding of a rare genetic disease: X-linked lymphoproliferative disease (XLP), which causes the immune system to go into overdrive, making normally mild viral infections fatal. In the late 1990s, researchers discovered that a mutation in an immune system protein called SAP caused XLP. SAP mutations lead to defects in many types of immune cells, including natural killer cells, the researchers found.

Veillette, based at the Clinical Research Institute of Montreal and the University of Montreal, decided to probe these findings further, examining just what happens to natural killer cells when SAP is missing. He genetically engineered mice that lack the SAP family of proteins. The mice developed

normally, but when Veillette looked at natural killer cells from them, he discovered something odd. The natural killer cells could destroy some types of cancer cells but not cancerous blood cells. The results, which appear in the September 2009 issue of *Nature Immunology*, suggest that, without SAP, natural killer cells don't recognize damaged blood cells, allowing them to pile up. The standard treatment for XLP is bone marrow transplantation, and that's unlikely to change, Veillette says. However, he thinks future research on SAP-related molecules could point toward better therapies for other viral infections or autoimmune diseases.

### MANAGING SALT

Researchers led by HHMI investigator Richard P. Lifton have uncovered clues to how cells manage their delicate interior balance of salts and water and how that affects cell volume. Too much salt inside a cell causes water to rush in, potentially bursting the cell, whereas too little salt can make a cell shrivel up and die. Specialized ion transporters regulate the flow of salts across a cell's outer membrane. Abnormalities in the regulation of intracellular chloride are believed to play a role in

diverse clinical disorders, including sickle cell anemia.

In 2001, Lifton discovered a pathway that helps control blood pressure. Since then, as his group investigated the key players in the pathway—protein kinases called WNKs—they found that the WNKs are involved in orchestrating the flow of chloride ions in and out of cells.

To explore this pathway, Lifton's lab group at the Yale School of Medicine used new tools of quantitative phosphoproteomics to identify key sites on chloride cotransporters. These sites are phosphorylated under resting conditions, which keeps the transporters inactive, but are rapidly dephosphorylated in low-salt environments, activating transport. This phosphorylation depends on WNK activity, the team concludes in the August 7, 2009, issue of *Cell*. With further research, they hope to reveal just how the pathway works.

### RANKING SPECIES WITH GOOGLE

The same method Google uses to rank the importance of Web pages can be used to rank the importance of species within an ecosystem, researchers have shown. Mercedes Pascual, an HHMI investigator at the University of Michigan,