Scientists identify another piece of the weight-control puzzle

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Controlling body weight is a complicated process, as any frustrated dieter might attest. But as scientists continue to investigate the brain's intricate neurocircuitry and its role in maintaining energy balance, they are forming a clearer picture of the myriad events that lead to weight gain and weight loss.

In the August 10 on-line issue of *Nature Neuroscience,* a study led by scientists at Beth Israel Deaconess Medical Center (BIDMC) identifies another piece of this complex puzzle, demonstrating that the neurotransmitter GABA --one of the master communicators among neurons – plays a role in controlling energy balance.

"Body weight maintenance is made up of three basic stages," explains the paper's senior author Bradford Lowell, MD, PhD, an investigator in the Division of Endocrinology, Diabetes and Metabolism at BIDMC whose laboratory is working to identify the specific neurocircuits responsible for controlling food intake and/or energy through functional neuroanatomical mapping studies.

"In the first stage, the brain receives sensory input from the body [including information provided by circulating hormones such as leptin and ghrelin and from fuels such as glucose and fatty acids]," says Lowell, who is also a Professor of Medicine at Harvard Medical School.

In the second stage, he adds, the brain integrates this sensory information with cues it has received from the environment (such as aromas and

other enticements) along with information gathered from the organism's emotional state. Then, in the final stage, the brain's neurocircuitry takes over, enabling the brain to make appropriate alterations in food intake and energy expenditure in order to maintain energy balance – and prevent weight gain and obesity.

Previous work had primarily focused on identifying the neuropeptides involved in this process. And indeed, this group of neurotransmitters often proves essential to maintaining energy balance – but not always.

"It is well known that AgRP [Agouti-related protein] neurons play a critical role in feeding and energy balance regulation," explains Qingchun Tong, PhD, a postdoctoral fellow in the Lowell laboratory and the study's first author. "However, the deletion of AgRP and NPY [two neuropeptides released from the AgRP neurons] produces little metabolic effect."

An alternate theory proposed that release of the GABA neurotransmitter was mediating the function of AgRP neurons, an idea that had long been postulated but never examined.

To test this hypothesis, Tong and his colleagues generated a group of mice with disrupted release of GABA specifically from the AgRP neurons. As predicted, the genetically altered mice exhibited profound metabolic changes.

"The mice with AgRP neuron-specific disruption of GABA release were lean, had higher energy expenditure and showed resistance to diet-induced obesity," says Tong. "We also found that these animals showed reduced food intake response to the hormone ghrelin. This suggests to us that the neurocircuit engaging GABA release from the AgRP neurons mediates at least part of ghrelin's appetite-stimulating action."

A series of studies to examine the function of glutamate and GABA release from other groups of neurons are currently underway as investigators continue to dissect the brain's neurocircuitry.

"As these new findings demonstrate, GABA release is an important component that mediates the function of AgRP neurons," says Tong. "Discoveries such as this will ultimately help us to design an efficient strategy to tackle the current epidemic of obesity and metabolic disease."

Source: Beth Israel Deaconess Medical Center