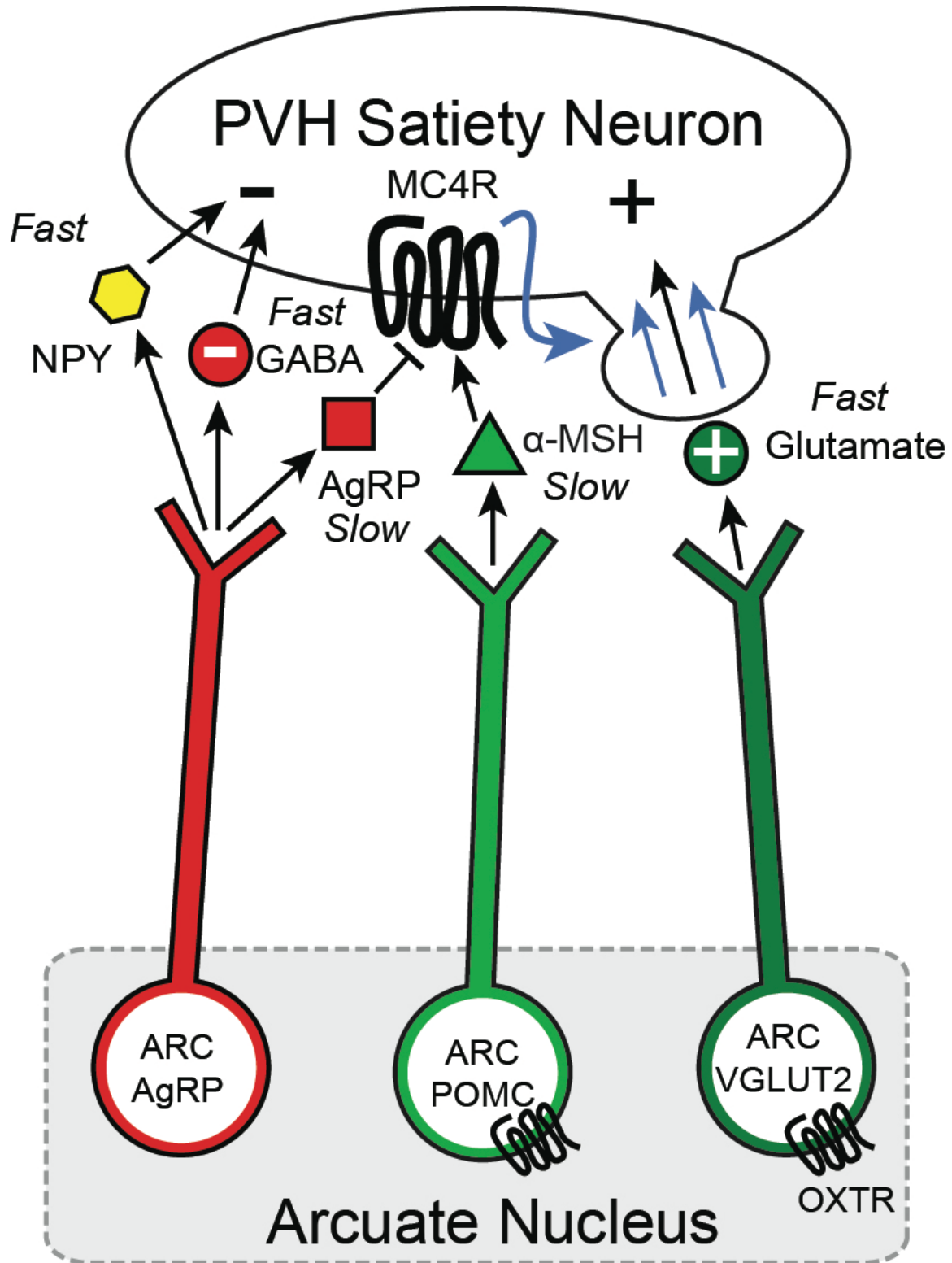


Insight into the brain's control of hunger and satiety

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Legend to Supplemental Figure 9: Current models for homeostatic control of hunger / satiety lack a rapidly-acting satiety mechanism that is temporally analogous to that provided by rapidly-acting, hunger-promoting ARCAgRP neurons. Our findings report the discovery of this missing component, namely glutamate-releasing oxytocin receptor-expressing neurons in the arcuate nucleus. These neurons converge with ARCAgRP and ARCPOMC neurons on downstream targets and rapidly increase / decrease satiety when experimentally activated / inhibited. Thus, in contrast to the hunger-promoting system where slow- (AgRP) and rapid-acting signals (GABA and NPY) are conveyed by one group of neurons (ARCAgRP neurons), the counteracting satiety-promoting system is split into two parallel-projecting neurons, the previously known ARCPOMC neurons which deliver slow-acting α -MSH, and the previously unknown ARCOxtr neurons which release the rapid-acting transmitter, glutamate. Importantly, these two satiety neurons interact as α -MSH released by ARCPOMC neurons postsynaptically increases glutamatergic transmission across the ARCOxtr?PVHMC4R synapse. This missing rapid-acting component, with ARCPOMC neurons, now provides the full 'yang' to the ARCAgRP neuron's 'yin'. Our work also provides a mechanism for α -MSH /MC4R regulation of satiety -- plasticity of the novel ARCOxtr?PVHMC4R synapse. Credit: B. B. Lowell

Beth Israel Deaconess Medical Center (BIDMC) researchers have identified previously unknown neural circuitry that plays a role in promoting satiety, the feeling of having had enough to eat. The discovery revises the current models for homeostatic control—the mechanisms by which the brain maintains the body's status quo—of feeding behavior. Published online today in *Nature Neuroscience*, the findings offer new insight into the regulation of hunger and satiety and could help researchers find solutions to the ongoing obesity epidemic.

"Current models lack a rapidly-acting satiety mechanism analogous to the [hunger](#)-promoting [neurons](#)," said corresponding author Bradford B.

Lowell, MD, PhD, a professor of medicine in the Division of Endocrinology, Diabetes and Metabolism at BIDMC. "This component we identified provides the full 'yang' to the hunger-promoting neurons' 'yin.'"

Researchers have long known that hunger is regulated by two kinds of neurons: Agouti-related protein (AgRP) neurons and pro-opiomelanocortin (POMC) neurons. AgRP neurons drive hunger; stimulating these nerves triggers eating within minutes. The opposing group of neurons, POMC, has been shown to promote satiety. Lab mice engineered to lack POMC neurons eat large quantities of food and become massively obese.

However, in recent years, new technology has allowed scientists to selectively manipulate neurons in living animals, demonstrating specific neurons' direct effect on behavior. About five years ago, this type of research revealed that POMC neurons act over the course of many hours—not minutes like their AgRP counterparts.

"The lack of a rapid effect strongly suggested that the POMC neurons, by themselves, are not the full counterpart to the AgRP neurons," said lead author Henning Fenselau, PhD, a postdoctoral fellow in Lowell's laboratory at BIDMC. "We hypothesized that an important but unknown neural component of the satiety system was missing from the current models."

What's more, because the team was looking for neurons that would suppress eating quickly, they narrowed their search for ones that release the fast-acting, excitatory neurotransmitter called glutamate. In the current paper, Lowell and colleagues investigated a third subset of neurons, Vglut2, the function of which was previously unknown.

In a series of experiments, Lowell and colleagues used optogenetics (the

use of light to activate genetically-modified neurons) and chemogenetics (the use of molecules to activate targeted neurons) to manipulate specific neurons to determine their roles in feeding behavior. First, the team demonstrated that, unlike POMC neurons, Vglut2 neurons could in fact rapidly suppress feeding behavior in mice. When the researchers chemically stimulated the neurons in question, it markedly decreased eating. When they inhibited the Vglut2 neurons, eating increased.

They also found that all three types of neurons—the hunger promoting AgRP neurons and the two satiety promoting neurons, Vglut2 neurons and POMC neurons—interact in the same circuit. All three converge downstream in a site in the hypothalamus known to suppress hunger, the subject of previous research by Lowell and colleagues. AgRP neurons inhibit activity in this downstream site, causing hunger, while the rapidly-acting Vglut2 neurons excite it, suppressing hunger. The third member of this circuit, POMC neurons, indirectly decrease hunger by releasing a hormone that bolsters Vglut2 neurons' ability to suppress hunger.

"We think this is very important because it may be one explanation why individuals lacking POMC genes become extremely obese, even if those neurons by themselves do not directly promote satiety," said Fenselau. "Without POMC, the Vglut2 neurons are ineffective in stimulating the downstream hypothalamic site. You need both POMC neurons and Vglut2 neurons for the satiety mechanism to work properly."

Finally, the team sequenced the genes expressed by this subset of neurons and found they possess receptors for the hormone oxytocin. Known to play a role in social bonding, oxytocin is linked to feelings of contentment and is already being investigated for its potential as a satiety-inducing weight loss medication. "Our findings could definitely explain why oxytocin is effective in satiety," said Fenselau.

To follow up, the scientists will further investigate the interactions

among the three types of neurons and the role they play in obesity.

More information: Henning Fenselau et al. A rapidly acting glutamatergic ARC→PVH satiety circuit postsynaptically regulated by α -MSH, *Nature Neuroscience* (2016). [DOI: 10.1038/nn.4442](https://doi.org/10.1038/nn.4442)

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