

Scientists find root cause of appetite loss during illness

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Credit: Maliz Ong

Loss of appetite during illness is a common and potentially debilitating phenomenon—in cancer patients, especially, it can even shorten lifespan.

Now scientists at The Scripps Research Institute (TSRI) have discovered how an immune system molecule hijacks a [brain circuit](#) and reduces appetite. Their research points to potential targets for treating loss of appetite and restoring a patient's strength.

"Treating loss of appetite won't cure an underlying disease, but it could help a patient cope," said TSRI Professor Bruno Conti, senior author of the study. "Many times, loss of appetite can compromise clinical outcome. A weak individual is less likely to be able to cope with chemotherapy, for instance."

On the flip side, the research, published May 4, 2016, in *The Journal of Neuroscience*, also points to possible drug targets to reduce appetite and possibly support weight loss for those with [metabolic disorders](#).

A Dangerous Phenomenon

If loss of appetite during illness sounds familiar, you're not alone.

Years ago, TSRI Associate Professor Walter Francesconi had to spend 20 days in the hospital. Being sick was bad enough, but what made things worse for Francesconi was his loss of appetite. He couldn't muster the desire to eat and ended up losing more than 10 pounds.

"When I got home, I was so weak that I was unable to walk," said Francesconi, who was first author of the new study.

Like Francesconi, many people recover their appetite after illness. But in patients with diseases such as cancer or AIDS, loss of appetite can turn into a wasting disease called cachexia, also known as "the last illness" because it can accelerate a patient's decline.

Previous studies had identified the biological players in loss of appetite.

One was an immune molecule called interleukin 18 (IL-18), which activates other cells to fight disease. Another was a brain structure called the Bed Nucleus of the Stria Terminalis (BST)—which has a subset of neurons that project to the Lateral Hypothalamus (LH), a brain region that controls appetite.

The challenge was to show how these elements interacted.

Identifying the Brain Circuit

The new research began with the discovery of the expression of IL-18 receptors in neurons of the anterior BST. With this finding, the researchers had a starting point for tracking the effects of IL-18 in this part of the brain.

Francesconi then used an electrophysiological technique called whole-cell patch clamp to record neuronal activity and uncovered a series of events regulating appetite.

In mouse BST brain slices not exposed to IL-18, an excitatory neurotransmitter called glutamate strongly activates a subset of BST neurons projecting to the LH. The activation of these BST-LH neurons leads to the release of an inhibitory neurotransmitter, called gamma-aminobutyric acid (GABA), on target neurons. The GABA release inhibits [neuronal activity](#) in the LH.

Put simply, normal amounts of GABA released into LH leads to a normal appetite.

IL-18 interferes with this system. When IL-18 binds to its receptors on a specific subset of BST-LH projecting neurons (type III), it reduces glutamate release, leading to less activation of type III neurons, reduced GABA signaling and a loss of appetite.

"IL-18 regulates feeding by locking directly into the neuronal circuitry," said Conti.

Studies of mouse behavior supported this finding. Mice with IL-18 injected directly into the anterior BST ate significantly less than mice that received a control substance.

Developing a Treatment

The researchers believe the circuit affected by IL-18 may be a potential drug target for treating [loss](#) of appetite. They also brought up the possibility of intervening with a molecular mimic of IL-18 to control [appetite](#) and reduce obesity in patients with metabolic disorders.

Next up, the researchers plan to investigate the specific biochemical pathways in this brain circuit. The better they understand the pathway, the better targets they'll have for potential therapies.

"This is just the beginning," Francesconi said.

More information: W. Francesconi et al, The Proinflammatory Cytokine Interleukin 18 Regulates Feeding by Acting on the Bed Nucleus of the Stria Terminalis, *Journal of Neuroscience* (2016). [DOI: 10.1523/JNEUROSCI.3919-15.2016](https://doi.org/10.1523/JNEUROSCI.3919-15.2016)

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