Signaling path in brain may prevent that 'I'm full' message, scientists discover

March 1 2011

Researchers at UT Southwestern Medical Center have identified a signaling pathway in the brain that's sufficient to induce cellular leptin resistance, a problem that decreases the body's ability to "hear" that it is full and should stop eating.

"Leptin resistance is a significant factor, yet the mechanisms that underlie the problem remain unclear," said Dr. Joel Elmquist, professor of internal medicine and pharmacology at UT Southwestern and senior author of the study appearing in the March issue of Cell Metabolism. "The fact that this cellular pathway may be involved is a novel observation."

Leptin is a hormone released by fat cells that is known to indicate fullness, or satiety, in the brain. If the body is exposed to too much leptin, however, it will become resistant to the hormone. Once that occurs, the body can't "hear" the hormonal messages telling the body to stop eating and burn fat. Instead, a person remains hungry, craves sweets and stores more fat instead of burning it.

Leptin resistance also causes an increase in visceral, or belly, fat, which has been shown to predispose people to an increased risk of heart disease , diabetes and metabolic syndrome.

For the current study, the researchers induced leptin resistance in organotypic brain slices from mice. This research technique, used commonly in neuroscience, enabled the researchers to maintain the

cellular and anatomical relationships and some of the network connections that normally exist within the brain.

"We're not dispersing cells. We're leaving them in a microenvironment that simulates what's going on in the brain," Dr. Elmquist said.

When the researchers began manipulating the network – known as cAMP-EPAC pathway – they found that activating this previously unexplored signaling avenue is enough to induce leptin resistance within hypothalamic neurons, a critical site of leptin action. They also found that when the pathway was blocked, the cells were no longer resistant to leptin.

"In the follow-up experiments, which we conducted in mice, we were able to induce leptin resistance simply by infusing activators of this pathway, further supporting our theory that this signaling pathway may contribute to leptin resistance in obesity," said Dr. Makoto Fukuda, instructor of internal medicine at UT Southwestern and the study's lead author.

Dr. Elmquist said that while the EPAC signaling pathway itself is not novel, this is the first time it has been studied in the hypothalamus and in the context of energy balance and leptin signaling.

The next step, Dr. Elmquist said, is to investigate how critical the EPAC pathway actually is in leptin responsive neurons and to determine its role in maintaining energy balance and leptin sensitivity.

"These results are potentially interesting and provocative, but the physiological importance remains to be seen," Dr. Elmquist said. "If, however, this pathway is indeed important, it will offer new insights into the mechanisms that high levels of leptin cause in leptin resistance."

Provided by UT Southwestern Medical Center