Discovery explains how cellular pathways converge to regulate food intake and body weight

BOSTON -- In the complex chain of molecular events that underlie eating behaviors and body weight, the AMP-activated protein kinase (AMPK) enzyme has proven to be a critical link.

Now, researchers at Beth Israel Deaconess Medical Center (BIDMC) have identified the mechanism responsible for inhibition of AMPK activity in the hypothalamus, a discovery that not only provides a deeper understanding of energy balance but also reveals a critical integration point where multiple signaling pathways, including PI3K-AKT and mTOR converge.

Described in the July 3 issue of Cell Metabolism, the findings could yield new opportunities for the development of treatments for both metabolic diseases and cancer.

"AMPK is an evolutionarily conserved 'fuel gauge,'" says senior author Barbara Kahn, MD, a scientist in the Division of Endocrinology, Diabetes and Metabolism at BIDMC and the George Richards Minot Professor of Medicine at Harvard Medical School. Activated when cellular energy supplies are low, AMPK also functions at the whole body level to regulate metabolism and energy balance.

The Kahn laboratory was the first to describe AMPK's critical role in mediating the actions of leptin, the hormone produced by fat cells that serves as a master regulator of neuroendocrine, metabolic, vascular, sympathetic and immune function. In 2002, Kahn demonstrated that AMPK is activated by leptin in skeletal muscle, thereby enabling the hormone to metabolize fatty acids. Subsequently, in 2004, her laboratory discovered that an opposing scenario takes place in the brain's hypothalamus, where AMPK is inhibited by leptin.

"Having determined that leptin's effects on food intake and body weight depend on the inhibition of AMPK in the hypothalamus, we wanted to determine the signaling events that were responsible for this effect," she explains.

The PI3K-AKT, mTOR-p70S6 kinase and AMPK pathways play distinct and critical roles in metabolic regulation, and each pathway is necessary for leptin's anorexigenic effects in the hypothalamus, which inhibit food intake. Through a series of experiments led by first author Yossi Dagon, PhD, a postdoctoral fellow in the Kahn lab, the scientific team showed that these pathways converge in an integrated phosphorylation cascade to mediate leptin action on the hypothalamus.

"Our findings identify a novel serine phosphorylation site on the AMPK alpha 2 catalytic subunit that mediates leptin's inhibitory effects and is critical for leptin

action on food intake and body weight, and further show that ribosomal p70S6 kinase is an inhibitory AMPK kinase," says Kahn. 'These discoveries unify what were thought to be multiple parallel pathways affecting leptin action including PI3 kinase and AKT into a coordinated phosphorylation cascade."

Adds study coauthor Lewis Cantley, PhD, Director of BIDMC's Cancer Center and a leader in the field of cancer metabolism, "Since PI3K, AKT, mTOR and p70S6K have all been shown to be important in cancer biology, this integration of these pathways may be important for cancer and other human diseases and could lead to improved therapeutic approaches."

Obesity has reached epidemic proportions worldwide and increases the risk for developing diabetes, cardiovascular disease and early mortality. "Maintaining normal body weight requires tight control of energy homeostasis, which necessitates a constant flow of metabolic input to the hypothalamus in the form of nutrients and hormones," says Kahn. "Our new results have broad biologic implications, since mTOR-p70S6 kinase and AMPK have multiple, fundamental and generally opposing cellular effects that regulate metabolism, cell growth and development."

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