Treating obesity via brain glucose sensing

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The past two decades have witnessed an epidemic spread of obesity-related diseases in Western countries. Elucidating the biological mechanism that links overnutrition to obesity could prove crucial in reducing obesity levels. In the July 26 issue of *PLoS Biology*, Dr. Dongsheng Cai and his research team at Albert Einstein College of Medicine describe a pathway that directs the brain to sense the body's glucose dynamics, and they find that a defect of this glucose sensing process contributes to the development of obesity and related disease. Importantly, the team also found that correction of this defect can normalize the whole-body energy balance and treat obesity.

The hypothalamus in the brain plays a key role in controlling energy and body weight balance. To maintain balance between energy intake and energy expenditure, the hypothalamus constantly gauges the whole-body's energy levels by sampling circulating hormones (e.g. insulin and leptin) as well as nutrients (e.g., glucose). Although we know quite a bit about the hormonal pathways in the hypothalamic regulation of feeding, the mechanisms for hypothalamic nutrient sensing are much less clear. Moreover, a causal link between a nutrient sensing defect and obesity remains to be established. The team led by Dr. Cai discovered a novel role of a protein complex, hypoxia-inducible factor (HIF), in hypothalamic glucose sensing and whole-body energy balance in mice.

HIF is a nuclear transcription factor which induces hypoxia response. When tissue oxygen level is low, HIF is activated to promote cellular metabolic adaption and survival. Recent research has appreciated the involvement of HIF in the metabolism of tumor cells. "However, an

intriguing but unexplored question is whether HIF can be important for the regulation of whole-organism metabolism, and if so, which tissue and cells are responsible." says Cai, who is an expert in neuroendocrinology and metabolism.

Cai and his group examined HIF in the hypothalamus and, surprisingly, found that it can be activated by glucose and that this regulation was associated with appetite control in mice. In identifying the cellular and molecular basis, the team found that in response to glucose, HIF acts in a unique group of hypothalamic nutrient-sensing neurons to induce expression of POMC gene - a gene which has been known to play a key part in hypothalamic control of feeding and body weight. Most excitingly, the team demonstrated the therapeutic potential of targeting hypothalamic HIF to control obesity. By enhancing the hypothalamic HIF activity via gene delivery, mice become resistant to obesity despite the condition of nutritional excess.

"It was an exciting discovery," explains Cai, "Our study is the first to show that beyond its classical oxygen-sensing function in many cells, HIF in the hypothalamic neurons can sense glucose to control the whole-body balance of energy intake and expenditure which is critical for body weight homeostasis." Overall, this study reveals a crucial role for neuronal HIF in bridging the brain's glucose sensing with the brain's regulation of body weight and metabolic physiology. These findings also highlight a potential implication for developing neuronal HIF activators in treating and preventing obesity and related diseases.

More information: Zhang H, Zhang G, Gonzalez FJ, Park S-m, Cai D (2011) Hypoxia-Inducible Factor Directs POMC Gene to Mediate Hypothalamic Glucose Sensing and Energy Balance Regulation. *PLoS Biol* 9(7): e1001112. doi:10.1371/journal.pbio.1001112