Fat or carbs?
The neural mechanism underlying food choices revealed

The intake of high-fat and high-carbohydrate diets is regulated separately by neuropeptide Y-producing neurons in the medulla oblongata and hypothalamus.

【Summary】

Neural pathways related to total calorie intake have been extensively studied. However, it remains unclear how these mechanisms control food choices. Yasuhiko Minokoshi and Ken-ichiro Nakajima's research team discovered that glucoprivation caused by 2-deoxy-D-glucose (2DG)[1] administration increases the intake of high-fat diet (HFD) and high-carbohydrate diet (HCD) in mice through two separate neural pathways in the paraventricular nucleus of the hypothalamus (PVH) [2]. These findings first demonstrate that fat and carbohydrate intake are regulated differently in the brain. This study was conducted collaboratively at NIPS, Nagoya University, and Sugiyama Jogakuen University. The results were published in "Metabolism".

【Results】

Feeding in mammals is controlled by a complex neural system. Although several key neural pathways related to total calorie intake have been extensively studied, it is still unclear how food choices are regulated and how they influence overall feeding behavior. Food selection among different types, such as an HCD and an HFD, is affected by various internal conditions. For example, mice usually consume only an HFD, but they will eat both an HCD and an HFD when glucoprivation occurs after 2DG administration. However, the neural mechanisms behind this remain unknown.

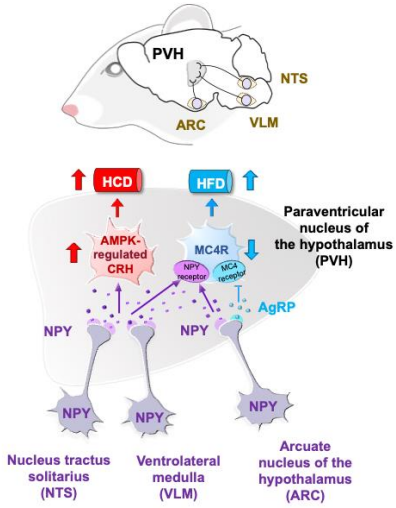
The research team examined the neural mechanisms influencing food choice between an HCD and an HFD in mice after administering 2DG. They found that the consumption of HCD and HFD after 2DG is independently controlled by AMP kinase[3] (AMPK)-regulated corticotropin-releasing hormone (CRH)[4] neurons and melanocortin 4 receptor (MC4R)[5]-expressing neurons in the PVH, respectively. The researchers also discovered that neuropeptide Y (NPY) neurons in the

nucleus of the solitary tract (NTS) and ventrolateral medulla (VLM) activate both AMPK-regulated CRH neurons and MC4R neurons in the PVH, promoting HCD and HFD intake following 2DG treatment. Conversely, NPY neurons in the arcuate nucleus of the hypothalamus (ARC) inhibit MC4R neurons in the PVH, resulting in increased HFD intake alone.

These findings first demonstrated that HCD and HFD intake are controlled by two separate neural pathways in the brain. This could offer new insights into understanding the neural mechanisms behind food choices among foods with different nutrient compositions.

Notes

1) 2-deoxy-D-glucose (2DG)
   Glucose analog. 2DG transiently causes glucopenia in the body when administered intraperitoneally.
2) The paraventricular nucleus of the hypothalamus (PVH)
   A critical hypothalamic nucleus that regulates appetite and the release of pituitary hormones.
3) AMP kinase (AMPK)
   AMPK is activated by cellular energy depletion, thereby stimulating glucose and lipid utilization in cells. In hypothalamic neurons, AMPK regulates feeding (Minokoshi, et al. Nature 428:569-574, 2004. doi: 10.1038/nature02440).
4) Corticotropin-releasing hormone (CRH) neuron
   This neuron is widely expressed in the brain. However, the neurons in the PVH regulate the hypothalamus-pituitary-adrenal axis, and its activation causes several stress-related behaviors. This research team discovered that activation of PVH AMPK-activated CRH neurons causes carbohydrate selection in mice (Okamoto S, et al. Cell Reports 22:706-721, 2018. doi: 10.1016/j.celrep.2017.11.10）.
5) Melanocortin 4 receptor (MC4R)-expressing neuron
   MC4R plays an essential role in the total calorie intake regulation. The gene mutations and polymorphisms cause obesity and increase its susceptibility in humans.



2DG-induced glucoprivation promotes high-carbohydrate diet (HCD) and high-fat diet (HFD) intakes in the paraventricular nucleus of the hypothalamus (PVH) by activating neuropeptide Y (NPY) neurons in the nucleus of the solitary tract (NTS), ventrolateral medulla (VLM), and the arcuate nucleus of the hypothalamus (ARC). Activation of NPY neurons in the NTS and VLM stimulates AMPK-regulated corticotropin-releasing hormone (CRH) neurons in the PVH, leading to increased HCD intake that helps offset the impaired glucose metabolism caused by 2DG. In contrast, PVH-projecting NPY neurons in the NTS, VLM, and ARC, which also release AgRP (agouti-related peptide), increase HFD intake after 2DG injection by inhibiting PVH melanocortin 4 receptor (MC4R) neurons.

Research member and collaborative researcher

Name: Nawarat Rattanajearakul, PhD
NIPS Research Fellow
Department: Department of Endocrinology and Metabolism
Institute: National Institute for Physiological Sciences, Japan
Present institution and position: Assistant Professor, Alimentary Neuroscience Laboratory, Department of Applied Life Sciences, Graduate School of Bioagricultural Sciences, Nagoya University, Nagoya, Aichi, Japan

Name: Kunio Kondoh, PhD
Assistant Professor
Department: Department of Endocrinology and Metabolism
Institute: National Institute for Physiological Sciences, Japan

Present institute and position: Associate Professor, Division of Integrative Physiology, Department of Physiology, Faculty of Medicine, Tottori University, Yonago, Japan

Name: Ou Fu, PhD
NIPS Research Fellow
Department: Department of Endocrinology and Metabolism
Institute: National Institute for Physiological Sciences, Japan
Present institute and position: Associate Professor, Laboratory of Food Perception Science, Science Center for Future Foods, Jiangnan University, Wuxi, China

Name: Shiki Okamoto, PhD, DVM
Associate Professor
Department: Laboratory of Veterinary Physiology and Biochemistry, Joint Faculty of Veterinary Medicine
Institute: Yamaguchi University, Yamaguchi, Japan

Name: Kenta Kobayashi, PhD
Associate Professor
Department: Section of Viral Vector Development
Institute: National Institute for Physiological Sciences, Japan

Name: Ken-ichiro Nakajima, PhD (co-corresponding author)
Associate Professor
Department: Department of Endocrinology and Metabolism
Institute: National Institute for Physiological Sciences, Japan
Present institute and position: Professor, Alimentary Neuroscience Laboratory, Department of Applied Life Sciences, Graduate School of Bioagricultural Sciences, Nagoya University, Nagoya, Aichi, Japan

Name: Yasuhiko Minokoshi, MD, PhD (co-corresponding author)
Professor (now Professor Emeritus)
Department: Department of Endocrinology and Metabolism
Institute: National Institute for Physiological Sciences, Japan
Present institute and position: Professor, Division of Nutrition Physiology, School

& Graduate School of Life Studies, Sugiyama Jogakuen University, Nagoya, Japan

Funding

This work was funded by KAKENHI grants from the Japan Society for the Promotion of Science (20H03736 and 23H02965 to Y.M., and 23K21182 to K.N.) and JST PRESTO program (JPMJPR21S8 to K.N.).

Journal article

Title: Glucoprivation-induced nutrient preference relies on distinct NPY neurons that project to the paraventricular nucleus of the hypothalamus.

Authors: Nawarat Rattanajearakul, Kunio Kondoha, Ou Fu, Shiki Okamoto, Kenta Kobayashi, Ken-ichiro Nakajima*, and Yasuhiko Minokoshi* (*Co-corresponding author)

Journal: Metabolism Issue: 156415. Date: October 10, 2025

URL (abstract):

https://www.sciencedirect.com/science/article/abs/pii/S0026049525002847?via%3Dihub

DOI: 10.1016/j.metabol.2025.156415.