Regulation of food intake by intestinal hormones in brain

In recent years, the obese and overweight population has continued to increase around the world, and the numbers of patients with conditions caused by obesity, such as diabetes, dyslipidemia, and hypertension, have increased. In order to alleviate obesity and overweight, it is important to make improvements to lifestyle in areas such as overeating, excessive lipid intake, and lack of exercise. It is reported that surgery to reduce weight has been effective for treating severe obesity in recent years. However, an evident solution regarding the body mass index in recent years has not been established.

Eating behavior is controlled by the neural network extending from the cerebral cortex to the spinal cord. This has the hypothalamus as its center, and is composed of neurons that promote eating behavior, such as those that produce neuropeptide Y (NPY) and agouti-related peptide (AgRP); and neurons that suppress eating behavior, such as those that produce proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART). By activation and suppression of the two types of neuron, eating behavior is initiated or halted, and food intake per day is regulated.

Insulin and leptin transmit information regarding the body's nutritional condition to the central nervous system, and they are involved in food intake. Leptin binds to the leptin receptor expressed on the arcuate nucleus (ARC) of the hypothalamus and suppresses NPY/AgRp neurons. Leptin also suppresses neurons in the lateral hypothalamic area (LHA) that produce orexin and melanin-concentrating hormone, which stimulate eating behavior; and it activates POMC/CART neurons. Insulin receptors are expressed on the paraventricular nucleus (PVN), dorsomedial hypothalamus (DMH), and ARC, and intracerebral or hypothalamic insulin administration inhibits food intake by the suppression of NPY/AgRp neurons and the activation of POMC/CART neurons.

Intestinal hormones secreted from enteroendocrine cells are involved in eating behavior. The blood–brain barrier (BBB) plays an important role in maintaining an environment favorable for neurological function. On the other hand, as the BBB controls the exchange of substances between the cerebral blood vessels and cerebral cells, intestinal hormones generally do not access the brain. However, in the hypothalamus, pituitary gland, medulla oblongata, and other circumventricular organs, restriction by the BBB is weaker than that in the cerebral cortex, and intestinal hormones present in blood vessels thus have the potential to enter the brain. Intestinal hormones act directly on the hypothalamus which controls eating behavior (Figure 1). Intestinal hormones also act directly on the solitary nucleus (NTS) and area postrema (AP) in the medulla oblongata. Activation of NTS and AP transmits electrical stimulation to the parabrachial nucleus (PBN) which induces food intake suppression. In addition, the intestinal hormones induce ascending neurotransmission from sensory nerves such as the vagus nerves and spinal nerves to the NTS/PBN. Hormones such as glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), peptide YY (PYY), and oxyntomodulin have appetite-suppressing effects, whereas ghrelin promotes appetite.

GLP-1 is secreted by enteroendocrine L-cells, and it is an incretin that stimulates insulin secretion from pancreatic β-cells. As antiobesity agents that make use of GLP-1 actions, dipeptidyl peptidase-4 (DPP-4) inhibitors and GLP-1 receptor agonists are used worldwide. In particular, as GLP-1 receptor agonists act strongly on the GLP-1 receptor, they markedly reduce gastric emptying and suppress food intake, in addition to their glucose lowering effect. The GLP-1 receptor is expressed on POMC/CART neurons in the hypothalamus, and activation of neurons that express the GLP-1 receptor has the effect of suppressing eating behavior. In addition, the GLP-1 receptor is expressed on the NTS and AP of the medulla oblongata, and binding of GLP-1 receptor agonists there has been reported. Furthermore, the GLP-1 receptor is expressed at intestinal vagus nerve endings, resulting in ascending neurotransmission from the peripheral afferent nerves to the brain. It is therefore considered that GLP-1 acts directly on the hypothalamus, and activates the NTS/PBN directly or is mediated by the afferent sensory nerves, resulting in suppression of food intake. In previous neuromodulatory studies, it was clearly shown that the vagus nerves are responsible for some of the food intake suppression action of GLP-1. However, the intraintestinal localization and transmission modes of the nerves that express the GLP-1 receptor remain unclear. Borgmann et al. have elucidated the characteristics of sensory nerves that specifically express the GLP-1 receptor, using mice expressing the gene for dual recombinase which facilitate mapping of the sensory nerves. It was clearly shown that the sensory nerves that express the GLP-1 receptor are the vagus nerves, with marked expression in the stomach and duodenal bulb, and that activation of neurons that express the GLP-1 receptor induces activation of c-FOS in the PBN, mediated by activation of c-FOS in the NTS, resulting in the suppression of food intake. It is hoped
that further clarification of the mechanism of the suppression of food intake by GLP-1 and other intestinal hormones will lead to full elucidation of the food intake regulation mechanism, and the development of drugs for the effective treatment of obesity.

DISCLOSURE
The authors declare no conflict of interest.

Norio Harada†, Nobuya Inagaki* Department of Diabetes, Endocrinology and Nutrition, Kyoto University Graduate School of Medicine, Kyoto, Japan

REFERENCES
1. Schauer PR, Kashyap SR, Wolski K, et al. Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med 2012; 366: 1567–1576.
2. Schwartz MW, Woods SC, Porte Jr, et al. Central nervous system control of food intake. Nature 2000; 404: 661–761.
3. Air EL, Benoit SC, Blake Smith KA, et al. Acute third ventricular administration of insulin decreases food intake in two paradigms. Pharmacol Biochem Behav 2002; 72: 423–429.
4. Schaeffer M, Hodson DJ, Mollard P. The blood-brain barrier as a regulator of the gut-brain axis. Front Horm Res 2014; 42: 29–49.
5. Chaudhri OB, Salem V, Murphy KG, et al. Gastrointestinal satiety signals. Annu Rev Physiol 2008; 70: 239–255.
6. Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: Properties, functions, and clinical implications. Am J Med 2011; 124: S3–18.
7. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. J Diabetes Investig 2010; 1: 8–23.
8. Adriaenssens AE, Biggs EK, Darwish T, et al. Glucose-dependent insulinotropic polypeptide receptor-expressing cells in the hypothalamus regulate food intake. Cell Metab 2019; 30: 987–996.
9. Gabery S, Salinas CG, Paulsen SJ, et al. Semaglutide lowers body weight in rodents via distributed neural pathways. JCI Insight 2020; 5: e133429.
10. Borgmann D, Ciglieri E, Biglari N, et al. Gut-brain communication by distinct sensory neurons differently controls feeding and glucose metabolism. Cell Metab 2021; 33: 1466–1482.e7.

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