Received: 19 September 2021
Revision received: 21, September 2021
Accepted: 29 September 2021
www.rriemd.com
DOI :10.33702/rriemd.2021.3.1.7

Editorial (Commentary)

The influence of Glucagon-Like Peptide 1 (GLP-1) for appetite, eating and weight

Hiroshi Bando

Medical Research / Tokushima University, Tokushima, Japan
Integrative Medicine Japan (IMJ), Shikoku Island Division, Tokushima, Japan
Japan Low Carbohydrate Diet Promotion Association, (JLCDPA), Kyoto, Japan

ABSTRACT
For humans, eating control is crucial. When metabolic homeostasis can be maintained, feeding function involves the hypothalamus and brain stem. When food intake exceeds metabolic homeostasis, reward system is involved such as dopamine neurons from the ventral tegmental area, the nucleus accumbens, and limbic system and to the neocortex. Physiological effects of Glucagon-Like Peptide 1 (GLP-1) include improving glucose metabolism, delaying gastric emptying, and suppressing appetite. GLP-1 receptor agonist (GLP-1RA) is supposed to cross the blood brain barrier (BBB) and act on the central nervous system (CNS), associated with weight reduction effect, delaying gastric emptying via the vagus nerve system.
Keywords: Glucagon-Like Peptide 1 (GLP-1), GLP-1 receptor agonist (GLP-1RA), blood brain barrier (BBB), Semaglutide, weight reduction

Citation: Hiroshi BANDO. (2021). The influence of Glucagon-Like Peptide 1 (GLP-1) for appetite, eating and weight. Recent Research in Endocrinology and Metabolic Disorder, 3(1)40-43. http://dx.doi.org/10.33702/rriemd.2021.3.1.7
Author for correspondence: *Hiroshi BANDO, Tokushima University, Tokushima, Japan.*

Email: pianomed@bronze.ocn.ne.jp

Recently, metabolic syndrome (Met-S), diabetes and obesity have been more prevalent internationally. In actual medical practice for type 2 diabetes mellitus (T2DM) and obesity, nutritional therapy such as low carbohydrate diet (LCD) has been known to be effective [1]. Current pharmacological topics include the efficacy of Glucagon-Like Peptide 1 receptor agonist (GLP-1RA) for diabetes [2,3]. Furthermore, the weight-reduction effect of GLP-1RA on obesity is now attracting attention [4]. This article describes basically the mechanism of Glucagon-Like Peptide 1 (GLP-1) on eating and clinically the effect of GLP-1RA for obesity.

For humans, eating control of the brain is a crucial mechanism. To the extent that metabolic homeostasis can be maintained, feeding function involves the hypothalamus and brain stem. On the other hand, when the amount of food intake exceeds metabolic homeostasis, some mechanisms are involved in the controls of the reward system, such as dopamine neurons from the ventral tegmental area, the nucleus accumbens (striatum), limbic system and to the neocortex [5xx].

For pathological condition of obesity, inflammation in the hypothalamus causes abnormalities in the reward system, resulting in disruption of feeding regulation [6]. The physiological effects of GLP-1 include improving glucose metabolism, delaying gastric emptying, and suppressing appetite in the central nervous system (CNS) [7]. Among them, the GLP-1 receptor suppresses appetite by being expressed in many parts of the CNS involved in the regulation of feeding. As regard to this, two mechanisms may exist.

Firstly, GLP-1 produced in the gastrointestinal (GI) tract activates the vagal afferents. Then, by conducting electrical stimulation to the solitary tract nucleus of the medulla oblongata, physiological signal is transmitted

to neurons toward the hypothalamus [8]. As a result, there is a mechanism by which appetite is suppressed. Secondly, GLP-1 is produced in neurons of the solitary tract nucleus of the medulla oblongata. Then, GLP-1 acts on the hypothalamus of the projection destination. As a result, an appetite-suppressing effect can be found [9]. However, considering the half-life of GLP-1 in the blood, it is very short which is approximately several minutes. Therefore, it is unlikely that GLP-1 produced in the GI tract crosses the blood-brain barrier (BBB) and acts on the CNS.

GLP-1RA has introduced to medical practice as a therapeutic agent for T2DM. GLP-1RA has been reported to cross the BBB and act directly, at least in part, on the CNS [10]. In addition to this effect, a weight reduction effect is found as well as the effect of delaying gastric emptying via the vagus nerve system. It has been reported that predecessor administration of liraglutide or semaglutide suppresses appetite. For this mechanism, activation of preproglucagon neurons that produce GLP-1 in the solitary tract would be also involved [11].

Furthermore, the function of inducing vomiting in GLP-1 receptor-expressing neurons has also been reported. Genome-related analysis of T2DM revealed that Japanese have a variant of the GLP-1 receptor. Therefore, it is expected that the effect of GLP-1 agonists on Japanese people is higher than others, and that the elucidation of the feeding regulation peculiar to Japanese people [12].

To date, several types of GLP-1RAs for the treatment of T2DM are found [13]. Each has a different molecular weight and duration of action. There are differences in administration method and diabetic agents that can be used in combination. When divided according to the administration method, four types are in the following. They are i) exenatide subcutaneously injected twice daily, ii) lixisenatide and liraglutide subcutaneously injected once daily, iii) exenatide, duraglutide and semaglutide once weekly subcutaneously injected, iv) oral type of semaglutide, which was examined in the PIONEER study. Then, the same or better hypoglycemic effect and weight reduction effect of semaglutide were observed for T2DM as compared with the injectable preparation. A domestic phase 3 clinical trial was conducted. As the results at 26 weeks after administration for oral semaglutide, weight reduction was observed for 1 kg with 7 mg and 2.2 kg with 14 mg [14]. Oral agent of semaglutide for 7 mg and 14 mg of the oral drug semaglutide have been used in clinical practice.

In the United States (US), liraglutide 3 mg is approved as an anti-obesity drug and has been used for non-diabetic patients [15]. The weight-loss effect of subcutaneous injections of semaglutide was investigated in 16 countries in Asia, Europe and US. The subjects were 1961 obese adults with a body mass index (BMI) of 30 or more, with an average body weight of 104 kg and an average BMI of 38. Randomly assigned, the active group was injected subcutaneously at 2.4 mg once weekly. All patients and the placebo group were provided with face-to-face or telephone counseling, dietary and exercise guidance, and motivation with a dietitian.

A 68-week intervention was performed. As a result, a 14.9% (15.3 kg) reduction was achieved in the semaglutide-administered group. This was found to have a large effect similar to that of weight reduction/ metabolism improvement surgery [16]. The average weight reduction in the placebo group was 2.6 kg. Temporary nausea and diarrhea were observed in 40% of the semaglutide group, of which 7% in the semaglutide group and 0.75% in the placebo group had discontinuation of treatment. Gallbladder-related disorders, such as the development of gallstones that may be associated with weight loss, were observed in 3% of the semaglutide and 1% of the placebo group. In the future, long-term effects and safety will be clarified, and it is expected as an option for the treatment of obesity and severe obesity.

In addition to GLP-1RA, some anti-obesity agents have been developed. They include growth differentiation factor 15 (GDF-15) [17], peptide YY (PYY) [18], cholecystokinin (CCK) [19] and glucagon [20] which are related to gastrointestinal (GI) hormones. Regarding ghrelin which brings appetite promotion, two agents with the opposite function have been found. They are i) enhancing the action of ghrelin inhibitor liver-expressed antimicrobial peptide 2 (LEAP-2) [21], and ii) reducing the action of ghrelin.

Conflict of interest: The authors declare no conflict of interest.
Funding- There was no funding received for this paper.

REFERENCES

[1] Bando H. Beneficial Effects of Ketone Bodies (KB) From Endocrine and Metabolic Points of View. SunText Rev Endocrine Care 2021;1(1): 101. DOI : 10.51737/endocrine.2021.001
[2] Hayashi K, Yasuoka T, Bando H, Miki K, Nakagawa M, Zushi T, et al. Useful Xultophy for Older Diabetic with Various Problems. SunText Rev Med Clin Res 2021; 2(2): 126. DOI : 10.51737/2766-4813.2021.027
[3] González CD, Girolamo GD. How do you treat obesity in the elderly pharmacologically?. Expert Opinion on Pharmacotherapy 2021; DOI: 10.1080/14656566.2021.1921150
[4] Kim BY, Kang SM, Kang JH, et al. Current Long-Term Pharmacotherapies for the Management of Obesity. *J Obes Metab Syndr*. 2020;29(2):99-109. doi:10.7570/jomes20010
[5] Perez-Bonilla P, Santiago-Colon K, Leinninger GM. Lateral hypothalamic area neuropeptides modulate ventral tegmental area dopamine neurons and feeding. Physiology & Behavior 2020;223:112986. doi.org/10.1016/j.physbeh.2020.112986.
[6] Perakakis N, Farr OM, Mantzoros CS. Fasting oxyntomodulin, glicentin, and gastric inhibitory polypeptide levels are associated with activation of reward- and attention-related brain centres in response to visual food cues in adults with obesity: A cross-sectional functional MRI study. Diabetes, obesity and metabolism 2021 May;23(5): 1202-1207. doi.org/10.1111/dom.14315
[7] Eren-Yazicioglu CY, Yigit A, Dogruoz RE and Yapici-Eser H. Can GLP-1 Be a Target for Reward System Related Disorders? A Qualitative Synthesis and Systematic Review Analysis of Studies on Palatable Food, Drugs of Abuse, and Alcohol. Front. Behav. Neurosci 2021; 14:614884. doi: 10.3389/fnbeh.2020.614884
[8] Holt MK, Rinaman L. Therole of nucleus of the solitary tract glucagon-like peptide-1and prolactin-releasing peptide neurons in stress: anatomy,physiology and cellular interactions. British Journal ofPharmacology 2021;1–17.https://doi.org/10.1111/bph.15576
[9] Diz-Chaves Y, Herrera-Pérez S, González-Matías LC, Lamas JA, Mallo F. Glucagon-Like Peptide-1 (GLP-1) in the Integration of Neural and Endocrine Responses to Stress. Nutrients. 2020; 12(11):3304. https://doi.org/10.3390/nu12113304
[10] Mathies M. Jepsen & Mikkel B. Christensen. Emerging glucagon-like peptide 1 receptor agonists for the treatment of obesity, Expert Opinion on Emerging Drugs 2021; DOI: 10.1080/14728214.2021.1947240
[11] Brierley DI, Holt MK, Singh A, de Araujo A, McDougle M, Vergara M, Afaghani MH, Lee SJ, Scott K, Maske C, Langhans W, Krause E, de Kloet A, Gribble FM, Reimann F, Rinaman L, de Lartigue G, Trapp S. Central and peripheral GLP-1 systems independently suppress eating. Nat Metab. 2021 Feb;3(2):258-273. doi: 10.1038/s42255-021-00344-4. Epub 2021 Feb 15. PMID: 33589843; PMCID: PMC7116821.
[12] Suzuki K, Akiyama M, Ishigaki K, Kanai M, Hosoe J, Shojima N, Hozawa A, Kadota A, Kuriki K, Naito M, Tanno K, Ishigaki Y, Hirata M, Matsuda K, Iwata N, Ikeda M, Sawada N, Yamaji T, Iwasaki M, Ikegawa S, Maeda S, Murakami Y, Wakai K, Tsugane S, Sasaki M, Yamamoto M, Okada Y, Kubo M, Kamatani Y, Horikoshi M, Yamauchi T, Kadowaki T. Identification of 28 new susceptibility loci for type 2 diabetes in the Japanese population. Nat Genet. 2019 Mar;51(3):379-386. doi: 10.1038/s41588-018-0332-4. Epub 2019 Feb 4. PMID: 30718926.
[13] Tak YJ, Lee SY. Anti-Obesity Drugs: Long-Term Efficacy and Safety: An Updated Review. *World J Mens Health*. 2021;39(2):208-221. doi:10.5534/wjmh.200010
[14] Yabe D, Nakamura J, Kaneto H, Deenadayalan S, Navarria A, Gislum M, Inagaki N; PIONEER 10 Investigators. Safety and efficacy of oral semaglutide versus dulaglutide in Japanese patients with type 2 diabetes (PIONEER 10): an open-label, randomised, active-controlled, phase 3a trial. Lancet Diabetes Endocrinol. 2020 May;8(5):392-406. doi: 10.1016/S2213-8587(20)30074-7. PMID: 32333876.
[15] Hasanzad M, Sarhangi N, Nikfar S, *et al.* A narrative review of current trends in liraglutide: insights into the unmet needs in management of type 2 diabetes and obesity. *J Diabetes Metab Disord* 2020;19:1863–1872. https://doi.org/10.1007/s40200-020-00619-9
[16] Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar 18;384(11):989. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.
[17] Ouyang J, Isnard S, Lin J, et al. GDF-15 as a Weight Watcher for Diabetic and Non-Diabetic People Treated With Metformin. *Front Endocrinol (Lausanne)*. 2020;11:581839. Published 2020 Nov 18. doi:10.3389/fendo.2020.581839

[18] Lafferty RA, Flatt PR, Irwin N. Established and emerging roles peptide YY (PYY) and exploitation in obesity–diabetes, Curr Opin Endocrinol Diabetes Obes: April 2021:28(2): 253-261. doi: 10.1097/MED.0000000000000612
[19] Cawthon CR, de La Serre CB. The critical role of CCK in the regulation of food intake and diet-induced obesity. Peptides 2021;138:170492. ISSN 0196-9781. doi.org/10.1016/j.peptides.2020.170492.
[20] Morita Y, Ohno H, Kobuke K, Oki K, Yoneda M. Variation in plasma glucagon levels according to obesity status in Japanese Americans with normal glucose tolerance. Endocrine J 2021;68(1): 95-102. doi.org/10.1507/endocrj.EJ20-0366
[21] Gupta D, Ogden SB, shankar K, Varshney S, Zigman JM. A LEAP 2 conclusion? Targeting the ghrelin system to treat obesity and diabetes. Molecular Metabolism 2021; 46:101128. ISSN 2212-8778. doi.org/10.1016/j.molmet.2020.101128.