Is ghrelin a glucagon-like peptide-1 secretagogue?

Glucagon-like peptide-1 (GLP-1), a 30-amino acid peptide processed from proglucagon protein by prohormone convertase 1/3, plays important roles in glucose and energy metabolism, including glucose-stimulated insulin secretion, inhibition of glucagon secretion and gut motility, and reduction of appetite. GLP-1 receptor agonists have been widely used as antidiabetic drugs, and high-dose liraglutide, a GLP-1 receptor agonist, has been approved for the treatment of obesity in the USA. GLP-1 is secreted by L cells, open-type endocrine cells located primarily in the lower intestine that directly sense nutrients transported into the gut. GLP-1 is released by various stimuli, including glucose, fats, protein, amino acids, long-chain fatty acids, short-chain fatty acids and bile acids. GLP-1 secretion is also regulated by the parasympathetic nervous system and circulating hormones, such as cholecystokinin, glucose-dependent insulinotropic peptide, insulin, gastrin-releasing peptide and leptin. Plasma GLP-1 levels in humans increase postprandially, and reach a peak within 1 h, and then gradually decrease to basal levels. Some clinical studies, including our own, showed a biphasic pattern of plasma GLP-1 concentrations, with an early postprandial peak at 15–30 min, and a second one at 90–120 min, whereas other studies described monophasic responses. This discrepancy appears to be attributable to differences in the methods used to measure GLP-1 and the contents of the test meals.

Ghrelin is a 28-amino acid peptide first isolated from the stomach. Acylation of its third residue, Ser-3, by the addition of a middle-chain fatty acid, n-octanoic acid, is essential for its biological activity, including the binding and activation of its receptor. Ghrelin stimulates feeding, gastric motility and secretion of growth hormone. Plasma ghrelin levels increase before meals and decrease afterward, the opposite pattern shown by plasma GLP-1. Fast ing plasma ghrelin levels are negatively correlated with body mass index in humans. Ghrelin administration has been reported to reduce glucose-stimulated insulin secretion, but in humans, ghrel lin’s effects on glucose metabolism and insulin secretion have not yet been fully clarified. Intravenous bolus administration of ghrelin under fasting conditions was found to induce hyperglycemia and reduce insulin secretion in humans. These findings, however, were not observed in other studies. Continuous infusion of ghrelin to healthy subjects over 16 h resulted in hyperglycemia, a reduced early insulin response, and an increased second-phase insulin response after meal. Further studies using various doses and timing of exogenously administered ghrelin are required to clarify ghrelin’s effects on glucose metabolism in humans.

Gagnon et al. recently reported that ghrelin enhanced GLP-1 secretion after oral glucose tolerance tests (OGTTs) in mice. They administered ghrelin (200 nmol/kg bodyweight) or saline intraperitoneally 15 min before OGTT. Relative to saline, ghrelin preadministration significantly increased plasma GLP-1 levels at 15 min after OGTT. Blood glucose levels at 60 and 90 min after OGTT were significantly lower in the ghrelin preadministration group. In addition, pretreatment with a ghrelin receptor antagonist reduced GLP-1 secretion after OGTT and impaired glucose tolerance in wild-type mice. High-fat diet-induced obese mice had lower basal plasma ghrelin levels and higher blood glucose levels after OGTT compared with controls, whereas ghrelin preadministration significantly increased plasma GLP-1 levels after OGTT and improved glucose tolerance. Gagnon et al. also showed that ghrelin receptors were expressed in L cells, and that ghrelin directly stimulated GLP-1 secretion from both murine and human L cell lines through an extracellular signal-related kinase 1/2-dependent pathway. These results suggest that ghrelin might function in the regulation of GLP-1 secretion. This group also showed that ghrelin administration without an oral glucose load did not alter basal GLP-1 levels, indicating that ghrelin is important for “priming” the L cells in preparation for glucose-stimulated GLP-1 secretion (Figure 1).

A variety of physiological phenomena are influenced by stratified hormonal secretion and feedback systems, such as the hypothalamus–pituitary–adrenal axis. When undigested nutrients reach the lower intestine, they cause inhibition of gastric emptying, small intestinal transit, gastric acid secretion, pancreatic enzyme secretion and bile acid secretion. This phenomenon in the gastrointestinal tract represents a negative feedback mechanism called the ileal brake (Figure 1). GLP-1 and peptide YY are mediators of the ileal brake, and the distal intestine controls the functions of the upper gastrointestinal organs. Conversely, ghrelin’s enhancement of GLP-1 secretion might represent one of the anterograde regulatory systems in the gastrointestinal tract.

Some early studies found that postprandial GLP-1 secretion in diabetic patients was lower than that in healthy subjects, whereas a recent meta-analysis showed no significant difference between the two groups in either Caucasian or Japanese subjects. Although the increases...
in GLP-1 after either a meal or OGTT varied widely in previous reports, it is important to pay attention to the methods used to measure plasma GLP-1, especially for active GLP-1 levels; blood collected in tubes containing a dipeptidyl peptidase-4 inhibitor, plasma extraction and antibodies used in ELISA kits\(^5\).

Postprandial GLP-1 secretion was reported to be lower or similar in obese subjects compared with lean controls. If ghrelin is important for postprandial GLP-1 secretion in humans as well as in mice, GLP-1 secretion after meals and after postprandial insulin secretion might be lower in obese subjects, because their plasma preprandial ghrelin levels are low. Even in lean subjects, postprandial GLP-1 secretion might be low if the individuals eat snacks between meals or have short intervals between meals, because plasma ghrelin levels do not increase much during the short fasting periods. Ghrelin resistance, which is caused by high-fat diets, could also further augment ghrelin’s enhancing effect on postprandial GLP-1 secretion in obese individuals. However, insulin secretion is generally increased by obesity, thus hyperinsulinemia cannot be explained only by ghrelin’s enhancing effect on GLP-1 secretion. Because the dose of ghrelin used in the report was pharmacological, it is uncertain whether physiological differences in plasma ghrelin levels influence human postprandial GLP-1 secretion in individuals with obesity or diabetes, or who are in the postprandial state.

Several kinds of orally available ghrelin receptor agonists, called growth hormone secretagogues, have been developed. For the treatment of obese patients with type 2 diabetes, preprandial ghrelin or growth hormone secretagogue administration might be useful to increase postprandial GLP-1 secretion. However, administration of ghrelin or growth hormone secretagogues under fasting conditions will increase appetite. Thus, both therapies might be less than ideal for the treatment of type 2 diabetes in patients who are obese. In addition, in our preliminary animal experiment, the anorexigenic effect of secreted GLP-1 might not be apparent. To apply ghrelin’s effect on GLP-1 release to diabetes treatment, the dose, timing, adverse effects and administration route of ghrelin should be examined in the future. Clarifying all mechanisms of postprandial GLP-1 secretion, including ghrelin’s effect, is important to facilitate the development of a novel strategy for diabetes treatment.

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**DISCLOSURE**

The authors declare no conflict of interest.

**REFERENCES**

1. Tolhurst G, Reimann F, Gribble FM. Nutritional regulation of glucagon-like peptide-1 secretion. *J Physiol* 2009; 587: 27–32.
2. Chabot F, Caron A, Laplante M, et al. Interrelationships between ghrelin, insulin and glucose homeostasis: physiological relevance. *World J Diabetes* 2014; 5: 328–341.
3. Vestergaard ET, Gormsen LC, Jessen N, et al. Ghrelin infusion in humans induces acute insulin resistance and lipolysis independent of growth hormone signaling. *Diabetes* 2008; 57: 3205–3210.
4. Gagnon J, Baggio LL, Drucker DJ, et al. Ghrelin is a novel regulator of GLP-1 secretion. *Diabetes* 2015; 64: 1513–1521.
5. Masuda K, Aoki K, Terauchi Y. Comparison of plasma active glucagon-like peptide-1 (GLP-1) levels assayed with or without plasma extraction in non-diabetic men. *Endocr J* 2012; 59: 435–438.

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