Bile-induced secretion of glucagon-like peptide-1: pathophysiological implications in type 2 diabetes?

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During the last decades it has become clear that bile acids not only act as simple fat solubilizers, but additionally represent complex hormonal metabolic integrators. Bile acids activate both nuclear receptors (controlling transcription of genes involved in for example bile acid, cholesterol, and glucose metabolism) and the cell surface G protein-coupled receptor TGR5 (modulating energy expenditure in brown fat and muscle cells). It has been shown that TGR5 is expressed in enteroendocrine L cells, which secrete the potent glucose-lowering incretin hormone glucagon-like peptide-1 (GLP-1). Recently it was shown that bile acid-induced activation of TGR5 results in intestinal secretion of GLP-1 and that enhanced TGR5 signaling improves postprandial glucose tolerance in diet-induced obese mice. This Perspectives article presents these novel findings in the context of prior studies on nutrient-induced GLP-1 secretion and outlines the potential implications of bile acid-induced GLP-1 secretion in physiological, pathophysiological, and pharmacological perspectives.

Bile-induced secretion of glucagon-like peptide-1: pathophysiological implications in type 2 diabetes? Am J Physiol Endocrinol Metab 299: E10–E13, 2010. First published April 27, 2010; doi:10.1152/ajpendo.00137.2010.—During the last decades it has become clear that bile acids not only act as simple fat solubilizers, but additionally represent complex hormonal metabolic integrators. Bile acids activate both nuclear receptors (controlling transcription of genes involved in for example bile acid, cholesterol, and glucose metabolism) and the cell surface G protein-coupled receptor TGR5 (modulating energy expenditure in brown fat and muscle cells). It has been shown that TGR5 is expressed in enteroendocrine L cells, which secrete the potent glucose-lowering incretin hormone glucagon-like peptide-1 (GLP-1). Recently it was shown that bile acid-induced activation of TGR5 results in intestinal secretion of GLP-1 and that enhanced TGR5 signaling improves postprandial glucose tolerance in diet-induced obese mice. This Perspectives article presents these novel findings in the context of prior studies on nutrient-induced GLP-1 secretion and outlines the potential implications of bile acid-induced GLP-1 secretion in physiological, pathophysiological, and pharmacological perspectives.
the blood stream has been described in detail by Holst in 2007 (13). As opposed to GLP-1-based therapy, Roux-en-Y gastric bypass (RYGB) surgery incurs remission of type 2 diabetes in the majority of patients (4), a “cure” of type 2 diabetes that has been linked to increased endogenous GLP-1 secretion (22). This indirectly supports the notion that increased endogenous GLP-1 may improve glucose metabolism. Thus, despite the fact that the hypothesis that endogenous GLP-1 activates neurons in lamina propria remains speculative, it seems expedient to find ways to stimulate endogenous GLP-1 secretion if the full glucose-lowering potential of GLP-1 is to be utilized medically. To improve the chances to do so, a detailed knowledge of the stimulus-secretion coupling in the intestine is required.

**Stimuli for GLP-1 Secretion**

Currently, it is well acknowledged that robust endogenous GLP-1 secretion is attained following ingestion of meals rich in fat and carbohydrates (44, 46); and protein ingestion has also been shown to elicit GLP-1 secretion (5). Most studies suggest that the interaction of nutrients with luminal microvilli of the L cells’ apical parts results in secretion of GLP-1 to the intestinal blood stream. In the L cell model, GLUTag, a direct association between glucose absorption (9) and metabolism (35), and GLP-1 secretion has been observed. Furthermore, in in vitro experiments with the L cell model GLUTag and in vivo experiments in dogs, it is possible to inhibit GLP-1 secretion by blocking the luminal L cell sodium-glucose transporter SGLT-1 (9, 40), suggesting that absorption of glucose is a key regulatory point. Furthermore, recent studies provide evidence for a direct secretion of several G protein-coupled receptors (for example GPR120), which can be activated by long-chain fatty acids and, hence, result in GLP-1 secretion (12). The mechanisms behind protein-induced GLP-1 secretion are even less well understood (5). In addition to nutrient-released GLP-1 secretion, studies suggest that paracrine [via somatostatin (11) and glucose-dependent insulinotropic polypeptide (37)] and neuroendocrine mechanisms [via vagus (37) and via sympathetic neural activation (7, 34)] play important roles for the regulation of postprandial GLP-1 secretion. Despite the aforementioned observations, there seems to be a direct way to a complete picture of the mechanisms responsible for meal-induced GLP-1 secretion. However, the findings of bile acid-induced stimulation of GLP-1 secretion from the 1980s and early 1990s have been revitalized by new studies, providing important pieces to the puzzle of mechanisms eliciting endogenous GLP-1 secretion.

**Bile-Induced GLP-1 Secretion—New findings**

Recently, the G protein-coupled receptor TGR5 was found in the enteroendocrine GLP-1-secreting cell line STC-1 (17) and in primary L cells from mice (36); and in 2009, Thomas et al. (42) took a giant leap in the understanding of the physiological function of TGR5 and endogenous GLP-1 secretion. In a detailed and carefully designed study, Thomas et al. used pharmacological and genetic gain-of-function and loss-of-function models to establish the physiological impact of TGR5 activation on GLP-1 secretion. First, they showed that the semisynthetic, potent, and selective TGR5 activator INT-777 (bile acid mimetic) increases intracellular levels of cAMP and the ATP/ADP ratio, causes calcium influx, and induces GLP-1 secretion in human L cells, effects potentiated by TGR5 overexpression and blunted by TGR5 RNA interference. Second, enhanced in vivo TGR5 signaling (transgenic overexpression of TGR5, restricted to tissues that express TGR5 normally) was shown to improve postprandial glucose tolerance in diet-induced obese mice, an improvement that was associated with robust postprandial GLP-1 release and insulin secretion. In contrast, TGR5+/− mice exhibited reduced glucose tolerance. Last, INT-777 was shown to increase GLP-1 release in TGR5−/− mice, whereas the effect of INT-777 on GLP-1 secretion was blunted in TGR5+/− mice. These findings suggest that postprandial gall bladder contraction and increased flow of bile acids to the intestine potentiate nutrient-induced GLP-1 secretion from the L cells via TGR5 activation.

**Bile and Type 2 Diabetes—Pathophysiological Implications?**

The new physiological understanding of endogenous GLP-1 secretion generated by Thomas et al. can have therapeutic potential. As mentioned, the current GLP-1-based antidiabetic treatments do not seem to increase endogenous GLP-1 secretion (14); and, if the hypothesis that major effects of endogenously secreted GLP-1 are mediated through local activation of sensory afferent nerves proves correct, they may exploit only a fraction of the significant physiological effects of GLP-1 (14, 21). Therefore, new treatment modalities enhancing L cell secretion [perhaps through TGR5 activation with bile mimetics, as suggested by Thomas et al. (42), or small molecule agonists] might provide a superior alternative.

Furthermore, the study of Thomas et al. (42) provides insights into physiological mechanisms that perhaps have pathophysiological implications in type 2 diabetes. Interestingly, reduced postprandial GLP-1 secretion has been suggested to play a role in type 2 diabetic pathophysiology, contributing to the exaggerated postprandial glucose excursions that characterize patients with type 2 diabetes (44). However, reduced GLP-1 responses in type 2 diabetic patients have been observed predominantly following meal tests (44, 45), with duration of diabetes being an important determinant of reduced GLP-1 secretion (44), whereas only a few (24, 27) among many studies (8, 18, 20, 31, 41, 47) utilizing oral glucose tolerance tests have been able to confirm the phenomenon. In fact, oral glucose elicited increased GLP-1 responses in some studies (8, 31, 41). Therefore, the question whether type 2 diabetic pathophysiology encompasses reduced nutrient-induced GLP-1 secretion is a subject of debate (26). The Thomas et al. study (42) might shift the focus of this debate from the “diabetic” L cells to the “diabetic” gall bladder. The newly described role of bile-induced TGR5 activation in L cell secretion combined with findings of reduced postprandial gall bladder emptying in type 2 diabetes (38, 39) [worsened by diabetic neuropathy typical for patients with long-standing disease (39)] suggests that reduced postprandial GLP-1 responses in patients with type 2 diabetes may, hypothetically, arise as a consequence of diabetic gall bladder dysmotility, which in turn might reduce postprandial bile flow to the intestine and, thereby, TGR5 activation in the L cells. Even though very few data on the quantitative provision of bile acids to the intestine exist (especially in diabetic patients) this hypothetical notion would, if it holds true, acquit the L cells of the ATP/ADP ratio, causes calcium influx, and induces GLP-1 secretion in human L cells, effects potentiated by TGR5 overexpression and blunted by TGR5 RNA interference. Second, enhanced in vivo TGR5 signaling (transgenic overexpression of TGR5, restricted to tissues that express TGR5 normally) was shown to improve postprandial glucose tolerance in diet-induced obese mice, an improvement that was associated with robust postprandial GLP-1 release and insulin secretion. In contrast, TGR5+/− mice exhibited reduced glucose tolerance. Last, INT-777 was shown to increase GLP-1 release in TGR5−/− mice, whereas the effect of INT-777 on GLP-1 secretion was blunted in TGR5+/− mice. These findings suggest that postprandial gall bladder contraction and increased flow of bile acids to the intestine potentiate nutrient-induced GLP-1 secretion from the L cells via TGR5 activation.
playing a “direct” role in type 2 diabetic pathophysiology and would explain why postprandial GLP-1 responses generally have been shown to be reduced in patients with type 2 diabetes [most pronounced in patients with long duration of diabetes (44)], whereas oral glucose (which presumably does not induce the same degree of gall bladder emptying) elicits normal GLP-1 responses in these patients (8, 18, 20, 31, 41, 47). However, it should be stressed that whether the type 2 diabetic state per se might reduce L cell secretion or not is still a subject of scientific debate.

The results in the study by Thomas et al. are also interesting in relation to the unexplained high prevalence of type 2 diabetes in cholecystectomized patients (and in patients with gall bladder disease) (6) and could pave the way for exploratory studies evaluating mechanisms behind these cross-sectional findings. Last, serum bile acids have been found to increase following RYGB (positively correlated with GLP-1 and negatively correlated with thyrotropic hormone) (33). As direct access of bile acids to L cell-rich parts of the small intestine is established following RYGB (from the secretory “blind” limb to the “ileal” alimentary limb) Thomas et al.’s findings may have implications for the description of mechanisms leading to RYGB-induced remission of type 2 diabetes.

Conclusions and Perspectives

In conclusion, the findings by Thomas et al. (42) suggest bile acids to play a significant role in postprandial glucose metabolism and outline new possibilities in antidiabetic treatment approaches. Furthermore, the findings could resolve the debate of reduced/normal GLP-1 secretion in type 2 diabetes and introduce the changed flow of bile following RYGB as a possible mechanism contributing to RYGB-induced remission of type 2 diabetes. A major weakness and a logical limitation of these hypotheses is the fact that the recent advances in the physiology of bile acid-induced GLP-1 secretion are based on studies in animals and cell models. Therefore, it should be noted that the perspectives on bile acid-induced GLP-1 secretion and its implication in type 2 diabetic pathophysiology offered in the present article remain speculative and might not be applicable to human (patho)physiology. Only clinical experiments can establish whether 1) postprandial gall bladder emptying and flow of bile acids to the small intestine control L cell secretion in humans, 2) reduced gall bladder emptying and reduced TGR5 activation have any pathophysiological implications in patients with type 2 diabetes, 3) bile acids or bile acid mimetics have therapeutic potential for treating patients with type 2 diabetes, and 4) bile acids play a potential role in the remarkable diabetes-“curing” effects of bariatric surgery.

DISCLOSURES

No conflict of interest is reported by the author.

REFERENCES


