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

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Abstract
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.
Introduction

During the last couple of years it has become clear that bile acids not only act as simple fat solubilizers in the digestive tract, but additionally represent complex hormonal metabolic integrators(43). In 1999 three groups independently of each other discovered that bile acids are ligands for the nuclear receptor FXR controlling transcription of genes involved in for example bile acid, cholesterol and glucose metabolism(23; 32; 48). In the early 2000’s it was shown that bile acids also act as signaling molecules (hormones) through the cell surface G protein-coupled receptor TGR5(25; 49). Bile acid activation of TGR5 results in increased intracellular cAMP levels, which in brown adipose tissue and muscle cells modulates energy expenditure by activating type 2 iodothyronine deiodinase, which in turn deiodinates thyroxine to the active thyroid hormone triiodothyronine(43). Accordingly it has been shown that bile acid-enriched diet increases energy expenditure and prevents diet-induced obesity in mice(49). Interestingly, already in the 1980’s intraluminal bile acids were shown to stimulate the secretion of gut glucagon-like immunoreactive materials (enteroglucagon; corresponding to glucagon-like peptide-1 (GLP-1)) in dogs(29; 30) and a few years later in human(1) and rat colon(34). However, the physiologic ‘purpose’ of and the mechanisms behind bile acid-induced GLP-1 release was not apparent; neither was the therapeutic potential of GLP-1 as a glucose-lowering drug for patients with diabetes fully developed. Nowadays it is well established that GLP-1 plays a crucial role in human glucose metabolism and new antidiabetic drugs based on GLP-1’s physiological effects have been developed(13). In this Perspectives article recent findings of bile acid-induced GLP-1 secretion will be described in the context of human GLP-1 physiology and possible implications for type 2 diabetic pathophysiology.

Glucagon-like peptide-1

GLP-1 is a 30-amino acid polypeptide produced in the endocrine L cells of the intestinal epithelium as a product of proglucagon gene expression(13). The hormone is secreted rapidly (within 10-15 min) in response to meal ingestion(13). It exerts strong glucose-dependent insulinotropic and glucagonostatic actions in the endocrine pancreas(13). Additionally, GLP-1 reduces gastrointestinal motility (e.g. brakes gastric emptying) and appetite whereby postprandial glucose excursions and food intake are kept down(13). As mentioned, these effects have been sought utilized in the development of GLP-1-based anti-diabetic treatment modalities(13). However, clinical studies on GLP-1-based therapy have not been able to show the GLP-1-induced remission of type 2 diabetes as anticipated from animal studies, and it is still uncertain whether these new drugs can halt the progression of type 2 diabetes(19). The reason for these limitations may be due to the fact that current GLP-1-based drugs exert their effects via elevated plasma levels of ‘GLP-1 receptor agonists’, and, therefore, allegedly, may not elicit the local effects that endogenous secreted GLP-1 might have. Such local effects may involve stimulation of local afferent sensory nerve fibers residing in lamina propria (arising from the nodose ganglion), sending impulses to the nucleus of the solitary tract and onwards to hypothalamus, which in turn could signal for example the pancreas to exert ‘GLP-1-induced effects’ (as proposed in 1999 by Hansen et al.(10)). This hypothesis is based on the observation that very little GLP-1 reaches the systemic circulation in intact form (in fact GLP-1 is degraded so extensively that a significant rise in the concentration of the intact peptide may not be detected after intake of smaller meals(45)), and has been supported by findings of GLP-1 receptor expression in nodose ganglion cells(28), reductions in GLP-1-induced insulin secretion following ganglionic blockade in rats(3) and loss of effect of ‘physiological’ doses
of GLP-1 on glucose-induced insulin secretion in mice rendered sensory denervated (by neonatal administration of the neurotoxin capsaicin)(2). Likewise, several findings suggest the inhibitory effects of GLP-1 on gastrointestinal motility and secretion to be - at least partially - mediated through sensory afferents(15; 16; 50-52) (The hypothesis that endogenous GLP-1 acts locally in the lamina propria before being degraded and before appearing in 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. In order 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 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 L cell expression 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 insulinoctropic polypeptide(37)) and neurohormonal mechanisms (via vagus(37) and via sympathetic neural activation(7; 34)) play important roles for the regulation of postprandial GLP-1 secretion. Despite the mentioned observations, there seems to be a long 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 1980’s and early 1990’s 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. took a giant leap in the understanding of the physiological function of TGR5 and endogenous GLP-1 secretion(42). 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. Firstly, they showed that the semisynthetic, potent and selective TGR5 activator INT-777 (bile acid mimetic) increases
intracellular levels of cAMP and ATP:ADP ratio, cause calcium influx and induces GLP-1 secretion in human L cells; effects potentiated by TGR5 overexpression and blunted by TGR5 RNA interference. Secondly, 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 which was associated with robust postprandial GLP-1 release and insulin secretion. In contrast, TGR5-/- mice exhibited reduced glucose tolerance. Lastly, 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, Thomas et al.’s study(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, which characterize patients with type 2 diabetes(44). However, reduced GLP-1 responses in type 2 diabetics have predominantly been observed 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 elicits 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). Thomas et al.’s 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 little 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 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 not induces the same degree of gall bladder emptying) elicits normal GLP-1 responses in these patients(8; 18; 20;
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.

Thomas et al.’s results 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. Lastly, 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 logic 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 in treating patients with type 2 diabetes, and 4) bile acids play a potential role in the remarkable diabetes-‘curing’ effects of bariatric surgery.


