MINI REVIEW

Targeting the TGR5-GLP-1 pathway to combat type 2 diabetes and non-alcoholic fatty liver disease

Cibler la voie de signalisation TGR5-GLP-1 pour combattre le diabète de type 2 et les stéatoses hépatiques non-alcooliques

T.W. H. Pols, J. Auwerx, K. Schoonjans*

Laboratory of Integrative and Systems Physiology (LISP), école polytechnique fédérale de Lausanne, 1015 Lausanne, Switzerland

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Summary Incretin-based therapies have shown promise in the treatment of type 2 diabetes. Here we review our current understanding of TGR5 as a target to induce glucagon-like peptide-1 (GLP-1) secretion. These new observations suggest that TGR5 agonists may constitute a novel approach to treat type 2 diabetes, as well as complications of diabetes, such as non-alcoholic fatty liver disease.

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Introduction

Type 2 diabetes is a common disease that is characterized by high blood glucose levels caused by perturbed insulin signaling. Diabetes is a major health concern as it is associated with several severe complications, among which are cardiovascular disease and non-alcoholic fatty liver disease (NAFLD). Promising treatment strategies for diabetes are the so-called incretin-based therapies [1,2]. Incretins are hormones secreted by the gastrointestinal tract after food ingestion that regulate insulin-secretion and glucose homeostasis. Incretins explain the physiological phenomenon that oral glucose delivery induces a much larger effect on insulin release as compared to intravenously administered glucose.

The two foremost incretins able to regulate insulin-secretion are gastric-inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) [3].

It has been demonstrated that the G-protein coupled receptor (GPCR) TGR5 (also known as GPR131, M-BAR or GPBAR1) regulates GLP-1 secretion [4,5]. As TGR5 was originally shown to be responsive to bile acids [6], this observation could explain some of the beneficial metabolic properties coupled to high circulating levels of bile acids, such as improved insulin sensitivity [7], and better post-prandial glycemic control [8]. In the latter study, it is of note that the increase in plasma bile acids observed in patients after bariatric surgery was also correlated with higher peak GLP-1 levels [8].

This review highlights some of the beneficial properties of TGR5 activation with regard to GLP-1 secretion and discusses TGR5 activation as an attractive strategy to improve diabesity and NAFLD.

* Corresponding author.
E-mail address: kristina.schoonjans@epfl.ch (K. Schoonjans).
GLP-1-based treatment strategies in type 2 diabetes

GLP-1 is produced by enterendocrine L-cells located in the distal ileum and colon [9,10]. Secretion of GLP-1 is stimulated by food ingestion, both directly via nutrients, particularly by fat and carbohydrates, as well as via neural signals [11,12]. GLP-1 exerts a variety of physiological effects to integrate nutrient processing and energy assimilation. Several of these effects are thought to be mediated through the GLP-1 receptor, which is highly expressed in the pancreas [13]. GLP-1 receptor activation potentiates glucose-dependant insulin-secretion in β-cells and reduces endogenous production of glucose in the liver as a result of its inhibitory effect on glucagon secretion in α-cells [3]. In addition to its impact on pancreatic hormone secretion, GLP-1 promotes islet neogenesis and survival, which is also thought to further contribute to its role in improving β-cell function and glycemic control.

Once secreted, bioactive GLP-1 is rapidly inactivated by the ubiquitous enzyme dipeptidyl peptidase-IV (DPP-IV) [14]. Two major therapeutic strategies exist today, which have used this feature to exploit the beneficial properties of GLP-1 in type 2 diabetes. The first approach involves the use of more stable GLP-1 mimetics, e.g. exenatide (Eli Lilly Pharmaceuticals) and liraglutide (Novo Nordisk Pharmaceuticals), while the second one involves treatment with DPP-IV inhibitors, e.g. sitagliptin (Merck Pharmaceuticals), vildagliptin (Novartis Pharmaceuticals) and saxagliptin (AstraZeneca and Bristol-Meiers Squibb Pharmaceuticals), which stabilize the half-life of endogenous GLP-1. These compounds have been approved for clinical use and improve glycemic control in diabetics [1,2]. Due to the glucose-dependent nature of GLP-1 action, GLP-1-based therapies are associated with a very low incidence of hypoglycemia. In addition, they do not increase body weight [1,2]. As a consequence, a lot of efforts are currently ongoing to further develop this class of compounds, which seem to have important advantages over some other commonly used anti-diabetic drugs.

Activation of TGR5 as novel treatment strategy in type 2 diabetes

We described recently that TGR5 controls glucose homeostasis in obese and insulin resistant mice [5]. The beneficial effects of TGR5 on glucose homeostasis were explained by the observation that TGR5 induces secretion of GLP-1. In agreement with the report that TGR5 induces GLP-1 secretion in cultured mouse enterendocrine STC-1 cells [4], we showed that the TGR5-specific agonist INT-777 (6-ethyl-23(S)methyl-cholic acid) induces GLP-1 secretion in both STC-1 cells as well as in human enterendocrine NCI-H716 cells. Silencing of TGR5 in STC-1 cells using short hairpin RNA prevented the secretion of GLP-1, illustrating the involvement of TGR5 in this response. Although the mechanism underlying TGR5-induced GLP-1 secretion is not yet completely established, stimulation of oxidative phosphorylation is without any doubt one of the early events that triggers this process. It is hypothesized that the resulting increase in ATP/ADP ratio will subsequently induce membrane depolarization and Ca²⁺ mobilization in a way reminiscent to the cascade of events that precedes insulin release in β-cells [5].

Using obese and insulin resistant mouse models, we showed that mice with a gain-of function of TGR5 became more glucose tolerant, whereas TGR5-deficient mice showed a delayed glucose clearance compared to their wild-type littermates [5]. This effect was correlated with a healthier pancreatic islet phenotype. The observation that TGR5 improves glucose clearance is at least partly explained by the regulation of GLP-1 secretion by TGR5.

Apart from the improved glucose tolerance and insulin sensitivity, obese animals treated with INT-777 also showed a significant reduction in liver steatosis along with a decreased liver damage as measured by plasma liver enzymes LDH, ASAT and ALAT [5]. This was correlated with decreased plasma triglyceride and non-esterified fatty acid levels and indicates that activation of TGR5 also prevents complications of diabetes, like NAFLD. Interestingly, exendin-4 has been shown to reverse hepatic steatosis in obese leptin-deficient Ob/Ob mice, which suggest that GLP-1 is also beneficial in NAFLD [15]. It will be interestingly to determine to which extent the beneficial effect of TGR5 activation on fatty liver formation is mediated through GLP-1. Additionally, it will be relevant to study whether activation of TGR5 may prevent other complications of diabetes, like cardiovascular disease.

Future perspectives

Incretin-based therapies, like the GLP-1 mimetic exenatide, have been shown to improve glycemic control in diabetic subjects as measured by an improvement of HbA₁c levels [1]. A potential alternative GLP-1 based therapy could consist of increasing endogenous GLP-1 secretion. This approach could in combination with DPP-IV inhibitors even further elevate GLP-1 levels, thereby improving the efficacy of this treatment.

One promising drugable target to induce endogenous GLP-1 secretion is TGR5. As outlined in the previous paragraphs, TGR5 activation improves glycemic control in animal models of diabetes, which is at least partly mediated by GLP-1 secretion (See Fig. 1). Another GLP-1-independent beneficial effect of activation of TGR5 within the metabolic realm is increased energy expenditure through the stimulation of mitochondrial oxidative phosphorylation in brown adipose tissue and muscle [16]. The effects of TGR5 activation on energy expenditure are very robust and could through the reduction of fat accumulation contribute in a significant manner to the beneficial effects of TGR5 activation in the context of the metabolic syndrome.

Effort has been put in identifying novel agonists for TGR5, which has resulted in the identification of several novel compounds that enhance the activity of TGR5. Next to the identification of INT-777, the natural compounds oleandric acid, betulinic acid, bile alcohols, as well as certain steroid hormones were recently identified as TGR5 agonists [17—20]. Progress has also been made on the search for synthetic TGR5 agonists, as 3-aryl-4-isoxazolcarboxamides were recently identified to activate TGR5, and found to
induce GLP-1 secretion in canines [21]. Thus, the arsenal of TGR5 agonists is steadily increasing allowing the optimal exploration of the pharmacology of this fascinating GPCR. The ultimate goal will obviously be to use such compounds in the clinical management of metabolic diseases.

Another point worth mentioning is the fact that TGR5 increases GLP-1 levels and glycemic control in obese animal models fed a high-fat diet but not in normal chow-fed mice. It is intriguing to speculate that TGR5 synergizes with the fat-sensing GPCRs GPR40, GPR119, and GPR120, which are also described to regulate GLP-1 levels in enteroendocrine cells [22–24]. This could open interesting combinatorial approaches to increase GLP-1 levels.

Finally, activation of TGR5 may potentially also have unfavorable side effects. For example, TGR5 was suggested to be implicated in the development of cancer promoted by bile acids, although evidence of such an effect was only ascertained in cultured cells [25, 26]. In addition, it has been demonstrated that TGR5-deficient mice have reduced severity of tauroliothocholic acid 3-sulfate sodium salt (TLCS)-induced pancreatitis [27]. The effects of TGR5 on pancreatitis may, however, be related to the induction of GLP-1, as the GLP-1 mimetic exenatide also increases the risk for pancreatitis [28].

In summary, based on recent literature evidence, it is reasonable to propose that enhancing GLP-1 secretion via TGR5 may represent a promising treatment strategy, as stand-alone therapy or in combination with other anti-diabetic agents, to improve glycemic control in diabetic subjects as well as to prevent complications of diabetes, such as NAFLD.

### References


