Introduction

Bile acids (BAs) possess an amphipathic steroid molecule which may facilitate the intestinal absorption, emulsification, and transport of lipophilic nutrients and vitamins. BA is mainly derived from the catabolism of cholesterol in the liver. Recently, BA has been introduced as the endogenous molecules showing pleiotropic responses [1], including glucose and energy homeostasis [2]. Some BAs escape the enterohepatic cycling to reach the systemic circulation [3]. Thus, they participate the functional processes such as lipid and glucose homeostasis, energy expenditure, intestinal mobility, inflammation [4], configuration, and the growth of gut microbiome or the skeletal muscle mass [5]. Dysregulated signaling of BAs have been indicated to involve in some disorders, including diabetes, obesity, dyslipidemia, fatty liver disease, atherosclerosis, cholestasis, gallstones, and cancer [6]. Basically, these effects of BAs were known to binding with the nuclear hormone farnesoid X receptor (FXR) and Takeda G protein receptor 5 (TGR5) in multiple organs [7]. In clinics, treatment of T2DM patients with the BA-like agent(s), or bariatric surgery in obese patients, results in a marked improvement in glycemic control that seems related with the changes in TGR5 and signaling. Therefore, we focus on the role of TGR5 in glucose homeostasis.

TGR5 belonged to G protein – coupled receptor that expressed in many tissues such as intestine, gallbladder, adipose tissues, skeletal muscle, brain, and pancreas. Therefore, TGR5 activated by BA induces the formation of the cyclic AMP (cAMP), which may activate protein kinase A (PKA) in cells and tissues [8]. Tauro-lithocholic acid (TLCA), lithocholic acid (LCA), deoxycholic acid (DCA), chenodeoxycholic acid (CDCA), and cholic acid (CA) can dose-dependently induce cAMP production in human TGR5-transfected CHO cells. The rank order of potency (EC50) is TLCA (0.33 μM) >LCA (0.53 μM) >DCA (1.01 μM) >CDCA (4.43 μM) >CA (7.72 μM), as described previously [9]. However, CDCA, DCA, LCA, ursodeoxycholic acid (UDCA) may also activate FXR [10]. Otherwise, TGR5 is also activated by linolenic acid and oleanolic acid [11], in addition to ursolic acid [12] and glycyrrhizic acid [13]. Additionally, we demonstrated triamterene as the useful blocker of TGR5 [14].

Oral glucose administration induces a more pronounced insulin secretion than an isoglycemic intravenous injection. Therefore, entero-endocrine K- and L-cells are identified and known to secrete the incretins, both glucose-insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP)-1. After transcription and translation into proglucagon, the action of prohormone convertase 1/3 in L-cells leads to GLP-1, GLP-2, oxyntomodulin, and IP2, whereas the action of prohormone convertase 2 in pancreatic α-cells leads to glucagon, glicentin-related polypeptide, IP1 and major proglucagon fragment [15]. In blood, GLP-1 half-life is about 1·5–5 min due to a rapid degradation by dipeptidyl peptidase 4 (DPP-4). Thus, DPP-4 inhibitors are successfully used to treat type 2 diabetes (T2DM) patients now.
Activation of TGR5 promotes GLP-1 secretion from intestinal L cells due to a closure of the ATP-dependent potassium channel (KATP) and a higher mobilization of intracellular calcium to enhance GLP-1 secretion. Glucose also enhances GLP-1 biosynthesis and secretion. However, GLP-1 secretion by intestinal L cells is negatively regulated by FXR through inhibition of pro-glucaon gene expression and suppression of GLP-1 secretion through the interfering with pathways activated by glucose [16]. Therefore, BA activation of both TGR5 and FXR in intestinal L cells can induce opposite effects on GLP-1 secretion and production. However, TGR5 activation in L cells likely occurs rapidly after food ingestion, whereas activation of FXR induces a more delayed response that requires transcriptional activation. Otherwise, pancreatic β cells express both TGR5 [17] and FXR [18], promoting glucose-stimulated insulin secretion by increasing intracellular calcium concentration. In pancreatic islet, TGR5 is identified in pancreatic α cells. Activation of TGR5 switches the α cell secretory phenotype from glucagon to GLP-1, thus promoting a paracrine effect on β cells to stimulate insulin secretion [19].

T2DM is known as a heterogeneous group of disorders, characterized by a decline in insulin-producing pancreatic β cells, an increase in peripheral insulin resistance, an increase in hepatic glucose production, or a combination of all the factors [20]. Therapies for T2DM are mostly focused on the reducing of hepatic glucose production, increasing of insulin secretion, and improving insulin sensitivity [21]. TGR5 as a receptor of bile acids has an effect on the regulation of glucose homeostasis. Activation of TGR5 could promote GLP-1 secretion in a murine enteroendocrine cell line STC-1 [8].

GLP-1 has the ability to enhance insulin secretion after oral administration of glucose. It suggested the potential treatment of T2DM through the management of glucose homeostasis by activating TGR5. Additionally, TGR5 can induce cAMP-dependent thyroid hormone activating enzyme type 2 iodothyronine deiodinase, causing elevated energy expenditure in brown adipocytes and skeletal muscles [22]. TGR5 also induces differential translation of the C/EBPβ isoform by AKT-mTOR pathway in macrophages. Thus, activation of TGR5 can alter adipose tissue macrophage function to improve insulin action for treatment of T2DM [23]. Another mechanism possibly connecting TGR5 signaling and elevated energy expenditure via modifications in the gut microbiome [24]. Therefore, TGR5 activation for T2DM is not totally dependent on GLP-1 only. Moreover, TGR5 inhibits renal disease in obesity and diabetes through inducing mitochondrial biogenesis and preventing renal oxidative stress and lipid accumulation [25]. The new roles of TGR5 in obesity has also been documented [26].

Systemic exposure to TGR5 agonists increases gallbladder volume in mice [27]. Recently, an agonist of TGR5, FC-92-EC85, has been investigated in mice and dogs showing hepatobiliary and cardiovascular effects limit the utility of systemic TGR5 agonist in Diabetes [28]. a novel topical intestinal agonist of TGR5 that was given orally to obese and insulin-resistant mice, leading to a prominent elevation in GLP-1 levels along with significant improvement in glucose tolerance. Intestinal TGR5 agonist did not cause a significant change in gallbladder size in lean mice [29]. Thus, an ideal TGR5 agonist would be intestinal-specific agonist reaching L cells without affecting other systemic tissues [7]. However, the impact of the intestinal TGR5 agonist on human gallbladder remained unclear and the therapeutic potential for T2DM in the clinic needs to confirm in advance.

Conclusion

Decreased pruritus in cholestatic liver disease, improvement of insulin resistance in type 2 diabetes, protection against obesity, and inhibition of atheroma development have been suggested as the potential therapeutic targets of TGR5 agonist(s). However, it still remains in animal studies. Clinical trials are required to confirm whether the new semi-synthetic TGR5 agonists have clinical efficacy. Additionally, once the subtype TGR5 could be distinguished between the gallbladder and metabolic tissues, development of new agonist(s) would be easier in basic research.

Acknowledgement

We thank Miss Y.L. Yen for the kindly help in the collection of references.

References


This work is licensed under Creative Commons Attribution 4.0 License

DOI: 10.19080/CRDOJ.2018.09.555759