

Opinion

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GPR119 and GPR131: Functional Difference?



Yingxiao Li^{1,2}, Kai Chun Cheng¹ and Juei-Tang Cheng^{2,3*}

¹Department of Psychosomatic Internal Medicine, Kagoshima University Graduate School of Medical and Dental Sciences, Japan

²Department of Medical Research, Chi-Mei Medical Center, Taiwan

³Institute of Medical Science, Chang Jung Christian University, Taiwan

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***Corresponding author:** Juei-Tang Cheng, Institute of Medical Sciences, Chang Jung Christian University, Gueiren, Tainan City, Taiwan 71101, Taiwan, Tel: +886-6-251-7864; Fax +886-6-283-2639; Email: jtcheng@mail.cjcu.edu.tw

Abstract

Recently, two strategies are generally applied in clinical practice to treat diabetes, namely, glucagon like peptide-1 (GLP-1) analogs and inhibitors of the enzyme dipeptidylpeptidase-IV (DPP-4) that degrades both GLP-1 and glucose dependent insulin tropic polypeptide (GIP). Physiologically, after food ingestion, enteroendocrine cells in the intestinal mucosa may release the incretins, including GLP-1 and GIP, that can stimulate insulin secretion from endocrine pancreas and thereby decrease blood glucose. GLP-1 is produced and released mainly by L-cells located in the distal ileum while GIP is secreted by enteroendocrine K-cells in the proximal gut. However, GIP is not focused in clinics because diabetic patients are mostly GIP resistant. Therefore, development of agent(s) that may enhance GLP-1 pathway received increasing attentions in recent.

Many G protein-coupled receptors (GPCRs) expressed in pancreatic islet and GLP-1 is known to be released in response to activation of two GPCRs, GPCR119 (GPR119) and GPCR 131 (GPR131). Physiologically, GPR119 regulates fatty acid while GPR131 also named as TGR5 is mainly activated by bile acid. Both receptors possess the ability to induce GLP-1 secretion and alleviate diabetes and obesity in animal studies. Interestingly, both receptors coupled Gs protein to activate cAMP signaling pathway. However, many functional variations are observed between GPR119 and GPR131. Therefore, clarification of the difference may help the reduction of adverse effect(s) during development of agent(s).

Herein, we cited the published reports showing the effects of GPR119 or GPR131 activation to conduct the difference between them. Also, we mentioned our opinions to call the attention(s) for avoiding the possible side effects during activation of each receptor.

Keywords: GPR119; GPR131; GLP-1; Diabetes; Obesity

Introduction

Diabetes mellitus (DM) is known as metabolic disorders showing hyperglycemia and hyperlipidemia due to the dysfunction of pancreatic islets [1]. The prevalence of DM in clinics is markedly increased and it will reach approximately 439 million in 2030 [2]. Generally, DM is mentioned to include two main subtypes, Type 1 (Insulin dependent diabetes) and Type 2 (Non-insulin dependent diabetes) subtypes, in addition to others. Clinically, type 2 DM (T2DM) characterized by insulin resistance in addition to hyperglycemia and/or hyperlipidemia is widely considered as metabolic disorder [3]. Many factors, such as reduced insulin secretion from pancreatic dysfunction, inadequate hepatic glucose production and peripheral insulin resistance, are introduced to involve in the development of

T2DM [4]. Therefore, therapeutic approaches have been the hot projects to develop critically.

After food ingestion, enteroendocrine cells in the intestinal mucosa may release the hormones that can stimulate insulin secretion from endocrine pancreas and thereby lower blood glucose; known as incretin effect [5]. Two types of incretins were identified in human, including glucose dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1 (GLP-1). Physiologically, GLP-1 is produced and released mainly by L-cells located in the distal ileum while GIP is secreted by enteroendocrine K-cells in the proximal gut [6]. In recent, GLP-1 has become a new target for therapeutics of T2DM due to its insulinotropic activity [5]. However, GIP is not focused in clinics

because patients with T2DM are mostly GIP resistant [7]. Two strategies have then been applied in clinical practice to treat T2DM, namely, GLP-1 analogs and inhibitors of the enzyme dipeptidylpeptidase-IV (DPP-4) that degrades both GLP-1 and GIP [5]. However, clinical practice meets some limitations, such as GLP-1 analogs shall be treated by injection only, and the effectiveness of DPP-4 inhibitors is mild [8]. Therefore, development of agent(s) that may enhance GLP-1 pathway received increasing attentions in recent.

Many G protein-coupled receptors (GPCRs) expressed in pancreatic islet and GLP-1 is known to be released in response to activation of two GPCRs, GPCR119 (GPR119) and GPCR 131 (GPR131), in addition to others such as GPR40 and GPR120. All of these GPCRs with a similar genomic sequence were coupled to G-protein while Taq Man Gene Expression Assays showed GPR119, mouse- Mm00731497, rat - Rn01648212 and GPR131, mouse -Mm04212121, rat - Rn00710093 for gene expression [9].

The GPR119 receptor for regulation of fatty acid was described as a class 1 (rhodopsin-type) orphan G-protein-coupled receptor [10]. The oleoylethanolamide (OEA) is identified as a potential endogenous ligand for GPR119 receptor that has been suggested as novel target for treatment of diabetes and obesity [11]. Activation of GPR119 by agonists showed an elevation of cAMP levels to stimulate GLP-1 secretion from cells. Similarly, activation of GPR 131 can result in same changes. GPR131 also named as Takeda G-protein-coupled receptor 5 (TGR5) or G-protein-coupled bile acid receptor 1 (GPBAR1) to bind bile acid in main [12]. Activation of GPR131 (TGR5) receptor may also promote the secretion of GLP-1 [13]. Knockout of GPR131 (TGR5) decreases energy expenditure and elicits obesity in female mice [14]. Similar to GPR119, GPR131 (TGR5) is also suggested as an attractive target for the treatment of diabetes and obesity [15]. However, functional difference between GPR119 and GPR131 remained obscure.

In intestinal L-cells, both GPR119 and GPR131 participated in GLP-1 secretion through cAMP signaling pathway. Gene of GPR119 or GPR131 from L-cells can be identified in pancreatic α -cell line while GLP-1 secretion was stimulated by the activation of GPR131 (TGR5) but not by GPR119 [9]. Selective secretion of GLP-1 by GPR131 (TGR5) agonist for glucose homeostasis has also been demonstrated [16]. Merit of GPR131 (TGR5) activation from basic research to clinical applications has been summarized [17]. However, GPR131 (TGR5) agonist may cause gallbladder filling in mice [18] probably due to the co-released peptide YY (PYY) while GLP-1 and PYY have been shown to act synergistically to slow gastric emptying and inhibit food intake [19]. Interestingly, the recently developed new compound OL3 is a low-absorbed TGR5 agonist that lowers blood glucose without inducing gallbladder filling [20]. But, similar effect from GPR119 agonist is still not reported.

For obesity, GPR119 activation by agonist OEA showed the merits in reduction of feeding behavior [21]. Similar results were observed during activation of GPR131 [15]. The effect on obesity is easily to link with GLP-1 because GLP-1 is known to cause gastric deceleration and increase satiety [22]. However, it has been reported that OEA is able to suppress the food intake to a similar level in both wild-type and GPR119-knockout mice [23]. Additionally, homology clustering analysis showed the closest relatives of GPR119 to be the cannabinoid receptors [24]. Otherwise, GPR131 agonist bile acids induce energy expenditure by promoting intracellular thyroid hormone activation [25]. Therefore, treatment of obesity by GPR119 agonist seems not the same as that induced by GPR131 (TGR5) agonist.

High mRNA levels of GPR131 (TGR5) were detected in human many organs with a gene located on chromosome position 2q35 and the open reading frame of 993 base pairs, encoding 330 amino acids [26]. Recently, functions of GPR131 (TGR5) have been extended to more than the metabolic regulation and included the inflammatory response, cancer and liver regeneration Guo et al. [27]. Therefore, different to GPR119, the agonist(s) of GPR131 (TGR5) will be developed to involve in many functional regulations in the future.

Conclusion

GPR119 and GPR131 (TGR5) have been identified in metabolic regulation for a long time. However, both receptors possess different role in another functional regulation. Development of the ligand(s) both agonist(s) and/or antagonist(s) shall be concerned the difference to avoid the adverse effect(s).

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