Annals of Diabetes Research

Editorial
Published: 30 May, 2017

New Target(s) for Diabetes Treatment

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Abstract

In clinic, two strategies are widely applied to treat the diabetes, Glucagon-Like Peptide-1 (GLP-1) analogs and inhibitors of the enzyme Dipeptidylpeptidase-IV (DPP-4) that degrades both GLP-1 and Glucose-Dependent Insulinotropic Polypeptide (GIP). However, GIP is not focused in clinics because diabetic patients are mostly GIP resistant. Moreover, these strategies had limitations in clinical practice: GLP-1 analogs can only be administered by injection and the effectiveness of DPP-4 inhibitors is mild. Therefore, development of agent(s) that may enhance GLP-1 pathway received increasing attentions at first. Basically, GLP-1 is released in response to activation of two G protein-coupled receptors (GPCRs); GPCR119 (GPR119) and GPCR 131 (GPR131). As described in our recent report, functional effects were different between GPR119 and GPR131. Natural product(s) may activate it to induce GLP-1 secretion and alleviate diabetes in animal studies. However, adverse reaction due to activating GPRs has been conducted and limited it to develop in clinical application. Interestingly, agonist for GLP-1 receptor from natural product has been developed and geniposide has been introduced as the potential one. However, GLP-1 receptor is distributed widely around human body. Therefore, clarification of the role of each function may help the reduction of adverse effect(s) during development of agonist(s). Moreover, gut microbiome(s) also involved in the regulation of glucose homeostasis. It will be the new target in the development of agent(s) for therapeutics of diabetes in the future. Herein, we discussed the potential of new target(s) that could be considered in the development of therapeutics for diabetes from the bench to bedside. Also, we suggest the suitable target(s) to call the attention(s) for better treatment of diabetes.

Keywords: Diabetes; GLP-1; Receptor agonist; Microbiota; Natural products

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Received Date: *15 May 2017*
Accepted Date: *23 May 2017*
Published Date: *30 May 2017*

Citation:
Li Y, Cheng KC, Cheng J-T. New Target(s) for Diabetes Treatment. Ann Diabetes Res. 2017; 1(1): 1002.

Introduction

Diabetes mellitus (DM) is introduced as one of the metabolic disorders mainly due to pancreatic dysfunction [1]. The prevalence is known to be raised critically while DM patients will reach approximately 439 million during 2030 [2]. Clinically, type 2 DM (T2DM) showing Insulin Resistance (IR) in addition to hyperglycemia and/or hyperlipidemia has widely been identified [3]. DM is a progressive disorder due to many factors in the development of T2DM [4]. Thus, new therapeutic approaches are focused critically.

Recently, two types of incretins were suggested in human, including Glucose-Dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 (GLP-1). In clinic, GLP-1 has become a new target for therapeutics of T2DM due to its insulinotropic activity [5], but GIP is less targeted because patients with T2DM are mostly GIP resistant [6]. 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 [7]. Therefore, development of agent(s) that may enhance GLP-1 pathway received increasing attentions.

Firstly, GLP-1 is secreted in response to activation of two G Protein-Coupled Receptors (GPCRs), GPCR119 (GPR119) and GPCR 131 (GPR131), in addition to others including GPR40 and GPR120 as described in our recent report [8]. Basically, GPR119 receptor for regulation of fatty acid is mentioned as a class 1 (rhodopsin-type) orphan G-protein-coupled receptor [9]. Oleoylethanolamide (OEA) as the endogenous agonist for GPR119 receptor has been used to treat diabetes and obesity [10]. Similarly, activation of GPR 131 can also result in an elevation of cAMP to stimulate GLP-1 secretion. Before now, GPR131 has another name, such as Takeda G

Protein-Coupled Receptor 5 (TGR5) or G-Protein-Coupled Bile Acid Receptor 1 (GPBAR1), for binding with bile acid [11]. However, GPR131 (TGR5) agonist caused gallbladder filling in mice [12] and higher expression of GPR131 (TGR5) gene has been identified in tumor [13]. Moreover, functions of GPR131 (TGR5) were also conducted to involve in the inflammatory response, cancer and liver regeneration [14]. Therefore, the agonist(s) for GPR131 (TGR5) shall be developed carefully in the future.

Agonist for GLP-1 receptor has been developed and used in clinical practice while the efficacy and tolerability of approved agonists (exenatide, dulaglutide, liraglutide, lixisenatide, and albiglutide) were recently compared [15]. Agonists are effective as a second-line therapy in improving glycemic parameters in patients with T2D. Reductions in glycated hemoglobin from baseline with agonists tended to be greater or similar compared with insulin therapy. Agonists were consistently more effective in reducing body weight than most oral glucose-lowering drugs as described [15]. However, the peptidic exenatide and GLP-1 are not orally-active, non-peptidic agonists has been expected. The natural product geniposide has been documented to activate GLP-1 receptor in PC-12 cells [16]. Then, iridoid analogs (catalpol, genipin, genipin methyl ether, 1,10-anhydrogenipin, loganin, shanzhiside methylester and 8-O-acetyl shanzhiside methylester) were also identified as the agonist-like substances [17]. Moreover, these orally-available agonists showed the merit to penetrate the central nervous system for antinociception and neuroprotection. Later, non-peptide agonist WB4-24 has also been demonstrated for pain hypersensitivity including inflammatory nociception [18]. The activation of GLP-1 receptor by agonist leads to a wide range of biological actions in the pancreas, such as the stimulation of glucose-dependent insulin synthesis and secretion, the reduction of glucagon levels and marked changes in β-cell proliferation and apoptosis [5]. Therefore, the reduction in HbA1c with agonists tended to be similar or smaller compared with the reductions achieved with insulin therapy, with less hypoglycemia. Moreover, reducing weight is more effective than oral glucose-lowering therapies and insulin. Additionally, the agonists appeared to have favorable effects on cardiovascular risk factors such as blood pressure and lipid levels [15]. However, these merits were not demonstrated in natural product(s) showing agonist-like activities. Moreover, functions of GLP-1 receptor remain obscure. It seems possible to result as that in GPR131 (TGR5) showing many adverse effects more than metabolic regulation. Therefore, development of non-peptidic agonist(s) received increasing attentions. Mainly, using the experience in metformin that was derived from phenformin, a natural product, chemical modification of original form isolated from the natural product to be more effective and less toxic would be useful in clinical practice.

Otherwise, the gut microbiota was hypothesized to play a critical role in metabolic diseases, including T2DM [19]. Because most of the herbal products were usually orally administrated, the modulation of the herbal products on the intestine microbiota has been new mechanistic understanding of the herbal products in DM treatment. Herbal treatment conspicuously modulated gut microbial metabolism by degradation of choline into methylamines, together with a decrease in fasting blood sugar and an expansion of islets in STZ and high-fat-diet-induced diabetic rats [20]. Herbal mixture could modulate the composition of the intestinal microbiota during T2DM clinical treatment, especially enrich the quantity of beneficial bacteria such as *Faecalibacterium* spp., and it was found that structural alterations in the gut microbiota were associated with the anti-diabetic effects of herbal mixture [19]. The quality and quantity of *Lactobacillus* and *Bacteroides* genus were significantly increased with the increasing concentration of Polysaccharides of Corn Silk (POCS). The results indicated that POCS could restore the intestinal microbiota balance for the treatment of T2DM [21]. Moreover, *Akkermansia muciniphila* is highly abundant in the gut microbiota (possibility as a result of an ecological advantage) and represents 1% to 5% of all intestinal bacteria [22]. Oral administration of *A. muciniphila* to mice fed a High-Fat Diet (HFD) reverses HFD-induced obesity, blunts metabolic endotoxemia — that is, it reduces proinflammatory bacterial Lipopolysaccharides (LPSs) in the circulation — and alleviates insulin resistance [23] and cardio-metabolic complications [24]. Amuc_1100*, a thermo stable outer-membrane protein of *A. muciniphila*, can reproduce these beneficial effects [25]. However, we still lack the enough data to understand the effect of natural product(s) on microbiota for DM treatment. Therefore, it is a good target in the development of new agent(s) in the future.

In conclusion, we suggest two targets for development of new agent(s) in diabetes treatment. Basically, GLP-1 has been identified in metabolic regulation. However, functions of GLP-1 receptor remain unclear. Therefore, development of the ligand(s) both agonist(s) and/or antagonist(s) shall be careful to enhance the effectiveness and avoid the adverse effect(s). Moreover, gut microbiota is also a good target for development of the agent(s) to treat diabetes in the future.

Acknowledgement

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

Disclosure

The authors declare no conflict of interests in this work.

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