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Free fatty acid receptor 1 as a novel therapeutic target for type 2 diabetes mellitus-current status

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ABSTRACT

The incidence of type 2 diabetes mellitus (T2DM) has been on the increase in recent times. Although several oral treatments for T2DM are available, some of them have been found to elicit undesirable side effects. This therefore underscores the need for new treatment options with lesser side effects than the existing ones for people with T2DM. Free fatty acid receptor 1 (FFAR1), also known as GPR40, belongs to a class of G-protein coupled receptors that are encoded by FFAR1 genes in humans. It is expressed in the pancreatic β-cells and it is activated by medium- and long-chain saturated and unsaturated fatty acids. Thus it responds to endogenous medium and long chain unsaturated fatty acids, resulting in enhancement of insulin secretion during increased glucose levels. The glucose dependency of insulin secretion has made this receptor a very good target for developing therapies that could be efficacious with fewer side effects than the existing therapies for the treatment of T2DM. Given that tremendous efforts have been made in recent times in developing novel FFAR1 agonists with antidiabetic potentials, this article provides a current status of knowledge on the efforts made so far in developing novel FFAR1 agonists that would be of relevance in the management of T2DM.

1. Introduction

The incidence of type 2 diabetes mellitus (T2DM) has been on the increase, making it a serious health care problem. It was estimated that about 415 million adults were living with diabetes globally in 2015 [1]. Although several synthetic drugs such as sulfonylureas, biguanides, alpha-glucosidase inhibitors and others are currently being used for the treatment/management of T2DM, some of them have been associated with adverse effects such as hypoglycemia, liver damage, gastrointestinal symptoms, and weight gain. This therefore underscores the need for new and safer treatment options for T2DM.

Free fatty acids (FFAs), which are obtained from dietary fat or endogenous synthesis, function as nutrients and signaling molecules. Studies have shown that free fatty acid receptors 1–4 which are G-protein coupled receptors, bind free fatty acids and serve as receptors for these FFAs. Short chain FFAs (SCFAs) activate FFA receptors 2 and 3 (FFAR2 and FFAR3) while medium-chain and long-chain FFAs (MCFAs/LCFAs) activate FFA receptors 1 and 4 (FFAR1 and FFAR4) respectively [2,3].

The G protein-coupled receptor, GPR40 (also called FFAR1) responds to medium and long chain unsaturated fatty acids, resulting in increase of insulin secretion during elevated glucose levels. The glucose dependency of insulin secretion makes this receptor a very good target for developing therapies with little or no adverse effects that could be useful for the treatment of T2DM. Whereas the mechanism of action of FFAR1 was not completely understood until now, previous studies suggested that FFAR1 is predominantly coupled with the G protein α-subunits of the Gq family [4].

Because of the efficacy and lesser side effects associated with FFAR1 agonists compared with existing therapies (such as insulin and sulfonylureas) for the treatment/management of T2DM, efforts are on gear towards developing novel FFAR1 agonists. This article therefore provides detailed information on the progress made so far in this direction.

2. Methods

Literature search was carried out in several electronic data bases such as Pubmed, Google Scholar, Medline, Agora and Hinari from 1972 to 2017 to identify the current status of knowledge on the role of free fatty acid receptor 1 as therapeutic targets for type 2 diabetes mellitus. The search terms used were G protein–coupled receptors, Free fatty acid receptor 1, Free fatty acid receptor 1 agonists, Free fatty acid receptor 1

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agonists with antidiabetic potentials, Mechanisms of hypoglycemic actions of Free fatty acid receptor 1, Adverse effects associated with the use of Free fatty acid receptor 1 or the agonists in the treatment of diabetes mellitus, Free fatty acid receptor 1 agonists with antidiabetic potentials in different stages of preclinical and clinical trials, and current status of use of Free fatty acid receptor 1 agonists in the treatment of diabetes mellitus. The language of the search was English. The findings from these data bases are thus reported in this review.

3. G protein-coupled receptor

G protein–coupled receptors (GPRs) constitute a large protein family of receptors found in eukaryotes and animals, that detect molecules outside the cell and activate internal signal transduction pathways, leading to cellular responses. The ligands that bind and activate these receptors include light-sensitive compounds, odors, pheromones, hormones, and neurotransmitters, and they vary in size from small molecules to peptides to large proteins [5]. The two major signal transduction pathways that involve the GPRs are: the cAMP signal pathway and the phosphatidylinositol signal pathway [5]. They are made up of sub-units which when activated lead to signal transmission [3].

3.1. Classes of GPR

The human genome contains more than 800 GPRs which are divided into six classes: Class A (Rhodopsin-like), Class B (Secretin receptor family), Class C (Metabotropic glutamate/pheromone), Class D (Fungal mating pheromone receptors), Class E (Cyclic AMP receptors) and Class F (Frizzled/Smoothened) [3,5].

Recently, GPRs were found to be multiple cell surface receptors for FFAs [6].

GPR41 is expressed in the adipose tissue and the gastrointestinal tract. Short-chain FFAs induce leptin secretion from adipocytes by stimulating GPR41, which suggests that GPR41 regulates energy homeostasis.

GPR43 was reported to be detected in immune cells, adipocytes and the gastrointestinal tract. It has also been reported to contribute to inflammatory responses and metabolic homeostasis [7].

GPR120, which is mainly expressed in the intestine and macrophages, promotes glucagon-like peptide-1 (GLP-1) secretion from the intestine and represses macrophage-I induced inflammation.

GPR40 (FFAR1) was reported to be strongly expressed in the pancreatic β-cells, in the enteroendocrine cells of the gastrointestinal tract (where the incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are also expressed), the intestine and to a lesser extent in the brain [5,8,9]. It also mediates insulin secretion upon stimulation by medium- and long-chain FFAs [8]. It is a class A G-protein coupled receptor which in humans is encoded by the FFAR1 gene [5,9]. FFAR1 binds FFAs, acting as a nutrient sensor for regulating energy homeostasis [10,11].

Expression of FFAR1 is stimulated by glucose in the human islets. This occurs at the transcriptional level and involves glucose-stimulated binding of PDX-1 to the HR2 region. FFAR1 contains two sites (Thr215 and Ser298) that bear potential protein kinase C (PKC) phosphorylation and two putative N-glycosylation ones (Asn155 and Asn165). Furthermore, the anchored sites of fatty acids are determined in amino residues Arg183, Asn244 and Arg258 located close to the extracellular domains of TM5, 6 and 7 when FFAR1 is stimulated. In the resting state, the Arg183 and Arg258 residues consist of an ionic lock with 2 glutamate residues (Glu145 and Glu172) located in TM2. In the presence of ligands, however, the ionic lock is broken, and then Arg183 and Arg258 are anchored by fatty ligands. It has been proven that the Arg211His and Gly180Ser polymorphisms in the GPR40 gene are strongly linked to receptor functionality and insulin secretion [12].

3.2. Regulation of the FFAR1 gene

FFAR1 gene expression was shown to be reduced under glucolipotoxic conditions (a condition of toxicity to β-cells due to the deleterious effects of elevated glucose and fatty acid levels) in rats and in islets from T2DM patients while a rare mutation in the human FFAR1 gene was associated with weak lipid-mediated enhancement of glucose stimulated insulin secretion (GSIS) [7,13]. Bioinformatics analysis carried out showed that the intergenic region between CD22 and GPR40 contains three evolutionarily conserved regions (HR1–HR3). Conserved sequences commonly correspond to sequences of functional significance. Analysis of the chromatin structure of the locus using the enzyme DNase I, a tool commonly used to reveal regulatory regions in genetic loci, showed that the GPR40 region in β-cells is preferentially accessible to DNase I digestion. Functional characterization of the GPR40 promoter performed by gene assay revealed that the 5′-flanking region of the GPR40 gene is capable of directing transcriptional activity selectively in β-cells [14]. An important component of this is attributable to a strong β-cell-specific enhancer that maps to the conserved region HR2. These regions were shown to be capable of binding the β-cell-specific transcription factors PDX-1 (pancreatic duodenal homeobox-1) and BETA2 both *in vitro* and *in vivo* [15]. The HR2 region also contains a site for the signal transducer and activator of transcription (STAT) family of transcription factors. Over expression of STAT proteins in β-cells leads to activation of the GPR40 promoter [14].

4. Physiological role of ffar in mediating insulin secretion

Elevated plasma FFAs often co-exist with type 2 diabetes and obesity, and fatty acids play an important role in insulin secretory functions of beta cells. Furthermore, an increase in blood FFA concentration augments GSIS.

4.1. FFAR1 expression in pancreatic islet

Through the use of reverse-transcription polymerase chain reaction, immunohistochemistry, and *in situ* hybridization, FFAR1 was found to be expressed in insulin-producing pancreatic islet cells [5]. Furthermore, the expression level of FFAR1 in pancreatic islets was reported to be two to 100 times higher than that in whole pancreas [16–19].

The importance of FFAR1 in *β*-cell function was demonstrated by loss of function studies in cultured cells and in *in vivo* experiments. In the absence of FFAR1, LCFA dependent insulin secretion is severely reduced, implicating FFAR1 as an important mediator of the acute action of LCFA on *β*-cells [19]. In addition, mice that lacked FFAR1 were reported to show protection from a number of the harmful effects of long-term high-fat diet. This findings suggest that FFAR1 may be a mediator of lipid-dependent *β*-cell dysfunction, and therefore a potential link between obesity and T2DM [19].

4.2. Mechanism of insulin secretion by FFAR1

The mechanism by which medium to long chain fatty acids stimulate insulin release was found to be that these fatty acids stimulate FFAR1 which enhances glucose dependent secretion of insulin from the pancreas by affecting several signaling pathways inclusive of protein kinase C. Earlier studies carried out by Liou and colleagues [4], suggested that FFAR1 is predominantly coupled with the G protein α-subunits of the Gq family (Gαq). When a free fatty acid binds to the FFAR1, the membrane protein becomes activated [5]. This activation causes one of its subunits to dissociate from the receptor, which then activates phospholipase C (PLC) that is found in the cell membrane. PLC in turn hydrolyzes phosphatidylinositol 4, 5-bisphosphate (PIP 2) (which is also in the membrane) to diacyl glycerol (DAG) which stays in the membrane, and inositol 1, 4, 5-triphosphate (IP 3). IP 3 diffuses into the cytoplasm from the plasma membrane and binds to receptors

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