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Review

Free Fatty Acid Receptor 1: A New Drug Target for Type 2 Diabetes?

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ABSTRACT

Free fatty acid receptor 1/G-protein-coupled receptor 40 (FFA1/GPR40) is activated by medium- to long-chain fatty acids (FA) and preferentially expressed in pancreatic β-cells. GPR40 mediates the acute potentiating effect of FA on glucose-stimulated insulin secretion, but not their chronic deleterious effects. As such, GPR40 is being considered as a new therapeutic target to enhance insulin secretion in type 2 diabetes mellitus. A number of preclinical studies and recent phase 2 clinical trials support the beneficial effects of a GPR40 agonist in type 2 diabetes. Recent studies from our laboratory identified protein kinase D as a downstream target of GPR40, which regulates cortical actin remodelling and amplifies the second phase of insulin secretion in response to fatty acids. We have also observed that glucose regulates the expression of the gene encoding GPR40 via a transcriptional mechanism that involves O-GlcNAcylation of the transcription factor pancreas-duodenum homeobox-1 and requires activity of phosphatidylinositol-3-kinase. These recent studies provide important mechanistic information as GPR40 agonists are being developed as new type 2 diabetes drugs; however, many questions remain to be answered regarding the biology of this receptor and its potential role in tissues other than the β-cell.

Mots clés:
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RÉSUMÉ

Le récepteur couplé aux protéines G FFA1/GPR40 est activé par les acides gras (AG) à chaînes moyenne et longue, et est préférentiellement exprimé dans les cellules bêta-pancréatiques. GPR40 est responsable de l'effet potentialisateur des AG à court terme sur la sécrétion d'insuline en réponse au glucose, mais non de leurs effets délétères à long terme. À ce titre, GPR40 est considéré comme une nouvelle cible thérapeutique pour améliorer la sécrétion d'insuline dans le diabète de type 2. Plusieurs études précliniques et de récents essais cliniques de phase 2 corroborent les effets bénéfiques d'un agoniste de GPR40 sur l'homéostasie glycémique. De récentes études dans notre laboratoire ont identifié la protéine kinase D comme une cible intracellulaire activée en aval de GPR40, qui régule le remodelage de l'actine corticale et amplifie la seconde phase de sécrétion d'insuline en réponse aux AG. Nous avons également observé que le glucose régule l'expression du gène codant pour GPR40 par un mécanisme transcriptionnel qui implique la glycosylation du facteur de transcription PDX-1 et requiert l'activité de la phosphatidylinositol-3-kinase. Ces récentes études apportent des informations importantes quant aux mécanismes d'action de GPR40, tandis que des agonistes de ce récepteur sont en cours de développement pour le traitement du diabète de type 2. Cependant, plusieurs questions restent à explorer concernant la biologie de GPR40 et son rôle potentiel dans les tissus autres que la cellule bêta.

Introduction

Type 2 diabetes mellitus is a global public health crisis and is expected to affect over 550 million people worldwide in 2030. Type 2 diabetes occurs when pancreatic β-cells are unable to compensate for insulin resistance induced by environmental factors such as obesity. Thus, insulin secretory defects are an integral part of the

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pathogenesis of type 2 diabetes, and as such one of the therapeutic approaches to treat type 2 diabetes is aimed at enhancing insulin secretion from pancreatic β-cells. To avoid iatrogenic hypoglycemia, such drugs should only be effective when circulating glucose levels are elevated.

Long-chain fatty acids (FA) do not initiate insulin secretion at low or normal glucose levels, but strongly potentiate glucose-induced insulin secretion (GSIS). Identification of the G-protein coupled receptor (GPCR) free fatty acid receptor 1/G-protein-coupled receptor 40 (FFA1/GPR40) as a medium- to long-chain FA receptor predominantly expressed in β-cells (1–3) and that mediates in large part the potentiation of GSIS by FA (2,4,5) sparked tremendous interest in the potential of this receptor as a novel drug target for type 2 diabetes treatment. A number of GPR40 agonists are under development as type 2 diabetes drugs, including one that showed promising results in recent phase 2 clinical trials (6,7).

From GPR40 physiological studies to the development of new type 2 diabetes drugs

Several groups have investigated the role of GPR40 in β-cell function, and the results from these studies concur to show that GPR40 plays a key role in mediating the potentiation of GSIS by FA. In different lines of mice with whole-body deletion of the gene encoding GPR40 (GPR40$^{-/-}$), a strong reduction of the potentiation of GSIS in response to acute stimulation by Intralipid in vivo or to medium- to long-chain saturated and unsaturated FA in vitro was observed, without changes in GSIS itself or other apparent defects under unchallenged conditions (5,8–10). Similar effects were seen in insulin-secreting cell lines transfected with small interfering RNA (siRNA) (2,11,12) or antisense oligonucleotides (13) against GPR40. In line with these observations, GPR40 agonists mimic the acute effect of FA on insulin secretion (14), and GPR40 antagonists block FA potentiation of GSIS (15). Importantly, potentiation of GSIS by FA is not completely abolished in the absence of GPR40, and the residual effect of FA is likely mediated by their intracellular metabolism and the generation of lipid-derived signalling molecules (Fig. 1 and reviewed in Nolan et al [16]).

In contrast to their acute, stimulating effects on insulin secretion, prolonged exposure to elevated levels of FA impairs β-cell function in the presence of high glucose, a phenomenon referred to as glucolipotoxicity (reviewed in Poitout and Robertson [17]). The possibility that GPR40 might be implicated in the mechanisms of glucolipotoxicity raised concerns that chronic administration of a GPR40 agonist could have undesirable, deleterious effects on the β-cell. In support of this possibility, Steneberg et al (10) showed that deletion of GPR40 was protective against high-fat diet-induced insulin resistance and glucose intolerance. Conversely, transgenic overexpression of GPR40 under the pancreas-duodenum homeobox-1 (PDX-1) promoter in mice led to impaired insulin secretion and hyperglycemia (10). These results led the authors to conclude that chronic activation of GPR40 is detrimental to β-cell function. Several subsequent studies, however, came to a different conclusion. First, we and others have shown that other lines of GPR40$^{-/-}$ mice are not protected from high-fat diet-induced obesity and insulin resistance (9,18). Second, Nagasumi et al (19) observed that transgenic overexpression of GPR40 under the control of the insulin II promoter in mice increases insulin secretion and protects from high-fat diet-induced glucose intolerance. Third, the impairment of GSIS (5) and induction of apoptosis (12) after chronic exposure to FA in vitro is similar in islets isolated from GPR40$^{-/-}$ and wild-type (WT) mice. Fourth, administration of a GPR40 agonist improves glucose intolerance and increases insulin secretion in rodent models of type 2 diabetes (14,20) and, most importantly, significantly lowers glycated hemoglobin (A1C) levels in type 2 diabetes patients (6). Overall, although the reasons for these discrepancies remain unknown, the majority of studies concur to suggest that GPR40 is not implicated in the mechanisms of glucolipotoxicity and that stimulating GPR40 might represent a suitable therapeutic approach in type 2 diabetes. This is supported by genetic evidence in humans, in which two loss-of-function single nucleotide polymorphisms within the *GPR40* gene were shown to be associated with impairment of insulin secretion (21).

GPR40 agonists as new drug for type 2 diabetes

Based on the preclinical evidence summarized above, several pharmaceutical companies have initiated programs to develop

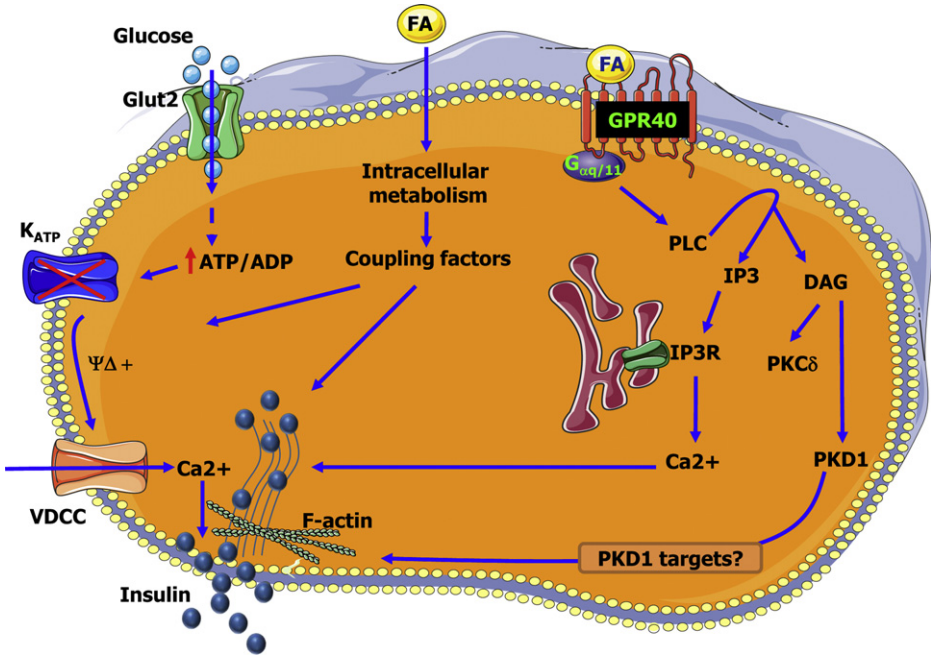

Figure 1. Model of GPR40-dependent and -independent potentiation of GSIS by FA.