

# GPR40 Modulators: New Kid on the Block

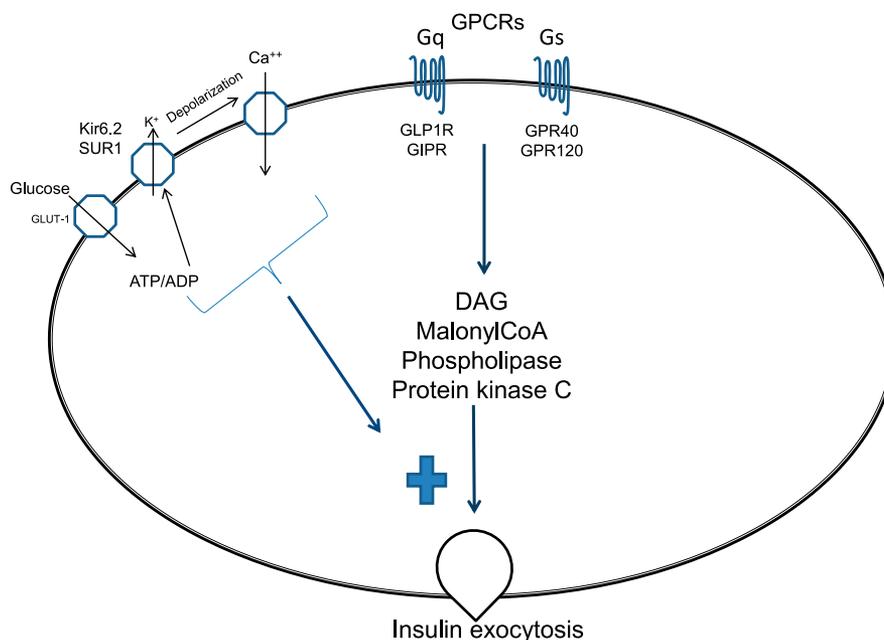
Impairments in insulin secretion and action are the pathophysiological hallmarks of type 2 diabetes (1,2). Pharmacological approaches to restore  $\beta$ -cell function have led to the use of insulin secretagogues that include sulphonylureas, glinides, and glucagon-like peptide-1–based therapies. Of these, the latter hold particular clinical advantage because glucagon-like peptide-1–modulated insulin secretion is glucose dependent (3,4), thereby minimizing the risk for hypoglycemia—the bane of clinicians managing diabetes across the world.

Fatty acids have long been known (5) to modulate human  $\beta$ -cell function. While acutely fatty acids amplify glucose-stimulated insulin secretion, chronic elevation of free fatty acid (FFA) levels has been thought to inhibit insulin secretion through the phenomenon of “lipotoxicity” (6,7). The cellular/molecular intermediates that are involved in this complex modulation, elegantly summarized in ref. 5, include malonyl CoA/long-chain acyl-CoA, triglyceride/FFA cycling through diacylglycerol, G-protein–coupled receptor 40 (GPR40) and phospholipase A2.

G-protein–coupled receptors have recently emerged as novel therapeutic targets because they appear to be closely involved in the pathology of various metabolic disorders including obesity, dyslipidemia, and type 2 diabetes (8). Since the seminal article (9) in 2003 about the role of GPR40 (also known as FFA1R: free fatty acid 1 receptor) in long-chain fatty acid–mediated glucose-stimulated insulin secretion from rodent and human  $\beta$ -cells, there have been over 60 publications investigating the properties and modulators of this receptor as yet another potential therapeutic approach for the management of type 2 diabetes. GPR40 is expressed most abundantly in humans in pancreatic  $\beta$ -cells and has also been found in the ileum and brain (9,10). It is a specific receptor for long-chain fatty acids unbound to albumin that induces glucose-stimulated insulin secretion through a calcium-dependent mechanism. Furthermore, there are tantalizing suggestions (8,11,12) that GPR agonists could regulate incretin secretion and thus further influence glucose-stimulated insulin secretion (Fig. 1).

This, however, remains to be proven in future investigations.

There have been uncertainties in pre-clinical studies as to whether a GPR40 antagonist/agonist should be developed for therapy of type 2 diabetes. An early study (13) demonstrated that while GPR40<sup>−/−</sup> mice on high-fat diet were protected from hyperinsulinemia, glucose intolerance, and hepatic steatosis, transgenic overexpression of GPR40 in  $\beta$ -cells in mice resulted in impaired  $\beta$ -cell function and diabetes. In contrast, Kebede et al. (14) showed that GPR40 knock-out mice on a C57/BL6 background developed fasting hyperglycemia and became as obese and glucose intolerant as their wild-type littermates when exposed to a high-fat diet. The field became even more confusing when Nagasumi et al. (15) demonstrated resistance to high-fat diet–induced glucose intolerance in transgenic mice on a C57/BL6 background overexpressing GPR40 in the pancreatic  $\beta$ -cells. Although it remains speculative, the apparent discrepancy could be explained, at least in part, by differences in the techniques used to generate the



**Figure 1**—A simplistic rendition of G-protein–coupled receptor (GPCR) modulation of glucose-stimulated insulin secretion in the  $\beta$ -cell. DAG, diacylglycerol; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP1R, glucagon-like peptide-1 receptor. (A high-quality color representation of this figure is available in the online issue.)



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