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 β-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 β-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 β-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 β-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 preclinical 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$^{-/-}$ mice on high-fat diet were protected from hyperinsulinemia, glucose intolerance, and hepatic steatosis, transgenic overexpression of GPR40 in β-cells in mice resulted in impaired β-cell function and diabetes. In contrast, Kebede et al. (14) showed that GPR40 knockout 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 β-cells. Although it remains speculative, the apparent discrepancy could be explained, at least in part, by differences in the techniques used to generate the

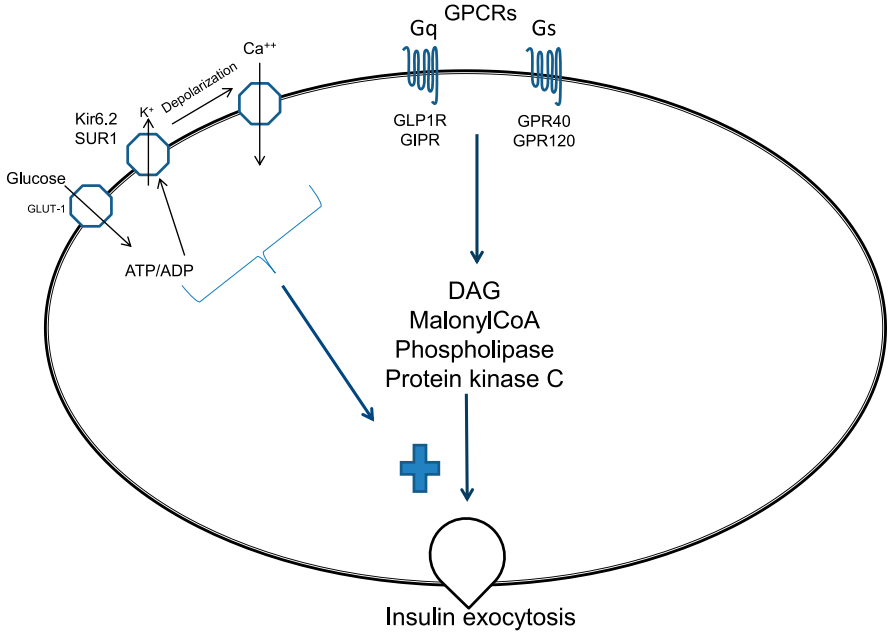

Figure 1—*A simplistic rendition of G-protein–coupled receptor (GPCR) modulation of glucose-stimulated insulin secretion in the β-cell. DAG, diacylglycerol; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP1R, glucagon-like peptide-1 receptor. (A high-quality color representation of this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

animals, genetic background of the mice used by each group, tissue expression based on the mouse line within each genetic manipulation experiment, etc.

The role of GPR40 in human diabetes was explored in a small study where variations in the coding region of GPR40 was not linked to type 2 diabetes or insulin secretion in response to an oral glucose challenge (16). However, in another study on human islets isolated from multiorgan donors, expression of GPR40 was found to be lower in islets from type 2 diabetes than control subjects (17), implying the possibility of involvement of this receptor in human type 2 diabetes.

Recent phase I studies in the U.S. of TAK-875, a GPR40 agonist, in individuals without (18) and with type 2 diabetes (19) demonstrated an elimination half-life of 28–36 h and substantial reductions in fasting and postoral glucose tolerance test glucose concentrations after once-daily oral dosing for 2 weeks. There was mild hypoglycemia in 2 out of 14 individuals with type 2 diabetes studied. Another recent phase II study (11) in the U.S. and Central America revealed up to 1% lowering of HbA_{1c} with 12 weeks of therapy with TAK-875 with rates of hypoglycemia similar to placebo and lower than glimepiride.

In an exploratory phase II randomized, double-blind, placebo-controlled, multicenter study (20) in Japanese patients with type 2 diabetes, 2 weeks of the same GPR40 agonist TAK-875 lowered postoral glucose tolerance test glucose concentrations while increasing insulin excursions. Fasting plasma glucose also decreased by 35–45 mg/dL with no episodes of hypoglycemia in 44 subjects who received 100 mg or 400 mg of the drug. Adverse events in which causality could not be ruled out included constipation, nausea, hematological changes, and flank pain.

The above study led to the current report (21) by the same investigators in which they studied TAK-875 (6.25–200 mg once daily) in a phase II, multicenter, randomized, double-blind, placebo-controlled, parallel-group, 12-week study with an open-label glimepiride arm. The study was conducted in lean patients with inadequately controlled type 2 diabetes (HbA_{1c} ~8.5%) on lifestyle management for their diabetes. Ninety-six percent of those enrolled completed the study, with adherence to protocol no different among study groups. There was dose-dependent lowering of HbA_{1c} with those receiving >50 mg/day of TAK-875 achieving reductions in HbA_{1c} similar to the glimepiride arm. Importantly, episodes of hypoglycemia were sixfold lower in the TAK-875 groups than in the glimepiride group, with no significant differences in adverse events among groups. The incidence of mild hypoglycemia in the TAK-875 groups was not dose dependent and did not result in drug withdrawal. However, the authors did not specify the definition of hypoglycemia in their report. Although multiple parameters of fasting and postoral glucose tolerance test glucose and hormonal excursions are reported, these changes need to be interpreted with caution, as sophisticated models and methods were not applied for precise estimation of insulin secretion and/or action. Importantly, there were no serious adverse events related to the drug. Other adverse events include nasopharyngitis, back pain, constipation, and headache.

It is noteworthy to recognize the fact that well within a decade of the initial discovery of the role of GPR40 on insulin secretion, phase II trials of GPR40 agonist have successfully been conducted in type 2 diabetes. This is a testament to the "crying need" for alternative and safe (especially from the standpoint of hypoglycemia) pharmacotherapy targeted to improve insulin secretion in these individuals. The significantly reduced episodes of hypoglycemia (compared with the sulphonylurea arm) in these trials is promising to the practicing clinician if and when these agents are approved for clinical use. The recent controversy and debate surrounding the safety of glucagon-like peptide-1–based approaches (22,23) underscore the need for novel agents that would stimulate insulin secretion without increasing the risk for hypoglycemia. Maybe GPR40 modulators will plug that gap if safety and efficacy profiles continue to be encouraging in future larger and longer-term clinical trials. Here's hoping for the best!

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