

## G-protein–coupled receptors in the pancreatic islets may be targets for treatment of type 2 diabetes

**It is known that islet dysfunction is the key to the pathophysiology of type 2 diabetes.<sup>1</sup> The islet defect is characterized by defective insulin secretion as regards the required demand caused by insulin resistance, inappropriately high glucagon secretion, and reduced  $\beta$ -cell mass.<sup>1-3</sup> For appropriate and pathophysiologically directed therapy, islet dysfunction is therefore a key target.**

Insulin and glucagon secretion are regulated by multiple mechanisms and factors. An important mechanism involves glucose, which stimulates insulin secretion and inhibits glucagon secretion. Several other factors affect these important actions of glucose, resulting in appropriate islet hormone secretion. During recent years, it has become evident that several factors affecting islet hormone secretion are in fact ligands for guanine nucleotide-binding protein (G-protein)–coupled receptors (GPCRs). These receptors are expressed in islet cells, and since they contribute to the regulation of islet function, they represent potential therapeutic targets.<sup>4</sup>

GPCRs are seven membrane–spanning receptors that couple through intracellular G-proteins, eliciting a response that may stimulate (Gs) or inhibit (Gi) formation of cyclic adenosine monophosphate (cAMP), thereby stimulating or inhibiting insulin secretion. Other GPCRs signal through Gq, which raises the intracellular calcium concentration. Several different GPCRs are expressed in islets.

Most important islet incretin hormone GPCRs are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic peptide (GIP) receptors. GLP-1 and GIP are gut incretin hormones, which are released into the circulation after meal ingestion, and which through incretin action, augment glucose-stimulated insulin secretion. They signal through Gs GPCRs, which increase the formation of cAMP in the islet  $\beta$ -cells, resulting in stimulated insulin secretion. The GLP-1 receptors have been particularly strong targets for therapy, since activation of these receptors also inhibits glucagon secretion, and at least in rodents, increases islet  $\beta$ -cell mass by inhibiting apoptosis.<sup>5</sup> Drugs based on GLP-1 are now on the market; these drugs are either GLP-1 receptor agonists or inhibitors of the enzyme dipeptidyl peptidase-4, the latter increasing the circulation of endogenously produced GLP-1. Both these strategies have been successful.<sup>5,6</sup> In contrast, the GIP receptor has not been so successful as a novel target, since the GIP receptor signal stimulates, rather than inhibits glucagon secretion, and GIP stimulation of insulin secretion is downregulated in type 2 diabetes.

Other islet GPCRs have lipid molecules as ligands. The most important of these are GPR40 (with fatty acids as ligands) and GPR119 (with lipid amides as ligands). They signal potentiation of glucose-stimulated insulin secretion, and are currently being explored as targets, in particular because GPR40 and GPR119 agonists also stimulate the release of GLP-1 from the gut.

Glucagon receptors, receptors for pituitary adenylate cyclase activating polypeptide and vasoactive intestinal polypeptide, neuropeptide Y receptors, ghrelin receptors, and GPR54 are islet pleiotropic GPCRs. They are mainly involved in paracrine, neural, or gastric regulation of islet function, and may stimulate or inhibit insulin secretion. Of particular interest is the neural regulation of islet function; the islets are densely innervated by autonomic nerves, which are involved in both the immediate islet hormone response to meal ingestion and the changes in islet hormone secretion during stress; the neurotransmitters in these responses are neuropeptides as well as classical neurotransmitters, and the signals are all transduced by GPCRs.<sup>7</sup>

Other islet GPCRs include adrenergic and melatonergic receptors (islet biogenic amine GPCRs), and muscarinic, endocannabinoid, and purinergic receptors. These are further away from being proven successful targets. The peptide, biogenic amine, and other GPCRs are also of potential interest as targets, although with a lower order of relative current pharmaceutical success compared with incretin hormone and lipid GPCRs.

**In conclusion, several different GPCRs are expressed in pancreatic islets. These are involved in the regulation of islet function, and they are also potential targets for treating the key islet defect in type 2 diabetes. Most successful so far in this respect is GLP-1–based therapy.**

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**References:**

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