

Editorial: *Molecular Endocrinology* Special Feature Minireviews for August 2013: GPCRs in Endocrine Physiology and Pathophysiology

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G protein-coupled receptors (GPCRs) are a large superfamily of plasma membrane receptors, which mediate a number of physiological regulatory mechanisms. They are also major drug targets used for a variety of diseases. Of particular importance to the field of endocrinology, GPCRs have recognized roles in the physiology, pathophysiology, and therapy of diabetes mellitus and metabolic syndrome. A GPCR forum held at ENDO2013 chaired by Agnes Schonbrunn, Deborah L. Segaloff, and Robert Peter Millar addressed this topic under the title, New light on GPCRs in the pathophysiology of diabetes and metabolic disorders. In this special issue, the editors of *Molecular Endocrinology* invited the speakers of this event to present their views and most recent results in this field.

Human pancreatic islets of Langerhans express a large number of GPCRs. Most of these receptors are present in insulin-producing β -cells, which is the main population of human islet cells. In these cells, as well as in other islet cells, GPCRs mediate sympathetic and parasympathetic actions and the effects of incretins, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide. However, the physiological and therapeutic relevance of the many GPCRs expressed in pancreatic islets are still unknown. GLP-1 mimetics are used successfully in the treatment of type 2 diabetes mellitus (T2DM), demonstrating the relevance of targeting specific GPCRs to the treatment of this disease. Therefore, GPCRs become a major target of drug development for antidiabetic therapy because they can increase insulin secretion, potentiate the effects of glucose, and increase β -cell mass by stimulating cell proliferation or decreasing apoptosis.

GLP-1 receptors are important targets for the therapy of T2DM. Patrick Sexton and colleagues describe the divergent effects of the responses of endogenous and exogenous GLP-1 receptor ligands on the function of the receptor. Their work suggests that naturally occurring polymorphisms of this receptor have the potential to produce differential responses to distinct GLP-1 receptor ligands. Furthermore, these findings reveal the importance of individualized therapy, which takes these variations into consideration.

Receptors for free fatty acids (FFAs) are either validated (FFA1) or potential (FFA2-FFA4) therapeutic targets for the treatment of T2DM and other diseases. Consistently, FFA1 receptors are highly expressed in pancreatic islets, whereas other FFA receptors are also expressed in this tissue. Graeme Milligan and his coworkers present data about the limitations of rodent models to study the human relevance of FFA receptors and demonstrate that their polymorphisms can have functional consequences. M3 muscarinic receptors are the major mediators of the effects of acetylcholine released during parasympathetic receptor on insulin and glucagon secretions.

Jürgen Wess and colleagues present their findings, which demonstrated physiological roles of M3 receptors in rodent models and present an innovative approach using an M3 receptor-based designer receptor, which enabled them to chronically activate in β -cells a Gq-coupled receptor by an otherwise pharmacologically inert drug. Their data show that chronic stimulation of this pathway protected mice against experimentally induced diabetes and glucose intolerance.

Ralph Jockers and his colleagues highlight the emerging relationship between defects in melatonin signaling/circadian rhythms and metabolic diseases, including T2DM. They use large-scale exon sequencing and show that functional and genetic associations between defective melatonin MT2 receptor signaling and T2DM risk provides a solid basis for the relationship between melatonin and T2DM in humans. They conclude that in the future defining the functional defects in carriers of rare MT2 receptor mutations can help to provide personalized therapies for these patients.

Ustione and his colleagues review the negative feedback role of dopamine in the regulation of insulin secretion. They report that L-DOPA, coming from the gut after a meal, can be converted to dopamine in β -cells and exerts an opposite effect on insulin secretion than incretins. This makes it a candidate antiincretin signal, which can con-

tribute to the positive effects of bariatric surgery on hyperglycemia.

Finally, Melanie Cobb and her coworkers highlight how the T1 receptor, a class C GPCR originally thought to be restricted to taste perception in gustatory neurons, can sense nutrients in many different tissues. Their data suggest that T1 receptor and other class C GPCRs have wider physiological roles than originally thought and present findings suggesting their possible function in metabolic regulation.

The papers presented in this special issue demonstrate the importance of targeting GPCRs for the treatment of other metabolic diseases, including T2DM.

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