A novel pharmacogenetic strategy to study the regulation of glucose and energy homeostasis by distinct GPCR signaling pathways

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Abstract

G protein-coupled receptors (GPCRs) play critical roles in maintaining proper glucose and energy homeostasis. During the past few years, clozapine-N-oxide (CNO)-sensitive designer GPCRs have emerged as valuable new tools to dissect the in vivo roles of distinct G protein signaling pathways in specific cell types or tissues. Structurally, these novel receptors (alternative name: designer receptors exclusively activated by designer drugs; DREADDs) are mutant muscarinic acetylcholine (ACh) receptors that are unable to bind the endogenous ligand, ACh. However, DREADDs can be activated by CNO with high potency and efficacy. Importantly, CNO is otherwise pharmacologically inert.

Seven transmembrane receptors (7TMRs), often termed G protein-coupled receptors (GPCRs), are the most common target of therapeutic drugs used today. Many studies suggest that distinct members of the GPCR superfamily represent potential targets for the treatment of various metabolic disorders including obesity and type 2 diabetes (T2D). GPCRs typically activate different classes of heterotrimeric G proteins, which can be subgrouped into four major functional types: Gαs, Gαi, Gαq/11, and G12/13, in response to agonist binding. Accumulating evidence suggests that GPCRs can also initiate β-arrestin-dependent, G protein-independent signaling. Thus, the physiological outcome of activating a certain GPCR in a particular tissue may also be modulated by β-arrestin-dependent, but G protein-independent signaling pathways. In this review, we will focus on the role of G protein- and β-arrestin-dependent signaling pathways in the development of obesity and T2D-related metabolic disorders.

Type 2 diabetes (T2D) is a complex, heterogeneous disease afflicting an increasing proportion of the population. In 2018, around 8.2% of the United States population had T2D (1). Insulin resistance is key to the pathogenesis of T2D, and obesity is the most common cause of insulin resistance in humans (2). As the worldwide prevalence of obesity is rising to epidemic proportions, a parallel epidemic of T2D is eminent (3). In most individuals, insulin resistance can be compensated by pancreatic β-cells through hyperinsulinemia. However, eventually β-cell dysfunction emerges and is characterized by a decrease in β-cell mass, as well as poor ability of β-cells to correctly secrete insulin in response to glucose. In this context, hyperinsulinemia is no longer able to compensate resulting in hyperglycemia and the development of T2D (2, 4, 5). Therefore, insulin resistance and lower insulin secretion are the two coexisting pathophysiological markers in most patients with T2D (2, 4, 5).

G protein-coupled receptors (GPCRs) regulate virtually all metabolic processes, including glucose and energy homeostasis. In this review, we focus on GPCRs that function in metabolic disorders, particularly in T2D and obesity-related diseases. Several endogenous ligands such as free fatty acids and their receptors (e.g., GPR40, GPR41, GPR43, GPR84, GPR119, and GPR120) have been extensively studied in the regulation of insulin secretion, insulin sensitization, β-cell expansion, and glucose homeostasis (Figure 1 and Table 1). Concomitantly, drugs that target these GPCRs in metabolic tissues have emerged as attractive T2D therapeutic targets as well (47). Thus, this review will discuss GPCRs and their signaling pathways (G protein-dependent and/or β-arrestin-dependent) that can be targeted pharmacologically to treat T2D by improving insulin sensitivity (Figures 1 and 2).

GPCRs are the most common target of therapeutic drugs today. These seven transmembrane receptors (7TMRs) are synthesized, folded, and assembled in the endoplasmic reticulum, packed in vesicles, and transported to the plasma membrane (48). Upon binding to its cognitive ligands, GPCRs undergo a conformational change, which is transmitted to the cytoplasmic portion to couple with a heterotrimer (α, β, and γ subunits) of GTP-binding protein (G proteins) (49). GPCRs typically couple into a specific G protein such as Gs, Gi, Gq/11, or G12/13. Coupling to Gs stimulates adenylate cyclase (AC) to increase cAMP levels, while coupling to Gi inhibits adenylate cyclase. Gq/11 activation simulates phospholipase C (PLC) to hydrolyze membrane phospholipids to release inositol 1,4,5,-triphosphate (IP3) and diacylglycerols (DAGs), which then leads to increased intracellular calcium concentrations. Gq/11 can also lead to PI3K and AKT activation (49–51).

Following G protein activation, a family of G protein-coupled receptor kinases (GRKs) can phosphorylate the cytoplasmic domain of the GPCR, which recruits β-arrestin adapter molecule. Once recruited to the GPCR, β-arrestin can facilitate internalization of the receptor or propagate a separate signaling cascade mediating distinct biological effects.

Biography

Jurgen Wess is the Chief of the Molecular Signaling Section, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH, Bethesda, Maryland, USA. He received his Ph.D. in Pharmacology from the Johann Wolfgang-Goethe University in Frankfurt/Main (Germany) and subsequently worked as a Postdoctoral Fellow at the National Institute of Mental Health (NIMH) and the National Institute of Neurological Disorders and Stroke (NINDS), NIH, Bethesda, Maryland, USA. One major focus of Dr. Wess' lab is to explore the roles of G protein-coupled receptors (GPCRs) in maintaining proper glucose and energy homeostasis.