

G protein-coupled receptor in hepatocytes

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G protein-coupled receptors (GPCRs) are cell surface receptors that mediate the function of extracellular ligands. Understanding how GPCRs work at the molecular level has important therapeutic implications, as 30-40% of the drugs currently in clinical use mediate therapeutic effects by acting on GPCRs. Like many other cell types, hepatocyte's function is regulated by GPCRs. A better understanding of the metabolic role of GPCRs in hepatocytes, the dominant constituent cells of the liver, could lead to the development of novel drugs that are clinically useful for the treatment of various metabolic diseases, including Type 2 diabetes, NAFLD, and NASH.

GPCR, Hepatocyte, Liver, NAFLD, Diabetes

1. Introduction

The liver is the crucial orchestrator of metabolism. In humans, approximately 11,000 genes are actively transcribed in hepatocytes, and many of them are related to the metabolic functions of the liver ^[1]. The liver mediates numerous physiological functions, including protein synthesis, macronutrient metabolism, cholesterol and lipid homeostasis, endocrine control of growth signaling pathways, and drug detoxification ^{[2][3][4][5][6]}. Metabolic hormones, nutrients, and sympathetic and parasympathetic neural signals tightly regulate liver function ^{[7][8]}. Alterations in these signaling pathways lead to the dysfunction of liver metabolism and can cause insulin resistance, type 2 diabetes (T2D), nonalcoholic fatty liver disease (NAFLD), nonalcoholic steatohepatitis (NASH), and cancer ^{[7][8][9]}. The liver consists of hepatocytes, biliary epithelial cells, stellate cells, smooth muscle cells, vascular endothelial cells, various immune cells, and sinusoidal endothelial cells ^{[10][11][12]}. Each of these cell types possesses a unique function and collectively regulates liver function at multiple levels. Hepatocytes are the primary cell type present in the liver and account for 80% of the liver cell population ^[12].

G protein-coupled receptors (GPCRs) are cell surface receptors and mediate the function of a vast number of extracellular ligands (neurotransmitters, hormones, etc.) ^{[13][14]}. Ligands-coupled GPCRs recognize and activate heterotrimeric G proteins, which comprise $G\alpha$, $G\beta$, and $G\gamma$. $G\alpha$ determines the functions of a G protein through the exchange of guanosine diphosphate (GDP) with guanosine triphosphate (GTP) ^[15]. The $G\beta$ and $G\gamma$ subunits are separately synthesized and form a complex to function as a single functional unit ^[16]. Both the $G\alpha$ and $G\beta\gamma$ subunits activate signaling molecules and trigger cellular responses. Based on their α subunit, G proteins are classified into four families: Gs, Gi, Gq, and G12/13 (Figure 1), where s and i represent stimulation and inhibition, respectively. Receptor-activated G proteins stimulate various downstream signaling pathways; for example, Gs and Gi proteins control adenylyl cyclase activity, Gq activates phospholipase C β , and G12/13 stimulates guanine nucleotide exchange factors for small GTPases of the Rho family ^{[17][18]}. The human genome contains about 800

different GPCR genes, which represent 3–4% of all human genes. Importantly, 30–40% of the drugs currently used in the clinic mediate their therapeutic effects via acting on GPCRs [13]. Understanding how GPCRs work at the molecular level is, therefore, of considerable therapeutic relevance.

Figure 1. G-proteins' classification and downstream signals.

2. Role of GPCRs in Liver Metabolism

2.1. Gs-Coupled GPCRs

The glucagon receptor (GCGR) is abundantly expressed by hepatocytes and is the most extensively studied Gs-coupled GPCR in the liver [19]. GCGR is activated by the 29 amino acid polypeptide glucagon, which is secreted by β cells of the endocrine pancreas, in particular during the fasted state or exercise [20]. The primary function of glucagon is to prevent hypoglycemia during fasting by increasing hepatic glucose production (HGP) from hepatocytes by stimulating both glycogenolysis and gluconeogenesis [21][22]. Activation of GCGR in hepatocytes results in increased intracellular cyclic adenosine monophosphate (cAMP) levels, followed by activation of protein

kinase A (PKA) and cAMP response element-binding (CREB) protein (Figure 2). Phosphorylated CREB (the active form of CREB) binds to CRE and increases the expression of essential gluconeogenic genes, including glucose 6-phosphatase (G6pc) and phosphoenolpyruvate carboxykinase (Pck1) [23]. The activated GCGR also stimulates Ca²⁺ release from the endoplasmic reticulum (ER) and activates calcium/calmodulin-dependent protein kinase II (CAMKII). This results in the translocation of FOXO1 to the nucleus that promotes the transcription of gluconeogenic genes [24]. In addition to transcriptional regulation of genes involved in glucose metabolism, GCGR activation also modulates the activity of enzymes involved in glucose metabolism via PKA-dependent phosphorylation. PKA phosphorylates phospho-fructokinase 2 (PFK-2), fructose 2,6-bisphosphatase (FBPase2), pyruvate kinase, and phosphorylase kinase. Phosphorylation of these enzymes increases HGP by increasing gluconeogenesis and glycogenolysis or by inhibiting glycolysis [25].

Figure 2. G protein-coupled receptors-mediated glycogenesis in hepatocytes.

2.2. Gi-Coupled GPCRs

GPCRs that preferentially couple to Gi proteins inhibit the function of adenylyl cyclase and thereby decrease intracellular cAMP. In a recent study, to understand the role of hepatic Gi signaling on whole-body glucose metabolism, Dr. Wess's group employed a chemo-genetic approach where a designer Gi-coupled receptor was

selectively expressed in mouse hepatocytes (Hep-GiD). This designer receptor can be selectively activated by clozapine-N-oxide (CNO), an otherwise chemically inert compound [26]. As activation of the Gs-coupled GCGR increases HGP, it was expected that activation of Gi in the liver would have opposite effects. Interestingly, activation of Gi signaling in hepatocytes also increased HGP by activating c-Jun N-terminal kinases (JNK) signaling [26]. Activation of Gi signaling in mouse liver impaired glucose tolerance and stimulated gluconeogenesis and glycogenolysis. Both in vivo and in vitro studies showed that enhanced Gi signaling in hepatocytes led to a JNK-dependent increase in the expression of *G6pc* (Figure 2). Similar results were obtained with the human hepatocytes. Activation of Gi signaling in the liver did not affect hepatic insulin signaling [26].

2.3. Gq-Coupled GPCRs

Stimulation of Gq signaling leads to the activation of phospholipase C β , followed by an increase in intracellular levels of inositol trisphosphate, diacylglycerol, and calcium (Figure 1). Further downstream effectors of the signaling pathway are dependent on the receptor and cell type. To understand the role of hepatic Gq signaling on glucose homeostasis, Dr. Wess's group expressed a Gq coupled, CNO-sensitive designer receptor selectively in mouse hepatocytes (Hep-GqD)[27]. Acute activation of this receptor with CNO increased blood glucose levels in a concentration-dependent manner. Hep-GqD mice showed impaired glucose and pyruvate tolerance. Impairments were predominately due to an increase in HGP [26]. Mechanistic studies confirmed an increase in the expression of various genes involved in gluconeogenesis and glycogenolysis. In particular, mRNA levels of *Pck1*, a rate-limiting enzyme of gluconeogenesis, were significantly increased (Figure 2). Similarly, the expression levels of genes involved in fatty acid syntheses such as *Acy1*, *Acc*, and *Fas* were also upregulated [26]. These data indicate that Gq signaling in hepatocytes plays a crucial role in glucose and lipid handling.

* The references listed here are based on the original article.

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