Effects of GPCRs on Type 2 Diabetes and Obesity

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Abstract. The escalating global prevalence of obesity and T2DM presents an increasingly grave challenge to humanity's well-being. These interconnected diseases demand urgent attention and innovative solutions. T2DM and obesity are deeply linked, and the GPCRs is significant in shaping the treatment landscape for both conditions. This article aims to undertaken with the primary goal of delving into the potential of GPCRs as a crucial avenue for addressing and treating obesity and diabetes more effectively. Among the array of GPCRs, GLP-1R emerges as a particularly pertinent player in this context. Presently, among the myriad therapies associated with GPCRs, GLP-1R agonists stand out as the most efficacious. These agonists demonstrate a distinct advantage over other anti-diabetic and anti-obesity medications. Their remarkable attributes include the absence of adverse effects, a diminished risk of hypoglycemia, and the capacity to increase insulin secretion in a way that depends on glucose. These qualities render GLP-1R agonists as a promising therapeutic approach. Furthermore, looking ahead, it is envisioned that GLP-1R agonist treatments will increasingly dominate the landscape of type 2 diabetes and obesity management. Their unique mechanisms and favorable outcomes suggest that GLP-1R agonists will likely emerge as the mainstream and preferred mode of addressing these widespread health concerns.

Keywords: Type 2 diabetes, Obesity, GPCRs, GLP-1R.

1. Introduction

Physical health is a life goal that is constantly concerned and discussed by all mankind. In the field of human diseases, T2DM and obesity have also attracted more and more attention, because these two diseases are extremely harmful to the human body and are accompanied by many complications. Diabetes affected 537 million persons globally in 2021. Diabetes and its complications killed about 6.7 million adults. Death from diabetes have one person every 5 seconds [1]. And 95% of people with diabetes is T2DM. Adult obesity prevalence grew from 30.5% to 42.4% between 2000 and 2018, and it causes many deaths in the United States [2]. In addition, the number of patients with obesity and diabetes has been on the rise in recent years. This means that more and more people will be exposed to the harms and impacts of obesity and diabetes. Therefore, how to effectively treat obesity and diabetes has become an important focus of social attention. At present, the major kind of therapy is metformin treatment for overweight or obese patients with type 2 diabetes. However, this treatment is a series of vice effect, has great limitations. Therefore, finding other effective treatment methods has become the focus of the treatment of obesity and diabetes. According to the studies that have been conducted, G protein coupled receptors (GPCRs) have been demonstrated to be crucial in the management of T2DM and obesity. In this paper, based on the existing data, GPCRs' significance in the management of diabetes and obesity is examined, and GPCRs' types, treatment methods, mechanism of action, advantages and prospects are described.

2. Diabetes and Obesity

2.1. Diabetes's Pathogenesis

A collection of metabolic illnesses known as diabetes are defined by glucose that develops as a result of deficiencies in insulin synthesis, activity, or both. Most cases of diabetes may be attributed to two primary etiopathogenetic groupings. Type 1 diabetes may be treated with injections of insulin

and has as its cause a complete absence of insulin production. Type 2 diabetes has an etiology that is combined with resistance to the action of insulin and an inadequate redeeming insulin response. T2DM has a more intricate etiology. It is generally known that T2DM is characterized by a deficient beta-cell reaction to the emergence of insulin resistance, which usually occurs with aging, inactivity, and weight increase [3]. The innate immune system is activated in T2DM and is mediated by cytokines [4]. This can provide new ideas to treat T2DM.

2.2. Pathogenesis of Obesity

Obesity is a term used to describe a level of overeating that is visible and a fat layer that is too thick. It specifically refers to a buildup of triglycerides that is the result of a situation. Excessive body fat buildup led to an abnormal increase in weight and causes physical and pathological alterations in one's body or latency because of excessive food intake or alterations in body metabolism. Unhealthy food and lifestyle choices are the main underlying causes of obesity, which is clearly a complex condition. It has been demonstrated that genetic variables can modify the phenotypic manifestation of obesity. In a limited proportion of cases, medications like steroids and endocrine conditions like hypothyroidism can also affect the normal physiology of weight regulation. The great majority of weight issues and obesity, however, are caused by an imbalance between energy intake and expenditure [5].

3. The Introduction of GPCRs

3.1. What is GPCRs

Most cell membrane receptors belong to the GPCRs' family. The human genome has 5% GPCRs genes. All seven of these receptors span seven membranes, albeit not all of them bind to G proteins, thus it's more convenient to call them GPCRs [6]. The peptide chain of G protein-coupled receptor is uniformly α-helical, with the N terminus bursting through the membrane and the C terminus bursting into it (Fig. 1). Notably, the most striking feature of GPCR is the complex transmembrane nature of its peptide chain, which zigzags across the cell membrane seven times to form seven α-helix bundles, which sometimes serve as ligand-binding domains. Three subunits, denoted by the letters, α, β and γ, make up a G protein.

Depending on the homology of the seven -helices imbedded in the cell membrane, GPCRs have been divided into five groups. GPCRs are categorized as rhodopsin (class A or one), adhesin (class B), secretin (still class B), glutamate (class C), and coiled-protein [7]. Class A is mostly odor receptors, about 400 of which are generally not used as drug targets. The N-terminal region of class B is particularly notable for having 120 amino acid molecules with two disulfide links. They often influence neuronal and endocrine signaling pathways since the only endogenous ligands they have are peptide hormones. Class B is a significant medicine target, especially for T2DM's treatment. Class C forces each other to exist as dimers, and their extracellular domains are broad. Such receptors are also considered effective drug targets for the central nervous system and obesity. coiled-protein receptors are rare and contain only coiled receptors and two taste receptors. The most prominent feature of these receptors is their unique Wnt signaling pathway [8].

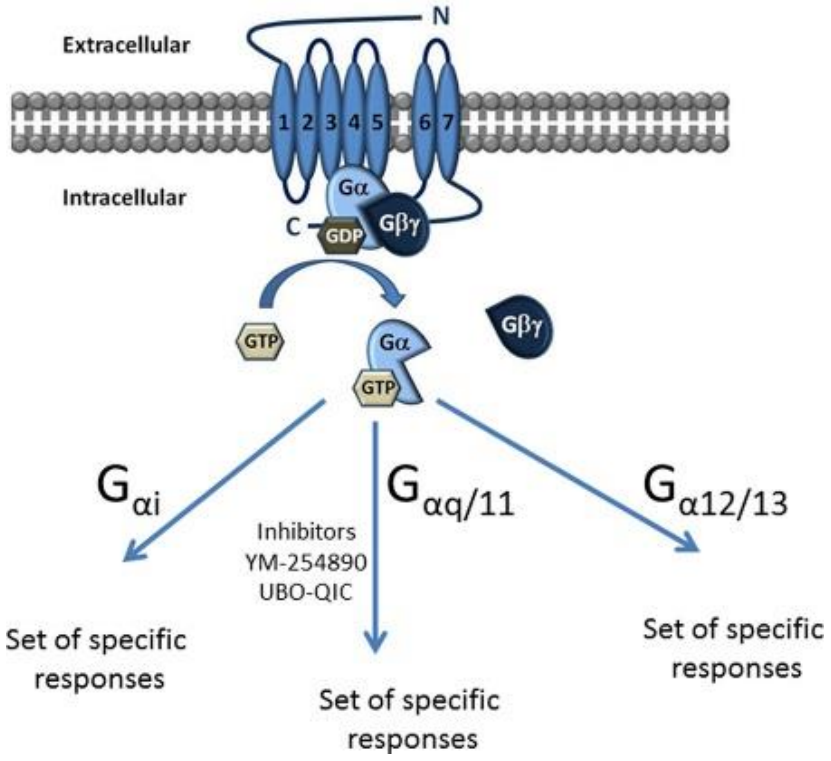

Figure 1. The GPCRs' structure [6]

3.2. Mechanism of Action of GPCRs

Numerous ligands can activate GPCRs, which then activate several downstream effector molecules by interacting with heterotrimeric G-proteins made up of three subunits (G, G, and G) (Fig. 2). Among other intracellular signaling mechanisms, G subunits may stimulate AC, cAMP, cAMP-regulated proteins such as PKA, and cyclic nucleotide-gated channels. Gi, Gq, Gs, and G12/13 are the four subfamilies into which they are separated. G-q can also activate PLC, which breaks down PIP2 into DAG as well as IP3. IP3 and DAG both can excite PKC and open a channel on the endoplasmic reticulum membrane. G-13 from the G12/13 family can activate the Rho guanine nucleotide transfer element, p115RhoGEF, along with other RhoGEF proteins linked to Rho activation more quickly. p120-caterin, cadherins, the Btk-family of tyrosine kinases, and Ras GTPase Activating Protein, and other proteins are known to interact with G-12. Additionally, G subunits can communicate with phospholipase C, voltage gated Ca^{2+} channels, and other molecules [9].

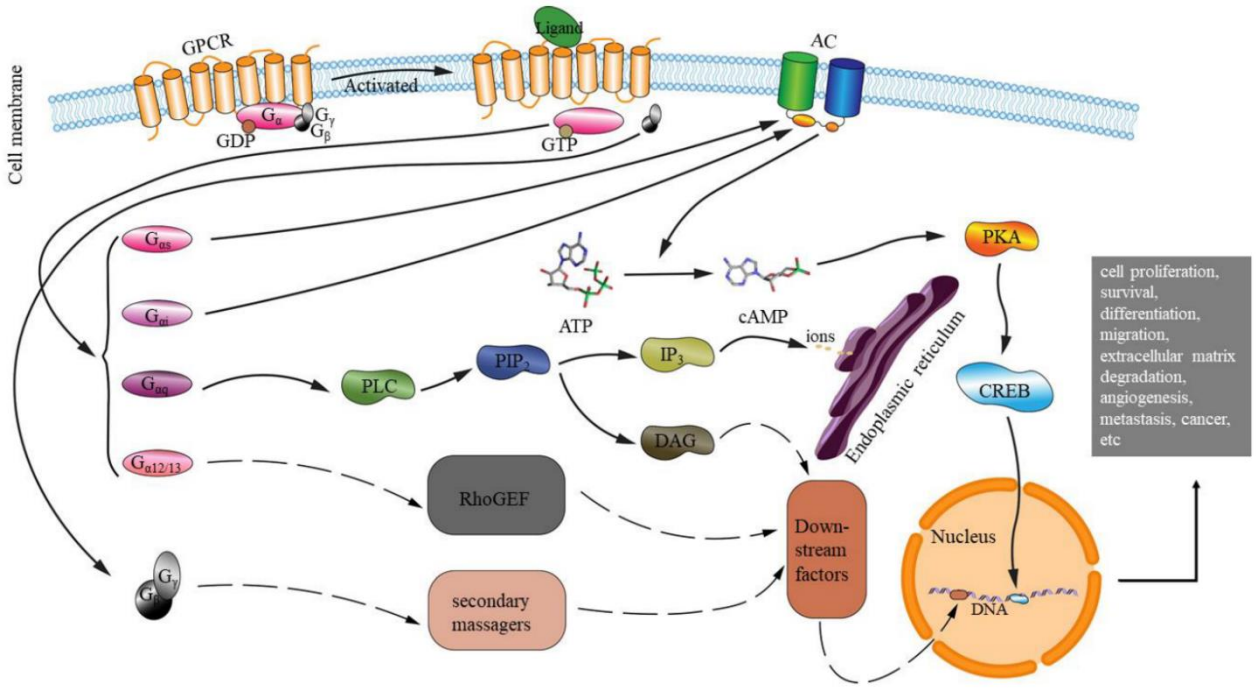

Figure 2. Locations of the regulatory pathways for GPCRs are shown graphically [9].

4. Introduction of the Application of GPCRs

4.1. Relevance Between Obesity and T2DM

Obesity and T2DM frequently combine; statistics reveal that 60 to 90 percent of those with T2DM are either obese now or had previously [10]. Insulin resistance is a side effect of increased lipid oxidation in obese individuals brought on by high plasma FFA levels. Because lipids are preferred as an energy source, muscle oxidation of glucose is persistently decreased, which restricts the usage of sugar from stored glycogen and prevents the glycogen synthase from working properly [11]. The increase in plasma levels of insulin and glucose following a meal counteracts this inhibitory impact [12]. Glycogen synthase activity may be hampered by the protracted decrease in glucose oxidation due to its preference for fats as a source of energy. This is because sugar from the stores of glycogen may not be able to be used as intended. The consequent increase in blood sugar and insulin levels cancels out this inhibition. Glycogen synthase activity may be hampered by the protracted decrease in glucose oxidation caused by the preference for lipids as an energy source. This is because glucose from the glycogen stores may not be able to be used as intended. The consequent increase in blood sugar and insulin levels cancels out this inhibition [10]. T2DM is the primary risk factor for obesity, hence treating T2DM and obesity follow the same principles.

4.2. GPCRs in the Therapy of Obesity and T2DM

Most of the molecules that signal outside the cell and biochemical pathways that are controlled depend heavily on GPCRs and GPCRs converse with one another to control glycemia in a balanced manner. This includes hormones and other extracellular signaling molecules. Here are some GPCRs and their effects. GLP-1R can enhance the release of insulin, reduce the release of glucagon, and clear the stomach. GIPR can weak rise in the production of insulin. GPR40 can both raise the levels of GLP-1 and insulin. GLP-1 is the reported endogenous ligands of GLP-1R. GPR120 can increase the release of GLP, decrease somatostatin production and emerge anti-inflammatory properties. GPR119 can decrease the production of GIP, GLP-1 and insulin. The best-characterized GPCR ligands for controlling blood sugar levels are the incretin hormones GLP-1, which work primarily by inducing glucose-dependent insulin release.

4.3. Mechanism of Action of GLP-1R Agonist

Glp-1 r belongs to a class B GPCRs family of 3 d across the membrane structure is a large structure of n-terminal domain with seven the alpha helix is made up of three cells and cell cycle, and the c terminal screw. The digestive tract primarily releases the incretin GLP-1 in response to meal consumption. Targeting merely pancreatic cells, with a higher level of GLP-1R in the pancreas endocrine/exocrine cells, acts by boosting insulin production that is dependent on glucose. This is true despite the fact that its pleiotropic, multi-tissue-involved, and highly reliant method of action. The heterotrimeric complex's G(s) protein component is activated when GLP-1 binds to its matching receptor. This stimulation of AC activity raises cAMP levels from ATP conversion. PKA and EPAC are both activated by rising cAMP levels. PKA stimulation prevents the voltage-gated potassium channel from opening, which delays membrane repolarization. Furthermore, PKA function leads on the phosphorylation of the enzyme's pathway goals, such as the SUR1 subunit of the KATP channel. This causes SUR1 to close, further depolarizing the cell membrane. Insulin secretion is ultimately triggered by the voltage-gated calcium channel opening as a result of membrane depolarization, which also increases Ca^{2+} inflow and, in turn, its cytoplasmic concentration [13].

4.4. Advantages of GLP-1R Agonist Over Other Treatment Modalities

Another small biological agonist GPR119 was unsuccessful and missed during the second stage of the clinical investigation, contradicting the encouraging findings from pre-clinical investigations [14]. Modern medications for diabetes promote insulin production, decrease kidneys glucose absorption, and boost the body's response to insulin. However, there are a few unfavorable side effects that these drugs might have, such as increased weight, stomach pain, swelling, an increased chance of broken bones, and hypoglycemia. The most effective, least expensive, and generally well tolerated treatment for T2DM is metformin, which increases the sensitivity of peripheral tissues to insulin. Yet, further insulin-lowering drugs are typically needed as T2DM proceeds gradually in order to keep safe levels of glucose in the blood [15]. In addition to lowering the chance of hypoglycemia, the agonists of GLP-1R also increase insulin production in a manner depending on glucose. To now, the agonists of GLP-1R are the sole drugs that reduce blood sugar levels while both acting as GPCR ligands. Because GLP-1 is physiologically quickly eliminated by DPP-4 and GLP-1R agonists imitate incretin, the concentration of GLP-1 is lowered in T2DM patients. According to the activities of these hormones, current therapies for T2DM offer a positive safety and effectiveness description, with extra-glycemic advantages [13].

5. Conclusion

Obesity and T2DM have a tight connection, which has great harm to human health. GPCRs play a significant role in the treatment of obesity and T2DM. GPCRs, as receptor proteins on the cell membrane, regulate various life activities and chemical reactions in cells. GLP-1R is one of a variety of GPCRs. The use of GIR-1R agonists is effective in the treatment of diabetes and obesity. Currently, GLP-1R agonists are the most effective of multiple therapies related to GPCRs. Compared with other anti-diabetic and anti-obesity drugs, GLP-1R agonists had no adverse effects, decreased the chance of hypoglycemia, and increased the production of insulin in a glucose-dependent way. With the advantages of better efficacy, lower cost, and longer duration of action, this treatment is bound to become the mainstream treatment for diabetes and obesity in the future.

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