REVIEW ARTICLE

Exploring the Therapeutic Promise of Free Fatty Acid Receptor 4 in Diabetes Mellitus: A Deep Dive into Molecular Mechanisms and Future Perspectives

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Abstract

Free fatty acid receptor 4 (FFA4) is encouraged by extended-chain fatty acids and has gained recognition as a promising agent for the treatment of diabetes mellitus (DM) treatment. Research indicates that FFA4 functions as a receptor for detecting unsaturated long-chain fatty acids, shedding light on the cellular pathways through which these fatty acids influence various biological functions. These mechanisms include the secretion of digestive tract peptide hormones and the control of glucose level. Activation of FFA4 is linked to enhanced insulin susceptibility and decreased release of glucagon-like peptide 1 from enteroendocrine cell types, making it an appealing target for developing therapies for overweight and diabetes. Agonists of FFA4 have demonstrated potential in enhancing satiety, stimulating incretin release, mitigating inflammatory metabolic responses, and boosting insulin sensitivity. As a result, drugs targeting FFA4 are anticipated to become available soon. This review explores FFA4's role in managing key metabolic processes, such as adipogenesis, lipid metabolism, and glucose regulation. It also assesses the potential of FFA4-based therapies for treating DM, emphasizing the progress and future directions in this evolving field of metabolic research.

Key words: Glucagon, glucose regulation, incretin, insulin sensitivity, lipid metabolism

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a long-term metabolic condition characterized by reduced insulin release, increased glucose generation in the liver and reduced glucose uptake in peripheral tissues. The pathophysiology of T2DM is complex, involving insulin unresponsiveness in fat tissue and the central nervous system, elevated glucagon levels, diminished incretin activity, increased renal glucose reabsorption, and other metabolic disturbances. Recent research has identified several new therapeutic targets currently in clinical development to address these challenges. These targets include agents aimed at improving insulin sensitivity, such as glucocorticoid receptor antagonists, as well as those focusing on reducing liver glucose output, such as antagonists of the glucagon receptor, inhibitors of glycogen phosphorylase, and inhibitors of fructose-1, 6-bisphosphatase.[1]

Conventional treatments for T2DM typically include biguanides, sulfonylureas, thiazolidinediones, and dipeptidyl

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peptidase-intravenous inhibitors. However, recent developments have brought new classes of medications, such as sodium-glucose co-transporter 2 inhibitors into use, which reduce blood glucose levels by reducing glucose reabsorption in the kidneys.[2] In addition, glucagon-like peptide-1 (GLP-1) receptor agonists, including exenatide, liraglutide, and lixisenatide, have been developed. These agents improve the activity of GLP-1, an intestinal hormone that is secreted in response to oral glucose. GLP-1 promotes insulin secretion and suppresses glucagon release, thus helping to control blood glucose levels.[3]

The FFA4 target is predominantly found in the lungs, fat tissue, and intestines; it interacts with long-chain lipids, particularly omega-3 fatty acids. Activation of FFA4 facilitates the movement of the glucose transporter across cellular compartments, leading to increased glucose uptake in 3T3-L1 adipocytes, which is crucial for energy metabolism. Chronic inflammation, a major contributor to insulin resistance, is closely associated with T2DM and obesity.[4]

This review examines the potential role of FFAR4 in managing metabolic disorders, highlighting how advancements in molecular pharmacology and innovative drug discovery methods can contribute to diabetes treatment. It underscores the importance of FFAR4 in developing new therapeutic strategies for more effective diabetes management.

FFAR4 AGONISTS: UNDERSTANDING SIGNALING PATHWAYS AND PHARMACOLOGICAL TOOLS THROUGH EXPERIMENTAL RESEARCH

Research has clarified the signaling pathways and pharmacological mechanisms of FFAR4 agonists, underscoring their potential as innovative therapeutic agents. Stimulation of FFAR4 leads to increased intracellular Ca^{2+} levels, implicating Gq and/or G11 G proteins and their association with phosphoinositide-specific phospholipase C. This was corroborated by findings showing that FFAR4 fails to induce inositol phosphate production or raise Ca^{2+} levels in HEK293 cells genetically modified to lack Gq and G11.[4] Furthermore, FFAR4's involvement in regulating ghrelin and somatostatin release suggests the engagement of Gi-family G proteins.[5,6] The receptor exhibits higher mRNA expression in pancreatic delta cells compared to beta cells, hinting at a possible therapeutic differentiation between Gq/11 and Gi-family G proteins.[7] In addition, FFAR4 activation by α-linolenic acid boosts GLP-1 and insulin production, presenting a promising strategy for enhancing glucose regulation and managing diabetes.[8]

Omega-3 fatty acids, acting through GPR120, decrease macrophage migration, resulting in fewer inflammatory macrophages in adipose tissue, as observed in genetically unmodified mice, but absent in GPR120-deficient mice.[9] This highlights GPR120's crucial role in mediating the anti-inflammatory properties and insulin-boosting properties of omega-3 fatty acids. Artificial targets such as GW9508 and TUG-891 have demonstrated high potency and selectivity for FFAR4, indicating their therapeutic potential for metabolic disorders.[10] In summary, FFAR4 agonists show promise for improving metabolic health by enhancing insulin secretion and reducing inflammation, making FFAR4 a promising agonist for managing hyperglycemia and obesity.

GPR120, found in tissues, such as the intestines, adipose tissue, liver, and the beta cells of the pancreas exerts a critical role in modulating metabolic processes. Activation of GPR120 enhances glucose utilization by activating the secretion of pancreatic protein -1 or GLP-1, which improves insulin sensitivity, influences anti-inflammatory pathways, and directly affects insulin signaling.[11] GLP-1, produced by enteroendocrine L-cells in response to food consumption, enhances insulin release, reduces glucagon secretion, delays gastric emptying, and induces feelings of fullness.[12]

THE ACTION OF FFAR4 ON ISLET FUNCTION IN THE PANCREATIC LANGERHANS ISLETS

GPR 120 is activated by dietary omega-3 fatty acids, particularly docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which activate intracellular signaling pathways that raise calcium levels and cause GLP-1 to discharge.[10] Research that has been performed in both *in vivo* and *in vitro* has corroborated this process, revealing that this activation substantially boosts the production of GLP-1 and the release of insulin. GLP-1 facilitates glucose-dependent insulin release, mitigates the risk of hypoglycemia, inhibits glucagon release, and reduces hepatic glucose production. Furthermore, GLP-1 improves insulin sensitivity and general metabolic wellness by promoting satiety and slowing down gastric emptying, which reduces food intake and leads to weight loss.[11,12]

Despite these encouraging preclinical results, translating FFAR4 activation benefits into clinical therapies faces several challenges. Developing effective FFAR4-based treatments involves addressing the complexities of human metabolism, potential off-target effects, and differences between species. Thorough clinical validation is required to guarantee the efficacy and long-term reliability of FFAR4 agonists.[9] In conclusion, while FFAR4 activation shows potential for treating metabolic disorders by enhancing GLP-1 secretion, improving insulin sensitivity, and offering anti-inflammatory effects, additional research is crucial to create effective and safe clinical therapies.

INVESTIGATING FFAR4 AS AN INNOVATIVE TARGET FOR DEVELOPING ANTI-DIABETIC MEDICATIONS

G-protein-coupled receptors (GPCRs) are known to interact with FFAs as their ligands, forming the largest family of human proteins, characterized by seven transmembrane helical segments joined by loops within and outside the cell.[13] FFA-activated GPCRs have drawn interest as possible targets for pharmaceutical development. GPR41 and GPR43 react to short-chain fatty acids, while GPR40 and GPR120 are especially engaged by small and long-chain fatty acids.[14]

GPR40, primarily expressed in β-cells of the pancreas exhibits a significant role in promoting insulin secretion. Various ligands targeting GPR40 have shown potential not only as antidiabetic agents but also for their wound-healing properties.[15] On the other hand, although they have been found in microglia, neurones, different malignancies, and inflammatory situations, GPR41 and GPR43 are less well characterized. Extensive research on GPR120 since its deorphanization has demonstrated that FFAs can enhance incretin secretion through this receptor.[16] Current studies emphasize GPR120's involvement in an array of ailments, such as cancer, inflammation, neuroprotection, additionally to T2DM. From a medicinal chemistry perspective, research focuses on the interconnections among structure and function of GPR120 agonists and their potential in managing T2DM, with valuable insights drawn from patent literature.[10]

STRUCTURAL FEATURES, PHARMACOLOGICAL CHARACTERISTICS, AND TISSUE LOCALIZATION OF GPR120

Human GPR120, a significant GPCR situated on chromosome 10q23.33, is characterized by its seven transmembrane domains (TMDs 1–7). Critical active sites for agonist binding and receptor activation include arginine at position 99 in the TMD2 and arginine at position 178 in the TMD4. The primary endogenous ligands for GPR120 are polyunsaturated fatty acids, including linoleic acid and DHA.[17]

GPR120 exists in two alternatively spliced forms: Showing 377 amino acids in the larger isoform (GPR120L) and 361 amino acids in the shorter version. The major distinction among these isoforms is a 16-amino-acid segment in the third cytoplasmic circuit of GPR120L, which affects their signaling characteristics. GPR120S engages with both Gq/G11 and β-arrestin pathways, facilitating Ca^{2+} mobilization, while GPR120L primarily activates the β-arrestin pathway without interacting with Gq/G11. GPR120S signaling involves inositol triphosphate inhibitors and is associated with Ca^{2+} signaling through Gαq/11 [Figure 1].[14]

Both isoforms can recruit β-arrestin proteins, leading to receptor internalization and degradation. They also exhibit accelerated phosphorylation of ERK1/2 through Gαq/11 signaling, resulting in the transformation of the protein for epidermal growth factor. Agonist binding triggers significant receptor internalization through β-arrestin interaction, involving phosphorylation at the cytoplasmic C-terminal component of the receptor includes serine and threonine residues.[17] This phosphorylation, particularly at clusters 1 (Thr347, Thr349, Ser350) and 2 (Ser357, Ser361), regulates β-arrestin 2 recruitment, receptor endocytosis, and Akt phosphorylation.[18]

NEGATIVE FEEDBACK REGULATION OF LIPOLYSIS AND ADIPOGENESIS THROUGH FFAR4 ACTIVATION

Extensive research underscores the critical role of FFAR4 in regulating adipocyte metabolism. FFAR4 is prominently expressed in different types of adipose tissues, including brown (BAT) and white (WAT) fat tissues, with its expression increasing during adipocyte differentiation. This receptor is also implicated in lipid droplet formation. Knockdown of FFAR4 using small interfering RNA has been shown to halt both the differentiation of adipocytes and lipoprotein build-up in 3T3-L1 cells. Conversely, activating FFAR4 with alpha-linolenic acid promotes the proliferation of fat cells 3T3-L1.[19]

Beyond its role in adipocyte metabolism, FFAR4 is crucial in regulating thermogenesis. It is notably expressed in BAT and its expression increases in mice's response to their exposure to cold. Initiation of FFAR4 by enhancing the quantities of BAT-specific proteins such as UCP1 to encourage the process of thermogenesis.[20] In addition, FFAR4 activation facilitates fatty acid absorption and metabolism, modifies mitochondrial respiration, and reduces adipose tissue mass in BAT. These effects are thought to result from FFAR4-mediated stimulation of Gq/11, which leads to increased calcium (Ca^{2+}) accumulation [Figure 2].[6]

FFAR4 also exerts a significant part in regulating lipolysis and insulin signaling. It improves glucose uptake by promoting the activation and translocation of GLUT4, which is the transporter of glucose to the cell membrane in adipocytes and 3T3-L1 cells. Disruption of FFAR4 results in decreased GLUT4 and IRS-1 expression, highlighting its role in insulin-stimulated glucose uptake. Studies comparing wild-type (WT) mice with FFAR4 knockout (KO) mice have shown that FFAR4 activation by omega-3 fatty acids enhances glucose uptake and insulin effectiveness in muscle and liver tissues.[21] Furthermore, FFAR4 regulates lipolysis, with FFAR4 agonist compound B reducing plasma FFAs and glycerol levels without affecting plasma insulin levels. Experiments demonstrating that compound B reduce glycerol flow from adipocytes in WT mice but not in FFAR4 KO mice provide additional evidence for this action. Recent research

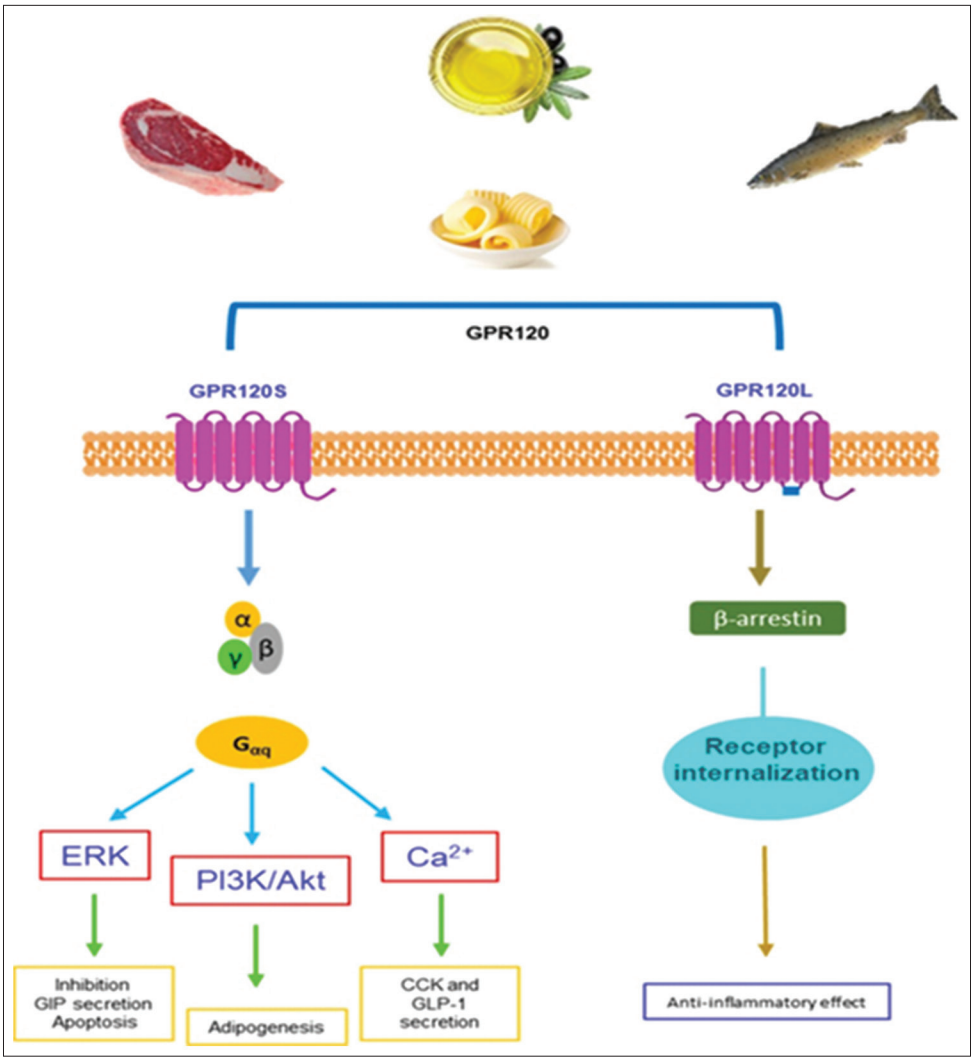

Figure 1: Mechanisms and pharmacological impact of GPR120: Insights and implications

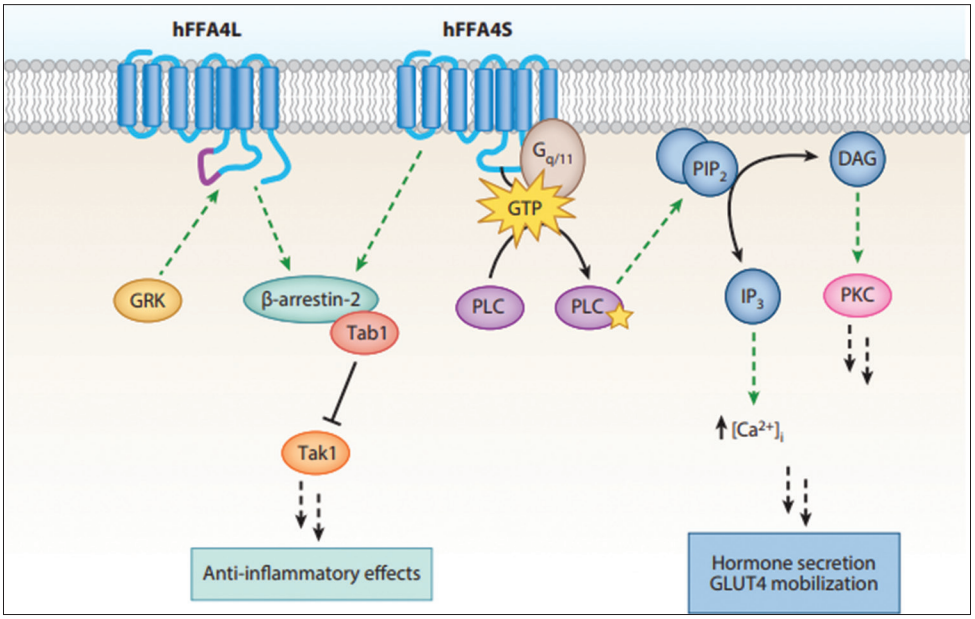

Figure 2: Human free fatty acid receptor 4 (hFFA4) is found in two isoforms: hFFA4S and hFFA4L. The former disturbs G protein signaling, while the latter activates β-arrestin-2 to produce anti-inflammatory effects, regulate hormone production, and control GLUT4 translocation through Gq/11 signaling and calcium mobilization

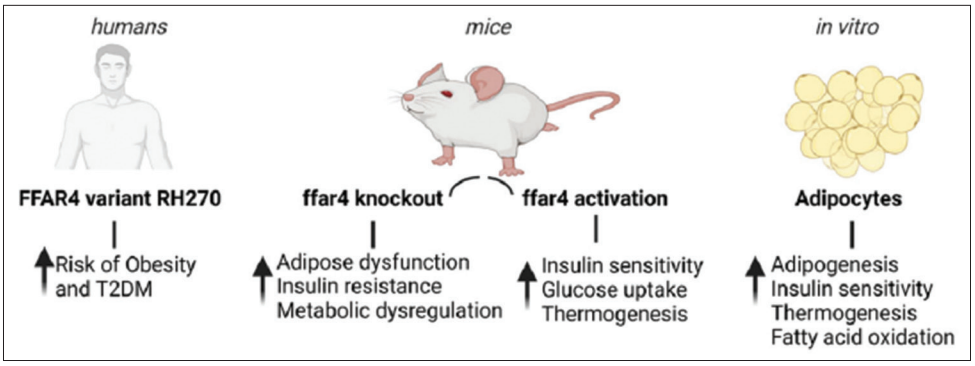

Figure 3: The function of free fatty acid receptor 4 in the metabolism of adipose tissue: Evidence from *in vitro*, human, and animal studies

indicates that FFAs released during adipocyte generation limit further lipolysis, with FFAR4's interaction with Gi/o being crucial for regulating this process.[22]

GPR120 DEFICIENCY AND REDUCED GLUCAGON SECRETION

GPR120 is particularly apparent in the colon, adipose tissue, and pituitary gland, but its presence in pancreatic islets is less well studied. Saturated fatty acids, such as palmitic acid and unsaturated fatty acids include DHA both stimulate GPR120. Research has shown that GPR120 KO islets have significantly reduced glucagon production in response to both palmitate and DHA. Notably, GPR40 KO mice also exhibit decreased glucagon release in reaction to fatty acids having long chain.[23]

Alpha-linolenic acid, an unsaturated long-chain fatty acid, stimulates the colon's production of GLP-1, which is how GPR120 was originally discovered.[24] In preclinical investigations, the incretin hormone GLP-1 promotes insulin production and supports cell survival and proliferation.[25] GPR120's function in lowering inflammation and easing insulin resistance in diet-induced diabetes models has also been linked to the impact of omega-3 fatty acids by recent studies.[8]

In mice, the absence of GPR120 results in glucose intolerance and obesity. Similarly, an increased incidence of obesity in European populations has been linked to genetic changes that affect GPR120 signaling.[26] Reduced GPR120 expression in human islets is linked to higher HbA1c levels, indicating poor long-term glucose control[13] based on these results, GPR120 agonists may enhance insulin sensitivity and cellular performance, as well as contribute to weight loss, making GPR120 a promising target for metabolic disease treatments [Figure 3].

TARGETING FFAR4 FOR OBESITY AND TYPE 2 DIABETES MANAGEMENT

Gustatory receptors, phagocytes, and lipocytes exhibit FFAR4, which binds with intermediate to long-chain lipids, such as omega-3 fatty acids. It plays a crucial part in insulin signaling, perception of taste, and inflammation reduction. Its presence in adipose tissue and macrophages highlights its importance in metabolic regulation. Activation of FFAR4 by omega-3 fatty acids, such as GW-9508, stimulates the adipocytes' phosphatidylinositol-4,5-bisphosphate 3-kinase resulting in increased glucose absorption and GLUT4 translocation to the cell membranes.[8]

In phagocytes, FFAR4 activation reduces pro-inflammatory responses triggered by lipopolysaccharide and tumor necrosis factor-α, leading to increased cytokines associated with the M2 macrophage phenotype and reduced M1 cytokine secretion. While another study showed that DHA could boost prostaglandin E2 (PGE2) production, Liu *et al*. stated that FFAR4 activation by DHA lowered COX-2 levels and PGE2 in RAW264.7 macrophages. Despite these conflicting results, both studies suggest a shift toward an M2 macrophage phenotype, characterized by reduced levels of pro-inflammatory cytokines, such as interleukin-6.[27]

FFAR4 is also present in the intestinal tract, where it stimulates GLP-1 release from enteroendocrine cells, similar to FFAR1.[10] In addition, FFAR4 is associated with anti-diabetic effects, reducing chronic inflammation linked to diabetes through its role in macrophages. In adipocytes, FFAR4 activation enhances glucose uptake, while in macrophages, in response to DHA, GW9508, and EPA, it lowers M1-linked cytokines.[13] Although FFAR4 is expressed at lower levels in the pancreas compared to FFAR1, its activation in pancreatic delta cells stimulates somatostatin production.[6] In addition, FFAR4 promotes the production of GLP-1 and serves an essential part in the secretion of gastric inhibitory peptide (GIP) by enteroendocrine K-cells. Considering FFAR4-deficient animals to WT mice, the GIP secretion after fat consumption was 75% lower in the latter group.[20]

CONCLUSION

FAR4 plays a crucial role in modulating metabolic processes, significantly influencing GLP-1 secretion and

insulin sensitivity through multiple pathways. The activation of FFAR4 by intestinal L-cells release GLP-1 in anticipation of long-chain FFAs, it thus slows stomach emptying, enhances perceptions of fullness, improves glucose-dependent insulin production, and restricts glucagon release. This multi-faceted effect not only supports improved glucose homeostasis but also contributes to better overall metabolic regulation.

Beyond its impact on glucose metabolism, FFAR4 activation offers substantial anti-inflammatory benefits. It enhances insulin signaling in both adipose tissue and pancreatic beta cells, which is vital for maintaining proper glucose levels and reducing inflammation linked to metabolic disorders. The anti-inflammatory action is particularly important to decrease the recurrent inflammation that frequently occurs in diseases, such as type 2 diabetes.

FFAR4's broad involvement in controlling inflammatory responses and metabolic processes highlights its potential as a therapeutic target. The ability of FFAR4 to influence GLP-1 release, insulin sensitivity, and inflammatory processes suggests that targeted therapies aimed at modulating FFAR4 activity could provide significant benefits for managing type 2 diabetes and other related metabolic disorders. Although, these results are encouraging, more study is necessary to completely comprehend the underlying mechanisms and create clinical treatments that are both secure and efficient. Strategies for treatment and patient outcomes in metabolic illnesses will be greatly improved by further investigation into the function of FFAR4 in metabolism and possible therapeutic uses.

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