Free fatty acid receptors in the endocrine regulation of glucose metabolism: Insight from gastrointestinal-pancreatic-adipose interactions

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Glucose metabolism is primarily controlled by pancreatic hormones, with the coordinated assistance of the hormones from gastrointestinal and adipose tissue. Studies have unfolded a sophisticated hormonal gastrointestinal-pancreatic-adipose interaction network, which essentially maintains glucose homeostasis in response to the changes in substrates and nutrients. Free fatty acids (FFAs) are the important substrates that are involved in glucose metabolism. FFAs are able to activate the G-protein coupled membrane receptors including GPR40, GPR120, GPR41 and GPR43, which are specifically expressed in pancreatic islet cells, enteroendocrine cells as well as adipocytes. The activation of FFA receptors regulates the secretion of hormones from pancreas, gastrointestinal and adipose tissue to influence glucose metabolism. This review presents the effects of the FFA receptors on glucose metabolism via the hormonal gastrointestinal-pancreatic-adipose interactions and the underlying intracellular mechanisms. Furthermore, the development of therapeutic drugs targeting FFA receptors for the treatment of abnormal glucose metabolism such as type 2 diabetes mellitus is summarized.

KEYWORDS
free fatty acid receptors, glucose metabolism, pancreatic islet cells, gastrointestinal hormones, adipose tissue

Introduction

Glucose homeostasis ensures continuous energy supply to all the cells of the body. It protects the body against hypoglycemic shock and hyperglycemia-induced damage to the cells such as vascular cells and neurons. In general, the uptake of glucose is intermittent while its consumption is a continual process. The fluctuation of blood glucose is well restricted to a limited range by the neuronal and hormonal regulatory molecules, which
constitute a complex network to target on the organs that are critical for the intake, absorption, storage, conversion and consumption of glucose (1, 2). In this regulation network, the hormones from pancreatic islet cells locate in the central position, with the assistance of hormones from gastrointestinal enteroendocrine cells (EECs) and adipocytes (3–5).

Similarly, to glucose, free fatty acids (FFAs) are important substrates and their metabolism is entangled with glucose for energy supply. FFAs show diverse regulatory effects on glucose metabolism according to their length and saturation (6). It is well known that FFAs enter into cells for β-oxidation and generate acetyl-CoA to link glucose metabolism via tricarboxylic acid cycle in mitochondria. Increasing studies have demonstrated that FFAs also function as extracellular ligands to activate G protein-coupled receptors (GPCR) on the plasma membrane. GPR40, GPR120, GPR84, GPR41 and GPR43 are identified as FFA receptors, and they are differently activated by long-chain, medium-chain, and short-chain FFAs (7–9).

FFA receptors are expressed in the cells that are critical to glucose metabolism. Pancreatic islet cells, EECs and adipocytes are equipped with FFA receptors in a cell-specific manner. At present, studies have shown that FFA receptors activation regulates the endocrine function of pancreatic islet cells, EECs and adipocytes, which takes part in the regulation of glucose homeostasis (8, 10). The integrated effects of FFA receptors on glucose metabolism via the hormonal gastrointestinal-pancreatic-adipose (G-P-A) interactions and the underlying intracellular molecular mechanisms are summarized in this review. The drug development targeting FFA receptors for the therapy of abnormal glucose metabolism such as type 2 diabetes mellitus (T2DM) is also discussed.

G-P-A interactions and glucose homeostasis

Insulin is secreted from islet β-cells and plays vital role in lowering blood glucose levels by acting on insulin-sensitive tissues and organs such as liver, skeletal muscles and adipose tissue. It stimulates the synthesis of glycogen and triglyceride and inhibits lipolysis to force the entry of blood glucose into cells (11). In contrast, glucagon is secreted from islet α-cells to elevate blood glucose levels by stimulating glycogenolysis, gluconeogenesis and lipolysis (12). Somatostatin (SS) and pancreatic polypeptide (PP) that are respectively secreted by islet δ-cells and γ-cells modulate insulin and glucagon secretion in a paracrine manner (13). The secretion of insulin and glucagon is primarily regulated by blood glucose, while it is also finely modulated by gastrointestinal hormones (GI hormones) and adipokines (14, 15).

GI hormones are a number of peptides that are secreted by different EECs (16). Glucagon like peptide-1 (GLP-1), cholecystokinin (CCK), gastric inhibitory peptide (GIP), ghrelin, gastrin and secretin are the well-known hormones that related to metabolism, and most of them take part in glucose metabolism by regulating insulin secretion or by acting directly on adipose tissue, liver, skeletal muscle and hypothalamus in central nervous system (CNS) (14) (17, 18). Adipokines are another group of proteins that are released by adipocytes. Among adipokines, leptin and adiponectin are well-known for their role in glucose metabolism (19). Leptin acts on CNS to inhibit appetite and stimulate sympathetic system to increase thermogenesis, and it also acts on islet β-cells to inhibit insulin secretion (20, 21). Leptin induces the loss of fat mass and the improvement of insulin sensitivity, which is beneficial to blood glucose control (22–24). However, leptin resistance occurs in obese subjects, which may contribute to the development of obesity and insulin resistance (25, 26). Adiponectin protects pancreatic islet β-cells against apoptosis and prevents islets loss after transplantation (27–29). Adiponectin also increases insulin sensitivity to improve glucose metabolism (30). The expression of leptin and adiponectin is regulated by islets hormones and GI hormones. For instance, leptin expression is increased by insulin (31), and adiponectin expression is upregulated by GLP-1 but inhibited by GIP (32–34).

The hormonal signals link pancreatic islet cells, EECs and adipocytes together to constitute a regulatory system for glucose metabolism (Figure 1). The G-P-A network responds to the fluctuation of blood glucose through a negative feedback mechanism to maintain glucose homeostasis. When the blood glucose level elevates after ingestion, insulin and some GI hormones increase to lower blood glucose by stimulating glycogen synthesis, inhibiting appetite, and reducing gluconeogenesis (35). Thus, the blood glucose is finely controlled in the normal range. Adipokines influence appetite, insulin secretion, insulin sensitivity and glucose utilization, which may be involved in the long-term mechanism for glucose metabolism.

The effects of FFAs on glucose metabolism

Glucose and FFAs are entangled in energy metabolism, and their interaction is crucial to the maintenance of glucose homeostasis. Fatty acids can be divided into short-chain (C2-C5), medium-chain (C6-C12) and long-chain fatty acids (C14-C26). All of them regulate insulin secretion. LCFFAs are divided into saturated and unsaturated FFAs, both of which are involved in insulin secretion. In general, FFAs exhibit rapid potentiation of glucose-stimulated insulin secretion (GSIS) on the basis of elevated blood glucose levels (6, 36, 37). Meanwhile, FFAs enhance the secretion of gastrointestinal hormones such as GLP-1, CCK and GIP, which are able to promote insulin
secretion (38). The acute potentiation of insulin secretion may be helpful for the control of postprandial elevation of blood glucose. However, long-term elevation of FFAs in combination with glucose damages GSIS, induces insulin resistance, and leads to the elevation of basal blood glucose (39). In addition, FFAs in long-term incubation induce lipotoxic β-cell damage and contribute to the occurrence of T2DM (40, 41).

During fasting, FFAs show the beneficial effects on glucose metabolism. LCFFAs are used as the main energy fuel and go to β-oxidation to generate energy during fasting, and they are also converted to ketone bodies for energy supply. Then blood glucose is saved, and the hypoglycemia is prevented. Blood glucose can not remain stable without the usage of LCFFA during fasting and starvation. LCFFAs are also vital for the recovery of high insulin-secreting ability of pancreatic β-cells in response to glucose after ingestion (42, 43), which is crucial to the control of glucose homeostasis after refeeding.

In summary, the influence of FFAs on glucose metabolism can be physiologically beneficial to remain glucose homeostasis at low glucose levels. On the other hand, they lead to the pathological change and the occurrence of metabolic diseases at high concentrations in accompanying high glucose.

**FFA receptors**

It was previously considered that FFAs regulate glucose metabolism through intracellular metabolism. The discovery of FFA receptors that include GPR40 (FFA1), GPR120 (FFA4), GPR41 (FFA3) and GPR43 (FFA2) unveils a new mechanism of FFAs for their regulation of glucose metabolism. GPR40 and GPR120 are activated by LCFFA, while GPR43 and GPR41 are activated by SCFAs (8). Being members of the GPCR family, all the FFA receptors couple to heterotrimeric G proteins that are composed of α-subunit, β-subunit and γ-subunit (44). FFA receptors have been reported to activate multiple signaling pathways that are mediated by Gαs, Gαi/o, Gαq/11 subunits and β-arrestins (8). In a cell specific manner, GPR40 is coupled to Gαs, Gαi/o and Gαq/11 subunits, while GPR120 is coupled to Gαq, Gαi/o and β-arrestin2, respectively. GPR41 and GPR43 are coupled to Gαi/o, and GPR43 also couples to Gαq/11 subunit (8). The diversity of linkage between FFA receptors and G proteins enables the FFA receptor to execute flexible regulatory functions. The signaling pathways for FFA receptors have not been fully discovered, and the details of the relationship
between intracellular signaling molecules and cellular responses needs to be further clarified.

It is well known that Gαs and Gαi/o affect the activity of adenylate cyclase (AC) and regulate intracellular cAMP levels and the relative signaling pathways (45). Gαq/11 is linked to phospholipase C (PLC) and activates the phosphatidylinositol signaling pathway (46). These signaling pathways regulate hormone secretion by altering the active state of many proteins including ion channels, vesicle trafficking proteins and exocytosis-related proteins. GPCR activation can recruit β-arrestins to the membrane for their binding to GPCR. β-Arrestins mediate the endocytosis of GPCR and negatively regulate GPCR signaling. Meanwhile, β-arrestins also interact with the intracellular signaling proteins (47). Mitogen-activated protein kinases (MAPK) cascade is an important signaling pathway for β-arrestin-activated intracellular signaling molecules (48).

**GPR40 and glucose metabolism**

GPR40 is distributed in pancreatic islet cells and EECs. The hormonal regulation of glucose metabolism by GPR40 is summarized in Figure 2. GPR40 activation by FFAs after fat ingestion potentiates the secretion of insulin, GLP-1, CCK and GIP, which restrain the elevation of blood glucose by acting on CNS, liver and skeletal muscle. Although GPR40 is not expressed in adipocytes, insulin and GI hormones act on adipocytes to improve glucose uptake and utilization as well as adipokine secretion.

**GPR40 and islet hormone secretion**

GPR40 was first discovered as a FFA receptor in pancreatic islet β-cells (49). GPR40 activation was reported to potentiate insulin secretion in primary cultured murine β-cells, INS-1 cells, MIN6 cells and human islets in vitro as well as in human and rodents in vivo (50–53). GPR40 knockout mice show approximately 50% reduction in FFAs-induced insulin secretion in vivo. It is suggested that postprandial increase of blood FFAs activates GPR40 to potentiate GSIS. The activation of PLC via Gαq/11 subunit and the increase in intracellular Ca²⁺ concentrations ([Ca²⁺]i) mediate GPR40-potentiated insulin secretion (51, 54). The coupling of GPR40 to Gαs subunit and the activation of AC are also suggested to
mediate the effects of GPR40 agonists on ion channels activities (55).

The potentiation of insulin secretion by GPR40 activation is glucose dependent. GPR40 activation increases insulin secretion at high glucose levels while it does not stimulate insulin secretion at low glucose levels (56). A conversion mechanism for GPR40 activation and insulin secretion may exist. Exocytosis of insulin granules is a complex process that is regulated by membrane potential, intracellular ATP levels, intracellular signaling molecules, and [Ca^{2+}] in β-cells (57, 58). Studies showed that GPR40 activation in rat pancreatic islet β-cells results in the opening of ATP-sensitive potassium channels (K_{ATP} channels) (59, 60). It is proposed that the intracellular environment of β-cells at low glucose levels facilitates the opening of K_{ATP} channels and GPR40 activation results in the opening of K_{ATP} channels. The opening of K_{ATP} channels hyperpolarizes membrane potential and then blocks insulin secretion. When the blood glucose level is up the stimulatory concentration for insulin secretion, there may be mechanism for the blockade of GPR40-induced opening of K_{ATP} channels. It is proposed that the state of K_{ATP} channels may be the reason for the glucose-dependence of GPR40 activation to stimulate insulin secretion.

GPR40 is also expressed in islet α-cells, and GPR40 activation potentiates glucagon secretion in rodent islets in vitro (61, 62). GPR40 agonists elicit the oscillatory increase in [Ca^{2+}] in α-cells by activating intracellular Ca^{2+} release from ER stores and the influx of extracellular Ca^{2+}, and the increase in [Ca^{2+}]x triggers exocytosis of glucagon granules (63, 64). When high fat diet (HFD) without sufficient glucose is consumed, hypoglycemia may occur, provided that glucagon does not elevate while insulin secretion increases. GPR40 activation by high FFAs promotes insulin secretion to store energy substrates. Meanwhile, GPR40 activation stimulates glucagon secretion to prevent hypoglycemia. Thus, the elevation of both insulin and glucagon after GPR40 activation may be a mechanism to harmonize between the uptake of energy in the forms of FFAs and the prevention of hypoglycemia under the intake of HFD.

Moreover, GPR40 is expressed in K cells and its agonists stimulate GIP secretion (68, 69).

GLP-1, CCK and GIP regulate glucose metabolism through multiple pathways. They potentiate insulin secretion by acting directly on β-cells in a glucose-dependent manner (70). Meanwhile, GLP-1 and CCK act on hypothalamus to inhibit food intake, which is a negative feedback mechanism for metabolic regulation (71). They also act on adipocytes. GLP-1 increases insulin sensitivity and promote fatty acid synthesis in adipocytes (72). Meanwhile, GLP-1 stimulates brown adipose tissue (BAT) thermogenesis and browning of white adipose tissue (WAT), which accelerate energy production and contributes to the lowering effects of GLP-1 on blood glucose levels (73–77). CCK and GIP promote fat deposit in adipocytes (78–81). The effect of CCK and GIP on fat deposit is a double-edged sword affecting glucose metabolism. To a certain extent, the induction of fat deposit may lower fatty acid levels and be beneficial to glucose metabolism. However, in the long run, it leads to obesity and insulin resistance and damage glucose metabolism. The action of GI hormones on adipocytes may be not involved in the acute regulation of blood glucose, but it may regulate glucose homeostasis in the long-term by changing the metabolic and secreting state of adipocytes.

Along with regulating adipocyte metabolism, GI hormones modulate the expression of adipokines. GLP-1 inhibits leptin expression in adipocytes. CCK antagonists increase leptin secretion from adipocytes (82). The physiological and pharmacological significance of GLP-1-inhibited leptin expression remains uncertain (83). GLP-1 and CCK upregulate adiponectin expression in adipocytes (33, 84, 85). Adiponectin exerts protective effects against inflammation and enhances insulin sensitivity in obese animals and humans (86, 87). Adiponectin also regulates glucose metabolism by stimulating fatty acids oxidation and glucose utilization in the skeletal muscle (88). The upregulation of adiponectin expression is suggested to be involved in GPR40-regulated glucose metabolism (86).

### GPR120 and glucose metabolism

GPR120 is expressed in adipocytes, EECs, pancreatic islet cells, immune cells and pulmonary Clara cells (89). GPR120 was first found as an orphan receptor and later was identified as a FFA receptor in enteroendocrine L cells (7, 90). As shown in Figure 3, the postprandial activation of GPR120 by LCFFAs stimulates the secretion of GLP-1, CCK and GIP, with the inhibition of ghrelin secretion. The GI hormones, directly or indirectly though regulating the secretion of insulin and adipokines, regulate glucose homeostasis by acting on liver, skeletal muscle and CNS. GPR120 regulates the secretion of SS and PP in islets and then may bring about paracrine regulation of insulin and glucagon secretion. In addition, GPR120 regulates...
the function of adipocytes directly and indirectly via modulating the cytokine release from macrophages in adipose tissue. Thus, GPR120 activation excites the G-P-A regulatory system and regulates glucose metabolism.

**GPR120 and GI hormone secretion**

GPR120-deficient mice developed more severe obesity and glucose intolerance when fed HFD compared with the wild type (WT) mice (91). GPR120 activation promotes GLP-1 secretion from enteroendocrine L cells in vitro (7). The increase in [Ca^{2+}]i and the activation of extracellular signal-regulated kinase (ERK1/2) are involved in GPR120-stimulated GLP-1 secretion (7). It was suggested that GLP-1 is responsible for the acute blood glucose-lowering effects of GPR120 agonists (92). However, other reports showed that GLP-1 secretion after fat ingestion did not differ between WT mice and GPR120-knockout mice (93, 94). In GPR120 and GPR40-double knockout mice, GLP-1 secretion is not induced by oil ingestion, indicating GPR120 and GPR40 are essential for fat-induced GLP-1 secretion. These results also suggest that GPR40 activation may compensate for the defect of GPR120 in enteroendocrine L cells.

In intestine, GPR120 is also expressed in K cells and I cells, and its activation stimulates the secretion of GIP and CCK (93, 95). It has been known that FFAs stimulate CCK secretion in humans in vivo. Knockdown of GPR120 expression significantly attenuates FFA-induced CCK secretion (95), which indicates that GPR120 mediates the stimulatory effects of FFA on CCK secretion. Cellular analysis in STC-1 cells and GLUTag cells indicates that FFAs increase [Ca^{2+}]i through the stimulation of intracellular Ca^{2+} release and extracellular Ca^{2+} influx (96). The activation of Gq/11-PLC signaling pathway and the resultant opening of monovalent cation-specific transient receptor potential channel type 5 (TRPM5) to increase [Ca^{2+}]i are responsible for GPR120-induced CCK secretion (97). GPR120 is expressed in K cells of the upper small intestine and mediates FFAs-stimulated GIP secretion in mice (93). Another study suggests that GPR120 activation stimulates CCK secretion and CCK acts on the K cells to stimulate GIP secretion (94, 98). Hormone secretion of endocrine cells such as K cells is finely controlled by many signal molecules. Some signal molecules are primary while the others are secondary, and they interrelate to regulate hormone secretion coordinately. Although the mechanism
of GPR120-regulated GIP secretion is inconclusive, it is clear that GPR120 activation stimulates GIP secretion.

In stomach, GPR120 is expressed in ghrelin-secreting P/D1 cells, and its agonists inhibit ghrelin secretion in mice in vivo (99). GPR120 activation inhibited ghrelin secretion by activating the pertussis toxin-sensitive Gαi/o protein and inhibiting cAMP-mediated signaling pathways (100). Ghrelin is an orexigenic protein and its blood level increases during fasting to motivate ingestion. Ghrelin administration enhances appetite and increases food intake in humans and in rodents (101, 102). The inhibition of ghrelin secretion by GPR120 activation is suggested to be postprandial negative feedback to stop ingestion, which coordinates with the increase in the anorexigenic hormones such as GLP-1, CCK and GIP to regulate glucose metabolism.

Since GLP-1 and CCK inhibit appetite while ghrelin motivates ingestion, GPR120-induced changes in GI hormones are proposed to reduce appetite (103). However, GPR120 knockout mice did not show significant changes in food intake, indicating that GPR120 is physiologically dispensable for appetite regulation (91, 104). GPR120 is expressed in hypothalamus and maybe take part in unsaturated fatty acids-induced improvement of hypothalamic inflammation in obesity (105). Intracerebroventricular injection of GPR120 agonist (TUG1197) exerts anti-inflammatory activity but has no effect on body mass and caloric intake in 6-days treatment in obese mice (106). In another study, chronic intracerebroventricular injection of GPR120 agonist (GPR120 agonist III) also does not affect the intake of HFD in 15-days treatment in normal-weight mice (107). However, intracerebroventricular injection of GPR120 agonist acutely inhibits food intake in 4 hours after the administration (107). It is suggested that GPR120 plays a role in hypothalamus, but its pharmacological regulation of appetite remain to be fully investigated in the future.

GPR120 and adipocyte function

GPR120 is expressed in white adipose tissue including subcutaneous and visceral WAT as well as BAT (108). In adipose tissue, it is expressed both in adipocytes and in macrophages (109). The expression level of GPR120 increases with the differentiation of preadipocytes. It is previously considered that GPR120 is expressed in mature adipocytes but not in preadipocytes. A study showed that GPR120 is expressed in the ciliary structure of preadipocytes and senses the extracellular FFAs and activate cAMP/EPAC (the exchange protein activated by cAMP/CTCF (CCCTC binding factor) signaling pathway, which results in remodeling of chromosome and promotion of expression of differentiation-related genes (110). 3T3-L1 cells exhibit a low differentiation rate when GPR120 is knocked down. Although GPR120-deficient mice exhibit an obese phenotype, they have decreased differentiation of adipocytes (91, 111). It is concluded that GPR120 activation in adipose tissue promotes the differentiation of preadipocytes. The adipocyte differentiation and triglyceride accumulation may benefit the decrease in blood glucose levels via the promotion of glucose transformation to triglyceride. Meanwhile, GPR120 activation in macrophages inhibits the release of inflammatory factors such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) to improve insulin sensitivity of adipocytes (112, 113), which promotes glucose entry into adipocytes and inhibits FFA release to favor the control of blood glucose (114, 115). Moreover, GPR120 activation promotes the browning of WAT via stimulating the secretion of fibroblast growth factor 21 (FGF21), and GPR120-deficient mice have impaired browning of WAT in response to cold exposure (116). The browning of WAT increases the thermogenesis and benefits the control of postprandial blood glucose levels. GPR120 is also highly expressed in BAT with upregulation by cold exposure in mice. A study showed that GPR120-deficient neonatal mice had reduced neonatal BAT activity and thermogenesis (117). GPR120 agonists have been shown to increase fatty acid uptake and oxidation, augment mitochondrial respiration, and reduce fat mass in mice (118). Thus, the promotion of thermogenesis is one mechanism of GPR120-regulated glucose metabolism.

GPR120 and islet hormone secretion

In pancreatic islets, GPR120 is not expressed in β-cells and α-cell. It is expressed in SS-secreting δ-cells PP-secreting γ-cells (119–122). GPR120 activation inhibits SS secretion but stimulates PP secretion in mouse islets (121, 122). The pertussis toxin-sensitive Gαi/o protein and its linked signaling pathway are suggested to mediate GPR120–inhibited SS secretion (121). The Gαq/11-PLC-Ca2+ signaling pathway is indicated to mediate GPR120-stimulated PP secretion (122). The physiological significance of this kind of cellular specificity of GPR120 expression in islets remains to be demonstrated. A recent study indicates the paracrine regulation of insulin secretion via GPR120–inhibited SS secretion (119).

GPR43/GPR41 and glucose metabolism

GPR43/GPR41 and hormone secretion

The SCFA receptor GPR43 and GPR41 are expressed in pancreatic β-cells and enteroendocrine L cells. GPR43-deficient mice showed a reduction of insulin secretion and developed more severe glucose intolerance when fed HFD compared with WT mice (123). GPR43 agonists increased insulin secretion via Gαq/11-PLC-Ca2+ signaling pathway in murine and human islets (123). Thus, GPR43 agonists directly act on β-cells to potentiate insulin secretion and regulate glucose metabolism. In addition, GPR43 agonists stimulate islet β-cell proliferation, and GPR43 deficiency caused a
reduction in β-cell mass due to increased β-cell death (124). GPR43 agonists are suggested to enhance the compensatory capacity of β-cells to insulin resistance, which makes them potential therapeutic candidates for T2DM (123).

In contrary to GPR43, loss of GPR41 enhances glucose tolerance in mice, and GPR41 overexpression has opposite effects (125). The islets from GPR41-deficient mice have increased insulin secretion under high glucose although the islets from GPR41-overexpressing transgenic mice did not show significant changes in insulin secretion under high glucose (125). GPR41 is coupled to the Gαq/o subunit, and its activation leads to the inhibition of AC activity and the decrease in cAMP levels, which may be responsible for the reduction of insulin secretion. Therefore, although both GPR43 and GPR41 are activated by SCFAs, they mediate opposite effects on insulin secretion in β-cells. It is interesting to demonstrate the dominant type of receptors and the net effect of SCFAs on insulin secretion. GPR43/GPR41 double knockout improves glucose tolerance and insulin secretion (126). It is suggested that GPR41 has a negative but dominant effect over GPR43 and GPR43/GPR41 mediate a net inhibition on insulin secretion under normal conditions.

GPR43 is expressed in enteroeendocrine L cells and mediates SCFAs-stimulated GLP-1 secretion in the mixed colonic cell cultures in vitro and in vivo (127, 128). GPR43-deficient mice show reduced SCFAs-induced GLP-1 secretion and impaired glucose tolerance (127). Gqα/11-PLC-Ca2+ signaling pathway was reported to mediate the effects of GPR43 activation on GLP-1 secretion in L cells (127). Although GPR41 is expressed in enteroeendocrine L cells (129), its role in GLP-1 secretion remains to be demonstrated.

**GPR43/GPR41 and adipocyte function**

GPR43 is expressed in adipocytes, but its role in adipocytes is not clear (130). GPR43 expression levels in WAT are higher in HFD-induced obese mice than in normal chow-fed mice. It was reported that SCFAs treatment suppresses lipolysis in 3T3-L1 adipocytes and adipocytes isolated from mice adipose tissue and that GPR43 knockdown inhibits adipogenesis (131). However, another report showed that GPR43-deficient mice tend to become obese easier when fed HFD than WT mice and GPR43 overexpression in adipose tissue leads to the lean phenotype in mice (132). Further studies are needed to elucidate the role of GPR43 in white adipose tissue. As to BAT, the other type of adipose tissue, GPR43-deficient old age mice exhibit the increase in BAT activity and increased energy expenditure, which may be responsible for the improved insulin sensitivity in the mice (133). GPR43 mediates the stimulatory effects of SCFAs on adipogenesis and mitochondrial biogenesis in brown adipocytes (134). It is proposed that the stimulation of BAT contributes to the lean phenotype of GPR43 overexpression. However, GPR43 expression in adipose tissue is not different between obese patients and lean subjects, and GPR43 agonists do not induce the differentiation of human preadipocytes isolated from omental adipose tissue (135). This study indicates that a species difference has to be considered between humans and mice in the study of GPR43 actions.

The role of GPR41 in regulating adipocytes function is also unsettled. GPR41 expression was found in adipocytes, and its activation stimulated leptin secretion from adipose tissues (136). However, other studies did not detect GPR41 expression in mouse adipose tissue, and the stimulation of leptin secretion by SCFA is suggested to be mediated by GPR43 rather than GPR41 (137). Male GPR41-deficient mice show higher body fat mass and plasma leptin levels as well as higher glucose levels than WT mice (138). Although this study does not resolve the controversial about the expression of GPR41 in adipocytes, it demonstrates that GPR41 surely regulates fat and glucose metabolism via direct or indirect actions on adipocytes. Immune cells such as macrophages distribute in adipose tissue and modulate adipocyte function via paracrine signaling cytokines such as IL-6, IL-1, and TNF-α (139, 140). GPR41 and GPR43 are expressed in macrophages (141, 142). Therefore, the involvement of macrophages in the regulation of fat accumulation and adipokine secretion in adipocytes may complicate the observation of GPR43/GPR41-regulated adipocyte function.

**Differences between SCFAs AND LCFFAs in metabolic regulation**

SCFAs are very different to LCFFAs in characteristics and its source in human body. SCFAs in humans are mainly obtained from colon as the products of bacterial fermentation from insoluble fiber and proteins but not from food intake (143, 144). Thus, the physiological significance of SCFAs in regulating metabolism is surely different to LCFFAs. Although both SCFA receptors and LCFFA receptor are involved in the regulation of glucose metabolism through targeting the secretion of insulin and GLP-1 as well as the function of adipocytes, they should have distinct effects on glucose metabolism in physiological and pathophysiological conditions. The details in differences of FFA receptors in glucose metabolism in different metabolic states are worth of further exploration.

**Targeting FFA receptors for drug development**

The development of drugs targeting FFA receptors has been going on for decades, and the earliest is the development of GPR40 agonists for the treatment of T2DM. GPR40 agonist TAK-875 exhibits the ability to improve blood glucose control in patients with T2DM. However, it stopped in clinical trial III because of its hepatotoxicity (145). The other GPR40 agonists including LY2881835, AMG837, CPL207280, SCO-267, CPU-014...
and AM-1638 are in the pipeline of drug development for T2DM treatment. Eli Lilly and Amgen initiated phase I/II clinical trials with LY2881835 and AMG837, respectively (146). Interestingly, GPR40 antagonists also have been developed for T2DM treatment. GPR40 antagonist DC260126 inhibits LCFA-stimulated increased in [Ca\textsuperscript{2+}]i and protect β-cells against palmitate-induced ER stress and cell apoptosis (147, 148).

GPR120 agonists have been shown to improve insulin sensitivity in obese subjects. GPR120 agonist TUG-891 has been indicated as therapeutic agent of diabetes and obesity (8, 146). The other GPR120 agonists including NCG75, GS137647A, AZI3581837 and CpdA all improve glucose tolerance in HFD-induced obese mice by increasing insulin sensitivity (146, 149, 150). Although a number of GPR120 agonists have been discovered, they have not moved to clinical trials. The insufficiency in both the understanding of GPR120 biology and the discovery of specific agonists with efficient effects in vivo may obstruct the development of drugs targeting GPR120.

GPR43 not only regulates glucose metabolism but also plays an important role in regulating immune function. GPR43 antagonists have been in development for anti-inflammation (151, 152). Since patients of T2DM are in the state of noninfectious microinflammation in multiple tissues such as adipose tissue, heart and liver (153), it is proposed that GPR43 antagonists may improve T2DM through anti-inflammation. GPR41 is also the therapeutic target for inflammatory diseases, but the development of drugs targeting GPR41 is relatively few compared with the other FFA receptors. There is still a long way to go for the development of drugs targeting GPR43/GPR41 for the treatment of metabolic diseases such as T2DM.

**Conclusion and prospect**

FFA receptors distribute in metabolism-related tissues to sense the fluctuation in extracellular FFAs and then regulate glucose metabolism through G-P-A regulatory system. The overlapping distribution of different types of FFA receptors in intestine indicates the importance of FFA receptors in nutrient sensing and metabolic regulation. This phenomenon also suggests that different FFA receptors may function differently and are distinguishingly activated in different nutritional states such as food intake, fasting, and obesity. Thus, the cells are able to response specifically to the changes in the level and composition of blood FFAs, which ensures the optimal fine-tuning of regulatory system for the maintenance of metabolism homeostasis. To date, the research in FFA receptor activation by different FFAs in vivo under different nutritional states is deficient. In the future, the detailed analysis of FFA receptor activation in different nutritional states will increase the understanding of FFA-regulated metabolism.

The regulatory effects of ligand-receptor interaction depend on not only the levels of ligands but also the levels of receptors. The changes in cellular expression of FFA receptors certainly influence the actions of FFAs on metabolism. It was found that HFD-induced obesity leads to the downregulation of GPR120 in intestine and in pancreatic islets in mice (122, 154). Due to the differentiation of adipocytes, GPR120 levels in subcutaneous fat and omental fat are increased in obese human subjects compared with those in lean subjects (91). However, morbidly obese human subjects (BMI 54.0 ± 5.7 kg/m\textsuperscript{2}) have lower GPR120 levels in visceral adipose tissue than nonobese subjects, indicating that the enlarged adipocytes goes to the other side for GPR120 expression (154). Demonstration of the expression level of FFA receptors in different nutritional states is essential for understanding their physiological and pathophysiological role and the strategies to regulate metabolism through FFA receptors. It is suggested that compounds that upregulate the expression of FFA receptors may improve metabolic disorders synergistically with FFA receptor agonists. A recent study shows that PPAR-γ agonist upregulates GPR120 expression in adipocytes and synergistically enhances the effects of GPR120 agonists on metabolism (114). This study gives an example of how-to-strength FFA receptors-FFAs interaction to regulate metabolism. More studies are expected to demonstrate the regulatory mechanism of the expression of FFA receptors in the future.

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**Conflict of interest**

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