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Short Chain Fatty Acids, pancreatic dysfunction and type 2 diabetes

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ABSTRACT

The microbiota living in gut influence the immune response, metabolism, mood and behavior. The diet plays a pivotal role in maintaining healthy gut microbiota composition and its fermentation leads to production of Short Chain Fatty Acids (SCFAs) mainly acetate, propionate and butyrate. During pancreatic dysfunction, insulin mediated suppression of glucagon is impaired leading to uncontrolled glucose production by liver and state of hyperglycemia. Insulin and glucagon balance is as important as insulin sensitivity which is reduced during Type 2 Diabetes (T2D). Glucagon like peptide-1 (GLP1) produced by Intestinal epithelial cells regulates insulin and glucagon secretion directly via GLP1 receptor on pancreatic cells or via nervous system. But half-life period of GLP1 is very short i.e. about 2 min, after which it is cleaved and inactivated. SCFAs are well documented to induce GLP1 but its direct effect on pancreatic dysfunction has not been reported. This review opens a new avenue to study the role of SCFAs as treatment to pancreatic dysfunction and T2D.

Introduction

Gut microbiota influence metabolism and immune response mainly by its fermentation products i.e. short Chain Fatty Acids (SCFAs). These SCFAs regulate glucose and lipid metabolism by activation of SCFA receptors on liver, adipose tissue, brain and pancreas. The pancreatic dysfunction affects secretion of insulin and glucagon by islet α and β cells, respectively, which has a pivotal role in glucose homeostasis and pathogenesis of Type 2 Diabetes [1] Apart from reduced insulin secretion and defects in insulin signaling, altered glucagon secretion affects liver glucose metabolism, leading to a state of hyperglycemia. During fasting conditions, glucagon induces gluconeogenesis and glycogenolysis in liver and fulfill the energy needs of the body while suppression of glucagon secretion in fed state inhibit hepatic glucose breakdown and allow storage of glucose in the form of glycogen [2]. However, pancreatic dysfunction results in disruption of insulin induced suppression of glucagon secretion, leading to uncontrolled production of hepatic glucose followed by hyperglycemia. In response to food intake, insulin and glucagon secretion are balanced via incretins produced by intestinal L cells [3]. Two incretins GLP1 (glucagon like peptide-1) and GIP (glucose dependent insulinotropic polypeptide) maintains glucose homeostasis via balancing secretion of insulin and glucagon. In pancreatic dysfunction and T2D, incretin activity is reduced leading to uncontrolled glucagon secretion and insulin resistance mediated hyperglycemia [4]. The inhibitors of dipeptidyl peptidase-4 (DPP-4) that inactivate GLP1 and analogues of GLP1 have been proved to reduce insulin resistance and increase glucose tolerance making GLP1 a target for improved glucose homeostasis and T2D [5]. The gut microbiota fermentation products, i.e., SCFA, have been shown to induce GLP1 and amylin secretion via activation of FFAR2 (SCFA receptor) [6]. SCFAs further increase pancreatic β cell mass, insulin secretion, reduce glucagon secretion and regulate glucose metabolism [7]. Although the gut microbiota alteration in T2D leading to altered SCFA profile is well documented, direct correlation between SCFA and pancreatic dysfunction is not looked upon in detail. (see Fig. 1)

Short Chain Fatty Acids (SCFAs)

SCFAs are products of gut microbiota mediated fermentation of resistant starch or dietary fiber which cannot be hydrolyzed completely in our digestive system due to lack of specific enzymes [8]. SCFAs with concentrations of about 60% acetate (C2), 25% propionate (C3), and 15% butyrate (C4) are found in the colon [9]. SCFAs are rapidly transferred from gut to the blood-stream, and the usual concentration in peripheral blood is around 100–150 μM for

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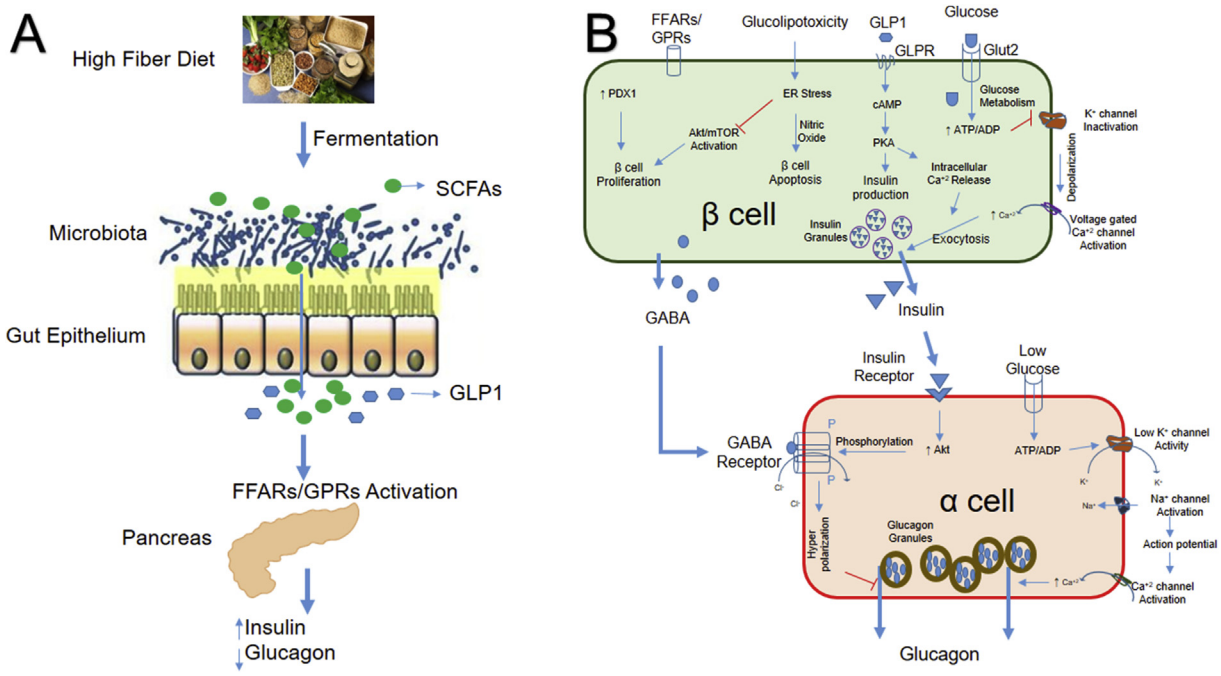

Fig. 1. A: Role of diet and gut microbiota in pancreatic function, High fiber diet consumption promotes healthy gut microbiota composition and its fermentation produces SCFAs regulate glucose metabolism via SCFA receptors, i.e. FFARs. The Intestinal epithelial cells produce GLP1 that up regulates insulin and down regulates glucagon secretion from pancreatic beta and alpha cells, respectively.
B: Pancreatic beta cell survival and regulation of pancreatic hormone secretion, Pancreatic beta cell survival is regulated by Akt/mTOR pathway activation via PDX1. Glucolipotoxicity induces ER stress, inhibit Akt/mTOR pathway and induces beta cell apoptosis via nitric oxide formation. Glucose up regulates ATP/AMP ratio and activates Ca^{+2} channel via KATP channel inactivation and depolarization. GLP1 receptor activation leads to release of intracellular Ca^{+2}, inducing exocytosis of insulin granules from beta cells. Insulin receptor activation leads to phosphorylation and translocation of GABAA receptor on alpha cell. GABAA receptor activation by GABA, released from beta cell, leads to hyperpolarization and inhibition of glucagon release. Low glucose increases action potential through activation of Na+ channel and moderate depolarization, leading to Ca^{+2} channel activation and release of glucagon in Ca^{+2} stimulated manner.

acetate, 4–5 μM for propionate, and 1–3 μM for butyrate. Butyrate is used as the major source of energy in colon, liver, brain and heart; propionate is utilized for gluconeogenesis in liver while acetate is utilized by peripheral tissues as fuel [10]. SCFAs are recognized by free fatty acid receptors FFAR2 and FFAR3. The receptor responsiveness is directly proportional to the length of carbon chain in SCFA molecule, i.e. FFAR2 is more responsive to acetate and propionate than to butyrate while FFAR3 is more responsive to butyrate and propionate than to acetate [11].

Pancreatic dysfunction and T2D

Pancreatic dysfunction is associated with impaired proliferation of beta cells as well as altered production and secretion of insulin and glucagon by islet beta and alpha cells respectively [1]. Glucose homeostasis is maintained by insulin and glucagon, while disrupted secretion of glucagon and insulin resistance in T2D leads to glucose intolerance. Following food ingestion insulin secretion is stimulated while glucagon secretion is suppressed. In case of T2D, pancreatic dysfunction increases alpha cells mediated production of glucagon as well as decreased insulin mediated suppression of glucagon leading to high concentrations of glucagon in circulation [12]. Collectively, hyperglucagonemia and lowered insulin to glucagon ratio mediates imbalance in glucose homeostasis [13]. Non-insulin-dependent diabetes mellitus (NIDDM) subjects have higher basal hepatic glucose output due to insulin resistance in liver leading to high fasting plasma glucose [14]. Ratio of alpha cell to beta cell increases in T2D due to higher instances of beta cell apoptosis and increased alpha cell proliferation as shown in one of the studies which can be correlated with levels of insulin and glucagon in T2D pathogenesis [15]. Although in some cases, alpha and beta cell dysfunction is shown without affecting proportion of islet cells due to impaired insulin secretion [16].

Alpha cell dysfunction

During alpha cell dysfunctioning, glucagon secretion is not suppressed by insulin and its excess production leads to hyperglucagonamea and T2D. Role of insulin in T2D has been studied in detail as insulin resistance and hyperglycemia are strongly associated with pathogenesis of this disease. However, glucagon also plays a pivotal role in maintaining glucose homeostasis via regulating glucose metabolism in liver. Glucagon stimulates glycogenolysis and gluconeogenesis in liver leading to increased glucose output in fasting condition [2].

In T2D, apart from insulin resistance, high level of glucagon is also found in circulation [17]. Following meal, elevated glucagon levels led to high post prandial glucose concentration in T2D [18]. Due to impaired insulin action on glucagon suppression, glucose production in liver increases which promote hyperglycemia and worsen T2D pathogenesis [19]. Although in early stages of T2D, glucagon levels are not elevated but in acute phase, insulin mediated glucagon suppression is impaired leading to hyperglucagonemia [17].

The glucagon receptor knockout prevents the onset of diabetes even if beta cells are completely destroyed, showing the pivotal role of glucagon in diabetes induction [20]. Even low plasma glucose is not sensed in case of T2D and insulin secretion is not inhibited, allowing insulin to suppress glucagon secretion and hypoglycemia persists [12].

Due to architectural proximity between alpha and beta cells within the islet, insulin regulates glucagon secretion in a paracrine manner. In vivo suppression of glucagon release is regulated not directly via glucose but via insulin acting on alpha cells. Insulin activates GABAA receptor translocation via AKT kinase pathway leading to membrane hyperpolarization in α cells and suppression of glucagon secretion [21]. Elevated levels of glucose and glucagon are found in alpha cell specific insulin receptor knock out [22]. Together these findings explain importance of insulin signaling in regulation of pancreatic alpha cells.

Glucagon secretion is regulated not only by insulin and other factors like γ-aminobutyric acid, Zn^{2+}, somatostatin and γ-hydroxybutyric acid but alpha cell itself also regulates glucagon secretion by sensing low glucose concentrations via ATP-sensitive K+ channel (KATP) channel. Hyperglycemia mediated increased ratio of ATP/ADP inhibits KATP channel in alpha cells. The membrane depolarization and inactivation of Na + channels thus, lead to reduced action potential and Ca + entry suppress glucagon secretion. KATP channel blocker has been shown to regulate glucagon secretion in glucose dependent manner in T2D [23,24].

One of the mechanisms by which GLP1 suppresses glucagon secretion is via cAMP accumulation and N type Ca^{+} channel inhibition in pancreatic alpha cells. Although SCFAs are reported to inhibit N type Ca^{+} channel via FFAR2 and FFAR3 in sympathetic neurons its effect in pancreatic alpha cells is not reported [25,26].

Beta cell dysfunction

Pancreatic beta cell dysfunction can be explained by impaired insulin praaoduction and secretion due to beta cell insufficiency leading to pathogenesis of diabetes. Insulin resistance is the major factor for pathogenesis of T2D as, unless beta cell dysfunction is associated with insulin resistance, healthy beta cells can compensate for the insulin demand via proliferation and overproduction of insulin [27].

Excess carbohydrate and fatty acids over stimulate pancreatic beta cells leading to beta cell dysfunction and impaired insulin secretion mediated T2D [28]. Beta cell mediated production and secretion of insulin is affected more, rather than loss of beta cell in T2D [29]. However, in patients with T2D, beta cell mass and insulin production is decreased showing pancreatic beta cell dysfunction. β cell dysfunction can occur due to oxidative stress, hypoxia, ER stress, cytokine induction etc. which lead to loss of beta cells due to apoptosis or inhibition of proliferation [30].

Mitochondrial oxidative stress and endoplasmic reticulum (ER) stress has been reported to play a major role in pancreatic beta cell death and impaired insulin secretion [31]. Misfolded proteins generate reactive oxygen species (ROS) in mitochondria while oxidative stress mediated disturbance in ER redox state leads to protein misfolding in ER. The reports suggest that ER stress and mitochondrial dysfunction along with AMP-activated protein kinase (AMPK) activation led to nitric oxide mediated apoptosis and loss of beta cells [32].

Pancreatic beta cell survival is controlled by mTOR pathway mediated suppression of mitochondrial stress, while in ER stress mediated dysfunction, inhibition of Akt/mTORC1 pathway leads to loss of beta cells and impaired insulin secretion [33]. ER stress mediated inhibition of PERK expression induces apoptosis of beta cells, inhibits beta cell survival and reduces insulin secretion leading to progressive diabetes with aging [34].

In pancreatic beta cells, maintenance of ER homeostasis is important for proper insulin secretion. During beta cell dysfunction, any unfolded protein response (UPR) generated due to impaired ER homeostasis could not restore ER function, leading to activation of death signal pathways, resulting in beta cell death. Hyperglycemia and hyperlipidemia has been shown to be associated with enhanced UPR mediated beta cell dysfunction and loss of beta cells [35].

Hyperglycemia mediated glycation and oxidation of ER folding sensor proteins has also been shown to induce ER stress while low levels of nitric oxide (acting as antioxidant) has role in cell survival [36]. In glucotoxicity and glucolipotoxicity mediated T2D models, mitochondria targeted antioxidant treatments showed reduced beta cell death and improved insulin secretion [37].

Recent reports indicate that beta cell de-differentiation to progenitor like cells as well as *trans*-differentiation to alpha cells is associated with pathogenesis of T2D. NKX6.1 knock out beta cells differentiated to δ-cells and its reduced expression is reported to induce insulin resistance and T2D [38].

Forkhead box protein O1 (FOXO1) is a multifunctional protein having role in pancreatic beta cell survival, signaling, apoptosis, autophagy, secretion etc. It accounts for the pancreatic beta cell de-differentiation and *trans*-differentiation leading to reduced beta cell mass and induce T2D [30,39]. FoxO1 inhibits pancreatic and duodenal homeobox 1 (PDX1) transcription via occupying FoxA2 DNA binding site in promoter region of PDX1 and thus inhibits β-cell proliferation as well as *trans*-differentiation [30]. Beta cell transcription factors like FOXO1, NKX6.1, PDX1, MAFA and RFX6 has a major role in de-differentiation of beta cells and pathogenesis of T2D [40]. Indirect evidence suggest that SCFA can prevent this differentiation via GLP1 mediated PI3K dependent inhibition of FOXO1 and upregulation of PDX1. Sodium butyrate has also been shown to induce pancreatic development factors and insulin secretion in presence of GLP1 by converting nestin EGFP progenitor cell to insulin secreting cells [41,42].

Butyrate is a well-known histone deacetylase (HDAC) inhibitor that promote beta-cell development, proliferation, differentiation, and function [43,44]. SCFA receptor mediated signaling is involved in pancreatic beta cell mass, glucose mediated insulin secretion and beta cell response towards insulin resistance [7]. The butyrate producing microbiota from lean donor improved insulin sensitivity in subject with metabolic syndrome [45]. Sodium butyrate has the potential to induce pancreatic development genes and beta cell differentiation in embryonic stem cells [46].

Incretins in pancreatic dysfunction and T2D

Insulin secretion is influenced more strongly by food ingestion than intravenous glucose infusion showing role of gut hormones in pancreatic hormonal regulation [47]. The gut hormones also known as incretins, regulate glucose homeostasis by influencing insulin and glucagon secretion. Incretins such as GLP1 and GIP are the hormones produced by the intestinal L cells which has role in glucose metabolism and T2D [3].

HbA1c, glycated hemoglobin, is the measure of diabetes and it reflects the average blood glucose levels over past 2–3 months. Effects on incretins are HbA1c dependent, as higher HbA1c levels are shown to inhibit incretin activity. Prediabetic and T2D groups have been categorized according to HbA1c differential response and levels of incretin and pancreatic secretion of glucagon and insulin from alpha and beta cells respectively. In prediabetics, pancreatic secretion is impaired while incretin effects are preserved whereas in type 2 diabetics, incretin effects are also reduced [48].

GIP has been reported to positively influence insulin mediated fatty acid synthesis and its esterification and glucose transport in adipose tissue [49]. Unlike GIP, GLP1 inhibits glucagon secretion and gastric emptying [49,50]. GLP1 is also associated with postprandial insulin secretion and has more significant role in humans. GLP1 levels are significantly reduced in T2D associated with

hyperglucagonemia and hyperglycemia [51].

During fasting conditions, GLP1 is low in circulation while high fat and carbohydrate diet induces GLP1 secretion from intestinal L cells. Unlike GIP which loses its activity in diabetic conditions, GLP1 can stimulate insulin secretion in high fat diet and sulfonylurea treated type 2 diabetic patients [52]. GLP1 induces pancreatic insulin secretion in glucose dependent manner and inhibits glucagon secretion directly via involvement of GLP1 receptor on pancreatic cells or indirectly via nervous system regulation [4].

SCFA receptors are highly expressed on GLP1 producing L cells located in distal ileum and colon hence, SCFA administration via gut has been shown to be more effective in GLP1 secretion via FFAR2 [53]. Butyrate enhances GLP1 secretion via upregulating genes responsible for GLP1 synthesis and secretion. Enhanced levels of butyrate are associated with reduced food intake, body weight loss, enhanced GLP1 activity and insulin sensitivity. FFAR3 is associated with butyrate mediated secretion of GLP1 as FFAR3 knockout shows attenuated GLP1 secretion [54]. Butyrate induces GLP1 and GIP secretion along with increased concentrations of insulin and amylin via stimulating pancreatic beta cells. Propionate administration also shows elevated levels of GIP, insulin and amylin without affecting GLP1. Butyrate requires FFAR3 for maximum induction of GLP1 while its effect on body weight and GIP stimulation is independent of FFAR3 [6]. GLP1 receptor regulates pancreatic hormone secretion by inducing insulin secretion and simultaneously suppressing glucagon secretion. It also induces proliferation and inhibits apoptosis of beta cells [55]. SCFA mediated GLP1 receptor activation improves PKB and PDX1 mediated islet proliferation and cytoprotection [42,56].

Glucose stimulated insulin secretion is affected by SCFA receptor FFAR2 and FFAR3. Glucose metabolism in pancreatic beta cells elevates ATP/ADP ratio which leads to closure of K^{+}-ATP channels and membrane depolarization. The opening of Ca^{+2} channel allows calcium influx and insulin release by exocytosis of insulin vesicles. SCFAs also improve insulin release via activation of FFAR2 and downstream pathway leading to phospholipase C (PLC) mediated hydrolysis of phosphatidylinositol 4,5 bisphosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP3) activating protein kinase C (PKC) leading to Ca^{+2} release from ER. FFAR2, like FFAR3, can also couple with G/i/o subunits and inhibit adenylate cyclase, which decreases the concentration of cAMP, inhibiting protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC) mediated insulin release [57].

Inflammation in pancreatic dysfunction and T2D

Nutrient overload and metabolic stress induces insulin resistance and also affect target tissues like liver and pancreas. Pancreatic inflammation is mainly governed by the cytokine IL-12 and IL1-β as well as chemokine CCL2 and CCL13. TNF-α, IL-1β and IFN-γ are elevated in type 2 diabetic islets which induce beta cell apoptosis and inhibit insulin secretion from pancreas [58]. In T2D, presence of different leukocytes are found in pancreas as well as in circulation which have a role in beta cell dysfunction [59]. During initial phase of T2D, $CD20^{+}$ B cells within the $CD45^{+}$ population are found in pancreas leading to inflammation and pancreatic dysfunction indicating role of adaptive immune response [60].

SCFAs, particularly propionate and butyrate have anti-inflammatory effects via down regulation of proinflammatory cytokines i.e. TNF-α, IL-1β, and IL-6 [61]. SCFA receptor i.e., FFAR2, influences the differentiation and activation of monocytes and neutrophiles mediated inflammation. SCFA-mediated activation of FFAR2 has been shown to trigger recruitment of circulating leukocytes to the inflammatory site via activation of intracellular signaling pathways including MAPK, Protein Kinase C (PKC), and Phospholipase C (PLC) [62]. SCFA butyrate down regulates TNF-α mediated expression of adhesion molecule VCAM-1 which prevents leucocyte migration [63]. Propionate and butyrate, but not acetate, can effectively suppress NF-kB activation, inflammatory cytokine gene expression and its release in vitro [64]. SCFA, mainly butyrate also induces IL-10 mediated T regulatory cell function and suppression of inflammation. SCFA mediated HDAC inhibition leads to mTOR pathway activation and IL-10 production [44].

Conclusion

In conclusion, SCFAs work as a mediator between gut microbiota and pancreas directly via receptor on pancreatic cells or via gut-brain- pancreatic axis. They have potential to improve glucose homeostasis and insulin sensitivity in case of T2D and can also regulate pancreatic insulin and glucagon secretion via GLP1 augmentation in pancreatic dysfunction. Pancreatic beta cell proliferation and reduced *trans*-differentiation to alpha cells can also be achieved by SCFA. Butyrate, being a potent HDAC inhibitor can also regulate inflammation and metabolism. Pancreatic dysfunction and T2D are also associated with metaflammation which can be regulated by anti-inflammatory role of SCFAs. Although SCFAs have potential to improve T2D and pancreatic dysfunction, detailed studies are yet to be done.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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