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Role of fatty acids in the pathogenesis of ß-cell failure and Type-2 diabetes

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ABSTRACT

Pancreatic ß-cells are glucose sensors in charge of regulated insulin delivery to the organism, achieving glucose homeostasis and overall energy storage. The latter function promotes obesity when nutrient intake chronically exceeds daily expenditure. In case of ß-cell failure, such weight gain may pave the way for the development of Type-2 diabetes. However, the causal link between excessive body fat mass and potential degradation of ß-cells remains largely unknown and debated. Over the last decades, intensive research has been conducted on the role of lipids in the pathogenesis of ß-cells, also referred to as lipotoxicity. Among various lipid species, the usual suspects are essentially the non-esterified fatty acids (NEFA), in particular the saturated ones such as palmitate. This review describes the fundamentals and the latest advances of research on the role of fatty acids in ß-cells. This includes intracellular pathways and receptor-mediated signaling, both participating in regulated glucose-stimulated insulin secretion as well as being implicated in ß-cell dysfunction. The discussion extends to the contribution of high glucose exposure, or glucotoxicity, to ß-cell defects. Combining glucotoxicity and lipotoxicity results in the synergistic and more deleterious glucolipotoxicity effect. In recent years, alternative roles for intracellular lipids have been uncovered, pointing to a protective function in case of nutrient overload. This requires dynamic storage of NEFA as neutral lipid droplets within the ß-cell, along with active glycerolipid/NEFA cycle allowing subsequent recruitment of lipid species supporting glucose-stimulated insulin secretion. Overall, the latest studies have revealed the two faces of the same coin.

1. Introduction

1.1. Glucose is the chief secretagogue for insulin secreting ß-cells

The ß-cells produce insulin, the main anabolic hormone of our body. Clustered with the other pancreatic endocrine cells (glucagon α-cells, somatostatin δ-cells, pancreatic polypeptide γ-cells, and ghrelin ε-cells) they compose the islets of Langerhans, representing less than 2 % of the whole pancreas. The islets can be considered as mini organs according to their extended vascularization and innervation [1]. The pancreatic islets control blood glucose homeostasis by finely regulating the secretion of both the only hypoglycemic hormone insulin and the glucose recruiting hormone glucagon. A rise in blood glucose stimulates insulin secretion, which in turn promotes glucose uptake and glycogen storage along with inhibition of lipolysis in adipocytes and glucose production in the liver [2]. These actions hold glycemia in the normal range (i.e. 3.9–5.6 mM). Under fasting conditions, glucagon is secreted by the α-cells and stimulates hepatic glucose production through glycogenolysis and eventually gluconeogenesis in order to maintain euglycemia [3].

Glucose-stimulated insulin secretion is characterized by a biphasic response [4]. The first phase, or triggering pathway, is induced by glucose-evoked elevation of intracellular calcium that releases the content of insulin granules already docked at the plasma membrane [5]. Glucose is the chief secretagogue for insulin secretion and continuous sensing of its blood levels by the ß-cells is mediated by the glucose transporter GLUT2 and glucokinase, the first rate-limiting enzyme of glycolysis with a high K_m conferring glucose sensor properties to the ß-cells; thus inducing insulin release only in response to a rise in glycemia [6,7]. Glycolysis produces pyruvate that is funneled into the mitochondria, thereby promoting the generation of ATP that raises the cytosolic ATP/ADP ratio closing the potassium channels. The subsequent cell membrane depolarization opens the voltage-sensitive calcium channels, which results in a rapid increase in cytosolic calcium triggering insulin granules exocytosis [8], see Fig. 1. The second sustained phase of glucose-stimulated insulin secretion, also refers to as the amplifying pathway, requires additional intracellular factors along with permissive cytosolic calcium concentrations [9]. Metabolism-derived molecules of the amplifying pathway include nucleotides (NADPH and

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ATP) and metabolites, such as glutamate and lipid species [10,11].These factors do not initiate insulin secretion by themselves but potentiate the secretory response.

Among the different intracellular factors modulating insulin exocytosis, some can also play a role as autocrine or paracrine signaling molecules. The release of ATP may activate P2Y purinergic receptors [12] and non-esterified fatty acids (NEFA) can activate their respective G-protein-coupled receptors [13], thereby enhancing the secretory response. Conversely, negative feedback on insulin exocytosis can be mediated by extracellular glutamate secreted by the islets acting on N-methyl-D-aspartate (NMDA) receptors of the ß-cell [14]. Finally, incretins (GIP, GLP-1) produced by the enteroendocrine cells potentiate glucose-stimulated insulin secretion [15,16].

1.2. Lipids can modulate glucose-stimulated insulin secretion

Lipids are mostly derived from food, a source that is particularly relevant for poly-unsaturated fatty acids (PUFA) as we lack dedicated desaturases for their synthesis. Upon a meal, digestive lipases hydrolyze triglycerides to long-chain fatty acids (Lc-FA, >12C), such as palmitate (saturated C16:0), oleate (mono-unsaturated C18:1) and linoleate (poly-unsaturated C18:2). Short-chain fatty acids (Sc-FA, <6C) are mainly produced in the colon by the gut microbiota through the fermentation of undigested carbohydrates [17]. Main function of Sc-FA is related to signaling targeting the NEFA receptors FFAR2 and FFAR3 (or GPR43 and GPR41, respectively). Sc-FA might play a role in the regulation of glucose and lipid homeostasis, in the gut-brain axis, as well as the in inflammatory response [18]. Lc-FA may also act as signaling molecules through the activation of their dedicated receptors FFAR1 (GPR40) and FFAR4 (GPR120) [19]. However, compared to Sc-FA, Lc-FA cover a larger set of biological functions [20] as they represent the major components of membranes under the form of phospholipids. Bound to glycerol, Lc-FA compose the neutral lipids triacylglycerols (TAG, or triglycerides), the most efficient energy store. Upon TAG hydrolysis, and once activated by Coenzyme-A (CoA), Lc-FA can serve as energy source for ATP production through mitochondrial ß-oxidation. Other lipid species have been shown to modulate glucose-stimulated insulin secretion; such as lysophosphatidylinositols that are upregulated in Type-2 diabetes and have been shown to support the secretory response of diabetic ß-cells [21]. Sphingolipids are also known to play a role in ß-cells and their metabolism is altered in Type-2 diabetes [22]. In particular, sphingosine-1-phosphate (S1P) enhances insulin release in a glucose dependent way [23], while ceramides are associated with ß-cell dysfunction, pointing to a dual effect of sphingolipid pathways (reviewed in Ref. [24]). Together with sphingolipids, cholesterol is required at the plasma membrane for proper assembly of the lipid rafts and formation of the secretory granules. However, intracellular accumulation of cholesterol is detrimental to the ß-cell, an effect counteracted by HDL particles [25]. Therefore, cholesterol metabolism must be accurately balanced to preserve ß-cell function, as illustrated by the association between statin use and diabetes progression (reviewed in Ref. [26]).

Both Sc-FA and Lc-FA receptors are expressed by pancreatic ß-cells and it's about 20 years ago that the FFAR1 was deorphanized, shown to be expressed mainly in ß-cells and human brain, and to involve $G\alpha_q$ signaling [27]. At the same time, FFAR1 was reported to potentiate glucose-stimulated insulin secretion through the elevation of intracellular calcium [28]. This led to intensive investigations on FFAR1 and the development of corresponding agonists as a potential target for the management of Type-2 diabetes. However, such efforts have not been very successful and have not been translated at the clinical level.

1.3. FFAR1 signaling in insulin secretion

Because of its potential therapeutic outcomes, FFAR1 has been the most widely studied fatty acid receptor in pancreatic ß-cells. Natural ligands of FFAR1 comprise medium and Lc-FA. Activation of FFAR1 by extracellular FFAs acutely potentiates glucose-stimulated insulin secretion through intracellular $G\alpha_q$ signaling, which activates phospholipase C (PLC) in turn hydrolyzing phosphatidylinositol-4,5-bisphosphate (PIP_2) into inositol trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 acts on its receptors at the endoplasmic reticulum (ER) membrane,

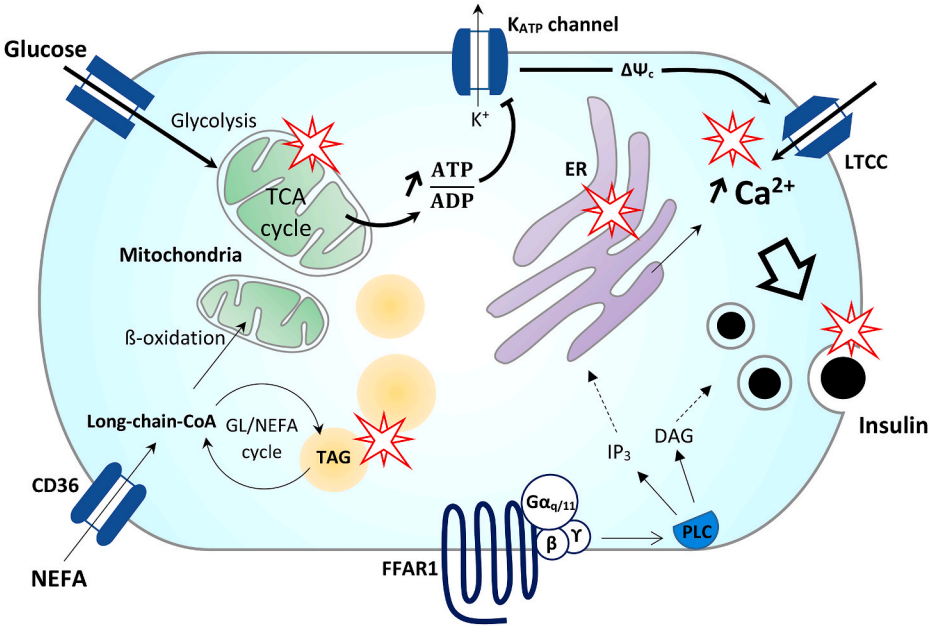

Fig. 1. Interactions between lipids and metabolism-secretion coupling in the ß-cell.
In the pancreatic ß-cell, glucose metabolism through glycolysis produces essentially pyruvate that activates mitochondria and the TCA cycle leading to the generation ATP. The thus formed ATP promotes the closure of the K-ATP channels on the plasma membrane, thereby inducing the depolarization of the plasma membrane and the opening of the voltage-sensitive L-type calcium channels (LTCC). The resulting elevation of cytosolic calcium concentration triggers insulin exocytosis. Inhibition of the ß-oxidation by glucose redirects long-chain-CoA to the glycerolipid/NEFA cycle. Stars are pointing to the main targets of intracellular injuries associated with lipotoxicity.

which induces calcium release from ER stores resulting in the further elevation of cytosolic calcium initiated by the glucose stimulation [29], see Fig. 1. DAG may also participate in the potentiation of insulin secretion by targeting protein kinase C (PKC) and favoring insulin granules exocytosis [30,31].

Although more than twenty synthetic FFAR1 ligands have been produced by universities and industries; none of them reached clinical use [32]. Despite the lack of therapeutical success, crystal structure analysis of FFAR1 bound to the agonist TAK875 was instrumental to uncover new binding pockets and various allosteric sites on the receptor [33,34]. Furthermore, the concept of biased agonism induced by FFAR1 ligands was introduced based on the observation of ß-arrestin and $G\alpha_q$ signaling being both involved in the insulinotropic activity, while differentially activated by FFAR1 ligands [35]. These findings underscore the complexity of FFAR1 signaling, and more generally of GPCR signal transduction, paving the way for innovative development of more selective anti-diabetic drugs.

2. Glucose-stimulated insulin secretion in a pathophysiological context

2.1. Pathophysiology of the ß-cell

Failure to maintain a critical and functional ß-cell mass leads to the development of diabetes. The loss of ß-cells along with detection of autoantibodies is a hallmark of Type-1 diabetes characterized by early onset of the disease and insulin dependency at diagnosis, while late onset Type-2 diabetes is first associated with insulin resistance followed by a progressive failure of ß-cell function [36]. Over the years, the classification criteria of the disease have been adjusted based on the diversity of diabetic subgroups [37]. Whether caused by genetic or environmental factors, or often a combination of both, diabetes mellitus is primarily characterized by hyperglycemia defined by fasting blood glucose above 7 mM [36]. According to the International Diabetes Federation, 537 million adults were living with diabetes in 2021, more than twice as much as in 1980. This increase correlates with the progression in the incidence of overweight (BMI 25–30 kg/m^2) and obesity (BMI >30 kg/m^2), which represents the main risk factor for Type-2 diabetes, although not all obese individuals develop diabetes [38]. A feature frequently observed in obese subjects is feeding behavior with frequent meals of energy-rich processed food and sweet beverages. This favors high glycemic index inducing robust insulin release, in turn promoting not only efficient nutrient storage but also rapid correction of glycemia eventually leading to transient low blood glucose, which then calls for anticipated repetition of food intake through hypothalamic feedback loop. Over years, such a vicious cycle promotes insulin resistance and potentially impairment of ß-cell function.

Excess feeding increases insulin exposure and promotes fat depots, which promotes obesity and insulin resistance along with glucose intolerance. Such individuals might not necessarily become diabetic, assuming compensatory insulin production and expansion of a non-deleterious adipose tissue [39]. However, imbalance in this system may lead to adipose tissue dysfunction and lipid spillover [40]. This favors the release of NEFA and the secretion of pro-inflammatory adipokines in the circulation, eventually promoting ectopic fat deposit, notably in the liver [41–45]. Accumulation of hepatic lipids promotes steatotic liver disease characterized by dysfunction and inflammation of the organ, a condition previously referred to as non-alcoholic fatty liver disease (NAFLD) and now named metabolic dysfunction-associated steatotic liver disease (MASLD) [46]. This condition potentially evolves toward cirrhosis and ultimately liver cancer [47,48]. Inflammation of metabolic organs (liver, adipose tissue, muscles) induces their resistance to the action of insulin, thereby promoting compensatory increased insulin secretion by the ß-cells. In these conditions, the ß-cells are chronically exposed to elevated circulating NEFA released by the adipocytes, including by local fat cells [49], and to glucose being overproduced by insulin resistant liver. Altogether, these factors favor glucose intolerance and hyperglycemia. The effects of chronically elevated glucose and fatty acids on ß-cell function have been widely investigated and gave rise to glucotoxicity and lipotoxicity models [50], followed by the concept of glucolipotoxicity [51].

2.2. Hyperglycemia and glucotoxic effects on the ß-cell

For diabetic patients, the maintenance of glycaemia within an overall 4–10 mM range represents a daily challenge. Any failure in this regard may lead to either hypoglycemic or hyperglycemic episodes with potentially severe complications. Recurrent hyperglycemia phases result in long-term deleterious effects, such as alterations of microvessels and nerves leading to nephropathies, neuro and retinopathies, and elevated cardiovascular risk [52–54]. Heart failure is a hallmark of Type-2 diabetes and is closely associated with poor glycemic control as well as the duration of diabetes [55]. Because hypoglycemia may have rapid devastating consequences, ranging from attention deficit to convulsion or even coma, the glucose-lowering strategies of diabetic patients are sometimes suboptimal allowing slightly chronic elevated glycaemia, assessed by HbA1c that is an independent marker of cardiomyopathy in diabetic patients. Therefore, it is crucial to better understand the effects of recurrent elevated blood glucose on insulin-secreting ß-cells and cardiovascular function.

Chronic hyperglycemia may lead to the loss of functional ß-cells as a consequence of ß-cell dedifferentiation. Lasting elevated glucose levels decrease expression of ß-cell specific transcription factors (e.g. *Pdx1/IPF1*, *MafA, Nkx6.1*) inducing ß-cell reversion to progenitor-like cells or transdifferentiation to α-cells [56–60]. Beside transcription factors, glucotoxicity alters the expression of several genes involved in mitochondrial function [61], energy sensing [62], glucose and lipid metabolism, exocytosis; collectively resulting in ß-cell dysfunction and/or death [63,64]. Glucotoxicity also favors inflammation, potentially through the production of IL-1ß that activates NF-κB altering ß-cell function [65]. Additionally, increased pro-inflammatory cytokines levels contribute to ß-cell dedifferentiation through *Foxo1* downregulation [66]. Such mitochondrial impairments and inflammation also operate on the heart promoting cardiac dysfunction [55].

2.3. Lipotoxicity, the lipid-induced ß-cell damage

Lipid-induced cellular damage, or lipotoxicity, has been considered as a major factor in the onset of Type-2 diabetes by promoting tissue inflammation and insulin resistance in peripheral tissues [45,67]. Moreover, it was suggested to further contribute to the development of the disease by directly altering ß-cell function and differentiation [50], while this model has been partially questioned recently [68].

Most of the studies on lipotoxicity and ß-cell viability have investigated the effects of palmitate and oleate; the former saturated fatty acid being more detrimental and promoting ß-cell death essentially via two mechanisms, i.e. ceramide formation and ER stress. Regarding ER stress, palmitate would favor apoptosis by inducing the depletion of ER calcium stores, thereby leading to the activation of the unfolded protein response (UPR) pathway [69,70]. This pathway was also shown to be activated by the unsaturated fatty acid oleate, although to a lesser extent [70]. This is indicative of various degrees of toxicity according to specific NEFA. Noteworthy, according to other studies also performed in rat insulinoma cells, oleate-induced apoptosis would be independent of the UPR pathway [71], as opposed to palmitate effects. The sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump is a key regulator of calcium homeostasis through its active transport of calcium from the cytosol into the ER. Lipotoxicity is accompanied by the release of cytokines, which downregulate SERCA2b in ß-cells, thereby promoting ER stress and apoptosis [72], an effect not directly contributed by NEFA. ER calcium stores can also be maintained by sorcin, a calcium binding protein that mediates termination of calcium-induced calcium release, thereby

preserving glucose-stimulated insulin secretion [73]. Sorcin has been reported to be downregulated in ß-cells exposed to palmitate and in islets isolated from mice fed a diet enriched in saturated fat, pointing to the role of palmitate in ER stress [73]. Alternative pathways have been associated with palmitate-induced ER stress, such as the aberrant palmitoylation of some proteins [74] or induction of oxidative stress upon NEFA exposure [75]. For the ß-cell, the various sources of reactive oxygen species (ROS) include the mitochondria, the peroxisomes, the ER, and microdomains of the cytosol [76]. When exposed to fatty acids, ROS are preferentially produced by both peroxisomes and mitochondria, while the latter organelle represents at the same time the primary targets of ROS [77]. In human pancreatic islets, lipotoxicity and ROS induce changes in key components of the mitochondrial machinery [63].

Palmitate is a precursor to the biosynthesis of ceramides, a form of fat that can contribute to lipotoxicity. Intracellular concentrations of ceramides are robustly increased following exposure to palmitate, which is associated with ß-cell dysfunction and apoptosis [78,79]. Practically, upon palmitate treatment upregulation of both palmitoyl transferase and ceramide synthases enhance the levels of ceramide in ß-cells [79]. Both the *de novo* and the salvage pathways of ceramides are induced by palmitate, while essentially the latter contributes to ß-cell damage. It remains unclear how ceramides promote apoptosis, possibly through ER stress and mitochondria permeabilization [78,80]. A recent study demonstrated that, upon palmitate exposure, ceramide could induce ferroptosis as a lipotoxic response in ß-cells [81], a mechanism promoting cell death and dependent on intracellular iron load and the accumulation of lipid peroxides. Following chronic exposure to NEFA, membrane and organelle structures may also be altered secondary to the changes in intracellular lipid composition. Rodent ß-cells exposed to palmitate or oleate exhibit lower membrane tension, pointing to modifications of their physicochemical properties [82].

2.4. Lipotoxicity revisited, the lipid-induced ß-cell adaptation

Upon the so-called lipotoxic conditions, unsaturated fatty acids such as oleate may exhibit some protective effects on ß-cells by preventing damages induced by the saturated fatty acids, primarily palmitate [79,83,84]. As opposed to high glucose, chronic exposure to NEFA does not result in major changes in gene expression or dedifferentiation, as observed in rodent ß-cells and human islets [85]. However, it was reported that chronic exposure of rat islets to palmitate decreases *MafA* expression and alters PDX-1 nuclear localization [86], both effects favoring ß-cell dedifferentiation. Stearoyl-CoA desaturase (SCD) is an ER enzyme that catalyzes the biosynthesis of monounsaturated fatty acids, such as palmitoleate and oleate from the saturated fatty acids palmitate and stearate, respectively. SCD was shown to confer protection against lipotoxicity and to maintain ß-cell identity in both rodent [87] and human [88] cells.

Lipid-induced ß-cell adaptation secondary to the exposure to fatty acids could be mediated by signaling upon binding to their dedicated receptors. The role of FFAR1 (or GPR40) in the acute potentiation of glucose-stimulated insulin secretion by long chain NEFA has been thoroughly described [28,89,90]. However, a putative contribution of FFAR1 in the lipotoxic response to chronic exposure to fatty acids remains controversial. About 20 years ago, FFAR1 was highlighted for its role in the harmful effects of chronic fatty acids on ß-cells [91]. This seminal study reported that the knockout of *Ffar1* protected mice against obesity-induced hyperinsulinemia and glucose intolerance and, conversely, its overexpression in the ß-cell was deleterious. Several additional *in vivo* and *in vitro* studies reported similar effects, although soon appeared controversies regarding the phenotype of *Ffar1* knockout mice [92–95]. For example, wild type versus *Ffar1* null mice showed no difference regarding glucose homeostasis and their isolated islets exhibited similar sensitivity to NEFA-induced impairment of glucose-stimulated insulin secretion [96]. Likewise, there was no difference when comparing control and *Ffar1* knockout mice fed either a standard chow diet or a high-fat diet [97]. Finally, deletion of both *Ffar1* and *Ffar4* did not alter the glucose tolerance in mice fed a high-fat diet [98].

Increasing expression of *FFAR1* in ß-cells sustains insulin secretion and ameliorates glucose tolerance in mice fed a high-fat diet as well as in diabetic KK mice [99]. Moreover, it was shown that FFAR1 signaling protects against palmitate-induced ß-cell death [100,101]. Taken together, these studies underscore the great challenge of defining the role of FFAR1 in the lipid-induced response of the ß-cells. Of note, the lack of reliable antibody against FFAR1 precludes its delineation at the protein level [102].

In addition to their action through FFAR receptors, fatty acids may trigger an inflammatory response upon binding to toll-like receptors of the innate immune system present in islets on both ß-cells and resident macrophages. This results in the activation of NF-kB and the production of proinflammatory cytokines, such as IL-1ß [103]. Like the FFAR1 response, acute versus chronic activation of this immune pathway may result in the potentiation or the inhibition of glucose-stimulated insulin secretion, respectively [104].

2.5. Glucolipotoxicity

In the course of obesity-induced Type-2 diabetes, high calorie intake promotes fat deposit and the associated insulin resistance favors elevated circulating NEFA levels, which may alter glucose clearance. Therefore, lipotoxicity and glucotoxicity are closely interconnected. In this context, it is thought that the effects of glucotoxicity and lipotoxicity are not only additive but might impair organ function in a synergistic way. These effects observed in experimental models paved the way to the concept of glucolipotoxicity, although its clinical relevance remains a matter of debate [68]. Practically, because glucose controls intracellular fatty acid partitioning, some lipotoxic effects develop only at high glucose [51,105,106]. Indeed, elevated glucose metabolism increases the cytosolic concentration of malonyl-CoA, thereby inhibiting fatty acid ß-oxidation and promoting intracellular accumulation of long-chain acyl-CoA [106]. In the same study, combining chronic high glucose with saturated fatty acids induced synergistic effects on apoptosis, whereas combined with unsaturated fatty acids the effects were much attenuated. These results highlight the cooperative nature of glucotoxicity and lipotoxicity, as well as the importance of the fatty acid double bounds in this process. Of note, the protective effects of the monounsaturated oleate to glucotoxic conditions does not apply to the polyunsaturated linolenate [82].

Regarding the intracellular mechanisms mediating glucolipotoxicity, different pathways in ß-cells have been considered [107], such as an increase in ceramide levels favoring ER stress [108] or induction of an inflammatory response through NF-κB activation [109]. Glucolipotoxic conditions may also favor ultrastructural changes in the ß-cells, mainly alterations of the mitochondrial architecture, as reported in different hyperglycemic rodent models (see review [110]) and in islets from Type-2 diabetic patients [111]. Continuous mitochondrial membrane fission and fusion events govern the balance between fragmented versus connected mitochondria, respectively. Rodent ß-cells exposed to high glucose plus palmitate exhibit a high degree of fragmented mitochondria [112]. Glucolipotoxic conditions also promote accumulation of lipid droplets in the ß-cells. Interestingly, the combination of high glucose with the unsaturated fatty acid oleate promotes massive storage of lipid droplets in rat ß-cells, whereas with the detrimental saturated palmitate the effect is way lower [85]. In a recent study, increased lipid storage capacity in rat INS-1E ß-cells, achieved by enhancing the recycling of sphingosine-1-phosphate, prevented oxidative stress and caspase-3 activation induced by either palmitate or oleate, while this protective effect was restricted to palmitate-induced apoptosis in human EndoC-ßH1 ß-cells [113]. These results suggest that increasing the capacity of the cell to drive fatty acids toward neutral lipids might serve as a safety sink limiting the formation of toxic metabolites.

3. Storage versus recruitment of intracellular lipids: the glycerolipid/NEFA cycle

3.1. The glycerolipid/NEFA cycle in action

As the chief coordinator of ß-cell function, glucose controls the metabolic fate of fatty acids. In case of glucose scarcity, recruited cytosolic fatty acids are activated to long-chain-CoA that can go into mitochondria for ß-oxidation and the supply of energy supporting basal cell functions (Fig. 1). Upon the elevation of blood glucose levels, the high capacity of glucose metabolism in the ß-cell efficiently raises glycolysis-derived pyruvate, resulting in the activation of the mitochondrial tricarboxylic acid (TCA) cycle, independently of a need of corresponding energy provision. Beside the generation of ATP, this favors the production of citrate that leaves the mitochondria to activate the cytosolic acetyl-CoA carboxylase (ACC). Its product malonyl-CoA inhibits the carnitine palmitoyltransferase I (CPT1). This shuts down ß-oxidation by preventing the entry of long-chain-CoA into mitochondria [114,115], which are rerouted towards the glycerolipid/NEFA cycle promoting the formation of lipid droplets made of TAG. The thus stored lipids might be subsequently recruited, completing the glycerolipid/NEFA cycle and potentially serving as a source of metabolic intermediaries involved in the potentiation of insulin secretion.

3.2. A role for glycerolipid/NEFA cycle in normal ß-cell

To be functional, the glycerolipid/NEFA cycle requires both lipogenic and lipolytic activities. As reported in INS-1E ß-cells and human islets, genes encoding enzymes of the glycerolipid/NEFA cycle are upregulated by glucotoxic conditions [85], which underscores the interplay between high glucose and intracellular lipid turnover. Paradoxically, in the ß-cell glucose can promote lipolysis [116–119], suggesting that glycerolipid/NEFA cycling is implicated in glucose-stimulated insulin secretion. This model was first substantiated by inhibition of lipolysis using the pan lipase inhibitor Orlistat, which resulted in impaired glucose-stimulated insulin secretion [120]. Similar effects were observed by knocking out either the hormone-sensitive lipase [121] or the adipose triglyceride lipase [122] in mouse ß-cells. Taken together, these studies revealed that the glycerolipid/NEFA cycle is playing a role in ß-cell function.

The glycerolipid/NEFA cycle has been suggested to generate derivatives of lipid metabolism serving as coupling factors in glucose-stimulated insulin secretion, although they remain to be thoroughly identified [19,123]. Both diacylglycerol and monoacylglycerol are intermediates of the glycerolipid/NEFA cycle and candidate molecules. Diacylglycerol can be derived from incomplete lipolysis of TAG or by lipogenesis from phosphatidic acid. Different pathways may produce different forms of diacylglycerol [124], eventually having signaling properties. Among those, 1,2-diacylglycerol can activate PKC resulting in the phosphorylation of proteins implicated in insulin exocytosis [31]. Insulin exocytosis is also the target of diacylglycerol through its binding to the synaptic protein Munc13-1 [125], thereby favoring the priming of the secretory vesicles; an effect also reported for monoacylglycerol [126,127].

3.3. The glycerolipid/NEFA cycling in diabetic ß-cells

In the course of obesity potentially leading to Type-2 diabetes, ß-cells increase their secretory capacity in order to compensate for obesity-induced insulin resistance, which might be followed by ß-cell decompensation triggering diabetes [107,128]. It has been proposed that the glycerolipid/NEFA cycling might be implicated in the initial adaptive response to insulin resistance [123]. In a model of obese rats, pancreatic islets exhibited both increased glucose-stimulated insulin secretion and enhanced activity of glycerolipid/NEFA cycle [129]. This points to a compensatory adaptation to cope with higher insulin demand by raising the generation of coupling factors such as diacylglycerol. Alternatively, this pathway could accommodate an excess of metabolic fuel [123]. Such a detoxification mechanism would drive part of glucose products to glycerol formation, leaving the ß-cell through aquaglyceroporins and reducing the glucotoxic load. Supportive of this model, ß-cells express a glycerol-3-phosphate phosphatase competing with the glycerolipid/NEFA cycle [130]. Alternatively, esterification of NEFA from long-chain-CoA and glycerol-3-phosphate into TAG can favor lipo-detoxification by limiting the production of NEFA and deleterious peroxidation products [113]. A similar effect is obtained with the transcription factor peroxisome proliferator-activated receptor alpha (PPARα) that reduces NEFA-induced ß-cell dysfunction by promoting storage of fatty acids into lipid droplets [131].

As of today, a putative role for the glycerolipid/NEFA cycle in ß-cells during the development of Type-2 diabetes remains speculative. In high-fat diet induced obese mice, pre-diabetes is associated with alteration of the islet glycerolipid/NEFA cycle, as suggested by reduced lipolysis and NEFA esterification [132]. An unbalanced glycerolipid/NEFA cycle has been reported in various rodent models of Type-2 diabetes [123]. In rodent and human islets exposed to glucolipotoxic conditions, the glycerolipid/NEFA cycle was shown to play a pivotal role in the maintenance of glucose-stimulated insulin secretion [85]. This protective mechanism requires both adaptive changes in the expression of genes implicated in the glycerolipid/NEFA cycle, as well as acute intracellular TAG mobilization [85].

4. Considerations about similarities between aging and Type-2 diabetes

The concept of lipotoxicity has been elaborated on various organs and, in parallel, in the context of aging. With advancing age, there is a redistribution of the white adipose tissue, with increased visceral fat and reduced subcutaneous fat mass [133]. This might induce some kind of synergism between obesity and aging as metabolically unhealthy obese subjects are characterized by decreased subcutaneous fat storage and increased fat mass in the visceral compartment [49]. Consequently, reactive lipids and their derivatives can accumulate in non-adipose tissues of metabolically active organs such as the liver, heart, skeletal muscle, and pancreatic ß-cells [40]. Type-2 diabetes is associated with obesity and its prevalence increases with age [134]. The reason for increased Type-2 diabetes with age is not clear but several factors have been proposed, such as higher adiposity and lower physical activity, eventually combined with a decline in ß-cell function [135]. This paradigm is very similar to the development of Type-2 diabetes in middle aged obese subjects, the main difference relying in the time scale of disease progression [136]. Although human studies have shown some discrepancies, collectively they point to an age-dependent failure of ß-cell function in parallel of peripheral insulin resistance [137]. For rodents, no clear consensus emerges regarding ß-cell dysfunction with age, although most of the studies report increased basal insulin release [137]. Islets of old senescence-accelerated SAMP1 mice exhibit a leftward shift of the glucose dose response with reduced insulin contents; a pattern also observed in young obese prediabetic db/db mice [138]. Human and mouse islets share similar age-associated mitochondrial failure [139], although aged mouse ß-cells compensate this metabolic deficiency by reducing the conductance of the K-ATP channel, thereby favoring the Ca^{2+} rise required for glucose-stimulated insulin secretion [139]. Overall, with increasing adiposity and reduced physical activity, age-dependent insulin resistance promotes ß-cell metabolic changes, similarly to the etiology of obesity-induced Type-2 diabetes.

5. Conclusion

In the mid-nineties, the role of lipids in ß-cell dysfunction and the pathogenesis of Type-2 diabetes was considered. The concept of lipotoxicity was born [50]. Three decades later, an amazing number of

studies have been conducted, mostly based on experimental *in vitro* and *in vivo* models. Collectively, these investigations point to free fatty acids as detrimental lipids with a special mention to saturated NEFA. The lipotoxic action might be exacerbated by the presence of high glucose, a synergistic effect referred to as glucolipotoxicity. Despite all these efforts, some interrogations remain with the lipotoxicity model as we lack robust corresponding evidence at the clinical level [68]. It is legitimate to ask ourselves if the experimental setups have been accurately designed, or if it could ever be realistic to mimic, in cell or mouse models, the etiology of a disease that takes several years to develop. Hopefully, time will tell; although it's been already about 30 years of intensive research. Potentially, novel non-invasive approaches, including the *in vivo* assessment of the functional mass ß-cell combined with lipidomics, will open new avenues in the complex and multifactorial development of Type-2 diabetes.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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