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Review

The molecular mechanisms of pancreatic β-cell glucotoxicity: Recent findings and future research directions

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ABSTRACT

It is well established that regular physiological stimulation by glucose plays a crucial role in the maintenance of the β-cell differentiated phenotype. In contrast, prolonged or repeated exposure to elevated glucose concentrations both *in vitro* and *in vivo* exerts deleterious or toxic effects on the β-cell phenotype, a concept termed as glucotoxicity.

Evidence indicates that the latter may greatly contribute to the pathogenesis of type 2 diabetes. Through the activation of several mechanisms and signaling pathways, high glucose levels exert deleterious effects on β-cell function and survival and thereby, lead to the worsening of the disease over time. While the role of high glucose-induced β-cell overstimulation, oxidative stress, excessive Unfolded Protein Response (UPR) activation, and loss of differentiation in the alteration of the β-cell phenotype is well ascertained, at least *in vitro* and in animal models of type 2 diabetes, the role of other mechanisms such as inflammation, *O*-GlcNacylation, PKC activation, and amyloidogenesis requires further confirmation. On the other hand, protein glycation is an emerging mechanism that may play an important role in the glucotoxic deterioration of the β-cell phenotype. Finally, our recent evidence suggests that hypoxia may also be a new mechanism of β-cell glucotoxicity.

Deciphering these molecular mechanisms of β-cell glucotoxicity is a mandatory first step toward the development of therapeutic strategies to protect β-cells and improve the functional β-cell mass in type 2 diabetes.

Contents

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1. Introduction

Pancreatic β-cells secrete insulin after meals to tighten blood glucose levels within a narrow range. The regulation of their function relies on a complex array of metabolic, neural, and hormonal factors. The most important factor is glucose itself, since most of the other modulators of insulin release exert their effects only in the presence of stimulatory levels of glucose. Thus, the rise in plasma glucose concentration triggers its rapid equilibrium across β-cell plasma membrane, its oxidation by glycolysis and the Krebs cycle, and an increase in the cytosolic ATP/ADP ratio. The latter event leads to the closure of ATP-sensitive K^+ (K_{ATP}) channels, plasma membrane depolarization, and opening of voltage-dependent Ca^{2+} channels. The ensuing Ca^{2+} influx induces a rise in cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$) which is the triggering signal for insulin secretion. This sequence of events is called the triggering pathway of glucose-stimulated insulin secretion (GSIS) (Henquin, 2000; Henquin et al., 2003). On the other hand, coupling factors produced by glucose metabolism, hormones, and neurotransmitters can amplify Ca^{2+}-induced insulin granule exocytosis. It is called the amplifying pathway of insulin secretion (Henquin, 2000; Henquin et al., 2003; Jitrapakdee et al., 2010; MacDonald et al., 2005).

The ability of β-cells to respond to an acute glucose challenge depends on adequate level of expression of several genes, including preproinsulin, the glucose transporter Glut2, glucokinase (Gck), etc. (Schuit et al., 2002). This level of expression is modulated by meals: it is reduced during fasting and rapidly restored upon feeding (Hinke et al., 2004). Interestingly, both chronic hypoglycaemia and chronic hyperglycemia induce the loss of β-cell differentiation, alter the stimulus-secretion coupling, and increase the rate of β-cell apoptosis, along with increased expression of genes under-expressed in normal β-cells (Blume et al., 1995; Butler et al., 2003b; Iwashima et al., 1994; Jonas et al., 1999; Laybutt et al., 2002). Similarly, *in vitro*, rodent β-cell function and survival are optimally preserved by culture in the presence of 10 mM glucose (G10) and markedly impaired by culture in either lower (2 to 5 mM glucose, G2–G5) or higher (30 mM glucose, G30) glucose concentrations (Bensellam et al., 2009; Efanova et al., 1998; Khaldi et al., 2004). It seems therefore that glucose stimulation exerts beneficial effects on the β-cell phenotype between G2 and G10 (Fig. 1). In contrast, supraphysiological glucose concentrations (between G10 and G30) are deleterious for β-cell function and survival, a concept termed as glucotoxicity (Fig. 1). The latter plays an important role in the alteration of the functional β-cell mass in type 2 diabetes (T2D), and contributes to the progressive worsening of glucose intolerance in these patients (Buchanan, 2003; Chang-Chen et al., 2008; Weir et al., 2009).

Rigorous investigation since the 1980s led to a progressive understanding of the molecular pathways that may underlie β-cell glucotoxicity. However, these mechanisms are not fully understood and some of them are debated. In this extensive review, we briefly emphasize the importance of regular physiological stimulation by nutrients in preserving the functional β-cell mass, and discuss the concept of β-cell glucotoxicity. We describe in details our current knowledge regarding the activation of these pathways by chronic hyperglycemia, how does each pathway contribute to the alteration of the β-cell phenotype, and their complex interaction. Finally, we present future research directions raised by these findings and highlight unsettled questions in the field.

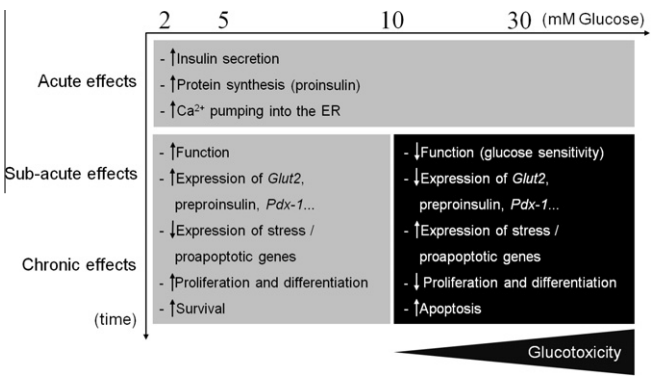

Fig. 1. Glucose exerts pleiotropic effects on the β cells depending on the intensity and the duration of stimulation. See the text for details. ER: Endoplasmic Reticulum; Glut2: Glucose transporter 2; Pdx-1: Pancreatic and duodenum homeobox-1.

2. Physiological effects of glucose and other nutrients on the β-cell differentiated phenotype

Regular stimulation by nutrients plays a key role in maintaining the functional β-cell mass through effects on β-cell survival and gene expression. The latter effects, which maintain β-cells in their differentiated state, include increased expression of "β-cell enriched genes" and repression of so-called "β-cell forbidden genes" (Quintens et al., 2008; Schuit et al., 2002). Physiological glucose stimulation differently affects the β-cell phenotype depending on the duration of the stimulation (Fig. 1).

2.1. Short-term effects

In the short-term (from minutes to a few hours), in addition to GSIS, glucose and other nutrients stimulate protein synthesis with a preferential effect on proinsulin and other granule proteins (Alarcon et al., 1993; Ashcroft, 1980; Grimaldi et al., 1987; Guest et al., 1989; Ling et al., 1996; Schuit, 1988; Skelly et al., 1996) (Fig. 1). Glucose regulates proinsulin biosynthesis predominantly by rapid stimulation of pre-existing preproinsulin mRNA translation (Gilligan et al., 1996; Gomez et al., 2004; Greenman et al., 2005; Itoh et al., 1978; Itoh and Okamoto, 1980; Vander Mierde, 2007; Welsh et al., 1986; Wicksteed et al., 2001). Proinsulin biosynthesis requires glucose metabolism but is independent from changes in $[Ca^{2+}]_i$ (Alarcon et al., 2002; Ashcroft, 1980; Leibowitz et al., 2003; Wicksteed et al., 2003).

In addition, glucose has been shown to induce rapid changes in the polysomal mRNA levels of several genes including those involved in oxidative stress response and endoplasmic reticulum (ER) stress response (Greenman et al., 2007).

In parallel, it is well established that the acceleration of β-cell metabolism upon acute glucose stimulation increases Ca^{2+} pumping into the ER via the sarcoendoplasmic reticulum Ca^{2+}-ATPase 2B (Moore et al., 2011; Ravier et al., 2011; Tengholm et al., 1999; Varadi and Rutter, 2002) (Fig. 1). Noteworthy, the ER Ca^{2+} concentration ($[Ca^{2+}]_{ER}$) plays a key role in proper function of several ER-resident molecular chaperones and foldases (Corbett et al., 1999; Gelebart et al., 2005; Suzuki et al., 1991), and in the processing of proinsulin (Guest et al., 1997). Therefore, this event may play a role in the modulation of chaperones activity, and in the adaptation of the ER folding machinery to the important increase in protein synthetic load triggered by glucose stimulation in β-cells (Ling and Pipeleers, 1996; Schuit, 1988).

These short-term effects are essential in refilling insulin cellular stores, maintaining β-cell glucose-responsiveness, and preparing β-cells for the next glucose challenge *in vivo* (Hinke et al., 2004).

2.2. Long-term effects

Besides the acute regulatory mechanisms, the maintenance of β-cell glucose responsiveness in the long-term (more than 12 h) relies on an adequate level of gene expression (Fig. 1). Indeed, it has been shown that extended physiological glucose stimulation regulates insulin gene transcription (Nielsen et al., 1985; Van Lommel et al., 2006; Wicksteed et al., 2003), translation (Permutt, 1974; Schuit, 1988; Wicksteed et al., 2003), preRNA splicing (Wang

et al., 1997), and mRNA stabilization (Tillmar et al., 2002; Welsh et al., 1985). The glucose-dependent regulation of insulin gene expression relies on a network of transcription factors that include principally pancreas duodenum homeobox-1 (PDX-1), V-maf musculoaponeurotic fibrosarcoma oncogene homologue A (MafA), and neurogenic differentiation 1 (NeuroD1). Glucose modulates the activity of these transcription factors through transcriptional/post-translational mechanisms that have been reviewed elsewhere (Andrali et al., 2008).

In addition to the insulin gene, prolonged stimulation (24 h) of purified primary rat β-cells within the physiological range of glucose concentrations (G10 vs. G3) has been shown to increase the mRNA levels of genes encoding proteins of several components of the triggering pathway of insulin secretion, including Glut2, subunits of the mitochondrial respiratory chain, both subunits of the K_{ATP} channel, genes involved in cataplerosis, fatty acid biosynthesis, and cholesterol biosynthesis (Flamez et al., 2002). Our previous microarray study testing the effects of 18 h culture in increasing glucose concentrations (G2, G5, G10 and G30) on the transcriptome of rat islets largely confirmed and extended these observations (Bensellam et al., 2009). In agreement, rat β-cells exposed to low glucose concentrations *in vivo* during prolonged fasting (72 h) showed a marked decrease in the mRNA levels of Glut2, voltage-dependent L-type Ca^{2+} channel α1 subunit, insulin, and Gck mRNA levels. These alterations were rapidly reversed following refeeding (Iwashima et al., 1994).

On the other hand, culture of rat and mouse islets in G10 vs. G2–G5 strongly inhibited the expression of several stress-response genes (Fig. 1), including oxidative stress response genes such as heme-oxygenase 1 (Hmox1) and metallothionein 1a (Mt1a), ER stress response genes such as heat shock 70kDa protein 5 (Hspa5/BiP), DNA-damage inducible transcript 3 (Ddit3 (Chop/Gadd153)), growth arrest and DNA-damage-inducible protein 34 (Gadd34), activating transcription factor 3 (Atf3) and tribbles homologue 3 (Trb3), and pro-apoptotic genes such as the proto-oncogene myelocytomatosis viral oncogene homolog (avian) (Myc) (Bensellam et al., 2009; Elouil et al., 2007; Jonas et al., 2009). Remarkably, these effects are accompanied by acute inhibition of mitochondrial oxidative stress (Hou et al., 2008b; Martens et al., 2005; Roma et al., 2012; Sarre et al., 2012).

In parallel to gene expression changes, physiological glucose stimulation is crucial for the preservation of optimal β-cell function. Thus, prolonged culture of primary rat β-cells, rat islets, and human islets in the presence of low non-stimulatory glucose concentrations noticeably decreased glucose-induced rise in $[Ca^{2+}]_i$, GSIS, and insulin biosynthesis (Bensellam et al., 2009; Flamez et al., 2002; Ling and Pipeleers, 1996). Similarly, islets of fasted rats (72 h) exhibited alterations of β-cell function that were reversed after refeeding (Iwashima et al., 1994).

Moreover, glucose is one of the most important stimuli for β-cell mass maintenance by stimulating proliferation-neogenesis-hypertrophy (Alonso et al., 2007; Bernard et al., 1999; Bonner-Weir et al., 1989; De Vroede et al., 1990; Hugl et al., 1998; Jetton et al., 2008; Kwon et al., 2006; Liu et al., 2009; Maedler et al., 2006; Steil et al., 2001; Swenne, 1982; Topp et al., 2004; Tyrberg et al., 1996) and inhibiting apoptosis (Bensellam et al., 2009; Costes et al., 2006; Efanova et al., 1998; Hoorens et al., 1996; Ling et al., 1994; Srinivasan et al., 2002; Van de Casteele et al., 2003) (Fig. 1).

3. Deleterious effects of supra-physiological glucose stimulation on the β-cell differentiated phenotype

3.1. The concept of glucotoxicity

While regular physiological glucose stimulation is essential to the maintenance of the β-cell differentiated phenotype as explained in the previous section, prolonged or repeated exposure to elevated glucose concentrations both *in vitro* and *in vivo* exerts toxic effects on the β-cell phenotype (Unger and Grundy, 1985) (Fig. 1). Thus, in the context of T2D, the inability of β-cells to adapt to the high organism's metabolic demand by secreting adequate amounts of insulin leads to the development of hyperglycemia (Beck-Nielsen and Groop, 1994; Kahn, 2003). The latter exerts additional damaging effects on β-cells, thus creating a vicious circle that contributes to the progressive decrease of the functional β-cell mass and thereby, to the worsening of the disease over time (Buchanan, 2003) (Fig. 2).

Of note, hyperglycemia exerts its deleterious effects either directly (glucotoxicity) or by unveiling the harmful effects of fatty acids (glucolipotoxicity). Although it is well established that elevated free fatty acid (FFA) levels exert deleterious effects on β-cells *in vitro*, there is no certainty about their role in β-cell demise in T2D subjects (Boden and Shulman, 2002; Grill and Bjorklund, 2009; Weir et al., 2001). Nevertheless, growing evidence points to a permissive effect of glucose on the deleterious actions of FFAs (Poitout and Robertson, 2008). In this review, we have only focused on β-cell glucotoxicity. The role of synergistic effects of the combination high glucose-elevated FFAs has been extensively reviewed elsewhere (Poitout et al., 2010). Other reactive metabolites including ketone bodies have been shown to alter β-cell function *in vitro* (Takehiro et al., 2005; Zhou and Grill, 1995). However, their potential contribution to β-cell glucotoxicity in T2D requires further proof.

Besides its role in β-cell demise in T2D, the hyperglycemic milieu also plays an important role in the loss of β-cell mass and the deterioration of β-cell differentiation after islet transplantation (Laybutt et al., 2007b; Montana et al., 1993). It is thus important to study the phenomenon of glucotoxicity and decipher its underlying mechanisms, toward the development of therapeutic solutions to protect and/or restore the functional β-cell mass (Fig. 2). However, despite rigorous investigations hitherto, the precise nature of these mechanisms and their contribution to the pathology of T2D is not fully understood.

The first source of confusion arises from the lack of consensus about the definition of glucotoxicity. One school of thoughts describes glucotoxicity as the irreversible alterations of β-cell function and gene expression resulting from prolonged exposure (several months or years rather than days) to supra-physiological glucose concentrations both *in vitro* and *in vivo* (Briaud et al., 1999; Gleason et al., 2000; Harmon et al., 2001; Robertson and Harmon, 2006; Tanaka et al., 1999). These authors maintain there is a clear distinction between glucose desensitization, which connotes a temporary reversible state of β-cell refractoriness to glucose stimulation due to β-cell exhaustion after exposition to elevated glucose concentrations (several hours to several days) (Kaiser et al., 1991; Sako and Grill, 1990), and the "true" glucose toxicity (Moran et al., 1997; Robertson et al., 1994; Robertson et al., 2003). Nonetheless, one can debate this distinction between glucose desensitization and glucose toxicity.

Concerning the dimension of time, numerous early high glucose-induced stress genes, such as Myc and Hmox1, have been shown to represent early signs of β-cell glucotoxicity that can profoundly affect the β-cell fate (Jonas et al., 2001; Jonas et al., 2003; Kaneto et al., 2002c; Laybutt et al., 2002a,b; Pascal et al., 2008; Van de Casteele et al., 2003). Besides, β-cell apoptosis, which represents the final stage of glucotoxicity, has been observed after culture of human and rodent islets for only several days in elevated glucose concentrations (Bensellam et al., 2009; Federici et al., 2001; Jonas et al., 2009; Khaldi et al., 2004; Leibowitz et al., 2001; Ling et al., 1994; Maedler et al., 2001; Piro et al., 2002), but also *in vivo* in animal models of T2D after few weeks of hyperglycemia, or even few days in some animal models (Donath et al., 1999; Finegood et al.,

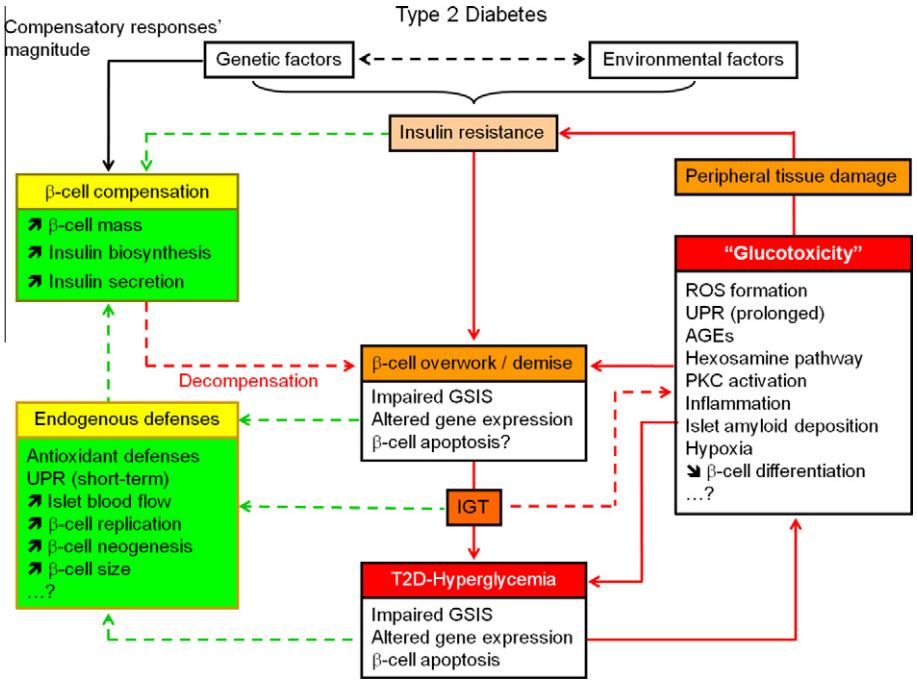

Fig. 2. Schematic representation of the different mechanisms underlying β-cell pathophysiology in T2D that precede and follow the establishment of hyperglycemia, and the role of glucotoxicity in the aggravation of insulin resistance and β-cell failure. T2D results from a complex interplay of genetic and environmental factors that affect whole body insulin sensitivity and GSIS. Although insulin resistance is thought to be the best clinical predictor of T2D that is found in most subjects with T2D, the development of frank diabetes mellitus requires an additional defect in insulin secretion. Thus, in the absence of a defect in GSIS, β-cells maintain normoglycemia at the price of hyperinsulinemia. The extent of β-cell compensation is thought to be predetermined genetically. This adaptation involves a coordinated increase in β-cell mass, insulin biosynthesis and insulin secretion. However, in genetically predisposed subjects, this phase is bypassed by a second phase of decompensation due to the inability of β-cells to sustain an adequate secretory response to match the organism demand (β-cell overwork). This phase is characterized by the alteration of GSIS, gene expression and likely β-cell apoptosis leading to the development of impaired glucose tolerance (IGT) and finally the establishment of hyperglycemia with reduction of functional β-cell mass. Chronic hyperglycemia leads to the exacerbation of β-cell overwork and the alteration of β-cell function and survival by several not fully understood mechanisms. In addition, hyperglycemia exerts toxic effects on peripheral tissues which contribute to the aggravation of insulin resistance. Very importantly, β-cell endogenous defenses are triggered in response to β-cell failure and elevation of glycemia to restore the functional β-cell mass. The imbalance between the protective effects of endogenous defenses and the deleterious effects of glucotoxicity is at the root of T2D pathology.

2001; Kluth et al., 2011; Leibowitz et al., 2001; Pick et al., 1998). Furthermore, it has been shown that even intermittent exposure of human islets, rat islets, and rat insulinoma cells (INS1) to high glucose concentrations for several days markedly impaired GSIS and triggered β-cell apoptosis (DelGuerra et al., 2007; Hou et al., 2008a). These observations suggest that postprandial glycemic fluctuations in prediabetic individuals with impaired glucose tolerance (IGT) may exert glucotoxic effects that contribute to the loss of functional β-cell mass and the progression toward frank diabetes (Fig. 2). Therefore, it seems that exposure of β-cells to high glucose levels for months or years is not an obligatory criterion to define glucotoxicity, at least *in vitro* and in animal models of T2D.

We therefore consider the early defects in GSIS and the concomitant or subsequent changes in gene expression and ultimate decrease of the functional β-cell mass as manifestations of glucose toxicity, regardless of the duration of the exposure to elevated glucose levels and whether these alterations are corrected after blood glucose normalization or not (Bensellam et al., 2009; Jonas et al., 1999; Khaldi et al., 2004; Laybutt et al., 2002).

Another source of confusion is the important discrepancy between evidences gained from *in vitro* and *in vivo* models of β-cell glucotoxicity and also between species. Such differences stem mainly from the variability of glucose concentrations at which β-cell glucotoxicity is observed. Thus, on the one hand, ~G10, which is the optimal glucose concentration for rodent β-cell function and survival *in vitro* (Bensellam et al., 2009; Efanova et al., 1998; Jonas et al., 2009), is already harmful *in vivo* (Finegood et al., 2001; Jonas et al., 1999; Laybutt et al., 2002) as well as for cultured human islets (Maedler et al., 2001) that are best preserved by culture in the presence of ~G5 (Ling and Pipeleers, 1996). On the other hand, the very high glucose levels that induce glucotoxicity *in vitro* (~G30–40) (Bensellam et al., 2009; Efanova et al., 1998; Jonas et al., 2009; Khaldi et al., 2004; Zraika et al., 2006) are unlikely to occur in T2D subjects (ADA, 2010). These differences between *in vitro* and *in vivo* models may result in part from the absence, *in vitro*, of other nutrients such as amino acids, incretin hormones such as GLP-1, and neurotransmitters such as acetylcholine that increase the sensitivity of β-cells to glucose, and also from the shorter periods of culture in the presence of elevated glucose concentrations that can be tested *in vitro*. Nevertheless, these differences do not disqualify totally *in vitro* studies. The latter have provided invaluable information about the role of glucotoxicity in β-cell damage, and several lines of evidence suggest that similar mechanisms of β-cell glucotoxicity are operative *in vitro* and *in vivo* (Chang-Chen et al., 2008; Jonas et al., 2009; Marchetti et al., 2010; Poitout and Robertson, 2008).

3.2. The mechanisms of β-cell glucotoxicity

Despite intensive therapy, β-cell function deteriorates during the years following the diagnosis of T2D (Turner, 1998; UKPDS Group, 1998), suggesting a role of the metabolic environment in β-cell demise. Therefore, persistent hyperglycemia has been proposed among the potential causes underlying these functional alterations based on earlier observations that blood glucose normalization partially reverses β-cell defects (Garvey et al., 1985; Glaser et al., 1988; Kosaka et al., 1980; Rossetti et al., 1987; Turner et al., 1976). Besides, it is now accepted that insufficient GSIS in

T2D may also result from a reduction in β-cell mass (Deng et al., 2004; Rahier et al., 2008; Sakuraba et al., 2002; Yoon et al., 2003). Our current understanding of the role of glucotoxicity in the loss of functional β-cell mass is based mainly on animal studies and *in vitro* experimentation on isolated islets and β-cell lines (Grill and Bjorklund, 2009; Jonas et al., 2009; Poitout and Robertson, 2008). Over several years, these studies revealed complex mechanisms behind β-cell glucotoxicity.

3.2.1. β-Cell overstimulation

It is well established that conditions of enhanced insulin secretory demand *in vivo* (insulin resistance, IGT, and hyperglycemia), or prolonged exposure to elevated glucose levels *in vitro* lead to β-cell overstimulation until a point where insulin biosynthesis is unable to cope with the high rates of insulin secretion (Fig. 2). This leads to the alteration of GSIS and the elevation of the circulating proinsulin to insulin ratio, likely as a consequence of β-cell insulin reserve depletion and the release of newly formed insulin granules before complete processing of proinsulin (Alarcon et al., 1995; Gadot et al., 1994, 1995; Ling et al., 2001; Marshak et al., 1999; Sempoux et al., 2001).

The role of overstimulation in β-cell glucotoxicity has been clearly demonstrated by β-cell rest interventions. Thus, it has been shown that the inhibition of GSIS and the depletion of islet insulin stores induced by prior culture of rat and human islets in the presence of high glucose concentrations was prevented by addition of K_{ATP} channel openers, such as diazoxide, to the culture medium (Bjorklund and Grill, 1993; Ma et al., 2007; Ritzel et al., 2004; Song et al., 2003; Yoshikawa et al., 2004). In agreement, the alteration of GSIS triggered by 48h glucose infusion in rats was opposed by co-infusion of diazoxide (Sako and Grill, 1990). Furthermore, long-term treatment of transplanted diabetic rats with K_{ATP} channel openers has been shown to markedly preserve the function of the graft even one week after drug withdrawal (Bjorklund et al., 2004).

Besides the restoration of islet insulin stores, the beneficial effects of diazoxide have been proposed to stem, at least in part, from the improvement of β-cell survival both *in vitro* and *in vivo* (Efanova et al., 1998; Huang et al., 2007b), direct effects on mitochondria (Grimmsmann and Rustenbeck, 1998; Lenzen and Panten, 1983; MacDonald, 1981), and important gene expression changes including: (i) upregulation of Pdx1, NK6 transcription factor related, locus 1, and genes of fatty acid synthesis, and (ii) downregulation of cAMP Response-Element Modulator (Crem), lactate dehydrogenase A (Ldha), uncoupling protein 2 (Ucp2), Caspase 7, and genes of fatty acid oxidation (Ma et al., 2007). Interestingly, previous reports in our laboratory have shown that diazoxide inhibited high glucose-induced expression of Myc and Hmox1 (Jonas et al., 2001, 2003). We also observed that high glucose-induced Mt1a expression was inhibited by diazoxide (MB and JCJ, unpublished results). These observations suggest that β-cell rest interventions may also improve the β-cell phenotype by reducing oxidative stress.

Noteworthy, although diazoxide has been shown to reduce fatty acid-induced ER stress in INS1 cells, murine insulinoma (MIN6) cells and rat islets (Sargsyan et al., 2008), we observed that it did not affect high glucose-induced upregulation of ER stress markers in rat islets (Elouil et al., 2007). This finding suggests that glucose activation of the ER stress response is independent from excessive insulin secretion induced by prolonged exposure to high glucose.

Previous clinical trials with diazoxide in T2D patients who were treated with bedtime insulin moderately improved several parameters of β-cell function, but failed to improve metabolic control (Guldstrand et al., 2002; Qvigstad et al., 2004). In addition, co-treatment with insulin has been shown to be required to obtain the beneficial effects of diazoxide (Radtke et al., 2007). Therefore, despite the well demonstrated beneficial effects of diazoxide, the exploitation of these findings in the development of a therapeutic strategy in T2D patients requires further investigation.

3.2.2. Oxidative stress

ROS delineates a group of free radicals and molecules derived from molecular oxygen that play an important role in both physiology and pathology of several cell types including β-cells (Pi et al., 2010; Robertson, 2004). Under physiological conditions, they are generated continuously by mitochondria as a byproduct of oxidative phosphorylation (Turrens, 2003), but cells bring into play various antioxidant systems to rapidly neutralize ROS and maintain an optimal redox environment for proper biological function. However, this equilibrium is lost in diabetic individuals where enhanced ROS formation overwhelmed and/or decreased the antioxidant defenses of the organism. Oxidative stress leads to cellular damage which plays a central role in the development of diabetic complications, insulin resistance and β-cell dysfunction (Ceriello, 2003; Evans et al., 2002; Robertson, 2009; Son, 2007).

β-cells are vulnerable to oxidative stress due to their low expression of the principal antioxidant enzymes superoxide dismutase 1 and 2 (SOD1-2), glutathione peroxidase 1 (GPX1), and catalase (CAT) (Lenzen et al., 1996; Tiedge et al., 1997; Tonooka et al., 2007). In addition, it has been recently suggested that islets have poor DNA repair capacity against oxidative damage (Modak et al., 2009).

The link between oxidative stress and glucotoxicity has been suggested by earlier studies in β-cell lines, isolated islets, and diabetic animal models showing that antioxidants can protect β-cells against the deleterious effects of high glucose levels on insulin secretion, insulin gene expression, islet insulin content and survival (Kaneto et al., 1996; Kaneto et al., 1999; Tajiri et al., 1997; Tajiri and Grill, 2000; Tanaka et al., 1999).

In agreement with these observations, it has been shown that high glucose increased ROS production in hamster insulinoma cells HIT-T15, MIN6 cells, rat islets, mouse islets as well as human islets (Bindokas et al., 2003; Morgan et al., 2007; Sakai et al., 2003; Tanaka et al., 2002; Zraika et al., 2006). Besides, it has been reported that islet cells of Zucker Diabetic Fatty (ZDF) rats and MKR mice presented a higher ROS content than their control littermates and showed in parallel, altered mitochondrial morphology and function (Bindokas et al., 2003; Lu et al., 2010). Although the mitochondrial respiratory chain is thought to be the major source of ROS, *in vitro* and *in vivo* observations support the involvement of NADPH oxidase (NOX) complexes also in this process (Morgan et al., 2007; Nakayama et al., 2005).

As shown in Table 1, high glucose has also been shown to increase oxidative stress markers and to stimulate the expression of several oxidative stress-response genes in β-cell lines, isolated islets, the islets of diabetic animals, and the islets of human T2D subjects. Furthermore, overexpression of several antioxidant enzyme genes including Cat, Gpx1, Hmox1, Mt, Sod1-2, peroxiredoxin 3, and thioredoxin has been shown to protect β-cells against ROS toxicity (Chen et al., 2001; Hotta et al., 1998; Lortz and Tiedge, 2003; Lortz et al., 2005; Tobiasch et al., 2001; Tanaka et al., 2002; Wolf et al., 2010). Thus, compelling evidence indicates that β-cells suffer from oxidative stress under prolonged hyperglycemia.

But how do ROS alter the β-cell phenotype? Oxidative stress-mediated inhibition of insulin gene expression has been shown to stem in part from the well-established diminution of PDX-1 binding to the insulin promoter (Olson et al., 1993, 1995), as a result of reduced expression and nuclear exclusion by a mechanism involving the activation of c-jun N-terminal kinase (JNK) (Kaneto et al., 2002a; Kawamori et al., 2003). JNK activation has been shown to play a central role in β-cell apoptosis induced by culture in low glucose via a mechanism involving ROS inhibition of JNK-

Table 1
Selection of oxidative stress markers and antioxidant response genes upregulated by high glucose levels in *in vitro* and *in vivo* models. 8-OHdG: 8-hydroxydeoxyguanosine; Cat: Catalase; Cox2: Cyclooxygenase 2; Gpx: Glutathione peroxidase; G6pd: glucose-6-phosphate dehydrogenase; Hmox1: Heme oxygenase 1; HNE: 4-hydroxy-2-nonenal; Mt: Metallothionein; Myc: myelocytomatosis viral oncogene homolog (avian); Nox: NADPH oxidase; Nrf2: NF-E2–related factor 2; Prxd: Peroxiredoxin; Sod: Superoxide dismutase; Srxn1: Sulfiredoxin1; Txnip: Thioredoxin-interacting protein; Txn: Thioredoxin; Ucp2: Uncoupling protein 2. *Our results contrast with another study showing that the expression and activity of G6pd is downregulated in mouse and human islets cultured in the presence of elevated glucose concentrations (Zhang et al., 2010).

Marker/ gene	*In vitro model*	*In vivo* model	Role	References
8-OHdG	INS1 cells, Rat islets	GK rat islets, OLETF rat islets, human T2D islets	Product of oxidative DNA damage	Hou et al. (2008a), Sakuraba et al. (2002), Nakayama et al. (2005), and Ihara et al. (1999)
HNE-modified proteins		GK rat islets, *Lepr*$^{db/db}$ mouse islets	Marker of lipid peroxidation	Gorogawa et al. (2002) and Ihara et al. (1999)
Cat		GK rat islets	Anti-oxidant	Lacraz et al. (2009b)
Cox2		GK rat islets	Pro-oxidant	Lacraz et al. (2010)
Gpx1		Px rat islets, *Lepr*$^{db/db}$ mouse islets, GK rat islets, human T2D islets	Anti-oxidant	Laybutt et al. (2002a), Kjorholt et al. (2005), Marchetti et al. (2004), and Lacraz et al. (2009b)
Gpx2	Rat islets		Anti-oxidant	Bensellam et al. (2009)
G6pd*	Rat islets	GK rat islets	Glucose metabolism, Anti-oxidant	Bensellam et al. (2009),Lacraz et al. (2009b)
Hmox1	Rat islets	Px rat islets, *Lepr*$^{db/db}$ mouse islets, GK rat islets	Anti-oxidant	Laybutt et al. (2002a), Jonas et al. (2003), Elouil et al. (2005), Kjorholt et al. (2005), and Lacraz et al. (2009b)
Mt1a	Rat islets		Anti-oxidant	Bensellam et al. (2009)
Mt1e, Mt1g, Mt1m, Mt1x		Human T2D islets	Anti-oxidant	Marselli et al. (2010)
Mt2a	Rat islets	Human T2D islets	Anti-oxidant	Bensellam et al. (2009) and Marselli et al. (2010)
Myc	Rat islets	Px rat islets, GK rat islets	Pro-apoptotic	Jonas et al. (2001), Elouil et al. (2005), and Lacraz et al. (2010)
Nox1		Human T2D islets	Pro-oxidant	Marchetti et al. (2004)
Nox2		GK rat islets	Pro-oxidant	Lacraz et al. (2010)
Nrf2/Nfe2l2		GK rat islets	Anti-oxidant	Lacraz et al. (2009b)
Prxd1		GK rat islets	Anti-oxidant	Lacraz et al. (2009b)
Prxd2		GK rat islets	Anti-oxidant	Lacraz et al. (2009b)
Sod1		Px rat islets, GK rat islets	Anti-oxidant	Laybutt et al. (2002a) and Lacraz et al. (2009b)
Sod2	Rat islets	Px rat islets, GK rat islets, human T2D islets	Anti-oxidant	Bensellam et al. (2009), Laybutt et al. (2002a), Marselli et al. (2010), and Lacraz et al. (2009b)
Srxn1	Rat islets		Anti-oxidant	Bensellam et al. (2009)
Txnip	INS1 cells, rat islets, Human islets	GK rat islets	Pro-apoptotic	Bensellam et al. (2009), Homo-Delarche et al. (2006), Shalev et al. (2002), and Shao et al. (2010)
Txn1		GK rat islets	Anti-oxidant	Lacraz et al. (2009b)
Txn2		GK rat islets	Anti-oxidant	Lacraz et al. (2009b)
Ucp2	Rat islets	Glucose-infused rat islets, Px rat islets, *Lepr*$^{db/db}$ mouse islets, *Lep*$^{ob/ob}$ mouse islets, ZDF rat islets	Anti-oxidant, impair GSIS	Khaldi et al. (2004), Laybutt et al. (2002a), Kjorholt et al. (2005), Kassis et al. (2000), Zhang et al. (2001), and Oberkofler et al. (2009)

upstream phosphatases (Hou et al., 2008b), but it is unclear whether this mechanism is operative under high glucose. Moreover, high glucose-induced oxidative stress has been shown to contribute to the loss of insulin gene expression by reducing MafA protein levels in HIT-T15 cells (Harmon et al., 2005). High glucose can also suppress insulin gene transcription by upregulating the expression of Myc (Jonas et al., 2001; Kaneto et al., 2002c), an oxidative stress-activated gene that has been shown to play an important role in β-cell dysfunction and apoptosis (Elouil et al., 2005; Pascal et al., 2008; Pelengaris et al., 2002; Van de Casteele et al., 2003).

In addition, it has been previously demonstrated in rat and mouse β-cells that hydrogen peroxide (H_2O_2) induced the loss of mitochondrial membrane potential and reduced the intracellular ATP concentration, leading to the opening of K_{ATP} channels, hyperpolarization of plasma membrane and thereby, inhibition of GSIS (Krippeit-Drews et al., 1999; Maechler et al., 1999). Interestingly, the deleterious effects of H_2O_2 on β-cell function and survival were prevented by genetic or pharmacologic inhibition of K_{ATP} channel activity, at least in part, as a consequence of increased activity of the antioxidant enzymes SOD, GPX and CAT (Gier et al., 2009).

Moreover, ROS-mediated alteration of GSIS has been proposed to be related to the downregulation of GAPDH activity (Sakai et al., 2003). The latter may lead to the accumulation of upstream glycolytic metabolites which flow into several glucotoxic pathways, including the Advanced Glycation End products (AGEs) pathway (Brownlee, 2001). The inhibition of GAPDH activity may also hamper the glycolytic flow and NADH shuttling, which results in the inhibition of mitochondrial ATP generation and thereby, inhibition of GSIS (Eto et al., 1999).

It is well established that excessive ROS production induces important macromolecular damage. Of note, mitochondrial DNA is particularly susceptible to oxidative stress owing to the absence of histones, and the poor DNA-repair mechanisms (Yakes and Van, 1997). In addition, several mitochondrial proteins such as aconitase and adenine nucleotide translocase have been shown to be targets for oxidative damage (Yan et al., 1997; Yan and Sohal, 1998).

In view of the various evidences that oxidative stress is central to the pathogenesis of T2D, antioxidant therapy should be theoretically very beneficial to these patients. Antioxidant (pre)treatment of diabetic animal models (*Lepr*$^{db/db}$ mice, ZDF rats, STZ-induced diabetic mice and rats etc.) provided some promising results over the last decade with regard to the protection against diabetic complications (Abiko et al., 2003; Fiordaliso et al., 2004; Pazdro and Burgess, 2010), the improvement of insulin sensitivity (Banday et al., 2005; Blouet et al., 2007; Houstis et al., 2006; Khamaisi et al., 1999; Song et al., 2005), and the enhancement of β-cell func-

tion and survival (Coskun et al., 2005; Dixit et al., 2010; Gorogawa et al., 2002; Harmon et al., 2009; Ihara et al., 2000; Kaneto et al., 1999; Kanter et al., 2004; Meghana et al., 2007; Sefi et al., 2011; Takatori et al., 2004; Tanaka et al., 1999).

Interestingly, clinical trials using seed extracts of *Silybum marianum* (Silymarin) alone or in combination with glibenclamide were very promising and showed a marked improvement of glycemic control in T2D patients (Huseini et al., 2006; Hussain, 2007). On the other hand, the few pilot trials of antioxidant supplementation in humans yielded unpersuasive results and were in sum disappointing (Bashan et al., 2009; Evans, 2007; Pazdro and Burgess, 2010). Even more, some reports proposed that selenium and vitamin E supplementation may increase T2D risk and all-cause mortality respectively (Miller et al., 2005; Stranges et al., 2007).

However, it is possible that the antioxidants used targeted H_2O_2 which plays also an important signaling role, while the central player in β-cell oxidative stress may be the superoxide anion. Interestingly, it has been shown in our laboratory that H_2O_2-induced alterations of rat islet function were prevented by addition of N-acetyl-L-cycteine (NAC) or the SOD mimetic agent, Mn(III)tetrakis(4-benzoic acid)porphyrin (chloride) (MnTBAP) to the culture medium. However, these antioxidants were unable to counter the functional alterations induced by prolonged exposure to high glucose (Khaldi et al., 2006). Alternatively, in the model of glucose infused rats, β-cell function was preserved *in vivo* and in isolated islets by co-infusion of the SOD mimetic 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl (Tempol). The latter completely prevented islet total and mitochondrial superoxide generation while NAC and taurine failed (Tang et al., 2007).

3.2.3. ER stress

During the last decades, the ER stress pathway has emerged as an important mechanism implicated in the pathogenesis of several diseases including diabetes (Delepine et al., 2000; Ladiges et al., 2005; Laybutt et al., 2007a; Senee et al., 2004; Thameem et al., 2006) and its ensuing complications (Lindenmeyer et al., 2008; Liu et al., 2008 ; Li et al., 2009; Morse et al., 2010).

The ER is a cellular organelle that fulfills vital biological roles including lipid synthesis, protein synthesis, posttranslational modifications and correct folding. The latter is mandatory for proper function of proteins. Therefore, the ER is endowed with a set of ER-resident molecular chaperones and foldases, and contains a high Ca^{2+} concentration to allow their proper activity. However, an increase in ER client protein load or a decrease in chaperone function leads to the exhaustion of the ER folding capacity and accumulation of unfolded proteins. Face to this "stress", a cellular adaptive response called the Unfolded Protein Response (UPR) is activated to restore ER homeostasis. The UPR is orchestrated by three master ER sensors: (i) the pancreatic ER kinase (PERK) which phosphorylates the α subunit of the translation initiation factor 2 (eIF2α) on serine 51, leading to rapid and transient global reduction in protein translation to reduce ER-client protein load, with a paradoxical increase in the translation of some rare transcripts, including activating transcription factor 4 (ATF4). The latter stimulates the expression of chaperones, antioxidant response genes, but also the proapoptotic effectors Ddit3, Atf3, and Trb3. Recently, it has been shown that eIF2α phosphorylation also upregulates the expression of the apoptosis antagonizing transcription factor, a novel UPR effector that promotes β-cell survival under ER stress through transcriptional upregulation of v-akt murine thymoma viral oncogene homolog 1 (Akt1) (Ishigaki et al., 2010) (Fig. 3); (ii) inositol requiring 1 (IRE1) which triggers the unconventional splicing of X-box binding protein 1 (Xbp1) pre-mRNA and subsequent increase in active XBP1. The latter, together with (iii) active ATF6, activates the expression of ER chaperone genes and ER-associated degradation (ERAD) genes in order to improve chaperone capacity, degrade the unfolded proteins and avoid ER proteotoxicity. Besides ERAD machinery, clearance of misfolded proteins may also occur through autophagy (Kaushik et al., 2010; Schroder and Kaufman, 2005; Schroder, 2008).

Importantly, since eIF2α phosphorylation can be activated by other kinds of cellular stress independently from the UPR (Harding et al., 2003; Ma and Hendershot, 2004), increased mRNA levels of Ddit3 and/or other ATF4-target genes alone should not be considered as signs of ER stress. It must be paralleled by PERK phosphorylation and/or the activation of IRE1 and/or ATF6. Therefore, we will designate the PERK arm of the UPR as the Integrated Stress Response (ISR) (Bensellam et al., 2009; Elouil et al., 2007; Ma and Hendershot, 2004).

If UPR activation fails to restore ER homeostasis under prolonged or intense ER stress, an apoptotic program is triggered, as depicted in Fig. 3. This program involves the complex action of several not fully identified effectors including Ddit3 (Oyadomari and Mori, 2004; Song et al., 2008), Trb3 (Bromati et al., 2011; Liew et al., 2010), Atf3 (Li et al., 2008), IRE1 (Han et al., 2009; Lipson et al., 2008; Pirot et al., 2007), and likely perturbations of Ca^{2+} homeostasis (Scorrano et al., 2003; Tsujimoto and Shimizu, 2007) (Fig. 3).

β-Cells are particularly sensitive to ER stress due to their high rate of proinsulin biosynthesis in response to glucose stimulation (see Section 2.1). Therefore, adequate UPR response is vital for the maintenance of the functional β-cell mass, whereas exaggerated activation and/or genetic disruption of the UPR triggers β-cell apoptosis and induces diabetes in man and rodents (Oslowski and Urano, 2010; Scheuner and Kaufman, 2008).

The first evidence suggesting a role of UPR signaling in β-cell glucotoxicity comes from several reports showing increased expression/activation of UPR-ISR markers in β-cells exposed to elevated glucose levels, either *in vitro* or *in vivo* (Table 2). However, despite the importance of these observations, upregulation of UPR makers alone do not prove a contributory role of ER stress in the glucotoxic alterations of the β-cell phenotype.

The second evidence linking UPR to β-cell glucotoxicity comes from genetic manipulations of UPR components and other genes in β-cell lines and mouse models. Thus, high glucose-induced downregulation of insulin gene expression in INS1 cells has been shown to be significantly prevented by Atf6 silencing. In contrast, active ATF6 overexpression in INS1 cells inhibited insulin secretion and gene expression in parallel to a marked reduction in PDX-1 and MafA mRNA and protein levels (Seo et al., 2008). In the same model, it has been shown that Trb3 overexpression inhibited GSIS, enhanced the deleterious effects of high glucose on cell growth, fostered high glucose-induced ROS production, and increased high glucose-induced apoptosis (Qian et al., 2008). Similarly, strong overexpression of Xbp1 in rat islet cells reduced the degree of β-cell differentiation, inhibited GSIS, and increased β-cell apoptosis (Allagnat et al., 2010). On the other hand, BiP overexpression in INS1 cells partially prevented the toxic effects of chronic high glucose on insulin gene expression and proinsulin biosynthesis (Zhang et al., 2009).

In vivo, it has been shown that Ddit3 deletion in $Lepr^{db/db}$ mice prevented fasting hyperglycemia and glucose intolerance as a consequence of enhanced β-cell function, increased proliferation, and inhibition of apoptosis (Song et al., 2008). Recently, a study in glucose-infused rats has shown that co-infusion of the chemical chaperones 4-phenylbutyrate (PBA) or tauro-ursodeoxycholic acid (TUDCA) prevented hyperglycemia-induced β-cell dysfunction and markedly reduced the activation of several ER stress markers. Very interestingly, this study has also established a link between ER stress and oxidative stress pathways since the chemical chaperones reduced superoxide generation while Tempol prevented eIF2α phosphorylation, Ddit3 upregulation, and Xbp1 splicing

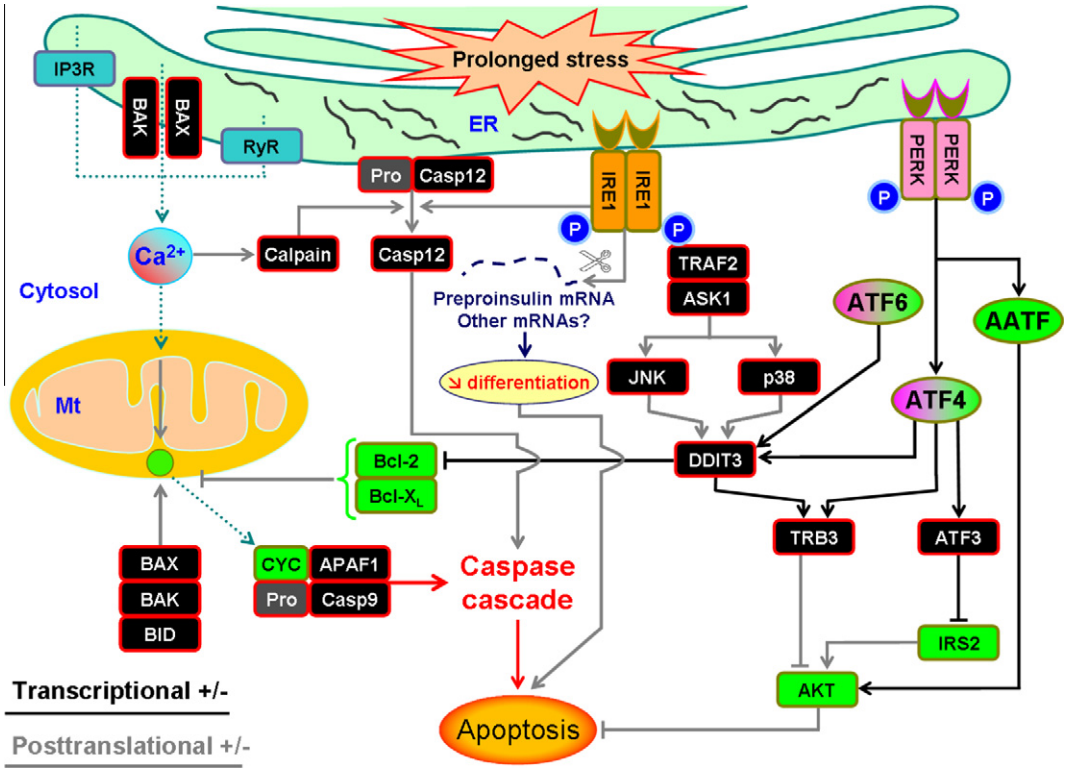

Fig. 3. Schematic representation of the cascade of molecular events triggered by unresolved ER stress leading to cell death. Besides stimulating the expression of chaperones, ATF4 induces the expression of the proapototic effectors Ddit3, Atf3, and Trb3 which act through the repression of Bcl2 and Irs2 gene expression and AKT activity respectively. On the other hand, hyperactive IRE1 stimulates proapoptotic effectors including JNK, Ddit3 and Casp12, and degrades preproinsulin mRNA and likely other mRNAs leading to a decrease in the degree of β-cell differentiation. AATF: apoptosis antagonizing transcription factor; AKT: thymoma viral proto-oncogene 1; APAF1: Apoptotic peptidase-activating factor 1; ASK1: apoptosis signal-regulated kinase 1; ATFX: Activating transcription factor X; CaspX: Caspase X; BAK: BCL-2 homologous antagonist/killer; BAX: BCL-2-associated X protein; BCL-XL: BCL-x long; BCL2: B cell leukemia/lymphoma 2; BID: BH3 interacting domain death agonist; CYC: Cytochrome c; Ddit3: DNA damage inducible transcript 3; ER: Endoplasmic reticulum; JNK: c-Jun NH2-terminal kinase; IP3R: Inositol 1,4,5-trisphosphate receptor; IRE1: Inositol requiring 1; IRS2: Insulin receptor substrate 2; Mt: Mitochondria; PERK: double-stranded RNA activated protein kinase (PKR)-like ER kinase; RyR: Ryanodine receptor; TRAF2: Tumor necrosis factor receptor-associated factor 2; Trb3: Tribbles homologue 3.

(Tang et al., 2012). These observations are in agreement with a previous study showing that prevention of eIF2α phosphorylation in β-cells induced oxidative stress (Back et al., 2009). However, it is unclear which pathway operates upstream of the other. It is possible that increased mitochondrial superoxide generation leaks into the ER. Alternatively, protein folding and particularly disulfide-bond formation may also generate ROS.

Altogether, these observations suggest that excessive stimulation of the UPR pathway under prolonged or unresolved ER stress in parallel to the activation of the ISR branch plays an important role in β-cell glucotoxicity.

3.2.4. Protein glycation and AGE-receptors

Glucose and other reducing sugars can spontaneously react with amine residues on proteins, lipids, and nucleic acids to form stable covalent adducts known as AGEs (Huebschmann et al., 2006) (Fig. 4). It is well established that hyperglycemia fosters this nonenzymatic glycation leading to intracellular AGEs accumulation and thereby, structural alterations of intracellular proteins (Brownlee, 2001). AGEs can also exert their toxic effects by diffusion out of the cell and modification of ECM proteins (Brownlee, 2001), and/or indirectly by binding to AGEs receptors (RAGE) and triggering various signalization cascades. Noteworthy, the activation of nuclear factor κB (NFκB) is a key target of RAGE signaling (Kim et al., 2005) (Fig. 4).

Evidence suggested that high glucose levels increase protein glycation and AGEs formation in rat and mouse islets (Pascal et al., 2010; Tajiri et al., 1997). Interestingly, it has been previously reported that aminoguanidine (AG) (an inhibitor of AGEs formation) can preserve insulin gene expression, proinsulin biosynthesis and GSIS in HIT-T15 cells, INS1 cells and rat islets cultured in the presence of high glucose levels (Tanaka et al., 1999; Tajiri et al., 1997; Tajiri and Grill, 2000), and a similar beneficial effect was observed in the islets of ZDF rats (Tanaka et al., 1999). However, the effects of AG in the latter study were also mimicked by NAC, suggesting that AG may act by reducing high glucose-induced oxidative stress (Tanaka et al., 1999). Another possibility is that AGEs formation exerts its deleterious effects by triggering oxidative stress. Interestingly, AGEs treatment has been recently shown to increase β-cell ROS generation *in vitro* and *in vivo* in parallel to functional alterations. These effects were countered using antioxidants (Coughlan et al., 2011; Lin et al., 2012). It has also been shown that AGEs inhibited GSIS via nitric oxide-dependent inhibition of cytochrome c oxidase and ATP production in mouse islets and INS1 cells (Zhao et al., 2009) (Fig. 4). In the latter model, AGEs treatment markedly reduced GSIS and increased apoptosis in a time and concentration-dependent manner in parallel to cytochrome *c* release from mitochondria, activation of effector caspases, and reduced insulin and Bcl2 gene expression (Zhu et al., 2011) (Fig. 4). These effects are thought to be mediated by the RAGEs since they were prevented by RAGE antibody or RAGE knockdown (Zhu et al., 2011). This concept was supported by the increased apoptosis rate observed in INS1 cells treated with RAGE ligands (Lee et al., 2010). AGEs have also been shown to decrease the expression and nuclear localization of PDX-1 together with increased levels of acetylated Forkhead box O1 (FoxO1) in HIT-T15

Table 2
Activation/upregulation of selected UPR-ISR markers in β-cells exposed to elevated glucose levels *in vitro* and/or *in vivo*. Atf: Activating transcription factor; BiP: Binding Ig Protein; Ddit3: DNA damage inducible transcript 3; Dnajc3: DNAJ (Hsp40) homologue C3; Edem1: ER degradation enhancer, mannosidase α-like 1; eIF2α: eukaryotic translation initiation factor 2α; Fkbp11: FK506 binding protein 11; IRE: Inositol requiring 1; PERK: double-stranded RNA activated protein kinase (PKR)-like ER kinase; Trb3: Tribbles homologue 3; Xbp1: X-box binding protein 1.

Marker/gene	Model	Reference
UPR		
IRE hyperactivation	INS1 cells	Lipson et al. (2008, 2006)
	Mouse islets	Lipson et al. (2008, 2006)
Xbp1 mRNA splicing	INS1 cells	Seo et al. (2008)
	Rat islets	Bensellam et al. (2009) and Elouil et al. (2007)
	Mouse islets	Jonas et al. (2009)
	Lepr$^{db/db}$ mouse islets	Laybutt et al. (2007a)
Activated ATF6	INS1 cells	Seo et al. (2008)
	OLETF rat islets	Seo et al. (2008)
BiP (chaperone)	INS1 cells	Wang et al. (2005b)
	Rat islets	Elouil et al. (2007)
	Lepr$^{db/db}$ mouse islets	Laybutt et al. (2007a)
	MKR mouse islets	Lu et al. (2008)
	Human T2D islets	Laybutt et al. (2007a)
Dnajc3 (chaperone)	Rat islets	Bensellam et al. (2009)
	Lepr$^{db/db}$ mouse islets	Laybutt et al. (2007a)
	MKR mouse islets	Lu et al. (2008)
	Human T2D islets	Laybutt et al. (2007a)
Fkbp11 (foldase)	Rat islets	Bensellam et al. (2009)
	Lepr$^{db/db}$ mouse islets	Laybutt et al. (2007a)
	MKR mouse islets	Lu et al. (2008)
Edem1 *(ERAD)*	Rat islets	Bensellam et al. (2009) and Elouil et al. (2007)
	Lepr$^{db/db}$ mouse islets	Laybutt et al. (2007a)
ISR		
PERK phosphorylation	INS1 cells	Hou et al. (2008a)
eIF2α phosphorylation	INS1 cells	Hou et al. (2008a) and Seo et al. (2008)
	OLETF rat islets	Seo et al. (2008)
	Lepr$^{db/db}$ mouse islets	Laybutt et al. (2007a)
Atf4	INS1 cells	Hou et al. (2008a)
	Rat islets	Hou et al. (2008a)
	Lepr$^{db/db}$ mouse islets	Laybutt et al. (2007a)
Atf3	Rat islets	Elouil et al. (2007)
	Lepr$^{db/db}$ mouse islets	Kjorholt et al. (2005)
	Human T2D islets	Hartman et al. (2004)
Ddit3	INS1 cells	Hou et al. (2008a), Seo et al. (2008), and Wang et al. (2005b)
	Rat islets	Elouil et al. (2007) and Hou et al. (2008a)
	Lepr$^{db/db}$ mouse islets	Laybutt et al. (2007a)
	Human T2D islets	Huang et al. (2007a), Laybutt et al. (2007a)
Trb3	INS1-rβ cells	Qian et al. (2008)
	GK rat islets	Qian et al. (2008)
	Lep$^{ob/ob}$ mouse islets	Liew et al. (2010)
	Human T2D islets	Liew et al. (2010)

cells, giving thus a new insight on the mechanism by which AGEs can alter insulin gene expression (Puddu et al., 2010) (Fig. 4).

On the other hand, studies on mice fed on a high AGE diet have shown that these animals become diabetic within 6 months and presented impaired pancreatic islet structure and function (Sandu et al., 2005). In agreement, *Lepr*$^{db/db}$ mice fed on a low AGE diet showed improved insulin sensitivity and a better preserved structure of the islets (Hofmann et al., 2002).

Together, these results suggest that the AGEs pathway may play an important role in the loss of functional β-cell mass in diabetes, at least in part through the induction of oxidative stress and the alteration of β-cell differentiation and survival (Fig. 4).

3.2.5. Hexosamine pathway

Evidence indicated that hyperglycemia can enhance glucose flux trough a pathway that converts fructose-6-phosphate and glutamine into glucosamine-6-phosphate and glutamate by the rate-limiting enzyme of the pathway, glutamine:fructose-6-phosphate amidotransferase (GFAT). Then, glucosamine-6-phosphate is further metabolized to uridine diphosphate-N-acetylglucosamine which is the substrate of the Olinked β-N-acetylglucosamine transferase (OGT). This enzyme catalyzes the transfer of N-acetylglucosamine (*O*-GlcNacylation) on serine and/or threonine residues of target proteins including PDX-1 (Gao et al., 2003) and FoxO1 (Housley et al., 2008; Kuo et al., 2008). These enhanced *O*-GlcNac posttranslational modifications lead to protein gain/loss of function and subsequently, important changes in gene expression that have been proposed to contribute to β-cell glucotoxicity.

Thus, GFAT overexpression in isolated rat islets or glucosamine treatment impaired GSIS in parallel to increased H_2O_2 production, reduced DNA binding activity of PDX-1, and reduced expression of insulin, Glut2 and Gck. These effects were reversed by NAC treatment (Kaneto et al., 2001). These results were confirmed and extended by another study showing that culture of rat islets in the presence of glucosamine inhibited GSIS and decreased the mRNA levels of Glut2 and Gck while increasing those of hexokinase

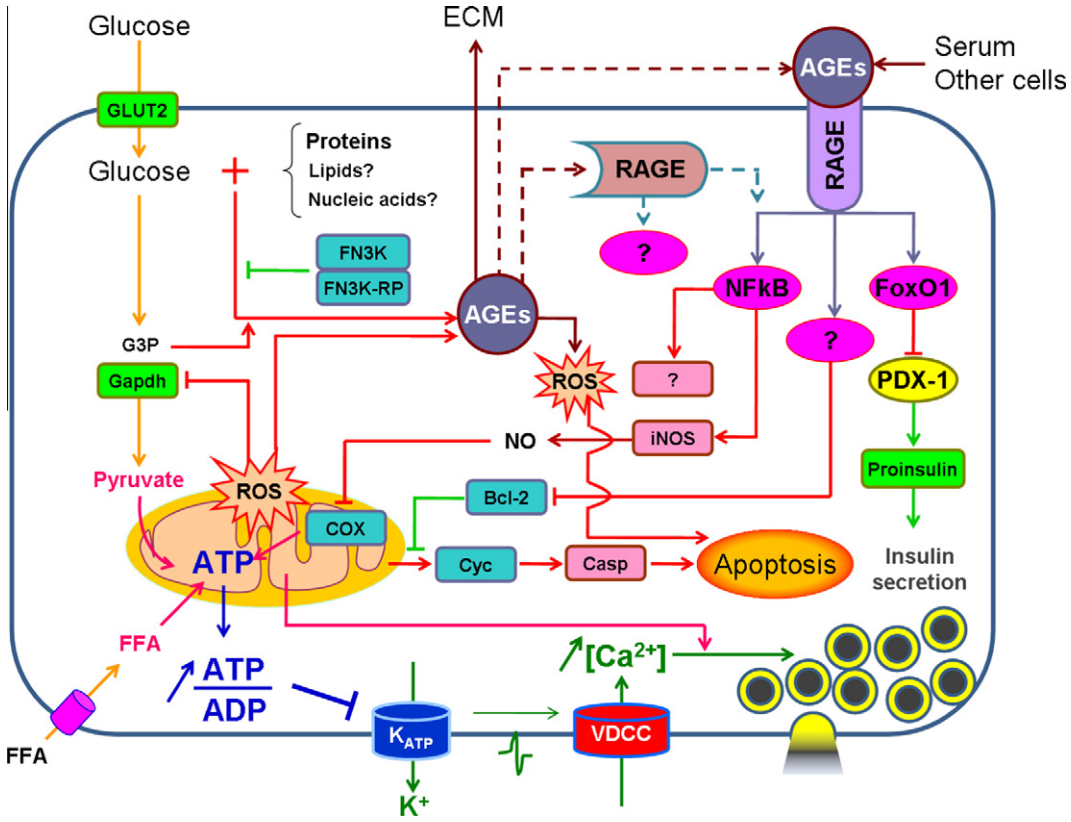

Fig. 4. Schematic representation of the molecular basis of the deleterious effects of AGEs on the β-cell phenotype. AGEs can either be formed inside β-cells or furnished by serum and adjacent cells such as endothelial cells. Mitochondrial ROS can stimulate AGEs formation by several mechanisms. One potential mechanism is the inhibition of GAPDH activity and subsequent accumulation of glyceraldehyde-3-phosphate (G3P), the precursor of methylglyoxal. Once formed, AGEs can stimulate ROS formation, thereby aggravating oxidative stress and leading to β-cell apoptosis. Recent evidence has shown that AGEs exert their deleterious effects predominantly by binding to their plasma membrane receptor RAGE and likely to other RAGE intracellular receptors. Activation of RAGE receptors triggers the expression of the acetylated form of FoxO1. The latter inhibits the expression and nuclear localization of PDX-1 leading to reduced insulin gene expression, which may explain in part the inhibitory effects of AGEs on GSIS and insulin content. In addition, AGEs-RAGE activates NFκB that stimulates the expression of inducible nitric oxide synthase (iNOS) and maybe other genes. Nitric oxide (NO) inhibits the cytochrome c oxidase (COX) leading to reduced ATP synthesis and GSIS. Moreover, RAGE activation inhibits the expression of the antiapoptotic gene Bcl2 and stimulates cytochrome c (Cyc) release into the cytosol, the activation of effector caspases (Casp) and β-cell apoptosis. ECM: Extracellular matrix; FN3K: fructosamine-3-kinase; FN3K-RP: FN3K related protein.

(Hk) (Yoshikawa et al., 2002). *In vivo*, the islets of diabetic Goto-Kakizaki (GK) rats exhibited increased expression and enzymatic activity of OGT alongside a global rise in islets protein *O*-GlcNacylation including PDX-1 (Akimoto et al., 2007). Besides, glucosamine infusion in rats markedly impaired GSIS (Shankar et al., 1998) and increased β-cell apoptosis (Liu et al., 2000). Finally, excessive activation of the hexosamine pathway has also been proposed to play a role in high glucose-induced human β-cells apoptosis (D'Alessandris et al., 2004).

However, if a growing body of data indicates that excessive *O*-GlcNac modification of proteins in β-cells may be deleterious, one should be aware that other evidence indicates that the hexosamine pathway plays an important physiological role. Thus, either pharmacological inhibition of GFAT by azaserine or OGT knockdown in MIN6 cells reduced insulin secretion (Akimoto et al., 2007; Gao et al., 2003).

3.2.6. PKC activation

PKC is a family of serine/threonine kinases that play an important role in both β-cell physiology and pathology. It encompasses at least 10 isoforms classified into three subfamilies: classical PKCs (α, βI, βII and γ) regulated by Ca^{2+} and diacylglycerol (DAG), novel PKCs (δ, ε, θ and η) regulated by DAG, and atypical PKCs (ζ and ιλ) regulated by neither Ca^{2+} nor DAG (Mellor and Parker, 1998).

Evidence from *in vitro* and *in vivo* experimentation has demonstrated that hyperglycemia preferentially activates PKCβII in several vascular tissues including retina, heart and aorta (Das Evcimen and King, 2007). Rat and mouse islets and β-cell lines express several isoforms of PKC including PKCβII (Carpenter et al., 2004; Kaneto et al., 2002b; Knutson and Hoenig, 1994). The activation of the latter has been shown to be partly involved in hyperglycemia-induced activation of Myc and subsequent reduction in insulin gene expression and GSIS (Kaneto et al., 2002c). In addition, PKCε inhibition has been shown to improve GSIS in the islets of *Lepr*$^{db/db}$ mice (Schmitz-Peiffer et al., 2007). In contrast, another report has shown that pharmacological activation of PKCε decreased mouse islet cell apoptosis after isolation without affecting GSIS (Kvezereli et al., 2008).

Inhibition of PKCβ has been shown to be a promising approach toward the treatment of microvascular complications in diabetic animals and humans (Clarke and Dodson, 2007; Ishii et al., 1996; Koya et al., 1997, 2000; Nonaka et al., 2000). However, until now and to our knowledge, no therapeutic approaches have been made toward the improvement of the functional β-cell mass in T2D subjects likely due to the multiplicity of PKC isoforms, their complex roles in β-cell pathophysiology, and the lack of specific inhibitors.

3.2.7. Inflammation

There is good evidence that inflammation is an important mechanism that contributes to the initiation, development, and progression of T2D (Donath and Shoelson, 2011; Kolb and Mandrup-Poulsen, 2005). The (pre)diabetic state is indeed characterized

by a low-grade inflammation as evidenced by increased plasma levels of several inflammatory markers, including C-reactive protein (CRP), interleukine-1β (IL-1β), IL-6, tumor necrosis factor alpha and white blood cell count (Donath and Shoelson, 2011; King, 2008). The proinflammatory cytokines and chemokines released by adipose tissue, endothelial cells, and immune cells under hyperglycemic conditions are thought to contribute to the inflammatory process in several tissues including the liver and pancreatic islets (Donath and Shoelson, 2011; King, 2008; Shoelson et al., 2006).

Thus, fibrosis, which generally results from inflammation, has been observed in the islets of ZDF rat (Pick et al., 1998), Otsuka Long Evans Tokushima Fatty (OLETF) rat (Ko et al., 2004), the Spontaneously Diabetic Torii rat (Masuyama et al., 2004), and GK rat (Homo-Delarche et al., 2006). In the latter model, islets fibrosis was accompanied by vascular alterations, overexpression of several genes involved in the inflammatory response, and increased macrophage and granulocyte staining around and inside the islets on pancreas sections (Homo-Delarche et al., 2006). These alterations have been proposed to stem from endothelial cell activation under hyperglycemic conditions, and subsequent increased expression of adhesion molecules and proinflammatory cytokines, including IL-1β, which can affect β-cells directly and also by recruitment of immune cells (Lacraz et al., 2009a). Islet macrophage infiltration and increased expression of IL-1β have also been reported in the pancreas sections of T2D patients (Ehses et al., 2007; Maedler et al., 2002).

Interestingly, IL-1β expression and secretion have been shown to be upregulated in human islets cultured in the presence of high glucose levels. This was paralleled by increased NFκB activation, reduced expression of endogenous IL-1 receptor antagonist (IL-1Ra), upregulation of the cell death receptor Fas, and increased β-cell death. These effects were opposed by addition of IL-1Ra to the culture medium, which prevented also high glucose induced inhibition of GSIS (Maedler et al., 2002). In agreement, a clinical trial using a recombinant human IL-1Ra in T2D patients showed improved glycemia, enhanced β-cell function, and reduced circulating levels of CRP and IL-6 even 39 weeks after IL-1Ra withdrawal (Larsen et al., 2007, 2009).

However, high glucose-induced activation of NFκB and subsequent stimulation of IL-1β expression have neither been confirmed in our laboratory in isolated rat islets (Elouil et al., 2005), nor by others in purified human β-cells (Cnop et al., 2005), cultured human islets, and islets from T2D subjects (Welsh et al., 2005). Moreover, a recent report has demonstrated that mouse islets deficient in IL-1 receptors or Fas are not protected against high glucose or ribose-induced apoptosis (McKenzie et al., 2010). One plausible explanation of these conflicting results is the use of culture dishes coated with ECM in the former studies, which allows the proliferation of contaminating non-endocrine cells. Besides, the beneficial effect observed after IL-1Ra treatment in T2D patients may be explained by a general effect on the whole body inflammation rather than a unique effect on β-cells.

Altogether, these observations highlight the intricate network of interactions between β-cells, immune cells, endothelial cells, and peripheral tissues in the hyperglycemic environment that contribute to the inflammatory process in T2D.

3.2.8. Islet amyloid deposition

The islets of T2D patients are characterized by the presence of amyloid deposits (Clark and Nilsson, 2004; Deng et al., 2004; Haataja et al., 2008). The latter are insoluble fibrils formed by the assembly of islet amyloid polypeptide (IAPP) soluble monomers (also known as amylin) into a linear rigid organization, which forms insoluble precipitates in the perivascular region and likely inside β-cells (Clark and Nilsson, 2004; Gurlo et al., 2010; Lin et al., 2007). IAPP is a 37-amino acid polypeptide of unclear physiological function, which is coexpressed and cosecreted with insulin by β-cells. IAPP has been shown to form amyloid in diabetic humans, monkeys, and cats but not in rodents due to proline substitutions in the hydrophobic amyloidogenic sequence (Clark and Nilsson, 2004).

Interestingly, amyloid deposits have also been observed in the islets of normoglycemic individuals. In addition, amyloid-containing islets presented only a slight decrease in proinsulin mRNA, refuting thereby a causative role of islet amyloidogenesis in the development of T2D (Sempoux et al., 2001). Nevertheless, *in vitro* and animal studies showed that it is small IAPP oligomers rather than amyloid fibrils that are toxic for β-cells. Thus, human IAPP (hIAPP) aggregates have been shown to induce β-cell death *in vitro* via a mechanism involving disruption of cell membrane (Janson et al., 1999). Besides, inhibition of IAPP expression in cultured human islets markedly reduced islet cell apoptosis, preserved islet architecture and enhanced β-cell function (Marzban et al., 2008). *In vivo*, it has been shown that IAPP oligomers are intracellular and do not colocalize with amyloid in transgenic mice overexpressing hIAPP in β-cells (Lin et al., 2007). These results are in agreement with previous observations that apoptotic β-cells in hIAPP-transgenic rodents were not adjacent to amyloid deposits (Butler et al., 2003a, 2004). In hIAPP-transgenic mice, IAPP oligomers were present in the secretory pathway including ER, Golgi apparatus, and the secretory vesicles. Interestingly, electron microscopy revealed that IAPP aggregates were adjacent to disrupted ER, secretory vesicle and mitochondrial membrane in agreement with *in vitro* observations. Similarly, IAPP oligomers were also found in the secretory pathway of human T2D β-cells (Gurlo et al., 2010).

IAPP oligomerization may stem from the saturation and dysfunction of ER machinery under hyperglycemic conditions, which reduces its capacity to clear IAPP oligomers as they form. Thus, overexpression of hIAPP in rodent β-cells has been shown to induce ER stress (UPR and ISR) in parallel with the accumulation of polyubiquitylated proteins (Costes et al., 2011; Huang et al., 2007a). This accumulation has been shown to result from hIAPP-related deficiency in ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1), an enzyme that allows access of proteins destined for degradation to the proteasome. Interestingly, UCH-L1 deficiency is also observed in human T2D islets (Costes et al., 2011). However, its dependence on IAPP aggregation in human T2D needs to be proven. Moreover, increased expression of hIAPP in rat β-cells has been shown to alter the autophagy pathway, which also plays an important role in the clearance of misfolded proteins (Rivera et al., 2011).

But until now, no report has demonstrated the colocalization of IAPP oligomers and apoptotic β-cells in T2D individual. Besides, the antibody used to detect these oligomers has been claimed to recognize other targets such as heat shock proteins (Zraika et al., 2010).

Overall, these observations suggest perhaps a role for amyloidogenesis in the alteration of the β-cell phenotype in T2D. The ER stress pathway may play a role in this process, particularly when the ER is overwhelmed under conditions of β-cell overstimulation.

3.2.9. Hypoxia

Hypoxia delineates a fall in tissue pO_2 below the normal level, which arises when O_2 demand exceeds O_2 supply. It leads to a metabolic crisis as manifested by reduced ATP production and increased mitochondrial ROS generation, and represents thereby a considerable threat to cell viability. Interestingly, hypoxic cells activate a master adaptive response orchestrated by the Hypoxia-Inducible Factor (HIF) family which enables cell survival through a switch from aerobic mitochondrial to anaerobic glycolytic ATP production, in parallel to the inactivation of pyruvate dehydroge-

nase and increased mitochondrial autophagy to prevent increased ROS generation (Semenza, 2010; Taylor, 2008).

HIFs are basic helix-loop-helix-PAS domain transcription factors composed of a regulated α subunit (either HIF1α or HIF2α), and a constitutively expressed HIF1β subunit (Aryl-hydrocarbon-Receptor Nuclear Translocator (ARNT)). Under normoxic conditions, HIFα subunits are hydroxylated by prolyl-hydroxylase-domain proteins in an O_2-, Fe^{2+}- and α-ketoglutarate-dependent manner. This hydroxylation promotes HIFα interaction with von Hippel-Lindau protein (VHL), leading to their polyubiquitylation and proteasomal degradation. Conversely, under hypoxic conditions, HIFα subunits are no longer degraded and translocate with their dimerisation partner ARNT to the nucleus to activate the transcription of HIF-target genes including glycolytic enzymes, pyruvate dehydrogenase kinase 1 (Pdk1), the vasodilating peptide adrenomedullin (Adm), vascular endothelial growth factors, erythropoietin, etc (Benita et al., 2009; Elvidge et al., 2006; Semenza, 2010).

The HIF pathway plays an imperative role in the modulation of β-cell function, survival/proliferation, and glucose homeostasis. Thus, either excessive repression or excessive activation are deleterious for β-cells as revealed by the phenotypical alterations observed in mice lacking vhl (Cantley et al., 2009; Choi et al., 2011; Puri et al., 2009; Zehetner et al., 2008), Arnt (Gunton et al., 2005), and Hif1α (Cheng et al., 2010), although the latter is controversial (Cantley et al., 2009). Besides, it has been previously reported that Hif1α and Arnt expression were downregulated in islets isolated from the pancreases of dead T2D patients (Gunton et al., 2005), although these observations were not confirmed by others (Marselli et al., 2010).

In the context of glucotoxicity, islet perifusion experiments have shown increased basal and reduced maximal GSIS in Vhl-KO islets (Zehetner et al., 2008), an effect similar to that observed in rat islets cultured for 18h or one week in the presence of high glucose levels (Bensellam et al., 2009; Khaldi et al., 2004). Glucose stimulation is also known to increase respiration in INS1 cells (Spacek et al., 2008), and to increase islet O_2 consumption rate and reduce intra-islet pO_2 in rodents, primates, and humans (Gilbert et al., 2008; Jung et al., 2000; Jung et al., 2009; Longo et al., 1991; Sweet and Gilbert, 2006; Wang et al., 2005a). Moreover, islet blood flow regulation has been shown to be altered in diabetic animals (Carlsson et al., 1996; Svensson et al., 2000; Svensson et al., 2005), and high glucose has been shown to induce human islet endothelial cell apoptosis *in vitro* (Favaro et al., 2008). In agreement, several rodent models of T2D displayed marked alteration of islet vasculature, including *Lepr*$^{db/db}$ mice (Shao et al., 2007), OLETF rats (Mizuno et al., 1999), GK rats (Homo-Delarche et al., 2006), and ZDF rats (Li et al., 2006). In the latter model, endothelium disruption was accompanied by increased islet expression of numerous HIF-target genes (Li et al., 2006).

Our microarray data revealed that most glycolytic enzymes and other HIF target genes, including Adm and Pdk1, were co-expressed and upregulated by glucose mostly between G10 and G30 (Bensellam et al., 2009), in agreement with previous observations in INS1 cells (Roche et al., 1997). Very interestingly, analysis of mouse islet proteome also revealed the upregulation of protein levels of several glycolytic enzymes after 24 h culture in the presence of G16.7 instead of G5.6 (Waanders et al., 2009). We have recently demonstrated in INS1 cells and rat islets that these gene expression alterations stem from the acceleration of mitochondrial metabolism and O_2 consumption upon stimulation with high glucose concentrations, subsequent β-cell hypoxia, and nuclear expression of HIF1 and HIF2 (Bensellam et al., 2012). These findings are congruent with a recent study showing that high glucose induced HIF1α activation in MIN6 cells, although only under mildly hypoxic conditions (10% O_2) (Sato et al., 2011). Interestingly, the glucose-dependent activation of HIF2α and its requirement for the regulation of Adm expression in pancreatic β-cells has never been reported before, HIF2α being usually considered absent from β-cells (Cantley et al., 2009; Heinis et al., 2010; Wiesener et al., 2003). Finally, we presented evidence suggesting that the high metabolic demand imposed by hyperglycemia in T2D may promote β-cell hypoxia *in vivo*. Thus, we observed increased mRNA levels of several HIF-target genes, including Adm, in the islets of *Lepr*$^{db/db}$ mice, in good agreement with our *in vitro* data. We also detected rare HIF1α-positive islet nuclei on pancreatic sections of *Lepr*$^{db/db}$ mice but not normoglycemic *Lepr*$^{db/+}$ mice, together with few islet cells exhibiting strong pimonidazole-protein adducts staining (a hypoxia marker) (Bensellam et al., 2012). In agreement, increased pimonidazole-protein adducts formation has been observed in isolated islets of other diabetic models (Sato et al., 2011).

These observations suggest that β-cells may suffer from hypoxia under conditions of hyperglycemia as a consequence of the acceleration of mitochondrial metabolism, increased ATP utilization, and limited O_2 supply, thereby leading to the alteration of islet gene expression (Fig. 5). Since increased staining of HIF1α and the proapoptotic HIF-target gene BCL2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) in hypoxic cultured or transplanted islets have been shown to correlate with increased β-cell apoptosis (Miao et al., 2006; Moritz et al., 2002), one could suggest that HIF activation and subsequent gene expression alterations in only a subpopulation of β-cells may contribute to the slow deterioration of β-cell function and survival in T2D.

3.2.10. Alteration of the β-cell differentiated phenotype

Differentiated cells, like β-cells, express characteristic transcription factors that coordinately activate or repress an array of genes, giving rise to a specific gene expression pattern. The latter allows these cells to have particular morphological and functional features. However, chronic hyperglycemia, through the activation of several glucotoxic pathways, down-regulates the expression of "β-cell enriched genes" and the transcription factors that regulate their expression (Table 3).

Down-regulation of "β-cell enriched genes" – The reduction of insulin gene expression is one of the earliest and most extensively studied glucotoxic alterations that has been characterized in β-cell lines and isolated rodent and human islets (Briaud et al., 1999; Marshak et al., 1999; Olson et al., 1998; Robertson et al., 1992). This reduction is observed after prolonged exposure to high glucose levels in β-cell lines, β-cells of diabetic animals, and β-cells of T2D patients. It has been shown to stem from decreased expression and binding of PDX-1 and MafA transcription factors to the insulin gene promoter (Gleason et al., 2000; Harmon et al., 1998; Marshak et al., 1999; Moran et al., 1997; Olson et al., 1995; Pino et al., 2005; Poitout et al., 1996; Sharma et al., 1995), increased expression of the transcriptional repressor CCAAT/enhancer-binding protein β (C/EBPβ) (Lu et al., 1997; Seufert et al., 1998), and increased expression of Myc (Kaneto et al., 2002c). Interestingly, since the decrease of insulin gene expression is prevented by antioxidants, it may result from high glucose-induced oxidative stress (Robertson and Harmon, 2006; Tanaka et al., 1999), but other pathways could also be involved including ER stress (Han et al., 2009; Lipson et al., 2008; Pirot et al., 2007).

Besides, the islets of several animal models of T2D including 90% pancreatectomized (Px) rats, ZDF rats, *Lepr*$^{db/db}$ mice, New Zealand Obese (NZO) mice and Psammomys obesus presented a marked decline in the expression of key islet transcription factors (Jonas et al., 1999; Kjorholt et al., 2005; Kluth et al., 2011; Leibowitz et al., 2001; Tokuyama et al., 1995). In parallel, these islets presented reduced expression of several GSIS key genes (Homo-Delarche et al., 2006; Jonas et al., 1999; Kjorholt et al., 2005; Laybutt et al., 2003; Thorens et al., 1992; Tokuyama et al., 1995; Zan-

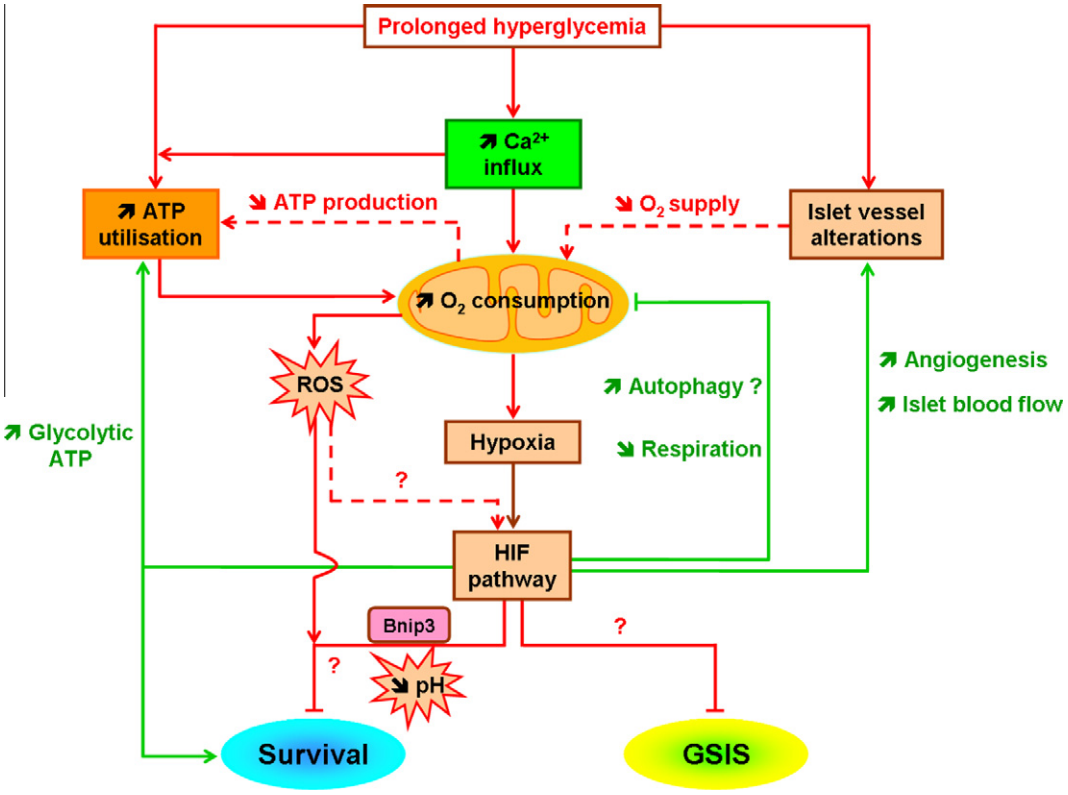

Fig. 5. Schematic representation of the hypothetic role of high glucose-induced hypoxia and subsequent activation of the HIF pathway in β-cell pathophysiology. Glucose stimulation increases O_2 consumption in β-cells following the acceleration of mitochondrial metabolism and the activation of ATP consuming processes like protein synthesis, plasma membrane Ca^{2+} ATPase (PMCA) and SERCA pump activity and exocytosis. Besides, hyperglycemia has been shown to alter islet vasculature leading thereby to limited O_2 supply. Therefore, prolonged stimulation with high glucose concentrations leads to relative hypoxia. The latter trigger an adaptive response by activating HIF1 and/or 2. This response may favor β-cell survival at the price of altered glucose-stimulated insulin secretion (GSIS) through i) the reduction of mitochondrial respiration and ROS generation by upregulating the expression of Pdk1 and likely, stimulating mitochondrial autophagy, ii) increasing anaerobic glycolytic ATP generation via the upregulation of glycolytic enzymes, and iii) promoting angiogenesis and increasing islet blood flow at the islet level by upregulating the expression of Vegf and vasomodulating factors including adrenomedullin (Adm). Mitochondrial ROS generation, which has been shown to activate HIF in other cell types, may also participate to the activation of the HIF pathway in β-cells. Finally, if hypoxia is prolonged or associated with other stresses like oxidative stress and/or acidosis, this may lead to β-cell apoptosis.

gen et al., 1997). A similar decrease in the expression of insulin, Pdx-1, Glut2, and Gck genes was observed in INS1 cells cultured for 48h in G30 (Wang et al., 2005b). On the other hand, studies in T2D patients confirmed some of these alterations, but not all (Table 3). Noteworthy, alterations in the expression of key metabolic genes resemble those observed in immature neonatal β-cells (Jermendy et al., 2011).

Interestingly, these alterations were normalized in the models of Px rats and *Lepr*$^{db/db}$ mice by phlorizin but not bezafibrate, supporting their dependence on hyperglycemia rather than hyperlipidemia (Jonas et al., 1999; Kjorholt et al., 2005).

Moreover, high glucose levels have been shown to down-regulate the expression of several components of the β-cell exocytotic machinery including N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex proteins in INS1 cells (Dubois et al., 2007), several T2D animal models (Chan et al., 1999; Gaisano et al., 2002; Zhang et al., 2002), and in the islets of human T2D patients (Dubois et al., 2007; Ostenson et al., 2006). These alterations were also reversed by phlorizin treatment in GK rats (Gaisano et al., 2002), and have been shown to involve the upregulation of several microRNAs (miRNAs) (Esguerra et al., 2011).

Up-regulation of "β-cell forbidden genes" – Concomitantly to the down-regulation of "β-cell enriched genes", β-cells exposed to elevated glucose levels *in vitro* and *in vivo* exhibited an abnormal upregulation of genes normally suppressed or expressed at very low levels (Table 3). They are characteristically induced by different kinds of stress and enclose both deleterious and protective genes that modulate in a complex manner the β-cell phenotype in response to hyperglycemia. They can be divided into three categories:

The first category encloses deleterious effectors. They include numerous transcription factors such as Cebp/β (Seufert et al., 1998), Myc (Jonas et al., 2001), Crem (Zhou et al., 2003), Ddit3 (Song et al., 2008), Atf3 (Hartman et al., 2004), and inhibitor of differentiation 1 (Id1) (Kjorholt et al., 2005; Akerfeldt and Laybutt, 2011), as well as several typical proapototic genes such as those of the Bcl2 family (Federici et al., 2001; Laybutt et al., 2007a; Piro et al., 2002), Fas (Maedler et al., 2001), and thioredoxin-interacting protein (Txnip) (Chen et al., 2008; Minn et al., 2005; Shalev et al., 2002). Other deleterious genes include the inhibitor of AKT Trb3 (Liew et al., 2010; Qian et al., 2008), the pro-oxydant enzyme Nox1 (Marchetti et al., 2004), and the controversial proinflammatory cytokine IL1β (Elouil et al., 2005; Maedler et al., 2002).

The second category encloses effectors with protective effects against glucotoxicity. They comprise principally several antioxidant defense genes and components of the UPR (Tables 1 and 2) (Bensellam et al., 2009; Elouil et al., 2005; Jonas et al., 2003; Jonas et al., 2009; Kjorholt et al., 2005; Lacraz et al., 2009b; Laybutt et al., 2002a; Marchetti et al., 2004; Marselli et al., 2010).

The third category encloses genes involved in metabolism including low-K_m Hk1 and Hk2 (Ghanaat-Pour et al., 2007; Jonas et al., 1999; Kjorholt et al., 2005; Laybutt et al., 2003), Ldha (Bensellam et al., 2009; Homo-Delarche et al., 2006; Jonas et al., 1999; Ma et al., 2007; Marselli et al., 2010), Mct1, Mct2, and

Table 3
Alteration of the β-cell differentiated phenotype. The table represents a selection of important "β-cell enriched genes" and "β-cell forbidden genes" that have been shown to be down-regulated and up-regulated respectively by high glucose levels in several *in vitro* and *in vivo* models of β-cell glucotoxicity as well as in human T2D islets for some of them. Abcc8: ATP-binding cassette transporter sub-family C member 8; Acly: ATP citrate lyase; C/EBPβ:CCAAT/enhancer-binding protein β; Crem: cAMP Response-Element Modulator; Fbp1: fructose-1,6-bisphosphatase; G6pase: glucose-6-phosphatase; Gck: Glucokinase; Glut2: Glucose transporter 2; Hnf: Hepatocyte nuclear factor; Hk: Hexokinase; Iapp: Islet amyloid polypeptide; Id1: Inhibitor of differentiation 1; Kcnj11: Potassium inwardly rectifying channel, subfamily J, member 11; Ldha: Lactate dehydrogenase A; MafA: V-maf musculoaponeurotic fibrosarcoma oncogene homologue A; Mct: Monocarboxylate transporter; mGpdh : mitochondrial glycerol-3-phosphate dehydrogenase ; Myc: myelocytomatosis viral oncogene homolog (avian); NeuroD1: neurogenic differentiation 1; Nkx6.1: NK6 transcription factor related, locus 1; Pc: Pyruvate carboxylase ; Pck1: phosphoenolpyruvate carboxykinase 1; Pdx-1: Pancreatic and duodenum homeobox-1; Serca: sarcoendoplasmic reticulum Ca^{2+}-ATPase; Ucp2: Uncoupling protein 2; Vdcc: Voltage-dependent Ca^{2+} channel.

Genes	Glucotoxicity model	Effect of hyperglycemia	References
β-Cell enriched genes			
Islet hormones			
Proinsulin	HIT-T15 cells	Down	Robertson et al. (1992) and Sharma et al. (1995)
	β-TC6 cells	Down	Poitout et al. (1996)
	INS1 cells	Down	Olson et al. (1998)
	Rat islets	Down	Briaud et al. (1999)
	Px rat islets	Down	Zangen et al. (1997)
	ZDF rat islets	Down	Tokuyama et al., 1995
	Rat islets transplanted into diabetic rats	Down	Laybutt et al. (2007b)
	Psammomys obesus	Down	Leibowitz et al. (2001)
	Human islets	Down	Marshak et al. (1999)
	Human T2D islets	Down	Marchetti et al. (2004) and DelGuerra et al. (2005)
Iapp	Px rat islets	Down	Laybutt et al. (2003)
	Rat islets transplanted into diabetic rats	Down	Laybutt et al. (2007b)
	Human T2D islets	Down	Marselli et al. (2010)
Transcription factors			
Pdx-1	INS1 cells	Down	Hou et al. (2008a) and Wang et al. (2005b)
	Rat islets	Down	Hou et al. (2008a)
	Px rat islets	Down	Jonas et al. (1999) and Zangen et al. (1997)
	Rat islets transplanted into diabetic rats	Down	Laybutt et al. (2007b)
	NZO mouse islets	Down (protein)	Kluth et al. (2011)
	Human T2D islets	Controversial: Slightly down, unchanged, up	Gunton et al. (2005), Marselli et al. (2010), Ostenson et al. (2006), and DelGuerra et al. (2005)
MafA	HIT-T15 cells	Down	Sharma et al. (1995)
	NZO mouse islets	Down (protein)	Kluth et al. (2011)
NeuroD1	Px rat islets	Down	Jonas et al. (1999) and Laybutt et al. (2003)
	Rat islets transplanted into diabetic rats	Down	Laybutt et al. (2007b)
Nkx6.1	Px rat islets	Down	Jonas et al. (1999) and Laybutt et al. (2003)
	NZO mouse islets	Down (protein)	Kluth et al. (2011)
	Rat islets transplanted into diabetic rats	Down	Laybutt et al. (2007b)
Hnf1α/ Tcf1	Px rat islets	Down	Jonas et al. (1999) and Laybutt et al. (2003)
	Human T2D islets	Down	Marselli et al. (2010)
Hnf4α	Px rat islets	Down	Jonas et al. (1999) and Laybutt et al. (2003)
	Human T2D islets	Down	Gunton et al. (2005)
Glucose metabolism			
Glut2	INS1 cells	Down	Wang et al. (2005b)
	Px rat islets	Down	Jonas et al. (1999) and Laybutt et al. (2003)
	$Lepr^{db/db}$ mouse islets	Down	Kjorholt et al. (2005
	Rat islets transplanted into diabetic rats	Down	Laybutt et al. (2007b)
	Human T2D islets	Down	Marselli et al. (2010)
Gck	INS1 cells	Down	Wang et al. (2005b)
	Px rat islets	Down	Jonas et al. (1999) and Laybutt et al. (2003)
	ZDF rat islets	Down	Tokuyama et al. (1995)
	Rat islets transplanted into diabetic rats	Down	Laybutt et al. (2007b)
Pc	Px rat islets	Down	Jonas et al. (1999) and Laybutt et al. (2003)
	$Lepr^{db/db}$ mouse islets	Down	Kjorholt et al. (2005)
	MKR mouse islets	Down	Lu et al. (2008)
mGpdh/ Gpd2	Px rat islets	Down	Jonas et al. (1999) and Laybutt et al. (2003)
	ZDF rat islets	Down	Tokuyama et al. (1995)
	MKR mouse islets	Down	Lu et al. (2008)
	Human T2D islets	Down	Marselli et al. (2010) and MacDonald et al. (2009)
Acly	GK rat islets	Down	Homo-Delarche et al. (2006)
	Human T2D islets	Down	Marselli et al. (2010) and MacDonald et al. (2009)
Ion channels and pumps			
Kcnj11	Px rat islets	Down	Jonas et al. (1999) and Laybutt et al. (2003)
	ZDF rat islets	Down	Tokuyama et al. (1995)
	$Lepr^{db/db}$ mouse islets	Down	Kjorholt et al. (2005)
Abcc8	Human T2D islets	Down	Marselli et al. (2010)

Table 3 (*continued*)

Genes	Glucotoxicity model	Effect of hyperglycemia	References
Vdccα1D	Px rat islets	Down	Jonas et al. (1999)
	ZDF rat islets	Down	Tokuyama et al. (1995)
	Human T2D islets	Down	Marselli et al. (2010)
Vdccβ	Px rat islets	Down	Laybutt et al. (2003)
Serca2b	Px rat islets	Down	Jonas et al. (1999)
	Lepr$^{db/db}$ mouse islets	Down	Kjorholt et al. (2005)
Serca3	Px rat islets	Down	Jonas et al. (1999)
	Lepr$^{db/db}$ mouse islets	Down	Kjorholt et al. (2005)
β-Cell forbidden genes			
Transcription factors			
C/EBPβ	HIT-T15 cells	Up	Lu et al. (1997)
	INS1 cells	Up	Lu et al. (1997)
	Px rat islets	Up	Seufert et al. (1998)
	ZDF rat islets	Up	Seufert et al. (1998)
Crem	Rat islets	Up	Bensellam et al. (2009) and Zhou et al. (2003)
Id1	*Lepr*$^{db/db}$ mouse islets	Up	Kjorholt et al. (2005)
	Human islets	Up	Wice et al. (2001)
	Human T2D islets	Up (protein)	DR. Laybutt (unpublished results)
Myc	Rat islets	Up	Bensellam et al. (2009), Elouil et al. (2005), and Kaneto et al. (2002c)
	Px rat islets	Up	Jonas et al. (1999, 2001)
	GK rat islets	Up	Lacraz et al. (2010)
Glucose metabolism			
Hk1	Px rat islets	Up	Jonas et al. (1999)
	ZDF rat islets	Up (enzymatic activity)	Cockburn et al. (1997)
	Lepr$^{db/db}$ mouse islets	Up	Kjorholt et al. (2005)
	Psammomys obesus	Up (enzymatic activity)	Nesher et al. (1999)
Hk2	Rat islets	Up	Ghanaat-Pour et al. (2007)
G6pase	Px rat islets	Up	Laybutt et al. (2002)
	GK rat islets	Up (enzymatic activity)	Ling et al. (2001)
Fbp1	Px rat islets	Up	Laybutt et al. (2002)
Pck1	Human islets	Up	Shalev et al. (2002)
	Human T2D islets	Up	Marselli et al. (2010)
Ldha	Rat islets		Bensellam et al. (2009), Ma et al. (2007) and Bensellam et al. (2012)
	Px rat islets	Up	Jonas et al. (1999) and Laybutt et al. (2003)
	GK rat islets	Up	Homo-Delarche et al. (2006)
	Rat islets transplanted into diabetic rats	Up	Laybutt et al. (2007b)
	Human T2D islets	Up	Marselli et al. (2010)
Mct1	Px rat islets	Up	Laybutt et al. (2002)
Mct2	Px rat islets	Up	Laybutt et al. (2002)
Mct4	Rat islets	Up	Bensellam et al. (2012)
	Px rat islets	Up	Laybutt et al. (2002)
Ucp2	Rat islets	Up	Khaldi et al. (2004)
	Glucose-infused rat islets	Up	Kassis et al. (2000)
	Px rat islets	Up	Laybutt et al. (2002)
	ZDF rat islets	Up	Oberkofler et al. (2009)
	Lep$^{ob/ob}$ mouse islets	Up	Zhang et al. (2001)
	Lep$^{ob/ob}$ mouse islets	Up	Kjorholt et al. (2005)
	Human islets	Up (protein only)	Li et al. (2008)
	Human T2D islets	Up (protein only)	Anello et al. (2005)

Mct4 (Bensellam et al., 2012; Laybutt et al., 2002), glucose-6-phosphatase, fructose-1,6-bisphosphatase (Laybutt et al., 2002), phosphoenolpyruvate carboxykinase 1 (Marselli et al., 2010; Shalev et al., 2002), and Ucp2 (Anello et al., 2005; Kassis et al., 2000; Khaldi et al., 2004; Kjorholt et al., 2005; Laybutt et al., 2002). Upregulation of these genes diverts glucose from its classical metabolism pathway, leading to the alteration of GSIS as evidenced in models of overexpression/deletion of some of these genes (Ainscow et al., 2000; Becker et al., 1994; Chan et al., 2001; Ishihara et al., 1994; Trinh et al., 1997; Zhang et al., 2001). Particularly, upregulation of Hks, and likely other glycolytic genes, could explain the reduced glucose threshold for basal insulin secretion in Psammomys obesus, Px rats, and cultured rat islets (Bensellam et al., 2009; Hosokawa et al., 1995; Khaldi et al., 2004; Nesher et al., 1999). On the other hand, upregulation of Ldha and Mcts may hamper GSIS by diverting the flux of carbon from oxidative phosphorylation and ATP generation toward lactate production and transport, and may represent a sign of β-cell hypoxia (Bensellam et al., 2009; Bensellam et al., 2012; Jonas et al., 2009).

4. Future research directions

Understanding the molecular basis of β-cell pathophysiology is a fundamental step toward the development of efficient therapeutic strategies for T2D. The present review draws attention to the complexity of the problem and the multitude of biological pathways involved in β-cell glucotoxicity.

Actual treatments of T2D aim at the control of hyperglycemia through life style interventions (dietary management and development of physical activity) and antidiabetic drugs that increase insulin levels (insulin, sulfonylureas, incretin mimetics, dipeptidyl peptidase 4 (DPP-4) inhibitors), decrease insulin resistance (thiazolidinediones (TZDs), biguanides), and/or slow postprandial glucose absorption (glucosidase inhibitors, amylin) (reviewed in Ahren (2011), Chia and Egan (2008), Drucker (2006), Israili (2011), Seino et al. (2012), Yki-Jarvinen (2004)). Besides alleviating hyperglycemia, emerging experimental and clinical evidences indicate that some pharmacological therapies, but not all, have a direct beneficial effect on β-cells (reviewed in Campbell and Mariz

Table 4
The principal medicines used or in development for the treatment of T2D and their effects on β-cells. DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide 1; IL-1Ra: Interleukine 1 receptor antagonist; SGLT2: Sodium-glucose cotransporter type 2; TZDs: thiazolidinediones.

Treatment	Effects on β-cell	Development phase	Outcome
Early intensive insulin therapy/Insulin	– Prevention of β-cell loss in an animal model of diabetes (Kautz, 2012) – Improvement of β-cell function in T2D patients, likely by opposing glucotoxicity (Glaser et al., 1988; Gormley et al., 1986; Yki-Jarvinen et al., 1988; Li et al., 2004; Ryan et al., 2004; Harrison et al., 2012)	Clinical use/ clinical trials	– Debated long-term beneficial effect (Gormley et al., 1986; Yki-Jarvinen et al., 1988; Li et al., 2004; Ryan et al., 2004; Harrison et al., 2012) – Progressive loss of β-cell function despite intensive therapy (Turner, 1998; UKPDS Group, 1998)
Sulfonylureas	– Closure of the K_{ATP} channel and stimulation of insulin secretion (Aguilar-Bryan and Bryan, 1999) – Controversial effect on insulin granule exocytosis *in vitro* (Eliasson et al., 1996; Garcia-Barrado et al., 1996; Mariot et al., 1998; Tian et al., 1998) – Potential antioxidant/antiapoptotic effect *in vitro* and *in vivo* through ROS scavenging and increased activity of antioxidant enzymes (DelGuerra et al., 2007; Gier et al., 2009; Jennings and Belch, 2000; O'Brien et al., 2000; Kimoto et al., 2003) – Controversial proapoptotic effect *in vitro* (Efanova et al., 1998; Maedler et al., 2005)	Clinical use	– Progressive loss of β-cell function despite intensive therapy (Turner, 1998; UKPDS Group, 1998; Harrower, 1994)
Metformin	– Indirect effect via insulin sensitization (Setter et al., 2003) – Protection of β-cells against glucotoxicity and restoration of GSIS in human T2D islets *in vitro* likely via an antioxidant/antiapoptotic effect (Marchetti et al., 2004; Lupi et al., 1999; Patane et al., 2000) – Delay of T2D incidence in high risk individuals through enhancement of insulin sensitivity and β-cell function (Knowler et al., 2002; Kitabchi et al., 2005)	Clinical use	– Progressive loss of β-cell function despite intensive therapy (Turner, 1998; UKPDS Group, 1998)
Diazoxide and other K_{ATP} channel openers	– Opening of the K_{ATP} channel and inhibition of insulin secretion and thereby induction of β-cell "rest" – Restoration of β-cell function altered by high glucose levels *in vitro* (Bjorklund and Grill, 1993; Song et al., 2003; Ritzel et al., 2004; Yoshikawa et al., 2004) and in animal models (Bjorklund et al., 2004; Huang et al., 2007b) in association with complex transcriptional changes (Ma et al., 2007) – Potential antiapoptotic effect *in vitro* and in a T2D animal model (Efanova et al., 1998; Huang et al., 2007b) – Moderate effect on β-cell function in T2D patients (Guldstrand et al., 2002; Qvigstad et al., 2004; Radtke et al., 2007)	Clinical trials	– Despite interesting experimental evidences, the impact on β-cell function in T2D patients is very moderate and it does not improve the metabolic control
TZDs	– Indirect effect via insulin sensitization (Yki-Jarvinen, 2004) – Protection of β-cells against high glucose induced apoptosis and loss of GSIS *in vitro* (Zeender et al., 2004) – Protection of β-cells against oxidative stress in vitro likely through upregulation of catalase gene expression (Chung et al., 2011) – Preservation of islet structure and improvement of pancreatic insulin content and β-cell function and survival in animal models of T2D (Finegood et al., 2001; Yajima et al., 2003; Diani et al., 2004) – Prevention/delay of T2D in animals and high risk individuals in parallel to the enhancement of β-cell function (Higa et al., 1999; Smith et al., 2000; Knowler et al., 2005; Gerstein et al., 2006; Xiang et al., 2006) – Improvement of the glycemic control in (pre)diabetic subjects in parallel to the improvement of β-cell function (Cavaghan et al., 1997; Miyazaki et al., 2002; Smith et al., 2004; Ovalle and Bell, 2004; Wallace et al., 2004; Miyazaki and DeFronzo, 2008)	Clinical use/ clinical trials	– Improvement of β-cell function in T2D patients and IGT subjects despite some controversies (Hung et al., 2005; Seufert and Urquhart, 2008)
Incretin-related medicines (GLP-1 analogues and DPP-4 inhibitors)	– Glucose-dependent stimulation of insulin secretion (Drucker, 2006) – Stimulation of the expression of β-cell enriched genes in the islets of T2D subjects *in vitro* (Lupi et al., 2008) – Inhibition of β-cell apoptosis induced by high glucose levels *in vitro* (Buteau et al., 2004) and in animal models of T2D (Farilla et al., 2002) likely through the activation of PKB (Buteau et al., 2004) and/or an antioxidant effect (Li et al., 2003; Pospisilik et al., 2003; Liu et al., 2012) – Potential restoration of β-cell function in the islets of T2D individuals *in vitro* (Lupi et al., 2008)	Clinical use/ clinical trials /	– Improvement of β-cell function in T2D patients and IGT subjects – Uncertain effect on β-cell mass in humans – Uncertain long-term beneficial effect

Table 4 (*continued*)

Treatment	Effects on β-cell	Development phase	Outcome
	– Stimulation of β-cell proliferation and neogenesis and restoration of β-cell mass in animal models of T2D (Farilla et al., 2002; Xu et al., 1999; Perfetti et al., 2000; Mu et al., 2006; Mu et al., 2009) – Improvement of glycemic control and β-cell function in diabetic animals and T2D patients (Mu et al., 2006; Mu et al., 2009; Greig et al., 1999; Young et al., 1999; Scherbaum et al., 2008; Bunck et al., 2009)		
IL-1Ra (Anakinra)	– Prevention of high glucose-induced inhibition of GSIS and β-cell apoptosis *in vitro* likely through the inhibition of NFκB, Fas and IL-1β expression (Maedler et al., 2002) – Improvement of glycemic control and β-cell function in parallel to the reduction of islet inflammation in an animal model of T2D (Ehses et al., 2009) – Improvement of glycemic control and β-cell function in T2D patients in parallel to the reduction of markers of systemic inflammation (Larsen et al., 2007)	Experimental/ clinical trials	– Improvement of glycemic control and β-cell function in T2D patients – Long-term beneficial effect only in a subpopulation of T2D individuals (Larsen et al., 2009) – Since high glucose-induced activation of NFκB and subsequent upregulation of IL-1β in β-cells is controversial (Elouil et al., 2005; Cnop et al., 2005; Welsh et al., 2005), the effect of IL-1Ra may be on whole body inflammation and not specifically on β-cells in T2D patients
Glucokinase activators	– Indirect effect via the modulation of hepatocyte glucose metabolism (Fyfe et al., 2007; Eiki et al., 2011) – Stimulation of the expression of β-cell enriched genes *in vitro* (Gill et al., 2011) – Stimulation of β-cell proliferation *in vitro* in association with increased expression of Irs2 (Nakamura et al., 2009; Wei et al., 2009) – Stimulation of β-cell hypertrophy *in vitro* (McGlasson et al., 2011) – Enhancement of GSIS *in vitro* (Fyfe et al., 2007; Eiki et al., 2011; Gill et al., 2011; Johnson et al., 2007) – Prevention of high glucose-induced β-cell apoptosis *in vitro* (Wei et al., 2009) and preservation of β-cell mass in an animal model of T2D (Futamura et al., 2012) – Prevention of H_2O_2 induced alterations of β-cell function and survival *in vitro* (Futamura et al., 2012) – Delay of the onset of diabetes in an animal model of T2D (Futamura et al., 2012) – Improvement of glycemic control in animal models of T2D (Fyfe et al., 2007; Eiki et al., 2011; Nakamura et al., 2009) – Improvement of glycemic control and β-cell function in T2D patients (Bonadonna et al., 2010)	Experimental/ clinical trials	– Improvement of glycemic control and β-cell function in T2D patients – Likely a promising therapy – Uncertain long-term beneficial effect (Meininger et al., 2011)
SGLT2 inhibitors	– Indirect effect via the inhibition of renal glucose reabsorption (DeFronzo et al., 2012) – Improvement of glycemic control and functional β-cell mass in animal models of T2D, likely by opposing glucotoxicity (Fujimori et al., 2008, 2009; Katsuno et al., 2009; Jurczak et al., 2011; Yamamoto et al., 2011; Suzuki et al., 2012) – Improvement of glycemic control in T2D patients (Komoroski et al., 2009; Wilding et al., 2009; Bailey et al., 2010; Ferrannini et al., 2010; Zambrowicz et al., 2012)	Experimental/ clinical trials	– Improvement of glycemic control in T2D patients – Potential negative effect on energy homeostasis in T2D patients – Uncertain long-term beneficial effect

(2007), Gupta et al. (2010), Marchetti et al. (2009), Wajchenberg (2007)). As summarized in Table 4, while the classical treatments such as metformin (biguanide), insulin and sulfonylureas are unable to avoid the progressive decline of β-cell function in already diabetic patients, the synthetic ligands of peroxisome proliferator-activated receptor γ TZDs, used primarily as insulin-sensitizers, as well as the incretin-mimetics and DPP-4 inhibitors have been shown to exert important beneficial effects on β-cell function and survival both *in vitro* and *in vivo*, at least in rodents. They are actually used in the treatment of T2D, mainly in combination with other drugs. However, the maintenance of their beneficial effect is not certain (Table 4). Besides, recent observations in humans suggest that they may represent a serious risk for the development of pancreatitis, several cancers and myocardial infarction (Elashoff et al., 2011; Friedland et al., 2012; Iyer et al., 2012; Nissen and Wolski, 2010). Other potentially interesting therapeutic agents in clinical development include the sodium-glucose cotransporter type 2 (SGLT2) inhibitors that oppose glucotoxicity through the inhibition of renal glucose reabsorption (DeFronzo et al., 2012) (Table 4). Long-term studies are however required to evaluate their safety and the upholding (or not) of their beneficial effects.

Altogether, given the central role of β-cell dysfunction in the pathogenesis of T2D, the development of safer and more specific β-cell-directed therapies is mandatory, and understanding the molecular and cellular basis of β-cell glucotoxicity opens new therapeutical horizons in this direction. Very interestingly, experimental evidence support that the beneficial effect of some of the above mentioned drugs on β-cells may be related, at least in part, to an antioxidant effect (Table 4). Indeed, the oxidative stress pathway occupies a central place among the glucotoxic mechanisms since it exerts its deleterious effects not only through ROS production, but the latter can also activate other glucotoxic pathways. Alternatively, several glucotoxic pathways can stimulate ROS generation (Brownlee, 2001; Kaufman et al., 2010; Robertson, 2004). Therefore, despite the negative results of antioxidant supplementation in humans, catalytic antioxidants such as SOD mimetics and other mitochondria-targeted antioxidants may be more appropriate alone or in combination with the actually available anti-diabetic drugs and deserve further work (Bottino et al., 2004; Lim et al., 2011; Tang et al., 2007, 2012).

However, next generation T2D medicines aiming the preservation of functional β-cell mass should target more than one glucotoxic pathway. For example, catalytic antioxidants could be tested in combination with chemical and/or pharmacological chaperones to improve the UPR. Interestingly, the improvement of β-cell function and survival in *Lepr*$^{db/db}$ mice after Ddit3 deletion was paralleled by increased islet expression of several UPR and antioxidant response genes (Song et al., 2008). Besides, given the emerging role of AGEs in β-cell glucotoxicity, RAGE antibodies also deserve additional work and should be included in the therapeutic scheme (Zhu et al., 2011). Other glucotoxic pathways that may also be targeted include inflammation (Larsen et al., 2007, 2009), and likely hypoxia (Bensellam et al., 2012). In addition, it has been reported that β-cell dysfunction and loss of differentiation in diabetes involves the upregulation of Id1 (Akerfeldt and Laybutt, 2011; Kjorholt et al., 2005). Therefore, pharmacological inhibition of this transcriptional repressor could also be promising and merits further investigation.

Regarding the glucotoxic alterations of gene expression, one should be aware that the activity level of a given gene under a given condition at a given moment is not regulated only by transcription and translation. In fact, the regulation of gene expression occurs also at other levels including mRNA stability (Tillmar et al., 2002), alternative mRNA splicing (Ortis et al., 2010), translational repression and/or mRNA degradation by miRNAs (Esguerra et al., 2011) and/or other mechanisms (Han et al., 2009), epigenetic regulation (Ng et al., 2010; Volkmar et al., 2012), and the modulation of protein levels (Waanders et al., 2009). Interestingly, the latter parameter is also subjected to an intricate regulation at several stages including translation (Greenman et al., 2007; Vander Mierde, 2007), post-translational modifications (including phosphorylation, hydroxylation, *O*-GlcNacylation, etc.) (Akimoto et al., 2007; Kluth et al., 2011), stabilization/degradation (Bensellam et al., 2012), and enzymatic activity (Ling et al., 2001). Accordingly, large scale studies combining different technologies in the same models are required to gain more complete insights about the mechanisms of β-cell glucotoxicity.

5. Conclusion

Increasing evidence indicates that high glucose levels exert deleterious effects on the β-cell phenotype through the activation of numerous glucotoxic pathways both *in vitro* and *in vivo*. These findings are however just the tip of the iceberg. A deeper understanding of each pathway, its components and their mode of regulation, and how the switch occurs from physiological to glucotoxic role under chronic hyperglycemia, such as for the ER stress pathway and the hexosamine pathway, may reveal new paths toward the restoration of a functional β-cell mass in T2D.

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