Appropriate therapy for type 2 diabetes mellitus in view of pancreatic β-cell glucose toxicity: “the earlier, the better”

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Received 12 May 2015; revised 16 July 2015; accepted 23 July 2015.
doi: 10.1111/1753-0407.12331

Abstract
Pancreatic β-cells secrete insulin when blood glucose levels become high; however, when β-cells are chronically exposed to hyperglycemia, β-cell function gradually deteriorates, which is known as β-cell glucose toxicity. In the diabetic state, nuclear expression of the pancreatic transcription factors pancreatic and duodenal homeobox 1 (PDX-1) and v-Maf musculoaponeurotic fibrosarcoma oncogene family, protein A (MafA) is decreased. In addition, incretin receptor expression in β-cells is decreased, which is likely involved in the impairment of incretin effects in diabetes. Clinically, it is important to select appropriate therapy for type 2 diabetes mellitus (T2DM) so that β-cell function can be preserved. In addition, when appropriate pharmacological interventions against β-cell glucose toxicity are started at the early stages of diabetes, β-cell function is substantially restored, which is not observed if treatment is started at advanced stages. These observations indicate that downregulation of pancreatic transcription factors and/or incretin receptors is involved in β-cell dysfunction observed in T2DM and it is very important to start appropriate pharmacological intervention against β-cell glucose toxicity in the early stages of diabetes.

Keywords: incretin receptor, insulin gene transcription factor, glucose toxicity.

Concept of pancreatic β-cell glucose toxicity

The main characteristics of type 2 diabetes mellitus (T2DM) are insulin resistance and pancreatic β-cell dysfunction. First, insulin resistance is developed as a result of overeating and the consequent development of obesity, but sufficient amounts of insulin are secreted from intact β-cells to compensate for the insulin resistance. Next, large adipocytes secrete larger amounts of free fatty acids (FFAs) and/or inflammatory cytokines, which gradually lead to a deterioration of β-cell function. This process is well known as β-cell lipotoxicity. In addition, it has been reported that when β-cells are exposed to FFAs, oxidative stress is induced and β-cell function gradually deteriorates. Finally, when β-cells are chronically exposed to hyperglycemia, β-cell function gradually deteriorates and β-cell mass decreases. These phenomena are well known as β-cell glucose toxicity. In addition, there is an important and recently proposed concept about β-cell failure. Specifically, it has been reported that loss of β-cell mass is due to β-cell dedifferentiation and not apoptotic β-cell death. Mature β-cells that produce insulin but do not express neurogenin3 (Ngn3) dedifferentiate to endocrine progenitor cells that express Ngn3 but do not produce insulin. Furthermore, it has been reported that insulin therapy facilitates β-cell redifferentiation from endocrine progenitor cells to mature β-cells. These findings suggest that the process of dedifferentiation of β-cells is involved in the β-cell failure found in T2DM and that insulin therapy protects β-cells through the facilitation of redifferentiation from endocrine progenitor cells to mature β-cells in addition to its suppression of apoptotic β-cell death.
Pancreatic transcription factors and β-cell glucose toxicity

It has been shown that oxidative stress is induced in the diabetic state and involved in β-cell glucose toxicity.5–17 Levels of various oxidative stress markers are increased in β-cells in the diabetic state.9 In addition, because the expression of several antioxidant enzymes is very low in β-cells, it seems that β-cells are rather vulnerable to oxidative stress. Indeed, when β-cells are exposed to oxidative stress, insulin gene expression is suppressed.13–19 In addition, DNA-binding activity of the pancreatic transcription factors pancreatic and duodenal homeobox 1 (PDX-1) and v-Maf musculoaponeurotic fibrosarcoma oncogene family, protein A (MafA). Therefore, reductions in the expression of these pancreatic transcription factors are likely involved in the β-cell dysfunction observed in type 2 diabetes.

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Figure 1 Natural course of the development of type 2 diabetes mellitus.
producing MafA conditionally, and in β-cells specifically in diabetic db/db mice. In addition, β-cell mass was preserved in the transgenic mice, and glucose-stimulated insulin secretion and insulin biosynthesis were restored. Together, these findings indicate that downregulation of MafA expression is particularly associated with β-cell dysfunction observed under diabetic conditions.

There are several other important transcription factors that are possibly involved in β-cell glucose toxicity. For example, neuronal differentiation 1 (NeuroD), a member of the basic helix-loop-helix (bHLH) transcription factor family, plays an important role in insulin gene transcription. It has been reported that the insulin enhancer elements E-box (NeuroD binding site) and A-box (PDX-1 binding site) are very important for enhancer elements E-box (NeuroD binding site) and A-box (PDX-1 binding site) are very important for insulins gene transcription. In NeuroD-knockout mice, the number of β-cells was markedly decreased, leading to severe diabetes and perinatal death. However, it has been shown that NeuroD expression was decreased under diabetic conditions. Therefore, downregulation of NeuroD expression may be involved in the β-cell glucose toxicity found in diabetes. NK6 homeobox 1 (Nkx6.1) is also an important transcription factor in β-cells. It is expressed in most epithelial cells during pancreatic development but its expression is restricted in mature β-cells. In Nkx6.1-knockout mice, β-cell neogenesis during the secondary transition was markedly reduced. In addition, MafA expression was not observed in Nkx6.1-knockout mice, suggesting that Nkx6.1 functions upstream of MafA during pancreatic development. It was shown that Nkx6.1 expression is decreased under diabetic conditions. Therefore, downregulation of Nkx6.1 expression may also be involved in the β-cell glucose toxicity found in diabetes.

Although it is known that various pancreatic transcription factors are sensitive to the oxidative stress that is provoked under diabetic conditions, it was recently reported that when a β-cell line was exposed to oxidative stress, cytoplasmic translocation of MafA and Nkx6.1 was observed. In parallel, DNA-binding of PDX-1 was markedly reduced, whereas the activity of other transcriptional factors was not affected. After chronic exposure to hyperglycemia in obese T2DM db/db mice, MafA expression was decreased, followed by reductions in Nkx6.1 expression. Furthermore, it was shown that in transgenic mice overexpressing the antioxidant enzyme glutathione peroxidase-1 (GPX-1) in β-cells of diabetic db/db mice, nuclear MafA and Nkx6.1 expression was restored and β-cell function was preserved. Together, these findings indicate that MafA, Nkx6.1 and PDX-1 activity likely determines β-cell function. Of these, MafA expression is decreased at an early stage of diabetes, with subsequent decreases in Nkx6.1 and/or PDX-1 expression leading to overt β-cell dysfunction found in T2DM.

Incretin signaling and β-cells glucose toxicity

Two incretin hormones, namely glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), are released by the gastrointestinal tract in response to the ingestion of food and stimulate insulin secretion, thereby regulating glucose homeostasis with a low risk of hypoglycemia. It is known that GLP-1 and GIP bind their incretin receptors in β-cells to increase intracellular cAMP levels, leading to stimulation of insulin secretion, suppression of β-cell apoptosis and an increase in β-cell growth. However, under diabetic conditions the action of incretin hormones is markedly reduced. It has been reported that the expression of GLP-1 and GIP receptors is quite low in various diabetic animals. This decrease was not observed after normalization of blood glucose levels, indicating that incretin receptor expression is downregulated by hyperglycemia. Furthermore, downregulation of incretin receptor expression was observed in T2DM subjects. Together, these findings suggest that downregulation of incretin receptors is involved in the impaired incretin effects found in diabetes that presumably lead to deterioration of β-cell function (Fig. 4).

Figure 4 Downregulation of incretin receptors in β-cells in the diabetic state. In the diabetic state, expression of the incretin receptors for glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) is downregulated, leading to a decrease in insulin secretion, an increase in β-cell apoptosis and a decrease in β-cell growth. Therefore, downregulation of incretin receptor expression is likely to be involved in the β-cell dysfunction observed in type 2 diabetes. IRS-2, insulin receptor substrate-2; TCF7L2, transcription factor 7-like 2; CREB, cAMP response element-binding protein.
Transcription factor 7-like 2 and incretin receptor

Transcription factor 7-like 2 (TCF7L2) is a transcription factor for the wingless-type integration site family (Wnt)/β-catenin signaling pathway. It is known that common genetic variations of TCF7L2 are associated with T2DM and that subjects with at-risk alleles of TCF7L2 exhibit impaired insulin secretion.\(^{58-62}\) It is also known that TCF7L2 plays a crucial role in the maintenance of β-cell function.\(^{63-65}\) Decreased expression of TCF7L2 under diabetic conditions leads to downregulation of GLP-1 and GIP receptor expression.\(^{63}\) Furthermore, recent studies have clearly shown that inactivation or a deficiency of TCF7L2 in β-cells downregulates GLP-1 receptor expression.\(^{64,65}\) In addition, inactivation of TCF7L2 leads to impaired insulin secretion and glucose tolerance, which is accompanied by a decrease in the expression of various genes, including those encoding insulin, MafA and the GLP-1 receptor.\(^{64}\) These observations indicate that TCF7L2 plays an important role in β-cells in glucose metabolism and that decreased expression of TCF7L2 leads to the downregulation of incretin receptor expression (Fig. 4).

Appropriate pharmacological interventions against β-cell glucose toxicity: “the earlier, the better”

Various studies have shown that thiazolidinediones (TZDs) and incretin-related drugs preserve both β-cell function and mass in animal models of diabetes, but many of these studies were performed during the early stages of diabetes\(^{66-69}\) and so the effects of these drugs in severe diabetic morbidity remained unclear. Recently, we reported that pioglitazone and liraglutide increased β-cell function and mass at an early stage of diabetes, but these effects were attenuated at an advanced stage of the disease.\(^{70}\) At the early stages, insulin biosynthesis and secretion were markedly increased by pioglitazone and liraglutide; these effects were not clearly observed at an advanced stage.\(^{70}\) Concomitantly with such phenomena, expression of various insulin gene transcription factors, such as MafA and PDX-1, was upregulated by pioglitazone and liraglutide in the early stages, but not at the advanced stage.\(^{70}\) We think that the increased expression of such factors at the early stage explains the increased insulin biosynthesis and secretion at the early stage of T2DM. It is likely that the recovery of MafA expression after treatment is particularly important for the recovery of β-cell function and amelioration of glycemic control, because MafA regulates not only insulin gene expression, but also various factors related to glucose-stimulated insulin secretion, such as the glucose transporter Glut2.\(^{43}\) In addition, increased expression of Glut2 and glucokinase\(^{43}\) could explain the augmentation of glucose-stimulated insulin secretion at the early stage of the disease. Furthermore, GLP-1 receptor expression is downregulated in the advanced compared with early stage of T2DM.\(^{70}\) Therefore, we assume that downregulation of some signal, such as protein kinase A, downstream of the GLP-1 receptor\(^{71-73}\) is involved in the ineffectiveness of antidiabetic drugs on insulin secretion in the advanced stages. In addition, it is known that pioglitazone reduces β-cell lipotoxicity; pioglitazone decreases serum FFAs concentrations and the triglyceride contents in β-cells.\(^{67}\) Therefore, we think that pioglitazone exerts its beneficial effects on β-cells by reducing lipotoxicity as well as glucose toxicity.

Chronically elevated concentrations of glucose, lipids and inflammatory cytokines induce not only oxidative stress, but also endoplasmic reticulum (ER) stress. Oxidative stress and ER stress contribute to inhibition of cell proliferation and the induction of apoptosis by suppressing the phosphatidylinositol 3-kinase signal or Bel2 family expression. Reductions in oxidative and ER stress by pioglitazone and liraglutide were more evident at the early rather than advanced stage of T2DM.\(^{70}\) Decreased expression of various pancreatic β-cell-related genes was associated with an improved metabolic state in the early stage of diabetes treated with pioglitazone and liraglutide in diabetic mice.\(^{70}\) Therefore, the effects of these drugs against oxidative and ER stress are likely mediated by improvements in glucose and lipid metabolism. In addition, we showed that the effects of such drug intervention on β-cell proliferation varied according to the degree of diabetic morbidity: the proportion of Ki67-positive β-cells was significantly increased by drug intervention only during the early stage of the disease but not at an advanced stage.\(^{70}\) In conclusion, the protective effects of pioglitazone and/or liraglutide on pancreatic β-cells are more powerful at an early stage of diabetes than at an advanced stage. These results suggest that the earlier the pharmacological intervention for T2DM, the better (Fig. 5).

Dipeptidyl peptidase (DPP) 4 is a promising target for the treatment of T2DM. It is a highly specific serine protease involved in the regulation and cleavage of the two incretin hormones GLP-1 and GIP. There are several kinds of DPP4 inhibitors that are often prescribed in clinical medicine. Taking into consideration the fact that GIP receptor and GLP-1 receptor expression in β-cells is downregulated, we think it would be better to use DPP4 inhibitors in the early stage of diabetes than in the later stage of diabetes that are accompanied by β-cell dysfunction.
Of the various types of treatment for diabetes, insulin is one of the best because it can decrease blood glucose levels without stimulating β-cells. Therefore, during insulin treatment, β-cells can take a rest; β-cells do not need to produce and/or secret large amounts of insulin. Thus, β-cell function is gradually restored and β-cells restart functioning appropriately. Although insulin treatment usually starts within a few years of the onset of T2DM, an even earlier start would be better. Indeed, it was reported that early intensive insulin therapy in subjects with newly diagnosed T2DM had a more favorable outcome in terms of the maintenance of β-cell function than conventional therapy.\textsuperscript{74,75}

### Acknowledgement

There is NO sources of support/funding, including federal and industry support.

### Disclosure

The authors report no conflicts of interest.

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