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H. KANETO [2005] MED HYPOTHESES RES 2: 379-391.

POSSIBLE MOLECULAR MECHANISM FOR GLUCOSE TOXICITY IN TYPE 2 DIABETES

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REVIEW

ABSTRACT. THE HALLMARK OF TYPE 2 DIABETES is pancreatic β-cell dysfunction and insulin resistance. Normal β-cells can compensate for insulin resistance by increasing insulin secretion and/or β-cell mass, but insufficient compensation leads to the onset of glucose intolerance. Once hyperglycemia becomes apparent, β-cell function gradually deteriorates and insulin resistance aggravates. This process is called "glucose toxicity". Under diabetic conditions, oxidative stress and ER stress are induced in various tissues, both of which are involved in the glucose toxicity. Induction of oxidative stress and/or ER stress leads to activation of the JNK pathway, which suppresses insulin biosynthesis and interferes with insulin signaling. In contrast, suppression of the JNK pathway in diabetic mice improves insulin resistance and ameliorates glucose tolerance. We assume that such phenomena can explain, at least in part, the molecular mechanism for glucose toxicity found in Type 2 diabetes.

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POSSIBLE MOLECULAR MECHANISM FOR GLUCOSE TOXICITY IN PANCREATIC β-CELLS

The development of Type 2 diabetes is usually associated with a combination of pancreatic β-cell dysfunction and insulin resistance. Normal β-cells can compensate for insulin resistance by increasing insulin secretion and/or β-cell mass, but insufficient compensation leads to the onset of glucose intolerance. Chronic hyperglycemia is a cause of impairment of insulin biosynthesis and secretion; once hyperglycemia becomes apparent, β-cell function gradually deteriorates and insulin resistance aggravates [1-4]. This process is called "glucose toxicity".

Under diabetic conditions, oxidative stress is provoked in various tissues including pancreatic β-cells [5-9]. β-Cells are thought to be a target of oxidative stress-mediated tissue damage [10-22], because expression levels of antioxidant enzymes such as catalase, and glutathione peroxidase were very low in β-cells compared to other tissues [23,24]. Thus, it is likely that oxidative stress is involved in β-cell deterioration in Type 2 diabetes. There are several sources of reactive oxygen species (ROS) productions in cells: the non-enzymatic glycosylation reaction [10,11], the electron transport chain in mitochondria [6,7], and the hexosamine pathway [17]. During the glycation reaction, superoxide anion (O^{2-}) is initially produced, and then hydrogen peroxide (H_2O_2) and hydroxyl radical are produced. Also, in the electron transport chain, superoxide anion (O^{2-}) is initially produced. It was previously shown that oxidative stress suppresses the insulin gene transcription in β-cells; when β-cell-derived HIT cells or isolated rat islets were exposed to oxidative stress, insulin mRNA expression was suppressed [11,17]. As a possible cause of the reduction in the insulin gene promoter activity by oxidative stress, it was shown that the DNA-binding activity of pancreatic and duodenal homeobox factor-1 (PDX-1) is rather sensitive to oxidative stress; when HIT cells or isolated rat islets were exposed to oxidative stress, PDX-1 binding to the insulin gene was markedly reduced [11,17]. PDX-1, also known as IDX-1/STF-1/IPF1 [25-27], is a member of the homeodomain-containing transcription factor family, and plays a crucial role in maintaining normal β-cell function by regulating multiple important β-cell genes, including insulin, GLUT2, and glucokinase [28-36]. Taken together, oxidative stress induced under diabetic conditions suppresses insulin biosynthesis, accompanied by reduction of PDX-1 DNA binding activity (FIG. 1).

Next, to evaluate the potential usefulness of antioxidants in treatment for Type 2 diabetes, obese diabetic C57BL/KsJ-db/db mice were treated with antioxidants (N-acetyl-L-cysteine plus vitamin C and E). The antioxidant treatment retained glucose-stimulated insulin secretion and moderately decreased blood glucose levels. The β-cell mass was significantly larger in the mice treated with the antioxidants. The amounts of insulin content and insulin mRNA were also preserved by the antioxidant treatment [12]. Similar effects were observed with Zucker diabetic fatty (ZDF) rats, another model for Type 2 diabetes [13]. These data indicate that antioxidant treatment can protect β-cells against glucose toxicity. In addition, treatment with probucol, an antioxidant widely used as an antihyperlipidemic agent, preserved β-cell mass, the insulin content, and glucose-stimulated insulin secretion, leading to improvement of glucose tolerance [9]. These data suggest potential usefulness of antioxidants for diabetes and provides further support for the implication of oxidative stress in β-cell glucose toxicity found in diabetes (FIG. 1).

The endoplasmic reticulum (ER) is an organelle which synthesizes various secretory and membrane proteins. These proteins are correctly folded and assembled by chaperones in the ER. During stressful conditions such as upon an increase in the misfolded protein level, the chaperons become overloaded and the ER fails to fold and export newly synthesized proteins, leading to ER stress [37-41]. Once ER stress is provoked in the cells, various pathway is activated (FIG. 2). It was previously reported that ER stress is involved in pancreatic β-cell apoptosis [42-46]. In Akita mice with a spontaneous mutation in insulin 2 gene, misfolded insulin protein increases ER stress, leading to decrease of β-cell mass. It was also reported that ER overload in β-cells causes ER stress and leads to apop-

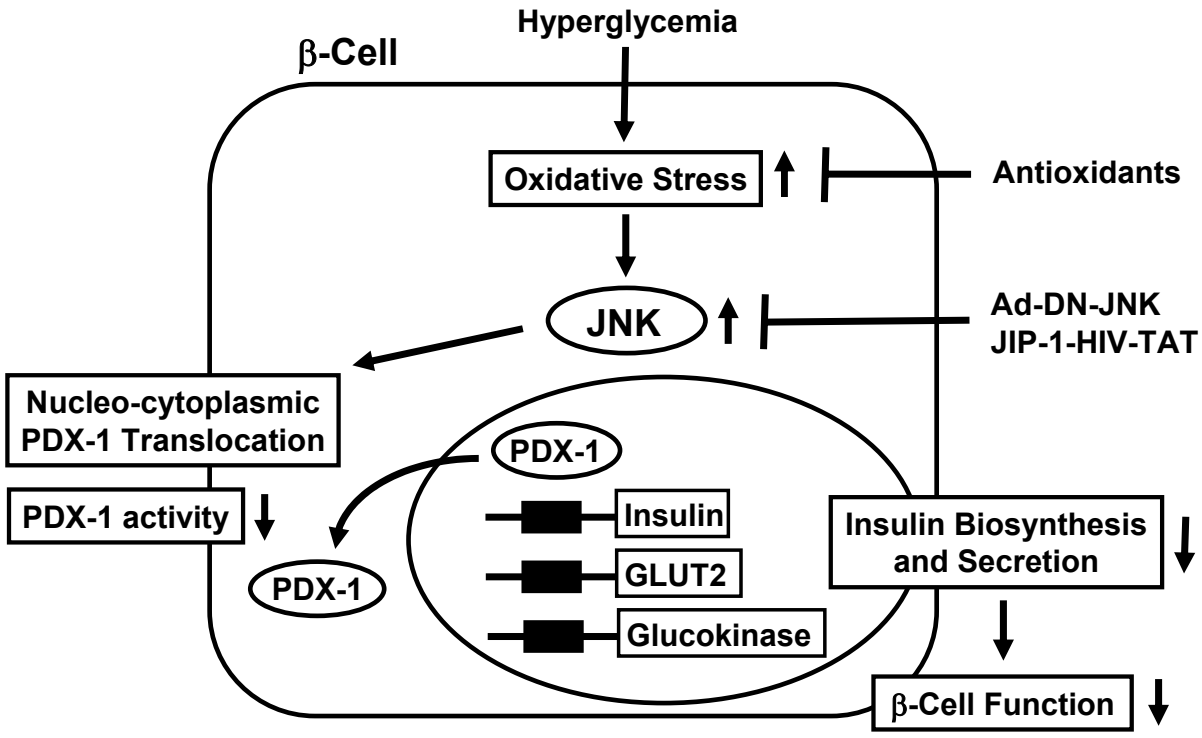

FIGURE 1. POSSIBLE MECHANISM FOR GLUCOSE TOXICITY IN PANCREATIC B-CELLS.

tosis through CHOP induction [46]. Therefore, it is likely that once ER stress is increased by some stimuli, ER stress triggers apoptosis in β-cells and thus ER stress is involved in progression of β-cell dysfunction and/or death found in diabetes.

It is known that c-Jun N-terminal kinase (JNK) [47-50] is activated by oxidative stress and/or ER stress in several cell types. It was reported that activation of JNK is involved in reduction of insulin gene expression by oxidative stress and that suppression of the JNK pathway can protect β-cells from oxidative stress [51]. When isolated rat islets were exposed to oxidative stress, the JNK pathway was activated, preceding the decrease of insulin gene expression. Adenovirus-mediated overexpression of dominant-negative type JNK1 (DN-JNK) protected insulin gene expression and secretion from oxidative stress. Moreover, wild type JNK1 (WT-JNK) overexpression suppressed both insulin gene expression and secretion [51]. These results were correlated with changes in the binding of the important transcription factor PDX-1 to the insulin promoter; adenoviral overexpression of DN-JNK preserved PDX-1 DNA binding activity in the face of oxidative stress, while WT-JNK overexpression decreased PDX-1 DNA binding activity [51]. Therefore, it is likely that activation of JNK pathway leads to decreased PDX-1 activity and subsequent suppression of insulin gene transcription in the diabetic state (FIG. 1). Furthermore, as a potential mechanism for JNK-mediated PDX-1 inactivation, it was recently reported that PDX-1 was translocated from the nuclei to the cytoplasm in response to oxidative stress. When oxidative stress was charged upon β-cell-derived HIT cells, PDX-1 moved from the nuclei to the cytoplasm [52] (FIG. 1). Addition of DN-JNK inhibited the oxidative stress-induced PDX-1 translocation, suggesting an essential role of JNK in mediating the phenomenon. In addition, leptomycin B, a specific inhibitor of the classical, leucine-rich nuclear export signal (NES), inhibited nucleo-cytoplasmic translocation of PDX-1 induced by oxidative stress [52].

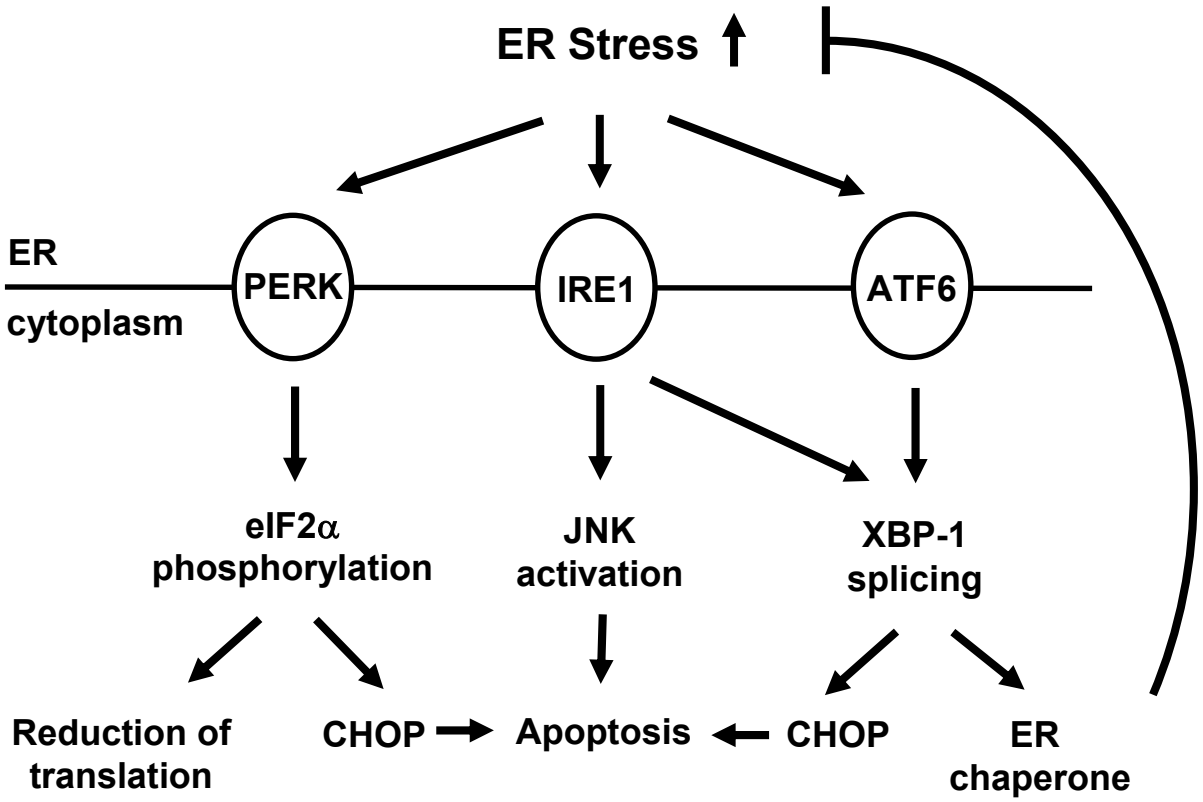

FIGURE 2. ER STRESS SIGNALING.

To examine whether DN-JNK can protect β-cells from the toxic effects of hyperglycemia and to explore the potential therapeutic application for islet transplantation, transplantation into diabetic mice was performed [51]. Isolated rat islets were first infected with dominant-negative JNK expressing adenovirus (Ad-DN-JNK) or Ad-GFP and cultured for 2 days, and 500 islets were then transplanted under kidney capsules of STZ-induced diabetic Swiss nude mice. Blood glucose levels were not significantly decreased by transplantation of islets infected with Ad-GFP, which was probably due to toxic effects of hyperglycemia upon a marginal islet number, but were markedly decreased by Ad-DN-JNK. Four weeks after transplantation of islets infected with Ad-GFP, insulin mRNA levels in islet grafts were clearly decreased compared with those before transplantation, but relatively preserved by DN-JNK overexpression [51]. These results suggest that DN-JNK can protect β-cells from some of the toxic effects of hyperglycemia during this transplant period, providing new insights into the mechanism through which oxidative stress suppresses insulin gene transcription in β-cells. Also, the finding that this adverse outcome can be prevented by DN-JNK overexpression suggests that the JNK pathway in β-cells could become a new therapeutic target for diabetes. It was reported that β-cell destruction by cytokines such as interleukin-1β (IL-1β) [53-55] can be prevented by inhibition of the JNK pathway [56-59], implying that JNK plays a role in autoimmune β-cell destruction found in early stage of type 1 diabetes. Also, it was reported that oxidative stress marker levels are increased in islets of Type 2 diabetic animal models [8,9] and that JNK activation by oxidative stress in islets actually reduces the PDX-1 DNA binding activity and insulin gene transcription [51]. In addition, the significance of JNK in the development of diabetes comes from the result of a genetic analysis

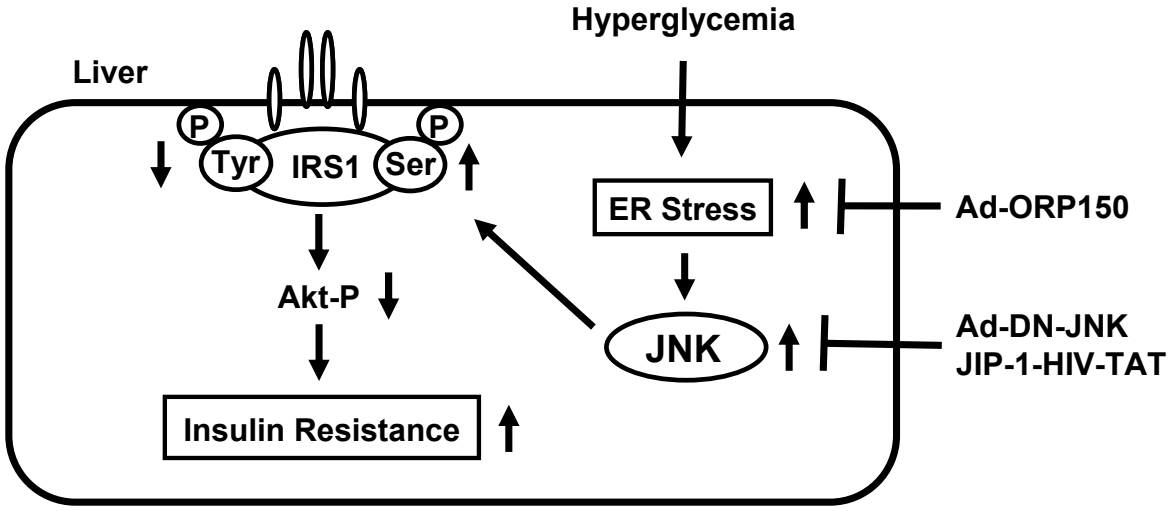

FIGURE 3. POSSIBLE MECHANISM FOR GLUCOSE TOXICITY IN INSULIN SIGNALING.

in humans; while islet-brain-1 (IB1), the human and rat homologue of mouse JNK-interacting protein-1 (JIP-1) [60,61], was known to selectively inhibit the JNK signaling [59], it was reported that a missense mutation within the IB1-encoding MAPKIP1 gene (S59N) is associated with a late onset Type 2 diabetes [62]. Thus, we propose that JNK is involved in deterioration of β-cell function in both Type 2 diabetes and the early stage of type 1 diabetes.

POSSIBLE MOLECULAR MECHANISM FOR GLUCOSE TOXICITY IN INSULIN SIGNALING

Under diabetic conditions, ER stress is increased in various tissues. Expression levels of immunoglobulin binding protein (Bip) and Lys-Asp-Glu-Leu (KDEL), both of which are ER stress markers, were much higher in the liver in the obese diabetic mice compared to non-diabetic C57BL6 mice [63]. It was also reported about the expression of several ER stress markers in dietary (high-fat diet-induced) and genetic (ob/ob) models of obesity. The pancreatic ER kinase (or PKR-like kinase) (PERK) is an ER transmembrane protein kinase that phosphorylates the α-subunit of translation initiation factor 2 (eIF2α) in response to ER stress (FIG. 2). Therefore, phosphorylation status of PERK and eIF2α is a key indicator of the presence of ER stress (64-66). PERK and eIF2α phosphorylation were increased in the liver of obese mice compared with lean control. It is known that the activity of c-Jun N-terminal kinase (JNK) is increased by ER stress (FIG. 2) [67]. Indeed, total JNK activity was also dramatically elevated in the obese mice [68]. It was also reported that when Fao liver cells were treated with tunicamycin or thapsigargin, both of which are ER stress inducers, insulin-stimulated tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1) was significantly decreased. IRS-1 is a substrate for insulin receptor tyrosine kinase, and serine phosphorylation of IRS-1, particularly mediated by JNK, reduces insulin receptor signaling. Indeed, pretreatment of Fao cells with tunicamycin produced a significant increase in serine phosphorylation of IRS-1 [68]. Furthermore, inhibition of JNK activity with the synthetic inhibitor, SP600125, reversed the ER stress-induced serine phosphorylation of IRS-1. These results indicate that ER stress promotes a JNK-dependent serine phosphorylation of IRS-1, which in turn inhibits insulin signaling (FIG. 2) [68].

Oxygen-regulated protein 150 (ORP150), a molecular chaperone found in the ER, has been shown to protect cells from ER stress (69). To examine a role of ER stress in insulin resistance in vivo, ORP150 expressing adenovirus (Ad-ORP) and a

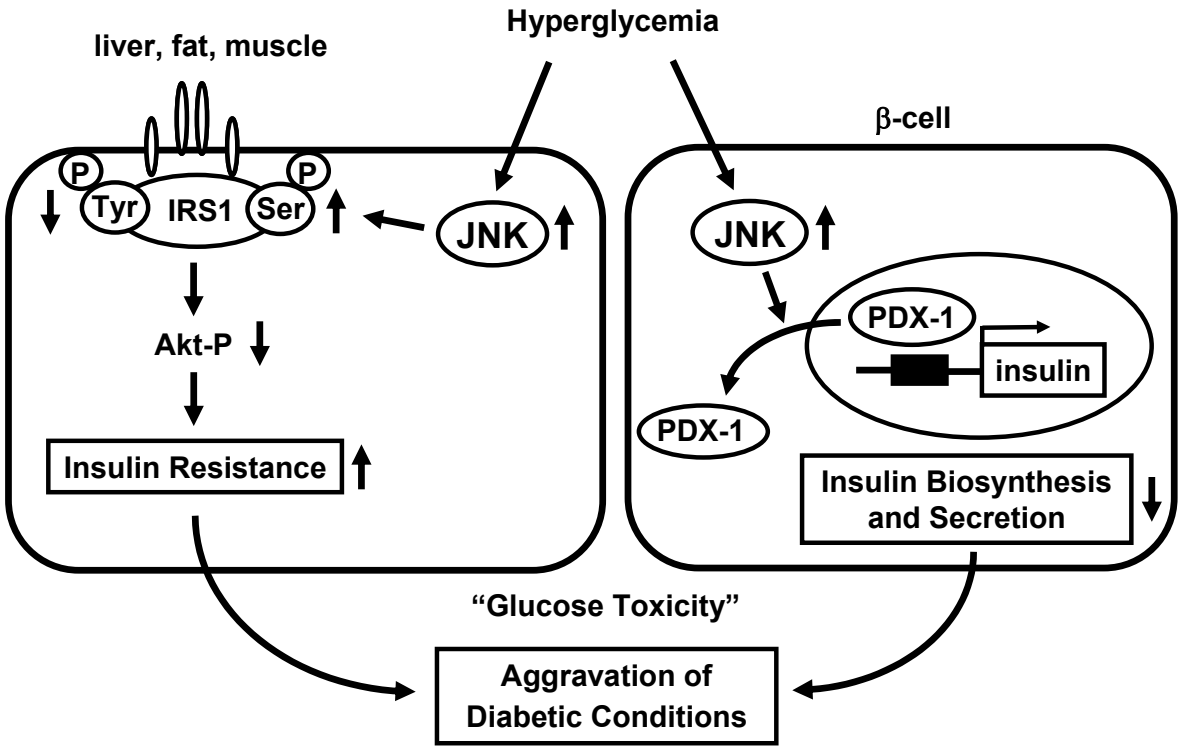

FIGURE 4. ROLE OF THE JNK PATHWAY IN GLUCOSE TOXICITY FOUND IN TYPE 2 DIABETES.

GFP expressing control adenovirus (Ad-GFP) were delivered to 8 week-old C57BL/KsJ-db/db obese diabetic mice from the cervical vein. An increase in ORP150 expression (~ 3-fold increase) in the liver was confirmed, but not in other tissues such as muscle and adipose tissue, was confirmed upon adenovirus injection. In addition, expression levels of KDEL and Bip in Ad-ORP-treated mice were lower compared to those in Ad-GFP treated db/db mice, indicating that ORP150 is actually acting to decrease ER stress in the liver. When C57BL/KsJ-db/db mice were treated with Ad-ORP, glucose tolerance was markedly ameliorated. In intraperitoneal insulin tolerance test (IPITT), the hypoglycemic response to insulin was larger in Ad-ORP-treated C57BL/KsJ-db/db mice compared to Ad-GFP-treated mice. Also, in the euglycemic hyperinsulinemic clamp test, the glucose infusion rates (GIR) of Ad-ORP-treated mice were significantly higher compared to Ad-GFP-treated mice, indicating that ORP150 overexpression in the liver reduces insulin resistance and thus ameliorates glucose tolerance in C57BL/KsJ-db/db mice. Endogenous hepatic glucose production (HGP) was significantly lower in Ad-ORP-treated mice compared to Ad-GFP-treated mice (FIG. 3) [63]. IRS-1 tyrosine phosphorylation was markedly increased in Ad-ORP-treated C57BL/KsJ-db/db mice compared to Ad-GFP-treated mice. Concomitantly, an increase in Akt serine 473 phosphorylation was observed in Ad-ORP-treated C57BL/KsJ-db/db mice compared to Ad-GFP-treated mice. These results indicate that reduction of ER stress enhances insulin signaling which leads to amelioration of glucose tolerance (FIG. 3) [63].

Furthermore, it was reported that mice deficient in X-box–binding protein–1 (XBP-1), a transcription factor that modulates the ER stress response, develop insulin resistance [68]. The spliced form of XBP-1 is a key factor in ER stress through tran-

scriptional regulation of various genes, including molecular chaperones (FIG. 2). In mouse embryo fibroblasts (MEFs) derived from XBP-$1^{-/-}$ mice, tunicamycin treatment resulted in increase of PERK phosphorylation. In these cells, there was also a marked activation of JNK in response to ER stress. When spliced XBP-1 expression was induced, there was a dramatic reduction in both PERK phosphorylation and JNK activation after tunicamycin treatment, indicating that XBP-$1^{-/-}$ cells are vulnerable to ER stress. Thus, it is likely that alteration in the level of spliced XBP-1 protein results in alterations in the ER stress response. Furthermore, tunicamycin-induced IRS-1 serine phosphorylation was significantly reduced in fibroblasts exogenously expressing spliced XBP-1. The extent of IRS-1 tyrosine phosphorylation was significantly higher in cells overexpressing spliced XBP-1. In contrast, IRS-1 serine phosphorylation was strongly induced in XBP-$1^{-/-}$ MEFs compared with XBP-$1^{+/+}$ controls even at low doses of tunicamycin treatment. Also, the amount of IRS-1 tyrosine phosphorylation was significantly decreased in tunicamycin-treated XBP-$1^{-/-}$ cells compared with tunicamycin-treated wild-type controls [68].

Since complete XBP-1 deficiency results in embryonic lethality, BALB/c-XBP-$1^{+/-}$ mice with a null mutation in one XBP-1 allele were used in order to investigate the role of XBP-1 in insulin resistance and diabetes in vivo [68]. XBP-$1^{+/-}$ mice treated with high fat diet developed continuous and progressive hyperinsulinemia. Blood glucose levels were also increased in the XBP-$1^{+/-}$ mice treated with high fat diet. During insulin tolerance test, the hypoglycemic response to insulin was also significantly lower in XBP-$1^{+/-}$ mice compared with XBP-$1^{+/+}$ littermates [68]. PERK phosphorylation was increased in the liver of obese XBP-$1^{+/-}$ mice compared with wild type control treated with high fat diet. There was also a significant increase in JNK activity in XBP-$1^{+/-}$ mice compared with wild type control. Consistently, Ser307 phosphorylation of IRS-1 was increased in XBP-$1^{+/-}$ mice compared with wild type control. There was no detectable difference in any of the insulin receptor signaling components in the liver and adipose tissues between genotypes taking regular diet. However, after treatment with high fat diet, major components of insulin receptor signaling in the liver, including IRS-1 tyrosine- and Akt serine-phosphorylation, were all decreased in XBP-$1^{+/-}$ mice compared with wild type control. A similar suppression of insulin receptor signaling was also observed in the adipose tissues of XBP-$1^{+/-}$ mice compared with XBP-$1^{+/+}$ mice [68]. Taken together, induction of ER stress leads to suppression of insulin receptor signaling in intact cells via IRE-1α-dependent activation of the JNK pathway. Furthermore, deletion of an XBP-1 allele in mice led to systemic insulin resistance and Type 2 diabetes. Thus, ER stress is involved in progression of insulin resistance and thus could be a potential therapeutic target for diabetes (FIG. 3).

The effects of modulation of the JNK pathway in the liver on insulin resistance and glucose tolerance was recently reported [70]. Overexpression of the dominant-negative (DN) type of JNK1 (Ad-DN-JNK) in the liver of obese diabetic C57BL/KsJ-db/db mice dramatically improved insulin resistance and markedly decreased blood glucose levels. In intraperitoneal insulin tolerance test (IPITT), the hypoglycemic response to insulin was greater in Ad-DN-JNK-treated C57BL/KsJ-db/db mice compared to Ad-GFP-treated mice. Furthermore, in euglycemic hyperinsulinemic clamp test, glucose infusion rate (GIR) in Ad-DN-JNK-treated mice was higher than that in Ad-GFP-treated mice, indicating that suppression of the JNK pathway in the liver reduced insulin resistance and thus ameliorated glucose tolerance in C57BL/KsJ-db/db mice. Furthermore, hepatic glucose production (HGP) was significantly lower in Ad-DN-JNK-treated mice. In contrast, there was no difference in the glucose disappearance rate (Rd) between these two groups [70]. These results indicate that reduction of insulin resistance and amelioration of glucose tolerance caused by DN-JNK overexpression are mainly due to an inhibition of hepatic glucose production.

It has been reported that serine phosphorylation of insulin receptor substrate-1 (IRS-1) inhibits insulin-stimulated tyrosine phosphorylation of IRS-1, leading to an increase in insulin resistance [71,72]. IRS-1 serine 307 phosphorylation was markedly decreased in Ad-DN-JNK-treated mice. An in-

crease in IRS-1 tyrosine and Akt serine 473 phosphorylation was also observed in Ad-DN-JNK-treated mice compared to control mice [70]. Therefore, an increase in IRS-1 serine phosphorylation may be closely associated with the development of insulin resistance induced by JNK overexpression. These results indicate that suppression of the JNK pathway enhances insulin signaling which leads to amelioration of glucose tolerance. Similar effects were observed in high-fat, high-sucrose diet-induced diabetic mice. Conversely, expression of wild-type JNK in the liver of normal mice decreased insulin sensitivity [70]. Taken together, these findings suggest that suppression of the JNK pathway in liver exerts greatly beneficial effects on insulin resistance status and glucose tolerance in both genetic and dietary models of diabetes (FIG. 3).

It has been also reported recently that JNK activity is abnormally elevated in the liver, muscle and adipose tissues in obese Type 2 diabetic mice and that insulin resistance is substantially reduced in mice homozygous for a targeted mutation in the JNK1 gene (JNK-KO mice) [71]. When the JNK-KO mice were placed on a high-fat, high-caloric diet, obese wild-type mice developed mild hyperglycemia compared to lean wild type mice. In contrast, blood glucose levels in obese JNK-KO mice was significantly lower compared to those in obese wild type mice. In addition, serum insulin levels in obese JNK-KO mice were significantly lower compared to those in obese wild type mice. Intraperitoneal insulin tolerance tests showed that hypoglycemic response to insulin in obese wild type mice was lower compared to that in obese JNK-KO mice. Also, intraperitoneal glucose tolerance test revealed a higher degree of hyperglycemia in obese wild type mice than in obese JNK-KO mice. These results indicate that the JNK-KO mice are protected from the development of dietary obesity-induced insulin resistance. Furthermore, targeted mutations in JNK were introduced in genetically obese mice (ob/ob) [71]. Blood glucose levels in ob/ob-JNK-KO mice were lower compared to those in ob/ob wild type mice, and the ob/ob wild type mice displayed a severe and progressive hyperinsulinemia. Thus, JNK deficiency can provide partial resistance against obesity, hyperglycemia and hyperinsulinemia in both genetic and dietary models of diabetes. Taken together, obese Type 2 diabetes is associated with activation of the JNK pathway, and the absence of JNK results in substantial protection from obesity-induced insulin resistance. These results strongly suggest that JNK plays a crucial role in progression of insulin resistance found in Type 2 diabetes. It is noted here that there are 3 isozymes of JNK: JNK1, JNK2, and JNK3, and that only JNK1 has been shown to be implicated in Type 2 diabetes [71]. Thus, it is likely that JNK1 is a crucial mediator of the progression of both insulin resistance and β-cell dysfunction found in Type 2 diabetes (FIG. 4).

Protein transduction domains (PTDs) such as the small PTD from the TAT protein of human immunodeficiency virus (HIV-1), the VP22 protein of Herpes simplex virus, and the third α-helix of the homeodomain of Antennapedia, a Drosophila transcription factor, are known to allow various proteins and peptides to be efficiently delivered into cells through the plasma membrane, and thus there has been increasing interest in their potential usefulness for the delivery of bioactive proteins and peptides into cells [73-79]. It was recently reported that the cell permeable JNK inhibitory peptide (amino acid sequence: GRK KRR QRR RPP RPK RPT TLN LFP QVP RSQ DT) is effective for the treatment of diabetes. This peptide is derived from the JNK binding domain of JNK-interacting protein-1 (JIP-1), also known as islet-brain-1 (IB-1), and has been reported to function as a dominant inhibitor of the JNK pathway [59]. To convert the minimal JNK-binding domain into a bioactive cell-permeable compound, a 20-amino acid sequence derived from the JNK-binding domain of JIP-1 (RPK RPT TLN LFP QVP RSQ DT) was covalently linked to a 10-amino acid carrier peptide derived from the HIV-TAT sequence (GRK KRR QRR R); then to monitor peptide delivery, this JIP-1-HIV-TAT peptide was further conjugated with fluorescein isothiocyanate (FITC). First, to examine the effectiveness of the JNK inhibitory peptide in vivo, this peptide was injected intraperitoneally to C57BL/KsJ-db/db obese diabetic mice. The FITC-conjugated peptide showed fluorescence sig-

nals in insulin target organs (liver, fat, muscle) and in insulin secreting tissue (pancreatic islets). In various tissues (liver, fat, and muscle), the JNK activity was actually suppressed by JIP-1-HIV-TAT-FITC in a dose-dependent manner [80].

To investigate whether suppression of the JNK pathway exerts beneficial effects on diabetes, C57BL/KsJ-db/db mice were treated with the intraperitoneal injection of the JNK inhibitory peptide, JIP-1-HIV-TAT-FITC or a scramble peptide as a control. Glucose tolerance in JIP-1-HIV-TAT-FITC-treated mice was significantly ameliorated compared to untreated or the scramble peptide-treated mice [80]. These data indicate that the JNK pathway is involved in the exacerbation of diabetes and that suppression of the JNK pathway could be a therapeutic target for diabetes. In insulin tolerance test, reduction of blood glucose levels in response to injected insulin was much larger in JIP-HIV-TAT-FITC-treated mice compared to untreated mice. Furthermore, in the euglycemic hyperinsulinemic clamp test, the steady-state glucose infusion rate (GIR) in JIP-1-HIV-TAT-FITC-treated mice was significantly higher than that in untreated mice, indicating that JIP-1-HIV-TAT-FITC reduces insulin resistance in C57BL/KsJ-db/db mice. Endogenous hepatic glucose production (HGP) and glucose disappearance rate (Rd) in the JNK inhibitory peptide-treated mice was also evaluated. It is noted that Rd reflects glucose utilization in the peripheral tissues. HGP in JIP-1-HIV-TAT-FITC-treated mice was significantly lower than that in untreated mice. In addition, Rd in JIP-1-HIV-TAT-FITC-treated mice was significantly higher than that in untreated mice [80]. These results indicate that JIP-1-HIV-TAT-FITC treatment reduces insulin resistance through decreasing HGP and increasing Rd. These data provide strong evidence that JNK is indeed a crucial component of the biochemical pathway responsible for insulin resistance in vivo. In addition, insulin mRNA level and insulin content were significantly higher in the peptide-treated mice. Thus, we assume that the JNK inhibitory peptide exerted some beneficial effects on the pancreatic islets. IRS-1 serine 307 phosphorylation was decreased in JIP-1-HIV-TAT-FITC-treated mice compared to control mice. An increase of IRS-1 tyrosine phosphorylation was observed in the peptide-treated wice compared to control mice. Concomitantly, increase of Akt serine 473 and threonine 308 phosphorylation both of which are known to be important for activation of the Akt pathway was observed in JIP-1-HIV-TAT-FITC-treated mice [80]. In conclusion, the cell-permeable JNK inhibitory peptide, JIP-1-HIV-TAT-FITC, improves insulin resistance and ameliorates glucose intolerance, indicating that the JNK pathway plays a crucial role and could be a potential therapeutic target for diabetes (FIG. 4).

CONCLUSIONS

Oxidative stress and ER stress are induced in various tissues under diabetic conditions, leading to activation of the JNK pathway. The JNK activation is involved in the progression of insulin resistance as well as deterioration of pancreatic β-cell function, and thus can explain, at least in part, the molecular mechanism for glucose toxicity found in Type 2 diabetes (FIG. 4).

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ABBREVIATIONS USED

Ad, adenovirus; Bip, immunoglobulin binding protein; DN, dominant-negative; eIF2α, α-subunit of translation initiation factor 2; ER, endoplasmic reticulum; IRS-1, insulin receptor substrate 1; IP-1, JNK-interacting protein-1; JNK, c-Jun N-terminal kinase; KDEL, Lys-Asp-Glu-Leu; ORP, oxygen-regulated protein; PERK, pancreatic ER kinase (or PKR-like kinase); PDX-1, pancreatic and duodenal homeobox factor-1; ROS, reactive oxygen species; XBP-1, X-box-binding protein-1.

RECEIVED ON 1-7-2005.
ACCEPTED ON 1-17-2005.