Islet Inflammation in Type 2 Diabetes

From metabolic stress to therapy

MARC Y. DONATH, MD
DESIREE M. SCHUMANN, PHD
MIRJAM FAULENBACH, MD
HELGA ELLINGSGAARD, PHD
AUREL PERREN, MD
JAN A. EHSES, PHD

Decreases in both mass and secretory function of insulin-producing β-cells contribute to the pathophysiology of type 2 diabetes. The histology of islets from patients with type 2 diabetes displays an inflammatory process characterized by the presence of cytokines, apoptotic cells, immune cell infiltration, amyloid deposits, and eventually fibrosis. This inflammatory process is probably the combined consequence of dyslipidemia, hyperglycemia, and increased circulating adipokines. Therefore, modulation of intra-islet inflammatory mediators, in particular interleukin-1β, appears as a promising therapeutic approach.

Diabetes Care **31 (Suppl. 2):S161–S164, 2008**

Inflammation is defined as the local response to tissue injury. It is characterized by immune cell invasion and local release of cytokines and chemokines and is sometimes accompanied by functional or structural damage of the invaded tissue. It is not in itself a disease, but a manifestation of disease. Inflammation has beneficial effects such as preventing spread of infections or promoting regeneration. Equally, it may exacerbate disease by tissue destruction due to inflammatory mediators, reactive oxygen species, and complement components. In this review, we propose to revisit the pathology of islet failure in type 2 diabetes and highlight evidence that this includes an inflammatory process in response to metabolic stress.

GLUCOSE-INDUCED β-CELL PRODUCTION OF INTERLEUKIN-1β: FROM ADAPTATION TO FAILURE

— Glucose is the main physiological regulator of insulin secretion. In addition to this acute effect, glucose also regulates the long-term adaptation of insulin production by affecting β-cell turnover. Indeed, short-term exposure of β-cells to increasing glucose concentrations induces proliferation (1–3). However, in *Psammomys obesus*, an animal model of type 2 diabetes, and in humans, the proliferative capacity of the β-cell is suppressed after a prolonged exposure to increased glucose concentrations (2,3). Moreover, elevated glucose concentrations induce β-cell apoptosis in cultured islets from diabetes-prone *Psammomys obesus* (2) and from humans (3,4).

Interleukin (IL)-1β is a pro-inflammatory cytokine acting during the autoimmune process of type 1 diabetes (5). IL-1β inhibits β-cell function and promotes Fas-triggered apoptosis in part by activating the transcription factor nuclear factor (NF)-κB. We tested the hypothesis that IL-1β may mediate the deleterious effects of high glucose on human β-cells (6). In vitro exposure of islets from nondiabetic organ donors to high glucose levels resulted in increased production and release of IL-1β, followed by NF-κB activation, Fas upregulation, DNA fragmentation, and impaired β-cell secretory function. The IL-1 receptor antagonist (IL-1Ra) protected cultured human islets from these deleterious effects. β-Cells themselves were identified as the islet cellular source of glucose-induced IL-1β. In vivo, IL-1β–producing β-cells were observed in pancreatic sections of type 2 diabetic patients but not in nondiabetic control subjects. These findings implicate an inflammatory process in the pathogenesis of glucotoxicity in type 2 diabetes and identify the IL-1β pathway as a target to preserve β-cell mass and function in this condition.

Recently, the role of IL-1β in type 2 diabetes has been challenged based on findings in islets isolated from patients with this condition (7). Unfortunately, these islets were placed in medium containing 5.5 mmol/l glucose for 3–4 days before experimentation. The reversibility of glucotoxicity is well documented (8) as well as the reversibility of glucose-induced IL-1β expression (6). It is therefore not surprising that increased levels of IL-1β were not detectable in these islets. Furthermore, there are numerous methodological differences, including the lack of use of extracellular matrix and the low number of organ donor samples that may account for some reported differences. Finally, a recent gene array analysis of near-pure populations of β-cells obtained by laser capture dissection displayed increased IL-1β mRNA expression in samples obtained from patients with type 2 diabetes (9).

Based on these findings, we conducted a clinical trial of IL-1 receptor antagonism in type 2 diabetes (10). The primary end-point, glycated hemoglobin, was significantly lower in IL-1Ra–treated versus placebo-treated patients, associated with enhanced insulin secretion. This study is proof of principle that antagonism of IL-1 has therapeutic potential in the treatment of diabetes, and supports the concept that islet inflammation is present and detrimental to islet function in type 2 diabetes.

From the Clinic of Endocrinology and Diabetes, Department of Pathology, University Hospital Zurich, Zurich, Switzerland.

Address correspondence and reprint requests to Marc Y. Donath, MD, Clinic of Endocrinology and Diabetes, Department of Medicine, University Hospital, CH-8091 Zurich, Switzerland. E-mail: marc.donath@usz.ch.

M.Y.D. is listed as the inventor on a patent (WO6709) filed in 2003 for the use of an interleukin-1 receptor antagonist for the treatment of or prophylaxis against type 2 diabetes. The patent is owned by the University of Zurich, and M.Y.D. has no financial interest in the patent. No other potential conflict of interest relevant to this article was reported.

This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.

Abbreviations: IL, interleukin; K_{ATP} channel, ATP-sensitive K^+ channel.

DOI: 10.2337/dc08-s243

DYSLIPIDEMIA, LEPTIN, AND CIRCULATING CYTOKINES: LINKING OBESITY TO β-CELL FAILURE

— Obesity is the main risk factor for the development of diabetes. It is often part of the metabolic syndrome and is accompanied by dyslipidemia and increased circulating leptin and cytokine levels. All of these factors have been shown to modulate β-cell function and survival. The influence of dyslipidemia on the β-cells of an individual will depend on his or her specific lipid profile. Whereas some free fatty acids and lipoproteins have been shown to be pro-apoptotic for the β-cell, others are protective. For example, long-term exposure of β-cells to saturated fatty acids such as palmitate appears highly toxic, whereas monounsaturated fatty acids such as oleate protect against both palmitate- and glucose-induced β-cell apoptosis (11,12). It is of interest to note that similar toxic effects are also observed in non–β-cells such as cardiac cells (13). These effects are paralleled by effects on β-cell function (i.e., saturated fatty acids are detrimental, whereas monounsaturated fatty acids are protective). Lipoproteins may also affect β-cell survival and function in a similar way, whereby VLDL and LDL are pro-apoptotic, while HDL is protective (14–16). These lipotoxic effects may also be influenced by the prevailing glycemia (17,18).

Leptin was initially identified as an adipocyte-derived satiety factor. Recently, leptin has also been considered as a proinflammatory cytokine because of its structural similarity with other cytokines and its receptor-induced signaling pathways (19). Interestingly, leptin accelerates autoimmune diabetes in NOD mice (20), providing an additional link between type 1 and type 2 diabetes (21). Of note, leptin also promotes other autoimmune diseases, including inflammatory bowel disease (22), multiple sclerosis (23), and rheumatoid arthritis (19). We have found that leptin, in addition to its established negative effect on insulin secretion (24,25), induces β-cell apoptosis via increasing release of IL-1β and decreasing release of IL-1Ra in human islets (26). Other cytokines released by adipocytes, including tumor necrosis factor-α and IL-6, may also modulate β-cell survival, although it is unclear if the amount released into the circulation is sufficient to affect β-cells (27,28). Furthermore, it may well be that these cytokines are only effective in the presence of other cytokines. Details regarding how all the above-mentioned factors affect β-cell secretory function have been reviewed elsewhere (27).

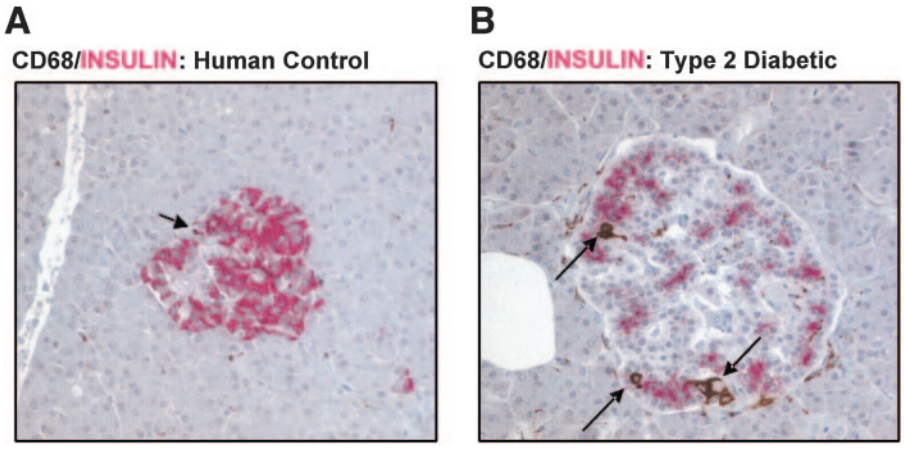

Figure 1—*Increased number of islet macrophages in type 2 diabetic islets. Pancreatic section from a nondiabetic patient* (A) *and a patient with type 2 diabetes* (B) *displaying increased numbers of islet-associated macrophages detected by double immunostaining for CD68 in brown (arrows) and insulin in red. For detailed methods and quantification, see Ehses et al. (38).*

IMMUNE CELL INFILTRATION IN ISLETS FROM TYPE 2 DIABETIC PATIENTS

— Pancreatic islets from type 2 diabetic patients are known to present with amyloid deposits, fibrosis, and increased cell death (29–31). All of these hallmarks are associated with an inflammatory response. Indeed, given that pancreatic β-cell mass is now known to decrease in type 2 diabetes (31–33), the immune system is most likely associated with the removal of these apoptotic or necrotic endocrine cells. However, before massive cell death and immune infiltration, pancreatic islets may respond to metabolic stress by producing inflammatory factors. As mentioned above, the human pancreatic β-cell produces increased IL-1β in response to glucotoxicity (6). Various other inflammatory factors and nutrients have also been shown to induce an islet inflammatory response in vitro (34–36). In support of this hypothesis, there is now evidence that islet macrophage infiltration occurs in the GK rat (37), the high-energy diet–fed mouse, the *db/db* mouse, and human type 2 diabetes before the onset or independently of significant islet cell death (Fig. 1) (38). Given that type 2 diabetes is characterized by hyperglycemia, dyslipidemia, and increased circulating inflammatory factors (so- called low-grade inflammation), increased cellular stress may be critical in precipitating islet inflammation in vivo.

ISLET INFLAMMATION: FROM PHYSIOLOGY TO FAILURE

— The impact of islet-derived inflammatory factors and islet inflammation on β-cell function and mass may be both beneficial and/or deleterious. Low concentrations of IL-1β promote β-cell function and survival (39). Other chronically elevated cytokines and chemokines in obesity and type 2 diabetes, such as IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1, may also play a role in pancreatic islet adaptation (28,40,41). Indeed, the immune system is classically involved in both adaptation and repair; however, if this response becomes prolonged, it may become deleterious to organ function. All this emerging evidence reinforces the paradigm that islet inflammation is involved in the regulation of β-cell function and survival in type 2 diabetes.

ANTI-DIABETIC DRUGS AND ISLET INFLAMMATION

— Understanding that islet inflammation is an important factor in the pathogenesis of type 2 diabetes raises a concern regarding the application of drugs potentially harmful to the remaining β-cells. Conversely, protection of β-cells from death presents itself as a new therapeutic target. In this context, modulation of the β-cell ATP-sensitive K^+ (K_{ATP}) channels (octamers composed of four inwardly rectifying K^+-channels [Kir 6.2] and four sulfonylurea receptors [SUR1]) appears particularly in-

teresting. Indeed, closure of the K_{ATP} channels by the sulfonylureas tolbutamide and glibenclamide may induce Ca^{2+}-dependent β-cell apoptosis in rodent and human islets (42–44). This effect was observed only in vitro and not consistently (45). However, in an important recent clinical study comparing insulin and sulfonylurea treatment of type 2 diabetes, it was shown that treatment with insulin preserved β-cell function more effectively than glibenclamide (46). It remains to be established whether it is the beneficial effects of insulin per se or the possible β-cell toxicity of glibenclamide that accounts for this observation. Whereas a deterioration of insulin secretion was seen in patients treated with sulfonylureas in the U.K. Prospective Diabetes Study, those treated with insulin were not evaluated in this regard (47). Given the possible deleterious effect of some sulfonylureas, alternatives to these as well as alternative insulin secretagogues may have to be considered. When applied at the concentration of their respective circulating half-lives in vitro, repaglinide and nateglinide do not appear to have an apoptotic effect on human islets (44). In contrast to sulfonylureas, K_{ATP} channel openers may exert protective effects on β-cells (48,49). In 1976, Greenwood et al. (50) were the first to report an improvement in insulin secretion after administration of diazoxide for 7 days to diabetic subjects. Similar protective effects were observed more recently in patients classified with type 1 and type 2 diabetes (51,52). Finally, other antidiabetic drugs that have emerged as putative protectors of β-cells include thiazolidinediones, GLP-1 analogs, insulin (44,53–55), and last but not least, IL-1Ra (10).

References

1. Chick WL, Like AA: Studies in the diabetic mutant mouse. 3 Physiological factors associated with alterations in beta cell proliferation. *Diabetologia* 6:243–251, 1970
2. Donath MY, Gross DJ, Cerasi E, Kaiser N: Hyperglycemia-induced beta-cell apoptosis in pancreatic islets of *Psammomys obesus* during development of diabetes. *Diabetes* 48:738–744, 1999
3. Maedler K, Spinas GA, Lehmann R, Sergeev P, Weber M, Fontana A, Kaiser N, Donath MY: Glucose induces beta-cell apoptosis via upregulation of the Fas-receptor in human islets. *Diabetes* 50:1683–1690, 2001
4. Federici M, Hribal M, Perego L, Ranalli M, Caradonna Z, Perego C, Usellini L, Nano R, Bonini P, Bertuzzi F, Marlier LN, Davalli AM, Carandente O, Pontiroli AE, Melino G, Marchetti P, Lauro R, Sesti G, Folli F: High glucose causes apoptosis in cultured human pancreatic islets of Langerhans: a potential role for regulation of specific Bcl family genes toward an apoptotic cell death program. *Diabetes* 50:1290–1301, 2001
5. Mandrup-Poulsen T: The role of interleukin-1 in the pathogenesis of IDDM. *Diabetologia* 39:1005–1029, 1996
6. Maedler K, Sergeev P, Ris F, Oberholzer J, Joller-Jemelka HI, Spinas GA, Kaiser N, Halban PA, Donath MY: Glucose-induced beta-cell production of interleukin-1beta contributes to glucotoxicity in human pancreatic islets. *J Clin Invest* 110:851–860, 2002
7. Welsh N, Cnop M, Kharroubi I, Bugliani M, Lupi R, Marchetti P, Eizirik DL: Is there a role for locally produced interleukin-1 in the deleterious effects of high glucose or the type 2 diabetes milieu to human pancreatic islets? *Diabetes* 54: 3238–3244, 2005
8. Thorens B, Wu YJ, Leahy JL, Weir GC: The loss of GLUT2 expression by glucose-unresponsive beta cells of db/db mice is reversible and is induced by the diabetic environment. *J Clin Invest* 90:77–85, 1992
9. Boni-Schnetzler M, Marselli L, Ehses JA, Weir GC, Donath MY: IL-1beta expression is induced by glucose and IL-1beta auto-stimulation, and increased in beta cells of type 2 diabetics (Abstract). *Diabetes* 56 (Suppl. 1):A413, 2007
10. Larsen CM, Faulenbach M, Vaag A, Volund A, Ehses JA, Seifert B, Mandrup-Poulsen T, Donath MY: Interleukin-1 receptor antagonist in type 2 diabetes mellitus. *N Engl J Med* 356:1517–1526, 2007
11. Maedler K, Oberholzer J, Bucher P, Spinas GA, Donath MY: Monounsaturated fatty acids prevent the deleterious effects of palmitate and high glucose on human pancreatic beta-cell turnover and function. *Diabetes* 52:726–733, 2003
12. Maedler K, Spinas GA, Dyntar D, Moritz W, Kaiser N, Donath MY: Distinct effects of saturated and monounsaturated fatty acids on beta-cell turnover and function. *Diabetes* 50:69–76, 2001
13. Dyntar D, Eppenberger-Eberhardt M, Maedler K, Pruschy M, Eppenberger H, Spinas GA, Donath MY: Glucose and palmitic acid induce degeneration of myofibrils and modulate apoptosis in rat adult cardiomyocytes. *Diabetes* 50:2105–2113, 2001
14. Cnop M, Hannaert JC, Grupping AY, Pipeleers DG: Low density lipoprotein can cause death of islet beta-cells by its cellular uptake and oxidative modification. *Endocrinology* 143:3449–3453, 2002
15. Roehrich ME, Mooser V, Lenain V, Herz J, Nimpf J, Azhar S, Bideau M, Capponi A, Nicod P, Haefliger JA, Waeber G: Insulin-secreting beta-cell dysfunction induced by human lipoproteins. *J Biol Chem* 278: 18368–18375, 2003
16. Rütti S, Ehses JA, Rohrer L, Prazak R, von Eckardstein A, Donath MY: High density lipoprotein protects human and mouse pancreatic islets from high glucose and interleukin-1 beta induced apoptosis (Abstract). *Diabetes* 56 (Suppl. 1):A27, 2007
17. El-Assaad W, Buteau J, Peyot ML, Nolan C, Roduit R, Hardy S, Joly E, Dbaibo G, Rosenberg L, Prentki M: Saturated fatty acids synergize with elevated glucose to cause pancreatic beta-cell death. *Endocrinology* 144:4154–4163, 2003
18. Poitout V, Robertson RP: Minireview: secondary beta-cell failure in type 2 diabetes: a convergence of glucotoxicity and lipotoxicity. *Endocrinology* 143:339–342, 2002
19. Otero M, Lago R, Lago F, Casanueva FF, Dieguez C, Gomez-Reino JJ, Gualillo O: Leptin, from fat to inflammation: old questions and new insights. *FEBS Lett* 579:295–301, 2005
20. Matarese G, Sanna V, Lechler RI, Sarvetnick N, Fontana S, Zappacosta S, La Cava A: Leptin accelerates autoimmune diabetes in female NOD mice. *Diabetes* 51:1356–1361, 2002
21. Donath MY, Ehses JA: Type 1, type 1.5, and type 2 diabetes: NOD the diabetes we thought it was. *Proc Natl Acad Sci U S A* 103:12217–12218, 2006
22. Barbier M, Cherbut C, Aube AC, Blottiere HM, Galmiche JP: Elevated plasma leptin concentrations in early stages of experimental intestinal inflammation in rats. *Gut* 43:783–790, 1998
23. Sanna V, Di Giacomo A, La Cava A, Lechler RI, Fontana S, Zappacosta S, Matarese G: Leptin surge precedes onset of autoimmune encephalomyelitis and correlates with development of pathogenic T cell responses. *J Clin Invest* 111:241–250, 2003
24. Kieffer TJ, Habener JF: The adipoinsular axis: effects of leptin on pancreatic beta-cells. *Am J Physiol Endocrinol Metab* 278: E1–E14, 2000
25. Roduit R, Thorens B: Inhibition of glucose-induced insulin secretion by long-term preexposure of pancreatic islets to leptin. *FEBS Lett* 415:179–182, 1997
26. Maedler K, Sergeev P, Ehses JA, Mathe Z, Bosco D, Berney T, Dayer JM, Reinecke M, Halban PA, Donath MY: Leptin modulates beta cell expression of IL-1 receptor antagonist and release of IL-1beta in human islets. *Proc Natl Acad Sci U S A* 101:8138–8143, 2004
27. Donath MY, Storling J, Maedler K, Mandrup-Poulsen T: Inflammatory mediators and islet beta-cell failure: a link between

type 1 and type 2 diabetes. *J Mol Med* 81: 455–470, 2003
28. Ellingsgaard H, Ehses JA, van Lommel L, Schuit FC, Donath MY: IL-6 regulates alpha-cell mass and function. *Diabetologia* 49 (Suppl 1):282–283, 2006
29. Hull RL, Westermark GT, Westermark P, Kahn SE: Islet amyloid: a critical entity in the pathogenesis of type 2 diabetes. *J Clin Endocrinol Metab* 89:3629–3643, 2004
30. Marzban L, Park K, Verchere CB: Islet amyloid polypeptide and type 2 diabetes. *Exp Gerontol* 38:347–351, 2003
31. Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC: Beta-cell deficit and increased beta-cell apoptosis in humans with type 2 diabetes. *Diabetes* 52: 102–110, 2003
32. Sakuraba H, Mizukami H, Yagihashi N, Wada R, Hanyu C, Yagihashi S: Reduced beta-cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese type II diabetic patients. *Diabetologia* 45:85–96, 2002
33. Yoon KH, Ko SH, Cho JH, Lee JM, Ahn YB, Song KH, Yoo SJ, Kang MI, Cha BY, Lee KW, Son HY, Kang SK, Kim HS, Lee IK, Bonner-Weir S: Selective beta-cell loss and alpha-cell expansion in patients with type 2 diabetes mellitus in Korea. *J Clin Endocrinol Metab* 88:2300–2308, 2003
34. Arnush M, Heitmeier MR, Scarim AL, Marino MH, Manning PT, Corbett JA: IL-1 produced and released endogenously within human islets inhibits beta cell function. *J Clin Invest* 102:516–526, 1998
35. Frigerio S, Junt T, Lu B, Gerard C, Zumsteg U, Hollander GA, Piali L: Beta cells are responsible for CXCR3-mediated T-cell infiltration in insulitis. *Nat Med* 8:1414–1420, 2002
36. Busch AK, Cordery D, Denyer GS, Biden TJ: Expression profiling of palmitate- and oleate-regulated genes provides novel insights into the effects of chronic lipid exposure on pancreatic beta-cell function. *Diabetes* 51:977–987, 2002
37. Homo-Delarche F, Calderari S, Irminger JC, Gangnerau MN, Coulaud J, Rickenbach K, Dolz M, Halban P, Portha B, Serradas P: Islet inflammation and fibrosis in a spontaneous model of type 2 diabetes, the GK rat. *Diabetes* 55:1625–1633, 2006
38. Ehses JA, Perren A, Eppler E, Ribaux P, Pospisilik JA, Maor-Cahn R, Gueripel X, Ellingsgaard H, Schneider MKJ, Biollaz G, Fontana A, Reinecke M, Homo-Delarche F, Donath MY: Increased number is islet associated macrophages in type 2 diabetes. *Diabetes* 56:2356–2370, 2007
39. Maedler K, Schumann DM, Sauter N, Ellingsgaard H, Bosco D, Baertschiger R, Iwakura Y, Oberholzer J, Wollheim CB, Gauthier BR, Donath MY: Low concentration of interleukin-1beta induces FLICE-inhibitory protein-mediated beta-cell proliferation in human pancreatic islets. *Diabetes* 55:2713–2722, 2006
40. Wellen KE, Hotamisligil GS: Inflammation, stress, and diabetes. *J Clin Invest* 115: 1111–1119, 2005
41. Schumann DM, Maedler K, Franklin I, Konrad D, Storling J, Böni-Schnetzler, Gjinovci A, Kurrer MO, Gauthier BR, Bosco D, Andres A, Berney T, Greter M, Bercher B, Chervonsky AV, Halban P, Mandrup-Poulsen T, Wollheim CB, Donath MY: The Fas pathway is involved in beta-cell secretory function. *Proc Natl Acad Sci U S A* 104:2861–2866, 2007
42. Efanova IB, Zaitsev SV, Zhivotovsky B, Kohler M, Efendic S, Orrenius S, Berggren PO: Glucose and tolbutamide induce apoptosis in pancreatic beta-cells: a process dependent on intracellular $Ca2^{+}$ concentration. *J Biol Chem* 273:33501–33507, 1998
43. Iwakura T, Fujimoto S, Kagimoto S, Inada A, Kubota A, Someya Y, Ihara Y, Yamada Y, Seino Y: Sustained enhancement of Ca(2+) influx by glibenclamide induces apoptosis in RINm5F cells. *Biochem Biophys Res Commun* 271:422–428, 2000
44. Maedler K, Carr RD, Bosco D, Zuellig RA, Berney T, Donath MY: Sulfonylurea induced beta-cell apoptosis in cultured human islets. *J Clin Endocrinol Metab* 90:501–506, 2005
45. Del Guerra S, Marselli L, Lupi R, Boggi U, Mosca F, Benzi L, Del Prato S, Marchetti P: Effects of prolonged in vitro exposure to sulphonylureas on the function and survival of human islets. *J Diabetes Complications* 19:60–64, 2005
46. Alvarsson M, Sundkvist G, Lager I, Henricsson M, Berntorp K, Fernqvist-Forbes E, Steen L, Westermark G, Westermark P, Orn T, Grill V: Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. *Diabetes Care* 26:2231–2237, 2003
47. U.K. Prospective Diabetes Study 16: Overview of 6 years' therapy of type II diabetes: a progressive disease: U.K. Prospective Diabetes Study Group. *Diabetes* 44:1249–1258, 1995
48. Maedler K, Storling J, Sturis J, Zuellig RA, Spinas GA, Arkhammar PO, Mandrup-Poulsen T, Donath MY: Glucose- and interleukin-1beta-induced beta-cell apoptosis requires Ca^{2+} influx and extracellular signal-regulated kinase (ERK) 1/2 activation and is prevented by a sulfonylurea receptor 1/inwardly rectifying K+ channel 6.2 (SUR/Kir6.2) selective potassium channel opener in human islets. *Diabetes* 53:1706–1713, 2004
49. Ritzel RA, Hansen JB, Veldhuis JD, Butler PC: Induction of beta-cell rest by a Kir6.2/SUR1-selective K(ATP)-channel opener preserves beta-cell insulin stores and insulin secretion in human islets cultured at high (11 mM) glucose. *J Clin Endocrinol Metab* 89:795–805, 2004
50. Greenwood RH, Mahler RF, Hales CN: Improvement in insulin secretion in diabetes after diazoxide. *Lancet* 1:444–447, 1976
51. Bjork E, Berne C, Kampe O, Wibell L, Oskarsson P, Karlsson FA: Diazoxide treatment at onset preserves residual insulin secretion in adults with autoimmune diabetes. *Diabetes* 45:1427–1430, 1996
52. Guldstrand M, Grill V, Bjorklund A, Lins PE, Adamson U: Improved beta cell function after short-term treatment with diazoxide in obese subjects with type 2 diabetes. *Diabetes Metab* 28:448–456, 2002
53. Drucker DJ: Glucagon-like peptide-1 and the islet beta-cell: augmentation of cell proliferation and inhibition of apoptosis. *Endocrinology* 144:5145–5148, 2003
54. Li Y, Hansotia T, Yusta B, Ris F, Halban PA, Drucker DJ: Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis. *J Biol Chem* 278:471–478, 2003
55. Zeender E, Maedler K, Bosco D, Berney T, Donath MY, Halban PA: Pioglitazone and sodium salicylate protect human beta-cells against apoptosis and impaired function induced by glucose and interleukin-1beta. *J Clin Endocrinol Metab* 89:5059–5066, 2004