Damaging Loss of Self-Control by Stressed β-Cells

Mark J. Holness and Mary C. Sugden

Only 15–20% of obese individuals with severe insulin resistance develop type 2 diabetes mellitus (T2DM). In healthy individuals, β-cell compensation ensures that enhanced glucose-stimulated insulin secretion (GSIS) balances the degree of insulin resistance. However, individuals predisposed to T2DM are unable to secrete the increased insulin required to compensate for insulin resistance in order to maintain glucose and lipid homeostasis. It is unclear why certain insulin-resistant individuals compensate with enhanced islet function and β-cell hyperplasia and remain healthy, while others develop β-cell failure characterized by insulin secretory defects coupled with relative loss of β-cell mass. In this issue of *Diabetes*, Halperin et al. (1) highlight the potential importance for β-cell dysfunction and T2DM of insulin resistance in the islet itself. Their observations provide novel insights into the battery of insults that can adversely impact β-cell function.

The endocrine pancreas contains ~1 million islets of Langerhans that comprise 2–3% of total pancreatic mass. Major cell types include β-cells that secrete insulin and glucagon-secreting α-cells. The integrated secretory responses of islet cells exceed those of segregated islet cell lines, indicating that interactions between individual islet cells are required for normal secretory function (2–5). The actions of individual cells comprising the islet may also be modulated by responses to their own secretions.

Insulin exerts its effects in target cells through binding to and activating its cell surface receptors. This is followed by an intricate and complex web of signaling pathways beginning with tyrosine phosphorylation of intracellular substrates including the insulin receptor substrate (IRS) proteins (Fig. 1). The finding that both the insulin receptor (IR) and the IRS proteins are expressed in rodent β-cells (6,7) and that all downstream elements belonging to the IR signaling pathway are expressed in human pancreatic β-cells (8) led to the prospect of a potential role of the insulin signaling cascade in regulation of β-cell function and/or mass (Fig. 1) (7). Autocrine effects of insulin regulate β-cell mass, as demonstrated in insulin-resistant mice engineered by ablation of IR, or IRS-1, or both genes (9–11). Disruption of insulin signaling at the level of the β-cell IR (the βIRKO mouse) did not change β-cell mass prenatally (12,13), but elicited age-dependent decreases in β-cell mass, with a selective loss of GSIS and β-cell insulin content, and development of a T2DM-like phenotype (14,15).

Insulin may also affect its own secretion. During insulin stimulation, tyrosine phosphorylation sites in IRS proteins bind specifically to SH2 domains in various downstream signaling molecules including phosphatidylinositide 3-kinase (PI3K). The stoichiometric balance between the p85 regulatory subunit (p85) of PI3K, the p110 catalytic subunit (p110) of PI3K, and the IRS proteins appears to be critical for signal transduction. Knockout of the p85α subunit (heterozygous knockout mice) improved insulin sensitivity in vivo (16,17). It would be predicted that the acute insulin response of the islet to glucose challenge in this knockout might be attenuated because the need to produce insulin is reduced. However, increased GSIS after inhibition of PI3K or with islets of p85-deficient mice (18,19) suggested that, in mice at least, insulin may have an acute negative effect on β-cell GSIS coupling. In these reports, inhibition of islet PI3K led to an increase in second-phase insulin release, which is often augmented in compensatory insulin secretion as a consequence of peripheral insulin resistance.

The study by Halperin et al. (1) builds on a previous study in human subjects reporting that, in contrast to the mouse, a 4-h infusion with a form of insulin (B28 Asp-insulin) that is immunologically distinct from endogenous insulin enhances β-cell function in healthy humans (20). Pre-exposure to exogenous insulin augmented endogenous insulin secretory responses to glucose by ~40% (Fig. 1). A follow-up study from the same group (20) evaluated whether the acute potentiating effect of pre-exposure to insulin on GSIS in healthy subjects was modulated through effects of insulin on circulating nonesterified fatty acid (NEFA) concentrations. GSIS was assessed after 4-h saline (low insulin/sham) or isoglycemic-hyperinsulinemic (high insulin) clamps with or without intralipid and heparin infusion. Glycemia was maintained at the same stimulatory concentration in all groups. Plasma NEFA concentrations fell during hyperinsulinemic clamps, reflecting the antilipolytic action of insulin. Despite preventing a drop in circulating NEFA during the hyperinsulinemic clamp by intralipid/heparin infusion, GSIS remained augmented compared with sham clamp. It was concluded that pre-exposure to insulin potentiates GSIS independently of its effect to suppress circulating NEFA concentration in healthy humans. However, this conclusion does not exclude the possibility that acute exposure to elevated NEFA could enhance GSIS, perhaps via stimulation of G protein–coupled receptor 40 (GPR40). In contrast, an analogous study (21) testing whether insulin exposure and insulin sensitivity modulated β-cell function in healthy humans concluded that while pre-exposure to physiological hyperinsulinemia affected β-cell response to acute hyperglycemia, this response depended on the antecedent degree of insulinization in a manner consistent with the degree of whole-body insulin sensitivity. β-Cell insulin resistance was not considered the main secretory abnormality in glucose-intolerant individuals, and a primary defect in the β-cell was suggested to be responsible.

From the Centre for Diabetes, Blizard Institute, St Bartholomew's and the Royal London School of Medicine and Dentistry, Queen Mary, University of London, London, U.K.

Corresponding author: Mark J. Holness, m.j.holness@qmul.ac.uk.

DOI: 10.2337/db11-1647

See accompanying original article, p. 301.

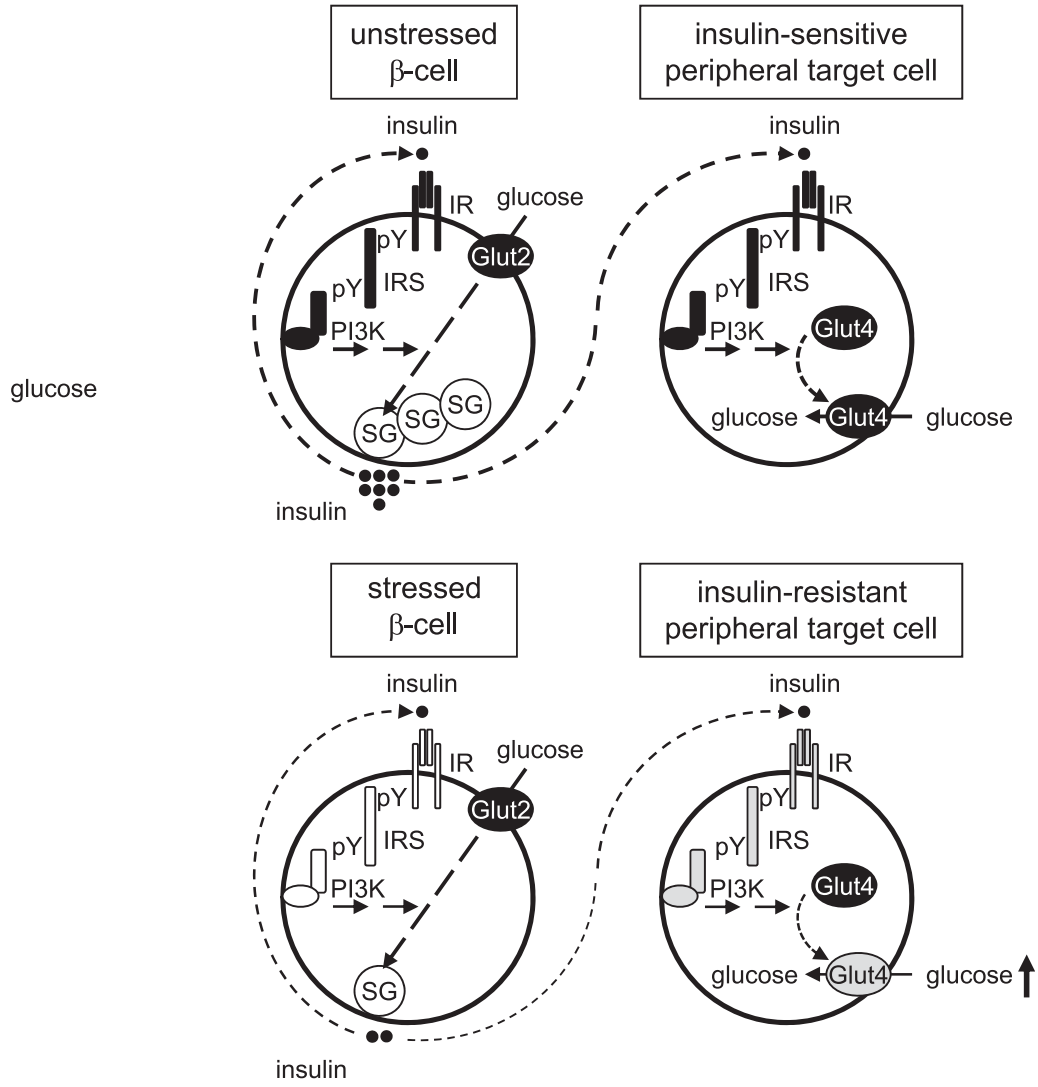

FIG. 1. In unstressed β-cells, insulin binding to IR, tyrosine phosphorylation of sites in the IRS proteins, and downstream signaling, including via PI3K, augment insulin secretory responses to glucose. This, combined with insulin sensitivity in peripheral target cells, will maintain normoglycemia, e.g., by enhancing GLUT4 translocation to the plasma membrane. The effect of insulin to augment GSIS is suppressed in stressed β-cells, e.g., in IGT or T2DM subjects, which combined with peripheral insulin resistance will lead to the development of hyperglycemia. SG, secretory granule.

To further explore the role of secreted insulin in augmenting β-cell function, Halperin et al. (1) examined the effect of pre-exposure to insulin on GSIS in two groups of insulin-resistant subjects. The rationale was that if insulin exerts its effect on GSIS via β-cells, insulin resistance at the level of β-cell insulin signaling could affect the ability of insulin pre-exposure to augment insulin secretion. In addition to control participants with normal glucose tolerance, the study groups included subjects with impaired glucose tolerance (IGT) as well as those with T2DM. These experiments aimed to evaluate whether insulin resistance or overt T2DM impaired GSIS after an isoglycemic-hyperinsulinemic clamp. During dynamic testing, it was observed that insulin's ability to regulate the insulin secretory response to glucose was variable in these subjects. The effect of insulin on GSIS was only observed at the highest rate of glucose infusion—a finding that may reflect the glucose dose or duration of exposure. Supporting the concept that β-cell insulin sensitivity is variable and dependent on the degree of hyperglycemia, it has been shown that chronic (48-h) exposure of insulin-secreting βTC6 cells to high glucose decreases insulin-induced tyrosine phosphorylation of IR in the absence of any change in the expression of IR (22). Using an insulin infusion rate to generate high physiological insulin for pre-exposure, Halperin et al. observed the clearest impairment of insulin-potentiated GSIS in the IGT group (Fig. 1), which was also the most obese group, a finding that raises questions regarding the impact of BMI on insulin modulation of β-cell function. It should be noted that the IGT group had a greater degree of insulin resistance than the T2DM subjects. Interestingly, the loss of the effect of insulin on GSIS is restored in the T2DM subjects, albeit at a lower level of GSIS.

In conclusion, Halperin et al. (1) present in vivo data that enhance our understanding of the autocrine effects of insulin on β-cell function. Their studies, together with those of Mari et al. (21) in healthy human subjects, raise interesting questions. Enhanced GSIS following acute insulin stimulation could potentially be maladaptive, unless it was balanced by suppressed insulin action. The effect of pre-exposure to insulin on augmentation of GSIS was suppressed in IGT subjects, who had lower β-cell dysfunction

relative to their degree of insulin resistance. That is, they were better able to secrete insulin and compensate for insulin resistance compared with the T2DM group, who retained the effect of insulin to stimulate GSIS, but who were unable to control glycemia. The latter observation could reflect a reduction in functional β-cell mass in the T2DM group. It would be informative in future studies to compare obese subjects who exhibit normal glucose tolerance to those with IGT and to compare the impact of pre-exposure to relatively high and relatively low physiological insulin levels on GSIS. One interpretation of these findings could be that insulin therapy, possibly in combination with agents ameliorating insulin resistance, could help the stressed β-cell recuperate its normal function. Indeed, as proposed by Halperin et al., insulin-sensitizing agents may exert their effects in part by restoring β-cell insulin sensitivity, thereby enhancing the capacity of the β-cell to respond to insulin with increased GSIS.

ACKNOWLEDGMENTS

M.J.H. and M.C.S. are supported in part by grants from Diabetes UK (BDA:RD07/0003568 and BDA:RD08/0003665).

No potential conflicts of interest relevant to this article were reported.

REFERENCES

1. Halperin F, Lopez X, Manning R, et al. Insulin augmentation of glucose-stimulated insulin secretion is impaired in insulin-resistant humans. Diabetes 2012;61:301–309
2. Halban PA, Powers SL, George KL, Bonner-Weir S. Spontaneous reassociation of dispersed adult rat pancreatic islet cells into aggregates with three-dimensional architecture typical of native islets. Diabetes 1987;36:783–790
3. Hopcroft DW, Mason DR, Scott RS. Structure-function relationships in pancreatic islets: support for intraislet modulation of insulin secretion. Endocrinology 1985;117:2073–2080
4. Pipeleers D, in't Veld PI, Maes E, Van De Winkel M. Glucose-induced insulin release depends on functional cooperation between islet cells. Proc Natl Acad Sci U S A 1982;79:7322–7325
5. Bosco D, Orci L, Meda P. Homologous but not heterologous contact increases the insulin secretion of individual pancreatic B-cells. Exp Cell Res 1989;184:72–80
6. Gazzano H, Halban P, Prentki M, et al. Identification of functional insulin receptors on membranes from an insulin-producing cell line (RINm5F). Biochem J 1985;226:867–872
7. Harbeck MC, Louie DC, Howland J, Wolf BA, Rothenberg PL. Expression of insulin receptor mRNA and insulin receptor substrate 1 in pancreatic islet beta-cells. Diabetes 1996;45:711–717
8. Muller D, Huang GC, Amiel S, Jones PM, Persaud SJ. Identification of insulin signaling elements in human beta-cells: autocrine regulation of insulin gene expression. Diabetes 2006;55:2835–2842
9. Brüning JC, Michael MD, Winnay JN, et al. A muscle-specific insulin receptor knockout exhibits features of the metabolic syndrome of NIDDM without altering glucose tolerance. Mol Cell 1998;2:559–569
10. Hennige AM, Ozcan U, Okada T, et al. Alterations in growth and apoptosis of insulin receptor substrate-1-deficient beta-cells. Am J Physiol Endocrinol Metab 2005;289:E337–E346
11. Kulkarni RN, Roper MG, Dahlgren G, et al. Islet secretory defect in insulin receptor substrate 1 null mice is linked with reduced calcium signaling and expression of sarco(endo)plasmic reticulum Ca2+-ATPase (SERCA)-2b and -3. Diabetes 2004;53:1517–1525
12. Kulkarni RN, Holzenberger M, Shih DQ, et al. beta-Cell-specific deletion of the Igf1 receptor leads to hyperinsulinemia and glucose intolerance but does not alter beta-cell mass. Nat Genet 2002;31:111–115
13. Kulkarni RN, Brüning JC, Winnay JN, Postic C, Magnuson MA, Kahn CR. Tissue-specific knockout of the insulin receptor in pancreatic beta cells creates an insulin secretory defect similar to that in type 2 diabetes. Cell 1999;96:329–339
14. Withers DJ, Gutierrez JS, Towery H, et al. Disruption of IRS-2 causes type 2 diabetes in mice. Nature 1998;391:900–904
15. Kido Y, Nakae J, Hribal ML, Xuan S, Efstratiadis A, Accili D. Effects of mutations in the insulin-like growth factor signaling system on embryonic pancreas development and beta-cell compensation to insulin resistance. J Biol Chem 2002;277:36740–36747
16. Fruman DA, Mauvais-Jarvis F, Pollard DA, et al. Hypoglycaemia, liver necrosis and perinatal death in mice lacking all isoforms of phosphoinositide 3-kinase p85 alpha. Nat Genet 2000;26:379–382
17. Terauchi Y, Tsuji Y, Satoh S, et al. Increased insulin sensitivity and hypoglycaemia in mice lacking the p85 alpha subunit of phosphoinositide 3-kinase. Nat Genet 1999;21:230–235
18. Zawalich WS, Zawalich KC. Effects of glucose, exogenous insulin, and carbachol on C-peptide and insulin secretion from isolated perifused rat islets. J Biol Chem 2002;277:26233–26237
19. Eto K, Yamashita T, Tsubamoto Y, et al. Phosphatidylinositol 3-kinase suppresses glucose-stimulated insulin secretion by affecting post-cytosolic [Ca(2+)] elevation signals. Diabetes 2002;51:87–97
20. Bouche C, Lopez X, Fleischman A, et al. Insulin enhances glucose-stimulated insulin secretion in healthy humans. Proc Natl Acad Sci U S A 2010;107:4770–4775
21. Mari A, Tura A, Natali A, et al.; for the RISC Investigators. Influence of hyperinsulinemia and insulin resistance on in vivo β-cell function: their role in human β-cell dysfunction. Diabetes 2011;60:3141–3147
22. Venieratos PD, Drossopoulou GI, Kapodistria KD, Tsilibary EC, Kitsiou PV. High glucose induces suppression of insulin signalling and apoptosis via upregulation of endogenous IL-1beta and suppressor of cytokine signalling-1 in mouse pancreatic beta cells. Cell Signal 2010;22:791–800