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# Islet adaptation to insulin resistance: mechanisms and implications for intervention

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**Abstract:** Insulin sensitivity and insulin secretion are reciprocally related such that insulin resistance is adapted by increased insulin secretion to maintain normal glucose and lipid homeostasis. The relation between insulin sensitivity and secretion is curvilinear and mathematically best described as a hyperbolic relation. Several potential mediators have been suggested to be signals for the beta cells to respond to insulin resistance such as glucose, free fatty acids, autonomic nerves, fat-derived hormones and the gut hormone glucagon-like peptide-1 (GLP-1). Failure of these signals or of the pancreatic beta cells to adequately adapt insulin secretion in relation to insulin sensitivity results in inappropriate insulin levels, impaired glucose intolerance (IGT) and type 2 diabetes. Therefore, treatment of IGT and type 2 diabetes should aim at restoring the normal relation between insulin sensitivity and secretion. Such treatment includes stimulation of insulin secretion (sulphonylureas, repaglinide and nateglinide) and insulin sensitivity (metformin and thiazolidinediones), as well as treatment aimed at supporting the signals mediating the islet adaptation (cholinergic agonists and GLP-1). Both, for correct understanding of diabetes pathophysiology and for development of novel treatment modalities, therefore, the non-linear inverse relation between insulin sensitivity and secretion needs to be acknowledged.

**Keywords:** GLP-1, glucose, insulin secretion, insulin sensitivity, lipids, metformin, thiazolidinedione, treatment

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## Introduction

It has been known since the 1960s that obesity is associated with increased insulin secretion [1–3]. After introduction of techniques for quantifying insulin sensitivity, it became clear that the hypersecretion of insulin in obesity is not caused by the obesity per se but to the accompanying reduced insulin sensitivity [4,5]. In fact, careful analysis of insulin sensitivity and insulin secretion in the same subjects identified a reciprocal relation between the two variables, such that insulin secretion is increased in reduced insulin sensitivity and reduced in increased insulin sensitivity [4–9]. When, for a given individual insulin sensitivity is reduced, such as during

pregnancy, in obesity, in polycystic ovary syndrome or after intake of glucocorticoids, insulin secretion is reciprocally increased. This is called the islet adaptation to insulin resistance, and the clinical importance is obvious from findings that when the adaptation is inadequate, i.e. when insulin secretion is insufficient for the degree of insulin resistance, hyperglycemia and impaired glucose intolerance (IGT), or type 2 diabetes develop [10–12]. Conversely, when insulin sensitivity is increased, as for example, after weight reduction in severe obesity or in elite sportsmen, insulin secretion is adaptively reduced [13,14]. A consequence of the inverse relation is that a correct measure of beta-cell function

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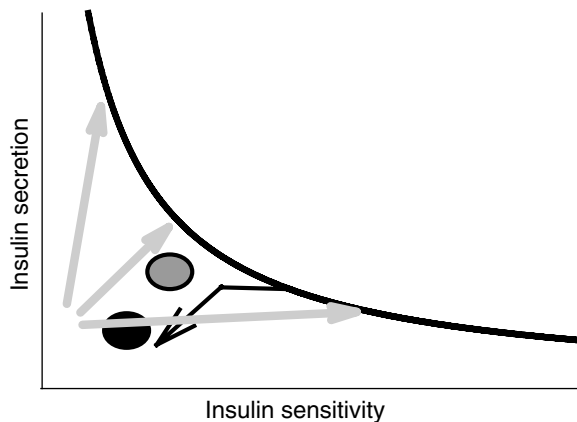
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requires that it is related to insulin sensitivity in the same subject. In fact, failure to acknowledge this relation may lead to incorrect conclusions on beta-cell function.

### Relationship between insulin sensitivity and secretion

Different mathematical relationships could represent the relationship between insulin sensitivity and secretion, as for example inverse linear or exponential functions. However, mathematical analysis of the relation in a large number of individuals has shown that the relation is non-linear in nature and best described as a hyperbolic function, as is illustrated in figure 1 [4,6–9,15]. This implies that the product of insulin sensitivity times insulin secretion is constant for a given degree of glucose intolerance. This product is usually called the disposition index. The asymptotic non-linear function describes also the physiological process that preserves a constant glucose uptake even in the presence of an elevated insulin release. In this situation, the body responds with reducing insulin sensitivity. This reduction however, after a certain value is very low, almost undetectable, despite an even excessive increasing of the secretion. The hyperbola fits with the representation of biological processes, especially enzymatic



**Fig. 1** The hyperbolic relation between insulin sensitivity and insulin secretion. Glucose tolerance is impaired if an individual is located below the hyperbolic line and good if an individual is located above the line. This is illustrated as the move from the normal hyperbolic line along the black arrow to the grey dot (representing impaired glucose tolerance, IGT) or the black dot (representing type 2 diabetes). Therapeutic approaches should aim at restoring the normal relation between insulin sensitivity and insulin secretion, i.e. to return the subject to the hyperbolic curve, as illustrated by the grey arrows.

reactions characterized by thresholds and saturation, which is not the case when testing for other mathematical relations.

### Mechanisms of islet adaptation to insulin resistance

The mechanism underlying the islet adaptation to insulin resistance, i.e. how the beta cells can sense a reduction in insulin sensitivity is not known. Several signals or mediators are, however, possible. One candidate is circulating glucose. If glucose levels were increased during development of insulin resistance, the hyperglycemia would be a stimulus for the beta cells to augment insulin secretion. This would therefore be a feedback loop because insulin secretion would then increase until the glycemia is normalized, which requires hyperinsulinemia due to the insulin resistance. In such a compensated state, therefore hyperinsulinemia exists in conjunction with normoglycemia. A problem with this hypothesis is that it lacks convincing experimental support because increased circulating glucose is rarely seen as long as beta cells are normally adapting to the insulin resistance, which maintains normoglycemia [15]. In fact, a study has shown that when insulin sensitivity is improved experimentally, insulin secretion is reciprocally reduced, and this was followed by increased and not reduced glucose levels [16], and one study using nicotinic acid showed that insulin resistance was followed by increased insulin secretion but a reduced circulating glucose [17]. It is thus not likely that glucose is a main signal for beta cells to adapt to insulin resistance.

Another candidate for being a signal increasing insulin secretion in insulin resistance would be the circulating free fatty acids (FFAs). In fact, during development of insulin resistance in adipocytes, FFAs levels increase due to reduced anti-lipolytic action of insulin [18]. Increasing levels of FFAs may therefore be a marker of insulin resistance in adipocytes, but FFAs may also be involved in the pathogenesis of whole body insulin resistance. Thus, an effect of FFAs is the induction of insulin resistance in muscle and liver [19]. However, FFAs may also be involved in the adaptation of insulin secretion to insulin resistance because FFAs, particularly longer chain FFAs, augment glucose-stimulated insulin secretion in humans and perfused rat pancreas, and reduction of circulating FFAs impairs insulin secretion in humans [20–22]. Mechanistically, this has been thought to rely on the formation of a long-chain acetyl CoA within the beta cells which by some as yet unidentified mechanisms, perhaps related to ionic changes or to kinase actions of

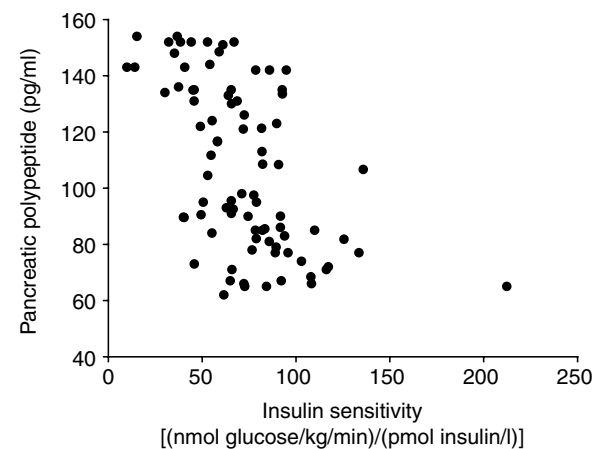
importance for the exocytosis, augments insulin secretion [23]. An alternate mechanism was recently suggested when it was shown that exogenous FFAs activate a specific G-protein coupled receptor, GPR40, in the beta cells [24], although it is not known whether this receptor signals a stimulation of insulin secretion. On the other hand, however, it may, like in the case for glucose, be argued that if the beta cells are functioning normally, the increased insulin secretion compensate for the insulin resistance thereby preventing FFAs from reaching insulinotropic concentrations. Furthermore, the increase in FFAs during insulin resistance in subjects with type 2 diabetes has usually been interpreted as being detrimental for beta-cell function because an increase in FFAs may result in lipotoxicity thereby impairing glucose-stimulated insulin secretion [25]. Hence, whether FFAs are of physiological relevance for the islet adaptation to insulin resistance remains an enigma.

A third candidate for the islet adaptation to insulin resistance might be the autonomic nerves. It is known that the pancreatic islets are innervated by parasympathetic, sympathetic and sensory nerves, and it is known that activation of the parasympathetic nerves through both cholinergic and non-cholinergic (peptidergic) mechanisms stimulate insulin secretion [26]. Furthermore, it has been shown that the hyperinsulinemia accompanying the obese fa/fa rat is partially dependent on the vagal nerves [27] and that the huge hyperinsulinemia, which accompanies the insulin resistance in ob/ob mice is sensitive to cholinergic antagonism by atropine [28]. Similarly, the islet hypertrophy in ob/ob mice is prevented by vagotomy [29]. It may therefore be suggested that insulin resistance is sensed by afferent nerves, which through a neural central circuit couples to increased vagal activity thereby increasing insulin secretion. Such a hypothesis is supported by a study on the increased insulin demand created by long-term glucose infusion in rats, in which the hyperinsulinemia was dependent on cholinergic activity [30]. Furthermore, both in humans [31] and in mice [32] with insulin resistance, insulin secretion is increasingly sensitive to cholinergic activation. A problem of verifying this hypothesis is the difficulty to determine vagal activity in humans. An indirect measure is, however, the circulating level of pancreatic polypeptide (PP), which is a marker of parasympathetic activity [33]. It has, thereby, been shown in insulin resistant Pima Indians that PP levels are increased, supporting a role of the parasympathetic nerves in the adaptations to insulin resistance [34]. Recently, we also verified this in a group of Caucasian women with normal glucose tolerance in whom insulin sensitivity was determined by the hyperinsulinemic,

euglycemic clamp technique. When their fasting PP levels were plotted against the insulin sensitivity, a linear relation was observed (figure 2). Thus, the autonomic nerves may contribute to the islet adaptation to insulin resistance.

In insulin resistance, the secretion of several adipocytokines from the adipocytes is altered [35]. For example, plasma levels of leptin are increased whereas plasma adiponectin is reduced in insulin resistance. As these adipocytokines may affect beta-cell function through the so-called adipoinsular axis [36], it may be hypothesized that they may contribute to the islet adaptation to changes in insulin sensitivity. This was recently explored in a population study where it was demonstrated that the islet adaptation in a large group of individuals independently correlated positively with circulating leptin and negatively with circulating adiponectin [37]. However, whether these correlations indicate causal relationship is not known, particularly because the effects of the adipocytokines on insulin secretion are far from being established.

Recently, it was interestingly suggested that the gut hormone glucagon-like peptide-1 (GLP-1) may contribute to insulin hypersecretion in insulin resistance [38]. GLP-1 is the most important incretin hormone in humans and has been shown to be extremely potent at augmenting glucose-stimulated insulin secretion [39–41]. It was thus shown in dogs fed a high-fat diet



**Fig. 2** Relationship between insulin sensitivity as determined by the euglycemic, hyperinsulinemic clamp technique, and fasting pancreatic polypeptide (PP) levels determined by radioimmunoassay, in 86 females, all 61 years of age. The relation was significant ( $r = -0.40$  and  $p < 0.001$ ). Fasting PP did also correlate positively with body mass index (BMI) ( $r = 0.51$  and  $p < 0.001$ ). However, also in a partial correlation analyses controlling for the influence of BMI, PP still correlated negatively with insulin sensitivity ( $r = -0.22$  and  $p = 0.039$ ).

for 12 weeks that the circulating levels of GLP-1 as well as the expression of GLP-1 receptors in the pancreas were increased, whereas FFAs or glucose did not increase [38]. Hence, also GLP-1 might contribute to hyperinsulinemia in insulin resistance.

### **Mechanism of impaired islet adaptation in diabetes**

It is clear that an islet adaptation to insulin resistance is important for maintaining glucose tolerance and therefore a defective insulin secretion in relation to insulin sensitivity, i.e. impaired islet adaptation to insulin resistance, is a major determinant of development of IGT and type 2 diabetes [10–12,15]. A reason for such defective adaptation may be limited beta-cell function. This may be a primary defect caused for example by impaired expression of transcription factors of importance for normal beta-cell function such as PDX-1 or the HNFs, the impaired expression of which underlies the various monogenetic MODY-forms of diabetes [42]. Another reason for defective beta-cell function may be secondary alterations of cellular function, like impaired processing of proinsulin, islet accumulation of amyloid, reduced beta-cell mass, or toxic perturbations by glucose or lipids on signalling mechanisms of importance for insulin secretion [43]. Besides defective beta-cell function per se, an inadequate islet adaptation may also result from inadequate function of any of the above-mentioned potential signals mediating the adaptation. Finally, it has also been proposed that a single, unifying, mechanism might be underlying both the insulin resistance and the islet dysfunction. A candidate for such a mechanism is defective function of the insulin receptor substrate-2 (IRS-2), which is expressed in insulin sensitive tissues, including the beta cells, and involved in the signalling of insulin [44]. Thus, a mouse model with knockout of the IRS-2 gene is associated with insulin resistance in association with defective beta-cell compensation [45]. In any case, therapeutic attempts in type 2 diabetes need to acknowledge that a major goal of treatment, from a mechanistic point of view, is to restore the normal relation between insulin sensitivity and insulin secretion in the individual patient, i.e. to return the subject above the hyperbolic line as illustrated in figure 1.

### **Approaches to therapeutic restoration of defective islet adaptation**

A first approach to restore islet adaptation is to increase the capacity of the beta cells to secrete insulin, as

this will allow the now augmented insulin secretion to match for the insulin resistance. Several compounds are known to be efficient stimulators of insulin secretion. Most commonly used are the sulphonylureas [46]. These compounds activate the specific-SUR1 receptor on the beta cells, which is coupled to closing the ATP-dependent K-channels thereby leading to depolarization, uptake of calcium and exocytosis of insulin. Although efficient also over a longer period of time and well documented through the use for several decays, drawbacks of sulphonylureas are the risk for hypoglycemia and that a substantial fraction of subjects fail in the longer run [47]. Recently, the more short-lived compounds, repaglinide and nateglinide, have been introduced. They are given in conjunction with meal intake to cope for the increased insulin demand in the prandial situation [48]. These compounds work through a similar mechanism as sulphonylureas. As they seem to exhibit a lower risk of hypoglycemia than sulphonylureas, they may be of advantage in the future. A different approach in restoring beta-cell function would be to remove factors underlying the dysfunction, like improving the processing of proinsulin, preventing or inhibiting the islet amyloid formation [49], or reducing the beta-cell lipid accumulation, the latter being a successful approach in experimental studies in Zucker Diabetic Fatty rats [49,50].

A second approach to restore defective islet adaptation is to increase insulin sensitivity. This will move the patient in the insulin sensitivity/insulin secretion diagram to the right and the capacity of the beta cells to secrete insulin might then be sufficient for the now increased insulin sensitivity. The most commonly used compound with this aim is metformin [51], which acts through lowering glucose production of the liver by inhibiting gluconeogenesis [52]. Metformin has been used since a long time and is considered safe, although a slight risk of lactic acidosis exists and, furthermore, adverse events in the form of gastrointestinal discomfort are not rare at high-dose levels. More recently, the thiazolidinediones (TZD) have been introduced. These compounds activate peroxisome proliferator-activated receptor- $\gamma$  (PPAR- $\gamma$ ), which through a complex transcriptional mechanism increases the expression of important signalling molecules for insulin action in insulin sensitive tissues, leading to translocation of GLUT-4 and increased fat oxidation, thereby reducing insulin resistance and increasing peripheral glucose uptake [53]. As PPAR- $\gamma$  also is expressed in the beta cells, it has been of interest that the TZDs also augment beta-cell function, perhaps by increasing fat oxidation thereby reducing the intracellular lipid accumulation

and preventing the lipotoxicity [50,53,54]. TZDs may therefore not only improve insulin sensitivity but also, apart from this action, improve beta-cell function, thereby aiming from two directions to restore the normal non-linear relation between insulin sensitivity and secretion. Although the initially introduced TZD, troglitazone, appeared unsafe due to hepatotoxicity, the currently used TZDs do not seem to adversely affect liver function. They do, however, increase the risk for oedema and heart failure. It should be emphasized, however, that the most important way of improving insulin sensitivity is life-style changes with weight reduction and increased physical activity [55]. This has been well documented in the important Malmö Preventive Trial in which life-style changes in subjects with IGT have been shown to prevent the development of type 2 diabetes as well as reduce cardiovascular morbidity and mortality [56].

A third therapeutic approach would be to support or increase the signals mediating the increased insulin secretion in insulin resistance. An idea behind this approach is that it may be the signals themselves that are not sufficient to cope with the reduced insulin sensitivity. Both the cholinergic system and GLP-1 have been proposed as such therapeutics in type 2 diabetes. Cholinergic agonism was thereby shown to improve the IGT and type 2 diabetes in experimental models in mice, where insulin secretion was markedly improved after long-term high-fat feeding [32]. Furthermore, GLP-1 has been explored in quite a detail for its use in treatment of type 2 diabetes during recent years [39–41]. Thus, GLP-1 has been shown to be anti-diabetogenic, and this effect is partially executed through stimulation of insulin secretion and, interestingly, in the longer run also through improvement of insulin sensitivity [57]. GLP-1 may thus be optimal in restoring the normal insulin sensitivity/secretion relation in subjects with type 2 diabetes. A problem has been that the peptide is so short-lived that it is not possible to administer unless a continuous infusion is given. As this short half-life is due to the activity of the degrading enzyme, dipeptidyl peptidase-4 (DPP-4) [58] attempts to overcome the problem include development of DPP-4 resistant analogs or development of agents inhibiting DPP-4 [59].

The fourth approach for restoring the normal relation between insulin sensitivity and insulin secretion would be to remove factors counteracting the signals mediating the insulin hypersecretion. Here, two candidates are obvious, and it is glucose and FFAs. Although both these factors, at least in the beginning of development of IGT and type 2 diabetes might mediate a normal beta-cell adaptation, when increased over certain levels, they create toxic effects in the beta cells, the so-called

glucotoxicity or lipotoxicity, which may counteract the normal islet adaptation [60,61].

### Concluding remarks

The reciprocal relation between insulin sensitivity and insulin secretion requires that both variables are estimated for accurate estimation of beta-cell function, as a main function of these cells is to adapt insulin secretion to insulin resistance. Defective islet adaptation is therefore a key mechanism underlying type 2 diabetes. In fact, type 2 diabetes may be regarded as a disease where the islet adaptation to insulin resistance fails. Therapeutic intervention should therefore aim at restoring the normal non-linear relation between insulin sensitivity and insulin secretion. Although the optimal treatment still awaits to be established, several approaches that are currently used serve this aim.

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### References

- 1 Karam JH, Grodsky GM, Forsham PH. Excessive insulin response to glucose in obese subjects as measured by immunochemical assay. *Diabetes* 1963; **12**: 197–204.
- 2 Perley MJ, Kipnis DM. Plasma insulin responses to oral and intravenous glucose: studies in normal and diabetic subjects. *J Clin Invest* 1967; **46**: 1954–1962.
- 3 Bagdade JD, Porte D Jr, Brunzell JD, Bierman EL. Basal and stimulated hyperinsulinism: reversible metabolic sequelae of obesity. *J Lab Clin Med* 1974; **83**: 563–569.
- 4 Kahn SE, Prigeon RL, McCulloch DK *et al.* Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes* 1993; **42**: 1663–1672.
- 5 Larsson H, Ahrén B. Islet dysfunction in obese women with impaired glucose tolerance. *Metabolism* 1996; **45**: 502–509.
- 6 Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man. *J Clin Invest* 1981; **68**: 1456–1467.
- 7 Clausen JO, Borch-Johnsen K, Ibsen H *et al.* Insulin sensitivity index, acute insulin response, and glucose

- effectiveness in a population-based sample of 380 young healthy Caucasians. Analysis of the impact of gender, body fat, physical fitness, and life-style factors. *J Clin Invest* 1996; **98**: 1195–1209.
- 8 Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999; **104**: 787–794.
  - 9 Larsson H, Ahrén B. Islet dysfunction in insulin resistance involves impaired insulin secretion and increased glucagon secretion in postmenopausal women with impaired glucose tolerance. *Diabetes Care* 2000; **23**: 650–657.
  - 10 Larsson H, Ahrén B. Insulin resistant subjects lack islet adaptation to acute dexamethasone-induced reduction in insulin sensitivity. *Diabetologia* 1999; **42**: 936–943.
  - 11 Ehrmann DA, Sturis J, Byrne MM *et al.* Insulin secretory defects in polycystic ovary syndrome. Relationship to insulin sensitivity and family history of non-insulin-dependent diabetes mellitus. *J Clin Invest* 1995; **96**: 520–527.
  - 12 Ward WK, Johnston CLW, Beard JC *et al.* Insulin resistance and impaired insulin secretion in subjects with histories of gestational diabetes mellitus. *Diabetes* 1985; **34**: 861–869.
  - 13 Guldstrand M, Ahrén B, Adamson U. Improved  $\beta$ -cell function after standardized weight reduction in severely obese subjects. *Am J Physiol* 2003; **284**: E557–E565.
  - 14 Ahrén B, Thorsson O. Increased insulin sensitivity is associated with reduced insulin and glucagon secretion and increased insulin clearance in man. *J Clin Endocrinol Metab* 2003; **88**: 1264–1270.
  - 15 Kahn SE. The relative contributions of insulin resistance and beta cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* 2003; **46**: 3–19.
  - 16 Kahn SE, Larson VG, Beard JC *et al.* Effect of exercise on insulin action, glucose tolerance, and insulin secretion in aging. *Am J Physiol* 1990; **258**: E937–E943.
  - 17 Kahn SE, Beaud JC, Schwartz MW *et al.* Increased  $\beta$ -cell secretory capacity as mechanism for islet adaptation to nicotinic acid-induced insulin resistance. *Diabetes* 1989; **38**: 562–568.
  - 18 Bergman RN, van Citters GW, Mittelman SD *et al.* Central role of the adipocyte in the metabolic syndrome. *J Invest Med* 2001; **49**: 119–126.
  - 19 Shulman GI. Cellular mechanisms of insulin resistance. *J Clin Invest* 2000; **106**: 171–176.
  - 20 Boden G, Chen X, Iqbal N. Acute lowering of plasma fatty acids lowers basal insulin secretion in diabetic and nondiabetic subjects. *Diabetes* 1998; **47**: 1609–1612.
  - 21 Dobbins RI, Chester MW, Daniels MB *et al.* Circulating fatty acids are essential for efficient glucose-stimulated insulin secretion after prolonged fasting in humans. *Diabetes* 1998; **47**: 1613–1618.
  - 22 Stein DT, Stevenson BE, Chester MW *et al.* The insulinotropic potency of fatty acids is influenced profoundly by their chain length and degree of saturation. *J Clin Invest* 1997; **100**: 398–403.
  - 23 Prentki M, Corkey BE. Are the beta-cell signaling molecules malonyl-CoA and cytosolic long-chain acyl-CoA implicated in multiple tissue defects of obesity and NIDDM? *Diabetes* 1996; **45**: 273–283.
  - 24 Itoh Y, Kawamata Y, Harada M *et al.* Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature* 2003; **422**: 173–176.
  - 25 Zhou VP, Grill VE. Long-term exposure of rat pancreatic islets to fatty acids inhibits glucose-induced insulin secretion and biosynthesis through a glucose fatty acid cycle. *J Clin Invest* 1994; **93**: 870–876.
  - 26 Ahrén B. Autonomic regulation of islet hormone secretion – Implications for health and disease. *Diabetologia* 2000; **43**: 393–410.
  - 27 Rohner-Jeanrenaud F, Hochstrasser AC, Jeanrenaud B. Hyperinsulinemia of preobese and obese fa/fa rats is partly vagus nerve mediated. *Am J Physiol* 1983; **244**: E317–E322.
  - 28 Ahrén B, Lundquist I. Modulation of basal insulin secretion in the obese, hyperglycemic mouse. *Metabolism* 1982; **31**: 172–179.
  - 29 Edvell A, Lindström P. Vagotomy in young obese hyperglycemic mice: effects on syndrome development and islet proliferation. *Am J Physiol* 1998; **274**: E1034–E1039.
  - 30 Balkan B, Dunning BE. Muscarinic stimulation maintains in vivo insulin secretion in response to glucose after prolonged hyperglycemia. *Am J Physiol* 1995; **268**: R475–R479.
  - 31 DelRio G, Procopio M, Bondi M *et al.* Cholinergic enhancement by pyridostigmine increases the insulin response to glucose load in obese patients but not in normal subjects. *Int J Obes Relat Metab Disord* 1997; **21**: 1111–1114.
  - 32 Ahrén B, Sauerberg P, Thomsen C. Increased insulin secretion and normalisation of glucose tolerance by cholinergic agonism in high-fat fed C57BL/6J mice. *Am J Physiol* 1999; **277**: E93–E102.
  - 33 Havel PJ, Taborsky GJ Jr. The contribution of the autonomic nervous system to changes of glucagon and insulin secretion during hypoglycaemic stress. *Endocr Rev* 1989; **10**: 332–350.
  - 34 Weyer C, Salbe AD, Lindsay RS *et al.* Exaggerated pancreatic polypeptide secretion in Pima Indians: can an increased parasympathetic drive to the pancreas contribute to hyperinsulinemia, obesity, and diabetes in humans? *Metabolism* 2001; **50**: 223–230.
  - 35 Havel PJ. Control of energy homeostasis and insulin action by adipocyte hormones: leptin, acylation stimulating protein, and adiponectin. *Curr Opin Lipidol* 2002; **13**: 51–59.
  - 36 Kieffer TJ, Habener JF. The adipoinsular axis: effects of leptin on pancreatic beta-cells. *Am J Physiol* 2000; **278**: E1–E14.
  - 37 Ahrén B, Pacini G. Signals adapting the beta cells to changes in insulin sensitivity. In: Crepaldi G, Tiengo A,

- Avojaró A eds. *The Metabolic Syndrome: Diabetes, Obesity, Hyperlipidemia and Hypertension*. New York: Elsevier, 105–113.
- 38 van Citters GW, Kabir M, Kim SP *et al*. Elevated glucagon-like peptide-1-(7–36)-amide, but not glucose, associated with hyperinsulinemic compensation for fat feeding. *J Clin Endocrinol Metab* 2002; **87**: 5191–5198.
- 39 Ahrén B. Glucagon-like peptide 1 (GLP-1) – a gut hormone of potential interest in the treatment of diabetes. *Bioessays* 1998; **20**: 642–651.
- 40 Drucker DJ. Biological actions and therapeutic potential of the glucagon-like peptides. *Gastroenterology* 2002; **122**: 531–544.
- 41 Holst JJ. Therapy of type 2 diabetes mellitus based on the actions of glucagon-like peptide-1. *Diabetes Metab Res Rev* 2002; **18**: 430–441.
- 42 Shih DQ, Stoffel M. Molecular etiologies of MODY and other early-onset forms of diabetes. *Curr Diabet Rep* 2002; **2**: 125–134.
- 43 Bergman RN, Finegood DT, Kahn SE. The evolution of  $\beta$ -cell dysfunction and insulin resistance in type 2 diabetes. *Eur J Clin Invest* 2002; **32** (Suppl. 3): 35–45.
- 44 Whitters DJ, Gutierrez JS, Towery H *et al*. Disruption of IRS-2 causes type 2 diabetes in mice. *Nature* 1998; **391**: 900–904.
- 45 Rhodes CJ, White MF. Molecular insights into insulin action and secretion. *Eur J Clin Invest* 2002; **32** (Suppl. 3): 3–13.
- 46 Gribble FM, Reimann F. Pharmacological modulation of K (ATP) channels. *Biochem Soc Trans* 2002; **30**: 333–339.
- 47 Salas M, Caro JJ. Are hypoglycemia and other adverse effects similar among sulphonylureas? *Adv Drug React Toxicol Rev* 2002; **21**: 205–217.
- 48 Davies MJ. Insulin secretagogues. *Curr Med Res Opin* 2002; **18** (Suppl. 1): s22–s30.
- 49 Höppener JWM, Ahrén B, Lips CJM. Mechanisms of disease: Islet amyloid and type 2 diabetes mellitus. *N Engl J Med* 2000; **343**: 411–419.
- 50 Shimabukuru M, Zhou YT, Lee Y, Unger RH. Troglitazone lowers islet fat and restores beta cell function of Zucker diabetic fatty rats. *J Biol Chem* 1998; **273**: 3547–3550.
- 51 Hsia SH, Davidson MB. Established therapies for diabetes mellitus. *Curr Med Res Opin* 2002; **18** (Suppl. 1): s13–s21.
- 52 Hundal RS, Krsiak M, Dufour S *et al*. Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes* 2000; **49**: 2063–2069.
- 53 Francis GA, Fayard E, Picard F, Auwerx J. Nuclear receptors and the control of metabolism. *Ann Rev Physiol* 2003; **65**: 261–311.
- 54 Cavaghan MK, Ehrmann DA, Byrne MM, Polonsky KS. Treatment with the oral antidiabetic agent troglitazone improves beta cell responses to glucose in subjects with impaired glucose tolerance. *J Clin Invest* 1997; **100**: 530–537.
- 55 Tudor-Locke CE, Bell RC, Meyers AM. Revisiting the role of physical activity and exercise in the treatment of type 2 diabetes. *Can J Appl Physiol* 2000; **25**: 466–482.
- 56 Eriksson KF, Lindgärde F. No excess 12-year mortality in men with impaired glucose tolerance who participated in the Malmö Preventive Trial with diet and exercise. *Diabetologia* 1998; **41**: 1010–1016.
- 57 Zander M, Madsbad S, Madsen JJ, Holst JJ. Effect of 6-week course of glucagon-like peptide 1 on glycemic control, insulin sensitivity, and beta-cell function in type 2 diabetes: a parallel-group study. *Lancet* 2002; **359**: 824–830.
- 58 Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. *Diabetes* 1998; **47**: 1663–1670.
- 59 Ahrén B, Simonsson E, Larsson H *et al*. Inhibition of dipeptidyl peptidase IV improves metabolic control over a 4 week study period in type 2 diabetes. *Diabetes Care* 2002; **25**: 869–875.
- 60 Poirier V, Robertson RP. Secondary beta-cell failure in type 2 diabetes – a convergence of glucotoxicity and lipotoxicity. *Endocrinology* 2002; **143**: 339–342.
- 61 Wang MY, Koyama K, Shimabukuro M, Newgard CB, Unger RH. OB-Rb gene transfer to leptin-resistant islets reverses diabetogenic phenotype. *Proc Natl Acad Sci USA* 1998; **95**: 714–718.