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Mechanisms linking obesity to insulin resistance and type 2 diabetes

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Obesity is associated with an increased risk of developing insulin resistance and type 2 diabetes. In obese individuals, adipose tissue releases increased amounts of non-esterified fatty acids, glycerol, hormones, pro-inflammatory cytokines and other factors that are involved in the development of insulin resistance. When insulin resistance is accompanied by dysfunction of pancreatic islet β-cells — the cells that release insulin — failure to control blood glucose levels results. Abnormalities in β-cell function are therefore critical in defining the risk and development of type 2 diabetes. This knowledge is fostering exploration of the molecular and genetic basis of the disease and new approaches to its treatment and prevention.

The increased prevalence of obesity has focused attention on a worldwide problem that is not one of famine or infection, but one of surplus. In the United States, only about a third of adults are considered to be of 'normal' weight[1], and similar trends are being observed worldwide[2]. Obesity is associated with several conditions, the most devastating of which may be type 2 diabetes. At the turn of this century 171 million individuals were estimated to have diabetes, and this is expected to increase to 366 million by 2030 (ref. 3).

Both obesity and type 2 diabetes are associated with insulin resistance[4]. But most obese, insulin-resistant individuals do not develop hyperglycaemia. Under normal conditions, the pancreatic islet β-cells increase insulin release sufficiently to overcome the reduced efficiency of insulin action, thereby maintaining normal glucose tolerance[5–7]. For obesity and insulin resistance to be associated with type 2 diabetes, β-cells must be unable to compensate fully for decreased insulin sensitivity[8]. β-cell dysfunction exists in individuals who are at high risk of developing the disease even when their glucose levels are still normal[8]. Non-esterified fatty acids (NEFAs) induce insulin resistance and impair β-cell function, making them a likely culprit.

Here we explore the interactions between obesity, insulin resistance and β-cell dysfunction that result in type 2 diabetes, and attempt to lay a framework to consider approaches that might lessen the burden of these epidemics that threaten modern society.

Insulin resistance and obesity

Fluctuations in insulin sensitivity occur during the normal life cycle, with insulin resistance being observed during puberty[9] and pregnancy[10], and with ageing[11]. Conversely, lifestyle variation such as increased physical activity[12] and increased carbohydrate intake[13] are associated with enhanced insulin sensitivity.

The most critical factor in the emergence of metabolic diseases is obesity. Adipose tissue modulates metabolism by releasing NEFAs and glycerol, hormones — including leptin and adiponectin — and proinflammatory cytokines[14–16]. In obesity, the production of many of these products is increased. Retinol-binding protein-4 (RBP4) induces insulin resistance through reduced phosphatidylinositol-3-OH kinase (PI(3)K) signalling in muscle and enhanced expression of the gluconeogenic enzyme phosphoenolpyruvate carboxykinase in the liver through a retinol-dependent mechanism[17]. By contrast, adiponectin acts as an insulin sensitizer, stimulating fatty acid oxidation in an AMP-activated protein kinase (AMPK) and peroxisome proliferator activated receptor-α (PPAR-α)-dependent manner[15,18].

In addition to adipocyte-derived factors, increased release of tumour necrosis factor-α (TNF-α), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1) and additional products of macrophages and other cells that populate adipose tissue might also have a role in the development of insulin resistance[14,19]. TNF-α and IL-6 act through classical receptor-mediated processes to stimulate both the c-Jun amino-terminal kinase (JNK) and the IκB kinase-β (IKK-β)/nuclear factor-κB (NF-κB) pathways, resulting in upregulation of potential mediators of inflammation that can lead to insulin resistance.

Pathways involving the induction of suppression of cytokine signalling (SOCS) proteins[20] and inducible nitric oxide synthase (iNOS)[21] may be involved in mediating cytokine-induced insulin resistance. Secretion of these proinflammatory proteins, particularly MCP-1 by adipocytes, endothelial cells and monocytes, increases macrophage recruitment and thereby contributes to a feedforward process[22,23].

The release of NEFAs may be the single most critical factor in modulating insulin sensitivity. Increased NEFA levels are observed in obesity and type 2 diabetes, and are associated with the insulin resistance observed in both[24,25]. Insulin resistance develops within hours of an acute increase in plasma NEFA levels in humans[26]. Conversely, insulin-mediated glucose uptake and glucose tolerance improve with an acute decrease in NEFA levels after treatment with the antilipolytic agent acipimox[27]. Increased intracellular NEFAs might result in competition with glucose for substrate oxidation leading to the serial inhibition of pyruvate dehydrogenase, phosphofructokinase and hexokinase II activity[28]. It has also been proposed that increased NEFA delivery or decreased intracellular metabolism of fatty acids results in an increase in the intracellular content of fatty acid metabolites such as diacylglycerol (DAG), fatty acyl-coenzyme A (fatty acyl-CoA), and ceramides, which, in turn, activate a serine/threonine kinase cascade leading to serine/threonine phosphorylation of insulin receptor substrate-1 (IRS-1) and insulin receptor substrate-2 (IRS-2), and a reduced ability of these molecules to activate PI(3)K[29]. Subsequently, events downstream of insulin-receptor signalling are diminished.

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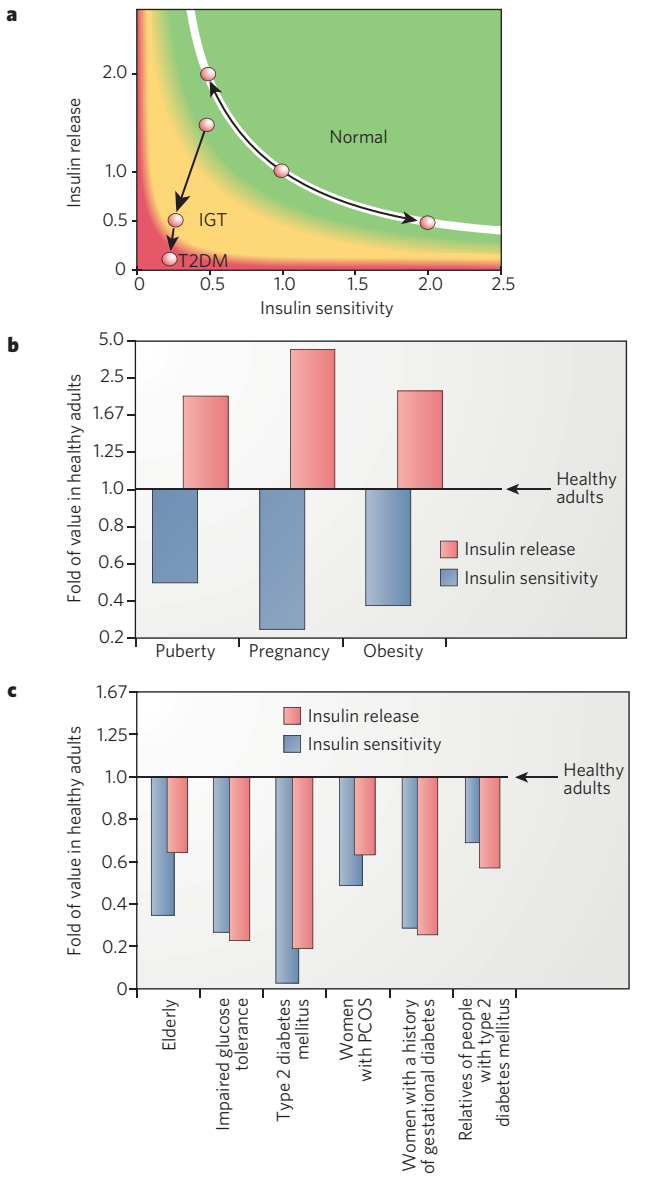

Figure 1 | Relationship between insulin sensitivity and insulin release in health and disease. **a**, Relationship between insulin sensitivity and the β-cell insulin response is nonlinear. This hyperbolic relationship means that assessment of β-cell function requires knowledge of both insulin sensitivity and the insulin response. Hypothetical regions delineating normal glucose tolerance (green), impaired glucose tolerance (IGT; yellow) and type 2 diabetes mellitus (T2DM; red) are shown. In response to changes in insulin sensitivity, insulin release increases or decreases reciprocally to maintain normal glucose tolerance — 'moving up' or 'moving down' the curve. In individuals who are at high risk of developing type 2 diabetes, the progression from normal glucose tolerance to type 2 diabetes transitions through impaired glucose tolerance and results in a 'falling off the curve'. Those individuals who do progress will frequently have deviated away from the curve even when they have normal glucose tolerance, in keeping with β-cell function already being decreased before the development of hyperglycaemia. **b**, Insulin sensitivity and insulin responses during puberty, during pregnancy and in obesity relative to that in healthy adults. On the basis of the hyperbolic relationship defining β-cell function, the product of insulin sensitivity and the insulin response is 1. In individuals with normal β-cells, glucose tolerance is preserved during puberty, during pregnancy and in obesity as the decrease in insulin sensitivity is matched by a reciprocal, compensatory increase in insulin release, maintaining the product of 1. **c**, Insulin sensitivity and insulin responses in groups of people with type 2 diabetes and those at increased risk of developing type 2 diabetes. In these groups, the decline in insulin sensitivity is not matched by a reciprocal increase in the insulin response. Instead, the insulin response also declines so the product is less than 1, which is compatible with the idea of β-cell dysfunction. PCOS, polycystic ovarian syndrome.

The distribution of body fat is itself a critical determinant of insulin sensitivity. Whereas simple obesity is typically associated with insulin resistance, insulin sensitivity also varies markedly in lean individuals because of differences in body fat distribution[30–33]. Lean individuals with a more peripheral distribution of fat are more insulin sensitive than lean subjects who have their fat distributed predominantly centrally — that is, in the abdominal and chest areas.

Differences in the characteristics of adipose tissue from these two depots might explain in part why the metabolic effects of intra-abdominal and subcutaneous fat differ. For example, intra-abdominal fat expresses more genes encoding secretory proteins and proteins responsible for energy production[34]. The amount of protein released per adipocyte also differs according to their location[19,35]. The secretion of adiponectin by omental adipocytes is greater than that of subcutaneous-derived adipocytes, and the amount released from these omental adipocytes is more strongly and negatively correlated with body mass index (BMI)[35]. Small adipocytes release more adiponectin than do larger cells, and omental adipocytes are typically smaller than subcutaneous fat cells[36]. Although each adipocyte from the intra-abdominal depot secretes more adiponectin, the subcutaneous depot represents a greater proportion of total body fat, and thus its contribution to total adiponectin levels will invariably be greater.

The delivery of NEFAs to the tissues might also be modulated by their source. Intra-abdominal fat is more lipolytic than subcutaneous fat and is also less sensitive to the anti-lipolytic effect of insulin[37]. This difference in adipocyte characteristics, combined with the proximity of the liver to the intra-abdominal fat depot, probably results in greater exposure of this organ than the peripheral tissues to NEFAs. This difference in exposure and the presence of a portal–peripheral NEFA gradient could explain why the liver can be insulin resistant at a time when the peripheral tissues are not[38].

β-cell function and mass

β-cells are markedly plastic in their ability to regulate insulin release, but at the same time do so in a very precise manner. The quantity of insulin released by β-cells varies according to the nature, quantity and route of administration of the stimulus, and the prevailing glucose concentration. In this manner, the β-cell is crucial to ensuring that in healthy subjects plasma glucose concentrations remain within a relatively narrow physiological range.

Insulin sensitivity also modulates β-cell function and is almost always decreased in obesity. Insulin-resistant individuals, whether lean or obese, have greater insulin responses and lower hepatic insulin clearance than insulin-sensitive individuals. In healthy individuals, there is a feedback loop between the insulin-sensitive tissues and the β-cells, with β-cells increasing insulin supply in response to demand by the liver, muscles and adipose tissue[7]. The relationship between insulin sensitivity and insulin levels is reciprocal and nonlinear in nature (Fig. 1a). In order for glucose tolerance to remain unchanged, changes in insulin sensitivity must be matched by a proportionate yet opposite change in circulating insulin levels. Failure of this feedback loop results in a deviation from normal glucose tolerance and underlies the development of diabetes.

Another important implication of this feedback loop is that interpretation of the β-cell's secretory response to a given stimulus must take into account the prevailing degree of insulin sensitivity. This ability of the β-cell to adapt to changes in insulin sensitivity seems to result from two parameters: the functional responsiveness of the cell and β-cell mass. In response to the insulin resistance observed in obesity[5–7], puberty[9] and pregnancy[10], human β-cells can increase insulin release to levels fourfold to fivefold higher than in insulin-sensitive individuals (Fig. 1b), whereas β-cell volume is only enhanced by about 50%[39,40].

The integration of the β-cell's response to changes in insulin sensitivity probably involves increased cellular glucose metabolism, NEFA signalling and sensitivity to incretins (Fig. 2). Increased β-cell glucose metabolism occurs in animal models of obesity that maintain normal blood glucose levels (euglycaemia)[41]. Glucose-stimulated insulin secretion requires the metabolism of glucose and thereby the generation of

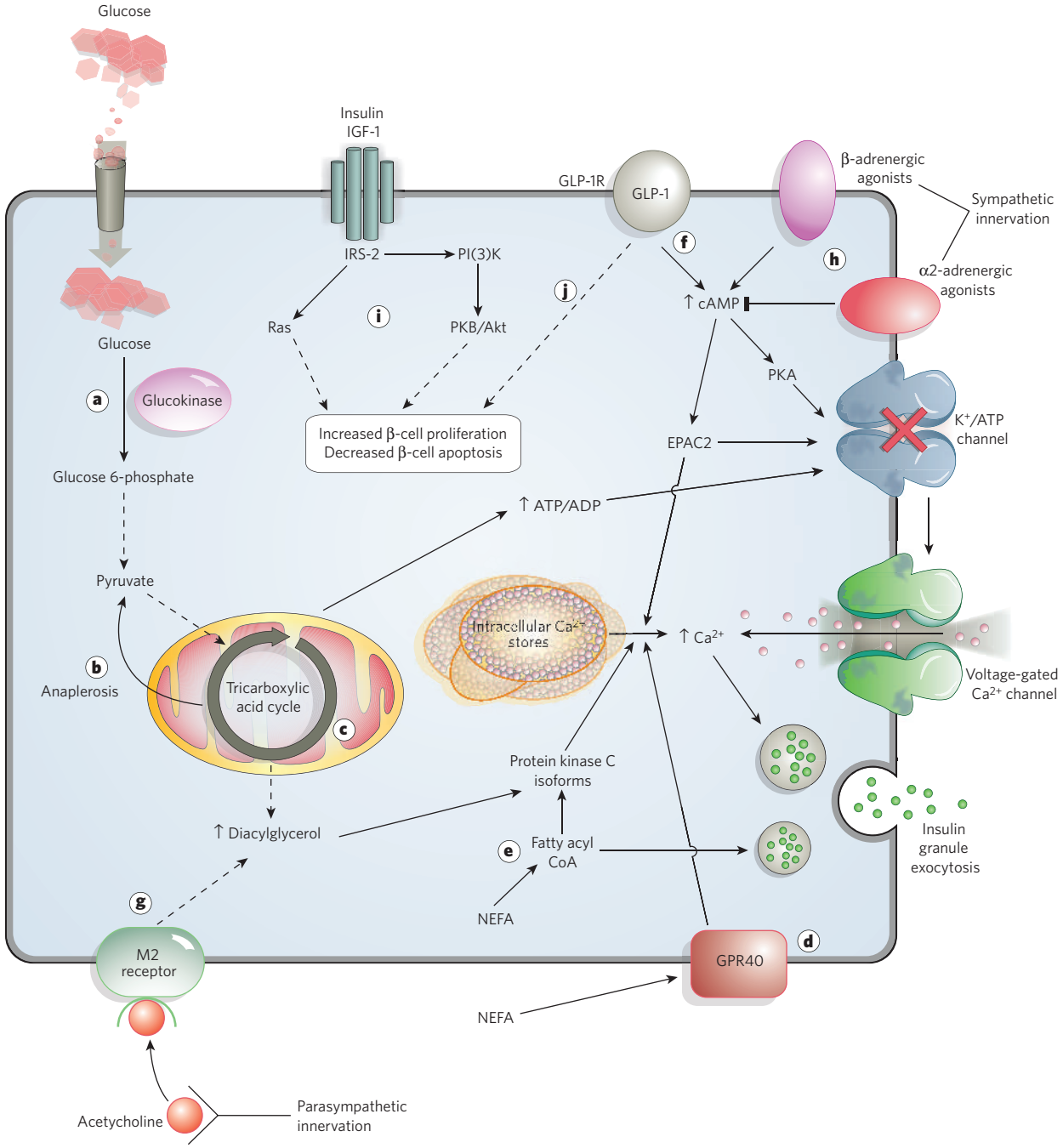

Figure 2 | Simplified model outlining potential cellular mechanisms of β-cell adaptation to insulin resistance. Glucose-stimulated insulin secretion occurs by oxidative metabolism of glucose, leading to an increase in the ATP/ADP ratio. This causes closure of K^+_{ATP} channels, depolarization of the plasma membrane, increased cytoplasmic calcium concentrations through voltage-gated calcium channels, and exocytosis of insulin-containing secretory granules. In conditions in which insulin demand is increased, β-cell glucose metabolism can be enhanced by increased glucokinase enzyme activity (**a**) and by replenishment of tricarboxylic acid cycle intermediates by anaplerosis (**b**). Glucose-induced increases in citrate levels lead to increased amounts of malonyl CoA (**c**), which, through inhibition of carnitine palmitoyl transferase-1 (CPT1), leads to increased levels of long-chain acyl CoA, increased diacylglycerol (DAG) and signalling through protein kinase C (PKC). Fatty acids influence insulin release by signalling through the G-protein-coupled receptor GPR40 (**d**) or through metabolism to fatty acyl CoA (**e**) and stimulation of insulin granule exocytosis, either directly or through PKC-dependent mechanisms. The incretin GLP-1 potentiates glucose-stimulated insulin release through its G-protein-coupled receptor (**f**) by means of mechanisms that include stimulation of protein kinase A (PKA) and the guanine nucleotide exchange factor EPAC2. Release of acetylcholine from parasympathetic nerve terminals activates the M2 muscarinic receptor (**g**), stimulating insulin release in a DAG- and PKC-dependent manner. Dual actions on insulin secretion have been described for sympathetic nerves (**h**), with α2-adrenergic agonists inhibiting and β-adrenergic agonists stimulating insulin secretion. Both pathways act through adenylyl cyclase, resulting in a decrease or increase in cAMP levels, respectively. β-cell mass can be positively regulated by the insulin/IGF-1 receptor signalling pathway (**i**) in which IRS-2 becomes phosphorylated, activating a cascade of downstream molecules including PI(3)K and PKB/Akt and Ras, resulting in enhanced β-cell survival. Finally, GLP-1 receptor (GLP-1R) signalling can similarly enhance β-cell survival and inhibit β-cell apoptosis (**j**) through several pathways, including transactivation of the epidermal growth factor receptor and stimulation of the IRS-2 pathway.

ATP. The resulting increase in the ATP/ADP ratio triggers the closure of the ATP-sensitive potassium (K^+_{ATP}) channel, depolarization of the cell membrane and influx of calcium through voltage-dependent calcium channels, resulting in insulin granule exocytosis. The increase in β-cell glucose metabolism involves an increase in the activity of glucokinase, the rate-limiting enzyme responsible for glucose phosphorylation after its entry into the cell[41] (Fig. 2a). There is evidence that glucose use rises as both oxidation and flux of glucose are increased, the latter through pyruvate carboxylase and the replenishment of tricarboxylic acid cycle intermediates in the mitochondria, a process known as anaplerosis[42] (Fig. 2b).

Increased citrate levels generated by glucose metabolism lead to generation of malonyl-CoA and increased long-chain acyl-CoA and diacylglycerol levels through inhibition of carnitine palmitoyl transferase 1. This leads to protein kinase C (PKC) activation and stimulation of insulin release (Fig. 2c). Despite these animal data, studies in humans suggest that increased glucose levels are not responsible for the adaptive increase in insulin release in response to decreased insulin sensitivity. For example, experimental insulin resistance was associated with increased insulin release both in the fasting state and after stimulation, yet the fasting plasma glucose level did not increase[43]. Improving insulin sensitivity by exercise training resulted in the expected fall in insulin levels, but the fasting glucose level was in fact higher after the intervention[44].

NEFAs are important for normal β-cell function, and potentiate insulin release in response to glucose and non-glucose secretagogues[45,46]. Studies in dogs suggest that it is the nocturnal elevations in NEFAs that might underlie the β-cell's adaptive response to insulin resistance[47]. This might involve two different mechanisms. The first relates to the binding of NEFAs to the G-protein-coupled receptor GPR40 on the cell membrane, resulting in the activation of intracellular signalling and a subsequent increase in intracellular calcium and secretory granule exocytosis[48] (Fig. 2d). The other involves generation of fatty acyl-CoA (Fig. 2e), which increases insulin release both by directly stimulating secretory granule exocytosis and by PKC activation[46].

A third possible mechanism, whereby a humoral factor could mediate increased β-cell output in response to decreased insulin sensitivity, is increased sensitivity to incretin hormones. These are produced in the intestinal mucosa and are responsible for the enhancement of the insulin response observed after oral — compared with intravenous — glucose administration[49]. Plasma levels of glucagon-like peptide-1 (GLP-1; Fig. 2f) are not increased in obese individuals and are, in fact, decreased in individuals who are morbidly obese[50]. However, the insulin response to nutrient ingestion in these individuals is increased, suggesting that, as with glucose and NEFAs, the β-cell might become more responsive to the effects of this peptide to modulate insulin secretion.

The extensive innervation of the islet by both parasympathetic and sympathetic neurons, and the intimate involvement of the central nervous system (CNS) in the regulation of metabolism suggest that the CNS might also have an important role in the functional adaptation to changes in insulin sensitivity. Increased insulin release is observed immediately after experimental lesioning of the ventromedial hypothalamus (VMH) and this effect is mediated by increased vagal activity, which can be blocked by vagotomy[51]. Parasympathetic stimulation of insulin release occurs through activation by acetylcholine of the M2 muscarinic receptor on the β-cell surface (Fig. 2g). The sympathetic nervous system is also important, with increased activity of the α2-adrenergic component being associated with decreased insulin release, whereas increased β-adrenergic activity enhances insulin output[52] (Fig. 2h).

Although changes in β-cell function are observed under conditions of increased secretory demand, the volume of β-cells also increases. In rodents fed a high-fat diet for 12 months to induce obesity and insulin resistance, islet size increases as a result of an increase in the number of β-cells rather than a change in β-cell size, and new islets do not form[53]. Pregnancy, and its accompanying insulin resistance, is associated with β-cell proliferation in rodents[54]. Human studies suggest that β-cell volume is increased by about 50% in healthy obese individuals, but that this increase might be more dependent on hypertrophy of existing cells than proliferation. Any formation of new β-cells probably occurs as a result of new islet formation derived from pancreatic exocrine ducts[39,40].

Glucose and/or NEFAs might mediate the increase in β-cell mass. In rats, infusion of glucose for up to 4 days results in β-cell hyperplasia and hypertrophy, together with a concomitant increase in glucose-stimulated insulin secretion[55,56]. But we failed to observe an increase in fed or fasted glucose levels during 12 months of increased dietary fat feeding, suggesting that glucose is unlikely to be the mediator of the observed increase in β-cell mass in this model[53]. By contrast, infusion of lipid for 4 days results in increased β-cell mass in rats owing to β-cell proliferation, with no sustained improvement in insulin release[56]. This is more consistent with our 12-month increased dietary fat feeding study, in which β-cell mass increased but glucose-induced insulin release did not, representing a disassociation between β-cell mass and secretory function.

Increased signalling by insulin and/or insulin-like growth factor 1 (IGF-1) is a potentially important pathway for modulation of islet mass. Activation of the insulin/IGF-1 receptor leads to phosphorylation of IRS-2 and downstream signalling through pathways including PI(3)K/protein kinase-B (PKB/Akt) and Ras, leading to activation of the mitogen-activated protein (MAP) kinases ERK-1 and ERK-2 (ref. 57; Fig. 2i). Increased β-cell expression of IRS-2 is associated with increased β-cell proliferation, neogenesis and survival[58]. In *Irs-2*-knockout mice, reintroduction of β-cell IRS-2 alone reversed the diabetic phenotype by increasing β-cell replication, resulting in an increase in β-cell number and mass[59].

The incretin GLP-1 is an insulin secretagogue but is also a β-cell mitogen, capable of increasing β-cell proliferation and reducing β-cell apoptosis in animal models[49] (Fig. 2j). Whether GLP-1 has similar effects in humans is not known.

Neural signalling might also regulate β-cell mass. Experimental lesions of theVMH produce a model of obesity and insulin resistance that is associated with vagal hyperactivity and proliferation of islet cells, particularly β-cells[60]. Thus, it is possible that increased vagal input associated with diet-induced obesity might also contribute to increased β-cell mass.

β-cell dysfunction

When the β-cell is healthy, the adaptive response to insulin resistance involves changes in both function and mass, and is so efficient that normal glucose tolerance is maintained. But when β-cell dysfunction is present, impaired glucose tolerance, impaired fasting glucose and, at the extreme, type 2 diabetes result.

The magnitude of the reduction in β-cell function in type 2 diabetes is compatible with a failure of the cell to respond adequately to secretagogue stimulation, an important contributor to reduced insulin release. This conclusion is based on a number of observations. First, the β-cell is unable to release insulin rapidly in response to intravenous glucose, despite the fact that the β-cells in individuals with type 2 diabetes clearly contain insulin[8]. Second, delivery of non-glucose secretagogues can acutely increase insulin release but does not result in equivalent responses to those seen with similar stimulation in healthy subjects[8]. Third, although the number of β-cells is clearly reduced by about 50% in type 2 diabetes[39,40], this degree of β-cell loss cannot fully account for the change in secretory function, because by the time the diagnostic level for diabetes occurs, the cell is operating at 25% or less of its functional capacity[61].

Type 2 diabetes is progressive, and one of the main factors responsible for this is a continued decline in β-cell function[8]. As a result of β-cell dysfunction and inadequate insulin secretion, postprandial and subsequently fasting glucose levels increase owing to incomplete suppression of hepatic glucose production and decreased efficiency of liver and muscle glucose uptake. The extremely elevated blood glucose levels frequently observed in diabetes might contribute to further disease progression through glucotoxic effects on the β-cell and harmful effects on insulin sensitivity, both of which can be ameliorated by therapeutically lowering the glucose level[62]. By contrast, raising the blood glucose

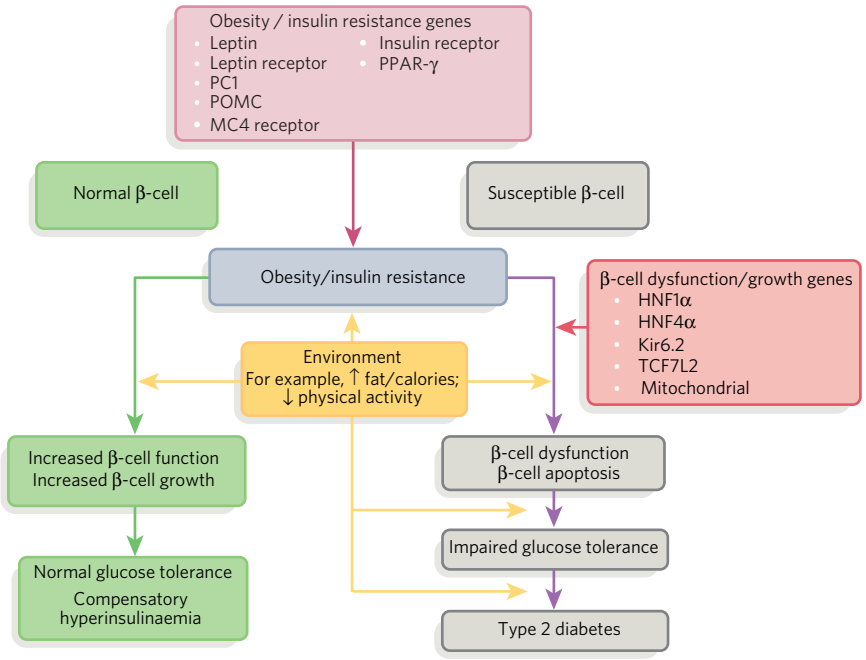

Figure 3 | Interaction of genes and the environment in individuals who maintain normal glucose tolerance and those who develop type 2 diabetes. Genes responsible for obesity and insulin resistance interact with environmental factors (increased fat/caloric intake and decreased physical activity), resulting in the development of obesity and insulin resistance. These increase secretory demand on β-cells. If the β-cells are normal, their function and mass increase in response to this increased secretory demand, leading to compensatory hyperinsulinaemia and the maintenance of normal glucose tolerance. By contrast, susceptible β-cells have a genetically determined risk, and the combination of increased secretory demand and detrimental environment result in β-cell dysfunction and decreased β-cell mass, resulting in progression to impaired glucose tolerance, followed, ultimately, by the development of type 2 diabetes. HNF, hepatocyte nuclear factor.

level for 20 hours in healthy subjects has exactly the opposite effect: it improves insulin sensitivity and enhances β-cell function[63]. This suggests that a pre-existing, and perhaps genetically determined, risk is crucial for β-cell dysfunction to occur. It is this pre-existing abnormality that results, with time, in a progressive impairment in insulin release and, ultimately, an increase in glucose levels, the latter of which further aggravates the situation and thereby contributes to β-cell failure.

A second metabolic derangement that might contribute in a feedforward manner to progressive loss of β-cell function is elevated plasma NEFA concentrations. Although NEFAs are critical for normal insulin release, chronic exposure to NEFAs *in vitro* and *in vivo* is associated with marked impairments in glucose-stimulated insulin secretion and decreased insulin biosynthesis[64,65]. Elevated NEFA levels produced by a lipid infusion *in vivo* contribute to the development of insulin resistance and also prevent the expected compensatory β-cell response in humans[66]. This dual effect makes them a good candidate to link insulin resistance and β-cell dysfunction in individuals with type 2 diabetes and those at risk of the disorder. This lipotoxic effect can also act synergistically with glucose to produce even greater deleterious effects, commonly referred to as 'glucolipotoxicity'.

Pathogenesis of type 2 diabetes

Given that β-cell function is decreased by about 75% when fasting hyperglycaemia is present, assessment of β-cell function in individuals at risk of developing diabetes has been of interest. Even when the glucose level is still within the normal range, β-cell function decreases progressively as the fasting glucose level increases[67]. Groups at increased risk of subsequently developing diabetes exhibit β-cell dysfunction well before they would be considered to have reduced glucose tolerance, in keeping with the idea of a pre-existing risk. Examples include women with a history of gestational diabetes[68] or polycystic ovarian syndrome[69], older subjects, who frequently develop hyperglycaemia as they continue to age[70], and individuals with impaired glucose tolerance[71,72] (Fig. 1c). First-degree relatives of individuals with type 2 diabetes, who are genetically at increased risk, also have impaired β-cell function, even though they may still have normal glucose tolerance[73] (Fig. 1c). Data from groups of first-degree relatives with different ethnic backgrounds highlight that common processes underlie the development of type 2 diabetes — namely insulin resistance and β-cell dysfunction — with the degree of abnormality of insulin release being the dominant determinant of differences in glucose tolerance between individuals[72].

Longitudinal data examining the progression to type 2 diabetes have been collected from the Pima Indians, in whom the prevalence of diabetes is higher than almost any other group in the world. In these individuals, who are insulin resistant, the transition from normal to impaired glucose tolerance and then on to diabetes is characterized by a progressive loss of β-cell function[74]. Those who did not progress to diabetes over time simply increased their insulin output as insulin sensitivity declined. In those individuals who progressed, the presence of a defect in insulin release was already manifest at their initial assessment, even though at that time there was nothing else to indicate that they would ultimately develop diabetes. These findings have been confirmed for non-Hispanic whites, African Americans and Hispanics participating in the Insulin Resistance Atherosclerosis Study (IRAS)[75].

Genes and environment

Many genes interact with the environment to produce obesity and diabetes (Fig. 3). In the case of obesity, the most frequent mutation is that in the melanocortin-4 receptor, which accounts for up to 4% of cases of severe obesity. Other rare causes include mutations in leptin and the leptin receptor, prohormone convertase 1 (PC1) and pro-opiomelanocortin (POMC)[76]. The gene variant most commonly associated with insulin sensitivity is the P12A polymorphism in *PPARγ*, which is associated with an increased risk of developing diabetes[77,78]. A number of genes associated with β-cell dysfunction have been identified, and include hepatocyte nuclear factor-4α and 1α — genes known to cause the monogenic disorder maturity onset diabetes of the young (MODY) — the E23K polymorphism in the islet ATP-sensitive potassium channel Kir6.2 (encoded by *KCNJ11*), two non-coding single-nucleotide polymorphisms in transcription factor 7-like 2 (*TCF7L2*) and mutations in the mitochondrial genome that are also associated with neurosensory hearing loss[77]. Work is ongoing on many candidate genes, including calpain 10, adiponectin, PPAR-γ coactivator 1 (*PGC1*) and the glucose transporter *GLUT2* (ref. 77).

Environmental factors are largely responsible for the modern day epidemic of obesity and type 2 diabetes. Increased caloric availability and fat consumption in the setting of decreased physical activity lead to overnutrition, increased nutrient storage and obesity. Long-term increased dietary fat intake is associated not only with the development of obesity but also with reductions in insulin release[79]. This effect has important consequences if β-cell function is already inherently abnormal owing to genetic susceptibility. Furthermore, changes in the proportions of dietary carbohydrate and fat can affect both insulin sensitivity and insulin release

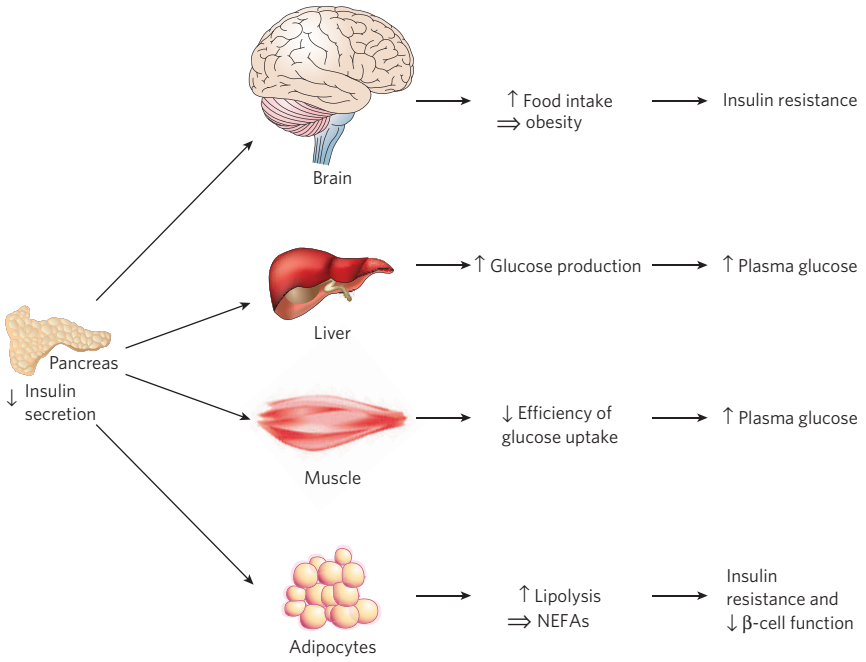

Figure 4 | Model of the critical role of impaired insulin release in linking obesity with insulin resistance and type 2 diabetes. Impaired insulin secretion results in decreased insulin levels and decreased signalling in the hypothalamus, leading to increased food intake and weight gain, decreased inhibition of hepatic glucose production, reduced efficiency of glucose uptake in muscle, and increased lipolysis in the adipocyte, resulting in increased plasma NEFA levels. The increase in body weight and NEFAs contribute to insulin resistance, and the increased NEFAs also suppress the β-cell's adaptive response to insulin resistance. The increased glucose levels together with the elevated NEFA levels can synergize to further adversely affect β-cell health and insulin action, often referred to as 'glucolipotoxicity'.

within three days of changing nutrient balance, at a time when obesity would not yet be a factor[13]. Another proposed environmental mechanism is thought to occur *in utero* and/or during the early postnatal period when poor nutrition alters metabolism, resulting in a tissue adaptation that favours the storage of nutrients[80]. The end result of these environmental changes is a deleterious interaction with genes that predispose to the development of obesity and type 2 diabetes.

A possible unifying mechanism

Having a single mechanism to explain the link between obesity, insulin resistance and type 2 diabetes would be ideal. A defect in insulin release by the β-cell could be crucial (Fig. 4). Decreased insulin release could result in disordered regulation of glucose levels by decreasing suppression of hepatic glucose production and reducing the efficiency of glucose uptake in insulin-sensitive tissues. Decreased insulin output could also impair adipocyte metabolism, resulting in increased lipolysis and elevated NEFA levels. Elevations in both NEFAs and glucose can occur simultaneously, and together are more deleterious to islet health and insulin action than either alone[46,81]. Thus the process may slowly feed forward, in keeping with observations that the onset of type 2 diabetes is usually a slow process that takes many years.

Even mild impairments of insulin release may have central effects on metabolic homeostasis. Insulin acts in the hypothalamus to regulate body weight, and impaired insulin signalling is associated with changes in food intake and body weight[82]. Thus, β-cell dysfunction resulting in a relative reduction in insulin release would be expected to result in decreased insulin action in this crucial brain region and be associated with weight gain and an aggravation of insulin resistance.

Insulin resistance at the level of the β-cell might have a role in the pathogenesis of defective insulin release. This idea is based mainly on studies using mice with a β-cell selective deletion of the insulin receptor and by subsequent work in which key molecules in the insulin signalling cascade within the β-cell have been manipulated[57,83]. However, deletion of the insulin receptor in the β-cell might also result in a loss of insulin receptors in the hypothalamus, so it is not clear whether the resultant effects are centrally mediated or truly β-cell specific. Although there is currently no evidence that insulin receptor mutations are commonly associated with type 2 diabetes, a reduction in insulin signalling in the β-cell remains an interesting possibility in further integrating defects in insulin action into the pathogenesis of obesity and type 2 diabetes.

Future directions

The past decade has seen major advances in our understanding of the relationship between obesity, insulin resistance and type 2 diabetes. However, despite these tremendous strides and the identification of the critical nature of β-cell dysfunction in the development of type 2 diabetes, there is still a great deal to be learned about the mechanisms linking obesity, insulin resistance and type 2 diabetes. Although clinical studies aimed at reducing the deleterious effects of these conditions have been undertaken and more are being launched, a better understanding of the genetic bases of these processes and the cellular events that underlie them should enhance our ability to devise new and better approaches to try to stem the deleterious effects of these diseases. ■

1. Hedley, A. A. *et al.* Prevalence of overweight and obesity among US children, adolescents, and adults, 1999–2002. *J. Am. Med. Assoc.* **291,** 2847–2850 (2004).
2. *World Health Organization Consultation on Obesity* 1–253 (World Health Organization, Geneva, 2000).
3. Wild, S., Roglic, G., Green, A., Sicree, R. & King, H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* **27,** 1047–1053 (2004).
4. Reaven, G. M. Role of insulin resistance in human disease. *Diabetes* **37,** 1595–1607 (1988).
5. Perley, M. & Kipnis, D. M. Plasma insulin responses to glucose and tolbutamide of normal weight and obese diabetic and nondiabetic subjects. *Diabetes* **15,** 867–874 (1966).
6. Polonsky, K. S., Given, B. D. & Van Cauter, E. Twenty-four-hour profiles and patterns of insulin secretion in normal and obese subjects. *J. Clin. Invest.* **81,** 442–448 (1988).
7. Kahn, S. E. *et al.* Quantification of the relationship between insulin sensitivity and B-cell function in human subjects. Evidence for a hyperbolic function. *Diabetes* **42,** 1663–1672 (1993).
8. Kahn, S. E. The importance of β-cell failure in the development and progression of type 2 diabetes. *J. Clin. Endocrinol. Metab.* **86,** 4047–4058 (2001).
9. Moran, A. *et al.* Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes* **48,** 2039–2044 (1999).
10. Buchanan, T. A., Metzger, B. E., Freinkel, N. & Bergman, R. N. Insulin sensitivity and B-cell responsiveness to glucose during late pregnancy in lean and moderately obese women with normal glucose tolerance or mild gestational diabetes. *Am. J. Obstet. Gynecol.* **162,** 1008–1014 (1990).
11. DeFronzo, R. A. Glucose intolerance of aging. Evidence for tissue insensitivity to insulin. *Diabetes* **28,** 1095–1101 (1979).
12. Goodyear, L. J. & Kahn, B. B. Exercise, glucose transport, and insulin sensitivity. *Annu. Rev. Med.* **49,** 235–261 (1998).
13. Chen, M., Bergman, R. N. & Porte, D. Insulin resistance and β-cell dysfunction in aging: the importance of dietary carbohydrate. *J. Clin. Endocrinol. Metab.* **67,** 951–957 (1988).
14. Wellen, K. E. & Hotamisligil, G. S. Inflammation, stress, and diabetes. *J. Clin. Invest.* **115,** 1111–1119 (2005).
15. Scherer, P. E. Adipose tissue: from lipid storage compartment to endocrine organ. *Diabetes* **55,** 1537–1545 (2006).
16. Shoelson, S. E., Lee, J. & Goldfine, A. B. Inflammation and insulin resistance. *J. Clin. Invest.* **116,** 1793–1801 (2006).
17. Yang, Q. *et al.* Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* **436,** 356–362 (2005).

18. Kadowaki, T. *et al.* Adiponectin and adiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. *J. Clin. Invest.* **116,** 1784–1792 (2006).
19. Fain, J. N., Madan, A. K., Hiler, M. L., Cheema, P. & Bahouth, S. W. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissues of obese humans. *Endocrinology* **145,** 2273–2282 (2004).
20. Mooney, R. A. *et al.* Suppressors of cytokine signaling-1 and -6 associate with and inhibit the insulin receptor. A potential mechanism for cytokine-mediated insulin resistance. *J. Biol. Chem.* **276,** 25889–25893 (2001).
21. Perreault, M. & Marette, A. Targeted disruption of inducible nitric oxide synthase protects against obesity-linked insulin resistance in muscle. *Nature Med.* **7,** 1138–1143 (2001).
22. Weisberg, S. P. *et al.* Obesity is associated with macrophage accumulation in adipose tissue. *J. Clin. Invest.* **112,** 1796–1808 (2003).
23. Xu, H. *et al.* Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. *J. Clin. Invest.* **112,** 1821–1830 (2003).
24. Reaven, G. M., Hollenbeck, C., Jeng, C. Y., Wu, M. S. & Chen, Y. D. Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM. *Diabetes* **37,** 1020–1024 (1988).
25. Boden, G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. *Diabetes* **46,** 3–10 (1997).
26. Roden, M. *et al.* Mechanism of free fatty acid-induced insulin resistance in humans. *J. Clin. Invest.* **97,** 2859–2865 (1996).
27. Santomauro, A. T. *et al.* Overnight lowering of free fatty acids with Acipimox improves insulin resistance and glucose tolerance in obese diabetic and nondiabetic subjects. *Diabetes* **48,** 1836–1841 (1999).
28. Randle, P. J., Garland, P. B., Hales, C. N. & Newsholme, E. A. The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* **i,** 785–789 (1963).
29. Shulman, G. I. Cellular mechanisms of insulin resistance. *J. Clin. Invest.* **106,** 171–176 (2000).
30. Carey, D. G., Jenkins, A. B., Campbell, L. V., Freund, J. & Chisholm, D. J. Abdominal fat and insulin resistance in normal and overweight women: direct measurements reveal a strong relationship in subjects at both low and high risk of NIDDM. *Diabetes* **45,** 633–638 (1996).
31. Cnop, M. *et al.* The concurrent accumulation of intra-abdominal and subcutaneous fat explains the association between insulin resistance and plasma leptin concentrations: distinct metabolic effects of two fat compartments. *Diabetes* **51,** 1005–1015 (2002).
32. Kahn, S. E. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. *Diabetologia* **46,** 3–19 (2003).
33. Fujimoto, W. Y. *et al.* Preventing diabetes — applying pathophysiological and epidemiological evidence. *Br. J. Nutr.* **84** (Suppl. 2)**,** S173–S176 (2000).
34. Maeda, K. *et al.* Analysis of an expression profile of genes in the human adipose tissue. *Gene* **190,** 227–235 (1997).
35. Motoshima, H. *et al.* Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J. Clin. Endocrinol. Metab.* **87,** 5662–5667 (2002).
36. Reynisdottir, S., Dauzats, M., Thorne, A. & Langin, D. Comparison of hormone-sensitive lipase activity in visceral and subcutaneous human adipose tissue. *J. Clin. Endocrinol. Metab.* **82,** 4162–4166 (1997).
37. Montague, C. T. & O'Rahilly, S. The perils of portliness: causes and consequences of visceral adiposity. *Diabetes* **49,** 883–888 (2000).
38. Kim, S. P., Ellmerer, M., Van Citters, G. W. & Bergman, R. N. Primacy of hepatic insulin resistance in the development of the metabolic syndrome induced by an isocaloric moderate-fat diet in the dog. *Diabetes* **52,** 2453–2460 (2003).
39. Kloppel, G., Lohr, M., Habich, K., Oberholzer, M. & Heitz, P. U. Islet pathology and the pathogenesis of type 1 and type 2 diabetes mellitus revisited. *Surv. Synth. Pathol. Res.* **4,** 110–125 (1985).
40. Butler, A. E. *et al.* β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. *Diabetes* **52,** 102–110 (2003).
41. Chen, C., Hosokawa, H., Bumbalo, L. M. & Leahy, J. L. Mechanism of compensatory hyperinsulinemia in normoglycemic insulin-resistant spontaneously hypertensive rats. Augmented enzymatic activity of glucokinase in β-cells. *J. Clin. Invest.* **94,** 399–404 (1994).
42. Liu, Y. Q., Jetton, T. L. & Leahy, J. L. β-cell adaptation to insulin resistance. Increased pyruvate carboxylase and malate-pyruvate shuttle activity in islets of nondiabetic Zucker fatty rats. *J. Biol. Chem.* **277,** 39163–39168 (2002).
43. Kahn, S. E. *et al.* Increased β-cell secretory capacity as mechanism for islet adaptation to nicotinic acid-induced insulin resistance. *Diabetes* **38,** 562–568 (1989).
44. Kahn, S. E. *et al.* Effect of exercise on insulin action, glucose tolerance and insulin secretion in aging. *Am. J. Physiol.* **258,** E937–E943 (1990).
45. Dobbins, R. L. *et al.* A fatty acid-dependent step is critically important for both glucose — and non-glucose — stimulated insulin secretion. *J. Clin. Invest.* **101,** 2370–2376 (1998).
46. Prentki, M., Joly, E., El-Assaad, W. & Roduit, R. Malonyl-CoA signaling, lipid partitioning, and glucolipotoxicity: role in β-cell adaptation and failure in the etiology of diabetes. *Diabetes* **51** (Suppl. 3)**,** S405–S413 (2002).
47. Bergman, R. N. *et al.* Why visceral fat is bad: mechanisms of the metabolic syndrome. *Obesity* **14** (Suppl. 1)**,** 16S–19S (2006).
48. Itoh, Y. *et al.* Free fatty acids regulate insulin secretion from pancreatic β cells through GPR40. *Nature* **422,** 173–176 (2003).
49. Drucker, D. J. The biology of incretin hormones. *Cell Metab.* **3,** 153–165 (2006).
50. Verdich, C. *et al.* The role of postprandial releases of insulin and incretin hormones in meal-induced satiety — effect of obesity and weight reduction. *Int. J. Obes. Relat. Metab. Disord.* **25,** 1206–1214 (2001).
51. Berthoud, H. R. & Jeanrenaud, B. Acute hyperinsulinemia and its reversal by vagotomy after lesions of the ventromedial hypothalamus in anesthetized rats. *Endocrinology* **105,** 146–151 (1979).
52. Ahren, B., Taborsky, G. J. & Porte, D. Neuropeptidergic versus cholinergic and adrenergic regulation of islet hormone secretion. *Diabetologia* **29,** 827–836 (1986).
53. Hull, R. L. *et al.* Dietary-fat-induced obesity in mice results in beta cell hyperplasia but not increased insulin release: evidence for specificity of impaired beta cell adaptation. *Diabetologia* **48,** 1350–1358 (2005).
54. Sorenson, R. L. & Brelje, T. C. Adaptation of islets of Langerhans to pregnancy: beta-cell growth, enhanced insulin secretion and the role of lactogenic hormones. *Horm. Metab. Res.* **29,** 301–307 (1997).
55. Bonner-Weir, S., Deery, D., Leahy, J. L. & Weir, G. C. Compensatory growth of pancreatic β-cells in adult rats after short-term glucose infusion. *Diabetes* **38,** 49–53 (1989).
56. Steil, G. M. *et al.* Adaptation of β-cell mass to substrate oversupply: enhanced function with normal gene expression. *Am. J. Physiol. Endocrinol. Metab.* **280,** E788–E796 (2001).
57. Rhodes, C. J. Type 2 diabetes — a matter of β-cell life and death? *Science* **307,** 380–384 (2005).
58. Bernal-Mizrachi, E., Wen, W., Stahlhut, S., Welling, C. M. & Permutt, M. A. Islet β cell expression of constitutively active Akt1/PKBα induces striking hypertrophy, hyperplasia, and hyperinsulinemia. *J. Clin. Invest.* **108,** 1631–1638 (2001).
59. Hennige, A. M. *et al.* Upregulation of insulin receptor substrate-2 in pancreatic β cells prevents diabetes. *J. Clin. Invest.* **112,** 1521–1532 (2003).
60. Kiba, T. *et al.* Ventromedial hypothalamic lesion-induced vagal hyperactivity stimulates rat pancreatic cell proliferation. *Gastroenterology* **110,** 885–893 (1996).
61. Røder, M. E., Porte, D. & Kahn, S. E. Disproportionately elevated proinsulin levels reflect the degree of impaired B-cell secretory capacity in patients with non-insulin dependent diabetes mellitus. *J. Clin. Endocrinol. Metab.* **83,** 604–608 (1998).
62. Garvey, W. T., Olefsky, J. M., Griffen, J., Hamman, R. F. & Kolterman, O. G. The effect of insulin treatment on insulin secretion and insulin action in type II diabetes mellitus. *Diabetes* **34,** 222–234 (1985).
63. Kahn, S. E., Bergman, R. N., Schwartz, M. W., Taborsky, G. J. & Porte, D. Short-term hyperglycemia and hyperinsulinemia improve insulin action but do not alter glucose action in normal humans. *Am. J. Physiol.* **262,** E518–E523 (1992).
64. Sako, Y. & Grill, V. E. A 48-hour lipid infusion in the rat time-dependently inhibits glucose-induced insulin secretion and B cell oxidation through a process likely coupled to fatty acid oxidation. *Endocrinology* **127,** 1580–1589 (1990).
65. Zhou, Y. P. & Grill, V. E. 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.* **93,** 870–876 (1994).
66. Carpentier, A. *et al.* Acute enhancement of insulin secretion by FFA in humans is lost with prolonged FFA elevation. *Am. J. Physiol.* **276,** E1055–E1066 (1999).
67. Utzschneider, K. M. *et al.* Impact of differences in fasting glucose and glucose tolerance on the hyperbolic relationship between insulin sensitivity and insulin responses. *Diabetes Care* **29,** 356–362 (2006).
68. Ward, W. K. *et al.* Insulin resistance and impaired insulin secretion in subjects with histories of gestational diabetes mellitus. *Diabetes* **34,** 861–869 (1985).
69. Ehrmann, D. A. *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.* **96,** 520–527 (1995).
70. Kahn, S. E. *et al.* Exercise training delineates the importance of B-cell dysfunction to the glucose intolerance of human aging. *J. Clin. Endocrinol. Metab.* **74,** 1336–1342 (1992).
71. Cavaghan, M. K., Ehrmann, D. A., Byrne, M. M. & Polonsky, K. S. Treatment with the oral antidiabetic agent troglitazone improves β cell responses to glucose in subjects with impaired glucose tolerance. *J. Clin. Invest.* **100,** 530–537 (1997).
72. Jensen, C. C. *et al.* β-cell function is the major determinant of oral glucose tolerance in four ethnic groups in the United States. *Diabetes* **51,** 2170–2178 (2002).
73. Knowles, N. G., Landchild, M. A., Fujimoto, W. Y. & Kahn, S. E. Insulin and amylin release are both diminished in first-degree relatives of subjects with type 2 diabetes. *Diabetes Care* **25,** 292–297 (2002).
74. Weyer, C., Bogardus, C., Mott, D. M. & Pratley, R. E. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J. Clin. Invest.* **104,** 787–794 (1999).
75. Festa, A., Williams, K., D'Agostino, R., Wagenknecht, L. E. & Haffner, S. M. The natural course of β-cell function in nondiabetic and diabetic individuals: the Insulin Resistance Atherosclerosis Study. *Diabetes* **55,** 1114–1120 (2006).
76. O'Rahilly, S. & Farooqi, I. S. Genetics of obesity. *Phil. Trans. R. Soc. B* **361,** 1095–1105 (2006).
77. Barroso, I. Genetics of type 2 diabetes. *Diabet. Med.* **22,** 517–535 (2005).
78. Andrulionyte, L., Zacharova, J., Chiasson, J. L. & Laakso, M. Common polymorphisms of the *PPAR-γ2* (*Pro12Ala*) and *PGC-1α* (*Gly482Ser*) genes are associated with the conversion from impaired glucose tolerance to type 2 diabetes in the STOP-NIDDM trial. *Diabetologia* **47,** 2176–2184 (2004).
79. Kaiyala, K. J. *et al.* Reduced β-cell function contributes to impaired glucose tolerance in dogs made obese by high-fat feeding. *Am. J. Physiol.* **277,** E659–E667 (1999).
80. Hales, C. N. & Barker, D. J. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* **35,** 595–601 (1992).
81. Leung, N. *et al.* Prolonged increase of plasma non-esterified fatty acids fully abolishes the stimulatory effect of 24 hours of moderate hyperglycaemia on insulin sensitivity and pancreatic beta-cell function in obese men. *Diabetologia* **47,** 204–213 (2004).
82. Schwartz, M. W., Woods, S. C., Porte, D., Seeley, R. J. & Baskin, D. G. Central nervous system control of food intake. *Nature* **404,** 661–671 (2000).
83. Otani, K. *et al.* Reduced β-cell mass and altered glucose sensing impair insulin-secretory function in βIRKO mice. *Am. J. Physiol. Endocrinol. Metab.* **286,** E41–E49 (2004).

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