

The role of adipokines in β -cell failure of type 2 diabetes

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Abstract

β -Cell failure coupled with insulin resistance is a key factor in the development of type 2 diabetes. Changes in circulating levels of adipokines, factors released from adipose tissue, form a significant link between excessive adiposity in obesity and both aforementioned factors. In this review, we consider the published evidence for the role of individual adipokines on the function, proliferation, death and failure of β -cells, focusing on those reported to have the most significant effects (leptin, adiponectin, tumour necrosis factor α , resistin, visfatin, dipeptidyl peptidase IV and apelin). It is apparent that some adipokines have beneficial effects whereas others have detrimental properties; the overall contribution to β -cell failure of changed concentrations of adipokines in the blood of obese pre-diabetic subjects will be highly dependent on the balance between these effects and the interactions between the adipokines, which act on the β -cell via a number of intersecting intracellular signalling pathways. We emphasise the importance, and comparative dearth, of studies into the combined effects of adipokines on β -cells.

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Introduction

Pancreatic β -cell failure, alongside insulin resistance, can be considered as one of the two key events that leads to the development of type 2 diabetes (Leahy *et al.* 2010). In the early stages of the disease, insulin resistance is countered by an increase in pancreatic β -cell mass and function (Chang-Chen *et al.* 2008) that can often delay diagnosis for a period of years. The β -cell eventually succumbs to rising insulin resistance via various mechanisms (including glucotoxicity, lipotoxicity and endoplasmic reticulum stress) and hyperglycaemia ensues (Jonas *et al.* 2009). What is key in preventing the onset of type 2 diabetes under these conditions is the ability of the body to maintain both pancreatic β -cell mass and function.

The relationship between the pancreas and adipose tissue was for many years believed to be something of a one-way street. It was accepted that insulin secretion from pancreatic islets in response to increased blood glucose

caused uptake of glucose into adipocytes via insulin receptor binding and signalling and thus led to increased storage of triacylglycerol. What was also accepted was that insulin resistance in adipose tissue contributed to β -cell failure (Weir *et al.* 2001), a phenomenon that highlighted the importance of the relationship between these two tissues. Our understanding of adipose tissue has grown immensely over the past few decades so that we now know that adipose tissue is not an inert storage depot for excess energy but an active endocrine organ with a wide, biologically active secretome (Deng & Scherer 2010).

The molecules released from adipose tissue are commonly referred to as adipokines (or adipocytokines). The list of molecules confirmed as adipokines grows every year, as both novel and existing molecules are seen to be secreted by adipose tissue or adipocytes. Most, but not all, adipokines are peptides/proteins with hormone-like properties (some are

known cytokines), but in this context, non-esterified fatty acids (NEFAs; free fatty acids) can also be considered to be adipokines. It has been widely demonstrated that the enlargement of adipose tissue depots seen in obesity can lead to dysregulated adipokine secretion, representing a potential pathophysiological link between obesity and type 2 diabetes (and vascular disease; Wellen & Hotamisligil 2005), and so research into their precise role in metabolic disorders is ongoing. It is becoming increasingly clear that adipokines form an important part of an 'adipo-insular axis' (see Fig. 1), dysregulation of which may contribute to β -cell failure and hence to type 2 diabetes.

Leptin: the 'first' adipokine

With the discovery of the product of the OB gene, leptin, in 1994 by Friedman and colleagues (Zhang *et al.* 1994), the first insights into adipose-derived hormonal factors that later became known as adipokines, and hence the bidirectional nature of the adipo-insular axis, were established. Leptin can claim to be the first adipokine to be associated with direct pancreatic effects, and certainly the most studied of all the adipokines with respect to its pancreatic effects. After initial clinical work suggested a possible relationship between circulating leptin levels and islet function (Ahren & Larsson 1997), basic laboratory studies confirmed effects of leptin exposure on glucose-stimulated insulin secretion (GSIS) in *ex vivo* pancreatic islets, although the initial few studies gave mixed results, with inhibitory (Kulkarni *et al.* 1997, Brown *et al.* 2002),

stimulatory (Tanizawa *et al.* 1997) and null (Leclercq-Meyer & Malaisse 1998) effects on insulin secretion being reported. It is now generally accepted that leptin has a potent inhibitory effect on insulin secretion from pancreatic β -cells *in vitro* and *in vivo* and has the additional effect of reducing pre-proinsulin gene expression (Laubner *et al.* 2005).

Our own research on this adipokine using human islets showed evidence of a U-shaped response (Brown *et al.* 2002), with lower concentrations inhibiting insulin release and higher levels having a relatively stimulatory effect, which may provide an explanation for some of the conflicting reports. This type of response is also consistent with the cytokine receptor-like nature of the leptin receptor and signalling cascade. We also demonstrated that leptin decreased uncoupling protein 2 (UCP2) expression in these islets and this may contribute to an effect of the adipokine in ameliorating β -cell apoptosis – further research in a clonal β -cell line from our group also showed an effect of leptin to alter the B-cell lymphoma 2/Bcl2-associated X protein (BCL2/BAX) expression ratio, which may also explain the reduction in apoptosis induced by this factor (Brown & Dunmore 2007). By contrast, a recent study by Chetboun *et al.* (2012) found no effect of leptin (or adiponectin) on apoptosis, although both adipokines caused a reactive oxygen species (ROS)-mediated increase in cell proliferation and leptin (but not adiponectin)-inhibited GSIS. This potential role of low levels of ROS in promoting β -cell mass may underline the importance of our aforementioned finding that leptin decreases UCP2 as this protein may also have a role in reducing ROS levels – generally thought to be beneficial to β -cells but possibly, in view of Chetboun *et al.*'s hypothesis, decreasing proliferation. This underlines the need for further research into the role of UCP2 in the β -cell.

It is apparent that leptin's effects on the β -cell are direct and it is clear that pancreatic β -cells express the leptin receptor, LepR (Ob-R), in both the functional long form (LepRb) and truncated shorter forms (Kieffer *et al.* 1996). Mechanistically speaking, it appears that leptin can activate multiple signalling pathways in the pancreatic β -cell. The classical pathway associated with leptin binding its receptor is activation of the Jak/STAT pathway where receptor-associated kinase JAK2 phosphorylates tyrosine residues on LepRb, which subsequently recruits and phosphorylates STAT family members that can then translocate to the nucleus and regulate gene transcription (Seufert 2004). Evidence also suggests that various members of the MAPK/ERK pathway are activated in

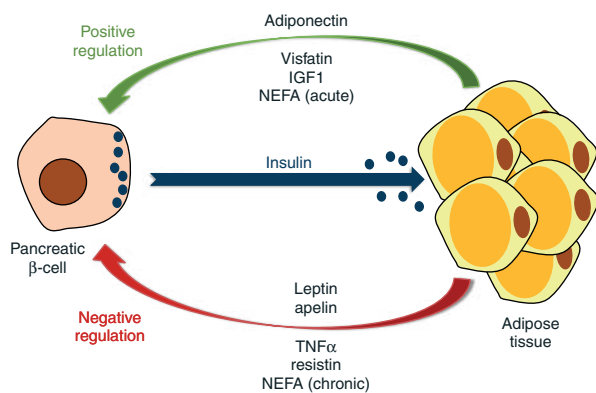


Figure 1
Diagrammatic representation of the interrelationship between adipose tissue and the pancreatic β -cell: the 'adipo-insular axis'. Positive regulation may include stimulation of insulin synthesis and secretion and cell proliferation. Negative regulation can involve inhibition of insulin synthesis and secretion and increased cell apoptosis and/or necrosis.

pancreatic β -cells by leptin, possibly through interaction with shorter forms of the leptin receptor (Tanabe *et al.* 1997). Another pathway affected by leptin is the phosphoinositide 3-kinase (PI3K) pathway (activated by insulin) – Ning *et al.* (2006) showed that this may involve inhibiting the protein and lipid phosphatase PTEN, which acts downstream of PI3K to dephosphorylate phosphatidylinositol (3,4,5) trisphosphate (PtdIns(3,4,5)P3) and decrease its levels – thus leptin may increase PtdIns(3,4,5)P3, which in turn leads to increased activation of ATP-dependent potassium channels, hyperpolarisation of the β -cell membrane and hence inhibition of GSIS. This potential role of PTEN is supported by the findings of Wang *et al.* (2010) who showed that deletion of PTEN protected against defects in β -cell function and mass in mouse models of type 2 diabetes including the leptin-deficient *ob/ob* mouse. The observations described earlier confirmed the presence of a genuine two-way endocrine relationship between the β -cell and adipose tissue and suggested a mechanism for the role of excess fat in pancreatic dysfunction.

In the years following the discovery of leptin and its β -cell-specific effects, many new, and some already identified, molecules came to be designated as adipokines. From this pool, a growing number of these secreted factors were shown to regulate either pancreatic β -cell function or mass, as the clamour for an understanding of an adipokine-based, hormonal link between obesity and diabetes grew.

Adiponectin

Adiponectin was one of the earlier adipokines identified (Scherer *et al.* 1995, Arita *et al.* 1999) and, unlike many others, has beneficial effects improving insulin sensitivity and vascular function, thus being both anti-diabetic (Pajvani *et al.* 2003) and anti-atherogenic (Ouchi *et al.* 1999). Increased adiposity is associated with decreased adiponectin secretion, apparently because hypertrophic adipocytes release less of the adipokine. Adiponectin has been suggested to circulate primarily as a multimeric (trimeric, hexameric and high molecular weight) association of full-length adiponectin and is locally proteolytically cleaved to a globular (trimeric) form in which the collagen-like amino-terminal domain is released (Pajvani *et al.* 2003). Adiponectin receptors (AdipoRs) are widely expressed and two forms have been cloned that exhibit 67% homology. Both AdipoR1 and AdipoR2 are seven transmembrane spanning proteins; however, by contrast with other G-protein-coupled receptors, they

have external carboxy-terminuses and cytoplasmic amino-terminuses; globular adiponectin has been shown to have a higher affinity for AdipoR1 (Kadowaki & Yamauchi 2005). Many of the effects of the adiponectin–AdipoR interaction have been suggested to be mediated by AMPK, peroxisome proliferator-activated receptor α (PPAR α) and p38 MAPK.

There is substantial evidence of adiponectin effects on β -cell function and survival. There is evidence that both AdipoRs are expressed in primary (Kharroubi *et al.* 2003) and clonal β -cells (Brown *et al.* 2010a, Wijesekara *et al.* 2010), with AdipoR1 generally being found to be expressed at much higher levels.

Studies using the NIT-1 mouse clonal β -cell line showed that AdipoR2 was expressed in these cells (Jung *et al.* 2009); however, although this report mentions measuring AdipoR1, no data are presented. It was found that incubation with the saturated fatty acid palmitate, well established to cause apoptosis in β -cells, for 24 h increased AdipoR2 expression, which then decreased again after 48 h; the PPAR α agonist clofibrate delayed palmitate impairment of AdipoR2 expression. Adiponectin increased AMPK phosphorylation compared with both control and palmitate alone – adding clofibrate as well increased AMPK phosphorylation still further and also partly reversed palmitate inhibition of GSIS.

Research employing the INS-1 clonal rat cell, in a novel ‘microfluidic chip’, found that intermittent high glucose (IHG) caused more impairment of β -cells than sustained high glucose (SHG) and that this was partly reversed by adiponectin (Lin *et al.* 2009a). IHG caused more apoptosis (and necrosis) than SHG, and the apoptosis alone was reversed in both situations by adiponectin; however, these changes were not quantified. IHG impaired GSIS more than SHG, but adiponectin partly reversed the impairment. Adiponectin also partly restored insulin content and insulin and pancreatic and duodenal homeobox 1 (*PDX1*) gene (mRNA) expression, which had been decreased by IHG more than SHG. The authors found similar effects on AMPK expression.

In our own studies of this adipokine (Brown *et al.* 2010a), we used the clonal β -cell line BRIN-BD11 and showed AdipoR1 expression to be much higher than that of AdipoR2. We also compared the effects of globular adiponectin (ADN) and the fragment ADN15–36. The protective monounsaturated NEFA oleate, but not the deleterious saturated NEFA palmitate, decreased *AdipoR1* mRNA, and a PPAR α , but not a PPAR γ , agonist decreased *AdipoR1* expression. By contrast, palmitate, not oleate, decreased *AdipoR2* mRNA but PPAR α and not PPAR γ

agonists decreased *AdipoR2* expression. gADN (which has a higher affinity for AdipoR1) but not ADN15–36 greatly increased lipoprotein lipase expression but slightly decreased that of *PDX1*. Neither fragment affected insulin expression.

Both gADN and ADN15–36 increased β -cell viability, which was reversed by leptin for ADN15–36 only. ERK1/2 inhibition reversed the effect of both ADN fragments. Neither fragment inhibited serum starvation-induced apoptosis. Both fragments increased ERK1/2 phosphorylation; leptin reversed this in case of ADN15–36 but not with gADN.

Wijesekara *et al.* (2010) also showed that ADN increased ERK phosphorylation in MIN6 cells (and mouse islets) but, in contrast to our studies, found that it protected against serum starvation-induced apoptosis – however, this was measured by cleaved caspase-3 assay. Chai *et al.* (2011) used gastric bypass surgery to ameliorate type 2 diabetes in an animal model, the Goto-Kakizaki (GK) rat, and showed that the resulting increase in adiponectin levels was associated with decreased islet β -cell apoptosis.

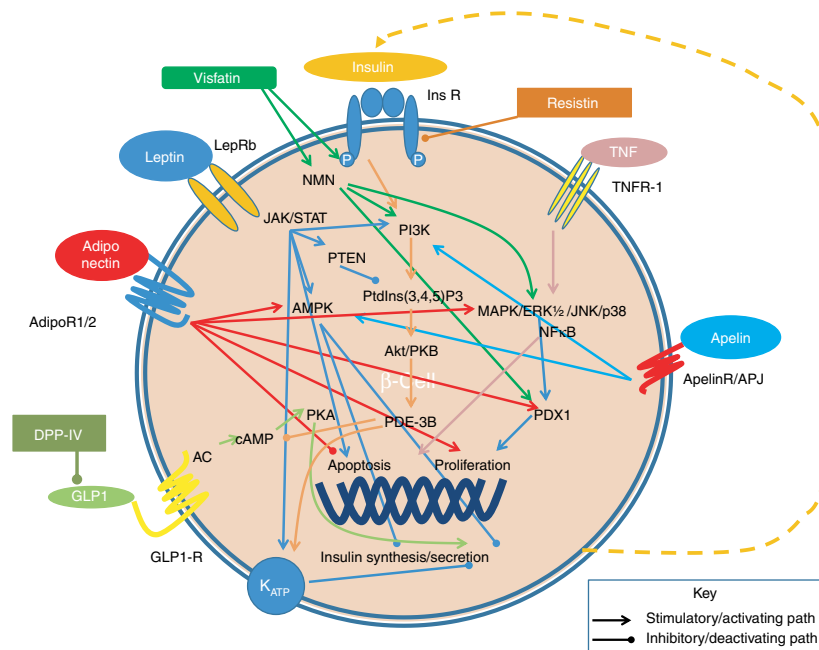
Scherer's *et al.* have recently produced convincing evidence that many of the actions of adiponectin are mediated through activation, via AdipoR1/R2, of a

ceramidase activity leading to generation of sphingosine-1-phosphate and suggest that AMPK is only involved via downstream activation. They have shown, using *in vivo* adiponectin gene overexpression or ablation in mice, that adiponectin protects against caspase-8-mediated apoptosis in β -cells. In INS-1 clonal β -cells, adiponectin protected against palmitate- or ceramide-induced apoptosis even in cells in which AMPK function was impaired by overexpression of a dominant negative mutant of the enzyme (Holland *et al.* 2011).

Chetboun *et al.* (2012), as mentioned earlier, also showed that adiponectin (and leptin) increased proliferation of clonal β -cells (RIN and MIN6) without affecting apoptosis. These effects appeared to involve generation of ROS possibly by inhibiting expression of antioxidant enzymes such as superoxide dismutase. The authors reported a beneficial effect of low levels of ROS including H_2O_2 contrasting with the deleterious consequences of high levels and suggest that these oxidant molecules can play a physiological role in regulating β -cell mass. They found, however, no effect of adiponectin on insulin secretion (by contrast with the inhibitory effect of leptin mentioned earlier). The authors did not investigate any combined effects of the two adipokines which, as is discussed below, may be an important issue.

Table 1 Summary of adipokines with demonstrated effects on pancreatic β -cells

Adipokine	Effect	References
Adiponectin	Increases GSIS Increases proliferation	Gu <i>et al.</i> (2006) Brown <i>et al.</i> (2010a)
Apelin	Inhibits insulin secretion	Guo <i>et al.</i> (2009)
DPP-IV	Inhibits GLP1	Lamers <i>et al.</i> (2011)
FGF	Increases β -cell proliferation Increases insulin transcription	Kilkenny & Rocheleau (2008) Wente <i>et al.</i> (2006)
IGF1	Increases β -cell mass	Dickson <i>et al.</i> (2001)
Interleukin-1 β	Increases nitric oxide Cytotoxic	Corbett <i>et al.</i> (1992) Mandrup-Poulsen <i>et al.</i> (1986)
Interleukin-6	Increases GSIS	Shimizu <i>et al.</i> (2000) and Suzuki <i>et al.</i> (2011)
Leptin	Inhibits GSIS Decreases pre-proinsulin levels Protects from apoptosis	Brown <i>et al.</i> (2002) Pallett <i>et al.</i> (1997) Brown & Dunmore (2007)
MCP1	Increased amylin expression	Cai <i>et al.</i> (2011a)
Non-esterified fatty acids	Increases GSIS (acute) Inhibits GSIS (chronic) Decreases insulin transcription Induces apoptosis	Thams & Capito (2001) Newsholme <i>et al.</i> (2007) Jacqueminet <i>et al.</i> (2000) Kharroubi <i>et al.</i> (2004)
Resistin	Decreases insulin receptor and increases cell viability	Brown <i>et al.</i> (2007)
TGF β	Regulates insulin transcription	Lin <i>et al.</i> (2009b)
TNF α	Inhibits GSIS Decreases insulin transcription Induces apoptosis	Zhang & Kim (1995) Tsiotra <i>et al.</i> (2001) Ortis <i>et al.</i> (2008)
Visfatin	Increases amylin but not pro-insulin gene expression Increases insulin secretion	Cai <i>et al.</i> (2011b) Brown <i>et al.</i> (2010b)

**Figure 2**

Complex interaction between adipokines in β -cell specific effects. Many adipokines act via post-receptor pathways in the β -cell which intersect in a number of places. In addition insulin itself, the release of which is affected by these adipokines, has autocrine effects on the β -cell. Signalling pathways which are negatively or positively affected by adipokines include one of the main pathways activated in insulin signalling the PI3K pathway as well as pathways such as MAPK/ERK1/2 and AMPK. AC, Adenyl cyclase; AdipoR, Adiponectin receptor; Akt/PKB, Protein Kinase B; AMPK, AMP-activated protein kinase; ApelinR, Apelin receptor (APJ receptor); DPP-IV, Dipeptidyl peptidase IV; ERK, Extracellular

signal-regulated kinases; GLP1, Glucagon-like peptide 1; GLP1-R, GLP1 receptor; InsR, Insulin Receptor; JAK/STAT, Janus Kinase/ Signal Transducer and Activator of Transcription; KATP, ATP-sensitive potassium channel/sulphonylurea receptor; LepR, Leptin receptor; MAPK, Mitogen-activated protein kinases (eg ERK, JNK, p38); NF κ B, nuclear factor kappa B; NMN, nicotinamide mononucleotide; PDE-3B, phosphodiesterase-3B; PDX-1, Pancreatic and duodenal homeobox 1; PI3K, phosphatidylinositol 3 kinase; PKA, protein kinase A (cAMP-dependent protein kinase); PTEN, Phosphatase and tensin homolog; TNFR-1, TNF α -receptor 1

Whether by inhibiting apoptosis of β -cells or by increasing proliferation, it is clear that the overall effect of high levels of adiponectin would be to preserve β -cell mass whereas low levels found in obesity and type 2 diabetes would contribute to its reduction. It is also likely that the ratio of adiponectin to leptin (and other adipokines) will be a significant factor in the overall effects of altered levels of adipokines resulting from increased adiposity on β -cell function (see below).

Tumour necrosis factor α

Tumour necrosis factor α (TNF α) is a pro-inflammatory cytokine with a well-established role in the immune system-mediated induction of β -cell death in type 1 diabetes. It is also an adipokine, and high circulating levels in obesity have been implicated in the induction of insulin resistance (Hotamisligil 1999). There is also evidence of TNF α effects on the β -cell, which may further contribute to type 2 diabetes (although one review asserts that the

elevation in TNF α in obese humans and animals does not reach levels concomitant with those known to deleteriously affect β -cell function or survival – see Zhao *et al.* (2006)). As in type 1 diabetes, TNF α can induce β -cell apoptosis via the nuclear factor kappa-light-chain enhancer of activated B cells pathway (Ortis *et al.* 2008, 2012).

There is a substantial number of reports on direct effects of TNF α inhibiting insulin secretion (for example Kim *et al.* (2008)), and one study (Cai *et al.* 2011b) reported that TNF α induces the expression of amylin from the β -cell. This latter study is of particular relevance in diabetes as the authors also report that there was no concurrent induction of proinsulin expression by TNF α . This may therefore lead to an increase in the ratio of amylin to insulin in the β -cell and potentially to a relative excess of amylin over insulin secretion. As amylin accumulating as amyloid is a potential factor in the destruction of β -cells in type 2 diabetes (Westermarck *et al.* 2011) and as it has also been suggested that an increase in circulating amylin/insulin ratio could

contribute to insulin resistance, this implies an additional potential role of TNF α in the link between obesity and type 2 diabetes. This would certainly point to a need for further studies of this fascinating hypothesis.

Resistin

In 2001, it seemed that a significant breakthrough in adipokine biology had been made. A new adipocyte-secreted molecule termed resistin was identified, which was shown, as the name would suggest, to potentially induce insulin resistance in rodents (Steppan *et al.* 2001). Resistin was discovered as a result of differential display of adipocyte genes induced and suppressed by treatment with the insulin-sensitising PPAR γ -acting thiazolidinedione drugs. Resistin was shown to be strongly down-regulated by rosiglitazone-induced PPAR γ activation, and a strong candidate for a 'diabetes gene' was suggested. Unfortunately, the observations of a potent effect on insulin resistance in rodents were not successfully reproduced in humans (Nagaev & Smith 2001), which reduced the interest of diabetes researchers in this molecule. Later research did, however, fascinatingly assign several distinct β -cell-specific effects to resistin.

Our research showed that resistin down-regulated insulin receptor expression levels (necessary for maintenance of β -cell mass) in clonal β -cells and hence decreased cell viability (Brown *et al.* 2007). This was then followed by a study that showed that resistin actually induced insulin resistance in pancreatic islets, causing a subsequent reduction in GSIS (Nakata *et al.* 2007). It should be noted that the islets and β -cells used in these studies were of mouse origin, and the findings have not as yet been repeated in human islets. What has been shown in human islets is that resistin is actually expressed within them and that its expression is up-regulated in type 2 diabetes (Minn *et al.* 2003, Al-Salam *et al.* 2011), so although the role of resistin in regulating human pancreatic β -cell mass/function as an adipokine may be yet to be demonstrated, it seems that it may nevertheless have an important role as an intracellular protein.

Visfatin/nicotinamide phosphoribosyltransferase

One of the more interesting recently described adipokines is visfatin. Visfatin, previously described as pre-B-cell colony-enhancing factor 1 (PBEF1), is actually a phosphoribosyltransferase enzyme (nicotinamide phosphoribosyltransferase (NAMPT)) that is secreted from adipose tissue

via a non-classical pathway. Originally reported as an insulin mimetic in a study (Fukuhara *et al.* 2005) subsequently partially retracted, research has actually shown that visfatin can act in an adipokine-like way to increase insulin secretion (Revollo *et al.* 2007, Brown *et al.* 2010b). Our studies showed that visfatin not only increased insulin secretion from β TC6 cells but it also had a direct effect activating β -cell insulin receptors, increasing their phosphorylation (Brown *et al.* 2010b). A recent study using the MIN6 cell line showed that visfatin stimulated β -cell proliferation and inhibited β -cell apoptosis induced by palmitate, via ERK1/2- and PI3K/Akt-mediated pathways (Cheng *et al.* 2011), findings that suggest the potential for visfatin to have positive effects on β -cell mass. The mechanisms behind the actions of visfatin in the β -cell are not yet fully understood but also appear to involve the enzymatic production of nicotinamide mononucleotide (Sheng *et al.* 2011), which can then regulate PDX1 expression and therefore insulin transcription. It is yet to be determined whether the overall effects of visfatin are beneficial or deleterious to β -cells – there is some evidence that the beneficial effects occur at lower physiological levels whereas higher pathological concentrations may have harmful effects (Brown *et al.* 2010b).

Dipeptidyl peptidase IV

In an exciting and potentially very important recent finding, dipeptidyl peptidase IV (DPP-IV) has been shown to be released from mature primary human adipocytes (Lamers *et al.* 2011). DPP-IV is a peptidase known to cleave the incretin glucagon-like peptide 1 (GLP1) at the NH2 terminus, thus reducing its half-life to several minutes (Drucker 1998). Although this interaction is not β -cell specific, it has clear implications for the β -cell. GLP1 is thought to stimulate as much as two-thirds of the insulin secreted postprandially (Kazafeos 2011) and therefore is a major player in β -cell function. Evidence also suggests that GLP1 can also stimulate proliferation of pancreatic β -cells and therefore positively regulates β -cell mass (Buteau 2008). It is therefore clear that the actions of this novel adipokine can have a potent effect on the pancreatic β -cell, and the ability of the pancreas to counteract rising insulin resistance.

Apelin

Apelin is a recently identified peptide with widespread expression including in adipose tissue and which therefore functions as an adipokine with effects on feeding behaviour

and glucose utilisation. The apelin receptor, the APJ receptor, is expressed in islets and apelin activation of its receptor inhibits insulin secretion (Sörhede Winzell *et al.* 2005), and it has been shown in clonal INS-1 β -cells that this is by activation of PI3K-phosphodiesterase 3B (Guo *et al.* 2009). Recent evidence suggests that apelin is itself expressed in pancreatic islets, particularly in β - and α -cells, raising the possibility of autocrine/paracrine effects (Ringström *et al.* 2010).

Interaction between adipokines in their effects on the β -cell

It is clear, as we have discussed earlier, that many adipokines have substantial effects on both the function and survival of β -cells; however, most of the reported studies have been done with individual adipokines in isolation (although there are a few studies such as that of Brown *et al.* (2010a) in which the interaction of the beneficial adipokine adiponectin with the mainly deleterious adipokine leptin was investigated). A summary of the main adipokines that have demonstrable effects in the β -cell, and of the nature of these effects, is given in Table 1.

It is obviously the case that *in vivo*, the β -cell is exposed to altered levels of the full range of adipokines in obese individuals and, as shown in Fig. 2, many adipokines act via pathways that intersect – for example signalling pathways involving PI3K, AMPK, MAPK/ERK1/2 and the insulin receptor itself are affected by many of the adipokines described earlier. The reported changes in circulating adipokine concentrations observed in metabolic diseases are complex and will require further elucidation; nevertheless, future studies are needed that focus on comparisons of the effects of combinations of adipokines at levels, which may be found in physiological (i.e. in lean individuals) and pathological (obese, diabetic and/or vascular disease) states.

Conclusion

In conclusion, a growing number of hormones and other active circulating factors have been found to be secreted by adipose tissue that have established roles in the maintenance or loss of β -cell mass or function. It remains to be seen whether these factors play a causative role in the development of diabetes, or if they contribute to progression of diabetes by affecting the speed at which the β -cell loses its ability to compensate for increases in insulin resistance seen in pre- and early type 2 diabetes. It can be stated with some confidence, nevertheless, based on the

evidence so far available that adipokines are likely to be a significant factor in β -cell failure and there is therefore a need for further research in the field, which may in the longer term suggest therapeutic approaches to ameliorating this growing disease.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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