REVIEW

Role of leptin in the pancreatic β-cell: effects and signaling pathways

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Abstract

Leptin plays an important role in the control of food intake, energy expenditure, metabolism, and body weight. This hormone also has a key function in the regulation of glucose homeostasis. Although leptin acts through central and peripheral mechanisms to modulate glucose metabolism, the pancreatic β-cell of the endocrine pancreas is a critical target of leptin actions. Leptin receptors are present in the β-cell, and their activation directly inhibits insulin secretion from these endocrine cells. The effects of leptin on insulin occur also in the long term, since this hormone inhibits insulin gene expression as well. Additionally, β-cell mass can be affected by leptin through changes in proliferation, apoptosis, or cell size. All these different functions in the β-cell are triggered by leptin as a result of the large diversity of signaling pathways that this hormone is able to activate in the endocrine pancreas. Therefore, leptin can participate in glucose homeostasis owing to different levels of modulation of the pancreatic β-cell population. Furthermore, it has been proposed that alterations in this level of regulation could contribute to the impairment of β-cell function in obesity states. In the present review, we will discuss all these issues with special emphasis on the effects and pathways of leptin signaling in the pancreatic β-cell.

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Introduction

A fine regulation of pancreatic β-cell function is essential for the control of plasma glucose homeostasis and nutrient metabolism. β-cell secretion and mass are dynamic features that adapt in the short and/or long term to the insulin requirements of the organism (Sachdeva & Stoffers 2009). These insulin needs depend on multiple factors, including nutritional status and metabolic, hormonal, and neural signals. This functional plasticity also occurs during physiological or pathological situations such as pregnancy or obesity respectively (Sachdeva & Stoffers 2009). The regulation of β-cell function in the short and long term allows for an adequate level of plasma insulin levels, which restores plasma glucose concentrations to normoglycemia by inducing glucose uptake and accumulation as glycogen and fatty acids, principally in muscle, liver, and adipose tissue. However, a decrease in β-cell mass or impaired β-cell function can lead to abnormal plasma insulin levels that can promote glucose intolerance and diabetes.

Among the different risk factors for the development of diabetes, obesity is a major one. The progression of obese individuals to diabetes is attributed to an altered compensation in β-cell mass and function in response to insulin demand (Sachdeva & Stoffers 2009). Obesity involves an increasing accumulation of adipose tissue and enhanced release of adipokines. Among others, leptin has been revealed as an important regulator of pancreatic β-cell function at different levels including insulin gene expression, insulin secretion, apoptosis, and cell growth. Thus, in addition to its central actions for the control of glucose metabolism (Morton & Schwartz 2011), leptin can modulate glucose homeostasis owing to these different direct effects on the β-cell. Additionally, it has been proposed that alterations in leptin signaling in the β-cell might be involved in diabetes in obese individuals (Seufert 2004). In the next sections we will focus on the different leptin actions in the pancreatic β-cell and how this hormone regulates the function of these endocrine cells.

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Leptin and glucose homeostasis

Leptin plays an important function in the control of food intake, energy expenditure, metabolism, and body weight (Fruhbeck 2006). It has been also demonstrated that this hormone has a key role in the regulation of glucose homeostasis acting through both central and peripheral mechanisms. Actually, animal models with defects in leptin or in leptin receptors such as *ob/ob* and *db/db* mice respectively develop insulin resistance, hyperinsulinemia, and impaired glucose homeostasis (Genuth *et al.* 1971, Dubuc 1976). Leptin administration to *ob/ob* mice reduces plasma glucose levels, an effect that is in part independent of any reduction in body weight (Pelleymounter *et al.* 1995, Schwartz *et al.* 1996). Additionally, leptin treatment reduces the hyperinsulinemia of these animals (Pelleymounter *et al.* 1995, Seufert *et al.* 1999*b*). Exogenous leptin treatment also improves plasma insulin and glucose concentrations in animal models of lipodystrophy, which lack adipose tissue and normal leptin levels (Shimomura *et al.* 1999). Moreover, central or peripheral leptin administration restores normoglycemia in animal models of type 1 (Chinookoswong *et al.* 1999, Fujikawa *et al.* 2010, Wang *et al.* 2010, Denroche *et al.* 2011) and type 2 diabetes (Park *et al.* 2010, Cummings *et al.* 2011). Similar observations have been reported in type 1 diabetic animals after adenoviral transfer of the leptin gene (Yu *et al.* 2008, Kojima *et al.* 2009). Likewise, cross-mating of leptin-expressing transgenic mice with Akita mice, a model of insulin-dependent diabetes, led to animals with better glucose tolerance and insulin sensitivity (Naito *et al.* 2011).

Although it has been reported that leptin affects glucose homeostasis mainly through actions on the hypothalamus (Coppari *et al.* 2005, Huo *et al.* 2009, Fujikawa *et al.* 2010, Hill *et al.* 2010, German *et al.* 2011), leptin peripheral actions are also involved. Leptin can directly affect glucose metabolism or interact with insulin actions in the skeletal muscle, liver, and adipose tissue (Berti *et al.* 1997, Ceddia *et al.* 1999*a*,*b*, Perez *et al.* 2004). Furthermore, besides these peripheral tissues, the pancreatic β-cell is a key target of leptin. Numerous *in vivo* and *in vitro* studies have shown that this hormone activates a diversity of events in the β-cell, which will be reviewed in the next sections. Additionally, experiments in knockout (KO) mice with specific deletion of the leptin receptor in the pancreas or in the β-cell and the hypothalamus have shown alterations in glucose homeostasis as well as in β-cell function and mass in these animals (Covey *et al.* 2006, Morioka *et al.* 2007). Leptin signaling defects in β-cells lacking the leptin receptor lead to hyperinsulinemia, which develops prior to insulin resistance (Gray *et al.* 2010). Moreover, administration of leptin antagonists to normal mice increases plasma insulin levels and promotes insulin resistance (Levi *et al.* 2011). Thus, leptin effects on β-cell function are also an important component of the leptin ability to regulate glucose homeostasis.

Leptin receptors in the pancreatic β-cell

Leptin, a peptidic hormone comprising 167 amino acids, is mainly released by adipocytes, but it is also detected in numerous tissues such as lymphoid tissues, placenta, and ovaries, among others (Mantzoros *et al.* 2011). Although its plasma concentrations are highly correlated with the adipose tissue mass, several factors, from circadian mechanisms to feeding behavior, can regulate its levels (Licinio *et al.* 1997). The leptin receptor (*OBR* (*LEPR*)) gene produces several splicing variants that lead to six isoforms (from ObRa to ObRf) (Fig. 1). All these variants have a common extracellular domain, but the intracellular site varies for each isoform. ObRb is the long full-length isoform and it is considered the main one involved in the transduction of intracellular signals (Mantzoros *et al.* 2011). Although some variants like ObRa may have some signaling capacity (Fruhbeck 2006), the function of the short isoforms has been attributed to leptin binding and transport in plasma, leptin transport across the blood–brain barrier, or renal leptin clearance (Meyer *et al.* 1997, Morton & Schwartz 2011). The long form of the leptin receptor has been reported in β-cell lines derived from mouse (βTC-3 and MIN-6), hamster (HIT), rat (INS-1 and RINm5F) as well as pancreatic islets of rat, mouse and human (Kieffer *et al.* 1996, 1997, Emilsson *et al.* 1997, Fehmann *et al.* 1997*b*, Tanizawa *et al.* 1997, Poitout *et al.* 1998, Seufert *et al.* 1999*b*). The expression of OBRB in the β-cell has been further confirmed by studies in KO mice with

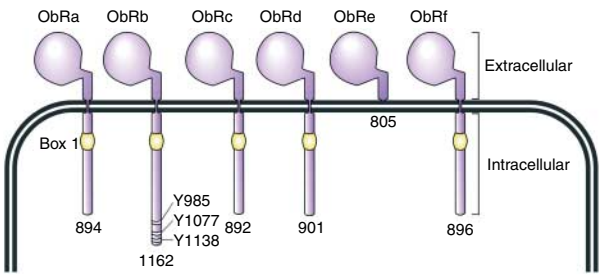

Figure 1 The leptin receptor has six isoforms obtained by alternative splicing, which are designated ObRa, ObRb, ObRc, ObRd, ObRe, and ObRf. While the extracellular domain is common for all of these isoforms, the intracellular domain differs from one variant to another. The number below each form indicates the number of amino acids characteristic of each isoform. The box 1 motif is required for JAK interaction and activation. However, only the long form (ObRb) contains motifs for the complete activation of the JAK/STAT pathway. Three tyrosine residues, whose phosphorylation is important for leptin signaling, are indicated in ObRb: Y985 interacts with the SH2-containing protein tyrosine phosphatase 2, Y1077 with STAT5, and Y1138 with STAT3.

specific disruption of the *Obr*(*Lepr*) gene either in the pancreas or in the β-cell and hypothalamus (Covey *et al.* 2006, Morioka *et al.* 2007).

The leptin receptor belongs to the class I cytokine receptor family (Fruhbeck 2006). The main signaling pathway initiated by this receptor family involves the activation of JAKs and STATs. In the case of ObRb, binding of leptin to the receptor activates JAK proteins that phosphorylate several tyrosine residues on the leptin receptor, allowing for the recruitment and phosphorylation of STATs. Then, STAT proteins dimerize, translocate to the nucleus, and act as gene transcription regulators (Fruhbeck 2006; Fig. 2). However, there are other pivotal signaling pathways, whose activation mediates the great diversity of leptin effects in the pancreatic β-cell, and that will be described in the following sections. These include PI3-kinase (PI3K), MAP kinase, c-Jun amino-terminal kinases (JNK), and nitric oxide (NO) among others (Lee *et al.* 2011).

Regulation of insulin secretion by leptin

Although some studies have indicated no effect or even a stimulatory action (Tanizawa *et al.* 1997, Leclercq-Meyer & Malaisse 1998, Ahren & Havel 1999), it is well accepted that leptin inhibits β-cell insulin secretion. Some of these discrepancies most likely come from the diverse conditions used in the different studies, including *in vivo* experiments, perfused pancreas, isolated islets, and β-cell lines, as well as from the different concentrations employed. Actually, several studies have reported U-shaped dose–responses for leptin (Zhao *et al.* 1998, Brown *et al.* 2002). At doses of 0·5–100 nM, leptin reduces insulin release in HIT-T15, β-TC6, and INS-1 cells (Kulkarni *et al.* 1997, Zhao *et al.* 1998, Tsiotra *et al.* 2001, Kuehnen *et al.* 2011). Similar observations have been obtained in isolated pancreatic islets of *ob/ob* and normal mice, rats as well as in perfused pancreas at concentrations ranging from 1 pM to 100 nM (Kieffer *et al.* 1997, Kulkarni *et al.* 1997, Pallett *et al.* 1997, Zhao *et al.* 1998). These effects have been reported for a variety of glucose concentrations from low to high levels. In contrast, in human islets, while some studies observed this inhibitory effect only at low glucose concentrations (Kulkarni *et al.* 1997, Seufert *et al.* 1999*b*), others reported reduced insulin secretion at high glucose levels (16–22 mM) with chronic leptin incubations (Brown *et al.* 2002). Thus, much work is necessary to address whether leptin effects on insulin secretion depend on glucose concentrations in human islets. Additionally, while no leptin effect has been reported in isolated human islets at 1–50 ng/ml during short-term incubations, significant changes in glucose-induced insulin secretion were observed under chronic leptin exposure (Lupi *et al.* 1999). The role of leptin in the regulation of insulin levels has been explored as well as *in vivo* in mice and rat confirming the suppressing function of this hormone (Kulkarni *et al.* 1997, Cases *et al.* 2001).

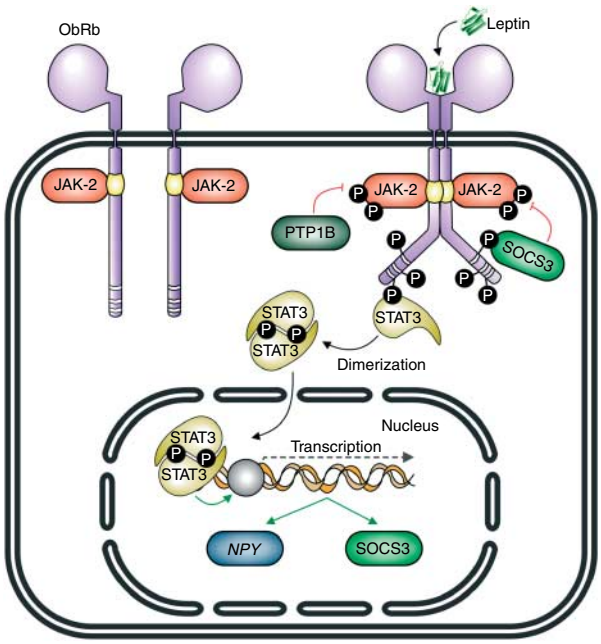

Figure 2 Leptin binding to its receptor activates the associated JAK-2 tyrosine kinase, which subsequently phosphorylates intracellular tyrosine residues of the receptor. This leads to the activation of STAT3, which dimerizes and migrates to the nucleus, where it works as a transcription factor, promoting the expression of genes like neuropeptide Y (*NPY*). STAT3 also induces the expression of SOCS3, a protein that acts as a negative regulator of the JAK/STAT pathway. Likewise, PTP1B is another protein that negatively regulates the JAK/STAT route.

Several signaling events seem to be involved in this inhibitory role of leptin in insulin secretion. In β-cells, glucose metabolism increases the intracellular ATP/ADP ratio, which blocks ATP-dependent K+ (K_{ATP}) channels, inducing a plasma membrane depolarization that activates voltage-dependent C^{2+} channels (VDCC). This activation leads to cytosolic Ca^{2+} influx and exocytosis. It has been reported that leptin activates K_{ATP} channels in β-cells from *ob/ob* mice, leading to diminished Ca^{2+} influx (Kieffer *et al.* 1997). Similarly, leptin reduces glucose-induced Ca^{2+} signals in human islets (Seufert *et al.* 1999*b*) and INS-1 cells (Kuehnen *et al.* 2011). In the rat cell line CRI-G1, K_{ATP} channel opening by leptin was associated with PI3K-induced reorganization of the actin cytoskeleton (Harvey *et al.* 2000), a process that was also confirmed in mouse pancreatic β-cells (Ning *et al.* 2006). Alternatively, it has been shown that leptin can reduce glucose transport and ATP levels in INS-1 cells, thereby affecting K_{ATP} channel activity (Lam *et al.* 2004). Conversely, leptin decreases glucose-induced expression of uncoupling protein-2 (UCP-2) in human islets (Brown *et al.* 2002), which should favor the coupling of ATP production from respiration, allowing for higher ATP/ADP levels.

Recently, it has been shown in INS-1 cells that reduced Ca^{2+} influx by leptin could also be related to a decreased activity of the protein phosphatase 1 enzyme (Kuehnen *et al.* 2011). In addition to the effect on K_{ATP} channels, leptin inhibits insulin secretion by PI3K-induced activation of phosphodiesterase 3B (PDE3B), which in turn decreases cAMP levels in rat pancreatic islets and HIT-T15 cells (Zhao *et al.* 1998). This would negatively affect the insulin secretion dependent on cAMP/protein kinase A (PKA). The physiological importance of this signaling mechanism is evidenced by the fact that leptin can suppress glucagon-like peptide 1-stimulated insulin secretion (Fehmann *et al.* 1997*a*,*b*, Zhao *et al.* 1998). Similarly, leptin inhibits insulin secretion in INS-1 cells in conditions of elevated cAMP levels (Ahren & Havel 1999). Moreover, leptin inhibits the phospholipase C (PLC)/protein kinase C (PKC) pathway in islets from *ob/ob* mice, decreasing insulin secretion when this route is activated (Chen *et al.* 1997). Therefore, several mechanisms may account for the inhibitory role of leptin in β-cell secretion (Fig. 3).

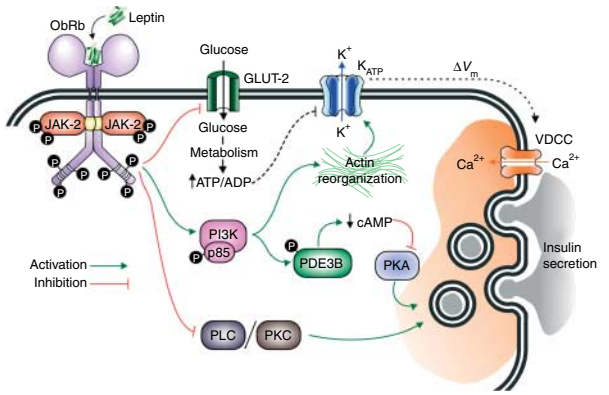

Figure 3 The stimulus–secretion coupling of pancreatic β-cells involves several steps. Glucose is incorporated into the cytosol through GLUT-2 transporters. Glucose mitochondrial metabolism allows for an increase of the intracellular ATP/ADP ratio. This increase closes K_{ATP} channels, inducing the plasma membrane depolarization and subsequent activation of VDCCs, which leads to an intracellular Ca^{2+} influx that triggers exocytosis. Leptin inhibits glucose transport through GLUT-2, and, thus, it would inhibit the subsequent events in the stimulus–secretion coupling. Leptin also activates PI3K-dependent reorganization of the actin cytoskeleton, leading to the opening of K_{ATP} channels and to plasma membrane hyperpolarization. Additionally, PI3K-dependent activation of PDE3B by leptin reduces cAMP levels, inhibiting the PKA pathway, which is involved in the regulation of Ca^{2+} channels and exocytosis. Leptin can also inhibit the PLC/PKC pathway.

Effect of leptin on insulin gene expression

Numerous studies have shown that leptin inhibits insulin gene expression. At 0·625–10 nM, leptin decreases proinsulin gene expression in the β-cell lines β-TC6, HIT-T15, and INS-1 after incubation with the hormone for 16–40 h (Kulkarni *et al.* 1997, Seufert *et al.* 1999*a*, Tsiotra *et al.* 2001). Analysis of proinsulin mRNA levels revealed a decrease in isolated rat islets after incubation with 1–10 nM leptin (Kulkarni *et al.* 1997, Pallett *et al.* 1997). This effect has also been observed in *ob/ob* mice treated *in vivo* with leptin and in *in vitro* experiments with isolated islets from these animals (Seufert *et al.* 1999*a*). In humans, *in vitro* experiments demonstrated that incubation of pancreatic islets with 6·25 nM leptin for 48 h also reduces proinsulin mRNA levels (Seufert *et al.* 1999*b*). This effect was observed at 11·2 mM glucose but not at 5·6 mM, indicating that leptin inhibition was dependent on stimulatory glucose levels. Consistent with these findings, leptin reduces proinsulin expression at 25 mM glucose but not at lower concentrations in INS-1 cells (Seufert *et al.* 1999*a*). Similarly, leptin inhibition of proinsulin mRNA transcription is higher at 16·7 mM glucose than at 7 mM in HIT-T15 cells (Tsiotra *et al.* 2001). Thus, it seems that leptin depends on stimulatory glucose concentrations to exert its action on insulin transcription.

This inhibitory function of leptin in the β-cell is mediated by the activation of JAK/STAT signaling. After the phosphorylation of JAK2 proteins, this pathway involves the recruitment of STAT proteins that work as transcriptional factors in the nucleus. It has been shown that leptin activates the STAT3 protein and promotes DNA binding of STAT proteins in nuclear extracts from RINm5F cells and isolated rat islets (Morton *et al.* 2011). In INS-1 cells, it was reported that STAT5b was involved in leptin-mediated repression of the rat insulin I gene promoter (Seufert *et al.* 1999*a*). More recently, this signaling pathway has been further characterized (Laubner *et al.* 2005). Although STAT1, -3, -5b, and -6 are present in INS-1 cells, it seems that leptin-mediated activation of JAK2 recruits basically STAT3 and -5b. Interestingly, it was shown that the inhibitory effect of leptin on insulin gene expression was not mediated by direct interaction of STAT3 or -5b with the proinsulin promoter (Laubner *et al.* 2005). By contrast, leptin-induced suppressor of cytokine signaling 3 (SOCS3) expression by STAT-dependent mechanisms was found to be responsible for the inhibition of the rat insulin I gene promoter activity (Laubner *et al.* 2005; Fig. 4). Thus, SOCS3 has another function in the pancreatic β-cell different from the well-known role as a negative regulator of the JAK/STAT pathway (Fruhbeck 2006). Given that leptin also increases SOCS3 expression in isolated human pancreatic islets and in islets from *ob/ob* mice treated *in vivo*, it seems that this mechanism may be general for various species (Laubner *et al.* 2005). Consistent with these findings, SOCS3 mRNA is decreased and proinsulin mRNA is increased in KO mice with a pancreas-specific disruption of the leptin receptor (Morioka *et al.* 2007).

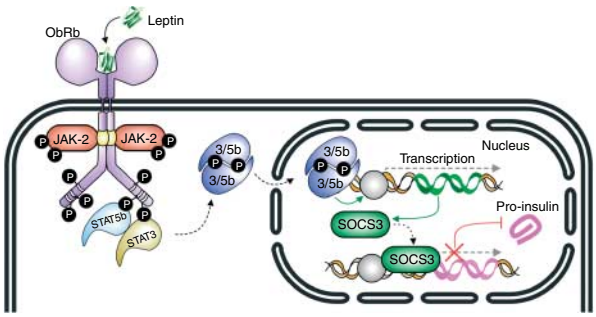

Figure 4 In the pancreatic β-cell, leptin induces the activation of STAT3 and STAT5B, which migrate to the nucleus and induce the expression of SOCS3. Although SOCS3 is a well-known inhibitor of the JAK/STAT pathway, in the β-cell it inhibits the expression of proinsulin.

Regulation of β-cell mass by leptin

The regulation of β-cell mass is essential for the compensatory response of the endocrine pancreas to situations of increased insulin demand such as obesity (Sachdeva & Stoffers 2009). Cell mass remodeling is the result of several processes, which include proliferation, neogenesis, cell size, and apoptosis. Several studies have reported leptin effects in the majority of these processes (Table 1). Experiments about the leptin effect on proliferation were initially performed in β-cell lines. Leptin mediates a proliferative response in RINm5F at concentrations of about 100 nM (Islam *et al.* 1997). In MIN-6 cells, this hormone at 1–10 nM increased proliferation as well through activation of the MAPK pathway (Tanabe *et al.* 1997). This proliferative response has been also observed in fetal islet cells and it has been postulated that it might have a role in β-cell mass at birth (Islam *et al.* 2000). Conversely, no proliferative action of leptin has been found in experiments with islets from adult rats (Okuya *et al.* 2001). Recent studies with disruption of the leptin receptor either in the pancreas (Morioka *et al.* 2007) or in β-cells and hypothalamus (Covey *et al.* 2006) indicate that leptin may have a negative role in β-cell mass expansion, since the average size of the islets from these KO mice was found to be increased. In one of these studies, no modification of proliferation was observed (Morioka *et al.* 2007). Instead, the enhanced islet mass in these KO mice was attributed to augmented β-cell size due to increased activity of p70S6 kinase and PKB. Thus, these latter studies using KO mice indicate that leptin may negatively contribute to β-cell mass expansion.

Both protective and deleterious effects have been attributed to leptin (Table 1). At 1–5 nM, leptin increases the viability of rat pancreatic islets by suppressing apoptosis, a process that was associated with decreases in both triglyceride content and inducible NO synthase (iNOS) expression, which probably would decrease the levels of NO as a proapoptotic factor (Okuya *et al.* 2001). Similarly, gene transfer of the leptin receptor to obese Zucker diabetic rats led to reduced triglyceride content, iNOS expression, and NO production when their pancreatic islets were incubated with leptin, indicative of a protective effect of this hormone against lipoapoptosis (Wang *et al.* 1998*a*,*b*). Consistent with this protective action, leptin modulates the expression of the anti-apoptotic gene β-cell leukemia 2 gene product (*Bcl2*), preventing against fatty acid-induced apoptosis (Shimabukuro *et al.* 1998). Likewise, leptin protects from apoptosis in the β-cell line BRIN-BD11 by increasing BCL2 and decreasing Bcl2 associated X protein (BAX; Brown & Dunmore 2007). On the contrary, other studies have shown leptin deleterious effects in the pancreatic β-cell. In human β-cells and INS-1 cells, chronically elevated concentrations of glucose (33·3 mM) and leptin (10 nM) induce apoptosis through activation of the JNK pathway (Maedler *et al.* 2008). Additionally, chronic exposure of human β-cells to leptin triggers apoptotic events by decreasing the expression of interleukin 1 (IL1) receptor antagonist and enhancing the release of IL1B (Maedler *et al.* 2004). Activation of the leptin receptor in RINm5F insulinoma cells also led to the upregulation of numerous genes related to inflammation as well as an increase of caspase proteolytic activity (Hekerman *et al.* 2007). Thus, given the diversity of effects observed in the islet, the role of leptin in the regulation of β-cell mass still deserves much attention.

Leptin resistance

Although leptin reduces food intake and body weight, obesity is characterized by high plasma leptin levels. In this regard, several studies have shown that attenuated leptin signaling is present in this metabolic disorder. This leptin resistance would explain why high leptin levels fail to induce the expected decreasing effects on feeding and body weight that would mitigate obesity. Several factors have been shown to mediate leptin resistance at the central level: impaired leptin transport in the blood–brain barrier, endoplasmic reticulum stress, and impaired leptin signaling, among others (Zhang *et al.* 2008, Morris & Rui 2009, Ozcan *et al.* 2009). Most of these alterations have been observed in models of diet-induced obesity. Several studies have also shown that attenuated leptin signaling in obesity models is related to increased levels or activity of SOCS3, protein tyrosine phosphatase 1B (PTP1B), and/or T-cell protein tyrosine phosphatase (TCPTP; Myers *et al.* 2010). Both proteins work as negative regulators of leptin-induced activation of the JAK/STAT pathway (Morris & Rui 2009). In addition to central leptin resistance, several

Table 1 Regulation of β-cell mass by leptin

Effect	β-cell model	Pathway/signaling molecules	Reference
Proliferative	RINm5F cells	c-fos	Islam *et al.* (1997)
Proliferative	MIN-6 cells	MAPK	Tanabe *et al.* (1997)
Proliferative	Rat fetal islet cells	c-fos	Islam *et al.* (2000)
No proliferative effect	Rat pancreatic islets	–	Okuya *et al.* (2001)
Increased islet area	KO mice with disruption of leptin receptor in hypothalamus and β-cells	–	Covey *et al.* (2006)
Increased islet area, increased cell size, no proliferation	KO mice with disruption of leptin receptor in pancreas	p70S6 kinase, PKB	Morioka *et al.* (2007)
Antiapoptotic	Rat pancreatic islets	↓ Triglyceride content, ↓ iNOS	Okuya *et al.* (2001)
Antiapoptotic	Gene transfer of leptin receptor in islets from Zucker diabetic rats	↓ Triglyceride content, ↓ iNOS, ↓ NO	Wang *et al.* (1998*a*,*b*)
Antiapoptotic	Islets from Zucker diabetic rats	↑ Bcl2	Shimabukuro *et al.* (1998)
Antiapoptotic	BRIN-BD11 cells	↑ Bcl2, ↓ Bax	Brown & Dunmore (2007)
Proapoptotic	INS-1 cells and human islets	JNK	Maedler *et al.* (2008)
Proapoptotic	Human islets	↓ IL1 receptor antagonist expression	Maedler *et al.* (2004)
Proapoptotic	RINm5F	↑ Caspase activity, ↑ expression of inflammation-related genes	Hekerman *et al.* (2007)

studies on obesity models have observed attenuated leptin signaling in peripheral tissues (Prpic *et al.* 2003, Lam *et al.* 2006, Steinberg *et al.* 2006, Nave *et al.* 2008). In most cases, an increase in PTP1B or SOCS3 levels was associated with this attenuated response to leptin. In the case of the endocrine pancreas, it has been proposed that leptin resistance in the β-cell may alter its function and could contribute to diabetes in obese individuals (Seufert 2004, Covey *et al.* 2006, Morioka *et al.* 2007). Since leptin signaling in the pancreatic β-cell triggers similar pathways as those activated in the hypothalamus or other tissues, it would be interesting to explore whether leptin resistance occurs in the β-cell during obesity and the mechanisms involved. For instance, although SOCS3 and PTP1B are implicated in several functions in the islet (Karlsen *et al.* 2001, Kushner *et al.* 2004, Laubner *et al.* 2005), their role in attenuated leptin signaling during obesity has not yet been studied in the pancreatic β-cell.

Conclusions

Among other functions, leptin modulates glucose homeostasis through central and peripheral actions. While several peripheral organs such as muscle, adipose tissue, and liver may participate in this process, the pancreatic β-cell is also an important player regulated by leptin. Numerous studies using different approaches and animal models have shown that leptin inhibits insulin gene expression and insulin secretion. Additionally, leptin produces distinct effects on proliferation, apoptosis, and cell size depending on the studied model. In this regard, much research is required to further determine the role of leptin in β-cell mass. Moreover, some studies have reported the effects of leptin on human β-cells that are different from those observed in animal models, particularly about the protective or deleterious actions of leptin. Thus, additional data will be necessary to contrast the function of leptin in animals and humans and to dissect the different roles. All this information is necessary to have a better understanding of the role of leptin in the β-cell and in the regulation of glucose homeostasis, as well as in the communication between the endocrine pancreas and the adipose tissue.

Declaration of interest

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

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