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Effects of leptin and adiponectin on pancreatic ß-cell function

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ABSTRACT

Leptin and adiponectin are hormones secreted from adipocytes that have important roles in metabolism and energy homeostasis. This review evaluates the effects of leptin and adiponectin on β-cell function by analyzing and compiling results from human clinical trials and epidemiologic studies as well as in vitro and in vivo experiments. Leptin has been shown to inhibit ectopic fat accumulation and thereby prevent β-cell dysfunction and protect the β-cell from cytokine- and fatty acid–induced apoptosis. However, leptin suppresses insulin gene expression and secretion as well as glucose transport into the β-cell. Adiponectin stimulates insulin secretion by enhancing exocytosis of insulin granules and upregulating the expression of the insulin gene; however, this effect depends on the prevailing glucose concentration and status of insulin resistance. In addition, adiponectin has antiapoptotic properties in β-cells. Available evidence concerning the role of these adipokines on insulin secretion, insulin gene expression, and apoptosis is not always entirely consistent; and many fundamental questions remain to be answered by future studies.

1. Introduction

Leptin and adiponectin are 2 important peptide hormones secreted by adipocytes that are involved in the regulation of metabolism and energy homeostasis. Although the hypothalamus has been identified as an important target organ for leptin to regulate food intake and energy expenditure, leptin is also known to exert direct actions in various peripheral tissues, including the pancreas. Leptin receptors are present in pancreatic β-cells [1]; and although a number of studies have been performed to elucidate the effects of leptin on β-cells during the past years, results have been controversial. Adiponectin induces fatty acid oxidation and glucose uptake, and suppresses gluconeogenesis in muscle and liver, thereby improving peripheral insulin sensitivity. In addition, adiponectin has antiatherogenic and anti-inflammatory properties, whereas leptin has proatherogenic and proinflammatory properties. Most studies have focused on the

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action of adiponectin in skeletal muscle, liver, and adipose tissue, whereas relatively fewer and rather inconsistent results are available regarding the "cross talk" between adiponectin and β-cells.

The purpose of this review is to investigate the complex relationship between pancreatic β-cells and these 2 important adipokines. Human clinical and epidemiologic studies as well as in vitro and in vivo experiments are reviewed and analyzed to present the current status of knowledge with respect to the role of leptin and adiponectin in β-cell function.

2. Effects of leptin on pancreatic β-cells

2.1. *In vitro studies*

Leptin receptors are expressed in primary rat pancreatic β-cells and in insulinoma cell lines [2]. Although both the long (ObRb) and the short (ObRa) leptin receptor isoforms are expressed in β-cells [1], ObRb is thought to be the main receptor mediating the actions of leptin. ObRb is expressed in insulinoma-derived β-cell lines and δ-cells [3], as well as in glucagon-producing α-cells [4]. The direct effect of leptin on pancreatic insulin secretion has been examined in several studies with various leptin concentrations (1.7-167 ng/mL). In physiological concentrations (1.7-10.0 ng/mL), leptin significantly downregulates insulin secretion from β-cells in the presence of high glucose concentrations [1,5] and has tonic inhibitory action on insulin secretion and insulin gene expression [1,5-9]. Leptin specifically inhibits glucose-stimulated insulin secretion (GSIS) via the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) or phospholipase C/protein kinase C (PKC) pathways [5,10]. This is in agreement with the finding that leptin decreases circulating insulin concentration in fed, but not in fasted, normal mice [1]. Furthermore, studies in human islets demonstrate that leptin inhibits insulin secretion in a similar manner to that described in rodent islets [1] and that this effect is mediated by ObRb [1,6]. Experiments using islets or perfused pancreatic tissue from *ob/ob* mice demonstrate inhibitory effects of leptin on basal and glucose-induced insulin secretion [3,6]. There are several mechanisms by which leptin may suppress insulin secretion by acting directly on β-cells. Depolarization of the β-cell membrane by closure of adenosine triphosphate (ATP)–sensitive potassium (K_{ATP}) channels in response to glucose or other insulin secretagogues is an essential step for the release of insulin from β-cells. Leptin hyperpolarizes the cell membrane by opening K_{ATP} channels leading to a decrease in intracellular Ca^{2+}, which is involved in the release of insulin vesicles out of the β-cell [3,11]. Although the exact molecular mechanism by which leptin opens K_{ATP} channels is not fully elucidated, 3 possible mechanisms have been proposed: (1) Leptin stimulates the activity of phosphodiesterase 3B (PDE3B) that hydrolyzes cAMP to AMP as well as the activity of phosphoinositide 3-kinase (PI3K), thereby reducing intracellular cAMP that is important for insulin secretion by closing K_{ATP} channels [9]. Treatment with PI3K inhibitors blocks the opening of K_{ATP} channels by leptin [11]. Similar results were obtained with selective inhibitors of PDE, which completely abolished the inhibitory effect of leptin on glucose- and glucagon-like peptide 1 (GLP-1)–induced insulin secretion [9]. In addition, leptin can affect PI3K activity and intracellular cAMP concentration by inhibiting phosphatase activity of phosphatase and tensin homolog (PTEN) [12]. (2) Leptin stimulates the formation of long-chain acyl-CoA esters that are known to be active mediators binding and opening K_{ATP} channels in β-cells. This is supported by the finding that leptin treatment induces triglyceride depletion and stimulates oxidation of free fatty acids (FFA) in islet cells [13]. (3) Leptin significantly reduces glucose transport into β-cells, thereby decreasing intracellular concentration of ATP; and the ratio of ATP to adenosine diphosphate is also thought to directly affect the opening of K_{ATP} channels [14].

Although leptin alone does not alter the phosphorylation status of glucose transporter 2 (GLUT2), leptin inhibits GLP-1–stimulated phosphorylation of GLUT2, resulting in an attenuation of glucose transport activity [14]. This suggests that leptin may have an antagonistic role to that of GLP-1. In addition, leptin inhibits phospholipase C/PKC-induced insulin secretion via a PI3K-dependent pathway, independent of PDE3B [15]. Calcium/calmodulin-dependent protein kinase, PKA or PKC are thought to be the possible mediators involved. Adenosine monophosphate–activated protein kinase (AMPK) is also related to the function of leptin. Leptin has tissue-specific effects on AMPK, activating it in skeletal muscle [16] and adipose tissue [17] but suppressing it in the hypothalamus [18]. Adenosine monophosphate–activated protein kinase activation in β-cells inhibits insulin secretion and insulin gene expression [19]; however, leptin does not appear to have an effect on AMPK activity in β-cells [20].

Many studies have demonstrated that leptin suppresses mRNA expression of preproinsulin in mouse β-cell lines [1], rat β-cell lines [8], *ob/ob* mouse islets [21], primary rat islets [1], and human islets [21]. The effect of leptin on insulin biosynthesis and gene expression is thought to be a transcriptional process [8] and is likely independent of the activation of K_{ATP} channels because the K_{ATP} channel opener diazoxide has no effect on leptin-induced suppression of insulin gene transcription in β-cells. Therefore, different signal transduction pathways should be involved in the inhibitory action of leptin on insulin gene expression and insulin secretion [8]. The inhibitory effect of leptin on preproinsulin mRNA expression requires prior stimulation of insulin gene promoter activity by GLP-1 or high glucose concentrations [8,21]. In human islets, leptin stimulates the expression of suppressor of cytokine signaling (SOCS) 3, which is a known inhibitor of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway [22]. Increased SOCS3 expression by leptin inhibits STAT3/5b-dependent preproinsulin I gene promoter activity in INS-1 β-cells [22].

Leptin has been identified as an important regulator of β-cell mass and cell survival, which is typically maintained by the balance between cell proliferation and cell death (including apoptosis). Studies in the leptin receptor–deficient Zucker diabetic fatty (ZDF) rats reveal that the reduction in β-cell mass in diabetes is primarily due to acceleration of β-cell death and not due to reduced proliferation [23]. Studies in this animal model demonstrate that triglyceride accumulation in islets is the cause of accelerated β-cell death [24]. Leptin reduces the triglyceride content of islets by increasing

intracellular FFA oxidation, thereby suppressing β-cell death [13]. Furthermore, leptin at 84 ng/mL (5 nmol/L), that is, at concentrations observed in obese human subjects with leptin resistance, inhibits inducible nitric oxide synthase expression in rat islets and hence decreases the amount of nitric oxide, which is related to apoptosis by depletion of calcium stores in endoplasmic reticulum and induction of C/EBP homologue protein expression [25]. Leptin also influences the antiapoptotic factor Bcl-2. Fatty acids inhibit Bcl-2 expression, thereby leading to apoptosis in islets from leptin receptor–deficient obese ZDF rats; however, following transfection with wild-type ObR, leptin completely blocks this effect [26]. Furthermore, apoptosis induced by depletion of serum in cultured cells is prevented by leptin treatment concomitant to increased levels of Bcl-2 mRNA expression and decreased levels of Bax protein [27]. In addition to apoptosis prevention, leptin increases DNA synthesis and induces cell proliferation in MIN6 cells through activation of both the mitogen-activated protein kinase and the JAK/STAT cascades [28]. Leptin-mediated suppression of PTEN has also been involved in β-cell proliferation by increasing the activity of cyclin-dependent kinase [29].

There are also reports of some deleterious effects of leptin on human β-cells [30,31]. Interleukin (IL)-1 receptor antagonist is known to protect human islets from glucose-induced IL-1β–mediated β-cell apoptosis and to improve β-cell function. Long-term exposure to leptin reduced the expression of IL-1 receptor agonist in β-cells and increased IL-1β secretion from macrophages residing in human islets, followed by impaired GSIS (β-cell dysfunction), caspase-3 activation, and β-cell apoptosis [30]. Furthermore, hyperleptinemia induced β-cell apoptosis and dysfunction through activation of the JNK pathway in human islets, whereas a JNK inhibitor abolished the unfavorable effects of leptin on apoptosis and impaired GSIS [31]. Moreover, studies in pancreas-specific leptin receptor-knockout mice demonstrate that both the number and the size of the islets were increased in the knockout mice [32,33]. However, other studies found that absence of leptin signaling does not affect mitosis of β-cells [32]. Therefore, the effect of leptin on β-cell proliferation has not been clarified; and further studies are needed.

2.2. *In vivo studies*

Leptin has been shown to protect β-cells from lipotoxicity in various rodent models. Adenovirus-mediated hyperleptinemia in streptozotocin-induced diabetic ZDF rats with islet transplantation prevents apoptosis of transplanted islet cells and preserves β-cell mass by blocking lipogenesis and lipid accumulation [34]. Hyperleptinemia inhibits the expression of lipogenic transcription factor sterol regulatory element binding protein–1c and its downstream lipogenic proteins in hepatocytes surrounding transplanted islets. However, in normal rats, hyperleptinemia induced by adenoviral gene therapy causes deprivation of both intracellular and extracellular lipids from β-cells, leading to β-cell dysfunction including suboptimal insulin secretory response to glucose [35]. This inhibition was reversibly restored by addition of FFA, underscoring the possible role of fatty acids as a signaling messenger. Recently, leptin therapy in insulin-deficient, nonobese diabetic mice was shown to reduce blood glucose and improve lipid profile through its inhibitory action on glucagon production and expression of lipogenic and cholesterologenic transcription factors [36].

In *ob/ob* mice, intraperitoneal injection of leptin reduces insulin secretion and inhibits transcription of the preproinsulin gene [8]. Preproinsulin mRNA expression is also decreased in INS-1 cells incubated with leptin at 25 mmol/L glucose, but not 5.6 or 11.1 mmol/L glucose [8], indicating that transcriptional suppression of the insulin gene by leptin is glucose concentration dependent. Leptin inhibits insulin synthesis via transcriptional repression [21], and SOCS3 is involved in this repression of preproinsulin gene by the leptin/JAK/STAT pathway [22]. Studies in dual β-cell and hypothalamus-specific leptin receptor–disrupted mice demonstrate that the β-cell is a major target of leptin for regulating glucose homeostasis independent of obesity [33]. Whereas whole-body leptin knockout results in increased food intake, this tissue-specific attenuation of leptin signaling does not alter food intake. Unlike in *ob/ob* or *db/db* mice, these mice exhibit fasting hypoglycemia due to increased basal insulin secretion from β-cells [33], consistent with previous studies showing an inhibitory effect of leptin on insulin secretion. Loss of leptin receptor signaling in β-cells leads to increased islet areas and glucose intolerance, which might be due to impaired GSIS caused by excessive triglyceride accumulation and decreased GLUT2 expression in β-cells. These results indicate that leptin regulation of glucose homeostasis extends beyond insulin sensitivity to influence β-cell function, independent of pathways controlling food intake, and collectively suggest that defects in this adipoinsular axis could contribute to diabetes associated with obesity. In fact, it has been demonstrated that hyperinsulinemia, not insulin resistance, is the primary pathophysiological consequence in mice lacking β-cell leptin signaling [37].

Studies in pancreas-specific leptin receptor knockout mice report improved glucose tolerance due to increased acute-phase insulin secretion and expanded β-cell mass [32]. This indicates that ablation of leptin signaling improves downstream insulin signal transduction in β-cells. Consistent with previous in vitro results, absence of leptin inhibited the induction of SOCS-3, which decreased preproinsulin expression, resulting in elevated fasting insulin concentration in the knockout mice. Notably, compared with control mice, knockout mice were more susceptible to high-fat diet leading to impaired β-cell function, poor compensatory islet growth, and glucose intolerance, suggesting a crucial role for leptin signaling in β-cell protection from lipotoxicity.

The effects of leptin on pancreatic β-cells delineated from in vitro and in vivo experiments in animal models are depicted in Fig. 1.

2.3. *Human studies*

Fat mass is the major determinant of plasma leptin concentrations in humans, and leptin levels directly correlate with body fat. Animal studies suggest that leptin inhibits insulin secretion and insulin gene expression. However, several cross-sectional studies in human subjects report that plasma leptin levels are positively associated with insulin

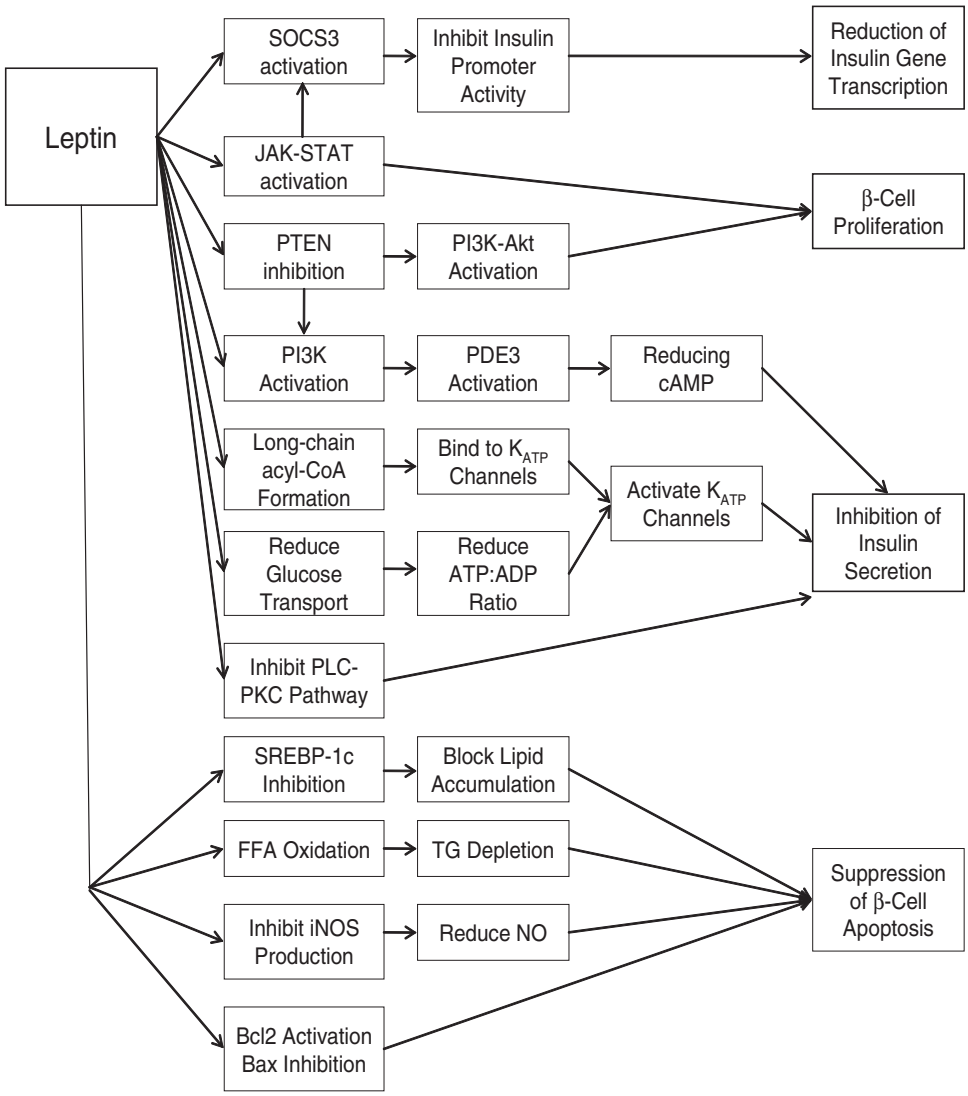

Fig. 1 – Schematic representation of the studied pathways of the effects of leptin on pancreatic ß-cells.

concentration and β-cell secretory function in healthy young adults [38,39] as well as in children [40]. In addition, fasting leptin concentration was more closely related to insulin secretory capacity of β-cells in healthy female subjects regardless of obesity [41,42]. Furthermore, significant positive correlations were found between fasting insulin and leptin in patients with type 2 diabetes mellitus [43]. These findings may be explained by the abundant experimental and clinical evidence showing that long-term treatment with insulin increases plasma leptin concentration in both humans and rodents [44-46]. As β-cells release more insulin to compensate for the underlying insulin resistance caused by increased body fat, insulin directly stimulates the synthesis and secretion of leptin [47], which may, in turn, regulate insulin release by a negative feedback mechanism in β-cells. The observation that obese subjects have greater leptin but also insulin concentrations indicates that there is state of leptin resistance [48]. Pancreatic leptin resistance in obesity might account for this loss of repressive control of insulin secretion by leptin [7]. Leptin resistance in β-cells results in abnormal insulin secretion in the fasting state and after feeding and leads to hyperinsulinemia, which could lead to the exhaustion and failure of β-cells [7,49]. Likewise, epidemiologic data demonstrate a strong association between leptin and insulin resistance in middle-aged subjects [50]. In leptin resistance, not only are the protective effects of leptin on β-cells attenuated; but also long-term exposure to leptin induces β-cell apoptosis via IL-1β signaling pathways [30]. β-Cell apoptosis is thus augmented; and eventually, islets lose the compensatory action to insulin resistance, and type 2 diabetes mellitus ensues.

One cross-sectional study with overweight adolescents reported that leptin was independently associated with insulin resistance, but not with insulin secretion, possibly due to pancreatic leptin resistance [51]. The effect of leptin on insulin resistance has been studied in many hypoleptinemic states such as congenital leptin deficiency [52], lipodystrophic syndrome [53], highly active antiretroviral therapy–induced lipodystrophy [54], and hypothalamic amenorrhea [55]. In these hypoleptinemic states, leptin treatment reduces insulin

levels and enhances insulin sensitivity by activating insulin-sensitive peripheral tissues, including the liver and adipose tissue [56], as well as by decreasing body weight and fat mass [57]. In addition, leptin replacement therapy was effective in ameliorating insulin resistance in patients with type 1 diabetes mellitus on a background of acquired generalized lipodystrophy [58]. Based on previous findings in rodents, hyperinsulinemia may precede the development of insulin resistance. Therefore, the correction of hyperinsulinemia with leptin therapy may be the underlying factor for the metabolic improvements in some of the hypoleptinemic conditions.

To date, several interventional studies have been performed to evaluate the effects and safety of leptin administration in lipoatrophic or obese patients with hypoleptinemia. Leptin replacement to children with congenital leptin deficiency remarkably ameliorates hyperinsulinemia and hyperlipidemia [59,60]. Recent randomized trials demonstrate that combination treatment with an amylin analog and human recombinant leptin significantly decreases not only body weight but also insulin levels in obese subjects [61]. With regard to hypoleptinemic men with human immunodeficiency virus–associated lipoatrophy, several clinical trials have shown that administration of recombinant leptin improves insulin resistance and suppresses fasting insulin concentration [54,62,63].

3. Effects of adiponectin on pancreatic ß-cells

3.1. *In vitro studies*

Following the discovery of adiponectin, 2 adiponectin receptors (AdR-1 and AdR-2) were cloned. Both AdR-1 and AdR-2 are abundantly expressed in β-cells [64], with AdR-1 being the predominant isoform [65,66]. Given that globular adiponectin has a stronger affinity for AdR-1, which is the dominant receptor in β-cells, the globular domain of adiponectin might be a potent and effective fragment affecting β-cell function.

The direct effect of adiponectin on insulin secretion in β-cells has been examined in several studies but with variable and inconsistent results. Although leptin only rescued fatty acid–mediated suppression of GSIS, globular adiponectin completely restored cytokine- and fatty acid–induced impairments in GSIS, indicating that adiponectin might protect β-cell dysfunction from autoimmunity or lipotoxicity [67]. Okamoto et al [68] demonstrated that adiponectin augments insulin secretion from isolated mouse islets by stimulating exocytosis of insulin granules without affecting ATP generation, K_{ATP} channels, membrane potential, Ca^{2+} influx, or activation of AMPK. Long-term treatment (24 hours) with both globular and full-length adiponectin augmented GSIS in isolated mice islets and increased expression of the insulin gene, as well as *Pdx-1* and *Mafa* [66], which are crucial transcriptional activators involved in the production of insulin and maintenance of β-cell viability. However, another study found a 45% decrease in *Pdx-1* expression in BRIN-BD11 cells incubated with globular adiponectin [65]. Winzell et al [69] showed a dual effect of adiponectin on insulin secretion in insulin-resistant mouse islets, which was dependent on prevailing glucose levels. In insulin-resistant islets, adiponectin inhibited insulin secretion at low glucose concentrations, but stimulated insulin secretion at high glucose concentrations, whereas insulin secretion in islets from normal mice was not affected by adiponectin. Experiments with human islets demonstrate that full-length adiponectin does not affect basal insulin secretion or GSIS [70].

Similar to the antiapoptotic effect of leptin on β-cells, adiponectin partially protects β-cells from IL-1β/interferon-γ or palmitate-induced apoptosis [67]. Another study showed that adiponectin prevents β-cell apoptosis against long-term serum deprivation and glucotoxicity [66,67]. These effects are mediated by both MEK–extracellular signal-regulated kinase (ERK) 1/2 and PI3K-Akt activation [66]. However, other studies reported that adiponectin does not prevent basal fatty acid–induced β-cell apoptosis of human islets, although it induces phosphorylation of acetyl-CoA carboxylase and subsequently increases lipid oxidation [70]. Globular adiponectin causes a significant ERK1/2-dependent increase in cell viability and a significant increase in *Pdx-1* expression in rat β-cell lines; however, this does not appear to protect the β-cells from apoptosis induced by serum depletion [65], in contrast to other reports [66,67].

Adenosine monophosphate–activated protein kinase is activated by adiponectin, resulting in inhibition of acetyl-CoA carboxylase activity by direct phosphorylation in β-cells [71]. Adiponectin-induced activation of AMPK inhibits glucose-stimulated lipogenesis in MIN6 cells. However, experiments with isolated mouse islets report that adiponectin does not affect the phosphorylation of AMPK at 5.6 mmol/L of glucose [68], indicating that adiponectin may not be able to activate AMPK under basal glucose concentrations because AMPK may already be activated by glucose itself [19]. In addition, globular and full-length adiponectin did not induce phosphorylation of AMPK and p38 mitogen-activated protein kinase in MIN6 cells following either short- or long-term treatment, although both forms of adiponectin stimulated ERK and Akt activation in MIN6 cells and isolated mouse islets [66]. These conflicting data may be due to differences among the various experimental conditions, for example, different prevailing glucose concentrations and duration of treatments.

3.2. *In vivo studies*

Adiponectin knockout mice exhibit impaired glucose tolerance in spite of normal or subnormal insulin levels [72]. Elevated blood glucose is not able to effectively stimulate insulin secretion in these mice. Globular domain adiponectin transgenic *ob/ob* mice exhibit increased insulin sensitivity and increased insulin secretion compared with nontransgenic mice [73]. This stimulatory effect of adiponectin on insulin secretion was independent of body weight. These results suggest that adiponectin has protective effects on β-cells. Contrary to leptin, pancreas-specific adiponectin receptor knockout animal models have not been developed so far. Despite inconsistent results from in vitro studies, in vivo studies in C57BL/6 mice demonstrate that intravenous adiponectin injection results in increased insulin secretion [68].

The studied pathways of the effects of adiponectin on pancreatic β-cells delineated from in vitro and in vivo experiments in animal models are depicted in Fig. 2.

3.3. *Human studies*

Currently, adiponectin is not available for administration to human subjects. Most epidemiologic studies have found that plasma adiponectin is associated with β-cell function as well as adiposity. An observational study in Asian children reported that adiponectin concentration inversely correlates with body weight, body mass index, and proinsulin levels in both boys and girls. In addition, insulin concentration and the homeostasis model assessment of insulin resistance (HOMA-IR) are inversely related to adiponectin in girls [40]. Contrary to leptin concentration, significant associations between adiponectin and insulin levels, insulin resistance, and β-cell function are abolished after adjustment for body weight [74]. In addition, the leptin-to-adiponectin ratio appears to be a better index of β-cell dysfunction than leptin or adiponectin alone, especially in females [40].

Adiponectin has been shown to positively correlate with insulin sensitivity and inversely correlate with fasting proinsulin concentration and the proinsulin-to-insulin ratio, a marker of β-cell failure [75]. Adiponectin concentration remains a significant independent determinant of the proinsulin-to-insulin ratio even after adjustment for percentage body fat [75]. This suggests that hypoadiponectinemia might be used as a surrogate marker for β-cell dysfunction. In addition, adiponectin is independently associated with insulin secretion-sensitivity index, that is, the product of insulin sensitivity and secretion, which in turn reflects β-cell function [76]. One study using the HOMA2 calculator [77], which is a mathematical tool for assessing insulin sensitivity (HOMA-%S) and β-cell function (HOMA-%B) from fasting insulin and glucose levels by using improved modeling algorithms than the original HOMA-IR score, demonstrated that circulating adiponectin is positively correlated with insulin sensitivity as measured by HOMA-%S and inversely related to β-cell dysfunction as expressed by HOMA-%B in obese subjects [78]. It has also been proposed that the decline in adiponectin concentration is longitudinally associated with attenuated β-cell compensation for insulin resistance in women with history of gestational diabetes [79]. However, hyperglycemic clamp studies in subjects with normal glucose tolerance found no significant association between fasting plasma adiponectin concentration and insulin secretion stimulated by glucose or GLP-1 [70]. A cross-sectional study in overweight Hispanic adolescents confirmed that leptin and adiponectin are independently associated with insulin sensitivity, but not with insulin secretion [51]. Other studies reported that the insulinogenic index [80], which reflects the pancreatic insulin secretory function, was not associated with adiponectin, whereas adiponectin was strongly associated with postprandial insulin and glucose concentrations and insulin sensitivity (HOMA-%S) [81]; this implies that adiponectin might be more closely related to insulin resistance rather than β-cell function. The precise role of adiponectin in β-cell function remains to be elucidated.

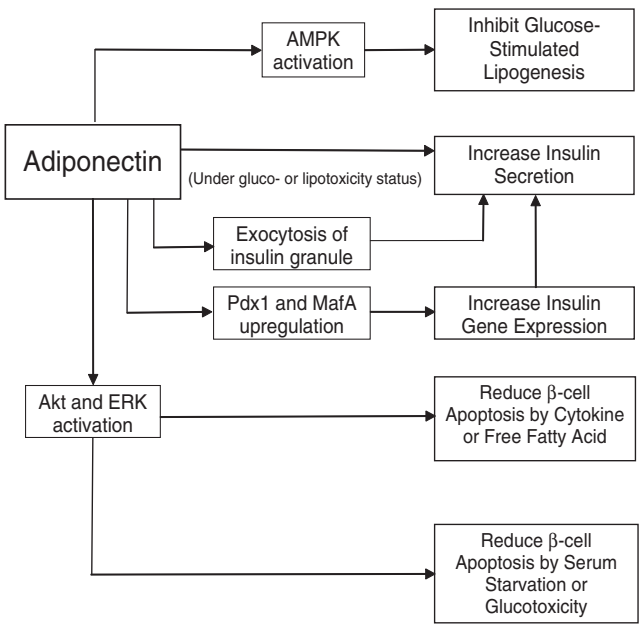

Fig. 2 – Schematic representation of the studied pathways of the effects of adiponectin on pancreatic ß-cells.

4. Summary and future directions

At present, a considerable amount of data has been published on the effects of leptin and adiponectin on β-cell function. However, evidence concerning the role of these adipokines in insulin secretion and β-cell apoptosis are inconsistent; and many fundamental questions remain unanswered. Under circumstances of overnutrition, leptin has a vital function in regulating lipogenesis by inhibiting ectopic fat accumulation in β-cells, thereby preventing β-cell dysfunction. In rodent models, leptin suppresses insulin gene expression and insulin secretion as well as glucose transport, resulting from activation and opening of K_{ATP} channels in β-cells. In addition, leptin protects β-cells from cytokine- and fatty acid–induced apoptosis by modulating Bcl protein family. These effects are mediated by activating JAK2/STAT pathway and inhibiting PTEN, followed by activation of PI3K and PDE3B. However, not all studies confirm these findings; and a study in human islets demonstrated a proapoptotic effect of leptin via activation of the JNK pathway.

The effects of adiponectin on β-cell function are still speculative. Although adiponectin stimulates insulin secretion by enhancing exocytosis of insulin granules and expression of the insulin gene and its transcription factors, it apparently has a dual effect on insulin secretion that is dependent on the prevailing glucose concentration and status of insulin resistance. The antiapoptotic properties of adiponectin are mediated by activation of PI3K-Akt and MEK-ERK1/2 pathways; however, it remains unclear whether adiponectin directly activates AMPK in β-cells. Considering the epidemiologic evidence demonstrating a close association between adiponectin and β-cell dysfunction, signaling pathways

downstream of adiponectin receptor and their effects on β-cell function remain to be determined.

Leptin and adiponectin are 2 important adipokines secreted by adipose tissue and affect metabolism by acting both centrally and peripherally. Besides the major peripheral tissues associated with glucose homeostasis (ie, liver and skeletal muscle), leptin and adiponectin may potentially affect many aspects of β-cell function and thereby modulate glucose control. A better understanding of the role of these adipokines in pancreatic function will likely have important implications in both research and clinical practice. Further research is needed to elucidate whether leptin will be effective in ameliorating β-cell dysfunction and maintaining β-cell mass in hypoleptinemic subjects with insulin resistance. Considering the therapeutic potential of adiponectin on β-cells as well as insulin-resistant peripheral tissues, it is crucial to develop adiponectin as a new medication available for human use. Although β-cell dysfunction is by no means the sole pathophysiological feature of type 2 diabetes mellitus, studies to elucidate the mechanisms by which leptin and adiponectin improve β-cell function would provide a means to preserve β-cells in humans and thereby contribute toward understanding, preventing, and controlling diabetes.

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Conflict of Interest

Disclosure: The authors have no conflicts of interest.

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