Regulation of pancreatic β-cell function by adipocytes

ZHAO Yu-Feng1,2, CHEN Chen1,*
1Endocrine Cell Biology, Prince Henry’s Institute of Medical Research, Melbourne, VIC 3168, Australia; 2Department of Physiology, the Fourth Military Medical University, Xi’an 710032, China

Abstract: Adipokines, the bioactive factors derived mainly from adipocytes, regulate pancreatic β-cell function including insulin secretion, gene expression and apoptosis. In this review, we propose that adipokines influence β-cell function through three interdependent pathways. The first is through regulating lipid and glucose metabolism in β-cells. The second implicates the change of ion channel opening and closing in β-cells. The third pathway is via the modification of insulin sensitivity of β-cells. The endocrine function of adipocytes is dynamic, and the secretion of various adipokines changes under different metabolic conditions. During the progression from the normal state to obesity and to type 2 diabetes, adipokines contribute to the occurrence and development of β-cell dysfunction in type 2 diabetes.

Key words: adipokines; insulin; β-cells; diabetes

The adipocyte is an endocrine cell that secretes many factors and plays an important role in energy metabolism[1]. Since the discovery of leptin in 1994, our view about the adipocyte has been greatly changed from that of a passive energy store to a dynamic endocrine entity[2]. Leptin is a protein that is exclusively expressed in the adipocyte and secreted into the blood stream. It circulates to the hypothalamus and acts on neurons, via its receptors, to inhibit appetite and stimulate energy expenditure[3]. The hormonal nature of leptin characterises the adipocyte as an endocrine cell. Adiponectin is another important adipocyte-secreted hormone[4]. The regulatory action of adiponectin on muscle and liver cells via its membrane receptors further strikingly supports the classification of the adipocyte as an endocrine cell with a complex secretory function. The adipocyte also secretes some cytokines such as tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which take part in the inflammatory action in many cell
types. In addition, free fatty acids (FFAs) that are released from the adipocyte under the condition of enhanced lipolysis, such as fasting or obesity, are involved in regulating the function of many kinds of cells via both the metabolic pathway and membrane receptor signalling pathway. A family of membrane receptors for FFAs has been discovered, which includes GPR41/43, GPR40 and GPR120\(^{[5]}\). The hormonal action of FFAs via its receptors gives a new insight into the regulatory function of the adipocyte in metabolism.

Adipokines form a complex endocrine system and have broad actions in the body. For example, leptin not only regulates appetite but also modulates other functions including reproduction, the immune system and the endocrine system, including insulin secretion. Adiponectin decreases triglyceride content in muscle by increasing expression of molecules involved in both fatty acid combustion and energy dissipation, and then improves insulin resistance\(^{[6]}\). FFAs stimulate insulin secretion through GPR40, and glucagon-like peptide-1 (GLP-1) secretion through GPR120\(^{[7,8]}\). In this review, we focus on the role of adipokines in regulating pancreatic \(\beta\)-cell function. Based on the published reports and our research results, we propose that adipokines regulate \(\beta\)-cell function through three interdependent pathways. One regulates lipid and glucose metabolism in \(\beta\)-cells. Another determines the activity of ion channels on \(\beta\)-cells. The third pathway is related to the change of insulin sensitivity of \(\beta\)-cells. The regulation of \(\beta\)-cell function by adipokines is summarized in Fig.1.

**Adipokines regulate glucose and lipid metabolism in \(\beta\)-cells**

The most important function of \(\beta\)-cells is to secrete insulin. Insulin secretion is under delicate modulation by many factors, with plasma glucose levels being the main regulator of insulin secretion. Glucose stimulates insulin secretion through ATP-sensitive potassium channel (K\(_{ATP}\) channel)-dependent pathways in \(\beta\)-cells. Glucose is transported into \(\beta\)-cells by glucose transporter 2 (GLUT2) and then phosphorylated by glucokinase. It follows an aerobic oxidation pathway to produce ATP from ADP. The increase in the ATP/ADP ratio closes K\(_{ATP}\) channels and leads to the depolarization of membrane potential and subsequent activation of voltage-gated calcium channels (Ca\(^{2+}\) channels).

---

Fig.1. Summary of the regulation of pancreatic \(\beta\)-cell function by adipokines. Adipokines influence \(\beta\)-cell function through modification of metabolic process of glucose and FFAs in \(\beta\)-cells, opening kinetics of ion channels, and sensitivity to insulin. Dash-lines indicate that the effect needs to be confirmed further.
The influx of calcium results in an increase in intracellular Ca\textsuperscript{2+} concentration ([Ca\textsuperscript{2+}]), which triggers exocytosis of insulin granules[9]. Glucose also activates several signalling pathways to potentiate insulin synthesis and secretion via K\textsubscript{ATP} channel-independent pathways[10]. The products of lipid metabolism, including phospholipids and diacylglycerol (DAG), also take part in the potentiation of insulin secretion[10].

Adipokines such as leptin, adiponectin and FFAs may influence insulin secretion via regulation of glucose and lipid metabolism. Fatty acid metabolism and glucose metabolism interact via a glucose-fatty acid cycle, known as the Randle cycle[11]. When FFA concentrations are high, glucose uptake and oxidation are inhibited. This is one reason for the attenuation of glucose-stimulated insulin secretion (GSIS) by long-term exposure of β-cells to high concentrations of FFAs. Another cause of FFA-induced inhibition of GSIS is that FFAs upregulate uncoupling protein-2 (UCP-2) expression in β-cells[12]. UCP-2 is located on the inner membrane of mitochondria and uncouples the oxidation from phosphorylation, thus inhibiting ATP production. UCP-2 overexpression leads to impairment of GSIS[10].

Leptin and adiponectin also influence β-cell function by regulating β-cell metabolism. An important function of leptin is to protect non-adipose tissues from damage by nonoxidative metabolic products of long-chain FFAs via increased β-oxidation of FFAs and reduction of lipogenesis[14]. Leptin receptor deficient rats (ZDF rats) exhibit reduction in FFAs oxidation and accumulation of triglyceride in β-cells, which leads to β-cell dysfunction and apoptosis through ceramide synthesis. Transgenic expression of normal leptin receptor into islets of ZDF rats restores the normal function of β-cells and inhibits β-cell apoptosis via increased FFA oxidation and decreased triglyceride content levels. Adiponectin also influences β-cell apoptosis. It is reported that adiponectin counteracts FFAs-induced apoptosis of INS-1 insulin-secreting cells[15]. AMP-activated protein kinase (AMPK) is suggested to be involved in the action of adiponectin on β-cells[10]. Adiponectin stimulates fatty acid oxidation in the muscle and liver cells. Although no direct evidence has been reported about the regulatory action of adiponectin on fatty acid oxidation in β-cells, adiponectin probably influences β-cell metabolism and secretion since functional receptors of adiponectin are expressed on β-cells. Further research into the function of adiponectin on β-cells is needed.

Adipokines modulate ion channel activity on β-cells

Adipokines are able to modulate ion channel activity and thereby influence insulin secretion. Ion channels are important participants in insulin secretion, as described above. It has been shown that leptin activates K\textsubscript{ATP} channels. K\textsubscript{ATP} channels regulate the resting membrane potential of β-cells. β-cells from leptin receptor deficient mice (db/db mice) have a more depolarized resting membrane potential than that from the normal mice, indicating that leptin may normally open K\textsubscript{ATP} channels on β-cells[17]. Patch-clamp electrophysiological analysis shows that leptin induces hyperpolarization of β-cells from ob/ob mice and CRI-G1 rat insulin-secreting cells, and single-channel recordings confirm that leptin increases the probability of K\textsubscript{ATP} channel opening[18]. The activation of K\textsubscript{ATP} channels by leptin involves the inhibitory effects of leptin on insulin secretion. Leptin-induced opening of K\textsubscript{ATP} channels may be due to the decrease in cytosolic ATP levels in β-cells, as leptin reduces glucose transport and decreases cytosolic ATP levels in β-cells[19].

The effects of FFAs on ion channels were studied in our laboratory. Firstly, we observed that linoleate inhibits K\textsubscript{(v)} channel activity in rat β-cells, which is mediated through the FFA receptor, GPR40. The PKA signalling system may take part in this process[20]. We also observed the effects of linoleate on Ca\textsuperscript{2+}\textsubscript{(v)} channels and K\textsubscript{ATP} channels. Linoleate inhibits Ca\textsuperscript{2+}\textsubscript{(v)} currents in rat β-cells in a calcium-dependent manner, as inhibition of the increase in [Ca\textsuperscript{2+}], induced by linoleate counteracts linoleate-induced inhibition of Ca\textsuperscript{2+}\textsubscript{(v)} currents. Moreover, we found that linoleate activates K\textsubscript{ATP} channels. Both the GPR40 signalling pathway and intracellular metabolic pathway are involved in linoleate-induced activation of K\textsubscript{ATP} channels (unpublished data). The inhibition of Ca\textsuperscript{2+}\textsubscript{(v)} channels and activation of K\textsubscript{ATP} channels may take part in FFAs-induced inhibition of GSIS in β-cells.

Although FFAs inhibit Ca\textsuperscript{2+}\textsubscript{(v)} channels and activate K\textsubscript{ATP} channels, they induce an increase in [Ca\textsuperscript{2+}], in β-cells. It was reported that FFAs stimulate an increase in [Ca\textsuperscript{2+}], in β-cells by activating GPR40, which links to the PLC/IP3 signalling pathway and stimulates calcium release from endoplasmic reticulum[17,21]. We found that linoleate stimulates an increase in [Ca\textsuperscript{2+}], in rat β-cells via two pathways. One pathway is mediated by GPR40, which leads to a transient increase in [Ca\textsuperscript{2+}], that is due to calcium release from the endoplasmic reticulum. Another pathway involves the intracellular metabolism of linoleate in β-cells. Inhibition of linoleate metabolism by acyl-CoA synthetase inhibitor Triacsin C blocks a metabolite-induced increase in [Ca\textsuperscript{2+}], in β-cells. We are now working on clarifying the FFA metabolites that are responsible for the induction of increased [Ca\textsuperscript{2+}], in β-cells, and on demonstrating which ion
channels are targets of FFA metabolites. In summary, FFAs influence activities of ion channels on the plasma membrane to inhibit GSIS, and, on the other hand, they mobilize intracellular calcium stores to increase [Ca\(^{2+}\)] and stimulate insulin secretion. This may be one reason for the hyperinsulinemia with blunted GSIS seen in obesity and at the early stage of type 2 diabetes.

**Adipokines influence insulin sensitivity of \(\beta\)-cells**

Insulin is critical to maintain the normal function of many cells, including the muscle, liver and fat cells. Insulin sensitivity of the cells is mainly regulated by adipokines. Some adipokines increase insulin sensitivity and others have the opposite effect. Insulin sensitivity of the cells is determined by this balance\(^{22}\). Adiponectin is the predominant adipokine which increases insulin sensitivity. Resistin, FFAs and TNF-\(\alpha\) are considered to be adipokines which decrease insulin sensitivity. Under the healthy condition, adiponectin is secreted sufficiently to maintain insulin sensitivity while the levels of resistin, FFAs and TNF-\(\alpha\) are low. In obesity and type 2 diabetes, adiponectin secretion decreases and the levels of resistin, FFAs and TNF-\(\alpha\) increase. This leads to insulin resistance in the various cell types.

Besides the peripheral action, insulin has an important autocrine action on \(\beta\)-cells, and is necessary for maintaining their normal function. For example, \(\beta\)-cell specific knock-out of insulin receptor substrate results in abnormal functioning of \(\beta\)-cells, which is similar to that seen in type 2 diabetes\(^{23}\). Our experiments showed that adipokines probably regulate insulin sensitivity of the \(\beta\)-cell itself and then influence \(\beta\)-cell function. We co-cultured the MIN6 insulin-secreting cells with 3T3-L1 adipocytes and found that 3T3-L1 adipocyte-derived factors induced dysfunction of MIN6 cells\(^{24}\). The phosphorylation of tyrosine kinase of the insulin receptor decreased in MIN6 cells after co-culture with 3T3-L1 adipocytes, indicating the impairment of insulin signalling in \(\beta\)-cells. The tyrosine kinase inhibitor, genistein, resulted in inhibition of glucokinase expression and Kir6.2 expression in MIN6 cells\(^{25}\). Moreover, treatment with genistein also leads to impairment of mouse primary cultured \(\beta\)-cells by inhibiting the expression of \(K_{ATP}\) and \(Ca^{2+}\)(\(\beta\)) channels, and by inhibiting exocytosis of insulin granules\(^{26}\). These results suggested that adipokines can reduce insulin sensitivity of \(\beta\)-cells and then impair \(\beta\)-cell function. However, the mechanisms involved in this process have not been clarified. We are now attempting to clarify the role of each adipokine, including leptin, adiponectin, resistin and TNF-\(\alpha\), in insulin action on \(\beta\)-cells.

Investigation into the role of adipokines in insulin resistance of \(\beta\)-cells provides new insight into the relationship between \(\beta\)-cell dysfunction and insulin resistance in type 2 diabetes, which are two major pathophysiological aspects of the disease. It is now accepted that adipokines induce insulin resistance in peripheral tissues such as the muscle, liver and fat, and \(\beta\)-cells compensate by secreting more insulin at the early stage of obesity. With the development of obesity, \(\beta\)-cells are exhausted and unable to compensate for insulin resistance and so type 2 diabetes occurs. Our study indicates that adipokines not only induce insulin resistance in peripheral tissues but also impair insulin action on the \(\beta\)-cell itself. Insulin resistance and \(\beta\)-cell dysfunction have one cause, the change of endocrine function of adipocytes.

**Role of adipokines in the changes of \(\beta\)-cell function in type 2 diabetes**

The endocrine function of adipocytes is dynamic, and the secretion of different adipokines changes with changes of metabolic condition. During the progression from the normal state to obesity and to severe diabetes, adipokines may contribute to the occurrence and development of \(\beta\)-cell dysfunction\(^{27}\). For example, leptin regulates FFA metabolism in \(\beta\)-cells and controls the contents of triglyceride in \(\beta\)-cells, which may prevent lipotoxicity of FFAs to \(\beta\)-cells under the normal condition. In obesity, although leptin levels increase, leptin resistance leads to less functioning of leptin to responding cells such as \(\beta\)-cells. The attenuation of leptin action on \(\beta\)-cells may deteriorate lipotoxicity of FFAs to \(\beta\)-cells. On the other hand, the attenuation of leptin action on \(\beta\)-cells may result in hypersecretion of insulin to compensate the insulin resistance. However, long-term hypersecretion of insulin will exhaust \(\beta\)-cells. Adiponectin may maintain insulin sensitivity of \(\beta\)-cells and protect them from abnormal secretion. Adiponectin levels decrease in obesity and type 2 diabetes, so its protective effect decreases, contributing to the development of type 2 diabetes. Elevation of FFAs in obesity also results in \(\beta\)-cell dysfunction by influencing activities of many ion channels and also glucose metabolism. Based on available information so far, influence of adipokines on pancreatic \(\beta\)-cell function is summarized in Fig.1.

The relationship between adipokines and \(\beta\)-cell function is complex. The changes that occur to \(\beta\)-cells during the progression from the normal state to obesity and to diabetes can be viewed hypothetically as five stages\(^{28}\).
Adipokines may have different effects on β-cell function at different stages. It is difficult to ascertain the effects of adipokines in each phase. Moreover, adipokines influence the expression and secretion of each other in an autocrine pathway. The network of adipokines makes it a challenge to elucidate the precise role of each factor in the regulation pathway. The network of adipokines makes it a challenge to elucidate the precise role of each factor in the regulation of β-cell function and in the contribution to β-cell dysfunction in the whole body.

Research into the effects of adipokines on β-cell function is at an early stage. Many more studies will be needed to demonstrate the role of adipokines in β-cell dysfunction, and indeed further adipokines may well be discovered. Therefore, the profile we provided in this review about the relationship between adipokines and β-cell function is but a piece of the jigsaw.

REFERENCES

1. Ahima RS. Adipose tissue as an endocrine organ. Obesity 2006; 14 (Suppl 5): 242S-249S.


