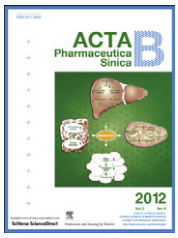
Acta Pharmaceutica Sinica B 2012;2(4):396–402

Institute of Materia Medica, Chinese Academy of Medical Sciences
Chinese Pharmaceutical Association

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

The role of fatty acid metabolism and lipotoxicity in pancreatic β-cell injury: Identification of potential therapeutic targets

Haopeng Yang, Xuejun Li*

Department of Pharmacology, School of Basic Medical Sciences, Peking University, Beijing 100191, China

Received 26 February 2012; revised 27 March 2012; accepted 28 April 2012

KEY WORDS

Lipotoxicity;
Pancreatic β-cells;
Insulin biosynthesis;
Insulin secretion;
Aquaporin

Abstract Over the last 20 years, intensive research has been focused on the specific mechanisms mediating the pancreatic β-cell injury. Both the decreased viability and the dysfunction of β-cells have become the key factors in the development of diabetes mellitus. Thus, it is of utmost importance to elucidate the discrete pathological changes in pancreatic β-cells within the context of the various lipotoxicity models. The goal of these studies is to generate evidence to improve not only the clinical treatment for diabetics, but also modulate the diet and activities of groups at high risk for diabetes. In this regard, we review the role of lipotoxicity in pancreatic β-cell injury and identify potential therapeutic targets in this cell model.

*Corresponding author. Tel.: +86 10 82802863; fax: +86 10 82801890.
E-mail address: xjli@bjmu.edu.cn (Xuejun Li).

Peer review under the responsibility of Institute of Materia Medica, Chinese Academy of Medical Sciences and Chinese Pharmaceutical Association.
http://dx.doi.org/10.1016/j.apsb.2012.05.003

Production and hosting by Elsevier

1. Introduction

Glucose and fatty acids are the two main nutrients in energy metabolism in most organisms, and are of particular interest in metabolic diseases such as diabetes and obesity. Though the specific pathogenesis of these metabolic diseases remains unclear, considerable evidence showing the deleterious effects of elevated glucose and fatty acid levels on pancreatic β-cell viability and function has been generated in recent years. Moreover, several hypotheses including glucotoxicity[1] and lipotoxicity[2] caused by chronic hyperglycemia and chronic dyslipidemia, respectively, have been well established. With prolonged exposure to these harmful conditions, pancreatic β-cell function and viability worsen over time, further impairing the metabolism of glucose and lipids in a detrimental cycle leading to further β-cell damage and, ultimately, diabetes.

Currently, a high fat diet has been considered as one of the causative factors in the decline of β-cell survival and function. The absorption of excess fatty acids can result in an elevated free fatty acid (FFA) level in blood and is worthy of close attention, as the extra FFAs that are not able to be appropriately metabolized can produce many negative effects *via* multiple pathways in pancreatic β-cells and may lead to β-cell apoptosis.

2. Fatty acid metabolism and lipotoxicity

Fatty acids and glycerol are mainly generated from triacylglycerol *via* catalysis by various lipases activated at the initial step of fatty acid metabolism, which is recognized as fat mobilization. Insulin and prostaglandin are able to inhibit fat mobilization, reduce the generation of fatty acid, and prevent the actions of many lipotropins such as adrenaline and glucagon, which can activate adenylate cyclase *via* cell membrane surface receptors and further stimulate the intracellular lipases *via* the phosphorylation of PKA. Free fatty acids are subsequently activated by long-chain fatty acid-CoA synthetase leading to the formation of long-chain fatty acid-CoA. In contrast to short-chain fatty acid-CoA (<C10), carnitine-acyl transferase (CAT) is needed for long-chain fatty acid-CoA transport into mitochondria. The activity of CAT-1, the rate-limiting enzyme of long-chain fatty acid-CoA transport and metabolism, is significantly increased in some conditions such as diabetes and chronic high fat or low sugar diet, indicating that CAT-1 could be recognized as a potential regulatory target in disorders of lipid metabolism. Therefore, chronic fatty-acid exposure could be deleterious through its various impacts on the intracellular fatty-acid metabolism.

Accordingly, malonyl-CoA, a product of glucose metabolism in the cytoplasm, possesses a beneficial effect by inhibiting CAT-1 activity[3], thereby blocking the transport of long-chain fatty acid-CoA into mitochondria. This would lead to the accumulation of long-chain fatty acid-CoA, potentially resulting in many deleterious effects on β-cell function and viability. The rise in apoptosis in INS-1E cells was partially reversed by the inclusion of the AMP-activated protein kinase (AMPK) agonist AICAR[4], which increased the oxidation of palmitate; during culture in low glucose palmitate-triggered apoptosis is accentuated both in human islets and β-cell lines when the carnitine-palmitoyl transferas-1 (CPT-1) inhibitor etomoxir was present. Etomoxir under these low glucose conditions decreased palmitate oxidation. However, in work by the group of Jun[5], treatment with carnitine and with carnitine-lipoic acid increased the mRNA levels of both CPT-1 and peroxisome proliferator activated receptor-γ (PPAR-γ), which controls lipid synthesis and storage in adipose tissue[6], in the presence of thiazolidinedione. Thus, carnitine and carnitine-lipoic acid can prevent lipotoxicity by increasing mitochondrial β-oxidation and reducing intracellular oxidative stress. Moreover, it has also been reported that CPT-1 was upregulated by the GW501516-induced activation of PPARδ, which further attenuated apoptosis and reduced basal insulin secretion induced by palmitate in HIT cells[7]. It was also observed that stearate, but not oleate, inhibited cell proliferation and induced cell death, and the activation of stearate in the form of stearoyl-CoA was a necessary element for the lipotoxic effects[8]. According to these data, it was concluded that the interruption of triacylglycerol synthesis in the endoplasmic reticulum, possibly because of the formation of a pool of oversaturated intermediates, represents a key event in the mechanism of saturated fatty acid-induced lipotoxicity.

3. Fatty acid metabolism and pancreatic β-cell damage

3.1. Ceramide formation

In recent years, research on cytokine-mediated cytotoxicity has gained extensive attention. Accumulating evidence reveals that the apoptosis of pancreatic β-cells has a direct relationship with ceramide formation (Fig. 1). An elevated level of ceramide has been found in the islets of Zucker Diabetic Fatty (ZDF) rats and the β-cell apoptosis mediated by the enhanced ceramide biosynthesis was effectively prevented by treatment with fumonisin B1, a ceramide synthase inhibitor, in these rats[9]. Moreover, C_2-ceramide, an analog of ceramide which can freely cross cell membranes, is able to potentiate the effects of palmitate on pro-apoptosis and anti-proliferation in β-cells[10].

3.2. Endoplasmic reticulum (ER) stress

The detailed mechanism of generation of ER stress induced by saturated fatty acids such as palmitate in β-cells mainly

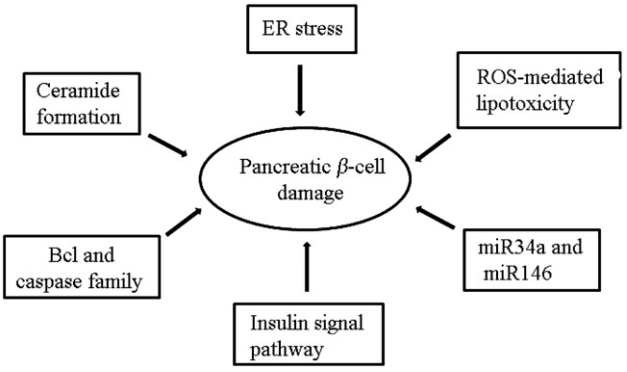


Figure 1 Cellular and molecular basis of pancreatic β-cell damage.