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Effect of the Endoplasmic Reticulum Stress on Diabetes Mellitus Type 2 in Hypothalamic Cells

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Abstract

Unfolded protein response is an adaptive cellular response that adjust protein translation rate to specific external stress. This response has been demonstrated to mediate programmed cell death and insulin resistance in pathophysiological conditions such as diabetes. More recently, it has been demonstrated that the pharmacological activation of UPR in the hypothalamus is able to stimulate food intake through mechanism not completely determined.

Keywords: Unfolded protein response (UPR); Hypothalamus; Glucocorticoids; Food intake; Diabetes mellitus

Introduction

The endoplasmic reticulum (ER) is a complex organelle in function and structure. It plays a critical role in several processes as synthesis, protein folding and transcription (1), it is responsible for the biosynthesis of almost one third of eukaryotic cells. The ER also contains the biggest concentrations of calcium ions (Ca^{2+}) inside the cell because of the active transportation of Ca^{2+} ions by calcium ATPases [1,2].

This organelle is a single environment for oxidative protein folding and modification after polypeptides transcription process. After the transcription process, the polypeptides are delivered to plasma membrane, intracellular organelles or extracellular environment [3].

Unfolded or misfolded proteins are retained within the ER. If the amount of protein increases excessively, there is a summoning of chaperones in an attempt of reestablishing the misfolded protein homeostasis. However, if balance is not reached, misfolded proteins are taken to cytoplasm through a mechanism called Endoplasmic Reticulum Associated Degradation (ERAD) and destroyed by proteasomes [4].

Recent researches point to a relation between the formation of misfolded proteins and several diseases incidence as such: diabetes, inflammation, neurodegenerative diseases, Alzheimer's, Parkinson's and bipolar disorder, also known as "conformational diseases" [4].

Diabetes Mellitus II (DMT2) is considered a multifactorial pathology related to obesity, dyslipidemia, endothelial dysfunction, inflammation and hypertension. DMT2 is one of the most common diseases in our world and considered a global healthy issue [5].

International Diabetes Federation (IDF) statistics indicates that, in 2013, 382 million people in the world have diabetes, this disease is responsible for about 4.6 million of deaths per year (IDF, Diabetes Atlas, 6th edition 2011). In 2030 diabetes incidence may reach 439 million adults [6].

Peripheral insulin resistance, glucose production dysfunction and inadequate insulin secretion are features of DMT2. This disease also changes the signalization pathway of the insulin, rising the concentration of endoplasmic reticulum stress as such: GRP78, XBP1s, this markers are found in the liver and in adipose tissue of fat patients with insulin resistance [7,8].

The accumulation of proteins inside the reticulum provides an overload of the folding capacity. These conditions incur in an imbalance of ER and cause its dysfunction and activate an adaptive called Unfolded Protein Response (UPR) [1,9].

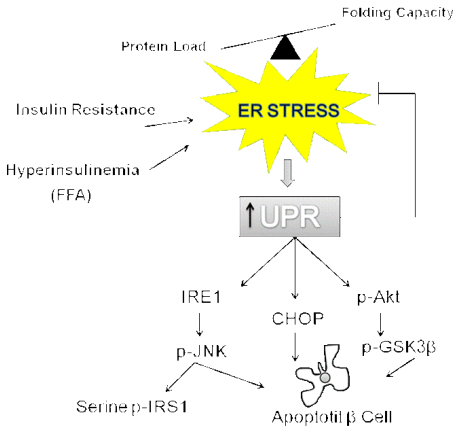

Figure 1: The activation of the UPR causes have activation of pro-apoptotic proteins that will cause to occur a decrease in the mass of beta cells in the pancreas as well as activation of proteins as p-JNK acting indirectly increasing the insulin resistance.

The main function of UPR is to reestablish the normal function of ER. The sensors that detect the ER stress are PERK, IRE1 and ATF6, these sensors act sometimes simultaneously and sometimes sequentially and control the transcription genes in stressed cells (Figure 1) [10].

Several researches point that β-cells failure and death occurs in consequence of unsolved ER stress leading to a chronicle activation of ER stress markers.

The stress response is a consequence of lifestyle. Inadvisable habits as smoking, air pollution and alcoholic drinks intake are related to development of metabolic diseases.

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