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REVIEW ARTICLE

Epigenetic Alterations Caused by Nutritional Stress During Fetal Programming of the Endocrine Pancreas

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Nutrition during critical periods of development is one of the pivotal factors in establishing a lifelong healthy metabolism. Different nutritional deficiencies such as a low availability of proteins in the maternal diet produce alterations in offspring that include changes in insulin and glucose metabolism, a decrease in the size and number of cells of pancreatic islets of Langerhans, and premature ageing of the secretory function of pancreatic β cells. Moreover, it has been reported that chronic nutritional stress is associated with epigenetic alterations in mechanisms of gene regulation during pancreatic development and function. These alterations can lead to dysfunctional states in pancreatic β cells, which in the long run are responsible for the onset of metabolic diseases like type 2 diabetes. The present review summarizes the most important evidence in relation to the participation of epigenetic mechanisms in the regulation of gene expression during the intrauterine programming of the endocrine pancreas in animal models. Such mechanisms include DNA methylation as well as modifications of histones and microRNAs (miRNAs). © 2015 IMSS. Published by Elsevier Inc.

Key Words: Malnutrition, β cells, Developmental programming, DNA methylation, Histones, miRNAs.

Introduction

Various clinical and experimental studies suggest that the nutritional environment in the womb and during the postnatal period strongly influences the health of an individual as an adult (1). It is known that when the fetus is exposed to adverse conditions *in utero*, it develops adaptive mechanisms to maintain homeostasis and assure survival. Nevertheless, these adaptations can increase the risk of disease in later stages of life (1).

Different situations of malnutrition such as a deficiency in the supply of proteins in the early stages of development produce changes in the structure and function of various organs. The pancreas is one of the organs that is negatively affected, leading later in life to metabolic disorders such as diabetes, dyslipidemia, hypertension and obesity (1,2). In this review we describe basic endocrine regulation by the pancreas and changes in epigenetic programming of the pancreatic endocrine function, particularly those related with alterations in carbohydrate metabolism of the offspring as a result of malnourished dams during pregnancy and lactation.

Physiological Role of the Endocrine Function of the Pancreas and Insulin Secretion

It is well known that the regulation of glucose levels in the blood constitutes one of the main pancreatic functions carried out by the endocrine cells of the islets of Langerhans. Hence, pancreatic β cells have a key role in the homeostasis of glucose, regulating insulin secretion according to the needs of the organism. As a consequence, insulin secretion is dependent on the metabolism and concentration of glucose.

In addition, glucose-induced insulin secretion is enhanced by the presence of other nutrients such as free

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fatty acids and amino acids. Nevertheless, these nutrients generally have little stimulatory effect on their own. A good description has already been published of the basic processes involved in glucose transport and insulin secretion, which take place after glucose uptake by β cells (3).

How a Low Dietary Supply of Proteins Programs Pancreatic Function and Carbohydrate Metabolism

Various studies with experimental animal models have demonstrated that a maternal diet deficient in proteins during critical periods of development (pregnancy and lactation) alters normal development of the pancreas and tissue sensitivity to the action of insulin (4–6). The latter condition in turn leads to hyperinsulinemia (7). However, the effects of protein restriction are dependent on the developmental window in which the restriction occurs.

A low-protein maternal diet during pregnancy and lactation produces an impaired glucose-stimulated insulin secretion (GSIS), a reduction in the mass of β cells, glucose intolerance, and insulin resistance in rat offspring. This protein restriction during pregnancy causes a reduction in the weight of the pancreas of newborns and a decrease in the quantity of β cells, a result of reduced replication and increased apoptosis (8–10). Moreover, there is a reduction in the size of the islets of Langerhans as well as the extent of pancreatic vascularization (9,11). If a low-protein gestational diet is followed by an adequate postnatal diet, the offspring show recovery of insulin secretion stimulated by glucose, the size of the islets, and the physiology of β cells (12). If protein deficiency takes place only during lactation, it produces a GSIS impairment and glucose intolerance in young adult life (13).

A low-protein maternal diet produces premature ageing of pancreatic β cells in the postnatal stage as well as a loss in sensitivity to glucose by pancreatic islets of Langerhans *in vitro*, causing alterations in glucose-stimulated insulin secretion (14,15). Additionally, this deficient maternal diet increases the duration of the cell cycle of pancreatic β cell cycle in offspring (8) and decreases the expression of genes for the production of insulin, glucokinase, the glucose transporter Glut2, and transcription factors like Pdx1 (pancreatic and duodenal homeobox-1) (10,16).

The aforementioned results constitute part of the evidence that a low-protein maternal diet modifies processes in offspring that have to do with the development and function of the endocrine pancreas as well as with carbohydrate metabolism and the sensitivity of tissues to the action of insulin. Recent research indicates that when a perturbed intrauterine environment leads to changes in the physiological function of pancreatic β cells, such changes are related to modifications in the epigenetic information and consequent cell reprogramming and function (17).

Epigenetic Factors in the Regulation of Gene Expression

The term "epigenetic" was first described in 1942 as phenotypical changes resulting from the interaction of an organism with its environment (18). Currently, this concept is understood as changes in the function of genes that occur without any change in the DNA sequence (19).

Epigenetic modifications are primarily responsible for the different patterns of gene expression that occur in certain cell types. Epigenetic changes within any given genotype provide certain phenotypical plasticity in the expression of genes, and this allows an organism to better respond to its environment and many different stimuli (2). Some epigenetic processes are related with DNA modifications such as methylation (20) and posttranslational modifications of histones (21). The latter include acetylation, methylation, phosphorylation, sumoylation, ubiquitination, and gene regulation by microRNAs (22).

The main epigenetic processes will be briefly described below to be discussed later in relation to the function of pancreatic β cells and carbohydrate metabolism.

DNA Methylation

DNA methylation (methylation of cytosines in the CpG dinucleotides) directly regulates gene transcription mainly by inhibiting the binding of transcription factors to specific regulatory regions (23,24). This epigenetic modification is associated with the formation of heterochromatin and therefore with the silencing of genes as well as with tissue-specific transcriptional regulation during cellular differentiation (25) and the recruitment of proteins that bind to the methylated cytosine (related to repressive remodeling of chromatin) (24).

Methylation of CpG dinucleotides (cytosine-guanine) consists of the enzymatic addition of a methyl group from S-adenosylmethionine to the carbon in position 5′ of the cytosine ring.

Approximately 70% of the CpG dinucleotides in the human genome are constitutively methylated, whereas the majority of the regions that contain unmethylated CpG dinucleotides are located in CpG islands. A CpG island is a region with at least 200 bp with a CG percentage $>50\%$ and an observed-to-expected CpG ratio $>60\%$. Approximately half of the genes of mammals have these CpG islands. These sites are kept methylated by the activity of methyltransferases (Dnmt) (25).

The majority of CpG islands remain unmethylated in transcriptionally active genes. However, under some circumstances they can be methylated *de novo*. This process is accompanied by local changes in histones and therefore in the structure of chromatin, modifications that vary according to the cellular context. Hence, CpG islands and the promoter that is subject to these modifications acquire a closed conformation that is incompatible with gene transcription (25).

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