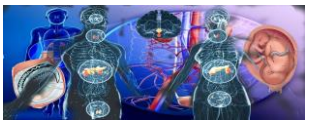
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A Pathophysiology of Insulin Resistance: Epidemiological Assessment

Malaisse J, Zuhlke H, Daniel G, De Lonlay T*, Ropero R, Riedel T, Cefalu E

Bushrod College of Science and Technology, Liberia

***Corresponding Author**: De Lonlay T, Bushrod College of Science and Technology, Liberia.

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Abstract

The centenary of insulin discovery represents an important opportunity to transform diabetes from a fatal diagnosis into a medically manageable chronic condition. Insulin is a key peptide hormone and mediates the systemic glucose metabolism in different tissues. Insulin resistance (IR) is a disordered biological response for insulin stimulation through the disruption of different molecular pathways in target tissues. Acquired conditions and genetic factors have been implicated in IR. Recent genetic and biochemical studies suggest that the dysregulated metabolic mediators released by adipose tissue including adipokines, cytokines, chemokines, excess lipids and toxic lipid metabolites promote IR in other tissues.

Keywords: Bovine insulin; biological activity; immunogenicity; lipid metabolism; glycogen synthesis; DNA synthesis

Introduction

Under normal physiological conditions, increased plasma glucose levels lead to increased insulin secretion and circulating insulin levels, thereby stimulating glucose transfer into peripheral tissues and inhibiting hepatic gluconeogenesis. Individuals with defected insulin-stimulated glucose uptake into muscle and adipocytes tissues, in addition to impaired insulin suppression of hepatic glucose output, are described as having 'insulin resistance'(IR). Several diseases are clinically associated with IR includes obesity, type 2 diabetes mellitus (T2DM), metabolic syndrome, cardiovascular disease, MAFLD, PCOS, and cancer.

The Insulin signaling and IR

Insulin is an endocrine peptide hormone with 51 amino acids and composed of an α and a β chain linked together as a dimer by two disulfide bridges along with a third intrachain disulfide bridge in the α chain. Insulin is released by pancreatic beta cells and is essential for glucose and lipid homeostasis. Insulin binds the insulin receptor (INSR) on the plasma membrane of target cells, leading to the recruitment/phosphorylation of downstream proteins, that primarily including insulin receptor substrate (IRS), PI3-kinase(PI3K), and AKT isoforms, that are largely conserved among insulin target tissues and that initiate the insulin response.

Insulin is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans and maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism and promoting cell division and growth through its mitogenic effects.

Insulin resistance is defined where a normal or elevated insulin level produces an attenuated biological response; classically this refers to impaired sensitivity to insulin mediated glucose disposal.

The Discovery of Insulin

In 1889 German scientists Minkowski and von Mering noted, from their experimental work with animals, that total pancreatectomy led to the development of severe diabetes. They hypothesised that a substance secreted by the pancreas was responsible for metabolic control. Others later refined this hypothesis, noting diabetes to be associated with destruction of the islets of Langerhans.

Structure and Chemical Properties of Insulin

Insulin was found to be a polypeptide in 1928 with its amino acid sequence identified in 1952. It is in fact a dipeptide, containing A and B chains respectively, linked by disulphide bridges, and containing 51 amino acids, with a molecular weight of 5802. Its iso-electric point is pH 5.5. The A chain comprises 21 amino acids and the B chain 30 amino acids. The A chain has an N-terminal helix linked to an anti-parallel C-terminal helix; the B chain has a central helical segment.

Synthesis and Release of Insulin

Insulin is coded on the short arm of chromosome 11 and synthesised in the β cells of the pancreatic islets of Langherhans as its precursor, proinsulin. Proinsulin is synthesised in the ribosomes of the rough endoplasmic reticulum (RER) from mRNA as pre-proinsulin. Pre-proinsulin is formed by sequential synthesis of a signal peptide, the B chain, the connecting (C) peptide and then the A chain comprising a single chain of 100 amino acids. Removal of the signal peptide forms proinsulin, which acquires its characteristic 3-dimensional structure in the endoplasmic reticulum.

Factors Influencing Insulin Biosynthesis and Release

Insulin secretion may be influenced by alterations in synthesis at the level of gene transcription, translation, and post-translational modification in the Golgi as well as by factors influencing insulin release from secretory granules. Longer-term modification may occur via influences on β cell mass anddifferentiation.

Mechanisms of Insulin Secretion:Increased levels of glucose induce the "first phase" of glucose-mediated insulin secretion by release of insulin from secretory granules in the β cell. Glucose entry into the β cell is sensed by glucokinase, which phosphorylates glucose to glucose-6-phosphate (G6P), generating ATP. Closure of K^+-ATP-dependent channels results in membrane depolarization and activation of voltage dependent calcium channels leading to an increase in intracellular calcium concentration; this triggers pulsatile insulin secretion.

Regulation and Mechanisms of Insulin Secretion at the Cellular Level

Synthesis and secretion of insulin is regulated by both nutrient and non-nutrient secretagogues, in the context of environmental stimuli and the interplay of other hormones. Nutrient secretagogues such as glucose appear to trigger insulin secretion from the β cell by increasing intracellular ATP and closing of K^+-ATP channels as outlined above.

Insulin Receptors and Insulin Binding

Insulin mediates its actions through binding to insulin receptors. The insulin receptor was first characterised in 1971. It consists of a heterotetramer consisting of 2 α and 2 β glycoprotein subunits linked by disulphide bonds and is located on the cell membrane. The gene coding for the insulin receptor is located on the short arm of chromosome 19. Insulin binds to the extracellular α subunit, resulting in conformational change enabling ATP to bind to the intracellular component of the β subunit.

Glucose Transporter Proteins

Glucose enters cells in an ATP-independent manner by means of glucose transporter proteins (GLUT), of which at least 5 subtypes have been identified Differing in characteristics such as *Km* for maximal glucose transport and insulin dependency, they enable different cell types to utilise glucose according to their specific functions. For example, most brain cells, having GLUT 1 as the principal transporter protein, are able to move glucose intracellularly at very low blood glucose blood concentrations without the need for insulin.

Lipid Metabolism

Insulin stimulates fatty acid synthesis in adipose tissue, liver and lactating mammary glands along with formation and storage of triglycerides in adipose tissue and liver. Fatty acid synthesis is increased by activation and increased phosphorylation of acetyl-CoA carboxylase, while fat oxidation is suppressed by inhibition of carnitine acyltransferase.

Conclusion

Insulin essentially provides an integrated set of signals allowing the balance between nutrient demand and availability. Impaired nutrition contributes to hyperlipidemia and insulin resistance causing hyperglycemia. This condition alters cellular metabolism and intracellular signaling that negatively impact cells. In the cardiomyocyte, this damage can be summarized into three actions: (1) alteration in insulin signaling. (2) Increased substrate accessibility, and (3) inflexibility in metabolism changes. All these effects induce cellular events including: (1) gene expression modifications, (2) hyperglycemia and dyslipidemia, (3) activation of oxidative stress and inflammatory response, (4) endothelial dysfunction, and (5) ectopic lipid accumulation, which, favored by obesity, perpetuates the metabolic deregulation.

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