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Review Article

Insulin; from Genome to Metabolome

Wala M Elfatih Mahgoub[1], Ibrahim A Ali[2]

[1]Department of Anatomy, Faculty of Medicine, The National Ribat University, Sudan. Email: walla_9@live.com
[2]Department of Physiology, Faculty of Medicine, The National Ribat University, Sudan. Email:hemamedicine@gmail.com

*Corresponding Author
Dr. Wala Mohamed Elfatih Mahgoub AbdAlla

Abstract: The preproinsulin precursor of insulin is encoded by the INS gene. A variety of mutant alleles with changes in the coding region have been identified. A read-through gene, INS-IGF2, overlaps with this gene at the 5' region and with the IGF2 gene at the 3' region. Several regulatory sequences in the promoter region of the human insulin gene bind to transcription factors. In general, the A-boxes bind to Pdx1 factors, E-boxes bind to NeuroD, C-boxes bind to MafA, and cAMP response elements to CREB. There are also silencers that inhibit transcription. The effects of insulin are initiated by its binding to a receptor present in the cell membrane. The receptor molecule contains an α- and β subunits. Two molecules are joined to form what is known as a homodimer. Insulin binds to the α-subunits of the homodimer, which faces the extracellular side of the cells. The β subunits have tyrosine kinase enzyme activity which is triggered by the insulin binding. This activity provokes the autophosphorylation of the β subunits and subsequently the phosphorylation of proteins inside the cell known as insulin receptor substrates (IRS). The phosphorylation of the IRS activates a signal transduction cascade that leads to the activation of other kinases as well as transcription factors that mediate the intracellular effects of insulin. Insulin affects the metabolism of different molecules in the body like CHO, proteins and lipids. It's essential for the continuity of life and the best example is, its strong homology in sequence of diverse species including humans, and how it preserved through different evolutionary periods of history.

Keywords: Insulin, Genome, Metabolome.

INTRODUCTION

Insulin (from the Latin word, *insula* meaning island) is a peptide hormone produced by beta cells of the pancreatic islets, and it is considered to be the main anabolic hormone of the body (Voet D, Voet JG, 2011) . It regulates the metabolism of carbohydrates, fats and protein by promoting the absorption of, especially, glucose from the blood into fat, liver and skeletal muscle cells. In these tissues the absorbed glucose is converted into either glycogen via glycogenesis or fats (triglycerides) via lipogenesis, or, in the case of the liver, into both (Stryer, Lubert, 1995). Glucose production and secretion by the liver is strongly inhibited by high concentrations of insulin in the blood (Sonksen P, Sonksen J, 2000). Circulating insulin also affects the synthesis of proteins in a wide variety of tissues. It is therefore an anabolic hormone, promoting the conversion of small molecules in the blood into large molecules inside the cells.

Beta Cells, Type 1 & 2 Diabetes Mellitus:

Beta cells are sensitive to glucose. When the glucose level is high, the beta cells secrete insulin into the blood; when glucose levels are low, secretion of insulin is inhibited (Koeslag, *et al.*, 2003). If beta cells are destroyed by an autoimmune reaction, insulin can no longer be synthesized or be secreted into the blood. This results in type 1 diabetes mellitus, which is characterized by abnormally high blood glucose concentrations, and generalized body wasting (American Society of Health-System pharmacists, 2009). In type 2 diabetes mellitus the destruction of beta cells is less pronounced than in type 1 diabetes and is not due to an autoimmune process. Instead there is an accumulation of amyloid in the pancreatic islets, which likely disrupts their anatomy and physiology (Koeslag, *et al.*, 2003). The pathogenesis of type 2 diabetes is not well understood but patients exhibit a reduced population of islet beta-cells, reduced secretory function of islet beta-cells that survive and peripheral tissue insulin resistance (Voet D, Voet JG, 2011). Type 2 diabetes is characterized by high rates of glucagon

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secretion into the blood which are unaffected by, and unresponsive to the concentration of glucose in the blood glucose. Insulin is still secreted into the blood in response to the blood glucose (Koeslag, *et al.,* 2003), as a result, the insulin levels, even when the blood sugar level is normal, are much higher than they are in healthy persons. There are a variety of treatment regimens, none of which is entirely satisfactory. When the pancreas's capacity to secrete insulin can no longer keep the blood sugar level within normal bounds, insulin injections are given.

Insulin Gene & Alleles

The preproinsulin precursor of insulin is encoded by the INS gene. A variety of mutant alleles with changes in the coding region have been identified. A read-through gene, INS-IGF2, overlaps with this gene at the 5' region and with the IGF2 gene at the 3' region (Bell GL, *et al.,* 1980).

Insulin Regulation

Several regulatory sequences in the promoter region of the human insulin gene bind to transcription factors. In general, the A-boxes bind to Pdx1 factors, E-boxes bind to NeuroD, C-boxes bind to MafA, and cAMP response elements to CREB. There are also silencers that inhibit transcription (Malloul D, *et al.,* 2002).

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Insulin as Metabolome:

Insulin Structure:

The human insulin protein is composed of 51 amino acids, and has a molecular mass of 5808 Da. It is a dimer of an A-chain and a B-chain, which are linked together by disulfide bonds. Insulin's structure varies slightly between species of animals. Insulin from animal sources differs somewhat in effectiveness (in carbohydrate metabolism effects) from human insulin because of these variations. Porcine insulin is especially close to the human version, and was widely used to treat type 1 diabetics before human insulin could be produced in large quantities by recombinant DNA technologies (Tof I, 1994), (Aggarwal SR, 2012).

The crystal structure of insulin in the solid state was determined by Dorothy Hodgkin. It is on the WHO Model List of Essential Medicines, the most important medications needed in a basic health system (19th WHO Model List of Essential Medicines, 2015).

The strong homology seen in the insulin sequence of diverse species suggests that it has been conserved across much of animal evolutionary history. The C-peptide of proinsulin, however, differs much more among species; it is also a hormone, but a secondary one. The primary structure of bovine insulin was first determined by Frederick Sanger in 1951 (Sanger F, Tuppy H, 1951). After that, this polypeptide was synthesized independently by several groups (Marglin A, 1966). The 3-dimensional structure of insulin was determined by X-ray crystallography in Dorothy Hodgkin's laboratory in 1969 (Blundell Tl, *et al.,* 1971).

Insulin is produced and stored in the body as a hexamer (a unit of six insulin molecules), while the active form is the monomer. The hexamer is an inactive form with long-term stability, which serves as a way to keep the highly reactive insulin protected, yet readily available. The hexamer-monomer conversion is one of the central aspects of insulin formulations for injection. The hexamer is far more stable than the monomer, which is desirable for practical reasons; however, the monomer is a much faster-reacting drug because diffusion rate is inversely related to particle size

Synthesis of Insulin:

In mammals, insulin is synthesized in the pancreas within the beta cells. One million to three million pancreatic islets form the endocrine part of the pancreas, which is primarily an exocrine gland. The endocrine portion accounts for only 2% of the total mass of the pancreas. Within the pancreatic islets, beta cells constitute 65–80% of all the cells.

Insulin consists of two polypeptide chains, the A- and B- chains, linked together by disulfide bonds. It is however first synthesized as a single polypeptide called preproinsulin in beta cells. Preproinsulin contains a 24-residue signal peptide which directs the nascent polypeptide chain to the rough endoplasmic reticulum (RER). The signal peptide is cleaved as the polypeptide is translocated into lumen of the RER, forming proinsulin (C. Roland, *et al.,* 2005). In the RER the proinsulin folds into the correct conformation and 3 disulfide bonds are formed. About 5–10 min after its assembly in the endoplasmic reticulum, proinsulin is transported to the trans-Golgi network (TGN) where immature granules are formed. Transport to the TGN may take about 30 min. Proinsulin undergoes maturation into active insulin through the action of cellular endopeptidases known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E (Steiner DF, Oyer PE, 1967). The endopeptidases cleave at 2 positions, releasing a fragment called the C-peptide, and leaving 2 peptide chains, the B- and A- chains, linked by 2 disulfide bonds. The cleavage sites are each located after a pair of basic residues (lysine-64 and arginine-65, and arginine-31 and −32). After cleavage of the C-peptide, these 2 pairs of basic residues are removed by the carboxypeptidase (Thomas E, 1993). The C-peptide is the central portion of proinsulin, and the primary sequence of proinsulin goes in the order "B-C-A" (the B and A chains were identified on the basis of mass and the C-peptide was discovered later). The resulting mature insulin is packaged inside mature granules waiting for metabolic signals (such as leucine, arginine, glucose and mannose) and vagal nerve stimulation to be

exocytosed from the cell into the circulation (Najjar S, 2001).

The endogenous production of insulin is regulated in several steps along the synthesis pathway; at transcription from the insulin gene, in mRNA stability, at the mRNA translation and in the posttranslational modifications.

Release of Insulin & Signal Transduction:

Beta cells in the islets of Langerhans release insulin in two phases. The first-phase release is rapidly triggered in response to increased blood glucose levels, and lasts about 10 minutes. The second phase is a sustained, slow release of newly formed vesicles triggered independently of sugar, peaking in 2 to 3 hours. This is the primary mechanism for release of insulin. Other substances known to stimulate insulin release include the amino acids arginine and leucine, parasympathetic release of acetylcholine (acting via the phospholipase C pathway), sulfonylurea, cholecystokinin (CCK, also via phospholipase C) (Cawston EE, Miller LJ, 2010) and the gastrointestinally derived incretins, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).

Release of insulin is strongly inhibited by norepinephrine (noradrenaline), which leads to increased blood glucose levels during stress. It appears that release of catecholamines by the sympathetic nervous system has conflicting influences on insulin release by beta cells, because insulin release is inhibited by α_2-adrenergic receptors (Nakaki T, *et al.*, 1980) and stimulated by β_2-adrenergic receptors (Layden BT, Lowe WL, 2010). The effects of insulin are initiated by its binding to a receptor present in the cell membrane. The receptor molecule contains an α- and β subunits. Two molecules are joined to form what is known as a homodimer. Insulin binds to the α-subunits of the homodimer, which faces the extracellular side of the cells. The β subunits have tyrosine kinase enzyme activity which is triggered by the insulin binding. This activity provokes the autophosphorylation of the β subunits and subsequently the phosphorylation of proteins inside the cell known as insulin receptor substrates (IRS). The phosphorylation of the IRS activates a signal transduction cascade that leads to the activation of other kinases as well as transcription factors that mediate the intracellular effects of insulin.

CONCLUSION

Insulin affects the metabolism of different molecules in the body like CHO, proteins and lipids. It's essential for the continuity of life and the best example is, its strong homology in sequence of diverse species including humans, and how it preserved through different evolutionary periods of history.

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