INTRODUCTION

Insulin is an anabolic hormone secreted by the endocrine pancreas.

• Endocrine pancreas: – Microscopic cluster of cells – Islets of Langerhans – 4 major cell types β-cells Insulin storage and anabolic hormone. α-cells Glucagon hyperglycemic facilitator δ-cells Somatostatin universal inhibitor of secretory cells. PP-cells Pancreatic polypeptide stim. secretion of GI & intestinal enzymes inhibit intestinal motility.

History. • 1921 – Dr. Frederick banting and Charles best discovered insulin

• 1923 – banting and best received nobel prize.

• 1956 – chemical structure of insulin was fully worked out by Sanger.

Chemistry. • Polypeptide containing 51 amino acids arranged in 2 chains A & B.

• A chain contains 21 AA.

• B chain contain 30 AA.

• linked by disulphide bonds.

. **Biosynthesis. • Insulin is** produced by the beta cell of pancreas

. • β-cells Islets of Langerhans Rough endoplasmic reticulum Preproinsulin Golgi apparatus Prohormone Convertase Proinsulin Secretory granules insulin + c- peptide.

Secretion. • Important trigger for the release of insulin is glucose.

• Intracellular transport of glucose is mediated by GLUT-2, an insulin- independent glucose transporter in β cells. Glucose undergoes oxidative metabolism in the β cell to yield ATP. ATP inhibits an inward rectifying potassium channel receptor on the β-cell surface; the receptor itself is a dimeric complex of the sulfonylurea receptor and a K+-channel protein. Inhibition of this receptor leads to membrane depolarization, influx of Ca2+ ions, and release of stored insulin from β cells.

Secretion.

Insulin receptor. • Combination of four subunits held together by disulphide bonds.

Two extracellular α subunits- lie entirely outside the cell -has insulin binding site.

Two transmembrane β subunits- penetrate through the membrane, protruding into the cytoplasm. -tyrosine protein kinase activity,

Insulin signalling • . Insulin binding to its receptor stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, such as insulin receptor substrates (IRS) (Fig. 2). IRS and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, resulting in the widespread metabolic and mitogenic effects of insulin. As an example, activation of the

phosphatidylinositol-3'-kinase (PI-3-kinase) pathway stimulates translocation of glucose transporters (e.g., GLUT4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signaling pathways induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes.

Insulin signalling cascade.

Regulation of insulin secretion. • Secretion of insulin from beta cells is regulated by the following mechanisms: Chemical Hormonal Neural mechanism

Chemical mechanism. • Mainly by glucose entry into the cells. • Other nutrients : amino acids, fatty acids and ketone bodies. • Note. – Glu induces a brief pulse of insulin output within 2min. – Glu and other nutrients are more effective when given orally than i.v coz they generate chemical signals "incretins" from the gut which act directly on β cells. immediate release of insulin.

Hormonal regulation. • Intra-islet paracrine interactions between the hormones produced by islets of langerhans. insulin glucagon somatostatin β cells α cells D cells

Cont.. • Growth hormone, corticosteroids thyroxine modify insulin release in response to glucose • PGE has shown to inhibit insulin release.

Neural regulation. • Islets of langerhans are richly innervated by both adrenergic and cholinergic nerves.

• α2 adrenergic receptor- inhibit insulin release.

• β2 adrenergic and vagal nerve-enhance insulin release.

• Note. – Any condition that activates the sympathetic branch of the ANS such as hypoxia, hypoglycemia, hypothermia suppresses the secretion of insulin by stimulation of α2 receptors.

Principle actions of insulin

• Rapid (seconds) Inc. transport of glu, AA and k^+ into insulin sensitive cells. Intermediate (minutes) Stimulation of protein synthesis. Inhibition of protein degradation Activation of glycolytic enzymes and glucogen synthesis. Inhibition of phosphorylase and gluconeogenic enzymes.

• Delayed (hrs)

• Inc. in mRNAs for lipogenic and other enzymes.

Effects of insulin on target tissues.

Fate of insulin. • It's a peptide: gets degraded in g.i.t when given orally. • Injected insulin or that released from pancreas is metabolized by liver and to a smaller extend in kidney and muscles.

• 50% of insulin entering portal vein is inactivated in the first passage through liver.

• Plasma t-half is 5-9 min.

Diabetes mellitus. • A chronic metabolic disorder characterized by hyperglycemia, glycosuria, hyperlipaemia..

• Results from a defective or deficient insulin secretory response

• Multi-organ damage – Kidney, eyes, nerves and blood vessels

• Two major types: 1.type 1 or insulin dependant DM. 2.type 2 or noninsulin dependant DM.

Type 1 DM. • "Insulin dependent diabetes" – both type 1 and type 2 DM eventually require insulin

• Early onset

• < 20 yrs.

• "juvenile diabetes" Immune mediated destruction of β-cells – by T-cells & – Autoantibodies.

• Decreased blood insulin

.**Type 2 DM. •** "Non-insulin dependent diabetes" – may eventually require insulin • Not immune mediated

• Later onset > 30 yrs.-old