Diabetes Mellitus and Insulin

Diabetes mellitus, recognised since ancient times, is named for the production of sugary urine in profuse volumes. Diabetes is rapidly increasing to epidemic proportions (in step with obesity, and 'insulin resistance' is closely related to obesity), and its consequences are dire – especially accelerated atherosclerosis (myocardial and cerebral infarction, gangrene or limb amputation), kidney failure, neuropathy and blindness. Diabetes, along with obesity, hypertension, dyslipidaemia, and fatty infiltration of the liver, comprise a 'metabolic syndrome', a common pathological cluster and a rapidly growing problem that is associated with many life-threatening conditions.

Type I DM (IDDM) is treated only by insulin whereas in the treatment of type II DM (NIDDM), orally active drugs are tried first in uncomplicated cases. Insulin is used in all the patients of type I diabetes mellitus and in the patients of type II diabetes who are not controlled with oral hypoglycemic agents (OHA), in pregnancy, to tide over stressful situations (like surgery) and in complications (like ketoacidosis and hyperosmolar coma).

Insulin

It was discovered by Banting and Best in 1921. It consists of 51 amino acids arranged in two chains; A (21 amino acids) and B (30 amino acids). Insulin was the first protein for which the amino acid sequence was determined (by Sanger's group in Cambridge in 1955). It consists of two peptide chains (of 21 and 30 amino acid residues) linked by two disulfide bonds. Like other peptide hormones, insulin is synthesised as a precursor (preproinsulin) in the rough endoplasmic reticulum. Preproinsulin is transported to the Golgi apparatus, where it undergoes proteolytic cleavage to proinsulin and then to insulin plus a fragment of uncertain function called C-peptide

Half life of insulin in plasma is about 5-6 minutes. Glucose is the main stimulus for the release of insulin from the β cells of pancreas. Glucose stimulates membrane glucose transporters (GLUT-2) and inhibits ATP sensitive K+ channels; factors that are responsible for the depolarization of β cells and release of insulin. α_2 receptor stimulation inhibits insulin secretion whereas β2 agonists and vagal stimulation enhances insulin release. Somatostatin inhibits whereas glucagon stimulates the release of insulin. Adrenergic system regulates insulin release via α_2 (decreases) and β_2 (increases) receptors.

Actions of Insulin:

1. It decreases blood glucose by

   • Stimulating the entry of glucose in muscle and fat (by increasing the synthesis of GLUT 4).

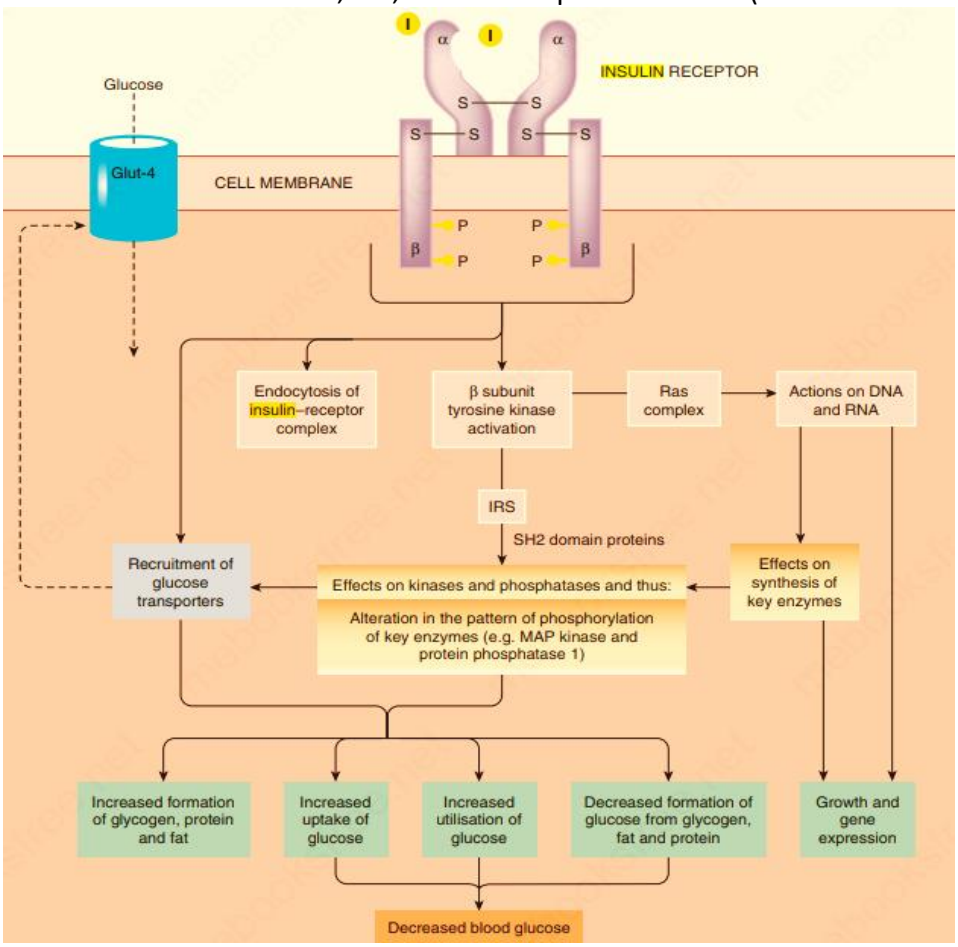
   • Inhibiting glycogenolysis (by inhibiting phosphorylase) and gluconeogenesis (by inhibiting phosphoenol pyruvate carboxykinase). These processes are inhibited at lower concentration of insulin.

   • Increasing glycolysis (by stimulation of glucokinase) and glycogenesis (by stimulating glycogen synthase). These require more concentration of insulin.

2. It inhibits lipolysis and thus favors triglyceride deposition. Insulin increases synthesis of fatty acid and triglyceride in adipose tissue and in liver. It inhibits lipolysis, partly via dephosphorylation – and hence inactivation – of lipases. It also inhibits the lipolytic actions of adrenaline, growth hormone and glucagon by opposing their actions on adenylyl cyclase.

3. Insulin stimulates uptake of amino acids into muscle and increases protein synthesis. It also decreases protein catabolism and inhibits oxidation of amino acids in the liver. Other metabolic effects of insulin include transport into cells of K+ , Ca2+ , nucleosides and inorganic phosphate.

Fig.: Insulin signalling pathways. I, insulin; Glut-4, an insulin-sensitive glucose transporter present in muscle and fat cells; IRS, insulin receptor substrate (several forms: 1–4).



Mechanism of action: Insulin binds to a specific receptor on the surface of its target cells. The receptor is a large transmembrane glycoprotein complex belonging to the tyrosine kinase-linked type 3 receptor superfamily and consisting of two α and two β subunits (see above Fig.). Occupied receptors aggregate into clusters, which are subsequently internalised in vesicles, resulting in downregulation. Internalised insulin is degraded in lysosomes, but the receptors are recycled to the plasma membrane.

Insulin Preparations

Conventional preparations are obtained from pork and beef. Addition of zinc makes it long acting Human insulin (humulin) is prepared by recombinant DNA technology and has rapid absorption (from s.c. route) and shorter duration of action. Recently ultrashort acting (insulin lispro, glulisine and aspart) and ultralong acting (insulin detemir and glargine) preparations have also been developed

S.No.	Type	Insulin	Onset	Duration	Comment
1	Rapid Acting	Lispro	15-20 min	3-4 hours	Present as monomers
		Apart	15-20 min	3-4 hours	Most rapidly acting
		Glulisine	15-20 min	3-4 hours	
2	Short Acting	Regular (Crystalline zinc)	30-60 min	5-8 hours	Regular insulin can be given i.v.
		Semi-Lente	1-2 hours	8-12 hours	
3.	Intermediate Acting	NPH or Isophane	2 hours	16-18 hours	
		Lente	2 hours	16-20 hours	
4.	Long Acting	Ultra–Lente	4-6 hours	20-36 hours	
		Glargine	4-6 hours	15-24 hours	Supplied at pH = 4
		Detemir	2-4 hours	20-24 hours	
		Degludec	2-4 hours	24-40 hours	