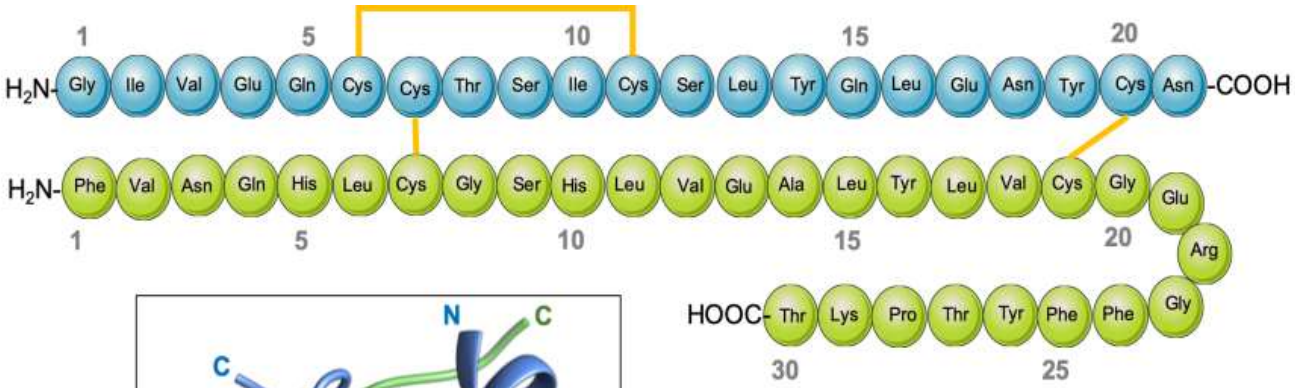
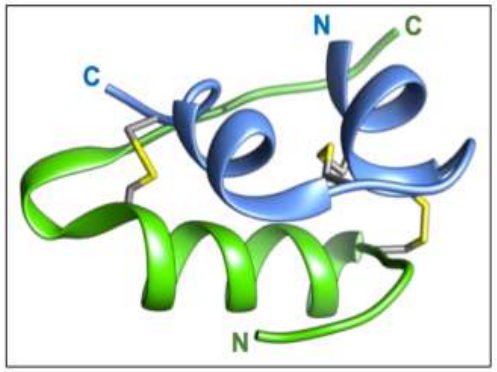
Endocrine function of pancreas is performed by the islets of Langerhans. The cells which make up the pancreatic islets (islets of Langerhans) are found in clusters irregularly distributed throughout the substance of the pancreas. Human pancreas contains about 1 to 2 million islets.

Islets of Langerhans consist of four types of cells:

1. A cells or α-cells, which secrete glucagon
2. B cells or β-cells, which secrete insulin
3. D cells or δ-cells, which secrete somatostatin
4. F cells or PP cells, which secrete pancreatic polypeptide.

INSULIN





Source of secretion

Insulin is secreted by B cells or the β-cells

in the islets of Langerhans of pancreas.

Chemistry and half-life

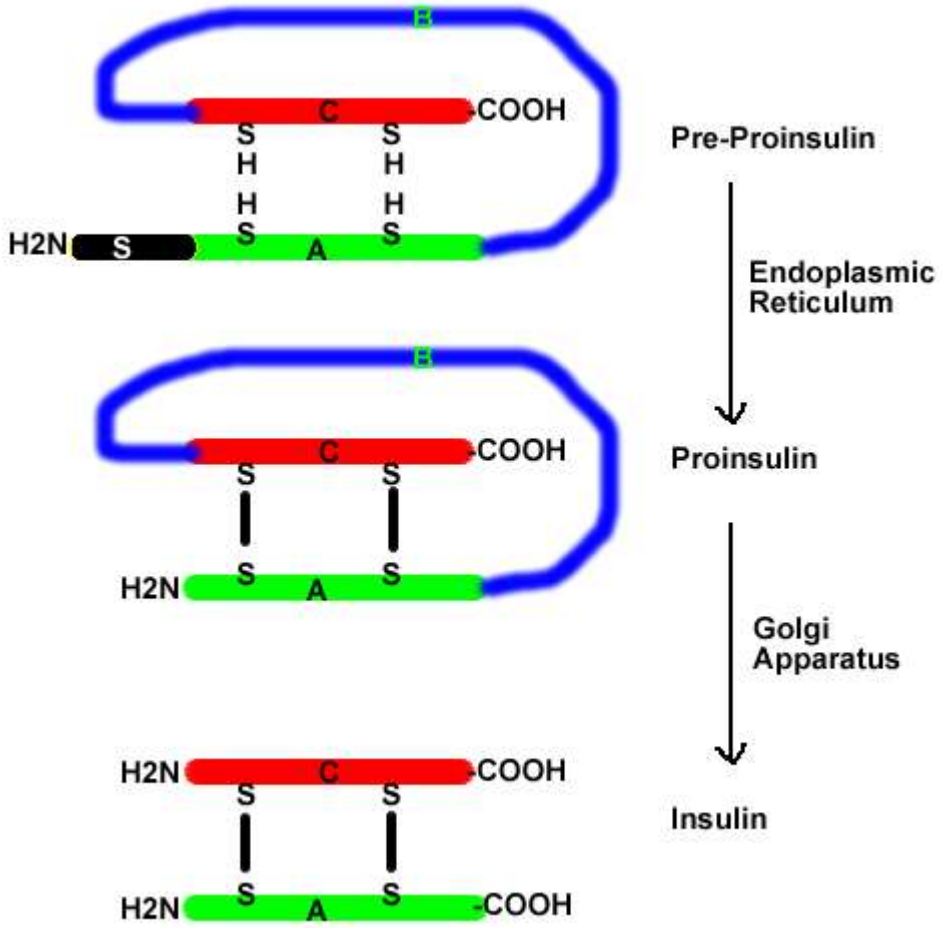
Insulin is a polypeptide with 51 amino acids and a molecular weight of 5,808. It has two amino acid chains (α and β chains), which are linked by disulfide bridges. The α-chain of insulin contains 21 amino acids and β-chain contains 30 amino acids. The biological half-life of insulin is 5 minutes.

Plasma level

Basal level of insulin in plasma is 10 μU/mL.

Synthesis of insulin

Synthesis of insulin occurs in the rough endoplasmic reticulum of β-cells in islets of Langerhans.



Actions of insulin

Insulin is the important hormone that is concerned with the regulation of carbohydrate metabolism and blood glucose level. It is also concerned with the metabolism of proteins and fats.

1. On Carbohydrate Metabolism

Insulin is the only antidiabetic hormone secreted in the body, i.e. it is the only hormone in the body that reduces blood glucose level. Insulin reduces the blood glucose level by its following actions on carbohydrate metabolism:

- Increases transport and uptake of glucose by the cells
- Promotes peripheral utilization of glucose
- Promotes storage of glucose – glycogenesis
- Inhibits glycogenolysis
- Inhibits gluconeogenesis

On Protein Metabolism

Insulin facilitates the synthesis and storage of proteins and inhibits the cellular utilization of proteins by the following actions:

i. Facilitating the transport of amino acids into the cell from blood, by increasing the permeability of cell membrane for amino acids

ii. Accelerating protein synthesis by influencing the transcription of DNA and by increasing the translation of mRNA

iii. Preventing protein catabolism by decreasing the activity of cellular enzymes which act on proteins

iv. Preventing conversion of proteins into glucose.

Thus, insulin is responsible for the conservation and storage of proteins in the body.

On Fat Metabolism

Insulin stimulates the synthesis of fat. It also increases the storage of fat in the adipose tissue.

Actions of insulin on fat metabolism are:

i. Synthesis of fatty acids and triglycerides

Insulin promotes the transport of excess glucose into cells, particularly the liver cells. This glucose is utilized for the synthesis of fatty acids and triglycerides. Insulin promotes the synthesis of lipids by activating the enzymes which convert:

a. Glucose into fatty acids b. Fatty acids into triglycerides.

ii. Transport of fatty acids into adipose tissue Insulin facilitates the transport of fatty acids into the adipose tissue.

iii. Storage of fat

Insulin promotes the storage of fat in adipose tissue by inhibiting the enzymes which degrade the triglycerides.

On Growth

Along with growth hormone, insulin promotes growth of body by its anabolic action on proteins.

It enhances the transport of amino acids into the cell and synthesis of proteins in the cells.

It also has the **protein-sparing effect,** i.e. it causes conservation of proteins by increasing the glucose utilization by the tissues.

Mode of action

On the target cells, insulin binds with the receptor protein and forms the insulin-receptor complex. This complex executes the action by activating the intracellular enzyme system.

Insulin Receptor

Insulin receptor is a glycoprotein with a molecular weight of 340,000. It is present in almost all the cells of the body.

Subunits of insulin receptor

Insulin receptor is a **tetramer,** formed by four glycoprotein subunits (two α-subunits and two β-subunits). The α-subunits protrude out of the cell and the β-subunits protrude inside the cell. The α and β subunits are linked to each other by disulfide bonds. Intracellular surfaces of α-subunits have the enzyme activity – **protein kinase (tyrosine kinase)** activity.

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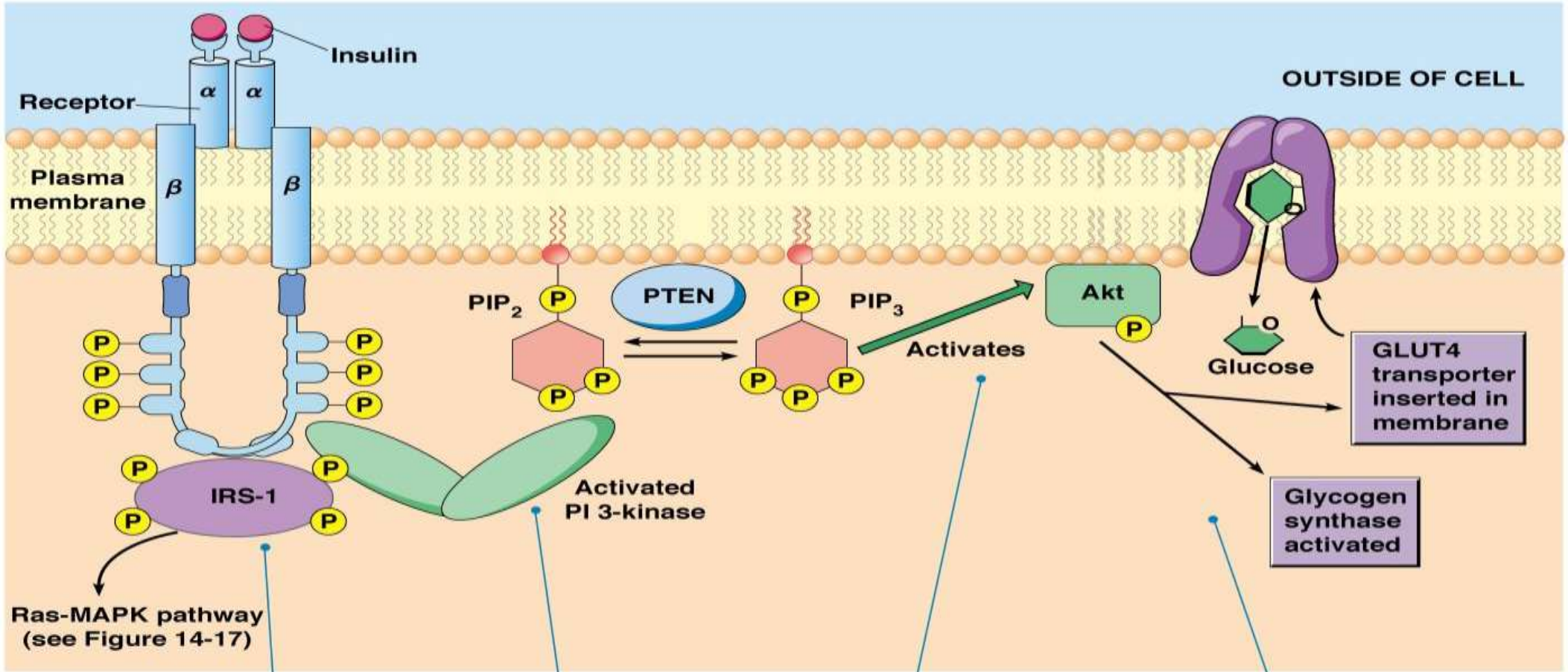
When insulin binds with α-subunits of the receptor protein, the tyrosine kinase at the β-subunit (that protrudes into the cell) is activated by means of autophosphorylation.

Activated tyrosine kinase acts on many intracellular enzymes by phosphorylating or dephosphorylating them so that some of the enzymes are activated while others are inactivated.

Thus, insulin action is exerted on the target cells by the activation of some intracellular enzymes and by the inactivation of other enzymes.



1. When the insulin receptor binds insulin, the activated receptor phosphorylates the IRS-1 protein. IRS-1 can lead to recruitment of GRB2, activating the Ras pathway.

2. IRS-1 activates PI 3-kinase, which catalyzes the addition of a phosphate group to the membrane lipid PIP_2, thereby converting it to PIP_3. PTEN can convert PIP_3 back to PIP_2.

3. PIP_3 binds a protein kinase called Akt, which is activated by other protein kinases.

4. Akt catalyzes phorphorylation of key proteins, leading to an increase in glycogen synthase activity and recruitment of the glucose transporter, GLUT4, to the membrane

REGULATION OF INSULIN SECRETION

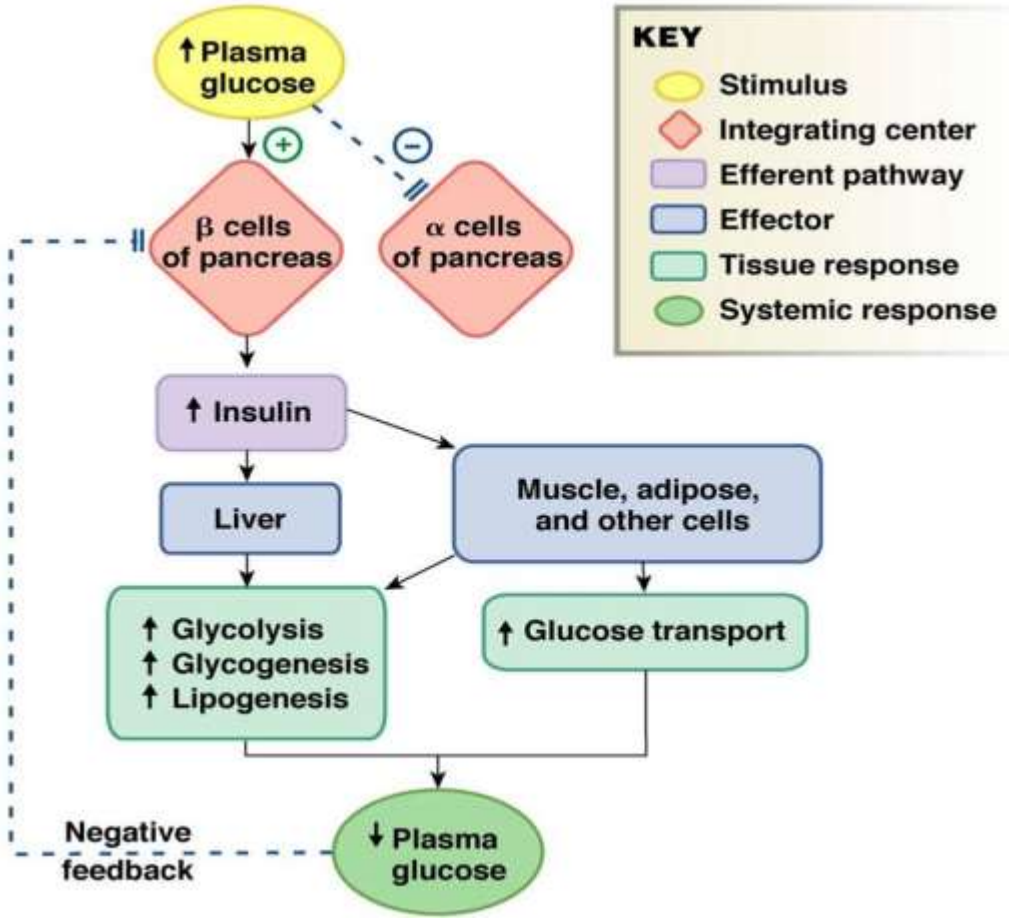
Insulin secretion is mainly regulated by blood glucose level. In addition, other factors like amino acids, lipid deriva tives, gastrointestinal and endocrine hormones and autonomic nerve fibers also stimulate insulin secretion.

1. Role of Blood Glucose Level

When blood glucose level is normal (80 to 100 mg/dL), the rate of insulin secretion is low (up to 10 μU/minute).

When blood glucose level increases between 100 and 120 mg/dL, the rate of insulin secretion rises rapidly to 100 μU/minute.

When blood glucose level rises above 200 mg/dL, the rate of insulin secretion also rises very rapidly up to 400 μU/minute.



Biphasic effect of glucose

Action of blood glucose on insulin secretion is biphasic.

i. Initially, when blood glucose level increases after a meal, the release of insulin into blood increases rapidly. Within few minutes, concentration of insulin in plasma increases up to 100 μU/mL from the basal level of 10 μU/mL.

It is because of release of insulin that is stored in pancreas. Later, within 10 to 15 minutes, the insulin concentration in the blood reduces to half the value, i.e. up to 40 to 50 μU/mL of plasma.

ii. After 15 to 20 minutes, the insulin secretion rises once again. This time it rises slowly but steadily. It reaches the maximum between 2 and 2½ hours. The prolonged increase in insulin release is due to the formation of new insulin molecules continuously from pancreas.

Role of Proteins

Excess amino acids in blood also stimulate insulin secretion. Potent amino acids are **arginine** and **lysin.** Without any increase in blood glucose level, the amino acids alone can cause a slight increase in insulin secretion. However, amino acids potentiate the action of glucose on insulin secretion so that, in the presence of amino acids, elevated blood glucose level increases insulin secretion to a great extent.

Role of Lipid Derivatives

The β-ketoacids such as acetoacetate also increase insulin secretion.

Role of Gastrointestinal Hormones

Insulin secretion is increased by some of the gastrointestinal hormones such as gastrin, secretin, CCK and GIP.

Role of Endocrine Hormones

Diabetogenic hormones like glucagon, growth hormone and cortisol also stimulate insulin secretion, indirectly.

All these diabetogenic hormones increase the blood glucose level, which stimulates β-cells of islets of Langerhans. So insulin secretion is increased.

Prolonged hypersecretion of these hormones causes exhaustion of β-cells, resulting in diabetes mellitus.

Role of Autonomic Nerves

Stimulation of parasympathetic nerve to the pancreas (right vagus) increases insulin secretion. Chemical neurotransmitter involved is acetylcholine. Stimulation of sympathetic nerves inhibits the secretion of insulin and the neurotransmitter is noradrenaline.

However, the role of these nerves on the regulation of insulin secretion under physiological conditions is not clear.