PANCREAS

The **pancreas** is an organ of the digestive system and endocrine system of vertebrates. In humans, it is located in the abdomen behind the stomach and functions as a gland. The pancreas has both an endocrine and a digestive exocrine function. As an endocrine gland, it functions mostly to regulate blood sugar levels, secreting the hormones insulin, glucagon, somatostatin, and pancreatic polypeptide. As a part of the digestive system, it functions as an exocrine gland secreting pancreatic juice into the duodenum through the pancreatic duct. This juice contains bicarbonate, which neutralizes acid entering the duodenum from the stomach; and digestive enzymes, which break down carbohydrates, proteins, and fats in food entering the duodenum from the stomach.

Inflammation of the pancreas is known as pancreatitis, with common causes including chronic alcohol use and gallstones. Because of its role in the regulation of blood sugar, the pancreas is also a key organ in diabetes mellitus. Pancreatic cancer can arise following chronic pancreatitis or due to other reasons, and carries a very poor prognosis, as it is often identified when it has spread to other areas of the body.

STRUCTURE

The pancreas is an organ that in humans lies in the abdomen, stretching from behind the stomach to the left upper abdomen near the spleen. In adults, it is about 12–15 centimetres (4.7–5.9 in) long, lobulated, and salmon-coloured in appearance.

Anatomically, the pancreas is divided into a head, neck, body, and tail. The pancreas stretches from the inner curvature of the duodenum, where the head surrounds two blood vessels: the superior mesenteric artery, and vein. The longest part of the pancreas, the body, stretches across behind the stomach, and the tail of the pancreas ends adjacent to the spleen.

Two ducts, the main pancreatic duct and a smaller accessory pancreatic duct, run through the body of the pancreas, joining with the common bile duct near a small ballooning called the ampulla of Vater. Surrounded by a muscle, the sphincter of Oddi, this opens into the descending part of the duodenum.

ULTRASTUCTURE:

The pancreas contains tissue with an endocrine and exocrine role, and this division is also visible when the pancreas is viewed under a microscope.

1.The majority of pancreatic tissue has a digestive role. The cells with this role form clusters (Latin: acini) around small ducts, and are arranged in lobes that have thin fibrous walls.

2.The cells of each acinus secrete inactive digestive enzymes called zymogens into the small intercalated ducts which they surround. In each acinus, the cells are pyramid-shaped and situated around the

intercalated ducts, with the nuclei resting on the basement membrane, a large endoplasmic reticulum, and a number of zymogen granules visible within the cytoplasm.

3.The intercalated ducts drain into larger intralobular ducts within the lobule, and finally interlobular ducts. The ducts are lined by a single layer of column-shaped cells. There is more than one layer of cells as the diameter of the ducts increases.

4.The tissues with an endocrine role within the pancreas exist as clusters of cells called pancreatic islets (also called islets of Langerhans) that are distributed throughout the pancreas.[

5.Pancreatic islets contain alpha cells, beta cells, and delta cells, each of which releases a different hormone. These cells have characteristic positions, with alpha cells (secreting glucagon) tending to be situated around the periphery of the islet, and beta cells (secreting insulin) more numerous and found throughout the islet..Enterochromaffin cells are also scattered throughout the islets.

6. Islets are composed of up to 3,000 secretory cells, and contain several small arterioles to receive blood, and venules that allow the hormones secreted by the cells to enter the systemic circulation.

FUNCTION

The pancreas is involved in blood sugar control and metabolism within the body, and also in the secretion of substances (collectively pancreatic juice) that help digestion. These are divided into an "endocrine" role, relating to the secretion of insulin and other substances within pancreatic islets that help control blood sugar levels and metabolism within the body, and an "exocrine" role, relating to the secretion of enzymes involved in digesting substances in the digestive tract.

Cells within the pancreas help to maintain blood glucose levels (homeostasis). The cells that do this are located within the pancreatic islets that are present throughout the pancreas. When blood glucose levels are low, alpha cells secrete glucagon, which increases blood glucose levels. When blood glucose levels are high beta cells secrete insulin to decrease glucose in blood. Delta cells in the islet also secrete somatostatin which decreases the release of insulin and glucagon.

Glucagon acts to increase glucose levels by promoting the creation of glucose and the breakdown of glycogen to glucose in the liver. It also decreases the uptake of glucose in fat and muscle. Glucagon release is stimulated by low blood glucose or insulin levels, and during exercise.[13] Insulin acts to decrease blood glucose levels by facilitating uptake by cells (particularly skeletal muscle), and promoting its use in the creation of proteins, fats and carbohydrates. Insulin is initially created as a precursor form called preproinsulin. This is converted to proinsulin and cleaved by C-peptide to insulin which is then stored in granules in beta cells. Glucose is taken into the beta cells and degraded. The end effect of this is to cause depolarisation of the cell membrane which stimulates the release of the insulin.

The main factor influencing the secretion of insulin and glucagon are the levels of glucose in blood plasma.Low blood sugar stimulates glucagon release, and high blood sugar stimulates insulin release. Other factors also influence the secretion of these hormones. Some amino acids, that are byproducts of the digestion of protein, stimulate insulin and glucagon release. Somatostatin acts as an inhibitor of both insulin and glucagon. The autonomic nervous system also plays a role. Activation of Beta-2 receptors of the sympathetic nervous system by catecholamines secreted from sympathetic nerves stimulates secretion of insulin and glucagon, whereas activation of Alpha-1 receptors inhibits secretion.M3 receptors of the parasympathetic nervous system act when stimulated by the right vagus nerve to stimulate release of insulin from beta cells.

INSULIN

Structure:

a) A single protein (monomer) of human insulin is composed of 51 amino acids, and has a molecular mass of 5808 Da. The molecular formula of human insulin is C257H383N65O77S6. It is a combination of two peptide chains (dimer) named an A-chain and a B-chain, which are linked together by two disulfide bonds.

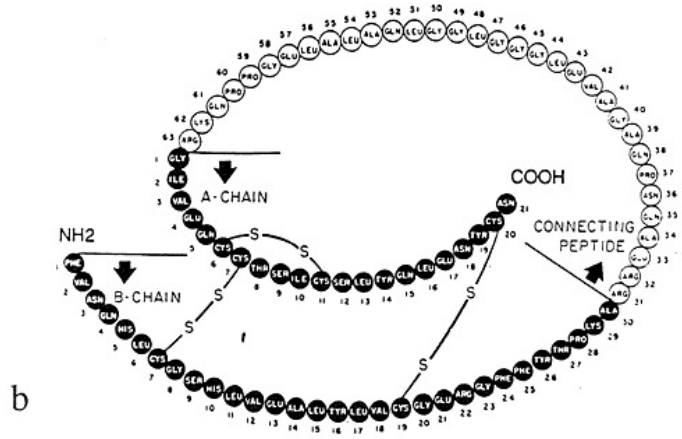
b) The A-chain is composed of 21 amino acids, while the B-chain consists of 30 residues. The linking (interchain) disulfide bonds are formed at cysteine residues between the positions A7-B7 and A20-B19. There is an additional (intrachain) disulfide bond within the A-chain between cysteine residues at positions A6 and A11.

c)The A-chain exhibits two α-helical regions at A1-A8 and A12-A19 which are antiparallel; while the B chain has a central α -helix (covering residues B9-B19) flanked by the disulfide bond on either sides and two β-sheets (covering B7-B10 and B20-B23).

d) The amino acid sequence of insulin is strongly conserved and varies only slightly between species. Bovine insulin differs from human in only three amino acid residues, and porcine insulin in one.

e) 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.

f)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 about 36000 Da in size. The six molecules are linked together as three dimeric units to form symmetrical molecule. An important feature is the presence of zinc atoms (Zn^{2+}) on the axis of symmetry, which are surrounded by three water molecules and three histamine residues at position B10.



Synthesis: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.[48] 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 minutes.[citation needed]

Proinsulin undergoes maturation into active insulin through the action of cellular endopeptidases known as prohormoneconvertases (PC1 and PC2), as well as the exoproteasecarboxypeptidase E.[49] 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.[50] 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).

Function:The actions of insulin on the global human metabolism level include:

Increase of cellular intake of certain substances, most prominently glucose in muscle and adipose tissue (about two-thirds of body cells).

Increase of DNA replication and protein synthesis via control of amino acid uptake

Modification of the activity of numerous enzymes.

The actions of insulin (indirect and direct) on cells include:

Stimulates the uptake of glucose – Insulin decreases blood glucose concentration by inducing intake of glucose by the cells. This is possible because Insulin causes the insertion of the GLUT4 transporter in the cell membranes of muscle and fat tissues which allows glucose to enter the cell.

Increased fat synthesis – insulin forces fat cells to take in blood glucose, which is converted into triglycerides; decrease of insulin causes the reverse.

Increased esterification of fatty acids – forces adipose tissue to make neutral fats (i.e., triglycerides) from fatty acids; decrease of insulin causes the reverse.

Decreased lipolysis – forces reduction in conversion of fat cell lipid stores into blood fatty acids and glycerol; decrease of insulin causes the reverse.

Induce glycogen synthesis – When glucose levels are high, insulin induces the formation of glycogen by the activation of the hexokinase enzyme, which adds a phosphate group in glucose, thus resulting in a molecule that cannot exit the cell. At the same time, insulin inhibits the enzyme glucose-6-phosphatase, which removes the phosphate group. These two enzymes are key for the formation of glycogen. Also, insulin activates the enzymes phosphofructokinase and glycogen synthase which are responsible for glycogen synthesis.

Decreased gluconeogenesis and glycogenolysis – decreases production of glucose from noncarbohydrate substrates, primarily in the liver (the vast majority of endogenous insulin arriving at the liver never leaves the liver); decrease of insulin causes glucose production by the liver from assorted substrates.

Decreased proteolysis – decreasing the breakdown of protein.

Decreased autophagy – decreased level of degradation of damaged organelles. Postprandial levels inhibit autophagy completely.

Increased amino acid uptake – forces cells to absorb circulating amino acids; decrease of insulin inhibits absorption.

Arterial muscle tone – forces arterial wall muscle to relax, increasing blood flow, especially in microarteries; decrease of insulin reduces flow by allowing these muscles to contract.

Increase in the secretion of hydrochloric acid by parietal cells in the stomach.[citation needed]

Increased potassium uptake – forces cells synthesizing glycogen (a very spongy, "wet" substance, that increases the content of intracellular water, and its accompanying K+ ions)[79] to absorb potassium from the extracellular fluids; lack of insulin inhibits absorption. Insulin's increase in cellular potassium uptake lowers potassium levels in blood plasma. This possibly occurs via insulin-induced translocation of the Na+/K+-ATPase to the surface of skeletal muscle cells.

Decreased renal sodium excretion.

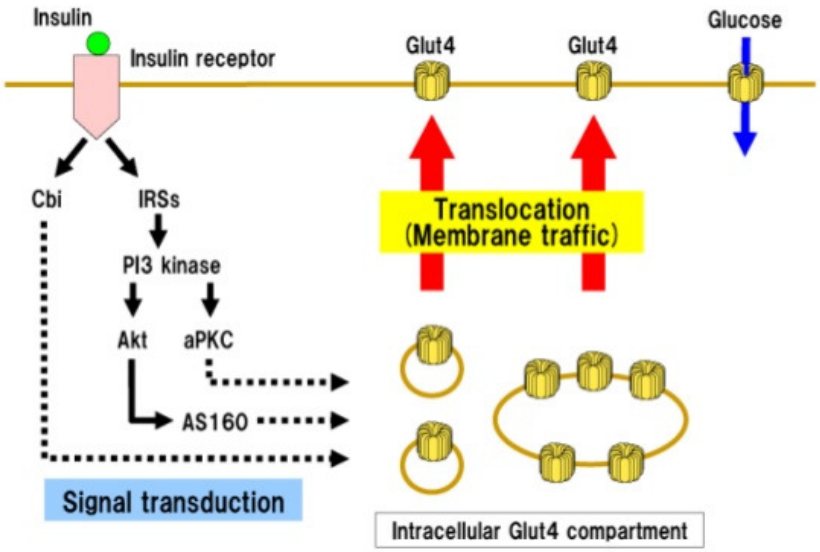
Insulin also influences other body functions, such as vascular compliance and cognition. Once insulin enters the human brain, it enhances learning and memory and benefits verbal memory in particular.[83] Enhancing brain insulin signaling by means of intranasal insulin administration also enhances the acute thermoregulatory and glucoregulatory response to food intake, suggesting that central nervous insulin contributes to the co-ordination of a wide variety of homeostatic or regulatory processes in the human body. Insulin also has stimulatory effects on gonadotropin-releasing hormone from the hypothalamus, thus favoring fertility.

The effects of insulin are initiated by its binding to a receptor, the insulin receptor (IR), 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.

The cascade that leads to the insertion of GLUT4 glucose transporters into the cell membranes of muscle and fat cells, and to the synthesis of glycogen in liver and muscle tissue, as well as the conversion of glucose into triglycerides in liver, adipose, and lactating mammary gland tissue, operates via the activation, by IRS-1, of phosphoinositol 3 kinase (PI3K). This enzyme converts a phospholipid in the cell membrane by the name of phosphatidylinositol 4,5-bisphosphate (PIP2), into phosphatidylinositol 3,4,5-triphosphate (PIP3), which, in turn, activates protein kinase B (PKB). Activated PKB facilitates the fusion of GLUT4 containing endosomes with the cell membrane, resulting in an increase in GLUT4 transporters in the plasma membrane.PKB also phosphorylates glycogen synthase kinase (GSK), thereby inactivating this enzyme. This means that its substrate, glycogen synthase (GS), cannot be phosphorylated, and remains dephosphorylated, and therefore active. The active enzyme, glycogen synthase (GS), catalyzes the rate limiting step in the synthesis of glycogen from glucose. Similar dephosphorylations affect the enzymes controlling the rate of glycolysis leading to the synthesis of fats via malonyl-CoA in the tissues that can generate triglycerides, and also the enzymes that control the rate of gluconeogenesis in the liver. The overall effect of these final enzyme dephosphorylations is that, in the tissues that can carry out these reactions, glycogen and fat synthesis from glucose are stimulated, and glucose production by the liver through glycogenolysis and gluconeogenesis are inhibited. The breakdown of triglycerides by adipose tissue into free fatty acids and glycerol is also inhibited.

After the intracellular signal that resulted from the binding of insulin to its receptor has been produced, termination of signaling is then needed. As mentioned below in the section on degradation, endocytosis and degradation of the receptor bound to insulin is a main mechanism to end signaling. In addition, the

signaling pathway is also terminated by dephosphorylation of the tyrosine residues in the various signaling pathways by tyrosine phosphatases. Serine/Threonine kinases are also known to reduce the activity of insulin.



Insulin-stimulated Glut4 translocation

GLUCAGON

Glucagon is a peptide hormone, produced by alpha cells of the pancreas. It works to raise the concentration of glucose and fatty acids in the bloodstream, and is considered to be the main catabolic hormone of the body.[3] It is also used as a medication to treat a number of health conditions. Its effect is opposite to that of insulin, which lowers extracellular glucose.[4] It is produced from proglucagon, encoded by the GCG gene.

The pancreas releases glucagon when the amount of glucose in the bloodstream is too low. Glucagon causes the liver to engage in glycogenolysis: converting stored glycogen into glucose, which is released into the bloodstream.[5] High blood-glucose levels, on the other hand, stimulate the release of insulin. Insulin allows glucose to be taken up and used by insulin-dependent tissues. Thus, glucagon and insulin are part of a feedback system that keeps blood glucose levels stable. Glucagon increases energy expenditure and is elevated under conditions of stress.[6] Glucagon belongs to the secretin family of hormones.

STUCTURE

Glucagon is a 29-amino acid polypeptide. Its primary structure in humans is: NH2-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Tyr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-COOH.

The polypeptide has a molecular mass of 3485 daltons.Glucagon is a peptide (nonsteroid) hormone.

Glucagon is generated from the cleavage of proglucagon by proproteinconvertase 2 in pancreatic islet α cells. In intestinal L cells, proglucagon is cleaved to the alternate products glicentin, GLP-1 (an incretin), IP-2, and GLP-2 (promotes intestinal growth).

FUNCTION

Glucagon generally elevates the concentration of glucose in the blood by promoting gluconeogenesis and glycogenolysis.Glucagon also decreases fatty acid synthesis in adipose tissue and the liver, as well as promoting lipolysis in these tissues, which causes them to release fatty acids into circulation where they can be catabolised to generate energy in tissues such as skeletal muscle when required.

Glucose is stored in the liver in the form of the polysaccharide glycogen, which is a glucan (a polymer made up of glucose molecules). Liver cells (hepatocytes) have glucagon receptors. When glucagon binds to the glucagon receptors, the liver cells convert the glycogen into individual glucose molecules and release them into the bloodstream, in a process known as glycogenolysis. As these stores become depleted, glucagon then encourages the liver and kidney to synthesize additional glucose by gluconeogenesis. Glucagon turns off glycolysis in the liver, causing glycolytic intermediates to be shuttled to gluconeogenesis.

Glucagon also regulates the rate of glucose production through lipolysis. Glucagon induces lipolysis in humans under conditions of insulin suppression (such as diabetes mellitus type 1).

Glucagon production appears to be dependent on the central nervous system through pathways yet to be defined. In invertebrate animals, eyestalk removal has been reported to affect glucagon production. Excising the eyestalk in young crayfish produces glucagon-induced hyperglycemia.