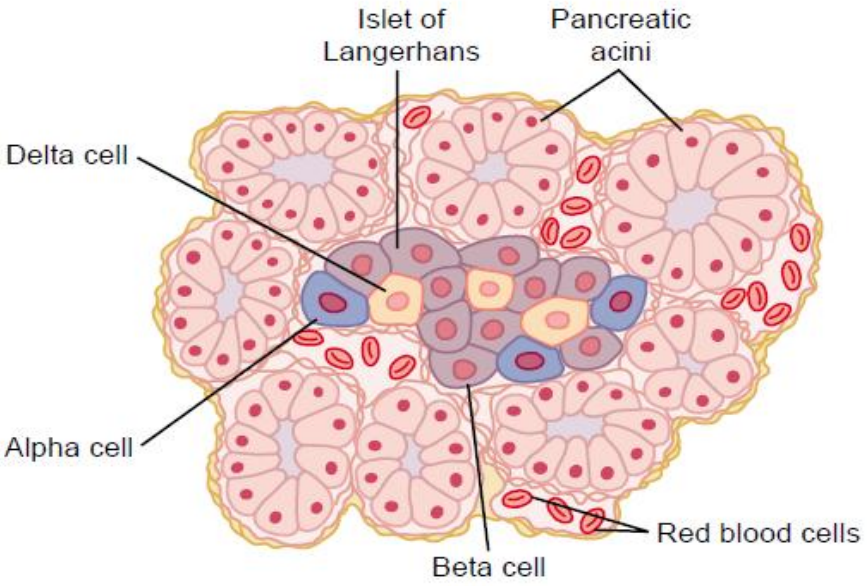
Lecture No:6



Insulin, Glucagon and Diabetes Mellitus

The pancreas, in addition to its digestive functions, secretes two important hormones, *insulin* and *glucagon*, that are crucial for normal regulation of glucose, lipid, and protein metabolism. Although the pancreas secretes other hormones, such as *amylin*, *somatostatin*, and *pancreatic polypeptide*, their functions are not as well established.

Physiologic Anatomy of the Pancreas.

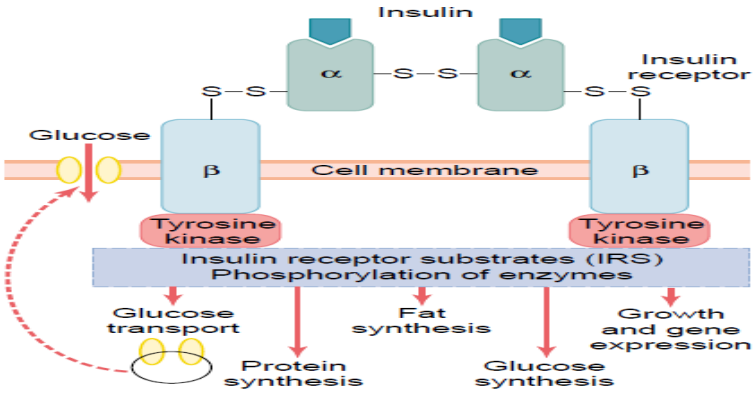
The pancreas is composed of two major types of tissues, as shown in above figure (1) the *acini*, which secrete digestive juices into the duodenum, and (2) the *islets of Langerhans*, which secrete insulin and glucagon directly into the blood. The human pancreas has 1 to 2 million islets of Langerhans, each only about 0.3 millimeter in diameter and organized around small capillaries into which its cells secrete their hormones. The islets contain three major types of cells, *alpha*, *beta*, and *delta* cells, which are distinguished from one another by their morphological and staining characteristics. The **beta cells**, constituting about 60 per cent of all the cells of the islets, lie mainly in the middle of each islet and secrete *insulin* and *amylin*, a hormone that is often secreted in parallel with insulin, although its function is unclear. The **alpha cells**, about 25 per cent of the total, secrete *glucagon*. And the **delta cells**, about 10 per cent of the total, secrete *somatostatin*. In addition, at least one other type of cell, the PP cell, is present in small numbers in the islets and secretes a hormone of uncertain function called *pancreatic polypeptide* .

Insulin Is a Hormone Associated with Energy Abundance

The insulin secretion is associated with energy abundance. That is, when there is great abundance of energy-giving foods in the diet, especially excess amounts of carbohydrates, insulin is secreted in great quantity. In turn, the insulin plays an important role in storing the excess energy. In the case of excess carbohydrates, it causes them to be stored as glycogen mainly in the liver and muscles. Also, all the excess carbohydrates that cannot be stored as glycogen are converted under the stimulus of insulin into fats and stored in the adipose tissue. In the case of proteins, insulin has a direct effect in promoting amino acid uptake by cells and conversion of these amino acids into protein. In addition, it inhibits the breakdown of the proteins that are already in the cells.

Activation of Target Cell Receptors by Insulin and the Resulting Cellular Effects

To initiate its effects on target cells, insulin first binds with and activates a membrane receptor protein that has a molecular weight of about 300,000 . It is the activated receptor, not the insulin, that causes the subsequent effects. The insulin receptor is a combination of four subunits held together by disulfide linkages: *two alpha subunits* that lie entirely outside the cell membrane and *two beta subunits* that penetrate through the membrane, protruding into the cell cytoplasm. The insulin binds with the alpha subunits on the outside of the cell, but because of the linkages with the beta subunits, the portions of the beta subunits protruding into the cell become autophosphorylated. Autophosphorylation of the beta subunits of the receptor activates a local *tyrosine kinase*, which in turn causes phosphorylation of multiple other intracellular enzymes including a group called *insulin-receptor substrates (IRS)*. Different types of IRS (e.g. IRS-1, IRS-2, IRS-3) are expressed in different tissues. The net effect is to activate some of these enzymes while inactivating others. In this way, insulin directs the intracellular metabolic machinery to produce the desired effects on carbohydrate, fat, and protein metabolism.



Insulin Promotes Muscle Glucose Uptake and Metabolism

During much of the day, muscle tissue depends not on glucose for its energy but on fatty acids. The principal reason for this is that the normal *resting muscle* membrane is only slightly permeable to glucose, except when the muscle fiber is stimulated by insulin; between meals, the amount of insulin that is secreted is too small to promote significant amounts of glucose entry into the muscle cells. However, under two conditions the muscles do use large amounts of glucose.

One of these is during moderate or heavy exercise. This usage of glucose does not require large amounts of insulin, because exercising muscle fibers become more permeable to glucose even in the absence of insulin because of the contraction process itself.

The second condition for muscle usage of large amounts of glucose is during the few hours after a meal. At this time the blood glucose concentration is high and the pancreas is secreting large quantities of insulin. The extra insulin causes rapid transport of glucose into the muscle cells.

Insulin Promotes Liver Uptake, Storage, and Use of Glucose

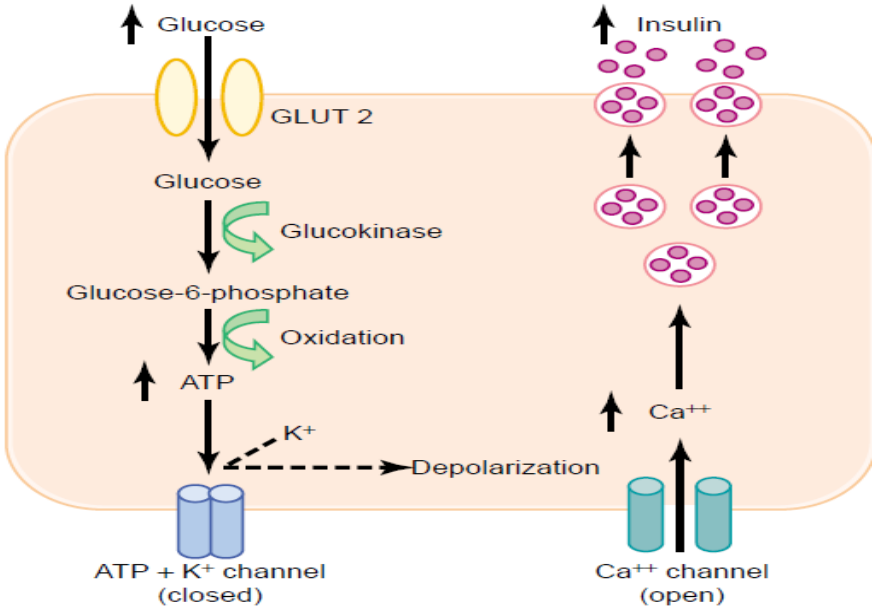
One of the most important of all the effects of insulin is to cause most of the glucose absorbed after a meal to be stored almost immediately in the liver in the form of glycogen. Then, between meals, when food is not available and the blood glucose concentration begins to fall, insulin secretion decreases rapidly and the liver glycogen is split back into glucose, which is released back into the blood to keep the glucose concentration from falling too low.

Insulin Promotes Conversion of Excess Glucose into Fatty Acids and Inhibits Gluconeogenesis in the Liver.

When the quantity of glucose entering the liver cells is more than can be stored as glycogen or can be used for local hepatocyte metabolism, *insulin promotes the conversion of all this excess glucose into fatty acids*. These fatty acids are subsequently packaged as triglycerides in very-low-density lipoproteins and transported in this form by way of the blood to the adipose tissue and deposited as fat. Insulin also *inhibits gluconeogenesis*. It does this mainly by decreasing the quantities and activities of the liver enzymes required for gluconeogenesis. However, part of the effect is caused by an action of insulin that decreases the release of amino acids from muscle and other extrahepatic tissues and in turn the availability of these necessary precursors required for gluconeogenesis.

Mechanisms of Insulin Secretion

The figure below shows the basic cellular mechanisms for insulin secretion by the pancreatic beta cells in response to increased blood glucose concentration, the primary controller of insulin secretion. The beta cells have a large number of *glucose transporters (GLUT- 2)* that permit a rate of glucose influx that is proportional to the blood concentration in the physiologic range. Once inside the cells, glucose is phosphorylated to glucose-6-phosphate by *glucokinase*. This step appears to be the rate limiting for glucose metabolism in the beta cell and is considered the major mechanism for glucose sensing and adjustment of the amount of secreted insulin to the blood glucose levels.



Factors and Conditions That Increase or Decrease Insulin Secretion

Increase Insulin Secretion

- Increased blood glucose
- Increased blood free fatty acids
- Increased blood amino acids
- Gastrointestinal hormones (gastrin, cholecystokinin, secretin, gastric inhibitory peptide)
- Glucagon, growth hormone, cortisol
- Parasympathetic stimulation; acetylcholine
- β-Adrenergic stimulation
- Insulin resistance; obesity
- Sulfonylurea drugs (glyburide, tolbutamide)

Decrease Insulin Secretion

- Decreased blood glucose
- Fasting
- Somatostatin
- α-Adrenergic activity
- Leptin

Glucagon and Its Functions

Glucagon, a hormone secreted by the *alpha cells* of the islets of Langerhans when the blood glucose concentration falls, has several functions that are diametrically opposed to those of insulin. Most important of these functions is to increase the blood glucose concentration, an effect that is exactly the opposite that of insulin.

Effects on Glucose Metabolism

The major effects of glucagon on glucose metabolism are (1) breakdown of liver glycogen (*glycogenolysis*) and (2) increased *gluconeogenesis* in the liver. Both of these effects greatly enhance the availability of glucose to the other organs of the body.

Glucagon Increases Gluconeogenesis.

Even after all the glycogen in the liver has been exhausted under the influence of glucagon, continued infusion of this hormone still causes continued hyperglycemia. This results from the effect of glucagon to increase the rate of amino acid uptake by the liver cells and then the conversion of many of the amino acids to glucose by gluconeogenesis. This is achieved by activating multiple enzymes that are required for amino acid transport and gluconeogenesis, especially activation of the enzyme system for converting pyruvate to phosphoenolpyruvate, a rate-limiting step in gluconeogenesis.

Somatostatin Inhibits Glucagon and Insulin Secretion

The *delta cells* of the islets of Langerhans secrete the hormone *somatostatin*, a polypeptide containing only 14 amino acids that has an extremely short half-life of only 3 minutes in the circulating blood. Almost all factors related to the ingestion of food stimulate somatostatin secretion. They include (1) increased blood glucose, (2) increased amino acids, (3) increased fatty acids, and (4) increased concentrations of several of the gastrointestinal hormones released from the upper gastrointestinal tract in response to food intake. In turn, somatostatin has multiple inhibitory effects as follows:

1. Somatostatin acts locally within the islets of Langerhans themselves to depress the secretion of both insulin and glucagon.
2. Somatostatin decreases the motility of the stomach, duodenum, and gallbladder.
3. Somatostatin decreases both secretion and absorption in the gastrointestinal tract.

Putting all this information together, it has been suggested that the principal role of somatostatin is to extend the period of time over which the food nutrients are assimilated into the blood. At the same time, the effect of somatostatin to depress insulin and glucagon secretion decreases

the utilization of the absorbed nutrients by the tissues, thus preventing rapid exhaustion of the food and therefore making it available over a longer period of time. It should also be recalled that somatostatin is the same chemical substance as *growth hormone inhibitory hormone,* which is secreted in the hypothalamus and suppresses anterior pituitary gland growth hormone secretion.

Summary of Blood Glucose Regulation

In a normal person, the blood glucose concentration is narrowly controlled, usually between 80 and 90 mg/ 100 ml of blood in the fasting person each morning before breakfast. This concentration increases to 120 to 140 mg/100 ml during the first hour or so after a meal, but the feedback systems for control of blood glucose return the glucose concentration rapidly back to the control level, usually within 2 hours after the last absorption of carbohydrates. Conversely, in starvation, the gluconeogenesis function of the liver provides the glucose that is required to maintain the fasting blood glucose level.

Diabetes Mellitus

Diabetes mellitus is a syndrome of impaired carbohydrate, fat, and protein metabolism caused by either lack of insulin secretion or decreased sensitivity of the tissues to insulin. There are two general types of diabetes mellitus:

1. *Type I diabetes*, also called *insulin-dependent diabetes mellitus (IDDM)*, is caused by lack of insulin secretion.
2. *Type II diabetes*, also called *non–insulin-dependent diabetes mellitus (NIDDM)*, is caused by decreased sensitivity of target tissues to the metabolic effect of insulin. This reduced sensitivity to insulin is often called *insulin resistance*.

In both types of diabetes mellitus, metabolism of all the main foodstuffs is altered.The basic effect of insulin lack or insulin resistance on glucose metabolism is to prevent the efficient uptake and utilization of glucose by most cells of the body, except those of the brain. As a result, blood glucose concentration increases, cell utilization of glucose falls increasingly lower, and utilization of fats and proteins increases.