Hormones of pancreas, insulin and glucagon

Insulin:

Insulin Is a Hormone Associated with Energy Abundance. In response to an influx of nutrients into the blood, insulin is secreted and permits these nutrients to be used by tissues for energy and anabolic processes; it also induces the storage of excess nutrients for later use when energy supplies are deficient. In the presence of insulin, stores of carbohydrates, fats, and proteins increase. Insulin has rapid (e.g., increased glucose, amino acid, and potassium uptake into cells), intermediate (e.g., stimulation of protein synthesis, inhibition of protein degradation, activation and inactivation of enzymes), and delayed (e.g., increased transcription) actions on carbohydrate, fat, and protein metabolism that occur within seconds, minutes, and hours, respectively.

Most of the Actions of Insulin Are Achieved through Autophosphorylation of Receptors. Insulin does not mediate its physiological effects through generation of second messengers as do most protein hormones; instead, signal transduction is achieved through autophosphorylation of the intracellular domains of its own receptor. The insulin receptor is a tetramer made up of two a-subunits that lie outside the cell membrane and two b-subunits that penetrate the cell membrane and protrude into the cytoplasm. Binding of insulin to the a-subunit of the receptor triggers tyrosine kinase activity of the b-subunits, producing autophosphorylation of the b-subunits on tyrosine residues. This results in phosphorylation of other intracellular proteins and enzymes, which mediates a multitude of responses.

Effects of Insulin on Carbohydrate Metabolism:

In Muscle, Insulin Promotes the Uptake and Metabolism of Glucose. An important effect of insulin in muscle is that it facilitates glucose diffusion down its concentration gradient from the blood into cells. This is achieved by increasing the number of glucose transporters in the cell membrane. These transporters are recruited from a cytoplasmic pool of vesicles to the cell membrane. The increased glucose transported into muscle cells undergoes glycolysis and oxidation and is stored as glycogen. Because glucose entry into muscle cells is usually highly dependent on insulin, glucose uptake by these cells is restricted to the postprandial period when insulin is secreted or periods of exercise when glucose transport is non–insulin-dependent. During exercise the insertion of glucose transporters into the cell membrane is insulin independent.

In the Liver, Insulin Promotes Glucose Uptake and Storage, and Inhibits Glucose Production: It also has the following actions in the liver:

• Increases the flux of glucose into cells. This is achieved not by increasing the number of glucose transporters in the cell membranes but by inducing glucokinase, which increases the phosphorylation of glucose to glucose-6-phosphate.

• Increases glycogen synthesis by activating glycogen synthase (as well as by increasing glucose uptake).

• Directs the flow of glucose through glycolysis by increasing the activity of key glycolytic enzymes (e.g., phosphofructokinase and pyruvate kinase).

• Decreases the hepatic output of glucose in several ways. First, insulin impairs glycogenolysis by inhibiting glycogen phosphorylase. Second, insulin decreases the exit of glucose from the liver by inhibiting glucose-6-phosphatase. Third, insulin inhibits gluconeogenesis by decreasing the amino acid uptake into the liver (see discussion on effects on protein metabolism) and by decreasing the activity or levels of key gluconeogenic enzymes (e.g., pyruvate carboxylase and fructose-1,6-diphosphatase).

• Enhances synthesis of fatty acids in two ways. First, insulin increases the flow of glucose to pyruvate (glycolysis) and the subsequent conversion to acetylcoenzyme A (acetyl-CoA). Second, insulin stimulates acetyl-CoA carboxylase, which converts acetyl-CoA to malonyl-CoA. This is the rate-limiting step in the synthesis of fatty acids.

In Adipose Tissue, Insulin Facilitates Glucose Entry into Cells. This is achieved in much the same way that insulin promotes glucose uptake into muscle cells—by increasing glucose transporters in the cell membrane. Subsequently, the metabolism of glucose to a-glycerol phosphate provides the glycerol that is needed for esterification of fatty acids for storage as triglycerides (see discussion of effects on fat metabolsim).

Insulin Has Little Effect on Glucose Uptake and Use by the Brain. In the brain, insulin has little effect on glucose transport into cells. Because brain cells are quite permeable to glucose and highly dependent on this substrate for energy, it is essential that the blood glucose concentration is maintained at normal levels. If the blood glucose concentration falls too low, symptoms of hypoglycemic shock appear, including fainting, seizure, and even coma.

Effects of Insulin on Fat Metabolism

In Adipose Tissue, Insulin Enhances Storage and Inhibits Mobilization of Fatty Acids. This effect of insulin is accomplished in several ways:

• Insulin inhibits hormone-sensitive lipase. This decreases the rate of lipolysis of triglycerides and the release of stored fatty acids into the circulation.

• Insulin increases glucose transport. The subsequent metabolism of glucose to a-glycerol phosphate increases the rate of esterification of fatty acids for storage as triglycerides.

• Insulin induces lipoprotein lipase. This enzyme is present in the capillary wall and splits circulating triglycerides into fatty acids, which is necessary for their transport into fat cells.

In the Liver, Insulin Promotes the Synthesis and Inhibits the Oxidation of Fatty Acids. As discussed previously, insulin promotes the synthesis of fatty acids from glucose in the liver. Because of the increased availability of a-glycerol phosphate from glycolysis, fatty acids are esterified to form triglycerides. Oxidation of fatty acids is impaired because of the increased conversion of acetyl-CoA to malonyl-CoA by acetyl-CoA carboxylase, as discussed. Malonyl-CoA inhibitscarnitine acyltransferase, which is responsible for shuttling fatty acids from the cytoplasm into the mitochondria for b-oxidation and conversion to ketoacids; insulin is antiketogenic.

Effects of Insulin on Protein Metabolism:

Insulin is an anabolic hormone. It increases the uptake of several amino acids from the blood into cells by stimulating transport across the cell membrane; this limits the rise in plasma levels of certain amino acids after a protein meal. In addition, insulin increases protein synthesis by stimulating both gene transcription and translation of mRNA. Finally, insulin inhibits catabolism of proteins and therefore decreases the release of amino acids from muscle.

Insulin, like growth hormone, is essential to growth. Diabetic animals fail to grow. The anabolic effects of insulin and growth hormone are synergistic.

Control of Insulin Secretion:

Glucose Is the Most Important Controller of Insulin Secretion. Although several factors can increase or decrease insulin secretion, the major control of insulin secretion is exerted by a feedback effect of blood glucose on the beta cells of the pancreas. When blood glucose concentration rises above fasting levels, insulin secretion increases. As a result of the subsequent effects of insulin to stimulate glucose uptake by the liver and peripheral tissues, the blood glucose concentration returns to normal levels. This provides an important negative feedback mechanism for controlling the blood glucose concentration.

Multiple Stimuli Other Than Hyperglycemia Increase Insulin Secretion. . These stimuli include the following:

• Amino acids, especially arginine, lysine, leucine, and alanine. As a result, dietary amino acids are removed from the blood and used by cells to synthesize proteins. Amino acids have a synergistic effect with glucose in stimulating insulin secretion.

• Gastrointestinal hormones, especially gastric inhibitory polypeptide and glucagon-like polypeptide 1. These hormones are released from the gastrointestinal tract after a meal is eaten and account for the greater increase in insulin secretion when glucose is administered orally than when comparable amounts are administered intravenously.

• Other hormones, including cortisol and growth hormone. These hormones increase insulin secretion in large part because they antagonize the effects of insulin on glucose uptake in peripheral tissues, leading to increased blood glucose concentration. Indeed, chronic increments in cortisol (with Cushing's syndrome) and growth hormone (with acromegaly) lead to hypertrophy and exhaustion of the beta cells of the pancreas and thereby cause diabetes mellitus.

• Autonomic nervous system, including both the sympathetic and parasympathetic nervous system. b-adrenergic stimulation increases insulin secretion, whereas a-adrenergic stimulation inhibits it. Activation of sympathetic nerves to the pancreas inhibits insulin secretion. Parasympathetic stimulation of the pancreas increases insulin secretion.

Glucagon

Most of the Actions of Glucagon Are Achieved by Activation of Adenylyl Cyclase. At physiological doses, the primary effects of glucagon occur in the liver and are opposite those of insulin. The binding of glucagon to hepatic receptors results in activation of adenylyl cyclase and generation of the second messenger cyclic AMP, which in turn activates protein kinase A, leading to phosphorylation that results in the activation or deactivation of a number of enzymes. **Glucagon Promotes Hyperglycemia in Several Ways:**

• Glucagon stimulates glycogenolysis. Glucagon has immediate and pronounced effects on the liver to increase glycogenolysis and the release of glucose into the blood. This effect is achieved through activation of glycogen phosphorylase and simultaneous inhibition of glycogen synthase.

• Glucagon inhibits glycolysis. Glucagon inhibits several key steps in glycolysis, including phosphofructokinase and pyruvate kinase. Consequently, glucose-6- phosphate levels tend to rise, leading to increased glucose release from the liver.

• Glucagon stimulates gluconeogenesis. Glucagon increases the hepatic extraction of amino acids from the plasma and increases the activities of key gluconeogenic enzymes, including pyruvate carboxylase and fructose-1,6-diphosphatase. Consequently, glucagon has delayed and protracted actions to promote glucose output by the liver.

Glucagon Is Ketogenic. Because glucagon inhibits acetyl-CoA carboxylase, there is decreased production of malonyl-CoA, an inhibitor of carnitine acyltransferase. Consequently, fatty acids are directed into the mitochondria for b-oxidation and ketogenesis.

Control of Glucagon Secretion:

Glucose Is the Most Important Controller of Glucagon Secretion. Glucose is the most important controller of both glucagon and insulin secretion; however, glucose has opposing effects on the secretion of these two hormones. Hypoglycemia increases glucagon secretion; as a result of the hyperglycemic actions of glucagon, blood glucose concentration returns toward normal. Conversely, increases in blood glucose concentration decrease glucagon secretion; glucagon and insulin provide important, but opposing, mechanisms for the regulation of blood glucose concentration.

Amino Acids, Especially Arginine and Alanine, Stimulate Glucagon Secretion. After a protein meal, both insulin and glucagon secretion are stimulated, but the glucagon response is depressed if glucose is ingested simultaneously. The glucagon response to a protein meal is valuable because without the hyperglycemic effects of glucagon, increased insulin secretion would cause hypoglycemia.

Fasting and Exercise Stimulate Glucagon Secretion. Under these conditions, the stimulation of glucagon secretion helps prevent large decreases in blood glucose concentration. b-adrenergic stimulation increases glucagon secretion, whereas a-adrenergic stimulation inhibits it. However, in contrast to the inhibitory effects of the sympathetic nervous system on insulin secretion, glucagon secretion increases during sympathetic activation.