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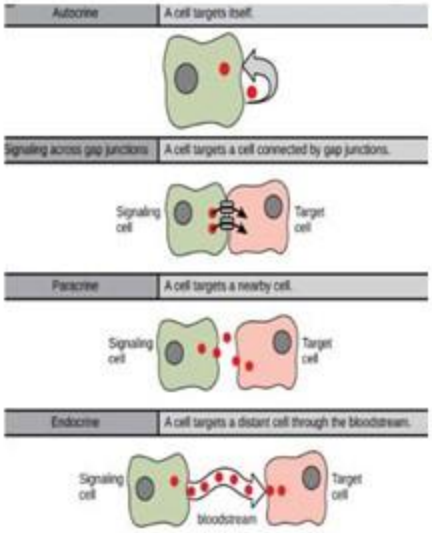
The liver and pancreas function



Paracrine

The cells that are near one another communicate (over relatively short distances) through the release of chemical messengers, is known as paracrine signaling. e.g. transfer of signals across synapses between nerve cells

Autocrine signaling

The cell signals to itself, releasing a ligand that binds to receptors on its own surface. The cytokine interleukin-1 in monocytes.

Endocrine

The signals are produced by specialized cells and released into the bloodstream, which carries them to reach far-away targets of the body are known as hormones. The hypothalamus, the pituitary, as well as the gonads (testes and ovaries) and the pancreas.

Exocrine gland

secretes substances through a duct opening in a gland onto an external or internal body surface. Salivary glands, sweat glands and glands within the gastrointestinal tract.

HEPATOBILIARY SYSTEM:

The liver produces and secretes bile. Bile is secreted by hepatocytes into canaliculi, then traverses a series of bile ducts, which become less numerous but progressively larger in diameter until they form the common hepatic duct. The bile can move through either the common bile duct into the duodenum or the cystic duct to the gallbladder. The sphincter of Oddi controls on this pathway. Sphincter relaxation is regulated primarily by CCK.

1- The sphincter is contracted, bile travels to the gallbladder.

2- The sphincter is relaxed, bile flows from the common hepatic duct and often from the gallbladder into the duodenum.

Bile components:

1. Bile acids: it labor on emulsify lipids for digestion by pancreatic lipase in association with colipase. Without bile acids, lipid digestion occurs slowly and is often incomplete because of decrease in the surface area available for enzymes. Bile acids are formed from cholesterol, and there are two general forms of bile acids: primary and secondary.

a. Primary bile acids: Cholic and chenodeoxycholic acids are synthesized in hepatocytes via 7-hydroxylase. Thus, the formation of these two bile acids is a principal route of cholesterol metabolism.

b. Secondary bile acids: Deoxycholic and lithocholic acids are not synthesized in hepatocytes. Instead, bacteria in the large intestine and terminal ileum contain 7-dehydroxylase, which converts cholic acid to deoxycholic acid and chenodeoxycholic acid to lithocholic acid. These bile acids are then passively reabsorbed and transported back to the liver via the enterohepatic circulation. These bile acids can be conjugated or unconjugated, where conjugation simply refers to a salt attachment. Bile acid type affects the specific intestinal or hepatocyte membrane transporter utilized.

2. Water and electrolytes: Ions including Na, K , Ca , Cl, and HCO3 are secreted from hepatocytes isotonically. Some additional water and HCO3 are secreted by duct cells. Bile concentration is completed in the gallbladder, and this concentration can be quite dramatic (up to tenfold). This occurs via Na and Cl

reabsorption, which causes isosmotic water reabsorption that occurs paracellularly and cellularly via aquaporins (AQPs).
3. Cholesterol and phospholipids: Besides the cholesterol converted to primary bile acids, small amounts of cholesterol are secreted in the bile. Phospholipids, primarily lecithin, are also secreted and help solubilize some of the bile constituents.
4. Pigments and organic molecules: The major pigment in bile is bilirubin. Bilirubin is formed from the catabolism of hemoglobin and is transported in the circulation in a complex with albumin. Hepatocytes secrete this bile pigment, which is either ultimately excreted directly in the intestines or temporarily reabsorbed and then excreted in the urine. Organic ions are also bile components which serve as a method for the liver to excrete toxins, drugs, and related compounds.

Gallbladder

The liver constantly produces bile but not in sufficient quantity to properly emulsify lipids in the small intestine. The gallbladder serves as the bile storage and distribution center. Therefore, when needed,a large quantity can be released. The stored bile in the gallbladder is concentrated. The gallbladder can contract to propel out the bile with:
1- CCK stimulation. CCK is the same substance that causes the sphincter of Oddi to relax.
2- Vagal stimulation also can cause weak gallbladder contraction.
3- somatostatin and norepinephrine inhibit bile acid secretion.

IV. NONBILIARY LIVER FUNCTIONS

A. Metabolism
1. Carbohydrate:
a- The liver plays a major role in the storage and subsequent breakdown of glycogen.
b- glycogenolysis: Glycogen breakdown to liberates glucose for released into the systemic circulation.
c- gluconeogenesis: a process by which the liver can convert fructose and galactose into glucose as well as convert amino acids and triglycerides into glucose.
2. Lipid: The liver contains the enzymes to undergo large amounts of lipid metabolism. Here the liver can mobilize fatty acids, through a process called lipolysis, to be released into the systemic circulation. The liver also produces lipoproteins, phospholipids, ketone bodies, and cholesterol and has the ability to convert amino acids and carbohydrates into new lipids.
3. Protein: The liver is involved in protein synthesis and amino acid uptake and metabolism. Proteins synthesized include plasma proteins, prohormones, clotting factors, apoproteins, and transport binding proteins. The liver also has the capacity to deaminate amino acids.
4. Vitamins and minerals: Many vitamins and minerals are delivered to the liver by the portal circulation. The liver has the capacity to store lipid-soluble vitamins such as vitamins A, D, E, and K. This storage of fat-soluble vitamins allows for a short-term reserve for when dietary sources are not available. The liver also stores certain minerals, such as iron and copper.
b- Detoxification
The liver participates in a number of detoxification and removal reactions:
1. Ammonia: The liver receives the majority of this ammonia via the portal circulation produced from intestines .The liver removes most of the circulating ammonia via the urea cycle reactions. Urea is released into the systemic circulation, where the majority can be excreted by the kidney.
2. Ethanol: The liver contains alcohol dehydrogenase, which facilitates the conversion of ethanol into acetaldehyde and reduced nicotinamide and adenine dinucleotide. These two products can then be converted into acetyl coenzyme A by peripheral tissues such as skeletal muscles.

3. Drug biotransformations reactions: involve two phases.

I. Phase I reactions: utilize cytochrome P450 enzymes to oxidize organic molecules. These reactions metabolize the majority of drug classes, Phase I reactions can also be used to activate some drugs.

II. Phase II reactions: conjugate the products to aid in solubility for release into the systemic circulation to be filtered and excreted in the kidney or to be secreted into the small intestine with bile for ultimate excretion.

C. Immune functions

The bacteria are also among the sampling of portal blood. Kupffer cells are specialized phagocytic macrophages located in the liver, which engulf and digest these intestinal bacteria. The liver is also the major site of both lymph production and immunoglobulin A release.

Liver endocrine:

The hypothalamic–pituitary–liver axis is unique in that both the second (GH) and third (IGF-1) secretions are hormones with widespread biological effects. .

Liver

The liver is a key target organ site of the hypothalamic–pituitary axis and produces IGF-1. IGF-1 is not solely produced in the liver, but, on average, hepatocytes contain 100-fold more IGF mRNA than do other tissues. It is thought that these extrahepatic tissues use IGF in autocrine or paracrine rather than endocrine signaling. GH receptors in the liver use a tyrosine kinase. Receptor activation increases IGF-1 production and release into the circulation.

GROWTH HORMONE GH:

is a peptide hormone. Preprohormone is produced in the rough endoplasmic reticulum (ER) of somatotropes"cells in the anterior pituitary". Once secreted, a portion of GH binds weakly to GH-binding protein and other plasma proteins before being ultimately broken down by the liver.GH has a number of targets: liver, cartilage and bone, muscle, and adipose tissue.

In cartilage and muscle, GH stimulates amino acid uptake and protein synthesis. Collagen formation and chondrocyte size and number increase in the presence of GH.

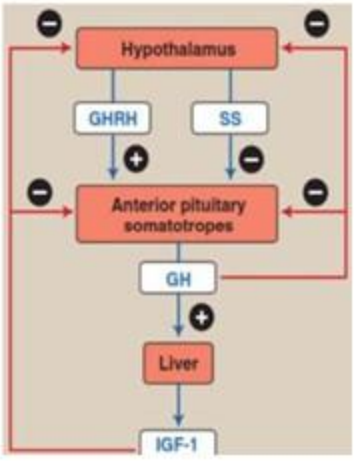
In adipose tissue, GH increases the breakdown of triglycerides and decreases glucose uptake. This decrease in glucose uptake is sometimes referred to as an " anti-insulin effect."

GH secretion is regulation:

1- the behavioral states, such as sleep, during exercise and stress, both of which increase its secretion and are thought to be related to growth and repair functions. GH is released in pulses and is cyclic throughout the day.

2- Increased secretion: Decreases in blood glucose concentration and fatty acids stimulate GH release.

3. Decreased secretion: Increasing blood glucose and fatty acids inhibits GH release. Conditions such as obesity as well as aging decrease release. Direct negative feedback is provided by GH and IGF-on both the anterior pituitary and the hypothalamus.



INSULIN-LIKE GROWTH FACTOR 1

IGF-1 (somatomedin C) is produced and secreted from hepatocytes. IGF-1 is a peptide hormone with some structural similarity to insulin (hence, "insulin-like"). Unlike GH, IGF-1 tightly binds plasma proteins.

IGF-1 functions very similar to GH. The majority of sustained actions of the hypothalamic–pituitary–liver axis are mediated by IGF-1. IGF-1 effects focus

more on the musculoskeletal system, increasing amino acid and glucose uptake and protein synthesis. Increased IGF correlates to growth spurts such as during adolescence.
IGF-1 secretion is mediated by GH levels. If GH is increased, IGF increases, and vice versa. Thus, the factors that alter GH secretion indirectly alter IGF-1 levels. IGF-1 participates in negative feedback regulation of the hypothalamic–pituitary–liver axis at the hypothalamus.

PANCREAS: have two functions:

A- EXOCRINE PANCREAS

The primary functions of the exocrine pancreas are to neutralize acid and deliver enzymes for macronutrient digestion within the duodenum. Enzymes and ion are secreted from small clusters of acinar cells are connected by intercalated ducts, which converge on the collecting duct. The cells lining the intercalated duct add ions and serous secretions.

Enzyme	Class/Action
Amylase	Carbohydrate enzyme
Chymotrypsinogen	Protein enzyme precursor
Deoxyribonuclease	Nucleic acid enzyme
Lipase	Lipid enzyme
Procarboxypeptidase A and B	Protein enzyme precursor
Proelastase	Protein enzyme precursor
Prophospholipase A2	Lipid enzyme precursor
Procolipase	Lipid enzyme precursor
Ribonuclease	Nucleic acid enzyme
Trypsinogen	Protein enzyme precursor

Regulation of pancreatic secretions is dependent on the phase of digestion:

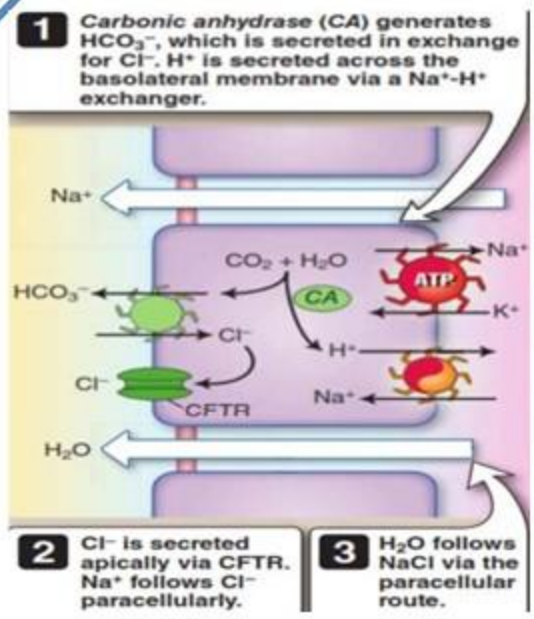
1. Cephalic phase: the vagus nerve stimulates pancreatic secretions by releasing acetylcholine (ACh) and vasoactive intestinal peptide (VIP) and is thought to account for about 25% of pancreatic secretions.
2. Gastric phase: about 10% of pancreatic secretions and is mediated by vagovagal reflexes stimulated by stomach distension.
3. Intestinal phase: The intestinal phase accounts for the majority of pancreatic secretions (65%) and is controlled hormonally control via secretin is released in response to H^+ and cholecystokinin (CCK) is released in response to amino acids, fatty acids, and monoacylglycerols.

The primary inhibitors of pancreatic secretions are somatostatin and a decrease in chyme macronutrients.

Enzyme secretion mechanisms

AAs +FAs in duodenum → released CCK into blood → binds to CCKA receptors on vagal afferents stimulate afferents → Eliciting the efferent stimulation → Vasoactive intestinal peptide VIP → pancreatic enzyme secretion from acinar cells

H^+ in duodenum → released secretin into blood → Vasoactive intestinal peptide VIP → pancreatic enzyme secretion from acinar cells



Ion secretion serous fluid mechanisms:

1. Acinar cells: Basolateral CCK and ACh binding stimulates Cl^- transport across the apical membrane, which facilitates paracellular Na^+ and water movement.
2. Intercalated duct cells: Basolateral secretin and ACh binding in intercalated duct cells activates cystic fibrosis transmembrane

conductance regulators (CFTRs), other Cl^- channels, and Cl -HCO_3 cotransporters. These transporters recycle Cl -and secrete HCO_3^-.

ENDOCRINE PANCREAS

are highly vascularized clusters of hormone producing cells known as the pancreatic islets (islets of Langerhans).A. Islet structure Islets contain four principal endocrine cell types, each of which produces a specific hormone. Hepatocytes are key targets for many of the pancreatic hormones.

1- α Cells secrete glucagon,
2- β cells secrete insulin,
3- δ cells secrete somatostatin,
4- F cells secrete pancreatic polypeptide. Self-Regulate pancreatic secretion activities (endocrine and exocrine). It also has effects on hepatic glycogen levels and gastrointestinal secretions.

Glucagon:

is a small peptide hormone synthesized by islet cells. Glucagon's half-life is 5–10 minutes after release into the circulation. It is degraded and removed from the circulation by the liver.

Function

Glucagon's main function is to mobilize and make energy substrates available for use by tissues during times of stress or between meals. Glucagon's primary target is the liver, but it has secondary targets that include striated myocytes and adipocytes.

Glucagon cellular effects including:

Increases in blood glucose, by glycogenolysis and gluconeogenesis
Increases fatty acid and lipolysis
Increases ketone body concentration and ketogenesis.

1. Glycogenolysis: Glucagon stimulates hepatic glycogen breakdown by glycogen phosphorylase and glucose 6-phosphatase, liberating glucose for release into the circulation. Glucose then exits the cell via GLUT2. Glucagon also stimulates glycogenolysis in muscle to support an increase in contractile activity.
2. Gluconeogenesis: Glucagon also stimulates glucose synthesis from noncarbohydrate sources, such as lipids and proteins. Gluconeogenesis is mediated by pathways that include glucose 6-phosphatase and fructose 2,6-bisphosphatase.

Glucagon simultaneously inhibits enzymes involved in glucose breakdown, including glucose kinase, phosphofructokinase, and pyruvate kinase.

3. Lipolysis: Glucagon also targets adipocytes, causing them to break down triglycerides into glycerol and free fatty acids. Lipolysis is mediated by hormone-sensitive lipase (HSL), thereby increasing plasma free fatty acids and fatty acid utilization as both direct (lipid metabolism) and indirect (converted back to glucose, then metabolized) substrates.
4. Ketogenesis: Ketone bodies (i.e., acetoacetate, β-hydroxybutyrate, and acetone) form in hepatocytes from incomplete oxidation of free fatty acids. Ketone bodies are released from the hepatocyte into the circulation. In extrahepatic tissues, where ketone bodies are converted back into acetyl coenzyme A for use in aerobic metabolism, liberating their stored energy.

Secretion Glucagon: release is regulated by circulating substrates (amino acids, ketone bodies, and glucose) and by neural and hormonal mechanisms.

1. Increased secretion:

a- Cholecystokinin (CCK) and higher blood concentrations of amino acids (such as result from consuming protein) stimulate glucagon secretion.
b- Glucagon is also stimulated by decreases in blood glucose via negative feedback.
c- The sympathetic nervous system (SNS) increases glucagon secretion during stressful events to increase energy substrate availability in the form of blood glucose, fatty acid, and ketone bodies to working tissues.
2. Decreased secretion:
a- Insulin and somatostatin decrease glucagon secretion by the islet.
b- Increases in blood glucose, fatty acids, and ketone bodies. Circulating glucagon-like peptide 1 (GLP-1) secreted from intestinal L cells also suppresses glucagon secretion.

INSULIN

Insulin is a protein hormone consisting of two peptide chains. Insulin's half-life is about 3–8 minutes. Insulin is degraded by the liver during its first pass.
A. Function Insulin's major function is to lower blood glucose levels. The primary insulin targets are the liver, skeletal muscle, and adipose tissue, which, when stimulated, allow for the uptake of glucose, fatty acids, glycerol, ketone bodies, and amino acids from the blood.
1. Glucose uptake: Insulin increases glucose uptake by upregulating and inserting GLUT4 transporters into muscle and adipose tissue. Cell membrane glucose transporters can be insulin sensitive, like GLUT4, or insensitive like GLUT2 (e.g., liver). Thus, muscle can dramatically decrease blood glucose levels when insulinis high (e.g., after meals) but does not appreciably affect blood glucose levels during periods of low insulin (e.g., between meals).
2. Glycogenesis: Insulin stimulates the formation of glycogen via stimulating glycogen synthase and inhibiting glycogen phosphorylase in muscle and liver. Glycogen formation is also increased by facilitating the conversion of glucose to glucose 6-phosphate. This facilitation is mediated by the insulin-sensitive glucokinase.
3. Glycolysis: Glycolysis is stimulated by insulin-induced activation of pyruvate dehydrogenase and phosphofructokinase in muscle and liver. This, coupled with the aforementioned increase in glucokinase, facilitates the utilization of glucose. The reverse pathway (gluconeogenesis) is being repressed in hepatocytes.
4. Lipogenesis: Insulin increases lipoprotein lipase (LPL) and decreases HSL activity in adipocytes. LPL facilitates the breakdown of chylomicrons and other low-density lipoproteins into free fatty acids, which then can be absorbed. The increase in cellular free fatty acids increases triglycerides and the formation of lipid droplets.
5. Ketone bodies: In hepatocytes, ketone body formation and secretion are inhibited in the presence of insulin because of insulin's inhibition of the rate-limiting carnitine shuttle (enzymes that move fatty acyl coenzyme A into the mitochondria for processing).
6. Protein synthesis: In skeletal muscle and hepatocytes, insulin promotes protein synthesis and inhibits protein catabolism. The anabolic effect of insulin involves:
a- Increase cellular uptake for amino acids.
b- The mTOR pathway decreases proteolysis
c- Increases ribosomal production and assembly.

Insulin secretion regulation

1. Increased secretion:
a- Increases in blood glucose, fatty acids, and amino acids stimulate insulin secretion by inhibiting ATP-sensitive K^+ channels efflux depolarizes membrane potential, which opens voltage-gated Ca_2^+ channels.

The subsequent increase in cytosolic Ca_2^+facilitates docking and fusion of the insulin-containing vesicles with the cell membrane to allow for insulin secretion.

b- Glucagon, glucose-dependent insulinotropic peptide GLP-1, CCK, acetylcholine, and β-adrenergic stimulation increase cytosolic Ca to increase insulin secretion

2. Decreased secretion:

Decreases in blood glucose provide negative feedback to decrease insulin secretion. Somatostatins from adjacent islet cells suppress insulin secretion, as does α-adrenergic stimulation by the SNS.