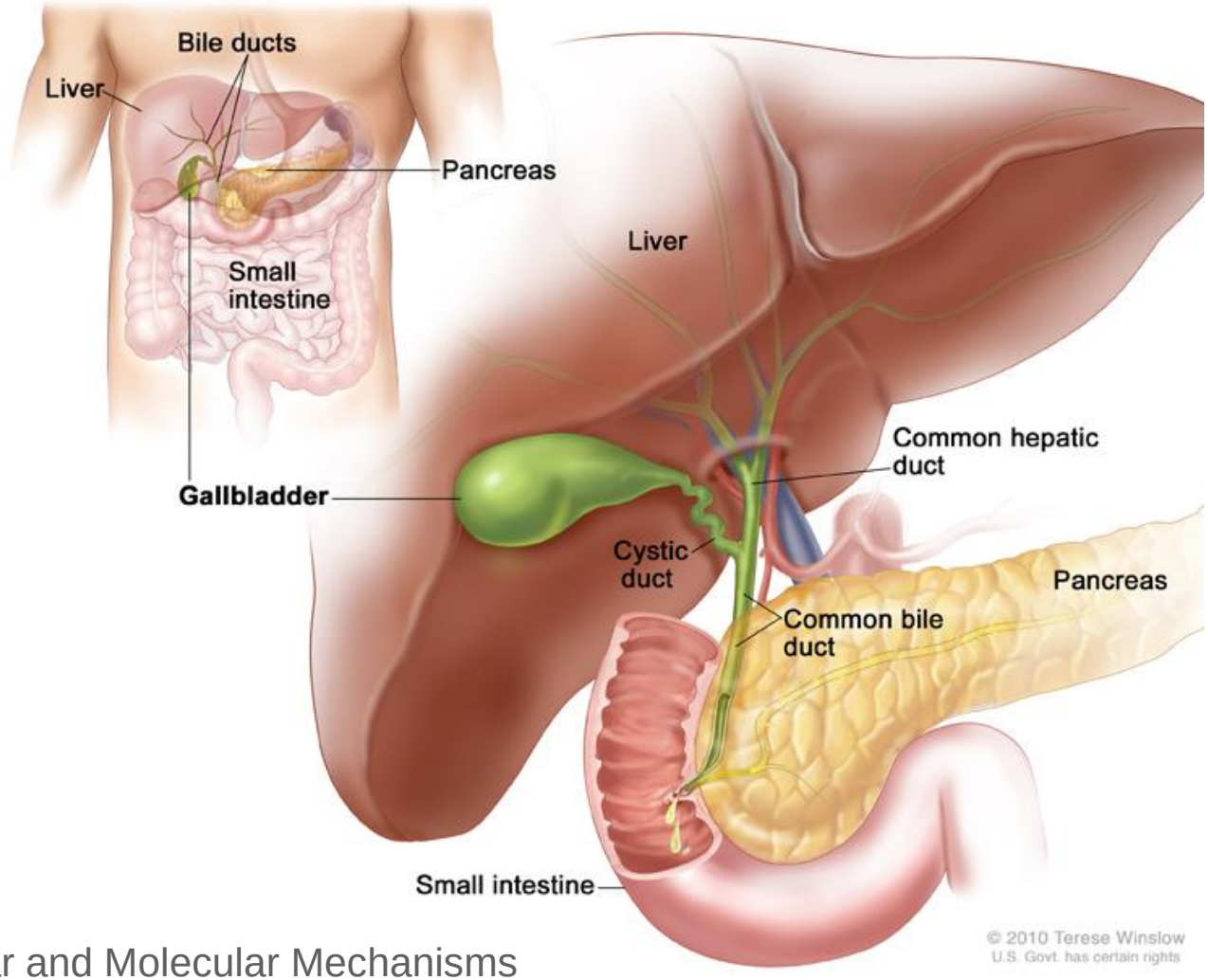
Pancreas


Bile ducts
Liver
Pancreas
Small intestine
Liver
Common hepatic duct
Gallbladder
Cystic duct
Pancreas
Common bile duct
Small intestine
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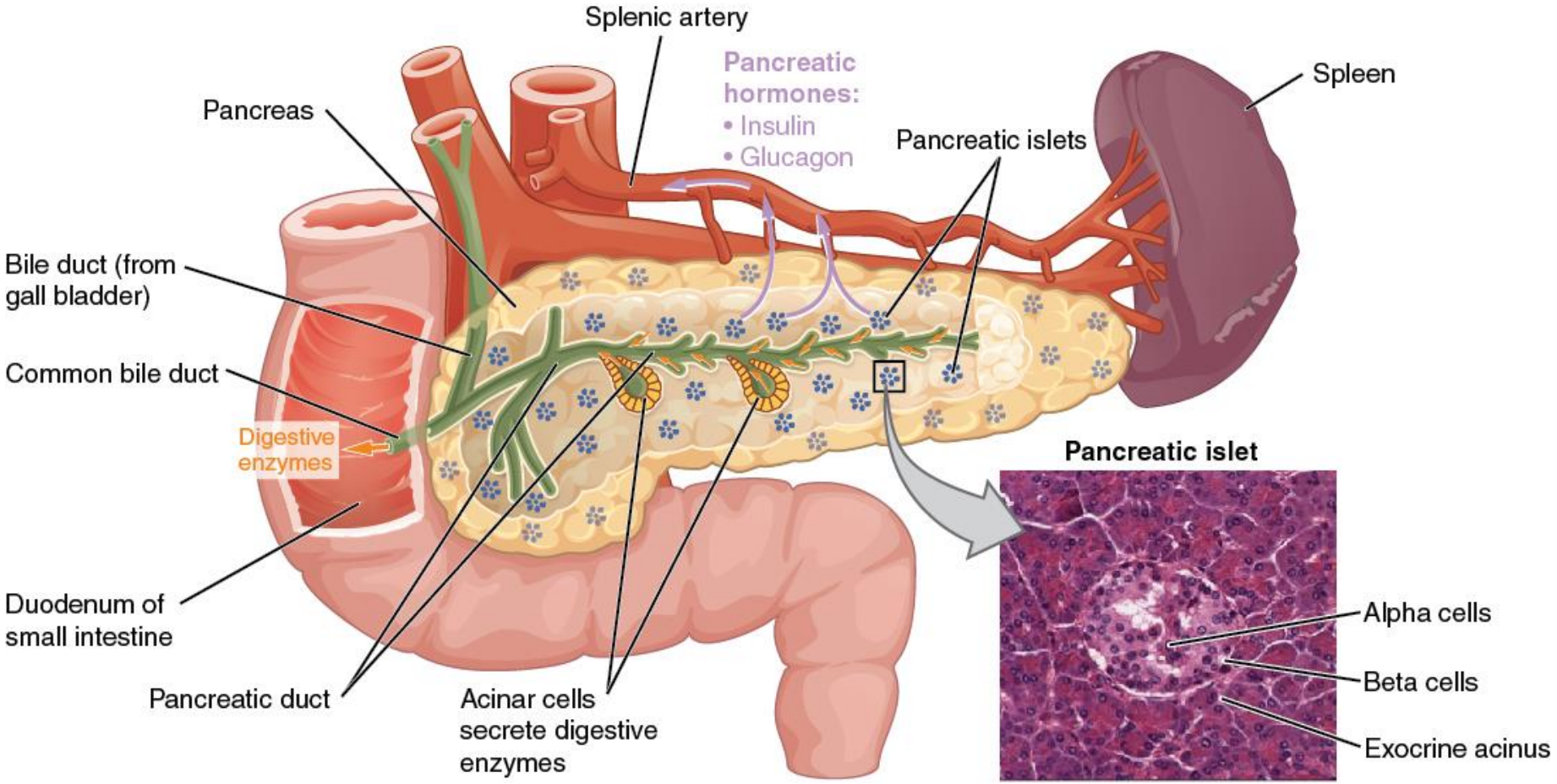
Pancreas

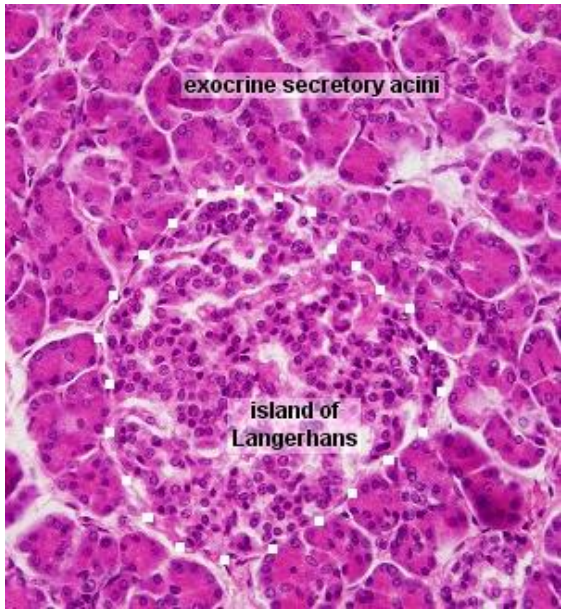
- behind stomach and under liver, the head of pancreas is next to duodenum
- approx. 15 cm; 60-90 g
- endocrine (1.5 - 4.5 % of volume) and exocrine function (production of pancreatic juice containing HCO_3^- and precursors of digestive enzymes)

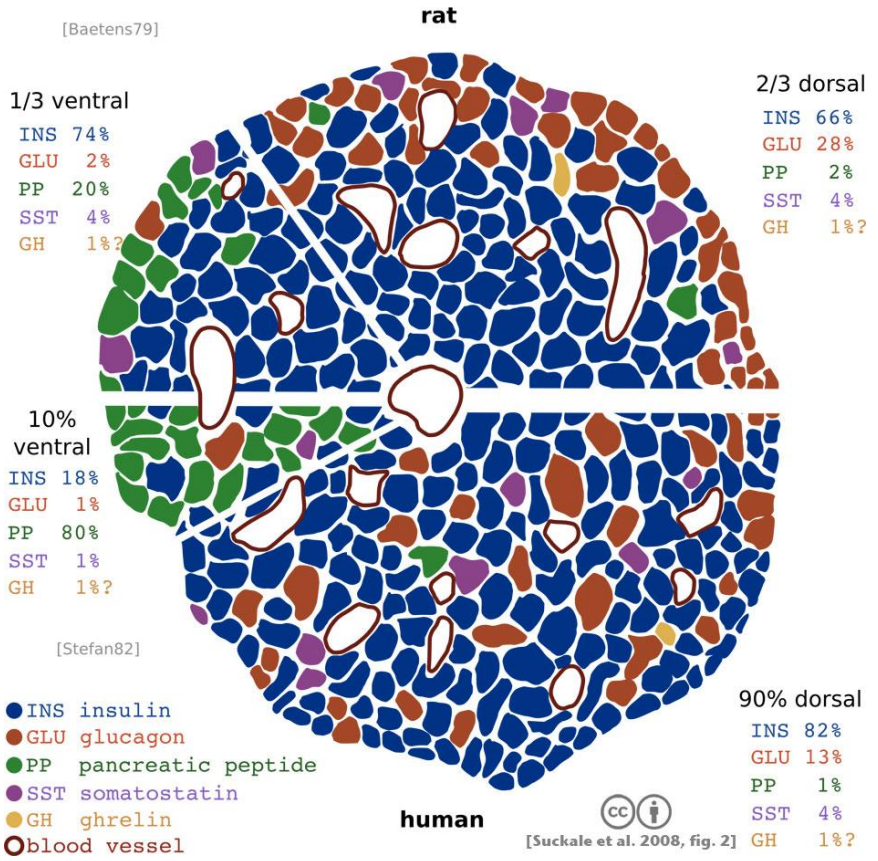


Microanatomy of pancreas

- fibrous sheath on the surface and septa reinforcing the inner tissue
- dense network of capillaries along septa
- exocrine alveolar gland divided into lobes (*acini*) – acinar cells + centroacinous cells
- **Islets of Langerhans** (approx. 1-3 mil.):

α-cells > glucagon
β-cells > insulin
PP (γ- / F) cells > pancreatic polypeptide
δ-cells > somatostatin
ε-cells > ghrelin





Pancreas - endocrine function

- hormones travel through the portal blood to the liver:

1. **nutrient storage** (glycogen, storage lipids)
2. **mobilization of energy reserves** during starvation, physical activity and stress (glucagon, adrenaline)
3. **regulation of glycemia**
4. **growth stimulation**

- humoral and paracrine regulation:

  adrenaline activates α-cells (glucagon) and inhibits β-cells (insulin)
  glucose inhibits α-cells (glucagon) and activates β-cells (insulin)
  glycogen activates α-cells (glucagon)
  somatostatin inhibits α- (glucagon) and β-cells (insulin)
  insulin inhibits α-cells (glucagon) located at the edge of islets

Insulin

1869 Paul Langerhans - described islets of Langerhans in the pancreas

1889 Oscar Minkowski - connection between pancreas and diabetes (dog surgery)

1920 Frederick Banting and Charles Best - pure isletin extracted

1922 the world's first insulin-treated diabetic patient

1923 Nobel Prize in Physiology or Medicine

(Banting and Macleod)

1958 Nobel Prize in Chemistry

(Frederick Sanger for describing the structure of insulin)

Insulin

- a peptide composed of 51 AMK (6 kDa)
- chain A and B connected by two disulfide bonds
- preproinsulin > proinsulin (84 AMK) > cleavage of chain C > insulin
- half-life 5-8 min
- degraded in liver and kidneys (endocytosis of the insulin-receptor complex)
- insulin released in pulses, the main stimulus is **increase in blood glucose**
- mechanism of insulin release:

↑ glucose in plasma > ↑ glucose in β-cells (GLUT2) > ↑ glc oxidation (Krebs cycle) > ↑ ATP > closing the ATP-controlled K^+ channels > depolarization > opening the potential-driven Ca^{2+} channels> ↑ Ca^{2+} in the cell > insulin exocytosis and opening of K^+ channels

- stimulation through vagal nerve, gastrin, secretin, GIP (gastric inhibitory polypeptide/enterogastron), GLP-1 (glucagon-like peptide/enteroglucagon)
- some AAs, free fatty acids, some pituitary and steroid hormones increase the secretion of insulin

Insulin: synthesis

translation (β-cells)

↓

preproinsulin

↓

translocation to the ER lumen
(cleavage of 24 AA signal peptide)

↓

proinsulin

↓

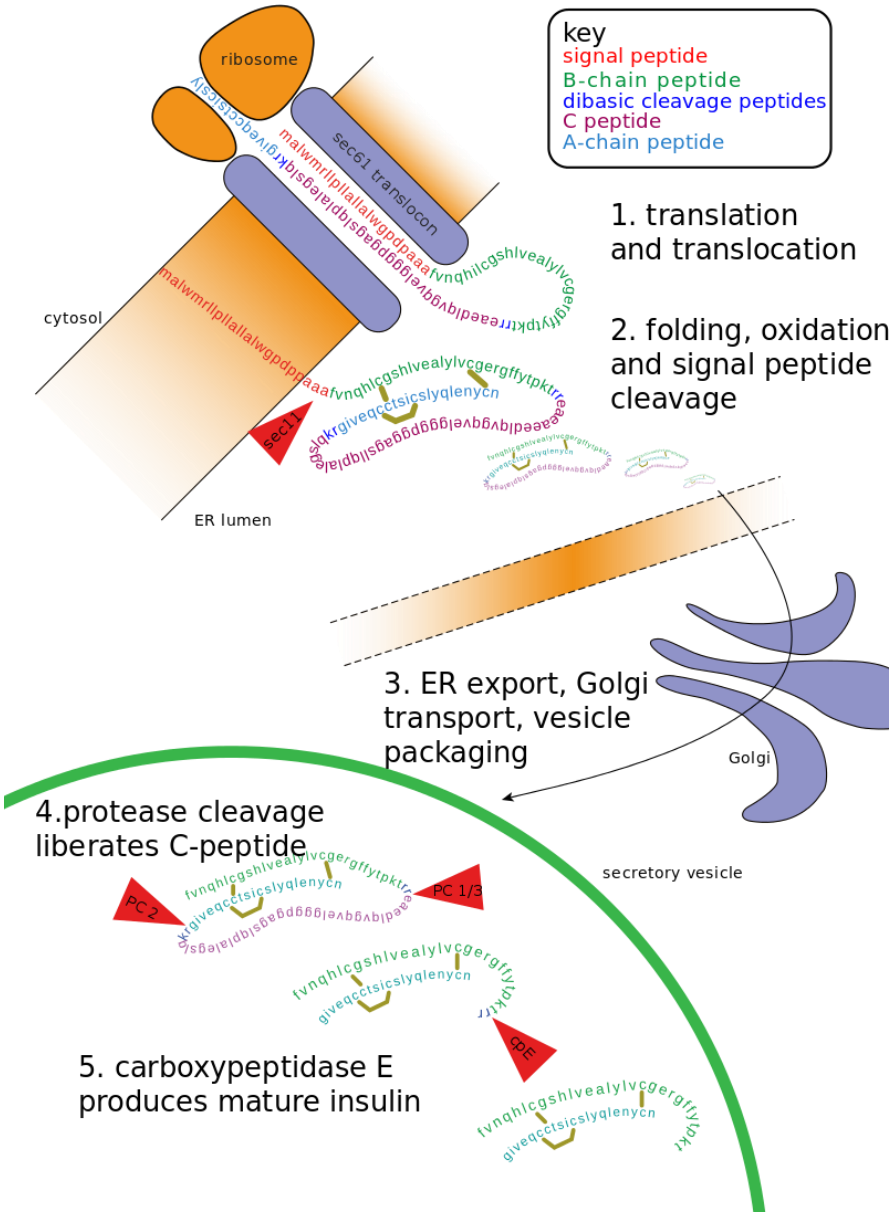
transport to GA

↓

convertases cleave out
C-peptide and stimulates synthesis
of **insulin**

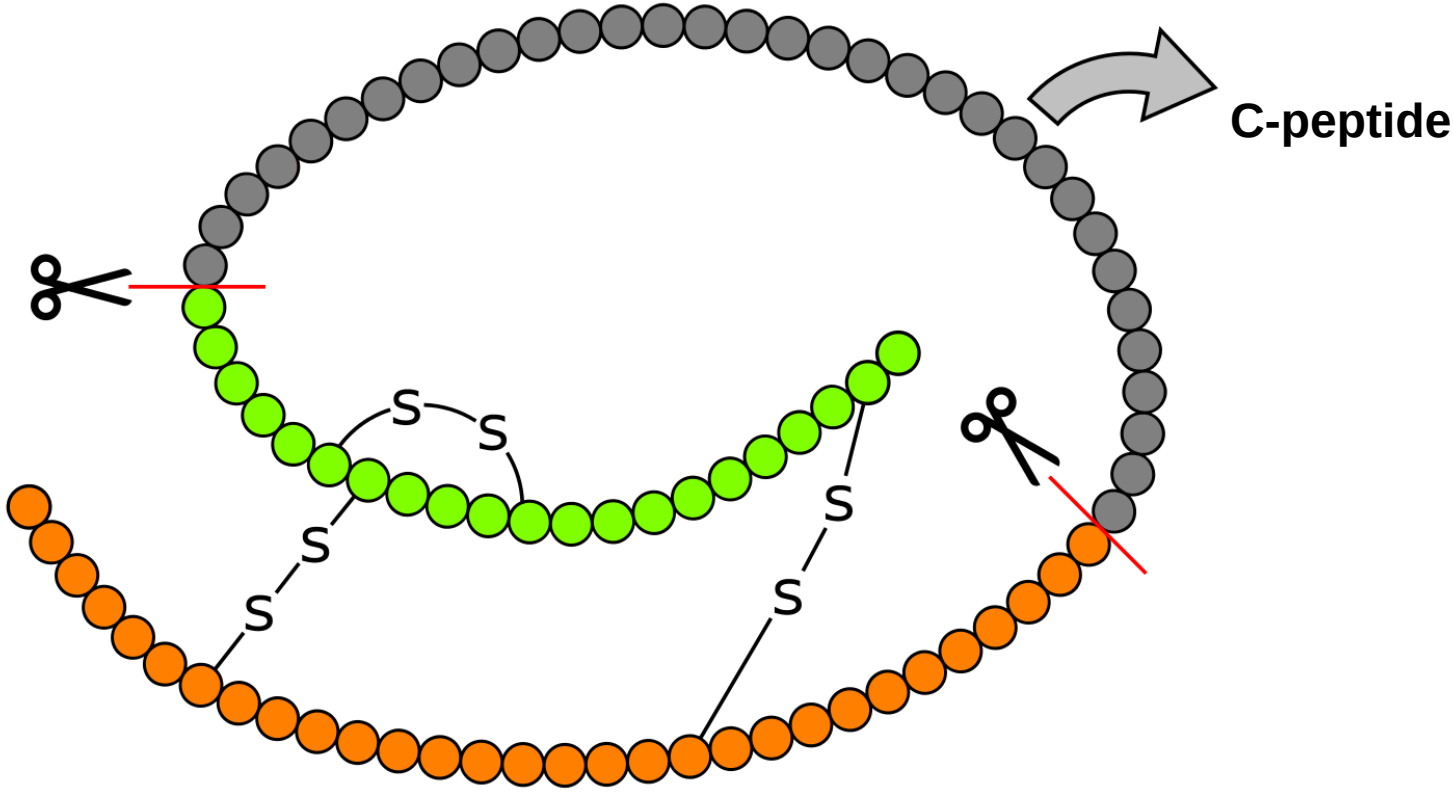
↓

stored in secretory granules before
stimulating exocytosis



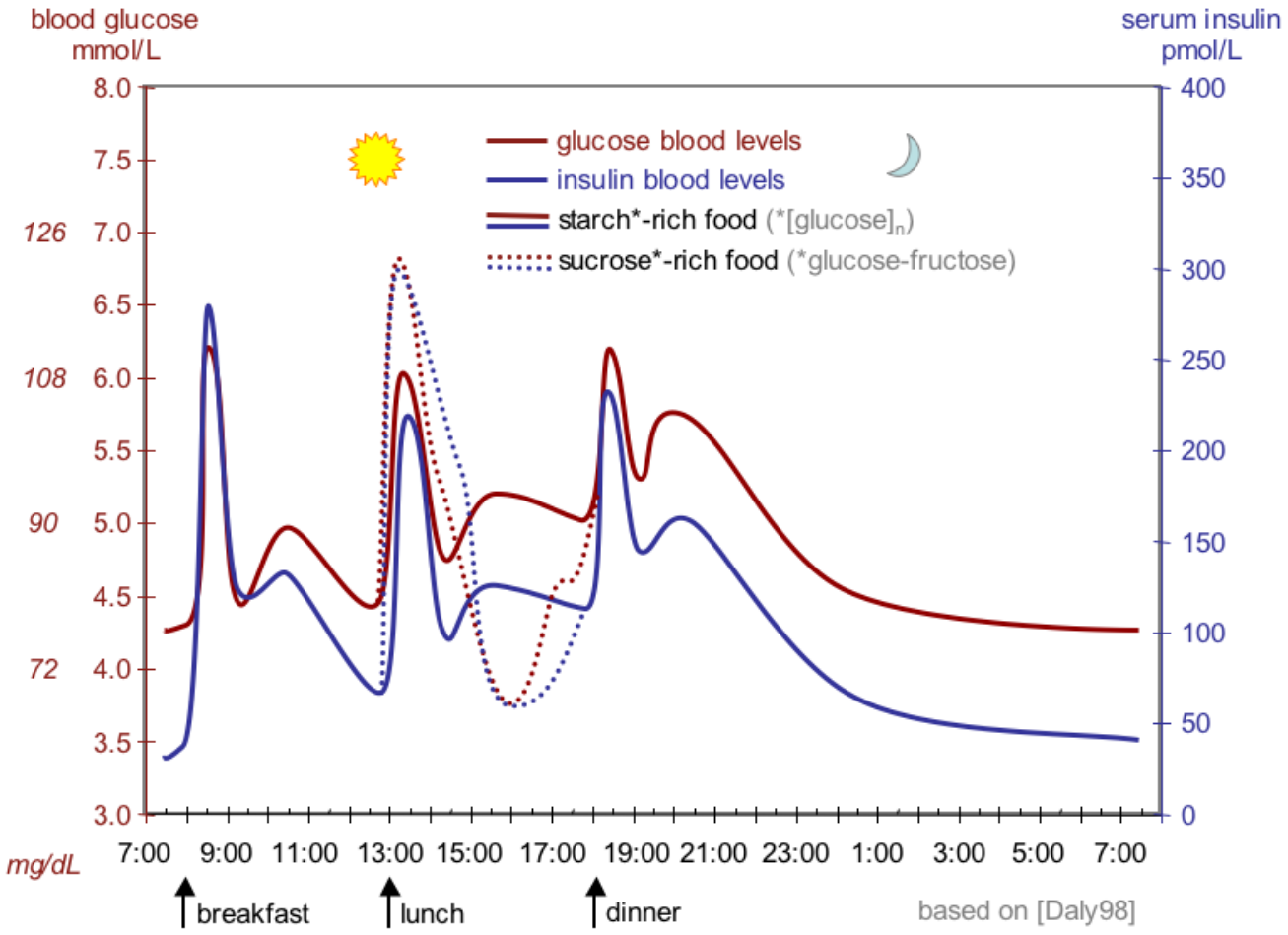
Insulin: synthesis

- chain A of 21 AAs stabilized by a disulfide bridge
- chain B of 30 AAs
- chains inter-connected by two disulfide bridges

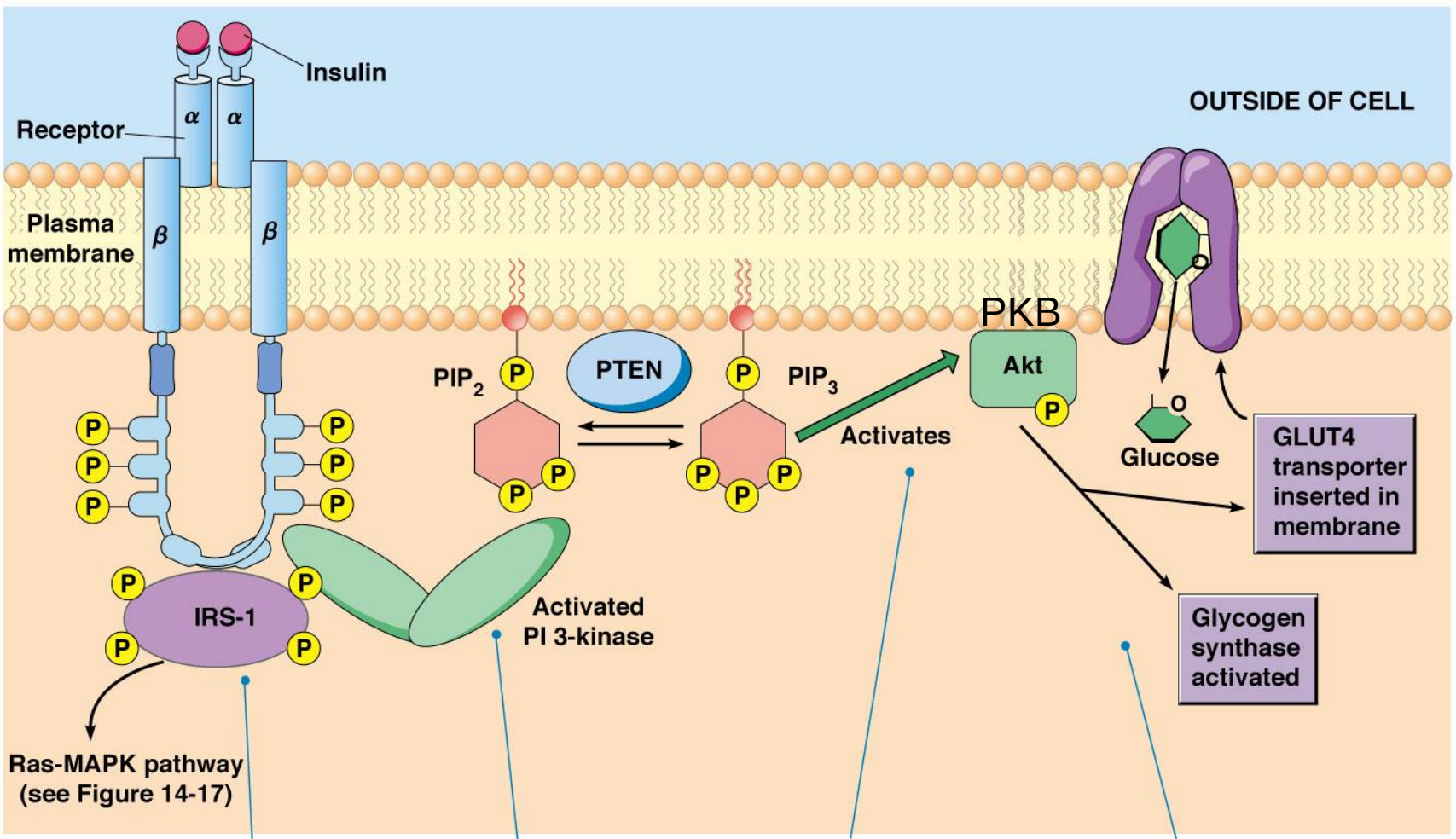


Insulin

- pulse release based on glycemia
- pancreas of a healthy adult contains about 6-10 mg of insulin, of which about 2 mg is used daily



Insulin



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

Insulin

insulin binding > autophosphorylation of receptor β subunit > insulin receptor substrate 1 (IRS-1) and its phosphorylation > phosphorylation of intracellular proteins with SH2-domains (protein kinase B = Akt) > increase of glycogen synthase activity and incorporation of GLUT4 glucose transporters into the cell membrane

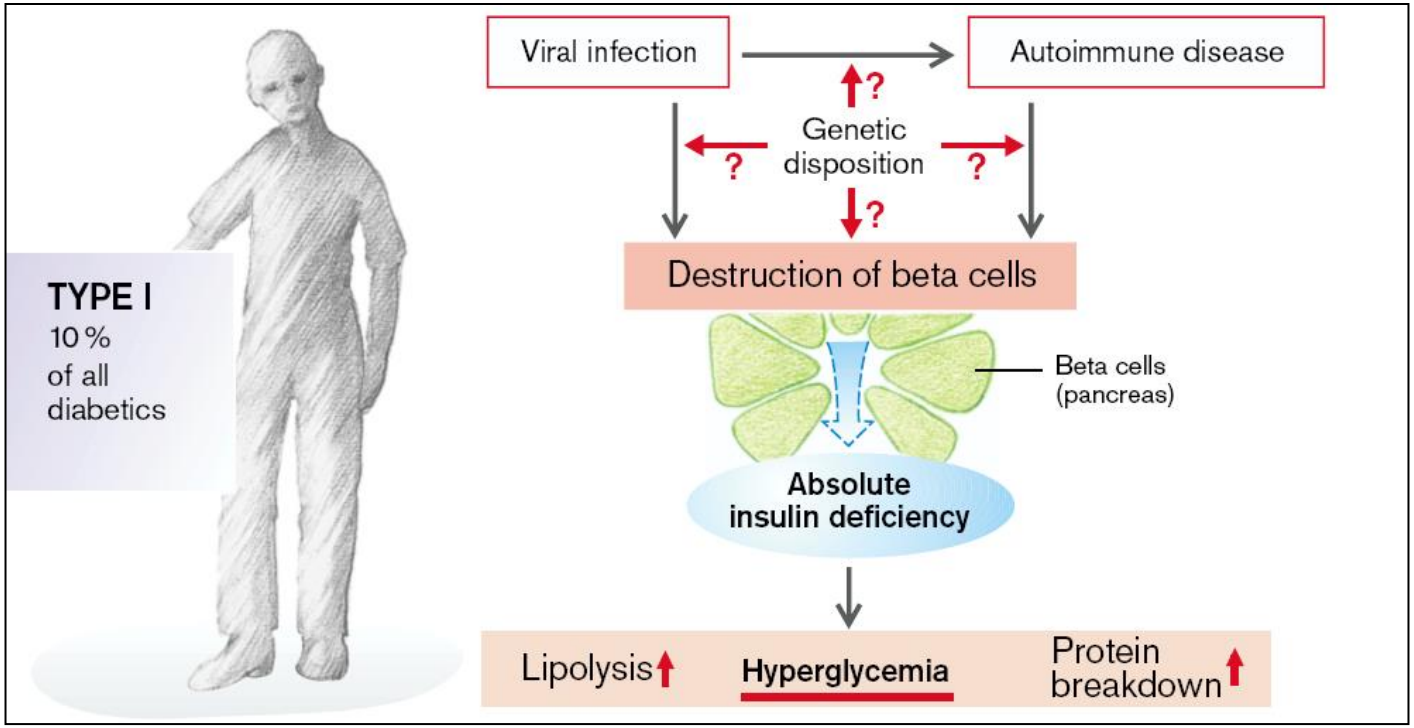
- concentration of insulin in between meals is about 57-79 pmol/l

Functions:

- **lowers blood glucose**
- **supports growth** (Ras-MAPK) **and anabolism** (fat formation, supports storing of glc in liver and AAs in the form of proteins in skeletal muscles)
- synthesis of glycogen in the liver
- **incorporation of GLUT4 into the membrane of skeletal muscle**
- stimulates Na^+/K^+-ATPase and thus supports re-uptake of dietary K^+

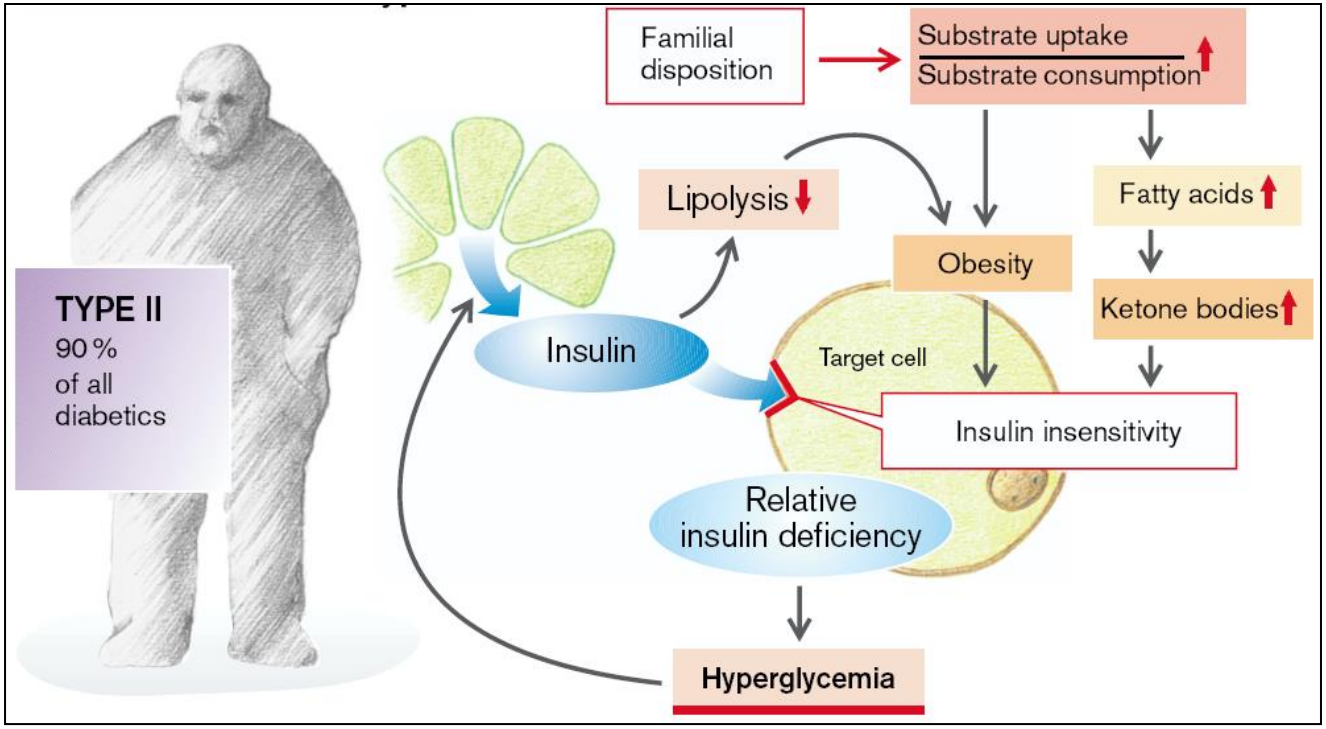
Diabetes mellitus type I: insulin-dependent (IDDM), juvenile diabetes

- insulin deficiency
- damaged β-cells, eg. after exposure to toxic substances or due to an autoimmune disease (often caused by a viral infection)
- most patients have detectable antibodies to islets of Langerhans or insulin
- genetic predispositions (more common in certain types of HLA)
- patients are given insulin



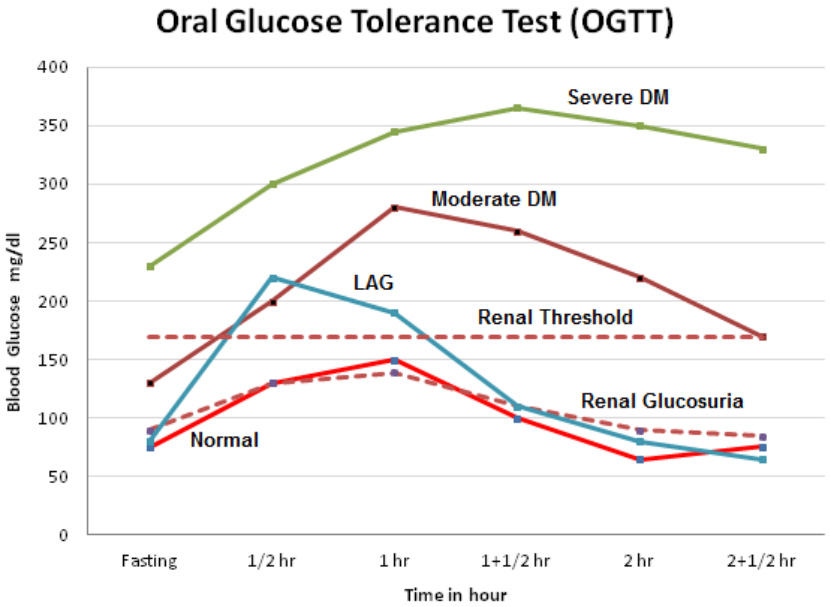
Diabetes mellitus type II: non-insulin-dependent (NIDDM), senile diabetes

- reduced sensitivity of target organs to insulin > relative insulin deficiency
- associated with normal or even higher insulin production
- genetic predisposition, obesity, autoantibodies to insulin or its receptors
- type II diabetes can develop even at a young age (**MODY** = *maturity onset diabetes of the young*)
- lifestyle modification, insulin administration only in more severe cases



Other types of diabetes mellitus:

- combined activity with hormones supporting growth and response to stress conditions:
  - somatotropin (growth hormone)
  - thyroid hormones
  - glucocorticoids (Cushing disease - **steroid diabetes**)
  - adrenaline
  - progestogens and human placental lactogen (**gestational diabetes**)
  - glucagon
- under normal circumstances, these hormones act synergistically and, by acting against insulin, keep glycemia normal



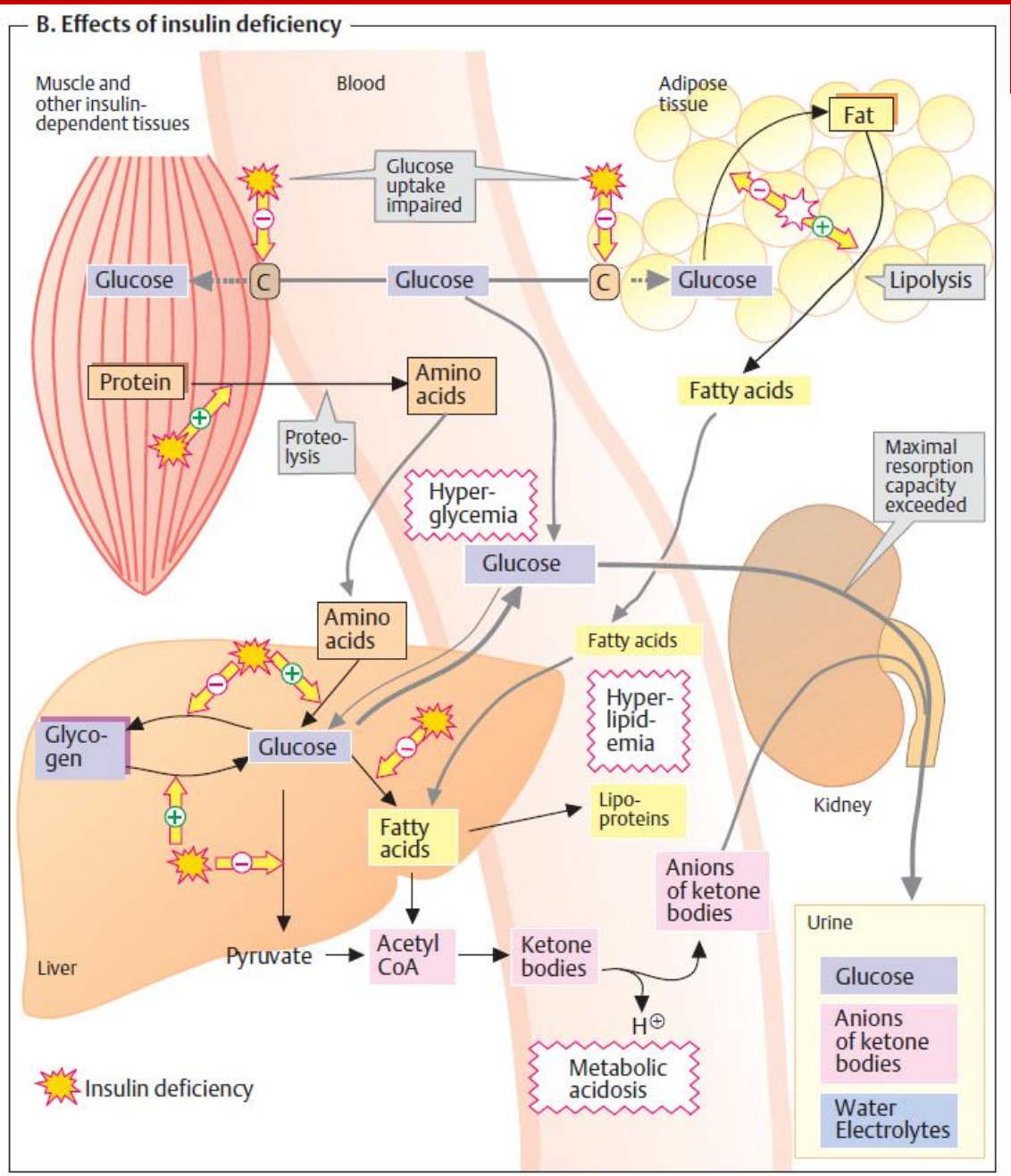
LAG - hyperthyroidism, pregnancy

Insulin: acute deficiency

- the main consequence is **hyperglycemia**
- high blood sugar > hyperosmolarity in extracellular environment > excretion of glucose in urine is associated with loss of water, Na^+ and K^+ > **dehydration > feeling thirsty**
- **breakdown of muscle proteins to release AA** > weight loss and muscle weakness
- **lipolysis in adipose tissue** > higher levels of fatty acids in the blood > conversion to other acidic metabolites in the liver > acidosis > **deep breathing** (Kussmaul) and breakdown into ketonic substances (**acetone in breath**)

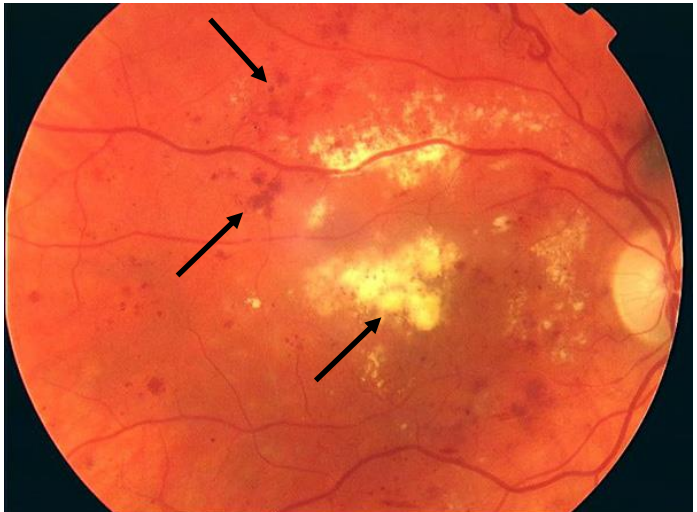
- disorders of metabolism, electrolytes and osmolarity can cause hyperosmolar or ketoacidic **coma**
- type I diabetes: hyperglycemia, hyperosmolarity
- type II diabetes: hyperglycemia, hyperosmolarity, increased proteolysis and lipolysis (ketoacidosis)

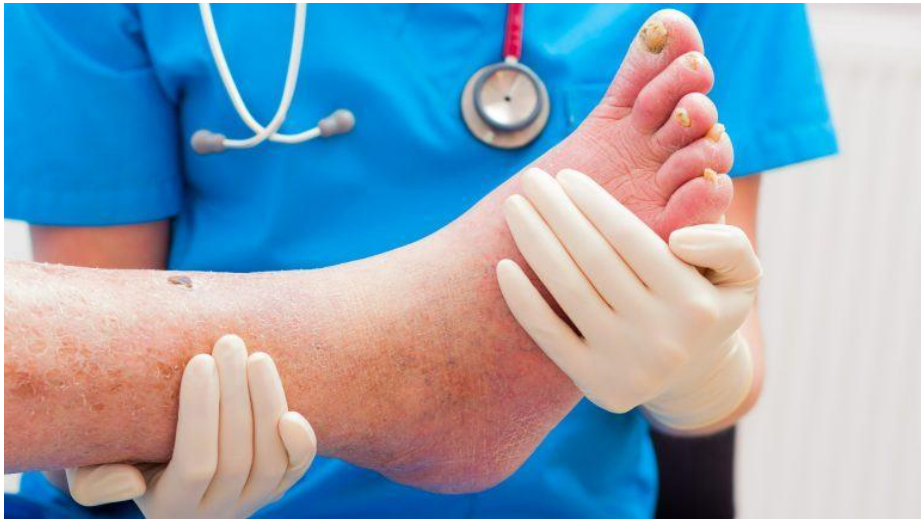
Insulin: acute deficiency



Insulin: chronic deficiency

- hyperglycemia leads to irreversible damage to the body after several years to decades
- glucose in cells reduced to **sorbitol** > accumulation in cells > osmotic edema (**clouding of the eye lens - cataract; nerve transmission disorders**)
- cells not absorbing glucose (eg. leucocytes) in hyperosmolar environment > weakened immunity > higher risk of **infection**
- glycated erythrocytes and walls of blood vessels > **microangiopathy** > blindness, kidney damage
- **macroangiopathy** > heart attack, stroke, kidney damage
- diabetic foot syndrome (microangiopathy + ischemia + infection)





Therapy - synthetic insulin

- pure insulin is administered in solution with zinc (six insulin molecules forming hexamer binds to two zinc atoms), peptide stabilizers and preservatives
- formerly porcine or bovine insulin extracted from the pancreas (minimal differences in AA chain); today predominantly human (**HM insulin**) is used produced by genetic engineering in *Escherichia coli* or *Saccharomyces cerevisiae*
- fast and depot insulins
- administration subcutaneously using insulin syringes, pens or pumps
- application 4 μg of insulin per 1 kg of human weight intravenously reduces blood glucose by about half (assuming a normal effect of the insulin receptor)
- it is not possible to administer orally due to degradation!

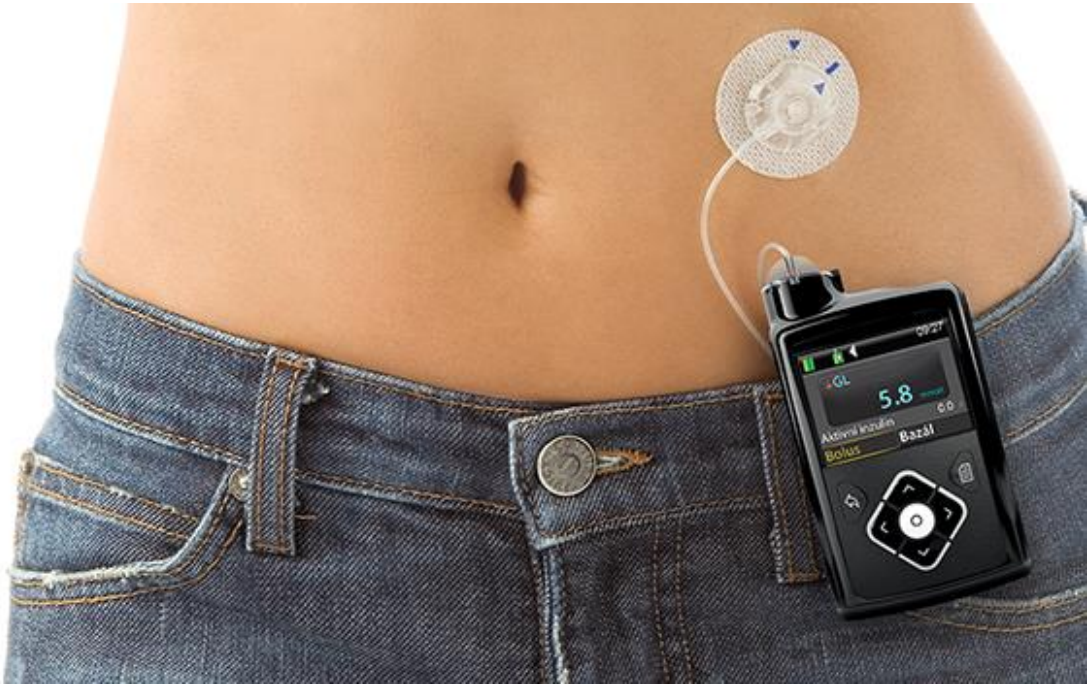
Therapy - synthetic insulin

Insulin pen

- cheaper
- repeated injections
- more manipulation
- different types of insulin

Insulin pump

- more expensive
- bolus doses when eating
- controlled by software
- fast insulin



Insulin: excess and hypoglycemia

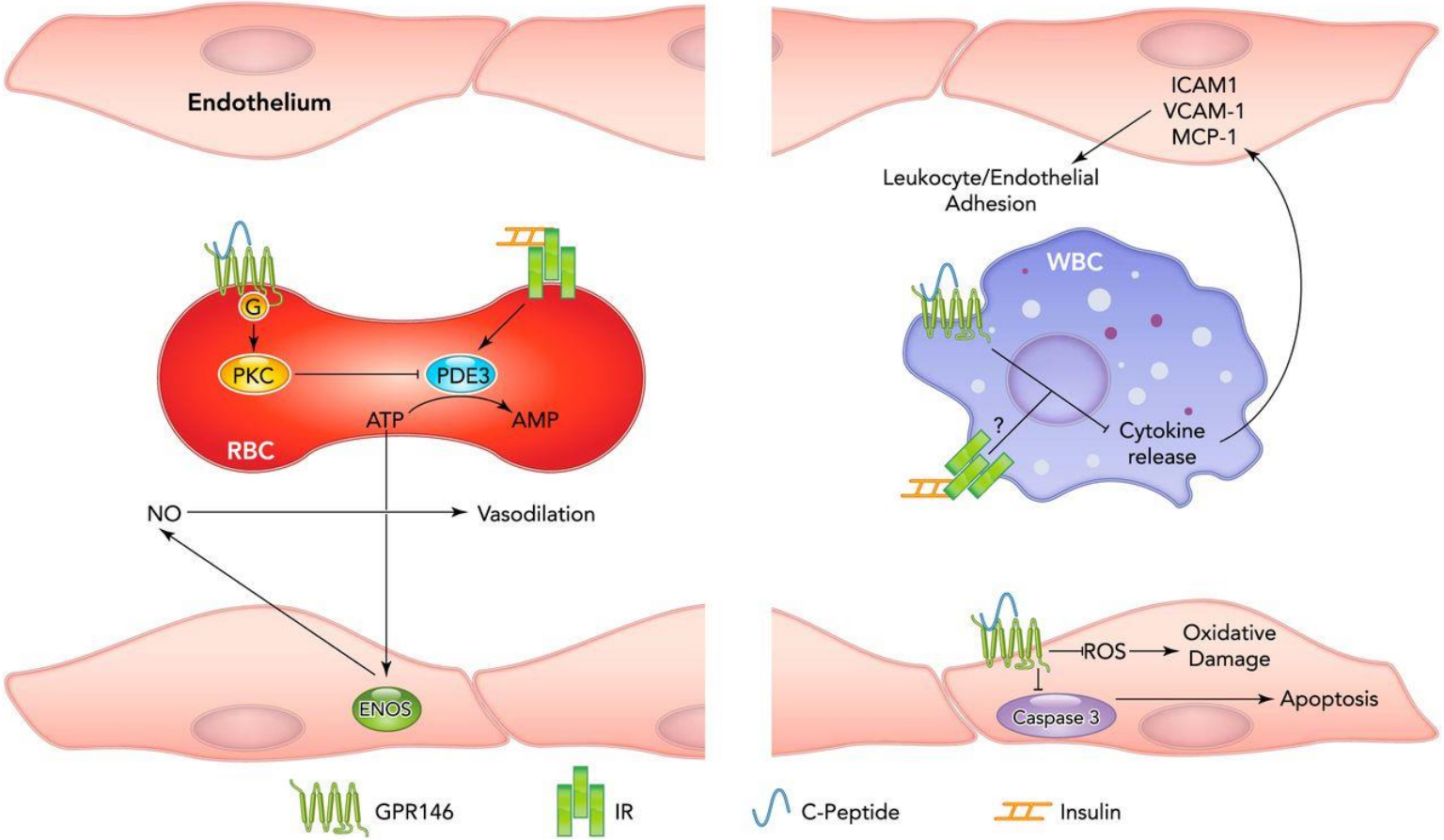
- most often caused by high level of insulin (eg. decreased insulin requirement during exercise)
- oral administration of antidiabetics
- genetic disorders, less frequently tumors or autoimmune disorders (antibodies that bind and gradually release insulin)

- hypoglycemia occurs naturally during intense work
- hypoglycemia can also be caused by a lack of insulin antagonists (glucagon, growth hormone, glucocorticoids and others)
- glucose disorders
- alcoholism

- **hypoglycaemia > hunger > sympathetic activation > increased heart rate, sweating, tremor > convulsions, loss of consciousness > irreversible brain damage**

C-peptide

- binding to endothelial cells, nerve cells, fibroblasts and renal duct cells
- action via G proteins
- ↑eNOS, ↑ Na^+/K^+-ATPases and others (eg vasodilation, nerve transmission)
- positive effects in patients with diabetes I (nervous activity, blood flow…)



Glucagon

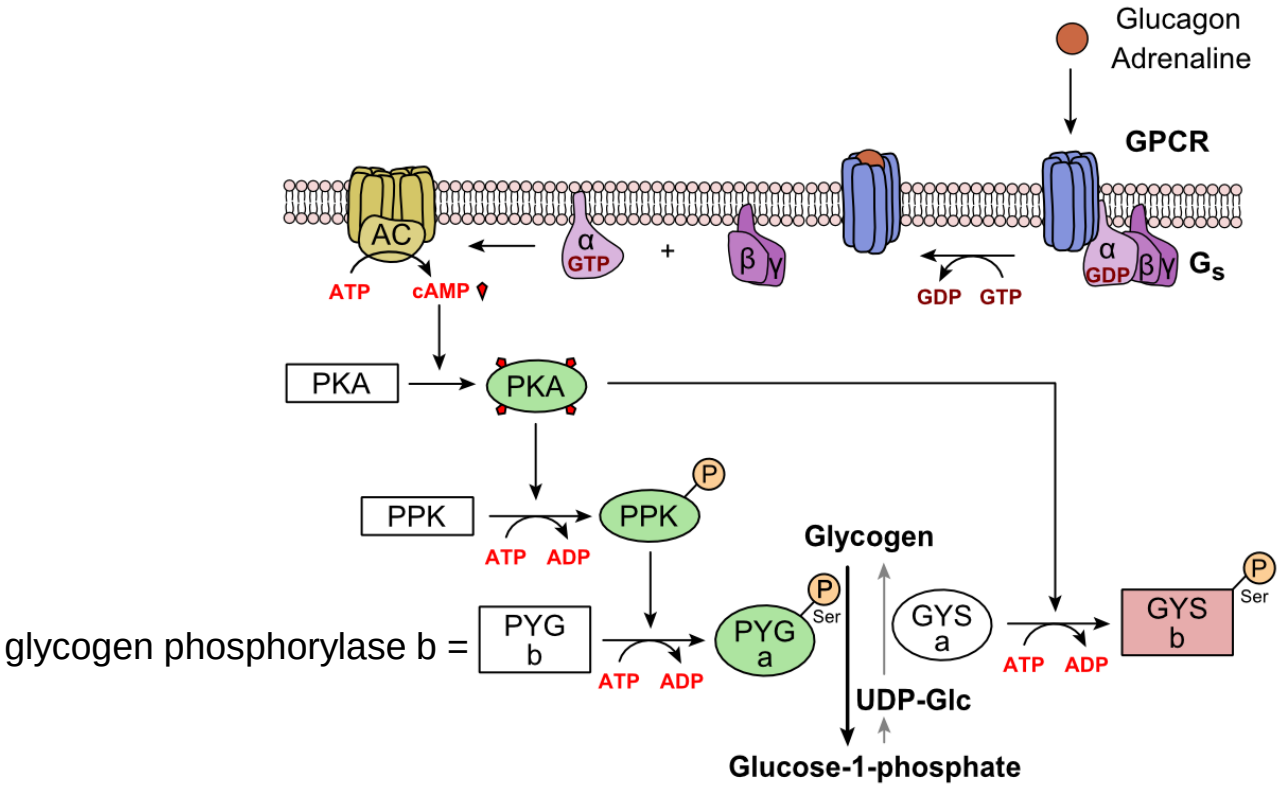
- α-cells of the islets of Langerhans
- 29 AA (3.5 kDa)
- **secretin protein family** (sekretin, somatoliberin, gastric inhibitory polypeptide GIP, vasoactive intestinal peptide and others)
- precursor called proglucagon > alternative products > some of them inhibit glucagon production and increase insulin production
- stored in secretory granules and released by exocytosis
- insulin antagonist

Regulation:

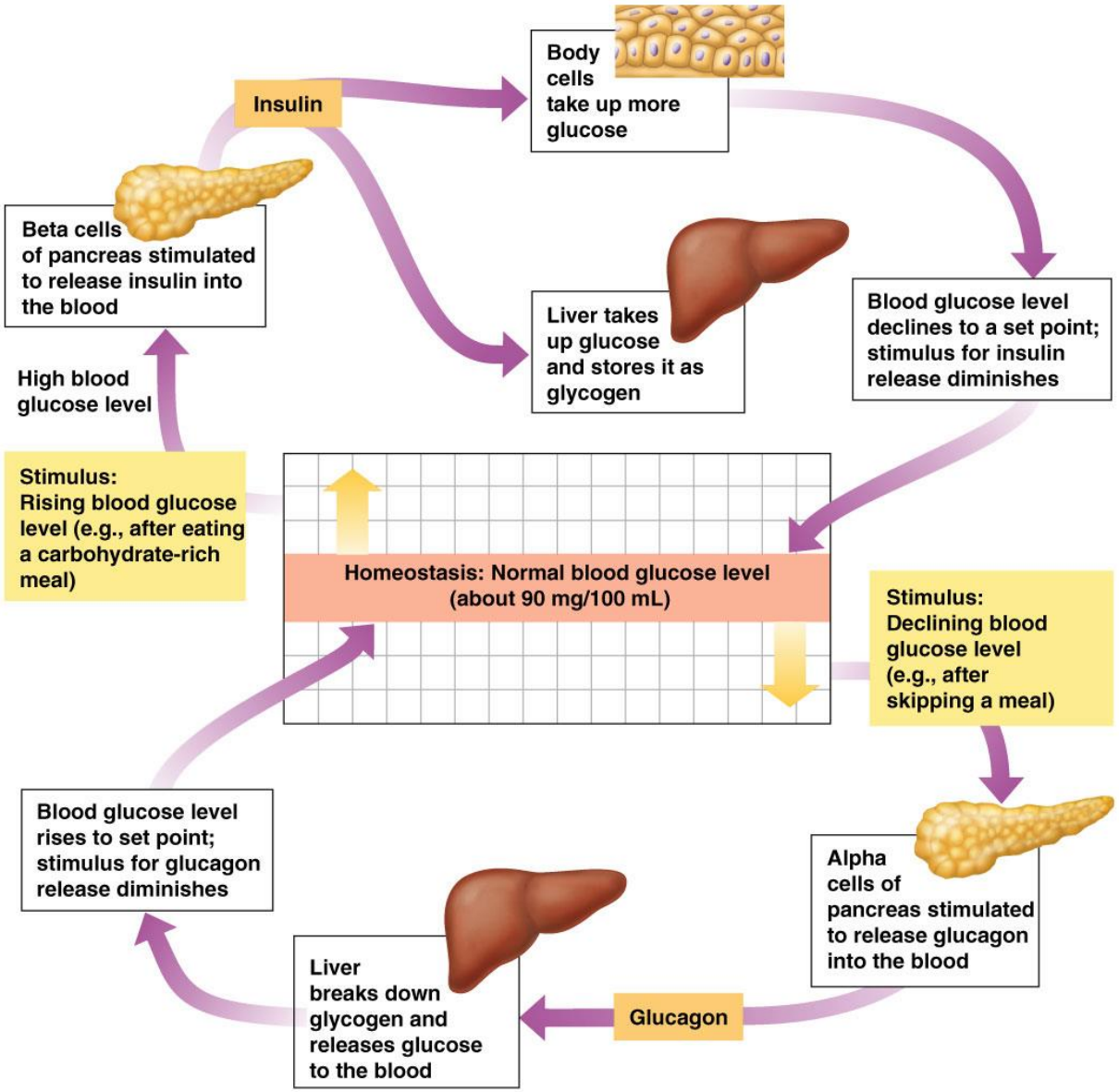
- hypoglycemia (released during starvation and prolonged exercise)
- stimulation by some AA from food (alanine, arginine)
- sympathetic stimulation via β_2-adrenergic receptors, cholecystokinin
- suppressed by glucose, high plasma levels of free AA, insulin and somatostatin

Glucagon

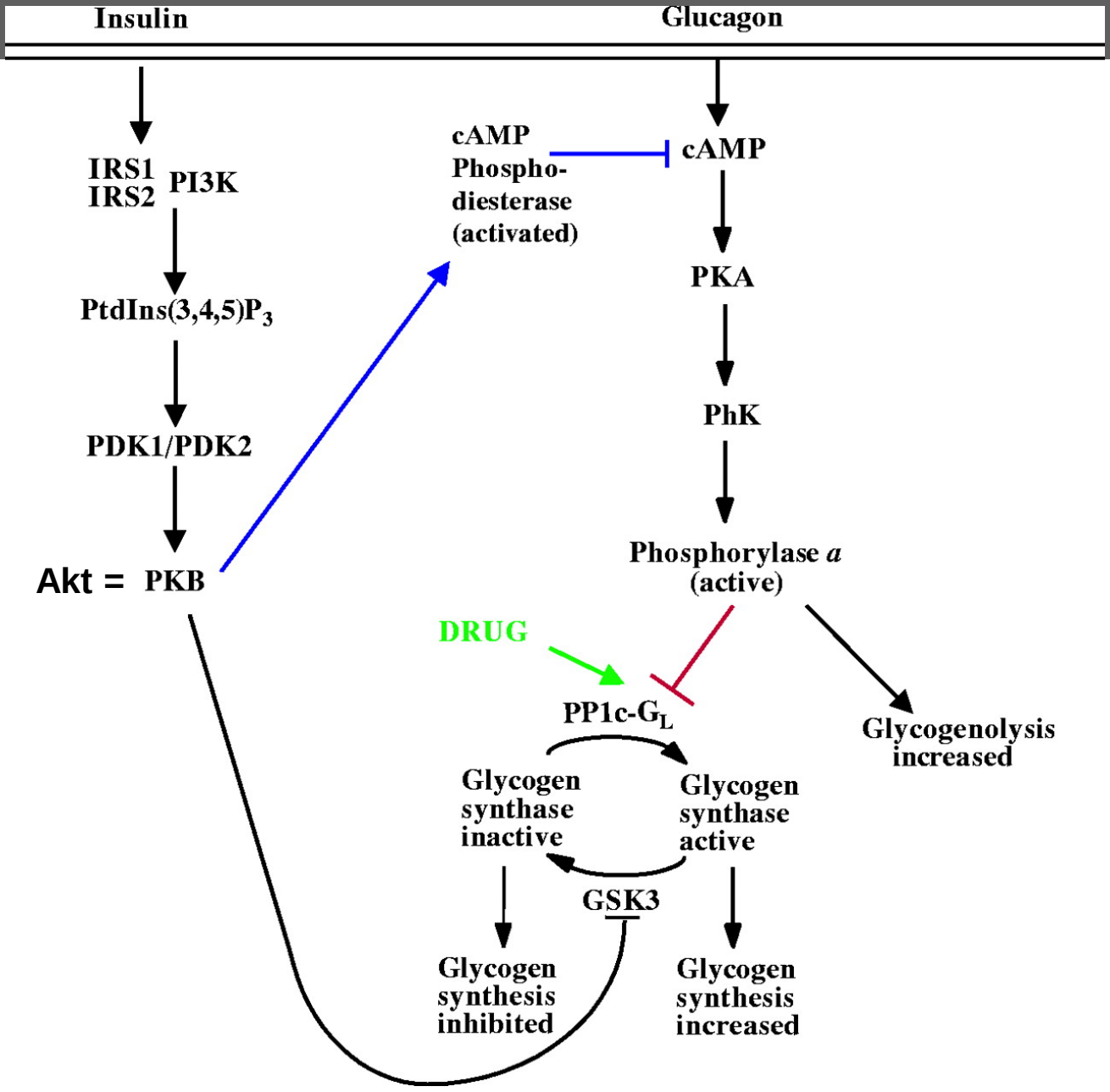
- acts through G proteins, cAMP, CREB
- **regulation of glycemia** (securing the energy source in the time between food intake and under increased activity)
- **increases glycogenolysis in the liver** (glucagon activates the enzyme glycogen phosphorylase a; not in the muscles!)
- **gluconeogenesis** from lactate, AA and glycerol (lipolysis)



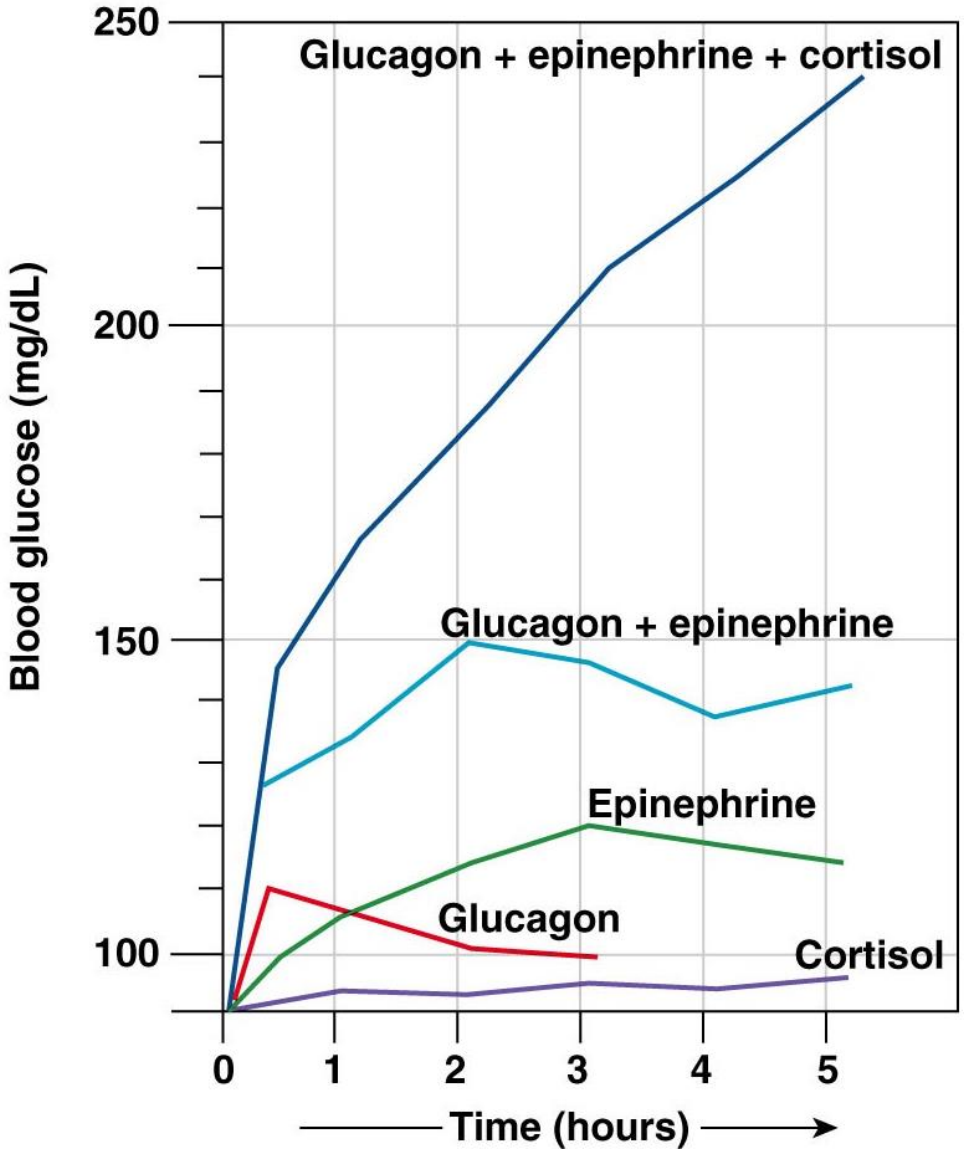
Insulin, glucagon and glycemia



Insulin, glucagon and glycogen metabolism



Synergistic action of hormones in the regulation of glycemia



Somatostatin (growth hormone–inhibiting hormone)

- **δ-cells of the islets of Langerhans, duodenum and intestine + neurosecretion in the hypothalamus** (inhibits growth hormone secretion in the adenohypophysis)
- encoded by a single gene in humans (other vertebrates mostly 6)
- homolog of cortistatin
- released with increased concentration of glucose and some AA (arginine) in the blood after a meal, induced by a low pH in the stomach
- endocrine and paracrine function

- acts through G proteins
- inhibits secretion of hormones in adenohypophysis (see earlier)
- inhibits release of insulin, glucagon, histamine, cholecystokinin, gastrin, secretin, motilin and other gastrointestinal hormones
- inhibition of gastric acid production (histamine antagonist), gastric emptying, smooth muscle contractions, intestinal blood flow and exocrine function of the pancreas

Pancreatic polypeptide (PP)

- PP (γ- /F) islets of Langerhans (especially the head of the pancreas)
- 36 AA (4.2 kDa)
- increased secretion during starvation, exercise, acute hypoglycemia and after protein intake x decreased secretion due to somatostatin and intravenous glucose
- stimulated by vagal nerve, cholecystokinin and gastrin

- regulation of endocrine and exocrine pancreatic secretion (antagonist of cholecystokinin), gastrointestinal secretion and hepatic glycogen levels
- **inhibits digestion**, including intestinal motility and gastric emptying
- **the exact physiological function is not yet clear**

- PP levels increased in patients with anorexia; administration of PP to rodents reduces food intake

Gastrointestinal tract

- the digestive tract is the largest endocrine organ
- endocrine cells are diffuse in the GI tract

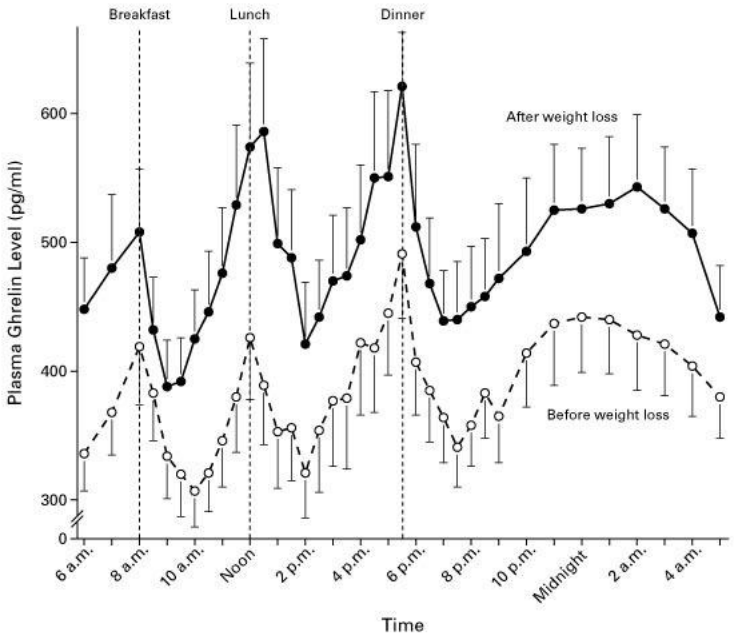
Hormones regulating the digestion:

- **ghrelin/leptin**
- **cholecystokinin (CCK)**
- **gastrin**
- **secretin**
- **motilin**
- **vasoactive intestinal peptide (VIP)**
- **gastric inhibitory polypeptide (GIP)**
- **glucagon-like peptide (GLP-1, enteroglucagon)**

and other hormones

Ghrelin ("Hunger hormone")

- CNS-affecting peptide
- belongs to the family of motilin peptides
- produced in **stomach and duodenum**, pancreas, small intestine, lungs, gonads, adrenal cortex, kidneys, placenta and brain
- produced by cleavage of preproghrelin (homolog of promotilin) > proghrelin > ghrelin (28 AA) and C-ghrelin (it is thought to produce hormone obestatin)
- secretion on an empty stomach x stops when the stomach stretches (secretion stops faster after intaking proteins or sugars than after lipid intake)
- ghrelin is able to cross the blood-brain barrier



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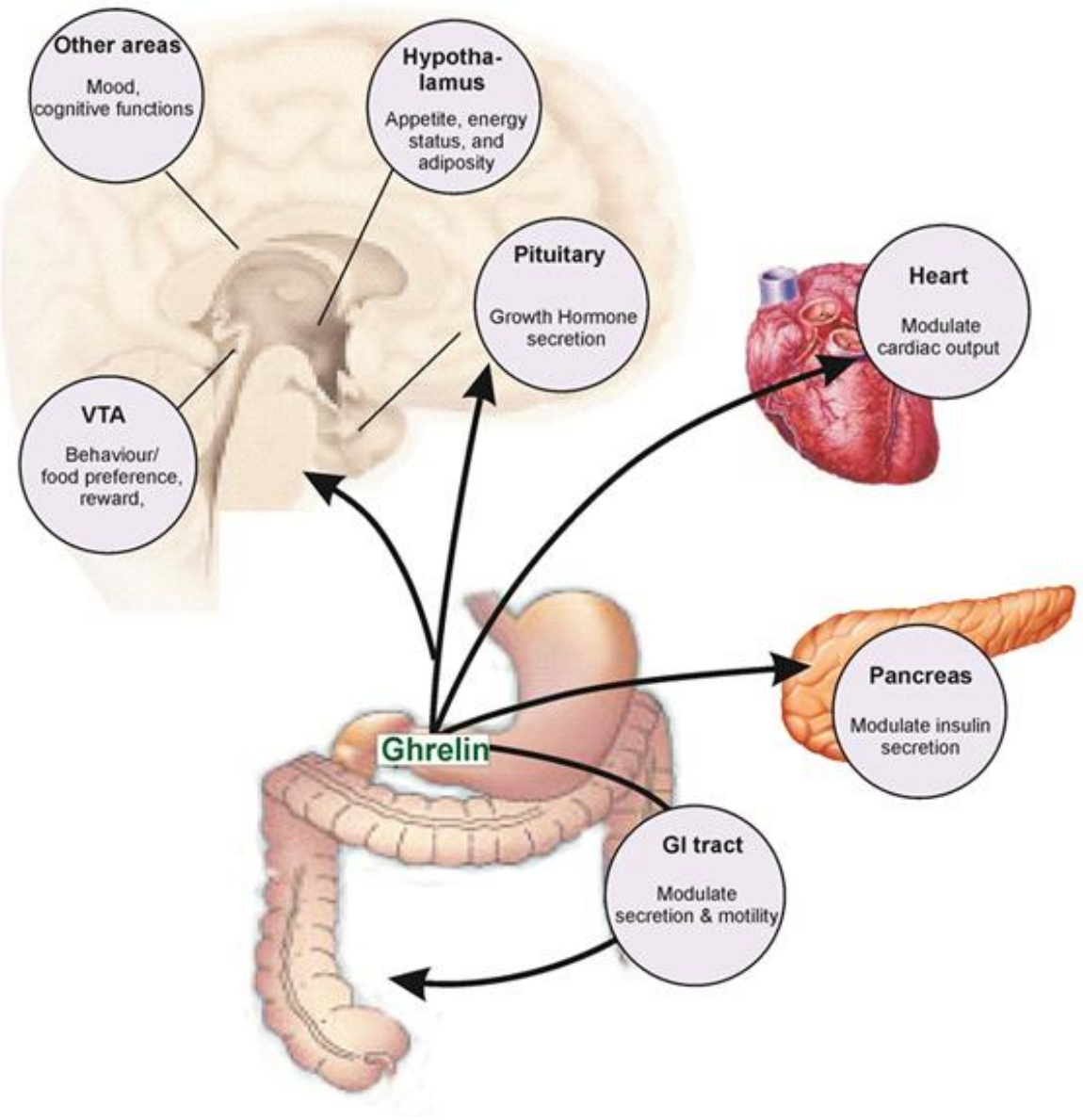
Ghrelin

- G protein-coupled receptors (the same target cells have also leptin and insulin receptors)

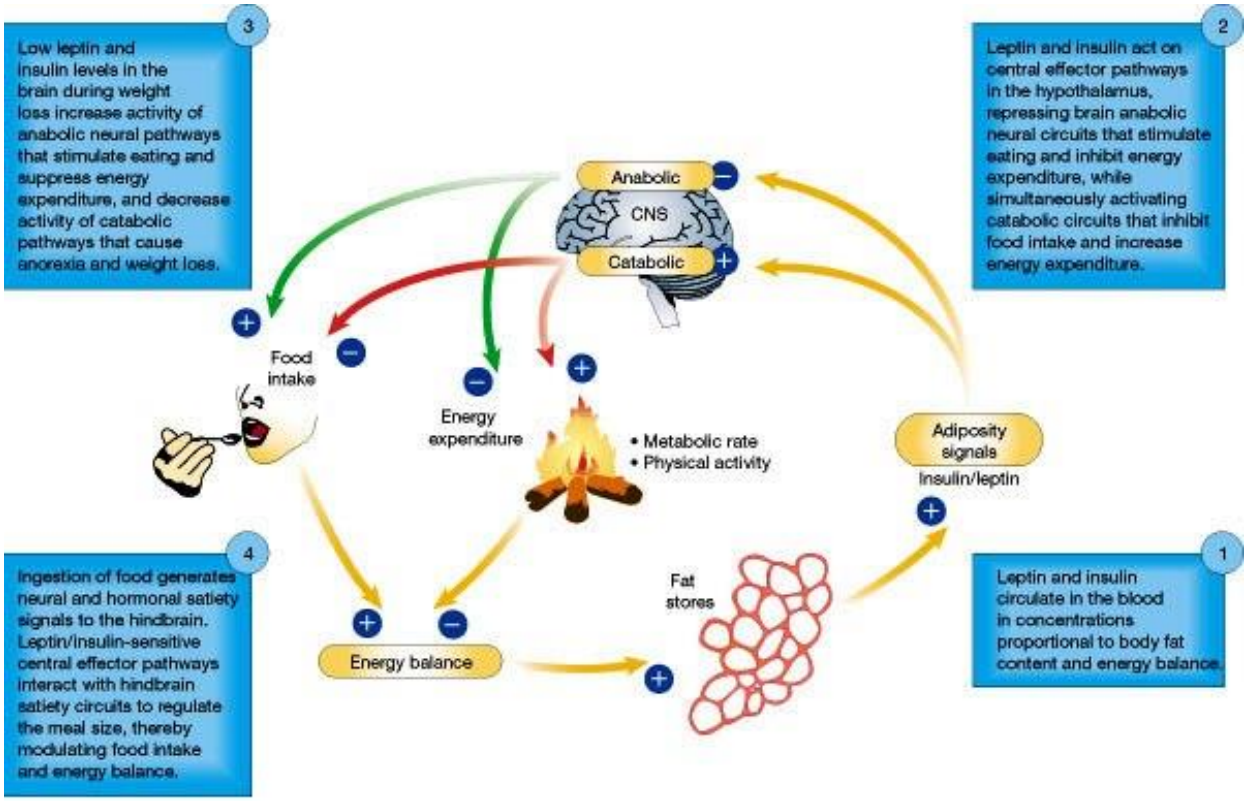
- **acts on the hypothalamic cells and increases hunger**
- activation of cholinergic-dopaminergic intermediate circuit mediating **reward reactions and appetite**
- signals to *orexigenic neuropeptide Y* (NPY) and *agouti-related protein* (AgRP) neurons > food intake
- motivation to search for food sources (confirmed by the effect of ghrelin injection), body weight regulator
- increases gastric acid production and intestinal motility (preparing body for food intake)
- energy management (reduced ATP production, fat and glycogen storage, heat production)
- antagonist of leptin and insulin

Ghrelin


Other areas
Mood, cognitive functions
Hypotha-lamus
Appetite, energy status, and adiposity
Pituitary
Growth Hormone secretion
Heart
Modulate cardiac output
VTA
Behaviour/ food preference, reward,
Ghrelin
Pancreas
Modulate insulin secretion
GI tract
Modulate secretion & motility

Leptin ("Satiety hormone")

- protein of 167 AA (16 kDa)
- produced by **white adipose tissue**, but also in brown adipose tissue, placenta, ovaries, skeletal muscles, stomach, bone marrow and other tissues
- leptin production grows exponentially with the amount of white fat
- the highest concentration in the blood between midnight and morning
- insulin and emotional stress increase level of leptin; reduced in sleep deprivation and starvation



Leptin

- acts **against ghrelin**
- **receptors in the arcuate nucleus of the hypothalamus > regulation of appetite and energy balance**
- 6 receptors encoded by one gene
- intracellular action eg. via JAK-STAT and MAPK
- reduced sensitivity to leptin observed in obese people

- stimulates satiety by irritating the nerves in the hypothalamus (**inhibition of *neuropeptide Y* and *agouti-related peptide***) and inhibits hunger
- outside the hypothalamus modulates energy expenditure, activates immune cells, pancreatic β-cells and acts as a growth factor

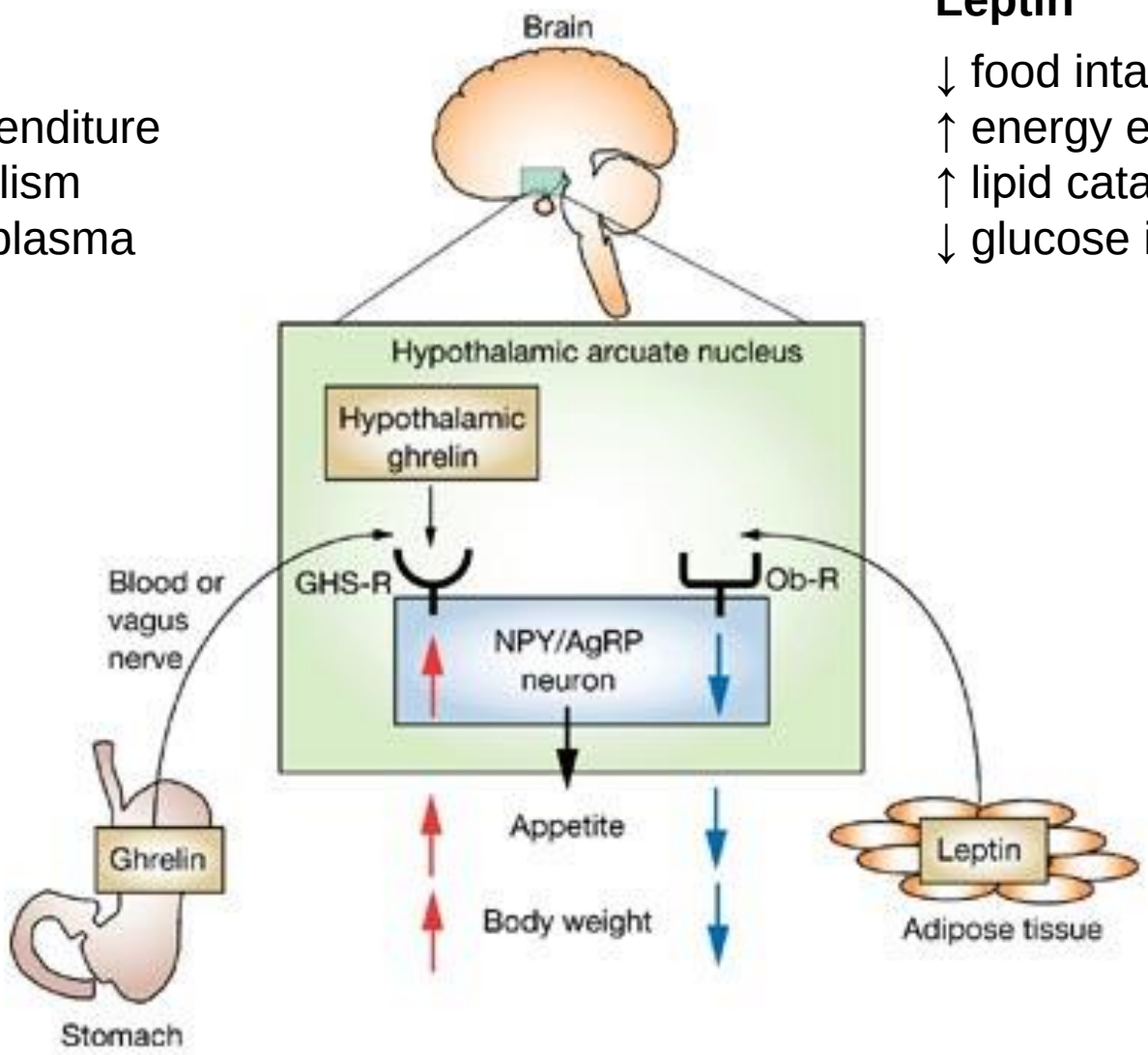
Ghrelin,leptin and metabolic control

Ghrelin

↑ food intake
↓ energy expenditure
↓ lipid catabolism
↑ glucose in plasma

Leptin

↓ food intake
↑ energy expenditure
↑ lipid catabolism
↓ glucose in plasma



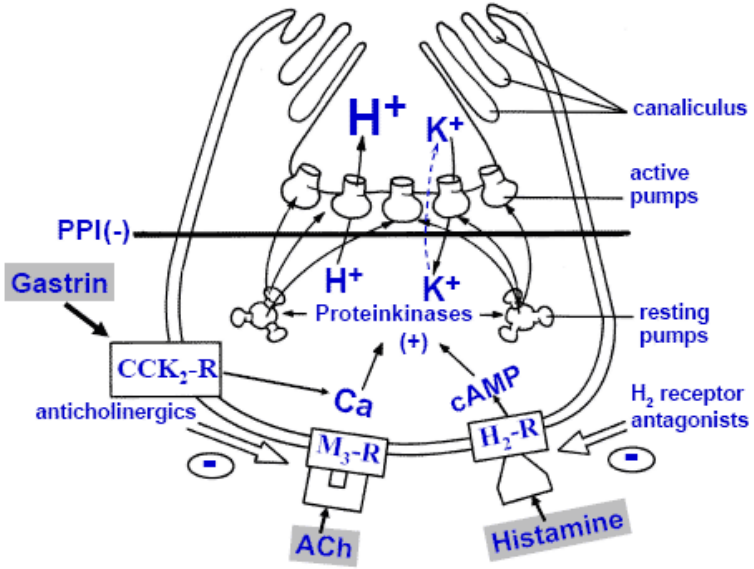
Hormones produced in GI tract

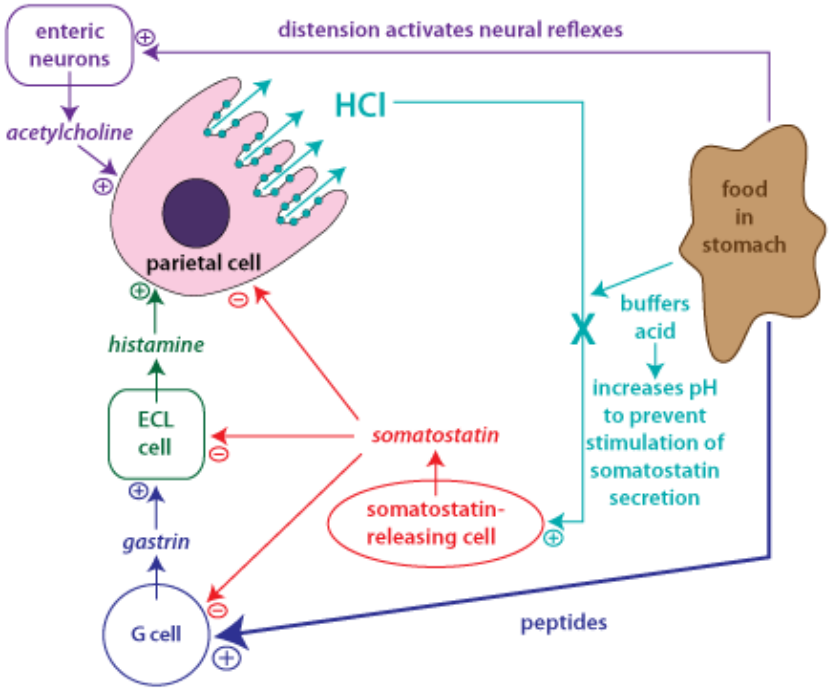
- peptides
- produced in endocrine cells of the mucosa, diffusely spread
- very similar in structure (peptide families) > similar effects at higher concentrations
- regulation neuronal, humoral, paracrine and endocrine
- **affect motility, secretion, blood supply and growth of GI tract**

HORMONE	LOCALIZATION	MAIN PHYSIOLOGIC ACTIONS
Gastrin	Gastric antrum, duodenum (G cells)	**-stimulate secretion of gastric acid and intrinsic factor from parietal cells** **-stimulate secretion of pepsinogen from chief cells** -promotes gastric and intestinal motility, mucosal growth
Cholecystokinin (CCK)	Duodenum, jejunum (I cells)	**-stimulate gallbladder contraction** **-stimulates release of pancreatic enzymes** **-relaxes sphincter of Oddi for release of bile and enzymes** -role in inducing satiety
Secretin	Duodenum, jejunum (S cells)	**-stimulate secretion of HCO_3 from pancreas** -inhibits gastrin and gastric acid secretion
Vasoactive intestinal peptide (VIP)	Enteric nerves	**-increases water and electrolyte secretion from pancreas and gut** -relaxes smooth muscles (via nitric oxide) of the gut
Gastric inhibitory polypeptide (GIP)	Duodenum, jejunum (K cells)	**-reduces gastric acid secretion** and intestinal motility **-stimulates insulin release**
Motilin	Throughout the gut (Mo cells and ECL cells)	**-increases small bowel motility (MMC during fasting) and gastric emptying**
Somatostatin	Stomach, small intestine, and pancreas (D cells)	**-inhibits secretion and action of many hormones, including all of the above**

Gastrin

- stomach antrum, duodenum (G cells)
- released when the stomach dilates, when levels of peptides and AA increase due to protein breakdown, nerve stimuli (parasympathetic, vagal nerve > gastrin-releasing peptide)
- release inhibited by low pH in the stomach and duodenum, by somatostatin
- **promotes the production of gastric juice (HCl;** directly by translocation of K^+/ H^+ ATPase pumps into the cell membrane, indirectly via histamine**), pepsinogen secretion and gastric mucosal growth**



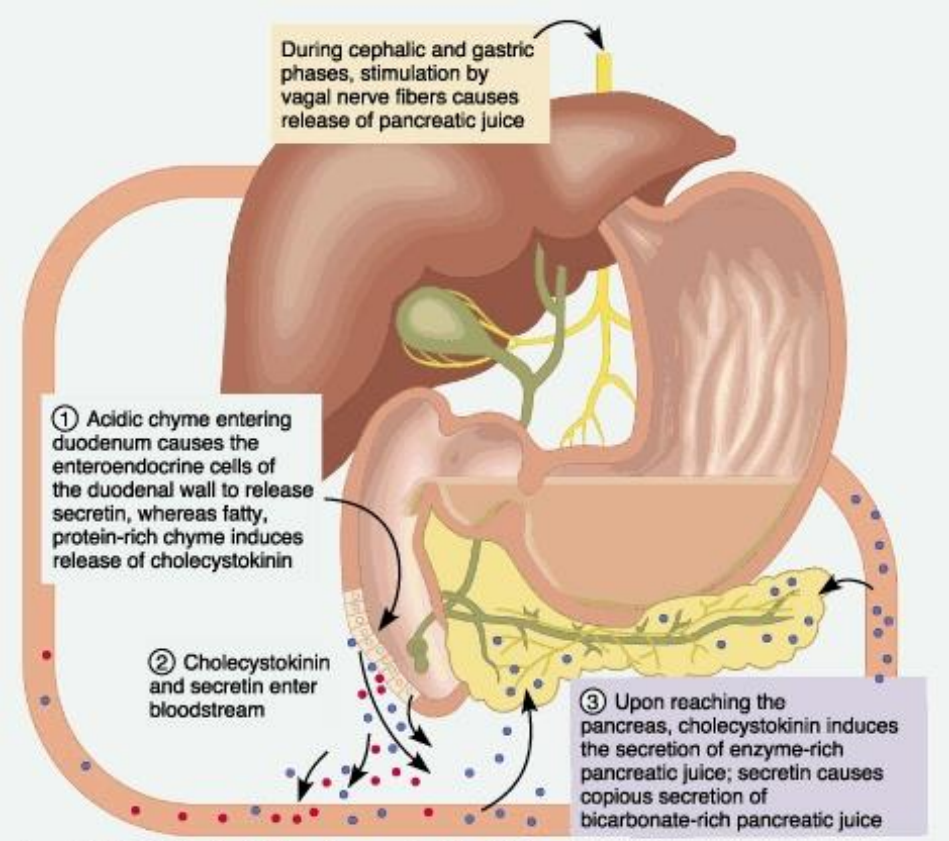


Cholecystokinin (CCK, pancreozymin)

- mucosa of the whole small intestine (I cells)
- gastrin/cholecystokinin family
- preprocholecystokinin 33 AA (posttranslational modification to produce many forms)
- stimulation via long chain fatty acids, AA, peptides in the lumen of the small intestine, nerve stimuli
- **causes contractions of the gallbladder, secretion of pancreas (digestive enzymes) and suppresses gastric emptying**

Secretin

- production mainly in the duodenum (S cells)
- 27 AA, stored as inactive prosecretin (low pH activation)
- stimulated by acidic chymus
- **suppresses secretion of HCl and growth of the gastric mucosa, stimulates HCO_3^- secretion**



Endocrine regulation of digestion - summary

- **gastrin** (HCl, pepsinogen)

- **CCK** (secretion of bile, pancreas): processing fat- and protein-rich diet

- **secretin** (secretion of the pancreas): neutralization of acid digestion

- **enterogastron** (gastric / digestive inhibitory polypeptide): negative regulation of digestion