Welcome to BCII lesson 12

Chimie Biologique II

Biological Chemistry II

BIO-213

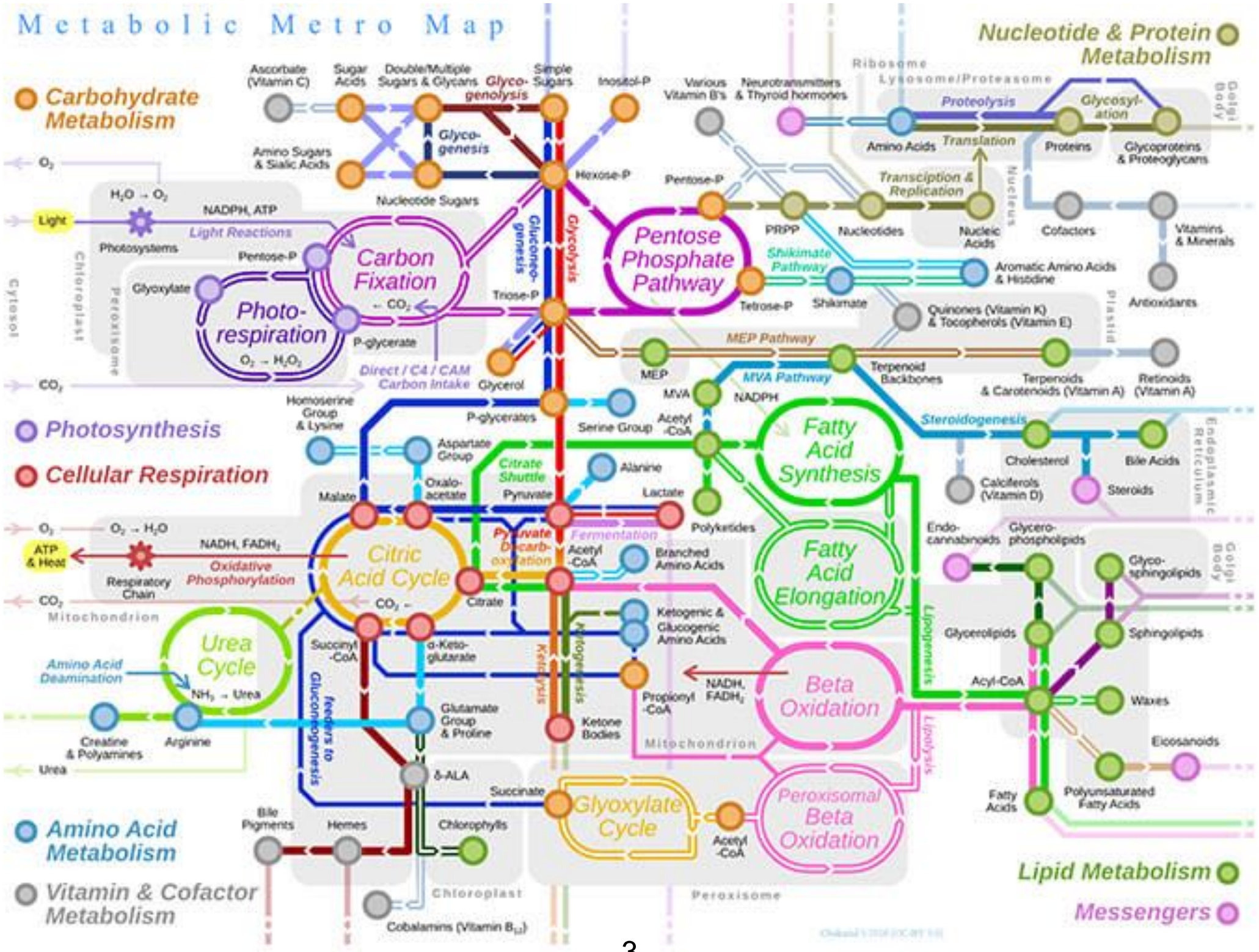
Teacher

Giovanni D’Angelo, IBI

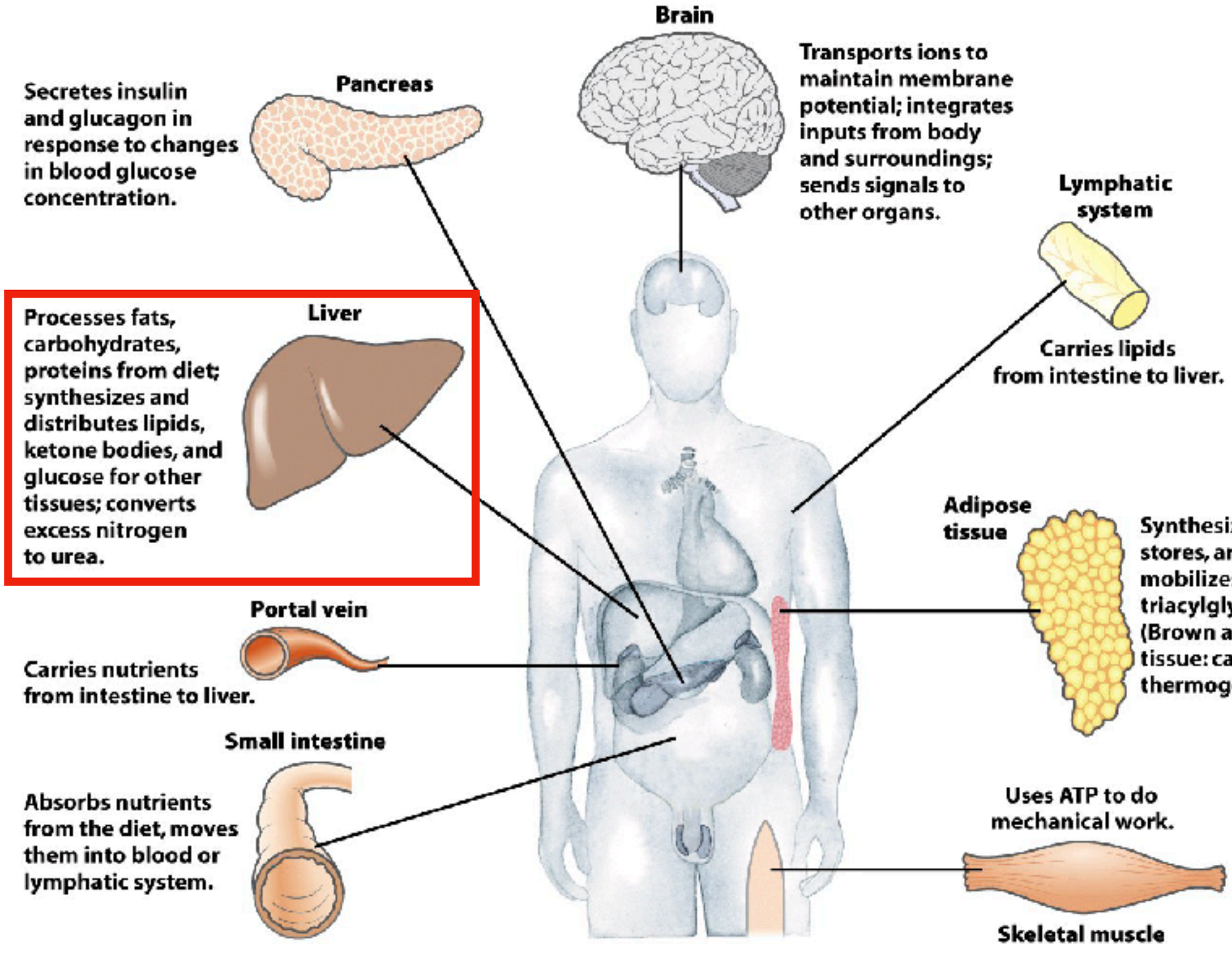
Lecture 12

Integration and regulation of metabolic pathways

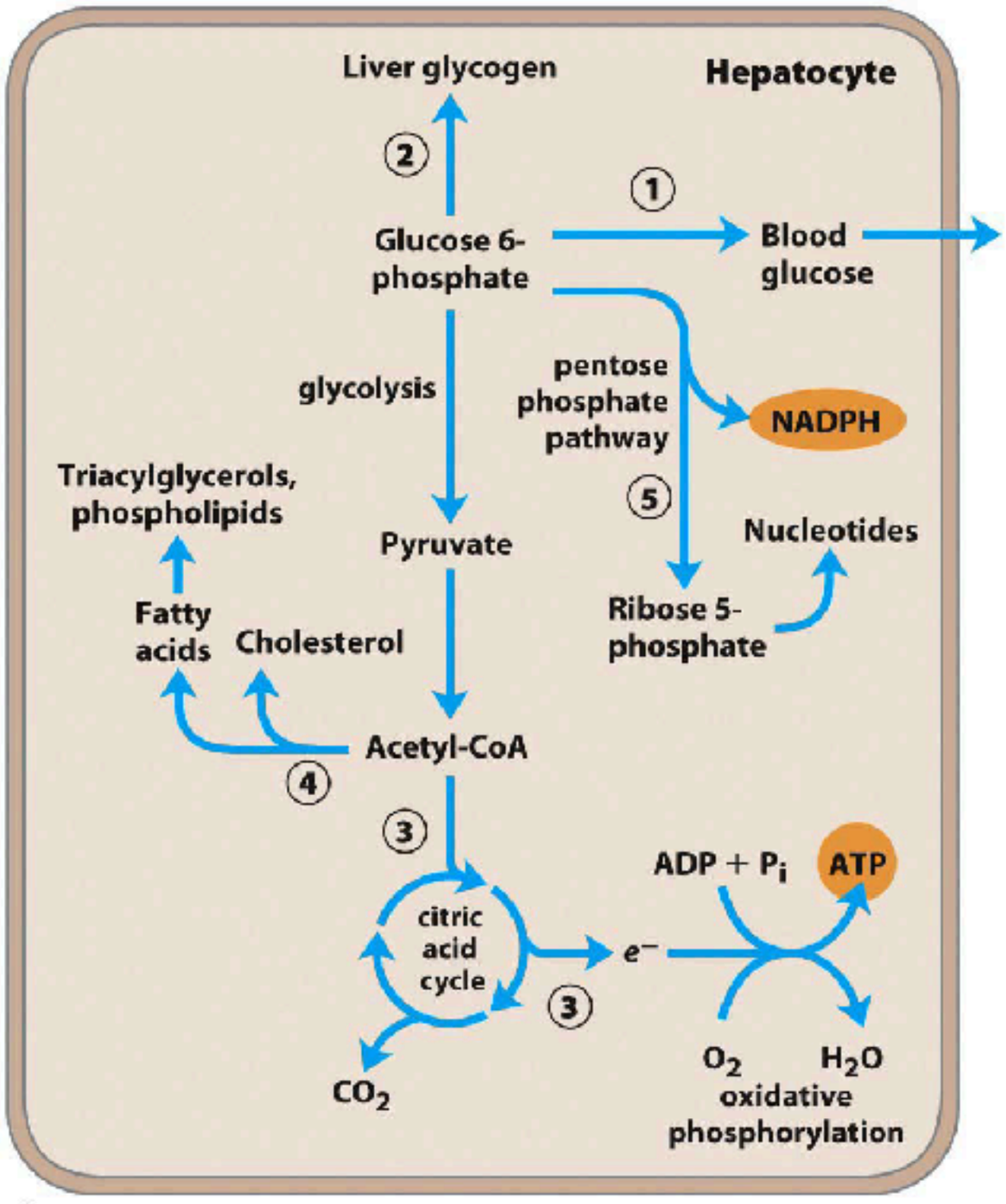
The Metabolic Metro Map



The Division of Labour



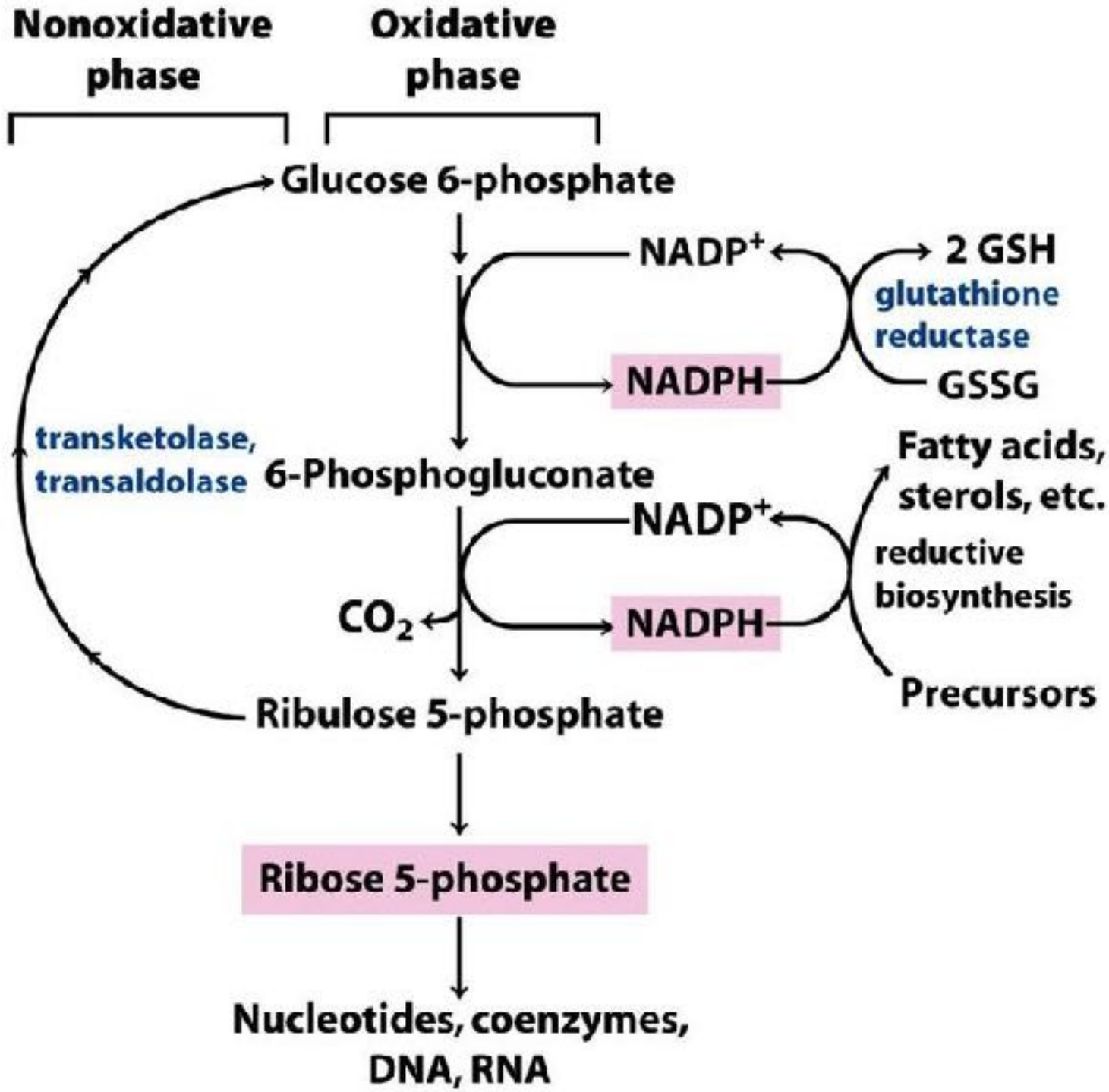
The Liver [sugars]



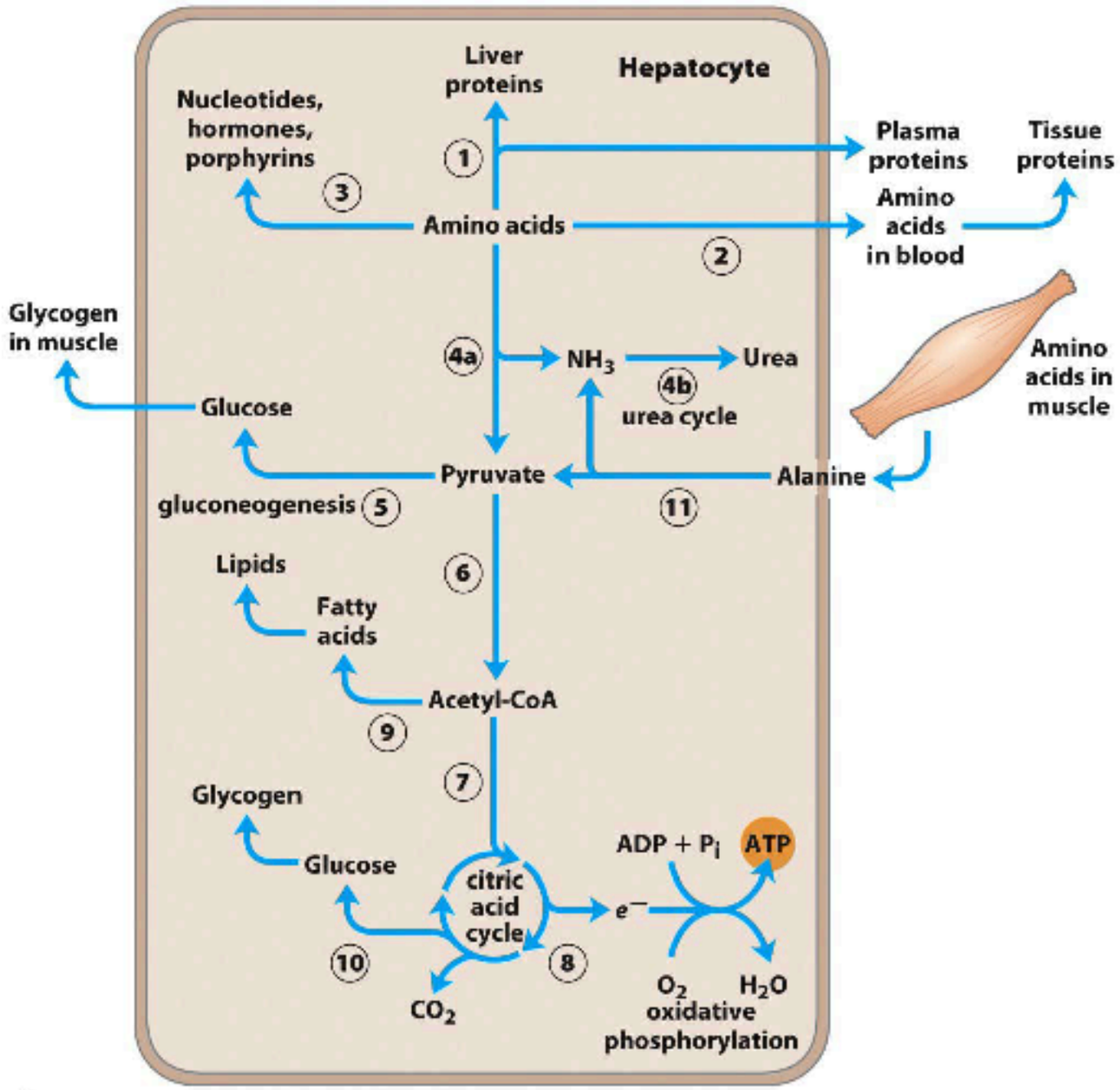
Once ingested, sugars are transported to the liver where they are converted to **glucose 6 phosphate**.
Here Glucose 6 phosphate can be:

1) Dephosphorylated and exported to the blood stream in the form of glucose
2) Incorporated into glycogen
3) Oxidised through the glycolytic and TCA pathways to fuel the oxidative phosphorylation system and produce ATP.
4) Following glycolysis, produce the Acetyl-CoA used in the synthesis of fatty phospholipids, triacylglyceols and cholesterol
5) feed into the **pentose phosphate** pathway that produces NADPH (required for fatty acid and cholesterol synthesis) and Ribose-5-phosphate that is required to produce nucleotides

The Pentose Phosphate pathway



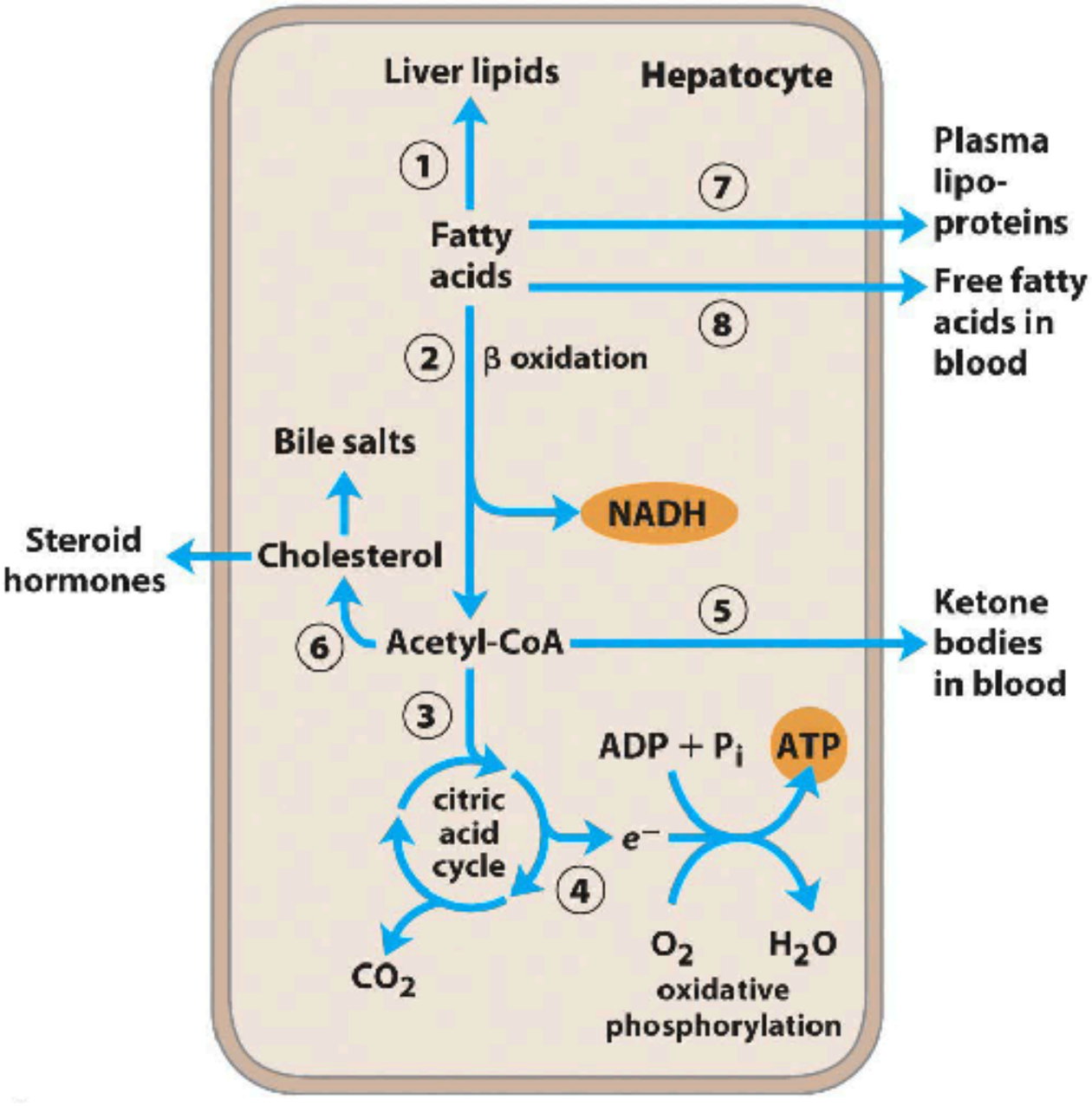
The Liver [amino acids]



Also amino acids (obtained by dietary proteins digestion are transported to the liver.
Here amino acids can be:

1) Used to make up liver proteins [plasma proteins are synthesised in the liver]
2) Be mobilised in the blood stream to reach other tissues
3) Used to produce nucleotides hormones and porphyrines
4) Deaminated and amide group can be secreted in the form of urea
5) (also 9 and 10) Re-routed into glucose or lipid metabolism
6) (also 7 and 8) Be used to produce ATP through the TCA cycle and the oxidative phosphorylationtides

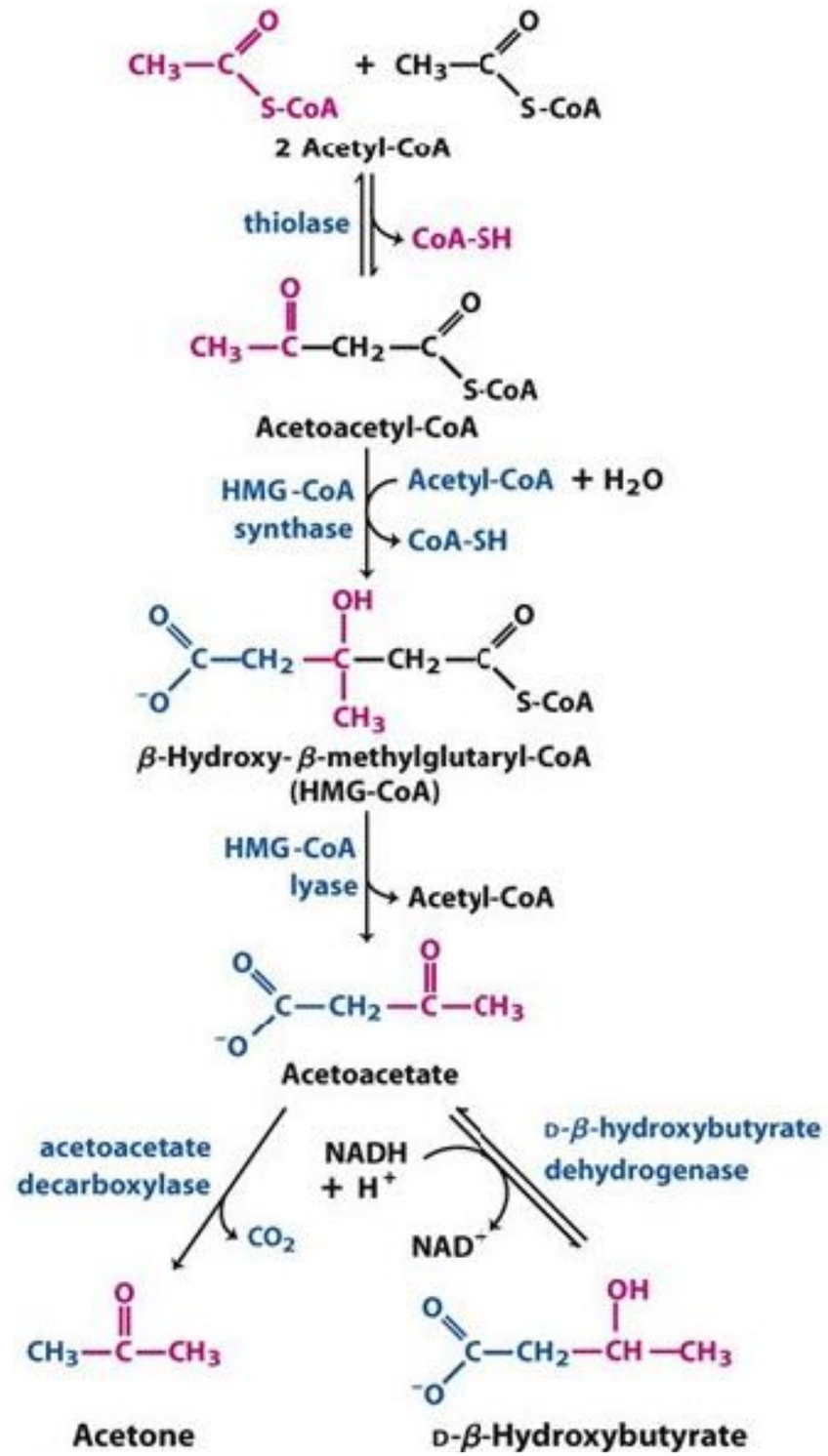
The Liver [Lipids]



Fatty acids (obtained by dietary fats are transported to the liver).
Here Fatty acids can be:

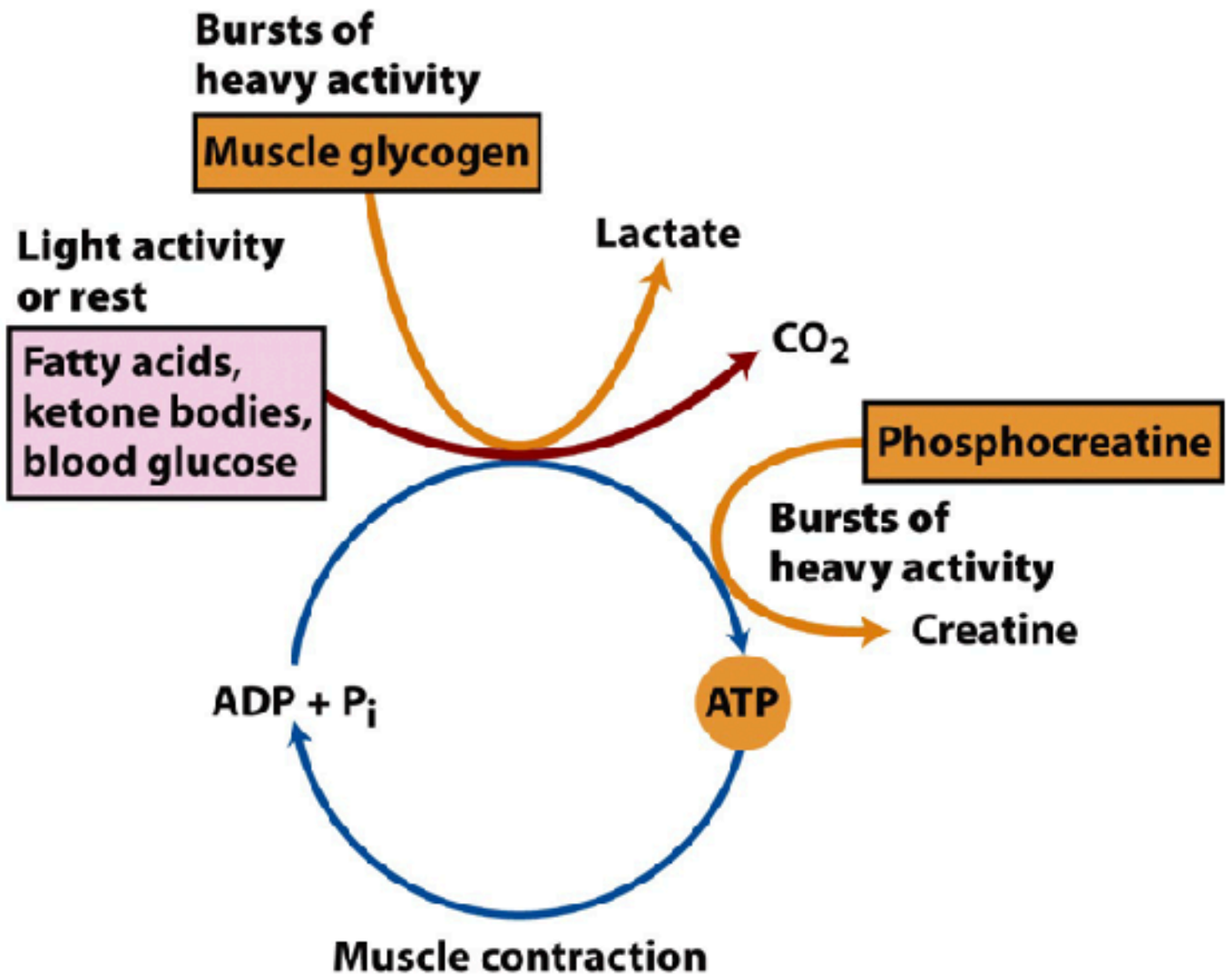
1) Used to produce liver lipids
2) Undergo B-oxydation to produce acetyl-CoA
3) Actyl-CoA can feed in the TCA cycle
4) to provide ATP through oxidative phosphorylation (lipids are the main energy source in liver)
5) Actyl-CoA can be conveyed to **ketone bodies**
6) Actyl-CoA can be used to produce sterols
7) (and 8) Fatty acids can be mobilised through the blood stream either as phospholipids/ triglycerides bound to lipoproteins or as free fatty acids bound to albumin

Ketone bodies



Ketone bodies are the **water-soluble** molecules (acetoacetate, beta-hydroxybutyrate, and the spontaneous breakdown product of acetoacetate, acetone) containing the ketone group that are produced by the liver from fatty acids during periods of low food intake (fasting), carbohydrate restrictive diets, starvation, prolonged intense exercise, alcoholism, or in untreated (or inadequately treated) type 1 diabetes mellitus. Ketone bodies are readily transported into tissues outside the liver and converted into acetyl-CoA, which then enters the citric acid cycle and is oxidized in the mitochondria for energy. In the brain, ketone bodies are also used to make acetyl-CoA into long-chain fatty acids.

The Muscles



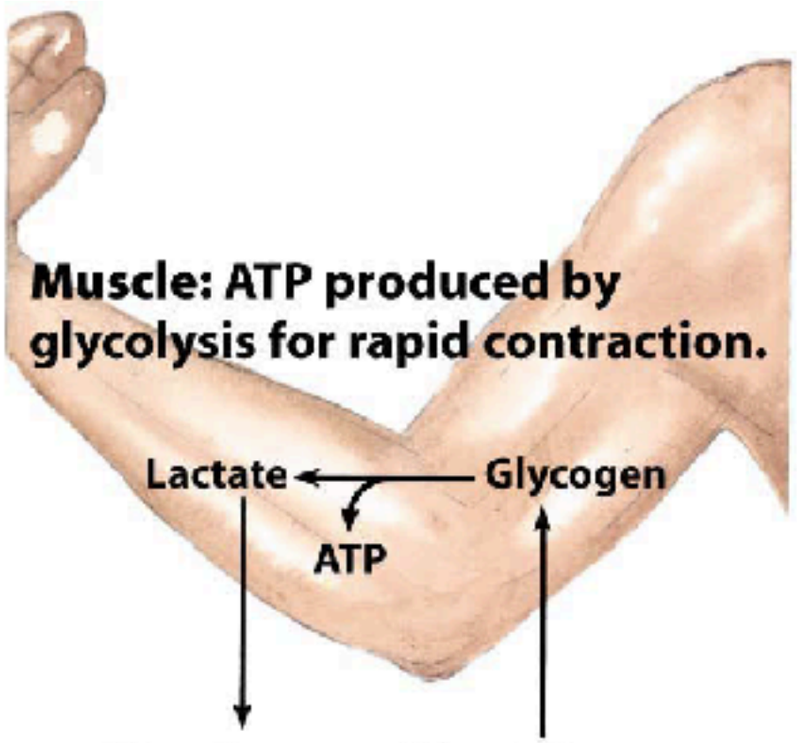
Muscles to contract consume ATP. Muscle activity accounts for 50% and 90% of the total oxygen consumption in a resting and exercising human being respectively. Muscle metabolism is thus committed to produce ATP.

Muscles use **fatty acids**, **glucose** and **ketone bodies** to produce ATP through oxidative phosphorylation under light activity or **resting conditions**.

Upon **increased energy demand** muscles their **glycogen** to get extra glucose that is primarily burned through glycolysis and **lactic fermentation**.

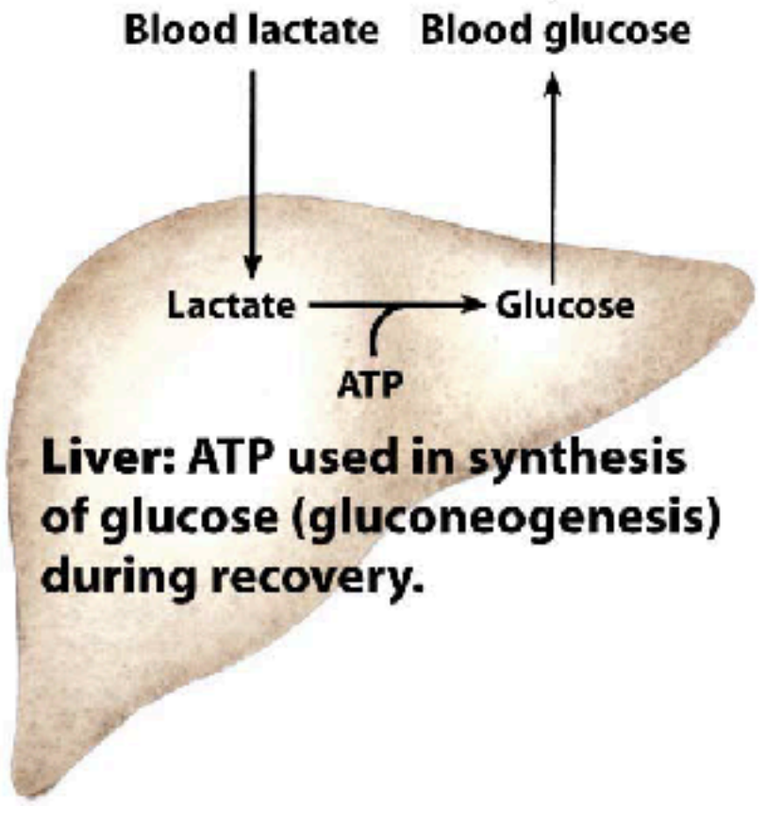
Phosphocreatine (derived from amino acids) constitutes a further readily spendable ATP source during **bursts of heavy muscular activity**.

The Muscles



After a period of intense muscle activity, respiration keeps being accelerated for a while. The oxygen intaken during this time is used by the liver to produce ATP through oxidative phosphorylation.

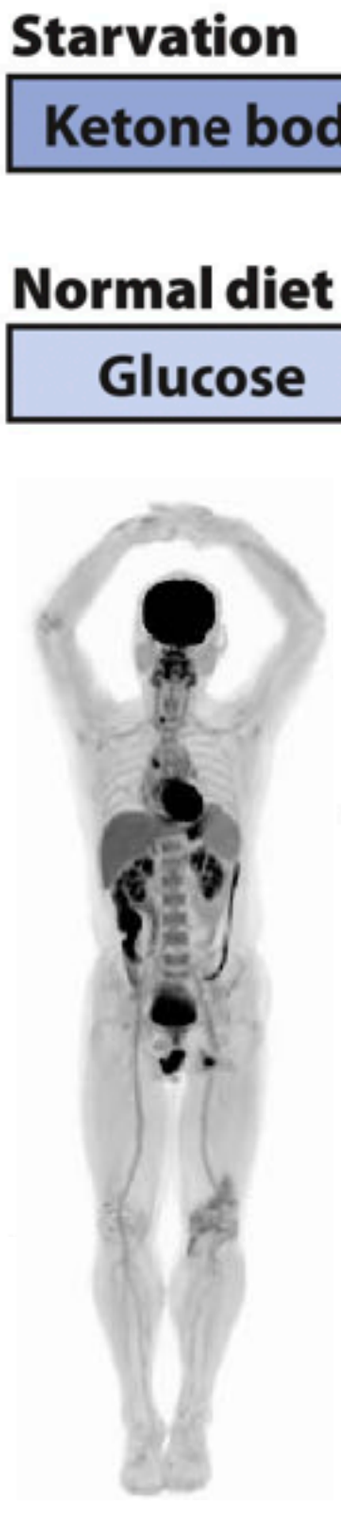
This ATP is then used to convert the lactate (resulting from lactic fermentation in the muscle) back to glucose.



Liver derived glucose is then released in the blood stream, reaches the muscles where it is used to re constitute the glycogen stores consumed during strenuous activity.

This metabolic circuit is known ad the **Cori cycle** named after its discoverers, Carl Ferdinand Cori and Gerty Cori,

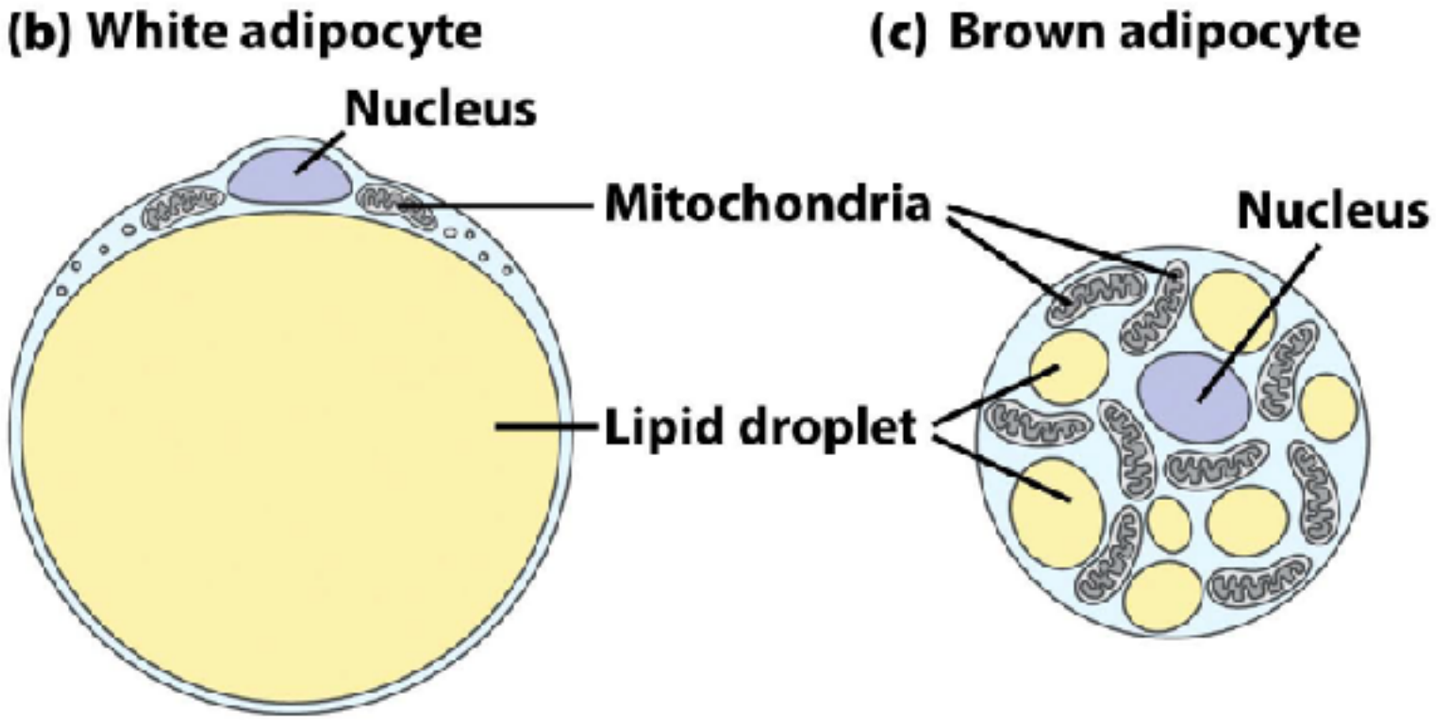
The Brain



The brain uses ATP to maintain the electrochemical gradient across the neuronal membranes [which is fundamental fo neural transmission]. Brain activity accounts for 20% of the total oxygen consumption in a resting human being. Brain uses primarily glucose [and ketone bodies during starvation] as a source of energy.

The brain has very limited glycogen stores and thus it depends heavily on circulating glucose. Glucose in the brain is channeled into glycolysis, TCA cycle and oxidative phosphorylation.

The Adipose Tissue

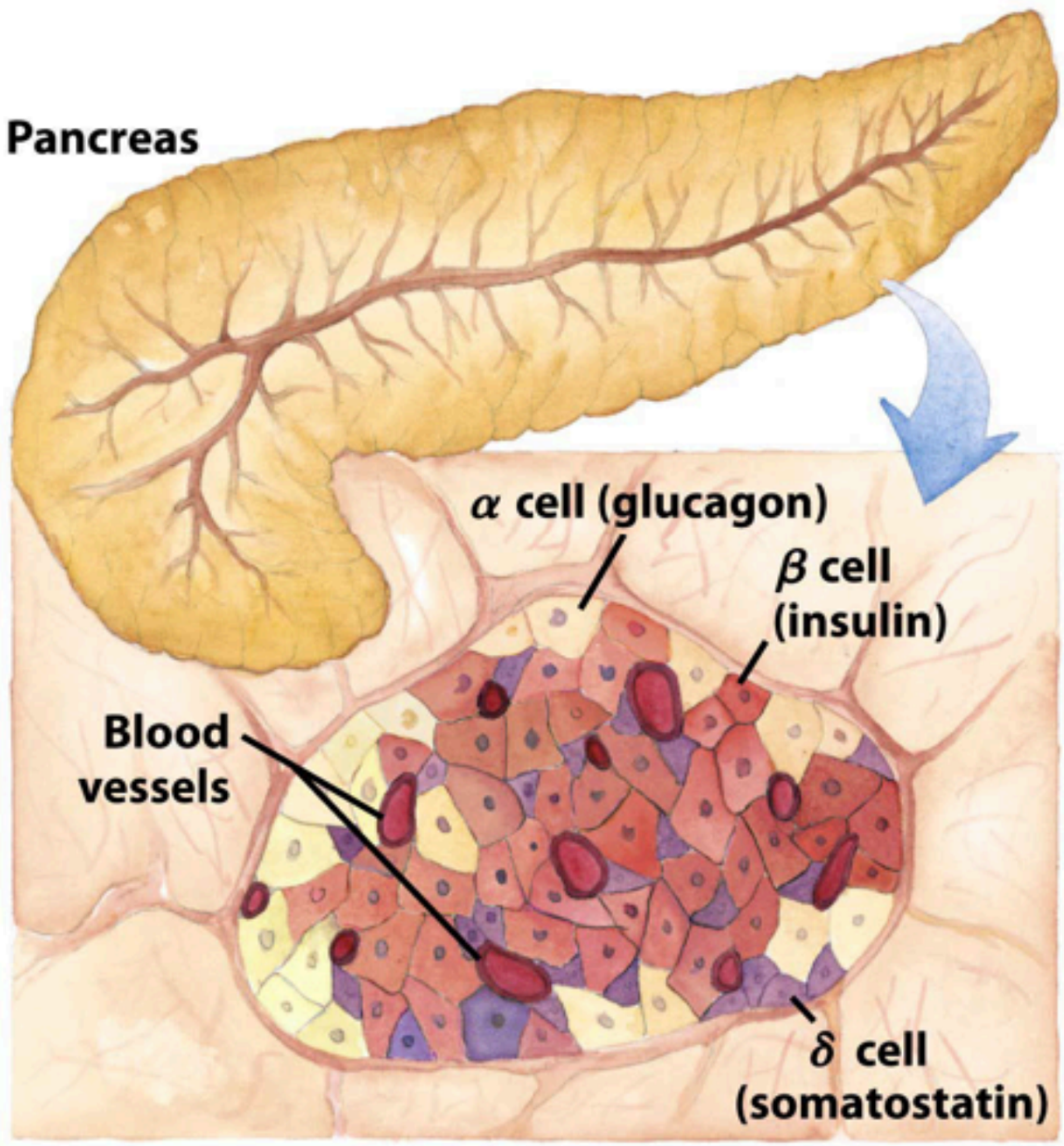


Adipose tissue, is a loose connective tissue composed mostly of adipocytes. Its main role is to store energy in the form of lipids and to insulate the body. The two types of adipose tissue are white adipose tissue (WAT), which stores energy, and brown adipose tissue (BAT), which generates body heat.

Free fatty acids are liberated from lipoproteins by **lipoprotein lipase** (**LPL**) and enter the adipocyte, where they are reassembled into triglycerides by esterifying them onto glycerol. Human adipose tissue contains about 87% lipids.

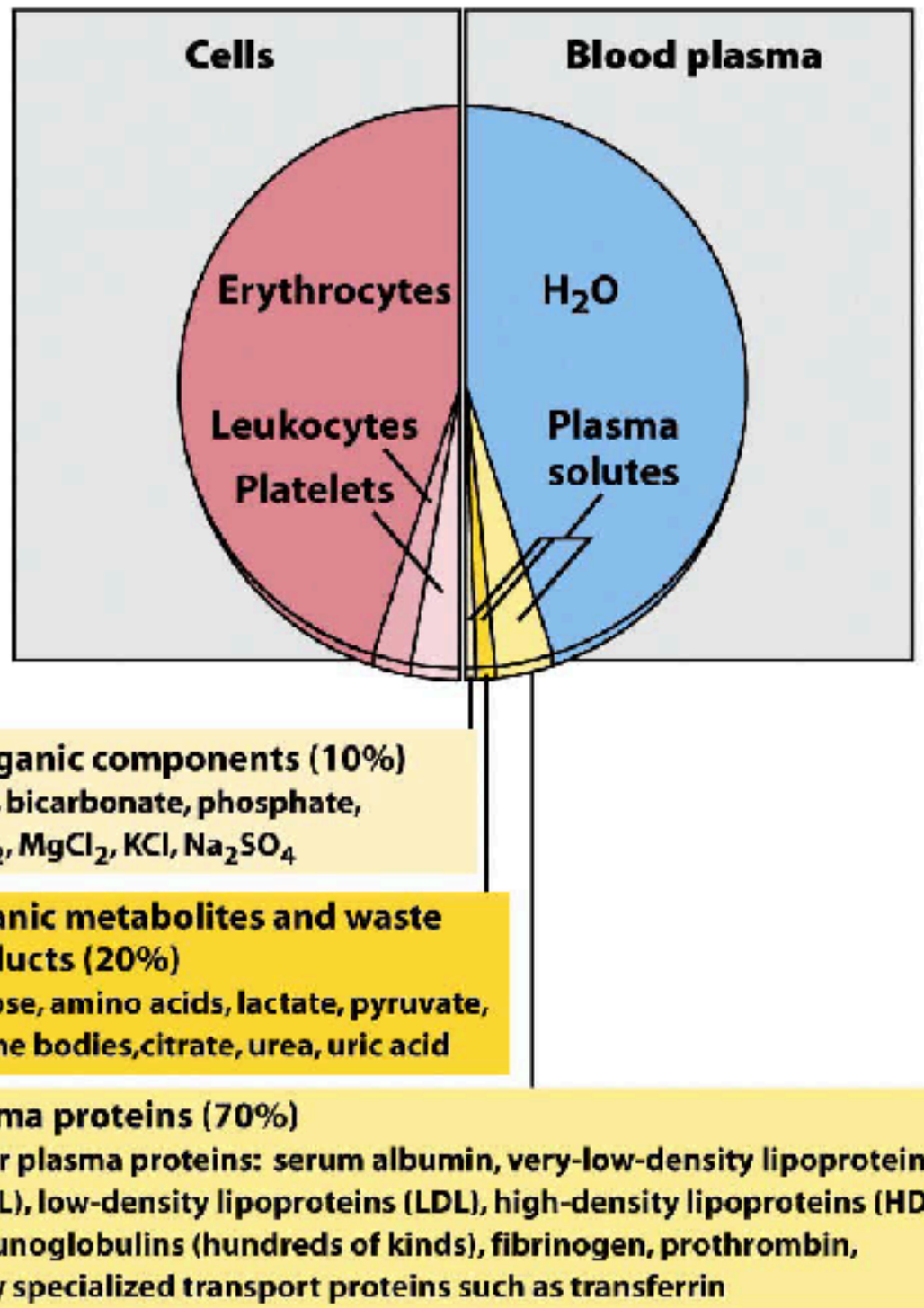
Upon demand the adipose tissue can release fatty acids fo they use as energy fuel in distal organs of burn them in mitochondria (BAT) to produce heat

The Pancreas



The **pancreas** has both an **endocrine** and a **exocrine** function. As an endocrine gland, it functions mostly to regulate **blood sugar levels**, secreting the hormones **insulin**, **glucagon**, **somatostatin**, and pancreatic polypeptide. The tissues with an endocrine role within the pancreas exist as clusters of cells called **pancreatic islets** (also called **islets of Langerhans**). 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. 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**.

The Blood



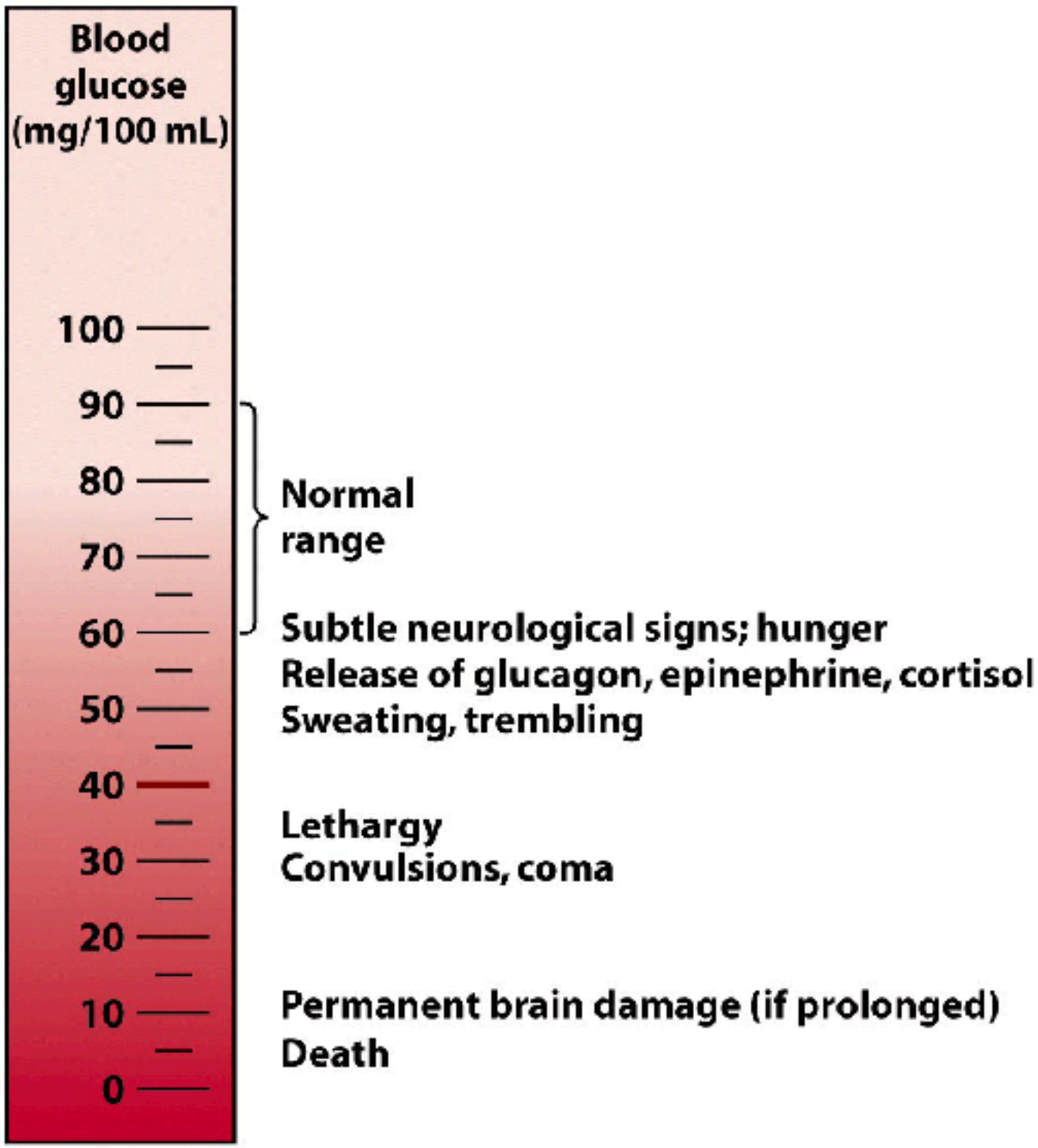
The blood is an important metabolic medium that transports metabolites among different organs and tissues.

It is composed by 50% of its volume of cells (erythrocytes, leukocytes, and platelets) and by 50% of plasma.

Plasma is then composed by 90% of H2O and for the remaining 10% by plasma proteins (albumin, immunoglobulins, lipoproteins, coagulation proteins, transferrin *etc.*); metabolites (glucose, amino acids, lactate, pyruvate, ketone bodies *etc.*); and inorganic components (NaCl, bicarbonate, phosphate, KCl *etc.*).

The concentration of the different solutes in blood is usually tightly controlled as small variations in their levels can cause serious probelms

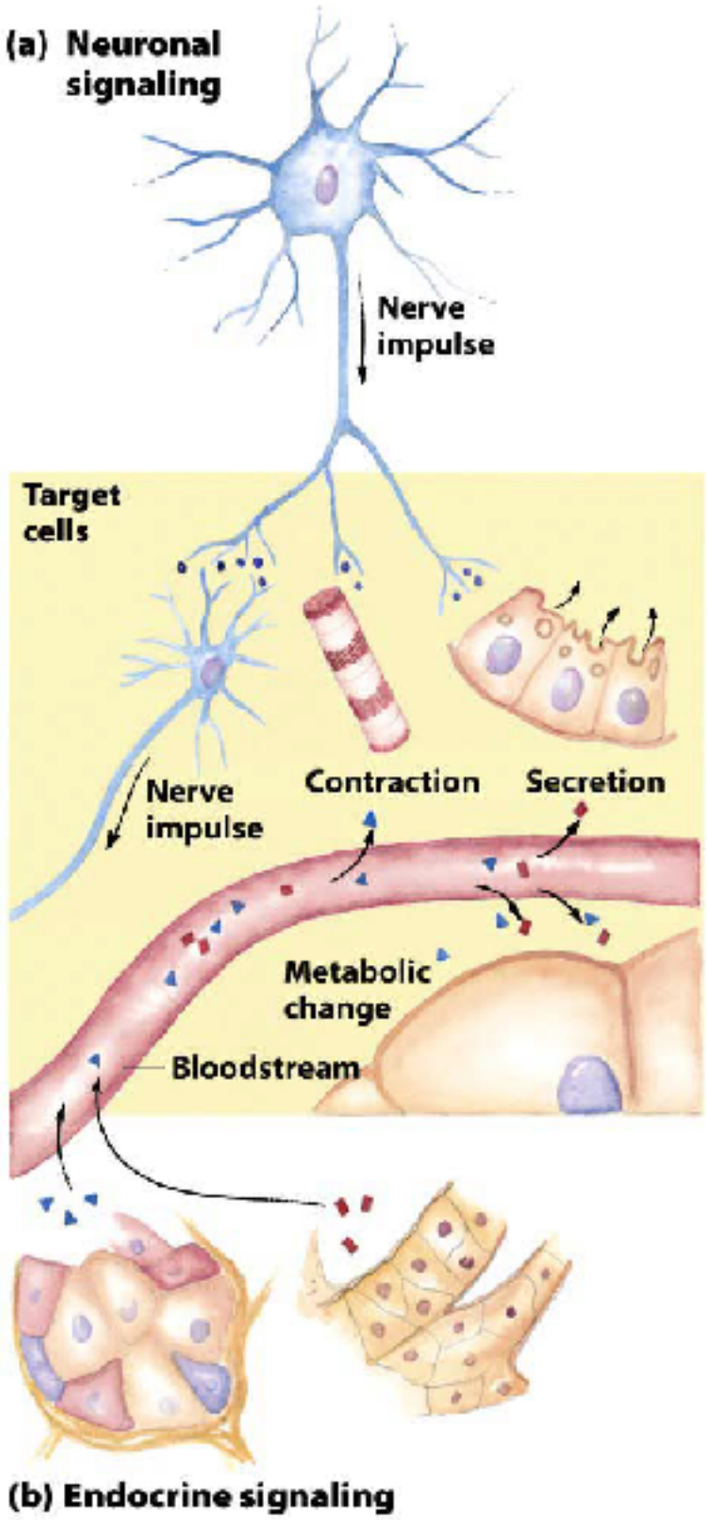
The Blood



The mean fasting plasma blood glucose level in humans is about **5.5 mM** (100 mg/dL). Despite widely variable intervals between meals or the occasional consumption of meals with a substantial carbohydrate load, human blood glucose levels tend to remain within the normal range. However, shortly after eating, the blood glucose level may rise temporarily up to **7.8 mM** (140 mg/dL) or slightly more.

Instances where blood glucose level drops below below **2.2 mM** or 40 mg/dL are called **hypoglycaemia**. Hypoglycaemia is a potentially fatal condition as those organs that are metabolically active or require a constant, regulated supply of blood sugar (the liver and brain are examples)

The NeuroEndocrine System



Metabolism is regulated across the different organs through **neuronal** and **hormone-mediated** signalling. Neurones transmit their signals through chemical messenger that travel for a limited space (below 1 µm) at the synapse to trigger a response in the post-synaptic cell. Hormones instead can travel long distances from the cell that produces them to its target cell. Also, while neurotransmitters have often a unique response to their release in the synapse hormones can elicit different responses depending to the target cell they encounter.

The nervous and endocrine systems often act together in a process called neuroendocrine integration, to regulate the physiological processes of the human body. in this context **Neuroendocrine cells** receive neuronal input (neurotransmitters released by nerve cells or neurosecretory cells) and, as a consequence of this input, release message molecules (hormones) into the blood.

Hormones

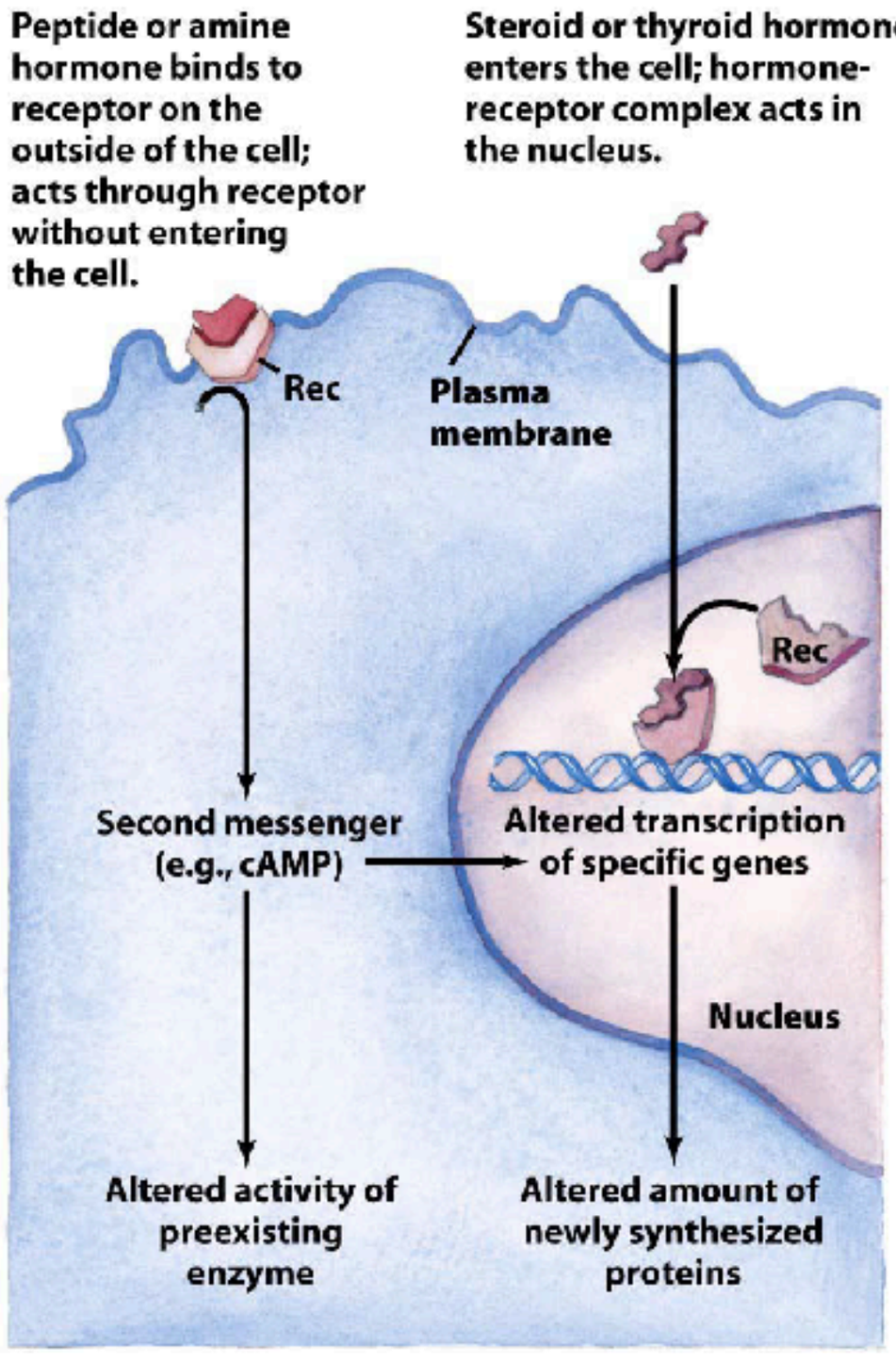
A **hormone** is a signalling molecule, produced by glands in multicellular organisms, that is transported by the circulatory system to regulate physiology.
Hormones can affect distant cells (endocrine signalling) nearby cells (paracrine signalling) or the secreting cell itself (autocrine signalling).
Hormones have diverse chemical structures.

1. Peptide hormones are made of a chain of amino acids that can range from just 3 to hundreds of amino acids.
2. Amino acid hormones are derived from amino acid, most commonly tyrosine
3. Eicosanoids hormones are derived from lipids such as arachidonic acid
4. Steroid hormones are derived from cholesterol.

TABLE 23–1 Classes of Hormones

Type	Example	Synthetic path	Mode of action
Peptide	Insulin, glucagon	Proteolytic processing of prohormone	Plasma membrane receptors; second messengers
Catecholamine	Epinephrine	From tyrosine	
Eicosanoid	PGE_1	From arachidonate (20:4 fatty acid)	
Steroid	Testosterone	From cholesterol	Nuclear receptors; transcriptional regulation
Vitamin D	1,25-Dihydroxycholecalciferol	From cholesterol	
Retinoid	Retinoic acid	From vitamin A	
Thyroid	Triiodothyronine (T_3)	From Tyr in thyroglobulin	
Nitric oxide	Nitric oxide	From arginine + O_2	Cytosolic receptor (guanylyl cyclase) and second messenger (cGMP)

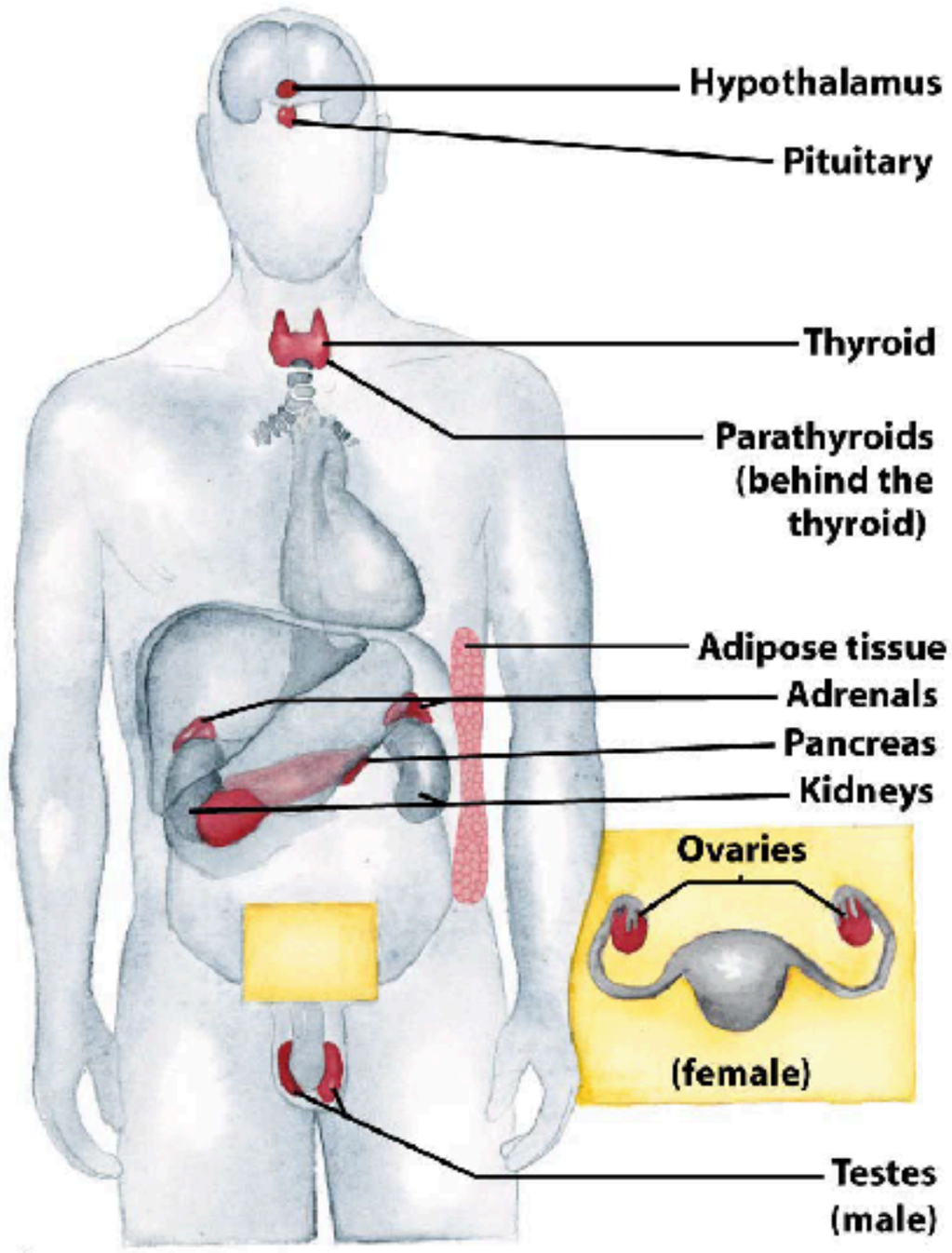
Hormones



Hormones affect distant cells by binding to specific **receptor proteins** in the target cell, resulting in a change in cell function. When a hormone binds to the receptor, it results in the activation of a **signal transduction pathway** that typically activates **gene transcription**, resulting in increased expression of target proteins; non-genomic effects which include **phosphorylation of effector proteins** and changes in **membrane trafficking** are more rapid, and can be synergistic with genomic effects. Peptide–based hormones (amines and peptide or protein hormones) are water-soluble and act on the surface of target cells binding to plasma membrane located receptors that initiate signalling through second messengers. Thyroid and steroid hormones, being lipid-soluble, cross the plasma membranes of target cells to interact with intracellular receptors (both cytoplasmic and nuclear) that upon hormone stimulation bind DNA and initiate transcription .

Break

Hormones work according to a hierarchy

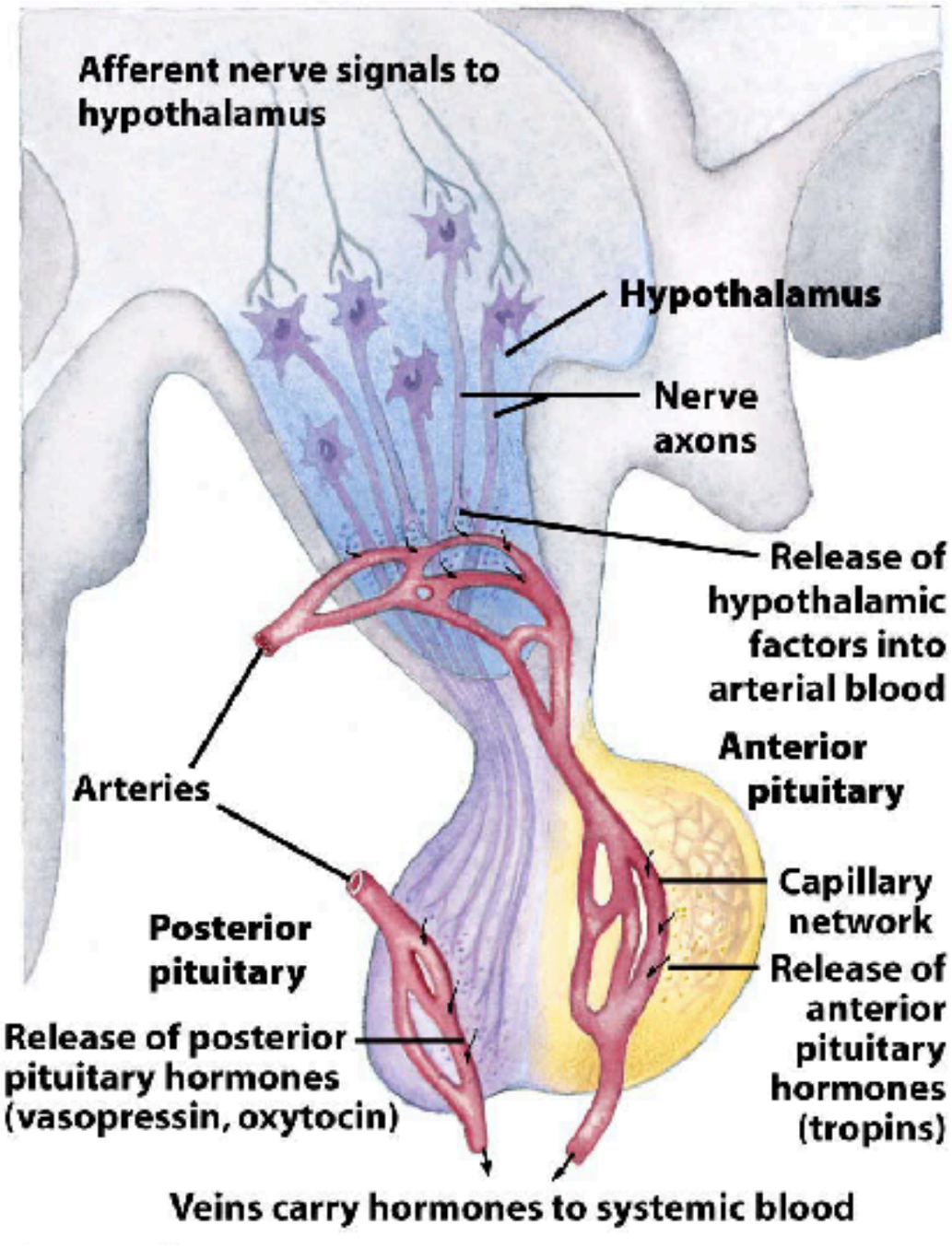


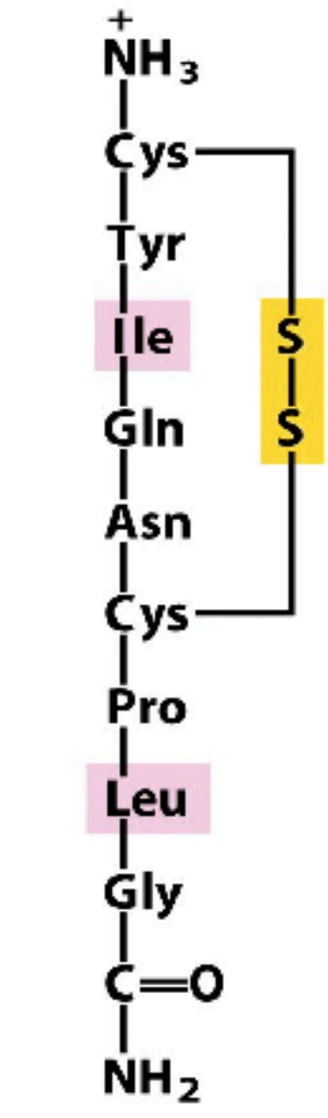
Hypothalamus: produces hormones that target the **anterior pituitary** and transmits neuronal signals to the **posterior pituitary** in response to nervous system stimuli

Anterior pituitary: produces hormones that target downstream endocrine organs including the **adrenal cortex**, the **thyroid**, **testis** and **ovaries** in response to nervous system stimuli.

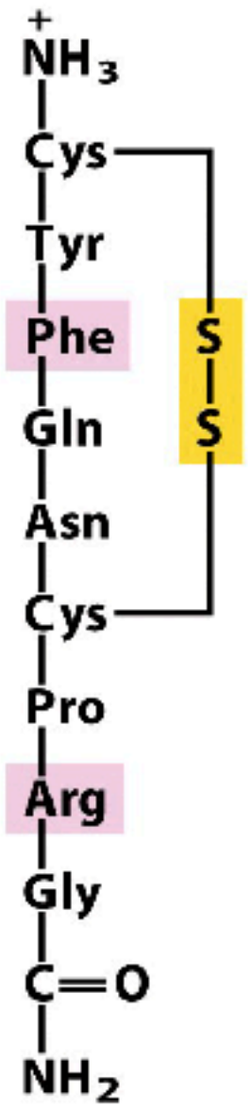
Posterior pituitary: contains the axons of neurones where their soma is in the hypothalamus. These neurones secrete **oxytocin** and **vasopressin**. Oxytocin targets the smooth muscle tissue in the uterus and mammary glands to induce labor and lactation respectively. Vasopressin controls blood pressure

Hormones work according to a hierarchy



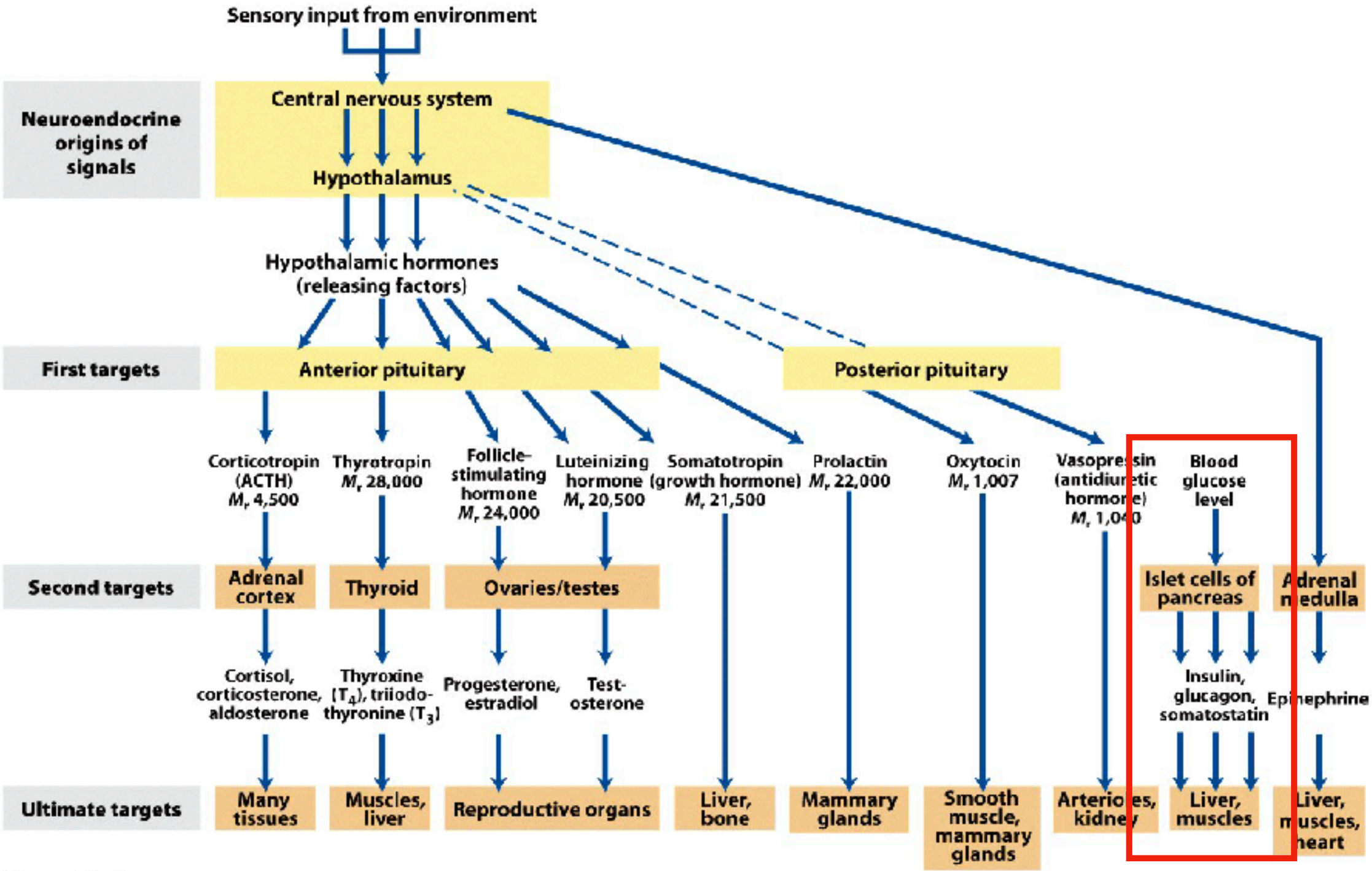


Human oxytocin

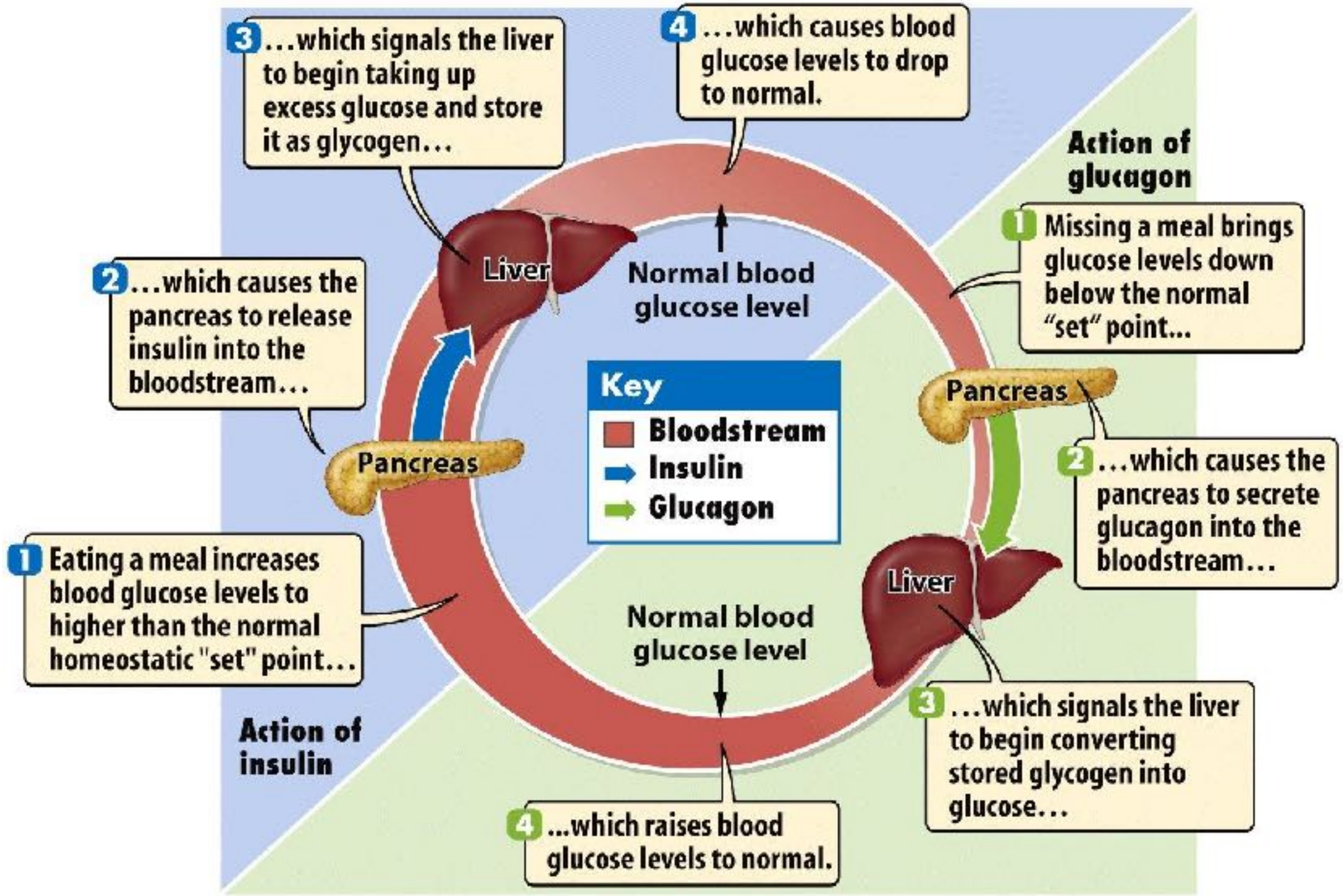


Human vasopressin (antidiuretic hormone)

Hormones work according to a hierarchy



Blood glucose homeostatic control



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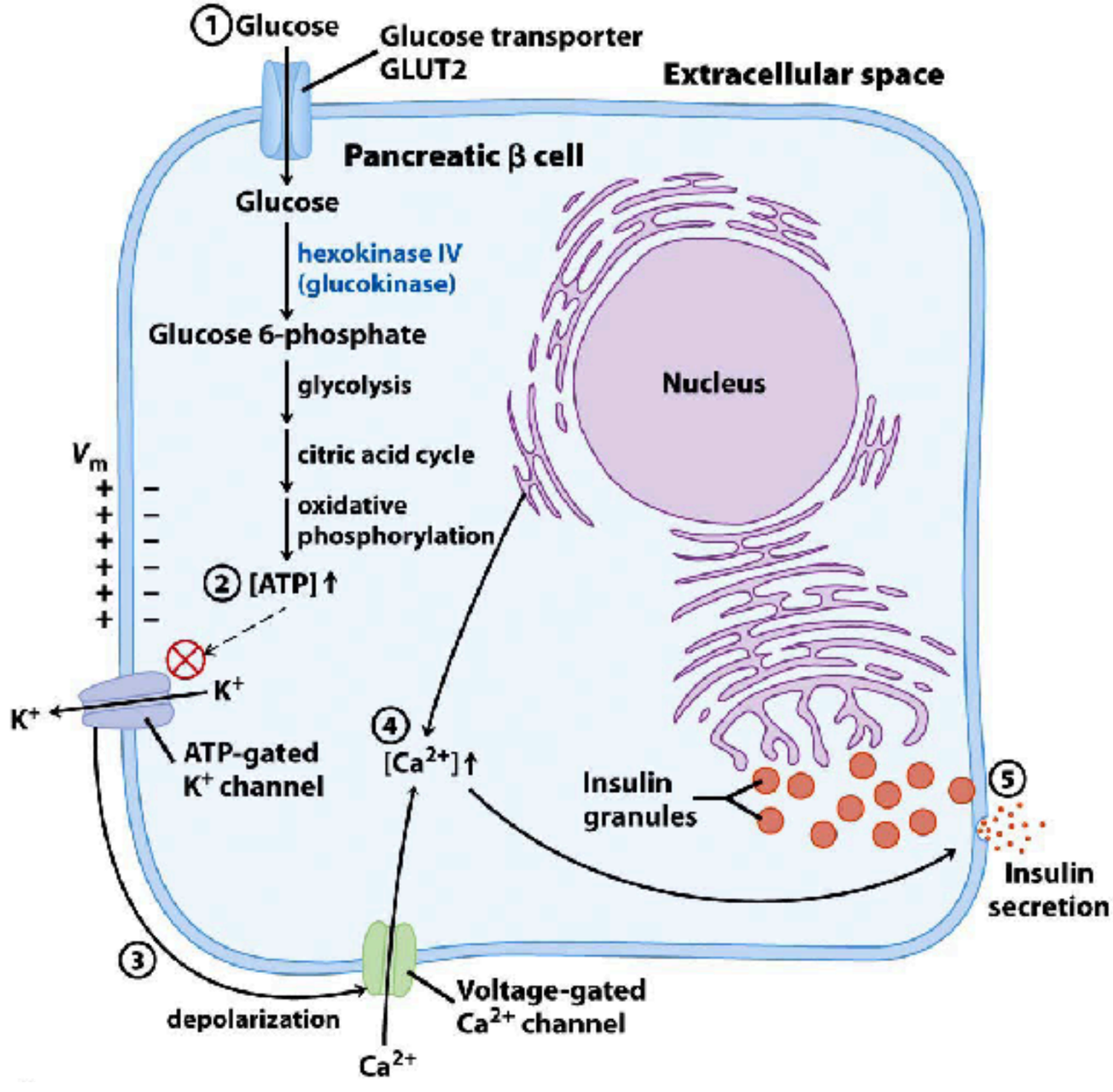
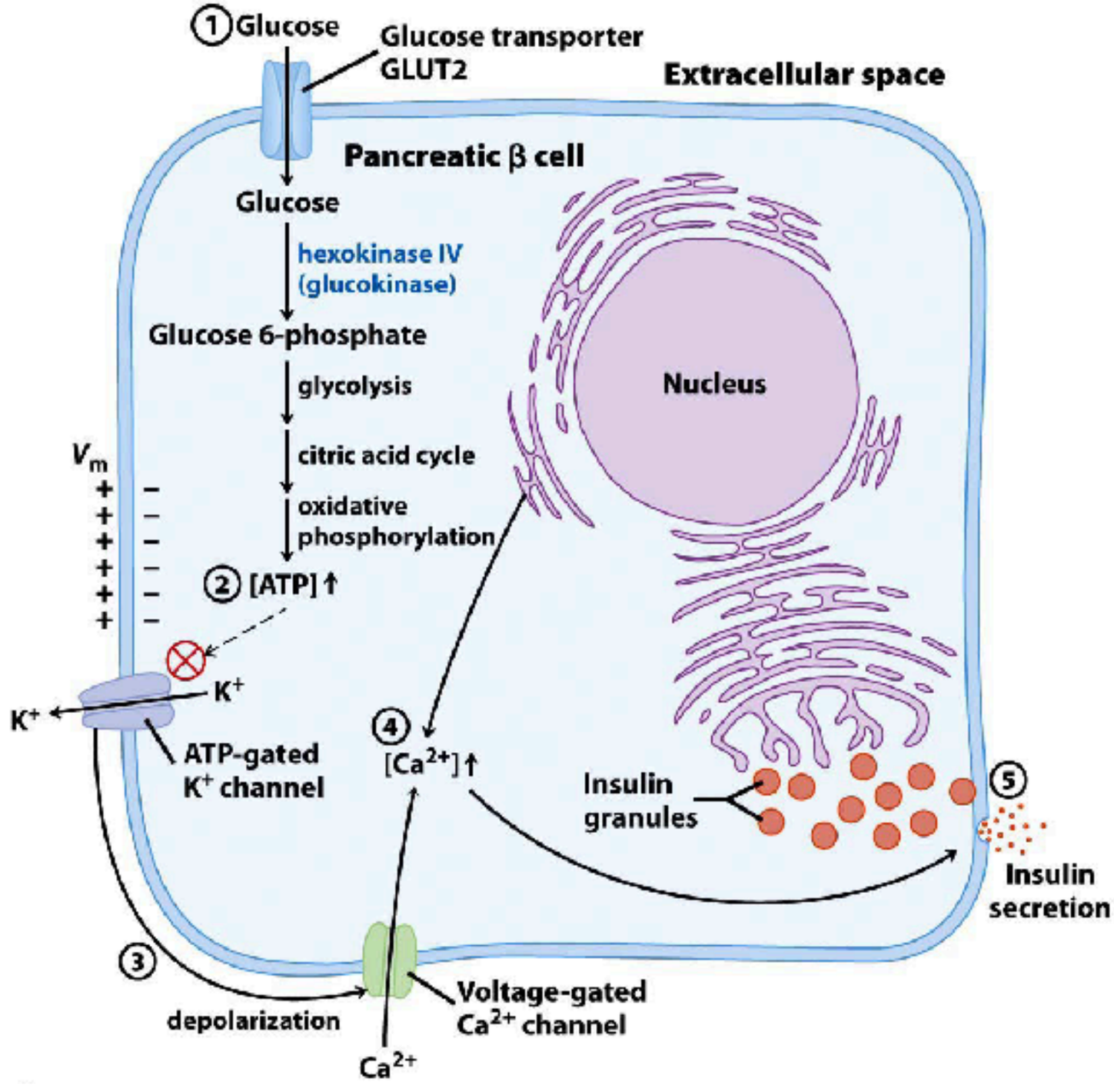
Beta Cells



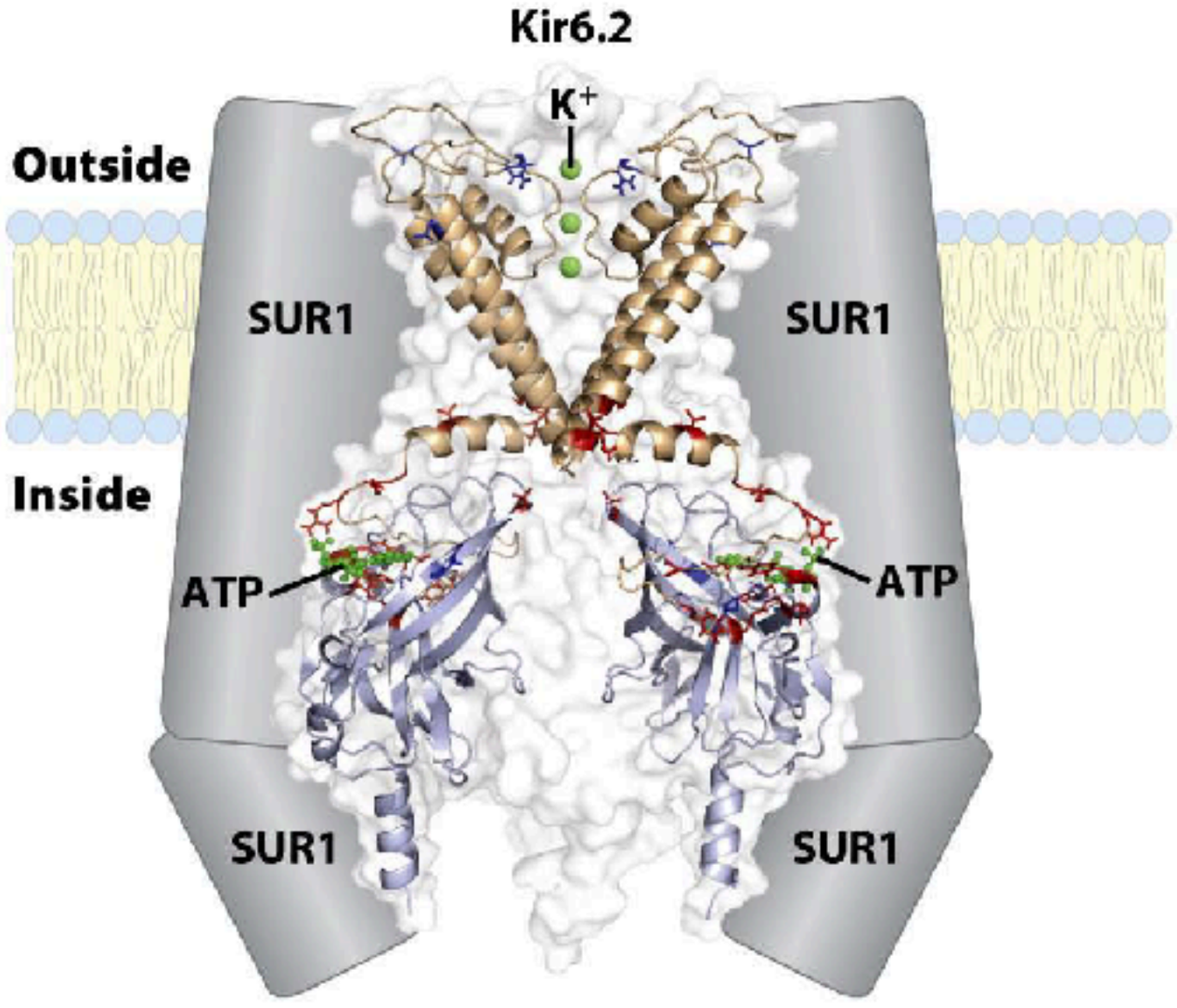
Beta-cells of the pancreatic islets of Langerhans act as **glucose sensors**, adjusting insulin output to the prevailing blood glucose level. The glucose-sensing mechanism of pancreatic β-cells can be roughly divided into two components: (i) the proximal events of glucose entry and metabolism and (ii) the distal mechanism of insulin secretion, spanning from mitochondrial signal generation and initiation of electrical activity to the ultimate effectors of insulin granule exocytosis.

Beta Cells



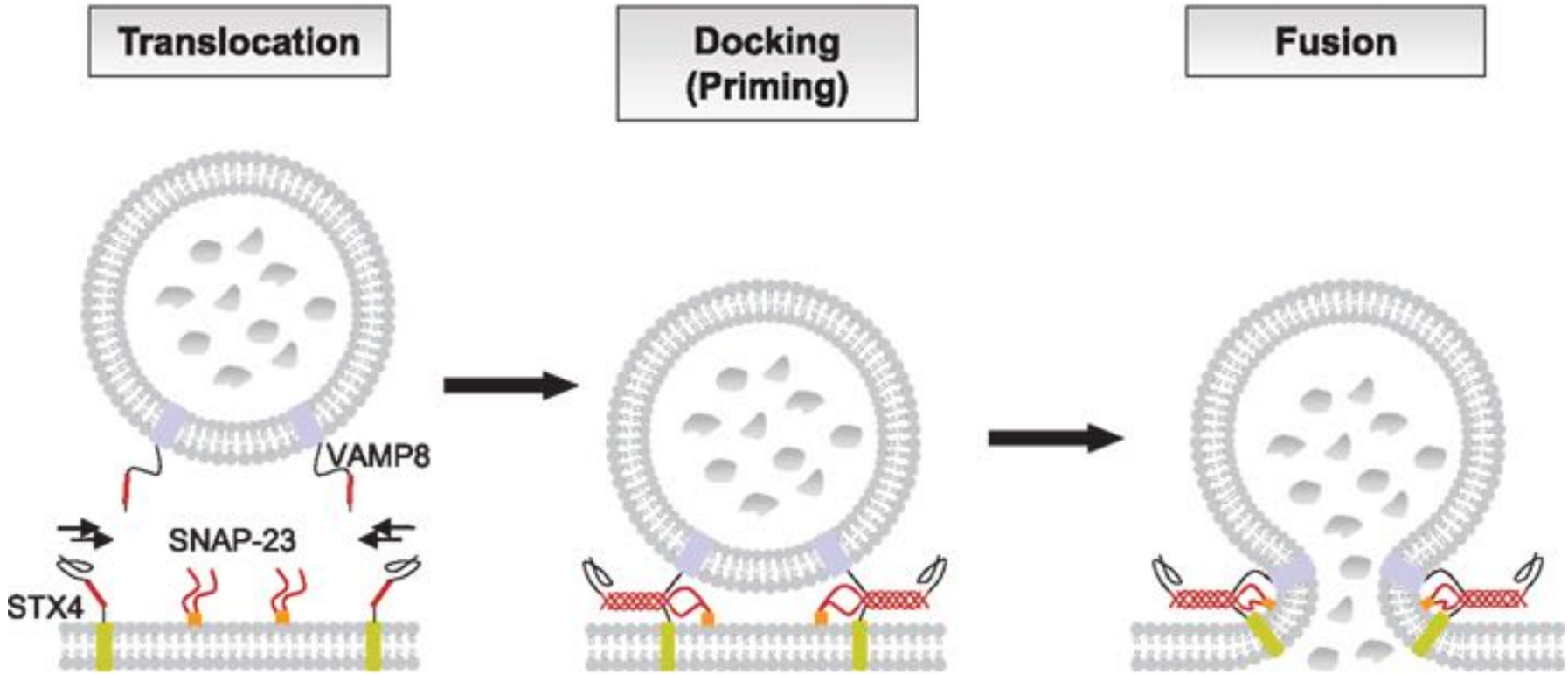
When glucose is available **ATP** is generated by β-cells. ATP inhibits an **ATP-gated K+ channel** which results in membrane depolarisation. As a consequence **Voltage-gated Ca2+ channels** on plasma membrane open allowing Ca2+ in. This is paralleled by a release of internal Ca2+ stores from the ER. The increase of cytosolic Ca2+ leads to the fusion of secretory granules containing insulin with the PM and release of this hormone in the blood stream.

Beta Cells- KATP channel



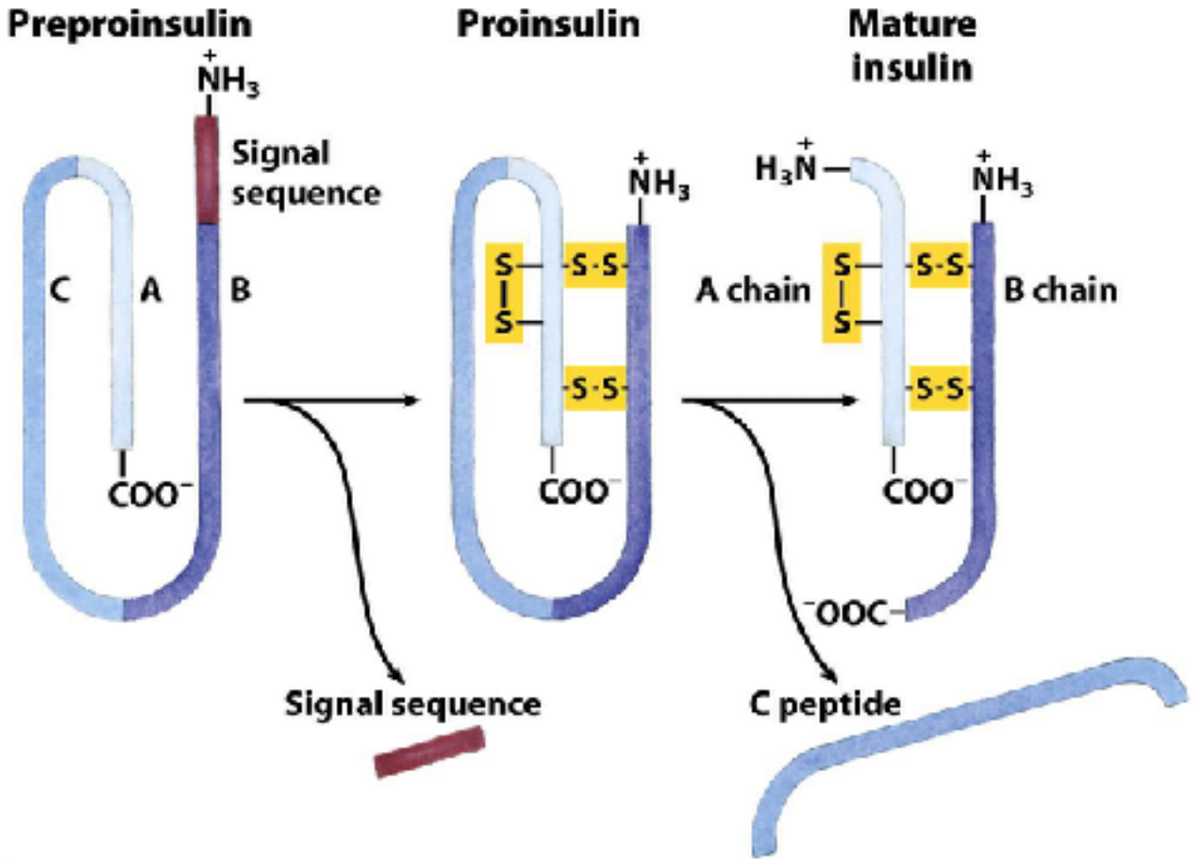
The **β-cell KATP channel** is associated with the regulatory sulphonylurea receptor (SUR) subunit. KATP channels are composed of four pore forming inward-rectifier K+ channel subunits (Kir6.2) and four regulatory sulphonylurea receptor subunits (SUR1). ATP inhibits KATP channels at the Kir6.2 subunit and point mutations within Kir6.2 attenuate the effect of ATP. A similar effect is mediated by the anti-diabetic sulphonylurea drugs through an interaction with SUR1, stimulating insulin secretion even in the absence of glucose.

Insulin granule secretion



Insulin exocytosis proceeds by formation of a "SNARE pair". In the particular case of insulin granules in beta cells, the SNARE protein on the granule is Synaptobrevin2/VAMP2 and the SNARE protein on the plasma membrane is Syntaxin1A in a complex with SNAP-25. Calcium dependence of membrane fusion is conferred by **Synaptotagmin**, which binds calcium ions and associates with the Syntaxin1A-Synaptobrevin2 pair. The exact mechanism of Synaptotagmin's action is unknown. Microscopically, exocytosis is seen to occur as a "kiss and run" process in which the membrane of the secretory granule fuses transiently with the plasma membrane to form a small pore of about 4 nm between the interior of the granule and the exterior of the cell. Only a portion of the insulin in a granule is secreted after which the pore closes and the vesicle is recaptured back into the cell.

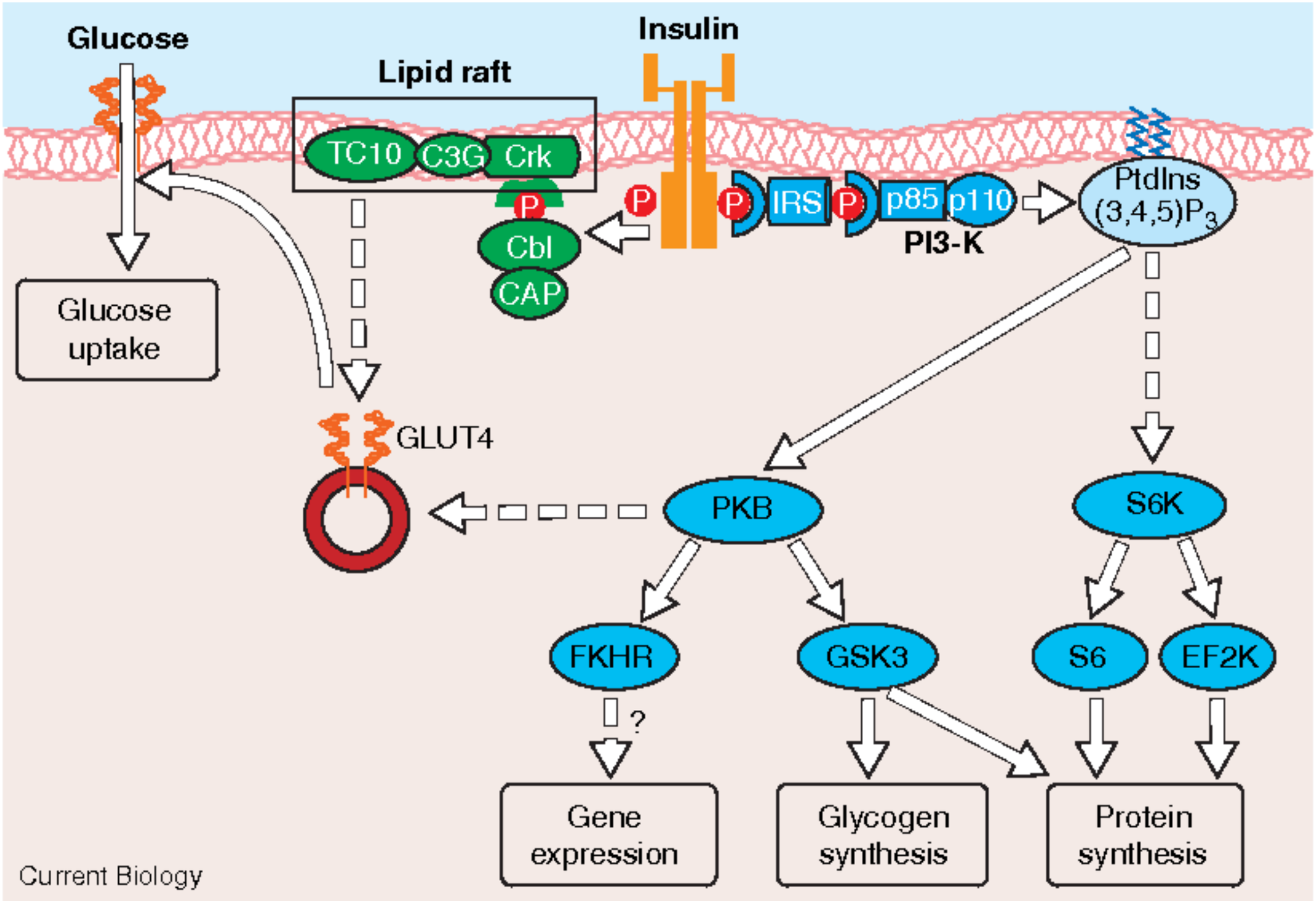
Insulin processing



Insulin consists of two polypeptide chains, the **A- and B- chains, linked together by disulfide bonds**. It is first synthesized as a single polypeptide called preproinsulin. Preproinsulin contains a 24-residue signal peptide which directs the nascent polypeptide chain to the ER. The signal peptide is cleaved as the polypeptide is translocated into lumen of the ER, forming proinsulin. In the ER the proinsulin folds into the correct conformation and 3 disulfide bonds are formed.

Proinsulin undergoes maturation into active insulin through the action of cellular endopeptidases known as prohormone convertases (PC1 and PC2), as well as the exoprotease carboxypeptidase E.[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 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). The resulting mature insulin is packaged inside mature granules.

Insulin signalling

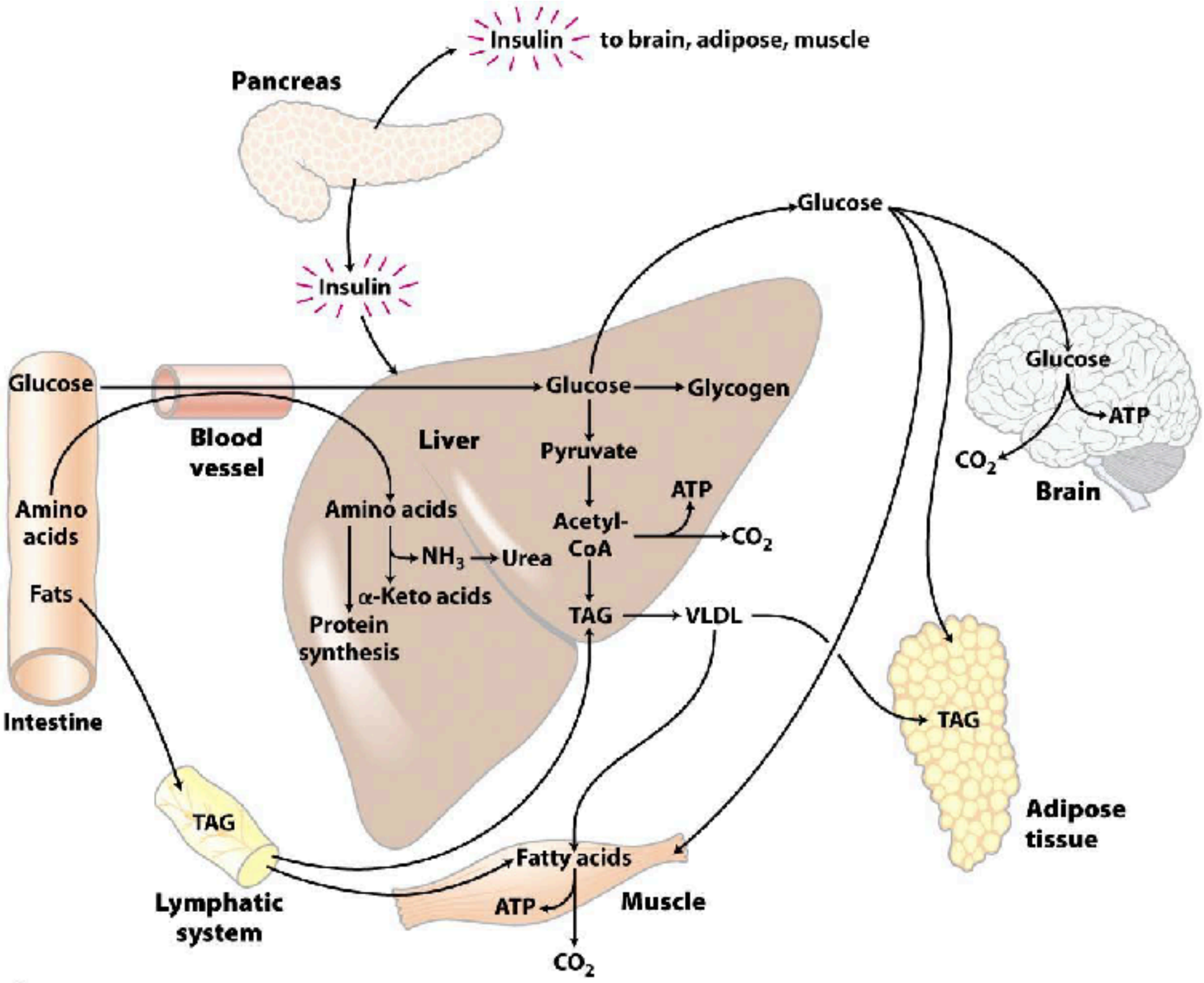


Insulin targets

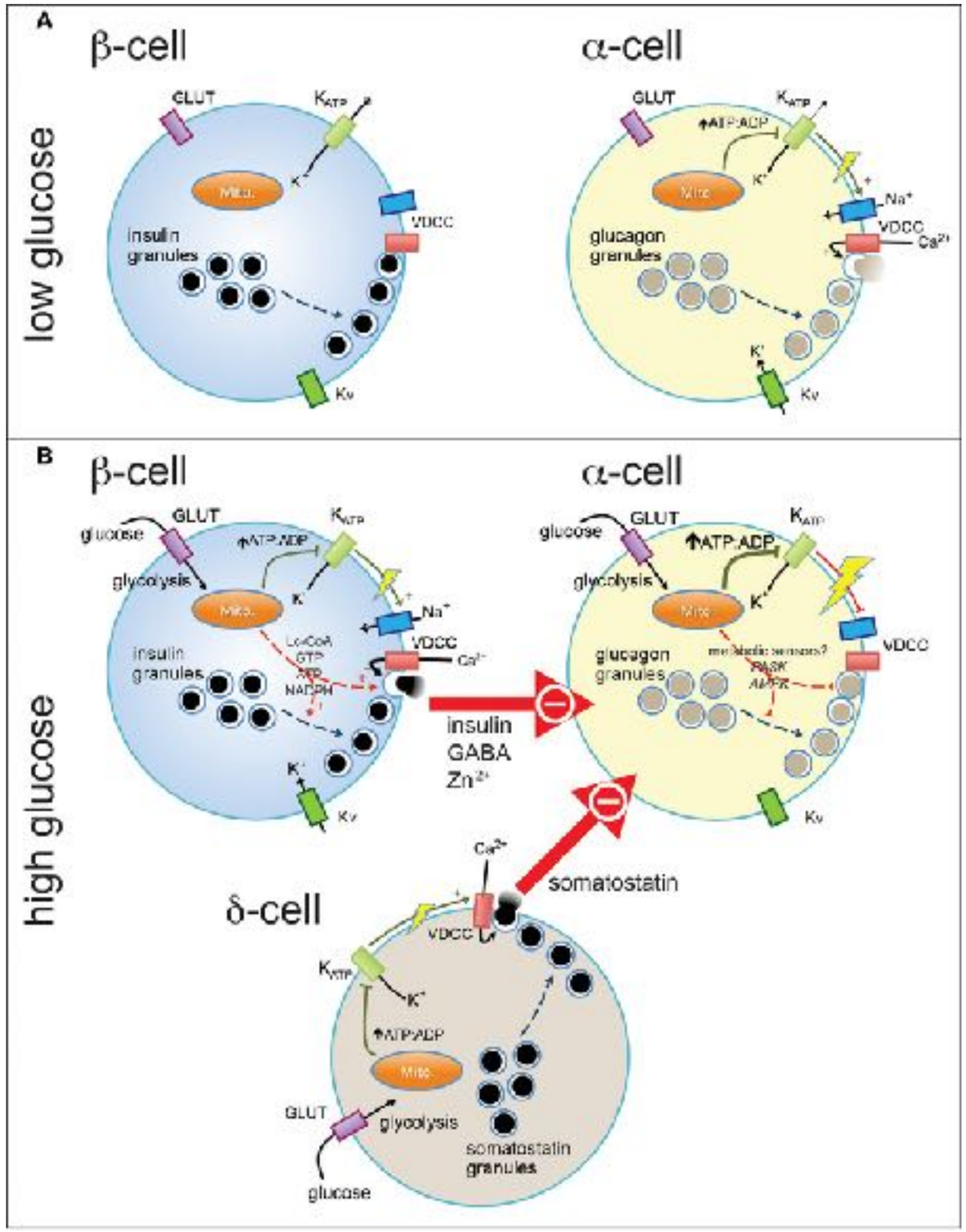
TABLE 23–3 Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

Metabolic effect	Target enzyme
↑ Glucose uptake (muscle, adipose)	↑ Glucose transporter (GLUT4)
↑ Glucose uptake (liver)	↑ Glucokinase (increased expression)
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA production (liver, muscle)	↑ PFK-1 (by ↑ PFK-2) ↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase

Insulin effects



Alpha Cells

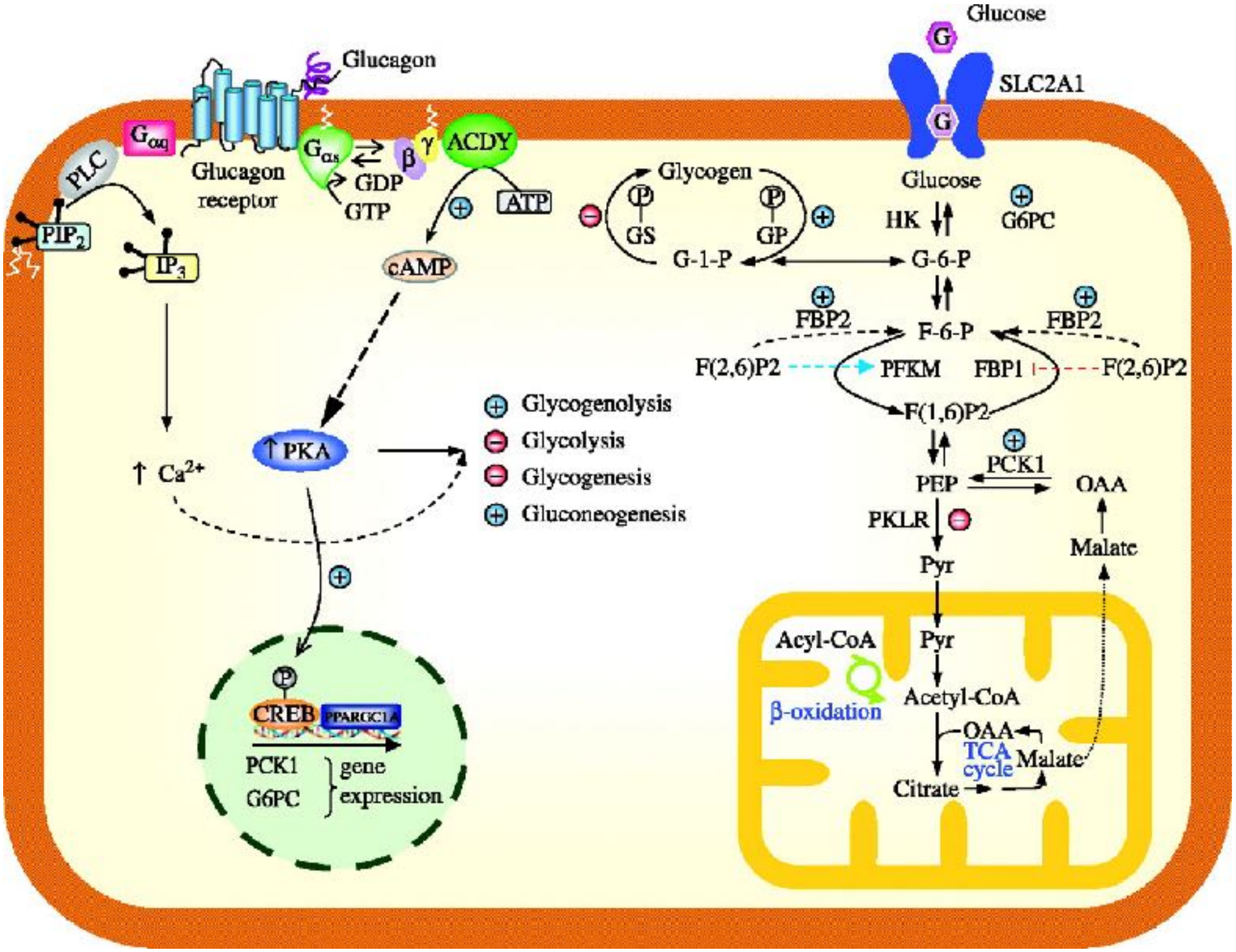


At **low glucose** levels α-cells are **electrically active**, due to a relatively elevated ATP (even at low glucose). This results in closure of KATP channels and a depolarized membrane potential that allows action potential firing mediated by a voltage-dependent channels. Entry of Ca2+ triggers the exocytosis of glucagon-containing secretory granules.

When plasma **glucose is increased**, this results in further increase in the intracellular ATP with further closure of KATP channels which further depolarizes the membrane to a point where **voltage-dependent channels stop operating**.

Glucagon secretion is also inhibited by paracrine factors secreted from β-cells and pancreatic δ-cells.

Glucagon signalling

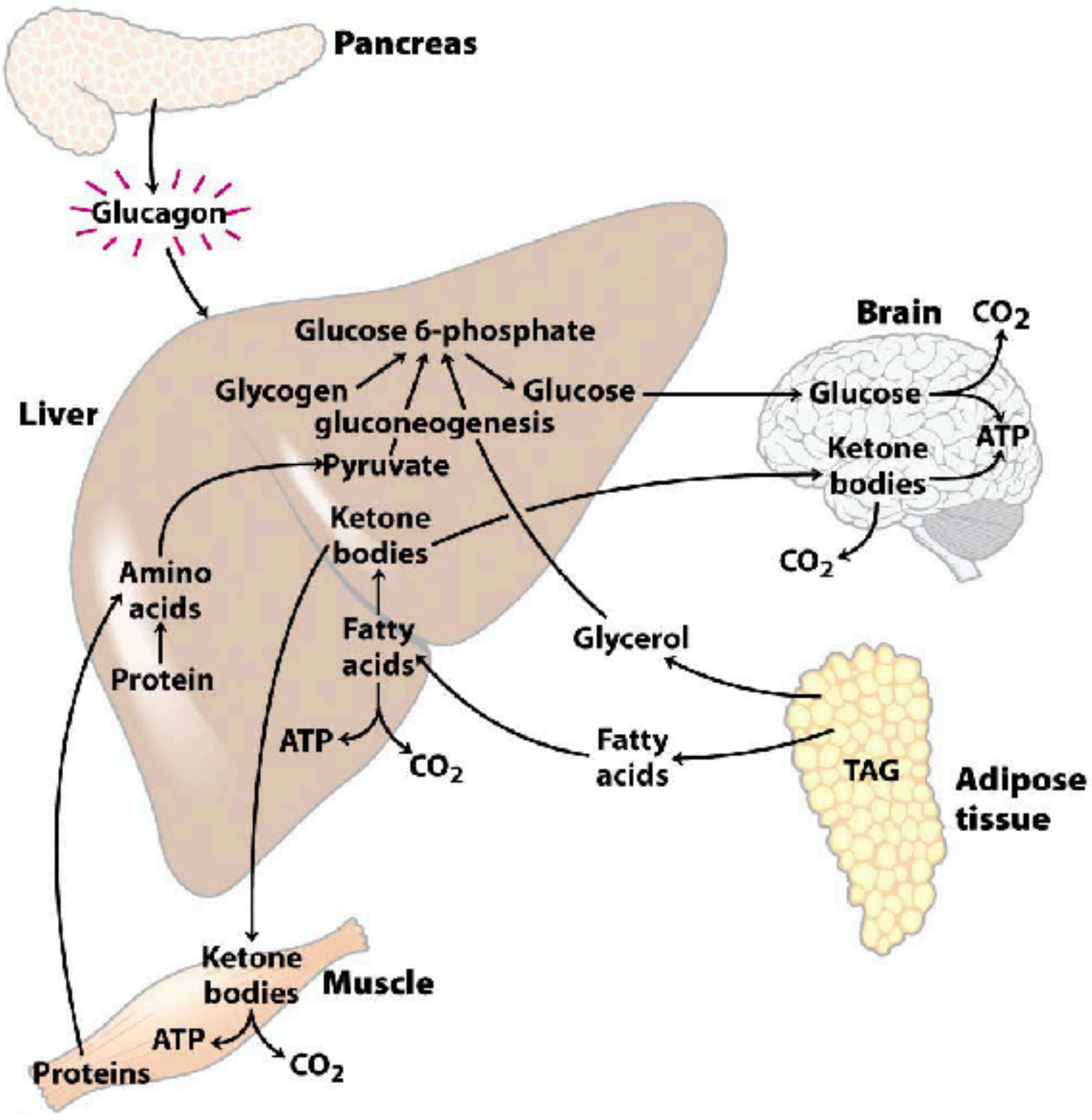


Glucagon targets

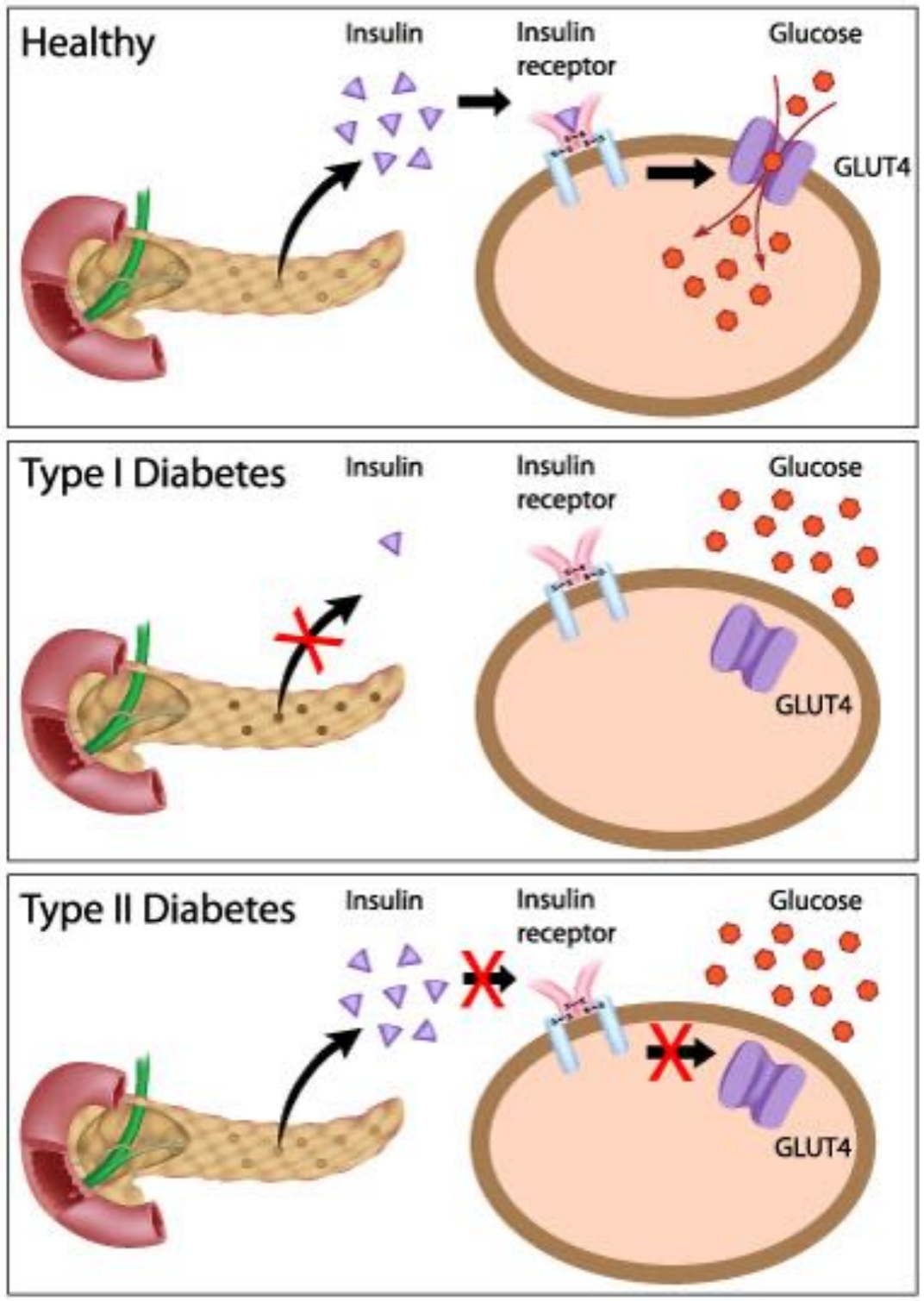
TABLE 23–4 Effects of Glucagon on Blood Glucose: Production and Release of Glucose by the Liver

Metabolic effect	Effect on glucose metabolism	Target enzyme
↑ Glycogen breakdown (liver)	Glycogen ⟶ glucose	↑ Glycogen phosphorylase
↓ Glycogen synthesis (liver)	Less glucose stored as glycogen	↓ Glycogen synthase
↓ Glycolysis (liver)	Less glucose used as fuel in liver	↓ PFK-1
↑ Gluconeogenesis (liver)	Amino acids, Glycerol, Oxaloacetate ⟶ glucose	↑ FBPase-2 ↓ Pyruvate kinase ↑ PEP carboxykinase
↑ Fatty acid mobilization (adipose tissue)	Less glucose used as fuel by liver, muscle	↑ Hormone-sensitive lipase ↑ PKA (perilipin—Ⓟ)
↑ Ketogenesis	Provides alternative to glucose as energy source for brain	↓ Acetyl-CoA carboxylase

Glucagon effects



Diabetes



The term diabetes mellitus refers to a group of metabolic disorders characterized by a high blood sugar level.

Symptoms include frequent urination, increased thirst, and increased appetite. If left untreated, diabetes causes serious acute and chronic complications .

Type 1 diabetes results from the pancreas's failure to produce enough insulin due to loss of beta cells due to autoimmune response.

Type 2 diabetes begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses, a lack of insulin may also develop. The most common cause is a combination of excessive body weight and insufficient exercise.

Diabetes

When glucose concentration in the blood remains high over time, the kidneys reach a threshold of reabsorption, and the body excretes glucose in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume is replaced osmotically from water in body cells and other body compartments, causing dehydration and increased thirst (polydipsia). In addition, intracellular glucose deficiency stimulates appetite leading to excessive food intake (polyphagia).

Take home messages

- The different organs in our body have specific metabolic functions still they are metabolically connected.
- The coordination among the metabolic activities operating at different organs is ensured by the neuroendocrine system
- Insulin and glucagon (which are produced by different cells in the pancreatic islets) represent an example of metabolic homeostatic circuit that controls blood sugar levels