MEDICAL UNIVERSITY – PLEVEN
FACULTY OF MEDICINE
DISTANCE LEARNING CENTER

Lecture № 17

Metabolism of carbohydrates, lipids and proteins and their regulation. Energetics and metabolic rate.

Body temperature regulation

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- **Metabolism is the sum of all chemical reactions, involved in**

  (1) producing energy from exogeneous and endogeneous sources,
  (2) synthesizing and degrading structural and functional tissue components, and
  (3) disposing of resultant waste products.

- ***Anabolic reactions*** provide substances for building up of cellular and extracellular structures and for adding body mass during growth.

- ***Catabolic reactions*** provide energy, that is expended for:

- mechanical work

- active transport across membranes

- maintaining body temperature

- synthetic metabolic reactions

- **According to the laws of thermodynamics:**
- **- in a closed system total energy is constant.**
- If the energy input is equal to the energy output, the body mass is constant. If energy balance is positive or negative, body mass changes.
- **- chemical transformations always result in a loss of free energy (as heat).**
- Energy, wasted as heat can never be zero or negative and chemical reactions can never be 100% efficient. This means that without food intake the total free energy of the body diminishes.

- ***Metabolism adapts to requirements of the body, which are not constant. Adaptation of metabolism is provided by control of the direction and velocity of chemical reactions.***
- **Both characteristics of chemical reaction in the body depend on:**

(1) ratio between quantity of reacting substances and quantity of end products

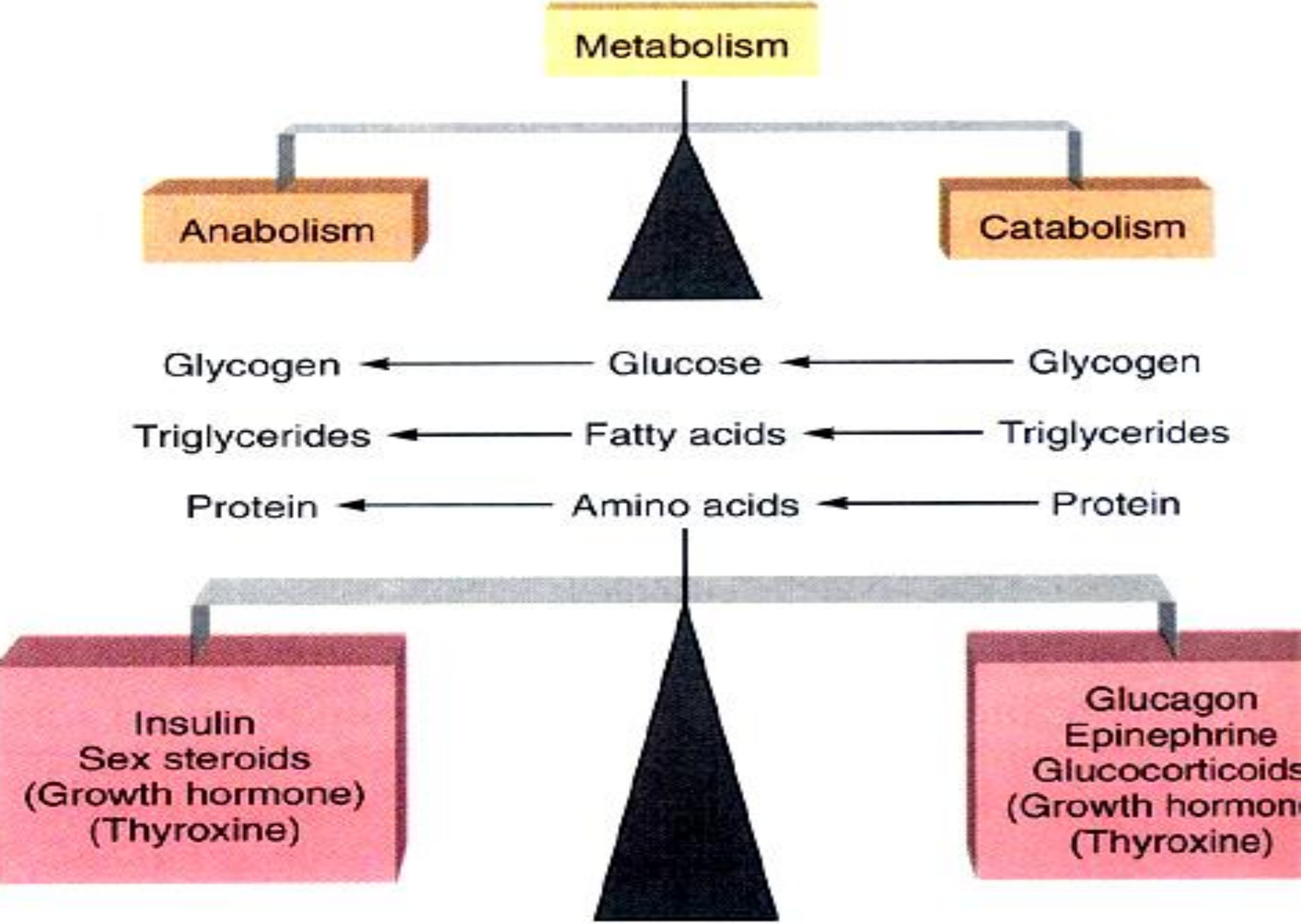
(2) enzyme activity, which depends on:

quantity of enzyme

alosteric activation and inhibition

covalent modification (most often regarding phosphorilation-dephosphorilation)

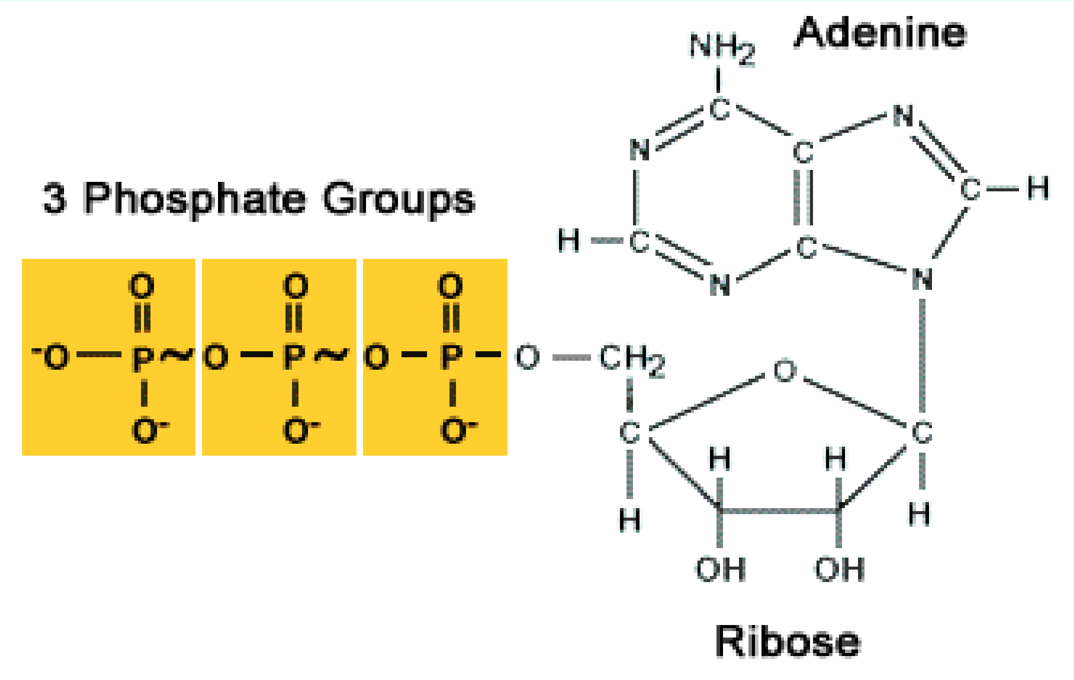
- **Most of these factors are the result of the influence of hormones and neurotransmitters on the cell's activity.**


Metabolism
Anabolism
Catabolism
Glycogen
Glucose
Glycogen
Triglycerides
Fatty acids
Triglycerides
Protein
Amino acids
Protein
Insulin
Sex steroids
(Growth hormone)
(Thyroxine)
Glucagon
Epinephrine
Glucocorticoids
(Growth hormone)
(Thyroxine)

Whole body metabolism

- The term **metabolism** is used to refer to all the chemical and energy transformations that occur in the body.
- The animal organism oxidizes carbohydrates, proteins and fats producing principally CO_2, H_2O and the energy necessary for life processes.
- **Energy can be stored** in the body in the form of **ATP** and **CP**.

- **ATP** is a labile chemical compound that is present in all cells and is a combination of **adenine, ribose and 3 phosphate radicals**.The last 2 phosphate radicals are connected with **the high- energy bonds**.



Whole body metabolism

- Removal of each of them liberates 12 000 cal of energy. ATP - P → ADP - P → AMP
- **The cells can transfer energy from the different foodstuffs to most functional systems only through this medium of ATP**.
- **The energy liberated** by catabolic processes in the body **appears as:**
  - an external work,
  - heat and
  - energy storage.

ENERGY METABOLISM

- *Energy balance: energy input is equal to the energy output.*

- ***Energy output consist of:***

1. **Basal (resting) metabolic rate** - absolute minimal energy expenditure. Basal metabolic rate is measured under standardized conditions in which the subject: (1) has had a full night of sleep, (2) has been fasting for 12 hours, (3) is in a neutral thermal environment, (4) has been resting physically for 1 hour, and (5) is free of psychic and physical stimuli.
2. **Diet-induced thermogenesis** (5% - 15% above the resting metabolic rate during 90 minutes after meal)
3. **Energy expenditure, related to profession, house work, sports etc.** It varies greatly among individuals.

Whole body metabolism

- **The energy is required for**:
  - Muscle activity
  - Secretion by the glands
  - Maintenance of the membrane potential by the nerve and muscle fibers
  - Synthesis of the substances in the cells
  - Absorption of the food-stuffs by the GIT and many other functions

Central role of glucose in carbohydrate metabolism

- The final digestive products of carbohydrates are about 80% of glucose and 20% of fructose and galactose. After absorption much of last two products are converted in the liver into glucose.
- Glucose thus becomes the final common pathway for transport of almost all carbohydrates to the tissue cells.

Transport of glucose through the cell membrane

- Active sodium-glucose co-transport (through the epithelium of guts and renal tubules)
- Facilitated diffusion(brain and liver cells, binding special membrane glucose carrier protein)
- Insulin dependent transport (muscles, connective tissue, fatty cells)

Central role of glucose in carbohydrate metabolism

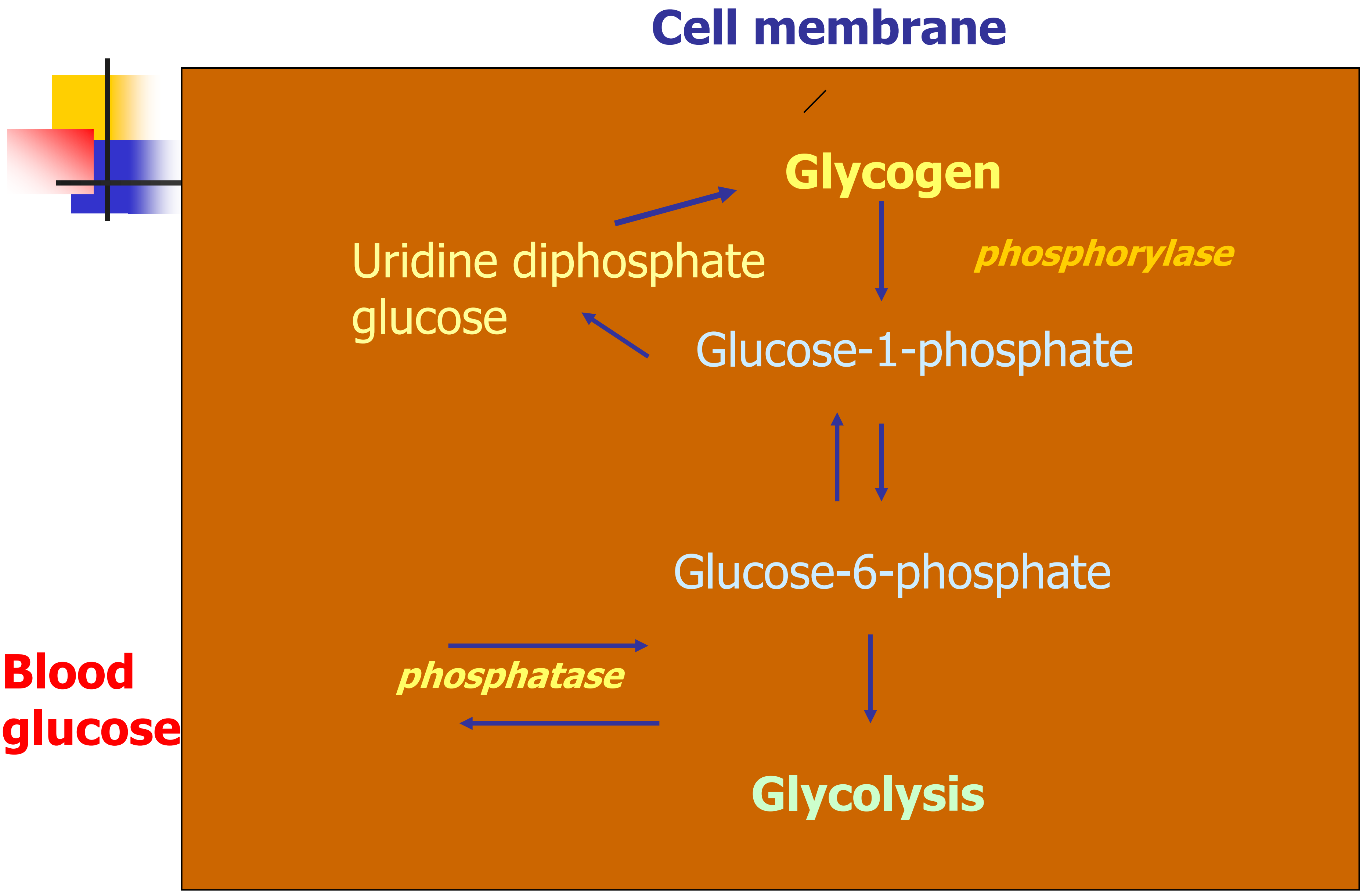
- Immediately on entry into the cells, **glucose** combines with a phosphate radical.This **phosphorylation** is promoted by the enzyme **glucokinase** in the liver or **hexokinase** in most other cells.
- After binding with phosphate, the **glucose** will not **diffuse back out** except **from the liver cells**, that have enzyme **glucose phosphatase.**

Glycogenesis

- After absorption into the cells, **glucose** :
  - can be used immediately for release of energy to the cells or
  - can be stored in the form of glycogen (a large polymer of glucose) in liver and muscles
- Several specific enzymes are required to cause the conversion of monosaccharides into a high-molecular weight precipitated compound make possible to store large quantities of carbohydrates without significantly altering the osmotic pressure of the intracellular fluids.This process is called **glycogenesis**.

Glycogenolysis

- The glycogen polymer is split away by phosphorylation, catalyzed by the **enzyme phosphorylase**.
- Under resting conditions, this enzyme is an inactive form.
- Two hormones **epinephrine and glucagon can specifically activate phosphorylase** and causing **rapid glycogenolysis**, elevate blood glucose concentration, when it is necessary.



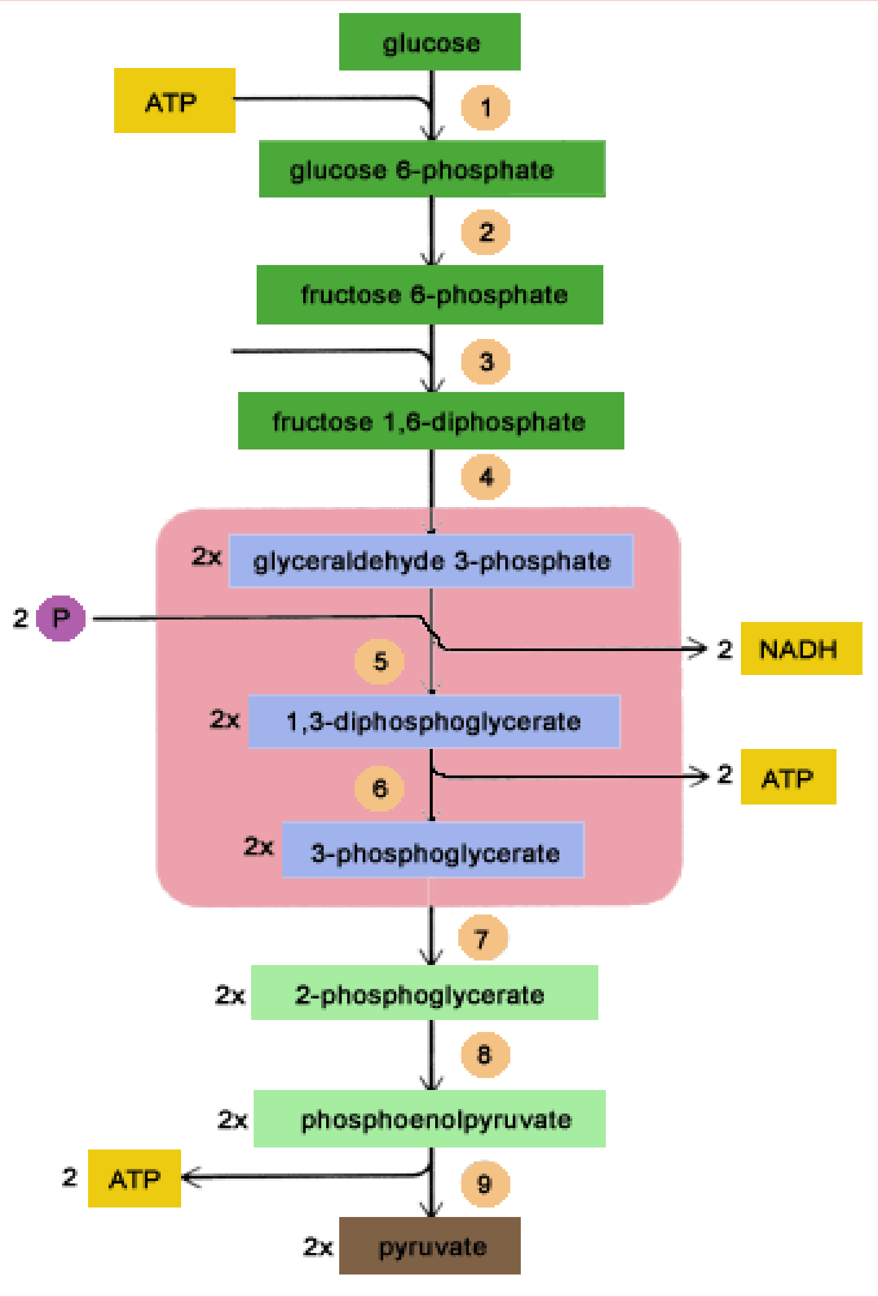
Cell membrane
Glycogen
phosphorylase
Uridine diphosphate glucose
Glucose-1-phosphate
Glucose-6-phosphate
Blood glucose
phosphatase
Glycolysis

Glycolysis

This means spliting of the glucose molecule to form 2 molecules of pyrovic acid.

This occures by 10 successive steps of

chemical reactions.

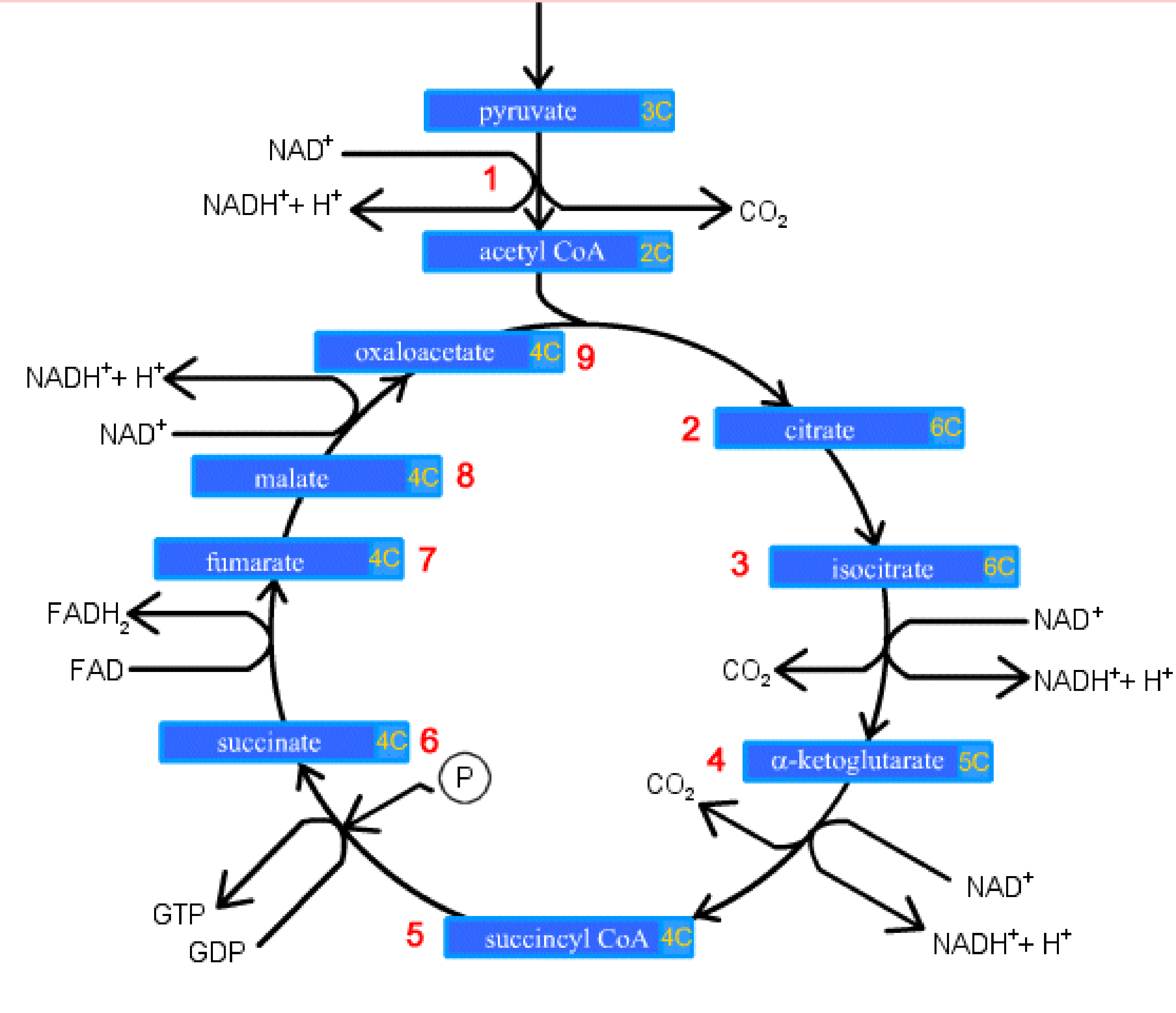


Oxidative phosphorylation

Citric acid cycle

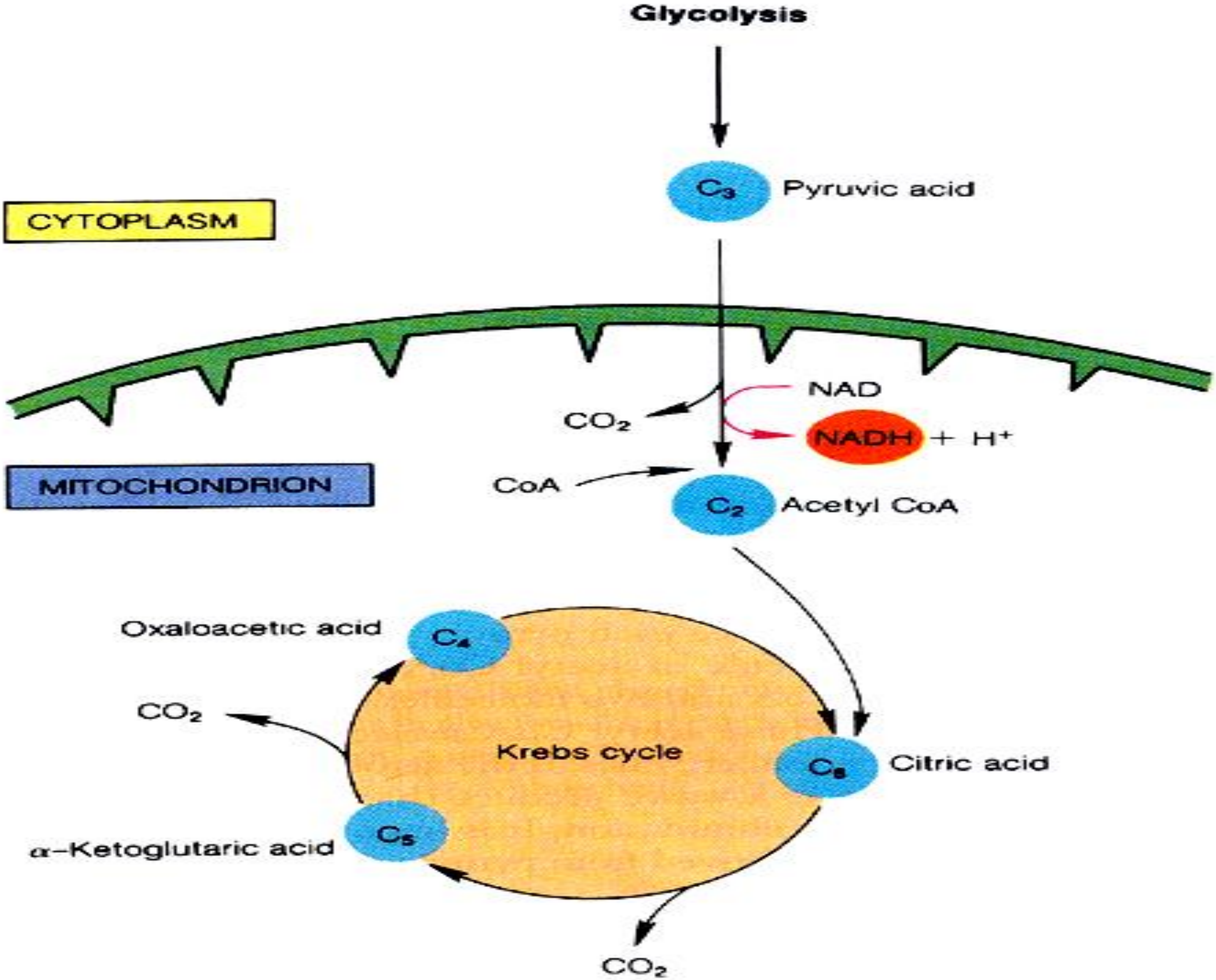
- Pyrovic acid is converted to acetyl-coenzyme A.
- **Acetyl-CoA is a common product of carbohydrate, lipid, and protein breakdown. It consists of an acetyl group attached to a coenzyme A molecule.** Coenzyme A is a large molecule that contains a molecule of ADP with two side chain groups stemming from its phosphate arms. Acetyl groups attach to the end of these side chains. In this way, **the coenzyme A acts as a carrier of acetyl groups.** When it is broken down by water, large amounts of energy are released.
- The next stage is called **citric acid cycle**. After that occur dehydrogenation and decarboxylation.
- During the sequence of oxidative reactions, tremendous quantities of energy are released to form ATP. This process is called oxidative phosphorylation.

Citric acid cycle



Citric acid cycle

- It occurs entirely in the mitochondria of the cells.
- **38 ATP molecules** are formed **for each molecule of glucose**, degraded to CO_2 and H_2O **under aerobic conditions**.
- 66% of energy stored in ATP can use for physiological functions of the cell.
- The remaining 34% of the energy becomes heat.



Glycolysis
C3
Pyruvic acid
CYTOPLASM
NAD
CO2
NADH + H+
MITOCHONDRION
CoA
C2
Acetyl CoA
Oxaloacetic acid
C4
CO2
Krebs cycle
C6
Citric acid
C5
α–Ketoglutaric acid
CO2

Glycolysis

- Under anaerobic conditions **anaerobic glycolysis** occurs**.** The great amount of lactic acid that forms during this process does not become lost from the body, because when O_2 is again available, the lactic acid either can be reconverted to glucose or can be used directly for energy.
- Heart muscle is especially capable of converting lactic acid to pyrovic acid and then using it for energy.

Release of energy from glucose occurs and by **pentose phosphate pathway**.

$$Gl + 12\ NADP^{+}\ \ 6\ H_2O \longrightarrow 6CO_2 + 12\ H + 12\ NADPH$$

Glucose conversion to glycogen or fat

- When glucose is not immediately required for energy the extra glucose that continually enters the cells is either stored as glycogen (in liver and muscles) or converted into fat (into liver and fat cells).

Gluconeogenesis

- When the body's stores of carbohydrates decrease below normal, moderate quantities of glucose can be formed from amino acids and the glycerol portion of fat. This process is called **gluconeogenesis**.
- It is controlled by hormones:
  - corticotropin and
  - cortisol.

Control of blood glucose level

- **Normal blood glucose (bl Gl) concentration**

  3,6 – 5,8 mmol/l (av. 90 mg/dl)

Nervous control (by hypothalamus)

- Activated sympathicus increases blood Gl concentration
- Hypothalamus secretes somatoliberin, corticoliberin, thyroliberin

Hormonal control

- ***hormones that increase blood Gl concentration***

(adrenalin, noradrenalin, glucagon, cortisol, growth hormone, thyroid hormones)

- ***a single hormone that decreases bl Gl level is insulin***

Lipid metabolism

- **Lipids include**: triglycerides, phospholipids, cholesterol.
- Triglycerides are used to provide energy for the different metabolic processes in the body.
- Phospholipids, cholesterol and small amount of triglycerides are used to form the membranes of all cells of the body and to perform other cellular functions.

Lipid metabolism

- During digestion most triglycerides are split into monoglycerides and fatty acids.
- All the fats of the diet with the principal exception of the short-chain fatty acids are absorbed from the intestines into the lymph.
- Then while passing through the intestinal epithelial cells, they are resynthesized into new molecules of triglyserides, that are aggregated and enter the lymph as **chylomicrons**, minute dispersed droplets.

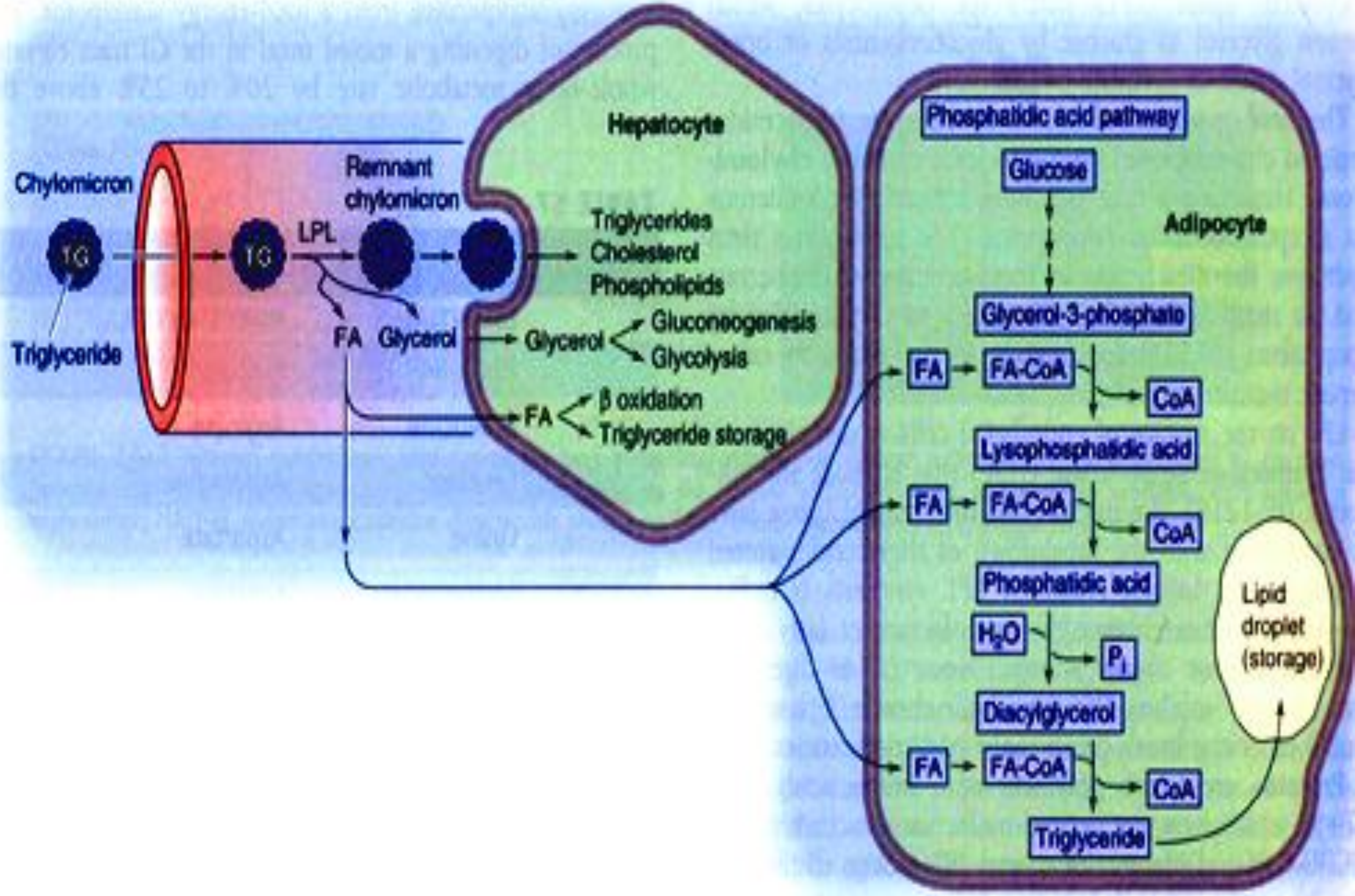
Lipid metabolism

- **Chylomicrons contain**: triglycerides; 9% phospholipids; 3% cholesterol and 1% appoprotein B.
- **Chylomicrons are removed from the circulating blood** as they pass through the capillaries of adipose tissue and the liver.
- These cells contain large quantities of the **enzyme lipoprotein lipase**, which hydrolyses the triglycerides of chylomicrons, that stick to the endothelial wall, releasing fatty acids and glycerol.
- **The fatty acids diffuse into the fat and liver cells.**

Lipid metabolism

- There **fatty acids are resynthesized** into triglycerides, new glycerol being supplied by the metabolic processes of the cells.
- **When the fat that has been stored in the adipose tissue is to be used elsewhere in the body**, usually to provide energy it must first to be transported to the other tissue.
- **It is transported in the form of free fatty acids**.This is achieved by hydrolysis of the triglycerides back into fatty acids and glycerol.On living the fat cells, the fatty acids ionize strongly **in the plasma and immediately combine with albumin molecules of the plasma proteins.**

B BREAKDOWN AND STORAGE OF DIETARY LIPIDS



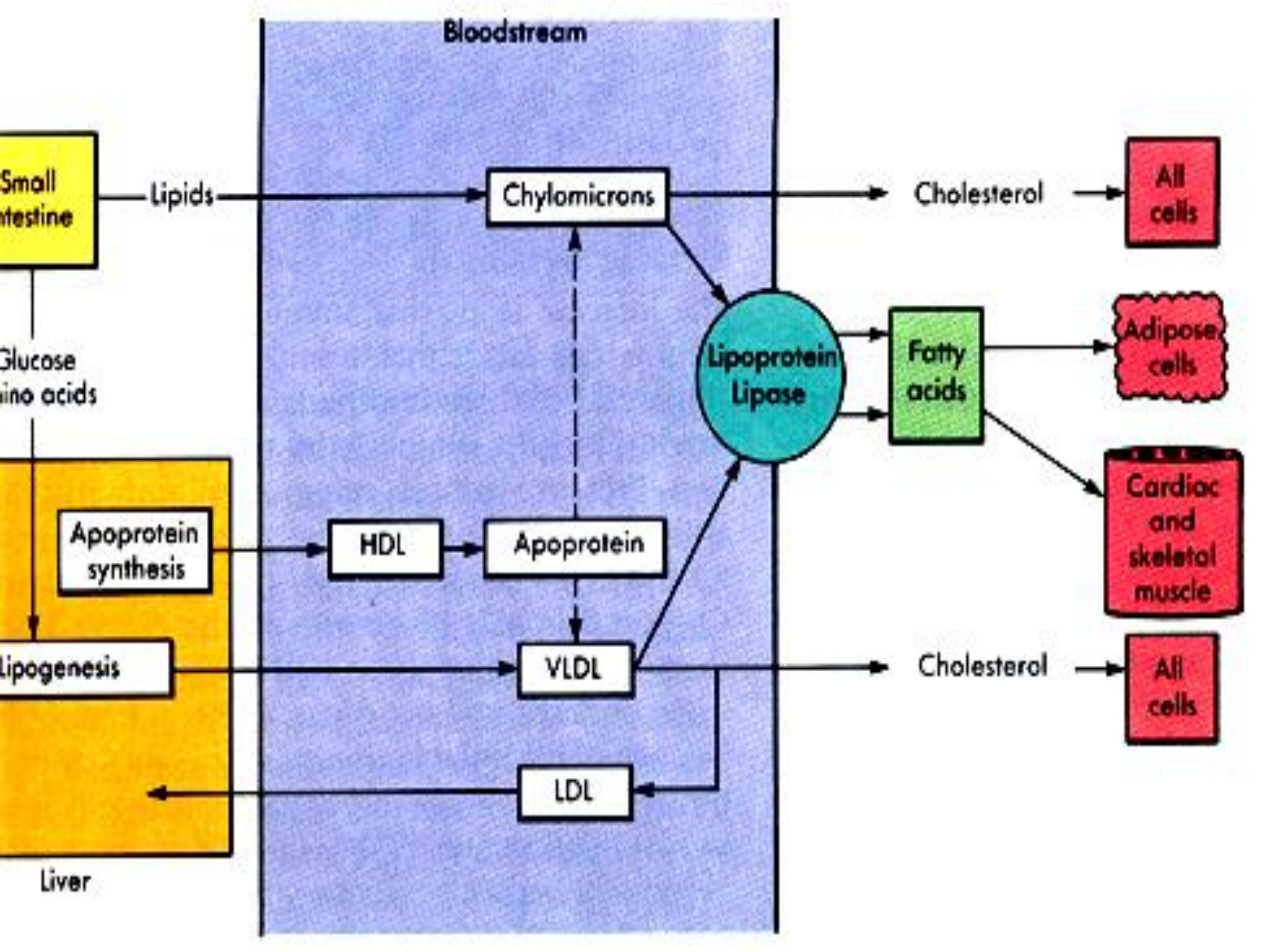
Lipoproteins

- In the postabsorbtive state, that is after all chylomicrons have been removed from the blood, **more than 95% of all lipids in the plasma are in the form of lipoproteins** (small particles containing triglycerides, cholesterol, phospholipids and protein).
- **The lipoproteins are classified by their densities**:

1. Very low density lipoproteins (**VLDL**)
2. Intermediate density lipoproteins (**IDL**)
3. Low density lipoproteins (**LDL**)
4. High density lipoproteins (**HDL**)

Lipid metabolism

- Almost all the lipoproteins are formed in the liver.
- The primary function of the lipoproteins is to transport their lipid components in the blood.
- Fat deposits are adipose tissue and the liver.
- Large quantities of lipases are present in adipose tissue. These enzymes catalyze the deposition of triglycerides from hylomicrons and VLDL.


Bloodstream
Small
ntestine
Lipids
Chylomicrons
Cholesterol
All
cells
Lipoprotein
Lipase
Fatty
acids
Adipose
cells
Cardiac
and
skeletal
muscle
Glucose
ino acids
Apoprotein
synthesis
HDL
Apoprotein
Lipogenesis
VLDL
Cholesterol
All
cells
LDL
Liver

Use of triglycerides for energy

- The first stage in the **use of triglycerides for energy** is their hydrolysis into fatty acids and glycerol.
- The degradation and **oxidation of fatty acids** occur only in the mitochondria.This process is called **ß oxidation.**
- The acetyl-Co A molecules formed by ß oxidation of fatty acids enter into the citric acid cycle. A net gain of making the **ATP mol** equals to **146**, during the complete **oxidation of 1mol of stearic acid.**

Lipid metabolism

- **Synthesis of triglycerides from carbohydrates is especially important for two reasons:**

1. The ability of different cells of the body to store carbohydrates,when greater quantity of them enter the body, in the form of glycogen is generally slight (except liver and muscle cells).
2. Each gram of fat contains almost 2.5 times as many calories of energy as each gram of glycogen.

- **Synthesis of triglycerides from proteins**

The excess of many amino acids can be converted into Acetyl-Co A and then be synthesized into triglycerides, stored as fat.

❑ Phospholipids

Phospholipids are synthesized in essentially all cells of the body, although certain cells have a special ability to form great quantities of them. Probably 90 % are formed in the liver cells; substantial quantities are also formed by the intestinal epithelial cells during lipid absorption from the gut.

Functions of the phospholipids are the following:

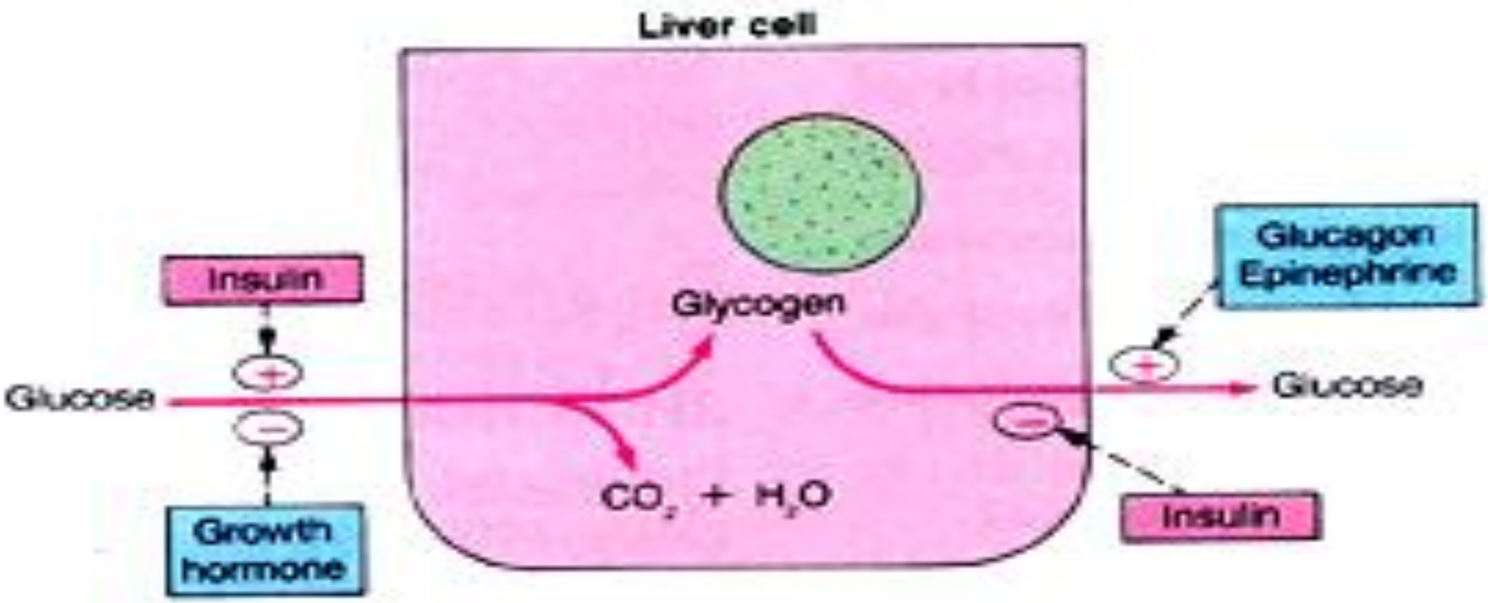
- (1) Phospholipids are an important constituent of lipoproteins in the blood and are essential for the formation and function of most of them. In their absence, serious abnormalities of transport of cholesterol and other lipids can occur.
- (2) Thromboplastin, which is needed to initiate the clotting process, is composed mainly of one of the cephalins.
- (3) Large quantities of sphingomyelin are present in the nervous system. This substance acts as an electrical insulator in the myelin sheath around nerve fibers.
- (4) Phospholipids are donors of phosphate radicals when these radicals are needed for different chemical reactions in the tissues.
- (5) Perhaps the most important of all the functions of phospholipids is participation in the formation of structural elements - mainly membranes in cells throughout the body.

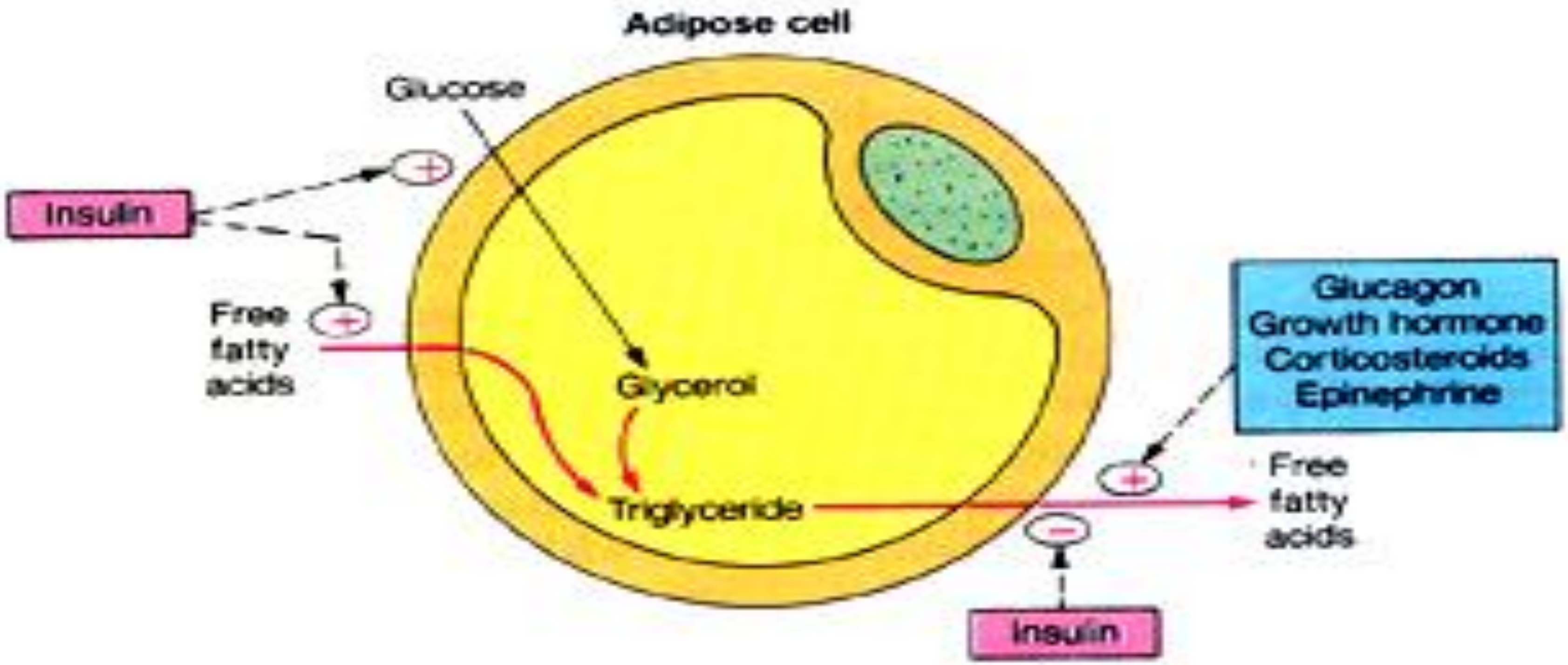
❑ Cholesterol

- Besides the cholesterol absorbed each day from the gastrointestinal tract, which is called ***exogenous cholesterol,*** an even greater quantity is formed in the cells of the body, called ***endogenous cholesterol.***
- Essentially all the endogenous cholesterol that circulates in the lipoproteins of the plasma is formed by the liver, but all other cells of the body form at least some cholesterol, which **is consistent with the fact that many of the membranous structures of all cells** are partially composed of this substance.
- A small quantity of cholesterol **is used** by the adrenal glands **to form** *adrenocortical hormones,* the ovaries to form *progesterone* and *estrogen,* and the testes to form *testosterone.*

Control of lipid metabolism

- Insulin – stimulates synthesis of fats from carbohydrates
- Stress → Sympathicus stimulation → epinephrine and norepinephrine – activate hormone-sensitive triglyceride lipase
- Growth hormone has the same effect
- Stress → corticotropin → cortisol → increases fat utilization
- Thyroid hormones → mobilization of fats


Liver cell
Insulin
Glycogen
Glucagon
Epinephrine
Glucose
Glucose
CO_2 + H_2O
Insulin
Growth
hormone


Adipose cell
Glucose
Insulin
Free
fatty
acids
Glycerol
Glucagon
Growth hormone
Corticosteroids
Epinephrine
Triglyceride
Free
fatty
acids
Insulin

Protein metabolism

- About 3 quarters of the body solids are proteins.
- These include structural proteins, enzymes, nucleoproteins, transport proteins in the blood and contractile proteins of the muscles.
- The proteins consist of amino acids, 20 of which are present in significant quantities.
- The proteins have several functions: structural, transport, regulatory, energetic.

Protein metabolism

- The end products of protein digestion are amino acids.
- They are absorbed trough the digestive tract into the blood by secondary active transport.
- The normal concentration of amino acids in the blood is 35 - 65 mg/dl.
- Significant quantities of amino acids can enter the cells only by facilitated or active transport using carrier mechanisms.

Protein metabolism

- After entry into the cells, amino acids combined by peptide linkages under the direction of the messenger RNA and ribosomal system, to form cellular proteins.
- There are reversible equilibrium between the plasma proteins and the tissue proteins.
- Many intracellular proteins can be rapidly decomposed again into amino acids under the influence of intracellular lysosomal digestive enzymes.

Protein metabolism

- The proteins in the chromosomes of the nucleus, structural and contractile proteins do not participate significantly in this reversible storage of amino acids.
- Each particular type of cell has an upper limit to the amount of proteins it can store.
- The excess amino acids in the circulation are then degraded in the liver and used for energy.

Protein metabolism

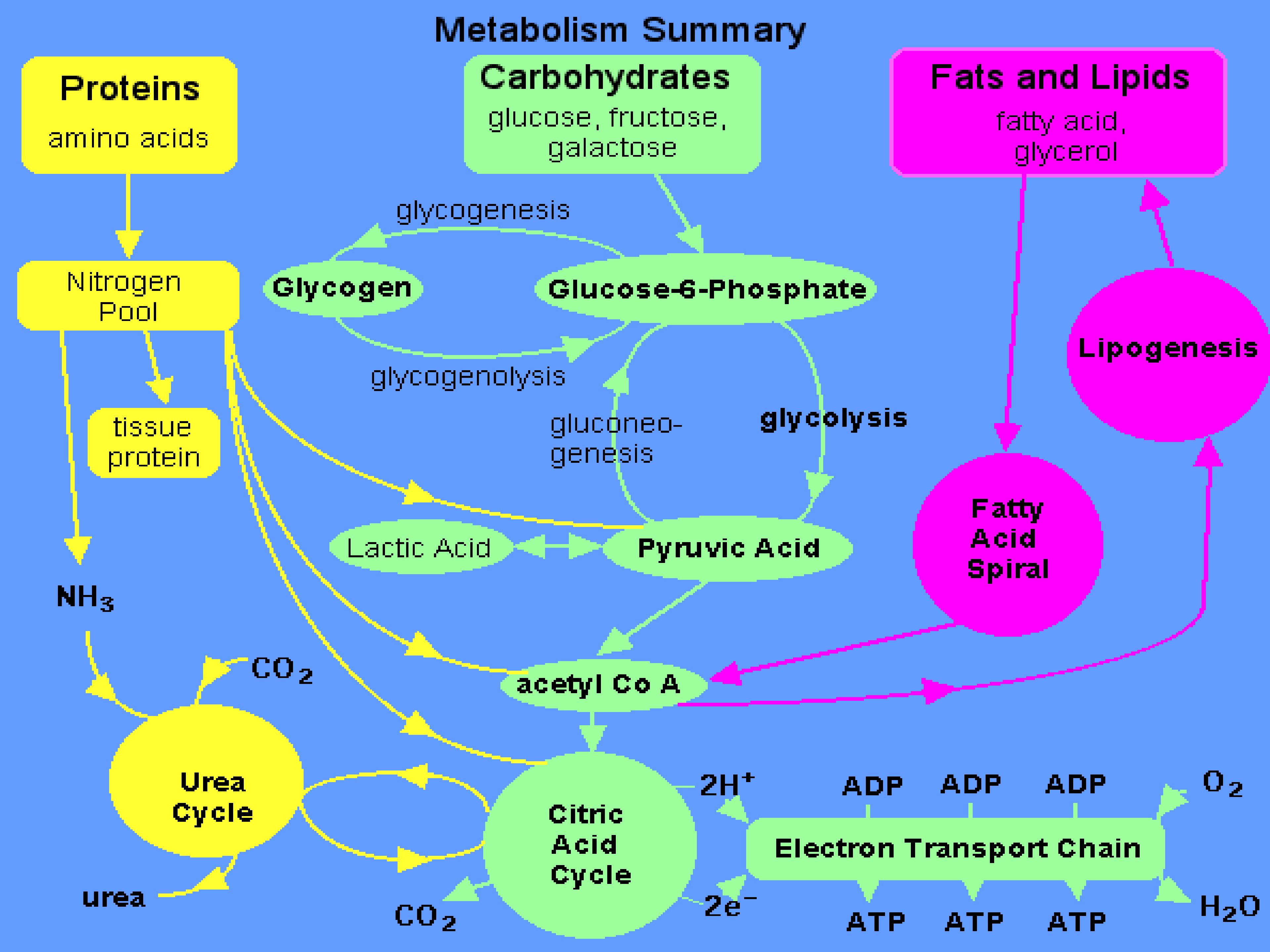
- This degradation begins with **deamination** under influence of aminotransferases.
- The ammonia released during this process is removed from the blood by conversion into urea.
- Once amino acids have been deaminated, the resulting keto acids products **can be oxidized to release energy for metabolic purposes**.
- The conversion of amino acids into glucose is called **gluconeogenesis,** and conversion into keto acids or fatty acids – **ketogenesis**.

Hormonal regulation of protein metabolism

- **Growth hormone** – enhances the transport of amino acids through the cell membranes, increases the rate of synthesis of cellular proteins.
- **Insulin** – accelerates transport of some amino acids into the cells, which could be the stimulus of protein synthesis.
- **Cortisol** – increases the rate of breakdown of extra hepatic proteins, making increased plasma concentration of amino acids. It stimulates gluconeogenesis and ketogenesis.

Hormonal control of protein metabolism

- **Testosterone** – causes increased deposition of proteins in the tissues, especially an increase in the contractile proteins of the muscles.
- **Thyroxin** – increases protein synthesis .
  - Deficiency of this hormone causes growth to be inhibited.
  - Excess removal of thyroxin has catabolic effect.


Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
glycogenesis
Glycogen
Glucose-6-Phosphate
Nitrogen Pool
glycogenolysis
Lipogenesis
tissue protein
gluconeo-genesis
glycolysis
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH_3
CO_2
acetyl Co A
Urea Cycle
Citric Acid Cycle
$2H^+$
ADP
ADP
ADP
O_2
Electron Transport Chain
urea
CO_2
$2e^-$
ATP
ATP
ATP
H_2O

Temperature regulation

Normal body temperature

- The temperature (T^0) of the deep tissues of the body – the "core" remains almost exactly constant = 37^0C.
- The skin temperature, in contrast to the core T^0 rises and falls with the T^0 of the surroundings.
- Body T^0 is controlled by balancing heat production against heat loss.

Body Temperature

- Normal internal body temperature is 37^0C.
- Temperatures above this:

  denature enzymes and block metabolic pathways
- Temperatures below this:

  slow down metabolism and affect the brain.

Heat production

- **The factors that determine the rate of heat production are:**
  1.basal rate of metabolism of all the cells of the body
  2.extra rate of metabolism caused by muscle activity
  3. extra rate of metabolism caused by the effect of thyroxin, growth hormone, epinephrine and norepinephrine

Heat production

4. extra rate of metabolism caused by the sympathetic stimulation

5. extra rate of metabolism caused by increased chemical activity in the cells themselves especially when the cell T^0 increases

Heat loss

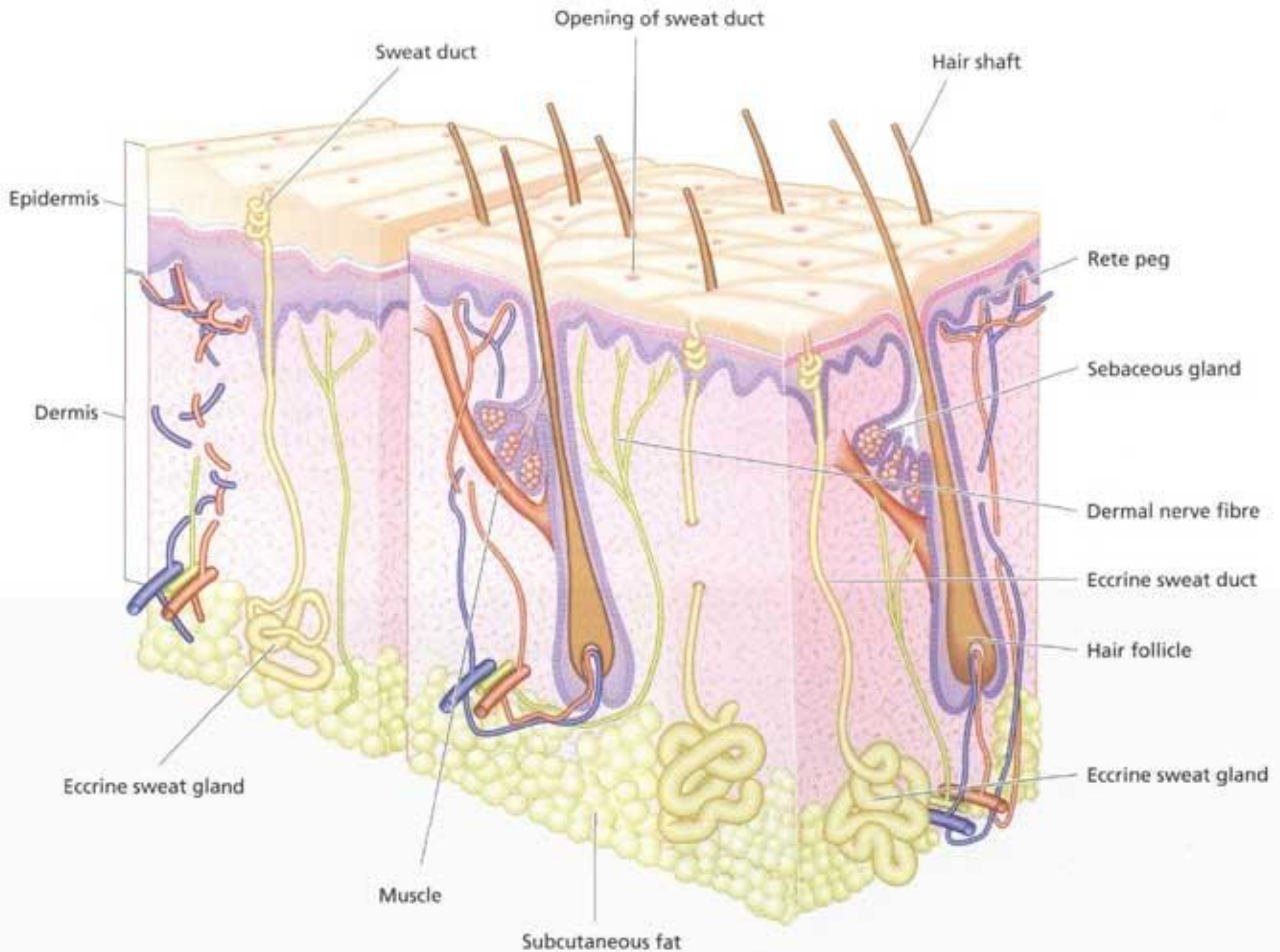
- Most of the heat produced in the body is generated in the deep organs, especially in the liver, brain, heart and the skeletal muscles during exercises.
- Then this heat is transformed from the deeper organs and tissues to the skin, where it is lost to the air and other surroundings.

Heat loss

- The rate at which heat is lost is determined by two factors:
  1. How rapidly heat can be conducted from the body core to the skin
  2. How rapidly heat can then be transferred from the skin to the surroundings.
- A high rate of blood flow causes heat to be conducted from the core of the body to the skin with great efficiency.

Heat loss

- Blood vessels penetrate the fatty subcutaneous insulator tissues and are distributed profusely immediately beneath the skin.
- Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries.
- In the most exposed areas of the body (the hands, feet and ears) blood is supplied to the plexus directly from the arteriovenous anastomoses.

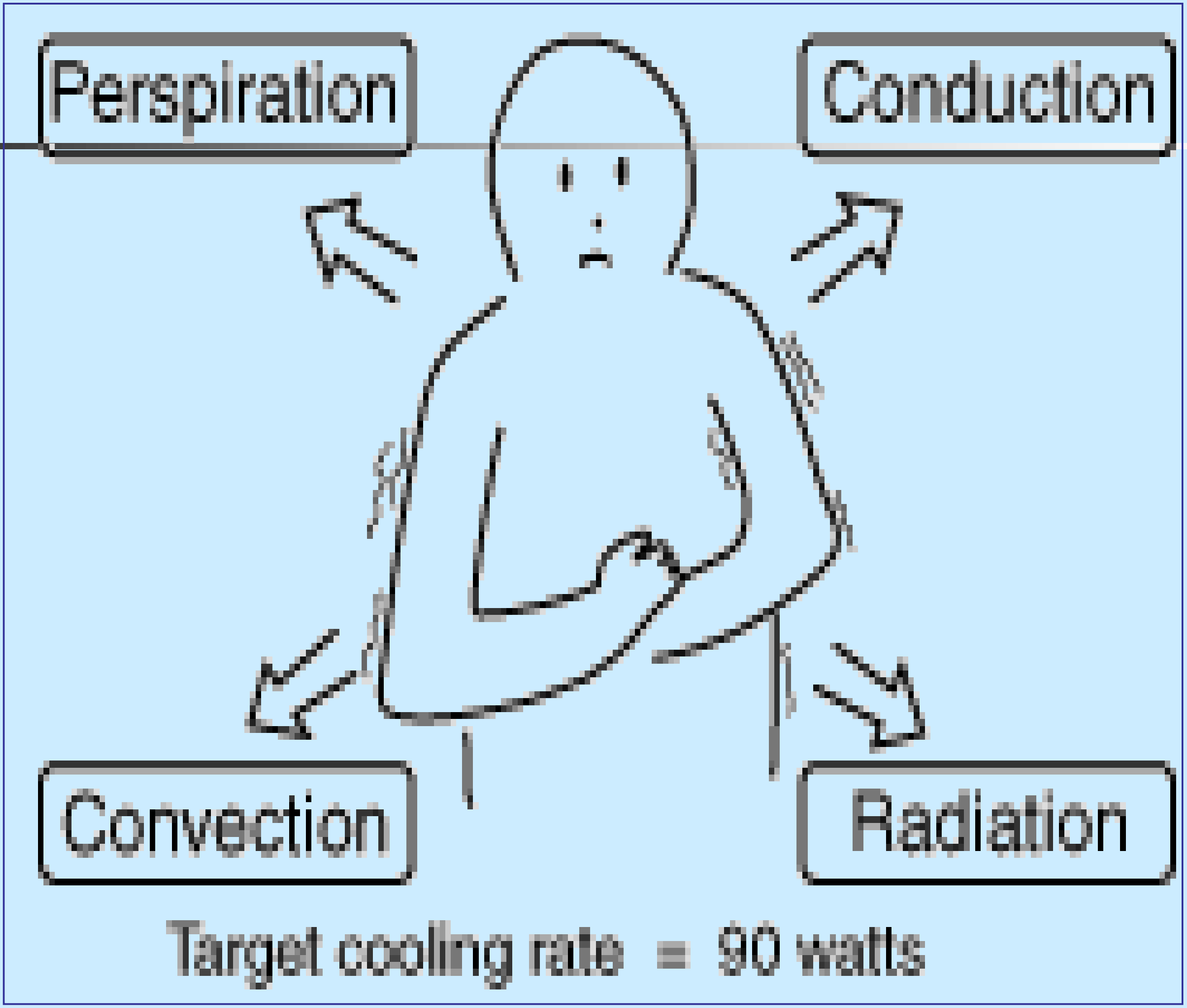


Opening of sweat duct
Sweat duct
Hair shaft
Epidermis
Rete peg
Sebaceous gland
Dermis
Dermal nerve fibre
Eccrine sweat duct
Hair follicle
Eccrine sweat gland
Eccrine sweat gland
Muscle
Subcutaneous fat

Basic physics of how heat is lost from the skin surface

- **1.Radiation** – loss of heat in the form of infrared heat rays (type of electromagnetic wave)
- **2.Conduction** – loss of heat by direct conduction from the surface of the body to other objects
- **3.Convection** – the removal of heat from the body by convection air currents
- **4.Evaporation**- is a necessary cooling mechanism, when the surrounding T^0 is higher than skin T^0, sweating increases

Basic physics of how heat is lost from the skin surface



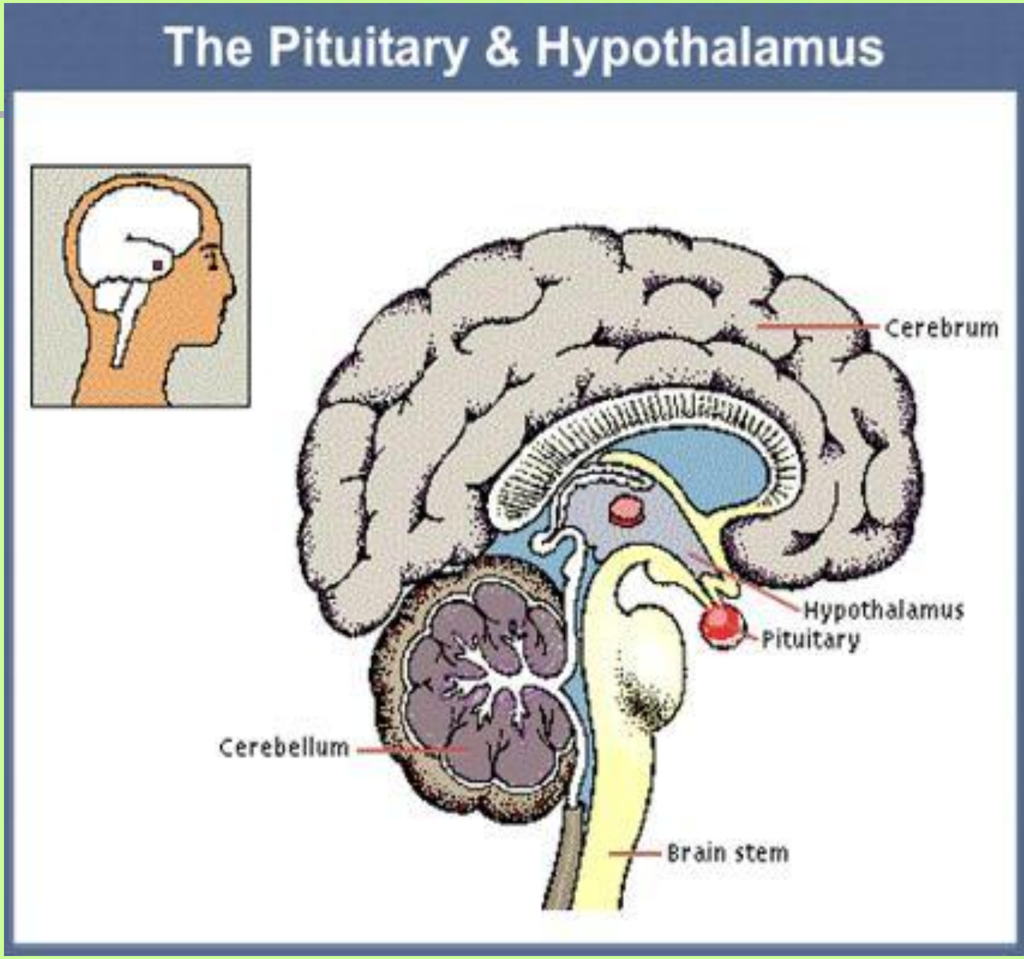
Regulation of body temperature

- The T^0 of the body is regulated by nervous feedback mechanisms, which operate through temperature-regulating centers located in the hypothalamus.
  - The anterior hypothalamic preoptic area has been found to contain large numbers of heat-sensitive neurons that function as temperature sensors.
  - Thermo-receptors of the skin also play important role in temperature regulation.

Body Temperature Control

- The hypothalamus acts as a thermostat and receives nerve impulses from heat and cold termoreceptors in the skin.

- There are also receptors in the hypothalamus- called central termoreceptors.



→ These detect changes in blood temperature.

3 basic components of a feedback system

- 1) receptor
  - sensor that responds to changes (stimuli)
- 2) control centre
  - sets range of values, evaluates input and sends output
- 3) effector
  - receives output from control centre and produces a response

Temperature regulation

The posterior hypothalamus summates the central and peripheral temperature sensory signals.

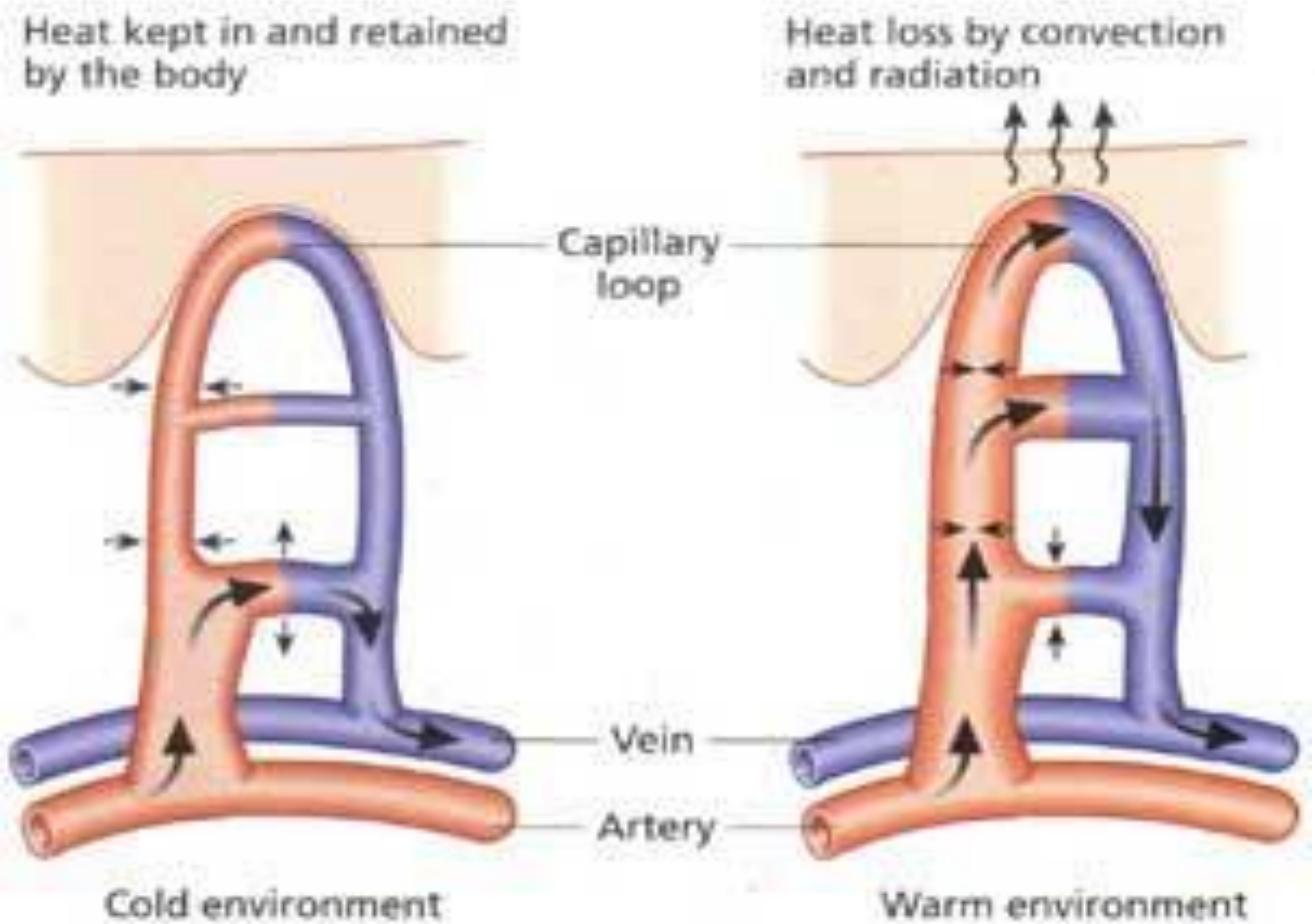
- **Temperature – decreasing mechanisms, when the body is too hot:**

  1.Vasodilatation – full vasodilatation can increase 8 fold the rate of heat transfer to the skin.

  2.Sweating – an additional 1^0C increase in body T^0 causes enough sweating to remove 10 times the basal rate of body heat production

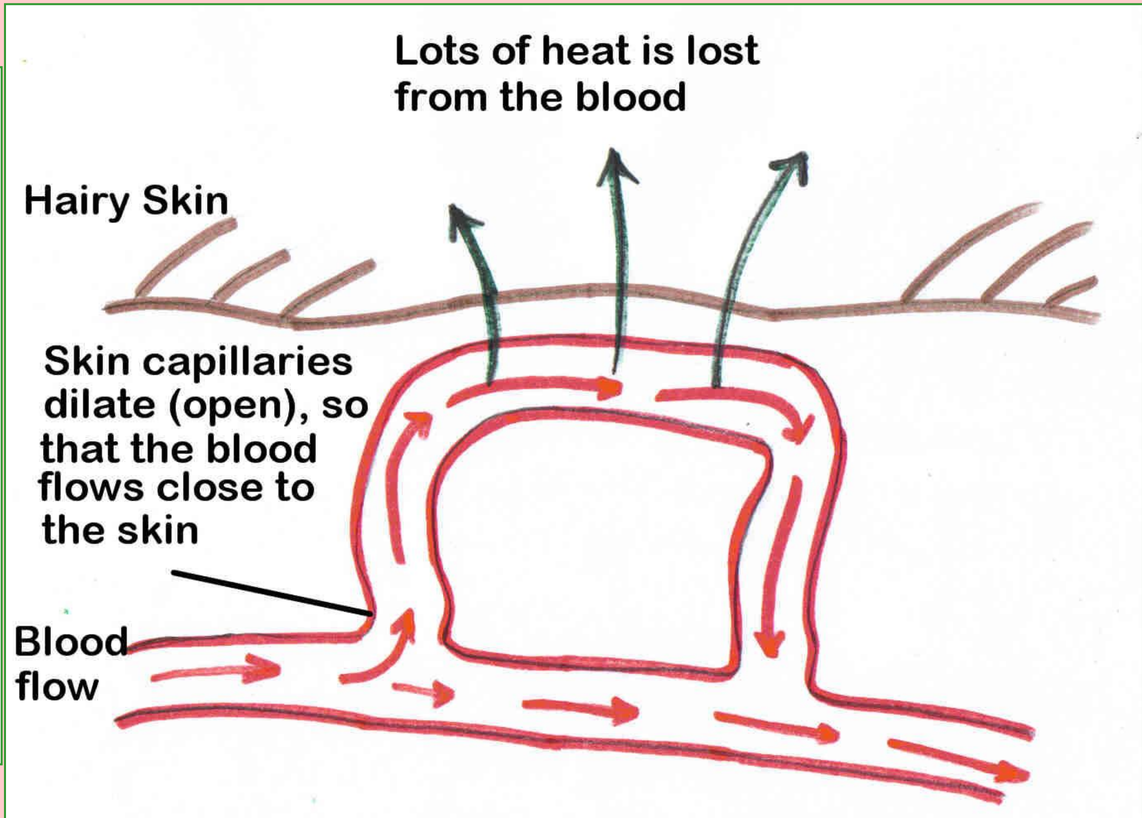
  3.Decrease of heat production – shivering and chemical thermo genesis are strongly inhibited.

Vasoconstriction and Vasodilatation

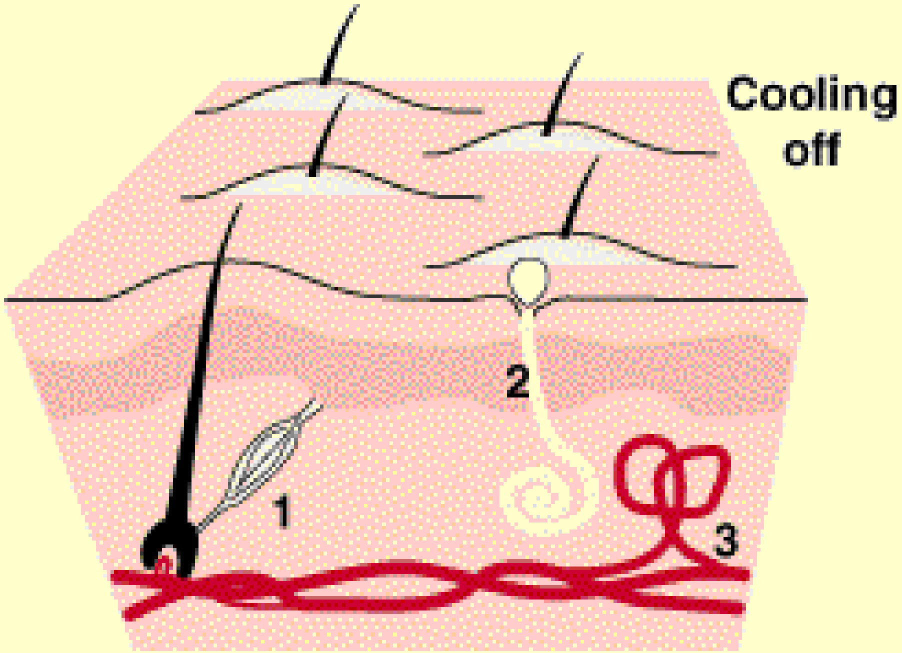


Correction of overheating

1. Detected by thermoreceptors in the hypothalamus.
2. Causes vasodilation.
3. Sweating

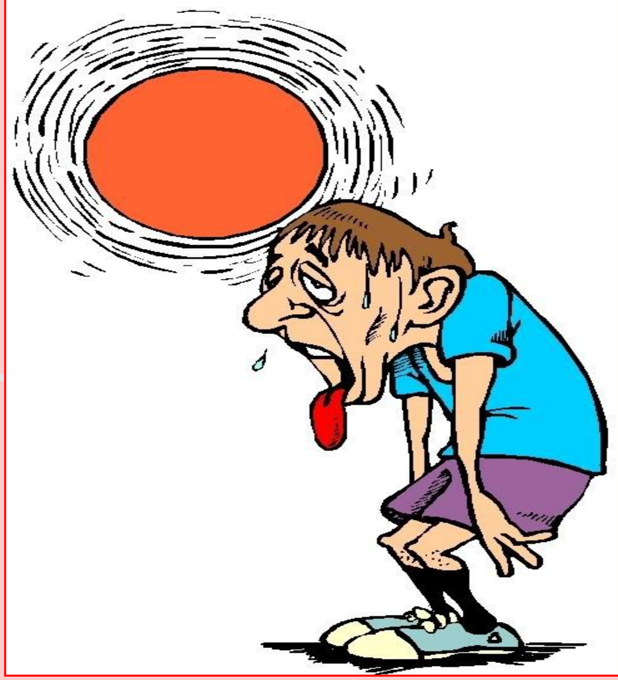


Cooling down



- When it's hot and you need to cool down, muscles at each hair relax.
- Hairs lie close to the skin.
- Air does not act as an insulating layer.

Sweating



How does it work?

Heat energy in the body is used to convert the water in sweat to vapour cooling down the body.

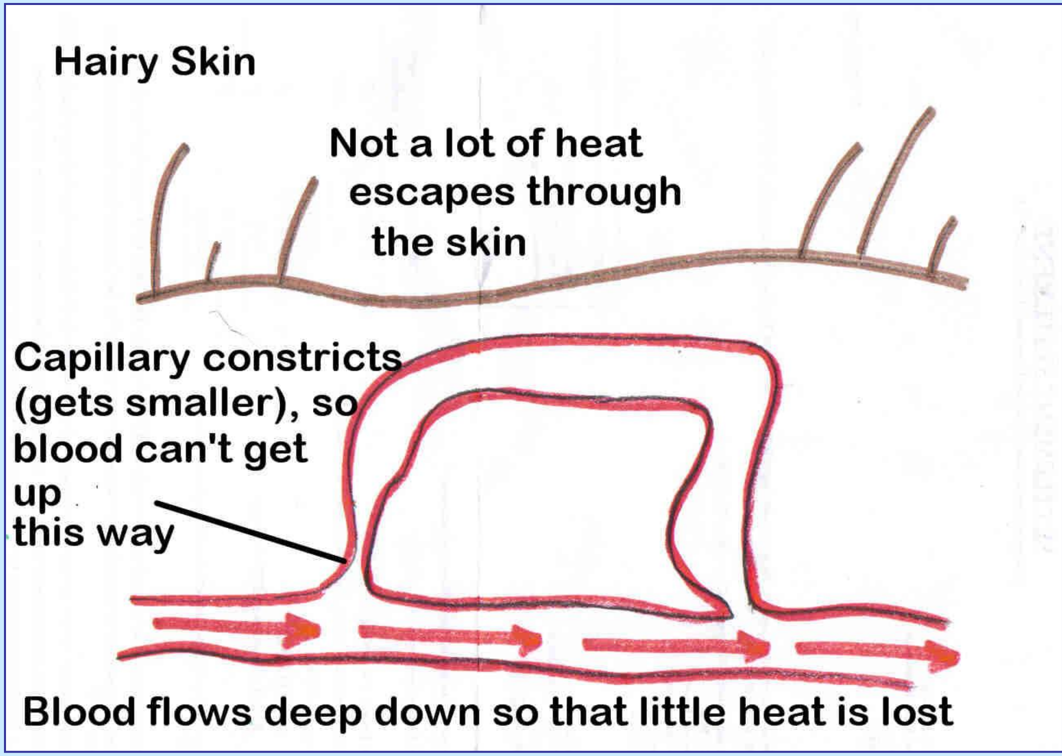
Temperature regulation

Temperature - increasing mechanisms, when the body is too cold:

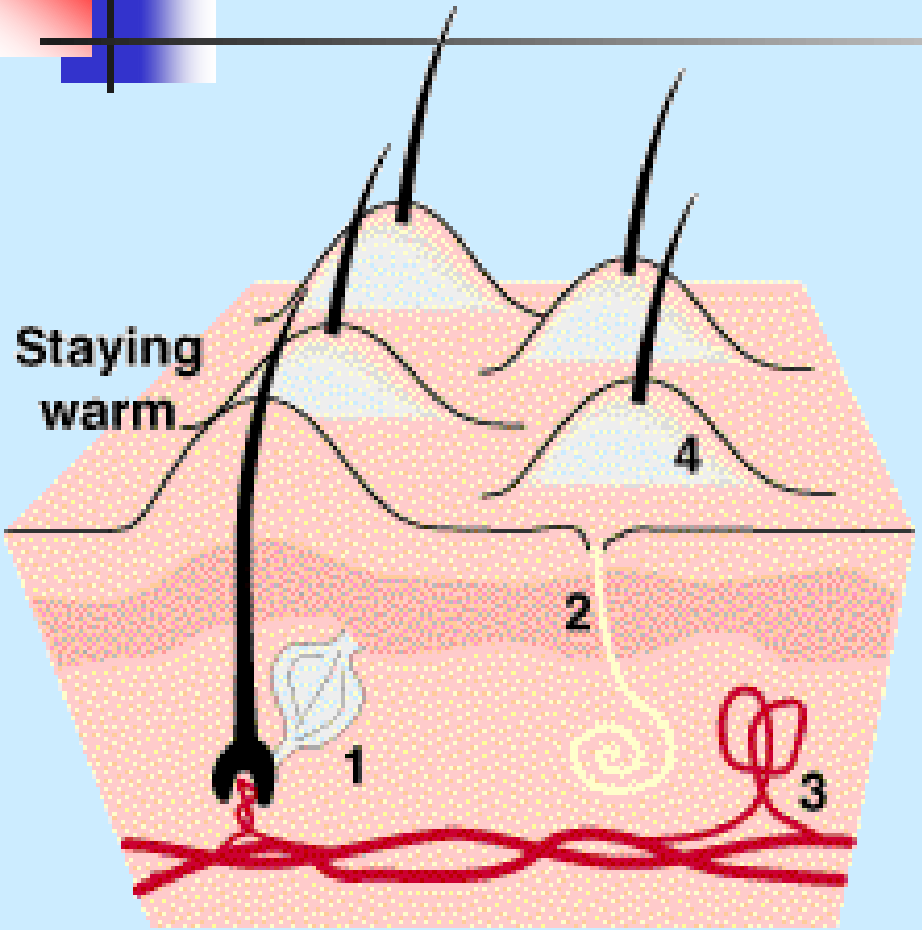
1. Skin vasoconstriction – this is caused by stimulation of the posterior hypothalamic sympathetic centers.
2. Piloerection
3. Increase of heat production – shivering activation; sympathetic excitation of heat production and thyroxin secretion

Correction of overcooling

1. Detected by thermoreceptors in the hypothalamus.
2. Causes vasoconstriction.
3. Decreased sweating
4. Shivering



Keeping warm



- When it's cold, the muscle contracts pulls the hair up.
- A layer of warm air accumulates around the hair and insulates the organism.
- Heat retained

Shivering

How does it work?

Located in the posterior hypotalamus is an area called primary motor centre of shivering. It is normally inhibited by the signals from the heat centre in the anterior hypotalamus-preoptic area, but it is exited by the cold signals from the skin and spinal cord. Increased muscular activity results in the generation of heat.

Voluntary responses

In humans the cerebrum “makes” people feel cold or hot.
They can then e.g. put on more clothes, eat a hot meal, exercise etc. as appropriate.

Thanks for your attention!