BIOCHEMISTRY **1st Year, 2nd Semester**

Prof. Catalin MARIAN, MD PhD Dr. Habil.
Email: cmarian@umft.ro

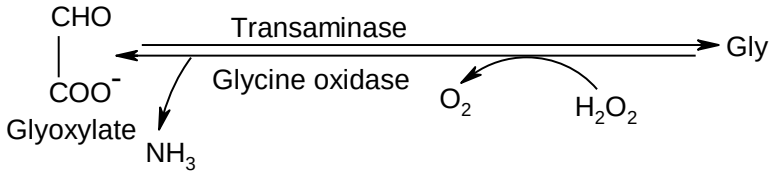
Lecture 9

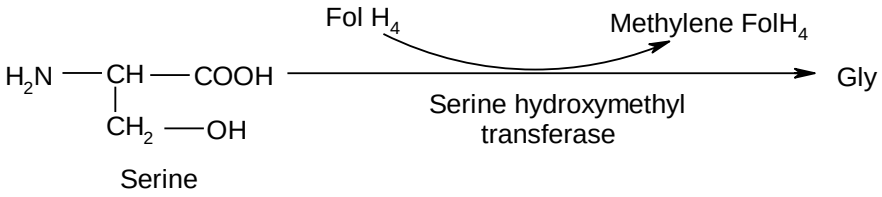
IV.6. The particular metabolism of amino-acids

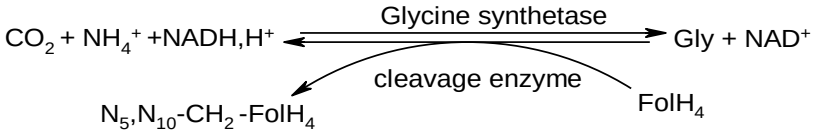
Glycine (glycocol)

It is a glucoplastic, biosynthesizable amino-acid.

The synthesis consists in the following three reactions:

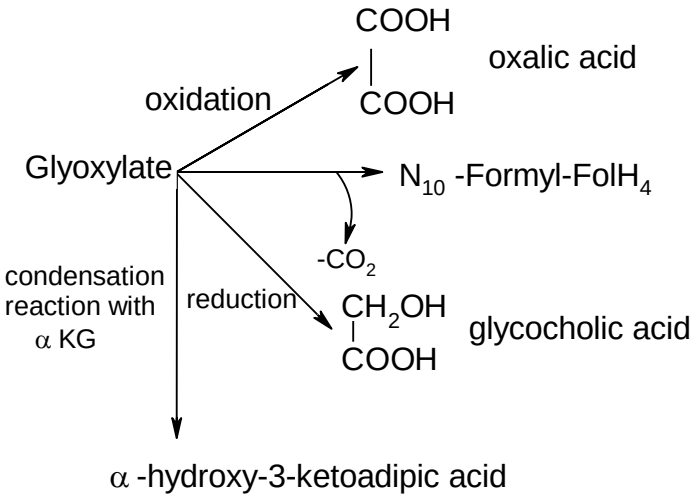






Catabolism

The first and last reactions from the synthesis can be used reversely within the catabolism process. The main catabolic pathway is transamination of Gly, forming glyoxilate. This, further on, will be transformed in several ways:



Biochemical and physiological role

- biosynthesis of porphyrins, purine bases, creatine, glutathione.
- conjugation with bile acids with which it forms conjugated bile acids (i.e. glycocolyc acid).
- conjugation with benzoic acid → hipuric acid

The conjugation processes are part of the mechanism of detoxification and xenobiotics elimination.

Pathology

1. Congenital non-ketonic hyperglycinemia, (0,6-1 g/day).

It is due to the deficit of glycine break up enzyme. The disease is deadly during childhood, the glycine excess inhibiting the neurotransmitters.

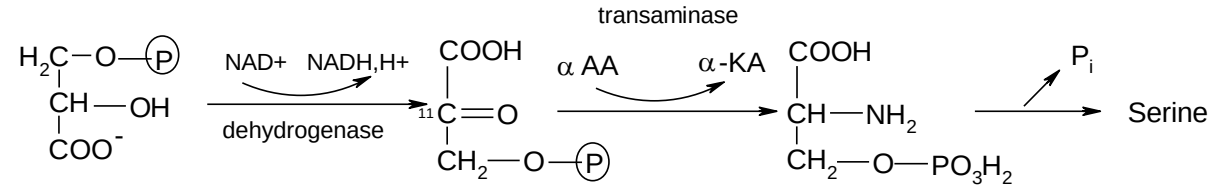
2. Metabolic oxalosis (occurs even in the absence of oxalates in food). It is due to the blocking of one or several pathways which metabolize the glyoxilate (the way of reducing to glycocalyc acid ⟶ oxalosis I, or condensation with α-KG ⟶ oxalosis II), compensatory increasing the oxidation way to oxalic acid, and the excess of oxalic acid forms renal calculi.

Alanine

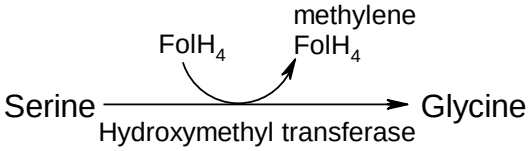
It is a biosynthesizable, glucoplastic amino-acid. Alanine metabolism is related to the pyruvic acid, by a transamination reaction. It is involved in the metabolism of amino-acids at the level of amino-acids catabolization by transamination and respectively in the amino-acids circulation within the late postprandial stage.

Serine

It is a glucoplastic biosynthesizable amino-acid. The main way of synthesis starts from the 3-phosphoglycerate.



Serine catabolism is mainly done through:



and secondarily by transforming in pyruvic acid in the presence of enzyme Ser-dehydratase.

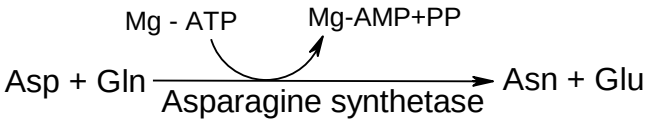
Regarding its role in the body, serine primarily represents the link between proteins and other molecules such as carbohydrates, lipids, vitamins, because of its hydroxyl group. Serine forms under these circumstances ester or ether bonds. Secondly, serine is an important precursor for the synthesis of amino-acids (glycine, cysteinee), amino-alcohols (colamine, coline, sphingosine) or lipids (phosphatidylserine).

Aspartic acid.

It is a non-essential, glucoplastic amino-acid whose metabolism is related to the oxaloacetic acid which it becomes reversibly through a transamination reaction. The aspartic acid plays an important role within ureogenesis, the purine nucleotide cycle, within the synthesis of the purine and pyrimidine bases.

Asparagine.

A non-essential glucoplastic amino-acid. It is formed of aspartic acid. The amide group is formed based on the nitrogen from Glu.



Glutamic acid.

It is a biosynthesizable glucoplastic amino-acid. The metabolism of the glutamic acid is related to that of the alpha-ketoglutaric acid, a compound of the tricarboxylic acids cycle. The glutamic acid plays an essential part within the metabolism of amino-acids, as the system glutamate–alpha ketoglutarate is the main system involved in the deamination of all amino-acids. The glutamic acid is a precursor in the synthesis of certain amino-acids such as Pro, Orn, Arg, Gln, His or of some important functional molecules such as the gamma-aminobutiric acid or glutathione. Within the blood coagulation process, the

gamma carboxylation of the first 10 residues of glutamic acid from prothrombin under the action of vitamin K leads to thrombin activation and the initiation of the blood clotting.

Glutamine.

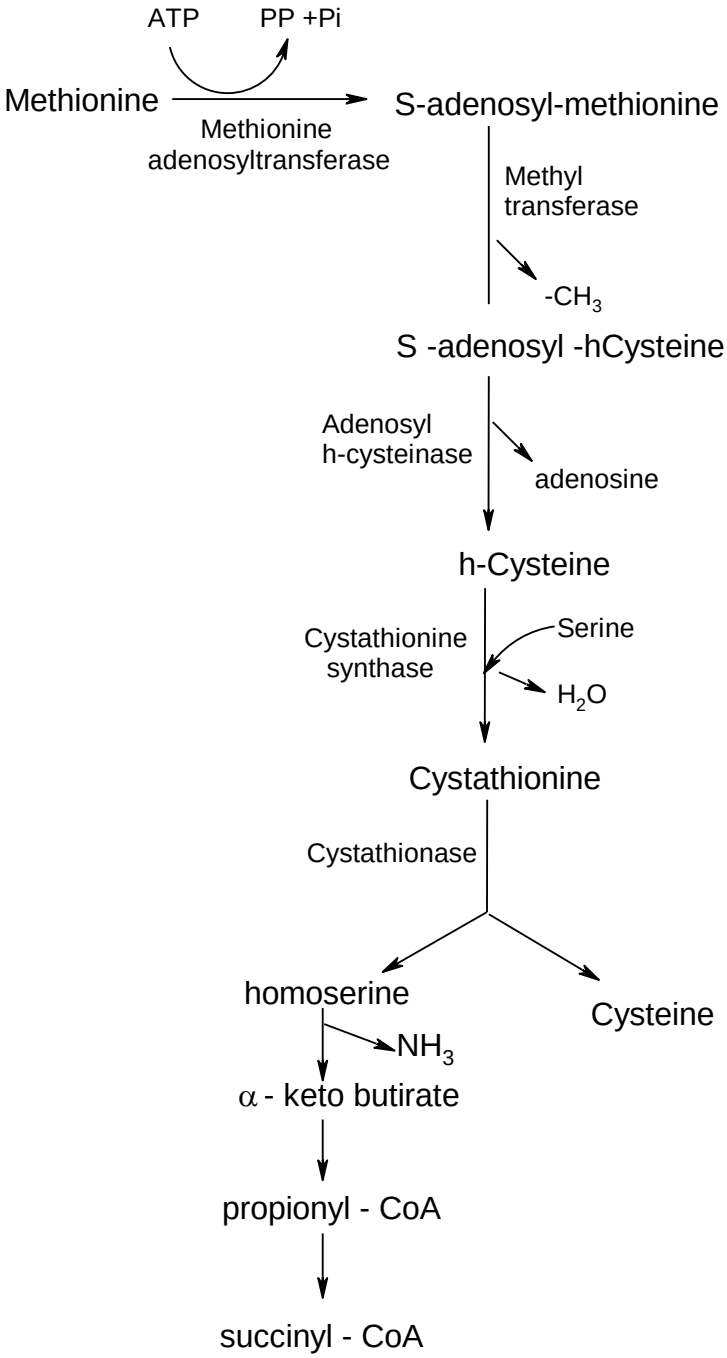
A glucoplastic biosynthesizable amino-acid, whose metabolism is related to that of the glutamic acid.

$$\text{Glutamate} + NH_3 + ATP \xrightarrow{\textbf{Glutamin syntethase}} Gln + ADP + Pi$$

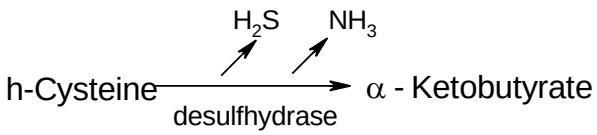
Glutamine plays a special role in transportation and reusing of the nitrogen within the body. Glutamine is involved in the process of ammonia-genesis, ureogenesis, transfer of amino group, synthesis of nitrogen bases.

Methionine and cysteinee.

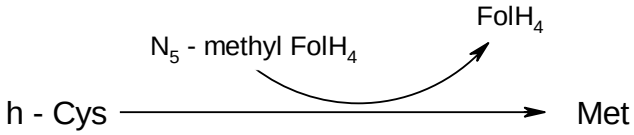
Methionine is an essential amino-acid, while cysteinee is formed by the transfer of a sulfur atom from methionine instead of the hydroxyl group of serine. Met and Cys are glucoplastic amino acids.



In the case of an urgent energy need, homocysteinee can be directed towards forming α–ketobutyrate.

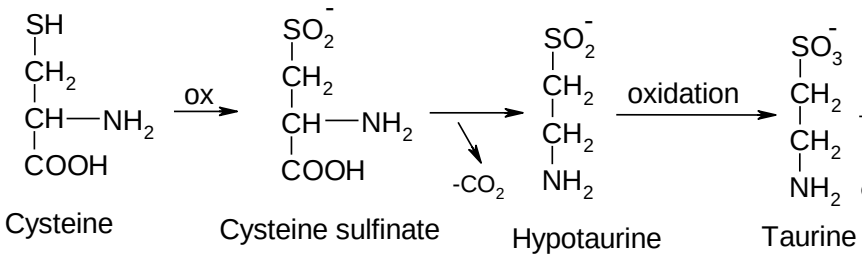


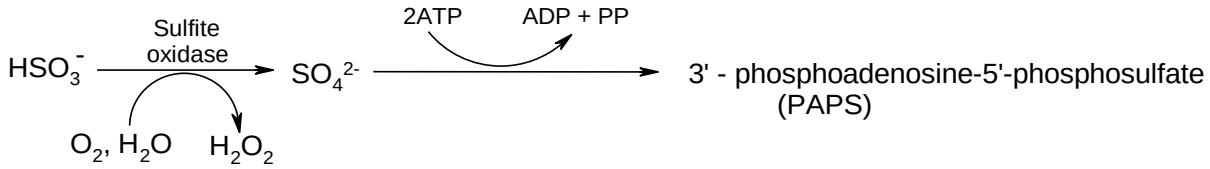
In the case of the methyonine needs, this can be made from homocysteinee.



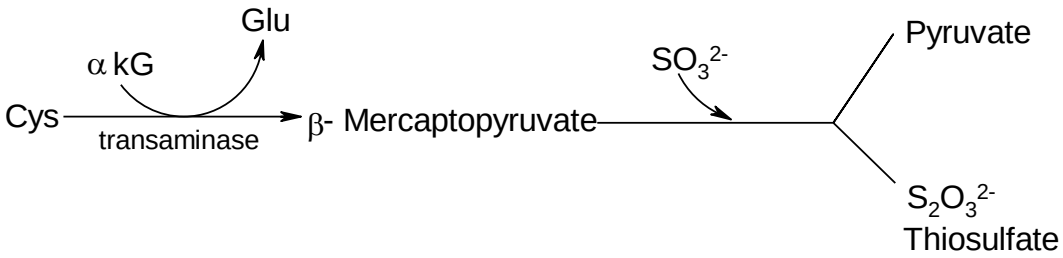
This reaction is the only case where FolH4 transfers a methyl group. S-adenosylmethionine is the main donor of methyl group in methylation reactions.

Cysteine is catabolized in several ways, according to the cell needs. The main way is:





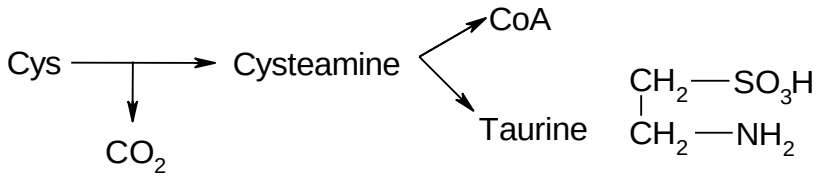
PAPS is the main agent of sulfation from the body, actively involved in the reactions of synthesis of sulfatides, gangliosides, heparin, etc. A secondary way is turning cysteine into pyruvate and tiosulphate, the latter playing a part in detoxification in the case of cyanides intoxication.



Cysteine plays in the body mostly a reductive role, due to the SH group. It constitutes an oxidoreduction system of the type:

2 Cysteine – SH ⟶ Cis – S – S – Cis + 2 H
Cystine

Furthermore, cysteine is the reduction part of glutation. By cysteine decarboxilation, cysteamine is obtained, a precursor for obtaining Coenzym A or taurine.

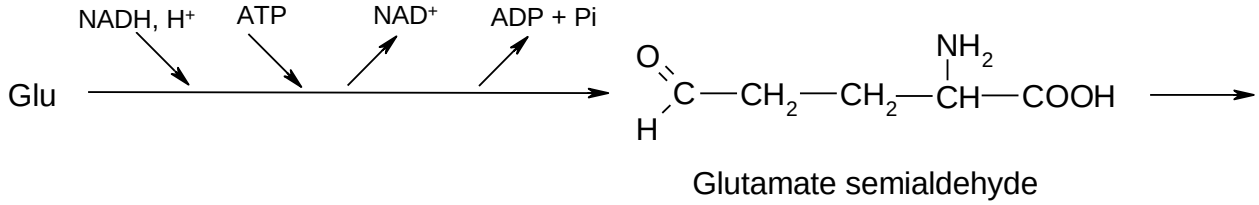


The pathology of cysteine and methionine metabolism

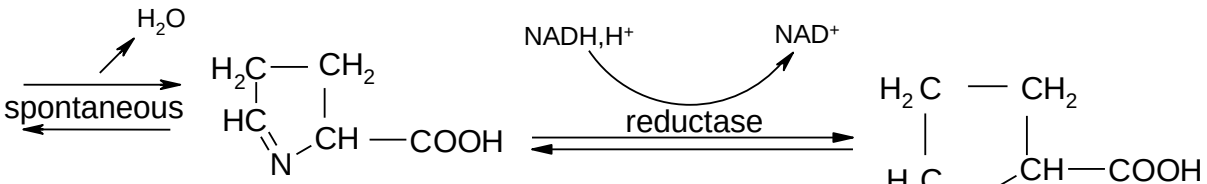
1. Hypermethioninemia. It is a congenial disease, due to the defect of the enzyme methyonyl-adenozyl-transferase. It manifests itself through mental retardation.
2. Congenital cystinuria. It is a malady generated by the defects of renal reabsorption of cysteine and of the basic amino-acids, a process leading to a massive elimination of the amino-acids mentioned. Cysteine, since it is hardly soluble, will form renal calculi. The necessary treatment includes removal of calculi, high liquid consumption, urine alcalinization by diet (vegetables), medication that conjugates cysteine.
3. Cystinosis. Accumulation of cysteine in lysosomes, due to the cysteine transportation defect through the lysosome membranes. The disease causes renal insufficiency in the first 10 years of life.
4. Hyperhomocysteinemia. It is a disease generated by the defect of cystationine synthetase, great quantities of h-Cis and Met accumulating into blood. The disease will manifest itself through atherosclerosis, mental retardation and retina dislocation after some years from the disease onset. 25% of the people suffering from atherosclerosis with an etiology with no risk factor have deficiency of cystathionine synthetase activity.

Proline.

It is an unessential, glucoplastic amino-acid. The proline synthesis has as precursor the glutamic acid.



Glutamate semialdehyde



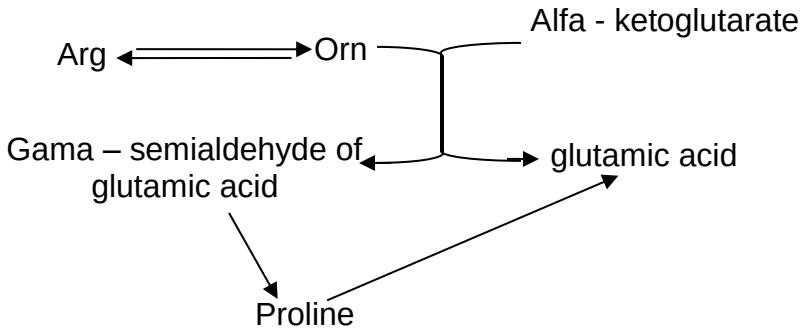
Δ^1-pyrolidin-5-carboxylate

Proline

Proline can be hydroxilated, resulting 3-, respectively 4–hydroxiproline. The catabolism of proline uses the same reactions from the synthesis process, but reversely, except that the enzymes catalyzing the reactions are different. The end product of catabolization is the glutamic acid. In the body, the proline and its hydroxilated derivatives are the main components of the collagen proteins.

Arginine.

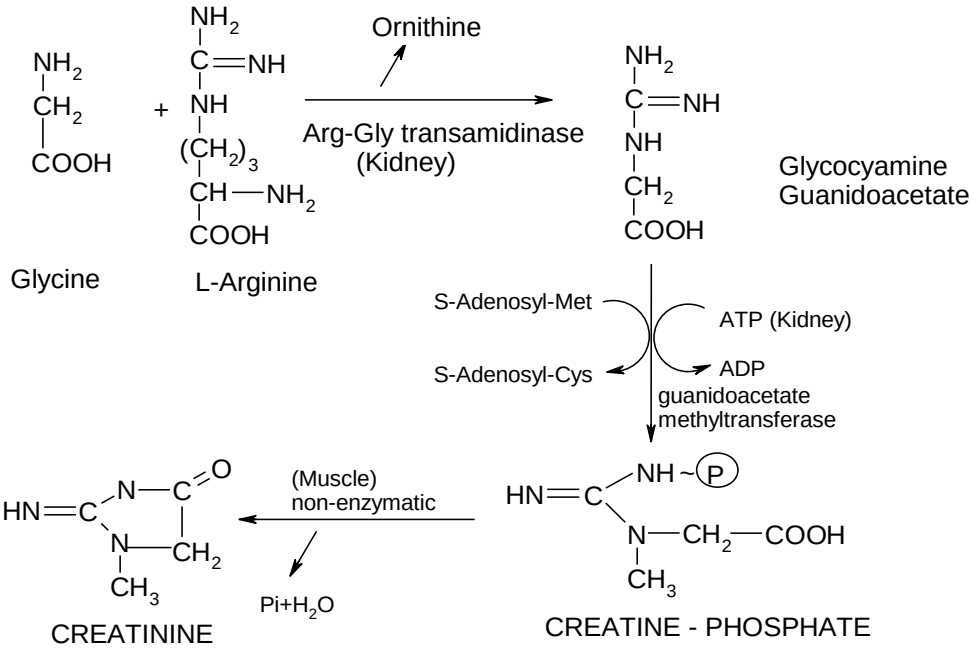
Arginine is a glucoplastic amino-acid, semi-essential, its food contribution being only necessary during the growing period. The arginine synthesis is made within the kidneys, where there are the enzymes of the ureo-genetic cycle, except for arginase. Citrulline can be regarded as the precursor of the synthesis, coming first of all from the intestinal mucosa. The catabolism occurs by means of ornithine.



Arginine is an intermediary of the ureo-genetic cycle and a precursor within the synthesis of proline, ornithine or glutamic acid. An important role is that of precursor of the nitrogen oxide synthesis, the main molecule involved in transmission of the vasodilatation signals.

$$\text{L – arginine} + \text{NADPH,H}^+ \xrightarrow{\text{NO-synthetase}} \text{L – citrulline} + \text{NO} + \text{NADP}^+$$

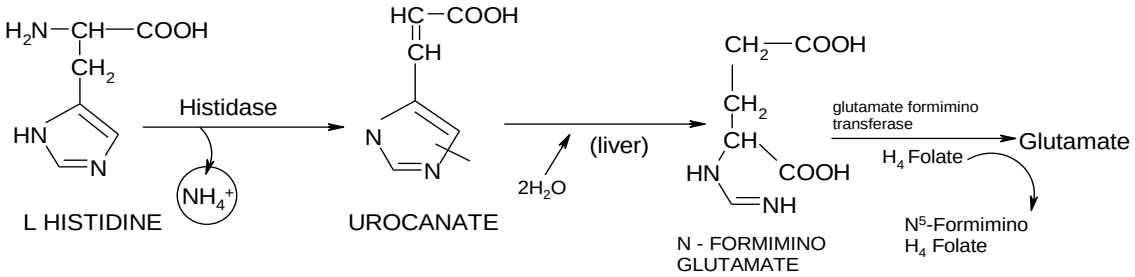
A very important part is related to creatine synthesis. Creatine, under the form of the macroergic compound creatine-phosphate, is the energetic reserve of the muscle. The creatinine resulting from the creatine catabolization, is a form of eliminating the nitrogen resulting during the amino-acids catabolization. Creatine is obtained in the muscle by transfering a guanidino- group from an arginine molecule to a glycine one, while the compound made will be subject to methylation.



Creatin-phosphate is a macroergic phosphate, with energy releasing role for the muscle tissue. The hydrolysis of the phosphate residue will produce, besides releasing the energy, a cyclization reaction forming creatinine. This can cross the muscle cell membrane, go into the plasma and be eliminated through the kidney. The creatinine quantity will depend on the muscle mass, daily 1 – 2 % of this turns into creatinine. The plasma creatinine concentration, 0,7 – 1,4 mg%, is very stable, as it depends only on the muscle mass. Because of this, it is used as an indicator of the renal function (renal clearance).

Histidine

It is a glucoplastic amino-acid, semi-essential. The catabolism of histidine will comprise the following stages:



Although the catabolism of His is an irreversible pathway, it has been found out that the body can go on for weeks with a His free diet, without any deficiency signs. This is due to the existence, within the muscles, of a special dipeptide, called carnosine (beta–alanyl–Histidine). This plays within the muscles a buffer role during contraction, when great quantities of lactic acid are released. Carnosine has a food origin or is made from

His and β-Ala with ATP consumption. Another compound is formed from carnosine by N-methylation, anserine. Both of them activate myosin ATP-ase.

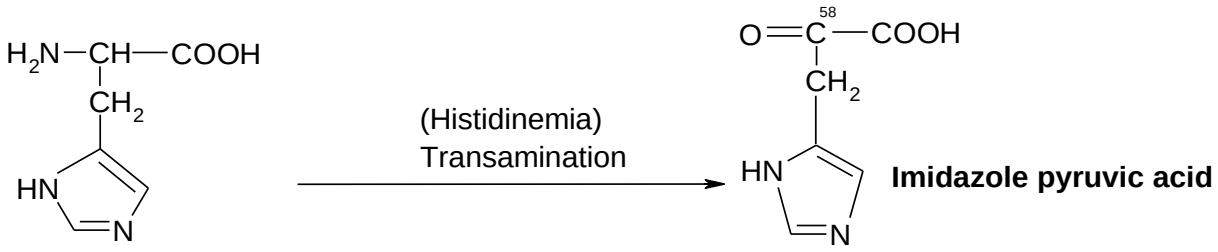
Synthesis of His needs 5-phosphoribosyl-1-pyrophosphate (PRPP) and ATP, leading to some common reactions with those of pyrimidine nucleotides synthesis.

Within the body, histidine plays several roles:

- The main binding element between proteins and metals, for instance the binding hem–Fe^{2+} - globin is accomplished by means of two histidine residues from the globin structure.
- Obtaining monocarbon groups
- Synthesis of carnosine and anserine
- Synthesis of histamine
- The $FolH_4$ deficiency test is made by loading histidine, when, in case of folic acid deficiency appears within urine as N-formiminoglutamic acid.

Pathology

The main disease related to histidine metabolism is histidinemia. It is a congenital disease (1:10 000) due to the histidase defect. Under the circumstances of disrupting the normal way of catabolization, a non-pHisiologic way is activated, producing imidazole-pyruvic acid coupled with an accumulation of histidine into blood and urine. The consequences of the disease: mental retardation, slurred speech.

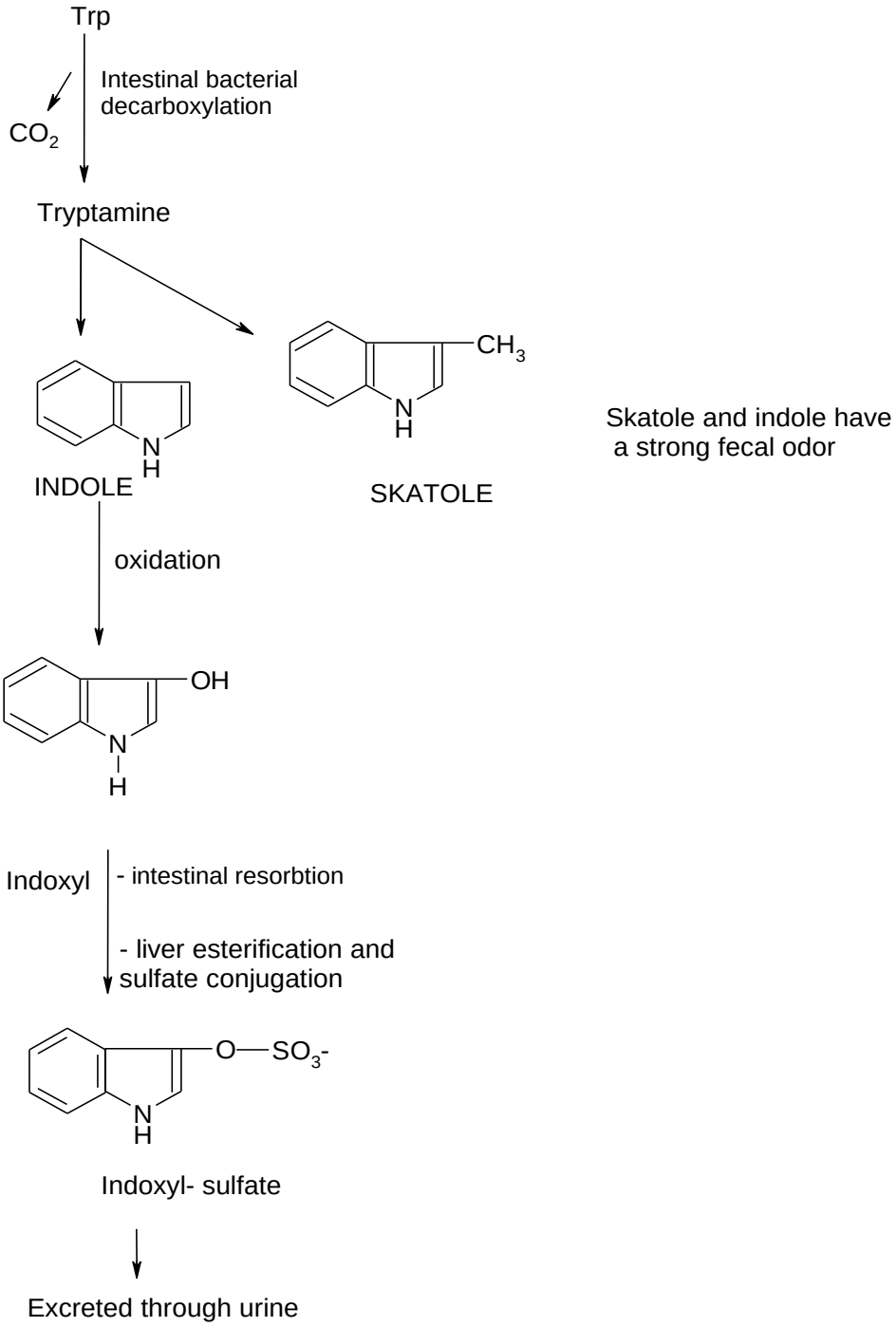


Tryptophan.

Tryptophan is an essential, mixed amino-acid**.** It undergoes several ways of metabolization, the main one leading to alanine (glucoplastic) and acetoacetate (ketoplastic).

Tryptophan is a precursor of the synthesis of alanine, serotonine, triptamine, melatonin. Tryptophan is also a precursor of the NAD^+ synthesis, being considered as a PP provitamin. For an adult, it is considered that the NAD^+ synthesis based on tryptophan provides all body needs and for this reason, nicotinamide would no longer meet the vitamin criteria.

Food rich in tryptophan causes sleep as the serotonine has this effect. Food rich in proteins inhibits sleep since the competition between amino-acids inhibits tryptophan turning into serotonine. Food rich in carbohydrates induces sleep because releasing insulin into the blood induces the storing of amino-acids which no longer compete with tryptophan.



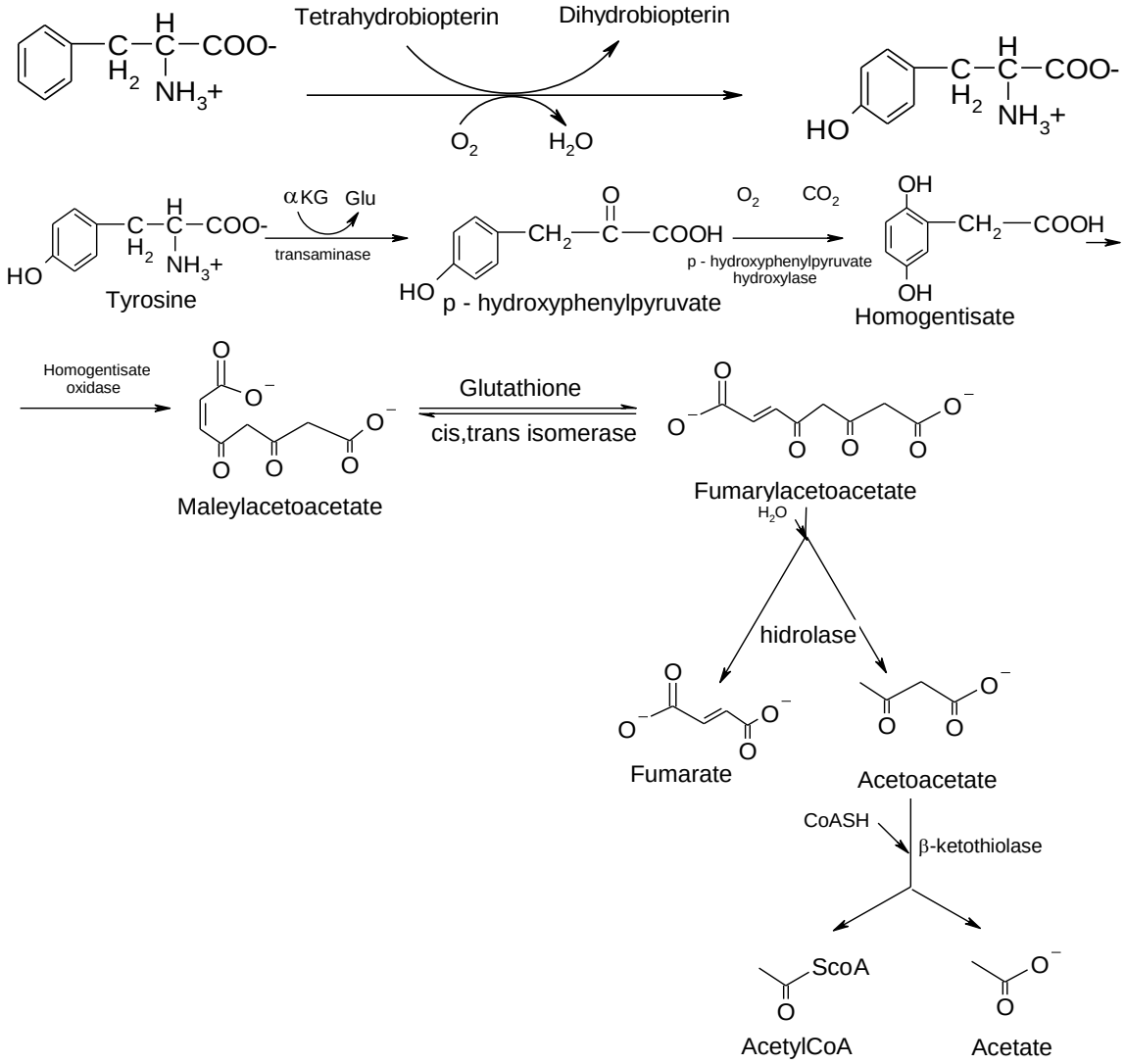
Pathology

1) Deficiency of B_6 vitamin – affects the activity of the *kynureninase* enzyme, with an outcome of urine elimination of *kynurenine* and *xanthurenic acid* (non-pHisiologic derivatives of kinurenine). Urine gets colored into a characteristic yellow-greenish color. This is also a symptom of being diagnosed with B_6 vitamin deficiency.

2) HARTNUP disease – is caused by a deficiency within the intestine absorption and the renal reabsorption of tryptophan. It will increase considerably the level of the urinary indican. Another negative effect is a decrease of NAD^+ production, with symptoms such as pelagra.

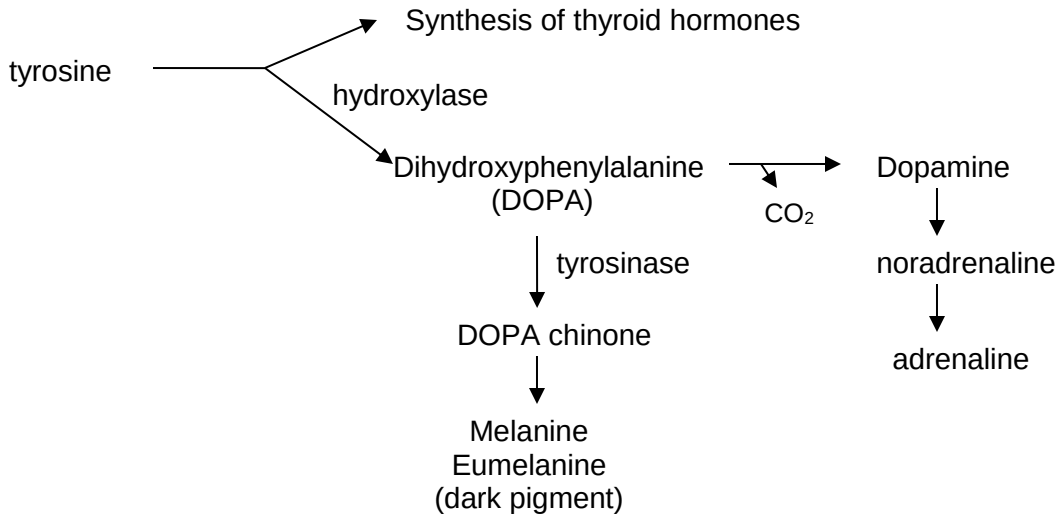
Phenylalanine and tyrosine.

Phenylalanine is an essential mixed amino-acid. Tyrosine is a non-essential mixed amino-acid, but whose synthesis depends completely on phenylalanine. In case of phenylalanine deficiency, tyrosine becomes an essential amino-acid.



Catabolism of phenylalanine and tyrosine

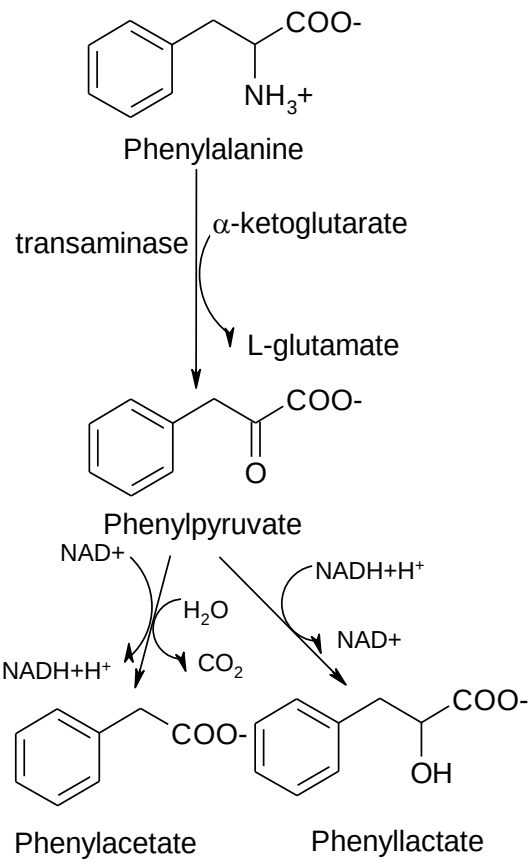
Tyrosine is the precursor of very important compounds, as thyroid hormones, catecholamines (adrenaline), pigments (melanine, eumelanine).



Pathology

The pathology of Phe and Tyr metabolism is the most important pathology related to the amino-acids metabolism, both due to the incidence (1: 5000) as well as due to the great number of enzymes affected.

1) Phenylketonuria – is the most important congenial defect within the amino-acids metabolism, with an incidence of 1/10000 for homozygotes and 1/50 for heterozygotes. The disease is due to the deficiency of the enzyme called *phenylalanine hydroxylase.* As a result of this enzymatic deficiency, great quantities of phenylalanine (50-100 mg %) will be accumulated, and a part of this will be catabolized abnormally to phenylpyruvic acid (ketoacid).



The excess of phenylalanine and phenylpyruvic acid from the blood will seriously harm the central nervous system (CNS) by blocking the synthesis of myelin within myelocytes and the synthesis of serotonine from tryptophan, which leads to a serious form of mental retardation called *phenylpyruvic idiocy.* In addition, the deficiency of tyrosine causes a depigmentation at the eyes and skin level. The presence of the phenylpyruvic acid will be determined by developing a greenish color of the urine of a newborn in contact with $FeCl_3$.

If the defect is identified within the first 2 weeks after birth, it can be treated by a diet poor in phenylalanine for 6 years, after which the body is able to get over this genetic flaw.

About 3% of the cases are due to the defect of *biopterine*. This is a more serious disorder as biopterine is also involved in the synthesis of catecholamines and of serotonine. The treatment is represented by the diet intake of biopterine.

2) Alkaptonuria (alkapton = the old name of the homogentisic acid) – it is a disease mentioned in the 16th century and described in 1859 by Garrod as an inherited metabolic disease. The disease is due to the deficiency of the enzyme *homogentisate oxygenase.* Under these circumstances, the catabolism of tyrosine will stop at the homogentisic acid, and this is accumulated into the blood and is massively eliminated through urine. Although the homogentisic acid is colorless, in contact with air it will be oxidized at quinone, which polymerizes, forming a dark pigment (black). Thus, the disease is easily diagnosed by the urine which becomes black in contact with air.

Within the body, in time, the pigment from the homogentisic acid will be deposited at the level of bones and articulations; a process named *ochronosis* (tissues darkening and necrosis) and the subject will also develop a form of arthritis.

3) Albinism – this term comprises a wide range of clinical syndromes characterized by hypomelanosis, due to the generic defects within the melanocytes from eyes and skin. The cause is represented by the absence of *tyrosinase*. At the skin level, there is sensitivity to sun with an increased risk for skin cancer, while at the eyes level there is photophobia.

4) Tyrosinemias – are affections due to the genetic defect of the enzymes involved in the tyrosine catabolism. The outcome is the accumulation of tyrosine in the blood with negative effects on the CNS.

• type I – is produced by the deficiency of *fumaryl-acetoacetate hydrolase*, which leads to the accumulation of fumaryl-acetoacetate and maleyl-acetoacetate. These are alkylation agents alkylating the DNA, with a role in carcinogenesis. There are also renal disorders, hepatic blockage and polyneuropathy.

• type II – is due to the deficiency of tyrosine *transaminases*, leading to the blood increase of tyrosine and causing mental retardation and eyes injuries.

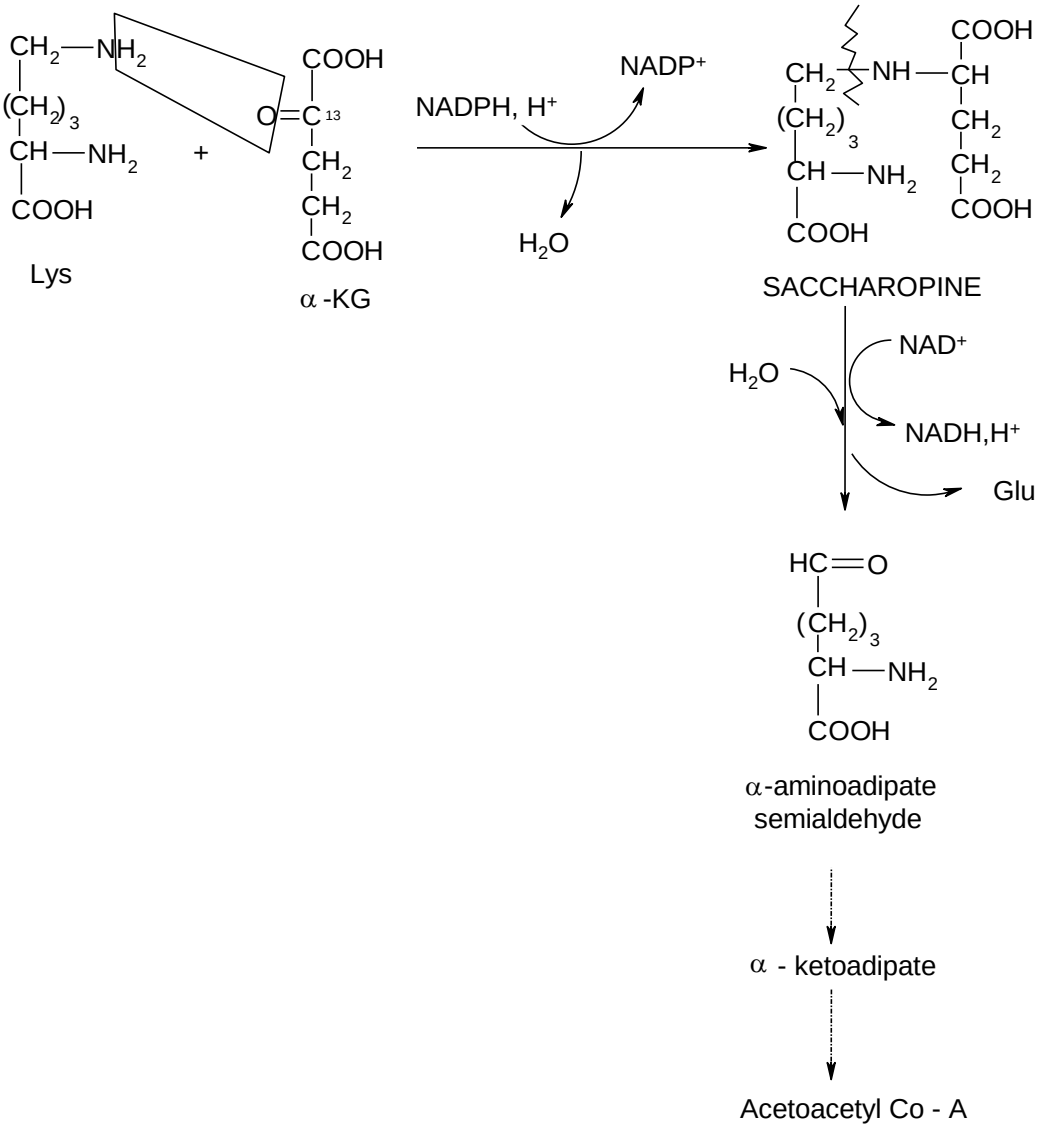
• type III – *tyrosinemia of the newborn* – is due to a flaw of *oxygenase* of the homogentisic acid.

Lysine.

Lysine is an essential ketoplastic amino-acid, synthesized by microorganisms. Lysine does not take part in transamination; still experiments with the radioactively marked lysine have proved the catabolism by transamination at the ε-NH_2 group.

Lysine is a basic amino-acid involved in determining the bindings between proteins and metals, proteins with nucleic acids, proteins and ubiquitine.

Lysine has a role in the synthesis of carnitine (a role in transporting the fatty acids into mitochondria).



Lysine catabolism

Pathology

Two metabolic disorders of lysine are known:

1) Hyperlysinemia – due to the deficiency of *saccharopine dehydrogenase*, as a result of which lysine and saccharopine are accumulated into the blood. This affection is benign.

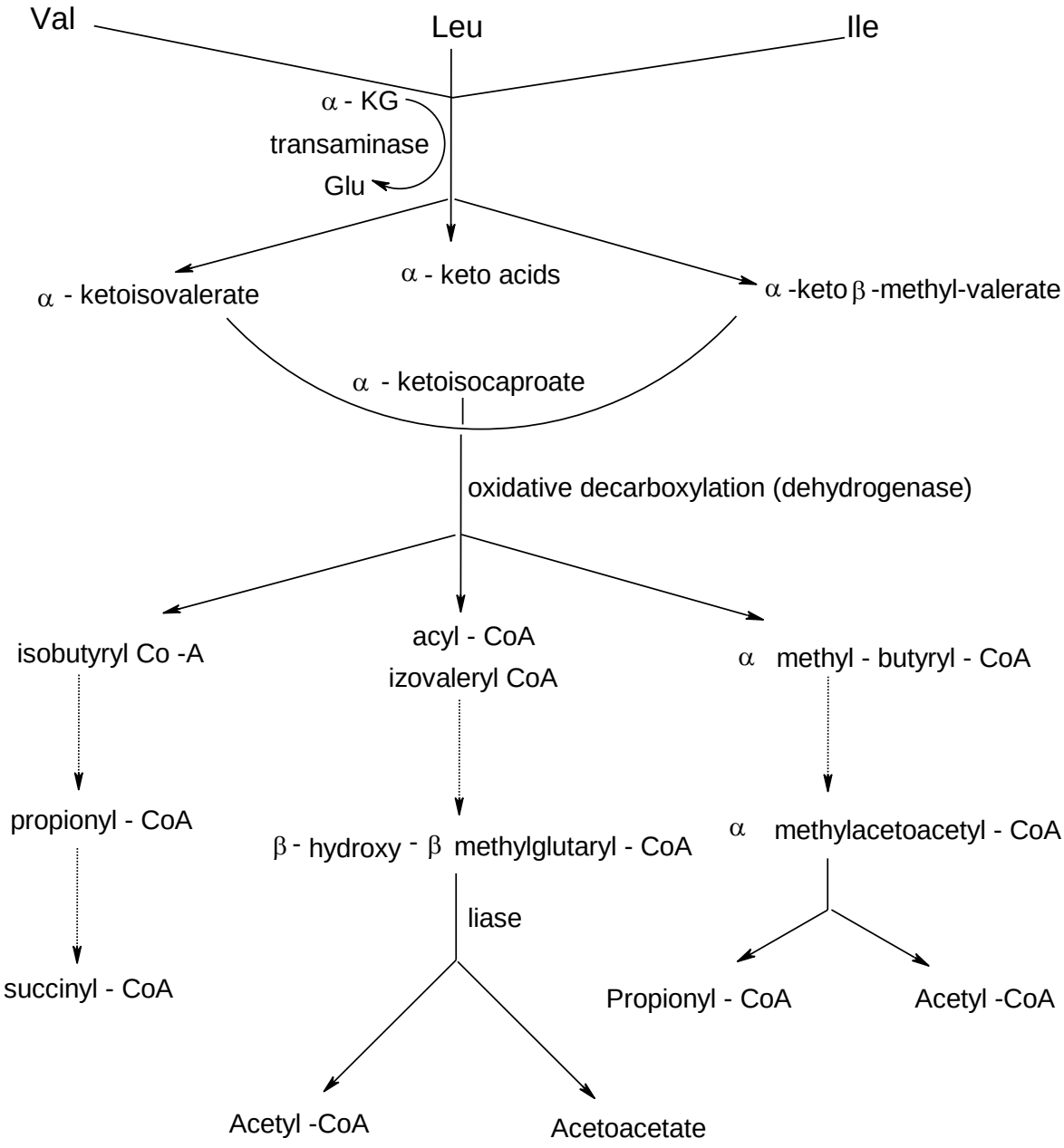
2) Lysinuria – due to the deficiency of transport of lysine at the level of the intestine mucosa and at the renal level. The plasma level of lysine, arginine, ornithine decreases to 1/3; hyperammonemia develops, hair thinning occurs, reduction of the muscular tissue, osteoporosis, all these reflecting the deficiency of Liz and Arg. Hyperammonemia is treated with citrulline.

Valine, leucine and isoleucine.

Valine, leucine and isoleucine are essential amino-acids, and from a gluco- and ketoplastic point of view: valine – glucoplastic, leucine – cytoplastic, isoleucine – mixed.

Pathology

The main genetic disease related to the metabolism of the branched chain amino-acids is called *maple syrup urine disease (branched-chain ketonuria)*, produced by the genetic deficiency of *dehydrogenases* of ketoacids resulted from branched chain amino-acids. The outcome of the disease is the accumulation of ketoacids and of amino-acids into the blood as well as their massive elimination by urine (ketonuria). Urine has a specific malt or maple syrup smell. The disease causes mental retardation, neurological disorders and, under extreme circumstances, the death in the first year of life.



Valine, leucine and isoleucine catabolism

IV.7. Hemoglobin metabolism

Hemoglobin is the protein responsible for transporting the oxygen into the body, having a key function for maintaining life.

Hemoglobin is a heteroprotein made up of a protein part – globin and a non-protein part – the heme (prosthetic group). The globin metabolism will follow the general pathways of proteins metabolism; however, the heme metabolism is a particular one.

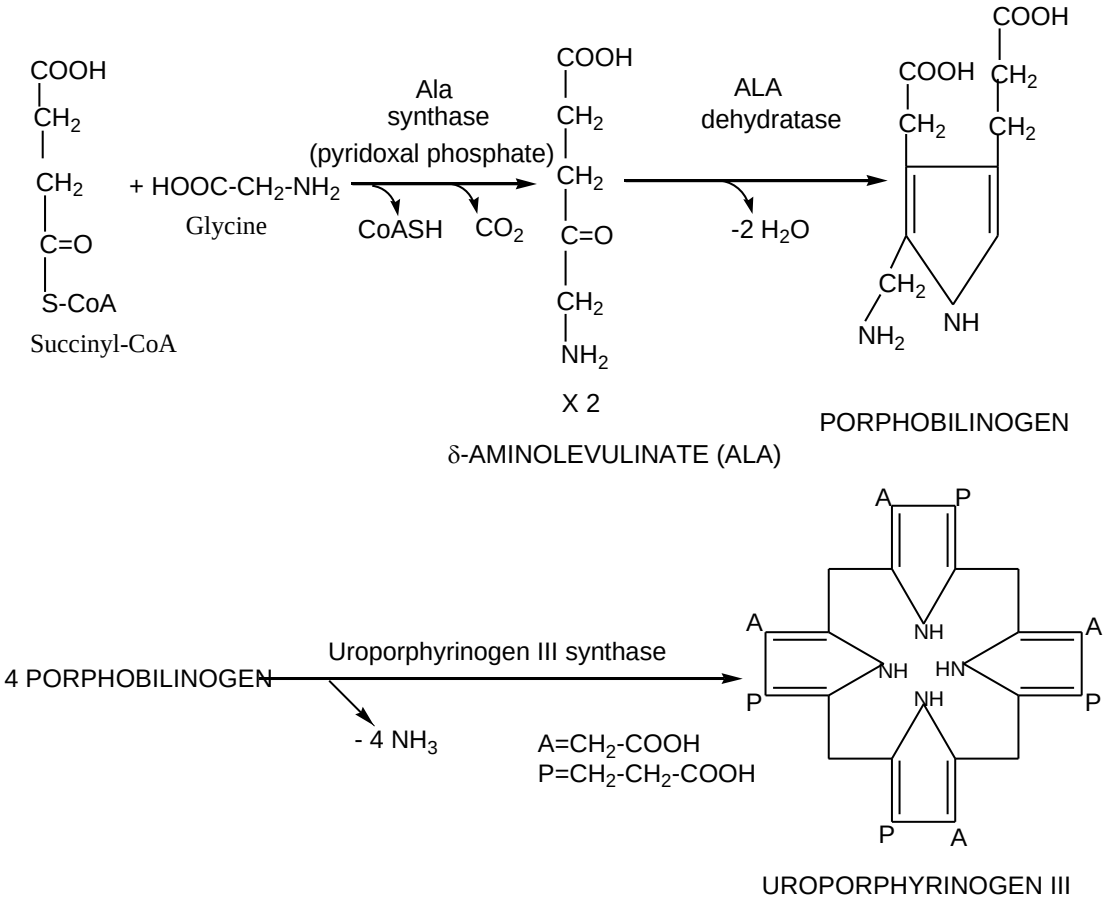
IV.7.1. Heme metabolism

Most of the heme from the body is found within hemoglobin, the 800-900g Hb from the adult body containing 30-35g heme. The rest is found within myoglobin, cytochromes and mehe enzymes (catalase, peroxidase).

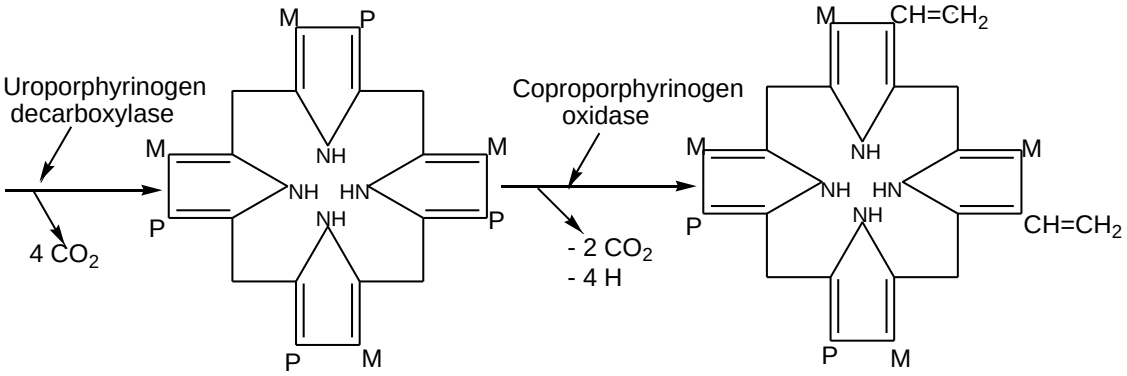
IV.7.1.1. Heme synthesis

Although heme is theoretically produced within all cells, most of the synthesis occurs at the level of the bone marrow (70% or 250-300 mg/day), within erythroblasts and proerythroblasts, and secondly within the liver (15% of the total), which produces great quantities of cytP450, catalase and cytochrome b_5.

Heme synthesis takes place within mytochondria (the first and the last 2 reactions) and within cytoplasm. The precursors of the synthesis are **succinyl-CoA** (mostly found within mytochondria) and **glycine**.

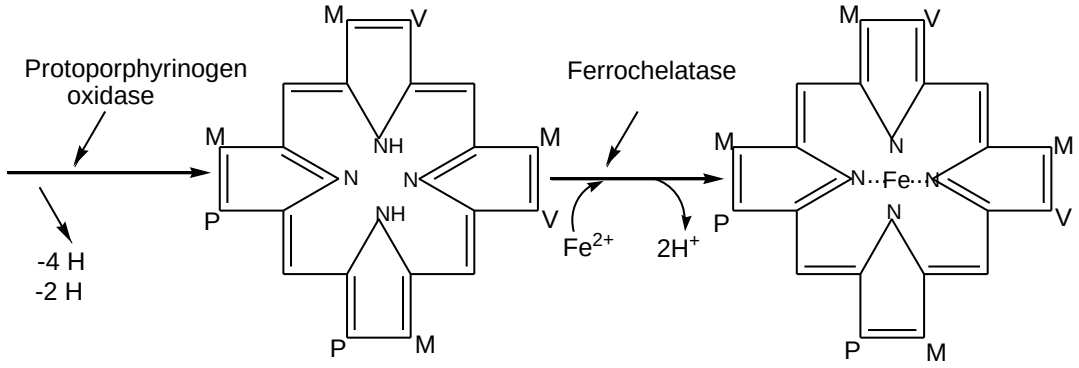


Theoretically, the substituents A and P can form 4 isomers I – IV, from which the enzyme isomerase acts only upon type III; the rest of them result in the case of defective enzymes, and are not functional.



COPROPORPHYRINOGEN III

PROTOPORPHYRINOGEN III



PROTOPORPHYRIN III

HEME

Although there are 15 possible isomers of protoporphyrin, only one, isomer 9 is physiological.

Regulation of heme synthesis

1. Substrate regulation – synthesis depends on the availability of succinyl–CoA (related to the Krebs cycle) and on Fe^{2+}. The Fe^{2+} deficiency causes ferriprive (iron-deficiency) anaemia.

2. Enzymatic regulation. The rhythm enzyme is the one catalyzing the first reaction, **δ-aminolevulinate synthase**. The enzyme is inhibited by the end product, the heme, by an allosteric mechanism and by the correpresion of the enzyme synthesis. The enzyme is inhibited by hematin and glucose. A series of drugs and metabolites induce the enzyme synthesis, for instance barbiturates and, especially 3,5–dicarbethoxy–1,4–dihydrocolidine (increases the enzyme level of over 40 times). The outcome of these pharmacological agents must be considered in case the patient has porphyria.

3. Influence of the oxygen pressure – decrease of pressure, for instance at high altitudes, intensifies the heme synthesis and induces the increase of the red blood cells number. In vitro experiments at high oxygen pressures have shown that the synthesis of several enzymes involved in the heme synthesis is inhibited.

Pathology

Porphyrias are disorders of the heme metabolism, congenital or contracted, where the making of non-physiologic intermediaries of the heme synthesis occurs. For the heme synthesis, only protoporphyrin III (9) is accepted, and the porphyrines catabolization takes place only for the entire system heme + Fe + globin. In case of flaws, the non-physiologic porphyrinic compounds resulted cannot be catabolized, accumulating within the blood, and they are either deposited within tissues, or are eliminated through urine. The porphyrogen intermediaries are colorless, but photo sensitive, so that, deposited at the level of the tissues, they will produce their necrosis upon exposure to light. The porphyrinic compounds are colored and are not photo sensitive.

Forming these non-physiological derivatives decreases the heme concentration, which activates δ-aminolevulinic synthase, the outcome being the progressive increase of the non-physiologic compounds concentration.

Disease	Affected tissue	Defect enzyme	Pathology
1. Congenital erithropoietic uroporphyria	Liver	Cosynthetase III(-)	- tissue necrosis - 0,6 g/day urinary elimination uroporphyrinogen I lethal in the first year of life
2. Variegate porphyria	Liver	ALA synthetasa (+) Protoporphyrinogen oxydase (-)	- affects the nervous system - skin (necroses)
3. Congenital protoporphyria	Bone marrow	Ferrochelatase (-)	- concretion - hephatic disease - skin disease
4. Acute intermittent porphyria (alcoholism)	Liver	ALA synthetasa (+) Porphobilinogen deaminase (-)	- red urine - affecting the nervous system

Treatment of porphyrias

- eliminating alcohol and anesthetics inducing the synthesis of cytP450, a substance activating the heme synthesis;
- food rich in carbohydrates, glucose;
- hematin administration;
- protection against sun rays (protection screens, β-carotene administration).

Since some symptoms are neurological, the patient is often treated for a neuropsychiatric disease (sedatives, hypnotic, anticonvulsive), which will worsen the porphyria by an increase of $cytP_{450}$ inducing the increase of the heme synthesis. In some cases, the treatment can be lethal.

IV.7.1.2. Heme catabolism

The catabolism takes place only for the integral system of heme + globin, other porphyrine derivatives without Fe being impossible to catabolize, being eliminated through urine. The catabolized heme mainly comes from the old red blood cells (120 days), about 85% of the total, and the rest of 15% from other heme proteins, mainly cytochromes, as well as from myoglobin, enzymes (catalase, peroxidase), etc.

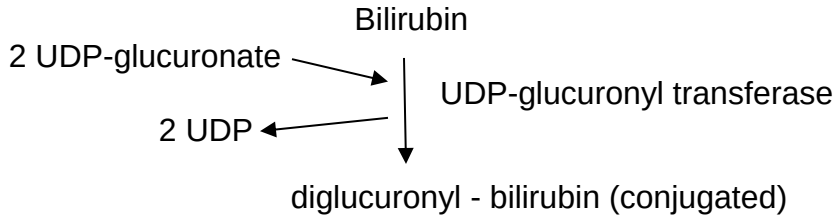
The first stages of catabolism take place within the cells of the reticuloendothelial system (portal vein, lymphatic ganglions, hematopoietic bone marrow and liver). About 1-2 x 10^8 erythrocytes/hour are destroyed, corresponding to 6,5 g hemoglobin degraded daily, hemoglobin which contains 0,4 g heme.

The first stage takes place within microsomes under the action of heme oxygenase which needs $3O_2$ and NADPH, H^+. The enzyme will break the porphyrin cycle at the level of α-methin bridge between the cycles that have vinyl as substituent. The carbon of the broken bridge will be eliminated under the form of **CO**, this being **the only source of CO** from the body. Part of the CO will be eliminated by breathing, being a measure of the degraded heme quantity.

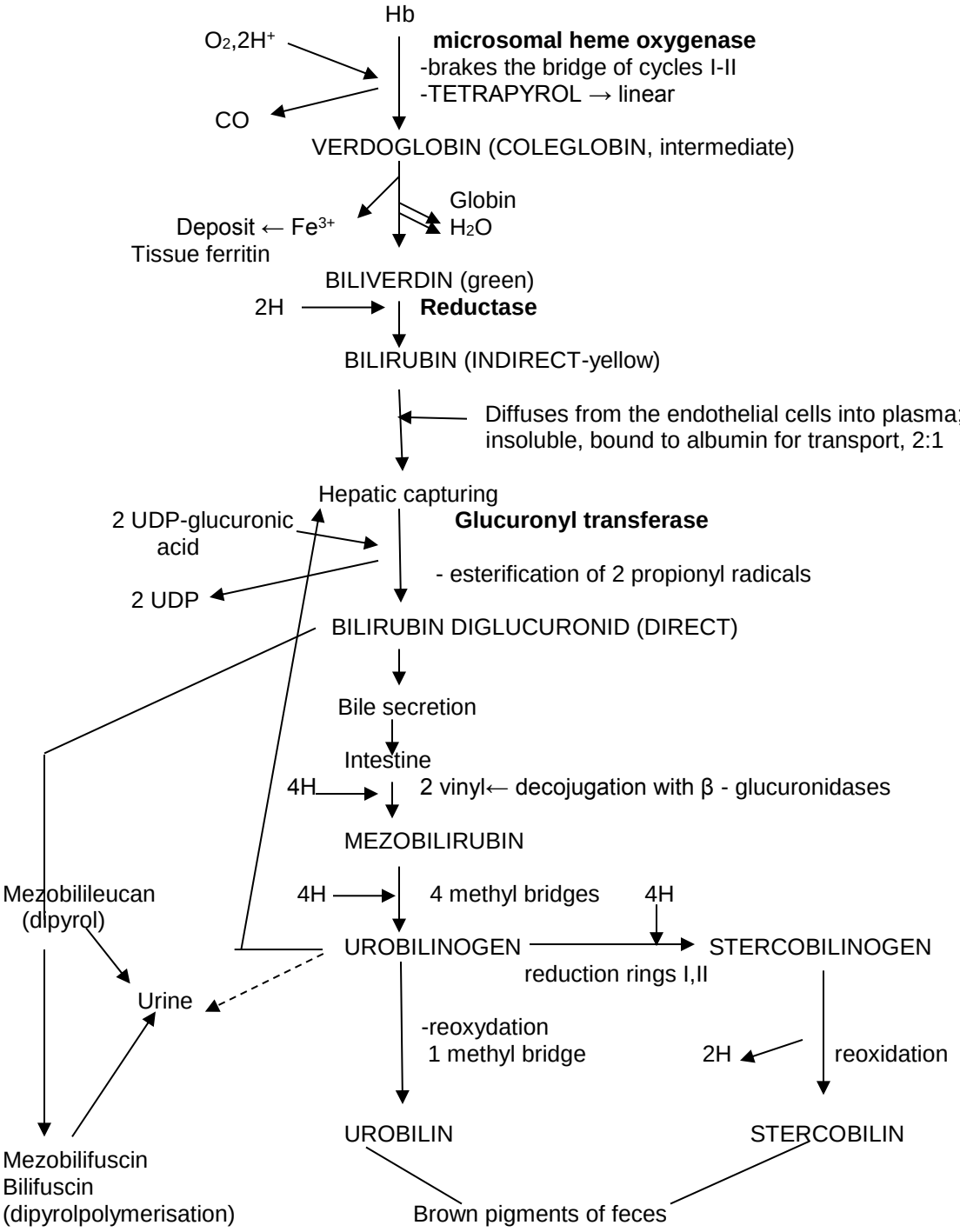
The end product of the catabolism is bilirubin.

Bilirubin difuses from the endothelial cells into the plasma. Being insoluble, it will attach to the serum albumin in a relation of 10^6 molecules/mol albumin. At a normal concentration of 4 g% serum albumin, about 70 mg/dL bilirubin can be linked. It has nevertheless been found out in certain diseases (kernicterus) that over a concentration of 25 mg/dL, bilirubin difuses freely, not being attached to albumin anymore. This type of bilirubin is called: prehepatic, insoluble, unconjugated or indirect.

At the hepatic level, the bilirubin-albumin complex is captured, bilirubin dissociates from albumin and enters passively into hepatocytes, where it is linked in 1:1 ratio to **ligandin (glutathione-S-transferase A),** a hepatic cytoplasmic protein (6% of the total of cytoplasmic proteins), and to FABP (fatty acid-binding protein), the binding to the cytoplasmic proteins removing the toxic effect of bilirubin. Within the liver, the propyonil radicals from the bilirubin molecule are estherified with glucuronic acid resulting the bilirubin diglucuronide.



The conjugated bilirubin is much more soluble, being named: soluble, post hepatic, conjugated or direct bilirubin. This favors its elimination through the bile into the intestine. Here, at the level of the terminal ileum, it is deconjugated, and the free bilirubin is reduced to a colorless tetrapyrrole derivative, called urobilinogen. This is reoxidated into colored products called urobilin and stercobilin, representing the brown pigments of the feces.



Hemoglobin catabolism

A part of urobilinogen (about 20%) is reabsorbed by the intestine mucosa into the blood, gets to the liver, where it is turned into bilirubin, which will be secreted freely. The conversion is not complete, a small part of urobilinogen, about 1% is eliminated through urine. The normal concentration of bilirubin within the plasma is between 0,3 - 1 mg%, of

which 0,2 - 0,7 mg% unconjugated bilirubin, and 0,1 - 0,3 mg% conjugated bilirubin. Daily, about 250 – 400 mg bilirubin is produced in the case of adults.

Unconjugated bilirubin being strongly linked to albumin or lipids cannot be eliminated through urine, unlike the conjugated one which can be eliminated, making urine (when eliminated in high concentrations) an intense yellow-brownish color.

Unconjugated bilirubin has great affinity for the membrane lipids, blocking the functioning of the cellular membranes, especially at the level of the nervous system.

IV.7.1.3. Pathology of the heme metabolism

For values of the bilirubin within blood which exceed 1 mg%, there is hyperbilirubinemia. Over 2 - 2,5 mg%, bilirubin diffuses within tissues which it colors characteristically (jaundice or “icterus“). According to the type of excessive bilirubin, unconjugated or conjugated, the color of skin and sclera varies from yellow to yellow-greenish.

Increased bilirubin concentration within the plasma can have various causes, each generating a specific pathology:

1. Physiologic jaundice of the newborn – as a result of immaturity of the bilirubin metabolism system at a hepatic level, and of lack of intestinal flora of the newborn, the unconjugated bilirubin from the intestine is either eliminated as such (meconium), or reabsorbed, passing into blood. As a result, 50% of the newborn babies have jaundice within the first few days:

- 1st day: 1 - 2 mg %
- 2nd day: 5 - 10 mg %
- the following weeks: 1 mg %

For about 10% of the newborn, the bilirubin level reaches values of 15-20 mg%, making possible the development of the malady **kernicterus** (nuclear jaundice). Thus, the excess of unconjugated bilirubin from the plasma exceeds the albumin binding capacity, crosses the blood-brain barrier and is deposited at the level of the basal substance, producing progressively hypotony, atony and death or permanent neurologic disorders. Treatment should be instituted fast and consists in:

- Phototherapy – the bilirubin from the skin is converted into more soluble isomers, eliminated through urine.
- Phenobarbital – inductor of diglucuronyl transferase.
- Binding agents (agar) attaching to the intestinal bilirubin, blocking its reabsorption and eliminating it with the feces.

2. Mechanical jaundice (due to the obstruction of the bile duct) – under the circumstances of bile duct obstruction, the conjugated, hepatic bilirubin passes into blood and is eliminated through urine.

3. Congenital jaundice – is due to affecting the hepatic processes of transforming unconjugated bilirubin into conjugated bilirubin, for instance the deficiency of UDP-glucuronyl transferase from the Crigler–Najar syndrome and from the Gilbert syndrome.

4. Hemolytic jaundice – is associated to the hemolytic diseases, where there is a hemoglobin excess which must be catabolized, generating the increase of all hemoglobin catabolism products.

5. Hepatitis – an inflammatory process of the hepatic tissue where the cellular destruction increases both the level of the conjugated bilirubin as well as of the unconjugated one.

For diagnosing the type of jaundice, the following will be investigated:
- the plasma level of the conjugated and the unconjugated bilirubin;
- the urinary urobilinogen level;
- the color of urine and feces.