Heme

This article has been translated from WikiSkripta; ready for the **editor's review**.

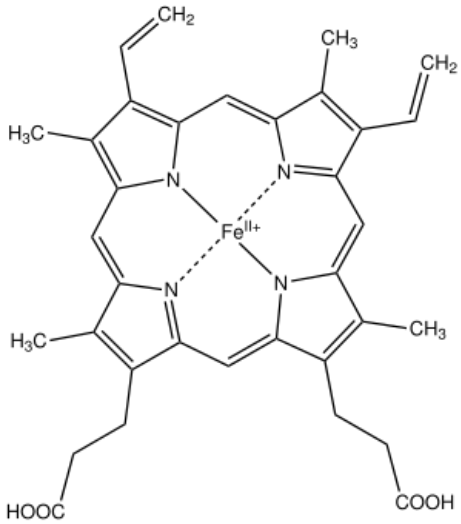
Heme is a prosthetic group of hemoproteins, which is formed by a tetrapyrrole core, in the middle of which the central Fe2+ atom is bound.

Hemoproteins

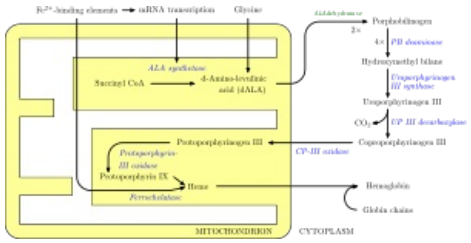
Hemoproteins are chemical structures that ensure many aerobic functions in the body. Through them, oxygen is not only transported, but also stored (hemoglobin, myoglobin). In addition, hemoproteins participate in the transport of electrons for the generation of energy in the respiratory chain, they are used for the synthesis and degradation of building or storage elements (steroids, lipids) and for the detoxification of xenobiotics. Their are also important for their role in controlling oxidative damage.

Heme biosynthesis

Heme biosynthesis takes place in all cells of the human body. It is most pronounced in erythroid cells of the bone marrow (70-80%)[1] and cells of the liver (15%)[1]. Heme in erythrocyte precursors becomes part of the transport protein - hemoglobin. In the liver, it is incorporated into enzymes from the cytochrome P450 family, and in the cells of other tissues it is part of working enzymes (catalase, peroxidase, etc.). The actual biosynthetic pathway is catalyzed by eight enzymes located in mitochondria and cytosol. Enzymes are produced firstly as "housekeeping"(operational) variants, present in cells of all tissues, secondly as specific variants within erythroid cells. The formation of different isoforms of enzymes is determined by the different localization of genes on chromosomes in the human genome, or by different expression of the same gene.



Heme structure



Heme biosynthesis

1. Synthesis of 5-aminolevulic acid (5-ALA)

5-Aminolevulinic acid is produced by the condensation of glycine with succinyl-CoA and subsequent decarboxylation of the intermediate of this reaction. The process is catalyzed by **5-ALA synthase** (ALAS) - an enzyme located in the matrix of mitochondria. Pyridoxal-5-phosphate participates as a cofactor in the reaction, which initially forms a Schiff base with glycine. ALAS exists in two isoforms. ALAS-1 is present in all cells, ALAS-2 is specific for erythroid cells. ALAS activity is sensitive to the presence of vitamin B6. This step is the most significant regulatory point of the entire synthesis.

2. Formation of porfobilinogen (PBG)

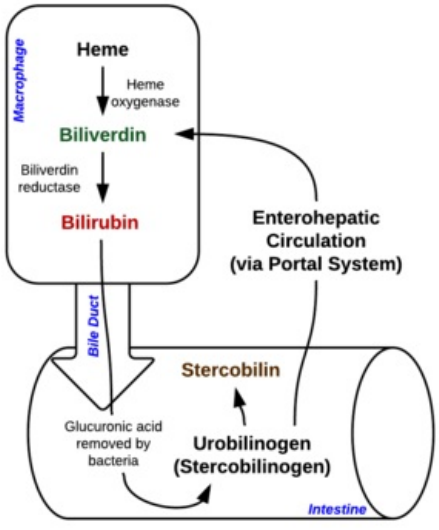
5-ALA passes into the cytosol after completion of its synthesis. Here, the condensation and simultaneous dehydration of 2 molecules of 5-ALA takes place to form porphobilinogen, which is the monopyrrole of the heme biosynthetic pathway. The reaction is catalyzed by **5-aminolevulate dehydratase** (ALAD) (porphobilinogen synthase). ALAD is an octameric -SH metalloenzyme containing eight Zn2+ molecules. The binding sites for Zn2+ are formed by -S- cysteine ligands and can be occupied by heavy metal cations, e.g. Pb2+, which leads to the inhibition of the entire reaction.

3. Formation of hydroxymethylbilane (HMB)

Hydroxymethylbilane is a linear tetrapyrrole whose synthesis is catalyzed by **HMB-synthase**. The essence of the reaction is the gradual condensation of four porphobilinogens (PBG) on the dipyrromethane group of the enzyme. Four ammonia molecules in total are released during the process

4. Formation of uroporphyrinogen III

Uroporphyrinogen-III-synthase (UROS) catalyzes the cyclization of HMB to uroporphyrinogen III. It is an octacarboxylate containing four acetate and four propion groups. It is a precursor for the formation of corins (cobalamin) and chlorins (chlorophyll).



Heme metabolism

5. Formation of coproporphyrinogen III

Coproporphyrinogen III is produced by the gradual decarboxylation of octacarboxylate (uroporphyrinogen III) to tetracarboxylate. The reaction is carried out by **uroporphyrinogen decarboxylase** (UROD). The essence is the conversion of four acetate residues of the side chains into methyl residues.

6. Formation of protoporphyrinogen IX

Coproporphyrinogen passes back into the mitochondria. Here, with the help of **coproporphyrinogen oxidase** (CPO), located in the intermembrane space, it is oxidatively decarboxylated to protoporphyrinogen IX. During the reaction the two propionates (at positions 2 and 4) are converted into vinyl groups.

7. Formation of protoporphyrin IX

Protoporphyrin IX is produced by splitting six H+ and six electrons using **protoporphyrinogen oxidase** (PPO) - an integral protein of the inner mitochondrial membrane. Its active site is oriented in the intermembrane space. Oxygen molecules participate in the reaction, to which hydrogen ions are transferred to form water. The methylene bridges of protoporphyrinogen IX are converted to methine bridges of protoporphyrin IX by this reaction. A **system of conjugated π-bonds** is formed, which is the cause of the coloring of porphyrin systems.

8. Formation of heme

Závěrečnou reakcí biosyntézy je vestavba Fe^{2+} do struktury protoporfyrinu IX. Průběh je katalyzován **ferrochelatasou** (hemsynthasou), jejímž kofaktorem jsou proteinové molekuly s [2Fe - 2S] klastrem. Reakce probíhá na vnitřní mitochondriální membráně, enzym je přivrácen do matrix mitochondrie.

The final reaction of biosynthesis is the incorporation of Fe2+ into the structure of protoporphyrin IX. The process is catalyzed by **ferrochelatase** (hemesynthase), the cofactor of which are protein molecules with a [2Fe - 2S] cluster. The reaction takes place on the inner mitochondrial membrane, the enzyme is turned to the mitochondrial matrix.

Links

Related articles

- Poruchy biosyntézy hemu - porfyrie (czech wikiskripta)
- Porphyria

Used literature

- MURRAY, Robert K – GRANNER, D. K – MAYES, P. A. *Harperova biochemie.* fourth czech edition. H&H, 1998. 872 pp. pp. 354-360. ISBN 80-7319-013-3.
- MATOUŠ, Bohuslav. *Základy lékařské chemie a biochemie.* first edition. Galén, 2010. 540 pp. ISBN 80-7319-013-3.
- KOOLMAN, Jan – RÖHM, Klaus-Heinrich – MAYES, P. A. *Barevný atlas biochemie.* first edition. Grada, 2012. ISBN 978-80-247-2977-0.

References

1. MATOUŠ, Bohuslav – ET AL.,. *Základy lékařské chemie a biochemie.* 1. edition. Galén, 2010. 540 pp. pp. 225. ISBN 978-80-7262-702-8.