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Review

Biosynthesis of heme in mammals

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Abstract

Most iron in mammalian systems is routed to mitochondria to serve as a substrate for ferrochelatase. Ferrochelatase inserts iron into protoporphyrin IX to form heme which is incorporated into hemoglobin and cytochromes, the dominant hemoproteins in mammals. Tissue-specific regulatory features characterize the heme biosynthetic pathway. In erythroid cells, regulation is mediated by erythroid-specific transcription factors and the availability of iron as Fe/S clusters. In non-erythroid cells the pathway is regulated by heme-mediated feedback inhibition. All of the enzymes in the heme biosynthetic pathway have been crystallized and the crystal structures have permitted detailed analyses of enzyme mechanisms. All of the genes encoding the heme biosynthetic enzymes have been cloned and mutations of these genes are responsible for a group of human disorders designated the porphyrias and for X-linked sideroblastic anemia. The biochemistry, structural biology and the mechanisms of tissue-specific regulation are presented in this review along with the key features of the porphyric disorders.

Keywords: Iron; Heme; Porphyrin; Porphyrias

1. Introduction

The total body iron content in adult humans is approximately 50 mg/kg in men and 40 mg/kg in women [1]. Almost all iron is incorporated into heme-containing proteins, particularly hemoglobin, myoglobin and cytochromes. The gender-based difference in body iron content is due to the smaller red cell, muscle and liver mass in women. The unique properties of heme, an iron molecule coordinated within a tetrapyrrole, allows heme to function both as an electron carrier and a catalyst for redox reactions. Heme is generated by the insertion of ferrous iron into the tetrapyrrole macrocycle of protoporphyrin IX, a reaction catalyzed by ferrochelatase, which resides in the mitochondrial matrix (Fig. 1). A highly conserved pathway involving both cytosolic and mitochondrial compartments is utilized to generate protoporphyrin IX but all of the heme biosynthetic genes are nuclear-encoded and translated in the cytoplasm.

Most heme synthesis takes place in developing red cells in the marrow but about 15% of the daily production takes place in the liver for the formation of heme-containing enzymes. The regulatory mechanisms controlling heme synthesis in these two organs differ. In the liver, heme biosynthetic enzymes are turned over rapidly, enabling the liver to respond to changing metabolic requirements. In erythroid progenitors, however, the pathway is regulated to permit a high steady-state level of heme synthesis and regulation is tied to the availability of iron. There are both "housekeeping" and erythroid genes for aminolevulinate synthase, the first and rate-limiting enzyme in the pathway and the next three genes have dual promoters allowing both erythroid-specific and non-erythroid regulation [2]. The remaining genes in the pathway have single promoters but nevertheless exhibit erythroid and non-erythroid expression differences. These differences will be discussed for each enzyme in the pathway.

Heme biosynthetic enzymes have been intensively studied in recent years. All of the genes involved have been cloned and the crystal structures of all of the enzymes have been determined. In this review we will dissect the complex heme biosynthetic pathway into four basic processes:

(1) Formation of the pyrrole.
(2) Assembly of the tetrapyrrole.
(3) Modification of the tetrapyrrole side chains.
(4) Oxidation of protoporphyrinogen IX to protoporphyrin IX and insertion of iron.

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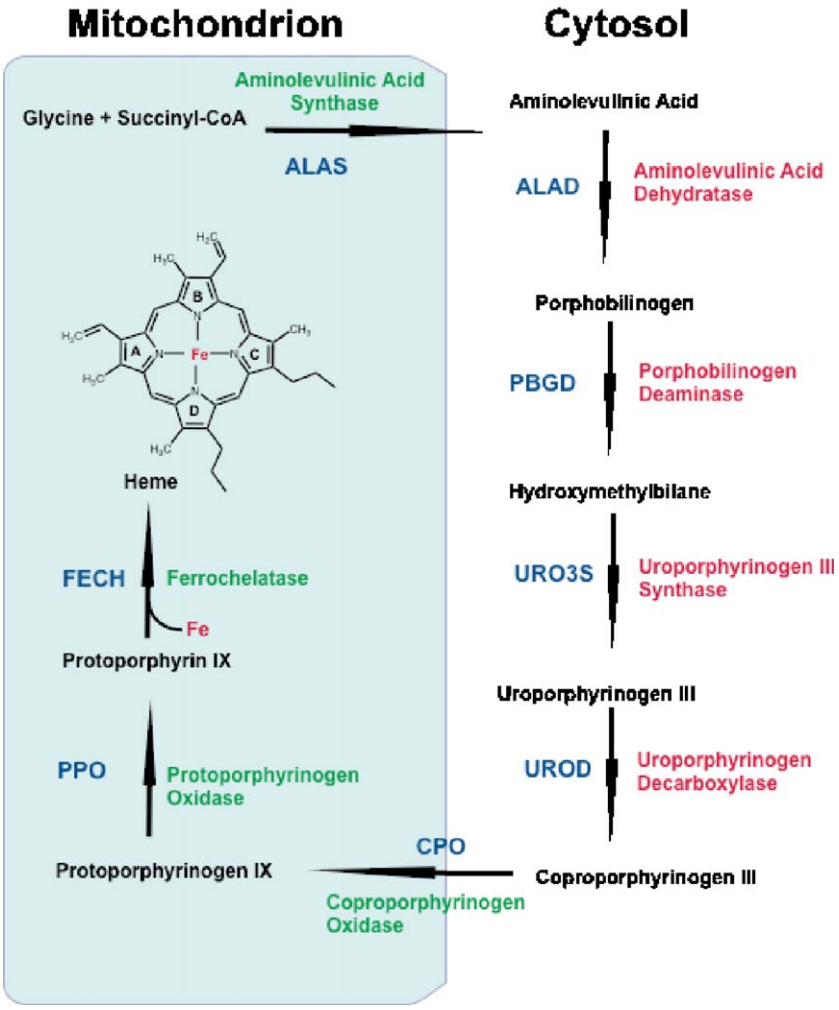

Fig. 1. The heme biosynthetic pathway. Mitochondrial enzymes are depicted in green and cytosolic enzymes in red. Abbreviations used in the text are capitalized.

Both inherited mutations and environmental factors may affect the pathway and lead to diseases including X-linked sideroblastic anemia, lead poisoning and the porphyrias. The porphyrias represent a group of disorders characterized by either acute neurovisceral attacks or photosensitivity and sometimes both. Accumulated substrates of defective pathway enzymes are responsible for disease symptoms. Compelling evidence has been generated indicating that neurovisceral symptoms are due to neurotoxic affects of porphyrin precursors. The photosensitivity is due to the fluorescent properties of porphyrins. A convenient way to classify the porphyrias is to divide them according to the dominant clinical feature (Table 1), although some authors prefer to divide the porphyrias based on whether excess substrate is generated in the liver (hepatic porphyrias) or the red cell (erythropoietic porphyrias). Here, each porphyric disorder will be described in the context of the step in the pathway which is defective.

1.1. Formation of the pyrrole

The first and rate-limiting reaction in the pathway is a condensation reaction between glycine and succinyl-CoA to form 5-aminolevulinic acid (ALA) (Fig. 2A). The reaction is catalyzed by two different ALA synthases, one expressed ubiquitously (ALAS1) and the other expressed only erythroid precursors (ALAS2). The gene encoding ALAS1 maps to the short arm of chromosome 3 [3] whereas ALAS2 is encoded on the X chromosome [4]. Regulation of these two forms of ALAS is mediated by different mechanisms but both forms require pyridoxal 5-phosphate (PLP) as a cofactor (Fig. 2B) and both are expressed as homodimers. PLP binds to a specific lysine of ALAS. A PLP-glycine Schiff base complex is then formed which reacts with succinyl-CoA. The crystal structure of ALAS from *Rhodobacter capsulatus*, which is highly homologous to

Table 1
Clinical features of the porphyrias

Photosensitivity only	Neurovisceral attacks and photosensitivity	Neurovisceral attacks only
Congenital erythropoietic porphyria	Hereditary coproporphyria	Acute intermittent porphyria
Porphyria cutanea tarda	Variegate porphyria	ALAD porphyria
Erythropoietic porphyria		