ejpmr, 2017,4(6), 213-221

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

STUDY OF HEME BIOSYNTHETIC PATHWAY, ITS REGULATION BY ENZYMES, DISORDERS AND DISEASES DUE TO HEREDITARY GENE ALTERCATIONS

Sikander Ali*, Maira Javed and Aniqa Zia

Institute of Industrial Biotechnology, GC University Lahore-54000, Pakistan.

***Corresponding Author: Sikander Ali**

Institute of Industrial Biotechnology, GC University Lahore-54000, Pakistan.

Article Received on 16/04/2017 **Article Revised on 07/05/2017** **Article Accepted on 28/05/2017**

ABSTRACT

Heme is synthesized naturally in almost all living organisms. There are various steps involved in the pathway of heme biosynthesis. Eight enzymes are involved in the making of heme. Liver and erythrocytes are two main sites for the heme synthesis as it forms cytochrome P450 that is important for the detoxification of xenobiotic compounds that are injected by individuals. Reticuloendothelial system at extracellular sites is involved in the removal and degradation of the old blood cells. Heme is released from hemoglobin and is degraded. Various factors are involved in regulating the expression of gene coding for the enzymes used in heme synthesis pathways. Heme oxygenase activity can be inhibited by other Porphyrins that contain certain metal ions other than iron (ferrous ion). Various disorders in heme biosynthesis can hinder the process; Porphyria is the main among them. Porphyria's are inherited and acquired disorders that are linked with the partially defective enzymatic activities of the heme biosynthesis pathway and increased level of precursors. Various types of Porphyria have been studied in this review. Here, a case report has also been included in which disease manifestation and symptoms have been illuminated. These attacks could be controlled by proper medication and hospitalization.

KEYWORDS: Heme, Metalloporphyrins, ALAS1, ALAS2, Feedback control, Protoporphyrin, Reticuloendothelial system, and AIP.

INTRODUCTION

Heme delegates hemoglobin the unique oxygen-binding ability. Heme in literal terms is the iron bound Porphyrin complex. Porphyrins are actually compounds made of four smaller pyrrole rings joined by four methane bridges. Thus due to association with metal atom they are also termed as metalloporphyrins. When globin protein is present along with it we term it as haemoglobin (Zhang, 2011). The distribution of heme is not uniform in the human body. In humans, 80% of the heme is formed and retained in RBCs; 15% is formed and kept in liver and remaining small portion goes to other tissues and body parts. Heme is also employed as a prosthetic group in many reactions.

Heme Biosynthesis

Living organisms, majority of them are able to synthesize heme naturally in their bodies. Organisms like *Caenorhabditis elegans*, who are unable to make it in their bodies acquire heme from external sources. The biosynthesis of heme involves eight enzymatic reactions that convert glycine and succinyl-CoA to heme (Zhang, 2011). All human cells need heme; for cellular respiration. The chief sites of formation of heme in human body are the liver, bone marrow and erythrocytes (Moore, 1990).

Steps of biosynthesis of heme

It should be known that at this stage eight steps are involved in the pathway. The first and last three steps of the biosynthesis of heme take place in mitochondria, and the intervening steps (i.e., four steps) take place in cytosol (Fig. 1). Essential precursors of reaction are conveniently found at this location (Ponka, 1999). Succinyl-CoA is produced by the Krebs cycle required for heme biosynthesis, and glycine is an amino acid that is already found in the cell. Since Krebs cycle occurs in mitochondria hence it proves to be an ideal location for heme making (Richard, 2006).

Enzymes

Typically formation of heme involves two groups of enzymes. They are erythroid-specific and housekeeping. Their specificity of function is clear from their names. The housekeeping enzyme (of first step of heme synthesis) is named ALAS1. Housekeeping enzymes are accountable for heme formation in about all body tissues other than for RBCs while Erythroid-specific enzymes are responsible for formation of heme only in the erythroid cells, which later form RBCs. Genes encoding ALAS1 and ALAS2 are present on the chromosomes no. 3 and X, respectively. (Kalle Möbius, 2010).

In humans, eight enzymatic reactions are involved for the biosynthesis of heme that eventually change succinyl-CoA and glycine to heme. In the **first step** a condensation reaction takes place between precursor's succinyl-CoA and glycine, resulting ALA. This reaction possibly occurs in two steps involving a Schiff base (Zhang, 2011). **The second step** of the formation of heme is done by the enzyme named as ALA dehydratase (Fig. 1), which catalyses the condensation of two molecules of ALA to form porphobilinogen (PBG). The cofactor for this reaction is the zinc metal ion and the suspected inhibitors are the lead metal ions. This enzyme protein is produced due to influence of gene on chromosome 9 that encodes for ALA dehydratase. It is important to consider at this point that this gene functions differently in both erythroid and housekeeping cells producing different enzyme in both cases (Messerschmidt et al., 2001). This is facilitated by the presence of two promoter regions on the gene, not only this but the gene also contains exon sites which are utilized alternatively in both types of cells. This implies that not whole of the gene portion is transcribed in any one type of the cell. When transcript of these genes was observed 11 of the 12 coding exons were found to be identical, which leaves their exclusiveness to the one exon only; which was the first one (Kaya, 1994). The **third** enzyme of heme biosynthetic reaction is porphobilinogen deaminase. In this step hydroxymethylbilane (HMB) is formed by the condensation of four molecules of porphobilinogen. They join in a linear manner one after another. HMB structurally is a tetrapyrole ring. As described in the previous step, a slightly different version of enzyme is required for both erythroid and housekeeping cells specific biosynthetic reaction to be carried out. So Porphobilinogen deaminase also has two forms which are both encoded by the same gene on chromosome 11 in humans (Meisler, 1980). This gene produces two separate transcripts by alternate splicing of exons; which again differ in their first exon.

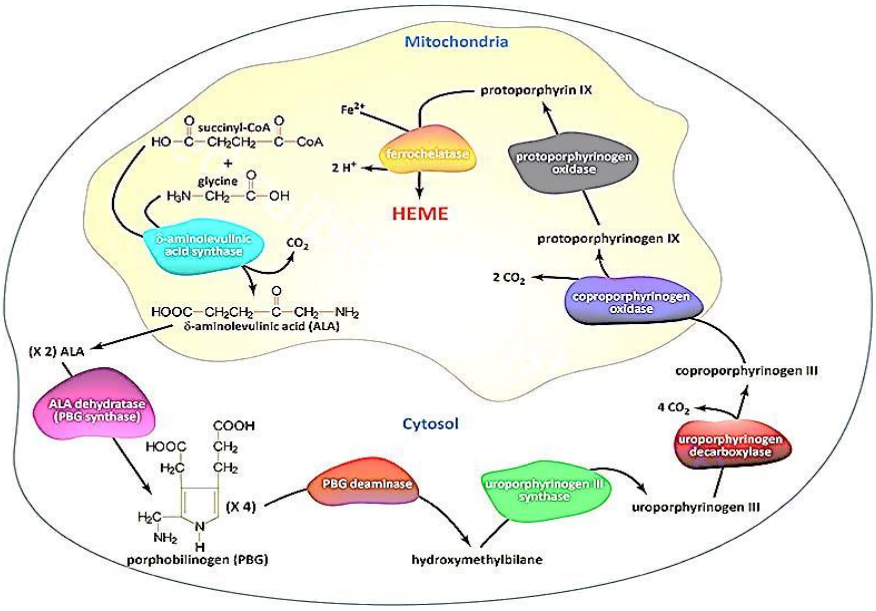

Figure 1: Animated figure depicting heme biosynthetic pathway

In the **fourth step** of heme biosynthetic pathway is catalysed by UROS (uroporphyrinogen III synthase) enzyme. In this step the intramolecular rearrangements of HMB takes place along with the closure of molecular ring which results in formation uroporphyrinogen III (URO) (Zhang, 2011). URO is a cyclic tetrapyrrole molecule which is flanked by eight carboxylic side chains. UROS exists in two forms produced by the erythroid specific and housekeeping cells respectively. The single gene on chromosome no 10 is controlling their production. There are separate promoters on the gene for the production of both of the isoforms of the enzyme. The modification for distinction in the final products of both types of cells is same; the alternate splicing of exons in the transcript produced (Xu, 1995). In the **fifth step** decarboxylation of the product of fourth step takes place by an enzyme UROD (Uroporphyrinogen decarboxylase), along with the formation of methyl groups. The result of decarboxylation reaction is formation of coproporphyrinogen III. (Meisler, 1980) The gene coding for this enzyme is located on chromosome number 1. There is a single form of this enzyme whose production is controlled by a single promoter located on the respective gene on chromosome 1 (Verneuil, 1984). In the **sixth step** in heme biosynthesis an enzyme, coproporphyrinogen III (CPO) catalyzes the successive oxidation and decarboxylation of coproporphyrinogen III, which results in formation of protoporphyrinogen IX (Zhang, 2011). Gene coding for this enzyme is located on chromosome no 3. The length of this gene is found to be 14 kb, with 7 exons along its length. Astonishingly the production of this enzyme (CPO) also controlled by a single promoter. Hence there is no isoform of this

enzyme in the metabolic pathway. (Kaya, 1994). The main reaction in the **seventh step (Figure 2)** in heme biosynthesis is the formation of methane bridges in protoporphyrin IX molecule. Reaction is catalysed by an enzyme protoporphyrinogen oxidase (PPO) (Zhang, 2011) (Meisler, 1980). The gene which controls its production is present on chromosome number 1. There is no alternate or iso-form of this enzyme; single form controls the reactions in both types of cells whether they are erythroid specific or non-erythroid in nature (Roberts, 1991). In the **eighth**, the last and final step of pathway heme formation takes place from protoporphyrin IX. The reaction involves insertion of Fe^{+2} (ferrous ion) in the center of protoporphyrin IX molecule; the reaction is catalysed by ferrochelatase enzyme. The production of this enzyme is catalysed by a single gene located along the chromosome 18, which was found to be 45 kb in size. This gene contains 11 exons in it (Taketani, 1992). The two of the enzymes, CPO and PPO, require oxygen as a substrate; due to such an implication the rate of heme biosynthesis may assumed to be controlled by oxygen levels in a certain concentration.

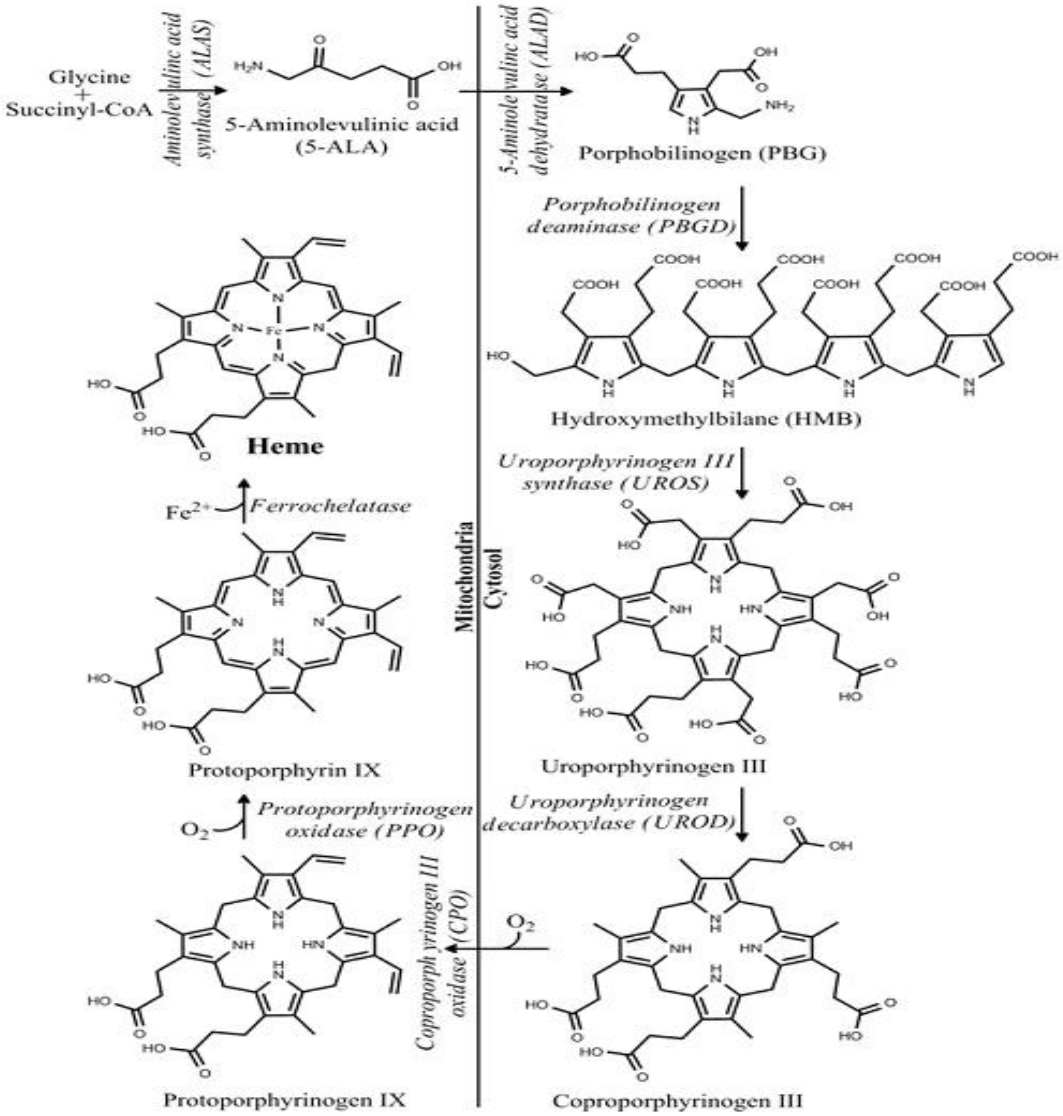

Figure 2: Heme biosynthesis with reaction precursors, enzymes and various intermediates of reaction pathway.

Synthesis Frequency (Supply and Demand)

The heme levels in several tissues of the human body oscillate according to the already present level of heme and the need for additional heme. Intracellular heme levels are precisely and dynamically controlled by modulating the rates of heme biosynthesis and degradation (Montellano, 2009). The two main sites of heme synthesis, as established earlier are the liver and erythrocytes. It plays a vital role in liver thus forming cytochrome P450; this compound is inevitable for the detoxification of xenobiotic compounds ingested by an individual. They may include aliphatic or aromatic hydrocarbons like benzene, toluene, methanol, ethanol, ethane etc; along with various drugs, food additives, and environmental contaminants (Granick, 1971). So the amount of heme formation may increase or decrease

according to the situation on hand. If an individual ingests drastic amount of toxic compounds then in order to carry out detoxification readily liver might start surplus heme production.

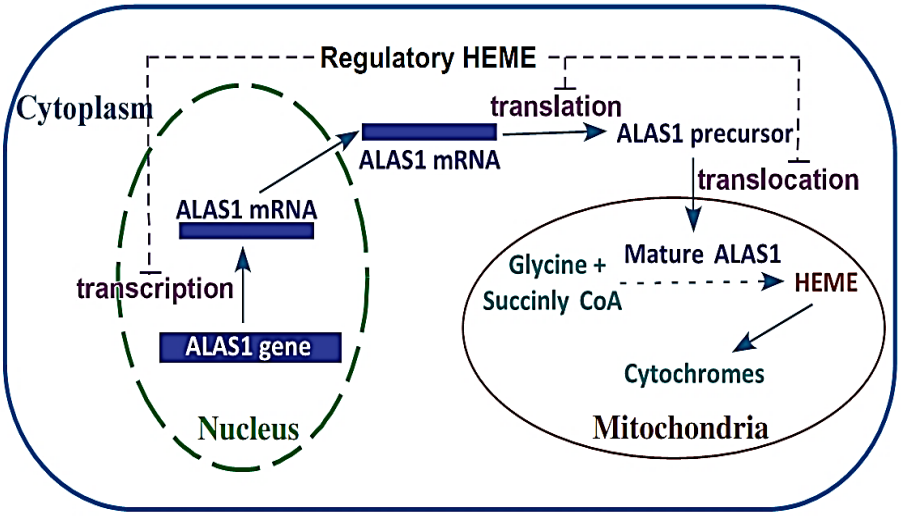

Figure 3: Two sites of heme synthesis in cell; mitochondria and, along with the gene regulation that controls the heme synthesis and feedback.

In liver the control on heme biosynthetic pathway is exerted from the very first step; where the synthesis of 5-ALA takes place. The enzyme controlling first reaction is ALAS1, which is naturally produced in lowest concentration from among the bulk of heme biosynthetic enzymes. Hence process is controlled and regulation is easy from the first step. ALAS1 amount is itself controlled by the negative feedback of heme (Figure 3), at the various stages of heme synthesis like translation, transcription, and translocation. It implies that if heme is in surplus amount then then these 3 steps would be inhibited; opposite would be true for the low heme concentration. Despite the above stated mechanism it is hypothesized by many researchers that intracellular heme exists as a vast free pool, which carries out various reactions but the origin of this pool is anonymous (Rutherford, 1979).

The major contribution of heme is hemoglobin synthesis which occurs in erythrocytes of bone marrow. Erythroid specific cells produce heme according to the need of hemoglobin for blood synthesis, here ALAS2 catalyses the first step of heme biosynthetic pathway. The transcriptional factor GATA-1 is found to regulate the production of heme in erythroid cells. Xenobiotic compounds degradation or concentration does not affect the rate of heme production for blood synthesis. Here feedback regulation is also not accounted for heme synthesis control instead greater amount of heme serves to increase the amount of reaction enzyme; its concentration is drastically found to increase the amount of other heme biosynthetic enzymes in MEL (Murine erythroleukemia) cells (Mense et al., 2006). The cascading effect of increase in amounts of other successive enzymes might be due to induction effect of ALAS2; that is saying it serves as a trigger for other pathway reactants production and preparation. Hence first step of heme synthesis in erythroid cells cannot be referred as the rate limiting step. The last step of heme biosynthesis can however lemmatize heme production if iron is not available for incorporation in the center of protoporphyrin IX. But once the eight steps of reaction are complete the growth factors like erythropoietin would continue to stimulate the growth and differentiation of erythrocytes; which would in turn produce hemoglobin. Hence iron non availability would only truly serve to inhibit the process of heme synthesis in erythrocytes in bone marrow and none other (Rutherford, 1979).

Natural Heme degradation

Red blood cells in human body have a total life span of approximately 120 days after which they are degraded inevitably. Reticuloendothelial system at extravascular sites is involved in removal and degradation of old blood cells. Heme is released from hemoglobin and is degraded (Fig 4). The first step of heme degradation is the oxygenation which takes place by the action of Heme oxygenase; it serves to break the α-methane bonds in Porphyrin ring and generate biliverdin (blue-green) in the presence of NADPH and oxygen. This oxygenation reaction cuts open the ring of heme. This activity is most prevalent in the spleen which functions primarily in disposing off the senescent red blood cells (Chowdhury, 2009). Kupffer cells and hepatocytes cells in liver also exhibit the heme oxygenase (degradation) activity. The two enzymes identified to be involved in this process are OH^{-1} and OH^{-2} (Dubart et al., 1986).

Various factors are involved in regulating the expression of genes coding for these enzymes. OH^{-1} is produced via very complex process; its production can be induced by metal ions, hydrogen peroxide, hypoxia, heme and degradation of glutathione.

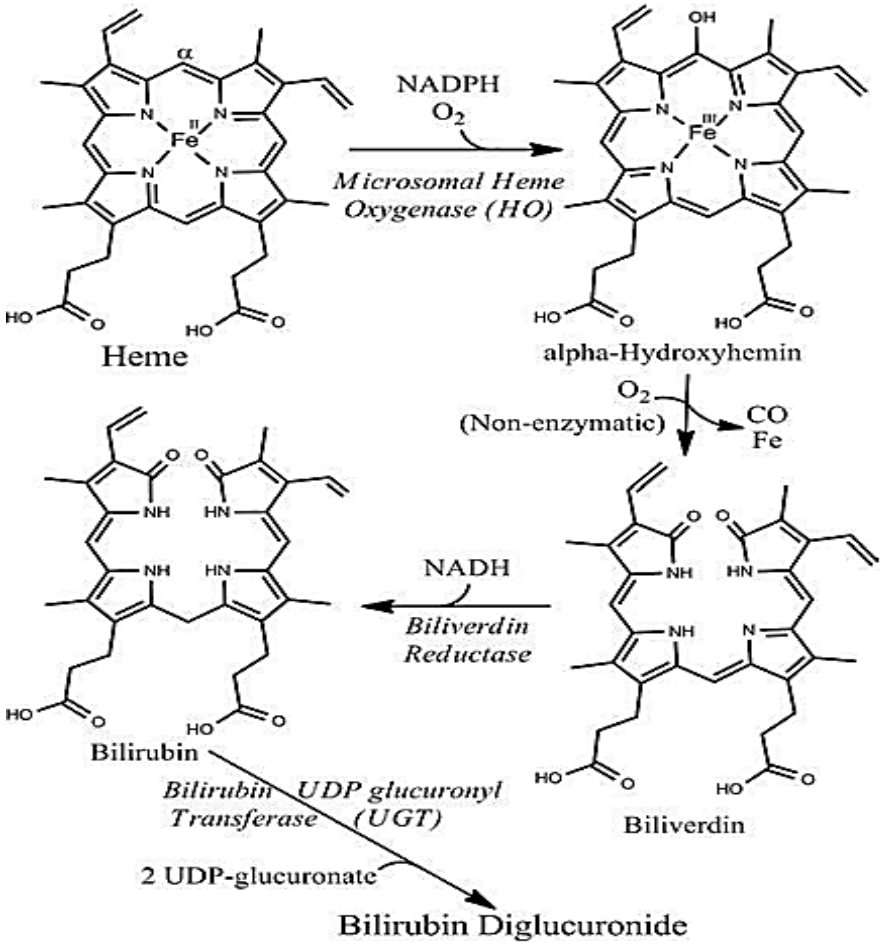

Figure 4: Heme natural degradation cycle.

The above stated factors are not the sole regulators, apart from them the cell type and specie of the organism also matters for the gene expression. For instance, hypoxia induces HO^{-1} expression in bovine, rodent, and monkey cells, but represses HO^{-1} production in several human cell classes, including those affected by lung cancer A549, glioblastoma cells umbilical vein, and endothelial cells (Lee, 1997).

Heme oxygenase activity can be inhibited by other Porphyrins which contain central metal ion other than iron (ferrous ion). They can be protoporphyrins containing tin or tungsten. The product after breaking of methane bridges of heme is known as biliverdin. Bilirubin (it is an orange coloured bile pigment) is the degradation product of biliverdin; this reaction is catalysed by biliverdin reductase. Bilirubin is released in the blood after its formation where it is bound by serum albumin; it is insoluble in water due to its lipophilic nature. It is responsible for the yellow colouration of bruises, wounds, and urine. Moreover patients suffering from jaundice get the yellow hue in their various body parts due to excessive breakdown of heme and bilirubin accumulation. 200-400 mg of bilirubin production per day has been estimated in humans, a major portion of which is comprised by the hemoglobin degradation (Takashi et al., 1998).

In order to be secreted in the bile bilirubin is rendered water soluble by its conjugation with glucuronic acid; this reaction is catalysed by bilirubin UDP-glucuronyl transferase. Bile salts play important role in emulsification of fats. Bilirubin acts as an antioxidant for human body and provides protection against any potential damage that may result from the oxidation reaction. The iron released by heme degradation can be reused in its biosynthetic pathway. The degradation pathway may also rid body of any kind of senescent Porphyrin, moreover in this pathway carbon monoxide is produced which acts as a neuromodulator. Above all normal body homeostatic conditions are reflected by hemoglobin degradation and heme biosynthesis; rates of both of these reactions are almost same in the normal conditions (Bosma, 1994).

Disease introduction

In the early 20th century, scientists started to investigate heme and its porphyrin precursors, due to their association with a class of interesting diseases called porphyrias. Porphyrias are inherited (mostly autosomal dominant) and acquired disorders associated with partially defective enzymatic activities of the heme biosynthetic pathway and increased levels of heme precursors. The term porphyria is derived from the Greek term ‘porphura’ which means “purple pigment” in

reference to the colour of body fluids in people suffering from a porphyria. Porphyrias are classified as hepatic or erythropoietic in type, depending on the primary organ in which excess production of porphyrins or precursors takes place (Sassa, 1981).

DISORDERS OF PORPHYRIA

An autosomal hepatic disorder that is a recessive trait, called ADP (5-Aminolevulinic acid Dehydrogenase Porphyria) is caused due to the poor activity of the enzyme 5-aminolevulinic acid dehydrogenase. The most common type of porphyria that is caused due to the reduced action of uroporphyrinogen decarboxylase is called PCT (Porphyria Cutanea Tarda). A recessive autosomal disorder that is caused by the noticeable general deficiency of the enzyme; uroporphyrinogen decarboxylase is called HEP (Hepatoerythropoietic Porphyria). A dominant autosomal type of porphyria that results from the semi-normal action of the enzyme; coproporphyrinogen oxidase, is called HCP (Hereditary coproporphyria). A dominant autosomal porphyria because of the semi-normal action of the enzyme; protoporphyrinogen oxidase, is called VP (Variegate porphyria). This is the major type of porphyria and is most common type acute porphyria, that is a dominant autosomal disease that results from the semi-usual activity of the enzyme; porphobilinogen deaminase and is called AIP (Acute intermittent porphyria).

AIP is the major type acute porphyria, resulting from the semi-usual activity of a specific enzyme known as porphobilinogen deaminase. It occurs often in women during the period between puberty and menopause. It is caused by the factors that participate in increasing the need for the biosynthesis of heme, such as contraceptive pills, sex steroids and other recommended medicines, alcohol, fasting, and stress. The pain caused due to porphyria may be about 10% of the pain that the women experience before their menstrual cycle. The cases or porphyria are very rare in US as they are found to be about 1-5 cases of acute porphyria per 10000 people, while there are an average of 60–100 cases per 100000 in Sweden that ranks top in the AIP patients. The experimental evidences of AIP show the disorders of peripheral, visceral and central nervous systems. The AIP patients experience the acute attacks of the neurovascular problems that are caused by the enhanced excretion of the precursors of porphyrin. The acute attacks often begin with the severe abdominal pain, constipation, and vomiting. The most common indication of the acute cases is the abdominal pain that occurs from 85% to 95%. The pain is poorly localized, steady and severe. In 80% of the acute cases, Tachycardia occurs. Primarily motor is involved in Peripheral neuropathy. Proximal muscles are often the sites from where muscle weakness begins, and occurs less frequently in the legs than in the arms. Confiscations may arise in the patients that experience the acute attacks. Disturbances that involve the CNS are highly variable but is common. The patients that experience acute attacks can have severe insomnia, anxiety, fear, illusions, confusion and depression and often suicidal tendencies (Zhang, 1999).

Acute Intermittance Porphyria (AIP) can be identified by a sample of urine. When the urine of AIP patients is compared with that of the usual laboratory standards, the AIP patients' urine will show enhanced levels of the porphyrin pioneers ALA and PBG. Because of the poor activity of PBGD, only the limited number of these metabolites will go forward in pathway to make heme. Usual lab Standards of PBG are about 3.4–9.5 nmol/L for men and approx. 5.3–9.2 nmol/L for women. The colour of urine turns dark red, and after exposure to Sunlight it is exposed to UV, the colour may darken to deep purple. The mixture of glucose, dextrose and organization of synthetic heme arginate are included in the treatments for acute attacks. The former prescription is contrived by only one company in US that is known by the name of its brand, Panhematin. The drugs such as barbiturates, diphenylhydantoin and sulfonamides increase the production of cytochrome P450 and the hem's need that may face acute attacks and must be escaped or avoided. Many drugs that are commonly used such as the pain killers and antibiotics can aggravate the snags of AIP and they should be escaped. It is important to note that an overall decrease in the heme biosynthesis can be related to the severe human disorders e.g., deficiency of heme changes the working of various neuronal cells, and forms the bases of the defects like those that are observed in the neurodegenerative disorders in the neuronal cells. A recent research tells us that the levels of ALA synthase and porphobilinogen deaminase; the two rate-limiting enzymes in the pathway of heme biosynthetic, are expressively decreased in brains of the patients of Alzheimer's disease, as compared to normal brains (Zhang, 1999).

The demonstration of AIP is nonspecific and inconstant, that may involve the peripheral, autonomic and CNS. There are few cases in the collected work in MRI findings of the cases of Porphyria with CNS participation. PRES is an experimental unit that is described by annexation, headache, conscious and optical disorder related to the neuroradiological outcomes, primarily white substance disturbances of parieto-occipital lobes (Narla, 2017).

AIP is caused due to the changes in the enzyme i.e., hydroxymethylbilane synthase (HMBS), gene that causes semi-usual HMBS enzymatic action, that is the third enzyme in pathway of heme biosynthesis (HMBS). The deficiency of this enzyme inclines the patients that are heterozygous to lethal acute attacks that are triggered by several factors comprising porphyrinogenic drugs (P450 inducers), infection, alcohol, depression, persistent fasting and enduring low nutrition, and the steroid hormones. These causes the start the production of ALAS1 (aminolevulinic acid synthase 1) the rate-limiting and first enzyme in the pathway of heme biosynthesis. The induction of hepatic ALAS1 limit the

partial HMBS deficiency of enzyme results in discernable buildup of the neurotoxic pioneers of porphyrin, ALA and PBG. The central and peripheral nervous systems produce acute psychiatric and neurovisceral symptoms by the action of these Porphyrins (Table 1). During an acute attack, the identification of AIP is usually performed by indicating evidently eminent urinary levels of PGB, and by diagnosing a pathogenic gene mutation in patient by HMBS. It is reported that AIP heterozygous experiencing acute attacks are 10-20% while most of the AIP patients are medically asymptomatic during the whole life of them. The patients of acute porphyria experience severe abdominal pain followed by constipation, vomiting and abdominal distension which may be called as the acute abdomen (Manisha, 2016).

Table 1: Types of Porphyria disorders

Porphyria	Deficient enzyme	Gene symbol	Chromosomal location	Inheritance	Main symptoms	Erythrocytes	Urine	Stool
Erythropoietic								
Congenital erythropoietic porphyria (CEP)	Uro-porphyrinogen III cosynthase	*UROS*	10q25.2	Autosomal recessive	Photosensitivity	Uroporphyrin Coproporphyrin	Uroporphyrin Coproporphyrin	Coproporphyrin
Erythropoietic protoporphyria (EPP)	Ferrochelatase	*FECH*	18q21.3	Autosomal dominant	Photosensitivity	Protoporphyrin	Absent	Protoporphyrin
Hepatic								
ALA dehydratase deficiency porphyria (ADP)	ALA dehydratase	*ALAD*	9q34	Autosomal recessive	Neurovisceral	Zn-Proto-porphyrin	ALA, Coproporphyrin	
Acute intermittent porphyria (AIP)	PBG deaminase	*PBGD*	11q23.3	Autosomal dominant	Neurovisceral		ALA, PBG, Uroporphyrin	
Hereditary coproporphyria (HCP)	Copro-porphyrinogen oxidase	*CPO*	3q12	Autosomal dominant	Neurovisceral photosensitivity		ALA, PBG, Coproporphyrin	
Variegate porphyria (VP)	Proto-porphyrinogen oxidase	*PPO*	1q23	Autosomal dominant	Neurovisceral and photosensitivity		ALA, PBG, Coproporphyrin	Coproporphyrin Protoporphyrin
Porphyria cutanea Isocopropophyrin tarda (PCT)	Uro-porphyrinogen decarboxylase	*UROD*	1p34	Variablel	Photosensitivity		Uroporphyrin, 7-carboxylate porphyrin	
Hepatoerythropoietic Isocopropophyrin porphyria (HEP)	Uro-porphyrinogen decarboxylase	*UROD*	1p34	Autosomal recessive	Photosensitivity and neurovisceral	Zn-Proto-porphyrin	Uroporphyrin, 7-carboxylate porphyrin	

Behavioural changes occur such as sleeplessness, emotional labiality; touchiness, tachycardia and hypertension due to the concerned increased action are important evidences for identification. Because of the changing medical demonstration and non-precise signs of the neurovisceral attacks and the studies show that such attacks are rare in children, a high catalogue of the notion is needed is needed to make the diagnosis of disease in children. Here we represent a case that shows the difficulty in identification and the progression of attacks in the boy prior to puberty and the porphyrinogenic medicines were injected in the boy for the treatment of infection and annexations that further aggravated, extended and increased the harshness of his acute attacks (Balwani, 2016).

Case study related to porphyria disorder

The patient was 9 years, pre-pubertal, developmentally normal Indian boy, who was having no previous medical history. He experienced the acute abdominal pain, followed by constipation and vomiting. He was suffering from fever that shows response to paracetamol one day before the acute pain. He was hospitalized due to severe pain for a supposed sub-acute intestinal hindrance, and the fluids were controlled (NPO). He was given antibiotics that were injected intravenously including metronidazole and ceftriaxone. An abdominal CT scan were performed that showed the mild ascites, but still no other source of his symptoms. On the 3rd day of his illness, an annexation was developed that was cured using the intravenous phenytoin and midazolamloading. The condition of the boy did not change and he was referred to another hospital where he was cured with IV fluids and variable antibiotics that also include amikacin and sulbactam (Kaplan, 1986). His reports showed hyponatremia and leukocytosis. Hyponatremia was cured with the intravenous saline. His abdominal pain and vomiting was reduced and he was discharged from the

hospital with the appetite stimulant and multivitamins. Stability was for a few days as after day 12 he felt weakness and pain in the lower fringes and feel like he was noticeable to support himself. The weakness increased to the severe pain in the fringes and back. He was admitted to hospital again on day 20 of his disease and also he was not able to sit without backing. He was now complaining tremors, headache and unbearable pain in limbs that was not relieved by pain killers. He had a poor appetite and was impatient and was suffering from insomnia (Solis, 2004). The pain was widespread in all limbs, back and trunk. There were no signs of swelling of joint. He was not able to stand without support as the deep tendon reflexes were extremely hard to stimulate and there were no meningeal signs. There was no indication of musculoskeletal disease. He was given tramadol as pain killer. The concentration of blood lead was 0.1µg/dL. He developed the urinary retention that was released by catheterization. His urine was red that lead to the notion of acute porphyria. His family studies showed that his mother and two brothers were having splice-site mutation and were heterozygous. The patient was treated with a high dose of dextrose infusion regimen (400g/day). The patient significantly improved himself and discharged on the physical therapy. After discharge, the patient had two successive attacks during the nine months triggered by respectively a slight pathological illness and deprived oral intake. These attacks were accomplished by intravenous dextrose (400g/day) and hospitalization (Anderson, 2005).

CONCLUSION

Heme biosynthesis is an inevitable natural process of living organisms whose proper regulation is very important for proper delivery of oxygen to various parts of body. For its mechanism to work properly the involvement of eight enzymes in proper order and on proper substrate or precursor compounds is important. Like its biosynthesis, the degradation of heme is also a natural process that occurs in body. Its various disorders that are result of accumulation of any of the compound of the biosynthetic pathway in body: Porphyria being the main among them. Although the disease results in adverse health deteriorating effects but cure is possible by hospitalization, proper medication, and regulation of diet. The expression of certain genes could be suppressed (in case of the overexpression of their protein) but it shall be only possible by the genetic modifications or gene regulating medicines that could be an important aspect of research in future for the scientists.

REFERENCES

1. A.G. Roberts, W. S. Partial characterization and assignment of the gene for protoporphyrinogen oxidase and variegate porphyria to human chromosome 1q23. Hum Genet, 1991; 1152–1154.
2. A.H. Kaya, P. M. Human delta-aminolevulinate dehydratase (ALAD) gene:Structure and alterna-tive splicing of the erythroid and housekeeping mRNAs. Genom, 1994; 19: 242–248.
3. C. Diosely Silveira, M. B. Acute intermittent porphyria presenting with posterior reversible encephalopathy syndrome and lateralized periodic discharges plus fast activity on EEG. Epilepsy & Behavior Case Reports, 2016; 58-60.
4. C. Solis, A. Martinez-Bermejo, T.P. Naidich, et al., Acute intermittent porphyria: studies of the severe homozygous dominant disease provides insights into the neurologic attacks in acute porphyrias, Arch. Neurol, 2004; 61: 1764–1770.
5. De Verneuil H, G. B. Assignment of the gene for uroporphyrinogen decarboxylase to human chromosome 1 by somatic cell hybridization and specific enzyme immunoassay. Hum Genet, 1984; 66: 202–205.
6. Dubart A, Mattei MG, Raich N, Beaupain D, Romeo PH, Mattei JF, Goossens M. Assignment of human uroporphyrinogen decarboxylase (URO-D) to the p34 band of chromosome 1. Hum Genet, 1986; 73: 277–279.
7. G.J. Arthue Bank. 1974. The Red Blood cell. Academic Press, London.
8. J.R. Chowdhury, W. A. Hereditary Jaundice and Disorders of Bilirubin Metabolism. The Metabol and Mol Bas of Inh Dises, 2009; 1-90.
9. K.E. Anderson, J.R. Bloomer, H.L. Bonkovsky, et al., Recommendations for the diagnosis and treatment of the acute porphyrias, Ann. Intern. Med., 2005; 142: 439–450.L. Zhang, 2011. Heme Biology The Secret Life of Heme in Regulating Diverse Biological Processes. Dallas, USA: Wor Sci Pub Co. Pte. Ltd.
10. M. Meisler, W. L. The UPS locus encoding uroporphyrinogen I synthase is located on human chromosome 11. Biochem Biophys Res Commun, 1980; 95: 170-176.
11. Mattoon J, Lancashire W, Sanders H, Carvajal E, Malamud D, Braz G,Panek A. Oxygen and catabolite regulation of hemoprotein biosynthe-sis in the yeast Saccharomyces cerevisiae. In Biosynthesis of Heme and Cholorophylls, ed. WJ Caughey, 1979; 421–435. New York: Academic Press.
12. Mense SM, Zhang L. Heme: A versatile signaling molecule controlling the activities of diverse regulators ranging from transcription factors to MAP kinases. Cell Res., 2006; 16: 681–692.
13. Messerschmidt A, Huber R, Poulos T, Wieghardt K.. Handbook of Metalloproteins. West Sussex: John Wiley & Sons Ltd, 2001.
14. Moore MR. Historical introduction to porphyrins and porphyrias. In Biosynthesis of Heme and Cholorophylls, ed. HA Dailey, 1990; 1–54. New York: Green Pub. Associates and Wiley-Interscience.
15. Ortiz de Montellano PR. Hemes in Biology. In Wiley Encyclopedia of Chemical Biology, 2009; 240–249. West Sussex: John Wiley & Sons Ltd.
16. P.J. Bosma, S.J. Bilirubin UDP-glu-curonosyltransferase 1 is the only relevant bilirubin

glucuronidating isoform in man. J. Biol. Chem., 1994; 17960–17964.
17. P.J. Lee, J. B. Hypoxia-inducible factor-1 mediates transcriptional activation of the heme oxygenase-1 gene in response to hypoxia. J. Biol Chem, 1997; 5375–5381.
18. Ponka P. Cell biology of heme. Am J Med Sci., 1999; 318: 241–256.
19. P.W. Kaplan, D.V. Lewis, Juvenile acute intermittent porphyria with hypercholesterolemia and epilepsy: a case report and review of the literature, J. Child Neurol, 1986; 1: 38–45.
20. R. Kalle Möbius, A.-C.-L.. Heme biosynthesis is coupled to electron transport chains for energy generation. Proc Natl Acad Sci., June 8, 2010; 10436-10441.
21. S. Richard, Ajioka, J. D. Biosynthesis of heme in mammals. Biochimica et Biophysica Acta, 2006; 723–736..
22. S. Sassa, K. A. Genetic, metabolic, and biochemical aspects of the porphyrias. Adva Hum Genet, 1981; 121–231.
23. S. Taketani, I. J. Structure of the human ferrochelatase gene. Exon/intron gene organization and location of the gene to chromosome 18. Euro J Biochem, 1992; 217–222.
24. S.S. Granick, S. δ-Aminolevulinic acid synthetase and the control of heme and chlorophyll synthesis. Metbol Regula, 1971; 77-89.
25. T. Rutherford, T. G. Heme biosynthesis in Friend erythroleukemia cells: Control by ferrochelatase. Proc Natl Acad Sci, USA, 1979; 833–836
26. Takahashi S, Taketani S, Akasaka JE, Kobayashi A, Hayashi N, Yamamoto M, Nagai T. Differential regulation of coproporphyrinogen oxidase gene between erythroid and nonerythroid cells. Blood, 1998; 92: 3436–3444.
27. W. Xu, K. C. Uroporphyrinogen-III synthase: molec-ular cloning, nucleotide sequence, expression of a mouse full-length cDNA,and its localization on mouse chromosome 7. Genomics, 1995; 26: 556-562.