READING GUIDE

PART 3: CONVERSION OF AMINO ACIDS TO SPECIALIZED PRODUCTS

Objectives

1. Diagram and describe the synthesis of heme and other porphyrins
2. Describe disorders of heme biosynthesis at the molecular level
3. Diagram and describe the metabolism of bilirubin and the disorders related to bilirubin metabolism
4. Describe the pathways by which catecholamines, histamine, serotonin, and creatine are synthesized and degraded

Read Chapter 21.

PORPHYRINS AND THE METABOLISM OF HEME

Big picture

- What are porphyrins, and what is the prevalent one in humans?
- What is heme?
- Heme is found in which proteins?
- How much heme is turned over (synthesized and broken down) each day?
- What are the main sites of heme synthesis?

Structure of porphyrins (Fig. 21.4, 21.5)

- What is the basic structure of a porphyrin?
- There are four types of porphyrins (I-IV). Which kind is important in humans?

Biosynthesis of heme

If you can pencil out the basic pathway to the formation of heme, you will be able to easily answer the following questions. It will also help you to organize the various porphyrias and their causes. (Fig. 21.8 is a very nice summary of this pathway.) I find this helpful for getting the flow of protoporphyrin IX (heme) synthesis (included in the slides for this topic).

What are the two initial building blocks (the starting material) of protoporphyrin IX and heme, and what do they combine to form?

What is the immediate precursor to porphobilinogen, the primary subunit of the heme structure?

What color is uroporphyrinogen?

What is the rate controlling step in porphyrin synthesis and what is the primary regulator?

Note that many drugs are metabolized by the cytochrome P450 monooxygenase system and consequently up-regulate the synthesis of these heme-containing proteins. This increase consumes available heme, decreasing end-product inhibition, and in turn up-regulates ALA synthase activity.

Porphyrias and other problems associated with heme biosynthesis

The porphyrias are defects in heme biosynthesis. Many are inherited and all are rare. If untreated, they result in accumulation of porphyrin intermediates to toxic levels.

There is a porphyria associated with an enzyme deficiency at every step of porphyrin synthesis downstream of porphobilinogen (Fig. 21.8).

- Porphyria cutanea tarda is the most common porphyria. Remember this one.
- The other hepatic porphyrias are all acute and occur in alphabetical order; acute intermittent porphyria – hereditary coproporphyria—variegate porphyria. These porphyrias tend to produce neurologic, gastrointestinal, and cardiovascular symptoms.
- The two erythropoietic porphyrias are also in alphabetical order and both have erythropoietic in the name; congenital erythropoietic porphyria and erythropoietic protoporphyria. These are characterized by skin rashes and are sometimes referred to as cutaneous porphyrias.
- The porphyrias that produce accumulation of tetrapyrrole rings cause photosensitivity (which is all of them except acute intermittent porphyria). Why do you suppose that is?

All the porphyrias are inherited as autosomal dominant except congenital erythropoietic porphyria (the first erythropoietic one). This one is recessive and the rarest porphyria.

To summarize

- Hepatic, acute = non-cutaneous presentation (neurologic, gastrointestinal, and cardiovascular)
- Hepatic, chronic = most common, cutaneous symptoms later in life
- Erythropoietic = cutaneous symptoms in early childhood

If you've committed the heme biosynthetic pathway to memory (at least for the moment), you'll be able to place these porphyrias on the synthetic pathway and to predict some of the precursor accumulations and symptoms. **Don't forget the steps of heme synthesis that are inhibited by lead.** Not really a porphyria but a complication of lead poisoning.

All the porphyrias result in decreased heme synthesis and consequently an activation (derepression) of ALA synthase. Given this fact, how would you treat a porphyria?

Degradation of heme

How long does a red blood cell routinely last in circulation before being turned over?

The degradation of heme and its transport to the liver is straight forward. If you know the major steps you will be able to answer the following questions. (Fig. 21.9, 21.10)

How is biliverdin formed from heme?

How is bilirubin produced from biliverdin?

How do you tell biliverdin from bilirubin?

How is bilirubin transported to the liver?

What happens to bilirubin once in the liver?

What happens to conjugated bilirubin in the gut?

What makes feces brown?

What happens to urobilinogen that gets taken back up into the blood stream?

Jaundice (Fig. 21.12, 21.13)

What is jaundice?

Describe the 3 main types of jaundice.

Which basic type of jaundice does the jaundice that occurs in newborns resemble?

Why do you need to extract blood with methanol to measure all the bilirubin?

OTHER NITROGEN CONTAINING DERIVATIVES OF AMINO ACIDS

Catecholamines (Fig. 21.5)

What are the primary three catecholamines and from what amino acid are they derived?

Which of these catecholamines is produced only outside the nervous system?

How are catecholamines inactivated? (Fig. 21.6)

Serotonin (Fig. 21.18)

How is serotonin synthesized?

How is serotonin degraded?

Histamine (Fig. 21.17)

How is histamine synthesized?

Creatine (Fig. 21.19)

What does creatine do?

Why is creatine clinically important and useful?

How is creatine synthesized?