



Problem 1 – Unit 6 – Biochemistry: Iron Metabolism & Heme Synthesis

Iron:

- Iron is an essential element which is not synthesized in the body and thus it must be provided by dietary intake. It function as electron donor when it is in its ferric state (Fe^{3+}) and as an electron acceptor when it is in its ferrous state (Fe^{2+}). Most of the iron is contained in Hb.
- When it is decreased ---> this will result in iron-deficiency anemia (most common type of anemia, red blood cells will be microcytic hypochromic).
- When there is iron overload (accumulation of free iron in the blood) ---> this can generate free radical which damage the cells but the effect of toxicity is limited by iron-binding proteins. Manifestations include:
 - Fever.
 - Vomiting & diarrhea.
 - Hyperglycemia & leukocytosis.
 - Hypotension & metabolic acidosis.
 - Lethargy, seizures & coma.Chronic iron overload is seen in patients receiving multiple blood transfusions.

Iron metabolism:

- Most of the iron is recycled in the reticuloendothelial system but there are some iron loss through sweating, shedding of skin & GIT mucosa.
- Normal iron loss in males is 1mg/day and in females 1.5mg/day (because of menstruation).
- Dietary iron (in food/supplements) is digested in its ferrous form (Fe^{2+}).

Iron deficiency can result from:

- Increased demand (in pregnancy & lactation).
- Bleeding (GIT or uterine).
- Nutritional deficiency (decreased dietary intake, alcohol, drugs...etc).
- Disease of the small intestine.

Symptoms of iron deficiency:

- Behavioral changes (such as irritability, poor concentration, apathy...etc).
- Pica: ingestion of unusual substances (clay & ice) and this is a reversible manifestation.
- Hair, skin, nails & tongue are affected.
- There is increased frequency of infection.

Iron sources & forms:

- In the blood, iron is bound to transferrin (Fe^{3+} -transferrin) to be carried to the target cells which express receptors for iron-transferrin complexes. The complex will be engulfed, iron will be released (due to the acidic nature inside the cells) and stored as ferritin and transferrin will be recycled. Liver is the major site for iron storage while bone marrow is the major site for iron utilization in heme synthesis.
- Ferrous iron (Fe^{2+}) exist in acidic pH & when combined with protoporphyrin IX will form heme. Ferric iron (Fe^{3+}) exist in neutral or alkaline pH.
- Iron is reduced from Fe^{3+} to Fe^{2+} and then transported across the intestinal enterocytes by the action DMT1. Then it will be oxidized again to Fe^{3+} and transported across the basolateral membrane of enterocytes by ferroportin to the blood where it will bind to transferrin to be carried to the liver (for storage in the form of ferritin. But if iron is exceeding the capacity for being stored as ferritin then it will form highly insoluble deposits known as hemosiderin).

Regulation of iron metabolism:

- Hepcidin: found in the liver and antagonize the action of iron transporters.
- Translation control by IREs (Iron Responsive Elements) which are recognized by IRBP (Iron Binding Proteins) and resulting in either increased or decreased transcription of mRNA.



Heme synthesis:

- Heme is a prosthetic group which is present in RBCs. Hemoglobin turnover is 6g/day. Sites of heme synthesis are erythroid cells (85%) and the rest in the liver.
- 4 pyrrole rings linked by methenyl bridges ---> protoporphyrin IX + ferrous iron ---> heme.

Heme synthesis reactions:

- Condensation of 1 glycine (from diet) + 1 succinyl CoA (from TCA cycle) to form aminolevulinic acid by the enzyme ALA synthase (this is the rate limiting step). Note: ALA is toxic to the brain when elevated and it is similar to the neurotransmitter GABA.
- Dimerization of 2 aminolevulinic acid molecules to form the pyrrole ring porphobilinogen.
- Head-to-tail condensation of 4 porphobilinogen to form hydroxymethylbilane by porphobilinogen deaminase.
- Enzymatic conversion of hydroxymethylbilane to uroporphyrinogen III
- Decarboxylation of uroporphyrinogen III to form coproporphyrinogen III by uroporphyrinogen decarboxylase.
- Coproporphyrinogen is decarboxylated to protoporphyrinogen IX.
- Protoporphyrinogen IX is converted to protoporphyrin IX by oxidation. Insertion of ferrous iron by ferrochelatase will produce heme.

Regulation of heme synthesis:

- Substrate availability: availability of Fe^{2+} for ferrochelatase.
- Feedback regulation: heme inhibits ALA synthase.
- Subcellular localization.
- Drugs & steroids: increasing heme synthesis.
- Heme availability: for globin synthesis to proceed.

Degradation of heme:

- Heme is converted to biliverdin by heme oxygenase.
- Biliverdin is converted to bilirubin by biliverdin reductase.
- Bilirubin is transported to the liver where bilirubindigluconide is going to be formed by UDP glucuronyl transferase.
- Bilirubindigluconide will be converted to urobilinogen by intestinal bacteria which then is either oxidized to urobilin in the kidneys and excreted in the urine (yellow color) or oxidized to stercobilin in intestines and excreted in feces (brown color).

Bilirubin forms:

- Unconjugated: water insoluble-tightly bound to albumin-not excreted in urine-increases in hemolysis-large increases cause kernicterus.
- Conjugated: water soluble-loosely bound to albumin-excreted in urine

