Inorganic Pharmaceutical Chemistry:

Essential & Trace Ions

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Iron

- Iron is a chemical element with the symbol Fe (Latin: **Ferrum**) and atomic number 26. Iron is one of the essential heavy metals for human nutrition.
- It plays a major critical role in oxygen and electron transport.
- The average 70-kg adult body contains around 4200 mg of iron ions.
- Free iron is, like most metal ions, highly toxic to the human body.
- Two types of iron can be found in foods, including **heme** and **non-heme**.
- Heme iron is absorbed with better efficiency from the intestine than nonheme iron.

The **Total Iron-Binding Capacity (TIBC)** test measures the blood's ability to attach itself to iron and transport it around the body. A transferrin test is similar. If you have iron deficiency anemia (a lack of iron in your blood), your iron level will be low but your TIBC will be high.

❑ **Iron electron configuration**

Fe ⟶ **Fe(II)** + **2e-**

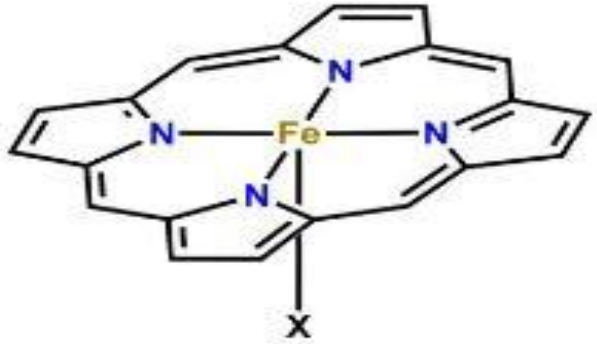
$[Ar]^{18}\ 3d^6\ 4s^2$ $3d^6\ 4s^0$

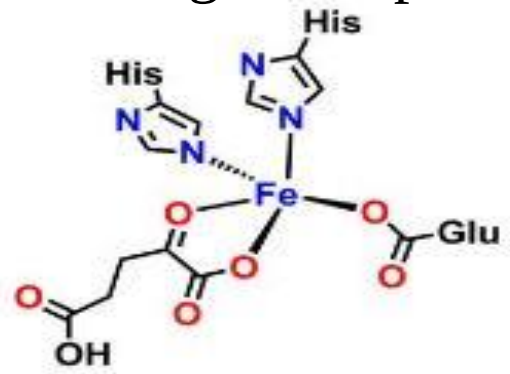
Fe ⟶ **Fe(III)** + **3e-**

$[Ar]^{18}\ 3d^6\ 4s^2$ $3d^5\ 4s^0$

- It plays a role in cell division and regulation of gene expression.
- Heme iron is present only in animal products such as meat, fish, and poultry, whereas nonheme iron is found in fruits, vegetables, dried beans, nuts, grain products, and meat.
- Heme is absorbed more easily without the need for absorption-enhancing cofactors. Nonheme iron, which is the most important dietary source in vegetarians, shows lower bioavailability; its absorption depends on the balance between dietary enhancers and inhibitors and body iron stores.
- Ascorbic acid is a well-known dietary factor improving iron bioavailability; however, calcium, polyphenols, and phytates reduce intestinal iron absorption.
- Iron deficiency anemia:

1. It negatively affects the cognitive development of infants, children, and adolescents.
2. Maternal iron deficiency anemia may cause low birth weight and preterm delivery.





Body Components Containing Iron

Occurrence	Iron Bound As	Mode of Linkage	Function	Iron Content	
				Total	% of Body Iron
Blood System	Haemoglobin	Heme	0_2 Transport	3 g	64.4
	Plasma	Transferrin	Fe Transport	4 mg	0.1
Tissues	Functional Iron (Myoglobin, Cell Hemes)	Heme	Cell Respiration	650 mg	14
	Storage Iron	Ferritin	Iron Pool	1 g	21.5
		Hemosiderin	Detoxication		

- Iron-dependent enzymes (enzymes that require iron as a cofactor): Cytochrome oxidase, Xanthine oxidase, peroxidase, and Catalase

- The advantage of **Fe^{3+}** salts is that they are not prone to oxidation in aqueous solutions.

- The reticuloendothelial system, which clears damaged RBCs by macrophages of the spleen, liver, and bone marrow, plays a role in systemic iron homeostasis.

- Dietary iron absorption is primarily performed through enterocyte cells on the duodenum and upper jejunum of the small intestine.

- Usually, iron is administered orally as **ferrous ion (Fe^{2+})** or **Ferric ion (Fe^{3+})** salts. Fe^{2+} compounds are more soluble at physiological pH. The most common medicinal preparations include $FeCl_3$, $FeSO_4$, Fe(II) fumarate, Fe(II) succinate and Fe(II) gluconate.

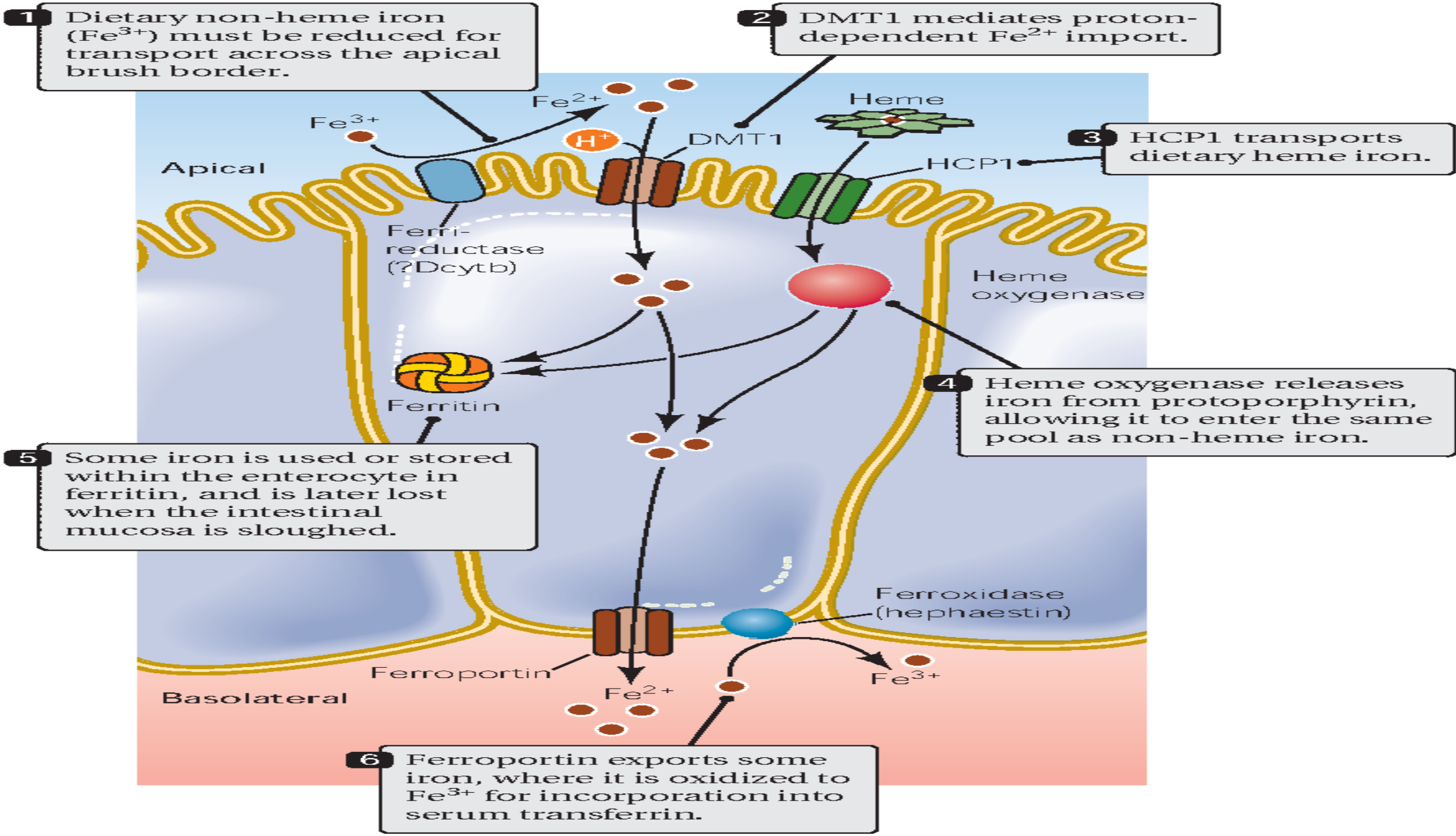
- Dietary iron can be absorbed as part of a protein such as **heme protein** or iron must be in its **ferrous Fe^{2+}** form.

Iron absorption

- A ferric reductase enzyme, **duodenal cytochrome B (Dcytb),** found in the brush border of enterocytes, reduces ferric **Fe^{3+}** to **Fe^{2+}**.

- A protein called **divalent metal transporter 1 (DMT1)** can transport some divalent metals across the cell membrane, transporting iron across the plasma membrane of enterocytes and into the cell.

- When iron is bound to heme, it is instead transported across the apical membrane by **heme carrier protein 1 (HCP1).** Heme is then catabolized to biliverdin by microsomal heme oxygenase, releasing **Fe^{2+}**.
- These intestinal lining cells can then store iron as ferritin, which is achieved by the binding of **Fe^{2+}** to apoferritin (in this case, when the cell dies, the iron leaves the body and shed in the feces), or the cells release iron into the body via the **ferroportin**, the only known iron exporter in mammals.

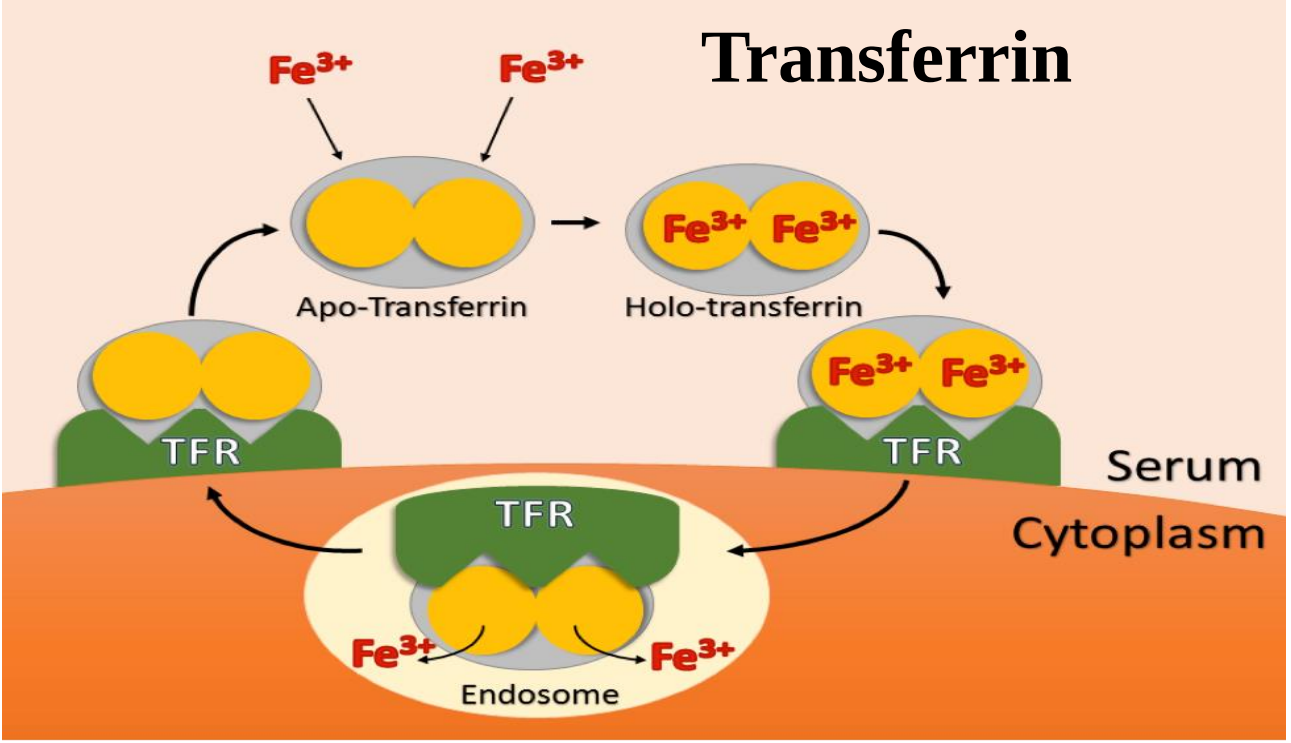

1 Dietary non-heme iron (Fe^{3+}) must be reduced for transport across the apical brush border.
2 DMT1 mediates proton-dependent Fe^{2+} import.
3 HCP1 transports dietary heme iron.
4 Heme oxygenase releases iron from protoporphyrin, allowing it to enter the same pool as non-heme iron.
5 Some iron is used or stored within the enterocyte in ferritin, and is later lost when the intestinal mucosa is sloughed.
6 Ferroportin exports some iron, where it is oxidized to Fe^{3+} for incorporation into serum transferrin.
Fe^{3+}
Fe^{2+}
H^+
DMT1
Heme
HCP1
Apical
Ferri-reductase (?Dcytb)
Heme oxygenase
Ferritin
Ferroxidase (hephaestin)
Ferroportin
Basolateral
Fe^{2+}
Fe^{3+}

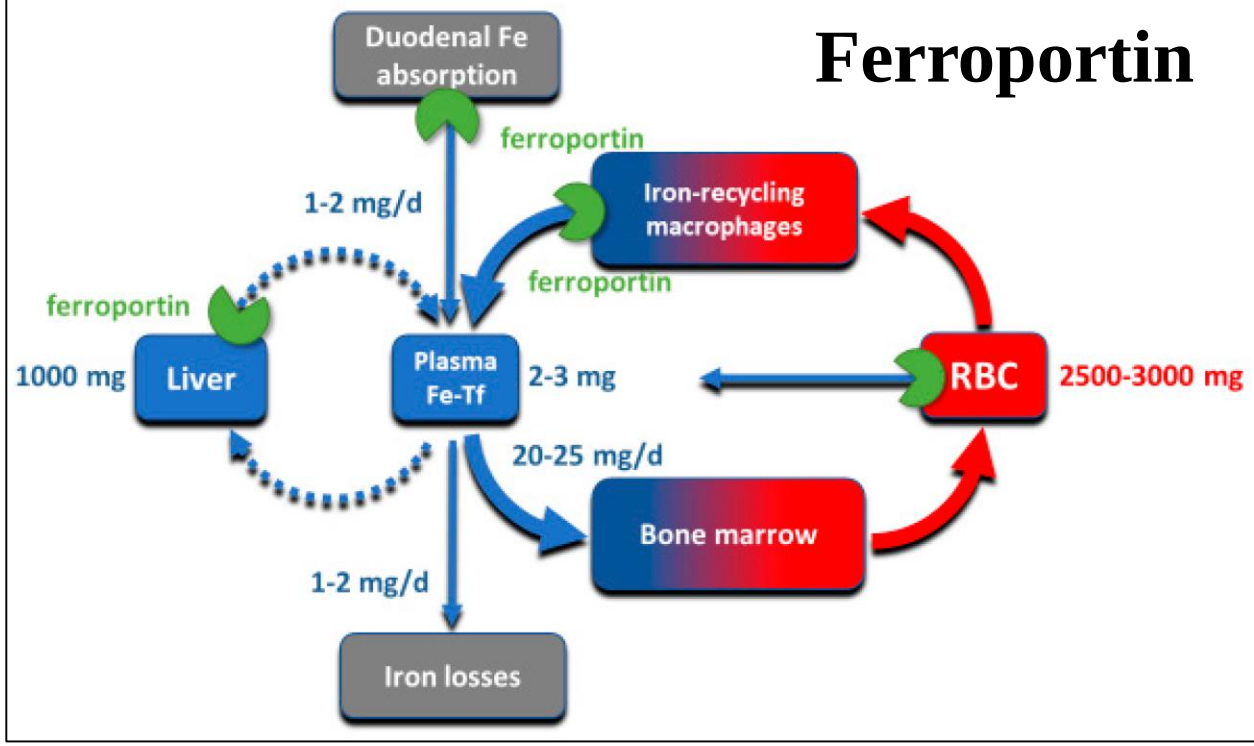
- Hephaestin is a ferroxidase that can oxidize **Fe^{2+}** to **Fe^{3+}** and is primarily present in the small intestine where the ferroportin helps transport iron across the basolateral end of enterocytes.

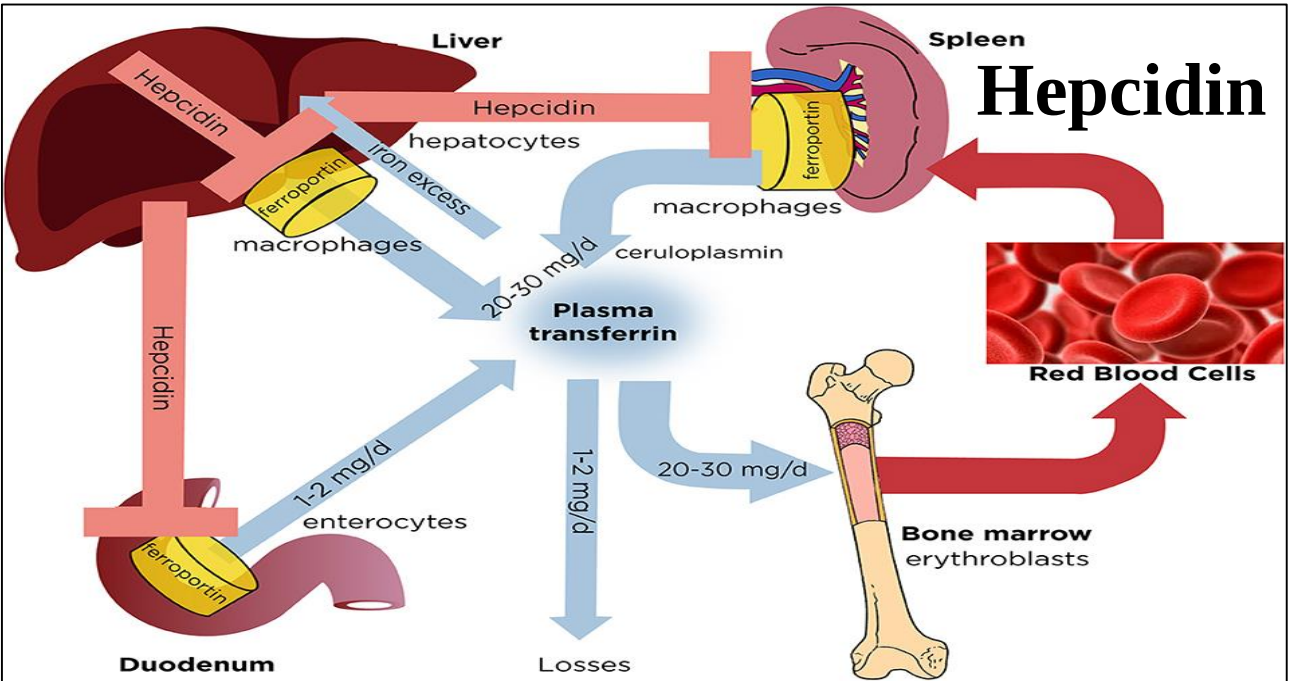
- Once released into the bloodstream, **Fe^{3+}** binds to transferrin and circulates in tissues. In contrast, ferroportin is post-translationally repressed by the 25-amino acid peptide hormone hepcidin.

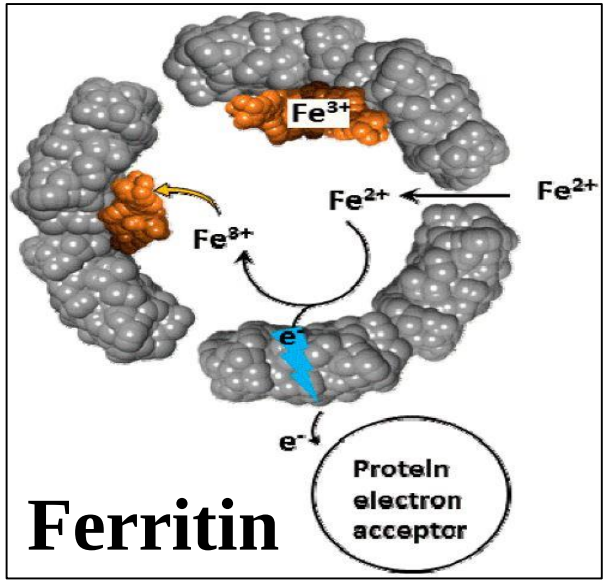
- The body regulates iron levels by regulating each of these stages. For example, enterocytes synthesize more Dcytb, DMT1, and ferroportin in response to iron deficiency anemia.

- The rate of iron absorption in the human body appears to respond to various interdependent factors, including total iron stores, and iron stores. Bone marrow produces new red blood cells and regulates the concentration of hemoglobin in the blood and the oxygen content of the blood. Also, during inflammation, the body absorbs less iron because it deprives bacteria of iron. Recent findings indicate that hepcidin regulation of ferroportin is responsible for the anemic syndrome of chronic disease.


Transferrin
Fe3+
Fe3+
Apo-Transferrin
Holo-transferrin
Fe3+ Fe3+
TFR
TFR
TFR
Fe3+
Fe3+
Endosome
Serum
Cytoplasm


Ferroportin
Duodenal Fe absorption
ferroportin
1-2 mg/d
Iron-recycling macrophages
ferroportin
ferroportin
1000 mg
Liver
Plasma Fe-Tf
2-3 mg
RBC
2500-3000 mg
20-25 mg/d
Bone marrow
1-2 mg/d
Iron losses


Hepcidin
Liver
Hepcidin
Hepcidin
hepatocytes
Iron excess
ferroportin
macrophages
Spleen
ferroportin
macrophages
20-30 mg/d
ceruloplasmin
Plasma transferrin
Red Blood Cells
Hepcidin
1-2 mg/d
enterocytes
ferroportin
Duodenum
1-2 mg/d
Losses
20-30 mg/d
Bone marrow
erythroblasts


Ferritin
Fe3+
Fe2+
Fe2+
Fe3+
e-
e-
Protein electron acceptor

- Iron reduction can proceed through two possible mechanisms that involve either a passive diffusion of reducing agents across the ferritin's shell or the transfer of electrons through specific pathways along the protein shell.
- A ferritin protein having 24 subunits binds to 4,000 iron molecules

- Ferroportin is a transmembrane protein that transports iron from the inside of a cell to the outside of the cell.

- Transferrins are glycoproteins that bind and mediate the transport of iron through blood plasma. They are produced in the liver and contain binding sites for two Fe^{3+} ions. Human transferrin is encoded by the TF gene.

- Hepcidin is the main iron regulatory hormone. It is a 25-amino acid peptide exclusively synthesized by the liver (encoded by the HAMP gene) and secreted into the circulation.
- It controls the delivery of iron to blood plasma from intestinal cells absorbing iron, erythrocyte-recycling macrophages, and iron-storing hepatocytes.

Factors Influence Iron Absorption

1. At physiological pH, ferrous iron (Fe^{2+}) is rapidly oxidized to the insoluble ferric (Fe^{3+}) form

2. A number of dietary factors influence iron absorption

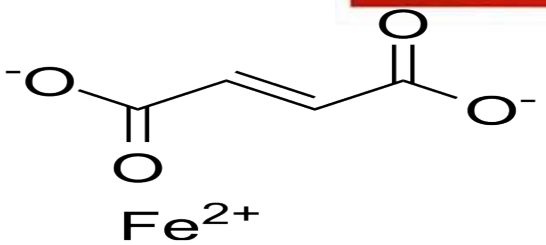
3. Lead is a particularly pernicious element to iron metabolism

4. Immaturity of the gastrointestinal tract can exacerbate iron deficiency in newborns

Medicinal Uses of Iron Products

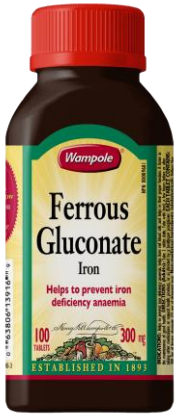
Ferrous Fumarate

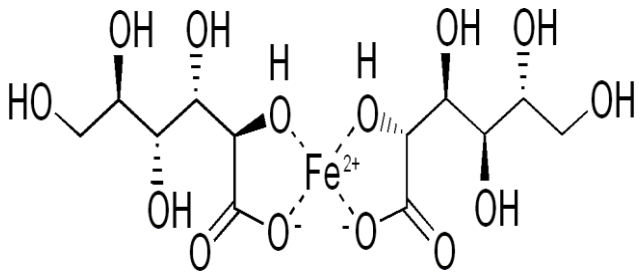
- (Mol. Wt. 169.9, Fe = 55.8 a.m.u)
- Iron content: (32.8% elemental iron)
- It has been assumed that Ferrous Fumarate is less irritating than ferrous sulfate if one administers equivalent doses of iron.
- One of the useful attributes of this salt is its resistance to oxidation on exposure to air.
- Usual Dose: 200 mg (the equivalent of 65 mg of elemental iron) two or three times a day.



Ferrous Gluconate

- (Mol. Wt. 482.18, Fe = 55.8 a.m.u)
- Iron content: (11.6% elemental iron)
- It was a great improvement as it has good bioavailability.
- It is doubtful if it is any less irritating than ferrous fumarate or sulfate when equivalent doses of iron are administered.
- Usual Dose: 300 mg
- Elemental iron= 36 mg



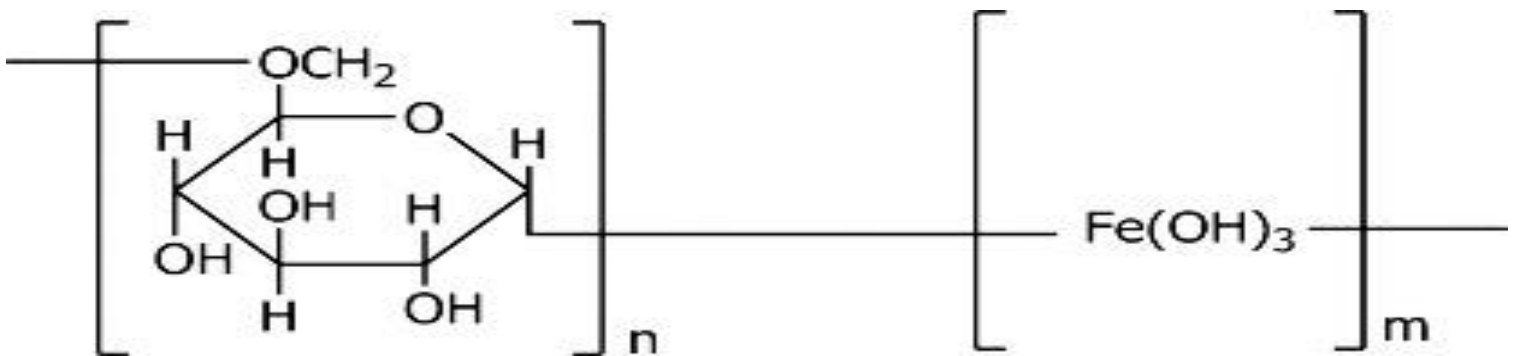


Ferrous Sulfate

- ($FeSO_4.7H_2O$; Mol. Wt. 278.02, Fe = 55.8 a.m.u) (20% iron)
- &Ferrous Sulfate oxidizes readily in moist air to form brownish-yellow basic ferric sulfate [$Fe_4(OH)_2(SO_4)_5$].
- Ferrous sulfate is the most widely used oral iron preparation and is considered the drug of choice for treating uncomplicated iron deficiency anemia.
- #It can be irritating to the gastrointestinal mucosa due to the astringent action of soluble iron.
- Usual Dose: 300 mg ==> 60 mg of elemental iron.

➢Iron Dextran Injection

- It is a sterile, colloidal solution of ferric hydroxide **$Fe(OH)_3$** complexed with partially hydrolyzed dextran (glucose polymer) of low molecular weight, in Water for Injectio.
- It is used only in confirmed cases of severe iron-deficiency anemia where oral therapy is contraindicated or ineffective, or if the patient cannot be relied upon to take oral medication.
- It should not be used in a prophylactic manner.
- Anaphylactic (severe allergic response) reactions, including three deaths, have been reported.
- A recent study indicates that iron dextran is effective in iron deficiency anemia only when the bone marrow iron stores are depleted.
- In iron-deficiency anemia Usual Dose: Intramuscular, the equivalent of 100 mg of iron once a day.



➢Ferric carboxymaltose

- Ferric carboxymaltose (**Ferinject®**) is a novel iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell.
- 50 mg of elemental iron per milliliter.
- The iron slowly dissociates from the complex and is used for hemoglobin synthesis.

✓ Doesn't contain dextran or modified dextrans and doesn't react with dextran antibodies therefore the risk of anaphylactic reactions is very low.

✓ Unlike iron sucrose, it has a near **pH (5.0 to 7.0)** and physiological osmolarity

✓ More stable than sodium ferric gluconate and iron sucrose, producing a slow delivery of iron to the binding site, and has an acute toxicity in animals 1/5 that of iron sucrose.

✓ Much higher doses over a short period of time can be administered:

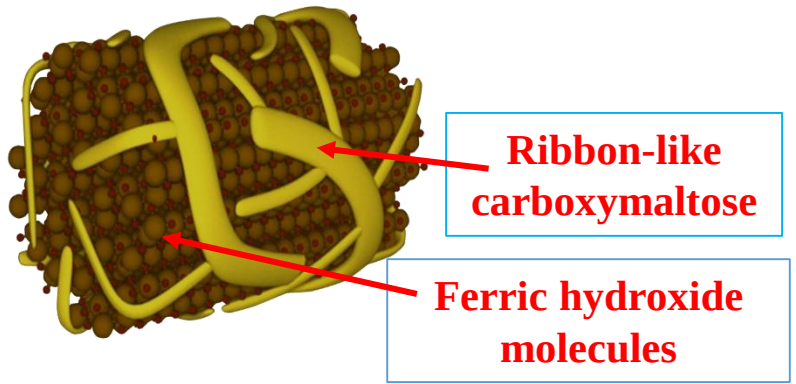
- Fewer administrations needed
- increase patient's comfort.

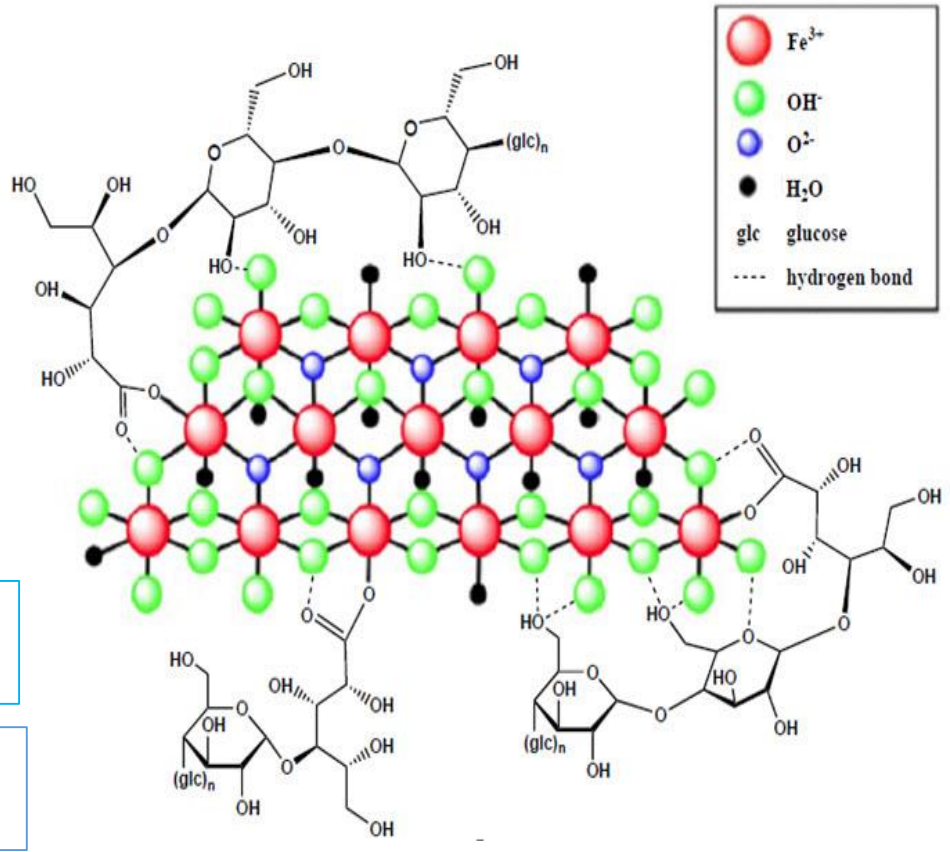
✓ Better suited for outpatient use:

-lesser number of infusions required

-test dose not required

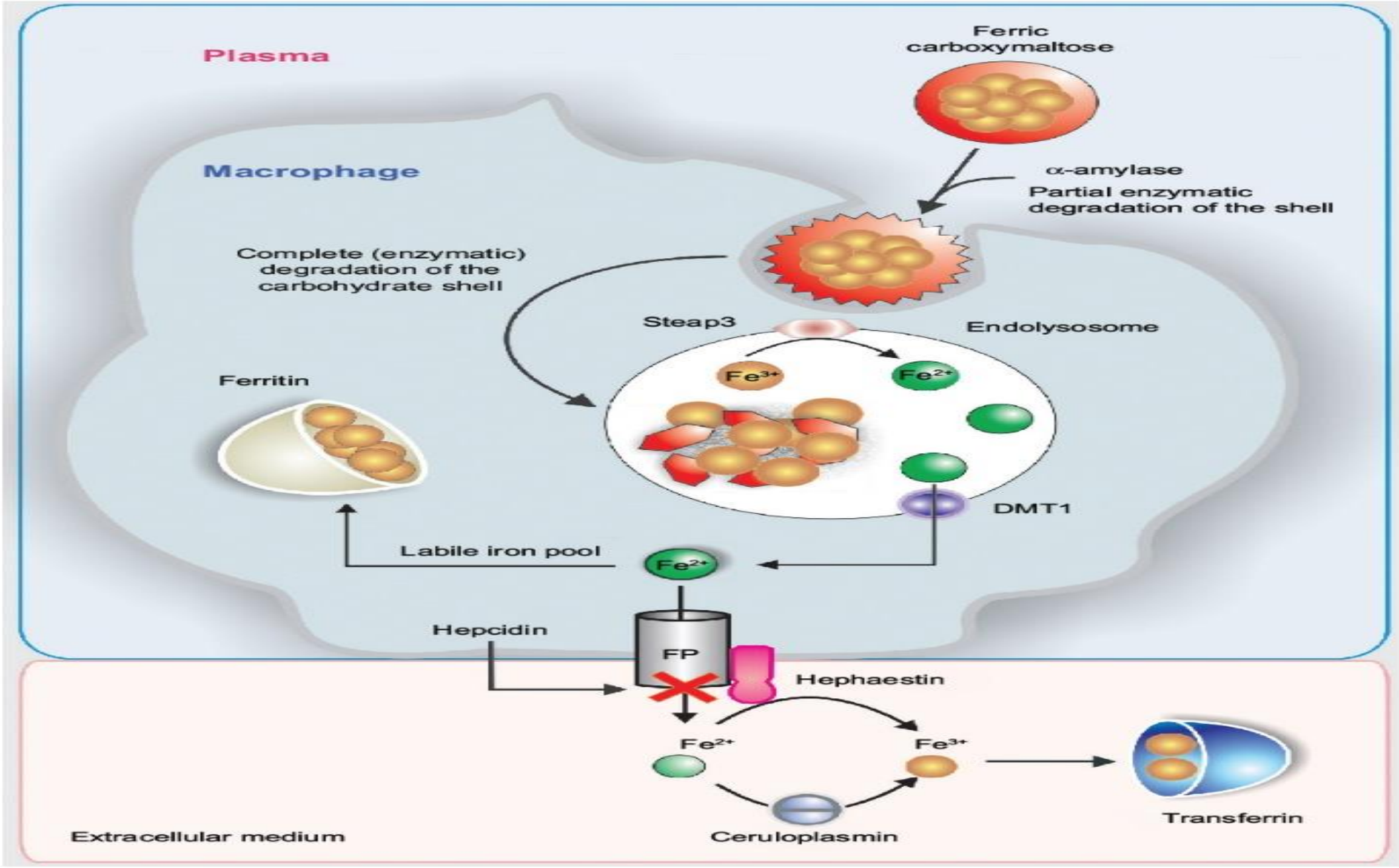
-higher dose can be administered





Mechanism Action of Ferric Carboxymaltose (FCM)

- # Once in the body, iron is released gradually, avoiding the acute toxicity of many other iron compounds but allowing large amounts of iron to be delivered.
- After IV FCM administration, the carbohydrate shell is incompletely broken down in the blood by α-amylase.
- Macrophages take the FCM by an endocytic mechanism by which the carbohydrate shell and the polynuclear iron core may be completely broken down in the endolysosomes to release Fe3+.
- A six-transmembrane epithelial antigen of the prostate 3 (Steap3) is likely to reduce the released Fe3+ into Fe2+.
- The Fe(II) is released by (DMT1) then by ferroportin and taken up by transferrin after oxidation by ceruloplasmin.
- Fe2+ is extruded from the endolysosomes to the cytosolic labile iron pool by the activity of DMT1 and from the cytosol to the plasma by FPN. Finally, it is transported by TF to the liver, bone marrow, and other tissues.
- The LD50 (i.e. the dose that kills 50% of experimental mice) is just 11 mg Fe/kg for iron sulfate (FeSO4), around 50 for Fe(III) gluconate, >200 for iron sucrose, >2500 for iron dextran1. For FCM the LD50 is >1000 mg Fe/kg body weight.
- In less stable complexes, iron is released rapidly from the complex causing high levels of transferrin saturation (60-100%) and therefore non-transferrin bound iron (NTBI). This NTBI, outside the macrophage, is highly toxic. Small amounts of iron in the serum (about 3 mg/l) can result in almost complete transferrin saturation.


Plasma
Ferric carboxymaltose
Macrophage
α-amylase
Partial enzymatic degradation of the shell
Complete (enzymatic) degradation of the carbohydrate shell
Steap3
Endolysosome
Ferritin
Fe3+
Fe2+
DMT1
Labile iron pool
Fe2+
Hepcidin
FP
Hephaestin
Fe2+
Fe3+
Transferrin
Extracellular medium
Ceruloplasmin

Copper

- In the human body, the majority of copper ions can be found as **Cu(II)**; nevertheless, the oxidation state shifts between the **Cuprous (Cu^{+})** and **Cupric (Cu^{2+})** forms.
- Copper is found in the brain in the form of **cerebrocuprein**, in blood cells as **erythrocuprein**.
- Typically, **50%** of the daily copper intake is absorbed in the **GI tract**. Copper is solubilized in stomach acid and absorbed from the stomach and upper small intestine, from intestine Copper moves into the blood where it exists first as **copper albumin complex**, then goes to the liver where the copper is either stored, incorporated into **ceruloplasmin** [Ceruloplasmin is the major copper-carrying protein in the blood], or excreted in the bile.
- A diet rich in copper: red meat, shellfish, water pumped through copper pipes
- The body content of copper is 80-120 mg

➢ Several roles in metabolism have been attributed to copper:

✓ Copper is utilized in hemoglobin formation.

✓ Copper is required to prevent anemic conditions through:

1. facilitates iron absorption.
2. Stimulates enzymes involving heme and globin biosynthesis.
3. Could be involved in the metabolism of stored iron.

✓ Copper is important in oxidative phosphorylation (ATP production) .

✓ Copper is associated with the formation of aortic elastin.

✓ Copper is a component of tyrosinase, an enzyme responsible for the conversion of tyrosine to the black pigment, melanin.

Wilson disease

- Wilson disease is a genetic disorder in which excessive amounts of copper build up in the human body.

- The copper is mainly stored in the liver and brain and therefore causes liver cirrhosis and damage to the brain tissue.

- The damage to the brain tissue occurs mainly at the lenticular nucleus and a typical brown ring is visible around the iris.

- The abnormal gene was identified to be ATP7B, a metal-transporting adenosine triphosphatase (ATPase) mainly expressed in hepatocytes, which has the main function of transporting copper across the membrane. This means that, in the absence of this gene, the excretion of copper via the liver is reduced. This leads to copper accumulation in the liver, which damages the liver and eventually releases copper into the bloodstream where it can further poison the organs.

- Mainly the brain, kidneys, and cornea are affected by copper accumulation.

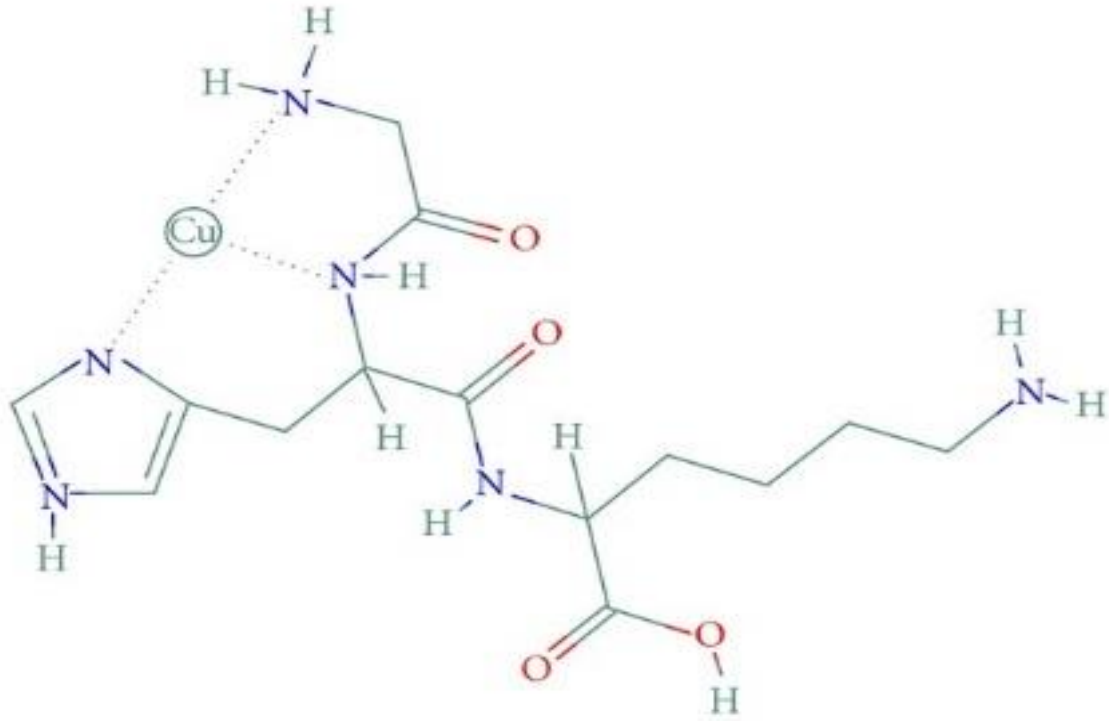
Glycyl-l-histidyl-l-lysine (GHK or GHK-Cu(II))

- GHK–Cu(II) is a tripeptide known for its high binding affinity to Cu(II) and its complex role in wound healing.
- GHK–Cu(II) has two main functions:

1) as an anti-inflammatory agent to protect the tissue from oxidative damage after the injury.

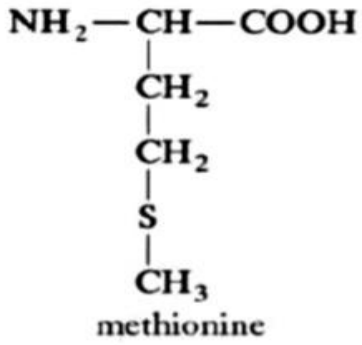
2) as an activator for wound healing itself as it activates the tissue remodeling.

❑ After the initial stages of wound healing are activated, such as blood coagulation and neutrophil invasion, a second stage of wound healing begins, **Mast cells**, which are located in the skin, secrete GHK, which accumulates Cu(II) and form the copper complex GHK–Cu(II) and therefore increases the metal–tripeptide concentration at the wound.

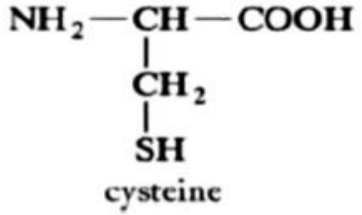


Sulfur

- Sulfur is widely distributed throughout the body as sulfhydryl groups of cysteine, disulfide linkages in protein from cystine, and sulfate salts and esters found in mucopolysaccharides and sulfolipids, Dietary sulfur comes from these same groupings found in plant and animal foodstuffs.
- The minimum daily requirements are 2-3 g.
- Currently, there seems to be no need for dietary supplements of sulfur.
- Sulfur is the third most abundant mineral in your body, it is an essential component of all living cells.
- Both of these amino acids (methionine and cysteine) are present in your skin, hair, and nails and they help to make these tissues strong and flexible.
- A 70 kg human body contains about 140 grams of sulfur.



methionine



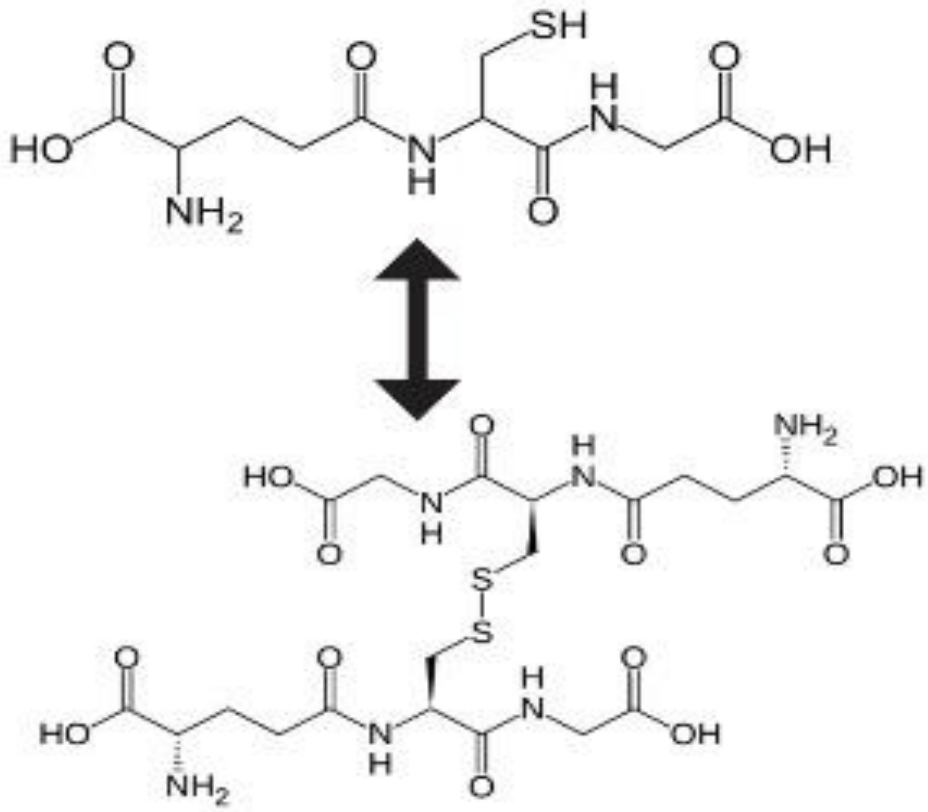
cysteine

Synthesis of Glutathione (GSH)

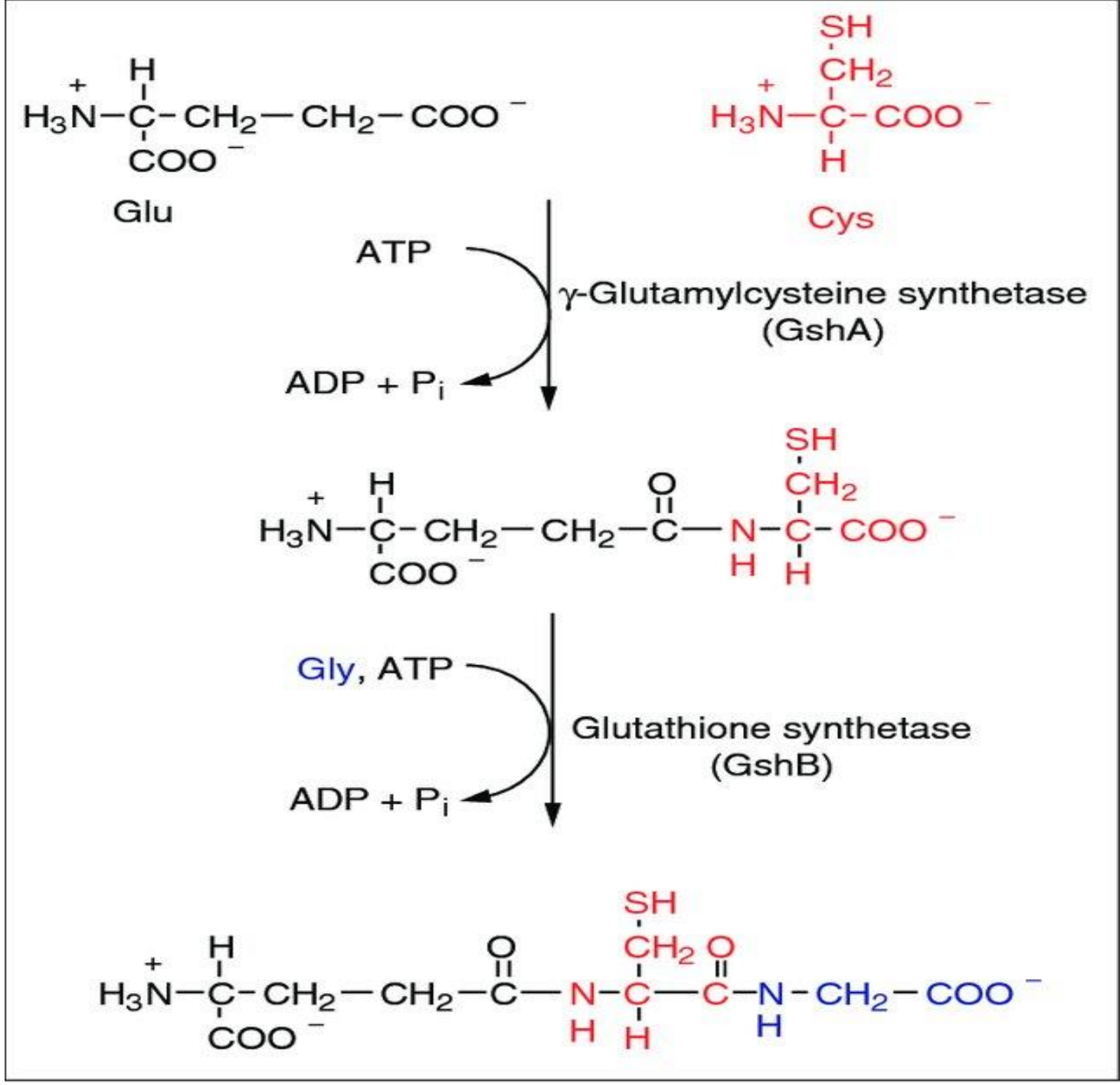
- **Glutathione** is a tripeptide (cysteine, glycine, and glutamic acid) found in surprisingly high levels—5 millimolar—concentrations in most cells.
- Glutathione exists in cells in 2 states: reduced (GSH) and oxidized (GSSG).
- GSH is synthesized in the cytosol of all mammalian cells in a tightly regulated manner.

❖Function of glutathione:

1. Antioxidant activity. Free radicals may contribute to aging and some diseases.
2. Preventing cancer progression.
3. Reducing cell damage in liver disease.
4. Improving insulin sensitivity.
5. Reducing symptoms of Parkinson's disease.
6. Reducing ulcerative colitis damage.
7. Treating autism spectrum disorders.

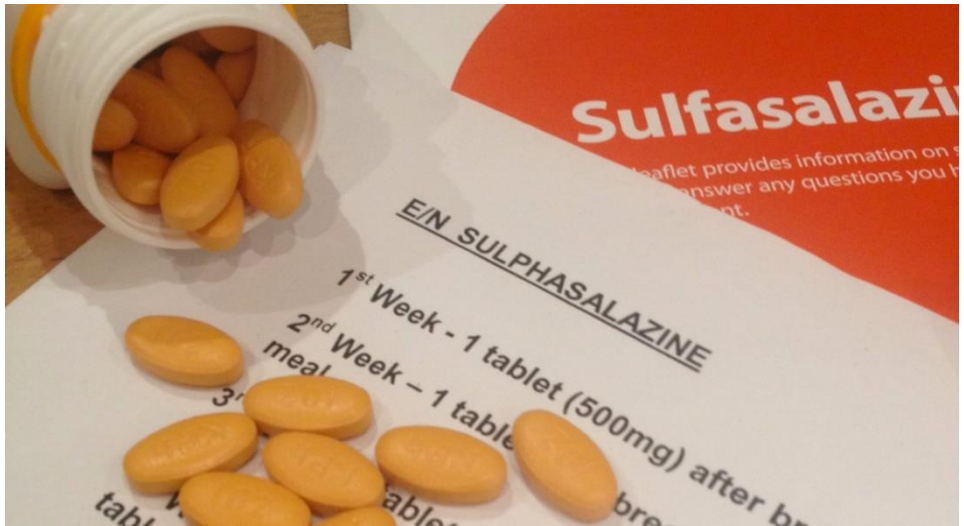


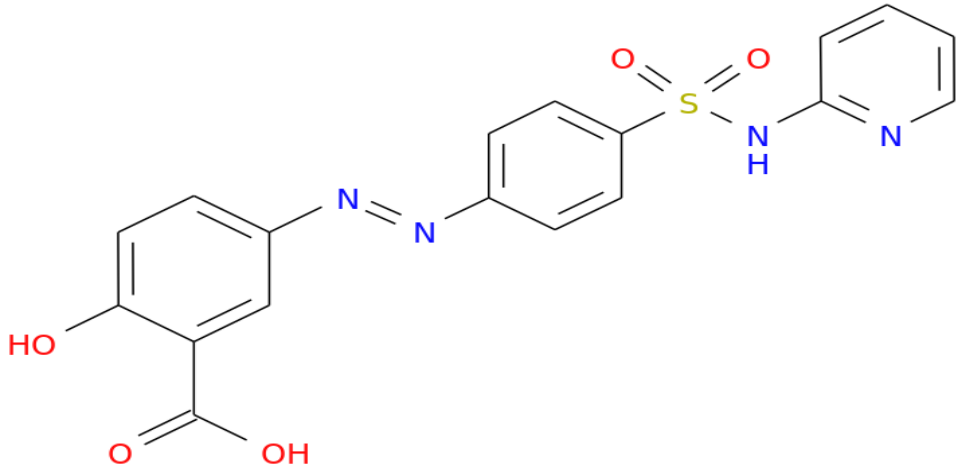
❖ The biosynthesis of GSH requires only two enzymes. γ-Glu-Cys ligase (GshA) catalyzes the formation of a peptide bond between the γ-carboxylate of glutamate and cysteine. GSH synthetase (GshB) catalyzes the subsequent formation of a peptide bond between the cysteinyl carboxylate of γ-Glu-Cys and the amino group of glycine. Each of these reactions requires hydrolysis of ATP to drive the formation of the peptide bond.



Sulfasalazine

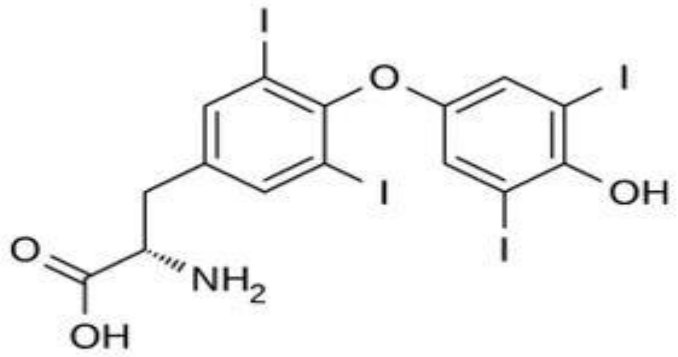
- Sulfasalazine is used to treat ulcerative colitis (UC) and rheumatoid arthritis
- Chemical Designation: **5-([p-(2-pyridylsulfamoyl)phenyl]azo) salicylic acid**.
- Drink plenty of fluids while taking sulfasalazine.
- Sulfasalazine can affect folate absorption, so you should also take folic acid (1 mg per day) while taking the medication and if you are pregnant, you should take 2 mg of folic acid a day.
- **Common side effects:** The most common side effects of sulfasalazine are headache, nausea, fever, rash, and reversible infertility in men.



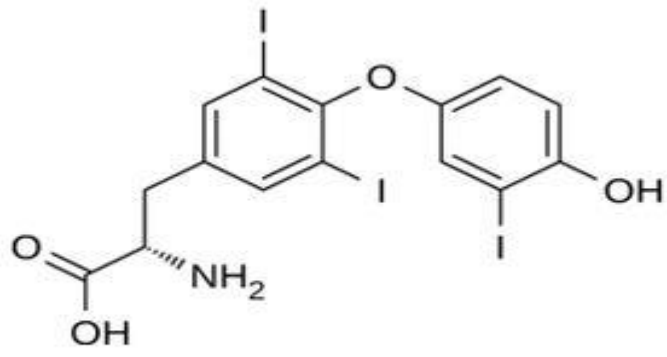


Iodine (Iodide)

- Iodide is an essential ion necessary for the synthesis of the two hormones produced by the thyroid gland, triiodothyronine (T_3) and thyroxine (T_4).



Thyroxine (T4)

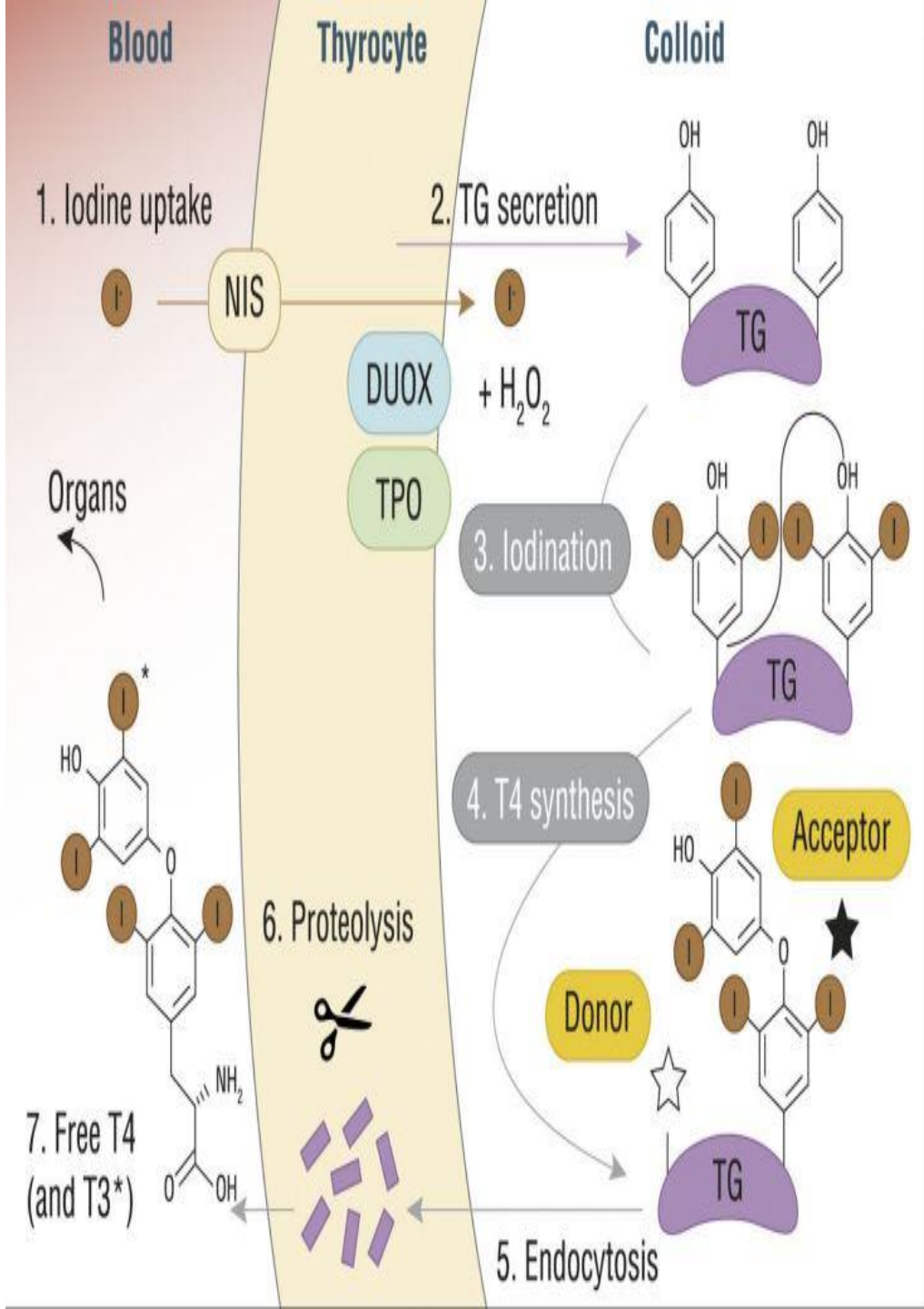


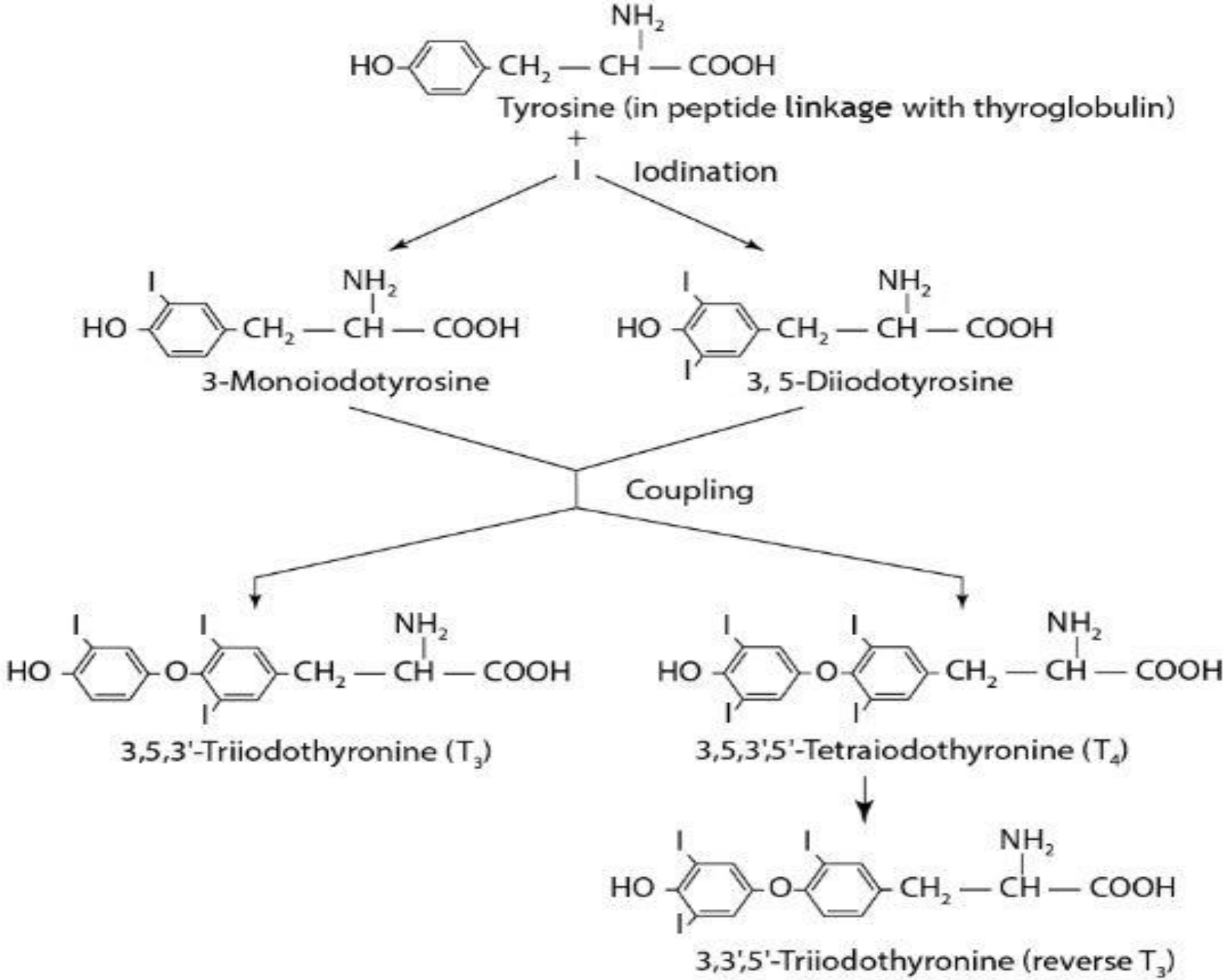
Triiodothyronine (T3)

- Internally iodine or iodide can be administrated since iodine is reduced to iodide in the intestinal tract. For solubility reasons, it is more common to administer an iodide salt.
- Iodine can be discussed from two standpoints: (1) its biochemical role in thyroid hormone formation; and (2) its pharmacological action as a fibrolytic agent, expectorant, and bactericidal agent.

- The usual daily iodine requirement for an average man is approximately 140 micrograms and for an average female about 100 micrograms.
- Lack of sufficient iodine in the diet results in an enlargement of the thyroid gland, known as simple or colloid goiter. It is characterized by a swelling at the neck.
- The enlargement of the thyroid gland is a compensatory mechanism whereby the body attempts to make up for the hormone deficiency by increasing the size of the gland.
- Endemic goiter is almost always the result of a dietary deficiency of iodine.
- Today adequate amounts of iodine are easily insured by the use of iodized table salt containing 0.01% potassium iodide.
- TH biosynthesis occurs at the interface between the follicular lumen and the apical plasma membrane of thyrocytes, and it depends on the interaction of essential components: iodine (I_2), a H_2O_2-dependent peroxidase called thyroperoxidase (TPO), and thyroglobulin (TG), which works as iodine acceptor.
- After intestinal adsorption, iodide enters the thyroid through the sodium/iodide symporter (NIS), a transport protein located in the basolateral plasma membrane of thyrocytes, and then it enters the follicular lumen crossing the apical membrane through a carrier called Pendrin.
- Once in the thyroid follicular lumen, iodide is incorporated into the TG, which is the predominant protein in the thyroid.

- TPO incorporates iodine into TG using H_2O_2 as the final electron acceptor.
- Once all the elements are present at the interface of the follicular lumen and at the apical plasma membrane of thyrocytes, the hormonogenesis process can occur in the follicular lumen. More specifically, TH synthesis comprises the following steps: 1) oxidation of TPO by H_2O_2; 2) oxidation of iodide ions by the TPO; 3) iodination of tyrosyl residues on Tg to form iodotyrosine moieties; 4) oxidation and coupling of iodotyrosine residues to form the final hormones, T3 and T4.
- After the incorporation of oxidized iodide into the TG, through a process of iodination or iodine organification that generates either monoiodotyrosine (MIT) or diiodotyrosine (DIT) residues, the final step consists of coupling neighboring residues to form the final hormones. Specifically, the coupling of two DIT residues yields T4, while the coupling of DIT with MIT yields T3. TPO and H_2O_2 catalyze the coupling reaction.




NH2
HO
CH2 — CH — COOH
Tyrosine (in peptide linkage with thyroglobulin)
+
I
Iodination
I
NH2
HO
CH2 — CH — COOH
3-Monoiodotyrosine
I
NH2
HO
CH2 — CH — COOH
I
3, 5-Diiodotyrosine
Coupling
I
I
NH2
HO
O
CH2 — CH — COOH
I
3,5,3'-Triiodothyronine (T3)
I
I
NH2
HO
O
CH2 — CH — COOH
I
3,5,3',5'-Tetraiodothyronine (T4)
I
I
NH2
HO
O
CH2 — CH — COOH
I
3,3',5'-Triiodothyronine (reverse T3)

- Internally iodine or iodide can be administered since iodine is reduced to iodide in the intestinal tract but more common iodide salts are administered because of solubility reasons.
- Iodine has:

1. biochemical role in thyroid hormone formation.
2. Pharmacological action as:
    I. Fibrinolytic agent.
    II. Expectorant.
    III. Bactericidal agent.

When iodine is administered its uptake by the thyroid gland is governed by three principal factors:

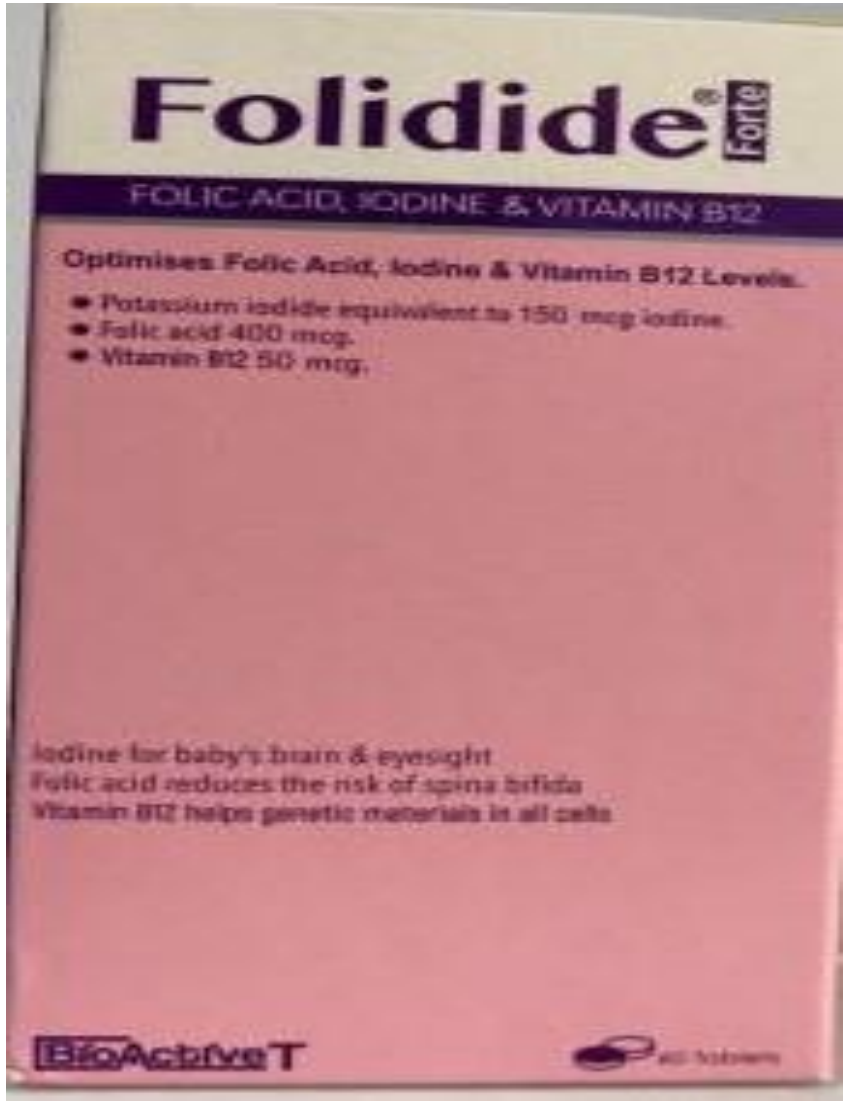
A. The character of local thyroid tissue because abnormal thyroid tissue (tumorous) has a slower uptake of iodide and a lower content of iodine than normal tissue.
B. Blood level of inorganic iodide because high level keeps the iodine at a high level in the colloids thus using up only a small part of the administered iodide.
C. The level of Thyroid-stimulating hormone (TSH) in the blood which is a hormone secreted by the pituitary gland that stimulates the uptake of iodide by the gland, incorporates iodine into thyroxin, and stimulates the release of thyroid hormones from the gland.

Excess of iodide inhibits the release of TSH and decreases the production of thyroid hormones.

Official Iodine Products

❑*Folidide*

- Strong Iodine Solution, U.S.P. (Lugol's Solution)
- Contains 5 g of iodine and 10 g of potassium iodide per 100 ml total volume.
- It is a transparent liquid having a deep brown color and odor of iodine.
- Category: Source of iodine.
- Usual Dose: 0.1 to 0.3 ml three times a day.
- Usual Dose Range: 0.1 to 3 ml daily.



❑*Amiodarone*

- Amiodarone is an antiarrhythmic medication used to treat and prevent a number of types of cardiac dysrhythmias.
- Amiodarone is structurally similar to thyroxine and also contains iodine. Both of these contribute to the effects of amiodarone on thyroid function.
- Amiodarone also causes an anti-thyroid action, via Wolff–Chaikoff effect, due its the large amount of iodine in its molecule, which causes bradycardia and arrhythmia.