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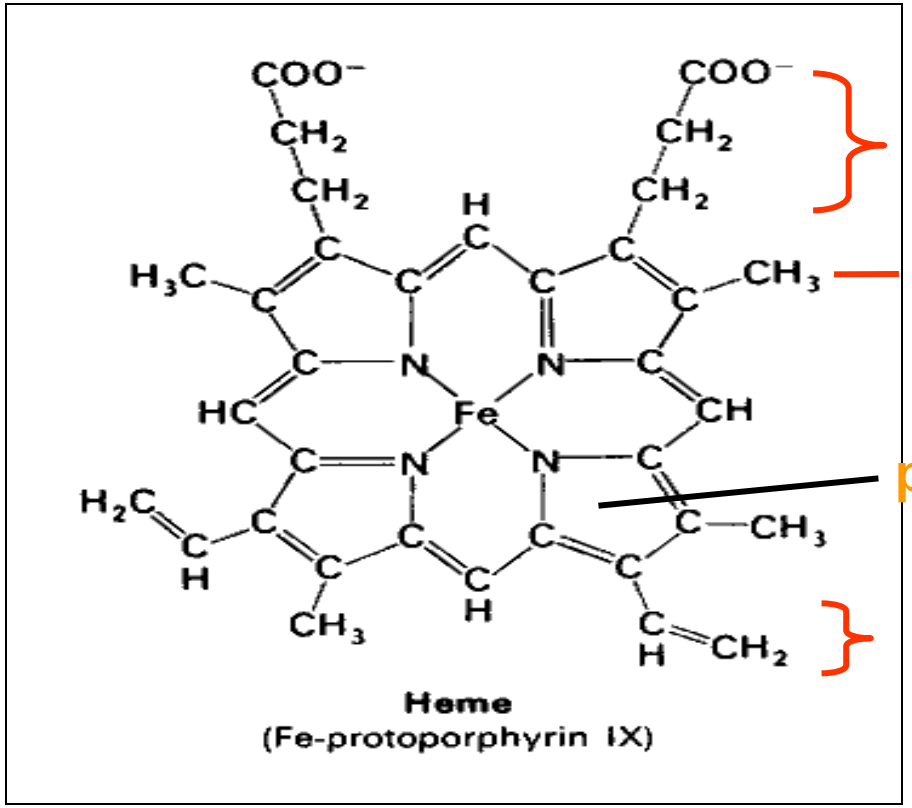
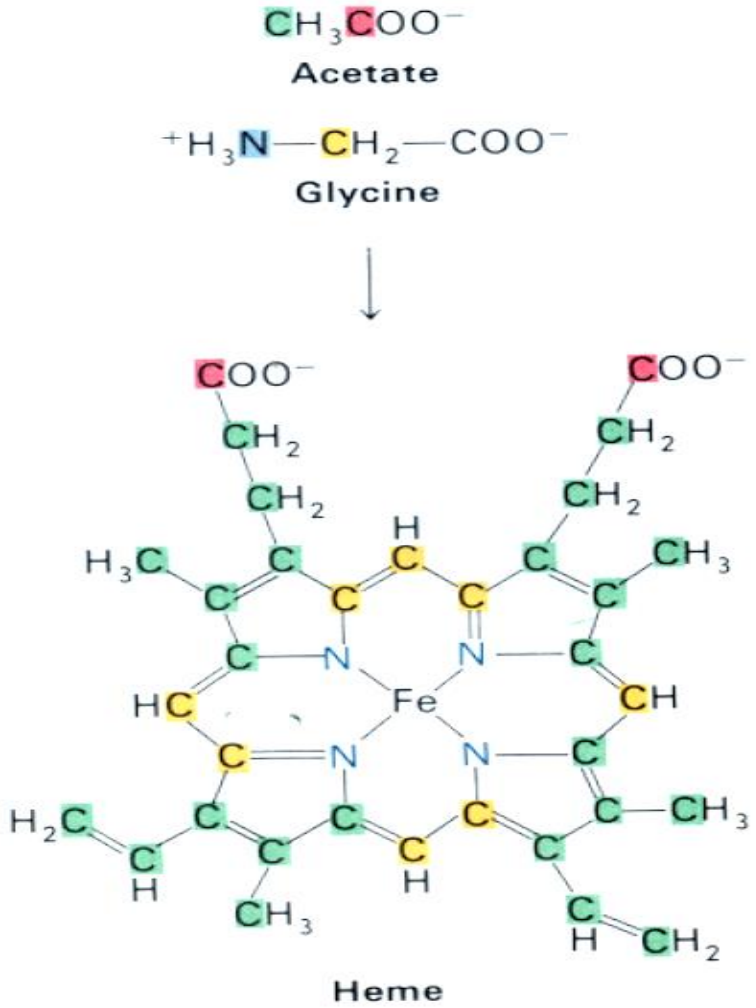
BIOSYNTHESIS OF PORPHYRIN, CREATINE AND CREATININE

Structure and Properties of Iron Protoporphyrin IX





Derived from protoporphyrin IX

Pattern of side chains defines isomer

Binds metals: Heme- Fe^{2+} (ferrous)

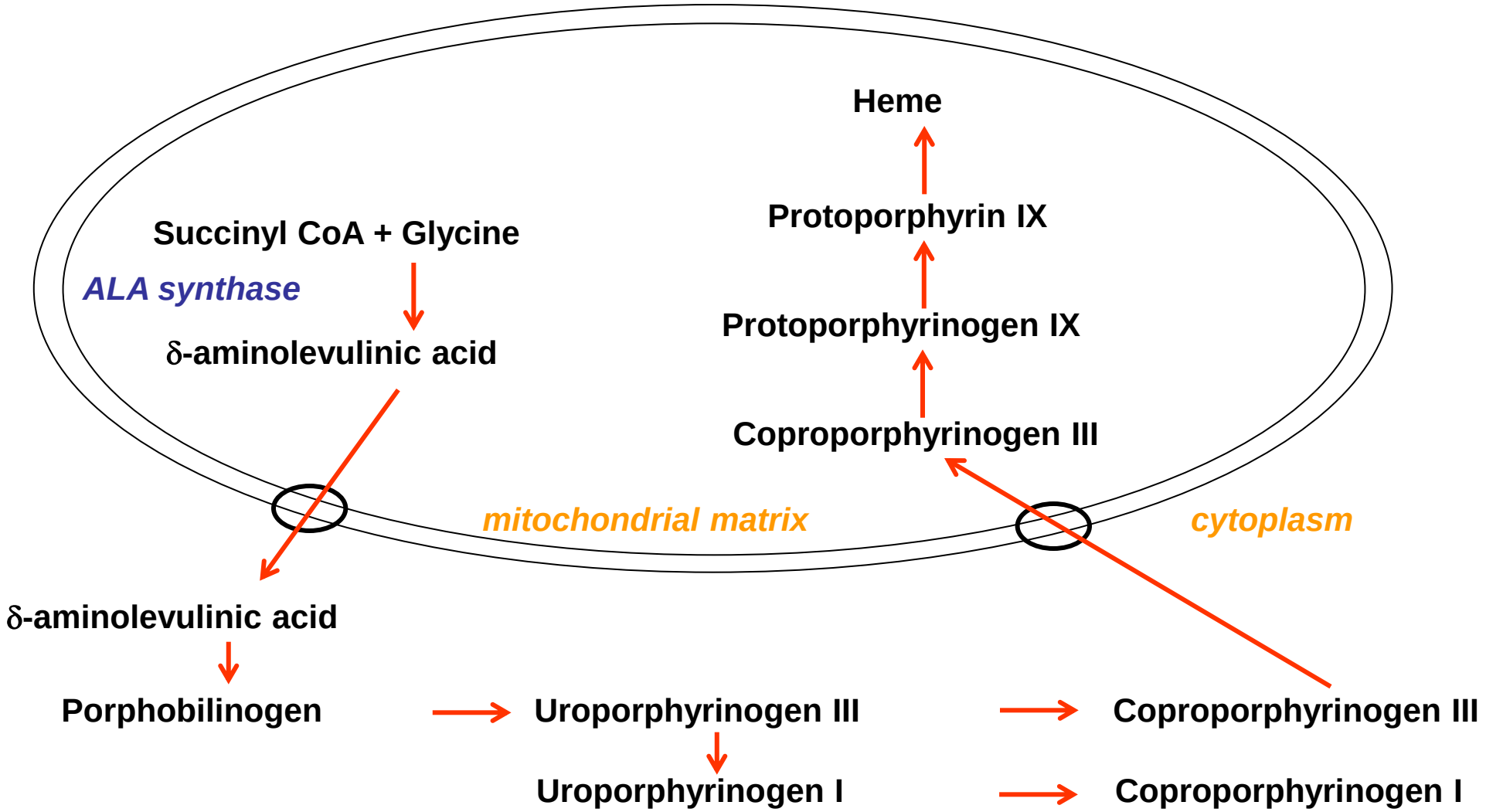
Hemin- Fe^{3+} (ferric)

Zinc protoporphyrin (ZnPP)- Zn^{2+}

Extended conjugation across ring system

Photoreactive generation of Reactive Oxygen Species (ROS)

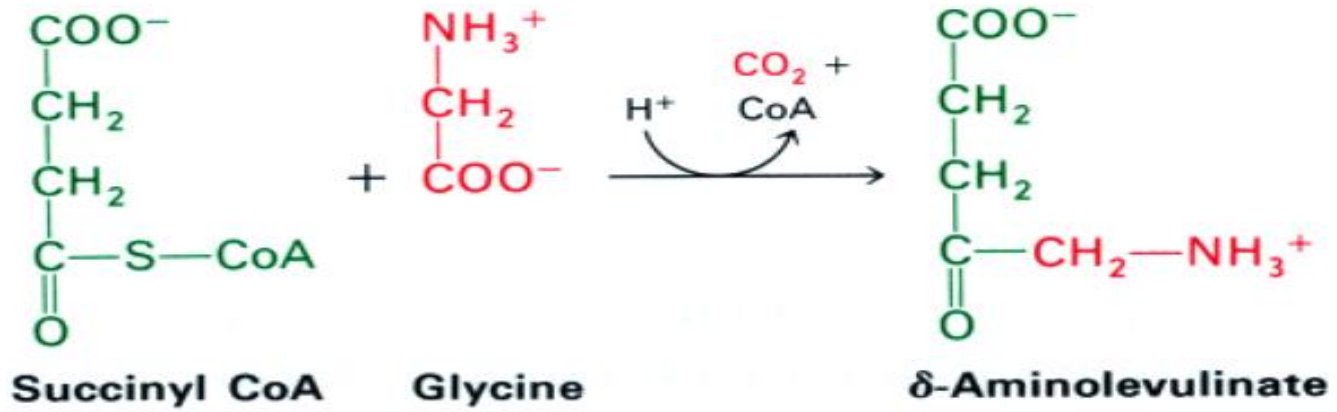
Overview of Heme Synthesis



Heme synthesis occurs in all cells due to the requirement for heme as a prosthetic group on enzymes and electron transport chain. By weight, the major locations of heme synthesis are the liver and the erythroid progenitor cells of the bone marrow.

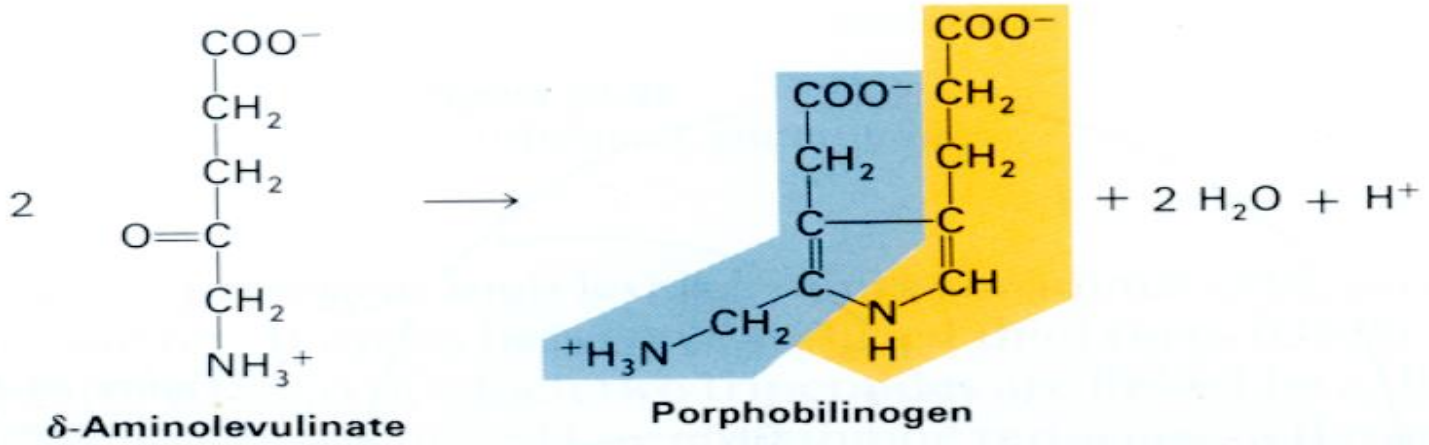
δ-Aminolevulinate (ALA) Synthase

is the Committed Step for Heme Biosynthesis



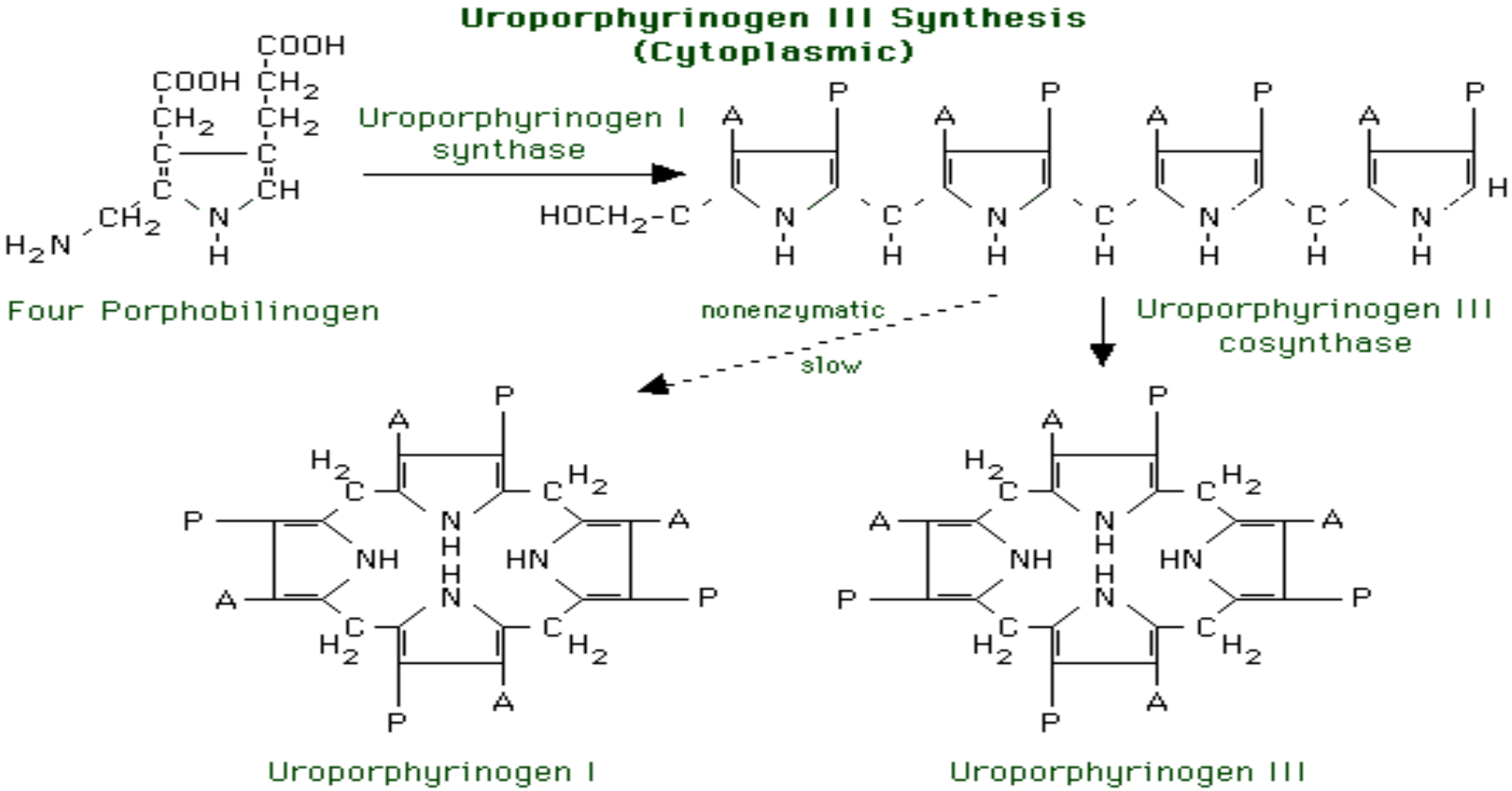
- Rate limiting committed step; requires pyridoxal-5'-phosphate as coenzyme
- Transcriptional regulation is the principal form of control since the enzyme has a short half life ($t_{1/2}$ = 1 hr). Heme and hemin repress transcription
- In erythrocytes heme synthesis is coordinated with that of the globin chains, all of which are stimulated by erythropoietin (Epogen©, Procrit©, and congeners)
- Heme and hemin allosterically inhibit ALA synthase
- Aromatic drugs, xenobiotics, and steroids induce synthesis of ALA synthase and can exacerbating certain porphyrias (later)

δ-Aminolevulinate (ALA) Dehydratase



- Asymmetry of the reaction results in acetate and propionate side chains
- The enzyme active site contains a required cysteine, making the enzyme sensitive to inactivation by lead (Pb^{2+}) and other heavy metals
- Increased urinary excretion of δ-aminolevulinate is a leading indicator of heavy metal poisoning

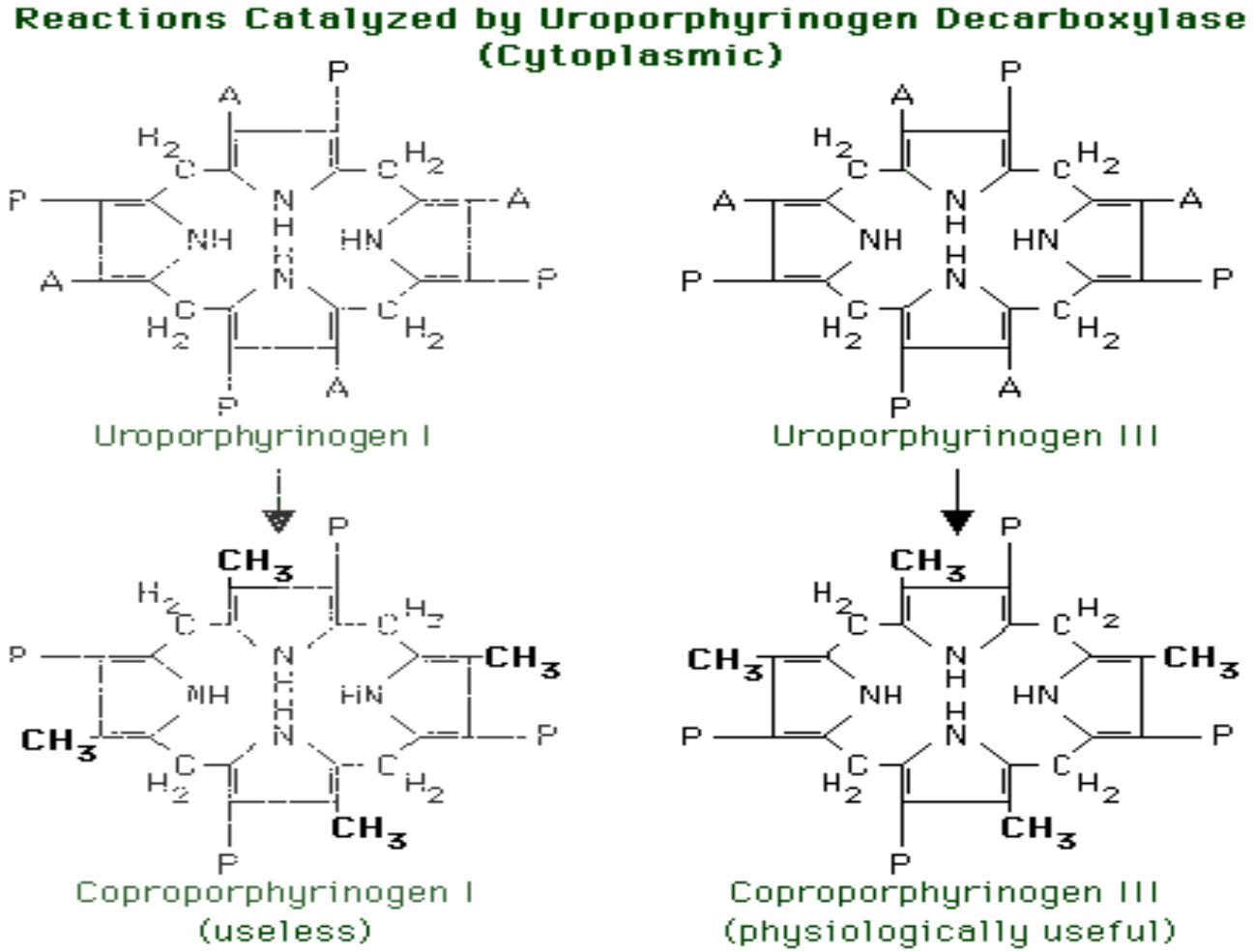
Formation of the Final Ring Requires a Bi-functional Enzyme



This step occurs by elimination of the primary amines as the methylene adds across the double bond of the pyrrole ring.

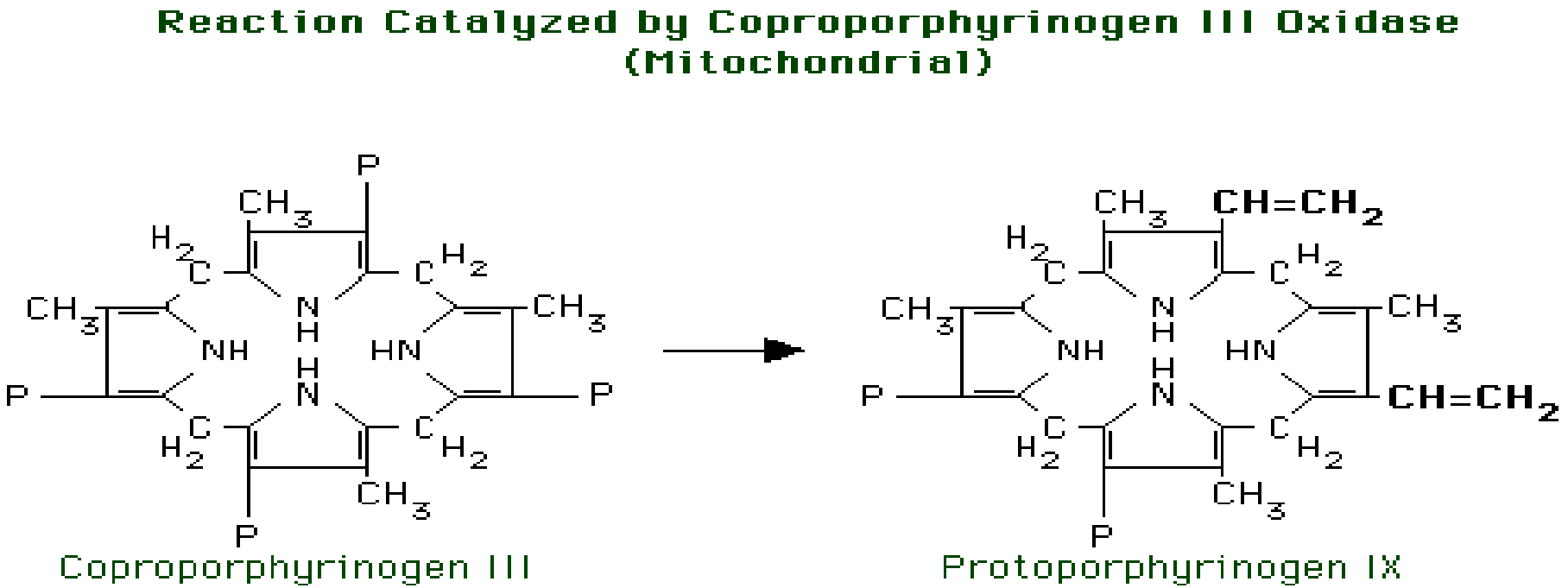
Note: Uroporphyrinogen I synthase is alternate name for Hydroxymethylbilane synthase

Uroporphyrinogen Decarboxylase Remodels the Acetate Side Chains

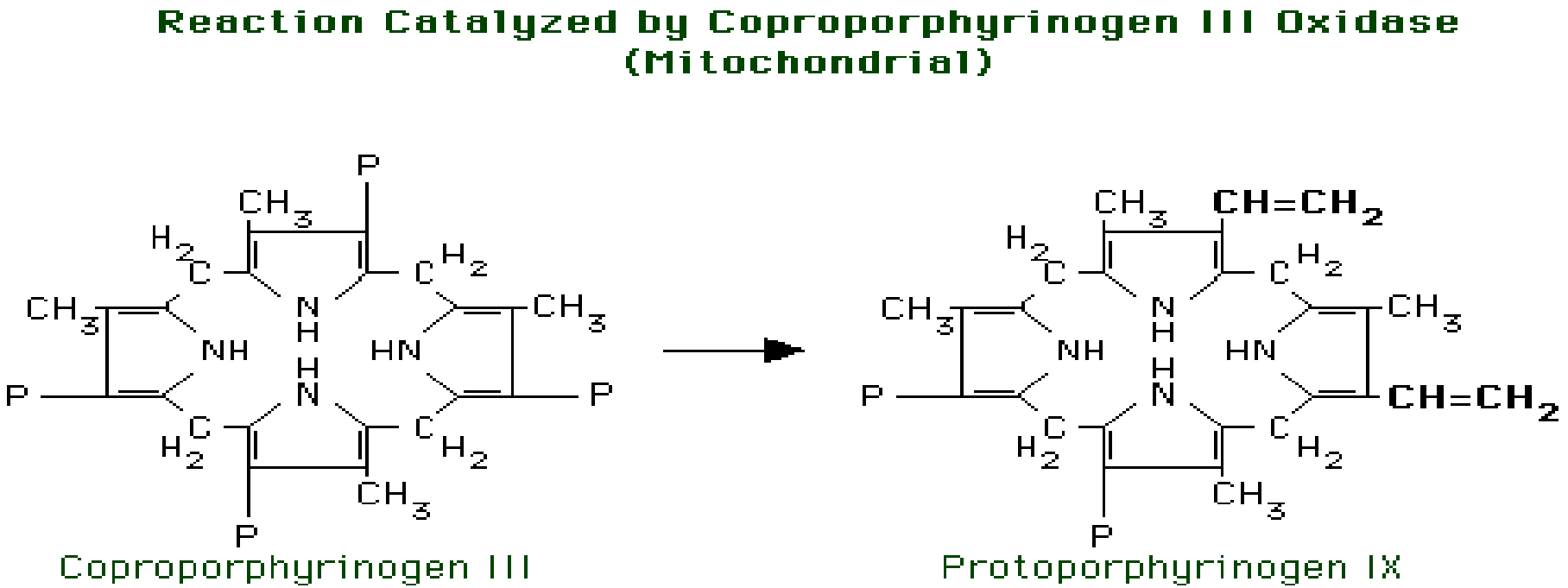


Spontaneously oxidizes to the biologically inactive Coproporphyrin I and III which are subsequently excreted in the urine

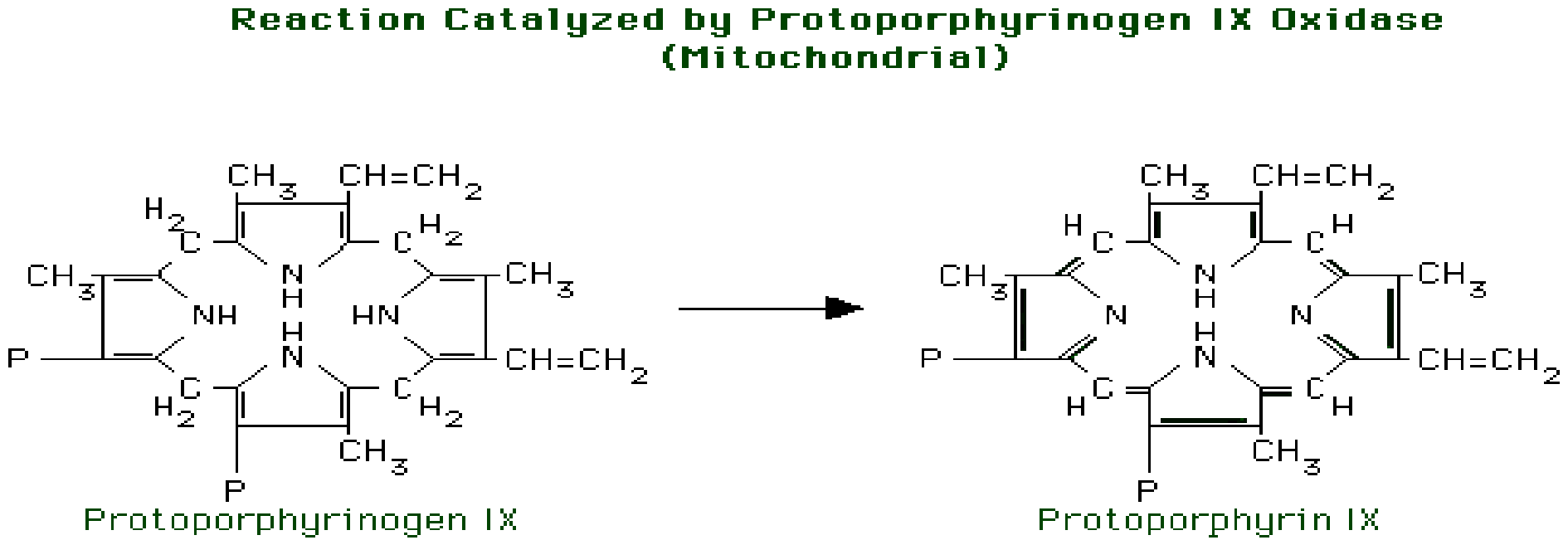
Coproporphyrinogen III Oxidase Catalyzes the Oxidative Decarboxylation of Specific Propionate Side Chains



Coproporphyrinogen III Oxidase Catalyzes the Oxidative Decarboxylation of Specific Propionate Side Chains

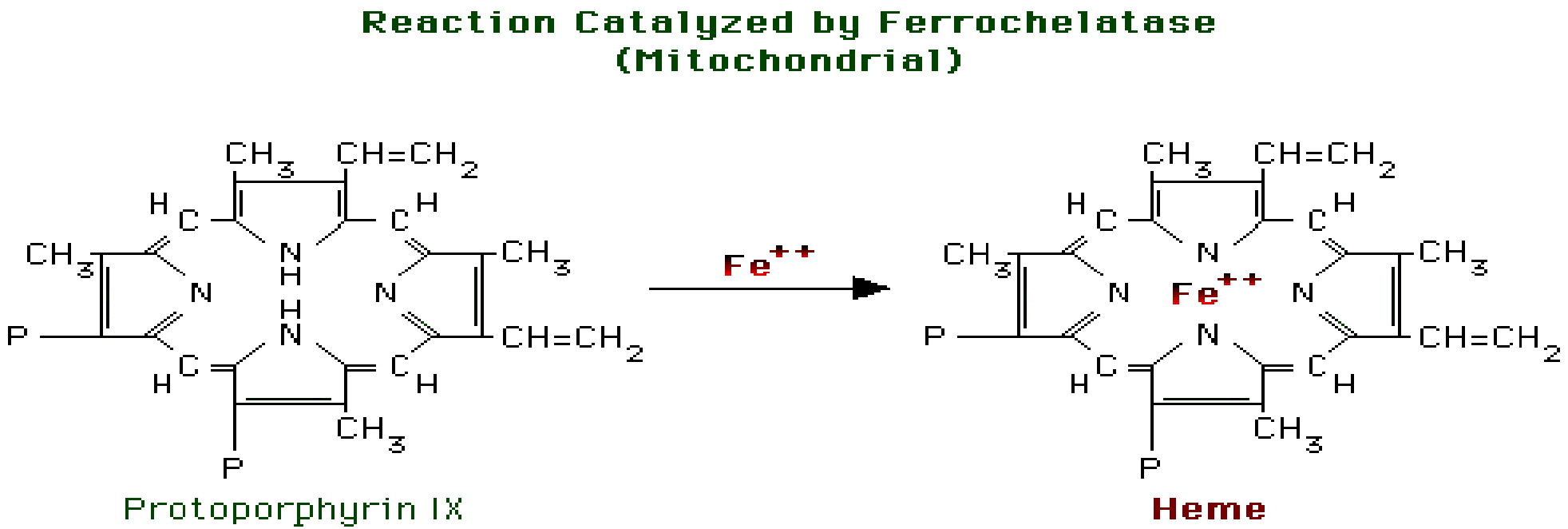


Protoporphyrinogen IX Oxidase



This reaction oxidizes the methylene bridge carbons between the pyrrole rings to methenyl bridge carbons, allowing extended conjugation through the entire tetrapyrrole ring system for the first time.

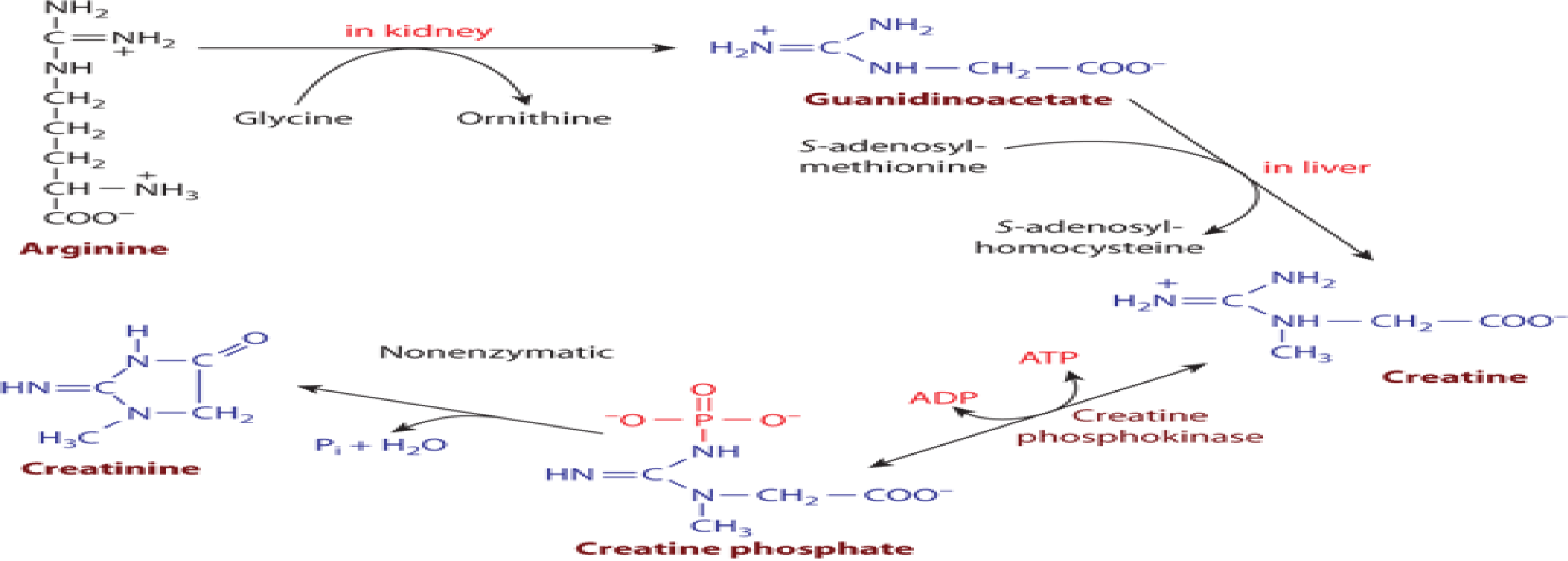
Ferrochelatase



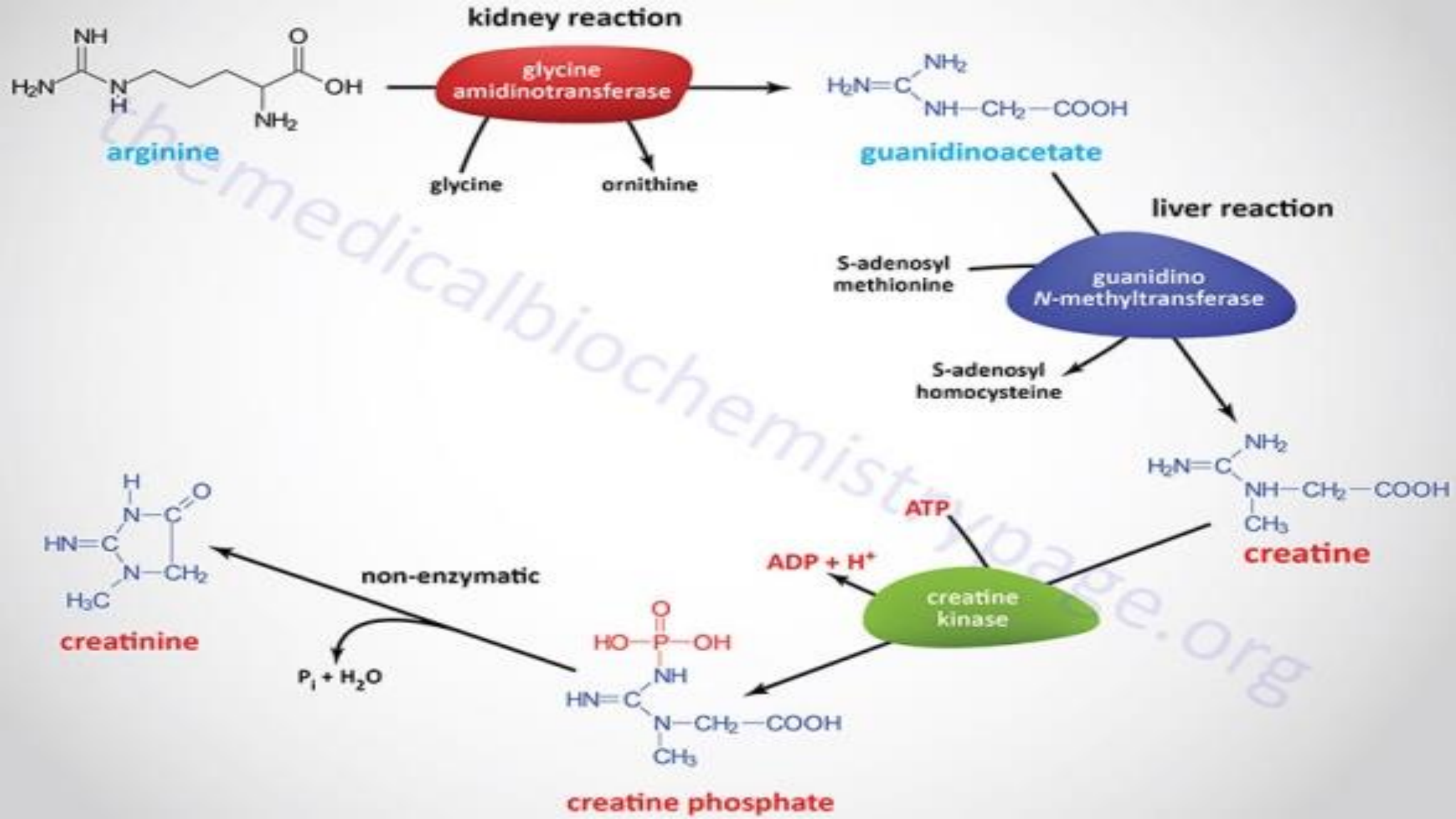
- Inserts Fe^{2+} into Protoporphyrin IX to yield heme
- The reaction also requires ascorbic acid and cysteine as reducing agents
- Lead (Pb^{2+}) acts as a competitive inhibitor of Fe^{2+} but does not insert into protoporphyrin IX

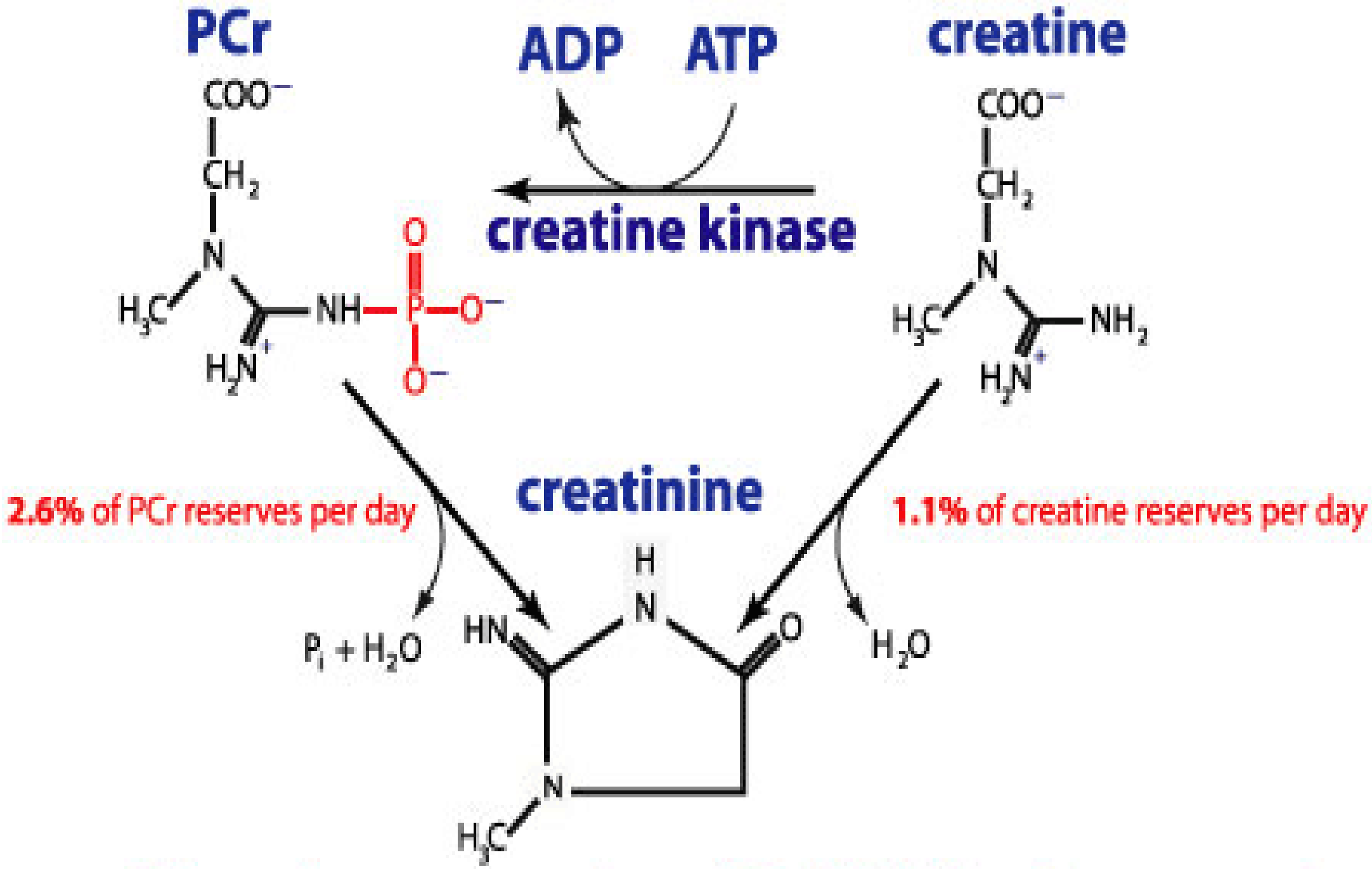
- Iron deficiency leads to insertion of Zn^{2+} to yield zinc protoporphyrin (ZnPP), an important clinical indicator of iron deficiency

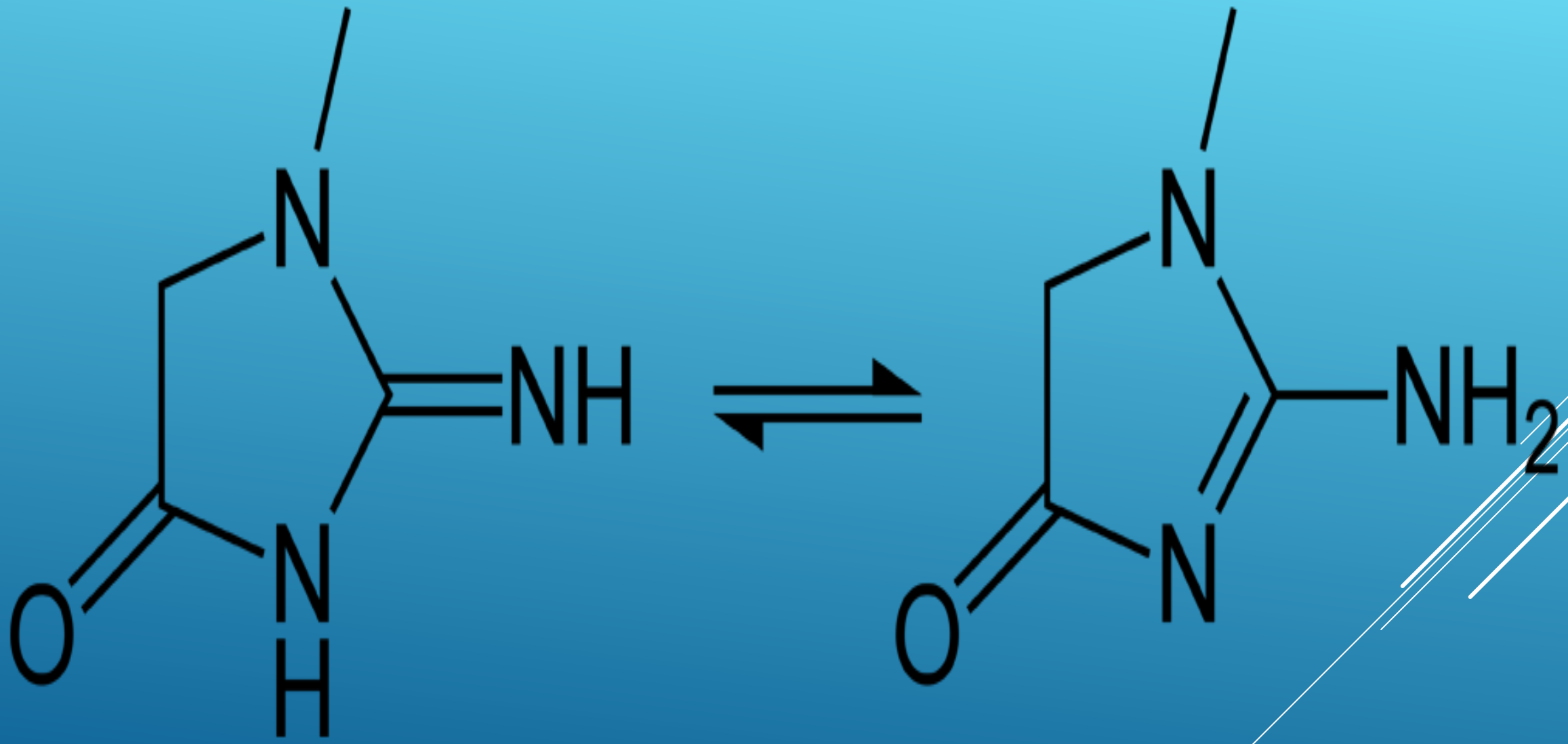
BIOSYNTHESIS OF CREATINE AND CREATININE



arginine:glycine amidinotransferase (AGAT, EC:2.1.4.1) to form guanidinoacetate, which is then methylated by guanidinoacetate N-methyltransferase (GAMT, EC:2.1.1.2), using S-adenosyl methionine as the methyl donor. Creatine itself can be phosphorylated by creatine kinase to form phosphocreatine, which is used as an energy buffer in skeletal muscles and the brain.




PCr
ADP
ATP
creatine
creatine kinase
creatinine
2.6% of PCr reserves per day
1.1% of creatine reserves per day
$P_i + H_2O$
H_2O


N
NH
O
N
H
N
NH2
O
N

Creatine Biosynthesis

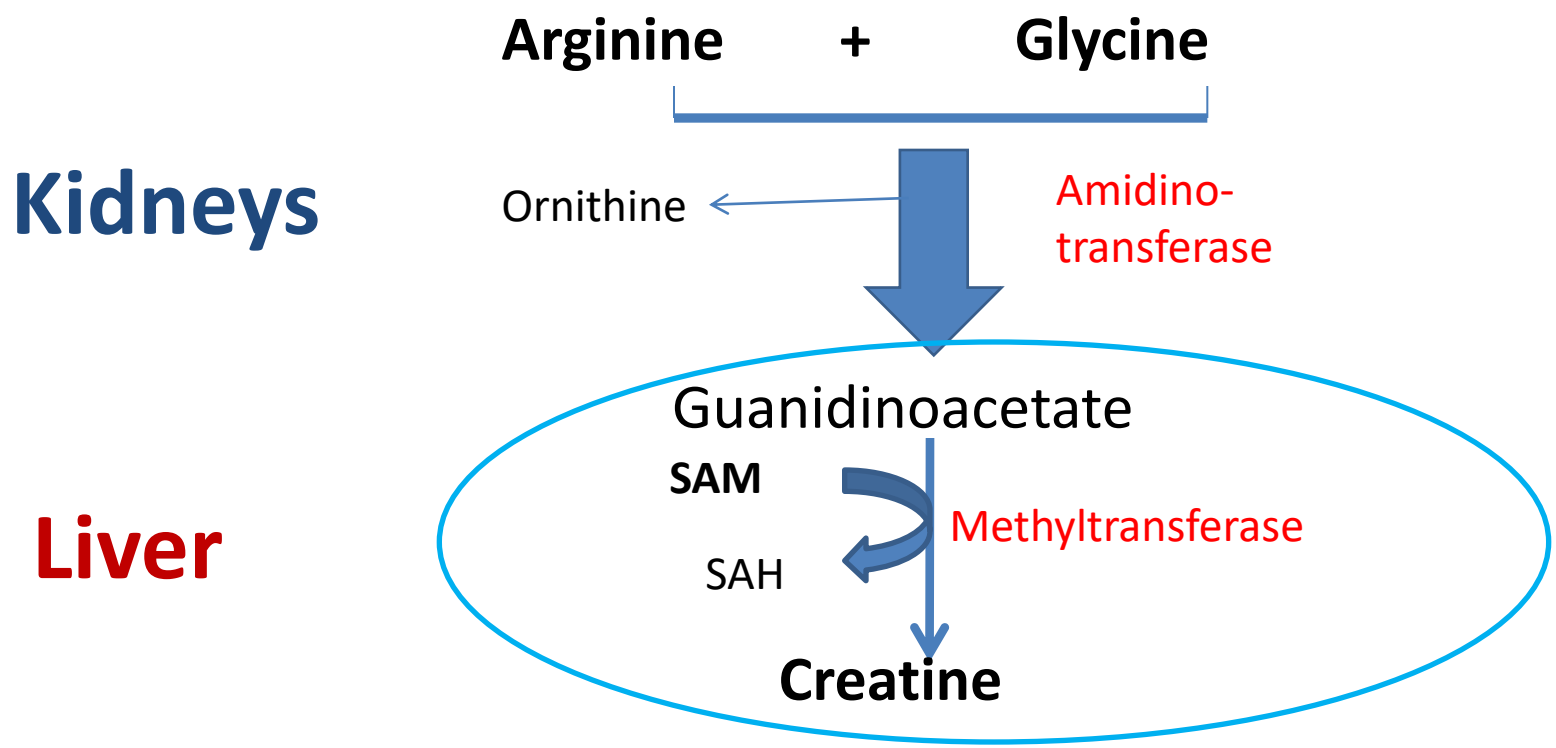
Three amino acids are required:

- Glycine
- Arginine
- Methionine (as S-adenosylmethionine)

Site of biosynthesis:

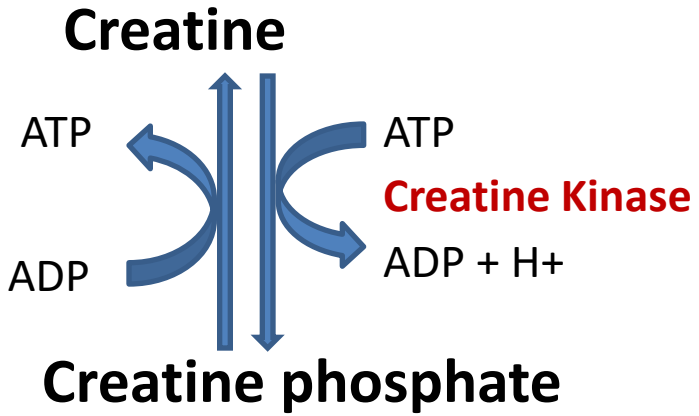
- Step 1: Kidneys
- Step 2: Liver

Creatine Biosynthesis



Distribution of body creatine

- From liver, transported to other tissues
- 98% are present in skeletal and heart muscles
- In Muscle, gets converted to the high energy source creatine phosphate (phosphocreatine)



Creatine Phosphate

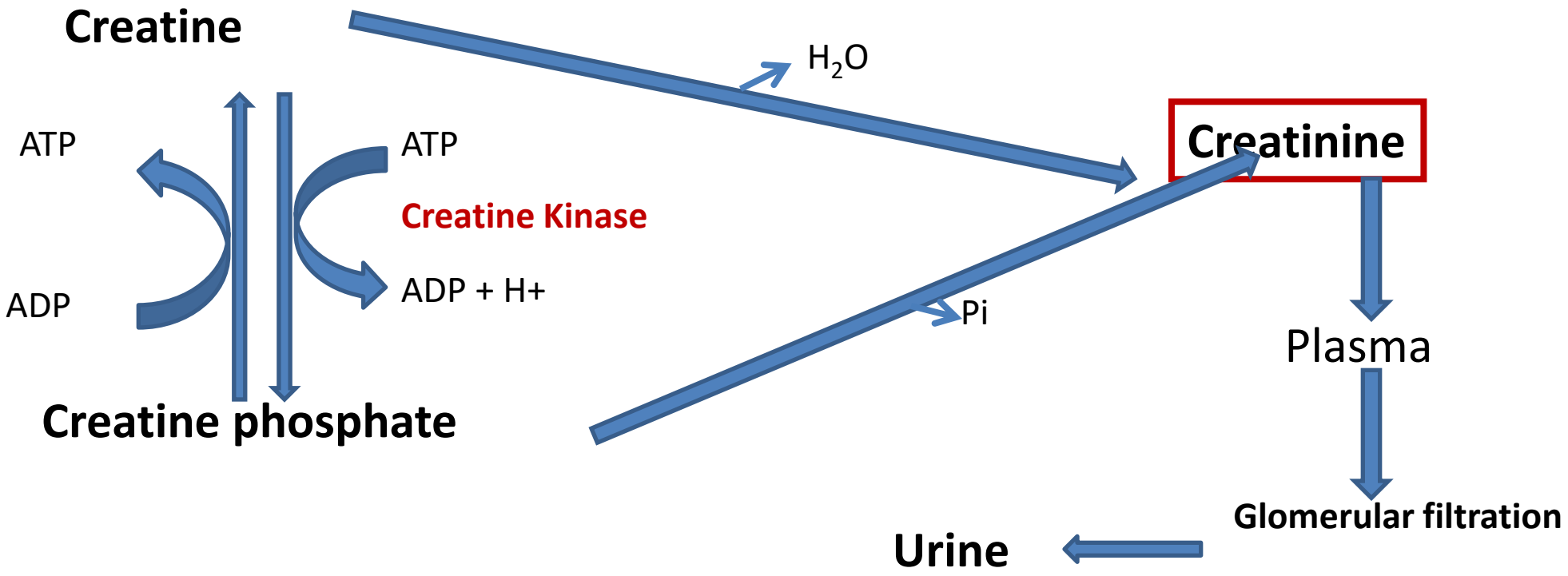
- Is a high-energy phosphate compound
- Acts as a storage form of energy in the muscle
- Provides a small but, ready source of energy during first few minutes of intense muscular contraction

The amount of creatine phosphate in the body is proportional to the muscle mass

Creatine Degradation

1. Creatine and creatine phosphate spontaneously form creatinine as an end product
2. Creatinine is excreted in the urine
3. Serum creatinine is a sensitive indicator of kidney disease (Kidney function test)
4. Serum creatinine increases with the impairment of kidney function

Creatine Degradation

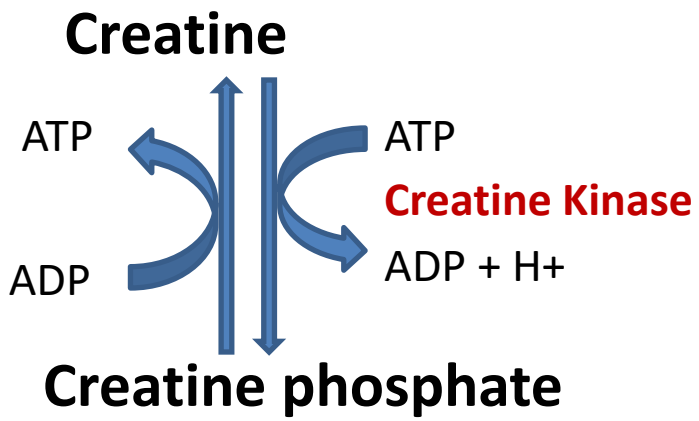


Urinary Creatinine

- A typical male excretes about 15 mmol of creatinine per day
- A decrease in muscle mass due to muscular dystrophy or paralysis leads to decreased level of creatinine in urine
- The amount of creatinine in urine is used as an indicator for the proper collection of 24 hours urine sample

Creatine Kinase (CK)

- CK is responsible for the generation of energy in contractile muscular tissues
- CK levels are changed in disorders of cardiac and skeletal muscle



Creatine Kinase (CK)

1. CK is required for conversion of creatine into creatine phosphate
2. CK has 3 isoenzymes:

   CK-MM mainly in skeletal muscle

   CK-MB mainly in heart muscle

   CK-BB mainly in brain

3. Serum total CK is increased in:

   Crush injuries (Damage of skeletal muscles)

   Myocardial infarction (Damage of heart muscle)


Many thanks all