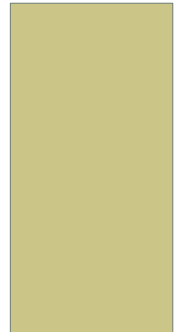


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CREATINE METABOLISM AND COLLAGEN DISEASES

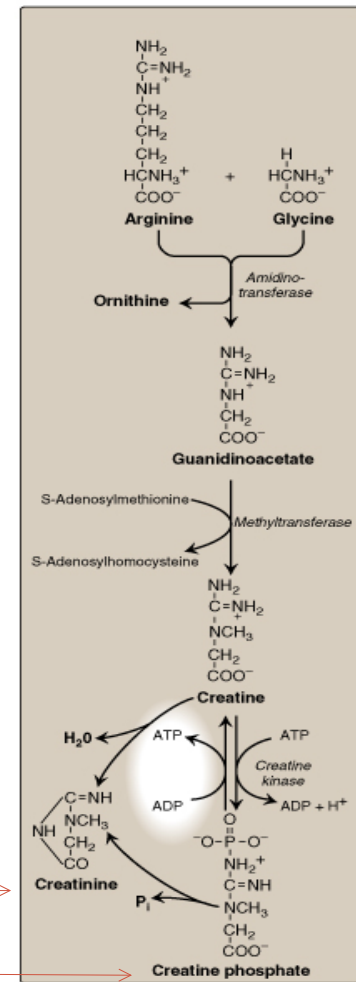


OBJECTIVES

By the end of this lecture the First Year students will be able to:

- Study the importance of creatine in muscle as a storage form of energy
- Understand the biosynthesis of creatine
- Study the process of creatine degradation and formation of creatinine as an end product
- Understand the clinical importance of creatinine as a sensitive indicator of kidney function
- Study the structure, function, types, and biosynthesis of collagen
- Understand different diseases associated with collagen

CREATINE METABOLISM



End product \longrightarrow

Energy source \longrightarrow

Figure 21.16
Synthesis of creatine.

CREATINE BIOSYNTHESIS

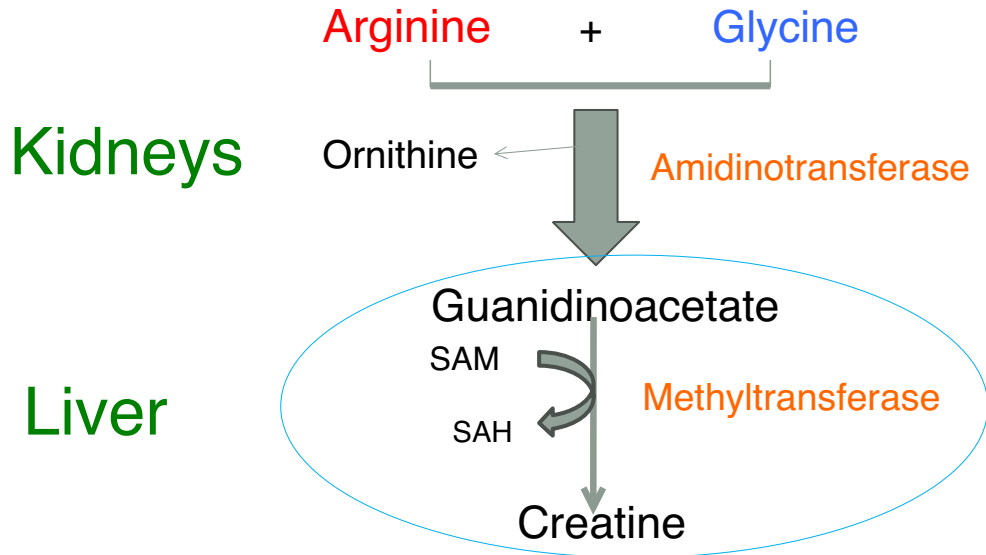
Three amino acids are required:

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

Sites of biosynthesis:

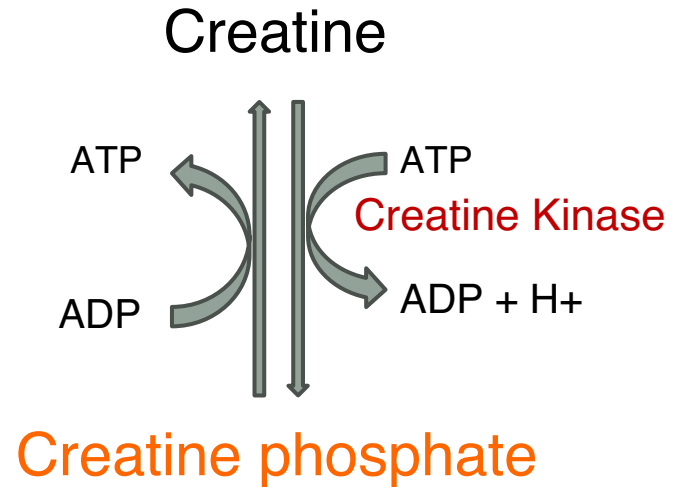
- Step 1: Kidneys
- Step 2: Liver

CREATINE BIOSYNTHEESIS



DISTRIBUTION OF BODY CREATINE

- Transported from liver to other tissues
- 98% present in skeletal and heart muscles
- In skeletal muscle it is converted to high-energy source **creatine phosphate** (phosphocreatine)



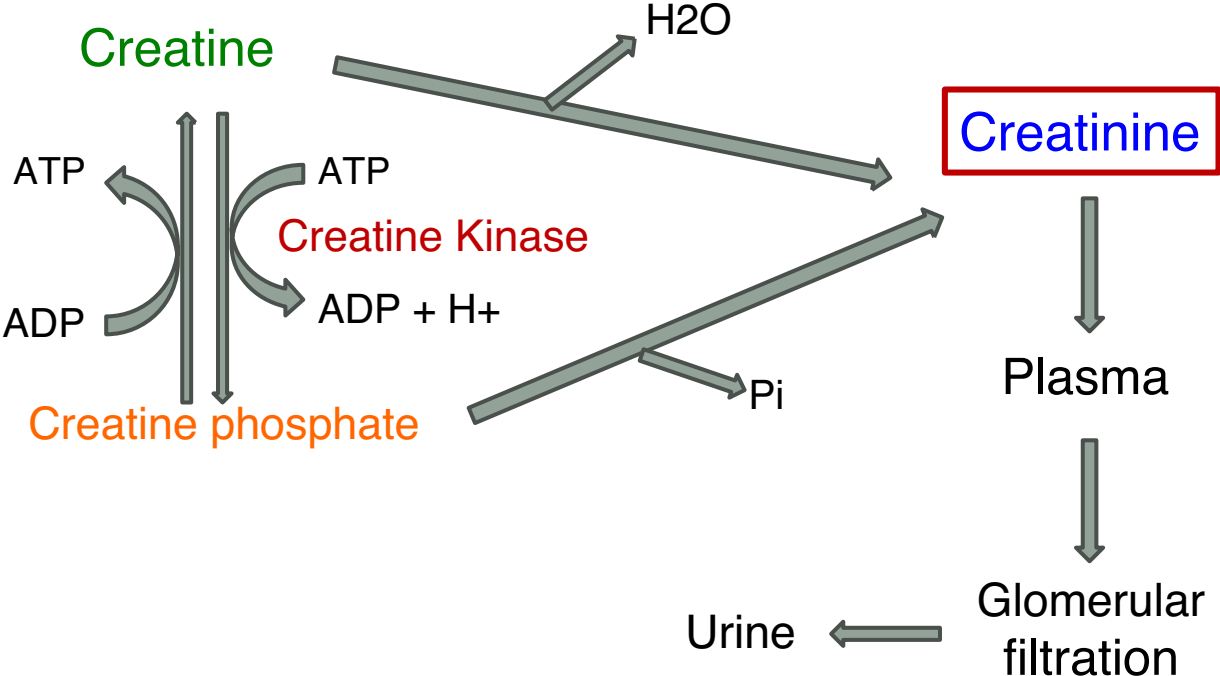
CREATINE PHOSPHATE

- A high-energy phosphate compound
- Acts as a storage form of energy in the muscle
- Provides small but, ready source of energy during first few seconds of intense muscular contraction
- **The amount of creatine phosphate in the body is proportional to the muscle mass**

CREATINE DEGRADATION

- **Creatine** and **creatine phosphate** spontaneously form **creatinine** as an end product
- **Creatinine** is excreted in the urine
- Serum creatinine is a sensitive indicator of kidney disease (kidney function test)
- Serum creatinine **increases** with the impairment of kidney function

CREATINE DEGRADATION

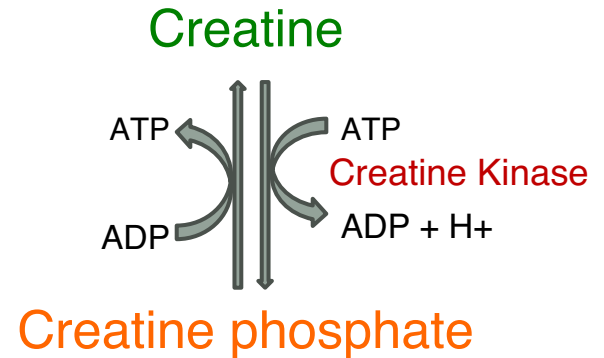


URINARY CREATININE

- A typical male excretes about 15 mmol creatinine/day
- Decrease in muscle mass (in muscular dystrophy, paralysis) leads to decreased level of urinary creatinine
- 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 generation of energy in contractile muscular tissues
- CK levels change in cardiac and skeletal muscle disorders



COLLAGEN

- Most abundant protein in the human body
- Collagen is a highly stable molecule with a half-life as long as several years
- A fibrous protein that serves structural functions
- Part of connective tissues, bone, teeth, cartilage, tendons, skin, blood vessels
- It has a long rigid structure

COLLAGEN STRUCTURE

- Collagen α -chain (~1,000 amino acids long) is rich in proline and glycine
- The glycine residues are part of a repeating sequence:
 - –Gly–X–Y–,
 - X = Frequently proline
 - Y = Often hydroxyproline
 - (–Gly–Pro–Hyp)₃₃₃
 - (Y can be also hydroxylysine)

COLLAGEN STRUCTURE

- Collagen consists of three α -chains wound around one another in a rope-like **triple helix**
- The three polypeptide chains are held together by hydrogen bonds
- Two examples of protein secondary structure: collagen helix and α -helix

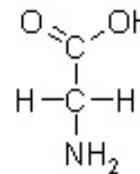
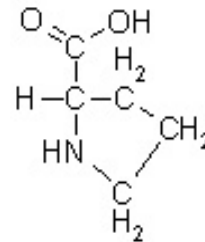
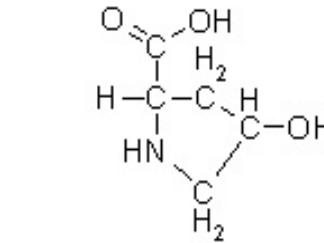
COLLAGEN STRUCTURE

- Rich in proline and glycine amino acids
- Proline prevents collagen chains to form α -helix because:
 - Proline has no back bone amino group (it is a ring structure with secondary amino group)
 - Therefore hydrogen bonding within the helix is not possible



NON-STANDARD AMINO ACIDS IN COLLAGEN

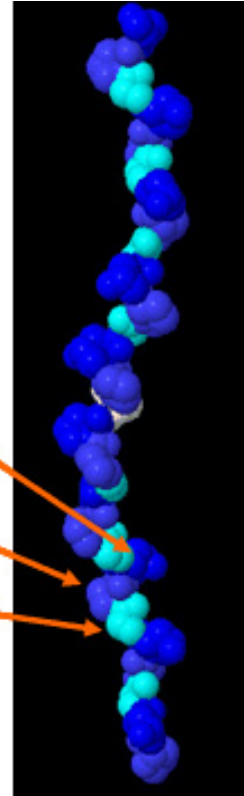
- Proline and lysine are converted to:
 - **Hydroxyproline** and **Hydroxylysine**
 - By **hydroxylase** enzymes
 - During post-translational modifications
- The enzyme requires vitamin C for its function



Hydroxyproline

Proline

Glycine



TYPES OF COLLAGEN

- Types of collagen depend on function
- Variations in the amino acid sequence of α -chains result in different properties

Examples:

- Type I: $(\alpha 1)_2 \alpha 2$
- Type II: $(\alpha 1)_3$

TYPE	TISSUE DISTRIBUTION
Fibril-forming	
I	Skin, bone, tendon, blood vessels, cornea
II	Cartilage, intervertebral disk, vitreous body
III	Blood vessels, skin, muscle
Network-forming	
IV	Basement membrane
VIII	Corneal and vascular endothelium
Fibril-associated	
IX	Cartilage
XII	Tendon, ligaments, some other tissues

BIOSYNTHESIS OF COLLAGEN

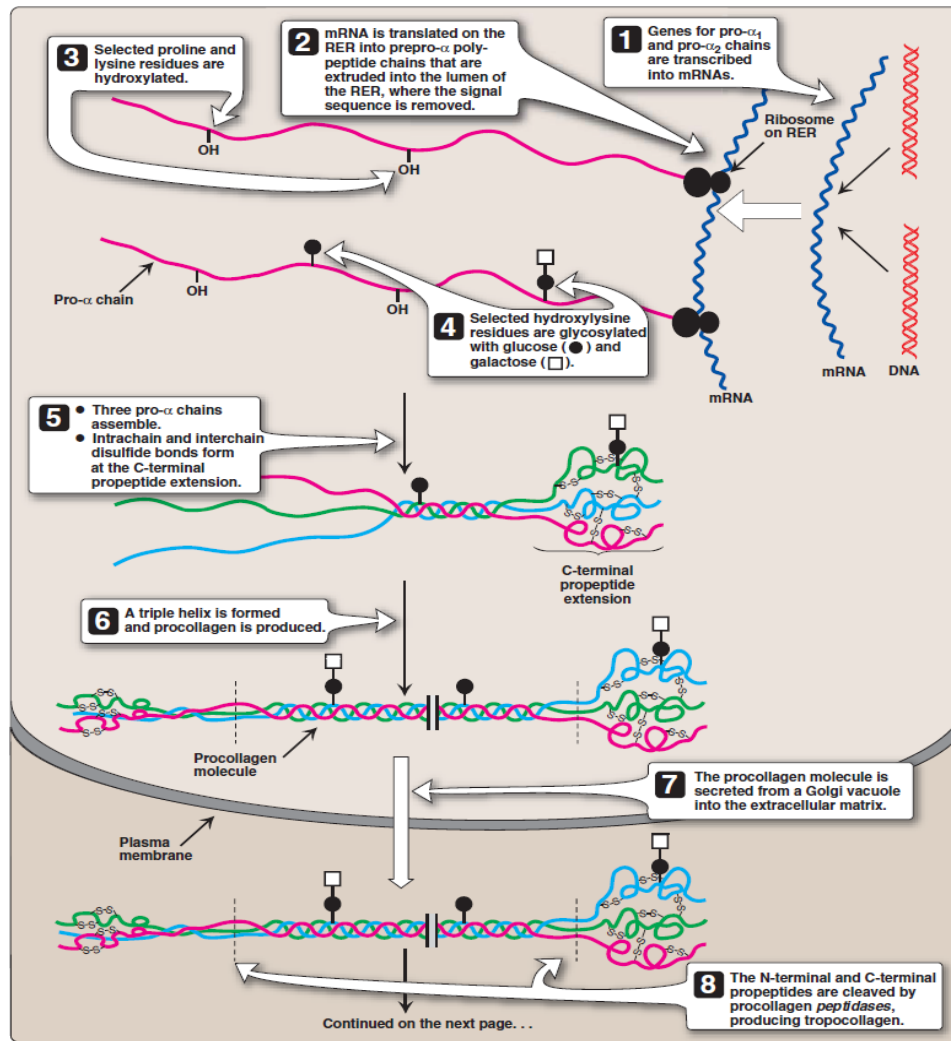
- Synthesized in fibroblasts, osteoblasts, chondroblasts
 - Pre-pro [?] Pro [?] Mature collagen
- Polypeptide precursors are enzymatically modified to form triple helix
- Hydroxylation of proline and lysine residues
- Glycosylation of some hydroxylysine residues with glucose or galactose

BIOSYNTHESIS OF COLLAGEN

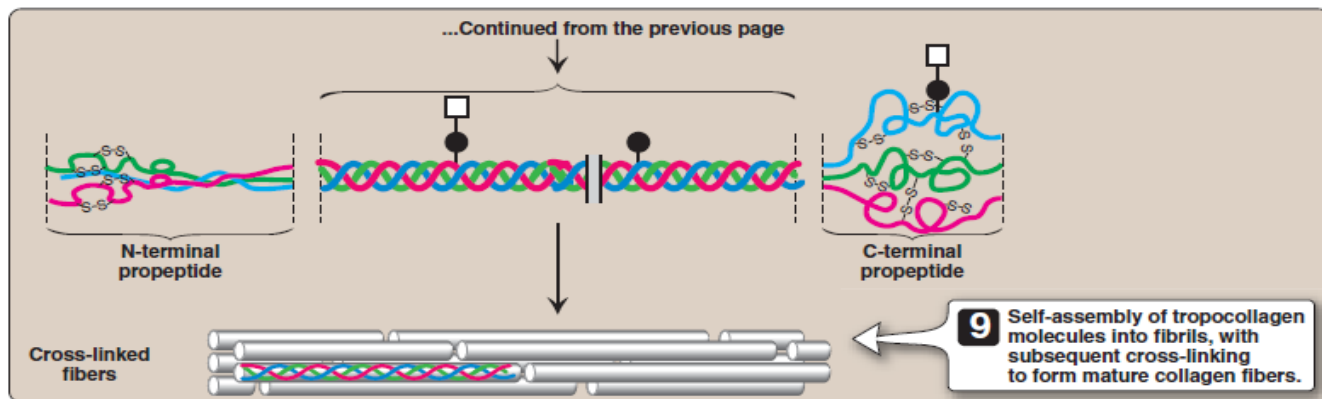
- Secreted from Golgi vacoules into the extracellular matrix as procollagen
- Cleaved by N- and C- procollagen peptidases to release triple helical tropocollagen molecules
- Tropocollagen molecules spontaneously associate to form collagen fibrils

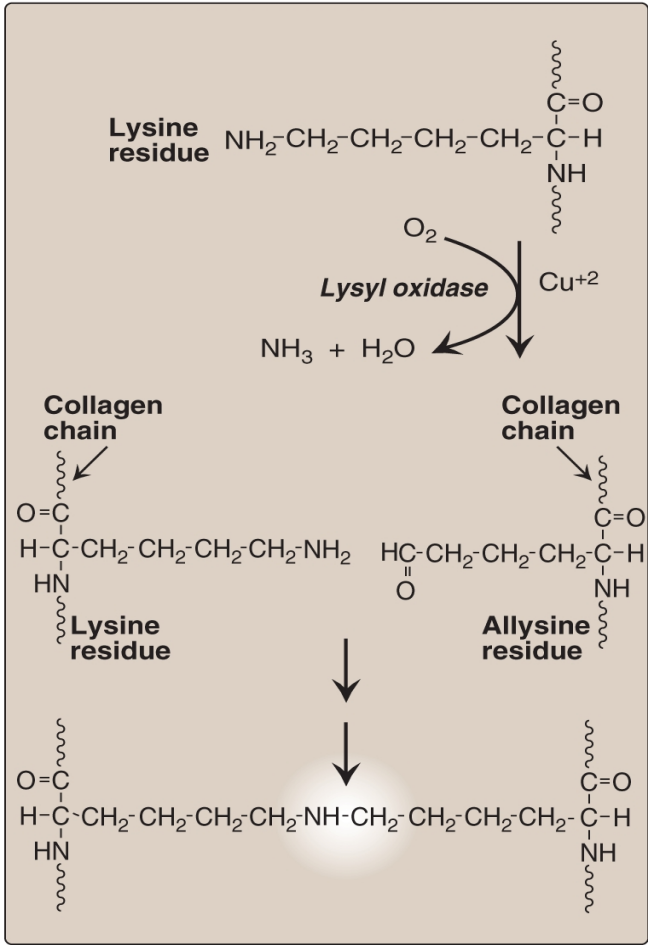
CROSSLINKING OF COLLAGEN FIBRILS

- **Lysyl oxidase** oxidatively deaminates some of the lysine and hydroxylysine residues in collagen
- The reactive aldehydes – **allysine** and **hydroxyallysine** condense with lysine or hydroxylysine residues in neighbouring collagen molecules to form covalent cross-links
- This produces **mature collagen fibres**



Continued on the next page...





COLLAGEN DISEASES

Acquired disease:

- Scurvy due to vitamin C deficiency

Genetically inherited diseases:

- Ehlers-Danlos syndromes (EDS)
- Osteogenesis imperfecta (OI)

COLLAGEN DISEASES

Ehlers-Danlos syndrome

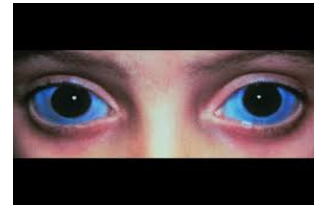
- Due to deficiency of **lysyl hydroxylase** or **N-procollagen peptidase**
- Mutations in the amino acid sequences of **collagen I, III and V**
- Characterized by hyper-extensibility of joints and skin



COLLAGEN DISEASES

Osteogenesis imperfecta (brittle bone disease):

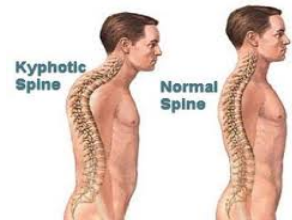
- Bones fracture easily with minor or no trauma
- Mutations **replace glycine with amino acids having bulky side** chains preventing the formation of triple helical conformation
- **Type I (most common)** characterized by mild bone fragility, hearing loss and blue sclerae



COLLAGEN DISEASES

Osteogenesis imperfecta (brittle bone disease):

- **Type II (most severe)** and lethal in the perinatal period (fractures in utero)
- **Type III (severe form)**
- Fractures at birth, short stature, spinal curvature
- Leading to a humped back (kyphotic) appearance and blue sclerae



REFERENCES

- Lippincott's Illustrated Reviews, Biochemistry, 6th edition, Denise R. Ferrier, Lippincott Williams & Wilkins, USA, pp. 43-49 and 287-288.
- Bishop's Clinical Chemistry 6th edition, pp. 223-227.