Protein

Protein structure determines function

DNA

(mRNA)

Translation:

Translation into 3D structure:

Modifications:

- Chemical modification of aminoacids
- Interaction with other molecules
- Proteolytic cleavage
- (Location)

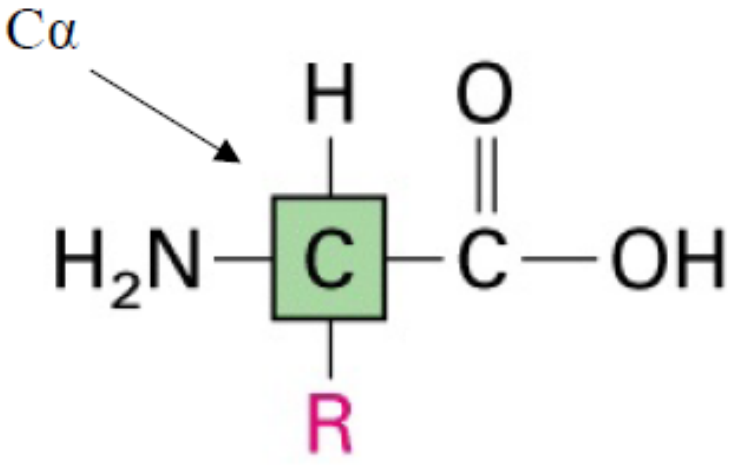
3D structure determines function:

New 3D structure

New function

- Proteins are single, unbranched chains of amino acid monomers
- There are 20 different amino acids
- The amino acid sidechains in a peptide can become modified, extending the functional repetoire of aminoacids to more than hundred different amino acids.
- A protein's amino acid sequence determines its three-dimensional structure (conformation)
- In turn, a protein's structure determines the function of that protein
- Conformation (=function) is dynamically regulated in several different ways

All amino acids have the same general structure but the side chain (R group) of each is different



Amino acid

R:	**Hydrophilic:**
	Basic
	Acidic
	Non-charged
	Hydrophobic
	"Special"

HYDROPHILIC AMINO ACIDS

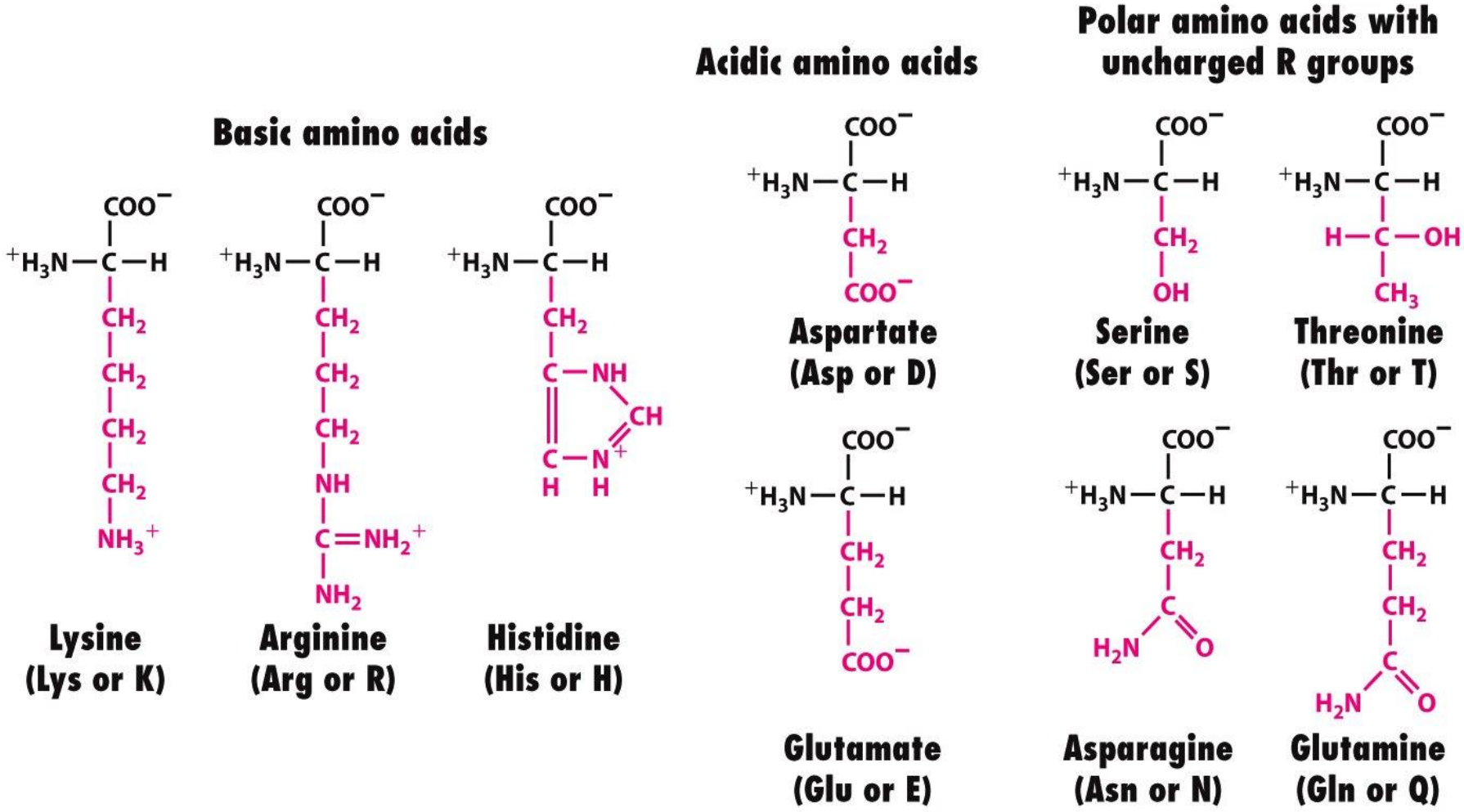


Figure 2-14 part 2
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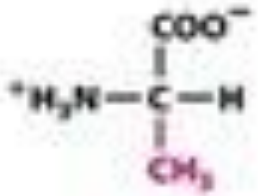
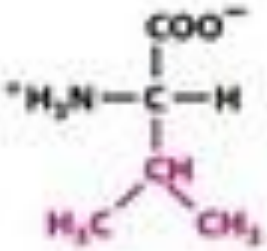
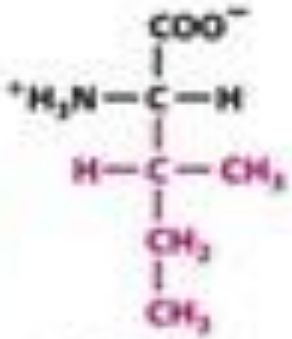
HYDROPHOBIC AMINO ACIDS



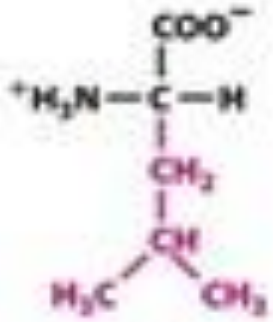
Alanine (Ala or A)



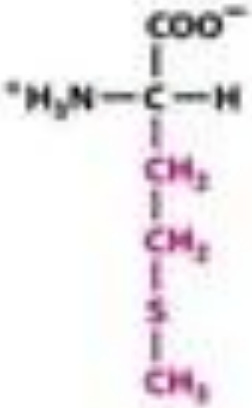
Valine (Val or V)



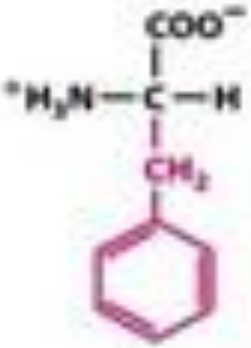
Isoleucine (Ile or I)



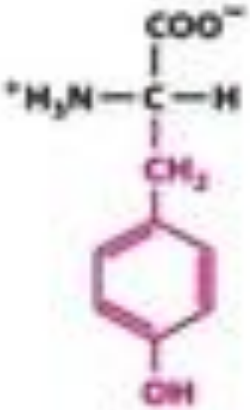
Leucine (Leu or L)



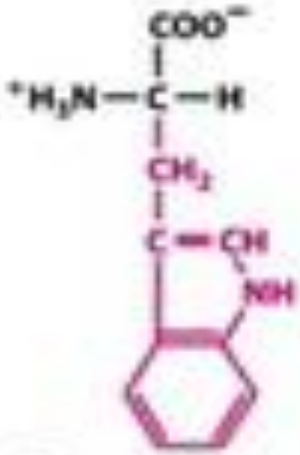
Methionine (Met or M)



Phenylalanine (Phe or F)



Tyrosine (Tyr or Y)



Tryptophan (Trp or W)

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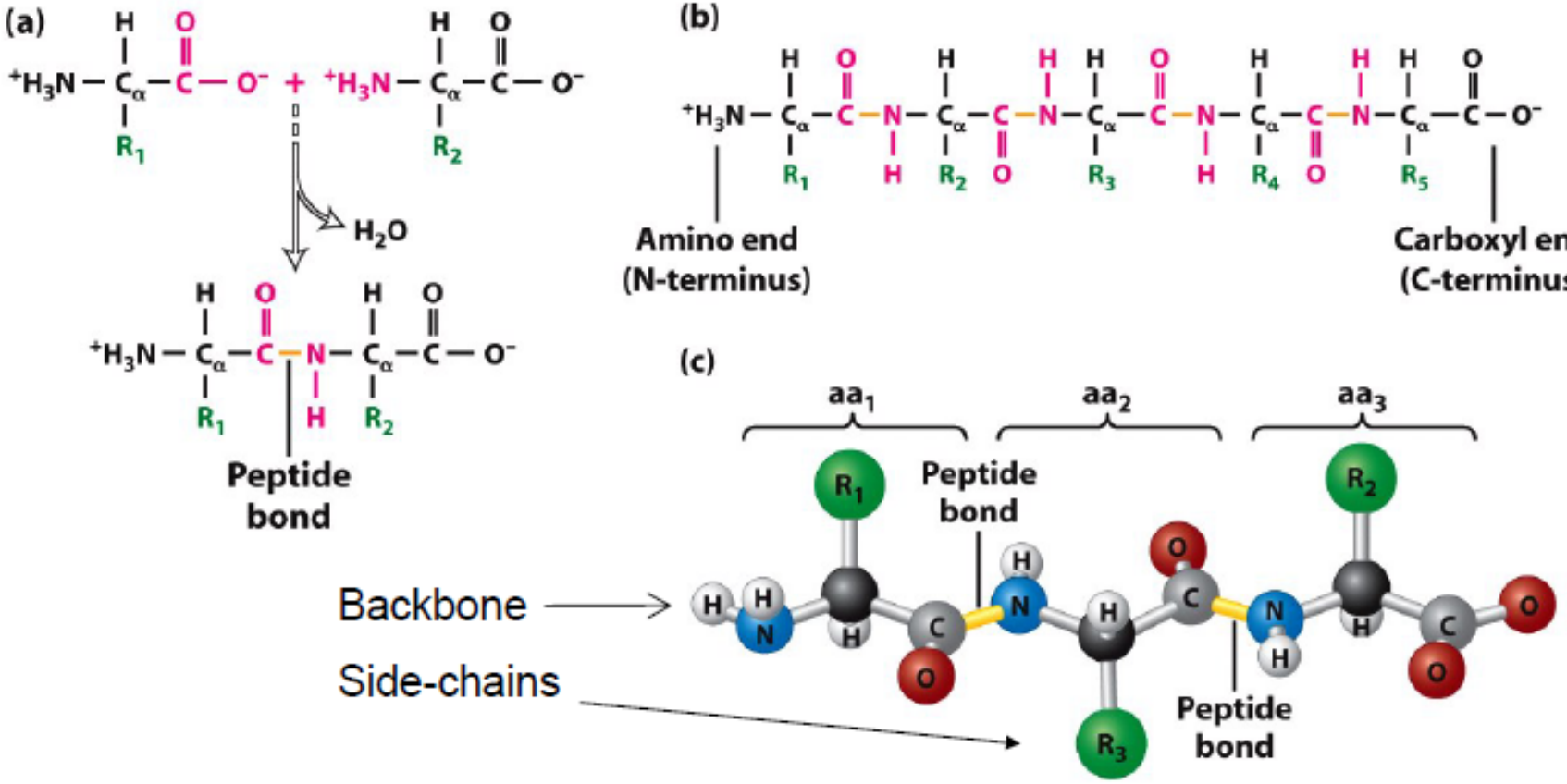
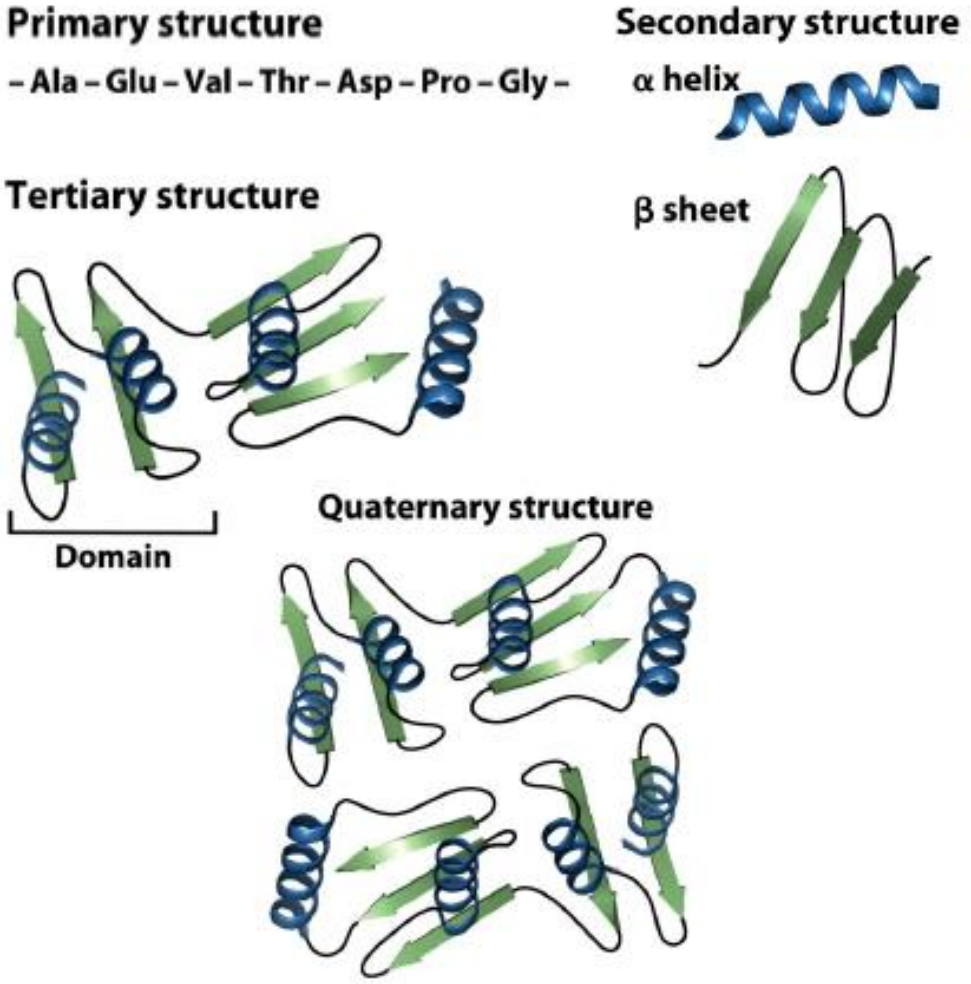
Peptide bonds connect amino acids into linear chains



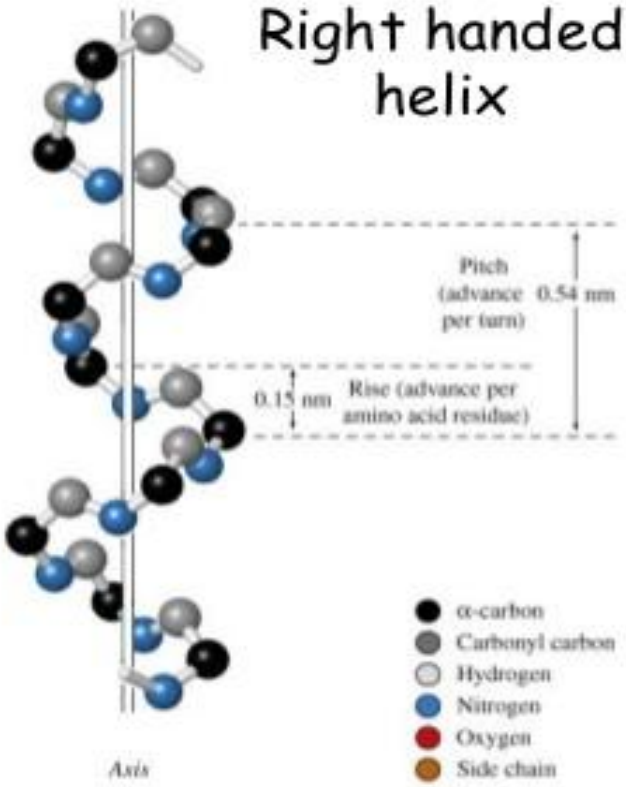
Four levels of structure determine the shape of proteins

- **Primary:** the linear sequence of amino acids
  peptide bonds
- **Secondary:** the localized organization of parts of a polypeptide chain (e.g., the α helix or β sheet)
  backbone hydrogen bonds
- **Tertiary:** the overall, three-dimensional arrangement of the polypeptide chain
  hydrophobic interactions, hydrogen bonds (non-covalent bonds in general) and sulfur-bridges
- **Quaternary:** the association of two or more polypeptides into a multi-subunit complex



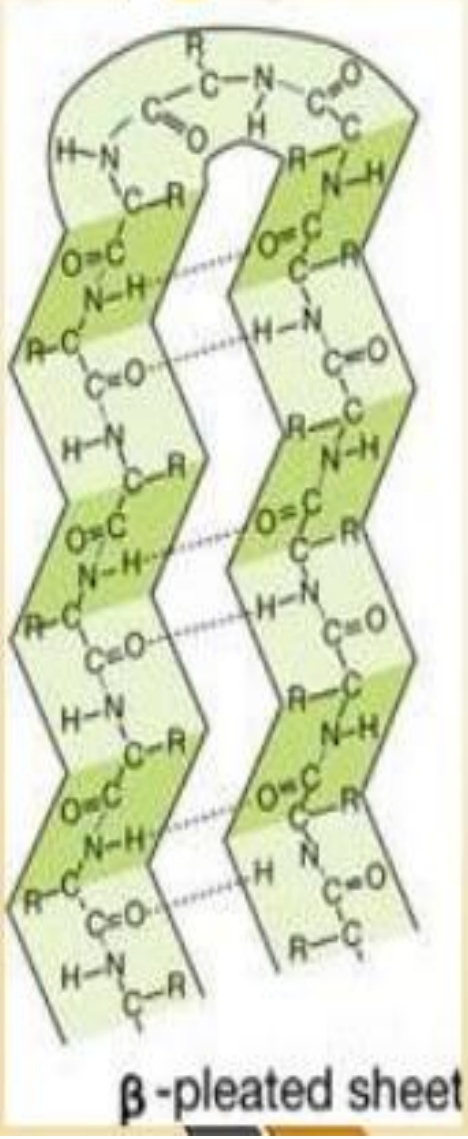
Alpha-Helix

Right-handed α-helix

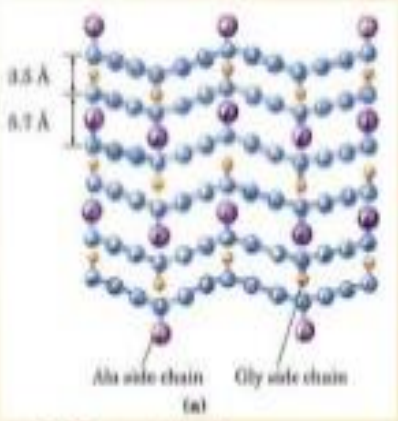


- Residues per turn: 3.6
- Rise per residue: 1.5 Angstroms
- Rise per turn (pitch): 3.6 x 1.5A = 5.4 Angstroms
- amino hydrogen H-bonds with carbonyl oxygen located 4 AA's away forms 13 atom loop

β-pleated sheet (β-sheets)



- The surfaces of β - sheets appear "**pleated**", and these structures are, therefore, often called " β - pleated sheets".
- Polypeptide chains - **fully extended**
- distance between adjacent a.a -3.5Å
- Stabilized by hydrogen bonds



2 types

Parallel — run in the same direction - **Flavodoxin**

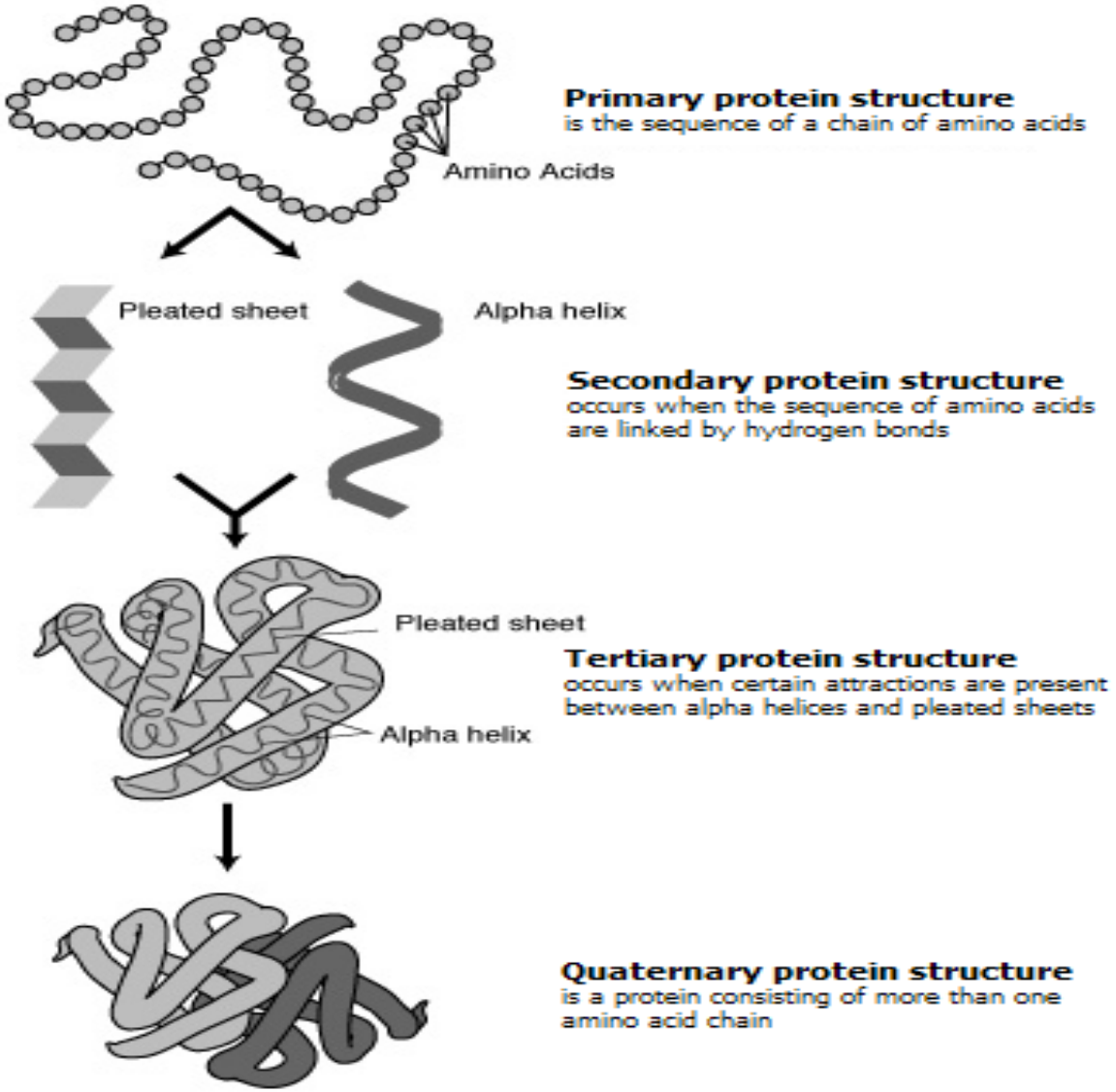
N → C
N → C

Anti -Parallel — strands in a sheet run in an opp. direction - **Silk fibroin**

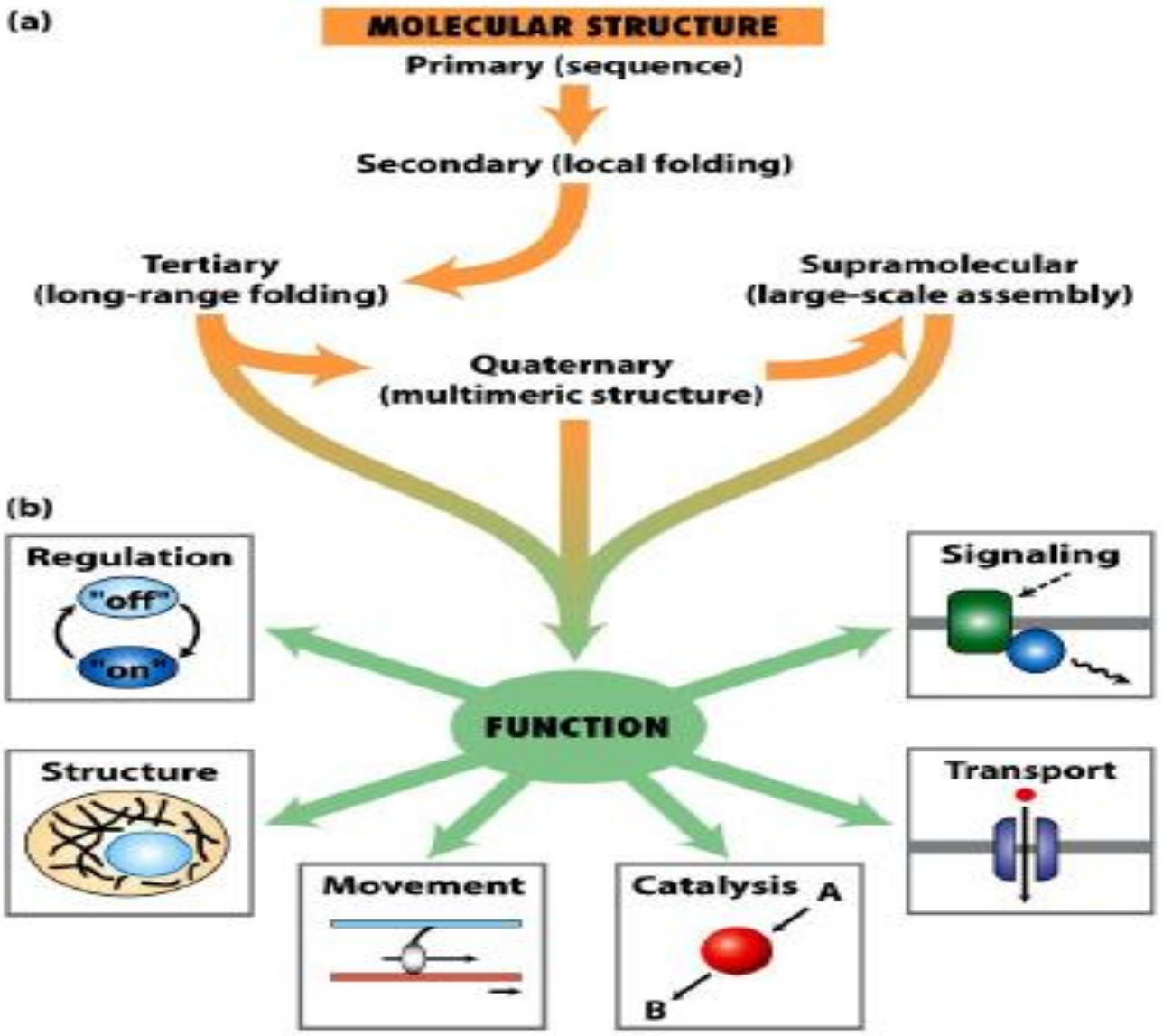
N → C
C ← N

Carbonic anhydrase - contains both

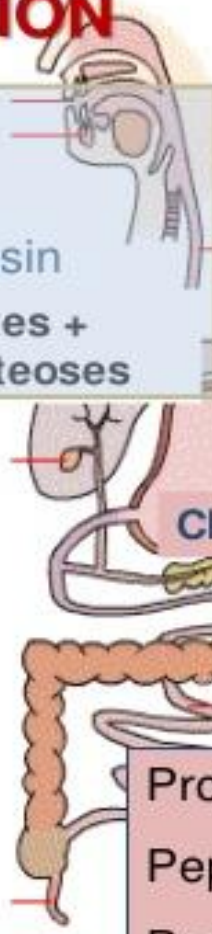
Levels of organization of proteins



Function


(a)
MOLECULAR STRUCTURE
Primary (sequence)
Secondary (local folding)
Tertiary
(long-range folding)
Supramolecular
(large-scale assembly)
Quaternary
(multimeric structure)
(b)
Regulation
"off"
"on"
Signaling
FUNCTION
Structure
Transport
Movement
Catalysis
A
B

PROTEIN DIGESTION



Buccal cavity

No protein digestion

Stomach

Pepsinogen —HCl→ Pepsin

Protein —Pepsin→ Peptones + Proteoses

Small intestine

Trypsinogen —Enterokinase→ Trypsin

Chymotrypsinogen → Chymotrypsin

Procarboxy peptidase → Carboxy peptidase

Proteins
Peptones
Proteoses

—Trypsin / Chymotrypsin, Carboxy peptidase→ Dipeptides

Dipeptides —Dipeptidase→ Amino acids

Peptones = larger peptides
Proteoses = smaller peptides

Classification of Proteins

Based on Conformation

Fibrous Insoluble in H_2O	Globular Soluble in H_2O
•α-Keratin •β-Keratin •Collagen	•Myoglobin •Hemoglobin •Lysozyme •Ribonuclease •Chymotrypsin •Cytochrome-c •Lactate dehydrogenase •subtilisin

Based on Composition

Simple	Conjugated	Derived
•Albumin •Globulin •Glutalins •Prolamins •Protamines •Histones •Scleroproteins	•Nucleoprotein •Lipoprotein •Phosphoprotein •Metalloprotein •Glycoprotein •Flavoprotein •Hemoprotein •chromoproteins	•Protiose •Peptones •Small peptides •Fibrin •Metaproteins •Coagulated proteins

Based on Nature of

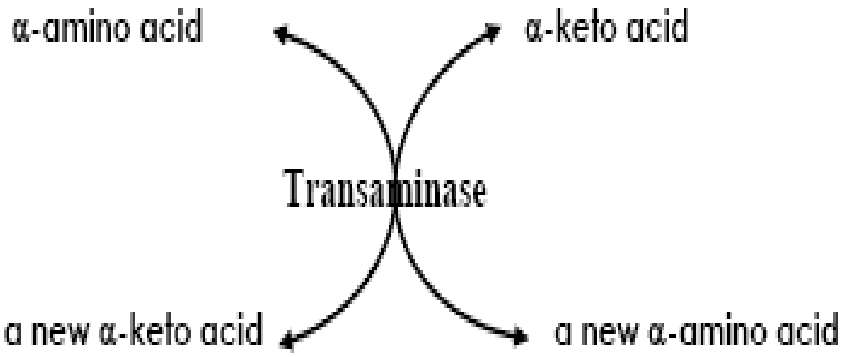
Acidic	Basic
•Blood proteins	•Histones

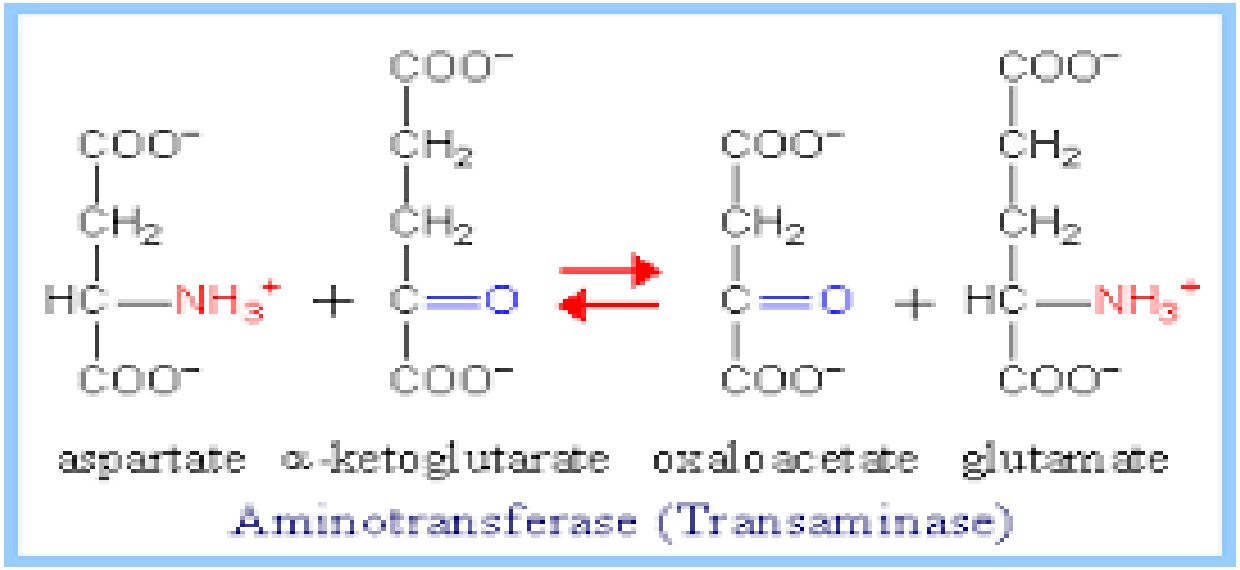
Classification based on function

Type of protein	Example	Function
Enzymes	Amylase	Digestion
Transport	Hemoglobin Myoglobin Albumin Lipoprotein	Transports O2 in blood Transports O2 in muscle Transports fatty acids Transports lipids
Storage	Ovalbumin Milk Ferritin	Egg-white protein Milk Iron storage in spleen
Contractile	Myosin, actin	Muscle movement
Protection	Antibodies Fibrinogen, thrombin	Fight infection Blood clotting
Hormones	Insulin Growth hormone	Carbohydrate metabolism Growth and regeneration
Structural	Glycoproteins Collagen Elastin	Cell walls, skin Tendons, bones, cartilage Ligaments
Toxins	Clostridium botulinum Ricin Snake venom	Botulism food poisoning Castor bean toxin Snake venom

Transamination reaction

(The transfer of an amino group from one molecule to another, especially from an amino acid to a keto acid.)

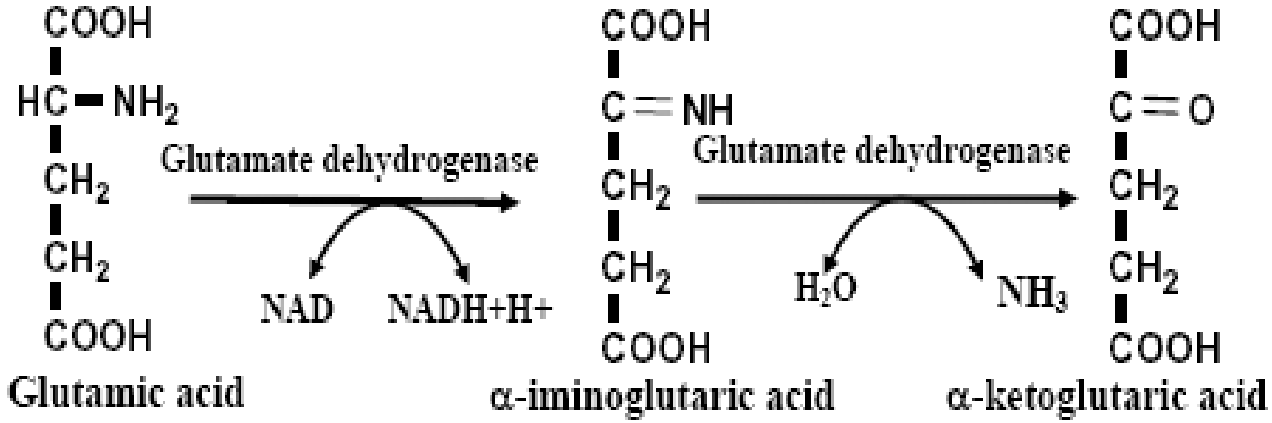




Occurs primarily in the liver cells.

Oxidative Deamination reaction

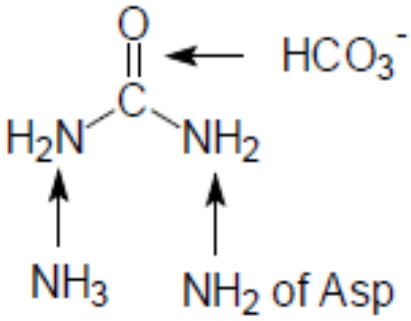
(During oxidative deamination, an amino acid is converted into the corresponding keto acid by the removal of the amine functional group as ammonia and the amine functional group is replaced by the ketone group. The ammonia eventually goes into the urea cycle.)



Occurs primarily in the liver and kidneys.

The Urea cycle

•Urea is formed from ammonia (NH3), amino group (NH2) of Asp, and bicarbonate (HCO3) by urea cycle in liver.



•Five enzymes are involved in urea synthesis in urea cycle.

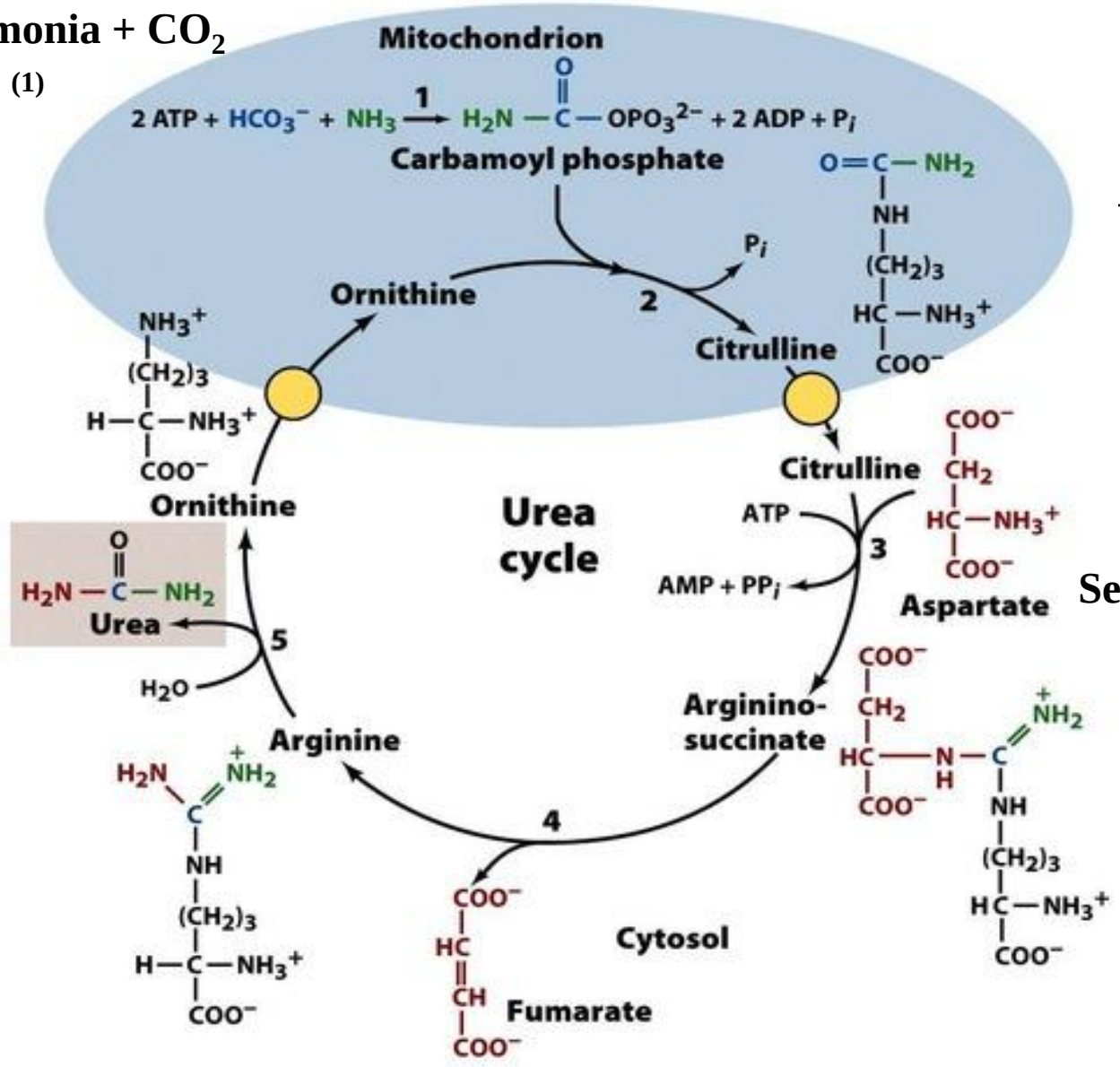
•Two enzymes are in mitochondrion.

•Three enzymes are in cytosol.

•Therefore, the urea cycle occurs partially in the mitochondrion and partially in the cytosol.

First ammonia + CO_2

(1)



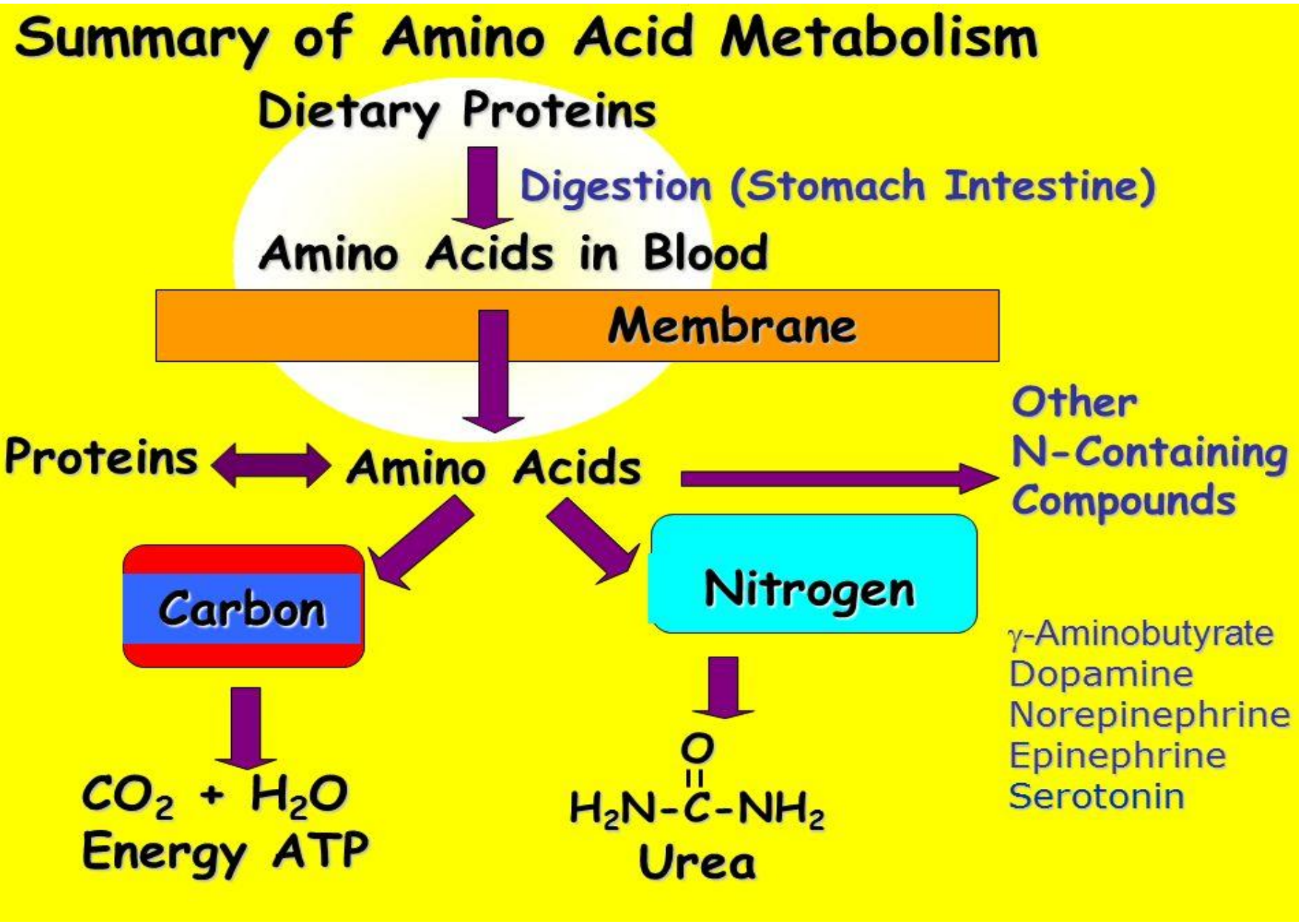
Second ammonia

(2)

Significance of the Urea cycle

- Major route of disposal of toxic ammonia.
- Synthesis of semi-essential amino acid **Arginine**.
- Urea cycle, citric acid cycle & transamination reactions are linked.

Summary of Amino Acid Metabolism



Disorders related to Amino acid & Protein metabolism

Contrasting Features of Kwashiorkor and Marasmus.

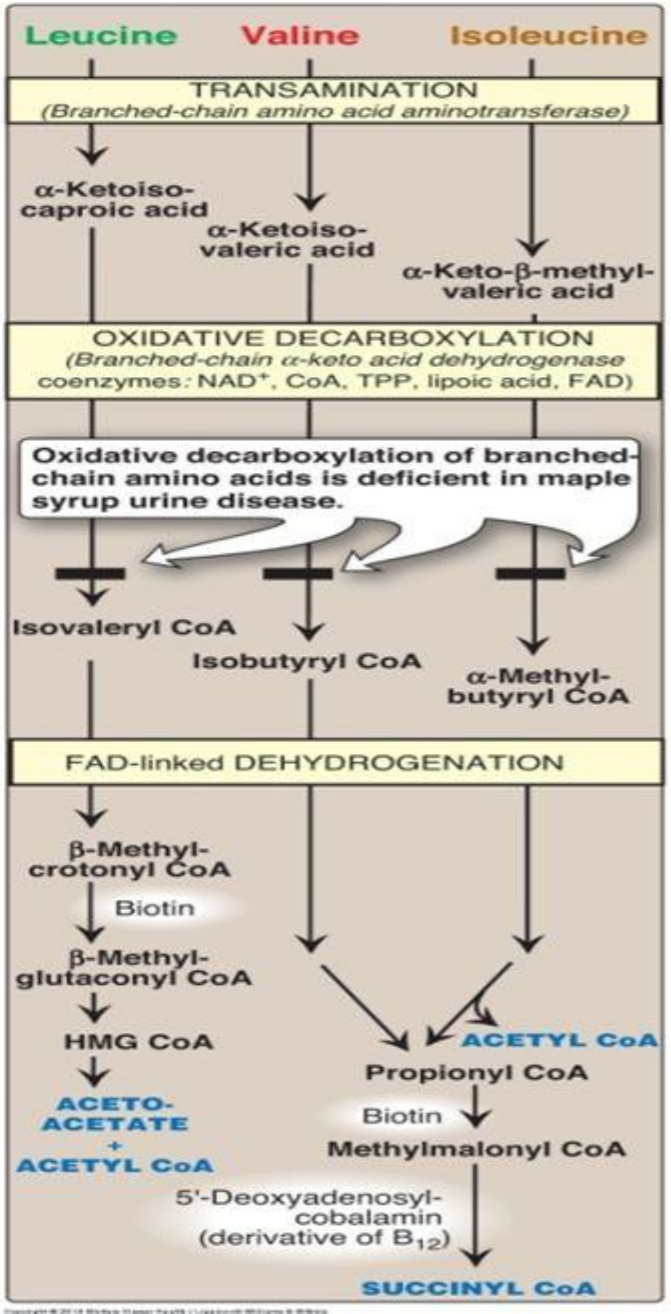
Feature	Kwashiorkor	Marasmus
Definition	Protein deficiency with sufficient calorie intake	Starvation in infants with overall lack of calories
Clinical features	Occurs in children between 6 months and 3 years of age	Common in infants under 1 year of age
	Growth failure	Growth failure
	Wasting of muscles but preserved adipose tissues	Wasting of all tissues including muscles and adipose tissues
	Oedema, localised or generalised, present	Oedema absent
	Enlarged fatty liver	No hepatic enlargement
	Serum proteins low	Serum proteins low
	Anaemia present	Anaemia present
	'Flag sign'—alternate bands of light (depigmented) and dark (pigmented) hair	Monkey-like face, protuberant abdomen, thin limbs
Morphology	Enlarged fatty liver	No fatty liver
	Atrophy of different tissues and organs but subcutaneous fat preserved	Atrophy of different tissues and organs including subcutaneous fat

Inborn Errors of Amino Acid Metabolism in Humans

Arginine and Urea cycle	Argininemia and hyperammonemia	Mental retardation	Arginase
	Hyperammonemia	neonatal death, convulsions, mental retardation	Carbamoyl phosphate synthetase
	Ornithinemia		Ornithine decarboxylase
Isoleucine, leucine, and valine	Branched chain ketoaciduria "maple syrup urine disease"	vomiting, convulsions and neonatal death, mental retardation in survivors	Branched-chain keto acid dehydrogenase complex
Methionine	Homocystinuria	mental retardation, several eye diseases, osteoporosis and frail bone structure	Cystathionine - beta - synthase
Tyrosine	Alkaptonuria	urine darkens upon standing, prone to arthritis	Homogentistic acid oxidase
	Albinism	white hair, pink skin	Tyrosinase in melanocytes is absent
Phenylalanine	Phenylketonuria	mental retardation	Phenylalanine hydroxylase

Maple syrup urine disease (MSUD)

- Autosomal recessive (1:185,000).
- Partial or complete deficiency in mitochondrial branched chain α-keto acid dehydrogenase (BCKD), that oxidatively decarboxylates Leu, Ile and Val.
- These BCAAs and their corresponding α-keto acids accumulate in blood, causing interference with brain functions (especially Leu and α-Kic acid).
- **Symptoms**: a characteristic maple syrup odor to the urine due to rise in Ile; feeding problems, vomiting, ketoacidosis, changes in muscle tone, neurologic problems that can result in coma; if untreated, disease is fatal; if treatment is delayed, intellectual disability results.
- **Treatment**: Synthetic formula free of BCAAs supplemented with limited amounts of Leu, Ile and Val to allow normal growth and development without producing toxic levels.



Inborn errors of amino acid metabolism

Disorder	Metabolic defect (enzyme / other)
1. Urea cycle	
(a) Hyperammonemia type-I	Carbamoyl phosphate synthase-I
(b) Hyperammonemia type-II	Ornithine transcarbamoylase
(c) Citrullinemia	Argininosuccinate synthase
(d) Arginosuccinic aciduria	Argininosuccinase
(e) Hyperargininemia	Argininase
2. Glycine	
(a) Glycinuria	Defect in renal reabsorption
(b) Primary hyperoxaluria	Glycine transaminase