Overview of amino acids metabolism

- Amino acids serve as substrates for the synthesis of protein,
- Amino acids provide nitrogen for the synthesis of other nitrogen-containing compounds,
- Amino acids are catabolized as fuels.

Classification of amino acids:

1. Chemical classification:

- ✓ According to the **chemistry** of the side chains.
- ✓ According to **polarity** of side chains.

2. Nutritional classification:

- ✓ Essential
- ✓ Non-essential

NOTE:

- ✓ All of the 20 amino acids present in proteins are essential for health.
- ✓ Some clinical conditions are associated with amino acid deficiency states, such as Kwashiorkor and Marasmus diseases.
- ✓ Kwashiorkor is protein deficiency with adequate energy intake whereas Marasmus is inadequate energy intake in all forms, including protein.

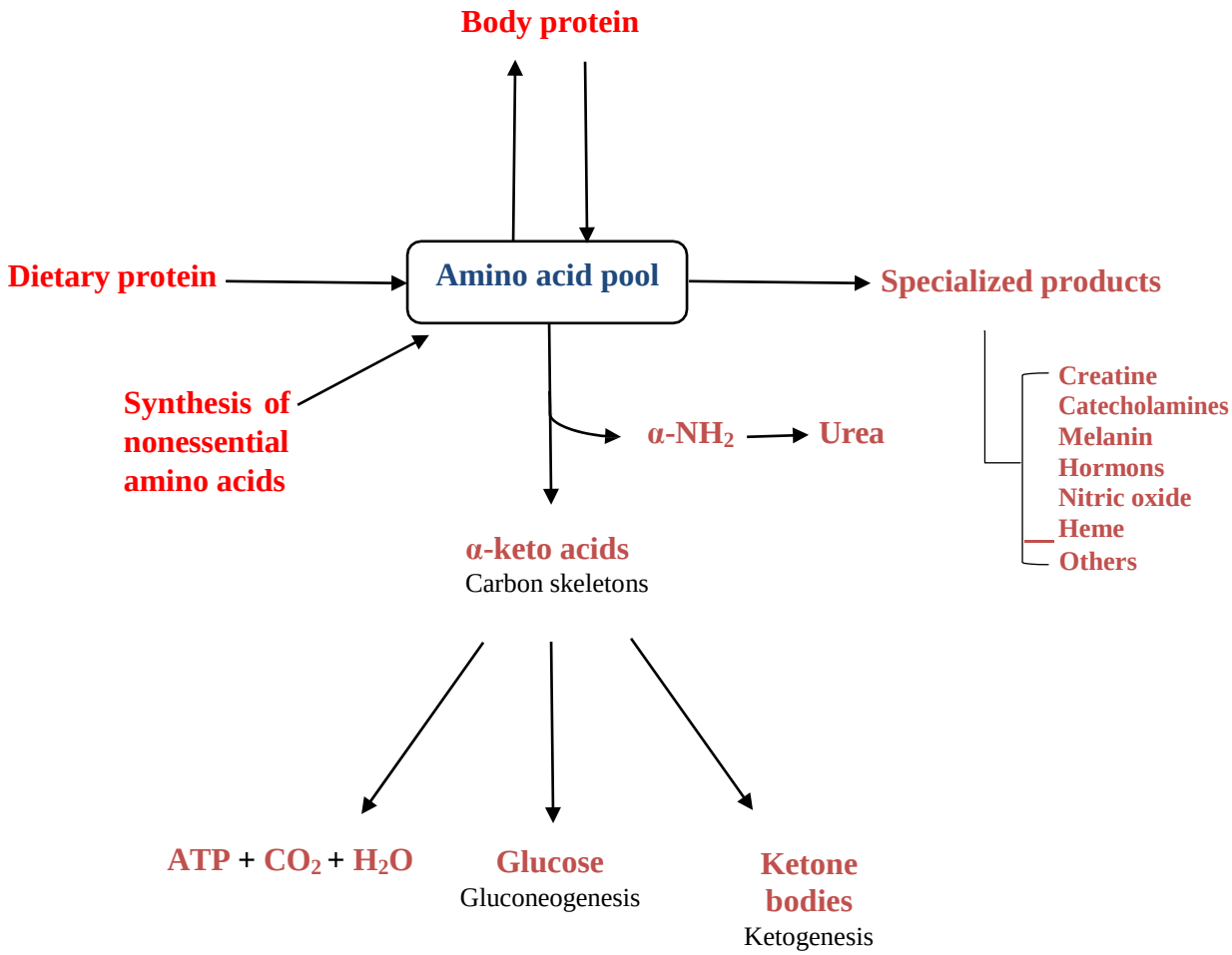
Amino acid requirements of humans

Nutritionally Essential	Nutritionally Nonessential
Arginine[1]	Alanine
Histidine	Asparagine
Isoleucine	Aspartate
Leucine	Cysteine
Lysine	Glutamate
Methionine	Glutamine
Phenylalanine	Glycine
Threonine	Hydroxyproline[2]
Tryptophan	Hydroxylysine[2]
Valine	**Proline**
	Serine
	Tyrosine

[1] *"Nutritionally semiessential." Synthesized at rates inadequate to support growth of children.*
[2] *Not necessary for protein synthesis but formed during posttranslational processing of collagen.*

3. Metabolic classification:

- ✓ Ketogenic (Leucine and Lysine)
- ✓ Both glucogenic and ketogenic (Isoleucine, Phenylalanine, Tryptophan, Tyrosine and Threonine)
- ✓ Glucogenic (all the remaining)



Overview of amino acid metabolism

Amino acids pool

The amount of free amino acids distributed throughout the body is called amino acid pool. Plasma level for most amino acids varies widely throughout the day. It ranges between 4–8 mg/dl. It tends to **increase** in the **fed state** and tends to **decrease** in the **post absorptive state**.

Sources of amino acid pool

1. Dietary protein.
2. Breakdown of tissue proteins.
3. Biosynthesis of nonessential amino acids.

NOTE:
In general, the rate of protein synthesis equals the rate of degradation (**steady-state**). However, there is a constant need for dietary intake of protein because:

- ✓ Some amino acids are also used for energy production and storage and for synthesis of non-protein molecules.
- ✓ There are situations where protein synthesis must exceed protein degradation, such as during growth, pregnancy, and recovery from illness.

Digestion of dietary proteins

- ✓ Protein digestion begins in the stomach.
- ✓ The highly acidic environment of the stomach denatures proteins. Denatured proteins are susceptible to proteolytic digestion.
- ✓ The primary enzyme involved in proteolytic digestion is **pepsin**, which catalyzes the **nonspecific hydrolysis** of peptide bonds at an optimal pH of 2.
- ✓ In the lumen of the small intestine, the pancreas secretes **zymogens** of **trypsin (**Trypsin cleaves peptide chains mainly at the carboxyl side of the amino acids lysine or arginine, except when either is followed by proline.), **chymotrypsin (**Chymotrypsin prefers large hydrophobic residues. Chymotrypsin preferentially catalyzes the hydrolysis of peptide bonds involving tyrosine, phenylalanine, and tryptophan), **elastase** etc.
- ✓ Proteolytic enzymes break the proteins down into free amino acids as well as dipeptides and tripeptides, which in turn are absorbed by the intestinal mucosa cells and subsequently are released into the blood stream where they are absorbed by other tissues.

Turnover of cellular proteins

- ✓ Turnover of cellular proteins (continuous degradation and synthesis) occur in all forms of life.
- ✓ Each day, humans turn over 1% to 2% of their total body protein, principally muscle protein.
- ✓ Approximately 75% of the amino acids liberated by protein degradation are reutilized, the remaining excess free amino acids are not stored for future use (i.e. amino acids not immediately incorporated into new protein are rapidly degraded).
- ✓ The relative susceptibility of a protein to degradation is expressed as its half-life ($t_{1/2}$).
- ✓ Half-lives of proteins may range from under 30 minutes to over 150 hours, or even the life time of an organ.

Cellular functions of protein degradation

1. The **recycling** of amino acids.
2. **Elimination** of misfolded and damaged proteins (due to environmental toxins, translationerrors and genetic mutations) when cannot be repaired.
3. **Regulation of cellular metabolism**, cellular growth and cell division (increase or decreasethe number of enzyme molecules and regulatory substances).
4. The **generation of active proteins** (the proteolytic cleavage of the precursor generates anactive enzyme).

Pathways of protein degradation

A. **General "non-specific" protein degradation** takes place in **lysosomes** (specialized organelles that operate at **low pH** (to denature proteins) and contain **proteases** for proteins, **lipases** for lipids, and many other **hydrolases** (~ 50 total)). By this pathway extracellular, membrane-associated, and long-lived intracellular proteins are degraded in lysosomes by **ATP-independent** processes.

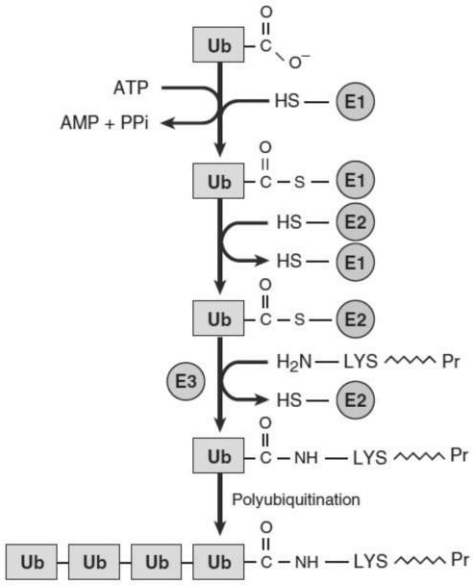
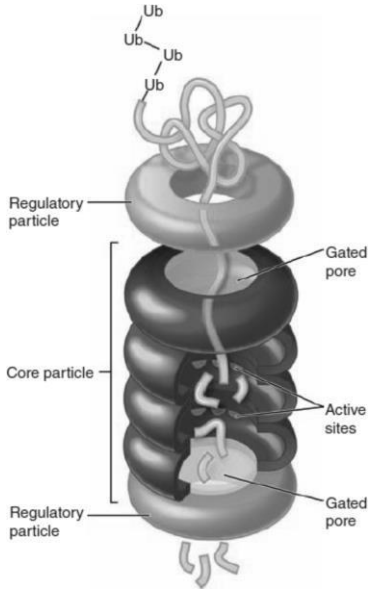
Many **normal** and **pathological** processes involve **increased lysosomal activity**, including:

- ✓ **Disuse atrophy of muscles** and **regression of the uterus after childbirth** (the muscular mass of the uterus is reduced from about 2 kg to about 50 g in just nine days).
- ✓ **Chronic inflammatory diseases** such as rheumatoid arthritis involve extracellular release lysosomal enzymes, which attack surrounding tissues.

B. **Controlled or programmed protein degradation involves the Ubiquitin-Proteasome system.**

Degradation of regulatory proteins with short half-lives and of abnormal or misfolded proteins occurs in the cytosol within the **proteasomes**, and **requires ATP** and **ubiquitin (Ub) (**a small polypeptide found in all eukaryotic cells, by which the cell distinguish between functional proteins and intracellular proteins that need to be degraded).

- ✓ Three different enzymes add progressively more **Ub** molecules, in tandem chains, an energy-requiring process (ATP). The more **Ub** molecules attached, the more rapid the degradation.
- ✓ Carboxyl terminal of Ub is attached to the ε-amino groups of lysyl residues in the target protein (isopeptide bond).
- ✓ The residue present at its amino terminus affects whether a protein is ubiquitinated. Amino terminal **Met**, or **Ser residues** retard, whereas **Asp**, or **Arg accelerate ubiquitination**.
- ✓ Subsequent degradation of Ub-tagged proteins **takes place** in the **proteasome**, a macromolecule that also is ubiquitous in eukaryotic cells.

	
Reactions involved in the attachment of ubiquitin (Ub) to proteins	**Representation of the structure of a proteasome** *The upper ring is gated to permit only polyubiquitinated proteins to enter the **proteosome**, where immobilized internal proteases degrade them to peptides.*

What controls the rate of protein degradation?

Different proteins are degraded at different rates. Abnormal proteins are quickly degraded, whereas the rate of degradation of normal proteins may vary widely depending on their functions. Enzymes at important metabolic control points may be degraded much faster than those enzymes whose activity is largely constant under all physiological conditions.

Degradation of normal proteins with comparable functions depends on:

- ✓ **N-terminal residue**, the residue present at its amino terminal affects whether a protein is ubiquitinated and subsequently degraded. Amino terminal **Met** or **Ser retards** whereas **Asp** or **Arg accelerates** **ubiquitination**.

- ✓ **PEST sequences**, regions rich in proline (P), glutamate (E), serine (S), and threonine (T), target **some** proteins for rapid degradation.

Interorgan exchange of amino acids

The net balance between release from endogenous protein stores and utilization by various tissues keeps the steady-state concentrations of circulating plasma amino acids between meals.

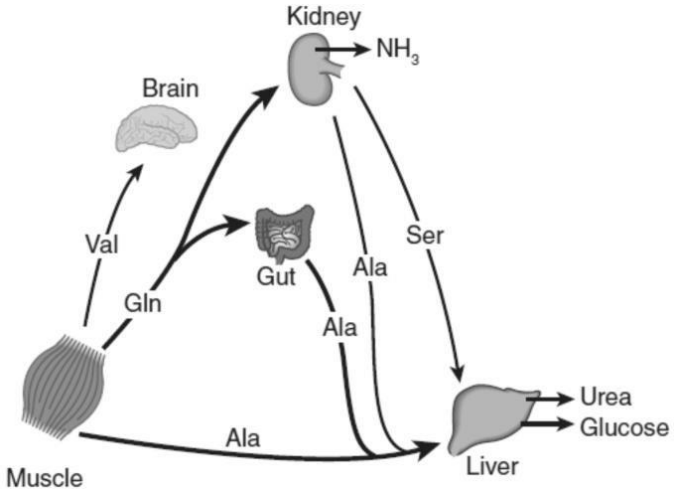
- In the **postabsorptive state**, free amino acids, particularly alanine and glutamine, are released from **muscle** into the circulation.

Alanine is extracted primarily by the liver, and glutamine is extracted by the gut and the kidney, both of which convert a significant portion to alanine. Alanine is a key **gluconeogenic amino acid**, and the rate of hepatic gluconeogenesis from alanine is far higher than from all other amino acids.

Glutamine also serves as a source of ammonia for excretion by the kidney.

Branched-chain amino acids, particularly valine, are released by **muscle** and taken up predominantly by the **brain**.

The **kidney** provides a **major source of serine** for uptake by peripheral tissues, including liver and muscle.



Interorgan amino acid exchange in normal postabsorptive humans

- In the **fed state (**following a protein-rich meal), the splanchnic tissues release amino acids while the peripheral muscles extract amino acids.