

Biochemistry
2nd stage

by

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Intermediary Metabolism

- **Intermediary metabolism:** the intracellular process by which nutritive material is converted into cellular components.
- **Metabolism:** is the entire network of chemical reactions carried out by living cells. It is also refer to the intermediate steps within the cells in which the nutrient molecules or foodstuffs are metabolized and converted into cellular components **catalysed by enzymes**.
- in cells, these reactions rarely occur in isolation, but rather are organized into multistep sequences called **pathways,** where the product of one reaction becomes the substrate for the next reaction, **such as glycolysis**. Most pathways can be classified as either catabolic (degradative) or anabolic (synthetic).

Catabolic pathways:

- involve reactions that **breakdown** complex molecules, such as proteins, polysaccharides, and lipids, to a few **simple molecules**, like, CO_2, NH_3 (ammonia) and water.
- Catabolism also allows molecules in the diet (or nutrient molecules stored in cells) to be converted into building blocks needed for the synthesis of molecules energy generation by degradation of complex molecules occurs in three stages :

1- Hydrolysis of complex molecules.

2- Conversion of building blocks to simple intermediates.

3- Oxidation of acetyl CoA.

Anabolic pathways:

- Anabolic pathways its reaction that form complex end products from simple precursors, like synthesis of **glycogen**, **polysaccharides from glucose**. Anabolic reaction required energy, which is generally provided by the **breakdown of ATP to ADP and Pi**. Also anabolic reactions involve chemical reductions in which the reducing power is most frequently provided by the electron donor NADPH.

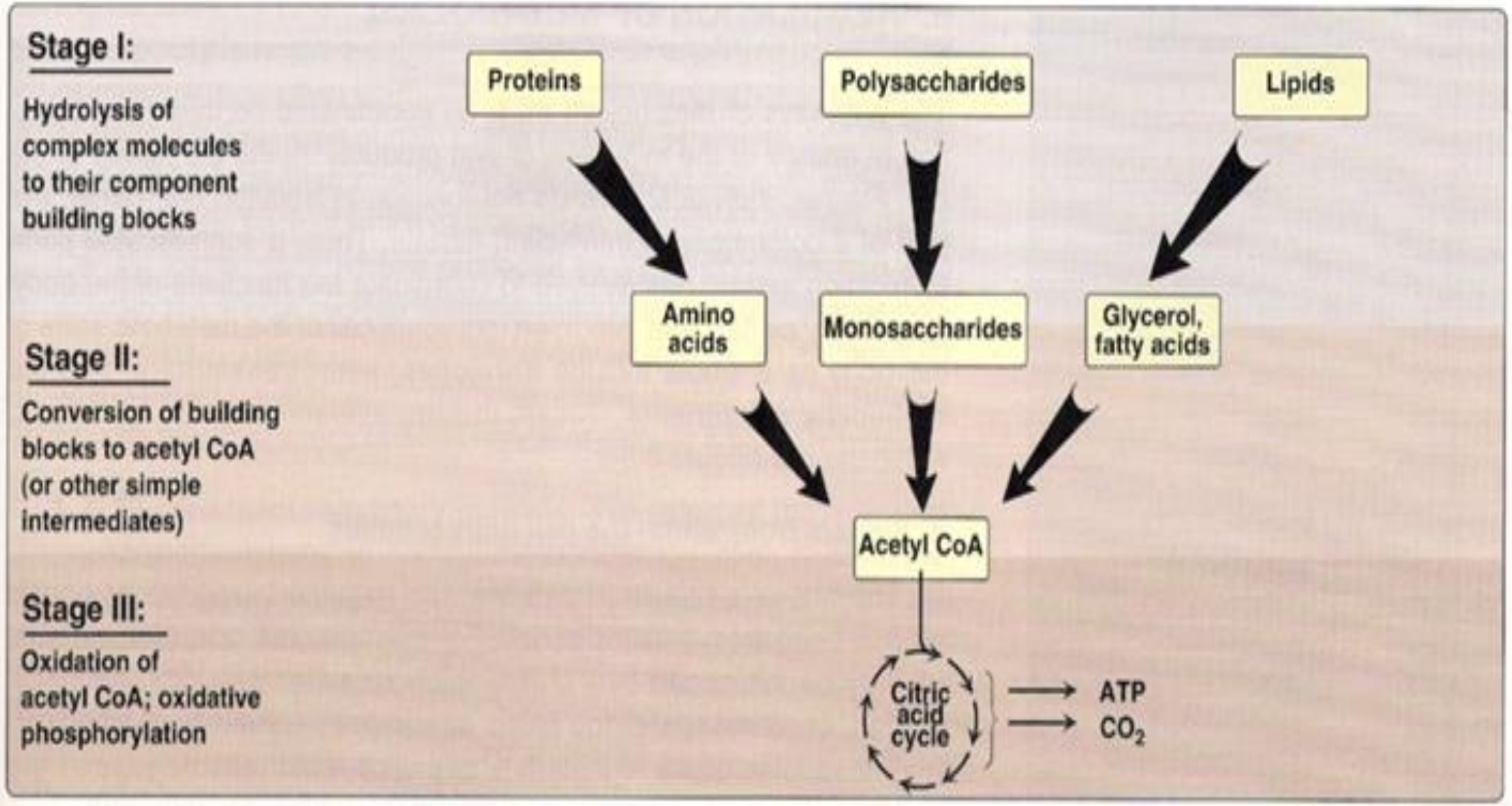


Figure 8.3
Three stages of catabolism.

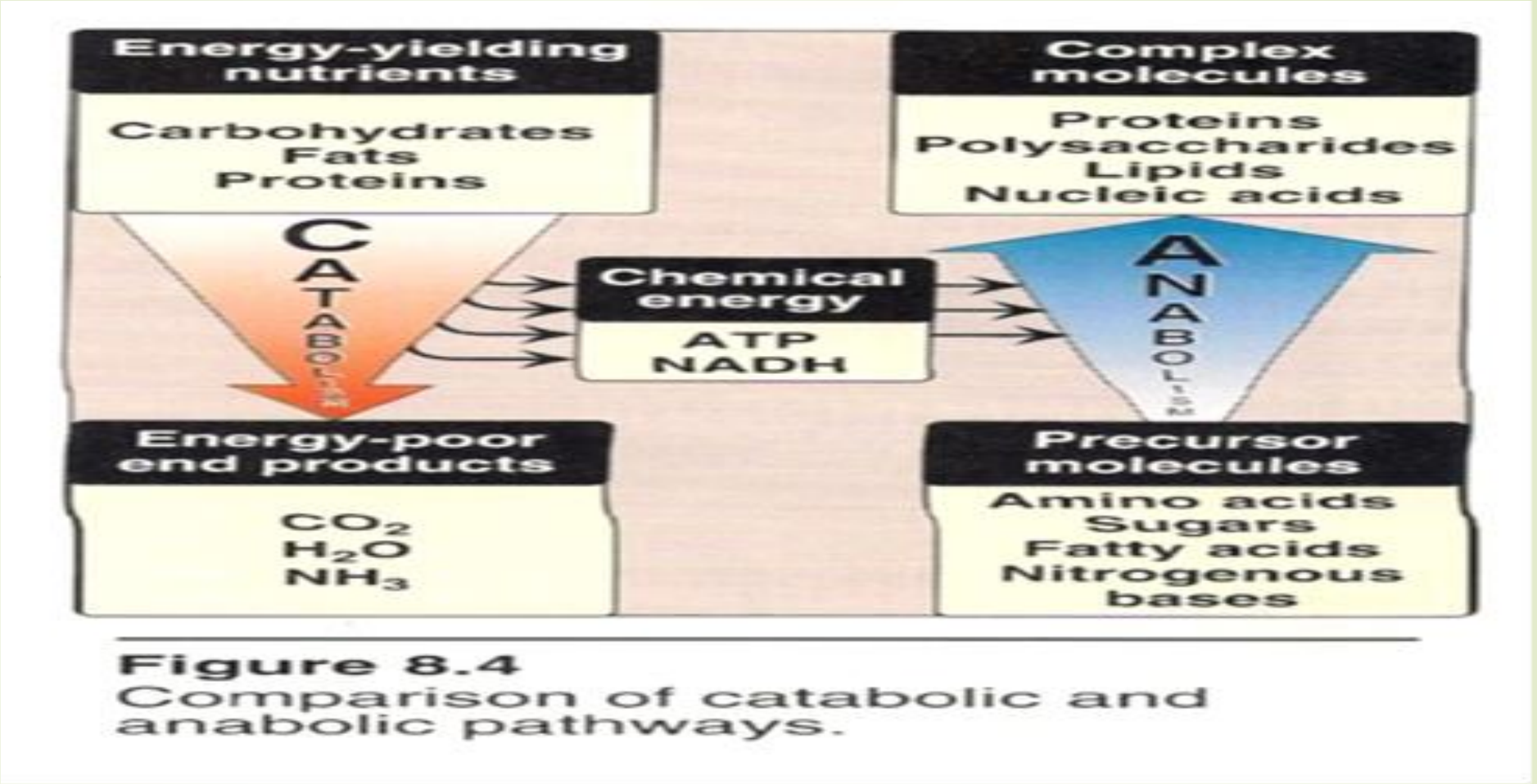


Figure 8.4
Comparison of catabolic and anabolic pathways.

- Metabolic pathways may have **a third category** called Amphibolic pathway occur at the "crossroads" of metabolism, acting as links **between** the anabolic and catabolic pathways, **e.g., citric acid cycle.**

Cellular Regulation of Metabolic Pathways:

- The regulation of metabolic pathways may occur at several levels.

1- The reaction rate is a function of pH, intracellular concentration of substrates, products and cofactors.

2- Control of metabolic sequence through the action of regulatory enzymes.

3- Regulation through the genetic control of the rate of enzyme synthesis.

4- Regulatory signals that inform an individual cell of the metabolic state of the body as a whole include hormones, neurotransmitters and the availability of nutrients.

Biomedical importance of Carbohydrates

- Chief source of energy.
- Constituents of compound lipid and conjugated proteins.
- Degradation products act as "promoters" or "catalysts".
- Certain carbohydrates derivatives are used as drugs like glycosides/antibiotics.
- Lactose principle sugar of milk, in lactating mammary gland.
- Degradation products utilized for synthesis of other substances such as fatty acids, cholesterol, amino acid…
- Constituents of mucocpolysaccharides which form the ground substances of mesenchymal tissues.
- Inherited deficiency of certain enzymes in metabolic pathways of different carbohydrates can cause diseases, e.g. galactosemia, glycogen storage diseases (GSDs), lactose intolerance…
- Derangement of glucose metabolism is seen in diabetes mellitus.

Digestion of carbohydrates:

- The major dietary carbohydrates are starch, sucrose, and lactose.
- Human can digest only polysaccharides consisting of □(1□ 4) glycosidic linkage or □(1□ 4) linkage with □(1□ 6) branch points.
- Liquid food materials like milk, soup, fruit juice escape digestion in the mouth as they swallowed, but solid foodstuffs are masticated thoroughly before they swallowed.

- **Digestion in Mouth:** Salivary α- amylase (ptyalin) (which requires Cl- ion for activation, pH about 6.7) will hydrolyzes α-(1-4) glycosidic linkage, **molecules** like starch, glycogen, and dextrin will produce smaller molecules: maltose, glucose and maltotriose.
- There **is no digestion** for carbohydrates in **stomach,** but some dietary sucrose may be hydrolyzed to glucose and fructose by HCl.
- **Digestion in the intestine**: food bolus reaches the duodenum from stomach where it meets the pancreatic juice. Pancreatic juice contain bicarbonate (HCO_3^-) neutralizes the stomach acid, raising the pH into the optimal range for the action of the intestinal enzymes.

1) Digestion of pancreatic enzymes:

- a- The pancreas secretes an α- amylase also called amylopsin, it is similar to salivary amylase, the enzyme hydrolyze α- (1-4) glycosidic linkages between glucose residues.
- b- The products of pancreatic α- amylase are the disaccharides maltose, maltotriose, and small oligosaccharides containing α- (1-4) and α- (1-6) linkages.

2) Digestion by enzymes of intestinal cells:

- Action of intestinal juice:

a- **intestinal amylase:** This hydrolyzes terminal α- (1-4) glycosidic linkage in polysaccharides and oligosaccharide molecules liberating free glucose molecule.

b- **Isomaltase:** It catalyze the hydrolysis of α-(1-6) glycosidic linkage, producing maltose & glucose.

c- **Maltase:** hydrolyze the α- (1-4) glycosidic linkage, producing two glucose molecules.

d- Lactase: It is a β **-galactosidase**. Lactose is hydrolyzed to glucose and galactose.

e- **Sucrase:** This enzyme converts sucrose to glucose and fructose.

Absorption of glucose, fructose and galactose:

- **Mechanisms of absorption:**

1-Simple Diffusion: This is dependent on sugar concentration gradients between the intestinal lumen, mucosal cells and blood plasma. All the monosaccharaides are probably absorbed to some extent by simple "passive" diffusion.

2- Active Transport Mechanisms:

- Glucose, fructose and Galactose, the final products generated by digestion of dietary carbohydrates, are absorbed by intestinal epithelial cells.
- Galactose and glucose are absorbed very fast, fructose and mannose intermediate rate and the pentoses are absorbed slowly. Galactose is absorbed more rapidly than glucose.
- They are transported into the cells on **transport proteins**, moving down a concentration gradient.
- **The carrier protein** has two binding sites one for **Na** and another for the **glucose**. The carrier protein is specific for sugar and it is mobile, a Na dependent and energy dependent.

Glucose Transporters (GluT)

- Glucose also moves into cells on transport protein called **glucose transporters (GluT)** that carries sodium ions in addition to the monosaccharide.
- Glucose Transporters(Glu-T) are several (Glu-T-1 to 7).The most **important are GluT-2 and GluT-4**
- GluT-2: Operates in intestinal epithelial cells; it is not Na dependent.
- GluT-4: Operates principally in **muscles** and **adipose tissue.**
- The **GluT-4 is under control of insulin** and moves between cytoplasm and membrane.

*** ((Note: Other "GluT" molecules are not under control of insulin)).**

- GluT-1 : is present mainly in RB cells and brain. Also present in **retina, colon** and **placenta.**

Absorption of other sugars:

- Sugars like **D-fructose** and **D-mannose** are probably absorbed by "facilitated transport" which requires the presence of **carrier protein** but does not require energy.
- Other sugars like **pentoses** and galactose are **absorbed passively** by **simple diffusion**.

Factors influencing rate of absorption:

Hormones: thyroid hormones **increase** hexoses absorption, while adrenal cortex hormones deficiency **decrease** the hexoses absorption due to decreased Na concentration in body fluids.

Vitamins: deficiency of **B-vitamins** decreased hexoses absorption.

Inherited enzyme deficiencies like **sucrase and lactase** can interfere with hydrolysis of corresponding disaccharides and their absorption

Utilization of Glucose:

1- Oxidation:

a- For provision of energy: In response to physiological needs, human body requires energy, oxidation of glucose or glycogen to pyruvate and lactate by EM pathways is called **"glycolysis". Glycolysis occurs in all tissues.**

b- HMP shunt: An alternative pathway for oxidation of glucose. It is not meant for energy. The pathway provides :

(1) NADPH which is used for reductive synthesis.

(2) Pentoses which is used for nucleic acids synthesis.

This pathway operates only in certain special tissues and not all tissues.

c- Uronic acid pathway: An alternative pathway for oxidation of glucose.

It provides **D-glucuronic acid** which is used for synthesis of mucopolysaccharides and conjugation reactions.

2- Storage: Excess of glucose taken is converted to glycogen in various tissues (glycogensis) especially liver and skeletal muscle and stored there for future needs.

3- Conversion to Fats: Excess of glucose is converted to FA and stored as "triacylglycerol" (TG) in Fat depots (lipogenesis).

4- Conversion to other carbohydrates: small amounts of glucose are used directly or indirectly in synthesis other carbohydrates or derivatives, which play important role in the body.

- **Formation of ribose and deoxyribose.**
- **Formation of fructose from glucose.**
- **Mannose, fucose, glucosamine and Neuraminic acid.**
- **Galactose.**
- **D – Glucuronic acid.**

5- Conversion to Amino acids.