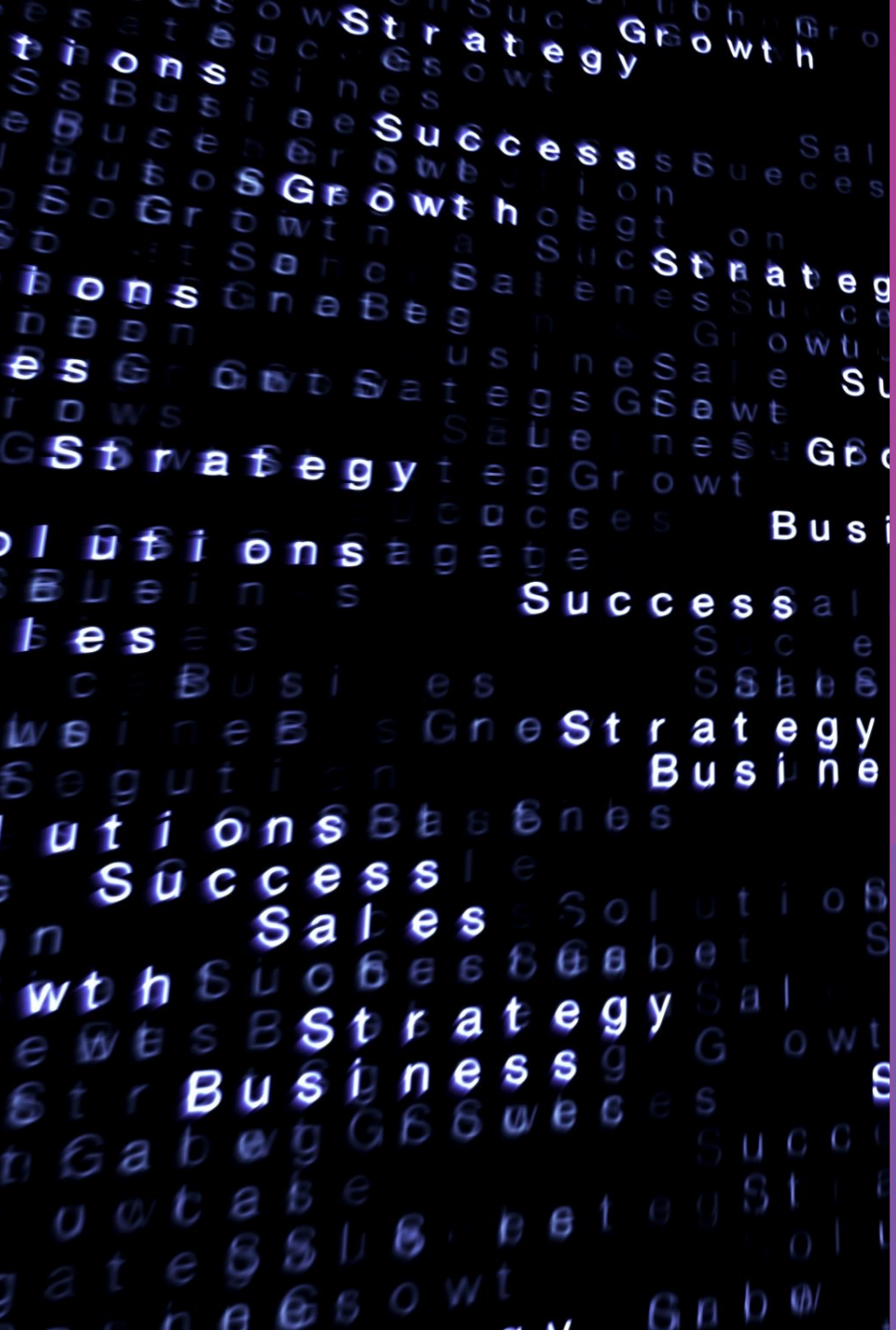
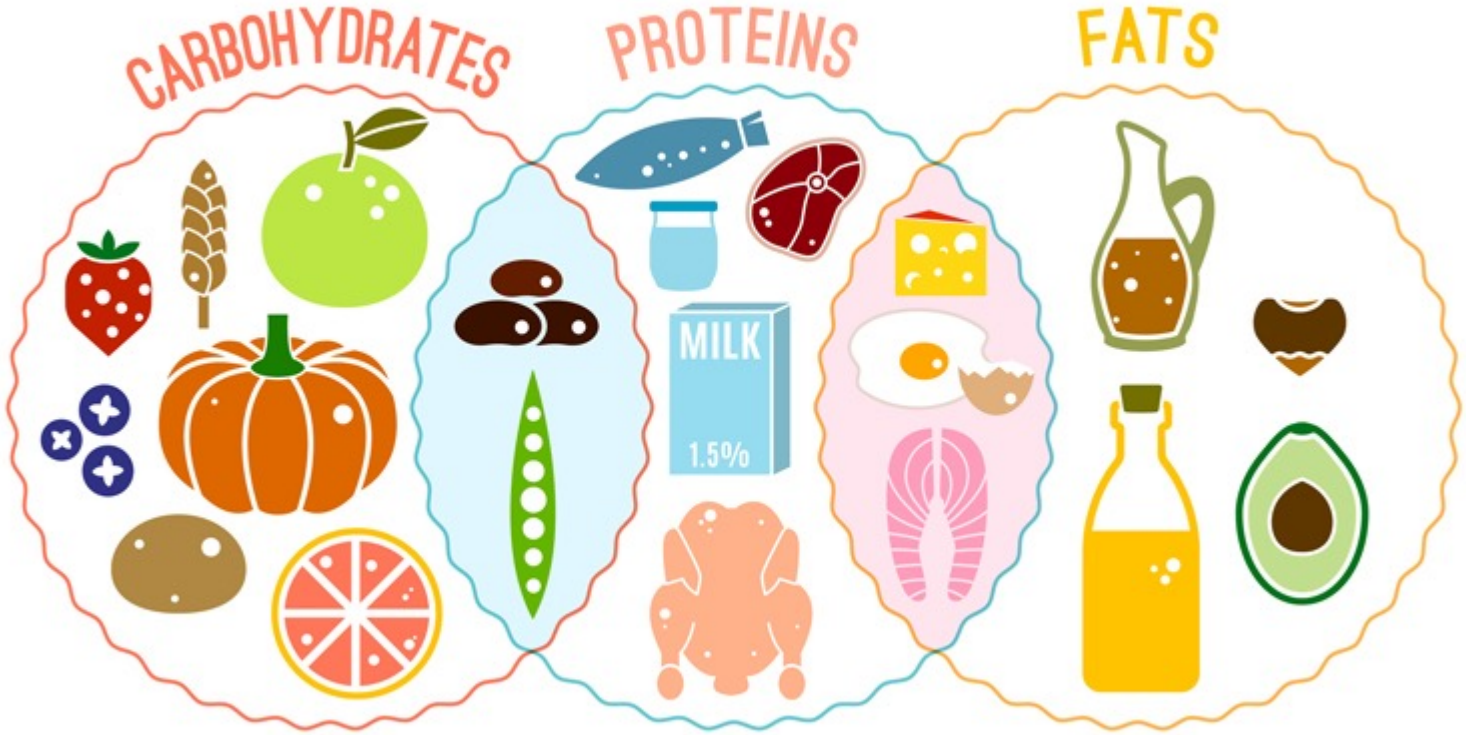


DINH DƯỠNG ĐA LƯỢNG (MACRONUTRIENTS)

DINH DƯỠNG VI LƯỢNG (MICRONUTRIENTS)

DINH DƯỠNG ĐA LƯỢNG(MACRONUTRIENTS)

- CARBOHYDRATE (CHO)
- LIPID
- PROTEIN
- CHẤT XƠ (FIBER)



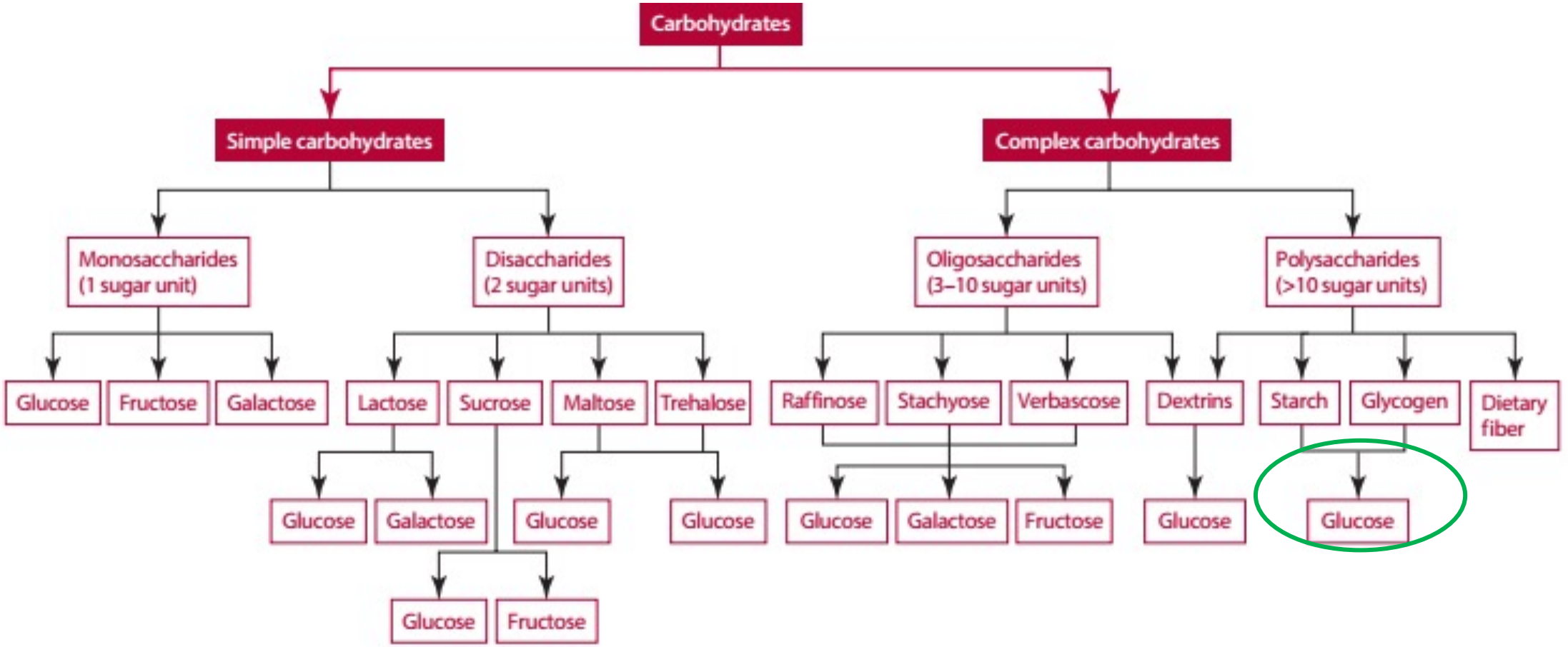


Figure 3.1 Classification of carbohydrates.
Source: Beerman/McGuire, Nutritional Sciences, 1/e. © Cengage Learning.

Fiber=cellulose → ĐV k tiêu hóa được do: beta (1-4) homopolysaccharide –X- alpha-amylase → alpha-polysaccharide (starch)

Tuy nhiên một số chủng VK đường ruột có thể tiêu hóa được chúng thành các acid béo chuỗi ngắn

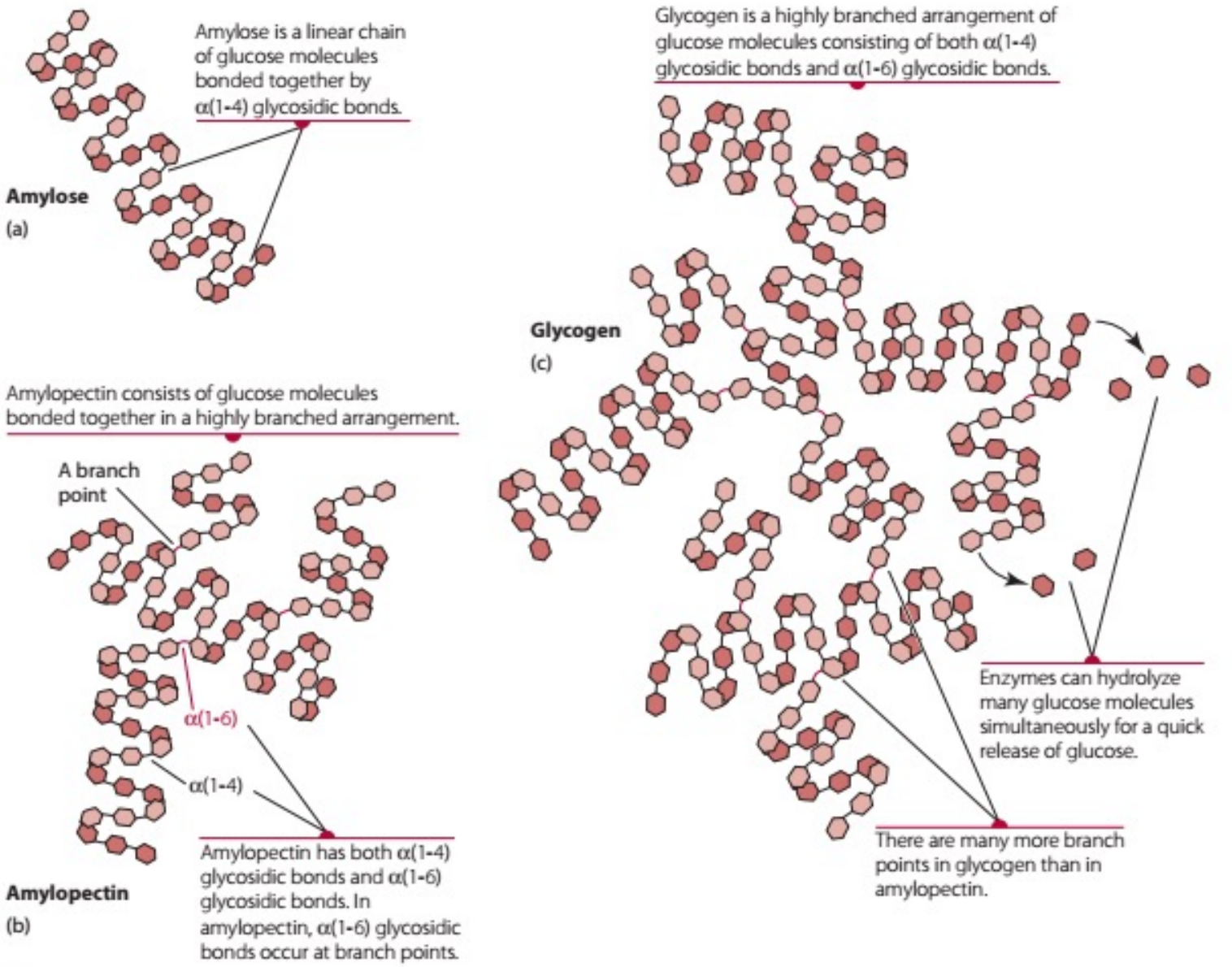
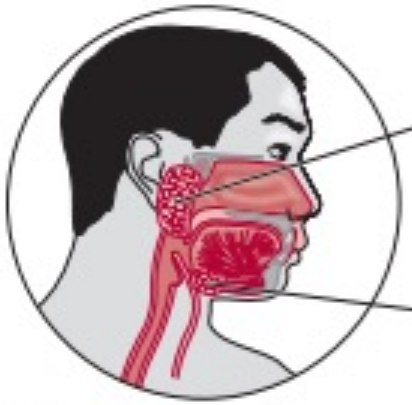


Figure 3.6 Structure of starches and glycogen.
Source: Beerman/McGuire, *Nutritional Sciences*, 1/e. © Cengage Learning.

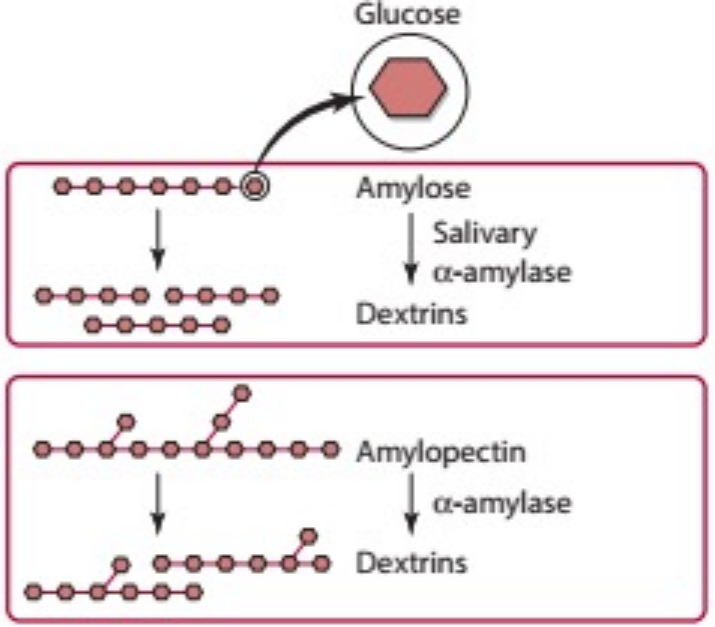
1



A. Digestion of amylose and amylopectin in the mouth

Amylose: Salivary glands release salivary α-amylase, which hydrolyzes α(1-4) glycosidic bonds in amylose, forming dextrins.

Amylopectin: Salivary glands release salivary α-amylase, which hydrolyzes α(1-4) glycosidic bonds in amylopectin, forming dextrins.



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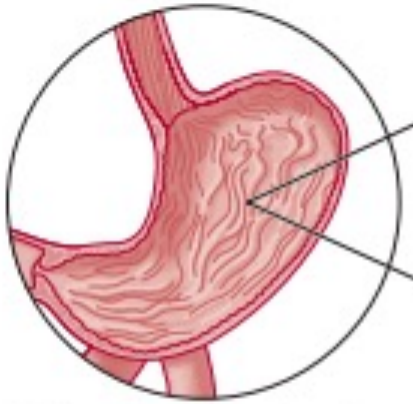


B. There is no digestion of amylose and amylopectin in the stomach

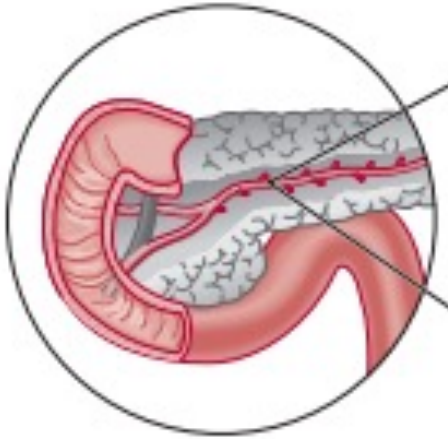
Amylose: Acidity of gastric juice destroys the enzymatic activity of α-amylase. The dextrins pass unchanged into the small intestine.

Amylopectin: Acidity of gastric juice destroys the enzymatic activity of salivary α-amylase. The dextrins pass unchanged into the small intestine.

No further digestion

No further digestion

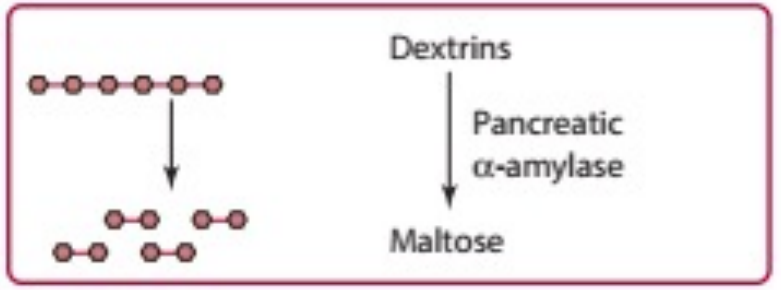
3

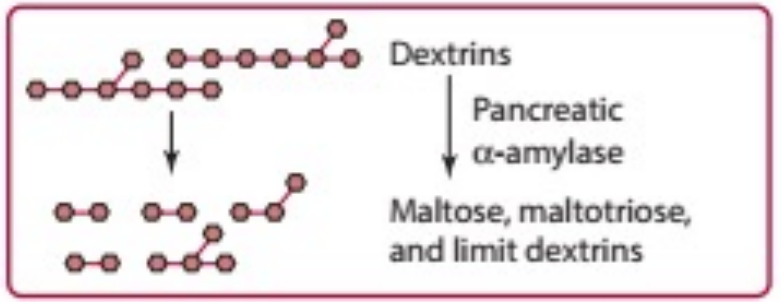


Amylose: The pancreas releases pancreatic α-amylase, which hydrolyzes α(1-4) glycosidic bonds, into the small intestine. Dextrins are broken down into maltose.

Amylopectin: The pancreas releases pancreatic α-amylase, which hydrolyzes α(1-4) glycosidic bonds to produce limit dextrins, maltotriose, isomaltose, and maltose. Hydrolysis stops four residues away from the α(1-6) bond.

C. Digestion of amylose and amylopectin in the small intestine





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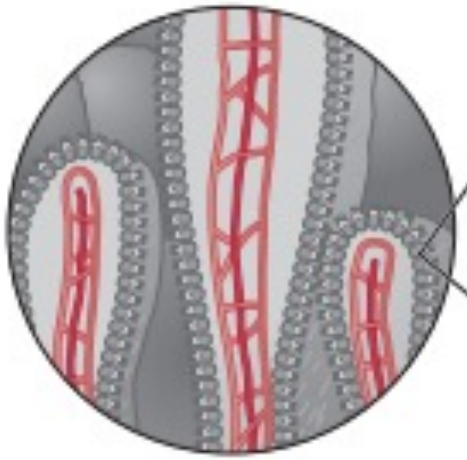
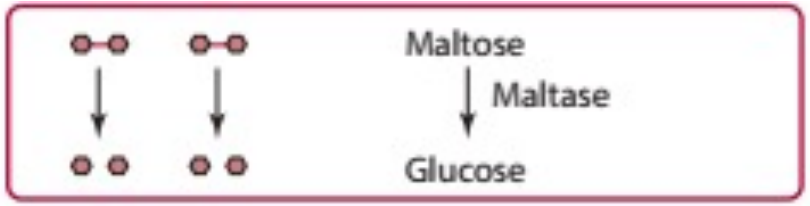
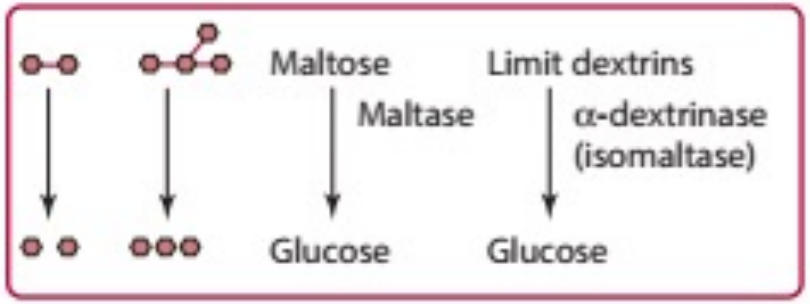


Amylose: Maltose is hydrolyzed by maltase, a brush border enzyme, forming free glucose.

Amylopectin: Maltose, maltotriose, and isomaltose are further hydrolyzed in the brush border by the enzyme maltase or α-dextrinase to glucose. α-dextrinase is the sole carbohydrase capable of hydrolysing α(1-6) glycosidic bonds.

D. Digestion of amylose and amylopectin on the brush border of the small intestine





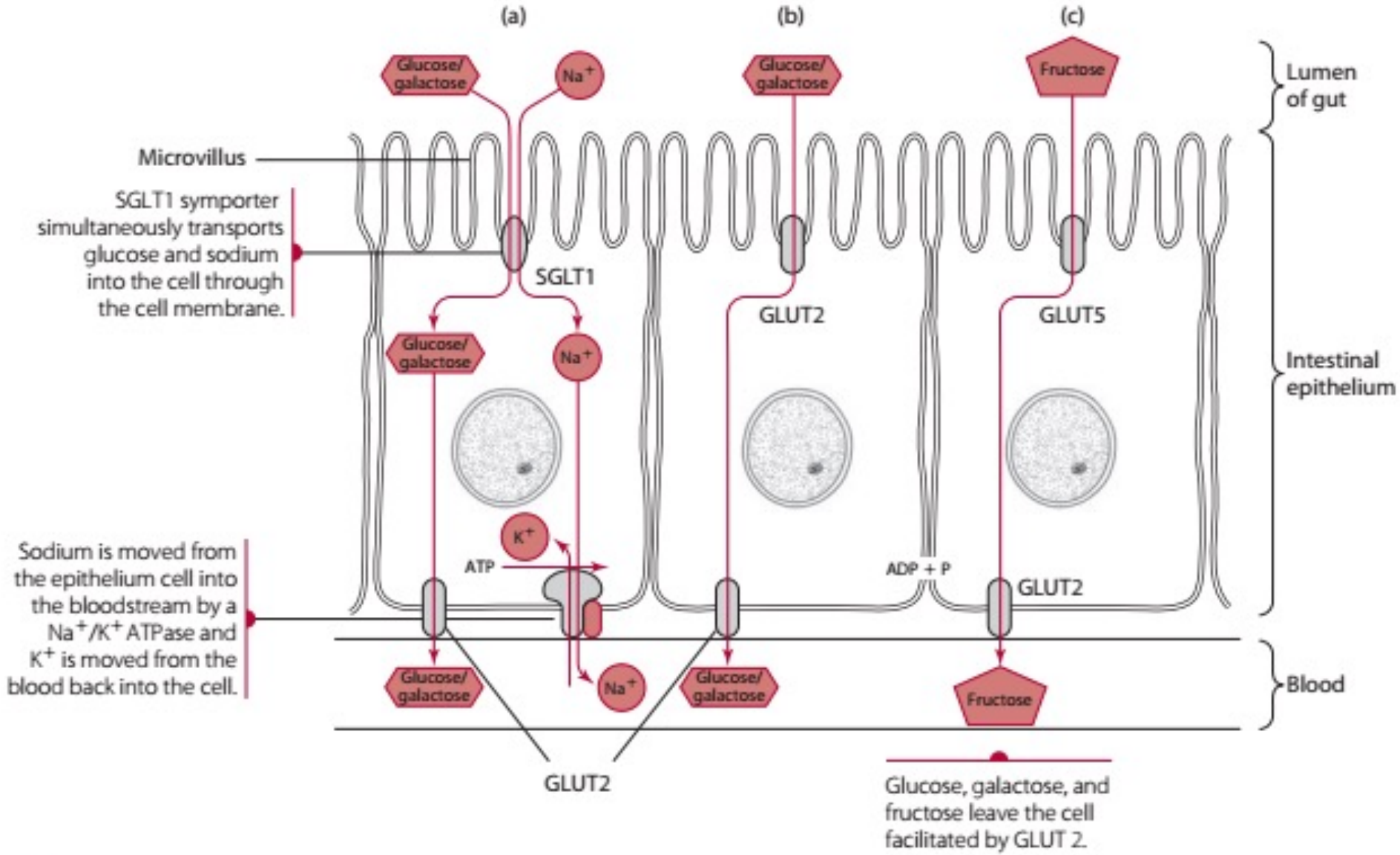


Figure 3.8 Transport of monosaccharides into enterocytes. (a) Active transport of glucose and galactose requiring ATP and Na^+. (b) Facilitated transport of glucose and galactose into the enterocyte by GLUT2 when the intestinal lumen glucose levels are high; glucose and galactose may also exit the cell with assistance from GLUT2. (c) Fructose entering the enterocyte via transport facilitated by GLUT5 and leaving the cell via transport facilitated by GLUT2.

Table 3.2 Glucose Transporters (GLUT)

Transporter Protein	Substrates	Major Sites of Expression
GLUT1	Glucose, galactose, mannose, glucosamine	Erythrocytes, central nervous system, blood–brain barrier, placenta, fetal tissues in general
GLUT2	Glucose, galactose, fructose, mannose, glucosamine	Liver, β-cells of pancreas, kidney, small intestine
GLUT3	Glucose, galactose, mannose, xylose, dehydroascorbic acid	Brain (neurons), spermatozoa, placenta, preimplantation embryos
GLUT4 (insulin dependent)	Glucose, glucosamine, dehydroascorbic acid	Muscle, heart, brown and white adipocytes
GLUT5	Fructose, but not glucose	Intestine, kidney, brain, skeletal muscle, adipose tissue

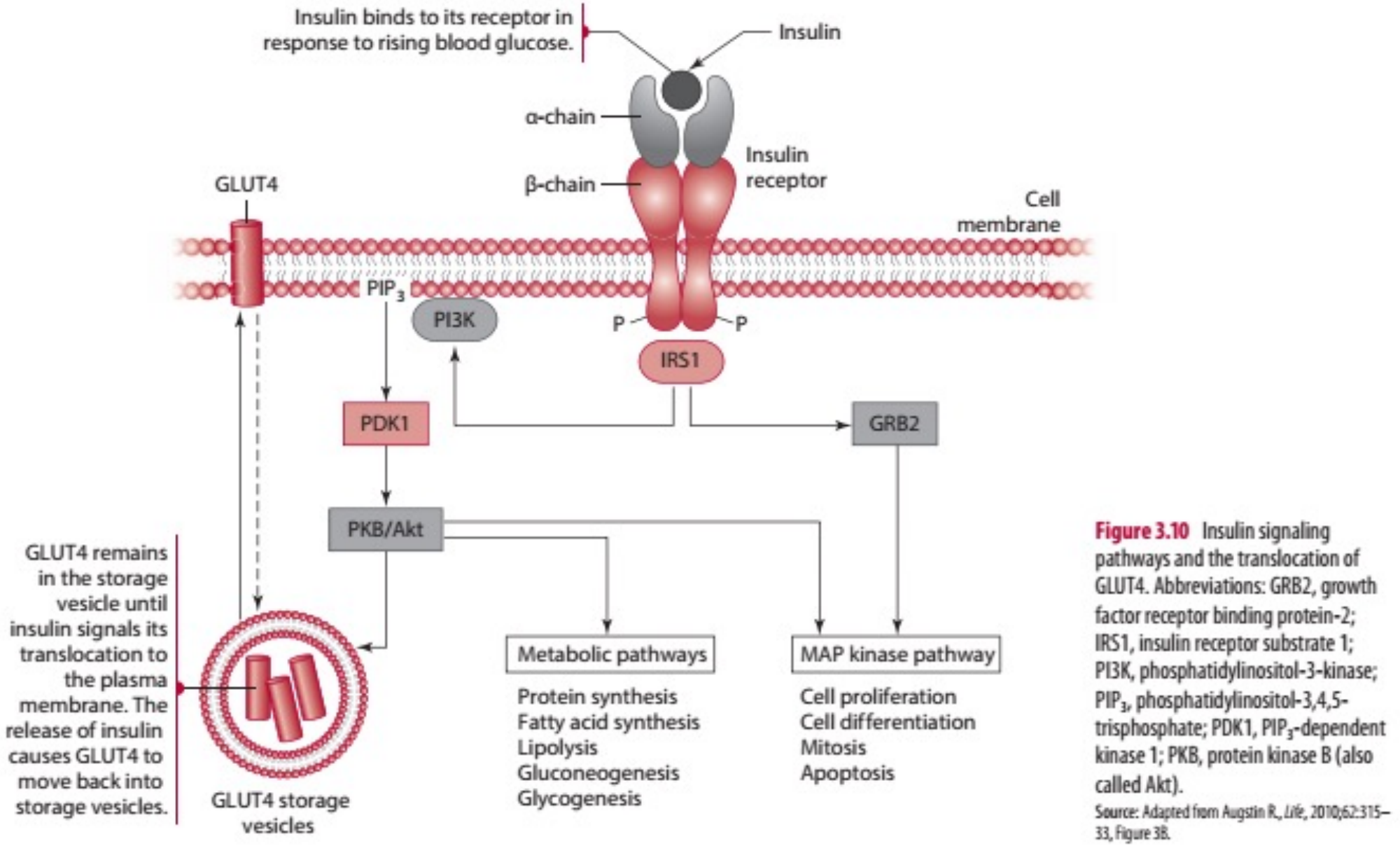


Figure 3.10 Insulin signaling pathways and the translocation of GLUT4. Abbreviations: GRB2, growth factor receptor binding protein-2; IRS1, insulin receptor substrate 1; PI3K, phosphatidylinositol-3-kinase; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PDK1, PIP_3-dependent kinase 1; PKB, protein kinase B (also called Akt).

Source: Adapted from Augstin R., *Life*, 2010;62:315–33, Figure 3B.

BIẾN DƯỠNG Ở MÔ

Glycogenesis
Glycogenolysis
Glycolysis
Gluconeogenesis
Pentose phosphate pathway
Tricarboxylic acid (TCA) cycle

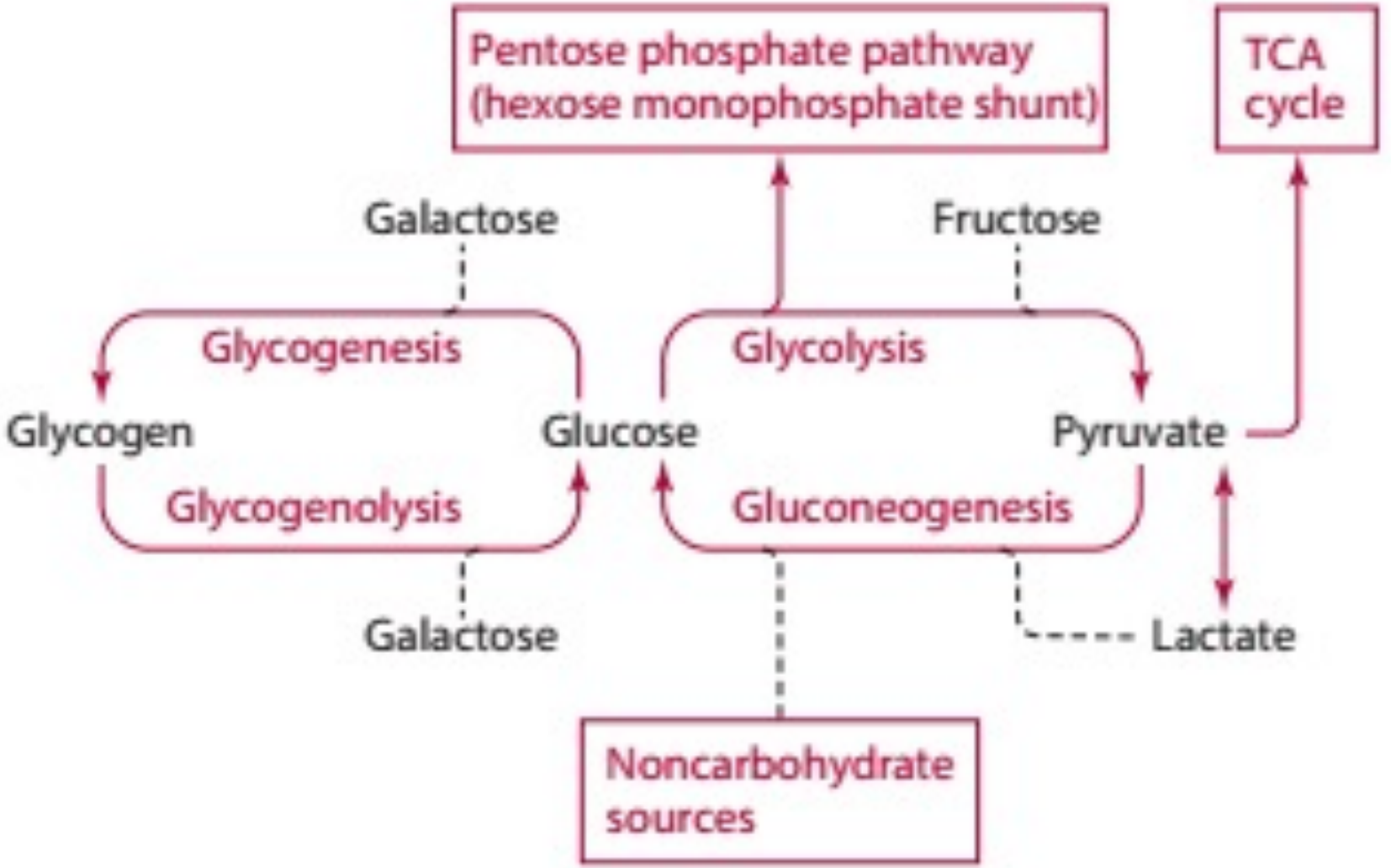
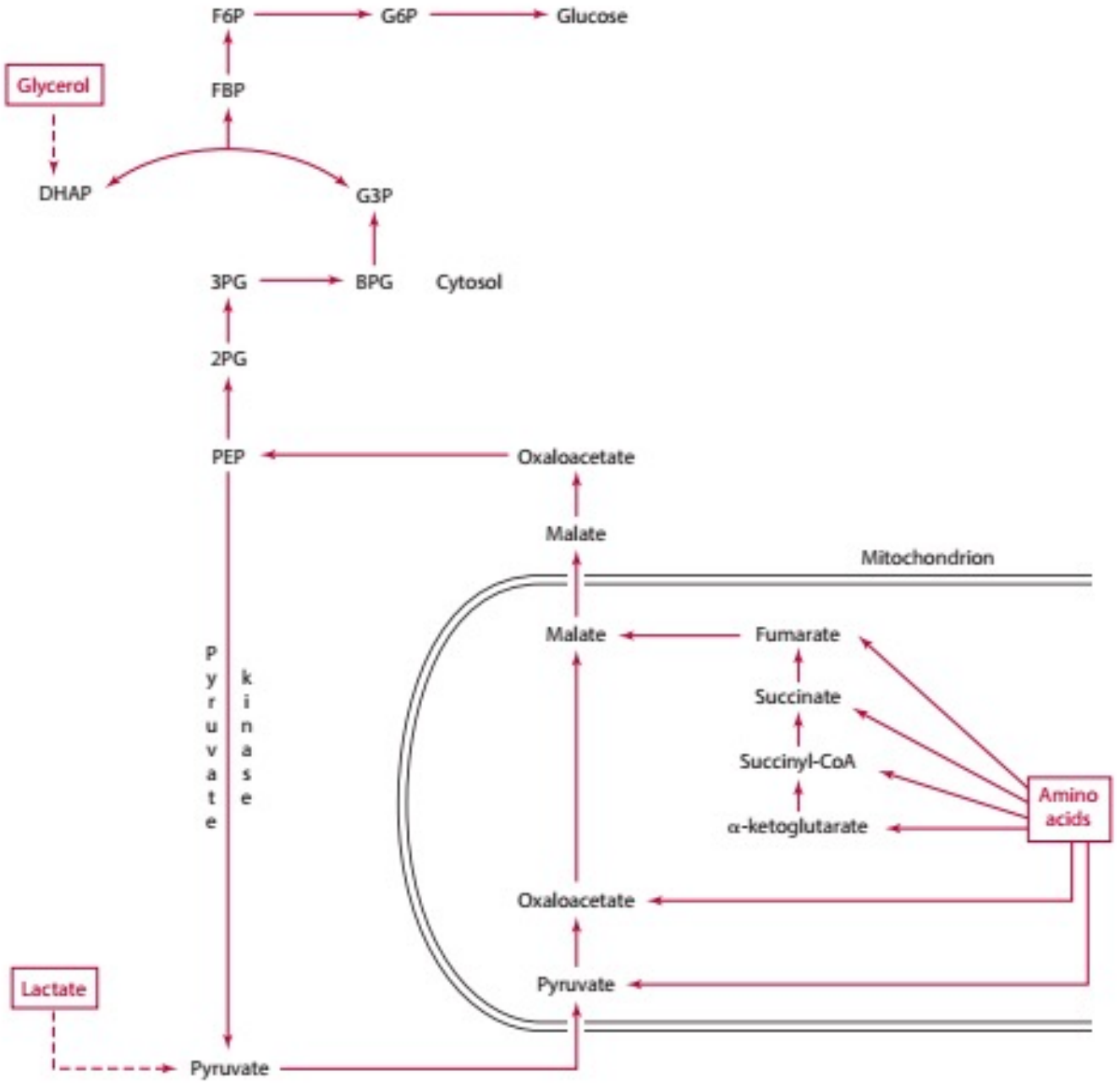


Figure 3.12 Integrated overview of carbohydrate metabolic pathways.

BIẾN DƯỠNG Ở MÔ

TÂN TẠO ĐƯỜNG



Chức năng chính của CHO

NĂNG LƯỢNG: TỔNG HỢP ATP (~ 4 KCAL/G)

TỔNG HỢP NEAA: BỘ KHUNG CARBON

TỔNG HỢP CHẤT BÉO: THÔNG QUA ACETYL-COA

TỔNG HỢP GLYCOGEN

CHẤT TRUNG GIAN CỦA CHU TRÌNH TCA

NUCLEOTIDES: PHẦN KHUNG ĐƯỜNG

GLYCOPROTEINS

GLYCOLIPIDS

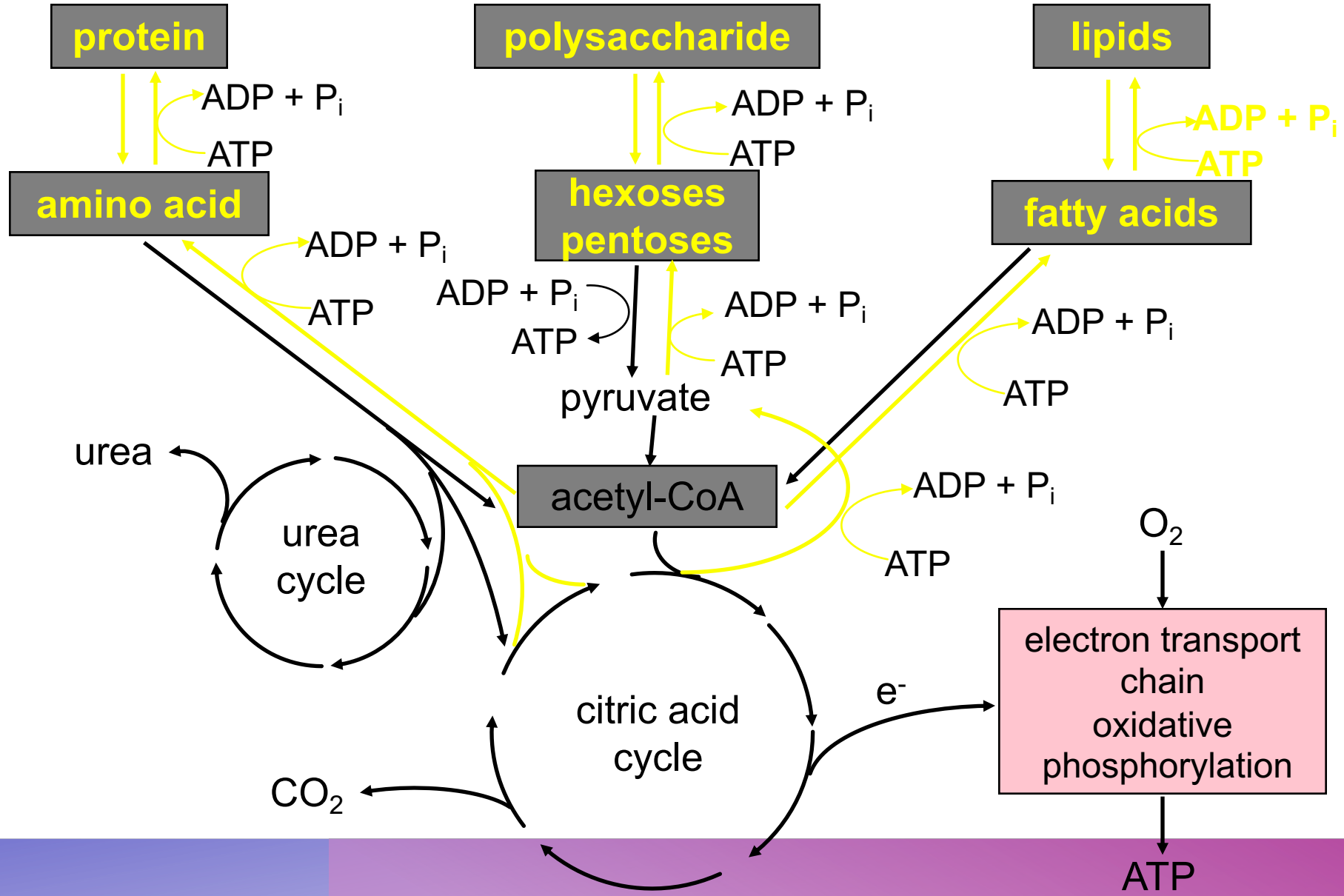

protein
polysaccharide
lipids
ADP + Pi
ATP
amino acid
hexoses
pentoses
fatty acids
pyruvate
acetyl-CoA
urea
urea
cycle
citric acid
cycle
CO2
O2
e-
electron transport
chain
oxidative
phosphorylation
ATP

TABLE 6.1 Amino Acids Found in the Human Body

Essential Amino Acids Found in Protein	Nonessential Amino Acids Found in Protein[a]	Nonessential Amino Acids Not Found in Protein
Tryptophan	Glycine	Ornithine
Valine	Aspartic acid	Taurine
Threonine	Asparagine	γ-aminobutyric acid (GABA)
Isoleucine	Proline	Beta-Alanine
Lysine	Glutamine	
Leucine	Glutamic acid	
Phenylalanine	Arginine	
Methionine	Cysteine	
Histidine	Tyrosine	
	Serine	
	Alanine	

[a]This list could also include post-translational derivatives of nonessential amino acids, such as hydroxyproline, hydroxylysine, homocysteine, and 3-methyl histidine.

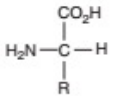


FIGURE 6.1. General Amino Acid Structure. Amino acids have an amino group, carboxyl group, hydrogen, and a side chain (R).

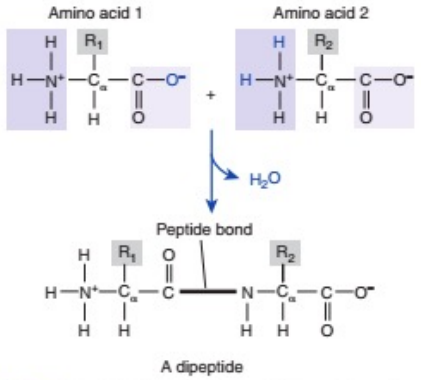


FIGURE 6.2. Peptide Bonds. A peptide bond forms from a reaction of an amino group with a carboxyl group between adjacent amino acids.

Dipeptide	Linkage of 2 amino acids
Peptide	Linkage of between 3 and 10 amino acids
Polypeptide	Linkage of more than 10 amino acids and typically fewer than 100 amino acids
Proteins	Very long linkages of amino acids (> 100) or more than one linkage complexed together (some scientists label amino acid links of more than 50 as proteins)

TABLE 6.2 Approximate Protein Content of Various Foods

Food	Protein (g)
Beef (3 oz)	25
Pork (3 oz)	23
Cod, poached (3.2 oz)	21
Oysters (3.2 oz)	17
Milk (1 cup)	8
Cheddar Cheese (1 oz)	7
Egg (1 large)	6
Peanut butter (2 tbsp)	8
Potato (1 large)	7
Bread (1 slice)	2
Banana (1 medium)	1
Carrots, sliced (2 cups)	1
Apple (1)	Trace
Sugar; oil	0

PROTEIN

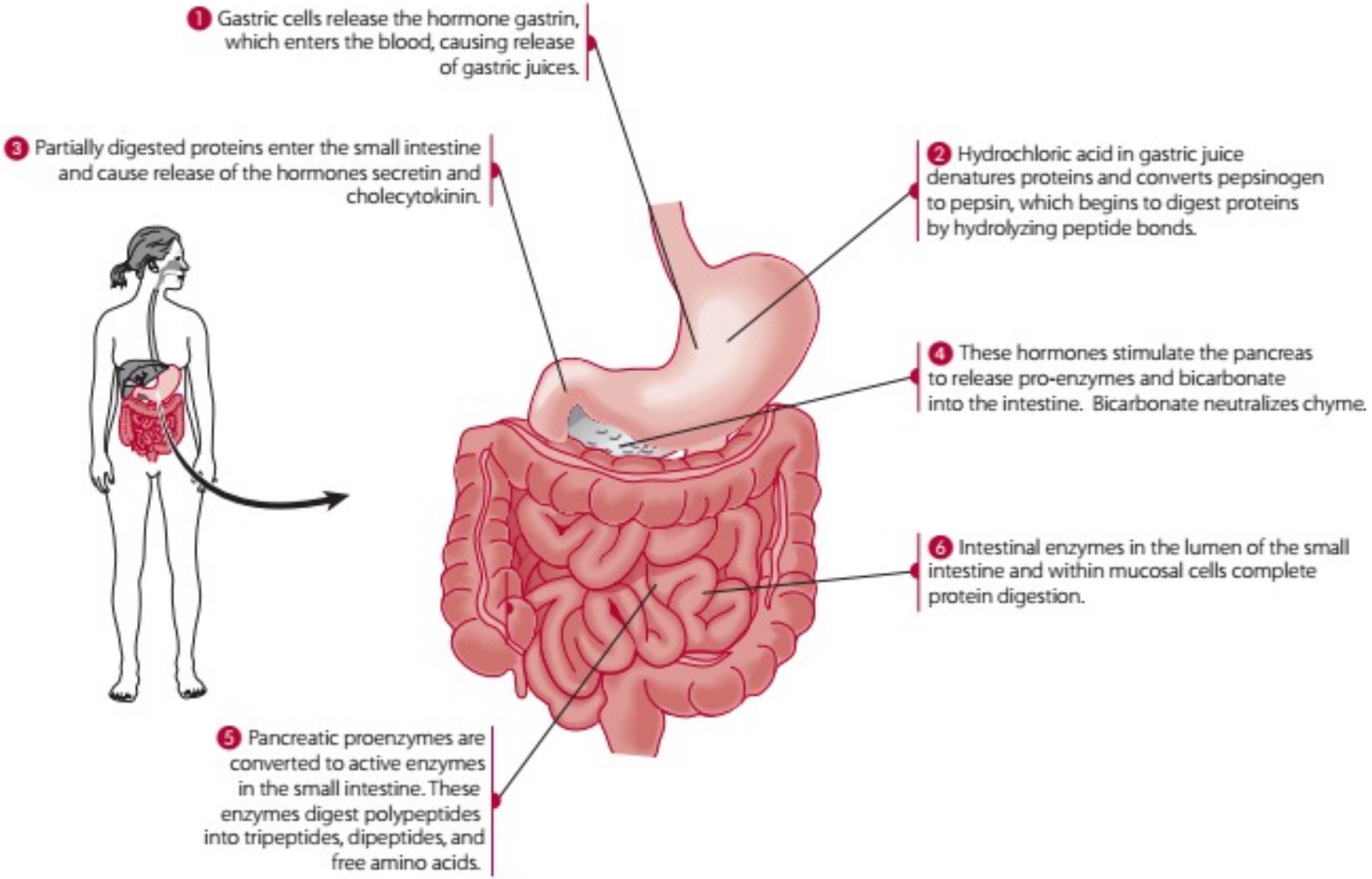
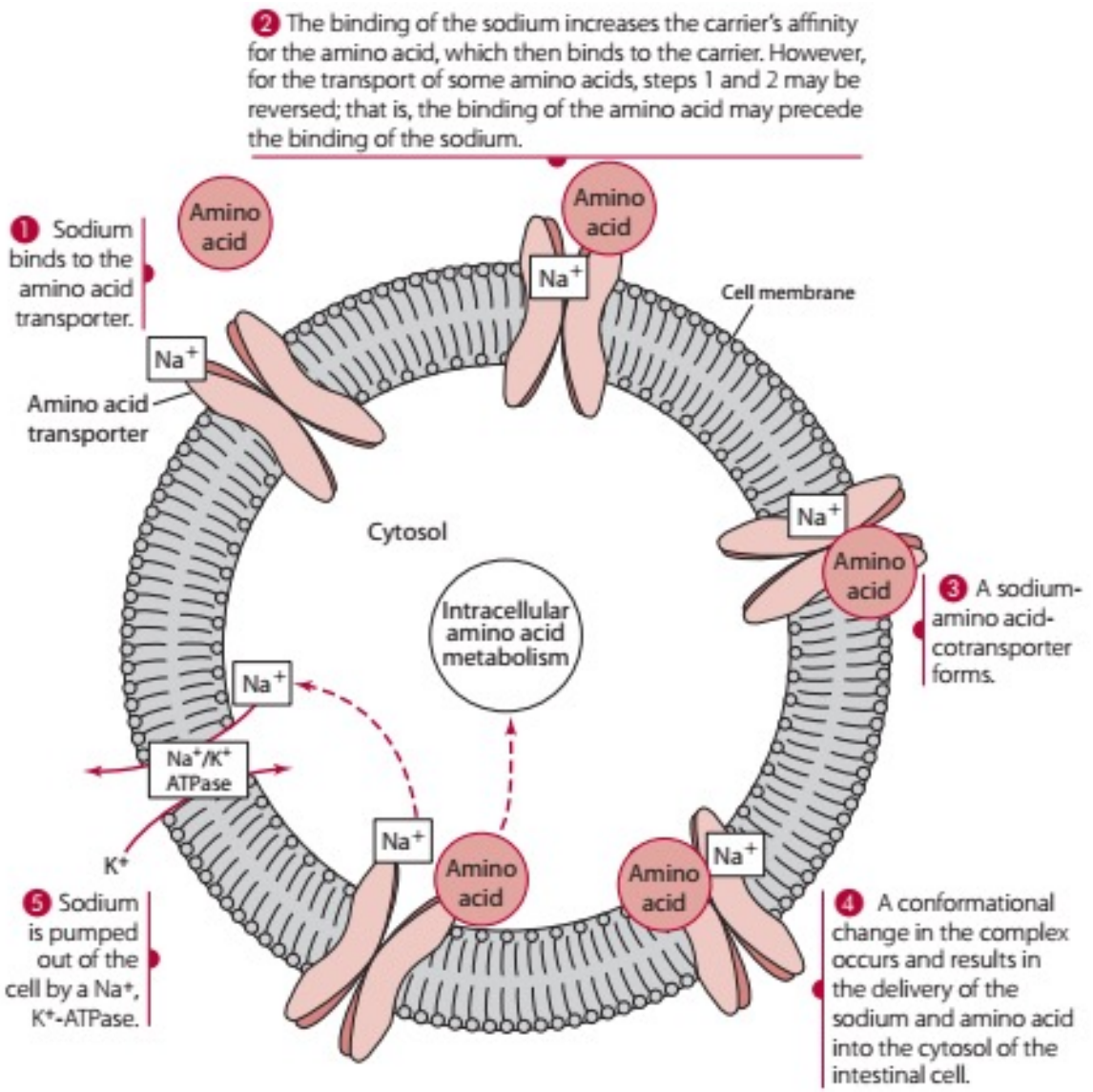


Figure 6.1 An overview of protein digestion.

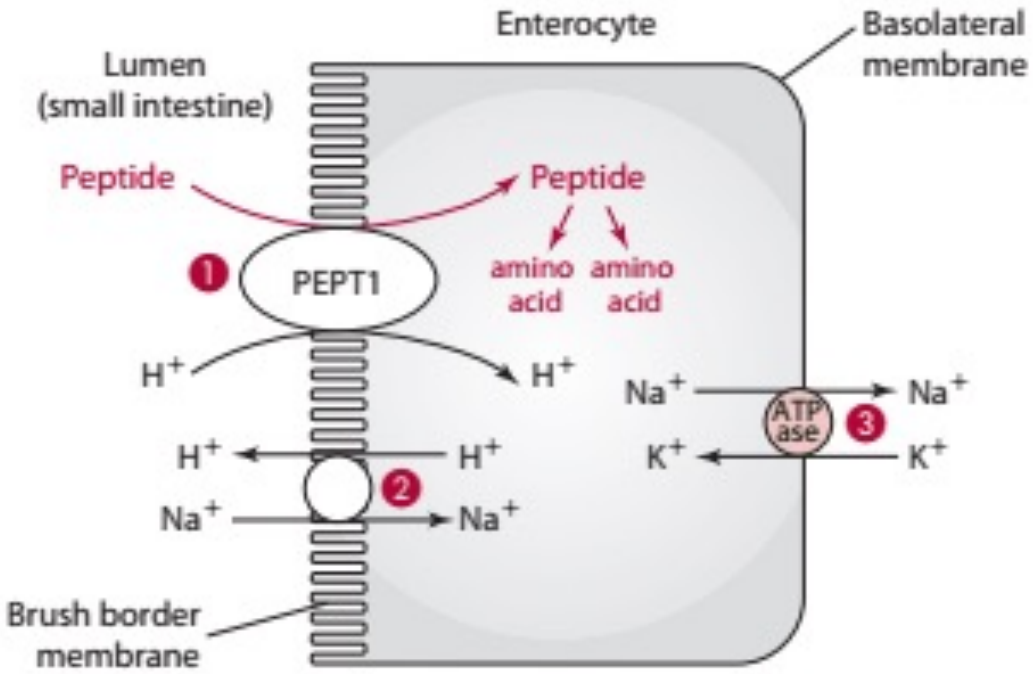
Source: Derived from Beerman/McGuire, Nutritional Sciences, 1/e. © Cengage Learning.

Table 6.4 Some Systems Transporting Amino Acids across the Intestinal Cell Brush Border Membrane

Amino Acid Transport Systems	Sodium Required	Some Amino Acids Carried
L	No	Leucine, other neutral amino acids
B^0	Yes	Most neutral amino acids
IMINO	No	Proline, hydroxyproline
PAT (imino acid)	No	Proline, glycine, alanine, β-alanine
y^+	No	Basic amino acids—arginine, lysine, histidine
X^-_{AG}	Yes	Acidic amino acids—aspartate, glutamate
$B^{0,+}$	Yes	Most neutral and basic amino acids, β-alanine
$b^{0,+}$	No	Arginine, lysine, ornithine, cysteine
ASC	Yes	Alanine, serine, cysteine, threonine, glutamine
N	Yes	Glutamine, asparagine, histidine
X^-_c	No	Glutamate, cystine



ure 6.2 Sodium (Na^+)–dependent transport of an amino acid into a cell.



❶ Peptides are transported into the intestinal cell along with H^+.

❷ The H^+ are pumped back into the intestinal lumen in exchange for Na^+.

❸ A Na^+, K^+–ATPase pumps Na^+ out of the cell in exchange for K^+ across the basolateral membrane.

Figure 6.3 Peptide transport. Peptides are transported across the brush border membrane of the intestinal epithelial mucosal cell.

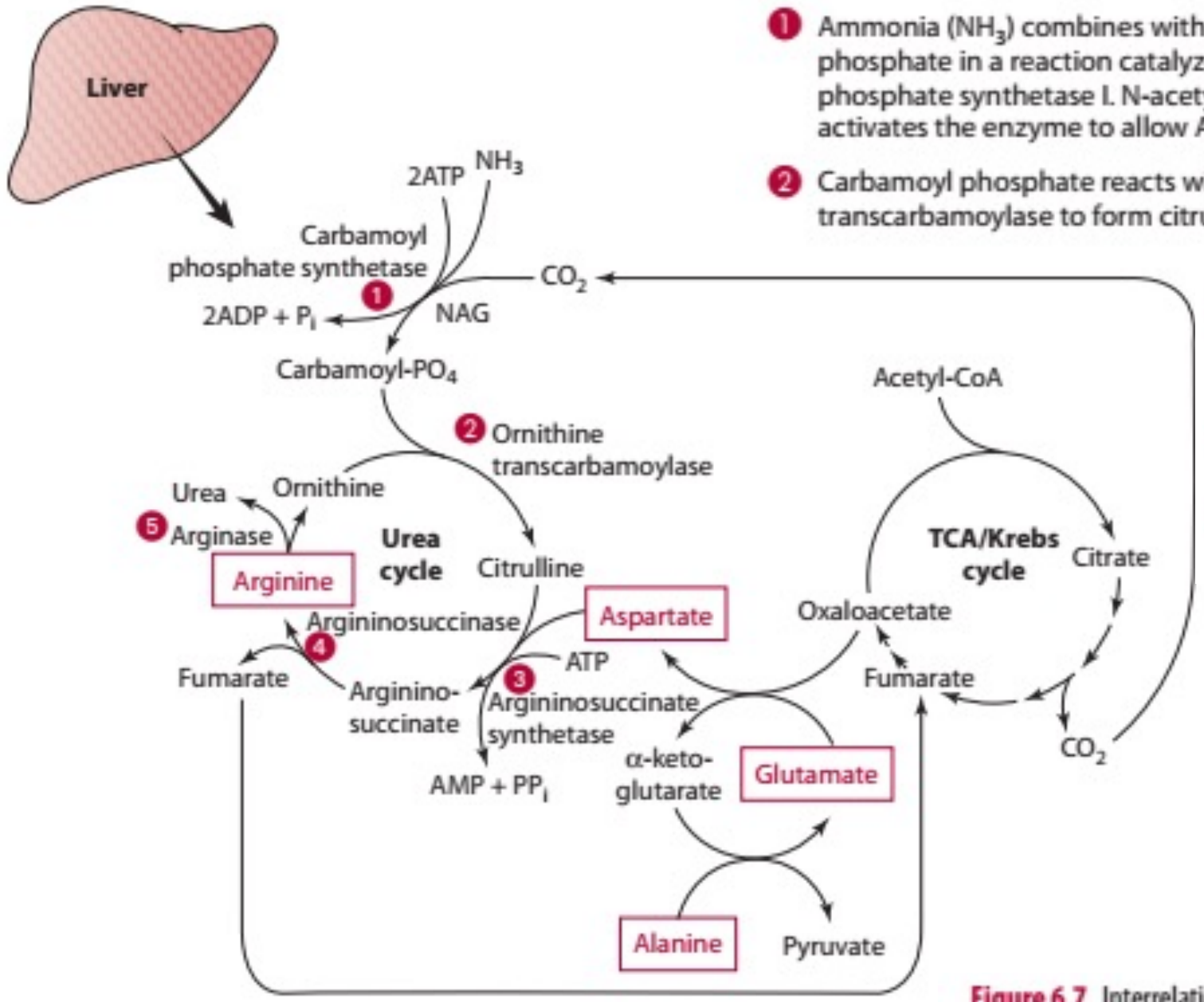
Peptide → aa hoặc diPP, triPP

phần lớn các acid amin được hấp thụ dưới dạng peptide

Peptide nguyên vẹn có được hấp thụ vào tế bào ruột không?

Table 6.5 Some Systems Transporting Amino Acids across the Intestinal Cell Basolateral Membrane

Amino Acid Transport System	Sodium Required	Some Amino Acids Carried
L	No	Leucine, other neutral amino acids except proline
T	No	Phenylalanine, tyrosine, tryptophan
X_c^-	No	Glutamate, cystine
A	Yes	Alanine, glycine, serine, proline, cysteine, methionine
y^+L	Yes	Lysine, arginine, histidine, glutamine, methionine, leucine, alanine, cysteine



1. Ammonia (NH_3) combines with CO_2 to form carbamoyl phosphate in a reaction catalyzed by mitochondrial carbamoyl phosphate synthetase I. N-acetyl-glutamate (NAG) allosterically activates the enzyme to allow ATP binding.
2. Carbamoyl phosphate reacts with ornithine using ornithine transcarbamoylase to form citrulline.
3. Aspartate reacts with citrulline once it has been transported into the cytosol. This step is catalyzed by argininosuccinate synthetase. ATP (two high-energy bonds) and Mg^{2+} are required for the reaction, and argininosuccinate is formed.
4. Argininosuccinate is cleaved by argininosuccinase in the cytosol to form fumarate and arginine.
5. Urea is formed and ornithine is re-formed from the cleavage of arginine by arginase, a manganese-requiring hepatic enzyme.

Figure 6.7 Interrelationships of amino acids and the urea and TCA/Krebs cycles in the liver.

Mini Review Article

Pharmaceutical Sciences and Research (PSR), 5(2), 2018, 72 - 80

L-citrulline as Alternative Pharmacological Substance in Protecting Against Cardiovascular Disease

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Faculty of Medicine, Universitas Indonesia

ABSTRACT

Cardiovascular disease (CVD) has taken up to average 30% of death diagnoses in the world. Prevalent attempts of physicians to treat this disease came down to focus on using drugs with their specific mechanism of action. Since the method only cures the symptoms and need to be pharmacologically monitored, physicians and scientists have been struggling to find other treatment strategies. This problem led us to search for another substance dealing with CVD via preventive therapy, which does not require such close monitoring by physicians in its use. The answer relies on using L-citrulline as potential therapeutics in treating and preventing CVDs. This compound, found mostly in *Citrus sp.*, contains chemical traits that could affect other bodily substances with its metabolic pathways. It has several functions, but boosting NO production is the dominant one in the cardiovascular system. By enhancing NO bioavailability, it suppresses the risk of having myocardial oxidative stress due to ischemia, cardiac pressure-overload, and post-infarct reperfusion. Thus, understanding of L-citrulline effects on endothelial NOS pathway in the generation of NO and its uncoupling mechanisms could be used as a foundation in developing alternative treatment and prevention of oxidative stress-induced CVD.

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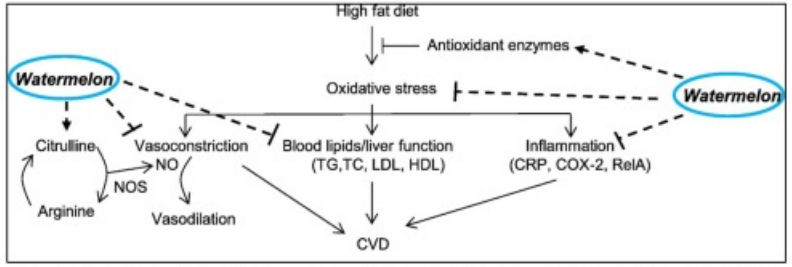


Figure 1. Watermelon (*Citrus vulgaris*) contains citrulline that promotes vasodilation, antioxidation, anti-inflammation, and healthy hepato-hematological functions Hong M *et al*., 2015. COX-2: cyclooxygenase 2, CRP: c-reactive protein, CVD: cardiovascular disease, HDL: high density lipoprotein, LDL: low density lipoprotein, NO: nitric oxide, NOS: nitric oxide synthase, RelA: NF-kappa-B p65 subunit, TC: total cholesterol, TG: triglyceride

Biochemistry of L-citrulline

Chemical Characteristics of L-citrulline

L-citrulline is a non-protein amino acid with $C_6H_{13}N_3O_3$ alpha-structured configuration withmolecular mass 175.19 Dalton. Its high solubility in water makes it perfect for oral administration via aqueous solution. Available in white powder form and alkalized-smell, its natural structure is often discovered in levorotatory stereoisomerization. Considering its hydrophilic custom, high intake of L-citrulline orally might cause osmotic diarrhea (Kaore & Kaore, 2014). Molecular structure of L-citrulline can be seen in Figure 2.

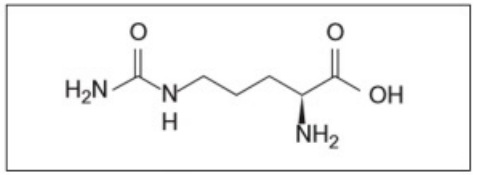


Figure 2. Molecular structure of L-citrulline (Kaore S *et al.*, 2014)

Metabolism and Biosynthesis of L-citrulline

L-citrulline is biosynthesized through nitric oxide and urea cycles. Urea cycle covers up to 90% production of L-citrulline in hepatocytes (*Frank et al*., 2017). Arginine is first transformed into ornithine by arginase, releasing urea into blood plasma to be further cleared via kidneys (Kaore & Kaore, 2014). Ornithine then combined with carbamoyl phosphate as constituents of ammonia to form citrulline by the enzymatic activity of ornithine carbamoyltransferase (*Frank et al*., 2017). Besides, citrulline could be metabolized back into arginine using argininosuccinate as intermediates by argininosuccinate synthase and lyase (Mori *et al.,* 2015).

Another process involved in the generation of L-citrulline is the nitric oxide cycle in blood vessels which covers up 10% production of plasma L-citrulline (*Frank et al*., 2017). Direct transformation of arginine into citrulline using nitric oxide synthase gives out NO into plasma. Reverse metabolism from citrulline into arginine is associated with the same pathway using argininosuccinate as biosynthetic intermediate (Jiang *et al.,* 2017). In double-blind randomized research cross-over design, supplementation of L-citrulline could remove any excess ammonia accumulation in blood, alleviating any central fatigue in athletes (Chen *et al.,* 2016). Detail schematic metabolism of L-citrulline can be seen in Figure 3 and 4.

Although nitric oxide cycle only constitutes tiny part of L-citrulline production, it gives the biggest point of information regarding mechanisms of L-citrulline towards cardiovascular system. Studies conducted to prove this hypothesis explained that consumption of *Citrus vulgaris* regularly would resist cellular damage due to its antioxidative activity. As *Citrus sp.* elevates plasma concentration of L-citrulline, it encourages the bioavailability of NO gas throughout systemic and pulmonary blood vessels. This condition provide basis for applying L-citrulline in promoting cardiovascular health (Hong *et al.,* 2015).

Physiological Mechanisms of L-citrulline in Cardiovascular System

L-citrulline: Nitric Oxide Production Booster

NO is a rapidly diffusing gaseous molecule that is released at several locations, such as vascular endothelial cells, neurons, and glial cells. It acts as vasodilator by relaxing vessels' smooth muscle. Production of NO gas is done by nitric oxide synthase using L-arginine as primary substrate in the NO cycle. L-citrulline, in this NO cycle, could be in paradoxical functions: precursor of L-arginine or byproducts of L-arginine metabolism while making NO as well (Lorin *et al.,* 2014). Supplementation

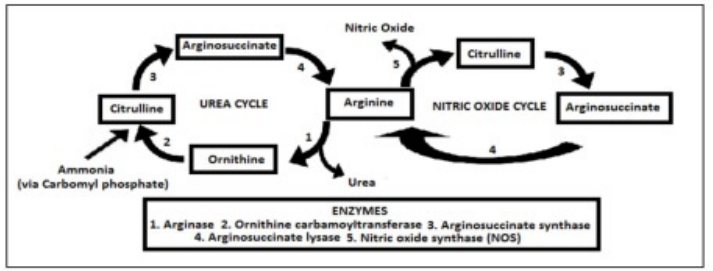


Figure 3. L-citrulline in metabolic pathways: urea and nitric oxide cycle (Frank *et al*., 2017).

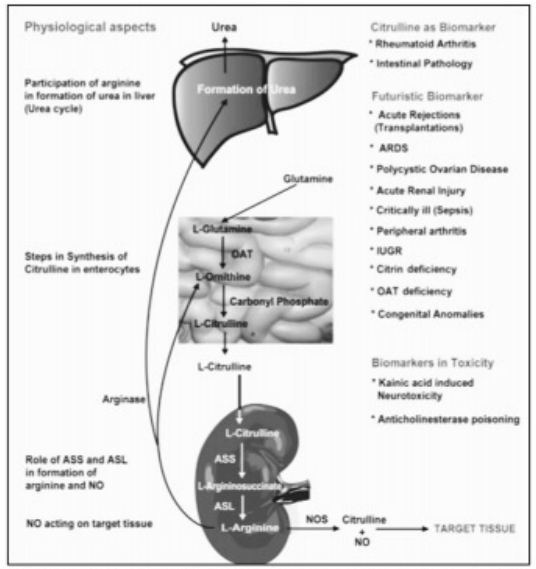


Figure 4. L-citrulline metabolism in liver, enterocytes, and kidneys. Note that L-citrulline could be used as biomarker (Kaore *et al*., 2014).

of L-citrulline orally increases plasma concentration of L-arginine. Additionally, arginine is then metabolized back into citrulline via either urea or nitric oxide cycle (Kurauchi *et al.,* 2017). Beside the use of L-citrulline as single agent, the combination of L-arginine and L-citrulline supplementation would further increase the amount of plasma citrulline (Suzuki *et al.,* 2017). Metabolic balance manages the whole concentration of arginine and citrulline itself in blood plasma. Graphical presentation between L-citrulline administration and amount of plasma citrulline is explained in Figure 5.

In vascular endothelium, NO is released by endothelial nitric oxide synthase (eNOS) involving L-arginine and L-citrulline as substrate and product respectively (Incalza *et al.,* 2017). Adequate L-citrulline supplementation gradually activates NO production due to recycling of L-citrulline into L-arginine. As a result, L-citrulline would indirectly increase NO levels in plasma (Mori *et al.,* 2015). Furthermore, NO does not exist long enough in plasma soon after its release. Its maximum distance of diffusion is 300 µm with half-life of 0.05-1.8 milliseconds (Mori *et al.,* 2015). Relationship between L-citrulline and plasma NO is explained in Figure 6.

Effects of L-citrulline on Plasma Amino Acids and other Substances

Not only L-citrulline increase nitric oxide levels in blood, but also it reduces plasma GSH which then dramatically decrease the degradation of NO by oxidation. As a matter of fact, serum nitrite (NO_2^-) concentration elevate significantly (Frank *et al.,* 2017). NO_2^- ion would be reduced to become NO under ischemic condition (Kaore & Kaore, 2014). Furthermore, L-citrulline affects certain substances in plasma; for example, glutamine, ornithine, and arginine. Arginine is transformed into L-citrulline

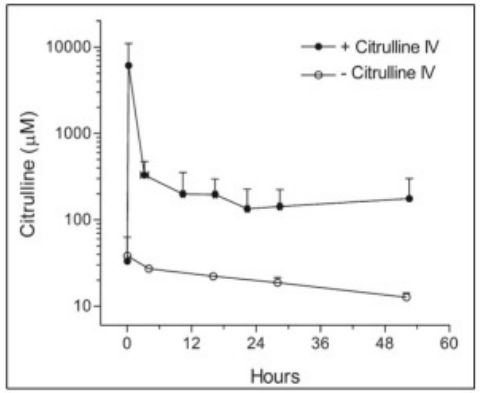


Figure 5. Plasma concentration-time profile of citrulline followed by continuous intravenous infusion after citrulline bolus administration. For comparison, citrulline plasma levels under similar procedures without citrulline treatments (Barr F *et al.*, 2007).

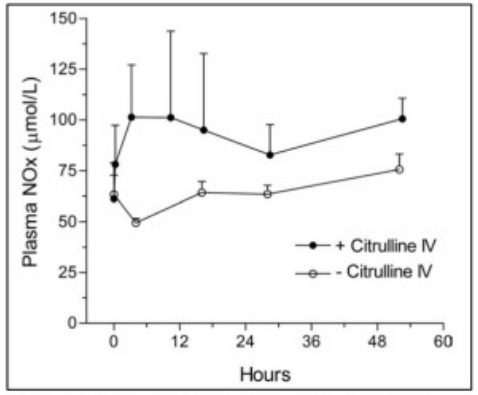


Figure 6. Plasma concentration-time profile of nitric oxide followed by continuous intravenous infusion after citrulline bolus administration. For comparison, citrulline plasma levels under similar procedures without citrulline treatments. (Barr F *et al.*, 2007).

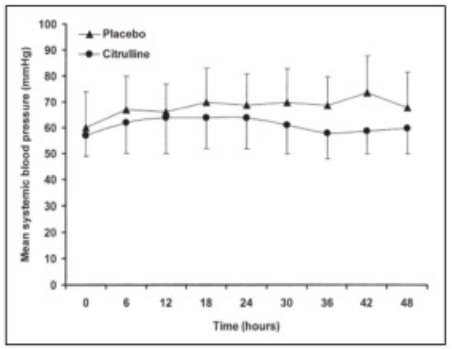


Figure 7. Mean blood pressure did not differ between oral and placebo groups. P = 0.53. Mean and standard deviation are shown for each group for 48-hour period (Xuan C *et al.*, 2015).

to generate ATP by enzymatic reaction of arginine deiminase, ornithine transcarbamoylase, and carbamate kinase. Because of sufficient L-citrulline is found in blood plasma, the backward mechanisms occur, which is the transformation of L-citrulline into arginine via argininosuccinate synthase (ASS) and argininosuccinate lyase (ASL) (Jiang *et al.,* 2017).

Other amino acids are not significantly affected. L-citrulline provides serum buffering effect through the retention of plasma bicarbonate, for it is absorbed as equally as the urea is excreted (Frank *et al.,* 2017). Since the urea is formed through urea cycle involving L-citrulline, it is therefore needed to be cleared along urine.

Other Functions of L-citrulline

L-citrulline is one of the potent hydroxyl radical scavengers that prevents excessive release of superoxide anion (O_2^-) as oxidative stress may happen in any ischemic tissues. L-citrulline could also become biomarker for certain inflammation, such as that citrullinated joint protein prone to autoantibodies attack in rheumatoid arthritis. (Kaore & Kaore, 2014) L-citrulline is also considered to be a powerful anabolic amino acid because it increases the rate of muscle protein synthesis. Therefore, weight gain is observed with massive reconstruction in muscular system (Jiang *et al.,* 2017).

Pharmacological Mechanisms of L-citrulline

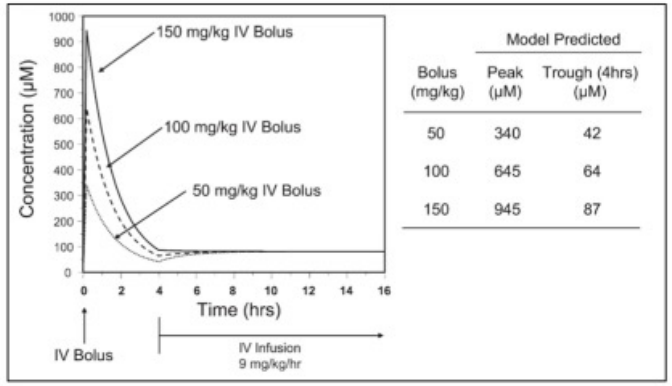
Pharmacodynamics of L-citrulline

No direct pharmacological effect of L-citrulline towards cells has been observed, but it is known to associate closely with the pharmacodynamics of NO gas. (Kaore & Kaore, 2014) Thus, L-citrulline balances systemic and pulmonary vascular tone by promoting vasodilation. This is done under the function of NO in activating membrane signaling enzyme, that is guanylyl cyclase. Dephosphorylation and cyclization of GTP into cGMP intensifies the amplification of Cyclooxygenase-1/cGMP signaling cascades that cause vessels' smooth muscles to relax (Mori *et al.,* 2015).

L-citrulline is observed to relieve pulmonary arterial hypertension since it manifests in its ability to vasodilate. However, it induces neither systemic hypotension nor tachycardia. Besides, that no dramatic reduction of

Table 1. Risk of pulmonary hypertension with plasma citrulline. Its relative risk of suffering pulmonary hypertension is significantly lower with more than 37 µM plasma citrulline treatment.[14]

Plasma Citrulline 12 h Postoperatively	Pulmonary Hypertension Absent	Pulmonary Hypertension Present	P value
< 37 µmol/L	18	9	.036
37 µmol/L	12	*0	



Bolus (mg/kg)	Model Predicted Peak (µM)	Model Predicted Trough (4hrs) (µM)
50	340	42
100	645	64
150	945	87

Figure 8. Pharmacokinetic modeling of IV administered bolus of citrulline, followed by 4 hours later by infusion. Bolus dose of 150 mg/kg was determined most likely to yield 4-hour trough of 80-100 µM, and infusion of 9 mg/kg/h was predicted to achieve steady state. Note that the plasma half time is 60 minutes with dose-dependent increase along with the added bolus dosage (Barr F *et al.*, 2007).

mean arterial pressure is seen after administration of L-citrulline is needed to be studied further (Heidi *et al.,* 2007). Association between citrulline and MAP can be seen in Figure 7. Additionally, protective effect of L-citrulline in relieving pulmonary hypertension risk is explained in Table 1.

Pharmacokinetics of L-citrulline

L-citrulline is well absorbed in enteral route. Its bioavailability in this route would be reduced to certain concentration, since it faces first-pass effect in the liver. Despite its conversion to other substances, constant supplementation of oral L-citrulline marked a linear and dose-dependent increase of plasma citrulline (Schwedhelm *et al.,* 2008). The optimal dosage of L-citrulline is controlled by liver and kidneys. As a result, latter restriction of plasma citrulline elevation occurs after excessive supplementation of oral L-citrulline. In addition, 83% of ingested citrulline will be taken up by kidneys to be transformed into L-arginine (Kaore & Kaore, 2014).

Enteral absorption of L-citrulline requires sodium-dependent cotransporter. Comparing to arginine, L-citrulline enters bloodstream much easier from intestinal lumen. It also provides buffering effect to other metabolic substances, especially arginine, involving urea cycle, NO cycle, and arginine biosynthesis. That is why it is safer and efficient to replenish plasma arginine using L-citrulline than directly using arginine (Kurauchi *et al.,* 2017).

Effective dosage of L-citrulline in human is estimated to be 40 mg/kg body weight with maximum 15 g of L-citrulline per oral administration (Frank *et al.*, 2017). Clearance of plasma citrulline in kidneys is estimated to be 0.6 L/kg/h with volume of distribution 0.9 L/kg for 60-minute plasma half-time (Barr *et al.,* 2007). Maintenance of certain plasma citrulline levels needs calculation involving citrulline infusion intravenously (Barr *et al.,* 2007) . Graphical presentations of L-citrulline pharmacokinetics in one study can be seen in Figure 8.

Protection of L-citrulline Against Cardiovascular Disease

Some CVDs has been recognized along to be related with oxidative stress; for example, hypertrophic cardiomyopathy, cardiac remodeling, and myocardial infarction. They manifest in the apoptosis or necrosis of normal cardiac myocytes. Some of these disorders are even maintained in certain body conditions or drug-induced states. Furthermore, molecular pathophysiology

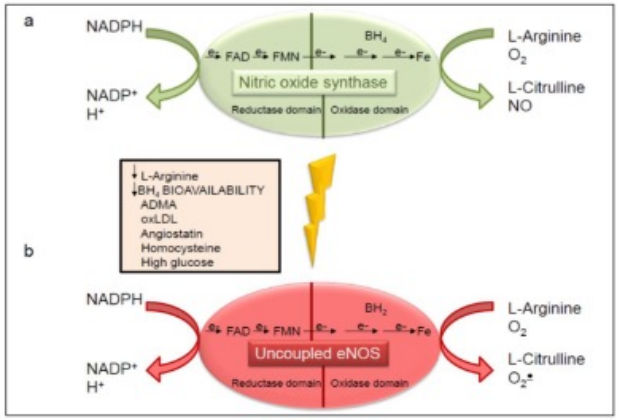


Figure 9. a) Generation of NO and L-citrulline via electron transfer in NOS pathway. Note that the electron is taken up from NADPH domain in order to reduce heme domain for both L-citrulline and NO synthesis. b) Uncoupling mechanisms compensating for low BH4 cofactor and substrate L-arginine. Note that superoxide anion replaces nitric oxide as byproducts of this pathway (Incalza M *et al.*, 2017).

involving the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) of these diseases is the ultimate 'culprit'. Hence, comprehension in the ROS/RNS generation mechanisms would give beneficial effect of using L-citrulline to counteract their pathological activities.

Pathophysiology of Oxidative Stress-induced Cardiovascular Diseases

Reactive oxygen species are hyperreactive intermediates of oxygen-related molecules, which are generated physiologically in mitochondria as byproducts of oxidative phosphorylation. RNS have similar chemical characteristics with ROS but with different element participated, that is nitrogen. Several examples of ROS/RNS are hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), oxygen nascent (O^-), and peroxynitrite ($ONOO^-$). They are generated as a result of incomplete amounts of electrons in their atomic valence shell. Destructive activities of these species, to fulfill their outer electron shell, are highly related to their oxidative reaction. Oxidation of nuclear materials, membrane fragmentation, cellular autolysis, and protein digestion are the devastating ones. Oxidative stress happens when ROS/RNS levels exceeds the capability of antioxidant defense system to suppress them. Cellular ischemia or hypoxia would be the most dominant factor in triggering oxidative stress. In this case, myocardial ischemia may happen to cause oxidative stress. Post-infarct angiogenesis and fibrosis may lead to ischemic-reperfusion injuries that cause more oxidative damages within nearby cells. In this way, myocardial infarction develops other complications as main effects of cellular oxidative stress (Incalza *et al.,* 2017). Besides myocardial infarction, cardiac remodeling also induces oxidative attacks. Excessive cardiac hypertrophy due to remodeling increased contractility, but with much lower end-diastolic blood volume. This means that it is designed to compensate reduced cardiac output due to aortic stenosis, high cardiac afterload, et cetera. Lower amount of blood stroked with powerful ventricular contraction would dramatically decrease the perfusion of blood into myocardium via coronary arteries. Greater and greater impact of oxidative stress could gradually deteriorate cardiac physiology into vicious cycle of heart failure.

In the situation where cells are experiencing oxidative stress, formation of peroxynitrite occurs most. Peroxynitrite is a radical molecule resulted from the combination of NO and O_2^- via a pathway called eNOS uncoupling (Moens *et al.,* 2011). The 'uncoupling' mechanism involves decreased amount of tetrahydrobiopterin (BH_4) which normally stabilize the dimerization of NOS enzyme (Moens *et al.,* 2011). This structure optimally facilitates the transfer of electron from NADPH in its reductase domain to heme group in its oxidase domain to convert arginine into citrulline by generating NO gas (Tang *et al.,* 2014). Relative subtraction of BH_4 cofactor in NOS is primarily caused by oxidation of BH_4 into dihydrobiopterin (BH_2) via oxidative stress (Moens *et al.,* 2011). As a result, partial transfer of electrons in non-dimer NOS might lead to generation of superoxide anion, instead of nitric oxide (Tang *et al.*, 2014). Further destruction of cells due to

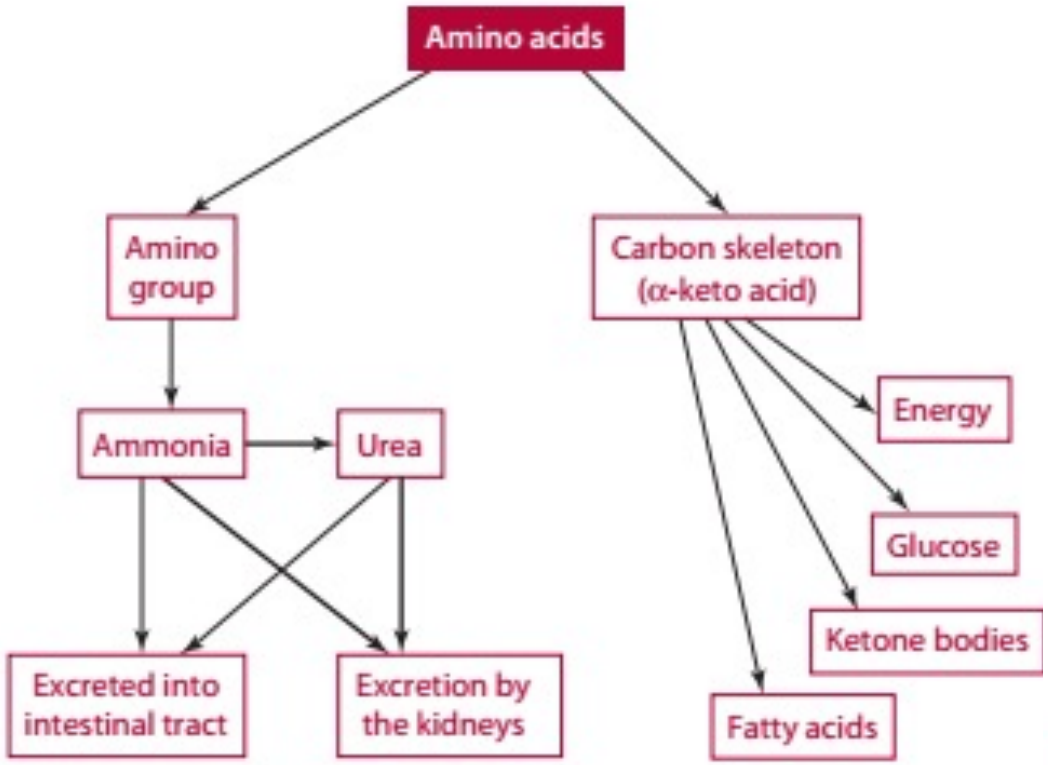


Figure 6.8 Possible fates of amino acids upon catabolism.

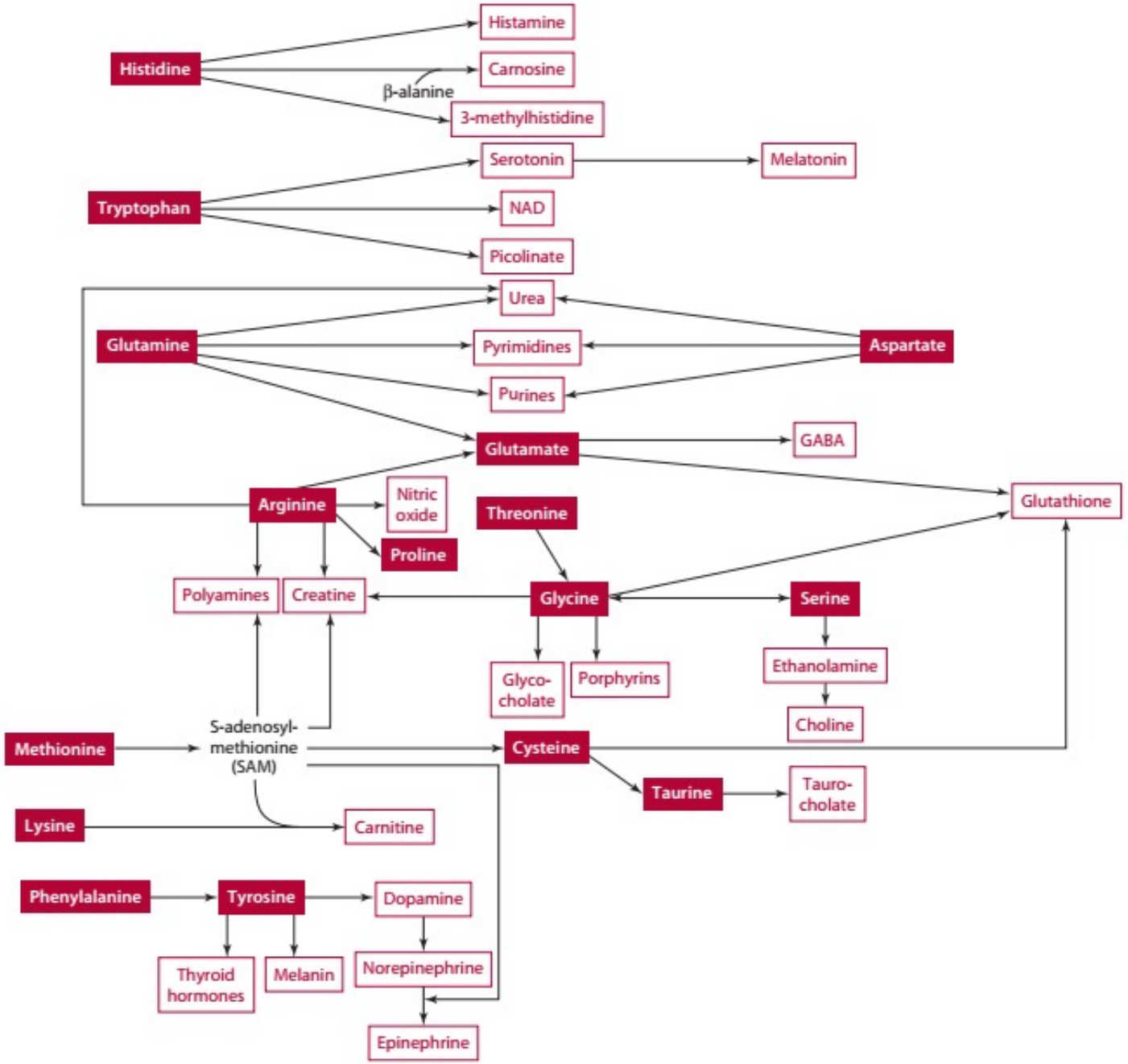
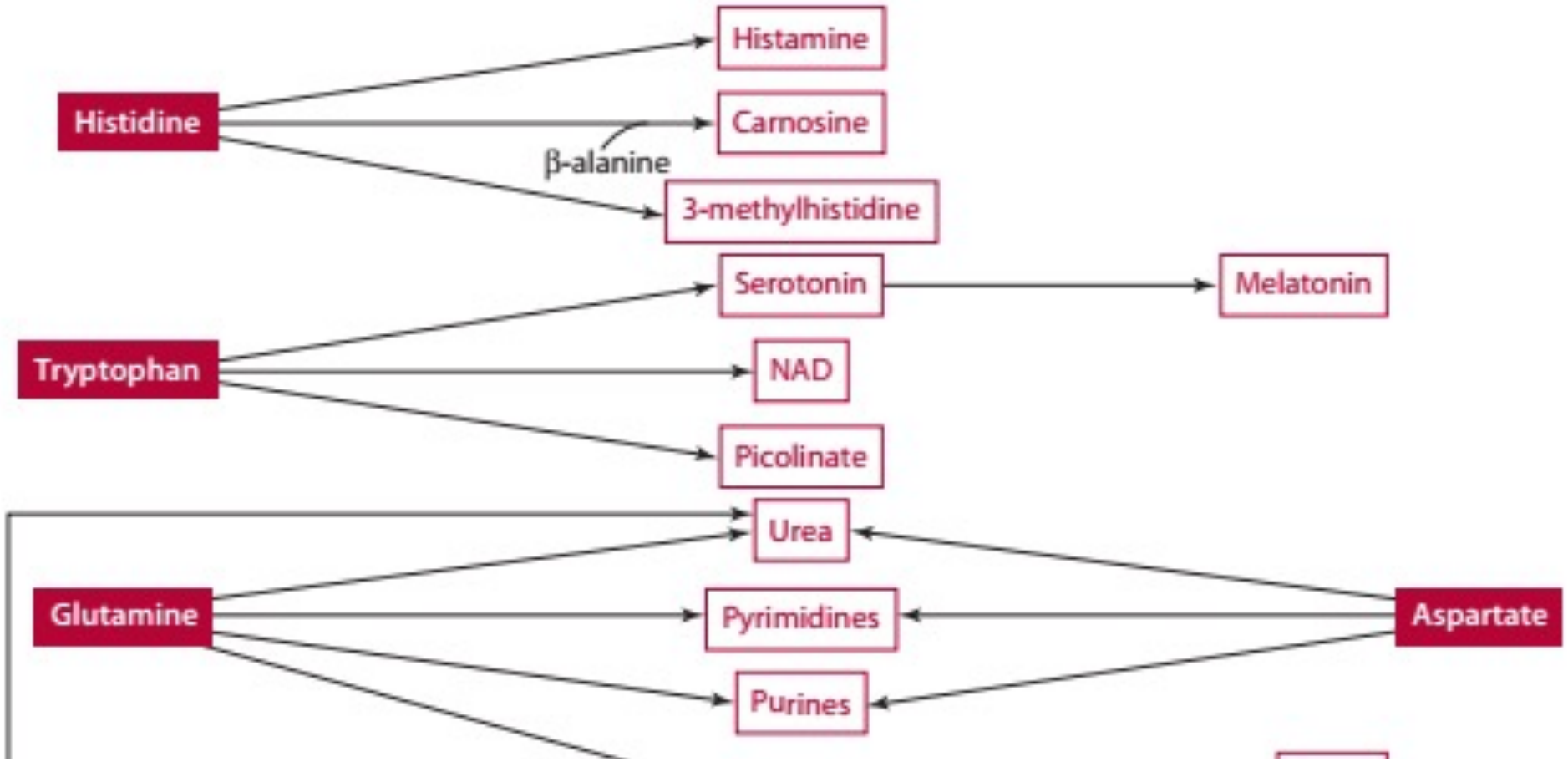


Figure 6.16 A summary of the uses of selected amino acids for the synthesis of nitrogen-containing compounds and selected biogenic amines, hormones, and neuromodulators.


Histamine
Histidine
Carnosine
β-alanine
3-methylhistidine
Serotonin
Melatonin
Tryptophan
NAD
Picolinate
Urea
Glutamine
Pyrimidines
Aspartate
Purines

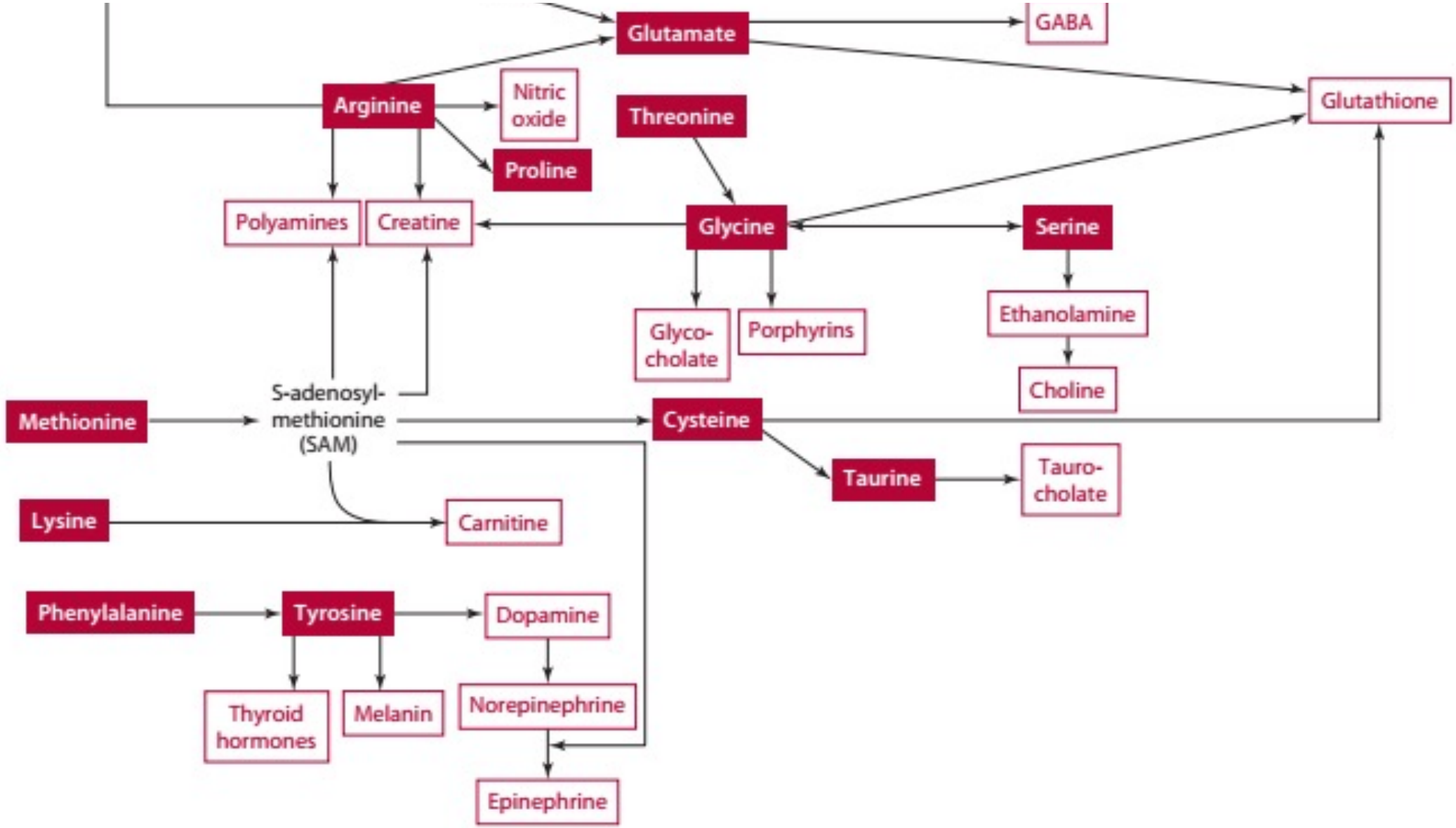
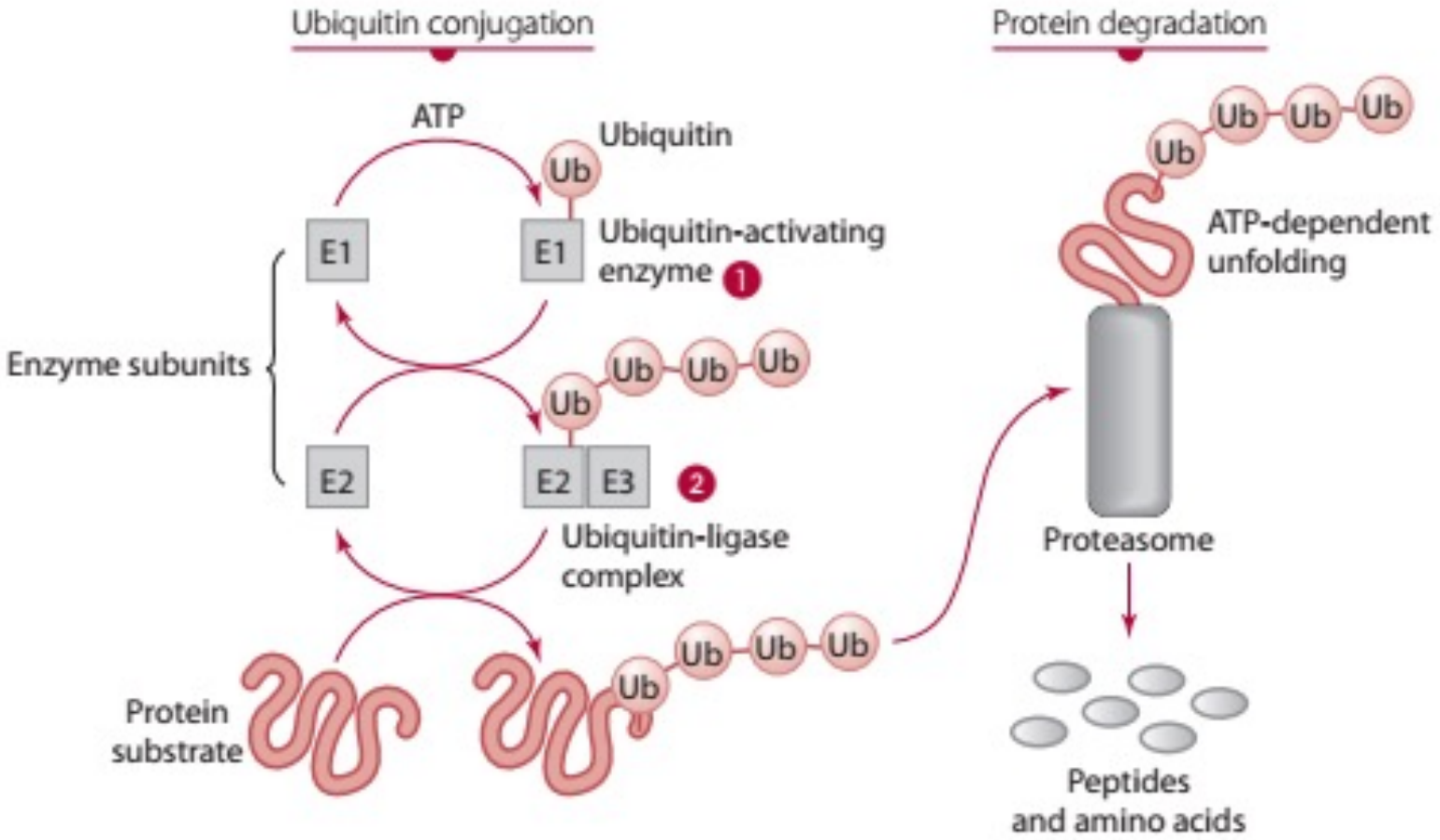


Figure 6.16 A summary of the uses of selected amino acids for the synthesis of nitrogen-containing compounds and selected biogenic amines, hormones, and neuromodulators.



1. The attachment of activated ubiquitin by E1, a subunit of the ubiquitin enzyme system, which hydrolyzes ATP to form a thiol ester with the carboxy end of ubiquitin. This activated ubiquitin is transferred to another enzyme protein, E2, referred to as ubiquitin-conjugating enzymes.
2. The carboxy end of ubiquitin is ligated by E3 to the protein substrate that is ultimately to be degraded. E3 has two distinct sites that interact with a targeted protein's N-terminal amino acid.

Figure 6.41 Proteasomal degradation of a protein.

Source: Adapted from "The ubiquitin-proteasome proteolysis pathway: potential for target of disease intervention" by Breen, H.B. and Espat, N.J., Journal of Parenteral and Enteral Nutrition 2004; 28:272–77. Copyright © 2004 by Sage Publications. Reprinted by permission of SAGE Publications.

Table 6.8 Body Composition of Reference Man and Woman

Reference Man	Reference Woman
Age: 20–24 yr	Age: 20–24 yr
Height: 68.5 in (174 cm)	Height: 64.5 in (164 cm)
Weight: 154 lb (70 kg)	Weight: 125 lb (56.8 kg)
Total fat: 23.1 lb (10.5 kg) (15.0% body weight)	Total fat: 33.8 lb (15.4 kg) (27.0% body weight)
Storage fat: 18.5 lb (8.4 kg) (12.0% body weight)	Storage fat: 18.8 lb (8.5 kg) (15.0% body weight)
Essential fat: 4.6 lb (2.1 kg) (3.0% body weight)	Essential fat: 15.0 lb (6.8 kg) (12.0% body weight)
Muscle: 69 lb (31.4 kg) (44.7% body weight)	Muscle: 45 lb (20.5 kg) (36.0% body weight)
Bone: 23 lb (10.4 kg) (14.9% body weight)	Bone: 15 lb (6.8 kg) (12.0% body weight)
Remainder: 38.9 lb (17.7 kg) (25. 3% body weight)	Remainder: 31.2 lb (14.2 kg) (25.0% body weight)

Sources: Adapted from Behnke A.R., Wilmore J.H., *Evaluation and Regulation of Body Build and Composition*. Englewood Cliffs, NJ: Prentice Hall, 1974; and Katch F.I., McArdle W.D., *Introduction to Nutrition, Exercise, and Health*, 4th ed., Philadelphia: Lea & Febiger, 1993, p. 235.

- Fatty acid
- Triacylglycerol
- Phospholipid
- Sphingolipids
- Sterols (cholesterol, bile acids, and phytosterols)
- Lipoprotein

1. Năng lượng
2. Cung cấp acid béo thiết yếu
3. Dung môi hòa tan các vitamin và sắc tố tan trong chất béo
4. Tín hiệu tế bào
5. …

Table 5.1 Some Naturally Occurring Fatty Acids

Notation	Common Name	Formula	Source*
Saturated Fatty Acids			
14:0	Myristic acid	$CH_3-(CH_2)_{12}-COOH$	Coconut and palm kernel oil, fish oils
16:0	Palmitic acid	$CH_3-(CH_2)_{14}-COOH$	All animal and plant fats, notably palm oil
18:0	Stearic acid	$CH_3-(CH_2)_{16}-COOH$	All animal and plant fats, notably cocoa butter
20:0	Arachidic acid	$CH_3-(CH_2)_{18}-COOH$	Peanut oil, wild-caught salmon oil
24:0	Lignoceric acid	$CH_3-(CH_2)_{22}-COOH$	Peanut oil
Unsaturated Fatty Acids			
16:1 Δ^9 (n-7)	Palmitoleic acid	$CH_3-(CH_2)_5-CH=CH-(CH_2)_7-COOH$	Fish oils, poultry fat
18:1 Δ^9 (n-9)	Oleic acid	$CH_3-(CH_2)_7-CH=CH-(CH_2)_7-COOH$	All animal and plant fats
18:2 $\Delta^{9,12}$ (n-6)	Linoleic acid	$CH_3-(CH_2)_4-CH=CH-CH_2-CH=CH-(CH_2)_7-COOH$	Most plant oils, poultry fat
18:3 $\Delta^{9,12,15}$ (n-3)	α-linolenic acid	$CH_3-(CH_2-CH=CH)_3-(CH_2)_7-COOH$	Linseed (flax), soybean, and canola oils
20:4 $\Delta^{5,8,11,14}$ (n-6)	Arachidonic acid	$CH_3-(CH_2)_3-(CH_2-CH=CH)_4-(CH_2)_3-COOH$	Fish oils
20:5 $\Delta^{5,8,11,14,17}$ (n-3)	Eicosapentaenoic acid	$CH_3-(CH_2-CH=CH)_5-(CH_2)_3-COOH$	Marine algae and fish that consume the algae
22:6 $\Delta^{4,7,10,13,16,19}$ (n-3)	Docosahexaenoic acid	$CH_3-(CH_2-CH=CH)_6-(CH_2)_2-COOH$	Marine algae and fish that consume the algae

* Fats and oils in the food supply contain many types of fatty acids of varying proportions. The sources listed here indicate foods that are comparatively enriched in the specific fatty acid.

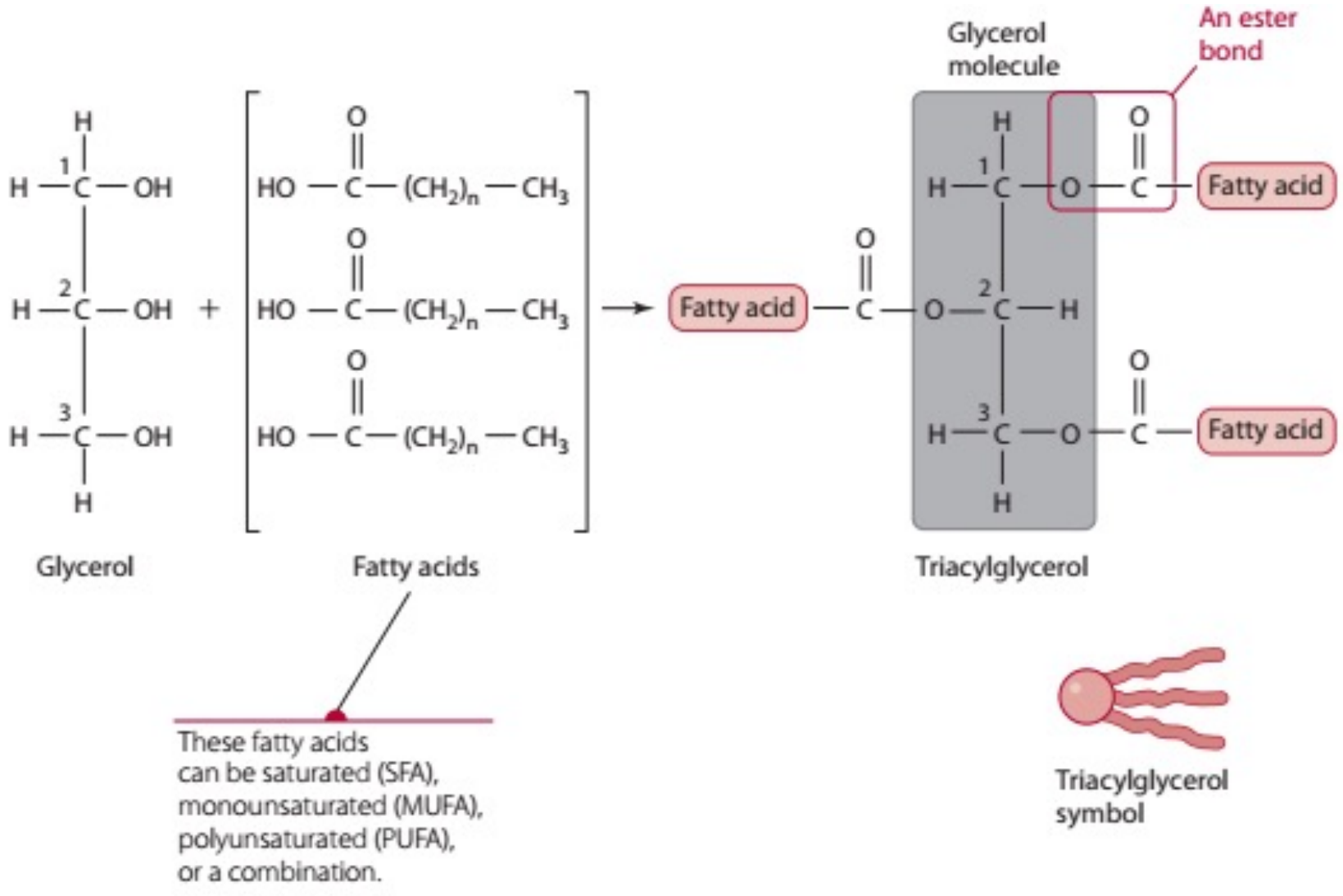
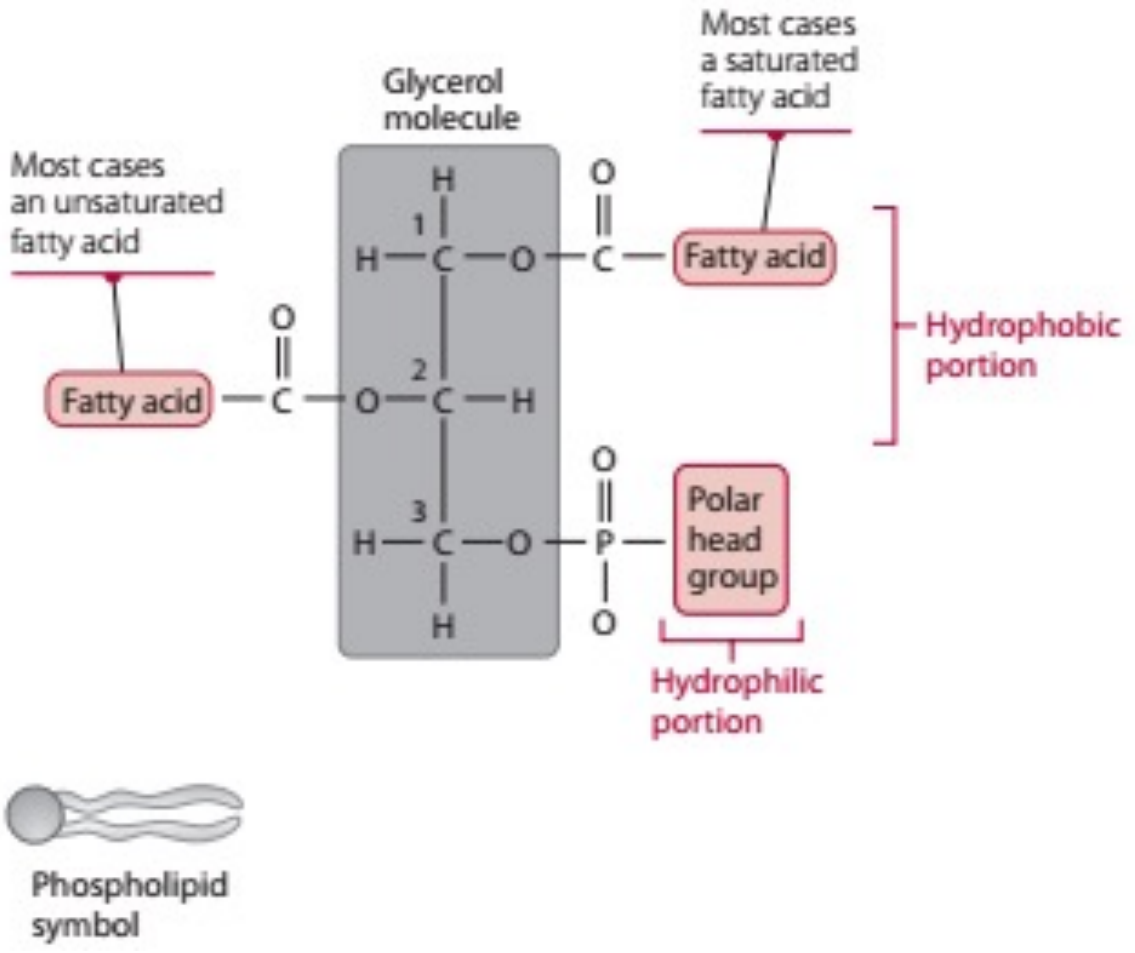


Figure 5.3 Linkage of fatty acids to glycerol to form a triacylglycerol. Chain length of fatty acid is (n + 2).

Source: Beerman/McGuire, Nutritional Sciences, 1/e.

PHOSPHOLIPID



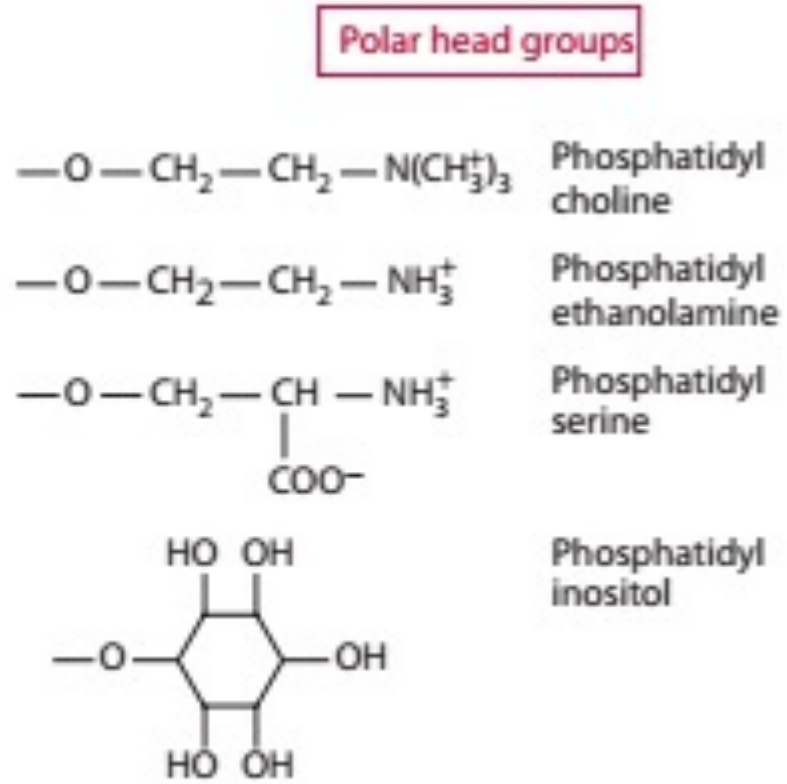


Figure 5.4 Typical structure of phospholipids.
Source: Beerman/McGuire, Nutritional Sciences, 1/e. © Cengage Learning.

Plasmalogen = fatty acid + phospho-choline, ethanolamine, hoặc serine.
Có ở nhiều mô, nhiều ở tim và não
Choline plasmalogen chiếm 40% trong số phospholipid ở tim
Ethanolamine plasmalogen chiếm 20% ở não và chủ yếu ở bao myelin

Platelet-activating factor

PHOSPHOLIPID

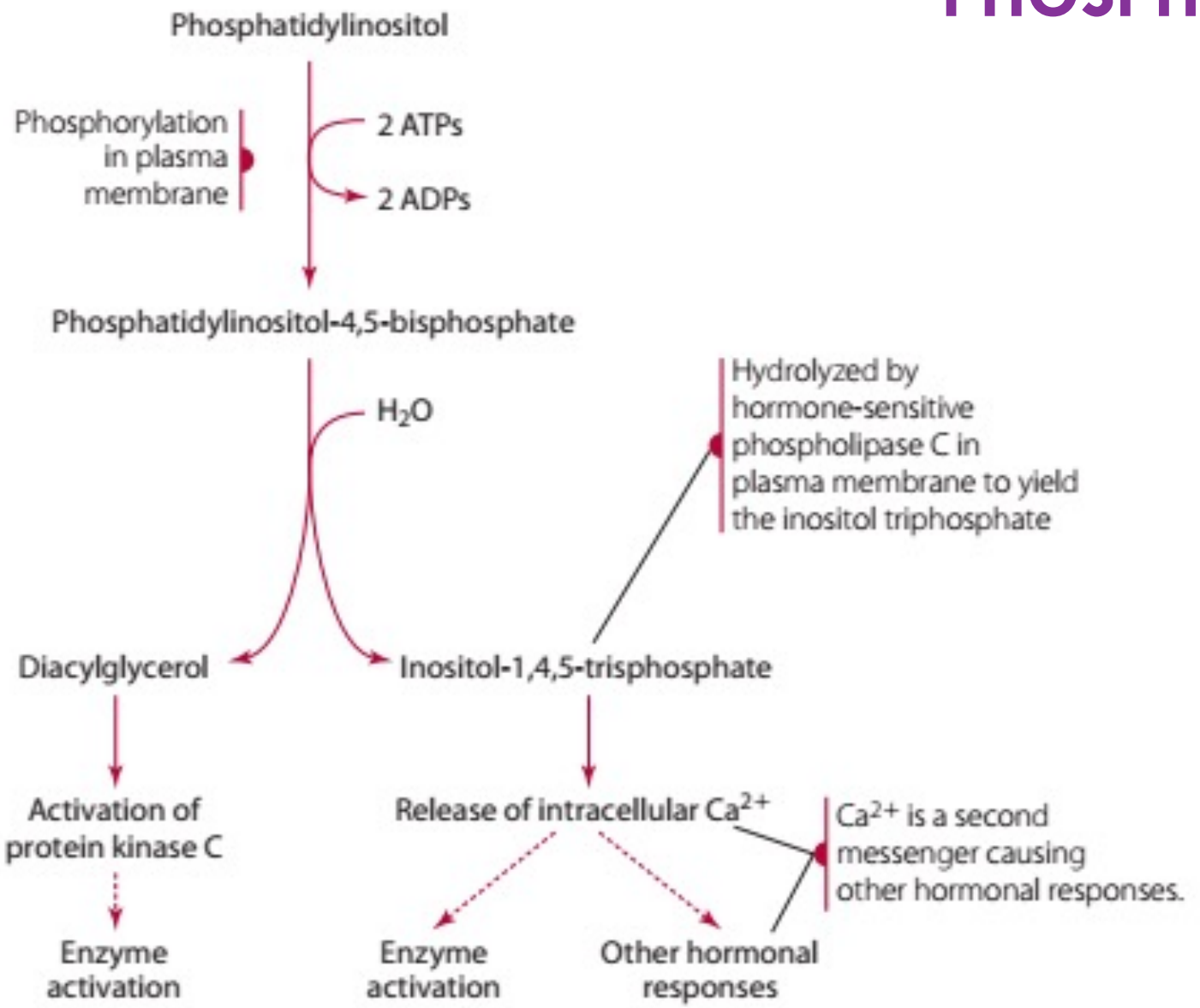


Figure 5.6 Inositol dual signaling system.

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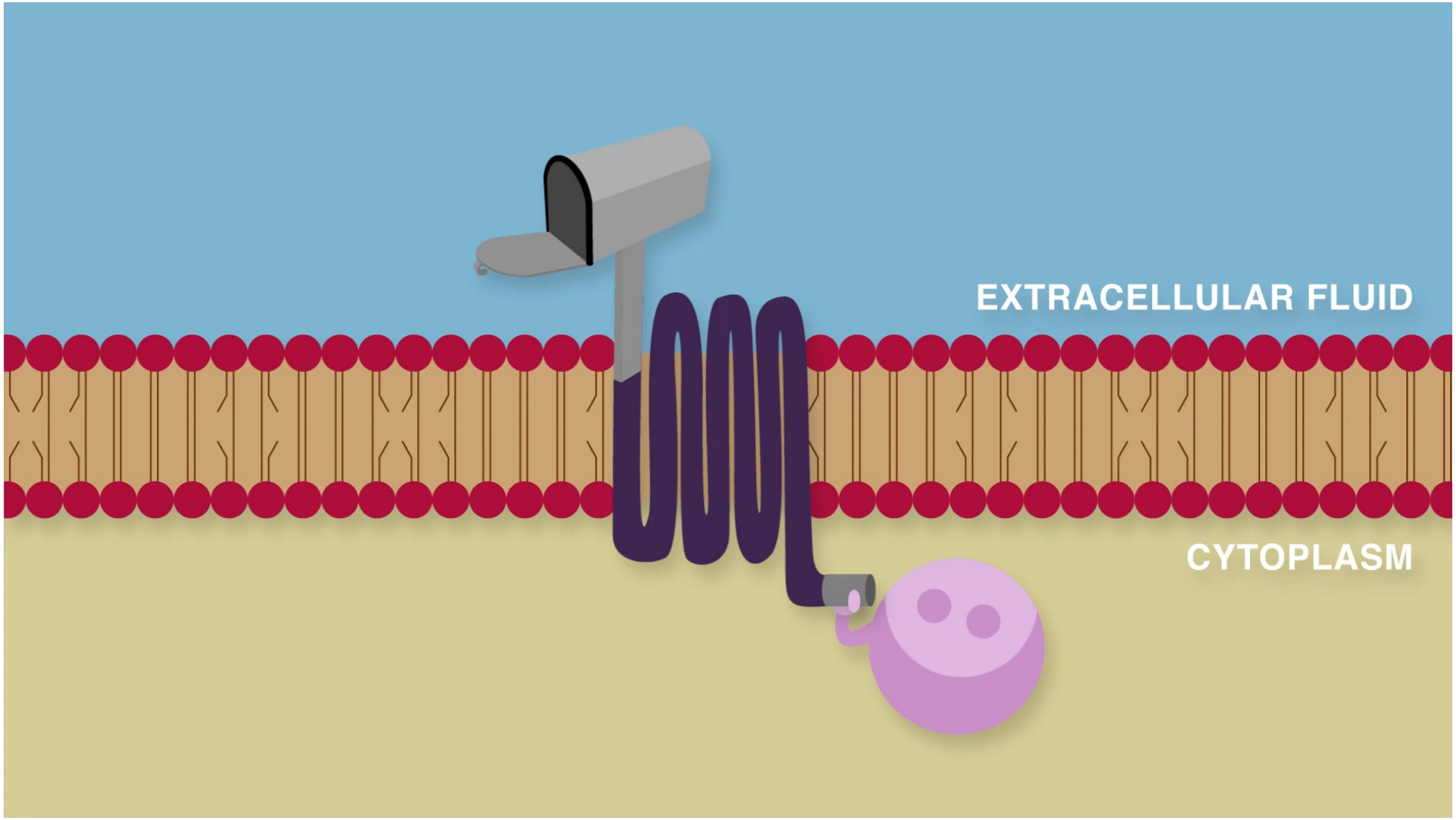


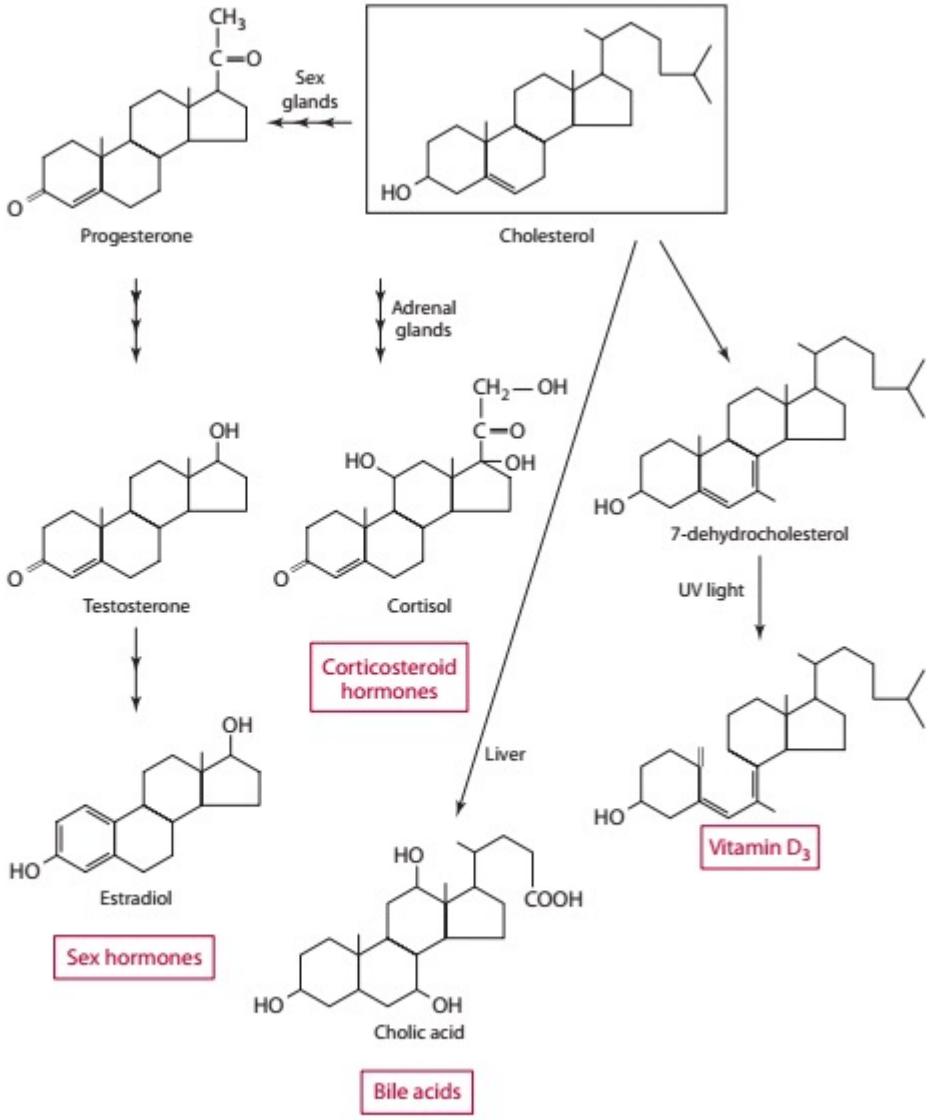
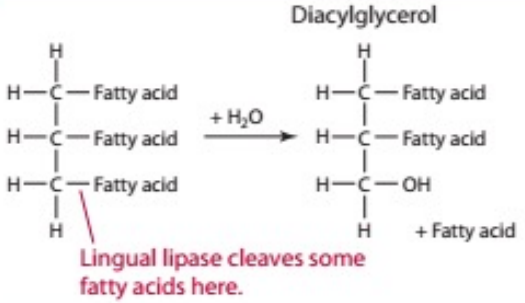
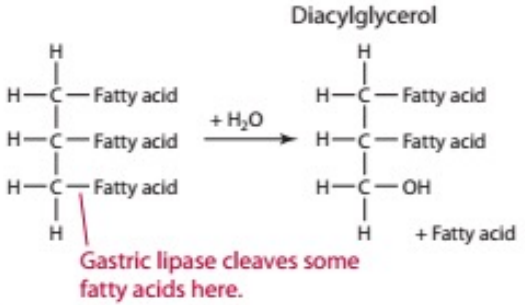
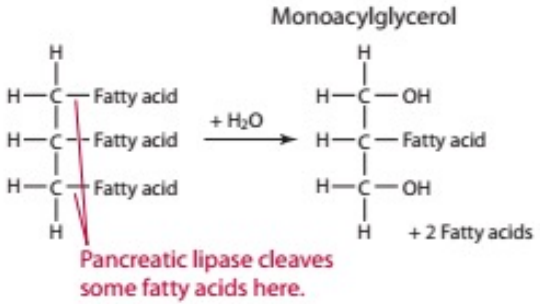
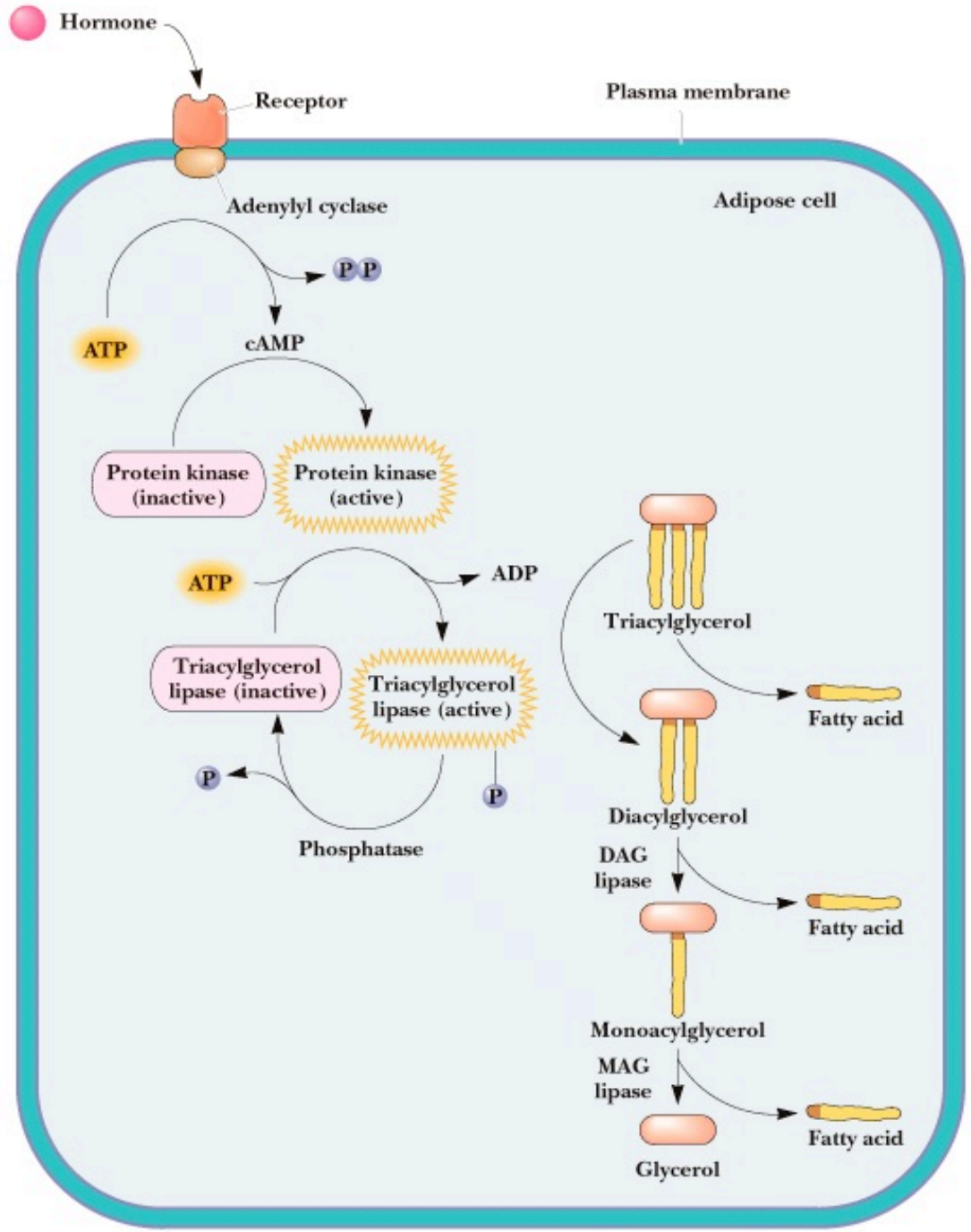


Figure 5.9 The formation of physiologically important steroids from cholesterol. Only representative compounds from each category of steroid are shown.

Table 5.4 Overview of Triacylglycerol Digestion

Location	Major Events	Required Enzyme or Secretion	Details
Mouth	Triacylglycerol ↓ *Minor amount of digestion* Triacylglycerols, diacylglycerols, and fatty acids	Lingual lipase produced in the salivary glands	
Stomach	↓ *Additional digestion* Triacylglycerol, diacylglycerol, and fatty acids	Gastric lipase produced in the stomach	
Small intestine	↓ *Phase I: Emulsification* Emulsified triacylglycerols, diacylglycerols, and fatty acid micelles ↓ *Phase II: Enzymatic digestion* Monoacylglycerols and fatty acids	Bile; no lipase Pancreatic lipase produced in the pancreas	


Hormone
Receptor
Plasma membrane
Adenylyl cyclase
Adipose cell
P P
ATP
cAMP
Protein kinase (inactive)
Protein kinase (active)
ATP
ADP
Triacylglycerol lipase (inactive)
Triacylglycerol lipase (active)
P
P
Phosphatase
Triacylglycerol
Fatty acid
Diacylglycerol
DAG lipase
Fatty acid
Monoacylglycerol
MAG lipase
Fatty acid
Glycerol

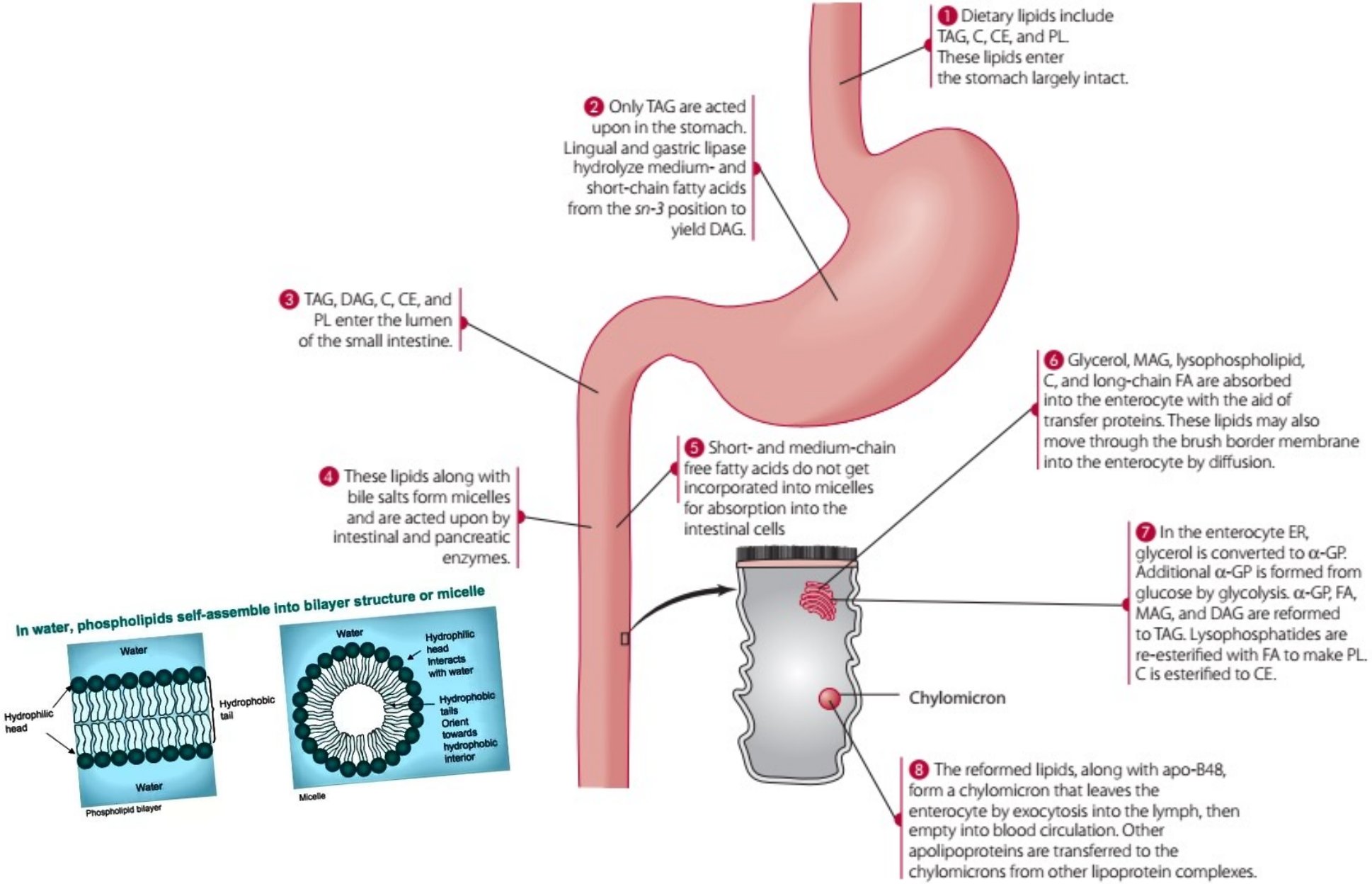


Figure 5.12 Summary of digestion and absorption of dietary lipids.
Abbreviations: TAG, triacylglycerol; C, cholesterol; CE, cholesterol ester; PL, phospholipid; DAG, diacylglycerol; MAG, monoacylglycerol; FA, fatty acid; and α-GP, α-glycerolphosphate.

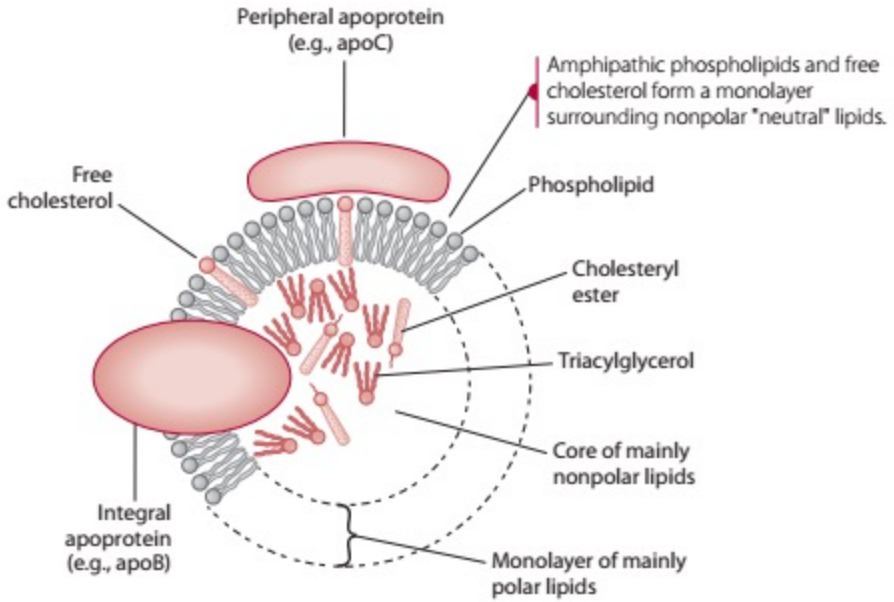


Figure 5.13 Generalized structure of a plasma lipoprotein.

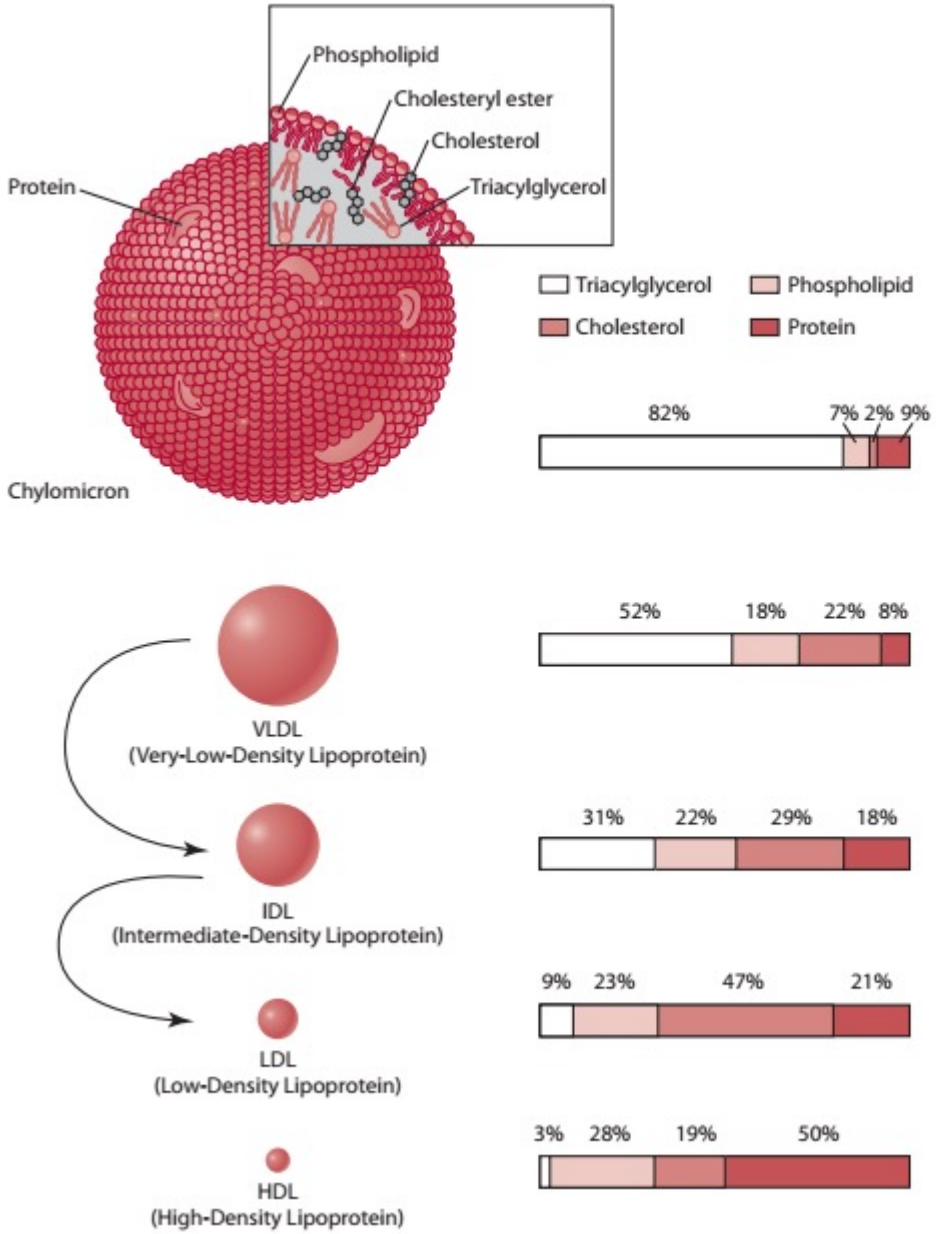


Figure 5.14 Lipid and protein of lipoprotein classes.
Source: Beerman/McGuire, *Nutritional Sciences*, 1/e. © Cengage Learning.

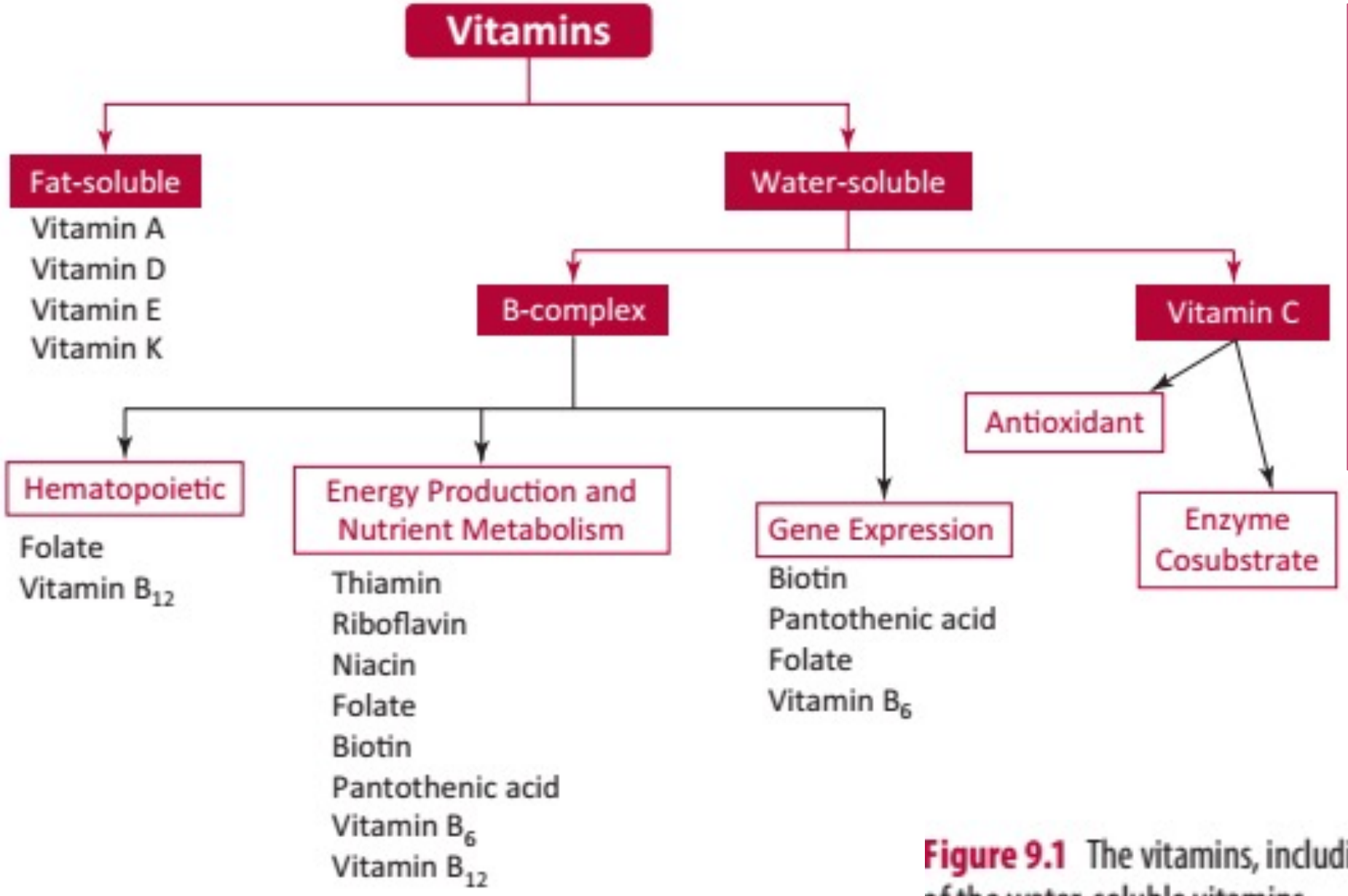
CHẤT BÉO

Table 5.6 n-3 and n-6 Fatty Acid–Derived Messengers and Their Physiological Effects

Messenger Classes	Arachidonic Acid (n-6)–Derived Messengers	Physiological Effects	EPA- and DHA (n-3)–Derived Messengers	Physiological Effects
Prostaglandins	PGD_2		PGD_3	
	PGE_2	Pro-arrhythmic	PGE_3	Anti-arrhythmic
	PGF_2		PGF_3	
	PGI_2	Pro-arrhythmic	PGI_3	Anti-arrhythmic
Thromboxanes	TXA_2	Platelet activator	TXA_3	Platelet inhibitor
	TXB_2	Vasoconstriction	TXB_3	Vasodilation
Leukotrienes	LTA_4		LTA_5	
	LTB_4	Pro-inflammatory	LTB_5	Anti-inflammatory
	LTC_4		LTC_5	
	LTE_4		LTD_5	
	LTD_4		LTE_5	
Epoxyeclosatrienoic derivatives	5,6-EET			
	8,9-EET			
	11,12-EET	Pro-inflammatory		
	14,15-EET			
Hydroxyleicosatetraenoic derivatives	5-HETE			
	12-HETE			
	15-HETE			
Lipoxins	LXA_4			
Resolvins			RVE1	Anti-inflammatory
			RVD	Anti-inflammatory
Neuroprotectin			NPD1	Anti-inflammatory

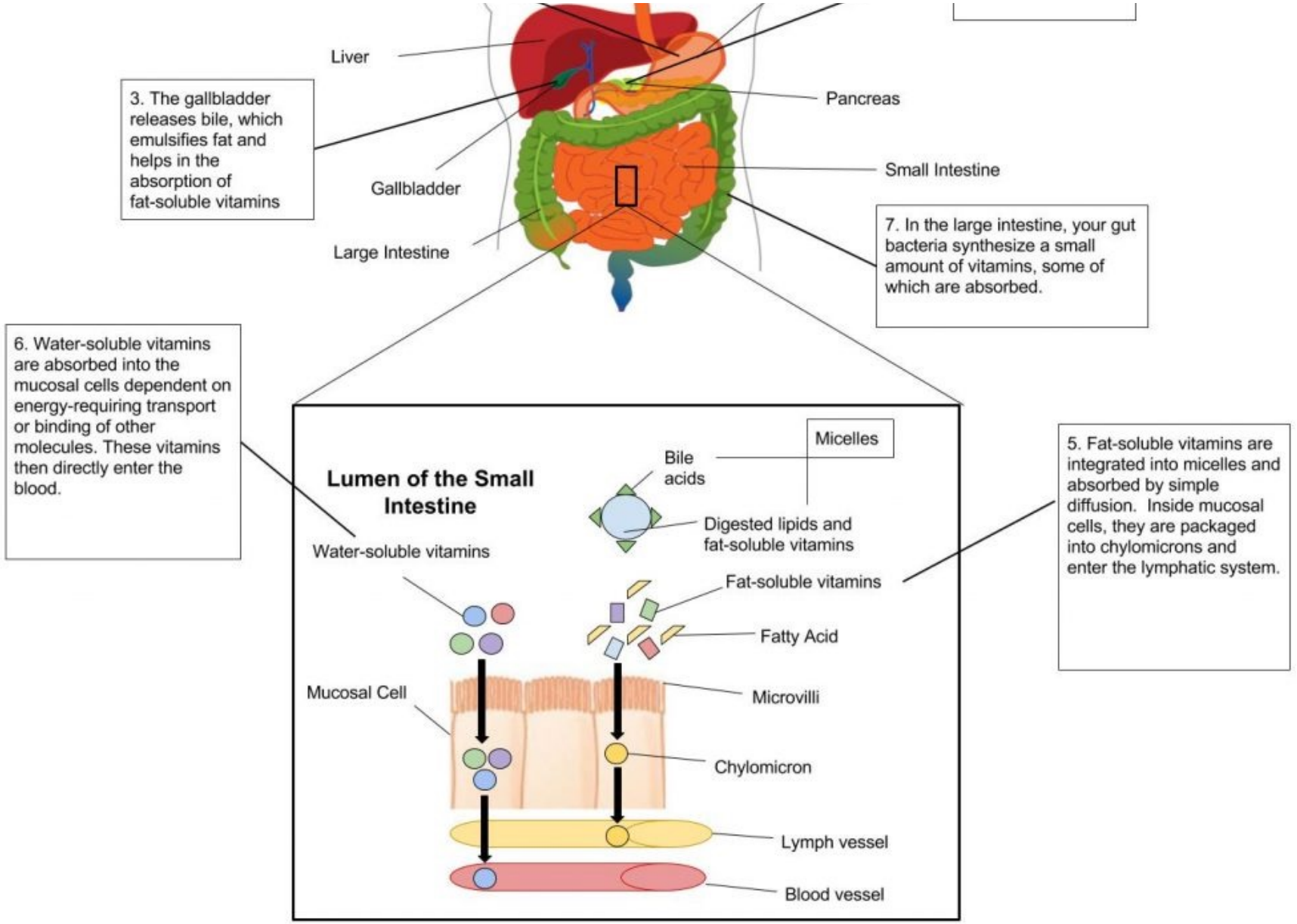
Source: Based on data from Heird W., Lapillonne A., The role of essential fatty acids in development. Annu Rev Nutr. 2005;25:549–71.

DINH DƯỠNG VI LƯỢNG



Thiamin (B1)
Riboflavin (B2)
Niacin (B3)
B6= pyridoxine, pyridoxal, pyridoxamine
B12= cobalamin
VitC = Ascorbic acid

Figure 9.1 The vitamins, including some functional roles of the water-soluble vitamins.



1. Vitamin tan trong nước
   - Protein VC và/hoặc
   - Na^+

2. Vitamin tan trong dầu
- Hấp thu như lipid

3. Vitamin B_{12}
   - có thụ thể CB
   - cần yếu tố phụ trợ

Table 9.3 Gastrointestinal Tract Absorption, Form in Systemic Circulation, and Storage Sites for the Water-Soluble Vitamins

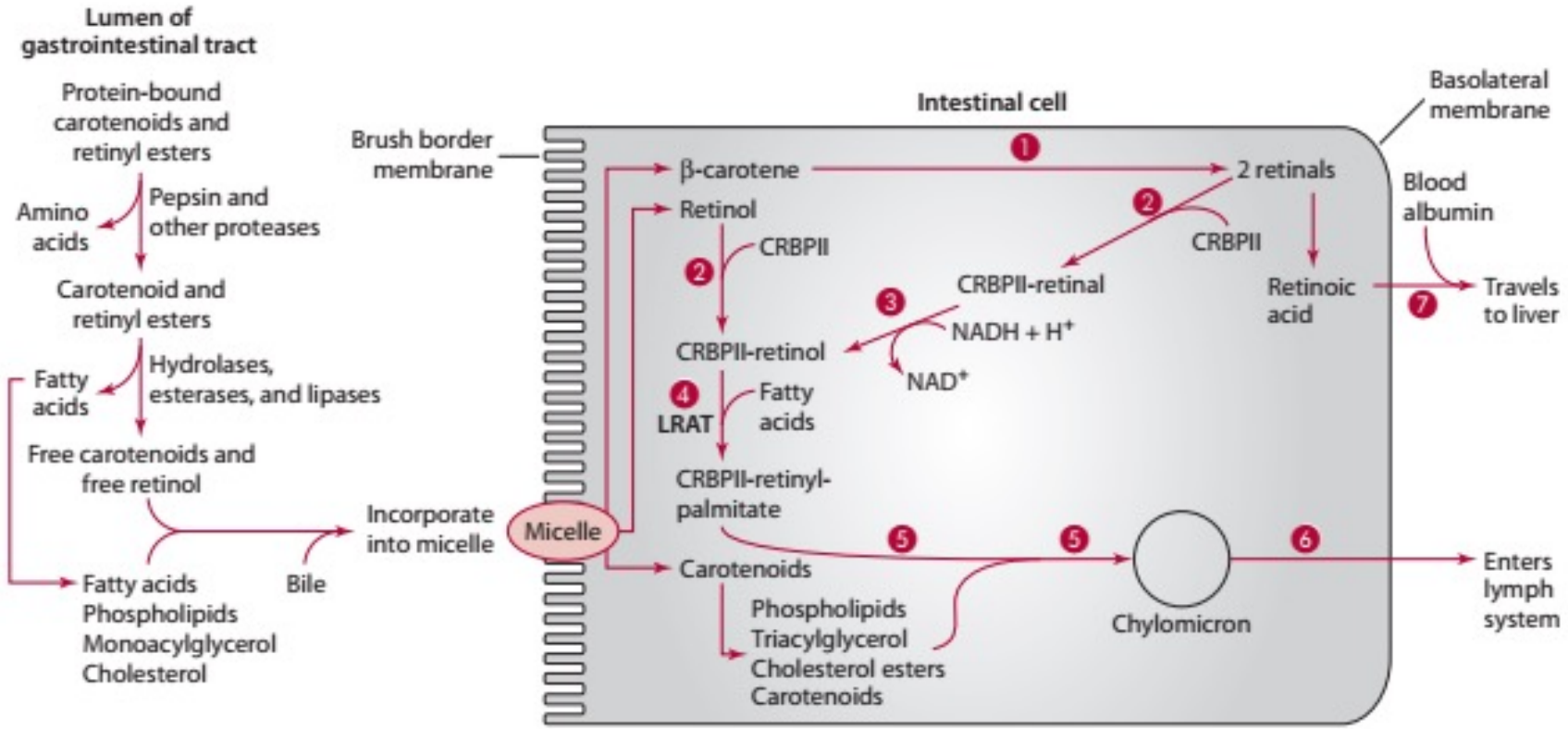
Vitamin	Absorption Site	Method	Form in Blood	Storage Sites(s)
C	Small intestine, jejunum	SDVT1*, SDVT2, diffusion	Free ascorbic acid, dehydroascorbic acid (minor)	Adrenal and pituitary glands, eyes, brain, white blood cells
Thiamin	Duodenum, jejunum, colon	ThT1*, ThT2, diffusion, other**	Free thiamine, TDP, possibly ThBP	Muscle, heart, brain, kidneys, liver
Riboflavin	Duodenum, jejunum, colon	RFVT3, RFVT1, diffusion	Riboflavin, FMN, and FAD usually bound to proteins (albumin, Ig, possibly RiBP)	Liver, kidneys, heart
Niacin	Small intestine, colon	Carrier (unnamed), diffusion	Free nicotinamide, free nicotinic acid, nicotinic acid bound to proteins	Liver
Pantothenic acid	Jejunum, colon	SMVT, diffusion	Free pantothenic acid	Liver, adrenal glands, kidneys, brain, heart
Biotin	Proximal small intestine, colon	SMVT, diffusion	Free biotin, biotin bound to proteins (albumin, biotinidase,...)	Liver, muscle, brain
Folate	Duodenum, jejunum, colon	PCFT*, RFC, diffusion	Free folate, (protein† bound — folate, THF, 5-methyl THF, 10-formyl THF)	Liver
Vitamin B_{12}	Ileum	IF receptor-mediated, diffusion	Methyl-, adenosyl-, cyano-, hydroxocobalamin-bound transcobalamins	Liver, muscle, pituitary gland, bone, kidneys, heart, brain, spleen
Vitamin B_6	Jejunum	Diffusion	Free PL, PLP bound to albumin	Muscle, liver, brain, kidneys, spleen

Abbreviations: SDVT, sodium-dependent vitamin transporter; ThTr, thiamin transporter; TDP, thiamine diphosphate; ThBP, thiamin binding protein; RFVT, riboflavin vitamin transporter; RiBP, riboflavin binding protein; Ig, immunoglobulin; SMVT, shared multivitamin transporter; PCFT, proton couple folate transporter; RFC, reduced folate carrier; IF, intrinsic factor; PL, pyridoxal; PLP, pyridoxal phosphate.

* Thought to be the primary carrier

** Possibly also organic cation transporter protein

† Proteins include mainly albumin, α2 macroglobulin, and a folate binding protein



1. β-carotene is converted into two retinal molecules. See Figure 10.3 for details of this reaction.
2. Cellular retinol-binding protein (CRBP) II binds to both retinol and retinal in the intestinal cell.
3. Retinal, while attached to CRBPII, is reduced to retinol by retinal/retinaldehyde reductase to form CRBPII-retinol.
4. Lecithin retinol acyl transferase (LRAT) esterifies a fatty acid (palmitic acid) onto the CRBPII-bound retinol to form CRBPII-retinylpalmitate.
5. Retinyl esters are incorporated along with phospholipids, triacylglycerol, cholesterol esters, carotenoids, and apoproteins to form a chylomicron.
6. Chylomicrons leave the intestinal cell and enter the lymph system and ultimately the blood.
7. Retinoic acid can directly enter the blood, where it attaches to albumin for transport to the liver.

Figure 10.3 Digestion and absorption of carotenoids and vitamin A, and re-esterification of retinol in the intestinal cell.

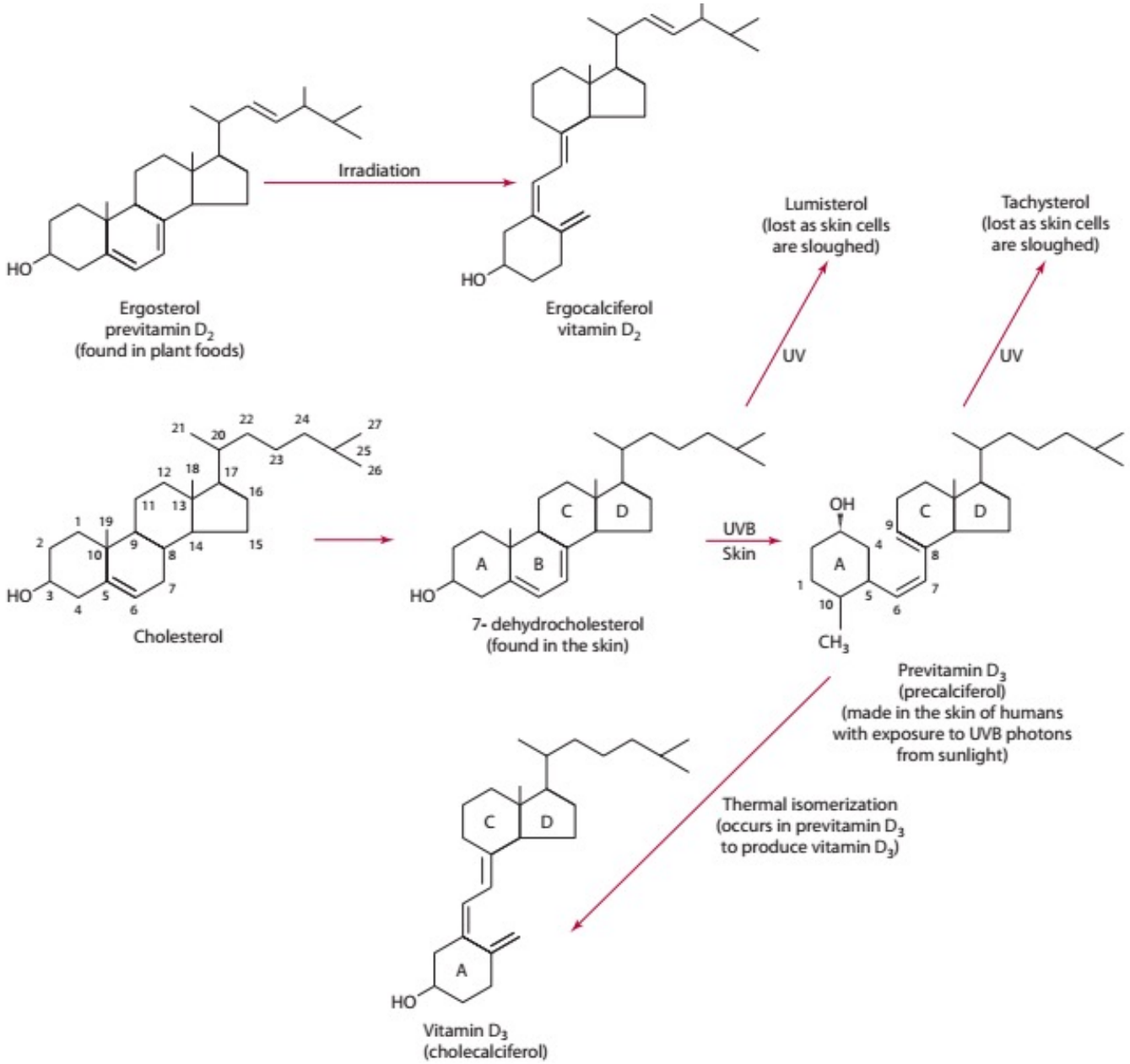


Figure 10.11 Production of ergocalciferol (vitamin D_2) and vitamin D_3 (cholecalciferol).

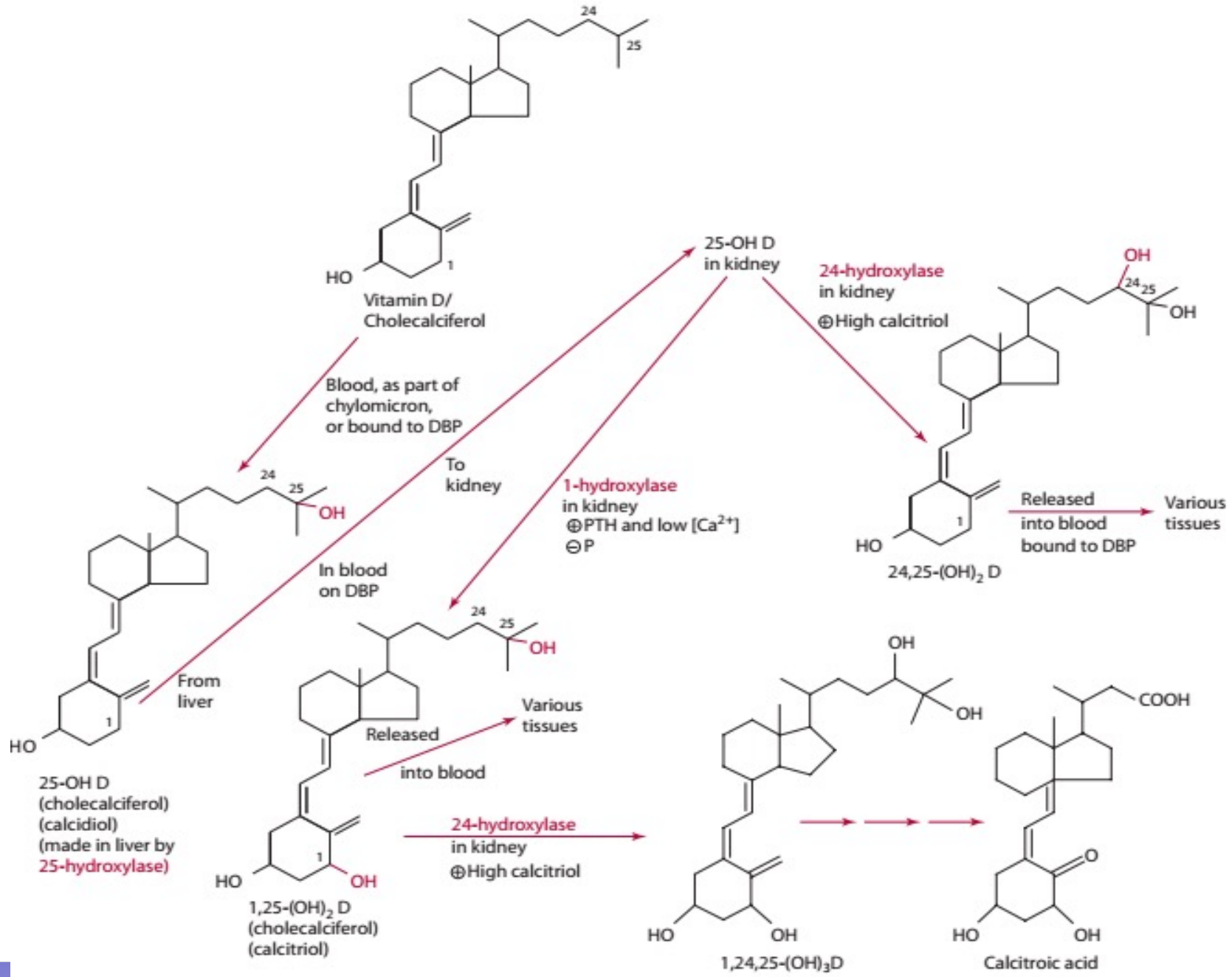


Figure 10.12 Hydroxylations of vitamin D.

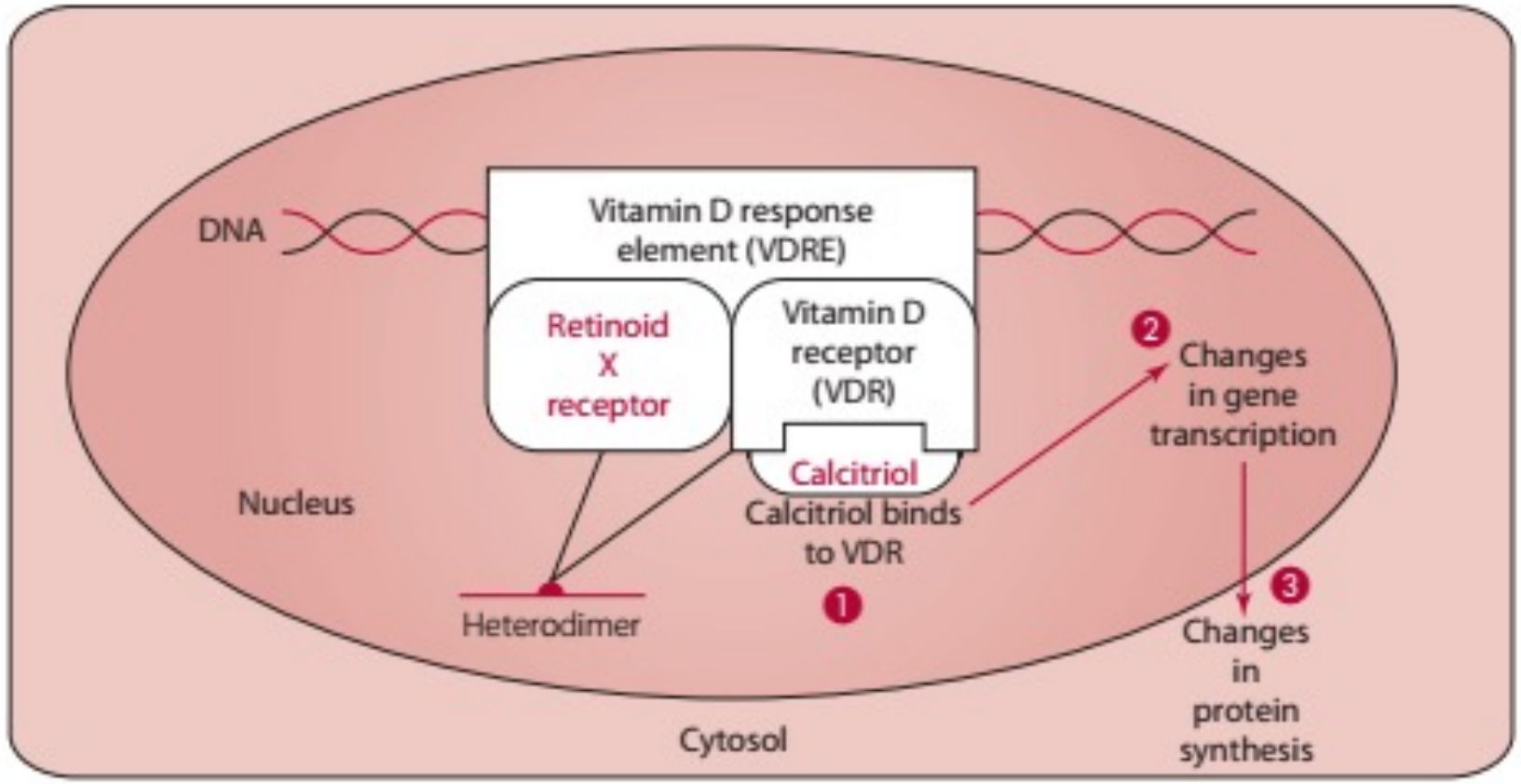


Figure 10.13 Proposed role of calcitriol bound to VDR on DNA in gene expression.

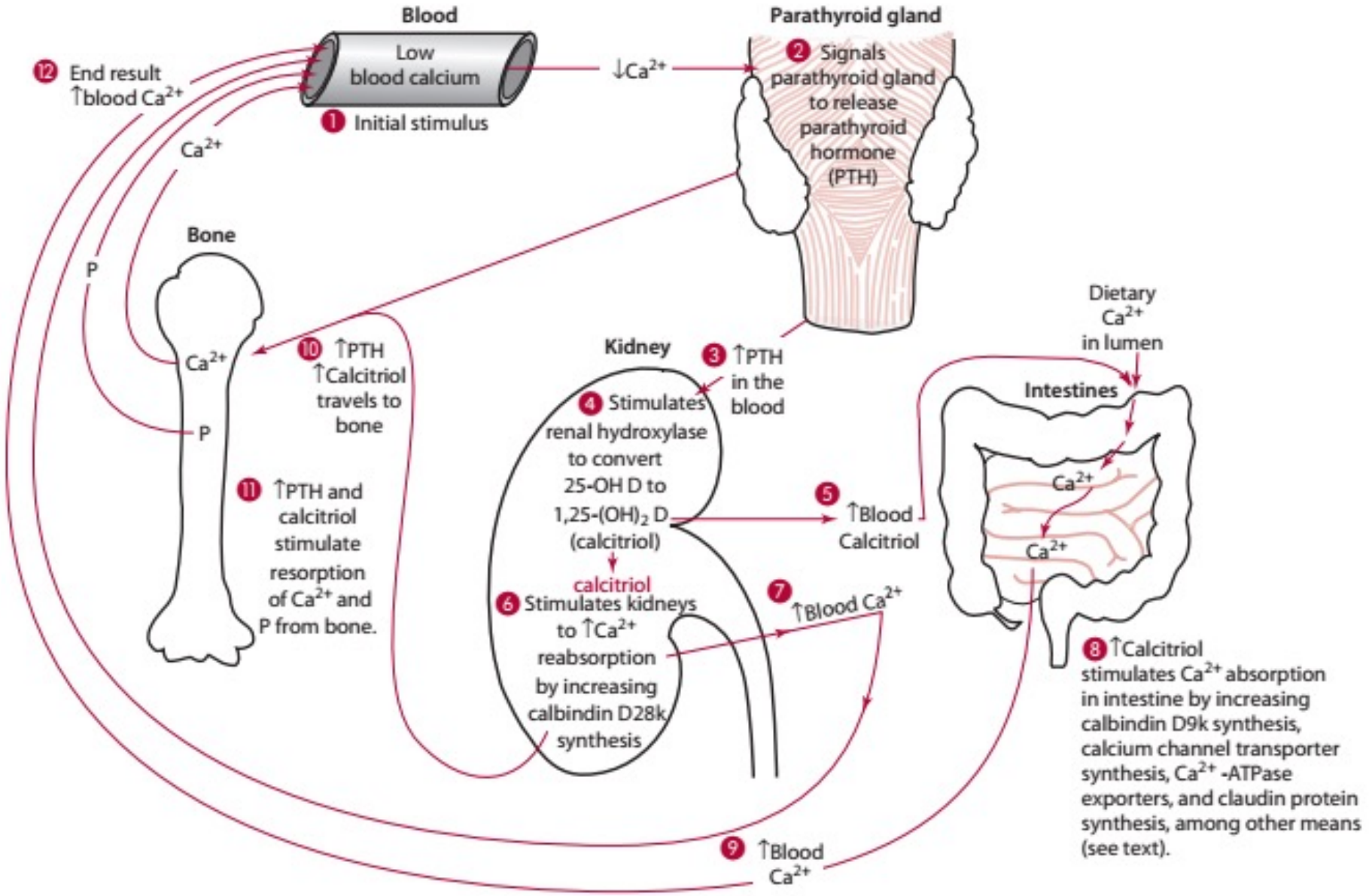


Figure 10.14 Calcitriol, 1,25-$(OH)_2$D, synthesis and actions with parathyroid hormone (PTH).