METABOLISM

= summary of all chemical (and physical) processes included in:

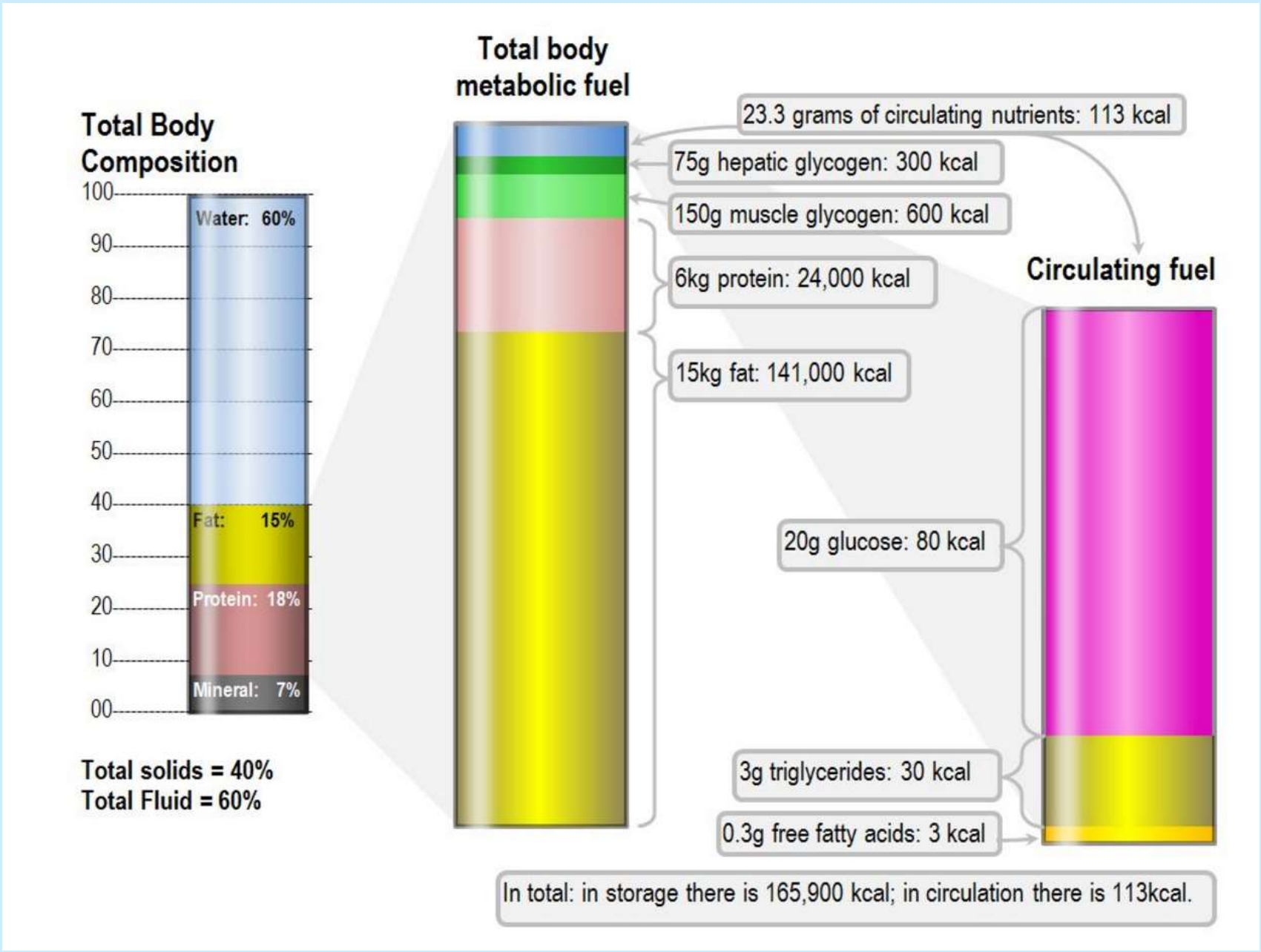
1. Production of energy from internal and external sources
2. **Synthesis** and **degradation** of structural and functional tissue components
3. Excretion of waste products and toxins from body

METABOLIC DISORDERS

1. **Inherited** metabolic disorders (enzymopathies)
2. **Combined** metabolic disorders (DM, gout, degenerative disorder of joints and bones)
3. Metabolic disorders from **external reasons**

METABOLISM

- Proteins
- Saccharides
- Lipids



http://www.derangedphysiology.com/main/required-reading/endocrinology-metabolism-and-nutrition/Chapter%203.1.8/physiological-adaptation-prolonged-starvation

DIET

Ballanced diet should contain:

– **sugars – saccharides (50 –55 %)**

– **fats (30 %)**

– **proteins (15 –20 %)**

– vitamines, innorganic compounds

– **water** – daily requirements correspond to **2,4 l:**

The daily energy requirement is:

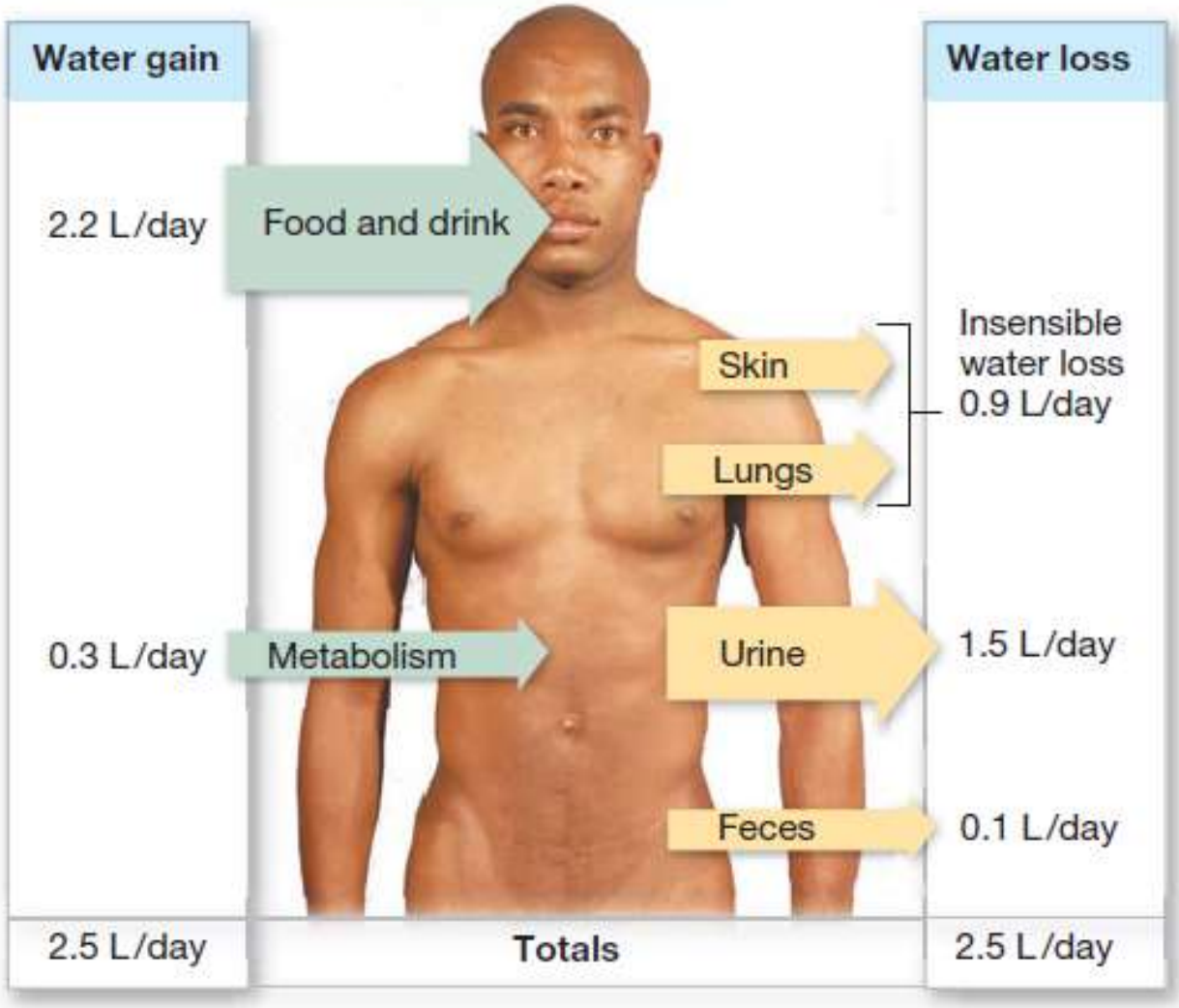
– an adult man ~12600 kJ

– an adult woman ~9200 kJ

– real consumption depends on:

- body weight
- the extent of physical activity
- other physiological and pathophysiological factors

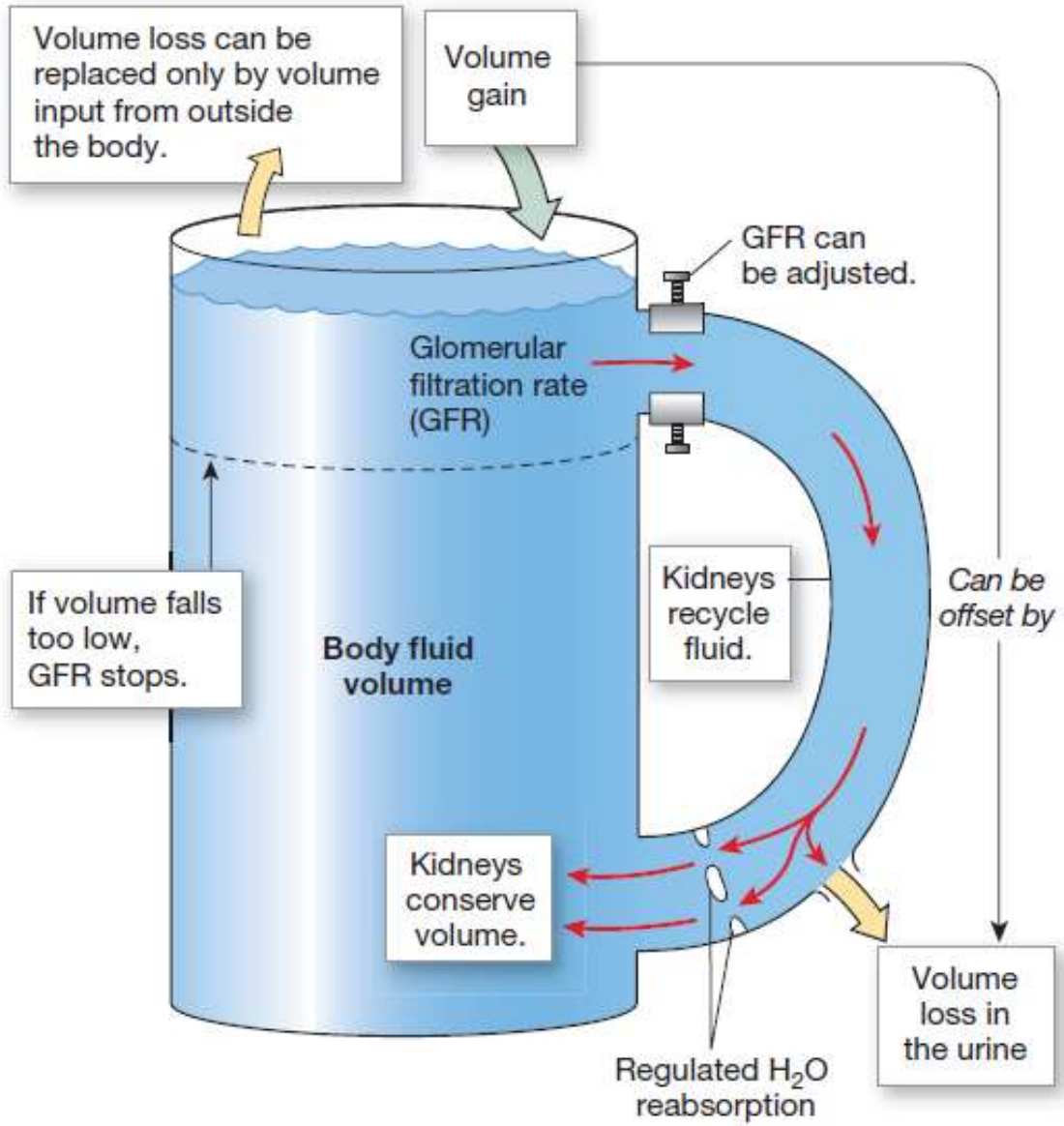
WATER BALANCE IN THE BODY



Intake 2.2 L/day + Metabolic production 0.3 L/day − Output 2.5 L/day = 0

THE KIDNEYS CONSERVE VOLUME

Kidneys cannot restore lost volume. They only conserve fluid.



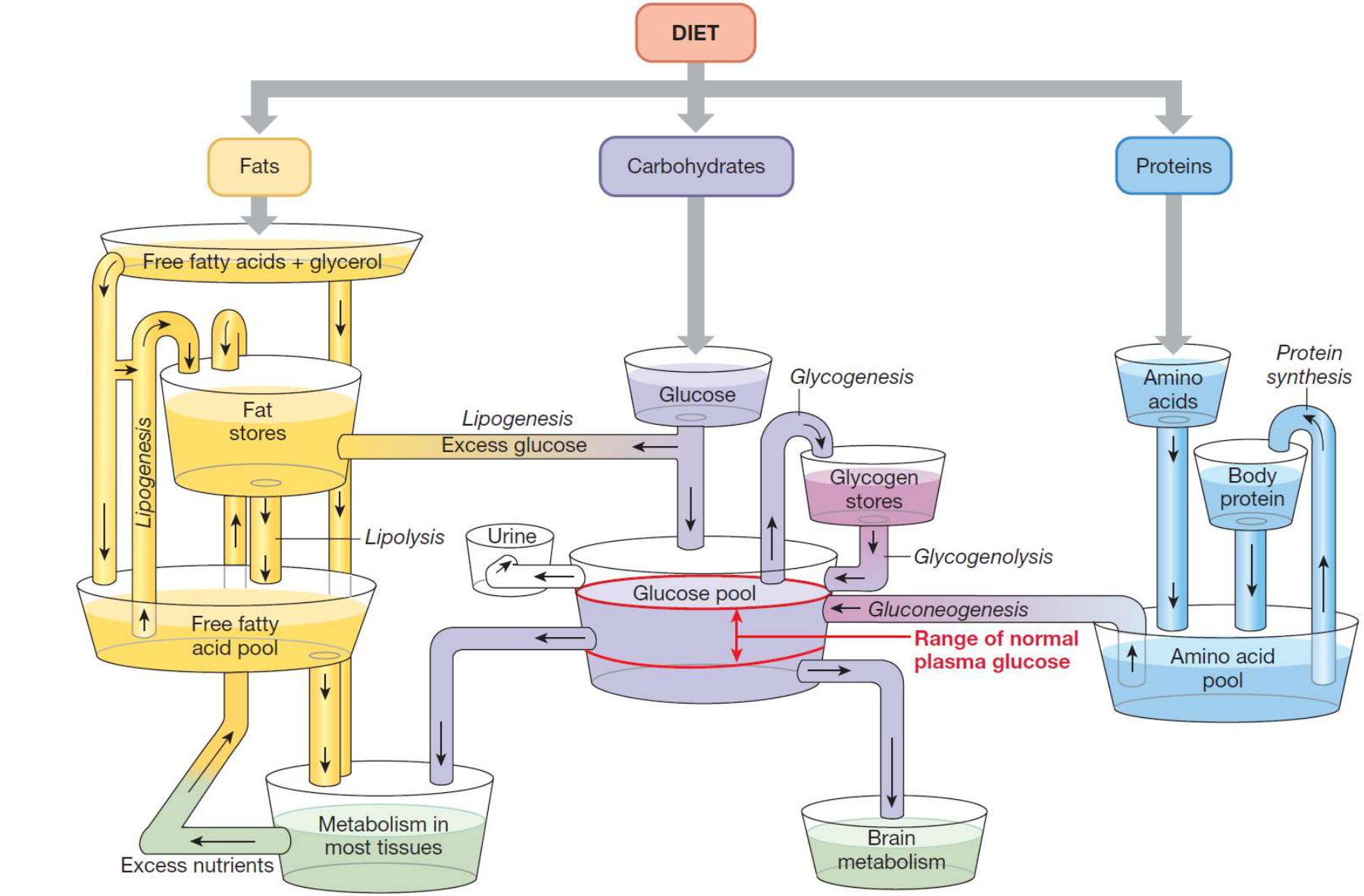
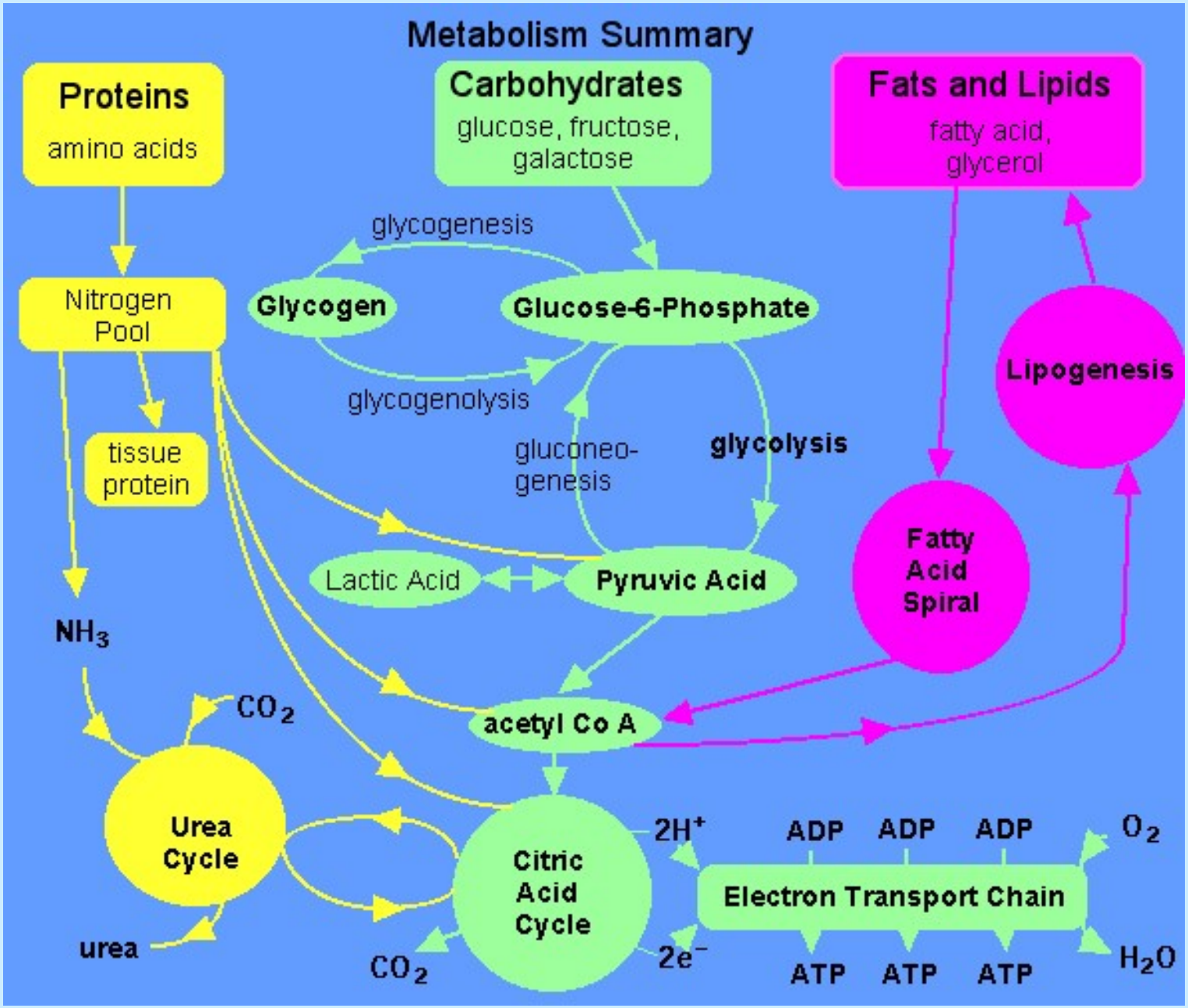
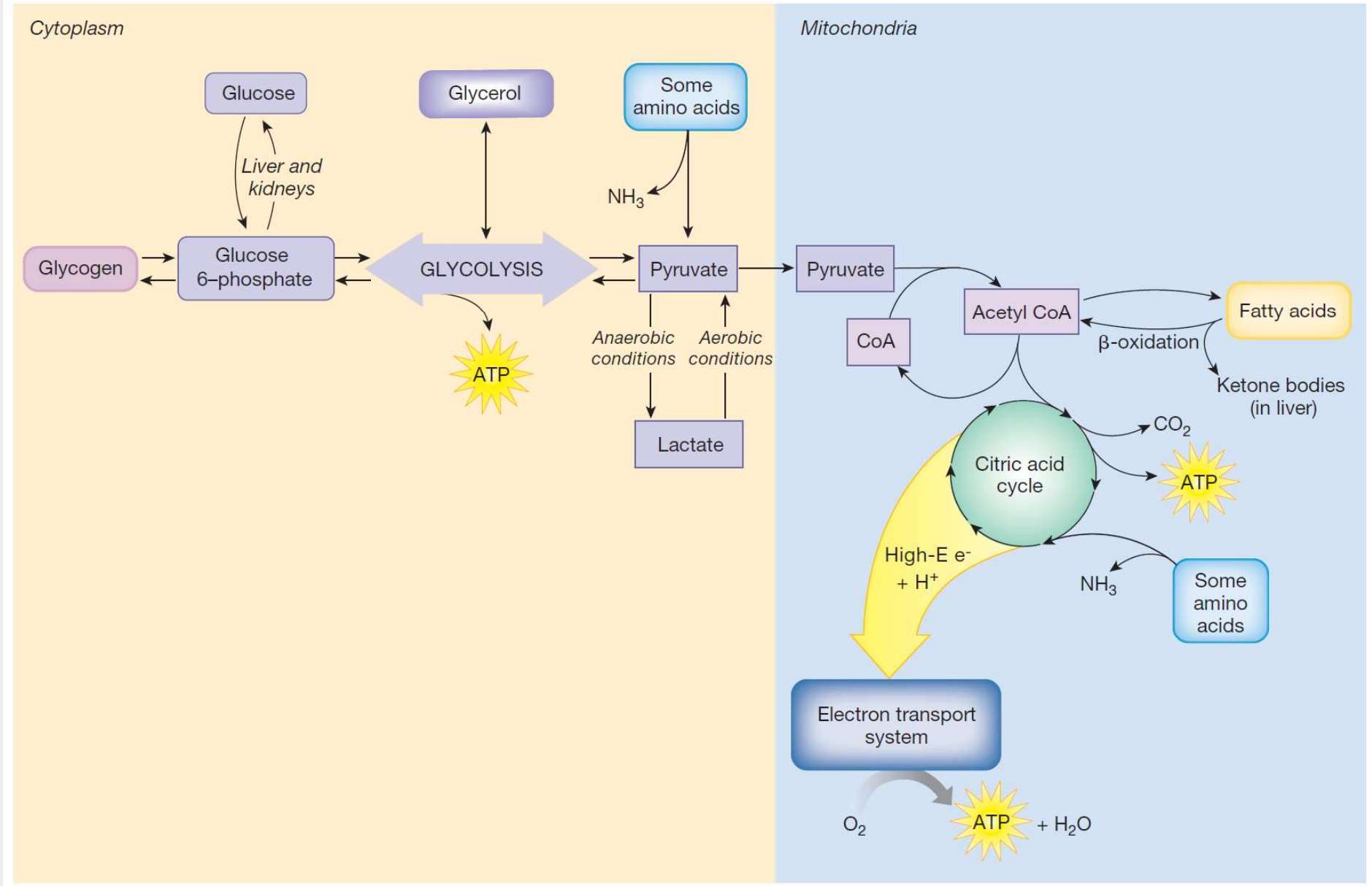


Fig. 22.3 Adapted from L. L. Langley, *Homeostasis* (New York: Reinhold, 1965).


Metabolism Summary
Proteins
amino acids
Carbohydrates
glucose, fructose, galactose
Fats and Lipids
fatty acid, glycerol
glycogenesis
Nitrogen Pool
Glycogen
Glucose-6-Phosphate
Lipogenesis
glycogenolysis
tissue protein
gluconeo-genesis
glycolysis
Fatty Acid Spiral
Lactic Acid
Pyruvic Acid
NH3
CO2
acetyl Co A
Urea Cycle
Citric Acid Cycle
2H+
ADP ADP ADP
O2
Electron Transport Chain
urea
CO2
2e−
ATP ATP ATP
H2O



(b) Fates of Nutrients in Fed-State and Fasted-State Metabolism

TABLE 18–1 Summary of Nutrient Metabolism during the Absorptive Period

1. Energy is provided primarily by absorbed carbohydrate.
2. There is net uptake of glucose by the liver.
3. Some carbohydrate is stored as glycogen in liver and muscle, but most carbohydrate and fat in excess of that utilized for energy are stored mainly as fat in adipose tissue.
4. There is some synthesis of body proteins, but many of the amino acids in dietary protein are utilized for energy or converted to fat.

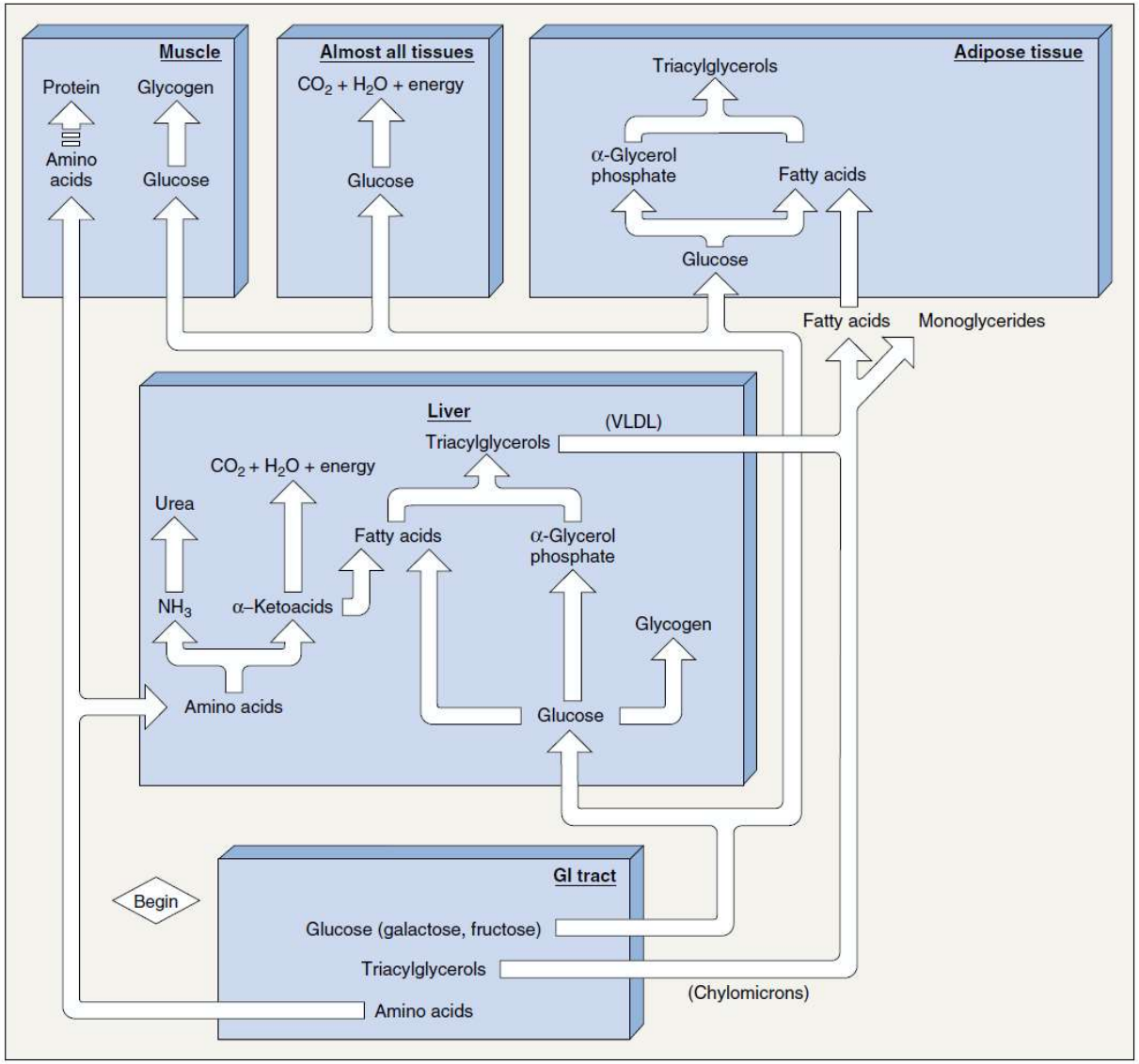


FIGURE 18–1
Major metabolic pathways of the absorptive state. The arrow from amino acids to protein in muscle is dashed to denote the fact that excess amino acids are not stored as protein (see text). All arrows between boxes denote transport of the substance via the blood. VLDL = very low density lipoproteins.

TABLE 18–2 Summary of Nutrient Metabolism during the Postabsorptive Period

1. Glycogen, fat, and protein syntheses are curtailed, and net breakdown occurs.
2. Glucose is formed in the liver both from the glycogen stored there and by gluconeogenesis from blood-borne lactate, pyruvate, glycerol, and amino acids. The kidneys also perform gluconeogenesis during a prolonged fast.
3. The glucose produced in the liver (and kidneys) is released into the blood, but its utilization for energy is greatly reduced in muscle and other nonneural tissues.
4. Lipolysis releases adipose-tissue fatty acids into the blood, and the oxidation of these fatty acids by most cells and of ketones produced from them by the liver provides most of the body's energy supply.
5. The brain continues to use glucose but also starts using ketones as they build up in the blood.

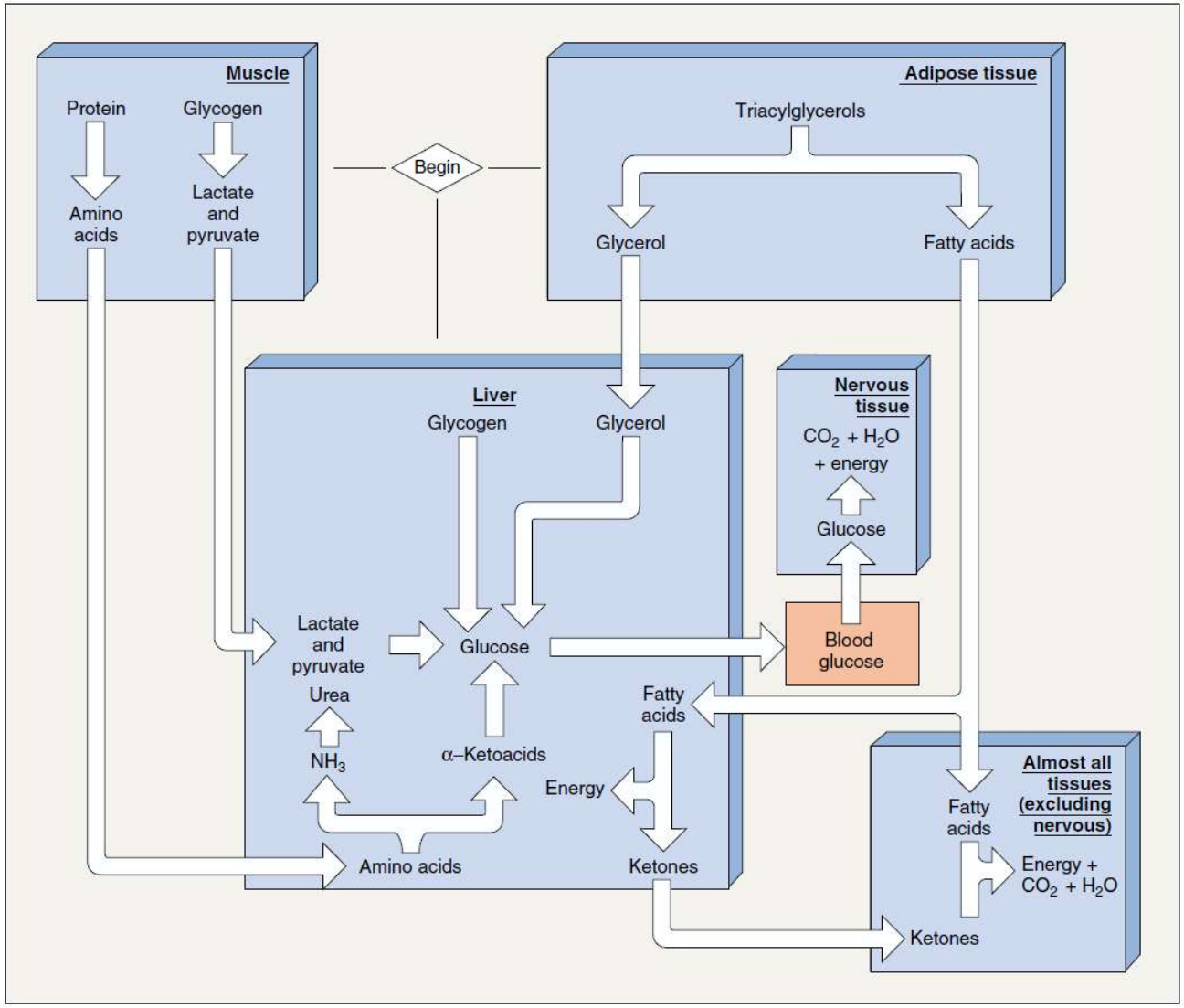
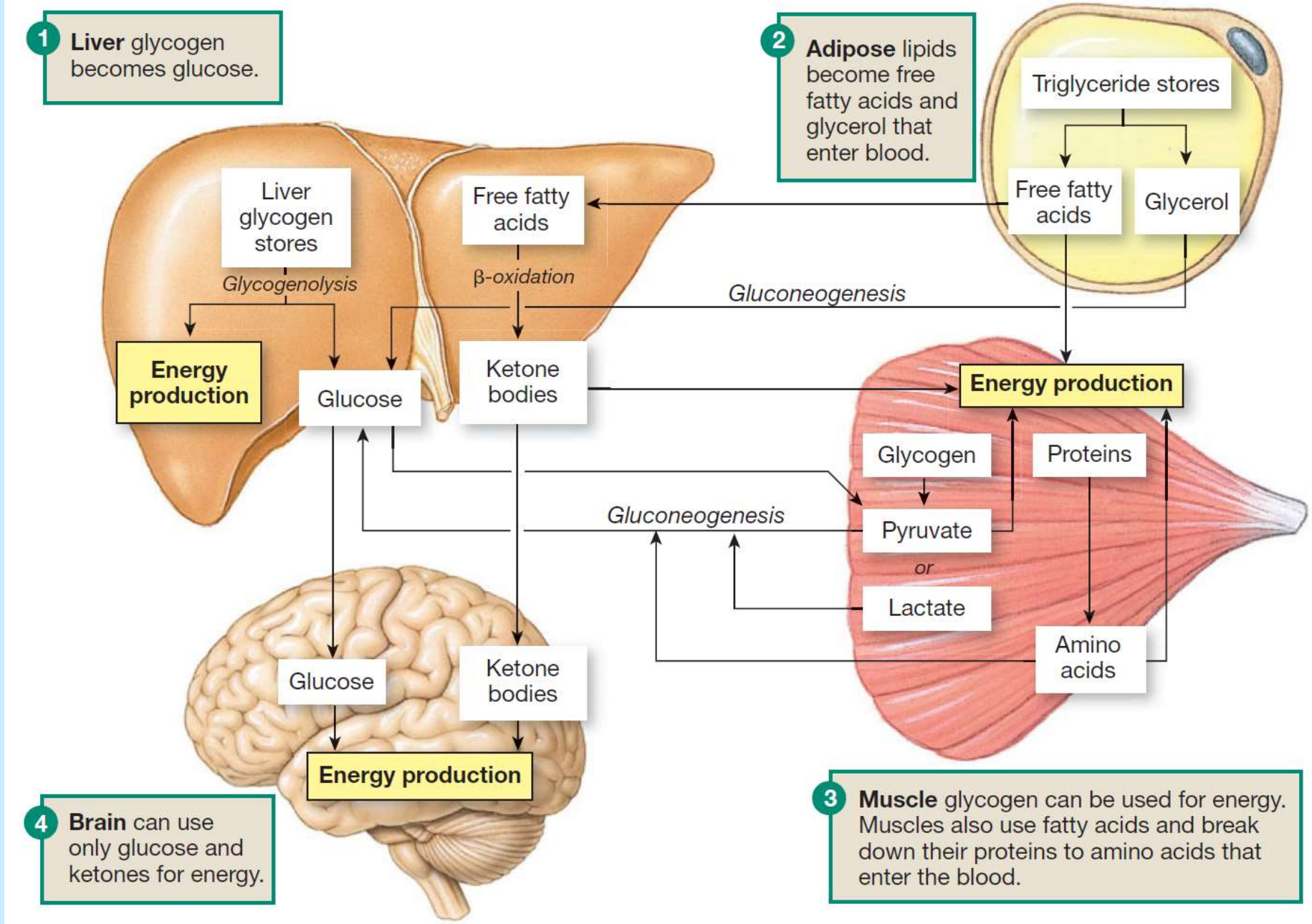


FIGURE 18–2
Major metabolic pathways of the postabsorptive state. The central focus is regulation of the blood glucose concentration. All arrows between boxes denote transport of the substance via the blood.


1 Liver glycogen becomes glucose.
2 Adipose lipids become free fatty acids and glycerol that enter blood.
Triglyceride stores
Free fatty acids
Glycerol
Liver glycogen stores
Free fatty acids
Glycogenolysis
β-oxidation
Gluconeogenesis
Energy production
Glucose
Ketone bodies
Energy production
Glycogen
Proteins
Gluconeogenesis
Pyruvate
or
Lactate
Amino acids
Glucose
Ketone bodies
Energy production
4 Brain can use only glucose and ketones for energy.
3 Muscle glycogen can be used for energy. Muscles also use fatty acids and break down their proteins to amino acids that enter the blood.

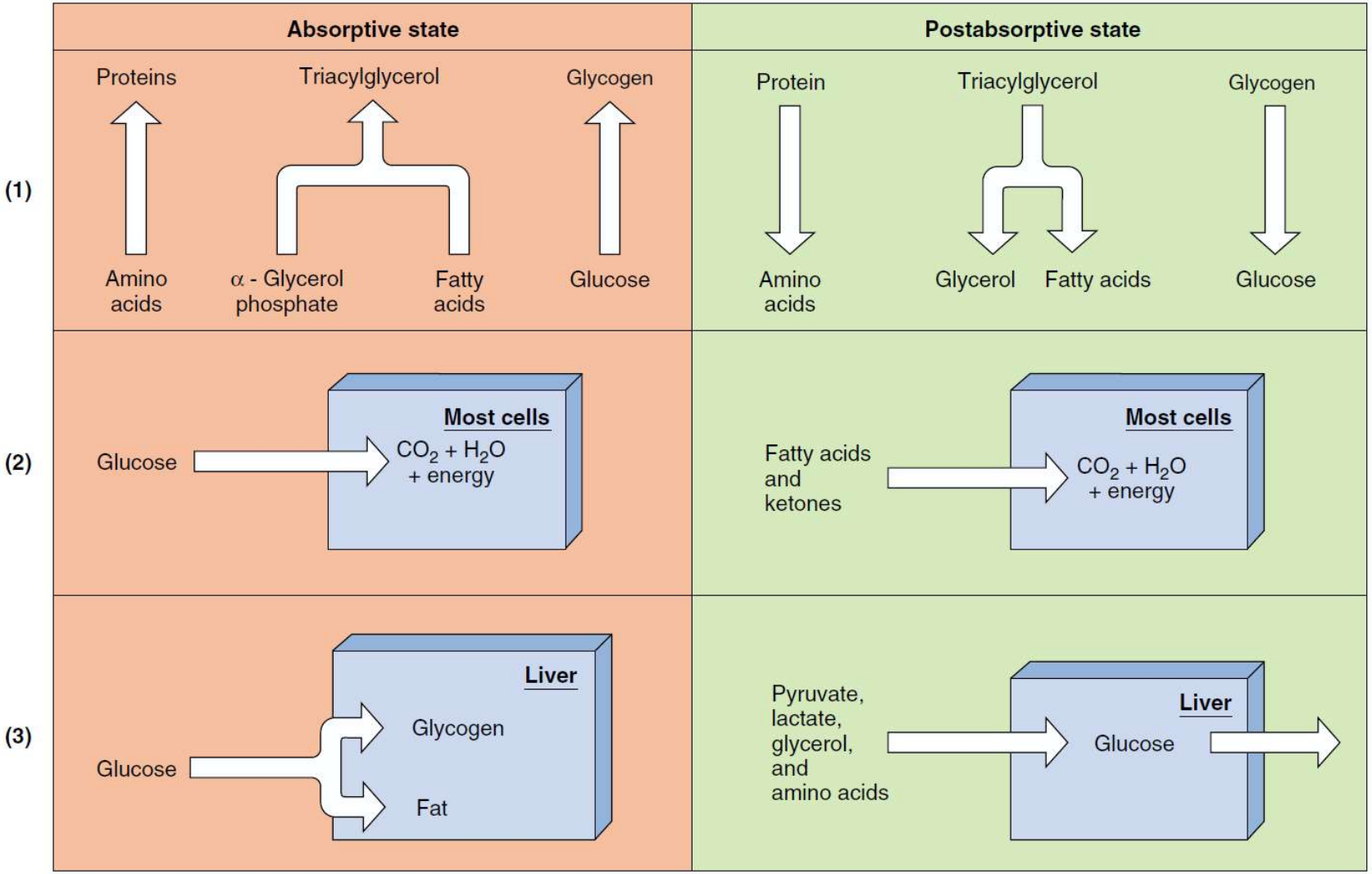


FIGURE 18–3

Summary of critical points in transition from the absorptive state to the postabsorptive state. The term "absorptive state" could be replaced with "actions of insulin," and the term "postabsorptive state" with "results of decreased insulin." The numbers at the left margin refer to discussion in the text.

NUTRIENT	ABSORBED AS	FED-STATE METABOLISM	FASTED-STATE METABOLISM
Carbohydrates	Glucose primarily; also fructose and galactose	• Used immediately for energy through aerobic pathways* (*glycolysis* and *citric acid cycle*) • Used for lipoprotein synthesis in liver • Stored as glycogen in liver and muscle (*glycogenesis*) • Excess converted to fat and stored in adipose tissue (*lipogenesis*)	• Glycogen polymers broken down (*glycogenolysis*) to glucose in liver and kidney or to glucose 6-phosphate for use in glycolysis
Proteins	Amino acids primarily plus some small peptides	• Most amino acids go to tissues for protein synthesis* • If needed for energy, amino acids converted in liver to intermediates for aerobic metabolism (*deamination*) • Excess converted to fat and stored in adipose tissue (*lipogenesis*)	• Proteins broken down into amino acids • Amino acids deaminated in liver for ATP production or used to make glucose (*gluconeogenesis*)
Fats	Fatty acids, triglycerides and cholesterol	• Stored as triglycerides primarily in the liver and adipose tissue* (*lipogenesis*) • Cholesterol used for steroid synthesis or as a membrane component • Fatty acids used for lipoprotein and eicosanoid synthesis	• Triglycerides broken down into fatty acids and glycerol (*lipolysis*) • Fatty acids used for ATP production through aerobic pathways (β-*oxidation*)

* Primary fate

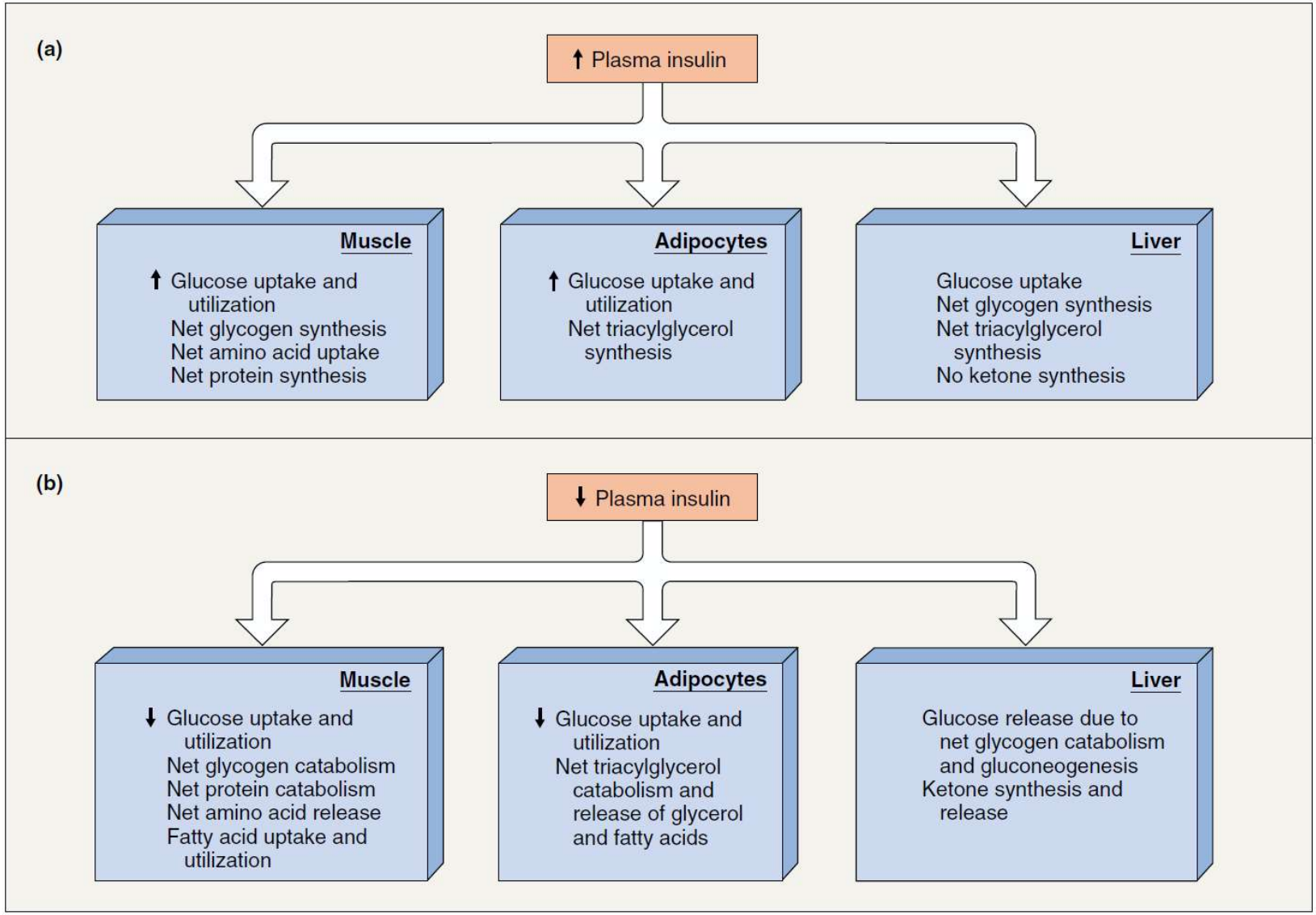


FIGURE 18–4

Summary of overall target-cell responses to (a) an increase or (b) a decrease in the plasma concentration of insulin. The responses in (a) are virtually identical to the absorptive state events of Figure 18–1 and the left panel of Figure 18–3; the responses in (b) are virtually identical to the postabsorptive state events of Figure 18–2 and the right panel of Figure 18–3. The biochemical events that underlie these responses to insulin are shown in Figure 18–6.

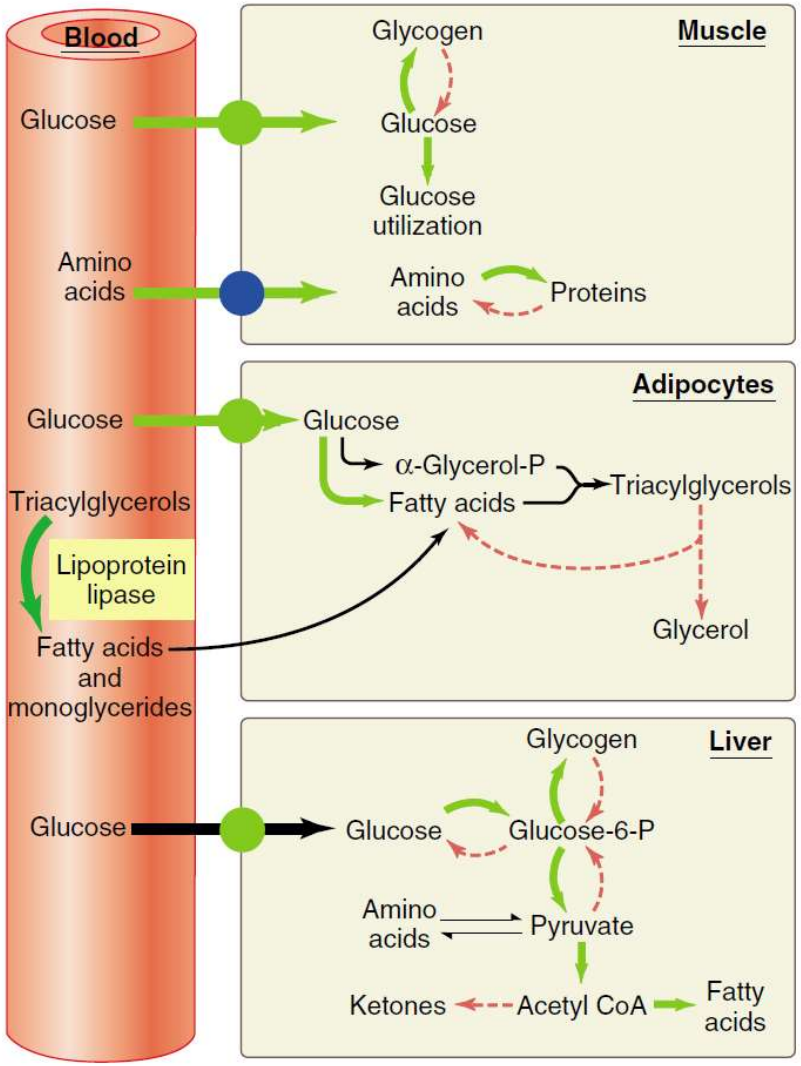


FIGURE 18–6

Reference illustration of the key biochemical events that underlie those responses of target cells to insulin summarized in Figure 18–4. Each green arrow denotes a process stimulated by insulin, whereas a dashed red arrow denotes inhibition by insulin. Except for the effects on the transport proteins for glucose and amino acids, all other effects are exerted on insulin-sensitive enzymes. The bowed arrows denote pathways whose reversibility is mediated by different enzymes (Chapter 4); such enzymes are commonly the ones influenced by insulin and other hormones. The black arrows are processes that are not *directly* affected by insulin but are enhanced in the presence of increased insulin as the result of mass-action.

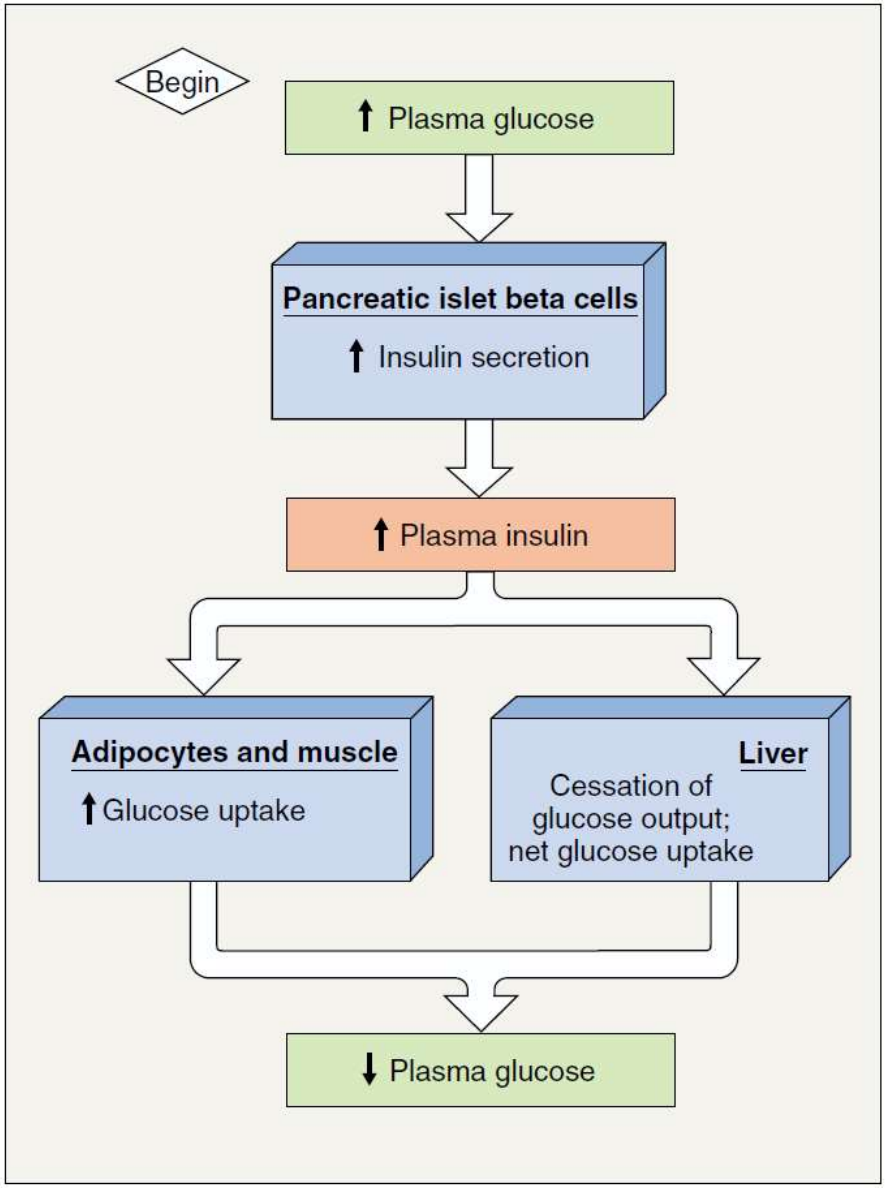


FIGURE 18–7
Nature of plasma glucose control over insulin secretion.

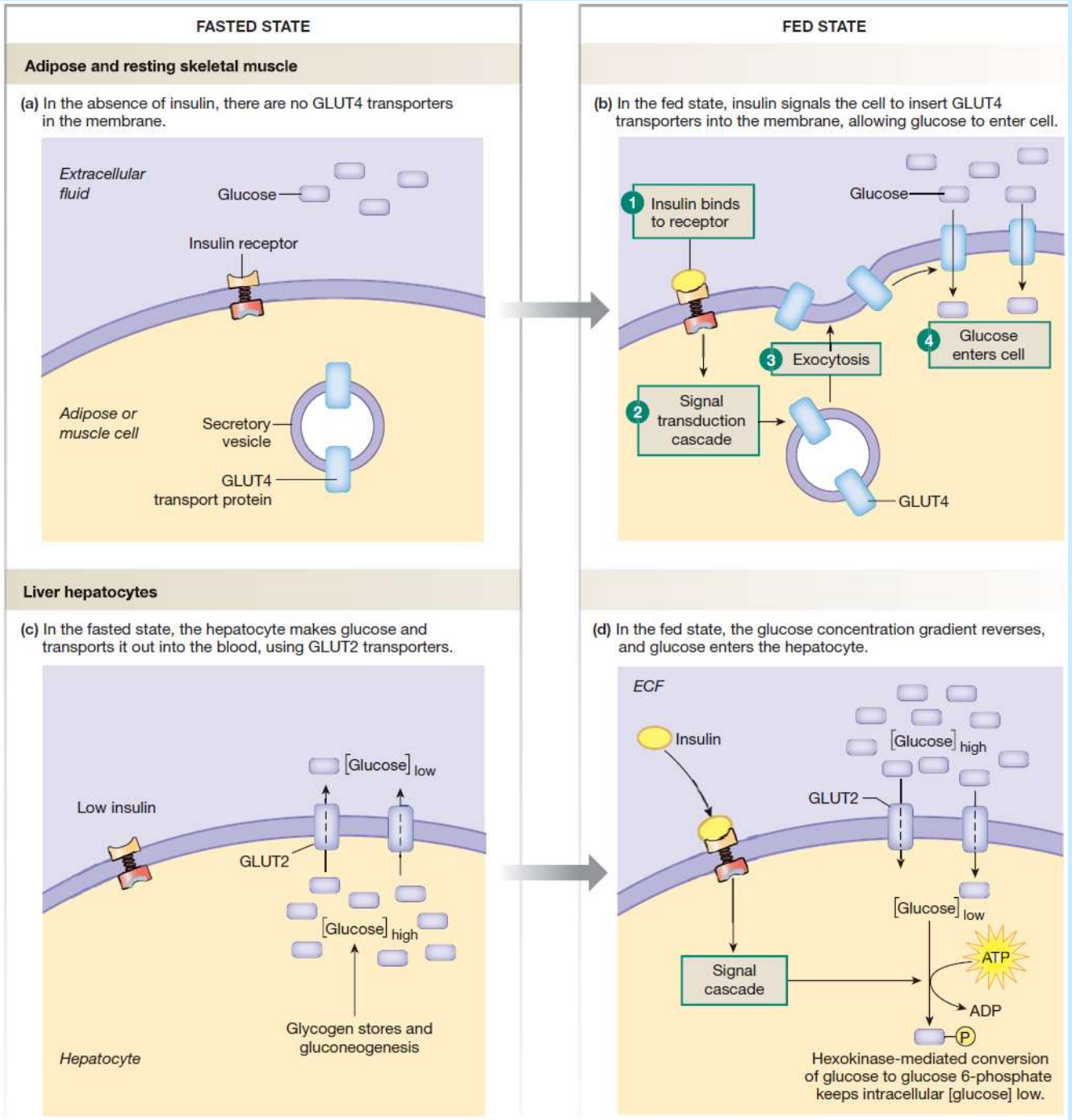


Fig. 22.17 ***Glucose transport in the fed and fasted states***

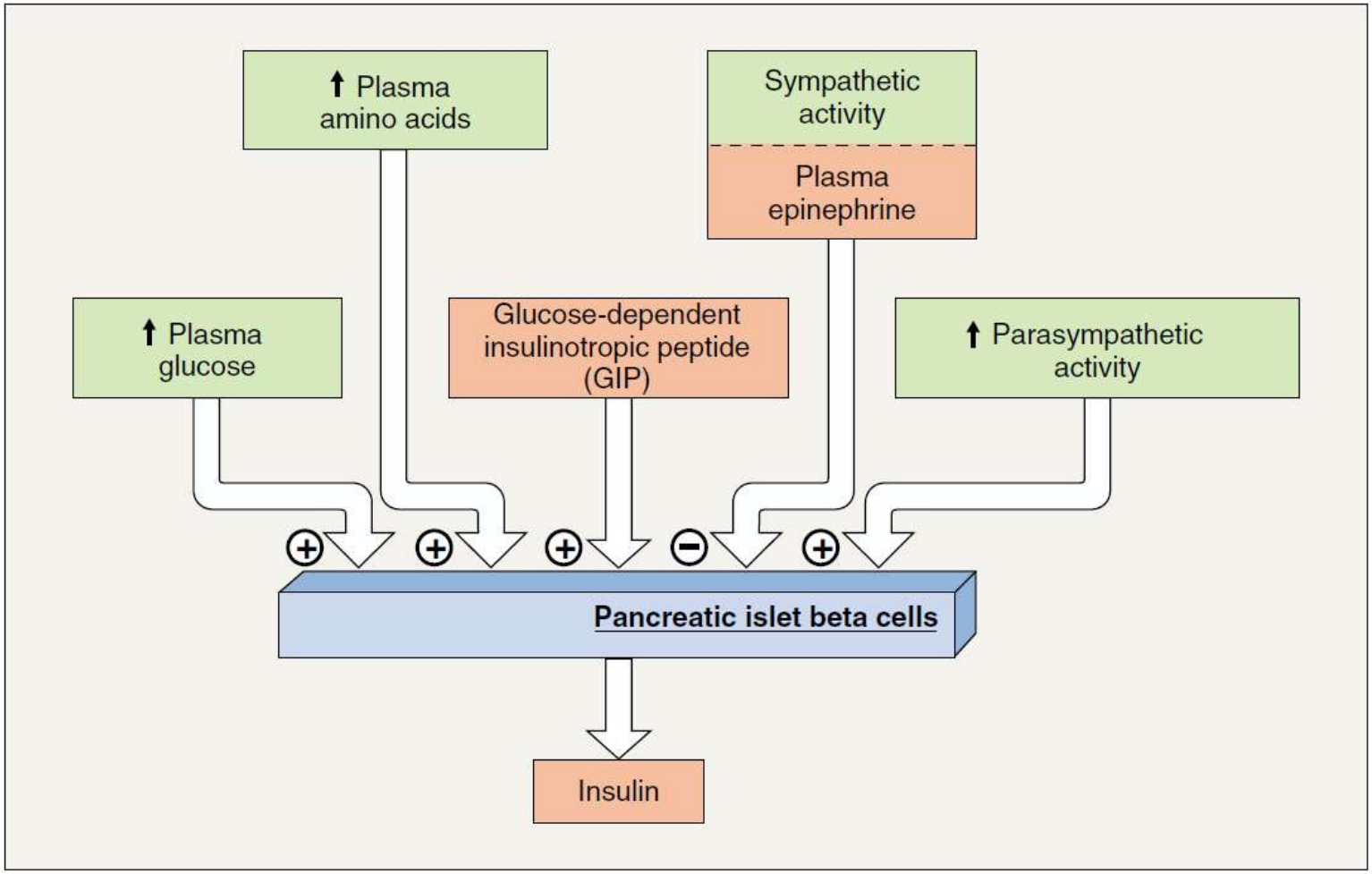


FIGURE 18–8

Major controls of insulin secretion. GIP is a gastrointestinal hormone.

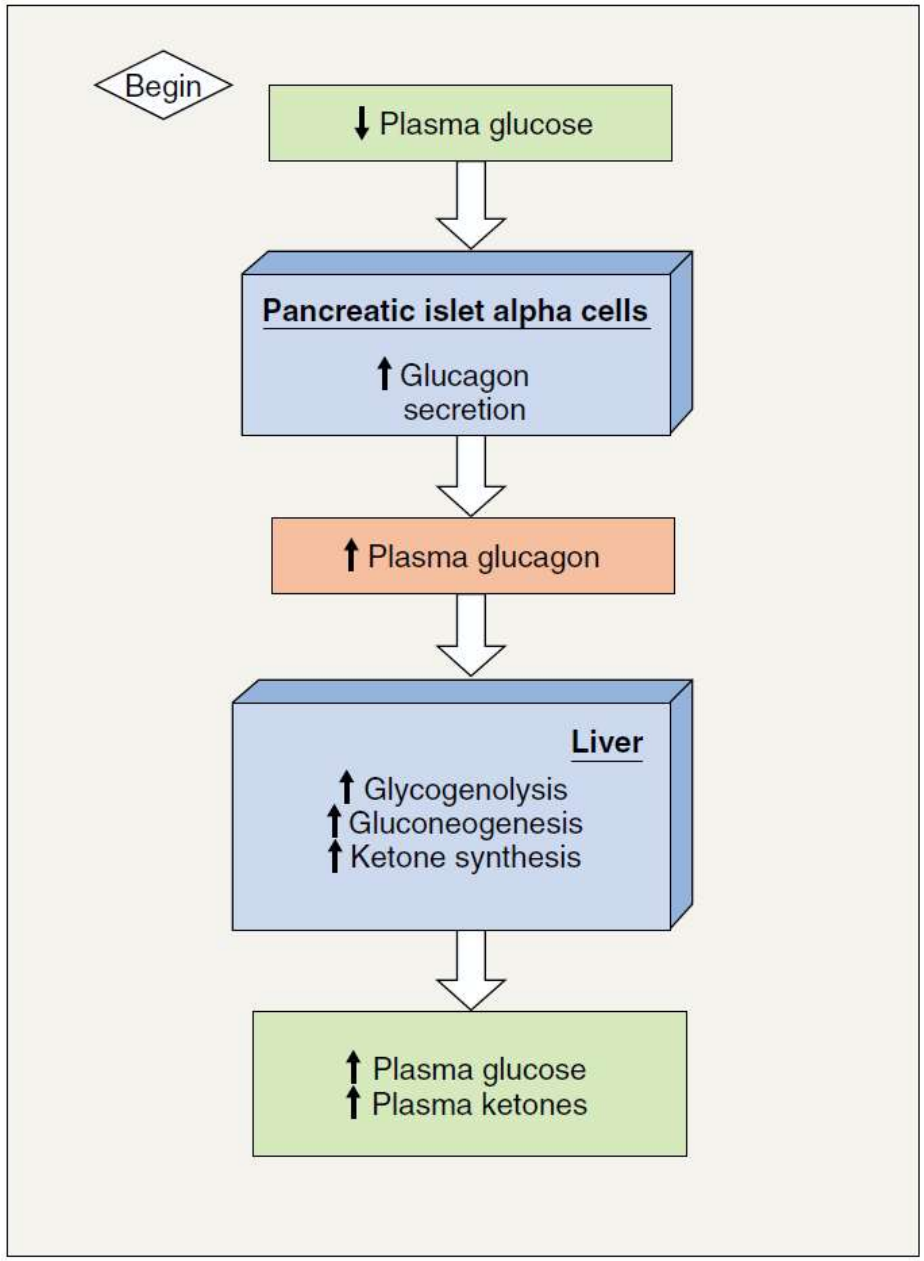


FIGURE 18–9

Nature of plasma glucose control over glucagon secretion.

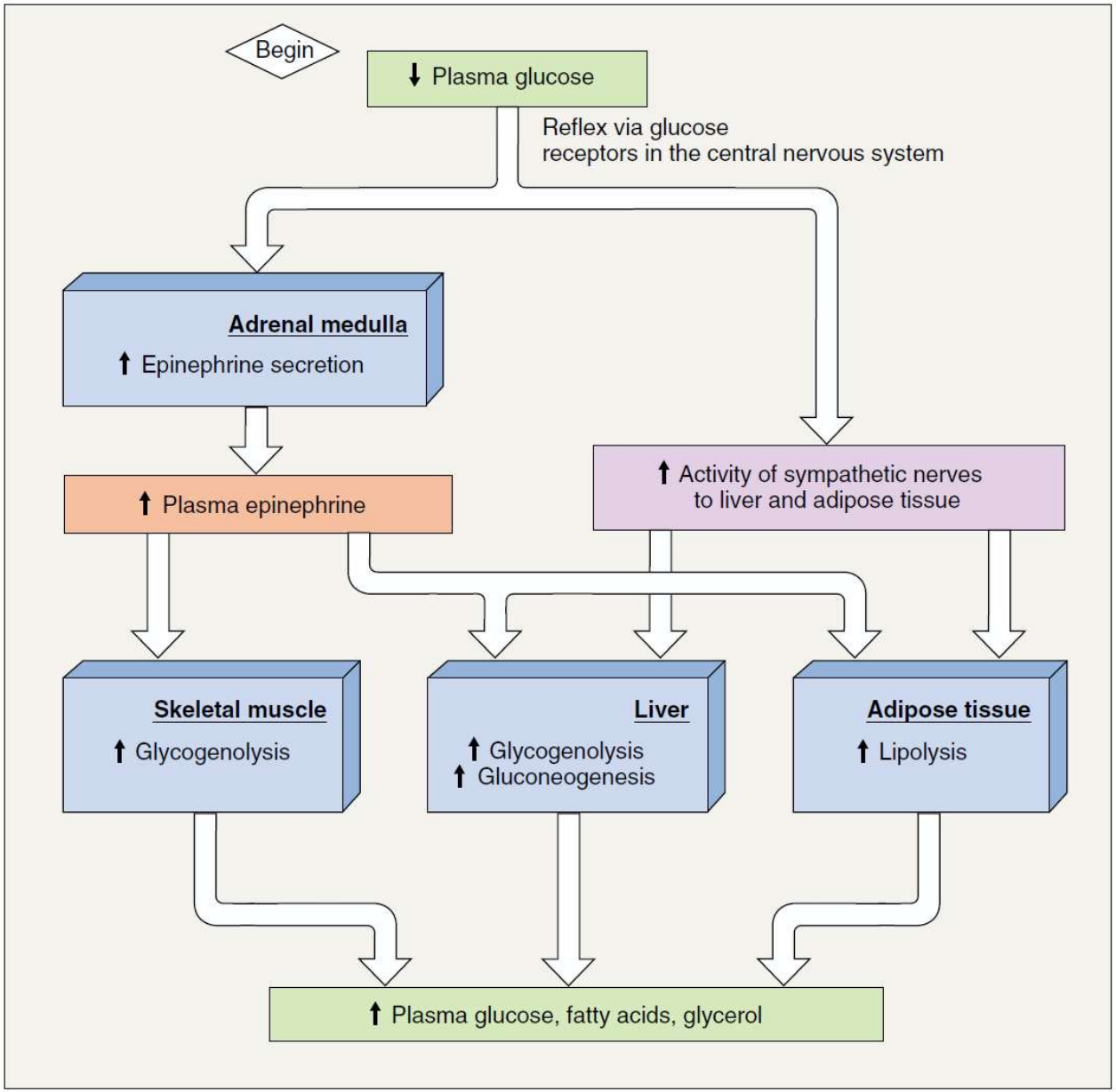
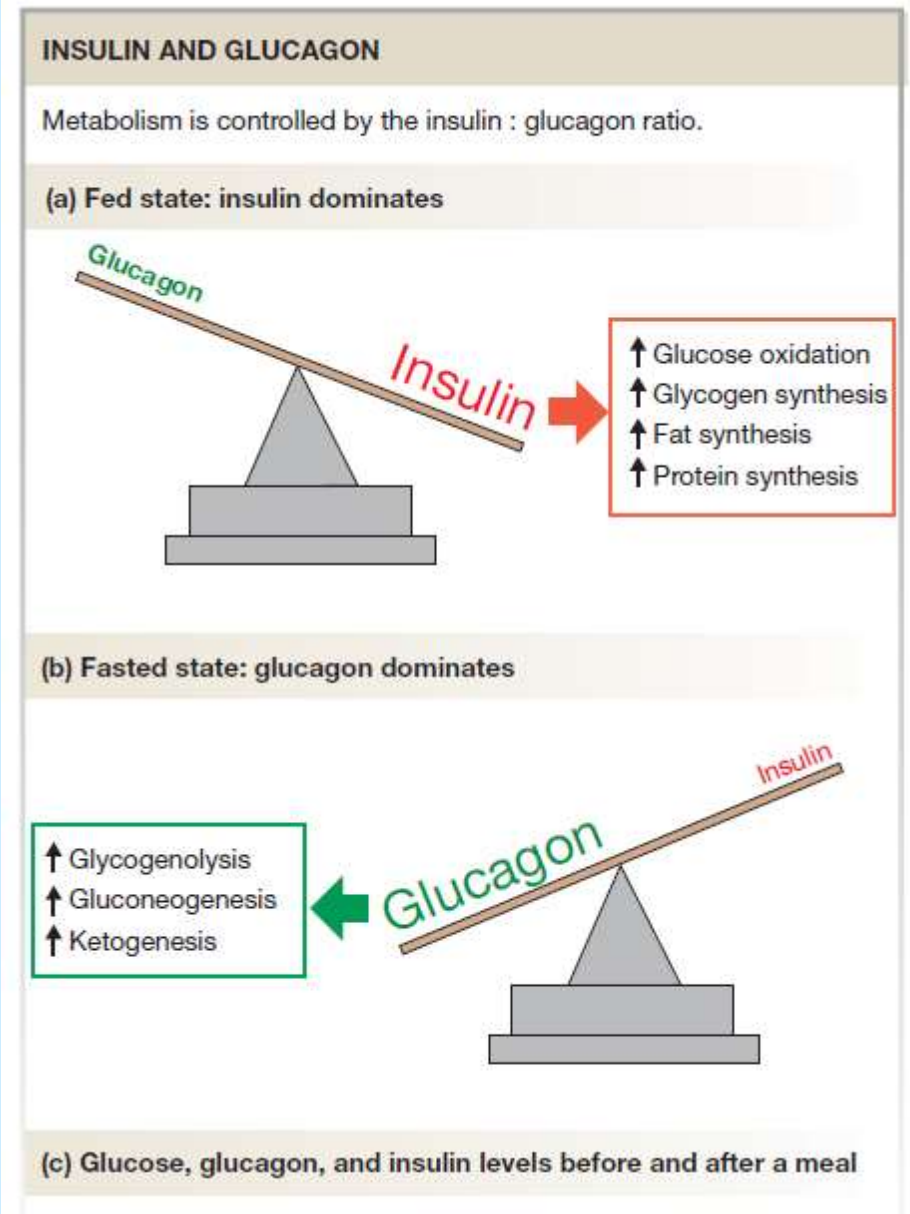
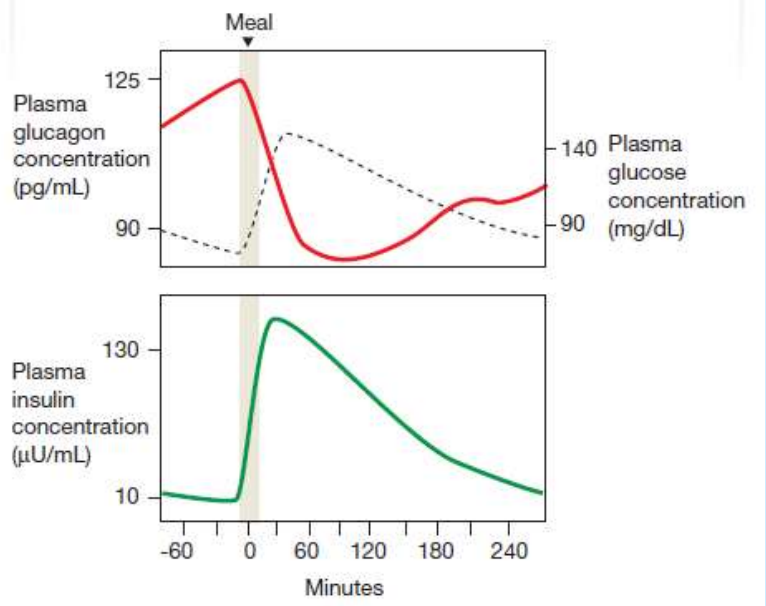


FIGURE 18–10

Participation of the sympathetic nervous system in the response to a low plasma glucose concentration (hypoglycemia). Glycogenolysis in skeletal muscle contributes to increased plasma glucose by releasing lactate and pyruvate, which are converted to glucose in the liver.

Insulin versus glucagon





Condition	Hepatic Glucose Storage (S) or Production (P)[a]	I/G
Glucose availability		
Large carbohydrate meal	4+ (S)	70
Intravenous glucose	2+ (S)	25
Small meal	1+ (S)	7
Glucose need		
Overnight fast	1+ (P)	2.3
Low-carbohydrate diet	2+ (P)	1.8
Starvation	4+ (P)	0.4

[a]1+ to 4+ indicate relative magnitude.

Courtesy of RH Unger.

TABLE 18-4 Summary of Glucose-Counterregulatory Controls*

	Glucagon	Epinephrine	Cortisol	Growth Hormone
Glycogenolysis	√	√		
Gluconeogenesis	√	√	√	√
Lipolysis		√	√	√
Inhibition of: glucose uptake by muscle cells and adipose-tissue cells			√	√

*A √ indicates that the hormone stimulates the process; no √ indicates that the hormone has no major physiological effect on the process. Epinephrine stimulates glycogenolysis in both liver and skeletal muscle, whereas glucagon does so only in liver.

SHORT-TERM VERSUS LONG TERM FASTING

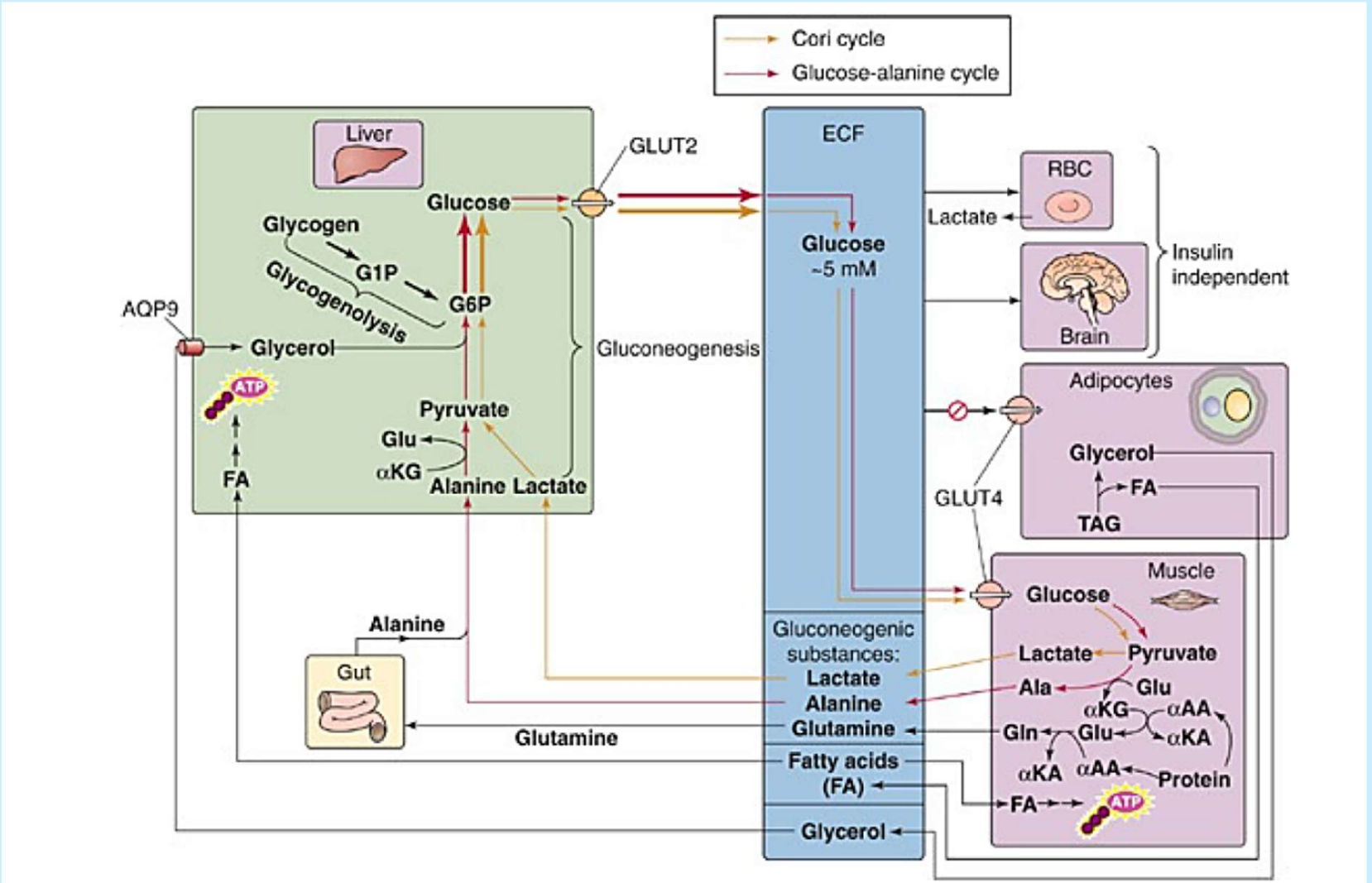
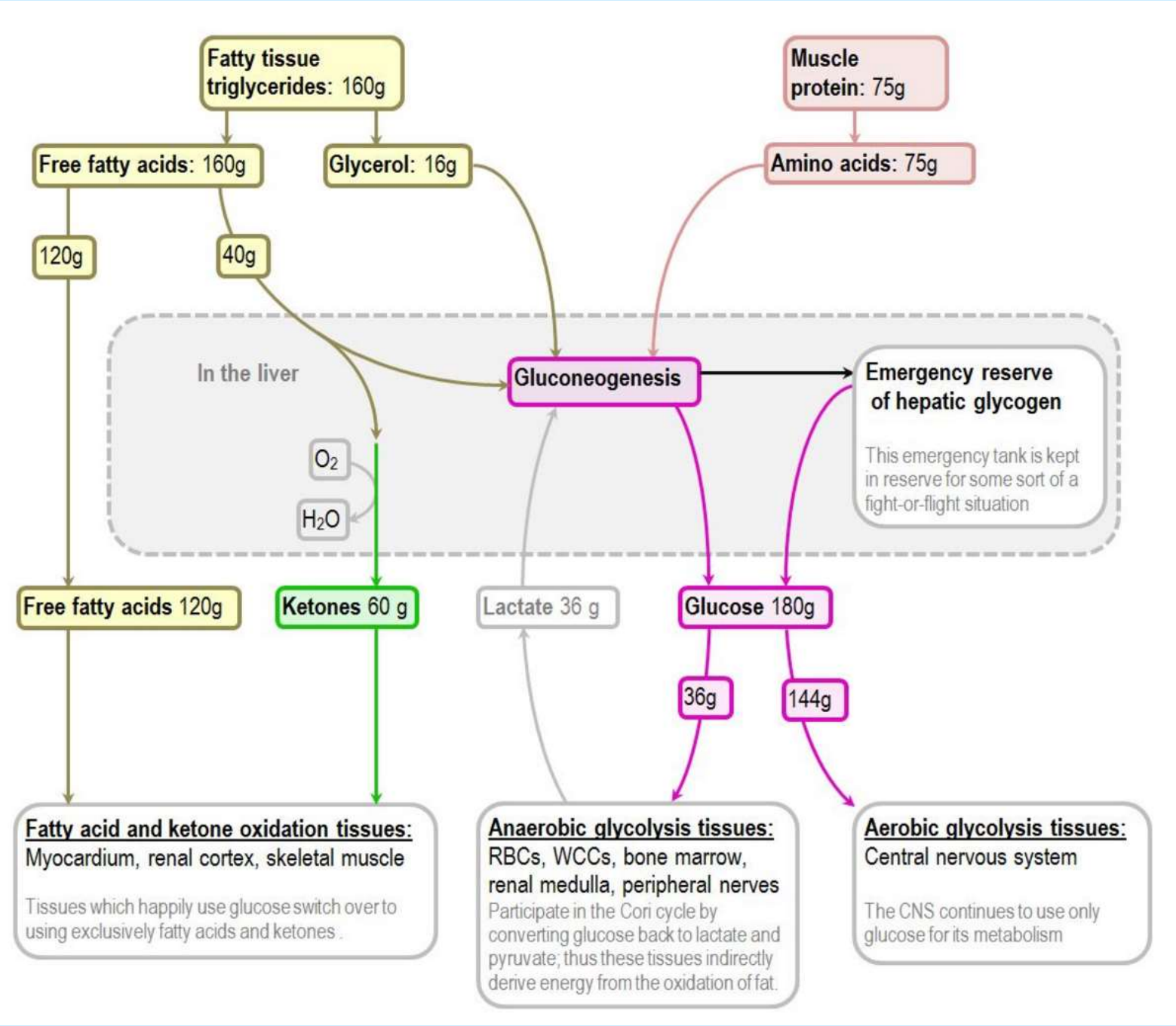
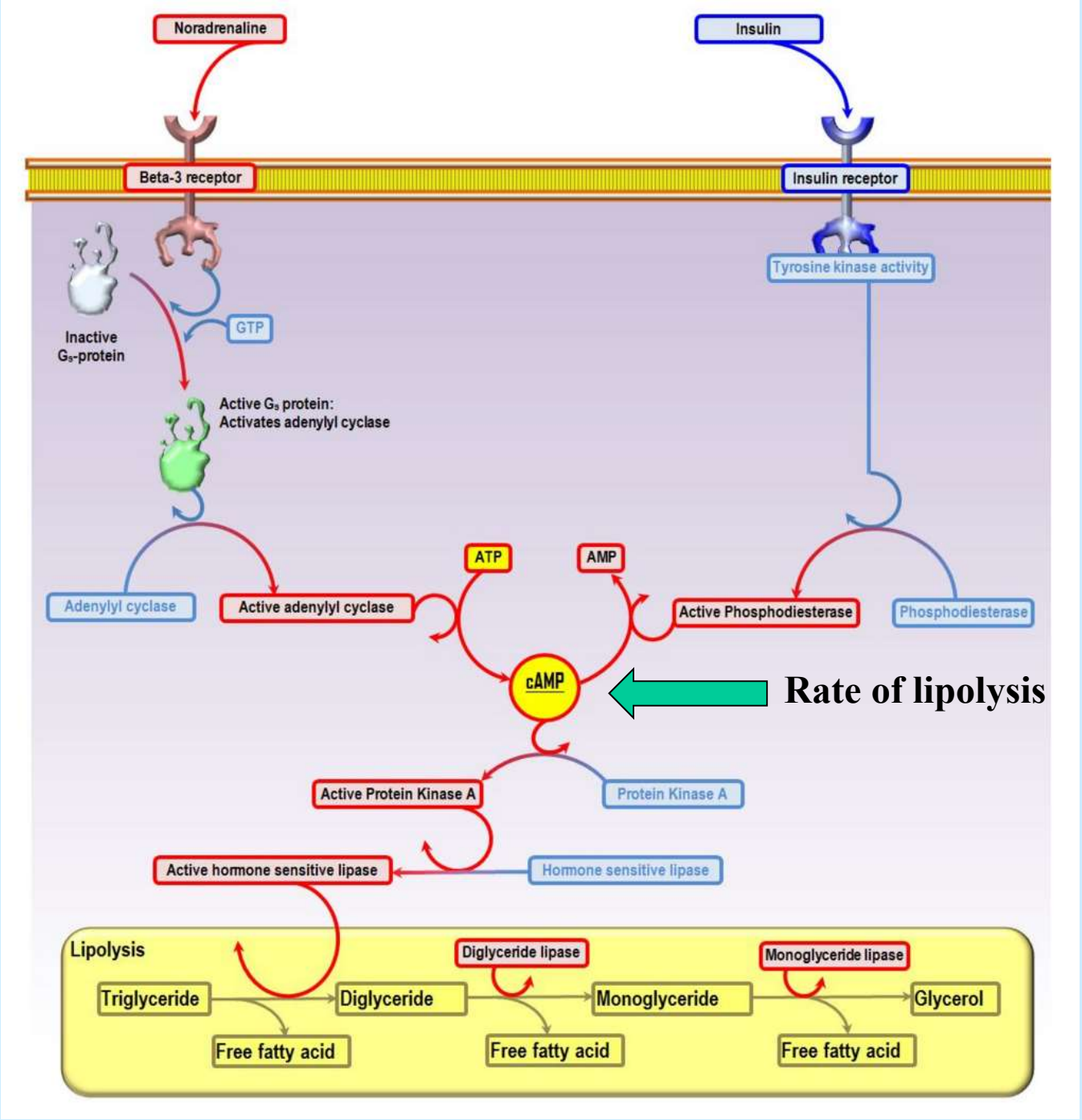


Figure 58-13 Overnight fast. αAA, α-amino acid; AQP9, aquaporin 9; ECF, extracellular fluid; αKA, α-keto acid; αKG, α-ketoglutarate.

24 h.


Fatty tissue triglycerides: 160g
Muscle protein: 75g
Free fatty acids: 160g
Glycerol: 16g
Amino acids: 75g
120g
40g
In the liver
Gluconeogenesis
Emergency reserve of hepatic glycogen
This emergency tank is kept in reserve for some sort of a fight-or-flight situation
O_2
H_2O
Free fatty acids 120g
Ketones 60 g
Lactate 36 g
Glucose 180g
36g
144g
Fatty acid and ketone oxidation tissues:
Myocardium, renal cortex, skeletal muscle
Tissues which happily use glucose switch over to using exclusively fatty acids and ketones.
Anaerobic glycolysis tissues:
RBCs, WCCs, bone marrow, renal medulla, peripheral nerves
Participate in the Cori cycle by converting glucose back to lactate and pyruvate; thus these tissues indirectly derive energy from the oxidation of fat.
Aerobic glycolysis tissues:
Central nervous system
The CNS continues to use only glucose for its metabolism


Noradrenaline
Insulin
Beta-3 receptor
Insulin receptor
Tyrosine kinase activity
GTP
Inactive
G_s-protein
Active G_s protein:
Activates adenylyl cyclase
ATP
AMP
Adenylyl cyclase
Active adenylyl cyclase
Active Phosphodiesterase
Phosphodiesterase
cAMP
Rate of lipolysis
Active Protein Kinase A
Protein Kinase A
Active hormone sensitive lipase
Hormone sensitive lipase
Lipolysis
Diglyceride lipase
Monoglyceride lipase
Triglyceride
Diglyceride
Monoglyceride
Glycerol
Free fatty acid
Free fatty acid
Free fatty acid

Prolonged starvation

- Decrease energy requirements
- BMR (- 20 to 25 kcal / kg / day)
- A majority of effects is given by hypoinsulinemia, effect on the liver is determined by glucagon
- The gradual increase in the ratio of gluconeogenesis
- Initially increase the rate of proteolysis
- Increasing the rate of lipolysis - activation of hormone-sensitive lipase = mobilization of glycerol and FAs

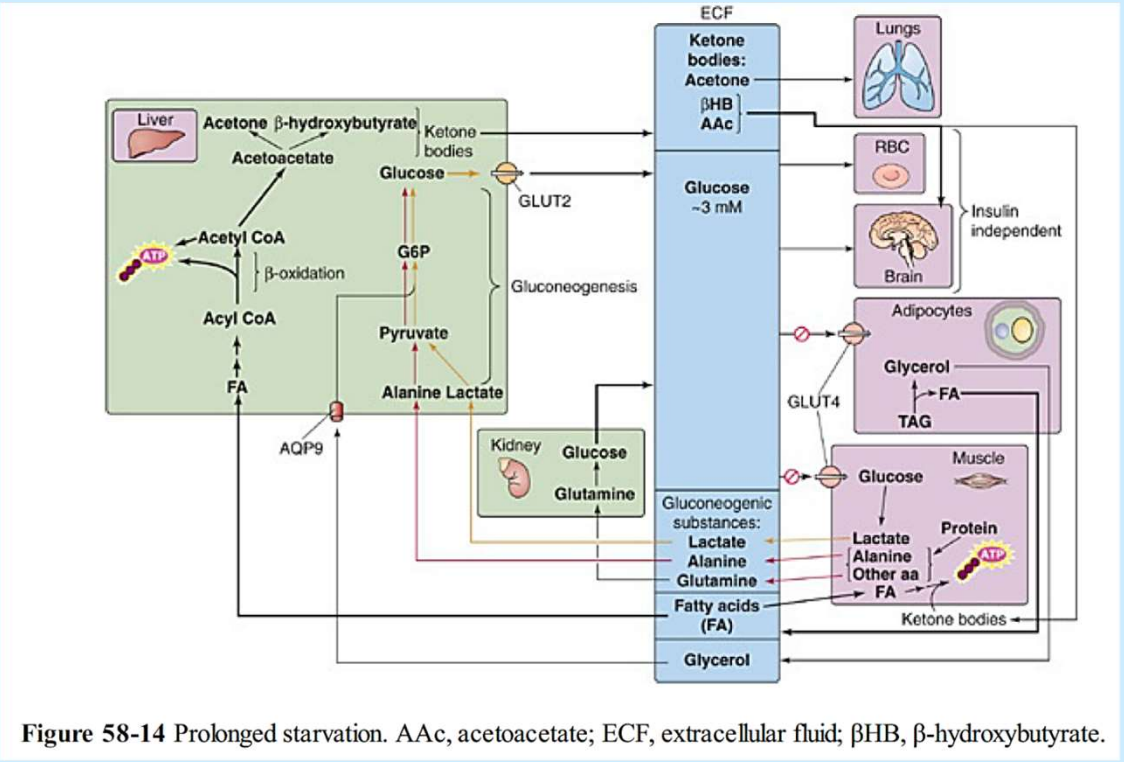
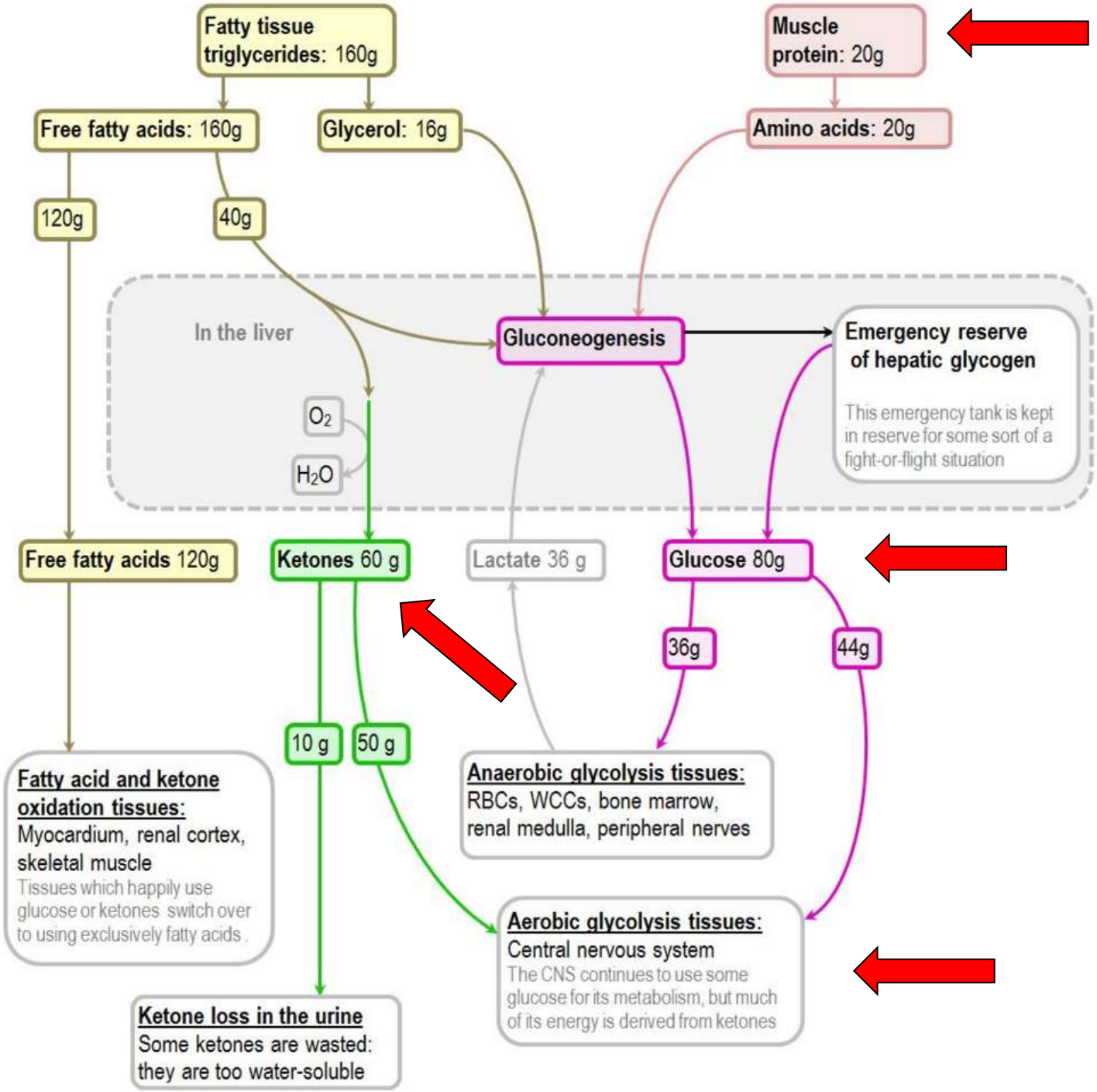
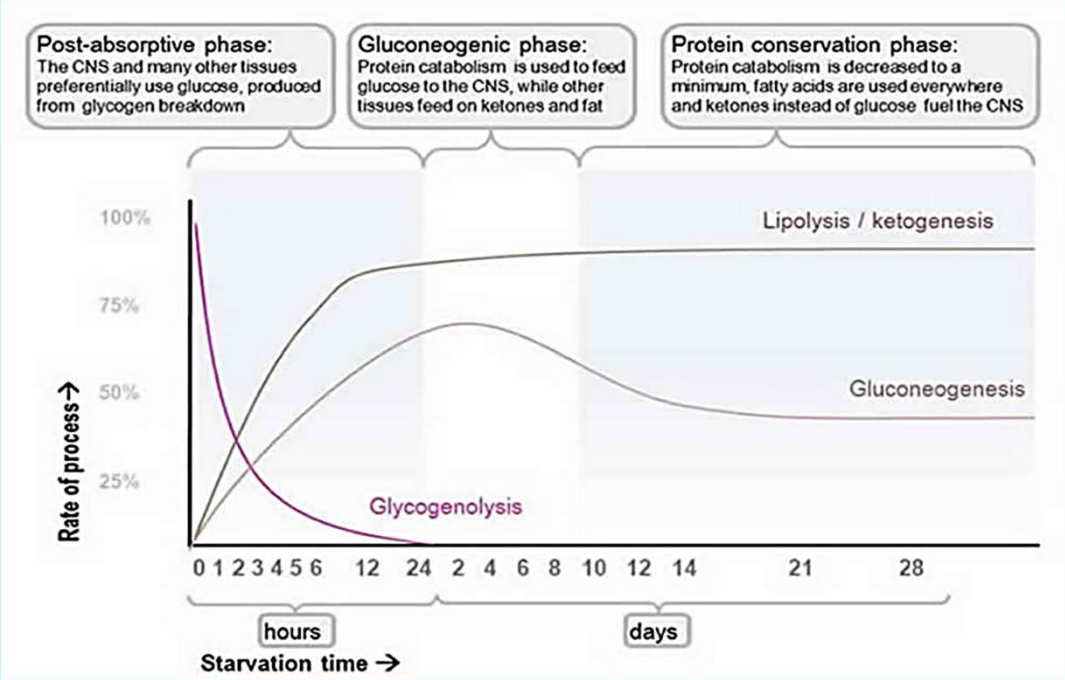
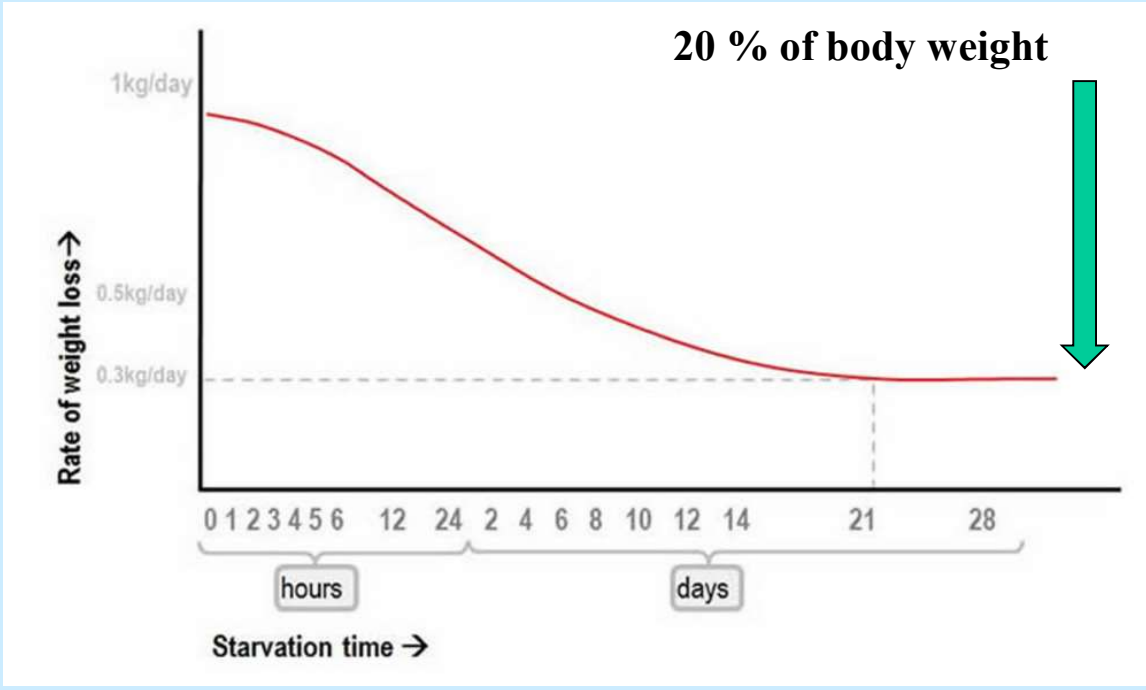


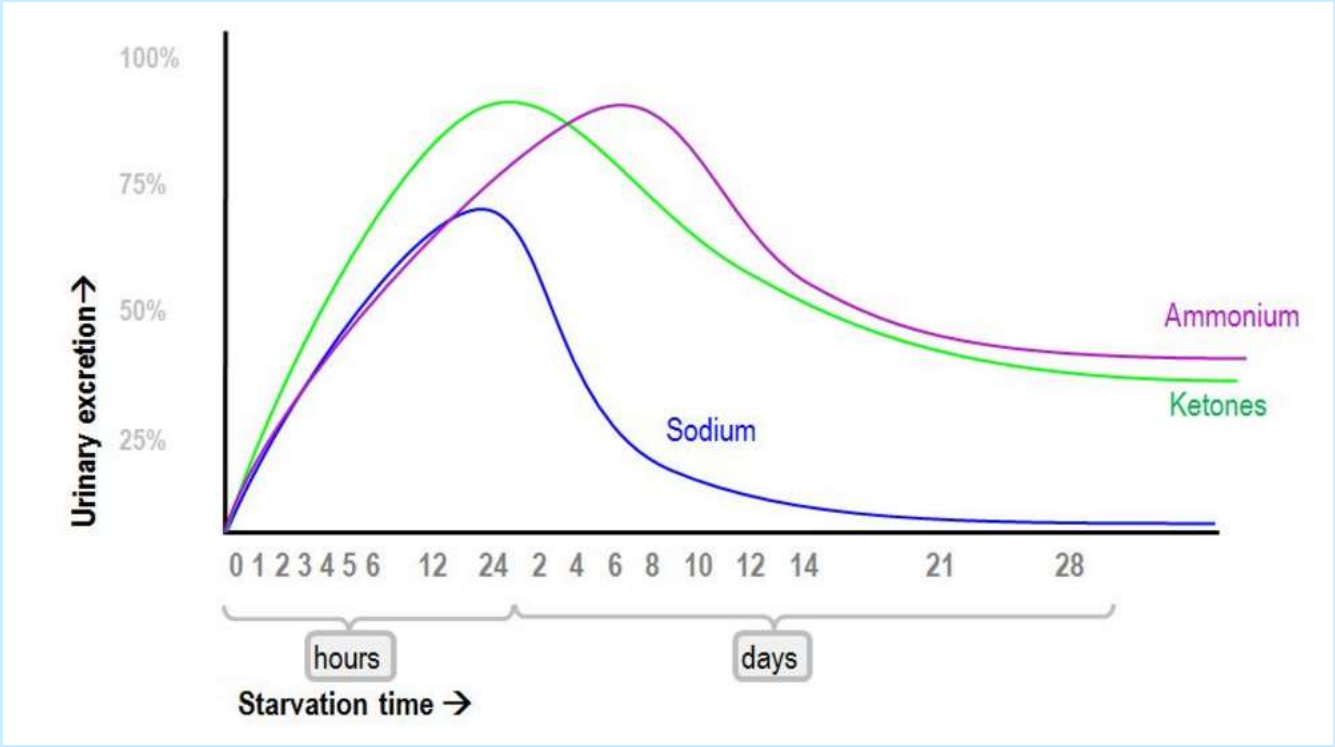
Figure 58-14 Prolonged starvation. AAc, acetoacetate; ECF, extracellular fluid; βHB, β-hydroxybutyrate.

- Glycerol = an additional substrate for gluconeogenesis; excess of FAs = substrate for muscles (insulin resistance, interference with "activation" of GLUT4) and peripheral tissues = enough glucose to nervous tissue
- Further starvation:
  - Reduction of proteolysis (= reduced production of urea = reduced excretion of water), increasing use of fat for ketogenesis
  - Use of ketones nervous tissue (b-hydroxybutyrate and acetoacetate)
  - Reduction of hepatic gluconeogenesis X increased gluconeogenesis in the kidney (40% of production)
  - Further mobilization of lipids = lipolysis = increase in hepatic ketogenesis (100 g d)
  - Further lipolysis = loss of adipose tissue, hormonal changes (leptin, FSH, LH - anovulation)


Fatty tissue triglycerides: 160g
Muscle protein: 20g
Free fatty acids: 160g
Glycerol: 16g
Amino acids: 20g
120g
40g
In the liver
Gluconeogenesis
Emergency reserve of hepatic glycogen
This emergency tank is kept in reserve for some sort of a fight-or-flight situation
O_2
H_2O
Free fatty acids 120g
Ketones 60 g
Lactate 36 g
Glucose 80g
36g
44g
10 g
50 g
Fatty acid and ketone oxidation tissues:
Myocardium, renal cortex, skeletal muscle
Tissues which happily use glucose or ketones switch over to using exclusively fatty acids.
Anaerobic glycolysis tissues:
RBCs, WCCs, bone marrow, renal medulla, peripheral nerves
Aerobic glycolysis tissues:
Central nervous system
The CNS continues to use some glucose for its metabolism, but much of its energy is derived from ketones
Ketone loss in the urine
Some ketones are wasted: they are too water-soluble


Post-absorptive phase:
The CNS and many other tissues preferentially use glucose, produced from glycogen breakdown
Gluconeogenic phase:
Protein catabolism is used to feed glucose to the CNS, while other tissues feed on ketones and fat
Protein conservation phase:
Protein catabolism is decreased to a minimum, fatty acids are used everywhere and ketones instead of glucose fuel the CNS
100%
75%
50%
25%
Rate of process →
Lipolysis / ketogenesis
Gluconeogenesis
Glycogenolysis
0 1 2 3 4 5 6 12 24 2 4 6 8 10 12 14 21 28
hours
days
Starvation time →


20 % of body weight
1kg/day
0.5kg/day
0.3kg/day
Rate of weight loss →
0 1 2 3 4 5 6 12 24 2 4 6 8 10 12 14 21 28
hours
days
Starvation time →


100%
75%
50%
25%
Urinary excretion→
Ammonium
Ketones
Sodium
0 1 2 3 4 5 6 12 24 2 4 6 8 10 12 14 21 28
hours
days
Starvation time →

Other changes as a result of starvation:

- Loss of K^+ in the initial stage, a stable concentration of 3 mmol/L
- Mg^{2+} - unchanged or only slight hypomagnesemia
- Ca^{2+} - unchanged
- Phosphates – unchanged
- Uric acid – increase (protein catabolism)
- Next changes:
  - Decreased heart rate (35 t/min, from 4. week slight increase)
  - Drop of blood pressure
  - ECG changes - flattening of the T wave, decrease of amplitude of QRS
  - In cases of extreme starvation - prolongation of the QT interval, T wave inversion, ST segment depression
  - Why?
    - The decrease of protein synthesis - myofibrils, myofilaments
    - Changes in the composition of the ECT/ICT
    - Losses of trace elements (Cu - ischemia)
    - Sympathetic (catecholamines) - Arrhythmia

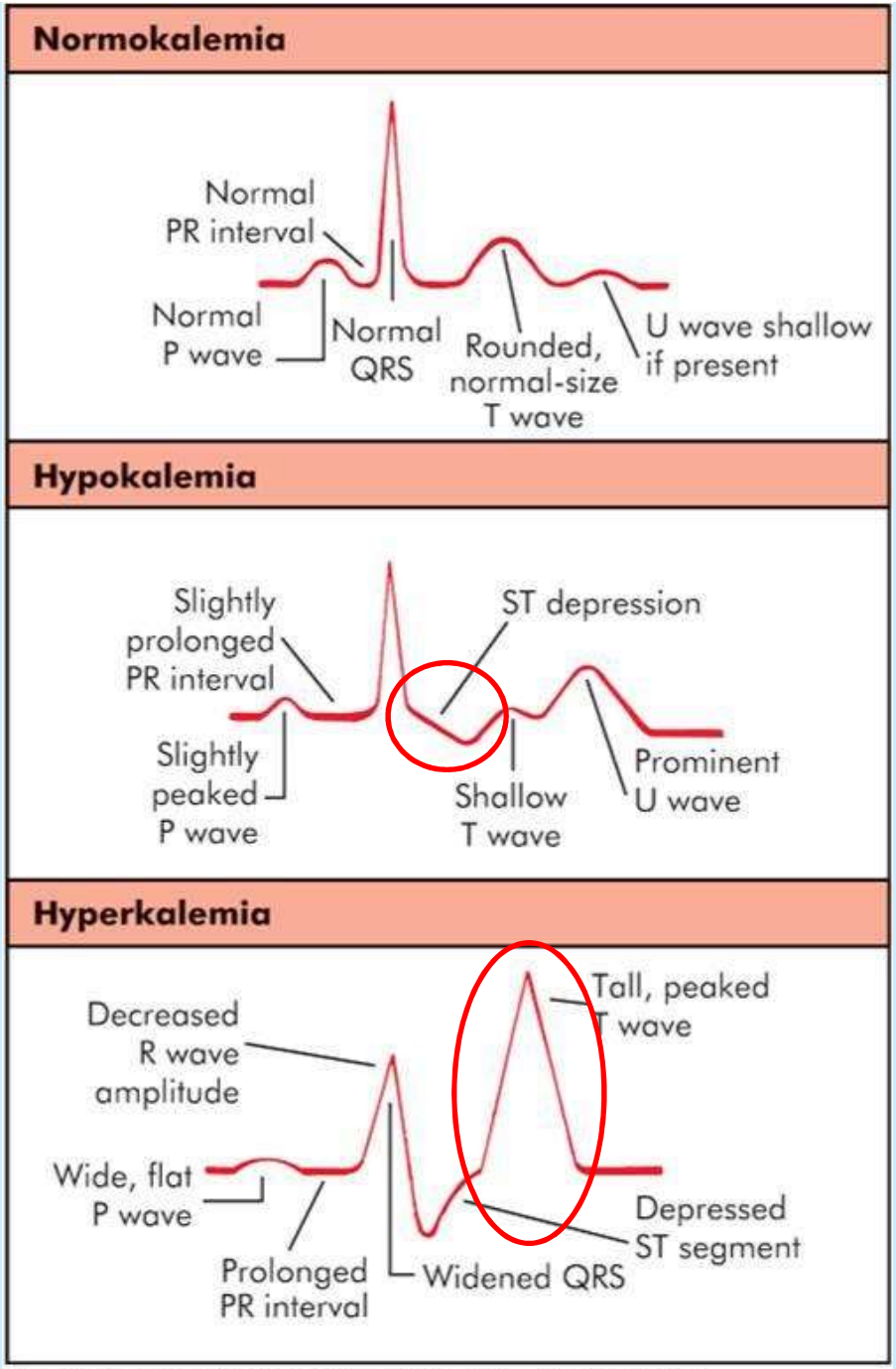


Fig. 4-7. Electrocardiogram Changes with Potassium Imbalance

METABOLIC DISORDERS EXAMINATION

LABORATORY METHODS (biochemistry)

- Lack or absence of metabolite (blood, urine, tissue, cells)
- Overproduction of metabolite
- Pathological storing of metabolite in tissues (histochemistry)
- Pathological metabolite

FINDINGS OF CAUSE OF METABOLIC DISORDER

- Disorder in resorption or excretion (functional load tests)
- Measurement of activity of certain enzymes or enzyme systems

GENEALOGIC EXAMINATION

SCREENING TESTS (fenylketonuria, hyperlipoproteinemia, aminoaciduria, thyroid gland hormones…)

METABOLISM OF SACCHARIDES

1.Source of **energy**
2.Part of glycoproteins, glycopeptides, glycolipids– structural or functional (collagen in basal membranes, mucopolysaccharides, myelin, hormones, receptors…)

Dietary carbohydrates– hexoses (glucose, fructose, galactose)
Key substrate – **glucose**.
Postprandial plasmatic levels of glucose: **3,5 – 6,5mmol/l**
Glycaemia. Hypoglycaemia, hyperglycaemia.
Hypoglycaemia: decreased oxygen supply of CNS
Glycolysis, gluconeogenesis. Humoral control of glycaemia.
Glycolysis: main products – lactate and pyruvate – mean plasmatic concentrations 0,7 and 0,07mmol/l (ratio **10:1** remains even at various turnover); during hypoxia – **30:1** (metabolic acidosis)

•Glucose **turnover**: 2mg/kg/min (11mmol/kg/min)~9g/hr~225g/day

•55% of glucose utilisation – terminal oxidation (CNS)
•20% - glycolysis, lactate back to liver, gluconeogenesis (Cori cycle)
•20% - absorption by liver and splanchnic tissues
•70% consumption of glucose at rest is insulin-independent

•Circulating glucose pool (**pool**) – only a little bigger than expenditure by liver per 1 hour
•Brain oxidation is kept by pool only for approx. 3 hrs
•NECESSITY OF CONTINUOUS GLUCOSE PRODUCTION FROM LIVER during **starving**
•80% - glycogenolysis, 20% - gluconeogenesis (more than 50% from lactate trapped by liver for gluconeogenesis, rest – AA, esp. alanine; lactate from glycolysis in muscles, ery, leu, etc.; AA – from proteolysis of muscles)

•Morning glucose intake – 70% is needed by peripheral tissues (muscles), 30% - splanchnic organs (liver)

•20-30% of consumed glucose – oxidised during 3-5 hrs to cover needs of GIT, 70-80% stored as glycogen (muscle, liver)

•Muscle glycogen – later transported to liver (lactate from glycolysis in muscles, re-uptake, gluconeogenesis in liver, glycogenolysis)

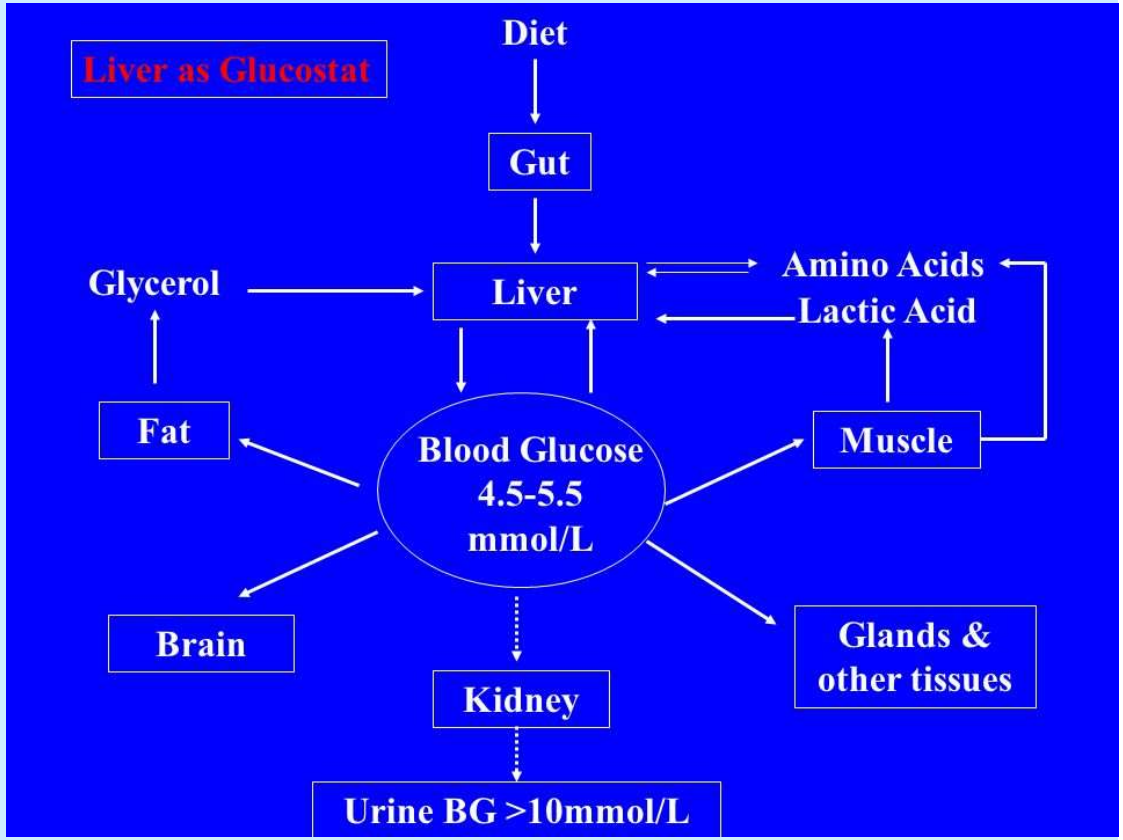
•During maximal absorption of exogenous glucose – release of glucose from liver is suppressed (insulin and glucagon facilitate this process)

LIVER GLUCOSTAT

- Maintaining the constant blood glucose

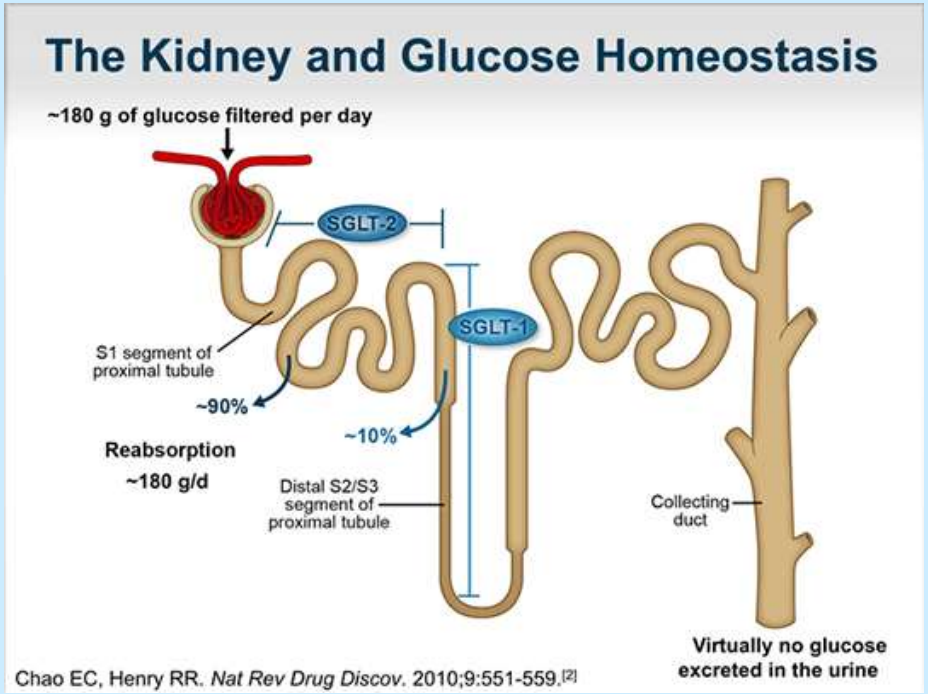
- Endocrine control:

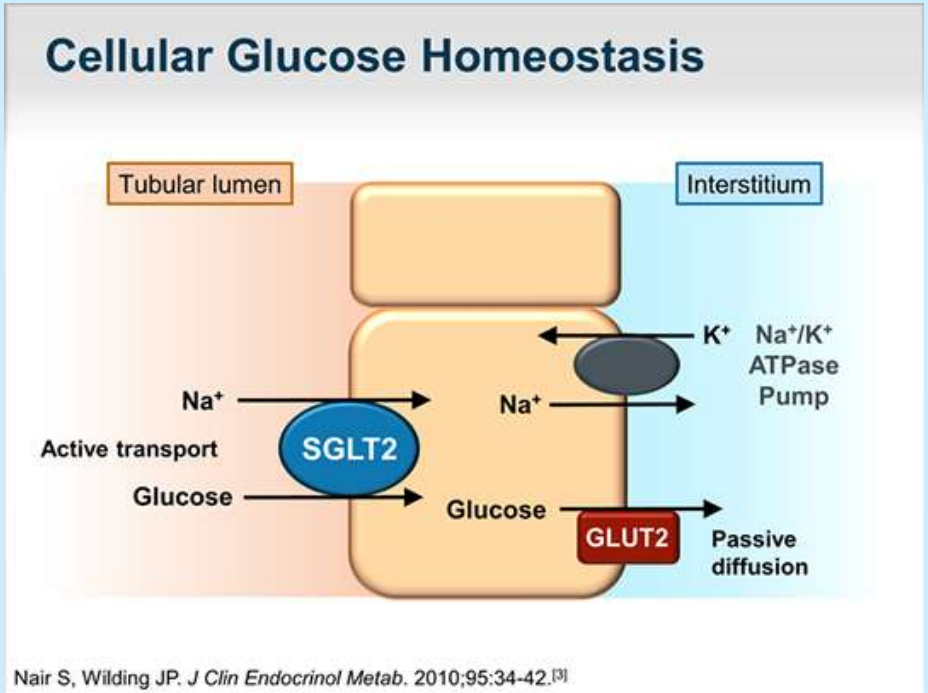
- glycogenolysis (glucagon, adrenaline, noradrenaline = activation of glycogen phosphorylase)
- why only liver and not muscles? (glucose-6-phosphatase in liver)
- gluconeogenesis (glucagon, adrenaline, noradrenaline, glucocorticoids, thyroid hormones)

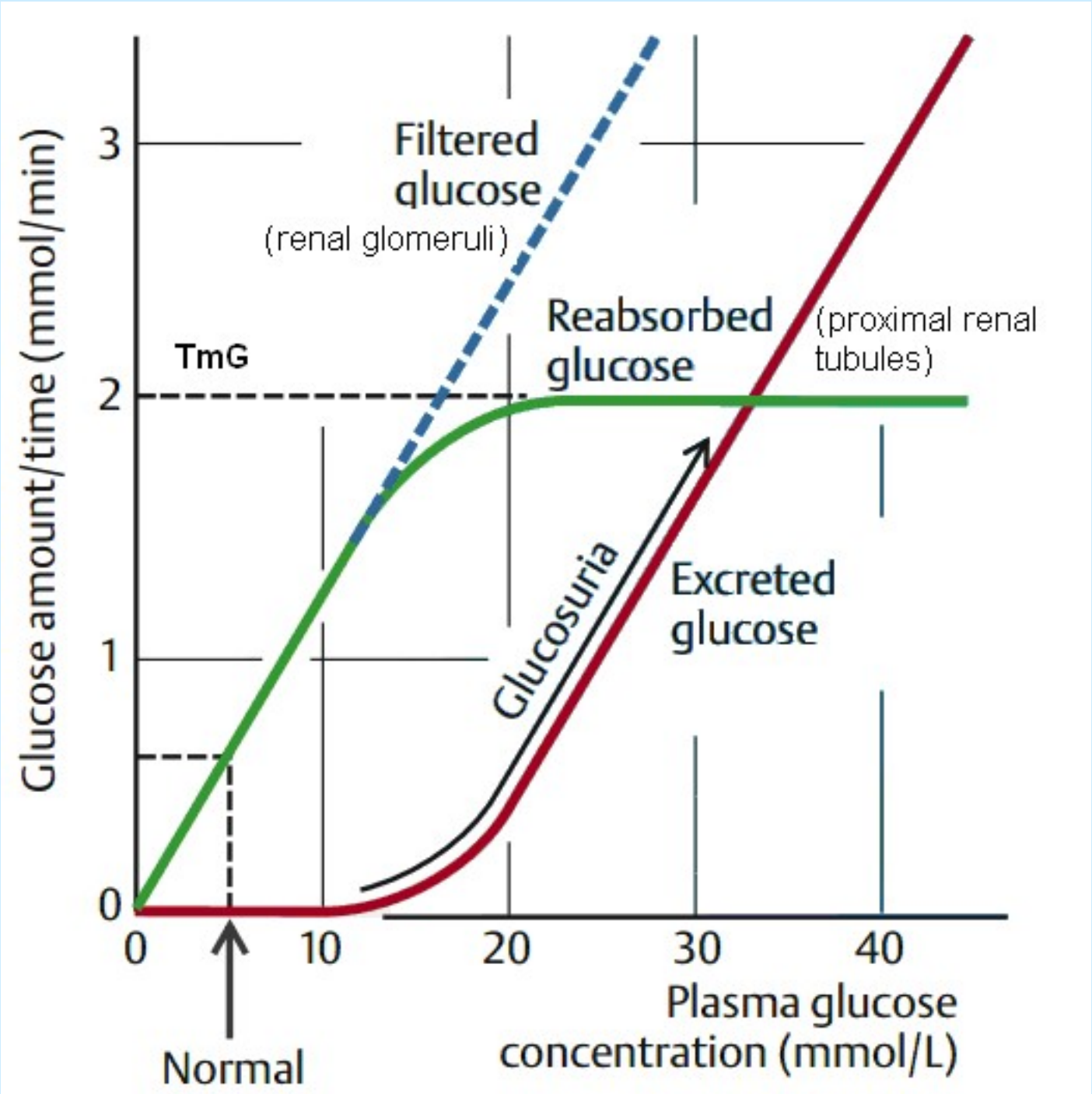


GLYCOSURIA

- **Renal glycosuria** (congenital deficiency of glucose transport in the kidneys, blood glucose is normal)
- **Alimentary glycosuria** (renal threshold for glucose = 10 mmol/l)
- Inhibitors of SGLT2






Glucose amount/time (mmol/min)
3
2
1
0
Filtered glucose
(renal glomeruli)
TmG
Reabsorbed glucose
(proximal renal tubules)
Glucosuria
Excreted glucose
0
10
20
30
40
Normal
Plasma glucose concentration (mmol/L)

METABOLISM OF LIPIDS

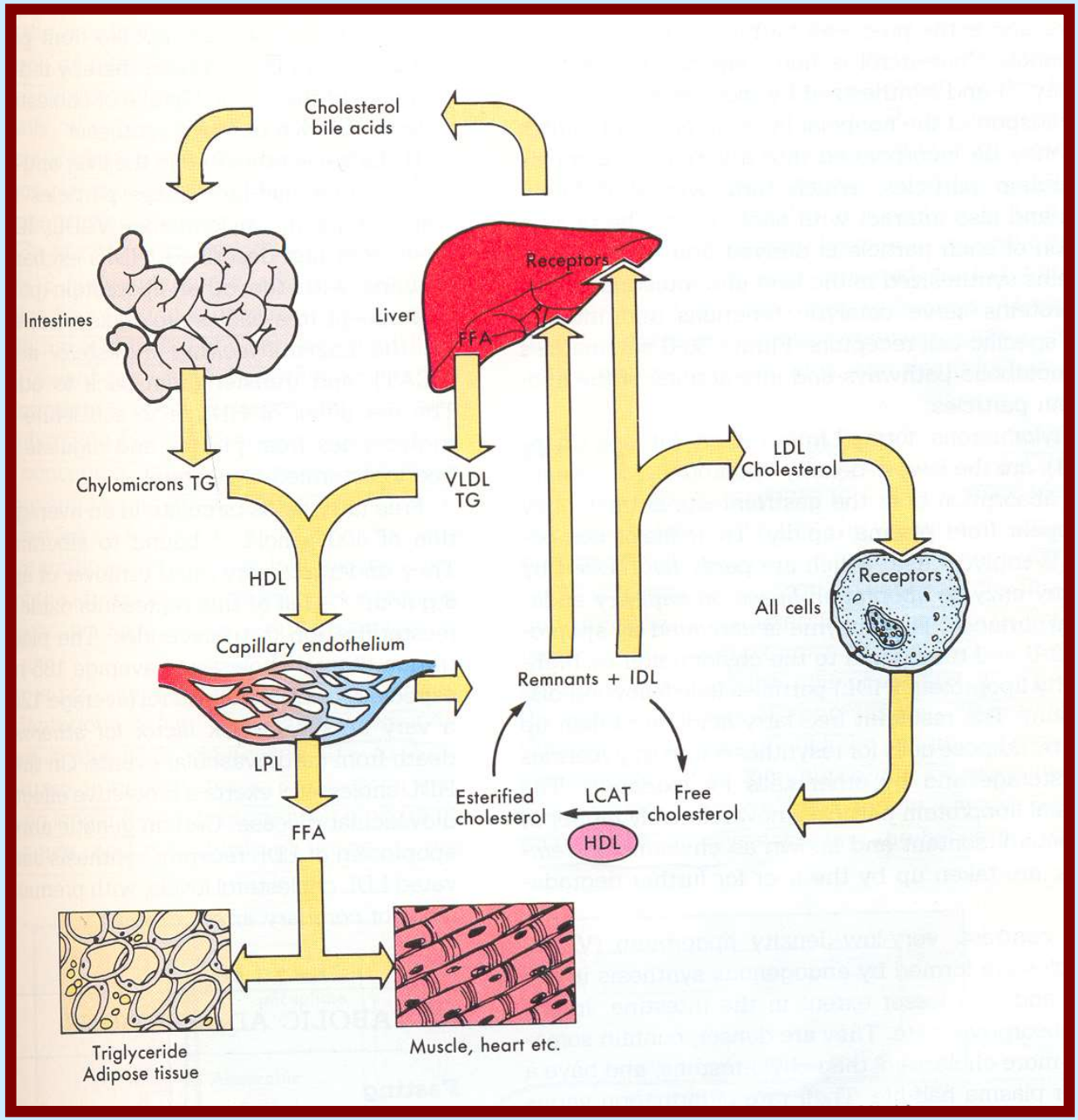
- Fat – approx. **50%** of daily amount of substrates for oxidation (100gr, 900kcal)
- Main and **most profitable** form of energy store
- Daily intake: approx. **100gr** (40% of daily diet)
- Main component of dietary sources and stores in body: **triglycerides**
- No strict dietary recommendation (part of FA synthetised in liver and adipose tissue)
- BUT: 3-5% of FA are polyunsaturated!!! – **ESSENTIAL FA**
- Precursors of membrane phospholipids, glycolipids, prostaglandins
- Cholesterol – part of membranes, precursor of bile acids, steroid hormones; daily intake – 300-600mg/day, synthesised too
- Lipoproteins: transport of lipids by blood plasma
- Apoproteins (from liver or intestine), catalytic function, receptors

•**Chylomicrons** – from diet, lowest density, **lipoprotein lipase** (endothelium of capillaries), activation by apoprotein C-II, transport of HDL
•Free FA absorbed by adipocytes (resynthesis of triglycerides, store) and other tissues (oxidation)
•Rest of lipoprotein particles (more cholesterol) – chylomicron rests – degradation in liver
•**VLDL** – endogenous synthesis in liver (less in intestine), in postabsorption phase
•Dense, more cholesterol, longer plasmatic half-time
•Speed of production: 15-90g/day
•Beginning of metabolism – see chylomicrons
•Products of lipoprotein lipase effect – **IDL** (intermediate-density lipoprotein)
•50% IDL – back to liver (as chylomicron rests)
•50% IDL – enriched by cholesterol – **LDL**
•Circulating LDL – transport of cholesterol into cells
•Absorption of LDL, IDL, rests of ch. – apoproteins, receptors, endocytosis
Uptake of **LDL-cholesterol** into cells – **down regulation** of LDL receptors (slowed resorption) and slowed synthesis de novo

•**HDL** – long plasmatic half-time, synthesis in liver and intestine
•Facilitation of other particles movement
•Exchange of key apoproteins
•They accept molecules of free cholesterol, estherify them (lecithin-cholesterol-acetyltransferase) and incorporate back to particles
•Main effect: acceleration of clearance of triglycerides from plasma and regulation of ration free:estherified cholesterol

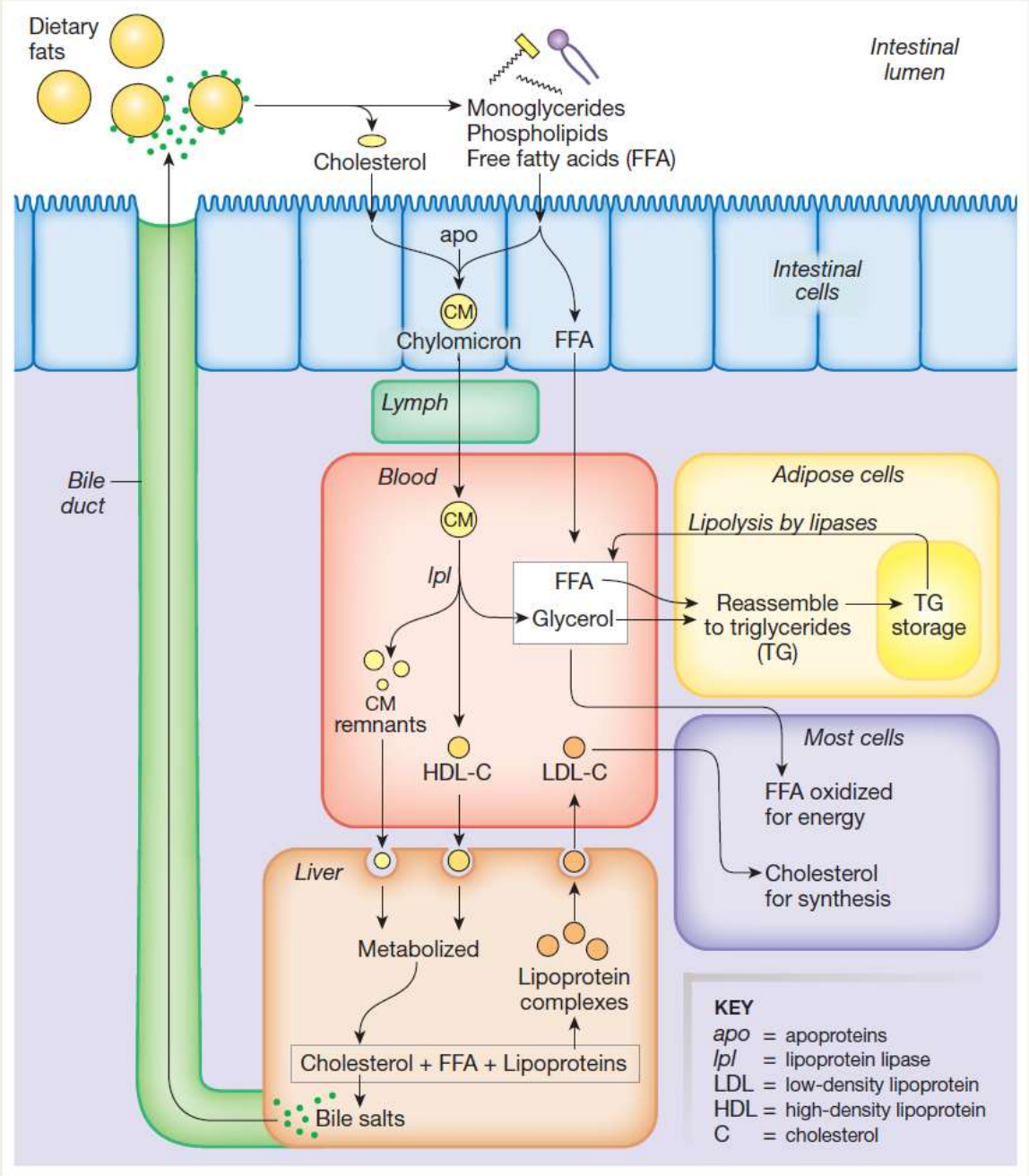
•**Free FA**
•Average concentration: 400μM/l
•Bound to molecules of albumins
•Fast turnover (approx. 8g/hr): 50% - oxidation, 50% - reestherification to triglycerides

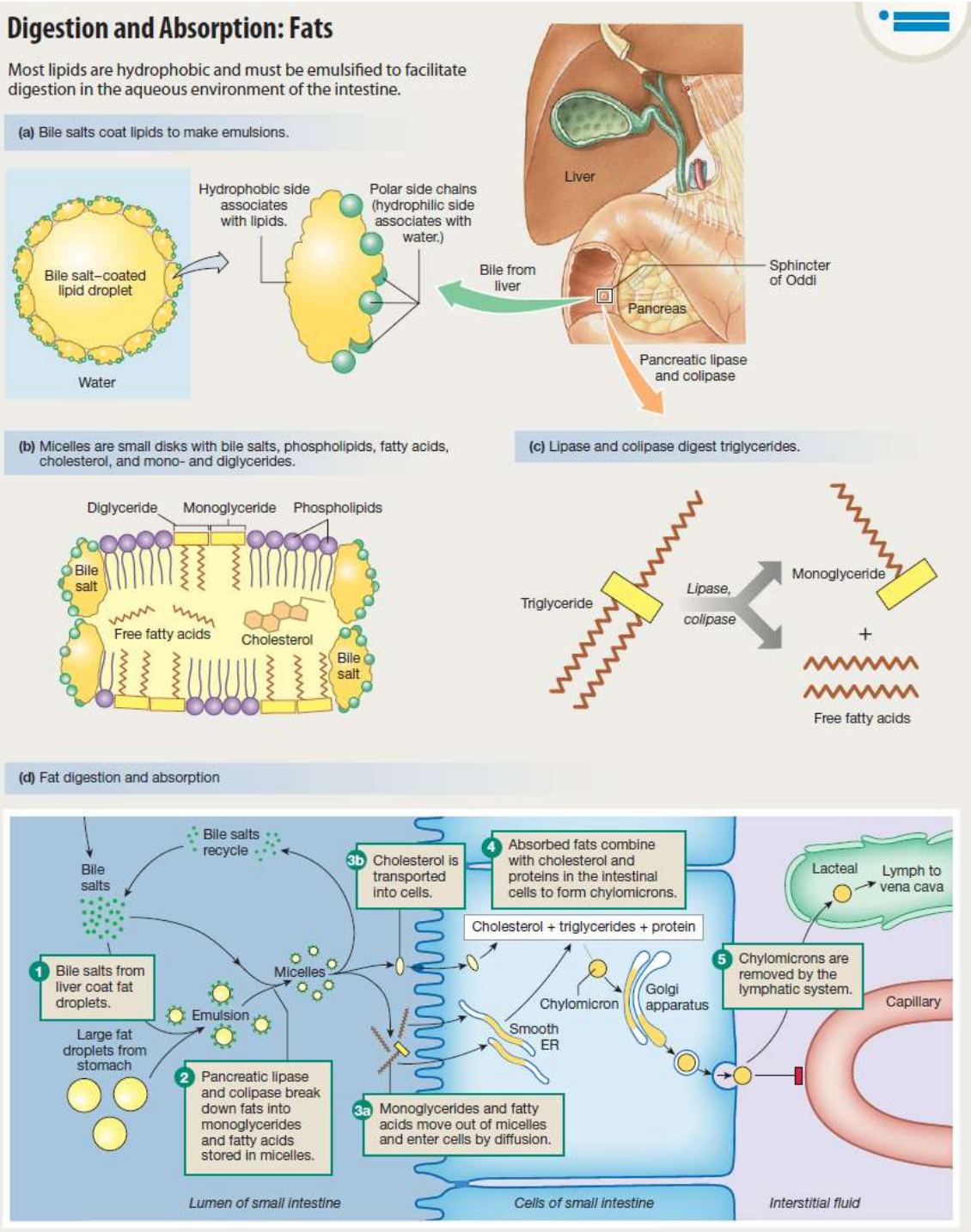
•Total **cholesterol**: 185mg/l
•LDL cholesterol: 120mg/l
•HDL cholesterol
•Arteriosclerosis, genetic predisposition (LDL apo or receptor)


Cholesterol
bile acids
Intestines
Liver
Receptors
FFA
Chylomicrons TG
VLDL
TG
LDL
Cholesterol
HDL
Capillary endothelium
Receptors
All cells
Remnants + IDL
LPL
Esterified
cholesterol
LCAT
Free
cholesterol
HDL
FFA
Triglyceride
Adipose tissue
Muscle, heart etc.

Fat Synthesis

(a) Transport and Fate of Dietary Fats





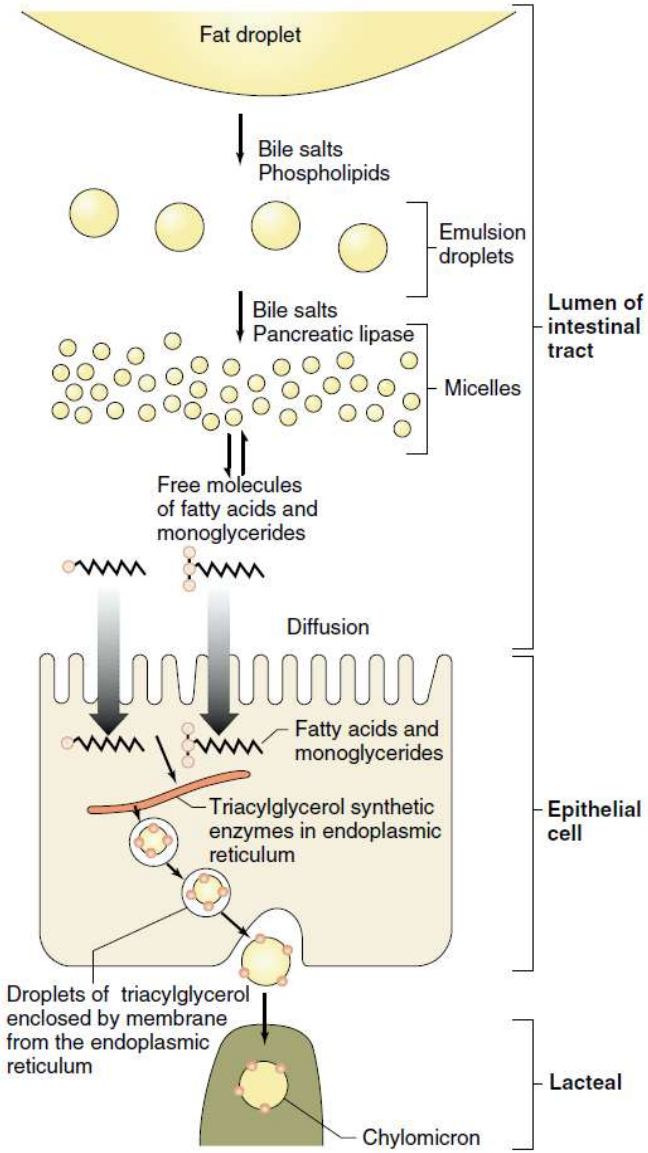
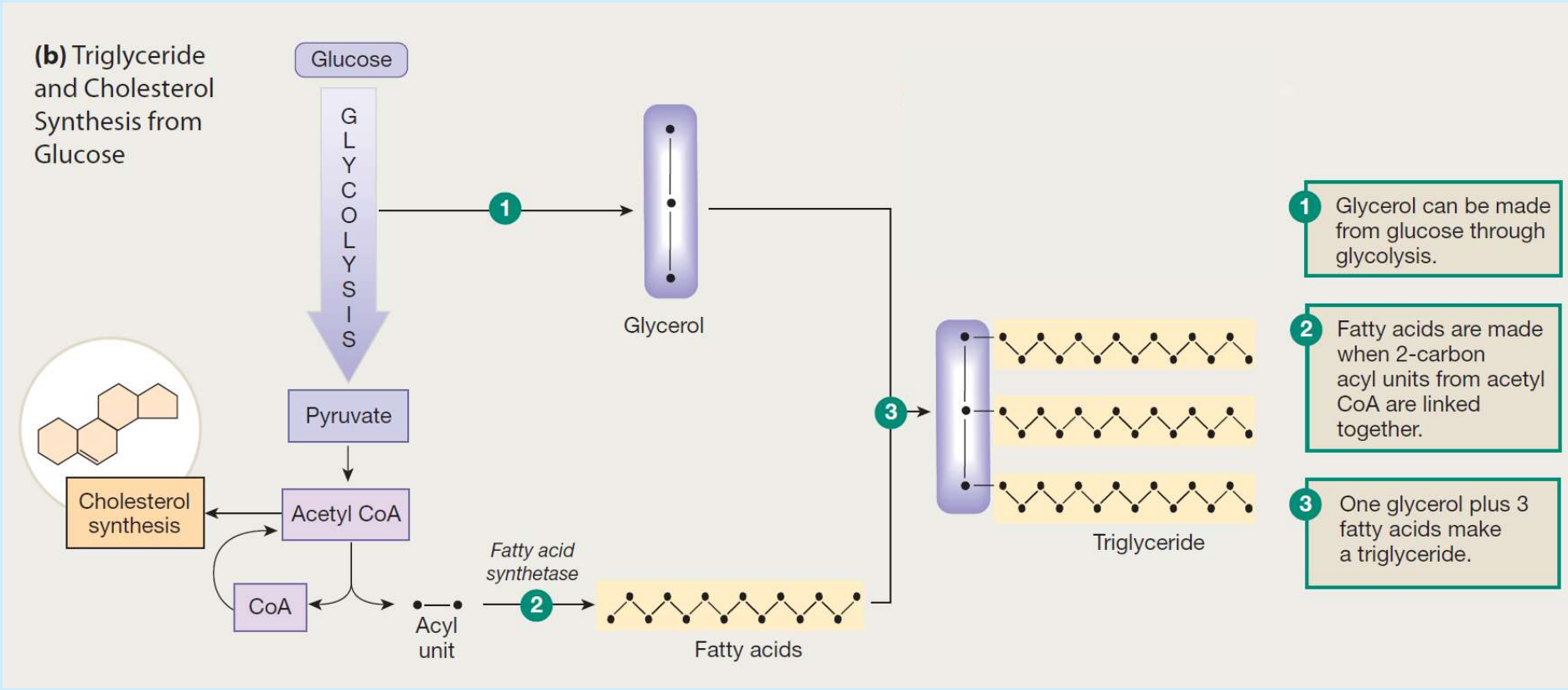
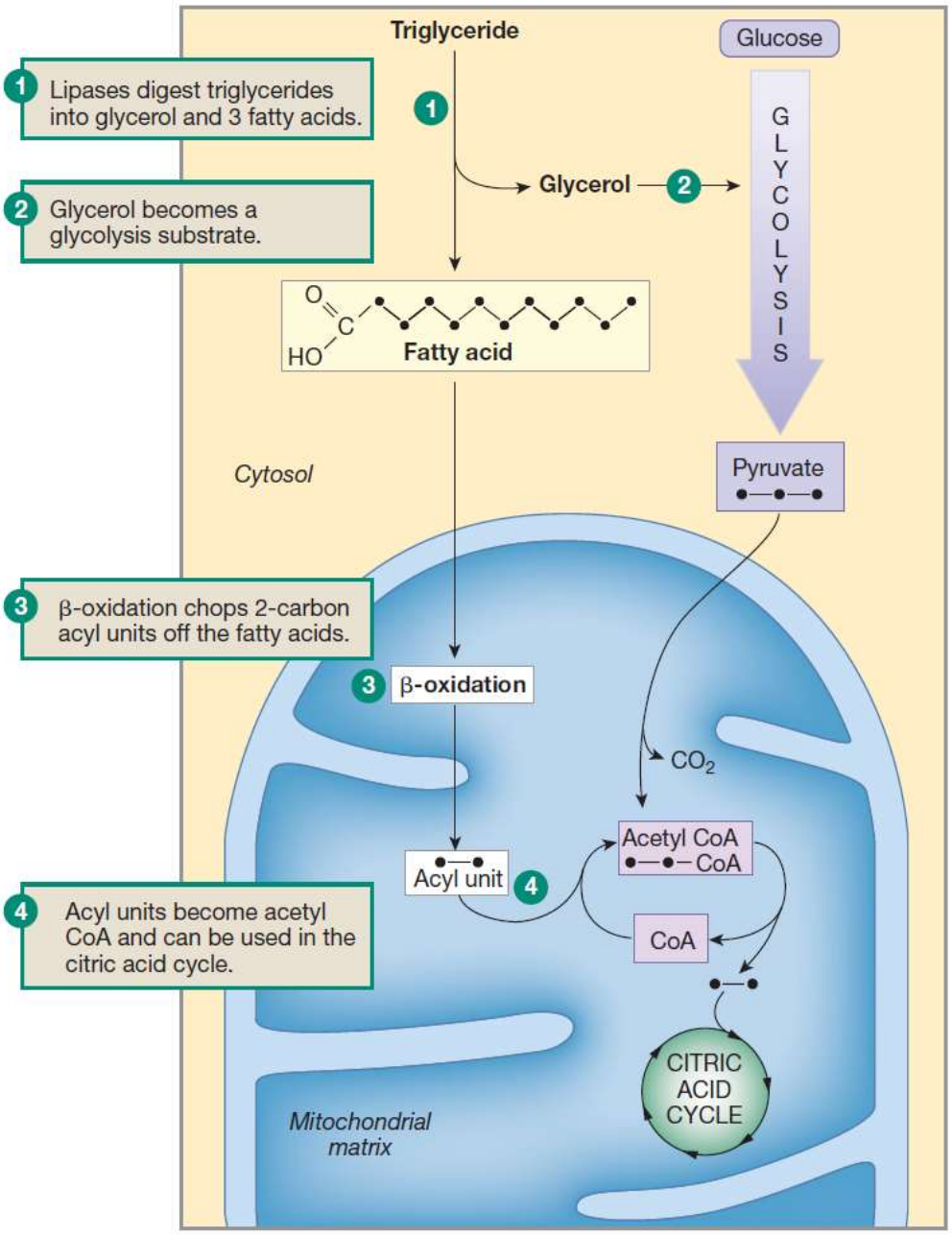


FIGURE 17–12
Summary of fat absorption across the walls of the small intestine.

Převzato. Silverthorn, D. U. Human Physiology – an Integrated Approach. 6th. edition. Pearson Education, Inc. 2012.x


(b) Triglyceride and Cholesterol Synthesis from Glucose
Glucose
GLYCOLYSIS
1
Glycerol
Pyruvate
Cholesterol synthesis
Acetyl CoA
CoA
Acyl unit
Fatty acid synthetase
2
Fatty acids
3
Triglyceride
1 Glycerol can be made from glucose through glycolysis.
2 Fatty acids are made when 2-carbon acyl units from acetyl CoA are linked together.
3 One glycerol plus 3 fatty acids make a triglyceride.

LIPOLYSIS


1 Lipases digest triglycerides into glycerol and 3 fatty acids.
2 Glycerol becomes a glycolysis substrate.
3 β-oxidation chops 2-carbon acyl units off the fatty acids.
4 Acyl units become acetyl CoA and can be used in the citric acid cycle.
Triglyceride
Glucose
1
Glycerol
2
GLYCOLYSIS
O
C
HO
Fatty acid
Cytosol
Pyruvate
3 β-oxidation
CO_2
Acetyl CoA
CoA
Acyl unit
4
CoA
CITRIC ACID CYCLE
Mitochondrial matrix

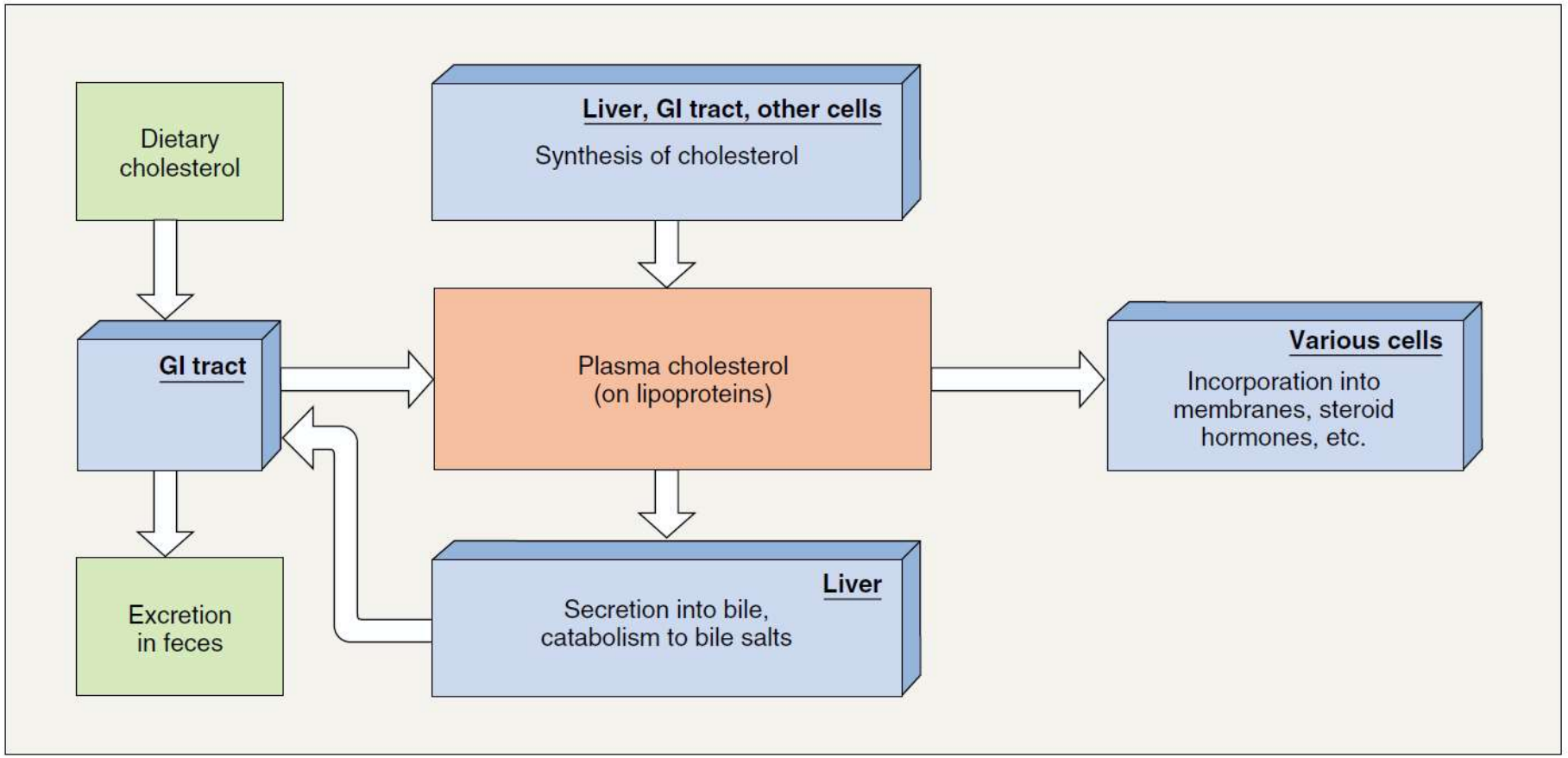


FIGURE 18–13
Cholesterol balance.

METABOLIC DISORDERS - SACCHARIDES

1. **Diabetes mellitus**
2. **McArdle syndrom:** glycogenesis from deficiency of myophosphorylase
   Accumulation of glycogen in muscles
   Muscle stiffness, rigor during exercise, lower tolerance of load
3. **Galactosemia** (inherited deficiency of phosphogalactosauridyltransferase; disorders of growths and development)

METABOLIC DISORDERS - LIPIDS

1. **HYPERLIPIDEMIA, HYPERLIPOPROTEINEMIA**
2. **INFREQUENT DISORDERS OF LIPID METABOLIS**

Ad 1) 5% of population
Primary and secondary forms
Arteriosclerosis
- **Hyperlipoproteinemia induced by lipids**
- **Familiar hypercholesterolemia (xantomatosis)**
- **Mixed hyperlipoproteinemia**
- **Familiar hypercholesterolemia with hyperlipemia**
- **Saccharides-induced triglyceridemia**
- **Secondary hyperlipoproteinemia** (dependent; alimentary)

Ad 2)
- **Lipidoses**
- **Abetalipoproteinemia** (LDL, VLDL)
- **Analfalipoproteinemia** (HDL)
- **Inherited defect acetyltranspherase LCAT** (accumulation of lecithin)

Adipose tissue

- = the long-term repository for excess energy
- = reflection of the imbalance between energy intake and energy expenditure, integrated over a long period

Lipogenesis

- TAGs in adipocytes (approx. 80 - 90% of the cell volume)
- Sources of FAs (free circulating, enzymatic hydrolysis of TAGs – chylomicrons, VLDLs, LDLs)
- *De novo* lipogenesis from non-lipid substrates (carbohydrates)
- Production of glycerol 3-phosphate (glycolysis, gluconeogenesis, glycerol kinase activity)
- TAG synthesis (G3P acyltransferases)

Regulation of lipogenesis

- Nutritional
  - feeding, fasting, and diet composition
  - Excessive carbohydrate consumption stimulates lipogenesis in both the liver and AT, increasing the availability of TAG in the postabsorptive state
  - Blood Glu! (lipogenic capability – substrate for lipogenesis)
- Hormonal
  - **Insulin** (+)
  - **GH** (dramatically reduces lipogenesis in AT; mechanism - decrease in insulin sensitivity and a reduction in the number of insulin receptors)
  - **Leptin** (limits lipid storage not only by inhibiting food intake, but also by affecting specific metabolic pathways in AT)

Lipolysis

- Lipolysis of TAG reserves
- Release of FFAs and glycerol
- Insulin
- Natriuretic peptides (especially during exercise-stimulated lipolysis)
- Catecholamines

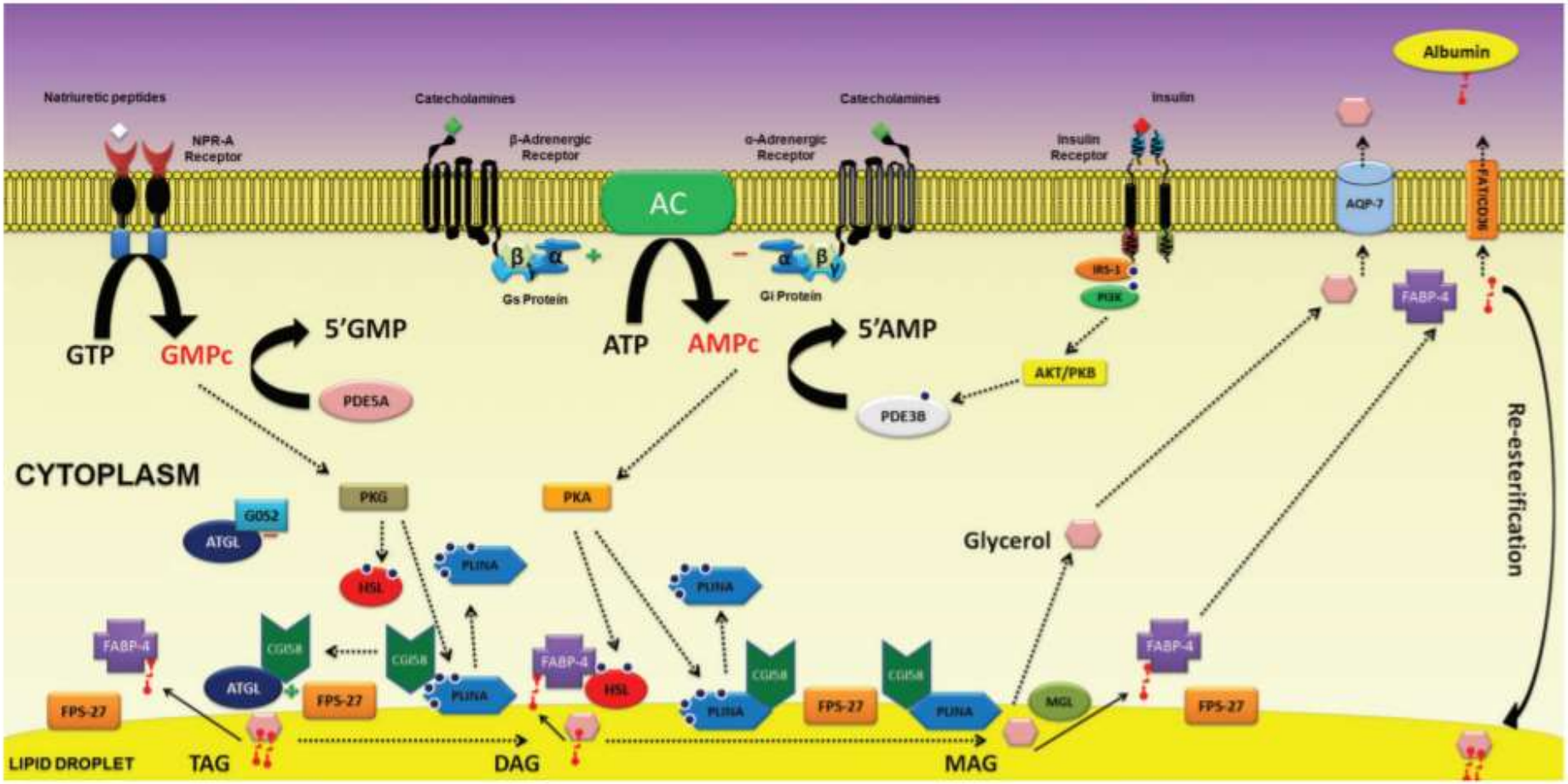
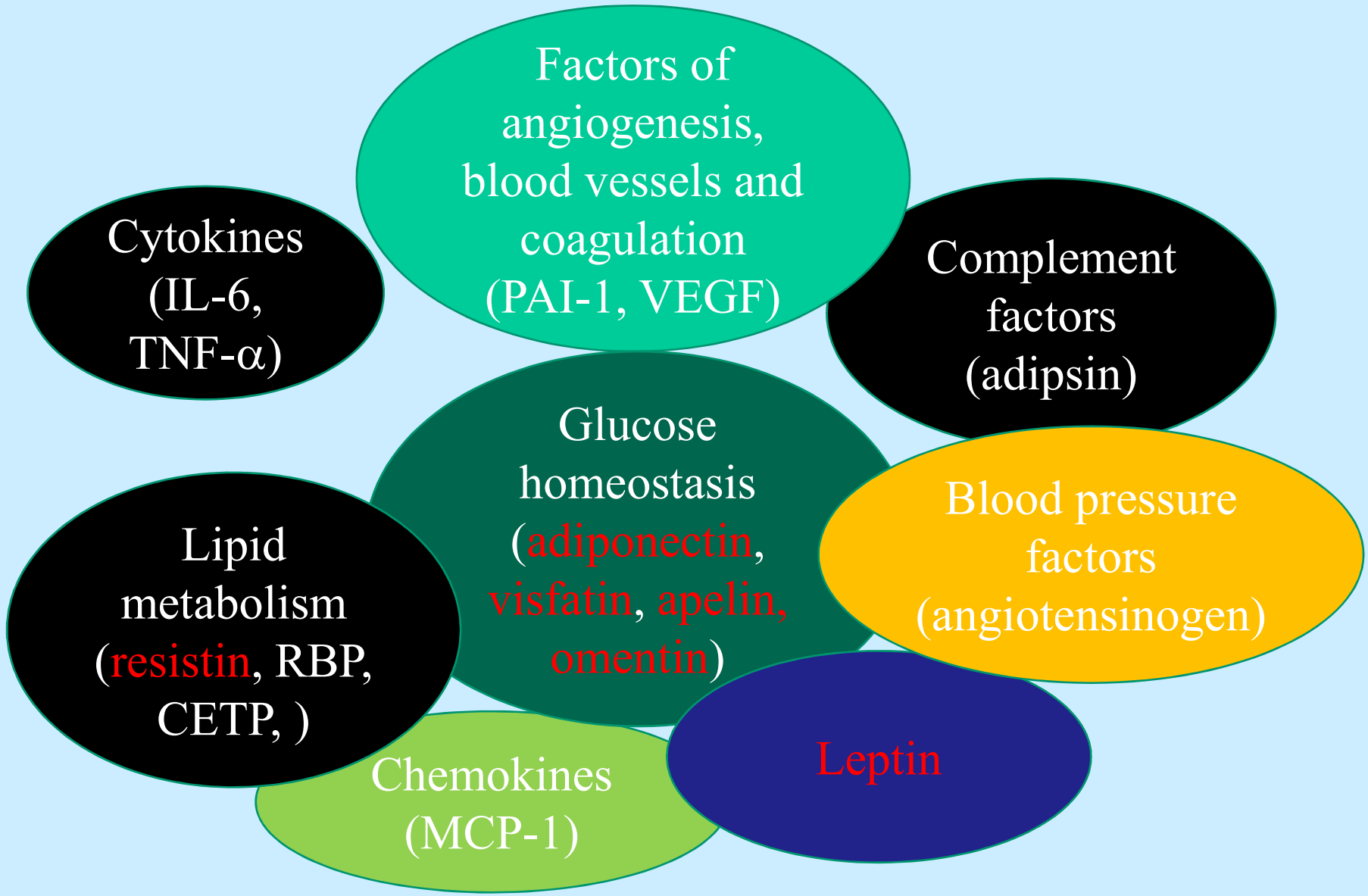


Figure 2. Major pathways involved in lipolytic regulation: the signal transduction pathways of catecholamines via adrenergic [(β) stimulatory and (α2) inhibitory] receptors and atrial natriuretic peptides via type A receptor (NPR-A); protein kinases (PKA and PKG) involved in the phosphorylation of target proteins; phosphorylation of HSL promoting translocation from cytosol to the surface of lipid droplets. Perilipin phosphorylation induces a major physical change on the droplet surface, which facilitates the action of HSL and starts lipolysis. Association of HSL with fatty acid binding protein (FABP-4) favors hydrolase action of HSL. Insulin anti-lipolytic action on adipocytes, through insulin receptors stimulation, leads to the activation of phosphodiesterase-3B (PDE-3B) promoting cAMP degradation. PDE-5A: phosphodiesterase 5A; ATGL: adipose tissue triacylglycerol lipase; FABP-4: fatty acid binding protein 4; GC: guanylate cyclase, Gi: inhibitory G protein; Gs: stimulatory G protein; HSL: hormone-sensitive lipase; PLINA: perilin; FPS-27: fat-specific protein 27; G0S2: G0/G1 switch gene 2; MGL: monoacylglycerol lipase; FFAs: free fatty acids; NPR-A: natriuretic peptide receptor-type A; TAG: triacylglycerol; DAG: diacylglycerol; MAG: monoacylglycerol.

Adipogenesis

- = transformation of undifferentiated preadipocytes in AT to adipocytes
- balance between adipogenesis, triglyceride synthesis, and lipolysis is responsible for the quantity of AT in an organism
- Three distinct phases - growth arrest, clonal expansion, and terminal differentiation
  - three CCAAT-binding proteins (C/EBPs) β, δ, and α and PPAR-γ, expressed in a defined sequence and thus coordinating the series of adipogenic stages

Endocrine role of AT



Adipose tissue secreted products regulated by energy balance

	Endocrine/paracrine	*Effect of obesity*	*Acute affect of food*	*Main regulators*
Leptin	Endocrine and paracrine	Increased	Increased	Multiple (please see text)
Adiponectin	Endocrine	Decreased	None	
Adipsin	Endocrine and paracrine	Increased	Increased	
TNFα	Paracrine	Increased	Increased	Multiple
IL-6	Endocrine and paracrine	Increased	None	Multiple
TNF-soluble receptors	Endocrine	Increased	None	
LPL	Mostly paracrine	Probably increased	Increased	Insulin
Resistin	Not known	Increased	Not known	
FIAF	Endocrine?		Reduced	
PAI-1	Paracrine	Increased		

This is not an exhaustive list of factors secreted by adipose tissue, but reflects those whose expression/secretion is regulated by energy balance. IL, interleukin; LPL, lipoprotein lipase; PAI-1, plasminogen activator inhibitor-1; TNF, tumour necrosis factor.

Crosstalk between AT and other tissues

- an effect on AT:
  - Endocrine function, regulating adipokine secretion
  - cell number in the fat pad, regulating cell turnover (adipogenesis and apoptosis
  - metabolic regulation of lipogenesis, lipolysis, and oxidation
- Muscle tissue
  - Myokines
  - IL-6 – lipolysis in AT
  - Irisin

BROWN ADIPOSE TISSUE

LIPIDS: structural, neutral and brown

Specific localisation

Sympathetic innervations of vessels and also adipocytes

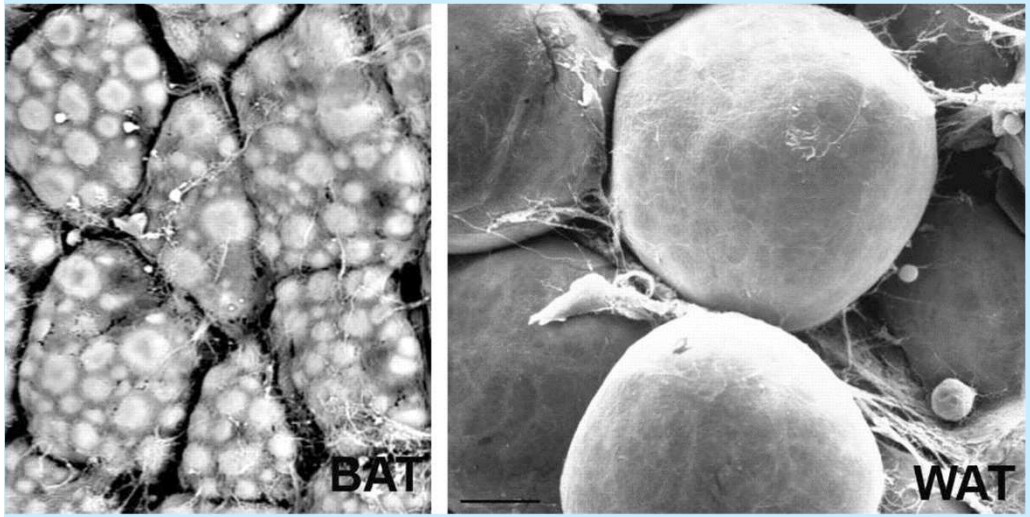
Several drops of fat in adipocyte

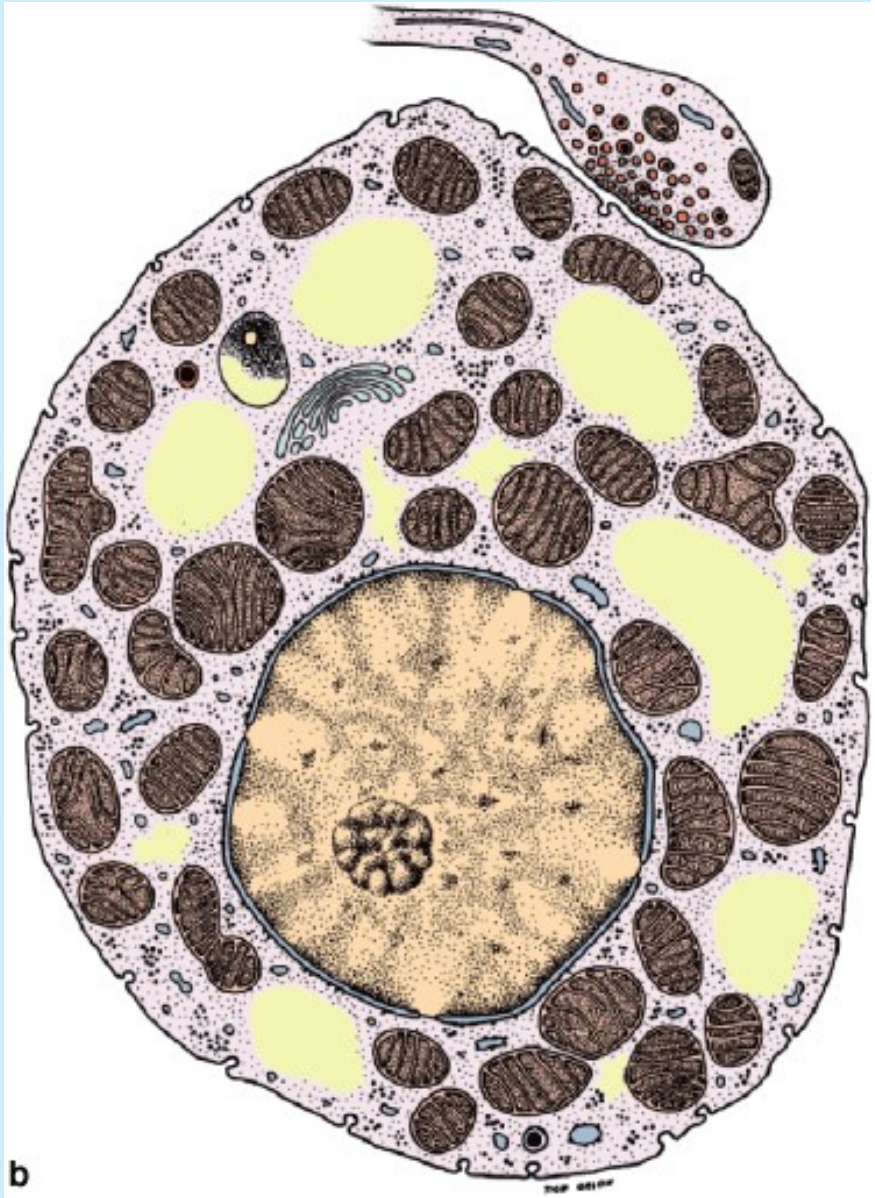
More mitochondria

Production of heat

Adaptation to cold

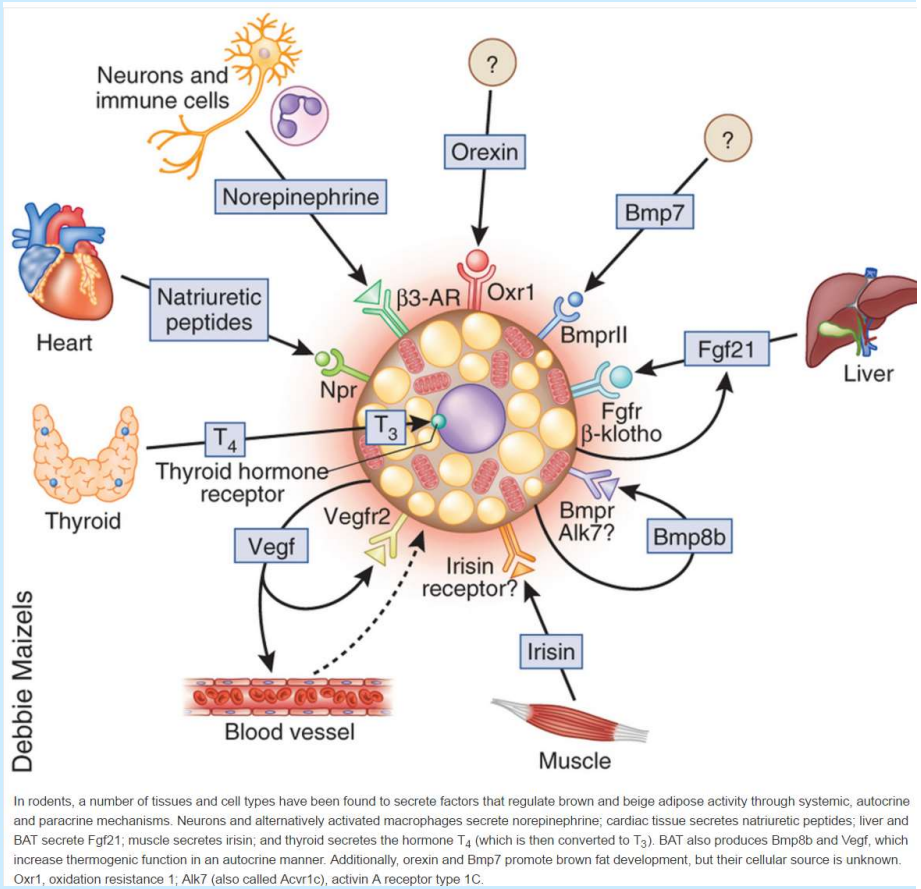
After meal – increased production of heat





Source: Mescher AL: *Junqueira's Basic Histology: Text and Atlas, 12th Edition:* http://www.accessmedicine.com

- Irisin = ??? (transformation of white fat to brown...), production increased during physical exertion?
- FGF21 = increased intake of Glu by peripheral tissues, increased oxidation of FAs
- Natriuretic peptides, ANP - increased lipolysis; protection against low temperatures?
- Bmp8b = produced by brown adipocytes and some hypothalamic nuclei - regulation of sympathetic activity
- T4/T3 - increasing the expression of thermogenic genes



In rodents, a number of tissues and cell types have been found to secrete factors that regulate brown and beige adipose activity through systemic, autocrine and paracrine mechanisms. Neurons and alternatively activated macrophages secrete norepinephrine; cardiac tissue secretes natriuretic peptides; liver and BAT secrete Fgf21; muscle secretes irisin; and thyroid secretes the hormone T_4 (which is then converted to T_3). BAT also produces Bmp8b and Vegf, which increase thermogenic function in an autocrine manner. Additionally, orexin and Bmp7 promote brown fat development, but their cellular source is unknown. Oxr1, oxidation resistance 1; Alk7 (also called Acvr1c), activin A receptor type 1C.

http://www.nature.com/nm/journal/v19/n10/fig_tab/nm.3361_F4.html

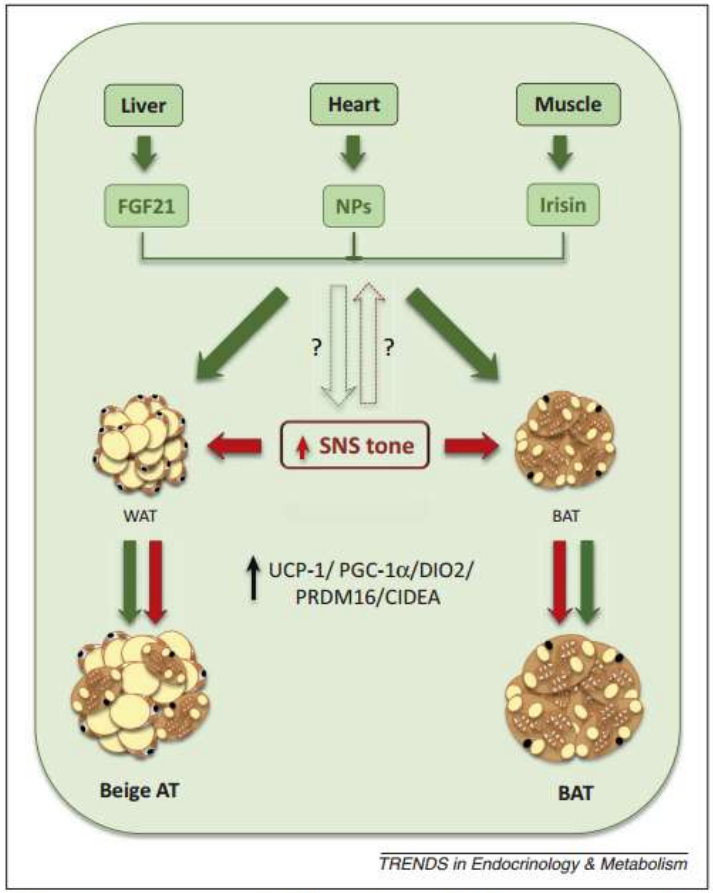


Figure 2. Endocrine factors affecting WAT and BAT depots. The SNS has been long known to upregulate the expression and activity of genes related to thermogenesis such as UCP-1, PGC-1α, DIO2, PRDM16, and CIDEA in both BAT and WAT depots. However, metabolically important peripheral organs including liver, heart, and muscle were recently shown to secrete factors such as FGF21, NPs (specifically ANP and BNP), and irisin, respectively, which could mediate similar effects. Although there is some evidence to indicate that NPs may work in concert with SNS to execute these effects, it remains to be determined whether FGF21 and irisin mediate their effects via the SNS or, alternatively, whether the SNS can contribute to the regulation of secretion of these factors from heart, liver, or muscle. Nonetheless, these observations point towards plausible crosstalk between various organs to regulate thermogenesis and hence overall energy expenditure in rodents and plausibly in humans.
Abbreviations: ANP, atrial natriuretic peptide; BNP, brain-derived natriuretic peptide; BAT, brown adipose tissue; CIDEA, cell-death inducing DFFA-like effector A; DIO2, type II iodothyronine deiodinase; FGF21, fibroblast growth factor 21; NPs, natriuretic peptides; PGC-1α, peroxisome proliferator activated receptor-γ coactivator-1α; PRDM16, PR domain-containing protein 16; SNS, sympathetic nervous system; UCP-1, uncoupling protein-1; WAT, white adipose tissue.

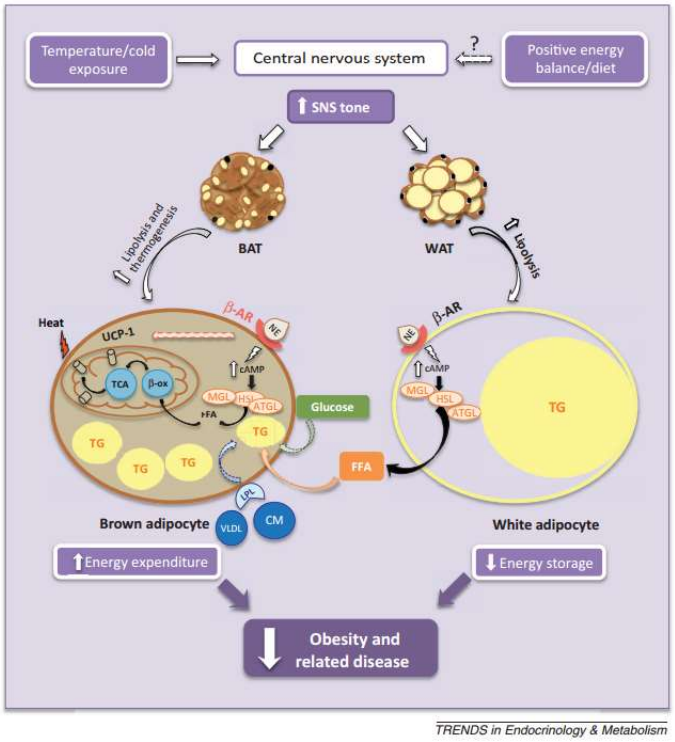
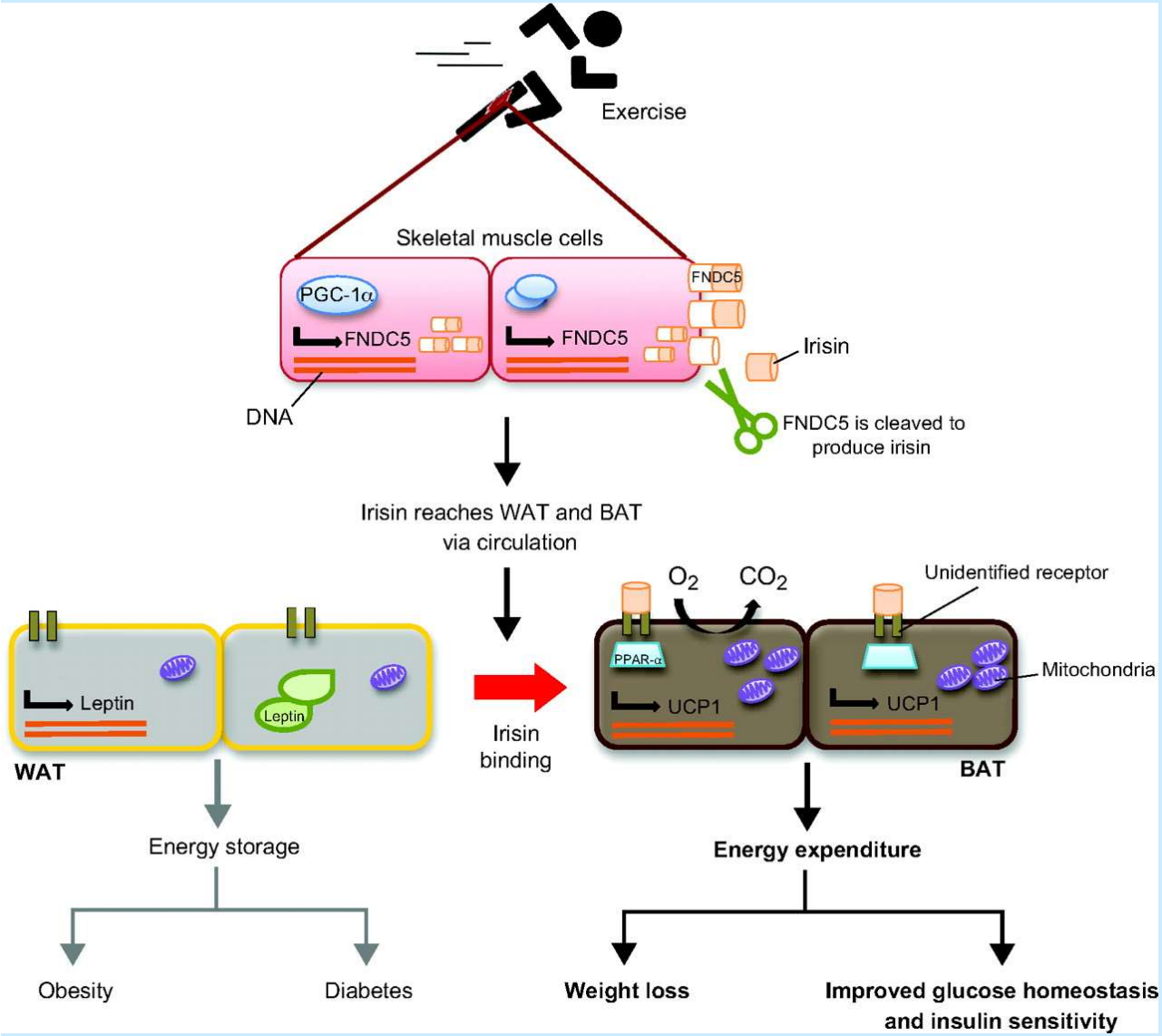


Figure 3. Metabolic implications of active BAT thermogenesis. Upon cold exposure, central mechanisms increase sympathetic tone and NE release to BAT and WAT that translates into lipolysis via β-ARs mediated increase in intracellular cAMP levels and activation of lipolysis mediated by ATGL, HSL, and MGL in both tissues. Although lipolysis in WAT results in breakdown of intracellular TG and hence increased release of FFA into circulation, lipolysis in BAT activates UCP1 and thermogenesis via β-oxidation of FFA. Once activated, brown adipocytes can significantly enhance energy expenditure by combusting intracellular TG stores. However, continued activity can result in the utilization of circulating glucose and FFA by brown adipocytes. An upregulation of LPL expression and activity of active BAT can also result in the increased uptake of TRLs by BAT. Together these mechanisms enhance whole-body energy expenditure and promote weight loss. In addition, active BAT is expected to aid in the clearance of circulating glucose, FFA, and lipoproteins, thereby ameliorating conditions of insulin resistance and hyperlipidemia. The role of diet in the stimulation of BAT thermogenesis in humans, however, remains unclear at this point.
Abbreviations: ATGL, adipose triglyceride lipase; BAT, brown adipose tissue; β-ox, β-oxidation; β-AR, β-adrenergic receptor; FFA, free fatty acids; HSL, hormone-sensitive lipase; LPL, lipoprotein lipase; MGL, monoacylglycerol lipase; NE, norepinephrine; SNS, sympathetic nervous system; TG, triglycerides; TCA, tricarboxylic acid cycle; TRLs, TG-rich lipoproteins; UCP1, uncoupling protein-1; WAT, white adipose tissue.

Chechi K, Carpentier AC, Richard D: Understanding the brown adipocyte as a contributor to energy homeostasis. Trends Endocrinol Metab 2013, 24(8):408-420.

Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α



Castillo-Quan JI: From white to brown fat through the PGC-1 alpha-dependent myokine irisin: implications for diabetes and obesity. *Disease Models & Mechanisms 2012, 5(3):293-295.*

Exercise-induced adipose tissue browning through PGC-1α and irisin. Exercise increases the expression levels of PGC-1α in the muscle. This, in turn, upregulates the expression of FNDC5, a type I membrane protein, which is C-terminally cleaved and secreted as irisin into the circulation. Binding of irisin to an unknown receptor on the surface of adipocytes in WAT changes their genetic profile. In particular, irisin induces the expression of PPAR-α, which is thought to be an intermediate downstream effector that increases the expression of UCP1 (highly expressed in BAT and a marker of browning). The browning of WAT is associated with augmented mitochondrial density and oxygen consumption. Browning is accompanied by an increase in the energy expenditure profile, leading to favourable effects on metabolism.

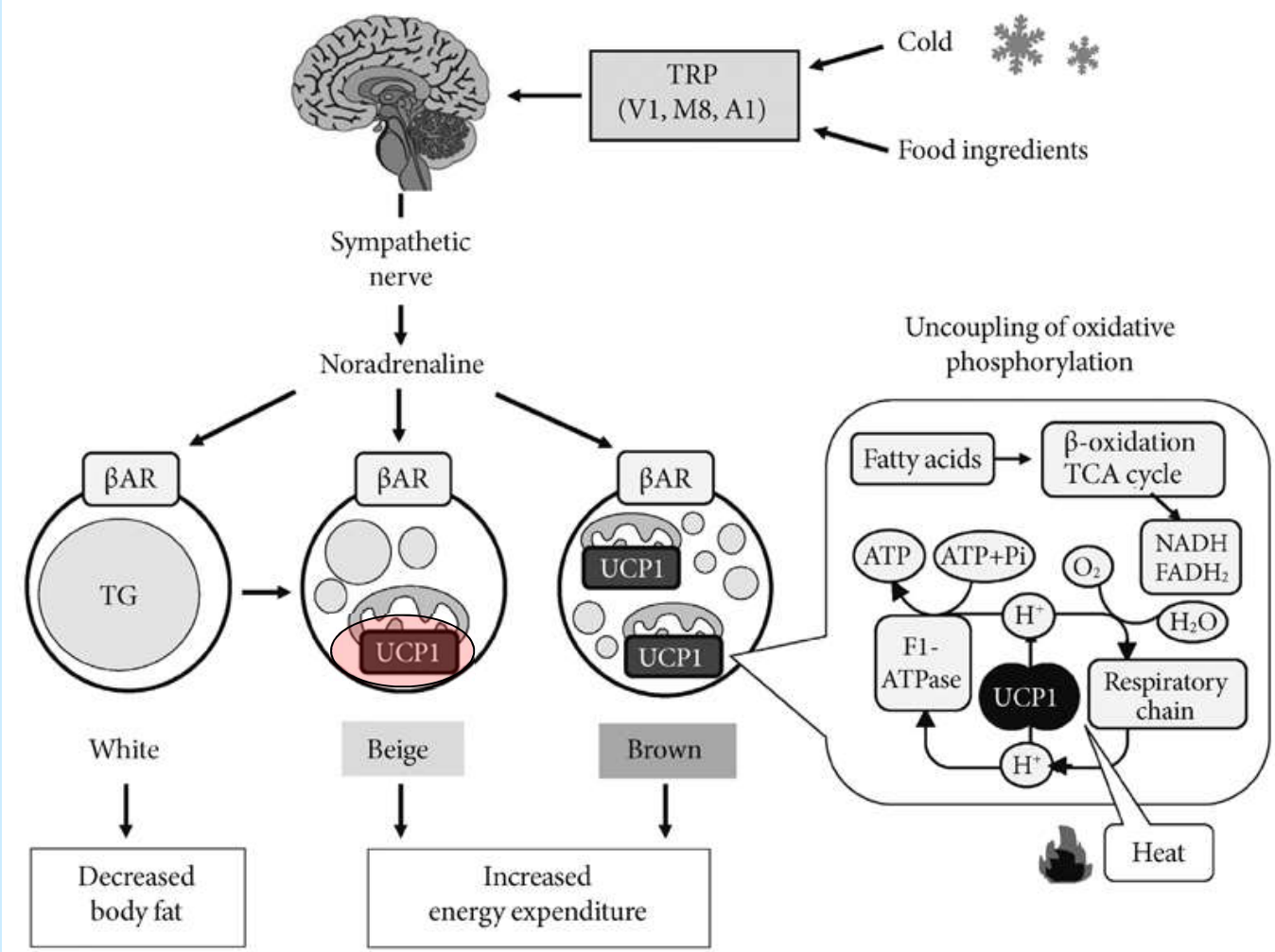
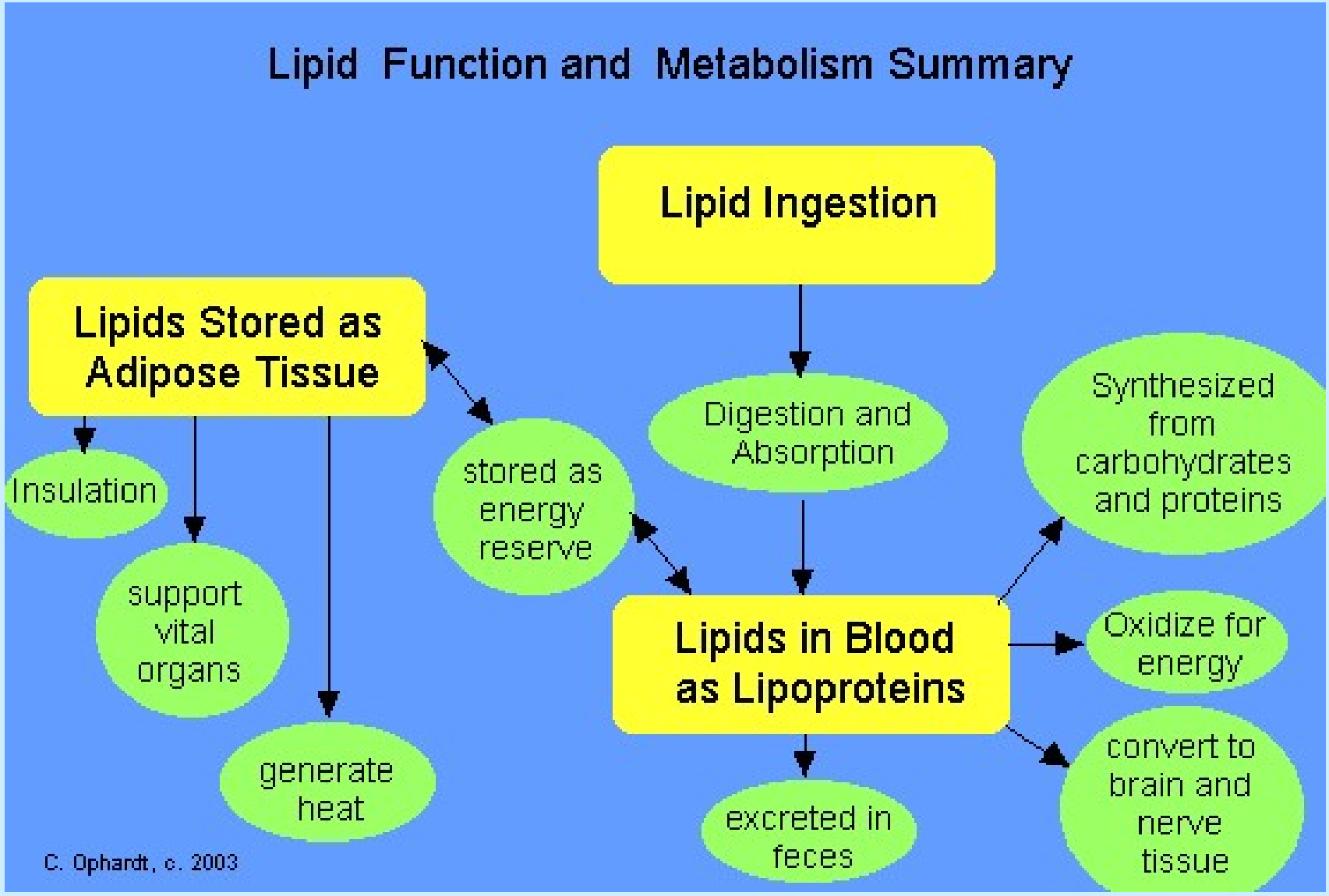


Fig. 1.

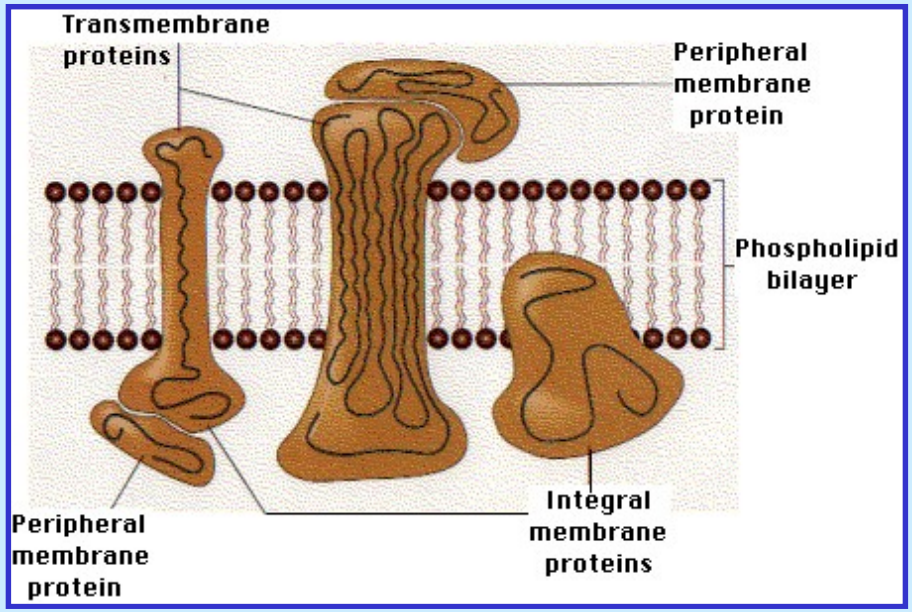
Sympathetically activated thermogenesis in brown adipose tissue, lipid mobilization from white adipose tissue, and induction of beige cells. Sympathetic nerve activity in adipose tissues is increased in response to cold exposure and oral ingestion of some food ingredients through the activation of transient receptor potential channels (TRP). Noradrenaline binds to β-adrenergic receptors (βAR) and initiates signaling cascades for triglyceride (TG) hydrolysis. The released fatty acids activate uncoupling protein 1 (UCP1) and are oxidized to serve as an energy source of thermogenesis. Activated UCP1 uncouples oxidative phosphorylation from ATP synthesis and dissipates energy as heat. Chronic sympathetic activation produces not only brown fat hyperplasia but also an induction of beige cells in white fat, thereby increasing whole-body energy expenditure and decreasing body fat.

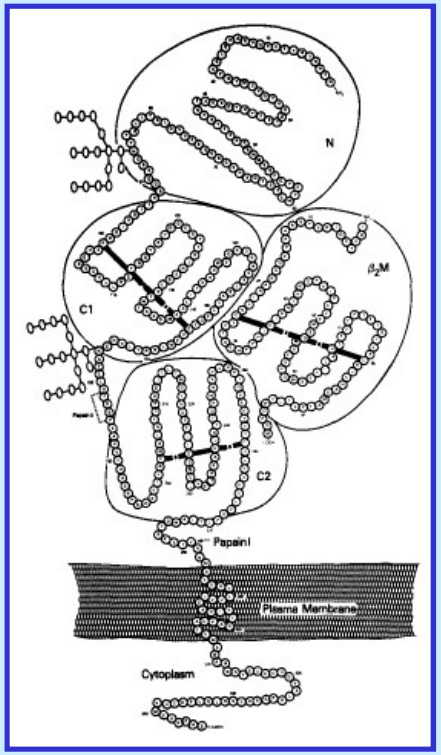
http://www.e-dmj.org/ViewImage.php?Type=F&aid=284781&id=F1&afn=2004_DMJ_37_1_22&fn=dmj-37-22-g001_2004DMJ

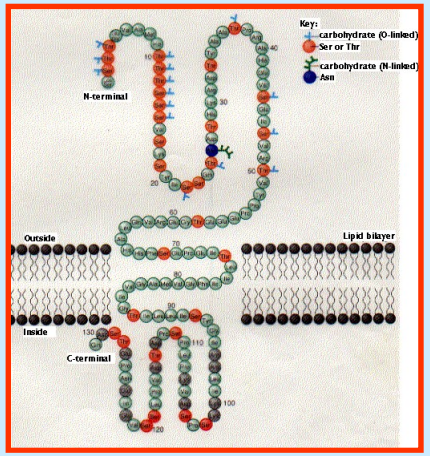

Lipid Function and Metabolism Summary
Lipid Ingestion
Lipids Stored as Adipose Tissue
Digestion and Absorption
Synthesized from carbohydrates and proteins
Insulation
stored as energy reserve
support vital organs
Lipids in Blood as Lipoproteins
Oxidize for energy
generate heat
convert to brain and nerve tissue
excreted in feces
C. Ophardt, c. 2003

METABOLISM OF PROTEINS

- Proteins = AA bound by peptide bonds (above 100 AA)
- Peptides (2-10 AA), polypeptides (10-100 AA)
- Primary, secondary, tertiary a quarterly structure of protein







Proteins, lipoproteins, glycoproteins

Structure of proteins

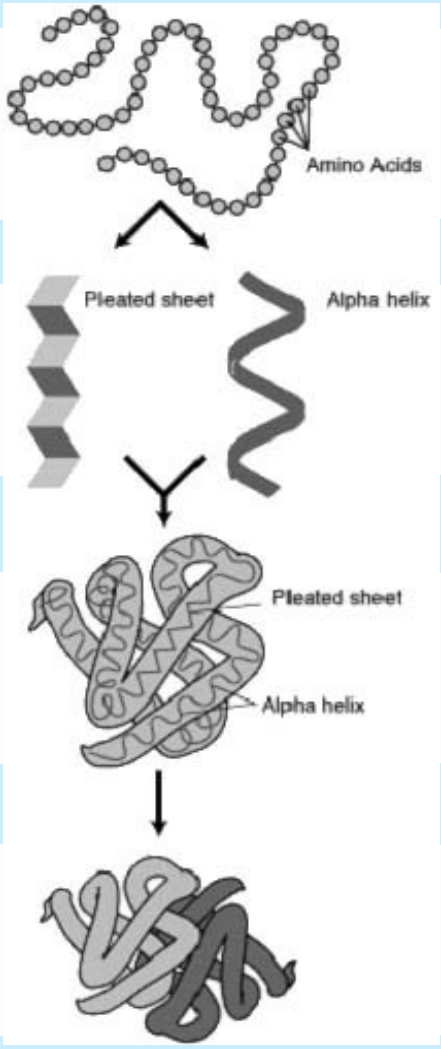
Structure

Primary

Secondary

Tertiary

Quaternary



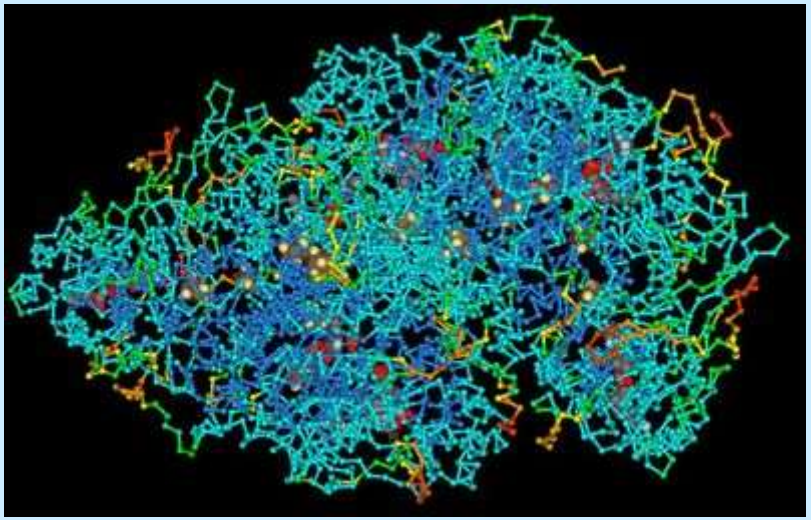
Assembly

Folding

Packing

Interaction

Proces



Total proteins in body: **10** kg

Metabolically active: **6** kg (e.g.60%)

Proteolysis of muscles: **50** g of proteins / day

Minimal daily intake: **50** g

Protein **minimum**: **0,5 g / kg** of body mass

Protein **optimum**: **0,7 g / kg** of body mass

Increased supply (growth, convalescence, pregnancy, lactation): **1,5 – 2,0**

AMINOACIDES

- Essential (not synthesised)
- Non-essential (from glucose metabolism – citrate cycle)
- **Aminoacid pool**
- Need of essential AA: **0,5 – 1,5 g / day**
- Disorders of proteosynthesis
- Optimal source of E-AA:NE-AA milk, eggs
- During growth: **40%** E-AA, in adults: **20%**

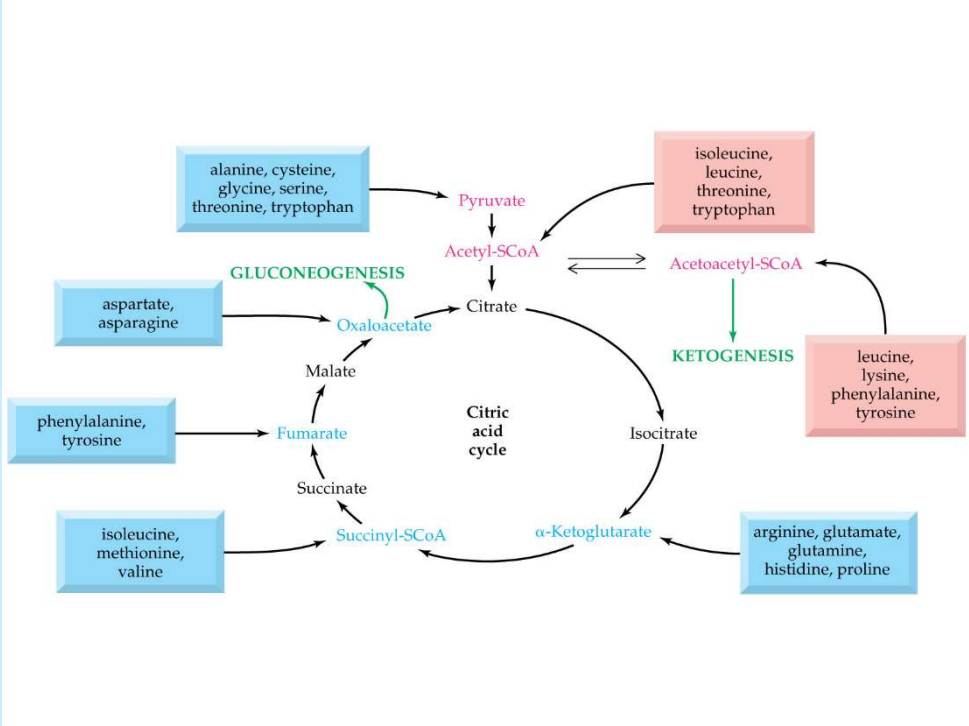
- **Precursors**: purines, pyrimidines, polyamines, phospholipids, creatin, carnitin, donors of methyl group, catecholamines, thyroid gland hormones, neurotransmitters

Amino acids - the surplus in food

Degradation, used as an energy source

AMK as other substrates:

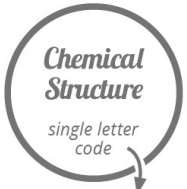
- Glucogenic AMK – synthesis of carbohydrates
- Ketogenic AMK – lipids and ketones



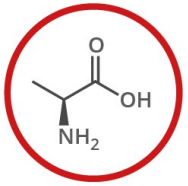
A GUIDE TO THE TWENTY COMMON AMINO ACIDS

AMINO ACIDS ARE THE BUILDING BLOCKS OF PROTEINS IN LIVING ORGANISMS. THERE ARE OVER 500 AMINO ACIDS FOUND IN NATURE - HOWEVER, THE HUMAN GENETIC CODE ONLY DIRECTLY ENCODES 20. 'ESSENTIAL' AMINO ACIDS MUST BE OBTAINED FROM THE DIET, WHILST NON-ESSENTIAL AMINO ACIDS CAN BE SYNTHESISED IN THE BODY.

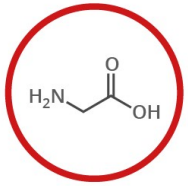
Chart Key: ALIPHATIC · AROMATIC · ACIDIC · BASIC · HYDROXYLIC · SULFUR-CONTAINING · AMIDIC · NON-ESSENTIAL · ESSENTIAL



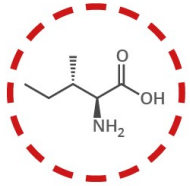
NAME (A)
three letter code
DNA codons



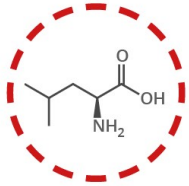
ALANINE (A)
Ala
GCT, GCC, GCA, GCG



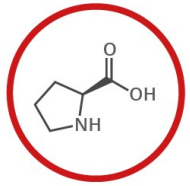
GLYCINE (G)
Gly
GGT, GGC, GGA, GGG



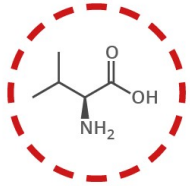
ISOLEUCINE (I)
Ile
ATT, ATC, ATA



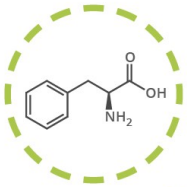
LEUCINE (L)
Leu
CTT, CTC, CTA, CTG, TTA, TTG



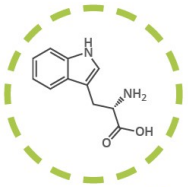
PROLINE (P)
Pro
CCT, CCC, CCA, CCG



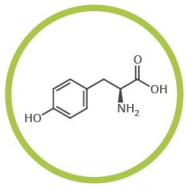
VALINE (V)
Val
GTT, GTC, GTA, GTG



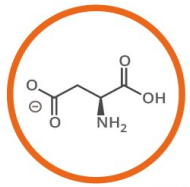
PHENYLALANINE (F)
Phe
TTT, TTC



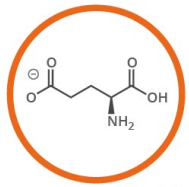
TRYPTOPHAN (W)
Trp
TGG



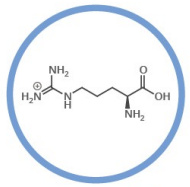
TYROSINE (Y)
Tyr
TAT, TAC



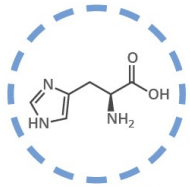
ASPARTIC ACID (D)
Asp
GAT, GAC



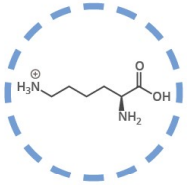
GLUTAMIC ACID (E)
Glu
GAA, GAG



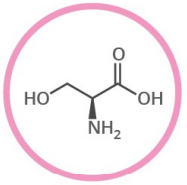
ARGININE (R)
Arg
CGT, CGC, CGA, CGG, AGA, AGG



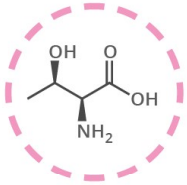
HISTIDINE (H)
His
CAT, CAC



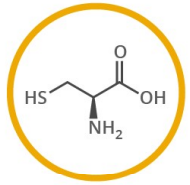
LYSINE (K)
Lys
AAA, AAG



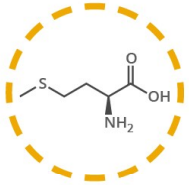
SERINE (S)
Ser
TCT, TCC, TCA, TCG, AGT, AGC



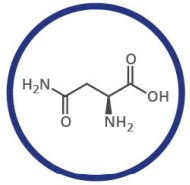
THREONINE (T)
Thr
ACT, ACC, ACA, ACG



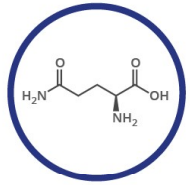
CYSTEINE (C)
Cys
TGT, TGC



METHIONINE (M)
Met
ATG



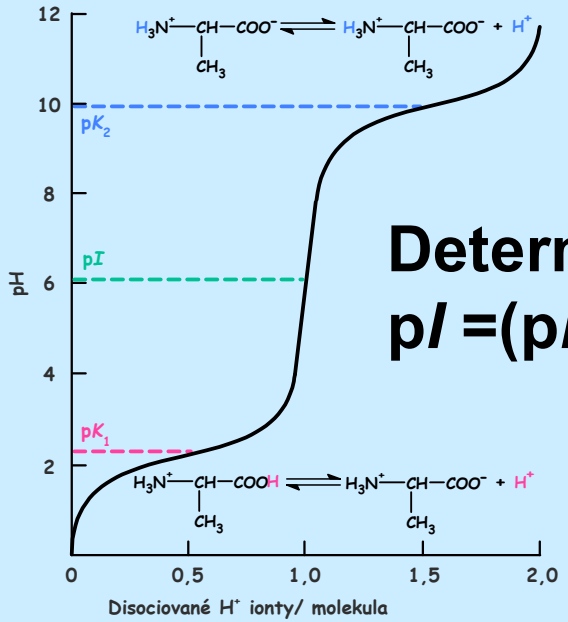
ASPARAGINE (N)
Asn
AAT, AAC



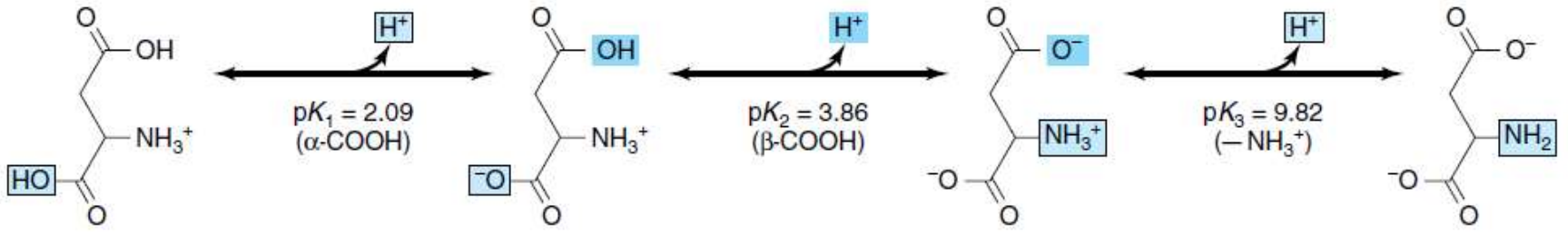
GLUTAMINE (Q)
Gln
CAA, CAG

Note: This chart only shows those amino acids for which the human genetic code directly codes for. Selenocysteine is often referred to as the 21st amino acid, but is encoded in a special manner. In some cases, distinguishing between asparagine/aspartic acid and glutamine/glutamic acid is difficult. In these cases, the codes asx (B) and glx (Z) are respectively used.

Ionization states of amino acids as a function of pH:



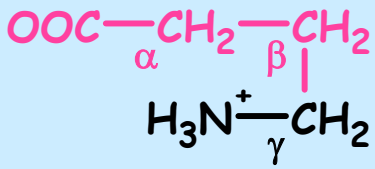
Determination of p*K*1, p*K*2 and p*I* of alanine
p*I* =(p*K*1 + p*K*2) / 2 (isoelectric point, p*I* = 6)



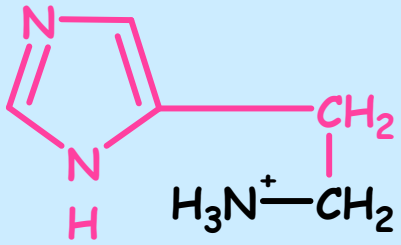
Isoelectric point = p*I*

Figure 3–1. Protonic equilibria of aspartic acid.

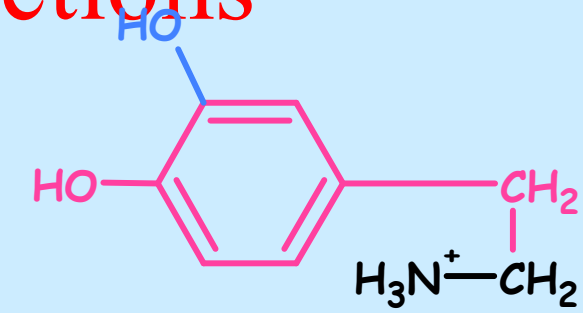
Derivatives of AMK with physiological functions



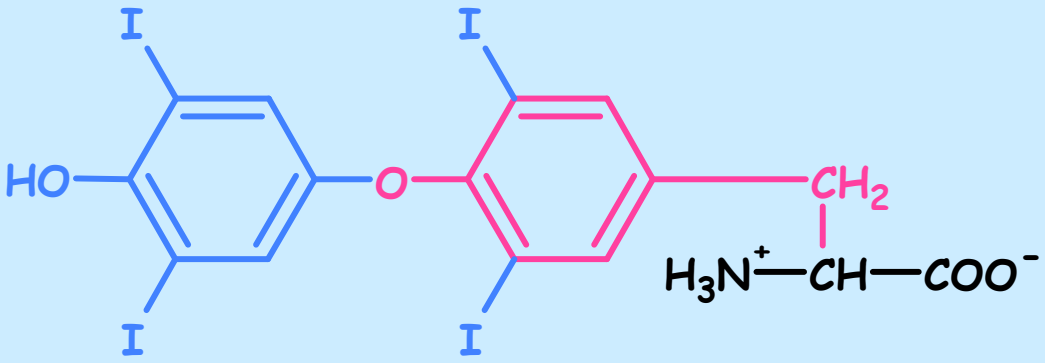
γ-Aminomáselná kyselina (GABA)



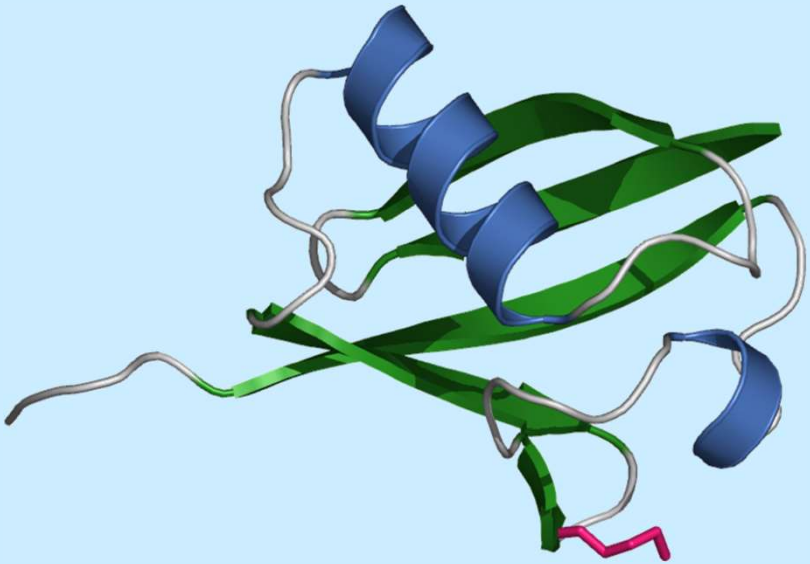
Histamin

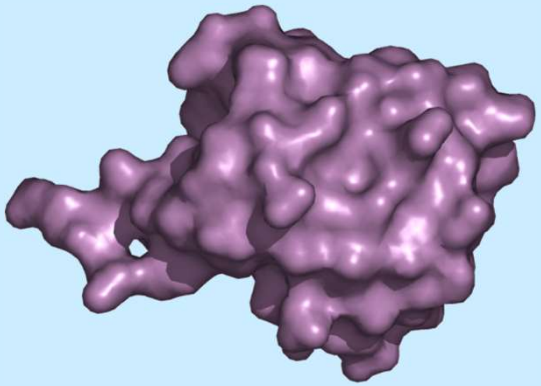


Dopamin



Thyroxin





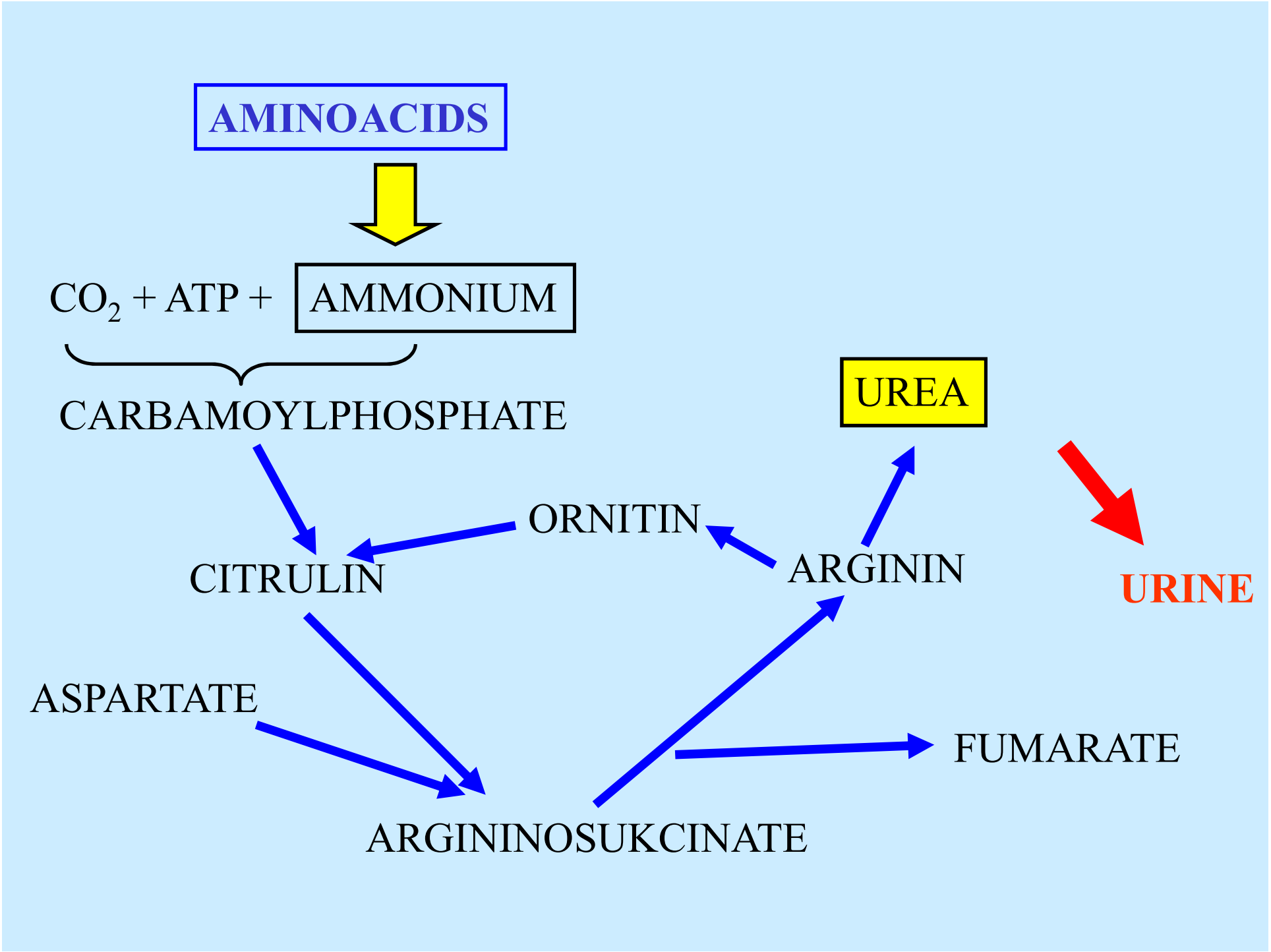
DEGRADATION OF PROTEINS

Binding to **ubiquitin** (74 AA).

Oxidation to CO_2 and H_2O after removing the amino-group (deamination).

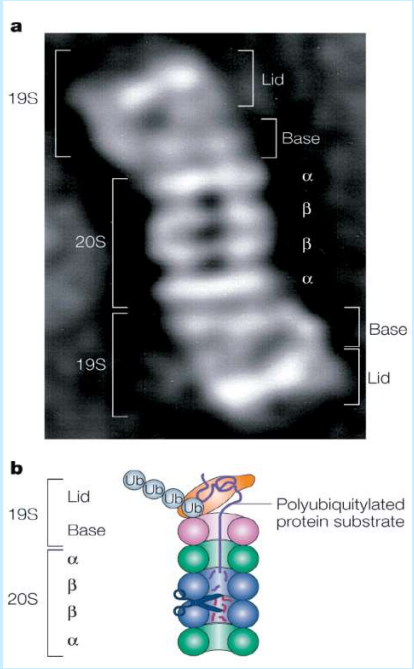
Gluconeogenesis (except of leucin), **ketogenesis** (5AA, acetoacetate or CoA precursors), **ureagenesis** (all AA, ammonium bound to glutamin or alanine, liver, Krebs-Henseleit cycle).

Regulated speed of degradation (muscle hypertrophy, atrophy of denerved or non-stimulated muscle).


AMINOACIDS
CO_2 + ATP +
AMMONIUM
CARBAMOYLPHOSPHATE
UREA
ORNITIN
CITRULIN
ARGININ
URINE
ASPARTATE
FUMARATE
ARGININOSUKCINATE

Degradation of proteins

- **lysozomes**
  - Extracellular proteins
  - Membrane proteins
  - Proteins with long half-time
  - Process does not require **ATP**
- **cytosol**
  - Metabolic proteins
  - Proteins with short half-time
  - Process requires ATP and *ubiquitin*



http://ebm.sagepub.com/content/231/7/1197.full.pdf+html

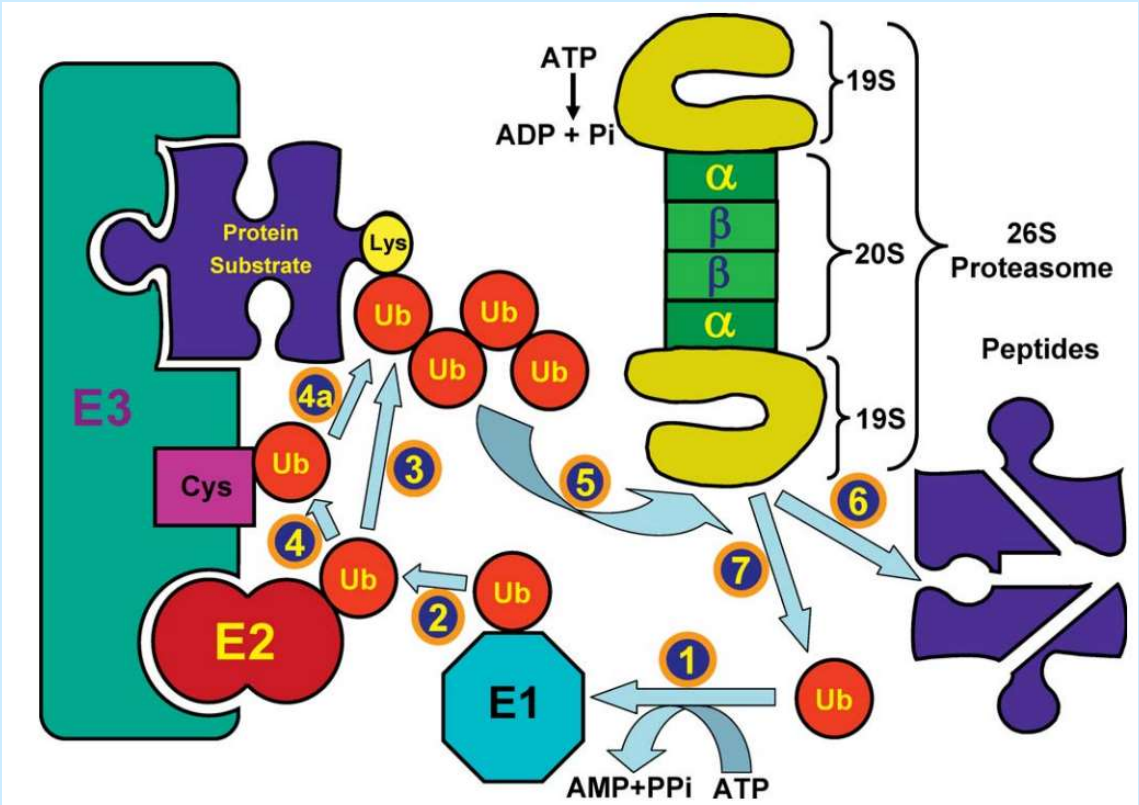


Figure 5. The ubiquitin-proteasome proteolytic system. Ubiquitin is activated by the ubiquitin-activating enzyme, E1 (1) followed by its transfer to a ubiquitin-carrier protein (ubiquitin-conjugating enzyme, UBC), E2 (2). E2 transfers the activated ubiquitin moieties to the protein substrate that is bound specifically to a unique ubiquitin ligase E3. The transfer is either direct ([3] in the case of RING finger ligases) or *via* an additional thiol-ester intermediate on the ligase ([4, 4a] in case of HECT domain ligases). Successive conjugation of ubiquitin moieties to one another generates a polyubiquitin chain that serves as the binding (5) and degradation signal for the downstream 26S proteasome. The substrate is degraded to short peptides (6), and free and reusable ubiquitin is released by de-ubiquitinating enzymes (DUBs) (7).

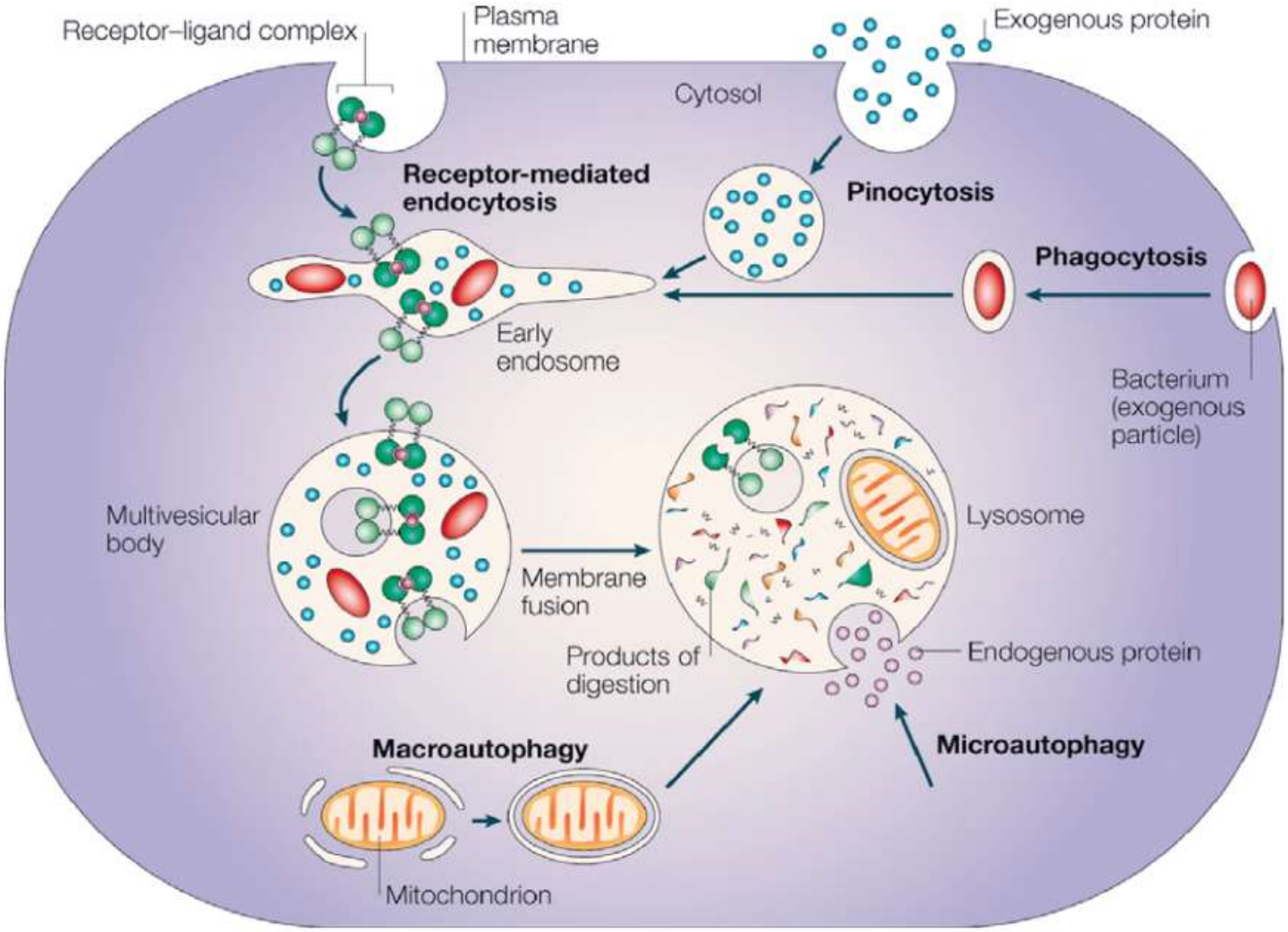


Figure 2. The four digestive processes mediated by the lysosome. (i) Specific receptor-mediated endocytosis, (ii) pinocytosis (non-specific engulfment of cytosolic droplets containing extracellular fluid), (iii) phagocytosis (of extracellular particles), and (iv) autophagy (micro- and macro-; of intracellular proteins and organelles). (Reprinted with permission from Ref. 83).

METABOLISM OF PURINES AND PYRIMIDINES

Purines and pyrimidines – physiological meaning of **nucleosides** (reactants with ribose); from diet or synthesis de novo from AA in liver; RNA is in balance with AA pool, DNA is stabile.

Recirculation or catabolism, eventually excretion in urine.
Pyrimidines – CO_2 and NH_3, purines – uric acid.

URIC ACID

Excreted in urine.
4mg/100ml of blood plasma
Kidney: filtration, resorption (98% filtration), tubular secretion (80%)
Daily: approx. 1g excreted in urine
Disorder in uric acid metabolism – gout.
Hyperuricemia – *primary* (overproduction) or *secondary* (reduced excretion, increased intake of purines in diet, blood disorders).

Synthesis of purines/pyrimidines

- **de novo (new synthesis of purine/pyrimidine ring)**
- **„saving“ reactions (synthesis from nucleotides and bases)**
  - **is more energy saving than de novo synthesis**
  - **They decrease the synthesis de novo**
  - **substrates:** **a) bases (adenine, guanine, hypoxanthine)**
    PRDP

    b) ribonucleosides
    ATP

Analogs of bases and nucleotides are used as cytostatics

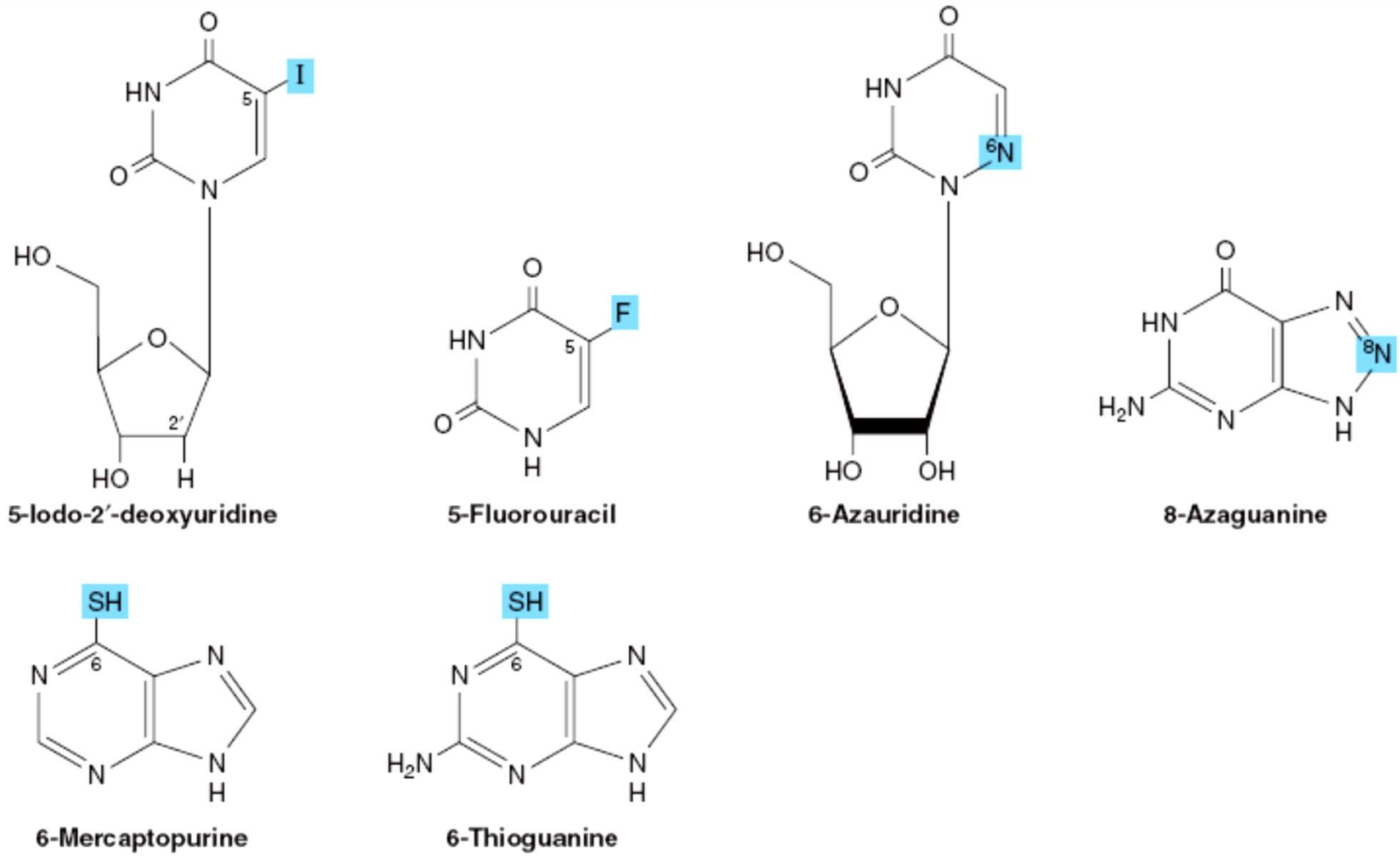


Figure 33–12. Selected synthetic pyrimidine and purine analogs.

Harper´s Illustrated Biochemistry 26th ed./ R.K.Murray; McGraw-Hill Companies, 2003, ISBN 0-07-138901-6.

GOUT (arthritis urica)

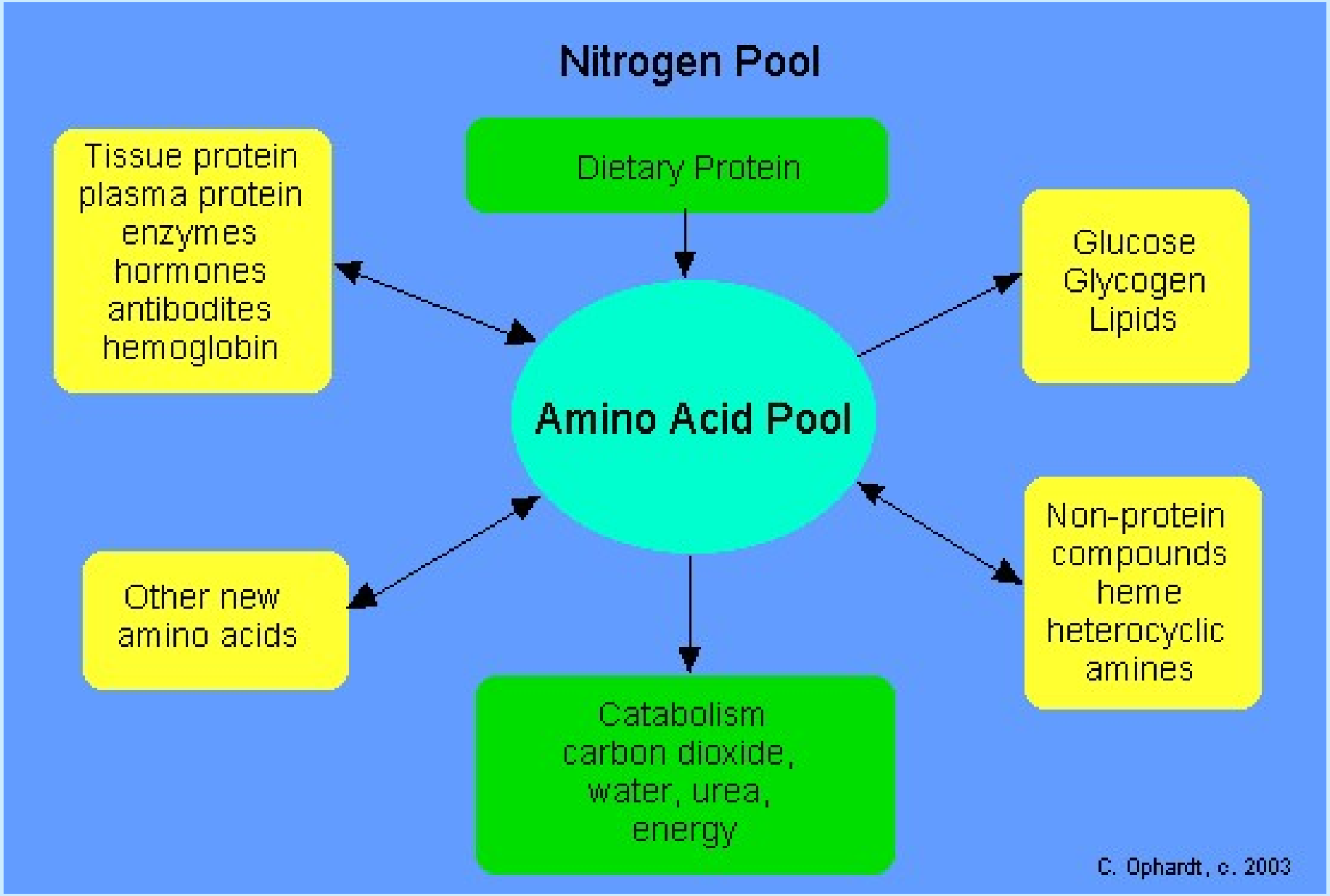
- Primary and secondary gout
- Acute (gouty attack) and chronic (chalkstones, urolithiasis) form
- General metabolic disorder - disease of purine metabolism
- Local **cumulating** of uric acid salts (urate) in tissues, urine (joints, kidneys), primary **hyperuricemia**
- Gouty attacks – repeated attacks of arthritis, typical localisation – metatarsophalangeal joint (**podagra**; omagra, cheiragra…)
- Hurtfulness during attack – phagocytosis of urates grains
- Therapy: NSA, colchicin – inhibition of fagocytosis, allopurinol – inhibition of xantinoxidase, phenylbutazon and probenecid – inhibition of resorption

NITROGEN BALANCE

Necessity to keep AA pool. AA mixtures.
Amount of N in urine – indicator of intensity of irreversible disintegration of proteins and AA.
Nitrogen balance: amount of N in urine = amount of N in dietary proteins

- Negative nitrogen balance: loss exceeds intake (starvation, immobilisation, catabolism, **lack of E-AA!!!**…)
- Positive nitrogen balance: intake exceeds loss (anabolic drugs, growth, convalescence…)

Synthesis and degradation of body proteins: 3–4g/kg of body mass (balanced diet)
From this amount: 5% - synthesis of albumins and proteins with fast-exchange in liver
In deficient diet (energetically, amount of proteins or E-AA) – proteosynthesis deceleration, compensatory –degradation deceleration (BUT of lower extent→ loss of body proteins)


Nitrogen Pool
Tissue protein
plasma protein
enzymes
hormones
antibodites
hemoglobin
Dietary Protein
Glucose
Glycogen
Lipids
Amino Acid Pool
Other new
amino acids
Non-protein
compounds
heme
heterocyclic
amines
Catabolism
carbon dioxide,
water, urea,
energy
C. Ophardt, c. 2003

CREATIN AND CREATININ

CREATIN

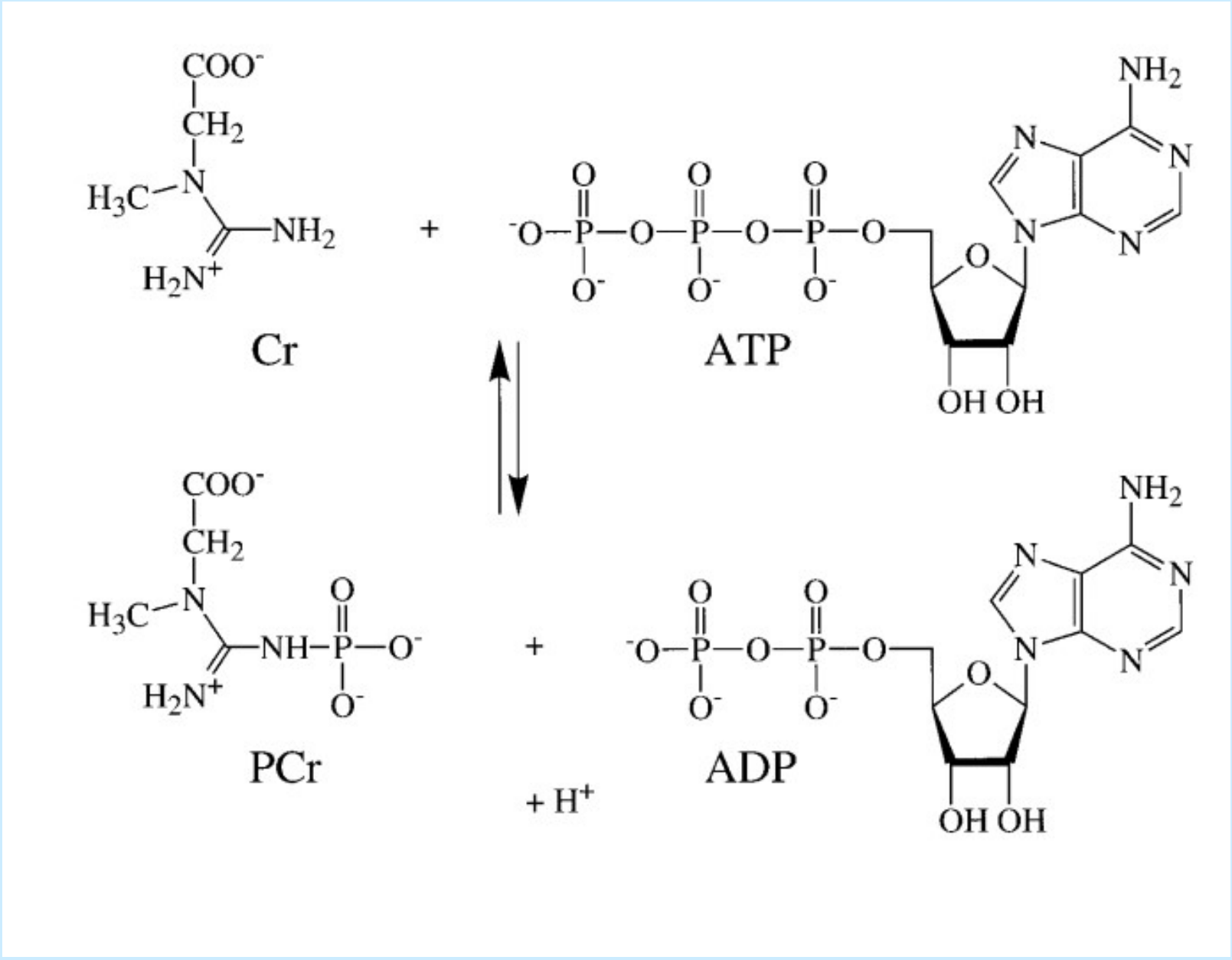
Synthesis in liver (methionin, glycin, arginin).
Phosphorylation in skeletal muscle – **phosphocreatin**.

CREATININ

From phosphocreatin, in urine.
Speed of excretion is relatively constant.

CREATINURIE

Physiological – in children, in pregnancy, after pregnancy, occasionally in non-pregnant.
During muscle catabolism – in enormous amounts (starving, DM, myopathy, thyreotoxicosis…)



Wyss M, Kaddurah-Daouk R: Creatine and creatinine metabolism. *Physiol Rev 2000, 80(3):1107-1213.*

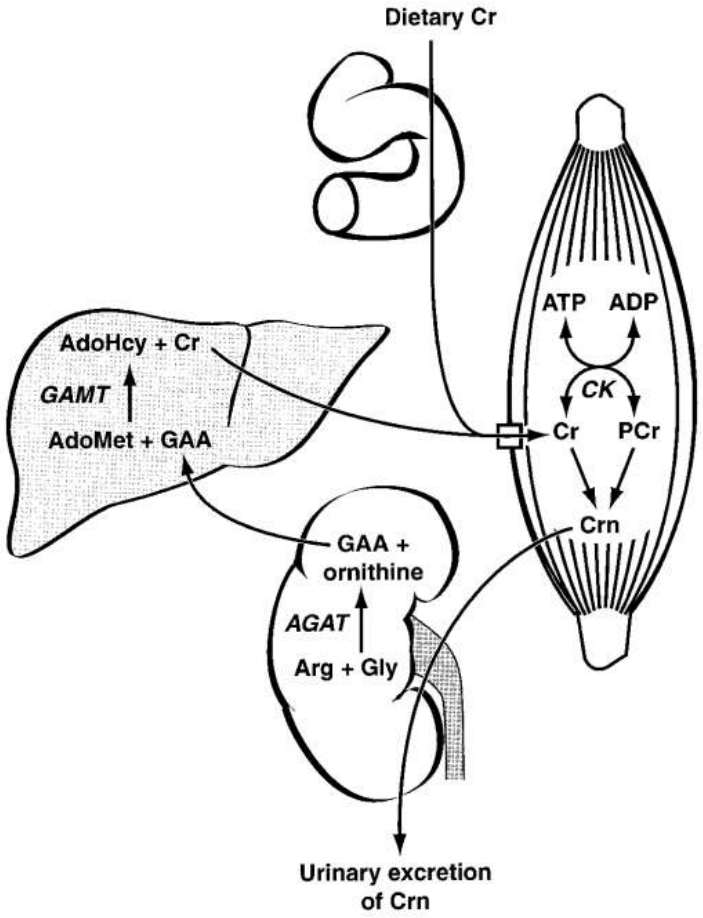
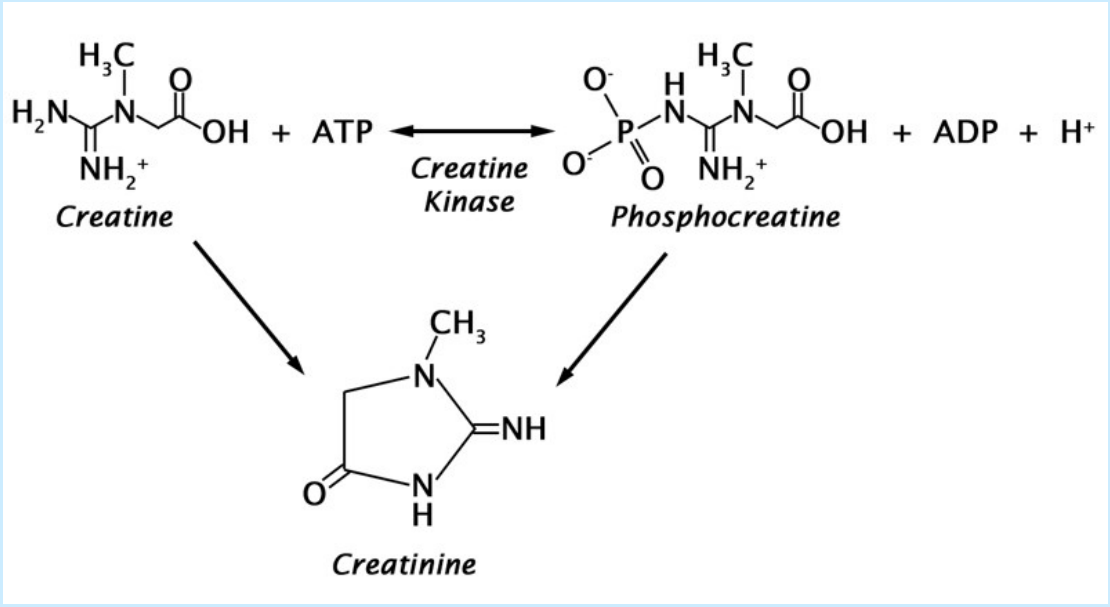


FIG. 4. Major routes of Cr metabolism in the mammalian body. The most part (up to 94%) of Cr is found in muscular tissues. Because muscle has virtually no Cr-synthesizing capacity, Cr has to be taken up from the blood against a large concentration gradient by a saturable, Na^+- and Cl^--dependent Cr transporter that spans the plasma membrane (□). The daily demand for Cr is met either by intestinal absorption of dietary Cr or by de novo Cr biosynthesis. The first step of Cr biosynthesis probably occurs mainly in the kidney, whereas the liver is likely to be the principal organ accomplishing the subsequent methylation of guanidinoacetic acid (GAA) to Cr. It must be stressed that the detailed contribution of different bodily tissues (pancreas, kidney, liver, testis) to total Cr synthesis is still rather unclear and may vary between species (see text). The muscular Cr and PCr are nonenzymatically converted at an almost steady rate (~2% of total Cr per day) to creatinine (Crn), which diffuses out of the cells and is excreted by the kidneys into the urine.



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METABOLIC DISORDERS – PROTEINS

QUANTITATIVE CHANGES

Proteinemia = plasmatic level of proteins.
Controlled:

1. Supply with full-value proteins and their use
2. Synthesis of proteins
3. Protein catabolism and loss from organism

Ad 1) nutrition disorders, special dietary trends
Ad 2) liver disorders, endocrine diseases
Ad 3) liver and muscles release E-AA when proteins are reduced in diet

METABOLIC DISORDERS – PROTEINS

QUALITATIVE CHANGES

1. Dysproteinemia = change in representation of particular proteins (fractions shift) – nephrotic syndrome, cirrhosis, acute inflammatory reactions, chronic inflammatory reactions, tumours

2. Paraproteinemia = presence of pathological imunoglobulines (with no antibodies specificity) – monoclonal immunopathy

3. Defect proteinemia = some components of plasma proteins are missing or lowered (1/10 – 1/1000 normal values) – syndromes of immunodeficiency, symptomatic hypo- and dysgamaglobulinemia (familiar lack of IgA), polyclonal hypergamaglobulinemia

METABOLIC DISORDERS – AMINOACIDES

1. Disorders of AA metabolism during hypovitaminoses and avitaminoses – vit.C (colagen synthesis– proline hydroxylation; metabolic osteopathy, haemorrhage, poor healing), vit.B6 (tryptophan metabolism – lack of nicotinic acid)

2. Disorders of AA metabolism during liver diseases – regulation of plasmatic level of AA (transamination, oxidation, decarboxylation, deamination, ammonia, urea, kidneys); badly soluble AA (cystine, tyrosine) may form crystals in urine; liver encephalopathy, liver coma, glutamine in coeliolymph

AMYLOIDOSIS

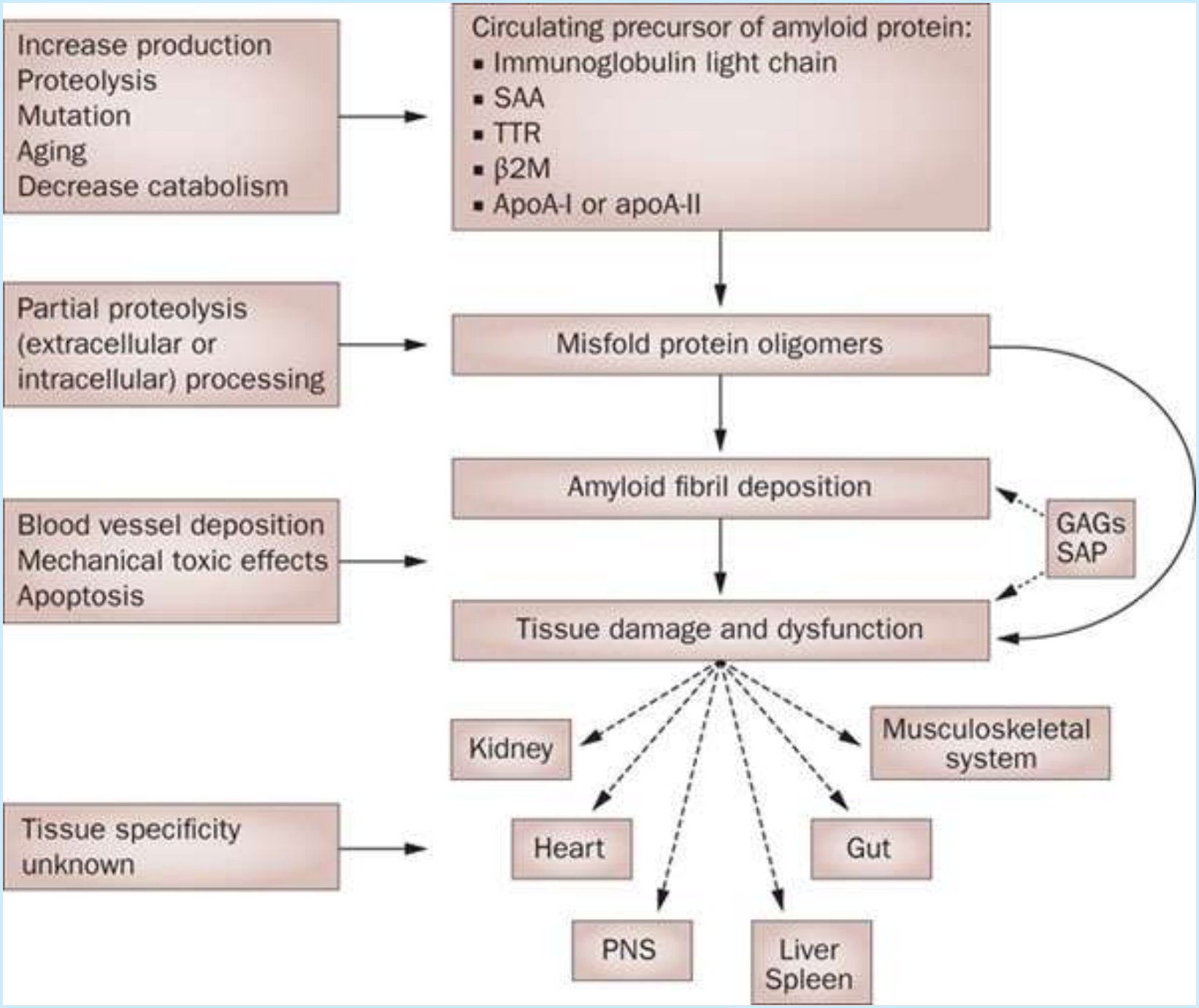
= infiltration of organs by amyloid (complex of protein with polysaccharide)

Mechanism of disease is alteration of immune system.

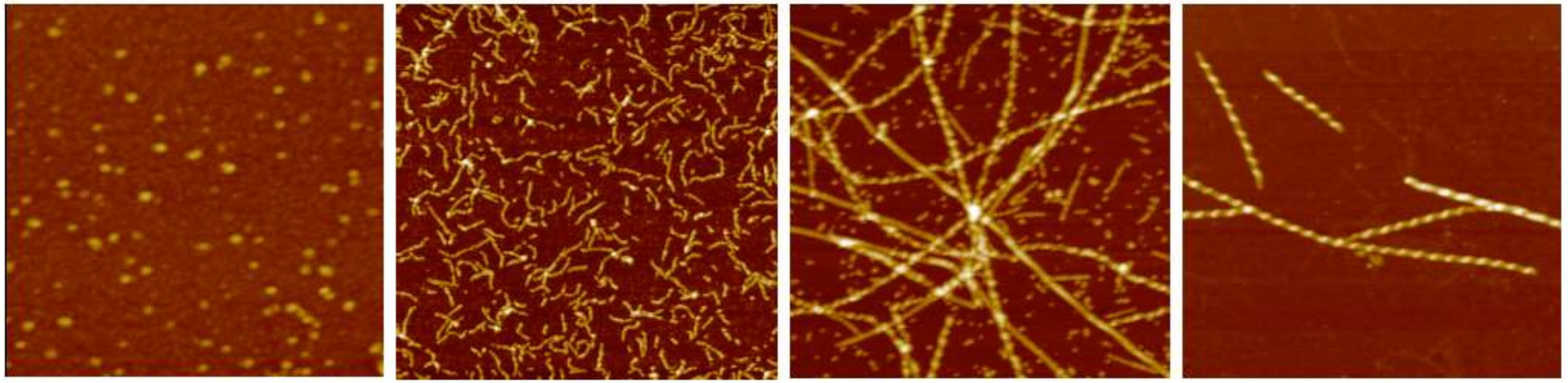
Primary and secondary amyloidosis

Primary – idiopathic; infliction of heart, muscles, GIT; elderly patients; no gender differences

Secondary – complication of chronic inflammatory diseases, tumours; more frequent; infliction of kidney (most often), lien, liver, adrenal glands


Increase production
Proteolysis
Mutation
Aging
Decrease catabolism
Circulating precursor of amyloid protein:
▪ Immunoglobulin light chain
▪ SAA
▪ TTR
▪ β2M
▪ ApoA-I or apoA-II
Partial proteolysis (extracellular or intracellular) processing
Misfold protein oligomers
Amyloid fibril deposition
GAGs
SAP
Blood vessel deposition
Mechanical toxic effects
Apoptosis
Tissue damage and dysfunction
Kidney
Musculoskeletal system
Tissue specificity unknown
Heart
Gut
PNS
Liver
Spleen

Aβ amyloidogenesis involves the transition from soluble protein to toxic oligomers and fibrils in AD



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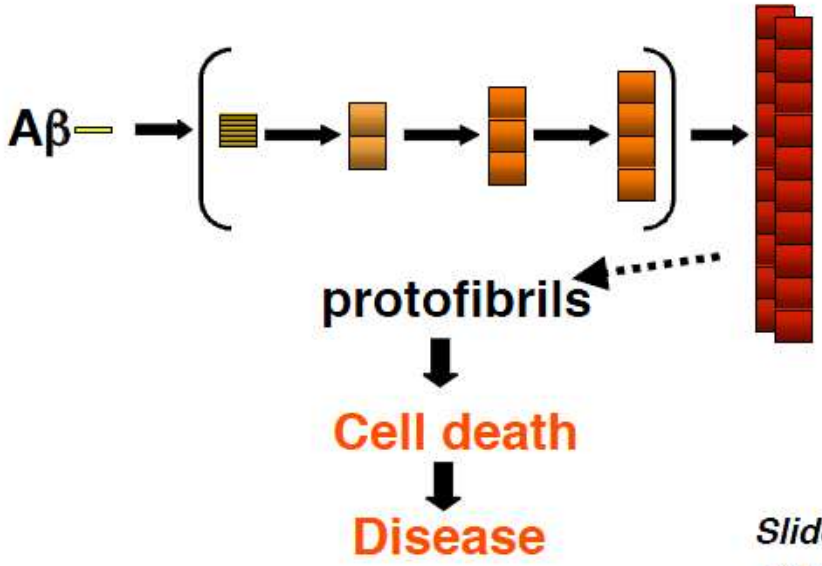
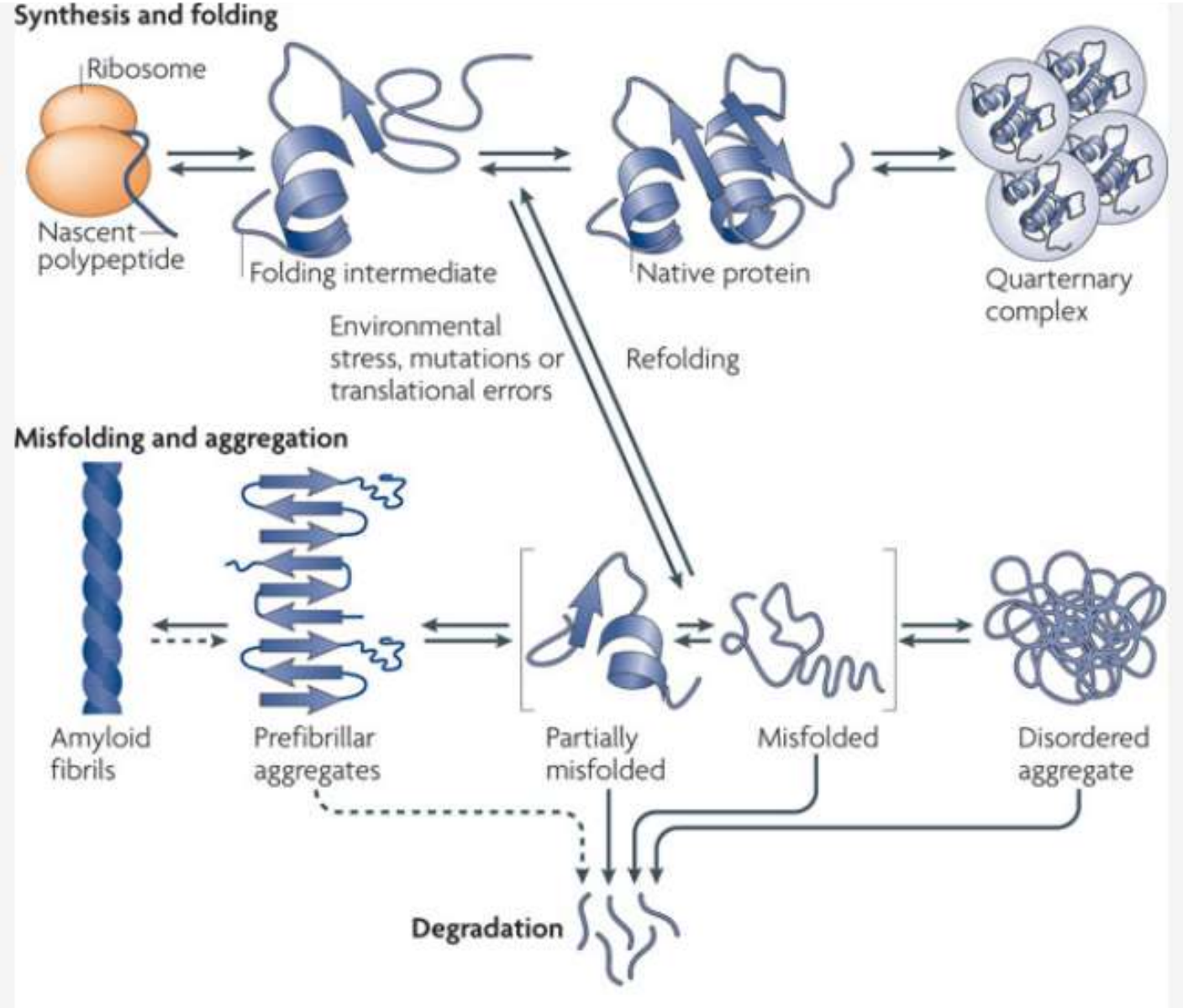
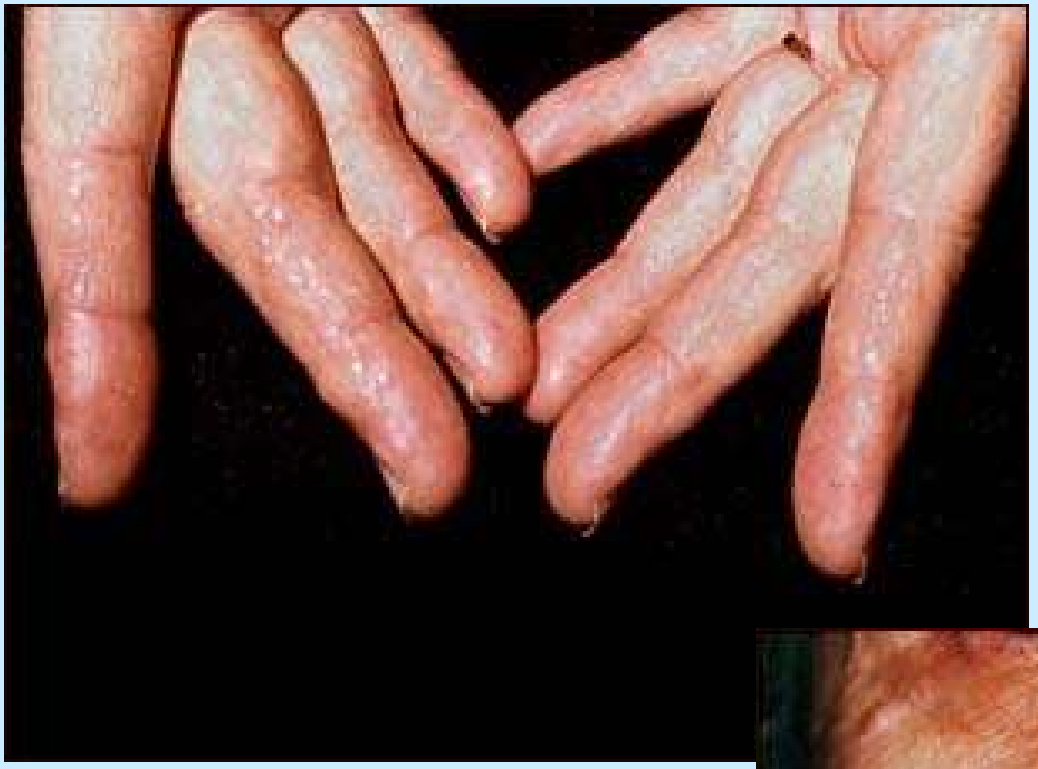


Slide courtesy of Jeff Kelly based on data of Teplow, Glabe, Krafft, and Lansbury

	Disease	Precursor protein
Loss-of-function	**Albinism**	**tyrosinase**
	Cancer	**P53 tumor suppressor**
	Cystic Fibrosis	**CFTR**
	Haemophilia disorders	**FV, FVII, FVIII, FIX, FX, FXI, FXIII**
	Marble brain syndrome	**carbonic anhydrase II**
	Phenyl keton uria	**phenylalanine hydroxylase**
Gain-of-toxic-function	**Alzheimer's disease**	**Ab-Protein**
	Primary systemic amyloidosis	**Ig Light Chain**
	Familial amyloidotic polyneuropathy	**transthyretin**
	Type II diabetes	**islet Amyloid Poly Peptide**
	ALS	**superoxide dismutase**
	Parkinson's disease	**α-synuclein**
Infectious misfolding	**Creutzfeldt Jakob disease**	**prion protein**
	Mad cow disease	**prion protein**
	Kuru	**prion protein**



A protein during and after its synthesis at the ribosome folds through different intermediates to its native, three-dimensional structure. Proteotoxic stresses, mutations in the synthesized protein or translational errors can cause protein misfolding. Once present, misfolded intermediates can be refolded to the native state or be degraded by different cellular proteolysis systems that prevent the accumulation of misfolded proteins. Once the quality-control network is overwhelmed — for example, through persisting harsh stress conditions, increased amounts of aberrant proteins or in aged cells — aggregates can form. Their formation can be guided by molecular chaperones. Forming aggregates can have varying degrees of structure, ranging from mostly unstructured, disordered aggregates to prefibrillar species and highly ordered β-sheet-rich amyloid fibrils. Disordered aggregates and intermediates during amyloid formation may be degraded. Arrows indicate a process that can include several single steps; dashed arrows indicate a process of minor significance.




A.D.A.M.