Metabolic Interrelationships

References:

Michael Lieberman Allan Marks: Basic Medical Biochemistry A Clinical Approach 3rd ed (2009) Section I- Chapters 1-3.

Thomas Devlin: Textbook of Biochemistry with Clinical Correlations 7th ed (2011) Chapter 21

Richard Harvey, Pamela Champe: Lippincott's Illustrated Review of Biochemistry 5rd ed (2011) Chapters 23 + 24.

David Nelson, Michael Cox: Lehninger-Principles of Biochemistry 5th ed. (2008) Chapter 15

Reginald Garrett, Charles Grisham: Biochemistry 3rd ed (2005) Chapter 25 (Integration of Metabolism)

OUTLINE

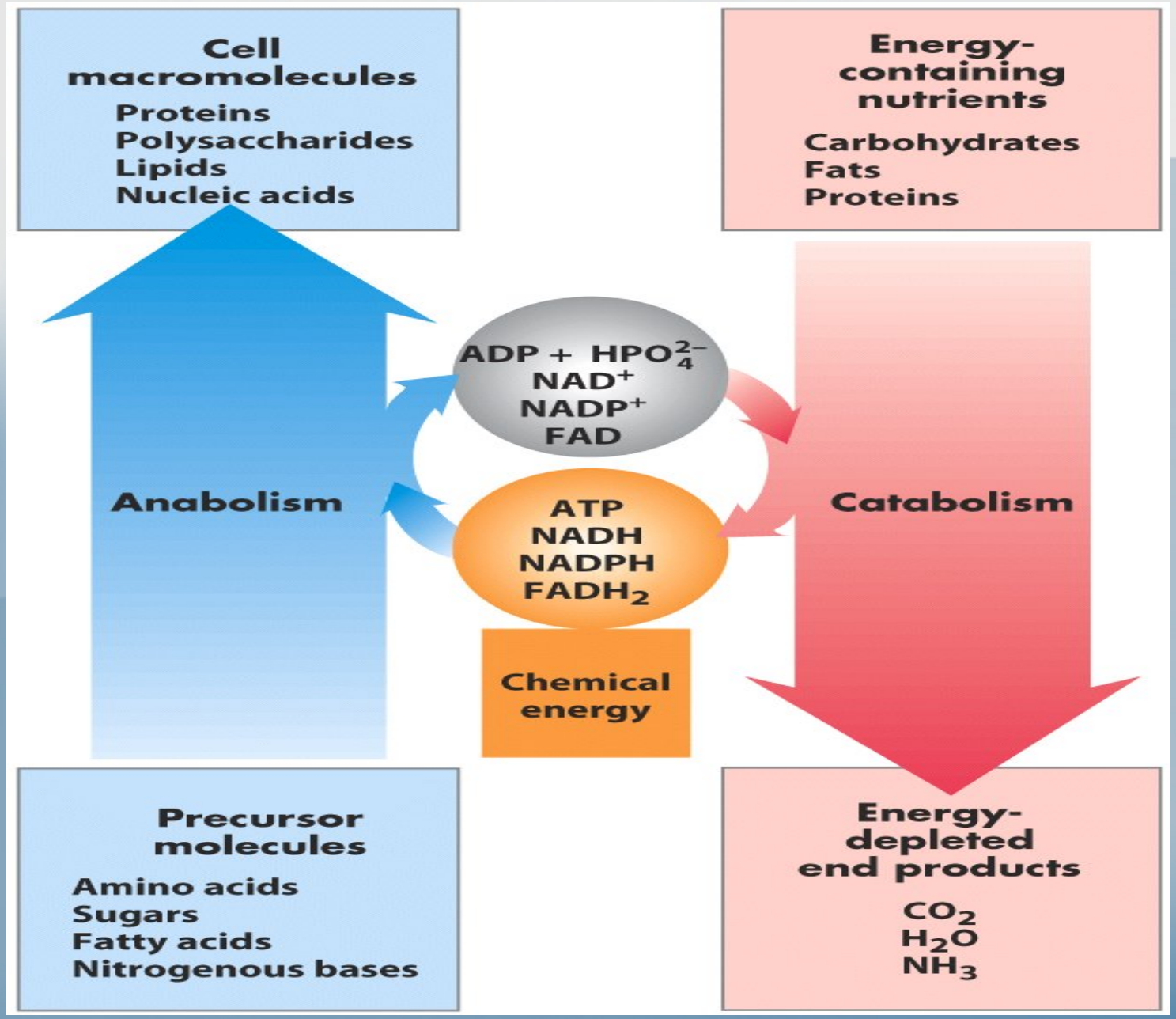
1. Metabolism - A Balance of Anabolic and Catabolic R_x's
   A. Production and Utilization of Energy and REDOX substances
2. Major Metabolic Pathways have Common Intermediates
3. Energy Charge Value
4. Control of Metabolism Occurs at 4 levels
   A. Substrate Availability
   B. Allosteric Modulation
   C. Covalent Modification
   D. Enzyme Synthesis
5. Metabolism – Cooperation between Tissues
   A. Liver
   B. Adipose Tissue
   C. Skeletal Muscle
   D. Brain

Outline (continued)

6. Metabolism Requires Hormonal Control
   - A. Insulin
   - B. Glucagon
   - C. Epinephrine
7. Tissue Interactions – Well Fed and Fasted States
   - A. Fuels and Pathways
8. Tissue Interactions – Under Various Conditions
   - A. Obesity and Dieting
   - B. Type I and Type II Diabetes
   - C. Cancer
   - D. Exercise
   - E. Pregnancy and Lactation
   - F. Stress and Injury
   - G. Liver and Kidney Diseases
   - H. Alcohol Ingestion
9. Respiratory Quotient

Metabolic Processes

- Glycogenolysis
- Gluconeogenesis
- Fatty Acid Synthesis
- Lipogenesis
- TCA Cycle Activity
- Amino Acid Oxidation
- Proteolysis
- Glycogenesis
- Glycolysis
- Lipolysis
- Glutaminolysis
- Ketogenesis
- Protein Synthesis
- Urea Synthesis


Cell macromolecules
Proteins
Polysaccharides
Lipids
Nucleic acids
Energy-containing nutrients
Carbohydrates
Fats
Proteins
ADP + HPO_4^{2-}
NAD^+
$NADP^+$
FAD
ATP
NADH
NADPH
$FADH_2$
Anabolism
Catabolism
Chemical energy
Precursor molecules
Amino acids
Sugars
Fatty acids
Nitrogenous bases
Energy-depleted end products
CO_2
H_2O
NH_3

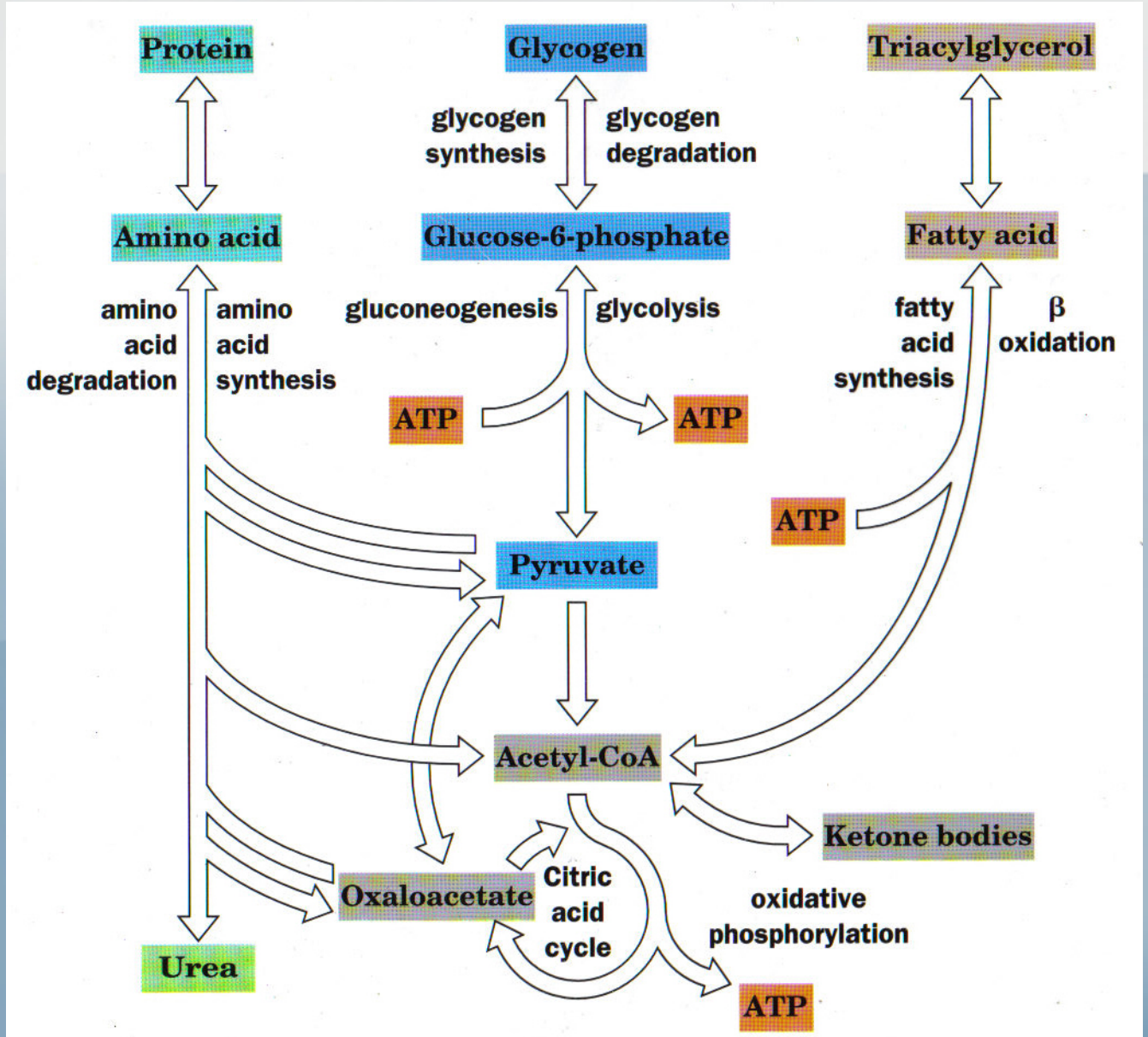


Figure 21-1. The major pathways of fuel metabolism in mammals.

ANAPLEROTIC REACTIONS

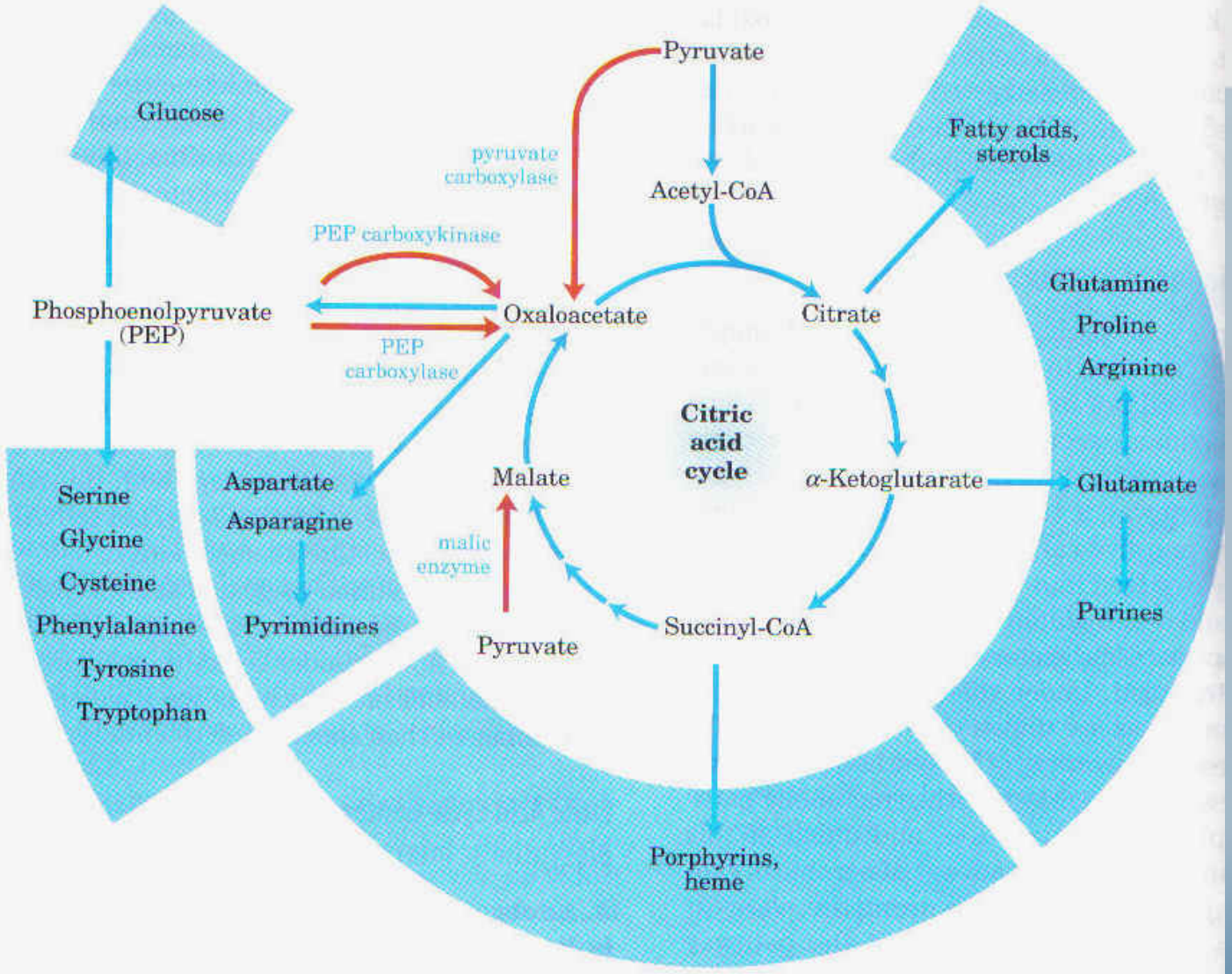


FIGURE 16–15 Role of the citric acid cycle in anabolism. Intermediates of the citric acid cycle are drawn off as precursors in many biosynthetic pathways. Shown in red are four anaplerotic plenish depleted cycle intermediates (see Table 16–2)

Metabolism
The "Big" Picture

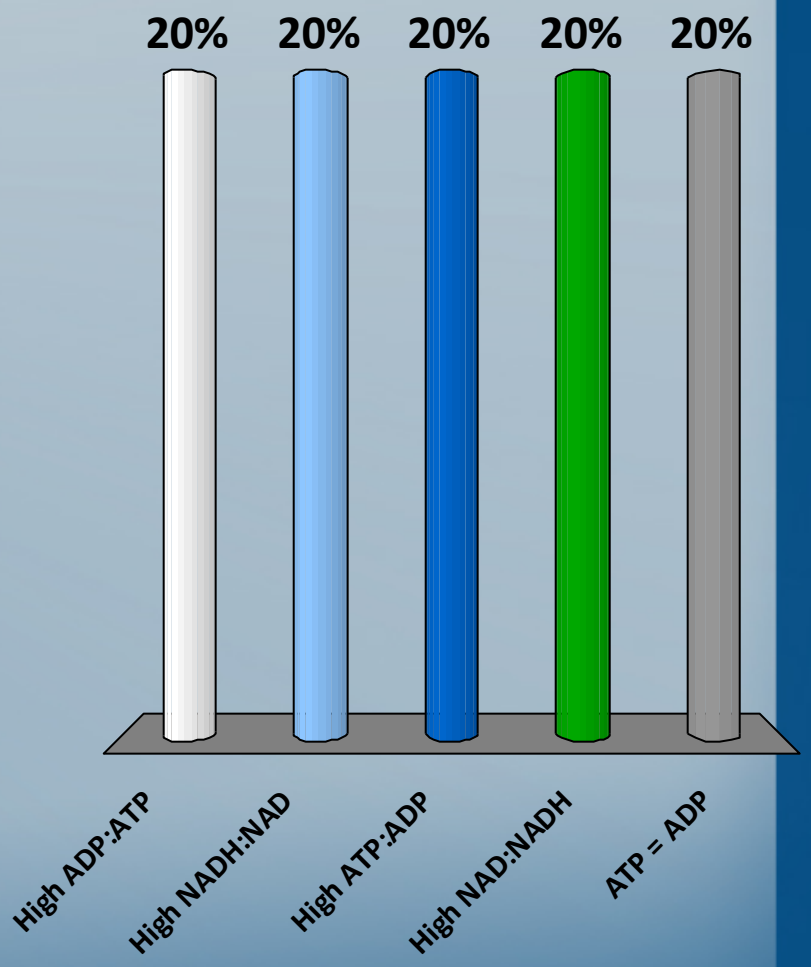
- Total available genes are the same for each cell but only a fraction of them are expressed (effective "genome" of that cell type).
- Of these expressed genes, some are used throughout the life of the cell but others (ie control of cell timing) are present only transiently. The set of proteins recovered at any moment in the life of a cell is called the "proteome."
- The complex set of small molecules in a cell represents its "metabolome." The metabolome is constantly changing. Maintaining the elements of the metabolome within certain ranges is called "homeostasis."

•Maintenance of Homeostasis

- In humans about 4,000 genes (12% of total) encode regulatory proteins including a variety of receptors, regulators of gene expression, and more than 500 different protein kinases.
- In many cases, the regulatory mechanisms overlap, one enzyme is subject to regulation by several different mechanisms.
- Homeostasis in living organisms occurs far from equilibrium which is a condition referred to as “steady state.” This requires expenditure of energy which is ATP.

Proliferating cells will have:

1. High ADP:ATP
2. High NADH:NAD
3. High ATP:ADP
4. High NAD:NADH
5. ATP = ADP



Importance of ATP as Energy Source

- In a typical cell, ATP is consumed within I minute of its formation
- Although total ATP in the body is only about 100g, the TURNOVER is very high
- For example a resting human consumes about 40 Kg of ATP in 24 hrs
- During strenuous exercise the rate of utilization of ATP may be as high as 0.5 Kg/min and for a 2 hr run, 60 Kg (132#) are utilized
- Motion, active transport, biosynthesis, etc require ATP as well. On the average an individual turns over his body weight in ATP every day.
- Clearly mechanisms for regenerating ATP are vital

- Ranges can be broad such as glucose (to be discussed later) or narrow such as intracellular ATP concentration.
- Example of ATP control is the “Energy Charge Value”

$$\text{Energy charge} = \tfrac{1}{2}\left(\frac{2\,[\text{ATP}] + [\text{ADP}]}{[\text{ATP}] + [\text{ADP}] + [\text{AMP}]}\right)$$

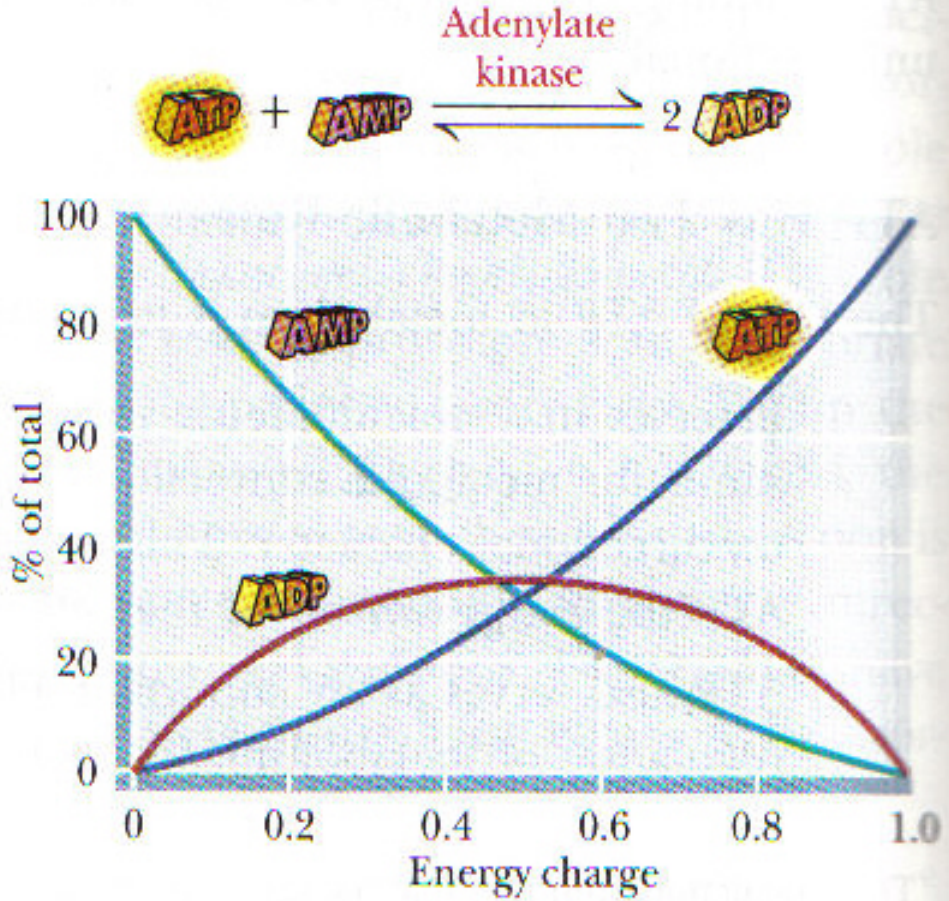


***Figure* 25.5** Relative concentrations of AMP, ADP, and ATP as a function of energy charge. (This graph was constructed assuming that the adenylate kinase reaction is at equilibrium and that $\Delta G^{\circ\prime}$ for the reaction is -473 J/mol; $K_{eq} = 1.2$.)

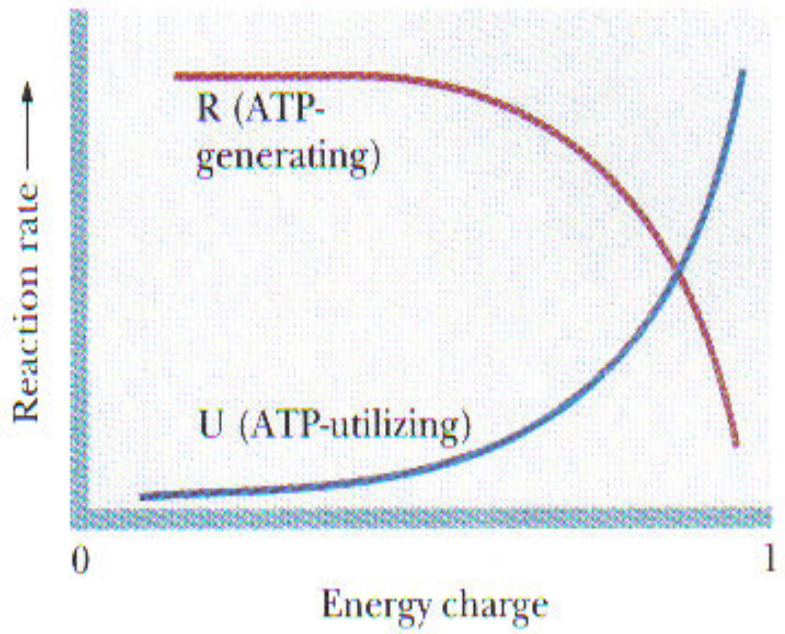


***Figure* 25.6** Responses of regulatory enzymes to variation in energy charge. Enzymes in catabolic pathways have as their ultimate metabolic purpose the regeneration of ATP from ADP. Such enzymes show an **R** pattern of response to energy charge. Enzymes in biosynthetic pathways utilize ATP to drive anabolic reactions; these enzymes follow the **U** curve in response to energy charge.

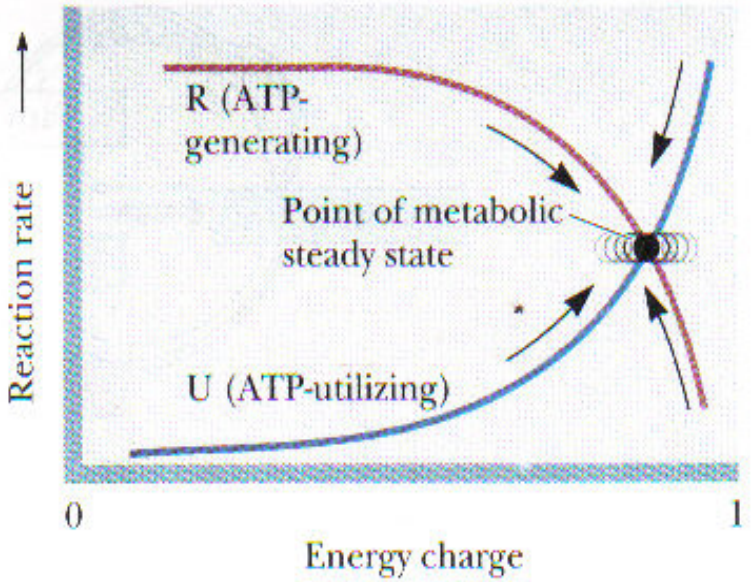


***Figure* 25.7** The oscillation of energy charge (E.C.) about a steady-state value as a consequence of the offsetting influences of **R** and **U** processes on the production and consumption of ATP. As E.C. increases, the rates of **R** reactions decline, but **U** reactions go faster. ATP is consumed, and E.C. drops. Below the point of intersection, **R** processes are more active and **U** processes are slower, so E.C. recovers. Energy charge oscillates about a steady-state value determined by the intersection point of the **R** and **U** curves.

•The flux through an enzyme-catalyzed reaction can be modulated b changes in the **number** of enzyme molecules or the **activity** of the enzyme.

•Such changes occur on a time scale from milliseconds to many hours in response to signals within and outside the cell.

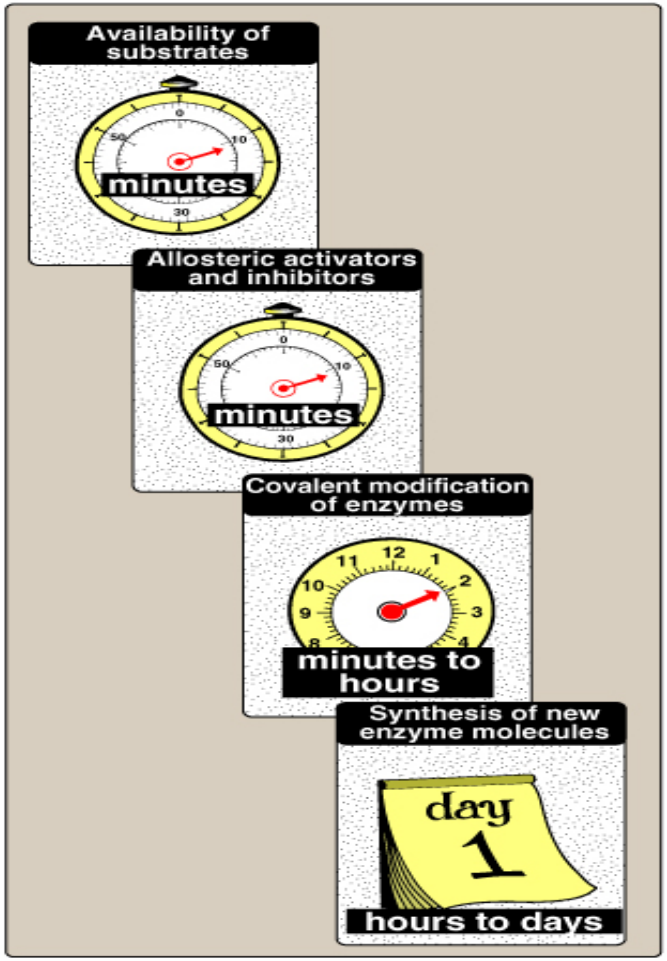


Figure 24.1
Control mechanisms of metabolism and some typical response times. [Note: Response times may vary according to the nature of the stimulus and from tissue to tissue.]

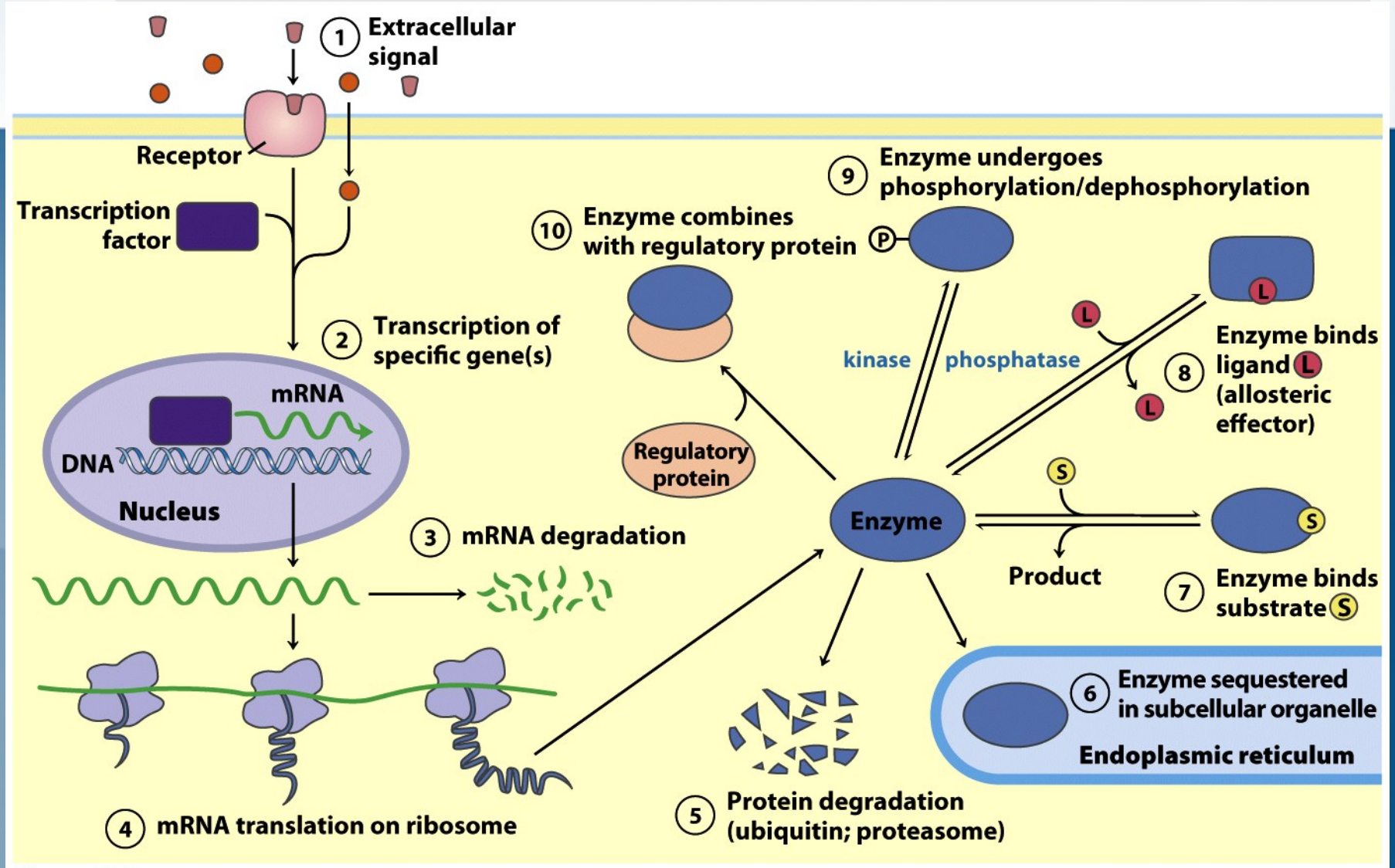


Figure 15-2

Lehninger Principles of Biochemistry, Fifth Edition

TABLE 15–1 Average Half-life of Proteins in Mammalian Tissues

Tissue	Half-life (days)
Liver	0.9
Kidney	1.7
Heart	4.1
Brain	4.6
Muscle	10.7

Table 15-1
Lehninger Principles of Biochemistry, Fifth Edition

Allosteric Effects

Involve Rate-determining Reactions

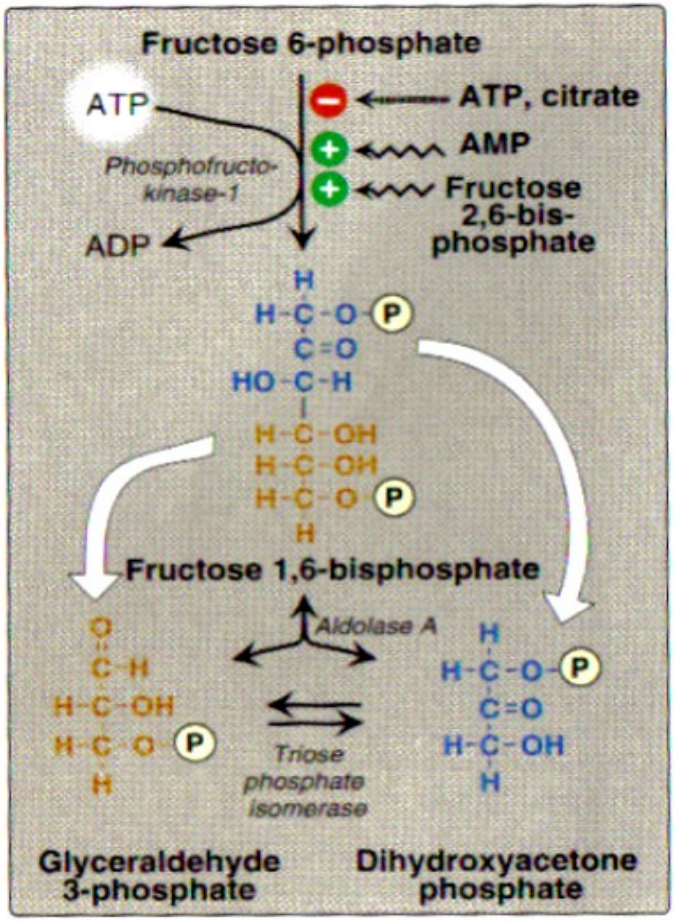


Figure 8.16
Energy investment phase (continued): Conversion of fructose 6-phosphate to triose phosphates.

Covalent Modification

Addition or removal of phosphate groups from specific threonine, serine or tyrosine residues

In the fed state most are in dephosphorylated form which are ACTIVE.

Exceptions are: glycogen phosphorylase, fructose bis phosphate phosphatase and hormone sensitive lypase of adipose tissue which are INACTIVE

In addition to phosphoylation, acylation of lysine residues in enzymes is being recognized as a regulator of metabolic pathways

Induction and Repression of Enzyme Systems

- Alterations in the number of active sites

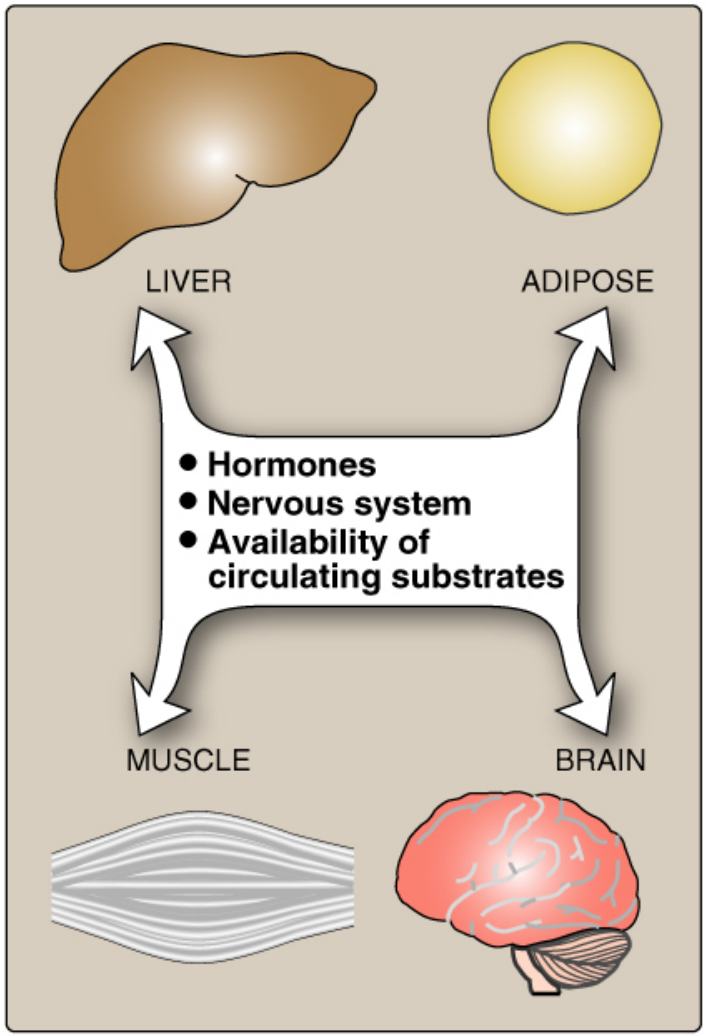


Figure 23.1
Mechanisms of communication between four major tissues.

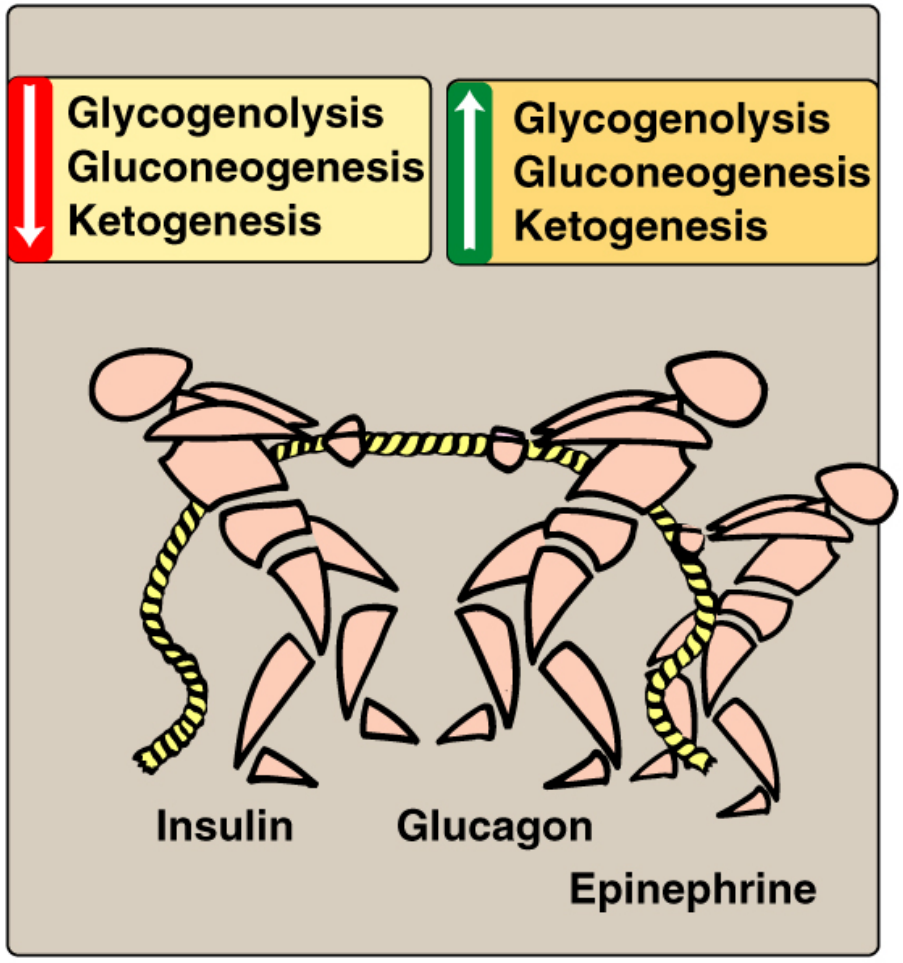


Figure 23.10
Opposing actions of insulin and glucagon plus epinephrine.

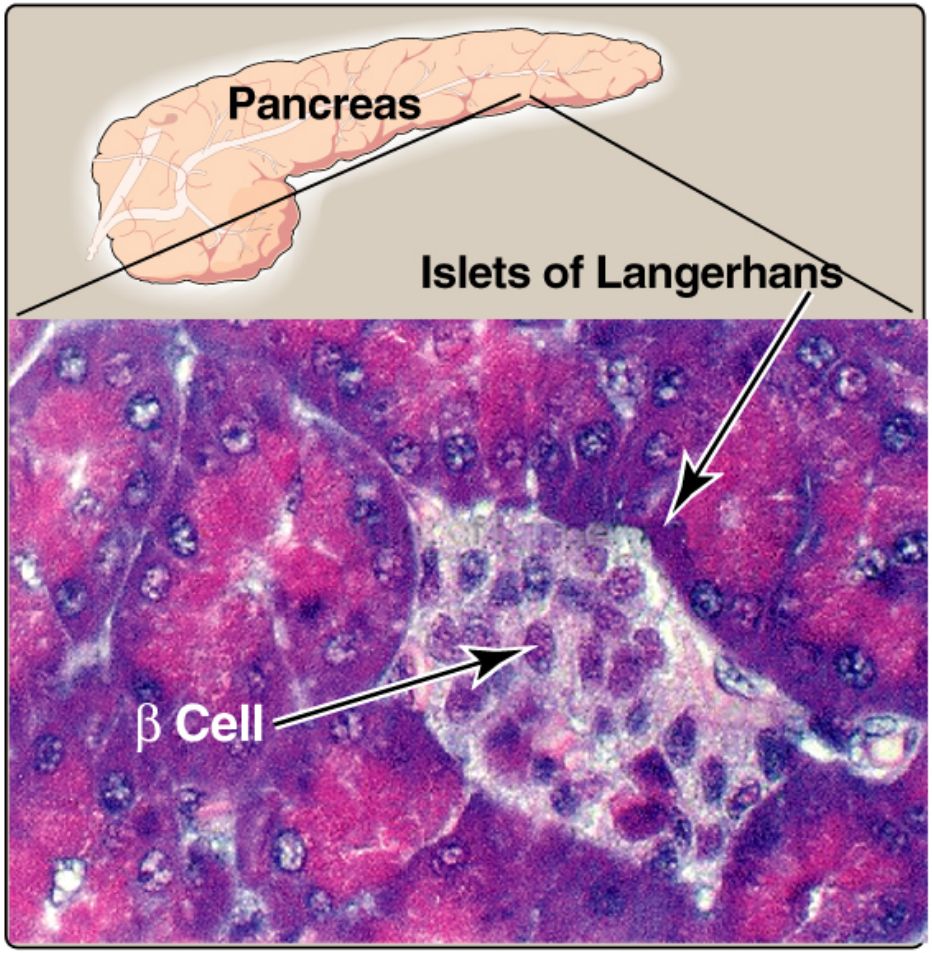


Figure 23.2
Islets of Langerhans.

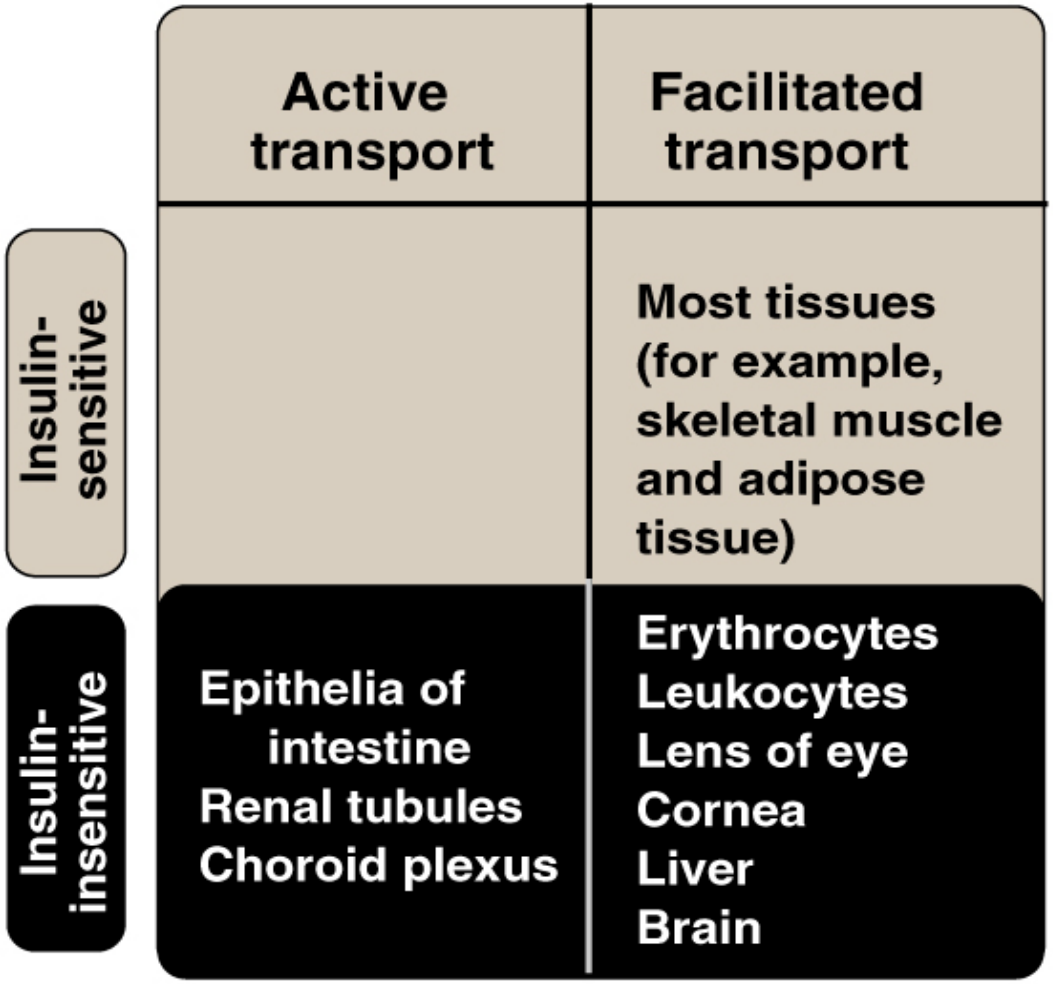
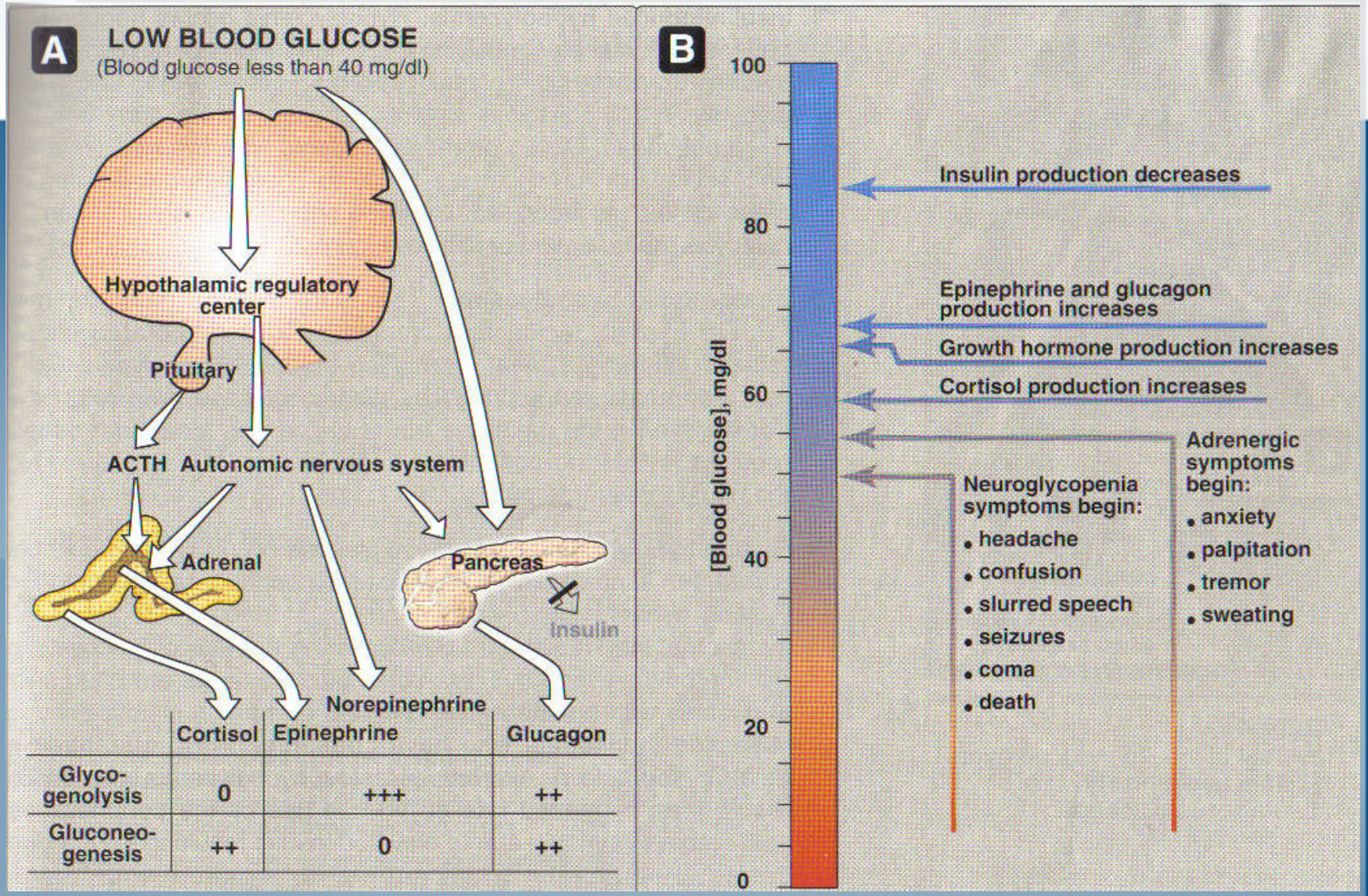


Figure 23.9
Characteristics of glucose transport in various tissues.

Table 22–5 Available metabolic fuels in a normal 70 kg man and in an obese man at the beginning of a fast

Type of fuel	Weight (kg)	Caloric equivalent (thousands of kcal (kJ))	Estimated survival time (months)*
Normal 70 kg man:			
Triacylglycerols (adipose tissue)	15	141 (589)	
Proteins (mainly muscle)	6	24 (100)	
Glycogen (muscle, liver)	0.225	0.90 (3.8)	
Circulating fuels (glucose, fatty acids, triacylglycerols, etc.)	0.023	0.10 (0.42)	
Total		166 (694)	3
Obese man:			
Triacylglycerols (adipose tissue)	80	752 (3,140)	
Proteins (mainly muscle)	8	32 (134)	
Glycogen (muscle, liver)	0.23	0.92 (3.8)	
Circulating fuels	0.025	0.11 (0.46)	
Total		785 (3,280)	14

* Survival time is calculated on the assumption of a basal energy expenditure of 1,800 kcal/day.


A
LOW BLOOD GLUCOSE
(Blood glucose less than 40 mg/dl)
Hypothalamic regulatory center
Pituitary
ACTH
Autonomic nervous system
Adrenal
Pancreas
Insulin
Norepinephrine
Cortisol
Epinephrine
Glucagon
Glyco-genolysis
0
+++
++
Gluconeo-genesis
++
0
++
B
[Blood glucose], mg/dl
100
80
60
40
20
0
Insulin production decreases
Epinephrine and glucagon production increases
Growth hormone production increases
Cortisol production increases
Neuroglycopenia symptoms begin:
• headache
• confusion
• slurred speech
• seizures
• coma
• death
Adrenergic symptoms begin:
• anxiety
• palpitation
• tremor
• sweating

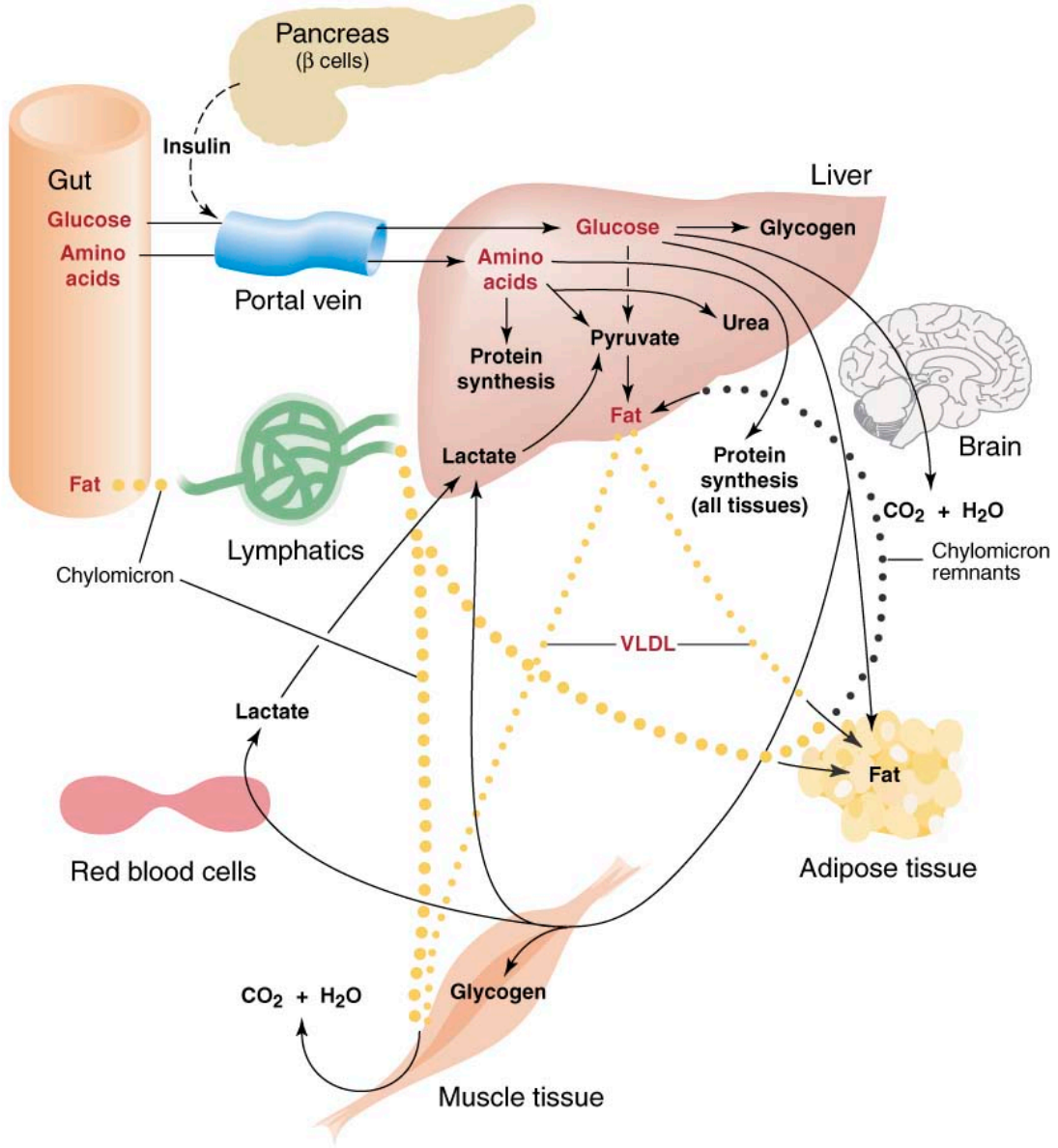


Figure 22.2. Disposition of glucose, amino acids, and fat by various tissues in the well-fed state.

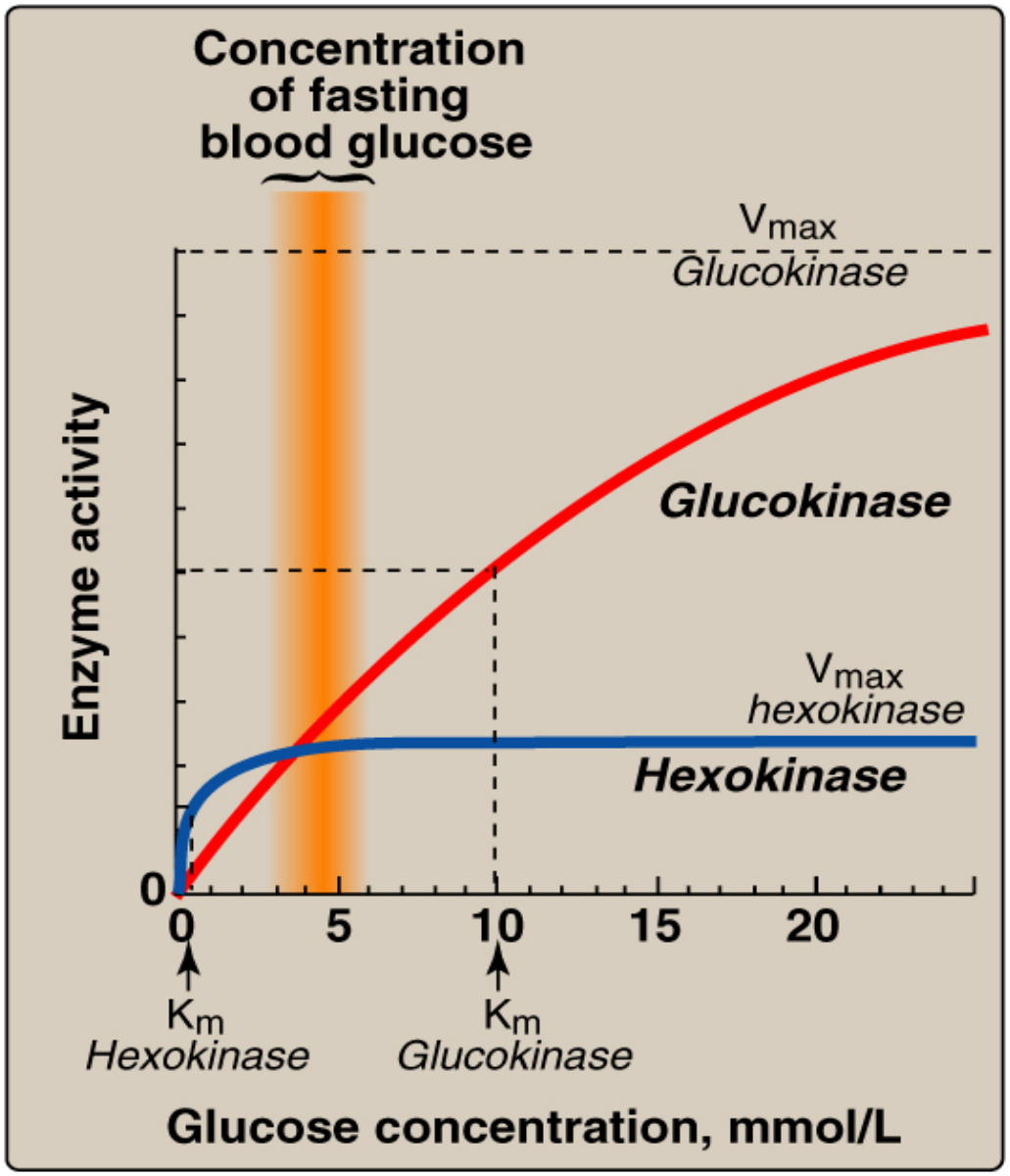


Figure 8.13
Effect of glucose concentration on the rate of phosphorylation catalyzed by *hexokinase* and *glucokinase*.

Possible Route for Diabetes Trtmt

While hexokinase is produced in most tissues, glucokinase is found only in liver and pancreas. Since glucokinase has higher Km than hexo-

kinase, it functions only when glucose concs. are high and its high Vmax allows the liver to take up large amounts so blood levels lower.

Pharmaceutical companies are currently searching for molecules that could activate glucokinase making it more efficient.

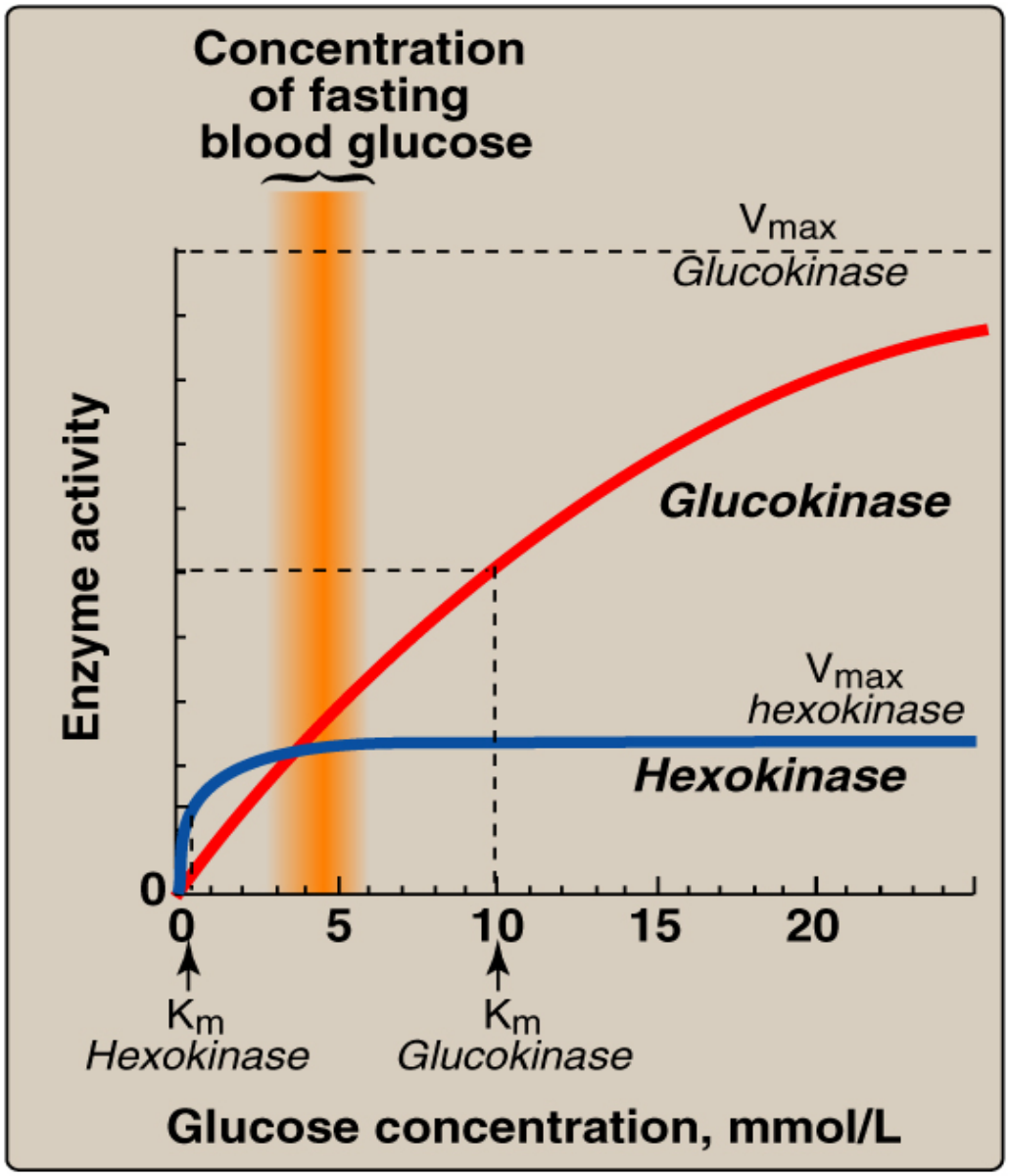


Figure 8.13
Effect of glucose concentration on the rate of phosphorylation catalyzed by *hexokinase* and *glucokinase*.

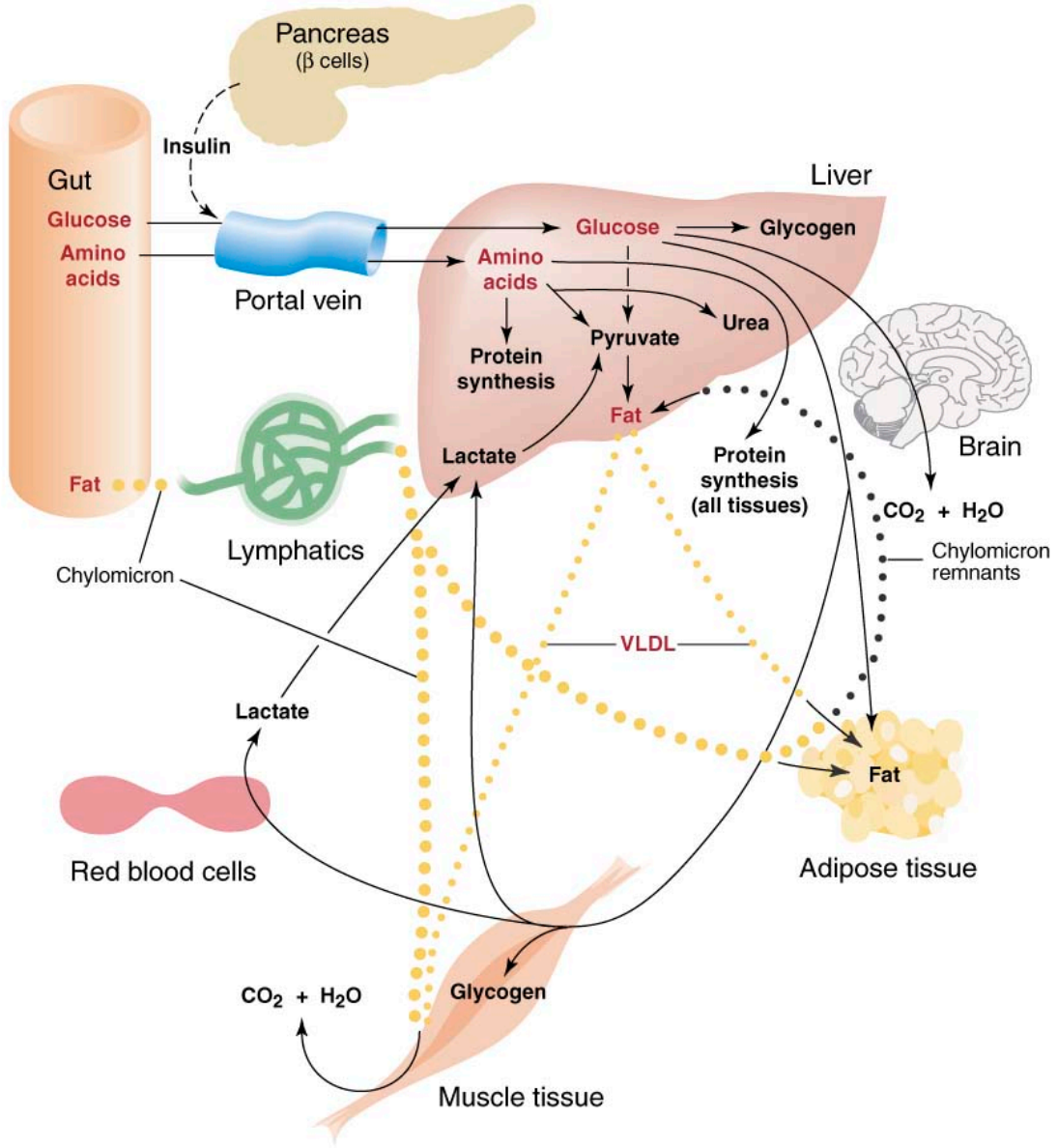


Figure 22.2. Disposition of glucose, amino acids, and fat by various tissues in the well-fed state.

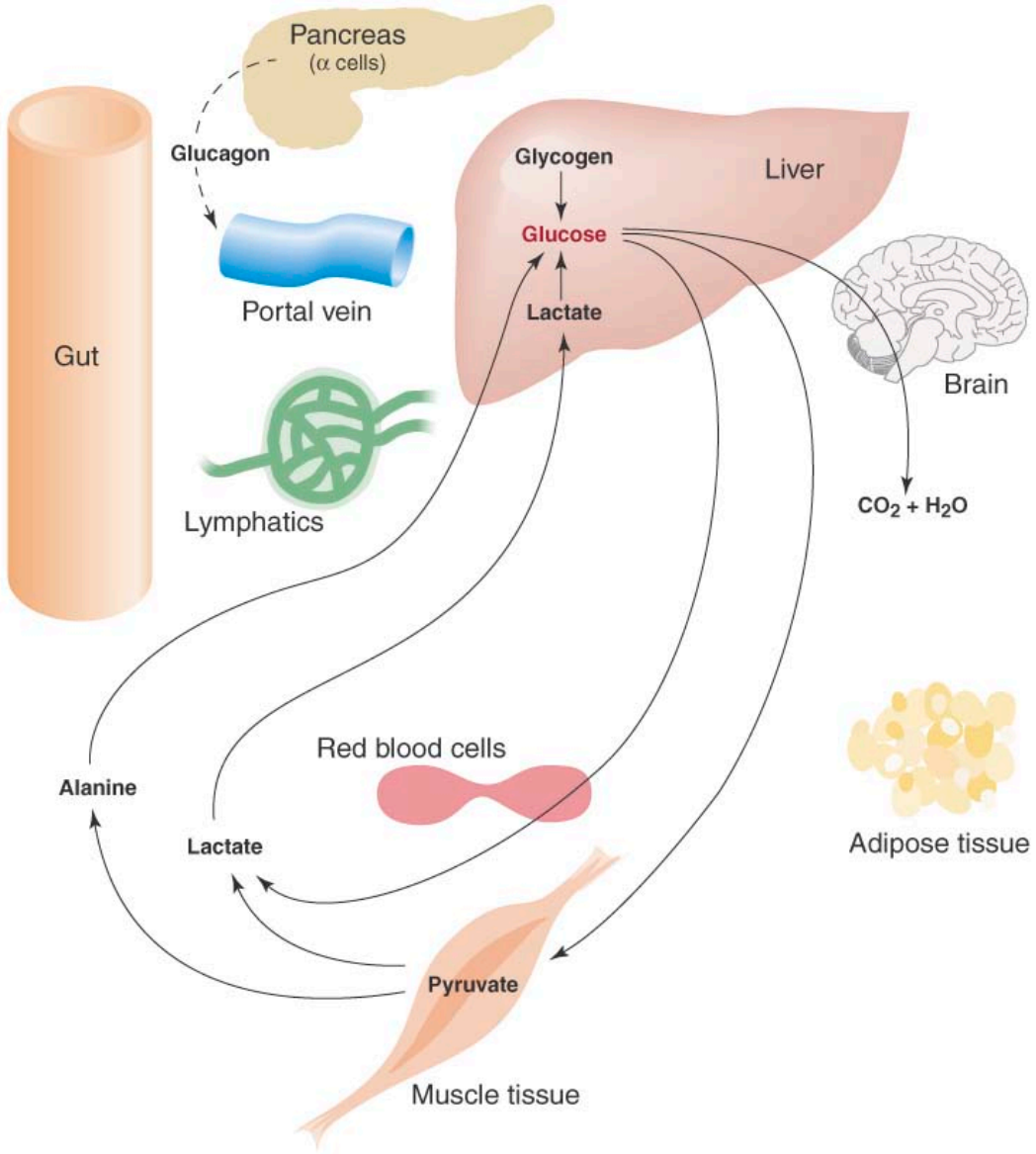


Figure 22.3. Metabolic interrelationships of major tissues in early fasting state.

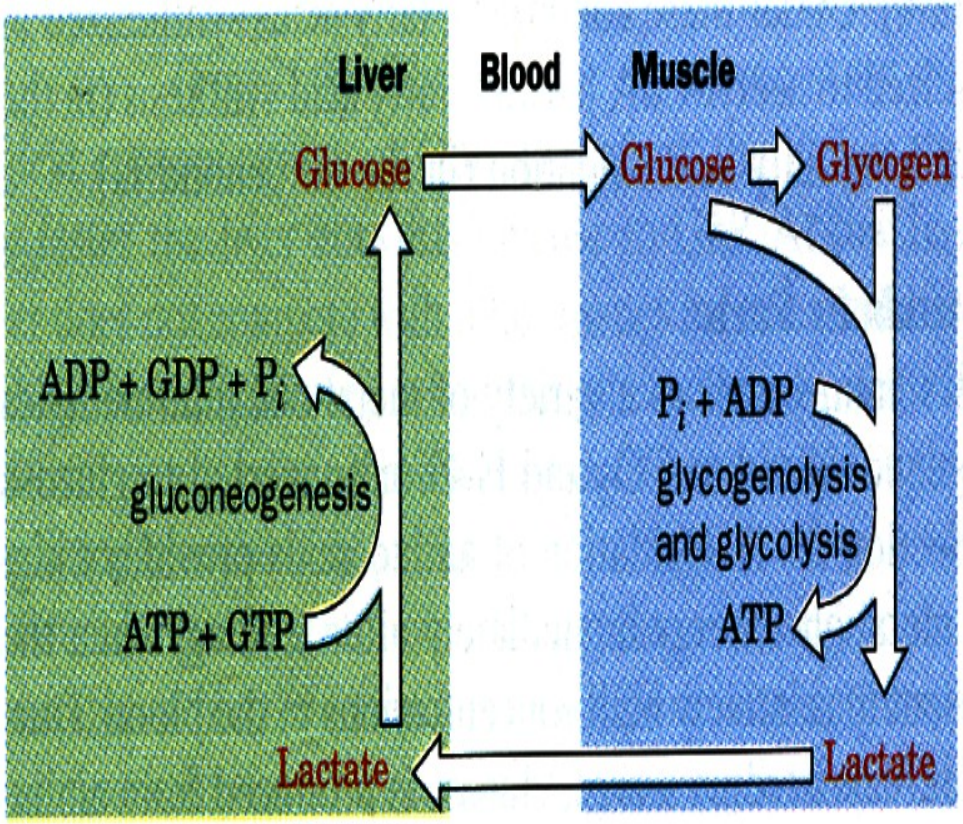


Figure 21-5. **The Cori cycle.** Lactate produced by muscle glycolysis is transported by the bloodstream to the liver, where it is converted to glucose by gluconeogenesis. The bloodstream carries the glucose back to the muscle, where it may be stored as glycogen. ✺ **See the Animated Figures.**

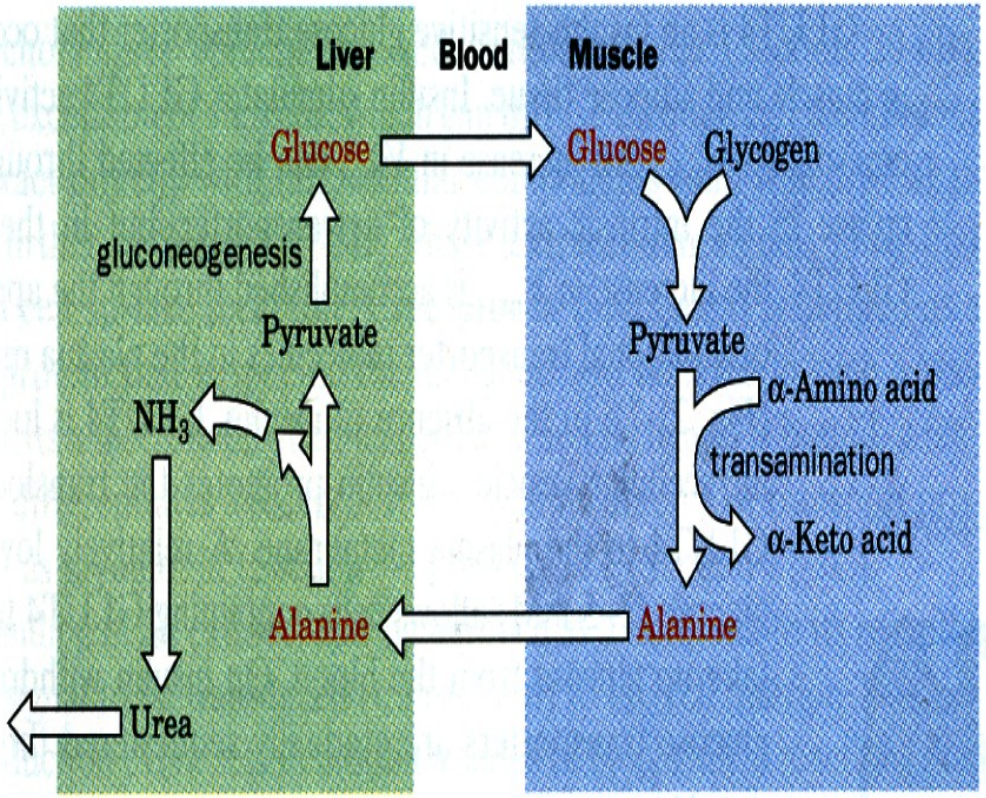


Figure 21-6. **The glucose–alanine cycle.** Pyruvate produced by muscle glycolysis is the amino-group acceptor for muscle aminotransferases. The resulting alanine is transported by the bloodstream to the liver, where it is converted back to pyruvate (its amino group is disposed of via urea synthesis). The pyruvate is a substrate for gluconeogenesis, and the bloodstream carries the resulting glucose back to the muscles.

✺ **See the Animated Figures.**

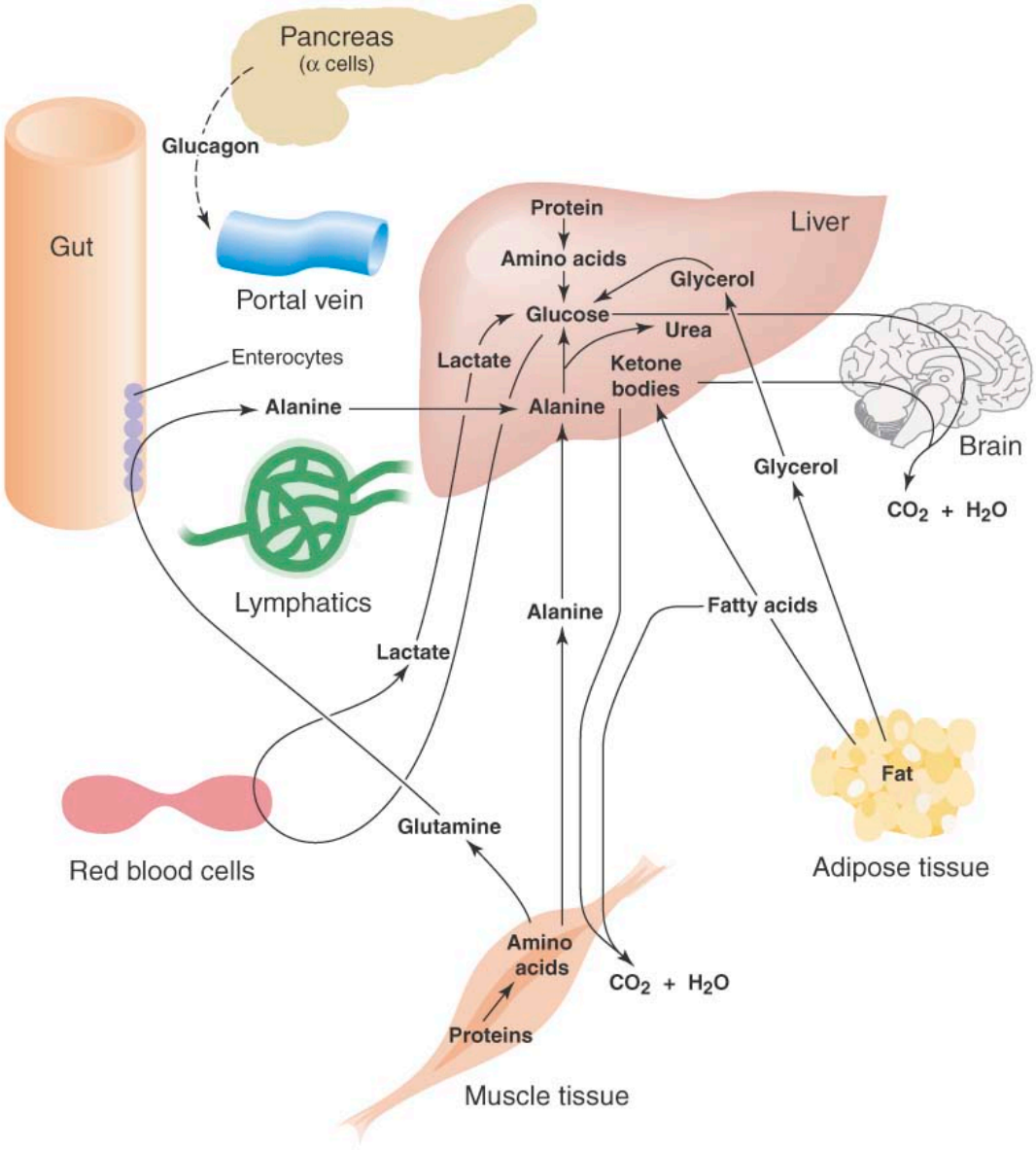


Figure 22.4. Metabolic interrelationships of major tissues in fasting state.

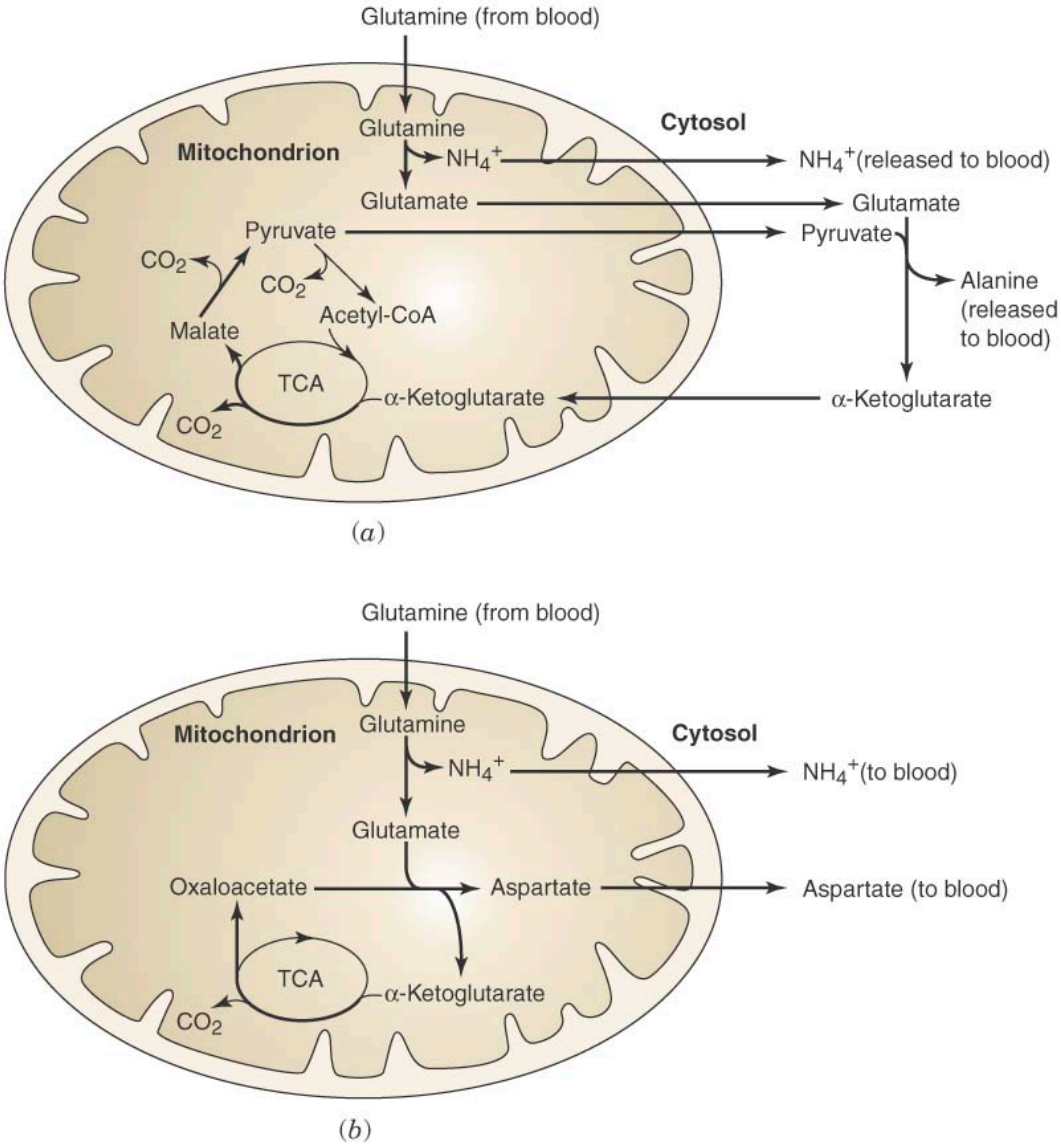


Figure 22.5. Glutamine catabolism by rapidly dividing cells. Part (*a*) redrawn from Duée, P.-H., Darcy-Vrillon, B., Blachier, F., and Morel, M.-T. Fuel selection in intestinal cells. *Proc. Nutr. Soc*. 54:83, 1995.

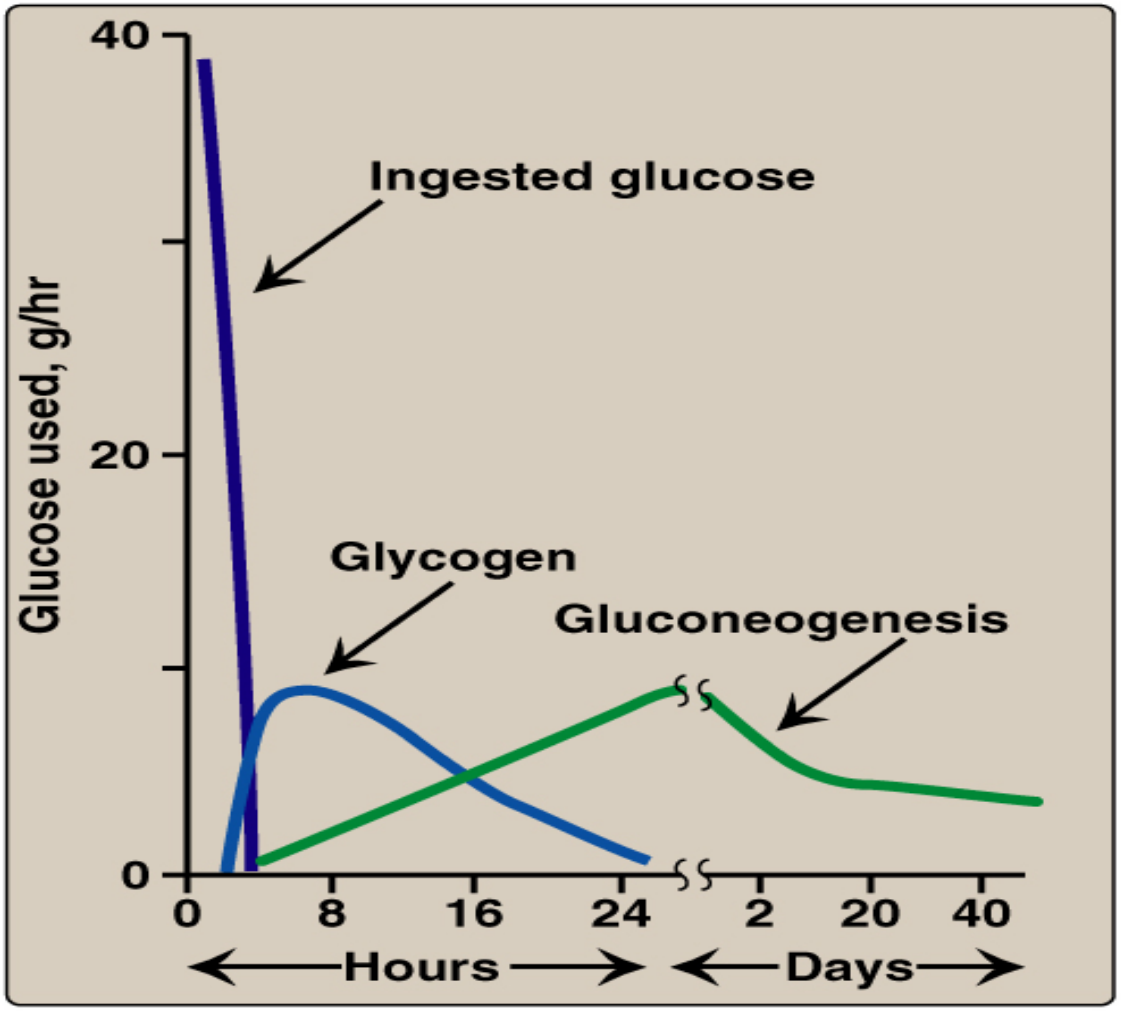


Figure 24.10
Sources of blood glucose after ingestion of 100 g of glucose.

TABLE 20.2 Substrate and Hormone Levels in Blood of Well-Fed, Fasting, and Starving Humans[a]

Hormone or Substrate (units)	*Very Well Fed*	*Postabsorptive 12 h*	*Fasted 3 days*	*Starved 5 weeks*
Insulin (μU mL^{-1})	40	15	8	6
Glucagon (pg mL^{-1})	80	100	150	120
Insulin/glucagon ratio (μU pg^{-1})	0.50	0.15	0.05	0.05
Glucose (mM)	6.1	4.8	3.8	3.6
Fatty acids (mM)	0.14	0.6	1.2	1.4
Acetoacetate (mM)	0.04	0.05	0.4	1.3
β-Hydroxybutyrate (mM)	0.03	0.10	1.4	6.0
Lactate (mM)	2.5	0.7	0.7	0.6
Pyruvate (mM)	0.25	0.06	0.04	0.03
Alanine (mM)	0.8	0.3	0.3	0.1
ATP equivalents (mM)	313	290	380	537

Source: From Ruderman, N. B., Aoki, T. T., and Cahill, G. F. Jr. Gluconeogenesis and its disorders in man. In: R. W. Hanson and M. A. Mehlman (Eds.), *Gluconeogenesis, Its Regulation in Mammalian Species*. New York: Wiley, 1976, p. 515.

[a]Data are for normal-weight subjects except for the 5-week starvation values, which are from obese subjects undergoing therapeutic starvation. ATP equivalents were calculated on the basis of the ATP yield expected on complete oxidation of each substrate to CO_2 and H_2O: 38 molecules of ATP for each molecule of glucose; 144 for the average fatty acid (oleate); 23 for acetoacetate; 26 for β-hydroxybutyrate; 18 for lactate; 15 for pyruvate; and 13 (corrected for urea formation) for alanine.

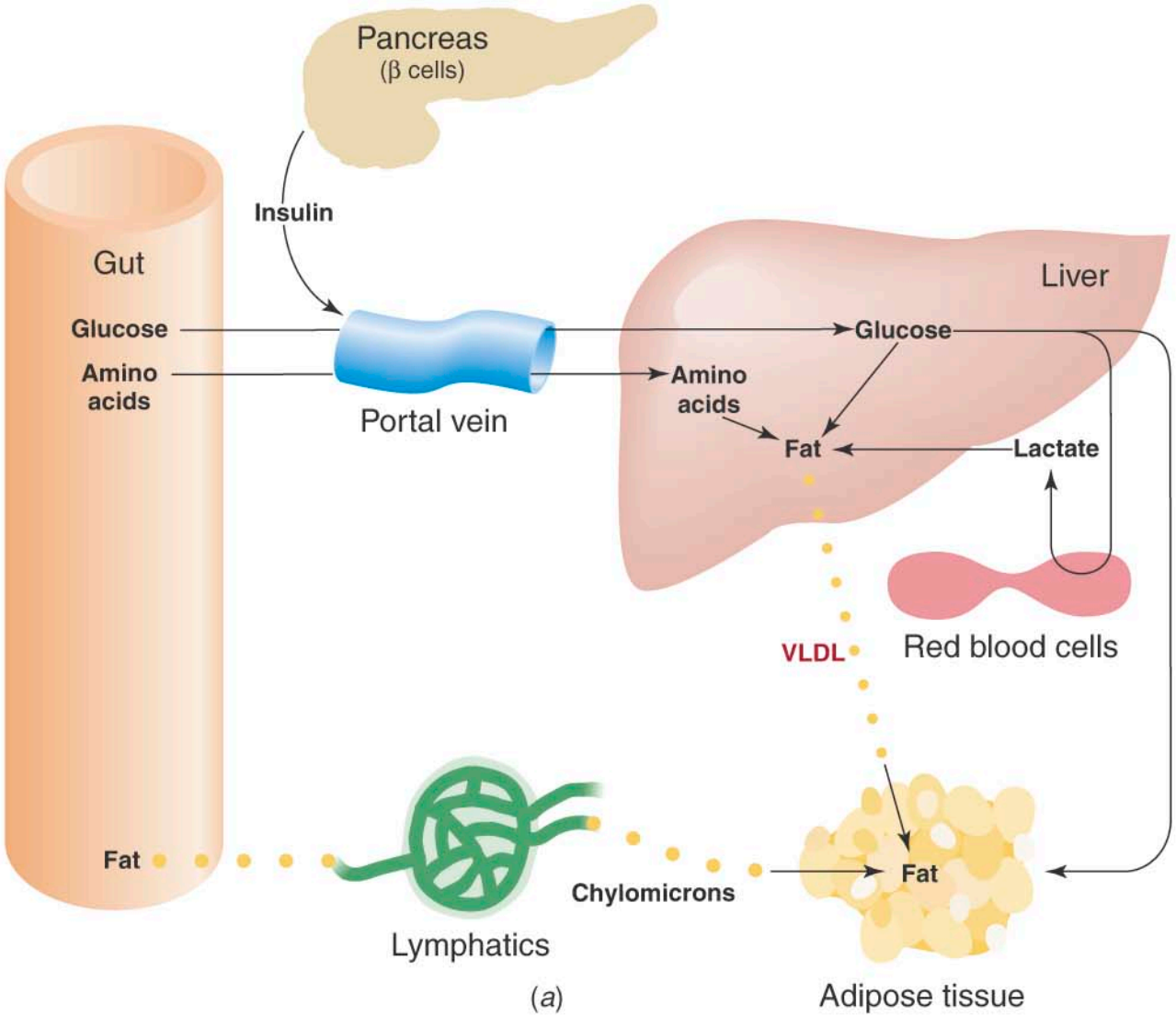


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*a*) Obesity.

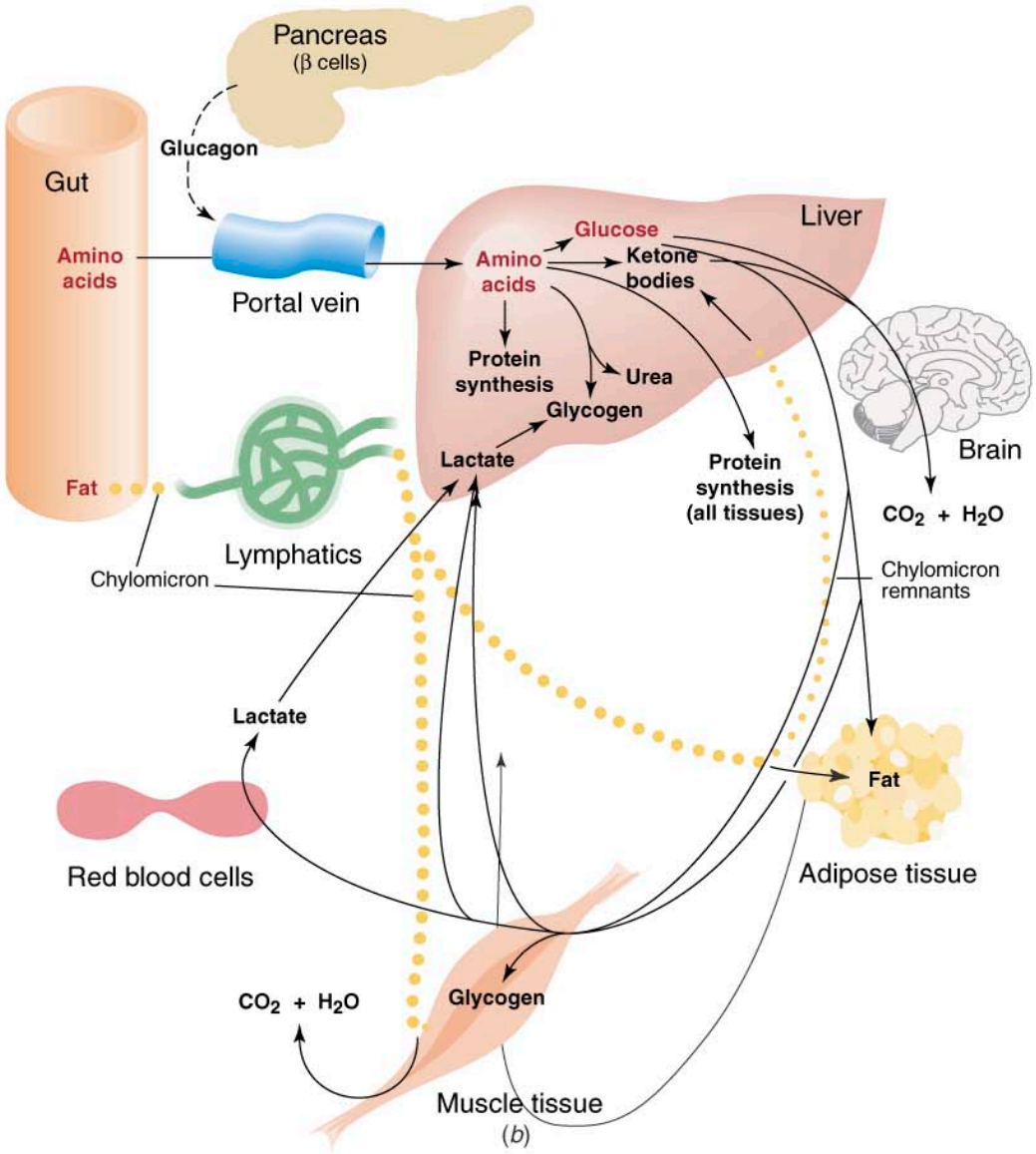
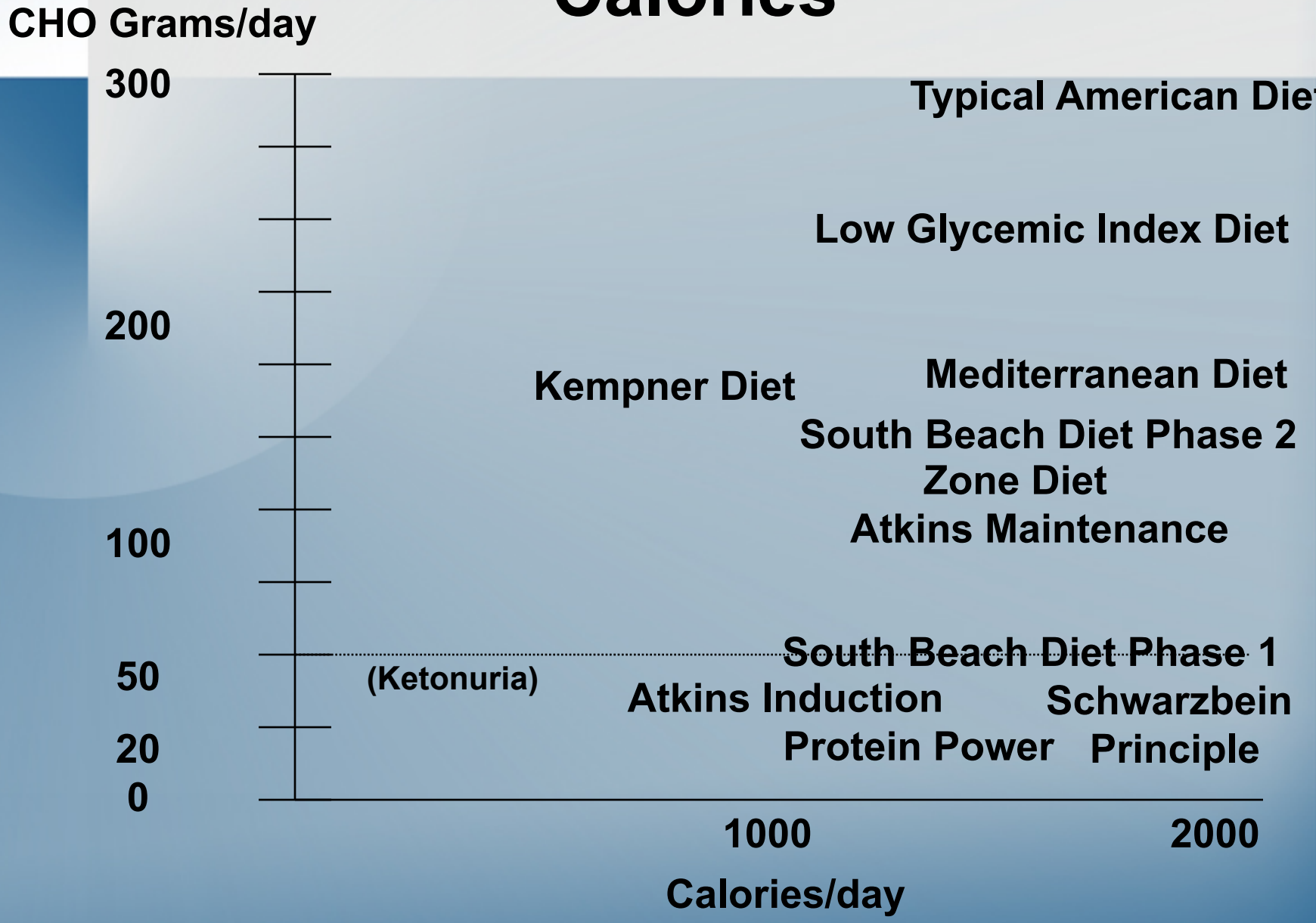


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*b*) Dieting.

Diets, Carbohydrates and Calories



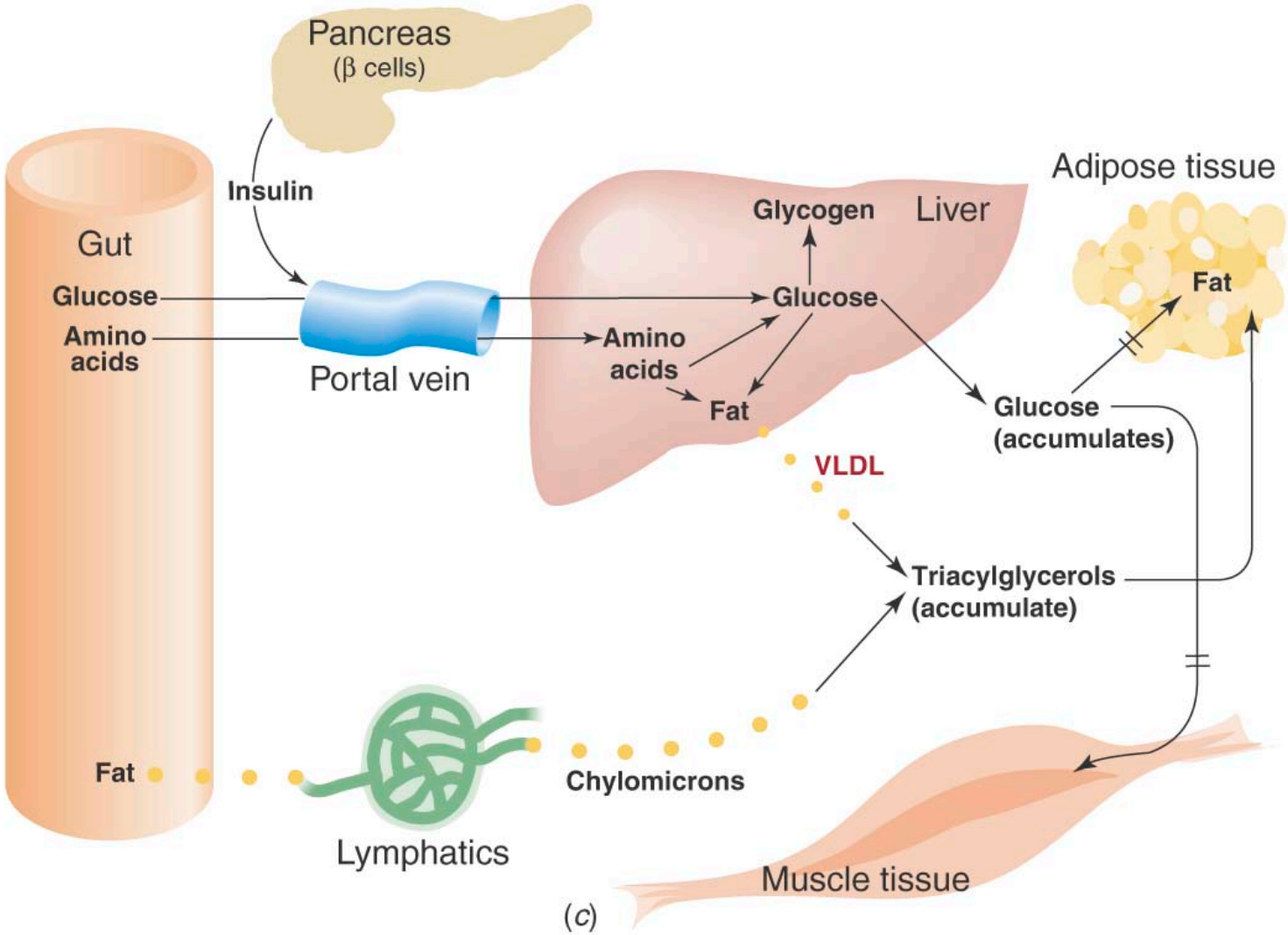


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*c*) Type 2 diabetes mellitus.

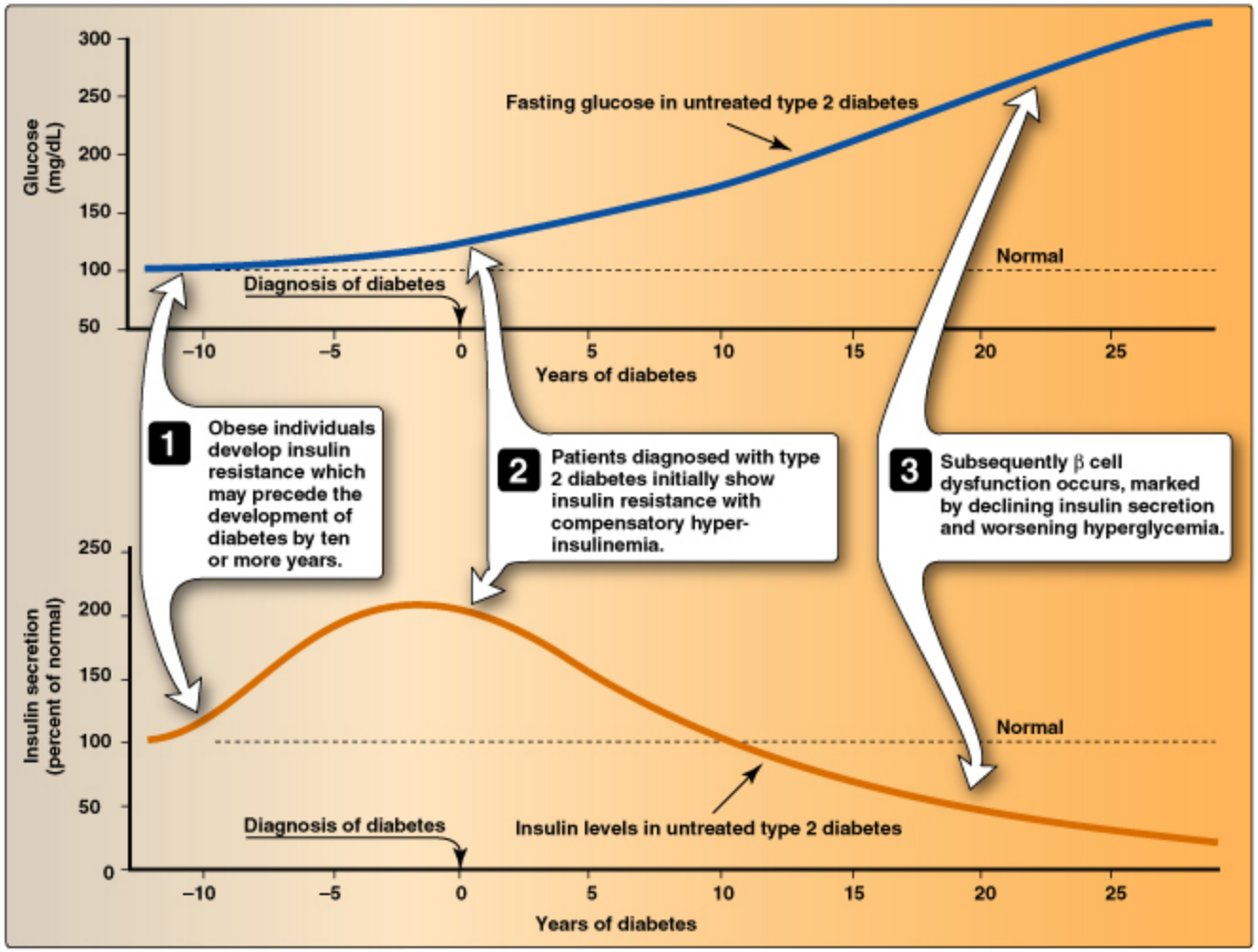


Figure 25.8
Progression of blood glucose and insulin levels in patients with type 2 diabetes.

Duration of Excess Weight and Risk of Diabetes

Ref: Lee JM et al Arch Pediatr and Adoles Med Sept 5, 2011

- Longitudinal survey of 8000 young adults – BMI's taken annually from 1981 til 2006 and diabetes status evaluated.
- Excess BMI yrs calculated by subtracting reference BMI (25) from actual BMI and cumulating sums for study duration.
- A higher level of excess BMI was associated with increased risk of diabetes. For example, an individual with 200 excess BMI-years had 3 times higher odds of developing diabetes than a person with 100 excess BMI-years.
- Conclusion: Excess and sustained BMI in young populations present a great risk for increased prevalence of diabetes.

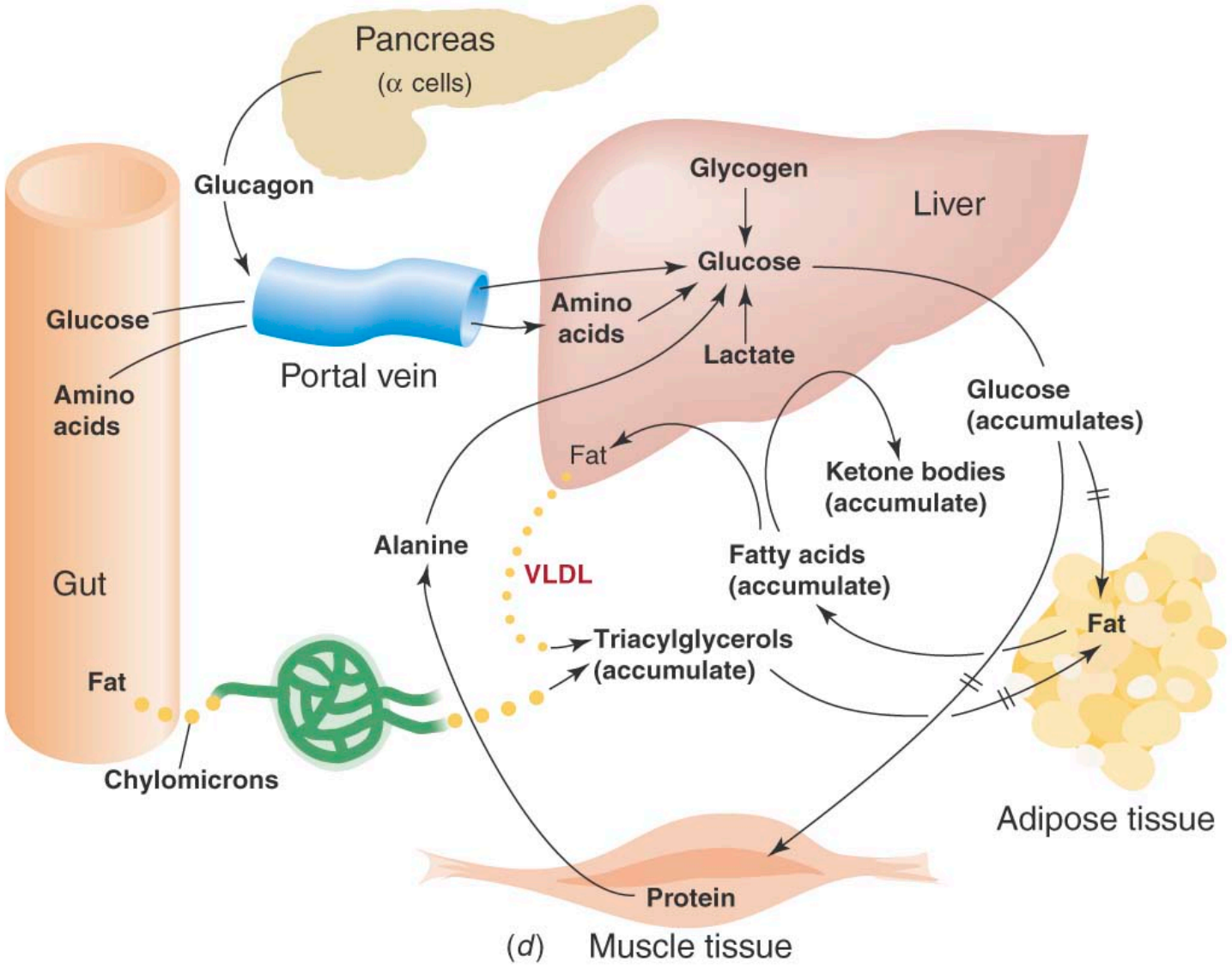


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*d*) Type 1 diabetes mellitus.

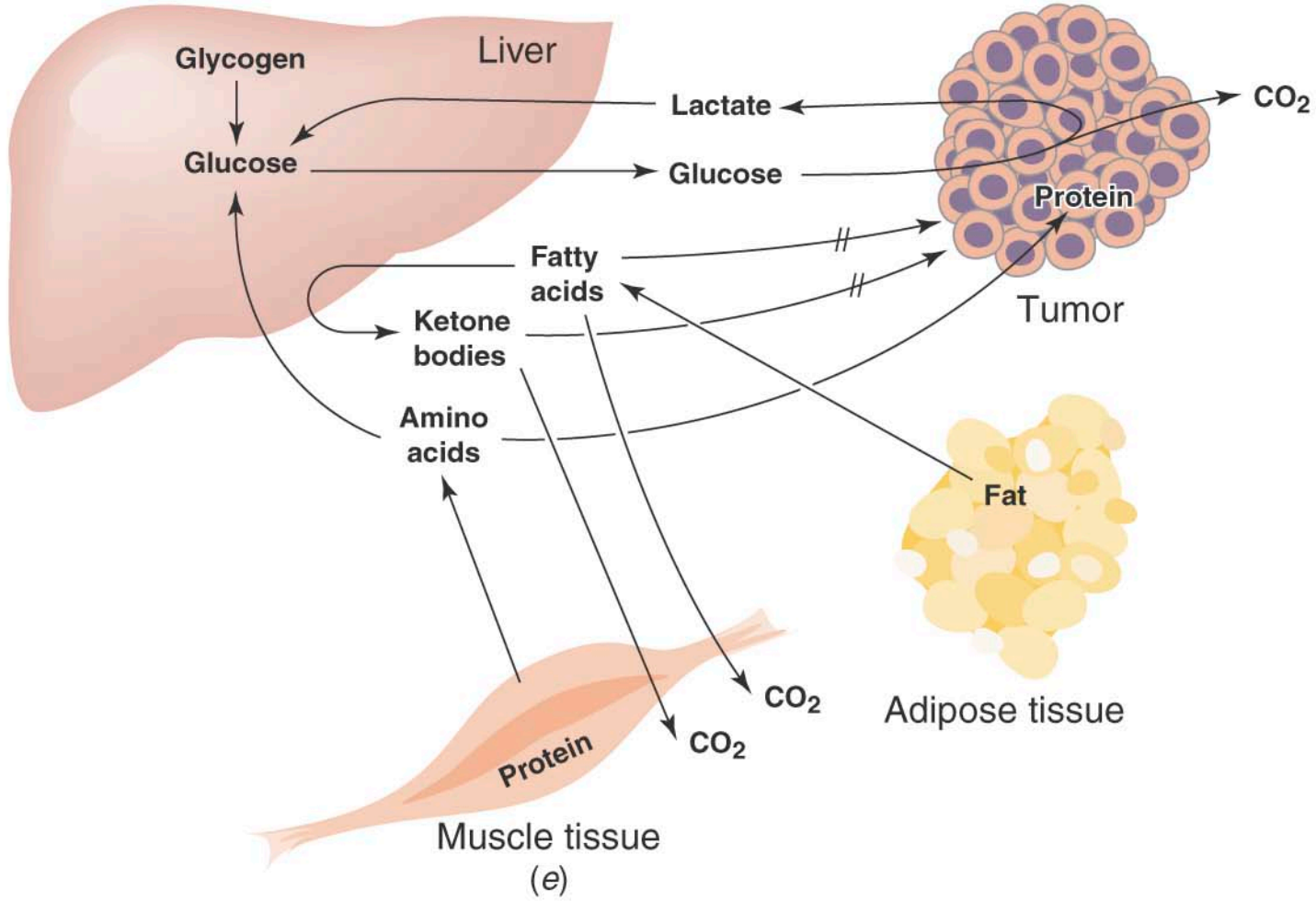


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*e*) Cancer.

Relationship of Cancer and Diabetes and Potential Drug Treatments

- Cancer cells use glucose to generate energy via glycolysis which produces lactic acid even when oxygen is present (Warburg Effect)
- Diabetics have high glucose levels but also high insulin which promote tumor growth
- Both these conditions lead to increased cancer rates
- Treatments are being designed to disrupt cancer cells by depriving them of energy however not all tumors use glycolysis and some normal cells do – a real challenge
- One drug called 2DG, an analog of glucose can be injected and is not metabolized so accumulates in the tumor and interferes with energy production but levels need to be high to compete with natural glucose in the bloodstream.
- Several other approaches are being planned

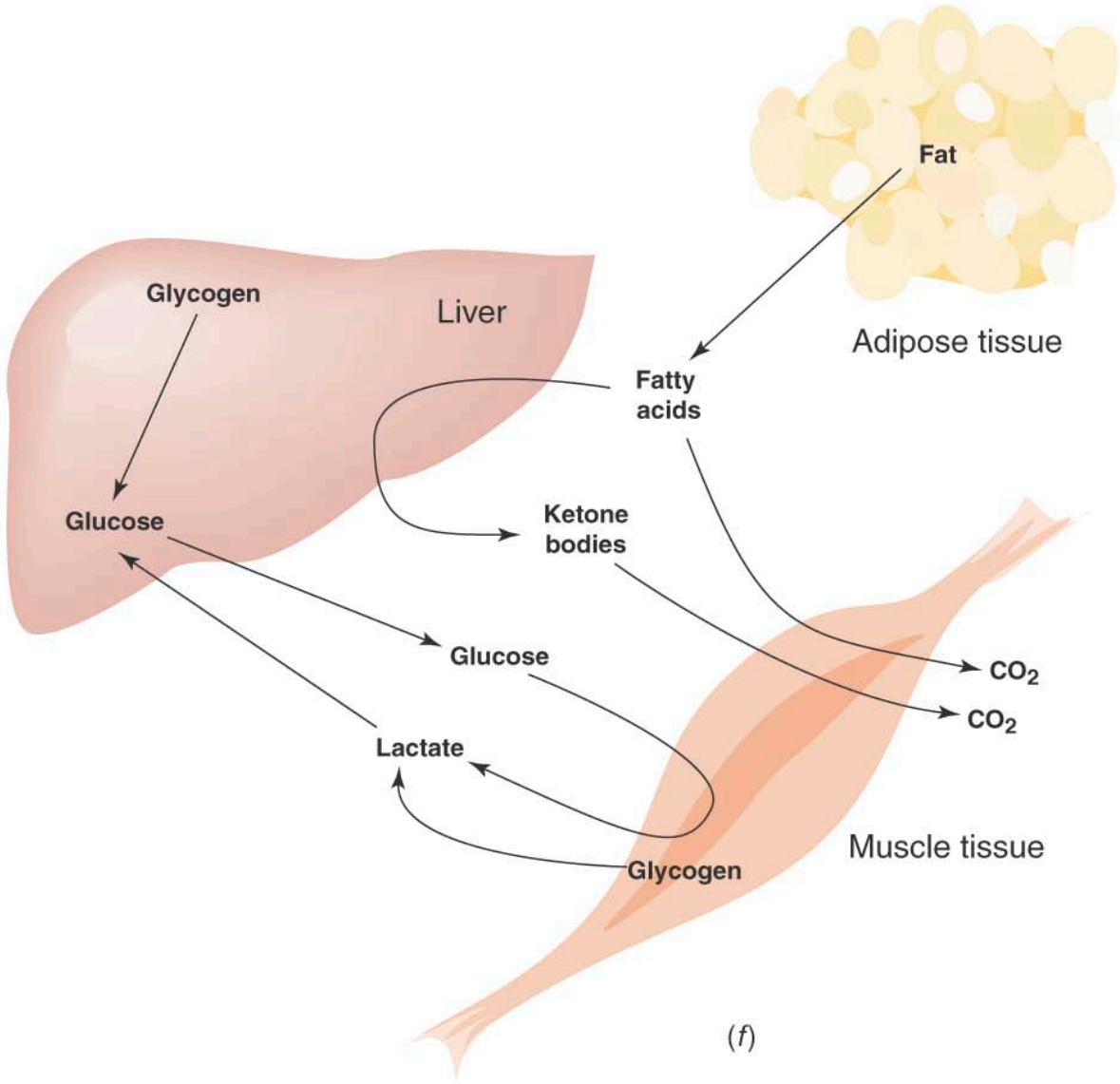


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*f*) Exercise.

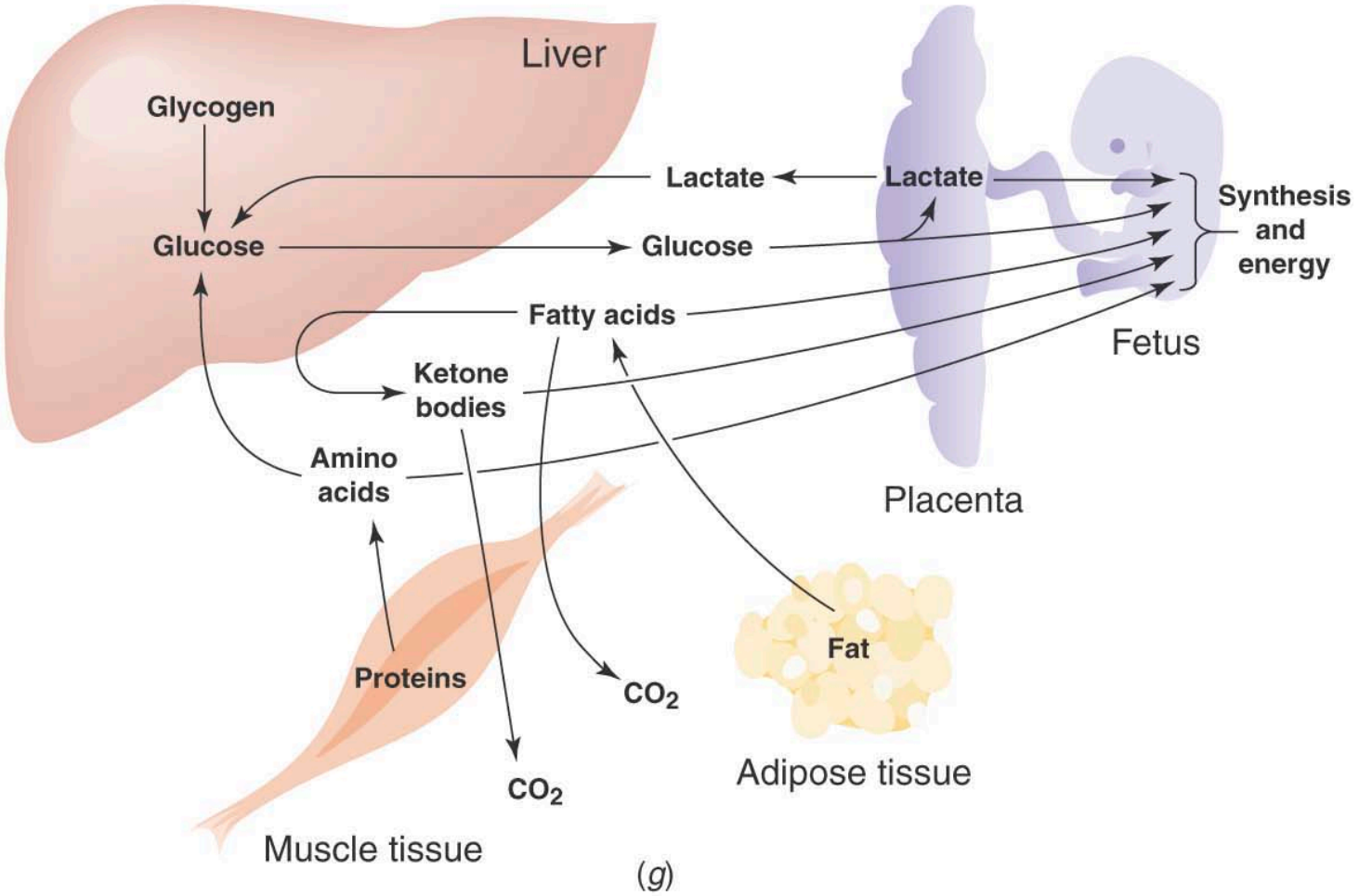


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*g*) Pregnancy.

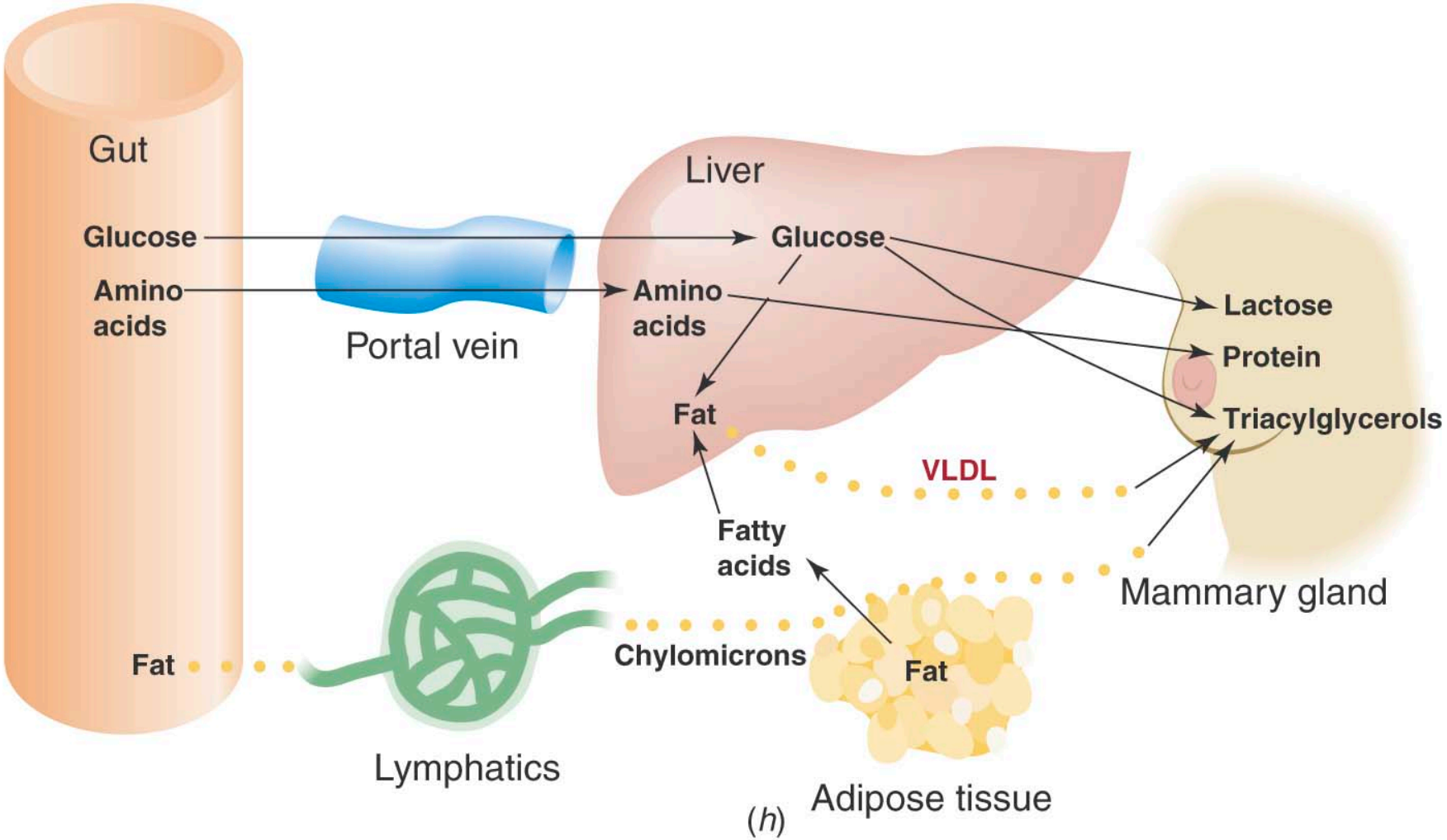


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*h*) Lactation.

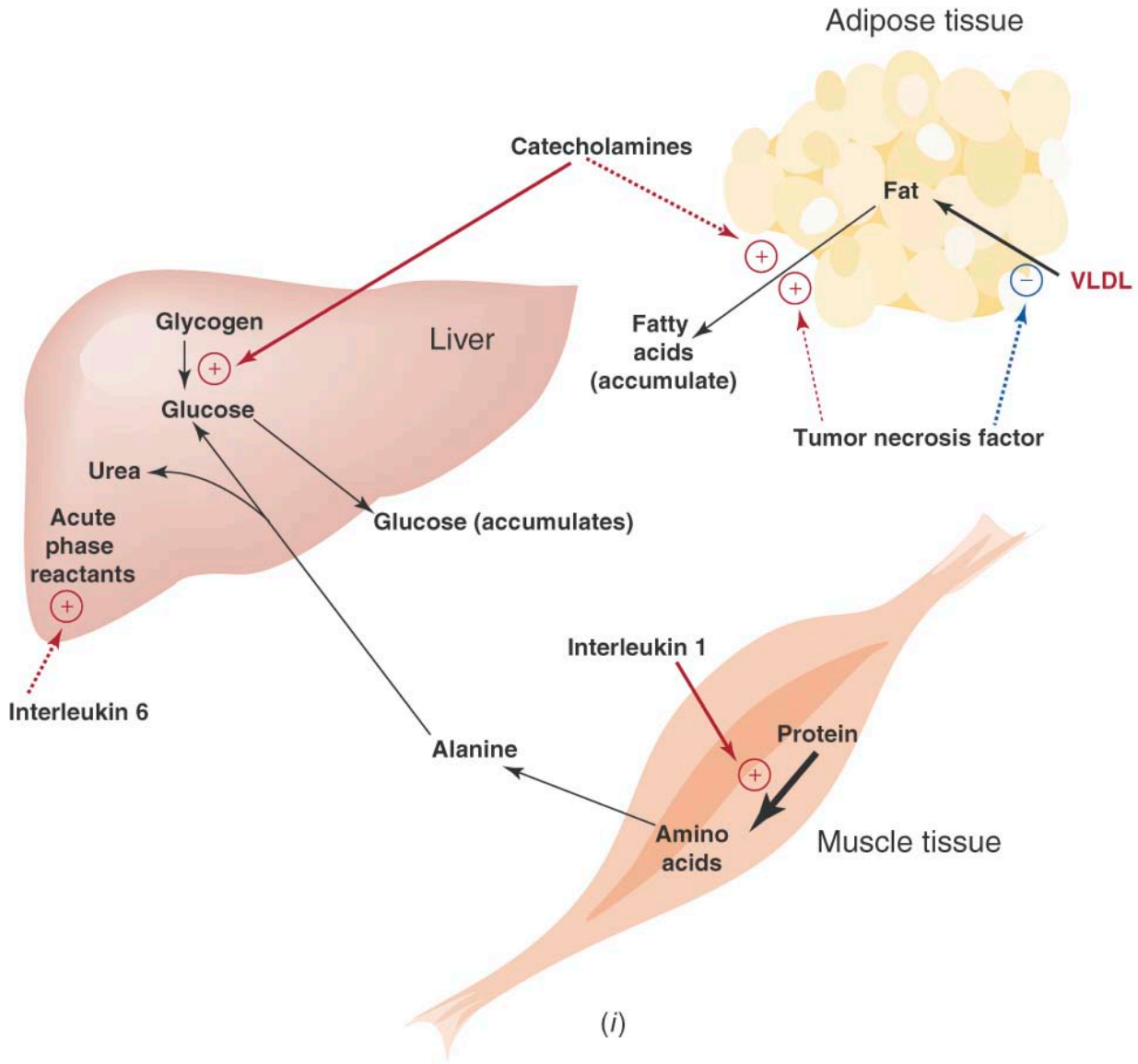


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*i*) Stress and injury.

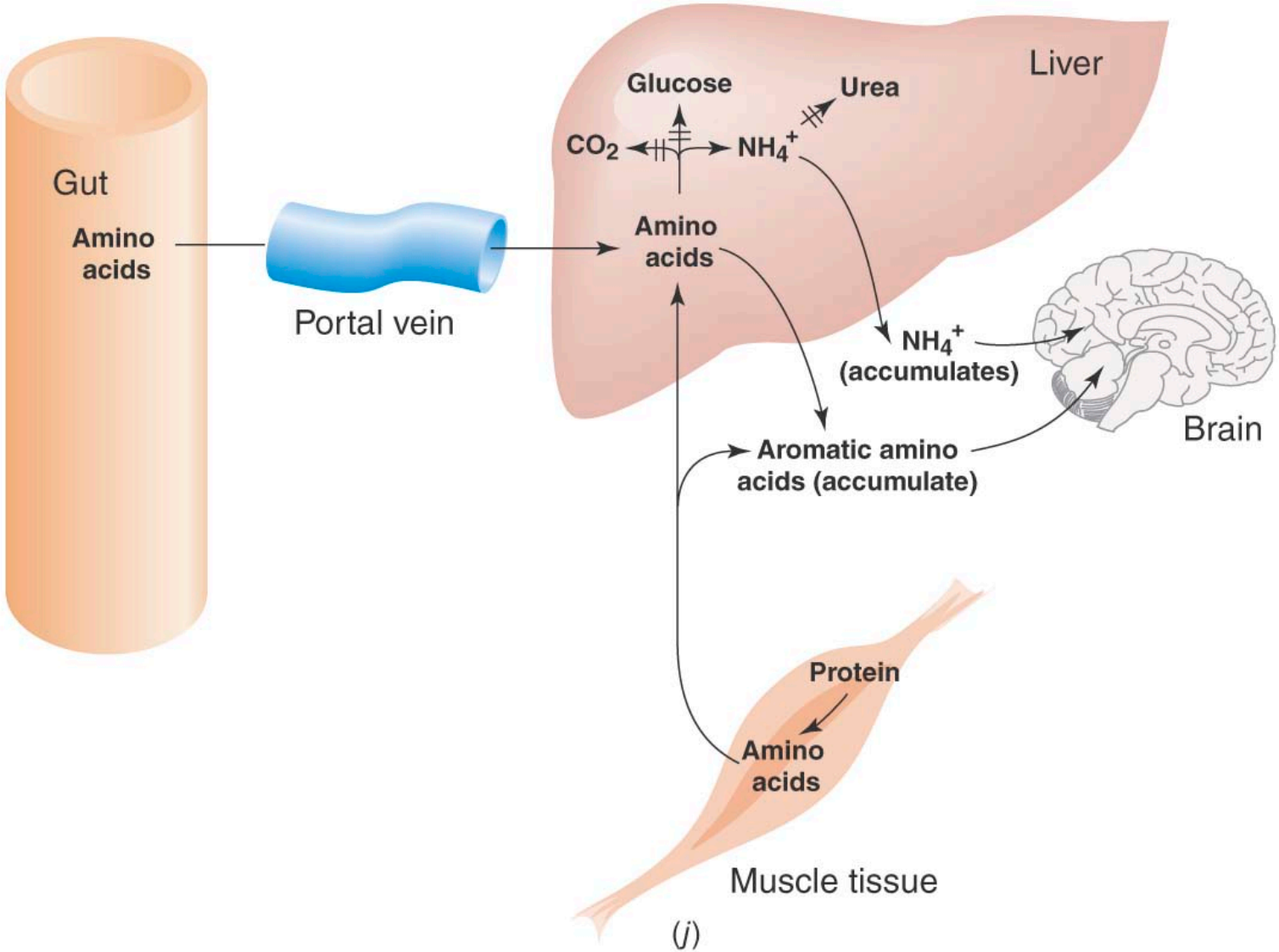


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*j*) Liver disease.

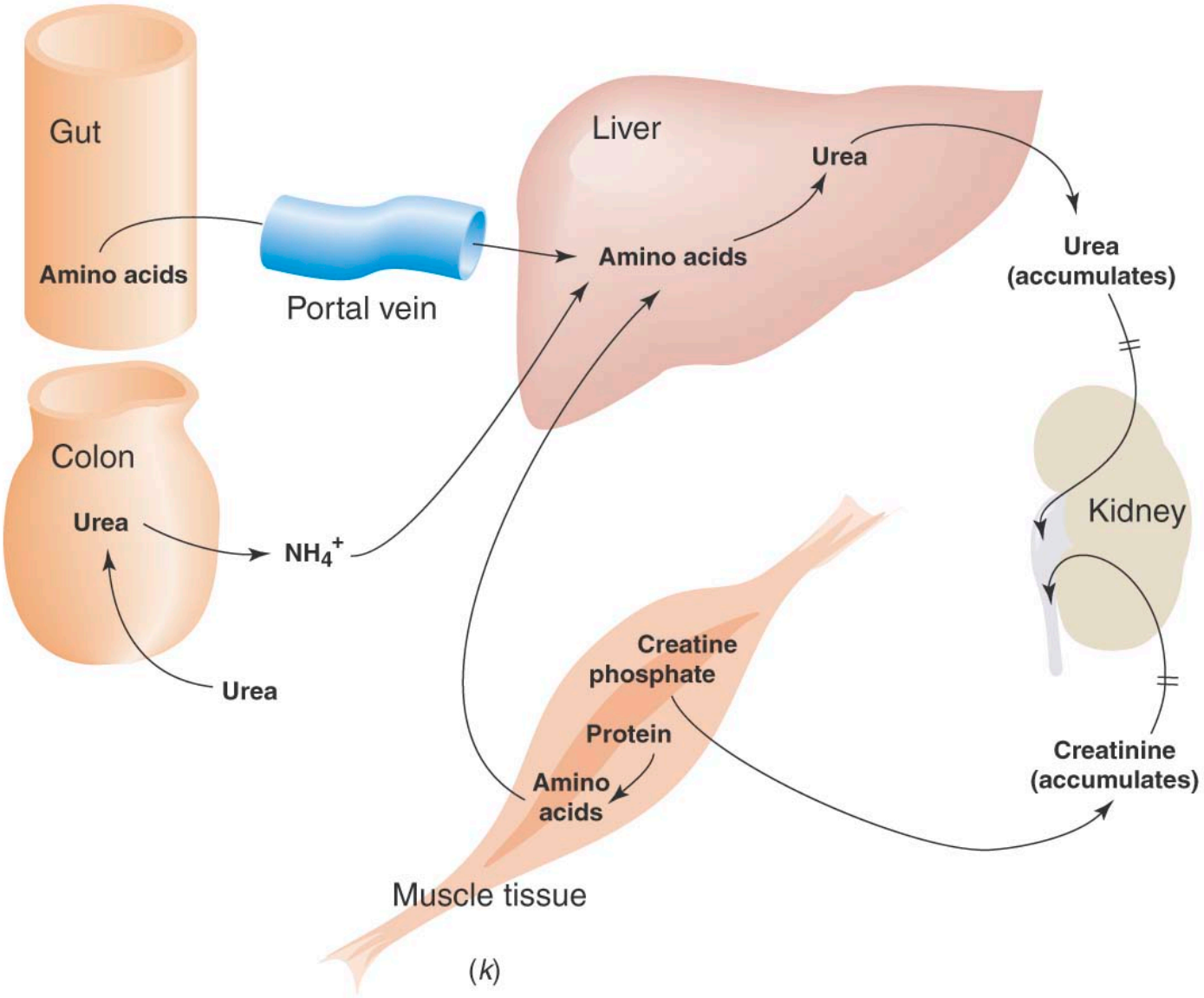


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*k*) Kidney failure.

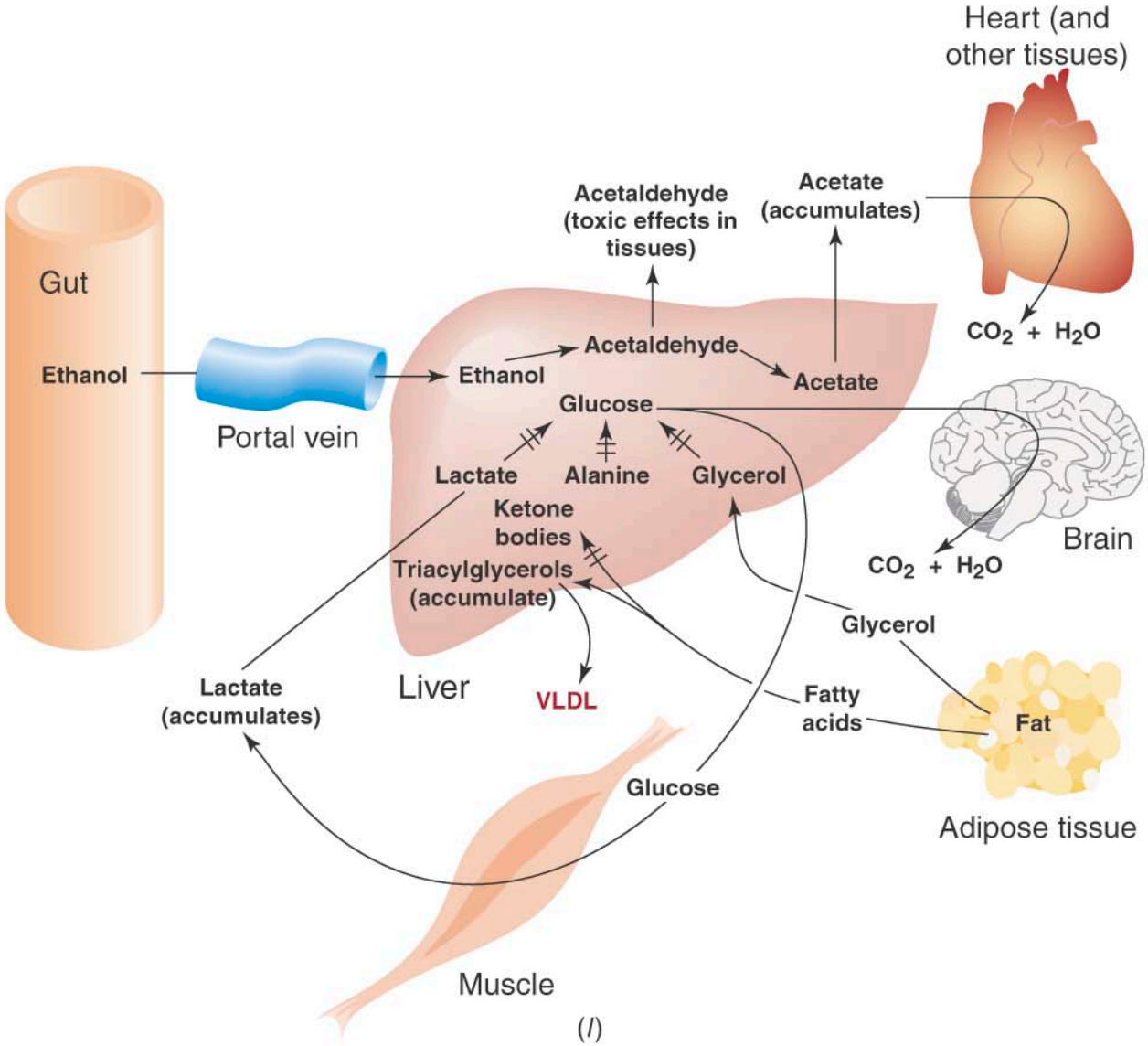


Figure 22.24. Metabolic interrelationships of tissues in various nutritional, hormonal, and disease states. (*I*) Alcohol.

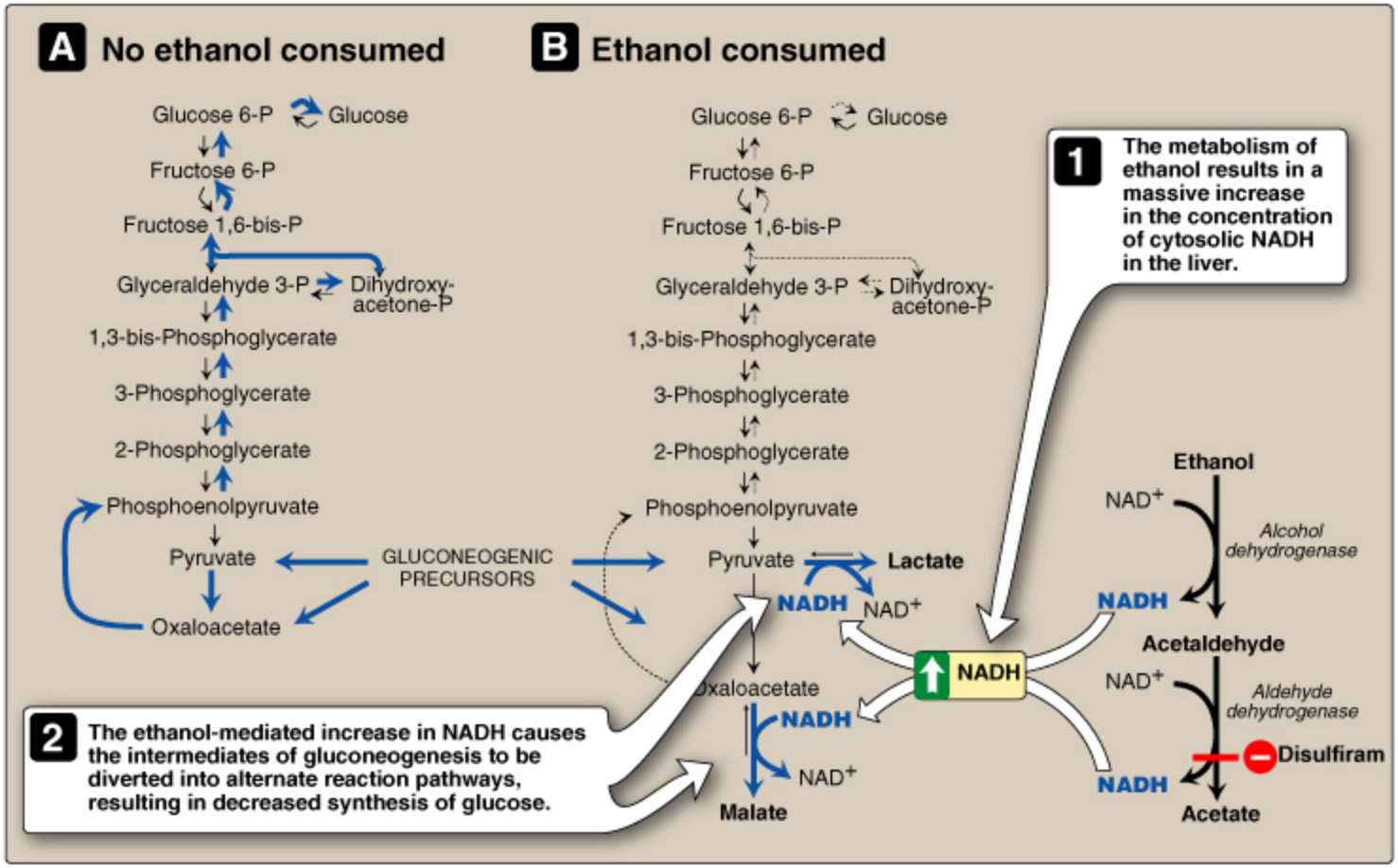


Figure 23.15

A. Normal gluconeogenesis in the absence of ethanol consumption. B. Inhibition of gluconeogenesis resulting from hepatic metabolism of ethanol.

RESPIRATION QUOTIENT (RQ)

def: Vol of CO_2 produced divided by the volume of O_2 consumed for Carbohydrate (i.e. glucose)

$$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O + E$$

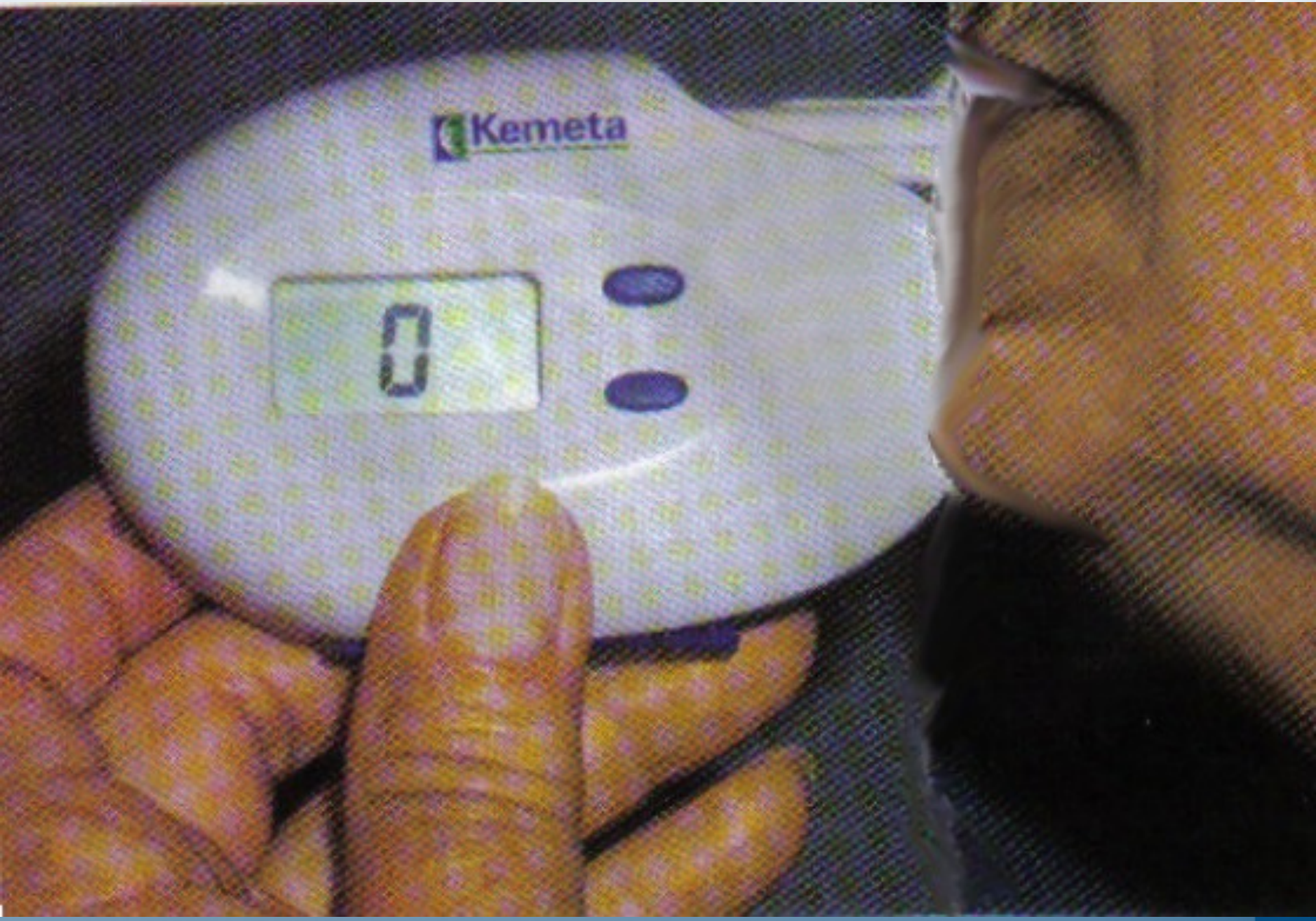
$$RQ = \frac{6CO_2}{6\ O_2} = 1$$

For lipid (i.e. 2 molecules stearic acid + 1 molecule palmitic acid)

$$2\ (C_{55}\ H_{106}\ O_6) + 157\ O_2 \rightarrow 110\ CO_2 + 106\ H_2O + E$$

$$RQ = \frac{110\ CO_2}{157\ O_2} = 0.70$$

For protein RQ = 0.80


Kemeta
0

"FAT BURNING ZONE"
(low intensity workouts)

	Low Intensity 60-65%MHR	High Intensity 80-85%MHR
Total Cal/min	4.86	6.86
Fat Cal/min	2.43	2.70
Total Cal/30 min	146	206
Total Fat Cal/30 min	73	82
Percent Fat Cal burned	50	39.9

Maximum fat oxidation occurs at 54% with heart rate at ca 130 beats/min

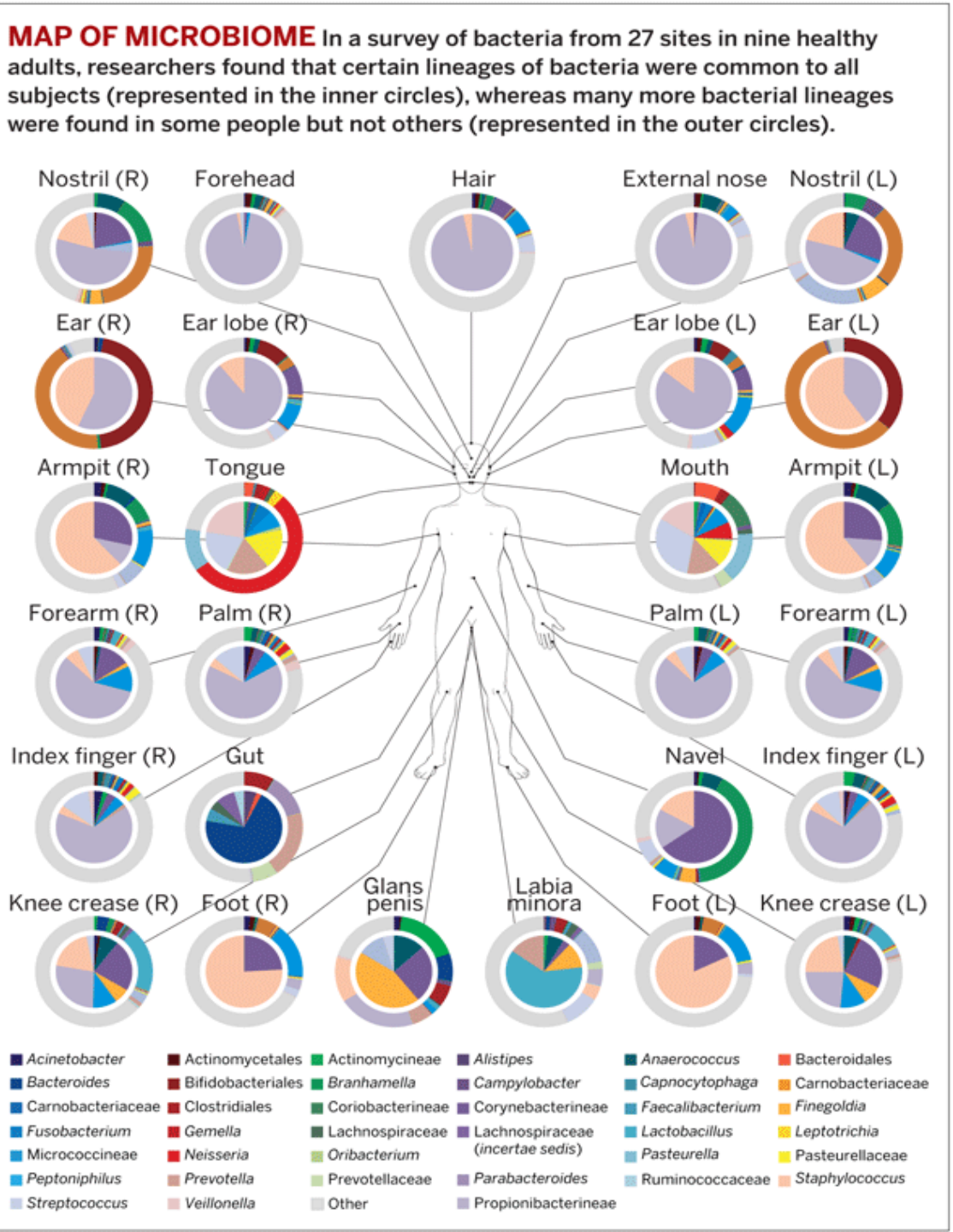
Data from 130# 25 yr old woman

MHR (old method) 220 – age

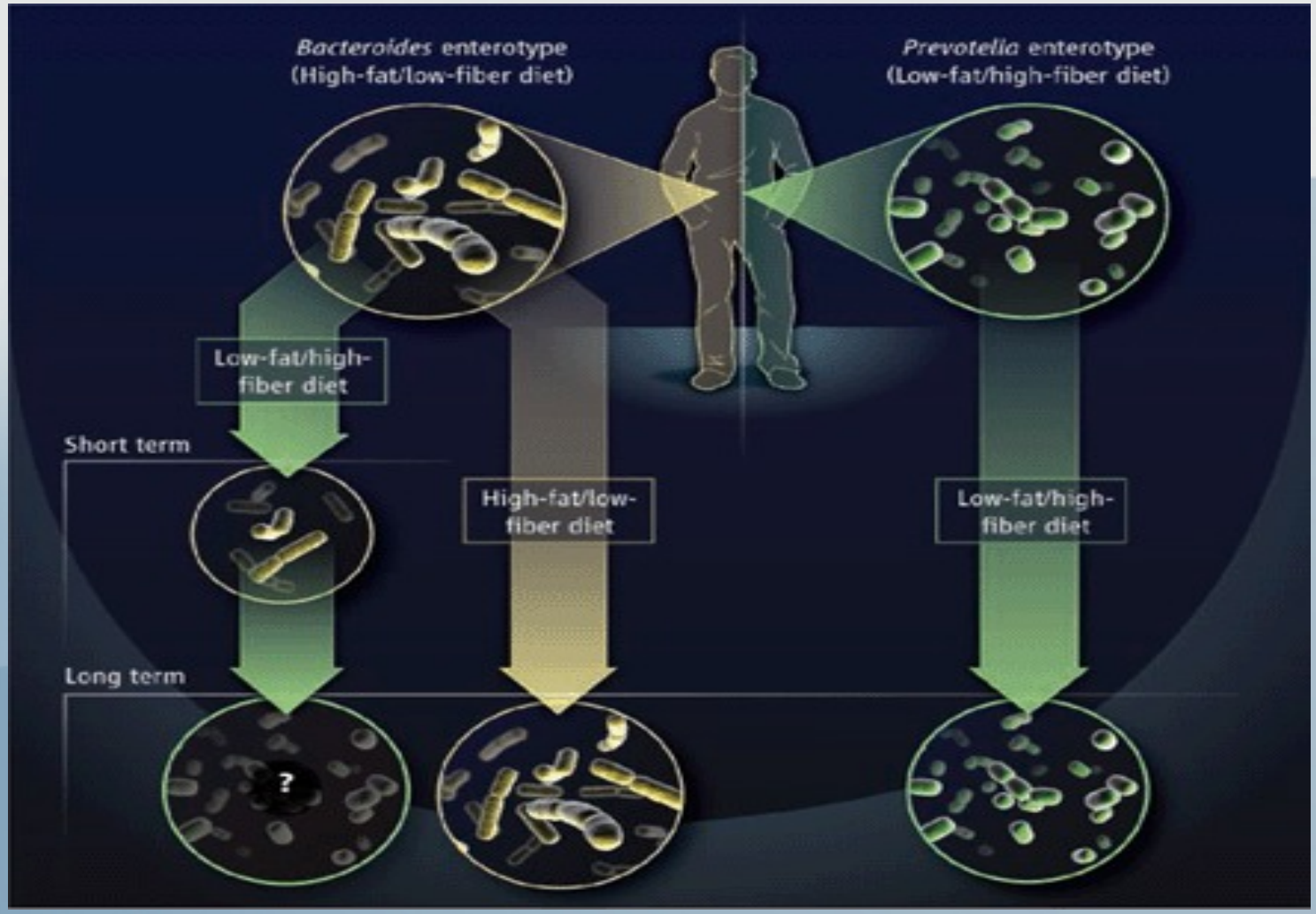
Karvonen Formula (corrects for resting heart rate)

Burning of extra fat colories in endurance athletes **after** exercise does **not** happen. "Afterburn" does not exist.

- We still have much to learn about metabolism
- The human body exists in a symbiotic relationship with microbes which outnumber human cells by a factor of 10 to 1.
- The genomes of the microbiota are collectively known as the microbiome.
- 90% of the protein-encoding cells in our body are microbes.
- Composition of the microbes can change over time and geographic regions (for example, the Japanese microbiome has acquired the gene for a seaweed digesting enzyme for sushi wrappers)



- Microbes co-inhabit our bodies.
- They protects us from pathogens, synthesize essential vitamins, enzymes for digestion and contribute to such human factors as obesity, food digestion and pill metabolism.
- Imbalances can result in autoimmune diseases such as Crohn's, skin disorders such as eczema and psoriasis and perhaps certain types of cancer



- Long- and short-term effects. Nutrients affect the composition of the intestinal microbiota. Two different long-term diets are associated with a distinct gut microbe population (enterotypes). These microbial profiles are stable, and short-term dietary changes are not sufficient to alter them.