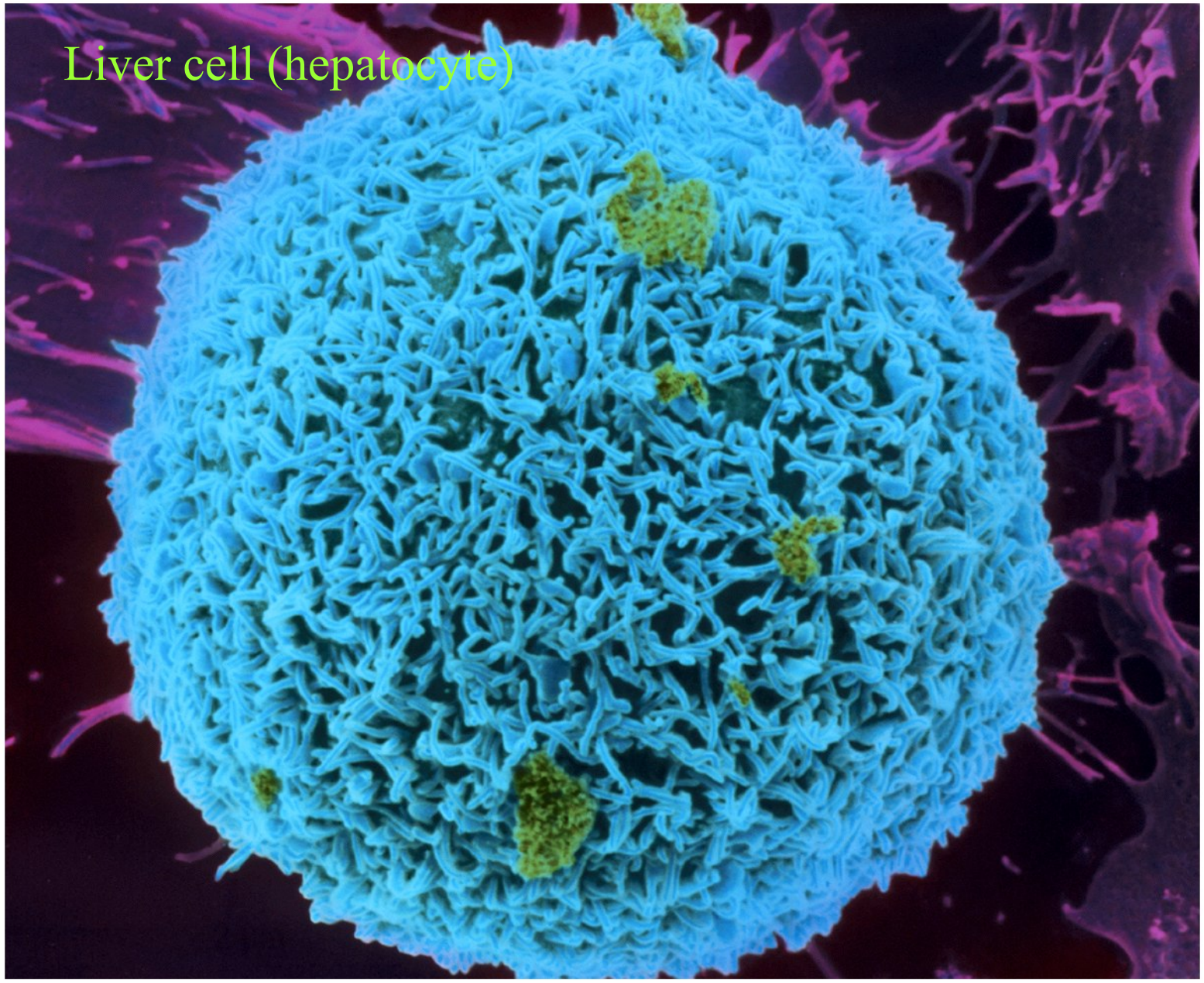
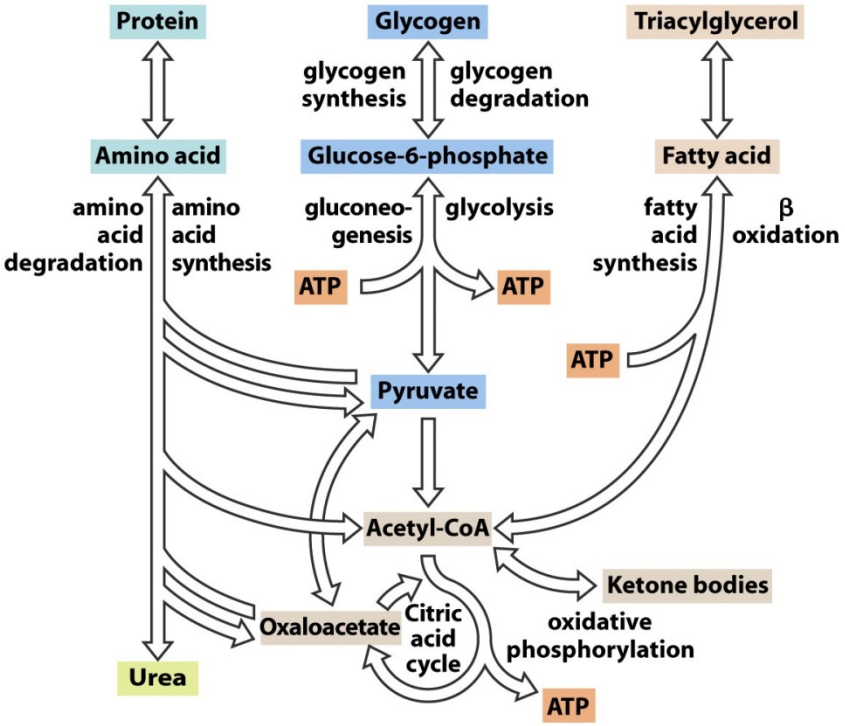
Chapter 9:
Mammalian Fuel Metabolism: Integration and Regulation


Liver cell (hepatocyte)

Organ specialization

- Glycolysis
- Gluconeogenesis
- Glycogen degradation and synthesis
- Fatty acid synthesis and degradation
- The citric acid cycle
- Oxidative phosphorylation
- Amino acid synthesis and degradation



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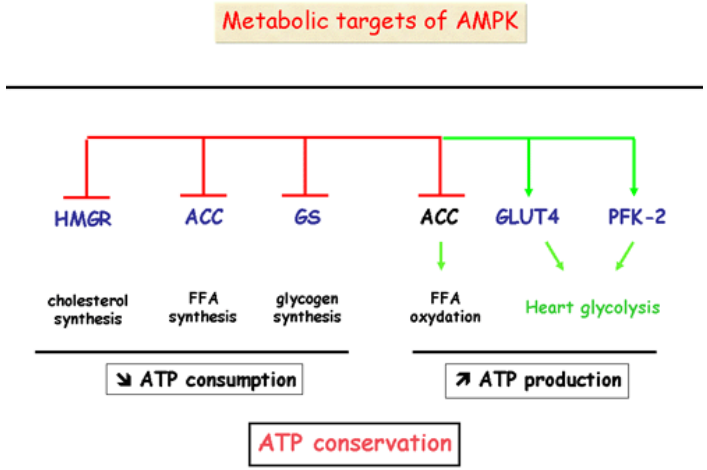
<u>Two key compounds</u>

Acetyl-CoA

Pyruvate

Need based control depending on organs: AMPK activation



The metabolic relationships among brain, adipose tissue, muscle, liver, and kidney

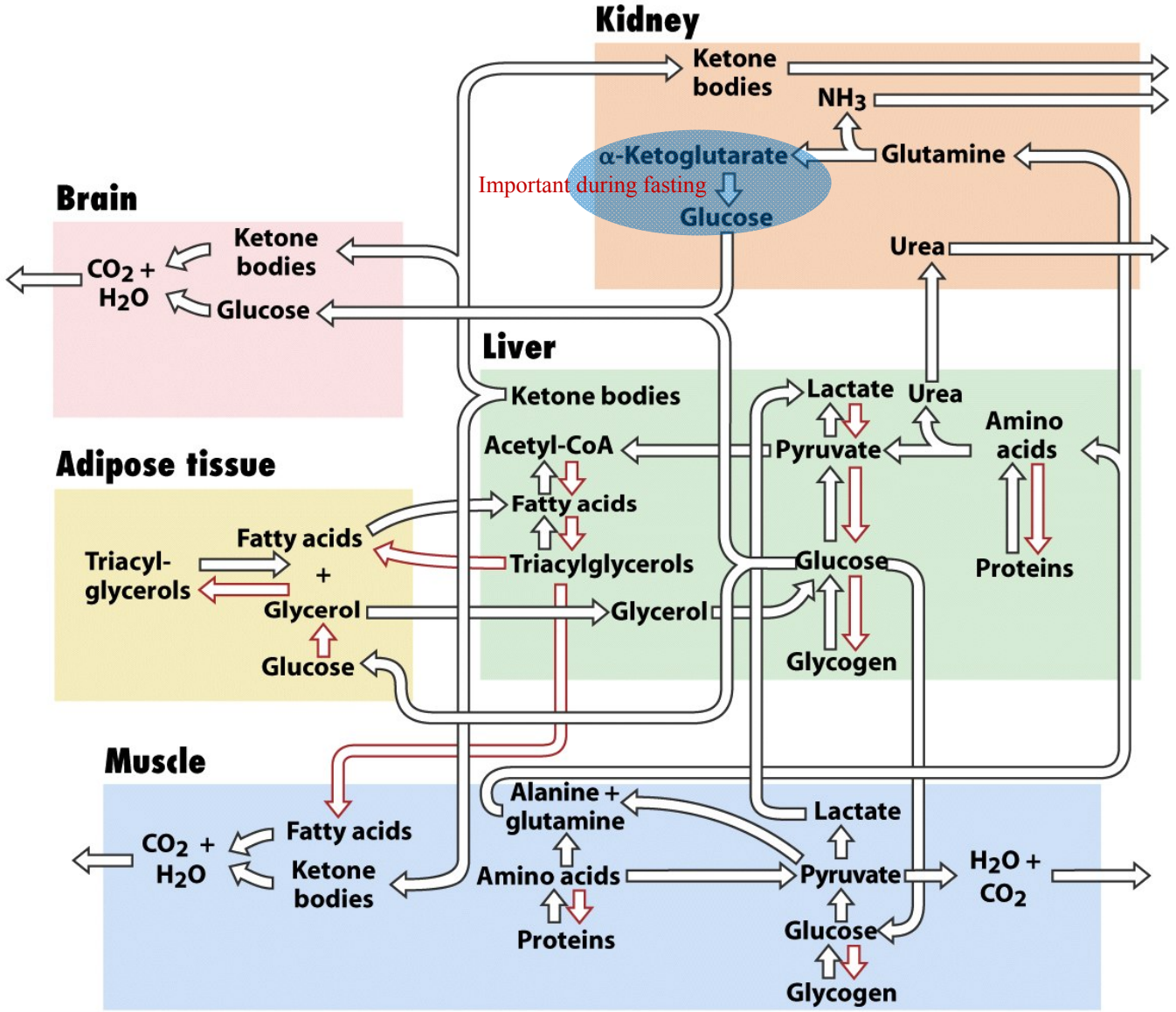


Figure 21-2 Fundamentals of Biochemistry, 2/e

1. Brain

Constitutes only ~2% of the adult body mass,

but is responsible for ~20% of its resting oxygen consumption

(Na^+-K^+)-ATPase: maintain membrane potential for nerve impulse transmission

Require a steady supply of glucose

- Glucose is the primary fuel
- Depends on ketone bodies under extended fasting condition
- Less than ~5 mM causes fatal problems
- Hypoglycemia in Type 1 diabetes mellitus
  - Hypoglycemia-Associated Autonomic Failure (HFFA)

Diabetic patients with good glycemic control become unable to recognize symptoms of hypoglycemia. Lack of symptoms, or hypoglycemia unawareness, is part of the syndrome called hypoglycemia associated autonomic failure. This syndrome also includes inadequate neuroendocrine hormonal responses and reduced glycemic thresholds for counterregulatory hormonal secretion.

2. Muscle

Major fuels: glycogen, fatty acids, ketone bodies
Glycogen (1-2% of mass) mobilize more rapidly and can be metabolized anaerobically

Muscle carbohydrate serves only muscle
Glycogen is converted to G-6-P
Synthesize glycogen but not glucose

Source of ATP during exercise in human

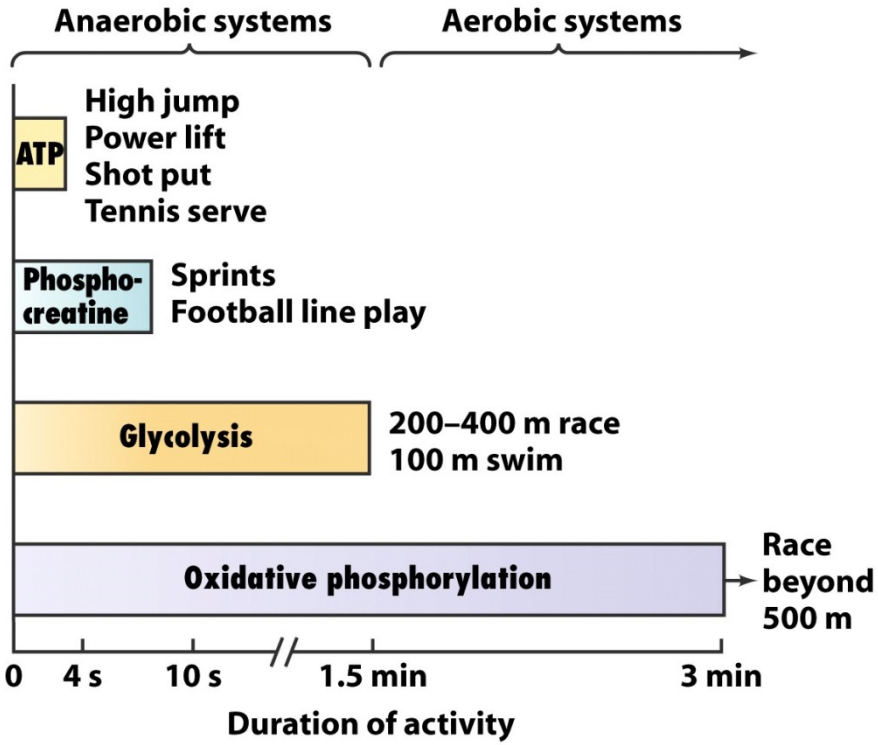


Figure 21-3 Fundamentals of Biochemistry, 2/e

Muscle types

Skeletal muscle: voluntary muscle

Two types: slow twitch, fast twitch

Smooth muscle: involuntary muscle within the walls of organs except heart

Cardiac muscle: involuntary muscle in heart

3. Heart

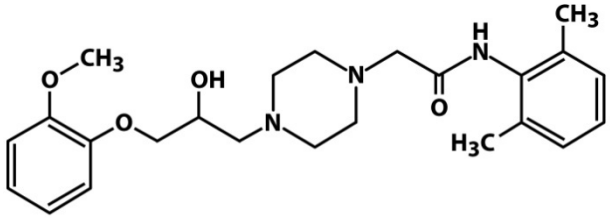
Largely aerobic

Continuous operation

Rich in mitochondria (up to 40% of cytoplasm)

Fatty acids are resting heart's fuel but depends on glucose during heavy work

Angina (heart pain) due to an insufficient oxygen supply



Ranolazine

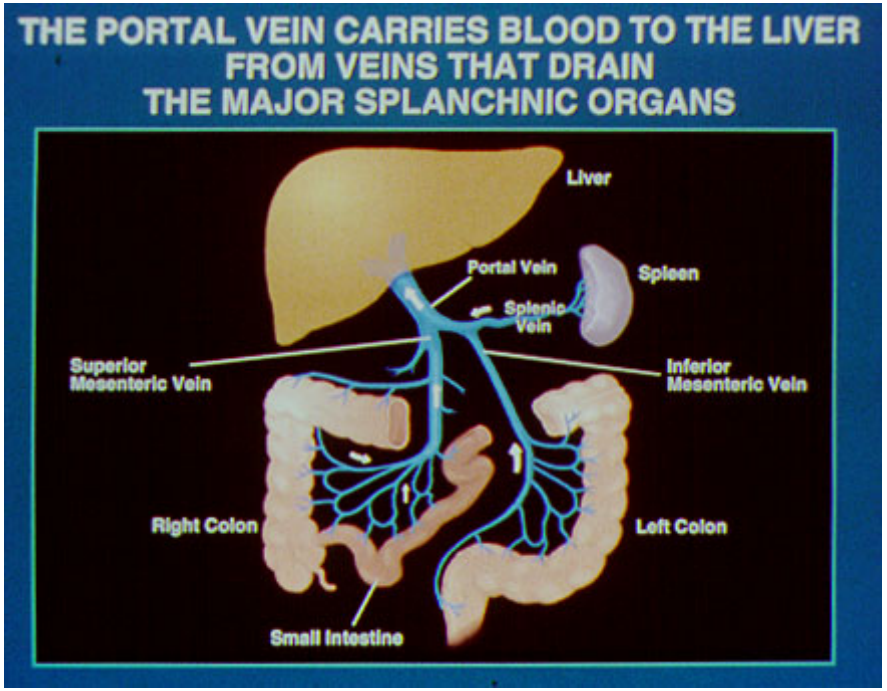
Fatty acid oxidation inhibitor,
making heart muscle depends on glucose

4. Adipose tissue

Fatty acid mobilization
Triacylglycerol by hormone-sensitive lipase
Metabolic need to fatty acids is signaled by decrease in [glucose]
[glycerol-3-P] determines the direction

5. Liver

Central metabolic clearinghouse
Portal vein from intestine: all the nutrients except fatty acids



Glucokinase in liver

Liver acts as a blood glucose "buffer"

Blood glucose to G-6-P by glucokinase (a liver isozyme of hexokinase)

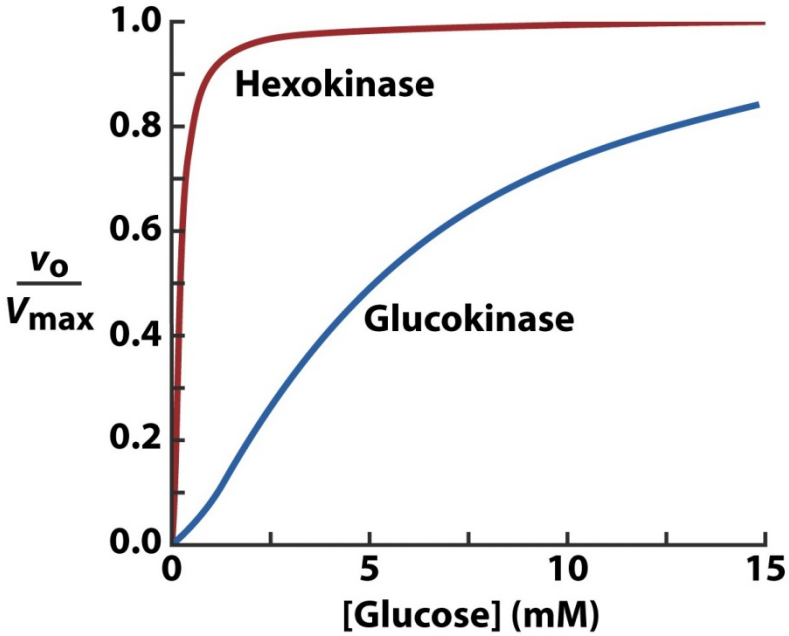
A monomeric enzyme but has sigmoidal kinetic behavior

Subject to metabolic control

Glucokinase regulatory protein: a competitive inhibitor in the presence of F6P

overcome by F1P: only available from dietary sources and signal the uptake of dietary glucose

Glucokinase is the β-cell's glucose sensor



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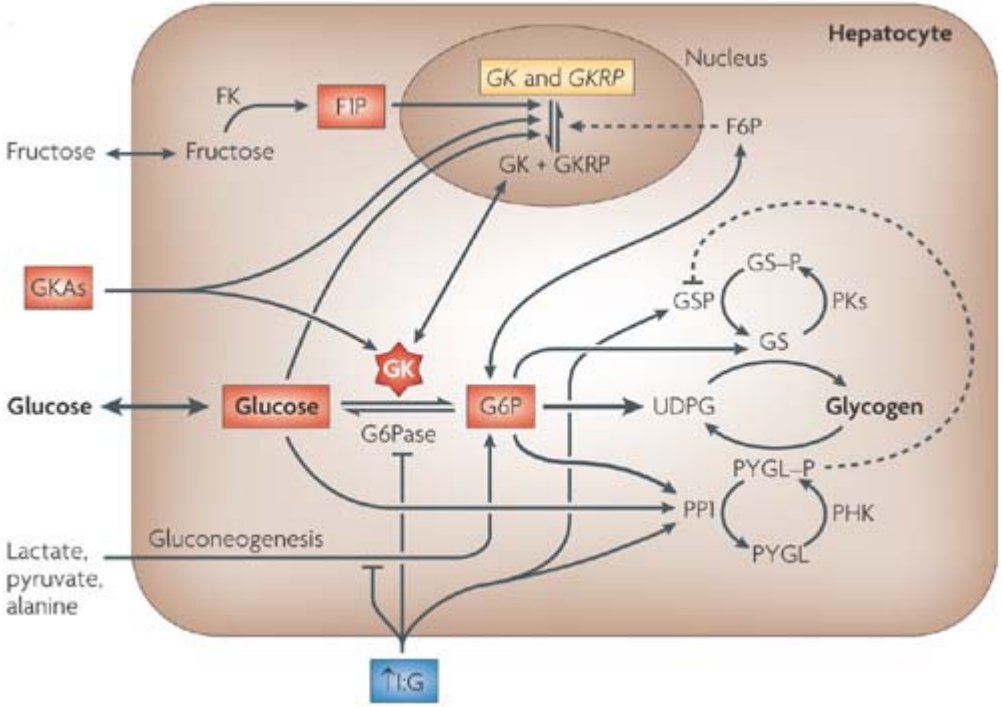
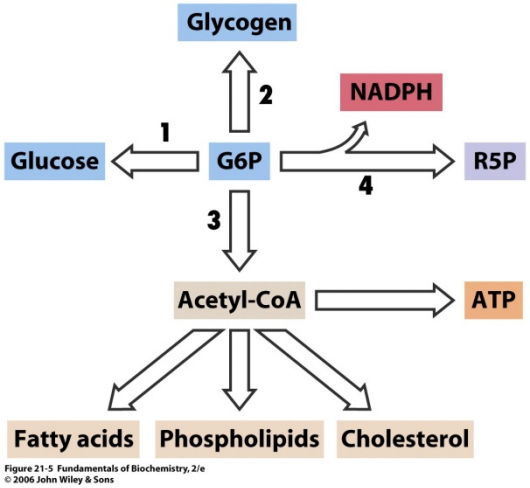


Nature Reviews Drug Discovery 8, 399-416 (May 2009)

Metabolic fate of glucose-6-P in liver
(at the crossroads)



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<u>The liver can synthesize and degrade triacylglycerols</u>

When the demand for metabolic fuels is high
Fatty acids to acetyl-CoA and then to ketone bodies for transport
Lack 3-ketoacyl-CoA transferase, which convert ketone bodies to acetyl-CoA

When the demand for metabolic fuels is low
Fatty acids to triacylglycerol and transported as VLDL

<u>Amino acids are metabolic fuels</u>

After feeding, dietary amino acids are completely oxidized or converted to glucose or ketone bodies
During a fast, muscle protein amino acids to glucose

6. Kidney

Filters urea and other waste products from the blood
Recovers important metabolites such as glucose

Maintains homeostasis

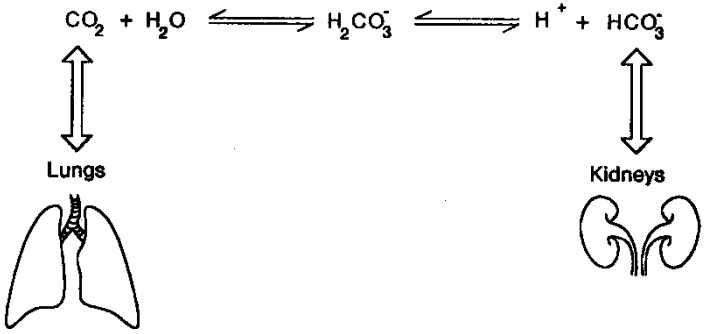
Acid-base balance: the blood's pH
By regenerating bicarbonate
By excreting excess H^+

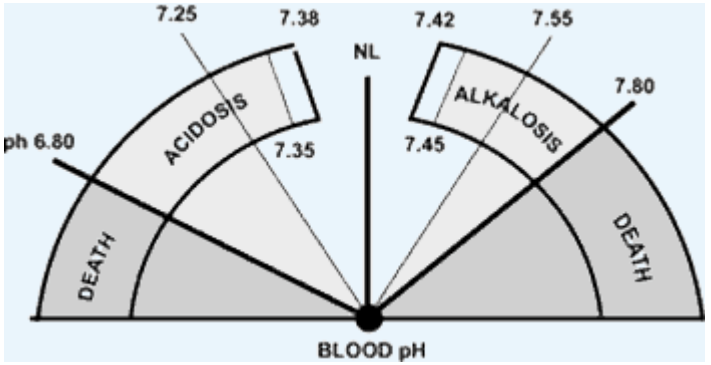
Blood pressure
Plasma volume

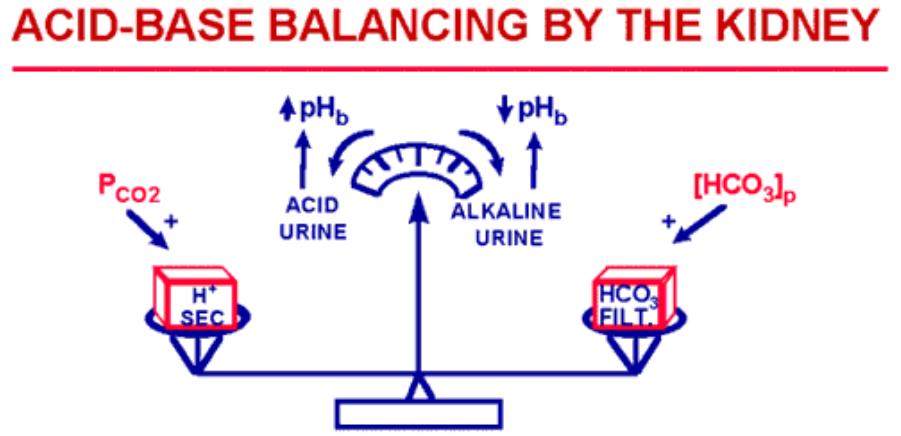
Gluconeogenesis from α-ketoglutarate

50% of the body's glucose

depends on kidney during starvation







http://www2.kumc.edu/ki/physiology/course/nine/9_7.htm

The kidney's ability to perform many of its functions depends on the three fundamental functions of *filtration*, *reabsorption*, and *secretion*, whose sum is renal excretion. That is:

Urinary excretion rate = Filtration rate – Reabsorption rate + Secretion rate (http://en.wikipedia.org/wiki/Renal_physiology)

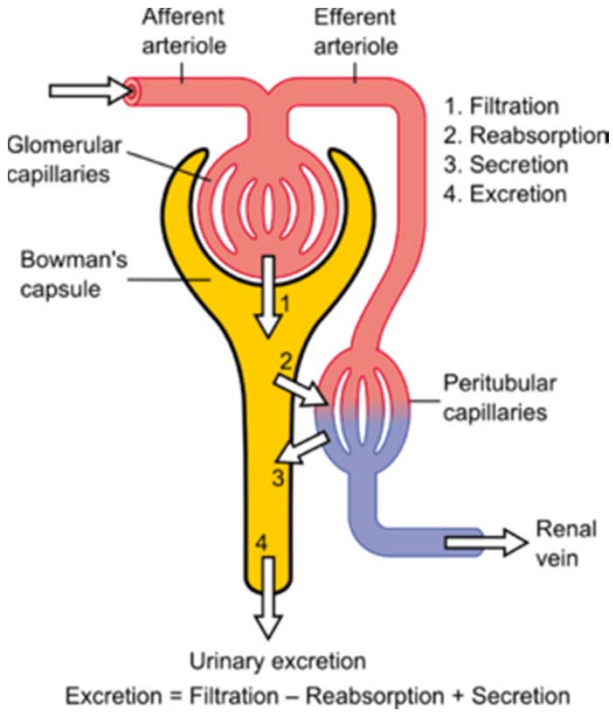
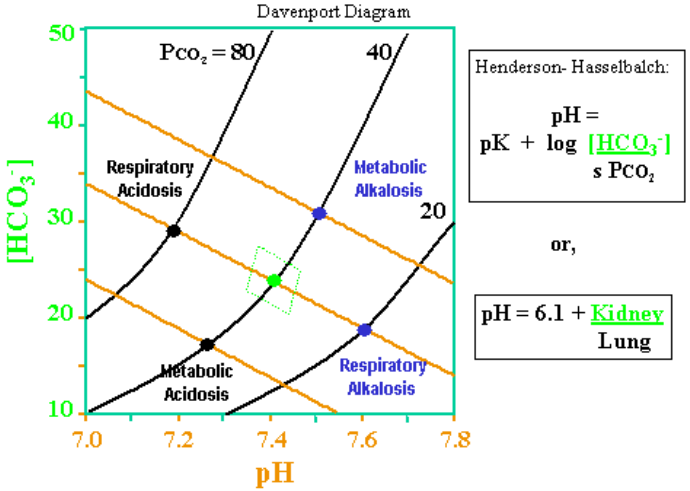


Figure 5: Diagnosis using Serum Acid-Base Values:



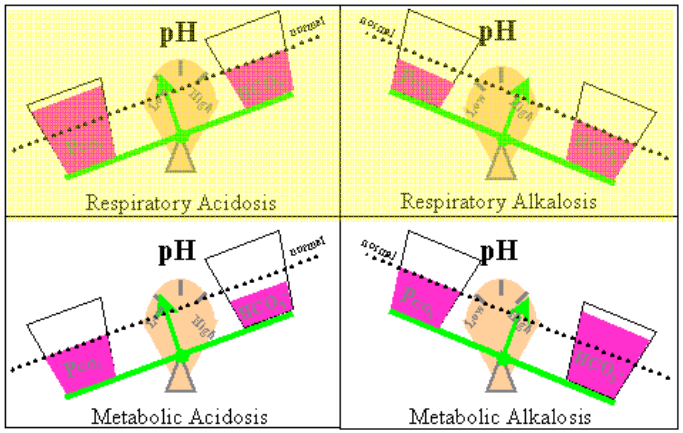
Henderson- Hasselbalch:

$$pH = pK + \log \frac{[HCO_3^-]}{s\,PCO_2}$$

or,

$$pH = 6.1 + \frac{\text{Kidney}}{\text{Lung}}$$

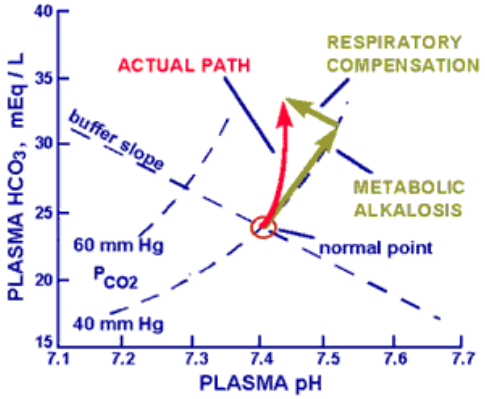
Figure 6: Primary Acid-Base Disturbances



http://romerosnap1.phol.cwru.edu/AcidBase-SOMy1.htm

METABOLIC ALKALOSIS

- The addition of alkali to the blood or the loss of acid causes the blood pH and $[HCO_3]_p$ to rise.
- The respiratory response to the high pH is hypoventilation. The rise in CO_2 titrates the blood buffers toa lower pH and a further small increase in $[HCO_3]_p$.

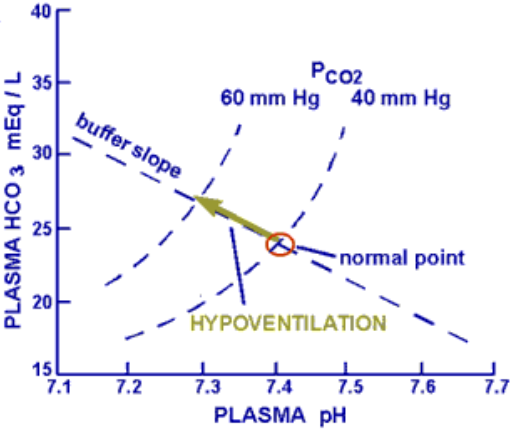


RESPIRATORY ACIDOSIS

- Hypoventilation causes the retention of acid (CO_2) in the blood.

$$CO_2 + H_2O \rightarrow H_2CO_3$$
$$\downarrow$$
$$H^+ + HCO_3^-$$

- The protons titrate the blood buffers to a lower pH and HCO_3 tends to accumulate in the blood.

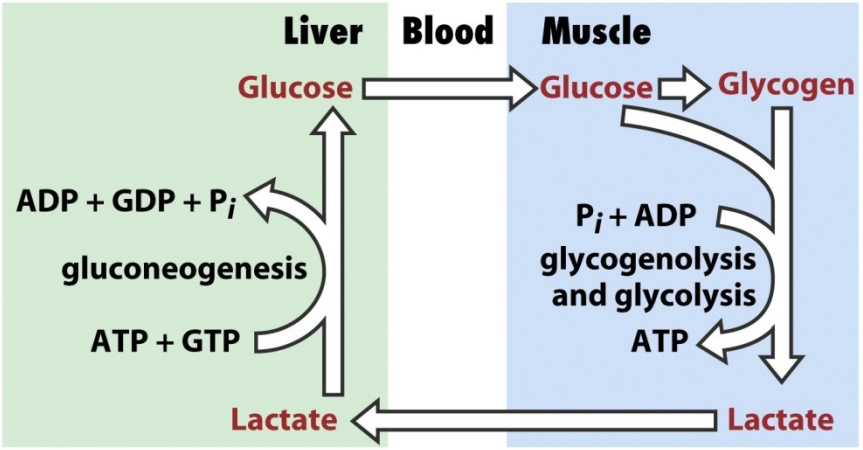


Interorgan metabolic pathways

The Cori cycle

resynthesis of glucose from lactate

oxygen debt: ?



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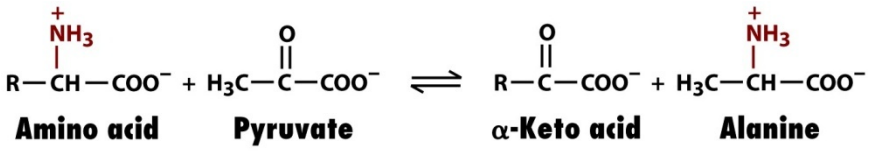
The glucose-alanine cycle

transport of nitrogen from muscle to liver



Unnumbered figure pg 752 Fundamentals of Biochemistry, 2/e
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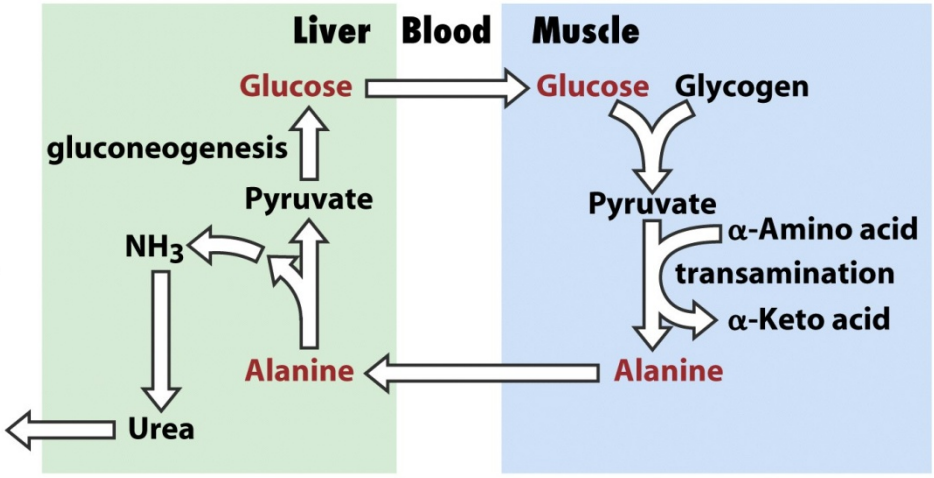

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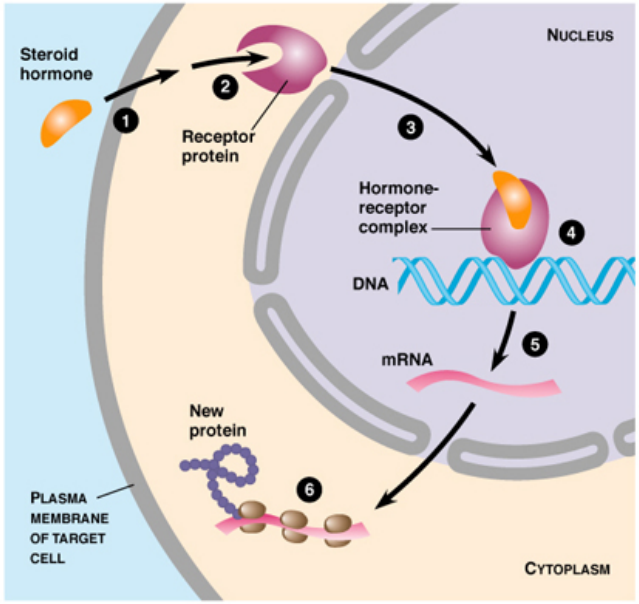
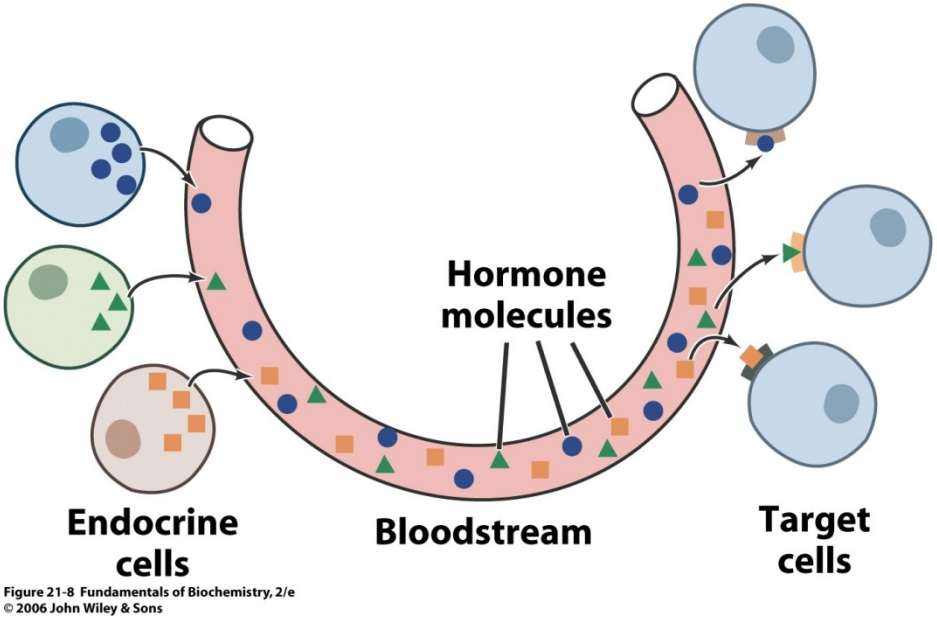
Hormonal control of fuel metabolism

Hormones: synthesis & release from endocrine glands
Maintain homeostasis
Response to external stimuli
Control cyclic and developmental programs

Receptors

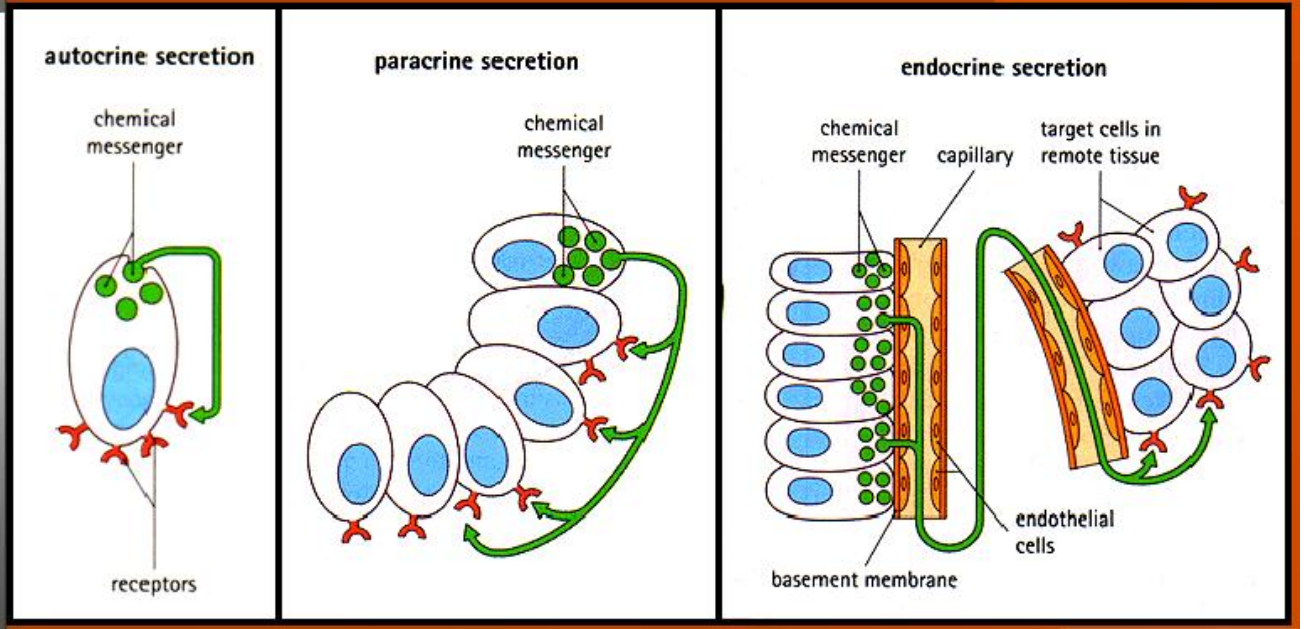
- Membrane receptor: nonsteroid hormones
- Intracellular protein receptor: steroid hormones





Endocrine signaling

Autocrine, Paracrine, and Endocrine

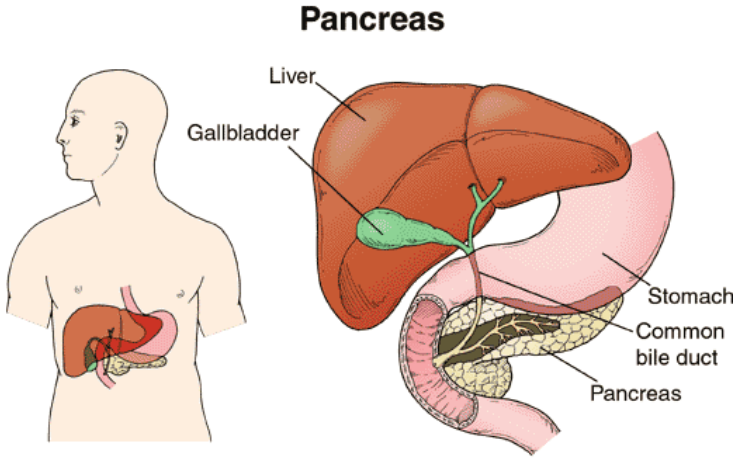


Stevens & Lowe 2nd, p 251

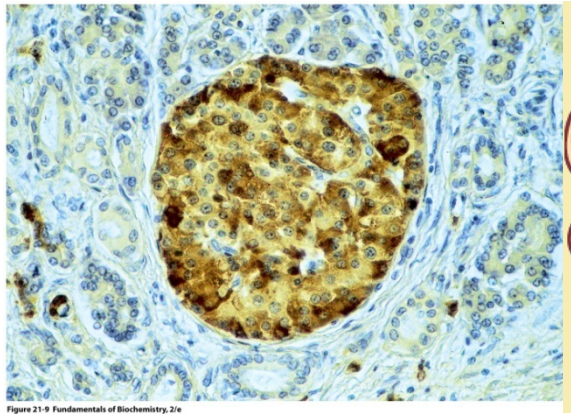
Biology 3431

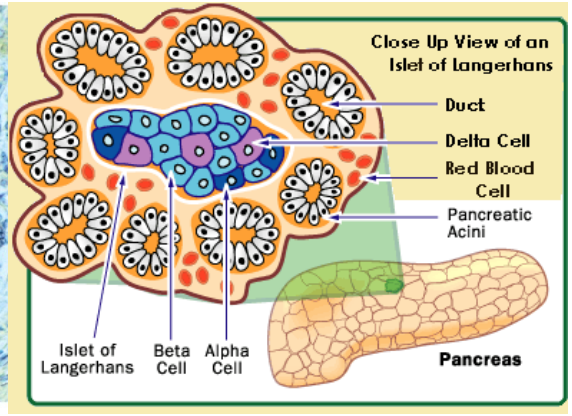
Pancreatic and adrenal hormones

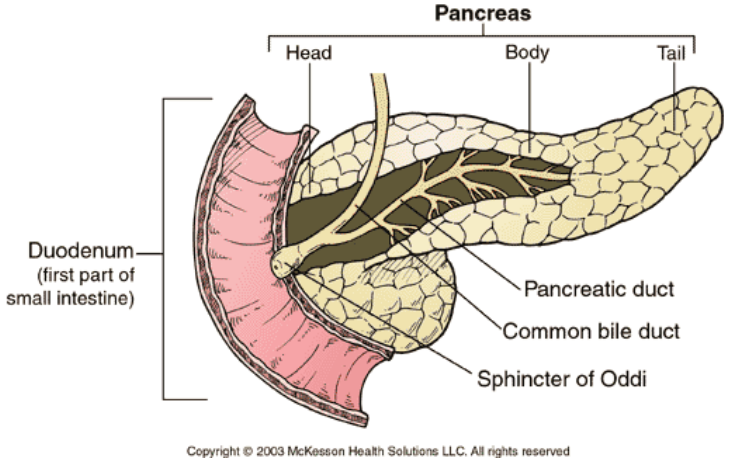
<u>Pancreas</u>
Digestive enzymes: trypsin, Rnase A, α-amylase, phospholipase A2
Islets of Langerhans: α-cells, β-cells



Pancreatic islet cells







Adrenal glands

Hormone release in response to neuronal signals
Medulla: an extension of the nervous system
    Catecholamine: norepinephrine, epinephrine

Cortex: synthesizes and secretes hormones
    Steroid hormones:
    glucocorticoids (e.g. cortisol): raising blood glucose
    mineralocorticoids (e.g. aldosterone): mineral metabolism
    androgens (e.g. testosterone, androgen):

Figure 1: Kidneys and Adrenal Glands

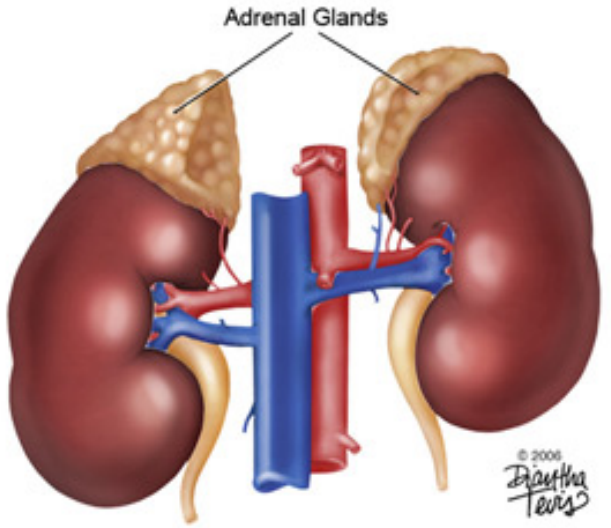
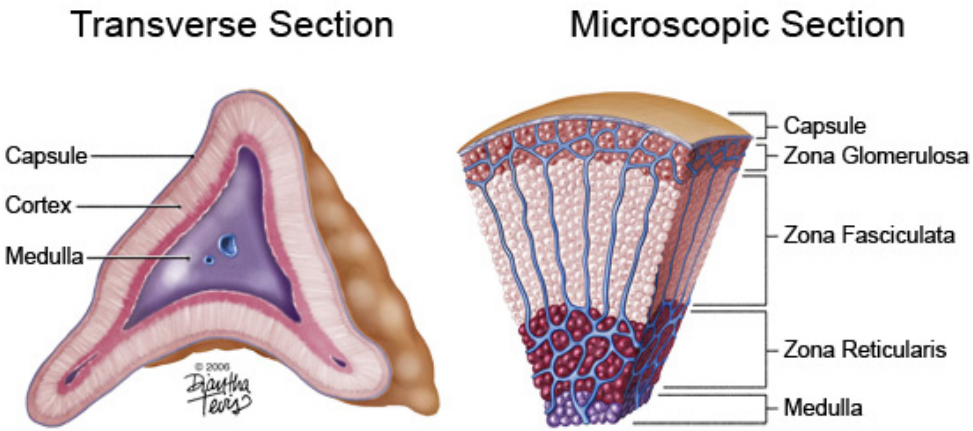


Figure 2: Adrenal Gland Cross Sections



Insulin release triggered by glucose

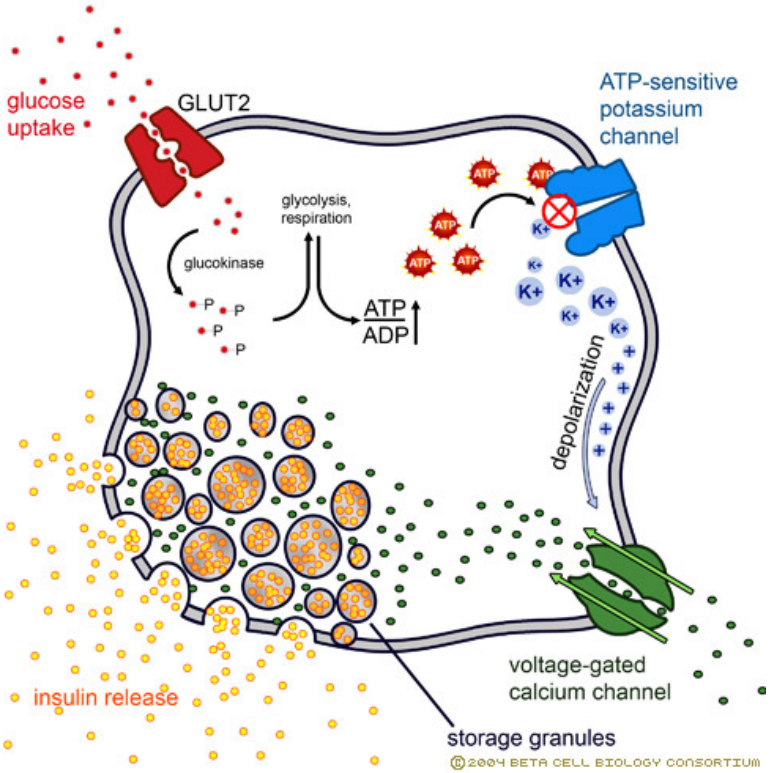
Normal blood glucose: 3.6-5.8 mM

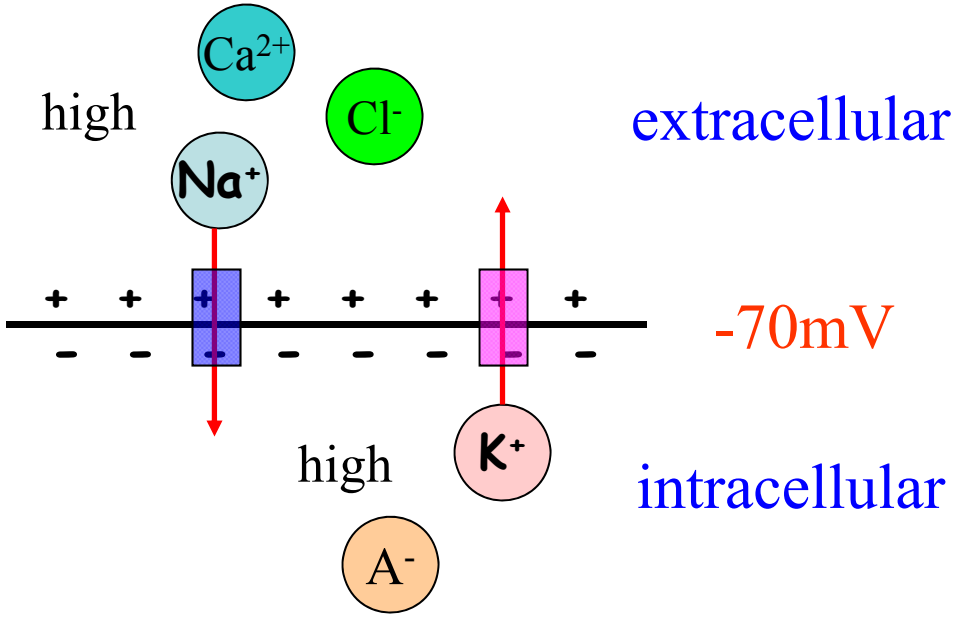
β-cells are sensitive to glucose at 5.5.-6.0 mM

Passive transport of glucose (GLUT2)

Glucokinase is a glucose sensor

The overall level of the β-cell's respiratory activity regulates insulin synthesis and secretion





Glucose transporter & receptor

http://en.wikipedia.org/wiki/Glucose_transporter

glucose transporter in muscle and adipose tissue
GLUT4: insulin-sensitive glucose transporter

glucose transporter in brain
Constitutive expression of insulin-insensitive glucose transporter (GLUT3)

glucose transporter in liver
GLUT2: low affinity for glucose
Receptor binding: inactivation of phosphorylase kinase & activation of glycogen synthase
control gene expression

Class I [edit]

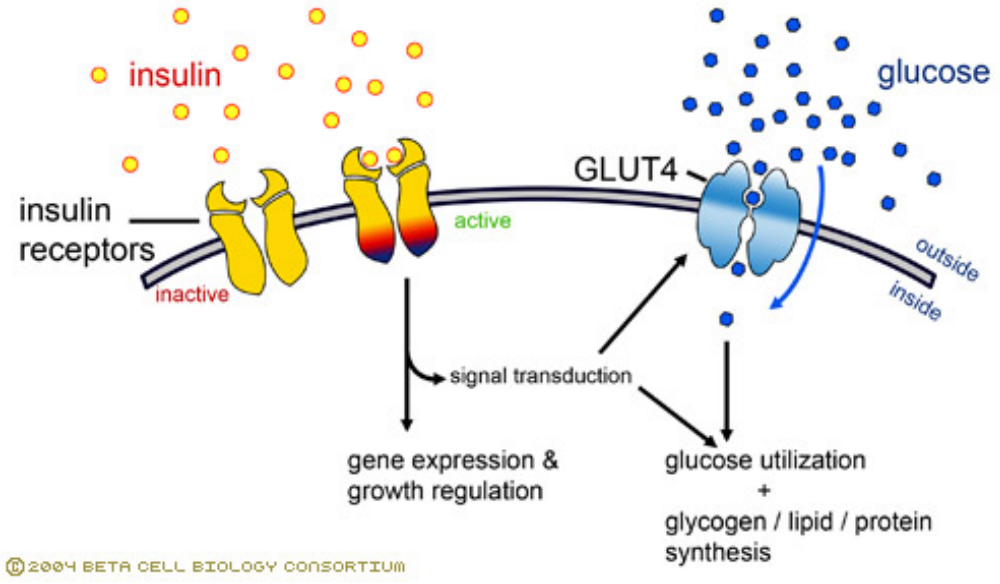
Class I comprises the well-characterized glucose transporters GLUT1-GLUT4.[11]

Name	Distribution	Notes
GLUT1	Is widely distributed in fetal tissues. In the adult, it is expressed at highest levels in erythrocytes and also in the endothelial cells of barrier tissues such as the blood-brain barrier. However, it is responsible for the low-level of basal glucose uptake required to sustain respiration in all cells.	Levels in cell membranes are increased by reduced glucose levels and decreased by increased glucose levels.
GLUT2	Is expressed by renal tubular cells and small intestinal epithelial cells that transport glucose, liver cells and pancreatic β cells. All three monosaccharides are transported from the intestinal mucosal cell into the portal circulation by GLUT2	Is a high capacity and low affinity isoform
GLUT3	Expressed mostly in neurons (where it is believed to be the main glucose transporter isoform), and in the placenta.	Is a high-affinity isoform
GLUT4	Found in adipose tissues and striated muscle (skeletal muscle and cardiac muscle).	Is the insulin-regulated glucose transporter. Responsible for insulin-regulated glucose storage.

Insulin receptors:

- The receptors for insulin are found on most mammalian cells – action of insulin is mediated through these receptors.
- Impaired action of insulin can result from defects in the receptors or defects in post-receptor events.

(Km for glucose is 2-5 mM)



Glucose uptake in muscle and fat cells
(insulin stimulated exocytosis and endocytosis)

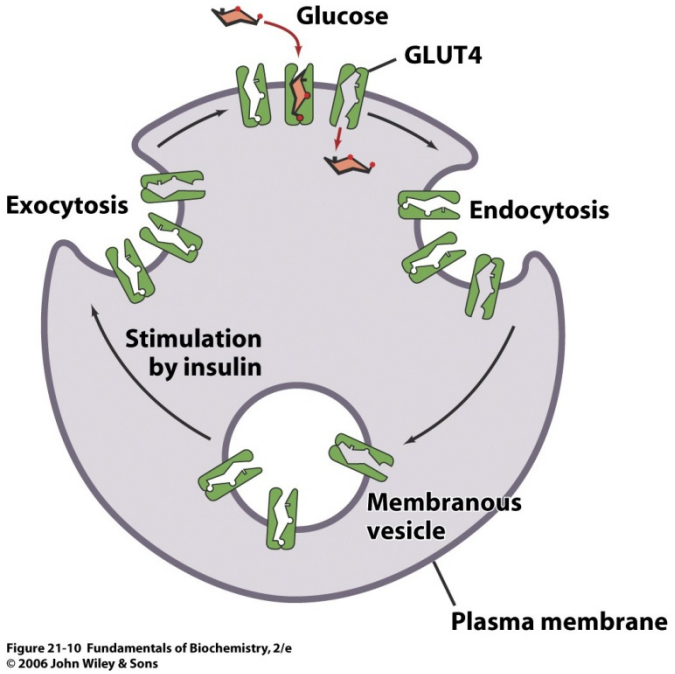


Table 21-1 Hormonal Effects on Fuel Metabolism

Tissue	Insulin	Glucagon	Epinephrine
Muscle	↑ Glucose uptake ↑ Glycogen synthesis	No effect	↑ Glycogenolysis
Adipose tissue	↑ Glucose uptake ↑ Lipogenesis ↓ Lipolysis	↑ Lipolysis	↑ Lipolysis
Liver	↑ Glycogen synthesis ↑ Lipogenesis ↓ Gluconeogenesis	↓ Glycogen synthesis ↑ Glycogenolysis	↓ Glycogen synthesis ↑ Glycogenolysis ↑ Gluconeogenesis

Table 21-1 Fundamentals of Biochemistry, 2/e

Overview of hormonal control of fuel metabolism

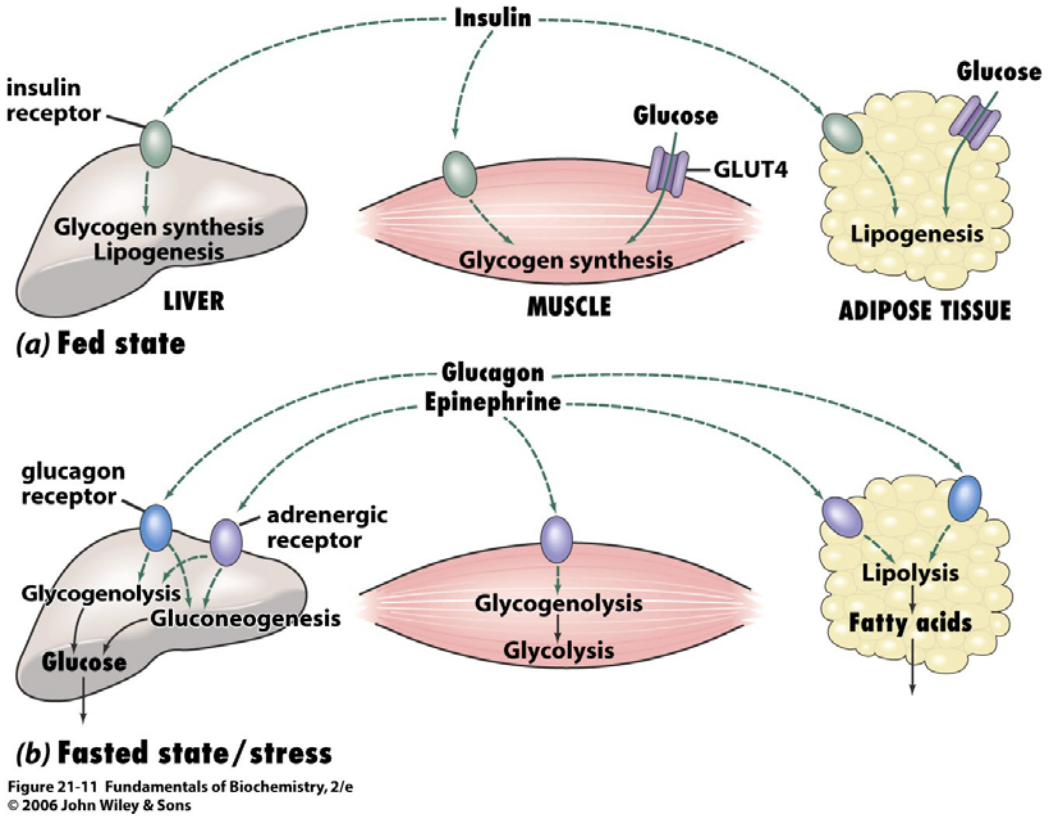


Figure 21-11 Fundamentals of Biochemistry, 2/e

Stimulate pancreas to secrete glucagon

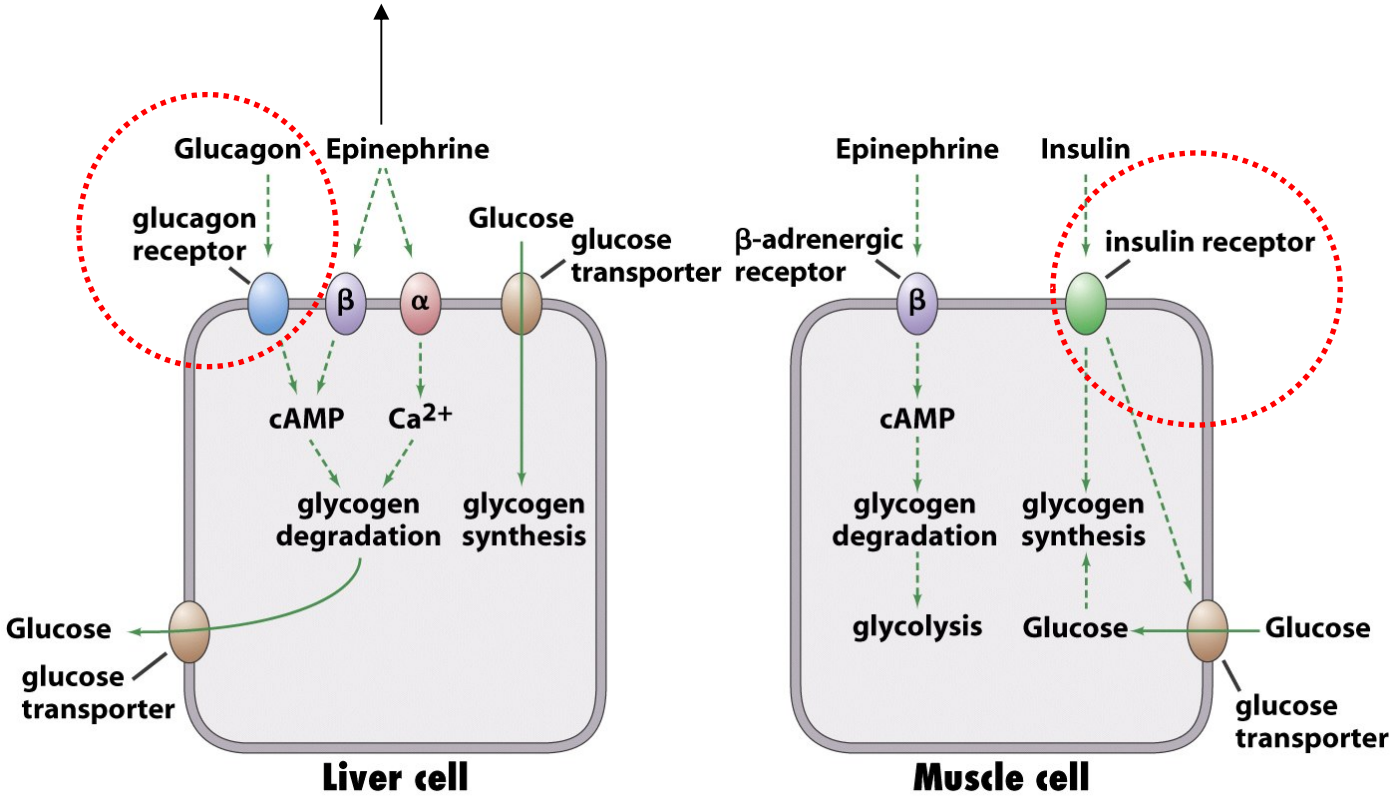
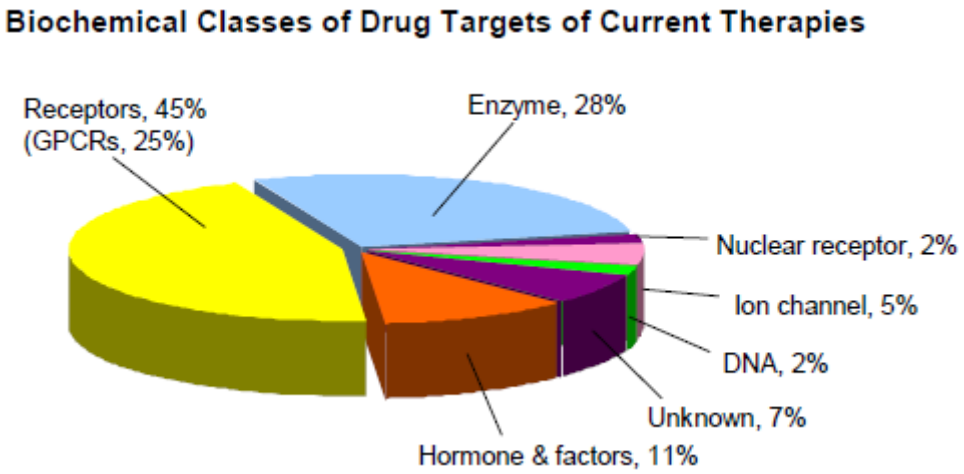


Figure 15-22 Fundamentals of Biochemistry, 2/e

Adrenergic receptors: β-adrenergic (cAMP), α-adrenergic (calcium ion)

Signal transduction



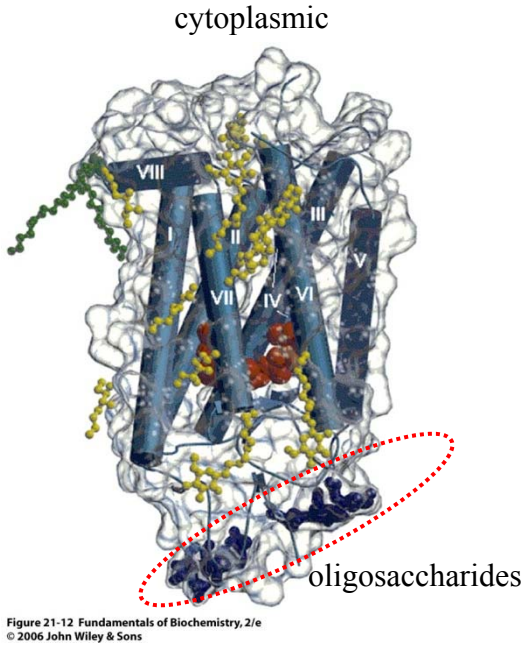
Signal transduction

Receptor mediated cellular response

G protein-coupled receptors (GPCRs)
>1000 different GPCRs in human genome
Alternate conformational changes on ligand binding

Heterotrimeric G proteins
Bind GTP and GDP
Hydrolyze GTP to GDP + Pi
heterogeneous α,β,γ subunits (45,37,9 kD)

Bovine rhodopsin



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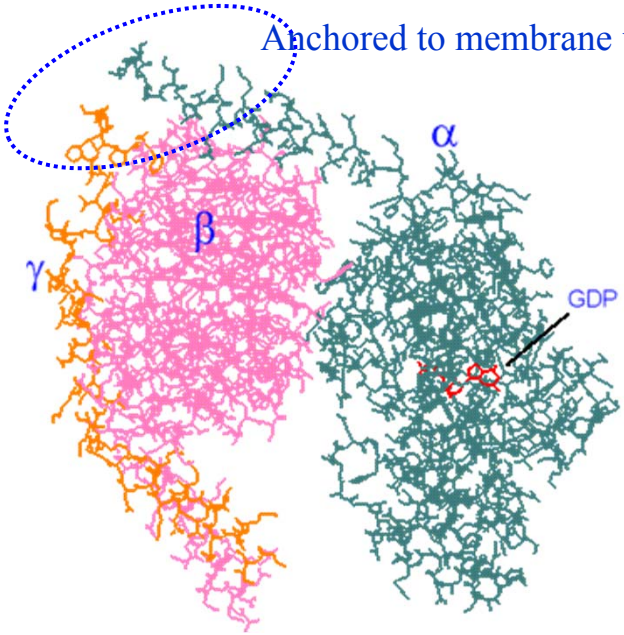
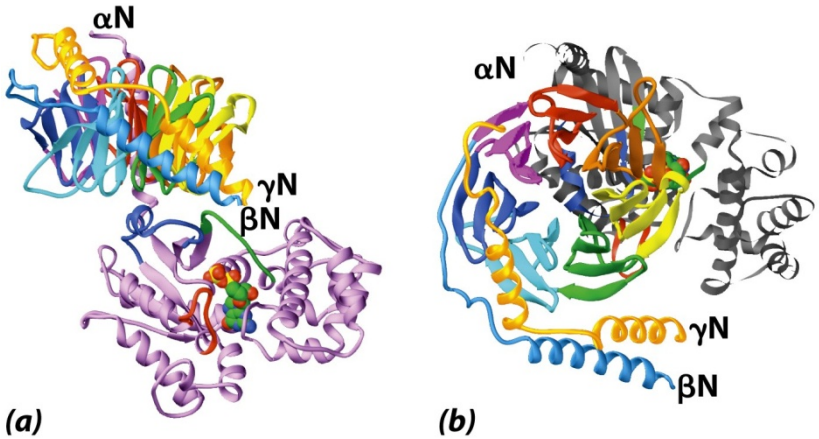


Heterotrimeric G protein



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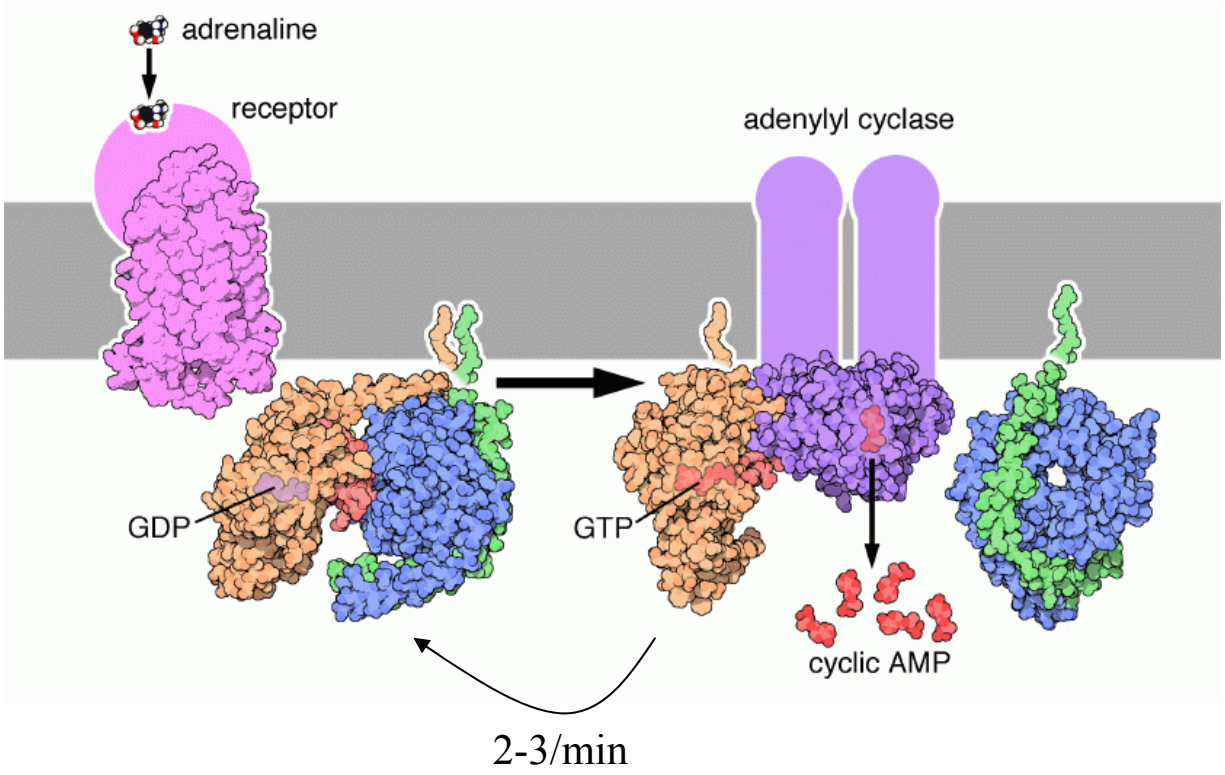


Accessory proteins

GTPase-activating protein (GAP): >2000-fold rate enhancement of GTP hydrolysis

Guanine nucleotide exchange factor (GEF): induces GDP release

Effecter proteins: adenylate cyclase

Stimulatory G protein, Gsα

Inhibitory G protein: Giα

A variety of mammalian G proteins (20 α subunits, 6 β subunits, 12 γ subunits)

Signal amplification

Adenylate cyclase

ATP → cAMP + PPi
Tissue specific 10 isoforms in mammals
Differ in their regulatory properties
$NM_1C_{1a}C_{1b}M_2C_{2a}C_{2b}$ sequence
C1a+C2a: catalytic core
C1b and C1a+C2a: bind regulatory molecules
Other regulators: Ca^{2+}, calmodulin, PKA, PKC
A variety of stimulus determines cAMP levels

Mammalian adenylate cyclase

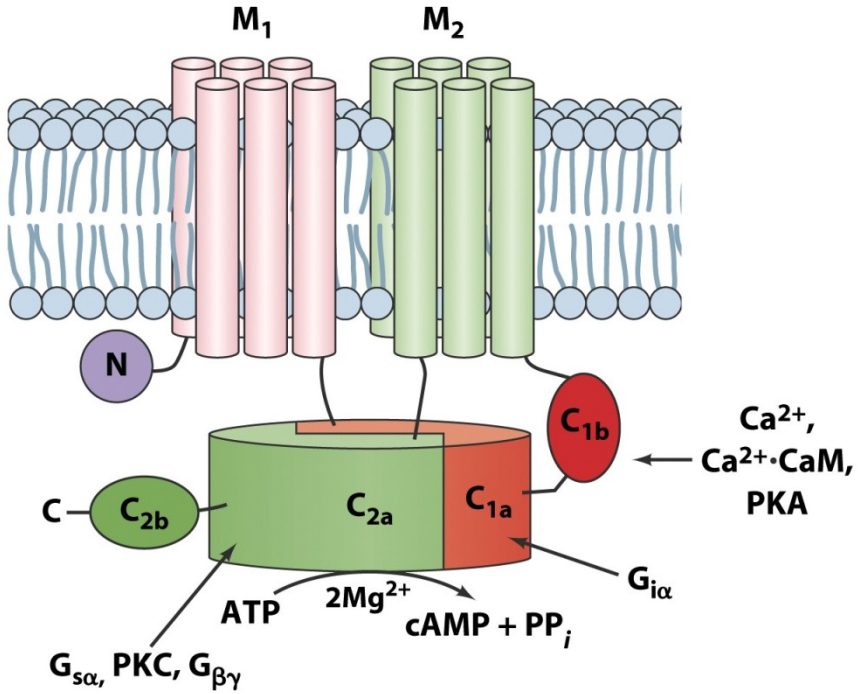
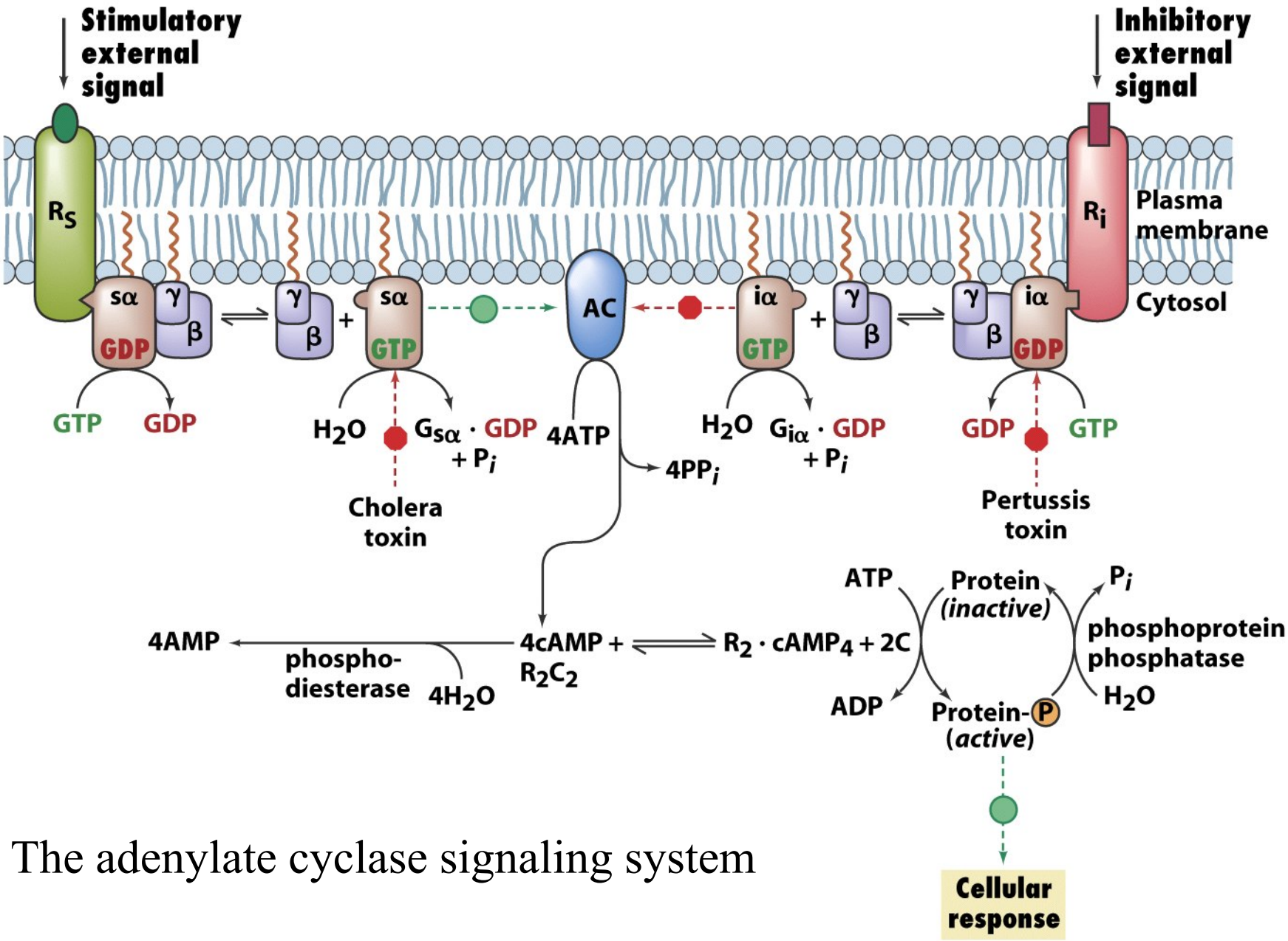


Figure 21-14 Fundamentals of Biochemistry, 2/e



The adenylate cyclase signaling system

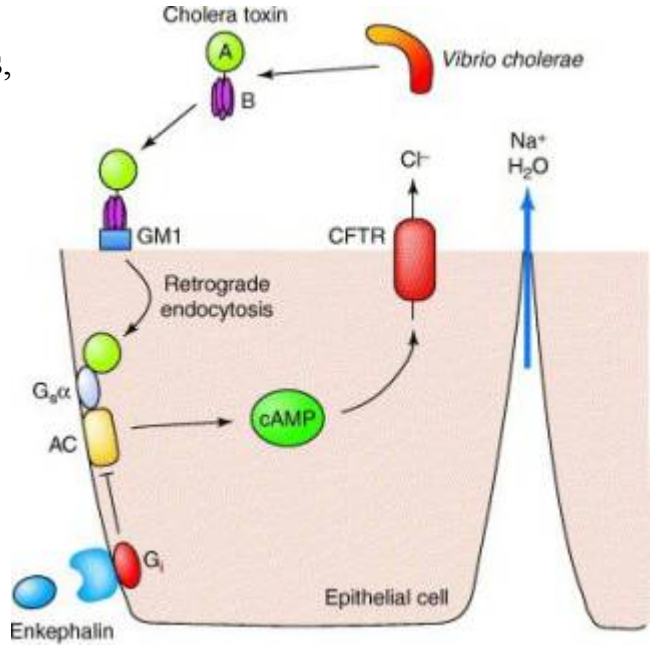
Figure 21-15 Fundamentals of Biochemistry, 2/e

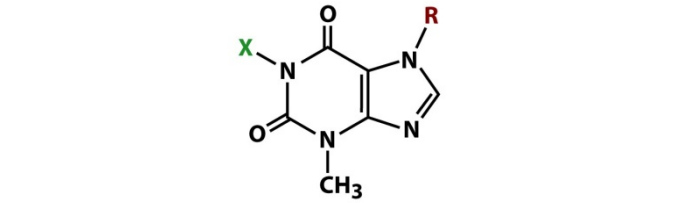
Drug and toxins that affect cell signaling

Methylated purine derivatives: nonspecific antagonist of adenosine receptors, which is GPCRs, thereby increasing cAMP

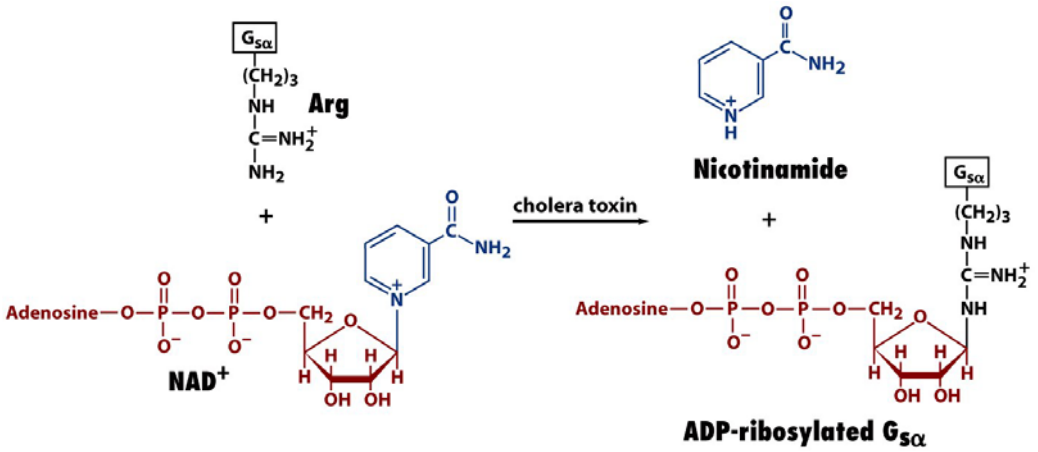
Cholera toxin: AB_5
~195 residue proteolytic fragment of A subunit
Transfer of ADP-ribose from NAD^+ to Gsα
Gsα activates adenylate cyclase but can't hydrolyze GTP
~100 fold increase of cAMP

Pertussis toxin
Homolog of cholera toxin
ADP-ribosylation of Giα
No exchange of GDP with GTP
Continued activation of adenylate cyclase





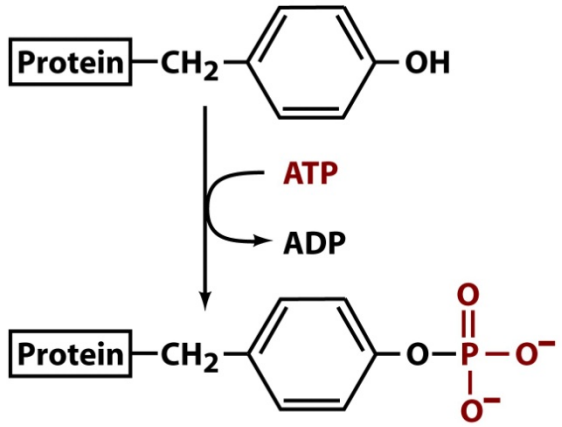
R = CH_3 X = CH_3 **Caffeine (1,3,7-trimethylxanthine)**
R = H X = CH_3 **Theophylline (1,3-dimethylxanthine)**
R = CH_3 X = H **Theobromine (1,7-dimethylxanthine)**



Receptor tyrosine kinases

Growth factors bind to receptor tyrosine kinases (RTKs)
Ligand-induced dimerization
(insulin receptor is a dimer in the unliganded state)

Autophosphorylation: cytoplasmic TK cross-phosphorylate
at 3 Tyr residues



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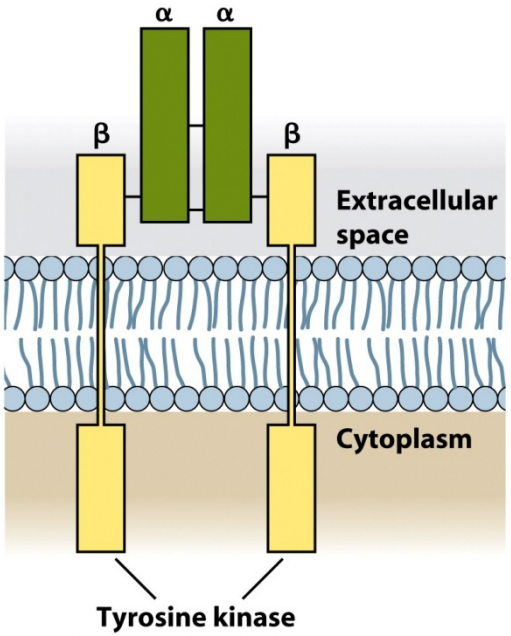

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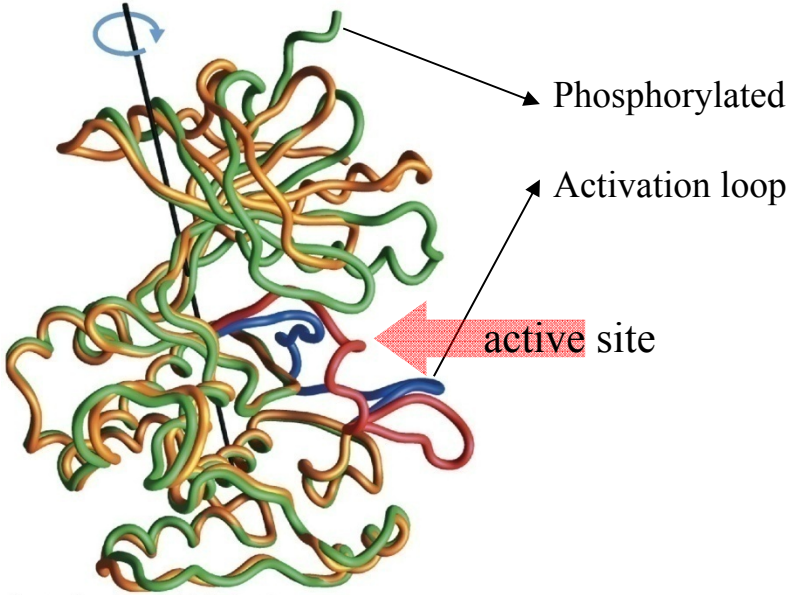
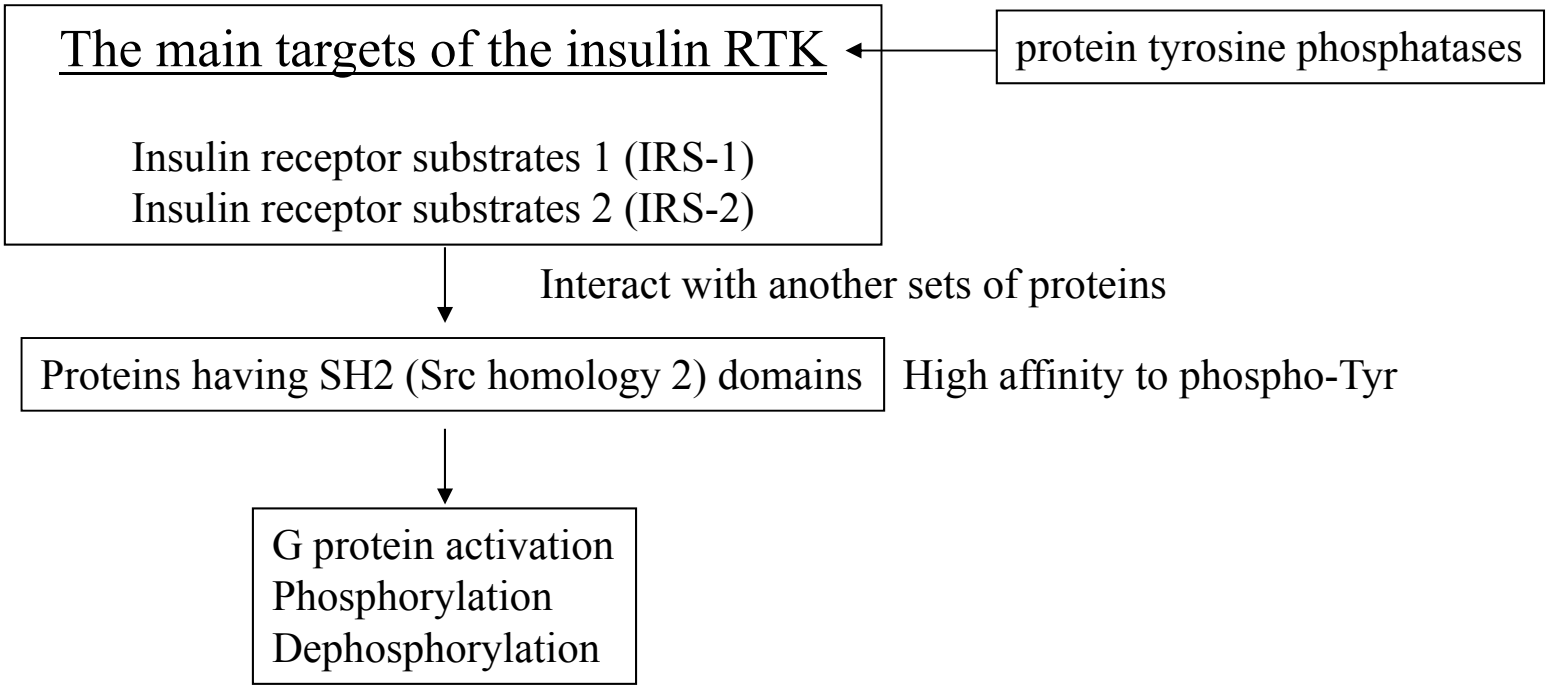


Figure 21-17b Fundamentals of Biochemistry, 2/e


The main targets of the insulin RTK
Insulin receptor substrates 1 (IRS-1)
Insulin receptor substrates 2 (IRS-2)
protein tyrosine phosphatases
Interact with another sets of proteins
Proteins having SH2 (Src homology 2) domains
High affinity to phospho-Tyr
G protein activation
Phosphorylation
Dephosphorylation

Growth factor RTK cascade

Grb2 protein (mammalian)
SH2 domain
2 SH3 domains (50~75 residues, binding Pro-rich sequences)
Sos protein (containing Pro-rich sequence)
Ras activation (a monomeric G protein)
Raf
MEK (MAP kinase/ERK kinase-activating kinase)/MAP kinase kinase
MAPK (mitogen-activated protein kinase)/ERK(extracellular-signal-regulated kinases)
Activation of transcription factors (Fos, Jun, Myc)

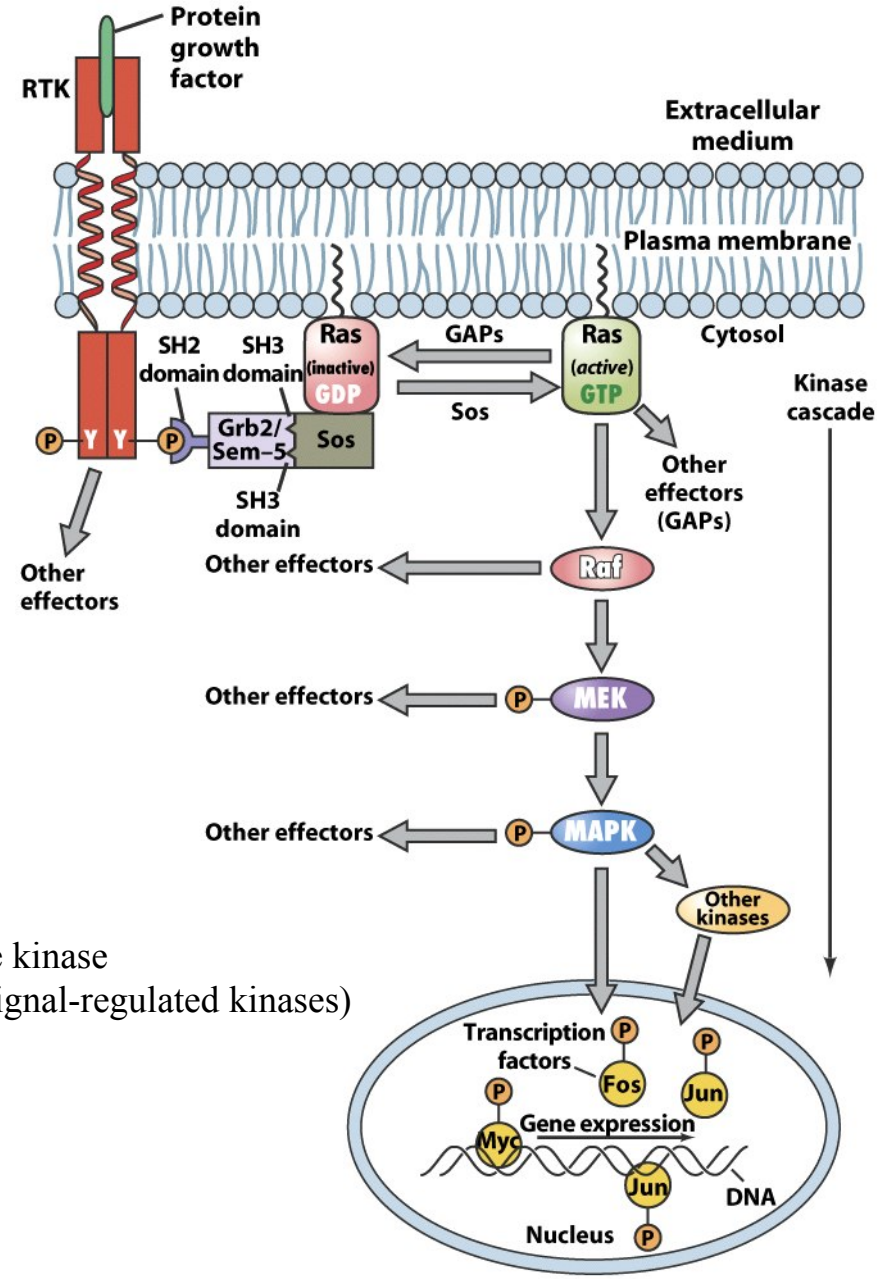


Figure 21-19 Fundamentals of Biochemistry, 2/e

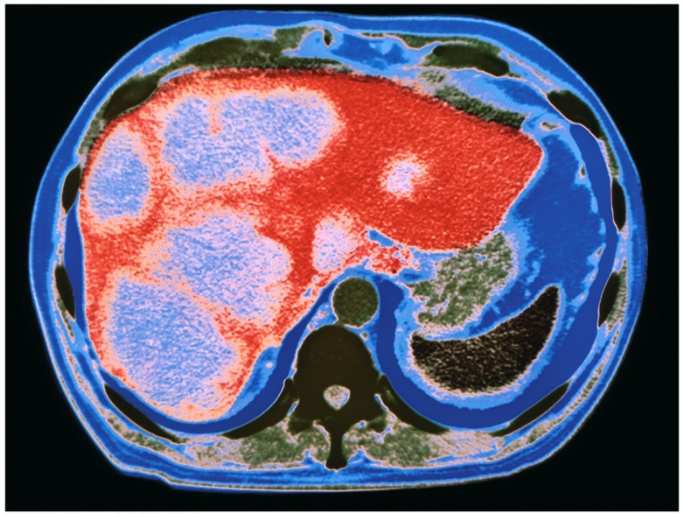
Oncogenes & cancer

Tumor: masses of cells in uncontrolled growth
Adult cells are largely quiescent

Malignant tumors (cancer): rapid growth, invasive
Benign tumors: slow growth, remain in place

<u>Oncogenes/protooncogenes</u>
v-src/c-src (60-kD tyrosine kinase): v-src is not regulated
v-erbB: EGF (epidermal growth factor) receptor lacking EGF-binding domain
phosphorylation without extracellular signal
v-ras: cellular G protein, hydrolyze GTP much more slowly

c-fos/v-fos
c-jun/v-jun



Liver cancer

Protein tyrosine phosphatases (PTPs)

- CX_5R motif (11-residue sequence [(I/V)HCXAGXGR(S/T)G])
- Membrane bound groups: similar structure to RTKs
- Intracellular groups: having SH-2 domain (SHP-2)

Protein Ser/Thr phosphatases: having binuclear metal ion

- PPP family: Fe^{2+} (or Fe^{3+}) and Zn^{2+}(or Mn^{2+}) in the catalytic centers (PP2A)
- PPM family: two Mn^{2+} ions in the catalytic centers (calcineurin)

SHP-2

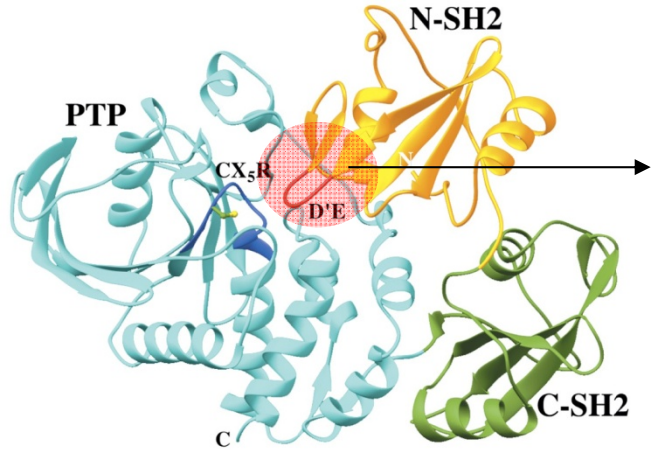


Figure 21-20 Fundamentals of Biochemistry, 2/e

Blocking active site

Figure 21-21 Fundamentals of Biochemistry, 2/e

The phosphoinositide pathway

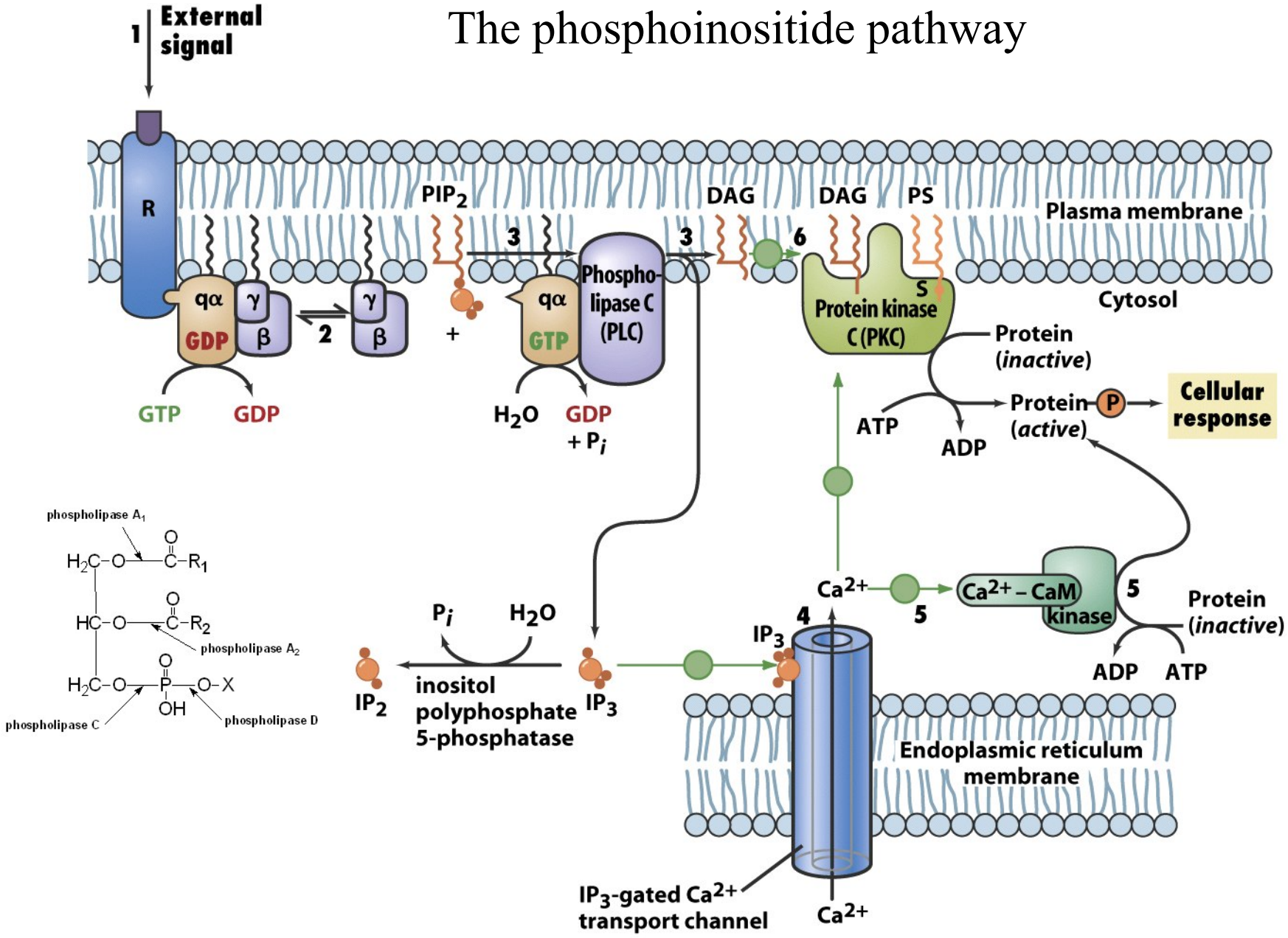
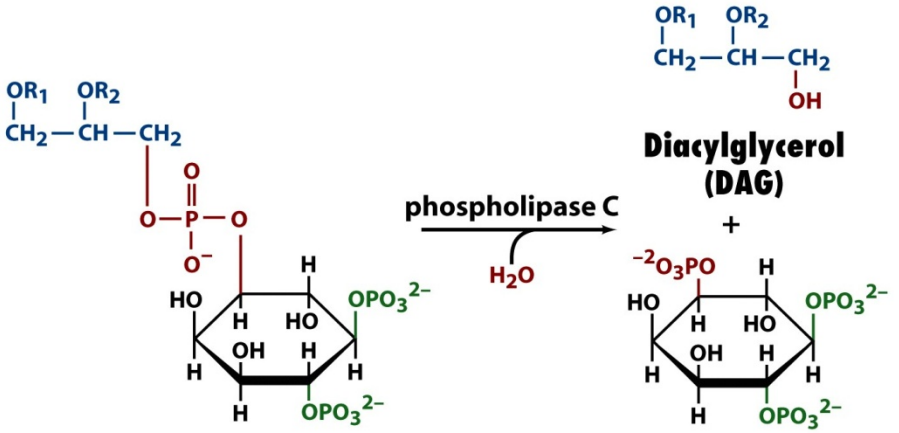


Figure 21-22 Fundamentals of Biochemistry, 2/e

PLC: 11 isozymes in mammals



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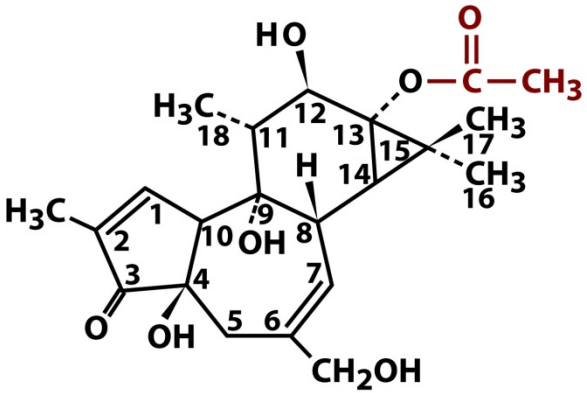
Phorbol-13-acetate (12-O-tetradecanoylphorbol-13-acetate, TPA)
Structurally similar to diacylglycerol
Tumor promoter (mitogen)



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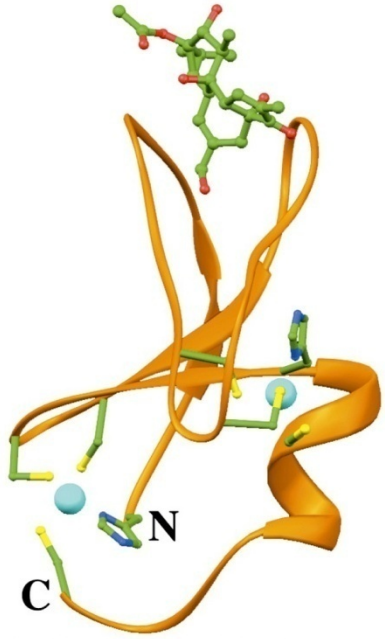

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Insulin signal transduction

Involves both the tyrosine kinase signaling cascade and phosphoinositides

PI3K (phosphoinositide 3-kinase) produces phosphoinositol 3,4,5-triphosphate which activates phosphoinositide-dependent protein kinase-1 (PDK1)

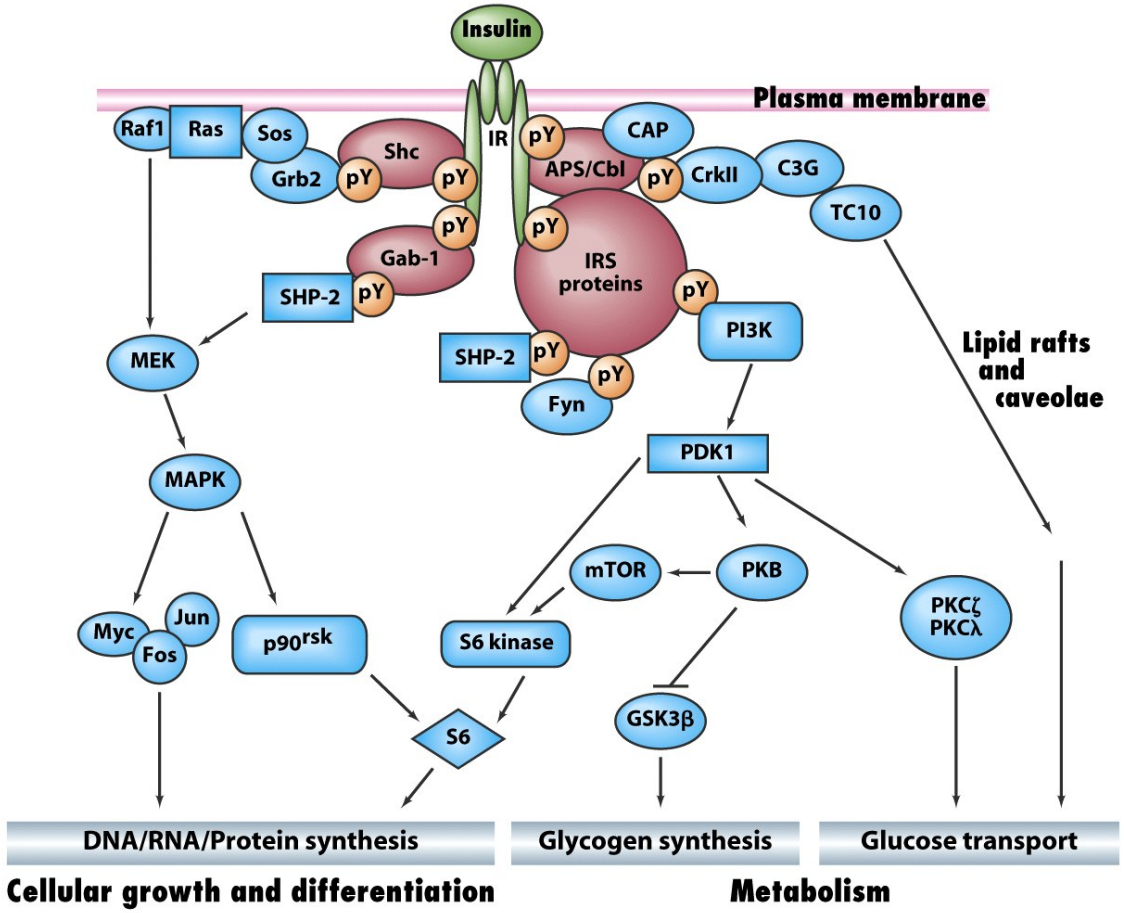


Figure 21-25 Fundamentals of Biochemistry, 2/e

Anthrax

Bacillus anthracis produces toxin

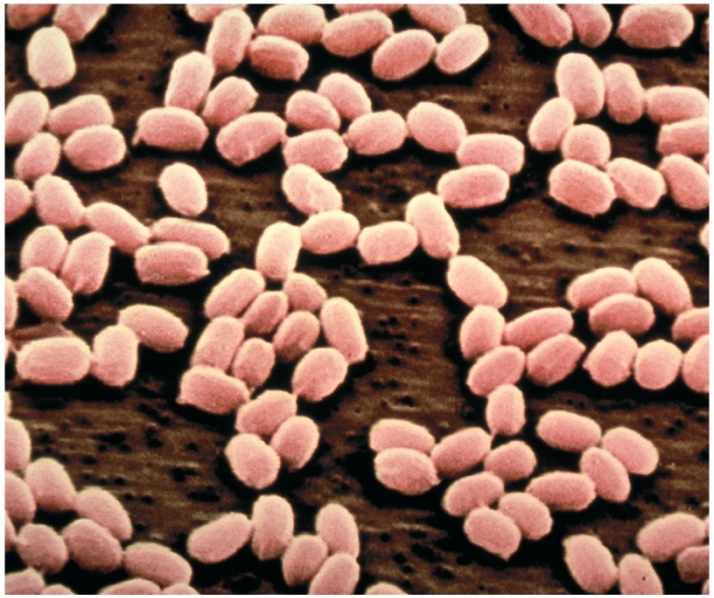
Anthrax toxin consists of three proteins

Protective antigen (PA): binding to receptor

Edema factor (EF): adenylate cyclase (requiring host calmodulin)

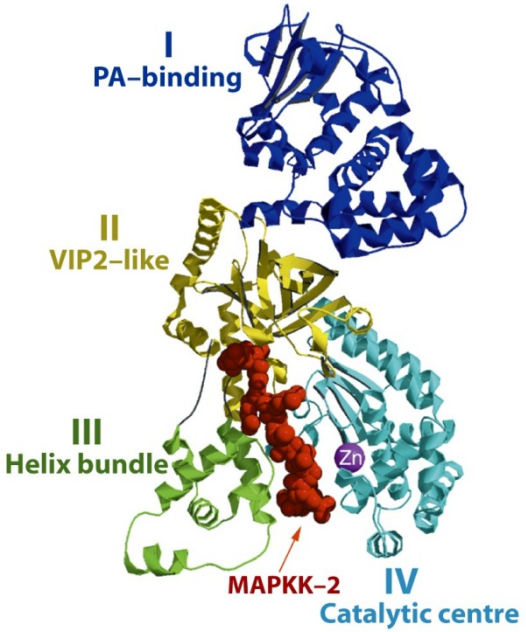
Lethal factor (LF): protease of MAPKK family

MAPKK (mitogen-activated protein kinase kinase)



Box 21-3 figure 1 Fundamentals of Biochemistry, 2/e

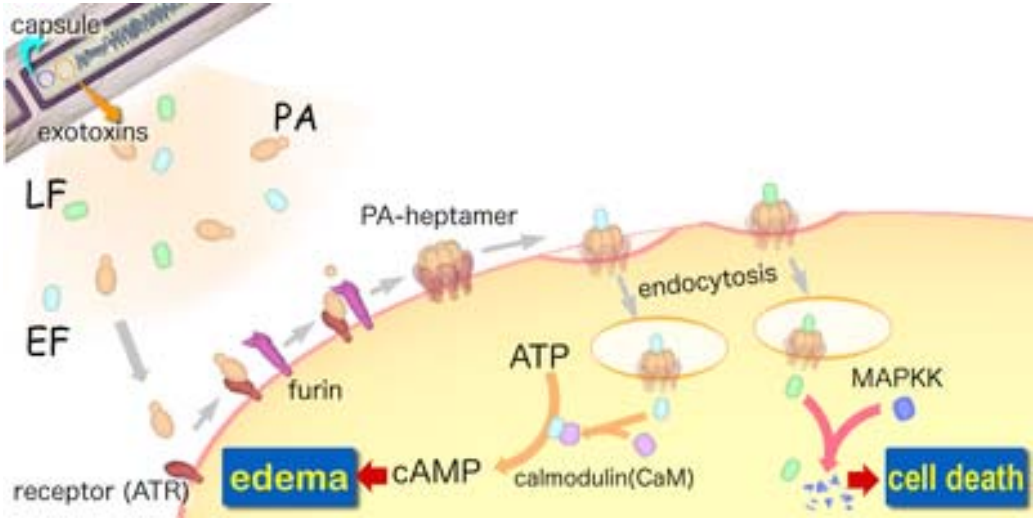
Lethal factor



Box 21-3 figure 2 Fundamentals of Biochemistry, 2/e

The pathways for toxin entry into cells and the points at which existing antitoxins can act.

LF triggered macrophage lysis, causing the sudden release of inflammatory mediators. This probably results in the massive septic shock that causes death.



http://en.wikipedia.org/wiki/Anthrax_toxin

Disturbances in fuel metabolism

Metabolic homeostasis

Metabolic changes in starvation, diabetes, and obesity

Dietary glucose

- 1/3 is converted to glycogen in the liver
- A half of the remainder is converted to glycogen in muscle cells
- The rest is oxidized for immediate needs
- Excess glucose is converted to triacylglycerol in the liver and exported for storage in adipose tissue

Table 21-2 Fuel Reserves for a Normal 70-kg Man

Fuel	Mass (kg)	Calories[a]
Tissues		
Fat (adipose triacyglycerols)	15	141,000
Protein (mainly muscle)	6	24,000
Glycogen (muscle)	0.150	600
Glycogen (liver)	0.075	300
Circulating fuels		
Glucose (extracellular fluid)	0.020	80
Free fatty acids (plasma)	0.0003	3
Triacylglycerols (plasma)	0.003	30
Total		***166,000***

[a]1 (dieter's) Calorie = 1 kcal = 4.184 kJ.

Source: Cahill, G.E., Jr., *New Engl. J. Med.* **282,** 669 (1970).

Blood glucose remains constant

Gluconeogenesis supplies glucose during starvation

- Muscle protein degradation
- Brain adaptation to ketone bodies

Liver glycogen depletion during fasting in 7 subjects

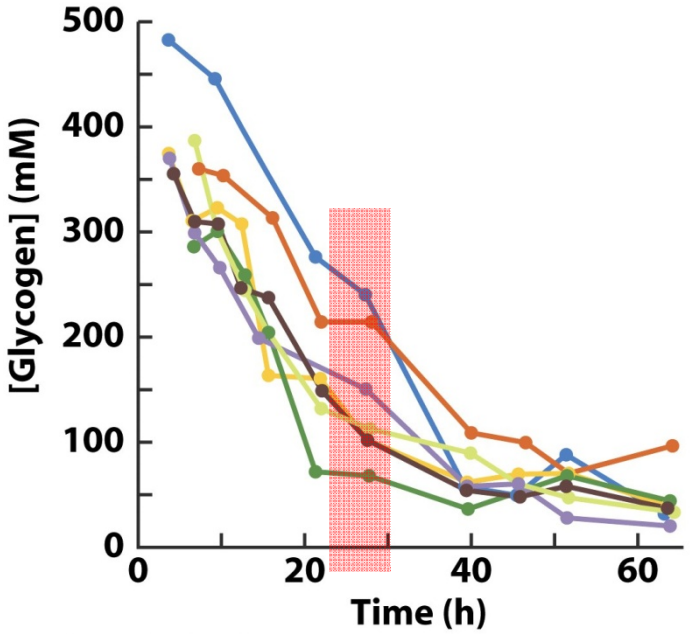


Figure 21-26 Fundamentals of Biochemistry, 2/e
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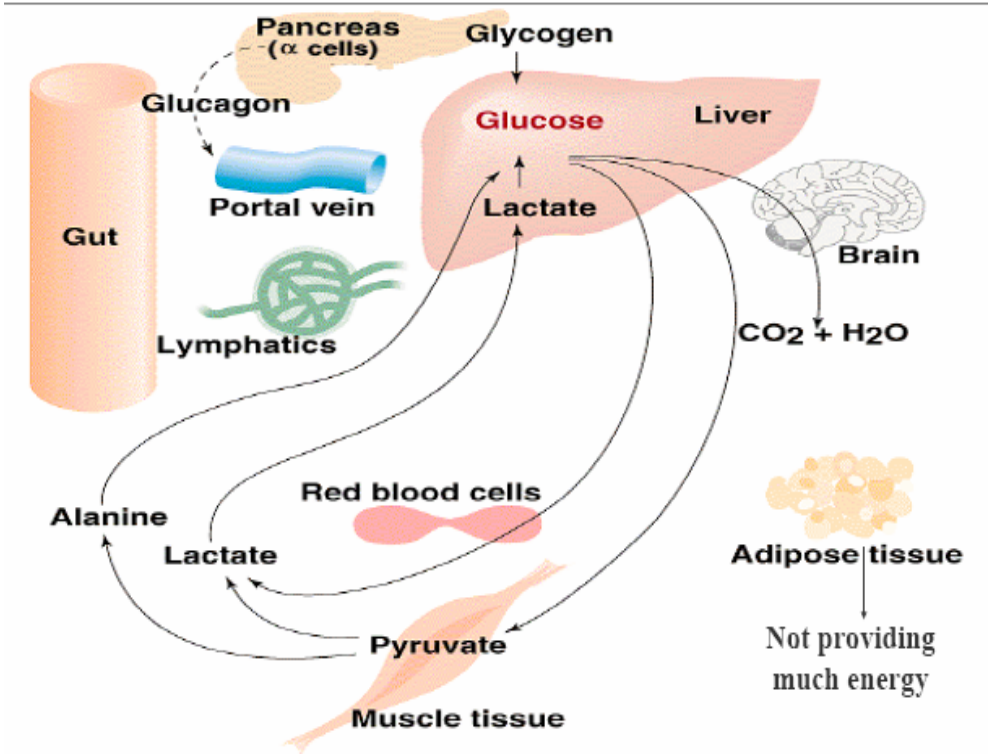
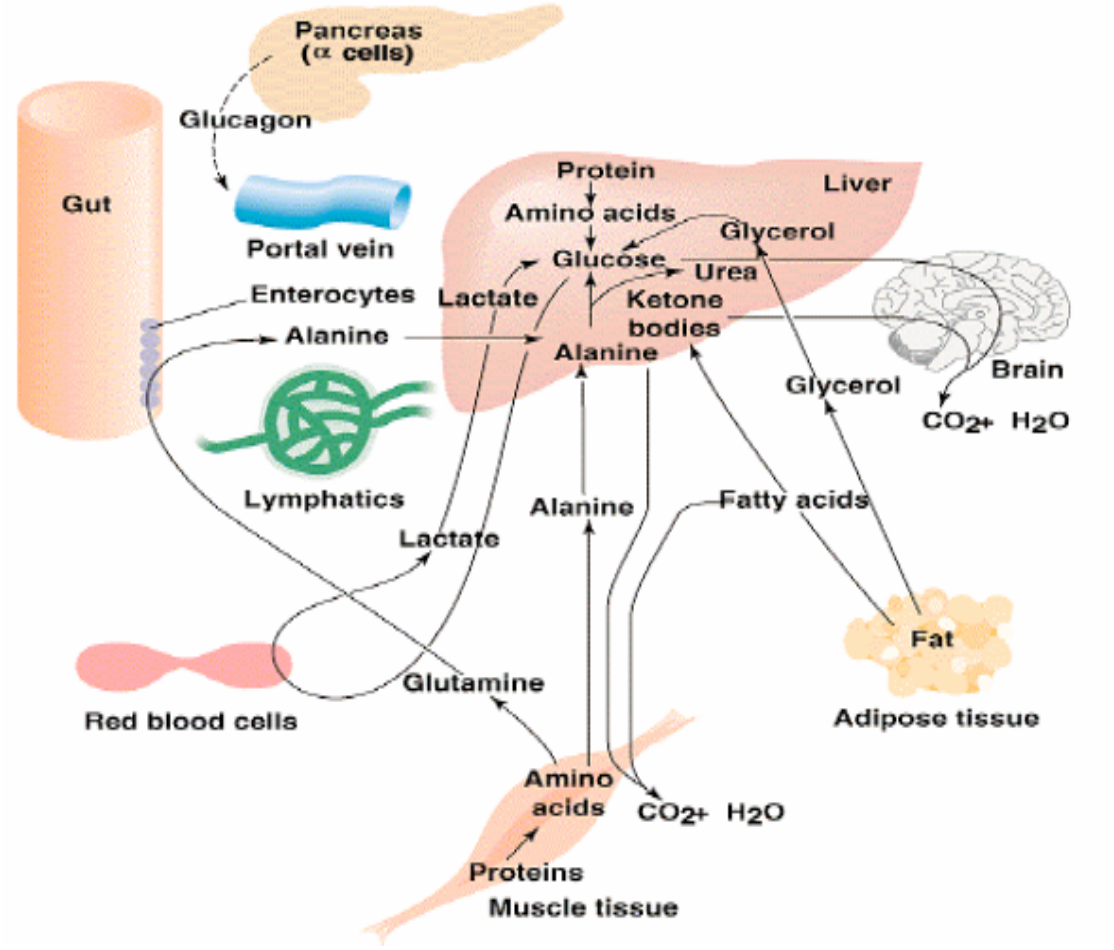
Metabolic interrelationships in the early fasting state (fig. 22.3)



Metabolic interrelationships in the fasting state (fig. 22.4)



Diabetes mellitus

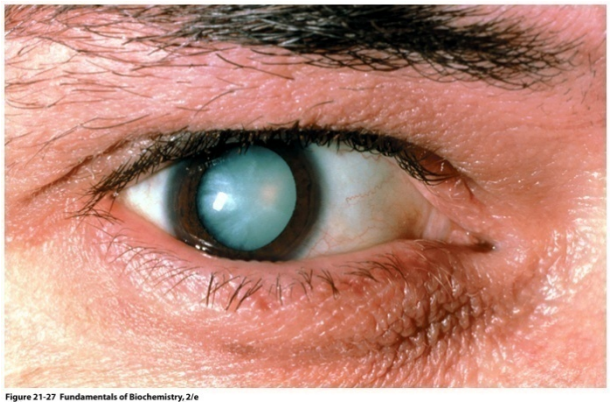
Heterogeneous clinical syndrome in which the central feature is a chronic elevation of the blood glucose concentration - this results in a range of pathologies.

Due to a deficiency of insulin (absolute) or a resistance to insulin (relative).

type I: insulin-dependent (juvenile-onset diabetes mellitus)
type II: non-insulin-dependent (maturity-onset diabetes mellitus)

The chronic hyperglycemia is associated with long term tissue damage, especially the blood vessels, nerves, heart, kidneys and eyes.

http://en.wikipedia.org/wiki/Diabetes
http://www.diabetes.org/home.jsp
http://diabetes.niddk.nih.gov/
http://www.latrobe.edu.au/podiatry/diabetesresources/diabetes_lecture_1.htm



Diabetic cataract

NIDDM: insulin resistant

insulin receptor or signal transduction
increased insulin production
diminished β cell response
increased blood glucose

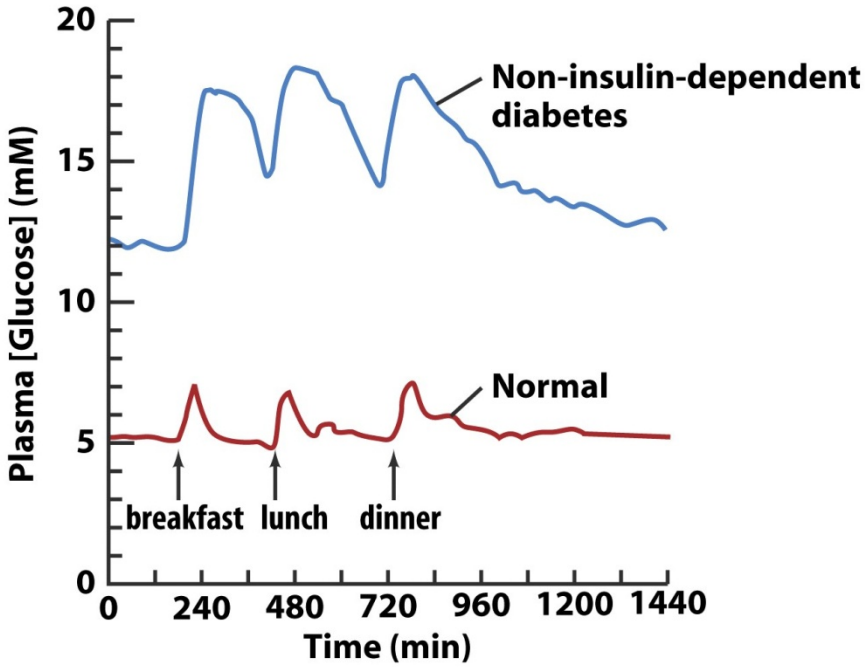
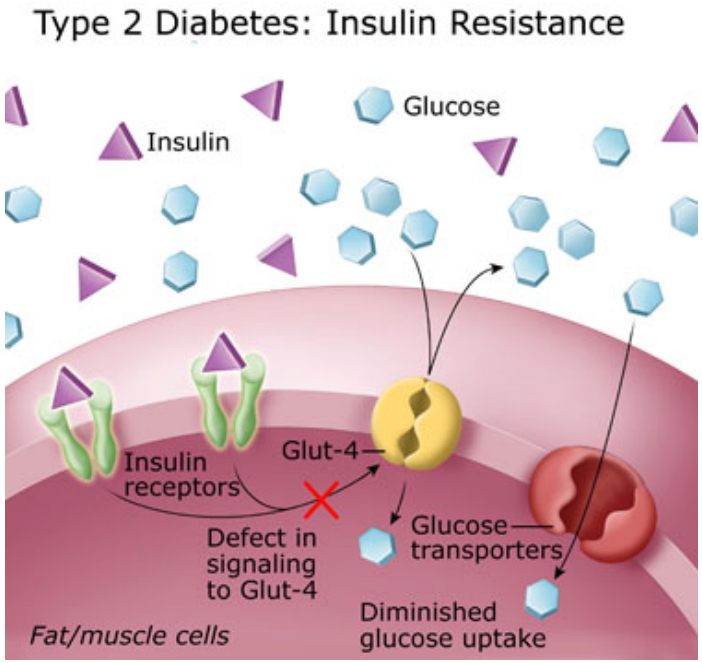


Figure 21-28 Fundamentals of Biochemistry, 2/e



Possible causes of NIDDM II

Overeating increases insulin production but eventually suppresses the synthesis of insulin receptors

Obesity causes elevated blood conc of free fatty acids, which decrease insulin signal transduction

Drugs decreasing insulin resistance by either

decreasing glucose release by the liver (metformin)

or increasing insulin-stimulated glucose disposal in muscle (TZD)

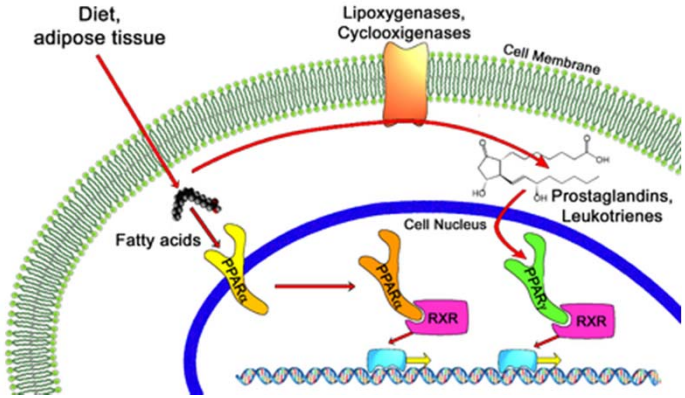
they target mito Complex I, thereby increasing [AMP]

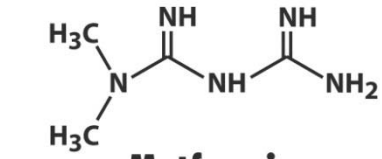
the resulting increase in AMPK activity

decreased liver gluconeogenesis and increased muscle glucose utilization

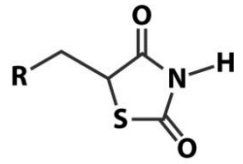
TZD also activates PPAR-γ in adipose tissue, leading to increased fatty acid uptake by them

PPAR (peroxisome proliferator-activated receptor)-γ is a group of nuclear receptor proteins acting as TF





Metformin



A thiazolidinedione (TZD)

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http://en.wikipedia.org/wiki/Peroxisome_proliferator-activated_receptor

Obesity

A chronic imbalance between fat and carbohydrate consumption and utilization
Increases the mass of adipose tissue
through an increase in the number of adipocytes or their size

Overeating mouse (ob/ob)
- lack leptin polypeptide produced by adipocytes
- satiety signal to the brain: decrease food intake & increase metabolism

Not identical to human
- increased fat body, increased leptin
- probably due to decreased leptin receptor

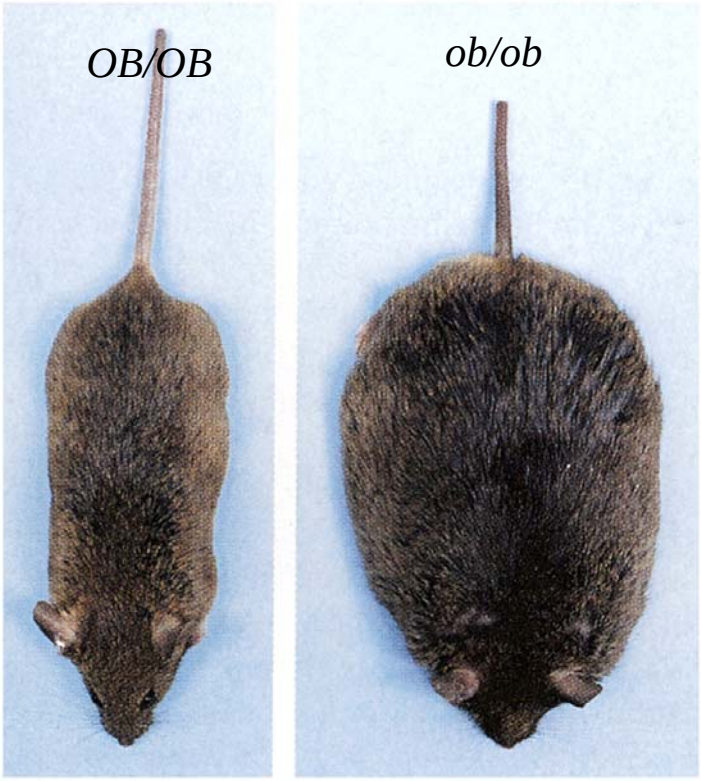


Figure 21-29 Fundamentals of Biochemistry, 2/e

Neuropeptide Y

Decreased leptin leads to high conc of neuropeptide Y from hypothalamus
Stimulates appetite and leads to fat accumulation

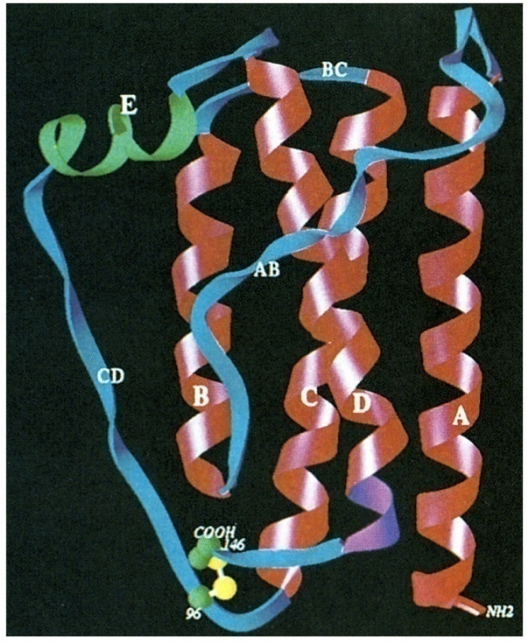
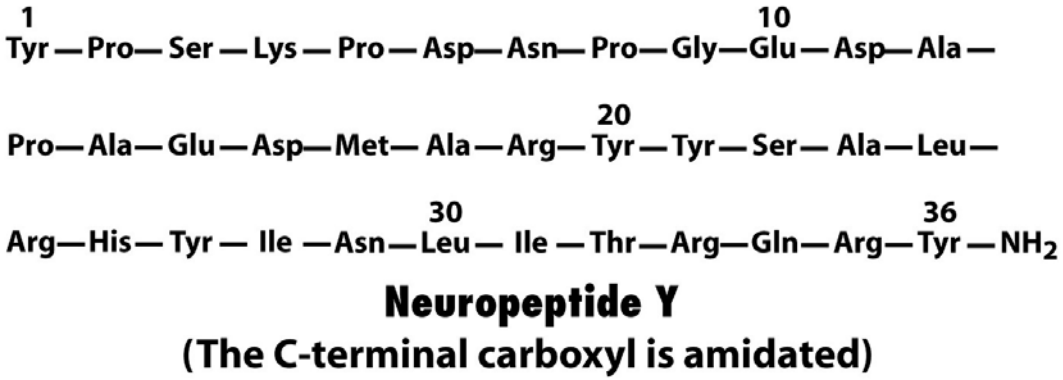


Figure 21-30 Fundamentals of Biochemistry, 2/e



Neuropeptide Y

(The C-terminal carboxyl is amidated)

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Fuel metabolism, body weight, and appetite are linked

Insulin receptors in the hypothalamus

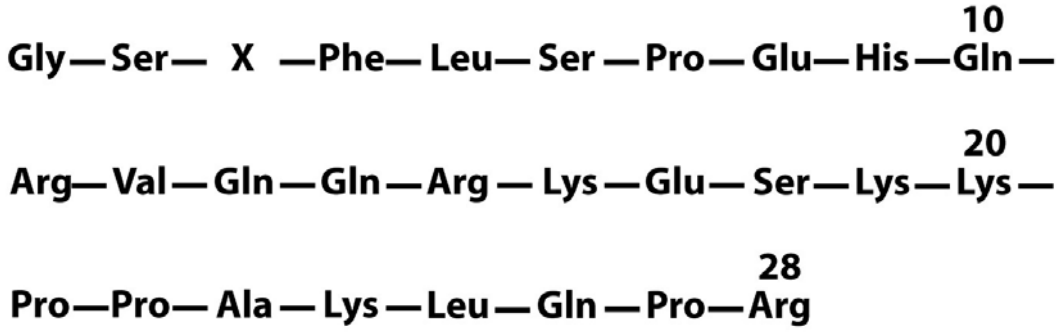
inhibit neuropeptide Y secretion

Ghrelin

appetite-stimulating peptide secreted by the empty stomach

most likely a short-term appetite control system (increase before meal & decrease just afterward)

boost levels of neuropeptide Y



Ghrelin

(X = Ser modified with *n*-octanoic acid)

Unnumbered figure pg 783b Fundamentals of Biochemistry, 2/e

PYY3-36

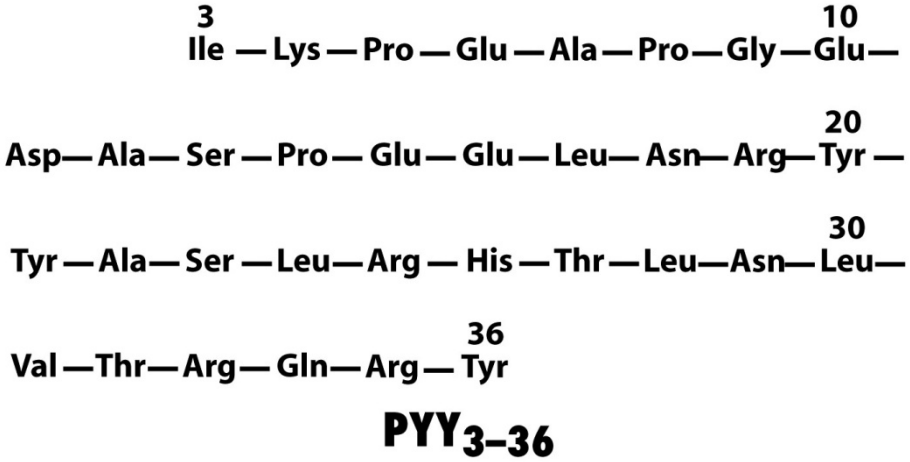
Appetite suppressing hormone from gastrointestinal tract

Decrease food intake by inhibiting neuropeptide Y secretion

Resistin

108-residue polypeptide from adipocyte

Block the action of insulin on adipocytes



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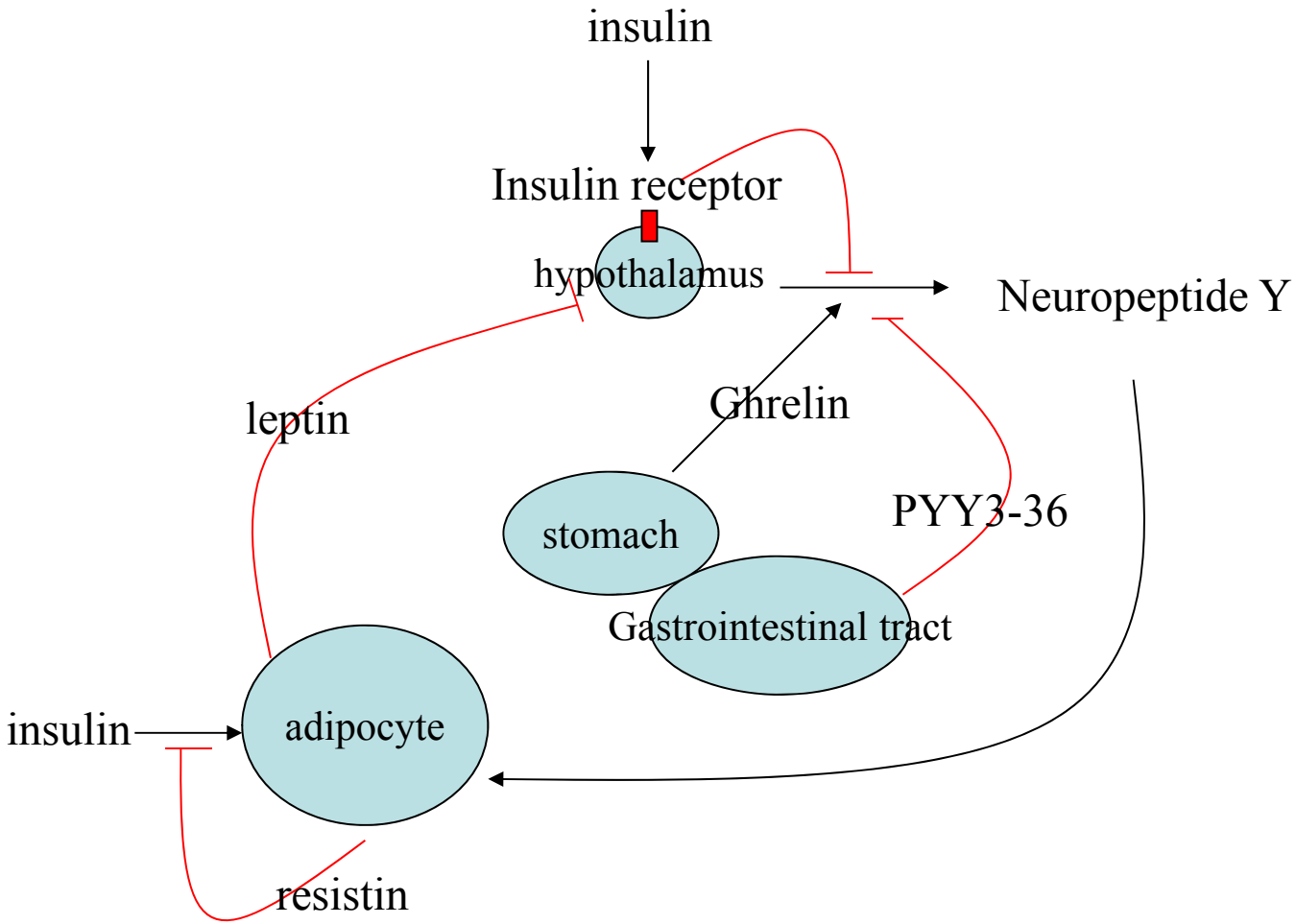

Leptin & insulin: blood circulation