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LEHNINGER
PRINCIPLES OF BIOCHEMISTRY

Sixth Edition

CHAPTER 23
Hormonal Regulation and Integration of Mammalian Metabolism
(포유류의 대사의 통합과 호르몬에 의한 조절)

CHAPTER 23
Hormonal Regulation and Integration of Mammalian Metabolism

Key topics:

- Basics of endocrine signaling
- Hormonal regulation of fuel metabolism: insulin
- Obesity

Neuronal vs. Hormonal Signaling

- In *neuronal* signaling, nerve cells release neurotransmitters that act on nearby cells
  - Distance may be small (~μm)
- In *hormonal* signaling, hormones are carried by the bloodstream to nearby cells *or* other organs
  - Distance may be great (1 m or more)

23.1 Hormones: Diverse Structures for Diverse Functions

- 다세포 생물(multicellular organism)의 특징: 세포 분화와 일의 분담.
  - 간: 대사의 진행과 배분의 중심적인 역할(당질, 아미노산, 지방 등의 대사). 영양소의 각 기관과 조직에 공급.
  - 간외(extrahepatic or peripheral) 조직: 간 이외의 조직
    - 지방조직(adipose tissue): 지방산의 지방형태로의 저장 및 방출.
    - 골격근(skeletal muscle): 운동
    - 뇌: ion을 pumping하여 신호전달
    - Etc.

신경계와 내분비계의 신호전달

- 신경계의 신경전달물질 (neurotransmitter)과 내분비계의 호르몬은 화학적 신호전달기전이 유사

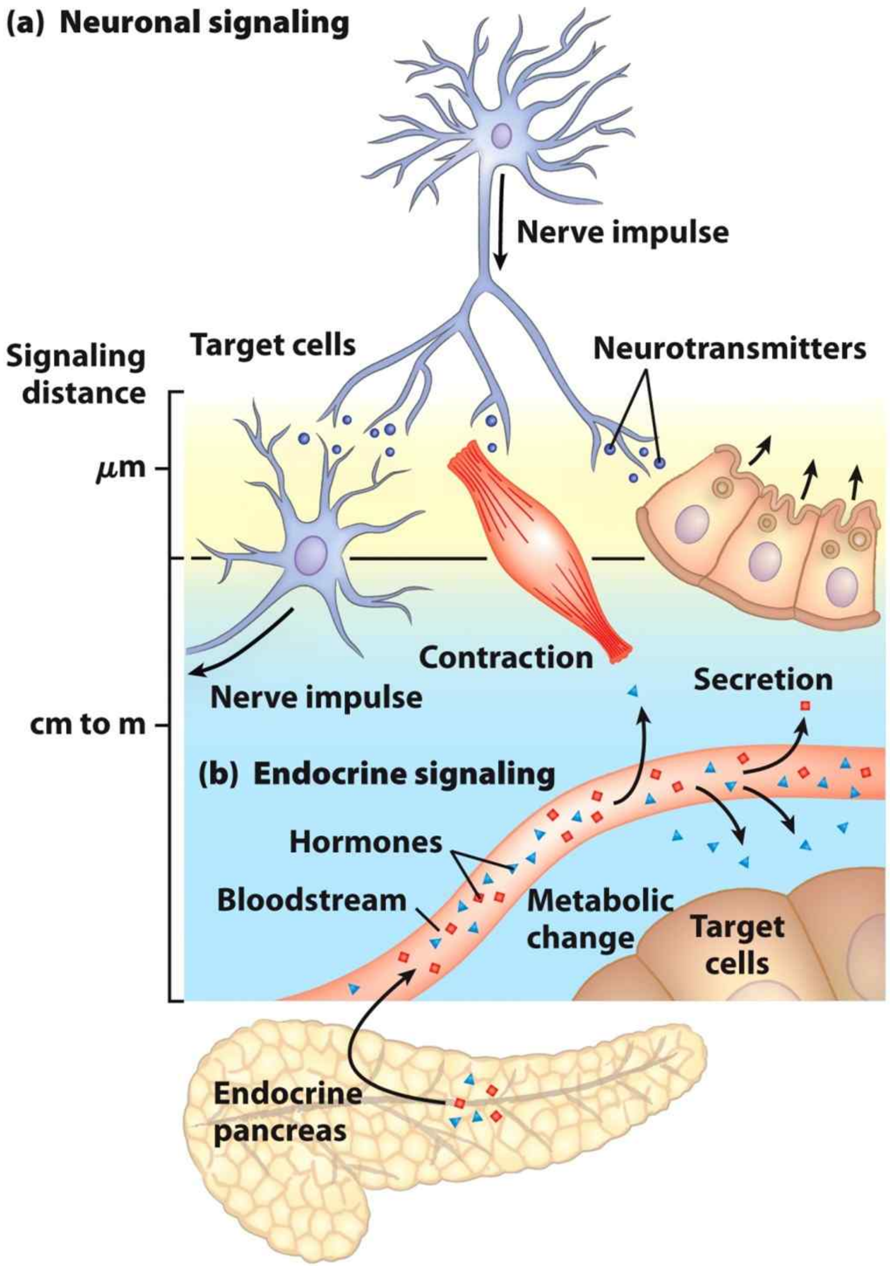

Figure 23-1
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호르몬연구는 충분한 양의 확보와 민감한 검색법의 개발을 통해 발전

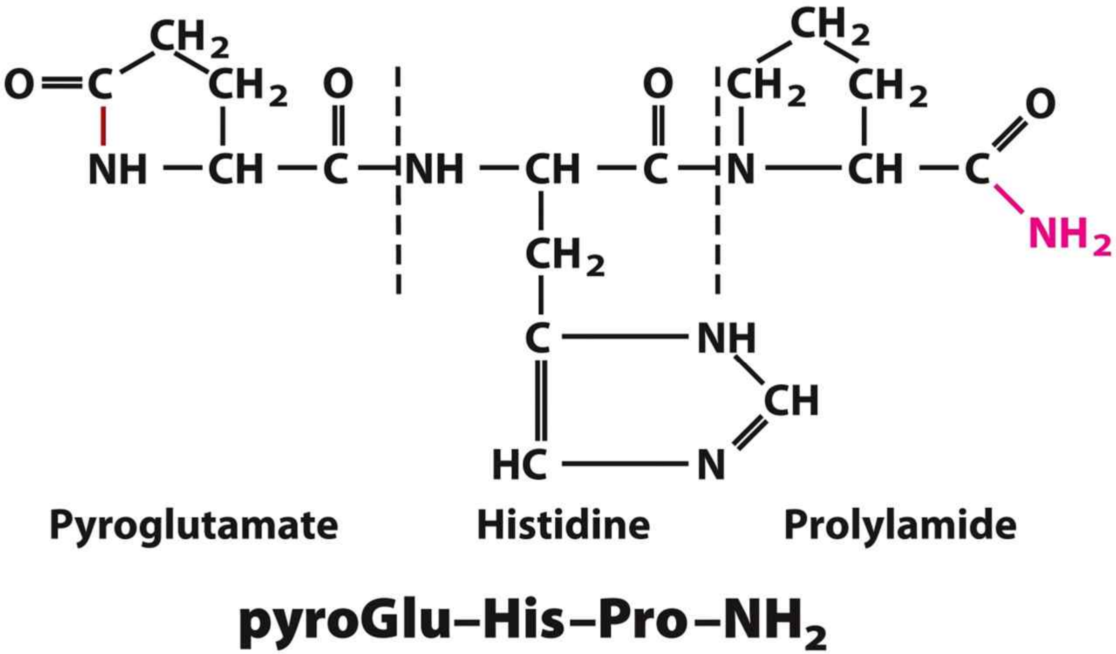

Figure 23-2
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Thyrotropin-releasing hormone(TRH)의 구조:

연구를 위해 백만마리의 돼지 또는 양의 시상하부에서 추출

Studying hormones presents some challenges

- **Produced in small amounts** so difficult to purify in appreciable quantity
  - Chemical analysis of thyrotropin-releasing hormone (TRH) from pigs required one million hypothalmuses (1,000,000 pigs)
    - See next slide
- **The Radioimmunoassay** (RIA) was developed to be a more sensitive way to measure hormones using radiolabeled antibodies

The ELISA (Enzyme-Linked Immunosorbent Assay) can detect and/or quantify hormones

- Purified hormone is injected into an animal
  - Animal makes an antibody to the hormone
- Antibody is purified, labeled with radioactive tag (for RIA) or an enzyme that produces a colored product (for ELISA)
- For a quantitative assay, a known amount of tagged antibody is added to a sample
- The fraction of the antibody bound is measured via photometry (for ELISA) or radiation detection (for RIA)

Water-Soluble Hormone (Insulin, etc.) Action vs. Nonpolar (Steroid, etc.) Hormone Action

호르몬작용의 2가지 기전:

1. 스테로이드 호르몬(steroid hormones):
   -세포막 투과 후 호르몬 수용체와 결합 → 핵 내로 들어가서 특정 단백질의 발현 유도
2. 비스테로이드 호르몬(nonsteroid hormones): 단백질, 펩타이드 등과 같이 세포막을 투과할 수 없는 호르몬. 세포표면의 수용체와 결합하여 신호전달

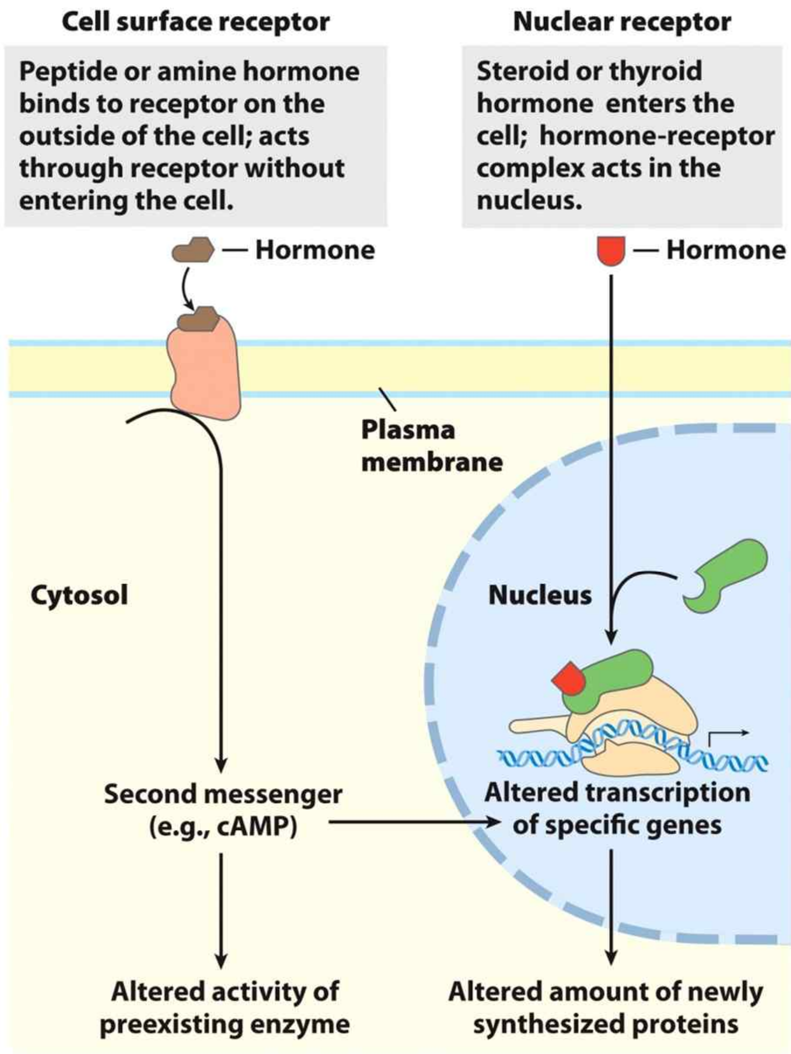

Figure 23-3
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호르몬의 분류

- 화학구조와 작용양식에 따른 분류 (Table 23-1)
- 전달거리에 따른 분류:
  - 내분비(endocrine): 분비된 세포에서 멀리 떨어진 표적세포에 작용
  - 측분비(paracrine): 분비된 세포에 인접한 세포들에 작용, prostaglandins, growth factors 등
  - 자가분비(autocrine): 분비된 세포의 세포표면의 수용체에 작용

TABLE 23–1 Classes of Hormones

Type	Example	Synthetic path	Mode of action
Peptide	Insulin, glucagon	Proteolytic processing of prohormone	Plasma membrane receptors; second messengers
Catecholamine	Epinephrine	From tyrosine	
Eicosanoid	PGE_1	From arachidonate (20:4 fatty acid)	
Steroid	Testosterone	From cholesterol	Nuclear receptors; transcriptional regulation
Vitamin D	1α,25-Dihydroxyvitamin D_3	From cholesterol	
Retinoid	Retinoic acid	From vitamin A	
Thyroid	Triiodothyronine (T_3)	From Tyr in thyroglobulin	
Nitric oxide	Nitric oxide	From arginine + O_2	Cytosolic receptor (guanylyl cyclase) and second messenger (cGMP)

Table 23-1
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펩타이드 호르몬계

- 시상하부(hypothalamus), 뇌하수체 (pituitary), 췌장 등에서 분비되는 호르몬이 여기에 속함
- 전구체(proform)로 생성되어 활성형으로 변환
- 일부의 경우 하나의 전구체로부터 여러 호르몬 생성(예: POMC로부터 여러 호르몬 생성)
- 분비소체(secretory vesicles)에 고농도로 저장되었다가 exocytosis 를 통해 방출

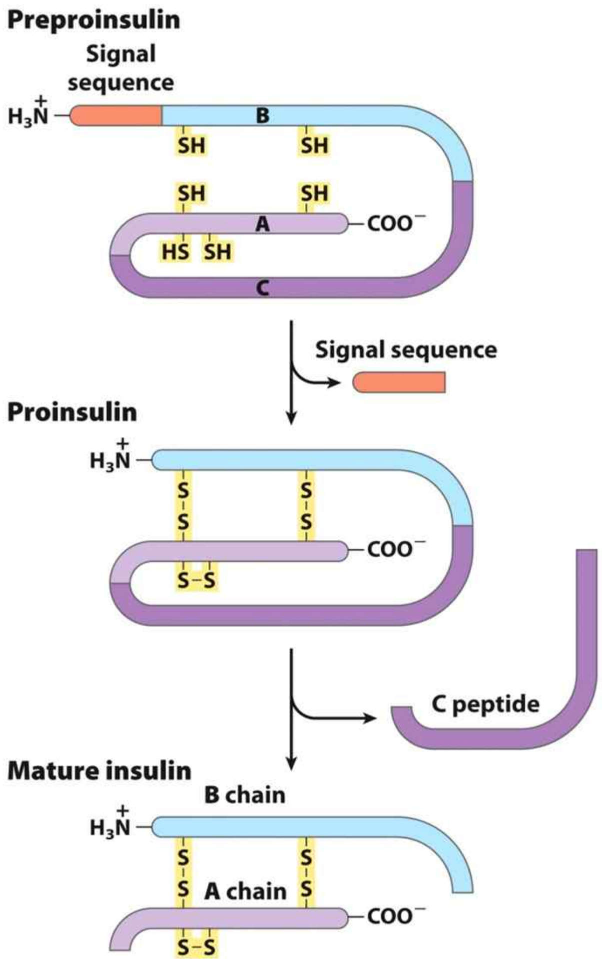

Figure 23-4
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인슐린의 생성과정

Proopiomelanocortin(POMC) 전구체의 분해를 통한 여러 호르몬의 생성:

뇌하수체 전엽(anterior pituitary)에서 생성

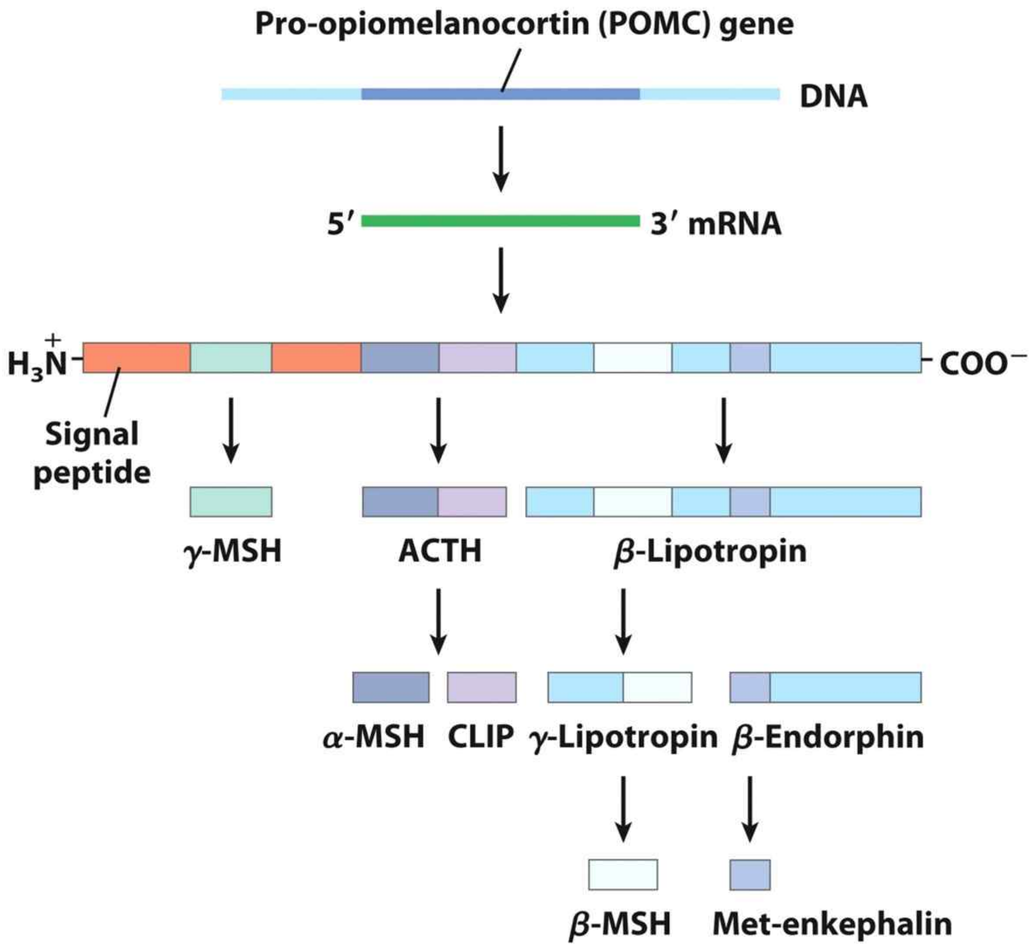

Figure 23-5
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카테콜아민 호르몬계

Tyrosine

↓

L-DOPA

↓

Dopamine

↓

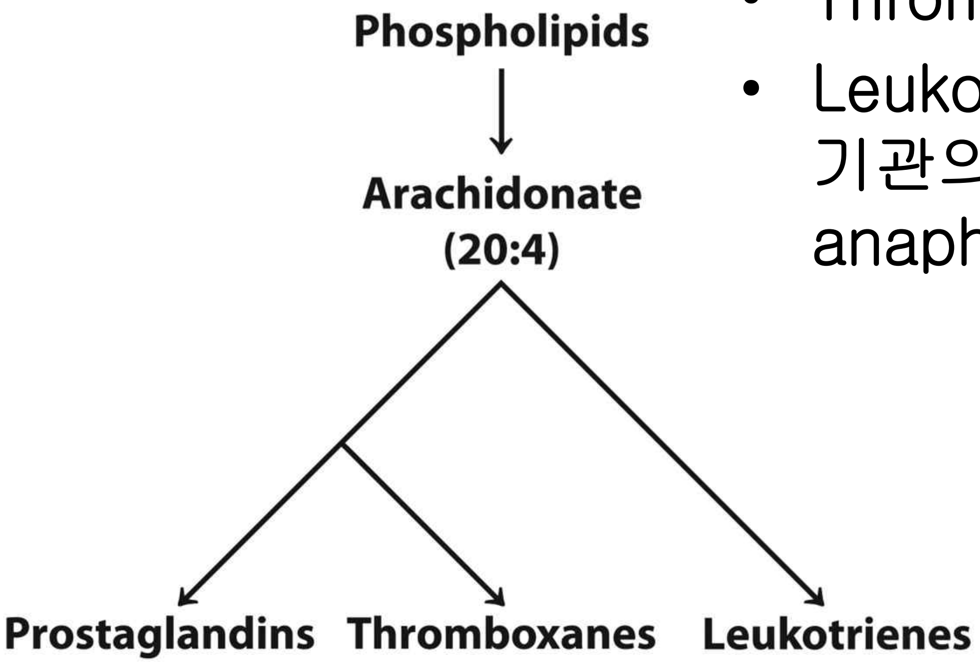
Norepinephrine

↓

Epinephrine

- 아미노산인 Tyr에서 생성
- epinephrine, norepinephrine 등
- 구조가 catechol과 유사하여 catecholamine이라 함
- 급성 스트레스에 주로 반응하여 방출
- 펩타이드 호르몬처럼 분비소체에 고농도로 저장되어 있다가 exocytosis를 통해 방출

에이코사노이드 호르몬계



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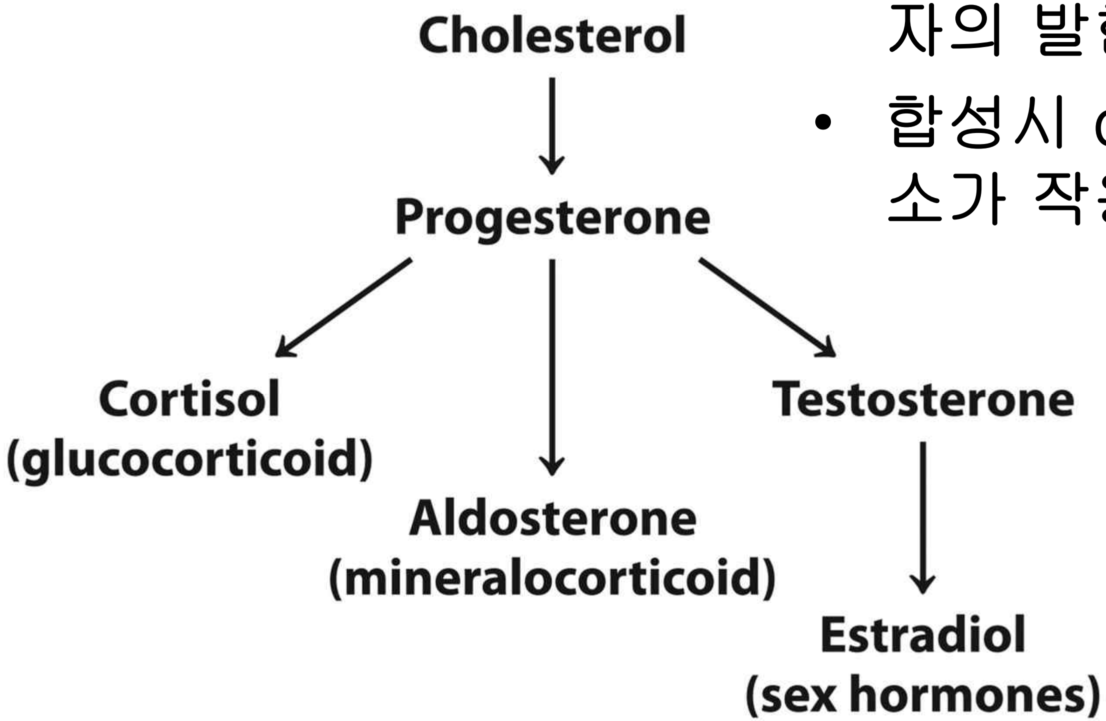
- Paracrine형태로 주변세포에 분비
- Prostaglandins: 소장, 자궁을 포함한 평활근 수축. 통증과 염증 매개
- Thromboxanes: 혈액응고에 작용
- Leukotrines: 소장, 폐의 기관지와 기관의 평활근 수축, anaphylaxis(과민성) 면역반응 매개

스테로이드 호르몬계



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- 부신피질호르몬, 성호르몬 등
- 콜레스테롤에서 합성
- 핵 내 수용체를 통해 특정 유전자의 발현 조절
- 합성시 cytochrome P-450 효소가 작용

비타민 D 호르몬

7-Dehydrocholesterol

$\downarrow$ **UV light**

Vitamin D_3
(cholecalciferol)

$\downarrow$

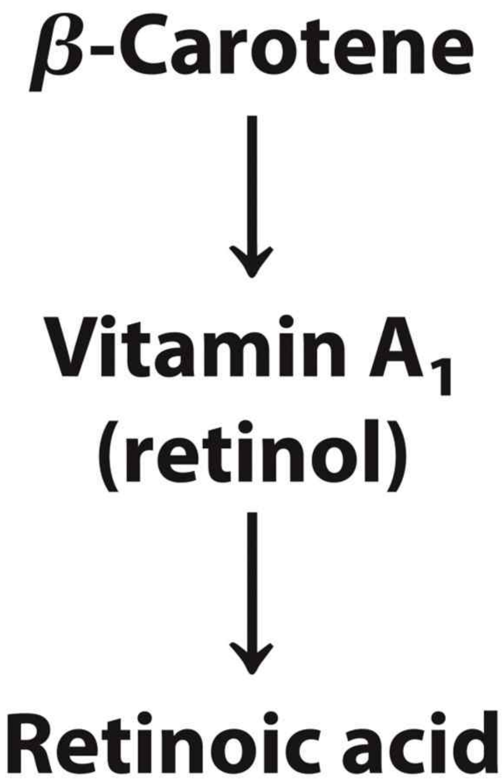
25-Hydroxycholecalciferol

$\downarrow$

1,25-Dihydroxycholecalciferol
(calcitriol)

- Vitamin D:
  - 음식으로 섭취 또는 피부에서 UV에 의해 7-dehydrocholesterol에서 생성
- Calcitriol:
  - 비타민 D가 간과 신장에서 칼시트리올로 변환
  - 부갑상선 호르몬의 협동작용으로 혈중 Ca^{2+}의 균형 유지
  - 소장에서 칼슘흡수 촉진
  - 부족하면 어린이에서 구루병 (rickets), 성인에서 골연화증

레티노이드 호르몬계



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- Retinoic acid: 세포 내 핵 수용체에 작용하여 성장이나 분화에 필수적인 단백질의 합성 조절
- β-카로틴 → retinol → retinal → retinoic acid로 바뀜

갑상선 호르몬(thyroid hormone)계

Thyroglobulin–Tyr

↓

Thyroglobulin–Tyr–I
(iodinated Tyr residues)

↓ proteolysis

Thyroxine (T_4),
triiodothyronine (T_3)

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- 갑상선에서 전구단백질인 thyroglobulin에서의 Tyr과 iodine들이 결합하여 생성. 이화효소의 발현을 활성화하여 에너지 대사 촉진
- Thyroxine(T_4): 작용전에 활성이 높은 T3로 변환. 일종의 프로호르몬
- Triiodothyronine(T_3): 갑상선 호르몬의 활성형분자

일산화질소(nitric oxide)

- NOS(nitric oxide synthase)에 의해 산소분자와 아르기닌으로부터 생성
- Guanylyl cyclase 활성화를 통해 cGMP 생성

주요 내분비선(endocrine glands)

- 신체 내외부의 신호를 중추신경이 받아들여 각 내분비기관을 통해 호르몬의 생산을 조절

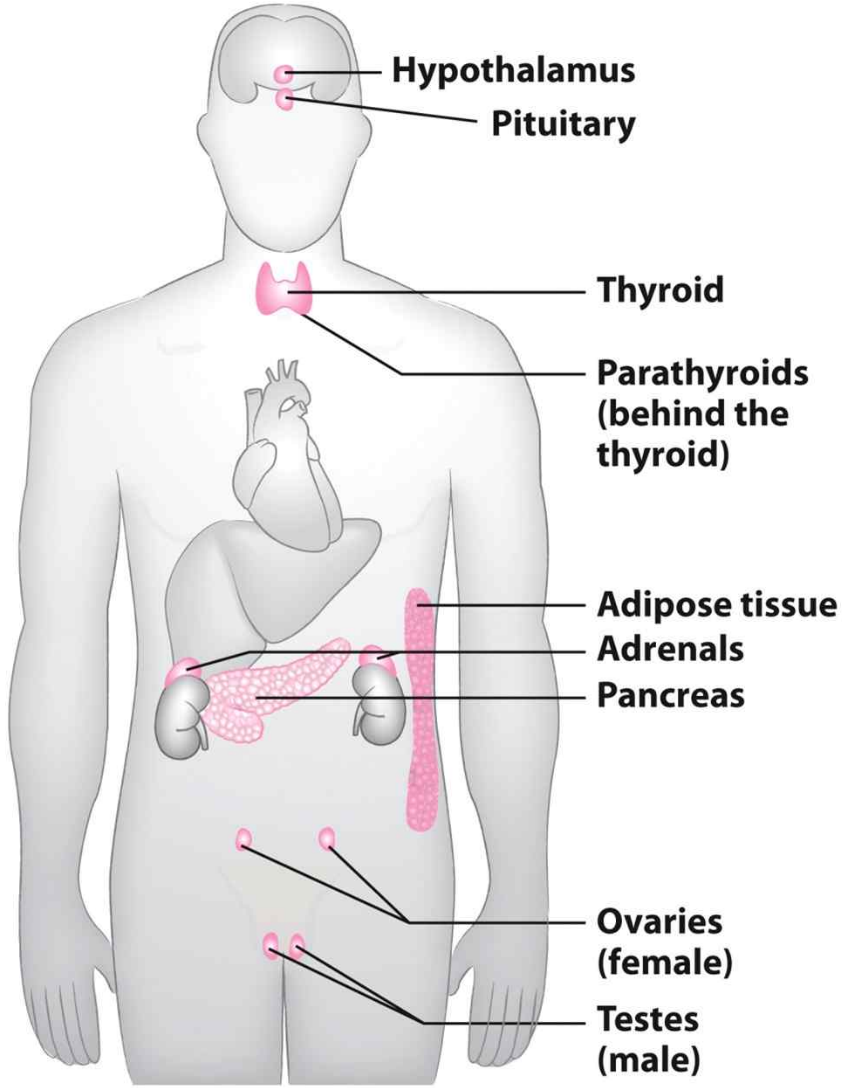

Figure 23-6
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호르몬과 표적조직

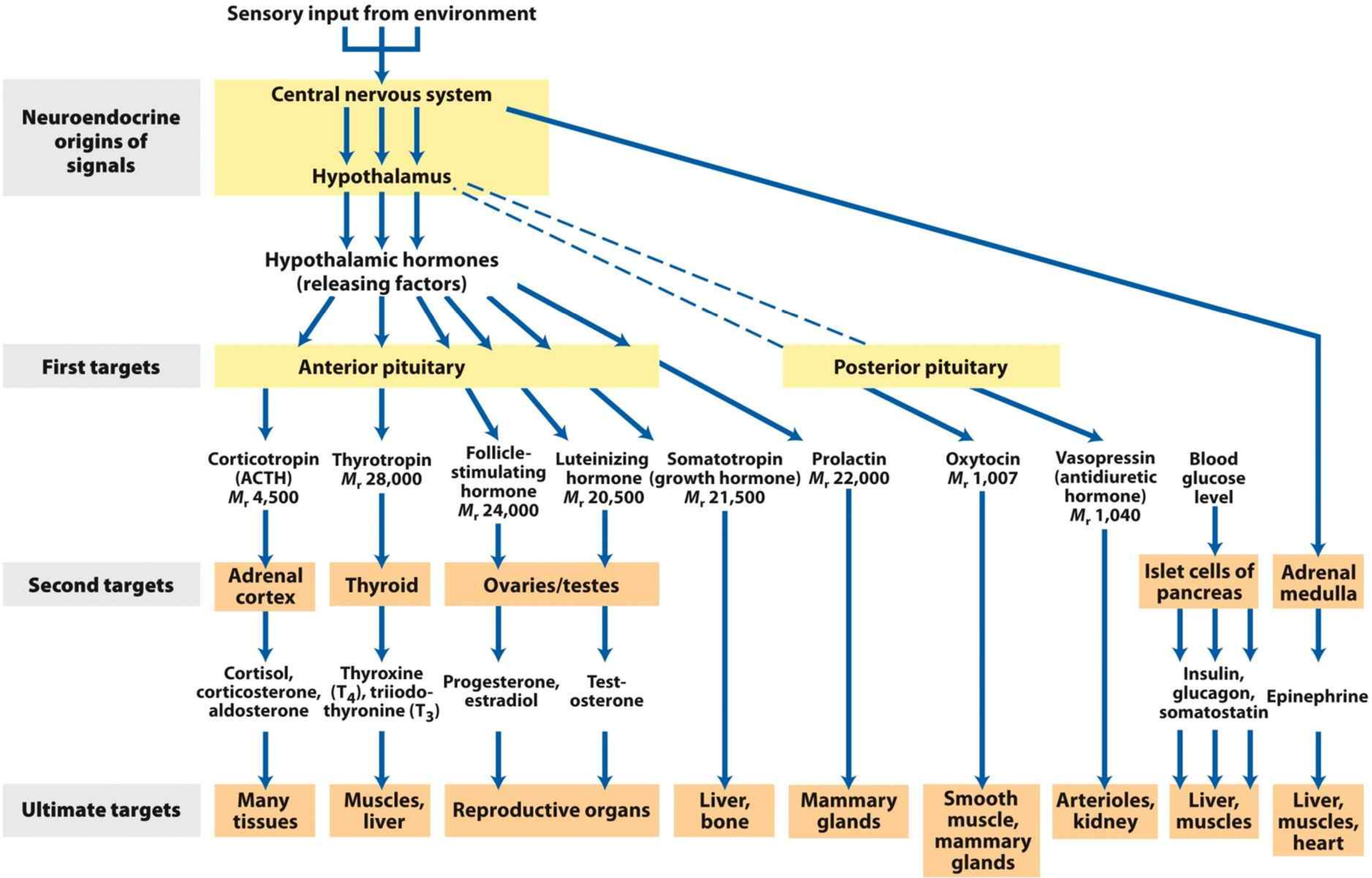

Figure 23-7
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호르몬 신호의 원류 신경계
(neuroendocrine origins of hormone signals)

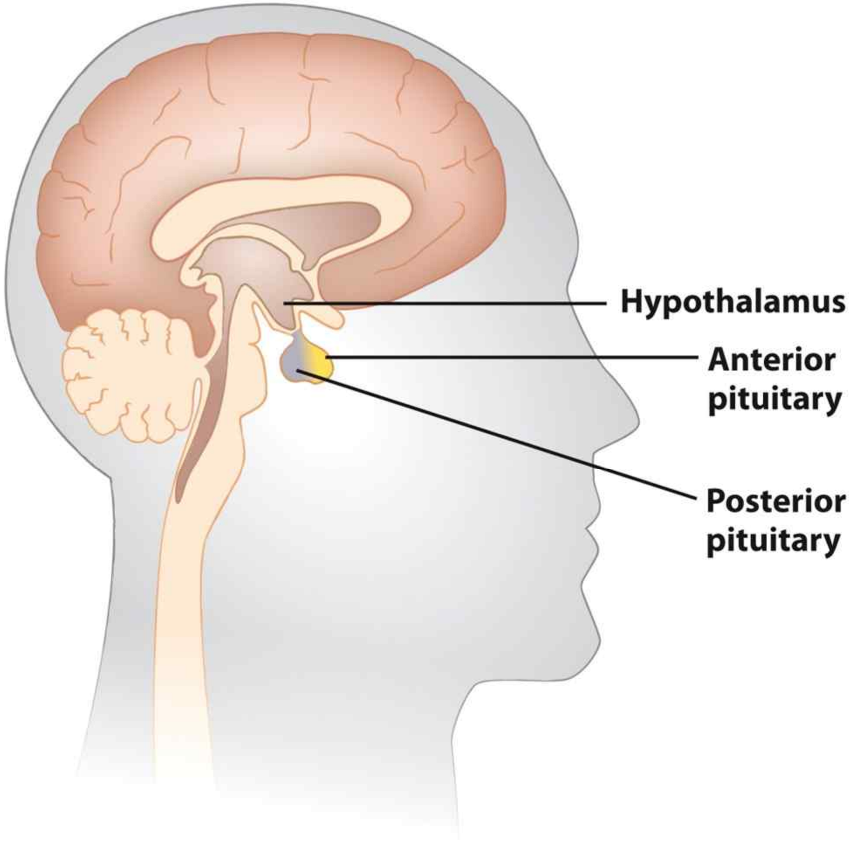

Figure 23-8a
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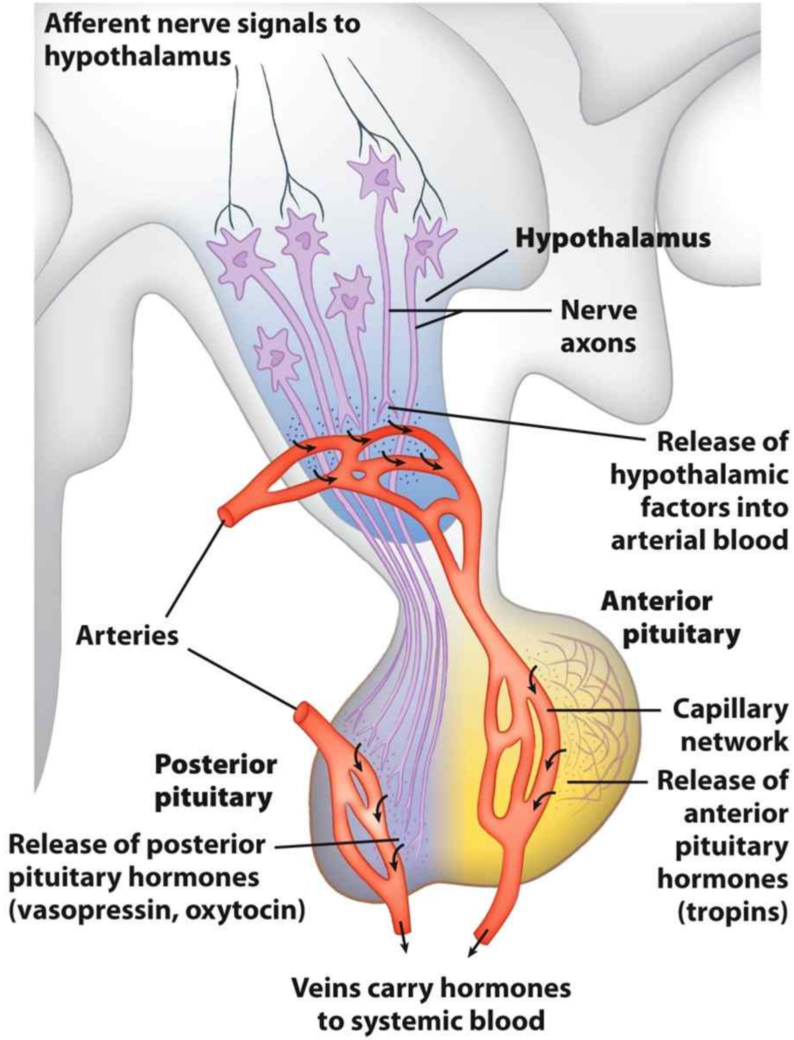

Figure 23-8b
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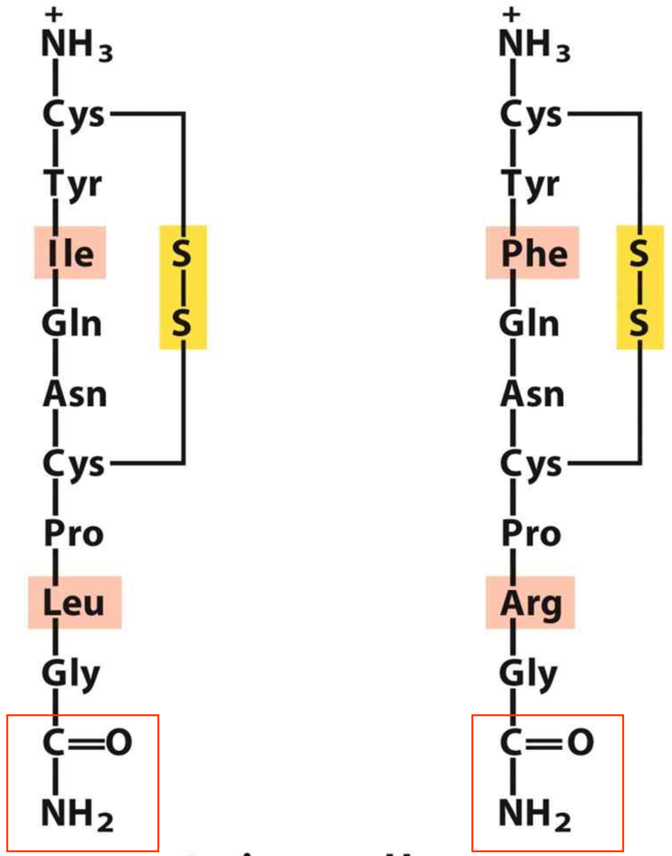
뇌하수체 후엽(posterior pituitary gland)의 2가지 호르몬



Human oxytocin

Human vasopressin (antidiuretic hormone)

Figure 23-9
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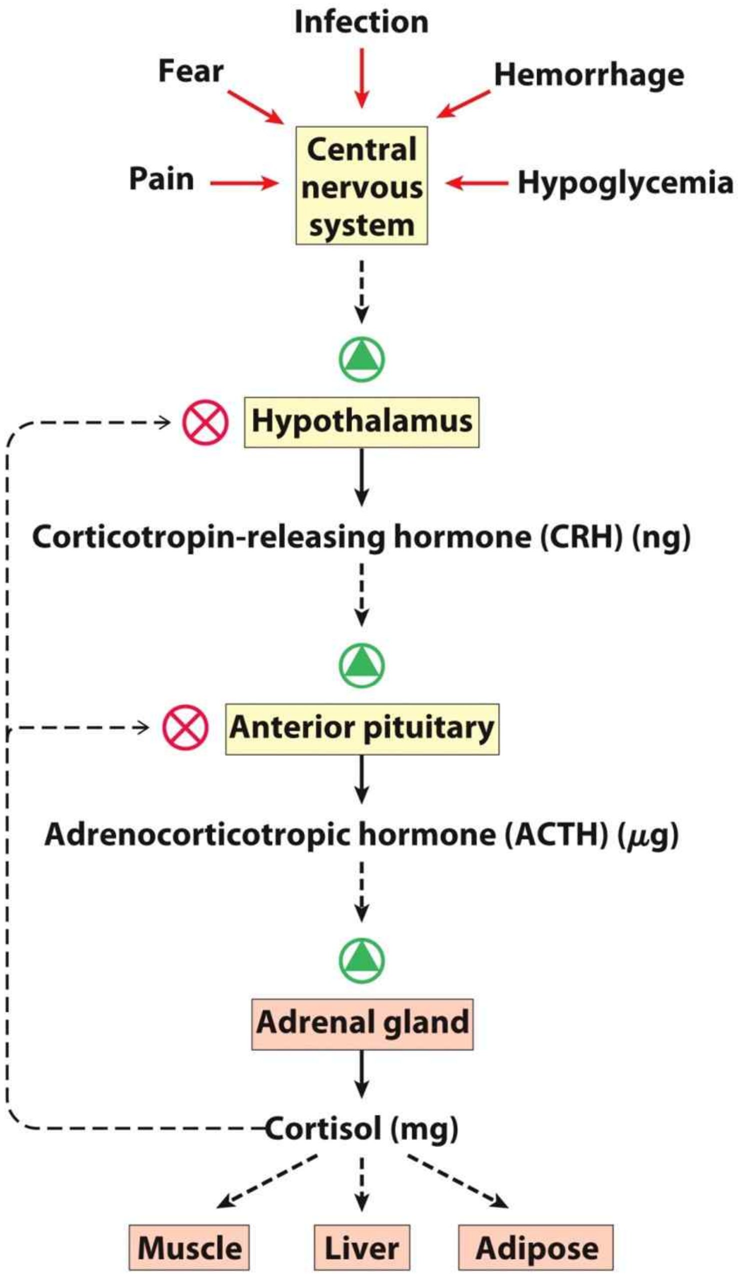
- 옥시토신: 자궁수축과 유선 자극을 통한 젖 분비 작용
- 바소프레신: 항이뇨호르몬 (antidiuretic hormone, ADH), 물의 재흡수증가, 혈관수축 작용
- 옥시토신, 바소프레신: 사랑호르몬으로 알려짐, devotion에 관여, 사랑, 이타심, 책임감 등

중추신경계에서 시상하부로의 신호전달후의 각종 호르몬 분비 cascade



Cortisol cascade

Figure 23-10
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23.2 Tissue-Specific Metabolism: The Division of Labor

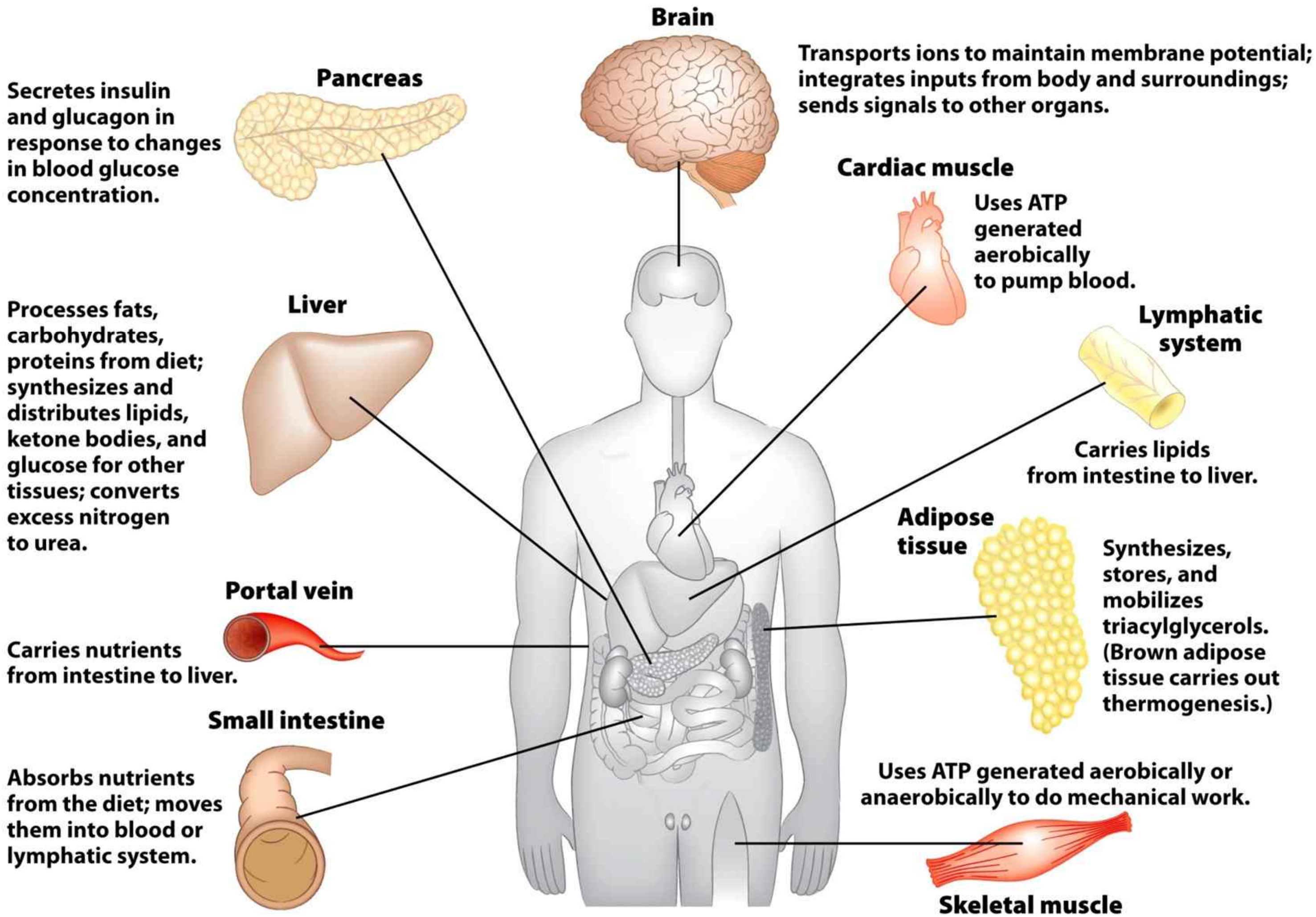

Figure 23-11
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The liver adapts to changing metabolic conditions

- Portal vein carries nutrients to liver
- Hepatocytes turn nutrients into fuel
- Hepatocyte enzymes turn over quickly
- Enzymes increase or decrease with changes in diet and needs of other tissues

간에서의 당질 대사경로

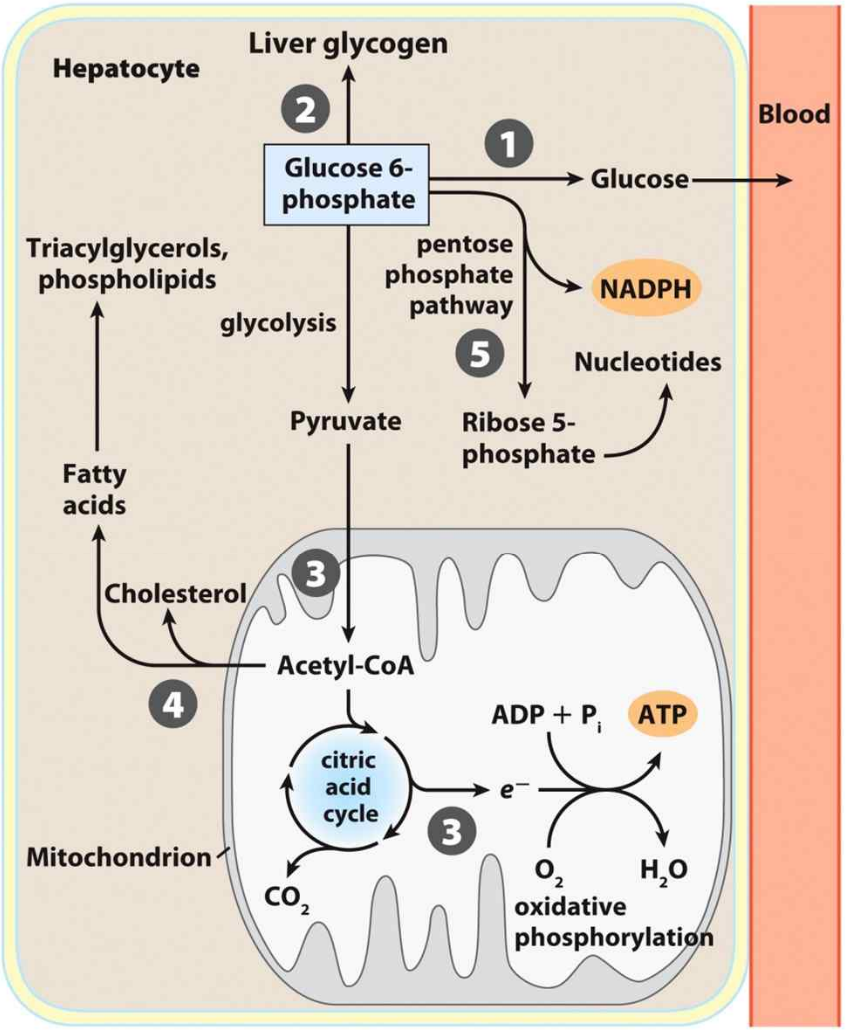

Figure 23-12
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- 글루코오스는 간에서 글루코오스-6-인산으로 변환되어 ①~⑤의 경로 중 하나로 변환
  - ①: 글루코오스로 변환되어 혈중으로 방출
  - ②: 글리코겐으로 변환
  - ③: 시트르산회로와 산화적인산화과정을 통해 ATP 생성
  - ④: 과잉의 글루코오스-6-인산은 지방으로 변환
  - ⑤: 지방산과 콜레스테롤 합성에 필요한 환원력(NADPH)과 nucleotide의 전구체인 D-리보스-5-인산 생성

TABLE 23–2 Pathways of Carbohydrate, Amino Acid, and Fat Metabolism Illustrated in Earlier Chapters

Pathway	Figure reference(s)
Citric acid cycle: acetyl-CoA $\longrightarrow$ $2CO_2$	16–7
Oxidative phosphorylation: ATP synthesis	19–19
Carbohydrate catabolism	
Glycogenolysis: glycogen $\longrightarrow$ glucose 1-phosphate $\longrightarrow$ blood glucose	15–27; 15–28
Hexose entry into glycolysis: fructose, mannose, galactose $\longrightarrow$ glucose 6-phosphate	14–11
Glycolysis: glucose $\longrightarrow$ pyruvate	14–2
Pyruvate dehydrogenase reaction: pyruvate $\longrightarrow$ acetyl-CoA	16–2
Lactic acid fermentation: glucose $\longrightarrow$ lactate + 2ATP	14–4
Pentose phosphate pathway: glucose 6-phosphate $\longrightarrow$ pentose phosphates + NADPH	14–22
Carbohydrate anabolism	
Gluconeogenesis: citric acid cycle intermediates $\longrightarrow$ glucose	14–17
Glucose-alanine cycle: glucose $\longrightarrow$ pyruvate $\longrightarrow$ alanine $\longrightarrow$ glucose	18–9
Glycogen synthesis: glucose 6-phosphate $\longrightarrow$ glucose 1-phosphate $\longrightarrow$ glycogen	15–32
Amino acid and nucleotide metabolism	
Amino acid degradation: amino acids $\longrightarrow$ acetyl-CoA, citric acid cycle intermediates	18–15
Amino acid synthesis	22–11
Urea cycle: NH_3 $\longrightarrow$ urea	18–10
Glucose-alanine cycle: alanine $\longrightarrow$ glucose	18–9
Nucleotide synthesis: amino acids $\longrightarrow$ purines, pyrimidines	22–35; 22–38
Hormone and neurotransmitter synthesis	22–31
Fat catabolism	
β Oxidation of fatty acids: fatty acids $\longrightarrow$ acetyl-CoA	17–8
Oxidation of ketone bodies: β-hydroxybutyrate $\longrightarrow$ acetyl-CoA $\longrightarrow$ CO_2 via citric acid cycle	17–20
Fat anabolism	
Fatty acid synthesis: acetyl-CoA $\longrightarrow$ fatty acids	21–6
Triacylglycerol synthesis: acetyl-CoA $\longrightarrow$ fatty acids $\longrightarrow$ triacylglycerol	21–18; 21–19
Ketone body formation: acetyl-CoA $\longrightarrow$ acetoacetate, β-hydroxybutyrate	17–19
Cholesterol and cholesteryl ester synthesis: acetyl-CoA $\longrightarrow$ cholesterol $\longrightarrow$ cholesteryl esters	21–33 to 21–37
Phospholipid synthesis: fatty acids $\longrightarrow$ phospholipids	21–17; 21–23 to 21–28

Table 23-2
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간에서의 아미노산 대사

- ①: 대부분의 혈장단백질은 간에서 생합성
- ②: 혈액으로 방출
- ③: 다른 질소화합물의 전구체 합성
- ④: 탈아미노화반응을 통해 글루코오스와 글리코겐 생성, 지방 생성, ATP 생성
- ⑤: 골격근의 아미노산을
- 피루브산으로 변환시켜 혈당 생성 → 근육에서 글리코겐으로 저장

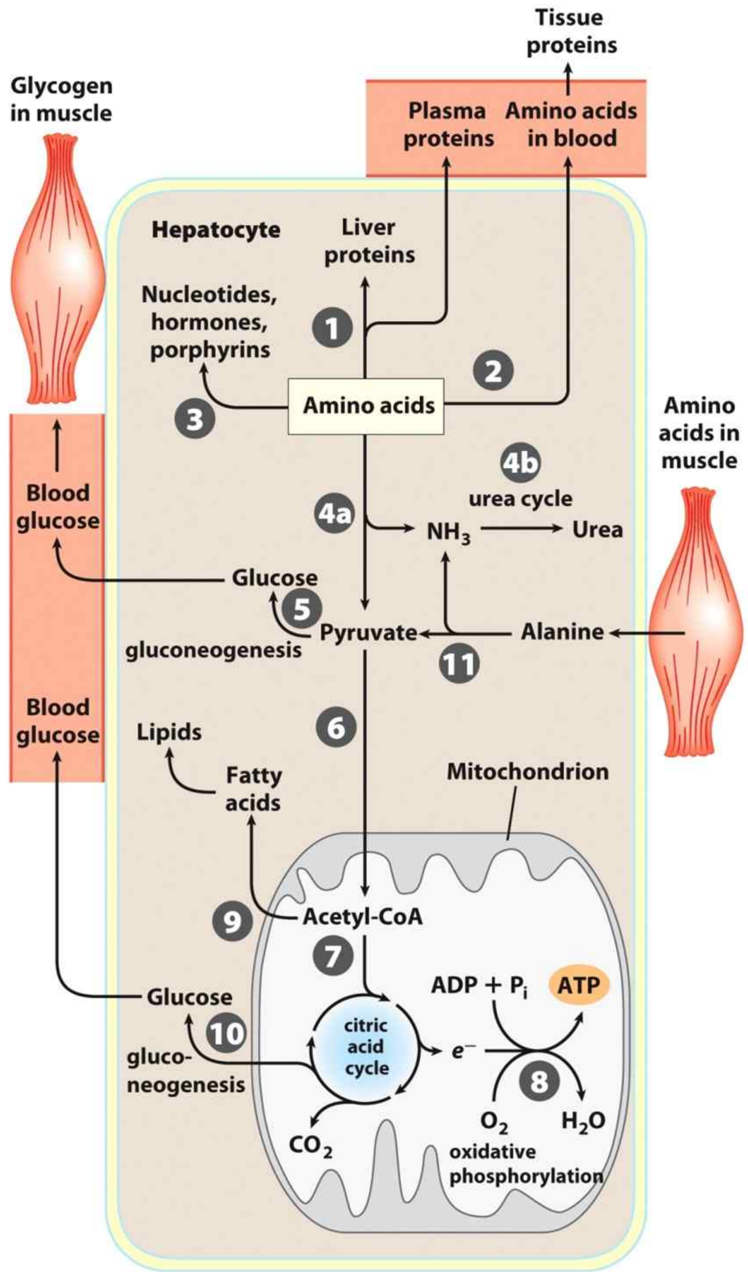

Figure 23-13
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간에서의 지방산 대사

①: 지방으로 변환

②: β-산화, 시트르산회로, 산화적인산화를 통해 ATP 생성

③: 아세틸기의 운반형인 케톤체(ketone bodies)를 형성하여 다른 조직에 에너지 공급(시트르산회로의 연료로 사용)

④: 콜레스테롤 생합성

⑤: 리포단백질 형태로 지방조직으로 운반

⑥: 혈청알부민과 결합하여 골격근과 심장에 운반되어 유리지방산이 연료로 산화

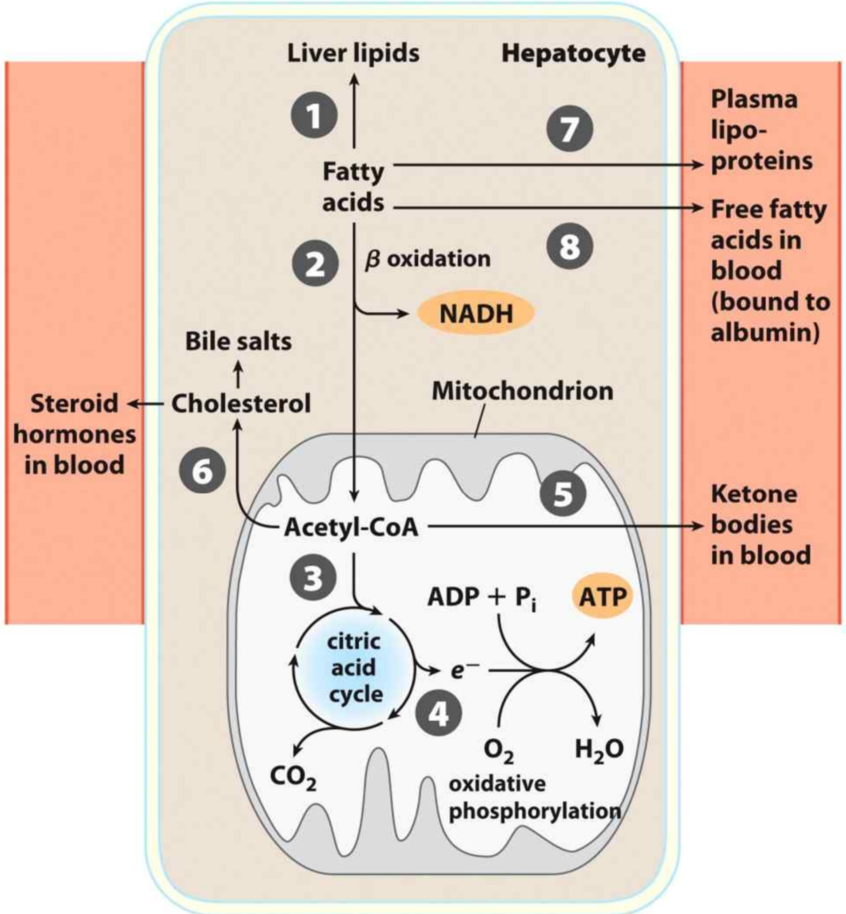

Figure 23-14
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Review of Liver Functions

- Provide glucose and ketones for other organs
- Process amino acids into urea, etc.
- Store nutrients (Fe ion, fat-soluble vitamins)
- Detoxify and solubilize organic compounds via cytochrome P450 system

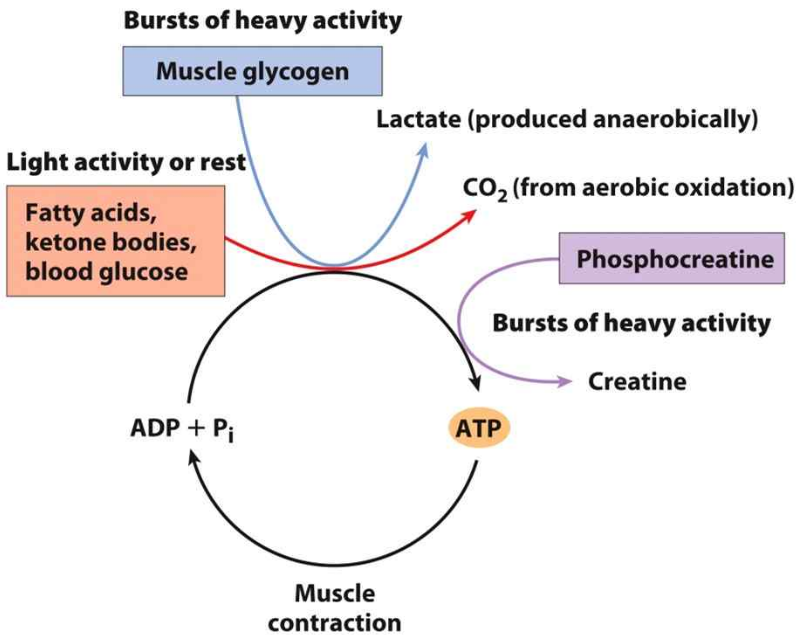
지방조직(adipose tissue)의 지방산 저장 및 공급

- 지방산을 지방으로 변환시켜 저장
- 지방조직은 성인 체중의 약 15% 차지
  (그 중 65%는 triacylglycerol이 차지)
- 지방 가수분해효소(triacylglycerol lipase)에 대한 호르몬의 작용:
  – Epinephrine(adrenalin): 지방가수분해효소의 활성화를 통한 지방산 방출
  – Insulin: 지방가수분해효소의 활성 억제를 통한 지방 축적

Muscle (Myocytes) – Two Types

- **Slow-twitch** (red muscle)
  - Fed by many blood vessels
  - Rich in mitochondria
    - to provide energy via slow and steady oxidative phosphosphrylation
- **Fast-twitch** (white muscle)
  - Fewer mitochondria and lower O_2 delivery
  - Uses ATP faster and fatigues faster due to greater demands (more tension, etc.) combined with reduced O_2 delivery
  - Endurance training can increase mitochondria

근육수축의 에너지원



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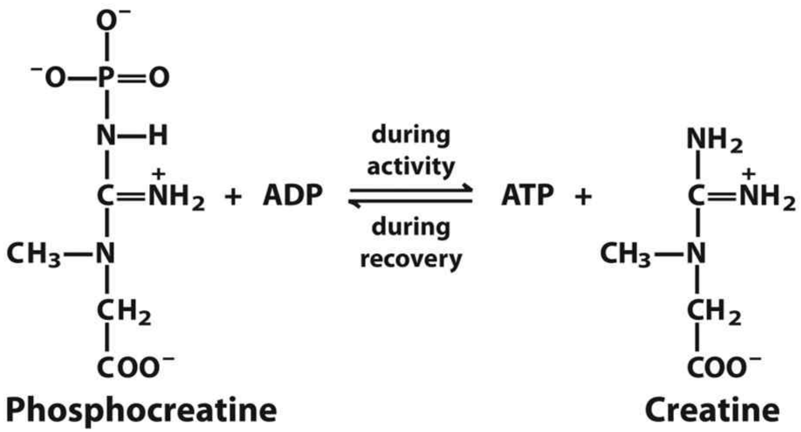

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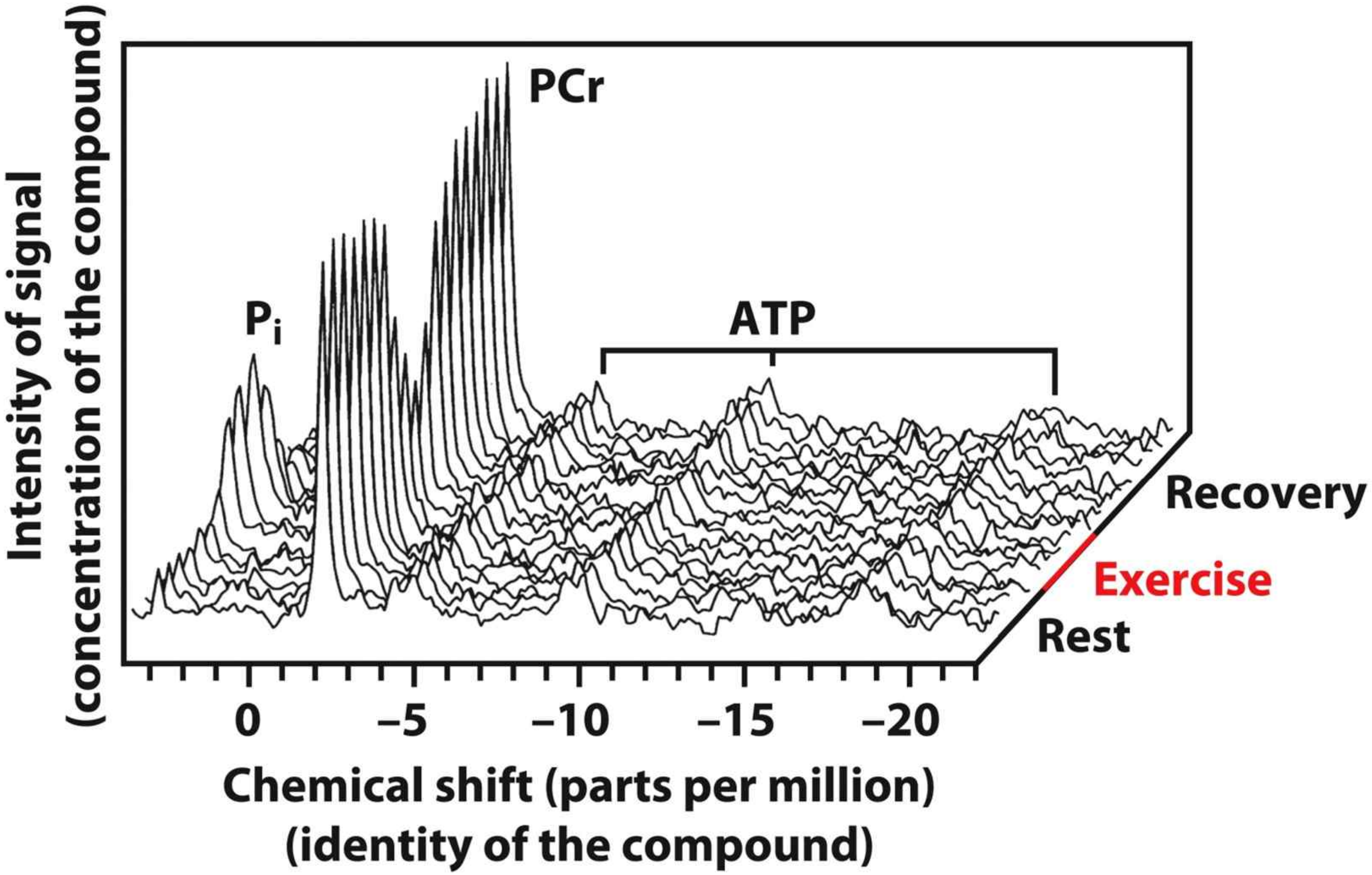
- 골격근은 쉬는 동안 인체 총산소 소비량의 50% 이상 소모, 격렬한 운동시 90% 까지 소비
- 쉬는 경우: 케톤체 이용 (→ 아세틸-CoA 생성 → 시트르산회로 → ATP생성)
- 보통의 활동: 유리지방산, 케톤체, 글루코오스 이용
- 격렬한 운동: 포스포크레아틴, 글리코겐 이용

Phosphocreatine buffers ATP concentration during exercise



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골격근과 간의 대사협동

- Cori 회로: glucose(간) → lactate(근육) → glucose(간)
- 근육에 저장된 글리코겐이 무산소운동시 분해되어 락트산으로 변환되고, 간에서 글루코오스 신생합성을 통해 글루코오스로 바뀐 후 다시 근육에서 글리코겐으로 저장됨

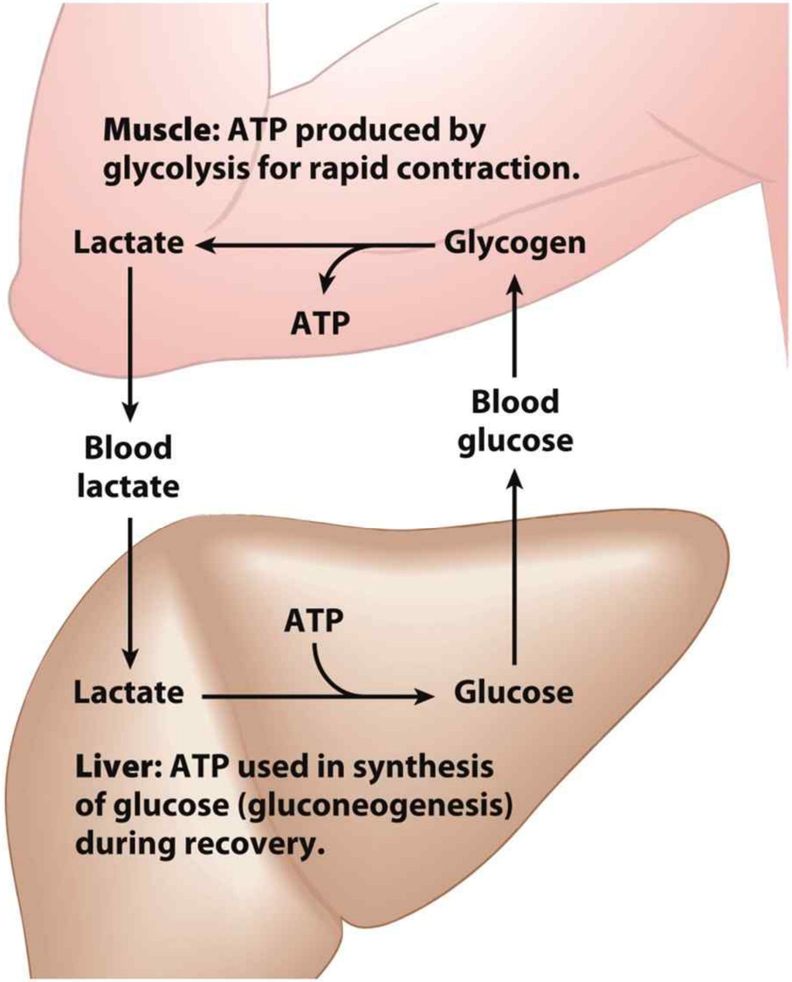

Figure 23-19
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뇌의 에너지원은 영양상태에 따라 변동

- 뇌는 전체 산소의 약 20% 소비
- 보통 글루코오스 이용(~130g/day). 기아나 단식시 케톤체의 일종인 β–hydroxybutyrate 이용(→ 아세틸-CoA로 전환 → ATP)

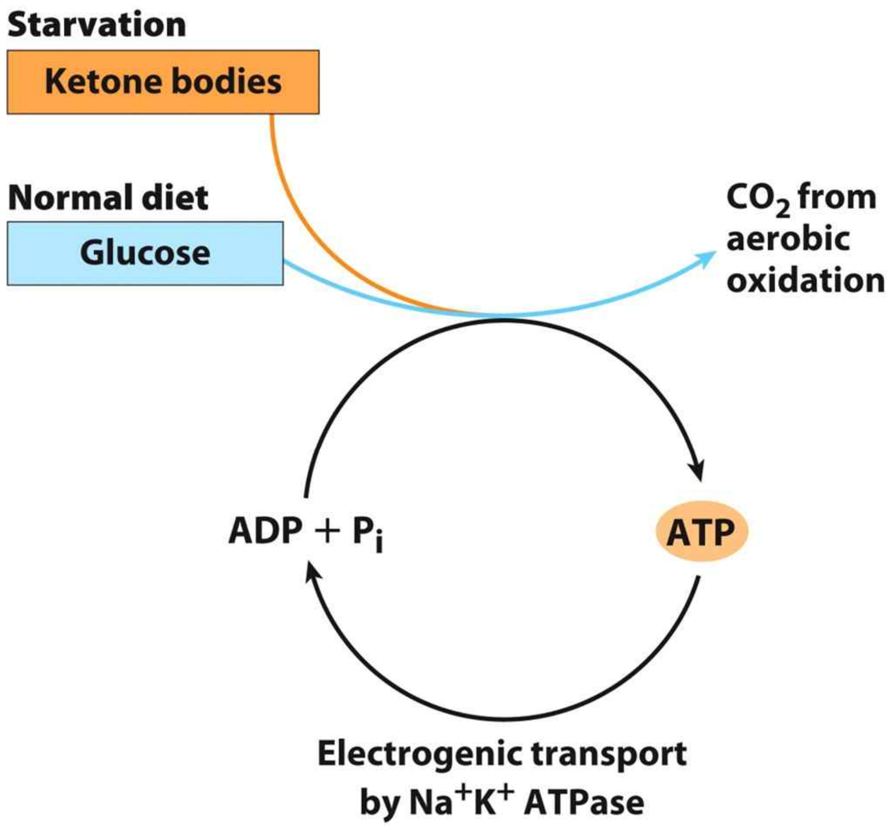

Figure 23-21
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혈액의 조성

- 혈액: 체중의 약 8% 차지 (5~6L 정도)
- 혈액의 조성:
  - –혈구: ~45%, 적혈구, 혈소판, 백혈구[과립형(중성, 산성, 염기성백혈구), 비과립형 (림프구, 단핵구)
  - –혈장: ~55%(물이 혈장의 90%), 알부민, 면역글로불린, 피브리노겐, prothrombin, 그외 70 여종
- 주요기능:
  - – 몸의 모든 조직에 물질과 열 운반
  - – 감염성 질병과 해로운 이물질로부터 몸을 방어

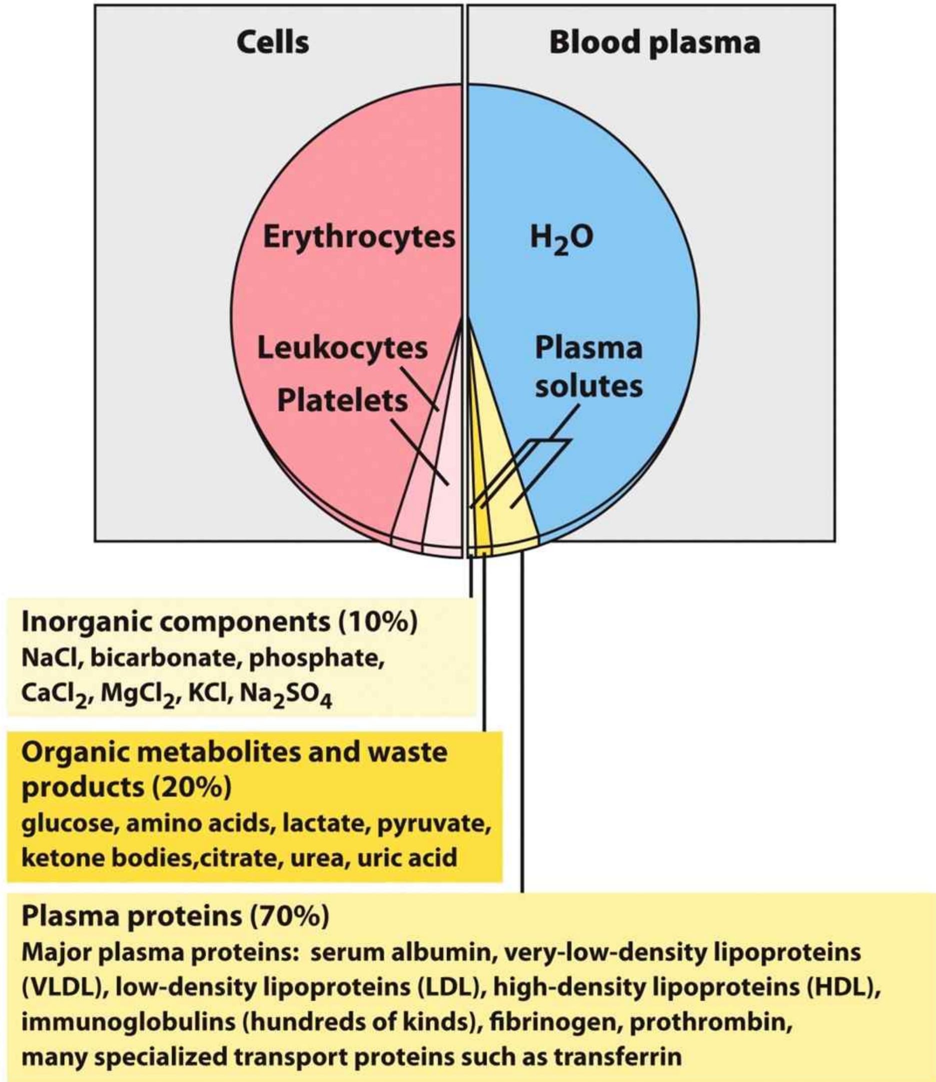

Figure 23-23
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사람의 저혈당이 미치는 생리적인 영향

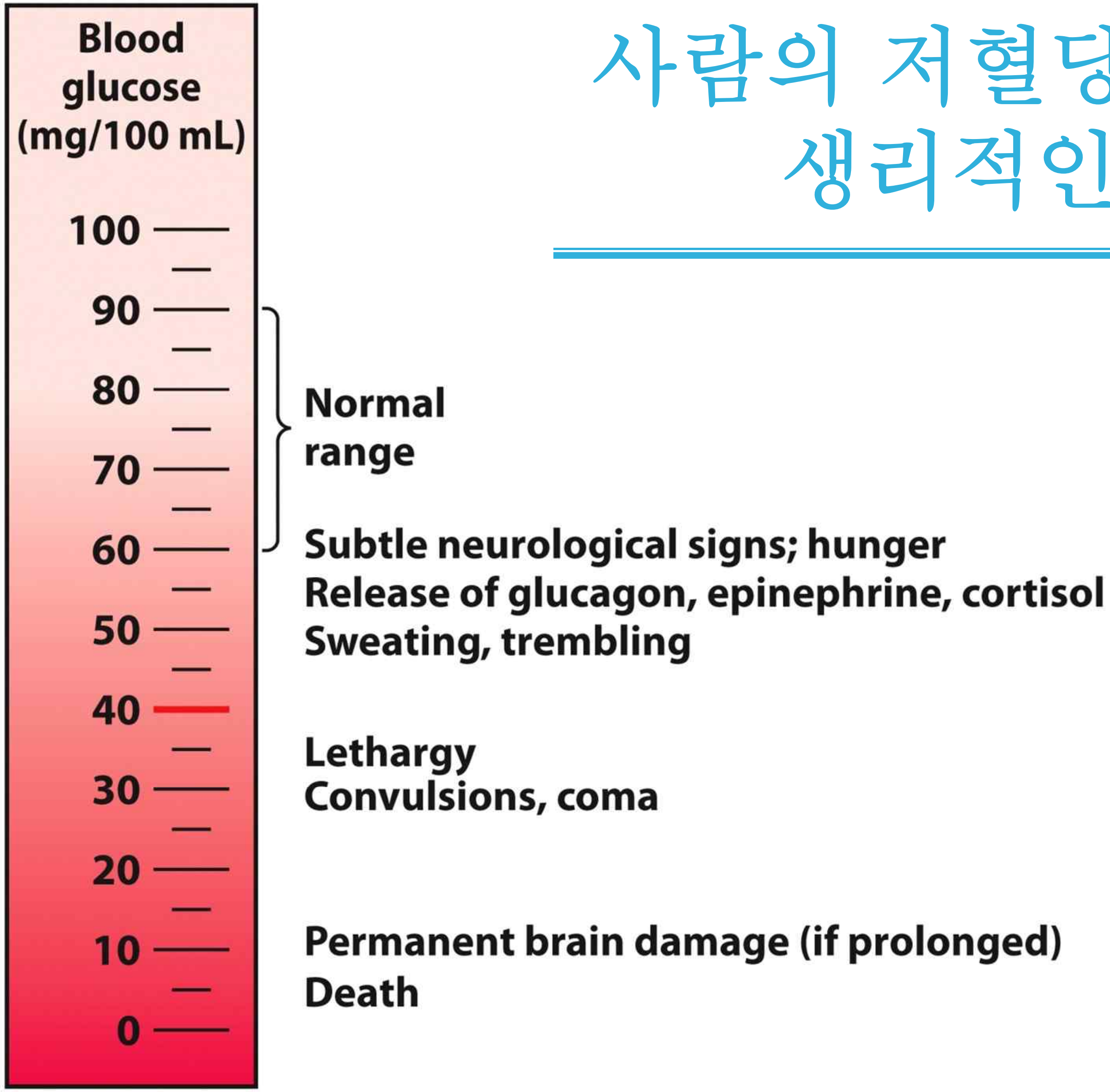

Figure 23-24
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23.3 Hormonal Regulation of Fuel Metabolism

- 격렬한 신체운동 요구시(예, 투쟁 또는 극단적 상황):
  - 부신수질(adrenal medulla)에서 epinephrine과 norepinephrine이 방출. 심박속도 증가를 통한 혈압상승, 기관지확장을 통한 산소유입 증가 (→ ATP 생성증가 → 활발한 근육운동)
    - Epinephrine: 근육, 지방조직, 간대사에 영향
    - Norepinephrine: epinephrine과 비슷한 작용
- 일반적인 혈당조절: 인슐린과 글루카곤의 길항작용
- 불안, 공포, 통증, 출혈, 감염 및 저혈당 등의 여러 스트레스시:
  - 부신피질(adrenal cortex)에서 cortisol 방출
    - Cortisol: 근육(비필수단백질 분해), 간(포도당 신생합성 촉진), 지방조직(지방산 유리 자극)에 작용.

Insulin stimulates conversion of excess glucose to glycogen

- Insulin stimulates glucose uptake in muscle and fat
  - Glucose → glucose 6-phosphate
- In liver, insulin stimulates glycogen synthase, inactivates glycogen phosphorylase
  - Glucose 6-phosphate → glycogen

Insulin stimulates conversion of excess glucose to fat

- Also in liver, insulin stimulates glycolysis
  - Glucose 6-phosphate → acetyl-CoA
- Also in liver, stimulates TAG synthesis
  - Acetyl-CoA → TAG, exported by VLDL
- In fat, stimulates TAG synthesis

Insulin can also act in the brain.

The endocrine system of the pancreas and glucose regulation by insulin

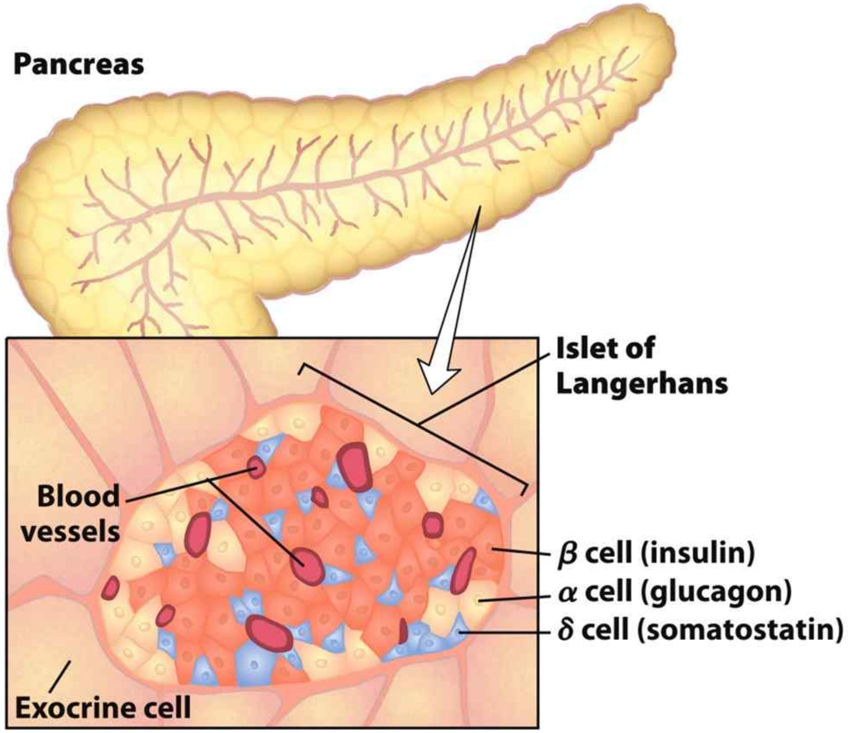

Figure 23-26
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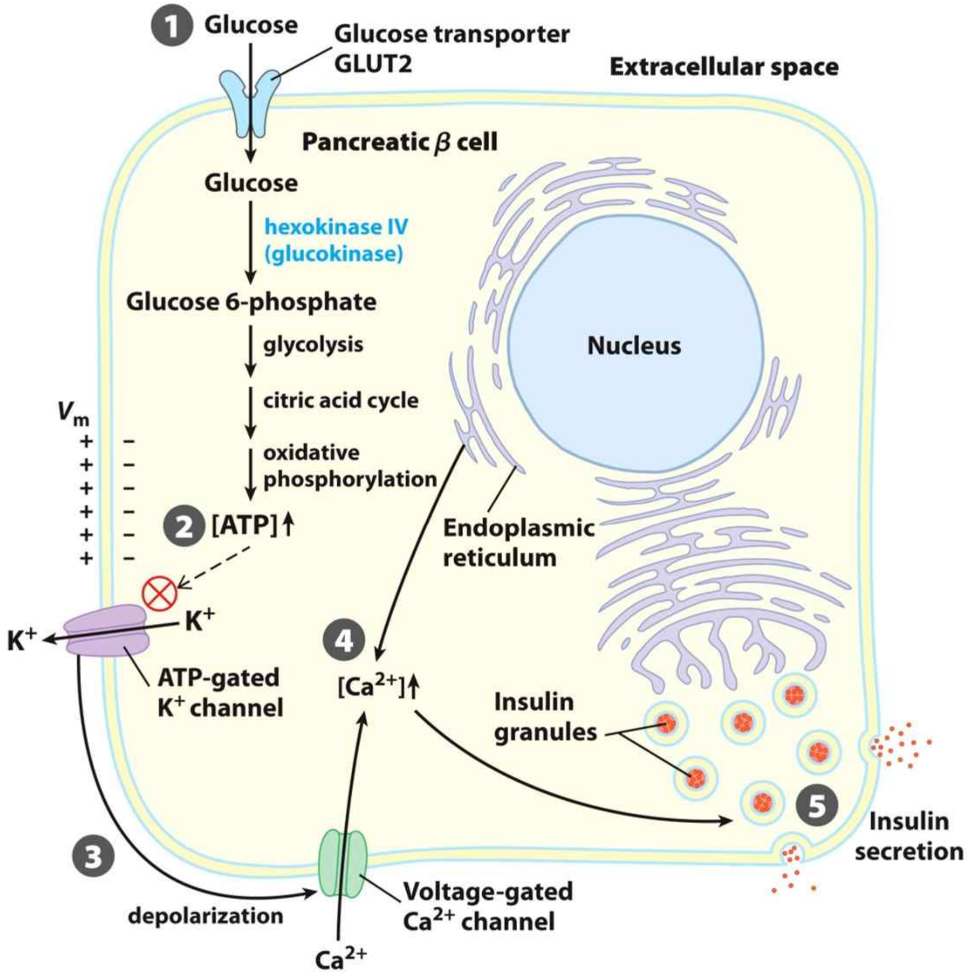

Figure 23-27
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TABLE 23–3 Effects of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

Metabolic effect	Target enzyme
↑ Glucose uptake (muscle, adipose)	↑ Glucose transporter (GLUT4)
↑ Glucose uptake (liver)	↑ Glucokinase (increased expression)
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA production (liver, muscle)	↑ PFK-1 (by ↑ PFK-2) ↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase

Table 23-3
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인슐린과 글루카곤에 의한 혈당의 조절

- Normal blood glucose metabolism에 관여하는 호르몬:
- 인슐린: 51개의 아미노산으로 구성. 췌장의 β–cell에서 분비. 혈당강하 기능
- 글루카곤: 29개의 아미노산으로 구성. 췌장의 α–cell에서 분비. 혈당상승 기능

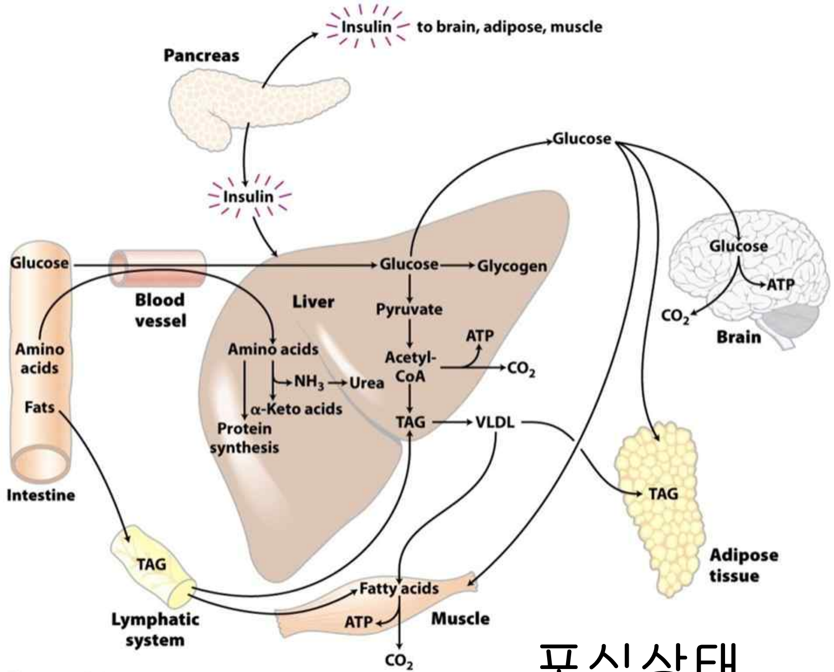

Figure 23-26
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포식상태

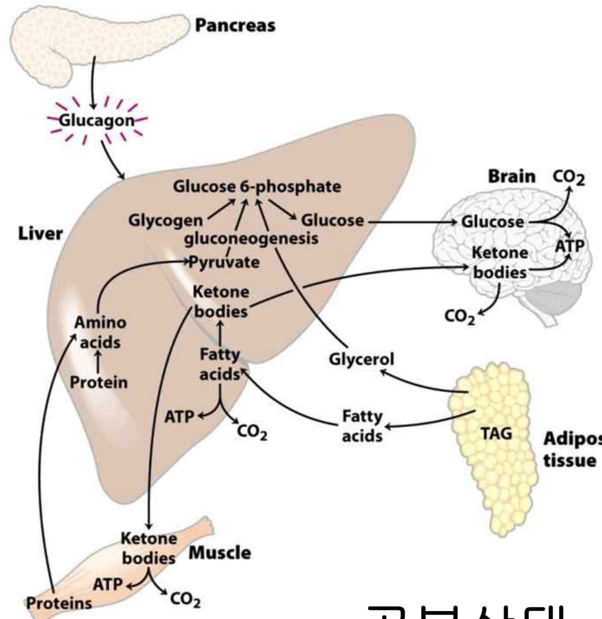

Figure 23-30
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공복상태

TABLE 23–4 Effects of Glucagon on Blood Glucose: Production and Release of Glucose by the Liver

Metabolic effect	Effect on glucose metabolism	Target enzyme
↑ Glycogen breakdown (liver)	Glycogen glucose	↑ Glycogen phosphorylase
↓ Glycogen synthesis (liver)	Less glucose stored as glycogen	↓ Glycogen synthase
↓ Glycolysis (liver)	Less glucose used as fuel in liver	↓ PFK-1
↑ Gluconeogenesis (liver)	Amino acids Glycerol Oxaloacetate } glucose	↑ FBPase-2 ↓ Pyruvate kinase ↑ PEP carboxykinase
↑ Fatty acid mobilization (adipose tissue)	Less glucose used as fuel by liver, muscle	↑ Hormone-sensitive lipase
		↑ PKA (perilipin–Ⓟ)
↑ Ketogenesis	Provides alternative to glucose as energy source for brain	↓ Acetyl-CoA carboxylase

Table 23-4
Lehninger Principles of Biochemistry, Sixth Edition

Effects of Prolonged Fasting

- Muscle begins to be used for fuel
  - Liver deaminates or transaminates amino acids
    - Converts amino groups to urea
    - C skeletons of glucogenic aa converted to pyruvate, then glucose via gluconeogenesis
    - Provides glucose for brain
  - FA oxidized to acetyl-CoA but oxaloacetate depleted to make glucose, so forms ketone bodies
    - Exported to other tissues

TABLE 23–5 **Available Metabolic Fuels in a Normal-Weight, 70 kg Man and in an Obese, 140 kg Man at the Beginning of a Fast**

Type of fuel	Weight (kg)	Caloric equivalent (thousands of kcal (kJ))	Estimated survival (months)*
Normal-weight, 70 kg man			
Triacylglycerols (adipose tissue)	15	140 (590)	
Proteins (mainly muscle)	6	24 (100)	
Glycogen (muscle, liver)	0.23	0.90 (3.8)	
Circulating fuels (glucose, fatty acids, triacylglycerols, etc.)	0.023	0.10 (0.42)	
Total		165 (690)	3
Obese, 140 kg man			
Triacylglycerols (adipose tissue)	80	750 (3,100)	
Proteins (mainly muscle)	8	32 (130)	
Glycogen (muscle, liver)	0.23	0.92 (3.8)	
Circulating fuels	0.025	0.11 (0.46)	
Total		783 (3,200)	14

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

Table 23-5
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Fuel Metabolism in Prolonged Fasting or Type 1 Diabetes

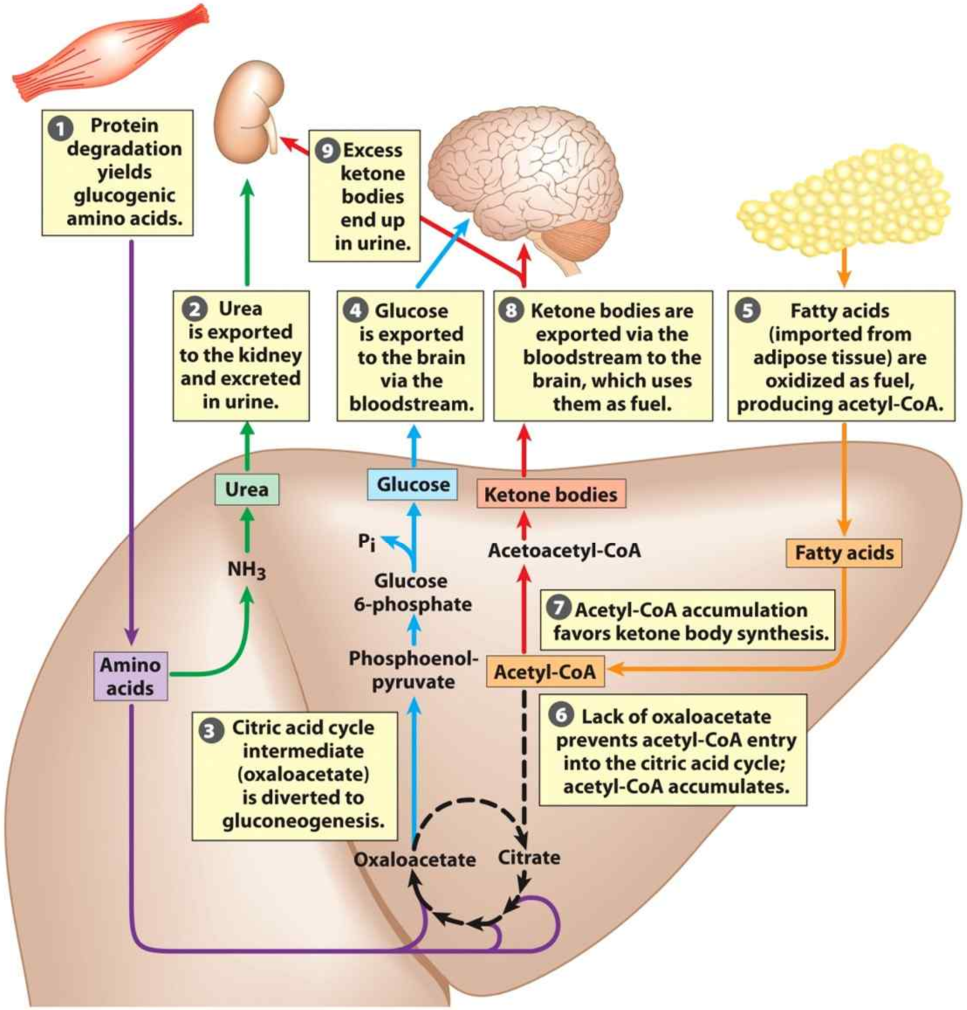

Figure 23-30
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Plasma Levels of Fatty Acids, Glucose, and Ketone Bodies During a One-Week Fast

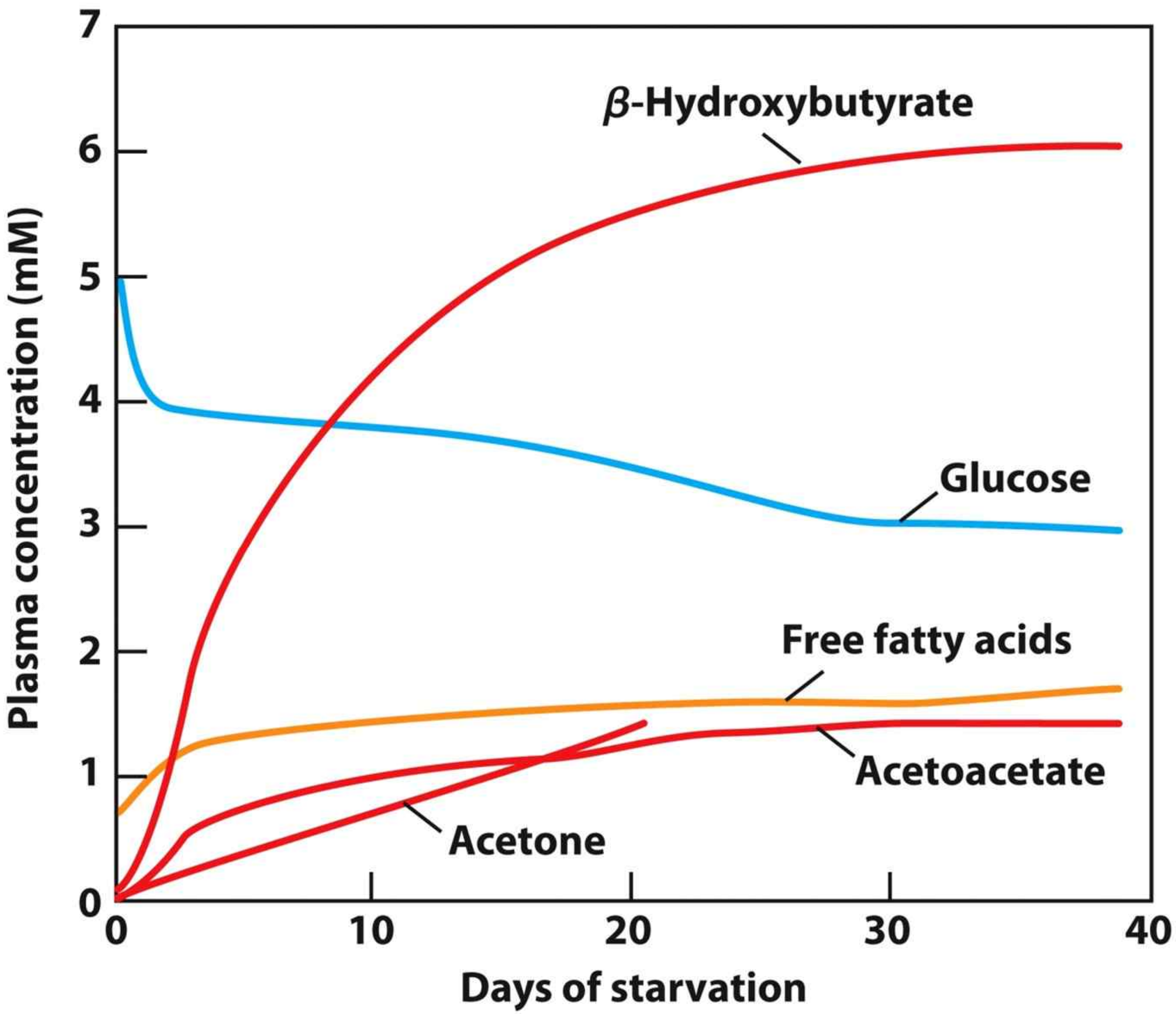

Figure 23-31
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Long-Term Effects of Elevated Blood Sugar

- Proteins can be glycosylated, especially at free amino groups
- Hemoglobin is abundant, has many exposed amino groups during formation, and entry of glucose into erythrocytes is not regulated
  - Hence, Hb easily glycosylated
  - Compromises O_2 delivery, especially in extremities (feet, etc.)
- Increases risk of cardiovascular disease, renal failure, and damage to small blood vessels and nerves

TABLE 23–6 Physiological and Metabolic Effects of Epinephrine: Preparation for Action

Immediate effect	Overall effect
Physiological	
↑ Heart rate ↑ Blood pressure ↑ Dilation of respiratory passages	Increase delivery of O_2 to tissues (muscle)
Metabolic	
↑ Glycogen breakdown (muscle, liver) ↓ Glycogen synthesis (muscle, liver) ↑ Gluconeogenesis (liver)	Increase production of glucose for fuel
↑ Glycolysis (muscle)	Increases ATP production in muscle
↑ Fatty acid mobilization (adipose tissue)	Increases availability of fatty acids as fuel
↑ Glucagon secretion ↓ Insulin secretion	Reinforce metabolic effects of epinephrine

Table 23-6
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23.4 Obesity and the Regulation of Body Mass

- 생체 내 체중 조절은 여러 단백질이 관여:
  - **Leptin(167 a.a.): adipocyte(**지방세포**)**에서 분비**, hypothalamus(**시상하부**)**의 **arcuate nucleus(**궁상핵**)**에 있는 **receptor**에 작용 → 식욕을 억제하는 호르몬인 **α-MSH**의 분비촉진 및 교감신경계에 작용하여 지방세포에서 **thermogenesis** 촉진**. Amgen**에서 비만치료제로의 개발 실패.
  - **Adiponectin(224 a.a.):** 지방세포에서 분비, 근육세포에 작용하여 **AMPK**를 활성화하여 지방산산화 촉진 및 지방산합성 억제.
  - **PPARs(peroxisome proliferator-activated receptors):** 지질변화에 반응하여 지방과 탄수화물대사에 관여하는 유전자들의 발현을 조절. **PPARδ**의 활성화가 지방산분해에 중요**(PPARδ**의 활성화는 비만치료의 주요 **target**임**, PPARγ**는 **inhibitor**개발 **target).**
  - **Ghrelin(28 a.a.):** 위에서 분비**, arcuate nucleus**에 있는 **orexigenic neuron(**식욕유발 뉴론**)**에 작용하여 식욕촉진.
  - **PYY3-36(34 a.a.):** 소장에서 분비**, orexigenic neuron**에 작용하여 **NPY**의 분비를 억제하여 식욕억제.

Hypothalamic regulation of food intake and energy expenditure

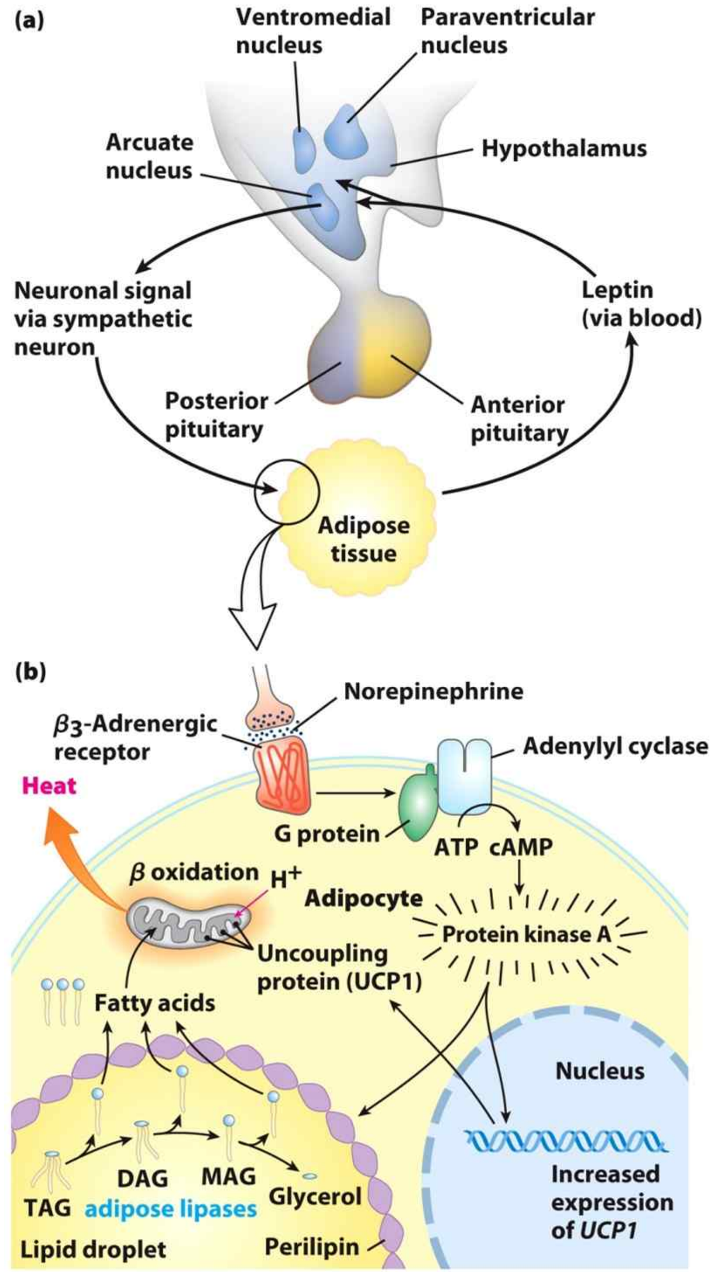

Figure 23-34
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Hormones that Control Eating

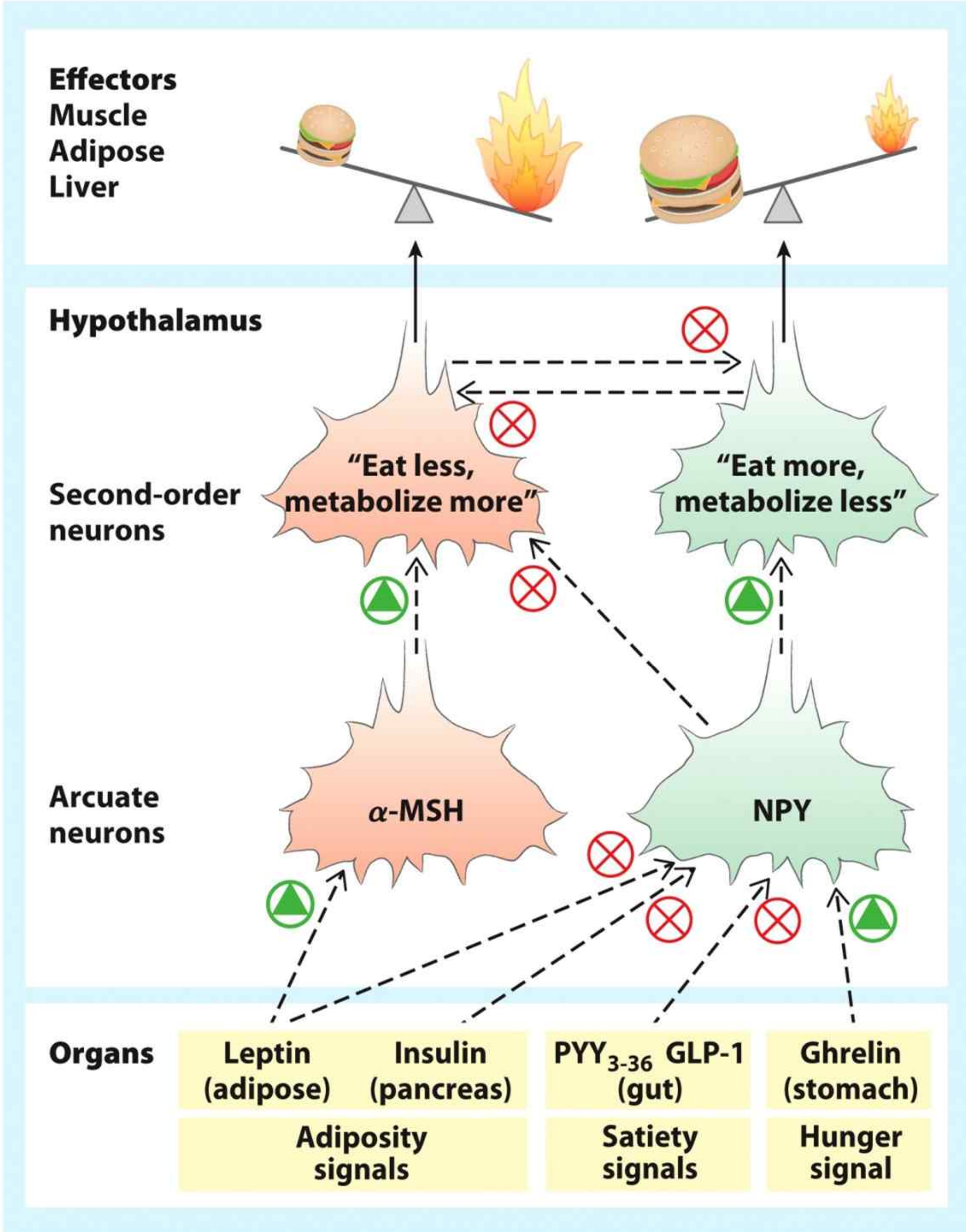

Figure 23-35
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Leptin is a fuel-burning, appetite-suppressing hormone

- Stimulates production of anorexigenic (appetite-suppressing) hormones
- Stimulates sympathetic nervous system
- Triggers cascade that regulates gene expression
- May be involved in hard-wiring of neuronal circuits during development

The JAK-STAT Mechanism of Leptin Signal Transduction

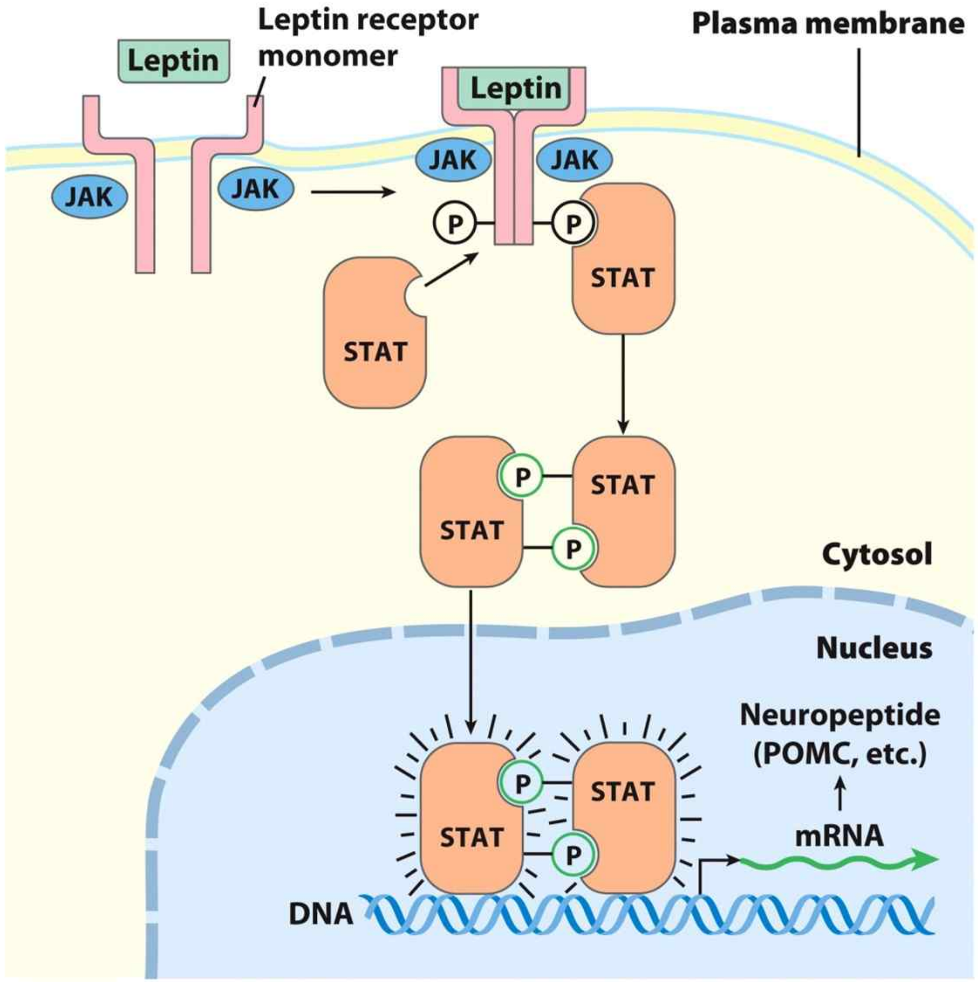

Figure 23-36
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Insulin also inhibits appetite by interacting with the hypothalmus

- The orexigenic neurons have insulin receptors
- Insulin binding:
  - Inhibits release of appetite-stimulating NPY
  - Stimulates appetite-suppressing α-MSH
- There may be cross-talk between insulin and leptin pathways!
  - Leptin makes liver and muscle more sensitive to insulin
  - A common 2° messenger may enable leptin and insulin to trigger the same downstream pathways

Proposed Mechanism for Cross Talk between Receptors for Insulin and Leptin

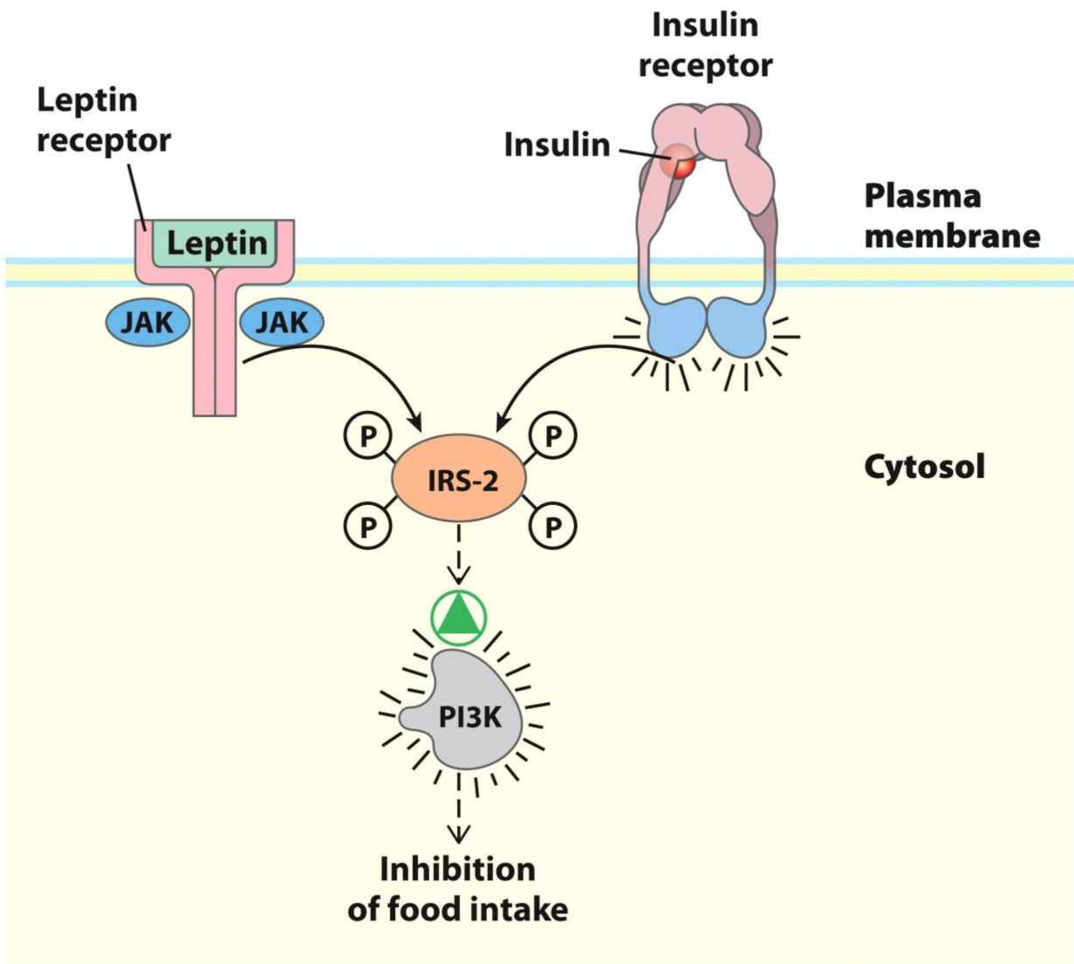

Figure 23-37
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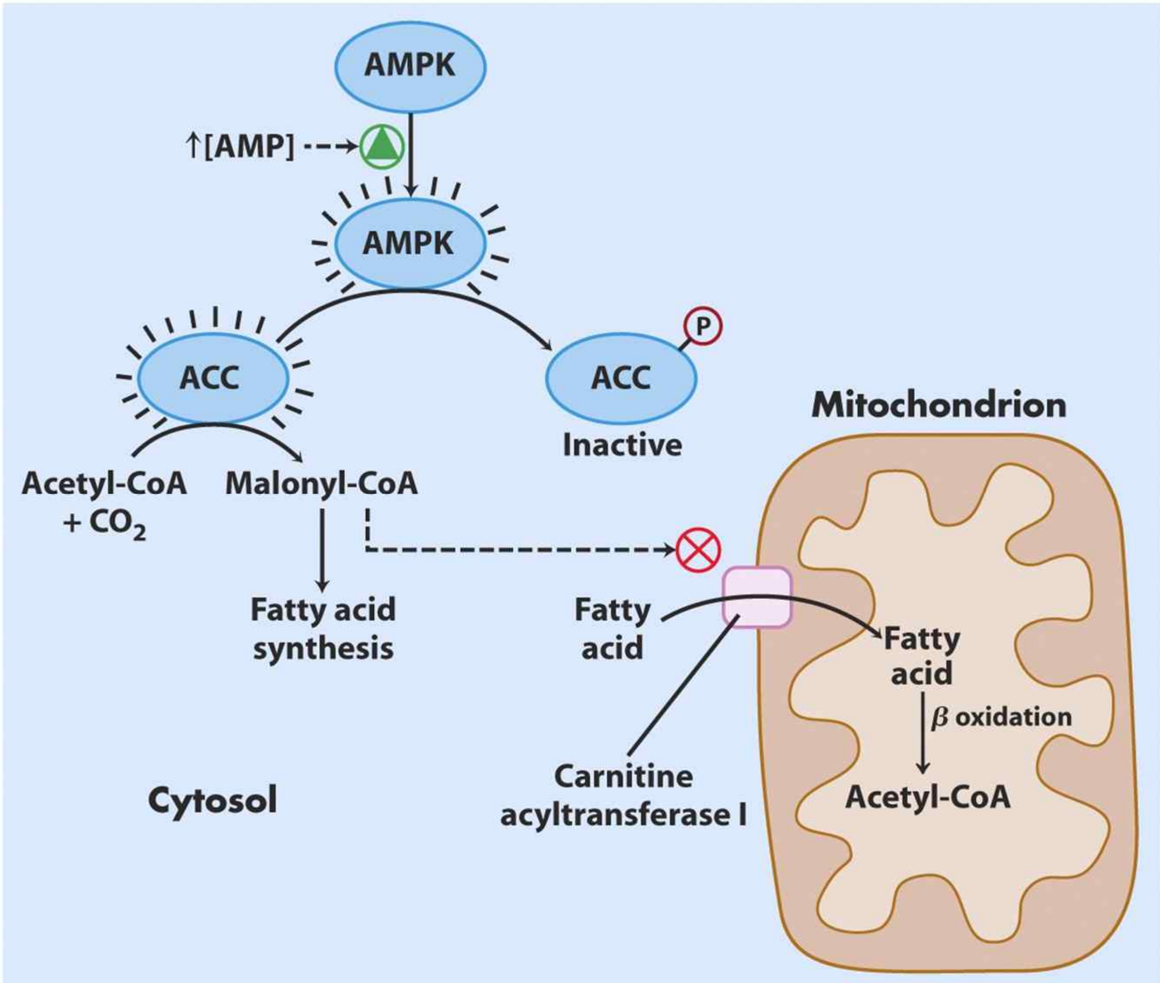
Adiponectin is made by adipose tissue and has receptors in the brain

- Circulates and makes other organs sensitive to insulin
- Protects against atherosclerosis, inflammation
- While incompletely understood, appears to work via AMP-activated kinase pathway

Adiponectin activates the AMPK pathway

- AMPK phosphorylates and inactivates acetyl-CoA carboxylase
  - Enzyme normally makes malonyl-CoA
    - Malonyl-CoA inhibits fatty acid import into mitochondria
  - Reduced acetyl-CoA carboxylase means that fatty acids are free to enter the mitochondria for oxidation
- AMPK pathway also inhibits cholesterol synthesis

Regulation of fatty acid synthesis and oxidation by AMPK action on acetyl-CoA carboxylase



Formation of Adiponectin and its Actions through AMPK

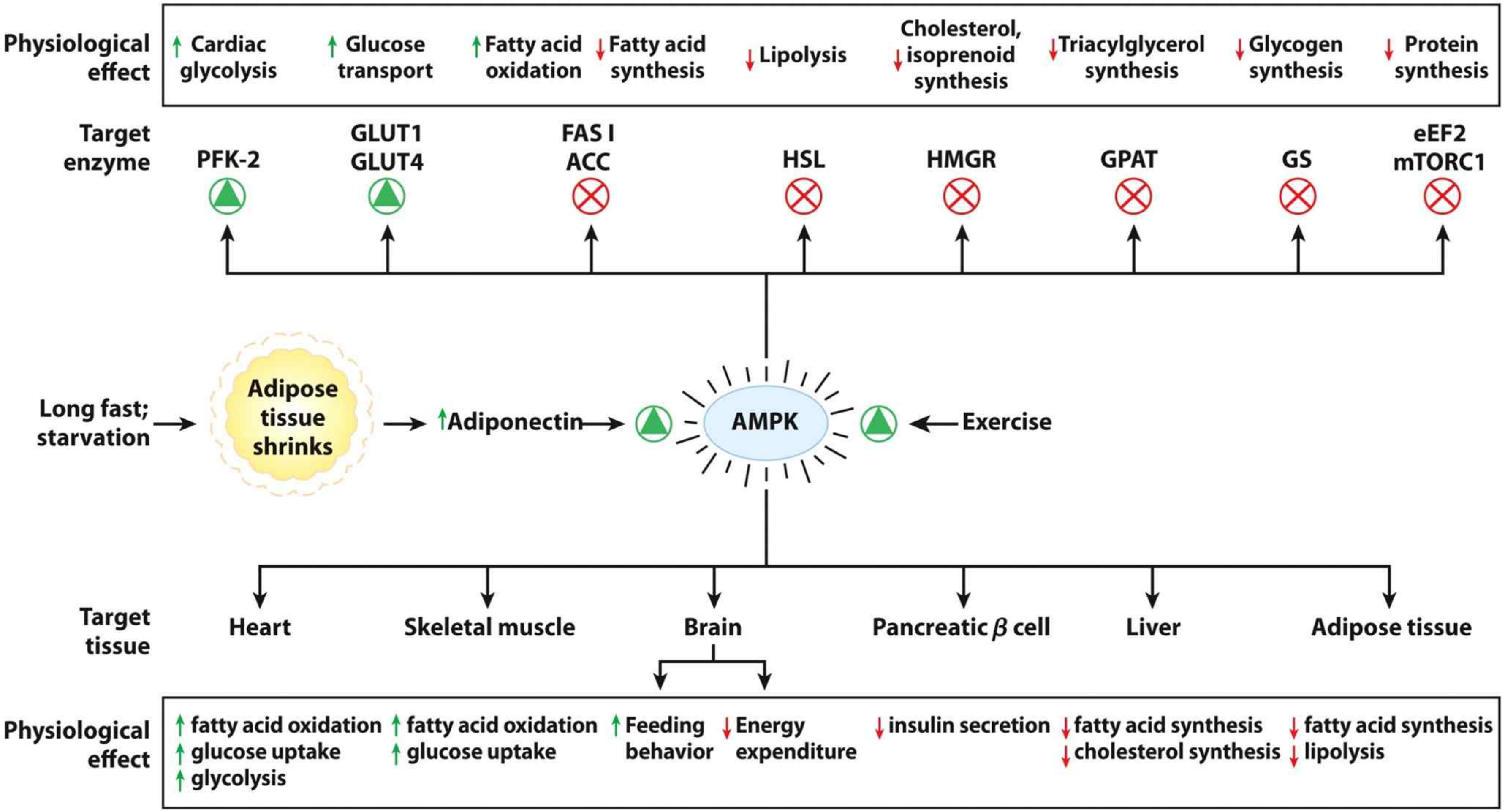


Figure 23-39
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Thiazolidinedione drugs activate the AMPK pathway and increase expression of adiponectin genes

- Thiazolidinediones are used to treat type 2 diabetes
  - Includes Avandia (rosiglitazone), Actos (pioglitazone)
- Targets include:
  - receptors that lead to activation of adiponectin gene transcription
  - AMPK pathway
  - PPARγ (next slides)
- Avandia limited due to increased heart disease risk

Peroxisome proliferator–activated receptors (PPARs) alter expression of genes for fat and carbohydrate metabolism

- PPARs so named because discovered in peroxisomes
- Bind fatty acids or derivatives
- Then bind to retinoid X receptor (RXR) and become powerful transcription factors
- Includes PPARγ, PPARα, and PPARδ

Function of PPARs

- PPARγ
  - in liver and adipose tissue
  - turns on genes for lipid synthesis and storage
  - activated by thiazolidinediones
- PPARα
  - in liver, heart, skeletal muscle, etc.
  - activated by FA and eicosanoids
  - turns on genes for uptake and oxidation of FA and for ketone body formation
- PPARδ
  - in liver and muscle
  - turns on genes for FA oxidation and mt uncoupling

Mode of Action of PPARs

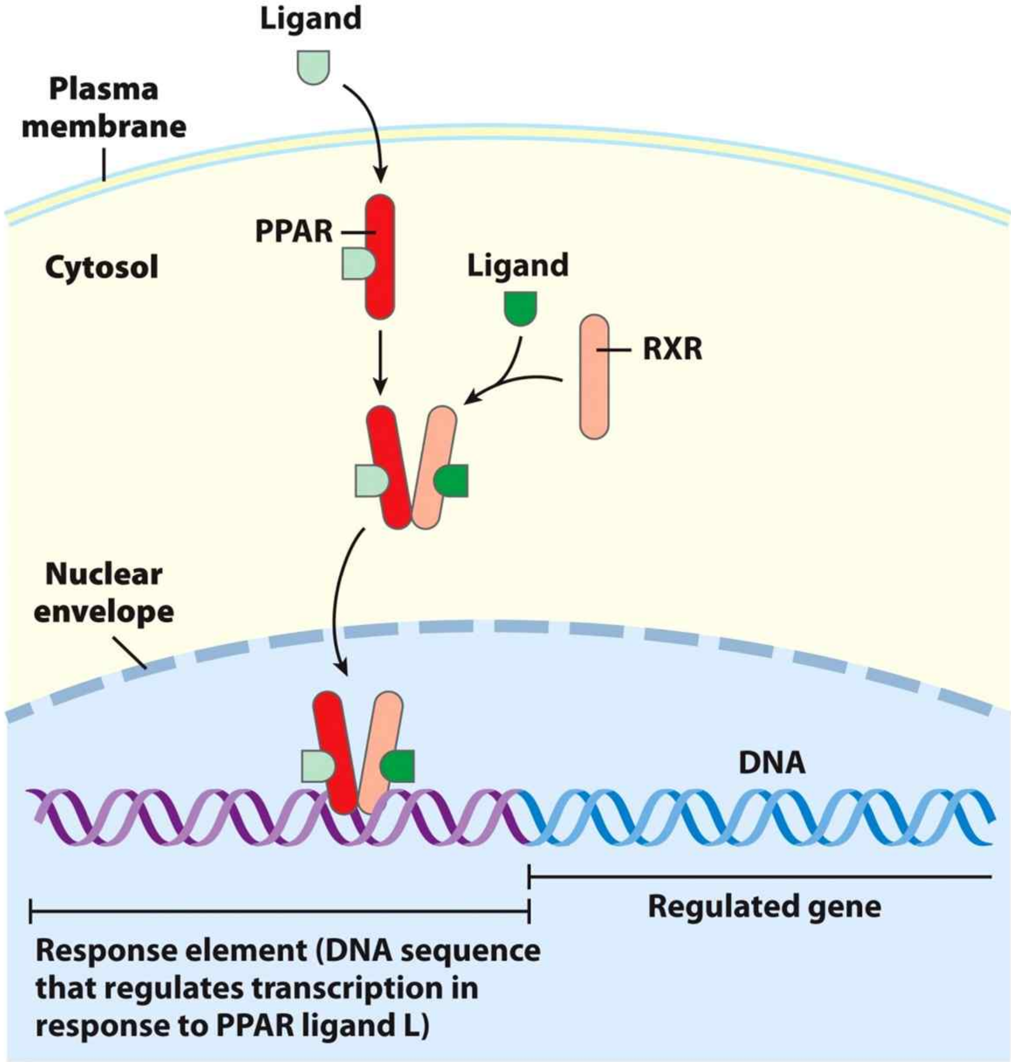

Figure 23-41
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PPARδ is a key regulator of fat metabolism

- Mice who are overfed do not become obese if PPARδ is constitutively active
- PPARδ activation even prevents obesity in db/db mice
- Major target seems to be mitochondrial uncoupling

Metabolic Integration by PPARs

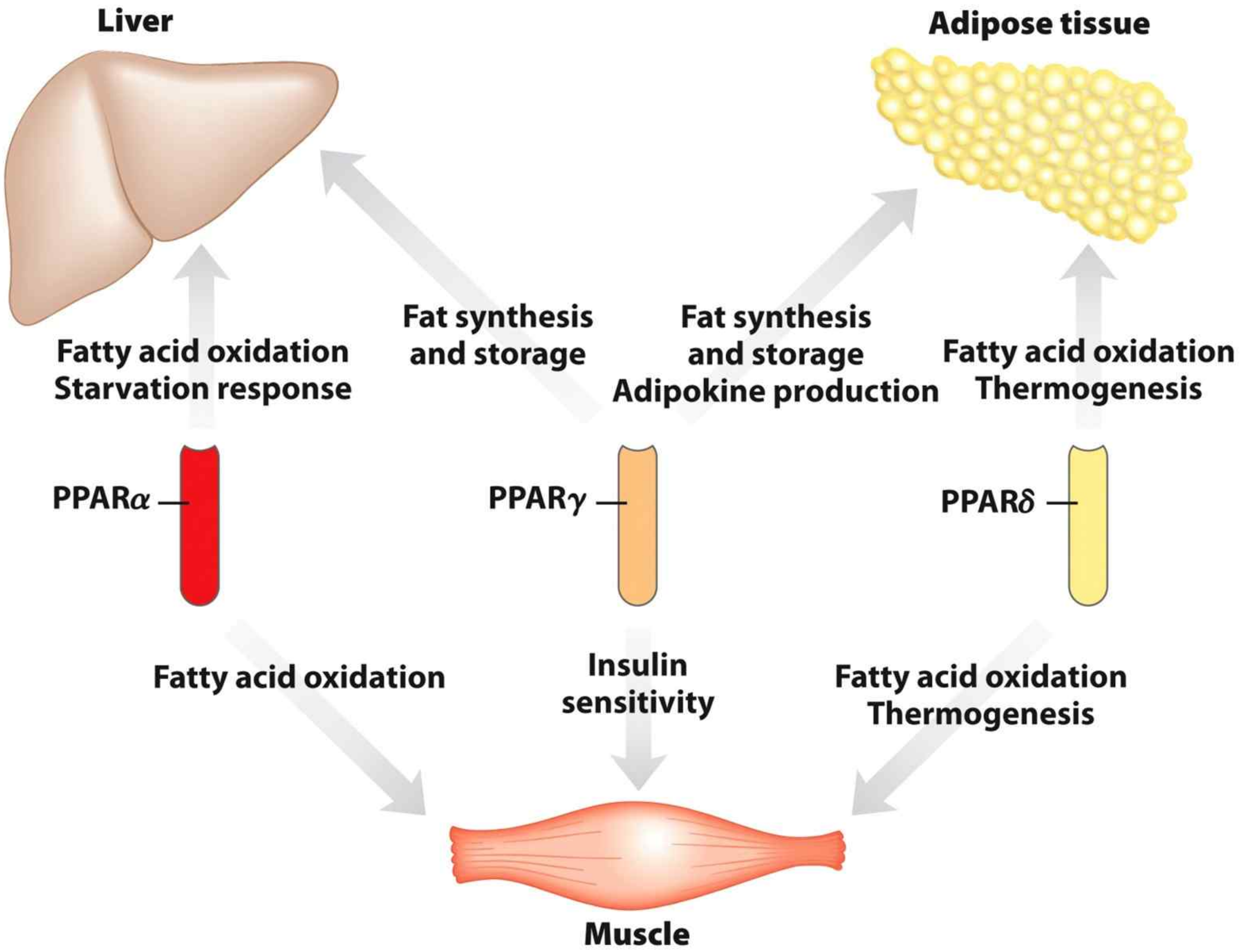

Figure 23-42
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Ghrelin is a short-term orexigenic peptide secreted in the stomach

- Ghrelin receptors appear in brain, heart, and adipose tissue
- Ghrelin is not well-understood
- Works via G-protein–coupled receptor to increase sensation of hunger
- Injections of ghrelin immediately increase appetite
- Prader-Willi Syndrome associated with high levels of ghrelin, insatiable appetite

Treatments for Type 2 Diabetes

- Diet and exercise to reduce obesity, manage blood glucose, increase insulin sensitivity of muscles
- Insulin, if endogenous insulin secretion is inadequate
- AMPK activator: Metformin (Glucophage)
- PPAR activators to increase adiponectin, stimulate adipocyte differential, and increase capacity for TAG storage: Thiozidinediones
- Stimulation of insulin by binding to ATP-gated K^+ channels: Sulfonylureas
- Preventing proteolytic degradation of glucagon-like peptide-1 (GLP-1), a peptide that stimulates insulin secretion (Dipeptidyl protease-4 inhibitors such as Januvia)

TABLE 23–7 Treatments for Type 2 Diabetes Mellitus

Intervention/treatment	Direct target	Effect of treatment
Weight loss	Adipose tissue; reduces TAG content	Reduces lipid burden; increases capacity for lipid storage in adipose tissue; restores insulin sensitivity
Exercise	AMPK, activated by increasing [AMP]/[ATP]	Aids weight loss; see Fig. 23–39
Sulfonylureas: glipizide (Glucotrol), glyburide (several brands), glimepiride (Amaryl)	Pancreatic β cells; K^+ channels blocked	Stimulates insulin secretion by pancreas; see Fig. 23–27
Biguanides: metformin (Glucophage)	AMPK, activated	Increases glucose uptake by muscle; decreases glucose production in liver
Thiazoladinediones: troglitazone (Rezulin),* rosiglitazone (Avandia),† pioglitazone (Actos)	PPARγ	Stimulates expression of genes, potentiating the action of insulin in liver, muscle, adipose tissue; increases glucose uptake; decreases glucose synthesis in liver
GLP-1 modulators: exenatide (Byetta), sitagliptin (Januvia)	Glucagon-like peptide-1, dipeptide protease IV	Enhances insulin secretion by pancreas

*Voluntarily withdrawn because of side effects.

†Prescriptions limited to patients not helped by other treatment, because of possible increased risk of cardiovascular disease.

Table 23-7

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Chapter 23: Summary

In this chapter, we learned:

- Nervous system controls the production of specific hormones via the hypothalamus-pituitary system
- Pituitary hormones stimulate other hormone-synthesizing glands or act directly on target tissues
- Blood glucose level is controlled by peptide hormone insulin
- Defective insulin production by pancreas or inadequate insulin sensing by target cells leads to diabetes
- Adipocytes influence brain's decision making about food intake and energy expenditure via protein hormone leptin