Vert Phys PCB3743

Endocrinology 1
Fox Chapter 11 part 1

Endocrinology

Secretion of hormones from endocrine glands into the circulation, and the action of those hormones on target tissues which have receptors for specific hormones.

Broadcast signal to distant tissues.
(as opposed to point-to-point communication by nerves)

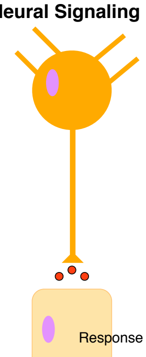
- **Exocrine** -- secretion **outside** the body (e.g. sweat glands)
- **Endocrine** -- secretion **into** the blood, acting on distant tissues
- **Paracrine** -- secretion acting on **nearby** cells
- **Autocrine** -- secretion acting on **same** cell

- Exocrine and Endocrine Cells that secrete chemicals are called **glands**

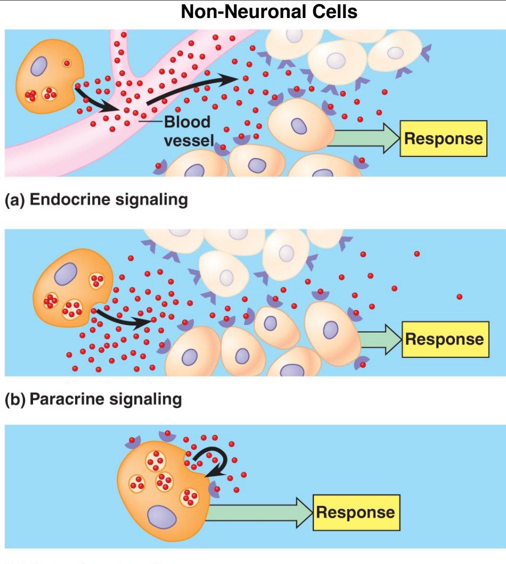
secreted chemicals act via receptors on the target cells

Intercellular Signaling

Neural Signaling



Non-Neuronal Cells



Endocrinology (Outline)

1. Leptin: Demonstration of endocrine system
   (see Chapter 19 p.12:666, p.13:669)

2. Types of hormones and hormone receptor systems

3. Examples of hormone systems:

   Hypothalamic Pituitary Axes

   i. Hypothalamic Piutitary Adrenal (HPA) Axis (Stress Response)

   ii. Hypothalamc Pituitary Thyroid Axis and Thyroid hormones
   (iodine, metabolism)

   iii. Insulin & Glucagon (see also chapter 19 p.12:672-678, p.13:675-685)

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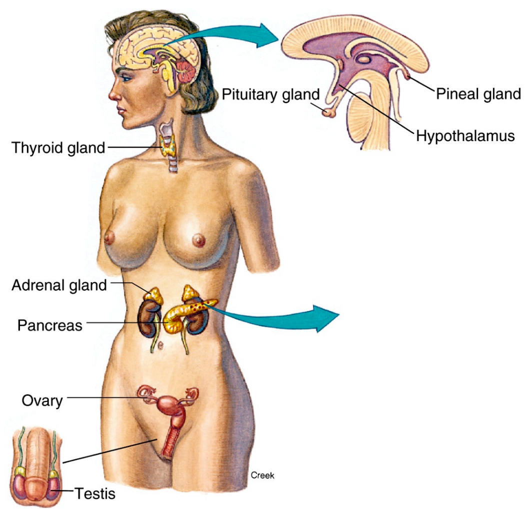

Fox Figure 11.1a

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Table 11.1

Table 11.1 | A Partial Listing of the Endocrine Glands

Endocrine Gland	Major Hormones	Primary Target Organs	Primary Effects
Adipose tissue	Leptin	Hypothalamus	Suppresses appetite
Adrenal cortex	Glucocorticoids Aldosterone	Liver and muscles Kidneys	Glucocorticoids influence glucose metabolism; aldosterone promotes Na^+ retention, K^+ excretion
Adrenal medulla	Epinephrine	Heart, bronchioles, and blood vessels	Causes adrenergic stimulation
Heart	Atrial natriuretic hormone	Kidneys	Promotes excretion of Na^+ in the urine
Hypothalamus	Releasing and inhibiting hormones	Anterior pituitary	Regulates secretion of anterior pituitary hormones
Small intestine	Secretin and cholecystokinin	Stomach, liver, and pancreas	Inhibits gastric motility and stimulates bile and pancreatic juice secretion
Islets of Langerhans (pancreas)	Insulin Glucagon	Many organs Liver and adipose tissue	Insulin promotes cellular uptake of glucose and formation of glycogen and fat; glucagon stimulates hydrolysis of glycogen and fat
Kidneys	Erythropoietin	Bone marrow	Stimulates red blood cell production
Liver	Somatomedins	Cartilage	Stimulates cell division and growth
Ovaries	Estradiol-17β and progesterone	Female reproductive tract and mammary glands	Maintains structure of reproductive tract and promotes secondary sex characteristics
Parathyroid glands	Parathyroid hormone	Bone, small intestine, and kidneys	Increases Ca^{2+} concentration in blood
Pineal gland	Melatonin	Hypothalamus and anterior pituitary	Affects secretion of gonadotrophic hormones
Pituitary, anterior	Trophic hormones	Endocrine glands and other organs	Stimulates growth and development of target organs; stimulates secretion of other hormones
Pituitary, posterior	Antidiuretic hormone Oxytocin	Kidneys and blood vessels Uterus and mammary glands	Antidiuretic hormone promotes water retention and vasoconstriction; oxytocin stimulates contraction of uterus and mammary secretory units
Skin	1,25-Dihydroxyvitamin D_3	Small intestine	Stimulates absorption of Ca^{2+}
Stomach	Gastrin	Stomach	Stimulates acid secretion
Testes	Testosterone	Prostate, seminal vesicles, and other organs	Stimulates secondary sexual development
Thymus	Thymopoietin	Lymph nodes	Stimulates white blood cell production
Thyroid gland	Thyroxine (T_4) and triiodothyronine (T_3); calcitonin	Most organs	Thyroxine and triiodothyronine promote growth and development and stimulate basal rate of cell respiration (basal metabolic rate or BMR); calcitonin may participate in the regulation of blood Ca^{2+} levels

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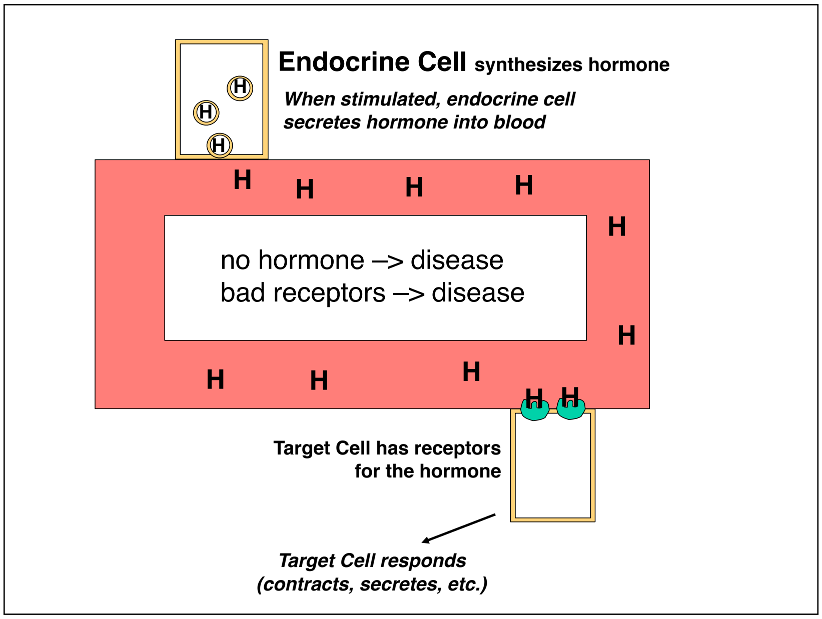
Endocrine Cell synthesizes hormone
When stimulated, endocrine cell secretes hormone into blood
no hormone –> disease
bad receptors –> disease
Target Cell has receptors for the hormone
Target Cell responds (contracts, secretes, etc.)

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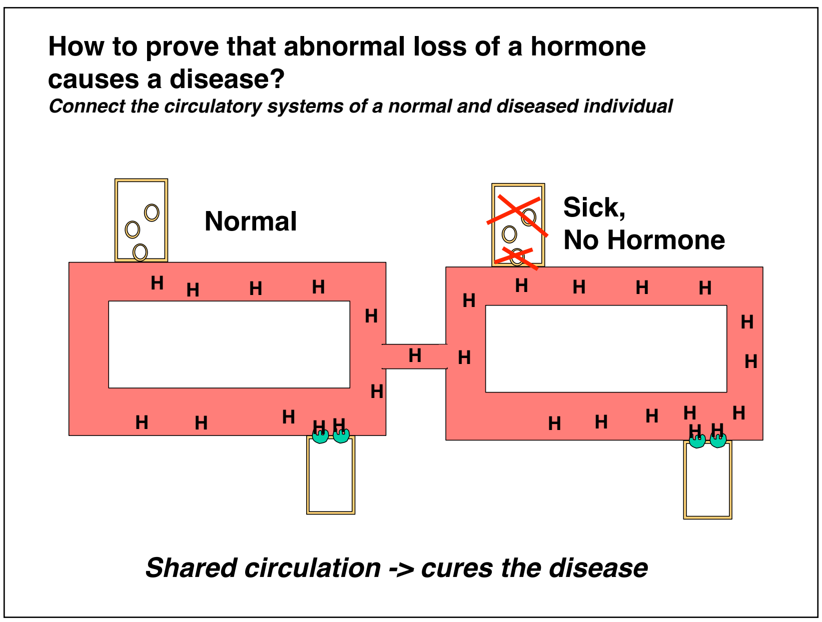
How to prove that abnormal loss of a hormone causes a disease?
Connect the circulatory systems of a normal and diseased individual
Normal
Sick,
No Hormone
Shared circulation -> cures the disease

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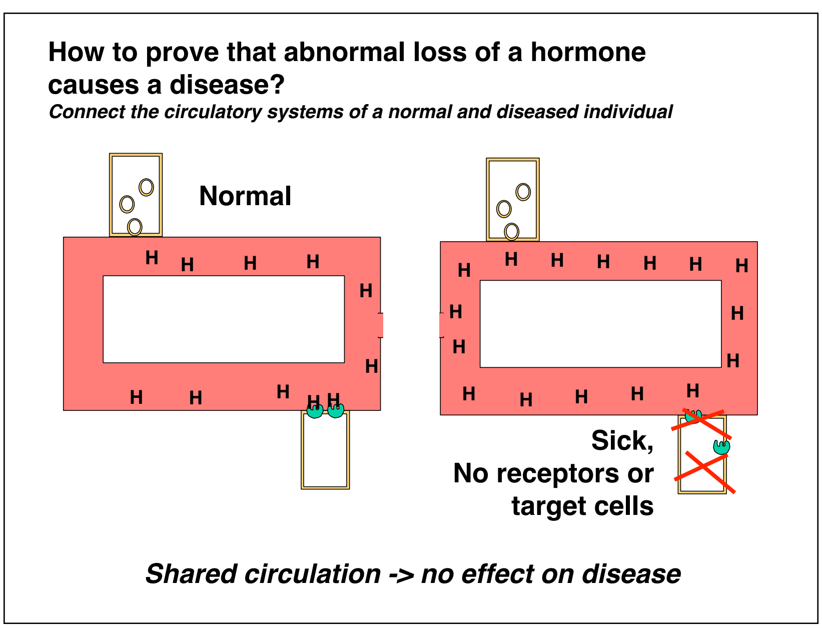
How to prove that abnormal loss of a hormone causes a disease?
Connect the circulatory systems of a normal and diseased individual
Normal
Sick,
No receptors or
target cells
Shared circulation -> no effect on disease

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Cloning of Leptin (leptos = thin) and receptor

Leptin = ~100 amino acid peptide hormone secreted by adipose tissue into the blood.

ob/ob mutation
-> extra stop codon terminates leptin transcript.
-> hypoleptinemia

db/db mutation
-> extra stop codon terminates leptin receptor
-> *functional* hypoleptinemia

There are rare human mutants homologous to mouse mutants:
Anglo-Pakistani brothers lack leptin,
French sisters lack leptin receptors.

However, exogenous leptin doesn't decrease appetite/body weight in most humans.

hypo - below (normal levels)
-emia - related to blood
hypoleptinemia - below normal levels of leptin in the blood

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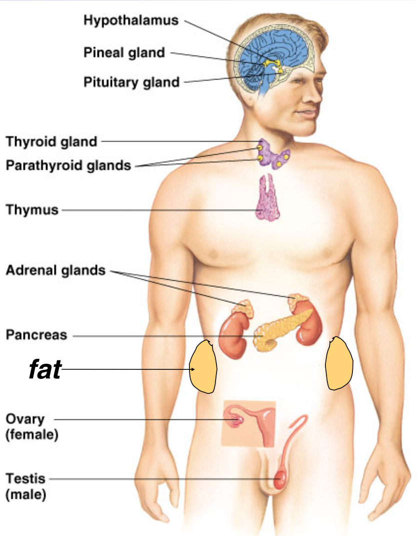
Figure 45.5 Human endocrine glands surveyed in this chapter



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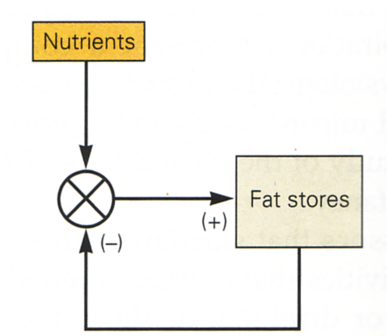
Feedback Regulation

High levels of regulated variable cause hypothalamus to downregulate behavior & physiology that drive the variable up.



Kandel

negative feedback loop balances positive input; no setpoint

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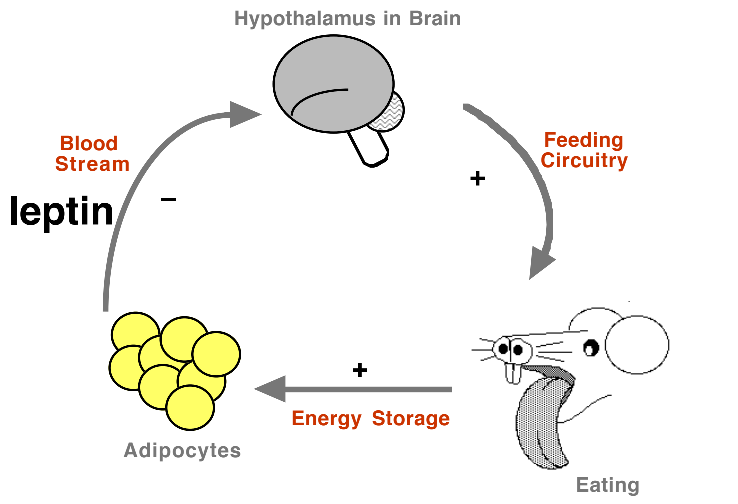
Feedback loops



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Obese Mutant Mice

ob/ob *obese* mouse
no leptin

db/db *diabetic* mouse
no leptin receptors

ob/ob mutants look identical to db/db mice: both over eat, are obese, become diabetic

	Body mass	Adiposity
wildtype (+/+):	18 g	12 %
obese (ob/ob)	64 g	60 %

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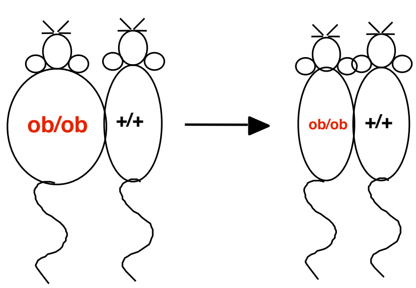
Parabiotic experiments with shared blood supply



wildtype blood normalizes **ob/ob**

∴ **wildtype** has hormone that **ob/ob** is missing

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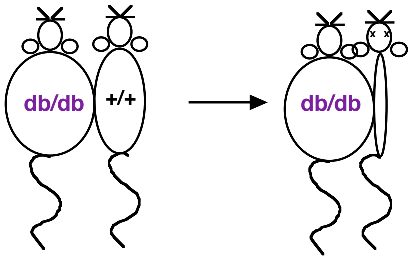
Parabiotic experiments with shared blood supply



db/db blood makes **wildtype** anorexic

∴ **db/db** has **excess** hormone that **wildtype** can detect

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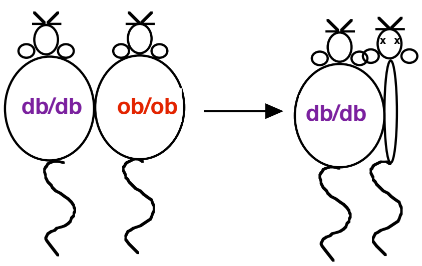
Parabiotic experiments with shared blood supply



db/db blood makes **ob/ob** anorexic

∴ **db/db** has **excess** hormone that **ob/ob** is missing

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hypoleptinemia and functional hypoleptinemia

ob/ob is missing hormone supplied by wildtype mouse.

db/db is missing receptor, while increased fatmass overproduces hormone. This is same hormone that ob/ob is missing, because it makes ob/ob anorexic.

ob/ob: no leptin hormone, so can't *produce* negative feedback signal and keeps putting on fat.
= hypoleptinemia

db/db : no leptin receptors, so can't *detect* negative feedback signal, and keeps putting on fat.
= functional hypoleptinemia

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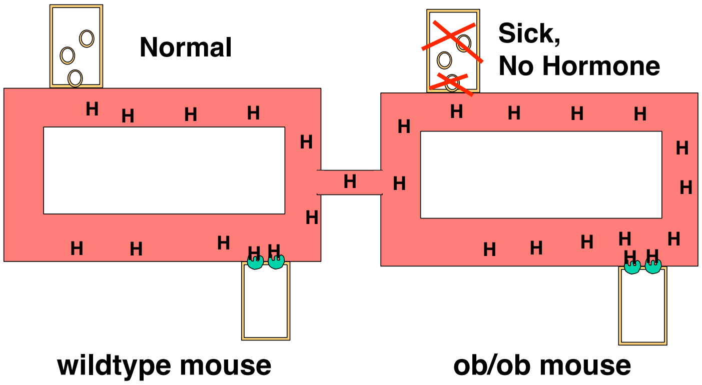
How to prove that abnormal loss of a hormone causes a disease?

Connect the circulatory systems of a normal and diseased individual



Shared circulation -> cures disease

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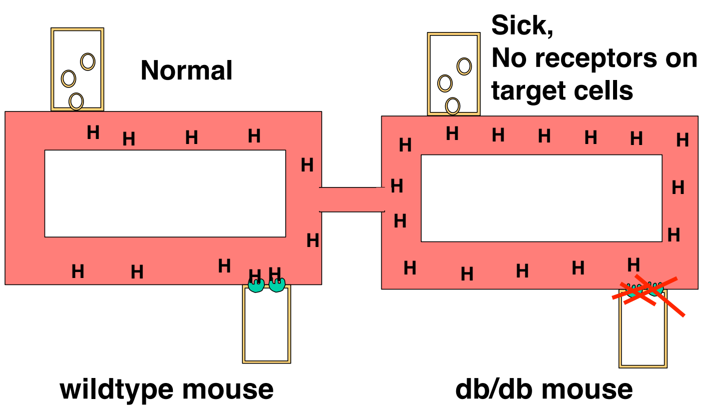
How to prove that abnormal loss of a hormone causes a disease?

Connect the circulatory systems of a normal and diseased individual



Shared circulation -> no effect on disease

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Do the Obese Rodent Models apply directly to human behavioral genetics?

1. Yes, there are occasional human mutants:

Anglo-Pakistani brothers lack leptin,

French sisters lack leptin receptors.

2. No, in fact leptin doesn't work well in most humans.

3. Polygenetic influences are clear.

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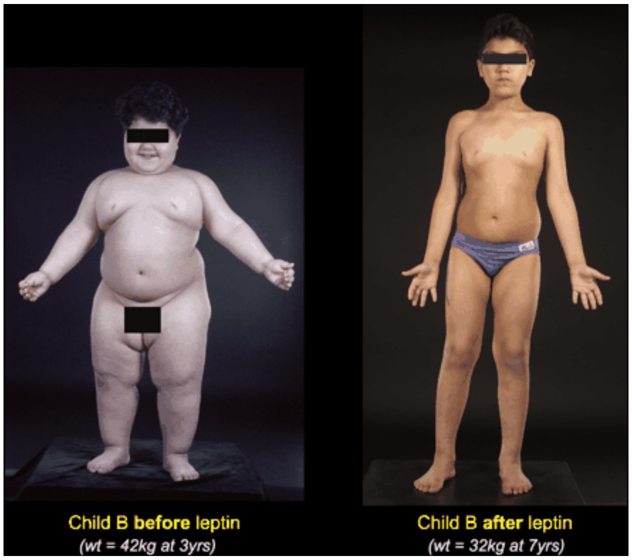

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Hormone Types

Nuclear Receptor Hormones
(Steroids, Thyroid Hormone, and Retinoic acid)

Polypeptide and Glycoprotein Hormones
(Second-Messenger Coupled Hormones)

i. GPCR linked to cAMP

ii. GPCR linked to phospholipase C and Ca++

iii. Tyrosine Kinase Receptors

Many hormones are converted from prohormones or prehormones
e.g. proinsulin is a polypeptide cleaved to form the smaller peptide, insulin
e.g. testosterone is a steroid that is converted to DHT or estradiol in target tissue
e.g. T4 is converted to the active T3 thyroid hormone

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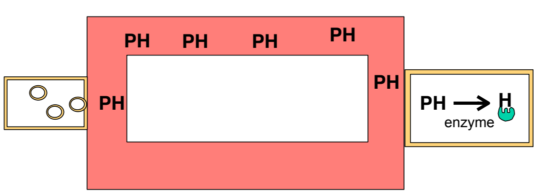
Table 11.3

Table 11.3 | Conversion of Prehormones into Biologically Active Derivatives

Endocrine Gland	Prehormone	Active Products	Comments
Skin	Vitamin D_3	1,25-Dihydroxyvitamin D_3	Conversion (through hydroxylation reactions) occurs in the liver and the kidneys.
Testes	Testosterone	Dihydrotestosterone (DHT)	DHT and other 5α-reduced androgens are formed in most androgen-dependent tissue.
		Estradiol-17β (E_2)	E_2 is formed in the brain from testosterone, where it is believed to affect both endocrine function and behavior; small amounts of E_2 are also produced in the testes.
Thyroid	Thyroxine (T_4)	Triiodothyronine (T_3)	Conversion of T_4 to T_3 occurs in almost all tissues.



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Nuclear Receptor Hormones
(Steroids, Thyroid Hormone, & Retinoic acid = lipophilic hormones)

1. Lipophilic molecules that pass through membranes (and skin)
made up of sterol ring structures (steroids) or long-chain hydrocarbons (thyroid hormone, retinoic acid) that easily cross lipid bilayers. Usually bound in the blood to **carrier proteins** (that have hydrophobic domain) that help them circulate through the body.

2. Coordinate peripheral physiological and central neural response
Because they can pass through membranes, they readily diffuse throughout body and brain to produce parallel physiological and behavioral responses. (Note: only cells that express the right receptors will respond to each hormone).

3. Release regulated by synthesis
Not easily contained in vesicles. Synthesized from lipid-soluble store by **enzymes** (so no gene for these hormones, although there are genes for synthesizing enzymes and for their receptors). eg, steroids synthesized from droplets of cholesterol in adrenal, ovaries, testes, etc.

4. Bind to cytoplasmic/nuclear receptors
Lipophilic hormones can **diffuse** across membrane and bind receptors on the **inside** of cells.

5. Receptors bind to DNA, affecting gene transcription
Receptors bind to specific sequences (**response elements**) in gene promoters. Because the nuclear receptors bind to DNA, their effects are necessarily genomic (e.g. not directly on ion channels or second messengers); i.e., they induce protein synthesis. It can take hours or days before the effect of nuclear receptor hormones is seen.

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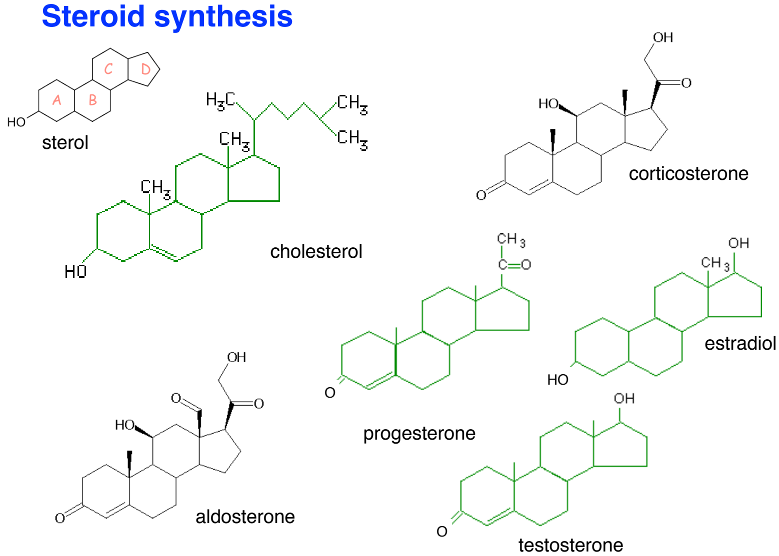
Steroid synthesis



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Steroid Hormones derived from cholesterol

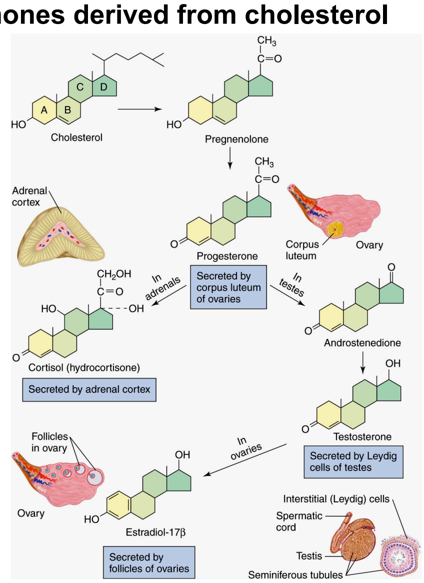

Figure 11.2

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Figure 11.4

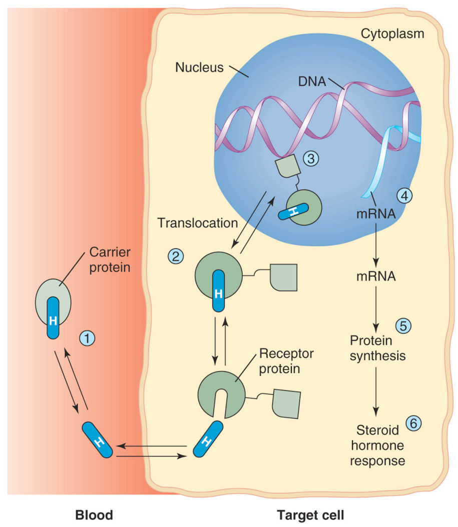

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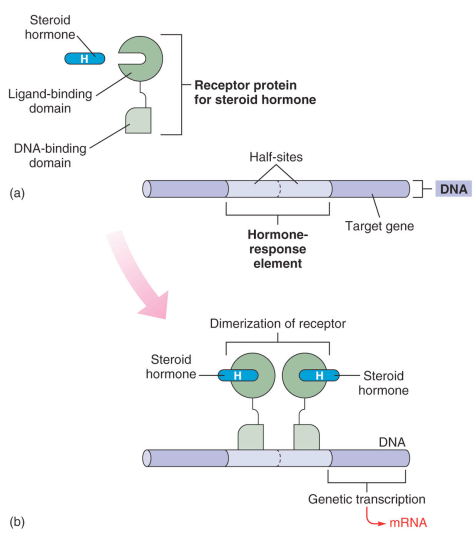
Figure 11.5



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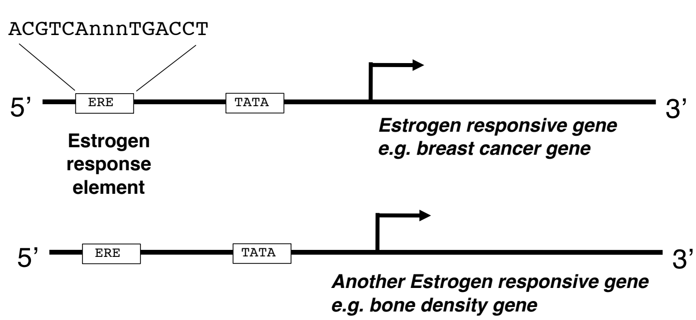
estrogen receptor in presence of estrogen binds to **estrogen response element**



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Estrogen responsive gene

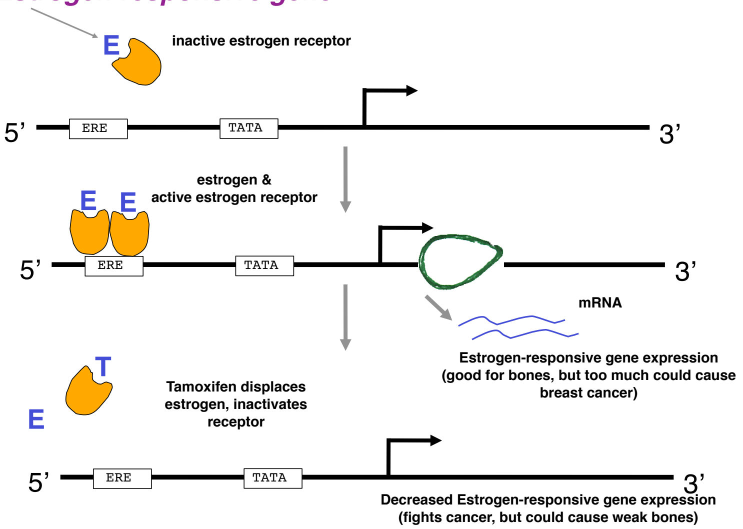

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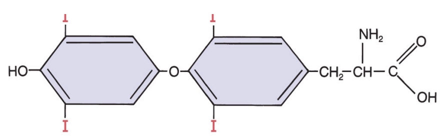
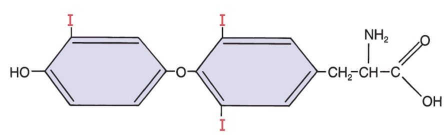
Figure 11.3

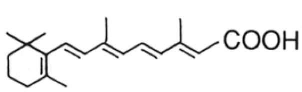


Thyroxine, or **tetraiodothyronine (T_4)**

T4 & T3 Thyroid Hormones



Triiodothyronine (T_3)



All-trans-Retinoic Acid (derived from Vitamin A)
(and other retinoic acid derivatives)

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Figure 11.6

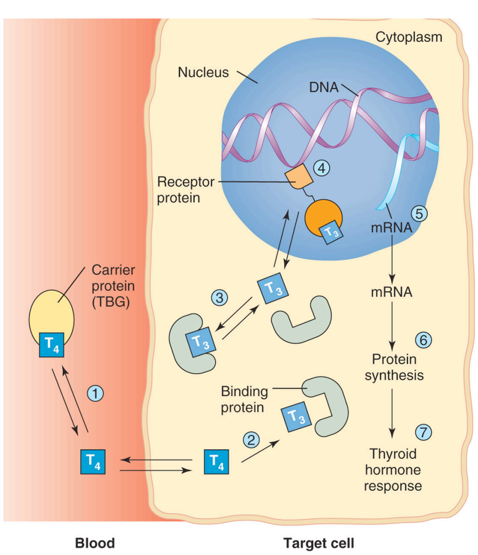

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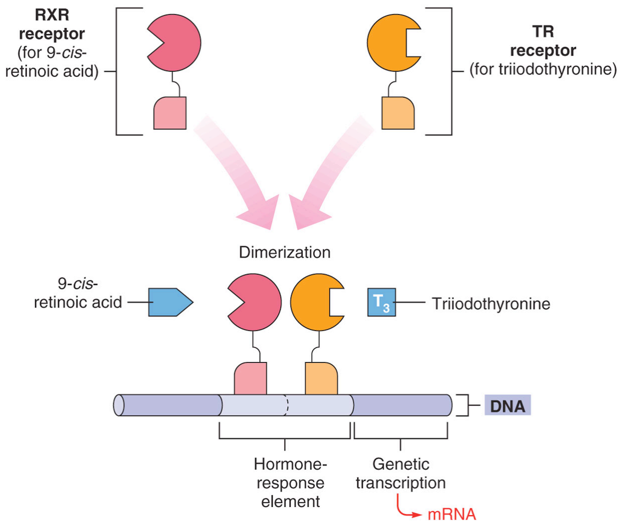
Figure 11.7



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Polypeptide and Glycoprotein Hormones
(Second-Messenger Coupled Hormones)

Small **peptides** 4-100 amino acids long. (often identical to neuropeptides used by neurons as neurotransmitters.)

Coded for by **genes**; processed in endoplasmic reticulum & Golgi apparatus; packaged in **vesicles** and secreted by endocytosis.

Many peptide hormones are converted from prohormones
e.g. proinsulin is a polypeptide cleaved to form the smaller peptide, insulin

Hydrophilic molecules so soluble in blood; circulate and act on **plasma membrane receptors** (on the surface of the cell) to induce **second messenger** signaling in the target cells.

3 Common Hormone Receptor Signaling Pathways:

i. GPCR linked to cAMP

ii. GPCR linked to phospholipase C and Ca++

iii. Tyrosine Kinase Receptors

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Table 11.2

Table 11.2 | Examples of Polypeptide and Glycoprotein Hormones

Hormone	Structure	Gland	Primary Effects
Antidiuretic hormone	8 amino acids	Posterior pituitary	Water retention and vasoconstriction
Oxytocin	8 amino acids	Posterior pituitary	Uterine and mammary contraction
Insulin	21 and 30 amino acids (double chain)	Beta cells in islets of Langerhans	Cellular glucose uptake, lipogenesis, and glycogenesis
Glucagon	29 amino acids	Alpha cells in islets of Langerhans	Hydrolysis of stored glycogen and fat
ACTH	39 amino acids	Anterior pituitary	Stimulation of adrenal cortex
Parathyroid hormone	84 amino acids	Parathyroid	Increase in blood Ca^{2+} concentration
FSH, LH, TSH	Glycoproteins	Anterior pituitary	Stimulation of growth, development, and secretory activity of target glands

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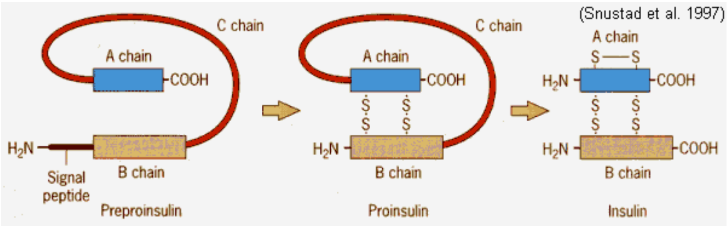
Processing of preproinsulin peptide



insulin gene product
is 110 amino acids

disulfide bonds between cysteine residues holds A & B chain together

A chain = 21 amino acids
B chain = 30 amino acids
C chain = 31 amino acids

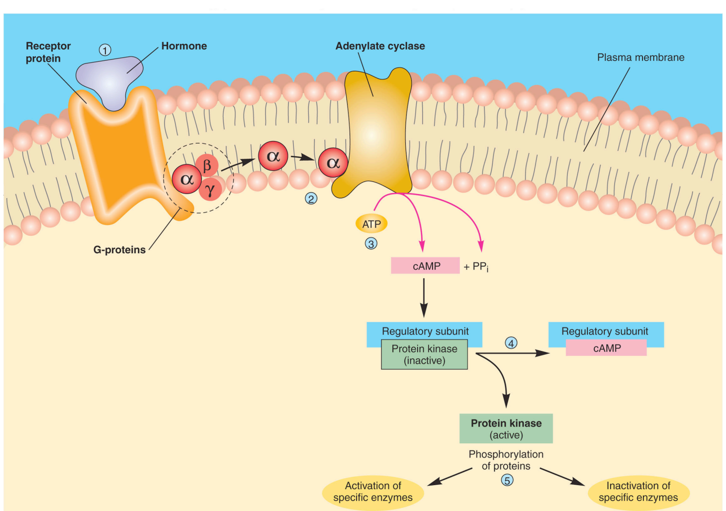
cAMP as a Second Messenger

1. Hormone binds to receptor on target cell's plasma membrane
2. Hormone-receptor interaction acts by G-proteins to stimulate adenylate cyclase on the cytoplasmic side of the membrane
3. Activated adenylate cyclase catalyzes conversion of ATP to cyclic AMP (cAMP) in the cytoplasm
4. Cyclic AMP activates protein kinase enzymes in the cytoplasm
5. Activated cAMP-dependent protein kinase phosphorylates (transfers phosphate groups) to activate/inhibit other enzymes in the cell.
6. Enzyme activity mediates the target cell's response to the hormone.

- gets the message across the membrane to inside of the cell
- amplifies the message by production of many cAMP molecules
- spreads the message by diffusion of cAMP throughout the cell

Fox Table 11.4

Figure 11.8



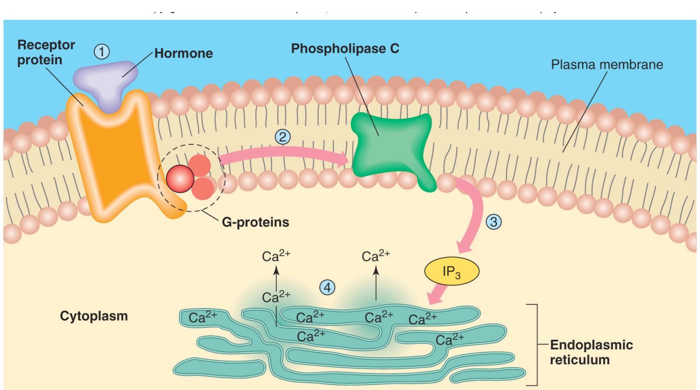
Intracellular Ca++ as a Second Messenger

1. Hormone binds to receptor on target cell's plasma membrane
2. Hormone-receptor interaction acts by G-proteins to stimulate phospholipase C enzyme in the membrane
3. Activated phospholipase C catalyzes the conversion of phospholipds in the membrane to inositol triphosphate (IP3) and diacylglycerol (DAG).
4. IP3 enters the cytoplasm and diffuses to the endoplasmic reticulum, binds to IP3 receptors, and causes Ca++ channels to open
5. Endoplasmic reticulum has high [Ca++]; Ca++ rushes out of endoplasmic reticulum unto cytoplasm.

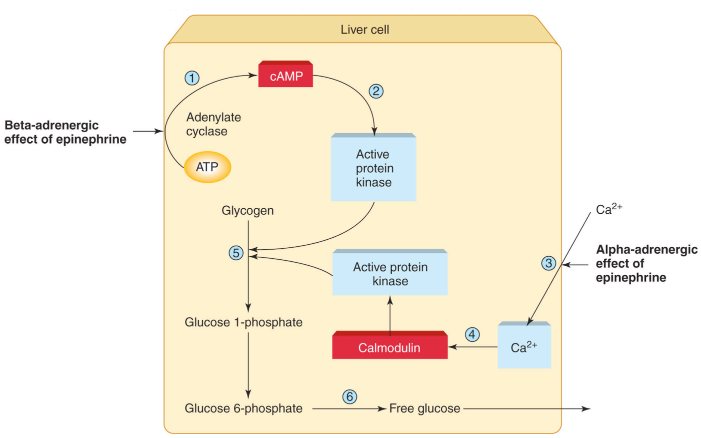
4. Ca++ in the cytoplasm binds to calmodulin protein.
5. Activated calmodulin activates protein kinases, which phosphorylate (transfers phosphate groups) to activate/inhibit other enzymes in the cell.
6. Enzyme activity mediates the target cell's response to the hormone.

Fox Table 11.5

Figure 11.9



cAMP and Ca++ can act together to enhance hormone effect
e.g. in the liver:
epinephrine -> beta-adrenergic receptors -> cAMP
epinephrine -> alpha-adrenergic receptors -> Ca^{++}



Fox Figure 11.10

Tyrosine Receptor Kinases

1. Hormone binds to receptor on target cell's plasma membrane
2. Receptors dimerize (form pairs)
3. Receptors phosphorylate each other (the receptors themselves are kinases)
4. Activated receptors phosphorylate target proteins ("tyrosine kinases" because add phosphate groups to tyrosine residues in target proteins)
5. Phosphorylated proteins activate/inhibit other pathways in the cell.
6. Enzyme activity mediates the target cell's response to the hormone.

examples: insulin, leptin, cytokines (like interleukin that induces fever)

Fox Table 11.5

Figure 11.11