Human Phys PCB4701

Endocrinology 1
Chapter 11

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.

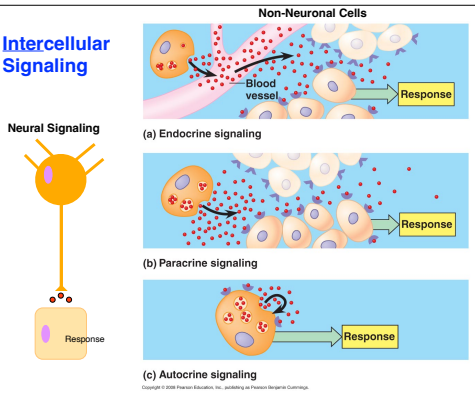
Broadcast signal to distant tissues.
(as opposed to point-to-point communication by nerves)

- **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**

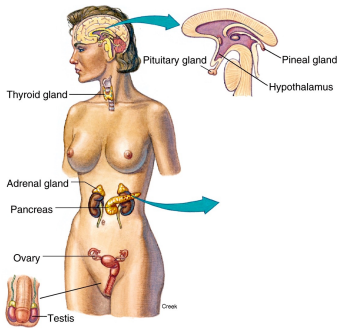
secreted chemicals act via receptors on the target cells

Intercellular Signaling



Endocrinology (Outline)

1. Leptin: Demonstration of endocrine system
2. Types of hormones and hormone receptor systems
3. Hypothalamic Pituitary Axes
   i. Hypothalamic Piutitary Adrenal (HPA) Axis (Stress Response)
   ii. Hypothalamic Pituitary Thyroid Axis and Thyroid hormones (iodine, metabolism)



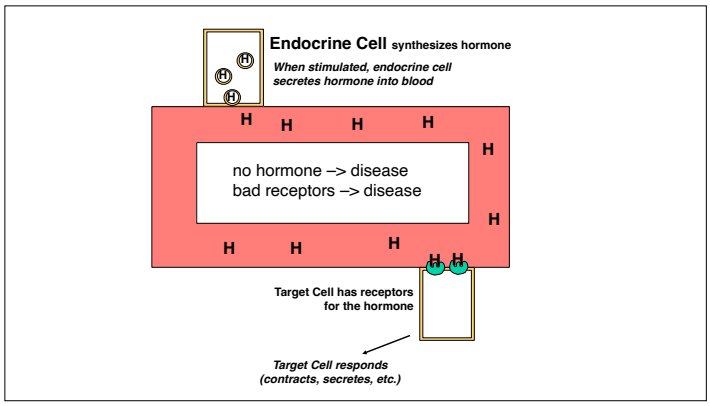
(a)

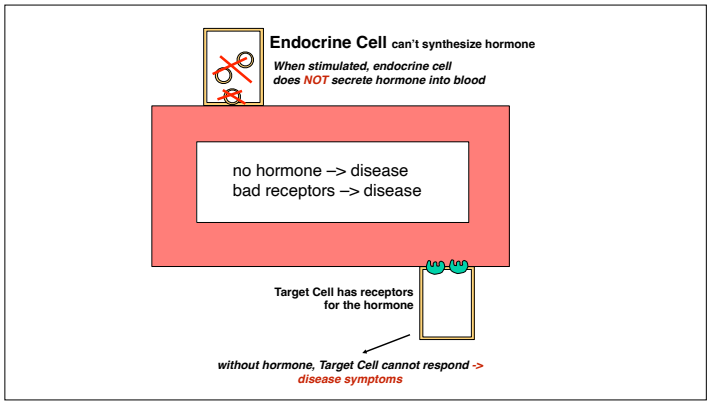
Fox Figure 11.1a

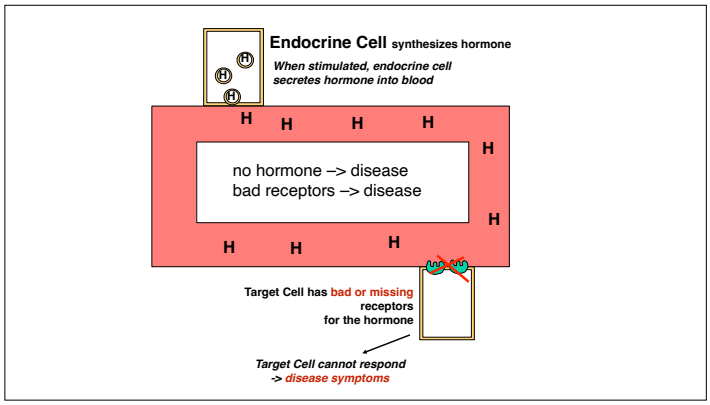
Table 11.1

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

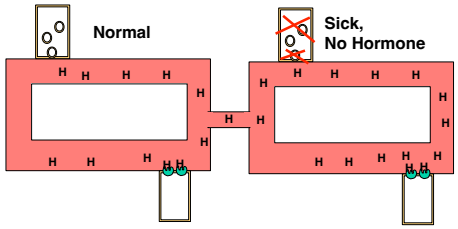

Endocrine Cell synthesizes hormone
When stimulated, endocrine cell secretes hormone into blood
no hormone –> disease
bad receptors –> disease
Target Cell has receptors for the hormone
Target Cell responds (contracts, secretes, etc.)


Endocrine Cell can't synthesize hormone
When stimulated, endocrine cell does NOT secrete hormone into blood
no hormone –> disease
bad receptors –> disease
Target Cell has receptors for the hormone
without hormone, Target Cell cannot respond -> disease symptoms


Endocrine Cell synthesizes hormone
When stimulated, endocrine cell secretes hormone into blood
no hormone –> disease
bad receptors –> disease
Target Cell has bad or missing receptors for the hormone
Target Cell cannot respond -> disease symptoms

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

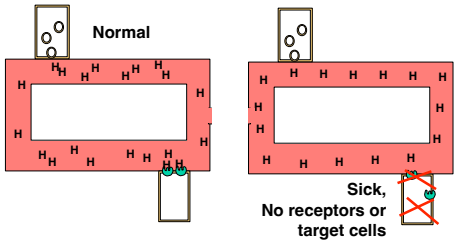
Connect the circulatory systems of a normal and diseased individual



Shared circulation -> cures the disease

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

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

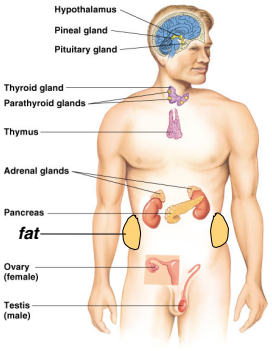
db/db mutation
–> extra stop codon terminates leptin receptor
–> *functional* hypoleptinemia

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.

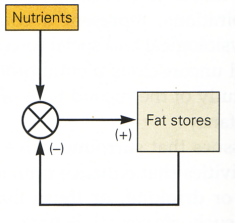
hypo - below (normal levels)
-emia - related to blood
hypoleptinemia - below normal levels of leptin in the blood

Figure 45.5 Human endocrine glands surveyed in this chapter



Feedback Regulation

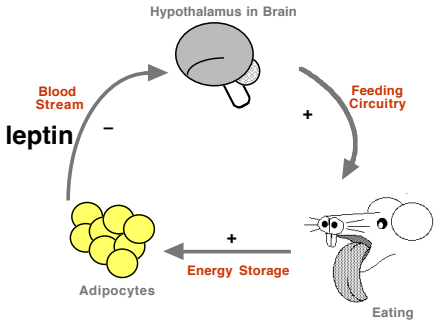
High levels of regulated variable cause hypothalamus to downregulate behavior & physiology that drive the variable up.



Kandel

negative feedback loop balances positive input; no setpoint

Feedback loops



Obese Mutant Mice

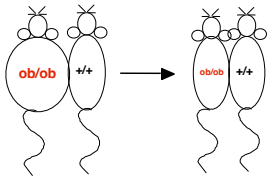
ob/ob ***obese*** **mouse**
no leptin

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 %

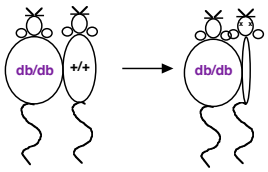
Parabiotic experiments with shared blood supply



wildtype blood normalizes **ob/ob**

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

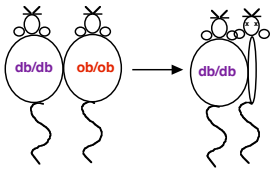
Parabiotic experiments with shared blood supply



db/db blood makes **wildtype** anorexic

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

Parabiotic experiments with shared blood supply



db/db blood
makes
ob/ob anorexic

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

hypoleptinemia and functional hypoleptinemia

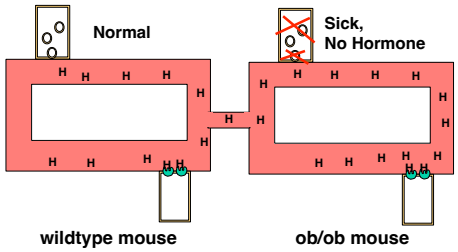
ob/ob is missing hormone supplied by wildtype mouse.

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*

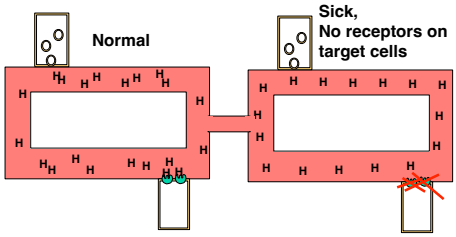
How to prove that abnormal loss of a hormone causes a disease?
Connect the circulatory systems of a normal and diseased individual



Shared circulation -> cures disease

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

Connect the circulatory systems of a normal and diseased individual



wildtype mouse **db/db mouse**

Shared circulation -> no effect on disease

in fact, normal mouse gets too much leptin from db mouse

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.

Hormone Dysfunction vs. Receptor Dysfunction

1. **Type 1 Diabetes Mellitus (lack of insulin)**
   vs.
   Type 2 Diabetes Mellitus (insulin receptor resistance)

2. **Central Diabetes Insipidus (lack of ADH)**
   vs.
   Nephrogenic Diabetes Insipidus (lack of ADH receptors)

3. **ob mutation (lack of leptin)**
   vs.
   db mutation (lack of leptin receptors)

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++

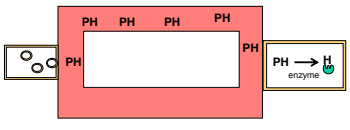
iii. Tyrosine Kinase Receptors

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

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.



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.

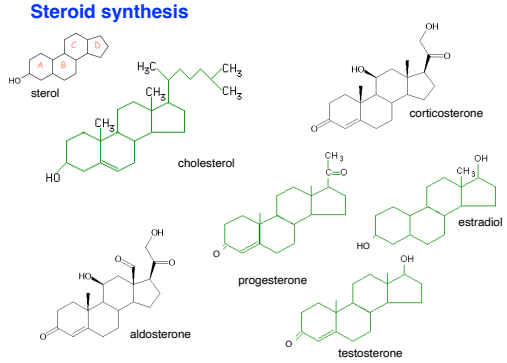
2. Coordinate peripheral physiological and central neural response
Because they can pass through membranes, they readily diffuse throughout body and brain to produce parallel physiological and behavioral responses. (Note: only cells that express the right receptors will respond to each hormone).

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.

Steroid synthesis



Steroid Hormones derived from cholesterol

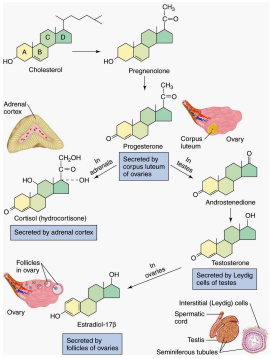


Figure 11.2

Figure 11.4

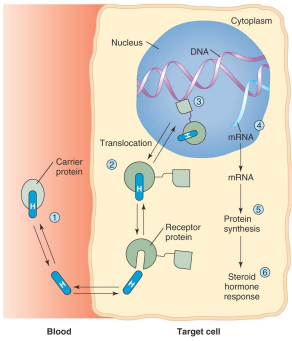
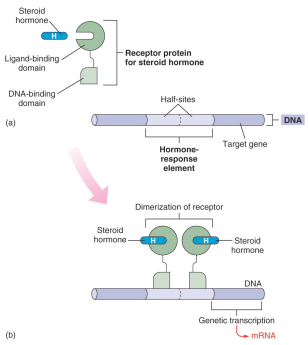
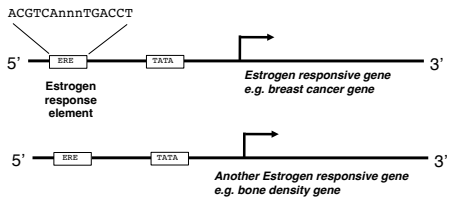


Figure 11.5



estrogen receptor in presence of estrogen binds to
estrogen response element



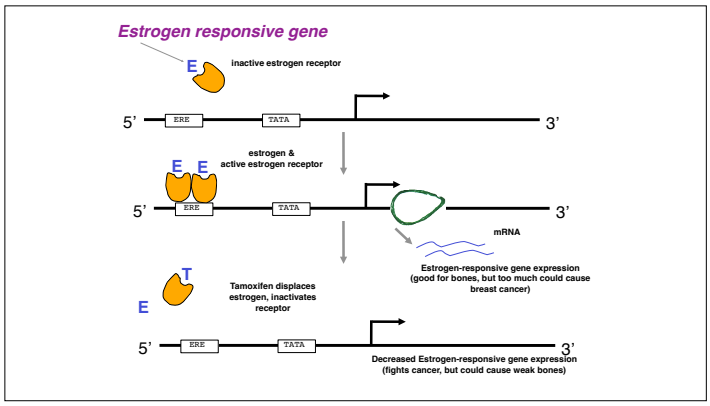


Figure 11.3

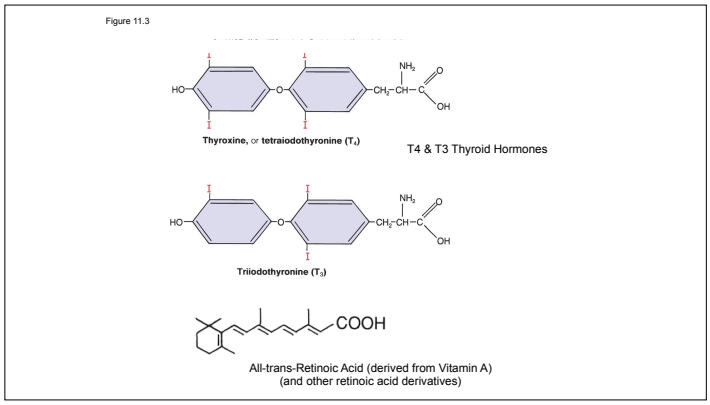


Figure 11.6

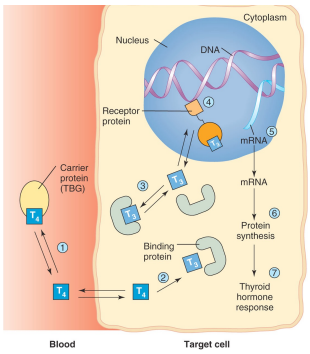
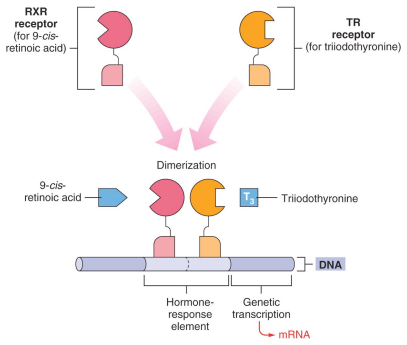


Figure 11.7



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++

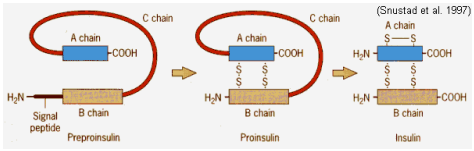
iii. Tyrosine Kinase Receptors

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

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

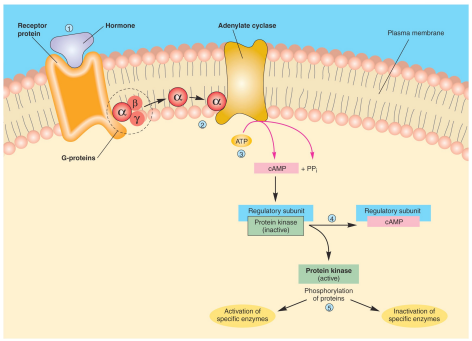
cAMP as a Second Messenger

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

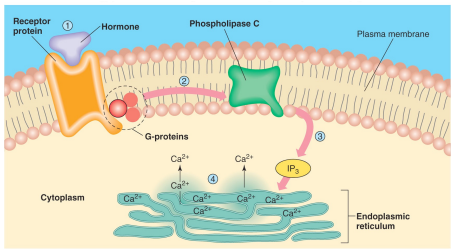


Intracellular Ca^{++} as a Second Messenger

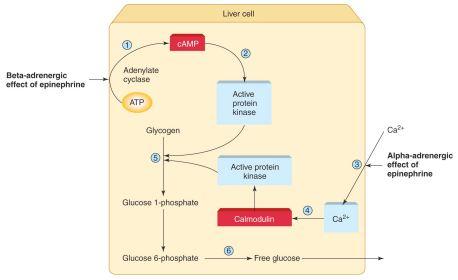
1. Hormone binds to receptor on target cell's plasma membrane
2. Hormone-receptor interaction acts by G-proteins to stimulate phospholipase C enzyme in the membrane
3. Activated phospholipase C catalyzes the conversion of phospholipds in the membrane to inositol triphosphate (IP3) and diacylglycerol (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

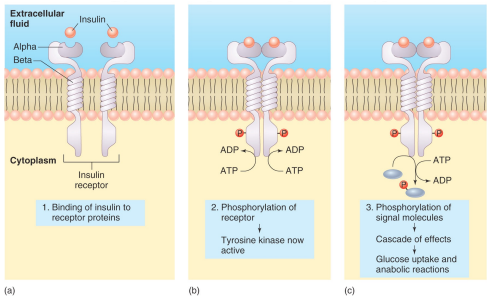
Tyrosine Receptor Kinases

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



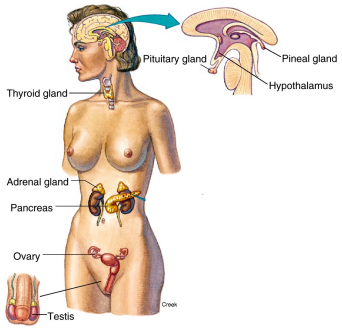
Hypothalamic-Pituitary Anatomy

Hypothalamus: brain region between brainstem and cerebrum that integrates sensory information and generates physiological responses to maintain homeostasis.

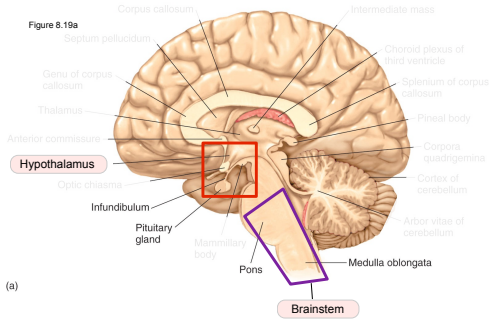
Pituitary Gland: attached to the underside of the hypothalamus by the **infundibulum** (pituitary stalk). Hypothalamus is connected to the pituitary by **hypothalamo-hypophyseal portal veins** that carry releasing hormones to the anterior pituitary, and by the **hypothalamo-hypophyseal tract** of axons projecting to the posterior pituitary.

Anterior Lobe: contains endocrine cells that secrete **tropic hormones** into the circulation that stimulate target organs in the body.

Posterior Lobe: contains axon terminals of **ADH and oxytocin** neurons that originate in the hypothalamus; releases ADH (water retention) and oxytocin (uterine contractions, milk release) into the blood stream.



Fox Figure 11.1a



Autonomic vs. Somatic Axes

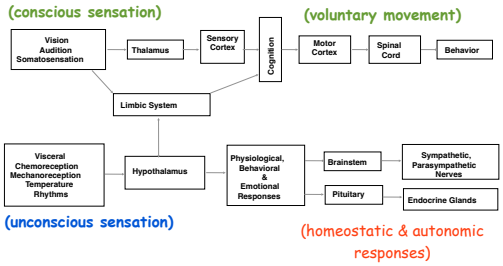


Figure 11.12

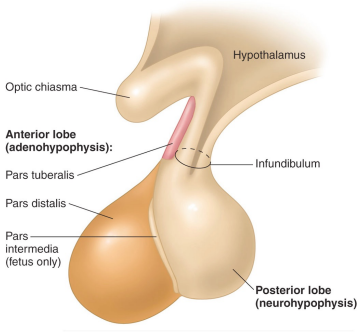


Figure 11.13

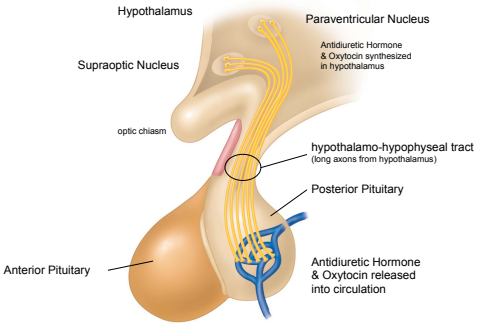
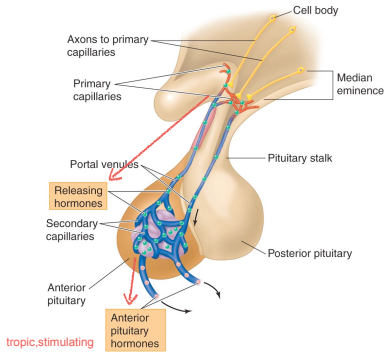


Figure 11.15



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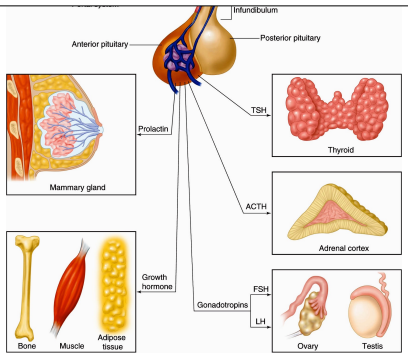

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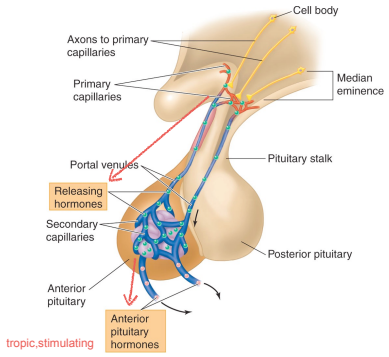


Hypothalamic Pituitary axes

Hypothalamus regulates pituitary function with releasing and release-inhibitory hormones

Releasing hormones –> pituitary to cause release of **stimulatory hormones** –> increase target glands activity

Inhibitory hormones –> pituitary to suppress release of stimulatory hormones –> decrease target gland activity
(esp. dopamine -> less prolactin)

Transection of infundibulum –> decrease of all pituitary hormones except **prolactin** increases.

Examples of Hypothalamic Pituitary Axes: HPA, HPG, HPT axes

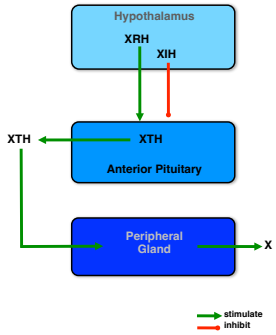
Target Hormones –> **negative feedback** to hypothalamus and pituitary –> **decreased levels** of releasing hormones and stimulatory hormones.

Feedforward Loop

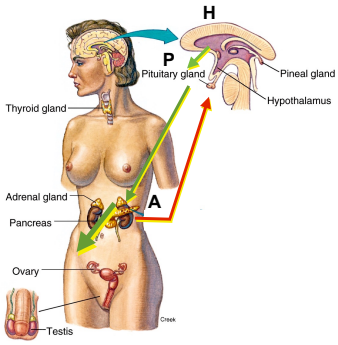
Releasing hormone:
hypothalamus –> pituitary

Tropic hormone:
pituitary –> target gland

target gland –> secretes X



Hypothalamic Pituitary Adrenal (HPA) Axis



(a)

FFox Figure 11.1a

Examples of Hypothalamic Pituitary Axes

	H-P-Adrenal Axis	H-P-Gonadal Axis	H-P-Thyroid Axis
Hypothal:	Corticotropin-releasing hormone (CRH)	Gonadotropin-releasing hormone (GnRH)	Thyrotropin-releasing hormone (TRH)
Anterior Pituitary:	Adrenocorticotropic hormone (ACTH)	Luteinizing hormone (LH)	Thyroid-Stimulating hormone (TSH)
Target Organ:	Adrenal Cortex	Ovaries & Testes	Thyroid Gland
Function:	Stimulate Corticosteroid Synthesis (Stress)	Stimulate Estrogen & Testosterone Synthesis (Reproduction)	Stimulate Thyroxine synthesis (Metabolism)

see Fox Table 11.6 & Table 11.7

Feedback Loops

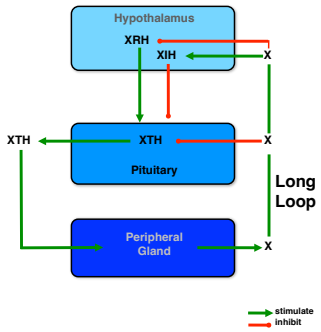


Figure 11.20

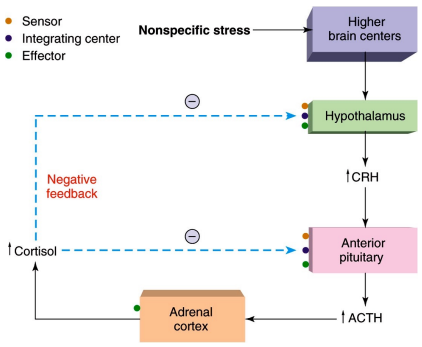


Figure 11.16

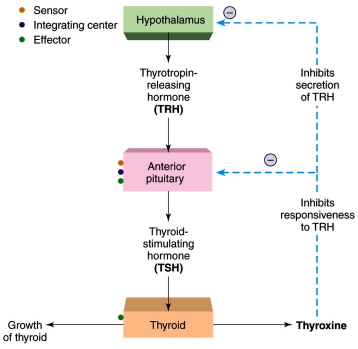
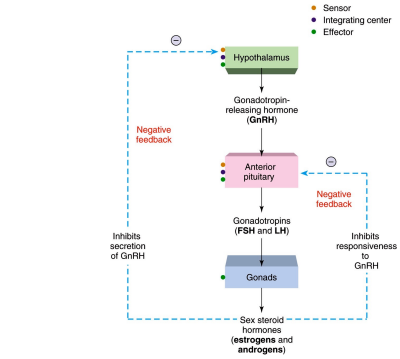


Figure 11.17



Hypothalamic-Pituitary pathologies:

Hypersecretion due to

- tumors
- lack of negative feedback
- inappropriate synthesis/degradation

Real or Functional Hyposecretion due to

- lack of releasing/tropic hormones
- lack of synthetic enzymes
- lack of receptors

Stress Response

Hypothalamic Pituitary Adrenal Axis (HPA) and Stress

Perturbation from homeostasis (maintenance of the constant internal environment)

"Fight or Flight" defined in 1900s by Cannon

Defined in 1930s as general response to "stress" by Selye in war veterans.

- increase in gastric secretion
- increase in adrenal secretion
- suppression of immune system

stress (neural input, disease, learned response)
-> hypothalamus **-> immediate** response & **long-term** response

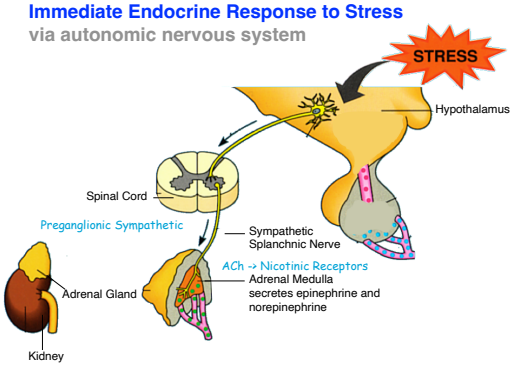
Immediate Endocrine Response via Autonomic Nervous System

hypothalamus –> brainstem
–> vagus –> increase heart-rate
–> spinal cord –> sympathetic activation
–> spinal cord –> splanchnic nerve –> adrenal medulla

Adrenal Medulla
–> epinephrine, norepinephrine into blood stream
–> cardiovascular effects (heart rate, blood flow, blood pressure)
–> mobilize glucose, increase metabolism

Immediate Endocrine Response to Stress

via autonomic nervous system



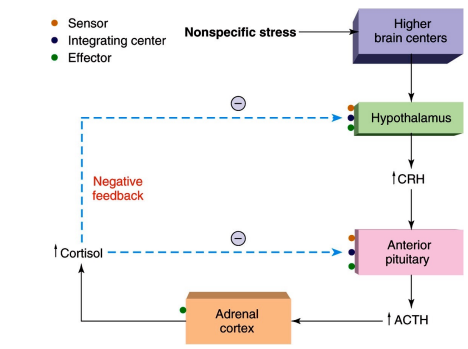
Long-term, transcriptional stress response mediated by glucocorticoids (GC):

CRH from hypothalamus
–> long portal vessels –> anterior pituitary
–> pituitary cells called **corticotropes**
–> adrenocorticotropic hormone (**ACTH**)

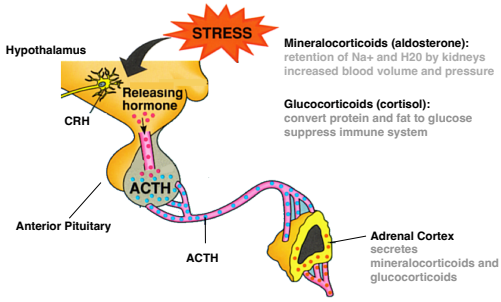
ACTH in blood
–> cortex of adrenal gland
–> ACTH receptors increase cAMP
–> increased cholesterol conversion to cortisol by enzyme P450 in mitochondria & increased cortical growth

Glucocorticoids
–> transcriptional effects on cells expressing GC receptors

Figure 11.20

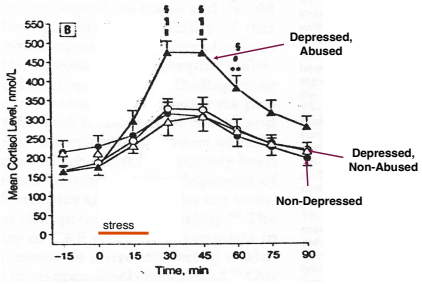


Long-Term Response to Stress:
secretion of mineralo- & glucocorticoids

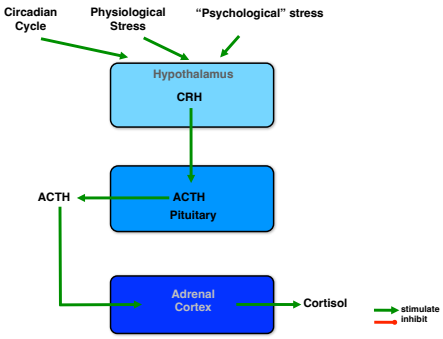


Enhanced Stress Response

Depressed women with Posttraumatic Stress Disorder (childhood abuse) show enhanced cortisol release in response to social stress.



HPA axis: Positive Feed forward



Corticotropes in Pituitary

Synthesize POMC -> ACTH

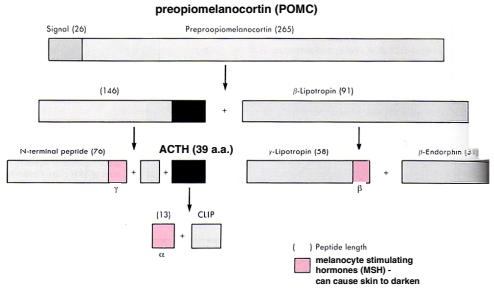
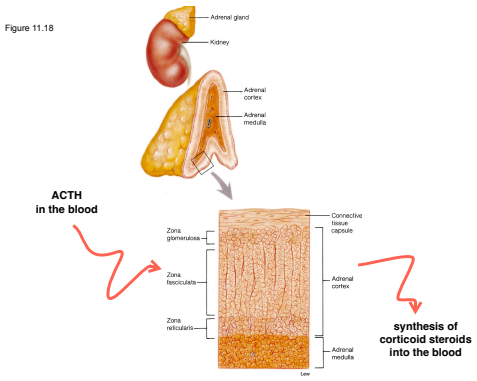


Figure 11.18



Adrenal gland anatomy

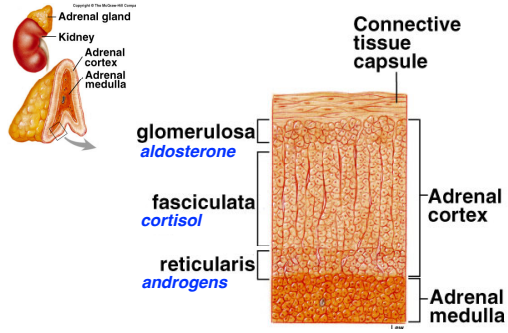
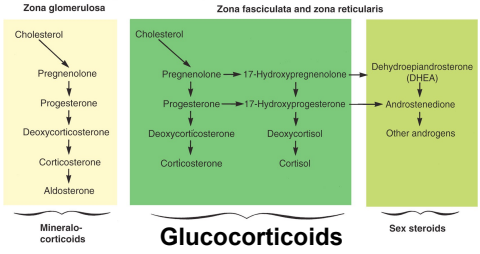
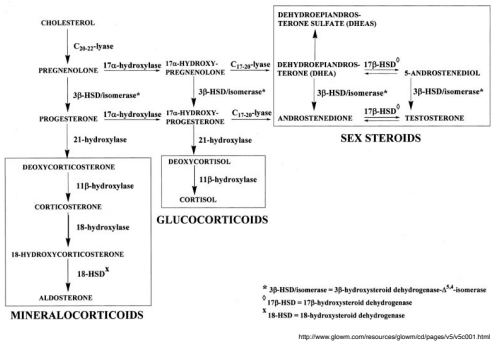


Figure 11.19



Steroid Synthesis in the Adrenal Gland



http://www.glowm.com/resources/glowm/cd/pages/v5/V5c001.html

Actions of Glucocorticoids (GCs)

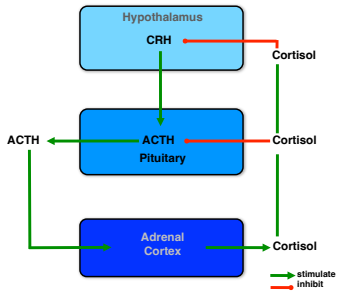
- Containment of stress response
- Suppression of swelling, suppression of immune system
  -> reduce tissue damage
- Mobilization of energy from muscle and fat
- Induce liver enzymes for detoxification
- Suppression of "optional" activities: reproduction, growth
- Adaptive in low doses, but problematic at high or chronic doses

Negative Feedback of Cortisol onto Hypothalamus and Pituitary

- Cortisol levels are controlled by negative feedback loop of HPA.
- High Cortisol levels in the blood act on GC receptors in the hypothalamus and pituitary to decrease CRH & ACTH synthesis and release
- If cortisol synthesis is **blocked** (by drug that blocks synthetic enzyme, or by a disease that damages adrenal cortex), then ACTH levels stay **elevated** (trying to elevate cortisol levels)
- If excess glucocorticoids are administered, HPA detects **high negative feedback**, so then ACTH and cortisol levels should **fall**.
- **Dexamethasone suppression test** administers an artificial glucocorticoid to confirm that HPA responds to negative feedback.

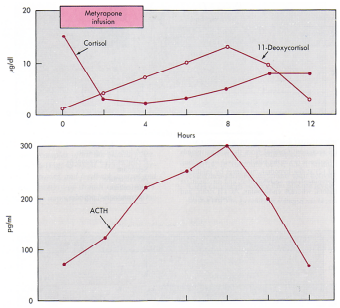
HPA axis: Negative Feedback

Cortisol feeds back to:
pituitary –> inhibit ACTH release
hypothalamus –> inhibit CRH release

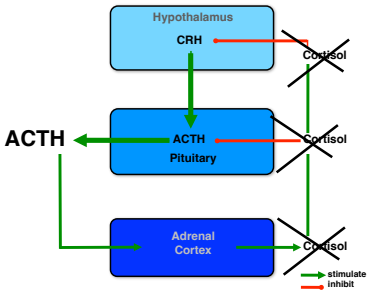


Feedback Loops: block negative feedback

metyrapone blocks conversion of 11-deoxycortisol -> cortisol;
so cortisol levels fall; pituitary responds by increasing ACTH levels



HPA axis: Remove Negative Feedback ACTH & CRH levels increase

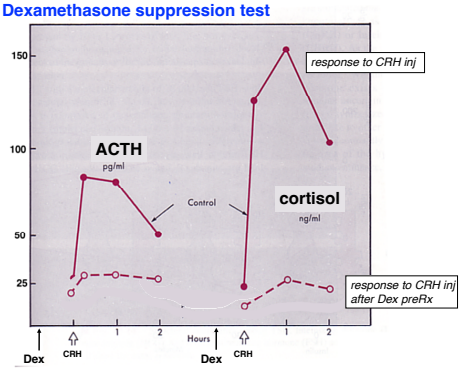


Dexamethasone suppression test

preRX with artificial GC (dexamethasone) suppresses cortisol response to CRH injection

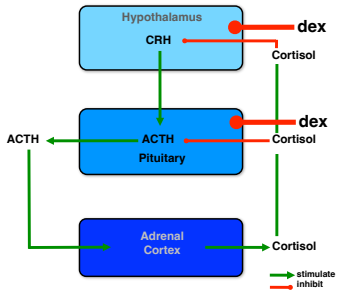
note:
can use suppression test to assay functioning of internal feedback loops

Dexamethasone suppression test



HPA axis: Enhanced Negative Feedback

Dex pretreatment -> blunted ACTH response to CRH



Pathologies of HPA

Points of steroid disregulation

Defects in cortisol synthetic enzymes can result in too much mineralcorticoids (-> high blood pressure) or too much sex steroids (progesterone & androgens -> masculinization)

Addison's Disease: autoimmune destruction of adrenal cortex causes loss of corticosteroids, but excess ACTH

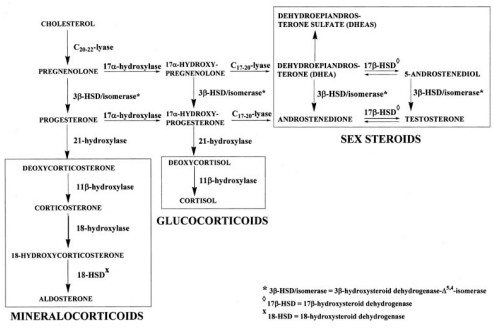
Tumors can oversecrete hormones.

Pheochromacytoma Tumors of adrenal medulla -> elevated epinephrine

Cushing's Syndrome: elevated cortisol
Tumors of Pituitary Gland (adenoma) or Lung (lung carcinoma) can produce too much ACTH -> too much cortisol

Tumors of Adrenal Gland can produce too much cortisol

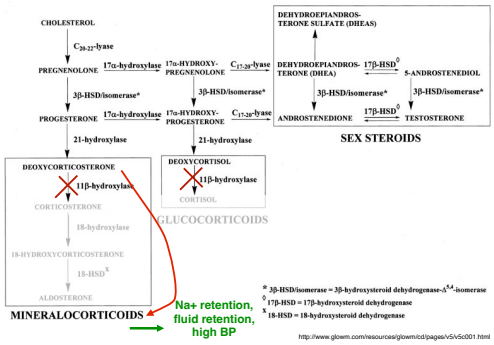
Steroid Synthesis in the Adrenal Gland



http://www.glowm.com/resources/glowm/cd/pages/v5/v5c001.html

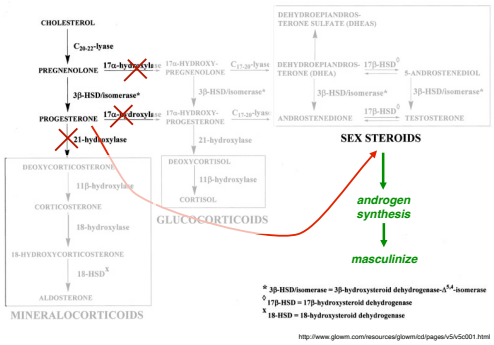
Steroid Synthesis in the Adrenal Gland

defect in 11-hydroxylase



http://www.glowm.com/resources/glowm/cd/pages/v5/v5c001.html

Steroid Synthesis in the Adrenal Gland
defect in 17- or 21-hydroxylase



http://www.glowm.com/resources/glowm/cd/pages/v5/V5c001.html

Pheochromacytoma tumors (1 in 100,000 people)

Hypersecretion of epinephrine and norepinephrine from tumors of the adrenal medulla

Dramatic clinical episodes after stress (or even just change in posture):

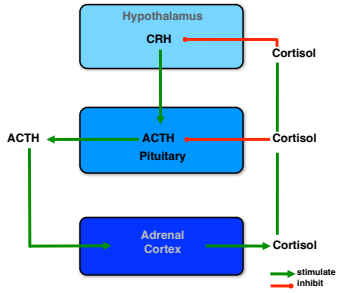
headache, palpatiations, chest pain, cold sweats, anxiety and impeding sense of death.

hyper-epinephrine –> increase heart rate

hyper-norepinephrine –> decreased heart rate

HPA axis: Negative Feedback

Cortisol feeds back to:
pituitary –> inhibit ACTH release
hypothalamus –> inhibit CRH release



Addison's disease (7 in 100,000 people)

Extreme adrenal steroid deficiency

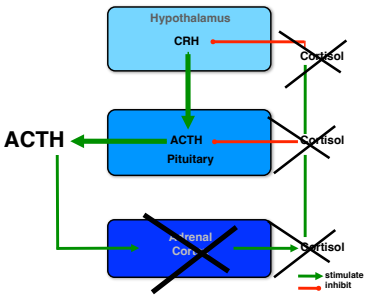
Caused by autoimmune or infectious **destruction of adrenal cortex**.

Extreme intolerance of stress, loss of appetite, malaise, fasting hypoglycemia, low blood pressure, salt craving

No glucocorticoids, so:
–> no negative feedback
–> hypersecretion of ACTH
–> hyperpigmentation of skin (because ACTH acts as melanocyte-stimulating hormone)

Treatment: administer exogenous corticosteroids to replace function of adrenal cortex

Addison's disease - low corticosteroids, elevated ACTH



Addison's disease - low corticosteroids, elevated ACTH

- Note the generalised skin pigmentation (in a Caucasion patient) but especially the deposition in the palmer skin creases, nails and gums.

www-clinpharm.medschl.cam.ac.uk

Cushing's Syndrome (1 in 100,000 people)
hypersecretion of cortisol

Loss of bone mass, loss of muscle mass, fragile skin and connective tissue(because cortisol mobilizes tissue for energy)

Obesity in abdomen and "hump" of hunchback

Enhanced infection without immune response (because cortisol suppresses immune system)

Insomnia, euphoria, or depression (because cortisol can cause mood swings)

Causes of Cushing's Syndrome:

Pituitary adenoma = **Cushing's Disease** (65%)

Ectopic ACTH production (e.g. lung tumor) (15%)

Adrenal adenoma (15%)

Adrenal carcinoma (5%)

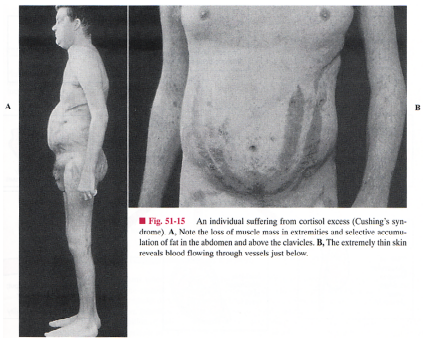
(**iatrogenic** induced by chronic glucocorticoid drug use)

Cushing's Syndrome

Harvey Cushing

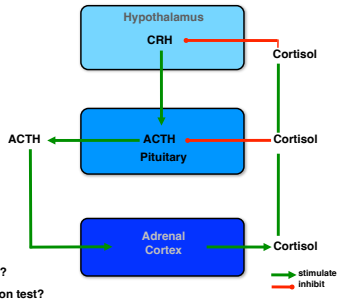
1st use of x-rays for surgery, blood pressure to monitor anesthesia, imported BP cuff from Europe, role of pituitary

Cushing's Syndrome



■ Fig. 51-15 An individual suffering from cortisol excess (Cushing's syndrome). **A**, Note the loss of muscle mass in extremities and selective accumulation of fat in the abdomen and above the clavicles. **B**, The extremely thin skin reveals blood flowing through vessels just below.

HPA axis: Analysis of Dysfunction

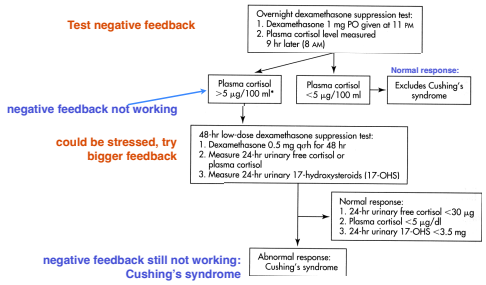


Response to CRH or ACTH?

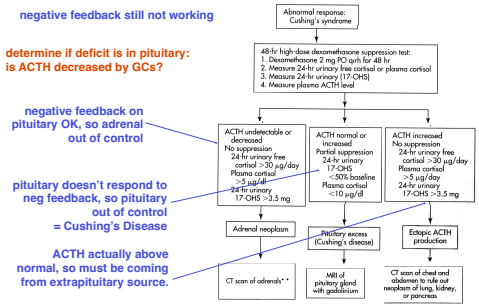
Dexamethasone suppression test?

Expression of Glucocorticoid receptors?

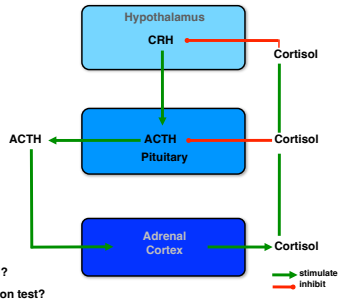
Diagnosis of Cushing's Disease



Diagnosis of Cushing's Disease



HPA axis: Analysis of Dysfunction



Response to CRH or ACTH?

Dexamethasone suppression test?

Expression of Glucocorticoid receptors?

Human Phys PCB4701

Endocrinology 3
Hypothalamic-Pituitary-Thyroid Axis

Hypothalamic-Pituitary-Thyroid Axis

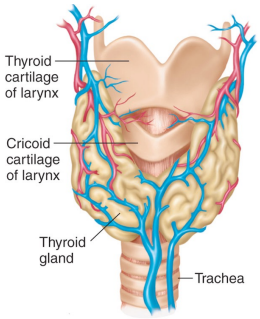
Hypothalamus secretes **Thyrotropin-Releasing Hormone** (TRH) into short portal vessels.

TRH stimulates thyrotroph cells in the pituitary to secrete **Thyroid-Stimulating Hormone** (TSH) into the blood

TSH stimulates **Thyroid Gland** to synthesize and release **thyroxine**.

Thyroxine (T_3) binds to nuclear thyroid hormone receptors to upregulate **metabolism**.

Figure 11.21

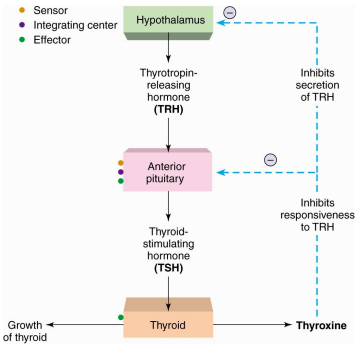


Examples of Hypothalamic Pituitary Axes

	H-P-Adrenal Axis	H-P-Thyroid Axis
Hypothal:	Corticotropin-releasing hormone (CRH)	Thyrotropin-releasing hormone (TRH)
Anterior Pituitary:	Adrenocorticotropic hormone (ACTH)	Thyroid-Stimulating hormone (TSH)
Target Organ:	Adrenal Cortex	Thyroid Gland
Function:	Stimulate Corticosteroid Synthesis (Stress)	Stimulate Thyroxine synthesis (Metabolism)

see Fox Table 11.6 & Table 11.7

Figure 11.16



Iodine & Thyroid Hormone Synthesis

Thyroid Gland:
Spherical follicles: **follicular cells** surrounding **colloid** (sticky glycoproteins).

Iodide (I^-) concentrated in follicular cells by **Na+/I- cotransporter**.
I- concentrated in colloid by transporter **pendrin**.

Synthetic enzymes and thyroglobulin secreted by follicular cells into colloid.

Thyroid peroxidase adds 1 or 2 iodine atoms to the amino acid tyrosine to form **monoiodotyrosine** (MIT) or **diiodotyrosine (**DIT). MIT and DIT are coupled to form T_3 or T_4. (synthesis occurs while attached to thyroglobulin).

Thyroid Stimulating Hormone (TSH) causes follicular cells to take up thyroglobulin, hydrolyze and release T_3 and T_4 into blood.

Figure 11.21

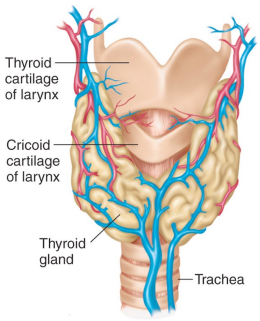


Figure 11.22

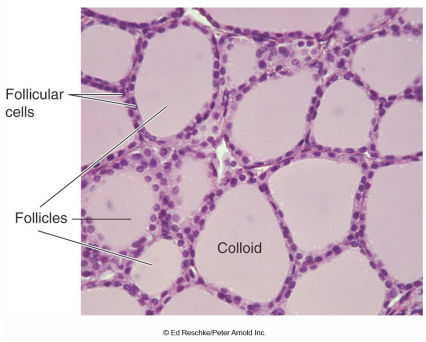
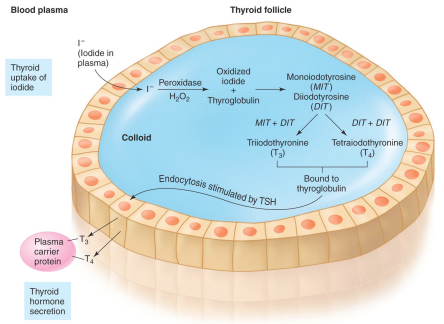


Figure 11.23



T4 & T3 Thyroid Hormones

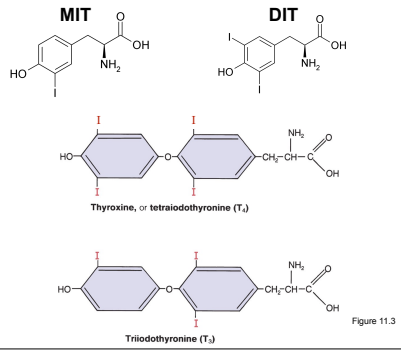


Figure 11.3

Figure 11.6

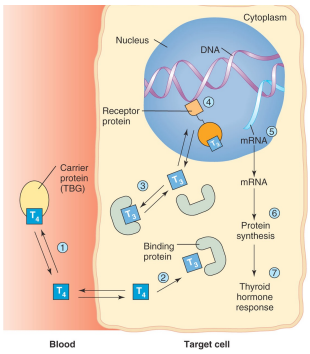
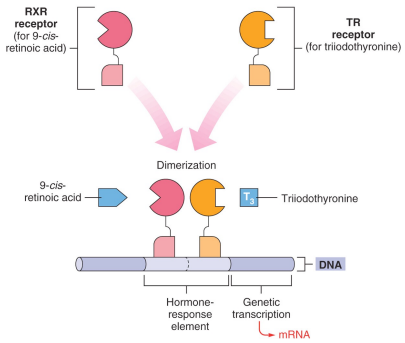


Figure 11.7



Thyroid Diseases

Goiter: hypertrophy (excessive growth) of thyroid gland

Endemic Goiter:
Lack of iodine in diet (increased incident with distance from sea)
-> low levels of thyroxine
-> no negative feedback on pituitary
-> high levels of TSH

Hypothryoidism
Primary: thyroid gland defect.
Secondary: insufficient TSH, or insufficient Iodine in diet.
Lethargy, low metablic rate, weight gain, sensitive to cold stress.
Cretinism: mental retardation due to hypothyroidism during pregnancy and after birth.

Hyperthyroidism
Over stimulation of thyroid gland; thyroid gland tumor
Graves Disease: autoimmune disease
antibodies bind to TSH receptors on thyroid
-> activate thyroid (antibodies **not** controlled by negative feedback)
-> hypertrophy of thyroid and **hyperthyroxemia**
-> goiter and **exophthalmos**

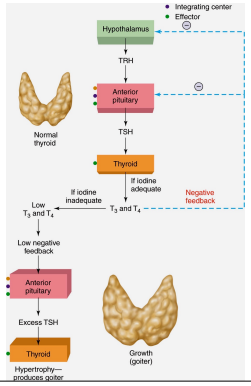


Figure 11.25

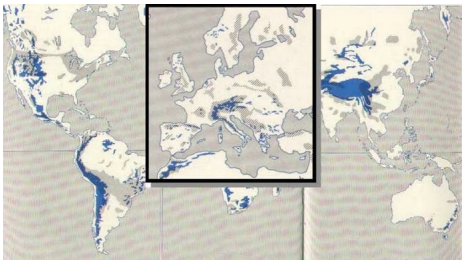
Goiter

Many children in southern Albania, like this 12 year old girl from Korçe, have visible goiter.

http://www.iccidd.org/media/IDD%20Newsletter/1991-2006/v22n1_0206.htm

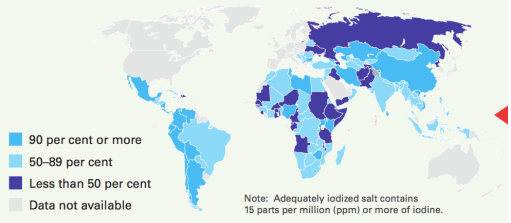
Figure 11.24

World map of prevalence of iodine-deficient goitre before iodine-prophylaxis



From Venturi 1985, http://sites.google.com/site/iodinestudies/epi

FIGURE 3. Household consumption of adequately iodized salt, worldwide, 2000–2006



Source: United Nations Children's Fund, *Progress for Children: A World Fit for Children statistical review*, UNICEF, New York, December 2007, p. 8.

34 countries have reached the universal salt iodization goal

Exophthalamus and Goiter in Grave's Disease

Figure 11.26

Table 11.8

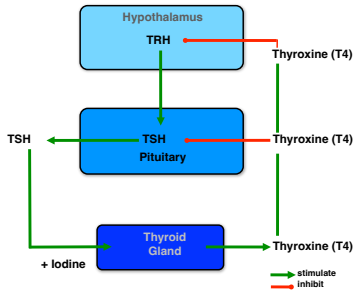
Table 11.8 | Comparison of Hypothyroidism and Hyperthyroidism

Feature	Hypothyroid	Hyperthyroid
Growth and development	Impaired growth	Accelerated growth
Activity and sleep	Lethargy; increased sleep	Increased activity; decreased sleep
Temperature tolerance	Intolerance to cold	Intolerance to heat
Skin characteristics	Coarse, dry skin	Normal skin
Perspiration	Absent	Excessive
Pulse	Slow	Rapid
Gastrointestinal symptoms	Constipation; decreased appetite; increased weight	Frequent bowel movements; increased appetite; decreased weight
Reflexes	Slow	Rapid
Psychological aspects	Depression and apathy	Nervous,"emotional" state
Plasma T_4 levels	Decreased	Increased
metabolism:	30% **less** O_2 consumption	50% **more** O_2 consumption

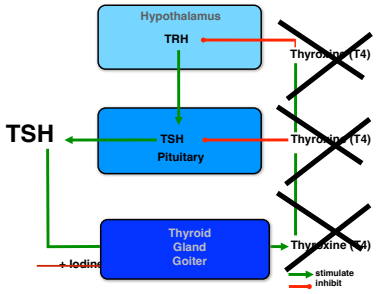
Hypothyroid Treatment: Iodized salt, T4 injections

Hyperthyroid Treatment: radioactive Iodine to kill thyroid gland cells

HP-Thyroid axis: Analysis of Dysfunction



HP-Thyroid axis: Analysis of Dysfunction
Iodine deficient Hypothroidism



HP-Thyroid axis: Analysis of Dysfunction
Grave's Disease: autoimmune hyperthyroidism