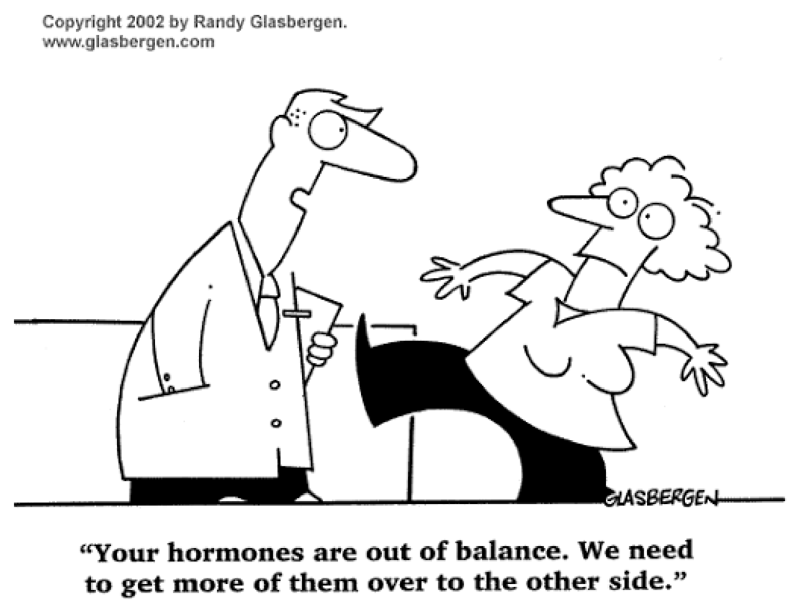
ENDOCRINE AND REPRODUCTIVE PHYSIOLOGY



GSSE PHYSIOLOGY TEACHING 2021

ANN HO

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10. **Reproductive Physiology**
    1. Prolactin
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HYPOTHALAMUS

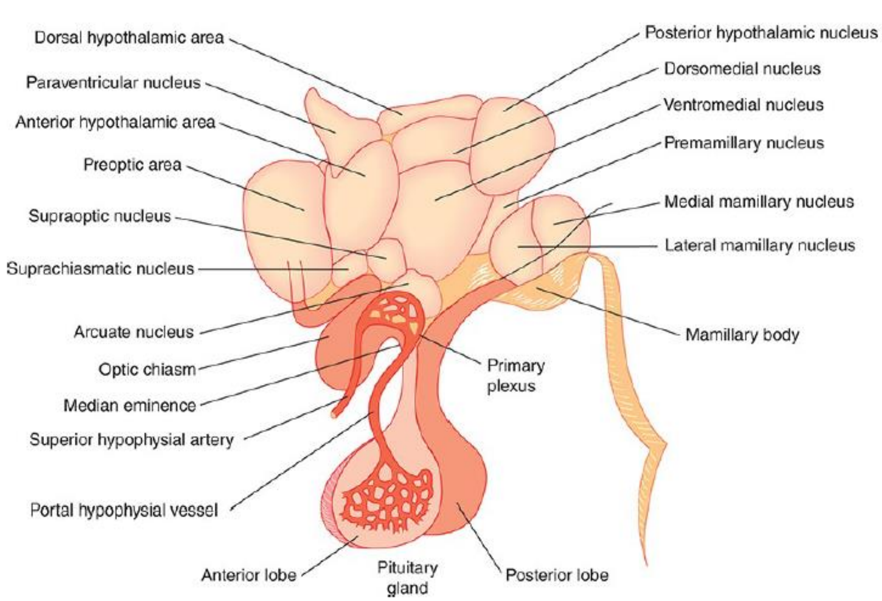

FIGURE 17–1 Human hypothalamus, with a superimposed diagrammatic representation of the portal hypophysial vessels.

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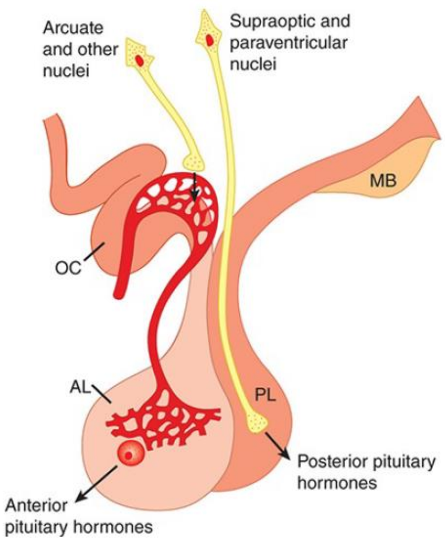

FIGURE 17–2 Secretion of hypothalamic hormones. The hormones of the posterior lobe (PL) are released into the general circulation from the endings of supraoptic and paraventricular neurons, whereas hypophysiotropic hormones are secreted into the portal hypophysial circulation from the endings of arcuate and other hypothalamic neurons. AL, anterior lobe; MB, mamillary bodies; OC, optic chiasm.

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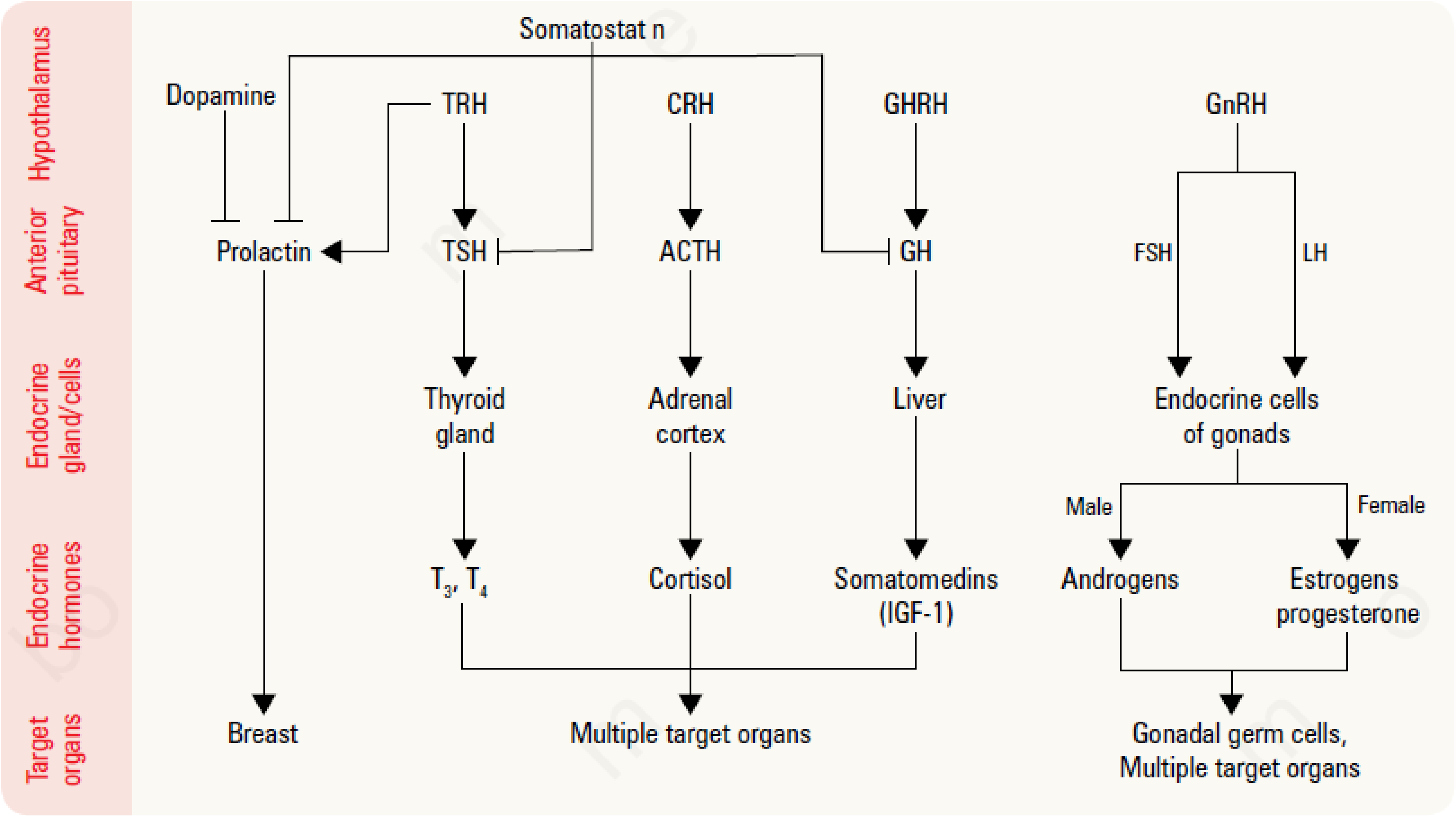
median eminence of hypothalamus – area which hypophysiotropic hormones are secreted → few nerve cell bodies, many nerve endings close to capillary loops from which portal vessels originate

HYPOTHALAMIC-PITUITARY HORMONAL AXES



Toronto Notes

3 GENERAL CLASSES OF HORMONES

Proteins (>100 AA) and polypeptides (<100 AA)

- Ant + post pituitary gland
- pancreas (insulin, glucagon)
- parathyroid hormone
- etc.

Steroids

- Adrenal cortex (cortisol and aldosterone)
- Ovaries and Placenta (oestrogen and progesterone)
- Testes (testosterone)

Derivatives of amino acid tyrosine

- Thyroid (thyroxine and triiodothyronine)
- Adrenal medullae (epinephrine and norepinephrine)

STRUCTURE OF HORMONES

Table 75–1

Cells and Hormones of the Anterior Pituitary Gland and Their Physiological Functions

Cell	Hormone	Chemistry	Physiological Actions
Somatotropes	Growth hormone (GH; somatotropin)	Single chain of 191 amino acids	Stimulates body growth; stimulates secretion of IGF-1; stimulates lipolysis; inhibits actions of insulin on carbohydrate and lipid metabolism
Corticotropes	Adrenocorticotropic hormone (ACTH; corticotropin)	Single chain of 39 amino acids	Stimulates production of glucocorticoids and androgens by the adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyrotropes	Thyroid-stimulating hormone (TSH; thyrotropin)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates production of thyroid hormones by thyroid follicular cells; maintains size of follicular cells
Gonadotropes	Follicle-stimulating hormone (FSH)	Glycoprotein of two subunits, α (89 amino acids) and β (112 amino acids)	Stimulates development of ovarian follicles; regulates spermatogenesis in the testis
	Luteinizing hormone (LH)	Glycoprotein of two subunits, α (89 amino acids) and β (115 amino acids)	Causes ovulation and formation of the corpus luteum in the ovary; stimulates production of estrogen and progesterone by the ovary; stimulates testosterone production by the testis
Lactotropes, Mammotropes	Prolactin (PRL)	Single chain of 198 amino acids	Stimulates milk secretion and production

IGF, insulin-like growth factor

Guyton and Hall

HORMONE RECEPTORS

Intracellular signalling after hormone receptor activation

- Ion channel-linked receptors
  - Neurotransmitters e.g. acetylcholine, norepinephrine
- G-protein-linked hormone receptors
- Enzyme-linked hormone Receptors
- Intracellular Hormone Receptors
  - Adrenal, gonadal steroid hormones, thyroid hormones, vit D (hormones are lipid soluble)

Intracellular Second Messenger Systems

- Adenylyl cylcase-cAMP second messenger system
- Cell membrane phospholipid second messenger system (phospholipase C)
- Calcium-calmodulin second messenger system

G-PROTEIN LINKED HORMONE RECEPTORS

G proteins (heterotrimeric GTP-binding proteins)

Indirectly regulate activity of target protein

- Alter activity of ion channels or intracellular enzymes (e.g. adenylyl cyclase or phospholipase C)

Can be stimulatory (G_s) or inhibitory (G_i)

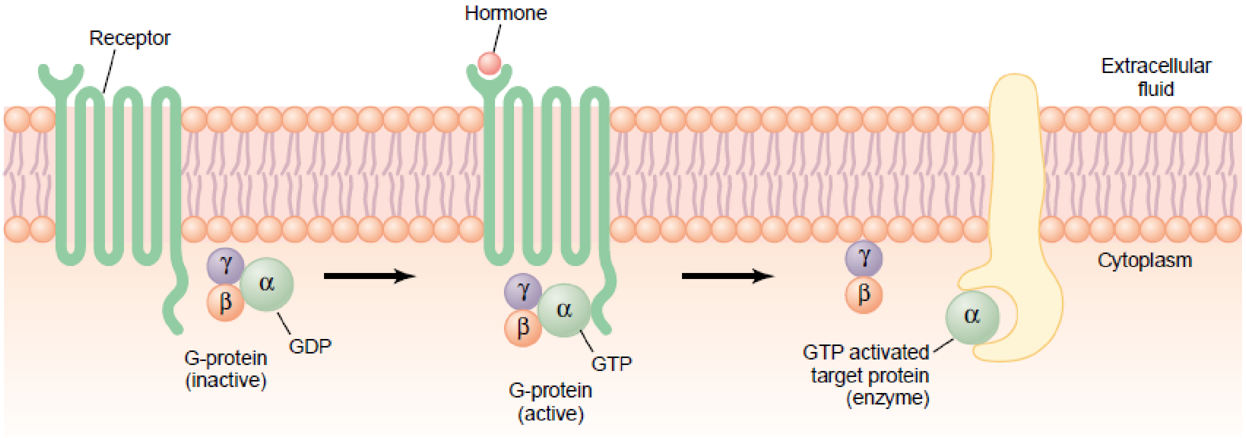


Figure 74–4

Mechanism of activation of a G protein–coupled receptor. When the hormone activates the receptor, the inactive α, β, and γ G protein complex associates with the receptor and is activated, with an exchange of guanosine triphosphate (GTP) for guanosine diphosphate (GDP). This causes the α subunit (to which the GTP is bound) to dissociate from the β and γ subunits of the G protein and to interact with membrane-bound target proteins (enzymes) that initiate intracellular signals.

Guyton and Hall

ENZYME-LINKED RECEPTORS

Hormone-binding site outside cell membrane

Catalytic/enzyme binding site on inside

Enzyme immediately activated when hormone binds to extracellular part

Examples

Cytokine receptors – signalling pathway includes phosphorylation of JAK2 molecules

- activate pathways such as STAT or MAPK or PI3K

Transmembrane receptor becomes activated enzyme *adenylyl cyclase*

- Cyclase catalyses formation of cAMP

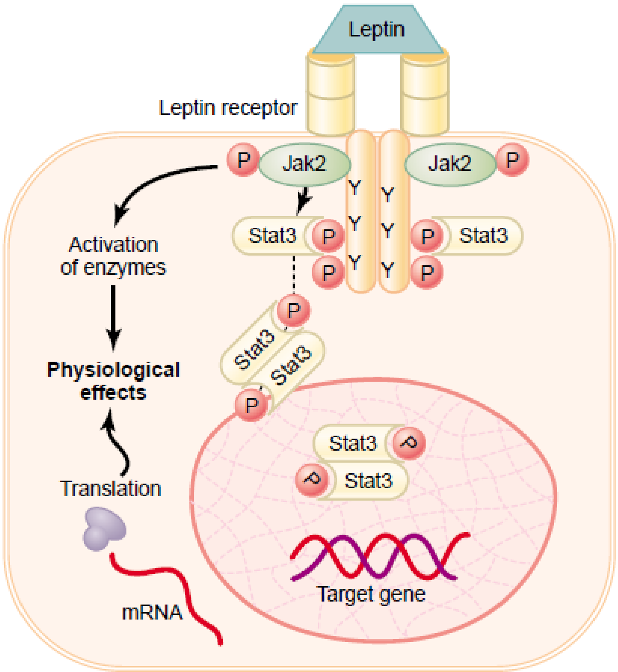


Figure 74–5

An enzyme-linked receptor—the leptin receptor. The receptor exists as a homodimer (two identical parts), and leptin binds to the extracellular part of the receptor, causing phosphorylation and activation of the intracellular associated janus kinase 2 (JAK2). This causes phosphorylation of signal transducer and activator of transcription (STAT) proteins, which then activates the transcription of target genes and the synthesis of proteins. JAK2 phosphorylation also activates several other enzyme systems that mediate some of the more rapid effects of leptin.

Guyton and Hall

INTRACELLULAR HORMONE RECEPTORS

- Lipid soluble hormones: Adrenal hormones, gonadal steroid hormones, thyroid hormones, vit D

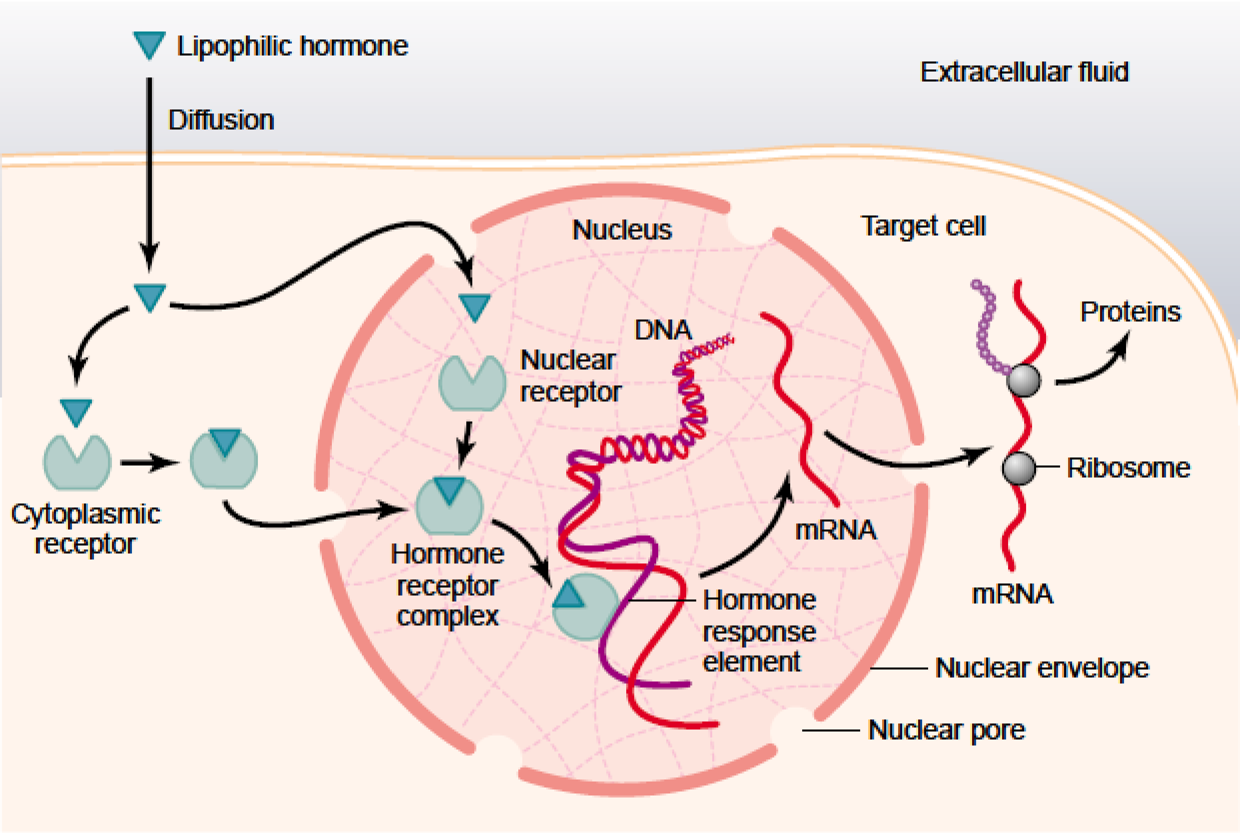


Figure 74–6

Mechanisms of interaction of lipophilic hormones, such as steroids, with intracellular receptors in target cells. After the hormone binds to the receptor in the cytoplasm or in the nucleus, the hormone-receptor complex binds to the hormone response element (promoter) on the DNA. This either activates or inhibits gene transcription, formation of messenger RNA (mRNA), and protein synthesis.

ADENYLYL CYCLASE-CAMP SYSTEM

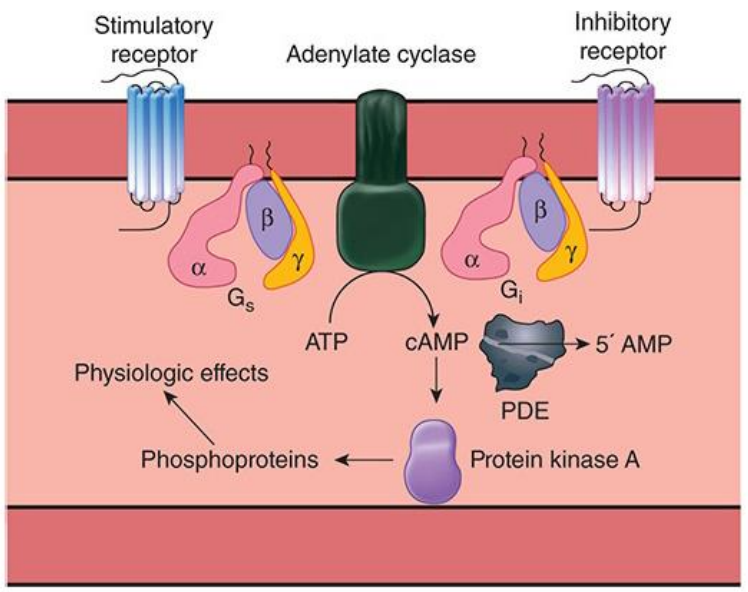


FIGURE 2–29 The cAMP system. Activation of adenylyl cyclase catalyzes the conversion of ATP to cAMP. Cyclic AMP activates protein kinase A, which phosphorylates proteins, producing physiologic effects. Stimulatory ligands bind to stimulatory receptors and activate adenylyl cyclase via G_s. Inhibitory ligands inhibit adenylyl cyclase via inhibitory receptors and G_i.

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Table 74–2

Some Hormones That Use the Adenylyl Cyclase–cAMP Second Messenger System

Adrenocorticotropic hormone (ACTH)
Angiotensin II (epithelial cells)
Calcitonin
Catecholamines (β receptors)
Corticotropin-releasing hormone (CRH)
Follicle-stimulating hormone (FSH)
Glucagon
Human chorionic gonadotropin (HCG)
Luteinizing hormone (LH)
Parathyroid hormone (PTH)
Secretin
Somatostatin
Thyroid-stimulating hormone (TSH)
Vasopressin (V_2 receptor, epithelial cells)

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PHOSPHOLIPASE C (PLC)

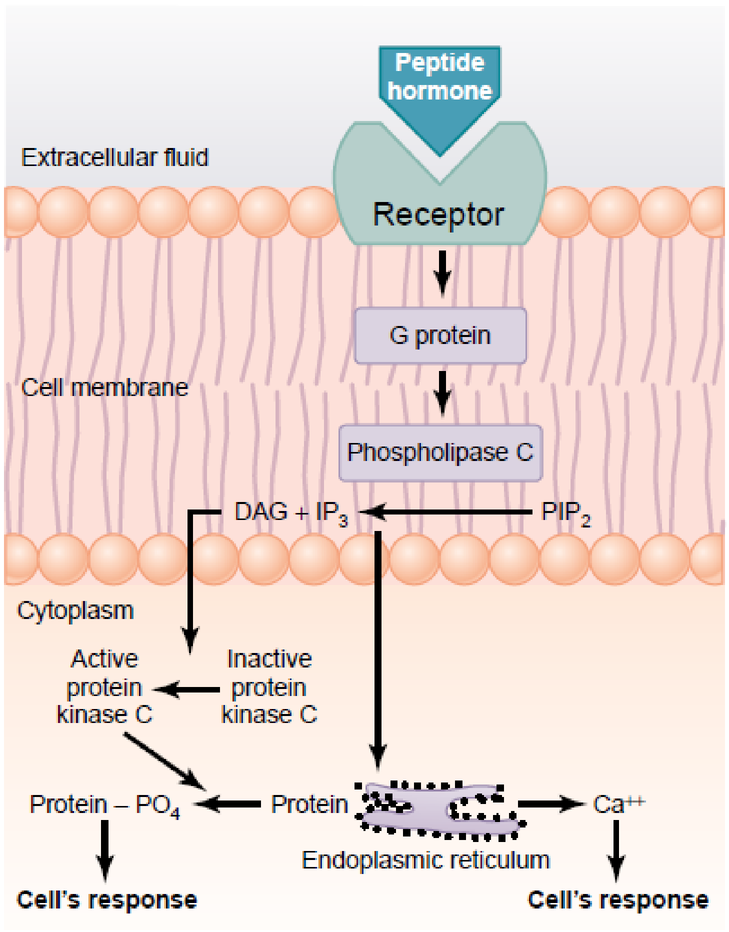


Figure 74–8

The cell membrane phospholipid second messenger system by which some hormones exert their control of cell function. DAG, diacylglycerol; IP_3, inositol triphosphate; PIP_2, phosphatidylinositol biphosphate.

PLC catalyse breakdown of some phospholipids in the cell membrane

Table 74–3

Some Hormones That Use the Phospholipase C Second Messenger System

Angiotensin II (vascular smooth muscle)
Catecholamines (α receptors)
Gonadotropin-releasing hormone (GnRH)
Growth hormone–releasing hormone (GHRH)
Oxytocin
Thyroid-releasing hormone (TRH)
Vasopressin (V_1 receptor, vascular smooth muscle)

Signaling pathways of endocrine hormones

cAMP	FSH, LH, ACTH, TSH, CRH, hCG, ADH (V_2-receptor), MSH, PTH, calcitonin, GHRH, glucagon	FLAT ChAMP
cGMP	ANP, BNP, NO (EDRF)	Think vasodilators
IP_3	GnRH, Oxytocin, ADH (V_1-receptor), TRH, Histamine (H_1-receptor), Angiotensin II, Gastrin	GOAT HAG
Intracellular receptor	Vitamin D, Estrogen, Testosterone, T_3/T_4, Cortisol, Aldosterone, Progesterone	VETTT CAP
Intrinsic tyrosine kinase	Insulin, IGF-1, FGF, PDGF, EGF	MAP kinase pathway Think growth factors
Receptor-associated tyrosine kinase	Prolactin, Immunomodulators (e.g., cytokines IL-2, IL-6, IFN), GH, G-CSF, Erythropoietin, Thrombopoietin	JAK/STAT pathway Think acidophils and cytokines PIGGLET

First Aid for USMLE

POSTERIOR PITUITARY GLAND (NEUROHYPOPHYSIS)

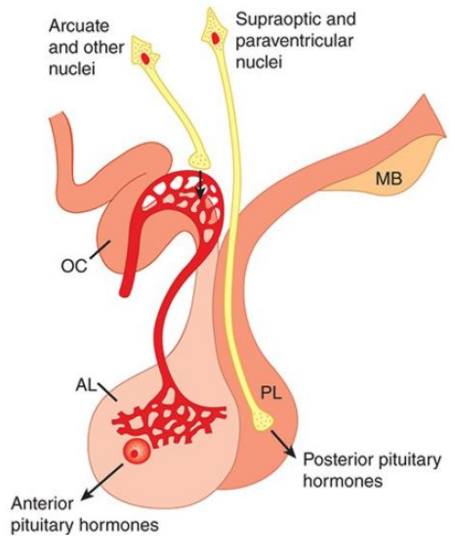
Neural hormones – made in paraventricular and supraoptic nuclei

Small and not bound in plasma → penetrate capillary wall easily

Polypeptides containing 9 amino acids

If pituitary stalk is cut, posterior pituitary hormones continue to be secreted normally (after transient decrease for a few days)

- Secreted by cut ends of hypothalamus



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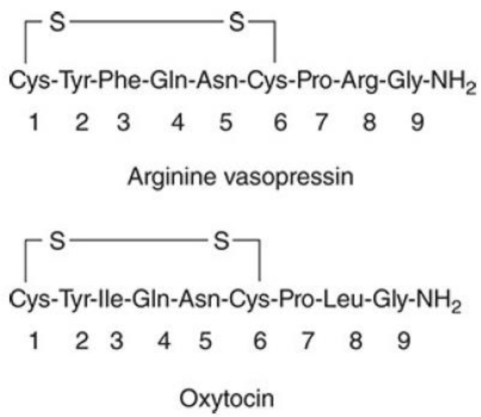

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VASOPRESSIN

Aka Antidiuretic Hormone (ADH) or Anginine Vasopressin (AVP)

Secretion affected by

- Osmoreceptor in hypothalamus
- Baroreceptors in great veins (carotid, aortic, pulmonary) and atria

Table 28–2

Regulation of ADH Secretion

Increase ADH	Decrease ADH
↑ Plasma osmolarity ↓ Blood volume ↓ Blood pressure	↓ Plasma osmolarity ↑ Blood volume ↑ Blood pressure
Nausea Hypoxia	
Drugs: Morphine Nicotine Cyclophosphamide	Drugs: Alcohol Clonidine (antihypertensive drug) Haloperidol (dopamine blocker)

Guyton and Hall

VASOPRESSIN

Effects (happens in 5-10 minutes):

- ↑permeability of **collecting ducts** in kidney (inserts aquaporin) → retention of water in excess of solute
- Increase urea absorption into renal medulla (due to high concentration of urea in tubular fluid after water is reabsorbed)
- Constrict vasa recta vessels in renal medulla → decrease blood flow in renal medulla

Attach receptors → activate adenylyl cyclase → cAMP → phosphorylation of elements in vesicles → vesicles insert into apical cell membranes

OXYTOCIN

Secretion increased by

- Nipple stimulation
- Stimulation of cervix

Effects:

- Contraction of pregnant uterus
- Milk letdown/ejection: Contraction of myoepithelial cells in breast → milk expressed from alveoli into ducts

Prolactin vs Oxytocin

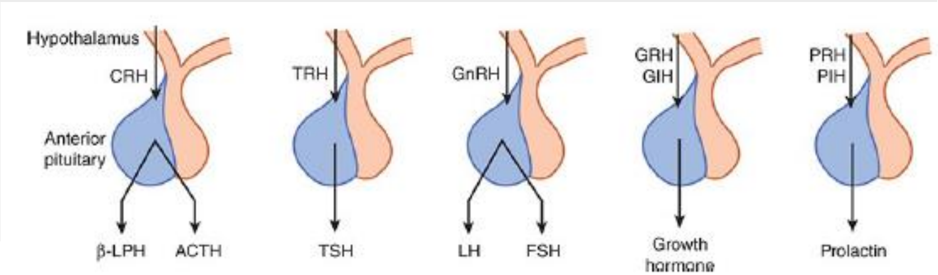
- Prolactin stimulates secretion of milk
- Oestrogen and progesterone inhibits it (hence milk not secreted during pregnancy)

ANTERIOR PITUITARY GLAND (ADENOHYPOPHYSIS)

Secretes 6 hormones (glycoproteins)

Secretion controlled by portal hypophysial vessels from hypothalamus

Released by Hypothalamus	Released by Anterior Pituitary
TRH – Thyrotropin-releasing hormone	TSH – thyroid stimulating hormone
CRH – Corticotropin-releasing hormone	ACTH – Adrenocorticotropic hormone
GnRH – gonadotropic-releasing hormone	FSH – Follicle Stimulating Hormone
	LH – leutinizing hormone
PIH – prolactin –inhibiting hormone *PRH – prolactin-releasing hormone (?)*	PRL – Prolactin
GRH – growth hormone-releasing hormone GIH – growth hormone-inhibiting hormone (somatostatin)	



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ANT PITUITARY CELL TYPES

Staining reactions	Secretory Cell Type	Percentage of cells	Secreted by anterior pituitary
Basophils = glycoprotein hormones	Thyrotrope	5	TSH – thyroid stimulating hormone
	Gonadotrope	20	FSH – Follicle Stimulating Hormone
			LH – leutinizing hormone
Basophilic / chromophobic	Corticotrope	10	ACTH – Adrenocorticotropic hormone
Acidophils	Lactotrope / Mammotrope	10-30	PRL – Prolactin
	Somatotrope	50	GH – Growth Hormone

GROWTH HORMONE

Aka somatotropic hormone or somatotropin

(+) GHRH, (-) somatostatin

Secreted in pulsatile pattern

- Adolescents have highest circulating levels
- After adolescence secretion decreases slowly with age, down to 25% of adolescent level in very old age

Half life of <20 minutes

Attach weakly to plasma proteins in blood (rapidly released into tissues)

Effect - Direct or indirect (through somatomedins)

SOMATOMEDINS

Polypeptide growth factors secreted by liver and other tissues

Attaches strongly to carrier protein in blood (released slowly from blood to tissues)

Half time ~20 hours (prolong growth promoting effects)

IGF-I (Somatomedin C/insulin-like growth factor 1)

- Secretion independent of GH before birth, stimulated by GH after birth

IGF-II

- Largely independent of GH
- Plays a role in foetal growth
- In adults, IGF-II only found in choroid plexus and meninges

GH REGULATION

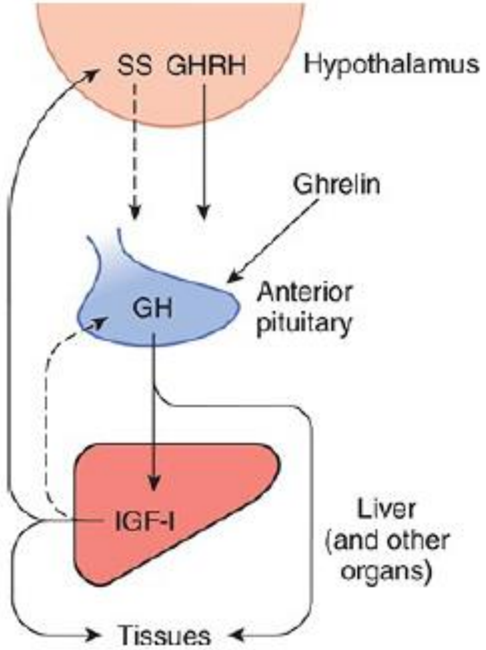


FIGURE 18–3 Feedback control of growth hormone secretion. Solid arrows represent positive effects and dashed arrows represent inhibition. GH, growth hormone; GHRH, growth hormone–releasing hormone; IGF-I, insulin-like growth factor-I; SS, somatostatin.

GH receptors are a member of the cytokine receptor superfamily

Activates many different intracellular signalling cascades

- JAK2-STAT pathway (cytoplasmic tyrosine kinase)
- Phospholipase C (PLC)
- Mitogen-activated protein kinases (MAPK)

GH STIMULI

Stimulate GH secretion	Inhibit GH secretion
GHRH Ghrelin	Somatostatin (GIH) IGF-I (somatomedins) GH (exogenous)
↓ BGL Fasting, starvation, protein deficiency	↑ BGL
↓ FFA	↑ FFA
Stressful stimuli = Trauma, stress, excitement, exercise	Aging, obesity
Sex steroids = Testosterone, Oestrogen	Medoxyprogesterone
Deep sleep (Stages II and IV)	Light or REM sleep
Increase in certain amino acids e.g. arginine	
Glucagons	
Lysine vasopressin	
L-dopa, α-adrenergic agonists that penetrate the brain	

Like Atkins diet!

GH EFFECTS

Direct Effect	Indirect Effect of GH (through Somatomedins)
Growth → ↑ mitosis, size of cells	IGF-I → Insulin-like activity - ↑ glucose uptake into cells - Anti-lipolysis - ↑ protein synthesis - Epiphysial growth
↑ protein synthesis = *anabolic protein effect (*↑ lean body mass)	
↑ lipolysis in adipose tissue → ↑ FFA in blood and for energy use = *in excess -> ketosis*	
↓ glucose utilisation (conserve carbohydrates) + ↓ *insulin sensitivity (diabetogenic)* → ↑ hepatic glucose output (inhibit gluconeogenesis) → ↓ glucose uptake in tissues (skeletal muscle + fat) → ↑ insulin secretion	
Epiphysial growth	

THE BANK

23219 – Growth hormone secretion is increased by

1: hypoglycaemia
2: exercise
3: fasting
4: L-dopa

13589 – Vasopressin or ADH

1: increases permeability to water of the proximal tubules
2: increase permeability to water of the collecting ducts of the kidney
3: decreases blood flow in the renal medulla
4: increases permeability of the collecting ducts of the inner medulla of the kidney to urea

THE BANK

23219 – Growth hormone secretion is increased by

1: hypoglycaemia
2: exercise
3: fasting
4: L-dopa

Answers: TTTT

Ganong 19th ed. CHAPTER: 22 PAGE: 387 (Table 22.3)

13589 – Vasopressin or ADH

1: increases permeability to water of the proximal tubules
2: increase permeability to water of the collecting ducts of the kidney
3: decreases blood flow in the renal medulla
4: increases permeability of the collecting ducts of the inner medulla of the kidney to urea

Answers: FTTT

Vasopressin or ADH is produced in the posterior part of the pituitary. It has its effect on the collecting ducts of the kidney, not on the proximal tubules (A false). In the collecting ducts it increases permeability to water (B true), urea (D true) and some other solutes. It also decreases the blood flow in the renal medulla (C true).

THE ADRENAL GLAND

Cortex = secrete steroid hormones

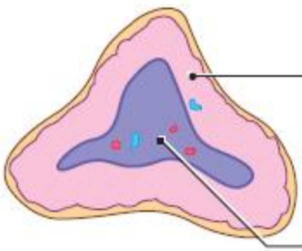
- Mineralocorticoids → affect Na and K secretion
- Glucocorticoids → glucose and protein metabolism predominate
- Androgens

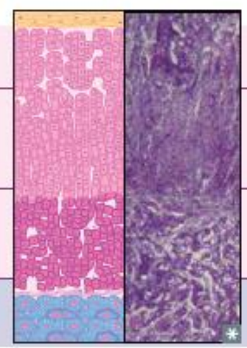
Medulla = secrete catecholamines

- Epinephrine
- Norepinephrine
- Dopamine

Adrenal cortex and medulla

Adrenal cortex (derived from mesoderm) and medulla (derived from neural crest).





	ANATOMY	PRIMARY REGULATORY CONTROL	SECRETORY PRODUCTS
CORTEX	Zona **G**lomerulosa	Renin-angiotensin	Aldosterone
	Zona **F**asciculata	ACTH, CRH	Cortisol, sex hormones
	Zona **R**eticularis	ACTH, CRH	Sex hormones (e.g., androgens)
MEDULLA	Chromaffin cells	Preganglionic sympathetic fibers	Catecholamines (epinephrine, norepinephrine)

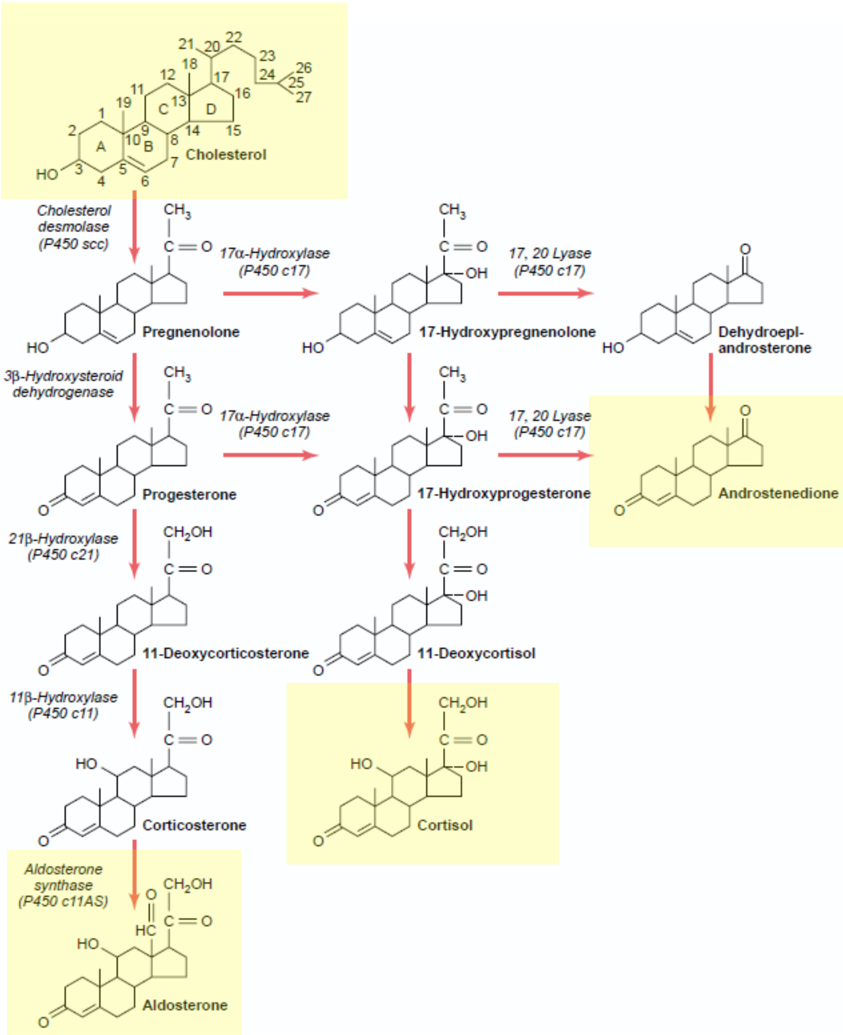
GFR corresponds with Salt (Na^+), Sugar (glucocorticoids), and Sex (androgens).
"The deeper you go, the sweeter it gets."

Pheochromocytoma—most common tumor of the adrenal medulla in adults. Episodic hypertension.

Neuroblastoma—most common tumor of the adrenal medulla in children. Rarely causes hypertension.

First Aid for USMLE

STEROIDOGENESIS



Hormones of adrenal cortex are derivatives of cholesterol

Contain cyclopentanoperhydrophenanthrene nucleus

Cortex secretes primarily 2 types

- C_{21} steroids (2 carbon side chains at position 17) → mineralocorticoid or glucocorticoid activity
- C_{19} steroids (keto/hydroxyl group at position 17) → androgenic activity

ALDOSTERONE

90% of mineralocorticoid activity

Half life ~20 min

60% bound to plasma proteins, 40% free form

Function – affects kidney (principal cells of collecting tubules), sweat glands, salivary glands and intestinal epithelial cells

- ↑ Na reabsorption → ↑ ECF volume and arterial pressure
- ↓ K secretion

Excess mineralocorticoid secretion:

- K depletion
- Na retention
- Hypertension
- Tetany
- Polyuria
- Hypokalaemic alkalosis (hyperaldosteronism) – Alkalosis due to secretion of H^+ in exchange for sodium in collecting tubules

ALDOSTERONE

Conditions that increase aldosterone secretion

Glucocorticoid secretion also increased
Surgery
Anxiety
Physical trauma
Hemorrhage
Glucocorticoid secretion unaffected
High potassium intake
Low sodium intake
Constriction of inferior vena cava in thorax
Standing
Secondary hyperaldosteronism (in some cases of heart failure, cirrhosis, and nephrosis)

ALDOSTERONE REGULATORS

ACTH → binds to receptors on plasma membrane of adrenocortical cells → activates adenylyl cyclase via G_s

RAAS = ANG II binds AT_1 receptors in zona glomerulosa → activate phospholipase C (via G-protein) → ↑ protein kinase C → convert cholesterol to pregnenolone and facilitate action of aldosterone synthase

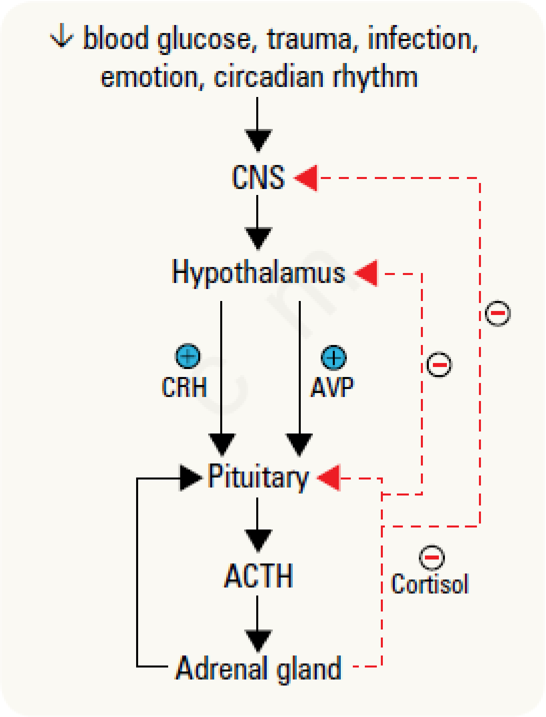


Figure 10. Regulation of CRH-ACTH-adrenal gland axis

Toronto Notes

CORTISOL

Accounts for 95% of all glucocorticoid activity

90-95% bound to plasma proteins – cortisol-binding globulin, transcortin, albumin

Half life ~60 to 90 min

Effects:

- ↑ gluconeogenesis
- ↓ GLUT4-mediated glucose uptake in skeletal muscle and adipose tissue (*opposes insulin*)
- ↑ lipolysis + ↑ oxidation of FFA
- ↑ proteolysis
- Reduces inflammatory response to injury
- Immunosuppression
- Inhibits growth (Decrease GH secretion)
- ↑ CP and BP
- Stimulate EPO synthesis

CATECHOLAMINES

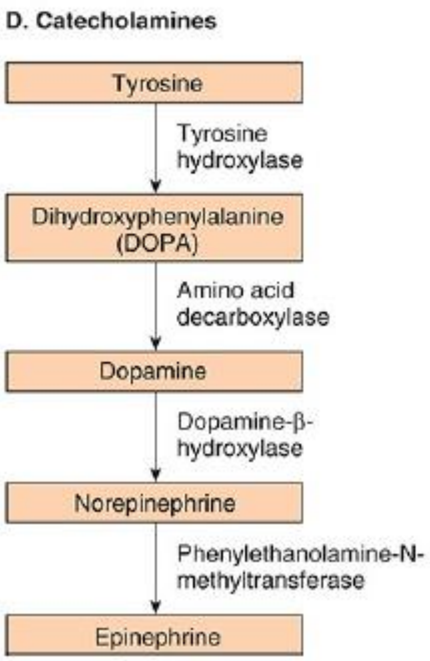
Secreted by chromaffin cells of Adrenal Medulla

- Epinephrine – 80%
- Norepinephrine – 20%
- Dopamine

PNMT (phenylethanolamine-N-methyltransferase) catalyses formation of E from NE

- Found in brain and adrenal medulla
- Induced by glucocorticoids

Half life ~2min



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ADRENERGIC RECEPTORS

Adrenergic receptors

- α: **NE** > E > Isoprenaline
- β: Isoprenaline > **E** > NE

α1	Vasoconstriction (in most organs) Pupil dilation, erect hairs, apocrine sweating ↑ glycogenolysis, gluconeogenesis
α2	Negative feedback ↓ insulin
β1	Ionotrope Chronotrope ↑myocardial excitability → extrasystole, arrythmias ↑ lipolysis ↑ O_2 consumption
β2	Vasodilation (in skeletal muscle and liver) ↑ glycogenolysis, gluconeogenesis ↑ insulin

NE increases SBP and DBP

E causes widening of pulse pressure

THYROID GLAND

composed of follicles

filled with colloid – major constituent is thyroglobulin

lined with cuboidal epithelial cells

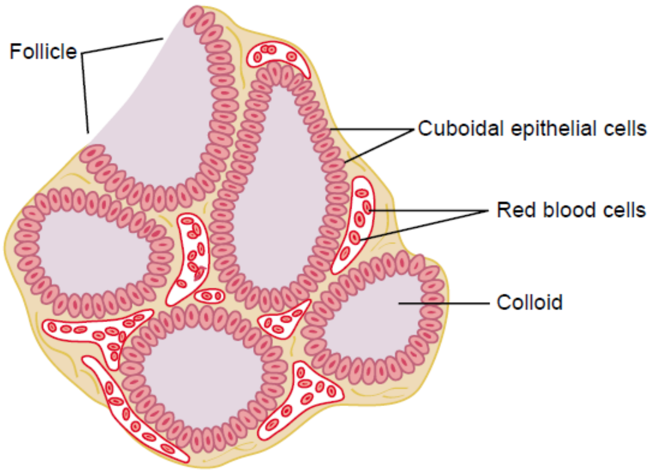
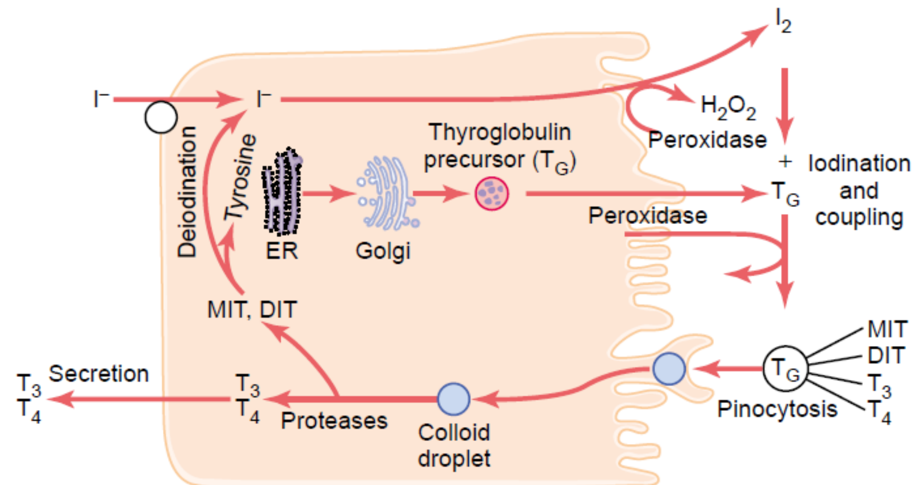


Figure 76–1

Microscopic appearance of the thyroid gland, showing secretion of thyroglobulin into the follicles.

THYROID HORMONE SYNTHESIS



Iodide trapping – concentrate iodide in cell

- Sodium-iodide symporter (NIS)
- Na-K ATPase transports Na out of cell

Formation of thyroglobulin

- Synthesised by ER and Golgi apparatus
- Secreted into follicle

Oxidation of I^- (iodide) to I_2 (iodine)

- By thyroid peroxidase on apical membrane

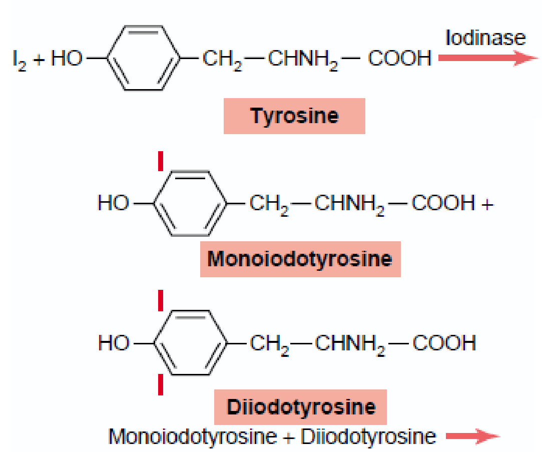
Organification of thyroglobulin

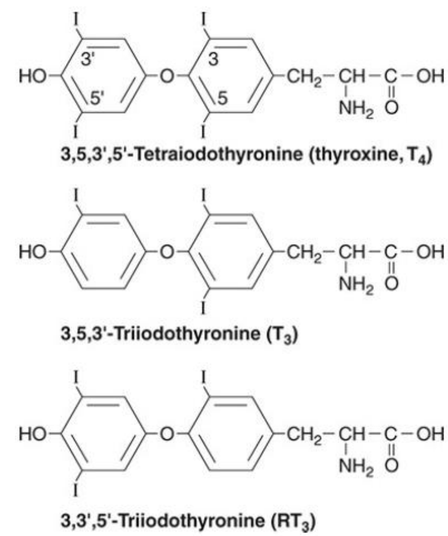
- Iodine binds with tyrosine amino acids within thyroglobulin molecule = MIT or DIT

Coupling reaction (among MIT and DIT) catalysed by thyroid peroxidase

- DIT + DIT = T_4 (thyroxine)
- MIT + DIT = T_3 (triiodothyronine)

Small amounts of RT_3 – unclear if biologically active





RELEASE OF T4 AND T3

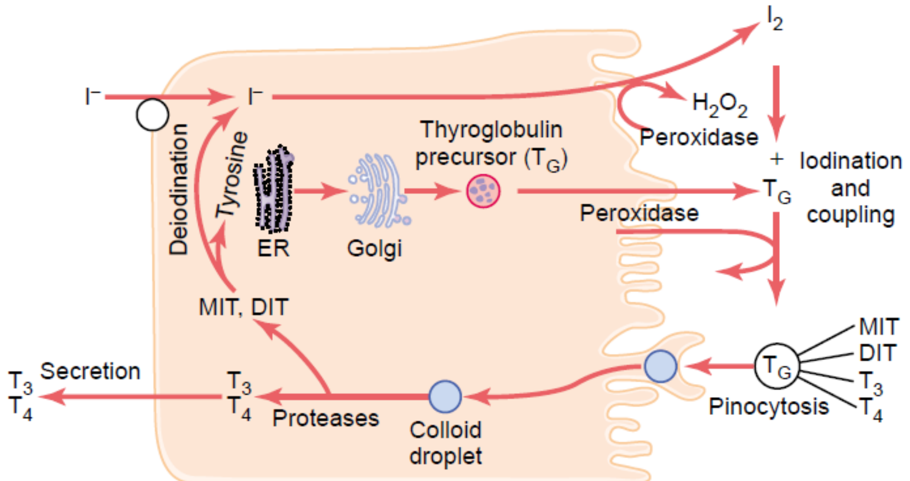
Pinocytosis - Pseudopod extension from apical surface close around small portions of colloid

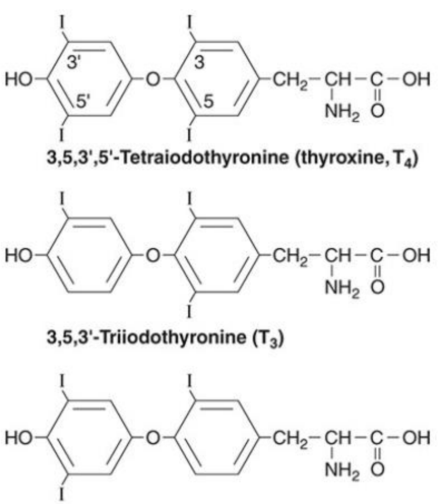
Proteases digest thyroglobulin molecules

- Release T4 (thyroxine) – 93%
- Release T3 (triiodothyronine) – 7%
- Release MIT and DIT → iodine cleaved by deiododinase enzyme

Half of T4 is slowly deiodinated to form additional T3

- Hence, mainly T3 delivered to tissue and T3 has higher concentration in plasma





TRANSPORT OF THYROID HORMONES

Mostly bound to plasma proteins

- Large pool of hormone ready to be mobilised as needed

Free forms are physiologically active and inhibit TSH

Plasma proteins that bind thyroid hormones

- Albumin
- Transthyretin
- Thyroxine-binding globulin (TBG)

Bind to intracellular hormone receptors (nuclear receptors) → initiate transcription process → ↑ mRNA

TSH / THYROTROPIN

Effect – ↑ production and secretion of thyroid hormones

- ↑ proteolysis of stored thyroglobulin
- ↑ iodide pump activity
- ↑ iodinisation of tyrosine
- ↑ size and secretory activity of thyroid cells
- ↑ number of thyroid cells

Act via cAMP

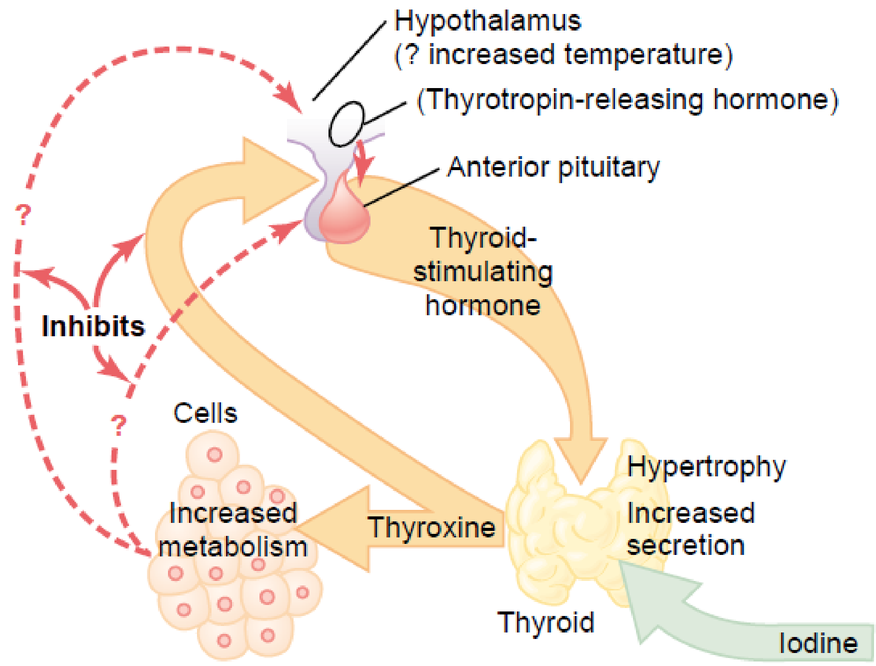


Figure 76–7

Regulation of thyroid secretion.

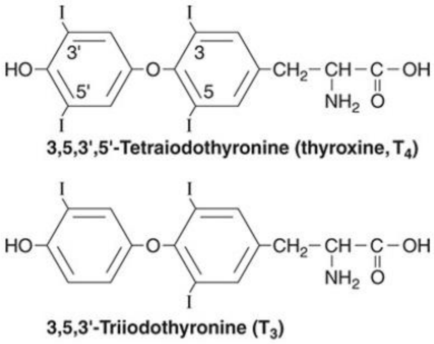
Guyton and Hall

T4

99.98% bound to plasma protein

0.02% free (~2ng/dL)

Half life ~6-7 days



More T4 produced but T3 concentration in plasma is higher

T3

0.15µg/dL found in plasma

0.2% is free

- Not bound as much as T4

99.8% protein bound – most to TBG and remainder to albumin

Half life 1-2 days (Shorter than T4)

More rapid actions on tissues than T4

EFFECT OF T3 AND T4

TABLE 20–3 Physiologic effects of thyroid hormones.

Target Tissue	Effect	Mechanism
Heart	Chronotropic and inotropic	Increased number of β-adrenergic receptors Enhanced responses to circulating catecholamines Increased proportion of α-myosin heavy chain (with higher ATPase activity)
Adipose tissue	Catabolic	Stimulated lipolysis
Muscle	Catabolic	Increased protein breakdown
Bone	Developmental	Promote normal growth and skeletal development
Nervous system	Developmental	Promote normal brain development
Gut	Metabolic	Increased rate of carbohydrate absorption
Lipoprotein	Metabolic	Formation of LDL receptors
Other	Calorigenic	Stimulated oxygen consumption by metabolically active tissues (exceptions: testes, uterus, lymph nodes, spleen, anterior pituitary) Increased metabolic rate

Modified with permission from McPhee SJ, Lingarra VR, Ganong WF (editors): *Pathophysiology of Disease*, 6th ed. New York, NY: McGraw-Hill; 2010.

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Decrease duration of tendon reflexes

Effects erythropoiesis

Increase FFA but decrease cholesterol, phospholipids and TGL in plasma (increase rate of cholesterol secretion in bile)

THE BANK

24359 – Cortisol
1: increases gluconeogenesis by the liver
2: decreases glucose utilisation by muscle cells
3: increases free fatty acid mobilization
4: increases ACTH secretion via a feedback control mechanism

23574 – Noradrenaline causes
1: increased cardiac contractility
2: vasodilation in skeletal muscle and liver
3: increased myocardial excitability
4: widening of the pulse pressure

9880 – S:There is very little free thyroxine in the plasma because R:thyroxine is bound to thyroxine-binding prealbumin in the plasma

THE BANK

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Answers: TTTF

Ganong, 19th Ed CHAPTER:20 PAGE: 353-358

23574 – Noradrenaline causes
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2: vasodilation in skeletal muscle and liver
3: increased myocardial excitability
4: widening of the pulse pressure

Answers: TFTF

Ganong 13th Edition CHAPTERS: 19 PAGES: 300

9880 – S:There is very little free thyroxine in the plasma because R:thyroxine is bound to thyroxine-binding prealbumin in the plasma

Answer: S is true, R is true but not a valid explanation of S

Ganong, 19th ed, Ch 2

CALCIUM/PHOSPHATE METABOLISM

1100g calcium in body

- 99% in skeleton
- 1% ICF
- 0.1% ECF

Regulated by 3 hormones

- Parathyroid hormone
- Vitamin D
- Calcitonin

500-800g phosphate in body

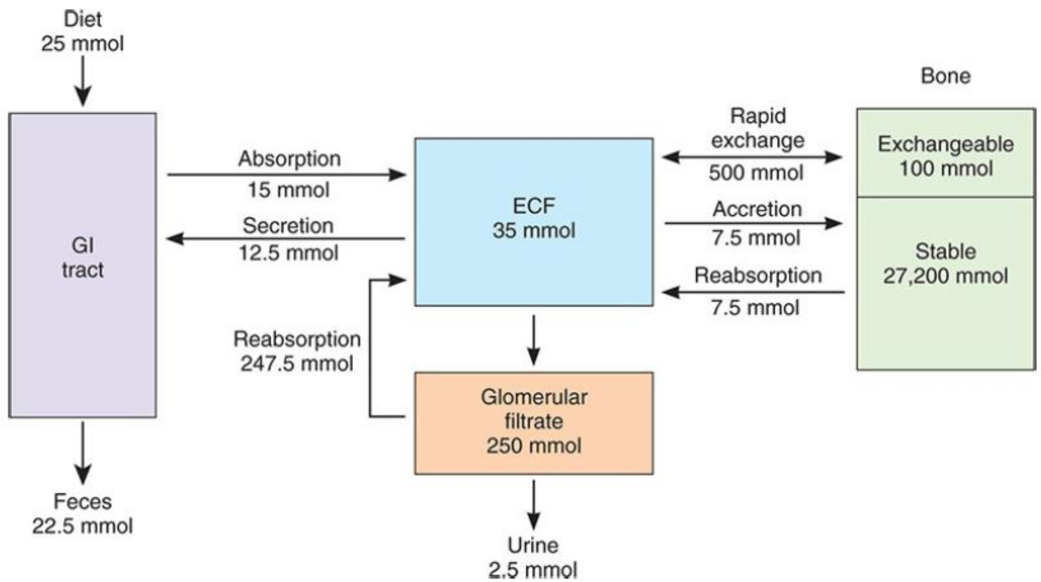


FIGURE 21–1 Calcium metabolism in an adult human. A typical daily dietary intake of 25 mmol Ca^{2+} (1000 mg) moves through many body compartments. Note that the majority of body calcium is in bones, in a pool that is only slowly exchangeable with the extracellular fluid (ECF).

PARATHYROID HORMONE

Secreted by chief cells of the parathyroid glands

↓Ca^{2+} in ECF → ↑ PTH secretion

Effects of PTH = ↑ Ca^{2+}

- Stimulate bone resorption
- Kidney: ↑ Ca^{2+} (increase reabsorption and decreased excretion)
- Kidney: ↓ PO_4^{2-} (decrease reabsorption and increased excretion)
- Stimulate conversion of vit D to active form → ↑ Ca^{2+} and PO_4^{2-} absorption in intestine

PTH receptor mediated by cyclic adenosine monophosphate (cAMP) second messenger system

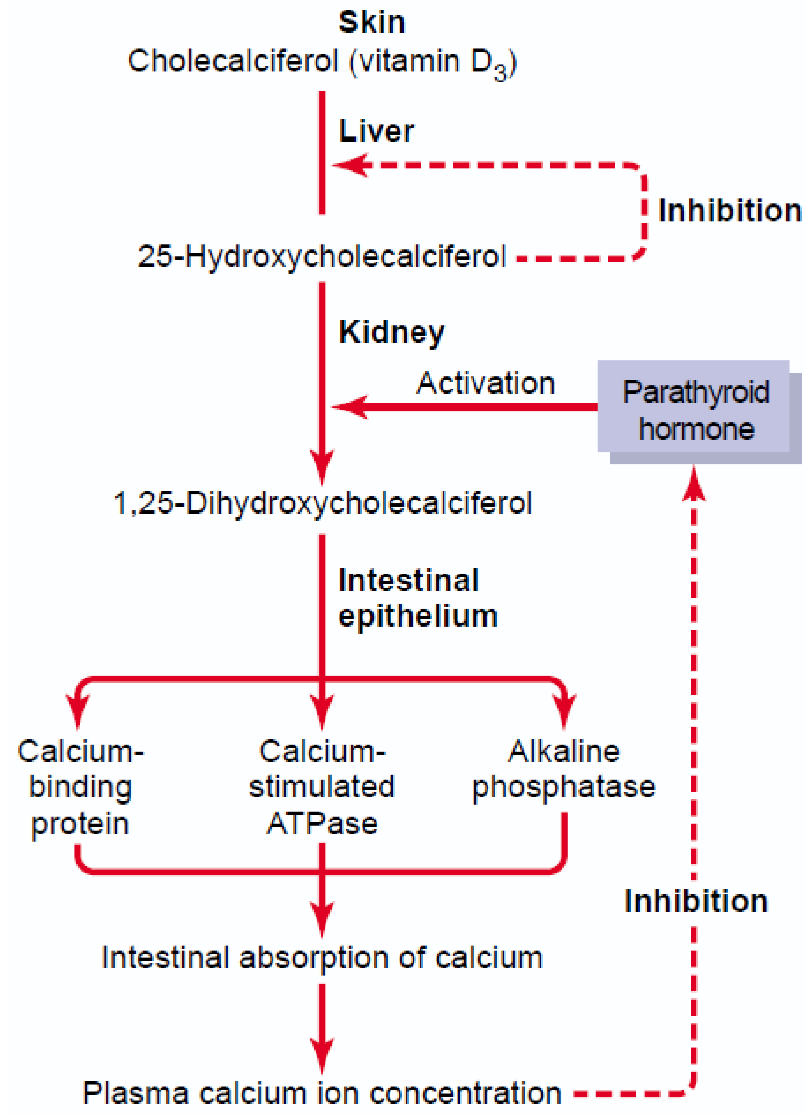
Changes in ECF Ca^{2+} detected by calcium-sensing receptor (CaSR) in parathyroid cell membranes

- G-protein coupled receptor → inhibits PTH secretion

VITAMIN D

Cholecalciferol (vit D_3) formed due to irradiation of 7-dehydrocholesterol

Active product is 1,25-dihydroxycholecalciferol (made active in kidney by PTH)



CALCITONIN

Peptide hormone secreted by parafollicular cells (C cells) of thyroid gland

Secreted in response to ↑Ca^{2+} in plasma (*opposite to PTH*)

Effects – weak in adult human

- Inhibit bone resorption (inhibit osteoclasts)
    - Transient as decreased osteoclasts also leads to decreased osteoblasts
- Increase Ca^{2+} excretion in urine (little importance)

Little long term effect on calcium homeostasis

Not involved in phosphate homeostasis

CALCIUM HOMEOSTASIS

GI tract

- ↑ Ca absorption promoted by **vit D**
- Ca^{2+} actively transported from brush border by Ca^{++} dependent ATPase

Bone – short term regulation (buffer system to keep plasma levels nearly constant)

- hydroxyapetite
- **PTH** mobilises Ca^{2+} from bone
- **Calcitonin** inhibits bone resorption

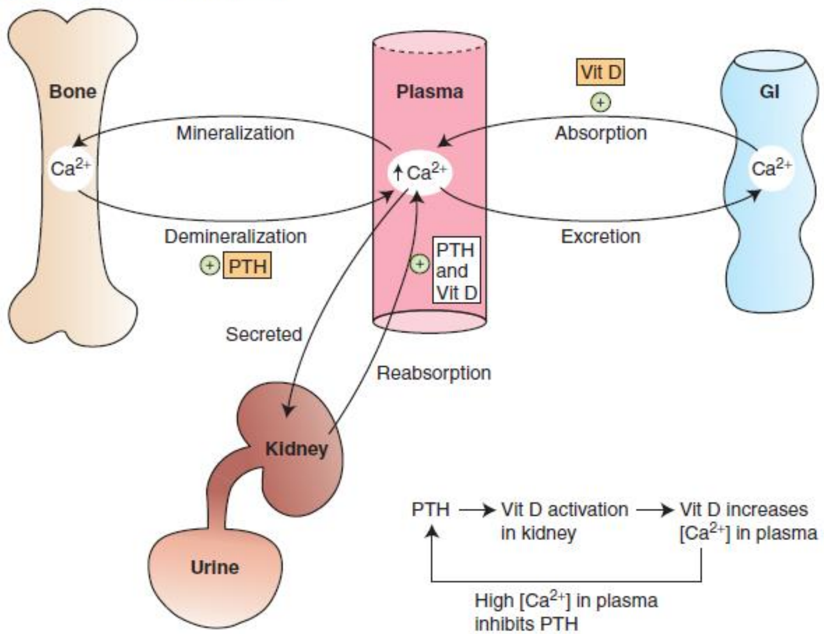
Kidneys – long term regulation

- Form active part of **vitamin D**
- **PTH** increase Ca^{2+} reabsorption in kidney
- **Calcitonin** increases Ca^{2+} in urine

Other factors affecting calcium

- Glucocorticoids
- Growth hormone
- Thyroid hormones
- Oestrogens
- Insulin

FIGURE 7-4 **Calcium homeostasis**



Ca^{2+}, calcium; GI, gastrointestinal tract; PTH, parathyroid hormone; Vit D, vitamin D.

First Aid for USMLE

THE BANK

15493 – The absorption of calcium from the upper small intestine is facilitated by

1: 1, 25 - dihydroxycholecalciferol
2: a calcium-binding protein in small intestinal epithelium
3: a low ionised calcium in plasma
4: phosphate in small intestine

21443 – PTH (parathyroid hormone)

1: increases mobilisation of Ca^{2+} from bone
2: increases reabsorption of Ca^{2+} from distal tubules of kidney
3: increases synthesis of 1, 25-Dihydroxycholecalciferol, the 'active' metabolite of vitamin D
4: increases phosphate reabsorption from renal tubules

23929 – Calcitonin

1: increases Ca^{2+} concentration of plasma
2: increases absorption of Ca^{2+} from bone
3: increases absorption of Ca^{2+} from small intestine
4: secretion is increased by a raised Ca^{2+} concentration of plasma

THE BANK

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2: a calcium-binding protein in small intestinal epithelium
3: a low ionised calcium in plasma
4: phosphate in small intestine

Answers: TTTF

Refer to Guyton, 7th Ed, Ch 79, page 937-939; Ganong, 19th Ed, Ch 25, page 456

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Ganong 16th Ed. CHAPTER: 21 PAGE: 356

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2: increases absorption of Ca^{2+} from bone
3: increases absorption of Ca^{2+} from small intestine
4: secretion is increased by a raised Ca^{2+} concentration of plasma

Answers: FFFT

Ganong 13th Ed. CHAPTER: 21 PAGE: 330

PROLACTIN

Similar structure to human GH

- Single chain of 198 amino acids

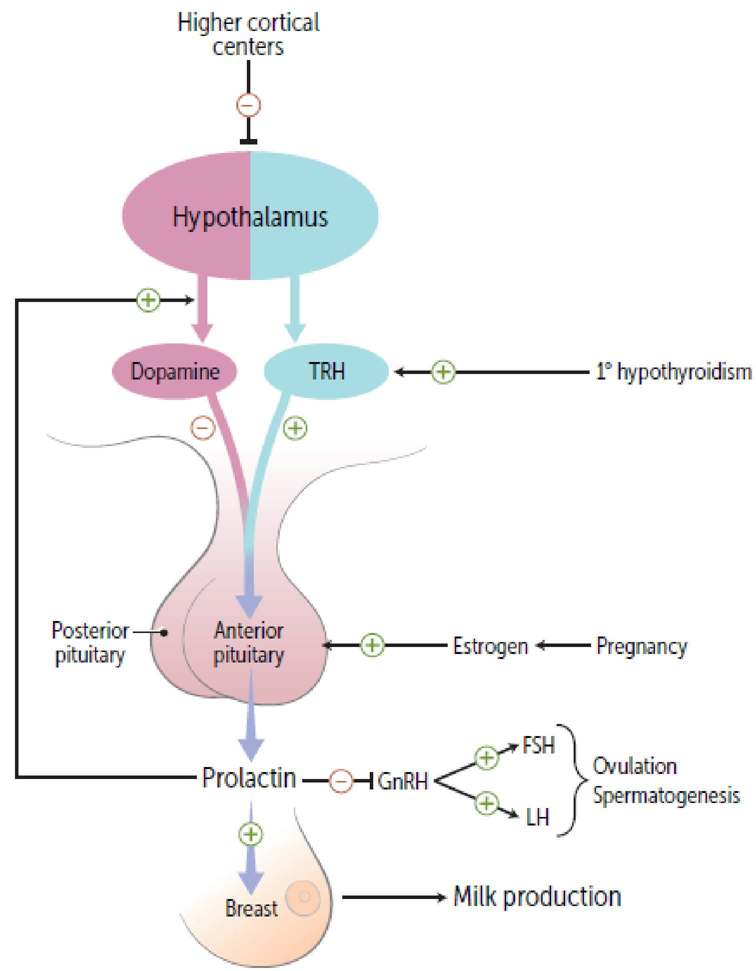
Prolactin receptors similar to GH receptors in structure and MOA

Half life ~20min

Secretion tonically inhibited by hypothalamus

- Dopamine = prolactin inhibiting hormone

Cut the stalk / damage hypothalamus → no dopamine inhibition → all ant pituitary hormone reduce, but prolactin level increase



First Aid for USMLE

PROLACTIN REGULATION

Prolactin increased in

- Exercise
- Surgical and psychological stresses
- Stimulation of nipple (non-lactating women)
- Sleep
- Pregnancy
- Oestrogen → act on lactotropes (slow increase)
- TRH
- Phenothiazines (block dopamine receptors)

Prolactin decreased in

- L-dopa
- Bromocriptine
- Chlorpromazine and related drugs (block dopamine receptors)
- Prolactin → ↑ dopamine secretion (negative feedback)

PROLACTIN EFFECTS

Milk secretion from breast (after oestrogen and progesterone priming)

- NOT milk ejection (that is oxytocin)

Inhibits effects of gonadotropins

- ↑ prolactin → ↓ actions of LH and FSH on gonads
- Infertility in male and female

Unknown effect on male – but excess prolactin from tumours causes erectile dysfunction

GONADOTROPINS

FSH and LH made of α and β subunit, glycoproteins

(+) gonadotrophs (GnRH)

GnRH secreted intermittently a few minutes at a time once every 1 to 3 hours. Intensity of stimulus determined by

- Frequency of cycles of secretion
- Quantity of GnRH released with each cycle
- LH secretion also cyclical following pulsatile release of GnRH
- FSH changes more slowly over period of many hours (in response to longer-term changes in GnRH)

FSH half life ~ 170min

LH half life~60min

Receptors – G-protein-coupled receptors coupled to adenylyl cyclase through a stimulatory G-protein

In target cells - Activate cyclic adenosine monophosphate second messenger system

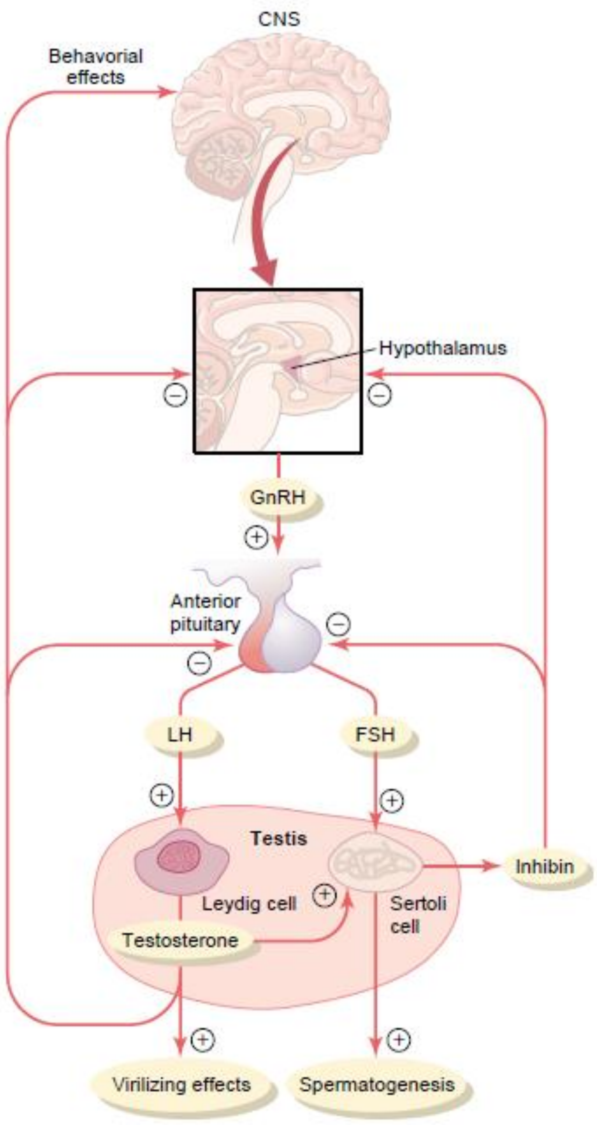
FSH AND LH EFFECTS IN MALES

FSH – stimulate spermatogenesis

- Stimulate Sertoli cells in seminiferous tubules
- Sertoli cells secrete Inhibin

LH – stimulate testosterone secretion

- Stimulate interstitial Leydig cells in testes



TESTOSTERONE

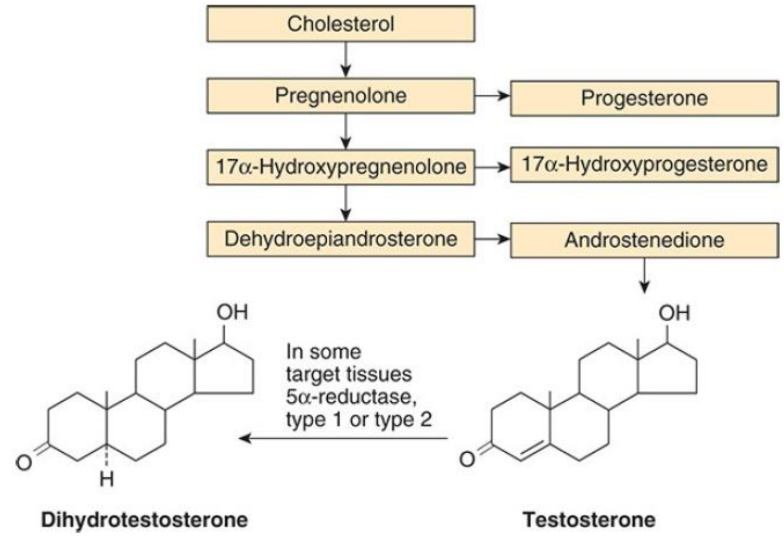
Secreted by Leydig cells

Stimulated by LH → cAMP via G-protein coupled LH receptor → stimulate protein kinase A → cholesterol converted to pregenenolone

Small amounts of testosterone secreted by female ovary and adrenals

Bound to

- 65% Gonadal steroid-binding globulin (BGB)
- 33% albumin



Effects
• Inhibit pituitary LH secretion • Develop and maintain male secondary sex characteristics • Anabolic → ↑ protein synthesis → ↑ growth • Maintain spermatogenesis • Moderate retention of Na, K, H_2O, Ca, SO_4, PO_4 • Increase libido

FSH AND LH EFFECTS IN FEMALES

Cyclical increase and decrease every month for FSH and LH

Follicular phase FSH>LH

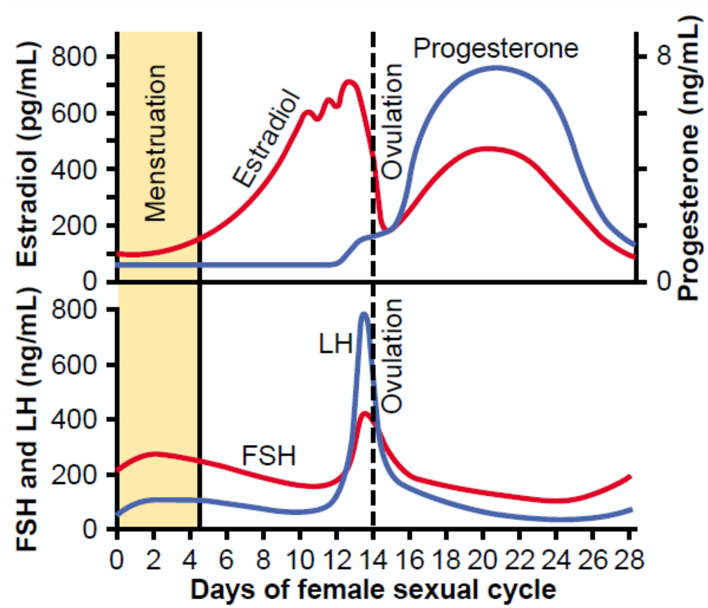
- growth of 6-12 primary follicles each month
- rapid proliferation of granulose cells + theca → secrete oestrogen and progesterone

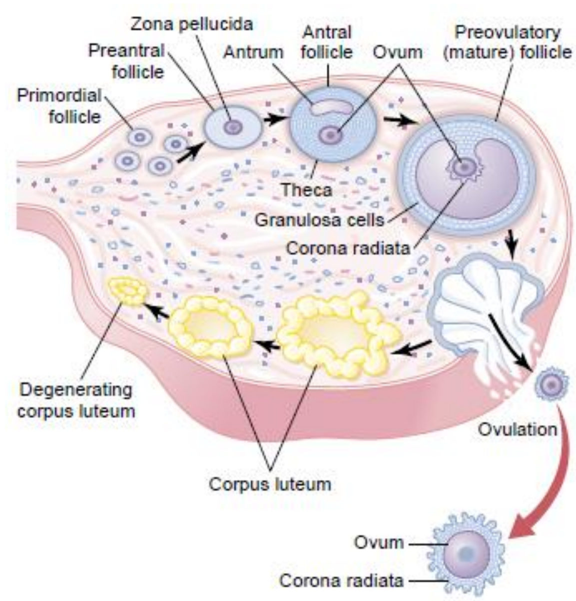
Ovulation <u>LH</u>>FSH

- Rapid swelling of follicle
- LH cause granulosa and theca cells to convert to progesterone-secreting cells
- → less oestrogen, more progesterone

Luteal phase LH

- Luteinisation – granulosa and theca interna cells change into lutein cells (fill with lipid inclusions)
- Oestrogen, progesterone and inhibin from luteal cells negatively feedback on FSH and LH
- ceases after final involution of corpus luteum





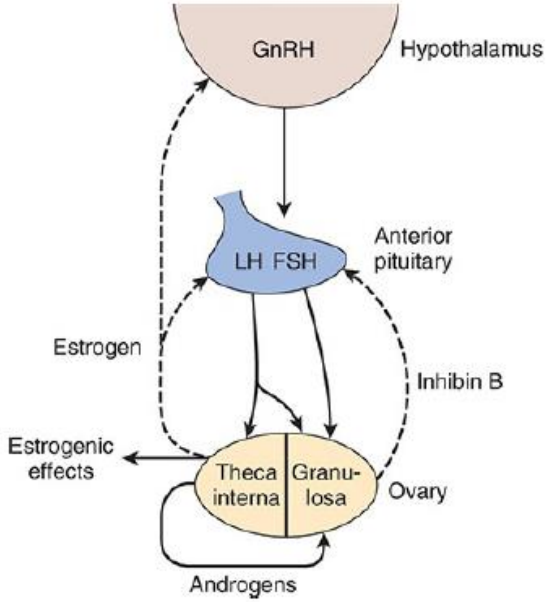


FIGURE 22–19 Feedback regulation of ovarian function. The cells of the theca interna provide androgens to the granulosa cells, and theca cells also produce the circulating estrogens that inhibit the secretion of GnRH, LH, and FSH. Inhibin from the granulosa cells inhibits FSH secretion. LH regulates the thecal cells, whereas the granulosa cells are regulated by both LH and FSH. The dashed arrows indicate inhibitory effects and the solid arrows stimulatory effects. FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone.

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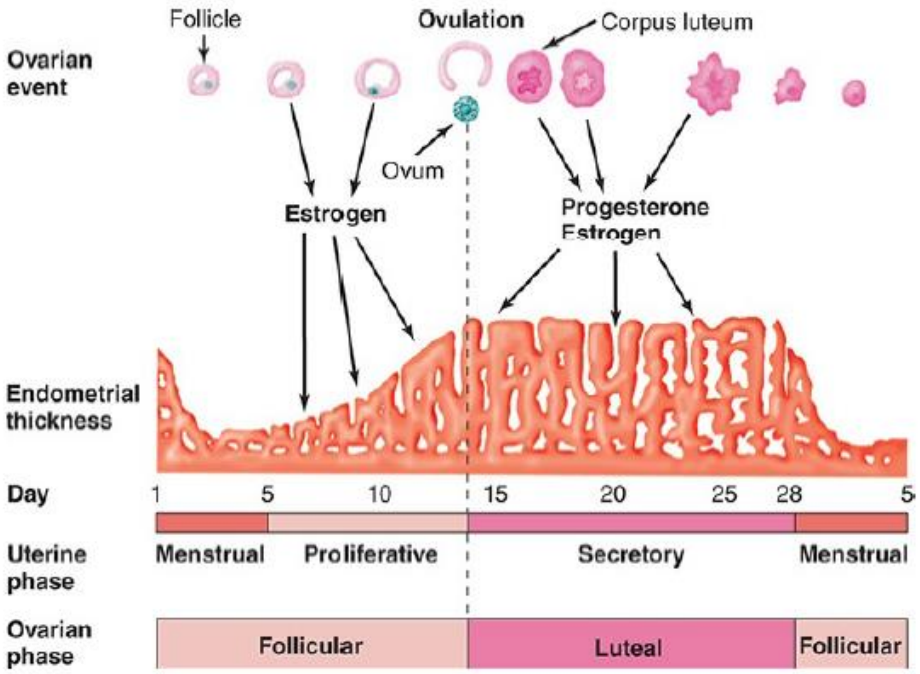

FIGURE 22–11 Relationship between ovarian and uterine changes during the menstrual cycle. (Reproduced with permission from Windmaier EP, Raff H, Strang KT: *Vander's Human Physiology: The Mechanisms of Body Function*, 11th ed. New York, NY: McGraw-Hill; 2008.)

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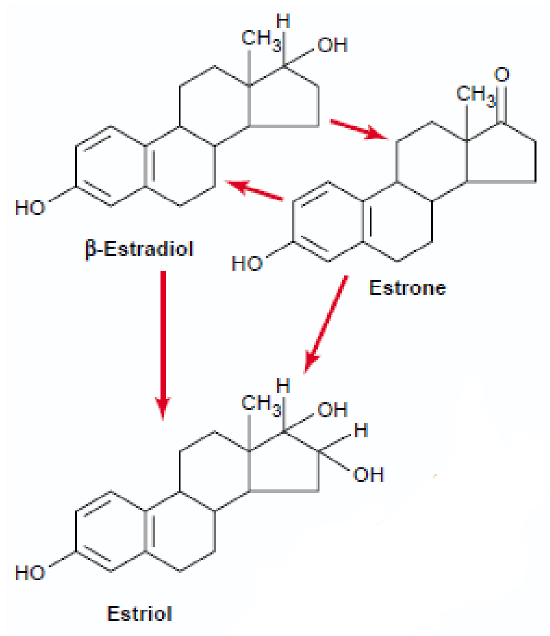
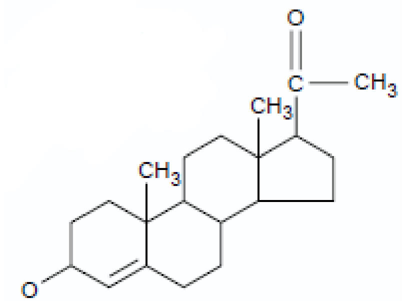
OESTROGEN

Effects

- Increase size of uterus , ovaries, fallopian tube and vagina in puberty
- Marked proliferation of endometrial stroma and development of endometrial glands
- Vaginal epithelium changed from cuboidal intro stratified type (more resistant to trauma and infection)
- Breast: Develop stromal tissues of breasts, growth of ductile system and deposition of fat in breast
- Bone: Inhibit osteoclastic activity in bones → stimulate bone growth. Unite epiphyses with shafts of long bones at puberty
- Slight increase in total body protein
- Increase whole body metabolic rate
- Increase deposition of fat in subcutaneous tissue
- Skin becomes softer, smoother and more vascular



PROGESTERONE



Progesterone

Effects

- Uterus
  - Promotes secretory epithelium in endometrium
  - Decreases excitability of myometrial cells – prevent expulsion of implanted ovum
- Increase secretion by mucosal lining of fallopian tubes
- Stimulate development of breast lobules and alveoli

THE BANK

22594 – Prolactin secretion is increased by
1: exercise
2: surgery
3: suckling
4: dopamine

23884 – With respect to breast development and lactation
1: prolactin initiates milk secretion
2: oxytocin induces milk ejection ('let-down')
3: oestrogen stimulates duct growth
4: growth hormone alone stimulates lobule-alveolar growth

10079 – With regard to the testis
1: normal spermatogenesis takes place under the effect of F.S.H. (Follicle Stimulating Hormone) alone
2: Sertoli cells secrete inhibin which has a negative feedback effect on the anterior pituitary
3: testosterone from Leydig cells inhibits the release of F.S.H. from the anterior pituitary
4: testosterone inhibits luteinising hormone secretion at the level of the hypothalamus

THE BANK

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Ganong 15th ed. Chapter: 23 Page: 398-399

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Guyton 7th Ed. Chapter: 82 Page: 994-995 Ganong 13th Ed. Chapter: 23 Page:378-379

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Answers: FTFT

THANKS