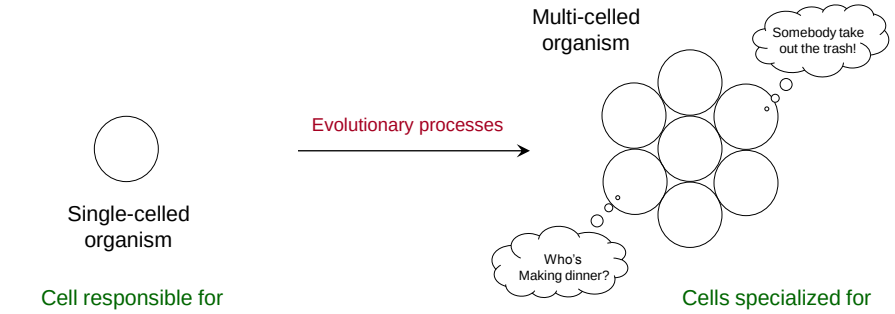
In the beginning…



Cell responsible for all physiological processes

Cells specialized for specific functions

How do cells communicate?

1) Nervous system (electrical / chemical signaling)
   - Rapid / conscious or sub-conscious / internal or external communication
2) Endocrine system (chemical signaling)
   - Slow / sustained / sub-conscious / internal or external communication

Hormone:

Any substance produced and secreted by one cell that regulates another cell

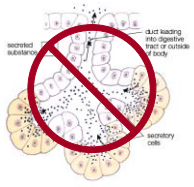
See Tables 9.1 / 9.2 (Costanzo – pgs. 380 – 381)

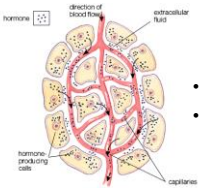
Marieb & Hoehn – Figure 16.1

Overview of Endocrine System:

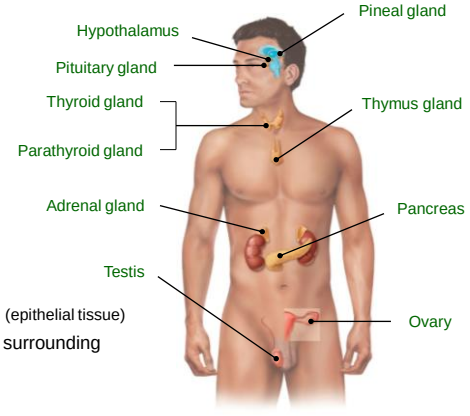
Endocrine System: Hormones and the various cells that secrete / receive them

Gland → Hormone → Target Cell → Effect





- Glandular secretory cells (epithelial tissue)
- Release substances into surrounding tissues (ductless)



We will focus on the classical endocrine system

Overview of Endocrine System:

Endocrine System: Hormones and the various cells that secrete / receive them

Gland → Hormone → Target Cell → Effect

Endocrine (classic definition):

Gland → Hormone —Blood→ Target Cell

Neuroendocrine:

Neuron → Hormone —Blood→ Target Cell

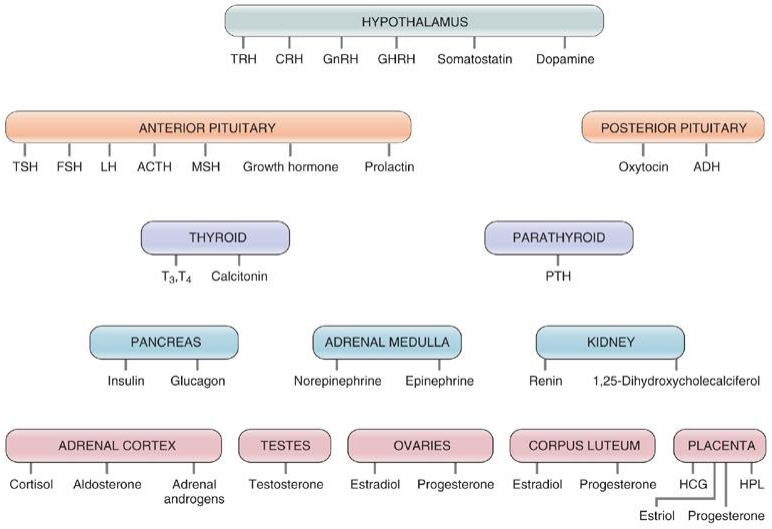
Paracrine:

Cell → Hormone —Interstitial Fluid→ Target Cell

Autocrine

Costanzo – Figure 9.1

Overview of Endocrine System:



Overview of Endocrine System:

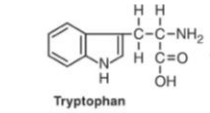
Endocrine System: Hormones and the various cells that secrete / receive them

Gland → Hormone → Target Cell → Effect

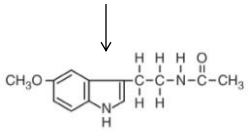
General Classes of Hormones:

1) Amines:

- Derived from individual amino acids

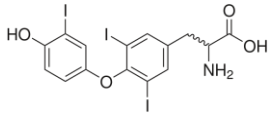


Tryptophan



Melatonin

- May incorporate inorganic ions



Triiodothyronine (T_3)

Majority of amines inactivated in liver or at site of action

Costanzo – Figure 9.2

Overview of Endocrine System:

Peptides inactivated by blood, liver, and kidney proteases

Endocrine System: Hormones and the various cells that secrete / receive them

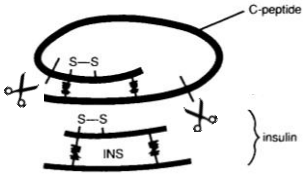
Gland → Hormone → Target Cell → Effect

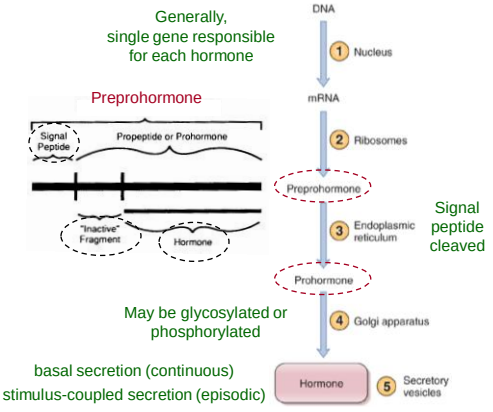
General Classes of Hormones:

2) Peptides:

- Most common type of hormone
- Composed of amino acids (3 – 200+ a.a.)
- Synthesis follows Central Dogma

Prohormone (e.g., insulin)





Overview of Endocrine System:

Steroids inactivated by liver; cleared through kidneys / intestines

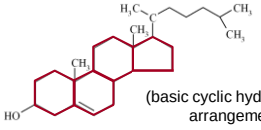
Endocrine System: Hormones and the various cells that secrete / receive them

Gland → Hormone → Target Cell → Effect

General Classes of Hormones:

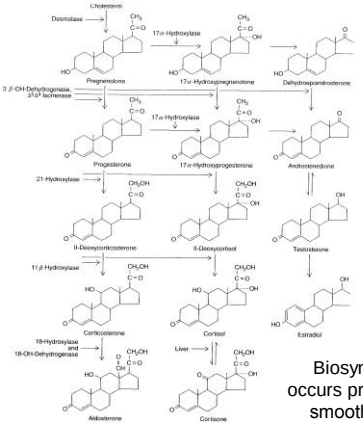
3) Steroids:

- Derived from cholesterol



(basic cyclic hydrocarbon arrangement)

- Complex biosynthetic pathways
- Very little stored (lipid soluble)



Biosynthesis occurs primarily in smooth ER…

Overview of Endocrine System:

Endocrine System: Hormones and the various cells that secrete / receive them

Gland → Hormone → Target Cell → Effect

Target Cells: Cells specialized to respond to hormones

↑ Specific receptors present (2000 – 10,000)

↳ Alter cells by changing identities, activities, or quantities of proteins

- Cell activity primarily regulated by # of active receptors present

**** Up Regulation / Down Regulation ****
Depends on affinity of receptors, but does not define why change has occurred (e.g., activation / inactivation)

- Cell changes may be: 1) prolonged and irreversible (e.g., puberty)
  2) transient and reversible (e.g., 'fight-or-flight")

Endocrine System

Overview of Endocrine System:

Endocrine System: Hormones and the various cells that secrete / receive them

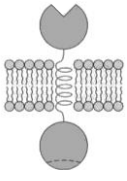
Gland → Hormone → Target Cell → Effect

- Hormones differ in mechanism of action:

2nd Messenger Systems

- Utilized by large, charged hormones (e.g., peptides)
- Receptors located on cell surface

A) Enzyme-linked receptors
   - Binding of hormone directly activates enzyme (e.g., kinase)



B) G protein-linked receptors

Endocrine System

Costanzo – Figure 9.6

Overview of Endocrine System:

Endocrine System: Hormones and the various cells that secrete / receive them

Gland → Hormone → Target Cell → Effect

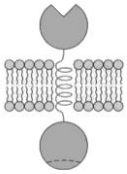
- Hormones differ in mechanism of action:

Primarily responsible for changing gene transcription rate

2nd Messenger Systems

- Utilized by large, charged hormones (e.g., peptides)
- Receptors located on cell surface

A) Enzyme-linked receptors
- Binding of hormone directly activates enzyme (e.g., kinase)

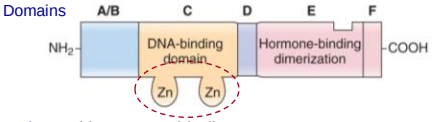


B) G protein-linked receptors

Primarily responsible for changing cell activity

Internal Receptor Systems

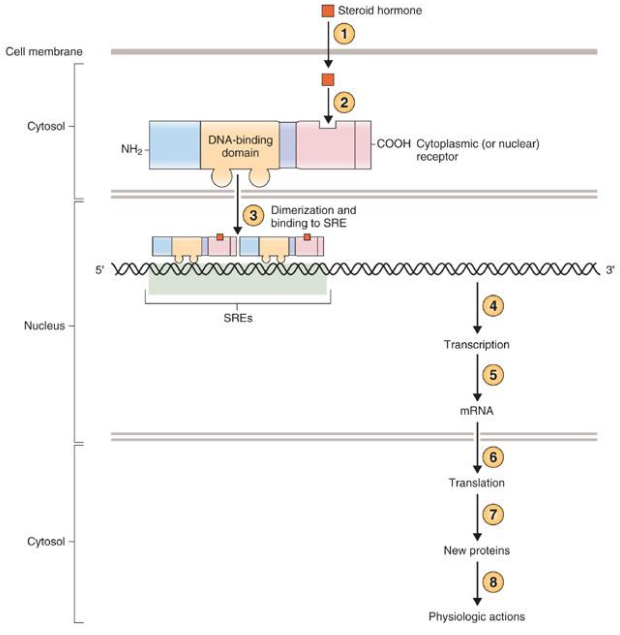
- Utilized by hydrophobic hormones (e.g., steroids)
- Receptors located in cytoplasm / nucleus



A / B: Initiates DNA binding (e.g., transcription factors)
C: Actively binds DNA (zinc fingers – highly conserved)
D: Hinge region (goes through conformational change)
E: Hormone-binding region

Endocrine System

Costanzo – Figure 9.7

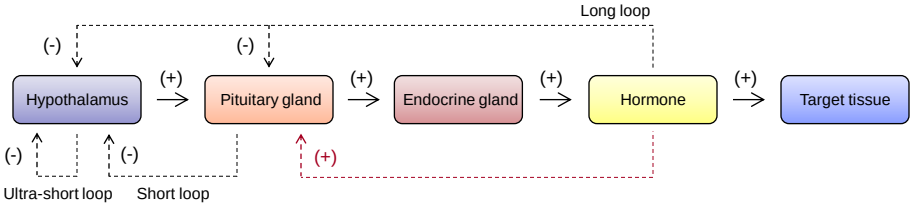


Overview of Endocrine System:

Endocrine System: Hormones and the various cells that secrete / receive them

Gland → Hormone → Target Cell → Effect

- Hormone levels maintained via feedback mechanisms:



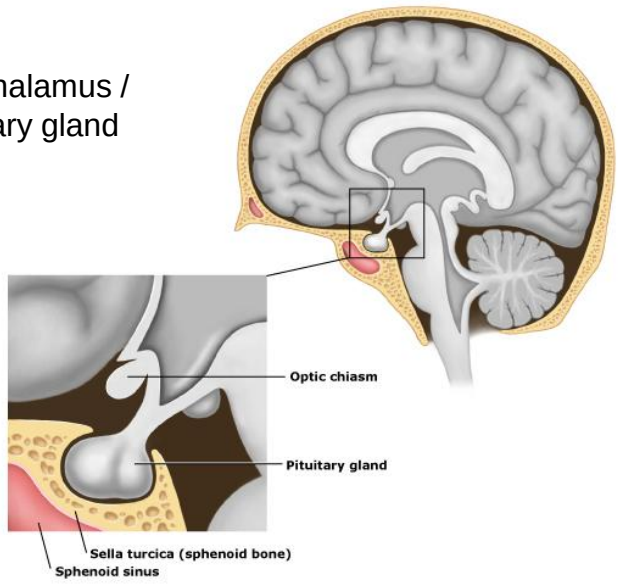
A) Negative Feedback: Some feature of hormone action, directly or indirectly, inhibits further secretion of the hormone

B) Positive Feedback: Some feature of hormone action, directly or indirectly, enhances further secretion of the hormone

Endocrine System

Property	Amines*	Peptides	Steroids
Feedback regulation of synthesis	Yes	Yes	Yes
Storage of hormone	Several days	One day	Very little
Mechanism of secretion	Exocytosis	Exocytosis	Diffusion
Plasma protein binding	Rarely	Rarely	Yes
Lifetime in blood	Seconds	Minutes	Hours
Time course of action	Seconds	Minutes – Hours	Hours – Days
Receptors	Plasma membrane	Plasma membrane	Cytosolic / Nuclear

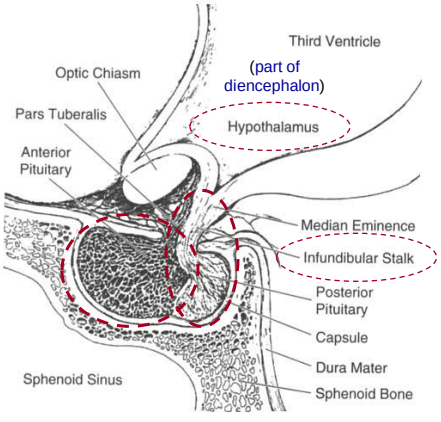
Hypothalamus / Pituitary gland



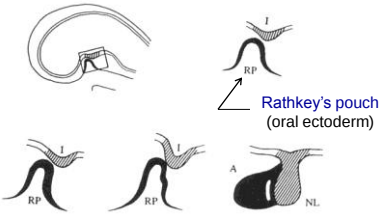
Norris (Vertebrate Endocrinology, 3rd ed.) – Figure 4.4

Hypothalamus / Pituitary Gland:

The hypothalamus and pituitary gland function in a coordinated fashion to orchestrate multiple endocrine system



Pituitary gland composed of both epithelial and neural tissue:



Anterior pituitary (adenohypophysis)

- Contains glandular cells

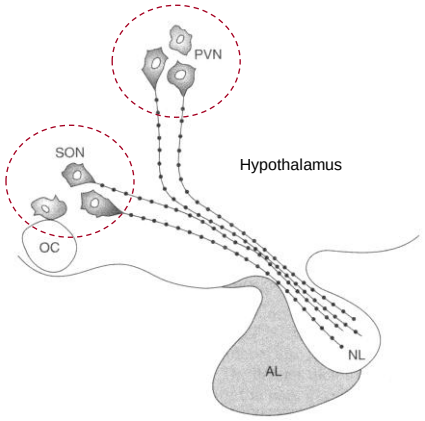
Posterior pituitary (neurohypophysis)

- Contains hypothalamic neurons

Hadley (Endocrinology, 5th ed.) – Figure 5.2

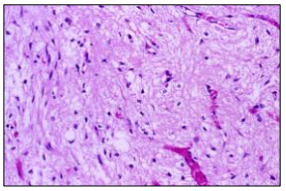
Hypothalamus / Pituitary Gland:

The hypothalamus is in direct control of the pituitary by both neural and hormonal mechanisms



The connection between the hypothalamus and posterior pituitary is neural:

- Neural cell bodies located in hypothalamus
  - Supraoptic nucleus (SON)
  - Paraventricular nucleus (PVN)
- Posterior pituitary collection of axons
  - Release neurohormones into neighboring capillary bed (oxytocin – OT; antidiuretic hormone – ADH)

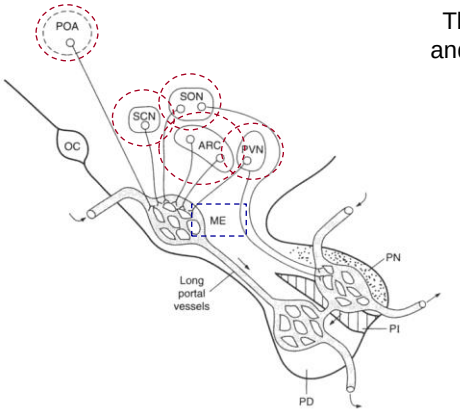


Hadley (Endocrinology, 5th ed.) – Figure 7.1

Endocrine System

Hypothalamus / Pituitary Gland:

The hypothalamus is in direct control of the pituitary by both neural and hormonal mechanisms



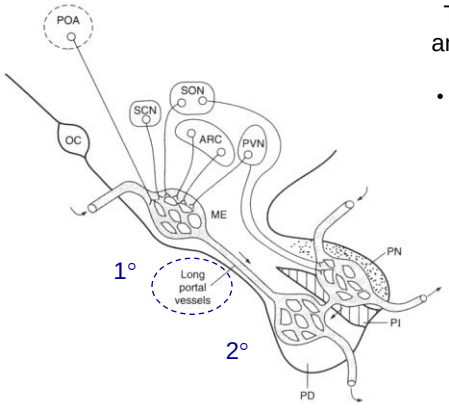
The connection between the hypothalamus and anterior pituitary is neural and endocrine:

- Neural cell bodies located in hypothalamus with axonal endings at median eminence (ME):
  - Supraoptic nucleus (SON)
  - Paraventricular nucleus (PVN)
  - Arcuate nucleus (ARC)
  - Preoptic area (POA)
  - Suprachiasmatic nucleus (SCN)
- Hypothalamic neurons release regulatory hormones at ME:
  - Releasing hormones (stimulatory effect)
  - Inhibiting hormones (inhibitory effect)

Hadley (Endocrinology, 5th ed.) – Figure 7.1

Hypothalamus / Pituitary Gland:

The hypothalamus is in direct control of the pituitary by both neural and hormonal mechanisms



Hadley (Endocrinology, 5th ed.) – Figure 7.1

The connection between the hypothalamus and anterior pituitary is neural and endocrine:

- Regulatory hormones travel to anterior pituitary via hypothalamic-hypophysial portal system:

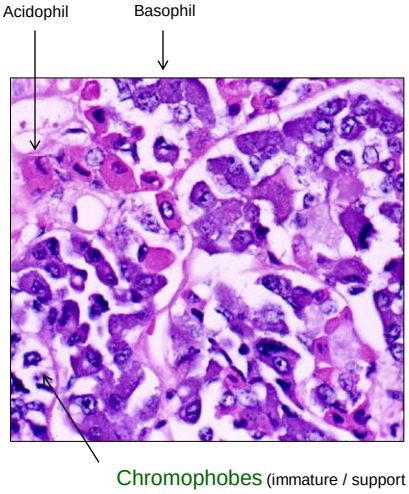
1° capillary bed
↓
Portal vessels
↓
2° capillary bed

Important Implications:

1) Regulatory hormones delivered to pituitary rapidly and in [high]
2) [High] of regulatory hormones do not appear in systemic circulation

Hypothalamus / Pituitary Gland:

The hypothalamus is in direct control of the pituitary by both neural and hormonal mechanisms



The connection between the hypothalamus and anterior pituitary is neural and endocrine:

- Regulatory hormones activate / inhibit cells in the anterior pituitary:

A) Acidophils: (granules bind acid stains)
   1) Somatotrophs (growth hormone – GH; ~ 20%)
   2) Lactotrophs (prolactin – PRL; ~ 15%)
      - Cell # varies according to sex / age

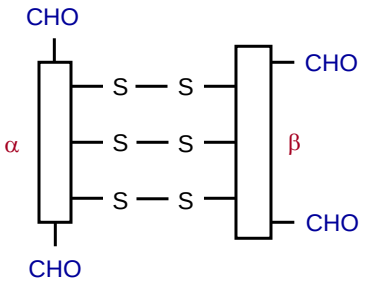
B) Basophils: (granules bind basic stains)
   1) Corticotrophs (adrenocorticotrophic hormone – ACTH; ~ 15%)
   2) Thyrotrophs (thyroid-stimulating hormone TSH; ~ 5%)
   3) Gonadotrophs (follicle-stimulating hormone – FSH; luteinizing hormone – LH; ~ 15%)

Anterior Pituitary Hormones:

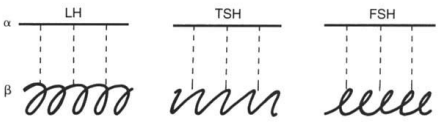
These hormones target endocrine glands
(TSH = thyroid gland; LH / FSH = gonads),
up regulating activity of glands

Group I: Glycoproteins (TSH / FSH / LH)

- Consists of two subunits: α-subunit (~ 92 – 93 a.a. residues) and β sub-unit (~ 110 – 145 a.a. residues); connected via disulfide bond



- Sub-units coded by different genes
- Biological activity dependent on variation in β sub-unit



- Large carbohydrate component (~ 15 – 30% MW of molecule)
  - Assists in folding protein / prevention of proteolytic breakdown

Human chorionic gonadotropin (HCG)
structurally related to glycoprotein family

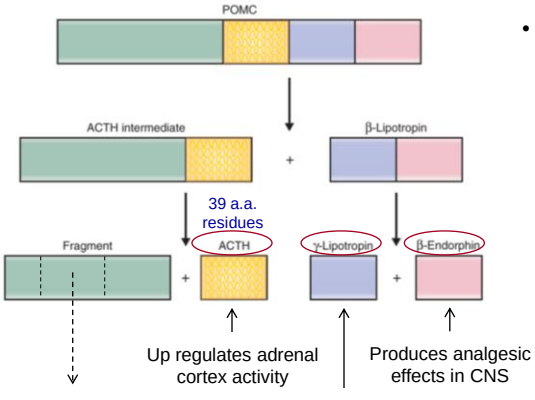
Norris (Vertebrate Endocrinology, 3rd ed.) – Figure 4.14

Costanzo (Physiology, 4th ed.) – Figure 9.9

Anterior Pituitary Hormones:

Group II: Pro-opiomelanocortin derivatives (ACTH)

- Post-translational modification of POMC (prohormone); results in production of multiple hormones



- Hormone production dependent on enzymes present

αMSH:
Controls color change in many vertebrates; little activity in humans

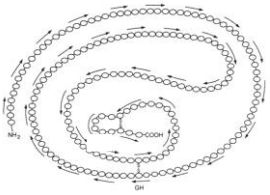
Addison's disease

Anterior Pituitary Hormones:

Group III: Single-chain peptide hormones (GH / PRL)

A. Growth Hormone:

- 191 a.a. residues; two internal disulfide bonds



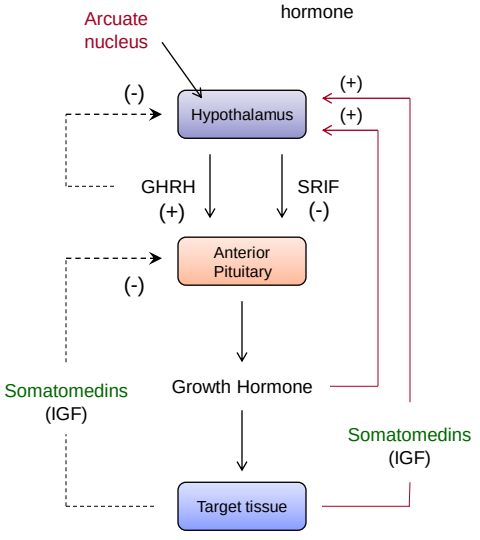
Regulation of GH Secretion:

- Secreted in pulsatile pattern (2 hr. bursts)
- ↑ rate during puberty (growth spurt)

Stimulatory Factors	Inhibitory Factors
Hypoglycemia	Hyperglycemia
Starvation	Obesity
Exercise / stress	Senescence

GHRH:
Growth hormone releasing hormone

SRIF (somatostatin):
Somatotropin release-inhibiting hormone



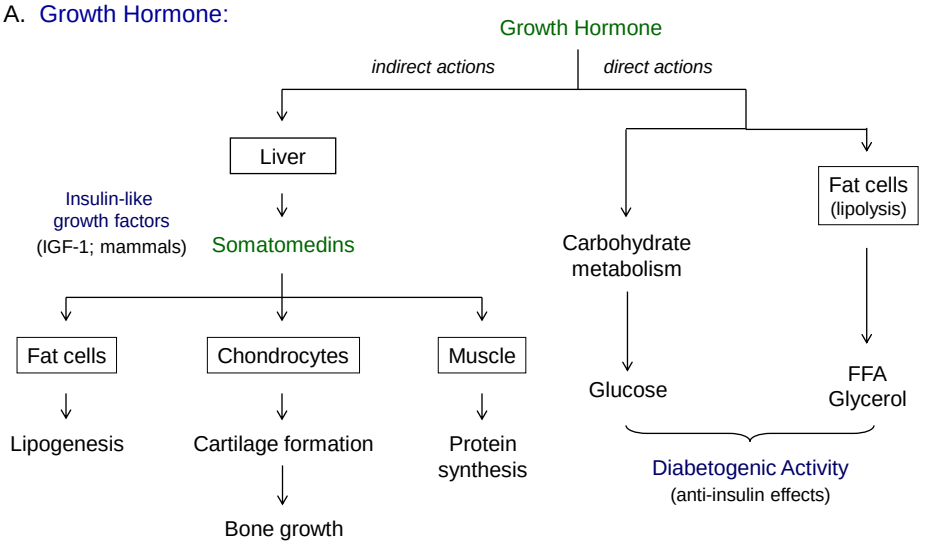
Endocrine System

Anterior Pituitary Hormones:

Synergisms with thyroid hormones / sex steroids

Group III: Single-chain peptide hormones (GH / PRL)

A. Growth Hormone:



Anterior Pituitary Hormones:

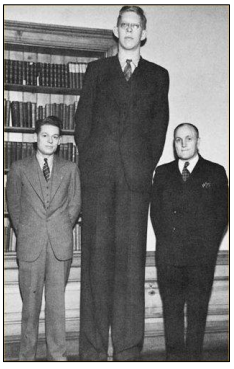
Group III: Single-chain peptide hormones (GH / PRL)

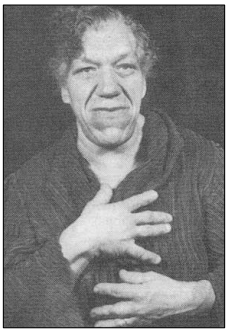
A. Growth Hormone:

Pathophysiology:

During early development:

In adulthood:





Gigantism (↑ GH)
Cause: Pituitary tumor
Treatment: Somatostatin analogs

Pituitary dwarfism (↓ GH)
Cause: Multiple causes
Treatment: Exogenous GH

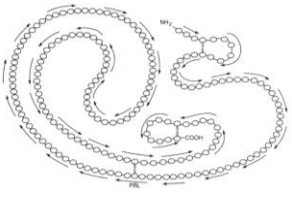
Acromegaly (↑ GH)
Cause: Pituitary tumor
Treatment: Somatostatin analogs

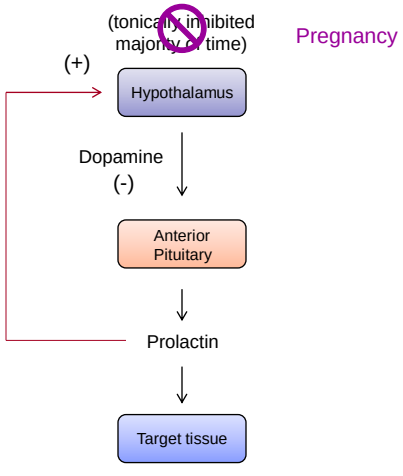
Anterior Pituitary Hormones:

Group III: Single-chain peptide hormones (GH / PRL)

B. Prolactin:

- 198 a.a. residues; three internal disulfide bonds





Regulation of GH Secretion:

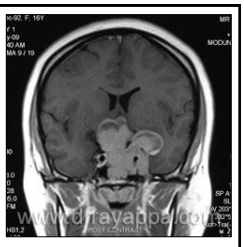
- Up regulated during pregnancy / lactation
- Primarily under inhibitory regulation

Stimulatory Factors	Inhibitory Factors
Sleep	Somatostatin

Anterior Pituitary Hormones:

Group III: Single-chain peptide hormones (GH / PRL)

B. Prolactin:



Pituitary tumor

Prolactin

Breast

- Simulates growth / development of mammary tissue (puberty / pregnancy)
- Simulates production of milk proteins / free fatty acids / lactose (suckling stimulation)

Work in conjunction with estrogen and progesterone

Inhibits ovulation

- Decreased fertility during breast-feeding

Pathophysiology:

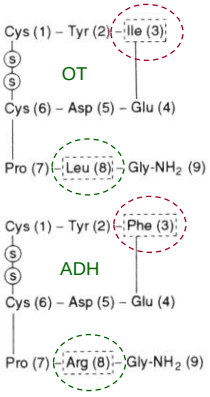
Hyperprolactinemia

Symptoms: Galactorhea / infertility
Cause: Multiple causes
Treatment: Bromocriptine (dopamine agonist)

Posterior Pituitary Hormones:

Oxytocin / Antidiuretic Hormone:

- Homologous 9 a.a. residues



OT / ADH genes on same chromosome but on different DNA strands

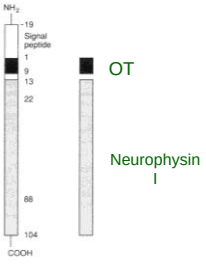
Hypothalamus

OT = paraventricular nuclei
ADH = supraoptic nuclei

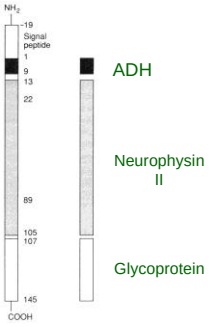
Posterior Pituitary

Neurophysins assist in transporting OT / ADH down axon (hormone binding proteins)

- Bioactive hormone synthesized from prohormones



Prooxyphysin



Propressophysin

Norris (Vertebrate Endocrinology, 3rd ed.) – Figure 6.2 / 6.3

Posterior Pituitary Hormones:

A. Oxytocin:

Stimulatory Factors
Infant cues (e.g., sound)

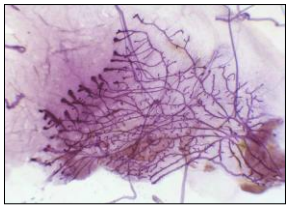
Inhibitory Factors
Opiods (endophins)

Oxytocin

Pitosin:
Synthetic agonist

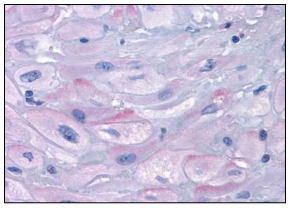
Breast (Suckling)

- Simulates movement of milk down duct system to nipple
  (milk letdown reflex)



Uterus (Dilation of cervix)

- Triggers powerful rhythmic contractions of uterus
  (child birth)



Posterior Pituitary Hormones:

B. Antidiuretic Hormone:

Stimulatory Factors
↑ plasma osmolarity
Hypovolemia

Inhibitory Factors
↓ plasma osmolarity
Ethanol

(Blocks ADH release
From pituitary)

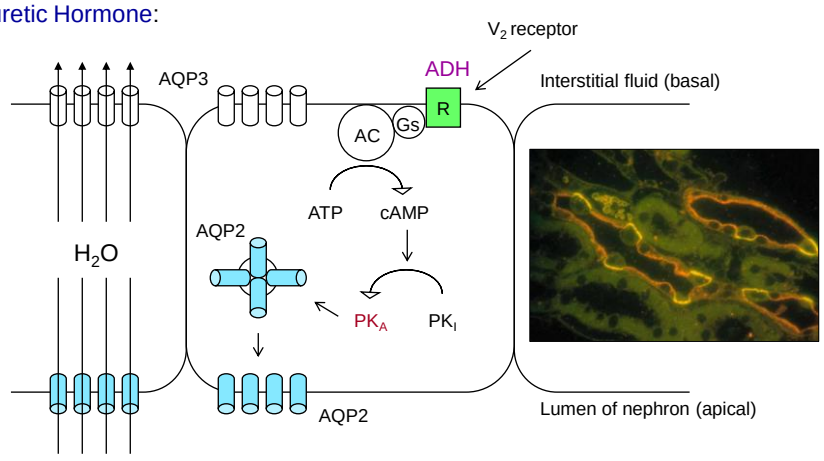
Antidiuretic Hormone

Kidneys

- Stimulates water reabsorption from kidney filtrate

Posterior Pituitary Hormones:

B. Antidiuretic Hormone:



1) ADH binds with receptor; activates cAMP pathway
2) Protein kinase triggers water channels (Aquaporin – 2) to embed in apical plasma membrane

Posterior Pituitary Hormones:

B. Antidiuretic Hormone:

ADH is also called vasopressin (AVP)

Stimulatory Factors
↑ plasma osmolarity
Hypovolemia
Blood pressure drop

Inhibitory Factors
↓ plasma osmolarity
Ethanol

Antidiuretic Hormone

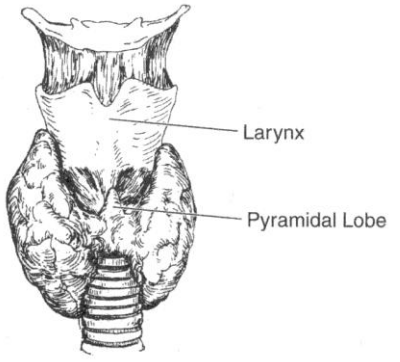
Kidneys
- Stimulates water reabsorption from kidney filtrate

Blood Vessels
- Triggers contraction of vascular smooth muscle

Pathophysiology:

Diabetes Insipidus
'a tasteless passer through'

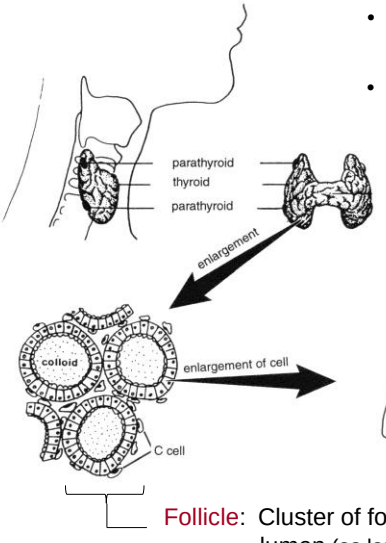
Symptoms: Large volumes of urine
Concentrated body fluids
Cause: No ADH produced (e.g., bad gene)
Unresponsive kidney (e.g., bad AQP2)
Treatment: ADH analogue (e.g., Desmopressin)

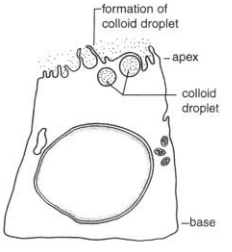


Thyroid gland

Thyroid Gland Anatomy:

- Bi-lobed gland located in throat region
  - Derived from endoderm of embryonic alimentary canal (Thyroglossal stalk)
  - Parathyroid gland embedded in tissue





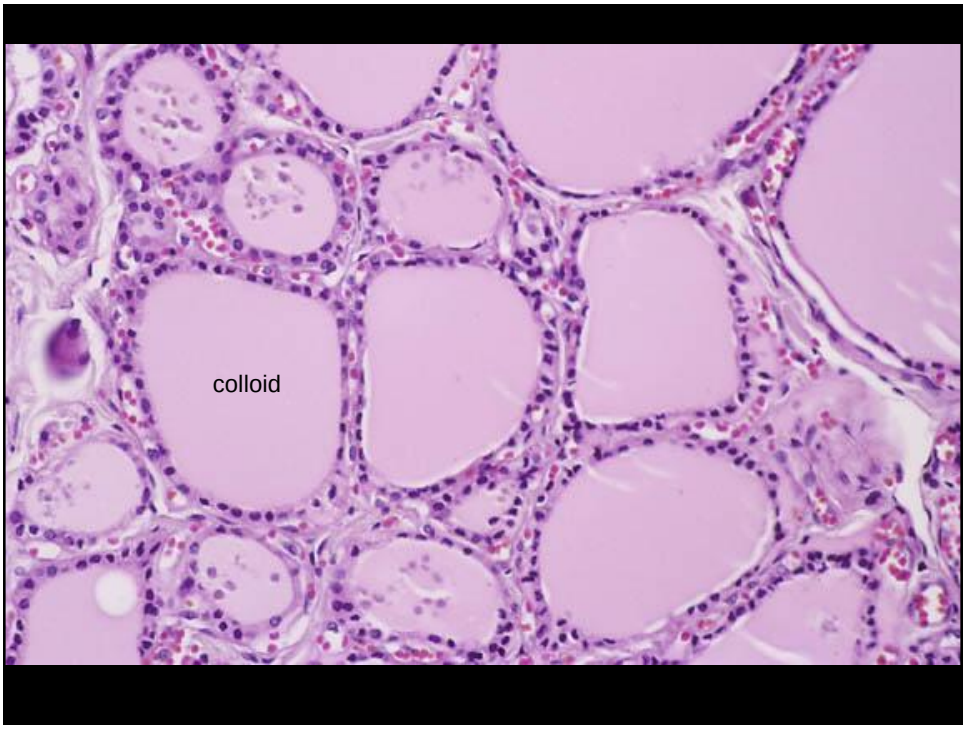
Colloid:
Thyroid hormone storage material
(located in lumen)

Can store 1 week worth of thyroid hormones

↑

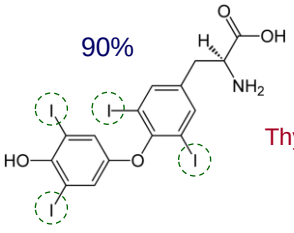
Production of hormones not tightly regulated

Follicle: Cluster of follicular cells (thyrocytes – simple cuboidal) surrounding lumen (as large as 1 cm)

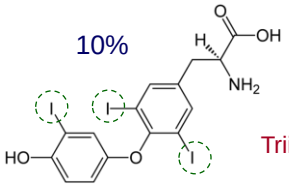


Thyroid Hormone:

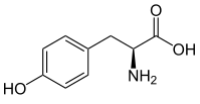
- Biogenic amine; derived from tyrosine
  - Requires iodine
- Two forms:



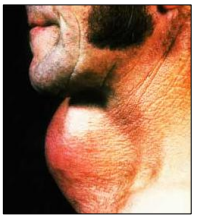
Thyroxine (T_4)
- 4 iodine atoms
- Tetraiodothyronine



Triiodothyronine (T_3)
- 3 iodine atoms



Tyrosine



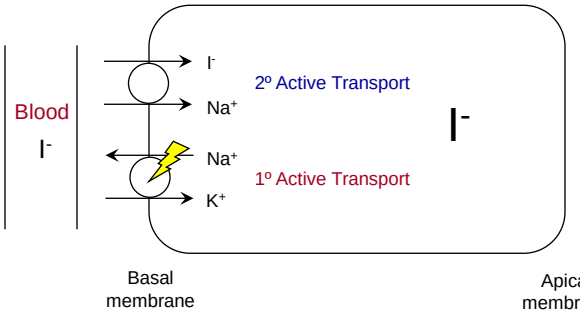
Goiter

Iodized salt…

Thyroid Hormone – Synthesis:

$[iodide]_{cell}$ 20x – 40x greater than $[iodide]_{plasma}$

Step 1: Accumulation of inorganic iodide (follicular cells):



Goitrogens:

Chemicals that block iodine uptake by the thyroid

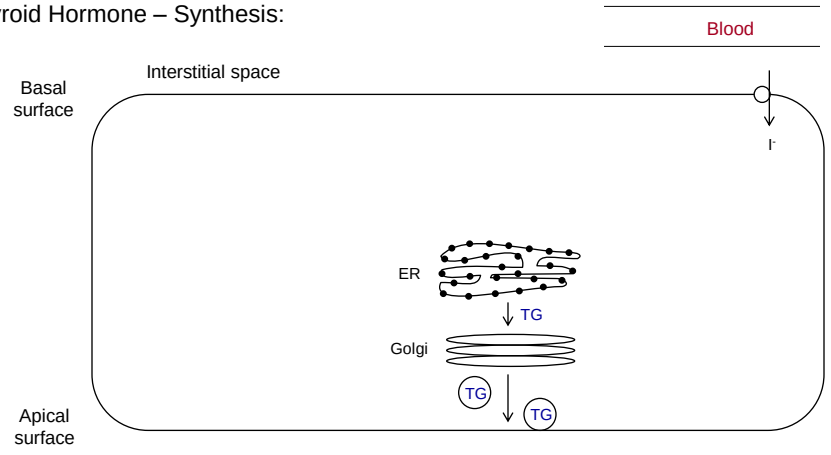
- Percholate ion (ClO_4^-)
- Thiocyanate (SCN^-)

} Competitive inhibitors

Dietary goitrogens exist:

Example:
Sweet potatoes
(cyanogenic glucosides)

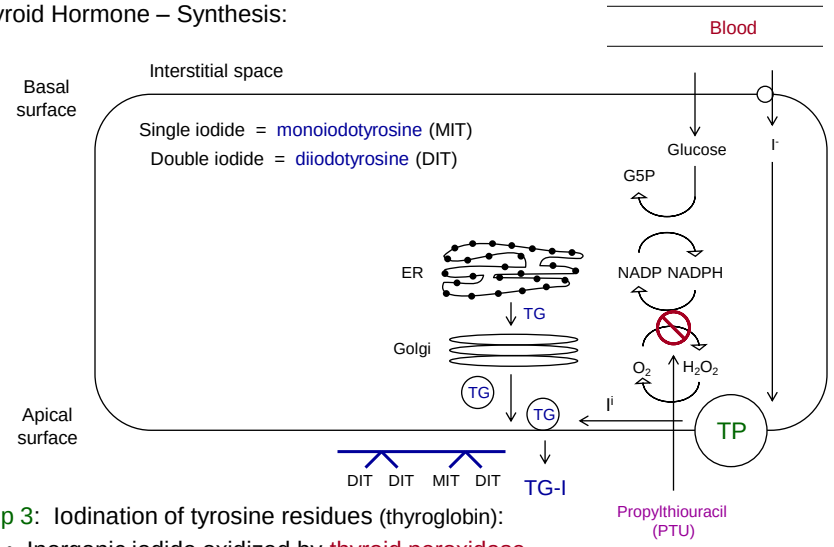
Thyroid Hormone – Synthesis:



Step 2: Synthesis of thyroglobin (TG):

- Glycoprotein (contains 4 – 8 tyrosine residues)
- Synthesized in rough ER; packaged in Golgi apparatus; stored as colloid

Thyroid Hormone – Synthesis:

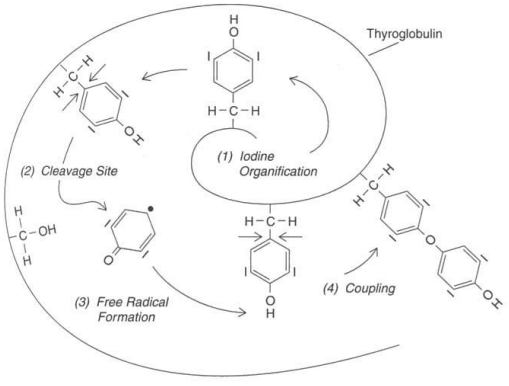


Step 3: Iodination of tyrosine residues (thyroglobin):

- Inorganic iodide oxidized by thyroid peroxidase
  - Requires hydrogen peroxide
  - Triggers iodination of tyrosine residues

Thyroid Hormone – Synthesis:

Only a fraction of tyrosine coupled (~ 10%)



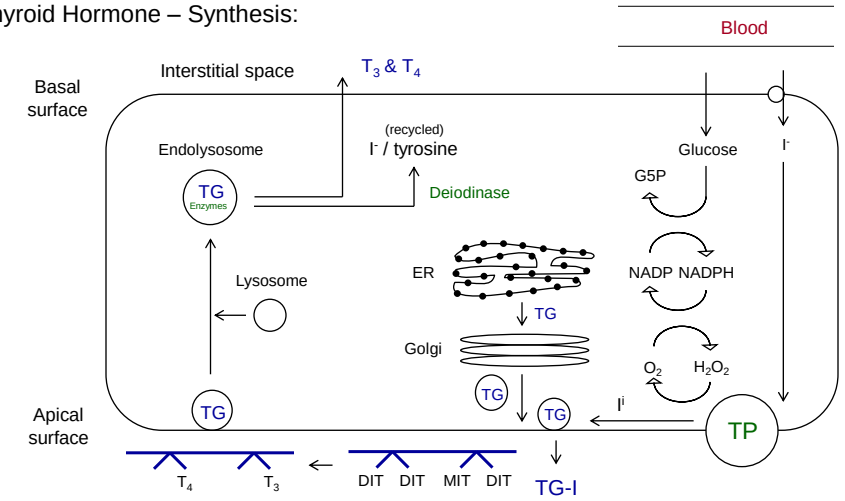
Step 4: Coupling of iodinated tyrosines

- Two iodinated tyrosines coupled together

  DIT + MIT = triiodothyronine; DIT + DIT = tetraiodothyronine

- Much more T_4 than T_3 synthesized (10x)

Thyroid Hormone – Synthesis:



Step 5: Hydrolysis of thyroglobin (releases hormone)

- Colloid engulfed to form endosome (endocytosis)
  - Endosome + lysosome (hydrolytic enzymes) = endolysosome
- T_3 / T_4 released into blood (passive transport)

T_3 / T_4 somewhat hydrophobic (↓ solubility)

Thyroid Hormone – Transport:

- Majority of circulating thyroid hormones bound to carrier proteins:

Thyroxine-binding globulin (~ 75%)

- Single polypeptide chain

Transthyretin (~ 20%)

- 4 polypeptide chains (2 binding sites)

Albumin (~ 5%)

- Single polypeptide chain

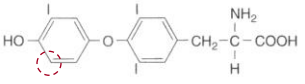
- Carrier proteins synthesized by liver
  - Protect hormones from clearance
    - Provide reservoir (T_4 half-life = 7 days)
  - Higher affinity for T_4

Thyroid Hormone – Activation:

T_3 is the more active form of thyroid hormone at the tissues

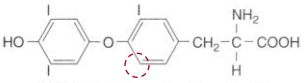
Remember: 10x more T_4 than T_3 in circulation

- Conversion occurs at tissue level:



3,5,3′-Triiodothyronine (T_3)

  A) ~ 45% of T_4 converted to T_3 (5'-iodinase)
    - Biologically active; lost via kidney after sulfur conjugation

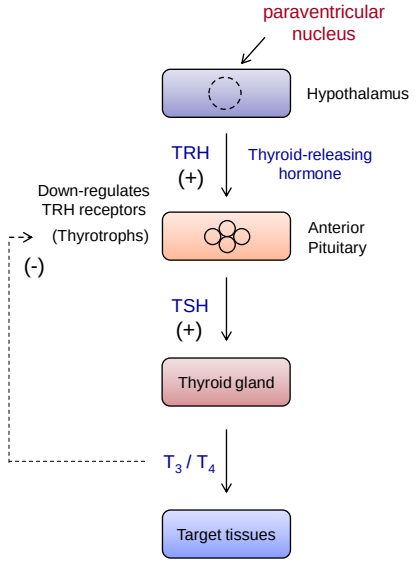


3,3′,5′-Triiodothyronine (Reverse-T_3)

  B) ~ 55% of T_4 converted to rT_3 (reverse T_3; 5'-iodinase)
    - Biologically inactive; lost rapidly via kidney

➢ During starvation, 5'-iodinase inhibited, thus lowering O_2 consumption and metabolic rate (brain 5'-iodinase not affected…)

Thyroid Hormone – Regulation:



TSH stimulates release of T_3 / T_4:

- ↑ iodide uptake
- ↑ synthesis of thyroglobulin
- ↑ endocytosis / hydrolysis of thyroglobulin

Mechanism of action = G-protein / cAMP pathway

Additional Stimulatory Factors	Additional Inhibitory Factors
Thyroid-stimulating immunoglobulins	I^- excess (Wolff-Chaikoff effect)

Thyroid Hormone – Action:

T_3 binds to intracellular receptor (nuclear)

Thyroid hormone (T_3)

Increases basal metabolic rate (BMR)

- ↑ Na^+/K^+ ATPase activity
  (↑ O^2 consumption)
  (↑ heat production)

Increases cardiac output

- ↑ heart rate
- ↑ stroke volume

(triggers synthesis of β_1-adrenergic receptors)

Promotes CNS maturation

(Newborn Hypothyroid Test)

Increases energy substrates

Synthesis of key metabolic enzymes

- ↑ glucose absorption
- ↑ glucogenolysis
- ↑ gluconeogenesis
- ↑ lipolysis
- ↑ proteolysis

Promotes growth

- ↑ bone formation
- ↑ bone maturation

(works in synergy with GH and somatomedins)

"Fountain of Youth"

Food restriction = ↓ thyroid hormones = longer life

Thyroid Hormone:

Pathophysiology:

First characterized endocrine disorder (~ 1850)

Cretinism

Hypothyroidism

(insufficient thyroid hormones)

Symptom(s):
- ↓ basal metabolic rate
- Weight gain / lethargy
- ↓ heat production (cold sensitivity)
- Decreased cardiac output
- Myxedema
- Growth / mental retardation (perinatal)

Cause(s):
- Thyroiditis (autoimmune)
- Hypothalamic / pituitary failure
- I^- deficiency
- Congenital (e.g., genetic)

Treatment(s):
- Hormone replacement therapy

Hyperthyroidism

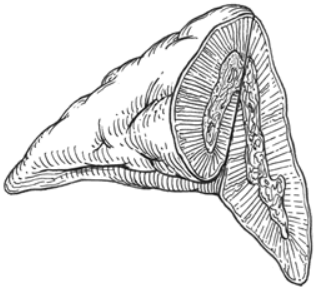
(excess thyroid hormones)

Symptom(s):
- ↑ basal metabolic rate
- Weight loss / excitability
- ↑ heat production (prolific sweating)
- Increased cardiac output
- Exophthalmos
- Goiter

↑ thyroid-stimulating immunoglobulins

Cause(s):
- Graves' disease
- Thyroid neoplasm (e.g., tumor)
- Hypothalamic / pituitary failure

Treatment(s):
- Drug administration (e.g., propylthiouracil)
- Thyroidectomy
- Radioactive ablation ($^{131}I^-$)



Adrenal gland

Marieb & Hoehn – Figure 16.13

Adrenal Gland Anatomy:

- 2 glands; located superiorly to each kidney
- Two disparate regions:

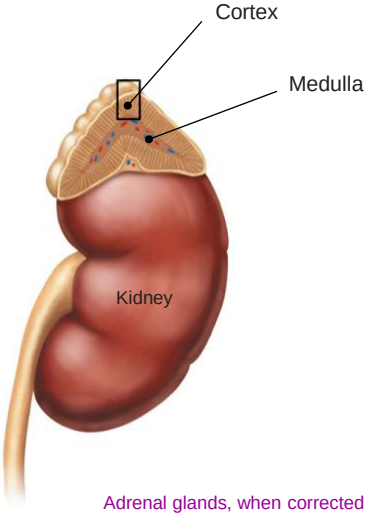
covered last term…

Adrenal medulla

- Inner zone (20% of tissue)
- Neuroectodermal origin (neural crest)
- Release catecholamines (epinephrine / norepinephrine)

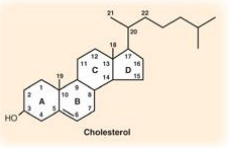
Adrenal cortex

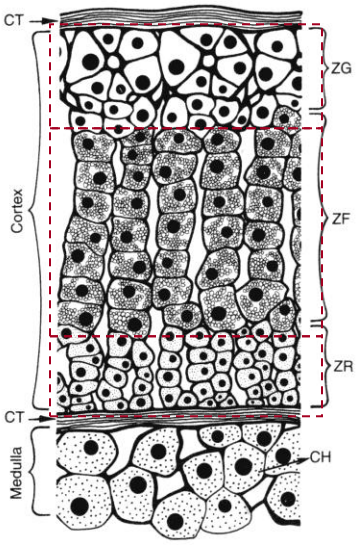
- Outer zone (80% of tissue)
- Derived from mesoderm (mesenchyme)
- Release steroid hormones



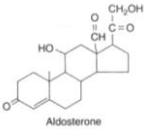
Adrenal glands, when corrected for weight, receive the highest blood flow of any organ in the human body

Adrenal Hormones:

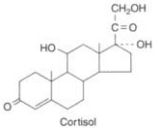




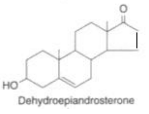
A) Zona glomerulosa
- Outermost layer; organized into whorls
- Synthesizes mineralcorticoids



B) Zona fasciculata
- Middle layer; organized into cords
- Synthesizes glucocorticoids



C) Zona reticularis
- Innermost layer; many reticular fibers
- Synthesizes androgens



Adrenal Hormones – Synthesis:

Step 1:
Uptake of cholesterol (plasma)
- Enters via LDL complexes
(LDL = low-density lipoproteins)

Step 2:
Synthesis of pregnenolone
- Occurs in mitochondria

Step 3:
Synthesis of various hormones

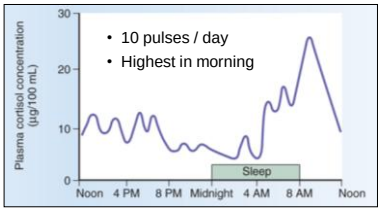
Blood
Cholesterol
adrenocortical cell
cholesterol desmolase (rate limiting step)
Pregnenolone

zona glomerulosa	zona fasciculata	zona reticularis
3β-hydroxysteroid dehydrogenase	17α-hydroxlase	17α-hydroxlase
Progesterone	17-hydroxypregnenolone	17-hydroxypregnenolone
21β-hydroxlase	3β-hydroxysteroid dehydrogenase	17,20-lyase
11 Deoxycorticosterone	17-hydroxyprogesterone	Dehydroepiandrosterone
11β-hydroxlase	21β-hydroxlase	3β-hydroxysteroid dehydrogenase
Corticosterone	11 Deoxycortisol	Androstenedione
aldosterone synthase	11β-hydroxlase	
Aldosterone	Cortisol	Lack of enzymes in various zones equates to different products

Adrenal Hormones – Regulation:

Cortisol / Adrenal androgens:

- Display diurnal pattern that is pulsatile

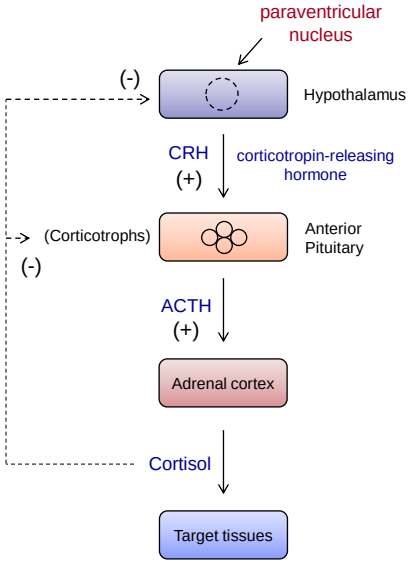


ACTH secretion drives pattern:

- ↑ cholesterol uptake by mitochondria
- ↑ cholesterol desmolase activity

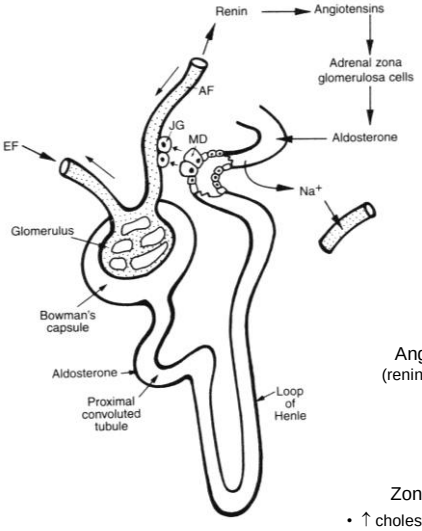
Mechanism of action = G-protein / cAMP pathway

Additional Stimulatory Factors	Additional Inhibitory Factors
Sleep-wake transition	Opiods
Stress	Somatostatins
ADH	



Adrenal Hormones – Regulation:

↑ [K+] in interstitial fluid directly stimulates aldosterone release



Aldosterone:

- Renin-angiotensin system (RAS) regulates release

Triggers:

1) Kidneys measure blood pressure
   - Juxtaglomerular cells (JG cells)
   - ↓ pressure = renin
2) Kidneys measure [Na^+] in filtrate
   - Macula densa cells
   - ↓ [Na+] = renin release

Angiotensinogen (renin substrate – liver) → (Renin) → Angiotensin I → (Angiotension – converting enzyme (ACE)) → Angiotensin II (2 min. half-life) → Zona glomerulosa

- ↑ cholesterol demolase activity
- ↑ aldosterone synthase activity

} G-protein / IP_3 & DAG pathway

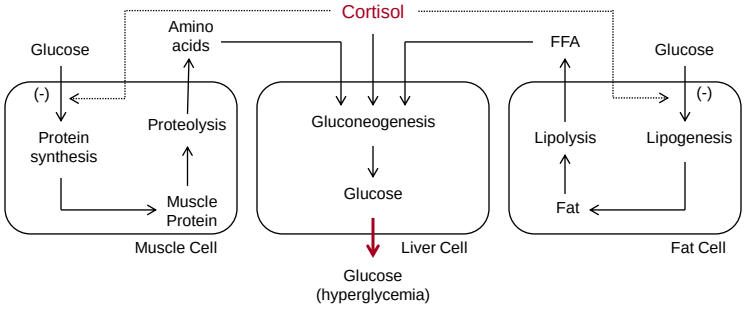
Adrenal Hormones – Action:

Adrenocortical steroids binds to Intracellular receptor

Cortisol

Stimulation of gluconeogenesis

Diabetogenic Activity
(anti-insulin effects)



Endocrine System

Adrenal Hormones – Action:

Adrenocortical steroids binds to Intracellular receptor

Cortisol

Stimulation of gluconeogenesis

Diabetogenic Activity
(anti-insulin effects)

Maintenance of vascular responsiveness

(triggers up-regulation of β_1-adrenergic receptors)

Manipulation of sleep cycles

- ↓ REM sleep
- ↑ awake time

Recall:
Largest bursts of cortisol just before waking

Suppression of Inflammation / immune response

- ↑ lipocortin synthesis
  (inhibits prostaglandin production)
- ↓ proliferation of T lymphocytes
- ↓ release of histamine

Inhibition of bone formation

- ↓ collagen synthesis
- ↓ osteoblast production
- ↓ intestinal Ca^{2+} absorption

Immunosuppressive drugs

Adrenal Hormones – Action:

Adrenocortical steroids binds to Intracellular receptor

Aldosterone

↓

- ↑ Na^+ reabsorption
- ↑ K^+ secretion
- ↑ H^+ secretion

} Kidney

Interestingly, aldosterone receptors in the kidney also have high affinity for cortisol – Potential problem?

YES – but…

11 β–hydroxysteroid dehydrogenase

cortisol → cortizone

cortisol: high receptor affinity

found in [high] In renal tissue

cortizone: low receptor affinity

Androgens

♂ = limited function

♀ = major androgen

↓

- development of pubic / axillary hair
- libido (sex drive)

Adrenal Hormones:

Pathophysiology:

Cushing's Syndrome

(Excess glucocorticoids; adrenal hyperplasia)

Addison's Disease

(Primary adrenocortical insufficiency)

Symptom(s): Hypoglycemia (corticosteroids)
Weight loss / weakness

Hyperkalemia (mineralocorticoids)
Metabolic acidosis
Hypotension

Loss of sex drive (androgens)
Decreased pubic / axillary hair

Hyperpigmentation:
↑ circulating ACTH

Cause(s): Adrenal cortex destruction (autoimmune)

Treatment(s): Hormone replacement therapy

Cushing's Disease

(Enhanced secretion of ACTH)

Symptom(s): Hyperglycemia
Central obesity / round face
Buffalo hump
Muscle wasting
Osteoporosis
Hypertension
Virilization(women)

Cause(s): Pituitary adenoma (tumor)

Treatment(s): Tumor removal

Adrenal Hormones:

Pathophysiology:

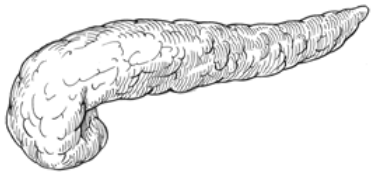
Conn's Disease

(Primary hyperaldosteronism)

Symptom(s): Increased ECF volume
Hypertension
Hypokalemia
Metabolic alkalosis

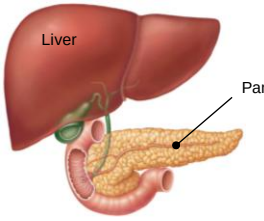
Cause(s): Adrenal hyperplasia

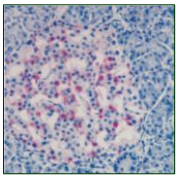
Treatment(s): Aldosterone antagonists
Tumor removal (surgery)



Pancreatic Hormones

Pancreas Anatomy:



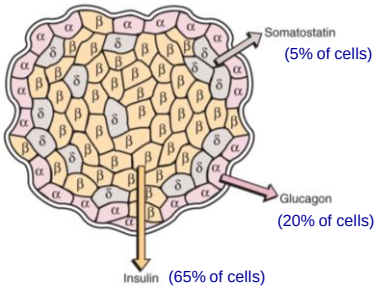


Embryonic origin:
Pancreatic duct (endoderm)

Endocrine cells clustered in
pancreatic islets (islets of Langerhans)

Both exocrine and endocrine function:

Exocrine = Digestive enzymes
Endocrine = blood glucose regulation



Pancreatic islets composed of:

α-cells: Periphery of islets; produce glucagon
β-cells: Center of islets; produce insulin
D-cells: Scattered; Produce somatostatin (SST)

Marieb & Hoehn (Human Anatomy and Physiology, 8th ed.)– Figure 16.13

Costanzo (Physiololgy, 4th ed.) – Figure 9.26

First hormone to:

1) Be isolated from animal source for therapy
2) Have protein structure determined
3) Have mechanism of action determined

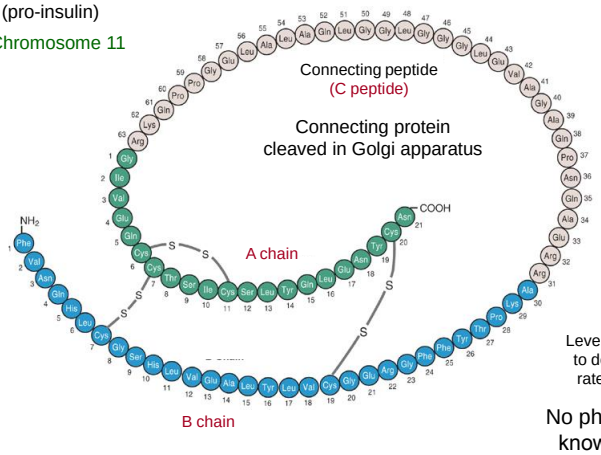
Pancreatic Hormones:

A. Insulin:

- Polypeptide; 2 chains (A = 21 a.a.; B = 30 a.a.) connected via two disulfide bonds

Synthesized from single chain (pro-insulin)

Gene = Chromosome 11



However:
Levels measured medically to determine endogenous rate of insulin production

No physiological function known for C peptide…

Costanzo (Physiology, 4th ed.) – Figure 9.27

Endocrine System

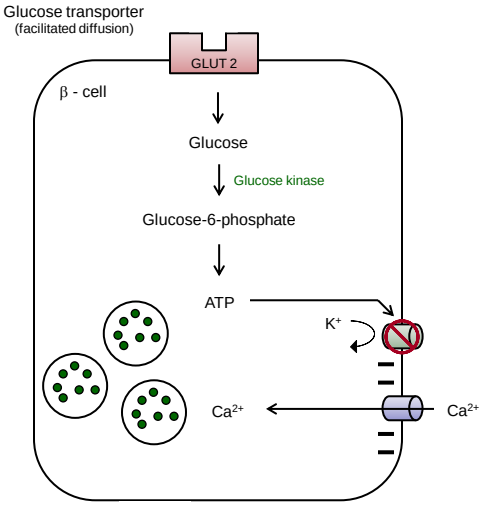
Pancreatic Hormones:

A. Insulin:

G

Additional Stimulatory Factors	Additional Inhibitory Factors
Increased [a.a.]	Fasting
Increased [fatty acids]	Exercise
Cortisol	Somatostatins

Regulation:



Glucose levels in blood most important regulator of insulin secretion:

1) Glucose transported into β cells
2) Glucose metabolized to produce ATP (substrate level phosphorylization)
3) ATP closes ATP-sensitive K^+ channels
   - Depolarizes membrane
4) Depolarization opens voltage-gated Ca^{2+} channels
5) Increased intracellular Ca^{2+} levels triggers insulin secretion

Endocrine System

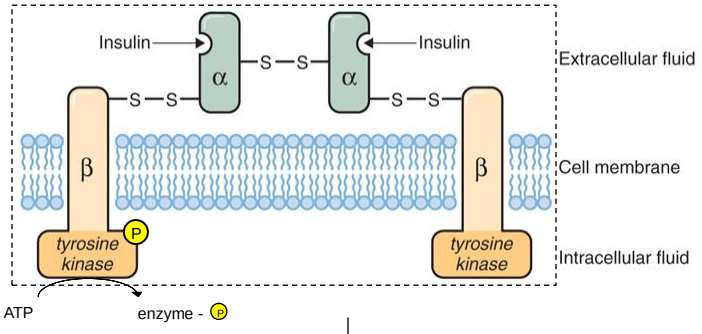
Pancreatic Hormones:

A. Insulin:

Insulin receptor:
Tetramer; composed of 2 α subunits and 2 β subunits

Mechanism of Action:

① Insulin binds to α subunits; triggers conformational change



② Tyrosine kinase autophosphorylates; phosphorylates intracellular enzymes / proteins

(endocytosis)

③ Insulin-receptor complex internalized; either degraded, stored, or recycled

Costanzo (Physiology, 4th ed.) – Figure 9.29

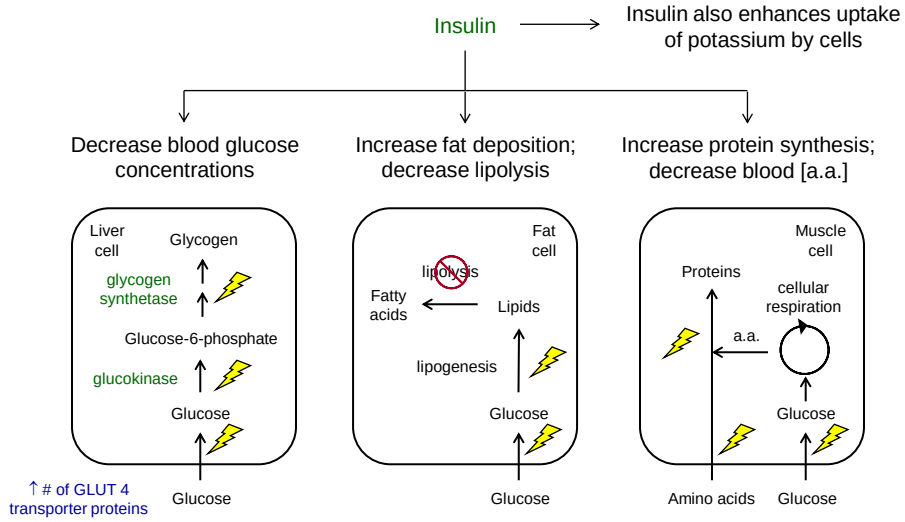
Pancreatic Hormones:

A. Insulin:

'Hormone of Abundance'

Ensures that excess nutrients are stored for future use

Actions on Target Tissues:



Pancreatic Hormones:

A. Insulin:

Diabetes mellitus

'a sweet passer through'

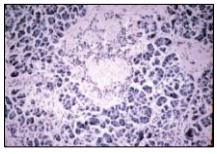
Pathophysiology:

Symptom(s)	Cause of symptom
• Increased blood concentrations of glucose, amino acids, and fatty acids	• Decreased glucose and amino acid uptake by cells; increased lipolysis of fats
• Metabolic ketoacidosis ('fruity' breath)	• Increased conversion of fatty acids to ketoacids
• Increased urine output and thirst	• Increased glucose load in kidney filtrate
• Hyperkalemia	• Increase in K^+ exiting cells

Biguanide drugs

Type I:

(insulin-dependent; juvenile-onset)



Cause:

Decrease in # of β-cells

(autoimmune)

Treatment:

Insulin replacement therapy

Type II:

(non-insulin-dependent; adult-onset)

Cause:

Down-regulation of insulin receptors

(target cells)

Treatment:

Caloric restriction / weight reduction

Pancreatic Hormones:

A. Insulin:

Diabetes mellitus

'a sweet passer through'

Pathophysiology:

Obesity linked with Type II diabetes:

Over-eating
(adulthood)

↓

Normal # fat cells; increased size → Reduced # of insulin receptors → ↑ insulin → Cellular desensitization to insulin

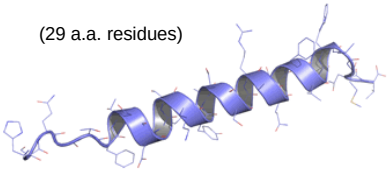
Word of warning:

Pancreatic Hormones:

B. Glucagon:

- Single chain polypeptide

(29 a.a. residues)



Regulation:

- Decreased blood glucose levels stimulate secretion

Additional Stimulatory Factors	Additional Inhibitory Factors
Increased [a.a.]	Insulin
Cholecystokinin (CCK)	Somatostatins
↑	
Digestive hormone	

'Hormone of Starvation'

Promotes mobilization and utilization of stored nutrients

Actions on Target Tissues:

Glucagon

↓

Increase blood glucose concentrations
- Stimulates glycogenolysis
- Stimulates gluconeogenesis

(targets liver cells)

Increase blood fatty acid concentrations
- Stimulates lipolysis

← Fatty acids used as substrate for gloconeogenesis

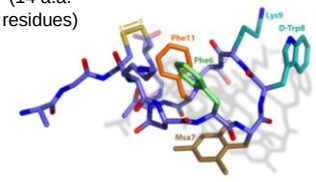
Mechanism of action = G-protein / cAMP pathway

Pancreatic Hormones:

C. Somatostatin:

- Single chain polypeptide

(14 a.a. residues)



Regulation:

- Increased blood levels of all nutrient forms stimulate secretion

Additional Stimulatory Factors	Additional Inhibitory Factors
Glucagon	Insulin

'Hormone of Moderation'

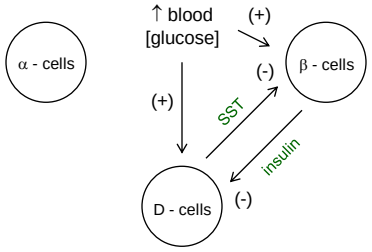
Regulates the responses of insulin and glucagon to ingestion of food

Actions on Target Tissues:

Somatostatin

↓

Decrease insulin secretion



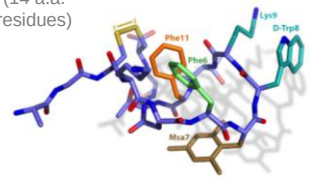
Endocrine System

Pancreatic Hormones:

C. Somatostatin:

- Single chain polypeptide

(14 a.a. residues)



Regulation:

- Increased blood levels of all nutrient forms stimulate secretion

Additional Stimulatory Factors	Additional Inhibitory Factors
Glucagon	Insulin

'Hormone of Moderation'

Regulates the responses of insulin and glucagon to ingestion of food

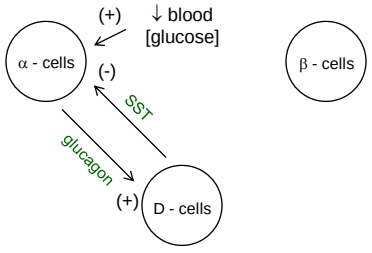
Actions on Target Tissues:

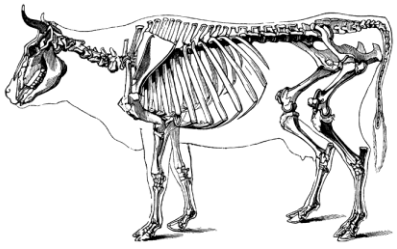
Somatostatin

↓

Decrease insulin secretion

Decrease glucagon secretion



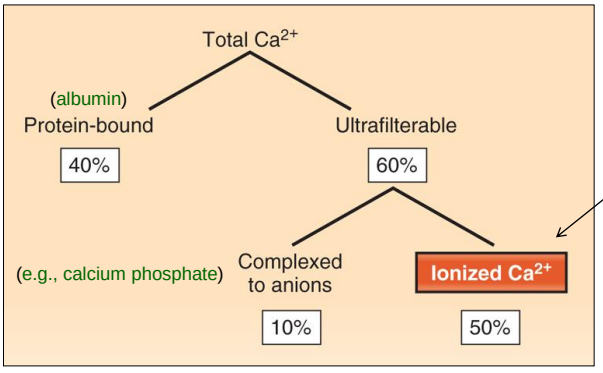


Calcium Regulation

Costanzo (Physiololgy, 4th ed.) – Figure 9.32

Forms of Ca^{2+} in Blood:

Key element in numerous physiological functions



Hypocalcemia:

Decrease in plasma $[Ca^{2+}]$

- Hyper-reflexia
- Spontaneous twitching
- Muscle cramps
- Tingling / numbness

Lowers threshold potential

Chvostek sign

Hypercalcemia:

Increase in plasma $[Ca^{2+}]$

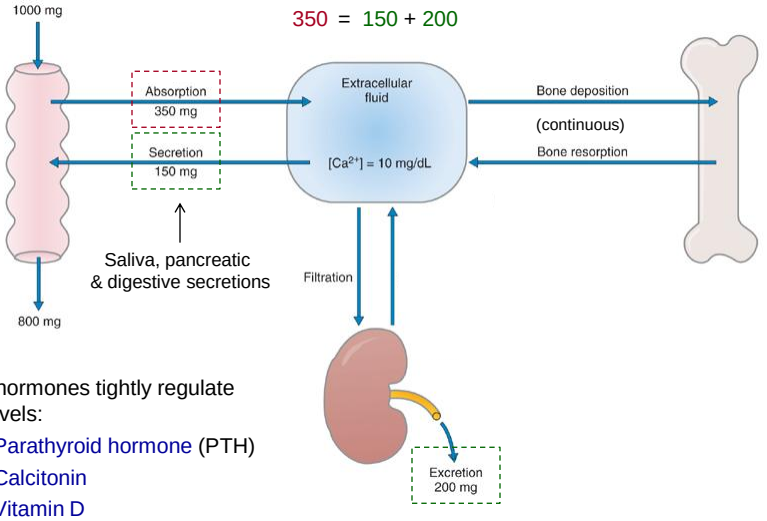
- Constipation
- Polyuria / polydipsia
- Hyporeflexia
- Lethargy / coma

Costanzo (Physiololgy, 4th ed.) – Figure 9.34

Overall Ca^{2+} Homeostasis:

Individual in Ca^{2+} balance:

350 = 150 + 200



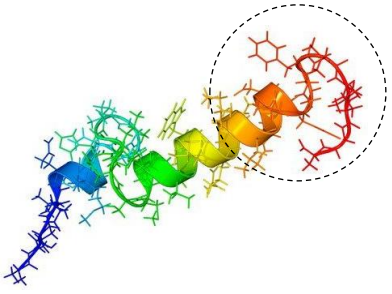
Three hormones tightly regulate Ca^{2+} levels:

1) Parathyroid hormone (PTH)
2) Calcitonin
3) Vitamin D

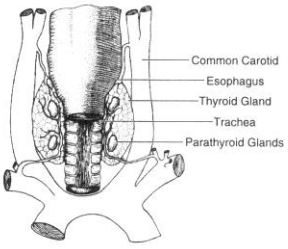
Calcium Regulation Hormones:

A. Parathyroid hormone:

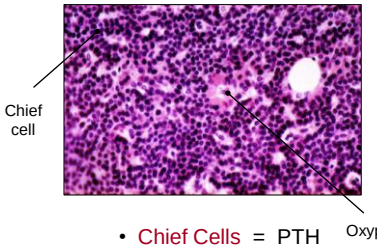
- Produced by parathyroid glands
- Single chain polypeptide (84 a.a. residues)



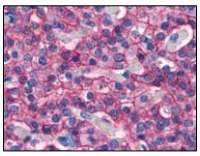
- ProPTH modified to active hormone in Golgi apparatus (6 a.a. removed)
- Biologic activity resides entirely in the N-terminal 34 amino acids



Small glands (~ 4) embedded on dorsal surface of thyroid gland



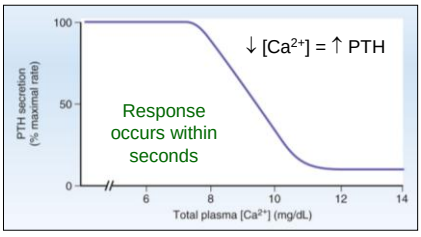
- Chief Cells = PTH
- Oxyphils = ?



Calcium Regulation Hormones:

A. Parathyroid hormone:

Regulation:

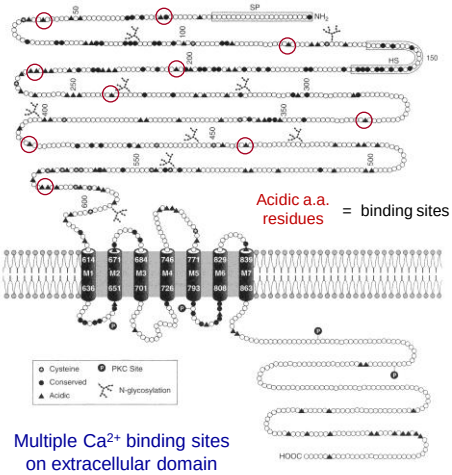


- Influenced directly by plasma [Ca^{2+}]

Activation of Ca^{2+} sensing receptors triggers G protein / IP_3 & DAG; shuts down PTH secretion

- Mg^{2+} triggers similar events

Ca^{2+} Sensing Receptors



Acidic a.a. residues = binding sites

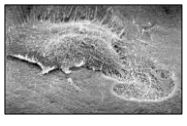
Multiple Ca^{2+} binding sites on extracellular domain

Costanzo (Physiololgy, 4th ed.) – Figure 9.34

Calcium Regulation Hormones:

Responsible for increase in plasma [Ca^{2+}]

A. Parathyroid hormone:



Actions on Target Tissues:

PTH

Increases bone resorption

PTH → Osteoblasts (bone marrow)

↓ Cytokines (e.g., IL-6)

↑ osteoclast activity / recruitment

↓

↑ resorption of bone

Increases Ca^{2+} reabsorption at kidney

&

Decreases PO_4^{3-} reabsorption at kidney

(phosphaturia)

Enhances Ca^{2+} resorption by lowering solubility constant ([Ca^{2+}] x [PO_4^{3-}]) at bone

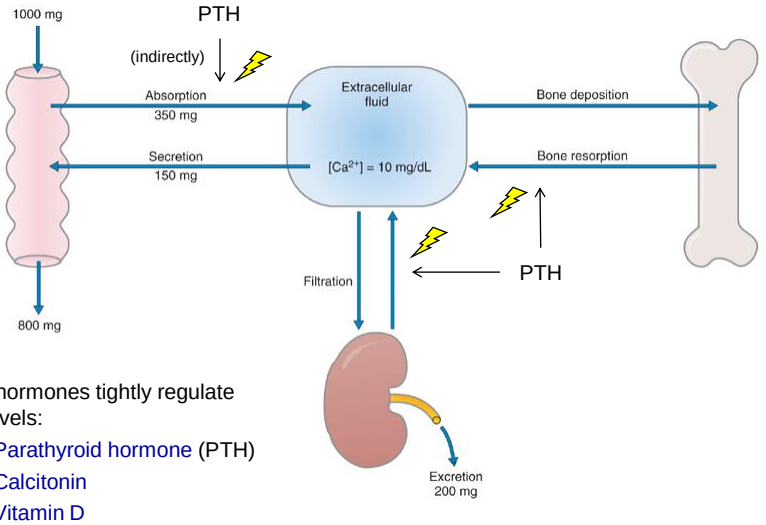
Increases Ca^{2+} absorption at small intestine

(indirect action; activates vitamin D production)

Mechanism of action = G-protein / cAMP pathway

Costanzo (Physiololgy, 4th ed.) – Figure 9.34

Overall Ca^{2+} Homeostasis:



Three hormones tightly regulate Ca^{2+} levels:

1) Parathyroid hormone (PTH)
2) Calcitonin
3) Vitamin D

Calcium Regulation Hormones:

A. Parathyroid hormone:

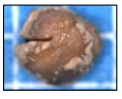
Humoral Hypercalcemia of Malignancy:

Tumors secrete PTH-related peptide; homologous with PTH

Pathophysiology:

Hyperparathyroidism

Symptoms:



- Hypercalcemia
  - ↑ bone resorption
  - ↑ kidney Ca^{2+} reabsorption
  - ↑ intestinal Ca^{2+} absorption
- Hypophosphatemia
  - ↓ kidney PO_4^{3-} reabsorption

Cause:

- Parathyroid adenoma (primary)
- Renal failure (secondary)

Treatment:

- Surgery (primary hyperparathyroidism)

Hypoparathyroidism

Symptoms:

- Hypocalcemia
  - ↓ bone resorption
  - ↓ kidney Ca^{2+} reabsorption
  - ↓ intestinal Ca^{2+} absorption
- Hyperphosphatemia
  - ↑ kidney PO_4^{3-} reabsorption

Cause:

- Thyroid surgery (cancers, etc.)
- Autoimmune / congenital

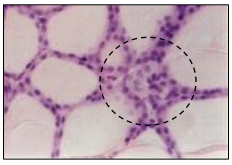
Treatment:

- Ca^{2+} / Vitamin D supplements

Calcium Regulation Hormones:

B. Calcitonin:

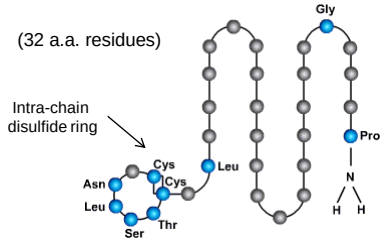
Produced by parafollicular cells (C cells) of thyroid gland



- Single chain peptide

(32 a.a. residues)

Intra-chain disulfide ring



Regulation:

- Increased plasma [Ca^{2+}] stimulates secretion
- Utilize calcium sensing receptors

Overall, physiological role uncertain; changes in levels do not trigger derangement Ca^{2+} metabolism

Actions on Target Tissues:

Calcitonin

↓

Decreases bone resorption

Calcitonin ⊘ Osteoclast activity / recruitment

↓

↓ resorption of bone

Mechanism of action = G-protein / cAMP pathway

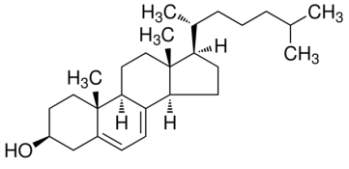
Calcium Regulation Hormones:

C. Vitamin D:

Vitamin:
An organic compound that must be obtained from the diet.

Diet →

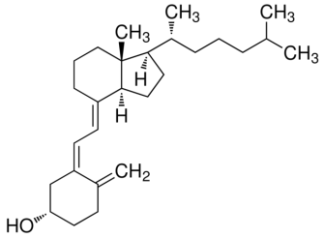
Precursor to cholesterol



7 - Dehydrocholesterol

↓ Photolysis

Diet →



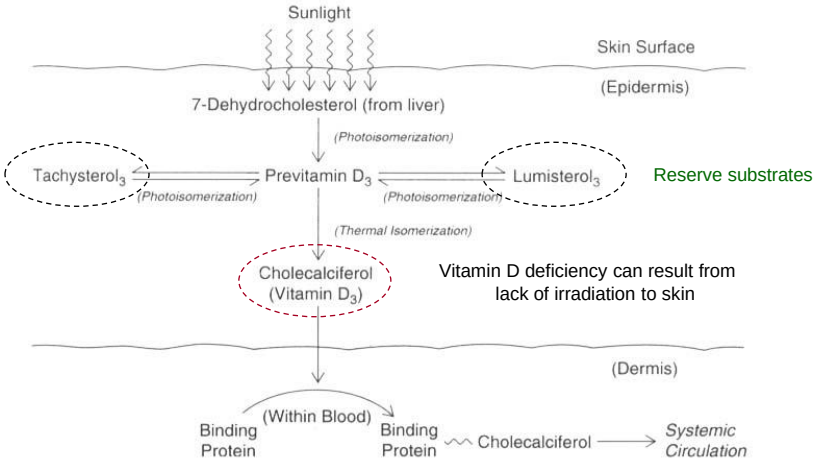
Cholecalciferol
(Vitamin D_3)

Calcium Regulation Hormones:

Irradiated food = adequate amount of vitamin (developed countries)

C. Vitamin D:

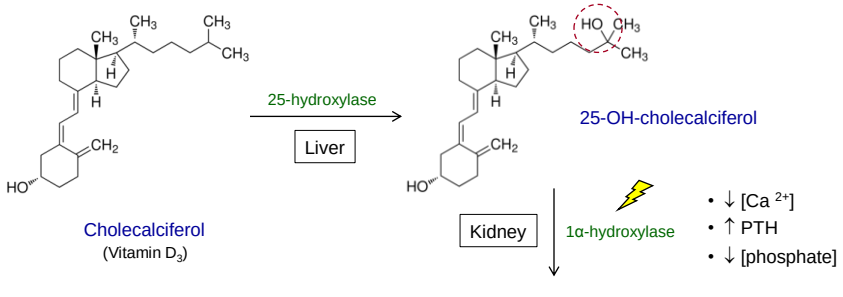
- Derived in skin of humans by action of ultraviolet light:



Calcium Regulation Hormones:

C. Vitamin D:

- Additional modifications necessary for activation of Vitamin D



Regulation:

- Regulation of Vitamin D synthesis occurs at the level of the kidney

Endocrine System

Calcium Regulation Hormones:

C. Vitamin D:

(steroid hormone)

Responsible for increase in plasma [Ca^{2+}] & [PO_4^{3-}]

(associated with laying down new bone)

Actions on Target Tissues:

Vitamin D

Increases Ca^{2+} & PO_4^{3-} absorption at small intestine

- Induces synthesis of calbindin D-28 K

↑

Cytosolic transport protein
(4 Ca^{2+} / protein)

Increases Ca^{2+} & PO_4^{3-} absorption at kidneys

(Unique from PTH which decreases PO_4^{3-} reabsorption)

Increases bone resorption

- Works with PTH to stimulate osteoclast activity

???

Mineralized old bone is resorbed to provide Ca^{2+} and PO_4^{3-} for new bone

Mechanism of action = Internal Receptor System

Endocrine System

Calcium Regulation Hormones:

C. Vitamin D:

Vitamin D Resistance:

Kidney unable to produce active hormone

- Absence of 1α-hydroxylase
- Chronic renal failure

Pathophysiology:

Vitamin D deficiency

Rickets: (children)

Symptoms:

- Growth failure / skeletal deformities

Cause:

- Inadequate sunlight / diet

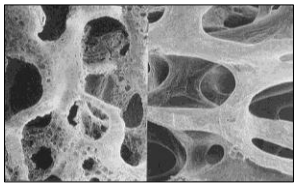
Treatment:

- Vitamin D supplements

(adults) Osteomalacia:

Symptoms:

- Softening of weight-bearing bones



Cause:

- Inadequate sunlight / diet

Treatment:

- Vitamin D supplements