MEDICINE 438's

ENDOCRINE PHYSIOLOGY

LECTURE III & IV: Anterior Pituitary Gland (Part I & II)

EDITING FILE

IMPORTANT | MALE SLIDES | EXTRA | FEMALE SLIDES | LECTURER'S NOTES

1 ANTERIOR PITUITARY GLAND

Lecture Three

OBJECTIVES

- **Anterior pituitary hormones (GH, Prolactin, TSH, FSH, LH, ACTH)**
- **Describe actions of Anterior Pituitary hormones**
- **Mechanism of action of hormones**
  - **Hormone receptors, down-regulation and up-regulation**
  - **Intracellular signaling**
  - **Second messenger mechanism**
- **Know conditions related to hypo or hyper secretion of Anterior Pituitary hormones**
- **Growth Hormone**
  - **Physiological functions**
  - **Regulation of GH secretion**
  - **Feedback mechanism**
  - **Factors controlling secretion**
- **Prolactin**
  - **Physiological functions**
  - **Regulation of prolactin secretion**

Stimuli for Hormonal Secretion

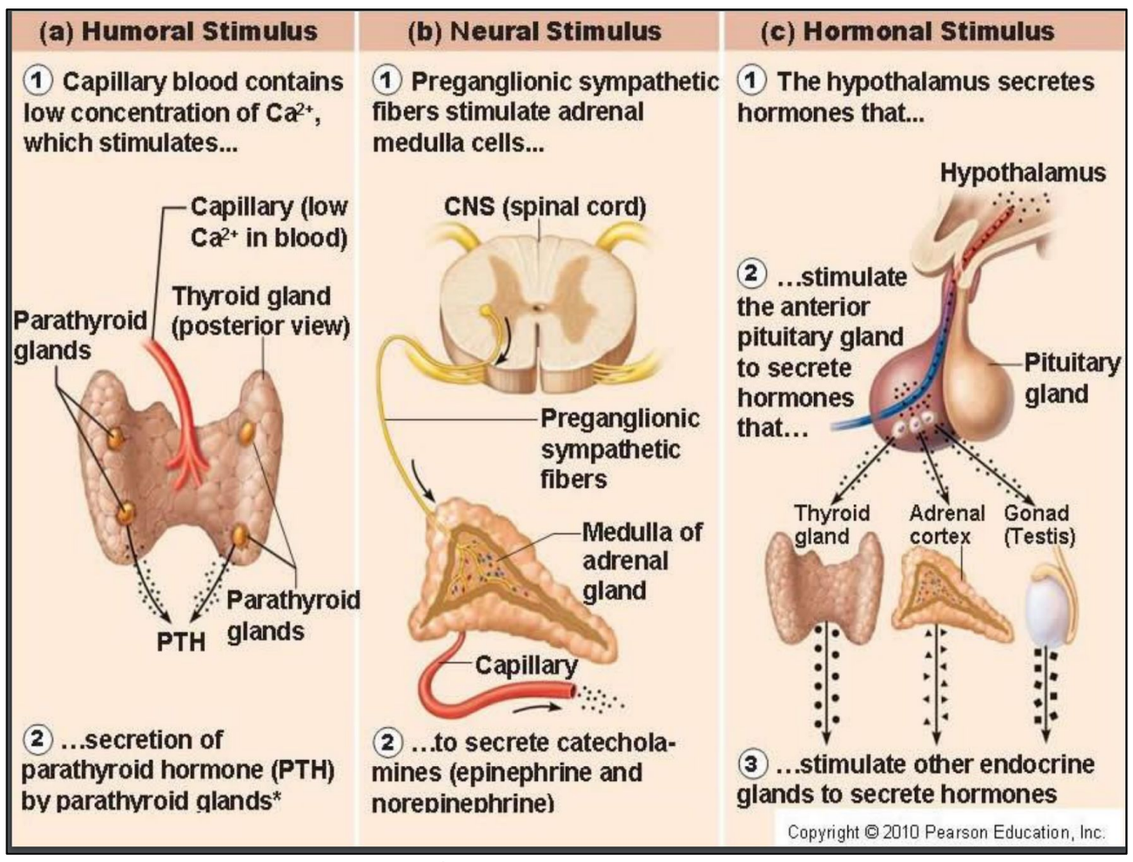


Figure 3-1

Anterior Pituitary Gland (Adenohypophysis)

- It is connected to hypothalamus by portal system: "hypothalamic-hypophysial portal vessels".

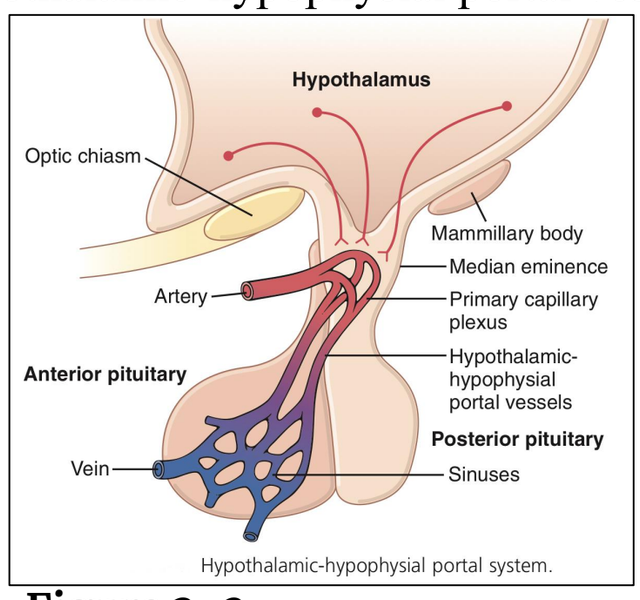


Figure 3-2

Anterior Pituitary Hormones

- Pituitary hormones are classified as peptide hormones.
- Six major hormones are secreted by the anterior lobe of the pituitary:

- **Growth hormone**[1]**:** promotes growth of the entire body by affecting protein formation, cell multiplication, and cell differentiation.
- **Prolactin:** promotes mammary gland development and milk production.
- **Adrenocorticotropin (corticotropin):** controls the secretion of some of the adrenocortical hormones, which affect metabolism of glucose, proteins, and fats.
- **Thyroid-stimulating hormone (thyrotropin):** controls the secretion rate of thyroxine and triiodothyronine by the thyroid gland.

Two separate gonadotropic hormones, control growth of the ovaries and testes, as well as their hormonal and reproductive activities:

- **Follicle-stimulating hormone**
- **Luteinizing hormone**

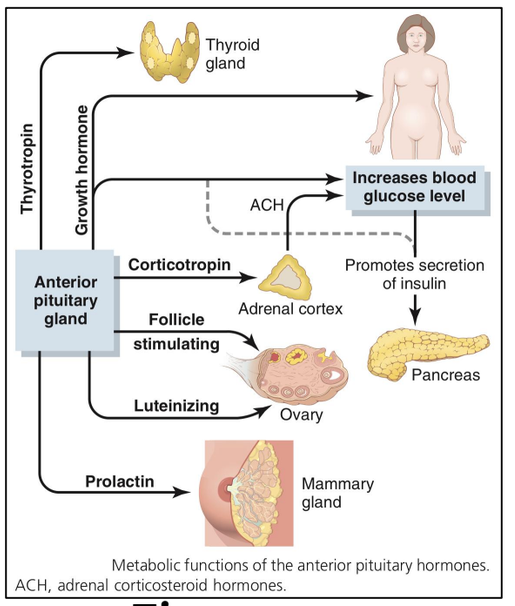


Figure 3-3

Growth Hormone (Somatotropic Hormone or Somatotropin)

- Synthesized and secreted by ***somatotrophs*** in the anterior pituitary.
- The synthesis of growth hormone is stimulated by GHRH & inhibited by Somatostatin (also known as somatotropin release–inhibiting factor [SRIF]).
- It is a small protein molecule that contains 191 amino acids.
- It has a molecular weight of 22,000.

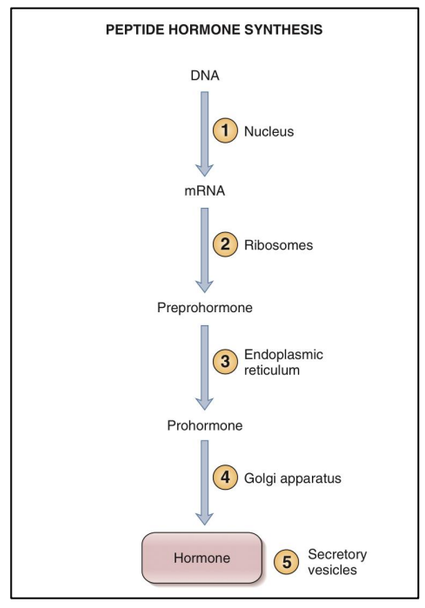


Figure 3-4 Steps involved in the synthesis of peptide hormones.

FOOTNOTES

1. All hormones secreted by the anterior pituitary glands function to act on other glands (e.g. prolactin on mammary gland), except GH, which acts directly on tissues.

Regulation of Growth Hormone Secretion

- **GHRH** → binds to a Gs-protein coupled receptor → activates either adenylyl cyclase or phospholipase C mechanisms → cAMP & IP3/Ca → secretion and synthesis of growth hormone.
- **Somatostatin** (SRIF) → binds to a Gi-protein coupled receptor → inhibits generation of cAMP → Decrease secretion.

Recall from the 1st lecture that peptide hormone exert their effect through 2nd messenger systems, which include:
(a) Adenylate Cyclase-cAMP mechanism, (b) Phospholipase C-IP3/DAG, (c) Tyrosine Kinase System.

- Remember that ***G proteins*** can be either stimulatory or inhibitory and are called, accordingly, ***Gs*** or ***Gi***. Stimulatory or inhibitory activity resides in the ***α*** subunit (α_s or α_i). Thus when ***GTP*** is bound to the α_s subunit of a G_s protein, the G_s protein stimulates the effector enzyme (e.g., ***adenylyl cyclase***). When ***GTP*** is bound to the α_i subunit of a G_i protein, the G_i protein inhibits the effector enzyme.

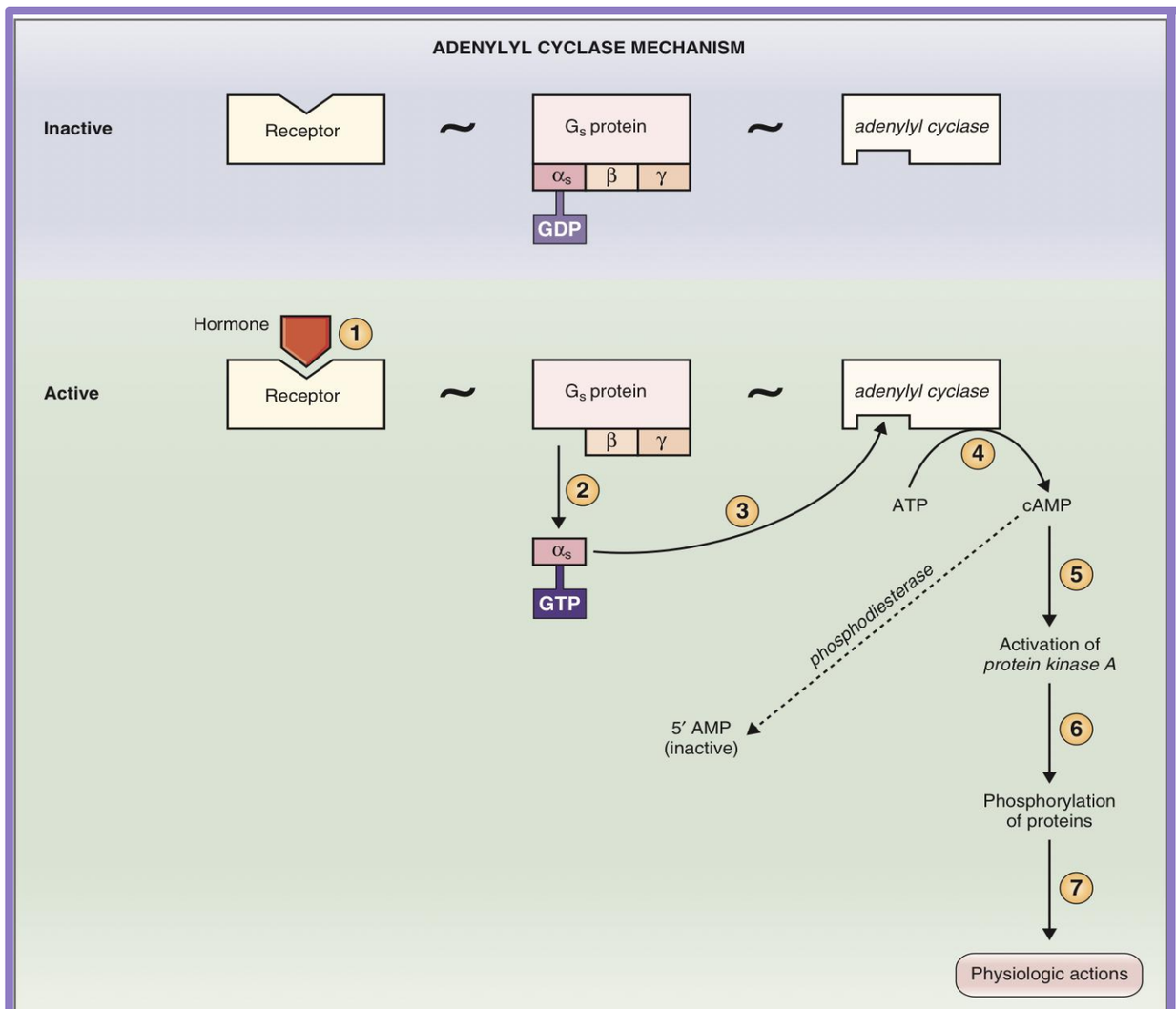


Figure 3-5 **Adenylyl Cyclase Mechanism:**
In this example, the hormone utilizes a ***Gs*** protein (rather than a ***Gi*** protein).
1. Hormone binds which produces two changes:
   - ***GDP*** is released from the α_s subunit and is replaced by ***GTP***
   - α_s subunit of ***Gs*** protein detaches
2. The α_s***-GTP*** complex activates ***adenylyl cyclase***.
   - Activated ***adenylyl cyclase*** converts ***ATP*** to ***cAMP*** (2nd messenger).
3. ***cAMP*** activates ***protein kinase A*** which phosphorylates intracellular proteins and produces the final physiologic actions.
4. Intracellular ***cAMP*** is degraded to an inactive metabolite (***5′AMP***), by the enzyme *phosphodiesterase*, thereby turning off the action of the second messenger.

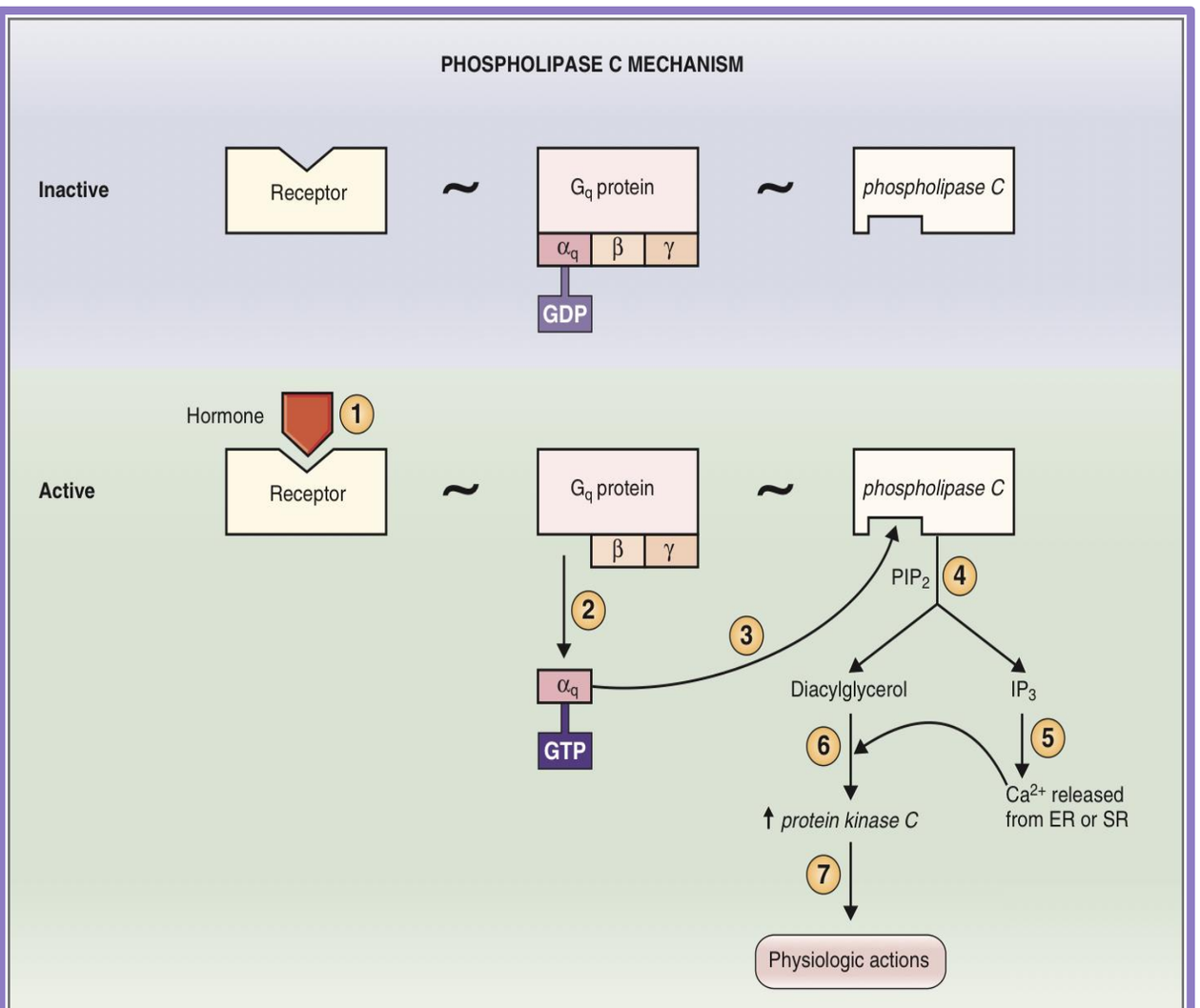


Figure 3-6 **Phospholipase C-IP3/DAG Mechanism:**
This mechanism involves utilizing a ***Gq*** protein.
1. Hormone binds which produces two changes:
   - ***GDP*** is released from the α_q subunit and is replaced by ***GTP***
   - α_q subunit of ***Gq*** protein detaches
2. The α_q***-GTP*** complex activates ***phospholipase C***.
   - Activated ***phospholipase C*** Cleaves (PIP_2) into ***DAG*** and IP_3
3. IP_3 releases calcium from mitochondria and sER. Calcium & DAG activate ***protein kinase C*** which phosphorylates intracellular proteins and produces the final physiologic actions.

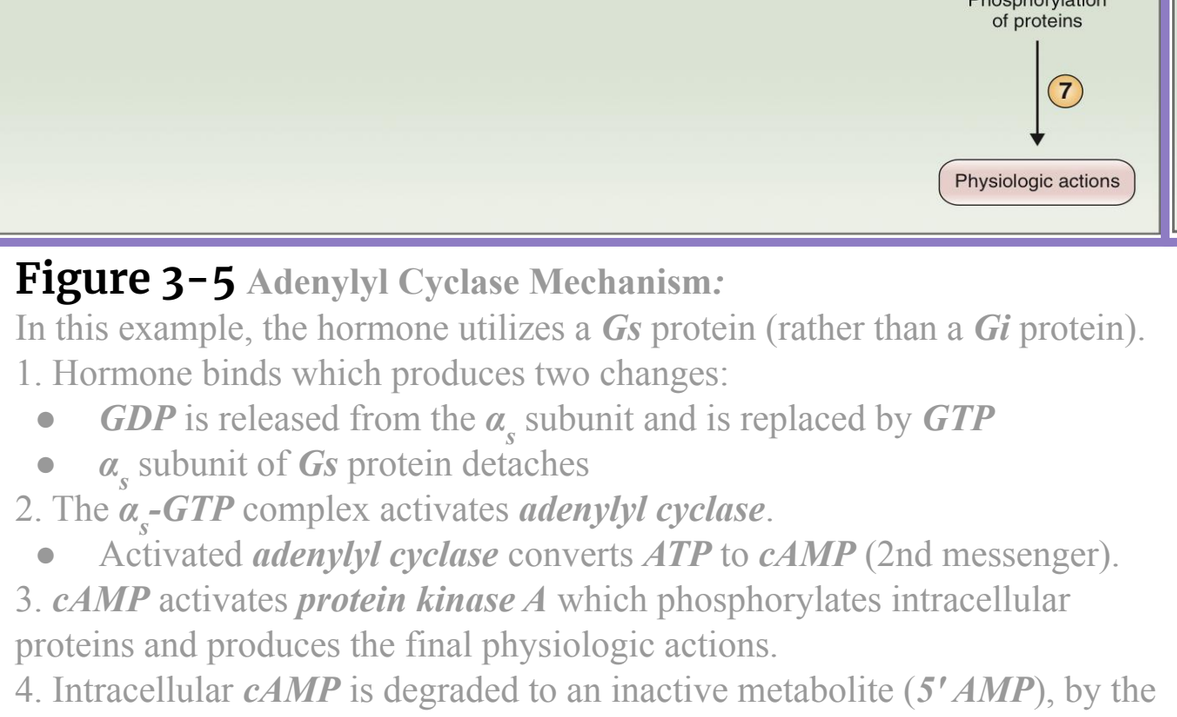


Figure 3-7 **Somatostatin** binds to its own membrane receptor, which is coupled to ***adenylyl cyclase*** by a ***Gi*** protein, inhibiting the generation of cAMP and decreasing growth hormone secretion.

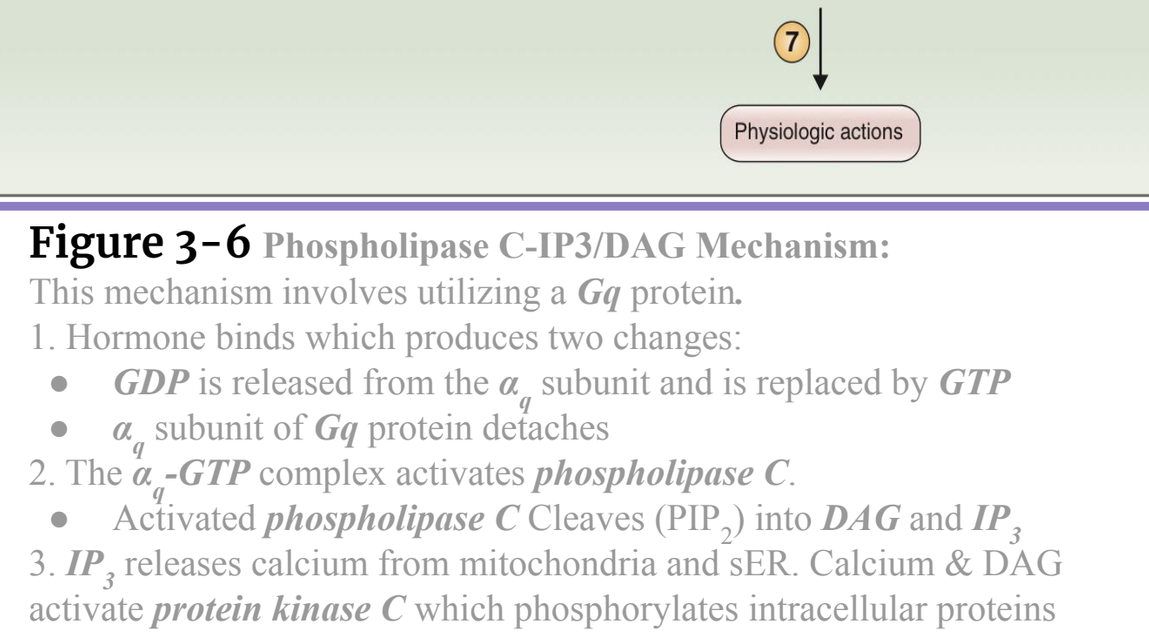
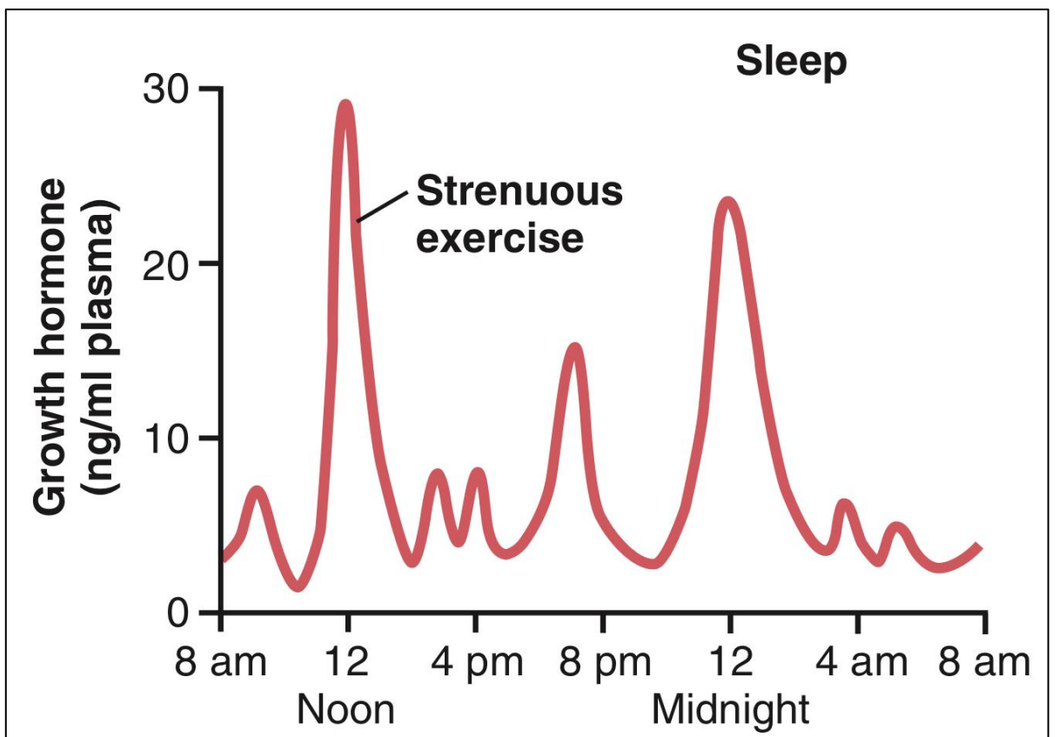


Figure 3-8 Regulation of growth hormone secretion

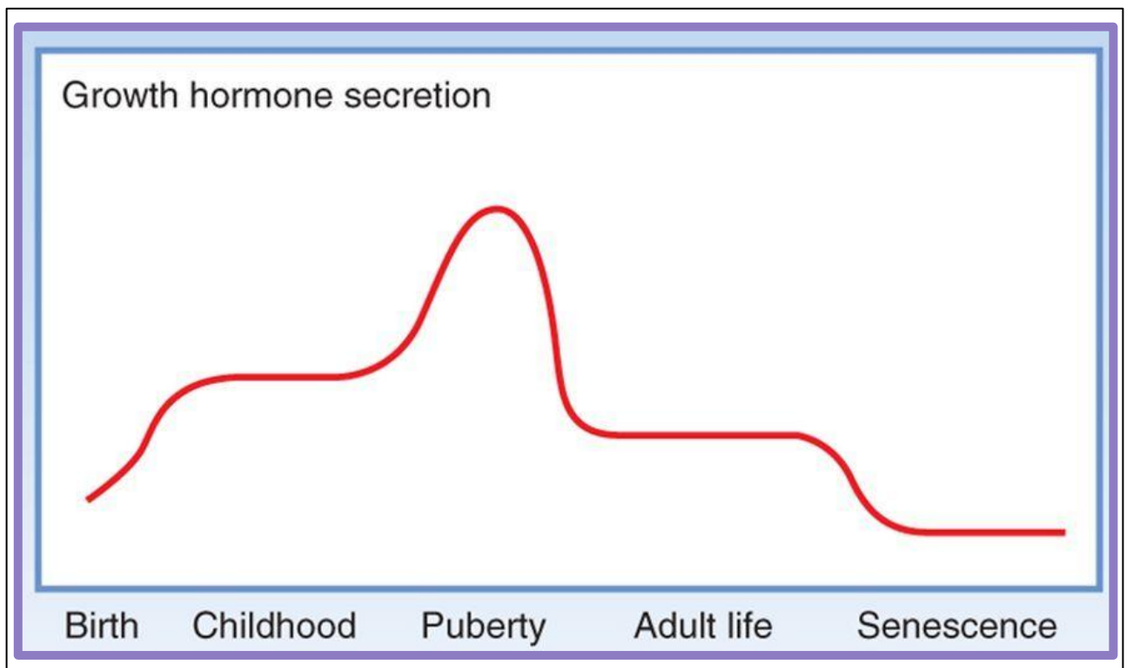
Regulation of Growth Hormone Secretion

- Growth hormone is secreted in a **pulsatile pattern,** with bursts of secretion occurring approximately every 2 hours.



Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

Figure 3-9

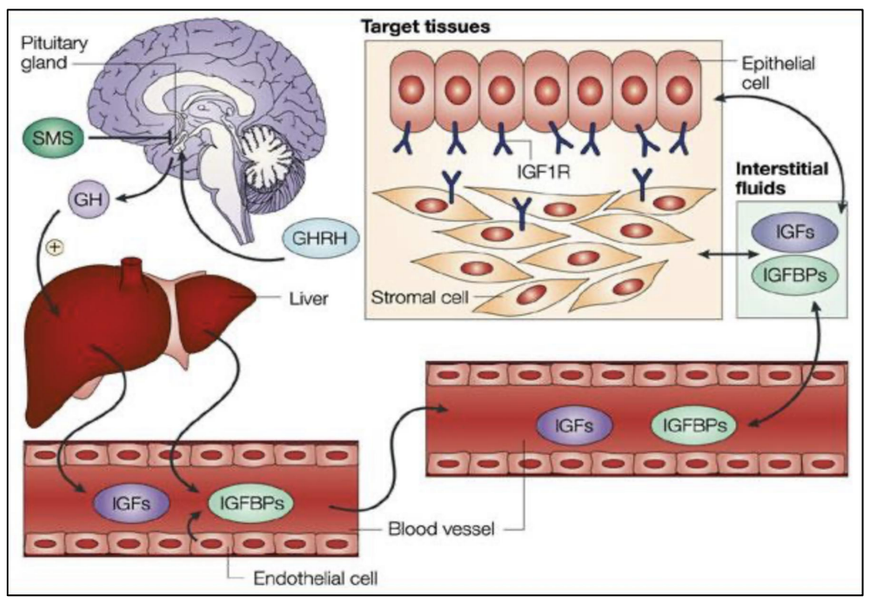
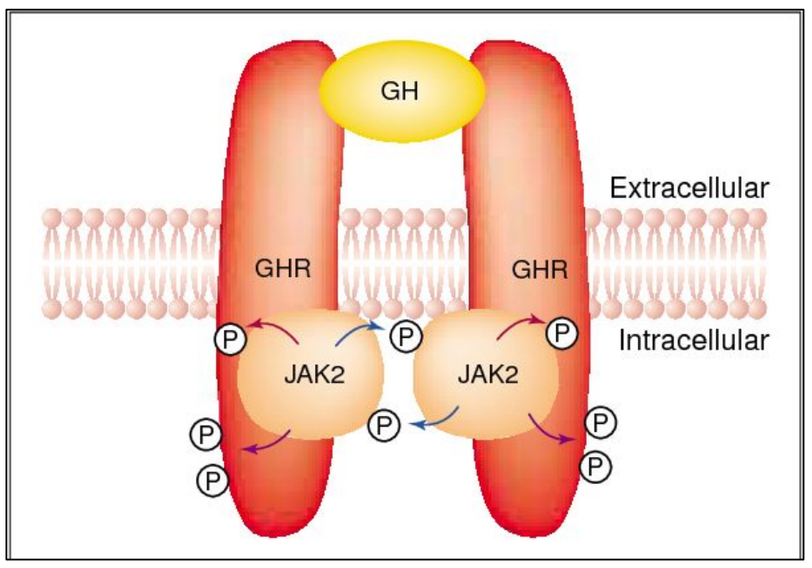


Growth hormone secretory rates are not constant over a lifetime.

- It increases steadily from birth into early childhood.
- During childhood, secretion remains relatively stable.
- At puberty, there is an enormous secretory burst, induced in females by *estrogen* and in males by *testosterone*. The high pubertal levels are responsible for the growth spurt of puberty.
- After puberty, the rate of growth hormone secretion declines to a stable level.
- Finally, in senescence, growth hormone secretory rates decline to their lowest levels.

Figure 3-10

Mechanism of Action

Indirect Effect (Somatomedins)	Direct Effect (GH)
	
• Mediated indirectly through the production of somatomedins (or insulin-like growth factors [IGFs][1]) in the liver. • The most important of the somatomedins is somatomedin C or IGF-1, It has a molecular weight of 4500-7500. • More potent.	• Target tissues: Skeletal muscles, liver and adipose tissue. • Mediated by tyrosine kinase–associated receptors.

FOOTNOTES

1. It's called IGFs because many of the somatomedin effects on growth are similar to the effects of insulin on growth. Including its effect on amino acid transport.

Functions of Growth Hormone

Long Term Effect	Short Term Metabolic Effects
Promotion of growth: ● ↑ cellular sizes & ↑ mitosis ● ↑ tissue growth & organ size **Indirect effect:** Depends on somatomedin 'insulin– like growth factor [IGF-I & II] secreted by the liver, which is responsible for effect of GH on bone & cartilage growth and increase the synthesis of protein in skeletal muscles.	**Protein metabolism (Anabolic):** Increase rate of protein synthesis in all cells through: ● Increase amino acids transport into cells. ● Increased nuclear transcription of DNA to form RNA. ● Enhancement of RNA translation to cause protein synthesis. ● Decrease protein catabolism "protein sparer". (because fatty acids are used as an energy source instead of proteins) ● Increases lean body mass.
1. Linear growth of long bones: ● Long bones grow in length at epiphyseal cartilages, causing deposition of new cartilage (↑collagen synthesis) followed by its conversion into bone. ● When bony fusion occurs between shaft & epiphysis at each end, no further lengthening of long bone occur.	**Fat metabolism (Catabolic):** ● Increase mobilization of free fatty acids from adipose tissue stores. ● Conversion of fatty acids to acetyl CoA to provide energy.[1]
2. Deposition of New Bone: ● Increase cell proliferation on surfaces of older bone & in some bone cavities. It also increase the thickness of bones. ● Occurs in membranous bones (flat bone), e.g. jaw and skull bones.	**CHO metabolism (Hyperglycemic):** ● Decreases glucose uptake by tissues (skeletal muscles and fat). ● Decreases the rate of glucose utilization throughout the body (fat is the alternative of glucose for energy). ● Increases glucose production by the liver (↑ gluconeogenesis) ● Increases Insulin resistance (↑FFA[2]) "Diabetogenic".

Other effects of growth hormone:

- Increases calcium absorption from GIT (stimulates activation of Vit. D by kidney)
- Strengthens and increases the mineralization of bone
- Retention of Na+ and K+ (through activation of RAAS, mechanisms are not clear)
- Increases muscle mass (increased protein synthesis)
- Stimulates the growth of all internal organs excluding the brain
- Contributes to the maintenance and function of pancreatic islets
- Stimulates the immune system (stimulates maturation of myeloid progenitors)

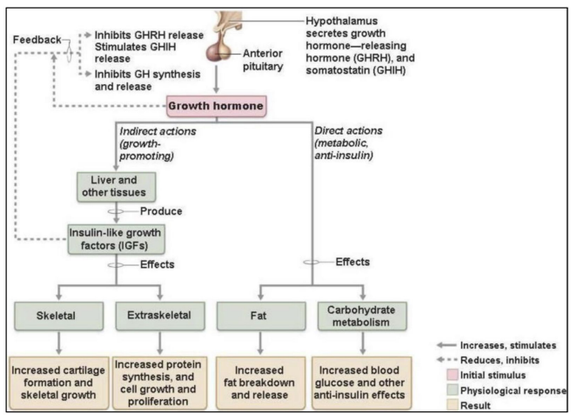


Figure 3-11

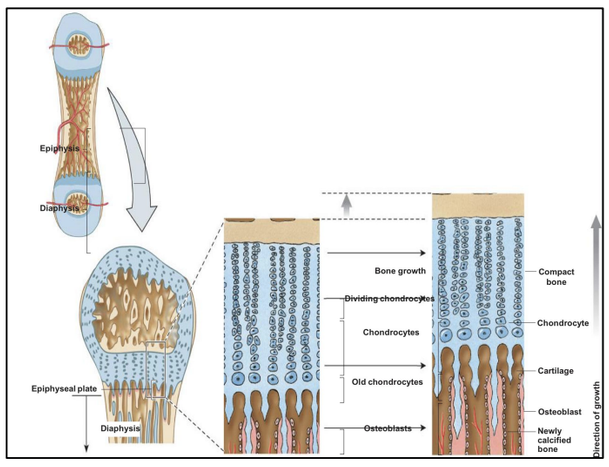


Figure 3-12

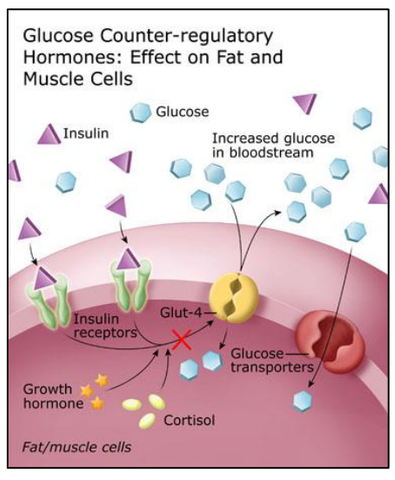


Figure 3-13 GH prevents the activation of Glut-4 by insulin, which stops the transport of glucose from blood into cells.

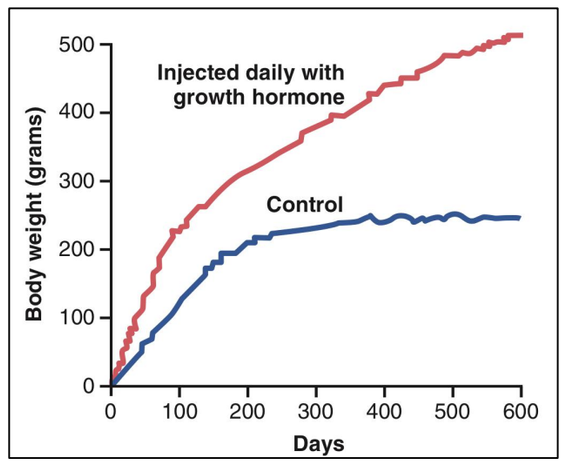


Figure 3-14 Comparison of weight gain of a rat injected daily with growth hormone with that of a normal littermate.

FOOTNOTES

1. **Diabetogenicity mechanism:** Growth hormone causes an increase in plasma free fatty acids, these fatty acids can act on inflammatory cells to cause the release of inflammatory mediators such as (TNF-alpha, IL-1 and IL-6), in turn, these cytokines can act on body tissues to antagonize the effect of insulin. This mechanism is also mainly responsible for the increased incidence of diabetes in obese individuals.
2. Fat must be converted to Acetyl-CoA to enter Krebs cycle, this conversion also results in the formation of ketone bodies, thus a person with GH excess may suffer from ketoacidosis or diabetic ketoacidosis.

Control of Growth Hormone Secretion

Stimulating Factors:

- The hypothalamus: GHRH
- Hypoglycemia (fasting)
- Muscular exercise (increased glucose consumption)
- Intake of protein or amino acids (after meals).
- During sleep (more in children)
- Stress conditions, e.g. trauma or emotions[1]
- Ghrelin (stomach) (released during hunger)

Inhibiting Factors:

- The hypothalamus: GHIH (somatostatin)
- Hyperglycemia (glucose intake)
- Increased free fatty acid concentrations

Stimulatory Factors	Inhibitory Factors
Decreased glucose concentration	Increased glucose concentration
Decreased free fatty acid concentration	Increased free fatty acid concentration
Arginine	Obesity
Fasting or starvation	Senescence
Hormones of puberty (estrogen, testosterone)	Somatostatin
Exercise	Somatomedins
Stress	Growth hormone
Stage III and IV sleep	β-Adrenergic agonists
α-Adrenergic agonists	Pregnancy

Figure 3-15 Factors Affecting Growth Hormone Secretion

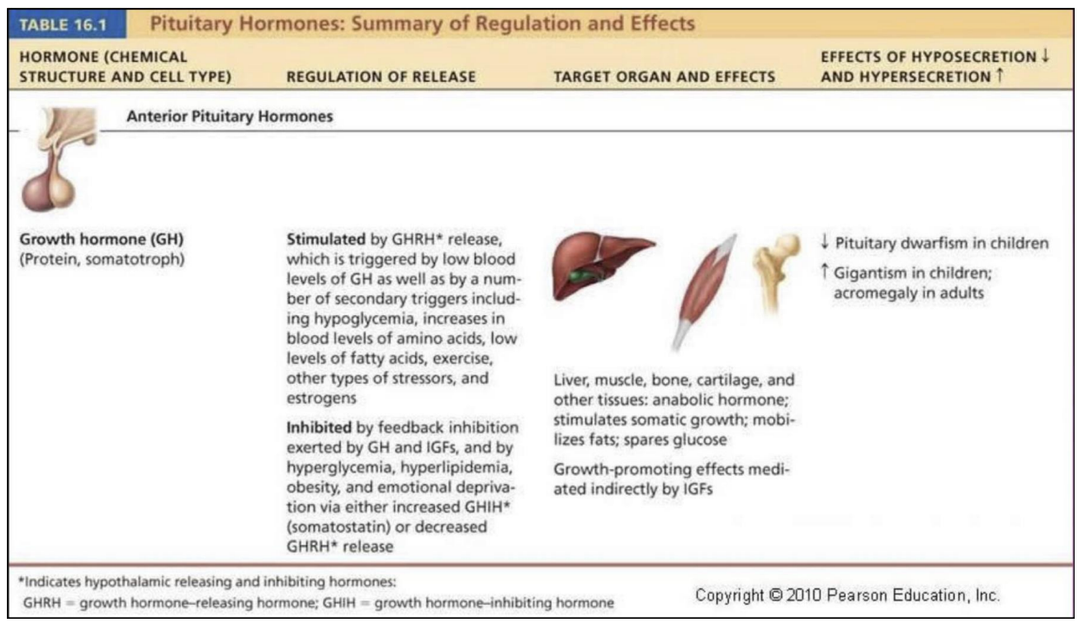


TABLE 16.1 Pituitary Hormones: Summary of Regulation and Effects

HORMONE (CHEMICAL STRUCTURE AND CELL TYPE)	REGULATION OF RELEASE	TARGET ORGAN AND EFFECTS	EFFECTS OF HYPOSECRETION ↓ AND HYPERSECRETION ↑
Anterior Pituitary Hormones			
Growth hormone (GH) (Protein, somatotroph)	**Stimulated** by GHRH* release, which is triggered by low blood levels of GH as well as by a number of secondary triggers including hypoglycemia, increases in blood levels of amino acids, low levels of fatty acids, exercise, other types of stressors, and estrogens **Inhibited** by feedback inhibition exerted by GH and IGFs, and by hyperglycemia, hyperlipidemia, obesity, and emotional deprivation via either increased GHIH* (somatostatin) or decreased GHRH* release	Liver, muscle, bone, cartilage, and other tissues: anabolic hormone; stimulates somatic growth; mobilizes fats; spares glucose Growth-promoting effects mediated indirectly by IGFs	↓ Pituitary dwarfism in children ↑ Gigantism in children; acromegaly in adults

*Indicates hypothalamic releasing and inhibiting hormones:
GHRH = growth hormone–releasing hormone; GHIH = growth hormone–inhibiting hormone

Figure 3-16

Abnormalities (Decreased GH secretion)

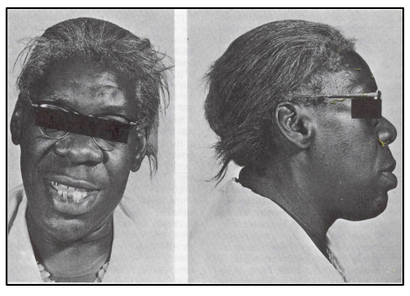
Dwarfism

Abnormalities (Increased GH secretion)

In adults

Acromegaly

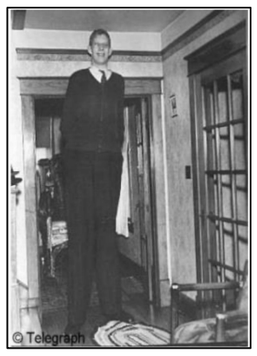
- Soft tissue continue to grow in thickness (e.g. skin, tongue, liver & kidneys)
- Enlargement of bones of hands & feet.
- Enlargement of membranous bones including cranium, nose, forehead bones, & supraorbital ridges.
- Protrusion of lower jaw.
- Hunched back (kyphosis, enlargement of vertebrae).
- Hyperglycemia (diabetes).
- Treated by Octreotide.



In children

Gigantism

- Height increases as it occurs before epiphyseal fusion of long bones with their shafts.
- Hyperglycemia (diabetes).
- Octreotide.



FOOTNOTES

1. Hypothalamus is connected to the limbic system, therefore the hypothalamus computes the person's emotional responses and randomly or accordingly fires off hormones that stimulate the secretion of pituitary hormones.

6 ANTERIOR PITUITARY GLAND

Lecture Three and Four

- TSH, FSH, and LH are all glycoproteins
- Each hormone consists of two subunits, α and β.
- The α subunits of TSH, FSH, and LH are identical and are synthesized from the same mRNA.
- The β subunits for each hormone are different and therefore confer the biologic specificity.
- The placental hormone human chorionic gonadotropin (HCG) is structurally related to the TSH-FSH-LH family.

Thyroid-Stimulating Hormone

- Synthesized by Thyrotrophs (5%)
- It is a glycoprotein, consists of two subunits (α and β)
- Related to LH and FSH.
- Actions:
  - Increased synthesis and secretion of thyroid hormone.
  - Trophic effect (size)
- Abnormalities:
  - Hyperthyroidism
  - Hypothyroidism

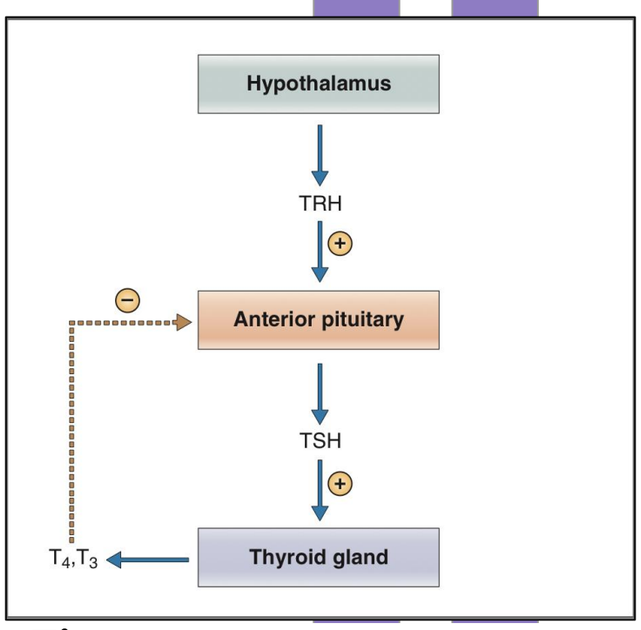


Figure 3-17 Regulation of thyroid hormone secretion.

Follicle-Stimulating Hormone (FSH) & Luteinizing Hormone (LH)

- Synthesized by Gonadotrophs (15%)
- It is a glycoprotein, consists of two subunits (α and β)
- Related to TSH.
- **FSH**: promotes gamete production & stimulates estrogen production in females.
- **LH**: stimulates sex hormone secretion; ovulation and corpus luteum formation in females; stimulates testosterone secretion in males.

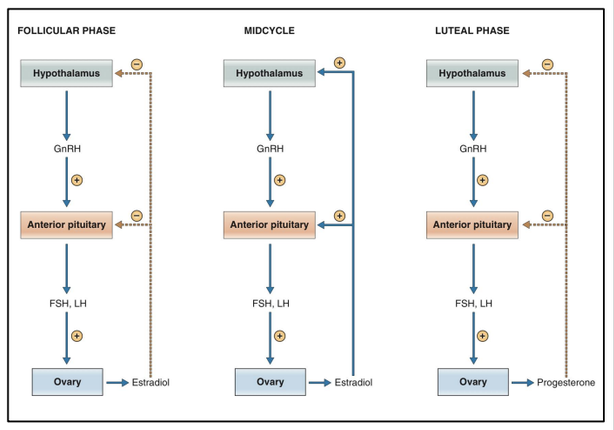


Figure 3-18 Control of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) secretion in females during the menstrual cycle.

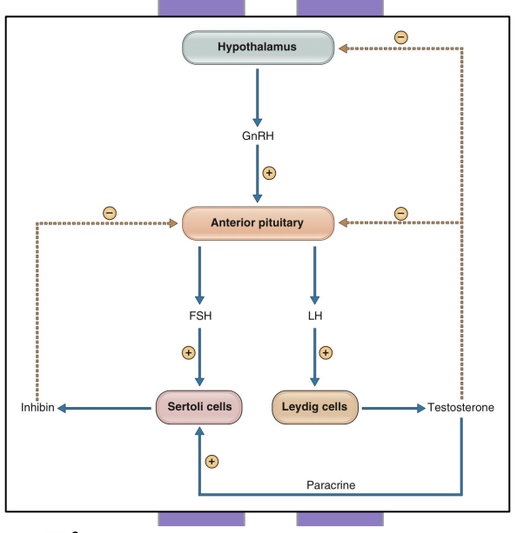


Figure 3-19 Control of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) secretion in males.

LECTURE IV: Anterior Pituitary Gland Part II

Prolactin

- Synthesized by lactotrophs (15%)
- Chemically, prolactin is related to growth hormone, having 198 amino acids.
- The major function of prolactin is milk production.
- Prolactin release is inhibited by PIH (dopamine).
  - In persons who are not pregnant or lactating, prolactin secretion is tonically inhibited by dopamine.
- Suckling response inhibits PIH release leading to increase prolactin release.

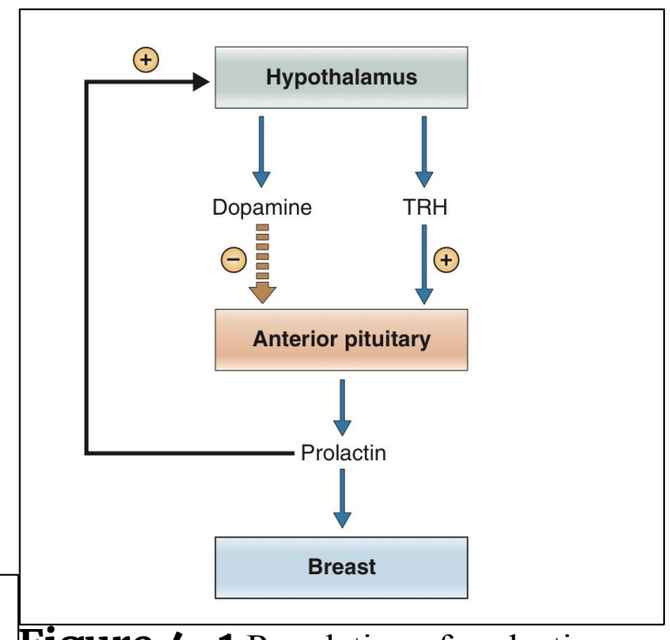


Figure 4-1 Regulation of prolactin secretion.

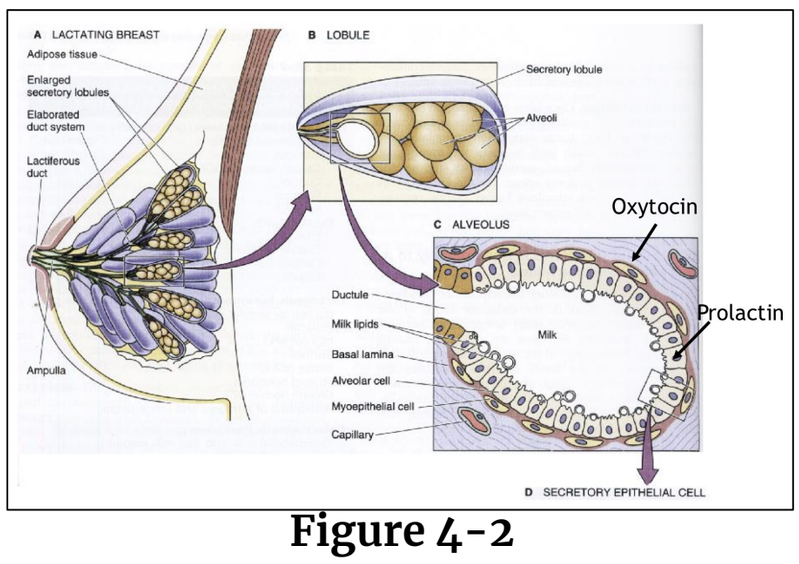


Figure 4-2

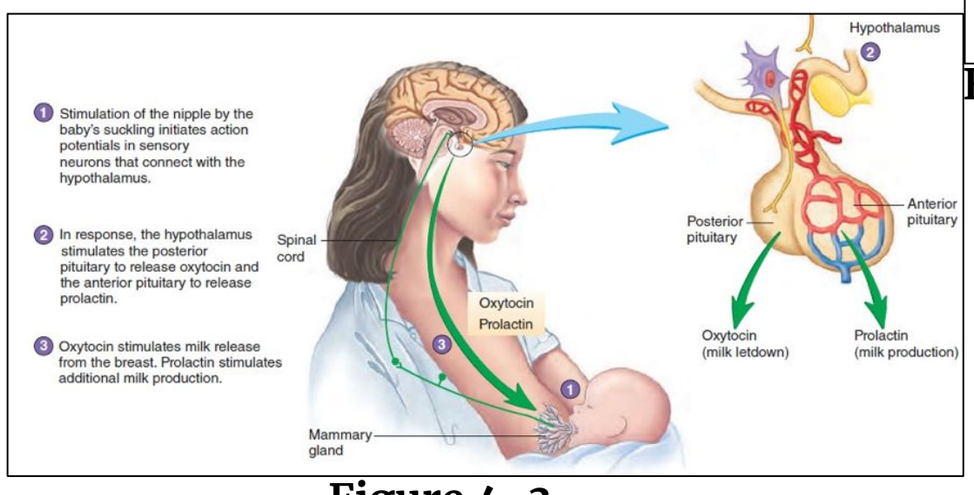


Figure 4-3

Sources of Dopamine

1. Dopaminergic neuron in the hypothalamus (major).
2. Dopaminergic neuron in the posterior pituitary gland.
3. Non lactotrophs cells of the anterior pituitary gland (very small amount).

Functions of Prolactin

Prolactin Effect on Breast:

- Increases mRNA
- Breast development (with estrogen and progesterone).
- Lactogenesis[1]:
  - increases production of lactalbumin, lipid and casein.
  - Parturition[2]

Other Effects of Prolactin:

- Dopamine:
  - Stimulates the secretion of dopamine in median eminence (inhibits its own secretion)
- Inhibition of ovulation[3]:
  - Inhibits the synthesis and release of gonadotropin-releasing hormone (GnRH).
  - Inhibition of ovulation account for the decreased fertility during breastfeeding.
  - In males with high prolactin levels (e.g., due to a prolactinoma), there is a parallel inhibitory effect on GnRH secretion and spermatogenesis, resulting in infertility.

Control of Prolactin Secretion

- PIH (Dopamine) inhibit its secretion
- Exercise increases PRL secretion
- Surgical & psychological stress increases PRL secretion
- Stimulation of the nipple increases PRL secretion
- During Sleep Prolactin level rises
- During pregnancy prolactin level rises
- TRH increases PRL secretion

Abnormalities

1. Prolactin deficiency.
   - Failure to lactate.
2. Prolactin excess.
   - Galactorrhea.
   - Infertility.
   - Treated by *Bromocriptine*.

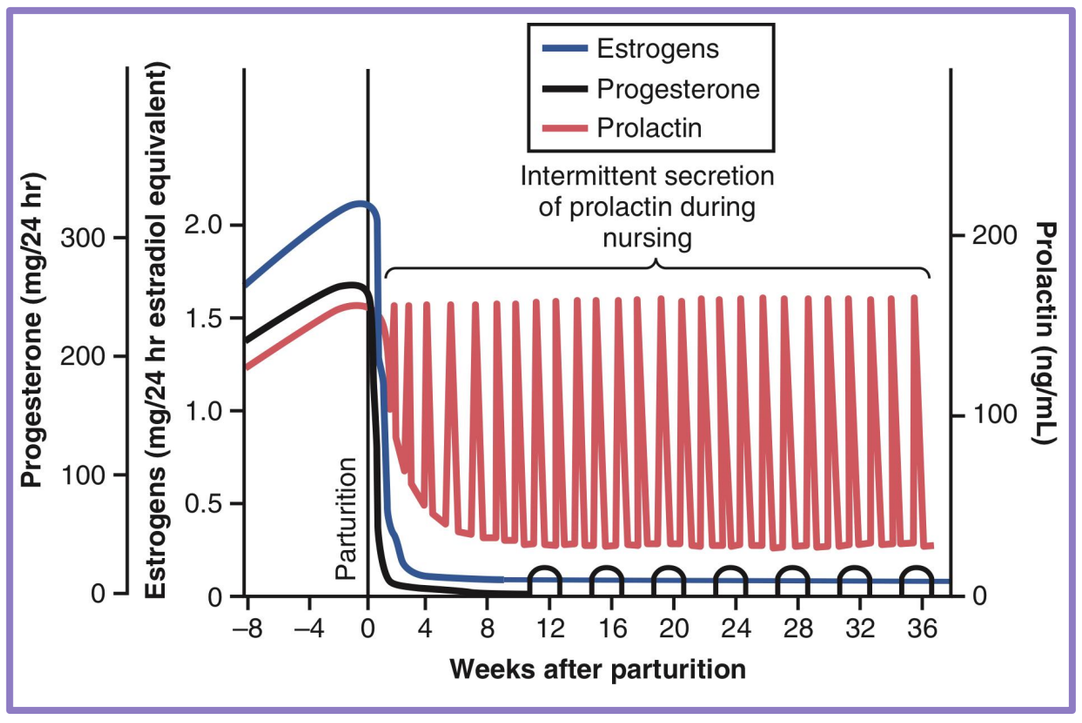


Figure 4-5 After the birth of the baby, the basal level of prolactin secretion returns to the nonpregnant level during the next few weeks. However, each time the mother nurses her baby, nervous signals from the nipples to the hypothalamus cause a 10 to 20-fold surge in prolactin secretion that lasts for about 1 hour. This prolactin acts on the mother's breasts to keep the mammary glands secreting milk into the alveoli for the subsequent nursing periods. If this prolactin surge is absent or blocked as a result of hypothalamic or pituitary damage or if nursing does not continue, the breasts lose their ability to produce milk within 1 week or so. However, milk production can continue for several years if the child continues to suckle, although the rate of milk formation normally decreases considerably after 7 to 9 months.

Stimulatory Factors	Inhibitory Factors
Pregnancy (estrogen)	Dopamine
Breast-feeding	Bromocriptine (dopamine agonist)
Sleep	Somatostatin
Stress	Prolactin (negative feedback)
TRH	
Dopamine antagonists	

TRH, Thyrotropin-releasing hormone.

Figure 4-4 Factors Affecting Prolactin Secretion

FOOTNOTES

1. Interestingly, pregnancy does not have to occur for lactation to be possible; if there is sufficient stimulation of the nipple, prolactin is secreted and milk is produced.
2. Although prolactin levels are high during pregnancy, lactation does not occur because the high levels of estrogen and progesterone down-regulate prolactin receptors in the breast and block the action of prolactin. At parturition, estrogen and progesterone levels drop precipitously and their inhibitory actions cease. Prolactin can then stimulate lactogenesis, and lactation can occur.
3. The reason seems to be that the same nervous signals from the breasts to the hypothalamus that cause prolactin secretion during suckling, inhibit secretion of GnRH.

Adrenocorticotropic hormone (ACTH)

- The ACTH family is derived from a single precursor, pro-opiomelanocortin (POMC).
- ACTH family includes ACTH, γ- and β-lipotropin, β-endorphin, and melanocyte-stimulating hormone (MSH)[1].
- Synthesized by Corticotrophs (15%)
- Stimulate synthesis and secretion of adrenocortical hormones.

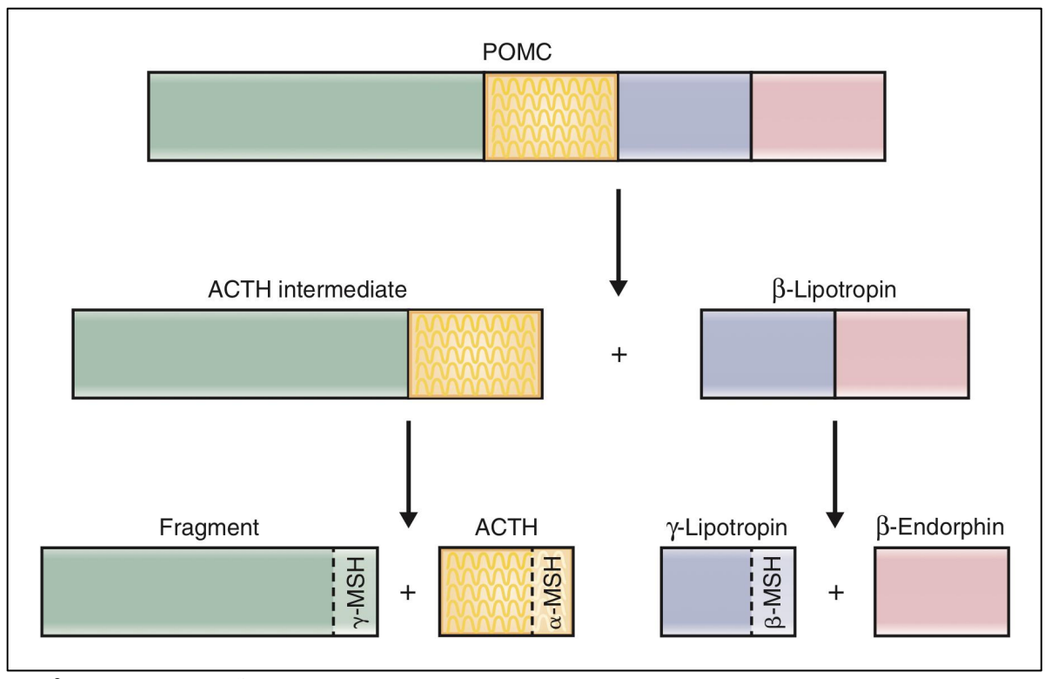


Figure 4-6 The hormones derived from pro-opiomelanocortin (POMC).

Stimulatory Factors	Inhibitory Factors
Decreased blood cortisol levels	Increased blood cortisol levels
Sleep-wake transition	Opioids
Stress; hypoglycemia; surgery; trauma	Somatostatin
Psychiatric disturbances	
ADH	
α-Adrenergic agonists	
β-Adrenergic antagonists	
Serotonin	

ADH, Antidiuretic hormone.

Figure 4-7 Factors affecting ACTH secretion.

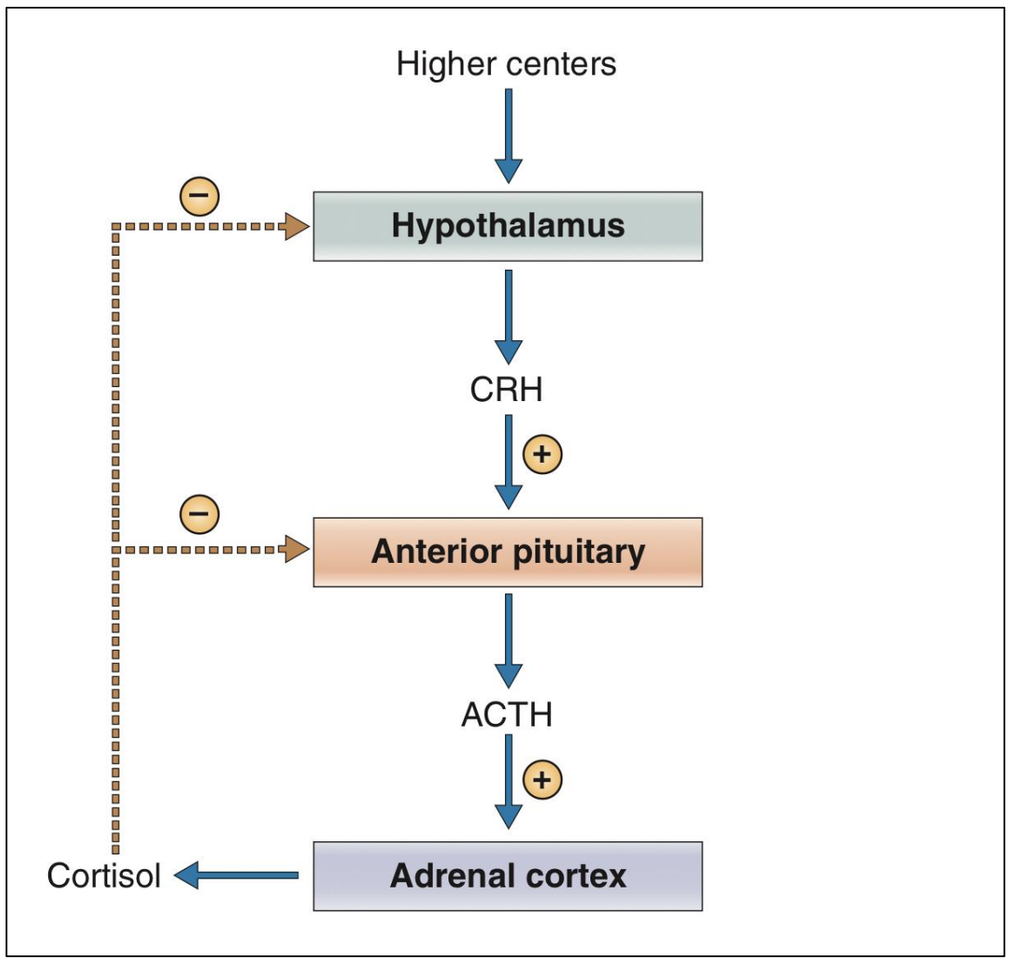


Figure 4-8 Regulation of cortisol secretion.

Summary

Table 11.6 | Anterior Pituitary Hormones

Hormone	Target Tissue	Principal Actions	Regulation of Secretion
ACTH (adrenocorticotropic hormone)	Adrenal cortex	Stimulates secretion of glucocorticoids	Stimulated by CRH (corticotropin-releasing hormone); inhibited by glucocorticoids
TSH (thyroid-stimulating hormone)	Thyroid gland	Stimulates secretion of thyroid hormones	Stimulated by TRH (thyrotropin-releasing hormone); inhibited by thyroid hormones
GH (growth hormone)	Most tissue	Promotes protein synthesis and growth; lipolysis and increased blood glucose	Inhibited by somatostatin; stimulated by growth hormone-releasing hormone
FSH (follicle-stimulating hormone)	Gonads	Promotes gamete production and stimulates estrogen production in females	Stimulated by GnRH (gonadotropin-releasing hormone); inhibited by sex steroids and inhibin
PRL (prolactin)	Mammary glands and other sex accessory organs	Promotes milk production in lactating females; additional actions in other organs	Inhibited by PIH (prolactin-inhibiting hormone)
LH (luteinizing hormone)	Gonads	Stimulates sex hormone secretion; ovulation and corpus luteum formation in females; stimulates testosterone secretion in males	Stimulated by GnRH; inhibited by sex steroids

FOOTNOTES

1. ACTH is the only hormone in this family with well-established physiologic actions in humans. β-Endorphin is an endogenous opiate.

QUIZ

MEDICINE438's ENDOCRINEPHYSIOLOGY

1. Which of the following increases secretion of GH?

A) Senescence
B) Insulin-like growth factor-1 (IGF-1)
C) Somatostatin
D) Hypoglycemia

2. Which anterior pituitary hormone plays a major role in the regulation of a nonendocrine target gland?

A) ACTH
B) TSH
C) Prolactin
D) FSH

3. Why is milk produced by a woman only after delivery, not before?

A) Levels of LH and FSH are too low during pregnancy to support milk production
B) High levels of progesterone and estrogen during pregnancy suppress milk production
C) The alveolar cells of the breast do not reach maturity until after delivery
D) High levels of oxytocin are required for milk production to begin, and oxytocin is not secreted until the baby stimulates the nipple

4. GH secretion would most likely be suppressed under which condition?

A) Acute hyperglycemia
B) Deep sleep
C) Gigantism
D) Exercise

5. Which of the following conditions or hormones would most likely increase GH secretion?

A) Hyperglycemia
B) Exercise
C) Aging
D) Somatomedin

ANSWER KEY: D, C, B, A, B

QUIZ

MEDICINE438's ENDOCRINEPHYSIOLOGY

1. Lipolytic effect of growth hormone is suppressed by
A) Glucose administration
B) Fasting
C) Stress
D) Hypoglycemia

2. Growth hormone increases the
A) Absorption of calcium from GIT
B) Excretion of sodium by kidney
C) Excretion of potassium by kidney
D) Excretion of magnesium by kidney

3. Growth hormone secretion is inhibited by
A) Glucagon
B) Estrogen
C) Androgens
D) Growth hormone

4. Growth hormone has all of the following effects on the protein metabolism except
A) Increased protein synthesis
B) Increased amino acid level in blood
C) Decreased protein catabolism
D) Increased nuclear transcription of DNA to form RNA

5. The effect of growth hormone on fat metabolism includes all of the following except
A) Breakdown of stored fat
B) Decreased conversion of fatty acids to acetyl CoA
C) Increased free fatty acid level in blood
D) Increase mobilization of free fatty acids from adipose tissue stores

ANSWER KEY: A, A, D, B, B

THIS LECTURE WAS DONE BY

Maha Alnahdi

FEMALE PHYSIOLOGY CO-LEADERS

Maha Alnahdi, Taif Alshammari

MALE PHYSIOLOGY CO-LEADERS

Nayef Alsaber, Hameed M. Humaid

PRESENTED BY

MEDICINE438's ENDOCRINE PHYSIOLOGY

REFERENCES

- Guyton and Hall Textbook of Medical Physiology
- Ganong's Review of Medical Physiology