Human Physiology Course

The Hypothalamus and the Pituitary Gland

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The Hypothalamic-Pituitary Axis

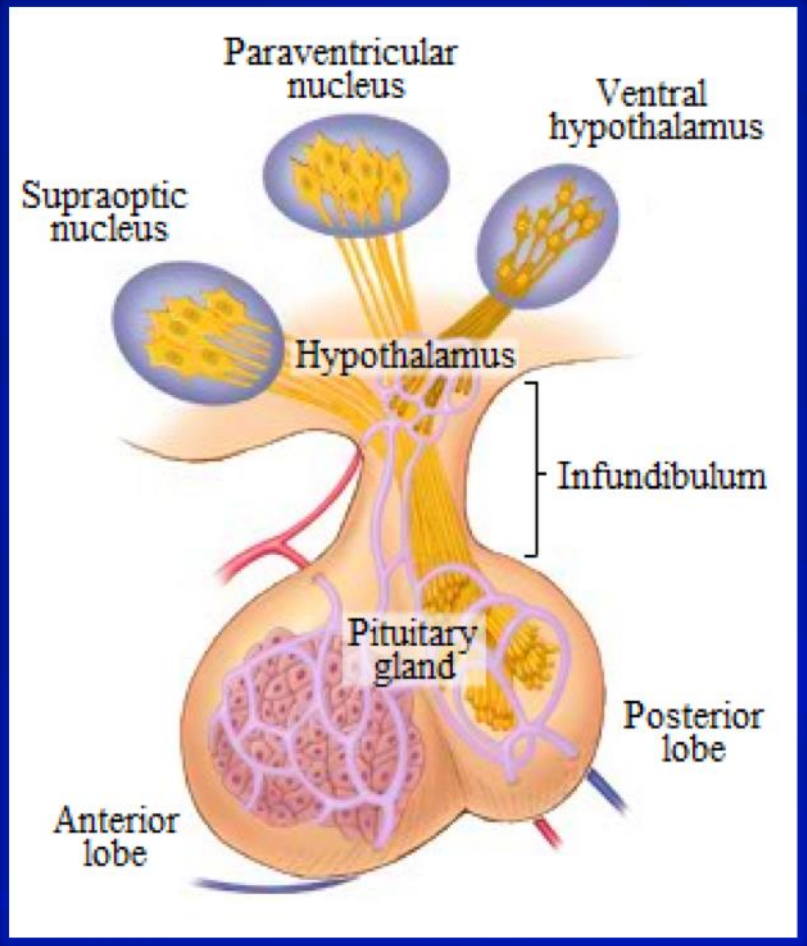
- The hypothalamus and pituitary gland form a complex interface between the NS and the endocrine system.

  (the brain links the pituitary gland to events occurring within or outside the body, which call for changes in pituitary hormone secretion)

- The brain can influence the activity of neurosecretory cells → hormones can influence release of other hormones.

- This important functional connection between the brain and the pituitary, is called *the hypothalamic-pituitary axis.*

The Pituitary Gland (Hypophysis)



- is located at the base of the brain and is connected to the hypothalamus by a stalk called the infundibulum
- it sits in a depression in the sphenoid bone of the skull called the sella turcica

- is composed of two morphologically and functionally distinct glands connected to the hypothalamus - *the adenohypophysis* and *the neurohypophysis*.

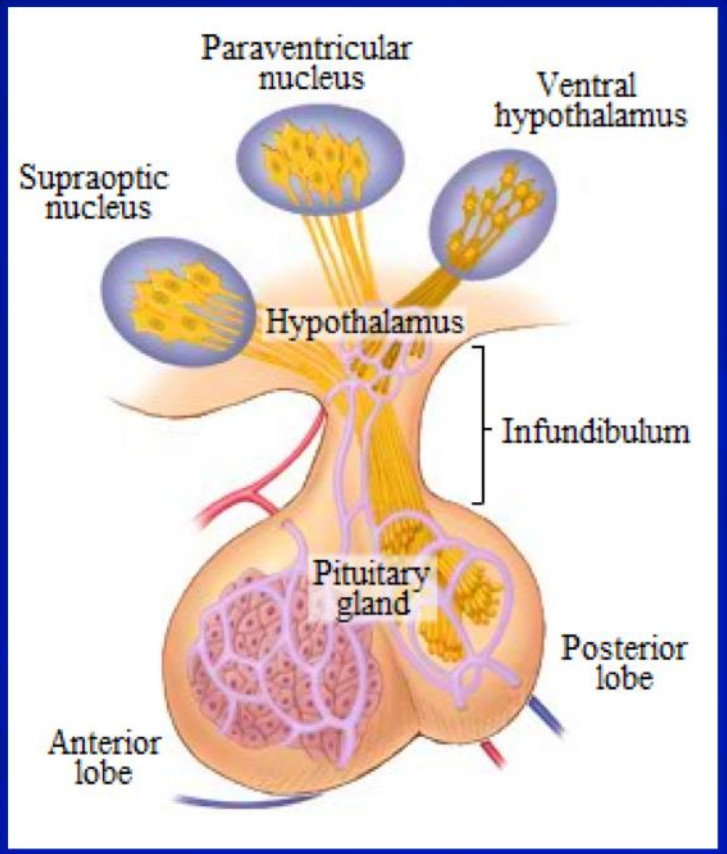
The Pituitary Gland (Hypophysis)

- The adenohypophysis consists of the *pars tuberalis*, which forms the outer covering of the pituitary stalk, and the *pars distalis* or *anterior lobe*.
- The neurohypophysis is composed of the median eminence of the hypothalamus, the *infundibular stem*, which forms the inner part of the stalk, and the *infundibular process* or *posterior lobe*.
- In adult humans, only a vestige of the intermediate lobe (the *pars intermedia)* is found as a thin diffuse region of cells between the anterior and posterior lobes. The intermediate lobe (often considered part of the anterior pituitary) synthesizes and secretes melanocyte-stimulating hormone.

The Pituitary Gland (Hypophysis)

- The adenohypophysis and neurohypophysis have different embryological origins:
  - The adenohypophysis is formed from an evagination of the oral ectoderm called Rathke's pouch.
  - The neurohypophysis forms as an extension of the developing hypothalamus, which fuses with Rathke's pouch as development proceeds.
- The posterior lobe is, therefore, composed of neural tissue and is a functional part of the hypothalamus.

The Pituitary Gland (Hypophysis)



- The anterior lobe of the pituitary gland is endocrine tissue.
- The posterior lobe of the pituitary gland is neural tissue.
- The anterior lobe and a small portion of the infundibulum make up the adenohypophysis, the posterior lobe and most of the infundibulum make up the neurohypophysis.

The Pituitary Gland (Hypophysis)

- a complex endocrine organ that secretes *peptide hormones* that have important actions on almost every aspect of body function:
  - preserving the volume/composition of body fluids
  - growth, blood pressure, metabolism, pain relief
  - reproduction, childbirth, lactation, nursing
  - stress/trauma response, temperature regulation, etc.
- The pituitary hormones produce physiological effects by:
  - acting directly on their target cells
  - stimulating other endocrine glands to secrete hormones

The Hypothalamic-Pituitary Axis

- Posterior Pituitary Hormones Are Synthesized by Hypothalamic Neurons Whose Axons Terminate in the Posterior Lobe
- Anterior Pituitary Hormones Are Synthesized and Secreted in Response to Hypothalamic Releasing Hormones Carried in the Hypophyseal Portal Circulation

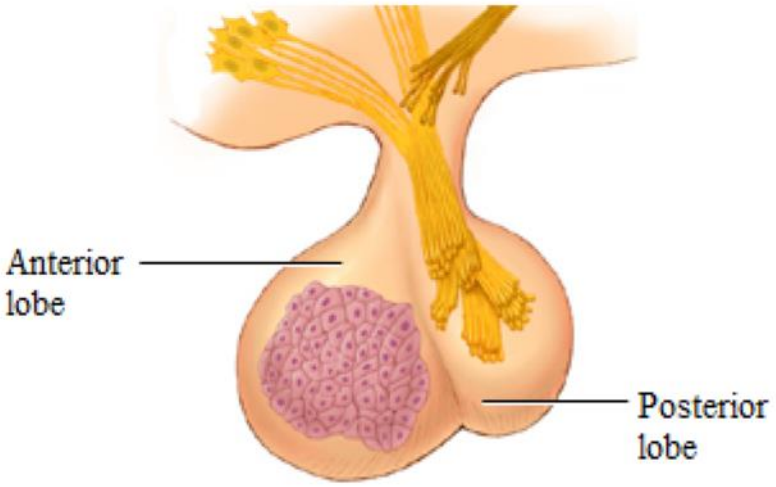
Hypothalamic Releasing Hormones *(hypophysiotropic hormones)*

Hormone	Chemistry	Actions on Anterior Pituitary
Corticotropin-releasing hormone (CRH)	Single chain of 41 amino acids	Stimulates ACTH secretion by corticotrophs; stimulates expression of POMC gene in corticotrophs
Thyrotropin-releasing hormone (TRH)	Peptide of 3 amino acids	Stimulates TSH secretion by thyrotrophs; stimulates expression of genes for α and β subunits of TSH in thyrotrophs; stimulates PRL synthesis by lactotrophs
Growth hormone-releasing hormone (GHRH)	Two forms in human: single chain of 44 amino acids, single chain of 40 amino acids	Stimulates GH secretion by somatotrophs; stimulates expression of GH gene in somatotrophs
Luteinizing hormone-releasing hormone (LHRH), gonadotropin-releasing hormone (GnRH)	Single chain of 10 amino acids	Stimulates FSH and LH secretion by gonadotrophs
Somatostatin, somatotropin release inhibiting factor (SRIF)	Single chain of 14 amino acids	Inhibits GH secretion by somatotrophs; inhibits TSH secretion by thyrotrophs
Dopamine	Catecholamine	Inhibits PRL synthesis and secretion by lactotrophs

Second messengers

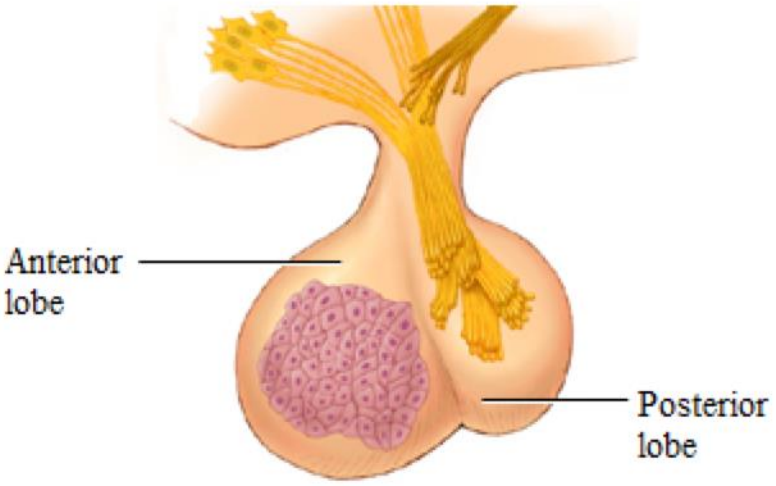
- GHRH increases cAMP and stimulates GH synthesis and secretion.
- Somatostatin decreases cAMP and inhibits GH synthesis and secretion from somatotrophs.
- TRH stimulates TSH secretion and the synthesis of the alpha and beta subunits of TSH by increasing inositol trisphosphate and calcium in thyrotrophs.
- cAMP stimulates ACTH synthesis in corticotrophs.

The Pituitary Gland (Hypophysis)



The **pituitary gland** has two major lobes:

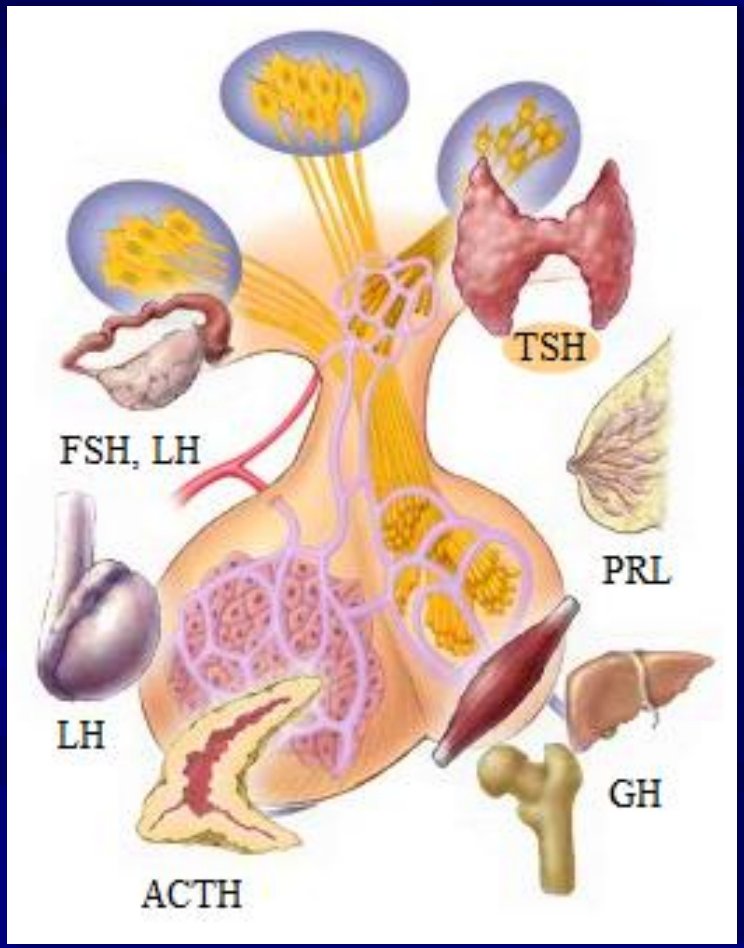
- Anterior lobe: glandular tissue, produces six well-understood hormones
- Posterior lobe: neural tissue, releases two hormones produced by neurons in the **hypothalamus**.



The **peptide hormones** of the anterior pituitary include:

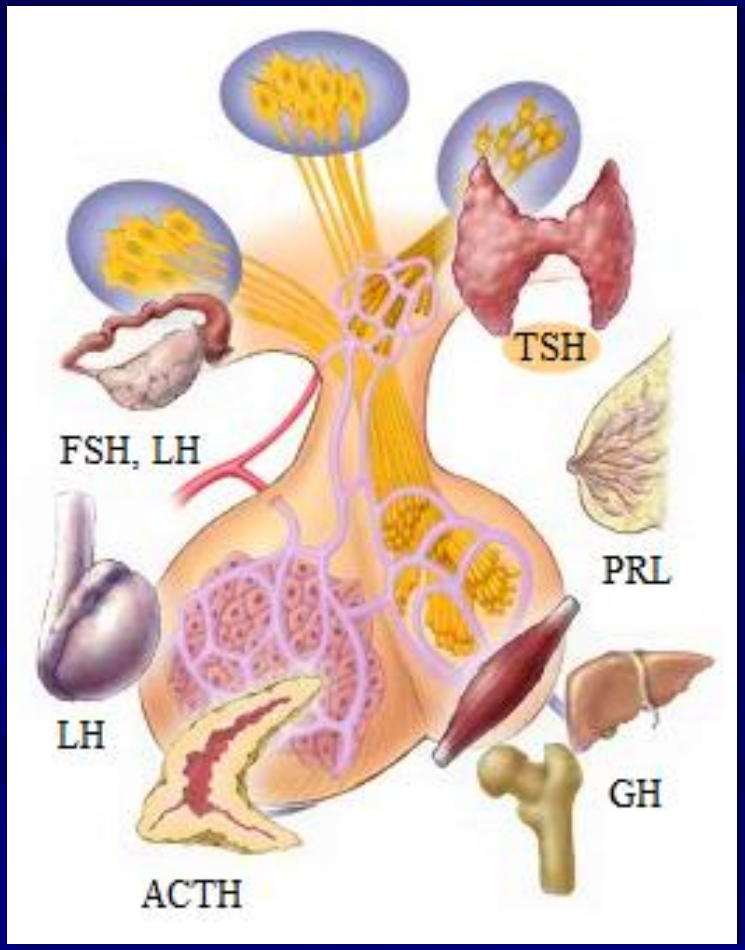
- **thyroid-stimulating hormone** *(TSH or thyrotropin)*
- **follicle-stimulating hormone** and **luteinizing hormone** *(FSH and LH, the gonadotropins)*
- **adrenocorticotropic hormone** *(ACTH or corticotropin)*
- **growth hormone** *(GH)*
- **prolactin** *(PRL)*

Anterior Pituitary Hormones



- The six classis anterior pituitary hormones are:
  - TSH (thyrotropin)
  - FSH (gonadotropin)
  - LH (gonadotropin)
  - ACTH (corticotropin)
  - GH
  - PRL

Anterior Pituitary Hormones



- Anterior pituitary hormones exert important growth effects on target tissues. The tropic hormones (TSH, FSH, LH, ACTH) cause the release of hormones from other endocrine glands.
- Anterior pituitary hormones are released from the anterior pituitary under the influence of the hypothalamus
- Hypothalamic hormones are secreted to the anterior lobe by way of a special capillary system - the hypothalamic-hypophysial portal system.

Anterior Pituitary Hormones

Somatotrophins:

- Growth hormone (GH; somatotropin) - is released under the influence of hypothalamic growth hormone-releasing hormone (GHRH), and is inhibited by hypothalamic somatostatin.
- Hypothalamic GHRH increases and hypothalamic somatotropin release-inhibiting factor (SRIF) decreases GH secretion from somatotrophs.
- GH secretion is regulated by the deep sleep, stress, exercise, hypoglycemia, sex hormones, ghrelin, fasting, niacin - stimulators, and by glucocorticoids, hyperglycemia, somatostatin, dihydrotestosteron, GH, IGF1, aging - inhibitors

Anterior Pituitary Hormones

Thyrotrophins:

- Thyroid-stimulating hormone (TSH) - is released under the influence of hypothalamic thyrotropin-releasing hormone (TRH) and is inhibited by somatostatin.
- Hypothalamic TRH stimulates TSH release from thyrotrophs, which, in turn, stimulates T3 and T4 release from the thyroid follicles, to comprise the hypothalamic-pituitary-thyroid axis.
- TSH secretion is regulated by the thyroid hormones, cold temperatures, and the sleep-wake cycle.

Anterior Pituitary Hormones

Corticotrophins:

- Adrenocorticotropic hormone (ACTH) and Beta-endorphin - are released under the influence of hypothalamic corticotropin-releasing hormone (CRH).
- Hypothalamic CRH stimulates ACTH release from corticotrophs, which, in turn, stimulates glucocorticoid release from the adrenal cortex, to comprise the hypothalamic-pituitary-adrenal axis.
- ACTH secretion is regulated by glucocorticoids, physical and emotional stress, ADH, and the sleep-wake cycle.

Anterior Pituitary Hormones

Lactotrophins:

- Prolactin (PRL; Luteotropic' hormone) – its release is inconsistently stimulated by hypothalamic TRH, oxytocin, vasopressin, VIP, angiotensin II, NPY, galanin, substance P, bombesin-like peptides (gastrin-releasing peptide, neuromedin B and C), and neurotensin, and inhibited by hypothalamic dopamine.

Anterior Pituitary Hormones

Gonadotrophins:

- Luteinizing hormone (LH; Lutropin), Follicle-stimulating hormone (FSH) - both are released under influence of Gonadotropin-Releasing Hormone (GnRH - LHRH that stimulates the secretion of FSH and LH from the anterior pituitary). These hormones, in turn, affect functions of the ovaries and testes.

Intermediate Pituitary Hormone

- The intermediate lobe synthesizes and secretes the Melanocyte–stimulating hormone (MSH)
- MSH is also produced in the anterior lobe
- when produced in the intermediate lobe, MSHs are sometimes called "intermedins"

Hormones of the Anterior Pituitary

Hormone	Chemistry	Physiological Actions
Adrenocorticotropic hormone (ACTH, corticotropin)	Single chain of 39 amino acids 4.5 kDa	Stimulates production of glucocorticoids and androgens by adrenal cortex; maintains size of zona fasciculata and zona reticularis of cortex
Thyroid-stimulating hormone (TSH, thyrotropin)	Glycoprotein having two subunits, α and β; 28 kDa	Stimulates production of thyroid hormones, T_4 and T_3, by thyroid follicular cells; maintains size of follicular cells
Growth hormone (GH, somatotropin)	Single chain of 191 amino acids; 22 kDa	Stimulates postnatal body growth; stimulates triglyceride lipolysis; inhibits insulin action on carbohydrate and lipid metabolism
Follicle-stimulating hormone (FSH)	Glycoprotein having two subunits, α and β; 28–29 kDa	Stimulates development of ovarian follicles; regulates spermatogenesis in testes
Luteinizing hormone (LH)	Glycoprotein having two subunits, α and β; 28–29 kDa	Causes ovulation and formation of corpus luteum in ovaries; stimulates production of estrogen and progesterone by ovaries; stimulates testosterone production by testes
Prolactin (PRL)	Single chain of 199 amino acids	Essential for milk production by lactating mammary glands

Posterior Pituitary Hormones

- ADH and oxytocin are synthesized in hypothalamic neurons whose axons terminate in the posterior pituitary.

Antidiuretic hormone (ADH, vasopressin, arginine vasopressin):

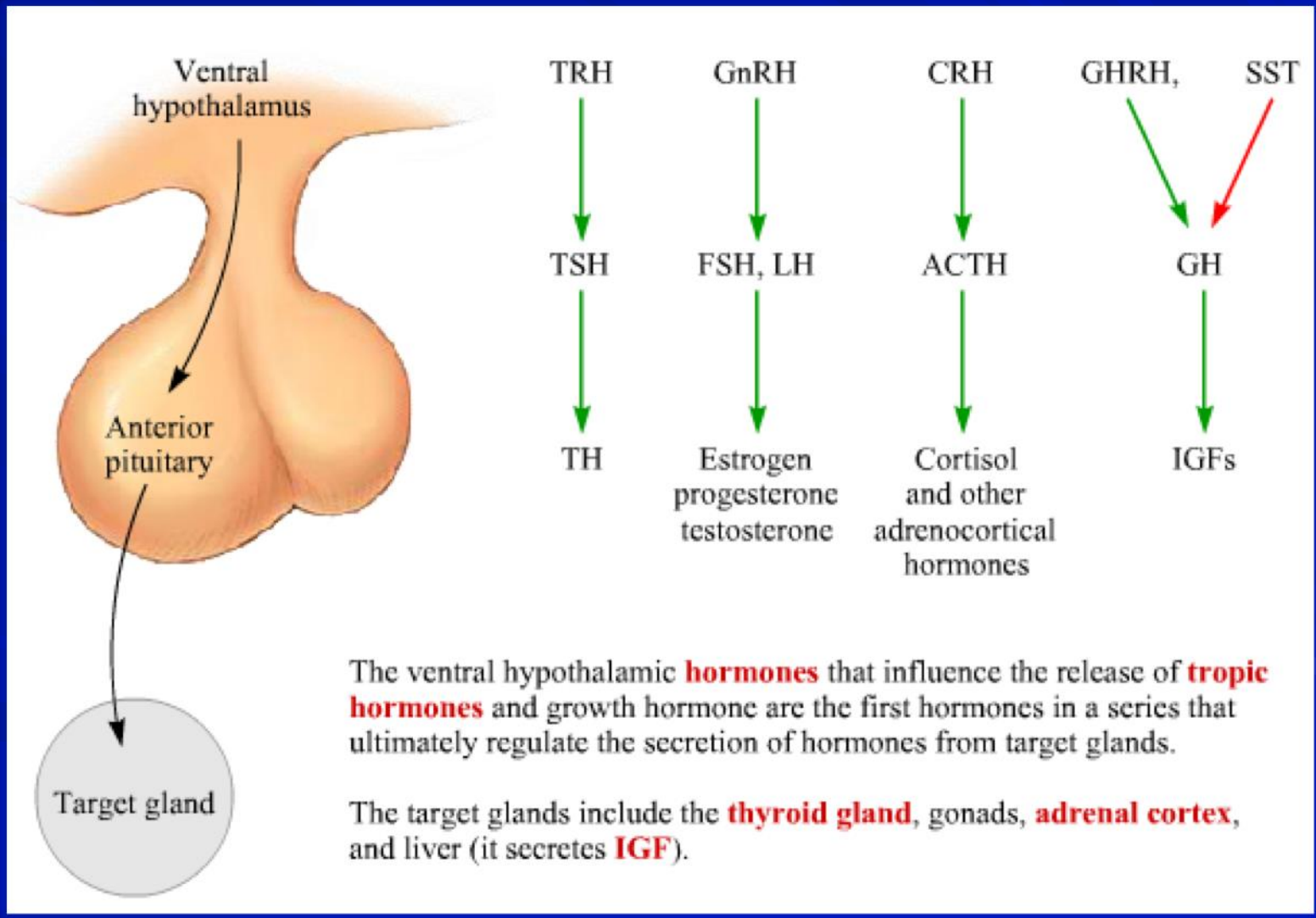
- the majority is released from the supraoptic nucleus in the hypothalamus.
- increases water reabsorption by the kidneys in response to a rise in blood osmolality or a fall in blood volume

Posterior Pituitary Hormones

Oxytocin:

- the majority is released from the paraventricular nucleus in the hypothalamus.
- Oxytocin stimulates milk letdown in the breast in response to suckling and muscle contraction in the uterus in response to cervical dilation during labor.
- Oxytocin creates a positive feedback loop -- uterine contractions stimulate the release of oxytocin from the posterior pituitary, which, in turn, increases uterine contractions. This positive feedback loop continues throughout labour.

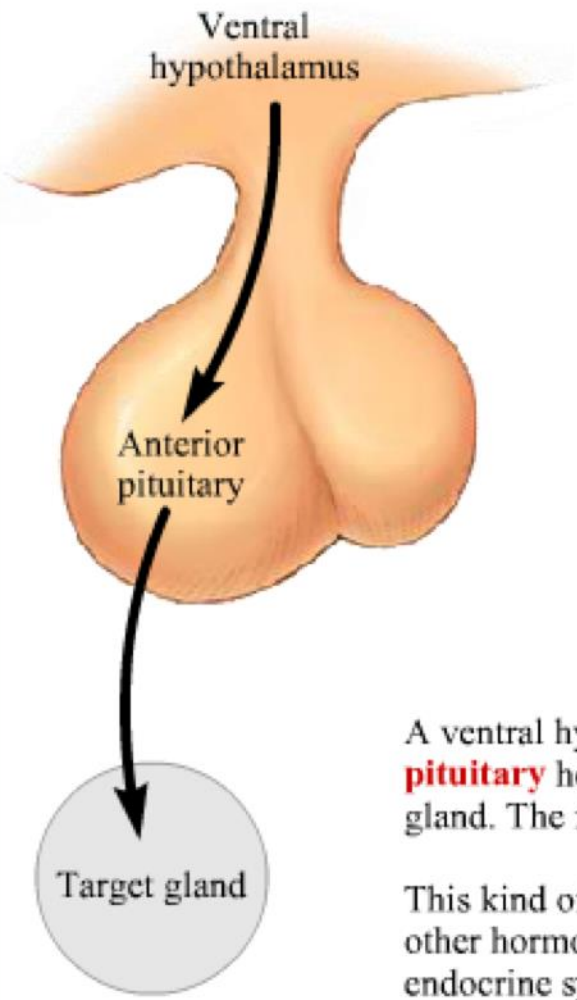
Endocrine Control of the Hypothalamic-Pituitary Axis



The ventral hypothalamic **hormones** that influence the release of **tropic hormones** and growth hormone are the first hormones in a series that ultimately regulate the secretion of hormones from target glands.

The target glands include the **thyroid gland**, gonads, **adrenal cortex**, and liver (it secretes **IGF**).

Endocrine Control of the Hypothalamic-Pituitary Axis (cont.)

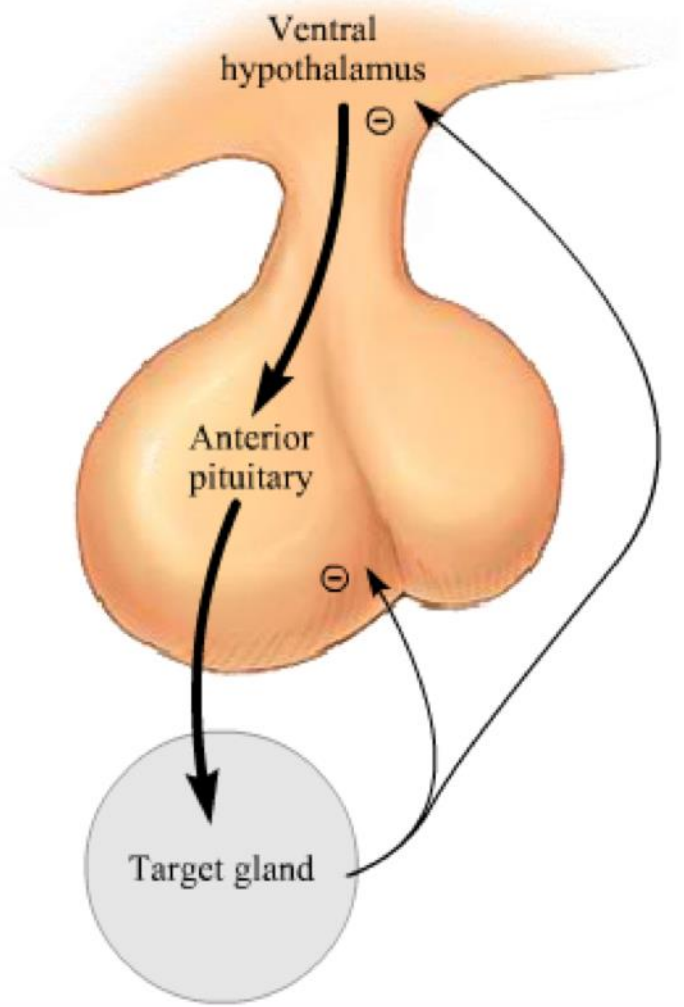


TRH	GnRH	CRH	GHRH, SST
TSH	FSH, LH	ACTH	GH
TH	Estrogen progesterone testosterone	Cortisol and other adrenocortical hormones	IGFs

A ventral hypothalamic hormone controls secretion of an anterior **pituitary** hormone that stimulates secretion of a hormone from a target gland. The final hormone in the chain acts on target tissues of the body.

This kind of complex control system provides many input sites where other hormones and **neurons** can act to achieve fine control over the endocrine system.

Endocrine Control of the Hypothalamic-Pituitary Axis (cont.)



For each hormone series, negative feedback loops control circulating levels of the target gland hormones.

Negative feedback exerted by the target hormone can be directed at the anterior pituitary, the ventral **hypothalamus**, or both.

Target hormones from one series can also influence the secretion of hypothalamic or anterior pituitary hormones from another hormone series.

– THYROID GLAND REGULATION
"negative Feed-back" axis

(negative effect)

– Hypothalamus

(TRH positive effect)

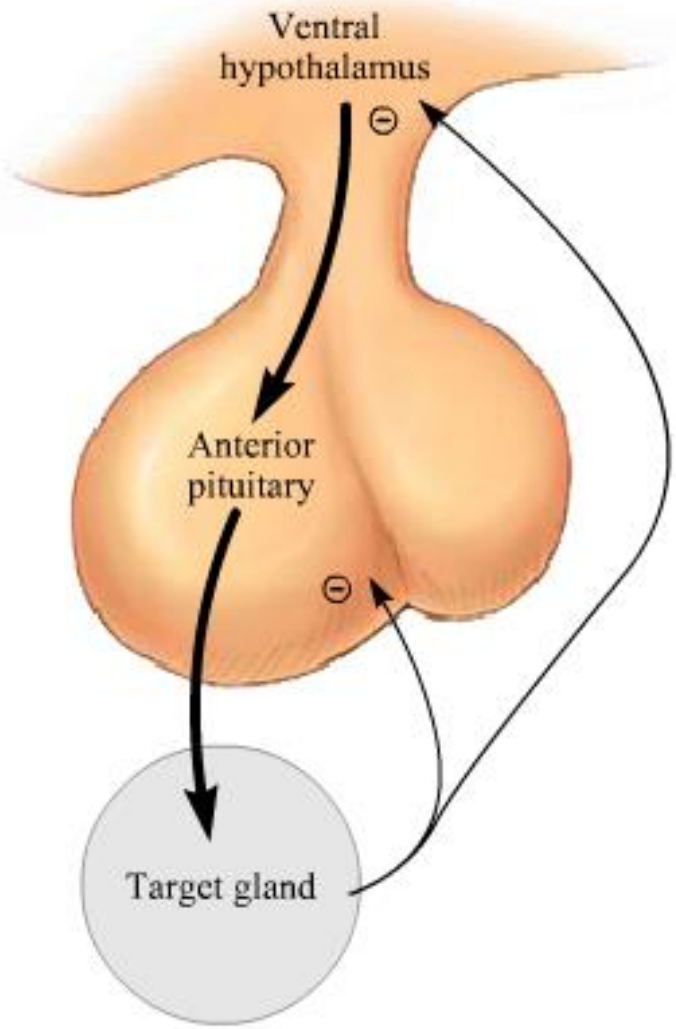
– Pituitary gland

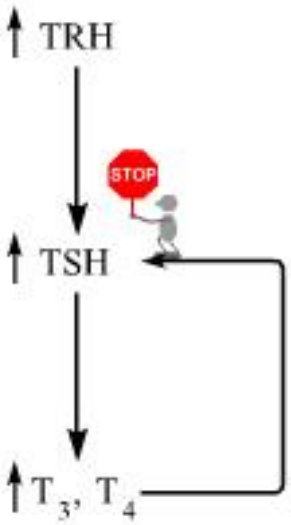
(TSH, positive effect)

– Thyroid gland

T3 & T4

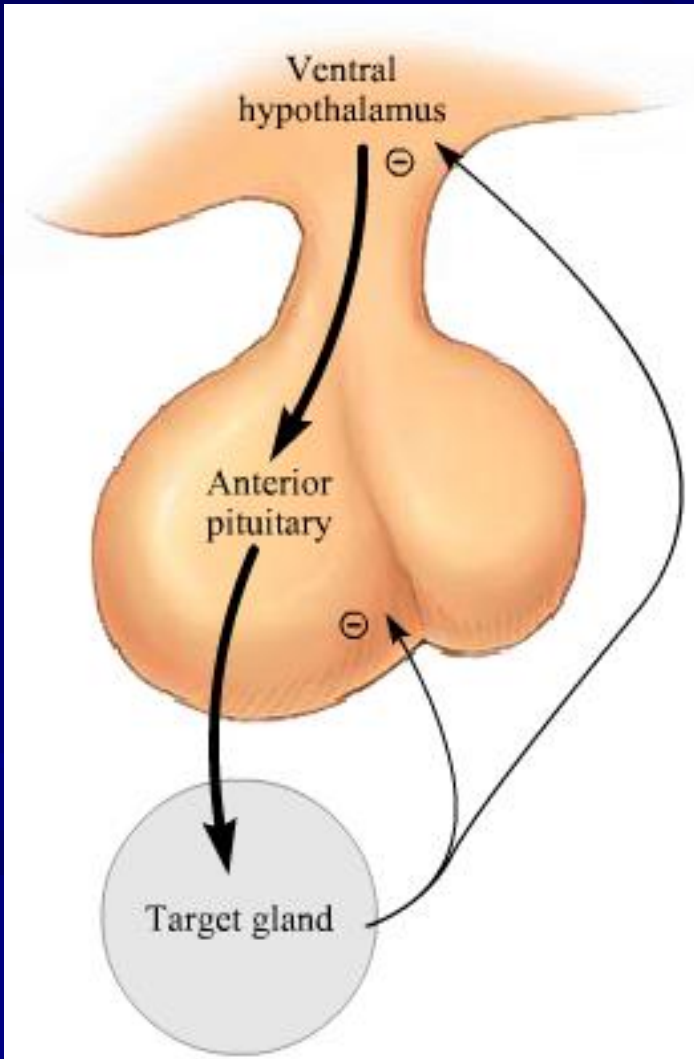
TRH -- TSH

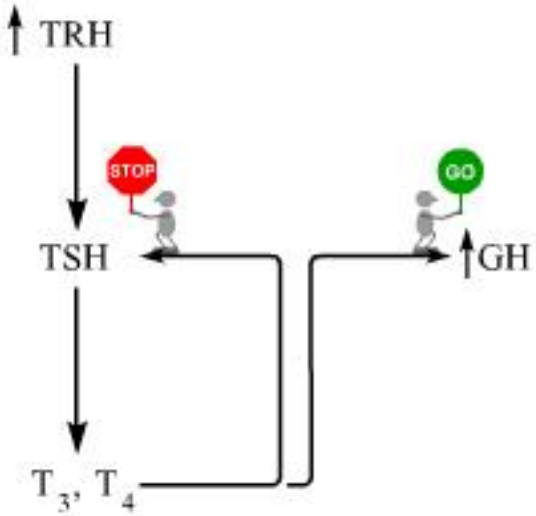




The **thyroid hormones** feed back almost exclusively to the anterior pituitary to inhibit secretion of **TSH**.

TRH – TSH – GH

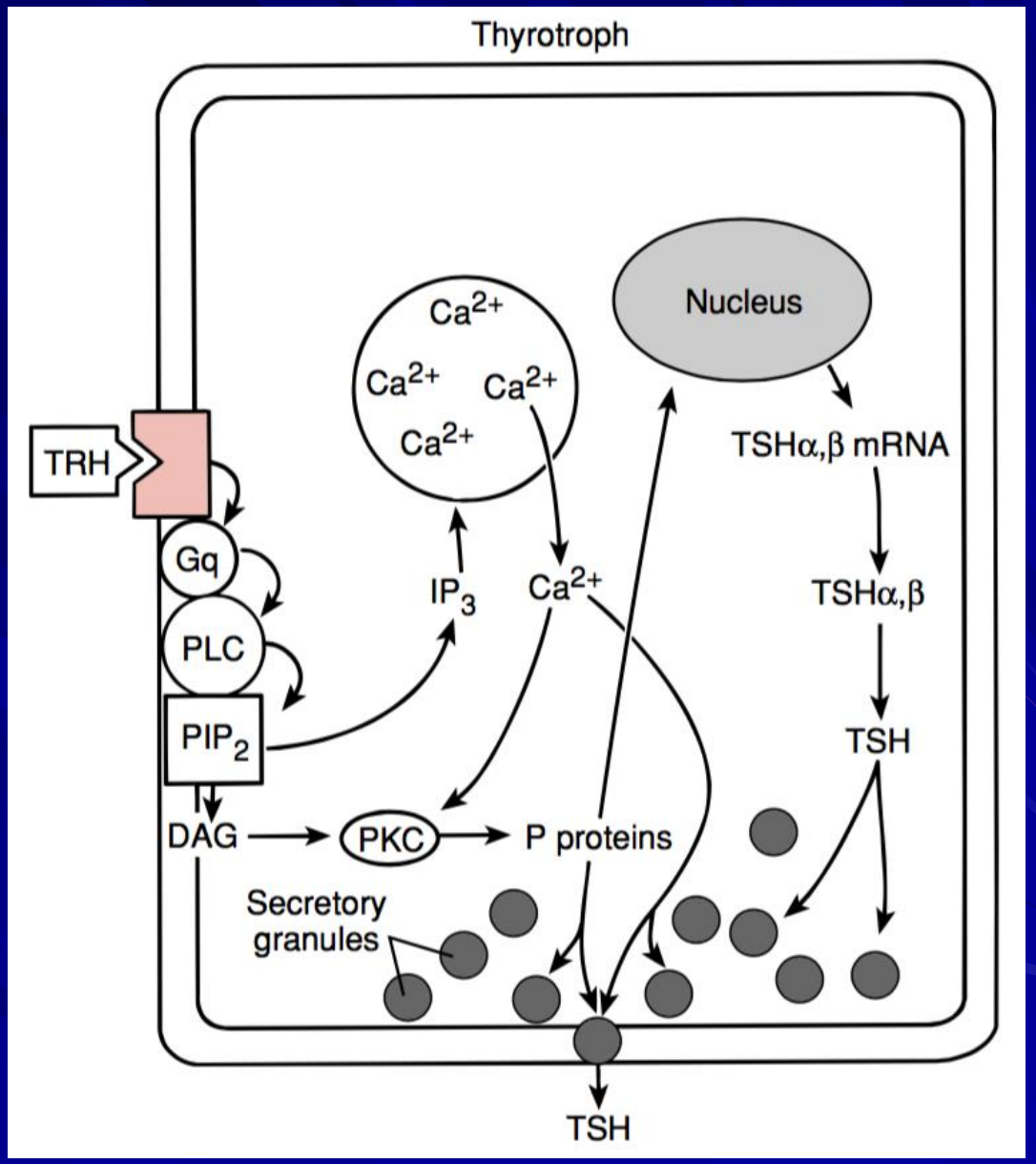




TH is also essential for the secretion of **GH**.

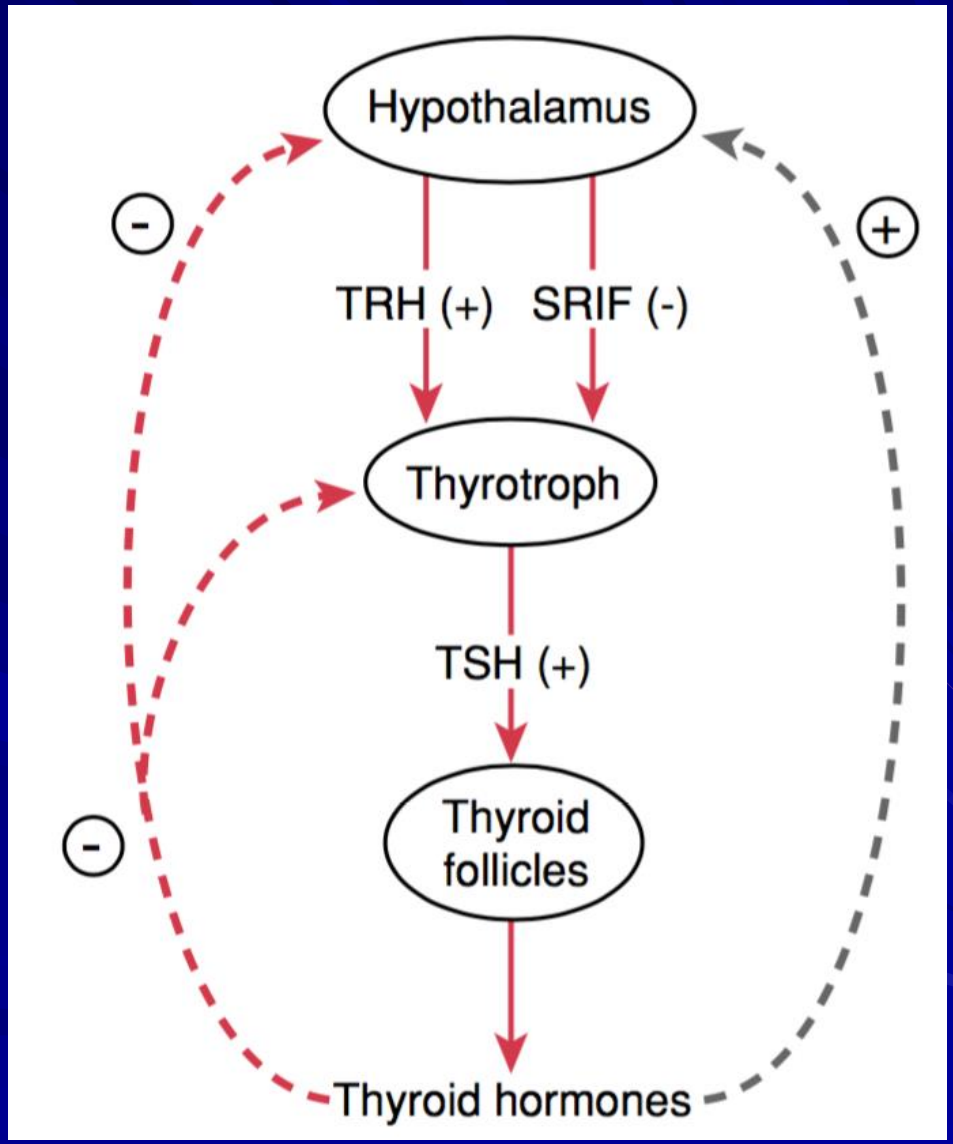
The actions of TRH on a thyrotroph

TRH binds to membrane receptors, which are coupled to phospholipase C (PLC) by G proteins (Gq). PLC hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP2) in the plasma membrane, generating inositol trisphosphate (IP3) and diacylglycerol (DAG). IP3 mobilizes intracellular stores of Ca2 . The rise in Ca2 stimulates TSH secretion. Ca2 and DAG activate protein kinase C (PKC), which phosphorylates proteins (P proteins) involved in stimulating TSH secretion and the expres-sion of the genes for the alpha and beta subunits of TSH.



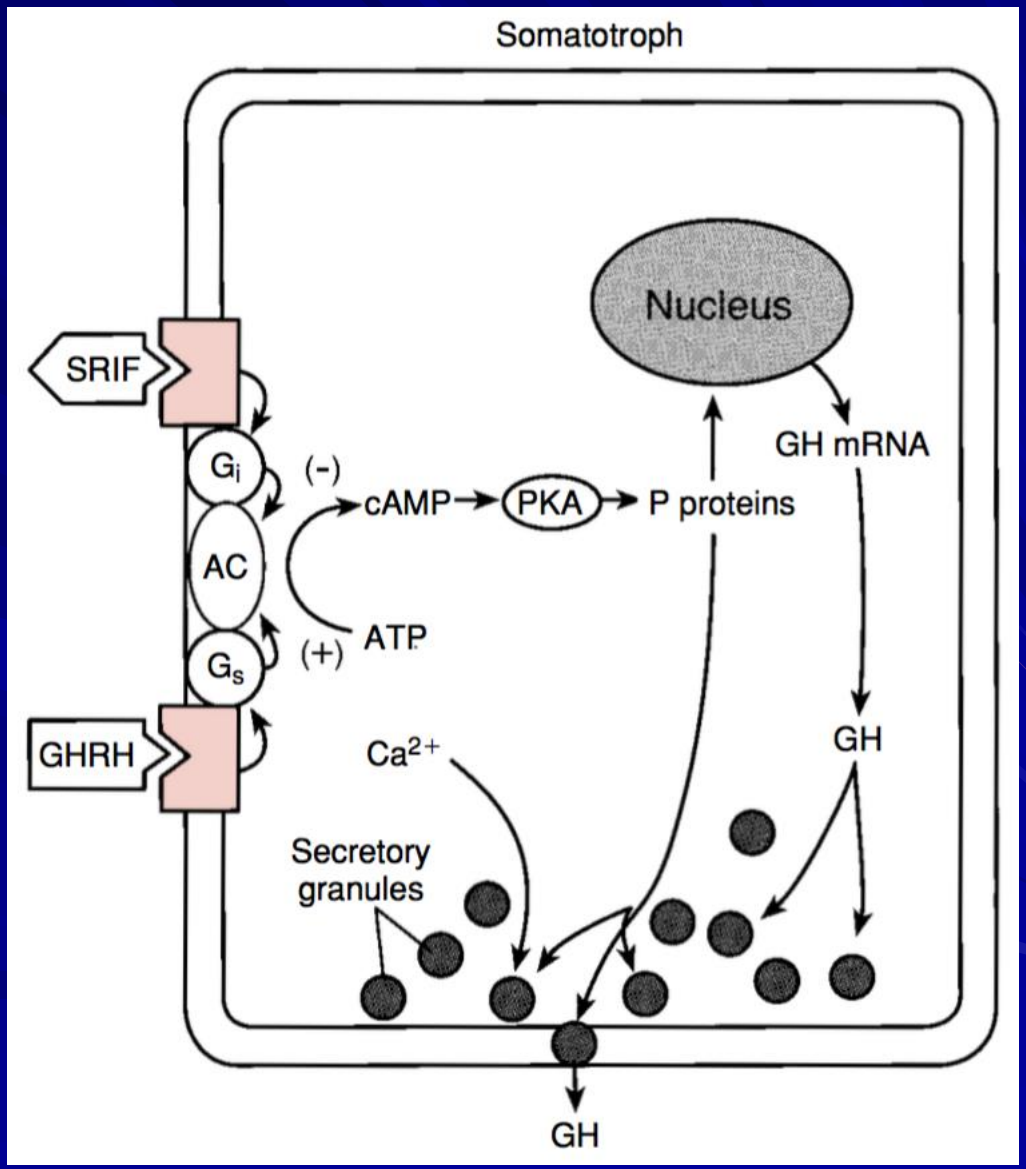
The hypothalamic-pituitary-thyroid axis

TRH stimulates and somatostatin (SRIF) inhibits TSH release by acting directly on the thyrotroph. The negative-feedback loops (-), shown in red, inhibit TRH secretion and action on the thyrotroph, causing a decrease in TSH secretion. The feedback loops (+), shown in gray, stimulate somatostatin secretion, causing a decrease in TRH secretion. SRIF, somatostatin, or somatotropin release inhibiting factor.



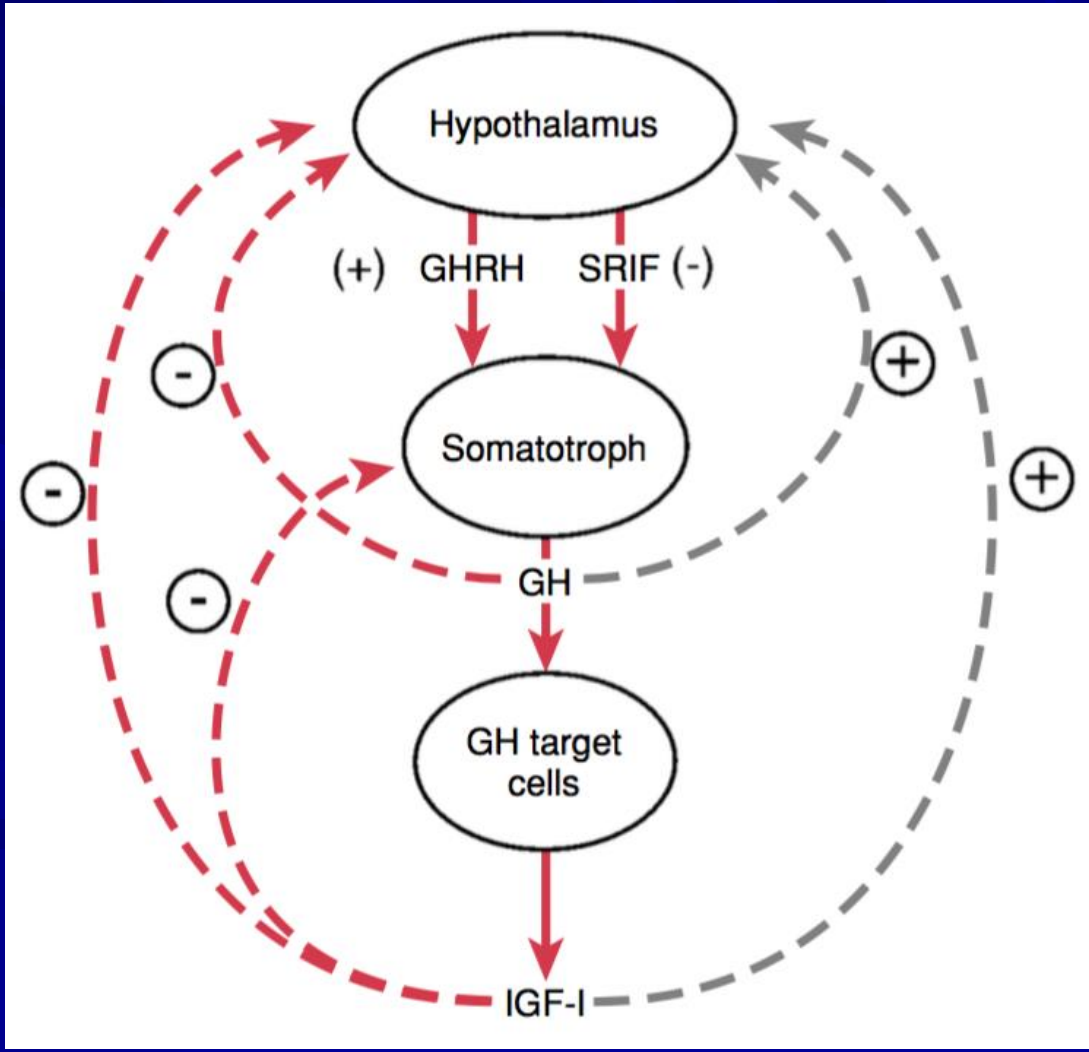
The actions of GHRH and somatostatin on a somatotroph

GHRH binds to membrane receptors coupled to adenylyl cyclase (AC) by stimulatory G proteins (Gs). Cyclic AMP (cAMP) rises in the cell and activates protein kinase A (PKA), which then phosphorylates proteins (P proteins) involved in stimulating GH secretion and the expression of the gene for GH. Ca2 is also involved in the action of GHRH on GH secretion. Somatostatin (SRIF) binds to membrane receptors coupled to AC by inhibitory G proteins (Gi). This action inhibits the ability of GHRH to stimulate adenylyl cyclase, blocking its action on GH secretion.



The hypothalamic-pituitary-GH axis

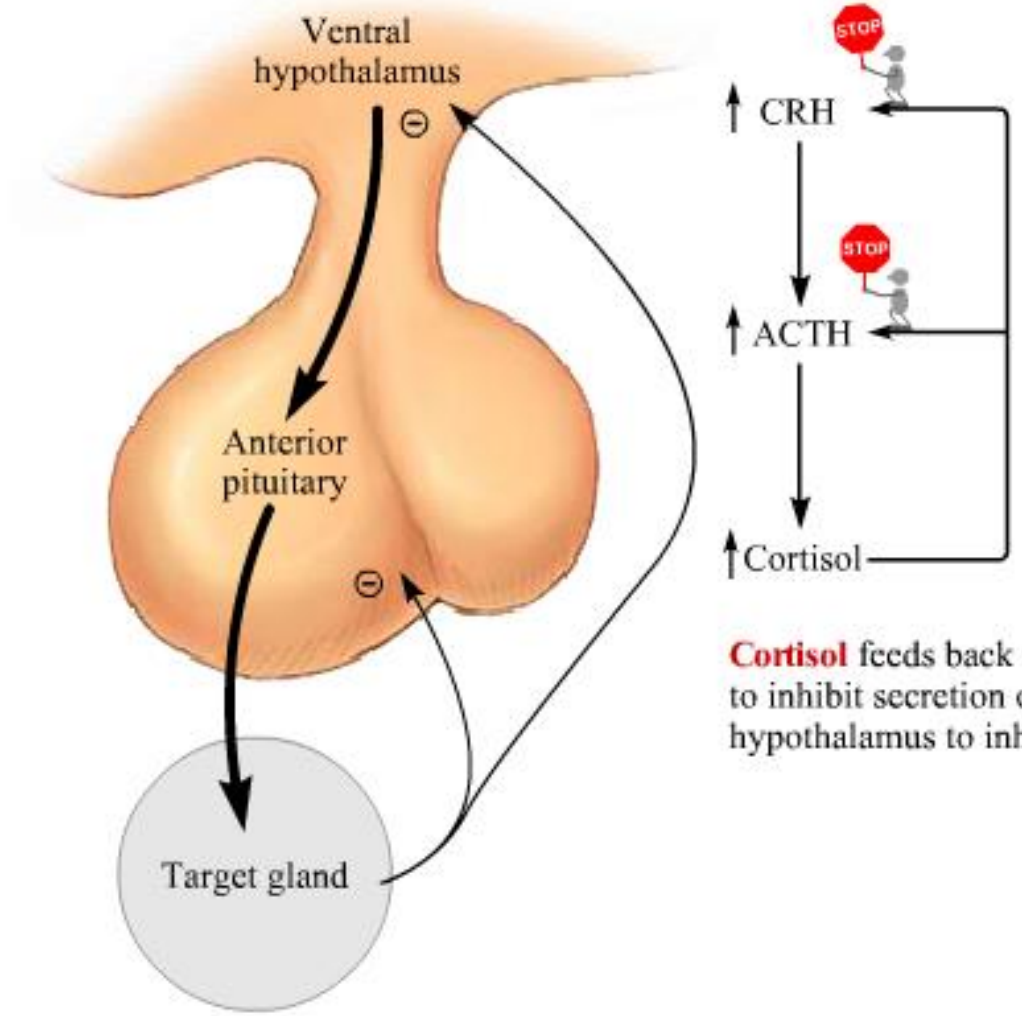
Growth hormone-releasing hormone (GHRH) stimulates, and somatostatin inhibits, GH secretion by acting directly on the somatotroph. The negative-feedback loops (-), shown in red, inhibit GHRH secretion and action on the soma- totroph, causing a decrease in GH secretion. The feedback loops (+), shown in gray, stimulate somatostatin secretion, causing a decrease in GH secretion. IGF-I, insulin-like growth factor I.



The Actions of Growth Hormone

Growth-promoting	Stimulates IGF-I gene expression by target cells; IGF-I produced by these cells has autocrine or paracrine stimulatory effect on cell division, resulting in growth
Lipolytic	Stimulates mobilization of triglycerides from fat deposits
Diabetogenic	Inhibits glucose use by muscle and adipose tissue and increases glucose production by the liver
	Inhibits the action of insulin on glucose and lipid metabolism by muscle and adipose tissue
Insulin-like	Transitory stimulatory effect on uptake and use of glucose by muscle and adipose tissue in GH-deficient individuals
	Transitory inhibitory effect on glucose production by liver of GH-deficient individuals

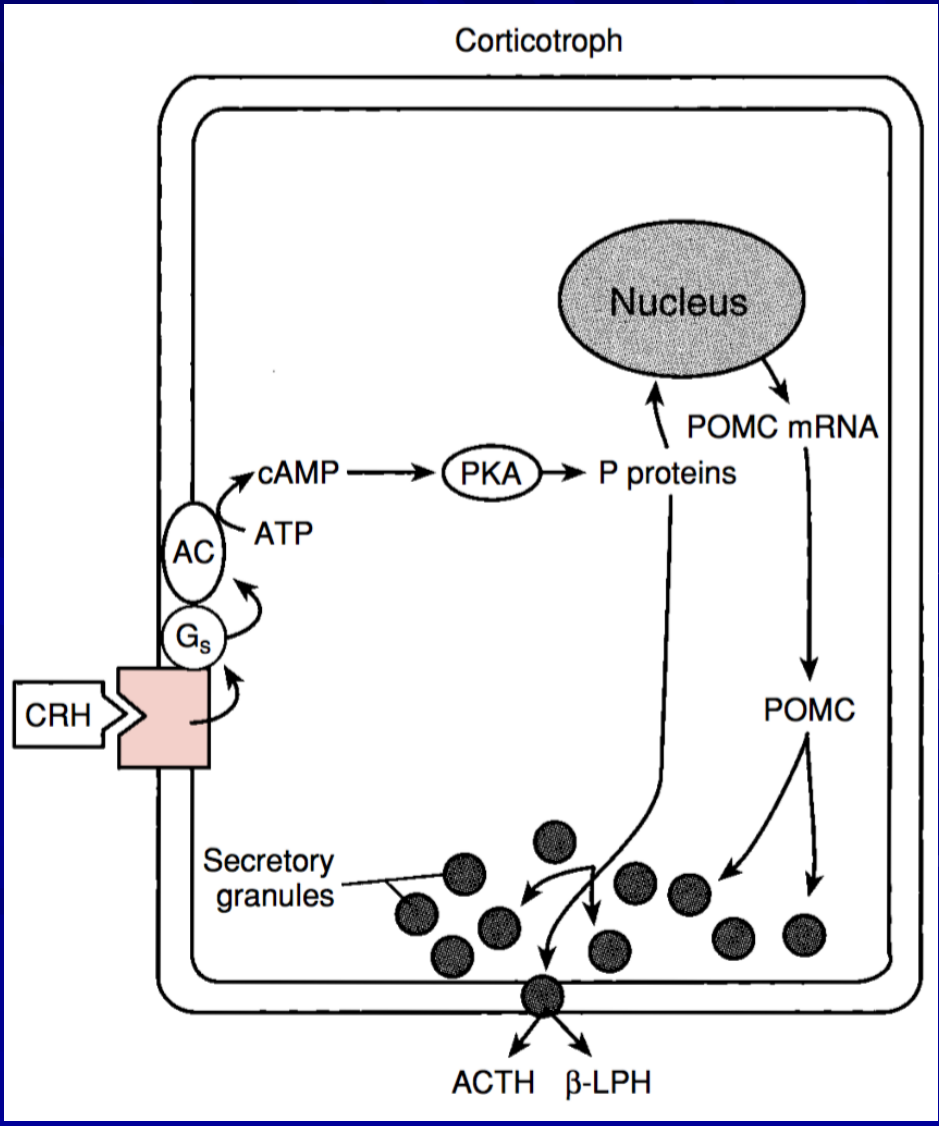
CRH -- ACTH



Cortisol feeds back to both the anterior pituitary to inhibit secretion of **ACTH**, and to the ventral hypothalamus to inhibit secretion of **CRH**.

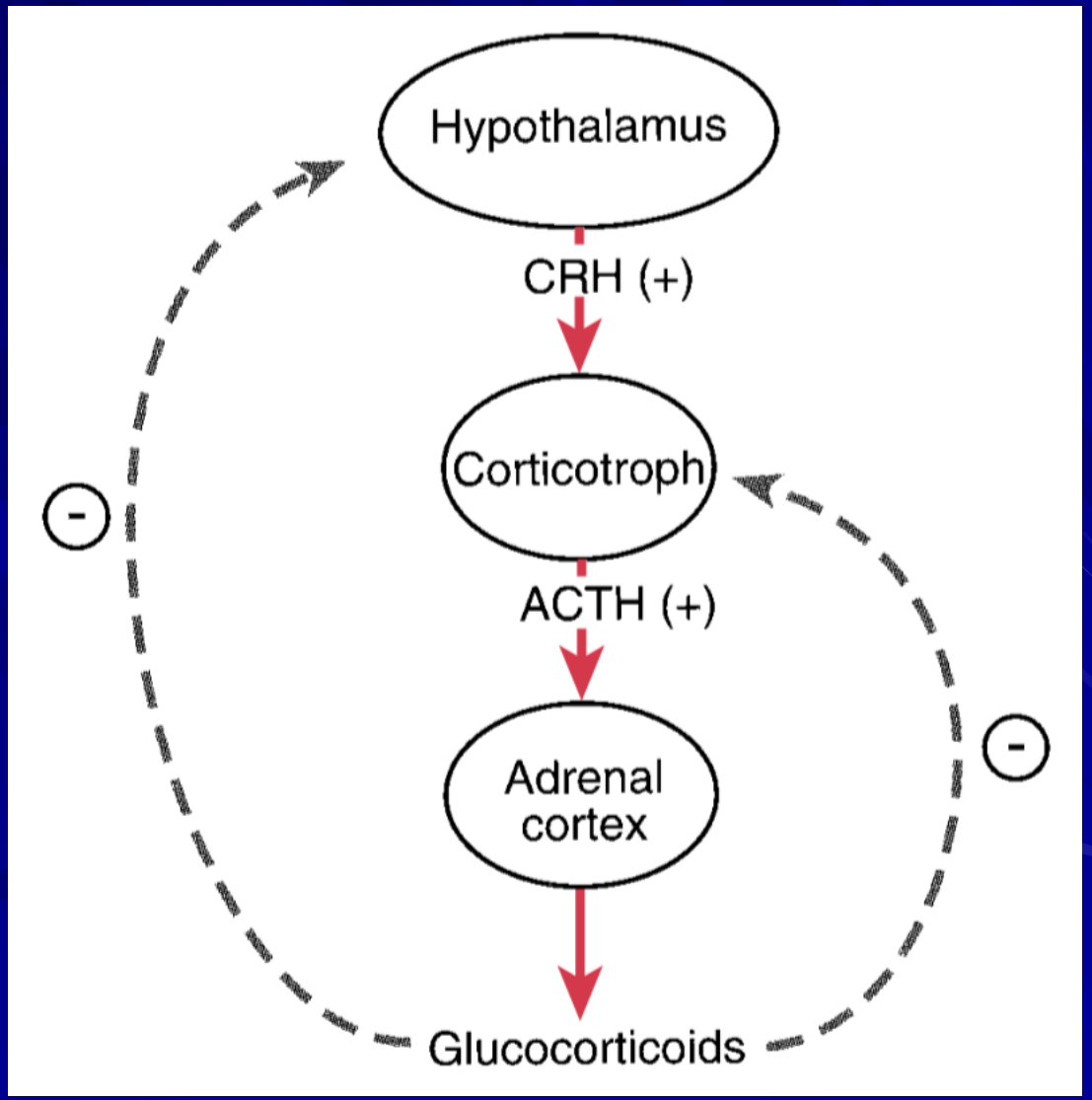
The main actions of corticotropin-releasing hormone (CRH) on a corticotroph

CRH binds to membrane receptors that are coupled to adenylyl cyclase (AC) by stimulatory G proteins (Gs). Adenylyl cyclase is stimulated, and cAMP rises in the cell. cAMP activates protein kinase A (PKA), which then phosphorylates proteins (P proteins) involved in stimulating ACTH secretion and the expression of the POMC gene.

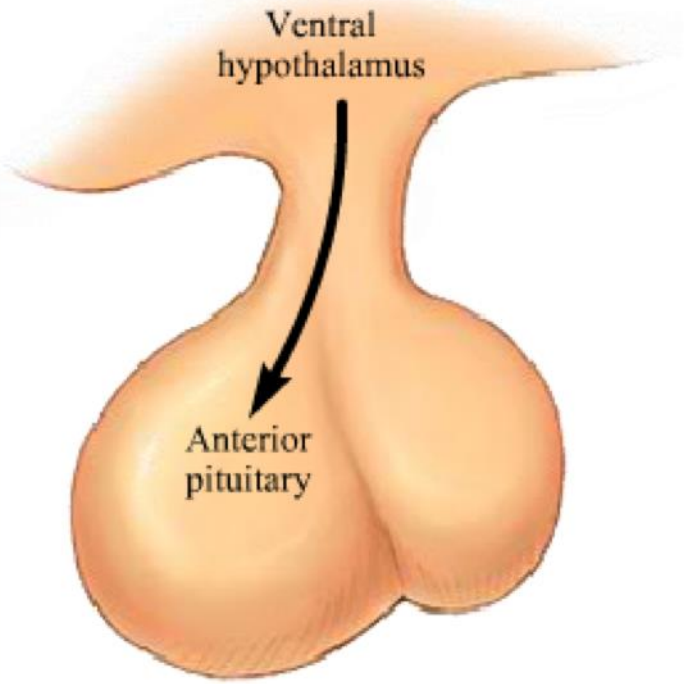


The hypothalamic-pituitary-adrenal axis

The negative-feedback actions of glucocorticoids on the corticotroph and the hypothalamus are indicated by dashed lines.



Prolactin

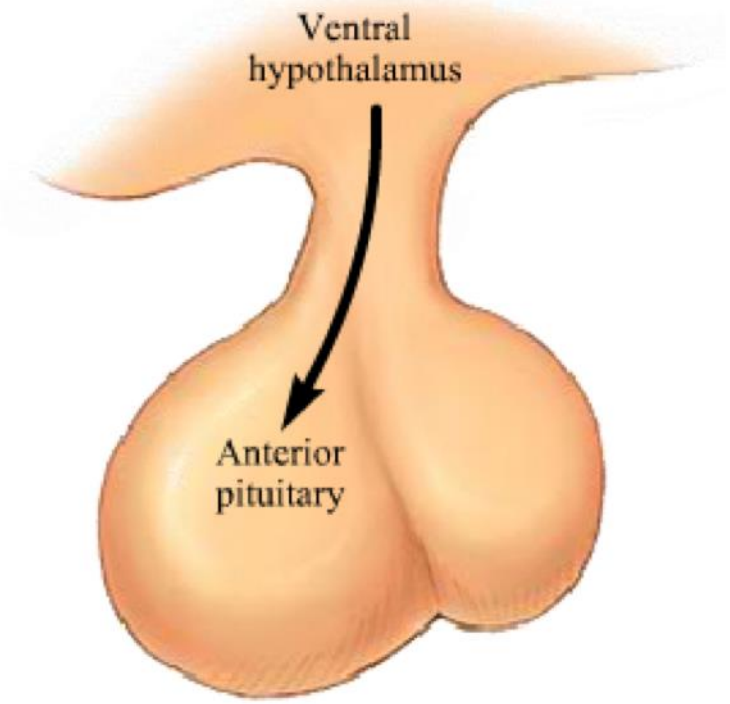


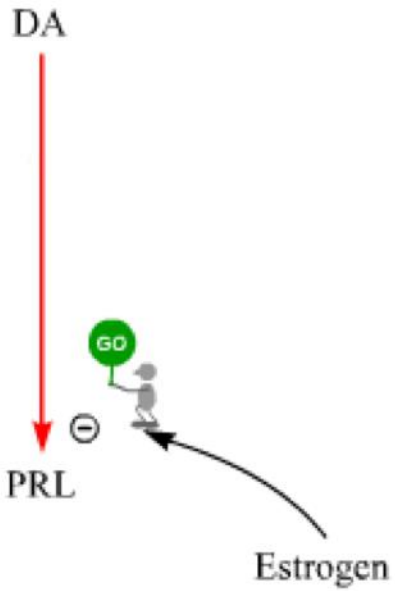
Prolactin differs from the other anterior pituitary hormones.

1) Its primary ventral hypothalamic drive is inhibitory.

2) It does not stimulate release of another hormone from a target gland.

Prolactin (cont.)

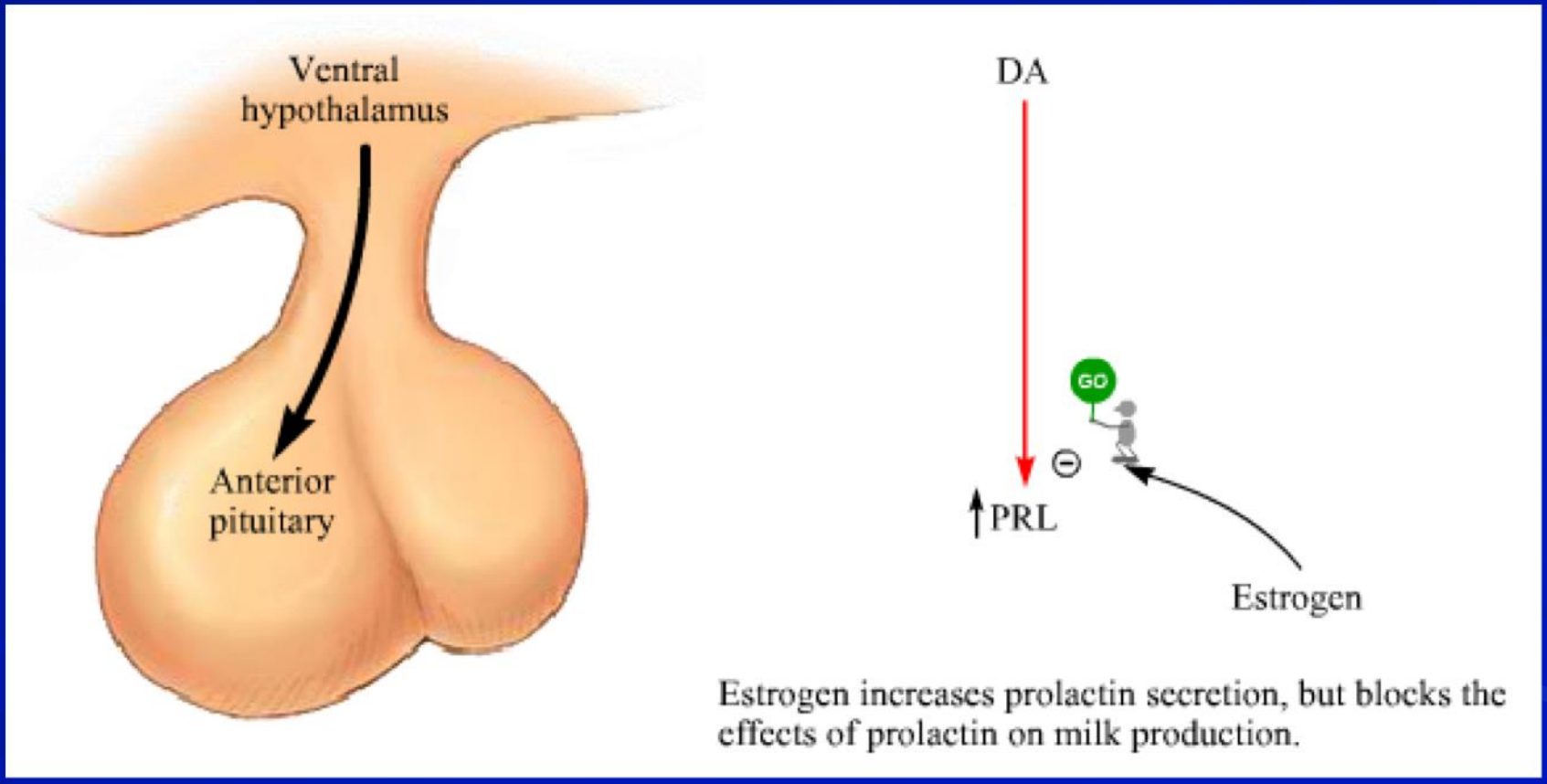




Prolactin is secreted in small amounts in both males and females.

The amount in adult females is slightly higher than the amounts in males and children because **estrogen** modulates its secretion.

Prolactin (cont.)

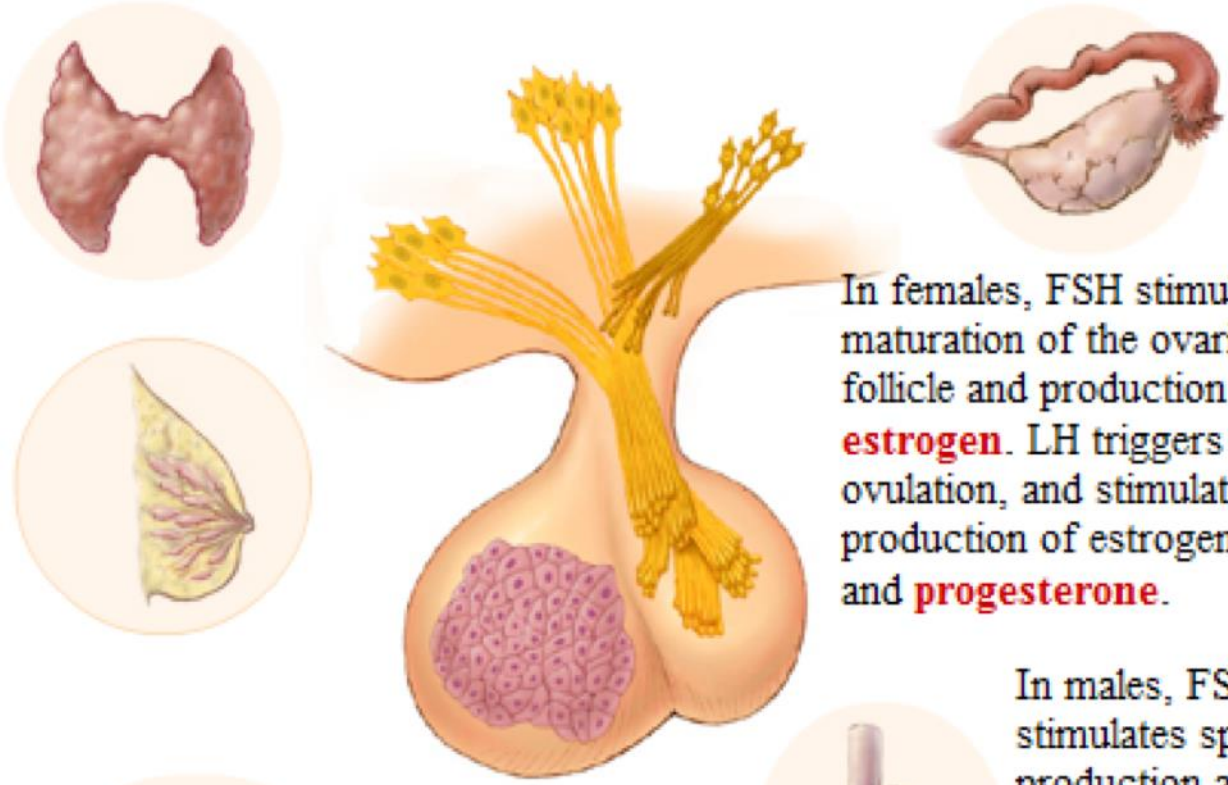


Estrogen increases prolactin secretion, but blocks the effects of prolactin on milk production.

The Hypothalamic-Pituitary Axis: Summary

TSH stimulates secretion of **thyroid hormones** by the **thyroid gland**.

PRL stimulates lactation in females. Although present in males, its action is uncertain.



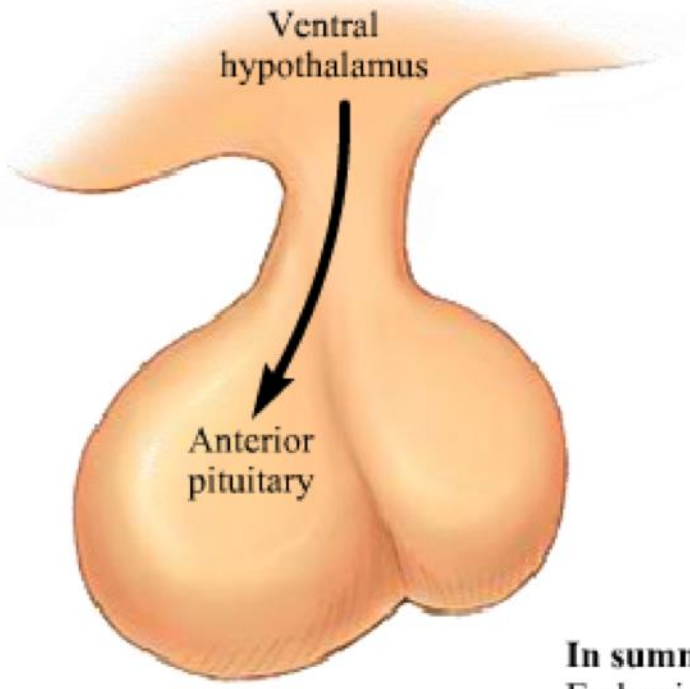
In females, FSH stimulates maturation of the ovarian follicle and production of **estrogen**. LH triggers ovulation, and stimulates production of estrogen and **progesterone**.

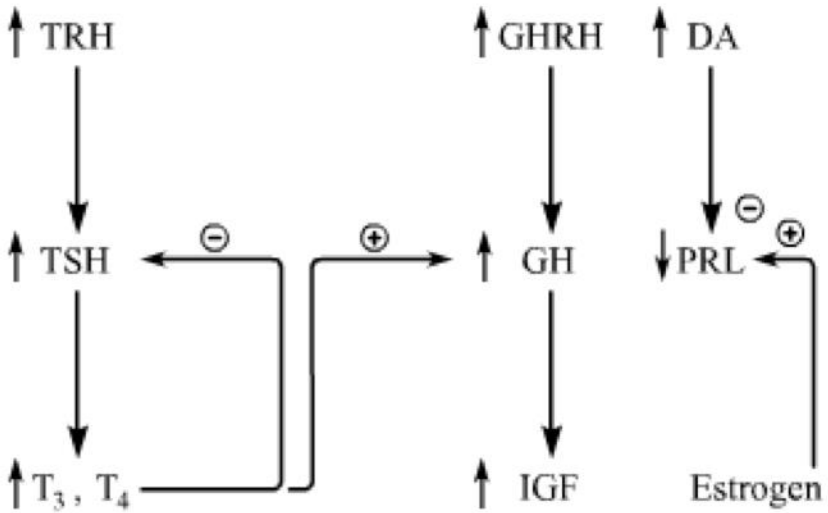
In males, FSH stimulates sperm production and LH stimulates production of **testosterone**.

GH stimulates growth and energy metabolism. Most of the growth effects of GH require intermediary proteins called **somatomedins** or **insulin-like growth factors (IGFs)**.

ACTH stimulates the secretion of **glucocorticoids** and other hormones of the **adrenal cortex**.

Endocrine Control of the Hypothalamic-Pituitary Axis: Summary





In summary:
Endocrine control of the hypothalamic- pituitary axis can be exerted by:

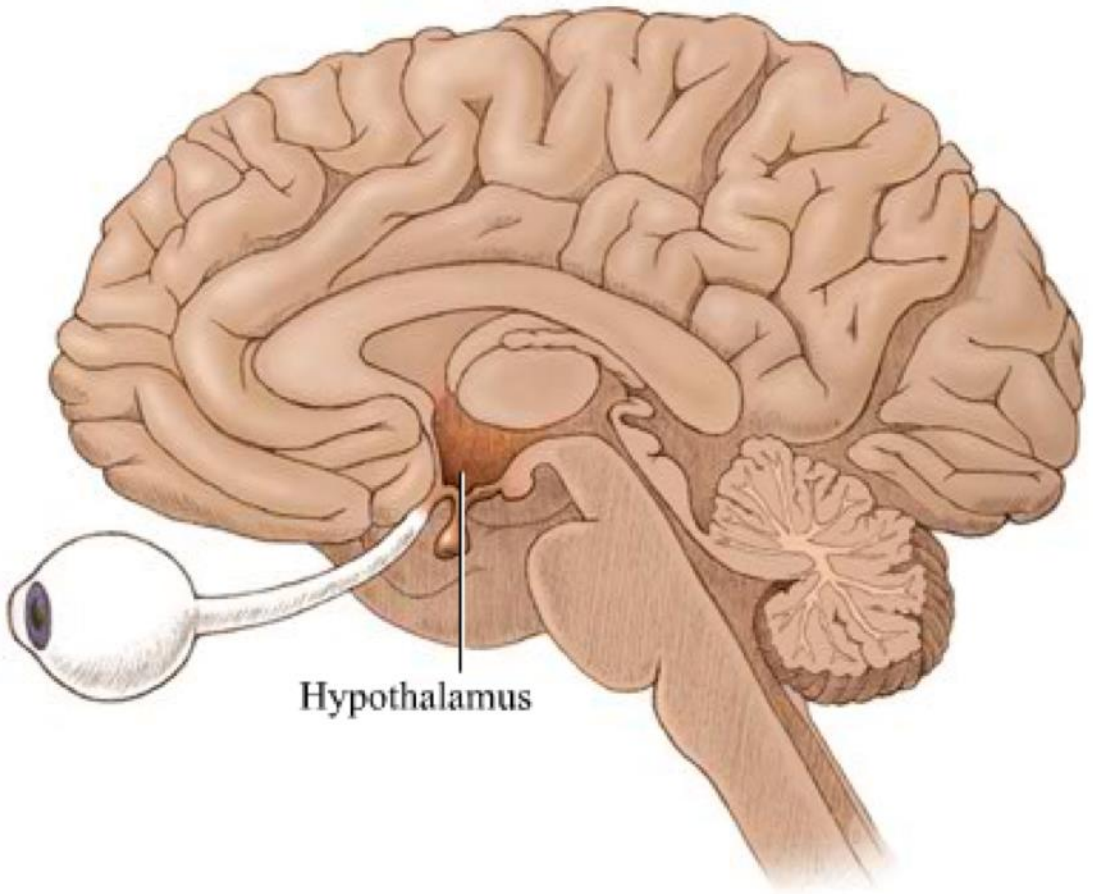
1) Negative feedback from a target hormone to a hormone of its own series

2) Modulation by a target hormone of one series to hypothalamic-pituitary hormones of another series.

Neural Control of the Hypothalamic-Pituitary Axis

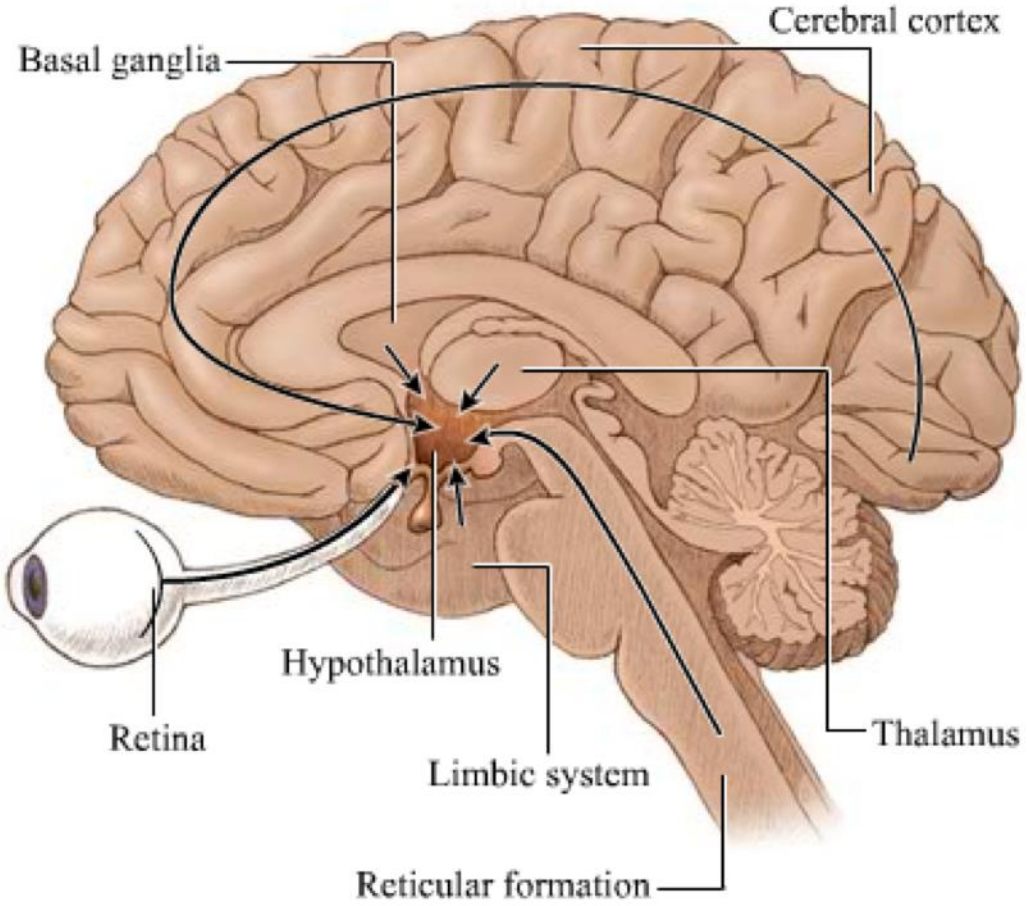
The **hypothalamus** is the highest level integrating center for the **autonomic nervous system**, and the coordinating center for neuroendocrine interactions.

Fibers from many parts of the brain influence the endocrine system via hypothalamic **neurons**.



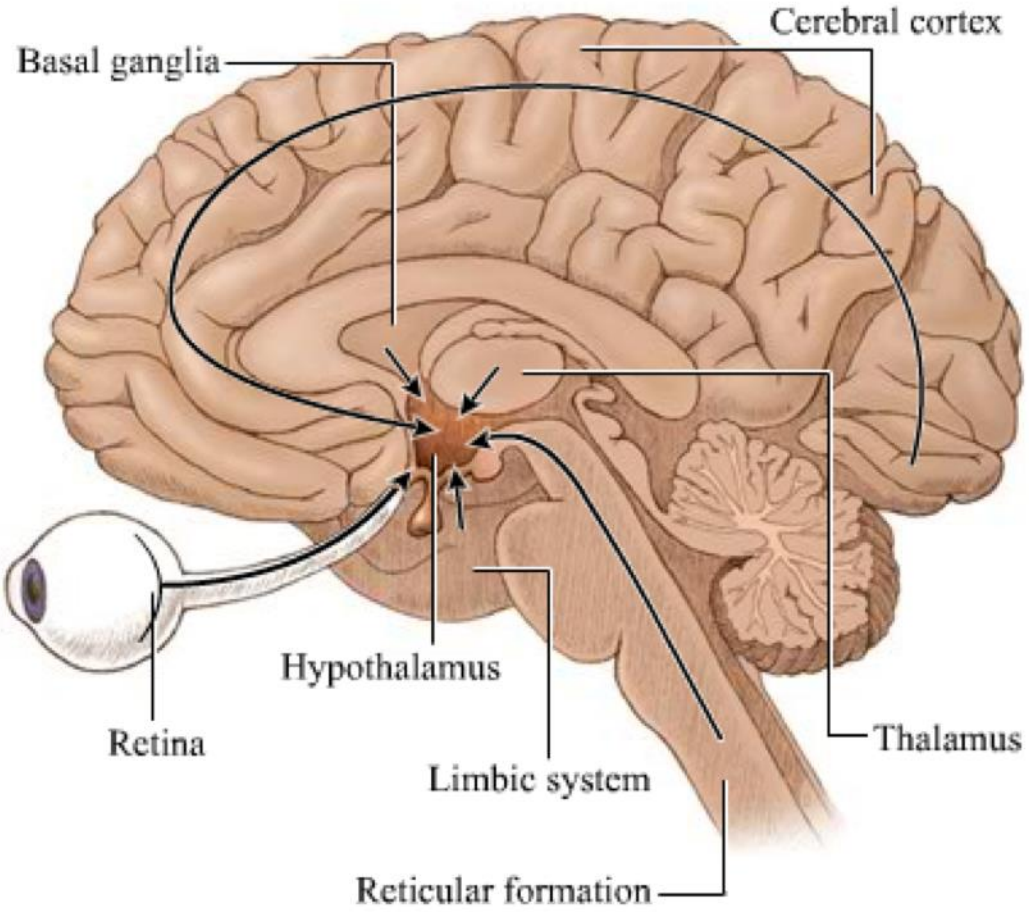
Neural Control of the Hypothalamic-Pituitary Axis

The **cerebral cortex** is widely connected both directly and indirectly to the hypothalamus. Parts of the **limbic system**, **thalamus**, **basal nuclei**, reticular formation of the **brainstem**, and the **retina** project to the hypothalamus.



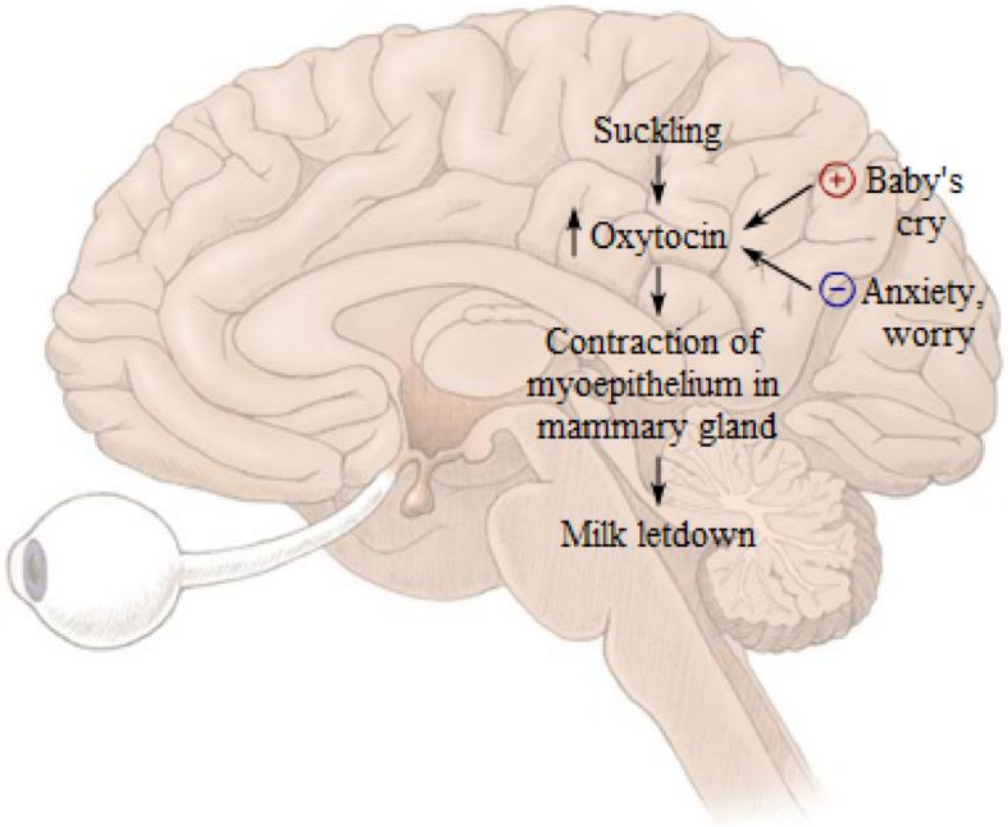
Neural Control of the Hypothalamic-Pituitary Axis

Strong emotions like fear, body housekeeping signals like ingestion of food, harmful stimuli that produce pain, trauma, or infection, environmental changes like extreme cold, and light signals from the retina can influence the endocrine system through these circuits.



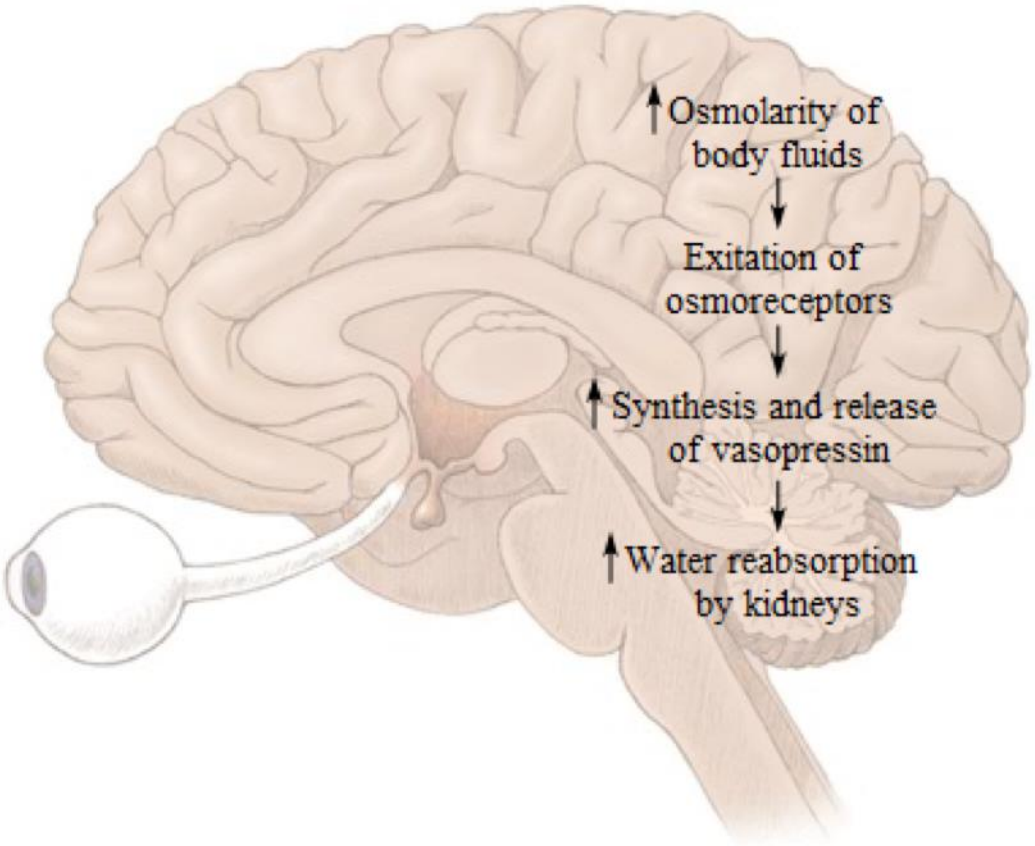
Neural Control of the Hypothalamic-Pituitary Axis

Neuroendocrine reflexes like the milk ejection reflex (milk letdown) are mediated in the hypothalamus.



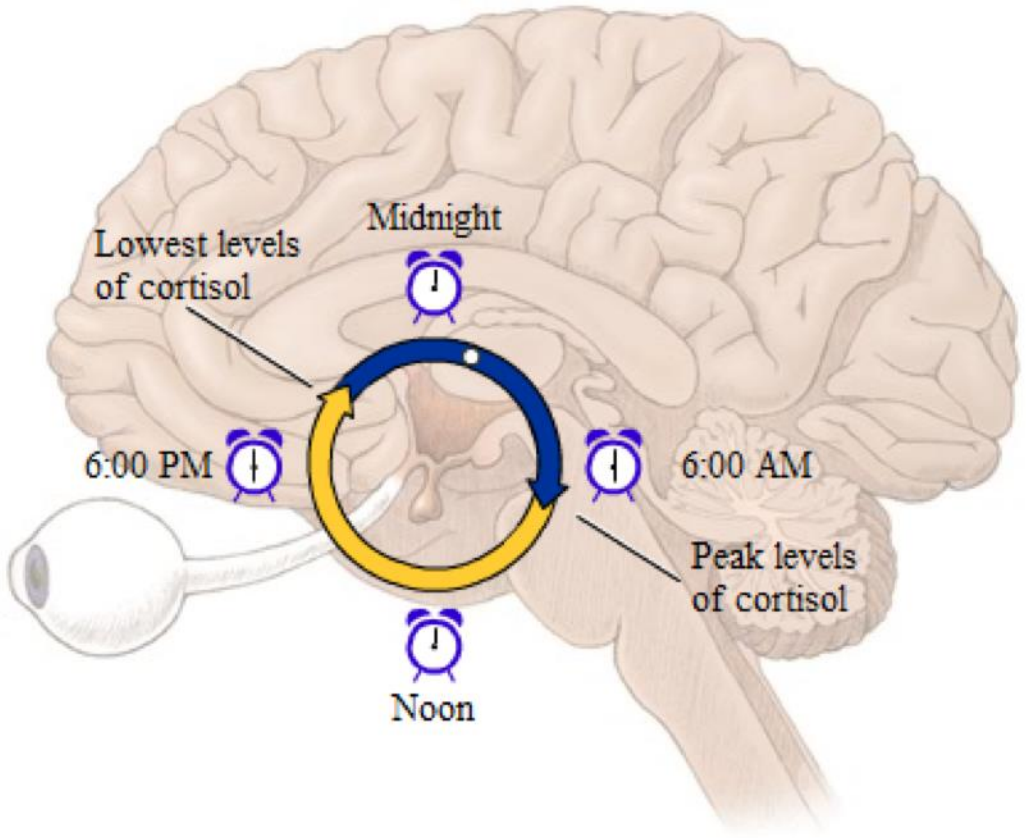
Neural Control of the Hypothalamic-Pituitary Axis

Hypothalamic neurons, including the **neurosecretory cells** that produce **vasopressin** (**ADH**), behave like **osmoreceptors**.



Neural Control of the Hypothalamic-Pituitary Axis

Neurons of the hypothalamus are pacemakers that generate circadian patterns of hormonal release by the hypothalamic-pituitary axis.



The Hypothalamic-Pituitary Axis

SUMMARY

- Hypothalamic neurons produce hormones
- Some hypothalamic hormones enter the systemic circulation from the posterior pituitary and others influence the anterior pituitary via the hypophyseal portal system
- TSH, FSH and LH, ACTH, and GH from the anterior pituitary influence secretion of a third hormone from a target gland
- Target gland hormones can exert negative feedback control of the hypothalamus and/or anterior pituitary
- Neurons throughout the brain influence the hypothalamus
- Hypo- and hypersecretion of thyroid hormone cause widespread metabolic consequences throughout the body.

Clinical significance

- Central diabetes insipidus caused by a deficiency of ADH.
- Gigantism and acromegaly caused by an excess of GH.
- Hypothyroidism caused by a deficiency of TSH.
- Hyperpituitarism, the increased secretion of one or more of the hormones normally produced by the pituitary gland.
- Hypopituitarism, the decreased secretion of one or more of the hormones normally produced by the pituitary gland.
- Panhypopituitarism a decreased secretion of most of the pituitary hormones.
- Pituitary tumors (adenomas)
- All of the functions of the pituitary gland can be adversely affected by an over or under production of associated hormones.

Summary

- The hypothalamic-pituitary axis is composed of the hypothalamus, infundibular stalk, posterior pituitary, and anterior pituitary
- Arginine vasopressin (AVP) and oxytocin are synthesized in hypothalamic neurons whose axons terminate in the posterior pituitary.
- AVP increases water reabsorption by the kidneys in response to a rise in blood osmolality or a fall in blood volume.
- Oxytocin stimulates milk letdown in the breast in response to suckling and muscle contraction in the uterus in response to cervical dilation during labor.

Summary

- The hormones ACTH, TSH, GH, FSH, LH, and PRL are synthesized in the anterior pituitary and secreted in response to hypothalamic releasing hormones carried in the hypophyseal portal circulation.
- Hypothalamic CRH stimulates ACTH release from corticotrophs, which, in turn, stimulates glucocorticoid release from the adrenal cortex, to comprise the hypothalamic-pituitary-adrenal axis.
- ACTH secretion is regulated by glucocorticoids, physical and emotional stress, AVP, and the sleep-wake cycle.

Summary

- Hypothalamic TRH stimulates TSH release from thyrotrophs, which, in turn, stimulates T3 and T4 release from the thyroid follicles, to comprise the hypothalamic-pituitary-thyroid axis.
- TSH secretion is regulated by the thyroid hormones, cold temperatures, and the sleep-wake cycle.
- Hypothalamic GHRH increases and hypothalamic SRIF decreases GH secretion from somatotrophs.

Summary

- GH secretion is regulated by the GH, IGF-I, aging, deep sleep, stress, exercise, and hypoglycemia.
- LHRH stimulates the secretion of FSH and LH from the anterior pituitary. These hormones, in turn, affect functions of the ovaries and testes.
- Dopamine inhibits the secretion of prolactin.