

HYPOTHALAMUS AND PITUITARY GLAND

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LEARNING OBJECTIVES

1. Contrast the anterior and posterior pituitary with respect to cell types and development.
2. Identify appropriate hypothalamic releasing factors that control the secretion of each of the anterior pituitary hormones.
3. Explain the importance of pulsatile and episodic secretion from the hypothalamus.
4. Diagram the short loop and long loop negative feedback control of the anterior pituitary hormone secretion. Predict changes in the secretory rates of hypothalamic, anterior pituitary and target gland hormones caused by over secretion or under secretion of any of these hormones or receptor deficit for any of these hormones.
5. Describe the regulation and roles of the posterior pituitary hormones, oxytocin and vasopressin (ADH). Name the stimuli and mechanisms that control their secretion.
6. Describe the causes and consequences of hypo-secretion of vasopressin (ADH).

INTRODUCTION

Growth, metabolism, response to stress and reproduction are complex physiological processes that require the integration of multiple systems. In the human body, the hypothalamus-pituitary gland axis serves as the "master" endocrine gland governing these functions. The release of hypothalamic neuropeptides and control of the pituitary function is regulated by afferent signals from the brain, viscera, and circulating levels of substrates and hormones. This neuroendocrine axis secretes at least 8 hormones which:

- Act directly on non-endocrine tissues [expl: growth hormone (GH), antidiuretic hormone (ADH)].
- Act to modulate the secretory activity of other endocrine glands [expl: adenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), lutenizing hormone (LH)].

ANATOMY & TERMS

Hypothalamus- is the area in the brain that is structurally and functionally connected to the pituitary gland.

Pituitary gland - is also called the hypophysis. It arises from two different tissue sources: posterior pituitary is nervous tissue (neurohypophysis) and anterior pituitary is glandular (adenohypophysis).

Posterior pituitary -is the neural portion derived from an extension of the hypothalamus (median eminence) which remains connected throughout life by a stalk, called the infundibulum (Fig 1).

Anterior pituitary – is the glandular portion derived from the mouth epithelium (Rathke's pouch) (Fig 1). It forms a cuff (pars tuberalis) around the infundibulum.

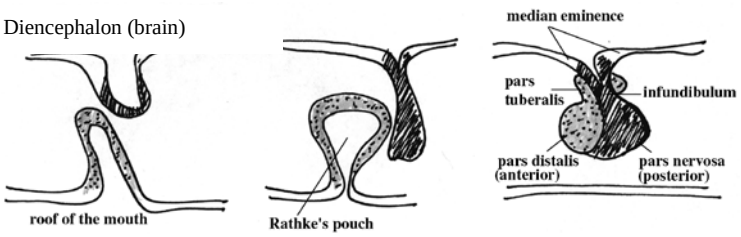


Figure 1. Embryological development of the pituitary gland.

Hypothalamic-hypophyseal portal tract. Nerve fibers from the hypothalamus terminate at capillaries in the infundibulum. The neuro-endocrine peptides secreted by these nerve fibers enter the blood and are carried by veins to a second capillary bed (portal system) in the anterior pituitary where they **govern the secretory activity of the endocrine cells in the anterior pituitary.**

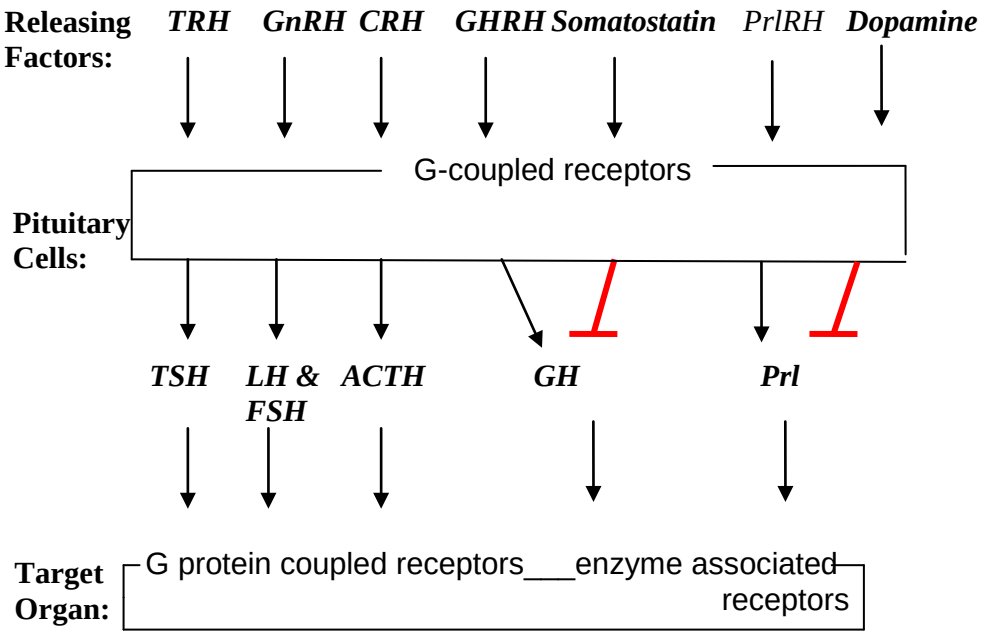
NEURO-ENDOCRINE CONTROL

Hypothalamic hormones are:

- peptides called releasing factors.
- secreted in an episodic and pulsatile manner. Why is this important?
- present at high concentrations at target cell
- present at very low concentration in systemic blood.

Actions of hypothalamic peptides include:

- binding to plasma membrane receptors.
- release of stored target hormones (in pituitary) via exocytosis.
- increase of transcription of target hormones.
- modulation of their receptor activity (up regulation; down regulation).



Summary of regulatory factors and targets for pituitary hormones

Pituitary Hormone	Hypothalamic Releasing Factor	Hypothalamic Inhibitory Factor	Target organ	Biological role
GH	GHRH	SRIF	Bone & liver	Growth
Prl	PrlRH	Dopamine	breast	milk
LH & FSH	GnRH		Gonads	Reproduction
TSH	TRH		Thyroid gland	Basal metabolic rate
ACTH	CRH		Adrenal	Response to stress

REGULATION BY FEEDBACK LOOPS

The hypothalamus regulates pituitary function with change in temperature, energy needs, or fluid balance. It is one of the few areas in the brain not sealed off from the blood (blood-brain barrier) and therefore can monitor and respond to substances within the blood, permitting hormonal feedback.

The negative feed back loops that govern the hypothalamic-pituitary axis include (Fig 2):

Long loop feedback: hormones from peripheral endocrine glands can exert feedback control on the hypothalamus and anterior pituitary. This feedback is usually negative.

Short-loop feedback: Negative feedback by pituitary hormones can inhibit the synthesis and/or secretion of the related hypothalamic hormones.

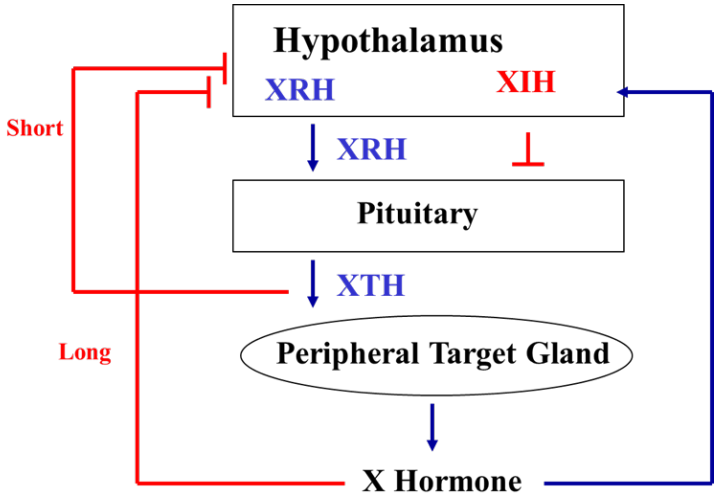


Figure 2. Negative feedback loops in a typical hypothalamus-pituitary-peripheral gland axis. X, a peripheral hormone: XTH, a pituitary tropic hormone; XRH, the releasing hormone; XIH, the inhibiting hormone.

GH SECRETION FROM ANTERIOR PITUITARY

Growth hormone (GH) secretion is governed by the hypothalamus in a pulsatile and episodic manner. Maximum secretion of GH occurs during sleep (Fig 3).

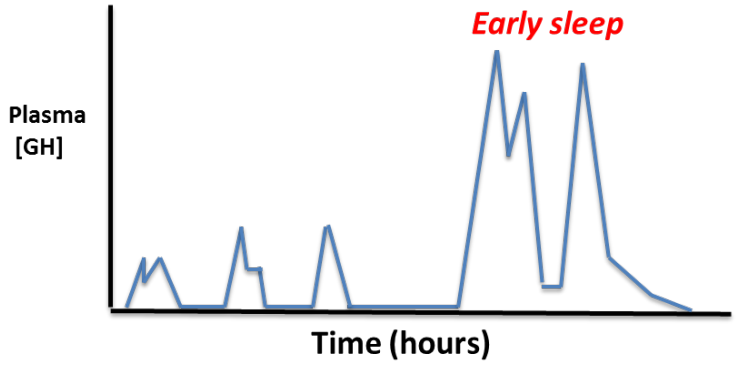


Figure 3. Growth hormone exhibits a circadian rhythm with maximal secretion during early sleep.

GH secretion is regulated in a positive manner by GHRH from the hypothalamus and in a negative manner by two hormones, insulin-like growth factor (IGF-1) from the liver and by somatostatin (SRIF) secreted by the hypothalamus (Fig 4).

Somatostatin (SRIF) and growth hormone releasing hormone (GHRH) bind to two different receptors coupled to the same second messenger but in opposing manner. Their net effect governs secretion of GH from the pituitary target cells.

What are the target organs and the effects of GH and IGF-1? After birth, GH governs longitudinal growth of the skeleton (body height). IGF-1 governs growth of the internal organs. During embryonic development, IGF-1 is essential for growth of the fetus.

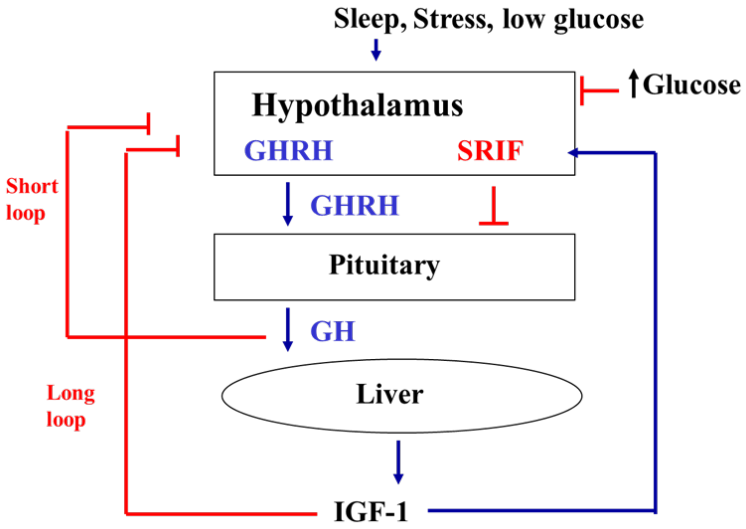


Figure 4. Regulation of GH secretion.

Note that GH alters metabolism (Fig 5) preventing glucose storage in muscle and fat. This effect raises circulating levels of glucose in the blood for ready access by growing tissues. Recently, GH has been shown to enhance growth of muscles used in anaerobic exercise such as weight lifting and to enhance the metabolism of lactic acid to glucose in the liver.

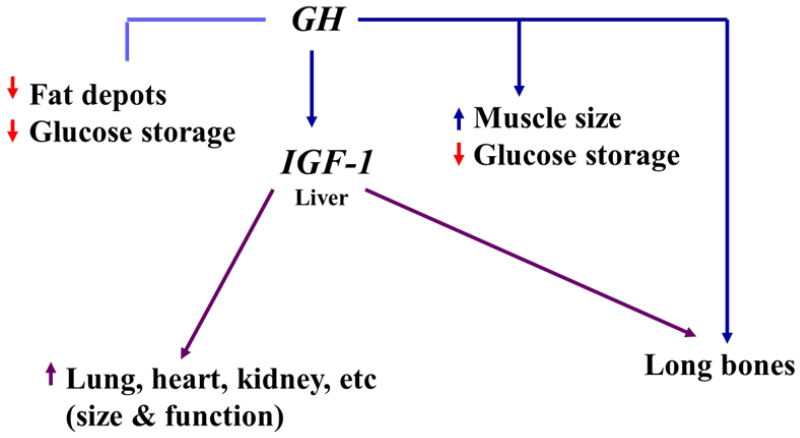


Figure 5. Effects of growth hormone (GH) on target tissues and organs.

PATHOLOGY

Hyper-secretion. Excess secretion of GH results in **acromegaly**. Acromegaly before puberty results in a **giant**. After puberty, acromegaly results in a thickening of the hands and feet and coarsening of facial features.

Hypo-secretion. Insufficiency of IGF-1 alone results in pygmies (found in Africa and Australia).
Receptor resistance for GH results in Laron Dwarfism.

Would administration of recombinant GH correct any of the phenotypes described above? If so which one(s)? What hormone would you chose to correct acromegaly?

The hypothalamus-anterior pituitary axis also regulates development and metabolism, response to stress, and reproduction. We will consider these axes in subsequent lectures.

SECRETION FROM POSTERIOR PITUITARY

Vasopressin (antidiuretic hormone, ADH) and oxytocin (OTC) are released from the posterior pituitary (Fig 1). Both are neuro-peptides which bind plasma membrane receptors in their target tissues.

Oxytocin is regulated by the suckling and the cry of an infant. It acts in both males and females to elicit "bonding" to the infant.

Antidiuretic hormone (ADH, Vasopressin) is regulated by cells in the hypothalamus that sense an increase in blood Na+ concentration (osmolality) (Fig. 6) and a significant decrease in blood volume (of 10% or more).

For example in response to dehydration, ADH is released. It acts on the kidney to retain water. At the same time the hypothalamus signals a thirst response. The intake of water and the movement of water from the urine to the blood dilute the plasma osmolality returning the blood to its normal 300 mOsM. This system is most sensitive to increases in osmolality but will be activated by a large loss in plasma volume (hemorrhage). ADH also acts on the vasculature to cause vasoconstriction of the blood vessels. Note that the net actions of this feedback loop increase blood pressure.

During osmotic stress, the posterior and anterior hypothalamus-pituitary axes interact. Activation of osmoreceptors by hyperosmolarity results in **ADH** secretion from axons terminating in the posterior pituitary, and from axons terminating in the median eminence. The ADH entering into the anterior pituitary potentiates the release of ACTH, a peptide hormone that regulates the secretion of cortisol from the adrenal glands. Cortisol acts to raise glucose in the blood during stressful states. Note that ADH alone does not increase ACTH secretion from the pituitary.

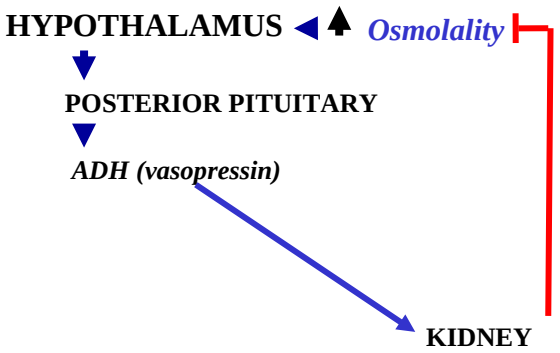


Figure 6. Feedback loop regulating body osmolality. Activation of ADH receptors in the kidney

causes the insertion of aquaporin channels into the cell surface. This enables water to move across these cells from the urine to the blood.

In the disease Diabetes Insipidus, the ADH axis is dysfunctional. If the problem is in hyposecretion of ADH, then the lesion is central. If the defect is ADH receptor resistance in the kidney, then it is a nephrogenic lesion. ADH receptor resistance can occur in one of two ways: 1) the ADH receptor is inactive or missing and 2) aquaporin (water) channels are defective or missing. An individual with receptor resistance is not able to concentrate urine.

DISRUPTION OF SIGNALLING IN H-P AXIS

As a general rule a partial or complete lesion at any step in the feedback loop results in loss of hormones downstream of the lesion and an increase in hormones upstream of the lesion.

KEY CONCEPTS

1. The hypothalamus of the brain regulates hormone secretion from the pituitary.
2. The pituitary consists of two distinct lobes (anterior and posterior) that have different embryonic origins, are regulated separately, and produce different hormone products.
3. Secretion from the hypothalamus-pituitary axis is pulsatile and episodic.
4. Regulation of the anterior pituitary is by negative feedback via hormones from target organs. There are four major feedback loops: GH, TSH, ACTH, LH and FSH.
5. The posterior pituitary secretes ADH in response to changes in osmolality and/or to volume. It secretes oxytocin in response to mechanical sensation (breast, birth canal).
6. The posterior and anterior H-P axes interact during the stressful condition of dehydration.
7. Many hypothalamic and pituitary hormones increase the survival (number and size) of their target cells and are called trophic hormones.

PROBLEMS

1. Why does hypo-secretion of GHRH in young children affect their stature? Are IGF-1 levels affected?

2. What phenotype would you expect from a defect in GH receptor signaling? What effect does this have on GH levels? What effect on IGF-1 levels?

3. What test(s) would you use to determine if an individual has excess secretion of GH?

4. Predict the effects of an insufficient release of ADH?

ANSWERS

1. Insufficient release of GHRH will diminish GH secretion. Since GH governs the growth of the long bones the affected individual will have a short stature. IGF-1 levels will be reduced because IGF-1 is a target hormone of GH.

2. A defect in GH receptor signaling would result in a loss or reduction in GH effects on the target tissues, so again short stature. GH levels will increase; IGF-1 levels will be reduced.

3. RIA to measure circulating GH and then a suppression test in which glucose is administered and then GH levels are measured in the blood by RIA. Secretion of GH should fall if the pituitary is responsive.

4. Insufficient release of ADH causes diabetes insipidus. These individuals can not concentrate their urine. They drink copious amounts of fluids to compensate.