

Chapter 4

The Hypothalamus and Pituitary Gland

The target cells for most of the hormones produced in these tissues are themselves endocrine cells, and a seemingly small initial signal is thus amplified to cause widespread effects on many cells and tissues. The close anatomical and functional relationships between hypothalamus and pituitary force an integrated discussion of these organs. The focus here is to introduce the major hormones produced by these organs, with significant emphasis on how

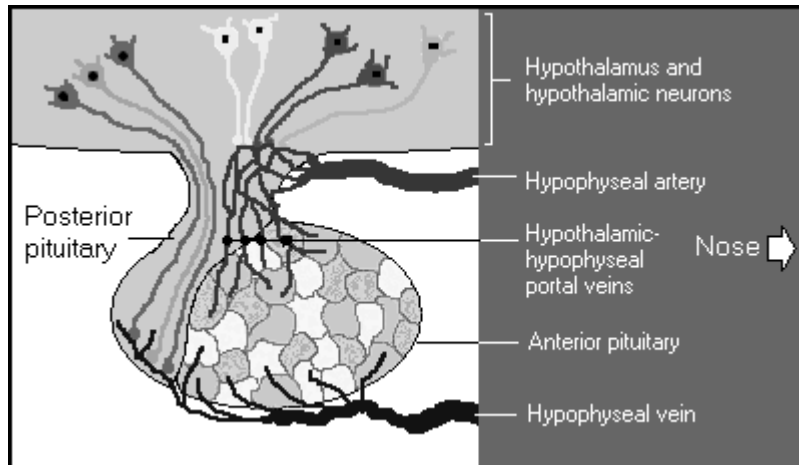
4.1. Functional Anatomy of the Hypothalamus and Pituitary Gland

The hypothalamus is a region of the brain that controls an immense number of bodily functions. It is located in the middle of the base of the brain, and encapsulates the ventral portion of the third ventricle. The pituitary gland, also known as the *hypophysis*, is a roundish organ that lies immediately beneath the hypothalamus, resting in a depression of the base of the skull called the *sella turcica*. The pituitary gland is composed of two distinctive parts:

- The **anterior pituitary** (adenohypophysis) is a classical gland composed predominantly of cells that secrete protein hormones.
- The **posterior pituitary** (neurohypophysis) is not really an organ, but an extension of the hypothalamus. It is composed largely of the axons of hypothalamic neurons which extend downward as a large bundle behind the anterior pituitary. It also forms the so-called **pituitary stalk**, which appears to suspend the anterior gland from the hypothalamus.

The anterior and posterior pituitary have separate embryological origins. In many mammals, there is also an intermediate lobe (*pars intermedia*) between the anterior and posterior pituitary. A key to understanding the endocrine relationship between hypothalamus and anterior pituitary is to appreciate the vascular connections between these organs. Secretion of hormones from the anterior pituitary is under strict control by hypothalamic hormones. These hypothalamic hormones reach the anterior pituitary through the following route:

A branch of the hypophyseal artery ramifies into a capillary bed in the lower hypothalamus, and hypothalamic hormones destined for the anterior pituitary are secreted into that capillary blood. Blood from those capillaries drains into **hypothalamic-hypophyseal portal veins** which branch again into another series of capillaries within the anterior pituitary. Capillaries within the anterior pituitary, which carry hormones secreted by that gland, coalesce into veins that drain into the systemic venous blood. Those veins also collect capillary blood from the posterior pituitary gland. The utility of this unconventional vascular system is that minute quantities of hypothalamic hormones are carried in a concentrated form directly to their target cells in the anterior pituitary, and are not diluted out in the systemic circulation

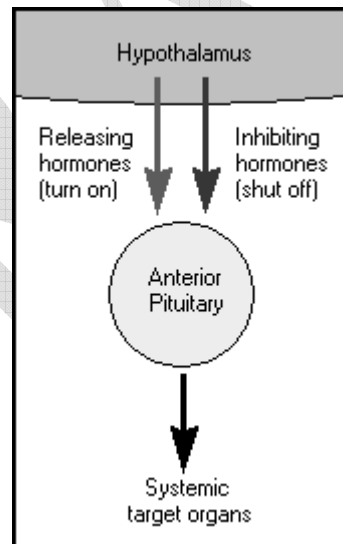


4.2. Histology of the Pituitary Gland

The pituitary gland or hypophysis is derived from two embryologically-distinct tissues. As such, it is composed of both neural and glandular tissue. Both tissues produce hormones that affect a large number of physiological processes.

4.3. Hypothalamic and Pituitary Hormones

The pituitary gland is often portrayed as the "master gland" of the body. Such praise is justified in the sense that the anterior and posterior pituitary secrete a battery of hormones that collectively influence all cells and affect virtually all physiologic processes.



The pituitary gland may be king, but the power behind the throne is clearly the hypothalamus. As alluded to in the last section, some of the neurons within the hypothalamus - neurosecretory neurons - secrete hormones that strictly control secretion of hormones from the anterior pituitary. The hypothalamic hormones are referred to as **releasing hormones** and **inhibiting hormones**, reflecting their influence on anterior pituitary hormones.

Hypothalamic releasing and inhibiting hormones are carried directly to the anterior pituitary gland via hypothalamic-hypophyseal portal veins. Specific hypothalamic hormones bind to receptors on specific anterior pituitary cells, modulating the release of the hormone they produce.

As an example, thyroid-releasing hormone from the hypothalamus binds to receptors on anterior pituitary cells called thyrotrophs, stimulating them to secrete thyroid-stimulating hormone or TSH. The anterior pituitary hormones enter the systemic circulation and bind to their receptors on other target organs. In the case of TSH, the target organ is the thyroid gland.

Clearly, robust control systems must be in place to prevent over or under-secretion of hypothalamic and anterior pituitary hormones. A prominent mechanism for control of the releasing and inhibiting hormones is negative feedback, as described in general in a previous section.

The following table summarizes the major hormones synthesized and secreted by the pituitary gland, along with summary statements about their major target organs and physiologic effects.

	Hormone	Target Organ (s)	Physiologic Effects
Anterior Pituitary	Growth Hormone (GH)	Liver, adipose	Promotes growth and metabolisms
	Thyroid-Stimulating Hormone (TSH)	Thyroid gland	Stimulates thyroid hormone secretion
	Adrenocorticotropic hormone (ACTH)	Adrenal cortex	Stimulates secretion of glucocorticoids
	Prolactin	Mammary glands	Milk production
	Luteinizing hormone (LH)	Gonads	Control of reproductive function
	Follicle Stimulating hormone (FSH)	Gonads	Control of reproductive function
Posterior Pituitary	Antidiuretic Hormone (ADH)	Kidney	Water retention
	Oxytocin	Uterus	Stimulates milk ejection and uterine contraction

As seen in the table above, the anterior pituitary synthesizes and secretes 6 major hormones. Individual cells within the anterior pituitary secrete a single hormone (or possibly two in some cases). Thus, the anterior pituitary contains at least six distinctive endocrinocytes. The cells that secrete thyroid-stimulating hormone do not also secrete growth hormone, and they have receptors for thyroid-releasing hormone, not growth hormone-releasing hormone.

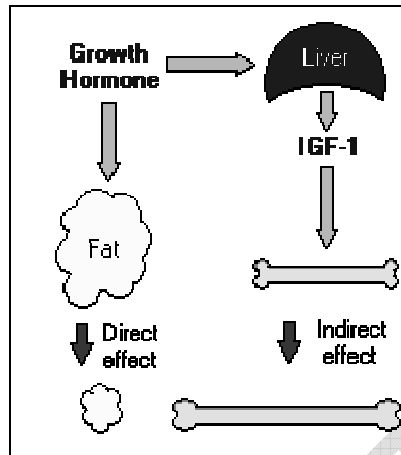
4.3. 1. Growth Hormone

Growth hormone, also known as *somatotropin*, is a protein hormone of about 190 amino acids that is synthesized and secreted by cells called *somatotrophs* in the anterior pituitary. It is a major participant in control of several complex physiologic processes, including growth and metabolism. Growth hormone is also of considerable interest as a drug used in both humans and animals.

(i) Physiologic Effects of Growth Hormone

Growth hormone has two distinct types of effects: direct and indirect effects.

- **Direct effects** are the result of growth hormone binding its receptor on target cells. Fat cells (adipocytes), for example, have growth hormone receptors, and growth hormone stimulates them to break down triglyceride and suppresses their ability to take up and accumulate circulating lipids.
- **Indirect effects** are mediated primarily by a **insulin-like growth factor-1 (IGF-1)**, a hormone that is secreted from the liver and other tissues in response to growth hormone. A majority of the growth promoting effects of growth hormone is actually due to IGF-1 acting on its target cells.



(ii) Effects on Growth

Growth is a very complex process, and requires the coordinated action of several hormones. The major role of growth hormone in stimulating body growth is to stimulate the liver and other tissues to secrete IGF-1. IGF-1 stimulates proliferation of chondrocytes (cartilage cells), resulting in bone growth. Growth hormone has a direct effect on bone growth in stimulating differentiation of chondrocytes. IGF-1 also is a key player in muscle growth. It stimulates both the differentiation and proliferation of myoblasts. It also stimulates amino acid uptake and protein synthesis in muscle and other tissues.

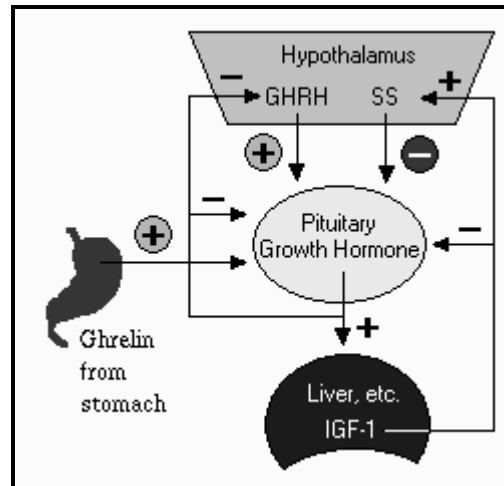
(iii) Metabolic Effects

Growth hormone has important effects on protein, lipid and carbohydrate metabolism. In some cases, there is a direct effect, in others, IGF-1 is the critical mediator, and some cases both direct and indirect effects are at play.

- **Protein metabolism:** In general, growth hormone stimulates protein anabolism in many tissues. This effect reflects increased amino acid uptake, increased protein synthesis and decreased oxidation of proteins.
- **Fat metabolism:** Growth hormone enhances the utilization of fat by stimulating triglyceride breakdown and oxidation in adipocytes.
- **Carbohydrate metabolism:** Growth hormone is one of a battery of hormones that serves to maintain blood glucose within a normal range. Growth hormone is often said to have anti-insulin activity, because it suppresses the abilities of insulin to stimulate uptake of glucose in peripheral tissues and enhance glucose synthesis in the liver. Somewhat paradoxically, administration of growth hormone stimulates insulin secretion, leading to hyperinsulinemia.

(iv) Control of Growth Hormone Secretion

Production of growth hormone is modulated by many factors, including stress, exercise, nutrition, sleep and growth hormone itself. However, its primary controllers are two hypothalamic hormones and one hormone from the stomach:



- **Growth hormone-releasing hormone (GHRH)** is a hypothalamic peptide that stimulates both the synthesis and secretion of growth hormone.
- **Somatostatin (SS)** is a peptide produced by several tissues in the body, including the hypothalamus. Somatostatin inhibits growth hormone release in response to GHRH and to other stimulatory factors such as low blood glucose concentration.
- **Ghrelin** is a peptide hormone secreted from the stomach. Ghrelin binds to receptors on somatotrophs and potently stimulates secretion of growth hormone.

Growth hormone secretion is also part of a negative feedback loop involving IGF-1. High blood levels of IGF-1 lead to decreased secretion of growth hormone not only by directly suppressing the somatotroph, but by stimulating release of somatostatin from the hypothalamus. Growth hormone also feeds back to inhibit GHRH secretion and probably has a direct (autocrine) inhibitory effect on secretion from the somatotroph.

Integration of all the factors that affect growth hormone synthesis and secretion lead to a pulsatile pattern of release. Basal concentrations of growth hormone in blood are very low. In children and young adults, the most intense period of growth hormone release is shortly after the onset of deep sleep.

(v) Disease States

States of both growth hormone deficiency and excess provide very visible testaments to the role of this hormone in normal physiology. Such disorders can reflect lesions in either the hypothalamus, the pituitary or in target cells. A deficiency state can result not only from a deficiency in production of the hormone, but in the target cell's response to the hormone.

Clinically, deficiency in growth hormone or receptor defects are as growth retardation or dwarfism. The manifestation of growth hormone deficiency depends upon the age of onset of the disorder and can result from either heritable or acquired disease.

The effect of excessive secretion of growth hormone is also very dependent on the age of onset and is seen as two distinctive disorders:

- **Giantism** is the result of excessive growth hormone secretion that begins in young children or adolescents. It is a very rare disorder, usually resulting from a tumour of somatotrophs.
- **Acromegaly** results from excessive secretion of growth hormone in adults. The onset of this disorder is typically insidious. Clinically, an overgrowth of bone and connective leads to a change in appearance that might be described as having "coarse features". The excessive growth hormone and IGF-1 also lead to metabolic derangements, including glucose intolerance.

(vi) Pharmaceutical and Biotechnological Uses of Growth Hormone

Human growth hormone is commonly used to treat children of pathologically short stature. Although growth hormone therapy is generally safe, it is not as safe as no therapy and does entail unpredictable health risks. Parents that request growth hormone therapy for children of essentially-normal stature are clearly misguided.

Growth hormone enhances milk production in dairy cattle and stimulate muscle growth and reduce deposition of fat in pigs.

(vii) Growth Hormone and Aging

Normal Changes in the Growth Hormone Axis with Aging

The rate of GH secretion from the anterior pituitary is highest around puberty, and declines progressively thereafter. This age-related decline in GH secretion involves a number of changes in the GH axis, including decreased serum levels of insulin-like growth factor-1 (IGF-1) and decreased secretion of growth hormone-releasing hormone from the hypothalamus. The cause of the normal age-related decrease in GH secretion is due to increased secretion of somatostatin, the GH-inhibiting hormone.

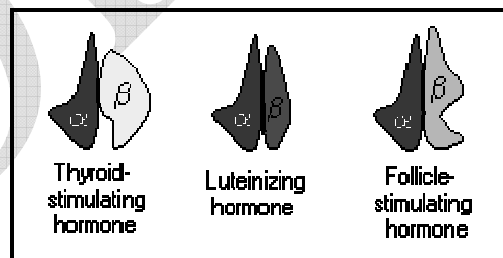
Normal aging is accompanied by a number of catabolic effects, including a decrease in lean mass, increase in fat mass, and decrease in bone density. Associated with these physiologic changes is a clinical picture often referred to as the *somatopause*: frailty, muscle atrophy, relative obesity, increased frequency of fractures and disordered sleep. These clinical signs of aging are, the manifestation of a very complex set of changes which involve, at least in part, the GH-axis.

GH Replacement Therapy in GH-deficient Adults

Adult-onset GH deficiency in humans is almost always due to pituitary disease, usually from a tumour or therapeutic efforts to treat a tumour. Such patients have increased risk of death from cardiovascular disease, and, relative to age-matched controls, show increased fat mass, reduced muscle mass and strength, lower bone density, and higher serum lipid concentrations. Additionally, they suffer from reduced vigor, sexual dysfunction and emotional problems.

4.3. 2. Thyroid-Stimulating Hormone (Thyrotropin)

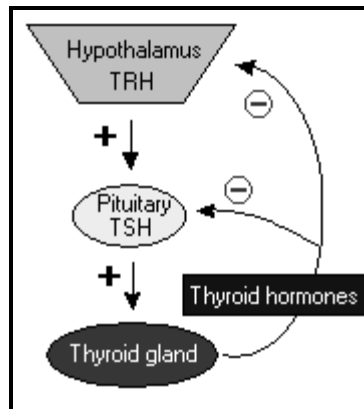
Thyroid-stimulating hormone, also known as thyrotropin, is secreted from cells in the anterior pituitary called *thyrotrophs*, finds its receptors on epithelial cells in the thyroid gland, and stimulates that gland to synthesize and release thyroid hormones.



TSH is a glycoprotein hormone composed of two subunits which are non-covalently bound to one another. The alpha subunit of TSH is also present in two other pituitary glycoprotein hormones, follicle-stimulating hormone and luteinizing hormone, and, in primates, in the placental hormone chorionic gonadotropin. Each of these hormones also has a unique beta subunit, which provides receptor specificity. In other words, TSH is composed of alpha subunit bound to the TSH beta subunit, and TSH associates only with its own receptor. Free alpha and beta subunits have essentially no biological activity.

The most important controller of TSH secretion is thyroid-releasing hormone. Thyroid-releasing hormone is secreted by hypothalamic neurons into hypothalamic-hypophyseal portal blood, finds its receptors on

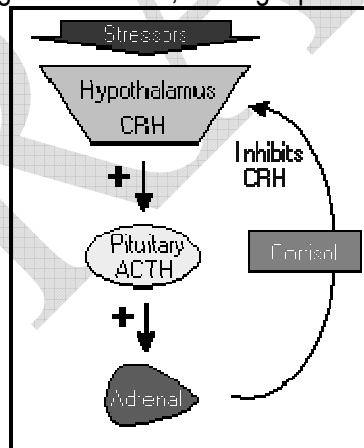
thyrotrophs in the anterior pituitary and stimulates secretion of TSH. TSH is only three amino acids long. Its basic sequence is glutamic acid-histidine-proline, although both ends of the peptide are modified. Secretion of thyroid-releasing hormone, and hence, TSH, is inhibited by high blood levels of thyroid hormones in a classical negative feedback loop.



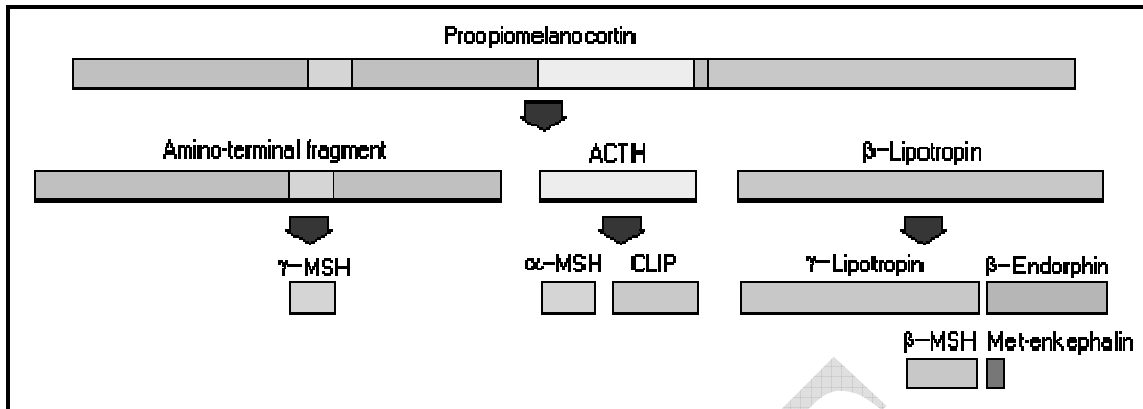
4.3. 3. Adrenocorticotrophic Hormone (ACTH)

Adrenocorticotrophic hormone, stimulates the adrenal cortex. More specifically, it stimulates secretion of glucocorticoids such as cortisol, and has little control over secretion of aldosterone, the other major steroid hormone from the adrenal cortex. Another name for ACTH is *corticotropin*.

ACTH is secreted from the anterior pituitary in response to corticotropin-releasing hormone from the hypothalamus. corticotropin-releasing hormone is secreted in response to many types of stress. Corticotropin-releasing hormone itself is inhibited by glucocorticoids, making it part of a classical negative feedback loop.



Within the pituitary gland, ACTH is produced in a process that also generates several other hormones. A large precursor protein named proopiomelanocortin (POMC) is synthesized and proteolytically chopped into several fragments as depicted below. Not all of the cleavages occur in all species and some occur only in the intermediate lobe of the pituitary.



The major attributes of the hormones other than ACTH that are produced in this process are summarized as follows:

- **Lipotropin:** Originally described as having weak lipolytic effects, its major importance is as the precursor to beta-endorphin.
- **Beta-endorphin and Met-enkephalin:** Opioid peptides with pain-alleviation and euphoric effects.
- **Melanocyte-stimulating hormone (MSH):** Known to control melanin pigmentation in the skin of most vertebrates.

4.3. 4. Prolactin

Prolactin is a single-chain protein hormone closely related to growth hormone. It is secreted by *lactotrophs* in the anterior pituitary. It is also synthesized and secreted by a broad range of other cells in the body, most prominently various immune cells, the brain and the decidua of the pregnant uterus. Prolactin is synthesized as a prohormone. Following cleavage of the signal peptide, the length of the mature hormone is between 194 and 199 amino acids, depending on species. Hormone structure is stabilized by three intramolecular disulfide bonds.

(i) Physiologic Effects of Prolactin

The conventional view of prolactin is that its major target organ is the mammary gland, and stimulating mammary gland development and milk production pretty well define its functions. *Such a picture is true as far as goes, but it fails to convey an accurate depiction of this multifunctional hormone.* Although the anterior pituitary is the major source of prolactin, the hormone is synthesized and secreted in many other tissues. Overall, several hundred different actions have been reported for prolactin. Some of its major effects are summarized here.

Mammary Gland Development, Milk Production and Reproduction. Prolactin induces lobuloalveolar growth of the mammary gland. Alveoli are the clusters of cells in the mammary gland that actually secrete milk. Prolactin stimulates lactogenesis or milk production after giving birth. Prolactin, along with cortisol and insulin, act together to stimulate transcription of the genes that encode milk proteins.

The critical role of prolactin in lactation has been confirmed in individuals with targeted deletions in the prolactin gene. Females that are heterozygous for the deleted prolactin gene (and produce roughly half the normal amount of prolactin) show failure to lactate after their first pregnancy.

Prolactin is also important in several non-lactational aspects of reproduction. It is necessary for maintenance of corpora lutea (ovarian structures that secrete progesterone) Females that are homozygous for an inactivated prolactin gene and thus incapable of secreting prolactin are infertile due to defects in ovulation, fertilization, preimplantation development and implantation.

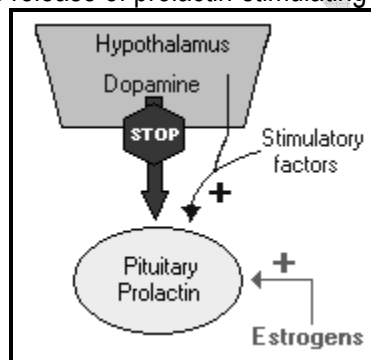
Finally, prolactin has a stimulatory effects on reproductive or maternal behaviours such care for the baby.

Effects on Immune Function: The prolactin receptor is widely expressed by immune cells, and some types of lymphocytes synthesize and secrete prolactin. Therefore prolactin act as an autocrine or paracrine modulator of immune activity. Prolactin has a modulatory role in several aspects of immune function, but is not strictly required for these responses.

(ii) Control of Prolactin Secretion

Dopamine serves as the major prolactin-inhibiting factor or brake on prolactin secretion. Dopamine is secreted into portal blood by hypothalamic neurons, binds to receptors on lactotrophs, and inhibits both the synthesis and secretion of prolactin. Agents and drugs that interfere with dopamine secretion or receptor binding lead to enhanced secretion of prolactin.

In addition to tonic inhibition by dopamine, prolactin secretion is positively regulated by several hormones, including thyroid-releasing hormone, gonadotropin-releasing hormone and vasoactive intestinal polypeptide. Stimulation of the nipples and mammary gland, as occurs during nursing, leads to prolactin release. This effect is due to a spinal reflex arc that causes release of prolactin-stimulating hormones from the hypothalamus.



Estrogens provide a positive control over prolactin synthesis and secretion. The increasing blood concentrations of estrogen during late pregnancy is responsible for the elevated levels of prolactin that are necessary to prepare the mammary gland for lactation at the end of gestation.

(iii) Disease States

Excessive secretion of prolactin - **hyperprolactinemia** - is a relative common disorder in humans. This condition has numerous causes, including prolactin-secreting tumours and therapy with certain drugs. Common manifestations of hyperprolactinemia in women include amenorrhea (lack of menstrual cycles) and galactorrhea (excessive or spontaneous secretion of milk). Men with hyperprolactinemia typically show hypogonadism, with decreased sex drive, decreased sperm production and impotence. Such men also often show breast enlargement (gynecomastia), but very rarely produce milk.

4.3. 5. Antidiuretic Hormone (Vasopressin)

Roughly 60% of the mass of the body is water, and despite wide variation in the amount of water taken in each day, body water content remains incredibly stable. Such precise control of body water and solute concentrations is a function of several hormones acting on both the kidneys and vascular system, but there is no doubt that antidiuretic hormone is a key player in this process.

Antidiuretic hormone, also known as **vasopressin**, is a nine amino acid peptide secreted from the posterior pituitary. Within hypothalamic neurons, the hormone is packaged in secretory vesicles with a carrier protein called neurophysin, and both are released upon hormone secretion.

(i) Physiologic Effects of Antidiuretic Hormone

(a) Effects on the Kidney

The single most important effect of antidiuretic hormone is to conserve body water by reducing the output of urine. A diuretic is an agent that increases the rate of urine formation. Injection of small amounts of antidiuretic hormone into a person or animal results in antidiuresis or decreased formation of urine, and the hormone was named for this effect.

Antidiuretic hormone binds to receptors in the distal or collecting tubules of the kidney and promotes reabsorption of water back into the circulation. In the absence of antidiuretic hormone, the kidney tubules are virtually impermeable to water, and it flows out as urine.

Antidiuretic hormone stimulates water reabsorption by stimulating insertion of water channels called aquaporins into the membranes of kidney tubules. These channels transport solute-free water through tubular cells and back into blood, leading to a decrease in plasma osmolarity and an increase osmolarity of urine.

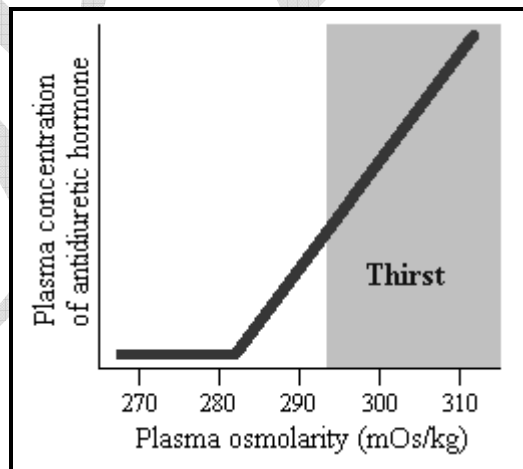
(a) Effects on the Vascular System

High concentrations of antidiuretic hormone cause widespread constriction of arterioles, which leads to increased arterial pressure. It was for this effect that the name vasopressin was coined. In healthy humans, antidiuretic hormone has minimal pressor effects.

(iii) Control of Antidiuretic Hormone Secretion

The most important variable regulating antidiuretic hormone secretion is **plasma osmolarity**, or the concentration of solutes in blood. Osmolarity is sensed in the hypothalamus by neurons known as an **osmoreceptors**, and those neurons, in turn, stimulate secretion from the neurons that produce antidiuretic hormone.

When plasma osmolarity is below a certain threshold, the osmoreceptors are not activated and antidiuretic hormone secretion is suppressed. When osmolarity increases above the threshold, the ever-alert osmoreceptors recognize this as a signal to stimulate the neurons that secrete antidiuretic hormone. Antidiuretic hormone concentrations rise steeply and linearly with increasing plasma osmolarity.



Secretion of antidiuretic hormone is also stimulated by **decreases in blood pressure and volume**, conditions sensed by stretch receptors in the heart and large arteries. Changes in blood pressure and volume are not nearly as sensitive a stimulator as increased osmolarity, but are nonetheless potent in severe conditions. For example, Loss of 15 or 20% of blood volume by haemorrhage results in massive secretion of antidiuretic hormone.

Another potent stimulus of antidiuretic hormone is nausea and vomiting, both of which are controlled by regions in the brain with links to the hypothalamus.

(iv) Disease States

The most common disease of man related to antidiuretic hormone is **diabetes insipidus**. This condition can arise from either of two situations:

- **Hypothalamic diabetes insipidus** results from a deficiency in secretion of antidiuretic hormone from the posterior pituitary. Causes of this disease include head trauma, and infections or tumours involving the hypothalamus.
- **Nephrogenic diabetes insipidus** occurs when the kidney is unable to respond to antidiuretic hormone. Most commonly, this results from some type of renal disease, but mutations in the ADH receptor gene or in the gene encoding aquaporin-2 have also been demonstrated in affected humans.

The major sign of either type of diabetes insipidus is **excessive urine production**. Some human patients produce as much as 16 liters of urine per day! If adequate water is available for consumption, the disease is rarely life-threatening, but withholding water can be very dangerous. Hypothalamic diabetes insipidus can be treated with exogenous antidiuretic hormone.

4.3. 6. Oxytocin

Oxytocin is a nine amino acid peptide that is synthesized in hypothalamic neurons and transported down axons of the posterior pituitary for secretion into blood. Oxytocin is also secreted within the brain and from a few other tissues, including the ovaries and testes. Oxytocin differs from antidiuretic hormone in two of the nine amino acids. Both hormones are packaged into granules and secreted along with carrier proteins called neurophysins.

(i) Physiologic Effects of Oxytocin

Oxytocin mediates three major effects:

- **Stimulation of milk ejection (milk letdown):** Milk is initially secreted into small sacs within the mammary gland called alveoli, from which it must be ejected for consumption or harvesting. Mammary alveoli are surrounded by smooth muscle (myoepithelial) cells which are a prominent target cell for oxytocin. Oxytocin stimulates contraction of myoepithelial cells, causing milk to be ejected into the ducts and cisterns.
- **Stimulation of uterine smooth muscle contraction at birth:** At the end of gestation, the uterus must contract vigorously and for a prolonged period of time in order to deliver the foetus. During the later stages of gestation, there is an increase in abundance of oxytocin receptors on uterine smooth muscle cells, which is associated with increased irritability of the uterus (and sometimes the mother as well). Oxytocin is released during labour when the foetus stimulates the cervix and vagina, and it enhances contraction of uterine smooth muscle to facilitate parturition or birth.
In cases where uterine contractions are not sufficient to complete delivery, physicians and veterinarians sometimes administer oxytocin ("pitocin") to further stimulate uterine contractions - great care must be exercised in such situations to assure that the foetus can indeed be delivered and to avoid rupture of the uterus.
- **Establishment of maternal behaviour:** Successful reproduction in mammals demands that mothers become attached to and nourish their offspring immediately after birth. It is also important that non-lactating females do not manifest such nurturing behaviour. The same events that affect the uterus and mammary gland at the time of birth also affect the brain. During parturition, there is an increase in concentration of oxytocin in cerebrospinal fluid, and oxytocin acting within the brain plays a major role in establishing maternal behaviour.
Both sexes secrete oxytocin - Males synthesize oxytocin in the same regions of the hypothalamus as in females, and also within the testes and perhaps other reproductive tissues. Pulses of oxytocin can be detected during ejaculation. Oxytocin is involved in facilitating sperm transport within the male and female reproductive systems and enhances male sexual behaviour.

(ii) Control of Oxytocin Secretion

The most important stimulus for release of hypothalamic oxytocin is initiated by physical stimulation of the nipples. The act of nursing or suckling is relayed within a few milliseconds to the brain via a spinal reflex arc. These signals impinge on oxytocin-secreting neurons, leading to release of oxytocin.

A number of factors can inhibit oxytocin release, among them acute stress. For example, oxytocin neurons are repressed by catecholamines, which are released from the adrenal gland in response to many types of stress, including fright

Both the production of oxytocin and response to oxytocin are modulated by circulating levels of sex steroids. The burst of oxytocin released at birth seems to be triggered in part by cervical and vaginal stimulation by the foetus, but also because of abruptly declining concentrations of progesterone.

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