Hypothalamus and Pituitary Gland

It would be difficult to overstate the influence of hypothalamic and pituitary hormones over physiologic processes. 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 hormone secretion and action are controlled. Links are provided to other sections of text containing additional information on the effects of these hormones.

Core information on physiology of the hypothalamus and pituitary is presented in the following topics:

- **Functional Anatomy of the Hypothalamus and Pituitary Gland**
- **Overview of Hypothalamic and Pituitary Hormones**
- **Anterior Pituitary Hormones and Their Releasing and Inhibiting Hormones**
    - **Growth Hormone**
    - **Thyroid Stimulating Hormone**
    - **Adrenocorticotropic Hormone**
    - **Prolactin**
    - **Gonadotropins: Luteinizing Hormone and Follicle Stimulating Hormone**
- **Posterior Pituitary Hormones**
    - **Antidiuretic Hormone (Vasopressin)**
    - **Oxytocin**

Advanced and supplemental information on the endocrine hypothalamus and pituitary:

- **Anatomy and Histology of the Pituitary Gland**
- **Anatomy of the Hypothalamus**
- **Growth Hormone**
    - **The Growth Hormone Receptor and Mechanism of Action**
    - **Growth Hormone and Aging**
    - **Agricultural Applications of Growth Hormone**

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 ("Turkish saddle"). In an adult human or sheep, the pituitary is roughly the size and shape of a garbonzo bean.

The image to the right, from the Visible Human Project, shows these anatomical relationships in the Visible Woman (click on the image to see a larger, unlabeled image).

Careful examination of the pituitary gland reveals that it 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.

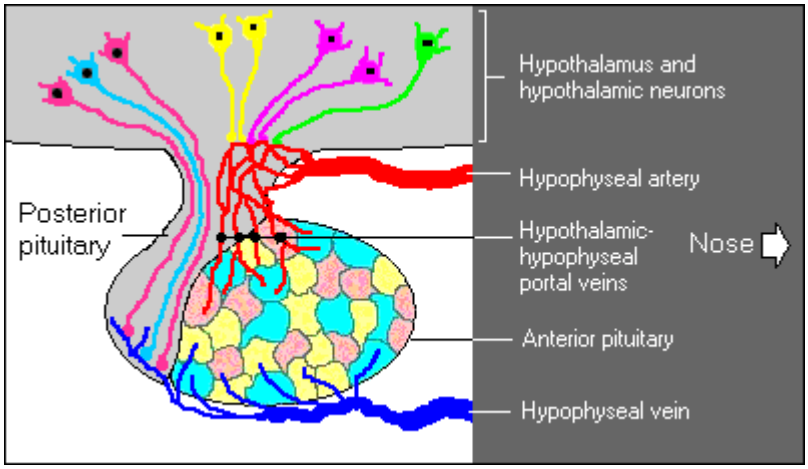
The image to the right shows a frontal view of a sheep pituitary gland and hypothalamus. The posterior gland can be seen peeking out behind the anterior gland; pass your mouse cursor over the image for labels (*image courtesy of T. Nett*).

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. As will be emphasized in later sections, 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 hypothalmic hormones destined for the anterior pituitary are secreted into that capillary blood.
- Blood from those capillaries drains into **hypothalamic-hypophyseal portal veins**. Portal veins are defined as veins between two capillary beds; the hypothalamic-hypophyseal portal veins 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.

This pattern of vascular connections is presented diagramatically below. Note also the hypothalamic-hypophyseal portal vessels in the image of a real pituitary gland seen above.



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.

Advanced and Supplemental Topics

- Anatomy and Histology of the Pituitary Gland

Endocrine Index	Glossary

Anatomy and 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.

Prior to embarking on the lessons below, it would be best to review the core section Functional Anatomy of the Hypothalamus and Pituitary Gland. The lessons below are somewhat graphics intensive and will be disappointing if your browser is not Java-enabled or your monitor is not capable of high resolution color.

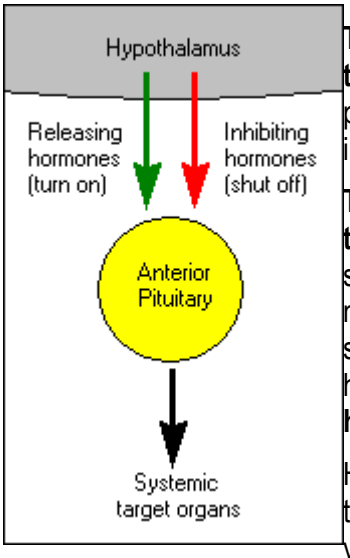
Summary of Lesson	Link

Close examination of a sectioned pituitary gland reveals two closely apposed, but distinctive tissues called the **adenohypophysis** (anterior or glandular pituitary) and **neurohypophysis** (posterior or neural pituitary). The adenohypophysis is further classified into several regions. The adenohypophysis and neurohypophysis have seperate embryological origins.

Microscopic examination of the conventionally-stained **adenohypophysis** reveals three distinctive cell types called **acidophils, basophils and chromophobes**. This pattern of staining reflects the chemical character of intracellular hormone-laden granules within the pituitary cells.

The **neurohypophysis** is an extension of the hypothalamus. It composed of bundles of axons from hypothalamic neurosecretory neurons intermixed with glial cells.

Overview of 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. Details on the control of specific hypothalamic and anterior pituitary hormones is presented in the discussions of those hormones.

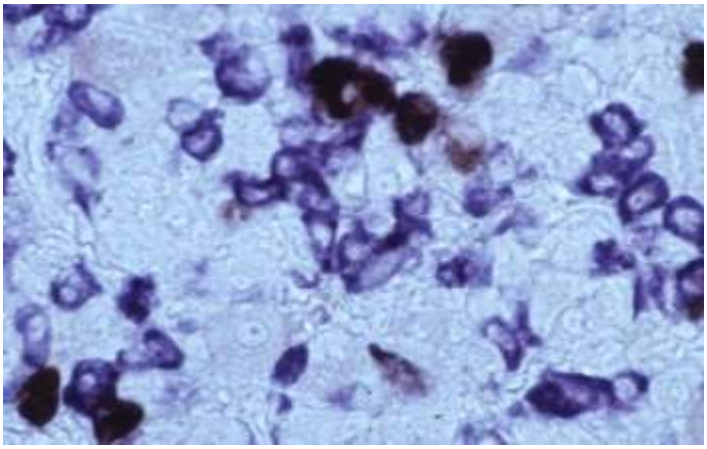
The following table summarizes the major hormones synthesized and secreted by the pituitary gland, along with summary statements about their major target organs and physiologic effects. Keep in mind that summaries are just that, and ongoing research continues to delineate additional, sometimes very important effects.

	Hormone	Major target organ(s)	Major Physiologic Effects
Anterior Pituitary	**Growth hormone**	Liver, adipose tissue	Promotes growth (indirectly), control of protein, lipid and carbohydrate metabolism
	Thyroid-stimulating hormone	Thyroid gland	Stimulates secretion of thyroid hormones
	Adrenocorticotropic hormone	Adrenal gland (cortex)	Stimulates secretion of glucocorticoids
	Prolactin	Mammary gland	Milk production
	Luteinizing hormone	Ovary and testis	Control of reproductive function
	Follicle-stimulating hormone	Ovary and testis	Control of reproductive function
Posterior Pituitary	**Antidiuretic hormone**	Kidney	Conservation of body water
	Oxytocin	Ovary and testis	Stimulates milk ejection and uterine contractions

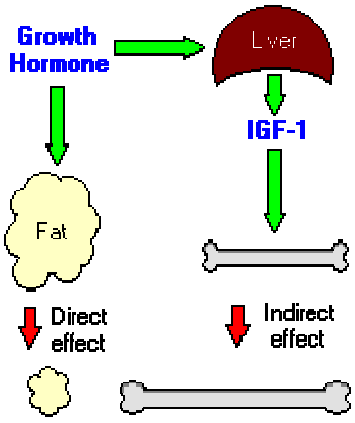
As seen in the table above, the anterior pituitary synthesizes and secreted 6 major hormones. **A**

final point to be made is that 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. The image below is of a section of canine anterior pituitary that was immunologically stained for luteinizing hormone (black stain) and prolactin (purple stain). The unstained cells in the image are those that secrete the other pituitary hormones.



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.

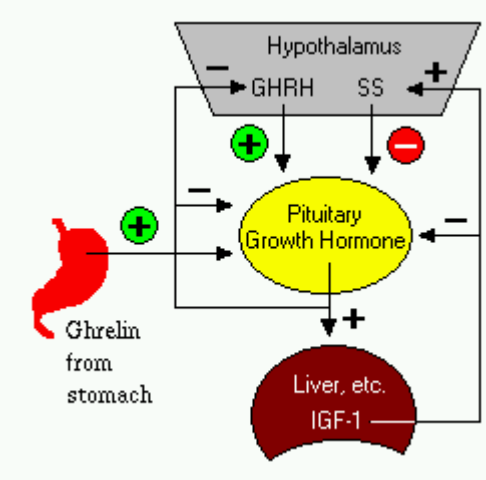
Physiologic Effects of Growth Hormone

A critical concept in understanding growth hormone activity is that it has two distinct types of 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 supresses 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.

Keeping this distinction in mind, we can discuss two major roles of growth hormone and its minion IGF-1 in physiology.



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 does seem to have a direct effect on bone growth in stimulating differentiation of chondrocytes.

IGF-1 also appears to be the 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.

Metabolic Effects

Growth hormone has important effects on protein, lipid and carbohydrate metabolism. In some cases, a direct effect of growth hormone has been clearly demonstrated, in others, IGF-1 is thought to be the critical mediator, and some cases it appears that 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 supresses 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.

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.

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 tumor of somatotropes. One of the most famous giants was a man named Robert Wadlow. He weighed 8.5 pounds at birth, but by 5 years of age was 105 pounds and 5 feet 4 inches tall. Robert reached an adult weight of 490 pounds and 8 feet 11 inches in height. He died at age 22.
- **Acromegaly** results from excessive secretion of growth hormone in adults. The onset of this disorder is typically insideous. 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.

Pharmaceutical and Biotechnological Uses of Growth Hormone

In years past, growth hormone purified from human cadaver pituitaries was used to treat children with severe growth retardation. More recently, the virtually unlimited supply of recombinant growth hormone has lead to several other applications to human and animal populations.

Human growth hormone is commonly used to treat children of pathologically short stature. There is concern that this practice will be extended to treatment of essentially normal children - so called "enhancement therapy" or growth hormone on demand. Similarly, growth hormone has been used by some to enhance atheletic performance. 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.

The role of growth hormone in normal aging remains poorly understood, but some of the cosmetic symptoms of aging appear to be amenable to growth hormone therapy. This is an active area of research, and additional information and recommendations about risks and benefits will undoubtedly surface in the near future.

Growth hormone is currently approved and marketed for enhancing milk production in dairy cattle. There is no doubt that administration of bovine somatotropin to lactating cows results in increased milk yield, and, depending on the way the cows are managed, can be an economically-viable therapy. However, this treatment engenders abundant controversy, even among dairy farmers. One thing that appears clear is that drinking milk from cattle treated with bovine growth hormone does not pose a risk to human health.

Another application of growth hormone in animal agriculture is treatment of growing pigs with porcine growth hormone. Such treatment has been demonstrated to significantly stimulate muscle growth and reduce deposition of fat.

- The Growth Hormone Receptor and Mechanism of Action (*not yet available*)
-

Growth Hormone and Aging

We've got plenty of youth. What we need is a fountain of smart.

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 not well understood, but is thought to result, in part, from 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, without doubt, the manifestation of a very complex set of changes which involve, at least in part, the GH-axis.** Naturally, this has spurred considerable interest in administering

supplemental GH as a "treatment" for aging in humans, and the availability of recombinant human GH has made such studies feasible.

In contrast to the view that GH deficiency contributes to the aging phenomenon, there is information suggesting that normal or high levels of GH may accelerate aging. Mice with genetic dwarfism due to deficiency in GH, prolactin and thyroid-stimulating hormone live considerably longer than normal mice, and the increased levels of GH seen with acromegaly in humans are associated with reduced life expectancy. Both of these findings are likely due to metabolic effects of GH.

GH Replacement Therapy in GH-deficient Adults

Adult-onset GH deficiency in humans is almost always due to pituitary disease, usually from a tumor or therapeutic efforts to treat a tumor. 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.

More than a dozen clinical trials have sought to evaluate GH replacement in patients with adult-onset deficiency. The goal has usually been to normalize serum IGF-1 concentrations by daily injections of GH. In essentially all cases, several months of GH replacement therapy led to increased lean mass and decreased adiposity (especially in visceral fat). The effects of GH treatment on bone density and hyperlipidemia has been inconsistent or minor, as have been the effects on strength and mental abilities. Common side effects observed in these trials included edema and joint/muscle pain, which appeared related to dose of GH. Since the first of these trials was conducted in 1988, long term risks are not yet known.

GH Therapy in the Elderly

Long before Ponce de Leon went in search of the legendary fountain of youth, people sought treatments to prevent or reverse the effects of aging. In 1990, considerable excitement was generated from a report by Rudman and colleagues which described wonderful effects of GH treatment in a small group of elderly men. These volunteers, who ranged in age from 61 to 81 years, showed increased lean body and bone mass, decreased fat mass and, perhaps most dramatically, restoration of skin thickness to that typical of a 50-year-old.

The study cited above and a handful of others have provided an initial understanding of the benefits, limitations and risks of sustained (6 to 12 month) GH supplementation in elderly men and women. A consistent finding in these investigations was a high incidence of adverse side effects - edema, fluid retention and carpal tunnel syndrome - which necessitated reductions in GH dose of cessation of treatment. GH treatment consistently induced an increase in serum IGF-1, a decrease in fat mass and increase in lean mass.

The effects on fat and lean masses may be viewed as positive effects, but, at the end of the day, it has to be asked whether GH treatment improved functioning in the elderly. In the studies in which function was objectively assessed, GH treatment did not improve cognitive function, and, despite the effects on lean body mass, was not any more effective than exercise alone in promoting strength. Long-term GH therapy in elderly postmenopausal women lead to significant increases in

bone mineral density, but these increases were less than what is routinely achieved with estrogen replacement. **While it must be acknowledged that a relatively small number of elderly patients have been treated for prolonged periods with GH, the controlled trials conducted thus far do not support is efficacy in aleviating age-related deficits in cognitive or somatic function.**

Another indication of potentially serious side effects of GH therapy in adults, including the elderly, has been provided by controlled clinical trials that assessed the utility of human GH treatment in critical illness, where endogenous GH secretion is typically suppressed. GH therapy was anticipated to attenuate the catabolic effects of illness and thereby decrease duration of hospitalization. The results of several clinical trials involving hundreds of patients, demonstrated a significant increase in mortality associated with high doses of GH. Additionally, those patients treated with GH that survived had longer periods of intensive care and hospitalization than those receiving placebos.

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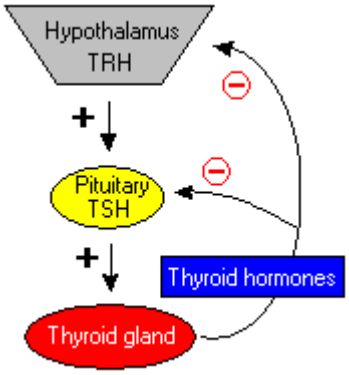
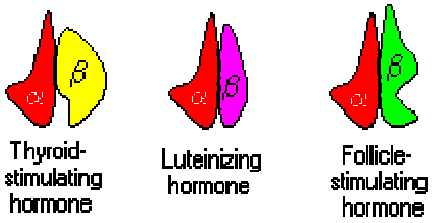
Thyroid-Stimulating Hormone (Thyrotropin)





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.

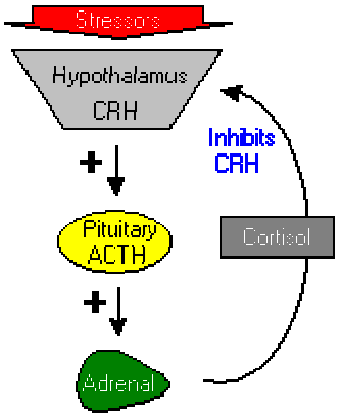
The most important controller of TSH secretion is thyroid-releasing hormone. Thyroid-releasing hormone is secreted by hypothalamic neurons into hypothalamic-hypophyseal portal blood, finds its receptors on thyrotrophs in the anterior pituitary and stimulates secretion of TSH.

One interesting aspect of thyroid-releasing hormone is that it 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.

Additional information about TSH and its effects and control are presented in the section on the thyroid gland.

Adrenocorticotropic Hormone (ACTH)

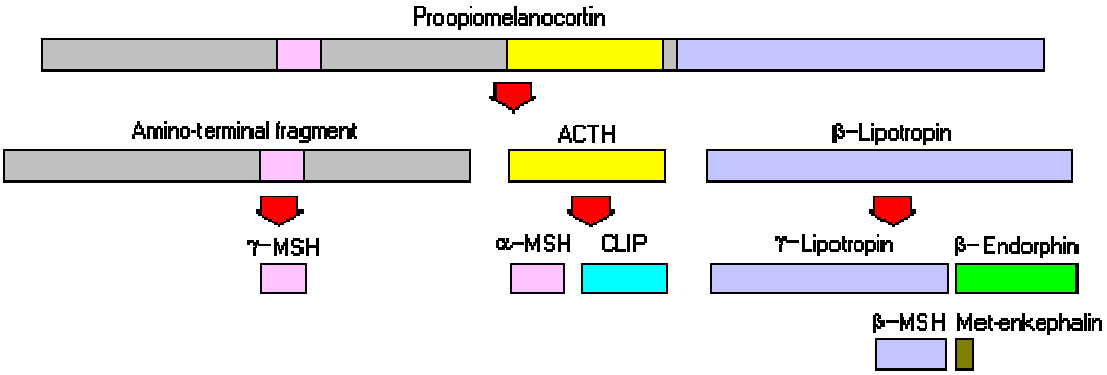


Adrenocorticotropic hormone, as its name implies, stimulates the adrenal cortex. More specifically, it stimulates secretion of glucocorticoids such as cortisol, and has little control over secretion of aldosterone, the other major steroid hormone from the adrenal cortex. Another name for ACTH is *corticotropin*.

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, which makes sense in view of the "stress management" functions of glucocorticoids. **Corticotropin-releasing hormone itself is inhibited by glucocorticoids**, making it part of a classical negative feedback loop.

Additional information on the role of ACTH in regulation of adrenal steroid secretion is presented in the sections on the adrenal gland *and* glucocorticoids.

Within the pituitary gland, ACTH is produced in a process that also generates several other hormones. A large precursor protein named proopiomelanocortin (POMC, "Big Mama") 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.

Prolactin

Prolactin is a single-chain protein hormone closely related to growth hormone. It is secreted by so-called *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.

Physiologic Effects of Prolactin

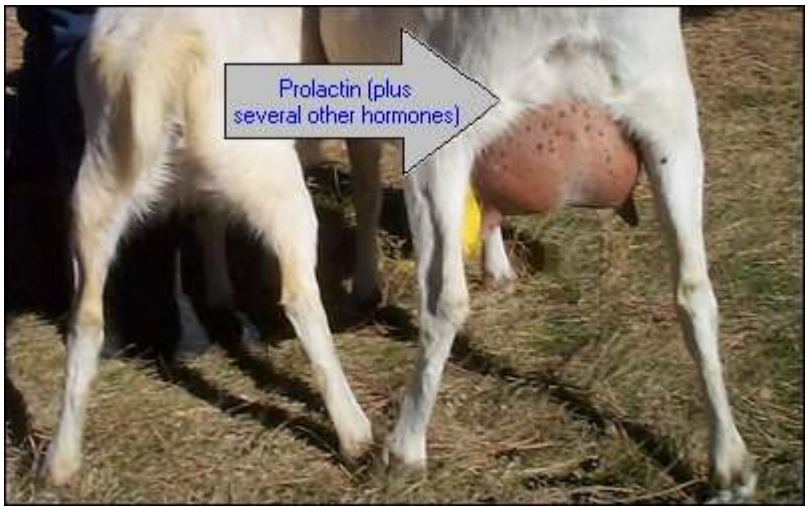
The conventional view of prolactin is that its major target organ is the mammary gland, and stimulating mammary gland development and milk production pretty well define its functions. *Such a picture is true as far as goes, but it fails to convey an accurate depiction of this multifunctional hormone.*

It is difficult to point to a tissue that does not express prolactin receptors, and 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 in various species. Some of its major effects are summarized here.

Mammary Gland Development, Milk Production and Reproduction

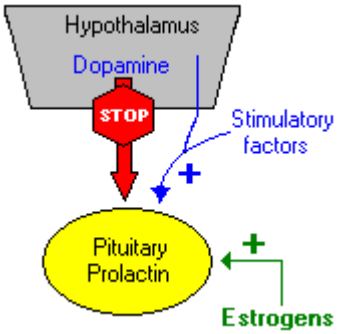
In the 1920's it was found that extracts of the pituitary gland, when injected into virgin rabbits, induced milk production. Subsequent research demonstrated that prolactin has two major roles in milk production:

- **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 mice with targeted deletions

in the prolactin gene. Female mice 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 also appears important in several non-lactational aspects of reproduction. In some species (rodents, dogs, skunks), prolactin is necessary for maintainance of corpora lutea (ovarian structures that secrete progesterone, the "hormone of pregnancy"). Mice 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 appears to have stimulatory effects in some species on reproductive or maternal behaviors such as nest building and retrieval of scattered young.

Effects on Immune Function

The prolactin receptor is widely expressed by immune cells, and some types of lymphocytes synthesize and secrete prolactin. These observations suggest that prolactin may act as an autocrine or paracrine modulator of immune activity. Interestingly, mice with homozygous deletions of the prolactin gene fail to show significant abnormalities in immune responses.

A considerable amount of research is in progress to delineate the role of prolactin in normal and pathologic immune responses. It appears that prolactin has a modulatory role in several aspects of immune function, but is not strictly required for these responses.

Control of Prolactin Secretion

In contrast to what is seen with all the other pituitary hormones, the hypothalamus tonically suppresses prolactin secretion from the pituitary. In other words, there is usually a hypothalamic "brake" set on the lactotroph, and prolactin is secreted only when the brake is released. If the pituitary stalk is cut, prolactin secretion increases, while secretion of all the other pituitary hormones fall dramatically due to loss of hypothalamic releasing hormones.

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 appears to be due to a spinal reflex arc that causes release of prolactin-stimulating hormones from the hypothalamus.

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

Disease States

Excessive secretion of prolactin - **hyperprolactinemia** - is a relative common disorder in humans. This condition has numerous causes, including prolactin-secreting tumors and therapy with certain drugs.

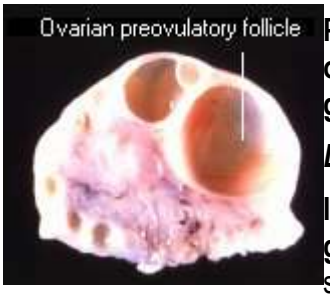
Common manifestations of hyperprolactinemia in women include amenorrhea (lack of menstrual cycles) and galactorrhea (excessive or spontaneous secretion of milk). Men with hyperprolactinemia typically show hypogonadism, with decreased sex drive, decreased sperm production and impotence. Such men also often show breast enlargement (gynecomastia), but very rarely produce milk.

Gonadotropins: Luteinizing and Follicle Stimulating Hormones

Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are called gonadotropins because stimulate the gonads - in males, the testes, and in females, the ovaries. They are not necessary for life, but are essential for reproduction. These two hormones are secreted from cells in the anterior pituitary called ***gonadotrophs***. Most gonadotrophs secrete only LH or FSH, but some appear to secrete both hormones.

As describef for thyroid-simulating hormone, LH and FSH are large glycoproteins composed of alpha and beta subunits. The alpha subunit is identical in all three of these anterior pituitary hormones, while the beta subunit is unique and endows each hormone with the ability to bind its own receptor.

Physiologic Effects of Gonadotropins

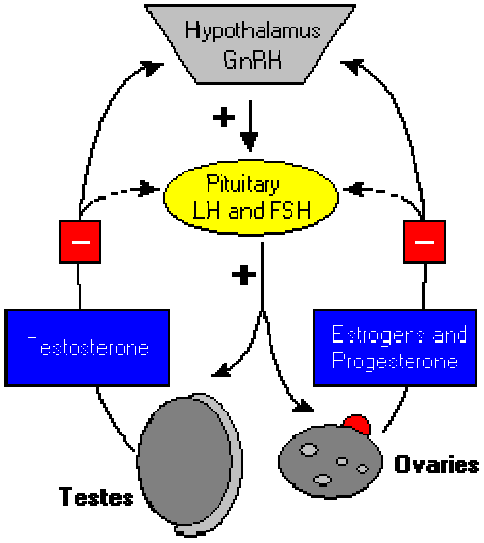


Physiologic effects of the gonadotrophins are known only in the ovaries and testes. Together, then regulate many aspects of gonadal function in both males and females.

Luteinizing Hormone

In both sexes, LH stimulates secretion of sex steroids from the gonads. In the testes, LH binds to receptors on Leydig cells, stimulating synthesis and secretion of **testosterone**. Theca cells in the ovary respond to LH stimulation by secretion of **testosterone**, which is converted into **estrogen** by adjacent granulosa cells.

In females, ovulation of mature follicles on the ovary is induced by a large burst of LH secretion known as the preovulatory LH surge. Residual cells within ovulated follicles proliferate to form corpora lutea, which secrete the steroid hormones **progesterone** and estradiol. Progesterone is necessary for maintenance of pregnancy, and, in most mammals, LH is required



for continued development and function of corpora lutea. The name luteinizing hormone derives from this effect of inducing luteinization of ovarian follicles.

Follicle-Stimulating Hormone

As its name implies, FSH stimulates the maturation of ovarian follicles. Administration of FSH to humans and animals induces "superovulation", or development of more than the usual number of mature follicles and hence, an increased number of mature gametes.

FSH is also critical for sperm production. It supports the function of Sertoli cells, which in turn support many aspects of sperm cell maturation.

Control of Gonadotropin Secretion

The principle regulator of LH and FSH secretion is gonadotropin-releasing hormone or GnRH (also known as LH-releasing hormone). GnRH is a ten amino acid peptide that is synthesized and secreted from hypothalamic neurons and binds to receptors on gonadotrophs.

As depicted in the figure to the right, GnRH stimultes secretion of LH, which in turn stimulates gonadal secretion of the sex steroids testosterone, estrogen and progesterone. **In a classical negative feedback loop, sex steroids inhibit secretion of GnRH** and also appear to have direct negative effects on gonadotrophs.

This regulatory loop leads to pulsatile secretion of LH and, to a much lesser extent, FSH. The number of pulses of GnRH and LH varies from a few per day to one or more per hour. In females, pulse frequency is clearly related to stage of the cycle.

Numerous hormones influence GnRH secretion, and positive and negative control over GnRH and gonadotropin secretion is actually considerably more complex than depicted in the figure. For example, the gonads secrete at least two additional hormones - inhibin and activin - which selectively inhibit and activate FSH secretion from the pituitary.

Disease States

Diminished secretion of LH or FSH can result in failure of gonadal function (hypogonadism). This condition is typically manifest in males as failure in production of normal numbers of sperm. In females, cessation of reproductive cycles is commonly observed.

Elevated blood levels of gonadotropins usually reflect lack of steroid negative feedback. Removal of the gonads from either males or females, as is commonly done to animals, leads to persistent elevation in LH and FSH. In humans, excessive secretion of FSH and/or LH most commonly the result of gonadal failure or pituitary tumors. In general, elevated levels of gonadotropins per se have no biological effect.

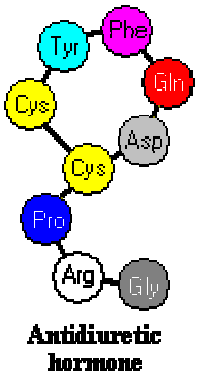
Pharmacologic Manipulation of Gonadotropin Secretion

Normal patterns of gonadotropin secretion are absolutely required for reproduction, and

interfering particularly with LH secretion is a widely-used strategy for contraception. Oral contraceptive pills contain a progestin (progesterone-mimicking compound), usually combined with an estrogen. As discussed above, progesterone and estrogen inhibit LH secretion, and **oral contraceptives are effective because they inhibit the LH surge that induces ovulation.**

Another route to suppressing gonadotropin secretion is to block the GnRH receptor. GnRH receptor antagonists have potent contraceptive effects in both males and females, but have not been widely deployed for that purpose.

Antidiuretic Hormone (Vasopressin)



Antidiuretic hormone

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.

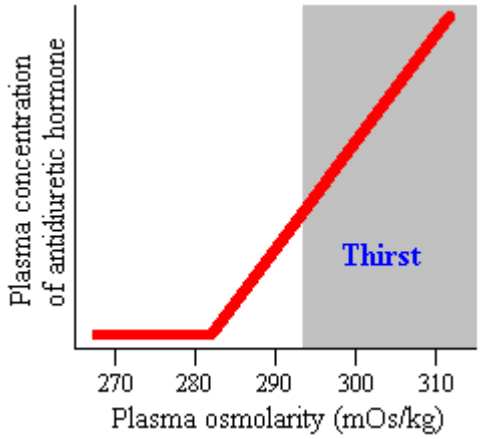
Antidiuretic hormone, also known as vasopressin, is a nine amino acid peptide secreted from the posterior pituitary. Within hypothalamic neurons, the hormone is packaged in secretory vesicles with a carrier protein called neurophysin, and both are released upon hormone secretion.

Physiologic Effects of Antidiuretic Hormone

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 reabsorbtion of water back into the circulation. In the absense of antidiuretic hormone, the kidney tubules are virtually impermiable to water, and it flows out as urine.

Antidiuretic hormone stimulates water reabsorbtion by stimulating insertion of "water channels" or 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.

Effects on the Vascular System

In many species, 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.

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, simulate 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 a the cue to stimulate the neurons that secrete antidiuretic hormone. As seen the the figure below, antidiuretic hormone concentrations rise steeply and linearly with increasing plasma osmolarity.

Osmotic control of antidiuretic hormone secretion makes perfect sense. **Imagine walking across a desert: the sun is beating down and you begin to lose a considerable amount of body water through sweating.** Loss of water results in concentration of blood solutes - plasma osmolarity increases. *Should you increase urine production in such a situation? Clearly not.* Rather, antidiuretic hormone is secreted, allowing almost all the water that would be lost in urine to be reabsorbed and conserved.

There is an interesting parallel between antidiuretic hormone secretion and thirst. Both phenomena appear to be stimulated by hypothalamic osmoreceptors, although probably not the same ones. The osmotic threshold for antidiuretic hormone secretion is considerably lower than for thirst, as if the hypothalamus is saying "Let's not bother him by invoking thirst unless the situation is bad enough that antidiuretic hormone cannot handle it alone."

Secretion of antidiuretic hormone is also simulated 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 hemorrhage 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.

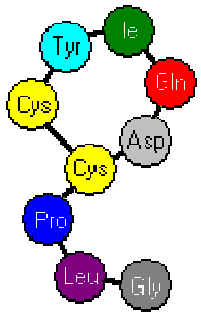
Disease States

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

- **Hypothalamic ("central") 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 tumors 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.

Oxytocin



Oxytocin

Oxytocin in 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.

Physiologic Effects of Oxytocin

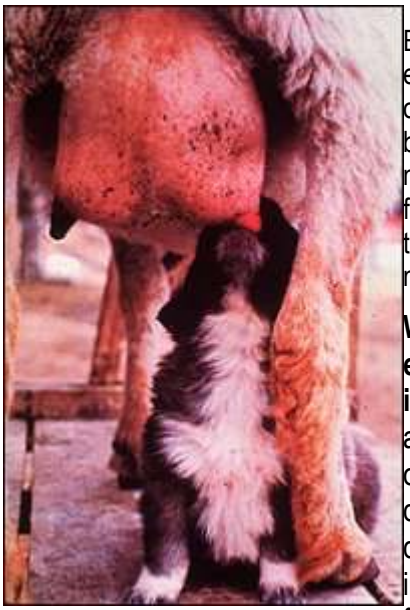
In years past, oxytocin had the reputation of being an "uncomplicated" hormone, with only a few well-defined activities related to birth and lactation. As has been the case with so many hormones, further research has demonstrated many subtle but profound influences of this little peptide. Nevertheless, it has been best studied in females where it clearly 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 prominant 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 fetus. 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 labor when the fetus 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 fetus can indeed be delivered and to avoid rupture of the uterus.

- **Establishment of maternal behavior:** 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 behavior. 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 behavior.**



Evidence for this role of oxytocin come from two types of experiments. First, infusion of oxytocin into the ventricles of the brain of virgin rats or non-pregnant sheep rapidly induces maternal behavior. Second, administration into the brain of antibodies that neutralize oxytocin or of oxytocin antagonists will prevent mother rats from accepting their pups. Other studies support the contention that this behavioral effect of oxytocin is broadly applicable among mammals.

While there is no doubt that oxytocin stimulates all of the effects described above, doubt has recently been cast on its necessity in parturition and maternal behavior. Mice that are unable to secrete oxytocin due to targeted disruptions of the oxytocin gene will mate, deliver their pups without apparent difficulty and display normal maternal behavior. However, they do show deficits in milk ejection and have subtle derangements in social behavior. It may be best to view oxytocin as a major facilitator of parturition and maternal behavior rather than a necessary component of these processes.

Both sexes secrete oxytocin - what about its role in males? 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. Current evidence suggests that oxytocin is involved in facilitating sperm transport within the male reproductive system and perhaps also in the female, due to its presence in seminal fluid. It may also have effects on some aspects of male sexual behavior.

Control of Oxytocin Secretion

The most important stimulus for release of hypothalamic oxytocin is initiated by physical stimulation of the nipples or teats. 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.

If you want to obtain anything other than trivial amounts of milk from animals like dairy cattle, you have to stimulate oxytocin release because something like 80% of the milk is available only after ejection, and milk ejection requires oxytocin. Watch someone milk a cow, even with a machine, and what you'll see is that prior to milking, the teats and lower udder are washed gently - this tactile stimulation leads to oxytocin release and milk ejection.

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. As a practical endocrine tip - don't wear a gorilla costume into a milking parlor full of cows or set off firecrackers around a mother nursing her baby.

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 fetus, but also because of abruptly declining concentrations of progesterone. Another well-studied effect of steroid hormones is the marked increase in synthesis of uterine (myometrial) oxytocin receptors late in gestation, resulting from increasing concentrations of circulating estrogen.
