# HYPOTHALAMUS AND PITUITARY GLAND

The hypothalamus and pituitary gland form a unit which exerts control over the function of several endocrine glands – thyroid, adrenals, and gonads as well as a wide range of physiologic activities.

The actions and interactions of the endocrine and nervous systems where by the nervous system regulates the endocrine system and the endocrine activity modulates the activity of the central nervous system constitute the major regulatory mechanisms for virtually all physiologic activities. The immune system also interacts with both the endocrine and the nervous system.

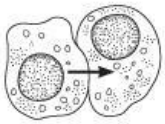
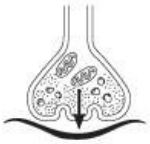
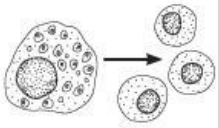
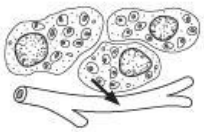
Nerve cells and endocrine gland cells, which are both involved in cell–to–cell communication, share certain characteristic features secretion of chemical messengers (neurotransmitters or hormones) and electrical activity. A single chemical messenger peptide or amine – can be secreted by neurons as a neurotransmitter or neural hormone and by endocrine gland cells as a classic hormone. Examples of such multifunctional chemical messengers are shown in Table 5-1. The cell communication may occur by four mechanisms:

**Table 5–1. Neuroendocrine Messengers: Substances that Function as Neurotransmitters, Neural Hormones, and Classic Hormones.**

| | **Neurotransmitter (Present in Nerve Endings)** | **Hormone Secreted by Neurons** | **Hormone Secreted by Endocrine Cells** |
|---|---|---|---|
| Dopamine | + | + | + |
| Norepinephrine | + | + | + |
| Epinephrine | + | | + |
| Somatostatin | + | + | + |
| Gonadotropin-releasing hormone (GnRH) | + | + | + |
| Thyrotropin-releasing hormone (TRH) | + | + | |
| Oxytocin | + | + | + |
| Vasopressin | + | + | + |
| Vasoactive intestinal peptide | + | + | |
| Cholecystokinin (CCK) | + | | + |
| Glucagon | + | | + |
| Enkephalins | + | | + |
| Pro-opiomelanocortin derivatives | + | | + |
| Other anterior pituitary hormones | + | | + |

1) Autocrine communication via messengers that diffuse in the interstitial fluid and act on the cells that secreted them.
2) Neural communication via synaptic junctions.
3) Paracrine communication via messengers that diffuse in the interstitial fluid to adjacent target cells (without entering the bloodstream), and
4) Endocrine communication via circulating hormones (Figure 5-1).

**Figure 5–1. Intercellular communication by chemical mediators**

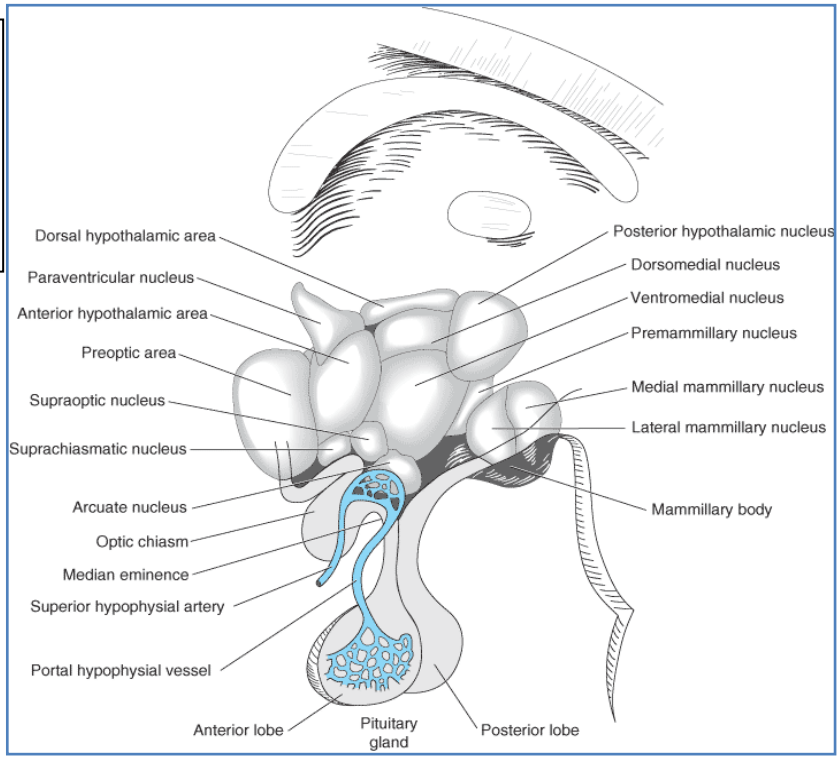
| | GAP JUNCTIONS | SYNAPTIC | PARACRINE | ENDOCRINE |
|---|---|---|---|---|
| |  |  |  |  |
| Message transmission | Directly from cell to cell | Across synaptic cleft | By diffusion in interstitial fluid | By circulating body fluids |
| Local or general | Local | Local | Locally diffuse | General |
| Specificity depends on | Anatomic location | Anatomic location and receptors | Receptors | Receptors |

The two major mechanisms of neural regulation of endocrine function are direct innervations and neuron secretion (neural secretion of hormones). The adrenal medulla, kidney, parathyroid gland, and pancreatic islets are endocrine tissues that receive direct autonomic innervation. An example of neurosecretory regulation is the hormonal secretion of certain hypothalamic nuclei into the portal hypophysial vessels, which regulate the hormone – secreting cells of the anterior lobe of the pituitary. Another example of neuronsecretory regulation is the posterior lobe of the pituitary gland, which is made up of the endings of neurons whose cell bodies reside in hypothalamic nuclei. These neurons secrete vasopressin and oxytocin into the general circulation.

## Anatomy and embryology

The anatomic relationships between the pituitary and the main nuclei of the hypothalamus are shown in Fig. 5-2.

**Figure 5–2. The human hypothalamus, with a superimposeed diagrammatic repre-sentation of the portal hypophysial vessels.**



The posterior lobe of the pituitary (neurohypophysis) is of neural origin. It consists of the axons and nerve endings of neurons whose cell bodies reside in the supraoptic and paraventricular nuclei of the hypothalamus and supporting tissues.

The human fetal anterior pituitary anlage is initially recognizable at 4-5 weeks of gestation, and rapid differentiation leads to a mature hypothalamic – pituitary unit at 20 weeks. The anterior pituitary (adenohypophysis) originates from Rathke's pouch, an ectodermal evagination of the oropharynx, and migrates to join the neurohypophysis. The pituitary gland, of which the anterior lobe constitutes two – thirds, weighs 500-900 mg; it may double in size during pregnancy.

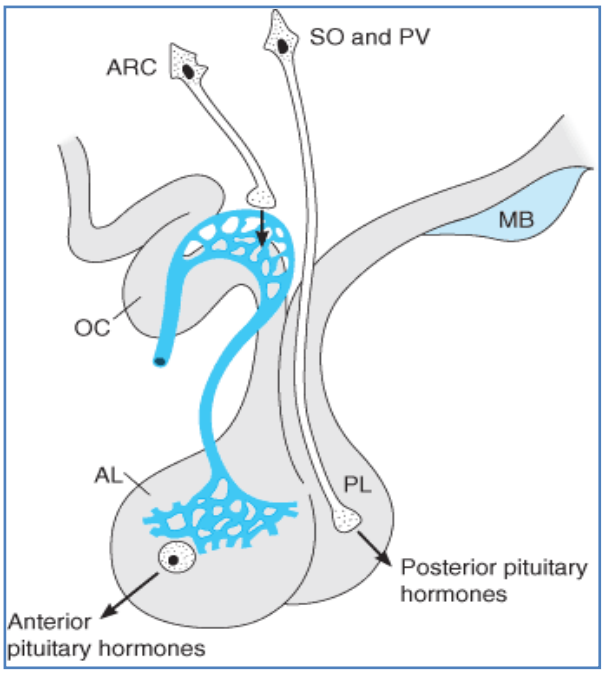



**Figure 5–5. Secretion of hypothalamic hormones**. The hormones of the posterior lobe (PL) are released into the general circulation from the endings of supraoptic and paraventricular neurons, whereas hypophysiotropic hormones are secreted into the portal hypophysial circulation from the endings of arcuate and other hypothalamic neurons (AL, anterior lobe; ARC, arcuate and other nuclei; MB, mamillary bodies; OC, optic chiasm; PV, paraventricular nucleus. SO, supraoptic nucleus).

The anterior pituitary is the most richly vascularized of all mammalian tissues, receiving blood from the portal circulation connecting the median eminence of the hypothalamus and the anterior pituitary. The axons of neurohypophysis terminate on capillaries that drain via the posterior lobe veins to the general circulation. The hypophysial – portal system of capillaries allows control of anterior pituitary function by the hypothalamic hypophysiotropic hormones secreted into the portal hypophysial vessels. This provides a short, direct connection to the anterior pituitary from the ventral hypothalamus and the median eminence (Fig. 5-5).

**Pituitary Histology**

Pituitary cells are classified according to their secretory products:

**Somatotrophs:** growth hormone (GH) secreting cells.
**Lactotrophs:** prolactin (PRL) secreting cells
**Thyrotrophs**: thyroid–stimulating hormone (thyrotropin; TSH) – secreting cells
**Corticotrophs:** cells secreting adreno-corticotropic hormone (corticotropin; ACTH) and related peptides.
**Gonadotrophs:** cells secreting gonadotropins: luteinizing hormone (LH) – and follicle stimulating hormone (FSH).

These highly specialized cells respond to specific hypothalamic and peripheral hormones. In addition, local (i.e. paracrine) factors also play a role in normal pituitary physiology. The six known major anterior pituitary hormone are listed in Table 5-2.

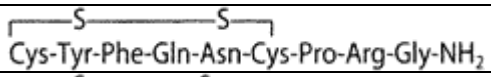
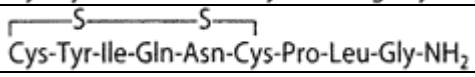
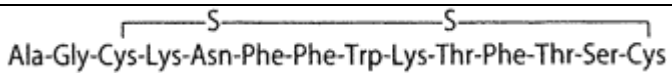
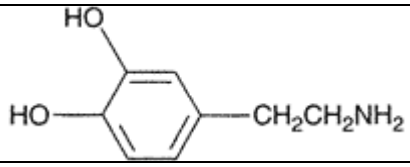
**Table 5–2.** Major Adenohypophysial Hormones and Their Cellular Sources.[1]

| Cellular Source and Histologic Staining | Main Hormone Products | Structure of Hormone | Main Functions |
|---|---|---|---|
| Somatotroph (acidophil) | GH; also known as STH or somatotropin | 191 amino acids, 22-kDa protein, mainly nonglycosylated | Stimulates the production of IGF-1 (the mediator of the indirect actions of GH). Also exerts direct actions on growth and metabolism. Modulator of immune function and hemostasis. |
| Lactotroph or mammotroph (acidophil) | PRL | 198 amino acids, 23-kDa protein, mainly nonglycosylated. (Note: most of the decidually produced PRL is glycosylated.) | Stimulation of milk production (protein and lactose synthesis, water excretion, and sodium retention). Inhibits gonadotropin. Immunomodulator. |
| Corticotroph (small cells with basophil granules with strong PAS positivity, indicating the presence of glycoproteins) | Derivatives of POMC, mainly ACTH and β -LPH | POMC: glycosylated polypeptide of 134 amino acid residues. ACTH: simple peptide of 39 amino acid residues, 4.5 kDa. β-LPH: simple peptide of 91 amino acid residues, 11.2 kDa. | ACTH: stimulation of glucocorticoids and sex steroids in the zona fasciculata and zona reticularis of the adrenal cortex, inducing hyperplasia and hypertrophy of the adrenal cortex. β -LPH: weak lipolytic and opioid actions. |
| Thyrotroph (large cells with "basophil" granules with PAS positivity) | TSH | Glycoprotein hormone consisting of a shared α (89 amino acid) and a TSH-specific (112 amino acid) subunit. Total size: 28 kDa. | Stimulation of all aspects of thyroid gland function: hormone synthesis, secretion, hyperplasia, hypertrophy, and vascularization |
| Gonadotroph (small cells) with "basophil" granules with PAS positivity) | LH: named after its effect in females. It is identical with the ICSH (interstitial cell stimulating hormone) originally described in males | Glycoprotein hormone consisting of a shared α and an LH-specific β (115 amino acid) subunit. Total size: 29 kDa | Females: stimulates steroid hormone synthesis in theca interna cells, lutein cells, and hilar cells; promotes luteinization and maintains corpus luteum. Males: stimulates steroid hormone production in Leydig cells. |
| | FSH | Glycoprotein hormone consisting of a shared and an FSH-specific β (115 amino acid) subunit. Total size: 29 kDa. | Females: targets the granulosa cells to promote follicular development. Stimulates aromatase expression and inhibin secretion. Males: targets the Sertoli cells to promote spermatogenesis and to stimulate inhibin secretion. |

## Hypothalamic Hormone

The hypothalamic hormones are secreted into hypophysial portal blood vessels and those secreted by the neurohypophysis directly into the general circulation. The structures of the eight major hypothalamic hormones are shown in Table 5-4.

**Table 5–4. Hypothalamic Hormones.**

| Hormone | Structure |
|---|---|
| **Posterior pituitary hormones** | |
| Arginine vasopressin |   |
| Oxytocin |   |
| **Hypophysiotropic hormones** | |
| Thyrotropin-releasing hormone (TRH) | (pyro)Glu-His-Pro-$NH_2$ |
| Gonadotropin-releasing hormone (GnRH) | (pyro)Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-$NH_2$ |
| Somatostatin[1] |   |
| Growth hormone–releasing hormone (GHRH) | Tyr-Ala-Asp-Ala-Ile-Phe-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Gly-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Met-Ser-Arg-Gln-Gln-Gly-Glu-Ser-Asn-Gln-Glu-Arg-Gly-Ala-Arg-Ala-Arg-Leu-$NH_2$ |
| Prolactin-inhibiting hormone (PIH, dopamine) |   |
| Corticotropin-releasing hormone (CRH) | Ser-Gln-Glu-Pro-Pro-Ile-Ser-Leu-Asp-Leu-Thr-Phe-His-Leu-Leu-Arg-Glu-Val-Leu-Glu-Met-Thr-Lys-Ala-Asp-Gln-Leu-Ala-Gln-Gln-Ala-His-Ser-Asn-Arg-Lys-Leu-Leu-Asp-Ile-Ala-$NH_2$ |

[1]In addition to the tetradecapeptide shown here (somatostatin 14), an amino terminal extended molecule (somatostatin 28) and a 12-amino-acid form (somatostatin 28 [1–12]) are found in most tissues.

## Hypophysiotropic Hormones

The hypophysiotropic hormones which regulate the secretion of anterior pituitary hormones include growth hormone releasing hormone (GHRH), somatostatin, dopamine, thyrotropin releasing hormone (TRH), corticotropin–releasing hormone (CRH), and gonadotropin–releasing hormone (GnRH). Most of the anterior pituitary hormones are controlled by stimulatory hormones, but growth hormone and especially prolactin are also regulated by inhibitory hormone. The hormones of the hypothalamus are secreted episodically and not continuously, and in some cause there is an underlying circadian rhythm.

## Posterior Pituitary Hormones

The hypothalamo–neurohypophysial system secretes two nanopeptides: antidiuretic hormone (ADH) (also known as arginine vasopressin) and oxytocin. They are synthesized in large cell bodies of neurons in the supraoptic nuclei (SON) and paraventricular nuclei (PVN). ADH is an important regulator of water balance; it also is a potent vasoconstrictor and plays a role in regulation of cardiovascular function. Oxytocin causes contraction of smooth muscle, especially of the myoepithelial cells that line the ducts of the mammary gland, thus causing milk ejection.

ADH and oxytocin are basic nanopeptides characterized by a ring structure with a disulfide linkage. They are synthesized by separate cells (i.e. there is no cosecretion or synthesis) from prohormones that contain both the peptide and an associated binding peptide or neurophysin specific for the hormone: neurophysin II for ADH and neurophysin I for oxytocin. In the secretory granules, further processing produces the mature nanopeptide and its neurophysin. Action potentials that reach the nerve endings increase the $Ca^{++}$ influx and initiate hormone secretion.

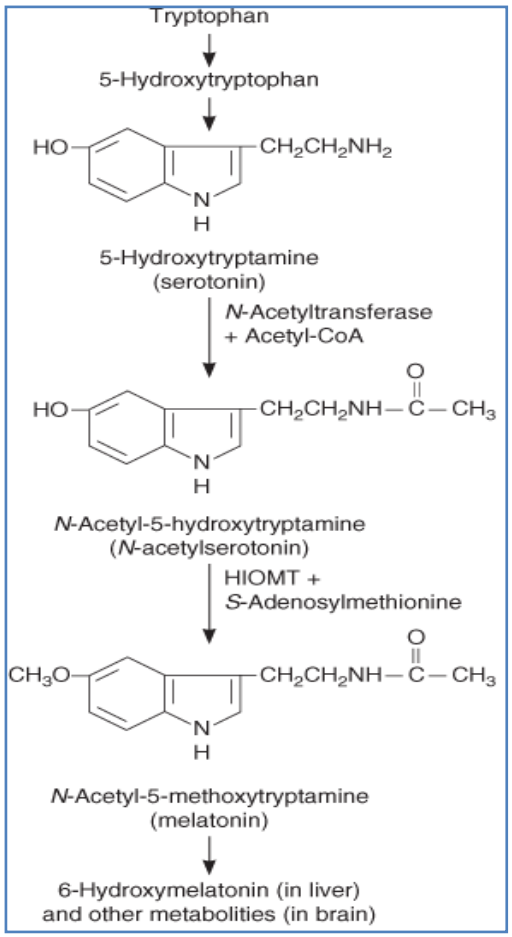



**Figure 5–9.** Formation and metabolism of melatonin. (HIOMT, hydroxyindole-O-methyltransferase).

## The Pineal Gland

The pineal gland is located at the roof of the posterior portion of the third ventricle. The pineal gland secretes melatonin, an indole synthesized from serotonin (Fig. 5-9). The pineal gland releases melatonin into the general circulation and into the cerebrospinal fluid (CSF). Melatonin secretion is regulated by the sympathetic nervous system and is increased in response to hypoglycemia and darkness. The physiologic roles of the pineal gland remain to be elucidated, but they involve regulation of gonadal function and development and chronobiological rhythms.

# Anterior Pituitary Hormones

## ACTH and Related Peptides

**Biosynthesis:** ACTH is a 39- amino acid peptide hormone (MW 4500) processed from a large precursor molecule, pro-opiomelanocortin (POMC) (MW 28, 500). Within the corticotroph, a single mRNA directs the synthesis and processing of POMC into smaller biological active fragments (Fig. 5-10) which include β-LPH, α-MSH, β MSH, β-endorphin, and the amino terminal fragment of pro-opiomelanocortin.

## Hypothalamic-Anterior pituitary Axis

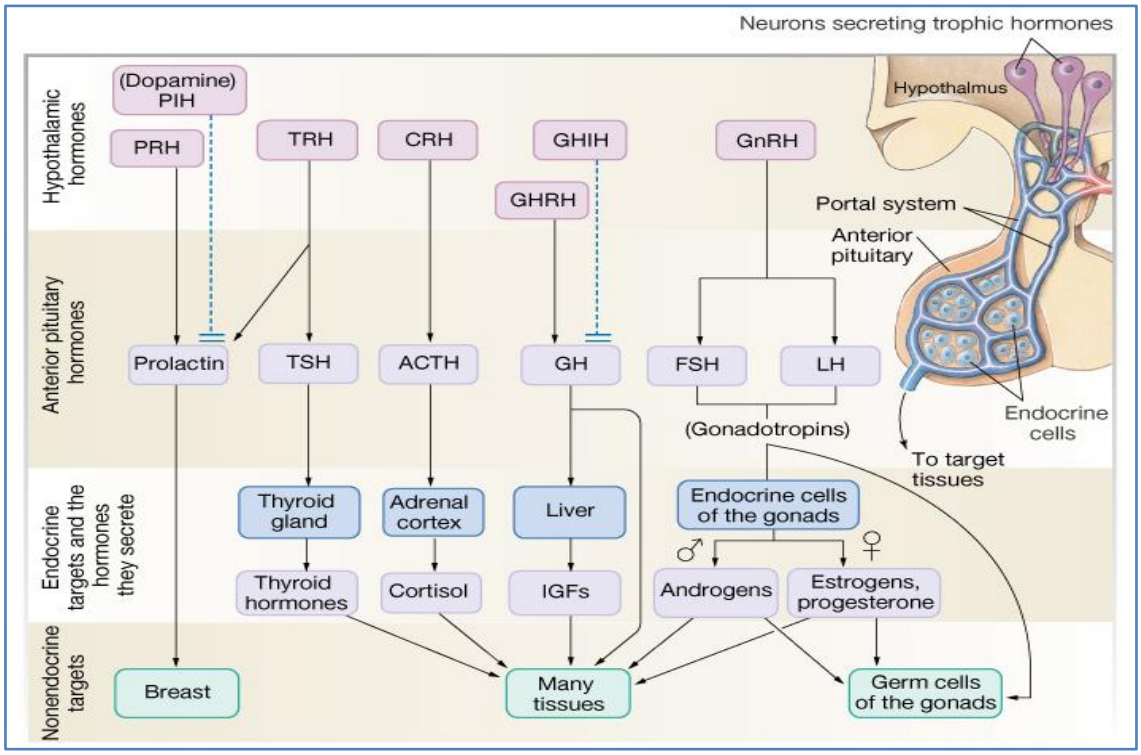
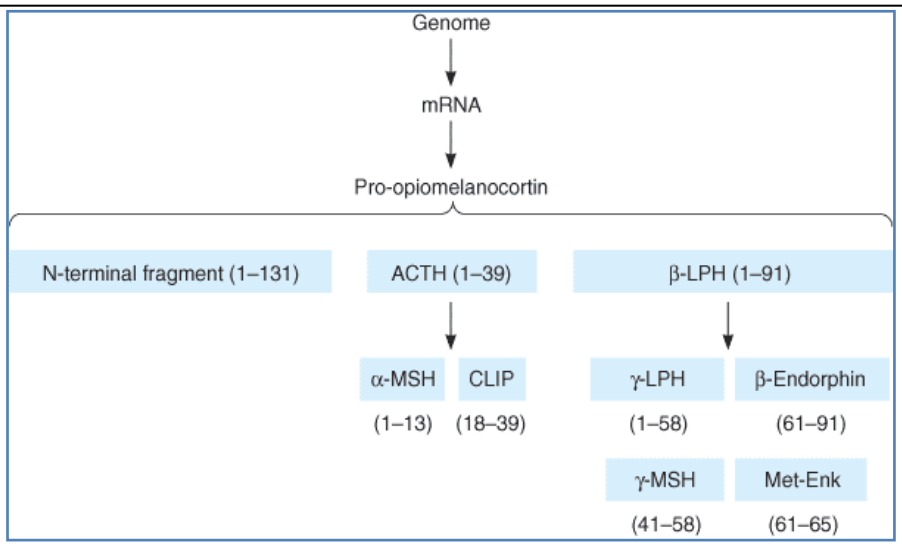
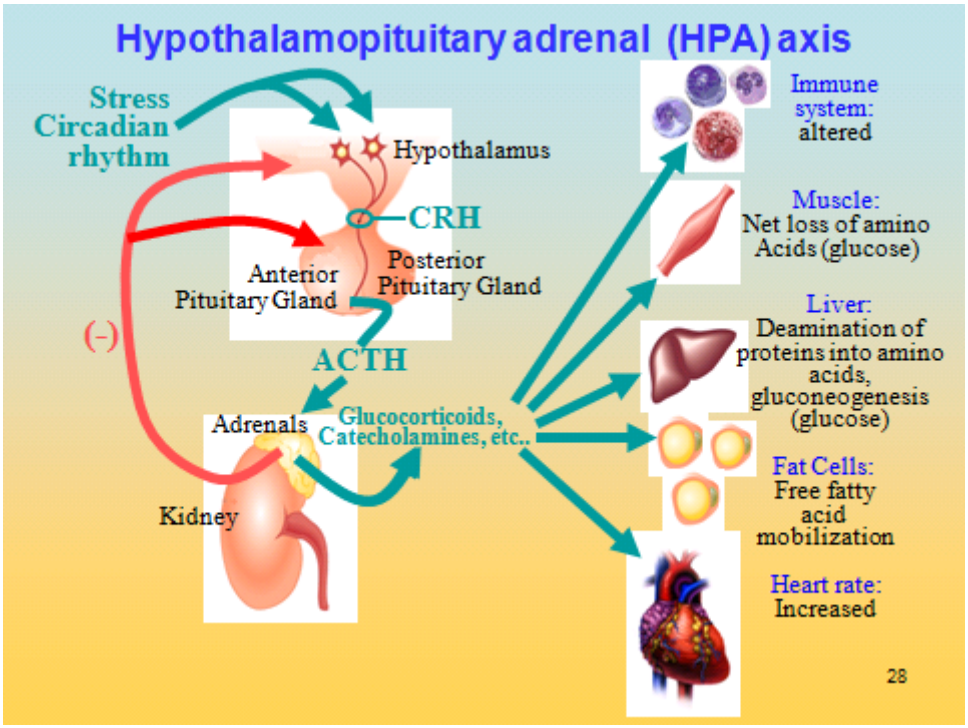



**Figure 5–10. The processing of pro-opiomelanocortin (MW 28,500) into its biologically active peptide hormones. Abbreviations are expanded in the text.**




**Function:** ACTH stimulates the secretion of glucocorticoids, mineralocorticoids, and androgenic steroids from the adrenal cortex. ACTH binds to receptors on the adrenal cortex and induces steroidogenesis using cAMP. The hyperpigmentation observed in states of ACTH hypersecretion (e.g. Addison's disease, Nelson's syndrome) appears to be primarily due to ACTH binding to the MSH receptor, because α-MSH and β-MSH do not exist as separate hormones in humans.




**Secretion:** The physiologic secretion of ACTH is mediated through neural influences by means of a complex of hormones, the most important of which is corticotropin–releasing hormone (CRH) (Fig. 5-11).

CRH stimulates ACTH in a pulsatile manner: diurnal rhythmicity causes a peak before awakening and a decline as a day progresses. This provokes diurnal secretion of cortisol from the adrenal cortex.

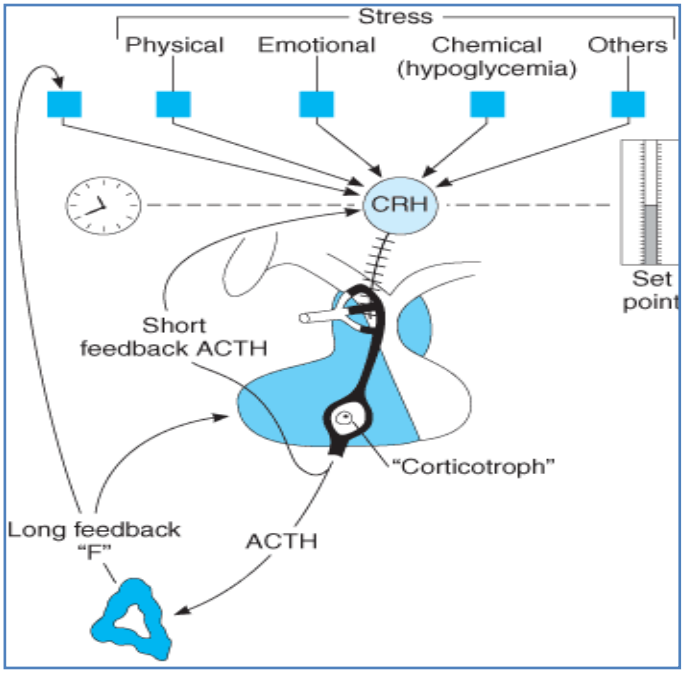



**Figure 5–11. hypothalamic-pituitary-adrenal axis, illustrating negative feedback by cortisol ("F") at the hypothalamic and pituitary levels. A short negative feedback loop of ACTH on the secretion of corticotropin-releasing hormone (CRH) also exists.**

Many stresses stimulate ACTH. Physical, emotional, and chemical stresses such as pain, trauma, hypoxia, acute hypoglycemia, cold exposure, surgery, depression, and interleukin-1 and ADH administration have been shown to stimulate ACTH and cortisol secretion. The increase in ACTH levels during stress is mediated by vasopressin as well as CRH.

Negative feedback of cortisol and synthetic glucocorticoids on ACTH secretion occurs at both the hypothalamic and pituitary levels via two mechanisms: "Fast feedback" is sensitive to the rate of change in cortisol levels, while "slow feedback" is sensitive to the absolute cortisol levels. The first mechanism is probably non nuclear. "Slow feedback" occurring later, may be explained by a nuclear– mediated mechanism and a subsequent decrease in synthesis of ACTH. ACTH also inhibits its own secretion (short loop feedback).

## Growth Hormone

**Biosynthesis:** Growth hormone (GH; somatotropin) is a 191-amino acid polypeptide hormone (MW 21,500) synthesized and secreted by the somatotrophs of the anterior pituitary. Its larger precursor peptide, pre GH (MW 28,000), is also secreted but has no physiologic significance.

**Function:** The primary function of GH is promotion of linear growth. Most of the growths–promoting effects are mediated by insulin–like growth factor I (IFG-1 previously known as somatomedin C).

GH, via IGF-1, increases protein synthesis by enhancing amino acid uptake and directly accelerating the transcription and translation of mRNA. In addition, GH tends to decrease protein catabolism by mobilizing fat as more efficient fuel source: it directly causes the release of fatty acids from adipose tissue and enhances their conversion to acetyl–CoA, from which energy is derived.

This protein–sparing effect is an important mechanism by which GH promotes growth and development. GH also affects carbohydrate metabolism. In excess, it decreases carbohydrate utilization and impairs glucose uptake into cells. This GH–induced insulin resistance appears to be due to post receptor impairment in insulin action.

**Secretion:** The secretion of GH is mediated by two hypothalamic hormones: growth hormone–releasing hormone (GHRH) and somatostatin (growth hormone–inhibiting hormone), both of which contribute to the episodic pattern of GH secretion.

GHRH binds to specific receptors, stimulating cAMP production by somatotrophs and stimulating both GH synthesis and secretion. The effects of GHRH are partially blocked by somatostatin (a tetradecapeptide, used also therapeutically in the management of GH excess).

Ghrelin, recently identified in the stomach, increases the release of GH by binding to a GH secretagogue receptor (GHS-R), suggests a new mechanism for regulation of GH secretion.

The neural control of basal GH secretion results in irregular and intermittent release associated with sleep and varying with age. Peak levels occur 1-4 hours after the onset of sleep. These nocturnal-sleep bursts, which form nearly 70% of daily GH secretion, are greater in children and tend to decrease with age.

The metabolic factors affecting GH secretion include all fuel substrates: carbohydrate, protein, and fat. Glucose administration lowers GH. In contrast, hypoglycemia stimulates GH release. A protein meal causes GH release. Fatty acids suppress GH responses to certain stimuli. Fasting stimulates GH secretion, possibly as a means of mobilizing fat as an energy source and preventing protein loss.

Responses to stimuli are blunted in states of cortisol excess and during hypo- and hyperthyroidism. Estrogen enhances GH secretion in response to stimulation. Many neurotransmitters and neuropharmacologic agents affect GH secretion. Dopaminergic, α-adrenergic, and serotonergic agents all stimulate GH release. β-adrenergic agonists inhibit GH.

## Prolactin

**Biosynthesis:** prolactin (PRL) is a 198-amino acid polypeptide hormone (MW 22.000) synthesized and secreted from the lactotrophs of anterior pituitary.

**Function:** PRL Stimulates lactation in the post partum period. During pregnancy, PRL secretion increases and in concert with many other hormones (estrogen, progesterone human placental lactogen-hPL, insulin, and cortisol), promotes additional breast development in preparation for milk production. Despite its importance during pregnancy, PRL has not been demonstrated to play a role in the development of normal breast tissue in humans. During pregnancy, estrogen enhances breast development but blunt the effect of PRL on lactation; the decrease in both estrogen and progesterone after parturition allows initiation of lactation. Accordingly, galactorrhea may accompany the discontinuance of oral contraceptives or estrogen therapy.

Although PRL does not appear to play a physiologic role in the regulation of gonadal function, hyperprolactinemia in humans leads to hypogonadism. In women, initially there is a shortening of the luteal phase; subsequently, anovulation, oligomenorrhea or amenorrhea, and infertility occur. In men, PRL excess leads to decrease testosterone synthesis and decreased spermatogenesis, which clinically present as decreased libido, impotence, and infertility. The exact mechanisms of PRL inhibition of gonadal function are unclear, but the principal one appears to be alteration of hypothalamic–pituitary control of gonadotropin secretion. Basal LH and FSH levels are usually normal – however, their pulsatile secretion is decreased and midcycle LH surge is suppressed in women.

PRL has also a role in immunomodulation. PRL modulates and stimulates both immune cell proliferation and survival.

**Secretion:** The hypothalamic control of PRL secretion is predominantly inhibitory, and dopamine is the most important inhibitory factor. TRH is a potent prolactin – releasing factor in addition to its role in stimulating TSH release PRL secretion is episodic. An increase is observed 60-90 min after sleep begins. Stress including surgery, exercise, and hypoglycemia, cause significant elevation of PRL levels. Estrogens augment basal and stimulated PRL secretion.

Dopamine agonists (e.g. bromocriptine) decrease PRL secretion, forming the basis for their use in states of PRL excess. Dopamine antagonists (e.g. receptor blockers such as phenothiazine and metoclopramide) augment PRL release.

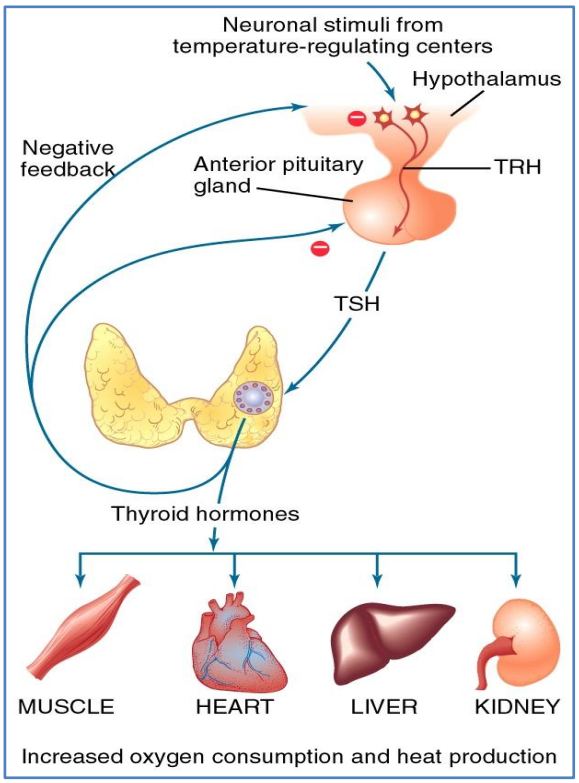
## Thyrotropin

**Biosynthesis:** Thyrotropin (thyroid–stimulating hormone, TSH) is a glycoprotein (MW 28.000) composed to two noncovalently linked α and β subunits. The structure of the α

subunit of TSH is identical to that of the other glycoprotein molecules – FSH, LH, and human chorionic gonadotropin (hCG) – but the β subunit differs in theses glycoproteins and is responsible for their biologic and immunologic specificity. The peptides of these subunits appear to be synthesized separately and united before the carbohydrate groups are attached.

**Function:** The β subunit of TSH attaches to high affinity receptors in the thyroid, stimulating iodide uptake hormone synthesis, and release of $T_4$ and $T_3$. This occurs through activation of adenylyl cyclase and the production of cAMP. TSH secretion also causes an increase in gland size and vascularity by promoting mRNA and protein synthesis.

**Secretion:** The secretion of TSH is controlled by both stimulatory (TRH) and inhibitory (somatostatin) influences from the hypothalamus. It is also modulated by the feedback inhibition of thyroid hormone on the hypothalamic–pituitary axis. Dopamine physiologically inhibits TSH secretion. Glucocorticoid excess has been shown to impair the sensitivity of the pituitary to TRH and may lower TSH to undetectable levels. However, estrogens increase the sensitivity of the thyrotroph to TRH; women have a greater TSH response to TRH than men do.




**Hypothalamic - thyroid axis**

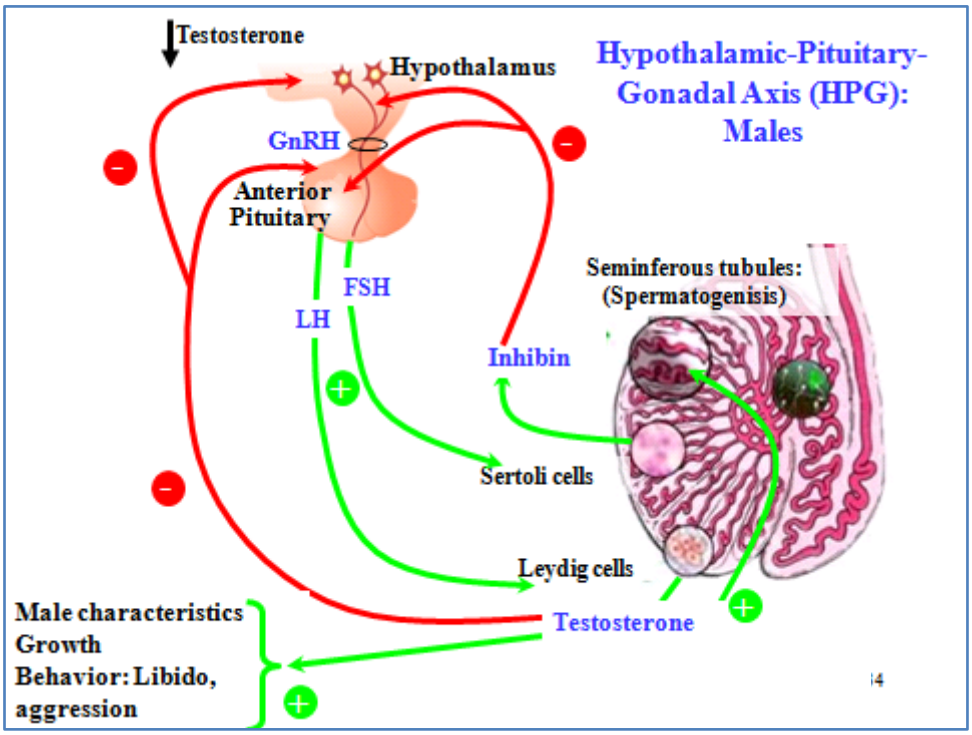
## Gonadotropins: Luteinizing Hormone, Follicle–Stimulating Hormone

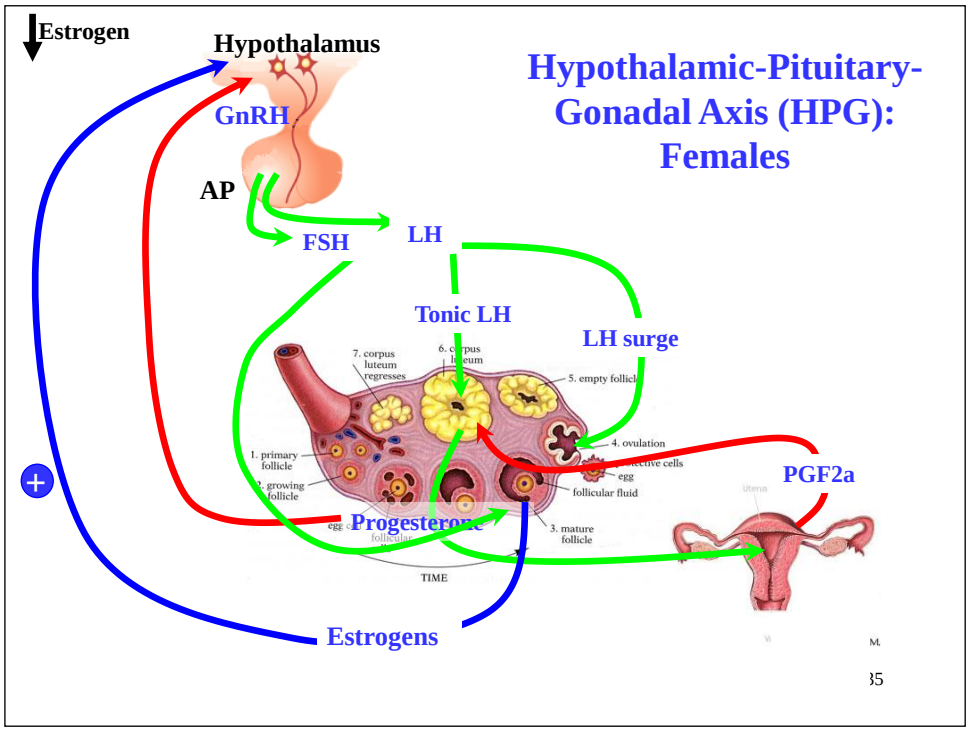
**Biosynthesis:** Luteinizing hormone (LH) and follicle stimulating hormone (FSH) are glycoprotein gonadotropins composed of α and β subunits and secreted by the same cell. The biologic activity of hCG, a placental glycoprotein, closely resembles that of LH. Human menopausal gonadotropin (hMG, menotropins) is a preparation with FSH – like activity. Menotropins and chorionic gonadotropin are used clinically for induction of spermatogenesis or ovulation.

**Function:** LH and FSH bind to receptors in the ovary and testis and regulate gonadal function by promoting sex steroid production and gametogenesis.

In men, LH stimulates testosterone production from the interstitial cells of the testes (Leydig cells). Maturation of spermatozoa, however, requires both LH and FSH. FSH stimulates testicular growth and enhances the production of an androgen–binding protein by the Sertoli cells, which are a component of the testicular tubule necessary for sustaining the maturing sperm cell. This androgen – binding protein promotes high local concentrations of testosterone within the testis, an essential factor in the development of normal spermatogenesis.

In women, LH stimulates estrogen and progesterone production from the ovary. A surge of LH in the mid menstrual cycle is responsible for ovulation; and continued LH secretion subsequently stimulates the corpus luteum to produce progesterone by enhancing the conversion of cholesterol to pregnenolone. Development of the ovarian follicle is largely under FSH control, and the secretion of estrogen from this follicle is dependent on both FSH and LH.



**Secretion:** the secretion of LH and FSH is controlled by gonadotropin – releasing hormone (GnRH), which maintains basal gonadotropin secretion, generates the phasic release of gonadotropins for ovulation, and determines the onset of puberty. Leptin, a recently described hormone made in adipocytes, is involved in regulation of this axis and may help to explain the suppression of gonadotropin secretion that accompanies caloric restriction.

In both males and females, secretion of LH and FSH is episodic, with secretory bursts that occur each hour and are mediated by episodic release of GnRH. The amplitude of these secretory surges is greater in patients with primary hypogonadism. The pulsatile nature of GnRH release is critical for sustaining gonadotropin secretion. A continuous, prolonged infusion of GnRH in women evokes an initial increase in LH and FSH followed by prolonged suppression of gonadotropin secretion. This phenomenon may be explained by down regulation of GnRH receptors on the pituitary gonadotrophs.

Circulating sex steroids affect GnRH secretion and thus LH and FSH secretion by both positive and negative (inhibitory) feedback mechanisms. During the menstrual cycle, estrogens provide a positive influence on GnRH effects on LH and FSH secretion, and the rise of estrogens during the follicular phase is the stimulus for the LH and the FSH ovulatory surge. Ovulation occurs about 10-12 hrs after the LH peak and 24-36 hrs after the estradiol peak. The remaining follicular cells in the ovary are converted, under the influence of LH, to progesterone – secreting structure, the corpus luteum.

Negative feedback effects of sex steroids on gonadotropin secretion also occur. In men, primary gonadal failure with low circulating testosterone levels is also associated with elevated gonadotropins. Inhibin, a polypeptide secreted by the Sertoli cells of the seminiferous tubules, is the major factor that inhibits FSH secretion by negative feedback.

## Pituitary and Hypothalamic Disorders

Hypothalamic–pituitary lesions present with a variety of manifestations, including pituitary hormone hypersecretion and hyposecretion. In adults, the commonest cause of hypothalamic–pituitary dysfunction is a pituitary adenoma, of which the great majority are hypersecreting. The earliest symptoms of such tumors are due to endocrinologic abnormalities-hypogonadism is the most frequent manifestation.

In children pituitary adenomas are uncommon. These also manifest as endocrine disturbances (low GH levels, delayed puberty, diabetes insipidus).

## Pituitary Hypersecretion

PRL is the hormone most commonly secreted in excess amounts by pituitary adenomas. Hypersecretion of GH or ACTH leads to the more characteristic syndromes of acromegaly and Cushing's disease.

## Pituitary Insufficiency

In children, short stature is the most frequent clinical manifestation of hypothalamic–pituitary dysfunction.

## Diabetes Insipidus

Diabetes insipidus is a common manifestation of hypothalamic lesions but is rare in primary pituitary lesions.

## Hypopituitarism

Hypopituitarism is manifested by diminished or absent secretion of one or more pituitary hormones. Hypopituitarism is either a primary event caused by destruction of the anterior pituitary gland or secondary phenomenon resulting for deficiency of hypothalamic stimulatory factors normally acting on the pituitary. Treatment and prognosis depend on the extent of hypo function, the underlying causes, and the location of the lesion in the hypothalamic–pituitary axis.

**Etiology:** The etiology considerations in hypopituitarism are diverse: invasive, infarction, infiltrative, injury, immunologic iatrogenic, infectious, idiopathic and isolated "nine I's". Most of these lesions may cause pituitary or hypothalamic failure (or both).

a. **Invasive:** space occupying lesions may cause hypopituitarism by destroying the pituitary gland or hypothalamic nuclei or by disrupting the hypothalamic – hypophysial portal venous system. Large pituitary adenomas cause hypopituitarism by these mechanisms, and pituitary function may improve after their removal. Small pituitary tumors – microadenomas – characteristically seen in the hypersecretory states (excess PRL, GH, ACTH) do not directly cause pituitary insufficiency.

b. **Infarction:** Ischemic damage to the pituitary has long been recognized as a cause of hypopituitarism. The mechanism for the ischemia is not certain. Hypotension along with vasospasm of the hypophysial arteries is currently believed to compromise arterial perfusion of the anterior pituitary. During pregnancy, the pituitary gland may be more sensitive to hypoxemia because of its increased metabolic needs or more susceptible states. Some degree of hypopituitarism has been reported in 32% of women with severe postpartum hemorrhage.

c. **Infiltrative:** hypopituitarism may be the initial clinical manifestation of infiltrative disease processes such as sarcoidosis and hemotochromatosis. Hypopituitarism particularly hypogonadotropic hypogonadism, is a prominent manifestation of iron storage disease, either idiopathic hemochromatosis or transfusional iron overload. If the diagnosis is established earl, hypogonadism in hemochromatosis may be reversible with iron depletion. Pituitary deficiencies of TSH, GH, and ACTH may occur later in the course of the disease and are not reversible by iron chelation therapy.

d. **Injury:** severe head trauma may cause anterior pituitary insufficiency and diabetes insipidus. Posttraumatic anterior hypopituitarism may be due to injury to the anterior pituitary, the pituitary stalk or the hypothalamus.

e. **Immunologic**: Lymphocytic hypophysitis resulting in anterior hypopituitarism is a distinct entity, occurring most often in women during pregnancy or in the postpartum period. An autoimmune process with extensive infiltration of the gland by lymphocytes and plasma cells destroys the anterior pituitary cells.

f. **Iatrogenic:** Both surgical and radiation therapy to the pituitary gland may compromise its function. The dose of conventional radiation therapy presently employed to treat pituitary tumors results in 50-60% incidence of hypothalamic and pituitary insufficiency.

g. **Infectious:** Although many infectious diseases, including tuberculosis, syphilis, and mycotic infections, have been implicated as causative agents in pituitary hypofunction, anti-infective drugs have now made them rare causes of hypopituitarism.

h. **Idiopathic:** In some patients with hypopituitarism, no underlying cause is found. Both autosomal recessive and x-linked recessive inheritance patterns have been reported.

i. **Isolated:** Isolated (monotropic) deficiencies of the anterior pituitary hormones have been described. Some of these have been associated with mutations in the genes coding for the specific hormones. Others, particularly GH deficiency, have been associated with mutations in genes necessary for normal pituitary development. Examples of isolated deficiencies: GH deficiency, ACTH deficiency, gonadotropin deficiency, TSH deficiency, PRL deficiency, multiple hormone deficiencies.

**Clinical Features**

The onset of pituitary insufficiency is usually gradual and the classic course of progressive hypopituitarism is an initial loss of GH and gonadotropin secretion followed by deficiencies of TSH, then ACTH, and finally PRL.

Impaired GH secretion causes decreased growth in children. Hypogonadism is manifested by amenorrhea in women and decreased libido or erectile dysfunction in men.

Hypothyroidism caused by TSH deficiency generally simulates the clinical changes observed in primary thyroid failure; however, it is usually less severe, and goiter is absent. Cold intolerance, dry skin, mental dullness, bradycardia, and anemia have all been observed.

ACTH deficiency causes adrenocortical insufficiency and its clinical features resemble those of primary adrenal failure. Weakness, nausea, vomiting, anorexia, weight loss, fever, and hypotension may occur. Since the zona glomerulosa and the renin–angiogenesis system are usually intact, the dehydration and sodium depletion in Addison's disease are uncommon. However, these patients are susceptible to hypotension, shock, and cardiovascular collapse since glucocorticoids are necessary to maintain vascular reactivity, especially during stress.

GH deficiency is associated with decreased muscle mass and increase fat mass. The only symptom of PRL deficiency is failure of postpartum lactation.

Laboratory findings may include anemia (related to thyroid and androgen deficiency), hypoglycemia, hyponatremia (related to hypothyroidism and hypoadrenalism, which cause inappropriate water retention, not sodium less). Hyperkalemia, which is common in primary adrenal failure, is not present. Adult GH deficiency is associated with decreased red blood cell mass, increased LDL cholesterol, and decreased bone mass.

**Diagnosis**

If endocrine hypofunction is suspected, pituitary hormone deficiency must be distinguished for primary failure of the thyroid, adrenals, or gonads. Basal determinations of each anterior pituitary hormone are useful only if compared to target gland secretion. Testosterone is a sensitive indicator of hypopituitarism in women as well as in men. Adrenocortical reserve should initially be evaluated by a rapid ACTH stimulation test.

Since hyperprolactinemia, regardless of its cause, leads to gonadal dysfunction, serum PRL should be measured early in the evaluation of hypogonadism.

In primary target gland hypofunction, TSH, LH, FSH, or ACTH will be elevated. Low or normal values for these pituitary hormones suggest hypothalamic – pituitary dysfunction.

Provocative endocrine testing may then be employed to confirm the diagnosis and to assess the extent of hypofunction.

## Pituitary Adenomas

Advances in endocrinologic and neuroradiologic research in recent years have allowed earlier recognition and more successful therapy of pituitary adenomas. Prolactinomas are the most common type, accounting for about 60% of primary pituitary tumors; GH hypersecretion occurs in approximately 20% and ACTH excess in 10%. Hypersecretion of TSH, the gonadotropins, or α subunits is unusual.

Pituitary microadenomas are defined as intrasellar adenomas less than 1cm in diameter that present with manifestations of hormonal excess without sellar enlargement. Pituitary macroadenomas are those large than 1cm in diameter and cause generalized sellar enlargement. Panhypopituitarism and visual loss increase in frequency with tumor size.

1. **Prolactinomas**

   PRL hypersecretion is the most common endocrine abnormality due to hypothalamic – pituitary disorders, and PRL is the hormone most commonly secreted in excess by pituitary adenomas.

   The classic clinical features are galactorrhea and amenorrhea in women and galactorrhea and decreased libido or impotence in men.

   a. **Galactorrhea:** Galactorrhea occurs in the majority of women with prolactinomas and is much less common in men. It may be present only transiently or intermittently. The absence of galactrorrhea despite markedly elevated PRL levels in probably due to concomitant deficiency of the gonadal hormones required to initiate lactation.

   b. **Gonadal Dysfunction:**
      1. **In women:** amenorrhea, oligomenorrhea with anovulation or infertility is present in ~ 90% of women with prolactinomas. Gonadal dysfunction in these women is due to interference with the hypothalamic-pituitary gonadal axis by the hyperprolactinemia, and is not due to distraction of the gonadotropin–secreting cells. This has been documented by the return of the menstrual function following

reduction of PRL levels to normal by drug treatment or surgical removal of the tumor. Although basal gonadotropin levels are frequently within the normal range, PRL inhibits both the normal pulsatile secretion of LH and FSH and the midcycle LH surge, resulting in an ovulation. Patients with hyperprolactinemia are usually estrogen – deficient.

2. **In men**: in men PRL excess may also occasionally cause galactorrhea; however, the usual manifestations are those of hypogonadism. Unfortunately, prolactinomas in men are often not diagnosed until late manifestations such as headache, visual impairment, or hypopituitarism appear; virtually all such patients have a history of sexual or gonadal dysfunction. Serum testosterone levels are low impotence also occurs in hyperprolactinemic males. Its cause is unclear, since testosterone replacement may not reverse it if hyperprolactinemia is not corrected.

## 2. Acromegaly and Gigantism

The characteristic clinical manifestations are the consequence of chronic GH hypersecretion, which in turn leads to excessive generation of IGF-1, the mediator of most of the effects of GH. Although overgrowth of bone is the classic feature, GH excess causes a generalized systemic disorder with deleterious effects and an increased mortality rate.

Acromegaly and gigantism are virtually always secondary to a pituitary adenoma. Ectopic GHRH secretion has been identified as another cause of GH hypersecretion. Ectopic secretion of HG per se is very rare but has been documented in a few lung tumors.

In adults, GH excess leads to acromegaly, the syndrome characterized by local overgrowth of bone, particularly of the skull and mandible. Linear growth does not occur, because of prior fusion of the epiphyses of long bones. In childhood and adolescence, chronic GH excess leads to gigantism.

Hypertension occurs in about 25% of patients and Cardiomegaly in about 15%. Cardiac enlargement may be secondary to hypertension or atherosclerosis. Renal calculi occur in 11% secondary to the hypercalciuria induced by GH excess. Other endocrine and metabolic abnormalities include glucose intolerance and hyperinsulinism due to GH–induced insulin resistance. Hypogandism occurs in 60% of female and 46% of male patients.

## 3. ACTH – Secreting Pituitary Adenomas: Cushing's Diseases

Pituitary ACTH hypersecretion (Cushing's disease) is now recognized as the most common cause of spontaneous hypercortisolism (Cushing's syndrome) and must be distinguished from the other forms of adrenocorticosteroid excess ectopic ACTH syndrome and adrenal tumors.

The endocrine abnormalities in Cushing's disease are as follows:

1. Hypersecretion of ACTH, with bilateral hyperplasia and hypercortisolism.
2. Absent circadian periodicity of ACTH cortisol secretion;
3. Absent responsiveness of ACTH and cortisol to stress;
4. Abnormal negative feedback of ACTH secretion by glucocorticoids; and
5. Subnormal responsiveness of GH, TSH, and gonadotropins to stimulation.

**Clinical Features**: Cushing's disease presents with the signs and symptoms of hypercortisolism and adrenal androgen excess. Obesity (with predominantly central fat distribution), hypertension, glucose intolerance, and gonadal dysfunction (amenorrhea or impotence) are common features. Other common manifestations include moon faces, hirsutism, poor wound healing, acne and easy bruisability. There is a female:male ratio of about 8:1

**4. Thyrotropin – Secreting Pituitary Adenomas**

Thyrotropin-secreting pituitary adenomas are rare tumors manifested as hyperthyroidism with goiter in the presence of elevated TSH.

**5. Gonadotropin – Secreting Pituitary Adenomas**

Most patients have hypogonadism and may have panhypopituitarism. Hormonal evaluation reveals elevated FSH in some patients accompanied by normal LH levels.

# Posterior Pituitary

## Antidiuretic Hormone (ADH; Vasopressin)

ADH acts through three receptors, termed V1, V2, and V3. The V1 receptors mediate vascular smooth muscle contraction and stimulate prostaglandin synthesis and liver glycogenolysis. Activation of V1 receptors increase phosphatidylinositol breakdown thus causing cellular $Ca^{++}$ mobilization. The V2 receptors, which produce the renal actions of ADH, activate Gs proteins and stimulate the generation of cAMP.

### Renal Actions

The major renal effect of ADH is to increase the water permeability of the luminal membrane of the collecting duct epithelium via the ADH-sensitive water channels, aquaporin–2. In the absence of ADH, permeability of the epithelium is very low, and reabsorption of water decreases, leading to polyuria. Water permeability of the luminal membrane is increased by increasing the number of aqueous channels at the luminal surface.

### Cardiovascular Actions

ADH pressor effects may be important during hypovolemia when plasma ADH levels are very high and maintenance of tissue perfusion is critical.

### Diabetes Insipidus

Diabetes insipidus is a disorder resulting from deficient ADH action and is characterized by the passage of large amounts of very dilute urine. Central (or neurogenic) diabetes insipidus is due to failure of the posterior pituitary to secrete adequate quantities of ADH.

Nephrogenic diabetes insipidus results when the kidney fails to respond to circulating ADH. The resulting renal concentrating defect leads to the loss of large volume of dilate urine i.e. free water. This causes cellular and extracellular dehydration, which stimulate thirst and cause polydipsia.

**A. Central diabetes Insipidus:**

Many of the disorders which cause hypopituitarism may also cause diabetes insipidus. Hypothalamic tumors or other primary central nervous system lesions and infiltrative and invasive lesions cause diabetes insipidus. These lesions cause diabetes insipidus by damage to the pituitary stalk, which interrupts the hypothalamic – neurohypophysial nerve tracts, or by direct damage to the hypothalamic neurons that synthesize ADH. These disorders cause varying degrees of ADH deficiency.

Diabetes insipidus can also be caused by trauma and is common following surgery for hypothalamic or pituitary tumors. Idiopathic diabetes insipidus presents in later childhood or adolescence and in adulthood. It is also associated with a decrease in the number of ADH – containing fibers. As many as 30-40% of these patients have antibodies directed against ADH–secreting hypothalamic neurons. Diabetes insipidus due to enzymatic destruction of circulating ADH by increased plasma levels of vasopressinase may occur during pregnancy.

**B. Nephrogenic Diabetes Insipidus**

This group of diseases is caused by renal unresponsiveness to the physiologic actions of ADH; thus ADH levels are normal or elevated. Chronic renal diseases, particularly those affecting the medulla and collecting ducts, can cause nephrogenic diabetes.

The electrolyte disorders hypokalemia and hypercalcemia reduce urinary concentrating capacity. Many drugs have been implicated in the development of nephrogenic diabetes insipidus. For example, lithium carbonate reduces the sensitivity of the renal tubule to ADH by reducing $V_2$ receptor density or aquaporin–2 expression.

## Oxytocin

Oxytocin primarily affects uterine smooth muscle. It increases both the frequency and the duration of action potentials during uterine contractions. Estrogen enhances the action of oxytocin by reducing the membrane potential of smooth muscle cells, thus lowering the threshold of excitation. Toward the end of pregnancy, as estrogen levels become higher, the membrane potential of uterine smooth muscle cells becomes less negative, rendering the uterus more sensitive to oxytocin. The number of oxytocin receptors in the uterus also increases at this time, and their activation causes cellular calcium to be mobilized through phosphatidylinositol hydrolysis.

**Actions**

**A. Parturition**

As a fetus enters the birth cancel the lower segment of the uterus, the cervix, and then the vagina are dilated, and this causes reflex release of oxytocin. Strong uterine contractions cause further descent of the fetus, further distension, and further release of oxytocin.

**B. Lactation**

Oxytocin is involved in lactation. Stimulation of the nipple produces a neurohumoral reflex that cases secretion of oxytocin. In turn, oxytocin causes contraction of the myoepithelial cells of the mammary ducts and the ejection of milk.