Biochemistry and Disorders of Hormones of the Hypothalamic and Pituitary Gland (Hypothalamus and Pituitary Axis)

1. Hormones of the hypothalamus

Prof. Dr. Hedef Dhafir El-Yassin 2013
Objectives:

1. to describe the structure and function of the hypothalamus
2. to list the hormones secreted from the hypothalamus
3. to understand how the hypothalamus controls the secretion of hormones of the pituitary gland.

1. Hormones of the hypothalamus

The hypothalamus is an integral part of the substance of the brain. A small cone-shaped structure, it projects downward, ending in the pituitary stalk, a tubular connection to the pituitary gland, which is a double lobed structure that produces the endocrine secretions when stimulated by the hypothalamus.
The hypothalamus controls each lobe of the pituitary slightly differently.

1. **control of Anterior lobe**
   a. The hypothalamus acts as an endocrine gland.
   b. Hormones are sent from the hypothalamus to the anterior pituitary via a blood vessel called the portal vein.
   c. The target tissue is the anterior lobe of the pituitary e.g. LH, TSH, and FSH.

2. **control of the Posterior lobe**
   d. Neuro-hormones are synthesized in the hypothalamus neurons. They are transported and stored in vesicles in the axon ending located in the posterior pituitary.
   e. Nerve impulses travel down the axon into the posterior pituitary. This causes the release of the vesicles of hormones into the bloodstream at the posterior pituitary e.g. oxytocin, and ADH.
Many hormonal systems involve hypothalamus.

Table: Hypothalamic hypophysial-target gland hormones form integrated feedback loops

<table>
<thead>
<tr>
<th>Hypothalamic hormones</th>
<th>No. of A.A in structure</th>
<th>Pituitary Hormone Affected(^1)</th>
<th>Target Gland Hormone Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Thyrotropin-releasing hormone (TRH)</td>
<td>3</td>
<td>TSH (PRL)</td>
<td>T(_3), T(_4)</td>
</tr>
<tr>
<td>2 Gonadotropin-releasing hormone (GnRH)</td>
<td>10</td>
<td>LH, FSH</td>
<td>Androgens, estrogens, progestins</td>
</tr>
<tr>
<td>3 Corticotropin-releasing hormone (CRH)</td>
<td>41</td>
<td>ACTH</td>
<td>Cortisol</td>
</tr>
<tr>
<td>4 Growth hormone-releasing hormone (GHRH or GRH)</td>
<td>49</td>
<td>GH</td>
<td>IGF-1</td>
</tr>
<tr>
<td>5 Prolactin release factor</td>
<td>Not established</td>
<td>PRL</td>
<td>neurohormones</td>
</tr>
<tr>
<td>6 Somatostatin (Growth hormone release-inhibiting hormone; somatotropin release-inhibiting hormone (GHRIH or SRIH)</td>
<td>14</td>
<td>GH (TSH, FSH, ACTH)</td>
<td>IGK-1; T(_3) and T(_4)</td>
</tr>
<tr>
<td>7 Prolactin-release-inhibiting hormones (Dopamine and GAP) (PRIH or PIH)</td>
<td></td>
<td>PRL</td>
<td>neurohormones</td>
</tr>
</tbody>
</table>

\(^1\)The hypothalamic hormone has a secondary or lesser effect on the hormones in parentheses.
1) **Thyrotropin-releasing hormone (TRH)**

Is the simplest of the hypothalamic neuropeptides. It consists essentially of three amino acids. Its basic sequence is glutamic acid-histidine-proline, The simplicity of this structure is deceiving for TRH is involved in an extraordinary array of functions. Some of which are:

   a. It stimulates the secretion of thyroid-stimulating hormone from the pituitary.
   b. It also affects the secretion of prolactin from the pituitary.

The TRH-secreting cells are subject to stimulatory and inhibitory influences from higher centers in the brain and they also are inhibited by circulating thyroid hormone.

2) **Gonadotropin-releasing hormone (GnRH)**

Also known as luteinizing hormone-releasing hormone (LHRH), is a peptide chain of 10 amino acids. It stimulates the synthesis and release of the two pituitary gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

3) **Corticotropin-releasing hormone (CRH)**

Is a large peptide consisting of a single chain of 41 amino acids. It stimulates not only secretion of corticotropin in the pituitary gland but also the synthesis of corticotropin in the corticotropin-producing cells (corticotrophs) of the anterior lobe of the pituitary gland. Many factors, both neurogenic and hormonal, regulate the secretion of CRH. Among the hormones that play an important role in modulating the influence of CRH is cortisol, the major hormone secreted by the adrenal cortex, which, as part of the negative feedback mechanism. Vasopressin, the major regulator of the body's excretion of water, has an additional ancillary role in stimulating the secretion of CRH.

Excessive secretion of CRH leads to an increase in the size and number of corticotrophs in the pituitary gland, often resulting in a pituitary tumor. This, in turn, leads to excessive stimulation of the adrenal cortex, resulting in high circulating levels of adrenocortical hormones, the clinical manifestations of which are known as Cushing's syndrome. Conversely, a deficiency of CRH-producing cells can, by a lack of stimulation of the pituitary and adrenal cortical cells, result in adrenocortical deficiency.
4) Growth hormone-releasing hormone (GHRH or GRH)
Like CRH, growth hormone-releasing hormone (GHRH) is a large peptide. A number of forms have been described that differ from one another only in minor details and in the number of amino acids (varying from 37 to 49). It is stimulated by stresses, including physical exercise, and secretion is blocked by a powerful inhibitor called somatostatin. Negative feedback control of GHRH secretion is mediated largely through compounds called somatomedins, growth-promoting hormones that are generated when tissues are exposed to growth hormone itself. Isolated deficiency of GHRH (in which there is normal functioning of the hypothalamus except for this deficiency) may be the cause of one form of dwarfism, a general term applied to all individuals with abnormally small stature.

5) Prolactin release factor (PRF):
Appears to be released from the hypothalamus in a pulsatile fashion and it is the fluctuation in PRF that regulates the circulating level of prolactin.

6) Somatostatin (Growth hormone release-inhibiting hormone; somatotropin release-inhibiting hormone (GHRIH or SRIH)
Somatostatin refers to a number of polypeptides consisting of chains of 14 to 28 amino acids. Somatostatin is also a powerful inhibitor of pituitary TSH secretion. Somatostatin, like TRH, is widely distributed in the central nervous system and in other tissues. It serves an important paracrine function in the islets of Langerhans, by blocking the secretion of both insulin and glucagon from adjacent cells. Somatostatin has emerged not only as a powerful blocker of the secretion of GH, insulin, glucagon, and other hormones but also as a potent inhibitor of many functions of the gastrointestinal tract, including the secretion of stomach acid, the secretion of pancreatic enzymes, and the process of intestinal absorption.
7) **Prolactin release-inhibiting hormones (Dopamine and GAP)**

GAP = GnRH-associated peptide

The hypothalamic regulation of prolactin secretion from the pituitary is different from the hypothalamic regulation of other pituitary hormones in two respects:

1. First, the hypothalamus primarily inhibits rather than stimulates the release of prolactin from the pituitary.
2. Second, this major inhibiting factor is not a neuropeptide, but rather the neurotransmitter dopamine. Prolactin deficiency is known to occur, but only rarely. Excessive prolactin production (hyperprolactinemia) is a common endocrine abnormality.

**Quick quiz 1:** which of the following statement is incorrect for hypothalamus?

1. it releases the hormones which regulate the secretion of anterior pituitary gland
2. hypothalamic hormones are absent from the tissues
3. the higher brain enters are necessary to control their secretion
4. the prolactin has no release hormone but has release inhibiting hormone

**Quick quiz 2:** one of the following hormones is synthesized in the hypothalamus but not secreted from it:

1. vasopressin
2. MSH
3. prolactin
4. serotonin

**Conclusion**

1. The hypothalamus is a small cone-shaped structure, part of the brain, it projects downward, ending in the pituitary stalk.
2. The pituitary gland, a roundish organ that lies immediately beneath the hypothalamus composed of two distinctive parts:
   a. The **anterior pituitary** (adenohypophysis).
   b. The **posterior pituitary** (neurohypophysis)
3. The hypothalamus controls the secretion of hormones from each lobe of the pituitary slightly differently
Biochemistry and Disorders of Hormones of the Hypothalamic and Pituitary Gland
(Hypothalamus and Pituitary Axis)

2. Hormones of the pituitary gland

Prof. Dr. Hedef Dhafir El-Yassin 2013
Lecture 4

Sunday 3/3

Objectives:

1. to describe the structure and function of the pituitary gland
2. to list the hormones secreted from the pituitary gland
3. state the peripheral effects of hormone release for each hormone synthesized or stored in the pituitary gland
4. to state the peripheral effects of increased and decreased hormone release for each hormone synthesized or stored in the pituitary gland.

2. Hormones of the Pituitary gland

The pituitary gland, also known as the hypophysis, is a roundish organ that lies immediately beneath the hypothalamus. Careful examination of the pituitary gland reveals that it composed of two distinctive parts:

1. The anterior pituitary (adenohypophysis) is a classical gland composed predominantly of cells that secrete protein hormones.

2. 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. The target cells for most of the hormones produced in these tissues are themselves endocrine cells.

The pituitary gland is often called the "master gland" of the body. The anterior and posterior pituitary secrete a number of hormones that collectively influence all cells and affect virtually all physiologic processes.
Table: The major hormones synthesized and secreted by the pituitary gland, along with summary statements about their major target organs and physiologic effects.

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

As seen in the table above, the anterior pituitary synthesizes and secreted six major hormones. **Individual cells within the anterior pituitary secrete a single hormone** (or possibly two in some cases). Thus, the anterior pituitary contains at least six distinctive endocrinocytes.

The cells that secrete thyroid-stimulating hormone do not also secrete growth hormone, and they have receptors for thyroid-releasing hormone, not growth hormone-releasing hormone.

**Hormonal cascade of signals from CNS to ultimate hormone.**

The target "gland" is the last hormone-producing tissue in the cascade, which is stimulated by an appropriate anterior pituitary hormone. Examples are thyroid gland, adrenal cortex, ovary and testes. Ultimate hormone feedback negatively on sites producing intermediate hormones in the cascade. Amounts (nanogram (ng), microgram (µg), and milligram (mg) represent approximate quantities of hormone released.
Overview of anterior pituitary hormones with hypothalamic releasing hormones and their actions

Anterior Pituitary Hormones

1. **Growth Hormone**

Growth hormone, also known as somatotropin, is a protein hormone of about 191 amino acids and two intramolecular disulfide bridges, that is synthesized and secreted by cells called somatotrophs in the anterior pituitary.

During daytime, its plasma concentration in health adults remain relatively low (<2 g/ml) with several secretory spikes occurring after meals or exercise.

However, it shows a marked rise in the evening in both adults and children and reach a peak value during the period of deepest sleep.

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 suppresses their ability to take up and accumulate circulating lipids.

- **Indirect effects** are mediated primarily by a insulin-like growth factor-1 (IGF-1), a hormone that is secreted from the liver and other tissues in response to growth hormone. A majority of the growth promoting effects of growth hormone is actually due to IGF-1 acting on its target cells. IGF-1 also appears to be the key player in muscle growth. It stimulates amino acid uptake and protein synthesis in muscle and other tissues.

**Metabolic Effects**

- **Protein metabolism**: In general, growth hormone stimulates protein anabolism in many tissues. This effect reflects increased amino acid uptake, increased protein synthesis and decreased oxidation of proteins.
- **Fat metabolism:** Growth hormone enhances the utilization of fat by stimulating triglyceride breakdown and oxidation in adipocytes.

- **Carbohydrate metabolism:** Growth hormone is one of a battery of hormones that serves to maintain blood glucose within a normal range. Growth hormone is often said to have anti-insulin activity, because it suppresses the abilities of insulin to stimulate uptake of glucose in peripheral tissues and enhance glucose synthesis in the liver.

- **Mineral metabolism:** promotes a positive calcium, magnesium and phosphate balance and causes the retention of Na⁺, K⁺ and Cl⁻.

**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. In children and young adults, the most intense period of growth hormone release is shortly after the onset of deep sleep.
Disease States

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 known 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:

- **Gigantism** 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.
- **Acromegaly** results from excessive secretion of growth hormone in adults. The excessive growth hormone and IGF-1 also lead to metabolic derangements, including glucose intolerance.

Quick quiz: Which of the following does not influence GH production?
1. Diet
2. Stress
3. Sleep
4. exercise

2. **Thyroid Stimulating Hormone**

Thyroid-stimulating hormone, also known as thyrotropin, is secreted from cells in the anterior pituitary called **thyrotophs**, 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. 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.
TSH has several acute effects on thyroid function. These occur in minutes and involve increases of all phases of T₃ and T₄ biosynthesis. TSH also has several chronic effects on the thyroid. These require several days and include increases in the synthesis of proteins, phospholipids, and nucleic acids and in the size of number of thyroid cells.

The most important controller of TSH secretion is thyroid-releasing hormone. Secretion of thyroid-releasing hormone, and hence, TSH, is inhibited by high blood levels of thyroid hormones in a classical negative feedback loop.

Quick quiz: All statements regarding TSH are true except:
1. It is not involved in protein and phospholipids synthesis
2. It provides NADPH by stimulating HMP pathway
3. It increases proteolysis of TBG to release T₃ and T₄
4. It increases uptake of iodine

3. Adrenocorticotropic Hormone

Adrenocorticotropic hormone, stimulates the adrenal cortex by enhancing the conversion of cholesterol to pregnenolone. 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.

Within the pituitary gland, ACTH is produced in a process that also generates several other hormones. A large precursor protein named proopiomelanocortin (POMC) is synthesized and proteolytically chopped into several fragments as depicted below.
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.

**Quick quiz**: All the statements regarding ACTH are true except:

1. It is a tropic hormone with 39 amino acids
2. It decreases insulin release
3. It promotes growth of the adrenal cortex
4. It increases pigmentation of the skin
4. **Prolactin (PRL)**

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.

Prolactin contains 199 amino acids and has three intramolecular disulfide bridges. PRL has effects on the immune system and is important in the control of osmolality and various events including:

- a. Metabolism of subcutaneous fat
- b. Carbohydrate metabolism
- c. Calcium and Vit D metabolism
- d. Fetal lung development
- e. Steroidogenesis

PRL binds to its receptor on the cell membrane of its target organs (breast, adrenal, ovaries, testes, prostate, kidney and liver) but with unknown intracellular mechanism.

**Control of Prolactin Secretion**

In contrast to what is seen with all the other pituitary hormones, the hypothalamus suppresses prolactin secretion from the pituitary.

Dopamine serves as the major prolactin-inhibiting factor or brake on prolactin secretion. In addition to inhibition by dopamine, prolactin secretion is positively regulated by several hormones, including thyroid-releasing hormone, gonadotropin-releasing hormone and vasoactive intestinal polypeptide.

**Estrogens provide a well-studied positive control over prolactin synthesis and secretion.**

**Quick quiz:** Secondary causes of hyperprolactinemia are:

1. Hypoglycemia
2. Hypothyroidism
3. Pituitary tumors
4. All the above
5. 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. As described 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 for each hormone with the ability to bind its own receptor.

a. Luteinizing Hormone

In both sexes, LH stimulates secretion of sex steroids from the gonads. In the testes, it stimulates the synthesis and secretion of testosterone. The ovary respond to LH stimulation by secretion of testosterone, which is converted into estrogen by adjacent granulosa cells.

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.

b. Follicle-Stimulating Hormone

FSH stimulates the maturation of ovarian follicles. 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. 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. Numerous hormones influence GnRH secretion, and positive and negative control over GnRH and gonadotropin secretion is actually considerably more complex than described 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.

Quick quiz  The following hormones have structural homology except:

1. TSH
2. LH and FSH
3. PRL
4. HCG
Posterior Pituitary Hormones

1. Antidiuretic Hormone (Arginine Vasopressin)

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

Antidiuretic hormone, also known as vasopressin, is a nine amino acid peptide secreted from the posterior pituitary. The single most important effect of antidiuretic hormone is to conserve body water by reducing the output of urine.

Effects of Antidiuretic Hormone

1. stimulates contraction of the muscles of the capillaries and arterioles, raising blood pressure
2. promotes contraction of the intestinal musculature, increasing peristalsis
3. stimulates water reabsorption 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.

Control of Antidiuretic Hormone Secretion

1. The most important variable regulating antidiuretic hormone secretion is plasma osmolarity, or the concentration of solutes in blood. 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 and stimulate the neurons that secrete antidiuretic hormone. As seen the figure, antidiuretic hormone concentrations rise steeply and linearly with increasing plasma osmolarity.
2. 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.

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.

**Quick quiz**: Increased reabsorption of water from the kidney is the major consequence of which of the following hormones?

1. cortisol
2. insulin
3. vasopressin
4. glucagons

**Quick quiz** Syndrome of inappropriate secretion of ADH (SIADH) is caused by:

1. malignant disease of lung/prostate
2. chest disease like pneumonia and TB
3. brain tumors and meningitis
4. all the above
2. **Oxytocin**

Oxytocin is a nine amino acid peptide that is synthesized in hypothalamic neurons and transported down axons of the posterior pituitary for secretion into blood. Oxytocin 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.

**Control of Oxytocin Secretion**

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.

**Quick quiz**  true or false

Oxytocin stimulates synthesis of steroids in ovary

**Conclusion**

1. The pituitary gland, a roundish organ that lies immediately beneath the hypothalamus composed of two distinctive parts:
   
   a. The **anterior pituitary** (adenohypophysis).
   
   b. The **posterior pituitary** (neurohypophysis)

2. knowledge of hormone structure and the ability to synthesize specific hormones permits the diagnosis of the disease states
Testing Activity of the Anterior Pituitary

Releasing hormones and chemical analogs, particularly of the smaller peptides, are now routinely synthesized. The gonadotropin-releasing hormone, a decapeptide, is available for use in assessing the function of the anterior pituitary. This is of importance when a disease situation may involve either the hypothalamus, the anterior pituitary, or the end organ. Infertility is an example of such a situation. What needs to be assessed in which organ is at fault in the hormonal cascade. Initially, the end organ, in this case the gonads, must be considered. This can be accomplished by injecting the anterior pituitary hormone LH or FSH. If sex hormone secretion is elicited, then the ultimate gland would appear to be functioning properly. Next, the anterior pituitary would need to be analyzed. This can be done by i.v. administration of synthetic GnRH; by this route, GnRH can gain access to the gonadotropic cells of the anterior pituitary and elicit secretion of LH and FSH. Routinely, LH levels are measured in the blood as a function of time after the injection. These levels are measured by radioimmunoassay (RIA) in which radioactive LH or hCG is displaced from binding to an LH-binding protein by LH in the serum sample. The extent of the competition is proportional to the amount of LH in the serum. In this way a progress of response is measured that will be within normal limits or clearly deficient. If the response is deficient, the anterior pituitary cells are not functioning normally and are the cause of the syndrome. On the other hand, normal pituitary response to GnRH would indicate that the hypothalamus was non-functional. Such a finding would prompt examination of the hypothalamus for conditions leading to insufficient availability/production of releasing hormones. Obviously, the knowledge of hormone structure and the ability to synthesize specific hormones permits the diagnosis of these disease states.

Clinical correlation

**Hypopituitarism**

The hypothalamus is connected to the anterior pituitary by a delicate stalk that contains the portal system through which releasing hormones, secreted from the hypothalamus, gain access to the anterior pituitary cells. In the cell membranes of these cells are specific receptors for releasing hormones. In most cases, different cells express deferent releasing hormone receptors. The connection between the hypothalamus and anterior pituitary can be disrupted by trauma or tumors. Trauma can occur in automobile accidents or other local damaging events that may result in severing of the stalk, thus preventing the releasing hormones from reaching their target anterior pituitary cells. When this happens, the anterior pituitary cells no longer have their signaling mechanism for the release of anterior pituitary hormones. In the case of tumors of the pituitary gland, all of the anterior pituitary hormones may not be shut off to the same degree or the secretion of some may disappear sooner than others.

In any case, if the hypopituitarism occurs, this condition may result in a life-threatening situation in which the clinician must determine the extent of loss of pituitary hormones, especially ACTH. Posterior pituitary hormones (Oxytocin and vasopressin) may also be lost, precipitating a problem of excessive urination (vasopressin deficiency) that must be addressed. The usual therapy involves administration of the end-organ hormones, such as, thyroid hormone, cortisol, sex hormones, and progestin; with female patients it is also necessary to maintain the ovarian cycle. These hormones can be easily administered in the oral form. Growth hormone deficiency is not a problem in the adult but would be an important problem in a growing child. The patient must learn to anticipate needed increases of cortisol in the face of stressful situations. Fortunately, these patients are usually maintained in reasonably good condition.

Question: Hypopituitarism may result from trauma, such as an automobile accident severing the stalk connecting the hypothalamus and anterior pituitary, or from tumors of the pituitary gland. In trauma, usually all of the releasing hormones from hypothalamus fail to reach the anterior pituitary. With a tumor of the gland, some or all of the pituitary hormones may be shut off. Posterior pituitary hormones may also be lost. Hypopituitarism can be life threatening. Usual therapy is administration of end-organ hormones in oral form.

1) If the stalk between the hypothalamus and anterior pituitary is severed, the pituitary would fail to cause the ultimate release of all of the following hormones except:
   a) ACTH.
   b) estradiol.
   c) oxytocin.
   d) testosterone.
   e) thyroxine.

Answers:

1) C Oxytocin is released from posterior pituitary. A, B, D, and E all require releasing hormones from hypothalamus for anterior pituitary to release them.