

SECTION

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# 59

## Hypothalamic and Pituitary Gland Hormones

Priscilla S. Dannies



### DRUG LIST

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Desmopressin	682	Oxytocin	683
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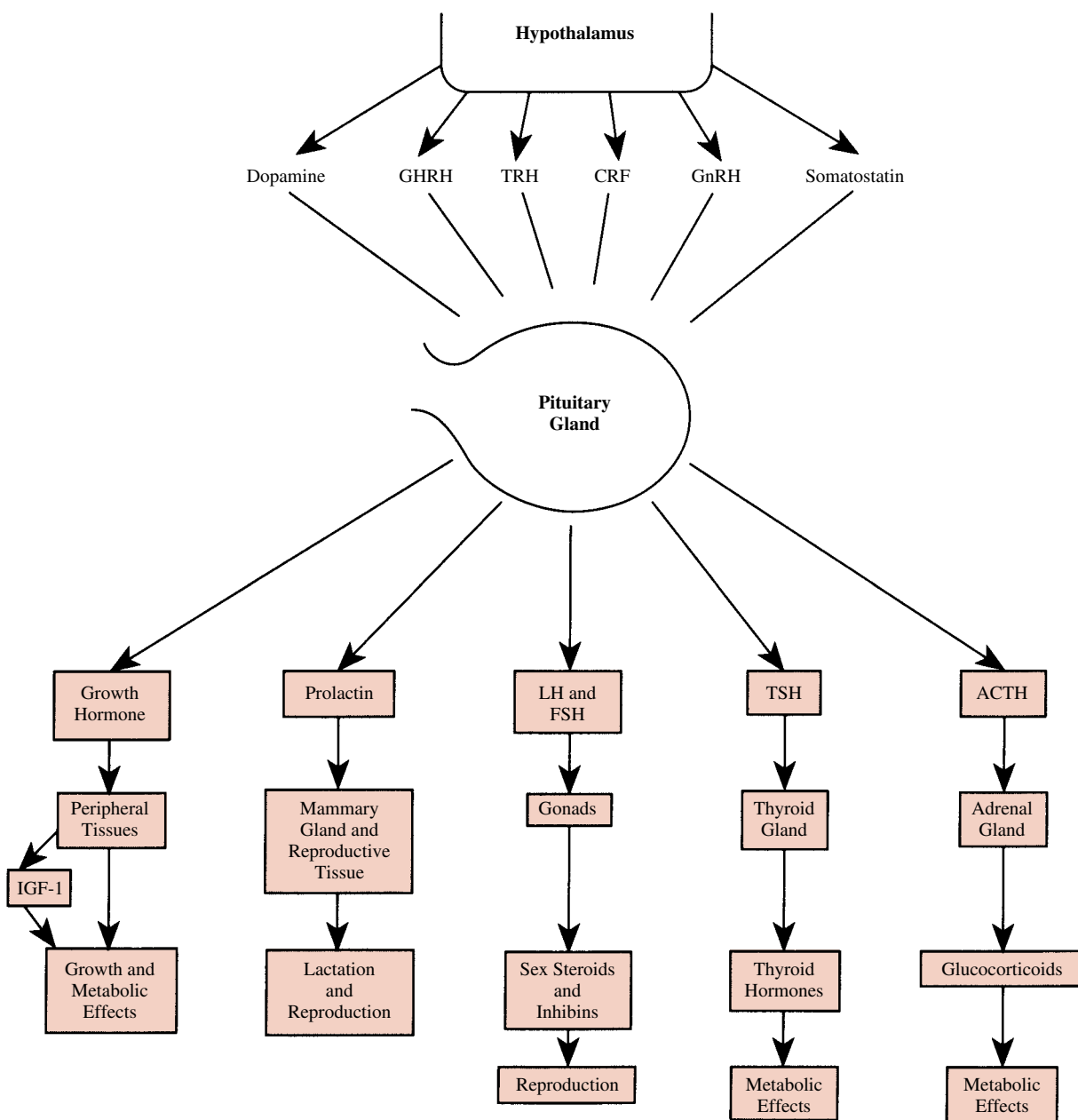
The hormones of the pituitary gland participate in the control of reproductive function, body growth, and cellular metabolism; deficiency or overproduction of these hormones disrupts this control. Clinical use of protein hormones in the past was limited because preparations had to come from glands or urine. The ability to prepare at least some of these hormones in large quantities by recombinant DNA techniques and the development of more stable analogues that can be injected in a depot form permit increased and more effective use of these hormones.

### ANTERIOR PITUITARY HORMONES

Six major hormones are secreted by the adenohypophysis, or anterior pituitary gland (Fig. 59.1). Cells in the anterior pituitary gland also secrete small amounts of a variety of other proteins, including renin, angiotensinogen, sulfated proteins, fibroblast growth factor, and other mitogenic factors. The physiological significance of these other secretory products is not known, but they may participate in autocrine regulation of the gland.

The secretion of anterior pituitary hormones is controlled in part by hypothalamic regulatory factors that are stored in the hypothalamus and are released into the adenohypophyseal portal vasculature. Hypothalamic regulatory factors so far identified are peptides with the exception of dopamine. Secretion of anterior pituitary hormones is also controlled by factors produced more distally that circulate in the blood. Predominant control of hormone production may be relatively simple, as with thyroid-stimulating hormone (TSH), the production of which is primarily stimulated by thyrotropin-releasing hormone (TRH) and inhibited by thyroid hormones, or it may be complex, as with prolactin, the production of which is affected by many neurotransmitters and hormones.

All anterior pituitary hormones are released into the bloodstream in a pulsatile manner; the secretion of many also varies with time of day or physiological conditions, such as exercise or sleep. At least part of the pulsatility of anterior hormone secretion is caused by pulsatile secretion of hypothalamic regulatory hormones. Understanding the rhythms that control hormone secretion has led to better uses of hormones in therapy.

**FIGURE 59.1**

Hormones of the hypothalamus and the anterior pituitary gland. Hormones released from the hypothalamus are one of the major means of controlling secretion from the anterior pituitary gland. GHRH, growth hormone releasing hormone; TRH, thyrotropin releasing hormone; CRF, corticotropin releasing hormone; GnRH, gonadotropin releasing hormone; LH, luteinizing hormone; FSH, follicle-stimulating hormone; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotrophic hormone; IGF-1, insulinlike growth factor 1.

### **Growth Hormone**

Growth hormone, or somatotropin, is a protein that stimulates linear body growth in children and regulates cellular metabolism in both adults and children. Growth hormone stimulates lipolysis, enhances production of free fatty acids, elevates blood glucose, and promotes

positive nitrogen balance. Many of its anabolic actions are mediated by enhanced production of an insulinlike growth factor (IGF-1), a protein produced in many tissues in response to growth hormone.

The episodic release of growth hormone is the most pronounced among the pituitary hormones. Serum levels between bursts of release are usually low (<5

ng/mL) and increase more than 10-fold when release is elevated. The marked variation in serum levels is in part the result of strong controls in opposite directions by the hypothalamic hormones, growth hormone–releasing hormone (GHRH), and somatostatin. Circulating factors, such as IGF-1 and ghrelin, a peptide produced in large amounts in neuroendocrine cells of the stomach, also affect growth hormone secretion. Growth hormone is released during sleep, with maximum release occurring an hour after the onset of sleep. Growth hormone is also released after exercise, by hypoglycemia, and in response to arginine and levodopa.

### Growth Hormone Deficiency

Growth hormone deficiency in children results in short stature and in adults increases fat mass and reduces muscle mass, energy, and bone density. Measurements of serum growth hormone levels are used for diagnosis of deficiency, but random measurements are not useful, because normal episodic release results in large variations in growth hormone levels. Growth hormone deficiency is most convincingly demonstrated by lack of response to provocative stimuli, such as administration of insulin, levodopa, or arginine. Recently a combination of GHRH and ghrelin have been used and have given large responses in normal subjects. Deficiencies are corrected by giving human growth hormone. Growth hormone is also sometimes given to individuals who are not growth hormone–deficient; it is used to increase the height of girls with Turner's syndrome and in certain conditions to counteract the wasting that may occur in AIDS.

In the past human growth hormone was prepared from human pituitary glands, but this source was discontinued after people who had received treatment contracted Creutzfeldt-Jakob disease. Now two forms of recombinant human growth hormone are available: somatropin (*Humatrope* and others), which has the same amino acid sequence as pituitary-derived growth hormone, and somatrem (*Protropin*), which has an *N*-terminal methionine that the pituitary form does not. Subcutaneous injections each evening, which mimic the natural surge that occurs at the start of sleep, are the usual regimen. Stimulation of growth in children is most effective when treatment begins early.

### Growth Hormone Excess

Acromegaly results from chronic secretion of excess growth hormone, usually as a result of pituitary adenoma. Long bones will not grow in adults because the epiphyses are closed, but bones of the extremities (hands, feet, jaw, and nose) will enlarge. The skin and soft tissues thicken, and the viscera enlarge. Excessive growth hormone secretion is demonstrated by elevated serum levels of growth hormone after glucose administration, since glucose is less effective in inhibiting

growth hormone secretion in acromegalics than it is in normal subjects. In addition, serum IGF-1 levels are elevated in acromegalics.

The primary treatment of acromegaly is surgery. Pharmacotherapy is used when surgical treatment is not successful. Two dopamine agonists (see Chapter 31), bromocriptine and cabergoline, are sometimes effective; they are taken orally. Although dopamine stimulates growth hormone release in normal individuals, it inhibits growth hormone release in up to 50% of acromegalics. The somatostatin analogue octreotide is usually more effective, and now that a long-acting form is available that requires only monthly injections, it is the preferred treatment. Another possible growth hormone antagonist, pegvisomant, is being investigated.

### Prolactin

Human prolactin is similar in structure to human growth hormone, and both are good lactogens. In women, prolactin acts with other hormones on the mammary gland during pregnancy to develop lactation and after birth to maintain it. Hyperprolactinemia causes impotence in men and amenorrhea and infertility in women. Chronically elevated levels of circulating prolactin are associated with suppression of 17- $\beta$ -estradiol and testosterone production in the ovaries and testes.

Prolactin serum levels increase during pregnancy and breast-feeding, at least immediately after the birth. In both men and women, prolactin increases after sleep starts, continues to increase during the night, and increases markedly during stress. Prolactin release is episodic during the day. More than 20 hormones and neurotransmitters affect prolactin production, but the dominant physiological control is primarily negative, mediated by dopamine from the hypothalamus. Dopaminergic agonists inhibit prolactin release and antagonists, such as the antipsychotic drugs, increase release.

There is no known therapeutic use for prolactin, but serum levels are measured to diagnose hyperprolactinemia. The normal range of serum prolactin is 1 to 20 ng/mL. Elevated prolactin levels ( $>100$  ng/mL) in the absence of stimulatory factors, such as antipsychotic drugs, are an indication of pituitary adenoma. Approximately one-third of women who need treatment for infertility have high serum prolactin levels. Galactorrhea, or inappropriate lactation, is sometimes associated with high prolactin levels. Hyperprolactinemia has been traditionally treated by the dopaminergic agonist bromocriptine (*Parodel*). The doses, usually 5 mg/day, are lower than those used to treat Parkinson's disease, and therefore, the side effects, nausea and postural hypotension, are less likely to cause problems. More recently, however, the more potent, long-lasting dopaminergic agonist cabergoline (*Dostinex*) has been found to be at least as effective and has a lower incidence of side effects.

### Thyroid-Stimulating Hormone

TSH, or thyrotropin, is a glycosylated protein of two subunits,  $\alpha$  and  $\beta$ . TSH stimulates the thyroid gland to produce thyroid hormones. Deficiencies are treated by giving thyroxine itself rather than TSH, but TSH is available for diagnostic purposes to differentiate between pituitary and thyroid gland failure as causes of hypothyroidism (see Chapter 65).

### Gonadotropins

Follicle-stimulating hormone (FSH), luteinizing hormone (LH), and human chorionic gonadotropin (hCG) are glycoproteins that are similar in structure to TSH. Glycosylation is not identical among the different hormones, and the type of glycosylation influences the half-life of the hormones. A sulfated *N*-acetylgalactosamine attached to LH but not FSH causes LH to be more rapidly metabolized; the half-life of LH is 30 minutes and that of FSH is 8 hours.

LH and FSH are pituitary hormones secreted in pulsatile fashion approximately every 2 hours. In women before menopause, this pattern is superimposed on much larger changes that occur during the normal menstrual cycle. FSH is released in substantial amounts during the follicular phase of the menstrual cycle and is required for proper development of ovarian follicles and for estrogen synthesis from granulosa cells of the ovary. Most LH secretion occurs in an abrupt burst just before ovulation. LH is required for progesterone synthesis in luteal cells and androgen synthesis in thecal cells of the ovary. FSH stimulates spermatogenesis and synthesis of androgen-binding protein in Sertoli cells of the testes. LH stimulates testosterone production from Leydig cells. Production of LH and FSH is controlled by gonadotropin-releasing hormone (GnRH) from the hypothalamus and by feedback control from target organs through steroids and multiple forms of a protein, inhibin.

Injections of these hormones are used to treat infertility in women and men. Traditional sources of gonadotropins are from human urine. Human menopausal gonadotropins (menotropins, *Humegon*, *Pergonal*) are isolated from urine of postmenopausal women and contain both FSH and LH. Purified preparations of FSH from the same source are also available (urofollitropin, *Fertinex*, *Fertinorm HP*). During early pregnancy, trophoblasts of the placenta produce hCG in large amounts. LH and hCG bind to the same gonadal receptors, but hCG is more stable and can be isolated from urine of pregnant women, so hCG preparations (*Pregnyl*, *Profasi*) are used to mimic the burst of LH secretion before ovulation. Recombinant preparations of FSH are also available (follitropin, *Gonal F*, *Follistim*).

Gonadotropins are used to treat infertility in women with potentially functional ovaries who have not responded to other treatments. The therapy is designed to simulate the normal menstrual cycle as far as is practical. A common protocol is daily injections of menotropins for 9 to 12 days, until estradiol levels are equal to that in a normal woman, followed by a single dose of hCG to induce ovulation. Two problems with this treatment are risks of ovarian hyperstimulation and of multiple births. Ovarian hyperstimulation is characterized by sudden ovarian enlargement associated with an increase in vascular permeability and rapid accumulation of fluid in peritoneal, pleural, and pericardial cavities. To prevent such occurrences, ovarian development is monitored during treatment by ultrasound techniques and by measurements of serum levels of estradiol.

Purified FSH is used to prepare follicles for in vitro fertilization because LH activity in menotropins may cause premature ovulation. Purified FSH is also used to treat infertility in women with polycystic ovarian disease; in this disease LH and androgen production may already be elevated.

Gonadotropins are used to induce spermatogenesis in hypogonadotropic hypogonadal men; a lengthy treatment is required to obtain mature sperm. For several weeks hCG is injected to increase testosterone levels, followed by injections of menotropins for several months. Prepubertal cryptorchidism can be treated by injections of hCG for up to several months.

### Adrenocorticotrophic Hormone

Adrenocorticotrophic hormone (ACTH), or corticotropin, a peptide of 39 amino acids, is first synthesized as a larger precursor from which ACTH is derived by proteolytic cleavage. ACTH stimulates production of glucocorticoids from the adrenal cortex (see Chapter 60). Release of ACTH depends on diurnal rhythms with serum levels highest in the early morning. Secretion of this peptide also increases under stress. It is easier and less expensive to treat patients having adrenocortical insufficiency with glucocorticoid replacement therapy than it is to use ACTH. Therefore, use of ACTH (*Acthar*) is restricted to diagnosis; a shorter 24-amino acid analogue (*Cosyntropin*) is also used. Intravenous administration of ACTH should result in peak plasma levels of glucocorticoids within 30 to 60 minutes if the adrenal gland is functional. Prolonged administration of ACTH in a repository form, however, may be necessary to stimulate steroid production, because ACTH has long-term trophic effects on adrenal cells in addition to the rapid stimulation of steroid production. If the cause of steroid deficiency is at the level of the pituitary gland, ACTH should eventually stimulate steroid production.

## HYPOTHALAMIC REGULATORY HORMONES

Five peptides isolated from the hypothalamus regulate release of one or more pituitary hormones. In addition, dopamine released from the hypothalamus inhibits prolactin production.

### Somatostatin

Somatostatin (or somatotropin release-inhibiting factor [SRIF]) occurs primarily as a 14-amino acid peptide, although a 28-amino acid form also exists. As with the other hypothalamic peptides, it is formed by proteolytic cleavage of a larger precursor. Somatostatin, originally isolated from the hypothalamus, is also in many other locations, including the cerebral cortex, brainstem, spinal cord, gut, urinary system, and skin. Somatostatin inhibits the secretion of many substances in addition to growth hormone (Table 59.1).

Somatostatin has a very brief half-life in serum and is not useful clinically. An 8-amino acid analogue with 2 D-amino acids substituted for the naturally occurring L-amino acids is more stable, and monthly injections of a depot form of this analogue (octreotide, *Sandostatin LAR*) have several uses. Long-acting octreotide is used to treat acromegaly, as described earlier. It is also used to counteract unpleasant effects caused by overproduction of secreted bioactive substances produced by neuroendocrine tumors, including hyperinsulinemia from insulinomas and secretions from carcinoid tumors that cause severe diarrhea. Octreotide may also control severe diarrhea associated with AIDS that has not responded to other treatments.

Transient side effects, gastrointestinal discomfort and decreased glucose tolerance, usually last only a few weeks after initiation of therapy. The most significant

side effect associated with prolonged use of octreotide is formation of gallstones resulting from reduced bile flow.

### Thyrotropin-Releasing Hormone

Thyrotropin-releasing hormone, or protirelin, consists of three amino acids. TRH (*Relefact TRH*) is used for tests to distinguish primary from secondary hypothyroidism (see Chapter 65).

### Gonadotropin-Releasing Hormone

GnRH (gonadorelin, luteinizing hormone-releasing hormone) is a decapeptide that stimulates production of LH and FSH. It is released in bursts from the hypothalamus at regular intervals, about every 2 hours, although in women the interval may lengthen in the luteal end of the menstrual cycle. The pituitary gland responds to these regular pulses by producing LH and FSH. The pattern of LH and FSH in cycling women, including the large burst of LH release before ovulation, can be stimulated by regular administration of GnRH pulses. The large burst of LH from the pituitary gland appears to be induced by feedback through estradiol and other products of the gonads that change the response of the pituitary gland to the GnRH pulses rather than by large changes in the amounts of GnRH secreted. The stimulatory response to GnRH depends on pulsatile administration and the timing of the pulses. Continual administration of GnRH does not have the same effects as pulsatile administration; although production of LH and FSH is stimulated initially, it is suppressed within a few days. Part of this desensitization to GnRH is caused by a decrease in the number of pituitary receptors for GnRH; additional postreceptor mechanisms are also important in this complete suppression.

GnRH itself has a short half-life, 7 minutes, if given intravenously. Structural variations of the decapeptide have resulted in more stable analogues with higher affinity for the GnRH receptor; a common modification is to substitute a D-amino acid for the sixth amino acid, glycine, in GnRH.

### Gonadotropin Stimulation

When stimulation of gonadotropin production is needed, the pituitary gland is usually capable of responding to appropriately administered GnRH, even in cases of hypogonadotropic hypogonadism, when LH and FSH levels are always low. Therefore, GnRH therapy can be substituted for gonadotropin therapy by administering GnRH (*Lutrepulse*) pulses intravenously via an indwelling pump. GnRH itself is used, since the short half-life is important to prevent accumulation between pulses. The advantage of this procedure compared with intramuscular injections of gonadotropins

**TABLE 59.1** Effects of Somatostatin

Inhibition of secretion of
Growth hormone
Thyroid-stimulating hormone
Prolactin
ACTH
Insulin
Glucagon
Pancreatic polypeptide
Gastrin
Cholecystokinin
Secretin
Vasoactive intestinal peptide
Exocrine pancreas secretion
Inhibition of bile flow
Inhibition of mesenteric blood flow
Decreased gastrointestinal motility

for treating infertility is that normal levels of LH and FSH should be maintained because of feedback from the gonads. This should reduce the risk of ovarian hyperstimulation and multiple births, since the procedure should not result in inappropriately high levels of gonadotropins (Table 59.2).

### Gonadotropin Suppression

Stable potent derivatives of GnRH include leuprolide (*Lupron*) and goserelin (*Zoladex*). Because these agonists are long acting, they suppress gonadotropin production after an initial stimulation. In some uses, the initial stimulation of gonadotropin is undesirable; a newer GnRH antagonist, ganirelix (*Antagon*) inhibits gonadotropin production without the stimulation and may ultimately replace the long-acting agonists. These compounds are formulated so they can be injected monthly or even less frequently.

In men, androgens stimulate growth of prostatic cancer; therefore, a reduction in androgen actions is used for palliative treatment (see Chapter 63). Estrogen use increases mortality in men primarily as a result of cardiovascular complications, and castration is not popular. Therefore, treatment with GnRH analogues to suppress gonadotropin release is favored. When long-acting agonists are given, signs and symptoms of prostatic cancer may increase shortly after initiation of therapy because of the initial stimulation of the pituitary gland. These analogues are also used to suppress puberty in young children with central precocious puberty.

In women, GnRH agonists are sometimes given along with FSH when stimulating follicles in fertility treatments; this addition prevents premature ovulation caused by the release of pituitary LH. Uterine leiomyomas and endometriosis regress when gonadotropin secretion is decreased. GnRH analogues relieve these conditions, but the relief usually lasts only as long as the analogue is administered, and the condition generally returns within a few months after therapy ceases. The main side effects are a result of estradiol deprivation

and include hot flashes (sudden intense surface temperature elevation and sweating), dry skin and vagina; long-term use may decrease bone density. The addition of estrogen and progesterone can reduce the adverse effects while maintaining gonadotropin suppression. However, there is a continuing need to address the recent cancer risk cautions issued for short-term versus long-term use of estrogen–progesterone combinations as hormonal replacement therapy.

### Corticotropin-Releasing Hormone

Corticotropin-releasing hormone consists of 41 amino acids; it stimulates ACTH release. It is used for investigational purposes.

## HORMONES OF THE POSTERIOR PITUITARY GLAND

Antidiuretic hormone (ADH) and oxytocin are synthesized in the supraoptic and paraventricular nuclei in the brain and are transported in secretory granules through axons to the posterior lobe. These hormones are cyclic peptides of eight amino acids. Each is synthesized as a larger precursor, which is processed into the hormone plus a protein that binds the hormone, called neurophysin. ADH and oxytocin have different amino acids at positions 3 and 8.

### Antidiuretic Hormone

ADH (vasopressin) is released primarily in response to increases in plasma osmolarity or decreases in blood volume. It produces its antidiuretic activity in the kidney, causing the cortical and medullary parts of the collecting duct to become more permeable to water, thereby increasing water reabsorption, reducing serum osmolarity, and increasing its volume. It produces this effect by binding to a subset of vasopressin receptors (Table 59.3) called  $V_2$  that have relatively high affinity for the hormone. ADH also has actions at sites other than the kidney.  $V_2$  receptors also mediate an increase in circulating levels of two proteins involved in blood coagulation: factor VIII and von Willebrand's factor. At higher concentrations, ADH interacts with  $V_1$  receptors to cause a general constriction of most blood vessels. It also interacts with  $V_3$  (or  $V_{1b}$ ) receptors to increase ACTH release, although the major control of ACTH release occurs through corticotropin-releasing hormone.

ADH itself is available for injections (*Pitressin*) but has a half-life of about 15 minutes. Desmopressin (*DDAVP*) is an analogue without an amino group at the first amino acid and with D-arginine instead of L-arginine. This analogue is more stable and has very little pressor activity. Desmopressin can be given subcutaneously or nasally, and the effects last for 12 hours.

**TABLE 59.2 Biological Actions of GnRH Agonists and Antagonists**

Drug	Dose and regimen	Effect
Agonist	Low, pulsatile	Pituitary and gonadal stimulation
Agonist	High, constant	Initial pituitary and gonadal stimulation followed by suppression within 2 weeks
Antagonist	Constant	Pituitary and gonadal suppression



**TABLE 59.3** Actions of ADH

Receptor type	Response
V <sub>1</sub>	Pressor
V <sub>2</sub>	Antidiuretic Hemostatic
V <sub>3</sub>	ACTH release

Because it is stable, desmopressin is preferred for treatments especially if pressor effects are not desired. The primary indication for therapy is central diabetes insipidus, a disorder that results when ADH secretion is reduced and that is characterized by polydipsia, polyuria, and dehydration. Desmopressin is also used to reduce primary nocturnal enuresis, or bedwetting, in children. It is useful in people with mild hemophilia A or with some types of von Willebrand's disease, in which von Willebrand's factor is present at low levels. In these cases, desmopressin is given when excessive bleeding occurs or before surgery to help reduce bleeding indirectly by increasing the amounts of coagulation factors.

A possible adverse effect of desmopressin is water intoxication if too much is taken.

ADH antagonists, including nonpeptide analogues that may be taken orally, have been developed with specificity for each of the receptor types. In the future, those that block V<sub>1</sub> receptors may be useful in treating hypertension, and those that block V<sub>2</sub> receptors may be useful in any condition of excessive water retention or hyponatremia, for which so far there is no satisfactory therapeutic treatment.

### Oxytocin

Oxytocin (*Pitocin*, *Syntocinon*) causes milk release (let-down) by stimulating contraction of the myoepithelial cells of the milk ducts in lactating mammary glands; this forces milk from the alveoli of the breast. Oxytocin release is stimulated by suckling and by auditory and visual stimuli, such as a baby's cry. Oxytocin is available as a nasal spray, which is used as an aid to lactation when milk ejection is impaired.

Oxytocin also stimulates contraction of uterine smooth muscle in late phases of pregnancy. See Chapter 62 for a full discussion of the use of oxytocin in labor and delivery.

### Study QUESTIONS

- A patient with severe diarrhea as a result of a carcinoid tumor is a candidate for which of the following treatments?
  - Pulsatile administration of GnRH
  - Nasal administration of desmopressin
  - Depot injections of octreotide
  - Oral administration of bromocriptine
- The actions of ADH include all of the following EXCEPT
  - Stimulation of ACTH release
  - Stimulation of bile secretion
  - Constriction of most blood vessels
  - Stimulation of coagulation factor VIII production
  - Production of concentrated urine
- A patient with endometriosis who is being treated with leuprolide has hot flashes and dry skin and vagina. What additional treatment would relieve these unpleasant effects?
  - Estrogen and progesterone
  - Ganirelix
  - Testosterone
  - Bromocriptine
- A 30-year-old woman has secondary amenorrhea and serum prolactin levels of 75 ng/mL. She has visited a fertility clinic to attempt to become pregnant. What treatment should be given?
  - Clomiphene
  - Ganirelix
  - Cabergoline
  - Estradiol
- Growth hormone deficiency in children must be determined by measuring hormone levels after giving an agent that stimulates release because
  - Normal growth hormone secretion in children is too low to be measured by current assays
  - Growth hormone secretion occurs only during sleep
  - Growth hormone secretion is episodic
  - A different form of growth hormone is secreted after stimulation

### ANSWERS

- C.** Carcinoid tumors arise from neuroendocrine cells of the gut and secrete serotonin and gastrointestinal hormones, which activate the gastrointestinal tract and result in diarrhea. Most of these tumors have receptors for somatostatin, which inhibit secretion when activated, resulting in reduced activity of the gut. Octreotide is a stable analogue of

somatostatin that is effective in treating carcinoid-induced diarrhea and that may slow tumor growth. The long-acting form requires only monthly injections to maintain effective levels. GnRH, desmopressin, and bromocriptine will not inhibit secretion from these neuroendocrine tumors.

2. **B.** ADH has many actions through three receptors but does not affect bile secretion. It stimulates ACTH release, although the predominant control occurs through corticotropin-releasing hormone. It has pressor activity by causing smooth muscles cells of most blood vessels to constrict. It stimulates production of coagulation factor VIII and von Willebrand's factor, and it increases the permeability of the collecting duct in the kidney to water, resulting in urine that has high osmolarity and low volume.
3. **A.** Endometriosis is growth of the endometrium beyond the uterine cavity. Leuprolide is a GnRH analogue that suppresses LH and FSH when present continuously, resulting in endometrial atrophy and low estrogen levels, causing hot flashes and skin dryness; long-term use may also reduce bone density. Low-dose estrogen and progesterone replacement therapy relieves the side effects caused by reduced estrogen levels, usually without stimulating endometrial growth. However, the recent warning of relative cancer risk of estrogen-progesterone combinations as short-term versus long-term hormonal replacement therapy must be carefully considered. Ganirelix, testosterone, and bromocriptine would not relieve the side effects.
4. **C.** High prolactin levels may cause amenorrhea and infertility through mechanisms not understood. Prolactin levels in normal women are less than 20 ng/mL. The primary control of prolactin is through inhibition of secretion by dopamine from the hypothalamus. Cabergoline is a stable dopamine agonist that reduces prolactin secretion. Clomiphene, an estrogen antagonist, is used to stimulate LH and FSH release to enhance fertility but should not be used until it has been determined whether reducing pro-

lactin levels alone is sufficient to cause fertility. Ganirelix and estradiol are not useful in treating infertility.

5. **C.** Growth hormone secretion is episodic, and a single measurement without stimulation may give a false impression of growth hormone levels that are too low (<5 ng/mL). Growth hormone release occurs not only immediately after sleep but also after eating and after exercise. A 20-kilodalton form of growth hormone is secreted with the normal 22-kilodalton form, but the former is present in about one-fifth the amount. Both forms have biological activity and are secreted basally and after stimulation of growth hormone release.

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**CASE Study** Changes in Body Size

A 53-year-old man visits his physician because he is bothered by headaches, which are becoming more intense and more frequent, so that he has one most of the time. The physician notices that the man's hands, feet, nose, and jaw are large and his voice is hoarse. The physician learns by questioning that the man has needed to purchase a larger wedding ring and larger shoes several times in the past 7 years. In a photograph of the man taken 10 years earlier, the nose and jaws are not large. The physician suspects acromegaly and finds after tests that the patient's serum growth hormone levels are elevated after oral glucose administration. A pituitary macroadenoma 1.1 cm in diameter is detected by magnetic resonance imaging. If surgery does not result in normal growth hormone levels, what treatment should be used?

**ANSWER:** Excessive growth hormone secretion in adults causes acromegaly, which is slow in onset but eventually results in growth of soft tissue and bones of the hands, feet, and parts of the face. Growth of nasopharyngeal soft tissue may result in hoarseness. Growth hormone is secreted episodically, so normal people may have briefly elevated levels of serum growth hormone through the day. In normal subjects but not acromegalics, oral glucose suppresses these spikes of growth hormone secretion. Surgical removal of the macroadenoma should help the headaches, but it returns serum growth hormone levels to normal only in 50% of cases. In patients whose levels are still elevated, treatment with long-acting somatostatin analogues, which inhibit growth hormone secretion, are the treatment of choice. Octreotide is available in a long-acting form that may be given biweekly to monthly. The dopamine agonists bromocriptine and cabergoline work in some acromegalic patients but are in general less effective than the somatostatin analogue.