**LECTURE 6: ENDOCRINE DRUGS**

**GROWTH HORMONE (SOMATOTROPIN)**

Growth hormone, an anterior pituitary hormone, is required during childhood and adolescence for attainment of normal adult size and has important effects throughout postnatal life on lipid and carbohydrate metabolism, and on lean body mass and bone density. Its growth-promoting effects are primarily mediated via IGF-I (also known as somatomedin C). Individuals with congenital or acquired deficiency of GH during childhood or adolescence fail to reach their midparental target adult height and have disproportionately increased body fat and decreased muscle mass. Adults with GH deficiency also have disproportionately low lean body mass.

**Pharmacodynamics**

Growth hormone mediates its effects via cell surface receptors of the JAK/STAT cytokine receptor superfamily. The hormone has two distinct GH receptor binding sites. Dimerization of two GH receptors is stimulated by a single GH molecule and activates signaling cascades mediated by receptor-associated JAK tyrosine kinases and STATs (see Chapter 2). The hormone has complex effects on growth, body composition, and carbohydrate, protein, and lipid metabolism. The growth-promoting effects are mediated principally, but not solely, through an increase in the production of IGF-I. Much of the circulating IGF-I is produced by the liver. Growth hormone also stimulates production of IGF-I in bone, cartilage, muscle, kidney, and other tissues, where it has autocrine or paracrine roles. It stimulates longitudinal bone growth until the epiphyseal plates fuse—near the end of puberty. In both children and adults, GH has anabolic effects in muscle and catabolic effects in adipose cells that shift the balance of body mass to an increase in muscle mass and a reduction in adiposity. The direct and indirect effects of GH on carbohydrate metabolism are mixed, in part because GH and IGF-I have opposite effects on insulin sensitivity. Growth hormone reduces insulin sensitivity, which results in mild hyperinsulinemia and increased blood glucose levels, whereas IGF-I has insulin-like effects on glucose transport. In patients who are unable to respond to growth hormone because of severe resistance (caused by GH receptor mutations, post-receptor signaling mutations, or GH antibodies), the administration of recombinant human IGF-I may cause hypoglycemia because of its insulin-like effects.

**GROWTH HORMONE ANTAGONISTS**

Antagonists of GH are used to reverse the effects of GHproducing cells (somatotrophs) in the anterior pituitary that tend to form GH-secreting tumors. Hormone-secreting pituitary adenomas occur most commonly in adults. In adults, GH-secreting adenomas cause acromegaly, which is characterized by abnormal growth of cartilage and bone tissue, and many organs including skin, muscle, heart, liver, and the gastrointestinal tract. When a GH-secreting adenoma occurs before the long bone epiphyses close, it leads to a rare condition, gigantism. Larger pituitary adenomas produce greater amounts of GH and also can impair visual and central nervous system function by encroaching on nearby brain structures. The initial therapy of choice for GH-secreting adenomas is endoscopic transsphenoidal surgery. Medical therapy with GH antagonists is introduced if GH hypersecretion persists after surgery. These agents include somatostatin analogs and dopamine receptor agonists, which reduce the production of GH, and the novel GH receptor antagonist pegvisomant, which prevents GH from activating GH signaling pathways. Radiation therapy is reserved for patients with inadequate response to surgical and medical therapies.

**Somatostatin Analogs**

Somatostatin, a 14-amino-acid peptide (Figure 37–2), is found in the hypothalamus, other parts of the central nervous system, the pancreas, and other sites in the gastrointestinal tract. It functions primarily as an inhibitory paracrine factor and inhibits the release of GH, TSH, glucagon, insulin, and gastrin. Somatostatin is rapidly cleared from the circulation, with a half-life of 1–3 minutes.

The kidney appears to play an important role in its metabolism and excretion. Somatostatin has limited therapeutic usefulness because of its short duration of action and multiple effects in many secretory systems. A series of longer-acting somatostatin analogs that retain biologic activity have been developed. Octreotide, the most widely used somatostatin analog, is 45 times more potent than somatostatin in inhibiting GH release but only twice as potent in reducing insulin secretion. Because of this relatively reduced effect on pancreatic beta cells, hyperglycemia rarely occurs during treatment. The plasma elimination half-life of octreotide is about 80 minutes, 30 times longer than that of somatostatin. Octreotide, 50–200 mcg given subcutaneously every 8 hours, reduces symptoms caused by a variety of hormone-secreting tumors: acromegaly, carcinoid syndrome, gastrinoma, glucagonoma, insulinoma, VIPoma, and ACTH-secreting tumor. Other therapeutic use indications include diarrhea—secretory, HIV associated, diabetic, chemotherapy, or radiation induced—and portal hypertension. Somatostatin receptor scintigraphy, using radiolabeled octreotide, is useful in localizing neuroendocrine tumors having somatostatin receptors and helps predict the response to octreotide therapy. Octreotide is also useful for the acute control of bleeding from esophageal varices. Octreotide acetate injectable long-acting suspension is a slowrelease microsphere formulation. It may be instituted after a brief course of shorter-acting octreotide has been demonstrated to be effective and tolerated. Injections into alternate gluteal muscles are repeated at 4-week intervals in doses of 10–40 mg. Adverse effects of octreotide therapy include nausea, vomiting, abdominal cramps, flatulence, and steatorrhea with bulky bowel movements. Biliary sludge and gallstones may occur after 6 months of use in 20–30% of patients. However, the yearly incidence of symptomatic gallstones is about 1%. Cardiac effects include sinus bradycardia (25%) and conduction disturbances (10%). Pain at the site of injection is common, especially with the long-acting octreotide suspension. Vitamin B12 deficiency may occur with long-term use of octreotide. A long-acting formulation of lanreotide, another octapeptide somatostatin analog, is approved for treatment of acromegaly. Lanreotide appears to have effects comparable to those of octreotide in reducing GH levels and normalizing IGF-I concentrations.

**THE GONADOTROPINS (FOLLICLE-STIMULATING HORMONE & LUTEINIZING HORMONE)**

The gonadotropins are produced by gonadotroph cells, which comprise 7–15% of the cells in the pituitary. These hormones serve complementary functions in the reproductive process. In women, the principal function of FSH is to stimulate ovarian follicle development. Both FSH and LH are needed for ovarian steroidogenesis. In the ovary, LH stimulates androgen production by theca cells in the follicular stage of the menstrual cycle, whereas FSH stimulates the conversion of androgens to estrogens by granulosa cells. In the luteal phase of the menstrual cycle, estrogen and progesterone production is primarily under the control first of LH and then, if pregnancy occurs, under the control of human chorionic gonadotropin (hCG). Human chorionic gonadotropin is a placental glycoprotein nearly identical with LH; its actions are mediated through LH receptors. In men, FSH is the primary regulator of spermatogenesis, whereas LH is the main stimulus for testosterone synthesis in Leydig cells. FSH helps maintain high local androgen concentrations in the vicinity of developing sperm by stimulating the production of androgen-binding protein in Sertoli cells. FSH also stimulates the conversion by Sertoli cells of testosterone to estrogen that is also required for spermatogenesis. FSH, LH, and hCG are available in several pharmaceutical forms. They are used in states of infertility to stimulate spermatogenesis in men and to induce follicle development and ovulation in women. Their most common clinical use is for the controlled ovarian stimulation that is the cornerstone of assisted reproductive technologies such as in vitro fertilization.

**Pharmacodynamics**

The gonadotropins and hCG exert their effects through G protein-coupled receptors. LH and FSH have complex effects on reproductive tissues in both sexes. In women, these effects change over the time course of a menstrual cycle as a result of a complex interplay among concentration-dependent effects of the gonadotropins, cross-talk of LH, FSH, and gonadal steroids, and the influence of other ovarian hormones. A coordinated pattern of FSH and LH secretion during the menstrual cycle is required for normal follicle development, ovulation, and pregnancy. During the first 8 weeks of pregnancy, the progesterone and estrogen required to maintain pregnancy are produced by the ovarian corpus luteum. For the first few days after ovulation, the corpus luteum is maintained by maternal LH. However, as maternal LH concentration falls owing to increasing concentrations of progesterone and estrogen, the corpus luteum will continue to function only if the role of maternal LH is taken over by hCG produced by syncytiotrophoblast cells in the placenta.

**PROLACTIN**

Prolactin is a 198-amino-acid peptide hormone produced in the anterior pituitary. Its structure resembles that of GH. Prolactin is the principal hormone responsible for lactation. Milk production is stimulated by prolactin when appropriate circulating levels of estrogens, progestins, corticosteroids, and insulin are present. A deficiency of prolactin—which can occur in rare states of pituitary deficiency—is manifested by failure to lactate. No preparation of prolactin is available for use in prolactin-deficient patients. In pituitary stalk section from surgery or head trauma, stalk compression due to a sellar mass, or rare cases of hypothalamic destruction, prolactin levels may be elevated as a result of impaired transport of dopamine (prolactin-inhibiting hormone) to the pituitary. Much more commonly, prolactin is elevated as a result of prolactin-secreting adenomas. In addition, a number of drugs elevate prolactin levels. These include antipsychotic and gastrointestinal motility drugs that are known dopamine receptor antagonists, estrogens, and opiates. Hyperprolactinemia causes hypogonadism, which manifests with infertility, oligomenorrhea or amenorrhea, and galactorrhea in premenopausal women, and with loss of libido, erectile dysfunction, and infertility in men. In the case of large tumors (macroadenomas), it can be associated with symptoms of a pituitary mass, including visual changes due to compression of the optic nerves. The hypogonadism and infertility associated with hyperprolactinemia result from inhibition of GnRH release. For patients with symptomatic hyperprolactinemia, inhibition of prolactin secretion can be achieved with dopamine agonists, which act in the pituitary to inhibit prolactin release.

**OXYTOCIN**

Oxytocin is a peptide hormone secreted by the posterior pituitary. Oxytocin stimulates muscular contractions in the uterus and myoepithelial contractions in the breast. Thus, it is involved in parturition and the letdown of milk. During the second half of pregnancy, uterine smooth muscle shows an increase in the expression of oxytocin receptors and becomes increasingly sensitive to the stimulant action of endogenous oxytocin.

**Pharmacodynamics**

Oxytocin acts through G protein–coupled receptors and the phosphoinositide-calcium second-messenger system to contract uterine smooth muscle. Oxytocin also stimulates the release of prostaglandins and leukotrienes that augment uterine contraction. In small doses oxytocin increases both the frequency and the force of uterine contractions. At higher doses, it produces sustained contraction. Oxytocin also causes contraction of myoepithelial cells surrounding mammary alveoli, which leads to milk letdown. Without oxytocin-induced contraction, normal lactation cannot occur. At high concentrations, oxytocin has weak antidiuretic and pressor activity due to activation of vasopressin receptors.

**VASOPRESSIN (ANTIDIURETIC HORMONE, ADH)**

Vasopressin is a peptide hormone released by the posterior pituitary in response to rising plasma tonicity or falling blood pressure. It possesses antidiuretic and vasopressor properties. A deficiency of this hormone results in diabetes insipidus.

**Pharmacodynamics**

Vasopressin activates two subtypes of G protein–coupled receptors. V1 receptors are found on vascular smooth muscle cells and mediate vasoconstriction via the coupling protein Gq and phospholipase C. V2 receptors are found on renal tubule cells and reduce diuresis through increased water permeability and water resorption in the collecting tubules via Gs and adenylyl cyclase. Extrarenal V2-like receptors regulate the release of coagulation factor VIII and von Willebrand factor, which increases platelet aggregation.

**THYROID PHYSIOLOGY**

The normal thyroid gland secretes sufficient amounts of the thyroid hormones—triiodothyronine (T3) and tetraiodothyronine (T4, thyroxine)—to normalize growth and development, body temperature, and energy levels. These hormones contain 59% and 65% (respectively) of iodine as an essential part of the molecule. Calcitonin, the second type of thyroid hormone, is important in the regulation of calcium metabolism.

**Thyroid Preparations**

These preparations may be synthetic (levothyroxine, liothyronine, liotrix) or of animal origin (desiccated thyroid). Thyroid hormones are not effective and can be detrimental in the management of obesity, abnormal vaginal bleeding, or depression if thyroid hormone levels are normal. Recent meta-analysis of T3 co-administered with antidepressants showed some depression benefits, but the results were inconclusive and further confirmation for its optimal use is required. Synthetic levothyroxine is the preparation of choice for thyroid replacement and suppression therapy because of its stability, content uniformity, low cost, lack of allergenic foreign protein, easy laboratory measurement of serum levels, and long half-life (7 days), which permits once-daily to weekly administration. In addition, T4 is converted to T3 intracellularly; thus, administration of T4 produces both hormones and T3 administration is unnecessary. Generic levothyroxine preparations provide comparable efficacy and are more cost-effective than branded preparations, It is preferable that patients remain on a consistent levothyroxine preparation between refills to avoid changes in bioavailability. A branded soft gel capsule (Tirosint) had faster, more complete dissolution and was less affected by gastric pH or coffee than a tablet formulation. Although liothyronine (T3) is three to four times more potent than levothyroxine, it is not recommended for routine replacement therapy because of its shorter half-life (24 hours), requiring multiple daily doses, and difficulty in monitoring its adequacy of replacement by conventional laboratory tests. T3 should also be avoided in patients with cardiac disease due to significant elevations in peak levels and a greater risk of cardiotoxicity. Using the more expensive thyroxine and liothyronine fixed-dose combination (liotrix) and desiccated thyroid has not been shown to be more effective than T4 administration alone. T3 is best reserved for short-term TSH suppression. Research is ongoing to clarify whether T3 might be more appropriate in patients with a polymorphism in the D2 gene or in those who continue to report fatigue, weight gain, and mental impairment while on T4 alone. The use of desiccated thyroid rather than synthetic preparations is never justified, since the disadvantages of protein antigenicity, product instability, variable hormone concentrations, and difficulty in laboratory monitoring far outweigh the advantage of lower cost. Significant amounts of T3 found in some thyroid extracts may produce significant elevations in T3 levels and toxicity. Exact equi-effective doses have not been determined. Approximate equivalence of desiccated thyroid 60 mg (1 gr) to 80 to 100 mcg of levothyroxine, and approximately 37.5 mcg of liothyronine has been reported. Any dosage conversions should be re-titrated based on laboratory and clinical response. The shelf life of synthetic hormone preparations is about 2 years, particularly if they are stored in dark bottles to minimize spontaneous deiodination. The shelf life of desiccated thyroid is not known with certainty, but its potency is better preserved if it is kept dry.

**ANTITHYROID THIOAMIDES**

The thioamides methimazole and propylthiouracil are major drugs for treatment of thyrotoxicosis. In the United Kingdom, carbimazole, which is converted to methimazole in vivo, is widely used. Methimazole is about ten times more potent than propylthiouracil and is the drug of choice in adults and children. Due to a black box warning about severe hepatitis, propylthiouracil should be reserved for use during the first trimester of pregnancy, in thyroid storm, and in those experiencing adverse reactions to methimazole (other than agranulocytosis or hepatitis). The chemical structures of these compounds are shown in Figure 38–5. The thiocarbamide group is essential for antithyroid activity.

**Pharmacodynamics**

The thioamides act by multiple mechanisms. The major action is to prevent hormone synthesis by inhibiting the thyroid peroxidase-catalyzed reactions and blocking iodine organification. In addition, they block coupling of the iodotyrosines. They do not block uptake of iodide by the gland. Propylthiouracil but not methimazole also inhibits the peripheral deiodination of T4 and T3 (Figure 38–1). Since the synthesis rather than the release of hormones is affected, the onset of these agents is slow, often requiring 3–4 weeks before stores of T4 are depleted.

**IODIDES**

Disadvantages of iodide therapy include an increase in intraglandular stores of iodine, which may delay onset of thioamide therapy or prevent use of radioactive iodine therapy for several weeks. Thus, iodides should be initiated after onset of thioamide therapy and avoided if treatment with radioactive iodine seems likely. Iodide should not be used alone, because the gland will escape from the iodide block in 2–8 weeks, and its withdrawal may produce severe exacerbation of thyrotoxicosis in an iodine-enriched gland. Chronic use of iodides in pregnancy should be avoided, since they cross the placenta and can cause fetal goiter. In radiation emergencies involving release of radioactive iodine isotopes, the thyroid-blocking effects of potassium iodide can protect the gland from subsequent damage if administered before radiation exposure.

**SYNTHETIC CORTICOSTEROIDS**

Glucocorticoids have become important agents for use in the treatment of many inflammatory, immunologic, hematologic, and other disorders. This has stimulated the development of many synthetic steroids with anti-inflammatory and immunosuppressive activity.

**Pharmacodynamics**

The actions of the synthetic steroids are similar to those of cortisol (see above). They bind to the specific intracellular receptor proteins and produce the same effects but have different ratios of glucocorticoid to mineralocorticoid potency.

CLINICAL PHARMACOLOGY

A. Diagnosis and Treatment of Disturbed Adrenal Function

1. Adrenocortical insufficiency

**a. Chronic (Addison’s disease)**—Chronic adrenocortical insufficiency is characterized by weakness, fatigue, weight loss, hypotension, hyperpigmentation, and inability to maintain the blood glucose level during fasting. In such individuals, minor noxious, traumatic, or infectious stimuli may produce acute adrenal insufficiency with circulatory shock and even death. In primary adrenal insufficiency, about 20–30 mg of hydrocortisone must be given daily, with increased amounts during periods of stress. Although hydrocortisone has some mineralocorticoid activity, this must be supplemented by an appropriate amount of a salt-retaining hormone such as fludrocortisone. Synthetic glucocorticoids that are long-acting and devoid of salt-retaining activity should not be administered to these patients.

**b. Acute**—When acute adrenocortical insufficiency is suspected, treatment must be instituted immediately. Therapy consists of large amounts of parenteral hydrocortisone in addition to correction of fluid and electrolyte abnormalities and treatment of precipitating factors. Hydrocortisone sodium succinate or phosphate in doses of 100 mg intravenously is given every 8 hours until the patient is stable. The dose is then gradually reduced, achieving maintenance dosage within 5 days. The administration of salt-retaining hormone is resumed when the total hydrocortisone dosage has been reduced to 50 mg/d.

**2. Adrenocortical hypo- and hyperfunction**

**a. Congenital adrenal hyperplasia**—This group of disorders is characterized by specific defects in the synthesis of cortisol. In pregnancies at high risk for congenital adrenal hyperplasia, fetuses can be protected from genital abnormalities by administration of dexamethasone to the mother. The most common defect is a decrease in or lack of P450c21 (21α-hydroxylase) activity.\* As can be seen in Figure 39–1, this would lead to a reduction in cortisol synthesis and thus produce a compensatory increase in ACTH release. The adrenal becomes hyperplastic and produces abnormally large amounts of precursors such as 17-hydroxyprogesterone that can be diverted to the androgen pathway, which leads to virilization and can result in ambiguous genitalia in the female fetus. Metabolism of this compound in the liver leads to pregnanetriol, which is characteristically excreted into the urine in large amounts in this disorder and can be used to make the diagnosis and to monitor efficacy of glucocorticoid substitution. However, the most reliable method of detecting this disorder is the increased response of plasma 17-hydroxyprogesterone to ACTH stimulation. If the defect is in 11-hydroxylation, large amounts of deoxycorticosterone are produced, and because this steroid has mineralocorticoid activity, hypertension with or without hypokalemic alkalosis ensues. When 17-hydroxylation is defective in the adrenals and gonads, hypogonadism is also present. However, increased amounts of 11-deoxycorticosterone are formed, and the signs and symptoms associated with mineralocorticoid excess—such as hypertension and hypokalemia— also are observed. When first seen, the infant with congenital adrenal hyperplasia may be in acute adrenal crisis and should be treated as described above, using appropriate electrolyte solutions and an intravenous preparation of hydrocortisone in stress doses. Once the patient is stabilized, oral hydrocortisone, 12–18 mg/m2 per day in two unequally divided doses (two thirds in the morning, one third in late afternoon) is begun. The dosage is adjusted to allow normal growth and bone maturation and to prevent androgen excess. Alternate-day therapy with prednisone has also been used to achieve greater ACTH suppression without increasing growth inhibition. Fludrocortisone, 0.05–0.2 mg/d, should also be administered by mouth, with added salt to maintain normal blood pressure, plasma renin activity, and electrolytes.

**b. Cushing’s syndrome**—Cushing’s syndrome is usually the result of bilateral adrenal hyperplasia secondary to an ACTHsecreting pituitary adenoma (Cushing’s disease) but occasionally is due to tumors or nodular hyperplasia of the adrenal gland or ectopic production of ACTH by other tumors. The manifestations are those associated with the chronic presence of excessive glucocorticoids. When glucocorticoid hypersecretion is marked and prolonged, a rounded, plethoric face and trunk obesity are striking in appearance. Protein loss may be significant and includes muscle wasting; thinning, purple striae, and easy bruising of the skin; poor wound healing; and osteoporosis. Other serious disturbances include mental disorders, hypertension, and diabetes. This disorder is treated by surgical removal of the tumor producing ACTH or cortisol, irradiation of the pituitary tumor, or resection of one or both adrenals. These patients must receive large doses of cortisol during and after the surgical procedure. Doses of up to 300 mg of soluble hydrocortisone may be given as a continuous intravenous infusion on the day of surgery. The dose must be reduced slowly to normal replacement levels, since rapid reduction in dose may produce withdrawal symptoms, including fever and joint pain. If adrenalectomy has been performed, long-term maintenance is similar to that outlined above for adrenal insufficiency.

**c. Primary generalized glucocorticoid resistance (Chrousos syndrome)**—This rare sporadic or familial genetic condition is usually due to inactivating mutations of the glucocorticoid receptor gene. The hypothalamic-pituitary-adrenal (HPA) axis hyperfunctions in an attempt to compensate for the defect, and the increased production of ACTH leads to high circulating levels of cortisol and cortisol precursors such as corticosterone and 11-deoxycorticosterone with mineralocorticoid activity, as well as of adrenal androgens. These increased levels may result in hypertension with or without hypokalemic alkalosis and hyperandrogenism expressed as virilization and precocious puberty in children and acne, hirsutism, male pattern baldness, and menstrual irregularities (mostly oligo-amenorrhea and hypofertility) in women. The therapy of this syndrome is high doses of synthetic glucocorticoids such as dexamethasone with no inherent mineralocorticoid activity. These doses are titrated to normalize the production of cortisol, cortisol precursors, and adrenal androgens.

**d. Aldosteronism**—Primary aldosteronism usually results from the excessive production of aldosterone by an adrenal adenoma. However, it may also result from abnormal secretion by hyperplastic glands or from a malignant tumor. The clinical findings of hypertension, weakness, and tetany are related to the continue renal loss of potassium, which leads to hypokalemia, alkalosis, and elevation of serum sodium concentrations. This syndrome can also be produced in disorders of adrenal steroid biosynthesis by excessive secretion of deoxycorticosterone, corticosterone, or 18-hydroxycorticosterone—all compounds with inherent mineralocorticoid activity. In contrast to patients with secondary aldosteronism (see text that follows), these patients have low (suppressed) levels of plasma renin activity and angiotensin II. When treated with fludrocortisone (0.2 mg twice daily orally for 3 days) or deoxycorticosterone acetate (20 mg/d intramuscularly for 3 days—but not available in the United States), patients fail to retain sodium and the secretion of aldosterone is not significantly reduced. When the disorder is mild, it may escape detection if serum potassium levels are used for screening. However, it may be detected by an increased ratio of plasma aldosterone to renin. Patients generally improve when treated with spironolactone, an aldosterone receptor-blocking agent, and the response to this agent is of diagnostic and therapeutic value.