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Pharmacology II

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Drugs used for thyroid disorders

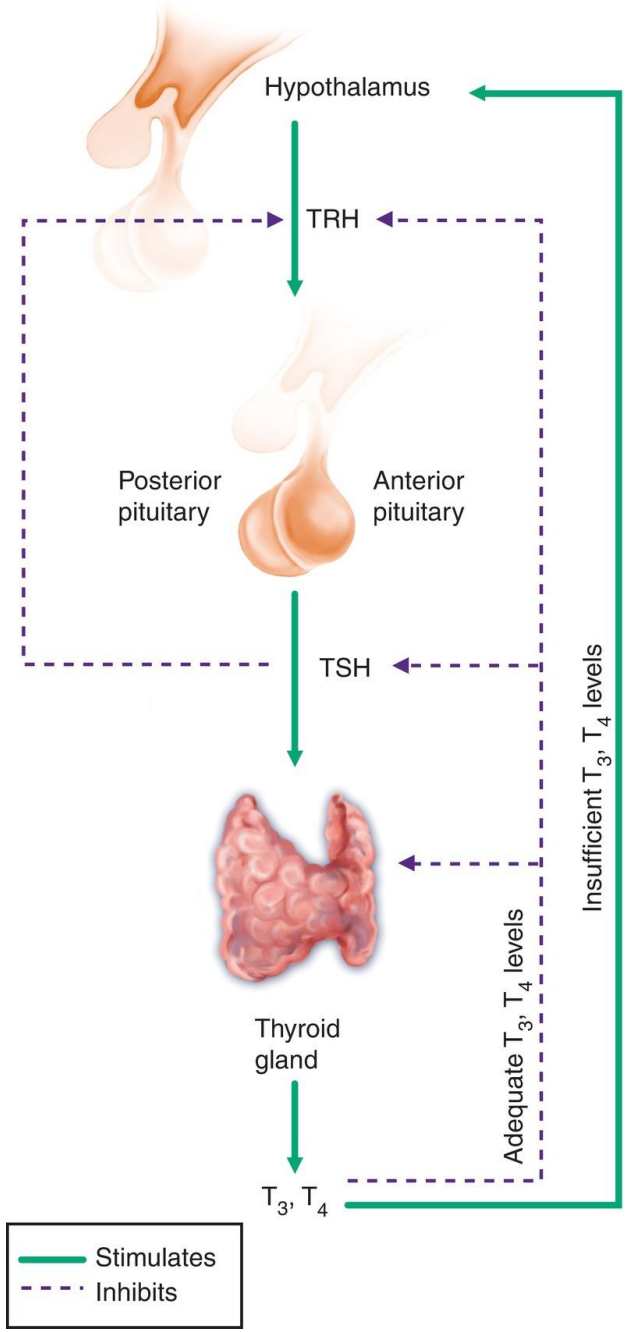
The thyroid gland produces three hormones:

- **thyroxine,**
- **triiodothyronine,**
- **calcitonin**.

Thyroxine (also called T4) contains four atoms of iodine, and triiodothyronine (also called T3) contains three atoms of iodine. Production of T3 and T4 depends on the presence of iodine and tyrosine in the thyroid gland. After they are formed, the hormones are stored within the chemically inactive thyroglobulin molecule. Tyrosine forms the basic structure of thyroglobulin. Thyroid hormones are released into the circulation when the thyroid gland is stimulated by thyroid stimulating hormone (TSH or thyrotropin) from the anterior pituitary gland through a negative feedback mechanism.

These hormones are thought to act mainly by controlling intracellular protein synthesis. Some specific physiologic effects include:

- Increased rate of cellular metabolism and oxygen consumption with a resultant increase in heat production
- Increased heart rate, force of contraction, systemic vascular resistance, and cardiac output (increased cardiac workload)
- Increased carbohydrate metabolism
- Increased fat metabolism, including increased lipolytic effects of other hormones and metabolism of cholesterol to bile acids
- Inhibition of pituitary secretion of TSH



Hyperthyroidism is characterized by excessive synthesis and secretion of thyroid hormone(s) by the thyroid and usually involves an enlarged thyroid gland that has an increased number of cells. Endogenous hyperthyroidism most commonly results from Graves' disease or nodular thyroid goiter. Other causes include thyroiditis, overtreatment with thyroid drugs, functioning thyroid carcinoma, and pituitary adenoma that secretes excessive amounts of TSH.

Hypothyroidism is characterized by diminished secretion of thyroid hormone. Primary hypothyroidism occurs when disease or destruction of thyroid gland tissue causes inadequate production of thyroid hormones. Common causes of primary hypothyroidism include chronic (Hashimoto's) **thyroiditis** , an autoimmune disorder characterized by inflammation of the thyroid gland, and treatment of hyperthyroidism with antithyroid drugs, radiation therapy, or surgery.

Antithyroid drugs

Propylthiouracil is the prototype of the thioamide antithyroid drugs for the treatment of hyperthyroidism more than 60 years ago

Methimazole is similar to propylthiouracil in terms of action, use, and adverse effects. It is also well absorbed with oral administration and rapidly reaches peak plasma levels.

Strong iodine solution (Lugol solution) and saturated solution of potassium iodide (SSKI) are iodine preparations sometimes used in short-term treatment of hyperthyroidism. These drugs inhibit release of thyroid hormones, causing them to accumulate in the thyroid gland.

Adjuvant medication used to treat hyperthyroidism

propranolol (Inderal) is a beta-adrenergic–blocking agent that is recommended in all patients with symptomatic hyperthyroidism.

Thyroid drugs

Levothyroxine a synthetic preparation of thyroxine, serves as the prototype thyroid drug and is considered the standard of care for long-term treatment of hypothyroidism. This potent form of T4 contains a uniform amount of hormone and can be administered orally and parenterally

Drug Therapy for Pituitary and Hypothalamic Dysfunction

Anterior Pituitary Hormones

The anterior pituitary gland produces seven hormones. Two of these, GH and prolactin, act directly on their target tissues; the other five act indirectly by stimulating target tissues to produce other hormones.

Corticotropin , also called adrenocorticotropic hormone (ACTH), stimulates the adrenal cortex to produce corticosteroids

Growth hormone (GH, also called somatotropin) stimulates growth of body tissues. It regulates cell division and protein synthesis required for normal growth and promotes an increase in cell size and number, including growth of muscle cells and lengthening of bone.

Prolactin plays a part in milk production by nursing mothers. It is not usually secreted in nonpregnant women because of the hypothalamic hormone prolact ininhibiting factor (PIF).

Thyroid-stimulating hormone (TSH; also called thyrotropin) regulates secretion of thyroid hormones. Thyrotropin secretion is controlled by a negative feedback mechanism in proportion to metabolic needs.
Follicle-stimulating hormone (FSH), one of the gonadotropins, stimulates functions of sex glands. In people of both sexes, the anterior pituitary produces FSH, beginning at puberty
Luteinizing hormone (LH; also called interstitial cell–stimulating hormone), another gonadotropin, stimulates hormone production by the gonads of both sexes. In women, LH is important in the maturation and rupture of the ovarian follicle (ovulation). After ovulation, LH acts on the cells of the collapsed follicular sac to produce the corpus luteum, which then produces progesterone during the last half of the menstrual cycle
Melanocyte-stimulating hormone (MSH) plays a role in skin pigmentation.

Posterior Pituitary Hormones

The posterior pituitary gland stores and releases two hormones that are synthesized by nerve cells in the hypothalamus

Antidiuretic hormone (ADH), also called **vasopressin**, functions to regulate water balance. ADH makes renal tubules more permeable to water. This allows water in renal tubules to be reabsorbed into the plasma and thus conserves body water. In the absence of ADH, little water is reabsorbed, and large amounts are lost in the urine.

Oxytocin functions in childbirth and lactation. It initiates uterine contractions at the end of gestation to induce childbirth, and it causes milk to move from breast glands to nipples so the infant can obtain the milk by suckling

Drugs for growth deficiency in children

The prototype anterior pituitary hormone is GH. Administered therapeutically, GH is not natural but rather synthesized from bacteria using recombinant DNA technology.

Somatropin is therapeutically equivalent to endogenous GH produced by the anterior pituitary gland.

Corticotropin which is obtained from animal pituitary glands. Corticotropin (ACTH) is effective in treating infantile seizures inpatients 2 months to 2 years of age.

Human chorionic gonadotropin (hCG) produces physiologic effects similar to those of naturally occurring LH. **In males**, it is used to evaluate the ability of Leydig cells to produce **testosterone**, to treat hypogonadism caused by pituitary deficiency

In females, recombinant hCG choriogonadotropin alpha is used in combination with menotropins to induce ovulation in the treatment of infertility.

Posterior pituitary hormone drugs for diabetes insipidus

Desmopressin acetate is the prototype posterior pituitary hormone medication. It is a synthetic analogue of ADH. It reduces urine volume and serum osmolality in patients with diabetes insipidus. It increases the reabsorption of water by the kidney.

Oxytocin (Pitocin) is a synthetic drug that exerts the same physiologic effects as the posterior pituitary hormone. Thus, it promotes uterine contractility and is used clinically to induce labor and in the postpartum period to control bleeding. It is essential that oxytocin be used only when clearly indicated and when the patient can be supervised by well-trained personnel, as in a hospital

Hypothalamic hormone drugs

Leuprolide acetate is equivalent to GnRH . The drug is more potent than the natural hormone

Goserelin (Zoladex), nafarelin ,and **triptorelin** are equivalent to GnRH. After initial stimulation of LH and FSH secretion, chronic administration of therapeutic doses inhibits gonadotropin secretion. This action results in decreased production of testosterone and estrogen, which is reversible when administration is stopped.

Drugs for acromegaly

Octreotide acetate has pharmacologic actions similar to the anterior pituitary hormone somatostatin. Scientists first synthesized this somatostatin analogue in 1979.

Lanreotide is administered subcutaneously for the treatment of acromegaly and gastroenteropancreatic neuroendocrine tumor. It is important to assess for GI symptoms

Pasireotide is administered deep intramuscularly for acromegaly and Cushing's disease

Drug Therapy for Adrenal Cortex Disorders

Pathophysiology

There are two forms of **adrenocortical insufficiency** .

Primary adrenal

insufficiency, or **Addison's disease**, occurs when adrenal cortical hormones are deficient. ACTH levels are elevated because the feedback mechanism is not working. Primary adrenal insufficiency most commonly results from an autoimmune disorder that has destroyed the layers of the adrenal cortex. Other causes of adrenal cortex destruction include metastatic carcinoma, fungal infections such as histoplasmosis, cytomegalovirus, amyloid disease, and hemochromatosis.

Secondary adrenal2221

insufficiency occurs when there is a disorder in the hypothalamic-pituitary-adrenal system. Secondary adrenal cortical insufficiency results from hypopituitariasm or surgical removal of pituitary gland

Drugs used to treat addison's disease

treatment of Addison's disease is to replace the adrenocorticoids to correct adrenal insufficiency. It is important to replace both the mineralocorticoid and adrenocorticoid. Lifetime hormone replacement is necessary.

Drug Class	Prototypes	Other Drugs in the Class
Adrenocorticoid/ mineralocorticoids	Hydrocortisone (Cortef, Solu-Cortef)	None
Mineralocorticoids	Fludrocortisone	None

Adrenocorticoids/mineralocorticoids

The prototype **hydrocortisone** a combination of a mineralocorticoid and adrenocorticoid, is useful in acute and chronic adrenal insufficiency.

Mineralocorticoids

If a patient with Addison's disease requires additional mineralocorticoid supplementation, then **fludrocortisone**, a synthetic steroid, is useful. A patient usually takes it in combination with a glucocorticoid. It is important to note that fludrocortisone has also proved effective for the treatment of orthostatic hypotension in older adults.

Cushing's disease

Pathophysiology

The cause of Cushing's disease is **adrenocortical excess** . In the majority of patients, the increased adrenocortical function results from excessive corticotropin, leading to hyperplasia of the adrenal cortex. In a smaller percentage of patients, it is the result of a cortisol-secreting adrenal tumor, whether from too much corticotropin (ACTH) or a primary tumor of the adrenal gland . Also long-term treatment with pharmacologic glucocorticoids leads to iatrogenic Cushing's syndrome.

Drugs used to treat cushing'sdisease

The treatment of Cushing's disease depends on the cause of the medical condition. The most common treatment of hypercortisolism is transsphenoidal surgery. Drug therapy is indicated in several situations: when surgery is contraindicated, in preparation for surgery, in occult ectopic ACTH syndrome, with a recurrence of hypercortisolism following surgery, and with treatment using radiation therapy to the pituitary

Drug Class	Prototype	Other Drugs in the Class
Glucocorticoid receptor antagonists	N/A	Ergot derivative: Cabergoline Somatostatin analog: Pasireotide (Signifor, Signifor LAR
11-Deoxycortisol inhibitors	Ketoconazole	Metyrapone (Metopirone) Etomidate (Amidate)
Antineoplastics	Mitotane (Lysodren)	None

Glucocorticoid receptor antagonists

Glucocorticoid receptor antagonists are administered when surgery to treat corticotroph tumors is delayed or contraindicated. The two medications used to normalize the 24-hour urinary cortisol are **cabergoline and pasireotide**.

Cabergoline is an ergot derivative. Its off-label use is to normalize urinary free cortisol levels in the treatment of Cushing's syndrome.

Pasireotide is a somatostatin analog to maximize the reduction of urinary free cortisol. The maximum reduction of cortisol is usually noted in approximately 2 months.


Thank you