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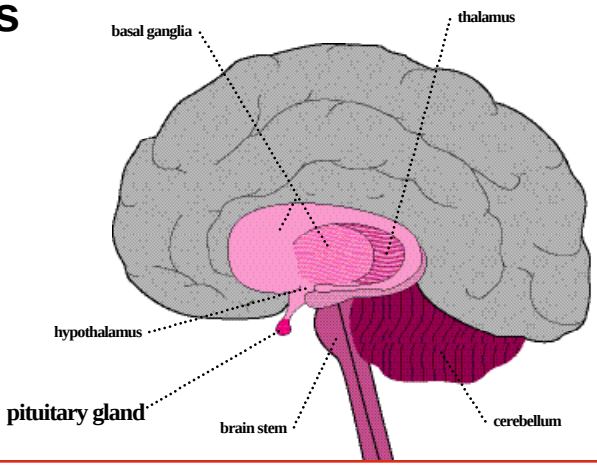
Hormones of the Human Pituitary Gland



The Pituitary Gland

As the primary regulator of the endocrine system, the pituitary gland is the most important of the endocrine glands. The major glands of the endocrine system include the pituitary, thyroid, and parathyroid glands, and the pancreas, adrenal cortex, ovaries, and testes. The pituitary regulates the actions of most of these glands and many other body functions. It, in turn, is regulated by the hypothalamus through nervous stimulation and through the production of various hormone-releasing factors. In humans the pituitary is located at the base of the brain, attached to the hypothalamus (see figure 1). It weighs approximately 700 mg and consists of posterior, intermediate, and anterior lobes, each with its own unique function.

The posterior lobe controls the release of two polypeptide hormones: vasopressin and oxytocin. These are synthesized in the hypothalamus and transported to the posterior lobe, where they are stored in secretory granules until release. Vasopressin (antidiuretic hormone) increases the reabsorption of water into the blood by the kidneys, thereby decreasing urine production. It also causes vasoconstriction of peripheral blood vessels, slowing the heart rate and increasing blood pressure. Oxytocin stimulates uterus contraction during labor and the milk release response during lactation.

The intermediate lobe releases melanocyte-stimulating hormone (melanotropin), which controls the darkening of the skin.

In the anterior lobe, releasing hormones from the hypothalamus stimulate the release of several hormones: prolactin (PRL) and human growth hormone (GH, somatotropin) from the acidophilic cells; follicle-stimulating hormone (FSH, follitropin), luteinizing hormone (LH, lutropin), and thyroid-stimulating hormone (TSH, thyrotropin) from the basophilic cells; and adrenocorticotropic hormone (ACTH, corticotropin) from the chromophobic cells. It is these anterior pituitary hormones that are the focus of this review.

Non-glycosylated Hormones of the Anterior Pituitary

The first pituitary hormones to be isolated and studied were PRL and GH, with studies dating back to the early 1940's.[1,2,3] These chemically related hormones are approximately 22,000 molecular weight (mol wt) and consist of single polypeptide chains with no covalently linked carbohydrate groups.[4] Extensive sequence homology and similarities in biological and immunological properties between PRL and GH, suggest that they evolved from a common ancestral precursor.[5,6,7]

prolactin

PRL is a single polypeptide chain comprised of 199 amino acid residues, containing two tryptophan residues and three disulfide bridges.[8,9,10] Its molecular weight is 22,800 daltons and its isoelectric point (pI) is approximately 5.7.[4,11]

The primary function of PRL is the development and maintenance of lactation. Several physiological conditions induce the release of PRL, the most notable being the stimulation of the breast and nipple during nursing.[12,13] Two other conditions giving rise to PRL release are severe stress and major surgery involving general anesthesia. The release of PRL into the bloodstream is thought to be under the control of a prolactin-inhibitory factor produced by the hypothalamus.[14]

Normal plasma levels of PRL range from 5 to 25 ng/ml in women and from 1 to 20 ng/ml in men. During pregnancy, PRL levels may elevate to as high as 300 ng/ml.[15] Several clinical conditions have been associated with abnormal levels of PRL in women, such as galactorrhea, anovulation with amenorrhea, hypoestrogenism, and hyperprolactinaemia. As such, diagnostic immunoassays for PRL are useful in the detection of these disorders.

growth hormone

Like PRL, GH is a single polypeptide, but is comprised of 191 amino acids, containing one tryptophan residue and two disulfide bridges.

Table 1. Approximate Molecular Weight, Carbohydrate Content, and pI of the Glycoprotein Hormones

		Carbohydrate content, g/100g				
Hormone	Molecular Weight	Neutral sugar	Acetyl hexosamine	Sialic acid	Fucose	pI
hCG	36,700	11.0 - 11.2	10.8 - 11.1	8.5 - 9.0	1.2	4.9
FSH	35,500	3.9 - 12.2	2.9 - 9.0	1.4 - 5.1	-	5.5
LH	28,500	11.3	4.9	2.0	-	7.4
TSH	25,000	5.9	4.1	-	0.5	-

Its molecular weight is 21,700 and its pI = 4.9.[4,16]

GH is an important anabolic, or protein-building, hormone. Its actions lead to nitrogen and potassium retention, decreased blood urea nitrogen, and increased serum phosphate. These indirect effects of GH are mediated through the production of secondary growth promoting peptides called somatomedins. The direct effects of GH include interactions with erythrocytes, resulting in decreased glucose utilization, and with diaphragm tissue, resulting in increased cAMP levels.[4]

Normal plasma levels of GH vary, but are generally under 10 ng/ml. Excessive secretion of GH, or hypersomatotropism, is often associated with liver and kidney disease and with acromegaly.[17,18] GH deficiency, or hypo-somatotropism, is associated with several types of dwarfism and with various pituitary or hypothalamic afflictions; in fact, GH is frequently prescribed for the treatment of such disorders.[19] As such, the measurement of GH is useful in the detection of both hyposomatotropism and hypersomatotropism.

The Glycoprotein Hormones

The pituitary hormones bearing carbohydrate moieties are considerably more complex and diverse than the single-chain polypeptide hormones PRL and GH. The glycosylated pituitary hormones include follicle stimulating hormone (FSH, follitropin), luteinizing hormone (LH, lutropin), and thyroid stimulating hormone (TSH, thyro-tropin). Included in most discussions of glycoprotein hormones is the placental hormone human chorionic gonadotropin (hCG). Thus, the glycoprotein hormones include TSH, FSH, LH, and hCG.

Structurally distinct from PRL and GH, the glycoprotein hormones are composed of two non-covalently linked subunits, designated α and ß. As with PRL and GH, physical evidence suggests that hCG, FSH, LH, and TSH have evolved from the same gene or set of genes.[20] The amino acid sequence of the α-subunit is identical among them and is encoded by the same gene.[15,21] The ß-subunit genes are distinct for each hormone, but share many conserved sequences; as such, the gene products are 40-45% homologous in their primary structure.[5,21] It is the differences in the ß-subunit genes, however, that account for the unique biological activity of each hormone.[15] In addition, it is reported that the individual subunits retain little or no biological activity; the α-ß dimer must be intact for the hormone to perform its physiological function.[22,23]

Structurally, the α- and ß-subunits are rich in cysteine residues and are highly cross-linked: the α-subunits contain five disulfide bridges and the ß-subunits contain six.[5] As glycoproteins, the reported mol wts of these hormones vary with the degree of glycosylation. Average mol wt, carbohydrate content, and pI (if available) are reported in Table 1.

thyroid stimulating hormone

TSH is a major regulating factor of thyroid hormone synthesis and secretion. It stimulates the thyroid to synthesize and release the thyroid hormones triiodothyronine (T3) and thyroxine (T4), and induces thyroglobulin production. In general, TSH stimulates the thyroid gland, increasing both blood circula-tion in the gland and iodine uptake.

TSH synthesis and secretion by the pituitary gland is under the direct control of the hypothalamus via thyrotropin releasing hormone (TRH). TSH is also regulated by the thyroid, as high plasma T3 and T4 concentrations inhibit TSH synthesis. In addition, TSH synthesis is thought to be under the control of factors such as dopamine, somatostatin, catecholamines, and various steroid hormones.[24]

As the thyroid gland is affected by the pituitary gland and the hypothalamus, immunoassays for TSH, T3 and T4, along with TRH stimulation assays, are routinely used as indicators of thyroid function. Thyroid dysfunction may be due to primary hyper-thyroidism, most often manifested as the autoimmune disorder Grave's Disease, but sometimes as thyroid adenoma, or nodular goiter.[25] In such afflictions, plasma TSH levels are usually well below normal, T3 and T4 levels are elevated, and TRH stimulation is subnormal.

Most cases of primary hypothyroidism are caused by yet another autoimmune disease, Hashimoto's thyroiditis. In such cases, TSH synthesis is increased and plasma levels are high. This is most likely due to the absence of T3-T4 negative feedback inhibition as plasma levels of T3 and T4 are low. In those cases of primary hypothyroidism caused by pituitary dysfunction, TSH levels are often normal, while levels of T3 and T4 are low. In such cases, TRH stimulation tests may help confirm pituitary dysfunction. Elevated TSH levels are usually, but not always, predictive of primary hypothyroidism. As such, TSH assays should be used in conjunction with T3 and T4 assays, and with TRH stimulation assays.

the gonadotropins: FSH, LH, and hCG

The remaining glycoprotein hormones, FSH, LH, and hCG, make up a subset of hormones called gonadotropins. As their name implies, the gonadotropins regulate gonadal function.

In males, FSH induces spermatogenesis and the development of seminiferous tubules, while LH stimulates testosterone secretion from Leydig cells.[26]

In females, FSH and LH are intricately involved in the reproductive cycle. LH stimulates the ovarian theca to produce several androgen precursors of estradiol. FSH, in turn, induces the conversion of these androgens to estradiol by the ovarian granulosa cells. FSH also stimulates the growth of the ovarian follicles in preparation for the LH-mediated release of a ripe ovum. LH then promotes the formation of the corpus luteum and the subsequent production of progesterone.[15]

The synthesis and secretion of FSH and LH are primarily controlled by the gonadotropin releasing hormone, luliberin, but are also thought to be regulated by an estrogen negative feedback inhibition. During the follicular growth phase, prior to ovulation, estradiol levels increase, while FSH levels decrease. As estradiol levels increase, the pituitary produces a mid-cycle surge of LH, which induces the rupture of the follicle and, subsequently, ovulation occurs. The follicular rupture of the ovulatory phase is thought to be triggered by the marked increase in estradiol secretion by the growing follicle. After ovulation, during the luteal phase, declining estradiol and progesterone levels are thought to give rise to the pituitary release of FSH, and the cycle begins again.[15] Table 2 summarizes the plasma levels of these hormones during the female reproductive cycle.

Measurements of FSH and LH are frequently used in the evaluation of disorders of reproduction and puberty, such as hypo-gonadism, ovulation timing and fertility studies, monitoring ovulation induction, and the clinical administration of gonadotropins.

Elevated LH (>25 IU/L) and FSH (>40 IU/L), along with decreased estradiol (<20 ng/L), are diagnostic of hypergonadotrophic hypogonadism (gonadal failure).[15] In such disorders, FSH levels are consistently higher than LH levels, since the absence of negative feedback by ovarian estradiol has a more pronounced effect on FSH. FSH values >40 IU/L are typically associated with ovarian failure. Four major areas of hyper-gonadotrophic hypogonadism are identified in Table 3.

Abnormally low levels of LH (<10 IU/L) and FSH (<10 IU/L) along with decreased estradiol (<20 ng/L) are diagnostic of hypogonadotrophic hypogonadism (central gonadal failure).[15] Such afflictions, also summarized in Table 3, are indicative of a pituitary or hypothalamic disorder.

While its role in the female reproductive cycle is not clear, hCG is instrumental in the maintenance of the corpus luteum at the beginning of the gestation period. Tests for hCG are routinely used for pregnancy detection, and can identify pregnancy as early as seven days after conception. hCG levels are also used to assist the verification of normal

Table 2. FSH, LH, estradiol, and progesterone levels of the premenopausal female menstrual cycle[15]

	Follicular Phase	Ovulatory Phase	Luteal Phase
LH	8-20 IU/L	>25 IU/L	8-20 IU/L
FSH	8-20 IU/L	10-30 IU/L	8-20 IU/L
Estradiol	30-150 ng/L	100-500 ng/L	50-250 ng/L
Progesterone	<2 µg/L	-	>10 µg/L

Table 3. Known Hypergonadotrophic and Hypogonadotrophic states[15]

	Estradiol	FSH and LH	Additional testing	Incidence
A. Hypergonadotrophic states				
Menopause	depleted	elevated		common
Gonadal dysgenesis	depleted	elevated	karyotype	uncommon
Premature ovarian failure	depleted	elevated	ovarian biopsy	rare
Ovarian resistance sydrome	depleted	elevated	ovarian biopsy	very rare
B. Hypogonadotrophic states				
Hyperprolactinemia	depleted	normal or depleted	TSH, PRL	common
Weight-loss amenorrhea	depleted	depleted		common
Exercise amenorrhea	depleted	depleted		common
Anorexia nervosa	depleted	depleted		uncommon
Kallman's syndrome	depleted	depleted		rare
Pituitary failure (Sheehan's syndrome, Ahumada-del Castillo syndrome)	depleted	depleted	anosmia testing somatotropin, TSH, ACTH	very rare

pregnancy: hCG levels are at the expected elevated levels in normal intrauterine pregnancy and in blighted intrauterine pregnancy, may be at low levels in ectopic pregnancy, and are elevated in pregnancies that involve the formation of hydatidiform moles. In addition, the structural similarity between hCG and LH has led to the pharmaceutical use of hCG as an LH analog for ovulation induction.[15]

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A Guide to Pituitary Hormone Reference Preparations

Glycoprotein hormones (FSH, LH, TSH) are assigned potencies based upon *in vivo* biological assays because chemically pure preparations have not been available and, due to carbohydrate moieties, considerable microheterogeneity is apparent in each of these hormones. In order to standardize glycoprotein hormone assay systems, the World Health Organization has prepared and distributed reference preparations for each of the pituitary glycoprotein hormones. Historically, these have been highly purified, but not chemically pure preparations, with assigned potencies based on biological assays relative to arbitrarily chosen preparations available at the time the reference materials were established. Since the establishment of these reference preparations, it has been necessary to replace them with additional materials, often more highly purified than the original reference, and to evaluate potencies based upon *in vitro* (e.g. RIA) as well as *in vivo* (e.g. bioassays) assay systems. In some cases, potencies vary as a function of the particular reference preparation being utilized and, in general, RIAs are more heterogeneous than *in vivo* bioassays.

The Table below is designed to aid in converting a potency based on one reference material, to a theoretical potency based on another reference preparation. It must be recognized, however, that converting potencies based upon one reference preparation to another can also be affected by assay peculiarities, and can only be accomplished by direct comparisons using the same assay procedures.

Definitions:

hMG - gonadotropin prepared from urine of menopausal and post-menopausal women.

IU - International Unit; the specified biological (*in vivo*) activity contained in a defined weight of the current International Standard.

IS - International Standard; a preparation to which an IU is assigned on the basis of an international collaborative study.

IRP - International Reference Preparation; similar to an IS, but established when a collaborative study indicates the preparation is not entirely suitable as an International Standard, or established before a complete collaborative study has been conducted.

Comparison Table of Hormone Reference Preparations

Hormone	Reference Preparation	Potency	Definition of Potency
FSH	1st IRP-hMG (1960)	No official units	Activity as "mg" 1st IRP-hMG
	2nd IRP-hMG (1964)	40 IU/ampoule	1 IU = 7 mg 1st IRP-hMG
	1st IRP-Pituitary FSH/LH for Bioassay (69/104)	10 IU/ampoule	By definition; equivalent to about 20 IU 2nd IRP-hMG
	2nd IRP-Pituitary FSH/LH for Bioassay (78/549)	10 IU/ampoule	Based on (69/104)
	1st IS-Pituitary FSH (83/575)	80 IU/ampoule	By definition; equivalent to 5 - 80 IU (78/549), depending on assay
GH	1st IRP (66/217)		By definition; 2.2 IU/mg for pure hormone; equivalent to NIAMDD-hGH-RP1
	1st IS (80/505)	4.4 IU/ampoule	Based on (66/217)
LH	1st IRP-hMG (1960)	No official units	Activity as "mg" 1st IRP-hMG
	2nd IRP-hMG (1964)	40 IU/ampoule	1 IU = 2 mg 1st IRP-hMG
	1st IRP-Pituitary FSH/LH for Bioassay (69/104)	25 IU/ampoule	By definition; equivalent to about 50 IU 2nd IRP-hMG
	2nd IRP-Pituitary FSH/LH for Bioassay (78/549)	25 IU/ampoule	Based on (69/104)
	1st IRP-Pituitary LH - Immunoassay (68/40)	77 IU/ampoule	By definition; equivalent to 15 - 75 IU (69/104), depending on assay
	2nd IS-Pituitary LH (80/552)	35 IU/ampoule	By definition; equivalent to 25 - 45 IU (68/40), depending on assay
PRL	1st IRP (75/504)		By definition; 30 IU/mg for pure hormone
IRP	2nd IS (83/562)	53/mIU/ampoule	By definition; equivalent to 53 mIU 1st (75/504)
IS	3rd IS (84/500)	53 mIU/ampoule	By definition; equivalent to 53 mIU 2nd (83/562)
TSH	1st IRP, human TSH (68/38)	150 mIU/ampoule	By definition.
	2nd IRP, human TSH (80/558)	37 mIU/ampoule	By definition; equivalent to 36 - 46 mIU (68/38), depending on assay