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HORMONES, ANTERIOR PITUITARY HORMONES

The hormones of the anterior pituitary gland play a significant role in the maintenance of normal health and body function. This master gland produces hormones involved in the regulation of somatic growth, metabolic rate, carbohydrate and lipid metabolism, lactation, reproduction, and response to stress. Eleven anterior pituitary hormones have been extensively characterized at the protein and genomic levels. These hormones fall into three classic categories, ie, pro-opiomelanocortin-related (POMC-related) hormones, proteins structurally related to prolactin and growth hormone (PRL/GH-related), and glycoproteins. Structural similarities exist within each biochemical category, and the structural data presented represent listings in the Protein Identification Resource (PIR) database, compiled by the National Biomedical Research Foundation, Washington, D.C. Table 1 provides summary information on the principal biologic roles of each of these hormones. The National Hormone and Pituitary Program at the NIH and the USDA Animal Hormone Program provide anterior pituitary hormones free of charge for nonprofit research purposes. All principal hormones of the anterior pituitary gland are available commercially as material purified from anterior pituitary gland extracts, synthetic peptides, or proteins produced by the expression of recombinant DNA. Excellent listings of commercial sources of anterior pituitary hormones are available (1, 2).

1. Pro-Opiomelanocortin-Derived Hormones

A single parent gene codes for the 267 amino acid glycoprotein which contains the sequences for adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), endorphin, and lipotropin (LPH) (3). This precursor has been named pro-opiomelanocortin [66796-54-1] (POMC), and the biosynthesis and structure have been reviewed (4, 5). The locations of the POMC-derived bioactive peptides relative to the precursor molecule are shown in Figure 1. Two disulfide bonds exist in the proximity of the N-terminus of the precursor, but there are no disulfide bonds in the bioactive peptides derived from the parent molecule. Glycosylation sites exist at Thr-45 and Asn-65. There also is evidence that Asp-29 of ACTH is glycosylated in the rat and mouse (6, 7). The biological significance of POMC glycosylation is unknown, but it has been postulated to stabilize the prohormone (8).

1.1. Adrenocorticotropic Hormone

Adrenocorticotropic hormone [9002-60-2] is required for maintenance and function of the adrenal cortex, which secretes potent steroid hormones regulating metabolism, ie, glucocorticoids. Insufficient secretion of the steroid hormones of the adrenal cortex, as in Addison's disease, may result in insulin hypersensitivity, inability to maintain blood sugar levels during food deprivation, hypotension, general weakness, fatigue, and psychological disturbances. Glucocorticoids regulate their own production by suppressing the synthesis and secretion of POMC-derived hormones, ie, negative feedback. Removal of the pituitary gland induces a pronounced physical atrophy of the adrenal cortex, which accompanies loss of function including a reduction

Table 1. Hormones of the Anterior Pituitary and Their Functions

Hormone	Acronym	CAS Registry Number	Number of amino acids[a]	Principal function
		Pro-opiomelanocortin-derived peptides		
adreno-cortico-tropin	ACTH	[9002-60-2]	39	stimulates cortex of adrenal gland to pro-duce steroid hormones, ie, glucocorticoids
β-endorphin		[59887-17-1]	31	functions as neurotrans-mitter; exerts opiate-like analgesia
lipotropin	LPH	[9035-55-6]		mobilizes fat; precursor for β-endorphin
β-LPH		[37199-43-2]	91	
γ-LPH		[60893-02-9]	58	
melanotropin	MSH	[9002-79-3]		darkening of the skin, ie, pigmentation
α-MSH		[37213-49-3]	13	
β-MSH		[9034-42-8]	22	
		Prolactin/growth hormone-related peptides		
prolactin		[9002-62-4]	199	supports lactation
growth hormone	GH	[9002-72-6]	191	stimulates body growth; anabolism
		Glycoproteins		
follicle-stimulating hormone	FSH	[9002-68-0]	210	supports maturation of ovarian follicles and sperm
luteinizing hormone	LH	[9002-67-9]	204	induces ovulation; main-tains testicular function
thyroid-stimulating hormone	TSH	[9002-71-5]	211	stimulates thyroid hor-mone production and thyroid gland growth

[a]From human amino acid sequence (PIR).

in steroid hormone secretion. The size and functional integrity of the adrenal gland can be restored by the administration of ACTH. The sequence of the first 24 N-terminal amino acids of ACTH cosyntropin [16960-16-0] confers full bioactivity at the adrenal gland and is highly conserved among species. Across species, the ACTH molecule differs slightly in structure and retains similar biologic function. It is a single-chain peptide, 39 amino acids in length (Fig. 1). Adrenocorticotropic hormone is not generally used for the treatment of adrenal insufficiency, because the adrenal steroids can be easily synthesized and administered. Clinically, ACTH is used for diagnostic testing of adrenal function. Commercial preparations of ACTH are available from Armour Pharmaceutical, Ciba Pharmaceutical, Hoechst-Roussel, Organon Inc., and Wyeth-Ayerst Laboratories.

1.2. Melanotropins

Two melanotropins, α-MSH and β-MSH, result from post-translational processing of POMC in the pituitary gland. The α-MSH peptide is comprised of the first 13 amino acids of ACTH, except that serine 1 is acetylated and valine 13 is amidated (Fig. 1). The cleavage of lipotropin (LPH) generates β-MSH (Fig. 1). In lower vertebrates, these hormones induce changes in melanin-containing cellular organelles which rapidly alter body pigmentation. While the physiologic role of MSH in mammals is questionable, MSH-secreting tumors and injections of MSH cause hyperpigmentation in humans. Darkening of the skin also occurs clinically with inadequate glucocorticoid secretion, which removes the negative feedback on POMC-derived hormone production and increases MSH secretion. α-MSH acts as a neurotransmitter within the central nervous system, where it may be involved in regulation of body temperature (9). Solid-phase synthesis is used to produce MSH for use in biomedical research. No other commercial applications exist.

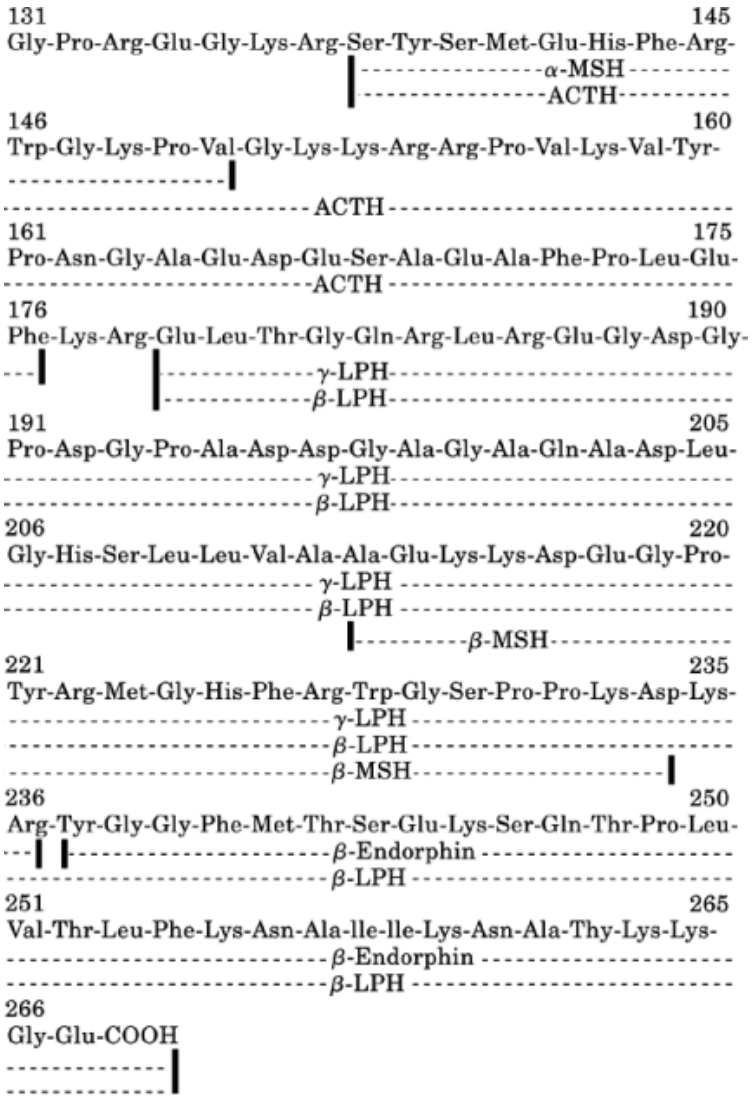

Fig. 1. Locations of bioactive peptides within human pro-opiomelanocortin for sites 131–267.

1.3. β-Endorphin

A peptide corresponding to the 31 C-terminal amino acids of β-LPH was first discovered in camel pituitary tissue (10). This substance is β-endorphin, which exerts a potent analgesic effect by binding to cell surface receptors in the central nervous system. The sequence of β-endorphin is well conserved across species for the first 25 N-terminal amino acids. Opiates derived from plant sources, eg, heroin, morphine, opium, etc, exert their actions by interacting with the β-endorphin receptor. On a molar basis, this peptide has approximately five times the potency of morphine. Both β-endorphin and ACTH are cosecreted from the pituitary gland. Whereas the physiologic importance of β-endorphin release into the systemic circulation is not certain, this molecule clearly has been shown to be an important neurotransmitter within the central nervous system. Endorphin

has been invaluable as a research tool, but has not been clinically useful due to the availability of plant-derived opiates.

1.4. Lipotropin

Lipotropin, first isolated from sheep pituitary glands (11, 12) in the course of research directed at optimizing ACTH purification techniques, has been determined to be distinct from the other known pituitary hormones and possesses lipolytic activity. The location of the two lipotropins, β-LPH and γ-LPH, within the POMC protein sequence is shown in Figure 1. Lipotropin is important as a precursor for β-endorphin, but the biological significance of its fat-mobilizing properties is unresolved. In the early 1990s LPH is used only for basic research.

2. Prolactin/Growth Hormone-Related Hormones

2.1. Prolactin

In 1928, bovine pituitary extract was shown to induce lactation in rabbits (13). Soon afterward, lactogenic activity was found in pituitary extracts from a variety of mammalian and nonmammalian species. The protein responsible for this activity has been appropriately named prolactin, although it is sometimes referred to as lactogenic hormone. The best-documented function of prolactin is to stimulate milk synthesis and secretion; however, a variety of other functions may exist. Advances in immunophysiology indicate an important role for this hormone in regulating immune function (14). In rodents, but not other species, prolactin acts to support the function of the corpus luteum, ie, the ovarian tissue which secretes hormones needed to maintain pregnancy. Prolactin also may be involved in the regulation of salt—water balance, growth, development, and metabolism (15).

The primary structure of prolactin consists of 199 amino acids in a linear sequence (see Hormones, anterior pituitary-like hormones). Similar to growth hormone (16), the tertiary structure of prolactin is thought to be arranged in a bundle of four α-helices (17). Detailed reviews of the structure—function relationships of prolactin among a variety of species have been published (17, 18). Only one gene for prolactin appears to exist (19). Although classically placed in the category of simple protein hormones, prolactin can be glycosylated. Carbohydrate attachment occurs at Asn-31, where the consensus glycosylation sequence Asn–X–Ser is found.

The abundance of glycosylated prolactin varies between species, but can be significant; in the pig, 50% of prolactin can be in the glycosylated form (20). The physiologic importance of glycosylated prolactin is uncertain, but depending on the bioassay used for potency testing, glycosylated prolactin may be less (21) or more (22) active than the nonglycosylated hormone. In addition to 23 kD prolactin, 21 and 25 kD forms of this hormone exist which may be generated from alternative mRNA splicing. Variants of prolactin also arise from proteolytic cleavage, phosphorylation, deamidation, sulfation, and polymerization. The biopotencies of these variants relative to 23 kD prolactin vary with different assay systems. While exceptions exist, prolactin variants generally exert equal or lower potency than the 23 kD form of the hormone; a summary of relative potencies is available (20). The N-terminal portion of prolactin appears to contain sequences which confer bioactivity, as the 16 kD N-terminal product of enzymatic cleavage retains potency (23). Site-directed mutagenesis of bovine prolactin has been used to produce hormone variants lacking disulfide bridges between amino acids 4–11, 191–199, or 58–174 (24). Mutant prolactin lacking the large (sites 58–174), but not small disulfide loops has a greatly reduced bioactivity. Prolactin is produced for research purposes. Clinical applications may develop as prolactin's role as an immune system modulator is elucidated (14).

2.2. Growth Hormone

The growth-promoting property of pituitary extracts was evident to early endocrinologists. Their observations have been confirmed upon the isolation of growth hormone (GH), also known as somatotropin, from bovine pituitary glands (25). While variable potencies have been observed when GH from one species is administered to another, this hormone is obviously a powerful stimulant of body growth. The lack of endogenous GH production is a cause of dwarfism in humans which can be overcome by clinical replacement therapy. Growth hormone produced from recombinant DNA is the commercial source of hormone for the clinical treatment of GH deficiency. Much of the growth-stimulating action of GH is mediated by insulin-like growth factors, originally called somatomedins, which are produced primarily in the liver in response to GH (26). Growth hormone also stimulates the production of insulin-like growth factors which have autocrine actions in a variety of non-hepatic target tissues (27).

In addition to its growth-stimulating properties, GH exerts potent metabolic actions. It induces a decrease in blood urea and amino acid levels; this action may be secondary to an increase in the rate of amino acid uptake and protein synthesis in peripheral tissues. Growth hormone antagonizes the blood sugar-lowering effect of insulin by suppressing glucose uptake and utilization, and promotes body leanness by decreasing fat synthesis and stimulating adipose breakdown. As a result of these desirable metabolic effects, recombinant GH preparations may find significant commercial applications as performance stimulators in domestic animals. Research has shown that growth hormone enhances milk production in lactating animals and improves feed efficiency, growth rate, and carcass lean meat-to-fat ratio in growing animals (see Growth regulators, animal). Interestingly, there is an increasing body of evidence to support the role of growth hormone as a stimulator of immune function, with the ability to reverse the aging-related decrease in thymus size (28).

Growth hormone from one species is not necessarily active when administered to other species. Bovine GH [66419-50-9], for example, is active in sheep and rodents, but not in primates. Growth hormone from primates, but not other species, exerts prolactin-like activity, which reflects its ability to bind to the prolactin receptor (18). The evidence supporting the ability of growth hormone to create a desirable physiological profile, ie, high protein—water and low fat body composition, and to enhance immunity has created a high degree of research interest in the pharmaceutical industry. U.S. Food and Drug Administration (FDA) approval has been granted for the use of a recombinant bovine GH preparation, produced by Monsanto Co., U.S.A., in lactating dairy cattle to increase milk production. Eli Lilly and Company, The Upjohn Company, and American Cyanamid Company also have interests in the commercial application of recombinant bovine GH. Recombinant porcine GH [9061-23-8] preparations from several companies, eg, The Upjohn Company, SmithKline Beecham Animal Health, Pitman-Moore, Inc., Monsanto Company, and American Cyanamid Company, are being evaluated for commercial use. Recombinant human GH for clinical use is marketed under such names as Protropin (Genentech), Umatrope (Eli Lilly), Genotropin (Sumitomo), and Somatonorm (Kabi-Vitrum) by a variety of pharmaceutical companies. A listing of additional suppliers is available (2).

Human chromosome 17 contains two genes that code for slightly different forms of GH (29). The products of these two gene copies differ in 12 amino acids, spread along the length of the molecule. These isohormones have been termed GH-normal (GH-N) and GH-variant [109675-94-7] (GH-V). GH-N is produced primarily in the pituitary gland, while GH-V is expressed in placental tissue (see Hormones, anterior pituitary-like hormones). As for prolactin, variants of the principal 22 kD form of pituitary GH exist; alternative mRNA splicing gives rise to a 20 kD form of GH, with residues 32–46 of 22 kD GH deleted. The 20 kD GH apparently does not bind the GH receptor as well as 22 kD GH, but exerts similar biological potency (16). Deamidated and acylated GH have been described which possess unaltered biopotency (16). A cluster of four α-helices comprises the tertiary structure of GH (16). Growth hormone's relation to prolactin and placental lactogen is evident, particularly in the preservation of two disulfide bonds which give rise to the so-called long and short loops (18). The synthesis of bovine GH from site-directed mutations of the encoding DNA has shown that the long rather than the short loop is needed for hormone secretion (30).

Full reduction and carbamidomethylation of the disulfide bonds of human GH does not affect bioactivity (31). However, there may be species differences in the role of the disulfide bonds on hormone action; for example, reduction followed by aminoethylation of porcine GH reduces bioactivity (32). Numerous studies have sought to determine the structural components of GH required for receptor binding. Site-directed mutagenesis shows that the N-terminus of GH, perhaps between residues 8 and 18, is required for receptor binding activity (33). On the other hand, the C-terminus also has been recognized to be important for the expression of full potency (18). The solution of the crystal structure of the GH-receptor complex has unified the results of earlier studies by showing that a number of sites over the length of GH are involved in the binding of one hormone molecule to two GH receptors (34).

3. Glycoprotein Hormones

There are three pituitary glycoprotein hormones, ie, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and thyroid-stimulating hormone (TSH). Luteinizing hormone and FSH control significant aspects of reproduction. These hormones are referred to as gonadotropins, owing to their trophic and stimulatory effects on gonadal tissues. Follicle-stimulating hormone is needed for maturation of the ovarian follicles, for maintaining the size of the ovary, and for stimulating the production of female sex steroid hormones, ie, estrogens. In the male, FSH is necessary for sperm production. Luteinizing hormone induces ovulation, ie, release of the egg, from the mature follicle. In the male, LH induces the synthesis of the male sex steroid hormones, called androgens (see Hormones, sex hormones). Thyroid-stimulating hormone is necessary for the proper development, growth, and function of the thyroid gland. Most importantly, TSH is responsible for maintaining thyroid hormone production. Inadequate levels of thyroid hormone give rise to a clinical profile characterized by sluggish mental processes, slow growth, sensitivity to cold, low basal metabolic rate, cardiac insufficiency, general weakness, and susceptibility to infection.

Luteinizing hormone, FSH, and TSH are comprised of two dissimilar, non-covalently bound α and β subunits. The α subunit is coded by a single gene ((35–37)). The β subunits differ in structure and confer specificity of biologic action. There is no significant bioactivity without α–β subunit association. Both subunits possess N-linked oligosaccharide chains which are found at consensus glycosylation sequences, ie, Asn–X–Thr, as generalized in Figure 2. Depending on the species and the hormone, both carbohydrate chains can terminate in sialic acid, sulfate, or a combination of both. A variety of complex glycosylation variants can occur, giving rise to closely related isoforms of LH, FSH, and TSH ((38–41)). There is a convincing body of evidence showing the importance of glycosylation on the biopotency of these hormones. Terminal sialic acid moieties create acidic, low pI, glycoprotein isoforms ((42, 41–43)). Sialic acids prolong hormone half-life in the circulation (45, 46), which confers significant *in vivo* potency (46, 47). Glycoprotein subunits have no free sulfhydryl moieties. Technical limitations have hindered the complete assignment of disulfide bridges, but the following assignments are likely correct: α11–35, α14–36, β93–100, β26–110, and perhaps β23–72 (48). A disulfide bond between β38–57 also has been reported for human chorionic gonadotropin, a placental LH-like hormone (49), and ovine LH [9002-67-9] (50).

Relative to other species, human glycoprotein α subunit has a 4 amino acid deletion between positions 6 and 9. A deletion spanning positions 1 and 6 exists in the porcine α subunit. A comparison of the primary structures of glycoprotein hormone subunits among species has been reviewed (48, 51). The α subunit possesses two carbohydrate moieties, Asn-56 and 82 (Fig. 3). The carbohydrate component of the α subunit is essential for post-receptor signal transduction. Deglycosylation of the α subunit increases receptor binding potency, but virtually eliminates the bioactivity of LH (52). Sites of the α subunit which participate in receptor binding may lie between amino acid positions 30–55 and 80–96 (48).

One glycosylation site exists on the β subunits of human LH [53664-53-2] and TSH [64365-92-0], ie, Asn-30 (Fig. 4). In some species, Asn-13 of LH-β is glycosylated (48). FSH-β subunit [58857-12-8] is glycosylated at two

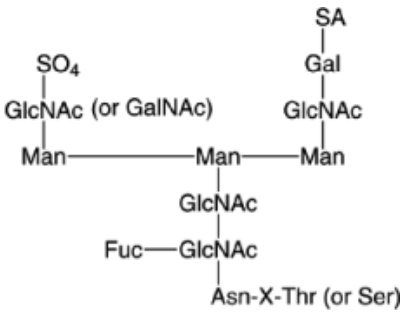

Fig. 2. Generalized structure of N-linked oligosaccharide of the pituitary glycoprotein hormones. SO_4=sulfate, GlcNAc=*N*–acetylglucosamine, GalNAc=*N*–acetylgalactosamine, Man=mannose, Fuc=fucose, SA=sialic(neuraminic) acid.

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1                                                              15
Ala-Pro-Asp-Val-Gln-—-—-—-—Asp-Cys-Pro-Gly-Cys-Thr-
16                                                             30
Leu-Gln-Glu-Asn-Pro-Phe-Phe-Ser-Gln-Pro-Gly-Ala-Pro-Ile-Leu-
31                                                             45
Gln-Cys-Met-Gly-Cys-Cys-Phe-Ser-Arg-Ala-Tyr-Pro-Thr-Pro-Leu-
46                                          ┌CHO                60
Arg-Ser-Lys-Lys-Thr-Met-Leu-Val-Gln-Lys-Asn-Val-Thr-Ser-Glu-
61                                                             75
Ser-Thr-Cys-Cys-Val-Ala-Lys-Ser-Tyr-Asn-Arg-Val-Thr-Val-Met-
76                                                             90
Gly-Gly-Phe-Lys-Val-Glu-Asn-His-Thr-Ala-Cys-His-Cys-Ser-Thr-
91                96
Cys-Tyr-Tyr-His-Lys-Ser
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Fig. 3. Human LH, FSH, and TSH α subunit [69431-84-1]. Amino acid numbering is relative to maximum homology between species (48). Note the 4 amino acid deletion in human α subunit between positions 6 and 9. Consensus glycosylation sites are at Asn-56 and 82. CHO=carbohydrate chain.

sites, Asn-13 and 30. Based on interactions of synthetic peptides with the LH receptor, loops formed by β93–100 and β38–57 may be essential for hormone bioactivity (48). Highly conserved sequences between residues 31–37 have been implicated in the formation of the α–β subunit dimer (48), which is absolutely necessary for the expression of bioactivity.

Preparations of FSH, usually containing equal or greater quantities of LH, are used for superovulation, ie, the production of a large number of ova, in human medicine and domestic animal production. Schering-Plough, U.S.A., and Vetipharm, Canada, market FSH for use in domestic animals. Preparations of FSH used in human fertility control are produced by two European companies, Serono and Organon; Serono produces the only FSH/LH approved for use in the United States. Luteinizing hormone does not have significant commercial value in the induction of ovulation in women since human chorionic gonadotropin (hCG) (see Hormones, anterior pituitary-like hormones) exerts potent LH activity, is resistant to biological degradation, and is readily available. A preparation of porcine LH [9061-23-8] is produced by Vetipharm, Canada; however, many superovulation procedures use gonadotropin-releasing hormone (GnRH) analogues rather than LH to induce ovulation. Gonadotropin-releasing hormone is a hypothalamic peptide which stimulates the pituitary to release LH and FSH. The use of recombinant DNA technology for the production of LH and FSH is being explored, and commercial preparations (ca 1993) of LH and FSH are derived from natural sources.

Thyroid-stimulating hormone can be used clinically to test thyroid function but has not found practical application in the treatment of human thyroid insufficiency. Direct replacement therapy with thyroid hormone

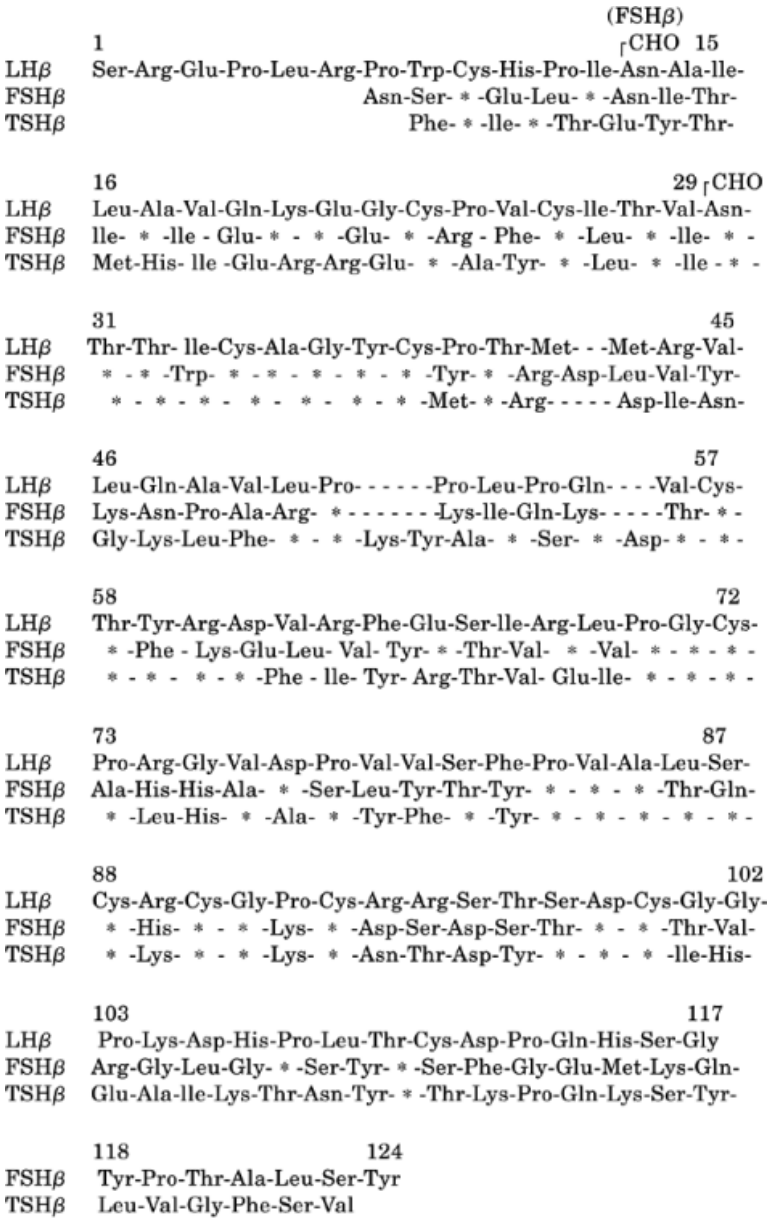

Fig. 4. Human LH, FSH, and TSH β subunits. Amino acid numbering is relative to maximum homology between the three subunits. Consensus glycosylation sites are at Asn-13 and 30. Note that carbohydrate attachment at Asn-13 only occurs in human FSH β. *indicates same amino acid as LHβ. CHO=carbohydrate chain (see Fig. 3).

is easy and effective, owing to a simple molecular structure. TSH has been used in the veterinary treatment of hypothyroidism, and preparations of TSH are produced by Cooper Animal Health, Inc. and Armour Pharmaceuticals.

Names are necessary to report factually on available data; however, the U.S. Department of Agriculture neither guarantees nor warrants the standard of the product, and the use of the name by the U.S. Department of Agriculture implies no approval of the product to the exclusion of others that may also be suitable.

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