UG CBCS Semester-IV (MJC-7: Endocrinology)
Chemical nature and physiological actions of hormones
Pituitary (Adenohypophysis)

TROPIC HORMONES OF THE ADENOHYPOPHYSIS

Numerous bioassays have been developed for quantitatively measuring tropic hormone activity, although current techniques for measuring gene action and immunological identification procedures generally have superseded the use of bioassays.

The tropic hormones are separable into three distinct chemical categories (Table 4-5). The hormones within each category exhibit considerable overlap in chemical structures (that is, amino acid sequences) and in some cases overlap in biological activities as well, especially when administered in pharmacological doses. Category I includes the glycoprotein hormones (GpHs): TSH, FSH, and LH. Each of these hormones is composed of two polypeptide subunits, each containing specific carbohydrate moieties. GH and PRL constitute the category 2 tropic hormones. Both PRL and GH are fairly large, folded polypeptide chains, and they exhibit considerable structural and some functional overlap. Category 3 includes smaller peptides: ACTH, a-MSH, LPH, and endorphins. These category 3 molecules have a common prohormone, have overlapping amino acid sequences, and exhibit some overlap in their biological actions. In addition to pituitary tropic hormones, certain tropic hormones of similar chemical structure and biological activity are produced in the placental mammals. As many as five tropic-like hormones have been isolated from the chorionic (fetal) portion of the placenta, including chorionic gonadotropin (CG), which is primarily LH-like in both structure and function, and chorionic somatomammotropin (CS), which has some GH but mostly PRL-like activity. A variant pituitary GTH that occurs in postmenopausal women is called menopausal gonadotropin (MG). Human MG is basically FSH-like and is produced by the postmenopausal adenohypophysis. Large amounts are secreted in response to failure of the ovaries to produce adequate levels of estrogens.

TABLE 4-5 Chemical Categories of Some Placental Peptide/Protein Hormones

Category	Name	Site of Synthesis
I	Thyrotropin (TSH)	Adenohypophysis: pars distalis
	Luteinizing hormone (LH)	Adenohypophysis: pars distalis
	Follicle-stimulating hormone (FSH)	Adenohypophysis: pars distalis
	Chorionic gonadotropin (CG)	Placenta
	Chorionic thyrotropin (CTSH)	Placenta
	Menopausal gonadotropin (MG)	Adenohypophysis: pars distalis
II	Growth hormone (GH)	Adenohypophysis: pars distalis; placenta
	Prolactin (PRL)	Adenohypophysis: pars distalis; placenta
	Chorionic somatomammotropin (CS)	Placenta
III	Corticotropin (ACTH)	Adenohypophysis: pars distalis
	α-Melanotropin (α-MSH)	Adenohypophysis: pars intermedia
	β-Endorphin	Adenohypophysis: pars distalis and pars intermedia
	Chorionic corticotropin (CC)	Placenta

A. Category I Tropic Hormones

All of the mammalian GpH tropic hormones examined to date are composed of two peptide subunits with an assortment of carbohydrate moieties attached. Molecular weights for these glycoproteins are about 32 kDa. The biological half-lives for TSH and LH in mammals are about 60 minutes, whereas that of FSH is about 3× longer. The longer half-life for FSH is attributed at least in part to differences in its unique carbohydrate components.

Glycoprotein hormones also show considerable specificity in their carbohydrate composition. For example, FSHs contain larger quantities of sialic acid than do the others, and the sialic acid is largely associated with the FSHβ-subunit. Sialic acid protects FSH from rapid degradation by the liver. Treatment of FSH with the enzyme neuraminidase selectively removes sialic acid, reduces the biological activity of FSH, and allows it to be degraded more rapidly.

1. LH Actions

Synthesis of androgens in both males and females is caused by LH action on the testes and ovaries. It also can be caused by CGs. LH acts through a membrane-bound G-protein-based receptor (GPCR) connected to a cAMP second-messenger system. Gamete release (sperm release in males and ovulation in females) also is under the control of LH. In females, LH causes formation of the corpus luteum from the ruptured ovarian follicles remaining after ovulation and also may stimulate the corpus luteum of the ovary to secrete progesterone.

Because three pituitary tropic hormones were named for their actions in females (PRL, FSH, and LH), an effort was mounted some years ago to rename LH for its action on the androgen-producing cells that occur between the seminiferous tubules of the testis rather than for inducing corpus luteum formation (luteinization) in the female. Hence, it was suggested that LHbe renamed the interstitial cell-stimulating hormone (ICSH) for its action on the steroidogenic interstitial cell of the testis (also called the Leydig cell) and the interstitial cell of the ovary. Although the use of ICSH occurs sporadically in the literature, LH has prevailed and is used today by most endocrinologists.

2. FSH Actions

Like LH, FSH binds to its GPCR and stimulates cAMP production as a second messenger. Whereas the major actions for LH are stimulation of androgen synthesis and gamete release in both sexes, FSH is primarily involved with gamete preparationdthat is, ovarian follicle development in females and spermatogenesis in males. In females and to a lesser extent in males, FSH also stimulates the conversion of androgens into estrogens through the induction of the enzyme P450aro. This enzyme also is very important in converting androgens to estrogens in the male brain.

3. TSH Actions

TSH also operates via a GPCR connected to a cAMP dependent mechanism to increase synthesis of thyroid hormones, cause release of stored thyroid hormones, and secondarily increase iodide uptake by cells of the thyroid. However, these measurements provide no consistent information concerning rates of thyroid hormone synthesis and release.

Humans may produce variant TSHs, one of which is associated with a pathological condition known as Graves' disease. Normal hTSH has a biological half-life of about 0.25 hours. The so-called long-acting thyroid stimulator (LATS) in Graves' disease has a biological half-life of 7.5 hours. Furthermore in rats, TSH causes maximal radioiodide uptake in 4 hours whereas LATS continues to produce elevated uptake 12 hours after administration. LATS is not a product of the pituitary but is an aberrant immunoglobulin that is not influenced by negative feedback of elevated thyroid hormones.

B. Category 2 Tropic Hormones

Two pituitary tropic hormones, GH and PRL, plus the placental tropic hormone, CS, comprise category 2. Multiple copies of the genes for hGH and hCS are found in humans on chromosome 17, whereas multiple copies of the hPRL gene occur on chromosome 6. Hence, multiple forms may occur in the plasma of one individual. PRL and GH are large, single polypeptide hormones of similar structure and molecular weight (about 22 to 23 kDa). Human CS is similar to both hGH and hPRL, although in other mammals CS may be structurally more like PRL than GH. There is an 85%homology between hGH and hCS as well as considerable overlap with hPRL, hence the name "somatomammotropin."

CS also is known as placental lactogen, but this older name, though still in use, does not reflect its GH like actions. It is estimated that duplication of the GH gene and evolution of the CS gene occurred between 85 and 100 MYBP. This is a relatively recent event compared to the separation of the GH and PRL genes, estimated to have occurred about 400 MYBP in non-mammals. The human placenta also produces the pituitary forms of GH and PRL. Placental PRL accumulates in amniotic fluid. A smaller (16 kDa) variant of pituitary PRL also has been isolated from the rat placenta. A 20-kDa variant of pituitary hGH is screted during the second half of pregnancy.

1. GH Actions

Growth hormone is often described as a protein anabolic hormone because it stimulates incorporation of amino acids into proteins and has a negative effect on nitrogen excretion. Growth hormone represents about one-half of the total hormone content of the human adenohypophysis, which emphasizes its importance in adults as well as during the years of maximal growth. It has been characterized chemically as a protein composed of 191 amino acids having a biological half-life in blood of 20 to 40 minutes. Growth hormone stimulates transport of amino acids intoccells and stimulates protein synthesis, especially by skeletalcmuscle cells. It cooperates with insulin to channel aminocacids, fatty acids, and carbohydrates into storage followingca meal. Furthermore, GH becomes an important regulator of blood glucose and amino acid utilization in the absence of insulin during short-term and long-term starvation. Circulating levels of hGHare highest during the period of maximal growth (ages 2 to 17 years). A daily secretory rhythm becomes established at about 4 years of age and continues throughout adult life. This pattern of GH secretion is both irregular and spontaneous, depending upon the physiological state of the individual, but episodes of GH release are frequently correlated with the onset of deep sleep.

Optimal growth-promoting actions of GH are obtained in hypophysectomized animals only when thyroid hormones are administered together with GH. This relationship between thyroid hormones and GH has been described as a synergism; that is, the growth response elicited by combined therapy with thyroid hormones and GH in hypophysectomized animals is greater than predicted by adding together the responses obtained with each hormone administered alone. Either thyroid hormones or GH will reinitiate some growth in hypophysectomized animals, but complete resumption of normal growth requires combined therapy. Furthermore, intact animals that exhibit thyroid deficiencies grow slowly and abnormally.

Thyroid hormones may influence synthesis of GH in intact rats but act peripherally to enhance GH potency in hypophysectomized animals. Thyroid hormones maintain a "responsive state" in target cells so they are more sensitive to GH and other regulators.

The effects of steroid hormones on growth are complex. Androgens and estrogens can increase the responsiveness of human tissues to hGH but to a lesser extent than do thyroid hormones. The mechanism of this steroid effect is not understood. Steroids, especially androgenic ones, have important effects on amino acid and carbohydrate metabolism unrelated to the roles of GH. Androgens are known to stimulate protein synthesis and hypertrophy of skeletal muscle, and estrogens selectively increase protein synthesis in the uterus. Conversely, the increase in androgens and estrogens associated with the onset of puberty causes cessation in proliferation of the epiphyseal plates at the ends of long bones of the appendicular skeleton and render these tissues unresponsive to GH. This results in a permanent cessation of growth in stature. Direct metabolic actions of GH on protein synthesis, amino acid transport, and lipolysis have been reported in several tissues. However, these growth effects of GH are mediated indirectly by the GH-stimulated production of two peptide regulators in the liver or, in some cases, directly in target tissues. These peptides were first called sulfation factors because of effects on incorporation of sulfate into cartilage during GH-stimulated cartilage growth, a phenomenon that could not be invoked by direct application of GH to cartilage cells in vitro. Later, they became known as somatomedins, as they mediated the actions of the somatotropic hormone, GH. We now know that these peptide growth stimulators are structurally related to insulin and have some insulin-like activity, in addition to their growth-promoting actions, due to their ability to bind to the insulin receptor. Later, they acquired the names of insulin-like growth factors (IGF-I, IGF-II).

IGF-II is secreted primarily during fetal growth, and IGF-I is secreted primarily in children and adults. The IGF-I receptor is a tyrosine kinase membrane receptor and acts by phosphorylating a variety of proteins in different target cells. The liver, then, can be considered a target endocrine gland for GH because it synthesizes and releases IGFs into the circulation, thus constituting the HPH axis. IGFs are transported in the blood while complexed to specific plasma IGF-binding proteins.

2. Prolactin Actions

Prolactin consists of a single chain of 199 amino acids (23 kDa) and, like GH, occurs as multiple isohormones. It produces a variety of distinctive actions in animals, including effects associated with reproduction, growth, osmoregulation, and the integument. Furthermore, PRL may produce synergistic actions with ovarian, testicular, thyroid, and adrenal hormones. The best-known action for PRL is the lactogenic effect on the mammary gland of females for which the hormone was named. PRL stimulates DNA synthesis, cellular proliferation, and the synthesis of milk proteins (casein and lactalbumin), free fatty acids, and lactose by the glandular epithelium of the mammary gland. hCS from the placenta produces a similar effect. In some species (e.g., rat, sheep), PRL may influence the synthesis of progesterone by the corpus luteum of the postovulatory ovary. This action was responsible for the older name for PRL, luteotropic hormone (LTH). There also is evidence in male mammals for effects of PRL on certain sex accessory structures.

Like the situation for GH, PRL actions on the mammary gland and possibly on other targets involve an interaction with additional hormones. Estrogens favor cell proliferation and growth of the mammary gland, making the mammary more responsive to PRL. Glucocorticoids also potentiate the actions of PRL in all species examined. Progesterone inhibits PRL actions on the mammary gland and can block lactogenesis. One hypothesis suggests that progesterone competes for glucocorticoid binding and/or blocks gene activation by glucocorticoids. The

stimulatory actions of insulin on the mammary gland may be related to its IGF-like activity that mimics an action of PRL.

C. Category 3 Tropic Hormones

This category comprises several hormones derived from the same precursor, a prohormone known as proopiomelanocortin (POMC) and includes ACTH, a-MSH, LPH, and the EOP β-endorphin. POMC-related peptides are found in cells of the brain, the pars distalis, and the pars intermedia (when this pituitary lobe is present). All of the category 3 molecules produced in the pituitary are a result of variations in posttranslational processing of POMC, and some products exhibit considerable overlap in their biological activities due to possession of similar amino acid sequences.

In the pars intermedia melanotropes, additional posttranslational modification of POMC end products occurs after prohormone convertase action on POMC. The C-terminus of a-MSH and b-endorphin are amidated by the enzyme peptidylglycine alpha-amidating monooxygenase (PAM). PAM and its isoforms also play an important role in amidating neuropeptides in hormone- and neurohormone-producing cells through the body. The N-termini of a-MSH and b-endorphin are acetylated by an interaction with N-acetyltransferase and acetyl coenzyme A. Virtually all of the a-MSH and b-endorphin secreted by melanotropes is acetylated prior to release. Interestingly, N-acetylation of b-endorphin eliminates the ability of this peptide to bind to mu (morphine) opioid receptors, thus eliminating its potency as an analgesic peptide.

1. Melanotropin (a-MSH)

In mammals, the epidermal melanin-producing cell is the melanocyte that synthesizes melanin under the influence of a-MSH but extrudes it into the extracellular compartment where it is accumulated in keratinocytes (keratin-containing epithelial cells). a-MSH acts on the melanocortin-1 receptor (MC1R) to stimulate cAMP and melanin synthesis in melanocytes. Animals that change from a white winter coat to a brown summer coat employ the services of a-MSH to stimulate melanin production for the summer coat. Hypophysectomy of the short-tailed weasel during the winters causes the summer coat to be white like the winter coat. Treatment of hypophysectomized weasels with either a-MSH or ACTH (which has some inherent a-MSH-like action) is sufficient to cause regrowth of the normal brown summer coat. The adenohypophyses of all vertebrates tested by bioassay possess a-MSH activity, including some mammals and all birds that lack a pars intermedia. This activity may reside in ACTH or possibly in LPH that also contains some MSH-like sequences. As mentioned above, α-MSH and CLIP are released following the hydrolysis of ACTH in melanotropes. α-MSH usually is acetylated prior to release, slowing its degradation and increasing its biological activity. It is not possible to distinguish MSH-like activity caused by α-MSH or by ACTH or ACTH fragments that also bind readily to α-MSH receptors and activate them. The physiological roles for a-MSH in pigmentation are not known in birds or in most mammals, but a role in feeding behavior has been observed.

2. Corticotropin (ACTH)

Corticotropin acts on a G-protein-coupled receptor called the melanocortin-2 receptor (MC2R) and stimulates the adrenal cortex to secrete glucocorticoids (cortisol and/or corticosterone), hormones that alter protein and carbohydrate metabolism. ACTH purified from several mammalian sources (e.g., bovine, porcine, ovine, human) consists of 39 amino acids in a single

peptide chain with a molecular weight of about 4500. Amino acids 1 to 23 of ACTH have full biological activity at the MC2R, 1 to 19 have 80% of full activity, but the fragment 1 to 16 has very little ACTH biological activity. Amino acids 24 to 39 are obviously outside of that region of the molecule responsible for its biological activity. All ACTH fragments containing residues 1 to 13 also have a-MSH activity because of the 'message' sequence His-Phe-Arg-Trp. Hence, although CLIP has considerable amino acid homology to part of the intact ACTH molecule, it has no ACTH-like or a-MSH-like biological activity because it lacks the essential first 13 amino acids. The presence of multiple-sized fragments of ACTH39 in the circulation has implications for the efficacy of RIA procedures for both ACTH and a-MSH with antibodies that may or may not have overlapping affinities.

3. Lipotropins (LPHs)

In addition to its role as a precursor for endorphins, LPHs have been proposed as hormones that stimulate lipolysis in adipose tissue (that is, hydrolysis of fats to free fatty acids and glycerol). Lipotropins, presumably of pituitary origin, have been identified in the systemic circulation, but levels of circulating LPHs have not been linked to observed changes in lipid metabolism, leaving open the question of any physiological role for LPHs. Other lipolytic hormones appear to be much more potent than the LPH peptides, further questioning their importance as lipolytic factors in vivo. LPHs may have some importance as sources for the production of endorphins.

4. The Endorphins and Enkephalins

Morphine is an opiate analgesic (pain-killing) drug that binds to mu opiate receptors in the central nervous system. Scientists postulated that there also would be endogenous compounds that produce analgesic opiate-like (morphine) effects on the central nervous system. A search for endogenous analgesics has resulted in identification and chemical characterization of two groups of EOPs. The larger EOPs include the dynorphins, β-endorphin, and some C-terminal hydrolysis products of β-endorphin that are acetylated at the N-terminal end. However, as mentioned previously, these additional alterations to β-endorphin markedly reduce its analgesic properties. The pentapeptide enkephalins also bind to opioid receptors. The distribution of endorphins in the pituitary and central nervous system parallels that observed for ACTH and LPHs, indicating that they are products of POMC hydrolysis. The enkephalins and dynorphins are produced from different prohormones by separate sets of neurons. Painful stimuli elevate levels of endorphins and enkephalins in the CSF, and they appear to exhibit the features required for endogenous opiate-like agents. The endorphins function as neuromodulators or neurotransmitters within the central nervous system through their morphine-like actions. The action of morphine, a non-peptide, is blocked by closely related pharmaceuticals such as naloxone. The effects of endorphins also are blocked by naloxone, implying closeness in mechanisms of action for morphine and the endorphins that bind to similar receptors. Three types of opioid receptors have been identified with differing affinities for the various opioids. In addition to their involvement with pain perception, endorphins influence release of neurotransmitters affecting tropic hormone release and can inhibit OXY release.

References

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