

MEDICINAL CHEMISTRY

Chemotherapy: Protein and Polypeptide Hormones

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Keywords

Corticotrophic hormone, somatotropin, hCG, FSH, LH, TSH, insulin, glucagon, GIT-hormones, oxytocin, vasopressin, PTH, peptides.

Nomenclature

1. General Principles: Naturally occurring oligo- and polypeptides are generally referred to by trivial names; their systematic names are so cumbersome that they are of little use. Most of the peptide hormones already have well-established trivial names indicating either natural source (e.g. insulin) or physiological action (e.g. relaxin, prolactin). However, some of the trivial names are so long that these hormones are known mainly by abbreviations (e.g. FSH for follicle-stimulating hormone). This is unfortunate, and it was therefore considered advisable to create suitable names for those peptide hormones not already having well established short trivial names. Three principles have been observed:

- (a) New names for hormones of the adenohypophysis bear the ending "-tropin";
- (b) Hypothalamic releasing factors (hormones) bear the ending "-liberin";
- (c) Hypothalamic release-inhibiting factors (hormones) bear the ending "-statin".

2. Trivial Names: The trivial names proposed for peptide hormones are given in the "Appendix." Abbreviations of the new names are not proposed, and the use of currently fashionable abbreviations is discouraged.

3. Species Designation: Since peptide hormones show species variation in their amino-acid sequence, their names are essentially "generic names", and are insufficient to specify a single chemical compound. It is therefore recommended that authors add to the name of each hormone the species from which the hormone was isolated, or at least indicate the biological source(s) where appropriate.

4. Special Groups of Hormones

a) **Hypothalamic Factors** (Hormones) - The hypothalamic "releasing factors" or "releasing hormones" have no well established trivial names. It is recommended that the trivial names given in the "Appendix" be used for the releasing factors (hormones). They are based on the ending "-liberin" added to the prefix of the pituitary hormone released by the factor. Thus, "thyroliberin" indicates the hypothalamic peptide stimulating the release (and perhaps also the biosynthesis) of thyrotropin, the corresponding tropic hormone, from the pituitary gland. (Note that the ending "-tropin" is no longer retained in the name; it is implied in the definition of "-liberin").

The names of those factors inhibiting the release (and perhaps the synthesis) of pituitary hormones are formed in a similar way with the suffix "-statin".

(b) **Pituitary Hormones** - Most of the hormones of the adenohypophysis have acceptable trivial names ending in -tropin. Follicle-stimulating hormone is known as "follitropin," and luteinizing hormone as "lutropin." It is recommended that pituitary hormones discovered in the future also be named with the ending -tropin. This suffix is restricted to pituitary and similar hormones and should not be used for, e.g. crustacean hormones acting on pigment cells.

Some placental hormones are physiologically very similar to pituitary hormones. They are named accordingly with the prefix "chorio-", e.g. choriogonadotropin for chorionic gonadotropin.

(c) **Invertebrate Peptide Hormones** -Though some of the invertebrate peptide hormones have been isolated in pure form and their amino acid compositions have been determined, the field has not yet developed to a stage where a list of names seems warranted.

It is, however, recommended that the suffixes defined above for hypothalamic and pituitary hormones are not used in invertebrates. Thus, a crustacean color change hormone acting on, e.g. erythrophores, should not be named "erythrotropin," a hormone causing release of eggs and/or sperm in sea urchins should not be called "gametoliberin."

List of Peptide Hormones^a

Trivial name	Other names	Current abbreviation^b
1. Hypothalamic Factors		
Corticoliberin	Corticotropin-releasing factor	CRF
Folliberin	Follicle-stimulating-hormone-releasing factor	FSH-RF
Gonadoliberin ^c	Gonadotropin-releasing factor	(LH/FSH-RF)
Luliberin	Lutemizing hormone-releasing factor	LH-RF (LRF)
Melanoliberin	Melanotropin-releasing factor	MFR
Melanostatin	Melanotropin release-inhibiting factor	MIF
Prolactoliberin	Prolactin-releasing factor	PRF
Prolactostatin	Prolactin release-inhibiting factor	PIF
Somatoliberin	Somatotropin-releasing factor; growth hormone-releasing factor	SRF GH-RF
Somatostatin	Somatotropin release-inhibiting factor	
Thyroliberin	Thyrotropin-releasing factor	TRF
2. Pituitary and Related Hormones		
Choriogonadotropin ^d	Chorionic gonadotropin	CG
Choriomammotropin	Chorionic somatomammotropin	CS
Corticotropin	Adrenocorticotrophic hormone	
Follitropin	Follicle-stimulating hormone	FSH
Gonadotropin ^e	Gonadotropin hormone	
Glunitocin ^f	Ocytocin ^j	
Isotocin ^g	Ocytocin ^j	
Lipotropin	Lipotrophic hormone	LPH
Lutropin	Luteinizing hormone; (Interstitial cell-stimulating hormone)	LH (ICSH)

Melanotropin ^h	Melanocyte-stimulating hormone	MSH
Mesotocin ⁱ	Ocytocin ^j	
Ocytocin ^j (Oxytocin)		OXT
Prolactin	Mammatropic hormone; mammatropin; lactotropic hormone; lactotropin	PRL
Somatotropin	Somatropic hormone; growth hormone	STH GH
Thyrotropin	Thyrotropic hormone	TSH
Urogonadotropin ^k	(Human) Menopausal gonadotropin	HMG
Vasopressin	Adiuretin; antidiuretic hormone	VP, ADH
Vasotocin	Ocytocin ^j	

3. Other Peptide Hormones

Angiotensin	Angiotensin II	
Bradykinin	Kinin-9	
Calcitonin	Thyrocalcitonin	
Erythropoietin		
Gastrin		
Gastrin sulphate	Gastrin II	
Glucagon	Hyperglycemic factor	(HGF)
Insulin		
Kallidin	Kinin-10	
Pancreozymin	Cholecystokinin	
Parathyrin ^l	Parathyroid hormone; Parathormone	
Proangiotensin	Angiotensin I	
Relaxin		
Secretin		
Somatomedin ^m	Sulfation factor	
Thymopoietin ⁿ	Thymine	

^a For convenience, some biologically active peptides that may not fulfill all criteria of a hormone are included.

^b Abbreviations, old or new, are not recommended; they are given here for identification purposes only.

^c This name indicates a hypothalamic substance releasing gonadotropin. It may also be used for the decapeptide isolated from pig hypothalamus and known as luteinizing hormone/follicle-stimulating hormone releasing factor, abbreviated LH/FSH-RF,^b since the peptide induces the release of both lutropin and follitropin in constant proportions and thus carries the activity of both luteinizing hormone and follicle-stimulating hormone (see also Footnote ^e).

^d The chorionic gonadotropins have in most species (including man) the action of both follitropin and lutropin and are therefore termed "gonadotropins."

^e Gonadotropin is to be used for hormones having the activity of both follitropin and lutropin, like the gonadotropins of cold-blooded vertebrates. It may also be used for impure preparations containing lutropin and follitropin.

^f In elasmobranch fishes.

^g In bony fishes.

^h Two peptides have been sequenced and designated α -melanotropin and β -melanotropin.

ⁱ In birds and reptiles.

^j The name of this hormone is derived from Greek $\omega\kappa\upsilon\tau\omicron\kappa\omicron\varsigma$ (OKYTOKOS = fast birth, prompt delivery), not from the Greek $\omicron\zeta\upsilon\varsigma$ (oxys = acid; fast). The spelling ocytocin should therefore be preferred; moreover, it avoids confusion with oxy, meaning "related to oxygen." However, oxytocin is in wide use, especially in the English language. Therefore, both spellings are listed as optional.

^k Most work has been done on the human hormone, known as Human Menopausal Gonadotropin (HMG); it is a pituitary hormone, chemically changed during passage through the kidney. Due to its occurrence in urine, it has been termed "urogonadotropin."

^l Parathyrin is a new name suggested here. The synonym Parathormone is a proprietary name.

^m The name "somatomedin" was suggested by a group working in the field (*Nature* **235**, 107 (1972)).

ⁿ A polypeptide from the thymus. The name proposed was suggested in a letter to *Nature* (**249**, 863 (1974)) to avoid confusion with the earlier "thymine" from nucleic acids. "Thymin" should be abandoned.

Structure and Function of Hormones

The integration of body functions in humans and other higher organisms is carried out by the nervous system, the immune system, and the endocrine system. The endocrine system is composed of a number of tissues that secrete their products, called endocrine hormones, into the circulatory system; from there they are disseminated throughout the body, regulating the function of distant tissues and maintaining homeostasis. In a separate but related system, exocrine tissues secrete their products into ducts and then to the outside of the body or to the intestinal tract.

Classically, endocrine hormones are considered to be derived from amino acids, peptides, or sterols and to act at sites distant from the tissue of their origin. However, the latter definition has begun to blur as it is found that some secreted substances act at a distance (classical endocrines), close to the cells that secrete them (paracrines), or directly on the cell that secreted them (autocrines). **Insulin-like growth factor-I (IGF-I)**, which behaves as an endocrine, paracrine, and autocrine, provides a prime example of this difficulty.

Hormones are normally present in the plasma and interstitial tissue at concentrations in the range of 10^{-7} M to 10^{-10} M. Because of these very low physiological concentrations, sensitive protein receptors have evolved in target tissues to sense the presence of very weak signals. In addition, systemic feedback mechanisms have evolved to regulate the production of endocrine hormones. Once a hormone is secreted by an endocrine tissue, it generally binds to a specific plasma protein carrier, with the complex being disseminated to distant tissues. Plasma carrier proteins exist for all classes of endocrine hormones.

Tissues capable of responding to endocrines have 2 properties in common: they possess a receptor having very high affinity for hormone, and the receptor is coupled to a process that regulates metabolism of the target cells. Receptors for most amino acid--derived hormones and all peptide hormones are located on the plasma membrane. Activation of these receptors by hormones (the first messenger) leads to the intracellular production of a second messenger, such as cAMP, which is responsible for initiating the intracellular biological response. Steroid and thyroid hormones are hydrophobic and diffuse from their binding proteins in the plasma, across the plasma membrane to intracellularly localized receptors. The resultant complex of steroid and receptor bind to response elements of nuclear DNA, regulating the production of mRNA for specific proteins.

Receptors for Peptide Hormones

With the exception of the thyroid hormone receptor, the receptors for amino acid-derived and peptide hormones are located in the plasma membrane. Receptor structure is varied: some receptors consist of a single polypeptide chain with a domain on either side of the membrane, connected by a membrane-spanning domain. Some receptors are comprised of a single polypeptide chain that is passed back and forth in serpentine fashion across the membrane, giving multiple intracellular, transmembrane, and extracellular domains. Other receptors are composed of multiple polypeptides. For example, the insulin receptor is a disulfide-linked tetramer with the β subunits spanning the membrane and the α subunits located on the exterior surface.

Subsequent to hormone binding, a signal is transduced to the interior of the cell, where second messengers and phosphorylated proteins generate appropriate metabolic responses. The main second messengers are cAMP, Ca^{2+} , inositol triphosphate (IP_3), and diacylglycerol (DAG). Proteins are phosphorylated on serine and threonine by cAMP-dependent protein kinase (PKA) and DAG-activated protein kinase C (PKC). Additionally a series of membrane-associated and intracellular tyrosine kinases phosphorylate specific tyrosine residues on target enzymes and other regulatory proteins.

The hormone-binding signal of most, but not all, plasma membrane receptors is transduced to the interior of cells by the binding of receptor-ligand complexes to a series of membrane-localized GDP/GTP binding proteins known as G-proteins. When G-proteins bind to receptors, GTP exchanges with GDP bound to the α subunit of the G-protein. The G_α -GTP complex binds adenylate cyclase, activating the enzyme. The activation of adenylate cyclase leads to cAMP production in the cytosol and to the activation of PKA, followed by regulatory phosphorylation of numerous enzymes. Stimulatory G-proteins are designated G_s , inhibitory G-proteins are designated G_i .

A second class of peptide hormones induces the transduction of 2 second messengers, DAG and IP_3 . Hormone binding is followed by interaction with a stimulatory G-protein, which is followed in turn by G-protein activation of membrane-localized phospholipase C- γ , (PLC- γ). PLC- γ hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to produce 2 messengers: IP_3 , which is soluble in the cytosol, and DAG, which remains in the membrane phase. Cytosolic IP_3 binds to sites on the endoplasmic reticulum, opening Ca^{2+} channels and allowing stored Ca^{2+} to flood the cytosol. There it activates numerous enzymes, many by activating their calmodulin or calmodulin-like subunits. DAG has 2 roles: it binds and activates protein kinase C (PKC), and it

opens Ca^{2+} channels in the plasma membrane, reinforcing the effect of IP_3 . Like PKA, PKC phosphorylates serine and threonine residues of many proteins, thus modulating their catalytic activity.

Hormones of Hypothalamic Origin

The hypothalamus, which is a relatively small organ that is located in the brain and responsible for thermoregulation, among other functions, is the secretory source of a number of peptide hormones that are transported to the pituitary gland situated immediately below it. These hormones regulate the synthesis of other peptide hormones produced by the anterior pituitary (adenohypophysis), and are thus called releasing hormones (RH) or releasing factors (RF), or inhibitory factors (IF), as the case may be. The release of these hypothalamic hormones is regulated via cholinergic and dopaminergic stimuli from higher brain centres, and their synthesis and release controlled by feedback mechanisms from their target organs.

Thyroliberin (Thyrotropin-Releasing hormone; TRH) is the hypothalamic hormone responsible for the release of the pituitary's thyrotropin. Thyrotropin stimulates thyroxine and liothyronin by the thyroid. The latter thyroid hormones, by feedback regulation, inhibit the action of TRH on pituitary. Thyroliberin is a relatively simple tripeptide that has been characterized as pyroglutamyl-histidyl-prolinamide. TRH possesses interesting biological properties. In addition to stimulating the release of thyrotropin, it promotes the release of prolactin. It also has some central nervous system effects that have been evaluated for antidepressant therapeutic potential.

Gonadoliberin, as the name implies, is the **gonadotropin-releasing hormone (Gn-RH)** (**Fig.1**), also known as **luteinizing hormone-releasing hormone (LH-RH)**. This hypothalamic decapeptide stimulates the releasing of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary. LH-RH is considered to be of potential therapeutic importance in the treatment of hypogonadotropic infertility in both males and females.

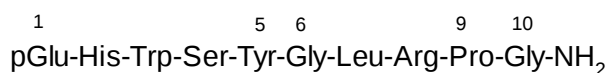


Fig. 1

It is known that GnRH can be degraded by preferential enzymatic cleavage between $\text{Tyr}^5\text{-Gly}^6$ and $\text{Pro}^9\text{-Gly}^{10}$. SAR studies of GnRH have shown that when Gly^6 is replaced with certain amino acids, as well as with changes in the peptide C-terminus, they usually undergo a reduced attack by proteolytic enzymes, resulting in a longer-lasting action and, for that reason, are referred to as superagonists. Moreover, when these D-amino acids at position 6 are hydrophobic, the half-life is enhanced.

Somatostatin is a tetradecapeptide possessing a disulfide bond linking two cysteine residues, 3-14, in the form of a 38-member ring (**Fig. 2**). Somatostatin suppresses several endocrine systems. It inhibits the release of somatotropin and thyrotropin by the pituitary. It also inhibits the secretion of insulin and glucagons by the pancreas. Gastrin, pepsin and secretin are intestinal hormones that are likewise affected by somatostatin.

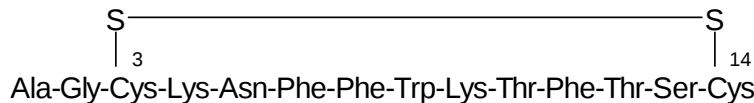


Fig. 2

Somatostatin has a shorter half-life (less than 3 minutes), and this, unfortunately, restricts its use as a therapeutic agent. Many derivatives of somatostatin have been prepared in order to increase its duration of action or to augment its selectivity of action. The culmination of these SAR studies has led to the development of octreotide acetate (**Fig. 3**), a longer-acting octapeptide analog of somatostatin, having a half-life of about 1.5 hours.

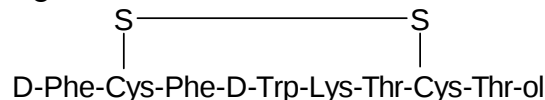


Fig. 3

Growth Hormone Releasing Factor (GRF) is a 44-residue-containing peptide, found in minute quantities in the hypothalamus. It is a positive effector in that it stimulates pituitary release of somatotropin.

Other hypothalamic hormones include the **luteinizing hormone release-inhibiting factor (LHRIF)**, **prolactin-releasing factor (PRF)**, **corticotropin-releasing factor (CRF)**, **melanocyte-stimulating hormone –releasing factor (MRF)**, and **melanocyte-stimulating hormone release-inhibiting factor (MIF)**.

Pituitary Hormones

The pituitary gland plays a major role in regulating activity of the endocrine organs, including the adrenal cortex, the gonads, and the thyroid. The posterior pituitary is responsible for the storage and secretion of hormones vasopressin and oxytocin, controlled by nerve impulses traveling from the hypothalamus. The anterior pituitary is under the control of hypothalamic regulatory hormones, and it secretes adrenocorticotrophic hormone (ACTH), growth hormone (GH), LH, FSH, prolactin, and others.

Table-1 summarizes the major hormones synthesized and secreted by the pituitary gland, along with summary statements about their major target organs and physiologic effects.

Table-1: Major hormones synthesized and secreted by the pituitary gland

	Hormone	Major target organ(s)	Major Physiologic Effects
Anterior Pituitary	Growth hormone	Liver, adipose tissue	Promotes growth (indirectly), control of protein, lipid and carbohydrate metabolism
	Thyroid-stimulating hormone	Thyroid gland	Stimulates secretion of thyroid hormones
	Adrenocorticotrophic hormone	Adrenal gland (cortex)	Stimulates secretion of glucocorticoids

	Prolactin	Mammary gland	Milk production
	Luteinizing hormone	Ovary and testis	Control of reproductive function
	Follicle-stimulating hormone	Ovary and testis	Control of reproductive function
Posterior Pituitary	Antidiuretic hormone	Kidney	Conservation of body water
	Oxytocin	Ovary and testis	Stimulates milk ejection and uterine contractions

The cells that secrete thyroid-stimulating hormone do not also secrete growth hormone, and they have receptors for thyroid-releasing hormone, not growth hormone-releasing hormone.

Careful examination of the pituitary gland reveals that it is composed of two distinctive parts:

- The **anterior pituitary or adenohypophysis** is a classical gland composed predominantly of cells that secrete protein hormones.
- The **posterior pituitary or neurohypophysis** is not really an organ, but an extension of the hypothalamus. It is composed largely of the axons of hypothalamic neurons, which extend downward as a large bundle behind the anterior pituitary. It also forms the so-called **pituitary stalk**, which appears to suspend the anterior gland from the hypothalamus.

Adrenocorticotrophic Hormone (ACTH, corticotrophin): ACTH is a very extensively studied single-chain peptide of 39 residues (**Fig. 4**). ACTH is secreted from the anterior pituitary in response to corticotropin-releasing hormone (CRH) from the hypothalamus, and is derived from a much larger precursor protein known as pro-opiomelanocortin, the latter is the precursor of the melanocyte-stimulating hormones (MSH). As the name implies, its major action is to regulate the function of the adrenal cortex. More specifically, it stimulates secretion of glucocorticoids such as cortisol, and has little control over secretion of aldosterone, the other major steroid hormone from the adrenal cortex.

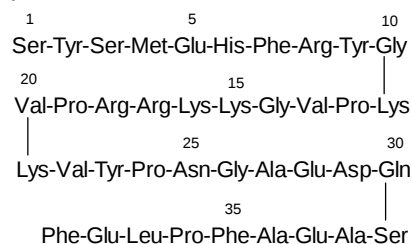


Fig. 4

The SAR studies of ACTH revealed that the COOH-terminal sequence is not particularly significant for biological activity. Removal of NH₂-terminal amino acid results in complete loss of steroidogenic activity. Complete activity has been reported for synthetic peptides containing the first 20 amino acids. A peptide containing 24 amino acids has full steroidogenic activity,

without allergenic reactions. This is significant since natural ACTH preparations at times cause clinically dangerous allergic reactions.

ACTH has a direct anti-inflammatory effect. It is not as potent as other anti-inflammatory agents, but has fewer side effects when the drug is withdrawn. ACTH may be better for long-term, low dose therapy in diseases such as rheumatoid arthritis, but it is normally prescribed for the treatment of multiple sclerosis. Withdrawal effects do exist, and they include malaise and intracranial hypertension.

Melanocyte stimulating hormone (MSH, Melanotropins) has no known function in mammals, but in reptiles and amphibians stimulate color changes in the epidermis. The receptors have been isolated are under study. Some speculate that it is involved in sleep, biorhythms, or pigmentation (note indicator of primary adrenal insufficiency below). MSH should not be confused with melatonin, a hormone produced by the pineal gland that stimulates lightening of skin in fish and amphibians and whose function in humans is also not well understood. Altered secretion of MSH has been implicated in causing skin pigmentation during the menstrual cycle and pregnancy. The two major types of melanotropin, α -MSH and β -MSH, are derived from ACTH and β -lipotropin, respectively.

α -MSH contains the same amino acid sequence as the first 13 amino acids of ACTH; β -MSH has 18 amino acid residues. A third melanotropin, γ -melanotropin, is derived from a larger peptide precursor, pro-opiomelanocortin (POMC).

Pro-opiomelanocortin (POMC) production is stimulated by Corticotropin-releasing hormone (CRH) of the hypothalamus. POMC is an ultra-cool 260 amino acid protein, which gets glycosylated (sugars added, probably at select arginine residues as for prolactin) and then cleaved to give a number of neurohormones. The anterior pituitary hormones, adenocorticotropin hormone (ACTH) and LPH (lipotropin hormone) are derived from POMC in the pars distalis of the anterior pituitary. In the pars intermedia area of the anterior pituitary, the ACTH derived from cleavage of POMC is cleaved further to produce α -MSH (melanocyte-stimulating hormone). Thus, POMC is processed differently in different areas of the pituitary. We can also get β -endorphin out of POMC cleavage, which means POMC is a source of an endogenous opiod peptide. In fact, POMC is the precursor to ACTH, α, β, γ -MSH, α, β, γ -endorphin, β -lipoprotein, and met-enkephalin. Besides the hypophysis (pituitary), the brain, gastrointestinal system, immune cells, placenta, and gonads are able to synthesize POMC products.

Lipotropins (Enkephalins and Endorphins) The isolation of two peptides with opiate like activity from pig brains was a breakthrough in the year 1975. These related pentapeptides, called **methionine-enkephalin** (Fig. 5) and **leucine-enkephalin** (Fig. 6), are abundant in certain terminals and have been shown to occur in the pituitary gland.

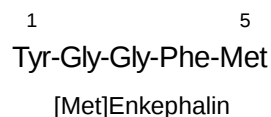


Fig. 5

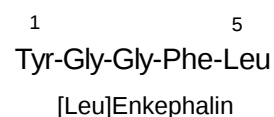


Fig. 6

The structure of enkephalins revealed that the amino acid sequence of met-enkephalin is identical with the sequence of residues 61-65 of β -lipotropin (β -LPH), a larger peptide found in the pituitary gland. This discovery suggested that β -LPH might be a precursor for other larger peptides containing the met-enkephalin sequence. Soon after the structural relationship between met-enkephalin and β -LPH was established, longer peptides, called **endorphins**, were isolated from the intermediate lobe of the pituitary gland. The endorphins (α , β and γ) contained the met-enkephalin amino acid sequence and possessed morphine like activity. **β -endorphin**, the longest of these peptides, is a 31 amino acid endogenous opiod peptide most important to the neuroendocrine regulation of human reproduction. Co-released with ACTH from the pituitary, β -endorphin is also produced in the medial-basal hypothalamus and widely distributed in the brain. Of the three major types of opiod receptors, μ , δ , and κ receptors, β -endorphin selectively binds μ receptors, the same that binds morphine with high affinity. Opioid μ receptors are mostly localized to the limbic system and hypothalamus. Opioid receptors regulate or modulate functions other than pain including temperature perception, hunger and thirst control, and reproduction. Only in the presence of steroids (such as estrogen or testosterone) can β -endorphin inhibit GnRH release from the mediobasal hypothalamus and consequently LH (leutinizing hormone) by the anterior pituitary. LH is important for ovulation.

The endorphins and enkephalins have a wide range of biological activities and most of their activities are in the CNS. They inhibit the release of dopamine in the brain tissue and acetylcholine from the neuromuscular junctions.

Growth Hormone (Somatotropin): Human placental lactogen (hPL), GH, and prolactin (PRL) comprise the growth hormone family. All have about 200 amino acids, 2 disulfide bonds, and no glycosylation. Although each has special receptors and unique characteristics to their activity, they all possess growth-promoting and lactogenic activity. Mature GH (22,000 daltons) is synthesized in acidophilic pituitary somatotropes as a single polypeptide chain. Because of alternate RNA splicing, a small amount of a somewhat smaller molecular form is also secreted.

While details of the method of signal transduction by the members of the GH family of tropic hormones remain unclear, PKC activity has been demonstrated to correlate directly with the biological effects of PRL and GH. This appears to indicate that the PKC signal transduction pathway is operative in transducing signals for the GH family of hormones.

The role of growth hormone in regulating IGF-1 production was noted above. Humans respond to natural or recombinant human or primate growth hormone with appropriate secretion of IGF-1, but growth hormone of other species has no normal biological effect in man. The latter is puzzling because interspecies GH homologies are quite high in many cases, and most other species respond well to human growth hormone. In humans, growth hormone promotes gluconeogenesis and is consequently hyperglycemic. It promotes amino acid uptake by cells, with the result that GH therapy puts an organism into positive nitrogen balance, similar to that seen in growing children. Finally, growth hormone is lipolytic, inducing the breakdown of tissue lipids and thus providing energy supplies that are used to support the stimulated protein synthesis induced by increased amino acid uptake.

There are a number of genetic deficiencies associated with GH. GH-deficient dwarfs lack the ability to synthesize or secrete GH, and these short-statured individuals respond well to GH therapy. Pygmies lack the IGF-1 response to GH but not its metabolic effects; thus in pygmies the deficiency is post-receptor in nature. Finally, Laron dwarfs have normal or excess plasma GH, but lack liver GH receptors and have low levels of circulating IGF-1. The defect in these individuals is clearly related to an inability to respond to GH by the production of IGF-1. The production of excessive amounts of GH before epiphyseal closure of the long bones leads to gigantism, and when GH becomes excessive after epiphyseal closure, acral bone growth leads to the characteristic features of acromegaly.

Prolactin (PRL): Prolactin is produced by acidophilic pituitary lactotropes. Prolactin is the lone tropic hormone of the pituitary that is routinely under negative control by prolactin inhibiting hormone (PIH), which is now known to be dopamine. Decreased hypophyseal dopamine production, or damage to the hypophyseal stalk, leads to rapid up-regulation of PRL secretion. A number of other hypothalamic releasing hormones induce increased prolactin secretion; as a result, it is unclear whether a specific PRH exists for up-regulating PRL secretion. PRL initiates and maintains lactation in mammals, but normally only in mammary tissue that has been primed with estrogenic sex hormones.

Placental Hormones

Human Chorionic Gonadotropin: Human chorionic gonadotropin (hCG) is a glycoprotein synthesized by the placenta. Estrogens stimulate the anterior pituitary to produce placentalotropin, which in turn stimulates hCG synthesis and secretion. It exerts effects that are similar to those of pituitary LH.

hCG is used therapeutically in the management of cryptorchidism in prepubertal boys. It is also used in women in conjunction with menotropins to induce ovulation when the endogenous availability of gonadotropin is not normal.

Human Placental Lactogen (hPL): Human placental lactogen is produced by the placenta late in gestation. At its height it is secreted at a rate of about 1 g/day, the highest secretory rate of any known human hormone. However, little hPL reaches the fetal circulation, and hPL has only about 1% the activity of PRL or GH in producing biological effects, leading some to question its functional importance in humans. It has been identified as a protein composed of 191 amino acid units in a single-peptide chain with two disulfide bridges. hPL resembles human somatotropin.

Gonadotropic Hormones

FSH, LH, and CG is each glycosylated to the extent of 16-30% of their molecular weight. each hormone is composed of two chains with combined molecular weights ranging from MW 30-38,000. The 89 amino acid alpha-chain for FSH, LH, and CG (89 + 3 N-terminal AAs) is essentially identical for each. The beta-chains, then, differ to confer selectivity with regards to their actions. For FSH and LH, the beta- chains have 115 AA, for CG the beta-chain has 145 AA. As in the case of TSH, the chains are held together by non-covalent forces (ionic, hydrogen bond, Van der Waals but not disulfide bonds). Within each chain, there are disulfide bonds, 5 in the alpha- and 6 in the beta-chains.

Functions: FSH, LH, and CG have different effects on women and men (not surprising), but the effects are consistent with the preparation for and development of the fertilized ova.

Follicle Stimulating Hormone (FSH)

Females:

- A. FSH promotes the development and maturation of ovarian follicles (many develop simultaneously, but at different rates)
- B. FSH stimulates estrogen synthesis and secretion by ovarian follicles. In follicles grown in tissue culture, addition of exogenous FSH causes estrogen secretion to increase at a rate much faster than development stimulation, indicating that the effect on estrogen level is independent of and not merely the consequence of increased follicle development.

Males:

- A. FSH is essential for gametogenesis and sperm formation.

Luteinizing Hormone (LH): In women, one function of LH is that it induces ovulation in the ovary (FSH alone cannot induce ovulation). At first, LH contributes to the final maturation and development of both the follicle and the ovum which it contains. After a period of time, a sharp increase in blood plasma estradiol (estrogen), a positive feedback to follicle development, is followed a day later by a near simultaneous release of FSH and LH from the anterior pituitary. In response to the burst of FSH and LH, one or more mature follicles rupture and release an ovum (egg).

A second function of LH in women is that it acts upon the ruptured follicle to stimulate its conversion to a corpus luteum, which provides an ovarian source of estrogen and subsequently progesterone. Progesterone exerts a negative feedback to depress the production of LH and hence prevent further follicle and ovum development until progesterone levels subside at the end of the menstrual cycle. If no positive stimulus to the corpus luteum is received from placental CG (chorionic gonadotropin) within seven days, the corpus luteum begins to recede or degenerate. As the corpus luteum degenerates, it stops secreting estrogen and progesterone, which then leads to a reinitiation of the cycle. The cycle begins again because low levels of estrogen and progesterone stimulate the anterior pituitary to increase its output of FSH and LH.

In men, LH stimulates the formation and secretion of androgens, especially testosterone, by the testes.

Chorionic Gonadotropin (CG) : CG is secreted by the chorion (the outermost extraembryonic membrane which gives rise to the placenta) seven (7) days after ovulation if the ovum has been fertilized (i.e. in pregnancy). CG stimulates the ovarian corpus luteum to secrete high levels of estrogen and progesterone.

The α (alpha) chains of FSH, LH, and CH are almost identical, as mentioned above, and are quite similar to the α (alpha) chain of TSH (thyroid stimulatory hormone). The differences in activity are caused by differences in the β (beta) chains. There is an 82% homology in AA 1-115 between the b chains of LH and CG. Individually, that is in the monomeric rather than dimeric state, the separated chains for any of the gonadotropins show no activity. However, due to the near identical nature of the α chains, separation of the α chain from one gonadotropin and reassembly

with the b chain of another gonadotropin produces a fully active hormone with the activity as specified by the β chain.

Each chain contains carbohydrate. The alpha-chains each have an Asn linked oligosaccharide. In the FSH beta-chain, there are two carbohydrates each Asn linked. The LH beta-chain contains one Asn linked carbohydrate. CG contains a total of six (6) carbohydrate chains, two (2) Asn-linked in a region similar to that of FSH and four (4) linked through Ser in a non-homologous region to FSH or LH.

Carbohydrate sidechains, as seen for PRL and TSH, are often found on proteins which are excreted and may contribute to stability or recognition. Such biological effects are the consequence of the carbohydrate's structure. The carbohydrates contribute complexities to the spacial structure which do not occur with nonglycosylated proteins. Carbohydrates are made up of numerous linked sugars. They can branch (at mannose) and offer multiple possibilities for formation of hydrogen bonds, esters, and ethers through use of the hydroxyl (-OH) groups which stick up or down around the sugar ring. Through such bonding interactions, particularly the non-covalent hydrogen bonding, they can be involved in the recognition of receptors. As an example of carbohydrate protection of the peptide backbone from enzymatic degradation, removal of one carbohydrate from FSH changes its half life from 90 minutes to 2-3 minutes.

A single DNA gene encodes for the protein which is the alpha-chain of FSH, LH, CG, and TSH. While the alpha-chain proteins are nearly identical, differences between them must be the consequence of alternative messenger RNA splicing or post-translational enzyme processing, such as alternative proteolysis or glycosylation.

The genes for the gonadotropin beta-chains are found on different chromosomes. While there are seven (7) genes that code for human CG (chorionic gonadotropin), only two appear to be transcribed (made from DNA into RNA) and translated (RNA to protein). The physiological impact of different forms for CG has yet to be evaluated.

The affinities for FSH, LH, and CG for their receptors are very high with a K_D of $\sim 10^{-10}$ M. The receptors exist in excess, so a receptor reserve exists. One gets maximal response when only 1% of the hormone receptors are occupied.

Prolonged exposure of receptors to hormones leads to down regulation of receptors. This decrease in the number of gonadotropin receptors in the plasma membrane of ovary or corpus luteum cells can result from either an internalization (endocytosis) of existing receptors, a decrease in their rate of synthesis or both. Due to the receptor reserve and the low percentage of receptor occupation needed for response, considerable down regulation of receptors is necessary before noticeable effects are observable.

The removal of the carbohydrate from a gonadotropin does not affect the binding affinity per se, but does markedly reduce the abilities of the hormones to stimulate adenylate cyclase or steroidogenesis. Deglycosylated hormones can act as a competitive antagonist. So FSH without carbohydrate can compete with FSH with carbohydrate.

Thyroid Stimulating Hormone (TSH)

Secretion of TSH (also called thyrotropin), the final member of the glycoprotein hormone family, is stimulated by thyrotropin-releasing hormone, TRH from the hypothalamus. While cAMP causes increased secretion of TSH by thyrotropes, it is not yet certain that cAMP is the physiological signal that regulates TSH production.

Circulating TSH binds to receptors on the basal membrane of thyroid follicles. The receptors are coupled through a G-protein to adenylate cyclase. The result is that ligand binding increases thyrocyte cAMP and PKA, leading in the short term to increased secretion of thyroxine (T4) and triiodothyronine (T3). Chronic stimulation of the receptor causes an increase in the synthesis of a major thyroid hormone precursor, thyroglobulin.

Thyroglobulin produced on rough endoplasmic reticulum has a molecular weight of 660,000. It is glycosylated and contains more than 100 tyrosine residues, which become iodinated and are used to synthesize T3 and T4. Thyroglobulin is exocytosed through the apical membrane into the closed lumen of thyroid follicles, where it accumulates as the major protein of the thyroid and where maturation takes place. Briefly, a Na^+/K^+ -ATPase-driven pump concentrates iodide (I^-) in thyroid cells, and the iodide is transported to the follicle lumen. There it is oxidized to I^+ by a thyroperoxidase found only in thyroid tissue. The addition of I^+ to tyrosine residues of thyroglobulin is catalyzed by the same enzyme, leading to the production of thyroglobulin containing monoiodotyrosyl (MIT) and diiodotyrosyl (DIT) residues. The thyronines, T3 and T4, are formed by combining MIT and DIT residues on thyroglobulin.

Mature, iodinated thyroglobulin is taken up in vesicles by thyrocytes and fuses with lysosomes. Lysosomal proteases degrade thyroglobulin releasing amino acids and T3 and T4, which are secreted into the circulation. These compounds are very hydrophobic and require a carrier protein for delivery to target tissues. In the plasma, T3 and T4 are bound to a carrier glycoprotein known as thyroxin-binding globulin and are disseminated throughout the body in this form.

Thyroid hormones act by binding to cytosolic receptors very similar to steroid hormone receptors, and for this reason T3 and T4 are often classified along with the hydrophobic steroid hormones. The principal role of thyroid hormones is also like that of steroid hormones. In adults, the ligand receptor combination binds to thyroid hormone response elements in nuclear DNA and is responsible for up-regulating general protein synthesis and inducing a state of positive nitrogen balance. In the embryo, thyroid hormone is necessary for normal development. Hypothyroidism in the embryo is responsible for cretinism, which is characterized by multiple congenital defects and mental retardation.

Thyroid stimulating autoantibodies (TSAb) also activate the human thyroid TSH receptor, leading to the hyperthyroidism of Graves' disease. TSABs bind to the TSH receptor and mimic the TSH stimulation of the gland by increasing intracellular cAMP.

The feedback loop that regulates T3 and T4 production is a single short negative loop, with the T3 and T4 being responsible for down-regulating pituitary TSH secretion. Meanwhile, continuously secreted hypothalamic TRH is responsible for up-regulating TSH production. The TSH actually secreted by thyrotropes is the net result of the negative effects of T3 and T4 and the positive effect of TRH.

Somatostatin is an oligopeptide (14 amino acid residues) and is referred to as somatotropin release-inhibiting factor (SRIF) (**Fig.7**). It acts by both endocrine and paracrine pathways to affect its target cells. A majority of the circulating somatostatin appears to come from the pancreas and gastrointestinal tract.

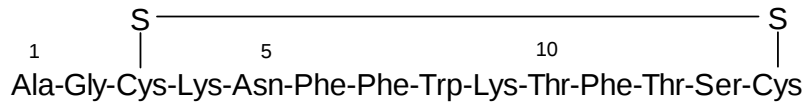


Fig. 7

If one had to summarize the effects of somatostatin in one phrase, it would be: "*somatostatin inhibits the secretion of many other hormones*".

Effects on the Pituitary Gland: Somatostatin was named for its effect of inhibiting secretion of growth hormone from the pituitary gland. Experimentally, all known stimuli for growth hormone secretion are suppressed by somatostatin administration. Additionally, animals treated with antiserum to somatostatin show elevated blood concentrations of growth hormone, as do animals that are genetically engineered to disrupt their somatostatin gene.

Ultimately, growth hormone secretion is controlled by the interaction of somatostatin and growth hormone releasing hormone, both of which are secreted by hypothalamic neurons.

Effects on the Pancreas: Cells within pancreatic islets secrete insulin, glucagon and somatostatin. Somatostatin appears to act primarily in a paracrine manner to inhibit the secretion of both insulin and glucagon. It also has the effect in suppressing pancreatic exocrine secretions, by inhibiting cholecystokinin-stimulated enzyme secretion and secretin-stimulated bicarbonate secretion.

Effects on the Gastrointestinal Tract: Somatostatin is secreted by scattered cells in the GI epithelium, and by neurons in the enteric nervous system. It has been shown to inhibit secretion of many of the other GI hormones, including gastrin, cholecystokinin, secretin and vasoactive intestinal peptide.

In addition to the direct effects of inhibiting secretion of other GI hormones, somatostatin has a variety of other inhibitory effects on the GI tract, which may reflect its effects on other hormones, plus some additional direct effects. Somatostatin suppresses secretion of gastric acid and pepsin, lowers the rate of gastric emptying, and reduces smooth muscle contractions and blood flow within the intestine. Collectively, these activities seem to have the overall effect of decreasing the rate of nutrient absorption.

Effects on the Nervous System: Somatostatin is often referred to as having neuromodulatory activity within the central nervous system, and appears to have a variety of complex effects on neural transmission. Injection of somatostatin into the brain of rodents leads to such things as increased arousal and decreased sleep, and impairment of some motor responses.

Pharmacological Uses: Somatostatin and its synthetic analogs are used clinically to treat a variety of neoplasms. It is also used in to treat gigantism and acromegaly, due to its ability to inhibit growth hormone secretion.

Pancreatic Hormones

The pancreas mainly produces two hormones, insulin and glucagon. Insulin is secreted by the β -cells and glucagon by the α -cells. The primary function of the pancreatic hormones is the regulation of whole-body energy metabolism, principally by regulating the concentration and activity of numerous enzymes involved in catabolism and anabolism of the major cell energy supplies.

Insulin: The earliest of the pancreatic hormones recognized was insulin, whose major function is to counter the concerted action of a number of hyperglycemia-generating hormones and to maintain low blood glucose levels. Because there are numerous hyperglycemic hormones, untreated disorders associated with insulin generally lead to severe hyperglycemia and shortened life span. Insulin is a member of a family of structurally and functionally similar molecules that include the insulin-like growth factors (IGF-1 and IGF-2), and relaxin. The tertiary structure of all 4 molecules is similar, and all have growth-promoting activities, but the dominant role of insulin is metabolic while the dominant roles of the IGFs and relaxin are in the regulation of cell growth and differentiation.

Proinsulin, which is a single-chain of 86 amino acid residues, is enzymatically transformed into insulin within the β -cells. The conversion involves the cleavage of a connecting C-peptide, which contains between 30-35 residues, the number and sequence varying among different species; human C-peptide consists of 35 residues. The resulting human insulin consists of two peptide chains, designated A (having 21 residues) and B (having 30 residues), which are inter-chain connected by two disulfide bonds. Furthermore, the A-chain also contains an intra-chain disulfide bond between Cys⁶ and Cys¹¹.

Actions of Insulin: The major function of insulin is to counter the concerted action of a number of hyperglycemia-generating hormones and to maintain low blood glucose levels. Because there are numerous hyperglycemic hormones, untreated disorders associated with insulin generally lead to severe hyperglycemia and shortened life span.

In addition to its role in regulating glucose metabolism, insulin stimulates lipogenesis, diminishes lipolysis, and increases amino acid transport into cells. Insulin also modulates transcription, altering the cell content of numerous mRNAs. It stimulates growth, DNA synthesis, and cell replication, effects that it holds in common with the insulin-like growth factors (IGFs) and relaxin.

Insulin, secreted by the β -cells of the pancreas, is directly infused via the portal vein to the liver, where it exerts profound metabolic effects. These effects are the response of the activation of the insulin receptor, which belongs to the class of cell surface receptors that exhibit intrinsic tyrosine kinase activity. The insulin receptor is a heterotetramer of 2 extracellular α -subunits disulfide bonded to 2 transmembrane β -subunits. With respect to hepatic glucose homeostasis, the effects

of insulin receptor activation are specific phosphorylation events that lead to an increase in the storage of glucose with a concomitant decrease in hepatic glucose release to the circulation.

In most nonhepatic tissues, insulin increases glucose uptake by increasing the number of plasma membrane glucose transporters: GLUTs. Glucose transporters are in a continuous state of turnover. Increases in the plasma membrane content of transporters stem from an increase in the rate of recruitment of new transporters into the plasma membrane, deriving from a special pool of preformed transporters localized in the cytoplasm. GLUT1 is present in most tissues, GLUT2 is found in liver and pancreatic β -cells, GLUT3 is in the brain and GLUT4 is found in heart, adipose tissue and skeletal muscle.

In liver glucose uptake is dramatically increased because of increased activity of the enzymes glucokinase, phosphofructokinase-1 (PFK-1), and pyruvate kinase (PK), the key regulatory enzymes of glycolysis. The latter effects are induced by insulin-dependent activation of phosphodiesterase, with decreased PKA activity and diminished phosphorylation of pyruvate kinase and phosphofructokinase-2, PFK-2. Dephosphorylation of pyruvate kinase increases its activity while dephosphorylation of PFK-2 renders it active as a kinase. The kinase activity of PFK-2 converts fructose-6-phosphate into fructose-2,6-bisphosphate (F2,6BP). F2,6BP is a potent allosteric activator of the rate limiting enzyme of glycolysis, PFK-1, and an inhibitor of the gluconeogenic enzyme, fructose-1,6-bisphosphatase. In addition, phosphatases specific for the phosphorylated forms of the glycolytic enzymes increase in activity under the influence of insulin. All these events lead to conversion of the glycolytic enzymes to their active forms and consequently a significant increase in glycolysis. In addition, glucose-6-phosphatase activity is down regulated. The net effect is an increase in the content of hepatocyte glucose and its phosphorylated derivatives, with diminished blood glucose.

In addition to the above described events, diminished cAMP and elevated phosphatase activity combine to convert glycogen phosphorylase to its inactive form and glycogen synthase to its active form, with the result that not only is glucose funneled to glycolytic products, but glycogen content is increased as well.

Insulin also has profound effects on the transcription of numerous genes, effects that are primarily mediated by regulated function of sterol-regulated element binding protein, SREBP. These transcriptional effects include (but are not limited to) increases in glucokinase, pyruvate kinase, lipoprotein lipase (LPL), fatty acid synthase (FAS) and acetylCoA carboxylase (ACC) and decreases in glucose 6-phosphatase, fructose 1,6-bisphosphatase and phosphoenolpyruvate carboxykinase (PEPCK).

Glucagon: is a 29-amino acid straight chain polypeptide (**Fig. 8**) synthesized by the α -cells of the Islets of Langerhans as a very much larger proglucagon molecule. Like insulin, glucagon lacks a plasma carrier protein, and like insulin its circulating half-life is also about 5 minutes. As a consequence of the latter trait, the principal effect of glucagon is on the liver, which is the first tissue perfused by blood containing pancreatic secretions. The role of glucagon is well established. It binds to plasma membrane receptors and is coupled through G-proteins to adenylate cyclase. The resultant increases in cAMP and PKA reverse all of the effects described above that insulin has on liver. The increases also lead to a marked elevation of circulating glucose, with the glucose being derived from liver gluconeogenesis and liver glycogenolysis.

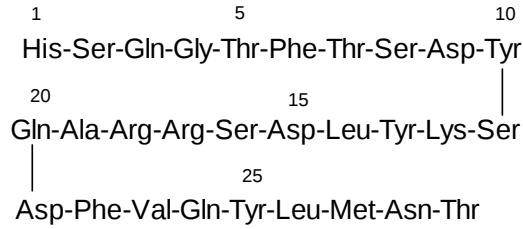


Fig. 8

Gastrointestinal Hormones and Peptides

There are more than 30 peptides currently identified as being expressed within the digestive tract, making the gut, the largest endocrine organ in the body. The regulatory peptides synthesized by the gut include hormones, peptide neurotransmitters and growth factors. As a matter of fact, several hormones and neurotransmitters first identified in the central nervous system and other endocrine organs have subsequently been found in endocrine cells and/or neurons of the gut.

The gastrointestinal hormones and peptides have significant physiological roles. These are tabulated below (**Table 2**).

Table 2: Gastrointestinal Hormones and Peptides

Hormone	Location	Major Action
Glucagon-like peptide 1 (GLP-1)	Enteroendocrine L cells predominantly in the ileum and colon	Potentiates glucose-dependent insulin secretion, inhibits glucagon secretion, inhibits gastric emptying
Glucose-dependent insulintropic polypeptide (GIP) originally called gastric inhibitory polypeptide	Enteroendocrine K cells of the duodenum and proximal jejunum	Inhibits secretion of gastric acid, enhances insulin secretion
Gastrin (17-residue polypeptide) (Fig. 9)	Gastric antrum, duodenum	Gastric acid and pepsin secretion
Cholecystokinin-Pancreozymin (CCK-PZ) (33-residue polypeptide) (Fig. 10)	Duodenum, jejunum	Stimulates gallbladder contraction and bile flow, increases secretion of digestive enzymes from pancreas
Secretin (27-amino acid polypeptide) (Fig. 11)	Duodenum, jejunum	Pancreatic bicarbonate secretion
Vasoactive intestinal peptide (VIP) (28-residue polypeptide) (Fig. 12)	Pancreas	Smooth muscle relaxation; stimulates pancreatic bicarbonate secretion
Motilin (22-residue polypeptide)	Small bowel	Initiates interdigestive intestinal motility

Pancreatic polypeptide (PP)	Pancreas	Inhibits pancreatic bicarbonate and protein secretion
Enkephalins	Stomach, duodenum, gallbladder	Opiate-like actions
Substance P	Entire gastrointestinal tract	CNS function in pain (nociception), involved in vomit reflex, stimulates salivary secretions, induces vasodilatation antagonists have anti-depressant properties
Bombesin-like immunoreactivity (BLI)	Stomach, duodenum	Stimulates release of gastrin and CCK
Neurotensin (13-amino acid peptide)	Ileal mucosa	Causes vasodilatation, increases vascular permeation and gastrin secretion, decreases gastric acid and secretin secretion

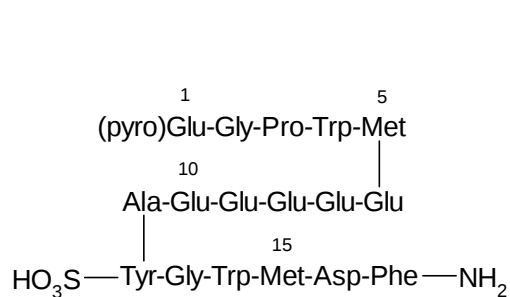
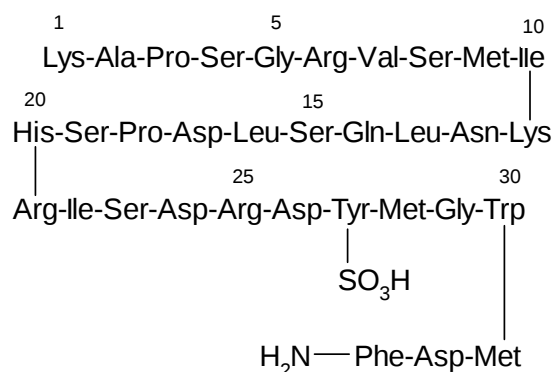


Fig. 9



Cholecystokinin

Fig. 10

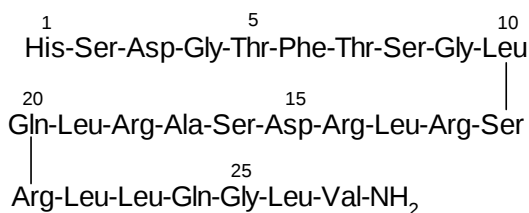


Fig. 11

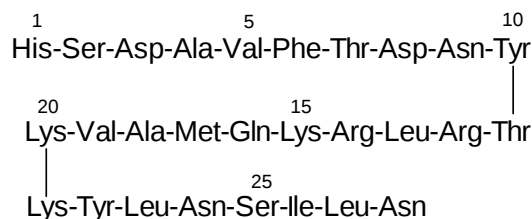


Fig. 12

Neurophyseal Hormones

The principal hormones of the posterior pituitary are the nonapeptides oxytocin and vasopressin. These substances are synthesized as prohormones in neural cell bodies of the hypothalamus and mature as they pass down axons in association with carrier proteins termed neurophysins. The

axons terminate in the posterior pituitary, and the hormones are secreted directly into the systemic circulation.

Vasopressin: is also known as **antidiuretic hormone (ADH)** (**Fig. 13**), because it is the main regulator of body fluid osmolarity. The secretion of vasopressin is regulated in the hypothalamus by osmoreceptors, which sense water concentration and stimulate increased vasopressin secretion when plasma osmolarity increases. The secreted vasopressin increases the reabsorption rate of water in kidney tubule cells, causing the excretion of urine that is concentrated in Na^+ and thus yielding a net drop in osmolarity of body fluids. Vasopressin deficiency leads to watery urine and polydipsia, a condition known as diabetes insipidus. Vasopressin binds plasma membrane receptors and acts through G-proteins to activate the cAMP/PKA regulatory system.

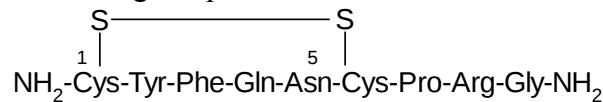


Fig. 13

Oxytocin : The mechanism of action of **oxytocin** (**Fig. 14**) is unknown. Oxytocin secretion in nursing women is stimulated by direct neural feedback obtained by stimulation of the nipple during suckling. Its physiological effects include the contraction of mammary gland myoepithelial cells, which induces the ejection of milk from mammary glands, and the stimulation of uterine smooth muscle contraction leading to childbirth.

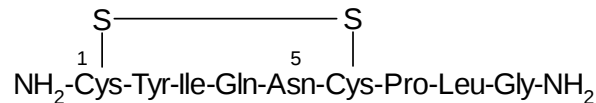


Fig. 14

Parathyroid Hormone (PTH)

Parathyroid hormone (PTH, molecular weight 9,500) is synthesized and secreted by chief cells of the parathyroid in response to systemic Ca^{2+} levels. The Ca^{2+} receptor of the parathyroid gland responds to Ca^{2+} by increasing intracellular levels of PKC, Ca^{2+} and IP_3 ; this stage is followed, after a period of protein synthesis, by PTH secretion. The synthesis and secretion of PTH in chief cells is constitutive, but Ca^{2+} regulates the level of PTH in chief cells (and thus its secretion) by increasing the rate of PTH proteolysis when plasma Ca^{2+} levels rise and by decreasing the proteolysis of PTH when Ca^{2+} levels fall. The role of PTH is to regulate Ca^{2+} concentration in extracellular fluids. The feedback loop that regulates PTH secretion therefore involves the parathyroids, Ca^{2+} , and the target tissues described below.

PTH acts by binding to cAMP-coupled plasma membrane receptors, initiating a cascade of reactions that culminates in the biological response. The body response to PTH is complex but is aimed in all tissues at increasing Ca^{2+} levels in extracellular fluids. PTH induces the dissolution of bone by stimulating osteoclast activity, which leads to elevated plasma Ca^{2+} and phosphate. In the kidney, PTH reduces renal Ca^{2+} clearance by stimulating its reabsorption; at the same time, PTH reduces the reabsorption of phosphate and thereby increases its clearance. Finally, PTH acts on the liver, kidney, and intestine to stimulate the production of the steroid hormone 1,25-dihydroxycholecalciferol (calcitriol), which is responsible for Ca^{2+} absorption in the intestine.

Calcitonin (CT, Thyrocalcitonin)

Calcitonin (CT) (**Fig. 15**) is a 32-amino acid peptide secreted by the parafollicular cells of the thyroid gland in response to hypocalcemia. Calcitonins as obtained from different species are identical at 7 of the first 9 residues, contain Gly at position 28, and all terminate with Pro-NH₂. The C-terminal proline amide (Pro-NH₂) is very important for the biologic function of CT, as is the disulfide-bridge between Cys residues at positions 1 and 7. Calcitonin is employed therapeutically to relieve the symptoms of osteoporosis, although details of its mechanism of action remain unclear. However, it has been observed that CT induces the synthesis of PTH in isolated cells, which leads *in vivo* to increased plasma Ca²⁺ levels. In addition, CT has been shown to reduce the synthesis of osteoporin (Opn), a protein made by osteoclasts and responsible for attaching osteoclasts to bone. Thus, it appears that CT elevates plasma Ca²⁺ via PTH induction and reduces bone reabsorption by decreasing osteoclast binding to bone.

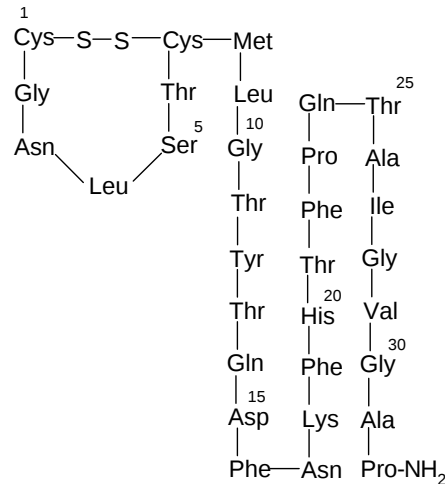


Fig. 15

Renin-Angiotensin System

The **renin-angiotensin system** is responsible for regulation of blood pressure. The intrarenal baroreceptor system is a key mechanism for regulating renin secretion. A drop in pressure results in the release of **renin** from the juxtaglomerular cells of the kidneys. Renin secretion is also regulated by the rate of Na⁺ and Cl⁻ transport across the macula densa. Higher the rate of transport of these ions, lower is the rate of renin secretion. The only function for renin is to cleave a 10-amino acid peptide from the N-terminal end of **angiotensinogen** (**Fig. 16**). This decapeptide is called **angiotensin I**. Angiotensin I is then cleaved by the action of **angiotensin-converting enzyme, ACE** to the active hormone, **angiotensin II** (**Fig. 16**), which is an octapeptide. ACE removes 2 amino acids from the C-terminal end of angiotensin I. Angiotensin II is hydrolyzed to angiotensin III, a heptapeptide, by an aminopeptidase. Angiotensin III preserves most of the pharmacological activities of its precursor. Further degradation of angiotensin III leads to pharmacologically inactive peptide fragments.

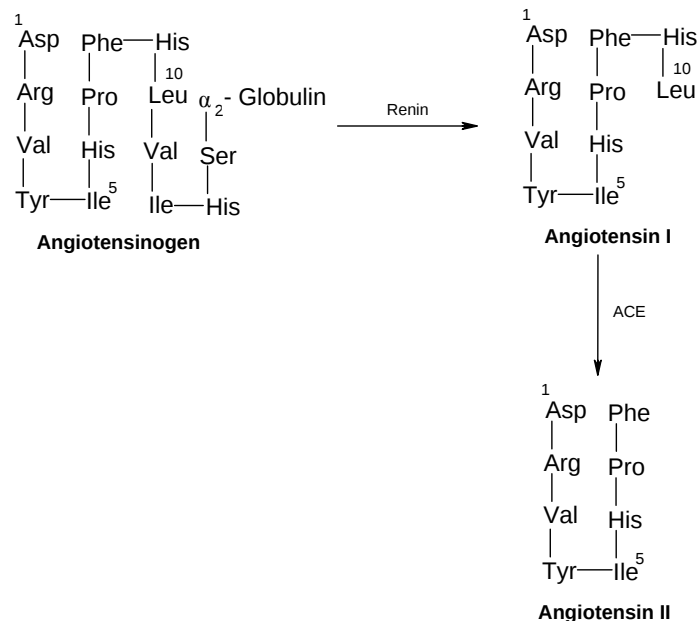


Fig. 16

Angiotensin II was also referred to as **hypertensin** and **angiotonin**. It is one of the most potent naturally occurring vasoconstrictors. The vasoconstrictive action of angiotensin II is primarily exerted on the arterioles and leads to a rise in both systolic and diastolic blood pressure. In individuals that are depleted of sodium or who have liver disease (e.g. cirrhosis), the pressive actions of angiotensin II are greatly reduced. These conditions lead to increased circulating levels of angiotensin II which in turn leads to a down-regulation in the number of angiotensin II receptors on smooth muscle cells. As a consequence, administration of exogenous angiotensin II to these individuals has little effect.

Other physiological responses to angiotensin II include induction of adrenal cortex synthesis and secretion of aldosterone. Angiotensin II also acts on the brain leading to increased blood pressure, vasopressin and ACTH secretion and increased water intake. Angiotensin II affects the contractility of the mesangial cells of the kidney leading to decreased glomerular filtration rate. One additional effect of angiotensin II is to potentiate the release of norepinephrine.

Two distinct types of angiotensin II receptors have been identified, AT₁ and AT₂. The AT₁ receptors are classical serpentine (7 transmembrane spanning) receptors. The AT₁ receptors are coupled to a G-protein that leads to activation of PLC- γ . Although the AT₂ receptors are also serpentine, they do not appear to be coupled to activation of G-proteins.

Natriuretic Hormones

Natriuresis refers to enhanced urinary excretion of sodium. This can occur in certain disease states and through the action of diuretic drugs. At least 3 natriuretic hormones have been identified. Atrial natriuretic peptide (ANP) was the first cardiac natriuretic hormone identified. This hormone is secreted by cardiac muscle when sodium chloride intake is increased and when the volume of the extracellular fluid expands. Active ANP is a 28-amino acid peptide containing a 17-amino acid ring formed by intrachain disulfide bonding. Two smaller forms of ANP have also been isolated from the brain. A brain natriuretic peptide (BNP) (first isolated from porcine

brain) has been identified and found in human heart and blood (but not human brain). BNP has different amino acids in its 17-amino acid ring and is encoded by a different gene. In humans, a third natriuretic peptide (CNP) is present in the brain but not in the heart.

The action of ANP is to cause natriuresis presumably by increasing glomerular filtration rate (its exact mechanism of action remains unclear). ANP induces relaxation of the mesangial cells of the glomeruli and thus may increase the surface area of these cells so that filtration is increased. Alternatively, ANP might act on tubule cells to increase sodium excretion. Other effects of ANP include reducing blood pressure, decreasing the responsiveness of adrenal glomerulosa cells to stimuli that result in aldosterone production and secretion, inhibit secretion of vasopressin and decreasing vascular smooth muscle cell responses to vasoconstrictive agents. These latter actions of ANP are counter to the effects of angiotensin II. In fact, ANP also lowers renin secretion by the kidneys thus lowering circulating angiotensin II levels.

Three different ANP receptors have been identified: ANPR-A, ANPR-B and ANPR-C. When ANP, BNP or CNP bind to receptor, an increase in guanylate cyclase activity results leading to production of cyclic GMP (cGMP). Both ANPR-A and ANPR-B proteins span the plasma membrane and their intracellular domains possess intrinsic guanylate cyclase activity. The exact function of the ANPR-C protein is unclear as this receptor does not contain an intracellular domain with intrinsic guanylate cyclase activity. It is hypothesized that it may act through a G-protein that activates PLC- β and inhibits adenylate cyclase or that it acts simply as a clearance receptor removing natriuretic peptides from the blood.

Suggested Reading:

1. K.D. Tripathi: Essentials of Medical Pharmacology.
2. Goodman Gilman's: The Pharmacological basis of Therapeutics by Alfred Goodman Gilman.
3. R.F. Doerge: Wilson & Gisvold's Text Book of Organic and Pharmaceutical Chemistry, J. Lippincott Co., Philadelphia.
4. H.P. Rang and M.M. Dale: Pharmacology
5. W.O. Foye: Principles of Medicinal Chemistry, Lea & Febiger, Philadelphia.
6. www.pubmed.com
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