Dr. Remington (*seated right*) reading galley proof. Galley proofs of USP monographs hang on the far wall, and USP Circulars are being collated on the billiard table.

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SOMATREM AND SOMATROPIN

SOMATREM

***N*-L-Methionylsomatotropin (human); Protropin**

[82030-87-3] $C_{995}H_{1537}N_{263}O_{301}S_8$ (22,256.21)

SOMATROPIN

Humatrope

Growth hormone, human; somatotropin (human) [12629-01-5] $C_{990}H_{1528}N_{262}O_{300}S_7$ (21,500.00)

Preparation—A single polypeptide chain of 191 aminoacids once obtained from the anterior lobe of the human pituitary gland. See US Pat 3,118,815.

Comments—Both somatrem and somatropin products are from recombinant DNA–directed syntheses. Humatrope is identical to human pituitary–derived somatropin. Somatrem (Protropin) is identical to natural growth hormone except it contains an additional methionine on the *N*-terminus of the molecule. However, the effects and potencies are identical; therefore, both peptides are considered together. Somatropin from pituitary extracts was discontinued because of reports that its use was sometimes the cause of Creutzfeldt-Jakob disease. For description, actions, and uses see *Growth Hormone* (page 1358).

Intramuscular administration of the hormone is preferred to subcutaneous injection because the hormone causes lipodystrophy or lipoatrophy at the cutaneous injection site. Pain and swelling usually occur on injection, so sites should be rotated. Hypercalciuria occurs frequently but usually regresses in 2 to 3 months. Hyperglycemia and frank diabetes mellitus due to insulin resistance may occur. Myalgia and early morning headaches are relatively frequent. Antibodies to the hormone may be found in 30 to 40% of recipients given somatrem, but patients rarely fail to respond to therapy. Approximately 2% of patients receiving somatropin developed antibodies, but growth responses have not been limited in such patients. Occasionally, somatotropin causes hypothyroidism. If the epiphyses are closed, the hormone should not be used because continued stimulation of growth of the phalanges and jawbone, but not other bones, can cause abnormal body proportions. Available products are exceedingly expensive.

THE POSTERIOR PITUITARY (NEUROHYPOPHYSIS)

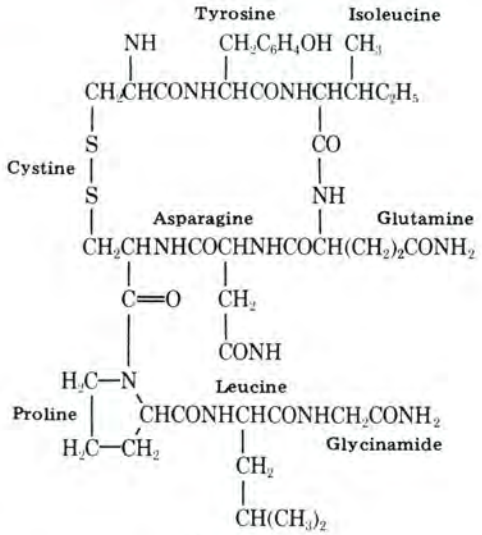
The posterior pituitary contains two peptide hormones, oxytocin and vasopressin. Neither is made in the posterior pituitary, but rather they are synthesized in neurons in the hypothalamus. Oxytocin is synthesized in the paraventricular nucleus, and vasopressin the supraoptic nucleus. The axons of the hormone-secreting nerve cells pass from the hypothalamus to the internal infundibular zone of the posterior pituitary (hence the name neurohypophysis). The hormones flow down the axons as granules or vesicles composed of a hormone and a carrier protein called neurophysin. Their release at the nerve terminals is effected by nerve impulses. Thus, the control of release is actually in the appropriate hypothalamic nuclei.

Human and most mammalian vasopressin is Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-GlyNH_2, called arginine vasopressin. An exception is pigs whose vasopressin called lypressin contains lysine at position 8. Vasopressin possesses antidiuretic hormone (ADH) and vasopressor activities. The ADH activity decreases urine flow by increasing the resorption of water from the distal convoluted tubules and collecting ducts of the kidney. The effect is a decrease in the osmolarity of the extracellular fluid.

When there is a defect in the hypothalamicopituitary secretion of ADH, diabetes insipidus results in a watery diuresis. Vasopressin is used mainly for its antidiuretic effects in this disease rather than for its vasoconstrictor actions, from which the name vasopressin is derived. However, not only does vasopressin stimulate vascular smooth muscle, but also it increases bowel motility, and it has been used to treat bowel stasis and to expel gas postsurgically. The vasoconstrictor and bowel spastic actions have special usefulness in arresting hemorrhage from peptic ulcers. The smooth muscle stimulant effects occur with pressin also has weak oxytocic activity. Vasopressin has a brief half-life (less than 20 min). Lypressin has much weaker smooth-muscle stimulant activity than vasopressin, the ratio of antidiuretic to pressor activity being about 1000:1.

Oxytocin stimulates the contraction of smooth muscle in the uterus and alveoli of the lactating breast. At coitus, uterine stimulation by oxytocin causes peristaltic activity that assists the migration of spermatozoa. During parturition, the hormone enhances the uterine contractions. The uses of oxytocin in labor and breast engorgement are described in Chapter 76. Neither vasopressin nor oxytocin survives the acid and enzymes of the gastrointestinal (GI) tract, so they must be given parenterally or intranasally.

Each of the octapeptides has been synthesized. Oxytocin has the structure

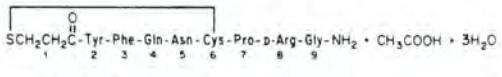


Oxytocin

The structure of vasopressin from human, monkey, dog, cat, ox, camel, rabbit, and rat pituitaries is identical with that of oxytocin, except that the isoleucine and leucine residues are replaced by residues of phenylalanine and arginine, respectively. The successful synthesis of the naturally occurring posterior lobe hormones has provided the impetus for the synthesis of a number of analogs of both oxytocin and vasopressin. Thus, substances in which one or more of the amino acids of the native hormones have been replaced by others or that contain fewer or additional amino acid residues have been prepared, and their pharmacological properties explored. One of these was the compound vasotocin, containing the pentapeptide ring of oxytocin and the tripeptide side chain of vasopressin. This substance possesses the biological properties of both neurohypophyseal hormones, although in lesser degree. Synthetic analogs of oxytocin and the two vasopressins, in which one or more of the amino acids of the native hormones have been replaced, are named by using numbers to denote the alterations represented in the synthetic. A synthetic vasopressin in which the moiety at position 8 is arginine is named simply 8-arginine vasopressin; if it is lysine, the peptide is 8-lysine vasopressin.

DESMOPRESSIN ACETATE

Vasopressin, 1-(3-mercaptopropionic acid)-8-D-arginine, monoacetate (salt), trihydrate; DDVAP; Concentraid



[62357-86-2] $C_{48}H_{68}N_{14}O_{14}S_2 \cdot 3H_2O$ (1183.22).

to be sent to the juxtaglomerular (JG) cells in the afferent arterioles, which then release renin. Renin secretion also is increased by low blood pressure at the JG cells and by sympathetic impulses, which work through β_1-adrenoreceptors. Renin then cleaves angiotensin I from angiotensinogen, both locally and in the blood. Angiotensin I is converted to angiotensin II by a converting enzyme (CE or kininase II), mainly in the lung. (Angiotensin III is a metabolite of II.) Thus, a variety of electrolyte, emotional, cardiovascular, and drug factors can affect aldosterone secretion indirectly.

STRUCTURE-ACTIVITY RELATIONSHIP—Clinical experience has indicated that the anti-inflammatory activity of adrenal cortical steroids in man correlates well with their glucocorticoid activity. The undesirable side effects of sodium retention and edema are associated with mineralocorticoid activity. Synthetic steroids possessing higher glucocorticoid and lower mineralocorticoid activity than cortisone or cortisol have been prepared and marketed. A comparison of some commonly used systemic corticosteroids is included in Table 77-2.

All adrenal corticoids require the 3-keto group and 4,5 unsaturation. Additional unsaturation in Ring A enhances the anti-inflammatory properties while at the same time reducing the sodium-retaining effect. The presence of oxygen at position 11 is necessary for significant glucocorticoid activity; the 11β-hydroxy group is more potent than the 11-keto group; the 11-keto group is converted to the active β-hydroxy group in the body. The 17α-hydroxy group also is important to glucocorticoid activity. Introduction of either a methyl or hydroxyl group at position 16 markedly reduces mineralocorticoid activity but only slightly decreases glucocorticoid and anti-inflammatory activity. The 9α-fluoro group enhances both glucocorticoid and mineralocorticoid activities, but the effects of substituents at the 6 and 16 positions override this effect.

BIOLOGICAL ACTIVITY—The glucocorticoids appear to affect all cells, although not all in the same way. Clinical interest primarily focuses on their anti-inflammatory and immunosuppressant effects. They prevent release of various lytic enzymes that extend tissue damage during inflammation and generate leukotactic substances. Glucocorticoids decrease phagocytosis by macrophages. Anti-inflammatory effects include the retardation of the migration of polymorphonuclear leukocytes, suppression of repair and granulation, reduction in the erythrocyte sedimentation rate, decreased fibrinogenesis, and diminished elaboration of C-reactive protein. Glucocorticoids suppress the production of cytokines (eg, IL-1,IL-6, interferon gamma, TNF-alpha, and others) by inflammatory cells (eg, monocytes, macrophages, and lymphocytes) that recruit eosinophils. They also decrease lipid eicosanoid and prostaglandin production by inhibiting the production of cytokines that induce cyclooxygenase-II in inflammatory cells. The immunosuppressant effects may be partly the result of the suppression of phagocytosis, gene expression of cytokines and a decrease in the number of eosinophils and lymphocytes, suppression of delayed hypersensitivity reactions, decrease in tissue reaction to antigen-antibody interactions, and reduction in plasma immunoglobulins.

Effects on carbohydrate, fat, and protein metabolism are responsible for both beneficial and untoward effects. These hormones increase hepatic gluconeogenesis and glycogen deposition, both lipolysis and lipogenesis (but increase fat deposition at only a few specialized sites), and protein catabolism in various tissues (especially skeletal muscle).

In addition to the above-mentioned changes brought about by glucocorticoids are the so-called permissive effects. In these, the steroids do not themselves cause change but physiological amounts are required for certain organs or structures to respond to stimuli. For example, neither the kidney can respond to a water load nor the arterioles to epinephrine in the absence of adequate levels of glucocorticoids.

Once a glucocorticoid hormone has permeated a cell membrane, it combines with a cytosolic glucocorticoid receptor that is inactive because it is bound to some specific proteins, including some heat shock proteins that prevent them from reaching the nucleus and binding to DNA. The glucocorticoid-receptor complex undergoes conformational changes that allow dissociation from the heat shock proteins and other immunomodulatory proteins, then it is translocated to the cell nucleus, where it attaches to glucocorticoid receptor elements in the DNA. The result is an enhancement or reduction of the gene transcription that leads to an increased or decreased synthesis of certain proteins. Other transcription factors also interact at the same DNA binding sites. The protein produced is determined, in part, by the glucocorticoid receptor, of which there is more than one kind within the cell. There are estimated to be from 10 to 100 glucocorticoid target genes per cell, but not all of them are expressed in every cell. Tissue selectivity for different steroid hormones seems to be considerably determined by steroid-metabolizing enzymes that differentially alter intracellular steroids that upon transport to the nucleus bind to specific hormone response elements in the DNA.

Mineralocorticoids act on the distal tubules and collecting ducts of the kidney to increase the expression of genes that encode for proteins that enhance reabsorption of Na^+ from the tubular fluid. The effects on electrolytes are associated with an increase in the number of open Na^+ and K^+ channels in the luminal membrane tubular cells, and they increase the activity of basolateral membrane Na^+/K^+-activated ATPase. The net result is a return of Na^+ to the systemic circulation in exchange for K^+. Similar electrolyte effects are promoted by mineralo-

Table 77-2. Major Adrenal Corticosteroids[a]

DRUG	RELATIVE ACTIVITY			DOSAGE FORM
	ANTI-INFLAM	TOPICAL	Na + RET	
Short- to medium-acting glucocorticoids				
Hydrocortisone (Cortisol)	1	1	1	Oral, Inj, Top
Cortisone	0.8	0	0.8	Oral, Inj, Top
Prednisone	4	0	0.3	Oral
Prednisolone	5	4	0.3	Oral, Inj, Top
Methylprednisolone	5	5	0	Oral, Inj, Top
Intermediate-acting glucocorticoids				
Triamcinolone	5	5–100	0	Oral, Inj, Top
Fluprednisolone	15	7	0	Oral
Long-acting glucocorticoids				
Betamethasone	25–40	10	0	Oral, Inj, Top
Dexamethasone	30	10–40	0	Oral, Inj, Top
Mineralocorticoids				
Fludrocortisone	10	10	250	Oral, Inj, Top
Desoxycorticosterone acetate	0	0	20	Inj, pellets

to be sent to the juxtaglomerular (JG) cells in the afferent arterioles, which then release renin. Renin secretion also is increased by low blood pressure at the JG cells and by sympathetic impulses, which work through β_1-adrenoreceptors. Renin then cleaves angiotensin I from angiotensinogen, both locally and in the blood. Angiotensin I is converted to angiotensin II by a converting enzyme (CE or kininase II), mainly in the lung. (Angiotensin III is a metabolite of II.) Thus, a variety of electrolyte, emotional, cardiovascular, and drug factors can affect aldosterone secretion indirectly.

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Dexamethasone	30	10–40	0	Oral, Inj, Top
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