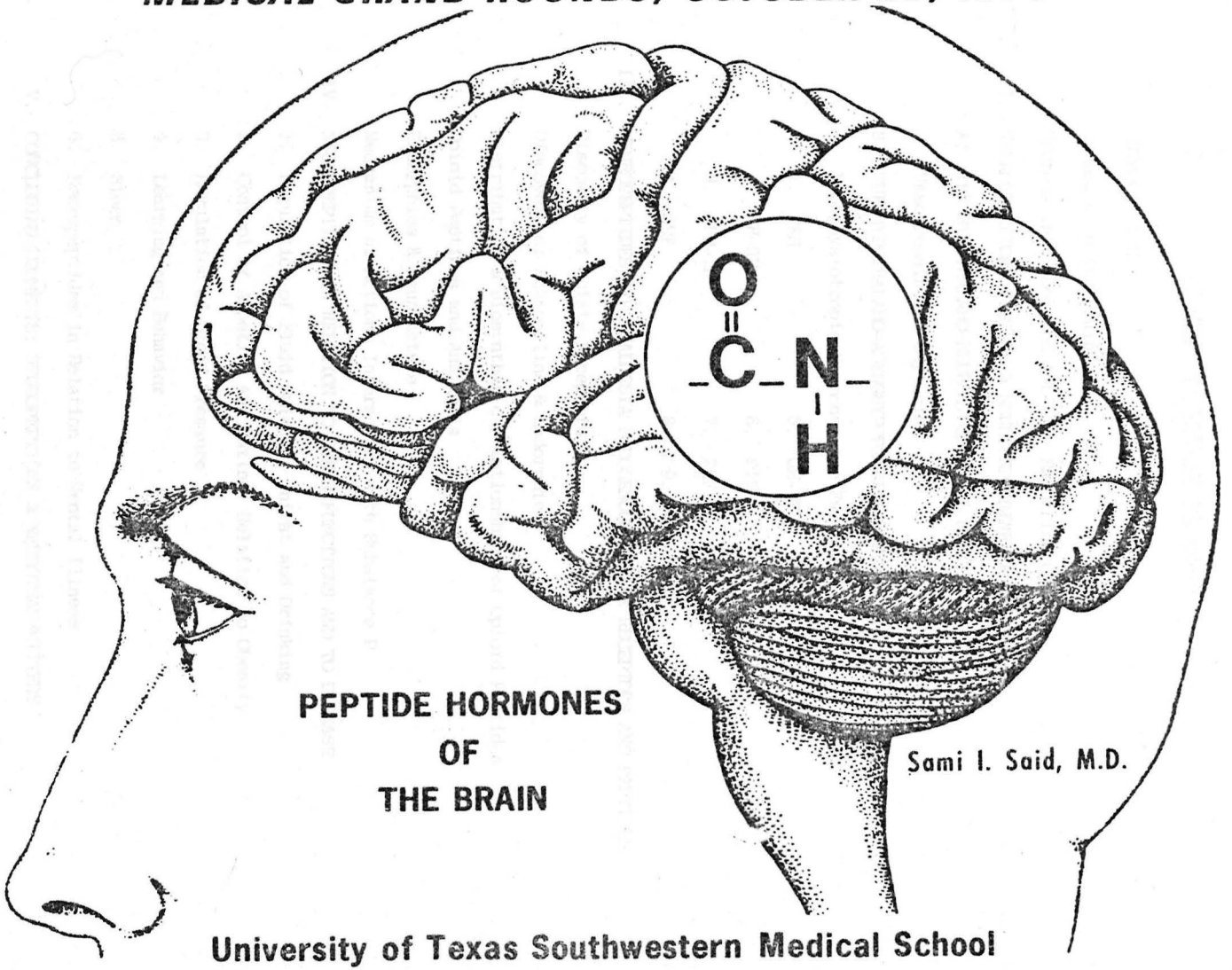
MEDICAL GRAND ROUNDS, OCTOBER 25, 1979



PEPTIDE HORMONES OF THE BRAIN

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PEPTIDE HORMONES OF THE BRAIN

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I. INTRODUCTION.

Hormones in the Brain?

The idea that the brain secretes hormones and that these hormones are vital regulators of many body functions, as well as of brain function itself, may still sound a little surprising. Although three Nobel Prizes in Medicine have gone to investigators in this field[1], and a great number of papers and meetings are currently devoted to the subject, the concept of peptide hormone secretion by the brain is a long way from being widely recognized. And the importance of these hormones in the understanding of physiology and disease has only begun to be appreciated.

As one who has recently ventured into this fast-developing area of research, and is fascinated and excited by its great potentials, I am anxious to tell others about it. Unlike many presentations from this forum, therefore, this will not be the last word from an expert, but a beginner's guide by a relative newcomer. After an introduction providing a historical perspective, I will focus on: the "classical" hypothalamic peptides and their key role in neuroendocrine regulation; peptides that mediate the perception of pain and its relief; peptides that participate in the regulation of a variety of basic functions, including fluid balance, food & water intake, reaction to stress, blood pressure, body temperature, sleep, learning & memory, and behavior; and finally, the possible link between brain peptides and mental illness.

Neurons that Look and Act Like Endocrine Cells.

In the 1930's, the late Ernst Scharrer reported that certain neurons showed morphologic features similar to those of endocrine gland cells[2]. He concluded that such neurons were capable of secreting hormonal substances, and called the phenomenon neurosecretion[3]. For the next 20 years, his ideas were ridiculed by some and rejected by most. In the early 1950's, however

Scharrer, his wife (Berta Scharrer) and Wolfgang Bargmann, reported that Gomori stains, designed for the demonstration of the secretory product of pancreatic ß-cells (insulin), selectively stained secretory material in the cell bodies of the supraoptic and paraventricular hypothalamic nuclei.[4-8] This secretory material also appeared in nerve fibers leading from these nuclei to the posterior pituitary. These pioneering observations, recently confirmed by specific immunohistochemical techniques[9], established the origin and anatomic pathways of the first neurosecretory system in the brain, and laid the foundation of the new science of neuroendocrinology.

II. THE HYPOTHALAMIC NEUROSECRETORY SYSTEMS:

A) THE HYPOTHALAMO-NEUROHYPOPHYSIAL SYSTEM.

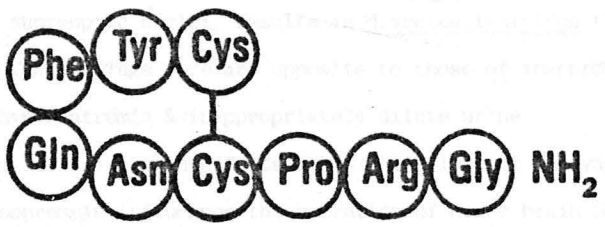
In this system, the peptides vasopressin (anti-diuretic hormone, ADH) and oxytocin are synthesized by cell bodies of the large supraoptic and paraventricular nuclei, also called the magnocellular system. The two peptides are bound to carrier proteins (called neurophysins), and transported along the axons to nerve terminals in the neurohypophysis, where they are stored and eventually released into the systemic circulation. The posterior pituitary thus serves as a storage-release center rather than a gland of internal secretion; the real source of its hormones being the hypothalamic nuclei. Note again that the terminals of the neurosecretory neurons forming the hypothalamic-neurohypophysial tract do not establish synaptic contact with other neurons or with any pituitary cells; instead, they release their secretions near the adjacent systemic capillaries. This is one example of hormonal release at a neuro-hemal junction. We will see other examples of this mechanism later.

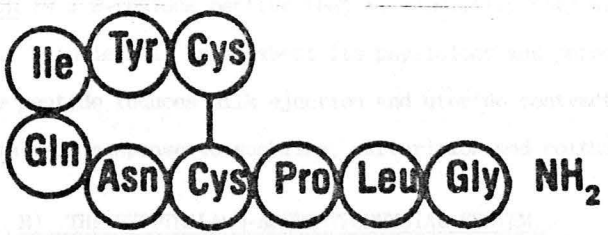
Vasopressin and Oxytocin.

Vasopressin (arginine-vasopressin) and oxytocin were the first biologically

active peptide hormones from brain, or anywhere, to be isolated to purity, chemically characterized, and synthesized. For these and other "epoch-making" achievements, the late Vincent du Vigneaud was awarded the Nobel Prize in 1955.[9a]

Vasopressin and oxytocin are closely related nonapeptides, each with a disulfide link and a terminal glycinamide (figure).





Although they originate in essentially the same areas of the hypothalamus, the two peptides have distinct and separate release mechanisms. Vasopressin (ADH) is secreted mainly in response to increased osmolality or reduced vascular volume, as by hemorrhage. In such conditions, the anti-diuretic and pressor activities of this hormone help maintain constant blood volume and osmotic content,

as well as blood pressure. Other stimuli of ADH release include angiotensin II, hypokalemia and nicotine. ADH release is inhibited by emotional stress and alcohol, as well as by increased blood volume. Inappropriate ADH secretion results in a well-known syndrome charactertized by hyponatremia, inappropriately concentrated urine, and increased urinary sodium concentration. The syndrome is most commonly associated with tumors and other lesions of the lung and CNS. Deficiency of ADH, as a consequence of massive destruction of the supraoptic nuclei, results in diabetes insipidus that is vasopressin-sensitive. The findings here are opposite to those of inappropriate ADH secretion: hypernatremia & inappropriately dilute urine.

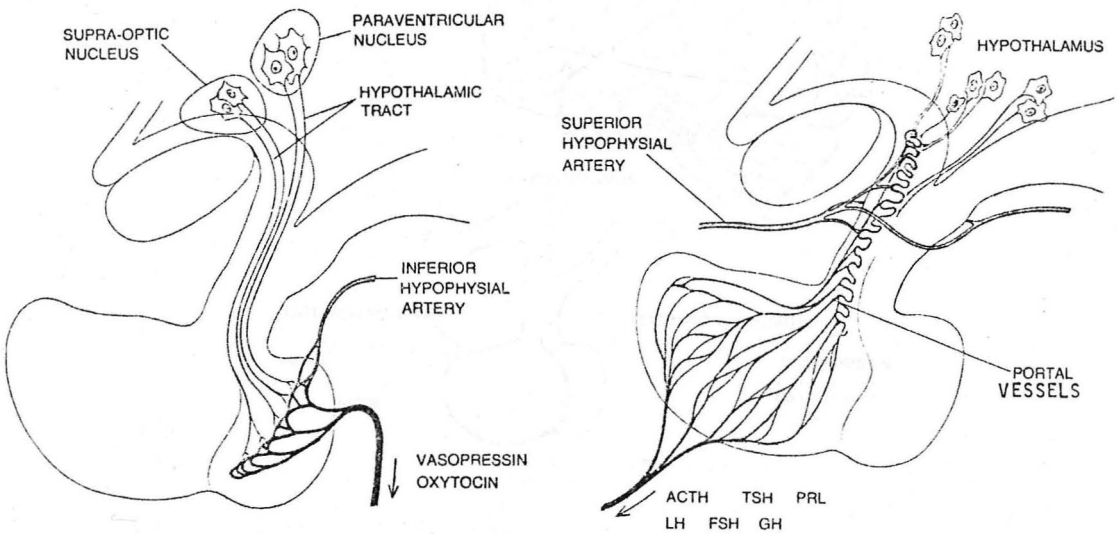
Besides its well-known effects as an anti-diuretic and vasopressin hormone, vasopressin influences the secretion of other brain hormones and other aspects of neuronal function. These effects are discussed in a later section.

Oxytocin is a 9-residue peptide that is chemically very similar to vasopressin. Much less is known about its physiology and pathophysiology in humans. The peptide induces milk ejection and uterine contractions. It is released mainly in response to suckling, parturition and coitus.

B) THE HYPOTHALAMO-ADENOHYPOPHYSIAL SYSTEM.

In the second major neurosecretory system, the source of the peptide hormones is, again, a group of hypothalamic secretory neurons. Located in the hypophysiotropic or tubero-infundibular area of the basal hypothalamus, they are also called parvicellular neurons, to distinguish them from the large magnocellular neurons of the supraoptic and paraventricular system. These neurons secrete a group of peptide hormones that control the release of adenohypophysial hormones and are therefore called hypophysiotropic or

releasing hormones. The manner in which these hormones reach the anterior pituitary is different from that in which vasopressin and oxytocin reach the posterior pituitary. Here there is no axonal transport; in fact, the innervation of the anterior pituitary is remarkably sparse. The crucial connection between the hypothalamus and anterior pituitary is a vascular one, by way of the hypophysial portal vessels (figure).

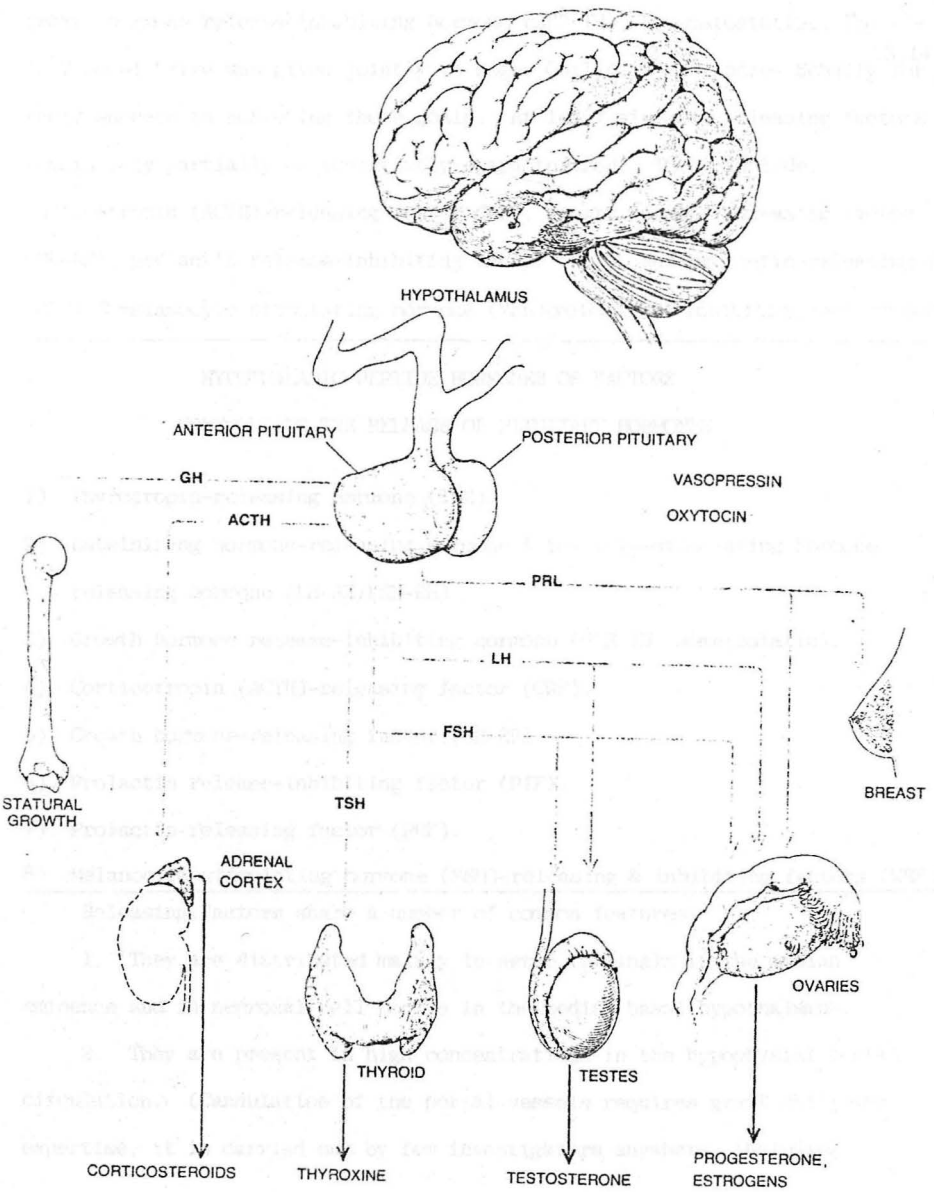


(From Ref. # 10)

The controlling influence of the hypothalamus on the anterior pituitary and the total dependence of that control on the portal vessels were established by the late G.W. Harris.[11] The hypophysiotropic neurons make contact with the portal vessels in the area of the median eminence of the tuber cinereum, located at the apex of the dome-shaped base of the hypothalamus. This is the second example of peptide release at a neuro-hemal junction. In comparison with the neurohypophysial hormones, which reach distant organs (e.g., kidney, uterus) via the systemic circulation, the hypophysiotropic hormones travel only to the anterior pituitary by means of the portal circulation (figure).

Hypophysiotropic Hormones and Factors.

Soon after Harris and others established the controlling influence of the hypothalamus on the hormonal secretion of the adenohypophysis — and thus on the functions of all the target endocrine glands (figure, ref.#10), an intensive search



began for the isolation of these hypothalamic hormones (also called releasing "factors" until they are chemically identified). This search has to date led to the chemical identification of three regulatory hormones: thyrotropin releasing hormone (TRH), luteinizing hormone-releasing hormone (LH-RH), and growth hormone release-inhibiting hormone (GHR-IH) or somatostatin. The 1977 Nobel Prize was given jointly to Roger Guillemin[12] and Andrew Schally[13,14] for their success in achieving these goals. At least six more releasing factors remain only partially or tentatively characterized. These include: corticotropin (ACTH)-releasing factor CRF), growth hormone-releasing factor (GH-RF), prolactin release-inhibiting factor (PIF), and prolactin-releasing factor (PRF) &melanocyte stimulating hormone (MSH)-releasing & inhibiting factors (MRF & MIF).

HYPOTHALAMIC PEPTIDE HORMONES OR FACTORS
CONTROLLING THE RELEASE OF PITUITARY HORMONES

1) Thyrotropin-releasing hormone (TRH).
2) Luteinizing hormone-releasing hormone & follicle-stimulating hormone-releasing hormone (LH-RH/FSH-RH).
3) Growth hormone release-inhibiting hormone (GHR-IH; somatostatin).
4) Corticotropin (ACTH)-releasing factor (CRF).
5) Growth hormone-releasing factor (GH-RF).
6) Prolactin release-inhibiting factor (PIF).
7) Prolactin-releasing factor (PRF).
8) Melanocyte stimulating hormone (MSH)-releasing & inhibiting factors (MRF & MIF).

Releasing factors share a number of common features:

1. They are distributed mainly in nerve terminals in the median eminence and in neuronal cell bodies in the medial basal hypothalamus.

2. They are present in high concentrations in the hypophysial portal circulation. (Cannulation of the portal vessels requires great skill and expertise, it is carried out by few investigators anywhere, including

John C. Porter, at this Medical Center).

3. They exert important actions on brain function over and above their effects on the secretion of adenohypophysial hormones. These actions are referred to in a later section.

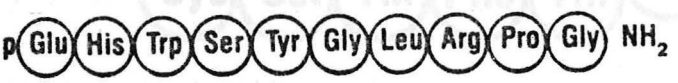
4. Like many other neural peptides, they also occur in extra-hypothalamic areas of the brain, as well as in the CSF, gastrointestinal tract, and other organs.[15]

1. Thyrotropin-Releasing Hormone (TRH).

The successful isolation, structure determination, and synthesis of TRH ended years of frustration and skepticism about the existence of the hypothalamic regulatory hormones.

The 3-residue peptide (figure) stimulates the synthesis and release of thyrotropin (thyroid-stimulationg hormone, TSH). This action makes TRH useful in differentiating between hypothalamic and pituitary hypothyroidism, although clinical use of the peptide has been largely on an investigational basis. TRH also stimulates prolactin release.

2. Luteinizing Hormone-Releasing Hormone (LH-RH).



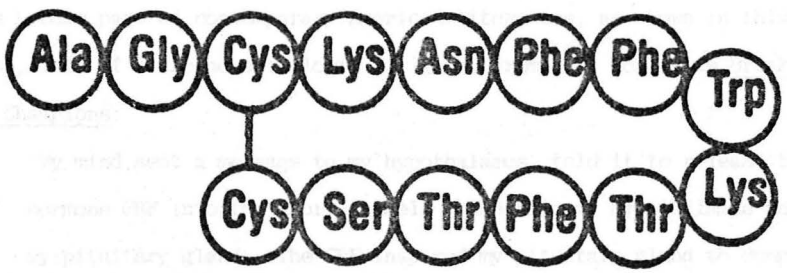
Like TRH, this decapeptide (figure) has pyroglutamyl histidyl resides at the N-terminus and an amide group at the C-terminus. LH-RH is the main link between the brain and the pituitary gland in the control of reproductive function. It releases both LH and FSH in men and women. LH-RH has been shown to be necessary for normal implantation and maintenance of pregnancy.

LH-RH has been used diagnostically to determine pituitary LH and FSH reserve, and to help in differentiating pituitary from hypothalamic causes of hypogonadism. LH-RH, alone or in combination with human gonadotropins, has been used to induce ovulation in amenorrheic women. Its use for this purpose is said to reduce the incidence of superovulation and the resultant multiple births sometimes seen with gonadotropin administration.

Synthetic analogs of LH-RH are available with many times (10-60 fold) the potency of the naturally occurring peptide, and with more prolonged activity. Such analogs are effective not only by injection but also by intranasal, intravaginal and oral administration.

Pharmacologic doses of LH-RH or its analogs may exert paradoxical, antifertility actions, blocking implantation and terminating gestation. Such actions have led to investigations of the possible usefulness of the hormone as a contraceptive.

3. Somatostatin (GHR-IH).



The presence of somatostatin was discovered in 1969 by Krulich and co-workers,[16] of our department of physiology. Three years later, it was isolated and chemically identified by Guillemin and his associates (as a cyclic 14-residue peptide, figure). Somatostatin inhibits not only GH but also TSH, insulin, glucagon, gastrin, secretin, CCK and VIP.

Because of the potent inhibitory effects of somatostatin on glucagon and GH release, and because of its presence in pancreatic islet cells, its possible role in the pathogenesis and management of diabetes has been actively investigated. Somatostatin lowers plasma glucose concentrations in normal subjects (despite its inhibition of insulin release). This effect has confirmed the important role of glucagon in carbohydrate homeostasis.[17] Somatostatin has also offered the potential for major advances in the treatment of diabetes. It reduces hyperglycemia in juvenile diabetics, and moderates or prevents diabetic ketoacidosis after the acute withdrawal of insulin from insulin-dependent diabetics.[12]

Somatostatin itself, however, is of little therapeutic value because of its multiple and short-lasting actions. Synthetic analogs with more selective and longer-lasting effects are being sought.[12,14]

4. Corticotropin (ACTH)-Releasing Factor (CRF).

The existence of corticotropin-releasing factor (CRF) and its importance has become part of contemporary American literature, as shown in this quotation, full of neuroendocrinologic insights, from Kurt Vonneguts Breakfast of Champions:

> "My mind sent a message to my hypothalamus, told it to release the hormone CRF into the short vessels connecting my hypothalamus and my pituitary gland. The CRF inspired my pituitary gland to dump the hormone ACTH into my blood stream. My pituitary had been making and storing ACTH for just such an occasion ..."

Although CRF was the first of all hypophysiotropic factors to be recognized (1955), its identity remains unknown. Vasopressin promotes ACTH release. For this reason, and because vasopressin occurs in high concentrations in

hypophysial portal blood, it was once thought to be CRF. This is unlikely since, for one thing, patients with diabetes insipidus lack vasopressin but can release ACTH in response to stress.

5. Growth Hormone-Releasing Factor (GH-RF).

Despite physiologic evidence for the presence of a hypothalamic factor controlling GH secretion, GH-RH has eluded all attempts to isolate it in pure form. Several known hormones stimulate GH release (e.g., ADH, glucagon, VIP) but none of them seems to be the primary GH-RF.

6. Prolactin-Release Inhibiting Factor (PIF).

Disconnecting the pituitary from the hypothalamus, as by section of the pituitary stalk, leads to decreased secretion of all pituitary hormones except that of prolactin, which is enhanced. Similarly, the isolated pituitary gland incubated *in vitro* secretes three times as much prolactin as the pituitary gland *in situ*. In other words, the hypothalamus exerts a net restraining effect on prolactin secretion. The identity of PIF is not known with certainty, but among the non-peptide agents possessing this activity are catecholamines, especially dopamine, and gamma-aminobutyric acid (GABA).

7. Prolactin-Releasing Factor (PRF).

Along with the dominant inhibitory influence of the hypothalamus on prolactin secretion, there is evidence for the occurrence of two or more prolactin-releasing factors. These include TRH and VIP: of the two, the latter is relatively more potent,[18] and is effective at concentrations similar to those found in hypophysial portal blood.[19]

8 & 9. Melanocyte Stimulating Hormone (MSH)-Releasing Factor (MRF), and MSH Release-Inhibiting Factor (MIF).

The release of MSH (melanotropin) from the pars intermedia of the pituitary gland is believed to be controlled by hypothalamic stimulating and inhibiting factors. MIF, which has a predominant role on melanotropin secretion, may have the structure, H - Pro - Leu - Gly - NH_2. This, as well as the identity of MRF, remain uncertain.

III. NEUROPEPTIDES AND ANALGESIA: ENDOGENOUS OPIATE RECEPTORS AND PEPTIDES.

Morphine and other active compounds from the opium poppy are among the oldest medicinal agents in use today. Abuse of these drugs and addiction to them create major health and legal problems. For these reasons, the discovery that the brain has specific receptors for opiates and makes its own morphine-like peptides has generated much excitement in the past few years. The fascinating story is best told by the men and women who participated in these discoveries. They include in alphabetical order: Hoda Akil,[20] Avram Goldstein,[21] John Hughes,[22] Hans Kosterlitz,[23] Howard Morris, Candace Pert,[24] Eric Simon,[25] Solomon Snyder[26] and Lars Terenius.[27]

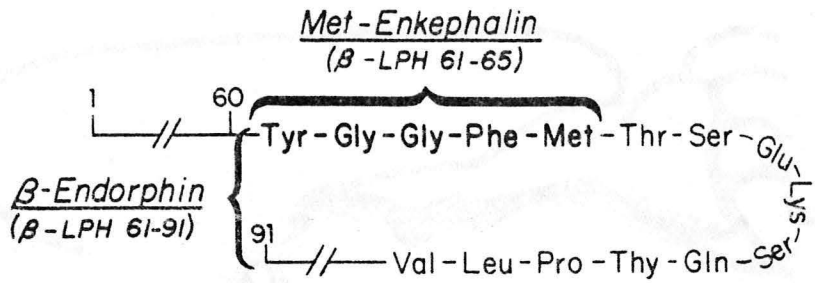
Discovery of Opiate Receptors.

The turning point probably was the finding that brain and other nervous tissues contain receptors that bind morphine and other opiates uniquely, but do not bind any known neurotransmitters. Another key observation (actually had been noted earlier, but its significance not fully realized) was that electrical stimulation of certain areas of the brain (especially the central grey) relieves pain. Then came the report that naloxone, a specific opiate antagonist, blocks the analgesia induced by electrical stimulation or by morphine. All of which raised the question: Does the brain make its own opiates?

Discovery of Enkephalins & Endorphins.

The search for opiate-like biological activity (relaxation of electrically stimulated guinea pig ileum) quickly suggested a "yes" answer to the above question. This opiate-like activity was later identified chemically as two pentapeptides, differing only in one (the C-terminal) amino-acid residue. These were called methionine-enkephalin and leucine-enkephalin (figure).

Further developments followed in rapid succession. A sharp-eyed chemist, examining the structure of β-lipotropin (β-LPH), a 91-residue molecule that had been isolated from the pituitary years earlier, noted that the sequence corresponding to positions 61-65 was identical to that of methionine-enkephalin. That is to say, the enkephalin structure was contained within that of β-LPH (figure). Next came the isolation from pituitary of another peptide with opioid properties. This new peptide (fig.), called β-endorphin, was larger than the enkephalins (31 residues) but its sequence, too, was contained within β-LPH ($\beta\text{-LPH}_{61-91}$, figure). Other endorphins that have been identified, also fragments of β-LPH, include α-endorphin ($\beta\text{-LPH}_{61-76}$) and γ-endorphin ($\beta\text{-LPH}_{61-77}$).



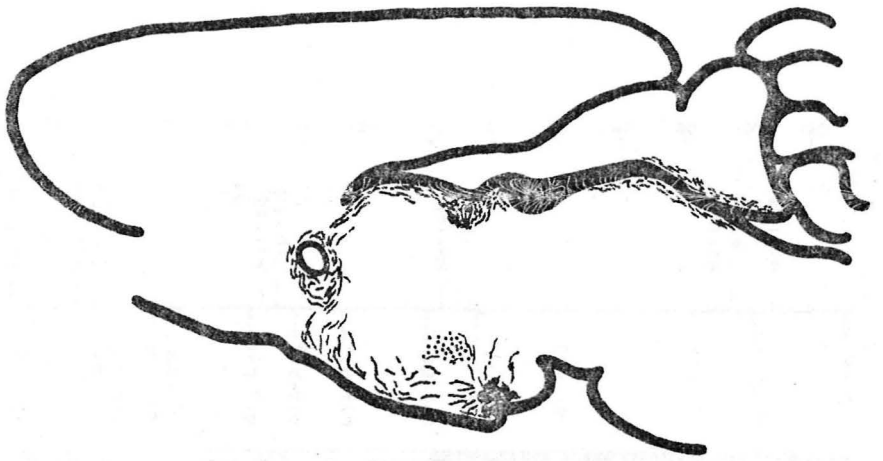
Leu-Enkephalin

Tyr-Gly-Gly-Phe-Leu

Structure of endogenous peptides. Sequence of β-endorphin corresponds to positions 61-91 of β-lipotropin (β-LPH), a 91-residue peptide. Structure of methionine-enkephalin corresponds to the first (N-terminal) 5 residues of β-endorphin. Leucine-enkephalin differs from methionine-enkephalin only in having leucine instead of methionine at C-terminus.

Distribution and Biosynthetic Relationships of Opioid Peptides.

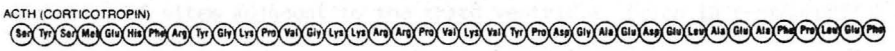
Enkephalins and endorphins are contained within separate and distinct neuronal systems in brain. β-endorphin is limited to one cluster of cell bodies in the basal hypothalamus, giving rise to fibers that innervate limbic and diencephalic structures close to the ventricular surface (figure). In contrast, enkephalin-containing neurons are widely distributed throughout the brain and spinal cord. Enkephalins are also present in the gastrointestinal tract, pancreas and adrenal medulla.

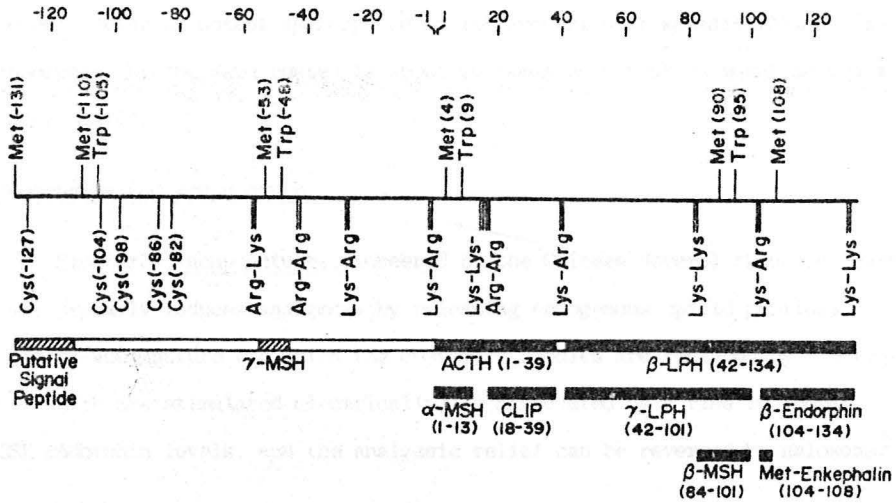


Schematic sagittal view of β-endorphin neurons in rat brain (from ref. #28).

The independent localization of enkephalins from that of endorphins is considered strong evidence that, contrary to what was thought earlier, endorphins are not the direct precursors of enkephalins.

On the other hand, neurons containing β-endorphin also contain β-LPH and ACTH (figure). This indirect evidence for a common derivation of these peptides has been recently confirmed by direct chemical proof. A common precursor has been identified for β-LPH, ACTH and β-endorphin, as well as for other naturally occurring peptides, including α-MSH. This large precursor, a 31,000 molecular weight protein, has been called pro-opiocortin. The structure of this precursor molecule has been elucidated through biochemical techniques including the cloning of its cDNA in E. coli (figure).[29]





Schematic representation of the structure of the ACTH-β-LPH precursor consisting of 4 repetitive units separated by paired basic residues. The closed bars represent the regions for which the amino acid sequence was known, and the open and the shaded bars represent the regions for which the amino acid sequence has been predicted from the nucleotide sequence of the ACTH-β-LPH precursor mRNA. (from ref. #29 , which should be consulted for further details).

Opioid Peptides and Analgesia.

It is now believed that endogenous opioid peptides are the major mediators of analgesia induced by intracerebral electrical stimulation. Electrical stimulation of sites adjacent to the third ventricle (rich in β-endorphin) relieves pain in animals and in patients; the analgesic response is antagonized by naloxone, and is associated with an elevation of the lumbar CSF levels of

endorphins. Exogenously administered enkephalins are inactive as analgesics. This is thought to be due to their rapid degradation by proteolytic enzymes.[30] Synthetic analogs with D-alanine in position 2 (replacing Gly) are more potent, being as potent as morphine on intraventricular administration. β-endorphin, by the same route, is about 20 times as potent as morphine (on a molar basis).

Endorphins and Acupuncture.

Similarly, acupuncture, pioneered by the Chinese several thousand years ago, probably induces analgesia by releasing endogenous opioid peptides. Electro-acupuncture (in which the customary needles are replaced by electrodes which are stimulated electrically) is associated by a rise in lumbar CSF endorphin levels, and the analgesic relief can be reversed by naloxone.[27]

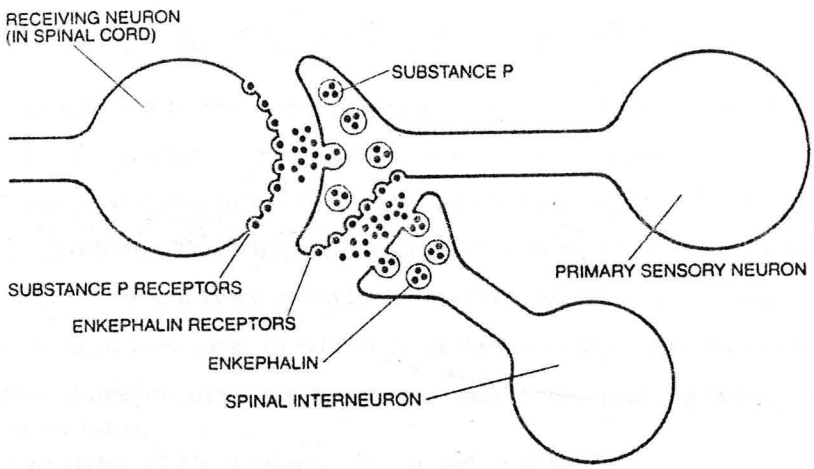
Mechanism of Action: Interaction with Substance P.

The mechanisms by which endorphins and enkephalins relieve pain are still unknown.

One possible mechanism lies in the interaction between endorphins and another neural peptide, substance P. The latter peptide, discovered almost 40 years ago, has now been characterized (figure) and found to occur widely in the brain and spinal cord, especially in the dorsal horn and dorsal roots (figure).

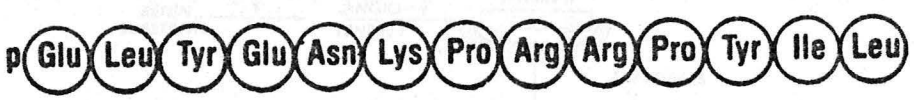
Immunohistochemical localization of Substance P in the dorsal horns of the spinal cord (from ref. #31).

Substance P is believed to play a major role in the transmission of pain signals. Recently, it has been shown that endorphins inhibit the release of substance P from the spinal trigeminal nucleus.[32] This action (figure) may explain, at least in part, the analgesic effect of endorphins.



Schema illustrating possible mechanism by which enkephalins and endorphins may produce analgesia. In the dorsal horn of the spinal cord, enkephalin neurons make synaptic contact with substance P neurons. Enkephalin inhibits the release of substance P, thereby reducing the excitatory stimulation of the receiving neuron in the spinal cord, resulting in fewer pain signals to the brain (from ref. # 31).

Another neuronal peptide that should be mentioned here is neurotensin, a tridecapeptide (figure) that causes vasodilation and hyperglycemia. Injected intracisternally in animals, neurotensin induces analgesia in minute doses, and may be at least 1000 times more potent than enkephalin as an analgesic.[33]



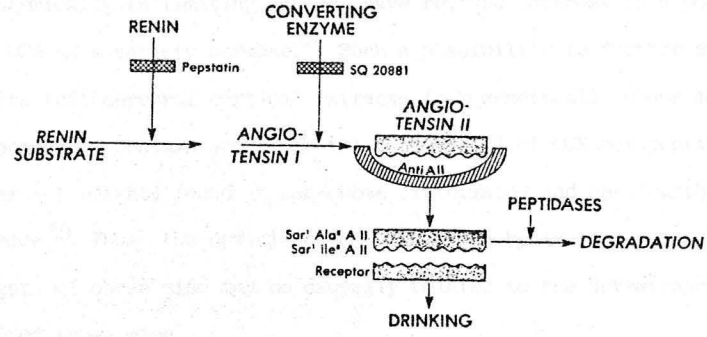
IV. NEUROPEPTIDES IN RELATION TO OTHER FUNCTIONS AND TO DISEASE.

In addition to the neuropeptides already mentioned above (neurohypophysial & hypophysiotropic peptides, enkephalins, endorphins, ACTH, substance P and neurotensin), the following peptides also occur in the nervous system: angiotensin, bombesin, bradykinin, cholecystokinin-pancreozymin (CCK), gastrin, motilin, prolactin, secretin (very recently discovered in brain) & VIP.[34,35] Many of these peptides have been shown to exhibit properties of neurotransmitters or neuromodulators.[33] Additional examples of the participation of some of these peptides in function & dysfunction are given below.

1. Regulation of Fluid Balance, Thirst and Drinking.

As referred to earlier, ADH plays a key role in regulating water clearance by the kidney. Angiotensin II, the potent octapeptide (figure), stimulates the release of ADH and of aldosterone.

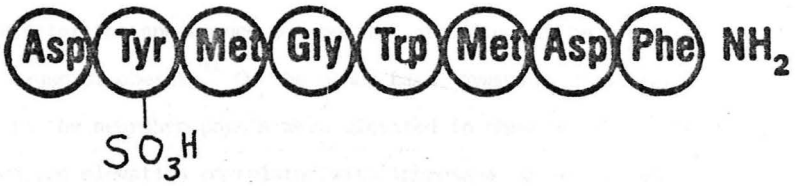
In addition, angiotensin II, acting centrally, has a pronounced dipsogenic effect, inducing thirst and drinking (figure).



Schematic summary of dipsogenic action of angiotensin II (A_2) and its suppression by competitive inhibitors of renin & converting enzyme, by anti-A_2 antibodies & by competitive analogs of A_2 (ref. # 36).

2. Control of Appetite and Eating; Relation to Obesity.

It has been known for years that parenteral administration of peptide preparations rich in CCK (figure) cause reduced food intake in mice, and that purified CCK or its octapeptide can elicit satiety-like behavior in several animal species.[37]



The C-terminal octapeptide of CCK.

Until recently, however, the physiological significance of these findings remained uncertain, since the required doses in these experiments resulted in circulating levels of the peptide that were considerably above those occurring postprandially. The demonstrated presence of high concentrations of CCK in cerebral cortex and other parts of the brain, and the recent observations that the peptide is far more effective given intraventricularly than systemically in limiting eating, have revived interest in a possible role of CCK as a satiety hormone.[38] Such a possibility is further supported by reports that cerebral cortical extracts from genetically obese mice (ob/ob) with hyperphagia contain about one-third the level of CCK-octapeptide-equivalent (per wet weight) found in non-obese littermates and one-fourth that in normal mice.[39] Thus, the deficiency of CCK in the brain (and possibly also in the gut) of obese mice may be causally related to the unrestrained appetite of these mice.

A report of elevated concentration of ß-endorphin in the pituitaries of genetically obese mice (ob/ob) and rats (fa/fa) and in the blood stream of the obese rats led to the suggestion that an excess of this peptide may play a causative role in the development of the overeating and obesity syndrome.[40] When measured in developing mice, however, the elevation in immunoreactive ß-endorphin (and α-melanotropin) was not evident until about 3months after the appearance of obesity, and thus may be a consequence rather than a cause of obesity.[41] On the other hand, immunoreactive Leu^5-enkephalin levels in the neurohypophysis were elevated in obese mice at 1 month of age, and the elevation correlated with increases in body weight.[41]

3. Regulation of Blood Pressure.

A number of the neural peptides can influence blood pressure. These include the vasopressor angiotensin II and vasopressin, and the vasodepressor VIP,[42,43] endorphins,[44] substance P, bradykinin and neurotensin.

It is too early to know the full significance of these peptides in the control of arterial blood pressure in normal and abnormal states. Already there is evidence, however, that endorphins may be important in the pathogenesis of systemic shock due to endotoxin,[45] general anesthesia,[46] blood loss, and acid aspiration in the airways. Such evidence is based on the protective effect of naloxone on the hypotension in experimental models of these conditions. VIP also is released in shock states, but its role as a mediator or modulator of the shock is still under investigation. Recently it was reported that the enkephalin content of adrenal medulla and other peripheral tissues is lower in spontaneously hypertensive rats than in normal control rats.[47] This finding raises the possibility of a role for endogenous opioid peptides (and possibly other vasodilator peptides) in the pathogenesis of essential hypertension.

4. Learning and Behavior:

There is evidence that ACTH, or active fragments thereof, affects learning by increasing motivation, improving the attentive ability, and enhancing the arousal state.[48,49] These effects have been noted in rats and in human volunteers.[48]

Vasopressin has been shown to have a role in memory processes.[49] Part of the evidence has come from the use of the Brattleboro strain of rats, which lack the ability to synthesize vasopressin and consequently have hereditary diabetes insipidus. These animals have severe memory deficits that can readily be corrected by vasopressin or its analogs.[50] Vasopressin also prevents puromycin-induced amnesia in mice and CO_2-induced and electroshock-induced amnesia in rats.[50]

β-endorphin, injected into the lateral ventricle of rats, produces not only analgesia but also catalepsy, with rigidity and locomotor inactivity.[51]

TRS increases motor activity, opposes the actions of barbiturates, and enhances the excitatory actions of acetylcholine and the lethality of strychnine.

Perhaps the most dramatic behavioral effects of any peptide are those of LH-RH.[52] This peptide induces in female rats readiness for and acceptance of sexual advances by the male, by assuming a lordotic posture with the hindquarters elevated. This effect can be shown after removal of the ovaries, hypophysis and even adrenals. The induction of lordosis begins 2-3 hours after injection of the hormone and reaches a peak 8 hours after injection.

5. Sleep:

The possibility that sleep might be induced by injection of humoral factors accumulating during wakefulness was first considered almost 70 years ago.[53] In more recent experiments, Pappenheimer found that infusing CSF from sleep-deprived goats into the ventricles of chronically implanted cats and rats caused a sleep-like state.[54] The responsible "sleep factor" is thought to be a peptide, but its precise nature has yet to be determined.

6) Neuropeptides in Relation to Mental Illness:

There already is strong evidence for a pathogenetic role for catecholamins and amino acid neurotransmitters in mental illness.[55] Evidence for a similar role for neuropeptides is still preliminary and merely suggestive:[55]

a) The bizarre behavioral effects of endorphins (see above) provide a link in what may be a causal relationship between endogenous opioid peptides and mental illness.

b) Endorphin concentrations have been reported to be altered in some psychiatric disorders.

c) Evidence has been presented that naloxone improves symptoms in some manics and some schizophrenics.

d) One group has suggested that a previously unknown peptide, leucine-endorphin, might be implicated in the reported ability of chronic renal dialysis to relieve schizophrenic symptoms.

Many more carefully designed and well controlled investigations need to be carried out to delineate the relationship of neuropeptides to mental illness.

V. CONCLUDING COMMENTS: NEUROPEPTIDES & NEUROTRANSMITTERS

It is clear that neuropeptides and neurotransmitters, all products of neuronal secretion, serve essentially the same physiologic purpose: that of mediating, modulating and regulating neuroendocrine functions. As B. & E. Scharrer first noted, it is useful to view the endocrine and nervous system as complementary, or even as two components of a single, broader system, the neuroendocrine system.[4,5]

In lower organisms, such as Hydra and sponges, neurons show evidence of neurosecretory activity comparable to that in higher animals. In such primitive animals, endocrine glands are missing, and the nervous system performs all of the existing endocrine functions. Thus, the undifferentiated "ancestral neuron" is a functionally versatile entity endowed with the means for long-distance as well as more or less localized chemical signalling. By the same token, neurohormones may be regarded as the phylogenetically oldest blood-borne messengers, capable of serving (as they do in lower animals) the dual functions of neurosecretions and hormones. In more advanced species, as in vertebrates with a developed endocrine system, many neurons are relieved of doing double duty. Even with this subspecialization fully developed, however, the close functional association between hormones and neurohormones (as well as neurotransmitters), or between neurons and endocrine cells, is fully maintained. Examples of such close and complementary relationship are: the release of peptide hormones by nerve stimulation, the stimulation of neuronal and neuroendocrine activity by peptide hormones, the modulation of actions of hypophysiotropic hormones by neurotransmitters and vice versa, the presence of some peptides in neurons as well as in endocrine cells, and the apparent presence in the same neuron of a peptide hormone together with a neurotransmitter. In short, the secretory products of the neuroendocrine system provide a spectrum of chemical messengers designed for communication at short range (neurotransmitters, paracrine secretions, hypophysiotropic hormones) or at long-range (blood-borne hormones).

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