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PHYSIOPATHOLOGY OF HYPOPHYSIAL DISTURBANCES AND DISEASES OF REPRODUCTION

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held in Buenos Aires, Argentina
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Editors

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Preface

This volume contains the papers presented at the International Symposium on Hypophysial Disturbances and Diseases of Reproduction held in Buenos Aires, July 29–31, 1981.

This meeting, organized and financed by the Fundación Argentina de Endocrinología (FAE), was the fourth of its kind sponsored by FAE in less than two years. In this manner the Foundation complies with its objective of advancement of endocrinology, both in its clinical and basic aspects, in Argentina.

The fields covered by the participants were: peptide hormones and their effect on pituitary function, regulation of prolactin secretion, aspects of the physiopathology of gonadal function, and immunology of reproduction.

The reader will find these topics of current interest. Practitioners are presented with state-of-the-art strategies to make their diagnosis more cunning and accurate while those engaged in basic research can read about newly developed concepts on hormone action and interactions. In summary, a volume appealing to all those whose interest is in endocrinology.

We must thank the participants for their willingness to share their most recent results and their experience with us.

Alejandro De Nicola
Jorge Blaquier
Roberto J. Soto

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BRAIN PEPTIDES

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Within the last decade, new findings have been presented concerning the presence of a number of peptides in brain and their concurrent localization in other tissues, especially the pituitary and gastrointestinal tract. This has been heralded as initiating an era of "new endocrinology." Hypothalamic releasing hormones have been reported to occur in extrahypothalamic sites and hormones previously described in the pituitary and gastrointestinal tract within the brain. Recent studies have been directed to assess the functional significance and mechanism of action of these peptides in the central nervous system. The concept of peptide secretion by neurons was first promulgated by Ernst and Berta Scharrer four decades ago (1940). Additionally, the concept of a substance being both a neurotransmitter and a hormone is not unique, and has long been accepted, as demonstrated by von Euler for norepinephrine in 1959. Whether or not there is concurrent regulation of the same peptide in brain and in other tissues still remains to be explored.

Evolutionary and Embryological Aspects

In addition to their important implications in the field of neurobiology, the concurrent presence of similar peptides in different tissues has raised important questions with regard to peptide evolution and embryological origins of peptides. Peptidergic neurotransmission is present in species that have no recognizable endocrine tissue (Dockray 1979). Concurrent brain and gastrointestinal localization of peptides has been noted at as early a stage

in invertebrate evolution as that of the lamprey. Substances similar to mammalian insulin have been described in unicellular eukaryotes (LeRoith et al. 1980), as has the presence of immunoreactive and bioreactive ACTH and endorphin (LeRoith et al. 1981). From another point of view, the presence of common sequences within the same peptide in two different species indicates conservation of function with mutation occurring in nonfunctional regions. The presence of common sequences in different peptides in a given species or different peptides possessing similar functions in a different species may indicate a common ancestral protein. Such findings may occur through gene duplication followed by point mutation or through amino acid substitution. Other types of mutations are also possible, such as phase shifts, deletions, or insertions in a structural gene. Two examples can be given. Vasoactive intestinal polypeptide and secretin are chemically similar. In mammals, VIP from any species studied does not stimulate pancreatic secretion, whereas VIP of avian and mammalian origin stimulates pancreatic secretion in birds. Conversely, porcine secretin only stimulates pancreatic secretion in mammals but not in birds. In the frog, caerulein, which is structurally similar to the terminal amino acid sequences of CCK-8 and of gastrin, stimulates both gastric secretion and gall bladder secretion, whereas in the mammal stimulation of the gall bladder and the stomach is mediated by the separate peptides CCK-8 and gastrin, and mammalian gastrin will not stimulate gastric acid secretion in the frog.

Reports of similar peptides in different tissues have been explained on an embryological basis by postulating that all tissues containing similar peptides were of neural crest origin (Pearse 1969). It is now realized, however, that the pineal gland, anterior pituitary, and hypothalamus arise not from the neural crest but from the neural ectoderm or specialized ectodermal placodes, while the embryological origin of the peptide-producing cells of the gastrointestinal tract remains uncertain. Another explanation for the diverse localization of peptides may come from observations indicating that peptide expression may be a common feature of many cells. Such secretion would be termed "paracrine" if the peptide were secreted locally to affect a neighboring cell; it would be termed hormonal or "endocrine" if the peptide were secreted into the bloodstream, i.e., from endocrine or gastrointestinal cells; it would be termed a "neurotransmitter" or a "neuromodulator" if the

peptide were synthesized by a neuron and released into the synaptic cleft through an axodendritic synapse or terminated presynaptically through an axo-axonic synapse; lastly, it would be termed "neurohormonal" if the peptide were present in a neuronal cell and released into the bloodstream--i.e., from the adrenal medulla or hypothalamus (Fig. 1).

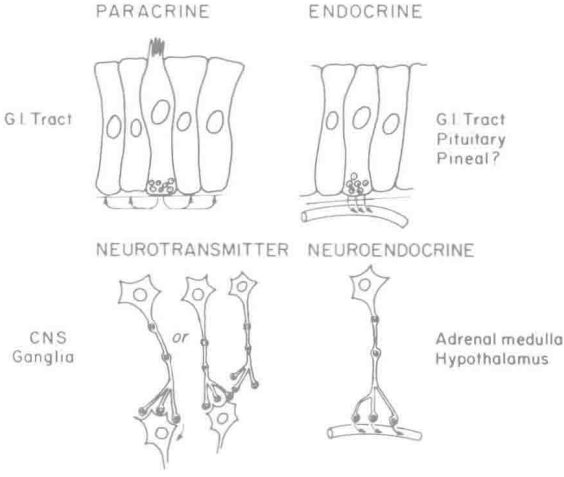

Fig. 1. Possible modes of peptide secretion (see text). From Krieger and Martin 1981.

Categories of Brain Peptides

Table 1 indicates those categories of peptides described in brain. It has been estimated that the number of synapses within the central nervous system that can be accounted for by "classic" neurotransmitters (acetylcholine, monoamines, and amino acids) represents only approximately 40% of the synapses known to be present within the central nervous system. It is therefore apparent that elucidation of the role of the recently discovered peptides and those that are still bound to be discovered will provide major new insights into central nervous system function.

Concentrations in the central nervous system of "pituitary" and "gastrointestinal" peptides are several orders of magnitude less than those of the "classic" neurotransmitters. (Such peptide concentrations range from 10^{-12} to

Table 1. Categories of Brain Peptides

Hypothalamic releasing hormones	Gastrointestinal peptides
Thyrotropin-releasing hormone (TRH)*	Vasoactive intestinal polypeptide (VIP)
Gonadotropin-releasing hormone*	Cholecystokinin (CCK-8)
Somatostatin*	Gastrin
Neurohypophyseal hormones	Substance P*
Vasopressin*	Neurotensin*
Oxytocin*	Methionine enkephalin*
Neurophysin(s)*	Leucine enkephalin*
Pituitary peptides	Insulin
Adrenocorticotropic hormone (ACTH)	Glucagon
β-endorphin*	Bombesin
α-melanocyte-stimulating hormone (α-MSH)	Secretin
Other pituitary peptides†	Somatostatin*
Prolactin	TRH*
Growth hormone	Others
Luteinizing hormone	Angiotensin II
Thyrotropin	Bradykinin
	Carnosine
	Sleep peptide(s)

*Peptides first isolated and characterized in the central nervous system.
†Not yet conclusively demonstrated in brain.
From Krieger and Martin 1981.

10^{-15} M per milligram of protein; biogenic neuroamine neurotransmitters are present in concentrations of 10^{-9} to 10^{-10} M per milligram of protein, while those of amino acid neurotransmitters are present in concentrations of 10^{-6} to 10^{-8} M per milligram of protein.) While pancreatic and hypothalamic concentrations of somatostatin are approximately equivalent, those of brain ACTH are approximately 1/1,000 of that found in the anterior pituitary, while the only peptide whose CNS concentration is greater than that described in the gastrointestinal tract appears to be cholecystokinin. Such lesser concentrations by no means minimize the importance of these peptides in the central nervous system. Evidence of concentration does not indicate turnover, and it may well be that regional, cellular, and subcellular distributions of peptides are of greater biological importance than concentrations in gross areas of

the central nervous system.

Characterization of Brain Peptides

With the rapid progress in the description of brain peptides and their commonality in several different tissues, it has become evident that there is need for criteria to characterize such peptides. Table 2 indicates the available methodologies designed to answer the numerous questions that have been raised by the presence of a given peptide in two or more different tissues. To date, the answers with regard to peptide forms present in different tissues and their anatomical localization have been obtained mainly by immunoassay and immunocytochemistry, with occasional confirmation by bioassay. Immunological techniques, however, cannot provide absolute identification; questions of specificity arise with respect to antibody cross-reactivity with similar amino acid sequences in known but unrelated peptides and potentially with similar sequences in unknown peptides. Immunocytochemistry presents additional problems such as decreased sensitivity when compared to radioimmunoassay, the presence of cross-reactivity with substances that is not detected by radioimmunoassay because of the low dilutions of the multivalent antisera used in immunocytochemical studies, as well as the potential inability to detect peptides in cell bodies if different forms are present in cell body vs. axon (i.e., precursor vs. product) when an antibody is employed which reacts only with the peptide but not with the precursor.

Localization of Brain Peptides

With the use of these methods, however, some generalizations may be made. Some peptides appear to be present with highest concentrations within cortical areas, such as cholecystokinin and vasoactive intestinal polypeptide. Others are present with highest concentrations in the hypothalamus. These include the hypophysiotropic hormones, the pro-opiocortin family, and angiotensin. There are also differences as to the localization of peptides in cell bodies. Some peptides are present in cell bodies restricted to one area. Examples of these are arginine vasopressin, oxytocin, and angiotensin, which are localized to the supraoptic and paraventricular nuclei; LHRH, which is found (depending on