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The Diffuse Neuroendocrine System[1]

Studies of This Newly Discovered Controlling System in Health and Disease

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Numerous peptides (neuropeptides) have been recently found to be present in both the nervous and endocrine systems composing what is now known as the diffuse neuroendocrine system. Two immunological methods, radioimmunoassay and immunocytochemistry, have been used here in combination to study their distribution and cellular localization. A number of these neuropeptides have recently been found to be abnormal in disease state, thus providing further information as to their role in normal and pathological conditions.

Key words: Neuropeptides; gut hormones; immunocytochemistry; radioimmunoassay.

Classical endocrinology and the fundamental concept of control of bodily functions by substances produced by distant organs was born after Brown-Séquard's classical experiments in recovery of bodily functions after treatment with extracts of the declining organ. Goiter was thereafter treated by thyroid extracts. Shortly afterwards, Bayliss and Starling (2) supported this concept by successfully eliciting an alkaline pancreatic response in dogs after intravenous injections by duodenal extracts. The idea of "control of bodily functions by circulating chemical messengers" (hormones) was thus strongly substantiated. However, recently it has become increasingly evident that the circulating hormones do not provide the complete answer in the problem of control of bodily functions.

Peptides Common to the Brain and Gut

In 1931 Von Euler and Gaddum (23) showed for the first time that an identical peptide was present in both the brain and the gut. Forty-four years later an explosively increasing number of peptides are being found to be common to these two sites, including the following neuropeptides: somatostatin, enkephalin, gastrin/CCK, bombesin and vasoactive intestinal polypeptide (VIP) (15).

Technology: Their distribution in health and disease is best investigated by two immunological procedures, radioimmunoassay and immunocytochemistry, which have been used in this study in combination (14).

Individual Peptides

Substance P

Substance P is an undecapeptide first discovered by Von Euler and Gaddum in 1931 (23).

Actions: Substance P shows a widespread spectrum of pharmacological actions in the gut, lung, brain and urogenital tract (22). It is regarded as a sensory neurotransmitter and powerful contracter of smooth muscle.

Distribution: Substance P is mostly found in the brain, gut, lung, urogenital tract and skin, where immunocytochemistry localizes it mainly to fine nerve fibers of the autonomic innervation. The distribution and the localization of the substance P nerve fibers support the theory that one of the main roles of this peptide is sensory transmission.

Pathology: Substance P nerve fibers are considerably reduced in the aganglionic segment of the gut affected by localized autonomic neuropathy, such as is found in Chagas disease and Hirschprung's disease. On the contrary, in a more generalized autonomic neuropathy, like that seen in the Shy-Drager Syndrome, this disease does not occur in the gut (3, 4).

Somatostatin

Somatostatin is a 14 amino acid peptide first isolated from the hypothalamus during the search for a controlling factor for the release of growth-hormone (6). It was later found that very large quantities of somatostatin are present in the gastrointestinal tract and pancreas, where it is localized by immunocytochemistry mostly to the D cells of the ultrastructural classification (20).

Actions: Somatostatin is a powerful endogenous inhibitor as it completely blocks the release not only of the pituitary hormones but also of most of the gut hormones as well as inhibits many gastrointestinal functions (5).

Pathology: The postulate that antral somatostatin deficiency is one of the numerous factors playing a part in the aetiopathogenesis of duodenal ulceration has recently been supported by quantitative immunocytochemical (18) and radioimmunological (7) findings indicating that there is a significant decrease of somatostatin content in the antrum of some patients with duodenal ulceration.

A significant decrease in the somatostatin content in children with "nesidioblastosis" of the pancreas and persistent neonatal hyperinsulinaemic hypoglycaemia has recently been reported (16); this may mean that lack of somatostatin is the cause of the uncontrolled insulin release in this disease.

Enkephalin

The enkephalins (leucine and methonine) are a group of two pentapeptides, one of which belongs to a much larger group of related peptides, all included under the generic term of endorphins (endogenous morphine) (10). The enkephalins are found principally in the gut, brain, adrenal medulla and some sympathetic ganglia (17).

Immunocytochemistry localizes enkephalin mostly to the gut au-

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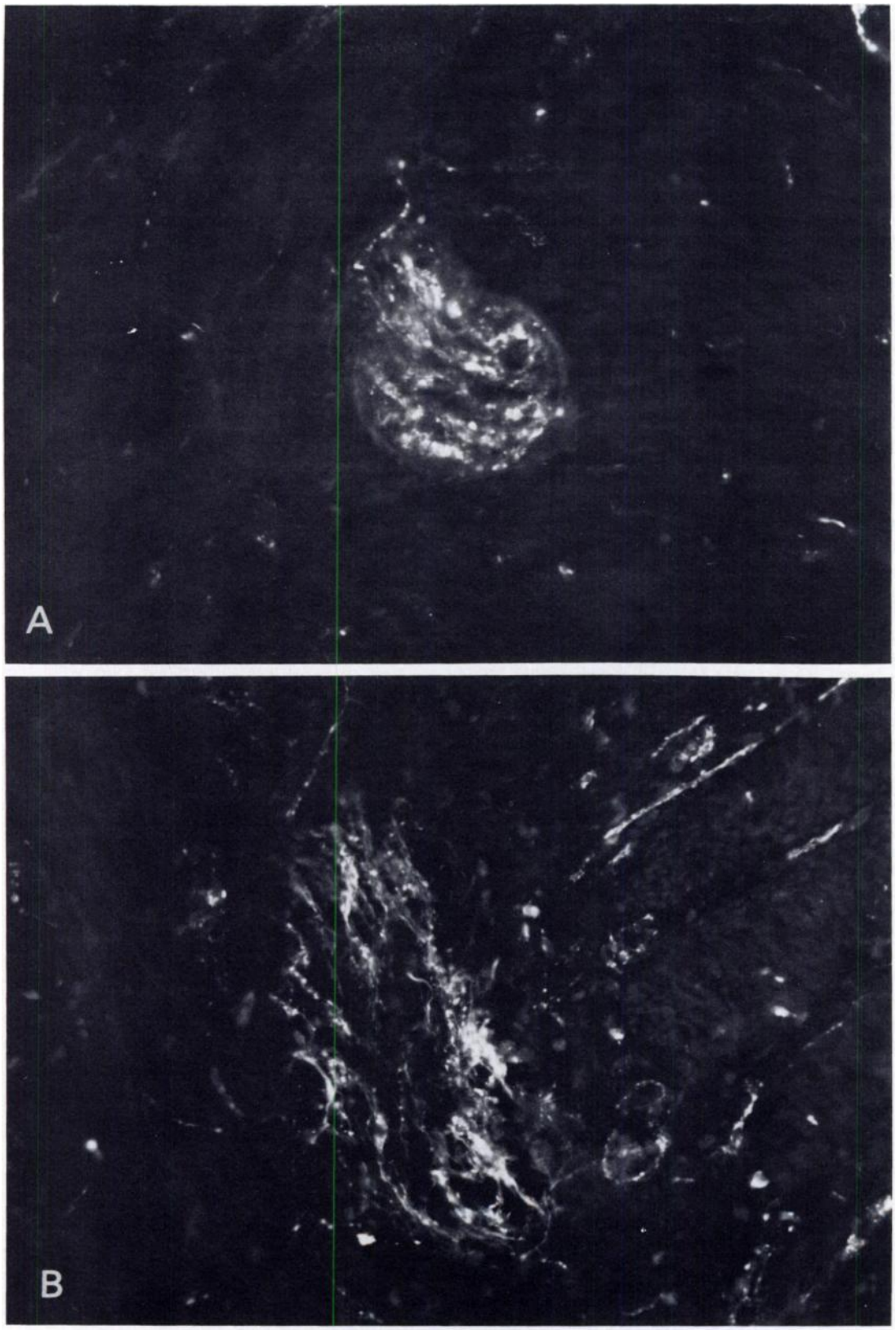

FIG. 1. A) Vasoactive intestinal polypeptide innervation of Auerbach's plexus in normal gut wall (×320). B) Vasoactive intestinal polypeptide innervation of highly abnormal Auerbach's plexus sprawling into the muscle layer in a patient with Crohn's disease (×320).

tonomic innervation. Denervation procedures as well as separate cultures of the Auerbach's and Meissner's plexuses conclusively demonstrate the intrinsic gut origin of these fibers (11). Identical experimental procedures have also been used with similar results to demonstrate the intrinsic origin of the substance P and VIP nerve fibers seen in the gut wall (11).

Bombesin

Bombesin is a 14 aminoacid peptide first extracted from the amphibian (Bombina bombina) skin (8). It was later found to have potent pharmacological actions on the mammalian gut, lung, urinary system and central nervous system.

Distribution: In man and other mammals bombesin is found in the brain, gut and lung where immunocytochemistry localizes it to typical "APUD" cells and the autonomic innervation (19).

Vasoactive Intestinal Polypeptide (VIP)

VIP is a 28 aminoacid peptide originally extracted from porcine gut. It has a wide spectrum of pharmacological actions (21). It is mainly a vasodilator, a smooth muscle relaxant and a secretory peptide.

Distribution: VIP is one of the most widely distributed peptides. It is found in the brain, gut, urogenital tract, upper respiratory tract, salivary glands and pancreas (17). A large number of neurophysiological experiments support its postulated role as a neurotransmitter. Immunocytochemistry also supports this view, as VIP is mostly present in the autonomic innervation.

Pathology: A significantly increased content of VIP, estimated by both radioimmunoassay and quantitative immunocytochemistry, has recently been found in segments of the gut affected by Crohn's disease (13). This exciting finding may possibly explain some of the poorly understood features of this disease, such as protracted diarrhea, often seen in patients with inflammatory bowel disease.

VIP levels, like substance P, are also significantly decreased in the aganglionic areas of the gut affected by Hirschprung's or Chagas' disease and remain unchanged in the generalized autonomic neuropathy seen in the Shy-Drager Syndrome (3, 4).

CONCLUSIONS

The finding of identical peptides in both the nervous and endocrine systems emphasizes the complete unity of this powerful controlling system, the diffuse neuroendocrine system. In addition, these findings reconcile two apparently opposing views, that of "nervism" postulated by Pavlov and that of Bayliss and Starling of "control of bodily functions by chemical messengers." The correctness of Feyrter's (9) concept of paracrine (local) control and that of Pearse (12), unifying by both function and origin the members of the diffuse neuroendocrine system, are further emphasized by these new and exciting discoveries.

It is thus possible to conceive that a single peptide may be acting in different ways, according to its localization and mode of release (17). This principally tripartite control system may be assumed to function: a) in a classical endocrine (circulating hormones) manner whereby peptides are released from a classical "APUD" cell, to the circulation, and act at a distance. b) in a paracrine (local) hormone manner whereby peptides are also released from "APUD" cells, but on this occasion to the vicinity, acting locally upon neighboring cells. c) in a neurocrine manner, whereby peptides are released from neuronal axons and act upon the target organ by axonal depolarization.

A peptidergic component of the autonomic innervation was suggested from the ultrastructural studies of Baumgarten et al. (1) as early as 1970. His concept was further supported by neurophysiologists who pointed out the presence of a nonadrenergic noncholinergic component of the autonomic innervation. The finding of a large and important peptidergic autonomic innervation fully supports these findings.

It is clear that the control of bodily functions is modulated by numerous factors acting in a synergistic or antagonistic manner. It is thus totally insufficient to analyse, separately, one single factor. A multidisciplinary and a multiprofile approach is what is needed. The explosive and exponential discovery of numerous neuropeptides, all with powerful controlling actions, and our increasing knowledge of their distribution, is beginning to open up the avenues for new ways of understanding the complexity of control of bodily functions and the unbalancing of this control in disease.

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