

Neuroimmunoendocrinology: Where is the Field for Study?

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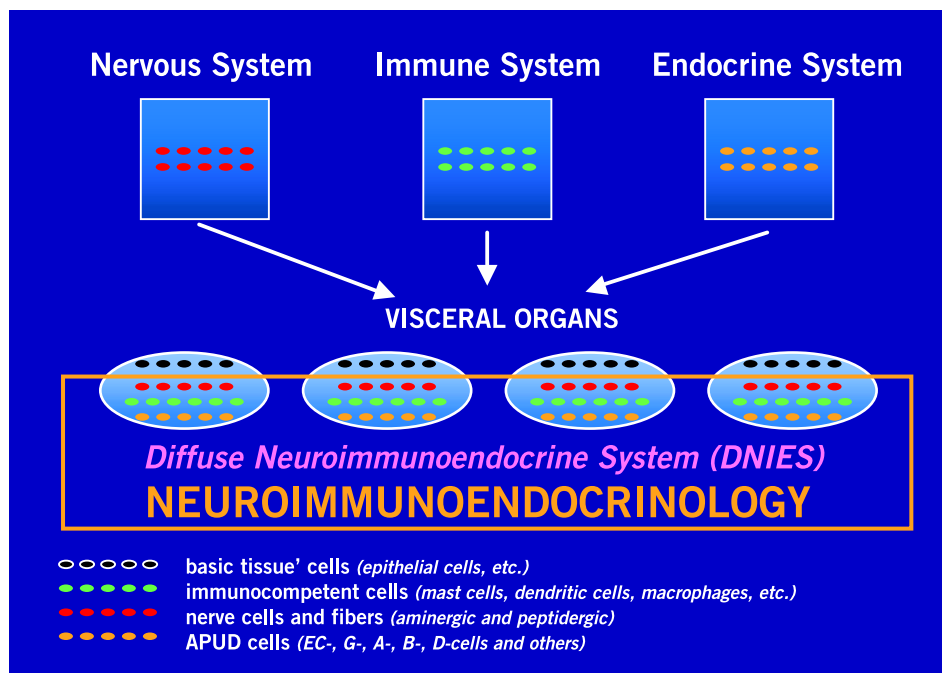
In last two decades there are more and more evidences that identical peptide hormones and biogenic amines are synthesized by different cells having neuronal, immune or endocrine assignment. Historically, Pearse was the first who in the late 1960's suggested that a specialized, highly organized cell system should exist in organisms, whose main feature was the ability of component cells to produce peptide hormones and biogenic amines. His concept was based on an extensive series of experiments for distinguishing endocrine cells in different organs, identifying endocrine cell-generated products and performing a thorough cytochemical and ultrastructural analysis of these cells. Pearse has shown that a variety of cell types, widely dispersed throughout the organism, have a common ability of absorbing monoamine precursors (5-hydroxytryptophan and L-dihydroxyphenylalanine) and decarboxylating them, thus producing biogenic amines. This ability accounts for the term APUD, an abbreviation of "Amine Precursor Uptake and Decarboxylation" used by Pearse to designate this cell series [1,2].

To date, the APUD series includes over 60 types of endocrine cells located in gut, pancreas, urogenital tract, airway epithelium, pineal gland, thyroid gland, adrenals, adenohypophysis and hypothalamus, carotid body, skin, sympathetic ganglia, thymus, placenta and other organs. Meanwhile the advent of radioimmunological methods and the rapid development of immunohistochemistry resulted in the establishment of a completely unexpected phenomenon, i.e., the same biogenic amines and peptide hormones were identified in neurons and endocrine cells. This year, 2002 marks the 25th Anniversary since Roger Guillemin had been awarded a Nobel Prize and presented his Nobel Prize Lecture entitled

"Peptides in the brain. New endocrinology of the neuron" [3].

The accumulated data did not fit the traditional concepts of hierarchical dependence within two main regulatory systems, viz., the nervous and endocrine systems. It became more and more evident that the mechanism of biological regulation should be based on the coordinated functional interaction between the endocrine system and the central and peripheral nervous systems considering the common type of information perception and transmission at subcellular, cellular and tissue levels. Many studies on identification of the same and similar physiologically active substances, acting within the nervous system as neurotransmitters and neurohormones, and locally or remotely as hormones within the endocrine system, enables both systems to be incorporated into the universal *diffuse neuroendocrine system (DNES)* [4]. Actually, it should be possible to unite in the organisms the structurally isolated nervous and endocrine systems by means of the functional relationships between biogenic amines and regulatory peptides and, to a certain extent, to provide a basis for the concept of integrated functions. Located in practically all organs and producing biologically active substances, the DNES cells play role of regulators of homeostasis acting via neurocrine, endocrine and paracrine mechanisms [5].

Later it was shown that the nervous and immune systems have well-established and very closely related interactions which regulate systemic homeostasis involving the production and secretion of a variety of cellular mediators known as *regulatory peptides* (peptide hormones, cytokines, chemokines, integrins and others) [6]. Peptide hormones, cytokines and other related molecules regulate homeostasis in the tissue of origin, either via local ac-



produce many peptides and biogenic amines which are identical to the same in the brain and central organs of the immune and endocrine systems (Figure).

Therefore, the close interrelationships between the three regulatory systems provide with anatomical/functional property – immune and nervous system have their representation in visceral organs through the peptidergic/aminergic neurons (and/or nerve fibers) as well as through the immunocompetent cells producing different peptide molecules; in its turn, the endocrine system represents in the central nervous system and immune organs through APUD cells (e.g. hypothalamic neurose-

cretory cells and others). Thus, it is obvious that cell types of all three classical regulatory systems (nervous, endocrine and immune) are represented in each visceral organ, including the central organs of homeostatic regulation (e.g. brain, thymus, thyroid, etc). Hence it follows to be possible to unite peptidergic/aminergic neurons, APUD cells and peptide-producing immunocompetent cells into a single common functional system and to extend the term *diffuse neuroendocrine system (DNES)* to a new term **DIFFUSE NEUROIMMUNOENDOCRINE SYSTEM (DNIES)**.

Exactly the DNIES is a field of the study for neuroimmunoendocrinology (Figure) as a new scientific biomedical discipline which integrates our knowledge about the signaling mechanisms of homeostatic regulation.

tions or by recruitment of external systems that facilitate restoration of local homeostasis. Studies on isolated-cell systems have confirmed that many regulatory peptides and biogenic amines are expressed within the brain. There are many peptidergic neurons and glial cells in the brain which can produce peptide hormones and biogenic amines; also besides neurons, immune cells, such as macrophages, T-lymphocytes, eosinophilic leukocytes and mast cells, which invade the brain after injury or inflammation, are a rich source of cytokines and other active molecules [7–9].

Such common chemical characteristics of three regulatory systems, namely: nervous, endocrine and immune systems stimulated the development of a new research field called *neuroimmunoendocrinology* which mainly studied the mutual interrelationships between these regulatory systems [10]. It seems necessary to underline that numerous investigations in this field of study fail to take one phenomenon into account which we consider as a very important fact: the nervous and immune cells together with APUD cells are present in most visceral organs, where they are available to

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