Pulmonary neuroendocrine cells in chronic renal failure

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Abstract

In patients with chronic renal failure, mechanical and haemodynamic changes could occur in the lungs without obvious pulmonary symptoms and findings, and their effects could pave the way to pulmonary functional disorders. Numerous studies have demonstrated that the respiratory system is a site of synthesis of many compounds, which play biological roles ascribed to hormones.

The present article is an attempt to make a synthesis of current opinions and views, based on the world literature survey and on our own studies, concerning the effect of homeostatic dysfunction of the kidneys on the morphology and action of DNES cells in the lung.

Key words: chronic renal failure, lung, DNES cells.

Introduction

A considerable progress has recently been observed in the knowledge on hormones, produced by dispersed neuroendocrine system cells (DNES). Using immunological methods, a number of APUD cells have been discovered and their hormonal activity linked to respective peptides [1, 2]. The epithelium, lining the airways and the peripheral air spaces of the lung contains, a population of amine and peptide-secreting pulmonary neuroendocrine cells (PNEC), which act as regulatory elements [3].

Pulmonary complications, such as pulmonary oedema, pleural effusions, pulmonary fibrosis, pulmonary calcification, pulmonary hypertension, haemosiderosis and pleural fibrosis are seen in patients with chronic renal failure [4, 5]. Partly, these symptoms may result from abnormal functioning of hormone-producing endocrine cells, which act in concert with higher neural and endocrine control systems to maintain the pulmonary structure and function [6].

Their precise roles remain unclear, but mediation of pulmonary response to uraemia appears to be an important function [7].

Basic characteristics of the Diffuse Neuroendocrine System (DNES). Apart from endocrine cells, which accumulate to form either distinct endocrine glands or isolated groups of cells in other specialized organs, there is an extensive system of neuroendocrine cells, found singly, among other epithelial cells, especially in the airways [3] and in the gastrointestinal tract [8]. The DNES family was proposed to include over 60 types of cells. As some relevant cells were shown to lack the APUD property and to be unable to produce bioactive peptides, the significance of the APUD concept became unclear, and the term APUD has been replaced by the term "diffuse neuroendocrine system" on the basis of the common characteristics of the endocrine-like cells and neurons [9].

Functionally, the neuroendocrine cell is a receptor-secretory cell, with surface receptors on the cellular membrane and reacting via secretion to a respective stimulus. The receptors of APUD cells have the ability to receive chemical stimuli from the blood or tissues [10].

The primary site of hormone action (paracrine effect) is situated in a direct vicinity of DNES cells, i.e., vascular endothelium and muscular coat, nerve fibres and the connective tissue. Distant target organs, according to the classic endocrine theory, are the further aim, following hormone absorption to the blood vessels [3].

Pulmonary neuroendocrine cells (PNEC). The pulmonary neuroendocrine system is represented in the bronchopulmonary tract by solitary neuroendocrine cells (NES) and the intra-epithelial innervated corpuscles to name them "neuroepithelial bodies" (NEB) (Fig.1). The precise function of interplay between these

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Figure 1. Bronchial section from the rat; a cluster and a solitary (arrows) of neuroendocrine cells. ABC method for somatostatin; mag. 200x.

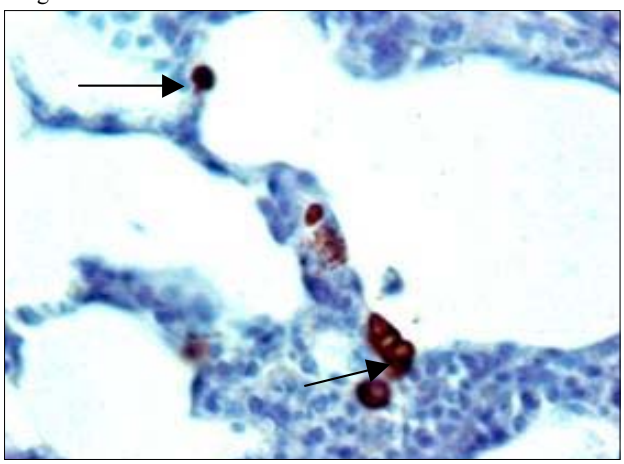


Figure 2. Photomicrograph of the lung of the rat. Haematoxylin and eosin; mag. 200x.

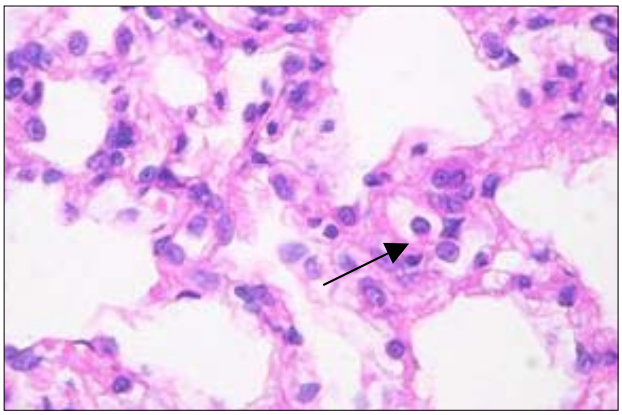


Figure 3. A fragment of the lung in the rat. Endocrine cell, impregnated with silver, according to Grimelius's method; mag. 400x.

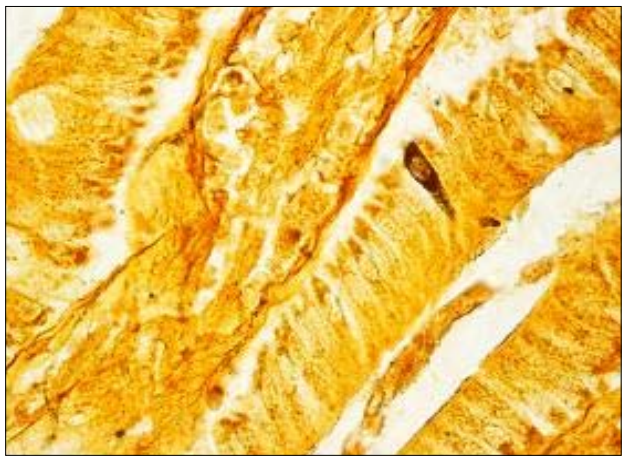
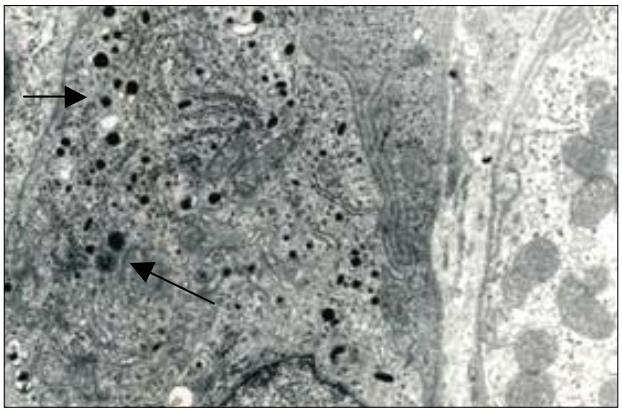


Figure 4. Electron micrograph of an enteroendocrine cell with secretory granules (arrows) from the rat lung; mag. 3000x.



two components under physiologic and pathologic conditions is not entirely clear. Current indications are such that NEB act as intrapulmonary chemoreceptors, sensitive to hypoxia and hypercapnia, whereas solitary NES cells may have a paracrine, regulatory function [11].

Morphological and histochemical properties of PNEC. In sections, stained with H+E, PNEC can be recognized by their clear cytoplasm (Fig. 2). However, with only H+E staining to prove the neuroendocrine character of the cells, PNEC determination is rather difficult. Before the advent of immunohistochemical techniques, argyrophilic stains had been used as a relatively reliable method to detect PNEC (Fig. 3).

Ultrastructure of PNEC. The apical surface of PNEC has small microvilli. In the cytoplasm of PNEC, cored dense granules are seen as a hallmark of members of the diffuse neuroendocrine system [12]. The size and electron density of the secretory granules vary, according to the animal species and their contents. (Fig. 4).

Chronic renal failure (CRF) is a pathological syndrome, developing, due to the progressive destruction of renal structures by chronic nephropathies, characterized by a gradually increasing function impairment. Direct causes of clinical symptoms of CRF and its final stage - uraemia - have not yet been recognized. Beyond argument is the assumption that most symptoms are due to metabolic disorders, caused by the accumulation of toxic substances in body fluids, which interfere with cellular processes.

Symptoms from the pulmonary tract. Lung changes in the course of uraemia attracted attention at the beginning of the 20th century. The radiological picture of pulmonary oedema was then described in patients with chronic renal failure as parahilar thickening with the shape of butterfly wings which occupy two thirds of the central pulmonary region and disappear towards the periphery, giving a zone of clearing up chest X-rays [5].

Clinical or subclinical pulmonary oedema and pleural effusions are the most common pulmonary complications. Other complications include pulmonary fibrosis, pulmonary calcification, pulmonary hypertension, haemosiderosis and pleural fibrosis in patients with chronic renal failure.

An analysis of our results [7, 13], together with literature data, indicates that PNEC cells actively participate in the pathogenesis of early dysfunctions of the bronchopulmonary tract in CRF and initiate the mechanism of subsequent adaptive response of DNES.

Conclusion

The above considerations, based on literature survey and our own results, allow the statement that CRF leads to severe

disorders in the system of endocrine cells of the lung. These disorders may involve quantitative changes and function impairment, that is, disturbances in the mechanisms of the release of polypeptide hormones (dysfunction, excessive accumulation of polypeptide in secretory granules).

Taking into consideration homeostatic disturbances of the organism, induced by the impairment of renal parenchyma and the key role of neuroendocrine cells in many organs, which regulate the functioning of the organism, it should be assumed that PNEC are greatly involved in the chain of physiological events, taking place in the lungs during uraemia. However, as long as the mechanisms of mutual relations and interactions are not elucidated, it is difficult to determine whether the clinical symptoms from the respiratory system result from the impairment of structure and function of single DNES cells, or if their occurrence is due to the reaction of enteroendocrine cells to homeostatic disorders. This can be explained by the fact that the products, synthesized in DNES cells, particularly biogenic amines (serotonin, catecholamines), act as tissue hormones which indirectly control and regulate homeostasis. A more detailed knowledge of the structure and function of neuroendocrine cells in the airways will undoubtedly contribute to better understanding of the pathological processes with PNEC involvement and may have a great practical significance in diagnostics; however, the issue still requires a number of investigations.

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