Gastrointestinal neuroendocrine cells in various types of hypertension – a review

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ABSTRACT

Recent years have witnessed a progressive increase in the number of people suffering from hypertension, which is one of the most serious health problems in the world. Hypertension results in changes leading to function disorders, not only of the organs and tissues, but also changes leading to the activation of many defense mechanisms in the cells in order to prevent damage. One of them is the expression of neuroendocrine (NE) hormones and biologically active substances, which has been the focus of extensive research for a number of years. Active involvement of NE cells and the biological and therapeutic properties of various substances synthesized by them have been confirmed in clinical trials and in various experimental models. Results obtained in many research studies indicate intense activity of enteroendocrine cells in the gastrointestinal tract in various pathological conditions, including hypertension. In the present review, we discuss the morphological and functional changes of gastrointestinal neuroendocrine cells under conditions of different types of hypertension.

Keywords: Neuroendocrine cells, gastrointestinal tract, hypertension

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Diffuse neuroendocrine system cells

In the human body, neuroendocrine (NE) cells are isolated or dispersed in many organs and systems in small concentrations. These cells are usually present in the epithelial cells lining the main body surfaces, but may also be present in the connective tissue. Despite the fact that they are anatomically independent and do not form separate organs, the endocrine cells that are distributed throughout the body constitute a particular functional system with common biochemical, cytological, and secretory properties as well as identical control mechanisms [1- 6]. On the other hand, they display a large number of morphological-functional distinctions, which form the basis for their classification [1,5,7].

The first mention of cells called neuroendocrine cells emerged in the 19th century. The term "Diffuse Neuroendocrine System" (DNES) is currently used. Those DNES cells secreting serotonin or certain other amine derivatives demonstrate amine precursor uptake and decarboxylation and are often referred to acronymically as APUD cells, e.g. [8]. This is one of the most important homeostasis systems [2, 4, 9, 10]. The system is a type of "link" between the nervous system and the hormonal system. Neuroendocrine crosstalk in the gut has been elaborated by Psichas et al. [11] and novel crosstalk in the intestinal immunoendocrine axis by Worthington [12].

The presence of DNES cells has been confirmed in many organs [11,13,14].

Morphology of neuroendocrine cells in the gastrointestinal tract

Neuroendocrine cells are located between the epithelial cells of the mucosa in the gastrointestinal tract. NE cells are morphologically different from other mucosal cells and exhibit a number of distinct neural phenotypic features, but function like endocrine cells [15]. EE cells in the GI tract are one of the fourth developmental cell lineages secreting over 30 different hormones [5]. At least 13 distinct gut NE cells exist, all of which may develop tumors oversecreting various bioactive peptides or amines [16].

Their number is estimated as $3x10^9$ [8]. Enteroendocrine cells have a variety of shapes [4, 5, 17], in H+E staining - a dark nucleus is surrounded by a bright, weakly stained cytoplasm. In terms of morphology, they can be divided into two types: the open type, when the top surface of the cell contacts the lumen of the digestive tract (Fig. 1); and the closed type, where the cells lie on the basal membrane but the top of the cell does not reach the gastrointestinal lumen (Fig. 2).

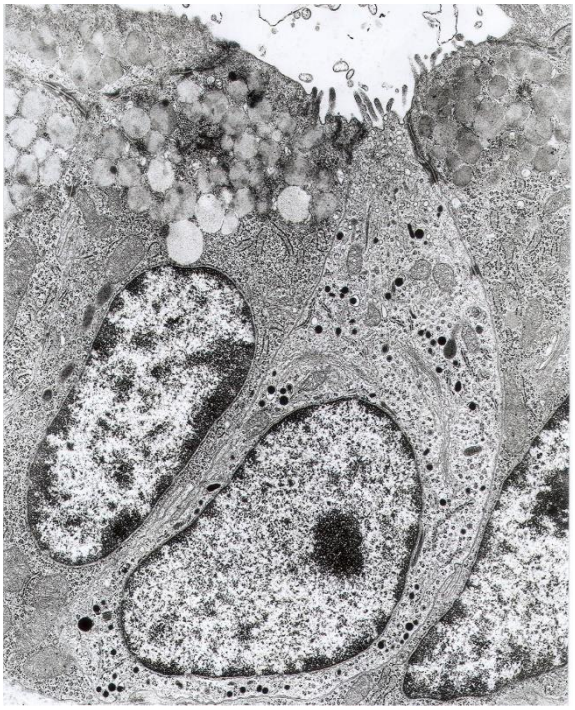

Figure 1. Neuroendocrine open-type cell with free surface microvilli and secretory granules in the cytoplasm. Magnification x4400 [Image is the property of Professor Irena Kasacka.]

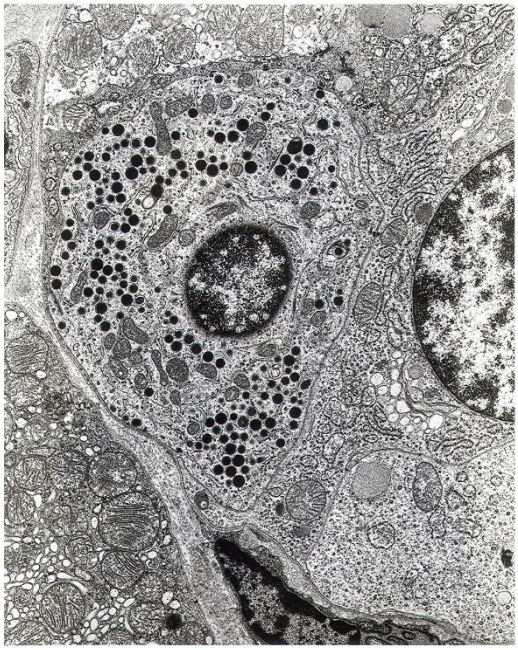

Figure 2. Neuroendocrine stomach cells of hypertensive rat. In the cytoplasm, numerous secreted grains, most of which are filled with high density electrons. Magnification x4400 [Image is the property of Professor Irena Kasacka.]

Very well developed microvillus and single pinocytic vesicles are often observed on the top surface of open cells. Since closed cells do not directly communicate with the gastrointestinal lumen, their function is probably not stimulated physicochemically by gastric or intestinal content, but their secretion is regulated by mediators from nerve endings or blood vessels [1]. Some enteroendocrine cells have long cytoplasmic protrusions thanks to which the secreted substances may be delivered directly to distant effector cells or blood vessels [18]. Effector cells can be other neuroendocrine cells, resulting in an extensive network of interconnected functional relationships [5, 18]. In electron microscopy, neuronal granules are stored in the cytoplasm of enteroendocrine cells, where biogenic amines and peptide hormones are stored (Fig.1, 2). Accurate identification and classification of enteroendocrine cells became possible only after the introduction of immunohistochemical staining methods [19], which enabled the detection of biogenic amines and peptide hormones, not only in granular secretions but also in nongranular form [5] in the cytoplasm of enteroendocrine cells (Fig. 3).

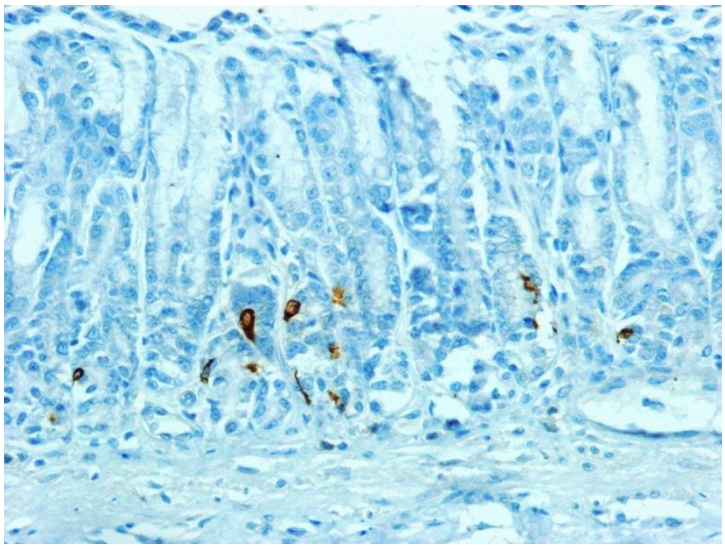

Figure 3. Microphotography of the gastric mucosa. Immunohistochemical staining of somatostatin in enteroendocrine cells. Magnification x200 [Image is the property of Professor Irena Kasacka.]

Hormones of the gastrointe-stinal tract and secretion cells

A great number of hormones secreted by different types of enteroendocrine cells present in the epithelium lining the gastrointestinal tract are now known. Their numbers have increased over the last few years (from 2011 to present) approximately over three fold [5, 20]. Intestinal enteroendocrine cells co-express six functionally related peptides [21].

These substances regulate not only the functions of the digestive system, but also contribute to maintaining the body's homeostasis. Neuroendocrine cells have been identified in each part of the gastrointestinal tract, starting with the mouth (e.g. taste bud cells) [22] to the large intestine and rectum.

The best known gastric peptide hormone is gastrin, which is secreted by G cells in the stomach and duodenum. Gastrin release occurs when food enters the stomach. Therefore, it is the main stimulant of gastric acid secretion. Its paracrine action leads to the release of histamine in the stomach [23]. Gastrin can affect the colon, pancreas, small intestine, liver, or the oesophagus. Gastrin as well as pure-ghrelin and histamine (ECL) cells are gastro-endocrine restricted [21]. In the human antral gastric mucosa, apart from the well-known endocrine cell secreting gastrin (G), somatostatin (D) and serotonin (EC), an unknown secretory product of D(1) cells and P cells has also been identified [18]. Ten years later, it appeared that P/D1 cells release ghrelin, which is distributed from the stomach to the colon (Table 1) [7]. Ghrelin is also secreted by A cells in the stomach (Table 1) [22].

However, its effects are not limited to the gastrointestinal tract, as it also affects the kidneys, ovaries, and the brain [24]. This hormone is an important regulator of sodium management, which has a direct impact on blood pressure regulation [25].

One of the first identified gastrointestinal hormones was secretin, secreted by S cells, whose secretion occurs both into the blood vessels and into the digestive tract. The primary function of secretin is the stimulation of bicarbonate secretion by the pancreas. Additionally, it affects motor activity, absorption, blood supply and metabolism, and intestinal secretion. The stomach relaxes the motility and secretion of hydrochloric acid, stimulates the synthesis of pepsin, and regulates the secretion of gastrin. Furthermore, secretin accelerates the heart rate, which may have a direct impact on blood pressure [8, 26].

Somatostatin is produced by D cells located in the stomach, the small and large intestine, and also the pancreas [27]. This hormone is an inhibitor of insulin, glucagon, and pancreatic juice production. Its action in terms of secretory cells of the gastrointestinal tract is similar [8]. Somatostatin and 5-HT are pan-GI tract enteroendocrine cell types [21]. In addition, somatostatin decreases saliva and bile secretion, inhibits gastric motility, reduces visceral blood flow, and increases and regenerates gastrointestinal cells [27].

D1 cells produce a vasoactive intestinal peptide (VIP) that inhibits acid secretion in the stomach and stimulates the endocrine pancreas. VIP also has a vasodilatory effect, thus leading to hypotension [8, 28]. VIP is secreted both by neuronal and immune cells, however the VIP-mediated action varies according to the target organ depending on the presence of a specific associated receptor, the involved immune cells, and the microenvironment of the organ [29].

Atrial Natriuretic Peptide (ANP), mainly secreted by atrial cardiomyocytes, participates in cardiovascular regulation, sodium resorption and additionally modulates gastric peristalsis and regulates gastric acid secretion by affecting the release of somatostatin and gastrin [30, 31].

Glucose-dependent insulinotropic peptide (GIP) secreted by K cells of the small intestinal mucosa, inhibits the secretion of gastrin, gastric acid, gastric and intestinal peristalsis, and stimulates insulin secretion [32, 33].

The glucose-like peptide (GLP-1) produced by the L cells of the large intestine and the final section of the small intestine inhibits exocrine pancreatic function, reduces the rate of gastric emptying, and further inhibits glycogenolysis in the liver. In experimental models, the administration of this neuropeptide increases pulse and blood pressure, reduces cardiomyocyte apoptosis, and improves heart function [34].

Cocaine- and amphetamine-regulated transcript (CARTs) peptides are recently described neuropeptides which impact, predominantly, on the body's energy metabolism [35]. The literature indicates the effect of CARTs on the hypothalamic-pituitary-adrenal axis, which plays an important role in the regulation of many processes occurring in the body, including blood pressure regulation [36]. A relatively numerous population of CART-positive neurons has been observed in the mucosal plexus of the stomach, and a co-localization of CART and VIP peptides has been observed in all segments of the digestive tract of various mammalian species [20].

Ghrelin is secreted by the parietal cells of the fundus and body of the stomach and is also produced in smaller quantities in the intestines, pancreas, kidneys, pituitary gland, and arcuate nucleus of the hypothalamus [37]. This hormone is responsible for controlling the energy balance of the body. It stimulates appetite, increases hydrochloric acid secretion, enhances gastrin secretion, regulates gastrointestinal motility, and protects the gastric mucosa. Its effect is not limited to the gastrointestinal tract, it affects the gonads, insulin

secretion, the cardiovascular system (inter alia, by suppressing cardiomyocytes and vascular endothelial cells) [38]. Ghrelin decreases arterial pressure and increases the cardiac index [2]. However, gastric ghrelin cells differ significantly from intestinal ghrelin-motilin cells [21].

Regulation of blood pressure

Arterial pressure is the result of cardiovascular system regulation, the diameter of blood vessels, and the composition and volume of extracellular fluid. Disorders of any of the systems are compensated for by the reflex action of the regulatory systems, stabilizing arterial pressure and determining blood pressure levels. Maintaining normal, constant blood pressure is aimed at maintaining proper blood flow in all organs of the body, especially the brain. Lowering or increasing mean BP beyond the scope of autoregulation constitutes a direct risk to life. Maintaining specific blood pressure through baroreceptor reflexes, arterial chemoreceptors, cardio-pulmonary mechanoreceptors, and venous reflexes occurs only while the stimulus is active and is called 'short-term regulation.' Its principle is to maintain constant blood pressure at the expense of a change in blood flow in major vascular systems (e.g. the digestive tract) as a result of neurogenic and humoral action [39].

Constant blood pressure is determined by long-term mechanisms, which act with a considerable delay. These mechanisms maintain a constant volume of extracellular fluid and consequently a constant volume of circulating blood. Cardiac capacity is the sum of organ flow, adjusted to the energy requirement and responsible for maintaining a constant oxygen level at the cellular level of a tissue or organ. The autonomic nervous system and the endocrine system participate in this regulatory mechanism. The effectiveness of regulating blood pressure depends on the functional dominance of autoregulation and vasoactive hormones over local factors that determine the adaptation of the flow to the current metabolic status of an organ or tissue [40, 41].

Etiology of hypertension

Hypertension is a chronic disease characterized by persistent or periodically elevated blood pressure above the upper reference value. Approximately 40% of the global population suffers from hypertension [42]. Hypertension is one of the most serious lifestyle diseases of the 21st century, frequently being a multifactorial impairment in the interaction between environmental and genetic components [43]. Hypertension leads to the dysfunction of many organs, cardiovascular disease, or renal disease [25, 44].

The etiology of hypertension is multifaceted. Despite considerable progress in research on hypertension, in almost 90% of the cases its cause remains undetermined. Such hypertension is called primary hypertension (idiopathic) [30]. The remaining 10% of hypertension cases are classified as secondary hypertension and are more likely to be complications or illnesses associated with other conditions (e.g. obesity, diabetes, heart disease) or vascular malformations [30, 40].

Systemic and local disorders and neuroendocrine cells of the gastrointestinal tract

The function of neuroendocrine cells is regulated by a number of factors. Secretion of substances produced by these cells remains under the control of the autonomic nervous system. It is also conditioned by calcium ion concentration and is regulated by interactions between cells. As demonstrated in a number of studies, any local lesions (e.g. inflammation or ulceration) and systemic conditions (e.g. hypertension) cause disorders of enteroendocrine cell function, reflected in changes in the number, morphology, location, and activity of these cells in the gastrointestinal tract. This illustrates the important role played by these cells in maintaining whole body homeostasis [45,46,47].

The earliest changes in hypertensive disease are changes in the structure and function of the myocardium and blood vessel walls, which results in a dysfunction of the whole body. In addition to the variety of organ complications associated with hypertension, gastrointestinal bleeding, intestinal ischemia associated with vasoconstriction, ulceration and intestinal fibrosis, or acute pancreatitis may occur. Organ changes are particularly dangerous since they are the most common causes of death [48-52].

Enteroendocrine cells of the gastrointestinal tract in arterial hypertension

In a number of experimental models [28, 30] and humans [25], changes in the position and the number of neuroendocrine cells in the gastrointestinal tract have been observed in the course of hypertension, despite an absence of significant changes in the histological structure of particular organs. Since some of the substances produced by neuroendocrine cells can affect blood vessel wall tension or heart function, they presumably play an important role in regulating blood pressure.

Research conducted on rats with experimental renal vascular hypertension demonstrated that the number of G, D, D1, and synaptophysin cells was elevated in comparison with control animals. The increase in the number of gastric secretion cells is likely to counteract the increased expression of secretory and gastric motility factors that accompany hypertension. The increased immunoreactivity of synaptophysin in the hypertonic stomach of the animals is presumably indicative of the intensification of intracellular transport of secreted grains in enteroendocrine cells [28]. The same experiment also demonstrated an increase in the number and immunoreactivity of VIP-containing cells in the pylorus of hypertensive rats [28]. These changes may be due to the inhibition of angiotensin converting enzyme (ACE) activity, leading to a decrease in the activity of the RAA [28].

In the gastrointestinal tract of animals with renal arterial hypertension, the number of cells containing atrial natriuretic peptide [30] was lower. An increase in ANP levels In the sera of these animals, which resulted in a decrease in blood pressure and normalization of heart activity, was observed [53]. The authors suggest that this may be the reason for a reduction in the immunoreactivity of ANP-producing cells in hypertensive animals.

Our own studies demonstrated an increase in the number of CART-containing cells throughout the GI tract in rats with renal arterial hypertension [35]. The mechanism of action of this peptide in hypertension has not been fully explained yet. It is assumed that by inhibiting pro-inflammatory factors CARTs participate in the body's adaptive process in hypertension, which is considered chronic inflammation [18].

Changes in enteroendocrine cell activity have also been observed in the course of intrinsic hypertension. Kasacka et al. [45] demonstrated a significant increase in the number of gastric, serotonin and somatostatin-producing cells in spontaneously hypertensive rats (SHR). The simultaneous increase in the number of gastrin-producing and somatostatin-producing cells present in the gastric mucosa of SHR may be due to the mutual functional relationships between these cells. A significant increase in the number of serotonin-producing cells is probably related to the paracrine effect of D cells which stimulate EC cells to produce serotonin. The authors of these studies suggested that a marked increase in immunoreactivity and the number of enteroendocrine cells in the stomach of SHR may be a compensatory phenomenon that alleviates, to a certain degree, homeostasis disorders caused by hypertension.

It was shown that the activity of neuroendocrine cells producing ghrelin was changed in hypertension [54,55]. Hamanda et al. [56] demonstrated increased immunoreactivity of ghrelin-containing cells in SHR compared with control Wistar Kyoto (WKY) animals.

A significantly higher number of immunopositive cells has also been reported in the stomach and duodenum of renal vascular hypertension [57]. This hormone has an antihypertensive effect, and the increase in the number of immunoreactive cells may be an adaptive response to homeostatic changes in the function and morphology of many organs in the course of hypertension, as suggested by Janiuk et al. [58].

The results of numerous studies have shown that ghrelin, by increasing the volume of excreted urine, can lower blood pressure, which may form the basis of a compensatory mechanism in hypertension. Research conducted on salt-induced hypertensive rats by Aoki et al. [59] demonstrated that ghrelin had antihypertensive effects in hypertensive animals. The effect of ghrelin on blood pressure has also been confirmed in humans [60].

In patients with hypertension, a postprandial increase in gastrin and a decrease in blood pressure have been observed [25]. One of the mechanisms responsible for regulating blood pressure is maintaining appropriate sodium levels and decomposing it in extracellular spaces [61]. Hypertension develops through prolonged accumulation of sodium, and compensatory mechanisms are unable to correct these disorders [62]. This is a mechanism frequently found in overweight or obese patients. It is believed that gastrin may impact renal receptors, resulting in excess sodium excretion, thus contributing to the maintenance of normal blood pressure [25, 61].

Our understanding of the biology and genetics of the intestinal endocrine lineage cells in normal and pathological states as well as novel immune mechanism in hypertension and cardiovascular risk improve available therapies considerably [4,16,57,63]. The present review contributes to the understanding of this topic.

CONCLUSION

We highlight that gut NE cells possess plastic morpho-biochemical properties in pathological conditions, similar to many other cells, including neurons. Morphologically, NE cells manifest their plasticity both in cytological and anatomical levels (cell parameters, their number, and distribution). The modified secretion process has been improved not only at the immunohistochemical level but also at the level of gene expressions showed by many other studies. From several NE cell types that have been studied, cells secreting SOM were distinct in their property of reaction to pathological conditions in various types of HT. The morpho-functional properties of NE cells depend on the cell

type, as well as on pathological conditions such HT type , its duration, and the age of the animals.

Conflicts of interest

The authors declare no conflicts of interest.

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