REVIEWS

Hormonal Function of Nonendocrine Cells: Role of New Biological Phenomenon in the Regulation of Homeostasis

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Recent studies revealed a new biological phenomenon: hormone synthesis in nonendocrine cells. Here we review hormone production by 4 types of nonendocrine cells of different origins, localizations, and functions and the role of this biological phenomenon in the maintenance of homeostasis. Our results and published data suggest that hormonal function is a general biological property not specific for only neuroendocrine cells, but rather typical of all living cells independently of their origin and role in the body.

Key Words: *hormones; nonendocrine cells; homeostasis regulation; biological functions*

The phenomenon of hormone synthesis by nonendocrine cells attracts much recent attention. Previous studies showed that neurons, some immunocompetent cells [15,18], mast cells, lymphocytes, eosinophils, endotheliocytes, thymic epitheliocytes, monocytes, platelets, chondrocytes, placental trophoblast and amniotic cells, testicular Leydig cells, endometrial cells, retinal photoreceptors and amacrine cells, skin Merkel cells, and macrophages produce various hormones, including serotonin, melatonin, histamine, endorphins, endothelins, matrilysin, natriuretic peptide, vasoactive intestinal peptide, thymosins, somatostatin, prolactin, and adrenocorticotropic hormone (ACTH, Table 1). Since nitric oxide (NO) is considered to be a gaseous hormonal substance [10], various NO-synthesizing cells can be also referred to hormone-producing.

Here we review the ability of 4 types of nonendocrine cells characterized by different origins, localizations, and functions to synthesize and secrete hormones and analyze the role of this biological phenomenon in the regulation of homeostasis.

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Lymphocytes. Recent studies showed that mammalian peripheral blood lymphocytes (PBL) synthesize melatonin, prolactin, ACTH, and somatotropin [11,28,32].

Melatonin (N-acetyl-5-methoxytryptamine) is synthesized by pinealocytes, enterochromaffin cells of the gastrointestinal tract, and other extrapineal cells of the neuroendocrine system [30]. This hormone acts as a universal regulator of biological rhythms, modulates cell differentiation and division, inhibits proliferation of some experimental tumors [3], and stimulates interferon production [25]. Chromatography and radioimmunoassay revealed melatonin synthesis and metabolism in lymphocytes [11].

Prolactin, the major adenohypophyseal hormone stimulating lactation is also synthesized and secreted by human PBL. Prolactin is produced in concanavalin A- or phytohemagglutinin-stimulated lymphocytes and acts as a growth factor promoting proliferation of lymphoid cells [32].

ACTH, the hormone produced by the adenohypophysis and stimulating corticosteroid synthesis in the adrenal cortex, was also found in lymphocytes [28,29]. In lymphocytes, ACTH regulates antibody production. Immunocytochemical assay showed the presence of

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serotonin, melatonin, and β-endorphin in secretory granules of natural killer cells [21,22]. These hormones are believed to regulate cytotoxic functions of natural killer cells.

Thymocytes. Previous studies showed that thymocytes synthesize luteinizing hormone [33]. Due to the presence of mitogenic activity, this hormone probably plays a role in the maturation of human T cells and acts as an autocrine/paracrine growth factor modulating thymocyte proliferation. Moreover, thymulin, α_1-thymosin, and thymopoietin possessing hormonal properties were shown to be synthesized in the thymus [1]. Thymic hormones regulate functions of the endocrine and nervous systems, but, surprisingly, produce less pronounced effects on the immune system.

Endothelial cells. Vascular endothelial cells synthesize and secrete vasoconstriction peptides [14,16]. Endothelin (ET) was isolated and characterized in 1988 [44]. It was shown that ET is produced not only by endotheliocytes, but also by other cells [19]. ET synthesis was revealed in the kidneys, liver, heart, intestine, smooth muscle cells, melanocytes, and parathyroid glands [36]. Three isoforms of this abundant molecule (ET-1, ET-2, and ET-3) are not genetically related and present in tissues in various ratios [19].

It was believed that the major function of ET is regulation of the vascular tone. However, the concentration of circulating ET is too low to cause systemic vasoconstrictive effects [41]. Probably, ET plays an important role in the mechanisms of local vasoconstriction [25].

It should be emphasized that endothelins act as hormones in the endocrine system. Endothelins formed in the reproductive glands are involved in the negative feedback regulation of pituitary functions by modulating secretion of various hormones [6,39].

The major physiological role of endothelins is still unclear. However, these compounds are suggested to produce various biological effects.

Retinal cells. Some retinal cells synthesize melatonin [36] and somatostatin [8]. The key enzyme catalyzing melatonin synthesis, hydroxyindole-O-methyltransferase (HIOMT), was found in the retina in 1971 [7]. It was shown that pinealectomy does not decrease the content of retinal melatonin [31,45]. Therefore, the hormone is synthesized (but not accumulated) in the retina.

Melatonin and HIOMT are localized in the cytoplasm of photoreceptors [40,43]. Taking into account the morphofunctional and histogenetic similarity be-

TABLE 1. Hormone Synthesis by Nonendocrine Cells

Cells	Hormones
Lymphocytes	ACTH, STH, prolactin, and melatonin
Mast cells (mastocytes)	Melatonin, serotonin, histamine, and VIP
Platelets	Serotonin and melatonin
Eosinophils	Serotonin, melatonin, and VIP
Macrophages	VNP
Natural killer cells	Serotonin, melatonin, and endorphins
Monocytes/macrophages	Matrilysin
Endotheliocytes	Endothelins, NO, and VNP
Retinal photoreceptors	Melatonin
Retinal amacrine cells	Somatostatin
Thymocytes	LH, thymulin, thymopoietins I and II, and α_1-thymosin
Thymic epitheliocytes	Serotonin, melatonin, and prostaglandins
Astrocytes	NO, endothelins, prostaglandins, nerve growth factor
Leydig's cells	Melatonin
Glomerulocytes	Endothelins
Atrial myocytes	ANP
Ventricular myocytes	VnNP
Merkel cells	Endorphins
Chondrocytes	Cartilage growth factor
Placental trophoblast and amniotic cells	Leptin and melatonin
Endometrial cells	Melatonin

Note. STH: somatotropic hormone (somatotropin); VIP: vasoactive intestinal peptide; VNP: vascular natriuretic peptide; LH: luteinizing hormone; ANP: atrial natriuretic peptide; and VnNP: ventricular natriuretic peptide.

tween the retina and pituitary gland and the evolutionary development of mammalian pineal gland from amphibian light-sensitive organs, the synthesis of melatonin in retinal photoreceptors is not surprising [17].

The role of retinal melatonin is poorly understood. Published data suggest that retinal melatonin acts as a neurotransmitter or local hormone responsible for synchronization of physiological processes in the retinal pigment epithelium with the light-dark cycle.

Somatostatin was found in retinal amacrine cells [9] of the cats [42], guinea pigs [38], rats [12], rabbits [34], and primates [35]. Published data show that 1% amacrine cells contain somatostatin [42] playing a role of a neurotransmitter [9].

Biological role of hormone synthesis in nonendocrine cells. Synthesis of hormones in lymphocytes, immunocompetent, and epithelial cells of the thymus confirms the reciprocal interrelation between the endocrine and immune systems. It was reported that thymectomy completely suppressed the postnatal development of ovarian follicles. On the other hand, transplantation of the thymus to athymic nude mice restored the dynamics of age-related changes in the content of follicle-stimulating and luteinizing hormones in the pituitary gland [33]. The synthesis and secretion of neuropeptides by immunocompetent cells justify the term neuroimmunoendocrinology [1].

Endothelins produced by the vascular endothelium are abundant substances regulating hormone secretion in endocrine organs [26]. Taking into account that endothelins found in various organs play an important role in the hypothalamopituitary axis of the neuroendocrine system, their presence in immunocompetent cells would indicate the existence of not only direct but also inverse relationships between the nervous, endocrine, and immune systems. This interaction is realized via ET-regulated neuropeptide production by immunocompetent cells in peripheral tissues.

At first sight, the synthesis and secretion of melatonin and somatostatin by retinal nonendocrine cells (photoreceptors and amacrine cells) are not related to hormonal functions of lymphocytes and endotheliocytes. However, since retinal cells synthesize ET [36], these compounds probably regulate hormone production in the retina.

We developed a new concept suggesting the existence of nonendocrine cells possessing hormonal functions and regulated by endothelins.

The effects of hormones on target cells are realized via the blood (endocrine mechanism), synapse (neurocrine mechanism), or extracellular space (paracrine mechanism). Therefore, various cells can be considered as hormone-producing independently on the chemical nature of synthesized substances.

A large body of data allows us to revise the general postulate of endocrinology: "hormonal function is specific for endocrine cells having the same origin and similar structure". This postulate was doubted when biogenic amines and peptide hormones were found in neurons and APUD cells in various organs referred to the diffuse neuroendocrine system [23,30]. It is now generally accepted that cells of the diffuse neuroendocrine system in various organs producing biologically active substances regulate homeostasis via the neurocrine, endocrine, and paracrine mechanisms [20,24].

Therefore, nonendocrine cells are an essential component of a universal system controlling and protecting the body. Hormones produced by these cells act as paracrine signal molecules, local regulators of cell, tissue, and organ interactions. Biologically active substances produced by nonendocrine cells act as hormones and reach target cells via the circulation. In both cases, some endocrine cells (mast cells, eosinophils, monocytes, platelets, and macrophages) absorb biologically active substances from the blood or extracellular spaces and transfer them to the site of action.

Thus, hormonal function is a general biological property of all living cells independently of their origin and role in the body, rather than specific function of neuroendocrine cells.

It is a striking fact that more than 100 years ago (in 1855) Claude Bernard hypothesized that not only endocrine glands, but also other organs in the body possess the property of internal secretion, the major mechanism involved in the maintenance of homeostasis [4]. This idea was confirmed by recent studies. The phenomenon of hormonal function of nonendocrine cells will elucidate the mechanisms of cell-cell interactions and their role in the maintenance of homeostasis under normal and pathological conditions.

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