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Ubiquitous expression and multiple functions of biologically active peptides

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ABSTRACT

Biologically active peptides are widely expressed throughout in human bodies. For example, endothelin-1 and adrenomedullin are expressed in almost all types of cells, including neurons, glial cells, fibroblasts, macrophages, cardiomyocytes, vascular endothelial cells, epithelial cells and cancer cells of various origins. Expression of both these peptides is induced by stimuli, such as hypoxia and inflammatory cytokines. They have a variety of biological functions, such as effects on brain function, hormone secretion, the cardiovascular system and cell proliferation. By contrast, orexins (hypocretins) and melanin-concentrating hormone (MCH) are specifically expressed in the hypothalamus, particularly in the lateral hypothalamus, although very low concentrations of these peptides are found in the peripheral tissues. Orexins and MCH play coordinated, but distinct physiological roles in the regulation of sleep-wake cycle, appetite, emotion and other brain functions. The cardiovascular system is regulated by cardiovascular peptides, such as natriuretic peptides, endothelins and angiotensin II. The renin-angiotensin system (RAS) is one of the most classical regulatory systems on blood pressure, electrolytes and kidney. (Pro)renin receptor is a novel member of the RAS and may be related to the pathophysiology of microvascular complications of hypertension and diabetes mellitus. Moreover, (pro)renin receptor forms a functional complex with vacuolar-type H^+-ATPase, which plays an important physiological role in maintaining the acidic environment of intracellular compartments including secretory vesicles. Perhaps, the complex of (pro)renin receptor and vacuolar-type H^+-ATPase may be important for the post-translational processing and secretion of many biologically active peptides.

Introduction

More than 45 years ago, A.G.E. Pearse showed that peptide-secreting cells have common morphological features and proposed the *Amine and Precursor Uptake Decarboxylation (APUD)* theory [64,65]. The APUD series comprised of pituitary corticotrophs and melanotrophs, pancreatic islet cells, thyroid C cells, adrenal medulla cells, gastrointestinal argyrophil or enterochromaffin cells, and lung endocrine cells. During the last 35 years, it has been shown that biologically active peptides are produced and secreted, not only by the APUD cells, but also by non-APUD cells. For example, atrial natriuretic peptide (ANP) and brain natriuretic peptide (B-type natriuretic peptide, BNP) are produced and secreted by cardiomyocytes [1,30], endothelin-1 (ET-1) by vascular endothelial cells [100], and leptin by adipocytes [19]. Thus, it is now known that biologically active peptides are expressed in almost all cell types of human and other animals, and have multiple biological functions.

In this review, we selected endothelins (ETs) [100], adrenomedullins (AMs) [35], melanin-concentrating hormone (MCH) [32] and orexins [15,70] from among numerous biologically active peptides, and discussed their distribution and regulation of expression, which were closely related to their multiple biological functions. We then discussed on (pro)renin receptor ((P)RR) [59], which may be related not only to the angiotensin generation, perhaps but also to the secretory pathway of many biologically active peptides.

Endothelins and adrenomedullins

ET-1 is a potent vasoconstrictor peptide discovered in porcine aortic endothelial cells [100]. ET-1 consists of 21 amino acids and has two disulfide bonds. ET-1 causes vasodilatation via the

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release of nitric oxide from the vascular endothelial cells. There are at least two other types of endothelins (ETs), ET-2 and ET-3 [28]. ETs act via the G-coupled receptors; ET type A receptor (ET_AR) [71] and type B receptor (ET_BR) [2]. The homozygous ET-1 gene knockout mice died of respiratory failure at birth and had morphological abnormalities of the pharyngeal-arch-derived craniofacial tissues and organs, suggesting that ET-1 is essential for normal development [36]. Defects in the gene encoding ET-3 or the ET_BR produced aganglionic megacolon and pigmentary disorders in mice and humans, indicating that interaction of ET3 with the ET_BR is essential in the development of neural crest-derived cell lineages [6]. Moreover, ETs have multiple biological actions including neurotransmitter/neuromodulator actions, modulatory actions on hormone secretion, and cell proliferatve and hypertrophic actions [5,80]. An antagonist against ET_AR is now used for the treatment of idiopathic pulmonary hypertension [46].

By contrast, adrenomedullin (AM) is a potent vasodilator peptide discovered from human pheochromocytoma tumor tissue [35]. Human AM consists of 52 amino acids and has one disulfide bond. There are five distinct AM cDNAs in the pufferfish, Takifugu rubripes (TrAM-1, -2, -3, -4, and -5) [61]. Human adrenomedullin 2/intermedin (AM2/IMD) was identified by genomic searching [67,93]. AM and AM2/IMD belong to the calcitonin/calcitonin gene-related peptide (CGRP) family, which includes calcitonin, CGRP, and amylin. The receptor system for CGRP, AM and AM2/IMD consists of the complex of calcitonin receptor-like receptor (CRLR) and receptor activity-modifying proteins (RAMPs) [45,67]. There are three RAMPs, RAMP1, RAMP2, and RAMP3. The complex of CRLR/RAMP2 or CRLR/RAMP3 forms the AM receptor, whereas the CRLR/RAMP1 complex forms the CGRP receptor. AM2/IMD binds non-selectively to all three CRLR/RAMP complexes: CRLR/RAMP1, CRLR/RAMP2 and CRLR/RAMP3.

Studies on the AM gene knockout mice showed that AM(−/−) embryos died at midgestation with extreme hydrops fetalis and cardiovascular abnormalities, including overdeveloped ventricular trabeculae and underdeveloped arterial walls [10]. These findings suggested that AM plays an essential role in normal development of cardiovascular system. In addition to the vasodilator action, AM and AM2/IMD have various biological actions, such as neurotransmitter/neuromodulator actions, anti-oxidative stress action, a positive inotropic action, natriuretic and diuretic actions, modulatory actions on hormone secretion, a modulatory action on cell proliferation, an anti-apoptotic action, and anti-bacterial action [18,34,78].

Both ET-1 and AM are ubiquitously expressed in various types of cells, including neurons, glial cells, fibroblasts, macrophages, cardiomyocytes, vascular endothelial and smooth muscle cells, epithelial cells and adipocytes [16,37,40,74,78,80,95]. ET-1 and AM are also produced and secreted by various types of cancer cells [37,52,78,85,92]. Fig. 1 shows expression of AM mRNA in human cancer cell lines by Northern blot hybridization [78], which indicates that AM is expressed not only in neuroblastoma cells, but also in non-APUD tumor cells. Moreover, expression of AM and ET-1 is induced by certain stresses, such as hypoxia, inflammatory cytokines and oxidative stress [22,31,52,53,68,77,85,92]. Exposure to hypoxia induced AM and ET-1 mRNA expression in cultured human coronary artery endothelial cells (Fig. 2), and augmented the secretion of AM and ET-1 peptides into the culture medium [53]. The cells may be able to secrete the AM and ET-1 peptides by such induction mechanism in the environmental emergency. By contrast, the induction of AM2/IMD expression by these stresses had not been reported [83]. It has recently been shown that the cAMP signaling by thyrotropin induces AM2/IMD expression in thyroid [49].

Both ET-1 and AM are ubiquitously expressed throughout in the body and may play an essential role in normal development and maintaining the life. The expression induction by certain stresses is another common feature of ET-1 and AM, and may help these peptides to act in the environmental emergency of cells.

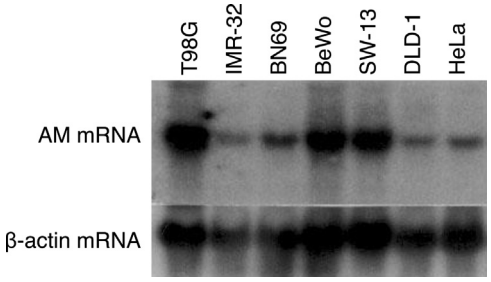

Fig. 1. Northern blot hybridization of adrenomedullin (AM) mRNA in various human tumor cell lines; T98G glioblastoma cells, IMR-32 neuroblastoma cells, NB69 neuroblastoma cells, BeWo choriocarcinoma cells, SW-13 adrenocortical carcinoma cells, DLD-1 colorectal carcinoma cells, and HeLa cervical carcinoma cells. Each lane contained 15 μg of total RNA. Lower panel shows β-actin mRNA as an internal control. Reproduced from Ref. [78] with kind permission from Tohoku University Medical Press.

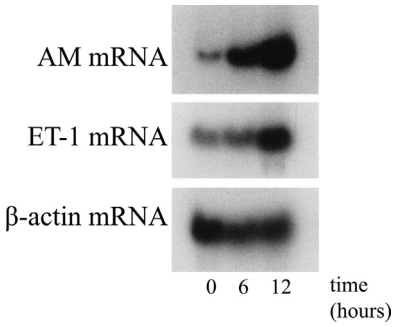

Fig. 2. Adrenomedullin (AM) mRNA and endothelin-1 (ET-1) mRNA expression in human coronary artery endothelial cells exposed to hypoxia for indicated time. In hypoxia experiments, the cells were cultured for 6 and 12 h at 37 °C in a chamber with 5% CO_2/94% N_2/1% O_2. Each lane contains 15 μg of total RNA. Lower panel showsβ-actin mRNA as an internal control. Expression of both AM mRNA and ET-1 mRNA was induced by hypoxia.
Reproduced from Ref. [53] with kind permission from Elsevier Science.

Melanin-concentrating hormone and orexins

Hypothalamic hormones are peptide hormones, which are produced by hypothalamic neurons, and regulate the production and secretion of anterior pituitary hormones [84]. They are transported to the median eminence by the axonal transport, where they are released and diffuse into the pituitary portal vessels to act on the anterior pituitary cells. Hypothalamic hormones comprise of corticotropin-releasing hormone (CRH), growth hormone-releasing hormone (GHRH), somatostatin, gonadotropin-releasing hormone (GnRH or luteinizing-releasing hormone, LHRH) and thyrotropin-releasing hormone (TRH). In addition to the hypothalamic hormones, many neuropeptides are present in the hypothalamus; neuropeptide Y (NPY), substance P, vasoactive intestinal polypeptide, and kisspeptin. They regulate the hypothalamic function, such as hormone secretion, reproduction, appetite, and sleep/wakefulness. These hypothalamic hormones and neuropeptides are expressed also in other brain regions and peripheral tissues, such as the gastrointestinal tract and adrenal gland. Among these neuropeptides, however, it is noteworthy that MCH [32] and orexins (hypocretins) [15,70] are mostly expressed in the hypothalamus (Figs. 3–5), particularly in the lateral hypothalamus. MCH and orexins play coordinated, but distinct physiological roles in the