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Review

Regulation of cell volume and water transport – An old fundamental role of the renin angiotensin aldosterone system components at the cellular level

Walmor C. De Mello*

School of Medicine, Medical Sciences Campus, UPR, San Juan, PR 00936, USA

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ABSTRACT

The expression and the role of renin angiotensin aldosterone system (RAAS) components on regulation of cell volume and water transport on vertebrates and invertebrates were reviewed. The presence of these components even in simple organisms like leeches and their relevance for the control of cellular volume and water transport supports the view that the expression of these components, at cellular level, is an acquisition which was preserved throughout evolution.

Contents

Introduction

The preservation of cell volume is fundamental for cell survival requiring the presence of regulatory mechanisms such as the regulatory volume decrease (RVD) or the regulatory volume increase (RVI). The inhibition of RVD has serious consequences for cellular function leading to activation of membrane ionic channels and of several kinases resulting in abnormalities of cellular function and is commonly associated with cell shrinkage through activation of AKt1 [21]. Furthermore, changes in cell volume can represent signals triggering cell migration, proliferation and release of hormones and transmitters [21]. Cell swelling occurs during hypothermia and hypoxia/ischemia, increase in the extracellular K+ concentration [K+] as well as intracellular acidosis/diabetic ketoacidosis. Variations in cell volume are not necessarily associated with extracellular hypotonicity or hypertonicity because increase of intracellular osmolarity due to synthesis or elimination of osmolytes, is responsible for cell swelling [21].

Evidence is available that in mammals, there are local renin angiotensin systems in different organs including the heart, kidney and possibly in the brain in which RAAS components have been identified intracellularly (see 7,11,13,10,40). These findings might indicate that the intracrine RAAS characterized by intracellular synthesis of RAAS components or their internalization, plays an important role on cellular functions. Here we review the question whether the expression and function of RAAS components on cell

* Tel.: +1 787 766 4441; fax: +1 787 766 4441.
E-mail address: walmor.de-mello@upr.edu

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volume and water transport is an old event preserved throughout evolution.

RAAS components are present in cells of invertebrates

Evidence is available, for instance, that components of the RAAS are present in invertebrates including annelids [38], crustaceans [5,6], molluscs [17], insects [20,32,34,35]. In leech (*Theromyzon tessulatum*), brain neurons immunoreaction to angiotensin II has been described [30] and immunocytes showed immunoreactivity to antihuman-Ang II and antihuman AT1 receptors [29,30]. Also, an asparyl protease of 32 kDa exhibiting 35% of sequence identity with mammalian renin, has been found in the leech [28,30]. Biochemically, renin, ACE- and AT1-like receptor were identified in the leech immune cells [28] and ACE has been found in bacteria [26]. So far, only soluble, single domain ACEs from invertebrates have been cloned, and these have been implicated in reproduction in insects [18]. Interestingly, bacterial DNA sequences could encode putative ACE-like proteins, strikingly similar to vertebrates enzymes [26]. ACEs from invertebrates have been isolated from insects like *Drosophila melanogaster* [5] showing kinetics very similar to mammalian ACE [26]. Immunochemical studies indicated ACE intracellularly co-localized with myotropine peptides suggesting a convertase activity [18]. Immunostaining of leech sections, revealed labeling in neurons and glial cells of the central nervous system (CNS), immunocytes, the nephridial canal canaliculi and the periphery of the ciliated funnel, as well as the epithelium lining nephridia. Renin is localized in the excretory system and in the nervous system of leech [29,30] and its first appearance has been detected in bony fish [16]. The first genomic characterization of non-mammalian vertebrates renin genes found in zebrafish was recently described [22]. According to Fournier et al. [16], practically all components of the renin angiotensin aldosterone system appear in bony fish with exception of Mas receptor of Ang (1–7) which appeared in amphibians.

On the functions of RAAS components in invertebrates

An important question is the physiological meaning of the expression of RAAS components. For many invertebrates, an important factor for survival when the medium changes, is the capability of the sodium pump to regulate the increased intracellular sodium concentration caused by an incremented osmolarity of the medium [25]. Evidence is, available that Ang II regulates water flow through aquaporins in clam worm [31] and experiments performed on leeches in vivo, indicated that Ang II amide is involved on the control of water balance [28]. Measurements of transepithelial short-circuit current in leeches, showed that Ang II amide reduced this current-an effect mediated by Cl− secretion [25,31] and in consequence, water follows the peptide eliciting water loss across the epithelium.

Cell swelling is known to activate ionic channels like the swelling-dependent chloride channel ($I_{Clswell}$) which plays an important role on the regulation of cell volume [3,7–9,19]. Eggs of the ascidian *Boltenia villosa* have an inwardly rectifying Cl− current whose amplitude varies by more than 10-fold during each cell cycle and osmotically produced swelling also increased Cl− current amplitude in unfertilized eggs [38]. These findings indicate that RAAS components play an important role on regulation of cell volume and water transport.

Components of RAAS are involved in cell volume regulation in vertebrates

The appearance of a sophisticated kidney function in mammals made it possible the efficient regulation of blood volume and blood pressure through the activation of the systemic renin angiotensin aldosterone system (RAAS). Independently of a circulatory RAAS, the expression of RAAS components at cellular level in vertebrates because immunodetection of renin–angiotensin system (RAS) components were found in anterior pituitary cells, particularly in lactotropes [36] and prorenin, renin and angiotensinogen were identified not only in lactotropes and gonadotropes but also in somatotropes, corticotropes, and thyrotropes. The highest levels of renin were detected in lactotropes and gonadotropes [37]. The detection of angiotensinogen and both its specific cleavage enzyme and its proenzyme within the same granule, suggests intragranular processing of this component [37] indicating an important intracrine mechanism involved in the secretory process.

In mammalians, components of the renin angiotensin system have been detected in several tissues including the heart, adrenal gland, kidney and in the brain [9,12,19,27,37,40] and many of the old properties of RAAS components as regulators of cell volume and water transport seen in invertebrates, are present in the mammalians. The RAAS is involved in the regulation of cell volume in normal mammalian heart as well as in the failing heart [7]. Indeed, in myocytes isolated from the failing ventricle and exposed to renin plus angiotensinogen or to Ang II, an increase of cell volume was seen concurrently with the inhibition of the sodium pump [7] while the intracellular administration of Ang II had an opposite effect [9]. The activation of the Na–K–2Cl cotransporter is involved in the effect of Ang II because bumetanide abolished the swelling induced by the peptide [9]. The regulation of cell volume, involves other components like ion channels and their voltage dependence. Cell swelling induced by Ang II in cardiac cells, causes the activation of ionic channels like the swelling-activate chloride current ($I_{Cl,swell}$) [3] leading to membrane depolarization, reduction of action potential duration [7] and consequent changes in cardiac excitability. The increase of ($I_{Clswell}$) in the failing and in the normal mammalian heart [3,8] elicited by changes in cell metabolism or by Ang II, is particularly relevant because the activation of this current seems involved in generation of cardiac arrhythmias including early after depolarizations [8].

In mammals, cell swelling also activates potassium channels (K(v) 4.2/4.3) which are the primary subunits of $I_{(to,fast)}$, through phosphorylation/dephosphorylation of serine/threonine phosphatases [39] in the mammalian heart [7,39]. It is known, for instance, that Ang II causes cell swelling and increases ICl_{swell} in the failing as well as in normal heart [3,8] and that the inability of the heart cell to regulate its volume through a lack of activation of the regulatory volume decrease (RVD) leads to serious impairment of heart cell function [21]. Components of the renin angiotensin system in the myocardium [19] play an important role on regulation of cell volume and water transport because extracellular Ang II or renin inhibit the sodium pump, counteracts the decline in cell volume. On the other hand, when the cell is exposed to hypotonic medium, the increment of cell volume can be reduced by intracellular Ang II or renin [7]. In this way, RAAS components contribute to the regulation of cell volume. This physiological property of Ang II is quite old because evidence is available that the peptide suppressed body weight loss of the clam worm *Perinereis* sp. under a hyper-osmotic condition, and enhanced body weight gain under a hypo-osmotic condition [31].

On the role of aldosterone and mineralocorticoid receptor

The earliest corticoid receptor have been found in lamprey and hagfish. The mineralocorticoid (MR) and the glucocorticoid (GR) first appear in skates and sharks while aldosterone first appears in lobe-finned fishes [1,24,33]. A mutation corresponding to His-950 in human MR may have been important in the physiological