Biomedicine & Pharmacotherapy 94 (2017) 317–325

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Original article

Renin-angiotensin-aldosterone (RAAS): The ubiquitous system for homeostasis and pathologies

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ARTICLE INFO

Article history:
Received 19 May 2017
Received in revised form 10 July 2017
Accepted 19 July 2017

Keywords:
Renin
Angiotensin II
Aldosterone
Vasopressin
Hypertension

ABSTRACT

Renin-angiotensin-aldosterone system (RAAS) is a vital system of human body, as it maintains plasma sodium concentration, arterial blood pressure and extracellular volume. Kidney-secreted renin enzyme acts on its substrate to form angiotensin II, a versatile effector peptide hormone. Every organ is affected by RAAS activation and the resultant hypertension, cell proliferation, inflammation, and fibrosis. The imbalance of renin and angiotensin II can result in an overwhelming number of chronic and acute diseases. RAAS is influenced by other enzymes, hormones, pumps and signaling pathways, hence, this review discusses important facets of this system, its crosstalk with other crucial factors like estrogen, thyroid, cortisol, kallikrein-kinin system, Wnt/β-catenin signaling, and sodium-potassium pump. The nexus of RAAS with the above-discussed systems was scantily explored before. So, this review furnishes a new perspective in comprehension of inflammation diseases. It is followed by the formulation of hypotheses, which can contribute to better management of an array of pathologies plaguing mankind. Manipulation of RAAS, by bending it towards ACE2 expression can regulate endocrine functions, which can be critical for a number of pathological management. Dietary intervention can restore RAAS to normalcy.

1. Introduction

Human body is a complex of numerous systems and organs, which interact for proper functioning. Out of the many systems, renin-angiotensin-aldosterone axis, or renin-angiotensin aldosterone system (RAAS) is a vital one, for survival [1]. This system maintains vascular tonicity by regulating extracellular fluid volume and arterial pressure [2]. By this system, water, blood, plasma, lymph and interstitial fluid are controlled tightly for functioning of the pulsating organ heart and filtration organ kidney, without the onslaught of either extremes. Perturbation of this system can disturb blood pressure, leading to chronic or acute diseases, or even sudden death [3]. As the name indicates, renin and angiotensin are two critical components forming the system. Renin (or angiotensinogenase), is secreted by the kidney granular cells [4]. The precursor of renin, named prorenin is a 406 amino acid-long protein, processing of which forms the active protein [5]. Prorenin can be proteolytically activated in the kidney by neuroendocrine convertase 1 (proprotein convertase 1) or cathepsin B, and non-proteolytically in many tissues by renin/prorenin receptor. Renin, in its active form has 340 amino acids [6]. It occurs in multiple isoforms, with antagonizing functions [7]. This enzyme is considered a hormone as well, for its signaling roles [8]. Low arterial blood pressure, low sodium chloride, and sympathetic nervous system activity (beta-1 adrenoceptor activation) lead to its expression [9]. It hydrolyzes the liver-secreted α-2-globulin protein angiotensinogen (about 118aa, though the length can vary) to angiotensin I, by acting on the bond between leucine (Leu) and valine (Val) [10]. Angiotensinogen is a member of the serpin family (SERPINA8), so a potential enzyme inhibitor [11]. Plasma level of angiotensinogen can be increased by corticosteroid, estrogen, thyroid hormone, and angiotensin II levels [10]. The decapeptide angiotensin I further undergoes cleavage in the lungs

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http://dx.doi.org/10.1016/j.biopha.2017.07.091
0753-3322/

capillaries, endothelial cells, and kidney epithelial cells by the endothelial-bound angiotensin-converting enzyme (ACE) (EC 3.5.15.1). This enzyme, a carboxypeptidase, also known as kininase II, peptidyl-dipeptidase A, or CD143, converts angiotensin I into the peptide angiotensin II [12,13]. Two C terminal amino acids of the angiotensin I is removed to form angiotensin II. ACE is a common component of the RAAS, as well as kinin- kallikrein system (KKS) [12]. This system is made of components as bradykinin, kallidin and serine protease kallikrein. Angiotensin II is a versatile effector molecule with intracrine/autocrine/paracrine role which cross-talks with almost all systems [14,15]. Angiotensin II has vasoactive role on all blood vessels (arteries and veins), as it constricts smooth muscle. It increases blood pressure, and pulsation speed of heart; stimulates plasminogen activator inhibitor protein PAI-1 and PAI-2, raising prothrombotic potential [16]. Also, it stimulates adrenal gland cortex to secrete aldosterone [17]. Aldosterone maintains sodium-potassium homeostasis by stimulating kidney proximal tubules to increase sodium reabsorption, hence, retaining sodium and loosing potassium [18]. RAAS acts on hypothalamus, a component of central nervous system (CNS) to stimulate thirst reflex (dipsogen) [19]. Thirst feeling is recognized by the osmoreceptors on hypothalamus [20]. Consequent secretion of antidiuretic hormone (ADH)/vasopressin, a nonapeptide from the posterior pituitary gland, reduces urinary loss [21]. Also, it influences adrenocorticotropic hormone (ACTH) secretion from the corticotrophs of anterior pituitary. ACTH is the principal hormone that regulates cortisol production from the adrenal glands [22]. Angiotensin II can also influence the release of prostaglandins, which can influence renal vasoconstriction. Cyclooxygenase (COX) 1-derived prostaglandin E(2) and its receptor have been identified crucial for the angiotensin II-dependent hypertension [23]. Also, angiotensin II can promote lipogenesis, thus increasing adipose tissue mass [24]. This aspect has been proven from the expression of RAAS on the adipose tissues and generation of angiotensin II [24,25]. Consequently, this enzyme is linked to adipose inflammation, glucose intolerance, and insulin resistance [26]. Multi-pronged functional mechanisms of angiotensin II has been studied extensively. It interacts with G-protein-coupled receptor (GPCR) AT1 by stimulating the Gq protein in vascular smooth muscle cells to activate phospholipase C, for increasing intracellular calcium [27]. So, angiotensin II is a critical regulator of blood volume, pressure, and pH. After binding to prorenin/renin receptors, circulating renin and prorenin trigger the local generation of angiotensin II, and mediate angiotensin II-independent signaling cascades. Angiotensin II has a half-life of 30 s [28]. It can be degraded into angiotensin III by aminopeptidase A enzymes on red blood cells [29]. There are other degraded forms of angiotensin II as well, with variable degree of affinity for angiotensin receptors. In fact, the degradation of angiotensin II with ACE2 enzyme is the basis of treating diabetic nephropathy [30–33]. ACE2 is critical for renal homeostasis and its deficit has been associated with albuminuria and glomerular injury (glomerulosclerosis) [30]. Thus, ACE and ACE2 have antagonistic functions, while the former is bad for kidney as well as heart, the latter is good for kidney [34]. Fig. 1 illustrates the above-described mechanism.

There are several prorenin and renin receptors (such as mannose-6-phosphate receptor (M6P-R), ATPase H(+)-transporting lysosomal accessory protein 2 (ATP6AP2)) [35]. The zymogen and the active enzyme bind to these receptors, which can influence their angiotensinogen-hydrolyzing ability. ATP6AP2 is a protein coded by the ATP6AP2 gene [36]. ATPases are vital for proton exchange, electromotive force, energy conservation, acidification, among other critical roles. Renin binding to the ATP6AP2 receptor quadruples renin activity as well as phosphorylates nucleophilic amino acid (serine (Ser) and tyrosine (Tyr)) of the ATPase [37].

Renin is coded by the gene REN. Mutation in this gene (deletion, amino acid substitution etc.) can hamper renin function and lead to multiple inflammatory conditions and diseases (such as hyperuricemia, anemia, chronic kidney failure) [38]. Renin concentration in healthy adult human plasma is 1.98–24.6 ng/L [39]. Beyond this level, above-mentioned pathologies ensue as both hypo- as well as hyper-activity can be harmful. In hypertensive patients, a mutation is associated with high plasma aldosterone and low plasma renin levels [40]. A high level of renin indicates adrenal gland insufficiency (Addison's disease), low filtrate NaCl concentration, drop in blood pressure, leading to hemorrhage, heart failure, liver cirrhosis, dehydration, and renal tumors [41]. Over-activity leads to vasoconstriction and retention of sodium and water [8]. This is the reason that during luteal phase (when uterus starts getting thicker for possible pregnancy) of menstrual cycle, plasma has high angiotensin II, which elevates aldosterone levels and resultant water retention [42]. High level of angiotensin II can constrict and reduce the area for glomerular filtration. Renin level fluctuation can be measured by an array of markers, some of which include high serum potassium, high

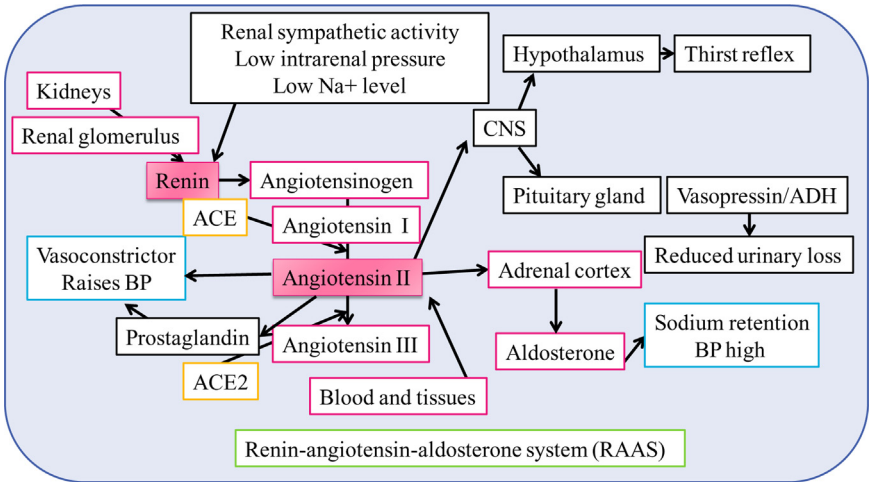

Fig. 1. The key mechanism of RAAS (renin-angiotensin-aldosterone system).