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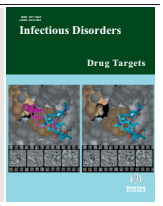
EDITORIAL

The Unsuspected Role of the Renin-Angiotensin System (RAS): Could its Dysregulation be at the Root of All Non-Genetic Human Diseases?



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The omnipresent RAS, also known as the renin-angiotensin-aldosterone system, is a hormonal and physiological system whose function is to control arterial pressure and circulating blood volume in humans [1, 2]. It also regulates pulmonary, cardiovascular, vegetative, renal, innate immune and gut microbiota functions [3, 4]. The RAS is a form of endocrine and enzymatic regulatory cascade. It is ubiquitous and found in every organ and tissue of the body. Components of the RAS are found both on cell plasma membrane and on the membranes of certain organelles, such as mitochondrial membranes [5, 6].

In the RAS, renin secreted by the kidney cleaves angiotensinogen (AGT) secreted by the liver to produce angiotensin I (Ang I). The latter is cleaved by angiotensin-converting enzyme (ACE) to produce angiotensin II (Ang II). Ang II binds to vasoconstriction-mediating type 1 (AT1R) and vasodilation-mediating type 2 (AT2R) receptors. Ang II is also cleaved by angiotensin-converting enzyme 2 (ACE2) to generate angiotensin (1-7) [Ang-(1-7)], which interacts with the proto-oncogene G protein-coupled receptor Mas (MasR) [4, 7], and the AT2R receptor. Ang II, by acting on the AT1R receptor, exerts several deleterious actions, such as vasoconstriction, profibrosis, proapoptosis, oxidative stress and pro-inflammation [8]. The ACE2 enzyme counterbalances the effects of Ang II/AT1R by cleaving Ang I and Ang II into Angiotensin (1-9) [Ang-(1-9)] and Ang-(1-7), respectively, which can favorably regulate the RAS. Thus, a balance between the different components of the RAS should always be present for proper system function and physiological regulation. Moreover, an imbalance in the RAS could be highly deleterious to the human body, as is the case with infection by the SARS-CoV-2 virus, which interacts with ACE2 (the SARS-CoV-2 receptor and a major RAS enzyme), leading to an imbalance in the RAS associated with overactivation of the AT1R receptor (Fig. **1**). The symptoms of COVID-19 will ultimately be linked to RAS dysfunction, as discussed in our previously published work [9-19].

Through this editorial, we claim that RAS dysfunction is also the root of many non-genetic human pathologies. Indeed, this extends much further than COVID-19. To understand this, we need to take into consideration the genetic polymorphism of the actors (different components) of RAS. In fact, numerous studies have described strong links between the genetic polymorphism of RAS components and the prevalence of specific human diseases [20, 21]. Therefore, we believe that genetic factors may predispose the host to varying degrees of susceptibility to different human pathologies. The prevalence and outcome of human disease have been shown to be linked to ACE polymorphism [22]. In fact, genetic polymorphism of the ACE1 and ACE2 genes can alter their biological activities and expression levels, leading to increased capillary permeability, coagulation, fibrosis and apoptosis in alveolar cells [23] and other cell types.

The Ang II/AT1R axis is the main pathway that can be affected during RAS dysregulation. We have previously reported that the deleterious episodes generated following SARS-CoV-2 infection, are the result of overactivation of the Ang II/AT1R axis [11-19]. Numerous deleterious effects can be produced by Ang II/AT1R signaling, such as vasoconstriction, fibrosis, inflammation, cell growth, migration, organ hypertrophy, thrombosis, production of reactive oxygen species (ROS), *etc*. [24, 25]. Mitochondrial dysfunction, DNA damage and cytokine storms result from overactivation of the Ang II/AT1R axis. Dysregulated RAS components can also alter and induce an imbalance in the innate/acquired immune response, with an unusual predominance of hyper-stimulated macrophages and neutrophilic granulocytes in affected human tissues. For example, experiments have shown that deletion of the AT1R gene in rodents significantly improved vital functions and reduced oedema formation [8, 9].

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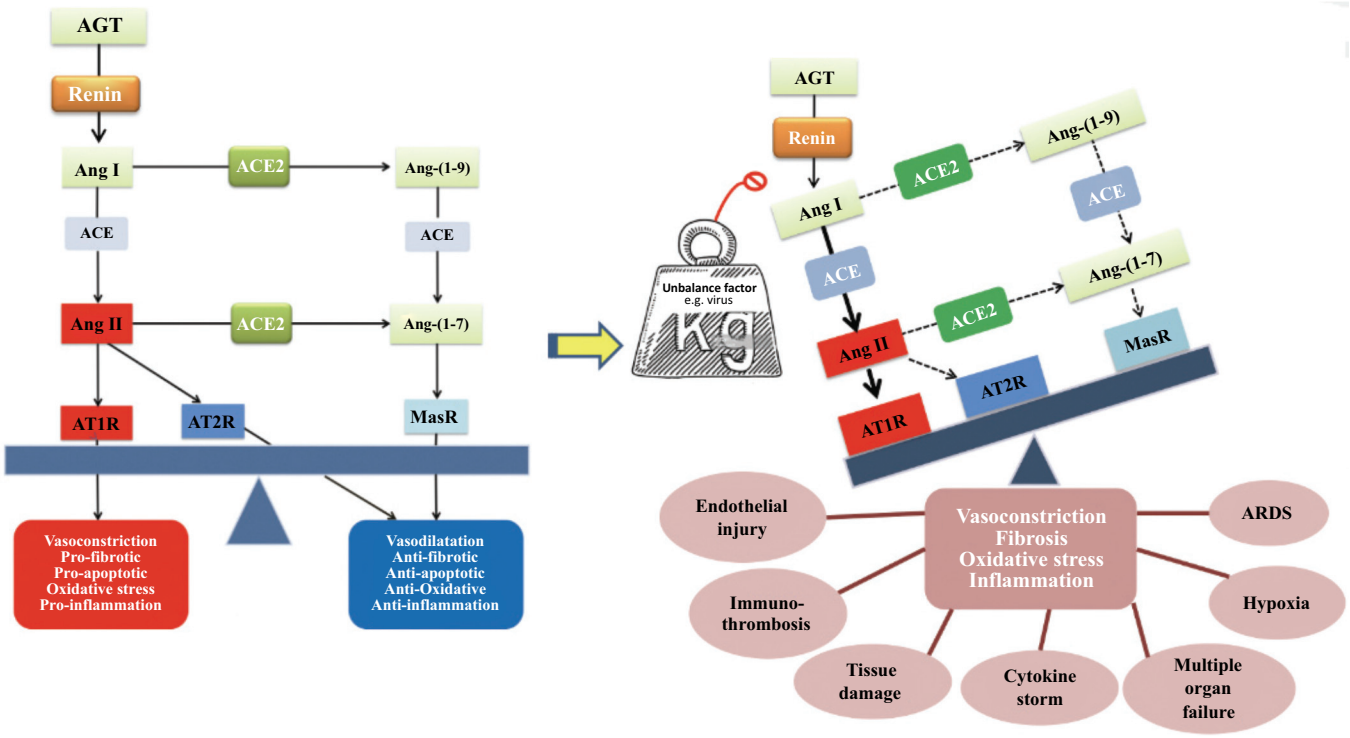

Fig. (1). Balance between the various components of the RAS in normal human physiology (left); imbalance of RAS caused by a dysregulation factor leading, for example, overactivation of the AT1R receptor, which can be highly deleterious for the human body (right). (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Even more, in the lung, the Ang II/AT1R axis can increase vascular permeability by releasing prostaglandins and vascular endothelial growth factor due to its proinflammatory, destructive and profibrotic properties. Indeed, in the case of SARS coronavirus infection, for example, the virus invades the airways, vascular endothelial cells and epithelial cells, which will be severely damaged, triggering an accumulation of protein-rich edema fluid in the alveoli and pulmonary interstitium, which will activate macrophages and neutrophil granulocytes to release a large number of inflammatory factors [9]. In the cardiovascular system, stimulation of the Ang II/AT1R axis has been associated with the development of various pathologies, including hypertension, vascular inflammation, atherosclerosis and heart failure [26, 27]. In the nervous system, increased levels of Ang II contribute to the loss of neurons in different regions of the brain. Ang II has been shown to cause the death of dopaminergic neurons, while losartan, an AT1R receptor antagonist, protects these neurons from apoptosis [28]. In the digestive system, the RAS has been shown to induce colonic inflammation by stimulating Th17 activation. In the colonic mucosa, Ang II induces colitis through AT1R *via* the JAK2/STAT1/3 pathway [29]. In addition, regulation of the Ang II/AT1R axis is also involved in the control of dietary amino acid homeostasis, antimicrobial peptide expression and intestinal microbial flora [30]. In the kidney, the overactivation of the RAS has been described as playing a central role in the progression of chronic kidney disease. Moreover, the Ang II/AT1R axis induces fibrosis and inflammation, which appear to contribute to renal pathologies [31].

In brief, the overactivation of the Ang II/AT1R axis induces deleterious effects in humans (and mammals in general) as previously mentioned. Nevertheless, a favorable regulatory system exists at the RAS level involving actors such as Ang-(1-7), the MasR [9], AT2R receptors, Ang-(1-9), angiotensin IV (Ang IV) and the AT4R receptor, which, through cellular signaling, can produce anti-inflammatory, anti-fibrotic, anti-proliferative, anti-oxidant (reducing), anti-hypertensive, anti-angiogenic, anti-hypoxemic, anti-hypoxic and anti-thrombotic effects.

It should also be noted that the RAS evolves throughout life (the RAS of infants differs from that of children, adults and the aged), from birth to death. RAS also differs between men and women (the gene coding for the ACE2 receptor is carried on the X chromosome). With its omnipresence in the body at the organ, tissue and cell level, the RAS controls all functions related to cellular life. It is this unprecedented global "vision" of the importance of the RAS in the total control of the functioning of the human body, as well as in the potential triggering of various neurological/neurodegenerative (Alzheimer's and Parkinson's diseases, schizophrenia, *etc*.), cardiovascular, gastrointestinal, immune (autoimmunity), cancerous and other pathologies, that is new because it has not been described until now. Thus, we emphasize the extreme importance of the RAS, a hormonal system initially identified in the kidneys and liver, but ultimately present in all tissues and organs. It controls all vital bodily functions, including brain function.

Ultimately, we argue that the ubiquitous RAS in the body (there are local variants in different tissues and organs, with the same receptors and ligands involved but in varying proportions and tissue distribution, adapted to the function of these tissues/organs) and cells (the RAS is found in the outer membrane of cells, but also in the membranes of the nucleus, mitochondria, endosomes, exosomes, lysosomes, endoplasmic or sarcoplasmic reticulum) is the key to all non-genetic pathologies. It acts as the operator of the human body's functions, and not the brain (itself controlled by the RAS). In fact, it controls the functions of neurons and other nervous system cell types such as oligodendrocytes, astrocytes and microglial cells.

The RAS is the "master" system of the human body and therefore offers unexpected therapeutic potential. The extensive study of the RAS should lead to major advances in applied medicine, with an immense field of research still untouched and medically unexplored.

LIST OF ABBREVIATIONS

ACE = Angiotensin-Converting Enzyme

AGT = Angiotensinogen

Ang I = Angiotensin I

Ang II = Angiotensin II

RAS = Renin-Angiotensin System

ROS = Reactive Oxygen Species

AUTHORS' CONTRIBUTIONS

- The authors have read and approved the manuscript.
- The authors were responsible for the study concept and design.
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- Disclosure : Part of this article has previously been published in “Angiotensin II Type I Receptor (AT1R): The Gate towards COVID-19-Associated Diseases”.

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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