

## Editorial

# Renin-Angiotensin System: Role in Chronic Diseases

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The renin-angiotensin system (RAS) is a developing endocrine system with new components discovered every year, which produces angiotensin peptides through an enzymatic cascade. The RAS initiates with angiotensinogen (AGT) expression at different tissues, a protein produced by several cell types, including, adipocytes, neurons and hepatocytes. However, in normal physiology, the liver is still considered the primary source of circulating AGT. Kidney enzyme Renin, cleaves AGT to produce angiotensin I (Ang I), a peptide that is hydrolyzed by angiotensin-converting enzyme (ACE) to the octapeptide Angiotensin II (Ang II), which acts through two specific receptors (AT1 and AT2). Besides Ang II, several other angiotensin peptides formed from AGT have biological activity; nevertheless the main one is Ang-(1-7), that generally opposes Ang II actions through the Mas receptor. Ang-(1-7) is a product of Ang II degradation by the action of the ACE-homologue enzyme (ACE2) and also directly from Ang I by prolylendopeptidase (PEP) and neutral endopeptidase (NEP). Recently, similar effects to Ang-(1-7) were described by Alamandine through MrgD receptor [1].

Several studies have associated chronic diseases with imbalances of RAS components, either at systemic level or at local/tissue level [2, 3]. Importantly, chronic diseases, such as diabetes, cardiovascular diseases, brain degeneration, cancer and kidney diseases are the leading cause of mortality in the world.

With the present PPL Special Issue on the “Renin-angiotensin system: Role in chronic diseases”, we have attempted to cover some of the chronic diseases associated with key components of RAS, and to address the most important aspects of its functional output. Furthermore, we aimed to include new tendencies and advances, some of them still controversial, but always contemplating what we consider as hot-points for research progress, drug developments and new treatments in a near future.

The articles of the Special Issue bring several chronic diseases related to different organs and with various systemic effects. Starting with preterm birth, Bertagnolli described the association between fetal RAS disturbances and chronic diseases, with evidence of important modifications in fetal organogenesis in premature children. Also, RAS can be persistently activated in these individuals in later life, suggesting that this imbalance can persist beyond intrauterine life. Moving on to the brain and central control of RAS in chronic disorders, Almeida-Santos *et al.* showed that RAS receptors and enzymes are widely distributed in the central nervous system, where they present complex effects. Several studies associated brain RAS alterations with neurodegenerative diseases such as Parkinson, Alzheimer, Huntington and Multiple Sclerosis. Considering that Angiotensin II is the most well documented RAS component, the paper contributed by Basmadjian *et al.* goes deeply into Ang II role in mental disorders, showing association of this peptide with stress and depression, and also with schizophrenia, Alzheimer and Parkinson. Considering that, together with neurodegenerative disorders, cancer is one of the most increasing prevalence diseases in elderly and adults, Fraga *et al.* examined the potential role of angiotensin-converting enzymes (ACE and ACE2) during the development of malignant epithelial neoplasias. The authors focused in oral squamous cell carcinoma and used bioinformatics analysis to access the potential network interactions.

The endogenous integrative role of RAS was contemplated in the reviews, focused on metabolic regulation. Rein and Bader revised the deleterious effects of augmented ACE/Ang II/AT1 activation during hyperglycemic conditions in diabetes; with opposition of these effects by an hyperactivation of the ACE2/Ang-(1-7)/Mas arm. The authors covered the effects of diabetes on kidney, heart, vessels, pancreas and retina. Evaluating the hormonal role of local and systemic RAS along with cytokines in chronic kidney (CKD) disease, da Silva *et al.* showed the closed relationship between RAS activation or blockade and cytokine modulation which deeply alters CKD progression. Continuing to study the metabolic effects, Andrade *et al.* screened the role of gut microbiota interaction with ACE2 enzyme and cardiovascular health. They linked amino acid uptake with ACE2 and gut microbiota, considering also the potential intestinal production of antimicrobial peptides by RAS. Nunes-Silva *et al.* assessed

one of the most important ways to increase body metabolism: thermogenesis/ physical training. The authors described new beneficial evidences of ACE2/Ang-(1-7)/Mas axis activation in humans and animal models of physical training.

Given the clinical relevance of the RAS, the Special Issue concludes with three original articles particularly focused on metabolism and cardiovascular disease. Pinheiro *et al.* evaluated the metabolic effects of pharmacotherapeutic association of the ACE inhibitor Enalapril and the Sirtuin activator- Resveratrol, on glucose and lipid profiles in mice. They found a possible potentiating effect on improving metabolic response. Considering the importance that obesity treatment achieved in the last decades, Crespo *et al.* investigated the effects of sleeve gastrectomy (SG) on metabolic profile and on RAS expression in adipose tissue of obese rats. The authors showed that SG leads to weight loss and improves metabolic parameters, improving adipose RAS. Finally, Moraes *et al.* described the vasodilator effect of Ang-(1-7) on vascular coronary bed of rats accessing the role of Mas, ACE and ACE2, suggesting that Ang-(1-7), at very low concentrations, has a direct vasodilator effect in the coronary bed of rats mediated by Mas and ACE enzymes.

We thank all the RAS researchers who contributed to this Special Issue - it is always your hard work and commitment that have made the progress of science bring new perspectives and hope for new chronic disease treatments.

## REFERENCES

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