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The Renin-Angiotensin System: Is there a limit to where it goes?

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Introduction

The renin angiotensin system (RAS) has been extensively studied since the Finnish physiologist Robert Tigerstedt described in 1898 that arterial pressure was elevated upon infusion of kidney extracts containing the “pressor substance” renin in anesthetized animals [1]. Its understanding is of unquestionable relevance for the cardiovascular homeostais since pharmacological agents (–sartans (AT1R blockers) or –pril (ACE inhibitors)) that blunt actions of the RAS has been extensively used in the management of various cardiovascular conditions and its benefits goes beyond the blood pressure reduction effects [2]. More recently, therapeutical strategies have also reached the inhibition of upstream molecules as the discoveries of renin inhibitors.

Although pharmacological therapies have been developed based on the classical view of the RAS, in which Ang II acts as the effector molecule of the system by its binding to the AT1 receptor, recent discoveries have been made regarding other functions within the RAS. Perhaps two of the most relevant discovery are: 1) the activation of molecules of the RAS independent of ligands by hemodynamic forces; and 2) the discovery of biased ligands to the AT1R that beyond blocking Ang II effects also elicits specific intracellular signaling.

The first evidence of AT1R activation by mechanical forces, independently of its ligand, was demonstrated in cardiomyocytes cells stimulated by stretch by Zou et al. [3]. Later it was found that this activation leaded to non-canonical AT1 receptor signaling, independent of the classical Gq activation but dependent of □-arrestin-2 recruitment and it has been shown to have beneficial effects on the heart beyond the blockade o Ang II-mediated affects [4].

Later, in 2013, Ramkhelawon et al. [5] and us [6,7] showed that the AT1R could also be activated by another mechanical stress, the shear stress, which shed light into a new possible molecular mechanism AT1R activation. Also as stated by Ramkhelawon et al. [5] and by us on our studies, although both stretch and shear stress are mechanical stresses, the molecular mechanisms that transduce these stimuli may differ greatly and both studies support that hypothesis. Now that the phenomenon of AT1R activation by shear stress has been elucidated, its biological relevance should be stressed. Recently, Carneiro at al. [5] did a step forward this understanding and showed that □-arrestin-2 recruitment, independently of the G-protein activation, is a key molecule in the NO generation by shear stress in endothelial cells. Besides the AT1R activation, we have also shown that ACE can also act as a mechanosensor to shear stress[8].

The second advance regarding RAS were the development of biased ligand to the AT1R (mainly the TRVs), which are into the phase II clinical trial of its developmental stage to treat patients with acute heart failure but so far any benefit over placebo with regards to the primary composite endpoint has been found [9]. Biased ligands are by definition molecules that specifically activate or block a subset of intracellular signaling repertoire. In this sense, TRV120027 targets the AT1R in such a way that blocks of the G-protein mediated adverse effects of Ang II while simultaneously unmasks beneficial pharmacology mediated by beta-arrestin. Its benefits to heart and kidney were already clearly demonstrated in animal models by us and others [10–12].

It is well know that AT1 receptor activation by its ligand angiotensin II has a central role to the pathogenesis of cardiovascular diseases through vascular inflammation, increased reactive oxygen species production, endothelial dysfunction and atherosclerosis. One possible mechanism of such response is the increase in NADPH activation and increase in reactive oxygen species (ROS) production that directly scavenges nitric oxide (NO) as well as decrease eNOS function by its uncoupling.

We are currently investigating the dichotomist possibility of AT1R activation by TRV versus Ang II in the vascular tissue. Our

research focus on the understanding of the effects of biased ligands AT1R, such as TRVs, on vascular function since this molecule has been shown to activate the AKT/PI3K/eNOS pathway. We believe that our findings will contribute to future studies towards the understanding of the RAS pathophysiological real meaning.

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