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The renin–angiotensin system in 2011: new avenues for translational research

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As pointed out by Nishimura [1], angiotensin II (Ang II) is an ancient peptide, even found in some primitive vertebrates and most probably evolved as a regulator of salt and water balance. Since the discovery of a pressor agent emanating from the mammalian kidney [2,3] focus on the rennin–angiotensin system (RAS) has been pivotal in fostering our understanding of the pathogenesis of a variety of cardiovascular and renal diseases. In this issue of *Current Opinion in Pharmacology* the emphasis is on novel mechanisms that involve the RAS and the mechanisms of its diverse functions. In a recent Pub Med search (1/28/2011) the term ‘angiotensin’ found 94,836 papers published since 1945. The impact of the physiology and pharmacology surrounding this peptide and its receptors is enormous. The treatment of hypertension and chronic heart failure has been revolutionized by drugs that target the production of Ang II and the blockade of its primary membrane target, the AT1 receptor. Angiotensin Converting Enzyme (ACE) Inhibitors and Ang II receptor blockers result in significant reductions in mortality and cardiovascular events for patients with hypertension and heart failure [4,5].

However, as pointed out by the articles in this issue the RAS has now been shown to participate in a wide variety of biological and pathological functions. The reviews in this issue focus on new progress in ACE biology, Ang II receptors, the possible therapeutic use of ACE2 and novel concepts relating to AT1 and AT2 receptor signaling. The classical view of the RAS has been significantly expanded and refined to include ACE2 and Ang (1–7). On the one hand, our knowledge of the function of the RAS has grown exponentially since Tiegerstedt and Bergman [2] first described this pressor substance in 1898. On the other hand, new components and biological effects of the RAS are continually being discovered.

While the majority of work on the RAS has targeted its role in blood pressure and salt and water balance it is clear from the articles in this issue that these peptides participate in very basic mechanisms of cell signaling and function. For instance, the review by Mederos y Schntzler, Storch, and Gudermann [6] describes a novel signaling pathway by which the AT1R (and perhaps other G-protein coupled receptors) can function as a mechanical transducer without the presence of agonist. Since AT1R’s are widely expressed in many cell types the potential for this mechanism to regulate cell excitability and function is intriguing. This mechanism may be extremely important in AT1R signaling in the central nervous system. Indeed, as pointed out in the reviews by Allen [7], Zimmerman [8], Gao and Zucker [9], and Diz *et al.* [10] Ang II participates in the regulation of sympathetic tone in key areas of the hypothalamus and brain stem. These brain regions include the rostral ventrolateral medulla (RVLM) that contains pre-sympathetic motor neurons that project to the spinal cord, and circumventricular organs that lack a blood–brain barrier, such as the subfornical

organ (SFO), which are capable of 'sensing' circulating Ang II and Ang (1–7). This area of investigation is especially important in understanding the pathogenesis of neurocardiovascular diseases such as chronic heart failure and various forms of hypertension. An important aspect of the central effects of Ang II and Ang (1–7) is their roles in modulating levels of reactive oxygen species (ROS), which are now well accepted signaling intermediates by which Ang II induces (patho)physiological responses in many tissues [11,12]. The reviews by Zimmerman [8] and Diz *et al.* [10] highlight the importance of the Ang II versus Ang (1–7) balance in regulating the autonomic nervous system. Expanding on the theme of the neural control of the circulation as a mediator of the hypertensive process, Marver and colleagues [13] review and provide evidence for a relationship between innate immunity in the central nervous system and T lymphocyte activation as a potentially important mechanism in the pathogenesis of hypertension.

While the emphasis has been largely on signaling through the AT1 receptor as the target of Ang II action, the role of the AT2 receptor has often been neglected. In this issue two papers are significant in this regard. Gao and Zucker [9] review recent data to support a controversial view that the AT2 receptor is not only expressed to a significant degree in the adult, but functions to suppress sympathetic nerve outflow in both normal and disease states. The concept that the AT2 receptor may be a potential therapeutic target in hypertension and other disease states has been supported by the recent development of a non-peptide agonist, Compound 21. Exciting data presented in the review by Steckelings *et al.* [14] provide support for the idea that AT2 receptor stimulation may be important in the end organ damage that occurs following myocardial infarction and in hypertension and inflammation.

While the production of Ang II and its downstream signaling pathways have been well described [15,16] equally important are novel advances in the enzymatic synthesis and degradation of Ang II. Bernstein *et al.* [17] show that manipulation of the N or C terminal domains of ACE in transgenic mice can have significant effects on blood pressure and fibrotic mechanisms. On the degradation side of the equation, the review by Raizada and colleagues [18] clearly shows that ACE2 and the generation of Ang (1–7) can be beneficial in the treatment of experimental pulmonary hypertension. The balance between Ang II and Ang (1–7) as well as their enzymatic parents could be a crucial factor in the development of new therapies to treat disorders dependent on the activation of the RAS. A good example of this concept is elucidated in the review by Schultz [19]. The peripheral chemoreflex modulation of respiration, sympathetic nerve activity, and arterial pressure has been shown to be sensitized in the setting of chronic heart failure in both humans and animals [20,21]. Recent studies show that Ang II plays a role in this sensitization at the level of the carotid body [22]. Furthermore, in studies summarized by Schultz [19] and by Zimmerman [8] the role of these substances in the modulation of ROS and ion channel function is clear. Additional support for the concept that the balance between Ang II and Ang (1–7) is important in the central control of blood pressure and sympathetic outflow is elaborated in the review by Diz *et al.* [10]. Once again, these studies provide rationale for development of translational paradigms targeting new components of the RAS for the treatment of cardiovascular disease.

The role of the intrarenal RAS in the pathogenesis of hypertension and most probably the activation of the RAS in heart failure has been well established and recognized since the initial observations of Goldblatt *et al.* [3]. It is generally assumed that intrarenal Ang II is produced by the action of juxtaglomerular cell release of renin working on plasma angiotensinogen. However, what has been less appreciated is the role of tubular renin and angiotensinogen in this process. Navar *et al.* [23] provide evidence for an intrarenal pathway that incorporates tubular production of renin/prorenin and angiotensinogen into the traditional way of thinking about this system. The implications of this pathway are far

reaching owing to the potential involvement of reabsorptive, vascular, and oxidative stress mechanisms, all impacting blood pressure regulation. Furthermore, activation of the intrarenal RAS may initiate a neural process that contributes to the maintenance of the hypertension [24].

One, of course, should not lose sight of the fact that vascular smooth muscle is still a primary target of the angiotensin peptides. As pointed out in the review by LaMarca *et al.* [25] activation of the AT1 receptor, in this case by autoantibodies during pregnancy, can evoke severe hypertension. More evidence is now accruing that this mechanism may play an important role in the pathogenesis of preeclampsia [26,27].

Finally, Ang II can play a role as a mitogen for fibroblasts [28,29] and stimulate myocyte growth [30]. Both Ang II and Ang (1–7) may play important roles in the proliferation of stem cells into vascular lineages. In the review by Roks *et al.* [31] evidence is provided for a novel concept that Ang II can participate in vasculogenesis by activation of endothelial progenitor cells. Ang (1–7) participates in the enhancement of endothelial function by virtue of its activation of the nitric oxide pathway and inhibition of the NADPH oxidase pathway. Once again, these observations support the view that the balance between Ang II and Ang (1–7) is crucial for normal cardiovascular function.

In summary, the role of angiotensin in neural, vascular, inflammatory and renal function as it pertains to the pathogenesis of cardiovascular disease has been broadened by an enhanced understanding of how this small peptide interacts with these systems. Figure 1 summarizes the many effects of the RAS that are outlined in the current issue. The reviews provided here clearly indicate the great potential for development of future therapies involving targets within the RAS.

Biographies

Irving H Zucker: is the Theodore F Hubbard Professor of Cardiovascular Research and Chairman of the Department of Cellular and Integrative Physiology at the University of Nebraska Medical Center. His research has focused on the neural control of the circulation in normal and disease states, especially chronic heart failure. His current research emphasis is on the regulation of angiotensin receptor expression in the central nervous system and the control of receptor expression in heart failure. The clinical relevance of this work stems from the fact that interventions such as exercise training and statin treatment may have profound effects on abnormal angiotensin II signaling through the AT1 receptor. Dr. Zucker obtained his BS degree in biology from The City College of New York and his PhD from New York Medical College in Physiology. He received post-doctoral training at the University of Nebraska Medical Center. Dr. Zucker serves on many editorial boards and is an Associate Editor of *The American Journal of Physiology: Heart and Circulatory Physiology*. He is a Past-President of The American Physiological Society.

Matthew C Zimmerman: is an Assistant Professor in the Department of Cellular and Integrative Physiology at the University of Nebraska Medical Center. Dr. Zimmerman earned his BS degree in biology from Marian College (now Marian University) in Fond du Lac, WI, and his PhD in Anatomy and Cell Biology from the University of Iowa in Iowa City, IA. He received post-doctoral training in the Free Radical and Radiation Biology Program at the University of Iowa. Dr. Zimmerman's research focuses on the role of superoxide and the sources of superoxide, particularly mitochondria and NADPH oxidases, on angiotensin II-induced neuronal activity and their relationship to autonomic function and the pathogenesis of hypertension. In collaboration with investigators in the Nebraska Center for Nanomedicine at the University of Nebraska Medical Center, Dr. Zimmerman's

laboratory is developing and evaluating the therapeutic efficacy of a nanomedicine-based delivery system for a protein called superoxide dismutase (SOD1), which specifically scavenges superoxide, on the pathogenesis of hypertension. Dr. Zimmerman's research is currently funded by the National Institutes of Health and the American Heart Association.

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Figure 1.

Multiple roles of the renin–angiotensin system (RAS) are depicted in this figure. The current issue describes novel research in areas concerned with the modulation and production of the main constituents of the RAS including pro-renin, renin, angiotensin converting enzyme (ACE), and angiotensin converting enzyme (ACE2). Three primary membrane receptors are activated by angiotensin II and angiotensin (1–7). The biological effects of these peptides are mediated, in part, by the generation of superoxide ($O_2^{\bullet-}$) and nitric oxide ($NO^{\bullet}$). The papers in this issue point to the multiple physiological and pathological effects of activation of the RAS on various organ systems including blood vessels, the kidney, the brain, the lungs, and inflammatory cells. Targets for therapeutic interventions and the discovery of potentially new pharmacological agents are also highlighted.