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What's new in the renin-angiotensin system?

A. I. Smith [1] and A. J. Turner [2, *]

[1] Department of Biochemistry and Molecular Biology, Monash University, Clayton, Victoria 3800 (Australia)
[2] School of Biochemistry and Microbiology, University of Leeds, Leeds LS2 9JT (United Kingdom),
e-mail: a.j.turner@leeds.ac.uk

In the sixty or so years since the Renin-Angiotensin System (RAS) and its pivotal role in regulating cardiovascular function was first described, the components and physiology of this endocrine axis has been the focus of an enormous research effort, the majority of which has concentrated on defining the precise role the various components within this axis play in the fine regulation of vascular tone and salt water homeostasis. As a consequence of this research, the production of angiotensin II, a potent vasoconstrictor, is currently considered the primary physiological RAS end product. Indeed, inhibitors of the angiotensin converting enzyme (ACE), a crucial player in the RAS catalysing the vital last step in angiotensin II production, have proven to be extremely effective therapeutics for the treatment of hypertension. However, recent findings published over the last three or four years have not only changed the way we think about the RAS but more importantly, have shown that the system is far more complex than first thought and clearly operates at physiological levels far beyond the simple regulation of vascular tone and body fluid homeostasis. This new research has uncovered new players in the system such as the ACE homologue ACE2, as well as new roles for what were largely considered inactive peptide congeners of angiotensin (e.g. angiotensin 1-7 and angiotensin IV). Molecular cloning studies and site directed mutagenesis have provided new insights into angiotensin receptor function, signalling and regulation and it is becoming clear that downstream receptor signalling pathways are far more extensive than first thought with evidence emerging for transactivation of other receptors utilising distinct signalling pathways. Finally, perhaps the most unlikely recent finding has been the observation that ACE 2 is a functional receptor for the SARS coronavirus.

Given that ACE is a well-validated therapeutic target and that unlike nearly all other zinc metallopeptidases the somatic enzyme has two catalytic sites, each subtly different, solving the crystal structure has been somewhat of a holy grail amongst the RAS research community. However, one of the major challenges structural biologists continue to struggle with is solving the crystal structure of heavily glycosylated membrane associated proteins such as ACE. In their article, 'The structure of Angiotensin Converting Enzyme', Sturrock et al., discuss their strategies that led to solving the crystal structure of testicular ACE and highlight the structural motifs within ACE that determine both catalytic access and specificity of the two ACE catalytic sites, this work opening the door to the rational design of the next generation, likely domain specific, therapeutic ACE inhibitors.

The alternate route for tackling the RAS in terms of therapeutic perturbation, is through treatment with selective type 1 (AT_1) angiotensin receptor antagonists. The generation of selective receptor agonists and antagonists along with selective site directed mutagenesis of expressed angiotensin receptors has not only paved the way for the development of new therapeutics but has also allowed unique insights into receptor structure and function. In the paper, 'When 6 is 9: 'Uncoupled' AT_1 receptors turn signalling on its head' Thomas et al provide strong evidence that some important downstream effects of AT_1 receptors are independent of classical G protein coupling, these include, receptor mediated endocytosis, tyrosine phosphorylation signalling and MAP kinase activation as well as transactivation of the epidermal growth factor receptor. These latter observations are particularly important, and support the concept of a functional partitioning between short-term angiotensin actions, for example vasoconstriction and the longer-term actions such as pathological cell growth. The issue and mechanisms of EGF receptor transactivation and pathological cell growth are very nicely covered in the paper by Hannan et al. 'Hijacking of EGF receptors by angiotensin II: new possibilities for understanding and treating cardiac hypertrophy'.

* Corresponding author.

It was perhaps the finding in late 2000 of an ACE homologue, ACE 2 that has probably had the biggest impact on the RAS field in recent years. The enzyme, although structurally quite similar to ACE, has a quite different catalytic profile. Within the RAS, ACE classically acts as a dipeptidylpeptidase generating angiotensin II from angiotensin through the removal of the C-terminal dipeptide His-Leu, while ACE 2, being a carboxypeptidase, is thought to catalyse the conversion of the vasoconstrictor angiotensin II into a putative vasodilator angiotensin$_{1\text{-}7}$ following the selective removal of the carboxy-terminal amino acid, phenylalanine. The article by Warner et al, 'ACE2: a novel ACE homologue, molecular and cellular perspectives', describes the discovery of ACE 2, its structural relationships with ACE and other ACE homologues along with some emerging, very interesting cell biology. In a paper titled 'The physiological functions of ACE2' the Penninger group describe ACE 2 substrate specificity and postulate that given the number of putative peptide substrates, ACE2 may have physiological functions outside the RAS. The paper also reviews the patterns of ACE 2 expression and the mapping of *ace* 2 gene to a quantitative trait loci affecting susceptibility to hypertension in rats. Finally, the authors also review the impact of both ACE2 and ACE gene knockouts in the mouse, confirming a role for ACE 2 in cardiovascular function. In the last paper examining functional aspects of ACE 2, Ferrario and Chappell focus on the precise role that ACE 2 and one of its catalytic products angiotensin$_{1\text{-}7}$ possibly play in regulating blood pressure as well as the putative pathological roles of angiotensin$_{1\text{-}7}$ in cardiac hypertrophy, heart failure, renal disease as well as hypertension. The hypothesis being that ACE 2 action on either angiotensin II or angiotensin$_{1\text{-}9}$ is a crucial catalytic step in the pathway(s) important for the generation of angiotensin$_{1\text{-}7}$.

It has been clear for some time that members of the RAS have functions beyond the simple regulation of vascular tone and salt-water homeostasis. The expression of many of the RAS players in the central nervous system for example opens up the possibility of central regulation of vascular function as well as actions beyond. For many years the hunt has been on for the elusive angiotensin 4/IV (AT_4) receptor. In their article on the angiotensin IV receptor Chai et al., describe the isolation, identification and function of the AT_4 receptor. Interestingly, although suggesting a role for this receptor in renal blood flow and sodium transport, this group also put forward evidence that the angiotensin IV system also involves memory and learning as well as glucose transport.

In the final article in this special issue, Khun, Li, Choe and Farzan describe one of the most unexpected findings to emerge from the many avenues of research into the RAS, that is 'ACE 2 is a functional receptor for the SARS coronavirus'. This fascinating observation that cellular entry of this enveloped virus is mediated by ACE2 not only has enormous value to those researching SARS, it also obviously opens new possibilities for the development of specific anti-SARS drugs by targeting ACE 2.

This special issue of Cellular and Molecular Life Sciences focuses on many of these new findings which hopefully when taken together may shed some light, not only on the complex physiology behind some of the new activities associated with some of the established players within the RAS, but also to try and define the roles some of the new RAS players may play.