New insights into mechanisms of hypertension

Rhian M. Touyz

Hypertension and its consequences contribute significantly to worldwide morbidity and mortality. Hypertension is the major cause of stroke, kidney disease and cardiac failure in the western world and it is predicted that by 2025 the number of adults with hypertension will increase by 60% [1–3]. This is attributed, in part, to the growing problem of associated risk factors including obesity and diabetes. Despite its widespread prevalence and intense research into its pathophysiology and cause, only 5% of patients with hypertension have an identifiable cause. Moreover, in spite of the enormous advances in antihypertensive drug therapy, the number of people with uncontrolled hypertension has continued to rise [4,5]. Reasons for these trends relate to the complex pathogenesis of hypertension.

Hypertension is the product of dynamic interactions between multiple genetic, physiological, environmental and psychological factors. In the past, much emphasis was placed on the autonomic nervous system and kidney as being major drivers of hypertension. More recently, the immune system has been implicated in the pathophysiology of hypertension, with many recent reviews detailing the role of T cells in the development of hypertension [6,7]. However, it should be kept in mind that most studies demonstrating immune activation/dysregulation in blood pressure elevation were performed in experimental models. Human studies confirming T cells as key players in essential hypertension are still needed.

Independent of the organ system playing a role in blood pressure elevation, it is clear that alterations in vascular function and structure are paramount. As such, there has been a paradigm shift wherein arterial hypertension may be considered a disease of vessels (vasculopathy) characterized by endothelial dysfunction, structural remodeling, vascular inflammation, increased stiffness and reduced distensibility. Initially these processes may be adaptive to elevated blood pressure, but once they are maladaptive they become contributing factors themselves. These vascular alterations impact on cardiac, cerebral and renal function, contributing to target organ damage leading to cardiovascular diseases including cardiac failure, stroke, renal failure and erectile dysfunction.

Cellular processes underlying these vascular perturbations include altered endothelial cell function, vascular smooth muscle cell growth/apoptosis, fibrosis, hypercontractility and calcification. Inflammation, associated with increased expression of redox-sensitive proinflammatory genes and recruitment, migration and infiltration of circulating cells, also participate in remodeling. These characteristics constitute the 'vascular phenotype' of hypertension [8], a phenomenon that may be determined by early life programming and imprinting [9]. Many of these features occur with aging, and the vascular phenotype in hypertension is increasingly considered a phenomenon of 'premature vascular aging' [10].

At the molecular level, abnormal signal transduction contributes to altered cellular function involving phospholipase C–inositol phosphate–diacylglycerol, mitogen-activated protein kinase, tyrosine kinases/phosphatases, RhoA/Rhokinase, transcription factors and NAD(P)H oxidase-derived reactive oxygen species [11–13]. These signaling pathways are stimulated in large part by prohypertensive peptides such as angiotensin (Ang) II and endothelin-1 (ET-1) that signal through membrane-associated G protein-coupled receptors [14,15]. In addition to classical vasoactive agents such as Ang II and ET-1, aldosterone, through its intracellular mineralocorticoid receptor, has been shown to influence cardiac and vascular function and structure in hypertension through nonrenal mechanisms [16]. The importance of aldosterone in the pathogenesis of hypertension has recently been highlighted by the findings of a mutation of the K^+ channel in hyperaldosteronism and hypertension [17].

Building on the concepts above are some new and recent insights that have contributed to the further understanding of mechanisms underlying

Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, Glasgow, Scotland, UK

Correspondence to Rhian M. Touyz, MD, PhD, Institute of Cardiovascular and Medical Sciences, BHF Glasgow Cardiovascular Research Centre, University of Glasgow, 126 University Place, Glasgow G12 8TA, Scotland, UK. Tel: +44 00141 330 7775; fax: +44 0 141 330 3360; e-mail: rhian.touyz@glasgow.ac.uk/rtouyz@uottawa.ca

Curr Opin Nephrol Hypertens 2012, 21:119–121

DOI:10.1097/MNH.0b013e328350a50f

hypertension and its consequences. The current issue highlights some of these, focusing on three major themes: vascular pathobiology: sodium and the kidney: and clinical conditions associated with hypertension, specifically preeclampsia and erectile dysfunction. Batchu and Korshunov (pp. 122–127) introduce us to receptor tyrosine kinases and their complex signaling networks with Ang II and other agonists in vascular remodeling. Of note, Ang II signaling through receptor tyrosine kinases involves Ang II type 1 receptor (AT_1) receptor-mediated transactivation of these kinases. We also learn about new functions of the AT_2 receptor through studies reviewed by Steckelings *et al.* (pp. 142–146), which show that AT_2R stimulation promotes cardiovascular protection through antifibrotic and anti-inflammatory actions without having antihypertensive effects. Such unexpected results challenge the dogma that AT_2R agonism may be an effective therapeutic strategy in the management of hypertension. Other provocative studies relating to the renin–angiotensin system have questioned the role of (pro)renin in Ang II-independent signaling. Reudelhuber (pp. 137–141) provides an up-to-date critical appraisal of the literature and concludes that the current data do not support a role for direct (pro)renin signaling through the (pro)renin receptor in vascular disorders. Rather, it is suggested that the main role of the (pro)renin receptor is a subunit of the vacuolar ATPase complex.

Other important systems modulating cardiovascular function and structure in hypertension are aldosterone and ET-1. Nguyen Dinh Cat and Jaisser (pp. 147–156) discuss the pleiotropic actions of aldosterone, signaling through rapid nongenomic and genomic pathways involving mineralorticoid-dependent and mineralorticoid-independent signaling, in the heart, the vessels and other nonepithelial tissues. Similar to Ang II, aldosterone is now recognized as a potent inducer of cardiovascular inflammation, fibrosis and progression of cardiovascular diseases including hypertension. Some of the effects of aldosterone may be mediated through ET-1 generation. For a while, the function of ET-1 in the pathogenesis of hypertension remained unclear. Recent studies reviewed by Rautureau and Schiffrin (pp. 128–136) provide strong evidence supporting the endothelin system in the development of hypertension, at least in animal models. New signaling pathways including calcitonin gene-related peptide, stromal interaction molecule-1/orai1 signaling, activation of p63RhoGEF and increases in O-GlcNAcylation, seem to be involved in the potent vascular contractile effects of ET-1. Data from genetically modified mice indicate that endothelial ET-1 is critically involved in the regulation of normal blood pressure and development of vascular disease.

Hypertension is a multiorgan disease and the kidney plays a central role in the development of hypertension, although at the same time being a target organ of hypertension-induced damage. The importance of the kidney probably relates in large part to the regulation of sodium excretion, which is a highly complex process and still not completely understood. Herrera and Coffman (pp. 171–178) review a series of recent studies of regulatory pathways affecting sodium excretion by the kidney including the renin–angiotensin system, the mineralocorticoid receptor, the endothelin system, nitric oxide and the WNK/SPAK pathway. They have highlighted studies that examined transgenic mouse models that provide a powerful mechanism for defining the role of proteins and pathways in sodium balance and blood pressure in the intact organism.

Many excellent reviews related to cardiovascular complications of hypertension are available, but underscored here are two human conditions, preeclampsia and erectile dysfunction, for which there are few good experimental models. George *et al.* (pp. 157–162) update us on new mechanisms implicated in preeclampsia, focusing on the vascular endothelial growth factor antagonist soluble fms-like tyrosine kinase 9sFlt-1) and immune factors, which seem to be key in maternal endothelial dysfunction. They also discuss the importance of ET-1 as a final common pathway in the pathogenic cascade of preeclampsia and suggest endothelin receptors blockers as potential therapeutic agents in managing preeclampsia. Considering the teratogenic effects of endothelin receptor blockers, the authors also discuss the limitations and concerns of such a therapy in preeclampsia.

It is becoming evident that there is an increased incidence of erectile dysfunction among patients diagnosed with cardiovascular disease. Both conditions, which may be a consequence of underlying endothelial dysfunction, share many risk factors including hypertension. Because vascular changes in the penile endothelium that lead to erectile dysfunction are similar to those that characterize the vascular phenotype in hypertension, it has been suggested that erectile dysfunction might be an early indicator for systemic endothelial dysfunction, hypertension and cardiovascular disease. Nunes *et al.* (pp. 163–170) discuss some of the molecular mechanisms associated with vascular changes in erectile dysfunction, focusing on cytokines, nitric oxide, hydrogen sulphide and the RhoA pathway. It is suggested that some of these systems may be interesting therapeutic targets to improve

vascular health not only in erectile dysfunction, but also in hypertension.

The comprehensive reviews in this issue present an update of some new directions regarding processes underlying aberrant blood pressure regulation and development of hypertension – from signaling molecules to transgenic mouse models to human disorders. A better understanding of such processes will contribute to improved therapies and new strategies to better manage hypertension so that the predicted trends of the growing epidemic of hypertension will be prevented.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kakar P, Lip GY. Towards understanding the aetiology and pathophysiology of human hypertension: where are we now? J Hum Hypertens 2006; 20:833–836.
2. Kannel WB. Hypertension: reflections on risks and prognostication. Med Clin North Am 2009; 93:541–558.
3. Mittal BV, Singh AK. Hypertension in the developing world: challenges and opportunities. Am J Kidney Dis 2010; 55:590–598.
4. Chobanian AV. Impact of nonadherence to antihypertensive therapy. Circulation 2009; 120:1558–1560.
5. Chobanian AV. Mixed messages on blood pressure goals. Hypertension 2011; 57:1039–1040.
6. Zubcevic J, Waki H, Raizada MK, Paton JF. Autonomic-immune-vascular interaction: an emerging concept for neurogenic hypertension. Hypertension 2011; 57:1026–1033.
7. Muller DN, Kvakan H, Luft FC. Immune-related effects in hypertension and target-organ damage. Curr Opin Nephrol Hypertens 2011; 20:113–117.
8. Savoia C, Burger D, Nishigaki N, *et al.* Angiotensin II and the vascular phenotype in hypertension. Expert Rev Mol Med 2011; 13:e11.
9. Lurbe E, Torró MI. Early vascular phenotypes in the genesis of hypertension. Pediatr Nephrol 2010; 25:763–767.
10. Nilsson PM. Early vascular aging (EVA): consequences and prevention. Vasc Health Risk Manag 2008; 4:547–552.
11. Kahle KT, Rinehart J, Giebisch G, *et al.* A novel protein kinase signaling pathway essential for blood pressure regulation in humans. Trends Endocrinol Metab 2008; 19:91–95.
12. Briones AM, Touyz RM. Oxidative stress and hypertension: current concepts. Curr Hypertens Rep 2010; 12:135–142.
13. Fisher SA. Vascular smooth muscle phenotypic diversity and function. Physiol Genomics 2010; 42A:169–187.
14. Higuchi S, Ohtsu H, Suzuki H, *et al.* Angiotensin II signal transduction through the AT1 receptor: novel insights into mechanisms and pathophysiology. Clin Sci (Lond) 2007; 112:417–428.
15. Bastin G, Heximer SP. Intracellular regulation of heterotrimeric G-protein signaling modulates vascular smooth muscle cell contraction. Arch Biochem Biophys 2011; 510:182–189.
16. Rautureau Y, Paradis P, Schiffrin EL. Cross-talk between aldosterone and angiotensin signaling in vascular smooth muscle cells. Steroids 2011; 76:834–839.
17. Choi M, Scholl UI, Yue P, *et al.* K+ channel mutations in adrenal aldosterone-producing adenomas and hereditary hypertension. Science 2011; 331:768–772.