Inflammation in the genesis of hypertension and its complications—the role of angiotensin II

Jun Li¹, Yvonne Doerffel², Berthold Hocher¹ and Thomas Unger¹

¹Center for Cardiovascular Research (CCR)/Institute of Pharmacology, and ²Outpatient Clinic, Charité – Universitätsmedizin Berlin, Germany

Keywords: hypertension; inflammation; angiotensin II

Inflammation and hypertension

Hypertension remains a major clinical syndrome characterized by small artery disease and subsequent accentuated development of atherosclerosis [1]. The affected arteries usually have diminished wall compliance and elevated stiffness resulting from arterial remodelling and atherosclerosis. With the progression of hypertension, the risk of cardiovascular complications such as myocardial infarction and stroke increases [2]. Recently, an emerging concept contends that inflammation plays a predominant role in the progression of hypertension and is also involved in the triggering of hypertension-associated cardiovascular complications.

Recent studies have indicated a close relationship between hypertension and inflammation, showing that tissue expression and plasma concentration of inflammatory mediators are increased in patients with essential hypertension and in experimental models of hypertension. These inflammatory mediators include C reactive protein (CRP) [3,4], interleukin (IL)-6, IL-1β [5], tumour necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) [6], and have been linked to the activation of the nuclear factor kappa B (NF-κB) system [7,8]. For example, in peripheral monocytes from hypertensive patients, the production of IL-1β and TNF-α was significantly increased upon lipopolysaccharide stimulation [9]. With this evidence for inflammation in hypertension, new questions arise. Does inflammation contribute to hypertensive vascular disease? Who are the players involved? Could vascular inflammation be a link between hypertension, atherosclerosis and aneurysm?
Besides mechanical stress and humoral factors, inflammation is considered an important stimulator for the activation of cellular elements resident in the media or adventitia layers of the arterial wall. Indeed, increased inflammatory molecules have been implicated in the regulation of vascular tone. For instance, it has been shown that circulating levels of CRP, IL-6 and TNF-α are positively related to aortic stiffness in patients with essential hypertension [10], and that CRP levels are associated with the future development of hypertension [4]. CRP may promote detrimental effects on the vascular wall by reducing nitric oxide bioavailability [3], promoting inflammatory activation of monocytes, vascular smooth muscle and endothelial cells, and inducing endothelial dysfunction and thrombotic complications [1].

Inflammation has not only been identified contributing to the pathway causing end-organ damage in hypertension as discussed above. Even more importantly, inflammation could turn out to be the hallmark of the pre-hypertensive state. Especially, pregnancy-induced hypertension seems to be such an ‘immune’ disease. Preeclampsia is derived from insufficient trophoblast invasion and poor remodelling of the uterine spiral arteries. It was suggested that this is due to failure of immune tolerance between mother and fetus. Placental hypoxia may ultimately lead to systemic effects through the secretion of cytokines and endothelial dysfunction. It is now believed that alterations of maternal immune tolerance to a fetal semi-allograft are important for the pathogenesis of hypertensive disorders in pregnancy [11]. Further work has shown that genes related to immune tolerance and inflammation are associated with blood pressure regulation, urinary protein excretion and oedema during pregnancy, which supports the hypothesis that genetically determined factors of maternal immune tolerance play a role in the pathogenesis of hypertensive disorders in pregnancy. In addition, there is recent evidence that this immune process is linked to the rennin–angiotensin system (RAS) [12].

Proinflammatory angiotensin II

The RAS is often activated in patients with hypertension as reflected, among others, by elevated levels of angiotensin II (Ang II), the effector peptide of the RAS. In addition to regulating vascular tone, Ang II acts as a major determinant of inflammatory reactions. For instance, infiltrated macrophages, which express high levels of angiotensin-converting enzyme (ACE), contribute to the production and accumulation of local Ang II surrounding ischaemic myocardium after experimental myocardial infarction [13]. Local Ang II, that has been found to colocalize with macrophages in intima-media of atherosclerotic vessels, decreases in parallel with a corresponding reduction of macrophage infiltration during the regression of experimental atherosclerosis [14]. In addition, it has been shown that peripheral blood monocytes from hypertensive patients are pre-activated and produce increased IL-1β upon Ang II stimulation when compared to that from healthy controls [9]. Ang II also induces NF-κB activation triggering the production of inflammatory cytokines, such as TNF-α and IL-6, and stimulates MCP-1 [7,8]. Furthermore, Ang II-induced hypertension is associated with increased vascular O2 production and impaired vascular relaxation [15]. In vascular smooth muscle cells, Ang II increases production of O2 anions via membrane-bound NADH and NADPH-driven oxidases [16]. Ang II exerts its (patho)physiological effects by binding to highly specific receptors located on the cell membrane. In humans and rodents, two pharmacologically distinct angiotensin receptors, AT1 and AT2, have been identified. Most of the known effects of Ang II involving inflammatory responses are mediated by AT1 receptors [17,18], while the AT2 receptor appears to be instrumental in tissue regeneration, repair process and anti-inflammation [19,20]. In this context, it has been reported that angiotensin AT2 receptors are required for the reduced infiltration of inflammatory cells and down-regulation of inflammatory cytokine expression in cuff-induced inflammatory vascular injury [21].

Anti-inflammatory effects by inhibition of the RAS

Pharmacologic inhibition of the RAS can be performed by inhibiting the generation of Ang II with an ACE inhibitor or by addressing the angiotensin AT1 receptor site with an AT1 receptor blocker (ARB) [17,18]. Clinical studies have revealed that both, ACE inhibitors and ARBs, significantly improve the clinical outcome in patients with hypertension and hypertension-related target organ damage [22,23]. In addition, inhibition of the RAS reduces the level of inflammatory reaction in the vessels, reverses most of the detrimental effects of Ang II on endothelial function, and offers additional tissue protection beyond blood pressure control in hypertension and its complications [21,24,25]. These experimental findings have been corroborated by clinical observations showing that treatment with ARBs can reduce the circulating levels of inflammatory mediators, such as CRP, IL-6, TNF-α and MCP-1 [26]. We and others recently demonstrated that a subset of ARBs induces the activity of peroxisome proliferator-activated receptor (PPAR)-γ by partial agonism [27]. PPAR-γ belongs to ligand-activated transcription factors involved in the transcriptional regulation of key metabolic pathways such as lipid metabolism and adipogenesis [28]. More recent in vivo and human studies suggest that PPAR activation may limit inflammation and atherosclerosis [28]. A potential advantage of ARBs over ACE inhibitors is that some of them partially activate or modulate PPAR-γ. Additionally, they do not antagonize the AT2 receptors but expose these to increased...
Ang II levels, which may indirectly contribute to the anti-inflammatory effects of ARBs. Given the fact that AT2 receptors seem to be required for the reduction of inflammatory cells and inflammatory cytokine expression [21], such an indirect activation of angiotensin AT2 receptors is likely to contribute to the well-documented anti-inflammatory effects of ARBs.

In summary, vascular inflammation is present in hypertension and contributes to hypertensive vascular disease. CRP and Ang II are major, but not the exclusive, players in hypertensive/infamy trial vascular and contribute to both inflammatory responses and hypertensive vascular remodelling at the same time. Finally, vascular inflammation may herald the development of hypertension, and may in the future even serve as a predictor of this disease.

Conflicts of interest statement. None declared.

References

5. Biasucci LM, Liuzzo G, Fantuzzi G et al. Increasing levels of interleukin (IL)-1Ra and IL-6 during the first 2 days of hospitalization in unstable angina are associated with increased risk of in-hospital coronary events. Circulation 1999; 99: 2079–2084
18. Unger T. Significance of angiotensin type 1 receptor blockade: why are angiotensin II receptor blockers different? Am J Cardiol 1999; 84: 9S–1S
27. Schupp M, Janke J, Clasen R, Unger T, Kintscher U. Evidence that macrophages in atherosclerotic lesions contain angiotensin II. Circulation 1991; 84: 9S–1S

Received for publication: 12.6.07
Accepted in revised form: 20.6.07