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Monocyte chemoattractant protein-1: a key mediator of angiotensin II-induced target organ damage in hypertensive heart disease?

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Hypertension is a leading risk factor for the development and progression of cardiovascular diseases. If it is left untreated, it often leads to target organ damage in resistance blood vessels, as well as the heart and kidney [1,2]. The prevalence of hypertensive vascular, heart and renal diseases is steadily increasing at an alarming rate both in the USA and worldwide. To prevent such a hypertension epidemic and/or treat target organ damage, several classes of therapeutic drugs including diuretics, β-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors (ACEI) have been developed and widely used over the last few decades [3]. In recent years a new class of compounds, angiotensin II type 1 (AT_1) receptor antagonists (ARB), has been added to the roster of antihypertensive agents [4]. Although most anti-hypertensive drugs are effective in treating certain experimental models of hypertension or hypertensive patients, the effectiveness and mechanisms of their actions are markedly different [3]. However, clinical trials have suggested that ACEI and ARB may be the drugs of choice in treating hypertension, cardiac hypertrophy and congestive heart disease, in which a circulating and tissue renin–angiotensin system (RAS) may be activated [5,6]. ACEI specifically block formation of the active molecule angiotensin II at the circulating and local tissue levels, whereas ARB block its actions at the AT_1 receptor level [5,6]. However, the cellular mechanisms by which ACEI and ARB exert their beneficial effects are not fully understood. The classic view is that the antihypertensive effects of ACEI and ARB are mediated at least partially, if not entirely, by lowering blood pressure and thus eliminating haemodynamic stimuli common to the disease process. However, evidence is also mounting that merely lowering blood pressure is not sufficient to account for the overall benefits of ACEI and ARB in treating hypertension and preventing target organ damage, because these benefits have been demonstrated in both animal and human studies with or without significant blood pressure-lowering effects [1,3–6]. In this issue of the journal, Behr *et al*. [7] report that long-term therapy with the AT_1 receptor blocker eprosartan markedly reduced cardiac hypertrophy, decreased morbidity and mortality, and therefore improved overall cardiac performance in a rat model of high-salt, high-fat hypertensive heart disease, stroke-prone spontaneously hypertensive rats (SHR-SP). In their study, the beneficial effects of eprosartan were associated with significant reductions in myocardial pro-inflammatory chemokine monocyte chemoattractant protein-1 (MCP-1) expression and production, with subsequent inhibition of monocyte and macrophage infiltration of the left ventricle [7]. Because only one-half the conventional dose of eprosartan was used, high blood pressure persisted in all three groups of SHR-SP rats with or without a high-salt, high-fat diet or eprosartan. Nevertheless, only the rats that received eprosartan exhibited decreases in MCP-1 mRNA expression and protein production, inhibition of monocyte and macrophage infiltration, and improvement of overall cardiac function [7]. Therefore, these novel findings suggest that increased MCP-1 expression

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may be a key mediator between angiotensin II and target organ damage in hypertensive heart disease.

MCP-1 as a powerful mediator of inflammatory responses in hypertensive cardiovascular diseases

Hypertension and cardiovascular diseases, including atherosclerosis, cardiac hypertrophy and ischaemic heart disease, are now increasingly recognized as inflammatory diseases. Munro and Cotran [8] were among the first to link inflammation to the pathogenesis of atherosclerosis [8]. Alexander [2] further proposed that hypertension and atherosclerosis should be viewed fundamentally as inflammatory diseases. In recent years, this hypothesis has led to heightened interest in studying the role of inflammatory cytokines, chemokines and growth factors in the pathogenesis of hypertension, atherosclerosis, cardiac hypertrophy, ischaemic heart disease and renal disease [9–13]. Consistent with this view, development and progression of these cardiovascular and renal diseases are often associated with increased expression and production of pro-inflammatory cytokines (leukocyte adhesion molecules, ICAM-1 and VCAM-1) [1,2], chemotactic proteins (MCP-1) [9–13], nuclear transcription factor (NFκB) [14–16], and growth factors (tumour necrosis factor, TNF-α, transforming growth factor, TGF-β) in endothelial cells, vascular smooth muscle cells and renal glomerular mesangial and tubular epithelial cells [1,2,9–16]. The key inflammatory molecule in initiating vascular, cardiac and renal inflammatory responses may be MCP-1, an important mediator of activation and recruitment of monocytes into the vascular endothelium, and from there to vascular smooth muscle cells or mesangial cells [9–15]. Indeed, the importance of MCP-1 in inflammatory diseases is highlighted by a careful MEDLINE search for MCP-1, which readily returns more than 3000 citations following its characterization in the late 1980s. MCP-1, a powerful chemokine, is synthesized and released by vascular, cardiac and renal cells in response to haemodynamic (shear stress, blood flow or oxidative stress) and humoral stimuli (such as angiotensin II and endothelin-1) [1,9–16]. Nuclear transcription factor NFκB appears to control expression of MCP-1 [14–16]. After release, it activates the CCR2 chemotactic receptor to induce chemotactic responses that mediate monocyte and macrophage migration into sites of active inflammation in various hypertensive and cardiovascular diseases [17,18]. Early studies demonstrated increased MCP-1 levels in human atherosclerotic arteries and experimental atherosclerotic lesions, where vascular smooth muscle cells and macrophages were identified as the major sources [9,10]. Increased expression of MCP-1, macrophage infiltration and inflammatory cytokines have subsequently been reported in hypertrophic and failing hearts with pressure overload due to aorto-caval fistula [12], ischaemic and reperfused rat hearts [19], and ischaemic or inflammatory renal diseases [15,20]. Behr *et al.* [7] used complementary approaches to quantify MCP-1 mRNA expression, MCP-1 protein production and macrophage infiltration in the myocardium of SHR-SP fed a high-salt, high-fat diet [7]. These rats are characterized by the development of severe hypertension, profound left ventricular hypertrophy, cardiomyocyte hypocontractility and eventually congestive heart failure [7]. In their study, MCP-1 mRNA expression in absolute copy numbers per nanogram of total RNA in the left ventricle, as analysed with quantitative real-time Taq-Man polymerase chain reaction, was four-fold higher in SHR-SP rats fed a high-salt and high-fat diet compared to those given a normal diet or genetic control WKY rats for 28 weeks. MCP-1 protein levels in the left ventricle, as determined by quantitative enzyme-linked immunosorbent assay, and MCP-1 immunoreactivity, as visualized by immunohistochemistry, also increased markedly. Interestingly, increased MCP-1 mRNA expression and MCP-1 protein in the left ventricle were accompanied by marked macrophage infiltration, a surrogate marker for MCP-1 activation. Thus, Behr *et al*. [7] provide solid evidence that MCP-1 expression and production are increased in the hearts of SHR-SP rats fed a high-salt, high-fat diet, suggesting that MCP-1 may mediate monocyte and macrophage infiltration and initiate inflammatory responses in the

myocardium of SHR-SP during the development and progression of hypertensive heart disease [7].

Angiotensin II as a powerful inflammatory cytokine and chemokine

Angiotensin II plays a critical role in the pathogenesis of a wide spectrum of cardiovascular and renal diseases, including hypertension, atherosclerosis, cardiac hypertrophy, ischaemic heart disease, cardiac and renal fibrosis [1–6,15,20]. At physiological levels (fentomoles), angiotensin II is an important physiological regulator of blood pressure, cardiac function and body salt and fluid homeostasis [3]. However, increased local or tissue angiotensin II formation in target organs such as blood vessels, heart and kidneys in the absence of elevated circulating angiotensin II may indeed be very deleterious [1,3–6]. Angiotensin II is not only a potent vasoconstrictor which elevates arterial blood pressure, but also a powerful pro-inflammatory cytokine, chemokine and growth factor [1,7,14–16]. There is accumulating evidence that angiotensin II can cause target organ damage by facilitating inflammatory and growth responses through activation of NFκB [1,14–16], the key nuclear transcription factor in inflammatory and fibrotic diseases. Activation of NFκB by angiotensin II may stimulate transcription of numerous inflammatory genes, including MCP-1, RANTES (Regulated on Active Normal T cell Expressed and Secreted) and interleukin (IL)-6, TNF-α and TGF-β [1, 14–16]. The view that MCP-1 is one of the most important chemokines in angiotensin II-induced inflammatory responses is supported by numerous studies, although the mechanisms by which angiotensin II increases MCP-1 expression and production are still not well understood [1,14–16]. In a rabbit model of atherosclerosis, the ACE inhibitor quinapril inhibited NFκB activity, expression and production of MCP-1 and neointimal macrophage infiltration at the injured sites [14]. In angiotensin II-induced hypertensive rats, vascular MCP-1 mRNA expression increased almost four-fold, which was significantly reduced by normalization of hypertension by the non-specific vasodilator hydralazine, but the effects of AT_1 receptor blockade were not studied [11]. Because similar results were reproduced in norepinephrine-induced hypertension, these data were interpreted as being mediated by mechanical factors [11]. However, in a different study, angiotensin II enhanced expression of MCP-1 mRNA and protein production in rat vascular smooth muscle cells in a dose- and time-dependent fashion, and these effects were mediated by AT_1 receptors involving the Rho-kinase pathway [21]. In mice, Wu *et al*. [22] showed that the AT_1 receptor antagonist valsartan, at a dose that did not influence systolic blood pressure, significantly reduced the expression of MCP-1 along with other inflammatory genes such as TNF-α, IL-6, IL-1β and monocyte/macrophage infiltration in injured vessels. Interestingly, the effects of valsartan on MCP-1 expression were attenuated in AT_2 receptor-deficient mice, suggesting that both AT_1 and AT_2 receptors are involved. Although Behr *et al*. [7] did not study the direct effects of angiotensin II on the expression of MCP-1 mRNA and protein or other pro-inflammatory cytokines or chemokines, they did extend those previous findings on MCP-1 expression further in a unique model of experimental hypertension (SHR-SP rats fed a high-salt, high-fat diet) using long-term therapy with a lower dose of a different AT_1 receptor blocker, eprosartan [7]. The advantage of using a lower dose of eprosartan is that the treatment does not reduce systolic blood pressure to the normotensive level, but retains clinical efficacy in inhibiting MCP-1 expression and improving cardiac function and mortality. Accordingly, the beneficial effects of eprosartan as demonstrated in this study may be explained by a mechanism other than high blood pressure. A direct effect of angiotensin II on MCP-1 expression and production may be implicated, as eprosartan specifically blocks AT_1 receptors [7].

Signalling mechanisms of angiotensin II-induced MCP-1 expression

Although the study by Behr *et al*. [7] clearly shows that long-term therapy with an ARB significantly reduces cardiac hypertrophy and the rate of morbidity and mortality and improves

cardiac performance in an animal model of hypertensive heart disease, it also raises many important unanswered questions. First, Behr *et al*. [7] suggest that the beneficial effects of ARB are not associated with blood pressure lowering; rather, a small decrease (16%) in systolic blood pressure may still be sufficient to activate angiotensin II-related signalling mechanisms [23]. Second, we do not know whether SHR-SP fed a high-salt, high-fat diet may be a proper model of angiotensin II-dependent hypertensive heart disease, because circulating or cardiac tissue angiotensin II was not measured. A high-salt diet may suppress angiotensin II production in the plasma and heart; and, if this is the case, how could an ARB produce such remarkable effects in this form of hypertensive heart disease? Third, it seems unlikely that MCP-1 is the only mediator for angiotensin II-induced target organ damage; other pro-inflammatory cytokines, chemokines and growth factors including TGF-β, TNF-α, IL-6 and IL-1β, and adhesion molecules such as ICAM-1 and VCAM-1 may be directly or indirectly involved [1, 2,15,22]. Blockade of AT_1 receptors with valsartan has been shown to attenuate expression of TNF-α, IL-6, and IL-1β [22]. Finally, the signalling mechanisms by which angiotensin II increases MCP-1 expression and production and induces end-organ damage remain to be elucidated. As mentioned previously, there is mounting evidence that NFκB may be one of the most important nuclear transcription factors that mediates angiotensin II-stimulated MCP-1 expression and production [1,14–16]. However, the signalling pathways by which angiotensin II directly or indirectly activates NFκB, which is then translocated into the nucleus to mediate MCP-1 transcription and synthesis, remain largely unknown. A local RAS may be activated in most, if not all, cardiovascular and renal diseases with consequently increased tissue or intracellular angiotensin II. Binding of extracellular angiotensin II to cell surface AT_1 receptors may stimulate MCP-1 mRNA expression through activation of different intracellular signalling cascades, likely involving protein kinase C-activated intracellular calcium mobilization [24], tyrosine kinase and mitogen-activated protein kinase [25], phospholipase A_2 [26] and redox-sensitive NADH/NAD(P)H oxidase [25]. Future studies further addressing these important issues could improve our understanding of the potential role of pro-inflammatory cytokines and chemokines in mediating angiotensin II-induced target organ damage and assist in further development of novel drugs to prevent and treat these diseases.

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