All because of the mast cell: blocking the angiotensin receptor-1 should be better than inhibiting ACE (theoretically)

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This editorial refers to ‘Contributions of ACE and mast cell chymase to endogenous angiotensin II generation and leukocyte recruitment in vivo’ by C. Company et al., pp. 48–56, this issue.

In cardiovascular disease, especially hypertension, chronic heart failure, and atherosclerosis, angiotensin II (Ang II) is generally a culprit while nitric oxide exerts beneficial effects. Accordingly, inhibiting angiotensin-converting enzyme (ACE) has become established as one of the most successful therapeutic options in the treatment of chronic cardiovascular disorders. However, an estimated 20–40% of patients do not respond to and/or tolerate ACE inhibition.1 The introduction of drugs selectively blocking Ang II receptors of type 1 (ARBs) has definitely brought some relief from unwanted side effects. In the paper by Company et al., appearing in the current issue of Cardiovascular Research,2 reasons are now given for why one should expect ARBs to be even more beneficial than ACE inhibitors in all cardiovascular conditions with an inflammatory component.

The reasoning and evidence are compelling and centre on the fact that the mast cell enzyme chymase is able to generate Ang II independently of the activity of ACE. In experiments conducted on the mouse cremaster muscle microcirculation, the authors show that degranulating mast cells release chymase in amounts great enough to circumvent the functional protection otherwise provided by an ACE inhibitor under non-inflammatory conditions. In contrast, stimulated mast cells lose much of their microcirculatory destabilizing potential if an ARB is applied instead of an ACE inhibitor.2 Proof of concept for the substantial involvement of mast cells was provided by corresponding studies performed in mast cell-deficient Kit+/Kit−/− mice (no added benefit from the use of an ARB), and in the presence of the chymase inhibitor chymostatin or the mast cell stabilizer cromolyn.2 Analogous utility of a mast cell stabilizer has previously been demonstrated for prevention of post-ischaemic release of tumour necrosis factor-alpha (TNF-α) from myocardial mast cells.3 Also, the Kit+/Kit−/− mouse model has successfully provided proof for the contribution of mast cells to the release of this particular cytokine and for the generation of Ang II in the murine heart.4,5

A particular merit of the present study of Company et al. is that it again brings to our attention the extraordinary importance of resident tissue mast cells in general physiological and pathophysiological responses. This numerically small population of immigrant cells, nestled into the perivascular spaces of the parenchymal tissue (Figure 1), is full of readily liberated, highly potent constituents and is, thus, also full of surprises. Among the plethora of inflammatory and vasoactive agents formed by and released from mast cells we find not only proteases such as chymase, tryptase, and metalloproteases but also histamine, leukotrienes, cytokines, and chemokines including TNF-α, monocyte chemoattractant and interleukins, renin (for Ang I synthesis), and the powerful sheddase heparanase. The latter has recently been found to be localized in the human myocardium exclusively in the resident mast cells (Figure 1).6 Its release upon stimulation probably accounts for the dramatic rise in plasma heparan sulphates observed both during on- and off-pump cardiac bypass surgery as a sign of shedding of the endothelial surface glycosaminoglycan.7 Interestingly, mast cells in the human myocardium express adenosine-A3 receptors (Figure 1). These stimulatory receptors respond to both adenosine and inosine. Elevated tissue purine levels may be expected not only in ischaemic states but also in atherosclerotic lesions, thus perhaps providing the necessary stimulus for mast cell degranulation and liberation of chymase. Incidentally, chymase and also tryp- tase are potential sheddases of proteinaceous components of the endothelial glycosaminoglycan.6,7

Although the potential of mast cell chymase to generate Ang II independently of ACE has been recognized before,5 we now have a quantitative evaluation of this contribution in vivo under inflammatory and non-inflammatory conditions.5 Atherosclerosis involves both stimulation by Ang II and an inflammatory setting. Chemokines from platelets and leucocytes are important for propagating atherosclerotic lesions,8 and platelets are known to express stimulatory AT-1 receptors.7 Thus, at first glance, the stage seems set for a greater benefit to be
derived from use of ARBs as opposed to ACE inhibitors. This all the more, since ACE is restricted to membrane surfaces, largely of the endothelial cells, whereas chymase, once released into the interstitial space, can spread everywhere, including the vascular system.10

So much for wishful thinking. Several objections to this theoretical expectation of ARBs being therapeutically more promising than ACE inhibitors immediately come to mind. For instance, pro-atherosclerotic cytokines formed by platelets bind to the glycosaminoglycans on the endothelial surface to attract and activate leukocytes.8 Shedding of the glycocalyx initiated by heparanase and proteases released from the mast cell would counter such a contribution,7 alleviating the role of chymase-generated Ang II on platelet activation (Figure 1). Also, the obligatory side effect of ACE inhibition, elevation of bradykinin, is not without merit in cardiovascular disease and atherosclerosis. Raising bradykinin should undoubtedly stimulate production of NO11 (Figure 1), an event absent in the case of sole blockade of the angiotensin receptor. Furthermore, chymase displays some species dependence with respect to preference of substrates. The principal ability of human mast cell chymase to generate Ang II seems to be clear,5 but the exact potential needs to be established. Finally, neither the mouse nor the vascular bed of the cremaster muscle is typically prone to atherosclerosis. Thus, extension of the findings reported by Company et al. to the situation pertaining to humans is a very long shot indeed. In at least one clinical study, ARBs were without beneficial effect.12 Despite extensive clinical trials undertaken to establish whether ACE inhibitor or ARB therapy is superior in various cardiovascular disorders, the only clear result thus far seems to be that the combination causes more problems than either therapeutic principle used singly.13–15

The message conveyed by these observations is that perhaps an entirely new option needs to be considered in the therapy of cardiovascular disease: namely, additional pharmacological stabilization of mast cells.2,3,5–7

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**References**


