Chymase: the other ACE?

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The therapeutic use of angiotensin-converting enzyme (ACE) inhibitors has been an integral part of the standard of care for hypertension and related diseases for decades. While the beneficial effects of these drugs are universally appreciated, there are a variety of physiological anomalies that remind us that there is still much to be learned about the mechanisms involved in the observed therapeutic effects of these agents, and the potential interaction with other related systems. For example, the limited relationship between plasma renin activity and the blood pressure response to ACE inhibitors remains rather puzzling to this day. In addition, with the advent of other inhibitors of the renin-angiotensin system, such as angiotensin receptor blockers (ARBs) and renin inhibitors (aliskiren), the effects of which resemble but do not mimic those of ACE inhibitors, it has become apparent that the mechanism of action of ACE inhibition is significantly more complex than simple lowering of circulating angiotensin II levels. This notion has been long appreciated through the observation that long-term treatments with ACE inhibitors is often associated with so-called “angiotensin escape,” characterized by the return of plasma angiotensin II concentration to pretreatment levels (although the beneficial effects on blood pressure usually persist). It is often assumed that this rebound generation of angiotensin II occurs through the action of the serine proteases such as cathepsin G and chymase (aka chymostatin-sensitive angiotensin II-generating enzyme or CAGE). A related, and perhaps more vexing anomaly is that in many diabetic patients, hypertension can be severe and is often resistant to antihypertensive therapies, including ACE inhibitors. This is indeed unfortunate since hypertension is a primary risk factor for the development of cardiovascular-related events in diabetic patients, and their target blood pressure is actually lower than in other patients. On the other hand, ACE inhibitors and/or ARBs remain the recommended drugs of first choice because they have been shown to be effective in preventing or delaying diabetic complications despite their blunted effectiveness in lowering blood pressure (1).

The study by Park et al. (4), appearing in the American Journal of Physiology-Renal Physiology, may provide important insights regarding diabetes-related resistance to antihypertensive treatment. This study explores the hypothesis that intrarenal angiotensin II can be generated from angiotensinogen by either of two pathways: a conventional ACE-dependent mechanism, and alternatively by an ACE-independent pathway, likely mediated by chymase. This study further suggests that non-ACE-dependent mechanisms predominate in diabetic kidneys and that this accounts for the ineffectiveness of ACE inhibitors in some diabetic patients. Chymase is a serine protease that cleaves angiotensin I at the same site as ACE, and has such a strong affinity that it converts angiotensin II to angiotensin II at a substantially greater rate than does ACE (6). Furthermore, whereas chymase is completely inhibited by serine protease inhibitors, it is highly resistant to ACE inhibitors. Through a comprehensive series of experiments using the lepin receptor-deficient/db/db type II diabetic mouse as a model, data are provided showing that the ACE activity and expression are markedly reduced in diabetic kidneys, whereas ACE2 levels are enhanced. Moreover, using the in vitro blood-perfused juxtamedullary nephron approach, these investigators demonstrated that the vasoconstriction produced by exogenously applied angiotensin I (as a precursor to angiotensin II) were blocked by ACE inhibition in control mice, but not in diabetic mice. Conversely, angiotensin I-induced constriction was blocked by serine protease inhibition in diabetic mice, but not in control mice. These data therefore confirm that a non-ACE-dependent mechanism for the generation of angiotensin II prevails in this form of diabetic nephropathy. The extent to which these findings can be extended into other diabetic models and to other species represents an important avenue of investigation with important clinical implications.

In total, chymases are a complex family of enzymes that can be classified into two subgroups, α and β, according to their structure and substrate specificity, and both subgroups can convert angiotensin I to angiotensin II. Interestingly, the β-chymases, which appear to be predominately found in rodents, do not appear to be expressed in humans, underscoring the need to extend such studies into other species, particularly humans. Vascular chymase has been previously implicated in the ACE-independent mechanism for local angiotensin II formation in human arteries (5), and chymase and renin derived from cardiac mast cells have been implicated in cardiac ischemia-reperfusion injury. Accordingly, it has also been reported that chymase expression is strongly upregulated in the human diabetic kidney, particularly in mesangial cells and in vascular smooth muscle cells (3), but the functional correlates of these changes have not been well studied. Along these lines, it has been suggested that the angiotensin II formed through the chymase pathway may not be involved in the regulation of blood pressure and hemodynamics, but rather that it is more likely involved in the structural remodeling associated with cardiovascular disease (2). The present findings by Park et al. (4) refute this notion and demonstrate that the non-ACE-dependent generation of angiotensin II plays a central role in the regulation of renal hemodynamics during the progression of diabetic nephropathy. In this regard, this study designates chymase as a potentially important therapeutic target in the treatment of diabetes-related hypertension and nephropathy.

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REFERENCES


