Renin-Angiotensin and Kallikrein-Kinin Systems Coordinately Modulate Angiogenesis

To the Editor:

We read with interest the article “Angiotensinogen and Its Cleaved Derivatives Inhibit Angiogenesis” by Celerier et al.1 At physiological concentrations, angiotensinogen (AGT), des(angiotensin I)angiotensinogen (des[Ang I]-AGT), and reactive center loop cleaved AGT affect endothelial cell (EC) phenotype toward antiangiogenesis. The renin-angiotensin system (RAS) and the kallikrein-kinin system (KKS), regarded as opposing forces in blood pressure control, share instead similarities as modulators of EC biology. Cleavage of kininogen (KNG) by kallikrein leads to formation of des(kinin)-KNG, which, similar to des(Ang I)-AGT, is antiangiogenic.2 Furthermore, angiotensin-converting enzyme (ACE) generates Ang II and degrades kinins, and both of these effects are considered proangiogenic. By extension, attention should be paid to the consequences that antihypertensive treatment, by interfering with RAS and KKS, might have on reparative or tumoral angiogenesis.

Under ACE inhibition (ACEI) or Ang II AT1 receptor blockade, compensatory increase in renin release leads to accelerated AGT cleavage, thereby augmenting angiogenesis inhibitors des(Ang I)-AGT and Ang (1-7). Furthermore, proangiogenic Ang II is lacking or displaced from receptor. Consequently, the equilibrium is shifted toward inhibition of vascular growth. How can we reconcile these concepts with the opinion that ACEI promotes neovascularization? One possibility involves the increased availability of angiogenic kinins.3 Accordingly, kinin B2-receptor disruption abrogates the healing effect of ACEI in a model of hindlimb ischemia.4 Yet, application of ACEI, ramipril, or AT1-receptor blocker, losartan, in coincidence with ischemic events reportedly leads to delayed and impaired postischemic recovery.5 Because the deleterious effects of ramipril are unaltered under combined kinin B1- and B2-receptor blockade, it is conceivable that kinins may not balance the negative impact of reducing the rate of Ang II formation. In light of the information provided by Celerier et al, des(Ang I)-AGT accumulation may have a role in negatively influencing reparative angiogenesis.

The above discrepancies should be reconsidered in accordance with the proposal introduced by Celerier that local environment may influence the final biological response. Furthermore, genetic alterations of system components may alternatively cause angiogenesis or antiangiogenesis to prevail. Therefore, in a therapeutic perspective, the most accurate scrutiny is required in the use of ACEI and AT1 antagonists under conditions where angiogenesis is necessary or undesired.

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_Hypertension_. 2002;39:e29
doi: 10.1161/01.HYP.000018956.63639.7F

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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