Angiotensinogen: An Attractive and Underrated Participant in Hypertension and Inflammation

To the Editor:

The Brief Review "Molecular Biology of Angiotensinogen" by Lynch and Peach1 provides a pertinent and complete analysis of the structure and regulation of this protein and its gene. However, more optimistic conclusions would have been appropriate, and the apparently unique role of angiotensinogen should certainly not be interpreted in a restrictive way. It may be true that angiotensinogen has the single classical role of being the unique substrate of renin, but this is still open to further research. In the meantime, angiotensinogen shares with the angiotensins it generates multiple roles in cardiovascular homeostasis. Moreover, angiotensinogen has introduced angiotensins into the current research on inflammation2 and some but not all of the inflammation models3 are characterized by an increased synthesis of angiotensinogen under dual regulation by cytokines and glucocorticoids.4 A local role of angiotensinogen in controlling vascular permeability and balancing the vasodilatory effects of kininogens might be suggested.

Whereas the role of angiotensinogen in inflammation is unknown, its importance in the control of blood pressure is debated. A selection of a few supplementary references from the literature, together with the results of our experiment performed at the time of publication of the Brief Review in Hypertension and described in this letter, should reinforce this function of angiotensinogen and bring a complementary physiological and physiopathological viewpoint to an excellent review focused primarily on angiotensinogen structure and expression.

Angiotensinogen's direct role in blood pressure regulation is demonstrated by the drop in blood pressure induced by angiotensinogen antibody administration.5 This drop is larger in rats on a salt-free diet than in those on a normal diet and is absent in binephrectomized animals. Experiments based on the passive transfer of antibodies are frequently criticized. Thus, to look for more direct evidence, we exposed male rats weighing 120–130 g to a salt-free diet for 1 month, after an initial treatment with 20 mg/kg furosemide subcutaneously, twice a day for 2 days (n=7).

These rats are characterized by a high plasma renin activity (PRA) (mean±SD) (22.1±7.1 pmol angiotensin I [Ang I]/ml/hr), and a high plasma renin concentration (PRC) (512±453 pmol Ang I/ml/hr). Their plasma angiotensinogen measured by an enzymatic assay (1,000±270 pmol angiotensinogen) was measured by a radioimmunologic assay (533±115 pmol Ang I/ml), which recognizes both angiotensinogen and des-Ang I-angiotensinogen.6 The presence of des-Ang I-angiotensinogen in plasma (389±60 pmol/ml) is a consequence of angiotensinogen consumption secondary to marked renin stimulation, as shown by the significant positive correlation between PRC and the ratio des-Ang I-angiotensinogen/angiotensinogen (r=0.913, n=7).

The acute administration of 250 μg pure rat angiotensinogen7 to four anesthetized rats increased blood pressure by 29±12 mm Hg, 2 minutes after injection and 16±6 mm Hg 10 minutes after injection, with a return to baseline levels at 60 minutes (Figure 1, upper panel). In these angiotensinogen-injected sodium-depleted rats, PRA increased from 23.1±11.2 to 63.7±16 pmol Ang I/ml/hr, PRC decreased from 598±442 to 225±141 pmol Ang I/ml/hr, and plasma angiotensinogen increased in both the enzymatic assay (584±200 pmol Ang I/ml) and the radioimmunologic assay (1,000±270 pmol angiotensinogen). A saline bolus had no hypertensive effect (n=3). When 250 μg pure angiotensinogen was administered intravenously to a binephrectomized salt-depleted rat, no rise in blood pressure was observed (middle panel), which confirms the unique role of the renal renin-angiotensin system in the short-term control of blood pressure.8 In three rats on a normal sodium diet, with normal plasma renin (PRA, 1±0.8 pmol Ang I/ml/hr; PRC, 7.3±1.9 pmol Ang I/ml/hr) and plasma angiotensinogen levels (enzymatic assay, 570±120 pmol Ang I/ml), the same dose of pure angiotensinogen had no blood pressure effect (lower panel).

This experiment provides direct evidence of the pressor effect of angiotensinogen dose that corrects a 73% reduction in plasma angiotensinogen, in a situation where PRC is increased by 70-fold. This pressor effect is not observed under normal circumstances and is mediated through the enzymatic effect of renin of renal origin.

The dual property of angiotensin II (Ang II) to stimulate angiotensinogen release9,10 and to decrease renin secretion through an intracellular mechanism of action similar to its vasoconstrictor effect11,12 creates within the renin-angiotensin system a complex and precise feedback regulation by components of the system.13 The in vivo adjustment between angiotensinogen and renin release through angiotensin II is a major determinant of the
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angiotensin decreased the messenger RNA level to 25-30% of control

| under the control of the mouse metallothionein I promoter

| encouraged us to continue the biochemical and genetic investiga-

| More recently, the investigation of angiotensinogen's role has

| benefited from two original experiments, aimed at discovering new

| ways of increasing or decreasing angiotensinogen production.

| Transgenic mice carrying the rat renin and angiotensinogen genes

| under the control of the mouse metallothionein I promoter

| developed a captopril-sensitive hypertension when supplied with ZnSO4 in drinking water.22 Transfer of stably transformed hepato
cells with antisense angiotensinogen RNA for angiotensinogen decreased the messenger RNA level to 25-30% of control values, a first attempt to use molecular genetic techniques to modify angiotensinogen production and, in the long term, locally generated angiotensin.23

References

8. Inagami T, Murakami T, Higuchi K, Nakajo S: Roles of renal and vascular renin in spontaneous hypertension and switching of the mechanism upon nephrectomy. Lack of hypotensive effects of inhibition of renin, converting enzyme and angioten-


cell lines. *J Mol Endocrinol* 1990;4:107-117

The following is in response:

To the Editor:

It appears that we have been taken to task by Dr. Menard and colleagues for insufficient "optimism" regarding possible roles of angiotensinogen in hypertension and inflammation. We suggest that perhaps our insufficiency is that of speculation, not optimism. In our judgment, the available data support the conclusion that angiotensinogen is simply an extracellular reservoir of angiotensin peptides and is inactive except as a substrate for renin or, perhaps, other proteases.

Assigning a role in inflammation to angiotensinogen is purely speculative; such a conclusion is unwarranted based solely on the observation that angiotensinogen messenger RNA levels increase (modestly) in response to cytokines and glucocorticoids. Angiotensinogen's purported "direct role in blood pressure regulation" apparently can be demonstrated only by the non-
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