Letters to the Editor

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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.6 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 (533±115 pmol Ang I/ml), which recognizes both angiotensinogen and des-Ang I-angiotensinogen,6 is much lower than measured by a 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 an angiotensinogen dose that corrects a 73% reduction in plasma renin activity.9,10 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 an 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 release8,10 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

![Figure 1. Representative tracings show blood pressure effects of the intravenous injection of pure rat angiotensinogen (250 μg) to a sodium-depleted rat (upper panel), a binephrectomized sodium-depleted rat (middle panel), and a sodium-repleted rat (lower panel).](http://hyper.ahajournals.org/lookup/fig/1)
renin-angiotensin system equilibrium. This is confirmed in our experiment by the fall in PRC that accompanies the rise in its substrate. This equilibrium is probably not perfect in women whose angiotensinogen is increased by an oestro-progestational treatment: their renal blood flow is reduced and their blood pressure is slightly increased. Another more practical consequence of this equilibrium is that the available angiotensinogen influences the interpretation of the various in vitro enzymatic assays of PRC and activity, for instance during pregnancy and oral contraceptive treatment or in patients with congestive heart failure.

In the epidemiological survey of Walker et al., angiotensinogen levels were significantly correlated with blood pressure. At least two cases of angiotensinogen-secreting hepatic tumors associated with hypertension have been reported. Slightly elevated levels of angiotensinogen have been observed in offspring of hypertensive patients. These observations should encourage us to undertake the biochemical and genetic investigations of angiotensinogen in hypertensive disorders.

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. Transfection of stably transformed hepatoma 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 generate angiotensinogen.
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