The Renin-Angiotensin System : Evidence from Gene Knock Out Studies

Iekuni Ichikawa, M.D., Ph.D.

Departments of Pediatrics and Medicine, Vanderbilt University Medical Center, USA

In order to identify the role of biologic substances, investigators have relied upon measures which inhibit the actions of the endogenous substances. A recently developed techique, gene targeting, allows complete and selective inactivation of a specific gene, thereby allowing identification of the consequences of complete absence of the gene product. We and others have recently produced several strains of mice deficient of a specific gene within the renin-angiotensin system[1-10]. Examination of these mustant mice revealed important bilogical functions of angiotensin (Ang) that have and have not been heretofore recognized.

Mice homozygous for a null mutation of angiotensinogen have a mean systemic blood pressure that is some 20-40mmHg lower than that of wild-type mice[1-3], indicating that Ang of endogenous origin is indeed a blood pressure-raising agent. Studies also showed that a subnormal level of Ang causes hypotension, as heterozygous and homozygous phenotypes for angiotensinogen are characterized by abnormally low blood pressure. In addition, the study by Kim et al[2]. raised the possibility that mutations of the angiotensinogen gene can be a cause of hypertension in humans, as mutant mice carrying targeted addition of extra copies of the aniotensinogen gene were hypertensive. This contrasts with the classic notion that the level of angiotensinogen is far in excess of the KD of renin so that upregulation of angiotensinogen should not increase the production of Ang I or Ang II.

Several animal studies using pharmacolgic Ang II inhibitors[11, 12] suggested an important role of Ang in the ontogeny of the kidney. To verify that Ang indeed regulates mammalian embryonic kidney development, the gene targeting strategy was recently employed[3]. Kidney specimens showed that, in the deep cortex, homozygous angiotensinogen null mutants have immature glomeruli, compared to wild-type. The study also revealed, however, that Ang has no significant role in the early process of initiating nephronogenesis.

In addition to delayed glomerular maturation, several other abnormal phenotypes became apparent in kidneys of homozygous angiotensinogen null-mutants after three weeks of age, many of which are proliferative in nature. Thus, the kidenys of homozygotes have, among other abnormalities, marked wall thickening in small arteries, despite marked hypotension. By contrast, in the heart, liver, or major vessels, these hypertrophic vascular lesions are not found. At 8 weeks, the papilla of wild-type mice displays normal elongation, whereas that of the targeted mouse is remarkably hypoplastic. Therefore, in mammals, Ang appears to have a heretofore unrecognized target tissue, namely, the papilla. In more recent study on mice carrying null-mutated angiotensin I converting enzyme (ACE) gene[10], an identical pat-

tern of hypoplastic papilla was noted, along with the presence of a concentration defect.

Since targeted null mutation of a given gene leads to complete absence of the gene product, this technique allows testing of whether some biological phenomena are indeed dependent upon a given product. In a recent study[13] with angiotensinogen gene (Agt) null mutant mice, Ang was shown to be nonessential for secondary hyperaldosteronism during extracellular fluid volume depletion, where potassium was found to function as an aldosterone induer alternative to Ang. The renin-angiotensin-aldosterone system has long been regarded as the primary hormonal cascade for extracellular fluid volume homeostasis in mammals[14]. In the study, wild-type (Agt+/+) and homozygous angiotensinogen null mutant (Agt-/-) mice were placed on normal or low Na diet to manipulate this system. Plasma aldosterone levels were comparable during normal Na diet, and similarly elevated during low Na diet in Agt+/+ and Agt-/- mice. Agt-/-mice were distinguished from Agt+/+ mice by their elevated plasma K levels, by ~1.5 and ~3.8 mEq/L during normal and low Na diets, respectively. Within the Agt-/-group, plasma aldosterone levels were directly proportional to plasma K levels. The importance of K for hyperaldosteronism during dietary Na restriction was verified by the observation that superimposition of K restriction led to hypotension in Agt+/+ and death in Agt-/- mice, along with a reduction in plasma aldosterone levels by 75 and 90%, respectively. Therefore, 1) a powerful angiotensin-independent mechanism exists for hyperaldosteronism during chronic extacellular fluid volume depletion; 2) high K is a central component of this mechanism; 3) the tonic effect of high K on plasma aldosterone does not involve Ang II or its receptors. In this context, when plasma K is regarded as a primary regulator for plasma aldosterone level during modulation in ECF volume, Ang II can be regarded as a modifier of this strong postive relationship between K and aldosterone.

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