Hypertensive and Hypotensive Mice Produced by the Introduction and Disruption of Genes on Renin-Angiotensin System.

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The renin-angiotensin system is an enzymatic cascade that produces a potent vasoconstrictor octapaptide angiotensin II, through its physiologically inactive intermediate decapeptide angiotensin I, from their precursor angiotensinogen.

We have constructed the chimeric renin-angiotensin cascade in mice comprising both human renin and human angiotensinogen as well as the endogenous angiotensin-converting enzyme and angiotensin II receptor by crossmating separate lines of transgenic mice carrying either the human renin or human angiotensinogen genes. Although each single gene carrier did not develop hypertension, despite the observed normal tissue specific expression of the transgenes, dual gene strains exhibited a chronically sustained increase in blood pressure (BP). The systolic BP was 129.1 ± 5 mm Hg.

Administration of a human renin-specific inhibitor (ES-8891) was effective in reducing the elevated blood pressure only against the cross-mated hybrid mice, but treatment of an angiotensin-converting enzyme inhibitor (captopril) and a selective antagonist (DuP 753) directed at the angiotensin II receptor decreased the basal level of blood pressure even in single gene carriers as well as in dual gene mice.

These results clearly demonstrated that the sustained increase in blood pressure of the hybrid mice was initiated by the interaction between the products of the two human genes. We named the hypertensive mice as "Tsukuba Hypertensive Mice".

On the other hand, we generated angiotensinogen-deficient mice by homologous recombination in mouse embryonic stem cells. These mice do not produce angiotensinogen in the liver, resulting in the complete loss of plasma immunoreactive angiotensin I. The systolic blood pressure of the homozygous mutant mice was 66.9 ± 4.1 mm Hg, significantly lower than that of wild-type mice (100.4 ± 4.4 mm Hg). We named the hypotensive mice as "Tsukuba Hypotensive Mice".

The blood pressure of Tsukuba Hypertensive Mice and Tsukuba Hypotensive Mice are shown below.

Blood Pressure (mm Hg)	Tsukuba Hypertensive Mice	Normal Mice	Tsukuba Hypotensive Mice
Systolic	129.1 $\pm$ 5.0	104.0 $\pm$ 4.4	66.9 $\pm$ 4.1
Diastolic	87.1 $\pm$ 7.2	66.8 $\pm$ 5.3	52.5 $\pm$ 1.9

Angiotensin (AT) II, exerts its multiple effects through the different types of AT receptors, AT1a, AT1b, and AT2. Previously, we showed chronic hypotension in angiotensinogen (the precursor of AT)-deficient mice and a dramatic increase in renin mRNA levels in its kidney, but it remains unclear which types of AT receptors regulate the blood pressure and renin gene expression.

In order to elucidate the physiological roles of AT1a receptor, we generated mutant mice with a targeted replacement of the AT1a receptor loci by the lacZ gene. In the heterozygous mutant mice, the strong lacZ staining was found in the glomerulus and juxtaglomerular apparatus of the renal cortex, which coincided with that of the signals detected by *in situ* hybridization. Chronic hypotension was observed in the heterozygous and homozygous mutant mice, with 10 and 22 mm Hg lower systolic blood pressure, respectively, than that of wild-type littermates.

Both the levels of renin mRNA in the kidney and plasma renin activity were markedly increased only in the homozygous mutant mice. These results demonstrated that an AT1a-mediated signal transduction pathway is, at least in part, involved in the regulation of blood pressure and renin gene expression.

In conclusion, the increase and decrease of genes of renin-angiotensin system caused hypertension and hypotension of these mutant mice, respectively, demonstrating that renin-angiotensin system play indispensable role not only in the hypertensive state but also in normotensive state which can not be replaced by any other hormonal and neuronal systems.

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