Renin-angiotensin System in Severe Hypertension of Stroke-prone SHR Rats

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It has been reported that either hypertension or onset of stroke of stroke-prone SHR (SHRSP) rats is accelerated by salt-loading. The present study was designed to investigate the participation of renin-angiotensin system in maintenance of salt-accelerated severe hypertension in male SHRSP rats.

Animals were kept on a standard laboratory chow and loaded with 1% NaCl solution as drinking water from about 10 weeks of age. The systolic blood pressure was measured by tail pulse-pick up method under unanesthetized conditions. Blood pressure responses to exogenous norepinephrine (NE) and angiotensin II (AII) were measured by the direct method under anesthesia with urethane. The effect of an AII-inhibitor, [1-sarcosine, 8-alanine] AII, on blood pressure was also measured directly in conscious rats. Blood samples for the plasma renin concentration (PRC) assay were collected from tail vein under unanesthetized conditions. PRC was measured by radioimmunoassay.

Changes of blood pressure and PRC during salt-loading were observed in 5 SHRSP rats. The blood pressure in these rats was 193±6 mmHg (mean±SD) at the start of experiment. After the salt-loading, the blood pressure gradually increased and became about 250 mmHg prior to the onset of stroke-signs. The stroke-signs were observed 21 to 41 days after salt-loading. PRC in these rats was initially 18.9±3.1 ng/ml/hr and was reduced to 10.5±3.1 ng/ml/hr 1 week after the salt-loading. And then, it gradually increased and reached 213±90.2 ng/ml/hr at the onset of stroke.

Blood pressure responses to NE and AII were measured in 23 SHRSP rats on 1% NaCl for 2–3 weeks, in 11 of which stroke signs were confirmed. The amounts of drugs producing a 30 mmHg rise of blood pressure (ED30) were used as an index of the pressure response. In individual analysis, ED30 for AII was positively correlated to PRC (n=23, r=0.796, P<0.01; ED30=0.687×PRC+14.4). In contrast, ED30 for NE did not change with the alteration of PRC. These results suggested an increase of plasma AII due to the elevated PRC in the salt-loaded SHRSP rats.

When the AII-inhibitor was infused at a rate of 10 µg/Kg/min for 40 min, SHRSP rats on tap water (n=7) showed no hypotensive response. SHRSP rats (n=8), which were loaded with 1% NaCl for 2–3 weeks and lower PRC (7.9±2.6 ng/ml/hr), also did not respond to the inhibitor. In contrast, salt-loaded SHRSP rats with higher PRC (30.1±16.0 ng/ml/hr, n=9) showed a marked hypotensive response. Moreover, a positive correlation was observed between the reduction of blood pressure by the inhibitor and PRC (n=24, r=0.755, P<0.01; mmHg= 655

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From these facts, the renin-angiotension system appears to participate in the maintenance of severe hypertension in salt-loaded SHRSP rats with hypereninemia.

Histological observation was performed on 12 rats loaded with 1% NaCl. Four rats, which had no stroke-signs but lower PRC (10.9 ± 1.1 ng/ml/hr), showed slight arteriosclerotic changes in the kidney. Four rats, which had higher PRC (78.5 ± 52.7 ng/ml/hr) but not stroke-signs, showed moderate to severe arteriosclerotic changes and fibrinoid necrosis in the renal artery. In the other 4 rats with both stroke-signs and higher PRC (96.4 ± 60.4 ng/ml/hr), the severe renovascular changes were observed. Thus, increase of PRC was accompanied by the advance of renal vascular changes.

From these results, it is concluded that salt-accelerated hypertension of SHR-SP rats is divided into benign and malignant hypertension and the active renin-angiotensin system participates in the latter phase.