31) Mechanisms of Blood Pressure Reduction by Converting Enzyme Inhibitor in SHR. Yukio Yamori*⁺, Akira Ooshima*⁺, and Robert C. Tarazi*. International Center*, Cleveland Clinic, Cleveland, Ohio, U.S.A., Japan Stroke Prevention Center⁺ and Department of Pathology[°], Shimane Medical University, Izumo 693.

INTRODUCTION

One of the recent progress in antihypertensive therapy is the introduction of a converting enzyme inhibitor (CEI). A mechanism of its blood pressure lowering effect is thought to be the suppression of angiotensin II formation, despite the fact that it was shown to decrease blood pressure efficiently in SHR in which renin-angiotensin system was not activated (JAPAN J PHARMACOL 29:133, 1979). Consequently, mechanisms other than reduction of circulating Ang II might be important in this regard. Our previous studies have indicated that both central mechanisms regulating sympathetic vasomotor tone and the degree of vascular protein synthesis inducing structural vascular changes, are playing dominant roles in the initiation and maintenance of spontaneous hypertension. In the present experiment, therefore, we have studied the central effect of CEI and its effect on vascular protein synthesis in SHR.

MATERIALS AND METHODS

(1) Young SHR (10 in total) at the age of 7 weeks were operated under pentobarbital anesthesia (40 mg/kg, i.p.) and Alzet osmotic minipumps (type 1702) were implanted, connected to a catheter, the tip of which was inserted into cisterna magna. CEI (SQ 14,225) was infused intracisternally at the rate of 25 μ g/0.5 μ l/h in 5 SHR, whereas in 5 controls the same amount of saline was infused intracisternally in the same way. Indirect blood pressure was measured at the tail by a pneumatic transducer every day for 10 days after the implantation. Dipsogenic effect was checked by observing water intake after water deprivation.

(2) Young SHRSP (10 in total) at the age of 7 weeks were divided into 2 groups and given either tap water containing SQ 14,225, 0.7 mg/ml or unmedicated tap water. Indirect blood pressure was measured daily for 2 weeks by the aforementioned method. A mixture of labelled lysine (L-¹⁴C(u)-lysine) and uridine (5-³H-uridine) was injected intravenously (0.08 μ C and 0.14 μ C per g body weight, respectively) 2 hours before sacrifice. After decapitation the heart (left and right ventricles), aorta and mesenteric arteries were quickly extirpated, weighed and kept frozen until analyses. These samples were homogenized in 95% ethanol and centrifuged for removing free lysine and uridine. The pellet, after being treated with 0.2 N perchloric acid (PCA) for extracting nucleotides, was mixed with hot 1 N PCA and centrifuged for separating DNA, RNA and collagen from noncollagenous protein; the latter was then dissolved in 0.1 N NaOH. Radioactive uridine and lysine incorporated into RNA, collagenous and noncollagenous protein, respectively were counted by a liquid scintillation counter.

RESULTS

(1) Blood pressure in young SHR was significantly reduced after continuous intracisternal infusion of CEI. Dipsogenic effect was less in treated than control rats.

(2) The peroral administration of CEI clearly blocked the development of hypertension in young SHRSP and significantly reduced noncollagen and collagen protein synthesis in left ventricle and aorta.

CONCLUSION WITH DISCUSSION

CEI reduced blood pressure in young SHR when administered either perorally or intracisternally, suggesting among various possibilities the involvement of central isorenin-angiotensin system in spontaneous hypertension. The suppression of vascular protein synthesis by the peroral administration of CEI indicated that the vascular response to CEI differed from that obtained by vasodilators which we have shown to decrease blood pressure without suppressing vascular protein synthesis. These central and peripheral effects of CEI might be important mechanisms of acute or chronic blood pressure reduction in young SHR although this model is not associated with activation of peripheral renin-angiotensin system.