26) Effects of a Specific Angiotensin II Receptor Antagonist on the Vascular Renin-Angiotensin System in Spontaneously Hypertensive Rats. Shang Jin Shi, Koichi Higashimori, Jitsuo Higaki, Hiroshi Mikami and Toshio Ogiwara. Department of Geriatric Medicine, Osaka University Medical School, Osaka 553.

CV-11974 is a newly synthesized potent nonpeptide angiotensin II (Ang II) receptor antagonist, which targets specifically for the vascular-type of Ang II receptors, designated the AT1 receptor. The main purpose of this study is to elucidate the effects of CV-11974 on Ang II release from isolated spontaneously hypertensive rats (SHR) and Wistar-Kyoto rats (WKY) mesenteric arteries.

Mesenteric arteries isolated from male SHR and WKY (12-week-old) were perfused with Krebs-Ringer solution aerated with a mixture of 5% CO₂ and 95% O₂ at a constant flow-rate of 4.5 ml/min. Released Ang II into the perfusate was extracted by Amprep C8 cartridges connected to the perfusion system and was determined by radioimmunoassay. CV-11974 was dissolved in 1N Na₂CO₃ and diluted to the appropriate concentrations with Krebs-Ringer solution, and added to the perfusion medium. The perfusion pressure was monitored by a pressure transducer connected to a polygraph.

No significant difference in the spontaneous release of Ang II from isolated mesenteric arteries was observed between SHR and WKY (10.7 ± 0.9 and 13.5 ± 1.4 pg/15min [n=7], respectively). CV-11974, added to the perfusion medium (10⁻⁹-10⁻⁶M), increased Ang II release from isolated mesenteric arteries of both strains in an almost identical dose-dependent fashion (Figure 1).

Figure 1

At the highest concentration used (10⁻⁶M), CV-11974 induced 148% and 144% increases of Ang II release from isolated mesenteric arteries of SHR and WKY, respectively. The perfusion pressure remained steady throughout the study.

The increment in Ang II release induced by CV-11974 may be not only due to inhibition of binding of the locally generated Ang II, but also due to stimulation of vascular renin by the lack of negative feedback of Ang II. These results suggest that the functional renin-angiotensin system (RAS) exists in vascular tissues and locally generated Ang II regulates the vascular RAS. However, no significant difference was observed in the Ang II release between SHR and WKY mesenteric arteries, suggesting that the vascular RAS may not have an important role for the maintenance of spontaneous hypertension.