

al.¹⁰ and Nakamoto et al.¹¹ proposed that Ang (1-7) counterbalances the pressor action of Ang II. This interpretation is based on 2 major lines of evidence. First, Ang (1-7) stimulated prostaglandin release in cultured cells.¹² Second, systemic administration of Ang (1-7) produced antihypertensive effects in spontaneously hypertensive rats (SHRs).¹³ Additional evidence suggests that the vasodilator actions of Ang (1-7) might be involved in the increased production of nitric oxide.¹¹ These data clearly demonstrate that Ang (1-7) might act as an endogenous inhibitor of the vasoconstrictional effect of Ang II. Another peptide, angiotensin (3-8), the (3-8) fragment of Ang II, was previously believed to be an inactive metabolite, but now its specific binding sites have been identified in the brain and many peripheral organs.¹⁴ Several studies have suggested that central administration of Ang (3-8) might produce a pressor effect and drinking behavior.⁶ Also, Ang (3-8) has been reported to dilate pial and renal cortical vessels,^{15,16} to increase middle cerebral artery blood flow,¹⁴ and to reverse cerebral vasospasm in rats with experimental subarachnoid hemorrhage.¹⁷ The metabolites of Ang (3-8) and Ang (4-8) have no any known physiological effects by now.^{1,2,6}

Anatomical and functional studies have provided evidence that enhanced activity of the tissue renin-angiotensin system plays a significant role in the pathogenesis and maintenance of hypertension in SHRs. In comparison to Wistar-Kyoto rats (WKYs), SHRs have shown increases in sympathetic tone, vasopressin secretion, densities of neuronal angiotensin II receptors, and pressor responsiveness to administration of Ang II.^{18,19} Because most of the pathophysiological findings in hypertension are attributed to the renin-angiotensin system, the roles of these angiotensin peptides in the development and maintenance of high blood pressure require further evaluation. In addition, there is abundant evidence for the existence of a localized renin-angiotensin system in the brain. Moreover Ang (1-7) and Ang (3-8) are newly found factors in the renin-angiotensin system and have been suggested to play physiological roles. Therefore, in this study, dipsogenic behavior, the pressor effect, and changes in renal functions induced by intravenous or intracerebroventricular administrations of Ang II, Ang (1-7), and Ang (3-8) in SHRs and WKYs were examined.

MATERIALS AND METHODS

Animals and Surgery

Adult male WKYs and SHRs at 20 weeks of age were used in this study. For intracerebroventricular (i.c.v.) cannulation, rats were anesthetized with intraperitoneal injection of sodium pentobarbital (50 mg/kg). The animal was placed on a stereotaxic apparatus (David Kopf instruments, Tujunga, CA) and the skull was exposed for intracerebroventricular cannulation. A sterile stainless steel cannula (24-gauge spinal needle with 30-gauge inner cannula) was implanted into the right lateral ventricle through a small hole drilled in the skull. The cannula was placed in the stereotaxic position of 1.0 mm posterior to the bregma, 1.5 mm lateral from the midline, and 4.5 mm inferior to the brain surface. The left femoral artery and vein were catheterized with cannulae tunneled under the skin. The free ends of the cannulae were externalized at the back of the neck. The cannula of the femoral artery was used for measurement of mean arterial blood pressure (MABP) and heart rate (HR). Before further experiments, the rat was allowed to recover from surgery at least 24 h.

Pressor Activity

The cannula of the femoral artery was used for measurement of mean arterial blood pressure (MABP) and heart rate (HR) via a Statham P23XL pressure transducer and RS 3800 polygraph (Gould Inc., Cleveland, OH, USA). The doses of intravenous and intracerebroventricular injections of angiotensin peptides were 100 pmol in 100 μ L phosphate-buffered saline [PBS; (in mM) 137 NaCl, 2.7 KCl, 0.9 NaH₂PO₄, 6.4 Na₂HPO₄, pH 7.4] and in 10 μ L artificial cerebrospinal fluid [aCSF; (in mM) 133.3 NaCl, 3.4 KCl, 1.3 CaCl₂, 1.2 MgCl₂, 0.6 Na₂HPO₄, 32 NaHCO₃, 3.4 D-(+)-glucose, pH 7.4]. Peptides were randomly injected into conscious rats. The pressor response was calculated at the peak of the response.

Dipsogenic Activity

The experiments were carried out in conscious and freely moving animals in their housed cages after a stabilization period of 30 min. Angiotensin peptides (Ang II, (1-7), (3-8), and (4-8)) at a dose of 100 pmol in 10 μ L of artificial cerebrospinal fluid were randomly in-