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Effects of Centrally Administered Angiotensin II Receptor Antagonists on the Cardiovascular and Hormonal Responses to Hemorrhage in Conscious SHR

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= ABSTRACT=

The role of endogenous brain angiotensin II (Ang II) in mediating the cardiovascular and vasopressin responses to hemorrhage was assessed in conscious spontaneously hypertensive rats (SHR), and normotensive Wistar-Kyoto (WKY) rats. Artificial cerebrospinal fluid (aCSF) with or without losartan (DuP 753), a specific Ang II receptor subtype I (AT_1) antagonist, and saralasin, a combined AT_1/AT_2 antagonist was administered into the cerebral lateral ventricle. Hemorrhage was performed at a rate of 3 ml/kg/min for 5 min.

Intracerebroventricular administration of losartan and saralasin had no effect on the basal blood pressure. However, in response to acute hemorrhage, central Ang II antagonists produced a remarkably greater fall in blood pressure, a reduced tachycardia, and an enhanced renin release compared with the aCSF control experiment in SHR, but effected no significant change in WKY rats. Central Ang II-blocked SHR showed significantly lower blood pressure and heart rate during the recovery period than the aCSF control rats. Vasopressin release following the hemorrhage was attenuated by icv Ang II antagonists: the effect was more pronounced in SHR than in WKY rats. Centrally administered losartan and saralasin produced remarkably similar effects on the cardiovascular function and vasopressin responses to hemorrhage.

These data suggest that brain Ang II acting primarily through AT_1 receptors plays an important physiological role in mediating rapid cardiovascular regulation and vasopressin release in response to hemorrhage especially in hypertensive rats.

Key Words: Intracerebroventricular, Losartan, Saralasin, Hemorrhage, Vasopressin, Renin, SHR.

INTRODUCTION

Accumulating evidence suggests that the brain renin-angiotensin system participates in the regulation of arterial pressure, body fluid balance (Severs & Daniels-Severs 1973; Phillips 1987a) as well as in the pathogenesis of hypertension (Phillips et al, 1977; Berecek et al, 1983). Central angiotensin II (Ang II) produces a variety of effects including elevation of arterial blood pressure, stimulation of drinking, increased secretion of vasopressin and cortico-

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tropin, and inhibition of renin secretion (Phillips, 1987a; Ahn et al, 1992; Ferguson & Wall, 1992). Centrally mediated responses to Ang II can be evoked by direct administration of the peptide into the central nervous system or via circulating Ang II acting on regions of the brain that lack a blood brain barrier (Hartle & Brody, 1984).

Central effects are mediated by brain circuits which begin with receptors accessible to Ang II injected into the lateral ventricle. Recently, competitive binding studies have revealed the existence of at least two Ang II receptor subtypes, AT_1 and AT_2 (Chiu et al, 1989; Bumpus et al, 1991). In adult rat brain, AT_1 receptors are the most numerous subtype and predominate in the structures where Ang II produces its pressor and dipsogenic actions (Obermüller et al, 1991; Rowe et al, 1991). In contrast, AT_2 receptors were found to be dominating in midbrain and thalamus, which have not been associated with cardiovascular effects directly. The function of AT_2 receptors remains unclear.

Doses of centrally administered Ang II in most studies have frequently been extremely high, producing concentrations of Ang II well above the physiological range. Limited data are available for estimation of a significant role of the endogenous brain Ang II in regulatory physiology, and thus it is still a matter of debate. We have therefore assessed the physiological importance of the endogenous brain Ang II in the cardiovascular regulation and vasopressin release in response to hemorrhage in conscious rats. Prior to conducting hemorrhage, we gave intracerebroventricular (icv) adminstration of either 1) artificial CSF (aCSF), 2) losartan (DuP 753), the specific Ang II-AT_1-receptor antagonist, or 3) saralasin, a combined AT_1/AT_2 receptor antagonist, in chronically catheterized unanesthetized rats.

Several lines of evidence have implicated brain Ang II in the pathogenesis of hypertension in spontaneously hypertensive rats (SHR) (Phillips et al, 1977; Berecek et al, 1983; Phillips & Kimura 1988). Thus, the cardiovascular and vasopressin responses to hemorrhage were compared between SHR, and normotensive Wistar-Kyoto (WKY) rats.

MATERIALS AND METHODS

Male SHRs and normotensive WKY rats, 13-16 weeks of age, were anesthetized with 40 mg/kg ip sodium pentobarbital. For icv injection, rats were stereotaxically instrumented with a stainless steel guide cannula (22 gauge) in the lateral ventricle and allowed to recover for at least 5 days. At 24 hours prior to an experiment, polyethylene catheters (PE 50) filled with heparin (50 U/ml) were placed into the bilateral femoral arteries for blood pressure measurement and bleeding, and also into a femoral vein. Penicillin (25 mg/kg, i.m) was administered after both surgical procedures.

On the morning of the experiment, rats remained unrestrained in their cages and the arterial catheter was connected to a Statham P50 pressure transducer coupled to a polygraph (model 7E, Grass Instruments Co., Quincy, Mass). Mean arterial pressure (MAP) and heart rate were recorded simultaneously throughout the experimental period. After a stabilization period, the obturator was removed from the guide cannula and replaced with an inner cannula (32-gauge stainless steel tubing) filled with the agent to be administered. The tip of the inner cannula extended 1 mm beyond the guide cannula. The inner cannula was attached to a 1 μl Hamilton syringe through polyethylene tubing (PE-20). Rats were randomly divided into 3 groups and administered with either artificial cerebrospinal fluid vehicle or 10 μg losartan (DuP 753, E.I. du Pont de Nemours and Company, Wilmington, Del.) in 2 μl, or saralasin (1 μg/μl/min). After 10 min, 2.5 ml of blood samples were taken through an arterial catheter into a heparinized syringe, while the same volume of donor blood was infused iv sim-ultaneously to minimize the hypovolemic effect on the hormonal levels. Then, arterial blood was withdrawn into an empty syringe at

a rate of 3 ml/kg/min for 5 min using a Harvard withdrawal pump. Additional blood samples were taken 10 min later. At the end of the experiment, Ang II (30 ng) was infused into the lateral ventricle for 20 min to test whether the pressor response to Ang II was blocked by the Ang II receptor antagonists.

Radioimmunoassay

Upon completion of the experiments, blood samples were centrifuged at 2,500 rpm for 20 min at 40℃. For determination of plasma renin concentration (PRC), 50 μl of plasma was stored in a tube containing 50 μg of EDTA. For arginine vasopressin (AVP) assay, the plasma was acidified with 1.0 N HCl. The prepared samples were stored at −20℃. Plasma concentrations of AVP and renin were determined using the radioimmunoassay methods described by Lee et al. (1987) and Cho et al. (1987), respectively.

Statistical Analysis

All data are presented as mean±SE. Differences among groups of the aCSF and Ang II receptor antagonists were analyzed by nonparametric Kruskal-Wallis's one-way analysis of variance. A Mann-Witney U-test was performed to assess the differences between SHR and WKY rats.

RESULTS

Baseline MAP and HR in WKY rats and SHRs prior to the initiation of experimental procedures were 116±2.6 mmHg and 357±13.4 beat/min, and 156±4.6 mmHg and 333±10.3 beat/min respectively (Table 1). Central administration of Ang II antagonists, losartan and saralasin, completely abolished the pressor response to icv Ang II (30 ng), but had no effect on basal MAP, HR and plasma concentrations of vasopressin (Fig. 3) and renin (Fig. 4) of both WKY and SHR.

The time course of changes in MAP and HR during and after blood withdrawal are illustrated in Fig. 1. During the 5 min bleeding period, basal MAP was maintained for approximately 4 min and then decreased thereafter in WKY controls given icv injection of the aCSF solution. In SHR, however, the latency for MAP to

Table 1. Changes in mean arterial pressure (MAP), heart rate (HR), and plasma concentrations of vasopressin and renin after hemorrhage (3 ml/kg/min for 5 min) in WKY rats and SHR pretreated with icv artificial cerebrospinal fluid (aCSF) and the Ang II receptor antagonists, losartan or saralasin

			Changes after hemorrhage		
		Baseline	aCSF	Losartan	Saralasin
MAP, mmHg	WKY	116±3	−26±3	−34±8	−35±9
	SHR	156±5$^{\#}$	−60±10$^{\#}$	−102±3$^{\#*}$	−95±5 $^{\#**}$
HR, beats/min	WKY	357±13	108±13	128±12	124±17
	SHR	333±10	130±20	43± 8	37±5
Vasopressin, pg/mL	WKY	4.0±0.6	41.7±3.5	30.0±4.3	31.8±3.2
	SHR	6.3±1.1	61.6±2.1$^{\#\#}$	36.1±2.9**	37.5±1.6**
Renin, ng AI/mL/hr	WKY	20.8±0.9	33.7±3.5	37.7±3.3	36.7±4.0
	SHR	17.4±1.3	33.9±3.8	46.0±3.4*	47.5±4.5$^{\#**}$

Values are mean±SE. $^{\#}p<0.05$, $^{\#\#}p<0.01$, WKY rat vs. SHR.
*$p<0.05$, **$p<0.01$, aCSF vs. losartan or saralasin-treated group.

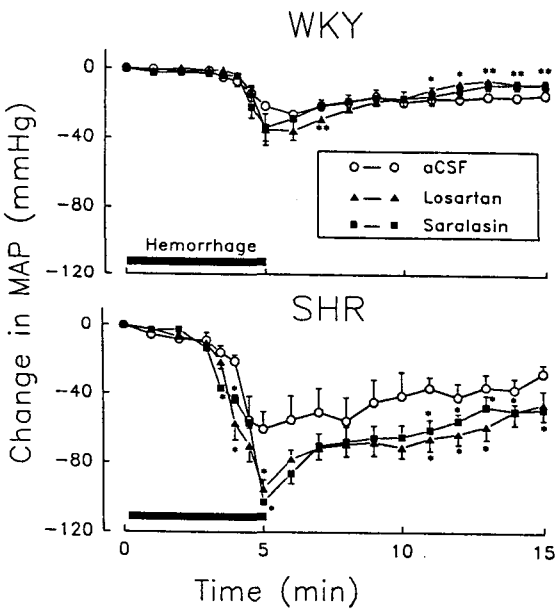

*Fig. 1. Changes in mean arterial pressure (MAP) during hemorrhage (3 ml/kg/min for 5 min) in WKY rats and SHR pretreated with icv aCSF and the Ang II antagonists, losartan or saralasin. *p< 0.05, **p<0.01, aCSF vs. losartan or saralasin-treated group.*

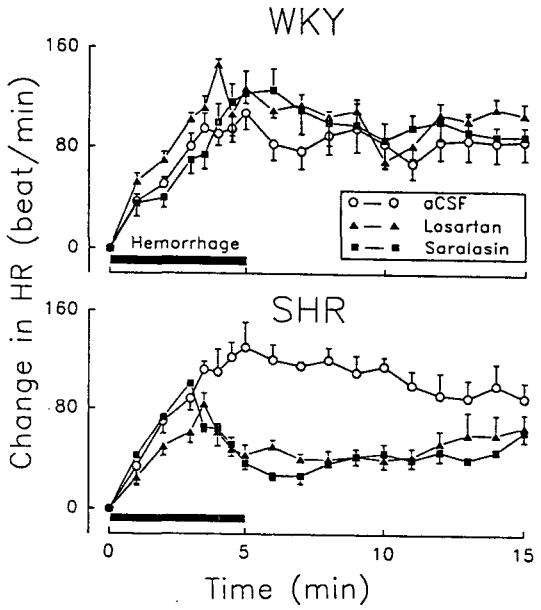

Fig. 2. Changes in heart rate (HR) during hemorrhage (3 ml/kg/min for 5 min) in WKY rats and SHR pretreated with icv aCSF and the Ang II antagonists, losartan or saralasin.

fall was about 3 min. The maximum fall in MAP at the end of bleeding was 26.0±2.6 mmHg in WKY and 60.4±10.0 mmHg in SHR controls. The magnitude of hemorrhage-induced hypotension was not significantly different between WKY controls and WKY pretreated with losartan or saralasin. In contrast, Ang II blocked SHR showed remarkably faster and greater falls in MAP during hemorrhage than the SHR controls: however, there was no difference in the effect of losartan and saralasin.

HR increased continuously throughout the full hemorrhagic period in both WKY and SHR controls, although MAP markedly decreased toward the end of blood withdrawal. The maximum increases in HR of WKY and SHR controls were 108±13.5 and 130±20.2 beat/min, respectively. HR responses of WKY to hemor-

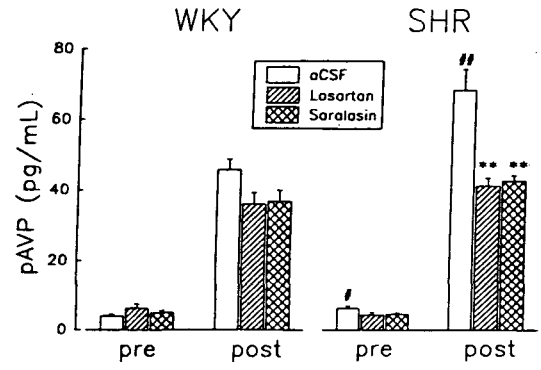

*Fig. 3. Plasma concentration of arginine vasopressin (AVP) pre and post hemorrhage (3 ml/kg/min for 5 min) in WKY rats and SHR pretreated with icv aCSF and the Ang II antagonists, losartan or saralasin. *p<0.05, **p<0.01, aCSF vs. losartan or saralasin-treated group. #p<0.05, ##p<0.01, WKY vs. SHR.*

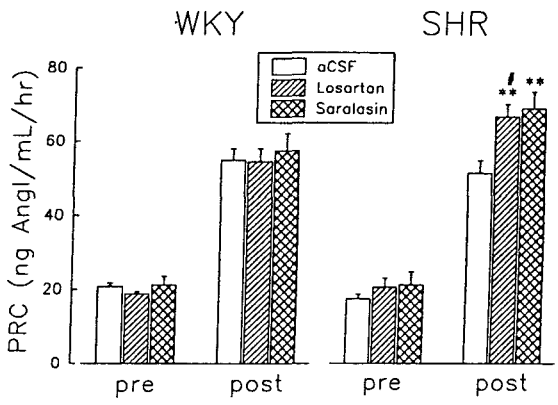

*Fig. 4. Plasma concentration of renin (PRC) pre and post hemorrhage (3 ml/kg/min for 5 min) in WKY rats and SHR pretreated with icv aCSF and the Ang II antagonists, losartan or saralasin. *p<0.05, **p<0.01, aCSF vs. losartan or saralasin-treated group. ‡p<0.05, WKY vs. SHR.*

rhage were not affected by Ang II blockade by either losartan or saralasin. However, in Ang II blocked SHR, the reflex tachycardia was not maintained and HR rapidly dropped along with the fall in MAP during hemorrhage.

Hemorrhage produced approximately a tenfold increase in plasma vasopressin concentration (Fig. 3), but less than a twofold increase in plasma renin concentration (Fig. 4) in both WKY and SHR controls. Icv losartan and saralasin attenuated the normal secretion of vasopressin following the hemorrhage: the effect was more pronounced in SHR than in WKY rats (mean differences from the aCSF control response were about 40% and 25%, respectively). Icv losartan and saralasin did not affect the plasma renin concentration in response to hemorrhage in WKY rats, but significantly increased the PRC in SHRs.

DISCUSSION

The present study demonstrated that icv administration of the Ang II-AT_1 antagonist, losartan, and a combined AT_1/AT_2 receptor antagonist, saralasin, aggravated the cardiovascular regulation and attenuated the increase in plasma vasopressin concentration in response to hemorrhage. The effects of AT_1 and combined AT_1/AT_2 blockade were remarkably similar. We found that icv losartan had no effect on the pressor response to intravenous injection of Ang II (unpublished observation) as reported by others (Fregly and Rowland, 1991). Tony and Porter (1993) observed that intravenous injection of 20 μg of losartan did not affect the central Ang II pressor response, either. Therefore, it seems that the effects produced by icv losartan in the present experiment were not due to leakage of the antagonist into the systemic circulation but via central sites of action.

The importance of endogenous brain Ang II in vasopressin release shown in the present study is consistent with other observations. First, icv infusion of angiotensin converting enzyme inhibitor, captopril, markedly reduced and delayed vasopressin and ACTH release during and after acute hemorrhage in conscious sheep (Cameron et al, 1986). Second, icv saralasin inhibited vasopressin release induced by hyperosmolality or hypovolemia produced by intraperitoneal injection of 900 mM NaCl or polyethylene glycol in rats (Yamaguchi et al, 1982). Third, the vasopressin response to an osmotic stimulus was reduced by icv losartan (Hogarty et al, 1993). Collectively, these observations support a physiologically important role for endogenous brain Ang II in the control of vasopressin secretion following both hypovolemic and osmotic stimuli.

In addition to vasopressin release, the present result implies the importance of brain Ang II in blood pressure regulation. Although the role of central Ang II has been extensively investigated, most of the studies have employed the administration of pharmacological doses of Ang II into the brain (Phillips, 1987: Ferguson & Wall, 1992). Thus, the present data provide the first demonstration of its physiological significance for cardiovascular regulation. Mechanisms underlying the impaired blood pressure

regulation during and after hemorrhage in central Ang II-blocked rats are not certain at present. However, the pressor response to centrally administered Ang II seems to be mediated by increased sympathetic nerve activity and vasopressin release. Pretreatment with a vasopressin V_1 receptor antagonist (Unger et al, 1981) or sympathectomy with 6-hydroxydopamine (Falcon et al, 1978) induced a partial decrease in the pressor response to central Ang II. But we recently showed a complete blockage of the pressor response to centrally administered Ang II in rats pretreated with both a V_1 receptor antagonist and a ganglionic blocker, pentolinium (Ahn et al, 1992).

On the basis of the above observations, it is reasonable to expect that blocking central Ang II receptors would decrease the sympathetic nerve activity and vasopressin release, and thus impair the blood pressure regulation during hemorrhage. However, limited data are available to substantiate this notion. Sheep given icv captopril did not show any increase in plasma epinephrine after hemorrhage unlike the intact animals, which might suggest a decreased sympathetic nerve activity (Cameron et al, 1986). However, they observed no consistent alterations in plasma norepinephrine response after hemorrhage. Retarded blood pressure recovery after hemorrhage in the central Ang II-blocked rats may be due, at least in part, to substantially lower levels of vasopressin. This possibility is supported by previous studies showing that the compensatory increase in blood pressure after hemorrhage was substantially retarded in homozygous Brattleboro rats virtually deficient in vasopressin, and in normal rats treated with an antipressor vasopressin analogue injected after hemorrhage (Zerbe et al, 1982).

The effects of icv Ang II receptor antagonists would be mediated by brain circuits which begin with receptors accessible to the lateral ventricle injections (Phillips 1987b), but exact regions for actions are not certain. A recent electrophysiological study suggested an activation of central angiotensinergic circuits in hemorrhaged rats. Tanaka et al, (1993) observed that hemorrhage produced activation of some of the subfornical organ neurons projecting to the paraventricular nucleus, and saralasin prevented the excitatory response of the neurons. Thus, they proposed that the neural circuits from the peripheral baroreceptors to the paraventricular nucleus through the subfornical organ neurons involve angiotensinergic pathways which may play an important physiological role in the control of cardiovascular function and body fluid balance.

In the present experiment, the effects of central AT_1 vs. combined AT_1/AT_2 blockade were remarkably similar. These data agree with the observations of Hogarty et al. (1993). They noted that vasopressin release due to an osmotic stimulus was significantly reduced by blockade of central AT_1 receptors or AT_1+AT_2 receptors (icv losartan+PD 123319). PD 123319 alone had no significant effect on vasopressin release. Collectively, these results suggest that endogenous Ang II in the brain, acting via AT_1 receptors, plays an important role in the regulation of blood pressure and vasopressin release, and the AT_2-mediated action of Ang II does not seem to contribute to it significantly. Anatomically, the vast majority of Ang II receptors in adult rats have been found to be of the AT_1 subtype (Obermüller et al, 1991; Rowe et al, 1991). AT_1 receptors were found in brain regions involved in cardiovascular regulation and body fluid homeostasis such as the circumventricular organs (subfornical organ, OVLT, area postrema), hypothalamus (paraventricular and supraoptic nuclei) and the nucleus of the tractus solitarius. AT_2 receptors were dominating only in the midbrain and cerebellum, which have not been associated with cardiovascular effects directly. The functions of AT_2 receptors are unknown at present.

There were strain differences in the responses to hemorrhage. The cardiovascular and vasopressin responses to hemorrhage of 15 ml/kg were significantly greater in SHR than normotensive WKY. Several experimental results suggested the contribution of an overactivated brain renin-angiotensin system to the pathogen-

esis of hypertension in SHR. Compared with normotensive WKY rats, SHR have elevated angiotensin-like immunoreactivity (Ganten et al, 1975; Weyhenmeyer & Phillips 1982), a higher number of Ang II receptors (Gehlert et al, 1986; Steckelings et al, 1992), stronger Ang II receptor binding (Gehlert et al, 1986), and greater levels of both AT_{1A}- and AT_{1B}- receptor mRNA (Raizada et al, 1993) in brain areas that are relevant to cardiovascular control. Suzuki et al. (1981) reported that icv saralasin or captopril decreased blood pressure in SHR and renal hypertensive rats, but increased blood pressure in DOCA-salt hypertensive rats. In contrast, many studies, including the present one, indicate that the basal blood pressure was not lowered in SHR when the brain renin-angiotensin system was blocked with an AT_1 antagonist (Wood et al, 1990; DePasquale et al, 1992), an AT_1/AT_2 antagonist (Bruner et al, 1987; Dudley et al, 1990), an ACE inhibitor (Baum et al, 1983) or by lesion of the anteroventral third ventricle (Gorden et al, 1982). Although the role of brain angiotensin for maintenance of basal blood pressure is still a matter of debate, the result of this study clearly shows that central Ang II blockade produces significantly more pronounced effects in hemorrhaged SHR than in WKY rats. Further studies are required to elucidate the mechanisms involved in the different sensitivity of the brain renin-angiotensin system in different rat strains.

Central Ang II blockade resulted in significantly enhanced renin release in response to hemorrhage in SHR and Wistar rats, but had no effect in WKY rats. One possible explanation for the increased renin response is the greater fall in blood pressure in those rats, since the major factor regulating renin release appears to be a fall in renal perfusion pressure (Wong et al, 1983). Another possible mechanism is that blockade of central Ang II may cause an increase in plasma renin level through removal of inhibition. Ang II given icv decreased plasma renin activity (Eriksson & Fyhrguist, 1976; Ahn et al, 1992) and icv captopril increased plasma renin activity (Brooks & Malvin, 1982). These results imply that endogenous brain angiotensin is involved in suppressing renin secretion. However, the relative importance of removal of inhibition of renin secretion after central Ang II blockade in the hemorrhaged rats remains to be elucidated.

In summary, central Ang II blockade impaired the cardiovascular regulation and vasopressin release in response to hemorrhage in conscious rats. SHR showed more sensitive responses to central Ang II blockers than WKY rats. The effects of central AT_1 and combined AT_1/AT_2 blockade on the responses to hemorrhage were remarkably similar. These findings suggest a physiological importance of endogenous brain Ang II for cardiovascular homeostasis and vasopressin release acting mainly through AT_1 receptors.

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