Role of central AT$_1$ and V$_1$ receptors in cardiovascular adaptation to hemorrhage in SD and renin TGR rats

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Numerous studies indicate that the cardiovascular brain regions are innervated by angiotensinergic and vasopressinergic neurons (5, 8, 13, 28) and that the intracranial administration of angiotensin II (ANG II) or arginine vasopressin (AVP) results in significant alterations of the cardiovascular functions (3, 13, 18, 20, 27, 42). However, the role of these two neuropeptides in the regulation of blood pressure under specific physiological and pathophysiological conditions is not yet well established. The evidence indicating increased release of ANG II and AVP in the central nervous system during hemorrhage (9, 29, 42, 43) may suggest involvement of these two neuropeptides in the central control of blood pressure in hypovolemic states. With regard to AVP, several lines of evidence indicate that it may interact with both the pressor and the depressor cardiovascular pathways (3, 27, 42). Our previous study (7) provided evidence that in normotensive Wistar-Kyoto rats the hypotensive and bradycardic effects of centrally released AVP become manifest during hemorrhage. Specifically, we have demonstrated that blockade of central V$_1$ AVP receptors reduces hemorrhagic hypotension and bradycardia in this strain. The above effects were absent in spontaneously hypertensive (SHR) rats (7), which suggested impaired function of the depressor component of the vasopressinergic system in this strain. SHR rats and rats with different forms of renin-dependent hypertension (two-kidney, one-clip, aortic stenosis) manifest significant changes in the content of angiotensin and vasopressin in the brain as well as several other neurochemical defects, the primary cause of which is not yet known (10, 13, 23, 26, 28, 39). Transgenic rats TGR(mRen2)27 (TGR) harboring the additional mouse renin gene develop significant hypertension (12). The advantage of this model is that it is primarily caused by an increased activity of the renin-angiotensin system. The renin TGR rat is therefore a valuable tool to study the consequences of prolonged activation of the renin-angiotensin system in isolation from the other pathological factors (kidney ischemia, hemodynamic disorders) that are necessary to produce renin-dependent hypertension in the other models. The available evidence indicates a significant increase of angiotensin peptides and of AVP in the brain of the renin TGR rats (22). Therefore, this model also creates a good opportunity to study the consequences of chronic upregulation of the brain angiotensinergic and vasopressinergic systems for blood pressure regulation. Our recent study (44) provided evidence for the enhancement of the pressor function of the angiotensinergic and vasopressinergic systems in the renin transgenic hypertension. The present investigation was aimed at elucidating whether the apparent upregulation of the angiotensinergic and vasopressinergic systems in the renin TGR rats may also influence blood pressure regulation in the hypovolemic state. To this end, blood pressure and heart rate (HR) responses to hemorrhage were determined in TGR(mRen2)27 rats and in their parent normotensive Hannover Sprague-Dawley (SD) strain under control conditions and during blockade of central AT$_1$ and V$_1$ receptors. The results reveal distinct differences in cardiovascular adaptation to hypovolemia between re-

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nin TGR and SD rats as well as a significant modification of these differences by blockade of central AT$_1$ and V$_1$ receptors. It is suggested that increased formation of ANG II and AVP in the brain accounts for significant modulation of the central control of blood pressure in renin transgenic hypertension. A preliminary account of these results has been published in abstract form (45).

MATERIALS AND METHODS

Animals

The experiments were performed on 22 hypertensive (mRen2)27 renin TGR rats weighing 430–490 g and on 25 normotensive Hannover SD rats weighing 366–470 g. The animals were 12–15 wk old. The TGR rats were the progeny of the line developed by Mullins et al. (see Ref. 12). Presence of mRen transcript was verified by polymerase chain reaction amplification in tissue samples taken from the tail. The normotensive Hannover SD rats were the progeny of the parent strain used to establish the renin transgenic line. Both groups were purchased from the Mollegaard Breeding and Research Center (Denmark). The rats were transferred to the Department of Experimental and Clinical Physiology in Warsaw when they were 8–9 wk old. Before the experiments they were maintained on 12 h light-12 h dark rhythm having free access to water and rodent dry pellet diet that contained 0.5% of sodium chloride. The experimental protocols were approved by the Ethical Committee on the Animal Research of the Medical University of Warsaw.

Surgery

The animals were implanted with the stainless steel guide tube (OD 0.6 mm) leading to the left lateral cerebral ventricle (LCV) and with an arterial catheter. The LCV cannula was implanted with each rat under general anesthesia (chloral hydrate 360 mg/kg body wt ip). The head was immobilized in the stereotaxic device (Kopff) and leveled between the bregma and lambda. The guide tube was placed vertically in the stereotaxic arm and lowered 3.00 to 3.50 mm below the level of the craniotomy. The guide tube was fixed in the skull with acrylic cement, and the guide tube was closed with the stainless steel obturator. After recovery from anesthesia, the rats were placed in individual cages. At least 1 wk was allowed for recovery from the intracranial surgery before implantation of the arterial catheter.

While the rat was under light ether anesthesia, we inserted the arterial catheter into the femoral artery. The intravascular part made from the polyvinyl tubing was placed in individual cages. At least 1 wk was allowed for recovery from the intracranial surgery before implantation of the arterial catheter.

Experimental Design

At the beginning of experiments, the rats were placed in the experimental cage in which they could move freely and have no access to water and food. Thirty minutes were allowed for the blood pressure and HR to stabilize before the measurements were started under resting conditions. Subsequently, the data were collected for 10 min before the start of LCV infusion. In each series, the experiment consisted of two parts: 1) a 40-min baseline period during which effects of LCV infusions on baseline blood pressure and HR were determined, and 2) a 50-min posthemorrhagic period. Hemorrhage was produced by bleeding the rat from the femoral artery. Volume of blood amounting to 1.3% of the body weight was removed at the rate of 2.5 ml/min. The LCV infusions were performed at a rate of 5 µl/h by means of the Harvard infusion withdrawal syringe pump (model 55–2219). Mean arterial pressure (MAP) and HR were recorded every 1 min during part 1 and the first 20 min of part 2 and every 5 min during the remaining 30 min of part 2 of the experiment.

Series 1. Time-Control Experiments

The experiments were performed to evaluate the cardiovascular responses to hemorrhage in SD and TGR rats: 1) under control conditions during LCV infusion of artificial cerebrospinal fluid (aCSF, series 1, time control), 2) during LCV administration of a selective blocker of AT$_1$ receptors (AT$_1$ANT, series 2), and 3) during LCV administration of a selective V$_1$ receptors antagonist (V$_1$ANT, series 3). Intracranial infusions of AT$_1$ and V$_1$ antagonists in series 2 and 3 were preceded by a 15-min-long baseline aCSF infusion and continued until the end of the experiment. LCV infusion of losartan (Merck) at a rate of 10 µg/h was used to block AT$_1$ receptors. It was shown previously that losartan-infused LCV at this rate effectively abolishes the pressor response to LCV administration of 100 ng of ANG II (44). A selective V$_1$ antagonist [d(CH$_2$)$_5$Tyr(Me)$_2$,Ala-NH$_2$]AVP (19) infused the LCV at a rate of 217 ng/h and was used to block V$_1$ receptors. We have found previously that LCV infusion of the other V$_1$ antagonist at the rat equivalent to that applied in the present study abolishes the pressor effect of centrally applied AVP but does not reduce the increase of blood pressure produced by intravenous injection of this peptide (7).

Measurements

MAP and HR were determined by means of the unit consisting of a transducer amplifier (Statham Gould P23-D) and an analog-digital converter connected to PC 386 computer. The following parameters were collected online during the experiment: systolic, diastolic, pulse, and MAP as well as HR period (HR$_p$), which corresponded to the interval (in ms) between the two consecutive peaks of the systolic pressure. The following formula was used to express HR in beats per minute: 60,000/HR$_p$.

Statistical Analysis

Values presented in the text and figures are expressed as means ± SE. In each series, values found during LCV infusion under baseline conditions during part 1 of the experiment were compared with those found under resting conditions preceding the part 1, whereas values found during part 2 were compared with those found at the end of the part 1. The changes of MAP and HR at consecutive time points in each experimental group were analyzed with one-way ANOVA for repeated measurements. Post hoc comparisons between time points were made with the Duncan test. The differences between the experimental groups were compared with planned contrasts. Statistica 5.0 was used to evaluate the data. The results were considered significant if $P < 0.05$.

RESULTS

Resting values of MAP and HR$_p$ in SD and TGR rats are presented in Table 1.

Series 1. Time-Control Experiments

Baseline conditions. Intraventricular infusion of aCSF did not cause significant changes of baseline MAP (Fig. 1)
and HRp (data not shown) in either SD or TGR rats. Neither were significant differences found in changes of MAP and HRp between SD and TGR rats.

Hemorrhage. Bleeding elicited a significant decrease of MAP in both SD [F(27,243) = 3.25; P < 0.001] and TGR rats [F(27,189) = 7.47; P < 0.001] (Fig. 2). The maximum decrease of MAP in TGR rats amounted to −26 ± 9 mmHg and was significantly greater (P < 0.05) than that in SD rats (−27 ± 9 mmHg). Significant differences between time courses of the hypotensive responses in SD and TGR rats were also confirmed by two-way ANOVA [F(1,16) = 8.31; P < 0.02]. The planned contrast test revealed significant differences during the whole posthypovolemic period. Hemorrhage resulted in nonsignificant fluctuations of HR in SD and in significant bradycardia in TGR rats [F(27,189) = 5.58; P < 0.001] (Fig. 3). Two-way ANOVA revealed significant differences in changes of HR between SD and TGR rats [F(1,16) = 6.21; P < 0.025].

Series 2. Effect of Blockade of AT1 Receptors

Baseline conditions. LCV infusion of losartan did not elicit significant changes of MAP in SD rats under baseline conditions (Fig. 1). On the other hand, in TGR rats it produced a significant reduction of MAP [F(24,144) = 3.25; P < 0.001], which was maintained during the whole observation period (Fig. 1). The maximum decrease of MAP in these experiments was equal to −17 ± 6 mmHg. As shown in Fig. 1, MAP was decreasing progressively during the first 8 min of LCV infusion of losartan and subsequently stabilized at a lowered level. No significant differences between fluctuations of MAP were found during the remaining period of losartan administration. Changes of MAP during infusion of losartan were significantly different from those found during aCSF infusion [F(1,14) = 2.70; P < 0.001] (Fig. 1). Significant differences were also found between changes of MAP in SD and TGR rats [F(1,12) = 26.70; P < 0.001]. HR was not significantly affected by LCV administration of losartan either in SD or in TGR(mRen2)27 rats (data not shown).

Hemorrhage. Administration of losartan did not significantly modify MAP and HR responses to hemorrhage in SD rats (Figs. 2 and 3). In TGR rats, hemorrhage performed during blockade of AT1 receptors produced a significant reduction of MAP [F(27,162) = 4.43; P < 0.001], which did not differ significantly from that found in time-control experiments of series 1 by two-way ANOVA (Fig. 2). Similarly, the difference between the maximum decreases of MAP observed in TGR rats immediately after bleeding during blockade of AT1 receptors (−39 ± 8 mmHg) and in time-control

### Table 1. Resting values of MAP and HRp

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<td>SD mRen2(27)</td>
<td>SD mRen2(27)</td>
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<tr>
<td>aCSF</td>
<td>115 ± 4</td>
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<td>AT1 ANT</td>
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Values are means ± SE; n, number of rats. MAP, mean arterial pressure; HRp, heart rate period; SD, Sprague-Dawley rats; mRen2(27), transgenic rats; aCSF, artificial cerebrospinal fluid; AT1 ANT and V1 ANT, AT1 and V1 antagonist, respectively.

![Fig. 1. Comparison of changes of mean arterial blood pressure (MAP) in Sprague-Dawley (SD, top panels) and renin transgenic TGR(mRen2)27 rats (bottom panels) under baseline conditions during infusion into lateral cerebral ventricle (LCV) of artificial cerebrospinal fluid (aCSF), aCSF plus V1 antagonist (V1 ANT; A), and aCSF with AT1 antagonist (AT1 ANT; B). (*) Significant difference in comparison with baseline; * significant difference between aCSF and V1 ANT or between aCSF and AT1 ANT.](http://ajpheart.physiology.org/)

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experiments of series 1 (−61 ± 9 mmHg) did not reach a level of significance. Summation of the maximum decreases of MAP produced by losartan alone (−17 mmHg) and by hemorrhage during losartan administration (−39 mmHg) resulted in a similar reduction of MAP (−56 mmHg) to that elicited by hemorrhage alone in time-control experiments (−61 mmHg).

As shown in Fig. 3, during blockade of AT₁ receptors hemorrhage did not produce significant changes of HR in either SD or TGR rats. Neither were significant differences found in time courses of HR changes in these two strains during losartan administration. Thus blockade of AT₁ receptors effectively abolished the bradycardic effect that was observed after hemorrhage in renin TGR rats in time-control experiments (Fig. 3).

Series 3. Effect of Blockade of V₁ Receptors

Baseline conditions. LCV administration of V₁ANT did not influence resting MAP in SD rats; however, a significant decrease of MAP was observed in renin TGR rats [F(1,14) = 12.31; P < 0.005]. HR was not significantly affected by infusion of V₁ANT in either SD or TGR rats (data not shown).

Hemorrhage. In SD rats, blockade of central V₁ receptors did not significantly modify changes of MAP caused by bleeding (Fig. 4). MAP decrease was significant [F(27,189) = 2.28; P < 0.001], and its time course was similar to that found in series 1 (Fig. 4). In contrast, in TGR blockade of central V₁ receptors abolished the posthemorrhagic hypotension (Fig. 4). Changes of MAP produced by hemorrhage in renin TGR rats during blockade of V₁ receptors were significantly different from those found in series 1 [F(1,13) = 14.12; P < 0.0025]. During treatment with V₁ANT, the posthemorrhagic decreases of MAP in SD and TGR rats were not significantly different.

After bleeding performed during blockade of V₁ receptors, HR tended to be maintained at a higher level than in time-control experiments. In SD rats, changes of HR during the whole posthemorrhagic period were not significant; however, significant acceleration of HR was found during the first 17 min after bleeding
Role of Central AT<sub>1</sub> and V<sub>1</sub> Receptors in Maintenance of Baseline Blood Pressure in SD and Renin TGR Rats

Blockade of central AT<sub>1</sub> receptors effectively decreased baseline blood pressure in renin TGR rats, exerting no significant effect in SD rats. In this respect, TGR rats behaved similarly to SHR, which respond with a decrease of blood pressure to the central administration of losartan (see Ref. 28). Increased pressor activity of the angiotensinergic system in the renin TGR rats may be relevant to the enhanced content of ANG II in the diencephalic and medullary structures, demonstrated in this strain by Senanayake et al. (35).

The finding that blockade of AT<sub>1</sub> receptors does not influence baseline blood pressure in SD rats is in agreement with reports of other authors (see Ref. 28), who were unable to demonstrate significant changes of blood pressure in normotensive rats after inhibition of the brain renin-angiotensin system.

In agreement with our previous investigation, the present results give evidence for significant involve-

DISCUSSION

The present investigation demonstrates significant differences in cardiovascular adaptation to hemorrhage between renin TGR and SD rats and provides evidence that these differences result from significantly greater activation of central AT<sub>1</sub> angiotensinergic and V<sub>1</sub> vasopressinergic systems during hypovolemia in TGR(mRen2)27 rats than in SD rats.

[F(18,126) = 1.91; P < 0.02] (Fig. 5). In TGR, bleeding during blockade of V<sub>1</sub> receptors did not change HR. This response was significantly different from the bradycardic effect observed in the same strain in time-control experiments [F(1,13) = 6.19; P < 0.05] (Fig. 5). The time courses of HR<sub>p</sub> changes in TGR in these two experimental situations were significantly different, as indicated by significant differences in interaction with time [F(26,338) = 3.38; P < 0.001]. During blockade of V<sub>1</sub> receptors, the posthemorrhagic changes of HR in SD and TGR rats did not differ.
blockade of central V1 receptors in SHR did not produce a decrease of blood pressure to that observed during the separate administration of either AT1- or V1-receptors antagonists (44). This suggested that ANG II and AVP can be elicited by LCV administration of an equimolar rate of [d(CH2)5Tyr(Me)2,Ala-NH2]AVP, a selective V1a-receptor antagonist (Ref. 19 and M. Manning, personal communication). Thus it appears that the increased pressor function of vasopressinergic system in renin transgenic hypertension is associated with enhanced activation of V1a receptors. Recently, we have found that the combined blockade of central AT1 and V1 receptors in renin TGR rats produces a similar decrease of blood pressure to that observed during volume withdrawal in SD rats (35), may directly stimulate vagal cardiovascular neurons, contributing thereby to hypovolemic bradycardia. The alternative hypothesis is that ANG II may act indirectly by stimulating vasopressinergic neurons on vagal motor neurons. The latter hypothesis is attractive from the evidence suggesting that ANG II regulates vasopressin content in the cardiovascular regions. Specially, Muders et al. (25) reported that chronic inhibition of angiotensin-converting enzyme with quinapril significantly alters vasopressin content in the brain stem cardiovascular regions.

Differences in Cardiovascular Adaptation to Hypovolemia in SD and Renin TGR Rats

The time-control experiments reveal that arterial bleeding of the same magnitude produces clearly different hemodynamic responses in SD and in TGR rats. The TGR rats were found to be more sensitive to blood loss as manifested by significantly greater postsensory hypotension and distinct bradycardic effect, which was absent in SD rats. It is likely that the differences between the two strains might have been caused by the leftward shift of the relationship between the blood volume decrease and the cardiovascular responses. Accordingly, it may be speculated that an adequately greater hemorrhage would cause similar bradycardia in SD as in TGR rats. Another factor that should be taken into consideration is the possibility that the percentage of blood loss might have been greater in TGR than in SD rats. However, this factor can be excluded because volume of the blood withdrawn in SD and TGR rats was a constant percentage of their body weight. Thus it is rather unlikely that the putative small differences in the initial circulating blood volumes between SD and TGR rats would be sufficient to explain striking differences in posthemorrhagic decreases of blood pressure and HR between the two strains.

Role of Central Angiotensinergic System in Regulation of Blood Pressure During Hypovolemia in SD and Renin TGR Rats

The present study does not provide convincing evidence for a significant role of central AT1 receptors in the regulation of blood pressure during hemorrhage in either SD or renin TGR rats. The negative results obtained in SD rats are in agreement with those presented in the study of Phillips et al. (32), who were unable to demonstrate a significant effect of intravenous administration of losartan on posthemorrhagic changes of blood pressure in this strain. In TGR rats decrease of blood pressure during blockade of AT1 receptors tended to be smaller than in time-control experiments, however, the difference did not reach a level of significance. Furthermore, the TGR rats were subjected to hemorrhage when their baseline blood pressure was already decreased by losartan, and the combined effect of losartan and hemorrhage in series 2 did not differ from the effect of hemorrhage itself in series 1.

Interestingly, blockade of AT1 receptors effectively abolished the bradycardic effect of hemorrhage seen in renin TGR rats in time-control experiments. AT1 receptors are present in the dorsal vagal complex (5). Therefore, it is likely that ANG II, which is produced in increased amounts in the medulla oblongata of the renin TGR rats (35), may directly stimulate vagal cardiovascular neurons, contributing thereby to hypovolemic bradycardia. The alternative hypothesis is that ANG II may act indirectly by stimulating vasopressinergic neurons (see below) or by potentiating effects of AVP on vagal motor neurons. The latter hypothesis is attractive from the evidence suggesting that ANG II regulates vasopressin content in the cardiovascular regions. Specially, Muders et al. (25) reported that chronic inhibition of angiotensin-converting enzyme with quinapril significantly alters vasopressin content in the brain stem cardiovascular regions.

Role of Central Vasopressinergic System in Regulation of Blood Pressure During Hypovolemia in SD Rats and Renin TGR Rats

In SD rats, blockade of V1 AVP receptors did not appreciably influence the hypotensive response during hypovolemia, although the small decrease of blood pressure observed in time-control experiments was no longer significant during V1ANT administration. The HR response was altered from nonsignificant fluctuations seen under control conditions to a significant although transient tachycardic response. In this respect, V1ANT acted in SD rats in the same direction as in WKY rats in which blockade of V1 receptors abolished bradycardia and caused transient tachycardia. In renin TGR rats, blockade of central V1 receptors effectively abolished posthemorrhagic hypotension and bradycardia. Thus in both groups of rats the posthemor-
rhagic HR was shifted toward the higher level. From the electrophysiological and biochemical evidence, it can be excluded that the effects of V1 antagonist might have been caused by its agonistic properties. Specifically, V1 antagonists do not alter the activity of single neurons responding to AVP (33, 40) and do not stimulate inositol triphosphate turnover in AVP-sensitive neurons (21, 37). Similarly, it is rather unlikely that V1 antagonist could exert its effects through blockade of oxytocin receptors. Although the antagonists of V1 receptors usually exhibit some affinity to the oxytocin receptors, their ability to block these receptors is significantly lower. The antioxytocic pA2 of [d(CH2)5Tyr(Me)2,Ala-NH2]AVP is not known; however, from its structure it may be assumed that it is close to that established for another V1 antagonist [d(CH2)5Tyr(Me)2]AVP (i.e., to 7.96 (M. Manning, personal communication). The rate of infusion of [d(CH2)5Tyr(Me)2,Ala-NH3]AVP in the present study was adjusted to its pA2 value of 8.75, which corresponds to its V1 antagonistic properties (19). Therefore, significantly higher rate of administration of this antagonist would be required to effectively block oxytocin receptors. In addition current evidence (24) indicates that centrally applied oxytocin promotes tachycardic responses. Thus far there are no data indicating that oxytocin could exert bradycardic or hypotensive effects.

A growing body of evidence points to an important role of the central nervous system in generation of hypotensive and bradycardic responses during hemorrhage (1, 7, 30, 34, 36) caused by both inhibition of the sympathetic system and activation of the parasympathetic system (34). Especially relevant to the present investigation is the study of Badoer et al. (2), who have shown that in conscious rats hemorrhage causes activation of neurons in several brain cardiovascular regions, which at the same time are either the source or the targets (8, 33, 42) of brain vasopressinergic innervation. Hemorrhage is a potent stimulus for central and peripheral release of vasopressin (8, 29, 43). The present and previous results (7) provide evidence that centrally released AVP plays a significant role in eliciting bradycardia and hypotension during hypovolemia. Regulation of the central release of AVP during hypovolemia in specific regions of the brain is only poorly recognized (9, 29). Therefore, the site of interaction of this peptide with the cardiovascular neurons cannot be defined at present. In the previous studies (7), we had proposed that the mechanism of hypotensive and bradycardic effect of centrally released vasopressin during hypovolemia may involve potentiation by this peptide of the central link of the Bezold-Jarisch reflex. According to some investigators, this reflex is initiated during hypovolemia from the cardiac receptors due to deformation of the cardiac walls by inadequate filling with blood (38). Vasopressinergic fibers are innervating medullary structures activated during the Bezold-Jarisch reflex (8, 14), and the AVP content in medullary brain regions is elevated in renin TGR rats (22). Therefore, it is tempting to hypothesize that potentiation of hemorrhagic bradycardia and hypotension seen in this strain may result from enhanced operation of the Bezold-Jarisch reflex by centrally released AVP. In our previous study, we proposed that the central bradycardic and hypotensive effects of AVP may be mediated by the activation of the brain nitricergic system (30). Interestingly, the hypotensive regulatory function of the brain nitricergic system appears to be impaired in SHR (30) and enhanced in renin TGR rats (31) in which the V1 vasopressinergic pathway seems to be upregulated. Therefore, it is likely that there exists a causal link between enhanced effectiveness of the hypotensive bradycardic function of the central V1-vasopressinergic system and increased activity of the brain nitricergic system in the renin TGR rats.

Hemorrhage is known to also stimulate systemic release of vasopressin (43). It is well established that systemically released AVP exerts significant pressor effect (41) and contributes to the central control of blood pressure via V1 receptors located in the area postrema (4, 6). Blockade of systemic V1 receptors during hemorrhage was found to exert the opposite effect to that reported in the present study; i.e., it impaired posthemorrhagic recovery of blood pressure (11, 15). However, this does not exclude the possibility that AVP receptors in the circumventricular organs, which are available for blood-borne vasopressin, do participate in the generation of bradycardia and hypotension during hemorrhage. Indeed systemic pretreatment with a V1 antagonist was found to abolish the posthemorrhagic bradycardia and inhibit renal sympathetic nerve activity (11, 15). It is likely that intrabrain and systemic release of vasopressin play a cooperative role in eliciting these effects. Accordingly, the final effect of vasopressin on the cardiovascular adjustments to hemorrhage would result from the interaction between the direct peripheral vasoconstrictive effect and central depressor functions of AVP.

It has been demonstrated that vasopressin may exert hemodynamic effects by stimulating V2 receptors (17). Some evidence indicates that the depressor effect of vasopressin becomes manifested during the blockade of central V2 receptors (18). Therefore, one can hypothesize that the effect of blockade of central V2 receptors during hemorrhage might have been modified by the simultaneous stimulation of central V2 receptors. However, the available information on the involvement of V2 receptors in cardiovascular adaptation to hemorrhage does not provide consistent information. Fujisawa et al. (11) have reported that in SD rats intravenous administration of nonpeptide V2 antagonist (OPC-31260) did not influence blood pressure recovery after hemorrhage; however, it intensified bradycardia and renal sympathoinhibition. On the other hand, Imai et al. (15) reported attenuation of hypotensive and bradycardic responses after administration of OPC-31260 by the same route to Long-Evans rats. In our previous investigation (7), LCV administration of peptide V2 antagonist [d(CH2)5-D-Ile2,Ala-Ile6,Ala-NH2]AVP did not exert a significant effect on posthemorrhagic changes of blood pressure and HR in WKY and SHR. However, further studies are needed to explore the role of central V2 receptors in
cardiovascular adaptation to hypovolemia in TGR rats, because reorganization of the brain vasopressinergic system in this strain may also involve altered activity of V2 receptors.

Effective elimination of hemorrhagic hypotension by V2 ANT in TGR contrasts with the ineffectiveness of blockade of V2 receptors in SHR (7) subjected to identical experimental paradigm. Comparison of these findings strongly suggests that the neurochemical alterations involved in the generation of hypertension in renin TGR rats are essentially different from those present in SHR rats. It is worth noting that SHR and renin TGR rats also manifest significant differences in the intrabrain distribution of AVP. In SHR, concentration of AVP is decreased in the brain stem and hypothalamus (39), whereas in the renin TGR rats it is decreased in the hypothalamus, being at the same time significantly elevated in the dorsal lower brain stem (22). Thus, one can speculate that upregulation of the brain angiotensinergic system in renin TGR rats may cause some reorganization of the central vasopressinergic system with a greater release of AVP in some specific cardiovascular brain regions. Probability of this hypothesis is intensified by the studies showing that the vasopressinergic neurons are innervated by angiotensinergic fibers, possess AT1 receptors, and respond with the release of AVP to local application of angiotensin (5, 13, 46). Strong evidence for significant involvement of ANG II in long-term regulation of the central release of AVP is provided by the recent study of Maders et al. (25) in which chronic treatment with quinapril, an inhibitor of angiotensin-converting enzyme, resulted in a significant decrease of vasopressin content in the regions innervated by PVN.

In conclusion, the present results strongly suggest that upregulation of the brain angiotensinergic system in renin transgenic hypertension is associated with significantly altered function of the brain vasopressinergic system under baseline conditions and during hypovolemia.

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