



Cardiovascular pharmacology

Angiotensin II and vasopressin are involved in the defense system against anaphylactic hypotension in anesthetized rats



Mofei Wang^{a,b}, Toshishige Shibamoto^{a,*}, Yuhichi Kuda^a, Lingling Sun^{a,c}, Mamoru Tanida^a, Yasutaka Kurata^a

^a Department of Physiology II, Kanazawa Medical University, Uchinada 920-0293, Japan

^b Department of Colorectal Surgery, The Fourth Affiliated Hospital of China Medical University, Shenyang 110032, China

^c Department of Hematology, The Fourth Affiliated Hospital of China Medical University, Shenyang 110032, China

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ABSTRACT

Anaphylactic shock is sometimes life-threatening, but the defense system against this circulatory failure was not fully understood. Ameliorating roles of angiotensin (ANG) II and vasopressin in anaphylactic hypotension were investigated in anesthetized ovalbumin-sensitized Sprague-Dawley rats. The sensitized rats were randomly allocated to the following pretreatment groups ($n=7/\text{group}$): (1) control (non-pretreatment), (2) ANG II synthesis inhibitor captopril, (3) ANG II receptor antagonist losartan, and (4) V1a vasopressin receptor antagonist. Anaphylactic shock was induced by an intravenous injection of the antigen. The systemic arterial pressure (SAP), central venous pressure (CVP), portal venous pressure (PVP) and portal venous blood flow (PBF) were measured, and splanchnic vascular resistance (Rspl: (SAP-PVP)/PBF) was determined. In the control group, SAP markedly decreased, followed by a gradual recovery toward baseline. Rspl transiently decreased immediately after antigen, and then increased 1.5-fold at 15 min and thereafter. The pretreatment with either losartan, captopril or V1a receptor antagonist augmented the initial fall of SAP and attenuated the SAP recovery along with augmentation of the late increase in Rspl. The 2-h survival rate was significantly smaller in either pretreatment group than in the control group (100%). Plasma levels of ANG II and vasopressin increased to 3.8- and 9.8-fold, respectively, at 30 min after antigen in the control group, whereas captopril pretreatment inhibited the increase in ANG II. In conclusion, inhibition of ANG II or vasopressin exacerbates anaphylaxis-induced hypotension in anesthetized rats.

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1. Introduction

Anaphylactic shock is a serious allergic reaction and is potentially life threatening (Brown, 1995). The knowledge on the defense system against hemorrhagic shock is well established: profound hemorrhage activates a number of compensatory mechanisms, including activation of the sympathetic nervous system and release of circulating vasoconstrictor hormones such as vasopressin and angiotensin (ANG) II, which act synergistically to achieve the subsequent cardiovascular recovery (Ponchon and Elghozi, 1997). In contrast, the defense system against anaphylactic shock is not well known. We have recently shown using the rat anaphylactic shock model that activation of the sympathetic nervous system is crucial against anaphylactic shock: β -adrenergic receptor activation is necessary to prevent early fatal outcome (Zhang et al., 2011a, 2011b); norepinephrine released from the sympathetic nerve endings and α -adrenergic receptor activation exerted beneficial effects at the recovery phase (Wang et al., 2013) in

anesthetized rats suffering from anaphylactic shock. However, the roles of other compensatory vasoconstrictor hormones such as vasopressin and ANG II in anaphylactic shock remain unknown. The patients administered of angiotensin converting enzyme synthesis inhibitors or its receptor antagonists show increased severity of anaphylactic shock (Sampson et al., 2005), suggesting the ameliorating action of ANG II against anaphylactic hypotension.

The purpose of this study was to determine the roles of ANG II and vasopressin in the compensatory defense system against anaphylactic shock. We studied the effects of pharmacological inhibition of ANG II and vasopressin on anaphylactic hypotension in anesthetized rats.

2. Materials and methods

2.1. Animals

The experiments conducted in the present study were approved by the Animal Research Committee of Kanazawa Medical University. Fifty male Sprague-Dawley (SD) rats (Japan SLC, Shizuoka, Japan) weighing

* Corresponding author. Tel.: +81 762 862 211; fax: +81 762 868 010.

E-mail address: shibamo@kanazawa-med.ac.jp (T. Shibamoto).

368 ± 5 g were used in this study. Rats were maintained at 23 °C and under pathogen-free conditions on a 12:12-hour dark/light cycle, and allowed food and water ad libitum.

2.2. Sensitization

Rats were sensitized by the subcutaneous injection of an emulsion made by mixing equal volumes of complete Freund's adjuvant (0.5 ml) with 1 mg ovalbumin (grade V, Sigma) dissolved in physiologic saline (0.5 ml). Two weeks after injection, rats were used for the following experiment (Shibamoto et al., 2005). Non-sensitized rats were injected with complete Freund's adjuvant and ovalbumin-free saline.

2.3. Surgical preparation and recording hemodynamic variables

Rats were anesthetized with pentobarbital sodium (50 mg/kg, ip) and placed supinely on a thermostatically controlled heating pad (ATC-101B; Unique Medical, Japan) that maintained body temperature at 36–37 °C throughout the experiment. The adequacy of anesthesia was monitored by the stability of blood pressure and respiration under control conditions and during a pinch of the hindpaw. Supplemental doses of anesthetic (10% of the initial dose) were given intraperitoneally as necessary. The trachea was intubated to facilitate spontaneous breathing. The right jugular vein was catheterized with a polyethylene tube (ID 0.4 mm, OD 0.6 mm) for measurement of the central venous pressure (CVP) at expiration. The right femoral artery and vein were also catheterized with a polyethylene tube (ID 0.3 mm, OD 0.5 mm) for measurement of the mean systemic arterial pressure (SAP) and continuous infusion of saline (10 ml/kg/h), respectively. Following a midline incision of the abdominal wall, a 22 gauge polyethylene catheter (Terumo, Tokyo, Japan) was inserted into the portal vein for continuous measurement of the mean portal venous pressure (PVP). A pulsed Doppler flow probe (MC2PSB, Transonic Systems, Ithaca, NY) was placed on the portal vein for continuous measurement of the mean portal venous blood flow (PBF).

The SAP, CVP and PVP were continuously measured with pressure transducers (TP-400T, Nihon-Kohden, Japan), and the reference level was set at the level of right atrium. Heart rate (HR) was measured by triggering the SAP. These hemodynamic variables along with PBF were digitally displayed and recorded at 40 Hz by PowerLab (AD Instruments, Castle Hill, Australia).

The vascular resistance of the splanchnic vascular beds (Rspl) was calculated as follows:

$$Rspl = (SAP - PVP) / PBF \quad (1)$$

2.4. Protocol

Sensitized rats were assigned to the control (non-pretreatment) group ($n=7$) and the following pretreatment groups: (1) the ANG II synthesis inhibitor captopril ($n=7$), (2) the ANG II receptor antagonist losartan ($n=7$), and (3) the vasopressin V1a receptor antagonist, [beta-mercapto-beta,beta-cyclopentamethylenepropionyl¹, O-me-Tyr², Arg⁸]-vasopressin ($n=7$). The non-sensitized group was also studied with the assignment of non-sensitized rats ($n=7$).

Hemodynamic variables were observed for at least 15 min after surgery until a stable state was obtained. After baseline measurement, losartan (6 mg/kg) or the V1a antagonist (60 µg/kg) was intravenously injected. At 10 min after the bolus injection of each antagonist, 0.6 mg ovalbumin antigen was intravenously injected. The doses of V1a antagonist and losartan used were high enough to eliminate the pressor response to an intravenous injection of 10 nmol/kg vasopressin (Zhang et al., 2012) and 3 nmol/kg ANG II (Zhao et al., 2009), respectively. Captopril was given by a bolus injection (2.5 mg/kg), followed by a continuously infusion (1 mg/kg/h) throughout the

experimental period. At 30 min after the bolus injection of captopril, the antigen was intravenously injected. The dose of captopril was reported to inhibit angiotensin converting enzyme activity (Isaacson and Reid, 1990; Heesch et al., 1996). The rats in the control and non-sensitized groups were pretreated with saline (500 µl) alone without any agents, and then 10 min later injected with the antigen.

2.5. Measurement of plasma ANG II and vasopressin concentrations

We measured plasma concentrations of ANG II and vasopressin after antigen injection in the separate experiments. The captopril-pretreated sensitized rats ($n=5$), control sensitized rats ($n=5$) and non-sensitized rats ($n=5$) were used with SAP measured in the same way as described above. At baseline, and 30, 60 and 120 min after antigen administration, blood (1.5 ml) was sampled from the right femoral artery with the same volume of saline being intravenously injected for replacement. Blood samples were transferred immediately to chilled tubes containing EDTA, and then centrifuged (1600g, 15 min, 4 °C). The plasma samples were separated and stored at -80 °C. Plasma concentrations of ANG II and vasopressin were determined using commercially available ELISA kits (Cloud-Clone Corp., Houston, USA for ANG II; Enzo life Sciences International, Inc., NY, USA for vasopressin) according to the manufacturers' instructions.

2.6. Statistics

Results are expressed as means $\pm$ SEM and survival rate as percentage. The Student *t* test was used to compare the basal variables before and after the pretreatment with antagonists. For the analysis of the variables after the antigen injection, intragroup and between-group comparisons were performed using one-way and two-way analysis of variance for repeated measures. When a significant difference was observed with the two-way analysis of variance, paired comparisons were made within a group and also between groups by using a Bonferroni posttest. Kaplan–Meier survival curves were analyzed by log-rank test. Significance was assumed when *P* value was less than 0.05 (two tailed). All statistical analyses were performed by StatView, version 5.0 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Hemodynamic basal levels

Table 1 shows the effects of the inhibitors on the basal levels of the variables. After pretreatment with losartan, captopril, or the V1a antagonist, SAP decreased significantly by approximately 20 mmHg.

3.2. Response of the control group

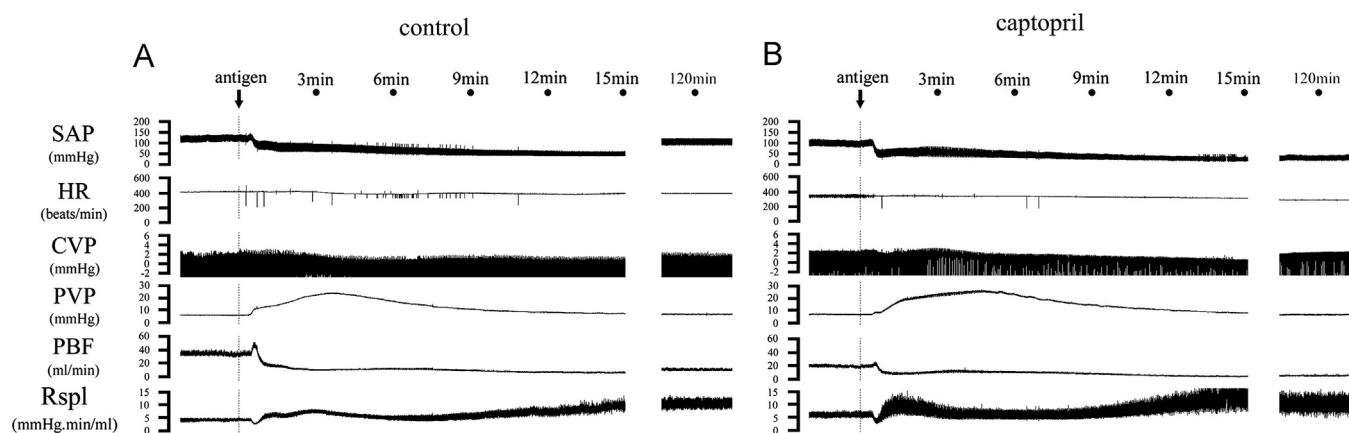
Fig. 1A shows representative recordings of the variables in a rat of the control group, and Fig. 2 shows the summarized data. An injection of the antigen caused systemic hypotension and portal hypertension in the control group: SAP decreased to a nadir of 33 ± 2 mmHg at 15 min after antigen injection, and then returned to 95 ± 5 mmHg at 120 min, which was not significantly different from baseline (Figs. 1A and 2A). Either CVP or HR did not change significantly after antigen injection, although CVP tended to decrease. PVP transiently increased with the peak of 21 ± 1 mmHg at 3 min (Fig. 2B). Immediately after antigen, PBF rapidly increased by 20%, and then decreased to a nadir of 17% at 15 min (Fig. 2C), followed by a gradual return to 44% at 120 min. Rspl initially decreased in accordance with an increase in PBF, and then did not change significantly until 15 min after antigen; thereafter,

Table 1

The basal levels of the variables before and after administration of an inhibitor, antagonists or saline.

Groups	Control (n=7)		Captopril (n=7)		Losartan (n=7)		V1a antagonist (n=7)		Non-sensitized (n=7)	
	Before	After	Before	After	Before	After	Before	After	Before	After
Systemic arterial pressure (mmHg)	120 ± 4	116 ± 4	120 ± 2	100 ± 5 ^{a,b}	119 ± 3	102 ± 3 ^{a,b}	117 ± 5	97 ± 5 ^{a,b}	117 ± 4	111 ± 4
Heart rate (beats/min)	380 ± 8	383 ± 10	355 ± 14	368 ± 10	352 ± 8	349 ± 8	352 ± 14	340 ± 10	350 ± 8	345 ± 10
Central venous pressure (mmHg)	2.2 ± 0.4	2.5 ± 0.4	2.6 ± 0.3	2.5 ± 0.4	2.4 ± 0.3	2.0 ± 0.2	2.5 ± 0.2	2.5 ± 0.2	2.5 ± 0.3	2.3 ± 0.3
Portal venous pressure (mmHg)	7.0 ± 0.3	6.5 ± 0.3	6.8 ± 0.5	5.3 ± 0.5	6.8 ± 0.5	5.4 ± 0.6	7.3 ± 0.2	6.6 ± 0.2	7.2 ± 0.4	6.8 ± 0.3
Mean portal venous blood flow (ml/min)	25.8 ± 1.9	24.6 ± 1.6	24.8 ± 1.0	23.0 ± 0.7	24.1 ± 1.2	21.9 ± 0.6	25.1 ± 1.0	22.9 ± 1.1	25.1 ± 0.7	24.8 ± 0.9
Splanchnic vascular resistance (mmHg min/ml)	4.1 ± 0.1	4.4 ± 0.2	4.6 ± 0.2	4.1 ± 0.2	4.7 ± 0.3	4.4 ± 0.1	4.3 ± 0.3	4.0 ± 0.1	4.4 ± 0.2	4.3 ± 0.3

Values are means ± SEM. In the control and non-sensitized groups, saline was injected instead of captopril, losartan or V1a antagonist.

^a $P < 0.05$ vs. before.^b $P < 0.05$ vs. the control group.**Fig. 1.** Representative recordings of the systemic arterial pressure (SAP), heart rate (HR), central venous pressure (CVP), portal venous pressure (PVP), portal venous blood flow (PBF), and splanchnic vascular resistance (Rspl) after an intravenous injection of the antigen of ovalbumin (0.6 mg) in a control rat (A), and a captopril-pretreated rat (B).

it significantly increased to 1.9-fold baseline at 120 min (Fig. 2D). The non-sensitized group showed no significant changes in the variables throughout the experimental period.

3.3. Responses of the pretreatment groups

In all the three pretreatment groups, the decrease in SAP was more rapid until 2.5 min after antigen injection, the nadir levels at 15 min were not significantly different from that of the control group. Thereafter SAP showed significantly lower values than that in the control group (Fig. 2A). As shown in Figs. 1B and 2B, PVP in either pretreatment group increased in a manner similar to that in the control group, and no significant differences were found among sensitized groups. Rspl in the pretreatment groups also changed similarly to that in the control group until 10 min after antigen injection, but after that it increased to higher levels at 15–60 min than in the control group (Fig. 2D). However, Rspl at 120 min after antigen was not significantly different among the sensitized rat groups.

Either CVP or HR did not significantly change after antigen injection in any pretreatment groups studied.

3.4. Survival rate

Fig. 3 shows the survival rate for individual groups. Three rats of the losartan and V1a antagonist groups and two rats of the captopril group died within 78 min after antigen, while all seven rats of both the control and non-sensitized groups were alive at 120 min after antigen. The survival rate was significantly smaller in the captopril, losartan, and V1a antagonist groups than in the control group.

3.5. Plasma concentrations of angiotensin II and vasopressin

Fig. 4 shows plasma concentrations of ANG II and vasopressin after antigen injection. In the control rats, ANG II increased significantly from the baseline of 1.2 ± 0.5 to 4.5 ± 0.9 pg/ml at 30 min after antigen injection, followed by a gradual return to baseline at 120 min. In contrast, ANG II did not increase significantly after antigen injection in the captopril-pretreated rats (Fig. 4A). Plasma vasopressin levels also significantly increased from the baseline of 7.0 ± 0.8 to 68.5 ± 18.5 and 39.8 ± 13.4 pg/ml at 30 and 60 min, respectively, after antigen injection. The antigen-induced increases in plasma vasopressin in the captopril-pretreated rats tended to be smaller, but not significantly, than in the control rats (Fig. 4B). Non-sensitized rats showed no significant changes in ANG II or vasopressin concentrations. Fig. 4C shows the SAP responses of these rats, which were essentially the same as those of the rats without blood sampling as described above: SAP of the captopril-pretreated rats was significantly smaller than that in the control sensitized rats at 5 min and 30–120 min after antigen injection.

4. Discussion

The major findings of the present study were that plasma levels of ANG II or vasopressin increased 3.8- and 9.8-fold, respectively, after antigen, and that blockade of these hormones not only augmented the initial fall of SAP, but also inhibited the SAP recovery from the nadir, resulting in a decrease in the survival rate in anesthetized rats with anaphylactic hypotension. These findings suggest that ANG II and

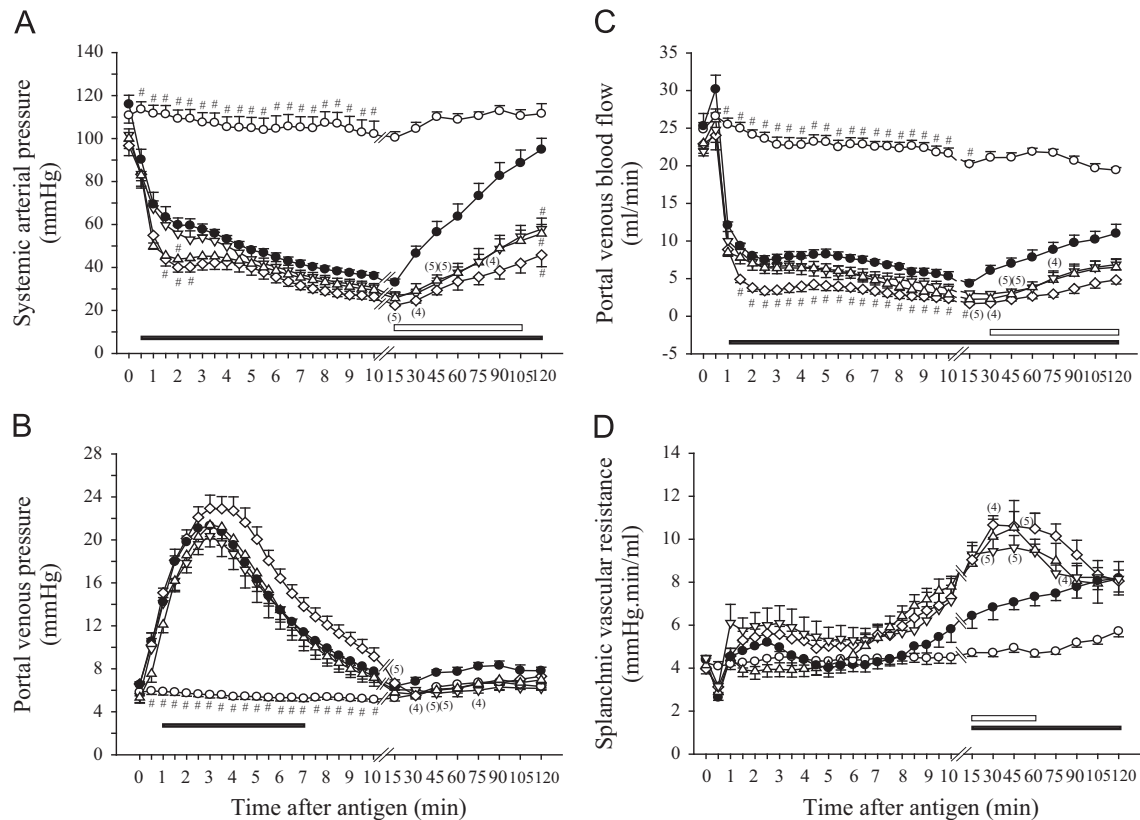


Fig. 2. Summary of the changes in the mean systemic arterial pressure (A), portal venous pressure (B), portal venous blood flow (C), and splanchnic vascular resistance (D) after an injection of the ovalbumin antigen. Open circle, non-sensitized group ($n=7$); closed circle, control group ($n=7$); open triangle, captopril group ($n=7$); open inverted triangle, losartan group ($n=7$); open diamond, V1a antagonist group ($n=7$). Values are means $\pm$ SEM; each point of variables for the control, captopril, losartan, and V1a antagonist groups during the time indicated by the black bar in the figure is significantly different from the corresponding baseline. $^{\#}P < 0.05$ vs. the control group; each point of variables during the time indicated by the white bar in A, C and D is significantly different from the corresponding value in the control group. The numbers in the parentheses indicate the sample numbers of the animals.

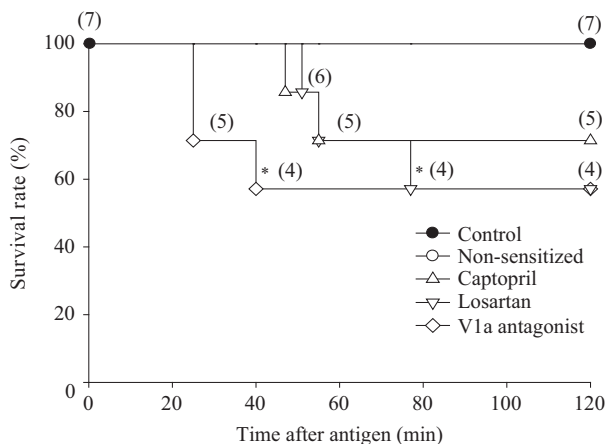


Fig. 3. The survival rates after an injection of the ovalbumin antigen. $^{\ast}P < 0.05$, vs. the control group. The numbers in the parentheses indicate the numbers of the surviving animals.

vasopressin play compensatory roles in both the early and recovery stages in rat anaphylactic shock.

It was reported that the blood pressure recovery from hemorrhagic shock was blunted by inhibition of vasopressin or ANG II (Ponchon and Elghozi, 1997). On the other hand, to the best of our knowledge, this is the first study to demonstrate that the blockade of ANG II and vasopressin augmented the severity of anaphylactic hypotension, with resultant deterioration of the survival rate and recovery from hypotension. This result suggests that vasoconstrictors

of ANG II and vasopressin play crucial roles in the defense system against anaphylactic hypotension.

The survival rates were smaller in the rats pretreated with either ANG II or vasopressin inhibitor (57%) than in the control rats which did not die but almost recovered from hypotension at 120 min (Fig. 2A). Actually 2 or 3 rats among 7 rats pretreated with inhibitors died within 60 min after antigen. This finding contrasts with the results of our previous studies using the same rat anaphylaxis model: all sensitized rats treated with α - (Wang et al., 2013) or β -adrenergic blockers (Zhang et al., 2011a, 2011b) survived or died, respectively, by 60 min after antigen. These results suggest that the detrimental action of inhibition of ANG II and vasopressin was stronger than that of α -adrenergic blockade, and was weaker than that of β -adrenergic blockade in rat anaphylactic hypotension: β -adrenergic blockade > antagonism of ANG II or vasopressin > α -adrenergic blockade. It is known that β -adrenoceptor activation increases renin release, and then ANG II production (DiBona and Kopp, 1997). This evidence suggests that β -adrenergic blockade results in ANG II reduction, which is consistent with the above conclusion on the order of the detrimental actions.

In the present study, measurement of plasma levels of ANG II and vasopressin revealed substantial increases of both vasoconstrictors after antigen (Fig. 4). This result provides a reason why blockade of ANG II and vasopressin deteriorated anaphylactic hypotension. In addition, absence of a significant increase in ANG II in the captopril-pretreated rats indicated the effectiveness of captopril, a ANG converting enzyme inhibitor, used in the present study. The basal levels of ANG II (1.2 ± 0.5 pg/ml) and vasopressin (7.0 ± 0.8 pg/ml) in anesthetized SD rats of the present

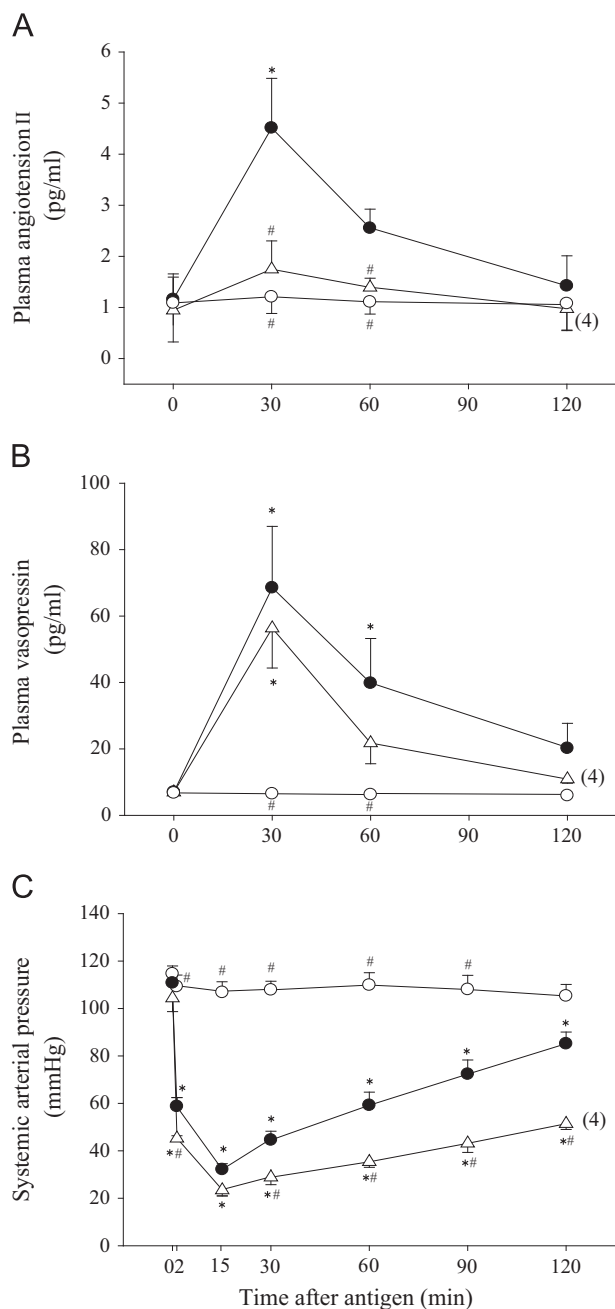


Fig. 4. Summary of the plasma angiotensin II levels (A), plasma vasopressin levels (B), and mean systemic arterial pressure (C) after an injection of the ovalbumin antigen. Open circle, the non-sensitized rats ($n=5$); closed circle, the control rats ($n=5$); open triangle, the captopril-pretreated rats ($n=5$). Values are mean $\pm$ SEM; * $P < 0.05$ vs. baseline; # $P < 0.05$ vs. the control rats. The numbers in the parentheses indicate the numbers of the surviving animals.

study were comparable with those in the previous studies (Chen et al., 2008; Sun et al., 2013). The anaphylaxis-induced peak levels of ANG II (3.8-fold baseline) were comparable to that found in anesthetized rats exposed to trauma-hemorrhage shock (Chen et al., 2008; Wang and Leung, 2013). Similarly, the peak levels of vasopressin (9.8-fold baseline) were comparable to that found in hypertonic saline-treated rats (Dunn et al., 1973).

The mechanism for increases in plasma levels of ANG II and vasopressin during anaphylactic hypotension may be similar to that during hemorrhagic shock. The high-pressure or arterial baroreceptors and low-pressure or atrial receptors are believed to participate in the reflex control of vasopressin and renin secretion: a

reduction in venous return or blood pressure causes a decrease in receptor activity and a reflex increase in secretion of both hormones (Thrasher, 1994). The renin-ANG system may be also activated via renal hypoperfusion, which was associated with anaphylactic hypotension. In addition, there is a possibility that anaphylaxis in the brain could stimulate release of ANG II and vasopressin: activation of brain mast cells induced by an intraventricular administration of antigen (Matsumoto et al., 2001) or compound 48/80, a mast cell degranulator (Matsumoto et al., 2008), evokes release of renin and vasopressin. Indeed, vasopressin release is stimulated by anaphylactic mediators such as histamine (Jochem, 2004a), serotonin (Ho et al., 2007), and prostaglandin D₂ (Summy-Long et al., 2002). Central histamine also increases plasma renin activity (Jochem, 2004b; Matzen et al., 1990).

It is well established that brain ANG II stimulates arginine vasopressin release by binding to the AT₁ receptor located on the paraventricular nucleus of the hypothalamus (Guggilam et al., 2008; Chiodera et al., 1998). Based on this evidence, it was expected that plasma vasopressin after antigen might have been smaller in the captopril-pretreated rats than in the control rats. As expected, a tendency of smaller vasopressin levels was observed in the captopril-pretreated rats although they showed a greater initial SAP fall than the control rats (Figs. 2A and 4C).

In the control group, Rspl, an indicator of the celiac and mesenteric arterial tone, initially and transiently decreased along with an increase in PBF, which indicated vasodilatation and represented the characteristic of rat anaphylaxis (Wang et al., 2013; Zhang et al., 2013). There followed an increase in Rspl at 15–120 min after antigen, which is probably caused by sympathoexcitation-induced vasoconstriction because chemical sympathectomy abolished it (Zhang et al., 2012). An interesting finding of the present study was that Rspl in the ANG II and vasopressin inhibitor groups showed a greater increase at 15–60 min after antigen than that in the control group (Fig. 2D). The mechanism for this marked increase in Rspl is possibly due to more activated sympathetic nervous system. This increased Rspl might serve as strong compensatory mechanism so as to recover the SAP fall by reducing the splanchnic blood flow, as shown in Fig. 2C, and redistributing the effective circulating blood to the heart and brain.

In summary, we determined the roles of ANG II and vasopressin in anaphylactic hypotension of anesthetized ovalbumin-sensitized SD rats. We found that plasma levels of ANG II and vasopressin increased substantially after antigen, and that the inhibition of these hormones exacerbates anaphylaxis-induced hypotension at early and the late phase, resulting in reduction of survival. In conclusion, ANG II and vasopressin constitute a crucial defense system against anaphylactic hypotension of anesthetized rats.

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