Alpha-adrenoceptor antagonists and chemical sympathectomy exacerbate anaphylaxis-induced hypotension, but not portal hypertension, in anesthetized rats

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Running head: Sympathetic nervous system and anaphylaxis

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ABSTRACT

Anaphylactic shock is sometimes life-threatening, and is accompanied by hepatic venoconstriction in animals, which in part accounts for anaphylactic hypotension. Roles of norepinephrine and α-adrenoceptor in anaphylaxis-induced hypotension and portal hypertension were investigated in anesthetized ovalbumin-sensitized Sprague-Dawley rats. The sensitized rats were randomly allocated to the following pretreatment groups (n=6/group): (1) control (non-pretreatment), (2) α1-adrenoceptor antagonist prazosin, (3) non-selective α-adrenoceptor antagonist phentolamine, (4) 6-hydroxydopamine-induced chemical sympathetectomy, and (5) surgical hepatic sympathetectomy. 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 (Rspl: (SAP-PVP)/PBF) and portal venous (Rpv: (PVP-CVP)/PBF) resistances were determined. Separately, we measured efferent hepatic sympathetic nerve activity during anaphylaxis. In the control group, SAP markedly decreased, followed by a gradual recovery toward baseline. PVP and Rpv increased 3.2- and 23.3-fold, respectively, after antigen. Rspl decreased immediately but only transiently after antigen, and then increased 1.5-fold later than 10 min. The α-adrenoceptor antagonist pretreatment or chemical sympathetectomy inhibited the late increase in Rspl and the SAP recovery. Pretreatment with α-adrenoceptor antagonists, or either chemical or surgical hepatic sympathetectomy did not affect the antigen-induced increase in Rpv. Hepatic sympathetic nerve activity did not significantly change after antigen. In conclusion, α-adrenoceptor antagonists and chemical sympathetectomy exacerbate anaphylaxis-induced hypotension, but not portal hypertension, in anesthetized rats. Hepatic sympathetic nerves are not involved in anaphylactic portal hypertension.

Key Words: anaphylactic shock; portal hypertension; hepatic sympathetic nerve
activity; chemical sympathectomy; prazosin; phentolamine; hepatic venoconstriction.
Introduction

Anaphylactic shock is a serious allergic reaction and is potentially life threatening (2). Decreases in blood pressure during circulatory shock such as acute hemorrhage reduce afferent impulses from arterial baroreceptors, thereby activating the sympathetic nervous system (14). The sympathoexcitation, as evidenced by increased renal sympathetic nerve activity (20) or circulating catecholamine levels (32), was also reported during anaphylaxis. However, the roles of norepinephrine released from the sympathetic nerve terminals in anaphylactic shock have not been determined, although those of β-adrenoceptors and epinephrine released from the adrenal gland have been reported (32). It remains unknown whether the peripherally released norepinephrine exerts beneficial actions against anaphylactic shock; the effects on anaphylaxis of the norepinephrine-selective neurotoxic drug 6-hydroxydopamine (6-OHDA), which destroys peripheral norepinephrine terminals (8, 18) have not been examined in animal models. In addition, the effect of inhibition of the α-adrenoceptor, which is the primary receptor for norepinephrine, on anaphylactic hypotension has not been determined.

Hepatic venoconstriction, as observed consistently in experimental anaphylaxis models (7, 11, 13), plays a significant role in the genesis of anaphylactic hypotension: anaphylactic hepatic venoconstriction produces acute portal hypertension, which then causes splanchnic blood pooling and plasma extravasation due to increases in both the capillary pressure and vascular permeability, resulting in decreased circulating blood volume, and finally anaphylactic hypotension. Hepatic venoconstriction in rats is caused by anaphylaxis-induced release of venoconstrictive mediators, such as leukotrienes, platelet-activating factor and cyclooxygenase metabolites (4, 5). As an alternative mechanism, activation of the sympathetic nervous system may evoke anaphylactic hepatic venoconstriction; electrical stimulation of the rat hepatic sympathetic nerve induced constriction of the hepatic vessel (3, 9). In addition, circulating norepinephrine increases during systemic anaphylaxis (32), and may constrict hepatic vessels via
activation of α-adrenoceptors (22). However, the response of the hepatic sympathetic nerve activity to anaphylactic hypotension or its role in anaphylactic portal hypertension remains unknown.

Therefore, there were two major purposes in this study regarding anaphylactic systemic hypotension and portal hypertension: The first was to determine the effects on anaphylactic systemic hypotension of chemical sympathetectomy with 6-OHDA and pharmacological blockade of α-adrenoceptors in anesthetized rats. The second was to determine the effects on anaphylactic portal hypertension of the aforementioned pharmacological interventions and surgical hepatic sympathetectomy, as well as the response of the efferent hepatic sympathetic nerve activity to anaphylaxis in anesthetized rats.

Materials and Methods

Animals

The experiments conducted in the present study were approved by the Animal Research Committee of Kanazawa Medical University. Sixty nine male Sprague-Dawley rats (Japan SLC, Shizuoka, Japan) weighing 362±3 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.

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) (23). Non-sensitized rats were injected with complete Freund’s adjuvant and ovalbumin-free saline.

Chemical sympathetectomy
Sensitized rats (n=6) and non-sensitized rats (n=6) for the 6-OHDA group and the 6-OHDA non-sensitized group, respectively, were intraperitoneally administered of 6-OHDA dissolved in sterile saline supplemented with 0.01% ascorbic acid three times at a dose of 40 mg/kg (1 ml) day 1, and 80 mg/kg (1 ml) day 2 and 3. The experiments with 6-OHDA–treated animals were performed at 3 days after the last injection. This procedure produces a highly effective sympathetic denervation (8, 18).

**Surgical preparation and recording hemodynamic variables**

Rats were anesthetized with pentobarbital sodium (50 mg·kg⁻¹, 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 0.4mm, OD 0.6mm) for measurement of the central venous pressure at expiration (CVP). The right femoral artery and vein were also catheterized with a polyethylene tube (ID 0.3mm, OD 0.5mm) 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 Fr polyethylene catheter (Terumo, Tokyo, Japan) was inserted into the portal vein, for continuous measurement of the mean portal venous pressure (PVP). Except for the experiments of measurement of the hepatic sympathetic nerve activity, 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). In the hepatic sympathectomy group, denervation was accomplished by cutting all visible nerves along the hepatic artery and by stripping the connective tissue passing next to and along
the course of the hepatic artery. Immediately thereafter, the hepatic artery was surrounded with cotton swabs previously soaked in 10% (v/v) phenol diluted in absolute ethanol.

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 resistances of the splanchnic vascular beds (Rspl) and the portal vein (Rpv) were calculated as follows:

\[
R_{spl} = \frac{(SAP - PVP)}{PBF} \quad (1)
\]

\[
R_{pv} = \frac{(PVP - CVP)}{PBF} \quad (2)
\]

α-adrenoceptor blockade and sympathetectomy studies

In addition to the chemical sympathetectomy (6-OHDA)-pretreated sensitized (6-OHDA group) rats (n=6) and non-sensitized (6-OHDA non-sensitized group) rats (n=6), sensitized rats were assigned to the control (non-pretreatment) group (n=6) and the following pretreatment groups: 1) α1-adrenoceptor antagonist prazosin (n=6), 2) non-selective α-adrenoceptor antagonist phentolamine (n=6), and 3) hepatic sympathetectomy (n=6). The non-sensitized group was also studied with the assignment of non-sensitized rats (n=6).

Hemodynamic parameters were observed for at least 15 min after surgery until a stable state was obtained. After the baseline measurements, prazosin (1 mg/kg) or phentolamine (2 mg/kg) was intravenously injected; 10 min later, 0.6 mg ovalbumin antigen was intravenously injected. The doses of phentolamine and prazosin used were high enough to eliminate pressor response to an intravenous injection of 100 nmol/kg norepinephrine (34). The rats in the hepatic sympathetectomy, control and
non-sensitized groups were pretreated with saline (500 μl) alone without any agents, followed by antigen injection.

**Hepatic sympathetic nerve activity study**

The sensitized (n=6) and non-sensitized (n=6) rats were instrumented under pentobarbital anesthesia for recording SAP and PVP in the same way as described above. Using a dissecting microscope, the hepatic sympathetic nerve running along the hepatic artery was exposed, and the distal end of the nerve was ligated, and then hooked up with a pair of silver wire electrodes for recording the efferent hepatic nerve activity, as described previously (29). The electrodes were fixed with a silicon gel to prevent dehydration and for electrical insulation. Electrical discharge was amplified 2,000-5,000 times with a band path of 100 to 1,000 kHz, and monitored by an oscilloscope. Raw nerve activity data were converted to standard pulses by a window discriminator, which separated discharge from electrical background noise that remained postmortem. Both the discharge rate and the neurogram were sampled with a PowerLab analog-to-digital converter for recording and data analysis on a computer. The rats were allowed to stabilize for 15 min after fixation of the electrodes and then intravenously injected with sodium nitroprusside (SNP: 30 μg/kg) to confirm baroreceptor-mediated sympathoexcitation. The animals which did not show sympathoexcitation in response to SNP-induced hypotension were excluded in this study. Thereafter the antigen was intravenously injected to induce anaphylactic hypotension, as described above. At the end of experiment, hexamethonium (10 mg/kg) was injected intravenously to ensure that post-ganglionic efferent sympathetic nerve outflow had been recorded.

**Measurement of plasma catecholamine concentrations**

To determine whether chemical sympathectomy with 6-OHDA was effectively performed, we measured the plasma concentrations of norepinephrine as
well as epinephrine during systemic anaphylaxis in the separate experiments. The 6-OHDA-pretreated sensitized rats (n=5), control sensitized rats (n=5) and non-sensitized rats (n=5) were used, in which SAP was measured in the same way as described above. At baseline, and 30 and 60 min after antigen administration, blood (2 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 (1,200 g, 10 min, 4°C). The plasma samples were separated and stored at -80°C. Plasma catecholamine concentrations were determined by high-performance liquid chromatography with a trihydroxyindole reaction.

Statistics

All results are expressed as the means ± SEM. Comparison of individual values within a group was made by the repeated measure analysis of variance followed by the Bonferroni posttest. Comparison of individual points between the five and two groups was made by one way analysis of variance followed by Bonferroni posttest and Student t-test, respectively. Differences were considered statistically significant at $P<0.05$.

Results

**α-adrenoceptor blockade and sympathetectomy studies**

Table 1 shows the effects of the α-adrenoceptor antagonists, and chemical and hepatic sympathetectomy on the basal levels of the variables. After pretreatment with prazosin or phentolamine, SAP decreased significantly, while PVP, CVP, and Rspl tended to decrease but not significantly. In the 6-OHDA groups, Rspl was significantly smaller than in the control group.

Figure 1A shows representative recordings of the variables from 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 by 218 $84 \pm 3$ mmHg from the baseline of 124±4 mmHg to a nadir of 38±1 mmHg at 10 min after antigen injection, and then gradually returned to 74±6 mmHg at 60 min (Fig. 2A). Either CVP or HR did not change significantly after antigen injection, although CVP tended to decrease. PVP increased from the baseline of 5.8±0.2 mmHg to the peak of 18.5±0.6 mmHg at 2.5 min (Fig. 2B). Immediately after antigen, PBF rapidly increased from the baseline of 24.6 ±1.6 to 36.2±1.8 ml/min (149%), followed by a profound decrease to 7.0±0.3 ml/min (29%) at 2.5 min (Fig. 2C). The increased PVP coupled with the decreased PBF yielded a marked increase in Rpv from 0.11±0.02 to 2.35±0.14 mmHg•min/ml at 2.5 min after antigen (Fig. 2D). In contrast, Rspl initially decreased in accordance with an increase in PBF, and then did not change significantly until 10 min after antigen; thereafter, it significantly increased and remained elevated 1.5-fold baseline to the end of the experimental period (Fig. 2E).

In the α-adrenoceptor antagonist and chemical sympathetectomy groups, SAP decreased to nadir levels, which were similar to that of the control group, at 10 min after antigen. Thereafter SAP in these pretreatment groups showed significantly lower values than that in the control group: significant differences were found at 10-60 min for the phentolamine group, at 40-60 min for the 6-OHDA group, and at 50-60 min for the prazosin group (Fig. 2A). As shown in Figs. 1B, 2B, and 2D, pretreatment with prazosin or phentolamine or chemical sympathetectomy did not significantly affect the antigen-induced increase in PVP or Rpv during the portal hypertension period (0.5-10 min after antigen) when PVP of the control group was increased significantly from the baseline. In contrast to the significant increase in Rspl of the control group at 10-60 min after antigen, no significant increase in Rspl was observed in the α-adrenoceptor antagonist and chemical sympathetectomy groups throughout the experimental period (Fig. 2E). There were significant differences in Rspl at 20-60 min after antigen injection, as indicated by the white bar in Fig. 2E, between the control groups and the other
groups except the hepatic sympathetectomy group.

Either CVP or HR did not significantly change after antigen injection in any groups studied. The non-sensitized group showed no significant changes in the variables throughout the experimental period (Fig. 2). None of the animals in this study died during the experimental period of 60 min after antigen administration.

**Surgical hepatic sympathetectomy study**

Figure 2 also shows the results of the hepatic sympathetectomy group. Hepatic sympathetectomy group showed responses similar to those in the control group. There were no significant differences in variables between these two groups.

**Hepatic sympathetic nerve activity study**

Normal responses of hepatic sympathetic nerve activity to a transient hypotension induced by an intravenous injection of SNP (30 µg/kg) were observed before challenging the antigen: the hepatic sympathetic nerve activity reflexively increased in response to SAP fall (136±8% at -20 mmHg, 180±19% at -40 mmHg). Figures 3 and 4 show the results of changes in the hepatic sympathetic nerve activity, along with SAP and PVP, after antigen challenge. The responses of SAP and PVP to the antigen in the sensitized rats in which hepatic sympathetic nerve activity was measured were similar to those of the control group for the other studies (Figs. 3A and 4A-B). Immediately after antigen, hepatic sympathetic nerve activity tended to decrease but not significantly (91±2% of the baseline at 1.5 min; P=0.087) in the presence of the SAP fall (-37±5 mmHg at 1.5 min). Thereafter, the nerve activity remained unchanged for 60 min (Figs. 3A and 4C).

**Plasma catecholamine concentrations**

To confirm the effectiveness of chemical sympathetectomy with 6-OHDA and
the possible roles of norepinephrine released from the sympathetic nerve endings in anaphylactic hypotension, the plasma levels of norepinephrine and epinephrine were measured in the separate experiments. As shown in Fig. 5A, at baseline the norepinephrine levels in the 6-OHDA pretreated rats (55±9 pg/ml) were significantly smaller by 56% than that of the control sensitized rats (125±3 pg/ml). At 30 and 60 min after antigen injection the 6-OHDA pretreated rats showed a much smaller norepinephrine (322±23 and 500±87 pg/ml, respectively) than the control sensitized rats (423±8 and 947±130 pg/ml, respectively). In contrast, the epinephrine levels at 30 min after antigen injection were significantly higher in the 6-OHDA pretreated rats (3,691±484 pg/ml) than in the control sensitized rats without 6-OHDA (1,604±72 pg/ml) (Fig. 5B). Figure 5C shows the blood pressure responses of these rats, which were essentially the same as those of the rats without blood sampling as described above: SAP in the 6-OHDA pretreated rats was significantly smaller than that of the control sensitized rats at 40-60 min after antigen injection.

Discussion

We obtained three major findings: (1) chemical sympathetectomy and \( \alpha \)-adrenoceptor blockade inhibited the recovery from systemic hypotension with inhibition of the late increase in Rspl; (2) neither chemical, nor hepatic sympathetectomy, or \( \alpha \)-adrenoceptor blockade attenuated anaphylaxis-induced hepatic portal hypertension, i.e. increase in PVP; (3) the hepatic sympathetic nerve activity did not increase in the presence of SAP fall after antigen. These findings suggest that norepinephrine released from the sympathetic nerve endings does not play a compensatory role in the initial fall of SAP but facilitates its recovery due to vasoconstriction, and that hepatic sympathetic nerve is not involved in anaphylaxis-associated hepatic venoconstriction in anesthetized rats.

To the best of our knowledge, this is the first study to determine the effects of
chemical sympathetectomy and α-adrenoceptor blockade on experimental anaphylactic shock models. We clearly showed that these interventions did not augment the severity of anaphylactic hypotension but attenuated recovery from hypotension. Furthermore, this elimination of recovery due to chemical sympathetectomy and α-adrenoceptor blockade may be caused by attenuation of delayed vasoconstriction because Rspl, as an indicator of the mesenteric and celiac arterial tone, did not increase at the late phase of 10-60 min in the chemical sympathetectomy and α-adrenoceptor antagonist groups (Fig. 2E).

Notably, the rats pretreated with either 6-OHDA, phentolamine or prazosin survived longer than 60 min after antigen in the present study. This finding contrasts with the results of our previous studies using the same anaphylaxis rat models (32, 33), in which all rats pretreated with the β2-adrenoceptor antagonists ICI118,551 or propranolol, died within 50 min after antigen; 40% of those pretreated with the β1-adrenoceptor antagonist atenolol died within 60 min. These results suggest that the detrimental action of α-adrenoceptor inhibition is less than that of β-adrenoceptor inhibition in anaphylactic adrenoceptor inhibition. One of the explanations for this predominance of β-adrenoceptor is that β2-adrenonergic receptor stimulation is essential for preventing protein extravasation across the microvascular walls in various states with enhanced vascular permeability (19,28). This difference may explain why the clinical reports which described the aggravation of anaphylactic shock in patients administered of α-adrenoceptor antagonists are limited (30) as compared with those on β-adrenoceptor antagonists (16).

As expected, in the 6-OHDA pretreated rats, basal norepinephrine level was as low as 44% of that in control sensitized rats. In addition, the increase of norepinephrine after antigen was much smaller in the 6-OHDA pretreated rats than in the intact sensitized rats (Fig. 5). We assume that the norepinephrine at baseline and post-antigen in the 6-OHDA pretreated rats was released from the adrenal glands. Actually, the
higher levels of epinephrine, which is released exclusively from the adrenal glands, at post-antigen in the 6-OHDA rats than those in the control rats suggest the facilitated activation of the adrenal glands to release catecholamine of norepinephrine and epinephrine in compensation for absence of norepinephrine release from the sympathetic nerve endings in the former rats. These findings indicate that the chemical sympathetectomy was effectively performed in the present study.

The finding that surgical hepatic sympathetectomy did not attenuate anaphylactic portal hypertension suggests that the hepatic sympathetic nerves are not involved in anaphylactic hepatic venoconstriction. Furthermore, the lack of attenuation by either chemical sympathetectomy or the pharmacological \(\alpha\)-adrenoceptor blockade reinforces the latter assumption. Finally, the absence of excitation of the hepatic sympathetic nerve activity supports this conclusion.

In the same rat anaphylaxis model as used in this study, the plasma level of norepinephrine increased 4-fold at 2.5 min after antigen (32). Thus, we suppose that the circulating norepinephrine released from organs other than liver may contribute to constriction of the hepatic vessels, even if hepatic sympathetic nerve activity does not increase. Nonetheless, portal hypertension was not attenuated by either prazosin or phentolamine. One explanation is that the circulating levels of epinephrine, which could dilate hepatic vessels via \(\beta\)-adrenoceptors (10, 25) increased much more than that of norepinephrine (32) counteracting the vasoconstrictor action of norepinephrine. However, this seems unlikely because \(\beta\)-adrenoceptor blockade did not affect the anaphylaxis-induced increases in PVP of anesthetized rats (32, 33).

We here for the first time demonstrated that hepatic sympathetic nerve activity did not increase, but tended to decrease, in response to anaphylactic hypotension. The absence of activation of the hepatic sympathetic nerve activity contrasts with the anaphylactic activation of renal sympathetic nerve activity in the previous study for rats (20). This indicates that the regional difference in sympathetic outflow (12) may exist
between kidney and liver during systemic anaphylaxis of anesthetized rats. On the other hand, the present result of no significant change in hepatic sympathetic nerve activity is not surprising because renal sympathetic nerve activity did not increase in the presence of SAP fall during anaphylaxis in dogs (15). It is likely that the baroreceptor-reflex may not operate normally during anaphylactic hypotension. Further studies are required in this respect.

The mechanism for the hepatic venoconstriction in the present study, other than hepatic sympathoexcitation, may be related to vasoactive chemical mediators released in response to the antigen. We previously reported using isolated blood-perfused rat livers sensitized with ovalbumin that cysteinyl leukotrienes and cyclooxygenase products are mainly involved in anaphylactic hepatic venoconstriction (5). Buxton et al. (4) also reported that the cyclooxygenase products and platelet-activating factor are responsible for the antigen-induced venoconstriction of crystalloid-perfused livers from rats sensitized with bovine serum albumin.

As a limitation of this study, the anesthesia of pentobarbital sodium might have substantial effects on the results. Pentobarbital decreases baroreceptor reflex control of both HR and renal sympathetic nerve activity in rats (26). Indeed, in the present study, HR did not significantly increase when SAP decreased after the antigen. The absence of tachycardia during anaphylactic hypotension of the pentobarbital-anesthetized SD rat was consistent with the previous studies reported by ourselves (6, 23, 24) and by others (20), and this finding contrasts with the tachycardia response of the unanesthetized SD rats that were sensitized and induced of anaphylaxis in the same manner as in the present study (31). Furthermore, as compared with the anesthetized anaphylactic rat, the sensitized unanesthetized rat recovered more quickly from the anaphylactic hypotension (31). In this respect, pentobarbital might have exerted direct depressant effects on the myocardium and systemic vasodilating action (1, 27), which could potentiate the circulatory effects of anaphylaxis and provide more serious reactions in this setting.
In summary, we determined the roles of norepinephrine and α-adrenoceptor in anaphylaxis-induced systemic hypotension and portal hypertension in anesthetized ovalbumin-sensitized Sprague-Dawley rats. We used pharmacological procedures to destroy the sympathetic nerve endings, and to inhibit α-adrenoceptors, as well as the surgical hepatic sympathetectomy. We also measured directly the efferent hepatic sympathetic nerve activity. We found that α-adrenoceptor antagonists and chemical sympathectomy exacerbate anaphylaxis-induced hypotension only at the late phase, but not survival. Anaphylactic portal hypertension was not affected by any perturbations studied. In conclusion, norepinephrine released from the sympathetic nerve endings does not play a compensatory role in anaphylactic hypotension at the early phase but at the recovery phase presumably via vasoconstriction. Hepatic sympathetic nerve activity is not involved in the antigen-induced hepatic venoconstriction during anaphylactic hypotension in anesthetized rats.

**Perspectives and Significance**

The hemodynamic regulation in anaphylactic shock has not been fully understood. Although the knowledge on the defense system against hemorrhagic shock is well established, that against anaphylactic shock is not well known. Activation of the sympathetic nervous system is crucial against hemorrhagic shock. The present study showed that the norepinephrine released from the sympathetic nerve endings and activation of α-adrenergic receptors exerted beneficial effects on anaphylactic hypotension at the recovery phase in rats. However, the sympathetic response to anaphylactic shock seems to be different depending on species: In response to the fall in SAP after antigen injection, the renal sympathetic nerve activity increases in rats (20, our unpublished observation), whereas it does not necessarily increase in dogs (15). In addition, the present study has demonstrated that the hepatic sympathetic nerve activity did not significantly change when SAP substantially decreased after antigen injection in
anesthetized rats. This finding indicates the presence of regional difference in sympathetic response to anaphylactic hypotension. Thus, it is required to clarify further the mechanism for the central regulation of hemodynamics during anaphylactic shock. In addition, the roles of other compensatory mechanisms such as the angiotensin and vasopressin system in anaphylactic shock remains unknown, although the patients administered of angiotensin II synthesis inhibitors or its receptor antagonists show increased severity of anaphylactic shock (21). There is a possibility that fatal outcome of anaphylactic shock might be due to impairment of these defense systems. Future studies in this respect are required.
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References


Figure legends

Figure 1. Representative recordings of the systemic arterial pressure, central venous pressure, heart rate, portal venous pressure, and portal venous blood flow after an intravenous injection of the antigen of ovalbumin (0.6 mg) in a control rat (A), and a prazosin-pretreated rat (B).

Figure 2. Summary of the changes in the systemic arterial pressure (A), portal venous pressure (B), portal venous blood flow (C), portal venous resistance (D), and splanchnic vascular resistance (E) after an injection of the ovalbumin antigen. Closed circle, control group (n=6); open square, prazosin group (n=6); open triangle, phentolamine group (n=6); open diamond, 6-OHDA group (n=6); open circle, hepatic sympathetectomy group (n=6); closed triangle, non-sensitized group (n=6); closed diamond, 6-OHDA non-sensitized group (n=6). Values are means ± SEM; *P<0.05 vs. baseline; each point of variables for the α-adrenoceptor antagonist and chemical sympathetectomy groups during the time indicated by the black bar in Figs. 2A-D is significantly different from the corresponding baseline value except for the non-sensitized and 6-OHDA non-sensitized groups. #P<0.05 vs. the control group; Each point of variables during the time indicated by the white bar in Figs. 2A and 2E is significantly different from the corresponding value in the control group except for the hepatic sympathetectomy group.

Figure 3. Representative recordings of the systemic arterial pressure, heart rate, portal venous pressure, hepatic sympathetic nerve activity, and integrated hepatic sympathetic nerve activity after an intravenous injection of the antigen of ovalbumin (0.6 mg) to a sensitized rat (A) and a non-sensitized rat (B).

Figure 4. Summary of the changes in the systemic arterial pressure (A), portal venous
pressure (B), and hepatic sympathetic nerve activity (C) after an injection of the ovalbumin antigen. Closed circle, the sensitized rats (n=6); closed triangle, the non-sensitized rats (n=6); Values are means ± SEM; *P<0.05 vs. baseline; #P<0.05 vs. the non-sensitized rats.

Figure 5. Summary of the plasma norepinephrine levels (A), plasma epinephrine levels (B), and mean systemic arterial pressure (C) after an injection of the ovalbumin antigen. Open diamond, the 6-OHDA pretreated rats (n=5); closed circle, the control sensitized rats (n=5); closed triangle, the non-sensitized rats (n=5); Values are means ± SEM; *P<0.05 vs. baseline; #P<0.05 vs. the sensitized rats.
Figure 1

A

Systemic arterial pressure (mmHg)

Central venous pressure (mmHg)

Heart rate (beats/min)

Portal venous pressure (mmHg)

Portal venous blood flow (ml/min)

B

Systemic arterial pressure (mmHg)

Central venous pressure (mmHg)

Heart rate (beats/min)

Portal venous pressure (mmHg)

Portal venous blood flow (ml/min)
Figure 2

A. Systemic arterial pressure (mmHg).

B. Portal venous pressure (mmHg).

C. Portal venous blood flow (ml/min).

D. Portal venous resistance (mmHg.min/ml).

E. Splanchnic vascular resistance (mmHg.min/ml).
Figure 3

A

- Systemic arterial pressure (mmHg)
  - 200
  - 150
  - 100
  - 50
  - 0

- Heart rate (beats/min)
  - 600
  - 400
  - 200
  - 0

- Portal venous pressure (mmHg)
  - 25
  - 20
  - 15
  - 10
  - 0

- Hepatic sympathetic nerve activity (μV)
  - 100
  - 50
  - 0
  - -50
  - -100

- Hepatic sympathetic nerve activity (integrals/τ)
  - 150
  - 100
  - 50

B

- Systemic arterial pressure (mmHg)
  - 200
  - 150
  - 100
  - 50
  - 0

- Heart rate (beats/min)
  - 600
  - 400
  - 200
  - 0

- Portal venous pressure (mmHg)
  - 25
  - 20
  - 15
  - 10
  - 0

- Hepatic sympathetic nerve activity (μV)
  - 100
  - 50
  - 0
  - -50
  - -100

- Hepatic sympathetic nerve activity (integrals/τ)
  - 150
  - 100
  - 50
Figure 5

A

Plasma norepinephrine (pg/ml)

Time after antigen (min)

B

Plasma epinephrine (pg/ml)

Time after antigen (min)

C

Systemic arterial pressure (mmHg)

Time after antigen (min)
### Table 1. The basal levels of the variables before and after administration of α-adrenoceptor antagonists or saline

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control (n=6)</th>
<th>Prazosin (n=6)</th>
<th>Phentolamine (n=6)</th>
<th>6-OHDA (n=6)</th>
<th>Hepatic sympathectomy (n=6)</th>
<th>Non-sensitized (n=6)</th>
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<td></td>
<td>121.5±4.0</td>
<td>123.9±3.5</td>
<td>124.1±2.3</td>
<td>90.7±8.3*#</td>
<td>123.7±4.2</td>
<td>90.6±8.6*#</td>
<td>103.2±3.3</td>
</tr>
<tr>
<td>Systemic arterial pressure (mmHg)</td>
<td>3.0±0.3</td>
<td>3.1±0.2</td>
<td>2.8±0.2</td>
<td>2.5±0.2</td>
<td>2.5±0.2</td>
<td>2.1±0.2</td>
<td>3.2±0.1</td>
</tr>
<tr>
<td>Central venous pressure (mmHg)</td>
<td>380±20</td>
<td>370±28</td>
<td>412±15</td>
<td>391±13</td>
<td>393±16</td>
<td>392±19</td>
<td>372±11</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>5.9±0.1</td>
<td>5.8±0.2</td>
<td>5.3±0.3</td>
<td>4.4±0.2#</td>
<td>5.4±0.4</td>
<td>4.7±0.5</td>
<td>5.8±0.2</td>
</tr>
<tr>
<td>Portal venous pressure (mmHg)</td>
<td>25.8±1.9</td>
<td>24.6±1.6</td>
<td>27.0±2.1</td>
<td>20.4±1.7</td>
<td>26.1±2.0</td>
<td>19.7±2.3</td>
<td>31.4±1.4</td>
</tr>
<tr>
<td>Mean portal venous blood flow (ml/min)</td>
<td>4.6±0.3</td>
<td>4.9±0.3</td>
<td>4.4±0.3</td>
<td>4.2±0.3</td>
<td>4.7±0.4</td>
<td>4.5±0.5</td>
<td>3.4±0.2#</td>
</tr>
<tr>
<td>Splanchnic vascular resistance (mmHg*min/ml)</td>
<td>0.11±0.02</td>
<td>0.11±0.02</td>
<td>0.09±0.02</td>
<td>0.10±0.02</td>
<td>0.11±0.01</td>
<td>0.14±0.03</td>
<td>0.09±0.01</td>
</tr>
<tr>
<td>Portal venous resistance (mmHg*min/ml)</td>
<td>0.11±0.02</td>
<td>0.11±0.02</td>
<td>0.09±0.02</td>
<td>0.10±0.02</td>
<td>0.11±0.01</td>
<td>0.14±0.03</td>
<td>0.09±0.01</td>
</tr>
</tbody>
</table>

Values are means ±SEM. In the control, non-sensitized, 6-OHDA, 6-OHDA non-sensitized, and hepatic sympathectomy groups, saline was injected instead of α-adrenoceptor antagonists. *p<0.05 vs. Before; #p<0.05 vs. the control group.