Portacaval shunting attenuates portal hypertension and systemic hypotension in rat anaphylactic shock

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Abstract Anaphylactic shock in rats is characterized by antigen-induced hepatic venoconstriction and the resultant portal hypertension. We determined the role of portal hypertension in anaphylactic hypotension by using the side-to-side portacaval shunt- and sham-operated rats sensitized with ovalbumin (1 mg). We measured the mean arterial blood pressure (MAP), portal venous pressure (PVP), and central venous pressure (CVP) under pentobarbital anesthesia and spontaneous breathing. Anaphylactic hypotension was induced by an intravenous injection of ovalbumin (0.6 mg). In sham rats, the antigen caused not only an increase in PVP from 11.3 cmH2O to the peak of 27.9 cmH2O but also a decrease in MAP from 103 mmHg to the lowest value of 41 mmHg. CVP also decreased significantly after the antigen. In the portacaval shunt rats, in response to the antigen, PVP increased slightly, but significantly, to the peak of 17.5 cmH2O, CVP did not decrease, and MAP decreased to a lesser degree with the lowest value being 60 mmHg. These results suggest that the portacaval shunt attenuated anaphylactic portal hypertension and venous return decrease, partially preventing anaphylactic hypotension. In conclusion, portal hypertension is involved in rat anaphylactic hypotension presumably via splanchnic congestion resulting in decreased venous return and thus systemic arterial hypotension.

Keywords Anaphylaxis · Hepatic circulation · Portal hypertension · Splanchnic congestion

Introduction

Anaphylactic hypotension is primarily caused by alterations in the systemic circulation that decrease blood flow to the heart, which is partly ascribed to hypovolemia presumably due to a decrease in effective circulating blood volume [1, 2]. This reduction of effective blood volume could be caused by vasodilation with the peripheral pooling and increased vascular permeability with a shift of intravascular fluid to the extravascular space [1, 2].

Anaphylactic shock in rats is characterized by antigen-induced hepatic venoconstriction and the resultant portal hypertension [3, 4]. We have proposed that anaphylactic portal hypertension plays an important role in the pathogenesis of circulatory collapse [5]; the antigen-induced hepatic venoconstriction causes an increase in portal venous pressure with resultant pooling of blood in upstream splanchnic organs, leading to decreased venous return. If the vascular permeability of the splanchnic vascular beds is increased by anaphylactic mediators [6, 7], the plasma extravasation is augmented, resulting in decreases in circulating blood volume and venous return. Indeed, we previously reported that the elimination of hepatic and splanchnic circulation by ligation of the celiac and mesenteric arteries combined with total hepatectomy attenuated the antigen-induced reduction of arterial blood pressure [4]. However, this acute surgical resection of liver and splanchnic vascular beds was invasive and could reduce the whole vascular surface area beds and produce non-physiological blood flow redistribution. Furthermore, elimination of the splanchnic vascular beds may also
reduce the total numbers of the anaphylaxis-associated effector cell, i.e., mast cells that are distributed abundantly in the mesentery and liver [8–10], and therefore the amount of anaphylactic chemical mediators released. This might have diminished the hemodynamic response to the antigen.

Thus, we here adopted the portacaval shunt in order to eliminate portal hypertension induced by anaphylactic hepatic venoconstriction, and determined the role of portal hypertension in anaphylactic hypotension of anesthetized rats.

Materials and methods

Thirty male Sprague-Dawley rats (Japan SLC, Shizuoka, Japan) weighing 309 ± 13 (SD) g were used in this study. Rats were maintained at 23°C and under pathogen-free conditions on a 12:12-h dark/light cycle, and allowed food and water ad libitum. The experiments conducted in the present study were approved by the Animal Research Committee of Kanazawa Medical University.

Rats were actively 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 physiological saline (0.5 ml). For non-sensitized control rats, complete Freund’s adjuvant (0.5 ml) without ovalbumin was injected.

Two weeks after sensitization, rats underwent either the side-to-side portacaval shunt or sham operation. The procedure for the side-to-side portacaval shunt in the rat was based on the method of Numata [11]. The abdomen was opened through a midline laparotomy. The intestines were retracted laterally to expose the portal vein and the inferior vena cava. The portal vein and the inferior vena cava were dissected from the surrounding tissues, and were hung up. Both of the veins were clamped together with a small double-angled Satinsky clamp. A small incision (6–8 mm) was made in both the portal vein and the inferior vena cava, and continuous sutures with 8-0 nylon were made. The clamps were then removed and the incision was closed. The approximate size of the long axis of the shunt was 5 mm. The sham-operated control rats underwent a similar abdominal surgery procedure, as did the portacaval shunt rats, i.e., handling of visceras, dissection, and clamping of the portal and caval veins for 10 min but without construction of the portacaval anastomosis. After closure of the incision, each rat received an intramuscular injection of a prophylactic antibiotic (gentamicin sulfate; 10 mg/kg). Both groups were then allowed to recover with free access to food and water.

Five or 6 days after the shunt operation, the rats were anesthetized with pentobarbital sodium (50 mg kg⁻¹, i.p.) and placed on a thermostatically controlled heating pad (ATC-101B; Unique Medical, Japan), which 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 initial dose) were given as necessary. The left carotid artery was catheterized to measure arterial blood pressure. The right external jugular vein was catheterized, and the catheter tip was positioned at the confluence of the superior vena cava and the right atrium. This catheter was used for an intravenous injection of antigen and measurement of the central venous pressure (CVP). Heart rate (HR) was measured by triggering the R wave of electrocardiogram. Following a midline incision at the lower abdomen, a catheter (ID 0.4 mm, OD 0.6 mm) was inserted into the portal vein via the cecal vein for continuous measurement of portal venous pressure. After closure of the abdomen, the baseline measurements were started. The sensitized and non-sensitized control rats were randomly divided into the portacaval shunt-operated and sham-operated groups. Thus, the in vivo rats were randomly assigned to one of the following four groups: shunt sensitized (n = 10), shunt control (n = 5), sham sensitized (n = 10), and sham control (n = 5) groups.

The arterial blood pressure, CVP, portal venous pressure and HR were continuously measured with pressure transducers (TP-400T; Nihon-Kohden, Japan). These pressures were continuously displayed on a thermal physiograph (RMP-6008; Nihon-Kohden). Outputs were also digitally recorded at 40 Hz by PowerLab (AD Instruments), and mean arterial blood pressure (MAP) and mean portal venous pressure (PVP) were obtained. The values of CVP were that measured at expiration. Hemodynamic parameters were observed for at least 20 min after surgery until a stable state was obtained. After the baseline measurements for 10 min, 0.6 mg of the ovalbumin antigen (0.3 ml in saline) was intravenously administered as a bolus via the jugular vein catheter. Then, the hemodynamic parameters were observed until 60 min after antigen administration.

All results are expressed as the mean ± SD. Statistical analyses for the data within a group were performed with repeated measures two-way analysis of variance, and a P value less than 0.05 was considered significant. When a significant difference was obtained, post hoc analysis was performed with the Bonferroni post-test method. Statistical analyses for the data between groups were performed with one-way analysis of variance, followed by the Bonferroni post-test method.

Results

Table 1 shows the baseline values of the hemodynamic variables of all 4 groups studied. There were no significant
MAP mean arterial blood pressure, ± Values are given as mean *P ± 84 41 351 then continued to decrease progressively to the nadir of ± 103 14 2 min after antigen, and CVP. MAP rapidly decreased from the baseline of 12 17.5 1.5 108 5 mmHg at 60 min. PVP increased from the baseline of 9.0 ± 1.3 cm H2O to the peak of 27.9 ± 3.8 cm H2O at 2 min after antigen, and then gradually decreased to 14.4 ± 1.7 cm H2O at 7 min. After that, PVP remained at this level, which was not significantly different from the baseline. Concomitant with the antigen-induced increase in PVP, CVP decreased significantly from the baseline of 5.3 cm H2O at 2 min after antigen, as shown in Figs. 1b and 2. PVP value of the shunt sensitized group was significantly smaller than that of the sham sensitized group, 41 ± 5 mmHg.

HR did not change significantly after antigen in any groups studied (Table 1). In either the sham control group or the shunt control group, the hemodynamic variables did not significantly change from the baseline after antigen injection, as shown in Fig. 2.

Discussion

The major finding of the present study was that the side-to-side portacaval shunt attenuated the antigen-induced decrease in MAP in anesthetized rats sensitized with ovalbumin. This finding is consistent with that of our previous study showing that surgical elimination of the blood flow to the liver and the splanchnic vascular beds attenuated anaphylactic hypotension in anesthetized rats [4]. Thus, the present result has reinforced the assumption that portal hypertension induced by anaphylactic hepatic venoconstriction is involved in anaphylactic hypotension in rats [4].

The beneficial effect of the portacaval shunt on the anaphylactic hypotension can be ascribed to prevention of splanchnic congestion following portal hypertension induced by anaphylactic hepatic venoconstriction. We assume that anaphylactic portal hypertension causes congestion of the upstream splanchnic organs, with resultant decrease in effective circulating blood volume. Moreover, portal hypertension could cause an increase in the capillary pressure of the splanchnic organs, which then increases fluid extravasation from the splanchnic vascular beds, resulting in a further decrease in effective circulating blood volume. Furthermore, if systemic anaphylaxis increased vascular permeability of the splanchnic vascular beds [6, 7], this increased splanchnic capillary pressure further augmented the increased transvascular fluid movement. Portacaval shunt might shift the blood flow from the portal veins to the vena cava inferior, resulting in maintenance of

Table 1  The baseline levels of the hemodynamic variables

| Groups          | Shunt sensitized (n = 10) | Sham sensitized (n = 10) | Shunt control (n = 5) | Sham control (n = 5) |
|-----------------|--------------------------|-------------------------|----------------------|---------------------|
| MAP (mmHg)      | 108 ± 12                 | 103 ± 12                | 109 ± 12             | 112 ± 17            |
| PVP (cmH2O)     | 9.2 ± 1.3*               | 11.3 ± 1.4              | 8.5 ± 2.0*           | 11.0 ± 1.4          |
| CVP (cmH2O)     | 1.6 ± 0.9                | 1.5 ± 1.0               | 1.8 ± 0.6            | 1.6 ± 0.5           |
| HR (beats/min)  | 429 ± 24                 | 452 ± 55                | 419 ± 30             | 420 ± 54            |

Values are given as mean ± SD

MAP mean arterial blood pressure, PVP mean portal venous pressure, CVP central venous pressure, HR heart rate

* P < 0.007 versus the sham groups
effective circulating blood volume and then the venous return. In contrast to the decreased CVP after antigen in the sham sensitized group, the absence of a decrease of CVP in the shunt sensitized group suggests the maintenance of the venous return.

It remains uncertain whether portal hypertension or anaphylactic hepatic venoconstriction plays a similar crucial role in human anaphylactic shock. Actually, there is no clinical study in which PVP was measured during anaphylactic shock in humans. However, anaphylactic hepatic venoconstriction, based on an increase in PVP, was observed in rat [4, 12], guinea pig [13], mouse [14], rabbit [15] and dog [16, 17]. Further study is required to determine whether hepatic venoconstriction or PVP increase is observed in humans suffering from anaphylactic shock.

In the present study, the portacaval shunting definitely attenuated, but did not abolish, anaphylactic hypotension. This indicates that the mechanisms other than portal hypertension should be responsible for the antigen-induced decrease in MAP in rats. There are several possibilities. First, it is reported that histamine, serotonin and nitric oxide are involved in the initial decrease in MAP after ovalbumin antigen in the sensitized Brown Norway rats [18]. Indeed, either histamine or serotonin administered intravenously into the anesthetized rats caused a short-lasting decrease in MAP, presumably due to dilatation of systemic arterioles [18]. We also found, by continuously measuring the aortic blood flow, MAP and CVP, that a transient decrease in total peripheral resistance, a finding consistent with arteriolar dilatation, occurs immediately after antigen in anesthetized SD rats [19]. The second possibility is the circulating blood volume reduction which was induced by increased plasma extravasation due to increased vascular permeability [20–22]. Indeed, in a similar rat model of anaphylactic hypotension, we demonstrated that the hematocrit increased markedly from 43 to 55% at 15 min after antigen [3]. The third possibility is related to cardiac dysfunction: cardiac dysfunction was reported during cardiac anaphylaxis in isolated rat hearts perfused with blood-free solutions [23]. Finally, anaphylactic pulmonary vasoconstriction and resultant right heart overload could decrease the venous return and then MAP [1]. However, in rats, pulmonary vasoconstriction was very weak during systemic anaphylaxis [19], and this possibility is unlikely. Further study is required to clarify the hemodynamic mechanism for anaphylactic shock.

In summary, we determined the roles of portal hypertension in the anaphylactic hypotension in anesthetized rats sensitized with ovalbumin. An intravenous injection of the antigen caused not only decreases in MAP and CVP but...
also an increase in PVP. The attenuation of portal hypertension by introduction of the side-to-side portacaval shunt ameliorated the antigen-induced decreases in MAP and CVP. Based on these findings, we conclude that portal hypertension is partly involved in anaphylactic hypotension: portal hypertension induced by anaphylactic hepatic venoconstriction and subsequent splanchnic congestion may cause a decrease in the venous return and then anaphylactic hypotension.

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