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Hepatic venoconstriction is involved in anaphylactic hypotension in rats

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Shibamoto, Toshishige, Sen Cui, Zonghai Ruan, Wei Liu, Hiromichi Takano, and Yasutaka Kurata. Hepatic venoconstriction is involved in anaphylactic hypotension in rats. *Am J Physiol Heart Circ Physiol* 289: H1436–H1444, 2005. First published May 27, 2005; doi:10.1152/ajpheart.00368.2005.—We determined the roles of liver and splanchnic vascular bed in anaphylactic hypotension in anesthetized rats and the effects of anaphylaxis on hepatic vascular resistances and liver weight in isolated perfused rat livers. In anesthetized rats sensitized with ovalbumin (1 mg), an intravenous injection of 0.6 mg ovalbumin caused not only a decrease in systemic arterial pressure from 120 ± 9 to 43 ± 10 mmHg but also an increase in portal venous pressure that persisted for 20 min after the antigen injection (the portal hypertension phase). The elimination of the splanchnic vascular beds, by the occlusions of the celiac and mesenteric arteries, combined with total hepatectomy attenuated anaphylactic hypotension during the portal hypertension phase. For the isolated perfused rat liver experiment, the livers derived from sensitized rats were hemoperfused via the portal vein at a constant flow. Using the double-occlusion technique to estimate the hepatic sinusoidal pressure, presinusoidal (R_{pre}) and postsinusoidal (R_{post}) resistances were calculated. An injection of antigen (0.015 mg) caused venoconstriction characterized by an almost selective increase in R_{pre} rather than R_{post} and liver weight loss. Taken together, these results suggest that liver and splanchnic vascular beds are involved in anaphylactic hypotension presumably because of anaphylactic presinusoidal contraction-induced portal hypertension, which induced splanchnic congestion resulting in a decrease in circulating blood volume and thus systemic arterial hypotension.

isolated perfused rat liver; anaphylaxis; hepatic circulation; portal hypertension; splanchnic congestion

ANAPHYLACTIC HYPOTENSION is primarily caused by alterations in the systemic circulation that decrease blood flow to the heart because left ventricular function is relatively well preserved during anaphylactic shock (4). Peripheral circulatory collapse is ascribed to hypovolemia, which results from a decrease in effective circulating blood volume. The latter could be because of vasodilation with the peripheral pooling and increased vascular permeability with a shift of intravascular fluid to the extravascular space (2).

In canine experimental models of anaphylactic shock, an increase in resistance to venous return is important in the pathogenesis of circulatory collapse (23); increased venous resistance decreases venous return with resultant decrease in stroke volume and systemic arterial pressure (P_{sa}). Indeed, eviscerated dogs did not develop anaphylactic shock (13). In addition, Enjeti et al. (5) reported that the severity of the anaphylactic shock could be decreased by occluding the descending aorta. In dogs, anaphylaxis-induced increase in venous resistance is partly caused by hepatic vasoconstriction, especially selective constriction of postsinusoidal hepatic veins

in dogs (26). Indeed, anaphylaxis-induced hepatic venous constriction induces pooling of blood in liver itself, as well as in upstream splanchnic organs. However, in the rat, the roles of the splanchnic bed, and particularly the liver, are not known in the pathogenesis of anaphylactic hypotension, although, in the rat, portal venous pressure (P_{pv}) was increased during anaphylactic hypotension induced by ovalbumin (8). Thus the first purpose of the present study was to determine whether lesions of liver and splanchnic vascular bed contribute to anaphylactic hypotension in anesthetized rats. To resolve this question, P_{sa} changes were observed in sensitized rats with and without hepatic and splanchnic circulation after the antigen was intravenously administered.

In addition to canine livers (26), the guinea pig liver shows the anaphylactic response characterized by significant contraction of postsinusoidal vessel with resultant hepatic congestion (16). On the other hand, it is not known whether anaphylactic reaction in rats causes constriction of postsinusoidal hepatic veins, resulting in hepatic congestion, although anaphylactic venoconstriction is observed in isolated perfused livers of the sensitized rats (8). To clarify the anaphylactic disturbance of hepatic circulation, we herein established anaphylactic models of isolated portally perfused rat livers in which the sinusoidal pressure was measured by the double-occlusion method (20, 26). Thus the second purpose of the present study was to determine effects of anaphylaxis on hepatic vascular resistance distribution and liver weight in isolated perfused rat livers.

MATERIALS AND METHODS

Animals. Forty eight male Sprague-Dawley rats (Japan SLC, Shi-zuoka, Japan) weighing 372 ± 28 g were used in this study. Rats were maintained at 23°C 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.

Sensitization. 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). Nonsensitized rats were injected with complete Freund's adjuvant and ovalbumin-free saline. After injection (2 wk), the rats were used for the following in vivo or isolated perfused liver experiments.

In vivo experiment. After sensitization (2 wk), 35 rats were anesthetized with pentobarbital sodium (70 mg/kg ip) and placed on a thermostatically controlled heating pad (ATC-101B; Unique Medical) 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 initial dose) were given as necessary. The left carotid artery was catheterized to measure P_{sa} . The right external jugular vein was

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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 (P_{cv}). Heart rate (HR) was measured by triggering the R wave of the electrocardiogram. The sensitized and nonsensitized animals were randomly divided into rats with gastrointestinal isolation and hepatectomy (GI-HptX) and intact rats. Thus the *in vivo* rats were randomly assigned to one of the following four groups: GI-HptX sensitized ($n = 11$), GI-HptX control ($n = 7$), intact sensitized ($n = 10$), and intact control ($n = 7$) groups. In the GI-HptX rats, through a 4-cm midline incision, ligation of the celiac artery and the mesenteric artery was followed by total hepatectomy, which consisted of resection of the median and left lateral lobe, the right lateral lobes, and the caudate lobes, as described by Gaub and Iversen (7). In the intact rats, after a midline incision, a catheter (0.47 mm ID, 0.67 mm OD) was inserted in the main portal vein without occlusion of the portal vein for continuous measurement of the P_{pv} . After closure of the abdomen, the baseline measurements were started.

The P_{sa} , P_{cv} , P_{pv} , and HR were continuously measured with pressure transducers (TP-400T; Nihon-Kohden) in the intact rats; P_{sa} , P_{cv} , and HR, but not P_{pv} , were measured in the GI-HptX rats. These pressures were continuously displayed on a thermal physiograph (RMP-6008; Nihon-Kohden). Outputs were also digitally recorded at 20 samples/s (PowerLab; ADInstruments). Hemodynamic parameters were observed for at least 20 min after surgery until a stable state was obtained. After the baseline measurements, 0.6 mg ovalbumin antigen was administered via the jugular vein catheter.

Isolated liver experiment. After sensitization (2 wk), these animals were anesthetized with pentobarbital sodium (70 mg/kg ip) and mechanically ventilated with room air. The basic methods for isolated perfused rat livers were described previously (18). In brief, a catheter was placed in the right carotid artery for later hemorrhage to obtain autologous blood for liver perfusion. After laparotomy, the hepatic artery was ligated, and the bile duct was cannulated with the polyethylene tube (0.5 mm ID, 0.8 mm OD). After intra-arterial heparinization (500 U/kg), 7–8 ml blood were withdrawn through the carotid arterial catheter. The intra-abdominal inferior vena cava (IVC) above the renal veins was ligated, and the portal vein was cannulated with a stainless cannula (1.3 mm ID, 2.1 mm OD) for portal perfusion. After thoracotomy, the supradiaphragmatic IVC was cannulated through a right atrium incision with a large-size stainless cannula (2.1 mm ID, 3.0 mm OD), and then portal perfusion was begun with the autologous blood diluted with 5% bovine albumin (Sigma-Aldrich, St. Louis, MO) in Krebs-Henseleit solution (in mM: 118 NaCl, 5.9 KCl, 1.2 $MgSO_4$, 2.5 $CaCl_2$, 1.2 NaH_2PO_4 , 25.5 $NaHCO_3$, and 5.6 glucose) at Hct 8%. The liver was rapidly excised, suspended from an isometric transducer (TB-652T; Nihon-Kohden), and weighed continuously throughout the experimental period.

The livers were perfused at a constant flow rate in a recirculating manner via the portal vein with blood that was pumped using a Masterflex pump from the venous reservoir through a heat exchanger (37°C). The recirculating blood volume was 40 ml. The perfused blood was oxygenated in the venous reservoir by continuous bubbling with 95% O_2 and 5% CO_2 . P_{pv} and hepatic venous pressure (P_{hv}) were measured with pressure transducers (TP-400T; Nihon-Kohden) attached by sidearm to the appropriate cannulas with the reference points at the hepatic hilus. To occlude inflow and outflow perfusion lines simultaneously for measurement of the double-occlusion pressure (P_{do}), two solenoid valves were placed in such a position that each sidearm cannula was between the corresponding solenoid valve and the liver. Portal blood flow rate (Q_{pv}) was measured with an electromagnetic flowmeter (MFV 1200; Nihon-Kohden), and the flow probe was positioned in the inflow line. Bile was collected drop by drop in a small tube suspended from the force transducer (SB-1T; Nihon-Kohden). One bile drop yielded 0.018 g, and the time between drops was measured for determination of the bile flow rate (11). The P_{pv} , P_{hv} , Q_{pv} , liver weight, and bile weight were monitored continu-

ously and displayed through a thermal physiograph (RMP-6008; Nihon-Kohden). Outputs were also digitized by the analog-digital converter at a sampling rate of 100 Hz. These digitized values were displayed and recorded using a personal computer for later determination of P_{do} .

Hepatic hemodynamic parameters were observed for at least 20 min after the start of perfusion until an isogravimetric state (no weight gain or loss) was obtained by adjusting Q_{pv} and the height of the reservoir at a P_{hv} of 0–1 cmH₂O and at a Q_{pv} of 37 ± 6 ml·min⁻¹·10 g liver wt⁻¹. After the baseline measurements, the perfused livers excised from the sensitized rats (anaphylaxis group, $n = 7$) and nonsensitized rats (control group, $n = 6$) were challenged with 0.015 mg ovalbumin injected in the reservoir.

The hepatic sinusoidal pressure was measured by the double-occlusion method (20, 26). Both the inflow and outflow lines were simultaneously and instantaneously occluded for 13 s using the solenoid valves, after which P_{pv} and P_{hv} rapidly equilibrated to a similar or identical pressure, which was P_{do} , using Liver software by Biomedical Science. In each experimental group, P_{do} was measured at baseline and at 3 and 6 min and then at 10-min intervals up to 30 min after antigen.

The total portal-hepatic venous (R_t) and presinusoidal (R_{pre}) and postsinusoidal (R_{post}) resistances were calculated as follows:

$$R_t = (P_{pv} - P_{hv})/Q_{pv} \quad (1)$$

$$R_{pre} = (P_{pv} - P_{do})/Q_{pv} \quad (2)$$

$$R_{post} = (P_{do} - P_{hv})/Q_{pv} \quad (3)$$

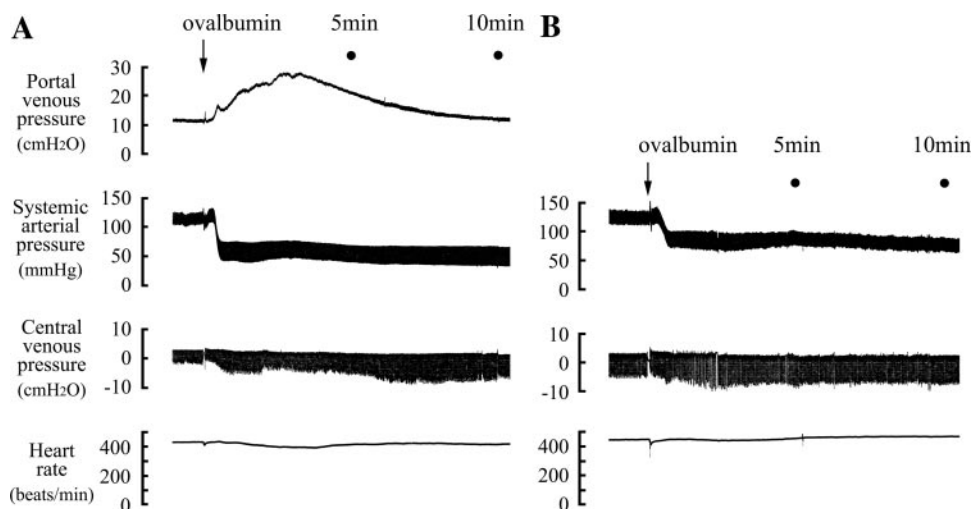
Statistics. All results are expressed as means $\pm$ SD. One-way ANOVA followed by Bonferroni's test was used to test for significant differences. Differences were considered as statistically significant at P values <0.05 .

RESULTS

The response of the anesthetized rats to antigen. Figure 1A shows a representative example of the response to an intravenous injection of the ovalbumin antigen in an anesthetized intact rat sensitized with ovalbumin (the intact sensitized group). Figure 2 shows the summary data of time course changes in P_{pv} and P_{sa} of all four groups of anesthetized rats. After an antigen injection in the intact sensitized group, P_{sa} and P_{pv} simultaneously began to increase and decrease, respectively. P_{sa} rapidly decreased from the baseline of 120 ± 9 to 65 ± 11 mmHg at 1 min after the antigen and then continued to decrease progressively to the nadir of 43 ± 10 mmHg at 16 min, followed by a gradual recovery to 79 ± 18 mmHg at 60 min. P_{pv} increased from the baseline of 9.8 ± 0.9 cmH₂O to the peak of 24.3 ± 4.6 cmH₂O at 2.5 min after antigen and then gradually decreased to 10.9 ± 1.9 cmH₂O at 20 min. After that, P_{pv} remained at this level, which was not significantly different from the baseline. The postantigen period of up to 20 min during which P_{pv} remained elevated above the baseline (Fig. 2) was designated as the portal hypertension phase in the present study.

The surgical procedures of ligation of the celiac and the mesenteric arteries combined with total hepatectomy (GI-HptX) did not significantly affect the hemodynamic variables. Although P_{sa} transiently increased immediately after occlusion of the arteries, it returned to the pre-GI-HptX level during the baseline measurement after hepatectomy. Figure 1B shows a representative example in the GI-HptX sensitized group. The mean P_{sa} rapidly decreased from the baseline of 117 ± 12 to 80 ± 15 mmHg at 1 min. These levels were significantly

Fig. 1. Representative recording of the response to ovalbumin antigen (0.6 mg) in the intact sensitized group (A) and the gastrointestinal isolation and hepatectomy (GI-HptX) sensitized group (B). Portal venous pressure was not measured in the GI-HptX sensitized group because of no blood flow in the portal veins resulting from liver resection.



higher than the corresponding values of the intact sensitized group of 65 ± 11 mmHg. Thereafter, it did not further decrease but remained at this level throughout the experimental period, as shown in Fig. 2. Thus P_{sa} from 1 to 20 min after antigen in the GI-HptX sensitized group was significantly greater than that in the intact sensitized group. It should be noted that this period corresponded to the portal hypertension phase.

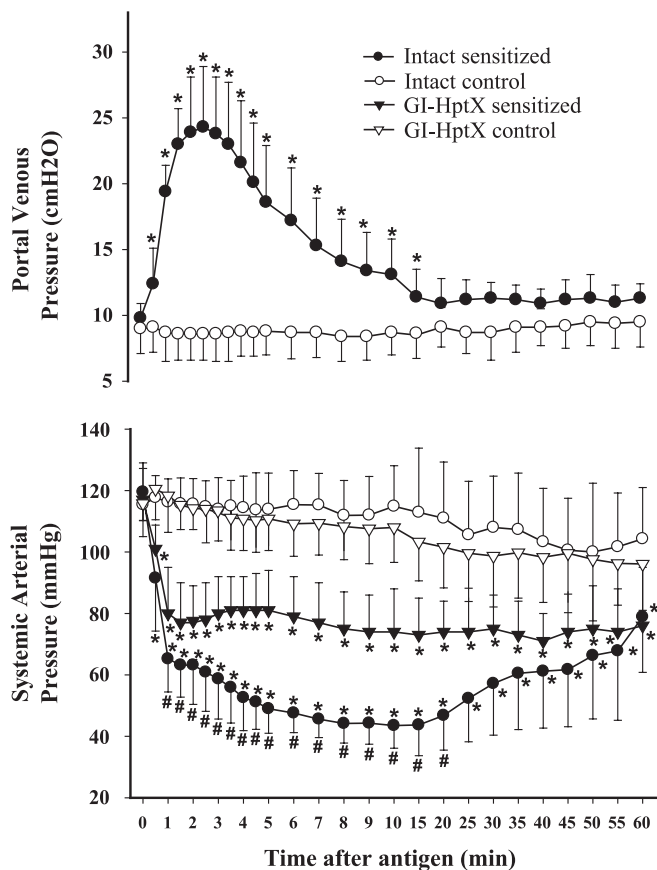


Fig. 2. Summary of changes in the systemic arterial pressure (P_{sa}) and portal venous pressure (P_{pv}) after antigen injection. Means $\pm$ SD; * $P < 0.05$ vs. baseline; # $P < 0.05$ vs. the intact sensitized group. P_{pv} was not measured in either the GI-HptX control or the GI-HptX sensitized group because the liver was excised.

At 10 min after antigen, P_{cv} in the intact sensitized group was significantly decreased from the baseline of 1.2 ± 0.3 to 0.1 ± 0.3 cmH₂O, whereas in the GI-HptX sensitized group, P_{cv} tended to decrease, but not significantly, from 0.8 ± 0.4 to 0.4 ± 0.8 cmH₂O. The changes in P_{cv} between the intact sensitized and GI-HptX sensitized groups at 10 min after antigen were significantly different (1.0 ± 0.3 vs. 0.4 ± 0.6 cmH₂O; $P < 0.05$). HR was not significantly changed after antigen in any groups studied, as shown in Fig. 1. Neither the P_{sa} nor the P_{pv} was significantly changed by the antigen in the control animals during the experimental periods of both the intact and GI-HptX groups (Fig. 2).

The response of the blood-perfused livers to antigen. The liver weight measured at the end of the perfusion experiment in the control and anaphylaxis groups was 9.3 ± 1.4 g ($n = 6$) and 9.0 ± 0.6 g ($n = 7$), respectively. The body weight in the control group was 0.288 ± 0.012 kg ($n = 6$), and that in the anaphylaxis group was 0.287 ± 0.021 kg ($n = 7$). There were no significant differences in the liver weight and body weight between the two groups. The liver weight-to-body weight ratio of all animals for the isolated perfusion study was 31.8 ± 3.1 g liver/kg body wt ($n = 13$).

An antigen injection caused hepatic venoconstriction, which was characterized by predominant presinusoidal constriction and liver weight loss, as shown in Fig. 3. Within 1 min after antigen, venoconstriction was evident by an increased P_{pv} that reached the peak value of 21.4 ± 4.9 cmH₂O from the baseline of 6.9 ± 0.1 cmH₂O (Fig. 4). The double-occlusion maneuver performed at 3 min after antigen revealed a P_{do} of 3.3 ± 0.3 cmH₂O that was significantly higher than that of the baseline of 2.3 ± 0.1 cmH₂O. Therefore, the P_{pv} -to- P_{do} gradient (in conjunction with the flow) defined the portal presinusoidal resistance (R_{pre} , Eq. 2). This resistance increased markedly from a baseline of 4.7 ± 0.2 to 18.1 ± 4.9 cmH₂O, whereas the P_{do} -to- P_{hv} gradient, the indicator of R_{post} , increased minimally, but significantly, from the baseline of 1.8 ± 0.1 to 2.8 ± 0.3 cmH₂O (Fig. 4). Thus R_{pre} increased by 250% the baseline from 0.13 ± 0.02 to 0.52 ± 0.19 cmH₂O $\cdot$ ml⁻¹ $\cdot$ min⁻¹ $\cdot$ 10 g liver wt⁻¹, whereas R_{post} increased by only 67% from the baseline level of 0.05 ± 0.01 to 0.08 ± 0.01 cmH₂O $\cdot$ ml⁻¹ $\cdot$ min⁻¹ $\cdot$ 10 g liver wt⁻¹ (Fig. 4). This indicates that an injection of the antigen almost selectively increased R_{pre} rather than

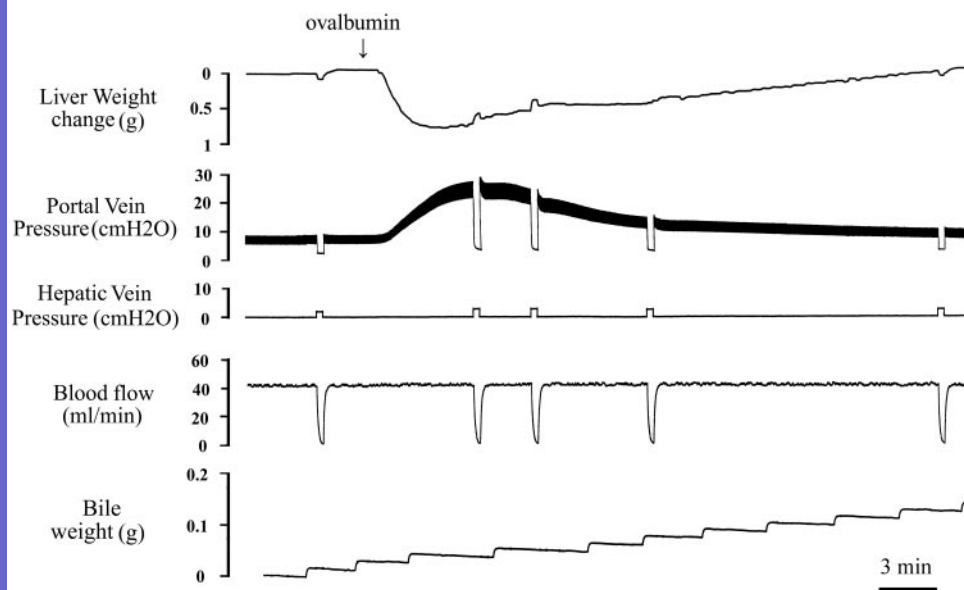


Fig. 3. Representative recording of the response to ovalbumin antigen (0.015 mg) in the blood-perfused liver isolated from a sensitized rat.

R_{post} , as reflected by a significant increase in the R_{pre} -to- R_{t} ratio from the baseline of 0.72 ± 0.01 to 0.86 ± 0.05 . P_{pv} , and thus R_{t} , returned to the baseline at 30 min after antigen. Concomitant with venoconstriction, the liver weight showed a gradual decrease, reaching the nadir, -0.5 ± 0.4 g/10 g liver wt, at 3 min. Along with P_{pv} , the liver weight returned to the baseline at 30 min after antigen. The bile flow decreased to 67% of the baseline level of 0.01 ± 0.001 g $\cdot$ min $^{-1}$ $\cdot$ 10 g liver wt $^{-1}$ during the maximal venoconstriction. In the control rat liver, no hemodynamic variables changed significantly after antigen (Fig. 4).

DISCUSSION

There are two major findings of the present study. The first finding (derived from the anesthetized rat experiments) is that

elimination of the blood flow to the liver and splanchnic organs attenuated the antigen-induced decrease in P_{sa} during the portal hypertension phase. Another finding (derived from the isolated perfused rat liver experiments) is that hepatic anaphylactic venoconstriction is characterized by almost selective presinusoidal constriction and liver weight loss.

Hepatic anaphylactic postsinusoidal venoconstriction plays a crucial role in anaphylactic hypotension in dogs (6). In the present study, we have shown that immunological damage to the liver and splanchnic vascular beds also participated in the anaphylactic hypotension in rats. This is based on the finding that the elimination of hepatic and splanchnic circulation by ligation of the celiac and the mesenteric arteries combined with total hepatectomy attenuated the antigen-induced reduction of P_{sa} (Fig. 2). The mechanism for the beneficial effect of GI-

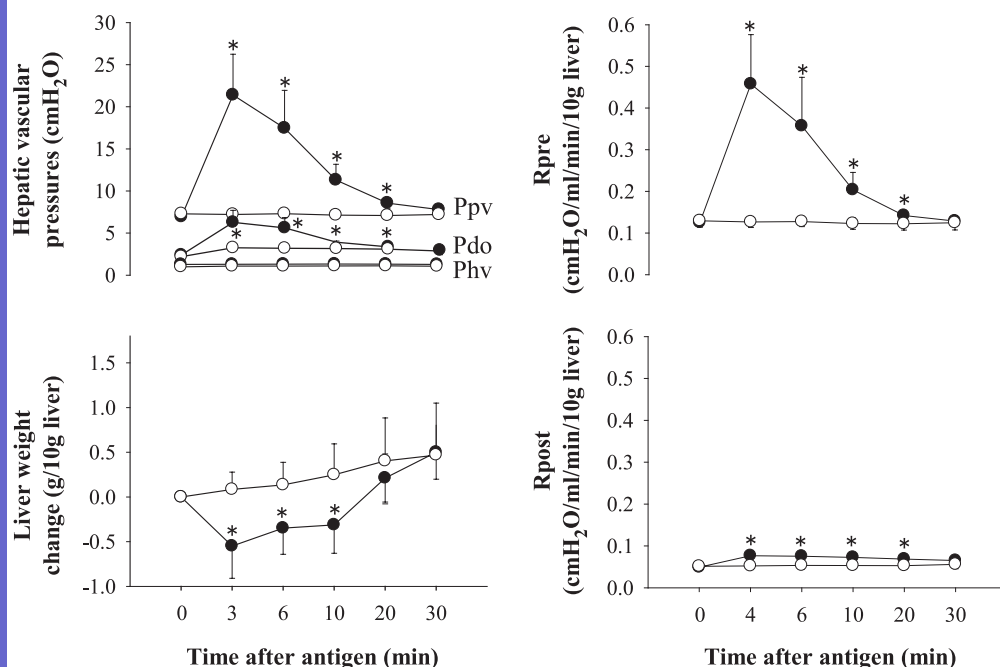


Fig. 4. Summary of changes in hepatic vascular pressures, liver weight changes, and pre (R_{pre})- and post (R_{post})-sinusoidal resistances after antigen injection in isolated perfused rat livers. Means $\pm$ SD; * P < 0.05 vs. baseline and the control group. P_{do} , double-occlusion pressure; P_{hv} , hepatic venous pressure; $\bullet$, anaphylaxis group; $\circ$, control group.

HptX on the anaphylactic hypotension is not known. However, we assume that anaphylaxis-induced portal hypertension may account for the profound decrease in P_{sa} because the period during which attenuation of anaphylactic hypotension was observed corresponded to the portal hypertension phase during which the elevation of P_{pv} was sustained (Fig. 2). We speculate the following pathophysiological process: anaphylaxis causes hepatic venoconstriction, as observed in the isolated perfused sensitized liver, resulting in portal hypertension that then causes congestion of the upstream splanchnic organs, with resultant decrease in venous return and effective circulating blood volume, and finally augmentation of anaphylactic hypotension.

Another possible explanation may be related to the sources of mast cells that release vasoactive chemical mediators in response to antigens. Although mast cells occur throughout most tissues, they are more prevalent in gastrointestinal tract as well as the skin and lungs, the areas that come in contact with the external environment (14). A large number of mast cells in the gastrointestinal tract, including liver and intestines, may release substantial amounts of anaphylactic vasoactive substances in the systemic circulation. The elimination of these sources by the procedure of GI-HptX might have decreased the release of the anaphylaxis-related chemical mediators, resulting in a weak anaphylactic response.

Finally, there is a third possibility that anaphylaxis might be associated with significant splanchnic arterial vasodilation, as observed when platelet-activating factor (PAF), one of the mediators of anaphylaxis, was injected in the conscious rats (21). Splanchnic arterial dilation could contribute to both the reduced systemic pressure and increased P_{pv} . Moreover, splanchnic arterial ligation would attenuate these responses. However, there is currently no data that demonstrated splanchnic arterial vasodilation during anaphylactic hypotension in rats.

With respect to the mechanism for the early stage of anaphylactic hypotension in anesthetized rats, Bellou et al. (1) reported that histamine, serotonin, and nitric oxide are involved in the initial decrease in P_{sa} after ovalbumin antigen in the sensitized Brown Norway rats. Actually, either histamine or serotonin administered intravenously in the anesthetized rats causes a short-lasting decrease in P_{sa} , presumably because of dilatation of systemic arterioles (1). The initial arterial hypotension after antigen in the GI-HptX sensitized rats might be induced by the same mechanism proposed by Bellou et al. (1).

Anaphylactic hepatic venoconstriction, based on an increase in P_{pv} , was observed in rats (8), guinea pigs (16), and dogs (25, 26). However, a species difference between dog and guinea pig has been found in the hepatic vascular segments that preferentially contract during anaphylaxis: selective postsinusoidal constriction occurs in sensitized canine livers (26), whereas predominant presinusoidal but significant and substantial postsinusoidal constriction occurs in guinea pig livers (16). Using isolated, perfused, and sensitized rat livers, we have shown that anaphylactic hepatic venoconstriction in rats was different from that in dogs or guinea pigs and was characterized by a large presinusoidal contraction and only a minimal postsinusoidal contraction based on the double-occlusion method (20, 26) to estimate the sinusoidal pressure (P_{do} ; see Figs. 3 and 4).

The mechanism for such a species-dependent response is not known. However, canine postsinusoidal hepatic veins anatom-

ically contain smooth muscle sphincters in hepatic initial sublobular veins (4). Maass-Moreno and Rothe (12) also reported that major pressure gradients must lie upstream from the large (>2 mm) hepatic veins in dogs. Indeed, these postsinusoidal veins vigorously contract in response to various mediators of anaphylactic reaction, such as histamine (22), thromboxane A_2 (22), and PAF (24). In guinea pig livers, the anaphylactic presinusoidal constriction may be caused mainly by PAF, whereas the postsinusoidal constriction is caused by cysteinyl leukotrienes (19). Actually, PAF predominantly contracts presinusoidal vessels in guinea pig livers (17). However, effects of anaphylaxis-related vasoactive substances are not currently known on the segmental vascular resistances of rat livers. Further study is required to identify the chemical mediators responsible for the anaphylactic hepatic venoconstriction in rats.

In contrast to the liver weight gain response to the antigen of dogs (26) and guinea pigs (16), a liver weight loss was induced by marked anaphylactic presinusoidal constriction in isolated perfused rat livers. With the constant perfusion of the liver, the mechanism of the weight loss is unknown. This liver weight loss may be the result of hepatic vascular blood loss. Theoretically, the interstitial fluid volume loss also could contribute to a liver weight loss (10). Further study is required in this respect.

There are limitations of the present study. The first is related to the finding that the HR was high at baseline, as shown in Fig. 1, and that HR did not change in response to the marked drop in blood pressure during the anaphylactic shock. One of the reasons for high HR could be ascribed to the vagolytic property of pentobarbital sodium used in the present study (15). It is reported that pentobarbital decreases cardioinhibitory parasympathetic activity that dominates the control of HR (15). Indeed, in the pentobarbital-anesthetized rat study of others (3), the basal HR showed ~ 400 beats/min, as observed in the present study. With respect to the absence of the increase in HR in response to the antigen-induced marked drop in P_{sa} , that is, impairment of normal arterial baroreceptor reflex, Koyama et al. (9) demonstrated that systemic baroreceptor reflex control of HR and renal sympathetic nerve activity is reduced during anaphylactic hypotension in pentobarbital-anesthetized dogs. A similar impairment of arterial baroreceptor reflex might occur in the rat anaphylactic shock. Another shortcoming is the absence of hepatic arterial perfusion in the present isolated perfused livers. Hepatic arterial perfusion with normally oxygenated blood would improve the metabolic milieu of the liver. However, the perfusate was well oxygenated by bubbling with 95% O_2 and 5% CO_2 , which provided perfusate oxygen tension of 290 ± 38 mmHg. Thus the isolated livers were perfused with hyperoxic blood, rather than hypoxic blood, and oxygenation was well done.

In summary, we determined the roles of splanchnic circulation in the anaphylactic hypotension in anesthetized rats sensitized with ovalbumin (1 mg). An intravenous injection of antigen (0.6 mg) caused not only a profound decrease in P_{sa} but also an increase in P_{pv} . The elimination of the splanchnic vascular beds, by the occlusions of the celiac and mesenteric arteries, combined with total hepatectomy attenuated anaphylactic hypotension during the portal hypertension phase. In addition, in isolated perfused sensitized rat livers, hepatic anaphylaxis caused almost selective presinusoidal constriction

and liver weight loss. Based on these findings, we conclude that liver and splanchnic vascular beds are partly involved in anaphylactic hypotension: anaphylactic presinusoidal contraction-induced portal hypertension and subsequent splanchnic congestion may cause a decrease in venous return and then hypotension.

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