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Liver Circulatory Response Caused by Prostaglandin E_1 in 90 Percent Hepatectomized Rats

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Summary. **The effects of prostaglandin E_1 (PGE) on portal venous blood flow (PVF) and hepatic arterial blood flow (HAF) were examined in hepatectomized rats. The jugular injection of PGE produced a dose-dependent increase in PVF in 90 percent hepatectomized rats. The magnitude of flow responses obtained in order of the PVF per wet liver weight due to PGE fell into the following order: the 66 percent hepatectomized rats, the 90 percent hepatectomized rats, and lastly, the 40 percent hepatectomized rats. Intramuscular injection of indomethacin failed to affect PVF in the 66 percent hepatectomized animals. PGE had no effect on HAF in hepatectomized rats.**

These results suggest that the PGE action on PVF is amplified according to the volume of liver resected, but such PGE action is diminished when 90 percent of the liver is resected, and endogenous prostaglandins are inactive in the hepatectomized situation.

Key words—prostaglandin, blood flow, hepatectomy, portal vein, rat.

INTRODUCTION

Increasing blood flow in the liver is important in providing an improved prognosis for liver disease, especially when the liver has been massively resected.[1,2] It has been shown that prostaglandin E_1 (PGE) increases portal venous blood flow (PVF) by dilating the vessels,[3,4] and that the action site of this agent is located in the superior mesenteric vascular bed.[5,6] Moreover, recent studies have revealed that PGE exerts a vasodilative effect on the portal vascular bed, and the PVF response due to PGE is amplified by hepatectomy.[7,8] However, in the above 66 percent hepatectomized condition, the effect of PGE on hepatic blood flow is unclear. On the other hand, effective concentrations of endogenous prostaglandins have been suggested in special pathological condition such as cell damage.[9]

This study was designed to investigate whether 90 percent hepatectomy influences the PGE effect on PVF, and to examine PVF following hepatectomy in relation to endogenous PGE activity.

MATERIALS AND METHODS

Forty-three male Wistar rats weighing 320-380 g were used. They had been kept for more than one week before the experiments in a room with a light-dark cycle of 12 : 12 with lighting on from 08 : 00 h, and at a temperature of 23.0±2.0°C. The animals were allowed free access to standard laboratory chow and tap water until immediately before the experiments. The experiments were performed in the afternoon between 13 : 00 and 18 : 00 h to eliminate diurnal changes in the animals associated with their circadian rhythm.

The animals were anesthetized with pentobarbital sodium (45 mg/kg, i.p.), and the depth of anesthesia was maintained with the same agent at 7.5 mg/kg, given subcutaneously every 30 min.[10] Tracheotomy was carried out to provide a patent airway. The PVF and hepatic arterial blood flow (HAF) were measured with a transit-time ultrasonic volume flowmeter (Transonic T201, Advance, NY, U.S.A.) connected to 2 mm RB probes.[8,11] The systemic arterial pressure (SAP) was recorded from the right carotid artery. Throughout the experiments, the rectal temperature was kept at 36.0±

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Table 1. Basal hepatic flow parameters following 0 (I), 40 (II), 66 (III) and 90 (IV) percent hepatectomy

	I	II	III	IV
PVF (ml/min)	13.8±1.3	9.7±1.7[a]	10.6±1.4[b]	4.0±0.1
HAF (ml/min)	5.7±0.2	5.2±0.1[c,d]	3.3±0.1	3.1±0.1
THF (ml/min)	19.2±1.3	14.5±1.5[e,f]	13.9±1.5[f]	7.2±0.2
HF/W(ml/min/g)	1.47±0.08	1.67±0.15	2.94±0.14[g]	2.41±0.11[g,h]

Values are the means ± SEM (n=6). [a]$p<0.01$ vs I and IV; [b]$p<0.01$ vs IV; [c]$p<0.05$ vs I; [d]$p<0.01$ vs III and IV; [e]$p<0.05$ vs I; [f]$p<0.01$ vs IV; [g]$p<0.01$ vs I and II; [h]$p<0.05$ vs III.

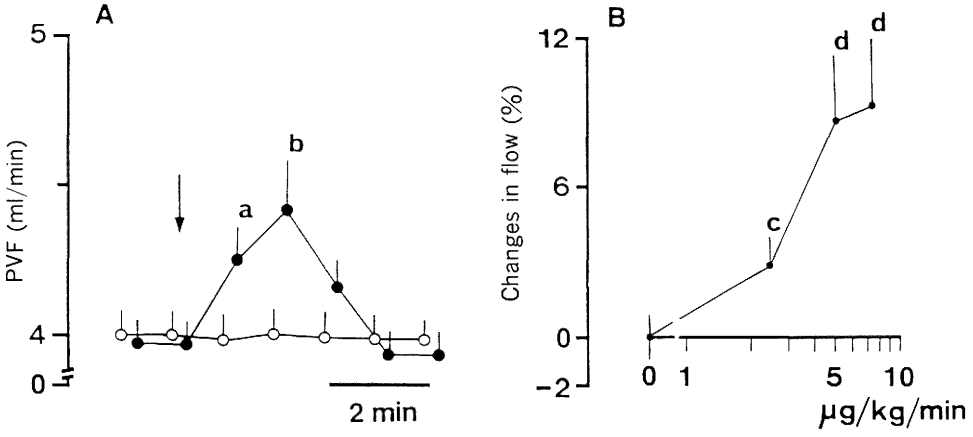

Fig. 1. A. Changes in PVF after PGE administration in 90 percent hepatectomized rats. PGE at 7.5 μg/kg/min (●) was jugularly injected, and saline (○) was injected as the control. The arrow indicates the time of injection. Values are the means ±SEM (n=6). [a]$p<0.05$ vs ○. [b]$p<0.01$ vs ○. **B.** Responses in PVF 2 min after PGE administration. PGE at 2.5, 5.0 and 7.5 μg/kg/min and saline were injected. Values are the means ±SEM (n=6). [c]$p<0.01$ vs 0. [d]$p<0.01$ vs 2.5.

0.5°C with a heating lamp.

Midline and transverse incisions were made to open the abdominal cavity, and the probes of the flowmeter were placed on the portal vein and the hepatic artery. The SAP, PVF and HAF were recorded continuously on a pen recorder (SAN-EI, Type 1237, Tokyo). During the experiments, the abdomen was covered with a piece of gauze moistened with saline to prevent the viscera from drying.

Partial hepatectomy was done by the methods previously described.[8,10,12] Either the median lobe, being about 40 percent, or the median and left lateral lobes, being about 66 percent, and forming a unit, was ligated and removed. Only the caudal lobe was left in the 90 percent hepatectomy.

Prostaglandin E_1 (PGE, Ono Pharmaceutical Co., Ltd., Osaka, Japan) dissolved in saline was administered through a catheter placed in the right jugular vein. The amount of the test injection was 46 μl, and each injection was completed in 2 min with a perfusion pump. Saline was injected as the control. Indomethacin (IM, Sigma, NY, U.S.A.) dissolved in 70% ethanol was injected into the back intramuscularily, and 70% ethanol was used as the control.

All data were analyzed by ANOVA and Duncan's range test, and $p<0.05$ was defined as significant.

RESULTS

Basal hepatic blood flow parameters (THF, total hepatic blood flow; HF/W, total hepatic blood flow per wet liver weight) are shown in Table 1.

The jugular injection of PGE at 7.5 μg/kg/min increased PVF in the 90 percent hepatectomized rats. Statistically, it was noted that the response reached its peak about 2 min after the injection, then returned to the control level within another 2 min (Fig. 1A). Based on

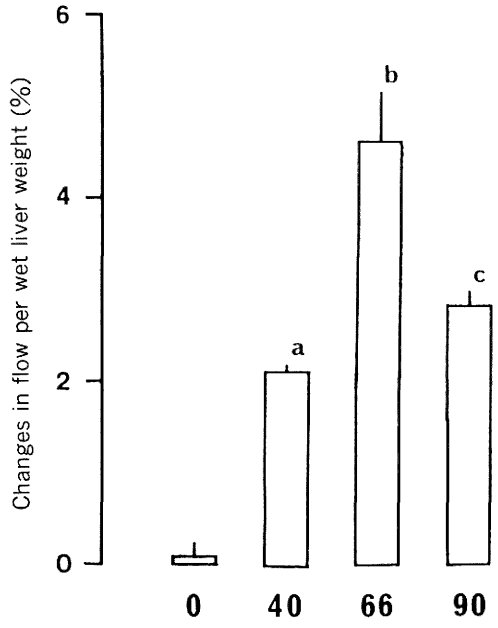

Fig. 2. Responses in PVF per wet liver weight after PGE administration. PGE at 5.0 μg/kg/min was jugulary injected into animals with 0, 40, 66 or 90 percent hepatectomy, and the responses 2 min after injection were compared. Each figure indicates the percentage of hepatectomy. Values are the means ± SEM (n=6). $^{a}p<0.05$ vs 0. $^{b}p<0.01$ vs 40 and 90. $^{c}p<0.01$ vs 40.

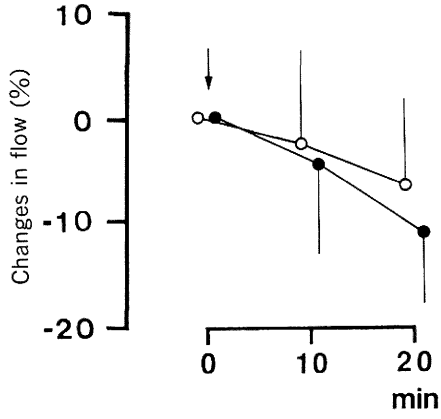

Fig. 3. Changes in PVF after IM administration in the 66 percent hepatectomized rats. The agent (●, 10 mg/kg) was injected intramuscularily, and ethanol (○, 70%) was injected as the control. An arrow indicates the time of injection. Values are the means ±SEM (n=6).

this finding, the changes in PVF 2 min after the PGE injection were compared.

The percent increases in PVF 2 min after PGE injections of 2.5, 5.0 and 7.5 μg/kg/min into the jugular vein tended to be dose dependent (Fig. 1B).

The PVF per wet liver weight was increased following the injection of PGE at 5.0 μg/kg/min in the three groups of hepatectomized rats (Fig. 2); the responses induced in order of magnitude ranged from the 66 percent hepatectomized rats, then the 90 percent hepatectomized rats, to the 40 percent hepatectomized rats.

In the 66 percent hepatectomized animals, the intramuscular injection of IM (10 mg/kg) provoked no significant change in PVF (Fig. 3). HAF was unchanged by PGE administration.

DISCUSSION

We found that the jugular injection of PGE brought about an increase in PVF in the 90 percent hepatectomized rats (Fig. 1). This supports the view that the intravenous administration of PGE increases PVF or hepatic blood flow.[7,8]

Hepatectomy has been shown to increase portal venous pressure and resistance according to the volume of liver resected.[13] and it has been demonstrated that hepatectomy increases PVF per wet liver weight,[14] though PVF per wet liver weight was less for the 90 percent hepatectomy than the 66 percent hepatectomy. It is therefore difficult to explain this from the viewpoint of portal venous pressure and resistance. It is considered that cardiac venous return reduced by a 90 percent hepatectomy causes systemic circulatory deterioration,[12] and hepatic hypoxia activates a vasoconstrictive substance such as endothelin-1 in the liver.[15,16]

Based on the fact mentioned above, it has also been thought that the increase in PVF after PGE administration may be a result of the reduction in the high portal venous resistance associated with hepatectomy. This speculation is supported by the recent finding that PGE produces a fall in portal venous pressure concomitant with an increase in PVF.[8] In the present study, the PVF response due to PGE was most evident in the 66 percent hepatectomized rats, and the response decreased when 90 percent of the liver was resected (Fig. 2). It is not easy to explain this phenomenon, but if excessive vasodilation due to a portal stream is presented in the 90 percent resected liver, the PGE effect on the residual vascular muscle will be diminished. Another possibility is that circulatory deterioration induced by 90 percent hepatectomy activated a hepatic vasoconstrictive peptide such as endothelin-1,[15,16] and the peptide counteracted the

effects of PGE.

Pharmacologically-active prostaglandins have been detected in the circulation during well identified pathologic conditions, including cell damage and inflammation.[9] IM has been shown to suppress vasodilating products of prostaglandin, and it has also been considered to change blood flow.[17] In the present study, the PGE action on PVF was substantially amplified by hepatectomy, but IM administration failed to change PVF. This is partially in line with a previous report stating that IM did not affect splanchnic hemodynamics in rats with portal hypertension.[18] It appears that endogenous prostaglandins are not related to the maintenance of hepatic blood flow in a partially resected liver.

Although PGE has been shown to dilate the hepatic arterial smooth muscles in the absence of hepatectomy,[9] no meaningful change in HAF was seen after PGE administration in this study, which supports the view that the agent was ineffective in dilating the muscles following hepatectomy or liver transplantation.[7,19] This could also be interpreted as indicating that PGE causes different pharmacological actions on the arterial wall according to the hepatic condition. The mechanism producing these differences needs to be clarified.

These observations suggest that PGE is capable of increasing PVF even when 90 percent of the liver has been resected, in which case the effect of PGE on PVF is reduced, and endogenous prostaglandins are not involved in the PGE action.

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