Prostaglandin E_1 (PGE_1) Attenuates Vasoconstriction Induced by PGE_2, PGD_2 and Phorbol Myristate Acetate in the Perfused Rat Liver

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It has been shown that prostaglandins (PGs) produced by Kupffer and endothelial cells play an important role in mediating physiological responses to various immunological stimuli. We studied the effect of prostaglandin E_1 (PGE_1) on the hemodynamic and metabolic changes induced by prostaglandin E_2 (PGE_2), D_2 (PGD_2) and phorbol 12-myristate 13-acetate (PMA), a potent inducer of PGs in the isolated rat liver perfused with Krebs-Ringer-bicarbonate (KRB) solution at a constant pressure of 12 cmH_2O. The liver was taken from overnight-fasted male Sprague-Dawley rats weighing 260 to 310g. Both PGE_2 and PGD_2 significantly decreased hepatic flow when their initial concentration was elevated to micromolar range. Although 1×10^{-6}M of PGE_1 did not have a major effect on hepatic flow, it significantly attenuauted the declines of hepatic flow produced by 4×10^{-6}M of PGE_2 and PGD_2. However, none of PGs tested influenced glucose and lactate concentrations in the medium. Continuous infusion of PGE_1 into the medium at a rate of 5 $\mu g \cdot min^{-1}$ significantly diminished the decreases in hepatic flow and oxygen consumption induced by 2×10^{-8}M of PMA. These results suggest that administration of PGE_1 may preserve hepatic blood flow by modifying the intrahepatic regulatory mechanism involving the activation of Kupffer and endothelial cells. (Key words: prostaglandins, Kupffer cells, endothelial cells, phorbol 12-myristate 13-acetate, isolated liver perfusion)

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Evidence has been accumulated that prostaglandins produced by nonparenchymal liver cells play fundamental roles in mediating physiological responses of the liver to various stimuli[1]. Vasoconstruction and increased glycogenolysis induced by administration of phorbol 12-myristate 13-acetate (PMA)[2,3], platelet-activating factor (PAF)[4], heat-aggregated immunoglobulin G[5] and opsonized zymosan[6] to the perfused liver have been shown to be inhibited by the phospholipase inhibitor bromophenacyl bromide or the cy-

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clooxygenase inhibitor indomethacin. Prostaglandin D_2 (PGD_2), E_2 (PGE_2) and $F_{2\alpha}$ ($PGE_{2\alpha}$) induce increases in portal pressure and glucose output in the fed rat liver perfused with constant flow[7,8]. Furthermore, PMA, PAF and zymosan fail to stimulate glycogenolysis in isolated parenchymal liver cells or hepatocytes, while PGE_2 and PGD_2 stimulate it[1,3,9,10]. Thus, it has been strongly suggested that prostaglandins produced by non-parenchymal cells may mediate the effect of these immunologically active agents on hepatocytes, and that the eicosanoids may alter hepatic metabolism by directly acting on hepatocytes and/or by producing hepatic ischemia or hypoxia. In the liver, prostaglandins are exclusively produced by Kupffer and endothelial cells[11,12]. The major eicosanoids produced by both cells have been reported to be PGD_2[12].

Recently administration of exogenous prostaglandin E series (PGE), particularly prostaglandin E_1 (PGE_1) infusion has been shown to have a beneficial effect on hepatic failure or dysfunction with a variety of causes, including toxins[13], viral hepatitis[14], immune-mediated diseases[15], hypoxia and ischemia[16,17]. The mechanism of the beneficial effect of PGE_1 remains to be understood. Increased blood flow to the liver, stabilization of endothelial cells, cytoprotective action and modulation of immune system have been proposed as the mechanism. Activation of non-parenchymal cells may be involved in inflammatory process in the liver. Revascularization of the ischemia liver may be accompanied by the stimulation of non-parenchymal cells by bacterial toxins or other immunologically active substances released into the portal circulation from the gut. Thus, exogenous PGE_1 may exert the beneficial effects by modulating the prostaglandin-mediated intercellular communication in the liver. However, little has been known about the direct actions of PGE_1 on the liver.

In the present study, we first studied the hemodynamic and metabolic effects of PGE_1, PGE_2 and PGD_2 on the isolated rat liver perfused at a constant pressure. Second, we examined the interaction of PGE_1 and PGE_2 or PGD_2. Finally, to clarify the effectiveness of PGE_1 for the prevention of hemodynamic and metabolic alterations associated with the activation of Kupffer and endothelial cells, we tested whether exogenous PGE_1 may antagonize PMA-induced vasoconstriction.

Materials and Methods

Animals and care

Male Sprague-Dawley rats weighing 260–310g were obtained from Nihon SLC (Shizuoka, Japan). They were kept on a 12h day-night rhythm with light on at 6 a.m. and light off at 6 p.m. They had free access to water and the standard laboratory chow. The animals were fasted overnight before the experiments.

Chemicals

Pure, PGE_1, PGE_2 and PGD_2 were obtained from Ono Pharmaceutical Co. LTD. (Osaka, Japan). They were dissolved in phosphate buffered saline (PBS) and stored as small aliquots in a freezer. PMA and fraction V bovine serum albumin (BSA) were purchased from Sigma Chemical (St. Louis, MO, USA). Dimethyl sulfoxide (DMSO) was from Wako Pure Chemical (Osaka, Japan). PMA was dissolved in DMSO and stored as aliquots in a freezer.

Solutions

Krebs-Ringer-bicarbonate (KRB) solution was used as the perfusion medium. The solution was composed of 117 mM NaCl, 4.7 mM KCl, 2.46 mM $CaCl_2$, 1.19 mM KH_2PO_4, 1.44 mM $MgSO_4$ and 24.8 mM $NaHCO_3$.

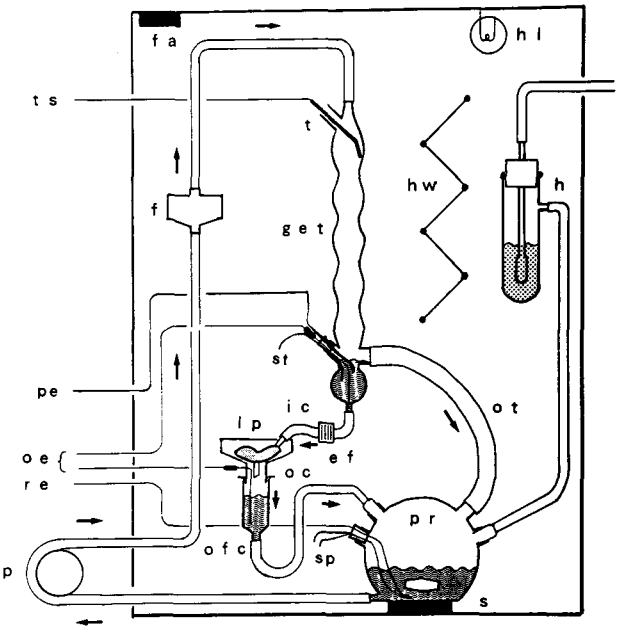

Fig. 1. Representation of the liver perfusion apparatus.

ef: electromagnetic flowmeter, f: filter, fa: fan, get: gas exchange tube "lung", h: humidifier, hl: heat lamp, hw: heat wire, ic: inflow catheter, lp: liver platform, oc: outflow catheter, oe: oxygen electrode (needle type), ofc: outflow chamber, ot: outflow tube (part of lung), p: pump, pe: pH electrode, pr: perfusate reservoir, s: stirrer, sp: sampling catheter in reservoir, st: sampling catheter in inflow chamber, t: thermometer, ts: thermostat.

KRB solution was saturated with a 95% O_2/5% CO_2 gas mixture, and pH was adjusted to 7.35 ± 0.05 at 37°C using 1 N $NaHCO_3$ or NaOH.

Recirculating perfusion of the rat liver with a constant pressure

Rats were anesthetized with pentobarbital sodium which was administered via penile vein at a dose of 30 to 35 $mg \cdot kg^{-1}$. The abdomen was opened through midline and midtransverse incisions. The inferior vena cava and portal vein were isolated. Five hundred units of heparin sodium was injected into the inferior vena cava. Three minutes later, the inferior vena cava was ligated above the renal vein. A polyethylene catheter (PE-240) was inserted into the portal vein and secured in place with 2–0 silk suture. The liver was immediately perfused with glucose-free KRB solution which had been warmed up to 37°C and saturated with 95% O_2 and 5% CO_2. The perfusion was continued during the following surgical procedure to minimize the anoxic time. The thorax was opened by transverse and longitudinal cephalad incisions. A polyethylene catheter (PE-260) was inserted through the right atrium and secured in place in the thoracic inferior vena cava. The liver was gently excised and placed on a liver platform. Finally the liver on the platform was placed in a modified Miller-type recirculating perfusion-aeration chamber with temperature control system by which the temperature of perfusate was kept at 37°C. The liver was perfused at a constant pressure of 12 cmH_2O with KRB containing 0.5% albumin and 10 mM D(+)-glucose. The recirculating perfusate volume was 200 ml. The general arrangement of the liver perfusion apparatus is illustrated in figure 1. In this system hepatic inflow was continuously measured by an electromagnetic flow transducer (Nihon Koden, Tokyo, Japan). Two needle-type oxygen electrodes (Intermedical, Nagoya, Japan) were placed in inflow and outflow chambers to monitor partial pressure of oxygen (Po_2).

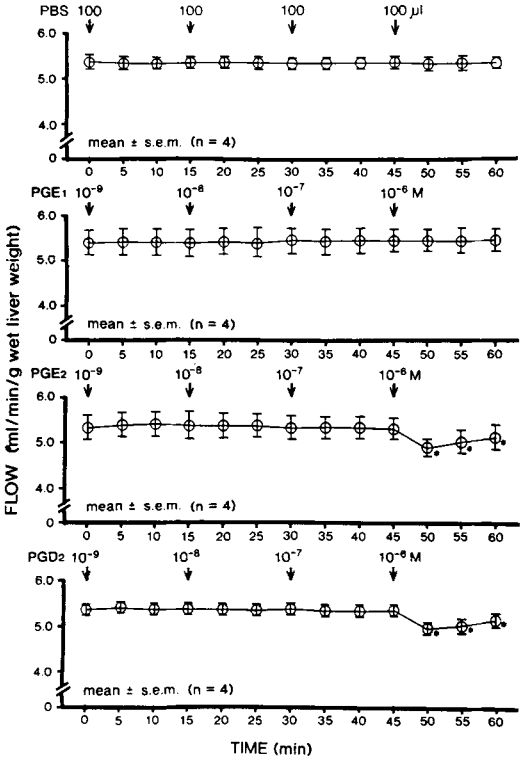

Fig. 2. Effects of incremental concentrations of PGE_1, PGE_2 and PGD_2 on hepatic flow.

*significant change from basal value.

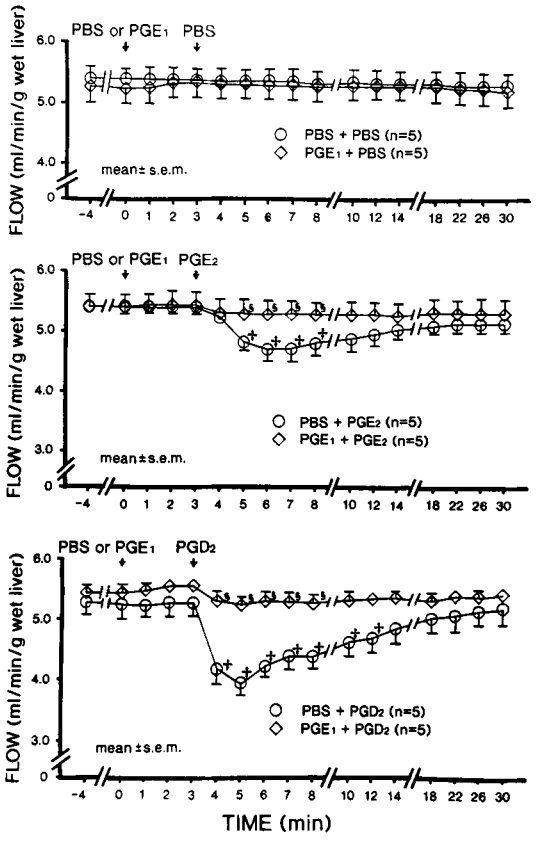

Fig. 3. Inhibition of PGE_2- or PGD_2-induced decrease in hepatic flow by PGE_1.

§ significantly different from PBS-PGE_2- or PBS-PGD_2-treated group in the same panel. + significantly different from PBS-PBS-treated group in the upper panel (one way-ANOVA followed by Duncan's multiple range test).

Dose-related alterations of hepatic flow by PGE_1, PGE_2 and PGD_2

The flow to the liver became stable approximately 20 min after the initiation of recirculating perfusion. In control group, 100 μl of PBS was administered to the perfusate reservoir every 15 min. In the other groups, we added PGE_1, PGE_2 or PGD_2 to the reservoir every 15 min to obtain an initial concentration of 10^{-9} M at time = 0 min, 10^{-8} M at 15 min, 10^{-7} M at 30 min and 10^{-6} at 45 min. The flow was recorded till time = 60 min.

Interaction of PGE_1 and PGE_2 or PGD_2

One hundred μl of PBS or 1×10^{-6}M of PGE_1 was added at time = 0 min. One hundred μl of PBS, 4×10^{-6}M of PGE_2 or PGD_2 was administered at time = 3 min. Approximately 40 μl of perfusate was collected from the reservoir at time = 0, 4, 8, 12, 18, 24 and 30 min, and was analyzed for glucose and L-lactate with YSI 2300 analyzer (Yellow Spring Instrument, U.S.A.). The flow was recorded till time = 30 min.

Effects of continuous administration of PGE_1 on PMA-induced alterations of hepatic flow and oxygen consumption

Table 1. Absolute changes in glucose concentration in perfusate

Groups	Time after the 1st treatments (minutes)					
	4	8	12	18	24	30
	Δ Changes in Glucose Concentration from Time = 0 ($mg \cdot dl^{-1}$)					
PBS + PBS	−2.8 ± 1.3	−3.2 ± 2.6	−2.0 ± 1.3	−4.4 ± 3.1	−2.6 ± 1.9	−4.4 ± 2.8
PGE_1 + PBS	−2.4 ± 3.1	−2.2 ± 2.7	−2.8 ± 0.9	−1.8 ± 1.7	−4.4 ± 2.9	−1.8 ± 1.7
PBS + PGE_2	−0.4 ± 2.0	0.6 ± 1.6	0.8 ± 1.7	0.0 ± 1.7	−3.2 ± 1.4	−1.8 ± 1.2
PGE_1 + PGE_2	0.0 ± 1.8	4.0 ± 2.2	5.0 ± 1.3	1.6 ± 3.0	3.4 ± 2.2	0.2 ± 1.4
PBS + PGD_2	−2.4 ± 2.2	−0.8 ± 2.8	−1.4 ± 2.6	−2.6 ± 1.7	−0.8 ± 1.8	−0.2 ± 1.7
PGE_1 + PGD_2	2.8 ± 2.3	−1.4 ± 3.8	−3.6 ± 2.5	−2.0 ± 1.1	0.4 ± 1.8	1.0 ± 3.4

Value are means ± s.e.m.

There was no significant difference among the groups at any sampling time (one-way ANOVA).

Fifty μl of DMSO or 2×10^{-8}M of PMA was added to the reservoir at time = 0 min. PGE_1 was continuously administered at a rate of 5 $\mu g \cdot min^{-1}$ from time = −15 min. Hepatic flow and partial pressure of oxygen (Po_2) in inflow and outflow chambers were recorded. Oxygen consumption of the liver was calculated by the following equation. Oxygen consumption ($\mu l \cdot min^{-1}$) = $\alpha/760 \times$ difference in Po_2 between inflow and outflow (mmHg) × flow ($ml \cdot min^{-1}$) where α is Bohr's coefficient (24 μl O_2/ml of water/760 mmHg at 37°C).

Statistical analysis

Alterations of variables in each group were analyzed using two-way analysis of variance (ANOVA) followed by Dunnet test. Comparisons among the groups were made by one-way ANOVA followed by Duncan's multiple range test. Changes or differences were considered to be significant when probability (P) values were less than 0.05. All values in Tables and Figures are expressed as mean ± s.e.m.

Results

Dose-related alterations of hepatic flow by PGE_1, PGE_2 and PGD_2

As shown in figure 2, hepatic flow was significantly decreased by PGE_2 and PGD_2 when their initial concentration was elevated to 10^{-6} M. Neither PBS nor PGE_1 produced any significant alteration of flow, though a small increase in hepatic flow was observed in some livers treated with PGE_1.

Interaction of PGE_1 and PGE_2 or PGD_2

Figure 3 demonstrates the alterations of hepatic flow in 6 groups. There was no significant difference in the flow between the two groups treated with PBS at 3 min (upper panel). Thus, 1×10^{-6}M of PGE_1 alone had no major effect on the flow. However, the flow reductions by 4×10^{-6}M of PGE_2 (middle panel) and PGD_2 (lower panel) were significantly suppressed by pretreatment with 1×10^{-6}M of PGE_1. In the groups pretreated with PBS at 0 min, the maximal reduction of flow was observed 4 min after PGE_2 administration (at time = 7 min) and 2 min after PGD_2 (at time = 5 min). The magnitude of the flow reduction was 25% in PGD_2-treatd group and 12% in PGE_2-treated group. Thus PGD_2 was a more po-

Table 2. Absolute changes in lactate concentration in perfusate

Groups	Time after the 1st treatments (minutes)					
	4	8	12	18	24	30
	Δ Changes in L-lactate Concentration from Time = 0 ($mmol \cdot l^{-1}$)					
PBS + PBS	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.02	0.08 ± 0.04	0.08 ± 0.02	0.12 ± 0.02
PGE_1 + PBS	0	0.04 ± 0.02	0.06 ± 0.02	0.06 ± 0.02	0.10 ± 0.03	0.12 ± 0.02
PBS + PGE_2	0.06 ± 0.02	0.08 ± 0.04	0.08 ± 0.04	0.10 ± 0.03	0.08 ± 0.02	0.10 ± 0.02
PGE_1 + PGE_2	0.06 ± 0.02	0.07 ± 0.03	0.08 ± 0.02	0.12 ± 0.02	0.10 ± 0.03	0.10 ± 0.03
PBS + PGD_2	0.08 ± 0.05	0.12 ± 0.05	0.12 ± 0.05	0.10 ± 0.03	0.12 ± 0.04	0.14 ± 0.05
PGE_1 + PGD_2	0.04 ± 0.02	0.08 ± 0.02	0.06 ± 0.02	0.12 ± 0.02	0.14 ± 0.02	0.16 ± 0.02

Values are means ± s.e.m.

There was no significant difference among the groups at any sampling time (one-way ANOVA).

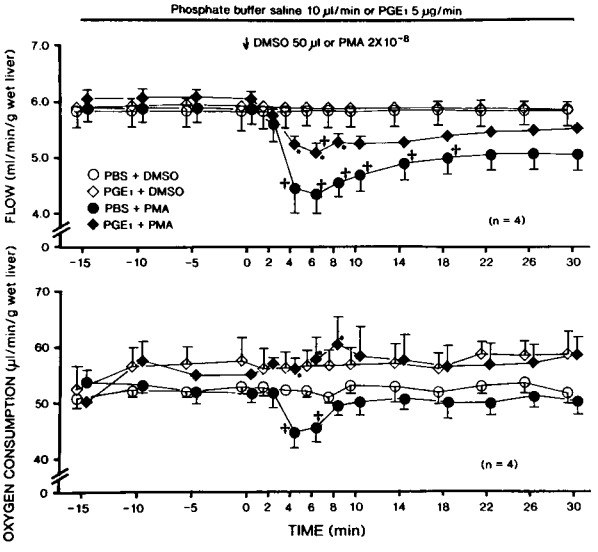

Fig. 4. Inhibition of PMA-induced decrease in hepatic flow by continuous administration of PGE_1.

*significantly different from PBS-PMA-treated group. + significantly different from corresponding control group (one way-ANOVA followed by Duncan's multiple range test).

tent constrictor of hepatic vessels than PGE_2.

Table 1 and table 2 show the absolute (Δ) changes in glucose and L-lactate concentrations from time = 0 min. Small changes in glucose concentration were observed in each group. Lactate concentration was gradually increased in all groups. There was no significant difference in Δ changes in glucose or lactate concentration among the groups. Thus, in the perfused liver from fasted rats, the prostaglandins had no significant effect on net glucose or lactate production.

Effect of continuous administration of PGE_1 on PMA-induced alterations of hepatic flow and oxygen consumption

Figure 4 demonstrates the alterations of hepatic flow and oxygen consumption in 4 treatment groups. There was no significant difference in hepatic flow or oxygen consumption among the two control groups treated

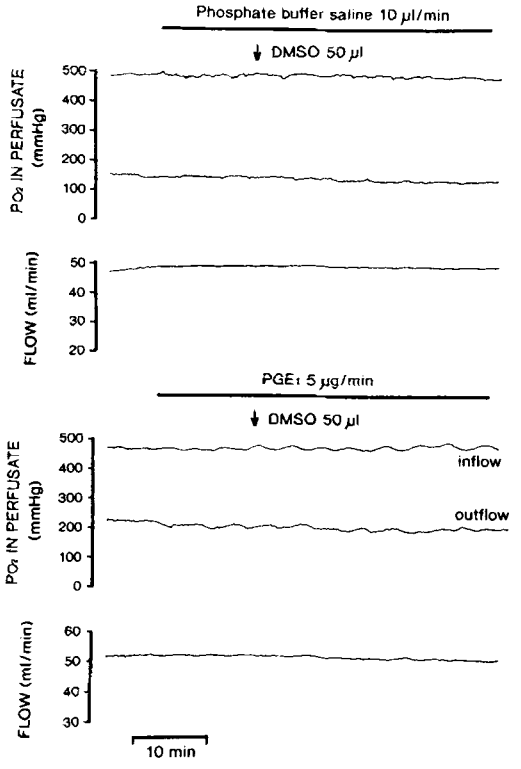

Fig. 5. Typical recordings of hepatic flow and P_{O_2} in DMSO-treated groups.

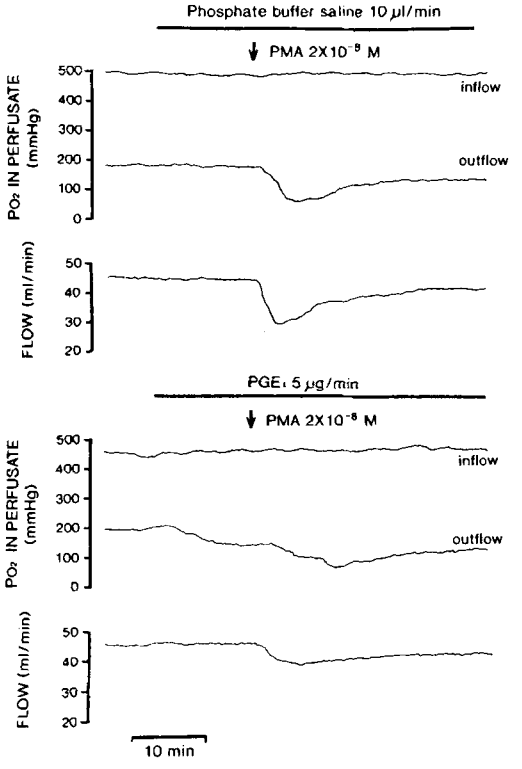

Fig. 6. Typical recordings of hepatic flow and P_{O_2} in PMA-treated groups.

with DMSO at 0 min, though oxygen consumption tended to be increased by the PGE_1 infusion. Thus, the continuous administration of PGE_1 did not exert a major effect on hepatic flow or oxygen consumption. However, the decreases in hepatic flow and oxygen consumption by 2×10^{-8}M of PMA were significantly attenauted by the continuous administration of PGE_1 at 5 $\mu g \cdot min^{-1}$. Typical recordings of hepatic flow and P_{O_2} in DMSO-treated and PMA-treated groups were shown in figure 5 and figure 6, respectively.

Discussion

It is well known that the blood flow through the hepatic vasculature is regulated by constriction of the portal venules and by sinusoids[18,19]. Evidence has been accumulated that the prostaglandins produced by Kupffer and endothelial cells play important roles in the transmission of physiological responses of the liver to various stimuli. Vasoconstrictive response of the isolated perfused liver to a number of immunologically active substances including PMA, PAF, heat-aggregated immunoglobulin G and opsonized zymosan has been shown to be inhibited by indomethacin[1-6]. Recent investigation has shown that the eicosanoids produced by the non-parenchymal liver cells may mediate the hemodynamic and metabolic alterations by sympathetic hepatic nerve stimulation[7]. Since cultured Kupffer and endothelial cells but not hepatocytes, extensively produce prostaglandins[11,12] and since PGD_2, PGE_2 and $PGF_{2\alpha}$ produce similar pattern of vasoconstrictive responses[3,5,7], the role of prostaglandins as intra-

hepatic and intercellular mediators has been emphasized[1].

In the present study, we confirmed the vasoconstrictive effect of PGE_2 and PGD_2 in the perfused liver from overnight-fasted rats. At a constant pressure of 12 cmH_2O, both agents significantly decreased hepatic flow when their initial concentrations were elevated to micromolar range. PGD_2 produced a quicker and sharper decline of flow than PGE_2. These results are comparable with previous findings that micromolar range of PGE_2, PGD_2 and $PGF_{2\alpha}$ increase portal pressure in the rat liver perfused at a constant flow rate[3,5,7]. However, 4×10^{-6}M of PGE_2 or PGD_2 exerted no significant effect on net glucose or lactate production in the liver from overnight-fasted rats. In the fed liver, both prostaglandins have been shown to increase net glucose and lactate production. Thus, the effects of PGE_2 and PGD_2 on carbohydrate metabolism may depend on the glycogen content of the liver, which is depleted by overnight-fasting.

The effectiveness of exogenous PGE, particularly PGE_1 administration in several critical conditions leading to hepatic failure has been reported. The benefit of PGE_1 has been shown in a variety of animal models for hepatic failure induced by toxic substances[13], hypoxia and ischemia[17]. Clinically intravenous PGE_1 has been demonstrated to improve hepatic function in patients with fulminant and subfulminant viral hepatitis[14]. Greig and others have reported that primary liver graft nonfunction after liver transplantation was attenuated by PGE_1 administration[16]. Activation of nonparenchymal cells may be involved in inflammatory liver diseases. Revascularization of the ischemic liver may be associated with exposure of the liver to immunologically active substances, which are released into the portal circulation from the gut. Thus, the beneficial effects of PGE_1 may be attributed to the modulation of function of non-parenchymal cells and/or action of mediators released from non-parenchymal cells.

In the present study, PGE_1 alone had no major effect on hepatic flow, but the pretreatment of PGE_1 attenuated PGE_2- and PGD_2-induced decline of hepatic flow. This property of PGE_1 is very unique, since almost all other prostanoids including $PGE_{2\alpha}$ and thromboxane A_2 have been reported to be vasoconstrictive in the isolated perfused liver[7]. The difference in hemodynamic action between PGE_1 and PGE_2 should be noted, because not only PGE_1 but also PGE_2 have been reported to be useful in toxic injury of the liver and hepatic failure[14,20,21]. Although the concentration of PGE_2 to induce vasoconstriction was much higher than the plasma concentration achieved by clinical dose of PGE_2 derivative, the disadvantage of PGE_2 should be taken into consideration in some types of hepatic injury.

Continuous administration of PGE_1 inhibited PMA-induced decreases in hepatic flow and oxygen consumption. PMA, recently identified to be a potent protein kinase C activator, has been known to stimulate prostaglandin synthesis in Kupffer cells and macrophages[22]. Vasoconstrictive response of the perfused liver to PMA has been shown to be blocked by the inhibitors of cyclooxygenase[3]. Since PGE_1 antagonized PGE_2- and PGD_2-induced decline in perfusion flow, it is highly possible that PGE_1 might inhibit the vasoconstrictive action of PMA by blocking the action of PGE_2 and PGD_2 produced by non-parenchymal cells in response to PMA. However, it is also likely that PGE_1 might suppress the reaction of Kupffer cells to PMA. The role of prostaglandins as immunomodulators has been demonstrated by a number of

experiments[23,24]. PGE_1 may modulate the Kupffer cell function by regulating cyclic AMP and/or GMP level, which have been considered to be important intracellular regulators of the immune reactions of macrophages[24,25].

The present study employed a recirculating perfusion technique with a constant pressure of 12 cmH_2O. This perfusion pressure adequately maintained the flow to the liver and hepatic oxygen consumption in the control groups of the livers. However, the decline of flow by PMA was associated with a decrease in oxygen consumption. This reduction of the oxygen consumption may not be due to the critical declines of hepatic flow and oxygen supply. Rather it may be due to the redistribution of flow within the liver which may cause local ischemia and hypoxia. Patel reported that PMA increased the perfusion pressure and decreased oxygen consumption in the isolated liver perfused with a constant flow, and that PMA may cause local hypoxia by redirecting flow through the liver[2].

The infusion rate of PGE_1 employed in the present study appears to be much higher than the rate clinically recommended. However, prostaglandins have been shown to be rapidly metabolized by hepatocytes in a flow-dependent manner[26]. Since the present study employed KRB solution as the perfusion medium, the hepatic flow was extremely high. Thus, the concentration of PGE_1 achieved by the infusion rate may be much lower than expected, though PGE_1 concentration in the perfusate was not determined in the present study.

In summary, we showed that PGE_1 antagonizes PGE_2- and PGD_2-induced declines of hepatic flow, and that continuous infusion of PGE_1 suppresses decreases in hepatic flow and oxygen consumption by PMA. These results suggest that PGE_1 may preserve hepatic blood flow by modifying the intrahepatic regulatory mechanisms involving the activation of Kupffer and endothelial cells.

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