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Hypotensive Response to Prostacyclin and 6-keto-PGE_1 following Hepatectomy in the Rat[1] (41895)

JACQUES VAN DAM, ROBERT B. STINGER, JUAN C. PENHOS, PETER W. RAMWELL, AND PETER A. KOT

Department of Physiology and Biophysics, Georgetown University Medical Center, Washington, D.C. 20007

Abstract. Prostacyclin (PGI_2) is metabolized to 6-keto-prostaglandin E_1 (6-keto-PGE_1) which is more stable yet equipotent to PGI_2 in lowering systemic arterial blood pressure in the dog. In this study, partial hepatectomy was performed to determine the role of the liver in the vasodepressor response to both intravenously administered PGI_2 and 6-keto-PGE_1. The magnitude and the duration of systemic hypotensive responses were measured in hepatectomized and sham-operated male Wistar rats following less than maximal, equidepressor doses of PGI_2 (0.3 μg/kg), 6-keto-PGE_1 (1.0 μg/kg), and also PGE_1 (3.0 μg/kg) and PGE_2 (3.0 μg/kg). Hepatectomy did not significantly alter the magnitude of the systemic hypotensive response to any of the prostaglandins tested. This indicates that the liver and hepatic circulation do not contribute significantly to the hypotensive effect of these prostaglandins by alterations of systemic vascular resistance, venous pooling of blood, or the generation of additional vasoactive metabolites as may be expected following administration of these prostaglandins. However, hepatectomy did significantly increase the duration of the hypotensive response to PGI_2 and 6-keto-PGE_1 but not PGE_1 or PGE_2. We conclude that *in vivo*, the liver has a more significant role in PGI_2 and 6-keto-PGE_1 inactivation than in the inactivation of PGE_1 and PGE_2 when administered intravenously. These results also support the relatively greater significance of the lung in the inactivation of PGE_1 and PGE_2 *in vivo*.

Prostacyclin (PGI_2) is presently considered to be one of the principal products of arachidonic acid metabolism of vascular endothelial tissue (1–3). This prostaglandin is a potent inhibitor of platelet aggregation (1–3), a vascular smooth muscle relaxing agent (2, 3), and a systemic hypotensive agent in rats, rabbits (4–6), dogs (7–10), baboons (11), and man (12–14). Prostacyclin is converted to 6-keto-prostaglandin E_1 (6-keto-PGE_1), a more stable metabolite, by 9-hydroxy-prostaglandin dehydrogenase (9-OH PGDH) which is present in the rabbit liver (15, 16) and human platelets (17). Unlike other metabolites of PGI_2, 6-keto-PGE_1 is equipotent to prostacyclin in inhibiting platelet aggregation (15, 17–19) and lowering systemic arterial blood pressure in the dog (20).

The liver is an important site of prostaglandin metabolism and inactivation (21–26) and therefore we evaluated the role of the liver and hepatic circulation on the relative vascular responses to exogenously administered PGI_2, 6-keto-PGE_1, PGE_1, and PGE_2.

Materials and Methods. Male Wistar rats (N = 60) weighing 250–350 g were anesthetized with intraperitoneal sodium pentobarbital (50 mg/kg). A tracheotomy was performed to maintain airway patency. Systemic arterial blood pressure (SAP) was continuously monitored through an indwelling catheter (PE 50) placed in the left common carotid artery. Bolus injections of test compounds were administered through an indwelling catheter (PE 20) placed in the left external jugular vein.

Hepatectomy was performed by the method of Higgins and Anderson (27). Following a midline peritoneal incision, individual liver lobes were ligated and excised. A small fraction of each lobe proximal to the ligature was left *in situ* to maintain the portal circulation. Following each experiment, the remaining fraction of liver tissue was excised and weighed. Total liver weight was determined by adding the weight of the liver excised to perform the hepatectomy to the weight of the fraction of liver tissue which remained *in situ*. Percentage hepatectomy was calculated as (weight of ex-

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cised liver/weight of total liver) × 100 and ranged from 65 to 93% with a mean of 81.1 ± 1.5%. Sham operations for the control group consisted of a midline peritoneal incision followed by manipulation of liver lobes. The abdominal incision in both sham-operated and hepatectomized rats was closed in layers with 2-O silk.

Stock solutions of PGI_2 (1 mg/ml) were prepared in 0.1 *M* Tris buffer (pH 9.0). PGE_1, PGE_2, and 6-keto-PGE_1 were prepared in ethanol (1 mg/ml). All solutions were stored at −20°C. On the day of each experiment, stock solutions of PGI_2 were diluted to 10–30 μg/ml with Tris buffer. PGE_1, PGE_2, and 6-keto-PGE_1 were evaporated under nitrogen and resuspended in 0.9% saline to 100 μg/ml, 100 μg/ml, and 10–30 μg/ml, respectively. Varying the concentration of PGI_2 and 6-keto-PGE_1 from 10–30 μg/ml ensured that the volumes administered were consistent and minimal for all doses of the compounds.

Changes in SAP were recorded by a direct writing physiograph (Gould Brush 2200). SAP was allowed to return to control value before subsequent doses of each agent were administered. The time to onset, time to maximal response and duration of the hypotensive response (time required for recovery to 50% of the maximum response) were measured in seconds from the time of prostaglandin injection.

Data are expressed as arithmetic mean ± standard error of the mean and were analyzed using Student's *t* test for either paired or unpaired observations where appropriate. Significance was judged at the $P < 0.05$ level. Linear regression lines were calculated by the method of least squares.

Results. The control values for mean systemic arterial blood pressure in sham-operated and hepatectomized rats were 127.1 ± 3.3 and 117.2 ± 3.5 mm Hg, respectively. Hepatectomy resulted in a lower, although normal baseline blood pressure. Vasodepressor responses were expressed as percentage decrease in order to compare dose–responses between the two groups. Neither the Tris buffer nor the 0.9% saline vehicles used for prostaglandin administration affected resting systemic arterial pressure.

Intravenous administration of PGE_1, PGE_2, PGI_2, and 6-keto-PGE_1 into nonhepatectomized rats decreased systemic arterial blood pressure in a dose-dependent manner (Fig. 1). The responses to PGE_1 and PGE_2 were similar over the dose range studied. Both PGI_2 and 6-keto-PGE_1 were significantly more potent systemic hypotensive agents than either PGE_1 or PGE_2 in the doses used. The dose–response curves for PGI_2 and 6-keto-PGE_1 do not significantly deviate from parallelism.

From these data, approximately equidepressor doses of PGE_1 (3.0 μg/kg), PGE_2 (3.0 μg/kg), PGI_2 (0.3 μg/kg), and 6-keto-PGE_1 (1.0 μg/kg), which were demonstrated to be less than maximal doses in sham-operated rats, were administered to both sham-operated and hepatectomized rats in order to determine the effect of hepatectomy on the systemic hypotensive action of these prostanoids. The selected doses decreased systemic arterial blood pressure by 25.9 to 31.6%. Hepatectomy did not significantly alter the magnitude of the systemic hypotensive response (Table I) or the time to onset of the hypotensive response.

In sham-operated animals, the time to the maximal vasodepressor response to 6-keto-PGE_1 (27.0 ± 1.3 sec) was significantly longer than that for PGE_1 (17.8 ± 1.0 sec). Similarly, the time to the maximal response to PGE_1 was significantly longer than that for PGE_2 (7.7 ± 0.4 sec). These values were not significantly changed following hepatectomy (Fig. 2). However, the time to the maximal vaso-

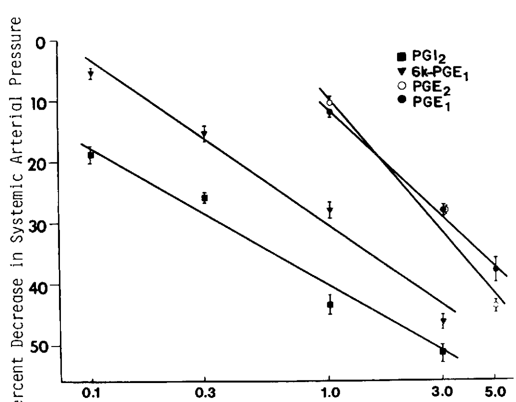

FIG. 1. Percentage decrease in systemic arterial blood pressure produced by intravenous administration of PGI_2 (N = 20); 6-keto-PGE_1 (N = 9); PGE_1 (N = 10); and PGE_2 (N = 12) in sham-operated rats.

TABLE I. PERCENTAGE DECREASE IN SYSTEMIC ARTERIAL PRESSURE PRODUCED BY INTRAVENOUS ADMINISTRATION OF PGE_1, PGE_2, PGI_2, AND 6-KETO-PGE_1 IN SHAM-OPERATED AND HEPATECTOMIZED RATS

	PGE_1 (3.0 μg/kg)	PGE_2 (3.0 μg/kg)	PGI_2 (0.3 μg/kg)	6-keto-PGE_1 (1.0 μg/kg)
Sham-operated	28.1 ± 1.0	28.3 ± 0.8	25.9 ± 0.9	28.3 ± 1.2
N^a	10	12	20	9
Hepatectomized	29.0 ± 0.8	31.6 ± 0.9	27.7 ± 0.9	29.3 ± 0.9
N	8	8	12	8

[a] N = number of animals in each group.

depressor response to PGI_2 was significantly increased in the hepatectomized rat.

The duration of the systemic hypotensive response to PGE_1 (51.9 ± 2.3 sec) and PGE_2 (29.8 ± 2.2 sec) was not significantly changed following hepatectomy (Fig. 3). However, the duration of the systemic hypotensive response to both PGI_2 (66.5 ± 3.1 sec) and 6-keto-PGE_1 (64.5 ± 6.4 sec) was significantly increased in the hepatectomized rat (112.4 ± 6.1 sec and 86.2 ± 3.8 sec, respectively). Furthermore, the increase in the duration of action following hepatectomy was greater for PGI_2 than for 6-keto-PGE_1.

Discussion. In this study, hepatectomy increased the duration of the systemic hypotensive response to intravenously administered prostacyclin and 6-keto-PGE_1 but did not significantly affect the response to PGE_1 and PGE_2. Because the magnitude of the hypotensive response was unaffected by hepatectomy but the duration of the hypotensive response was prolonged, we conclude that the liver and hepatic circulation do not contribute significantly to the systemic hypotensive effect of these prostaglandins but inactivate PGI_2 and 6-keto-PGE_1 more than PGE_2 and PGE_1.

Although PGE_1 and PGE_2 activity are reduced more than 70% following a single transit through the isolated perfused liver (23, 32), the role of the liver *in vivo* is negligible in the metabolism of intravenously administered PGE_1 and PGE_2. Removal of the liver in this study did not significantly decrease the magnitude nor increase the duration of action of these prostaglandins. The lung represents the major site of PGE_1 and PGE_2 inactivation and

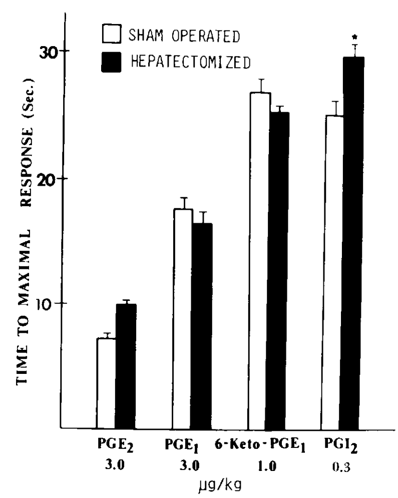

FIG. 2. Time to maximal response (sec) to intravenously administered PGE_2 (N = 20); PGE_1 (N = 18); 6-keto-PGE_1 (N = 32); and PGI_2 (N = 17) in sham-operated and hepatectomized rats. *$P < 0.05$ vs sham-operated rats.

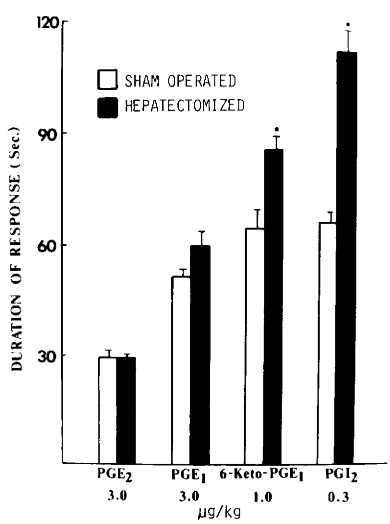

FIG. 3. Duration of response (sec) to intravenously administered PGE_2 (N = 20); PGE_1 (N = 18); 6-keto-PGE_1 (N = 32); and PGI_2 (N = 17) in sham-operated and hepatectomized rats. *$P < 0.05$ vs sham-operated rats.

approximately 90% of the activity of these compounds is removed in a single pass through the pulmonary circulation (9, 30, 32, 33). Therefore, hepatectomy is unlikely to significantly alter the magnitude or duration of the systemic hypotensive response to intravenously administered PGE_1 and PGE_2.

In contrast, prostacyclin and 6-keto-PGE_1 are not inactivated during pulmonary transit (4, 9, 15, 16, 20, 28, 30, 31, 34). The liver therefore receives a large concentration of these compounds following intravenous administration and hepatectomy would be expected to significantly alter the systemic hypotensive response to prostacyclin and 6-keto-PGE_1.

Hepatic conversion of prostacyclin to 6-keto-PGE_1 is reported to account for the 10-fold increase in the dose of prostacyclin required to achieve an equivalent hypotensive response in eviscerated rats when compared to intact rats (28). However, based on the results of our study, hepatectomy did not alter the magnitude of the systemic hypotensive response to PGI_2. We therefore suggest that the alteration in the magnitude of the hypotensive action of PGI_2 following evisceration is due primarily to the removal of the splanchnic circulation and not the liver alone. Prostacyclin has been shown to cause dilatation in the mesenteric vascular bed (10) which may account for part of the hypotensive response to PGI_2.

In summary, the role of the liver in the cardiovascular response to prostacyclin was found to be one of inactivation. Both the time to maximal response and the duration of action of prostacyclin were significantly increased following hepatectomy. The decreased elimination of prostacyclin following removal of the liver indicates the loss of some hepatic factor(s) responsible for the binding or inactivation of this compound. Prostacyclin inactivation occurs in other tissues, but the liver appears to play a significant role in PGI_2 degradation.

Although hepatectomy did not significantly alter the magnitude of the systemic hypotensive response nor increase the time to maximal response to 6-keto-PGE_1, its duration of action was also significantly increased following removal of the liver. The degree to which the blood pressure responses to 6-keto-PGE_1 were affected by hepatectomy suggests that it is less dependent on the liver for inactivation than is prostacyclin.

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