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Portal Injection of Dopamine Directly Increases Portal Venous Blood Flow in 66 Percent Hepatectomized Rats

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Summary. **Portal venous blood flow (PVF) and systemic arterial pressure (SAP) were examined after dopamine (DA) injection into the portal or femoral vein in 66 percent hepatectomized rats. The portal injection of DA at 25 μg/kg/min evoked an increase in PVF without any change in SAP. PVF response due to portal DA injection tended to be dose dependent, and when portal venous resistance was defined as portal venous pressure/PVF, the resistance was reduced concomitant with an increase in PVF. The same dosage of DA injected into the femoral vein increased PVF with an increase in SAP.**

These results suggest that DA directly contributes to the PVF control under a hepatectomized condition, and that DA receptor in the portal vasculature is involved in this response.

Key words—hepatic blood flow, hepatectomy, liver.

INTRODUCTION

Increasing blood flow in the liver can contribute to an improved prognosis for liver disease when the liver has been partially resected. It has been shown that exogenously administered dopamine (DA) increases portal venous blood flow (PVF) by dilating the vessels, and that the action site of this agent is located in the superior mesenteric vascular bed.[1-3] In connection with this, it has also been suggested that there is a vasodilative action of DA in the portal vascular bed,[4-7] but the contribution of DA to PVF control has not yet been evaluated directly. On the other hand, partial hepatectomy has been shown to increase portal venous pressure (PVP) and portal vascular resistance (PVR).[8,9]

This study was therefore designed to investigate whether DA directly injected into the portal vein influences PVF in relation to a hepatectomized condition.

MATERIALS AND METHODS

Thirty male Wistar rats weighing 280-300 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, 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.

The animals were anesthetized intraperitoneally with 45 mg/kg pentobarbital sodium, and the depth of anesthesia was maintained with the same agent at 7.5 mg/kg, given subcutaneously every 30 min.[10] A Tracheotomy was carried out to provide a patent airway. The systemic arterial pressure (SAP) was recorded from the right carotid artery. Throughout the experiments, the rectal temperature was kept at 36.0±0.5°C with a heating lamp.

Midline and transverse incisions were made to open the abdominal cavity. The PVF was measured with a transit-time ultrasonic volume flowmeter (Transonic T201, Advance, NY) connected to a 2 mm probe,[11,12] and the probe of the flowmeter was placed on the portal vein. The PVP was recorded from the extrahepatic portion of the portal vein. The SAP,

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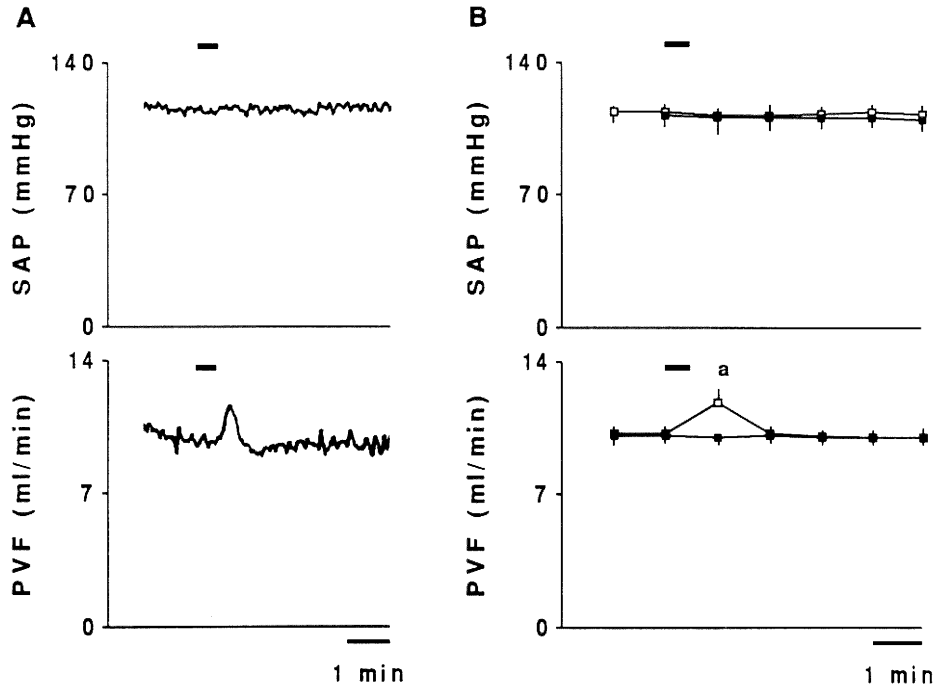

Fig. 1. Changes in SAP and PVF caused by DA injection into the portal vein in 66 percent hepatectomized rats. **A.** SAP and PVF after DA 25 μg/kg/min injection. *Bars* show the time of injection. **B.** Mean SAP and PVF after DA 25 μg/kg/min injection (□). The control received saline (■). *Bars* indicate the time of injection. Values are the mean ± SEM (n=6). [a]$p<0.01$ vs ■.

PVF and PVP were recorded continuously with a pen recorder (SAN-EI, Type 1237, Tokyo; SR6221, Graphtec, Tokyo). PVR was defined as PVP/PVF. During the experiments, the abdomen was covered with a piece of gauze moistened with saline to prevent the visceral organs from drying.

The liver was partially resected by methods previously described.[11,12] The median and left lateral lobes, forming a unit-structure comprising about 66 percent of the total were ligated and removed.

DA (Kyowa Hakko Kogyo Co., Ltd., Tokyo) dissolved in saline was administered through a catheter placed either in the left femoral vein or in the portal vein. The amount of a test injection was 11.5 μl, and each injection was completed in 30 s with a perfusion pump. Saline was injected as a control. All data were analyzed by ANOVA and Duncan's multiple range test, with $p<0.05$ being defined as significant.

RESULTS

The portal injection of DA at 25 μg/kg/min increased PVF without any change in SAP in the 66 percent hepatectomized rats (Fig. 1A). It was noted that the response reached its peak about 45-60 s after the injection, then returned to the control level within another 60 s (Fig. 1B). Based on this finding, the changes in PVF and SAP 60 s after DA injection were compared.

PVF response due to portal DA injection ranging from 6.25 to 25 μg/kg/min tended to be dose dependent, but no further increase in PVF was seen when 50 μg/kg/min DA was injected. PVF response showed a dose dependent fashion when DA was injected into the femoral vein. It was also noted that PVF was increased when DA at 6.25 μg/kg/min was injected into the portal vein, but not when the same dose of DA was injected into the femoral vein (Fig. 2).

PVF was increased following the portal injection of DA at 25 μg/kg/min in the 66 percent hepatectomized rats. In the liver intact animals, however, there was no appreciable change in PVF (Table 1a).

In the 66 percent hepatectomized animals, the portal injection of DA at 25 μg/kg/min evoked no significant change in SAP with an increase in PVF, but the same dosage in a femoral DA injection resulted in an increase in SAP and PVF (Table 1b).

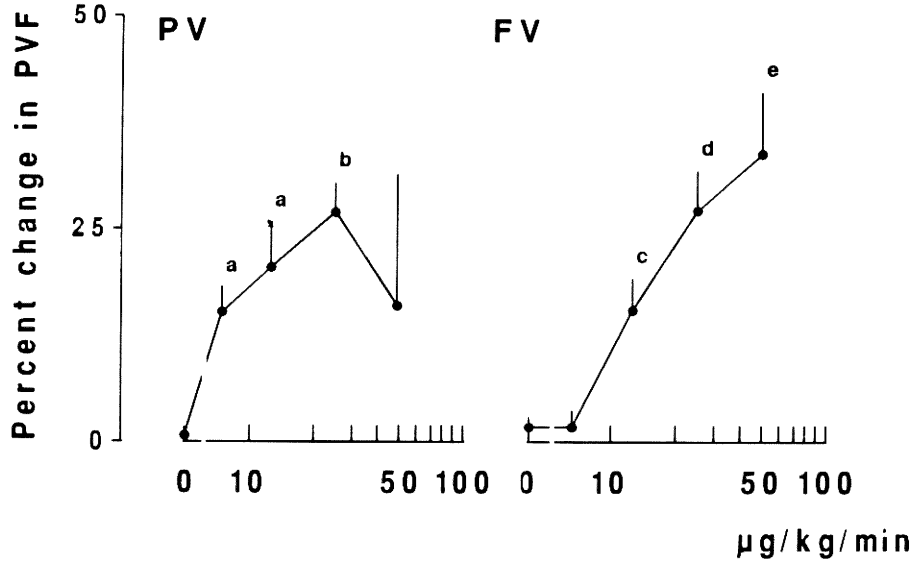

Fig. 2. Responses in PVF after DA injection into the portal vein (PV) or into the femoral vein (FV) in 66 percent hepatectomized rats. Percent changes in PVF after DA injection at 6.25, 12.5, 25 and 50 μg/kg/min are shown. The control received saline. Values are the mean ± SEM (n=6). [a]p<0.01 vs 0. [b]p<0.01 vs 6.25. [c]p<0.01 vs 0 and 6.25. [d]p<0.01 vs 6.25. [e]p<0.01 vs 12.5.

When DA at 25 μg/kg/min was administered, a monophasic reduction in PVR was induced after a portal injection, while there was an increase in PVR following a femoral injection (Fig. 3).

DISCUSSION

We found that DA substantially contributes to PVF control; DA directly injected into the portal vein increases PVF in the 66 percent hepatectomized condition. This is partially consistent with the view that the intravenous administration of DA increases PVF.[13,14] The DA action on the portal vasculature seemed to be peculiar to DA because the PVF response caused by DA tended to be dose dependent.

Concerning the active site of DA, DA receptor has been thought to be localized in the superior mesenteric vascular bed, based on the finding that DA inhibits the nerve stimulation-induced mesenteric vasoconstriction in the dog, the rat and the rabbit,[1,2] and that a venous injection of DA could increase PVF, whereas a portal injection of DA failed to increase PVF in the dog.[15] In the present study, however, DA was effective in increasing PVF when injected into the portal vein. This increase in PVF may be the result of

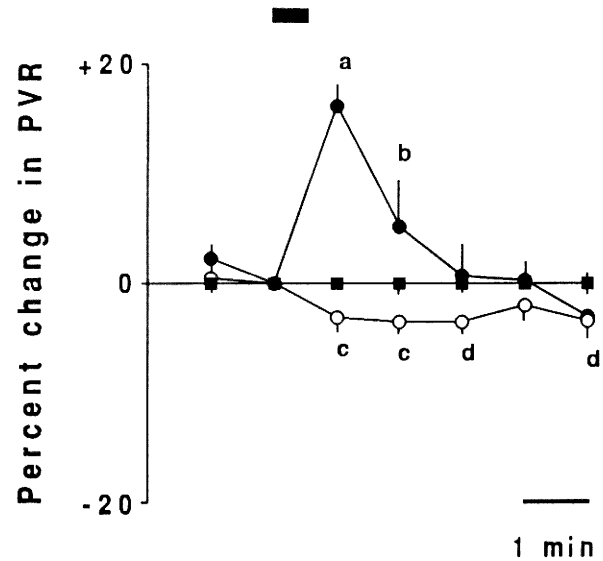

Fig. 3. Responses in PVR caused by DA in 66 percent hepatectomized rats. DA 25 μg/kg/min was injected into the portal vein (○) or into the femoral vein (●). The control received saline (■). A bar shows the time of injection. Values are the mean ± SEM (n=6). [a]p<0.01 vs ■. [b]p<0.05 vs ○. [c]p<0.05 vs ■. [d]p<0.01 vs ■.

Table 1a. SAP and PVF 60 s after DA 25 μg/kg/min injection into the portal vein in liver intact (I) and 66 percent hepatectomized (II) rats

	I	II
SAP (mmHg)	114±5	112±2
PVF (ml/min)	10.2±0.2	11.9±0.2[a]

Table 1b. Percent change in SAP and PVF caused by DA 25 μg/kg/min injection into the portal vein (I) or into the femoral vein (II) in 66 percent hepatectomized rats

	I	II
SAP	+1.3±1.1	+34.8±6.0[a]
PVF	+26.7±3.7	+26.8±4.9

Values are the mean ± SEM (n=6). [a]$p<0.01$ vs I.

the dilation of the portal vessels, especially since PVR was decreased following an increase in PVF. This could mean that the active site of DA is localized not only in the mesenteric vascular bed but also in the portal vascular bed.

The PVF response to portal DA injection was greater in the hepatectomized rats than in the liver intact rats (Table 1a). Considering this result together with the fact that the rat PVP is increased according to the volume of liver resected,[8,9] it is possible that DA may reduce the increased PVP associated with hepatectomy, and that this phenomenon is characterized by a DA action. Further study on this point is necessary, however.

The femoral administration of DA at 25 μg/kg/min produced an increase in PVF with an increase in SAP. This is in keeping with the view that DA increases SAP by enhancing the cardiac output.[16] In contrast with this, PVF was increased without any change in SAP following the portal injection of DA at 25 μg/kg/min (Table 1b). Because the liver has been shown to inactivate the biological activity of DA,[17] it is believed that the DA injected into the portal vein was metabolized by the liver before it reached the heart.

Hepatic blood flow is proportionate to cardiac output,[18] but the relation of cardiac output to hepatic blood flow is controversial: hepatic blood flow is enhanced secondarily by increased cardiac output[19] or hepatic blood flow is increased primarily by an action on the hepatic vasculature.[20] In this study, portal DA injection had an effect on PVF without any change in SAP. The notion therefore arises that DA could enhance hepatic blood flow independent of cardiac output.

DA has been considered for use in circulation emergency.[21-23] This study proposes that DA is useful in improving hepatic and systemic circulation in the partially hepatectomized condition (Table 1). This may hold true for clinical use, and add further weight to DA application in the case of circulatory deterioration. In this case, portal DA administration should be the consideration.

These observations suggest that DA is active in increasing PVF when the liver is partially resected, in which case the portal vascular bed is involved in the action site.

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