SHORT COMMUNICATION

Portal vein prostacyclin activity in experimental portal hypertension in rats

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Summary

1. Portal hypertension was produced experimentally in rats by partial ligation of the portal vein.
2. One week later portal veins of these animals were shown to release significantly greater amounts of prostacyclin than control animals.
3. It is postulated that if this response occurs in man, local vasodilatation and inhibition of platelet aggregation may be exacerbatory factors in the severity of haemorrhage from oesophageal varices that complicate portal hypertension.

Key words: experimental portal hypertension, oesophageal varices, prostacyclin (PGI$_2$).

Introduction

Arterial and venous endothelium of many species, including the rat and man, produce prostacyclin (PGI$_2$), a potent vasodilator and inhibitor of platelet aggregation (Moncada, Higgs & Vane, 1977; Moncada, Vane & Whittle, 1977). It has been suggested that not only is PGI$_2$ an important mediator of platelet–vessel wall interaction, but that it is a circulating hormone, one of the functions of which is to counteract the proaggregatory property of thromboxane A$_2$, a prostaglandin derivative generated endogenously in stimulated platelets (Moncada & Vane, 1978).

The demonstration of alterations in the PGI$_2$-stimulating or -inhibiting activity of plasma from patients with one of a number of diseases associated with haemorrhage or thrombotic complications has reinforced the assertion that this prostaglandin has some clinical relevance (Remuzzi, Misiani, Marchedi, Livio, Mecca, De Gaetano & Donati, 1978). Amongst these observations is one by Van Hoof, Chamone & Vermlyen (1979) that some patients with liver or renal disease have a raised level of PGI$_2$-stimulating factors in their plasma. This finding has led us to consider the possibility that excessive production of PGI$_2$ might contribute to a local haemostatic defect in patients with portal hypertension where massive haemorrhage from oesophageal varices is frequent. As a first step we have measured local PGI$_2$ production in rats where portal hypertension had been induced by partial ligation of the portal vein.

Materials and methods

Portal hypertension was produced in 20 Sprague–Dawley rats (150–200 g) by partial ligation of the portal vein. The animals were anaesthetized with ether and the peritoneal cavity was opened via an upper midline incision. Pressure in the portal vein was measured by simple manometry, taking the level next to the portal vein at the porta hepatis as 0 cm water. With care to avoid the hepatic artery and bile duct the portal vein was mobilized. A Teflon tube approximately half the diameter of the vessel was placed alongside it and a polyamide ligature tied firmly around, both as near to the porta hepatis as possible. The tube was then removed leaving the vein constricted to about half its original diameter. The abdomen was closed and the animal allowed to recover.
Four control groups were examined to establish the effect of surgical manipulation, short of prolonged ligation, on PGI₂ production and portal vein pressure. In the first group portal veins were obtained from 10 rats 1 week after ether anaesthesia for 15 min without surgery. In the second group portal veins were obtained from 10 rats after identical anaesthesia and laparotomy alone. In the third group of 10 animals the portal vein was fully dissected but not ligated and in the fourth group (10 animals) ligation, as described in the original group, was carried out and the ligature removed after 60 s.

One week later all groups were anaesthetized, laparotomy was carried out to establish the presence of any areas of congestion or necrosis in gut or liver and the venous pressure measurements were repeated. About 2–3 cm of the portal system distal to the ligature was excised and the animal killed.

Because of the lability of PGI₂ the venous tissue was cleaned immediately of connective tissue, placed in a plastic tube containing Tris/sodium chloride buffer [Tris (0·01 mol/l) in sodium chloride solution (145 mmol/l: saline), pH 8·0] at 4°C and transported to the laboratory for assay. Tissue extracts were prepared and PGI₂ was assayed as described by Hutton, Dandona, Chow & Craft (1980). The tissue was chopped into small pieces and suspended in fresh Tris/saline to a concentration of 50 mg of tissue/ml of buffer. After 3 min incubation at room temperature the supernatant was removed and placed at 4°C; PGI₂ was assayed by its inhibitory effect on ADP-induced platelet aggregation (Hutton et al., 1980). Platelet-rich plasma (0·4 ml) was incubated in a Payton aggregometer at 37°C with 0·05 ml of tissue extract (or pure PGI₂ as standard) for 60 s, at which time 0·05 ml of ADP (100 μmol/l) was added. The fall in absorbance was determined 3 min after addition of the ADP and expressed as ng of PGI₂-like activity/50 mg of tissue. The assay was repeated with supernatants obtained after incubation at 37°C for 20 min.

ADPase activity in the tissue extracts was determined as described by Hutton et al. (1980). The results were analysed statistically by Wilcoxon's two-sample test and Student's t-test.

Results

There were no areas of gut or liver necrosis or congestion noted in any of the animals. In the control groups no significant changes in portal venous pressure were noted. In contrast to this there was a highly significant increase in portal venous pressure from 10·4 ± 2·4 to 16·6 ± 1·75 (sd) cm water 1 week after ligation (P < 0·01).

The results of the PGI₂ assays are shown in Fig. 1. The highest levels were found in the group with partial ligation of the portal vein and this was significantly greater than activity in any of the four control groups (P < 0·01). PGI₂ activity in control groups 2, 3 and 4 was significantly greater than in control group 1 where no surgery had been carried out (P < 0·01). Groups 3 and 4 had slightly greater PGI₂ activity than group 2 where there was no direct trauma to the portal vein but these differences were not significant.

Discussion

The assay technique used in these studies is not specific for PGI₂ and so we feel obliged to use the term PGI₂-like activity for the anti-aggregatory effects observed. However, the production of
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other prostaglandins by vascular tissue is low and no ADP-degrading activity was detected in any of the samples tested. Moreover the anti-aggregatory activity observed was, like that of pure PGI₂, destroyed on incubation of the extracts at 37°C for 20 min and we therefore believe that the major inhibitory substance generated by the vessels was PGI₂. Our results indicate that sustained partial ligation of the portal vein sufficient to induce portal hypertension is associated with a significant increase in local production of the PGI₂-like activity when compared with sham-operated animals, including those subjected to ligation.

Whether this local response is initiated by trauma or by the hypertension is uncertain. Trauma without prolonged ligation caused a lesser, but still significant, increase in PGI₂ which was sustained up to 7 days. This suggests that part of the PGI₂ response was a non-specific effect of surgical manipulation unrelated to hypertension. Conversely, similar increases in PGI₂ have been demonstrated in aortic extracts from spontaneously hypertensive rats by Pace-Asciak, Carrara, Rangaraj & Nicolau (1978) who suggest that the increased PGI₂ production may be sufficient to induce a systemic fall in blood pressure and that this may be an adaptive response to hypertension. We have not measured circulating levels of PGI₂ and are therefore unable to comment on these points, but it seems reasonable to suggest from our data that local vasodilatation and anti-aggregatory effects would occur. If these same effects occur in portal hypertension in man, this might contribute to the excessive bleeding from oesophageal varices which commonly complicates this condition.

We have not so far examined vascular tissue other than the portal vein to determine the extent of the PGI₂ response in our model. If further studies confirm increased PGI₂-like activity in other vessels after surgery, failure of this response may be implicated in the hypercoagulability associated with surgery.

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References