**LEADING ARTICLE**

**Endothelin and vascular function in liver disease**

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The endothelins are a group of three related peptides with two receptor subtypes, ETA and ETB. Following the discovery of endothelin 1 as a potent vasoconstrictor, there has been intense interest in the role of endothelin on vascular function in liver disease. Speculation on the role of endothelin in the pathogenesis of acute renal failure, including hepatorenal syndrome, has also been speculated.

The endothelins are a group of three related peptides of 21 amino acids, first isolated as endothelin 1 (ET-1) from porcine endothelial cells. Molecular studies have shown that there are two receptor subtypes, namely ETA and ETB. In vascular smooth muscle both receptor subtypes are expressed, and mediate vasoconstriction. ETA receptors are also found on endothelial cells where they cause vasodilatation through an nitric oxide dependent mechanism.

**HEPATOrenal SYNDrome**

Following the discovery of ET-1 as a potent vasoconstrictor by Yanigasawa and colleagues, there has been intense interest in the role of endothelin on vascular function in liver disease. Demonstration that infusion of ET-1 causes a profound decrease in glomerular filtration rate and renal blood flow in normal rats was immediately followed by speculation about the role of endothelin in the pathogenesis of acute renal failure, including hepatorenal syndrome.

Hepatorenal syndrome (HRS) is caused by renal vasoconstriction and impaired glomerular perfusion, both of which may be mediated by ET-1.

In 1992, there were three simultaneous publications which reported increased plasma concentrations of ET-1. In the largest and most detailed study, it was observed that circulating ET-1 and ET-3 concentrations were increased in patients with severe liver disease, with a more marked increase in plasma ET-1 concentrations in patients with HRS due to alcoholic hepatitis or acute liver failure (type 1 HRS). Eight years on it was shown that the high plasma ET-1 levels in patients with HRS decreased rapidly within one week after orthotopic liver transplantation, and this was followed by an improvement in renal function. Further evidence supporting the role of circulating or autocrine ET-1 in the pathogenesis of HRS is the observation that acute occlusion of a TIPS shunt to cause acute portal hypertension leads to a significant increase in arterial concentrations and renal synthesis of ET-1, and a 40% reduction in renal plasma flow. However, whether these are causally related is unknown.

To investigate the role of ET-1 in the pathogenesis of HRS that occurs in acute liver failure, we have recently investigated a rat model of acute liver failure which shares some of the hallmarks of HRS—namely, a reduction in renal blood flow, normal renal histology, development of renal impairment, and increased ET-1 concentrations. In this model, the development of renal failure is reversed or prevented by administration of Bosentan, a combined ETA and ETB receptor antagonist. Further studies using endothelin antagonists in patients with type 1 HRS are needed however before the role of this circulating peptide is elucidated in the pathogenesis of HRS.

**Endothelin and the liver**

Gandhi et al were the first to show that infusion of ET-1 into an isolated rat liver leads to increased portal pressure. This has led to great interest among hepatologists on the role of ET-1 on portal hypertension. It is now known that infusion of ET-1 into the isolated rat liver causes a sustained and dose dependant increase in portal pressure associated with increased glycolysis and oxygen consumption. Moreover, ET-1 stimulates phosphoinositide turnover and repetitive sustained intracellular calcium transients in isolated rat hepatocytes. Other studies...
have shown that ET-1 also has important interactions with non-parenchymal liver cells. Cultured sinusoidal endothelial cells from rat liver have been shown to release ET-1 and preferential binding sites for ET-1 have been identified both in vivo and in vitro on hepatic stellate cells.\textsuperscript{14,15} ET-1 induces a dose dependant increase in intracellular free calcium in hepatic stellate cells coupled with cell contraction.\textsuperscript{15,20} In addition, activated rat hepatic stellate cells have been shown to express ET-1 mRNA, thus raising the possibility of an autocrine action of ET-1. Therefore, ET-1 may act as a potent vasoconstrictor agonist regulating intrahepatic blood flow. Pinzani et al have investigated expression of ET-1 in human cirrhotic liver using in situ hybridisation and immunohistochemistry.\textsuperscript{15,20} They observed that ET-1 expression was markedly enhanced in cirrhotic liver tissue where activated hepatic stellate cells were shown to be the major sites of ET-1 synthesis. ET-1 exerts several biological actions on hepatic stellate cells, including mitogenecity, activation of mitogen activated protein kinase, and a rapid increase in intracellular calcium coupled with reversible cell contraction. All of these effects appear to be mediated by ET\textsubscript{A} receptors, and studies have shown upregulation of ET\textsubscript{A} and ET\textsubscript{B} receptors in human cirrhotic liver.\textsuperscript{20,21}

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Based on these data, it seems reasonable to assume that endothelin has a functional effect on portal pressure and the hepatic microcirculation. Several studies have since evaluated the synthesis of ET-1 in the liver. Levels of ET-1 in the portal vein are increased compared with arterial concentrations, suggesting that there is increased ET-1 synthesis in the splanchic circulation. Studies by Moller and Gerbes have also shown that there is net hepatosplanchnic release of ET-1 in cirrhosis, and in particular they observed that levels of ET-1 correlated positively with portal pressure, cardiac output, and inversely with central blood volume.\textsuperscript{20,25} These results are consistent with the hypothesis that ET-1 is involved in the development and perpetuation of portal hypertension. Increased hepatic venous concentrations of ET-1 suggest that the liver is a site of ET-1 synthesis, and ET-1 levels are increased in hepatic tissue in cirrhosis and correlate with disease severity.\textsuperscript{20,22} Recent studies by Nagasue et al have suggested that increased concentrations of ET-1 in the portal vein arise from the spleen as a major source of ET-1 in liver disease.\textsuperscript{26}

Thus there is increased synthesis of ET-1 in the liver and spleen with upregulation of ET\textsubscript{B} receptors in liver tissue. Endothelin may modulate sinusoidal blood flow in liver disease through contraction of hepatic stellate cells. There may also be further interactions with endotoxin as injection of endotoxin increases the sensitivity of the portal circulation to infusion of ET-1.\textsuperscript{27–30} This may be secondary to endotoxin mediated upregulation of ET\textsubscript{B} receptors. The mechanisms leading to increased ET-1 synthesis in liver disease are unknown, with conflicting data on the role of endotoxin, central blood volume, or regional hypoxia.

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Reichen et al have shown that administration of a mixed endothelin antagonist lowers portal pressure in vivo, presumably by acting on hepatic stellate cells, and counteracts the microvascular effects of ET-1 in vitro.\textsuperscript{27–30} Similar results were obtained by Kojima et al when they observed that a mixed ET receptor antagonist decreased portal pressure in a rat model of biliary cirrhosis.\textsuperscript{30}

ENDOTHELIN AND VASCULAR FUNCTION IN PATIENTS WITH CIRRHOSIS

Some years ago, Moller et al tentatively suggested that endothelins might contribute to vasodilatation.\textsuperscript{23} At the time, I thought this was a daft idea. However, recent data suggest that they may not have been too far from the truth. Two studies have been published in the past 12 months which have evaluated the effect of exogenous ET-1 infusion on forearm blood flow (FFB). Helmy et al have shown that compensated cirrhotic patients exhibit decreased responsiveness to infused ET-1.\textsuperscript{31} In normal subjects, ET-1 caused a 30–40% reduction in FBF whereas in child A cirrhosis an equivalent dose caused a ~20% reduction in FBF. They subsequently observed that infusion of BQ-123, an ET\textsubscript{A} receptor antagonist, caused more vasodilatation in cirrhotic patients than controls.\textsuperscript{32} In a recent issue of Gut, Vaughan et al described infusion of ET-1 into patients with advanced cirrhosis (Child Pugh C).\textsuperscript{33} They observed that infusion of ET-1 into normal subjects caused a decrease in FBF but most interestingly, infusion of ET-1 into cirrhotic patients caused an increase in FBF, and this reverted to normal following liver transplantation. They also observed that infusion of an ET\textsubscript{B} receptor antagonist (BQ123) caused vasodilatation in both normal controls and cirrhotic patients. Conversely, Helmy et al have shown that infusion of an ET\textsubscript{B} receptor antagonist into mild cirrhotic patients causes a reduction in FBF.\textsuperscript{34}

“More studies on the differential regulation of ET\textsubscript{A} and ET\textsubscript{B} receptors in patients with differing severities of liver disease are required”

These data have important implications in the design of therapeutic studies. It suggests that there is upregulation of ET\textsubscript{B} receptors in the systemic vasculature, such as the forearm, and which mediate vasodilatation. Clearly, more studies on the differential regulation of ET\textsubscript{A} and ET\textsubscript{B} receptors in patients with differing severities of liver disease are required to establish why such different responses are observed. But if the response in the forearm to infused ET-1 is opposite to that observed in normal controls, what happens in other circulatory beds, such as the kidney or portal circulation? Only further studies will bridge the gap between scientific endeavour and credibility.

REFERENCES

A 19 year old female smoker was admitted with an eight week history of cramping lower abdominal pain, per rectal bleeding, weight loss, and loose stools. Past medical history included iritis and she was taking the oral contraceptive pill. There was a positive family history of Crohn’s disease (mother). Routine bloods revealed raised inflammatory markers, normal haemoglobin, and white cell count, but raised platelet count and fibrinogen levels. Stool culture was negative. The findings at colonoscopy were consistent, both macro- and microscopically, with Crohn’s colitis. She was commenced on intravenous fluids, oral asacol 800 mg three times daily, and prednisolone 40 mg daily. Her bloody diarrhoea started to settle within 48 hours. She then developed sustained central visual loss in the left eye. Immediate ophthalmic review highlighted bilateral papilloedema, greater on the left than on the right, and signs of chronic uveitis. What was the diagnosis made from the urgent magnetic resonance imaging brain scan requested in this patient? See page 206 for answer

GI SNAPSHOT

Cerebral venous thrombosis in acute inflammatory bowel disease

Question
A 19 year old female smoker was admitted with an eight week history of cramping lower abdominal pain, per rectal bleeding, weight loss, and loose stools. Past medical history included iritis and she was taking the oral contraceptive pill. There was a positive family history of Crohn’s disease (mother). Routine bloods revealed raised inflammatory markers, normal haemoglobin, and white cell count, but raised platelet count and fibrinogen levels. Stool culture was negative. The findings at colonoscopy were consistent, both macro- and microscopically, with Crohn’s colitis. She was commenced on intravenous fluids, oral asacol 800 mg three times daily, and prednisolone 40 mg daily. Her bloody diarrhoea started to settle within 48 hours. She then developed sustained central visual loss in the left eye. Immediate ophthalmic review highlighted bilateral papilloedema, greater on the left than on the right, and signs of chronic uveitis. What was the diagnosis made from the urgent magnetic resonance imaging brain scan requested in this patient? See page 206 for answer

Figure 1 Magnetic resonance venogram shows central venous sinus thrombosis. There is flow of blood in the right transverse and sigmoid sinus but absence of flow on the left side.
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