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Cirrhosis

Role of endothelin in systemic and portal resistance in cirrhosis

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Endothelin may be involved in many of the vascular abnormalities in patients with cirrhosis, and its overall effects in different tissues may depend on differential expression of endothelin receptors on smooth muscle and endothelial cells

Many of the complications of cirrhosis result from haemodynamic changes involving the systemic circulation and regional vascular beds. Typically, patients with advanced cirrhosis and portal hypertension have a hyperdynamic vasodilated circulation characterised by high cardiac output and low blood pressure, and this leads to compensatory activation of vasoconstrictor systems, including the sympathetic nervous system and renin-angiotensin-aldosterone systems.[1] Much of this picture can be attributed to vasodilatation of the mesenteric vascular bed which in turn contributes to portal hypertension by increasing portal inflow. While vascular resistance in the mesenteric bed is reduced, another major contributor to portal hypertension is an increase in vascular tone within the liver which is at least partly mediated by hepatic stellate cells. Altered local vascular tone contributes to other important complications of cirrhosis—intrarenal vasoconstriction can result in the hepatorenal syndrome, while in the lung pathological vasodilatation can result in the development of the hepatopulmonary syndrome, and less commonly pulmonary vasoconstriction may result in portopulmonary hypertension. As a result there has been intense interest in understanding the mechanisms and vascular mediators responsible for these systemic and regional changes in vascular tone with the hope that this will lead to the development of new treatments.

Endothelin 1 (ET-1) is a potent endothelium derived vasoactive peptide that plays a central role in regulating vascular tone in healthy individuals but has multiple other actions that may be of importance in disease, including stimulation of cellular growth and proliferation, and involvement in the wound healing response and tissue fibrogenesis.[2 3] For more than a decade there has been major interest in the possible role of ET-1 in the pathogenesis of cirrhosis, its contribution to portal hypertension, and the possibility that endothelin antagonists might be used in the treatment of portal hypertension and other complications of cirrhosis.[4 5] Plasma endothelin levels are increased in cirrhosis, and correlate with the severity of liver disease and portal pressures.[6 7] The hepatosplanchnic circulation, including the splenic vascular bed and the liver itself, appears to be the major source of this increased endothelin production.[8–11] Importantly, while in health the vascular endothelium is the major source of endothelin production, in the cirrhotic liver ET-1 appears to be largely derived from activated stellate cells.[10] Recent studies suggest that in cholestatic liver injury, cholangiocytes are another important source of ET-1.[12]

A number of lines of evidence suggest that this increased ET-1 production may contribute to portal hypertension. Endothelin receptor expression is upregulated in liver disease and hepatic stellate cells express the highest levels of endothelin receptors.[13–15] Furthermore, endothelin induced contraction is enhanced in stellate cells from cirrhotic rat livers and in the intact liver endothelin causes sustained vasoconstriction.[16] Thus it has been proposed that increased hepatosplenic production of endothelin contributes to portal hypertension by mediating intrahepatic stellate cell contraction and an increase in hepatic sinusoidal tone. This concept has been supported by studies in animal models of portal hypertension which have shown that administration of endothelin antagonists reduces portal pressure.[17–19] The weight of evidence is that this effect is largely due to a reduction in hepatic and collateral resistance rather than to changes in mesenteric blood flow.[17 19]

Thus there is strong experimental evidence that endothelin contributes to increased intrahepatic vascular tone in cirrhosis. However, there is also evidence that altered responsiveness to ET-1 may contribute to changes in the systemic and mesenteric circulation. Despite elevation of circulating endothelin and vasopressin levels and activation of the renin-angiotensin system and adrenergic nervous systems, peripheral and mesenteric vascular tone is reduced in patients with advanced liver disease, with the degree of activation of vasoconstrictor responses being greatest in those in whom vasodilatation is most prominent.[20] This suggests vascular responsiveness to these endogenous vasoconstrictors is impaired. Helmy *et al* have shown that peripheral vascular responses to angiotensin II are diminished in cirrhotic patients but can be restored by inhibition of local nitric oxide production.[21] Using a similar experimental approach, these workers observed that in patients with compensated cirrhosis, vasoconstrictor responses to ET-1 were significantly reduced compared with controls.[5 22] We have recently shown that infusion of ET-1 into the forearm of patients with

advanced liver disease and marked systemic vasodilatation actually elicits a vasodilation response but that following liver transplantation normal vasoconstriction responses to endothelin are restored.[23]

How can these altered peripheral vascular responses to endothelin be explained? Although in normal individuals the predominant response to ET-1 is vasoconstriction, it is known that this peptide has the capacity to produce both vasoconstrictor and vasodilatory responses. Two endothelin receptor subtypes, nominated endothelin A and endothelin B (ET-A and ET-B), have been cloned and characterised. Both receptors are present on vascular smooth muscle, and binding of ET-1 to these receptors leads to vasoconstriction.[24] However, ET-B receptors are also found on endothelial cells and binding of endothelin at this site mediates the release of vasodilators, including nitric oxide and prostacyclins.[25] Thus the overall response to an exogenous infusion of ET-1 reflects the balance of the effects of these various receptors and could be affected by changes in their individual activity or levels of expression on different cell types.

Helmy *et al* proposed that the diminished response to exogenous ET-1 might simply reflect greater basal ET-1 activity. This idea is supported by their finding of increased vasodilatation following ET-A antagonism in cirrhotics compared with controls[5 22] (that is, in cirrhotics there is a greater contribution of ET1, acting through the ET-A receptor, for maintenance of vascular tone). Alternatively, it could reflect an increase in ET-B mediated release of vasodilators in response to ET-1 that dampens ET-A mediated vasoconstriction. During ET-A blockade, endogenous ET-1 is able to act unopposed on ET-B receptors and this enhanced ET-B response is revealed. Our finding that the forearm vasculature of decompensated cirrhotics dilated in response to ET-1 is consistent with this concept of enhanced ET-B mediated vasodilatation, an effect that in these patients outweighs the normal ET-A mediated vasoconstrictor response and thus contributes to vasodilatation. The novel idea that ET-1 might contribute to vasodilatation of some vascular beds is supported by studies that have shown enhanced vasodilatation in response to a number of endothelium and nitric oxide dependent vasodilators in cirrhotics. Furthermore, ET-1 induced vasodilatation has recently been demonstrated in the pulmonary circulation of cirrhotic rats.[26]

Whether these intriguing findings in the forearm of cirrhotics reflect a general disturbance in endothelin responses in the systemic vascular or mesenteric circulation remains unclear. However, they emphasise that ET-1 and its antagonists could have quite different effects in patients with varying severity of liver disease and that the effects of endothelin antagonism might be beneficial in some parts of the circulation but harmful in others. For example, while ET-A antagonism might reduce ET-A mediated intrahepatic vasoconstriction, this beneficial effect could be outweighed by an increase in mesenteric and peripheral vasodilatation that could increase portal inflow and further exacerbate portal hypertension and systemic hypotension. In the liver, ET-1 binding to ET-B receptors increases sinusoidal resistance presumably because ET-B mediated vasoconstriction outweighs ET-B mediated release of vasodilators from the sinusoidal endothelium.[27 28] This effect may be enhanced in cirrhosis, since in the injured liver endothelial nitric oxide production is impaired.[2] Thus ET-B antagonism might be expected to lower portal pressure, by both reducing intrahepatic tone and reducing ET-B mediated vasodilatation of the peripheral and mesenteric circulatory bed. However, the ET-B receptor functions as a clearance receptor for endothelin and the potential beneficial effects of ET-B blockade may be counteracted by the unopposed action of displaced ET-1 on ET-A receptors.

Given this wealth of experimental data but an almost total lack of systemic interventional studies, the paper by Tripathi and colleagues[29] published in this issue of *Gut* is of considerable interest ***(see page 1290)***. This is the first study to examine the effects of systemic ET-A and ET-B receptor antagonism on systemic and portal haemodynamics in patients with cirrhosis. In keeping with findings in normal subjects, ET-A receptor blockade produced a reduction in blood pressure, reflecting a reduction in systemic vascular resistance, while ET-B blockade had the opposite effect. As might be predicted from studies in the forearm, ET-A antagonism appeared to produce a greater fall in blood pressure than has been observed in normals, including significant hypotension in one subject, and this may limit its therapeutic usefulness. Neither acute intervention produced a statistically significant effect on portal pressure, leading the authors to conclude that endothelin-1 does not contribute to portal haemodynamics in early cirrhosis.

However, there are a number of important caveats. Intravenous administration of antagonists may not be the optimal approach for blocking endothelin receptors in the hepatosplanchnic circulation as the drugs may be cleared by receptors in the lungs and systemic vascular bed and not reach the liver in sufficient concentrations to affect intrahepatic vascular tone. There was also considerable variability in portal pressure measurements in all treatment groups that may have contributed to failure to find statistically significant differences. Indeed there was a trend towards reduced hepatic venous pressure gradient with both blocking agents towards the end of the study period which might have reached significance with longer observation. Finally, most of the studies that have shown a beneficial effect of endothelin receptor antagonism in animal models of portal hypertension have used a combined ET-A/ET-B antagonist.[17–19] Combined blockade may be more effective as blockade of one receptor may simply allow unopposed action of the other. Clearly, further studies are needed to address these issues, and to identify whether changes in administration, dosage, or a combination of endothelin antagonists can lead to more therapeutically attractive effects on systemic and portal haemodynamics.

In the meantime, there are several other complications of cirrhosis in which ET-1 may play an important pathogenic role, and treatment with endothelin antagonists may be beneficial. Cirrhosis is commonly associated with changes in the pulmonary vasculature. Intriguingly, both pathological pulmonary vasodilatation[30] (hepatopulmonary syndrome) and vasoconstriction[31] (portopulmonary hypertension) have been described, and in some patients the two problems may even coexist. The mechanisms leading to these contrasting clinical problems remain unclear but there is both experimental and clinical evidence to suggest that ET-1 may be involved.[26 32] Increased ET-B receptor mediated pulmonary nitric oxide production, which is reversed by ET-B receptor antagonism, has been shown to play a central role in an animal model of hepatopulmonary syndrome but whether these findings are applicable to human hepatopulmonary syndrome is unknown.[12 26] The hypothesis that ET-1 contributes to pulmonary vasoconstriction in portopulmonary hypertension is supported by recent small studies which have shown that oral treatment with the mixed endothelin receptor antagonist bosentan is well tolerated and leads to reduced pulmonary vascular resistance.[33 34]

There is also major interest in the possible role of endothelin in hepatorenal syndrome.[7] Recent work in an animal model showed that renal failure could be reversed by treatment with

bosentan.[35] Furthermore, a small study in patients with advanced cirrhosis and hepatorenal syndrome showed an improvement in renal function following infusion of an ET-A receptor antagonist, without major effects on systemic haemodynamics.[36] Further studies of endothelin antagonism in patients with hepatorenal syndrome are awaited with interest, but once again achieving an appropriate balance between inhibition of local pathological endothelin mediated vasoconstriction and possible exacerbation of peripheral and mesenteric vasodilatation may prove difficult.

For the moment we are left with compelling experimental evidence that endothelin may be involved in many of the vascular abnormalities in patients with cirrhosis, and that its overall effects in different tissues may depend on differential expression of endothelin receptors on smooth muscle and endothelial cells. Whether inhibition of ET-A and/or ET-B responses proves to be therapeutically useful may well depend on the balance between systemic and local effects in different patient groups. The study of Tripathi *et al*, while largely negative, shows that systemic studies of ET blockade can be safely performed in cirrhotic patients and provides a stimulus for further investigation of the role of endothelin antagonists in the treatment of cirrhosis and its complications.

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