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Role of Endothelins

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Key Words
Liver cirrhosis · Portal pressure · Hepatic stellate cells · Sinusoidal endothelial cells · Kupffer cells · Ischemia-reperfusion injury

Hyperdynamic circulation as well as increased hepatic resistance contribute to portal hypertension in cirrhosis of the liver [1]. Hyperdynamic circulation with increased cardiac output, heart rate and plasma volume and decreased arterial blood pressure and systemic vascular resistance are characteristic in advanced cirrhosis. Systemic and splanchnic *vasodilatation* is pivotal for the hyperdynamic circulation. This has prompted intense research into a number of endogenous neurohumoral mediators with vasodilating properties (nitric oxide, natriuretic peptides, glucagon, etc.) [2, 3].

In recent years, however, mechanisms augmenting *intrahepatic vascular resistance* and thus contributing to portal hypertension have received increasing attention. In this respect, endothelins (ETs) are of particular interest [4–8].

ETs are a family of 21-amino acid polypeptides with potent vasoactive properties. ET-1 was first isolated in the supernatant of vascular endothelial cells [8] but later synthesis of both circulating isopeptides, ET-1 and ET-3, was shown in other organs such as the gastrointestinal tract [9]. ET-1 has mainly vasoconstrictive properties by acting on the ET_A receptor on smooth muscle cells. ET-1 binds with lower affinity also to the ET_B receptor on endothelial cells inducing a vasodilatation by the release of NO and prostacyclins. ET-1 exhibits a much higher affinity to the ET_A receptor than ET-3, whereas the ET_B receptor exhibits similar affinity for both isopeptides. Vascular response to ETs thus depends on the ratio of different receptors which seem to vary in different vascular regions [5–8] and can be affected by gender or culture conditions. The role of ET-3, particularly regarding portal pressure, has not been fully elucidated yet. Therefore, mainly ET-1 will be covered in this article.

ET Plasma Concentration and Hepatic Release in Cirrhosis

In patients with cirrhosis of the liver elevated arterial and venous plasma concentrations of ET-1 and ET-3 have been described [2, 10–16]. Interestingly, there is an increased hepatosplanchnic release of ET in these patients. Release of ET-1 (fig. 1) as well as arterial and venous plasma concentrations were found to correlate with the hepatic venous pressure gradient [13, 14]. These findings could indicate augmented hepatic ET-1 synthesis in cirrhosis and/or a role of ET-1 in the increase in portal pressure. Indeed, in the liver of cirrhotic rats increased concentrations of ET-1 protein and moreover an increased ET-receptor density has been described [17]. Furthermore, release of ET from isolated perfused liver as well as from

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Table 1. Synthesis of and receptors for endothelin-1 in nonparenchymal and parenchymal cells of the liver

Synthesis	Receptors
Sinusoidal endothelial cells	Hepatic stellate cells
Hepatic stellate cells >>	Sinusoidal endothelial cells >>
Kupffer cells	Kupffer cells
	Hepatocytes

sinusoidal endothelial cells upon stimulation by transforming growth factor-β have been observed [18, 19]. These findings raise the question as to which cells of the liver synthesize ET and whether this is stimulated in liver damage or cirrhosis.

ET Synthesis in Various Cell Types of the Liver

Expression of ET-1 in isolated liver cells was detected mainly in sinusoidal endothelial cells and stellate cells and to a lesser extent in Kupffer cells (table 1). Following liver injury by bile duct ligation, prepro ET-1 mRNA increased mainly in stellate cells and to a lesser extent in endothelial cells [20]. These data support the finding of ET-1 overexpression in stellate cells and sinusoidal endothelial cells of human cirrhotic liver [21]. Hepatic stellate cells are located in the space of Disse and surround the sinusoidal capillary composed of endothelial cells and Kupffer cells. This anatomic location suggests a role of stellate cells in the regulation of the diameter of liver sinusoids and thus of portal pressure possibly by endocrine or paracrine effects.

ET Effects on Various Cells of the Liver

ET receptors have been found mainly on stellate cells and sinusoidal endothelial cells, but also on Kupffer cells and hepatocytes (table 1) [22–24]. As shown recently, the ET-induced decrease in the hepatic microvascular blood flow is predominantly mediated by the contraction of stellate cells [23, 25–27]. Furthermore, recent evidence suggests an effect of ET on hepatic microvascular exchange in cirrhosis, possibly by affecting the fenestration of sinusoidal endothelial cells [28]. This might be another mechanism contributing to a decrease of hepatic function in cirrhosis.

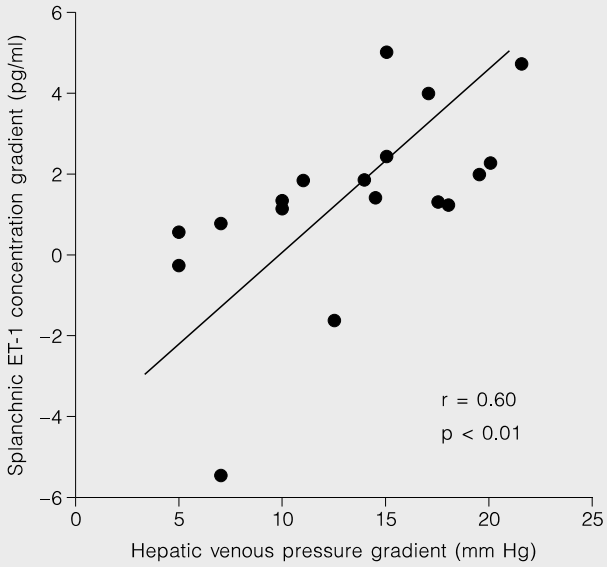

Fig. 1. Hepatosplanchnic release of endothelin-1 in patients with cirrhosis is related to the degree of portal hypertension as indicated by the hepatic-venous pressure gradient. Data adapted from Gerbes et al. [13].

ET and Portal Pressure

ET causes an increase of portal pressure in vivo as well as in isolated perfused liver [29, 30]. In cirrhotic liver, but not in controls, portal pressure decreases upon administration of an ET-receptor antagonist [31]. These data suggest a role of ET in modulating portal pressure, particularly in portal hypertension. In liver injury or cirrhosis as well as with ischemia-reperfusion injury, there is Kupffer cell activation as well as an increase in portal pressure. Interestingly, the activation of Kupffer cells seems to contribute to the increase of portal pressure. This is partly mediated by ET as was recently shown in isolated perfused rat liver [32].

Conclusions

Plasma concentrations of ETs are increased in cirrhosis which may be due to increased hepatosplanchnic release. This could reflect increased hepatic synthesis of ET-1, mainly by stellate and sinusoidal endothelial cells.

ET increases portal pressure, and ET-receptor blockade decreases portal hypertension in cirrhosis. ET also seems an important mediator of the increase in portal pressure upon Kupffer cell stimulation. Thus, ET modulates portal pressure and is involved in the pathophysiology of portal hypertension.

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