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Endothelin and Other Mediators in the Pathophysiology of Portal Hypertension

Key Words
Liver cirrhosis · Portal pressure · Hepatic stellate cells · Sinusoidal endothelial cells · Kupffer cells

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 *vasodilatation* is pivotal for the hyperdynamic circulation. This has prompted intense research of a number of endogenous neurohumoral mediators with vasodilating properties (NO, 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 (ET) are of particular interest [4–8].

ET 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 ET thus depends on the ratio of different receptors which seems to vary in different vascular regions [for reviews, see 5–8]. The role of ET-3, particularly regarding portal pressure, has not been fully elucidated yet. Therefore, mainly ET-1 will be covered in the following text.

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 (fig. 1). Release of ET-1 as well as arterial and venous plasma concentrations were found to correlate to the hepatic-venous-pressure gradient [13, 14]. In the liver of cirrhotic rats, increased concentrations of ET-1 and an increased ET receptor density have been described [17]. Furthermore, release of ET from isolated perfused liver as well as from sinusoidal endothelial cells upon stimulation by TGF-β have been observed [18, 19]. These findings raise the question 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

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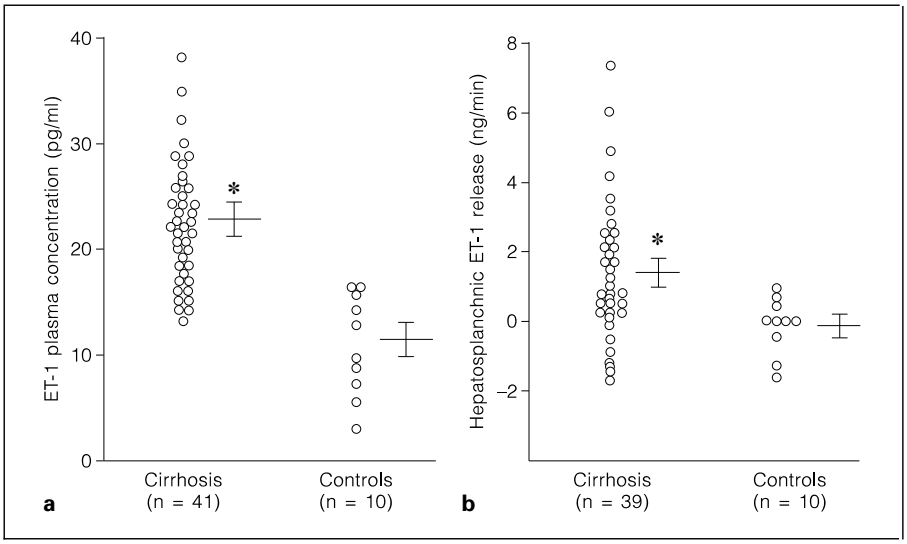

Fig. 1. ET-1 plasma concentrations in hepatic venous samples (**a**) and in femoral artery (data not shown) of patients with cirrhosis were significantly ($p < 0.0001$) higher than in control sujects. In the same patients, hepatosplanchnic release of ET-1 was increased ($p < 0.01$) compared to controls (**b**) [Data adapted from 14].

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

Synthesis	
Endothelial cells	> Stellate cells ⩾ Kupffer cells, Hepatocytes
Receptors	
Stellate cells	> Endothelial cells, Kupffer cells, Hepatocytes

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. The data on increased hepatic synthesis of ET in liver damage raise the issue of how ET affects portal pressure and whether there might be endocrine or paracrine effects involved.

ET and Portal Pressure

ET causes an increase of portal pressure in vivo as well as in isolated perfused liver [22, 23]. In cirrhotic liver, but not in controls, portal pressure decreases upon administration of an ET receptor antagonist [24]. These data suggest a role of ET in modulating portal pressure particularly in portal hypertension.

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) [25–27]. As shown recently, ET-induced decrease of the hepatic microvascular blood flow is predominantly mediated by the contraction of stellate cells [26, 28–30]. Therefore, an autocrine effect of ET appears as an interesting pathomechanism of portal hypertension: in liver damage, increased ET synthesis from stellate cells may induce an increase of portal pressure by contraction of these cells. Furthermore, recent evidence suggests an effect of ET on hepatic microvascular exchange in cirrhosis, possibly by affecting the fenestration of sinusoidal endothelial cells [31]. This might be another mechanism contributing to a decrease of hepatic function in cirrhosis. Finally, the increase of portal pressure upon Kupffer cell stimulation seems to be partly mediated by ET as was recently shown in isolated perfused rat liver [32].

In summary: In conclusion, plasma concentrations of ET 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 pres-

sure with sinusoidal constriction by stellate cells playing an important role. Thus, ET modulates portal pressure and is involved in the pathophysiology of portal hypertension.

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