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Review

Arachidonic acid metabolites and endothelial dysfunction of portal hypertension

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ABSTRACT

Increased resistance to portal flow and increased portal inflow due to mesenteric vasodilatation represent the main factors causing portal hypertension in cirrhosis. Endothelial cell dysfunction, defined as an imbalance between the synthesis, release, and effect of endothelial mediators of vascular tone, inflammation, thrombosis, and angiogenesis, plays a major role in the increase of resistance in portal circulation, in the decrease in the mesenteric one, in the development of collateral circulation. Reduced response to vasodilators in liver sinusoids and increased response in the mesenteric arterioles, and, viceversa, increased response to vasoconstrictors in the portal-sinusoidal circulation and decreased response in the mesenteric arterioles are also relevant to the pathophysiology of portal hypertension. Arachidonic acid (AA) metabolites through the three pathways, cyclooxygenase (COX), lipoxygenase, and cytochrome P450 monooxygenase and epoxygenase, are involved in endothelial dysfunction of portal hypertension. Increased thromboxane-A2 production by liver sinusoidal endothelial cells (LSECs) via increased COX-1 activity/expression, increased leukotriens, increased epoxyeicosatrienoic acids (EETs) (dilators of the peripheral arterial circulation, but vasoconstrictors of the portal-sinusoidal circulation), represent a major component in the increased portal resistance, in the decreased portal response to vasodilators and in the hyper-response to vasoconstrictors. Increased prostacyclin (PGI2) via COX-1 and COX-2 overexpression, and increased EETs/heme-oxygenase-1/K channels/gap junctions (endothelial derived hyperpolarizing factor system) play a major role in mesenteric vasodilatation, hyporeactivity to vasoconstrictors, and hyper-response to vasodilators. EETs, mediators of liver regeneration after hepatectomy and of angiogenesis, may play a role in the development of regenerative nodules and collateral circulation, through stimulation of vascular endothelial growth factor (VEGF) inside the liver and in the portal circulation. Pharmacological manipulation of AA metabolites may be beneficial for cirrhotic portal hypertension.

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1. Introduction

Portal hypertension, a common complication of chronic liver diseases, is defined as an increase in portal pressure above normal values of 10 mmHg. It is the result of an increase in portal vascular resistance and an elevated portal inflow (Fig. 1), and it causes the development of esophageal varices, ascites and hepatorenal syndrome, the hepatopulmonary syndrome, porto-pulmonary hypertension, encephalopathy [1–5]. Hypotension, low systemic vascular resistance, and reduced sensitivity to vasoconstrictors are common features of the hyperdynamic syndrome in portal hypertension, and are pathogenetic factors [3].

Endothelial cell (EC) signaling plays a pivotal role in the control of flow and pressure in the splanchnic circulation, and, on the other hand, the altered hemodynamic profile in portal hypertension, influences EC signaling, structure, and function in cirrhotics [6–9]. Endothelial-derived dilating factors, nitric oxide (NO), carbon monoxide (CO), prostacyclin (PGI2), and endothelial-derived hyperpolarizing factors (EDHF) are released from the arterial endothelium in response to both humoral and mechanical stimuli and can profoundly affect the function of the underlying vascular smooth muscle. Endothelial-derived contracting factors such as endothelin (ET), angiotensin II, thromboxaneA2 (TxA2), leukotrienes (LTs), are powerful vasoconstrictors released from the endothelium that are hormonally and mechanically induced, and can also affect vascular smooth muscle cells tone [8,9].

2. Endothelial function and dysfunction

Since the discovery in 1980 that acetylcholine (ACh) requires the presence of ECs to elicit vasodilation [10], the importance of the EC layer for vascular homeostasis has been increasingly appreciated. Dysfunction of the endothelium has been implicated in the pathophysiology of different forms of cardiovascular disease, including hypertension, coronary artery disease, chronic heart failure, peripheral artery disease, diabetes, and chronic renal failure. ECs sense mechanical stimuli, such as pressure and shear stress, and hormonal stimuli, such as vasoactive substances, releasing agents that regulate vasomotor function, trigger inflammatory processes, and affect hemostasis. The endothelium also contributes to mitogenesis, angiogenesis, vascular permeability, and fluid balance.

Endothelial dysfunction was initially identified as impaired vasodilation to specific stimuli such as ACh or bradykinin. A broader understanding of the term would include vasodilation, vasoconstriction, a proinflammatory and prothrombic state.

Endothelial dysfunction in liver sinusoidal endothelial cells (LSECs), and possibly in portal venules, decreases the production of vasodilators, and favours vasoconstriction. EC dysfunction in the splanchnic and systemic arterial circulation overproduces vasodilator molecules, leading to arterial vasodilatation. In addition, portal hypertension leads to the formation of portosystemic collateral vessels.

This review will examine the contributory role of AA metabolites in endothelial dysfunction of portal hypertension, considering the hepatic venous dysfunction and splanchnic arterial dysfunction separately.

3. Porto-sinusoidal circulation

There are several potential morphological sites for regulating blood flow through the sinusoids: the various segments of the afferent portal venules and hepatic arterioles, the sinusoids themselves, the central and hepatic venules. All these vessels contain several types of contractile cells and respond to pharmacologic agents [11]. The principal site of regulation of blood flow through the sinusoids is thought to reside in the sinusoid itself, where the major blood pressure drop occurs in the liver. The sinusoidal lining cells are responsive to a variety of pharmacologic substances. By contracting (or swelling), they may selectively reduce the patency of the sinusoid lumen and act like sphincters. The participation of perisinusoidal, stellate cells (far-storing, Ito cells) in regulating sinusoidal diameter has also been reported. ET-1 has been shown to cause contraction of isolated stellate cells in culture and to narrow the lumens of sinusoids in isolated perfused livers, although the principal site of vasoconstriction elicited by ET-1 was shown to be the preterminal portal venule [11].

Hepatic sinusoidal endothelium is discontinuous and possesses large (100–200 nm) membrane-bound, nondiaphragmed round cytoplasmic holes or fenestrae (occupying 6–8% of the endothelial surface) [12]. The fenestrae are arranged in sieve plates, which are approximately 0.1 μm in diameter and comprise 20–50 aggregated pores. Sinusoidal ECs also display gaps and lack an organized basement membrane. The sinusoidal endothelium functions as a selective sieve allowing for passage of small particles (up to medium-sized chylomicrons) from blood to hepatocytes via the space of Disse, and also contributes to vasomotor tone [13]. Cirrhosis is characterized by phenotype changes of LSEC, with capillarization, i.e. loss of fenestrae and abnormal deposition of a basement membrane matrix on the abluminal face, and endotheliopathy. Further, LSEC dysfunction results in increased inflammation due to impaired immune tolerance and defenestration [14–16]. One of the first demonstrations that vasoconstriction in the cirrhotic hepatic portal circulation contributes to portal hypertension, was given by Bhathal and Grossman in 1985 [17]. They showed that the isolated perfused cirrhotic liver has a mean resistance which is approximately 110% higher than the normal liver. The vascular tone of the normal liver is minimal as assessed by the response to a variety of vasodilator agents, including sodium nitroprusside, magnesium sulphate, papaverine hydrochloride, and cytochalasin B. In contrast, these agents reduce the perfusion resistance of the cirrhotic livers by approximately 15%. Prostaglandin E1 produces a lesser fall in resistance which nevertheless is greater in cirrhotic livers than controls. Gupta et al. [18] showed that after preconstricting the intrahepatic microcirculation with methoxamine, vasorelaxation to cumulative doses of receptor-mediated endothelial agonist, ACh, and to receptor-independent endothelial agonist, calcium ionophore A23187, is significantly less in cirrhotic livers as compared with normal livers. The impaired vasorelaxation is a result of a decrease in both NO-mediated and non-NO-mediated components of vasorelaxation. In human cirrhotic portal hypertension, NO donors are effective in reducing hepatic resistance to portal flow [19].

Furthermore, also vasoconstriction to endothelin-1 (ET-1) [20] methoxamine [21], leukotriene-D4 [22] is increased in the cirrhotic portal hepatic circulation.

EC dysfunction seen in the portal intrahepatic/sinusoidal microcirculation contributes to the increased intrahepatic vascular resistance, and, thus, to portal hypertension. LSECs have far-reaching effects regulating liver functions, including blood clearance, vascular tone, immunity, hepatocyte growth [23] and angiogenesis/sinusoidal remodeling [24]. Thus, LSEC dysfunction results in a pathology contributing to impaired vasomotor control (primarily vasoconstrictive), inflammation, fibrosis, liver regeneration [23] and pathological angiogenic/sinusoidal remodeling [24]. These factors facilitate the development of cirrhosis and portal hypertension [13].

Oxidative stress is a main cause of EC dysfunction. Patients with cirrhosis have elevated oxidative stress [25] and administration of the antioxidant vitamin C markedly attenuates postprandial increases in portal pressure, suggesting that increased oxidative stress in cirrhotic patients contributes to portal hypertension. In