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Molecular Mechanisms Leading to Splanchnic Vasodilation in Liver Cirrhosis

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Abstract
In liver cirrhosis, portal hypertension is a consequence of enhanced intrahepatic vascular resistance and portal blood flow. Significant vasodilation in the arterial splanchnic district is crucial for an increase in portal flow. In this pathological condition, increased levels of circulating endogenous vasodilators, including nitric oxide, prostacyclin, carbon monoxide, epoxyeicosatrienoic acids, glucagon, endogenous cannabinoids, and adrenomedullin, and a decreased vascular response to vasoconstrictors are the main mechanisms underlying splanchnic vasodilation. In this review, the molecular pathways leading to splanchnic vasodilation will be discussed in detail.

Introduction

Portal venous pressure results from intrahepatic resistance and portal flow, expressed as a mathematical function of resistance and flow across the hepatic vasculature (pressure = resistance · flow). A pathological increase in portal pressure is called portal hypertension.

In liver cirrhosis, increases in portal pressure are primarily caused by a high resistance to outflow in the portal district due to structural modifications and a vasoactive component. When portal hypertension is established, splanchnic arterial vasodilation, a hyperdynamic circulatory syndrome with an enhanced cardiac output, and opening of portosystemic collaterals occur, causing an enhanced splanchnic flow that perpetuates and aggravates the portal pressure increase, promoting decompensation in cirrhotic patients (Fig. 1). Portal hypertension plays a fundamental role in the development of ascites, hepatic encephalopathy, gastric and esophageal varices, and hepatorenal syndrome, which are among the most serious clinical complications in these patients [1–3]. Therefore, understanding the mechanisms responsible for splanchnic vasodilation is crucial for planning strategies to prevent and treat the complications that occur in cirrhosis.

In cirrhosis with portal hypertension, splanchnic arterial vasodilation occurs both in mesenteric and in splenic vascular beds, and a low splanchnic vascular resistance depends mostly on precapillary resistance arteries [4]. The underlying molecular pathways have not been entirely delineated, but an increased production of vasodilating substances and an impaired vascular response to vasoconstrictors are the main mechanisms proposed [5, 6]. The aim of this review is to discuss in detail the principal systems and substances that have been identified as mediators in this context.

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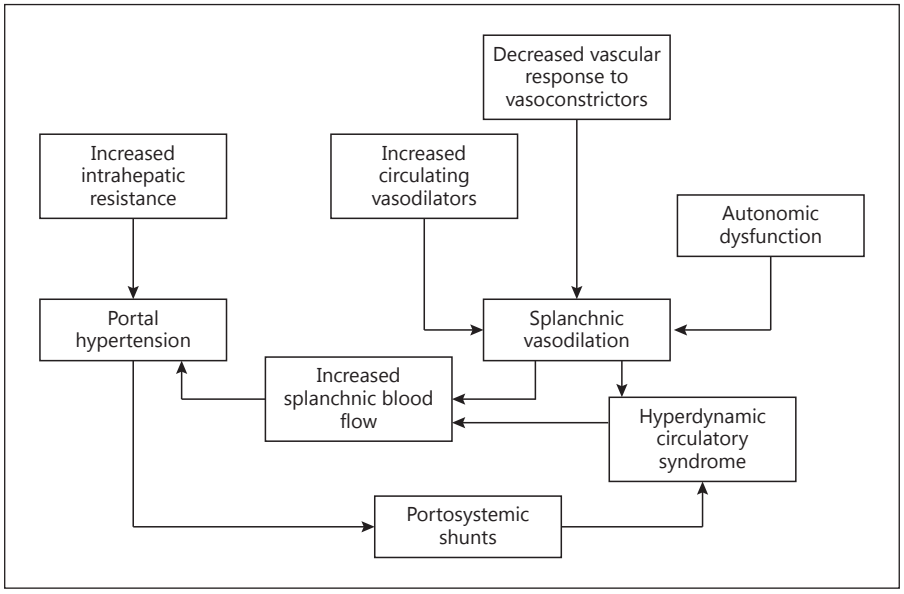

Fig. 1. Crucial role of splanchnic vasodilation in the onset and worsening of portal hypertension in liver cirrhosis.

Increased Circulating Vasodilators

Nitric Oxide

Nitric oxide (NO) is a brief-half-life (20–30 s) free-radical gas that freely passes through the membranes of cells. It exerts its vasodilating effect via the activation of guanylyl cyclase to synthesize cGMP and the subsequent relaxation of vascular smooth muscle cells. It is generated by NO synthase (NOS), of which 4 major isoforms exist: inducible NOS (iNOS), endothelial NOS (eNOS), neuronal NOS (nNOS), and mitochondrial NOS. While a reduced production of NO has been observed in cirrhotic livers [7], there is general agreement in considering an increased NO production in the mesenteric vasculature as the crucial factor responsible for the decrease in splanchnic resistance in cirrhosis. In decompensated cirrhotic patients, plasma levels of NO-hemoglobin complexes are increased [8]. Moreover, in the portal vein plasma NO concentrations are higher than in peripheral veins, indicating an increased synthesis in the splanchnic vasculature. NOS inhibition effectively contrasts the increase in splanchnic flow in cirrhotic rats [9], confirming its fundamental role in determining the hemodynamic alterations typical of this pathological condition. In rats with ligation of the portal vein, an overproduction of NO by eNOS in the endothelium of superior mesenteric arteries occurs before the onset of a splanchnic hyperdynamic circulation [10], suggesting that in portal hypertension NO is a fundamental participant in the generation of hyperdynamic circulation.

The increased NO bioavailability is secondary to the increase in both NOS expression and activity. In cirrhotic rats, iNOS and eNOS expression is enhanced in arterial vessels [11], and eNOS concentrations in extracts of mesenteric arteries are more than double compared to values in control rats [12]. In this animal model, also the vascular levels of mRNA for the enzyme are significantly higher [11]. In rats with portal hypertension, even a small increase in portal pressure is associated with an increased eNOS expression [13], while in eNOS knockout mice injected with carbon tetrachloride a reduced splanchnic blood flow is present [14]. In their portal vein and superior mesenteric artery, also eNOS activity is elevated, as shown by the measurement of the conversion to citrulline of M-arginine [15]. Activation of eNOS has been observed already 10 h after ligation of the portal vein [16]. In cirrhosis, eNOS is activated in the vasculature by several stimuli that originate from the endothelium, such as inflammatory cytokines, shear stress, and VEGF [17]. Other mechanisms have been shown to be involved in activation of the eNOS signaling pathway under this pathological condition, including upregulation of GTP cyclohydrolase I, mediated by bacterial translocation, with production of tetrahydrobiopterin (cofactor of eNOS) [18], phosphorylation of eNOS by Akt [19], and coupling of eNOS with chaperone heat shock protein 90 [20]. Recently, a new mechanism for eNOS modulation in cirrhosis, involving the renin-angiotensin system, was shown [21]. Angiotensin-converting enzyme (ACE) 2 cleaves angiotensin II to generate the vasodilator angio-

tensin-(1–7), which binds to the receptor Mas (MasR), leading to the activation of eNOS and the endothelial production of NO. In the mesenteric arterial vasculature of cirrhotic rats, ACE2 and MasR expression and the production of angiotensin-(1–7) are increased, contributing to vasodilation in this vascular district. Even though all of these studies suggest that eNOS mediates the splanchnic vasodilatory response in cirrhosis, another study reported that, after portal vein ligation, in eNOS-knockout mice the portal pressure still rose and a hyperdynamic circulation developed [22], suggesting the involvement of other NOS isoforms or other pathways. Indeed, bacterial infection, cytokines, and endotoxins promote also iNOS production. In patients with cirrhosis, intestinal bacterial overgrowth frequently occurs and is associated with systemic endotoxemia. Because endotoxin enhances the expression of iNOS, it has been hypothesized that in cirrhosis circulating endotoxin stimulates the vascular production of NO [23]. In patients with cirrhosis, selective iNOS inhibition causes peripheral vasoconstriction [24]. In the adventitia of mesenteric vessels from cirrhotic rats, higher levels of activated macrophages that express iNOS have been documented [25]. Therefore, activation of iNOS in these cells may induce, in a paracrine way, an increase in splanchnic flow, contributing to the worsening of portal hypertension. Also nNOS may induce splanchnic vasodilation, even if its role seems less relevant [26].

Carbon Monoxide

Carbon monoxide (CO) is an endogenous gaseous molecule similar to NO. In humans, the main source of CO is the enzyme heme oxygenase (HO), which catalyzes the degradation to biliverdin of heme. The two main HO isoenzymes are HO-1, the inducible isoform, and HO-2, which is constitutive. In arterial vessels, CO, generated both in smooth muscle and in endothelial cells, promotes smooth muscle myocyte relaxation through stimulation of soluble guanylyl cyclase and activation of large conductance Ca^{2+}-activated K^+ channels (BK_{Ca}s) [27]. The vasodilating properties of CO are also due to its capability to inhibit formation of the vasoconstrictor molecule 20-hydroxyeicosatetraenoic acid [28]. Patients with cirrhosis exhibit significant increases in carboxyhemoglobin plasma levels [29]. An increase in HO-1 expression has been documented in the mesenteric vasculature of rats with prehepatic portal hypertension [30] and common bile duct ligation [31] and in rats treated with CCl_4 [32]. In CCl_4-cirrhotic rats, also an enhanced HO-2 expression has been observed [33]. In different animal models of cirrhosis and portal hypertension, HO inhibition ameliorated both the mesenteric vascular response to vasoconstrictors and the alterations in systemic hemodynamics. Moreover, we have demonstrated that in the advanced stages of cirrhosis an increased HO expression has a determinant role in impairing the contractile response of mesenteric arteries to phenylephrine, while overexpression of NOS is the main responsible factor in early stages [32]. In advanced cirrhosis, induction of HO-1 could be the cause of the diminished NO generation, and the mechanisms involve the competition between NOS and HO for the use of NADPH, the heme degradation necessary to assemble NOS, and the binding of CO to the NOS prosthetic heme group. NO levels, oxidative stress, glucagon, and angiotensin II induce the expression of HO-1, and in cirrhosis they may be the determiners of its increase in the periferic vascular system [34, 35]. In cirrhotic rats, especially in ascitic animals, along with an increased HO-1 expression, an enhanced BK_{Ca} α-subunit expression has been observed in mesenteric arteries, and inhibition of BK_{Ca} and HO normalized the increased response to acetylcholine [36]. CORM-3, a molecule that releases CO, induced mesenteric arterial vasodilation in cirrhotic ascitic rats, and this was amplified by pretreatment with the HO-inhibitor chromium mesoporphyrin. Furthermore, the dilation induced by CO was abolished after the inhibition of not only soluble guanylyl cyclase but also BK_{Ca}, underlining the crucial role of those channels in modulating the vascular effects of CO in decompensated cirrhosis. Moreover, in cirrhosis, the impaired responsiveness of mesenteric arteries to acute flow variations, which is likely secondary to a preexistent overproduction of vasodilators by the endothelium, seems to be due to a product of HO [37]. The mechanism leading to this HO-enhanced expression and activity in the vasculature still needs investigation, but it is probably multifactorial since several factors contributing to the development of portal hypertension, including oxidative stress, cytokines, and endotoxins, are known HO inducers.

Prostacyclin (Prostaglandin I2)

Prostaglandin I2 (PGI_2) is another vasodilator derived from the endothelium. It is synthesized by cyclooxygenases (COX) in response to both humoral and physical stimuli, including shear stress and proinflammatory substances. In vascular smooth myocytes, PGI_2 induces relaxation by promoting adenylyl cyclase activation and, as a consequence, inducing cyclic adenosine monophosphate production. In portal-hypertensive rats, an increased basal synthesis of PGI_2 seems pivotal in determining vascular hypocontractility and vasodilation [38]. In

patients with cirrhosis, the circulating PGI_2 concentrations are increased [39]. Moreover, in this group of patients, PGI_2 inhibition with indomethacin significantly increases the peripheral vascular resistance and reduces the hepatic blood flow, with a decrease, even if slight, in portal pressure, suggesting a role for PGI_2 in the induction of splanchnic vasodilation and, as a consequence, portal hypertension [40]. Also in cirrhotic rats and rats with ligation of the portal vein, plasma and urinary levels of PGI_2 are higher than in controls [41]. In the same study it was demonstrated that the increase in PGI_2 plays a role in the elevation of portal pressure and hyperdynamic circulation development in experimental cirrhosis. In portal-hypertensive animals, indomethacin significantly reduced circulating levels of PGI_2, decreasing splanchnic blood flow, but it failed to modify the splanchnic blood flow in control rats, suggesting a minor role of PGI_2 under physiological conditions [42]. In contradiction with this study, in which it was shown that in the mesenteric artery of rats with portal hypertension COX-1 expression was enhanced while COX-2 expression was not detectable, other authors showed that also selective COX-2 inhibition could be effective in improving portal hypertension [43]. The increase in PGI_2 levels preceded the development of hemodynamic changes, suggesting that hyperdynamic circulation is mostly a consequence and not a primary cause of the enhanced PGI_2 release within the splanchnic vasculature.

Probably, in the development of portal hypertension, a PGI_2 and NO interaction promotes splanchnic hyperemia. In rats with portal vein stenosis, both short- and long-term treatment with indomethacin decreased the mesenteric arterial flow; however, after long-term treatment it remained higher. Interestingly, the impaired effect of long-term treatment with indomethacin was associated with increased sensitivity to the NOS inhibitor NG-nitro-L-arginine methyl ester, suggesting an enhanced NO production after long-term PGI_2 inhibition [44]. In portal hypertension, several stimuli, including shear stress and proinflammatory substances, induce COX in endothelial cells to produce PGI_2. In patients with cirrhosis, its production may be induced also by circulating microparticles, released by various cells, that carry arachidonic acid into endothelial cells, stimulating COX activity [45].

Epoxyeicosatrienoic Acids

Epoxyeicosatrienoic acids (EET), derived from the arachidonic acid metabolism by cytochrome P-450 (CYP) epoxygenase enzymes, exist in 4 regioisomeric epoxides: 5,6-EET, 8,9-EET, 11,12-EET, and 14,15-EET. Vascular endothelial cells are major sites for the production of EET, which have various biological activities (e.g., an effect on vascular tone among others). In particular, with regard to portal hypertension progression, they have a dual behavior: in the peripheral vascular beds they have a dilating effect, but in the portal and sinusoidal circulation they are vasoconstrictors [46]. EET are important mediators in endothelium-dependent mesenteric relaxation in cirrhosis, but their effect is only mild under physiological conditions. In fact, inhibition of epoxygenase modifies the mesenteric vasodilatory response to acetylcholine only in rats with cirrhosis [47], indicating that an altered EET balance in the splanchnic vascular bed is characteristic of cirrhosis. Plasma EET concentrations increase significantly in cirrhotic patients compared to healthy individuals, but the ratios between 8,9-EET, 11,12-EET, and 14,15-EET are similar [48]. Moreover, in these patients, the peripheral vasoconstriction induced by miconazole, a nonspecific inhibitor of EET synthesis, is increased compared to healthy subjects. In cirrhosis, changes in the vascular expression of CYP may be crucial for the increase in circulating EET [49]. Endothelium-derived 11,12-EET exerts a hyperpolarizing effect through the activation of calcium-activated potassium channels [50, 51]. Moreover, a strong interaction between EET and the HO system is well documented [52]. In rat mesenteric arteries, 11,12-EET exerts a dilator effect through a mechanism that is HO dependent, acting via calcium-activated potassium channels. Also 5,6-EET, 8,9-EET, and 14,15-EET vasodilate mesenteric arteries, but only 8,9-EET acts similarly to 11,12-EET, while 5,6-EET promotes vasodilation independently of guanylyl cyclase and HO, and HO inhibition only partly impairs the effect of 14,15-EET [53]. In mesenteric arteries from cirrhotic rats, enhanced vasodilation, independent of NO and PGI_2, is promoted by increased reactivity to 11,12-EET via an enhanced myoendothelial gap junction expression (in particular connexins 40 and 43) [54]. Recently, we demonstrated that, in experimental cirrhosis, treatment with a specific inhibitor of epoxygenase significantly reduces the portal blood flow and pressure, in association with normalization of the response to acetylcholine of mesenteric arteries [47].

Glucagon

Glucagon is a peptide hormone released by pancreas α-cells that, apart from regulating glucose levels by promoting gluconeogenesis and glycogenolysis, is known to reduce vascular resistance. In cirrhosis, due to the poor hepatic function and the presence of numerous vascular portosystemic collaterals, glucagon escapes immediate

hepatic degradation. In portal hypertension, hypersecretion from pancreatic α-cells also contributes to hyperglucagonism [55]. In patients with cirrhosis, compared to normal subjects, glucagon levels are much higher and hemodynamic responses are blunted after glucagon administration [56]. In portal hypertension, glucagon contributes to the onset and progression of hyperdynamic circulation and the decrease in mesenteric arterial reactivity to circulating vasoconstrictors, as indicated by the observation that in portal-hypertensive rats the decrease in portal blood flow and pressure induced by somatostatin is secondary to the inhibition of glucagon secretion [57]. In cirrhotic patients with active gastrointestinal bleeding, the efficacy of somatostatin analogs is ascribable to the capability of reducing portal hypertension [58].

Endogenous Cannabinoids

Endogenous cannabinoids (EC), such as anandamide, are ubiquitous lipid signaling molecules that are synthesized from membrane phospholipids. CB1 is a specific EC receptor present in perivascular nerves and in smooth muscle and endothelial cells [59]. High concentrations of circulating EC have been documented in patients with cirrhosis [60]. In the splanchnic vasculature, the effects of EC are likely secondary to an increased production of NO [61] but also to mechanisms independent of NO. Indeed, in mesenteric arteries of cirrhotic rats, NOS inhibition or endothelial denudation did not abolish vasodilation [62]. Overactivation of vascular CB1 receptors is implicated in mesenteric blood flow and portal pressure elevation in cirrhosis. In this pathological condition, due to bacterial translocation and endotoxemia, the release of EC by macrophages and monocytes is increased, leading to activation of CB1 in the vessels and perivascular nerves and vasodilation [63]. In CCl_4-cirrhotic rats, administration of a CB1 receptor antagonist caused a significant reduction in ascite formation [64]. Apart from CB1, other receptors, such as TRPV1, may be implicated in the EC-dependent vasorelaxation of liver cirrhosis. TRPV1, expressed in perivascular nerves, has been shown to mediate the hypotensive effect of EC in cirrhosis [65]. Moreover, it has been shown that in cirrhotic rats pretreatment with a molecule blocking the response of sensory nerves impairs the mesenteric artery vasorelaxation induced by anandamide, suggesting that the signaling pathway leading to relaxation is located in the adventitia of the vessels, where primary sensory nerves are situated. Anandamide determines a dose-dependent vasodilator response in mesenteric but not in femoral arteries of cirrhotic rats, highlighting the selectivity of EC effects in the splanchnic circulation [66].

Adrenomedullin

Adrenomedullin (ADM) is a peptide with a potent vasodilating effect, produced in the endothelial cells of vessels. In the aorta and portal vein of cirrhotic rats, ADM gene expression is enhanced compared to controls [67]. Moreover, levels of circulating ADM are significantly higher in patients with cirrhosis [68]. The elevation is more prominent in patients with ascites, suggesting that circulating levels of ADM correlate with the severity of hemodynamic changes [69, 70]. ADM production increases after stimulation with bacterial endotoxin and cytokines [71]. In cirrhosis, ADM plasma levels correlate with nitrate-nitrite levels [72]: ADM seems to modulate endothelium-dependent vasorelaxation by phosphorylating and activating Akt with a consequent increase in cGMP production [73]. Interestingly, in aortas of cirrhotic rats, anti-ADM antibody administration reversed the blunted contractile response to phenylephrine [67].

Impaired Reactivity to Circulating Vasoconstrictors

Concomitant with the increased circulating levels of vasodilating substances, splanchnic arteries exhibit a decreased contractile response to vasoconstrictors. A decreased expression or sensitivity of the receptors for vasoconstrictor substances is the probable mechanism accounting for the occurrence of a marked vasodilatation in the splanchnic arterial bed in spite of the increased levels of vasoconstrictors.

In portal hypertension, the downregulation of neuropeptide Y, involved in adrenergic neurotransmission, causes a reduction in reactivity to noradrenaline [74]. In cirrhosis, the increased systemic levels of norepinephrine may induce the presynaptic α_2-adrenergic inhibition of neuropeptide Y production [75]. Moreover, the activity of dipeptidyl-peptidase IV, which degrades neuropeptide Y, is increased in cirrhosis [76]. In CCl_4-induced cirrhotic rats, neuropeptide Y administration enhanced the mesenteric arterial contractility and decreased the portal blood flow and pressure [77].

Endothelin-1, despite its marked vascular constrictor capability, induces vasodilation when it binds to ETB1 receptor [78]. In the splanchnic circulation of bile duct-ligated cirrhotic rats, levels of endothlin-1 were decreased, while ETB receptor expression was increased [79]. Moreover, the expression of phosphorylated G protein-coupled receptor kinases, that desensitize the vasoconstriction-promoter ETA receptor, was substantially increased in cirrhotic rats.

In cirrhosis, the renin-angiotensin-aldosterone system activates to homeostatically compensate the intense vasodilation. In cirrhotic rats, the vascular hyporesponsiveness to angiotensin II is a consequence of the increased interaction between β-arrestin-2 and angiotensin II type 1 receptor, and the consecutive change in receptor activity [80].

In cirrhosis, a reduced expression or activity of Rho kinase represents another mechanism that contributes to the impaired contractile response [81].

Neural Autonomic Dysfunction

Other studies have reported a contribution of neural autonomic dysfunction in the pathogenesis of the decreased splanchnic arterial resistance. The neural regulation of splanchnic vascular tone occurs through the central and peripheral efferent and afferent nervous system. In portal-hypertensive and cirrhotic rats, neurons in the cardiovascular regulatory nuclei are persistently activated [82]. In these animal models, denervation of the primary afferent nerves normalized systemic vascular resistance [83, 84]. In portal hypertension, the reactivity to noradrenaline is also altered due to mesenteric sympathetic nerve atrophy, which is caused by processes of axonal retraction and apoptosis taking place in the neurons of sympathetic ganglia [85]. A sustained overactivation of the sympathetic nervous system could be accountable for desensitization in the splanchnic vascular bed, thus worsening vasodilation [86].

Conclusion

NO, the circulating levels of which are increased in cirrhosis, seems to be the fundamental, but not the only, factor mediating splanchnic vasodilation. The involvement of CO, PGI_2, EET, glucagon, EC, and ADM, among other endogenous vasodilators, has been shown. A decreased reactivity to vasoconstrictors in the splanchnic vasculature and neural autonomic dysfunction also play a role in this process.

Disclosure Statement

The authors declare that there is no conflict of interests regarding the publication of this paper.

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