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The Molecules: Abnormal Vasculatures in the Splanchnic and Systemic Circulation in Portal Hypertension

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1. Introduction

Portal hypertension, defined as an increase in pressure within the portal vein, is a detrimental complication in liver diseases. The increased intrahepatic resistance as a consequence of cirrhosis is the primary cause of portal hypertension (Figure 1). Once it is developed, portal hypertension influences extrahepatic vascular beds in the splanchnic and systemic circulation. Two major consequences of portal hypertension in this regard are excessive arterial vasodilation/hypocontractility and the formation of portosystemic collateral vessels. Both excessive arterial vasodilation and portosystemic collateral vessel formation help to increase the blood flow through the portal vein and worsen portal hypertension. This facilitates the development of the abnormal hemodynamic condition, called the hyperdynamic circulatory syndrome, and ultimately leads to variceal bleeding and ascites (Bosch 2000; Bosch 2007; Groszmann 1993; Iwakiri 2011; Iwakiri & Groszmann 2006).

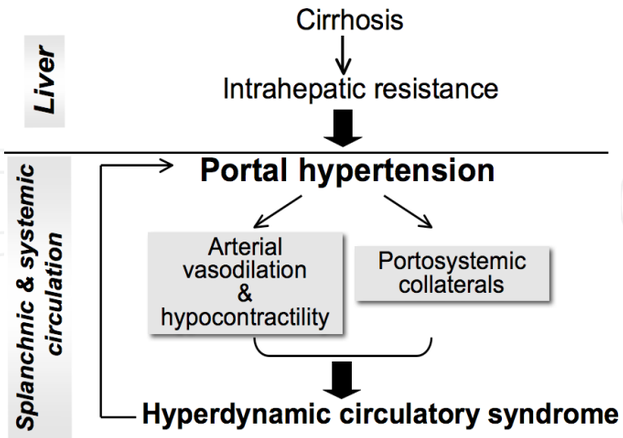

Fig. 1. Overview of portal hypertension.

This chapter summarizes current knowledge of molecules and factors that play critical roles in the development and maintenance of excessive arterial vasodilation and portosystemic collateral vessels in the splanchnic and systemic circulation in cirrhosis and portal

hypertension. The chapter concludes with a brief discussion about the future directions of this area of study.

2. Key molecules and factors – Excessive arterial vasodilation/hypocontractility

This section addresses molecules and factors that are involved in the development and maintenance of excessive arterial vasodilation/hypocontractility in cirrhosis and portal hypertension.

2.1 Key molecules

The molecules discussed here include nitric oxide (NO), carbon monoxide (CO), prostacyclin (PGI_2), endocannabinoids, Endothelium-derived hyperpolarizing factor (EDHF), adrenomedullin, tumor necrotic factor alpha (TNFα), bradykinin and urotensin II. In addition to these vasodilatory molecules, decreased response to vasoconstrictors, such as neuropeptide Y, also contributes to hypocontractility of mesenteric arterial beds (i.e., arteries of the splanchnic circulation).

2.1.1 Nitric oxide

Nitric oxide (NO) is the most potent vasodilatory molecule in vessels and contributes to excessive arterial vasodilation in the splanchnic and systemic circulation in portal hypertension perhaps to the most significant degree. NO, synthesized by endothelial NO synthase (eNOS) in the endothelium, defuses into smooth muscle cells and activates guanylate cyclase (GC) to produce cyclic guanosine monophosphate (cGMP) (Arnold, et al. 1977; Furchgott & Zawadzki 1980; Ignarro, et al. 1987), facilitating vessel relaxation.

In portal hypertension, elevated eNOS activity causes overproduction of NO and the resultant excessive arterial vasodilation in the splanchnic and systemic circulation. As for the other two NOS isoforms, neuronal NOS (nNOS) and inducible NOS (iNOS), a couple of studies suggest that nNOS, which resides in the nerve terminus and smooth muscle cells of the vasculature, also contributes to excessive arterial vasodilation in portal hypertension, although its effect is small (Jurzik, et al. 2005; Kwon 2004). In contrast to eNOS and nNOS, which are constitutively expressed, iNOS is generally expressed in the presence of endotoxin and inflammatory cytokines and generates a large amount of NO. Interestingly, however, despite the presence of bacterial translocation and endotoxin in cirrhosis, iNOS has not been detected in arteries of the splanchnic and systemic circulation in cirrhosis and portal hypertension (Fernandez, et al. 1995; Heinemann & Stauber 1995; Iwakiri, et al. 2002; Morales-Ruiz, et al. 1996; Sogni, et al. 1997; Weigert, et al. 1995; Wiest, et al. 1999). This paradox remains to be elucidated. Accordingly, eNOS would be the most important among the three isoforms of NOS for excessive vasodilation observed in arteries of the splanchnic and systemic circulation in portal hypertension (Iwakiri 2011; Iwakiri & Groszmann 2006; Wiest & Groszmann 1999).

eNOS is regulated by complex protein-protein interactions, posttranslational modifications and cofactors (Sessa 2004). A summary of mechanisms that activate eNOS is shown in Figure 2. Below presented are several proteins that have been reported to increase eNOS

activity in the superior mesenteric artery (i.e., an artery of the splanchnic circulation) of portal hypertensive rats.

2.1.1.1 Heat shock protein 90 (Hsp90)

This figure shows a general idea of eNOS regulation, not limited to portal hypertension. Caveolin-1 inhibits eNOS activity, while eNOS is activated through interactions with heat shock protein 90 (Hsp90), tetrahydrobiopterin (BH_4), guanosine triphosphate (GPT) and calcium calmodulin (CaM). Additionally, eNOS is phosphorylated and activated by Akt, also known as protein kinase B. VEGF; vascular endothelial growth factor, TNFα; tumor necrosis factor alpha.

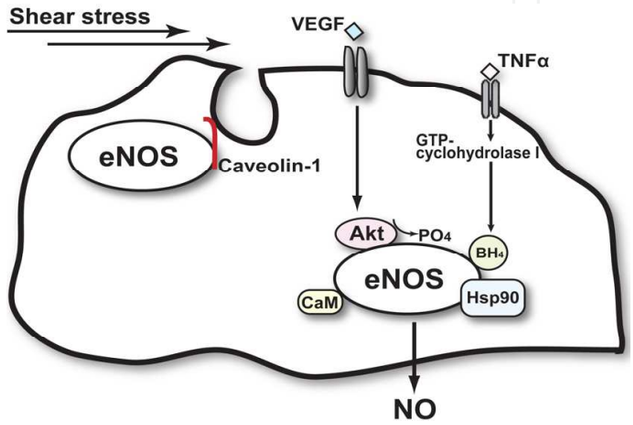

Fig. 2. Endothelial nitric oxide synthase (eNOS) is regulated by complex protein-protein interactions and posttranslational modifications.

A molecular chaperone, Hsp90, acts as a mediator of a signaling cascade leading to eNOS activation (Garcia-Cardena, et al. 1998). In the superior mesenteric artery isolated from portal hypertensive rats, an Hsp90 inhibitor, geldanamycin (GA), partially attenuated excessive vasodilation (Shah, et al. 1999). This observation suggests that Hsp90, at least in part, plays a role in elevated activation of eNOS, which causes overproduction of NO in the superior mesenteric artery in portal hypertensive rats.

2.1.1.2 Tetrahydrobiopterin (BH4)

eNOS requires BH_4 for its activity (Cosentino & Katusic 1995; Mayer & Werner 1995). Cirrhosis increases circulating endotoxin, which elevates activity of guanosine triphosphate (GPT)-cyclohydrolase I, an enzyme that generates BH_4. One study shows that increased levels of BH_4, as a result of cirrhosis, enhance eNOS activity in the superior mesenteric artery (Wiest, et al. 2003). Thus, an increase in BH_4 production in the superior mesenteric artery of cirrhotic rats is thought to be one of the mechanisms by which eNOS contributes to excessive arterial vasodilation.

2.1.1.3 Akt/protein kinase B

Akt, a serine/threonine kinase, can directly phosphorylate eNOS on Serine1177 (human) or Serine1179 (bovine) and activates eNOS, leading to NO production (Dimmeler, et al. 1999; Fulton, et al. 1999). We have shown that portal hypertension increases eNOS

phosphorylation by Akt in the superior mesenteric artery and that wortmannin, an inhibitor of the phosphatidylinositol-3-OH-kinase (PI3K)/Akt pathway, decreases NO production and excessive vasodilation in the superior mesenteric artery isolated from portal hypertensive rats (Iwakiri, et al. 2002). These observations suggest that Akt-dependent phosphorylation and activation of eNOS play a role in excessive NO production and the resulting vasodilation in the superior mesenteric artery of portal hypertensive rats.

Since eNOS is the major NOS that generates NO in arteries of the splanchnic and systemic circulation, understanding the mechanisms by which eNOS is activated in these arteries is essential and allows us to develop critical strategies to block excessive arterial vasodilation and the subsequent development of the hyperdynamic circulatory syndrome.

2.1.2 Carbon monoxide (CO)

CO is an end product of the heme oxygenase (HO) pathway and a potent vasodilatory molecule that functions in a similar mechanism to NO (Figure 3). It activates sGC in vascular smooth muscle cells and regulates the blood flow and resistance in several vascular beds (Naik & Walker 2003). HO has two isoforms, HO-1 and HO-2. HO-1, also known as heat shock protein 32, is an inducible isoform. HO-2, a ubiquitously expressed constitutive isoform, is also found in blood vessels (Ishizuka, et al. 1997; Zakhary, et al. 1996). In pathological conditions, HO activity increases markedly due to the up-regulation of HO-1 (Cruse & Lewis 1988). Several experimental and clinical studies have shown a possible relationship between HO pathway and several complications of cirrhosis and portal hypertension, such as cardiac dysfunction (Liu, et al. 2001), renal dysfunction (Miyazono, et al. 2002), hepatopulmonary syndrome (Carter, et al. 2002), spontaneous bacterial peritonitis (De las Heras, et al. 2003) and viral hepatitis (Tarquini, et al. 2009).

Increased portal pressure alone contributes to the activation of HO pathway in mesenteric arteries and other organs (Angermayr, et al. 2006; Fernandez & Bonkovsky 1999). In a study using rats with partial portal vein ligation, a surgical model that induces portal hypertension, HO-1 was up-regulated in the superior mesenteric arterial beds (Angermayr, et al. 2006). When rats with partial portal vein ligation were given an HO inhibitor, tin(Sn)-mesoporphyrin IX, intraperitoneally immediately after surgery for the following 7 days, a significant reduction in portal pressure was observed in the HO inhibitor-treated group compared to the placebo group. However, the HO inhibition did not affect the formation of portosystemic collaterals in portal hypertensive rats (Angermayr, et al. 2006).

Like those surgically induced portal hypertensive rats, rats with cirrhosis exhibit enhanced HO pathway to mediate excessive vasodilation in arteries of the splanchnic and systemic circulation (Chen, et al. 2004; Tarquini, et al. 2009). Rats with bile duct ligation (a surgical model of biliary cirrhosis) showed an increase in HO-1 expression in both the superior mesenteric artery and the aorta, compared to sham-operated rats. In contrast, HO-2 expression did not differ between the two groups of rats. Importantly, aortic HO activities as well as blood CO levels were positively related to the degree of the hyperdynamic circulatory syndrome assessed by mean arterial pressure, cardiac input and peripheral vascular resistance. Acute administration of an HO inhibitor, zinc protoporphyrin (ZnPP), ameliorated the hyperdynamic circulatory syndrome in cirrhotic rats with 4 weeks after bile duct ligation (Chen, et al. 2004; Tarquini, et al. 2009).

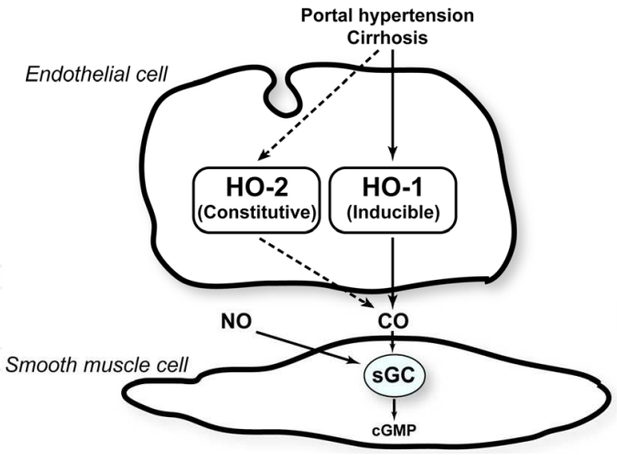

Fig. 3. Hemeoxygenase (OH) pathway in the arterial splanchnic and systemic circulation in cirrhosis and portal hypertension. HO-1 is an inducible isoform, while HO-2 is a constitutive isoform. Both nitric oxide (NO) and carbon monoxide (CO) activate soluble guanylate cyclase (sGC) in smooth muscle cells and facilitate vasodilation.

In contrast to other studies, a study by Sacerdoti et al. (Sacerdoti, et al. 2004) reported that HO-2, not the inducible HO-1, was up-regulated in mesenteric arteries of cirrhotic rats. In their study, cirrhotic rats were generated by giving carbon tetrachloride (CCl_4) in gavage for 8 to 10 weeks. Consistent with other studies, however, administration of an HO inhibitor, tin(Sn)-mesoporphyrin IX, ameliorated excessive arterial vasodilation in cirrhotic rats. Collectively, these observations may suggest that different experimental models of cirrhosis and portal hypertension cause different effects on HO pathway in the aorta and mesenteric arteries, thus resulting in up-regulation of different types of HO isoforms.

Studies with cirrhotic patients also showed an increase in plasma CO levels (De las Heras, et al. 2003; Tarquini, et al. 2009). Spontaneous bacterial peritonitis further accelerated blood CO levels in cirrhotic patients (De las Heras, et al. 2003). Furthermore, Tarquini et al. (Tarquini, et al. 2009) documented that plasma CO levels as well as HO expression and activity in polymorphonuclear cells were significantly increased in patients with viral hepatitis and the hyperdynamic circulatory syndrome. Importantly, plasma CO levels were directly correlated with the severity of the hyperdynamic circulatory syndrome. Collectively, these clinical studies with cirrhotic patients also suggest that enhanced circulating CO levels are associated with the development of the hyperdynamic circulatory syndrome.

2.1.3 Prostacyclin (PGI_2)

PGI_2 is generated by the activity of cyclooxygenase (COX) in endothelial cells and facilitates smooth muscle relaxation by stimulating adenylate cyclase to produce cyclic adenosine monophosphate (Claesson, et al. 1977) (Figure 4). There are two isoforms of COX. COX-1 is a constitutively expressed form, and COX-2 is an inducible form (Smith, et al. 2000; Smith, et al. 1996).

PGI_2 is an important mediator in the development of experimental and clinical portal hypertension (Hou, et al. 1998; Ohta, et al. 1995; Skill, et al. 2008). Increased COX-1

expression contributed to increased arterial vasodilation in the splanchnic circulation in portal hypertensive rats (Hou, et al. 1998). COX-2, however, was not detected in the superior mesenteric artery of those rats. These observations suggested that COX-1, not COX-2, would be responsible for the increased vasodilation in the superior mesenteric artery of portal hypertensive rats. However, inhibiting COX-1 only neither decreased PGI_2 levels nor ameliorated the hyperdynaic circulatory syndrome in portal hypertensive mice (Skill, et al. 2008). A study using both COX-1-/- and COX-2-/- mice in combination of selective COX-2 (NS398) and COX-1 (SC560) inhibitors, respectively, showed that blockade of both COX-1 and COX-2 ameliorated the hyperdynamic circulatory syndrome in portal hypertensive mice. Therefore, it is suggested that both COX-1 and COX-2 need to be suppressed to reduce PGI_2 production and to ameliorate the hyperdynamic circulatory syndrome (Skill, et al. 2008). Similar to experimental portal hypertension, circulating PGI_2 levels are also elevated in cirrhotic patients (Ohta, et al. 1995).

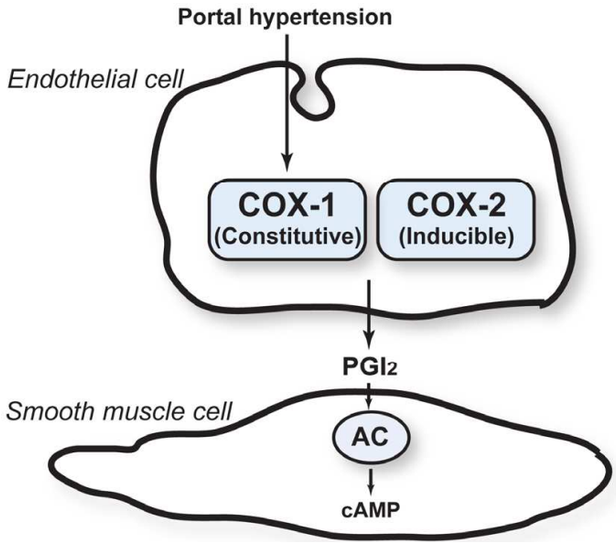

Fig. 4. Cyclooxygenase (COX) pathway in the arterial splanchnic and systemic circulation in cirrhosis and portal hypertension. COX-1 is a constitutive form, while COX-2 is inducible form. Both COX-1 and COX-2 seem to play a role in production of prostacyclin (PGI_2), which activates adenylate cyclase (AC) in smooth muscle cells to produce cyclic adenosine monophosphate (cAMP), thereby leading to vasodilation.

2.1.4 Endocannabinoids

Endocannabinoid is a collective term used for a group of endogenous lipid ligands, including anandamide (arachidonyl ethanolamide) (Wagner, et al. 1997). Endocannabinoids bind to their receptors, CB1 receptors, and cause hypotension (Figure 5). The bacterial endotoxin lipopolysaccharide (LPS) elicits production of endocannabinoids (Varga, et al. 1998) and thus develops hypotension.

Cirrhotic patients are generally endotoxemia, which is characterized by elevated endotoxin/LPS levels in the blood. Thus, it is not surprising that circulating anandamide levels are elevated in cirrhotic patients (Caraceni, et al. 2010; Fernandez-Rodriguez, et al. 2004). Cirrhotic rats also exhibit endotoxemia. Thus, antibiotic treatment to suppress

endotoxemia decreased hepatic endocannabinoid levels and ameliorated the hyperdynamic circulatory syndrome in those rats (Lin, et al. 2011).

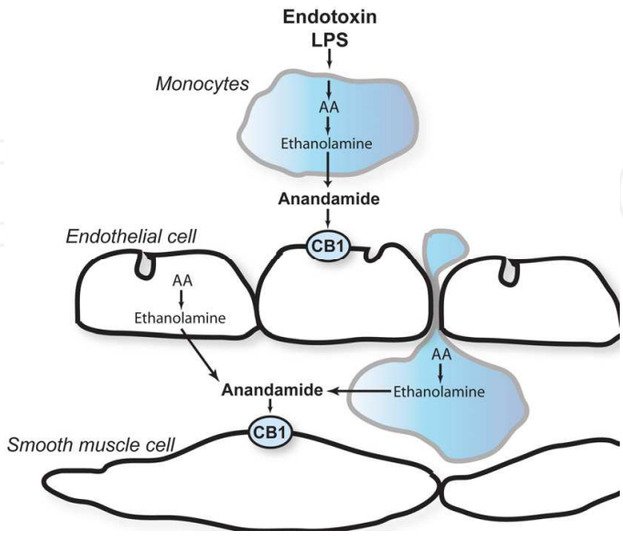

Fig. 5. Anandamide produced by circulating monocytes causes hypotension in cirrhotic rats and patients. Anandamide (arachidonyl ethanolamide) is an endogenous lipid ligand that belongs to endocannabinoids (Wagner, et al. 1997) and generated from arachidonic acid (AA). The bacterial endotoxin lipopolysaccharide (LPS) elicits production of anandamide in monocytes and endothelial cells (Varga, et al. 1998). Anandamide binds to CB1 receptors located on endothelial cells and smooth muscle cells and causes hypotension.

Monocytes and platelets are the two major sources of endocannabinoids in endotoxemia (Batkai, et al. 2001; Ros, et al. 2002; Varga, et al. 1998). When monocytes and platelets were pre-exposed to LPS and then injected to normal rat recipients, hypotension was developed (Varga, et al. 1998). Hypotension was however prevented by pretreatment of recipient rats with a CB1 receptor antagonist, SR141716A. Thus, endotoxemia elicits production of endocannabinoids in monocytes and platelets, leading to hypotension.

Anandamide levels were also elevated 2- to 3-fold and 16-fold in monocytes isolated from cirrhotic rats and patients, respectively, compared to their corresponding controls (Batkai, et al. 2001). Transplantation of monocytes isolated from cirrhotic rats or patients via intravenous injection, but not those monocytes from control rats, to normal recipient rats gradually caused the development of hypotension. In contrast, when normal recipient rats were pretreated with a CB1 receptor antagonist, SR141716A, the monocytes from the same cirrhotic rats or patients did not cause hypotension in those rats. Besides elevated anandamide levels, CB1 receptor levels were 3 times higher in hepatic arterial endothelial cells isolated from cirrhotic human livers than in those isolated from normal human livers. Importantly again, blocking CB1 receptor by SR141716A ameliorated arterial hypotension and the hyperdynamic circulatory syndrome in cirrhotic rats. Collectively, these results suggest that CB1 receptor can be a therapeutic target to ameliorate the hyperdynamic circulatory syndrome in cirrhosis and portal hypertension.

2.1.5 Endothelium-Derived Hyperpolarizing Factor (EDHF)

Endothelium-derived hyperpolarizing factor (EDHF) is also an important vasodilatory molecule that regulates vascular tone (Cohen 2005; Feletou & Vanhoutte 2006; Feletou & Vanhoutte 2007; Griffith 2004). It is associated with hyperpolarization of vascular smooth muscle cells and facilitates vasodilation. The term EDHF might be confusing, since it implies a single molecule (Feletou & Vanhoutte 2006). Currently, it is not still fully characterized what molecule EDHF is. However, accumulating evidence suggests that HDHF could be multiple molecules, including PGI_2 (Feletou & Vanhoutte 2006), NO (Cohen, et al. 1997; Plane, et al. 1998), epoxyeicosatrienoic acids (EETs) (Fleming 2004; Gauthier, et al. 2004; Li & Campbell 1997; Oltman, et al. 1998; Quilley & McGiff 2000; Widmann, et al. 1998), lipoxygenase [12-(s)-hydroxyeicosatetraenoic acid (12-S-HETE)] (Barlow, et al. 2000; Faraci, et al. 2001; Gauthier, et al. 2004; Pfister, et al. 1998; Zhang, et al. 2005; Zink, et al. 2001), hydrogen peroxide (H_2O_2) (Beny & von der Weid 1991; Chaytor, et al. 2003; Ellis, et al. 2003; Gluais, et al. 2005; Matoba, et al. 2002; Matoba, et al. 2003; Matoba, et al. 2000; Morikawa, et al. 2003; Shimokawa & Matoba 2004), potassium ions (K^+), C-type natriuretic paptides (Banks, et al. 1996; Wei, et al. 1994) and hydrogen sulfide (Mustafa, et al. 2011). It has also been suggested that EDHF function may be mediated through direct coupling between endothelial and smooth muscle cells at myoendothelial gap junctions composed of connexins (Cohen 2005; Feletou & Vanhoutte 2007; Griffith 2004) (Figure 6).

Most recently, a study by Mustafa et al. (Mustafa, et al. 2011) suggested that H_2S could be an EDHF. H_2S is synthesized endogenously from L-cystathionine-γ-lyase (CSE) and cystathionine-β-synthase (Hosoki, et al. 1997; Stipanuk & Beck 1982). The H_2S-mediated vasodilation occurs through the opening of ATP-sensitive potassium channel (K_{ATP} channel) and is independent of the activation of cGMP pathway (Zhao, et al. 2001). In the superior mesenteric artery of mice lacking CSE, hyperpolarization is virtually abolished. Most interestingly, H_2S covalently modifies (i.e., S-sulfhydrating) K_{ATP} channel and leads to relaxation of vessels.

EDHF seems to be more important in smaller arteries and arterioles than in larger arteries. This tendency has been recognized in a number of vascular beds, including mesenteric and cerebral arteries and arteries in ear and stomach (Tomioka, et al. 1999; Urakami-Harasawa, et al. 1997; You, et al. 1999).

It has not been established whether EDHF is involved in vasodilation and hypocontractility of arteries of the splanchnic and systemic circulation in cirrhosis and portal hypertension. Barriere et al. (Barriere & Lebrec 2000) reported that EDHF contributed to hypocontractility in the superior mesenteric artery isolated from cirrhotic rats when NO and PGI_2 production were inhibited. This hypocontractility was abolished when the vessels were further treated with inhibitors of small conductance Ca^{2+}-activated K^+ channel (SK channel), such as apamin and charybdotoxin, suggesting that EDHF blunts contractile response in cirrhotic rats (Barriere & Lebrec 2000). In contrast, a study by Dal-Ros et al. (Dal-Ros, et al. 2010) showed that the contribution of EDHF to vasodilation in mesenteric arteries was even smaller in cirrhotic rats than in normal rats. It was speculated that decreased expression of connexins (Cx), such as Cx37, Cx40, and Cx43, as well as Ca^{2+}-activated K^+ channel contributed to this smaller contribution of EDHF to vasodilation in the superior mesenteric

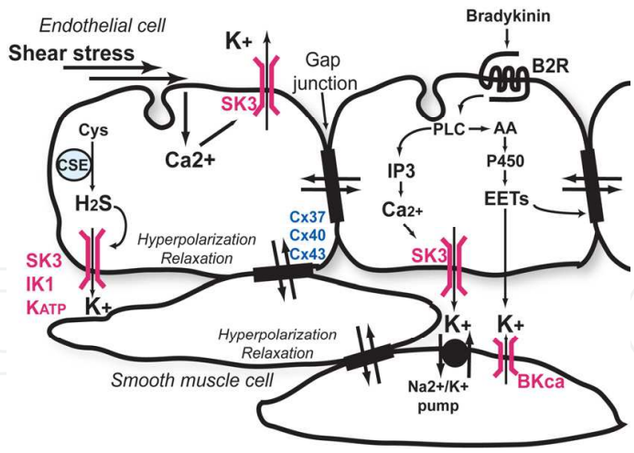

Fig. 6. Overview of endothelium-derived hyperpolarizing factor (EDHF) in the superior mesenteric artery. Shear stress generated by an increase in portal pressure increases endothelial Ca^{2+} concentration and produces hyperpolarization by activating ion channels, such as small conductance calcium-activated potassium channel (SK3) and intermediate conductance calcium-activated potassium channel (IK1). Hydrogen sulfide (H_2S) is formed in vascular endothelial cells from cysteine by L-cystathionine-gamma-lyase (CSE). H_2S causes hyperpolarization through activation of SK3, IK1 and ATP-sensitive potassium channel (KATP). Connexins (Cx) 37 and 40 are predominant gap junction proteins in endothelial cells and contribute to EDHF-mediated response. Connexin 43 (Cx43) is also present at the gap junction, but it does not play a major role in this context. Potassium ion (K+) activates Na+/K+-ATPase pump, preventing the effects of any substantial rise of potassium during endothelium-dependent hyperpolarization. Bradykinin, through its G-protein coupled receptor (B2R), activates the metabolism of arachidonic acid (AA) via cytochrome P450 monooxygenase (P450). Bradykinin also activates phospholipase C (PLC) that stimulates inositol trisphosphate (IP3) to increase cytosolic Ca^{2+} concentration. Epoxyeicosatrienoic acids (EETs) cause hyperpolarization/relaxation, acting through the voltage-gated potassium channel (BKCa) and gap junction.

artery of cirrhotic rats (Dal-Ros, et al. 2010). However, Bolognesi et al. (Bolognesi, et al. 2011) presented that mesenteric arteries isolated from cirrhotic rats exhibited elevated Cx40 and Cx43 expression, which increased sensitivity to epoxyeicosatrienoic acids (EETs) in those arteries and contributed to enhanced vasodilation.

2.1.6 Tumor necrosis factor α

A proinflammatory cytokine, tumor necrosis factor α (TNFα), is produced by mononuclear cells upon activation by bacterial endotoxins. In cirrhosis and portal hypertension, therefore, TNFα levels are elevated (Lopez-Talavera, et al. 1995; Mookerjee, et al. 2003). Inhibition of TNFα action by an anti-TNFα antibody resulted in a significant reduction in hepatic venous pressure gradient (HVPG) of patients with alcoholic hepatitis (Mookerjee, et al. 2003). Similarly, inhibition of TNFα synthesis by thalidomide also prevented the development of the hyperdynamic circulatory syndrome in portal hypertensive rats (Lopez-Talavera, et al. 1996). The mechanism of TNFα action in cirrhosis and portal hypertension is not fully understood.

TNFα stimulates NOS activity by increasing BH_4 production through stimulation of expression and activity of guanosine triphosphate-cyclohydrolase I, a key enzyme for the regulation of BH_4 biosynthesis in endothelial cells (Katusic, et al. 1998; Rosenkranz-Weiss, et al. 1994). Enhanced BH_4 production directly increases eNOS-derived NO production (Katusic, et al. 1998; Rosenkranz-Weiss, et al. 1994; Wever, et al. 1997). In biliary cirrhotic rats, it was demonstrated that TNFα, through the activation of iNOS in the aorta and lung, plays a role in the development of the hyperdynamic circulatory syndrome and the hepatopulmonary syndrome (Sztrymf, et al. 2004).

2.1.7 Adrenomedullin

Adrenomedullin is an endogenous vasodilatory peptide consisting of 52 amino acid residues in human and 50 amino acid residues in the rat (Kitamura, et al. 1993; Kitamura, et al. 1993; Nuki, et al. 1993). The major producers of circulating adrenomedullin are vascular smooth muscle cells (Sugo, et al. 1994) and endothelial cells (Sugo, et al. 1995). Adrenomedullin binds to and induces its signaling through the G-protein-coupled calcitonin receptor-like receptor/receptor activity-modifying protein (RAMP)2 and 3, which are expressed in multiple tissues, including blood vessels, kidney, lung, atrium, gastrointestinal tract, spleen, endocrine glands, brain and heart. Receptor RAMP2 is essential for angiogenesis and vascular integrity (Ichikawa-Shindo, et al. 2008). Adrenomedullin expression is up-regulated by hypoxia (Nagata, et al. 1999; Wang, et al. 1995) and inflammation (Sugo, et al. 1995; Ueda, et al. 1999), both of which are associated with neovascularization.

The vasodilatory action of adrenomedullin was considered in the beginning to be solely due to elevated cAMP production, i.e., endothelium-independent vasodilation. However, endothelial denudation substantially reduced its vasodilatory action in rodent aortic rings (Hirata, et al. 1995; Nishimatsu, et al. 2001). Furthermore, this adrenomedullin-induced endothelium-dependent vasodilation was exerted mostly through activation of the phosphatidylinositol 3-kinase (PI3-K)/Akt pathway (Nishimatsu, et al. 2001). It has been well established that this pathway is involved in various important actions in endothelial cells, such as activation of eNOS. While one study demonstrated in a mouse model of ischemia that adrenomedullin-induced collateral vessel formation in ischemic tissues was eNOS-dependent (Abe, et al. 2003), no study has so far shown that adrenomedullin activates eNOS through Akt activation.

Several studies have reported that in liver cirrhotic patients, circulating adrenomedullin levels are elevated and are associated with increased levels of plasma nitrite (a stable NO metabolite) and plasma volume expansion (Guevara, et al. 1998; Kojima, et al. 1998; Tahan, et al. 2003). Furthermore, the increased circulating adrenomedullin levels in those patients are inversely related to peripheral resistance (Guevara, et al. 1998). These observations indicate that adrenomedullin may promote excessive vasodilation and the hyperdynamic circulatory syndrome in cirrhotic patients. It is not surprising, therefore, that administration of an anti-adrenomedullin antibody prevented the occurrence of the hyperdynamic circulatory syndrome in the early sepsis (Wang, et al. 1998) and ameliorated blunted contractile response to phenylephrine in the aorta isolated from cirrhotic rats (Kojima, et al. 2004).

Portal hypertension alone, regardless of the presence of cirrhosis, increases adrenomedullin production. One clinical study showed that adrenomedullin and NO levels are elevated not only in patients with cirrhotic portal hypertension, but also in those patients with non-cirrhotic portal hypertension (Tahan, et al. 2003). How an increase in portal pressure influences production of adrenomedullin is an interesting and important question to be investigated.

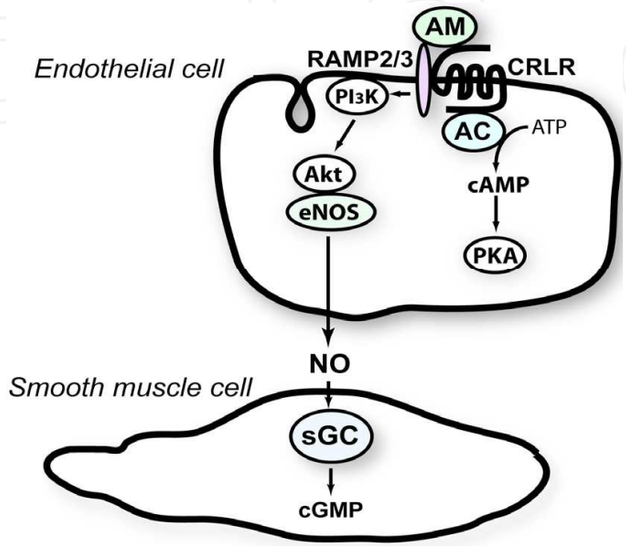

Fig. 7. Adrenomedullin causes vasodilation and hypotension. Adrenomedullin (AM) binds to and induces its signaling through the G-protein-coupled calcitonin receptor-like receptor (CRLR)/receptor activity-modifying protein (RAMP)2 and 3. The vascular action of adrenomedullin was at first considered to be solely due to elevated cAMP production by activation of adenylate cyclase (AC) in endothelial cells, thereby causing endothelium-independent vasodilation. Adrenomedullin-induced endothelium-dependent vasodialation is exerted mostly through activation of the phosphatidylinositol 3-kinase (PI3-K)/Akt pathway, which activates eNOS to produce NO. NO then diffuses into smooth muscle cells to activate soluble guanylate cyclase (sGC) and produce cyclic GMP (cGMP), leading to vasodilation.

2.1.8 Bradykinin

Bradykinin is a nine amino acid peptide and known to facilitate vasodilation (Antonio & Rocha 1962). Bradykinin leads to endothelium-dependent hyperpolarization through activation of phospholipase C (PLC), which could raise Ca^{2+} concentration and also stimulate production of EETs (Feletou & Vanhoutte 2006) (Figure 6). Bradykinin reduces sensitivity to glypressin (a long lasting vasopressin analogue) in both portal hypertensive and cirrhotic rats (Chen, et al. 2009; Chu, et al. 2000), thereby advancing vasodilation.

2.1.9 Urotensin II

Urotensin II is a cyclic peptide and has a structural similarity to somatostatin. It can function both as a vasoconstrictor and a vasodilator depending on vascular beds (Coulouarn, et al.

1998). In the systemic vessels including the aorta and coronary artery, urotensin II serves as the strongest vasoconstrictor known (Ames, et al. 1999; Douglas, et al. 2000). In rat mesenteric arteries, however, urotensin II causes vasodilation (Bottrill, et al. 2000). In biliary cirrhotic rats, plasma urotensin II levels were increased, and hypocontractility/vasodilatation was advanced in mesenteric arteries. An urotensin II receptor antagonist, palosuran, improved this hypocontractility/vasodilatation, by increasing RhoA/Rho-kinase expression and Rho-kinase activity (thereby more contraction) and decreasing nitrite/nitrate levels (Trebicka, et al. 2008). These observations may suggest that elevated levels of urotensin II also lead to hypocontractility/excessive vasodilation in the mesenteric arteries of patients with cirrhosis and portal hypertension. Thus, blocking the urotensin II-mediated signaling pathway may be an effective way to treat those patients.

2.1.10 Neuropeptide Y

Neuropeptide Y is a sympathetic neurotransmitter and known to cause α-adrenergic vasoconstriction (Tatemoto 1982; Tatemoto, et al. 1982). RhoA/Rho-kinase modulates various cellular functions such as cell contractility through phosphorylation of myosin light chain (Uehata, et al. 1997; Wang, et al. 2009). It was suggested that impaired RhoA/Rho-kinase signaling was responsible for excessive vasodilation and vascular hypocontractility in biliary cirrhotic rats (Hennenberg, et al. 2006). Acute administration of neuropeptide Y improved arterial contractility in the mesenteric arteries of cirrhotic rats by restoring impaired RhoA/Rho-kinase signaling (Moleda, et al. 2011). These observations may suggest that neuropeptide Y can be used for the treatment of hypocontractility/excessive vasodilation of the arterial splanchnic circulation in cirrhosis and portal hypertension.

2.2 Key factors

An increase in portal pressure alone can induce excessive arterial vasodilation and hypocontractility in the splanchnic and systemic circulation. In addition, chronic liver cirrhosis and portal hypertension are known to cause arterial wall thinning in these circulations. This arterial wall thinning is a critical factor that maintains excessive arterial vasodilation and hypocontractility and facilitates the development of the hyperdynamic circulatory syndrome in advanced portal hypertension.

2.2.1 Portal pressure

Using rats with partial portal vein ligation (Abraldes, et al. 2006; Fernandez, et al. 2005; Fernandez, et al. 2004; iwakiri 2011), which enables induction of different degrees of portal hypertension in animals (Iwakiri & Groszmann 2006), Abraldes et al. (Abraldes, et al. 2006) showed that portal pressure is detected at different vascular beds depending on the stage of portal hypertension. A small increase in portal pressure is first detected by the intestinal microcirculation. Then, further increased portal pressure is sensed by the arterial splanchnic circulation (e.g., the mesenteric arteries), finally followed by the arterial systemic circulation (e.g., the aorta). Thus, the intestinal microcirculation functions as a "sensing organ" to portal pressure. It is postulated that mechanical forces generated as a result of increased portal pressure, presumably cyclic strains and shear stress, activate eNOS and thus lead to NO production (Abraldes, et al. 2006; Iwakiri, et al. 2002; Tsai, et al. 2003).

When mild portal hypertension is generated in rats using partial portal vein ligation, an increase in portal pressure is too small to cause splanchnic arterial vasodilation. However, the level of vascular endothelial growth factor (VEGF) is significantly elevated in the intestinal microcirculation, followed by increased eNOS levels (Abraldes, et al. 2006). This model of mild portal hypertension may likely correspond to the portal pressure changes observed in early-stage cirrhosis, in which the progression of portal hypertension is generally slow. When portal pressure is further increased to a certain level, vasodilation develops in the arterial splanchnic circulation. Once vasodilation is established in the intestinal microcirculation and the arterial splanchnic circulation, arterial systemic circulatory abnormalities seem to follow (iwakiri 2011).

Like the above study using rats with partial portal vein ligation, portal pressure modulates intestinal VEGF and eNOS levels during the development of cirrhosis in rats (Huang, et al. 2011). We have shown that there is a significant positive correlation between portal pressure and intestinal VEGF levels ($r^2 = 0.4$, $p<0.005$). While plasma VEGF levels were significantly elevated in cirrhotic rats with portal hypertension (63.7 pg/ml, $p<0.01$) compared to controls (8.5 pg/ml), no correlation was observed between portal hypertension and plasma VEGF levels.

2.2.2 Arterial wall thinning

Endothelial NO plays a critical part in regulating the structure of the vessel wall (Rudic, et al. 1998). Studies using cirrhotic rats with ascites documented the occurrence of arterial wall thinning. Those rats exhibited decreased thickness of the vascular walls of the thoracic aorta, abdominal aorta, mesenteric arteries and renal artery (Fernandez-Varo, et al. 2007; Fernandez-Varo, et al. 2003). Administration of a NOS inhibitor significantly ameliorated wall thickness and attenuated the hyperdynamic circulatory syndrome, by increasing arterial pressure and peripheral resistance (Fernandez-Varo, et al. 2003). Since NO is predominantly derived from endothelial cells in these arteries, these observations suggest that increased eNOS-derived NO, at least in part, is responsible for this profound arterial wall thinning. Therefore, understanding the mechanisms of arterial wall thinning is important for the development of useful therapies for patients with portal hypertension.

3. Key molecules and factors – Portosystemic collateral vessel formation

In addition to excessive arterial vasodilation/hypocontractility in the splanchnic and systemic circulation, the formation of portosystemic collateral vessels is also thought to exacerbate portal hypertension (Bosch 2007; Iwakiri & Groszmann 2006). The portosystemic collateral vessel formation is probably an adaptive response to increased portal pressure, which, by releasing the pressure, may transiently help to delay the progression of portal hypertension. However, these collateral vessels eventually contribute to an increase in the blood flow through the portal vein and advance portal hypertension (Langer & Shah 2006). In addition, the formation of these vessels can also lead to detrimental complications. Since the vessels are fragile, they tend to rupture easily, causing esophageal and gastric variceal bleeding. Furthermore, since these vessels have the portal blood bypass the liver, toxic substances carried by it, such as drugs, bacterial toxins and toxic metabolites, returns to the

systemic circulation and can cause portal-systemic encephalopathy and sepsis (Bosch 2007; Iwakiri & Groszmann 2006). The enlargement of pre-existing vessels as well as angiogenesis facilitate the development of these collateral vessels (Langer & Shah 2006; Sumanovski, et al. 1999). Studies have shown that vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) play critical roles in the development of portosystemic collateral vessels in cirrhosis and portal hypertension.

3.1 Vascular Endothelial Growth Factor (VEGF)

The process of angiogenesis is regulated by growth factors exhibiting vasodilatory activity, such as VEGF. How are these angiogenic growth factors elevated in cirrhosis and portal hypertension? One mechanism may be initiated by an increase in portal pressure. As described previously, studies using portal hypertensive rats showed that a sudden increase in portal pressure is signaled to the intestinal microcirculation and induces intestinal VEGF expression (Abraldes, et al. 2006; Fernandez, et al. 2005). This sudden increase in portal pressure may create local mechanical forces, such as cyclic strains and shear stress, which may trigger VEGF induction.

It has been documented that administration of anti-angiogenic agents, such as blockers of VEGF receptor-2 (SU5416, anti-VEGFR2 monoclonal antibody) (Fernandez, et al. 2005; Fernandez, et al. 2004) and inhibitors of receptor tyrosine kinases (Sorafenib and Sunitinib) (Mejias, et al. 2009; Tugues, et al. 2007), reduces the formation of portosystemic collateral vessels and decreases portal pressure.

3.2 Placental growth factor

In addition to VEGF, placental growth factor (PlGF), another member of the VEGF family, has also been found to be increased in the intestinal microcirculation of portal hypertensive mice (Van Steenkiste, et al. 2009). In portal hypertensive mice lacking PlGF or given an anti-PlGF monoclonal antibody, both portal pressure and portosystemic collateral vessel formation were decreased. Collectively, these VEGF and PIGF studies suggest that blocking angiogenic activities, thereby decreasing the formation of portosystemic collateral vessels, has potential for the treatment of portal hypertension.

4. Summary

There are two major factors that contribute to excessive arterial vasodilation/hypocontractility in arteries of the splanchnic and systemic circulation in portal hypertension. One is an intrinsic factor and the other is a structural factor. The intrinsic factor includes vasodilatory molecules such as NO, CO, PGI_2, endocannabinoids, EDHF, adrenomedullin, TNFα, bradykinin and urotensin II. Decreased response to vasoconstrictors, such as neuropeptide Y, also facilitates hypocontractility of mesenteric arterial beds in cirrhosis and portal hypertension. The structural factor includes thinning of arterial wall (Fernandez-Varo, et al. 2007; Fernandez-Varo, et al. 2003). NO plays a critical role for arterial wall thinning in cirrhotic rats. However, its mechanism is not clear. In addition to excessive arterial vasodilatation/hypocontractility in the splanchnic and systemic circulation, the development of portosystemic collateral vessels is also regarded as the major factor that worsens portal hypertension (Bosch 2007; Iwakiri & Groszmann 2006).

4.1 Future direction

Both experimental and clinical studies of cirrhosis and portal hypertension have documented that a wide variety of molecules are involved in excessive arterial vasodilation/hypocontractility in the splanchnic and systemic circulation. This accumulation of knowledge allows us to further investigate molecular and cellular mechanisms in which these molecules exert excessive arterial vasodilation/ hypocontractility in cirrhosis and portal hypertension. In particular, it is interesting and important to address how changes in portal pressure, along with these molecules, influence the function and structure of vasculatures in the splanchnic and systemic circulation. Furthermore, it is not fully elucidated how these molecules are excessively induced in portal hypertension. Another important investigation would be to elucidate paracrine and autocrine regulations of vascular cells (e.g., endothelial cells, smooth muscle cells and fibroblasts) by these molecules. While the roles of these molecules in the vasculature per se have been described, few studies have investigated cell specific regulations and cell-cell communications exerted by these molecules.

Among those molecules introduced in this chapter, there are at least two molecules that are particularly anticipated for further investigation in the context of excessive arterial vasodilation and portosystemic collateral vessel formation in portal hypertension. One is hydrogen sulfide (H_2S). An increasing body of evidence suggests that H_2S is a crucial vasodilatory molecule in the superior mesenteric artery. However, it is not known whether H_2S is also involved in excessive arterial vasodilation in the splanchnic circulation in portal hypertension. Another molecule of interest is adrenomedullin. Studies using mice lacking adrenomedullin or its receptors indicated that adrenomedullin plays a critical role in the regulation of blood vessel integrity, including vascular stability and permeability (Caron & Smithies 2001; Fritz-Six, et al. 2008; Ichikawa-Shindo, et al. 2008; Shindo, et al. 2001). Given that increased vascular permeability and decreased vessel integrity are typical of vessels in cirrhosis and portal hypertension, this aspect of adrenomedullin should be explored in cirrhosis and portal hypertension.

5. Conclusion

To date, there are only limited options for the treatment of portal hypertension, despite the fact that portal hypertension leads to the most lethal complications of liver diseases such as gastro-oesophageal varices and ascites. Facing this situation, there is a strong need for studies of the vascular abnormalities associated with cirrhosis and portal hypertension (Shah 2009). These studies will have potential to lead us to develop novel targets for the treatment of portal hypertension.

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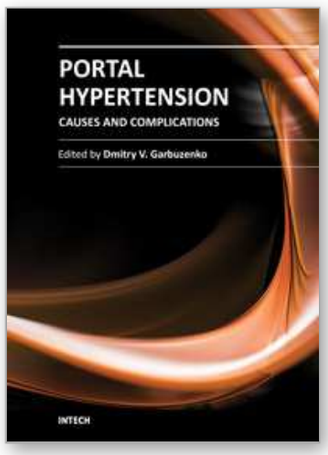

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Portal hypertension is a clinical syndrome defined by a portal venous pressure gradient, exceeding 5 mm Hg. In this book the causes of its development and complications are described. Authors have presented personal experiences on conducting patients with various displays of portal hypertension. Moreover, the book presents modern data about molecular mechanisms of pathogenesis of portal hypertension in liver cirrhosis, the information about the original predictor of risk of bleeding from gastro-esophageal varices and new methods for their conservative treatment.

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