Pathophysiology of Portal Hypertension and Its Clinical Links

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Portal hypertension is a major cause of morbidity and mortality in patients with liver cirrhosis. Intrahepatic vascular resistance due to architectural distortion and intrahepatic vasoconstriction, increased portal blood flow due to splanchnic vasodilatation, and development of collateral circulation have been considered as major factors for the development of portal hypertension. Recently, sinusoidal remodeling and angiogenesis have been focused as potential etiologic factors and various researchers have tried to improve portal hypertension by modulating these new targets. This article reviews potential new treatments in the context of portal hypertension pathophysiology concepts. (J CLIN EXP HEPATOL 2011;1:87–93)

Portal hypertension is a major cause of morbidity and mortality in patients with liver cirrhosis. It is defined as an abnormal increase in the pressure in the veins that carry blood from the splanchnic organs to the liver.¹ According to Ohm's law ($\Delta P = F \times R$), pressure (P) can be increased by increased portal blood flow (F) and/or increased resistance to blood flow (R).² Therefore, any event that can cause an increase in the portal blood flow or resistance to portal blood flow can contribute to the development of portal hypertension.³

In the normal liver, portal pressure is maintained within a normal range despite the dynamic change in portal flow by adjustment of intrahepatic vascular resistance. In liver cirrhosis, disruption of the sinusoidal architecture due to the progression of fibrosis and formation of regenerative nodules formation and intrahepatic vasoconstriction due to imbalance in vasoregulatory mediators, such as nitric oxide (NO) and endothelin-1 (ET-1), lead to an increase in the intrahepatic vascular resistance. In addition, splanchnic vasodilatation and hyperdynamic circulation lead to an increase in portal blood flow. Therefore, the cirrhotic liver is not able to maintain portal pressure within a normal range and portal hypertension develops. Furthermore,

portosystemic collateral vessels develop to compensate portal hypertension, which in turn contribute not only to the development of life-threatening complications such as bleeding from gastroesophageal varices, but also to the additional increase in the portal blood flow and portal hypertension. Recently, many studies suggested that angiogenesis and sinusoidal remodeling also play an important role in the development of portal hypertension, and treatments targeting these new mechanisms have been tried by various investigators (Figure 1). Although various mechanisms are involved in the development of portal hypertension, current therapies are mainly targeted to the increased portal blood flow, such as beta-blockers or splanchnic vasoconstrictors. In this review, pathophysiology of portal

Figure 1 Pathophysiology and promising targets for the treatment of portal hypertension in liver cirrhosis.

Keywords: angiogenesis, pathophysiology, portal hypertension, sinusoids, treatment

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Abbreviations: AT: angiotensin; ET-1: endothelin-1; eNOS: endothelial nitric oxide synthase; HSC: hepatic stellate cell; HVP: hepatic venous pressure gradient; NO: nitric oxide; PDGF: platelet-derived growth factor; PlGF: placental growth factor; RAS: renin-angiotensin system; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor

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hypertension including new concepts, current therapies and trials, and promising treatments for portal hypertension will be discussed.

Pathophysiology of Portal Hypertension

Increase in Intrahepatic Vascular Resistance

The progression of liver fibrosis and regenerative nodule formation in the cirrhotic liver leads to a distortion of the sinusoidal structure and narrowing of the vascular lumen, which in turn leads to increased resistance to the portal blood flow and portal hypertension. These mechanical factors developed from the disruption of the liver vascular architecture have been considered as the main cause of the increase in the intrahepatic resistance in cirrhotic liver. However, besides these mechanical factors, intrahepatic vasoconstriction also plays an important role in the development of portal hypertension. A previous study, which presented the decrease in portal pressure by vasodilators, suggested that intrahepatic vasoconstriction might contribute 10–30% of the increase in portal resistance,⁴ while other recent studies suggest that the role of intrahepatic vasoconstriction in the portal resistance might be even greater in the cirrhotic liver.⁵ Enhanced contractility of hepatic stellate cells (HSCs) plays an important role in the development of intrahepatic vasoconstriction.⁶ They are involved in the regulation of the sinusoidal blood flow in the normal liver⁷ and HSC contractility is regulated by a balance between vasoconstrictors and vasodilators in normal condition.^{8,9} In cirrhotic liver, the decrease in the vasodilators, such as NO, and the increase in the vasoconstrictors, including ET-1, angiotensin II (AT-II), and α -adrenergic stimulus, promote intrahepatic vasoconstriction. Intrahepatic vasoconstriction in turn increases portal pressure and impairs adaptability of the intrahepatic vessels to respond to changes in portal blood flow thus accentuating the effect of increase in portal blood flow on portal pressure.¹⁰

Because of its potential reversibility, intrahepatic vasoconstriction has been considered as a promising target for portal hypertension. In addition, treatments targeted to intrahepatic vasoconstriction were suggested to be effective in reducing the portal pressure and safe in animal studies.^{11–16} Supported by these results, various treatments had been tried to reverse intrahepatic vasoconstriction including ET-1 receptor antagonists¹⁷ and NO donors such as mononitrate^{18,19} or NO-releasing derivative of ursodeoxycholic acid, NCX-1000.²⁰ However, unfortunately, clinical studies could not prove the benefit of these treatments, which could not reduce the portal pressure in patients with portal hypertension. In addition, side effects including potential hepatotoxicity of ET-1 antagonist^{21,22} or systemic hypotension of NO donors²⁰ further limit their use in clinical practice. Further below, we will discuss some new therapeutic directions to target intrahepatic vasoconstriction.

Splanchnic Vasodilatation and Hyperdynamic Circulation

In contrast to the vasoconstriction of intrahepatic vessels, vasodilation develops in the splanchnic vasculature. Although the exact mechanism for splanchnic vasodilation is still unclear, an overproduction of endogenous vasodilator and a decrease in vascular reactivity to vasoconstrictors are associated with its development. Splanchnic vasodilation is the main cause of the increase in the portal blood flow in liver cirrhosis.²³ In addition, extrahepatic vasodilation reduces effective arterial blood volume, which is compensated by increase in the heart rate and cardiac output.^{24–26} However, effective blood volume eventually cannot be maintained with this mechanism with the progression of liver cirrhosis, and arterial hypotension develops.²⁷ Arterial hypotension activates high pressure baroreceptor, which in turn activates sympathetic nervous system and renin-angiotensin system (RAS) and promote secretion of vasoconstrictors including norepinephrine and angiotensin II to compensate to the reduced effective arterial blood volume.^{24–26} However, splanchnic vessels are resistant to these vasoconstrictors because of increased vasodilators including NO.^{28,29} Therefore, maintenance of effective blood volume is achieved by vasoconstriction of peripheral vessels other than splanchnic vessels.^{30–33} These mechanisms lead to the development of hyperdynamic circulation, which is characterized by peripheral and splanchnic vasodilation, reduced mean arterial pressure, and increased cardiac output. In addition, many collateral vessels are developed to connect the high pressure portal veins with systemic veins with lower pressure. However, this process is insufficient for normalizing portal pressure and causes serious complications of portal hypertension, such as development of gastroesophageal varices, which are prone to rupture, and shunting of portal blood flow into the systemic circulation, which leads to hepatic encephalopathy and sepsis.³⁴

Sinusoidal Remodeling and Angiogenesis

The HSCs are located in the space of Disse in close contact with sinusoidal endothelial cells and their density and coverage of the sinusoidal lumen are enhanced in liver cirrhosis.³⁴ This process, which is called as sinusoidal remodeling, could contribute to increased intrahepatic vascular resistance. Sinusoidal remodeling encompasses the recruitment of HSCs to the sinusoidal walls and activation of HSCs with extension of their tentacle-like structures which encircle the vascular lumen and adjacent endothelial cells. Recently, platelet-derived growth factor (PDGF) signaling is considered to be crucial for angiogenesis and sinusoidal remodeling.³⁵ It acts as a potent mitogen for HSCs and their expression is up-regulated in chronic liver disease.³⁶ Consistently, a recent study demonstrated that PDGF promotes an angiogenic phenotype of HSCs and

enhances HSC coverage of sinusoids.³⁷ This study also suggested that ephrin-B2 may play a key role in this process.³⁷

Recent studies suggested that angiogenesis plays an important role in the development and maintenance of increased splanchnic blood flow and the formation of collaterals.^{38–40} Angiogenesis is a hypoxia-stimulated and growth factor-dependent process in which new vascular structures are formed from the pre-existing blood vessels and it contributes to disease progression when it occurs during chronic inflammatory liver diseases.⁴¹ Although endothelial cells are the most recognized cell type during angiogenesis, HSCs also contribute to the angiogenesis by their ability to stabilize the new vessels or by secreting angiogenic molecules that recruit and stimulate endothelial cells, such as vascular endothelial growth factor (VEGF) and angiopoietin-1.⁴² The VEGF is a potent angiogenic factor, which is triggered by binding to its tyrosine kinase VEGF receptor-2.^{43–45} The expression of VEGF and VEGF receptor-2 is up-regulated in portal hypertensive mice⁴⁰ and administration of anti-VEGF receptor-2 monoclonal antibodies decreases the angiogenesis in the splanchnic vascular bed and the formation of collateral vessels in the portal hypertensive animal models.^{39,40} These results support the role of VEGF-dependent angiogenesis in the development of increased splanchnic blood flow and the formation of portosystemic collaterals.

CURRENT THERAPIES FOR PORTAL HYPERTENSION

Most of currently available pharmacologic therapies for patients with portal hypertension target the increase in portal blood flow. They include nonselective beta-blockers or other splanchnic vasoconstrictors such as terlipressin, somatostatin, or its analog, octreotide. Other specific therapies for individual complications of portal hypertension, such as vasopressin receptor antagonists, vaptan, for dilutional hyponatremia or lactulose for hepatic encephalopathy are beyond scope and will not be discussed in this review.

Nonselective beta-blockers are effective in reducing portal pressure and in preventing bleeding from esophageal varices. They reduce portal pressure by inhibition of both β_1 - and β_2 -adrenergic receptors, which lead to reduction in cardiac output and to inhibition of splanchnic vasodilatation, respectively.² However, the reduction of portal pressure achieved by beta-blockers is only 15%⁴⁶ and this drug cannot be used in significant proportion of patients because of contraindications or intolerance. Furthermore, beta-blockers could not satisfactorily reduce portal pressure in > 30% of patients even though they had taken them with adequate dosage.⁴⁷

Terlipressin, a semisynthetic analog of vasopressin, is a powerful agonist for vasopressin V1 receptors. When its glycylic residues are cleaved by endothelial peptidases, it is transformed into lysine vasopressin, the biologically active form. By activating V1 receptors, it causes splanchnic

vasoconstriction, and subsequent reduction in portal blood flow and portal pressure.² Several studies recommended terlipressin, rather than somatostatin or octreotide, as a first-line treatment for acute variceal bleeding because only terlipressin reduced relative mortality in meta-analyses.^{48,49}

Somatostatin, a 14-amino-acid peptide, reduces portal pressure and collateral blood flow by inhibiting release of glucagon.⁵⁰ In addition, this drug shows beneficial effects in portal hypertension by reducing postprandial splanchnic blood flow.⁵¹ Furthermore, a previous animal study suggested that somatostatin could inhibit the contractile effect of ET-1 on activated HSC by stimulation of somatostatin receptor subtype 1.⁵² In addition, a synthetic long-acting somatostatin analog, octreotide, inhibits secretion of glucagon more potently than somatostatin.⁵³ It also could contribute to reducing portal pressure by its local vasoconstrictive effect on vascular smooth muscle of the mesenteric area via interaction with other vasoconstrictors.⁵⁴ A recent animal study suggested that octreotide reduces splanchnic angiogenesis, VEGF expression, and portal pressure in early cirrhosis by binding to the somatostatin receptor subtype 2.⁵⁵

Treatments on the Horizon

Simvastatin

Because insufficient NO production by endothelial cells in the liver is considered as the major factor for the increased intrahepatic vasoconstriction and portal hypertension in the cirrhosis, NO supplementation selectively in liver may be beneficial in patients with portal hypertension. Therefore, several studies supplied NO donors, such as isosorbide-5-mononitrate and NCX-1000. However, in patients with advanced cirrhosis, non-liver-selective NO donors, such as organic nitrates, enhanced peripheral vasodilation, further decreasing the arterial blood pressure and activating endogenous vasoactive systems.⁵⁶

Defective phosphorylation of Akt caused by overexpression of G-protein-coupled receptor kinase-2 could contribute to the impaired activity of eNOS in SECs.⁵⁷ In a cirrhotic animal model, adenoviral delivery of myr-Akt restored endothelial nitric oxide synthase (eNOS) phosphorylation and lead to normalization in portal pressure and a significant increase in the mean arterial pressure.⁵ Simvastatin, 3-hydroxyl-3-methylglutaryl-coenzyme A reductase inhibitor, rapidly enhanced Akt phosphorylation and Akt-dependent eNOS phosphorylation, which resulted in the increase in the endothelial NO production.⁵⁸ In addition, simvastatin decreases the expression of caveolin-1, an eNOS inhibitory protein.⁵⁹ In a previous study, simvastatin acutely increased hepatic vein NO levels and reduced hepatic resistance in patients with liver cirrhosis and portal hypertension, although their portal pressure did not change.⁶⁰ A recent double-blind randomized controlled trial (RCT)

evaluated the effects of continuous simvastatin administration on the hepatic and systemic hemodynamics in patients with liver cirrhosis and portal hypertension.⁶¹ Simvastatin administration for 1 month significantly decreased hepatic venous pressure gradient (HVPG) in patients with cirrhosis and severe portal hypertension with an excellent safety profile. Simvastatin decreases HVPG independent of the concomitant treatment with beta-blockers, which suggests that its effect on the portal pressure could be additive with the current standard treatment of portal hypertension and may increase the number of patients who are protected effectively from portal hypertension-related complications. Therefore, simvastatin could be considered as a promising therapy for portal hypertension by enhancing NO production in the intrahepatic circulation.

Carvedilol

Carvedilol, a potent non-cardioselective beta-blocker with mild anti- α_1 adrenergic activity, decreases heart rate and cardiac output and causes splanchnic vasoconstriction.⁶² This results in reduced portal blood inflow and in a fall in portal pressure. In addition, through its α_1 adrenoceptor blocking effect, carvedilol decreases the hepatic vascular tone and hepatic resistance, resulting in a further decrease in portal pressure.⁶² Carvedilol showed a greater portal hypotensive effect than propranolol in randomized controlled hemodynamic studies.^{63,64} However, the vasodilating activity of carvedilol may enhance arterial hypotension and sodium retention, a risk which is especially relevant in patients with advanced, decompensated cirrhosis.^{63,64} A recent RCT compared the efficacy of carvedilol and endoscopic band ligation for prevention of the first variceal bleeding in patients with cirrhosis and esophageal varices grade II or larger in size.⁶⁵ The incidence of the first variceal bleeding was significantly lower in the carvedilol arm than in the banding arm, although there were no significant differences in overall mortality (35% vs 37%, $P=0.71$).⁶⁵ Carvedilol certainly represents a promising drug for further study.

Angiotensin Antagonists

It is suggested that AT-II plays a role in the pathogenesis of portal hypertension in cirrhosis.⁶ Plasma levels of AT-II are elevated in cirrhosis due to the activation of RAS,⁶⁶ and administration of angiotensin II to perfused cirrhotic livers leads to an increase in intrahepatic vascular resistance.⁶⁷ In patients with cirrhosis, angiotensin II is of major importance for both the regulation of the peripheral vascular tone⁶⁸ and the sodium and fluid homeostasis.^{69,70} AT-II induces the release of catecholamines and stimulates the SNS.⁷¹ Furthermore, AT-II regulates sinusoidal blood flow by inducing contraction of the HSCs.⁷² These findings suggest that treatments that prevent activation of RAS or block the activity of AT-II might be beneficial in patients with portal hypertension. However, because RAS is

stimulated to compensate the splanchnic vasodilatation-induced decrease in the effective arterial volume,²⁷ interfering with RAS could lead to arterial hypotension and renal dysfunction. Consistently, AT-II receptor antagonist salarasin⁷³ and AT-converting enzyme inhibitor captopril⁷⁴ resulted in a marked hypotension in patients with portal hypertension.

Treatment for 1 week with 25 mg of losartan, an orally active nonpeptide AT-II antagonist, caused significant decreases in HVPG (approximately 45% reduction of HVPG) in patients with portal hypertension.⁷⁵ Although there was a significant reduction in the mean arterial pressure with losartan treatment, no deterioration in the renal function was observed in patients treated with losartan. Therefore, the authors suggested that AT-II blockade with losartan is safe and highly effective in the treatment of portal hypertension.⁷⁵ Meanwhile, a recent double-blind RCT suggested that 1-week treatment of irbesartan (150 mg/day), a structurally similar nonpeptide AT-II antagonists that exert their hemodynamic effects by specifically blocking AT1 receptors, only moderately reduced HVPG (12.2%), but induced marked arterial hypotension and renal impairment in patients with advanced cirrhosis.⁷⁶ Irbesartan was not tolerated in 22% of the patients because of an induction of a marked, symptomatic arterial hypotension.⁷⁶ Similarly, a recent RCT compared the effects of 6-week treatment with losartan versus propranolol in patients with liver cirrhosis and esophageal varices.⁷⁷ In contrast to the previous study, 6-week treatment with losartan did not modify the HVPG ($-2\% \pm 12\%$, $P=NS$), while propranolol caused a significant reduction of HVPG ($-10\% \pm 11\%$, $P=0.003$).⁷⁷ Furthermore, losartan caused arterial hypotension and reduced the GFR in patients with moderately impaired liver function.⁷⁷ Thus, the data with this approach are mixed and no firm conclusions can be made at this time. The concept is compelling though since this class of drugs may have antifibrotic effects in addition to their vascular effects.

Antibiotics/TLR4 Antagonists

Toll-like receptors (TLRs) are a family of pattern-recognition receptors that recognize different classes of molecular pattern-specific pathogens.⁷⁸ Binding of ligand to TLRs lead to signaling and activate subsequent immune responses. Among the family of TLR proteins, TLR4 recognizes lipopolysaccharide, a gram-negative bacteria wall component that is enriched within the intestinal lumen and its associated portal circulation.⁷⁹ TLR4 is expressed by all parenchymal and non-parenchymal cell types and contributes to tissue damage. TLR4 in HSCs mediates responses including inflammation, fibrogenesis, and anti-apoptosis.⁸⁰ A recent study suggested that TLR4 signaling within liver endothelial cells contributes to angiogenesis, sinusoidal remodeling, and cirrhosis.⁸¹ Clearly, the role of intestinal microbiota in fibrosis development and portal

hypertension perpetuation merits further investigation, especially as antibiotic therapy has already been proven to benefit specific groups of patients with cirrhosis and portal hypertension. However, further refinement of drugs and indications is required before a broad expansion of their use could be proposed due to the relevant concern of antibiotic resistance.

Anti-Angiogenesis Agents

Recent studies suggested that the angiogenesis in the splanchnic bed and the formation of portosystemic collaterals in portal hypertension could be inhibited by interfering with VEGF/VEGF receptor-2 pathway. Selective blockade of VEGF angiogenic activity by administration of an anti-VEGF receptor-2 monoclonal antibody (DC101) resulted in a significant decrease in the formation of portosystemic collaterals in portal hypertensive mice.⁴⁰ Similarly, administration of SU5416, a potent anti-angiogenic agent that selectively inhibits VEGF-stimulated VEGF receptor-2 autophosphorylation by interfering with the tyrosine kinase domain of the VEGF receptor-2, significantly decreased the formation of portosystemic collaterals.³⁹ This treatment also significantly decreased portal venous inflow and increased splanchnic arteriolar resistance.³⁹ However, despite the reduction in portal venous inflow after SU5416 treatment, portal pressure did not decrease because of the concomitant inhibition in the formation of portosystemic collaterals.³⁹

The ineffectiveness of selective inhibition of VEGF signaling on portal pressure could be explained by the fact that angiogenesis is regulated by multiple factors. Not only VEGF, but also PDGF plays an important role in development of angiogenesis and portal hypertension and is secreted by endothelial cells and binds to PDGF receptor on HSCs.⁸² The PDGF signals are now considered as a crucial factor for angiogenesis.^{35,37} Combined inhibition of VEGF and PDGF signaling by rapamycin (VEGF signaling inhibitor) and Gleevec (PDGF signaling inhibitor) significantly reduced splanchnic neovascularization, superior mesenteric arterial blood flow, as well as portal pressure in experimental models.⁸² In addition, this combined treatment decreased the portal pressure.⁸² In addition, treatment with multiple kinase inhibitors, such as sorafenib⁸³ and sunitinib,⁸⁴ significantly decreased the portal pressure as well as the formation of portosystemic collaterals. However, it should be kept in mind that angiogenesis is a critical process for healing and repair.⁴¹ Furthermore, angiogenesis develops in liver cirrhosis to compensate the high portal pressure. Therefore, inhibition of angiogenesis could impair these physiologic and compensatory mechanisms. In this regard, several studies suggested that placental growth factor (PlGF) could be a promising target.^{85,86} PlGF is a member of the VEGF family and has angiogenic activity. In contrast to VEGF which binds to VEGFR-2, PlGF binds to VEGFR-1 selectively and does not affect

physiological angiogenesis.⁸⁷ PlGF expression was up-regulated in cirrhotic animal model and PlGF inhibition resulted in a significant reduction in not only pathologic angiogenesis in the splanchnic area and portal blood flow, but also portal pressure.^{85,86} Neuropilin-1 (NRP-1), a VEGF co-receptor protein, also modulates PDGF signaling by forming receptor complexes with PDGFR.⁸⁸ In a recent study, NRP-1 neutralizing antibodies ameliorated fibrosis and portal hypertension in experimental models.⁸⁹ Because it modulates both PDGF and VEGF, targeting this molecule could be promising for treatment of portal hypertension.

CONCLUSION

Various recent studies broaden our understanding of the pathophysiology of portal hypertension and suggest promising targets to improve portal hypertension. Especially, identification of the role of angiogenesis and sinusoidal remodeling on the development of portal hypertension provide new promising targets including VEGF, PDGF, and PlGF. However, their clinical benefits are still unclear. In addition, we should keep in mind that angiogenesis and sinusoidal remodeling are the results of compensatory mechanism for elevated portal pressure, and therapeutic inhibition could lead to serious side effects. Therefore, not only their clinical efficacy, but also their safety, especially in patients with liver cirrhosis, should be confirmed by various clinical trials before their clinical application.

CONFLICTS OF INTEREST

All authors have none to declare.

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