NEW INSIGHT ABOUT RENIN-ANGIOTENSIN SYSTEM IN PORTAL HYPERTENSION

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Abstract

Background: A key role for the renin-angiotensin system (RAS) in portal hypertension has been demonstrated in both animal and human . The classical RAS enzyme angiotensin converting enzyme (ACE) is responsible for the conversion of angiotensin I (Ang I) to angiotensin II (Ang II). This, in turn, stimulates hepatic fibrosis, increases intrahepatic vascular tone and portal pressure through stimulation of the Ang II type 1 receptor (AT1R). Although conventional RAS inhibitors, which are commonly used by hypertensive patients, have inhibited liver fibrosis in animal models, sufficiently powered clinical trials have not yet evaluated their effectiveness in human liver disease. These medications may reduce portal pressure, however, can cause off-target side effects including systemic hypotension and kidney failure, according to small studies in cirrhotic individuals.Recent research has linked the alternative RAS—consisting of the enzyme ACE2 and the effector peptide angiotensin-(1-7) (Ang-(1-7)—to the development of liver fibrosis and portal hypertension through the putative receptor Mas (MasR) . It is now widely known that the alternative RAS counter-regulates many of the harmful effects of the ACE-dependent classical RAS; this system is active in both preclinical animal models and human chronic liver disease. Drugs which block the alternate RAS may be useful in treating portal hypertension, according to recent studies. This is because these drugs increase splanchnic vascular resistance in cirrhotic animals, which will improve portal hypertension .With a focus on potential new treatment methods targeting the ACE2-driven alternative RAS, this review highlights the RAS's role in liver fibrosis and portal hypertension.

Keywords: Renin-Angiotensin System, Portal Hypertension, Olmesartan

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Introduction

Fibrosis of the liver is initiated as a part of the wound healing response to tissue injury. The end result of chronic fibrotic injury to the liver is cirrhosis, in which there is extensive scar formation, distortion of liver parenchyma by septae and nodule formation, and alterations in blood flow and this can finally lead to liver failure [1,2]. A major outcome of cirrhosis is the development of portal hypertension which is responsible for many complications including life-threatening variceal bleeding [3]. Cirrhosis has become the 11th most common cause for deaths in humans and was responsible for approximately 1.2 million deaths worldwide in 2016 [4]. The most common causes for chronic liver disease (CLD) include chronic viral infections (e.g., hepatitis B and C), excessive alcohol consumption, non-alcoholic fatty liver disease (NAFLD) and cholestatic diseases such as primary biliary cholangitis and primary sclerosing cholangitis [2,5,6].

Despite being a major health problem, there is no specific medical treatment for cirrhosis. Therefore, treatments that target the causative factors and managing complications associated with cirrhosis including portal hypertension are the only currently available options. Thus, if the causative agent is viral hepatitis C (Hep C), treatment with antiviral therapies leads to cessation and even reversal of tissue fibrosis [7]. Treatment options for established cirrhosis and portal hypertension are limited with the major therapy being non-selective beta-blockers (NSBB). Previous research shows that the renin angiotensin system (RAS) is activated during the development of cirrhosis and contributes to the pathogenesis of both liver fibrosis and portal hypertension [3,6]. This review presents an update on new aspects of the RAS, with special emphasis on novel mechanisms via which the RAS can be manipulated.

The Renin Angiotensin System (RAS)

In normal physiology, the RAS plays a very important role in vascular resistance and regulation of blood pressure, sodium and water homeostasis, and tissue remodeling during tissue injury. The RAS comprises two arms known as the "classical arm" and the "alternate arm" (protective arm). The alternate arm of the RAS plays a major role in counter-balancing many of the deleterious effects of the classical RAS [8].

1.1.1. The Classical Arm of the Renin Angiotensin System

The classical arm of the RAS can be thought of as a linear cascade where angiotensinogen is converted to the effector peptide of the system, angiotensin II (Ang II). Angiotensinogen is produced mainly in the liver by hepatocytes and released into the circulation. Circulating angiotensinogen is converted to the decapeptide angiotensin I (Ang I) by renin, an enzyme produced by the juxtaglomerular apparatus of the kidney. Thereafter, angiotensin converting enzyme (ACE), mainly present in the lungs, converts Ang I to Ang II [9]. There is also an ACE independent pathway of Ang II production from Ang I, which is regulated via a serine endopeptidases named chymase [10,11]. Ang II mediates its effects through two G-protein-coupled receptors, Ang II type 1 receptor (AT1R) and Ang II type 2 receptor (AT2R). AT1R is the predominant receptor type during adult life whereas AT2R, although having some functional role in adults, has been postulated to function mainly during fetal life [12].

Ang II by binding to the AT1R mediates classical RAS functions which include vasoconstriction, sodium homeostasis (by increasing sodium reabsorption from renal tubules and by stimulating the adrenal gland to release aldosterone), increasing thirst (by acting on AT1R in the brain), induction of inflammation and the wound healing response via secretion of cytokines, chemokines, and extracellular matrix proteins. Ang II also acts as a prooxidant and prothrombotic agent and interferes at several steps of intracellular insulin signaling pathways such as the phosphoinositide 3-kinase (PI3) kinase and mitogen activated protein kinase (MAP) kinase pathways [13,14].

1.1.2. The Alternate Arm of the Renin Angiotensin System

Whilst the physiological role of the classical RAS is well-established, the discovery of a new RAS enzyme, ACE2, a homologue of ACE, has dramatically changed our understanding of the RAS physiology [15,16]. The 'alternate or the protective arm' of the RAS driven by ACE2 is considered as the counter-regulatory arm of the classical RAS [3].

In the late 80s, researchers discovered a biologically active heptapeptide angiotensin-(1–7) (Ang-(1–7)) of the RAS [17]. The enzymatic pathway responsible for producing Ang-(1–7) came to light when ACE2 was discovered in the year 2000 by two independent laboratories [15,16]. It is now known that Ang-(1–7) peptide is produced by ACE2 after cleavage of a carboxyl terminal single amino acid from the 8-amino acid peptide Ang II. ACE2 is a zinc-metalloproteinase and a type-1 transmembrane protein which consists of 805 amino acids with a single transmembrane alpha-helical portion, an extracellular N-terminus portion containing the catalytically active domain

and an internal inactive C-terminus [9]. ACE2 is structurally similar to ACE; however, it is functionally different with different substrate affinities than that of ACE, and ACE2 is resistant to ACE inhibitors (ACEi). The major action of ACE2 is to break down Ang II to Ang-(1–7), which acts through the Mas receptor (MasR), a G protein-coupled receptor (GPCR). Ang (1–7) is subsequently metabolized via ACE into Ang-(1–5) and via the other neutral endopeptidases (NEP), neprilysin into Ang-(1–4) [18]. The ACE2/Ang-(1–7)/MasR arm counter-regulates many of the actions of the classical RAS, thus producing opposing effects to those of the classical RAS, including antihypertensive, anti-inflammatory, antithrombotic, antiproliferative, and antifibrotic effects (Figure 1).

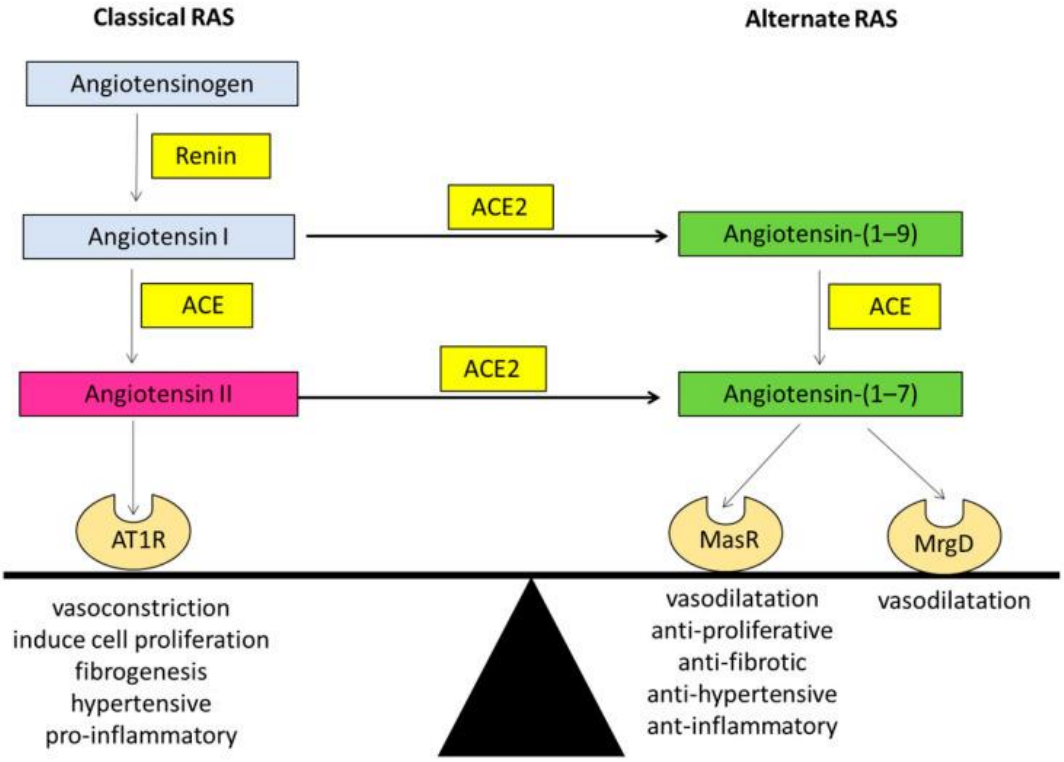

Figure 1

The 'balance' between the two arms of the renin angiotensin system (RAS). Graphical representation of the classical arm (ACE/Angiotensin II/AT1R) and the alternate arm (ACE2/Angiotensin-(1–7)/MasR) of the RAS where the alternate arm counter-balances the deleterious effects of the classical arm. Angiotensin II can exert its effects via the angiotensin II type 1 receptor (AT1R). Whilst angiotensin-(1–7) of the alternate RAS acts mainly via the Mas receptor (MasR), recent evidence suggests that it also transduces its signal via the Mas related G protein-coupled receptor type-D (MrgD). ACE: angiotensin converting enzyme; ACE2: angiotensin converting enzyme 2. [18].

Although the MasR is recognized to be the functional receptor for Ang-(1–7) [19], Santos and colleagues in 2003 suggested that certain effects of Ang-(1–7) may not be mediated through MasR [20]. This was supported by the finding that MasR blocker D-Ala7-Ang-(1–7) (A779) could not block the Ang-(1–7) mediated vasodilatation in the rat aorta, however, these effects were completely blocked by the Ang-(1–7) antagonist D-Pro7-Ang-(1–7) (D-Pro) [21]. Subsequently, a study by Gembardt and colleagues showed that upon stimulation with Ang-(1–7), Chinase hamster ovary (CHO)cells overexpressing MasR or a newly characterized Ang-(1–7) receptor, the Mas related G protein-coupled receptor type-D (MrgD), releasing arachidonic acid [22]. Lautner and colleagues later showed that in addition to Ang-(1–7), the RAS peptide alamandine also activates the MrgD, and the vasodilatory effects produced by alamandine were blocked by the MrgD blocker D-Pro [23]. Other studies provided further evidence by showing that D-Pro blocked Ang-(1–7) mediated vasodilatation in perfused cirrhotic rat livers whilst the MasR blocker A779 had no effect [24].

In a recent study, it was shown that when transfected with either the MasR or MrgD, mesangial cells release cyclic adenosine monophosphate (cAMP) in the presence of Ang-

(1–7) [25]. Moreover, in MasR or MrgD transfected human embryonic kidney (HEK293) cells, blockade of MasR and MrgD with A779 and D-Pro, respectively, abolished the release of cAMP. Moreover, the effects of MrgD stimulation in-vitro were confirmed by in-vivo functional studies by showing that the hemodynamic responses to a bolus injection of Ang-(1–7) were blunted in MrgD knockout (MrgD-KO) mice compared with the controls. With these findings, it is now considered that the alternate arm of the RAS consists of ACE2/Ang-(1–7)/MasR/MrgD [25].

ACEi and Angiotensin II Type 1 Receptor Blockers (ARBs) can be used in treatment of Liver Fibrosis. Since Ang II plays a major role in liver fibrosis, ACEi and ARBs have been studied as potential antifibrotic therapies in liver disease [40]. ACE inhibitors are widely used in patients with high blood pressure and chronic heart failure. Studies in preclinical models suggest that ACEi attenuate the expression of transforming growth factor beta 1 (TGF-β1), collagen and other extra cellular matrix (ECM) proteins including matrix metalloproteinase (MMP)-2 and MMP-9, leading to attenuation of fibrosis [26-33].

There have also been several animal studies which have examined the effects of ARBs in liver diseases. Studies in bile duct ligated (BDL) rats have shown that ARB, telmisartan decreased gene expression of ACE, AT1R, collagen type III, and TGF-β1 while increasing the expression of ACE2 and MasR with concomitant reduction in hepatic fibrosis [37-40]. Another ARB, losartan, significantly ameliorated the progression of hepatic fibrosis induced by carbon tetrachloride (CCl4) in rats along with significant reductions in gene expression levels of AT1R and TGF-β1 [41]. Moreover, a study performed in rats with NASH induced by feeding methionine-choline deficient (MCD) diet showed that another ARB, olmesartan, attenuated serum aspartate transaminase (AST) levels, hepatic stellate cell(HSC) activity, oxidative stress, gene expression of TGF-β1 and collagen, collectively leading to improved liver fibrosis likely resulting from reduced activation of HSCs [42-50].

Despite evidence from animal studies there is a relative lack of clinical studies of RAS inhibition in human liver fibrosis. A retrospective study carried out by Corey and colleagues suggested a reduction in liver fibrosis and necroinflammation in patients with chronic hepatitis C who received ACE inhibitors and ARBs as a treatment for hypertension [51-53]. The study reviewed 284 liver biopsies from the patients who were evaluated at an outpatient hepatology clinic during a 5 year period. The patients were classified into three groups: Group 1—hypertensive patients (n = 143) who received ACEi (captopril, enalapril, lisinopril, quinapril, and trandolapril) or ARBs (losartan, valsartan and irbesartan); Group 2—hypertensive patients (n = 91) treated with β-adrenergic antagonists, calcium channel antagonists, diuretics, α-adrenergic antagonists, or vasodilators; Group 3—patients (n = 50) with chronic hepatitis C infection who did not have hypertension. The results showed a significantly low mean Ishak fibrosis score in patients included in the Group 1 who received ACE inhibitors and ARBs compared to the patients in Group 2 who were treated with other treatments for hypertension. The patients with no hypertension included in the Group 3 showed the lowest mean fibrosis score supporting the theory that hypertension and activation of RAS contributes to fibrosis progression. Another register-based cohort study of patients (n = 70,546) with a first-time diagnosis of chronic liver disease between 2005 and 2012 in Sweden revealed a marked reduction in liver-related mortality among patients with alcoholic liver disease who received ACEi [52,53].

Only a small number of randomized studies have evaluated the effects of RAS blockade in liver fibrosis. A randomized open-label controlled study performed by a group of researchers from South Korea in 2012 investigated the antifibrotic effect of ARBs in patients with compensated alcoholic liver disease [54]. They treated 42 patients with candesartan and ursodeoxycholic acid (UDCA), and the control group (n = 43) received UDCA alone for 6 months. There was a reduction in Laennec fibrosis score, area of fibrosis, hydroxyproline level, and α-smooth muscle actin in the candesartan treated group. Another randomized clinical trial performed in 2011 in a group of selected patients with cirrhosis compared those who received (n = 24) and those who did not receive (n = 24) olmesartan treatment for one year. There was a reduction in TGF-β1 in the olmesartan treated group but not in hepatic fibrosis markers which include serum hyaluronic acid, type IV collagen, and procollagen III N-terminal propeptide levels [55]. In 2007, Debernardi-Venon and colleagues from Italy published data from a randomized clinical trial of candesartan treatment conducted in 47 compensated Child A and Child B cirrhotic patients. The results showed a significant reduction in serum fibrosis marker hyaluronic acid in candesartan treated patients compared to the untreated patients [56]. Although there is a reduction in hyaluronic acid level in treated patients, the results were not supported by

histological data. Between 2004 and 2006, a 48-month follow up study was conducted on 89 patients with cirrhosis associated with hepatocellular carcinoma (HCC) in Japan using combination therapy with branched-chain amino acid (BCAA) granules and an ACE inhibitor, perindopril [57]. The serum fibrosis markers hyaluronic acid and type IV collagen 7S were measured in groups of patients who received a combination therapy with BCAA granules and perindopril and two single-treatment groups who received either perindopril or BCAA and compared to a control group. The patients included into this study were confirmed to be free of any residual HCC, alcohol consumption and also the status of insulin resistance (IR). The results of this study show that combination therapy of BCAA and perindopril improved serum fibrosis markers as compared to either ACE inhibitor or BCAA alone. Another randomized study conducted in 30 patients with early stages of chronic hepatitis C in Japan showed that oral losartan and UDCA administration has the potential to reduce serum type IV collagen and TGF-β1 compared to UDCA alone, but not liver fibrosis as indicated by METAVIR fibrosis score [58].

Thus, there are some studies which suggest beneficial effects of ACE inhibitors and ARBs as antifibrotic agents, [52,53,57]; however, the evidence is conflicting and there is a definite need for further large randomized placebo controlled clinical trials [60]. In addition, it should be noted that there are also concerns about the use of RAS inhibitors in advanced cirrhosis [61-70] as they can induce arterial hypotension and renal function impairment.

The Role of RAS in Portal Hypertension

Almost 90% of the patients with cirrhosis eventually develop portal hypertension. This condition prequels to several complications that occur in the patients with decompensated cirrhosis, such as gastro-esophageal varices and variceal bleeding, ascites, hepato-renal syndrome (HRS), and hepato-pulmonary syndrome (HPS) [73-89].

In cirrhosis, the development of portal hypertension is due to the combined effects of increased hepatic resistance to the incoming portal venous flow which results from the changes to the normal tissue architecture within the fibrotic liver and increased sinusoidal vasoconstriction, and elevated portal venous blood flow secondary to the splanchnic vasodilatation [90,91]. There is currently a lack of therapeutic options for treating portal hypertension and associated complications. The pharmacological mainstay is the use of NSBBs. NSBBs reduce portal pressure via decreasing cardiac output and increasing splanchnic vascular resistance and thus reducing mesenteric blood flow. However, NSBBs are poorly tolerated thus contraindicated in up to 15–20% of the patients. Moreover, in up to 60% of the patients, NSBB treatment fails to produce a clinically significant therapeutic response, defined as a fall of hepatic venous pressure gradient of to a value less than 12 mmHg or reduction in portal pressure greater than 20% from baseline [92,93,94,95]. Since there have been no new drug classes introduced for the long-term management of portal hypertension for more than 30 years, there is an ongoing need for the development of more effective and tolerable drugs to treat this condition in cirrhotic patients.

Previous studies suggest that the RAS plays a major role in the development of portal hypertension in cirrhosis [86,96,97,98]. Many experimental and clinical studies have shown that modulation of the RAS improves portal pressure in cirrhotic animal models and human patients [24,95,99,100,101], suggesting that this system is a potential target in formulating future therapies to treat portal hypertension in cirrhosis.

Role of the renin angiotensin system in cirrhotic portal hypertension. Development of portal hypertension in cirrhosis is a combined effect of the changes that occur within the intrahepatic and splanchnic vascular beds. In the cirrhotic liver, vasoconstrictor peptide Ang II signals through its receptor AT1R in activated HSCs to increase the ECM proteins deposition, creating a fixed barrier to the incoming portal blood flow which raises portal pressure. In addition, Ang II also promotes the contraction of the activated HSCs and vascular smooth muscle cells (VSMCs), further increasing intrahepatic vascular tone, exacerbating portal pressure. Increased intrahepatic resistance is further augmented by the reduced release of vasodilatory molecules such as nitric oxide (NO) from vascular/sinusoidal endothelial cells (VECs) in the cirrhotic livers. In addition, the intrahepatic vasodilatory function of Ang-(1–7) peptide produced from Ang II by ACE2 action is also diminished, further contributing to intrahepatic resistance. In contrast, in the cirrhotic splanchnic vascular bed, circulating Ang-(1–7) increases the release of NO via its putative receptor Mas (MasR) and possibly other factors are released from VECs such as endothelium-derived hyperpolarizing factors (EDHFs) via activation of the Mas related G protein-coupled receptor type-D (MrgD). This promotes the relaxation of VSMCs which leads to dilatation of the splanchnic vascular bed leading to an increased portal blood flow. This further aggravates portal pressure. Splanchnic

vasodilatation is also aggravated by intrinsic splanchnic vascular hypocontractility to vasoconstrictors such as Ang II. [102].

The Role of RAS in Increasing Hepatic Resistance in the Cirrhotic Liver

As outlined above, the components of the classical RAS, such as ACE and Ang II, are significantly upregulated in the systemic and hepatic circulations of the cirrhotic livers [63]. Ang II is a potent profibrotic peptide which promotes HSC proliferation and ECM formation in the fibrotic liver [31,39], and the subsequent elevation in intrahepatic resistance to blood flow contributes to the development of portal hypertension in cirrhosis. Increased intrahepatic vascular resistance is also mediated by the contraction of the activated perisinusoidal contractile HSCs. These cells overexpress the AT1R and contract in response to elevated Ang II, and it is through this mechanism that Ang II contributes to sinusoidal vasoconstriction, thus increasing the intrahepatic resistance to blood flow [32,41]. Previous work from our laboratory supported this concept by showing that in response the infusion of Ang II, perfused cirrhotic rat liver preparations had a greatly increased vasoconstrictive response when compared to healthy rat livers, likely due to the effects of Ang II on the upregulated AT1R in vascular smooth muscle cells and sinusoidal myofibroblastic HSCs [101]. Previous studies also showed that cirrhotic livers have an elevated local Ang II production, thus potentially driving AT1R-mediated vasoconstriction and resistance to portal flow. Therefore, it is expected that the inhibition of Ang II via ACEi and/or ARBs would improve portal hypertension not only by attenuating hepatic fibrosis but also by improving intrahepatic resistance to blood flow in cirrhosis [48,103,104].

Previous studies suggest that the detrimental effects of the classical RAS on hepatic resistance could be counteracted by increasing the overexpression of the alternate RAS in the cirrhotic livers [3]. Previous studies showed that the addition of Ang-(1–7) or the MasR agonist AVE0991, decreases the activation of primary rat HSCs in cell culture, whereas the addition of MasR blocker A779, increases the activation of HSC, as reflected by increased αSMA expression. Previous study also showed that infusion of Ang-(1–7) in-vivo, suppressed HSC activation in cirrhotic rats [32]. In keeping with these findings, another study showed that Ang-(1–7) has profound vasodilatory effects in cirrhotic livers [24]. In addition, the local overexpression of ACE2 in cirrhosis [36] not only ameliorated liver fibrosis but also reduced hepatic perfusion pressure in experimental mouse models by decreasing the levels of vasoconstrictor peptide Ang II whilst simultaneously increasing the levels of vasodilator peptide Ang-(1–7) in the cirrhotic livers [36,64].

The Role of RAS in Mesenteric Vasodilatation in Cirrhosis

In contrast to the profound vasoconstrictive effects produced by Ang II in the intrahepatic vasculature, the systemic and splanchnic vessels are hyporesponsive to circulatory Ang II, and therefore these vessels remain dilated in cirrhosis [105].

Experiments with the isolated mesenteric, omental and/or peripheral vascular bed preparations from cirrhotic animals have indicated that the dilatation of the splanchnic vascular bed in cirrhosis is also attributed to the development of intrinsic vascular hyporesponsiveness to the circulatory vasoconstrictors such as Ang II [109]. Supporting the above in-vitro vessel work, in-vivo experiments in human patients showed that cirrhotic patients had a diminished vasoconstrictive response to intra-arterially administered Ang II as reflected by no significant change in the forearm blood flow, compared to healthy controls [110]. However, despite the evidence of reduced Ang II activity, AT1R is either unchanged or upregulated in splanchnic vessels of the cirrhotic patients [111,112], suggesting that splanchnic vascular hyporesponsiveness to Ang II may probably as a result of the changes that occur downstream of the AT1R [113,114].

Systemic vasodilatation in cirrhosis may also be facilitated by overexpression of the alternate RAS [32,35,115]. Importantly, ACE2, MasR and Ang-(1–7) are elevated in the splanchnic vascular bed of cirrhotic rats and human patients, suggesting that the alternate RAS may play a role in the splanchnic vasodilatation and thereby in the development of portal hypertension in cirrhosis [99,100]. Ang-(1–7) acting via the MasR is shown to increase the release of nitric oxide (NO) from the VECs, which promotes the relaxation of VSMCs leading to splanchnic vasodilatation [99]. It is also shown that Ang-(1–7)/Ang II ratio is significantly elevated in the splanchnic compared to systemic circulations in the cirrhotic patients undergoing liver transplant, which is also negatively correlated with the systemic vascular resistance, suggesting that the augmented Ang-(1–7) activity contributes to the splanchnic vasodilatation in cirrhosis [115]. Supporting this, a previous study showed that infusion of Ang-(1–7) produced hypocontractility in the cirrhotic

splanchnic vasculature but not in controls [99]. Consistent with this, preincubation of cirrhotic mesenteric vascular bed preparations with MasR blocker A779 inhibited the vasodilatory effects produced by Ang-(1–7) [99]. These ex vivo findings were in agreement with in vivo findings showing that a bolus intravenous injection of Ang-(1–7) reduced both splanchnic vascular resistance and hepatic vascular resistance and that a bolus dose of the MasR antagonist A779 increased the resistance in both splanchnic and hepatic vascular beds with a net effect of a significant improvement of portal pressure in CCl4-induced cirrhotic rats [99].

Not only the MasR, but the alternate receptor for Ang-(1–7), MrgD, is also upregulated in the splanchnic vessels of the cirrhotic rats . Moreover, the injection of both MasR and MrgD blockers improved portal hypertension in cirrhotic animal models, presumably via the inhibition of Ang-(1–7) mediated splanchnic vasodilatation in cirrhosis [100]. Although the mechanism(s) through which Ang-(1–7) regulates the MrgD-mediated vasodilatory effects in the splanchnic vessels not well explained, it is possible that in addition to the release of NO, Ang-(1–7), by acting via the MrgD, may enhance the release of other vasodilators such as endothelium-derived hyperpolarizing factors (EDHFs) including epoxyeicosatrienoic acids in splanchnic vessels [101-117].

Manipulation of the RAS in Portal Hypertension

Thus, much research evidence supports the contribution of the RAS in the pathogenesis of portal hypertension,so it is expected that the inhibition of the classical RAS or increasing local expression or activity of the alternate RAS may reduce intrahepatic vascular tone, resulting in a reduced portal pressure. On the other hand, inhibition of the alternate RAS in the splanchnic vasculature is expected to increase splanchnic vascular resistance, thereby improving portal hypertension by reducing portal inflow. These findings therefore suggest that both the classical and alternate RAS are potential targets for the development of novel therapies to treat portal hypertension in human cirrhotic patients.

Targeting the Classical RAS in Portal Hypertension

Many experimental and clinical studies have shown that portal hypertension in cirrhosis could be treated with the inhibitors of the classical RAS, such as ACEi and ARBs. In addition to RAS regulation of portal hypertension, some studies have also suggested that chymase inhibitors are potential drugs to reduce portal pressure by inhibiting intrahepatic Ang II production [10,11]. These drugs are expected to reduce portal pressure via decreasing Ang II mediated increase in intrahepatic resistance. ACEi also prevents the degradation of Ang-(1–7), and thus would increase the intrahepatic Ang-(1–7) levels promoting vasodilatation. However, although they have been widely used in the treatment of systemic hypertension, the ACEi such as enalapril and captopril, and ARBs such as candesartan, losartan, and irbesartan have only been used in a limited number of clinical trials to study their antifibrotic and antiportal hypertensive effects in cirrhotic patients [111,118,119,120,121,122].

The outcomes of clinical trials studying the effects of ACEi and ARBs in cirrhosis were summarized by Tandon and colleagues in a comprehensive meta-analysis published in 2010, which included the findings of three and nine studies on ACEi ARBs, respectively [95]. This analysis concluded that in early Child Pugh A cirrhosis, ACEi and/or ARBs are of similar efficacy to NSBBs in reducing the hepatic venous pressure gradient (HVPG) (17% and 21% with ACEi/ARBs and NSBBs, respectively). However, in advanced Child Pugh B or C cirrhosis, ACEi/ARBs only produced a 3% reduction of HVPG, whilst NSBBs produced a similar reduction of HVPG to that in Child Pugh A cirrhosis. This study, therefore, concluded that although the RAS plays an important role in increasing intrahepatic resistance in early stages of cirrhosis, the effects of RAS on increasing intrahepatic vascular tone in advanced cirrhosis are likely to be overridden by the activation of other powerful vasoconstrictive systems such as the endothelin and/or the sympathetic nervous system [95,107,123]. However, an undesirable side effect of ACEi/ARBs is that in patients with advanced cirrhosis these drugs produce significant systemic hypotension and renal impairment, since the baseline activation of the RAS plays a pivotal role in maintaining adequate arterial pressure and renal perfusion in these patients [95,124,125].

Targeting the Alternate RAS in Portal Hypertension

It is shown that the vasodilatory effects of Ang-(1–7) in cirrhotic splanchnic vessels appear to be mediated via its receptor MasR. Administration of the specific MasR blocker A779 increased the resistance in splanchnic vessels, reduced splanchnic blood flow and thereby improved portal hypertension in cirrhotic rat models [99]. However, the effectiveness of MasR blockade in

lowering portal pressure by increasing splanchnic resistance may be compromised by its ability to increase intrahepatic resistance by blocking Ang-(1–7) mediated vasodilatation in the liver [99]. Indeed, in contrast to the results of MasR antagonism, the nonpeptide Ang-(1–7) agonist AVE0991 was shown to lower portal pressure by reducing intrahepatic resistance [126]. Supporting this, another study showed that neutral endopeptidase (NEP) inhibitor candoxatrilat also significantly reduced intrahepatic resistance thereby portal pressure in cirrhotic rats, via reducing Ang-(1–7) metabolism in the cirrhotic livers [127].

As has been discussed, in addition to the MasR, the novel receptor MrgD is also shown to mediate the vasodilatory effects of Ang-(1–7) [25]. Consistent with this, it was documented that similar to the MasR, MrgD is also significantly upregulated in the cirrhotic splanchnic vessels, and blockade of MrgD with a bolus injection of D-Pro led to a significant reduction of portal pressure in cirrhotic rat models, which was similar to that produced by the MasR blocker A779 [100]. However, in that study both these blockers failed to reduce portal pressure up to clinically significant levels (i.e., <20% from the baseline). Moreover, these drugs failed to sustain their portal pressure lowering effect for more than 20–25 min, possibly attributed to the rapid metabolism of these peptide blockers within the rat circulation [100]. This study therefore warrants further studies to determine whether these blockers could maintain adequate plasma concentrations when given as a continuous infusion over time, and thereby produce a clinically sustainable effect on portal pressure in experimental cirrhosis.

Importantly unlike MasR, MrgD is not upregulated in the hepatic vascular bed of the cirrhotic animals, suggesting that the effects of MrgD likely to be limited to the splanchnic vascular bed in cirrhosis. Thus, in contrast to the MasR blocker A779, MrgD blockade with D-Pro may not increase intrahepatic resistance, thus enhancing its antiportal hypertensive effect in cirrhosis [99]. This finding that the MrgD has tissue-specific expression in splanchnic vessels in cirrhosis has significant potential implications for the development of pharmacotherapies that specifically target splanchnic vasodilatation in cirrhotic patients.

Role of Olmesartan in Liver Diseases

The pathophysiology of organ fibrosis may be significantly influenced by the RAS, according to a number of recent lines of evidence [116].

Ang II has been demonstrated to stimulate collagen synthesis and proliferation in mesangial cells as well as other cell types. Furthermore, Ang II increases the expression of transforming growth factor-β (TGF-β) [120].

It has been demonstrated that inhibiting the RAS using AT1 antagonists or ACE inhibitors will inhibit organ fibrosis. Ang II is thought to be involved in the control of intrahepatic circulation in the liver [116].

According to recent reports, AT1 receptors primarily mediate the proliferation and contraction of human HSCs as well as the production of TGF-β in rat HSCs induced by Ang II, indicating that the advancement of liver fibrosis in vivo is inhibited by ACE inhibitors or AT1 antagonists. According to these results, Ang II and RAS may be crucial in the development of liver fibrosis. Conversely, angiogenic chemicals secreted by active HSCs stimulate LSECs, thereby increasing angiogenesis. The significance of angiogenesis in fibrogenesis is demonstrated by the amelioration of liver fibrosis caused by certain angiogenesis-inhibiting medications, such as those that target vascular endothelial growth factor receptor-2 (VEGFR-2). Several studies show that angiotensin II is a powerful vascular smooth muscle cell growth factor that upregulates VEGF and promotes angiogenesis. Furthermore, it has been demonstrated that the AT1R antagonist reduces angiogenesis in hepatocellular carcinoma by inhibiting the VEGF pathway [120].

(3) gastrointestinal tract microorganisms

The gut and liver are anatomically related by portal circulation [36]. The liver is continuously exposed to microbial products, food-derived antigens, poisons, nutrients, and germs from the gastrointestinal system. Bacterial translocation is a common factor in the development of hepatic encephalopathy and spontaneous bacterial peritonitis, and upper gastrointestinal hemorrhage, three consequences of liver cirrhosis. The inflammatory reaction that results from bacterial translocation causes a rise in portal hypertension, which exacerbates the patients' hyperdynamic circulation [113].

(4) Decreased vasodilators

It has been stated that one of the most significant contributing causes to the rise of intrahepatic vascular resistance is a deficiency in the intrahepatic bioavailability of the endogenous vasodilator NO. The reduced NO is caused by two mechanisms:

First, negative regulators (such caveolin-1), which are up-regulated during cirrhosis, inhibit the NO generating enzyme endothelial eNOS; as a result, NO production declines [112].Second, cirrhosis is associated with elevated oxidative stress. During

cirrhosis, increased superoxide radicals spontaneously react with NO to form peroxynitrite (ONOO-), an endogenous toxicant Thereby decreasing NOs bioavailability as a vasodilator. Numerous substances, including ethanol, viruses, bacteria endotoxins, and medications, can cause oxidative stress in LSECs [113].

(5) Increased vasoconstrictors

In addition to vasodilators being reduced in cirrhosis, there is a rise in vasoconstrictors, such as thromboxane A2 (TXA2). TXA2 is generated in LSECs by COX-1 activity. Another significant vasoconstrictor that increases intrahepatic vascular resistance is endothelin (ET-1), which binds to its receptors on HSCs [112].

(B) Increased portal blood flow:

Unlike the hepatic vasculature, where endothelial dysfunction to vasodilators is present, Cirrhotic splanchnic vessels experience vasodilatation due to local over-production of vasodilators and intrinsic vascular hypocontractility, leading to increased blood flow through these vessels [113]. The excess production of NO in splanchnic arteries is mainly caused by eNOS. NO is produced by endothelial cells and diffuses into VSMCs, where it directly induces the release of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate by membrane-bound soluble guanylate cyclase. Following this, cGMP causes K+ efflux, additionally, it activates protein kinase reliant on cGMP, which dephosphorylates myosin light chain kinase and causes vasodilatation. [4]. Despite the development of portosystemic collaterals, systemic arterial vasodilation leads to increases in splanchnic blood flow to the portal system and consequently, higher portal pressure. [114]. This illness exacerbates portal hypertension and promotes the hyperdynamic circulation, which is defined as lower peripheral resistance, greater cardiac index, lower mean arterial pressure, and lower systemic vascular resistance. Combined with increased blood flow to portosystemic collaterals, hyperdynamic circulation leads to clinically severe consequences such gastric varices [115].

Conclusion

Recent advances in our understanding of the complexities of the RAS have led to the development of new ideas regarding the therapeutic potential of manipulating the RAS in liver disease. Whilst the classical RAS via its effector peptide Ang II is strongly implicated in liver scarring, there remains a lack of clinical evidence to support the routine use of classical RAS blockers as antifibrotic agents. Ang II is also strongly implicated in the pathogenesis of portal hypertension via its ability to promote constriction of contractile cells in the cirrhotic liver. This has prompted a number of clinical trials of classical RAS blockers in cirrhosis; however, available evidence suggests that this class of drugs is of limited efficacy and has serious adverse effects in patients with advanced cirrhosis. The possible role of the alternative RAS and its suitability as a therapeutic target in liver cirrhosis is less well-studied. There is intriguing evidence that drugs targeting the MasR could have efficacy as antifibrotic agents. On the other hand, a greater therapeutic interest and importance is the possibility that drugs targeting the receptors of the alternate arm could be used to treat portal hypertension. Very recent evidence suggests that the MrgD may be a particularly attractive therapeutic target because in cirrhosis, unlike MasR, the expression of MrgD is minimal in the liver but markedly upregulated in splanchnic vessels. This could allow for the potential development of mesenteric vasculature selective drugs which reduce splanchnic flow but do not adversely affect resistance and blood flow in the liver.

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