Received: 7 March 2022 | Accepted: 13 May 2022

DOI: 10.1002/poh2.17

REVIEW

PH&C PORTAL HYPERTENSION & CIRRHOSIS

Endothelins and liver cirrhosis

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Managing Editor: Ningning Wang

Funding information
None

Abstract

Endothelins are a family of 21-amino acid oligopeptides, called endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin 3 (ET-3). Endothelins act on hepatocytes, liver endothelial cells, and Kupffer cells in a paracrine or autocrine manner through two G protein-coated receptors, called endothelin A and B receptors, which are mainly located in interlobular veins, interlobular artery endothelial cells and hepatic stellate cells (HSCs). ET B receptor (ETBR)-1 is responsible for the induction of endothelial nitric oxide synthase, resulting in nitric oxide release and vasodilatation, whereas ETBR-2 is located on HSCs and is responsible for vasoconstriction. Endothelins are not stored in the organs. Approximately 20% of endothelins are secreted into the circulation system, and are rapidly cleared by the lungs, liver, heart, and kidneys. As a potent vasoconstrictor, endothelins may have a key role for the treatment of hypertensive vascular diseases, inflammation, fibrosis, and metabolic diseases. By clearing ET-1 from the circulation, endothelin A receptor (ETAR) antagonists can reduce intraportal vascular resistance by dilatating the portal vein, reducing the contraction of HSCs, increasing the diameter of sinusoids, facilitating the regression of liver fibrosis, and restoring liver parenchyma. ET-1 induces nitric oxide synthase and upregulates cyclooxygenase 2 mRNA levels, making it a key factor during the onset of fibrosis and in the prognosis of patient outcomes. Endothelins can be used to treat porto-pulmonary hypertension, portal hypertension, angiogenesis, and liver fibrosis and have been approved for the treatment of porto-pulmonary hypertension. Endothelins are produced on mesangial cells, podocytes, tubular epithelium, and renal collecting tubes in high amounts. Activation of ETAR supports the progression of kidney diseases, whereas activation of ETBR has protective effects on the kidneys. ET-1 plays an important role in normal cardiovascular homeostasis. Endothelins are closely associated with severe systemic hypertension, congestive heart failure, atherosclerosis, and pulmonary hypertension. Dual ET receptor antagonists reduce blood pressure, but have several side effects, including liver toxicity, acute liver failure, accumulation of salt and water, testicular toxicity, headache, and teratogenicity. Liver enzymes should be checked in all patients who have received ET receptor antagonists, and women of childbearing years should use contraception.

KEYWORDS
cirrhosis, endothelin, portal hypertension

1 | INTRODUCTION

Endothelins are a family of 21-amino acid oligopeptides, called endothelin-1 (ET-1), endothelin-2 (ET-2), and endothelin 3 (ET-3), with two intramolecular disulfide bonds. Endothelins are mainly located in interlobular veins, interlobular artery endothelial cells, and hepatic stellate cells (HSCs). Endothelins bind to two G protein-coated endothelin receptors, called endothelin receptors A (ETAR) and B (ETBR).[1,2] ETBRs, which are located on

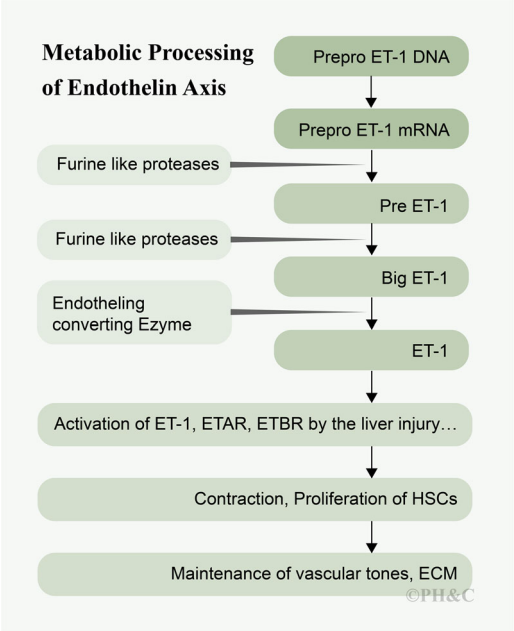

FIGURE 1 Metabolic processing of endothelin axis. ECM, extracellular matrix; ET, endothelin; ETAR: endothelin A receptor; ETBR, endothelin B receptor; HSC: hepatic stellate cell.

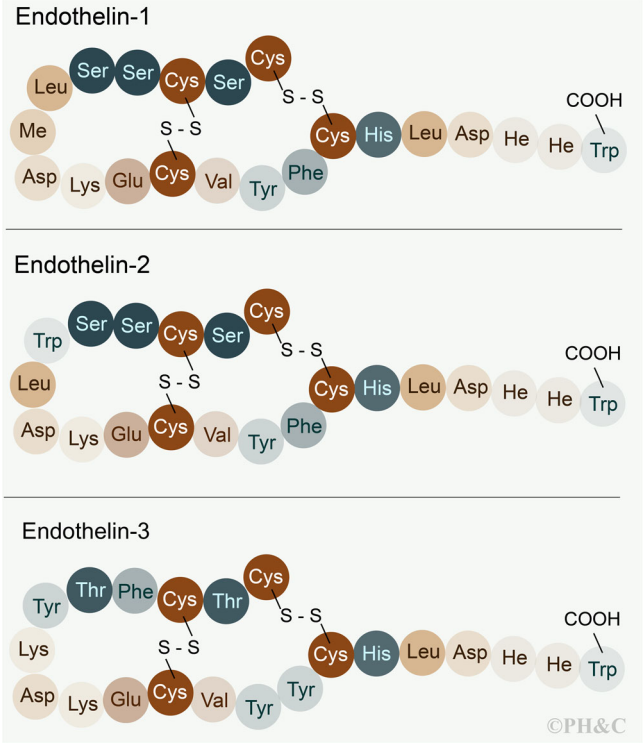

FIGURE 2 Endothelin's family. There are several aminoacide differences which are shown by gray color among endothelins.[12]

cells lining the endothelium and on HSCs, have two subtypes, ETBR-1 and ETBR-2.[3,4] ETBR-1 is responsible for the induction of endothelial nitric oxide synthase, resulting in nitric oxide release and vasodilatation, whereas ETBR-2 on HSCs is responsible for vasoconstriction.[5] ET-1 mRNA is synthesized by the activation of the preproendothelin gene through liver injury and inflammation. The translational product, that is, preproendothelin, is cleaved by a two-step process involving furin-like endopeptidases to form big endothelin, which, in turn, is cleaved by endothelin converting enzyme (ECE) to form ET-1 (Figure 1).[6]

The levels of ET-1, ETAR, and ETBR in tissue have respectively been shown to be 7-, 5-, and 4.6-fold higher, respectively, in patients with liver cirrhosis than in controls.[7,8] Moreover, acute administration of CCl4 into the peritoneum of rats has been shown to increase ET-1, ETAR, and ETBR levels 7.2-, 7.4-, and 4.9-fold, respectively, whereas big ET-1 levels are unaffected by bile duct ligation.[9,10]

The genes that encode ET-1, ET-2, and ET-3 are localized on chromosomes 1, 6, and 20, respectively, whereas the genes that encode ETAR and ETBR are located on chromosomes 4 and 13, respectively.[11] Endothelins are homologous to each other, although they difference in several amino acids (Figure 2).[12] ET-1, which induces long-lasting vasoconstriction through ETAR and vasodilatation through ETBR, was first isolated from porcine aortic endothelial cells in 1988.[13]

ET-1 acts by binding to endothelin A and/or B receptors, which are located on the membranes of endothelial cells and HSCs in the liver, and on other cell types, including vascular smooth muscle cells, Kupffer cells, polymorphonuclear cells, macrophages, and cells in the heart, brain, lungs, kidneys, and liver.[14,15] Platelet activating factors (PAF) in Kupffer cells and on membranes are increased 2- and 1.48-fold, respectively, in cirrhotic rats treated with by CCL4. Kupffer cells are the main reservoir of PAFs.[16] ET-1 has over 100-fold greater affinity for ETARs than ET-2 and ET-3, whereas all three endothelins have equal affinity for ETBRs.[17]

ETs are not stored in the organs. Approximately 20% of synthesized endothelins are secreted into the circulation. Endothelins are cleared quickly from the circulation by the lungs, liver, heart, and kidneys, with the lungs removing about 50% of the circulating ET-1 through ETBRs.[18] Although ET-1 is normally metabolized by healthy livers, ET-1 metabolism is reduced, while ET-1 is overexpressed, in cirrhotic livers.[19–21] Endothelin receptor antagonists bind to ETBRs, reducing their degradation.[18] ET-1 acts on hepatocytes, liver endothelial cells and Kupffer cells in a paracrine or autocrine fashion.[5,22] Several vasoconstrictors, such as angiotensin II, thromboxane A2, and carbon monoxide, and vasodilators, such as NO, maintain balance in the hepatic circulation, controlling fenestrae and the diameter of sinusoids.[5] A cadaveric study showed that ETBRs are decreased and ETAR/ETBR ratios increased in patients with terminal stage liver cirrhosis.[23]

Urinary ET-1 excretion was shown to be greater in patients with liver cirrhosis than in healthy control individuals, which may explain the overexpression of ET-1 in the kidneys of patients with liver cirrhosis.[24] Both ET-1 and the ETBR agonist sarafotoxin increase HSC contractility, whereas bosentan, a mixed ET antagonist, decreases portal vein pressure in rats with portal hypertension.[25] Many types of hepatic injury, including viral hepatitis, alcoholic and nonalcoholic steatohepatitis, autoimmune hepatitis, and drug-induced liver injuries, activate Kupffer cells and HSCs.

Kupffer cells interact with hepatocytes and secrete significant levels of cytokines such as interleukin (IL)-1, IL-6, IL-10, and tumor necrosis factor (TNF)-alfa; as well as radical oxygen species (ROS), PAF, and eicosanoids. These mediators stimulate liver endothelial cells to express ET-1. Lysosomal enzymes may exacerbate inflammation and tissue injury.[5] Endothelin synthesis is inhibited by nitric oxide, natriuretic peptide, heparin, and prostaglandins.[26]

HSCs constitute approximately 5%–10% of all cells in the liver. Under normal conditions, they play a role in the storage of vitamin A and exhibit a quiescent phenotype. Activation of HSCs by transforming growth factor (TGF)-beta, platelet derived growth factor (PDGF), TNF-alfa and cytokines increases ET-1 expression, as well as inducing HSCs to undergo striking morphological and functional transition to a myofibroblast-like phenotype, with increased fibrogenic, contractile, immunomodulatory and migratory potential.[5,27,28] Cells with a myofibroblast-like phenotype express alfa-smooth muscle actin and respond to endothelin-1, TGF-beta, PDGF, Krüppel-like factor 6 (KLF-6), matrix metalloproteinases (MMPs), tissue inhibitors of MMPs (TIMPs) and other signaling molecules secreted by injured hepatocytes, liver sinusoidal endothelial cells, and Kupffer cells. This process leads to HSC contraction, migration, and proliferation and the accumulation of extracellular matrix proteins, including fibril forming collagens. These changes are accompanied by the closure of endothelial fenestrae and portal hypertension in the portal system.[5]

Acute blockage of ETAR with a selective ETAR receptor antagonist, ambrisentan, does not affect portal hemodynamics, whereas blockage of ETBR with bosentan reduces body weight and portal venous pressure. The combination of ambrisentan and bosentan reduces vascular endothelial growth factor (VEGF) levels, the severity of fibrosis, portosystemic vascular collaterals, and mesenteric vascular density (i.e., vascular length per unit window area) but had no effect on ALT, AST and bilirubin levels compared with bosentan or ambrisentan alone. The combination of bosentan and ambrisentan also significantly reduced angiotensin, inducible nitric oxide synthase (iNOS), cyclooxygenase 2 (COX-2), VEGF, and phospho-VEGF receptor 2 levels, as well as downregulating the expression of Akt and phospho-Akt protein.[1] ETAR antagonists reduce intra-portal vascular resistance by dilatation of the portal vein. This, in turn, reduces the contraction of HSCs, increases the diameter of sinusoids, facilitates the regression of liver fibrosis, and restores liver parenchyma, by clearing ET-1 from the circulation.[29]

High plasma concentrations of ET-1 reduce bile flow, whereas low plasma concentrations of ET-1 increase bile flow, indicating that ET-1 induces bile flow under physiological conditions and plays a role in the pathogenesis of cholestatic liver diseases.[12] In addition, endothelin receptor antagonists are hepatotoxic, with bosentan increasing ALT levels 7.6%. Loss of appetite and fatigue are frequent side effects of ET receptor antagonists.[1] CCL4-induced liver cirrhosis has been shown to increase ET overexpression in the renal medulla of rats, as well as reducing glomerular filtration rates.[30] ET overexpression is reduced and glomerular filtration rates enhanced in these rats after Bosentan administration.[30]

1.1 | Endothelin and portal hypertension

Patients with portal hypertension and liver cirrhosis demonstrate characteristic hemodynamic changes, including systemic hyperkinetic circulation, abnormal distribution of blood volume, and neurohumoral dysregulation.[31] The activation of both HSCs and Kupffer cells was shown to be independent of the etiology of liver injury, such as HBV, HCV, and HDV infection; alcohol, drugs, or metabolic or autoimmune diseases.[32] These agents alter HSCs to a myofibroblast phenotype, with characteristic morphologic and functional diversifications.[33] This activation results in the release of interferon (IFN)-gamma, TNF-alfa, free oxygen species, and proteases.[34] Although activated HSCs express endothelins and angiotensin-I receptors, their expression of nitric oxide synthase and nitric oxide is reduced decreases and intrahepatic vascular resistance is increased.[35] Splanchnic vasodilatation results in an increase in blood at the peripheric microcirculatory area. Cardiac outflow increases due to activation of the renin-angiotensin system resulting in portal hypertension.[34] Increases in the extracellular membrane (ECM), nodule formation, thrombosis, and fibrosis alter the hepatic microcirculation, resulting in angiogenesis.[34,36]

Bile duct ligation was found to increase portal pressure and ET-1 concentrations in humans and in animal models. Treatment of rats with the ETAR antagonist, LU135252, at a dose of 80 mg/day for 1–6 weeks after bile duct ligation improved liver histology, reduced liver collagen by 60%, and reduced the levels of messenger RNA encoding hepatic procollagen alfa 1 and TIMP-1 (two major effectors of fibrosis) and serum procollagen type III.[37] These results showed that ETAR antagonists can be used as anti-fibrotic drugs in chronic parenchymal diseases.[37]

Intraperitoneal administration of 0.15 mg/kg CCl4 twice weekly for 8 weeks to rats induced liver cirrhosis, whereas intravenous administration of the ET-1 antagonist TAK-044 reduced portal pressure, improved hepatocellular necrosis about 35%, and reduced the concentrations of liver enzymes.[38] Similarly, TAK-044 treatment of rats with CCl4-induced liver cirrhosis decreased ET-1 concentrations and ET receptor densities to normal levels.[39] Although lipopolysaccharide (LPS) induces cirrhosis in rats, administration of LPS plus tezosentan, a mixed ET receptor antagonist, reduced liver enzyme and plasma TNF-alfa levels, along with hepatic myeloperoxidase activity and hepatic neutrophil levels, while increasing survival rates when compared with rats that received only LPS.[40]

Intraportal administration of ET-1 or sarafotoxin, an ET-B receptor agonist, at a dose of 0.5 nmol/kg increased portal pressure progressively in both cirrhotic

and healthy control rats. Portal pressure was not reduced by administration of ETAR and ETBR antagonists alone, but was reduced in rats treated with both ETAR and ETBR antagonists. These results indicate that ET-1 plays a major role in portal hypertension accompanying liver cirrhosis.[41]

ET-1 also plays an important role in upregulating the expression of inducible nitric oxide synthase (iNOS) and Cox-2 mRNA. Intravenous administration of bosentan (30 mg/kg) blocked the upregulation of ET-1, iNOS, and Cox-2 mRNA induced by bile duct ligation, whereas intraperitoneal administration of 1 mg/kg LPS induced cirrhosis in Sprague Dawley rats.[42]

Two weeks after bile duct ligation or sham operation, hepatic hemodynamics were measured before and after intraportal administration of ETAR, ETBR, and mixed ET receptors. The ETAR antagonist, B123, reduced portal vein pressure in cirrhotic rats but did not in noncirrhotic rats. In contrast, the ETBR antagonist, BQ788, had no effect on cirrhotic rats but increased portal vein pressure in noncirrhotic rats. Administration of both the ETAR and ETBR antagonists reduced hepatic blood flow, whereas administration of the mixed ET receptor, bosentan, reduced portal vein pressure but had no effect on hepatic blood flow.[42] A similar study showed that administration of ET-1 at a dose of 3 nmol/kg into the portal vein progressively increased portal pressure and systemic arterial pressure in both normal and cirrhotic rats. Administration of a mixed ET antagonist, SB209670, at a dose of 5.4 mmol/kg reduced portal vein pressure but had no effect on systemic artery and renal artery pressure.[43] Taken together, these results indicate that mixed ET receptor antagonists can be useful for the treatment of portal hypertension.[44]

In a double-blind, randomized multicenter study, 18 patients with liver cirrhosis and six healthy control subjects were administered a mixed ET-1 receptor antagonist, tezosentan, at a dose of 3 mg/hour for 2–3 h. Infusion of tozosentan, however, had no effect on hepatic wedge pressure gradient, hepatic blood flow, arterial blood pressure, or heart rate.[45] Moreover, tezosentan was excreted unchanged exclusively via the liver bile ducts into the feces, and it was well tolerated.[17] In another double-blind, randomized study, 16 patients with liver cirrhosis and portal hypertension were treated with the selective ETAR antagonist, BG123, at doses of 1000 and 3000 nmol/min (Group 1), the selective ETBR antagonist B788 (Group 2) or saline solution (Group 3). BQ123 reduced mean arterial pressure (MAP) and pulmonary vascular resistance index (PVRI), but did not affect hepatic vein pressure gradient (HVPG), cardiac index or systemic vascular resistance index in cirrhotic patients compared with the control group. In contrast, B788 increased MAP and systemic vascular resistance index and decreased cardiac index but had no effect on HVPG or PVRI compared with the control group. These findings indicated that ET-1 did not affect acute HVPG but did contribute to the maintenance of systemic and pulmonary hemodynamics.[46]

ET-1 plays roles as a key factor both during the onset and the progression of fibrosis. ET-1 levels were shown to increase in broncho-alveolar lavage fluid and lung tissue in patients with idiopathic pulmonary fibrosis. Moreover, ET-1 receptor antagonists were found to limit bleomycin-induced lung fibrosis.[47] Bosentan has been found to inhibit endothelin-induced fibroblast proliferation, ECM deposition and contraction. Activation of the ET system was found to reduce cardiac, hepatic, pulmonary and renal fibrosis, with ET-1 reversing fibrosis by activating MMP-1.[48]

1.2 | Endothelins and pulmonary hypertension

The pulmonary circulation is a major site of ET-1 expression, with human lung tissue having high affinity for binding ET receptors. ETARs are located in large pulmonary arteries, whereas ETBRs are located in more distal pulmonary arteries. ET-1 plays a major role in the pathogenesis of pulmonary arterial hypertension.[49] Hepatopulmonary syndrome arises from intrapulmonary vasodilatation in the presence of portal hypertension and liver cirrhosis.[50] Selective ETBR expression in the pulmonary vasculature increases in animals following portal vein or common bile duct ligation. Increased ETBR leads to increases in iNOS and NO levels, resulting in hepatopulmonary syndrome in animals with cirrhosis and portal hypertension.[51] ETBR levels are significantly increased in patients with pulmonary hypertension, whereas ETAR levels are not changed.

Lung fibroblasts derived from patients with systemic sclerosis showed increased expression of procontractile proteins, such as alfa smooth muscle actin (α-SMA), ezvin, paxillin, and myosin, along with augmented contraction ability of the collagen matrix. Blockage of ET-1 decreases pulmonary scar formation associated with lung fibrosis.[52] ET-1, ETBR, endothelial NOS (eNOS) and NO levels have been shown to increase in experimental hepatopulmonary syndrome. Increased pulmonary microvascular endothelial ETBR expression in prehepatic portal hypertension and liver cirrhosis shows positive a correlation with increased shear stress, which is a modulator of ETBR expression. This finding indicates that ETBR overexpression, rather than eNOS activation by ET-1, contributes to hepatopulmonary hypertension.[50] ETBR overexpression both alters pulmonary vasodilatation and prevents pulmonary hypoxic hypertension in patients with hepatopulmonary syndrome.[53] ETAR and ETBR both inhibit pulmonary apoptosis, and decrease the levels of the MMPs MMP2 and MMP9, as well as the levels of pro-inflammatory cytokines.[49]

Oral administration of bosentan results in a rapid decrease in pulmonary arterial pressure and an increase in cardiac index.[18] Bosantan treatment of a patient with portopulmonary hypertension due to cryptogenic cirrhosis for 16 and 31 weeks reduced pulmonary artery pressure from 88 mmHg to 43 and 58 mmHg, respectively, and reduced hepatic portal vein pressure gradient from 26 mmHg to 7 and 17 mmHg, respectively.[54] Similarly, bosentan treatment of a patient with portopulmonary hypertension due to alcoholic cirrhosis for 9 months reduced pulmonary vascular resistance 60%

and mean pulmonary artery pressure from 55 to 44 mmHg. Moreover, bosentan was well tolerated.[55]

ET-1 plays an important role in normal cardiovascular homeostasis. ET was shown to be closely related to severe systemic hypertension, congestive heart failure (CHF), atherosclerosis, and pulmonary hypertension.[56] Treatment with dual ET receptor antagonists reduced blood pressure. ET-1 levels are increased in rats with CHF. Treatment with ET-1 receptor antagonists reduced myocardial contraction in rats with CHF, but had no effect on myocardial contraction in healthy rats. Although ET-1 has positive inotropic effects in rats with CHF, long-term treatment can reduce coronary blood flow and induce ventricular arrhythmias. ET-1 shows potent hypertrophic effects on cardiac myocytes by having direct toxic effects on these cells. Treatment with ET receptor antagonists for 12 weeks extended the survival of rats with CHF, with increased ET-1 concentrations in hypertrophic hearts causing pulmonary hypertension.[57] ET-1 and sarafototoxin S6C, a potent ETBR agonist, were found to stimulate the activation of cultured HSCs. This process was inhibited by administration of bosentan, which also reduced collagen-1, alpha SMA, extracellular matrix, and cellular fibronectin mRNAs. These findings indicated that ET-1 contributes to fibrogenesis by activating HSCs.[58]

In a double blind, placebo controlled, multinational, multicenter study, patients with porto-pulmonary hypertension were randomized to receive macitentan 10 mg/day ($n = 43$) or placebo ($n = 42$) for 12 weeks. Macitentan reduced pulmonary vascular resistance 35% compared with placebo. During the double-blind period of the study, 84% of patients in the macitentan group and 79% in the placebo group experienced adverse events, such as peripheral edema, with 9% and 0% having adverse events leading to discontinuation.[59] Several selective and nonselective ET receptor antagonists have been approved in Europe for the treatment of patients with pulmonary hypertension. Macisentan, ambrisentan, and bosentan have been shown effective drugs, reducing mortality and morbidity rates and improving exercise capacity in patients with pulmonary hypertension.[60–62]

1.3 | Endothelin and hepatorenal syndrome

Endothelins are highly expressed on mesangial cells, podocytes, tubular epithelium, and renal collecting tubes. Activation of ETAR enhances the progression of kidney diseases, whereas activation of ETBR has protective effects on the kidneys.[63] Endothelins act in a paracrine or autocrine fashion on renal blood flow, glomerular hemodynamics, and the regulation of sodium and water.[64,65] These peptides modulate cortical and medullary or locational blood flow, mesangial contraction, podocyte function, acid–base balance and the stimulation of ECM production. ETs may cause increasing renal vascular resistance, acute ischemic renal failure, calcineurin inhibitor toxicity, endotoxemia, and hepatorenal syndrome.[66]

ET-1 infusion in normal healthy rats results in severely reduced renal blood flow, renal vasoconstriction, glomerular filtration rate (GFR), and finally hepatorenal syndrome.[26,67] ET-1 and ET-3 levels were shown to be significantly higher in patients with hepatorenal syndrome due to acute liver failure or alcoholic hepatitis. One week after liver transplantation, ET-1 levels decrease, and renal functions improve. Administration of bosentan increases renal blood flow in healthy people and ameliorates renal failure in patients with chronic kidney diseases. ET-1 levels increase in normal healthy, cirrhotic, and endotoxemic rats.[26,68] These results indicate that endogenous endothelins play important roles in the maintenance of renal vascular tone. Similarly, treatment of Alport rats with sitaxentan, an ETAR antagonist, reduced proteinuria, normalized glomerular MMP and pro-inflammatory cytokine expression, and increased survival rates.[69] Blockage of ET-1 receptors results in nephroprotection due to the normalization of growth factors, the attenuation of MMP activity and the reversal of ECM storage.[70]

2 | SUMMARY

ETs are potent vasoconstrictors that may play a key role in the treatment of hypertensive vascular diseases, inflammations, fibrosis, and metabolic diseases. The ET axis can be inhibited by the blockage of big endothelin, ECE, and/or ETARs and ETBRs. Dual ET antagonists were reported to have several side effects, such as liver toxicity, acute liver failure, accumulation of salt and water, testicular toxicity, headache, and teratogenicity. Liver enzymes should be monitored in all patients who have received ET receptor antagonists, and women of childbearing ages should use contraception. ET receptor antagonists may be an important target for the treatment of patients with idiopathic pulmonary arterial hypertension, CHF, hypoxia and lung diseases, and chronic pulmonary thromboembolic diseases. Large, multicenter, randomized trials are required to assess the safety and efficacy of ETs in patients with liver cirrhosis, including in the treatment of portal hypertension, angiogenesis, and liver fibrosis.

AUTHOR CONTRIBUTION

Necati Örmeci: Conceptualization; writing.

ACKNOWLEDGMENTS

Not applicable.

CONFLICT OF INTEREST

Necati Örmeci is the Editorial Board Member of Portal Hypertension & Cirrhosis, who is therefore excluded from the peer-review process and all editorial decisions related to the publication of this manuscript. The remaining author declares no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used in the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

Not applicable.

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How to cite this article: Örmeci N. Endothelins and liver cirrhosis. *Port Hypertens Cirrhos*. 2022;1:66-72. doi:10.1002/poh2.17