Renin–angiotensin system (RAS) and hepatic fibrosis

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Hepatic fibrosis is a dynamic condition between fibrogenesis and fibrolysis. Hepatic fibrosis is characterized by inflammation, the involvement of several liver cell types such as hepatic stellate cells (HSCs) and Kupffer cells (KCs) and the activation of multiple signaling mechanisms including cytokines, chemokines and growth factors that result in the deposition of extracellular matrix (ECM). To date, many animal models and clinical studies indicate that the renin-angiotensin system (RAS) plays a major role in the progression of liver fibrosis. Angiotensin II (ANT II) is a key component in RAS that plays an important role in hepatic fibrosis via activated HSCs. At the same time, ANT II is implied in the hemodynamic balance of cirrhosis and portal hypertension. So, ANT II has been an important therapeutic target to inhibit fibrosis and reduce the risk of complications of portal hypertension.

Role of RAS in hepatic fibrosis

The RAS is classically conceived as a hormonal cascade responsible for controlling cardiovascular, renal and adrenal functions that regulate hydro-electrolytic balance and blood pressure through ANT II actions. Many studies have defined a role for the involvement of the RAS in the pathogenesis of hepatic fibrosis in animal models. HSCs activation by liver injuries induce angiotensin II type 1 receptor (AT1) and angiotensin converting enzyme (ACE) expression and ANT II secretion. ANT II induce oxidative stress, increase concentration of proinflammatory cytokines, tumor necrotizing factor-α (TNF-α) and interleukin (IL)-1β and upregulate the expression of inflammatory proteins, such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (Cox2). ANT II also increase hepatic transforming growth factor-β (TGF-β) concentration, collagen deposition, accumulation of smooth muscle alpha-actin (α-SMA) positive cells and lipid peroxidation products. AT1 antagonist such as losartan, suppressed the number of activated HSCs, TGF-β expression and the amount of hepatic fibrosis. While AT1 play an important role in the development of fibrosis, the AT2 signal has antifibrogenic and/or cytoprotective effects on oxidative stress-induced liver fibrosis therefore, hepatic fibrogenesis by RAS may be determined by the balance between AT1 and AT2 signals. In the other hand, ANT (1-7)/Mas axis is alternative pathway of RAS and ANT (1-7) is also increase in chronic liver disease. Through many animal studies, ANT (1-7) showed the improvement of hepatic fibrosis and this pathway is considered as counter-regulatory response to RAS-mediated hepatic injury and one of future therapeutic for hepatic fibrosis.
Figure 1. The renin-angiotensin system (RAS). Renin cleaves the decapeptide, ANT I, from angiotensinogen, and ANT I is converted to ANT II by ACE. In the alternative pathway, ANT II can be converted to ANT (1-7) by ACE2. Several additional enzymes that can participate in the conversion of ANT I to ANT II are also shown. ACE, angiotensin-converting enzyme; ANT, angiotensin; AT1, angiotensin receptor type 1; AT2, angiotensin receptor type 2; ARB, angiotensin receptor blocker; ACEi, angiotensin-converting enzyme inhibitor

Clinical application of ARBs and ACE inhibitors in patients with chronic liver disease

Several clinical studies have been tried to elucidate the effect of blocking of RAS in hepatic fibrosis using AT1 receptor blocker (ARB) or ACE inhibitor.\textsuperscript{13, 21-26} Overall, these small studies indicate that utilization of ARBs and ACE inhibitors might be beneficial for patients with hepatic fibrosis except recent one study data from HALT-C trial cohort which showed that ACE inhibitor or ARB therapy did not retard the progression of hepatic fibrosis.\textsuperscript{26} However, these studies have limitations because the majority of them were composed of small study population and chronic hepatitis C and evaluated retrospectively. In addition, ARB or ACE inhibitor could induce serious side effects such as renal impairment or systemic hypotension. So, the answer for the anti-fibrotic effects of ARB and ACE inhibitor have been remained as unsolved and well designed large scale controlled trial should be done in near future.

Conclusion

Much evidence through many studies indicated that the RAS plays a key role in hepatic fibrosis. Many studies using animal models of liver fibrosis has shown that both ARBs and ACE inhibitors are effective at attenuating hepatic fibrosis and clinical studies have also been promising. However, large, controlled trials are needed to determine the effectiveness of ARBs and ACE inhibitors in treatment of hepatic fibrosis.

Reference


