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Review

The role of renin-angiotensin system modulation on treatment and prevention of liver diseases

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ABSTRACT

The renin-angiotensin system (RAS) is now recognized as an important modulator of body metabolic processes. The discovery of angiotensin-converting enzyme 2 (ACE2) has renewed interest in the potential therapeutic role of RAS modulation. Recent studies have pointed out the importance of the local balance between ACE/Ang-II/AT1 and ACE2/Ang-(1-7)/Mas arms to avoid liver metabolic diseases. Furthermore, non-alcoholic fatty liver disease is an increasing health problem that includes a spectrum of hepatic steatosis, steatohepatitis and fibrosis. Some new studies revealed that RAS imbalance appears to promote hepatic fibrogenesis; while the activation of ACE2/Ang-(1-7)/Mas counter-regulatory axis is able to prevent liver injuries. In this context, the aim of the present review is to discuss the importance of RAS in the development and prevention of liver disease. AT1 receptor activation by Ang II induces hepatic stellate cell contraction and proliferation, causes oxidative stress, endothelial dysfunction, cell growth and inflammation. In addition, both AT1 blocker administration and ACE inhibitors lead to a reduction in inflammation and improvement of hepatic fibrosis. Conversely, Ang-(1-7) infusion reduces fibrosis and proliferation mainly by suppression of hepatic stellate cell activation; Mas receptor antagonism aggravates liver fibrosis and severe liver steatosis. In conclusion, the use of ACE/Ang II/AT1 axis inhibitors associated with ACE2/Ang(1-7)/Mas axis activation is a promising new strategy serving as a novel therapeutic regimen to prevent and treat chronic liver diseases as well as acute liver injury.

Contents

Abbreviations: ACEi, ACE inhibitors; AT1 ARBs, blockers; CDAA, choline-deficient L-amino acid-defined; DMN, dimethyl nitrosamine; ECM, extracellular matrix; ERK, extracellular-signal-regulated kinases; HSCs, hepatic stellate cells; ac-HSC, HSCsfrom quiescent to activated; IL, interleukin; KC, Kupffer cells; MMPs, matrix metalloproteinases; TIMPs, metalloproteinases; NAFLD, Nonalcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-B, nuclear factor-B; PPAR-γ, peroxisome proliferator-activated receptor gamma; ROS, reactive oxygen species; Sal B, Salvianolic acid B; α-SMA, smooth muscle actin; TGF-β1, transforming growth factor-β1; TNF, tumor necrosis factor; CCL_4, carbon tetrachloride; OLETF, Otsuka Long-Evans Tokushima fatty.

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Introduction

Liver disorders are caused by a variety of insults, including viral hepatitis, alcohol, drug abuse and autoimmune hepatitis. Chronic injury, over months or years, causes liver fibrosis and eventually results in liver cirrhosis [36]. One of the major risk factors for hepatic fibrosis is type 2 diabetes mellitus, commonly associated with obesity and fat deposition in the liver [79] (steatosis). In recent years the renin-angiotensin system (RAS) has been recognized as an important metabolic system, which plays an important role in lipid and glucose homeostasis [6,63,65,66,70]. Moreover, RAS is known to be altered during the pathogenesis of liver fibrosis [27,50] and there is a new therapeutic group, called RAS blockers, which inhibits hepatic fibrosis both in rats [23] and humans [11,82,91]. Thus, the aim of the present review was to analyze the participation of both arms: ACE/Ang II/AT1 and ACE2/Ang-(1-7)/Masn in the development and prevention of liver disease, and demonstrate the participation of ACE inhibitors (ACEi) and AT1 blockers (ARBs) as important options for treating patients with liver disorders.

Metabolic role of renin-angiotensin system

The liver is considered the primary source of circulating angiotensinogen in normal physiology [64]. In the classical view, RAS is described as a single cascade where renin converts angiotensinogen into angiotensin I (Ang I), which is converted to angiotensin II (Ang II) by angiotensin converting enzyme (ACE).

Ang II mediates biological responses through two G-protein-coupled receptors, the Ang II receptor type 1 (AT1) [34] and Ang II receptor type 2 (AT2), however, the main described effects are AT1 mediated [35]. In the current view of RAS, another counter regulatory arm was described [68] where ACE2 cleaves Ang I to generate the Ang-(1-9) peptide; which can be converted to the vasodilator peptide Ang-(1-7) by ACE or other peptidases [12,68,93]. ACE2 also generates Ang-(1-7) by directly metabolizing Ang II with greater efficiency than converting Ang I to Ang-(1-9) [84]. Thus, the ACE2/Ang-(1-7) axis can be advocated as a compensatory pathway in RAS also during liver injury [12,64,69,70,85,88] (Fig. 1).

RAS also has effects on cellular metabolism. Ang II is a proinflammatory, pro-oxidant, and prothrombotic agent that interferes in several steps of intracellular insulin signaling [53]. On the other hand, ACE2 plays a pivotal protective role in diabetes: a relative ACE2 deficiency may lead to the impaired degradation and accumulation of Ang II, contributing to decreased insulin secretion. Furthermore, ACE2 also plays a role in kidney disease and several other conditions in which increased Ang II is undesirable. ACE2 regulates the degradation of Ang II and the formation of Ang-(1-7), and may have beneficial effects on both kidneys and the pancreas [4], whereas ACE2 deficiency promotes adipose tissue inflammation and augments obesity-induced glucose intolerance. Several studies support the idea that ACE2 is a good ACE, and highlight the importance of seeking therapies that increase their activity in the prevention and treatment of diabetes and its complications [4]. In line with this hypothesis, recent studies have shown that Ang-(1-7)/Mas axis deficiency in FVB/N mice induces glucose intolerance, dyslipidemia, increased insulin levels, increased abdominal fat mass, reduced insulin sensitivity [65] and a RAS imbalance with increased Ang II/AT_1 arm activation in the heart induced by exercise [21]. Furthermore, transgenic rats with increased Ang-(1-7) plasma levels show enhanced glucose tolerance, insulin sensitivity, insulin-stimulated glucose uptake, decreased triglycerides and cholesterol levels, and a significant decrease in abdominal fat mass [63]. Ang-(1-7) has been demonstrated to decrease liver gluconeogenesis [6], and the Mas receptor is an essential component of the insulin receptor signaling pathway [67]. Recently, new studies recognized that systemic infusion of Ang-(1-7) increases both volume and flow of muscle microvascular associated with a significant increase in insulin-mediated glucose disposal. These effects were blocked by Mas receptor inhibitor A-779 demonstrating that Ang-(1-7) by activating Mas recruits muscle microvasculature and enhances the metabolic action of insulin [18]. Also recently, the relationship between insulin resistance, RAS, and oxidative stress in vascular tissues was discussed and accessed [31]. Corroborating these data, ACE2/Ang-(1-7)/Mas axis increases glucose uptake, decreases glycogen synthesis, and reduces the stress in hepatic cells improving hepatic insulin resistance through the Akt/PI3K/IRS-1/JNK insulin signaling pathway [8]. Indeed, Ang-(1-7) decreases the release of inflammatory mediators by adipose tissue in obesity animal models [30].

Confirming all these pieces of evidence, a recent study showed that some RAS components were up-regulated in rat liver fibrosis and the ACE/Ang II/AT1 axis was increased to a greater extent than the ACE2-Ang(1-7)-Mas axis [95]. Similarly, studies showed that RAS is frequently activated in patients with chronic liver diseases, since angiotensin II-blocking agents reduced fibrosis in patients with chronic hepatitis C virus and non-alcoholic steatohepatitis (NASH) [11,91].

Liver fibrosis pathogenesis

Hepatic fibrosis and its end-stage diseases (cirrhosis and liver cancer) are major causes of morbidity and mortality throughout the world, and their prevalence is rising, largely due to the increasing impact of chronic viral hepatitis. There are many primary causes of liver fibrosis with the most common being chronic hepatitis B and C, alcohol and the increasingly important problem of non-alcoholic fatty liver disease (and obesity) [86]. Liver fibrosis is characterized by an overall increase in the concentration of matrix proteins in liver tissue, including collagens, elastin, glycoproteins, proteoglycans and pure carbohydrates (hyaluronan), that alter the matrix composition profile [19]. The most prominent producers of extracellular matrix are hepatic stellate cells (HSCs) and especially Kupffer cells (KC) [21,71,87,92] which are fundamental in the development of hepatic fibrosis.

HSCs are perivascular mesenchymal cells found in the space of Disse, among endothelial cells and hepatocytes. These cells represent approximately 15% of the total number of hepatic cells. The main function of HSCs is to metabolize vitamin A and produce cytokines, growth factors and inflammatory mediators. They are a major fibrogenic cell type in the liver, which also contributes to the induction of hepatic inflammation through cytokines and increased expression of AT1 receptors in liver [17]. During some injuries, Kupffer cells are activated by oxidative stress increasing the production of pro-inflammatory cytokines that change HSCs from quiescent to activated (ac-HSC), and subsequently producing collagen which leads to liver fibrosis [80]. The Ac-HSC