Chapter 10
Role of Renin-Angiotensin System in the Pathogenesis and Progression of Non-alcoholic Fatty Liver

Amira M. Badr, Iman O. Sherif, Yasmen F. Mahran, and Hala A. Attia

Abstract Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver diseases and is increasing simultaneously with obesity and Type 2 Diabetes Mellitus, which are on the rise. Currently, no FDA-approved drug exists to treat NAFLD, and pharmacological treatments are directed at managing its associated comorbidities. Therefore, a better understanding of NAFLD pathogenesis and converging pathways helps in improving prognosis and preventing progression to non-alcoholic steatohepatitis (NASH). Renin-angiotensin system (RAS) plays an important role not only in regulating blood pressure but was also found to contribute to obesity, insulin resistance, lipotoxicity, and inflammation, which are considered the key players in NAFLD pathogenesis. Moreover, a prominent role of RAS has been identified in hepatic fibrosis; activated hepatic stellate cells (HSC) express renin, angiotensin-converting enzyme (ACE), and angiotensin II (AngII), which cause HSC to proliferate and produce reactive oxygen species and inflammatory mediators. On the other hand, the inhibition of RAS improved insulin resistance and inhibited hepatic fibrogenesis. The maintenance of the balance between the two arms of RAS showed to play a meaningful role. One of the two arms is known as the classical arm; ACE-AngII-Angiotensin I receptor arm, and the other is the new one; ACE2/Ang1-7/Mas/MasII. Ang1-7 was found to increase insulin sensitivity and counteract the effects of AngII. Therefore, RAS blockers have emerged as a promising therapeutic modality for NAFLD. Accordingly, the present review will discuss the role of RAS in NAFLD and the potential therapeutic value of RAS modulators.

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Introduction

As a major contributor to chronic liver diseases, non-alcoholic fatty liver disease (NAFLD) incidence has recently increased along with obesity and Type 2 Diabetes epidemics. It is universally recognized as the hepatic manifestation of metabolic syndrome, a global public health concern associated with the involvement of multiple systems and resulting in high mortality rates. A sedentary lifestyle, increased dietary fructose consumption, and obesity are the root causes of NAFLD. NAFLD includes a wide range of liver conditions, from simple steatosis to the more serious non-alcoholic steatohepatitis (NASH). Simple steatosis is known as NAFL and is considered benign. However, NASH is characterized by liver injury, hepatocellular ballooning, inflammation, and various degrees of fibrosis [1].

The renin-angiotensin-system (RAS) is a body system known for decades ago to consist mainly of a single hormonal cascade responsible for controlling cardiovascular and renal functions [2]. Evidence that RAS contributes to NAFLD pathogenesis do exist through both experimental and clinical studies. A discussion of the role of RAS in the development and prevention of NAFLD will be presented in this context.

RAS

RAS is one of the body's hormonal systems with multiple functions. Members of this system include mainly renin and Angiotensin II (Ang II). Through the circulating Ang II, RAS functions in the homeostatic control of blood volume, systemic vascular resistance, hormone secretion, and renal function in a prolonged manner [2, 3]. It has been reported that RAS is present in the systemic circulation and is also produced in local tissue [4]. There is evidence that some cell types express several RAS components intracellularly, such as adrenal medullary chromaffin cells and pituitary glandular cells [5], adipocytes [6], and renal cortical cells [7]. Both local and systemic RAS operate in an integrated way and have diverse physiological roles through autocrine and paracrine actions [8, 9]. Cell proliferation, differentiation, apoptosis, the generation of reactive oxygen species (ROS), tissue inflammation, and fibrogenesis are some of the physiological pathways they can modulate [8, 10, 11].

The renal juxtaglomerular cells secrete renin in response to the stimulation of β-adrenergic receptors located on the cell walls [12]. Renin, the rate-limiting step in the RAS cascade, interacts with a plasma protein called angiotensinogen to create a decapeptide prohormone; Ang I, Fig. 10.1 [13]. Ang I is then rapidly hydrolyzed through the angiotensin-converting enzyme (ACE) action to form the major biologically active peptide generated by RAS, Ang II, Fig. 10.1 [14]. ACE is located on the

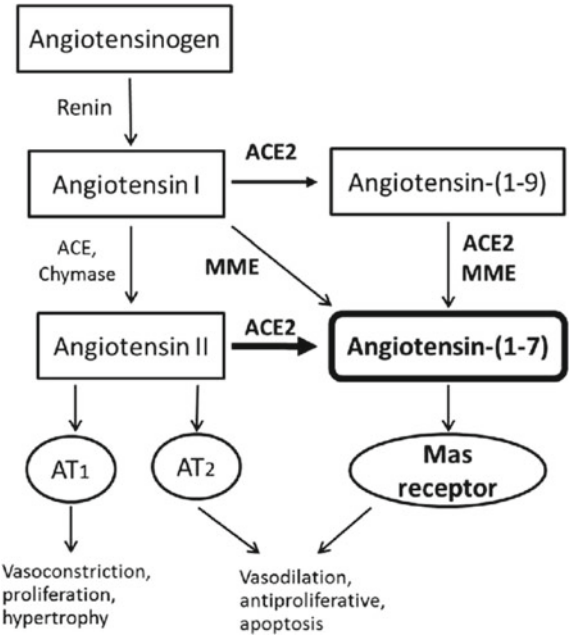

Fig. 10.1 Members of the RAS system; Ang II, Ang-(1-7), their receptors and producing enzymes. ACE: Angiotensin 1-converting enzyme; ACE2, Angiotensin 1-converting enzyme2; AT1, Angiotensin II type 1 receptor; AT2, Angiotensin II type 2 receptor; MME, Membrane metallo-endopeptidase; RAS: Renin-Angiotensin System. The figure is adopted from Ghadhanfar et al. [18]

luminal side of the vascular endothelium, predominantly in the lung and the kidney, besides other organs [15, 16]. In 2000, a new gene in the ACE gene family was discovered, ACE2 [16]. ACE 2 is also expressed on the endothelial cell surface with a limited expression pattern compared to ACE [17].

Ang II

The most crucial active peptide of the RAS is Ang II. Two main receptors, angiotensin type-1 and type-2 receptors (AT1R and AT2R) mediate the Ang II functions in the body. AT1R mediates most of the significant physiological effects of Ang II, such as regulating blood pressure, salt and water retention, hormone secretion, kidney function, as well as the modulation of cell proliferating and migrating [8, 19]. Also, the AT1R axis mediates much of the disease change associated with chronic RAS activation, such as fibrosis, inflammation, angiogenesis, vascular aging, and atherosclerosis [20]. While the AT1 receptor is abundant in adult tissues, AT2R is mainly expressed in fetal tissues and is upregulated in pathological conditions. AT2R is generally reported to mediate antagonistic effects to those pathophysiological conditions induced by AT1R with harmful consequences [16, 19].

Other Angiotensins

In addition to Ang II's primary function in the RAS, Ang I and Ang II's other metabolites may also possess significance in the body. There are three bioactive angiotensin fragments, Ang III (Ang 2-8), Ang IV (Ang 3-8), and Ang (1-7) derived from Ang II by the action of various enzymes. Angiotensin III and IV are generated after the aminopeptidases removed amino acids from Ang II's N terminus. Similar activities are shared between Ang III and Ang II via AT1R and AT2R [21, 22]. Furthermore, Ang IV through acting on Angiotensin receptor 4 is also involved in regulating cardiac hypertrophy, angiogenesis, and plasminogen activator inhibitor 1 (PAI-1) expression, among other physiological functions and pathological conditions [23, 24].

A1-7 is produced either by ACE2 or by endopeptidases from Ang I. ACE2 can also convert Ang I to Ang-1-9, which is further metabolized to A1-7 by ACE, Fig. 10.1. The MAS1 oncogene (Mas) receptor appears to be primarily in charge of mediating the angiotensin (1-7) effects, which mostly counteract Ang II. The ACE2-angiotensin-(1-7)-Mas axis appears to favor vasodilation, to exert antiproliferative, anti-inflammatory, antifibrotic, and antithrombotic activities [8, 25, 26, 18].

The Two Arms of the RAS

Based on previous information, RAS can be described as having two arms, the classical ACE-AngII-AT1R arm and the new one consisting of ACE2/Ang1-7/Mas/Mas II and is known to antagonize the classical pathway, Fig. 10.1. A combination of the two biologically active peptides, Ang II stimulates inflammation, oxidation, fibrosis, and vasoconstriction by activating AT1R, whereas Ang1-7 inhibits and reduces many of Ang II's detrimental effects [27, 28]. The role of the new arm has been evolving recently [29, 30]. According to research, ACE2 is involved in the pathophysiology of cardiovascular diseases, and a reduction of ACE2 directly correlates with hyperactivation of the ACE/Ang II/AT1R axis [31].

The Pathogenesis of NAFLD

NAFLD is a heterogeneous group of liver diseases in which excess triglycerides (TG) are accumulated in the liver. The liver is the main organ responsible for fatty acids (FA) metabolism. FA acquirement is attained by hepatocellular uptake from the plasma and de novo lipogenesis. However, elimination of FA occurs via β-oxidation in the cell or through exportation into plasma in the form of TG-rich very-low-density lipoproteins (VLDL). Under normal conditions, only small TG are stored in the liver

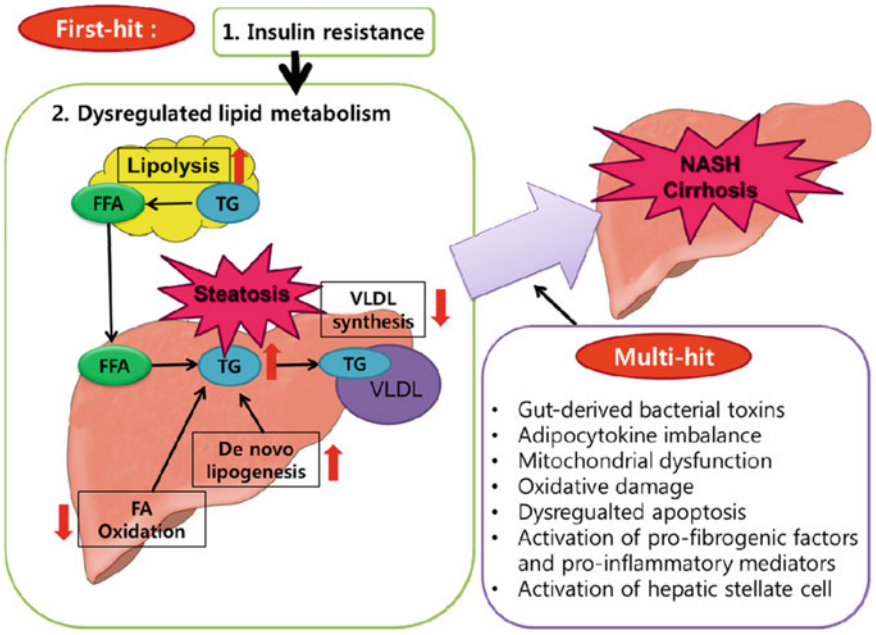

Fig. 10.2 IR and dysregulated lipid metabolism is associated with increased release of FFA from the adipose tissue to the liver, increased glucose production, and TG accumulation. Simple steatosis renders the hepatocytes susceptible to "multiple hits" which include gut-derived bacterial toxins, adipocytokine imbalance, mitochondrial dysfunction, oxidative damage, activation of pro-fibrogenic factors, and pro-inflammatory mediators ultimately leading to NASH and cirrhosis. FFA: Free fatty acids, IR: Insulin Resistance, TG: Triglycerides. The figure is adapted from [35]

in cytoplasmic lipid droplets. Under certain conditions, if an imbalance between lipid acquirement and lipid elimination is settled, a clinical state of NAFLD occurs [32].

The pathogenesis of NAFLD can be described as a "multiple-hits hypothesis". Hepatic steatosis development through TG accumulation in the liver and insulin resistance (IR) is considered the first hit. The first hit subsequently prepares the liver to be vulnerable to the other hits; such as lipotoxicity, oxidative stress, mitochondrial dysfunction, gut-derived bacteria, and inflammatory cytokines/adipokines, that promote inflammation and fibrosis, Figs. 10.2 and 10.3 [33, 34].

Lipotoxicity

As a part of lipid metabolism, the liver imports free FA (FFA), synthesizes, stores, and exports lipids. Disturbances in any of these processes may result in NAFLD. Adipose tissue lipolysis produces FFA that plays a critical role in developing lipotoxicity; which occurs when they accumulate in non-adipose tissues, and lead to hepatic

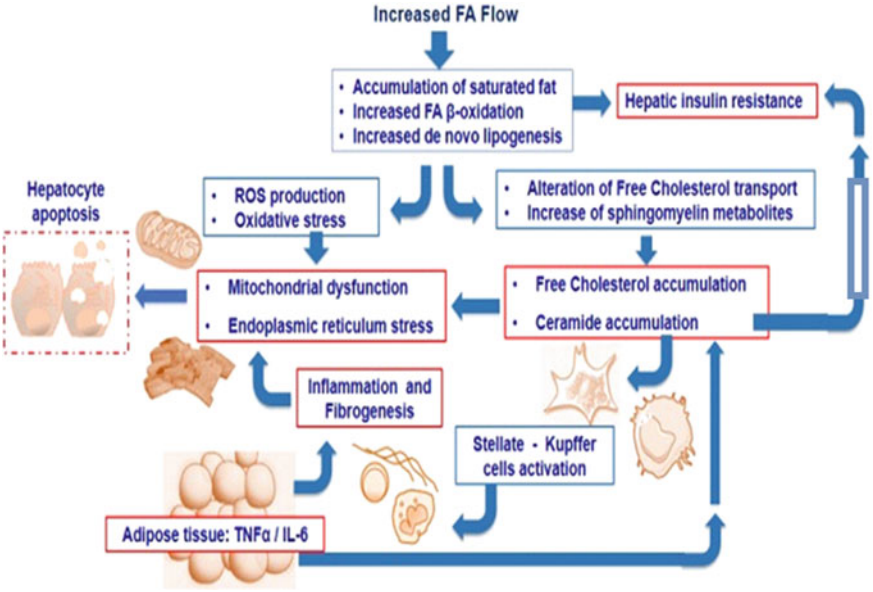

Fig. 10.3 The major pathogenic pathways involved in NAFLD: IR is associated with increased FFA flux that contributes to increased TG production. In parallel, the accumulation of free cholesterol and ceramides enhances the activation of inflammatory pathways; TNF-α and IL-6 from adipose tissue enhance the inflammatory process. Fat accumulation in the liver culminates in oxidative stress, lipotoxicity and increased inflammatory markers. ROS generation induces oxidative mitochondrial damage and ER stress, ER: Endoplasmic Reticulum, FFA: Free fatty acids, IL-6: Inteleukin-6, IR: insulin resistance, NAFLD: Non-alcoholic fatty liver, ROS: reactive oxygen species, TG: Triglycerides, TNF-α: Tumor necrosis factor-α. Figure is adapted from Gaggini et al. [36]

dysfunction and death. When the liver is in a physiological state, FFA are either transported to the mitochondria for β-oxidation, esterified to be excreted in VLDL, or stored as lipid droplets. However, when the liver is in a pathological state, FFA and phospholipids accumulate in the hepatocytes. Accumulated long-chain saturated FA such as palmitate and stearate can stimulate pattern recognition receptor, toll-like receptor4 (TLR4), which activates the pro-inflammatory cytokines. Additionally, uncontrollable lipotoxicity leads to increased production of ROS, which results in hepatic endoplasmic reticulum (ER) stress and mitochondrial dysfunction, which are critical in the pathogenesis of NAFLD as will be discussed, Fig. 10.2 [37].

IR

A growing body of evidence from experimental and clinical studies consider IR the key pathophysiological hallmark of NAFLD and its progression to NASH. Insulin plays a crucial role in lipid metabolism; it suppresses adipose tissue lipolysis, thus

decreasing plasma FA levels and promoting TG storage in adipose tissue [38]. Thus, hyperinsulinemia promotes hepatic FA and TG uptake, de-novo lipid synthesis and impaired β-oxidation of FA by negative feedback, leading to TG accumulation [38, 39]. IR is necessary for lipotoxicity establishment, oxidative stress, and the activation of inflammatory cascades, Fig. 10.2 [40].

Mitochondrial Dysfunction and Oxidative Stress

Subsequently to increased FFA in the hepatocytes, the process of FA β-oxidation will increase as an adaptive mechanism, which will be associated with ROS production. Fat oxidation in the liver is critical for preventing fat accumulation, but too much FA oxidation is detrimental to the liver through oxidative stress, which reduces antioxidant defences [37]. The oxidative stress further increases the hepatocyte's susceptibility to toxic stimuli. Mitochondria are the first organelle to be impaired due to aggressive lipids like FFA and cholesterol accumulating there, resulting in decreased mitochondrial FA oxidation. At the same time, the minor pathways of ER α- and ω-oxidations will be activated leading to overproduction of ROS, which can lead to lipid peroxidation producing malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) that can enhance inflammation, activate cell necrosis and apoptosis, and be implicated in fibrosis [33, 37].

Adipocytokine Imbalance and Inflammation

The cross talk between lipotoxicity, IR, and other factors can activate the inflammatory cascades and stimulate the release of pro-inflammatory cytokines such as nuclear factor-κB (NF-κB), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) [41]. In addition, excessive FFA and oxidative stress encountered in NAFLD can activate pattern recognition receptors like TLRs and NOD-like receptors (NLRs). Researchers have reported that NLRP-3 inflammasomes may contribute to fibrosis progression in NAFLD [40, 41], and they observed higher levels of NLRP3, pro-IL-1b, and pro-IL-18 protein expression in NASH patients compared to those with simple steatosis [42].

Moreover, adipose tissue macrophages are the primary source of local and systemic inflammatory mediators. TNFα and IL-6 are two important pro-inflammatory adipocytokines, and their expression is markedly increased in the adipocytes of obese subjects and patients with IR. Thus, excess caloric intake, obesity, and adipose tissue expansion lead to a chronic mild inflammatory state that plays a pivotal role in the onset of IR [43]. On the other hand, adiponectin is a prototypic anti-inflammatory and anti-diabetic adipocytokine which inhibits the phagocytic activity in macrophages and stimulates the release of the anti-inflammatory IL-10. Thus, high TNFα and low adiponectin lead to IR and NAFLD [44].

Endoplasmic Reticulum Stress

In hepatocytes, the main site of lipid synthesis is the ER [45]. Many insults including physiological, pathological, and environmental can cause accumulation of unfolded/misfolded protein, leading to disruption of ER homeostasis, a condition that is known as ER stress [46]. It has been reported that there is a crosstalk between ER stress and progression of NAFLD, as increased ER stress was found to induce IR in both human and rat and impair Glucose Transporter Protein-4 (GLUT4) production and insulin-induced glucose uptake [47]. Furthermore, an increasing body of evidence demonstrates that ER stress plays an important role in the activation of hepatic Sterol regulatory element-binding proteins (SREBP-1); the most important transcription factor that regulates the expression of the enzymes for FA synthesis; and thus the development of NAFLD [48]. Moreover, a close association between ER stress and the inflammatory response was reported [49]. ER stress is well documented to activate JNK and NF-κB as a consequence of unfolded protein response (UPR) signalling, resulting in the impairment of hepatic metabolism [50]. The major pathogenic mechanisms involved in the pathogenesis of NAFLD were illustrated in Figs. 10.2 and 10.3.

Genetic Factors

Finally, though hepatic steatosis is prevalent in patients with obesity and IR, only a small percentage of these patients proceed to NASH and cirrhosis, implying a complex interaction between genetics and environmental factors. One of the evolving treatments of NAFLD is the inhibitors of RAS, emphasizing the role of RAS in the pathogenesis and development of NAFLD. Moreover, it has been documented that single nucleotide polymorphisms (SNP) in angiotensin II type I receptor (ART1) are linked with increased risk of NAFLD and its related fibrosis [51]. Therefore, the RAS and its contribution to NAFLD will be further discussed in this chapter.

The Role of RAS in NAFLD

In recent years, RAS has become more widely acknowledged as a modulator of body metabolism. Many studies demonstrated that the classical RAS axis is upregulated in the liver during NAFLD [8, 27, 51, 52]. Ang II causes many deleterious effects that contribute to a wide range of histological changes observed in NAFLD and NASH. Among these effects are the stimulation of IR, de novo lipogenesis, mitochondrial toxicity, endothelial dysfunction, ROS generation, and the release of pro-inflammatory cytokines like TGF-β and IL-6, Fig. 10.4 [8, 42, 53, 54]. Thus, NAFLD pathogenesis and progression may be influenced by RAS.

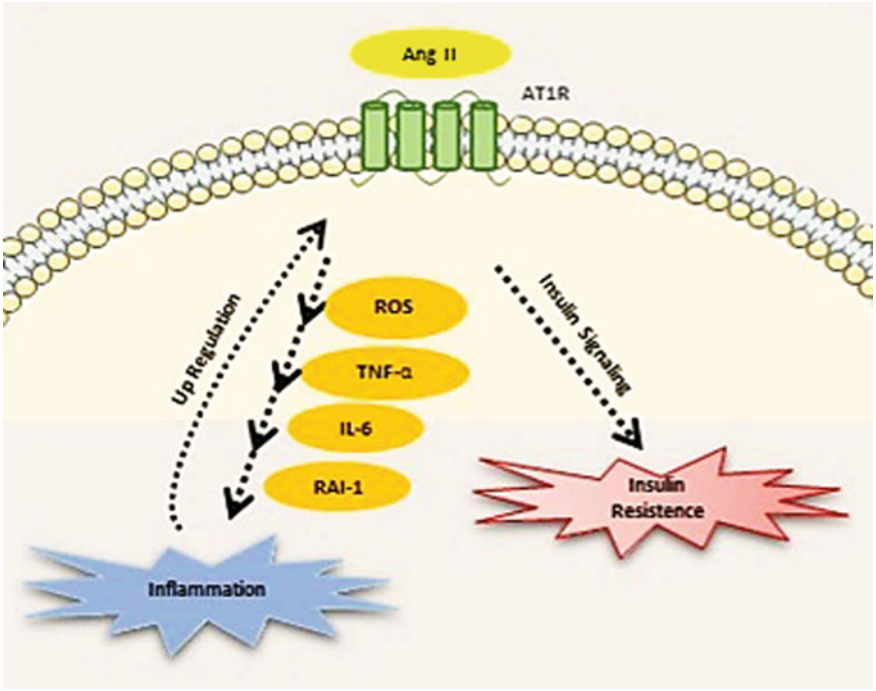

Fig. 10.4 Ang II is a major player in NAFLD. It impairs intracellular insulin signaling contributing to IR. It also induces the generation of ROS, initiating and propagating the production of pro-inflammatory mediators, including TNF-α, IL-6, and PAI-1. These results in inflammation, additional impairment of insulin signaling, and upregulation of the AT1R genes, contributing to the vicious cycle of steatosis–necroinflammation–fibrosis. Ang II: Angiotensin II, AT1R: Angiotensin type 1 receptor, IL-6: Inteleukin-6, IR: insulin resistance, NAFLD: Non-alcoholic fatty liver, PAI-1: plasminogen activator inhibitor-1, ROS: reactive oxygen species, TNF-α: Tumor necrosis factor-α [55]

Evidence that the two axes of RAS contribute to NAFLD pathogenesis do exist. In experimental models of NAFLD, the two axis of hepatic RAS were imbalanced with the upregulation of the ratios ACE/ACE2, AngII/Ang (1-7), and Mas/AT1R, which ultimately lead to liver steatosis [27, 56]. Accordingly, it was demonstrated that the maintenance of local balances of the two axis is important for the prevention of liver metabolic diseases [57], in which the activation of ACE2/Ang (1-7)/Mas inhibits liver injury. This was further supported by the findings that the use of AT1R blockers [52, 58], inhibition of ACE/Ang II/AT1R by gene knockout animal models [59], or/and the activation of the alternative ACE2/Ang1-7/Mas axis [60, 61] can ameliorate NAFLD. In humans with liver disease, increased expression of both ACE2 gene and plasma Ang-(1-7) was reported, confirming that the alternative axis of the RAS is upregulated in response to hepatic injury as a protective remedy [62]. Taken together, the above studies demonstrate the essential participation of the RAS in NAFLD. In harmony with these findings, recent research have explored the therapeutic efficacy

of RAS inhibitors (RASi) for the treatment of NAFLD and they are now considered as a promising evolving treatment of NAFLD, and thus emphasizing the role of RAS in its pathogenesis and progression [63].

The Role of RAS in the Development of IR and Lipogenesis

Results from experimental animals and humans suggest that obesity activates the ACE/Ang II/AT1R arm. In fact, NAFLD's altered hepatic lipid metabolism and IR has been linked to an alteration in Ang II, and rodent models that lack renin, ACE, and liver-specific deletion of ATR1 showed reduced hepatic steatosis and improved IR [64]. Further evidence of the contribution of Ang II to IR is provided by increasing number of experimental and clinical studies showing improved insulin sensitivity following the use of RASi; ACE inhibitors and AT1R Blockers (ARBs) [65, 66]. Recent studies have shown that the signaling pathways of insulin and Ang II cross talk at several levels and share downstream effectors. Insulin activates the phosphoinositide-3-kinase (PI3K)/Akt pathway, which stimulates the translocation of GLUT-4 in insulin-dependent tissues. Ang II inhibits insulin-mediated PI3K pathway activation, which results in impaired GLUT-4 translocation, resulting in IR [67]. Moreover, Ang II can induce the generation of ROS and regulate the production of pro-inflammatory mediators, resulting in the impairment of insulin signalling, Fig. 10.5 [68, 69].

Moreover, Ang II induces IR by its effect on the adipose tissue. The adipocytes express components of RAS, including angiotensinogen, ACE, AT1R, and AT2R. Adipocyte differentiation is inhibited by Ang II via the AT1R, resulting in increased secretion of inflammatory cytokines or diabetogenic adipokines, which inhibit insulin signalling and lead to increased hyperglycemia and weight gain [71]. These effects were also ameliorated by ARBs [66, 72]. Additionally, elevated plasma Ang II has been associated with increased FFAs, resulting in augmented hepatic FFA uptake and promoting the hepatic lipogenesis [73].

On the other hand, there is increasing evidence that the Ang-1-7/Mas axis has beneficial effects by reducing obesity, via improving insulin sensitivity and glucose tolerance, decreasing body fat, increasing adiponectin production, and reverting IR [74, 55]. Cao et al. proposed that Ang-(1-7)/ACE2/Mas pathway can ameliorate fatty liver through regulating lipid-metabolizing genes and via its ability to improve Akt signalling and, thus improving insulin sensitivity [61]. Recently, Song et al. found that Mas deletion in mice has contributed to the severe glucose intolerance, IR, and hepatic steatosis. Meanwhile, the upregulation of Ang (1-7)/Mas arm or Ang-(1-7) administration attenuated NAFLD by downregulating the expression of hepatic lipogenic enzymes, and improving the Akt-induced insulin signaling [75].

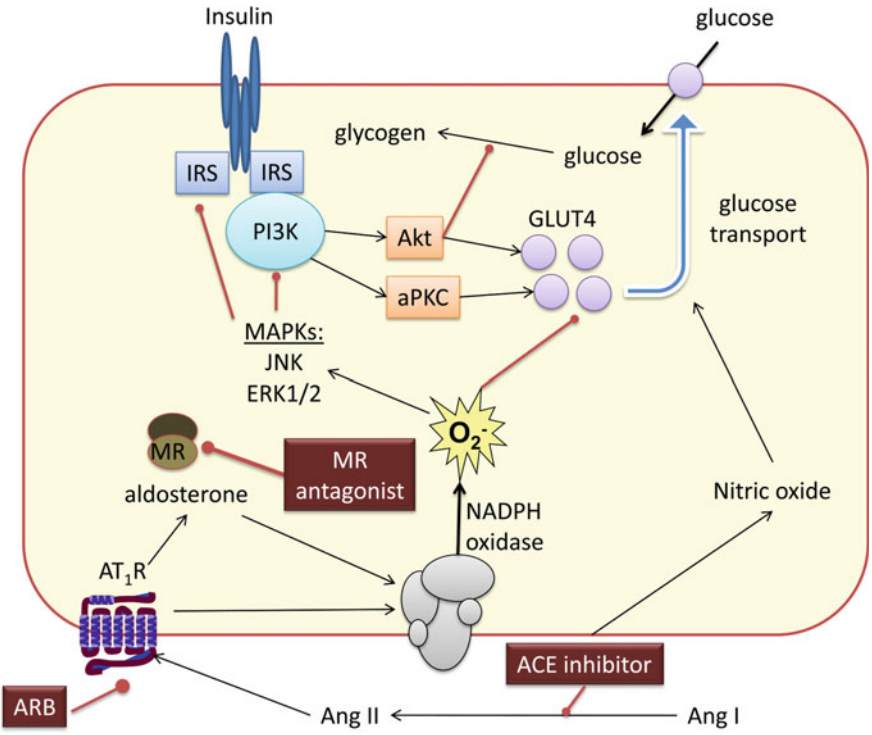

Fig. 10.5 Ang II activates NADPH oxidase to generate ROS (O_2^-). Activation of redox-sensitive serine kinases such as JNK and ERK-1 induced the phosphorylation of IRS-1 and reduced binding with PI3K, with decreased translocation of GLUT4 and reduced glucose transport. The use of ARBs prevents these effects of Ang II. Direct renin inhibitors and ACE inhibitors improve IR by decreasing the formation of Ang II and Aldosterone. ACE inhibitors also increase glucose transport via a nitric oxide-dependent mechanism. ACE: Angiotensin converting enzyme, AKt: protein kinase A, Ang II: Angiotensin II, ARBs: Angiotensin receptor blockers, ERK: extracellular signal-regulated kinase, GLUT4: Glucose transporter protein 4, IR: Insulin Resistance, IRS-1: insulin receptor substrate-1, JNK: c-jun N-terminal kinase, NADPH: nicotinamide adenine dinucleotide phosphate hydrogen, PI3K: phosphatidylinositol 3 Kinase, PKC: protein kinase C. ROS: Reactive oxygen species [70]

The Role of RAS in Promoting Hepatic Oxidative Stress, Inflammation, and Fibrosis

RAS system is also a contributor to hepatic oxidative stress and inflammation. Ang II can induces the generation of ROS mainly by activating the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [69]. Moreover, it regulates the production of pro-inflammatory mediators, including TNF-α, IL-6, and Plasminogen Activation Inhibitior (PAI-1) [76]. Previous studies in transgenic rats with elevated plasma AngII levels indicated that AngII-induced NAFLD is primarily caused by oxidative stress-mediated mitochondrial dysfunction and impaired mitochondria-mediated

FA β-oxidation via AT1R [54]. The Ang II-mediated ROS formation induces mitochondrial damage with the depletion of mitochondrial genes and proteins leading to reduced FA oxidation, thereby contributing to the development of NAFLD. Both increased activity of NADPH oxidase and decreased activity of cytosolic Cu–Zn superoxide dismutase (SOD) contribute to mitochondrial oxidative stress in these transgenic rat livers. Excessive ROS formation causes lipid peroxidation and release of reactive aldehydes such as 4-HNE. Lipid peroxidation has been shown to increase mitochondrial permeability and reduce gene transcription [77].

Ang II-induced ROS production also mediates inflammation and further impairment of insulin signalling [68, 69]. Furthermore, a high Ang II expression level was proven to trigger inflammatory cell recruitment into the liver and, as a result, induces NAFLD [54, 78]. In accordance, Ang II-infused rats expressed higher levels of IL-6 in the liver, as well as higher levels of monocyte recruitment and inflammation [57, 61]. Moreover, It has also been reported that RAS is linked to fibrosis in NAFLD, and RASi have been shown to prevent stellate cell activation. Activated hepatic stellate cell transforms into hepatic myofibroblasts (HMs), which possess a localized RAS that continuously produces Ang II and stimulates fibrogenesis, in addition to the production of pro-inflammatory cytokines and tissue growth factor (TGF)-β1. HMs thus aggravates hepatic inflammation and fibrogenesis in a vicious manner. Accordingly RASi has the potential to slow down the vicious cycle originating from steatosis to necroinflammation and fibrosis [79].

On the other hand, Cao et al. documented that the ROS levels were increased in the liver of *ACE2* knockout mice, whereas in HepG2 cells, Ang-(1-7) could protect against oxidative stress by inhibiting NADPH oxidase expression. In parallel, ACE2 downregulation led to increased activation of JNK and NF-κB, that is associated with increased induction of pro-inflammatory cytokines; TNFα and IL-6, and both ACE2 overexpression and Ang-(1-7) ameliorated that effect [80, 81]. Thus, ACE2 can protect against inflammatory stress by inhibiting pro-inflammatory cytokines expression [61].

Role of RAS in ER Stress

A recent work revealed that ameliorating ER stress contributes to the role of ACE2 in maintaining hepatic metabolic homeostasis. In ACE2 knockout mice, several ER-related genes were activated while, and importantly, ACE2 upregulation alleviates ER stress and restores hepatic metabolic homeostasis in the HepG2 cells. Interestingly, the protein levels of SREBP-1c protein, as well as FA synthas and acetyl coA carboxylase, which are SREBP-1c targeting enzymes for de novo FA synthesis, were downregulated in ACE2- overexpressed HepG2 cells. This provides an avenue to treat fatty liver disease and other ER stress-associated pathologies [80]. It is well known that Akt is associated with ER stress [82], and an evidence showed that the suppression of Akt signalling can induce ER stress subsequent apoptosis [83, 84]. Previous data revealed that ACE2 downregulation decreased the activity of Akt [81], however,

the activation of Akt increased markedly in ACE2-overexpressing HepG2 cells [80], indicating that the Akt signalling pathway may be involved in the regulation of the ER stress by ACE2 in hepatic cells.

The Potential Therapeutic Efficacy of RASi in the Treatment of NAFLD

According to previous illustration of the potential implication of RAS in NAFLD, growing interest in the therapeutic efficacy of RASi such as ACE inhibitors (ACE-I) and ARBs, in patients with NAFLD has emerged, supported by their widespread use and excellent safety profile [55]. Different clinical studies were conducted [85–89]. A recent one by Kim et al., showed that RASi significantly reduced NAFLD development and progression in obese patients, especially with increased cumulative dose [63]. They also reported that ACE-I use was superior compared to other RASi, in terms of reducing the risk of NAFLD progression, and suggested that additional hepatoprotective effects of ACE-I may be mediated through increasing bradykinin. However, others propose ARBs to be more effective, as ACE-I blocks both ATR1 and ATR2, with the loss of the counterbalancing effects of AT2R on the actions of AT1R [63, 90].

A meta analysis conducted by Li et al., of clinical studies using ARBs, concluded that an efficient lowering of low density lipoprotein and cholesterol was observed, however the data is still insufficient to support the efficacy of ARBs in preventing the progression of NAFLD to fibrosis [65]. The limitation is that most studies in the RAS field have focused only on the progression to liver fibrosis, not NAFLD itself, and were restricted to limited study populations or rodent models. Thus, further well-designed randomized controlled trials of RASi in NAFLD patients should be encouraged [91]. Several investigations have demonstrated that RASi improve IR, hepatic steatosis and inflammation in NASH models [92, 93]. ACE-I and ARBs not only inhibit the ACE/Ang II/AT1 arm, but they also stimulate the activity of the ACE2/Ang-(1-7)/Mas axis and increase Ang-(1-7) level by several times [94]. Both showed significant effects in improving lipid and glucose metabolism [55, 80, 92, 93]. The effect of ARBs on hepatic fibrosis in different animal models is also well-established, e.g. ARBs inhibit stellate cell activity in obese mice, leading to a decrease in hepatic fibrosis [63, 95]. Evidence in humans show that NAFLD patients using ARBs commonly have decreased fibrotic markers [85]. However, ARBs are not the same, they differ in their receptor selectivity and binding mode. Telmisartan ranks higher among the ARBs from the standpoint of safety and efficacy in the treatment of NAFLD. It ls also the only ARB to have partial Perixesome Proliferator Activated Receptor (PPAR)-γ agonist activity, Fig. 10.6 [96]. Recently, the use of RASi in managing NAFLD was recommended in Japan, when hypertension is a comorbidity [97].

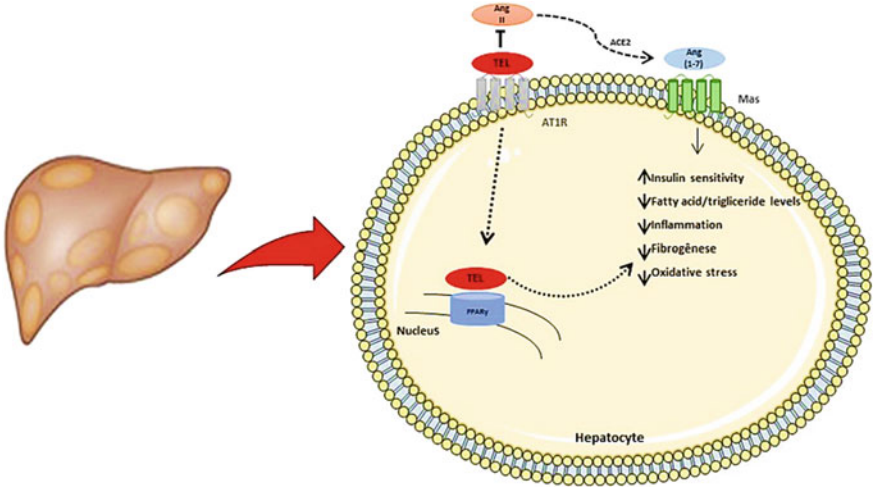

Fig. 10.6 The liver-protecting actions of telmisartan, an AT1R in NAFLD are shown. It indirectly stimulates the Ang-(1-7)/Mas axis, improves insulin sensitivity, lipid metabolism, and decreases the expression of proinflammatory cytokines, with the suppression of macrophage infiltration into the liver. The result is morphological improvement in hepatic steatosis and in fibrogenic markers. It also has anti-oxidative properties and works as a partial agonist of the nuclear receptor PPAR-γ. Ang: Angiotensin, AT1R: angiotensin type 1 receptor blocker, NAFLD: Non-alcoholic fatty liver disease, PPAR: Peroxisome Proliferator Activity Receptor. The figure is adopted from [55]

Conclusion

Collectively, RAS has been found to be highly associated with NAFLD pathogenic pathways. Thus, scientists can speculate that by inhibiting RAS, NAFLD progression can be halted. RASi can do so by improving insulin signaling, controlling adipokines and inflammatory cytokines production, reducing oxidative stress, and inhibiting fibrosis. Although not yet approved as a treatment for NAFLD, future clinical studies are expected to provide better understanding of RASi value and their therapeutic potential.

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