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Role of Angiotensin II in Hepatic Inflammation through MAPK Pathway: A Review

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Abstract

Renin Angiotensin system (RAS) regulates multiple physiological, pharmacological and pathological functions throughout the body by interacting with angioteinsin II (Ang II) receptor type 1 (AT_1R) and Ang II receptor type 2 (AT_2R). However, Ang II is being blamed for damaging several organs like kidney, heart, adrenal cortex, smooth muscles, brain, pancreas, endothelial function and liver. On the other hand, mitogenactivated protein kinase (MAPK) signal transduction pathways are normally observed everywhere and extremely regulated process for a eukaryotic cell cycle. Like Ang II, MAPK also contributes several physiological and pathological functions once it is activated. Moreover, MAPK cascade is also considered as a key signaling pathway that strictly controls various stimulated cellular processes, including proliferation, differentiation, inflammation, fibrosis and apoptosis. We have explained that how Ang II is responsible for MAPK activation and its further consequences in cytoplasm and nucleus for regulation of several inflammatory and proinflammatory cytokines. Overall, all signaling components may appear as an important regulatory messenger in the induction of hepatic cellular inflammation, and therefore, it could serve as targets for therapeutic intervention diseases like hepatitis and other related complications.

Keywords: Liver dysfunctions; RAS; AT_1R; MAPK; Inflammation

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Introduction

Both acute and chronic hepatic dysfunctions are increasing globally which contributes to hepatic failure [1]. Consumption of alcoholic beverages, fatty foods, taking unnecessary over the counter (OTC) drugs and leading a sedentary lifestyle serves as the main contributing factor for the development of hepatic damages [2]. As the extent of mortality and morbidity is increasing at an alarming rate, consequently it is capturing the attention of current public health care professionals [3]. Drugs induced liver toxicity has often been observed when a therapy fails or shows harmful adverse drug reaction (ADR) [4]. However, in most of the cases, normal hepatic functions are being hampered by either free radicals mediated oxidative stress or inflammatory cytokines [5]. Taken together, hepatic disturbances often assist in collagen production, extra cellular matrix deposition [6], mast cell accumulation [7], hemeoxygenase degradation [8], migration and infiltration of various immune cells [9] which lead to cirrhosis, hepatitis, hypertrophy, carcinoma and liver failure [10].W

Liver dysfunction is often observed due to overproduction of Ang II in the liver, activating local RAS that helps in free radicals generation, vascular damage, cellular growth and apoptosis through immune cell migration [11]. In addition, Ang II concentration in serum is found higher in patients suffering from chronic hepatitis C or prone to genetic polymorphism [12]. Inside the liver, Ang II generally binds with AT_1R which activates Hepatic stellate cells (HSC) that further initiates its downstream pathway [13]. Furthermore, Ang II-AT_1R interaction also activates local macrophages to release various cytokines like nuclear factor and-κβ (NF-κβ) macrophage inflammatory protein (MIP), SMAD,

Cyclooxygenase 2 and other chemokines [14,15]. Study also revealed that mice lacking AT_1R genetically were able to attenuate hepatic inflammation [16]. Other studies also discussed that hepatic Ang II also attracts several downstream molecules like α-smooth muscle actin, β-actin, human leukocyte antigen (HLA), and other chemokines [18,19].

Mitogen activated protein kinases (MAPKs) have been extensively studied and found to be responsible for several types of inflammation through AT_1R interaction [20]. MAPK also plays a pivotal role in the progression of several pathophysiologies like hepatitis, fibrosis, iron deposition, hypertrophy and apoptosis [21]. It is noticed that MAPK, which is a signaling pathway is activated when an extracellular molecules binds on it and then transmitting signals to the intracellular machinery process through G protein-coupled receptor [22]. Interestingly, MAPK has been also blamed as stress activated protein kinases (SAPKs), mostly activated by environmental as well as chemical stress, that further plays a key role in the processing of different chemical and cellular responses [23]. Surprisingly, it is experimented that MAPK is solely responsible for hepatic inflammatory signaling like nuclear factor–κβ, interleukin-6, endothelin-1 (ET-1), activating protein-1 too [24]. Furthermore, MAPK mediated signaling significantly contribute to several cancers [25,26]. Not only for clinical significance but also for therapeutic approaches, MAPK and Ang II-AT_1R interaction have been exclusively important for elucidating several diseases as well as to make a target molecule against MAPK. Therefore, this review will try to explore the molecular mechanisms inside liver involving various inflammatory signaling that leads to hepatic inflammation.

Angiotensin II and MAPK

RAS is a very wide and important pathway which coordinate several biological functions like regulation of blood pressure, cellular growth, production of extra cellular matrix, stimulation of proinflammatory or inflammatory cytokines and initiates apoptosis if necessary [27]. This pathway is generally activated once renin is available inside circulation. Renin, which is a protease enzyme produced from the kidney, converts liver angiotensinogen to angiotensin I. Furthermore, angiotensin I is converted to Angiotensin I and Angiotensin II when either

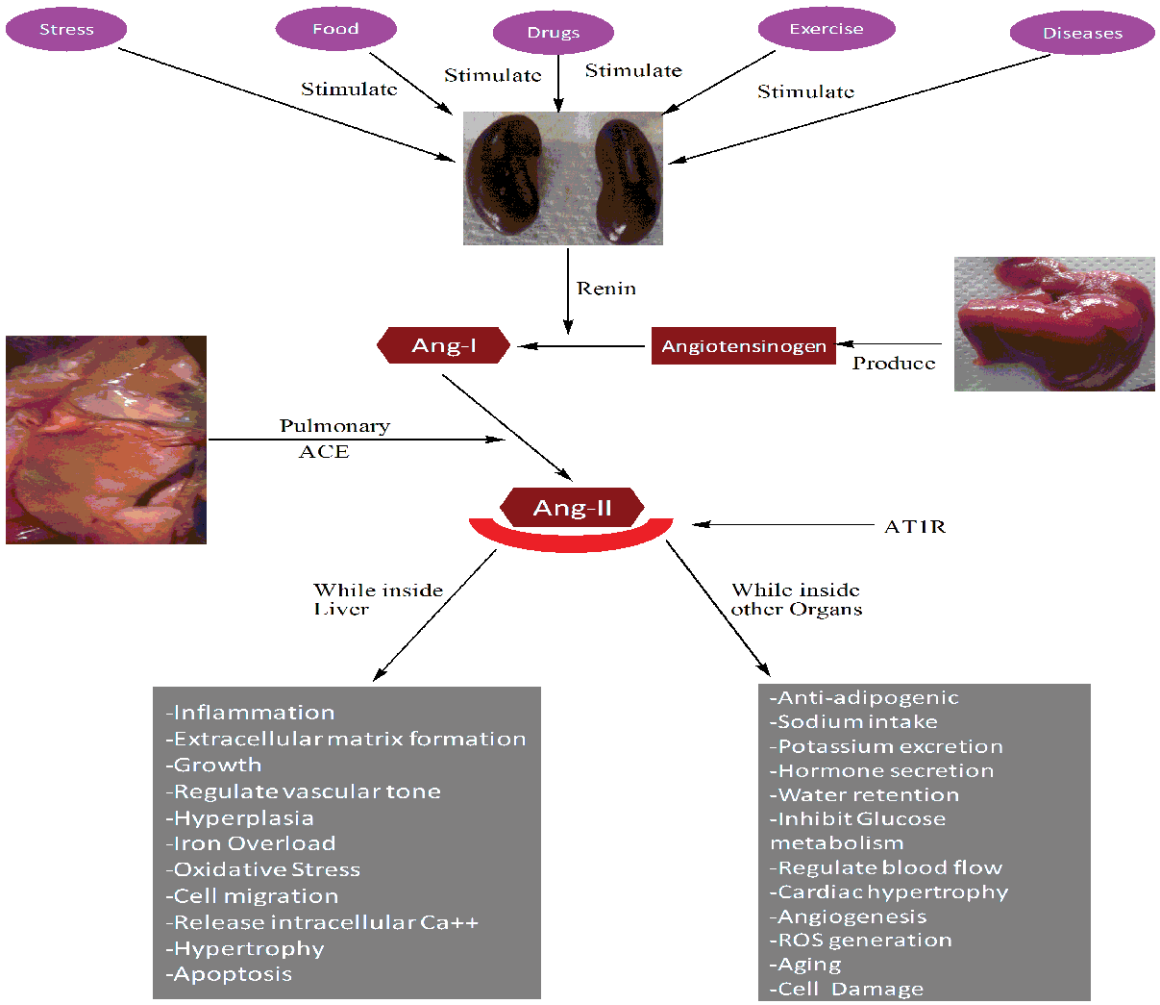

Figure 1 Production of AngiotensinII and related organ dysfunctions.

pulmonary ACE or tissue chymase or cathepsin are available via G protein-coupled receptor **(Figure 1)** [28]. So far, several types of angiotensin (I-XII) have been isolated from various models and those are activated through AT_1R and AT_2R [29]. Angiotensin can be activated in both circulation and tissue due to the availability of its receptors throughout the body [30]. It has been also noticed that activation of AT_2R often brings some protective effects like reduced inflammation via epoxyeicosatrienoic acid and by inhibiting nuclear factor -κβ [31]. Another study explained that Ang II induce arterial pressure can be reduced by the activation of AT_2R in rat model [32].A cross study has also been found which explained that deletion of AT_2R may protect from dietinduced obesity and insulin resistance in rats [33].

On the other hand it is highly established that Ang II-AT_1R binding mostly signals through MAPK pathway that promotes cellular growth and inflammation [34]. However, MAPK often serves a huge number of fundamental cellular processes to exchange extracellular and intracellular information [35]. Within the endoplasmic reticulum (ER), generally three core types of MAPK are found which are MAP3K, MAPKK, and MAPK. Beside this, downstream kinase (MAPKAPK) and upstream kinase (MAP4K) are also noticed. Inside the mammalian MAPK cascade, four different kinds of MAPK were isolated and named as MAPK p38, ERK5, cJun N terminal kinase (JNK) and extracellular signal-regulated kinase 1 and 2 (ERK1/2) respectively [36].

Ang II and MAPK in hepatic free radicals generation

Free radicals are highly reactive molecules which directly damage cell membrane, cytoplasm as well as nucleus [37]. The prime members of this family are reactive oxygen species and reactive nitrogenous species that hamper the normal cellular activity and produces oxidative stress [38]. However, free radical as well as oxidative stress mediated hepatic dysfunction has been noticed enormously by disturbing liver Cytochrome $_p$450 system [39]. Oxidative stress markers have also been identified inside the serums who were suffering from chronic hepatitis C [40]. Furthermore, hepatic tissue injuries are very common when free radicals like •OH, $•O_{2^-}$, and H_2O_2 are generated inside liver [41]. Although Ang II is mainly responsible for controlling blood pressure, it also significantly generates free radical when it is attached with AT_1R [42]. Study also suggested that Ang II-AT_1R interaction stimulates NAD(P)H oxidase (NOX) and generates ROS and RNS which further stimulates several proinflammatory cytokines [11,43]. Mitogen activate protein kinase also participates in generation of free radicals which is mostly noticed via NAD(P)H oxidase (NOX) 4 and AKT1-AKT2 (protein kinase B) pathway [44,45]. Another study explained that activation of p38MAPK was observed in ATP depleted hepatic stellete cells (HSCs) culture. The study also described that p38MAPK depended reactive oxygen species (ROS) declined number of normal HSCs [46,47]. One of the crucial studies explored that reactive oxygen species contribute significantly in development of several cancers by stimulating different cytokines [48].

Ang II and MAPK in diabetes

Diabetes, a heterogeneous metabolic disorders which not only affects pancreas but also hampers normal functioning of liver [49]. Nonalcoholic liver diseases and diabetes are the two major components of metabolic syndrome [50]. Inside the liver, high glucose concentration may alter cellular homeostasis [51] and might induce several pathological events [52]. Taken together, the complication of diabetes can activate hepatic Ang II [53] which further induces MAPK family [54] that possesses several inflammatory cytokines like activated protein-1,tumor necrosis factor-α, and nuclear factor-κβ, and many others [55]. Inflammatory cytokines further responsible for the development of liver cirrhosis, cancer and liver failure if not treated with care [56]. However, chronic diabetic status also triggers collagen and extracellular matrix production in liver which further develop hepatic fibrosis [57,58].

Ang II and MAKP in hepatic inflammation

Biological subjects are always exposed to its surrounding environment, at the same time they also need food and air to survive. Unfortunately, environment carries several foreign harmful elements which often invade inside biological system and activates host immunity [65]. On the other hand, liver serves various protective roles by producing several growth factors, antibody and other immune components to fight against harmful stimuli [66]. Once those foreign elements invade into hepatic tissue, liver immediately attracts neutrophil, T cell, local macrophages, β integrin and natural killer cells [67]. The evidences for the role of Ang II and MAPKs in the development of hepatic inflammation are summarized in **Table 1.** It is highly suggested that Angiotensin II often stimulates immune cells by activating kupffer cell to invite monocytes, killer cells, tumor necrosis factor and interleukins [68]. Local hepatic renin angiotensin system is also regulated by chronic liver injury which simultaneously activates some events such as recruitment of inflammatory cells and generation of free radicals [69]. Angiotensin related hepatic inflammation often showed elevated level of liver marker such as AST, ALP and ALT which confirms hepatic tissue injury [70]. Study also explored that MAPK which is activated by Ang II solely participates in hepatic inflammation [71]. Another study disclosed that MAPK-JNKs remarkably serve inflammation [72]. A hypothetical mechanism for Ang II and MAPKs mediated inflammatory response has been proposed in **Figure 2**.

New promising molecules against MAPK family

Researchers always try hard to develop a potent molecule against any kind of pathogenesis. Various molecules have been tested against angiotensin and related family. There is no such potent MAPK inhibitor has been established yet. Some good activities have been showed by few molecules but they need proper trial [73,74] and their effects on various experimental animal models are summarized in **Table 2**. BI78D3, an inhibitor of JNK showed prevention of JNK phosphorylation and ameliorates JNK dependent liver damage [75]. Another JNK inhibitor SP600125 showed promising effect on preventing the JNK expression and its activity in HeLa cells [76]. Furthermore, animal studies also showed that CNI1493 may prevent p38 MAP kinase signalling cascade and reduced TNF-α level in collagen induced arthritis rats [77]. Inhibition of p38 MAP kinase signalling cascade by SB203580

also restored the development and cellular proliferation in developing liver [78]. However, these newly developed molecules showed promising results in various *in vitro* and *in vivo* assays, their side effects and adverse drug reaction profiles are not established fully. A selective inhibitor of p38 mitogenactivated protein kinase, BIRB796, is such a molecule which activates the

Table 1 Role of Ang II on hepatic inflammation via several members of MAPK family.

Models	Outcomes of the study	References
HSCT6 cells	Ang II caused HSC to produce ECM via activation of ERK and cJun.	[59]
	Expression of AT_1R found high due to Ang II.	
Male Sprague Dawley rats	Angiotensin (1-7) blocked liver inflammation by inhibiting MAPK expression.	[60]
	Reduced TLR-4 and NF-κβ expression in liver.	
Male Sprague Dawley rats	Activation of liver injury is mediated by MAPK over expression.	[61]
	Ang II induces oxidative stress, hepatic inflammation, and vascular damage and thus resulting liver injury.	
Male Sprague Dawley rats	Ang II increased phosphorylation of cJun and ERK-2.	[11]
	It signaled proinflammatory cytokines via MAPK signaling.	
Male Sprague Dawley rats	MAPK family caused proinflammatory cytokine synthesis such as IL-6, and TNF-α in HSCs.	[62,63]
Sprague Dawley wild-type rats	Ang II causes the activation of Janus Kinase 2 in liver dysfunction via several cytokines productions.	[64]

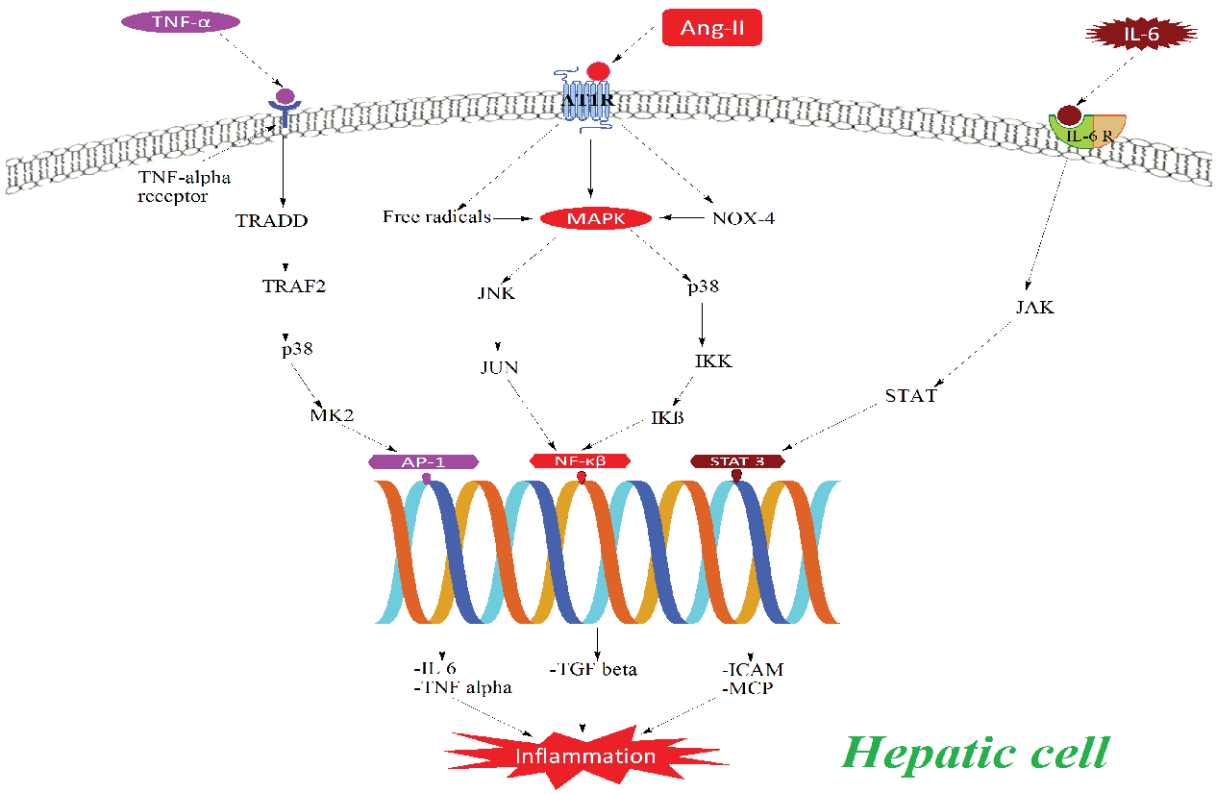

Figure 2 The possible pathway describes when Angiotensin 2 binds with angiotensin type 1 receptor it activates the mitogen activated protein kinase (MAPK), at the same time generation of free radicals and NADPH oxidase(NOX4) also gets activated, but these molecules also activates MAPK. Activation of NF-kβ is caused either by JNK-JUN pathway or by p38-IKK-IKB pathway; these activation will facilitate the production of mRNA of Proinflammatory cytokines such as TGF-β, TNF-α, and IL-6. Produced Interleukin(IL-6) binds with IL-6 receptor, and activates STAT-3 through JAK-STAT pathway to produce ICAM, MCP which assist in inflammation. Tumor Necrosis Factor(TNF-α) after binding with its receptor within the cell membrane activates Tumor necrosis factor receptor type 1associated DEATH domain (TRADD) which triggers TNF receptor-associated factor 2 (TNFR2) that stimulates Activated protein(AP 1) by p38MK2 pathway to initiate the production of proinflammatory cytokines.

Table 2 Role of new molecules on MAPK family.

Molecules	Models	Outcome of the study	References
BI78D3	Diabetic Mice and Human prostate tissue	Inhibited the phosphorylation of JNK substrates in the cell	[75,80]
		Blocked JNK dependent liver damage and restores insulin sensitivity.	
SP600125	HeLa cell culture	Inhibited JNK catalytic activity	[76]
CNI1493	Rat model	Reduced TNF-α and macrophage mediated inflammation through p38 MAP kinase signalling cascade	[77]
SB203580	Fetal rat hepatocytes	Inhibited p38 mitogen-activated protein kinase pathway in hepatocyte	[78]
BIRB796 Male mice The selective activity of BIRB796 induced [79] nuclear factor (erythroid -derived 2)- like 2 signaling in the liver.			

nuclear factor (erythroidderived 2)like 2 signaling pathway [79]. However, a reactive intermediate of BIRB796 could be found both in mouse and human liver microsomes which is responsible for the development of BIRB796's hepatotoxicity [79].

Conclusion and Future Directions

Ang II induced hepatic inflammation via MAPK suggests several pathways. Firstly, Ang II interacts with AT_1R, stimulates Gprotein couple receptor (GPCR) and then activates MAPK, resulted free radicals generation, later sends stimulation for inflammatory and proinflammatory molecules and production of other growth factors which finally contribute hepatic inflammation or hepatitis. MAPKs are important signaling molecules in several pathways in liver physiology and disease pathogensis. In many pathologic processes, JNK1 is found responsible. MAPK and other members of this family regulate multiple pathophysiologic processes, including liver cell death, steatosis, inflammation, fibrosis and many more. So a therapy must be established against hepatitis inducted by MAPK. Several other molecules are already in development processes which need to be properly testified through clinical trial.

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