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Review Article

Anti-inflammatory Role of Blocking the Renin-angiotensin System: Future Prospective

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Abstract

The renin-angiotensin system (RAS) was thought to be in charge of managing blood pressure and electrolytes. It has been established that angiotensin II is also responsible for controlling inflammation in addition to blood pressure and potassium levels. Angiotensin converting enzyme 2 (ACE2), angiotensins (1–7), angiotensins (1–9), and other additional RAS components have been identified, and have anti-angiotensin II effects. Both angiotensin receptor blockers (ARBs) and angiotensin converting enzyme inhibitors (ACEIs) are utilized as anti-hypertensive medications and protecting the heart and kidneys, and counteract the part played by Ang II in the initiation of inflammation. This review provides crucial details that help explain how ACEI and ARBs reduce inflammation. Using reliable websites like Google Scholar, PubMed, and ResearchGate, the most recent publications were reviewed. Search terms have included "RAS role of Ang II in inflammation," "influence of ACEI," and "effect of ARBs on PPAR-gamma." The data were gathered from controlled clinical trials, in vitro studies, and animal-based studies; preprints, article reviews, and meta-analysis studies were excluded. Both ACEIs and ARBs reduce inflammation via a variety of mechanisms, which explains their cardioprotective and nephroprotective effects. They reduce inflammation by modulating an inflammatory pathway through either similar or dissimilar mechanisms.

Keywords: Angiotensin II, ACE inhibitor, ARBs, anti-inflammatory effects

الدور المضاد للالتهابات لمنع نظام الرينين أنجيوتنسين: المستقبل المحتمل

الخلاصة

كان يعتقد أن نظام الرينين أنجيوتنسين هو المسؤول عن إدارة ضغط الدم والإلكتروليتات. وقد ثبت أن الأنجيوتنسين II مسؤول أيضا عن السيطرة على الالتهاب بالإضافة إلى ضغط الدم ومستويات البوتاسيوم. تم تحديد الإنزيم المحول للأنجيوتنسين (ACE2)، والأنجيوتنسينات (1-7) و (1-9)، ومكونات RAS الإضافية الأخرى، ولها تأثيرات مضادة للأنجيوتنسين II. يتم استخدام كل من حاصرات مستقبلات الأنجيوتنسين ومثبطات الإنزيم المحول للأنجيوتنسين كأدوية مضادة لارتفاع ضغط الدم وحماية القلب والكلى، ومواجهة الدور الذي لعبه Ang II في بدء الالتهاب. توفر هذه المراجعة تفاصيل حاسمة تساعد في شرح كيفية تقليل ACEI و ARBs للالتهابات. باستخدام مواقع ويب موثوقة مثل Google Scholar و PubMed و ResearchGate، تمت مراجعة أحدث المنشورات. تضمنت مصطلحات البحث "RAS ، دور Ang II في الالتهاب ، تأثير ACEI ، وتأثير ARBs على PPAR-gamma تم جمع البيانات من التجارب السريرية الخاضعة للرقابة، والدراسات المخبرية، والدراسات القائمة على الحيوانات. تم استبعاد المطبوعات المسبقة ومراجعات المقالات ودراسات التحليل التلوي. كل من ACEIs و ARBs تقلل من الالتهاب عبر مجموعة متنوعة من الآليات، مما يفسر آثارها القلبية والكلوية. أنها تقلل من الالتهاب عن طريق تعديل مسار التهابي من خلال آليات مماثلة أو مختلفة.

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INTRODUCTION

Normal bodily function and the integrity of organ structures depend on inflammation as a protective mechanism, yet persistent inflammation damages tissue [1]. A peptide structure called the Renin-Angiotensin System (RAS) controls blood pressure [2]. For many years, it was believed that the RAS is a hormonal system in charge of blood pressure regulation and electrolyte balance. It also controls the homeostasis of many important organs, such as the kidneys and heart [3,2]. Many new RAS components, such as ACE2, Ang (1-7), Ang (1-9), the Mas receptor, and alamandine (Figure 1), have been identified recently [4]. Traditional RAS components included angiotensinogen, Renin, Ang I, ACE, Ang II, and Ang II-receptor. The juxtaglomerular apparatus of the kidney cells produces the enzyme renin, which is then converted by hepatocytes to angiotensinogen to produce Ang I [4,5,1]. The other classic element of RAS, ACE, transforms angiotensin I into angiotensin II [1,5,6,7]. Additionally, ACE facilitates the conversion of bradykinin into inactive metabolites [6]. Ang II is broken down into Ang (1-7) or Ang (1-9) by the newly identified RAS enzyme ACE2 [6,1,4]. The metallopeptidases ACE and ACE2 are both tethered to the cell membrane [8].

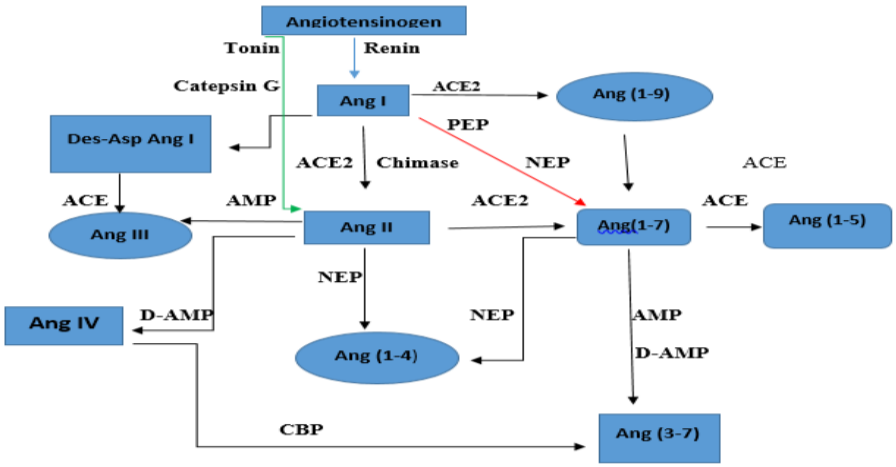

Figure 1: Schematic representation of Traditional and new components of RAS. Angiotensinogen converted to Ang I by Renin. Then Ang I converted to Ang II by ACE or chimase. Ang II can be synthesized directly by Tinin or Catepsin G. Many enzymes can degrade Ang II to different metabolite such as Amp, PEP, NEP, Ang I cleaved directly by ACE2 to Ang (1-9) or to Ang (1-7) by NEP and PEP. Other components such as Ang IV, Ang (1-4), Ang (3-7), Ang III and Ang (1-5) are produced through CBP, ACE, AMP, NEP.

ACE/Angiotensin II/AT1R Axis and Inflammation

Organ injury is caused by the activation of ACE/Ang II/AT1R axis, which increases blood volume, fibrosis, and inflammation [1]. Angiotensin II is an octapeptide that is produced when ACE breaks down angiotensinogen I [9,6]. It functions physiologically by binding to the Ang II receptor type 1 and type 2 G-protein-coupled receptors. It is believed that Ang II is a crucial RAS effector [5,2,9,11,12]. It's responsible of igniting the chain of events that causes inflammation [9]. The pro-inflammatory mediator Ang II was discovered [2]. It stimulates the NF-kB pathway by activating the AT1-receptor. Atherosclerosis develops in large part due to the transcription factor NF-κB. Inflammatory mediators like interleukin-6 (IL-6), C-X-C chemokine, and vascular cell adhesion molecule-1 (VCAM-1) are increased as a result [2,5,6]. By triggering the creation of particular chemokines such monocyte chemoattractant 1 (MCP-1), Ang II encourages the migration of inflammatory cells into blood vessel cells [13,6]. Additionally, it involved a complicated process of white blood cell infiltration that resulted in a rise in the production of a variety of mediators, including integrins, ICAMs, cytokines, chemokines, and selectins. By changing the expression of VCAM-1 and ICAM-1, TNF-α, and interleukin-6, Ang II also lessens inflammation [9]. Some of the pro-inflammatory effects of Ang II can be attributed to dendritic cells, which are crucial for immunological response and inflammation and have AT1 and AT2 receptors. Ang II stimulates dendritic cell infiltration, maturation, and antigen binding [6]. Due to the presence of local RAS that regulate their migration to the site of inflammation, the formation of free radicals, and NADPH activity, T-cells also contribute to Ang II-induced inflammation. The release of particular cytokines and chemokines that

control T-cell infiltration to the site of inflammation is regulated by the activation of AT1R by Ang II, which leads to T-cell rearrangement [6]. Ang II decreases endothelial NO production, raises TNF-α levels, and increases ROS formation through boosting the activity of the NADPH oxidase enzyme through AT1R activation [6,2]. Ang II stimulates the hormone aldosterone [1,9]. Aldosterone encourages inflammation by boosting leukocyte migration to the site of inflammation [2]. Additionally, it enhances the production of reactive oxygen species (ROS) [9].

METHODS

We searched the web for pertinent articles. Searching has been done on reputable scientific websites including Google Scholar, PubMed, and ResearchGate. Animal-based studies, *in vitro* investigations, and randomized controlled trials were all included in the included papers. Preprints, review articles, and articles containing meta-analyses have all been left out. Thirty-two articles were reviewed; 29 of them were used in this review, and 3 weren't. Then, to produce this manuscript, the data and supporting arguments from those articles were utilized.

RESULTS AND DISCUSSION

Studies relating RAS activation to inflammation have led to research and studies on the anti-inflammatory properties of ACEI and ARBs. The impact of RAS activation inhibitors on vascular and systemic inflammation was examined in various types of studies. By controlling RAS and stifling pro-inflammatory biomarkers, ACEIs and ARBs both have anti-inflammatory effects. By raising levels of Ang (1–7), which function as a natural ACE inhibitor and has strong anti-inflammatory capabilities, ACEIs and ARBs primarily reduce inflammation. Expression of ACE2 is increased by the use of both medication groups [14,15]. Angiotensin II is then changed into Ang (1-7) and Ang (1-9) by ACE2. Recombinant ACE2 was employed to assess its impact on RAS in a prospective, randomized, double-blind animal trial, and data analysis showed that ACE2 successfully decreased levels of Ang II and TNF-α [16]. In addition to enhanced ACE2 expression, other factors elevated Ang (1-7) levels. ARBs raise Ang (1-7) levels by blocking angiotensin I receptor (AT1R), whereas ACEI prevents ACE from degrading angiotensin I, which is then converted to Ang (1-7) and Ang (1-9) [11,4,17]. Protein kinase C (PKC), c-SRC kinase, and members of the MAPK family (p38, ERK1/2, and JNK), were only a few of the intracellular signaling molecules that Ang (1-7) efficiently suppressed. Its anti-inflammatory activities are due to this inhibition [3]. Additionally, Ang (1-7) has a cardioprotective effect [18]. In rats fed lipopolysaccharide, a new study on captopril discovered that it decreased lung inflammation. The total WBC, neutrophil percentage, INF-γ, PGE2, TGF-β1, and the INF-γ/IL-4 ratio all experienced significant declines, according to data analysis [11]. The synthesis of pro-inflammatory mediators is inhibited by ACEI. It was investigated how efficiently enalapril lowered cytokines and hence frailty. Enalapril suppressed the majority of the measured cytokines, including MCP-1 and MCP-1alpha [19]. By preventing its breakdown, captopril and other ACEIs raise the level of the anti-inflammatory peptide N-Acetyl Seryl Asparatyl Lysyl Proline (Ac-SDKP) in the plasma, which helps Ac-SDKP to reduce inflammation and fibrosis while promoting angiogenesis [1]. A wonderful investigation was conducted on 12-week-old male BALB/c mice to ascertain captopril's anti-fibrotic efficacy through Ac-SDKP regulation [20]. The data analysis (Table 1) showed that captopril increased Ac-SDKP, CCL-2, and macrophage recruitment, all of which have been demonstrated to be inhibited by captopril [20], while decreasing MAPK and TGF-β1 levels. There is evidence that thrombospondin 1 (TSP-1) lowers inflammation. It functions via the CD47 receptor, which is present on T-cells and polymorphonuclear cells [21]. The level of TSP-1 in patients receiving perindopril is higher than in patients receiving other antihypertensive drugs such beta blockers, according to results from a study on perindopril to establish its impact on TSP-1, the attenuated levels of the highly specific C-reactive protein (hs-CRP) and pentraxin related protein (PTX3) confirmed this effect. The author claims that long-term perindopril users have decreased endothelial inflammation levels. TSP-1 plasma levels in conjunction with PTX3 induce this impact [17]. ARBs boost the expression of ACE2 and Mas receptors while lowering AT1R levels. Different ARBs have different effects on the ACE-AngII-AT1 and ACE2-Ang (1-7)-Mas axes. For instance, olmesartan, candesartan, and losartan improved cardiac dysfunction in all Ang II knockdown scenarios, whereas telmisartan, valsartan, and irbesartan improved cardiac dysfunction only when Ang II was present *in vivo* [22] (Table 2). ARBs also lessen inflammation by lowering reactive oxygen species (ROS). ROS production contributes to increased vascular penetration, white blood cell movement, fibrosis, and cell proliferation at the early stages of inflammation. End-organ damage is occasionally brought on by ROS [9]. For instance, data analysis from a study using doxorubicin and valsartan to evaluate valsartan's cardioprotective efficacy showed that ROS were significantly decreased in the valsartan + doxorubicin-treated H9C2 cells compared to the doxorubicin-treated group. This shows that ARBs can successfully reduce inflammation brought

on by ROS. An in vitro study was performed to determine how effectively candesartan reduces the innate immune system's response to LPS in human monocytes. Data interpretation revealed that at a dose of 1 micromole/L, candesartan effectively reduced LPS-induced IL-6 release. Candesartan also CD14 mRNA expression was significantly reduced, but TLR4 remained unaffected. Candesartan significantly reduced the expression of inflammatory mediators stimulated by LPS, such as TNF-α, IL-1β, IL-6, lipoxygenase-1 (LOX-1), and IκB-α mRNA.

Table 1: Selected Studies Evaluating Anti-inflammatory Effects of ACEIs, Ang (1-7) and ACE2

Drug	Author & year	Type of study	Main result
Ang (1-7)	Khajah *et al.*, 2016 [3]	Animal study	Male and female BALB/c mice involved in this study, DSS polymer used to induce colitis, while control group received tap water only. Ang 1-7 mitigated Ang II expression at doses of 0.01-0.1 mg/kg, furthermore, daily intake of Ang 1–7 at 0.06 mg/kg dose attenuate Ang II to the basal levels seen in the UT group. Ang II level increased sufficiently when high dose of Ang 1–7 (1.0 mg/kg) injected in DSS/i.p saline group. Ang (1-7) mitigated colitis inflammation via modulating the expression/activity of several signaling molecules such as Ang II, p38 MAPK, ERK1/2, and Akt.
Recombinant ACE2	Treml *et al.*, 2010 [16]	Animal study.	In this study 15 piglet are used, 6 piglets received recombinant ACE2, 6 piglets considered as control and 3 of the received ACE2 without LPS pre-treatment. The result showed that ACE2 effectively reduced level of Ang II and TNF-a.
Captopril	Boskabady *et al.*, 2018 [11]	Animal study	The results showed that captopril dose-dependently reduced total and differential WBC counts, while it improved serum oxidant/antioxidant biomarkers and histopathological changes in LPS-treated rats. These results indicate a therapeutic potential for captopril on systemic inflammation and oxidative stress against LPS-induced lung injuries.
Enalapril	Keller *et al.*, 2019 [19]	Animal study	Male and female mice were involved in this study, middle age (male n=30, female n=32), older age (male n= 38, female n= 28). Enalapril reduced most cytokines such as IL-6, TNF-a, IL-1 alpha, but reduce level of MCP-1 and MCP-1 alpha significant.
Captopril	Chan *et al.*, 2018 [20]	Animal study	12-week-old male BALB/c mice underwent unilateral ureteric obstruction (UUO). UUO mice treated with either a vehicle, captopril, or captopril in conjunction with S17092 (prolyl oligopeptidase inhibitor). 7 days' post treatment, mice were k and kidneys used for analyses. Data analysis illustrated that Captopril decrease level of MAPK and TGF-B1 also increase level of Ac-SDKP. Captopril mitigated level of CCL-2 also macrophage recruitment.

Candesartan significantly reduced the LPS-induced release of the pro-inflammatory cytokines TNF-α and IL-6, but not the anti-inflammatory cytokine IL-10 [12]. On PPARs (peroxisome proliferator-activated receptors), some ARBs have a partial agonistic effect [24–26]. Because they boost the activity of kinases and transcription pathways like NF-κB and nuclear factor of activated T-cells while lowering the synthesis of IL-1β and TNF-α, and PPARs are crucial for controlling inflammation [24]. ARBs like telmisartan, which activate PPAR-γ, cause a rise in adiponectin levels [27]. By lowering oxidative stress, adiponectin possesses anti-inflammatory effects [28]. In a different study, the AB oligomer caused inflammation in BV2 cells, and telmisartan's ability to reduce inflammation was examined. Telmisartan significantly raises levels of the anti-inflammatory cytokine IL-10 while significantly decreasing pro-inflammatory mediators including IL-1β and TNF-α generated by ABO in BV2 cells. Telmisartan dramatically boosted PPAR-γ expression and blocked the NF-κB pathway by preventing ABO-mediated activation of Akt and ERK [29]. The acute inflammatory mediator (hs-CRP) is decreased by ARBs [27,25,9]. Patients with hypertension received irbesartan for three months as part of a trial. The acute inflammatory marker hs-CRP (before irbesartan, 2.8±0.54; after irbesartan, 2.66±0.50) and the oxidative stress marker d-ROM (before irbesartan, 338±74; after irbesartan, 305±62) were both decreased, the researchers found when they evaluated inflammatory mediators. Irbesartan may also operate as an antioxidant by promoting antioxidant enzymes, albeit this effect hasn't been clinically demonstrated yet [25]. In a 2015 study, the role of irbesartan in reducing adhesion molecule levels was examined. Data analysis revealed that irbesartan efficiently decreased TNF-α-induced release and the production of adhesion molecules (VCAM-1 and ICAM-1) and E-selectin. Irbesartan also prevented TNF-α-induced nuclear translocation of NF-κB, P65, and IκB-α phosphorylation [30]. Telmisartan has been shown to reduce the chronic inflammation brought on by formalin and the granuloma brought on by cotton pellets in rats, and Al-Hejjaj *et al*. demonstrated this in 2011 [31]. These benefits can possibly be ascribed to telmisartan's PPAR-γ agonist action, which may suppress inflammatory processes [32]. The anti-inflammatory activity of Azilsartan and Aliskiren is responsible for their ability to reduce adipogenesis in a rat model of high-fat diet-induced NAFLD when

RAS activity is inhibited [33,34]. Azilsartan enhances methotrexate's impact on clinical ratings and specific inflammatory markers in individuals with active rheumatoid arthritis, according to research by Mahmood *et al*. (2018) [35]. Additionally, giving individuals with active rheumatoid arthritis who are not responding to methotrexate azilsartan along with the biological drug etanercept enhances the anti-inflammatory action and lessens pain and disease severity [36].

Table 2: Selected Studies Evaluating Anti-inflammatory Effects of ACEIs and ARBs

Drug	Author & year	Type of study	Main result
Perindopril	Buda *et al.*, 2019 [21]	Randomized control trial	351 participant included in this study, control group, group B treated with other antihypertensive drugs, group C treated with perindopril. Significant association was reported between TSP-1 levels and the inflammatory biomarker (Hs-CRP, PTX3) in groups C and B. Perindopril increases plasma level of TSP-1 effectively at dose 10 mg, and as a result inflammation reduced.
ARBs	Wang *et al.*, 2016 [22]	Animal study	ARBs increased expression of ACE2 and MAS 1 receptor, but AT1R has been downregulated by ARBs, level of Ang II mitigated after 4 weeks of treatment with ARBs.
Valsartan + doxorubicin	Cheng *et al.*, 2020 [23]	Animal study + in vitro study	- In vivo: 40 rats are used in this study; control group, rats treated with Doxorubicin, rats treated with Doxorubicin and valsartan. - In vitro: using H9C2 cell line. Valsartan effectively reduces doxorubicin-induced ROS; also it attenuates the expression of cytokines such as TNF-a, IL-6.
Candesartan + LPS	Zhao *et al.*, 2013 [12]	In vitro	Unstimulated human circulating monocytes gained from healthy volunteer by counter low centrifugal elutriation. Then Monocytes have been tested by incubation with LPS (50 ng/ml) with or without candesartan 1 mmol/l. Candesartan effectively attenuated the inflammatory mediator cytokines such as TNF-1-a, IL-1B and interleukin-6. Furthermore, candesartan mitigated the activation of the NF-kB pathway, also decreased the ROS formation induced by LPS, without affecting the secretion of interleukin-10
Telmisartan + AβO	Wang *et al.*, 2020 [29]	In vitro	AβO has been used to induce inflammation in BV2 cell. Telmisartan decreased level of TNF-a and IL-1 also enhanced release of IL-10. Telmisartan cause a significant increasing in PPARγ transcriptional activity.
Irbesartan	Taguchi *et al.*, 2013 [25]	Clinical study	118 patients enrolled in this study, male (n=94), female (n=24). Irbesartan mitigated level of d-ROM and hs-CRP, also reduced oxidative stress
Irbesartan	Jiang *et al.*, 2015 [30]	*In vitro* study	HUVECs has been used as cell culture. The data revealed that Irbesartan suppressed NF-kB and inhibit TNF-a induced VCAM, ICAM and E-selectin expression and secretion.
Telmisartan	Al-Hejjaj *et al*., 2011 [31]	Animal study	Rats were used to study of the anti-inflammatory activity of different doses of telmisartan in formaldehyde-induced chronic inflammation, and cotton pellet-induced granuloma compared with dexamethasone. Telmisartan decreased formaldehyde-induced chronic inflammation and cotton-pellet induced granuloma in rats in a dose-dependent pattern.
Telmisartan	Abbas *et al*., 2011 [32]	*In vitro* study	Incubation of both intact erythrocytes and the lysate with different concentrations of telmisartan resulted in a concentration-dependent slowing in the rate of Hb oxidation, as predicted by the increment in the time required to form 50% MetHb.
Azilsartan and Aliskiren	Utba *et al*., 2016 [33]	Animal study	The effects of blocking RAS with azilsartan, aliskiren or their combination on the body weight and adipogenesis in rat's model of NAFLD were evaluated. Administration of azilsartan attenuates adipogenesis and obesity in rat's model of high-fat diet induced NAFLD, while aliskiren affects adipogenesis only.
Azilsartan and Aliskiren	Hussain *et al*., 2017 [34]	Animal study	Both azilsartan and aliskiren protects the rats against high-fat diet induced NAFLD with predominant effects for the former, and their combination showed no beneficial synergistic or additive effects.
Azilsartan	Mahmood *et al*., 2018 [35]	Clinical study	Azilsartan improved the effects of methotrexate on the clinical scores and certain inflammatory biomarkers of patients with active RA.
Azilsartan	Mahmood *et al*., 2018 [36]	Clinical study	Blocking RAS with azilsartan may improve the effects of etanercept on the clinical markers of pain and disease severity of patients with active RA not responding to methotrexate.

Conclusions

Both drug classes share some similar anti-inflammatory mechanisms, and each has a different mechanism to mitigate inflammation, such as telmisartan activating PPAR-gamma and captopril decreasing Ac-SDKP breakdown. Both ARBs and ACEIs have anti-inflammatory properties unrelated to their antihypertensive effects, primarily by reducing the pro-inflammatory effects of Ang II. Finally, we can draw the conclusion that the cardioprotective and

renoprotective properties of ACEI and ARBs are due to their anti-inflammatory properties.

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Conflict of interests

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