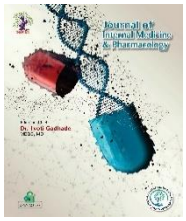
Journal of Internal Medicine & Pharmacology (JIMP)

[E-ISSN: 3049-0049]

Journal Homepage: https://sennosbiotech.com/JIMP/1



Review Article

Angiotensin Signaling in the Brain and Blood Vessels: Implications for Neurological and Cardiovascular Disorders

Kanhopatra Wable

Agnihotri Institute of Pharmacy Wardha, India, 442001

ARTICLEINFO ABSTRACT

Angiotensin signalling is found to be significant in the regulation of the system that maintains the cardiovascular and neurological balance. This regulatory mechanism affecting blood pressure, volume control, and vasomotor tone is probably mainly controlled through the renin-angiotensin system or RAS. Recent data demonstrate that although Ang II is an important regulator of brain and blood vessel function, it may also be involved in the development of pathological changes. Within the brain tissue, Ang II binds to certain receptors, such as AT1 and AT2; participating in the regulation of neuronal firing, stress and neuroinflammation. Abnormality of this signalling pathway has been linked to neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and stroke through free radical-mediated damage, compromised blood-brain barrier integrity and neuronal death. In the vascular compartment, activates endothelial dysfunction, vascular remodelling hypertrophy and inflammation, and oxidative and proliferative changes in the vascular smooth muscle cells. These effects form the basis of the formation of cardiovascular diseases such as atherosclerosis, aneurysms and ischemic heart diseases. Interactions between central and peripheral angiotensin pathways worsen these conditions through nervous and vascular adaptation feedback loops. More recent therapies aimed at individual elements of RAS, including ACEIs, ARBs, and novel receptor ligands, reveal good potential for averting these detrimental consequences.

Keywords: Angiotensin Signaling, Blood-Brain Barrier, Cardiovascular Disorders. Renin-Angiotensin System

⁎⁎ Corresponding author

Kanhopatra Wable

Agnihotri Institute of Pharmacy Wardha, India, 442001

E-mail addresses: Kanhopatrawable@gmail.com

Received date: 10-Nov-2024 Revised date: 05-Dec-2024 Accepted date:17-Dec-2024

DOI: https://doi.org/10.61920/jimp.v1i04.38

1. Introduction

Overview of the Renin-Angiotensin System (RAS)

The kinds of hormones involved in RAS the renin-angiotensin system is a key hormonal pattern that controls circulatory homeostasis, fluid levels, and blood pressure. Originally ascribed to have a systemic function, RAS is nowadays viewed as a local tissue renin-angiotensin system that uses a variety of enzymes, receptors, and effector molecules such as angiotensinogen, renin, angiotensin I, angiotensin II (ANG II) and their receptors. Ang II, the primary effector of RAS, convey its biological effects through the angiotensin type 1 receptor (AT1R) and type 2 receptor (AT2R mainly). AT1R leads to direct vasoconstriction, and sodium retention thereby having pro-inflammatory effects, on the other hand, AT2R has consequences of vasodilation and anti-inflammatory effects. Apart from the traditional organizational RAS, there is emerging evidence of tissue containing RAS within diverse organs such as the brain and vessels, and therefore, with a more comprehensive role in physiological and diseased states [1-2].

Importance of Angiotensin in Physiological and Pathological Processes

Angiotensin II is a peptide hormone that has a dual function and impacts the various body's vital activities. In the vasculature, angiotensin II acts on the arterioles K+ channels controlling the direct vasoconstriction and consequently blood pressure [3]. It is also involved in the pathogenesis of vascular remodelling and endothelium, so it is an important factor in vascular health [4]. In the CNS, Ang II has multiple functions and impacts such as modulation of neuronal excitability as well as neuroinflammation and preservation of the blood-brain barrier [5]. However, aberrant regulation of Ang II signalling is involved with diverse diseases like hypertension, stroke, neurodegenerative diseases, and vascular diseases, including atherosclerosis. The novel biology of Ang II based on hypertensive and physiological profiles indicates its duality in influencing hemodynamic parameters [6].

Rationale for Exploring its Dual Role in the Brain and Blood Vessels

The connection between the structure of the nervous system and the blood vessels together with its management form the neurological vascular unit that is key to the overall well-being of the brain [7]. Thus, angiotensin II as a master of both S and L-RAS is conveniently placed to interfere with this neurovascular unit. This must be brought about by modulation of neuronal activity, change in vascular tone and regulation of distinct inflammatory channels which culminate in the complex interplay with the neurological and cardiovascular systems. Appreciation of this dual function is critical for unravelling the mechanisms of pathology manifested in neurogenic hypertension, stroke and other cerebrovascular diseases, and neurodegenerative diseases. Further, antagonizing the Ang II signalling has been rapidly investigated as a therapeutic approach that has been studied for ACE inhibitors and ARBs in the context of cardiovascular diseases. It is, therefore, crucial to have a further understanding of Ang II effects in both the brain and the vessels when extending this therapeutic schema to treat neurovascular disorders. This review intends to discuss those mechanisms and reveal the presence of synergistic therapeutic strategies [1-2].

2. **The Renin-Angiotensin System: An Overview**

Components and Pathways of RAS

RAS is a much integrated hormonal system which involves a series of enzymes and proteins and is well documented to be involved in adjustments of BP, fluid load and vessel compliance [8]. Starting with a protein called angiotensinogen which is produced in the liver, it is cleaved, by an enzyme called renin, which is released by the kidneys in conditions of low BP or low sodium. Angietensus I is then cleaved by the angiotensin-converting enzyme (ACE) mainly in the lungs to produce angiotensin II (Ang II). The major effector of the molecule Ang II produces diversified physiological effects after binding with specific receptors like AT1R and AT2R. Whereas AT1R stimulation results in vasoconstriction and sodium and immune activation, AT2R has opposite effects including vasodilation, anti-inflammatory, and tissue remodelling [1-2].

Role of Angiotensin II as a Key Effector Molecule

Under physiological conditions, Ang II is a key component of RAS, whereas, under pathological conditions, it is a component of the activated RAS. Ang II links to AT1R and leads to systemic vasoconstriction, rise in systemic vascular resistance, and secretion of aldosterone from adrenal glands which in turn favours reabsorption of sodium and water in the kidneys. This cascade plays a crucial role in the regulation of blood pressure and balance of fluids in the human body. Ang II has impacts on vascular remodelling, endothelial dysfunction, and inflammatory response, and causes hypertension, atherosclerosis and organ damage. However, this interaction with AT2R can reduce such effects through vasodilation, anti-inflammatory activity, and cell protection activities although the potential of these effects may vary with the background circumstances [9-10].

Localized RAS in the Nervous System and Vasculature

Formerly, RAS was thought to act as a systemic hormonal system, however, new information pointed out that there exist local RAS within individual organs and tissues such as the brain and blood vessels. Within the nervous system, Ang II has the importance for modulation of neuronal excitability, synaptic plasticity and neuroinflammation. It is also involved in the maintenance of the blood-brain barrier and neurovascular response or coupling. Local RAS located at the vascular level regulates vascular tone and endothelial function making it an essential modulator of vascular function. Abnormality in the spatial regulation of RAS is associated with neurogenic hypertension, cerebrovascular diseases and neurodegenerative ailments. This indicates how studying localized and systemic RAS may provide deeper insights into the biphasic effects of Ang II on the nervous system and blood vessels for a plethora of diseases [11].

3. Angiotensin Signaling in the Nervous System

Mechanisms of Angiotensin Receptor Activation (AT1R and AT2R) in the Brain

Angiotensin II (Ang II) exerts its effects in the brain through the activation of two primary receptor subtypes: There are two subtypes of receptors, angiotensin type 1 receptor (AT1R) and angiotensin type 2 receptor (AT2R) [12]. These receptors are expressed in many regions of the brain, such as the hypothalamus, brain stem and cerebral cortex and are associated with cardiovascular and neuroimmune regulations. These signalling alterations consist of AT1R-mediated pathways such as PKC, MAPKs and NADPH oxidase. These pathways promote the constriction of blood vessels

and the release of inflammatory proteins while also causing oxidative stress [13]. On the other hand, AT2R usually counteracts the actions of AT1R through exercising actions including vasodilation neuroprotection, and anti-inflammation. AT2R is known to produce favourable effects through phosphatases, nitric oxide (NO) generation and cyclic GMP changes [14]. The differential regulation of these two receptors in the brain appears to have physiological and pathological importance as the balance between the widths of the two curves may represent the respective influences of AT1R and AT2R in the regulation of brain homeostasis [9].

Role in Neuroinflammation, Oxidative Stress, and Blood-Brain Barrier Integrity

Angiotensin II is involved in the mediation of neuroinflammation and oxidative stress, two essential pathogenic factors for numerous neurological diseases [16]. Stimulation of AT1R in the brain increases levels of pro-inflammatory cytokines, IL-6 and TNF-α and raises the production of ROS via NADPH oxidase. This oxidative stress will affect the neuronal cells and also disrupt the mitochondria and accentuate the neuronal disorder [13]. Also, Ang II signalling negatively affects the blood-brain barrier, upregulates endothelial permeability and downregulates the expression of programmes that regulate the tight junctions hence enabling the movement of immune cells and escalating the inflammation process. By comparison, AT2R activation has protective effects against these conditions because of its ability to inhibit inflammation, scavenge free radicals and maintain the structural integrity and function of the BBB which makes it a promising target [16].

Implications for Neurological Disorders

Several neurological disorders are attributable to the dysregulation of signalling involving the angiotensin receptor in the nervous system. In stroke, increased AT1R signalling leads to ischemic brain injury by vasoconstriction, inflammation, and oxidative stress while increased AT2R signalling reduces brain damage probably by increasing blood flow. In Alzheimer's disease, Ang II promotes amyloid-beta deposition and tau pathogenesis through oxidative stress and pro-inflammatory pathways; however, AT2R may reverse neurodegeneration through neuronal regeneration and anti-inflammatory effects. In the same way, the role of Ang II as a pro-producer through the activation of AT1R in Parkinson's disease has been identified as causing dopaminergic neuron loss by oxidative stress and inflammation, while the activation of AT2R offers neuroprotection. Such outcomes support the biphasic role of Ang II signalling and its scope for further treatment of multiple neurological diseases [10].

4. Angiotensin Signaling in Blood Vessels

Vascular Smooth Muscle Contraction and Endothelial Dysfunction

Several of the actions of angiotensin II (Ang II) are particularly important in vascular physiology because they influence both vascular smooth muscle cells (VSMCs) and endothelial cells. By binding to AT1R on VSMCs, Ang II effect vasoconstriction through the raise of intracellular calcium concentration and activation of PKC [17]. This results in an improved vascular tone and plays a role in either increasing or decreasing blood pressure in normal physiological conditions. However, sustained activation of AT1R impairs vascular function and contributes to endothelial dysfunction, which features include reduced NO production,

increased generation of O,- and inflammation. Dysfunctional endothelium becomes unable to control vascular tone and permeability and, therefore, becomes susceptible to pathological states of vascular function [18].

Effects on Vascular Tone, Inflammation, and Remodeling

Thus, angiotensin II impact on the vascular tone goes beyond solely constriction of blood vessels. As scholars interpret it, it is a pro-inflammatory mediator by enhancing the secretion of cytokines including IL-6 and TNF-α [19]. These cytokines attract other immune cells within the vascular wall thus escalating inflammation levels. In addition, Ang II stimulates NADPH oxidase and causes the formation of ROS which in turn promotes oxidative stress [13]. The ROS not only affect endothelial function negatively but also function as informational phases which regulate vascular alteration such as hypertrophy and fibrosis. These structural changes within the blood vessels elevate arterial rigidity and also decrease vascular pliability, essential components towards the chronicity of vascular disease [19].

Contributions to Hypertension and Atherosclerosis

The deleterious consequences of Ang II signalling are considered to play a pivotal role in the generation of high blood pressure and the formation of atherosclerotic plaque. These changes are mediated through the potent proconstrictor effect of Ang II via activation of AT1R which leads to chronic vasoconstriction, inflammation vascular remodelling increased blood pressure and afterload on the heart. Ang II also induces precocious atherosclerotic plaque formation by increasing VSMCs' proliferation and migration, as well as the extracellular matrix deposition and lipids lesions in the arterial walls. Here, inflammation and oxidative stress, endothelial dysfunction result in monocyte adhesion and macrophages transform into foam cells, which event characterizes atherosclerosis. In addition, activation of Ang II increases other pro-coagulant factors incidences of thrombosis that compound the advancement of vascular diseases.

The present findings of Ang II signalling in blood vessels shed light on molecular pathways that underlie normal function and pathogenesis. The use of ACE inhibitors and ARBs that act on Ang II can be recognised as a modern principle of the treatment of vascular disorders. These interventions not only reduce blood pressure, but also inhibit the inflammatory process, oxidative stress and changes in vessels that are associated with the development of cardiovascular diseases, and offer vast protection for the blood vessels [17-18].

5. Neurovascular Interactions Mediated by Angiotensin

Cross-Talk Between the Nervous System and Blood Vessels

From this closed-loop system, angiotensin II (Ang II) has been identified as the principal peptide that serves multiple functions in fine-tuning neurovascular interactions [20]. Ang II interacts with the autonomic nervous system as a neuromodulator binding to AT1R in several areas within the brain including the hypothalamus and the brainstem [21]. This results in increased sympathetic drive and therefore has a direct impact on vascular resistance and arterial blood pressure. At the same time, the signalling of Ang II contributes to endothelial as well as smooth muscle cell content of blood vessels as far as the dilation and constriction of vessels is concerned about the nervous system input. These pro- and anti-facilitation mechanisms

prevent dyssynchronization of microcirculation regulation in the brain and stabilization of systemic blood pressure. Nevertheless, the disturbance of such interactions can result in organ diseases, particularly in the nervous vascular field along with hypertension [22].

Role in Neurogenic Hypertension and Cerebral Autoregulation

Sympathnorthism, including the overactivation of the sympathetic nervous system, is connected to Ang II-mediated pathogenic cascades with neurogenic hypertension. Here, through the activation of AT1R in the brainstem and the hypothalamus, sympathy tone is augmented by Ang II and hence vasoconstriction becomes prolonged, and blood pressure is compounded [2]. This dysregulated Ang II signalling also exhibits a negative effect of cerebral autoregulation which is the ability of cerebral circulation to regulate the constant blood flow in the brain despite changes in systemic blood pressure [21]. Ang II and oxidative stress along with inflammation in the brain increase endothelial dysfunction and there is further loss of autoregulatory abilities. As a result, reduced CA plays a role in ischemic injury, cognitive dysfunction, and stroke risk [18].

Implications for Neurovascular Coupling in Cognitive Impairment

Neurovascular coupling which refers to the regulation of local microcirculation by neuronal activity is of paramount importance to the healthy functioning of the brain. ERP alterations that result from Ang II-induced changes in neurovascular coupling have particularly important signs as far as cognitive impairment and neurodegenerative diseases are concerned [15]. Overstimulation of AT1R in the CNS impairs antioxidant/oxidant balance and increases inflammation, injures the endothelium and decreases NO availability. This has the effect of hindering vasodilation and reducing how oxygen and nutrients can access the active regions of the brain, thus interfering with neuronal function [14]. Repeated exposure to Ang II has untoward effects on vascular function including, vascular dementia and Alzheimer's disease where there is a failure for neurovascular coupling plus impaired cognition. [10] .On the other hand, activation of AT2R has been shown to have a potentially beneficial effect in reversing some of the above deleterious effects through increases in vascular dilation, reduced oxidative stress and maintained endothelial integrity. This underscores the therapeutic value of modulating angiotensin signalling with the hope of promoting the recovery of the neurovascular couch and reversing cognitive dysfunction [18].

6. Angiotensin and Its Role in Neurological Disorders

Hypertension-Induced Brain Damage and Stroke

Angiotensin II (Ang II) is implicated in hypertension which is a significant risk factor for brain injury and stroke. This results from the consistent organisation of the renin-angiotensin system and hypertension that results in morphological and physiological alterations in the blood vessels of the brain. Ang II by acting on the AT1R, increases vasoconstriction, elevated vascular stiffness and impaired endothelial function. These effects adversely affect the ability of the human brain to precariously regulate blood supply to the brain increasing the risks of ischemic events, and hemorrhagic strokes. Ang II also increases oxidative stress and inflammation within the cerebral blood vessels therefore increasing BBB dysfunction and neuronal damage. In stroke, these

pathways contribute to post-ischemic inflammation and oxidative stress leading to increased brain infarct volume and impaired functional recovery [23].

Angiotensin's Involvement in Neurodegenerative Diseases

There are just recent trends to show that Ang II has certain functions in neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). That is, in AD, Ang II promotes the formation of amyloid-beta plaques and hyperphosphorylation of tau protein by oxidative stress and inflammation. The current proposal reaffirms that stimulation of AT1R accelerates neuronal injury and cognitive deficits through detrimental effects on synapses and inflammation within the brain. Thus, in the frame of PD, oxidative stress and mitochondrial impairment of dopaminergic neurons due to Ang II are associated with the latter's degeneration. Additionally, as we described above, Ang II also affects neurovascular coupling and the BBB integrity and allows for the infiltration of more inflammatory mediators into the brain to which these diseases are prone [24].

Evidence from Preclinical and Clinical Studies

Animal studies have shown the deleterious action of Ang II signalling in neurological disease animal models. In hypertensive models,/Wang et al/observed that chronic Ang II infusion induced neuro oxidative stress inflammation and increased permeability of the BBB and increased cognitive impairment and neuronal damage [15]. Likewise in models of AD, antagonizing AT1R with ARBs lowered amyloid-beta levels, enhanced synaptic plasticity and prevented cognitive impairment [10]. These observations have been supported by clinical studies as well. Some patients with hypertension take RAS inhibitors like ACE inhibitors and ARBs and from large studies, it is shown that these patients had less likeliness to get AD and stroke. There has also been evidence of enhanced global cognitive functioning and minimized cerebral vascular events among patients receiving RAS-targeting therapeutic products [25].

7. Angiotensin and Cardiovascular Disorders

Angiotensin-Driven Mechanisms in Cardiac Hypertrophy and Heart Failure

Interactions of Ang II with the cardiac tissue's structural and functional characteristics contribute to the pathophysiology of cardiac hypertrophy and heart failure. Ang II binding to AT1R is cytostimulatory and results in the activation of effectors such as MAP kinases and TGF- β that cause hypertrophy of myocytes, and increased accumulation of extracellular matrix molecules. This leads to raised myocyte stiffness and namely cardiac contractility. In heart failure, chronic activation of Ang II signalling impairs cardiomyocyte survival, causing fibrosis remodelling, a decline in LV systolic function, and reduced LVEF. It also fueled oxidative stress and inflammation in cardiac tissue and directly contributed to worsening heart failure through increased oxidation of cardiomyocytes damage and disruption of mitochondrial functionality.[26].

Vascular Complications Associated with Overactivation of RAS

Components of the renin-angiotensin system (RAS) are upregulated in diabetes with Ang II as the major operational molecule associated with vascular disease. Ang II directly enhances intracellular calcium levels in VSMCs and causes constriction of vessels thereby increasing system vascular

resistance and hypertension. It also provokes endothelial dysfunction through cytokine production by releasing pro-inflammatory cytokines, chemotactic factors, and activation of NADPH oxidase that produces ROS. These mechanisms cause endothelial dysfunction, reduce the availability of nitric oxide, and raise vascular stiffness. Chronic exposure to Ang II causes vascular remodelling, including VSMC proliferation and fibrosis, to promote atherosclerosis and augmentation of peripheral arterial and coronary artery diseases. Ang II also has promoted plaque instability of atherosclerosis leading to thrombosis and myocardial infarction [27].

Therapeutic Approaches Targeting Angiotensin Signaling

Angiotensin II signalling is currently one of the most important pharmacologic targets in the management of cardiovascular diseases, with several therapeutic strategies developed to minimize adverse Ang II effects [28]. One of the most commonly employed methods includes Angiotensin-Converting Enzyme (ACE) Inhibitors, including enalapril and lisinopril which prevent enzymatic alteration of Angiotensin I to Angiotensin II [29]. Through lowering Ang II levels, ACE inhibitors thereby reverse vasoconstriction, inflammation, and oxidative stress that have a therapeutic value in hypertension, heart failure, as well as recovery after myocardial infarction [30]. Another category of drugs is the Angiotensin Receptor Blockers (ARBs) comprised of losartan and valsartan which specifically block the angiotensin type 1 receptor (AT1R) [31]. It attenuates the undesirable actions of Ang II including vasoconstriction and fibrosis, however, the beneficial effects involve the type 2 receptor (AT2R) [32]. ARBs are most beneficial in reducing hypertension, reversing left ventricular hypertrophy, altering myocardial structure and slowing the progression of heart failure. Potentially a little higher on the Renin-Angiotensin System (RAS) chain are Direct Renin Inhibitors like aliskiren. As will be discussed under the mechanisms of action, both drug classes suppress the activity of renin thereby reducing the production of Ang I and consequently Ang II providing an effective alternate therapy to antihypertensive and cardiovascular diseases. Co-supporting these therapies is Aldosterone Antagonists a class of drugs that work against the downstream effect of Aldosterone that results from Ang II. In enhancing cardiovascular protection these agents also decrease sodium retention, vascular stiffness and myocardial fibrosis [28]. Together, these approaches of therapy form a conceptual foundation for intervention against the pathobiological effects of the AngII signalling pathway and have substantially enhanced the secondary prevention of cardiovascular disease in patients [17].

8. Therapeutic Implications and Future Perspectives

Therapies developed in the current era on cardiovascular and neurological diseases arising from angiotensin signalling include ACE inhibitors, ARBs, and DRI. These therapies have been brought out to reverse the pathological progression of hypertension to ameliorate cardiac remodelling and offer some end-protective effects against organ damage by counteracting the pathogenic impact of Ang II [33]. Not only do they work on key nodes of the RAS but also attenuate vasoconstriction and inflammation these drugs are effective in improving clinical outcomes in heart failure, stroke, and vascular dementia [23]. However, the requirement

for advanced and selective solutions has led to the search for novel approaches to treat RAS...This newest cancer treatment has an emphasis on targeted pathways and molecules in the RAS [24]. For instance, drugs specifically targeting the AT2R are being designed to take advantage of its anti-inflammatory action, vasodilator action, and neuroprotection without stimulating the adverse routes invoked by the AT1R [31-32]. Furthermore, those blocking ACE2 have been considered to target the degradation of the remaining beneficial Ang-(1-7), a bioactive peptide with vasoprotective effects [30]. Similarly, the systematic modulation of the RAS especially using gene editing technologies like CRISPR/Cas9 in isolating certain components of the RAS to Alzheimer's pathogenesis is proving promising for the development of biomarker-defined personalized medicine [34]. Thus, future direction in neurovascular medicine will seek to enhance understanding of the crosstalk between angiotensin signalling and neurovascular unit pathophysiology including; irritation and dysfunction of BBB [15]. Studies related to the contribution of localized RAS in the brain and its relation with neurovascular coupling and cognition are useful given the increasing incidence of neurodegenerative disorders. Further, the enhanced application of molecular approaches, biomarkers, and novel delivery systems creates additional opportunities for enhancing therapeutic effectiveness and selective toxicity. Such work shows that angiotensin-directed therapies may become a multipurpose approach towards managing a variety of cardiovascular and neurological diseases and improve patients' outcomes in the future decades [11].

Conclusion

Angiotensin II has a built-in dual role in the nervous system and blood vessels; it is a major controller of physiological processes and a signifier of pathophysiological changes [17]. In the nervous system, Ang II modulates neuroinflammation, oxidative stress, and blood-brain barrier disruption that may compromise neurological diseases including stroke, Alzheimer's disease, and Parkinson's disease [10]. Ang II has the same effects in the vascular system is very similar; Ang II controls the vascular tone and remodelling in the same system but also contributes to endothelial dysfunction, inflammation and hypertension leading to pathologies like atherosclerosis and HF. This interaction of the nervous and vascular systems demonstrates the complex and global consequences of Ang II signalling. Angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and renin inhibitors have become cornerstones of neurovascular and cardiovascular disease care because they selectively block the pathogenic actions of Ang II while preserving its physiological functions [28]. New drugs that target the AT2R and new horizons such as gene modification therapies provide new approaches to future therapies [32]. These studies of Ang II signalling along with its restricted roles in the brain and vasculature can provide a point to fine-tune these therapies for better patient care in the future. Overcoming the multifaceted effects of Ang II, such developments will alleviate patient's quality of life with neurovascular and cardiovascular diseases on a global scale [17].

Acknowledgement

The authors are grateful for the assistance given by Agnihotri Institute of Pharmacy. Wardha throughout this research work. We would like also

to acknowledge the support of colleagues and the encouragement of families during the work on this study.

Declaration of Competing Interest

The authors report no competing financial interests or other relationships that might be perceived as having influenced the work reported in this article.

References

1. Cantero-Navarro E, Fernandez-Fernandez B, Ramos AM, Rayego-Mateos S, Rodrigues-Diez RR, Sánchez-Niño MD, Sanz AB, Ruiz-Ortega M, Ortiz A. Renin-angiotensin system and inflammation update. Molecular and cellular endocrinology. 2021 Jun 1;529:111254.
2. Martyniak A, Tomasik PJ. A new perspective on the renin-angiotensin system. Diagnostics. 2022 Dec 21;13(1):16.
3. Gaur P, Saini S, Vats P, Kumar B. Regulation, signalling and functions of hormonal peptides in pulmonary vascular remodelling during hypoxia. Endocrine. 2018 Mar;59:466-80.
4. Wang X, Khalil RA. Matrix metalloproteinases, vascular remodeling, and vascular disease. Advances in pharmacology. 2018 Jan 1;81:241-330.
5. Lu Y, Hao R, Hu Y, Wei Y, Xie Y, Shen Y, Rui Q, Yu G. Harpagide alleviate neuronal apoptosis and blood-brain barrier leakage by inhibiting TLR4/MyD88/NF-κB signaling pathway in Angiotensin II-induced microglial activation in vitro. Chemico-Biological Interactions. 2021 Oct 1;348:109653.
6. Yi W, Chen F, Zhang H, Tang P, Yuan M, Wen J, Wang S, Cai Z. Role of angiotensin II in aging. Frontiers in Aging Neuroscience. 2022 Dec 2;14:1002138.
7. Mastorakos P, McGavern D. The anatomy and immunology of vasculature in the central nervous system. Science immunology. 2019 Jul 12;4(37):eaav0492.
8. de Barcelos Ubaldo Martins L, Jabour LG, Vieira CC, Nery LC, Dias RF, Simoes e Silva AC. Renin Angiotensin System (RAS) and Immune System Profile in Specific Subgroups with COVID-19. Current Medicinal Chemistry. 2021 Jul 1;28(22):4499-530.
9. Miesbach W. Pathological role of angiotensin II in severe COVID-19. TH open. 2020 Apr;4(02):e138-44.
10. Ahmed HA, Ishrat T. The brain AT2R—a potential target for therapy in Alzheimer's disease and vascular cognitive impairment: a comprehensive review of clinical and experimental therapeutics. Molecular neurobiology. 2020 Aug;57:3458-84.
11. Leung PS, Leung PS. Local RAS. The Renin-Angiotensin System: Current Research Progress in The Pancreas: The RAS in the Pancreas. 2010:69-87.
12. Elsaafien K, de Kloet AD, Krause EG, Sumners C. Brain angiotensin type-1 and type-2 receptors in physiological and hypertensive conditions: focus on neuroinflammation. Current hypertension reports. 2020 Jul;22:1-3.
13. Al Razee A. Pharmacologic Neuromodulation Targeting Neuroinflammation as a Novel Therapeutic Strategy for Experimental Pulmonary

Hypertension. University of California, Los Angeles; 2023.

14. Zhang YH. Neuronal nitric oxide synthase in hypertension–an update. Clinical hypertension. 2016 Nov 3;22(1):20.

15. Bild W, Vasincu A, Rusu RN, Ababei DC, Stana AB, Stanciu GD, Savu B, Bild V. Impact of the renin-angiotensin system on the pathogeny and pharmacotherapeutics of neurodegenerative diseases. Biomolecules. 2022 Oct 6;12(10):1429.

16. Guan Z, Lan H, Cai X, Zhang Y, Liang A, Li J. Blood–Brain barrier, cell junctions, and tumor microenvironment in brain metastases, the biological prospects and dilemma in therapies. Frontiers in Cell and Developmental Biology. 2021 Aug 24;9:722917.

17. Eguchi S, Kawai T, Scalia R, Rizzo V. Understanding angiotensin II type 1 receptor signaling in vascular pathophysiology. Hypertension. 2018 May;71(5):804-10.

18. Engin A. Endothelial Dysfunction in Obesity and Therapeutic Targets. Obesity and Lipotoxicity. 2024 Sep 18:489-538.

19. dos Passos RR, Santos CV, Priviero F, Briones AM, Tostes RC, Webb RC, Bomfim GF. Immunomodulatory activity of cytokines in hypertension: a vascular perspective. Hypertension. 2024 Jul;81(7):1411-23.

20. Dorey TW. Phosphodiesterases mediate neurohumoral regulation of sinoatrial node and atrial arrhythmogenesis.

21. Singh MR. *Angiotensin-II Signaling in the Pars Reticulata GABA-Ergic Neurons in the Substantia Nigra and Its Implications in Nigral Neurotransmission* (Doctoral dissertation, Colorado State University).

22. Ma J, Li Y, Yang X, Liu K, Zhang X, Zuo X, Ye R, Wang Z, Shi R, Meng Q, Chen X. Signaling pathways in vascular function and hypertension: molecular mechanisms and therapeutic interventions. Signal transduction and targeted therapy. 2023 Apr 20;8(1):168.

23. Sayed MA, Eldahshan W, Abdelbary M, Pillai B, Althomali W, Johnson MH, Arbab AS, Ergul A, Fagan SC. Stroke promotes the development of brain atrophy and delayed cell death in hypertensive rats. Scientific reports. 2020 Nov 19;10(1):20233.

24. Abiodun OA, Ola MS. Role of brain renin angiotensin system in neurodegeneration: an update. Saudi journal of biological sciences. 2020 Mar 1;27(3):905-12.

25. Ribeiro VT, de Souza LC, Simoes e Silva AC. Renin-angiotensin system and Alzheimer's disease pathophysiology: from the potential interactions to therapeutic perspectives. Protein and Peptide Letters. 2020 Jun 1;27(6):484-511.

26. Re RN. Role of intracellular angiotensin II. American Journal of Physiology-Heart and Circulatory Physiology. 2018 Apr 1;314(4):H766-71.

27. de Miranda FS, Guimarães JP, Menikdiwela KR, Mabry B, Dhakal R, layeequr Rahman R, Moussa H, Moustaid-Moussa N. Breast cancer and the renin-angiotensin system (RAS): Therapeutic approaches and related metabolic diseases. Molecular and Cellular Endocrinology. 2021 May 15;528:111245.

28. Ferrario CM, Mullick AE. Renin angiotensin aldosterone inhibition in the treatment of cardiovascular disease. Pharmacological research. 2017 Nov 1;125:57-71.

29. Wu C, Yin Z, Wang Y, Chen X, Li B, Wang Q, Yao L, Zhang Z, Liu X, Zhang R. The first bioactive (angiotensin-converting enzyme-inhibitory) peptide isolated from pearl matrix protein. Heliyon. 2024 Apr 15;10(7).

30. Bhullar SK, Shah AK, Dhalla NS. Mechanisms for the development of heart failure and improvement of cardiac function by angiotensin-converting enzyme inhibitors. Scripta Medica. 2022;53(1):51-76.

31. Mansour AM, Khattab MM, El-Khatib AS, Awaad AK, El-Refaie WM, El-Mezayen NS. Valsartan as a prophylactic treatment against breast cancer development and niche activation: What molecular sequels follow chronic AT-1R blockade?. Life Sciences. 2024 Sep 15;353:122939.

32. Juillerat-Jeanneret L. The other angiotensin II receptor: AT2R as a therapeutic target. Journal of medicinal chemistry. 2020 Feb 7;63(5):1978-95.

33. Nandave M. The Effect of ACE Inhibitors Vs. Angiotensin Receptor Blockers on Insulin Resistance in Hypertensive Patients. InAngiotensin-converting Enzyme Inhibitors vs. Angiotensin Receptor Blockers: A Critical Analysis of Antihypertensive Strategies: A Machine-Generated Literature Overview 2024 Oct 27 (pp. 223-275). Singapore: Springer Nature Singapore.

34. Kaur G, Arora J, Sodhi AS, Bhatia S, Batra N. Nanotechnology and CRISPR/Cas-Mediated Gene Therapy Strategies: Potential Role for Treating Genetic Disorders. Molecular Biotechnology. 2024 Oct 24:1-23.