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Review Article

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Mini-Review: Role of Drugs Affecting Renin-Angiotensin System (RAS) in Traumatic Brain Injury (TBI): What We Know and What We Should Know

Mohammad Kazem Sarpolaki [1,*], **Ali Vafaei** [2,*], **Mohammad Reza Fattahi** [3], **and Arad Iranmehr** [1]

[1]Neurological Surgery Department, Imam Khomeini Hospital Complex (IKHC), Tehran University of Medical Sciences (TUMS), Tehran, Iran
[2]Experimental Medicine Research Center, Department of Pharmacology, Tehran University of Medical Sciences (TUMS), Tehran, Iran
[3]Multiple Sclerosis Research Center, Neuroscience Institute, Tehran University of Medical Sciences (TUMS), Tehran, Iran

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Address for correspondence:
Arad Iranmehr
Neurological Surgery Department, Imam Khomeini Hospital Complex (IKHC), Tehran University of Medical Sciences (TUMS), Tohid Squre, Tehran 1419733141, Iran.
Email: arad.iranmehr@gmail.com

*Mohammad Kazem Sarpolaki and Ali Vafaei contributed equally to the work and should be considered co-first authors.

ORCID iDs
Mohammad Kazem Sarpolaki
https://orcid.org/0000-0001-7400-0503
Ali Vafaei
https://orcid.org/0000-0001-5747-1792
Mohammad Reza Fattahi
https://orcid.org/0000-0002-0770-0654
Arad Iranmehr
https://orcid.org/0000-0002-5932-9375

ABSTRACT

Traumatic brain injuries (TBIs) are among the most important clinical and research areas in neurosurgery, owing to their devastating effects and high prevalence. Over the last few decades, there has been increasing research on the complex pathophysiology of TBI and secondary injuries following TBI. A growing body of evidence has shown that the renin-angiotensin system (RAS), a well-known cardiovascular regulatory pathway, plays a role in TBI pathophysiology. Acknowledging these complex and poorly understood pathways and their role in TBI could help design new clinical trials involving drugs that alter the RAS network, most notably angiotensin receptor blockers and angiotensin-converting enzyme inhibitors. This study aimed to briefly review the molecular, animal, and human studies on these drugs in TBI and provide a clear vision for researchers to fill knowledge gaps in the future.

Keywords: Traumatic brain injury; Brain injury; Angiotensin; Renin-angiotensin system

INTRODUCTION

Traumatic brain injuries (TBIs) are among the most important clinical and research fields in neurosurgery, primarily because of their significant impact on society but also because of their prevalence.[8] TBIs are the leading cause of disability and mortality among young people, particularly in low-income countries. While there is an increased incidence of TBI in young people in developing countries (probably related to the increased use of motor vehicles), high-income or developed countries are facing a change in TBI patterns in which more older adults are also affected by TBIs (possibly related to decreased road accident injuries and increased prevalence of elderly falls).[31] Moreover, cases of TBI still persist in sports and the military. Therefore, TBI is a significant public health concern.[7,37]

In addition to surgical interventions, many studies have focused on pharmacological interventions for the treatment of TBI.[38] The pathophysiology of neural tissue damage

Conflict of Interest
The authors have no financial conflicts of interest.

following TBI is commonly divided into two types: primary and secondary. The primary injuries are caused by direct trauma. A range of mechanisms can cause secondary injury, including apoptosis, inflammation, and axonal degeneration.[3,26] Preventive strategies are the primary solutions for the first type of injury. Secondary injuries resulting from TBI are less well known but could play a crucial role in reducing morbidity and mortality. A variety of studies have been conducted in this field. Some have examined the molecular basis of pharmacological interventions to understand cellular damage pathways,[12] whereas others have examined the impact of a specific drug on TBI in animals[41] or humans.[43]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are drug groups used primarily to treat hypertension and have recently become the focus of TBI research.[4] The renin-angiotensin system (RAS), which is generally associated with the cardiovascular regulatory system, also significantly affects the brain, making it a potential target for developing new TBI treatments.[16,40,52,53] Following TBI, local RAS activation in the brain tissue may result in cellular damage and insult, contributing to neuroinflammation and progressive brain atrophy. Therefore, pharmacological interventions targeting the RAS have become an important research area for preventing and reducing brain injuries after trauma.[36]

RAS-related drugs mostly target the three main axes, which are discussed later in this paper. The rationale for using these drugs is to attenuate the pro-inflammatory effects of angiotensin (Ang) receptor type 1 (AT1R) and enhance the anti-inflammatory effects of angiotensin receptor type 2 (AT2R) and Ang-(1-7)/MasR pathways. Stimulation of AT1R by Ang-II activates the nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase complex, leading to pro-inflammatory and oxidative stress-promoting neurodegenerative processes. These effects are mediated by regulatory RAS (rRAS; Ang-[1-7]) signaling through the Mas receptor (MasR) and AT2R.[4,36]

In this narrative review, we discuss the drugs that affect the RAS in the context of TBI pathophysiology, animal studies, and clinical trials.

LOCAL AND SYSTEMIC RAS

RAS is an essential regulatory system for blood pressure and sodium levels. Angiotensinogen (ATG) is produced and secreted into the bloodstream by the liver and converted to Ang-I by renin, a protein synthesized by the kidneys. Subsequently, Ang-I is converted to Ang-II by ACE, which is produced in the lungs. Owing to its action on AT1R, Ang-II increases sodium reabsorption and water retention in the body. Although this has historically been known as the RAS pathway, recent studies have shown that the pathway is more complicated and detailed than previously thought.[4,16,40]

Studies have shown that organs such as the brain have a local RAS in addition to the body's systemic RAS. Early animal studies in the 1970s showed both the presence of renin and Ang-II in the brain, as well as the neuroactivity of Ang-II. Ang-II, in addition to its direct peripheral action on the vascular smooth muscles, was shown to have a central hypertensive effect acting directly on the brain.[6,18] Because renin and Ang-II are unable to cross the blood-brain barrier (BBB), later studies suggested that the brain produces all these enzymes and peptides independent of the systemic RAS via its own local RAS.[24,52,53]

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Another important breakthrough in understanding the local RAS in the brain was the discovery of novel peptides, receptors, and enzymes other than Ang-I and Ang-II in the pathways. Ang-IV, a derivative of Ang-III, which is derived from Ang-II, has been shown to have cognitive enhancing effects in animal models of learning and memory and to exert its effects via angiotensin receptor type 4 (AT4R), which is primarily distributed throughout the brain.[19] Ang-(1-7), a vasodilator derived mainly from Ang-II by ACE2, acts primarily via MasR, a receptor found in the brain as well as other parts of the body.

Overall, three main axes can be distinguished: ACE/Ang-II/AT1R, Ang-II/AT2R, and ACE2/Ang-(1-7)/MasR. The rationale behind the nomenclature of the axes is that AT1R, AT2R, and MasR are mainly activated by Ang-II (produced by ACE), Ang-II, and Ang-(1-7) (produced by ACE2), respectively. The effects of each axis are exerted through the downstream pathways of its receptors. In addition to natural ligands, receptors can be activated or inhibited through pharmacological or genetic manipulation.[4,40] AT1R activation leads to neuroinflammation, the induction of oxidative stress, BBB disruption, and cell death. In contrast to AT1R, AT2R induces DNA repair and cell differentiation.[16] In addition to its vasodilatory effect, Ang-(1-7) enhances learning and memory while providing neuroprotection. Additionally, genetically engineered MasR-knockout rats have been shown to have memory deficits.[16,40] Therefore, the ACE/Ang-II/AT1R axis is considered an antagonist of the other two axes (**FIGURE 1**). Ang-IV, which acts on AT4R, is also considered a neuroprotective pathway.[17]

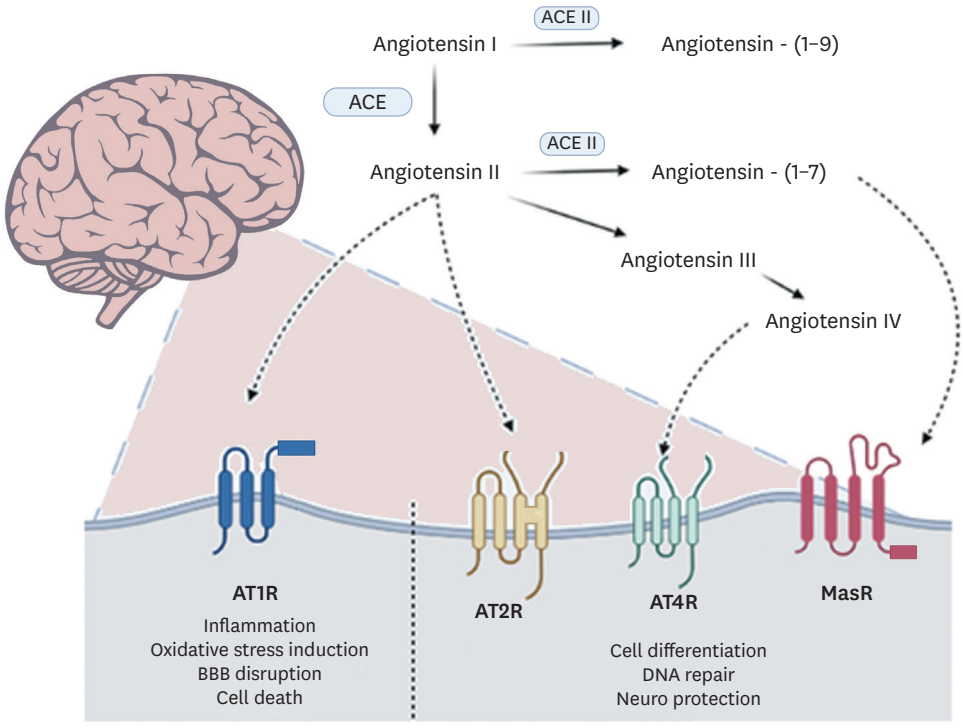

FIGURE 1. Overview of the suggested axes of the local RAS in the brain.
RAS: renin-angiotensin system, ACE: angiotensin-converting enzyme, AT1R: angiotensin receptor type 1, AT2R: angiotensin receptor type 2, AT4R: angiotensin receptor type 4, MasR: Mas receptor, BBB: blood-brain barrier.

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RAS IN TBI

The RAS network and its relationship to TBI can be classified into four main mechanisms: the direct mechanical effect of TBI on RAS, microglia-related effects of RAS, angiogenic effects of RAS, and intracellular RAS-mediated damage.[48]

Previous studies on cardiac myocytes have shown that AT1Rs can be activated by stretching alone, without ligands.[35,44] Similarly, it has been suggested that the mechanical impact of head injury on the brain could cause ligand-independent activation of AT1Rs, which may result in the induction of oxidative stress and the release of numerous inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-1, ultimately leading to cell death and apoptosis. Another interesting finding was that AT1R activation in the cerebral arteries of mice led to intense vasoconstriction following head injury. This can lead to decreased cerebral blood flow and secondary brain injury.[1,36,42]

Microglia are a specific type of glial cell that act as resident macrophages in the brain. In addition to their critical role in protecting the brain against different pathogens and infections, they play an important role in both cell differentiation and death in the brain.[22] Microglia respond differently to various microenvironments and circumstances. They also either induce inflammation or act as anti-inflammatory agents. Any change in the brain can result in the multidirectional activation of silent microglia.[13,30] TBI is no exception. Microglia play a pivotal role in both damage and recovery following TBI. Studies have shown a close relationship between these cells and RAS pathways in TBI. Animal studies have shown that some microglia in specific brain areas express AT1R mRNA. Specifically, microglia respond to oxidative stress via AT1R and differentiate into pro-inflammatory microglial cells. These cells then release inflammatory cytokines including IL-1, IL-6, and TNF-α which mediate cell apoptosis and death.[33,54] However, studies have suggested that microglia release anti-inflammatory cytokines (e.g., IL-10) in response to activation by IL-3 and IL-4. However, there is no evidence of a relationship between the anti-inflammatory responses of microglia and the RAS. These microglia produce low levels of reactive oxygen species (ROS) and nitric oxide (NO), promoting stem cell proliferation and differentiation.[15]

Furthermore, the RAS and TBI are linked by their role in angiogenesis. Neovascularization is crucial for functional recovery after TBI.[48] Studies have shown links between the RAS and angiogenic growth pathways. Specifically, there is evidence that vascular endothelial growth factor (VEGF) is regulated by AT1R via Ang-II.[23]

Studies have suggested that the RAS also acts intracellularly. For example, dopaminergic brain cells have been shown to express AT1R and AT2R, which primarily exist on the cellular and mitochondrial membranes. These two receptors act as regulatory systems for superoxide formation within the cells, thereby increasing or decreasing respiration.[27,39,45,49,50]

In a study on human and mouse brain tissue, treatment with recombinant human ACE2 suppressed the TBI-induced increase of Ang-II and decrease of Ang-(1-7) in the brain, mitigated neural cell death, reduced the activation of NLR family pyrin domain containing 3 and caspase-3, decreased phosphorylation of mitogen-activated protein kinases and nuclear factor kappa-light-chain-enhancer of activated B cells, and reduced inflammatory cytokines TNF-α and IL-1β.[32]

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RAS-RELATED DRUGS IN TBI

A number of drug classes which target different elements of the RAS pathway may be useful in treating TBI, given the significant role the RAS pathway plays in secondary injuries following TBI. Three main drug classes can be used to antagonize the development of the pro-inflammatory AT1R axis: ACE inhibitors, ARBs, and renin inhibitors. Additionally, AT2R and Ang-(1-7) receptor agonists and human recombinant ACE2 can be considered as potentially beneficial drugs because of their role in activating the AT2R and MasR axes, which antagonize AT1R. Currently, no clinical studies have examined the effects of these drugs on TBI, and only a limited number of animal studies have been conducted on their neuroprotective effects in TBI models.[48]

Over the past few decades, specific drug-induced alterations and pathways have been investigated in detail. For example, ARBs have different mechanisms for affecting the RAS, including the regulation of NO production[20,55] and brain-derived neurotrophic factor,[5,25] activation of peroxisome proliferator-activated receptors[51,56] and matrix metalloproteinase, and heat shock protein upregulation.[21,28,29,46] However, some evidence indicates that the non-RAS-related effects of ACE inhibitors (such as elevated bradykinin and substance *p* levels) could lead to increased brain swelling and damage. Several studies have shown that Ang-II receptors are present in the choroid plexus, and that ACE inhibitors affect CSF production. Therefore, local or systemic administration of ACE inhibitors could influence CSF production and result in intracranial pressure alterations in patients with TBI.[10,11,34]

Despite several non-TBI clinical studies showing the neuroprotective effects of RAS-regulating drugs, insufficient clinical studies address these drugs in TBI. However, animal studies have yielded promising results. The most commonly studied drugs are candesartan and telmisartan, which are both ARBs. Currently, there are limited studies on long- and short-term neurological outcomes, mortality, and secondary outcomes such as lesion volume and brain edema. Evidence for other drugs is limited because only one such study has been published.[48]

Animal studies have shown that candesartan and telmisartan have neuroprotective effects in rodents following TBI; lesion volume, neuronal injury and apoptosis, microglial activation, astrogliosis, and pro-inflammatory signaling were decreased, and cerebral blood flow was protected 1–3-days post-injury.[51] Another study treated mice with candesartan showed a significantly lower mortality rate following TBI than those in the control group.[47] In the aforementioned study, the mortality rates were reported in both adult and aged mice. All adult mice survived the experiment; however, post TBI mortality was significantly lower in the candesartan-treated group than in the control group (12.5% and 30%, respectively). These results seem to conflict with those of human studies that showed higher mortality rates after TBI among patients who used ACE inhibitors prior to the incident.[9] However, some essential factors need to be considered. First, it is important to note that human studies are limited to only one retrospective heterogeneous study, which administered various forms and unknown doses of ACE-I to patients prior to injury. Second, antihypertensive medications are typically prescribed to elderly patients. Because older age is an independent risk factor for higher morbidity and mortality following TBI, these patients are more likely to experience post-TBI insults. Third, ACE polymorphisms should be considered.[2] Fourth, published heterogeneous human studies are not considered strong evidence due to different drug usage among patients and varying effects of AT1R, AT2R, and AT4R on TBI.[14] Fifth, drug dosage is an important aspect. Previous animal studies used low-dose candesartan and

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telmisartan without significant effects on blood pressure. In future human studies, this is an important factor to consider as hypotension reduces cerebral blood flow and contributes to brain damage following TBI.[4,47,51]

CONCLUSION

TBI is a leading cause of mortality and morbidity. Over the past few decades, a growing body of evidence has demonstrated the crucial role of the local RAS pathway in secondary injuries after TBI. However, limited studies have currently been conducted on this topic. ACE inhibitors and ARBs are accessible drugs with known cardiovascular effects that can be investigated for their pre- and post-TBI effects. Further studies are required to determine the effects of ACE inhibitors and ARBs on TBI outcomes. We do not propose a multicenter retrospective human study among patients with TBI, because these drugs are generally prescribed for hypertension management. In the future, it may be beneficial to conduct a human randomized clinical trial with low-dose candesartan and blood pressure monitoring. Furthermore, specific AT2R and AT4R agonists may be interesting targets for animal studies.

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