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REVIEW ARTICLE

Involvement of the Renin-Angiotensin System in Stress: State of the Art and Research Perspectives

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Abstract: ***Background*:** Along with other canonical systems, the renin-angiotensin system (RAS) has shown important roles in stress. This system is a complex regulatory proteolytic cascade composed of various enzymes, peptides, and receptors. Besides the classical (ACE/Ang II/AT_1 receptor) and the counter-regulatory (ACE2/Ang-(1-7)/Mas receptor) RAS axes, evidence indicates that non-classical components, including Ang III, Ang IV, AT_2 and AT_4, can also be involved in stress.

***Objective and Methods*:** This comprehensive review summarizes the current knowledge on the participation of RAS components in different adverse environmental stimuli stressors, including air jet stress, cage switch stress, restraint stress, chronic unpredictable stress, neonatal isolation stress, and post-traumatic stress disorder.

***Results and Conclusion*:** In general, activation of the classical RAS axis potentiates stress-related cardiovascular, endocrine, and behavioral responses, while the stimulation of the counter-regulatory axis attenuates these effects. Pharmacological modulation in both axes is optimistic, offering promising perspectives for stress-related disorders treatment. In this regard, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are potential candidates already available since they block the classical axis, activate the counter-regulatory axis, and are safe and efficient drugs.

Keywords: Renin-angiotensin system, stress, neurobiology, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers.

1. INTRODUCTION

The renin-angiotensin system (RAS) is a complex regulatory proteolytic cascade composed of various enzymes, peptides, and receptors that are classically involved in a variety of physiological functions, including the humoral control of blood pressure and hydro electrolyte balance [1-3]. The generation of the RAS peptides begins with the angiotensinogen (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-Ile…), an α-2-globulin mainly produced by the liver, which is cleaved in the amino-terminal portion by renin, an aspartyl protease, forming the decapeptide angiotensin (Ang) I (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu). Ang I is then converted into the octapeptide Ang II (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe) by the carboxyl dipeptidase angiotensin-converting enzyme (ACE). Other enzymes can also make this conversion, such as tonin, chymase, and cathepsin G. Ang II acts through two main G-protein-coupled receptors, AT_1 and AT_2. However, the majority of the effects of Ang II are conveyed by the AT_1 receptor. In addition to the classical components, there are other biologically active peptides, such as Ang III [Ang-(2-8)] and Ang IV [Ang-(3-8)] [1, 4, 5].

Over the past few decades, several new components have been identified and added to the RAS. Most of these components are described as having counter-regulatory effects against the classical ACE/Ang II/AT_1 receptor axis. Ang-(1-7) (Asp-Arg-Val-Tyr-Ile-His-Pro) is a heptapeptide, which can be formed directly from Ang II with high catalytic efficiency by the monopeptidyl carboxypeptidase ACE homolog enzyme, ACE2, or other peptidases, including prolyl endopeptidase (PEP) and prolyl carboxypeptidase (PCP) [6-9]. ACE2 can also cleave Ang I to generate Angiotensin (1-9) (Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu). In addition, Ang-(1-7) can be formed directly from Ang I by endopeptidases including neprilysin, PEP, neutral endopeptidase (NEP) and thimet oligopeptidase (TOP). Ang-(1-7) is a ligand of the G protein-coupled Mas receptor [10], which is expressed in the brain, testis, heart, blood vessels, and kidney among other organs [11, 12]. The ACE2/Ang-(1-7)/Mas receptor axis counteracts or modulates the actions of the classical RAS axis [8].

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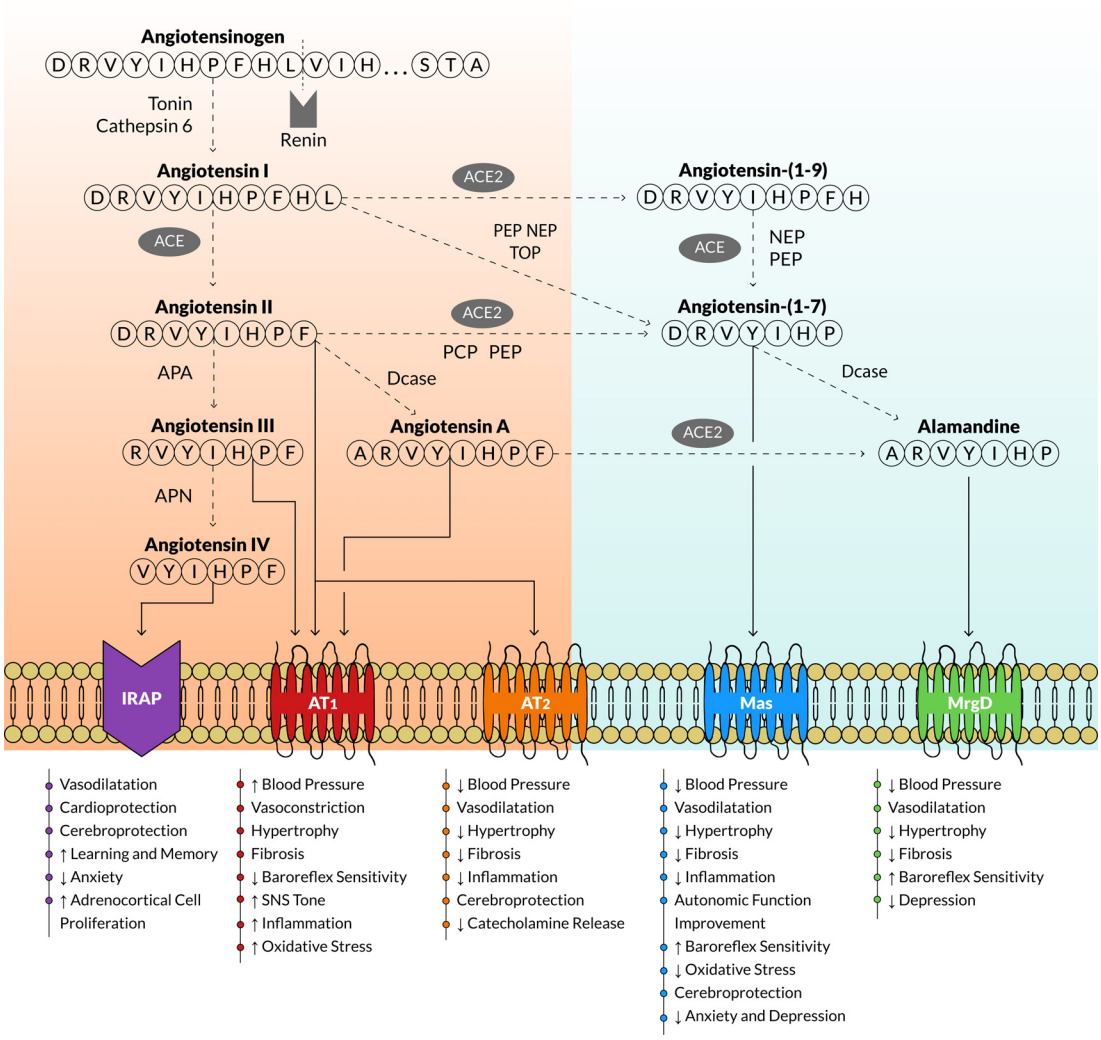

Fig. (1). The renin-angiotensin system cascade: updated simplified view.
Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Ang I, angiotensin I; Ang II, angiotensin II; Ang-(1-7), angiotensin-(1-7); Ang-(1-9), angiotensin-(1-9), Ang A, angiotensin A; AT_1, angiotensin type-1 receptor; AT_2, angiotensin type 2 receptor; Mas, Ang-(1-7) receptor Mas; MrgD, Mas-related G-protein coupled receptor; IRAP, insulin-regulated amino peptidase; APA, aminopeptidase A; APN, aminopeptidase N; DCase; DC, decarboxylase; NEP, neutral endopeptidase; PEP, prolyl endopeptidase; PCP, prolyl carboxypeptidase; Thimetoligopeptidase (TOP); SNS, sympathetic nervous system. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

More recently, Alatensins (Ang A and Alamandine) and Mas-related G-protein-coupled (MrgD) receptors have been described [13, 14]. Ang A [Ala^1-Ang II] is an octapeptide and only differs from Ang II by having an Ala^1 instead of Asp^1 due to decarboxylation of Asp^1 residue. Ang A has the same affinity for AT_1 receptors as Ang II, with a slightly higher affinity for AT_2 receptors [13]. Alamandine [Ala^1-Ang-(1-7)] is a heptapeptide, which can be formed directly from Ang A by the ACE2. Moreover, this peptide can be produced directly from Ang-(1-7) through decarboxylation of the N-terminal aspartate amino acid residue. Alamandine stimulates the MrgD receptor [14, 15]. Fig. (**1**) shows a simplified updated view of the RAS.

Stress is a state of threatened homeostasis, mobilizing adaptation mechanisms, searching for survival and for the return to body homeostasis [16]. The stress generates psychological, cardiovascular, and neuroendocrine effects, such as tachycardia, cortisol (human trials) and catecholamine (experimental models) release [17-19]. Different stressors interact with the brain networks, leading to a quick hypothalamus-pituitary-adrenal (HPA) and sympathetic-adrenal-medullary (SAM) axes activation. This promotes the release of stress related hormones, like glucocorticoids and Ang II. However, stress responses differ in conformity with the duration and its consequences at long and short term [20].

Many central nervous system (CNS) regions are involved in stress response, especially the limbic structures, including prefrontal cortex (PFC), amygdala, hippocampus, paraventricular nucleus of the hypothalamus (PVN), and dorsomedial hypothalamus (DMH) [21-24]. Among these regions, it is worth noting that the PFC is a sensitive brain region for detrimental stress exposure effects and is vulnerable to impacts in cognitive abilities and behavioral plasticity [25, 26]. Additionally, damage to the pre limbic cortex (PL), one

of PFC's sub regions, upregulates glucocorticoid plasma levels [27, 28].

Ang II modulates the neuroendocrine system and is considered an important stress hormone [29-32]. Enhancement of Ang II produced by stress seems to contribute to the cardiovascular, neurological, and renal disorders [33-41]. On the other hand, increasing evidence indicates that the counter-regulatory RAS axis modulates and attenuates the physiological responses to stress [42, 43].

In this paper, we review the literature regarding studies that examined the contribution of RAS and its classical axis inhibitors and blockers in different adverse environmental stimuli stressors, including air-jet stress, cage switch stress, restraint stress, chronic unpredictable stress (CUS), neonatal isolation stress and post-traumatic stress disorder (PTSD).

2. RAS AND ADVERSE ENVIRONMENTAL STIMULI

Adverse environmental stimuli are a stress phenomenon related to the way the organism feels and behaves in response to the environment. The animal perceives the environment and usually its external aspects, including luminosity, isolation, scents, temperature, weather, and many others [44]. How the organism deals with comforting or damaging situations in life are both also intrinsically related to this concept. In this regard, psychological and social factors result in the activation of mechanisms that interact with RAS, such as the autonomic nervous system and the HPA axis. This explains the relationship between RAS and its regulating role in environmental changes [45-49].

2.1. Air-jet Stress

The air-jet stress model consists of puffing compressed air against subjects, immobilized or not, for a defined period of time, which can vary from pulse to continuous airflow. This type of stress produces marked increases in sympathetic output, especially to the cardiovascular system, that is modulated by RAS components [50, 51].

In 1995, Coste *et al*. (1995) [52] proposed that RAS could be relevant for the increment of stress-induced hypertension in borderline hypertensive rats. Chronicle exposure to air-jet stress significantly increased blood pressure in these rats, but the treatment with captopril, an angiotensin converting enzyme inhibitor (ACEi), prevented this effect, even with the maintenance of higher plasma renin levels.

De Matteo *et al*. (2006) [53] suggested that Ang II modulates the cardiovascular response to air-jet stress through DMH. The group demonstrated that bilateral microinjection of candesartan, an angiotensin-receptor blocker (ARB), into the DMH in mice attenuated pressor and tachycardic stress reactions. These findings indicated that Ang II participates in cardiovascular stress regulation and that it occurs, at least in part, via DMH region. Veelken *et al*. (1996) [54] observed that Ang II also modulated renal sympathetic nerve activity (RSNA) mediated responses evoked by the air-jet stress protocol. The group observed that ZD7155, an AT_{1A} receptor blocker was able to suppress the anti-natriuretic and antidiuretic effects in response to air-jet stress. Indeed, ZD7155 successfully inhibited or annulled this sympathetic renal nerve mediated effects, demonstrating the modulation role of endogenous Ang II renal sympathetic functional effects related to this type of stress.

An exaggerated RSNA after air-jet stress protocol was observed in Wistar-Kyoto rats that had a chromosome 1 blood pressure quantitative trait locus introgressed from stroke-prone spontaneously hypertensive rats (WKYpch1.0). Yamazato *et al*. (2006) [50] noticed that intracerebroventricular (ICV) injection of candesartan suppressed the sympathetic overreaction induced by the stress procedure to a greater extent in WKYpch1.0 than in Wistar-Kyoto mice. Thus, the study reinforced that this RSNA exaggerated response against air-jet stress is mediated by the RAS. Moreover, Lim *et al*. (2015) [55] demonstrated that chronic Ang II treatment elevated RSNA by recruitment of neurons, which is similar to chemo reflex stimulation, but not to stress or baroreceptor activation, suggesting that parasympathetic pathways activated by Ang II may be common to those activated by chemoreceptors. Of importance, Ang II enhanced total RSNA responses to air jet stress.

Nonetheless, Martins Lima *et al.* (2013) [56] investigated the counter-regulatory RAS axis involvement in this scenario, showing the effects of the peripheral and central administration of Ang-(1-7) and XNT (1-[(2- dimethylamino) ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl) sulfonyloxy]-9H-xanthene-9-one), an ACE2 activator, on cardiovascular responses evoked by air-jet stress. The heptapeptide attenuated the tachycardic response induced by this stress protocol, likely due to a modulatory action on ß-adrenergic mechanisms in cardiomyocytes. Furthermore, peripheral injection of the ACE2 activator compound, XNT, abolished the tachycardia induced by acute stress.

Taken together, these studies indicated that RAS modulates the sympathetic cardiovascular response elicited by air-jet stress. However, more experiments are needed to provide an expanded view of RAS responses in this type of stress protocol.

2.2. Cage Switch Stress

Cage switch stress consists in removing a rat from its home cage and placing it into another identical cage [57]. These placements vary in accordance with the time interval chosen for putting the animals in different cages [58]. The procedure commonly generates cardiovascular alterations, such as tachycardia and increased blood pressure.

In 2009, Davern *et al*. (2009) [59] analyzed the importance of AT_{1A} receptors in mice for neuronal responsiveness and cardiovascular reaction to stress. After cage switch stress, AT_{1A} knockout mice had attenuated heart rate and increased blood pressure, along with a preserved spontaneous baroreflex sensitivity that was not inhibited by stress in these animals. It was identified a lower c-Fos immunoreactivity in PVN, DMH nucleus, and rostral ventrolateral medulla in AT_{1A}knockout mice. Conversely, higher immunoreactivity was also observed in the medial nucleus of the amygdala, nucleus of the solitary tract and caudal ventrolateral medulla. The results indicating that the greater activation of the amygdala in AT_{1A} knockout mice, when compared with wild type, may suggest that AT_{1A} receptors are involved in the attenuation of anxiety induced by stress. On the other hand, The weaker activation in the hypothalamus

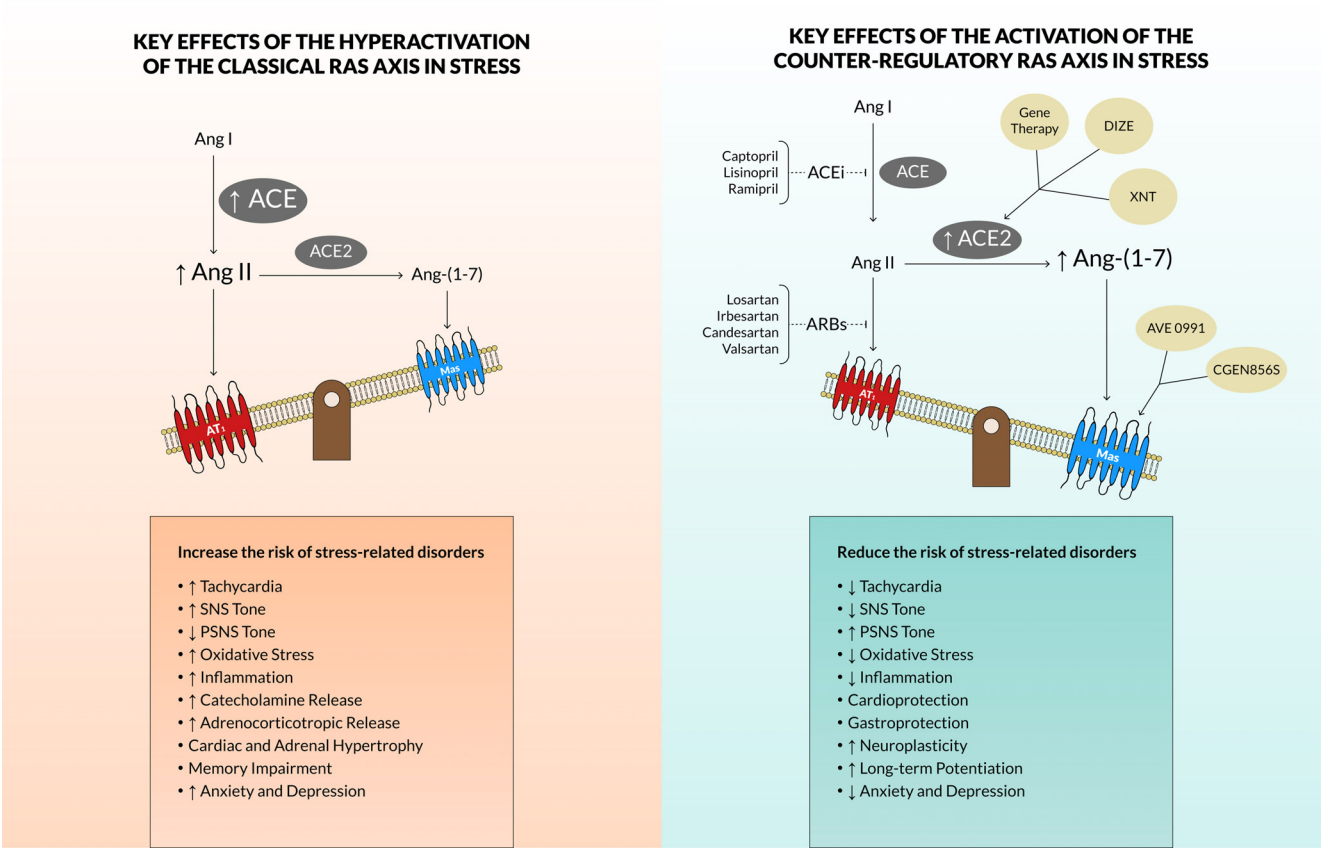

Fig. (2). Schematic diagram of the RAS axis in stress-related disorders.
Abbreviations: ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Ang I, angiotensin I; Ang II, angiotensin II; Ang-(1-7), angiotensin (1-7); AT_1, angiotensin type-1 receptor; Mas, Ang-(1-7) receptor Mas; ACEi, angiotensin-converting enzyme inhibitor; ARBs, angiotensin-receptor blockers; DIZE, diminazene aceturate; XNT, 1-[(2-dimethylamino)ethylamino]-4-(hydroxymethyl)-7-[(4-methylphenyl)sulfonyloxy]-9H-xanthene-9-one; AVE0991, Mas-receptor agonist; CGEN-856S, Mas-receptor agonist; SNS, sympathetic nervous system; PSNS, parasympathetic nervous system. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

and rostral ventrolateral medulla activation may be due to the AT_{1A} receptors importance in autonomic cardiovascular reactions triggered by cage switch stress, as well as in stress-induced inhibition of the baroreflex.

In Schlager mice (an animal with naturally increased blood pressure due to over activation of the sympathetic nervous system), losartan, an AT_{1A} receptor antagonist, attenuated the sustained pressor response provoked by cage switch stress. Palma-Rigo *et al*. (2011) [60] analyzed this result and suggested that RAS has crucial roles in sympathomodulatory activity through the inhibition of sympathetic vasomotor tone and long-lasting sympathetic activation during long periods of stress. Moreover, to better understand the pressor response provoked by cage switch stress, Chen *et al*. (2012) [61] investigated the influence of AT_1 receptors expressed and located in the majority of C1 neurons of the rostral ventrolateral medulla. During this stress model, AT_1 receptor expression in these neurons produced higher and sustained pressor responses. This finding indicates that AT_1 expression in C1 neurons is the key for pressor response through Ang II in cage switch stress.

Oscar *et al*. (2015) [43] observed that microinjection of Ang-(1-7) into the BLA of rats attenuates the pressor and tachycardic responses triggered by the cage switch stress model. These effects were completely reversed by the Mas-receptor antagonist, A779. More recently, Silva *et al*. (2020) showed that the tachycardic response was also attenuated in rats injected with diminazene aceturate (DIZE), another ACE2 activator, into the basolateral amygdala (BLA), a brain region related to sympathetic reactions during acute stress [62].

Furthermore, Tazumi *et al*. (2016) [63] analyzed how estrogen replacement affects RAS activation in cardiovascular responses generated in cage switch stress. Ovariectomized female mice were subcutaneously implanted with 17β estradiol or placebo. The animals were submitted to cage switch stress, increasing blood pressure, and heart rate differently in both groups. The increase in heart rate and blood pressure was attenuated in the estradiol group and it was identified higher plasma renin activity and Ang II in the placebo group. Since losartan abolished the pressor response in both groups, authors suggested that, during stress, the inhibitory effects of

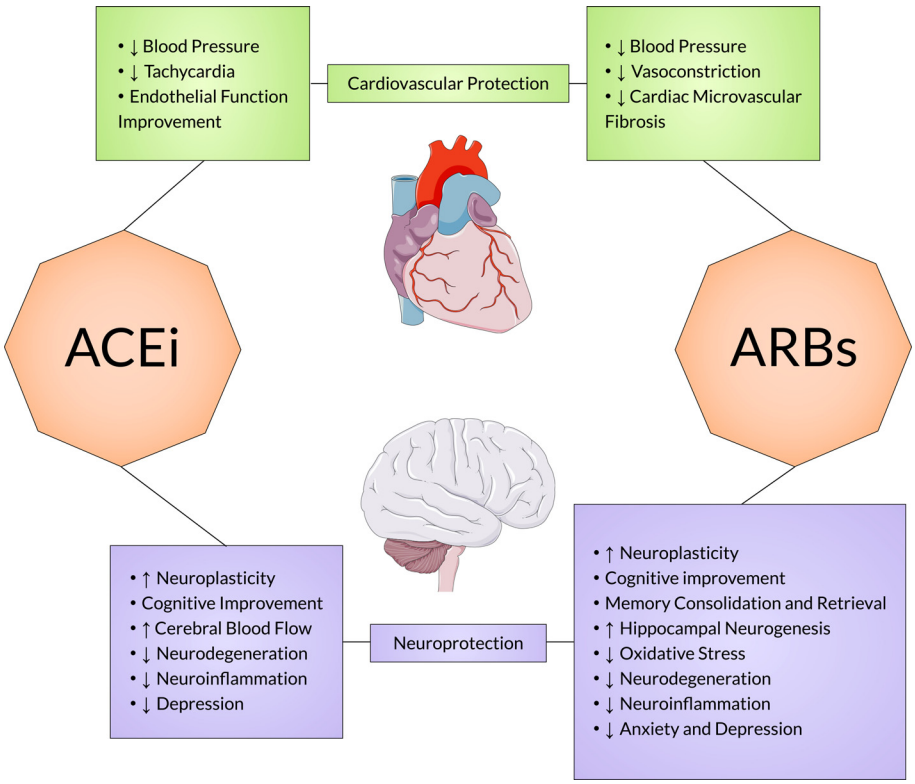

Fig. (3). Main effects of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin-receptor blockers (ARBs) in stress-related disorders. *(A higher resolution/colour version of this figure is available in the electronic copy of the article).*

estrogen on RAS activation are partially due to the suppression of pressor response in this type of psychological stress.

The neuropharmacological perspective for ACEi as a possible therapy for attenuating stress-mediated autonomic responses was also explored in the cage switch model. Lee *et al*. (2004) [64] observed that captopril blocked the pressor response provoked by cage switch stress exposure. The result indicates the participation of ACE in this sympathetic mediated response.

In order to improve the treatment strategies for stress reactions, non-classical RAS compounds also have proven to participate in thermic reactions triggered by the cage switch stress model. Watanabe *et al.* (1999) [65] detected that brain AT_2 receptors participate in immunological stress-induced fever in mice. During cage switch stress, AT_2KO mice exhibited greater hyperthermia, proposing the participation of this receptor in hyperthermia induced by stressful occurrences.

To sum up, cage switch stress is strongly associated with cardiovascular disturbances. Most studies associated the classical RAS axis with these sympathetic autonomic responses. Preliminary evidence indicates that the counter-regulatory RAS axis may become a potential neuropharmacological strategy for the treatment development.

2.3. Restraint Stress

Restraint stress (rendering the animal immobile) activates the hypothalamus, the amygdale, and the locus coeruleus [66], resulting in marked sympathetic activation. The increase in sympathetic activation evoked by acute restraint stress (ARS) upregulates tissular and circulating Ang II concentrations as a consequence of renin release [40, 67-77]. This experimental model was used in a substantial number of studies investigating the role of RAS components in stress effects. Restraint stress results in varied effects, including tachycardia, catecholamine release, anxiety and ulcers [78-82]. Thus, cardiovascular, neuroendocrine and gastrointestinal effects were discussed below in separate subtopics.

2.3.1. Cardiovascular Effects

Ang II and the sympathetic nervous system synergistically increase the heart rate and exert short-term cardiovascular control in response to restraint stress [47, 83, 84]. In accordance, Busnardo *et al*. (2014) [85] found that bilateral microinjection of losartan or lisinopril (an ACEi) in the PVN inhibited the pressor response to ARS, but without interfering in tachycardic response.

In rats, microinjection of lisinopril into the prelimbic cortex reduced the pressor response, but without avoiding the ARS-evoked tachycardia. When pretreated with candesartan, there was a reduction of the ARS-evoked pressor response, but still no alteration in the tachycardia effect. Surprisingly, the pretreatment with PD123177, an AT_2 receptor antagonist, reduced the tachycardia effect, but no changes were noted in the ARS pressor response. The study suggested the contribution of RAS receptors in the PL region in regulating ARS cardiovascular reactions. Further, PL AT_{1A} receptors seemed to be associated with pressor response, while PL AT_2 receptors, to the tachycardic component of the response [86].

Uresin *et al*. (2004) [87] investigated the effects of losartan in heart rate and the changes in plasma corticosteroids

associated with stress-induced cardiovascular alterations by restraint stress. Losartan significantly inhibited the elevation of plasma corticosteroids in both acute and chronic protocols. However, in agreement to previous studies, the heart rate variability provoked by ARS was not prevented by AT_{1A} blockade. Additionally, Costa Ferreira *et al*. (2016) [88] verified that losartan inhibits autonomic activity and baroreflex impairment provoked by this stress type.

Lu *et al*. (2017) [89] identified an increase in serum levels of corticosterone and Ang II in an experiment that combined restraint and acoustic stress. This association of stressors induced heart failure in C57BL/6 mice that were previously submitted to transverse aortic constriction surgery, a model of pressure-overload heart failure. The treatment with irbesartan, an ARB, reduced vasoconstriction, lowering the vulnerability to stress responses and premature hypertension development. Results showed lower survival probability for stressed animals and reinforced the role of Ang II production in modulating cardiovascular effects produced by stress [90].

To evaluate the RAS pathway in these cardiovascular alterations evoked by restraint stress, rats were treated with subcutaneous infusions of Ang II or Ang-(1-7) for one week. Unexpectedly, Ang II attenuated the increase in mean arterial pressure and produced bradycardia in the first 3 days of restraint stress protocol but progressively returned to a similar heart rate frequency of the control period. This result indicates that Ang II can influence brain response to stress and blood pressure without altering heart rate fluctuations. On the other hand, the Ang-(1-7) infusion reduced baseline mean arterial pressure but did not alter mean arterial pressure response to the restraint stress, supporting only a regulatory role for Ang-(1-7) on basal mean arterial pressure, while produces a small but significant and sustained bradycardia [91]. These findings are intriguing since they contradict the current view of the classic versus the counter-regulatory RAS axes in physiological responses.

2.3.2. Neuroendocrine Effects

Repeated restraint stress increases AT_{1A} receptor expression in the anterior parvocellular division of the PVN, where corticotropin-releasing factor (CRF) a stimulator of adrenocorticotropic hormone synthesis, can be formed [92]. This indicates that AT_{1A} may be involved in the mediation of CRF production in endocrine stress response [93]. Corroborating this finding, Saavedra *et al*. (2006) [78] identified that pretreatment with candesartan avoided the increase in CRF levels observed in rats submitted to restraint stress. Therefore, since stress is a state with higher corticosteroid levels, increased brain AT_{1A} receptor expression is possibly associated with this hormonal and sympathoadrenal response.

Nostramo *et al.* (2012) [80] observed that the AT_2 receptor is extremely sensitive to restraint stress, presenting a reduction of its mRNA expression. On the other hand, AT_{1A} receptors remained at the baseline levels after the stress protocol. This was one of the first studies that investigated the modulatory effect of Ang II receptors on catecholamine synthesis. Tyrosine hydroxylase and dopamine β-hydroxylase mRNA levels in PC12 cells, a cell line in the adrenal medulla with endogenous catecholamine modulated by both hydroxylases, were reduced following the administration of AT_1 (ZD7155) and AT_2 (CGP42112) receptors antagonists. Therefore, it was shown that restraint stress on adrenomedullary AT_{1A} and AT_2 receptors could lead to allosteric alterations, including the modulation of catecholamine biosynthesis. This type of stress also alters the binding of receptors when catecholamine biosynthetic enzymes levels are elevated [94].

Even further, restraint stress was used to investigate gene expression alterations through the classical and non-classical RAS receptors in rat's adrenal medulla [95]. Nostramo *et al*. (2015) [95] identified an increase in the expression of some RAS receptors before repeated restraint stress. The AT_2 receptor expression was the most increased, followed by AT_{1A}, AT_4 and Mas receptors, in this order. After the stress protocol, it was found a transient reduction of all these receptors, except for AT_1. Additionally, the model provided an elevation in angiotensinogen and ACE gene expression after repeated exposure, suggesting an important role for Ang II production in prolonged stress. Accordingly, the expression of ACE2 mRNA was reduced after both single and repeated stress, which may reduce non-Ang I and non-Ang II compounds' formation in order to increase Ang II levels as an adaptive response to constant and repeated stress exposure. These findings indicate the participation of classical and non-classical RAS components in adrenomedullary mechanisms to stress.

Despite the role of the AT_4 receptor in the adrenal still being unclear, the authors showed an AT_4 predominance in both the medulla and adrenal cortex's outer layer. This result supports previous studies reporting AT_4 expression in the same regions in bovines [96] and relates with the investigations of Pawlikowski *et al.* (2001) [97] that identified Ang IV as capable of stimulating adrenocortical cell proliferation through the AT_4 receptor. More studies are still required to further understand how Ang IV and AT_4 receptors can act upon this model of stress.

The counter-regulatory RAS axis involvement in neuroendocrine effects related to restraint stress was also investigated. Through a bilateral infusion of Ang-(1-7) into the ventral hippocampus in combination with Ro256981, an NMDAR receptor antagonist, results confirmed anxiolytic effects of this RAS peptide due to its modulation. The study also indicated that Ang-(1-7) ameliorates 5-HT neurotransmitter imbalance and anxiety provoked by chronic restraint stress. The heptapeptide was able to restore mood processing of the ventral hippocampus during emotional stress-related episodes, reinforcing a role for Ang-(1-7) mediation of anxiety-like behaviors in this brain area [98].

2.3.3. Gastrointestinal Effects

Zhu *et al.* (2014) [81] suggested a gastro protective potential for Ang-(1-7) in restraint stress. During the conduction of the study, gastric mucosal lesions were induced in rats by a two-hour cold-restraint stress exposure. These lesions were attenuated after ICV treatment with Ang-(1-7), preventing the increase of stress mediators levels such as Ang II, corticosterone, norepinephrine, serotonin, and dopamine in the brain regions associated with stress. Additionally, these Ang-(1-7) effects were inhibited by A779, a Mas receptor antagonist. The anti-stress property of Ang-(1-7)

could restore the gastric environment and its circuitry, being a potential target for gastric diseases, such as stress-associated ulcerations. Moreover, after conducting restraint stress in rats, Yisireyili *et al*. (2018) [99] suggested that AT_1 antagonists can have a potential therapeutic effect in stress-induced intestinal inflammation, and that irbesartan could be beneficial for the treatment of irritable bowel syndrome in patients suffering from stress. Overall, given that restraint imposes several physiological responses, this model has been widely used to investigate the contribution of RAS components in cardiovascular, neuroendocrine, and gastrointestinal effects produced by stress.

2.4. Chronic Unpredictable Stress

Chronic unpredictable stress (CUS) is extensively used in preclinical research. The protocol of this model is composed of random, sporadic, varied, and unexpected stress exposure factors on animals for continuous weeks [100]. CUS generates behavioral and physiological alterations including depressive-like behavior, anxiety [100-102], and cardio metabolic dysregulations [103-106]. The reactions to CUS involves activation of HPA and SAM axes [107] with central consequences, such as hippocampal synaptic deficits [108], lowered brain-derived neurotrophic factor (BDNF) [109] and decreased hippocampal volume [101].

Firoozmand *et al.* (2018) [103] described that CUS causes a state of microvascular disease associated with increased production of catecholamines and an Ang II/Ang-(1-7) imbalance in the cardiac tissue, favoring Ang II production and promoting perivascular fibrosis. The group also found that low doses of losartan recovered the Ang II/Ang-(1-7) balance through the blockade of Ang II effects, offering a protective effect on cardiac microvascular impacts by preventing the increase of perivascular collagen deposition. It is known that ACEi and ARBs upregulate Ang-(1-7) levels presumably by NEP or ACE2 pathways [110-112]. Besides, similarly to the effects presented in restraint stress, losartan has also proven to inhibit baroreflex impairment and autonomic reactivity in CUS [88].

It was demonstrated that CUS could upregulate hypothalamic Ang I, Ang II, and Ang IV concentrations, and increase plasma levels of corticosterone, adrenaline and noradrenaline, besides inducing depressive-like behavior and loss of learning and memory ability in mice. Interestingly, an enriched environment was capable of attenuating this behavior and related endocrine alterations, presenting a protective property against CUS consequences [106, 113, 114]. Hypothalamic Ang-(1-7) levels were not altered in experiments, indicating that CUS responses to stress mainly involve classical RAS pathways [114].

Evidence indicates that depressive-like behavior is related to the generation of reactive oxygen species. In stress situations, these molecules derived from mitochondria are overproduced and take place in the lipid peroxidation of brain lipid rich membranes, causing oxidative stress and apoptosis or necrosis [115-118]. These effects can be measured by stress markers in the brain, such as thiobarbituric acid reactive substances (TBARS), tissue glutathione (GSH), and *in situ* catalase (CAT). Ayyub *et al.* (2017) [118] showed that chronic treatment with irbesartan significantly elevated the brain monoamines levels and decreased oxidative stress after CUS protocol. These changes were consistently associated with antidepressant effects, since it was observed an increase of 5-HT levels in the brain and a reduction of oxidative stress by reducing TBARs levels and increasing CAT and GSH levels. This highlights a relevant action of ARBs against oxidative stress and its consequences.

It is well known that depression and anxiety models provide suppression in the generation of hippocampal progenitor cells and in the survival of hippocampal neurons, which can be reverted by antidepressants and even by exercises [119]. Interestingly, Ping *et al.* (2014) [102] found that the treatment with valsartan, an AT_1 receptor antagonist, stimulated hippocampal neurogenesis and BDNF expression in mice submitted to CUS, resulting in an antidepressant-like effect. The evidence not only reinforced the potential effects of ARBs against depression and anxiety-like behavior induced by stress but also indicated a promising antidepressant and anxiolytic mechanism related to RAS that deserves better understanding.

The neuronal effects of CUS protocols are also related to neurodegenerative disorders. These conditions act like psychiatric risk factors, such as psychological, psychosocial, and physical stress [120], worsening neurological disease progression [121-123], especially age-related ones, such as Alzheimer's disease (AD) [124]. It was observed that Ang II production in animals decreased the neurodegeneration in experimental AD models [124, 125] as well as slowed cognitive deterioration in AD patients [126-130].

According to AbdAlla *et al*. (2015) [131], the CUS-associated neurodegeneration involves ACE. Hippocampal ACE levels and gene expression were upregulated not only in brain vessels but also in neuronal cell bodies. This overexpression is associated with CUS activation of the HPA axis since ACE expression seems to be linked to the glucocorticoid levels and its receptor stimulation [132-134]. The study also found that captopril minimizes the CUS effects on neurodegeneration, slowing AD progression [131]. However, this neuroprotective effect produced by ACEi is still not completely elucidated.

Despite several studies indicating that RAS peptides are responsible for ACEi antidepressant effects in CUS models, a recent research suggested that they actually would only mediate these effects indirectly. According to Luo et al. (2020) [135], ACEi produced a rapid and long-lasting annulment of stress-induced depressive-like behaviors by enhancing the BK-B2R-Cdc42-mTORC1 signaling pathway. The group found that the downregulation of Ang II function is apparently insufficient to perform antidepressant effects in CUS mice. These effects seem to be independent of the RAS molecules, but dependent on the bradykinin (BK) system, since captopril reversed the CUS induced reduction of BK in stressed mice. By activating the mammalian target of rapamycin complex 1 (mTORC1) pathway, captopril quickly reversed the stress-induced loss of dendritic spines, which is a result of the hypofunction of the downstream effector of BK, the cell division control protein 42 (Cdc42) homolog. Furthermore, ACE seemed to block the mTOR signaling

pathway [136, 137], but more studies are required to understand this mechanism.

In order to investigate the mechanism of ACEi rapid antidepressant effects, the authors also tested if other RAS-acting agents could mimic this action [135]. It was observed that renin inhibitors and ARB drugs could present antidepressant responses against CUS, but none of them produced this effect as quickly as ACEi did, suggesting that the inhibition of ACE is the most effective pharmacological strategy. Furthermore, when comparing ACEi drugs, lisinopril demonstrated a much faster response due to its better blood-brain barrier permeability [138].

In conclusion, RAS involvement on alterations associated with CUS protocols still need further investigations, but the preliminary findings indicate that interference with RAS components can attenuate CUS effects. Pharmacological modulation of both classical and counter-regulatory RAS axes seems to counteract the depressant and angiogenic effects produced by this model.

2.5. Neonatal Isolation

Some studies have shown that early adverse environmental experiences can be related to the development of vulnerability to stress factors at an older age. A variety of newborn's experiences of adversity, such as neonatal isolation, can affect postnatal development [139]. Studies also described this condition as a chronic behavioral stress model that imitates the effects of early life stress on cardiovascular, neuroendocrine, and metabolic responses [140, 141].

Most studies have focused on neonatal separation effects regarding hypertension, obesity, and Ang II dependent activation in the adipose tissue. Female mice exposed to neonatal isolation and early weaning displayed an Ang II-dependent hypertension through RAS upregulation in the adipose tissue. The rats exposed to this model of stress and fed with a high-fat diet showed increased arterial pressure associated with higher Ang II concentration in adipose tissue. The expression of ACE was similar in the low-fat diet group, suggesting an upregulation of the angiotensinogen peptide. In consequence, these effects contribute to obesity and its related disorders. Along with these interpretations, chronic ACEi treatment diminished mean arterial pressure in these rats submitted to neonatal isolation, proposing it as a possible pharmaceutical strategy for lowering the risk of associated cardiovascular diseases, such as uncontrolled hypertension [142].

Adequate levels of Ang II in postnatal development are necessary for normal maturation of the kidney [143,144]. Male rats exposed to maternal separation continued normotensive but expressed higher sex-specific renal function reduction and higher Ang II-mediated vascular reactions during adulthood [145,146]. In order to understand further short- and long-term effects of these stress mechanisms, Dalmasso *et al*. (2020) [146] analyzed the renal tissue from rats submitted to maternal separation and observed lower renal filtration capacity and increased renal expression of AT_1 and AT_2 receptors, which were associated with a reduction of Ang II intrarenal levels. These effects were hypothesized as being caused by Ang III increased degradation by amino peptidase A, but this theory still requires further elucidation.

Moreover, it was identified an increase in ACE expression and a decrease in ACE2 expression and activity, along with the attenuation of the known anti-angiogenic effects of Ang-(1-7) [147-149]. The authors suggested that rats exposed to maternal separation might have further changes within the renal microvascular response to intrarenal RAS imbalance due to unusual upregulation of angiogenic factors [146]. In summary, RAS components play a role in neonatal isolation stress effects by influencing cardiovascular and metabolic responses.

2.6. Post-traumatic Stress Disorder

PTSD is a complex psychiatric disorder characterized by the intrusive re-experiencing of past trauma, hypervigilance, increased reactivity to unpredictable versus predictable threat signals, enhanced fear, deficits in fear extinction, and an inability to discriminate between threat and safety. This type of stress is generated by exceptional life events and is associated with mood disorders, anxiety, substance abuse and higher risk for suicidal behavior [150].

In terms of neurobiology, the PTSD state involves similar physiological characteristics in comparison to chronic stress, such as reduced hippocampal volume, higher CRF concentration, and modulation of catecholamine levels in the CNS. Additional PTSD observations differ from the common stress reaction pattern, including lower plasma and urinary cortisol levels. This reduction is generated by increased negative feedback produced by cortisol due to higher sensitivity of glucocorticoid receptors in specific tissues. On the other hand, the sensitization of the HPA axis is in consonance with the hyper reactivity and hyper responsiveness phenotypes encountered in PTSD patients [151, 152].

In the neuroendocrine picture, many ARBs are being considered as potential treatments of CNS disorders, considering the Ang II participation in the cerebral circulation, inflammation, learning, and memory [153-155]. Indeed, US veterans using ACEi and ARBs for cardiovascular disorders presented a reduction of PTSD symptoms [156]. This confirms the association of the antihypertensive properties of ACEi and ARBs with a reduction of PTSD symptoms [157].

Aiming to understand the role of Ang II in PTSD avoidance-like symptoms and memory impacts, Bonini *et al*. (2006) [158] tested memory retention in rats after infusion of Ang II into the CA1 region of the dorsal hippocampus. In rats tested in the inhibitory avoidance training, open field test and elevated plus maze test, it was observed that the Ang II effects in amnesia were blocked by PD123319, an AT_2 receptor antagonist, but not by losartan. These results also indicated that intra-CA1 Ang II hinders retrieval of avoidance memory, involving the activation of AT_2 receptors. Additionally, Benicky *et al.* (2011) [159] analyzed cerebral inflammation, a frequent PTSD consequence [160], and found that systemic administration of candesartan decreased the acute brain inflammatory response evoked by PTSD. Altogether, these studies [158, 159] indicate that AT_1 and AT_2 receptors may be targets for PTSD treatment.

Table 1. Summary of key RAS effects and mechanisms related to stress.

Air-jet Stress	• Renal sympathetic nerve activity overreaction against air-jet stress is mediated by the RAS [50]. • Ang II modulates cardiovascular stress regulation through the dorsomedial hypothalamus [53]. • Activation of ACE2/Ang-(1-7)/Mas receptor axis attenuates the cardiac reactivity to air-jet stress [56].
Cage Switch Stress	• Ang-(1-7) injected into the basolateral amygdale attenuated the pressor response evoked by cage switch stress [43]. • AT_{1A} receptors have important roles in autonomic cardiovascular responses [59]. • ACE2 activator injected into basolateral amygdala successfully attenuated tachycardic response [62]. • Inhibitory effects of estrogen on stress-induced RAS activation could be partially responsible for suppressing the pressor response to psychological stress [63]. • Captopril treatment decreased mean arterial pressure enhancement induced by cage switch stress [64]. • AT_2 receptors play important roles in stress-induced hyperthermia in mice [65].
Restraint Stress	• Ang-(1-7) prevents stress-induced gastric lesions in rats [81]. • Through prelimbic treatment, ACEi and ARBs showed potential in reducing pressor response and tachycardia [86, 88]. • Losartan inhibits plasma corticosterone elevation, autonomic sympathetic activity and baroreflex impairment [87, 88]. • Ang-(1-7) presents a regulatory role on basal mean arterial pressure by reducing baseline mean arterial pressure [91]. • AT_1 receptors seem to be involved in the mediation of corticotropin-releasing hormone production [93]. • Restraint stress alters the binding of receptors when catecholamine biosynthetic enzymes are upregulated [94]. • AT_4 and Mas receptors genes expression were transiently decreased in the adrenal medulla [95]. • Ang IV was capable of stimulating adrenocortical cell proliferation through AT_4 receptor [97]. • Ang-(1-7) can ameliorate 5-HT neurotransmitter imbalance in anxiety-like behavior during stress [98]. • Irbesartan inhibits stress-induced intestinal inflammation through AT_1 signaling and activation of the ACE2 pathway [99].
Chronic Unpredictable Stress	• Losartan seems to have a protective effect on the cardiac tissue by reverting the disbalance of Ang II/Ang-(1-7) induced by CUS [103]. • ARBs presented antidepressant and anxiolytic effects. Authors suggested BDNF protagonism in this phenomenon by regenerating the hippocampal neurogenesis [102]. • Irbesartan elevated brain monoamine levels and reduced oxidative stress [118]. • ACEi performed a rapid antidepressant effect, especially lisinopril due to its better blood-brain barrier permeability [135, 138].
Neonatal Isolation Stress	• ACEi treatment diminished mean arterial pressure [142]. • Rats exposed to maternal separation displayed lower renal filtration capacity and increased renal expression of AT_1 and AT_2 receptors, which were associated with a reduction of Ang II intrarenal levels [146]. • Rats exposed to maternal separation displayed an increase in kidney ACE expression and a reduction in ACE2 expression and activity in postnatal life [146].
Post-traumatic Stress Disorder	• Veterans treated with ARBs showed improvement in PTSD symptoms [155]. • Intra-CA1 Ang II difficult the retrieval of avoidance memory by a mechanism that involves activation of AT_2 [158]. • Candesartan reduces the acute brain inflammatory response, a common PTSD symptom [159]. • Upregulation of the brain RAS and proinflammatory cytokines contribute to sensitization of the hypertensive response to Ang II [163].

Abbreviations: Ang II, Angiotensin II; Ang-(1-7), Angiotensin-(1-7); ARBs, angiotensin-receptor blockers; AT_1 angiotensin type-1 receptor; AT_2, angiotensin type 2 receptor; ACE, angiotensin-converting enzyme; ACEi, angiotensin-converting enzyme inhibitor; CUS, chronic unpredictable stress; PTSD, post-traumatic stress disorder; RAS, Renin-angiotensin system.

In 2012, Khoury *et al*. (2012) [161] made the first analysis examining the effects of ACEi in individuals after exposed trauma. The study showed a considerable association between ACEi/ARBs treatment and reduction of PTSD symptoms. These medications could attenuate hyper arousal and other common intrusive reactions.

Furthermore, Marvar *et al.* (2014) [155] administered losartan in mice submitted to the classical Pavlovian fear conditioning and analyzed gene alterations in neuroendocrine imbalances, including brain and cardiovascular responses. Authors found an enhancement of consolidation of extinction memory for both acute and chronic losartan administered groups, but the chronic treated group also presented reduced AT_1 receptor expression in the amygdala. These findings suggest a capability of AT_1 receptor antagonists in enhancing extinction of fear memory, being beneficial for PTSD treatment.

Recently, Parrish *et al.* (2019) [162] evaluated adult female SD rats with losartan injected intraperitoneally and tested fear extinction procedures. The study showed that ovariectomy and hormonal contraceptives, associated with higher estradiol levels, are capable of producing deficits of fear consolidation extinction. Losartan treatment diminished these deficits, but much remains to be cleared about sex properties. The study suggests that AT_1 receptors antagonists, associated with lower estradiol levels, can minimize these symptoms of PTSD in females.

Additionally, in the same year, Xue *et al*. (2019) [163] demonstrated enhanced hypertensive reactions in rats infused subcutaneously with Ang II after being submitted to the resident-intruder paradigm procedure. An upregulation in the mRNA expression of RAS components and proinflammatory cytokine were identified, possibly contributing to the sensitization of the hypertensive reaction generated by Ang II. The results indicate a potential for further analysis in relation to PTSD, Ang II and predisposal of hypertension development.

Interoceptive triggers, such as CO_2 inhalation, threaten physiological homeostasis and raise emotional responses in PTSD subjects. In order to test fear behavior, Winter *et al*. (2019) [164] tested the effect of ICV injections of losartan and identified an attenuation of the freezing reaction induced by CO_2 inhalation. This indicated a probable action of the AT_1 receptor in modulating contextual fear.

Recently, Xue *et al*. (2020) [31] found that the hypertensive and anxiety-like behavior evoked by predator scent stress, a PTSD model, are related to RAS components and inflammatory state. Clinical signs of anxiety detected in the elevated plus-maze test were associated with higher plasma levels of Ang II and increased expression of proinflammatory cytokines in stress-related brain regions, such as the PVN. ACEi blocked these effects, reinforcing that the upregulation of some RAS components and inflammatory markers are linked with blood pressure control and anxiety. In conclusion, just a few studies identify a direct association between RAS peptides and PTSD. Most of them are related to a symptom generated by this type of stress and that is why the contribution of RAS components in PTSD deserves further investigation. Table **1** summarizes the relevant findings in each stress model and (Fig. **2**) represents a schematic diagram of the RAS axis in stressrelated disorders.

CONCLUSION

In this review, we show that the RAS components are strongly associated with the response of different adverse environmental stimuli stressors, which is confirmed by studies using air-jet stress, cage switch stress, restraint stress, CUS, neonatal isolation stress, and PTSD. Some components of the classical RAS axis have been reported to contribute to several conditions associated with emotional stress, including hypertension, depression, anxiety, and even neurodegenerative diseases. On the other hand, the counter-regulatory RAS axis seems to have a protective role, reducing the effects mediated by the classical axis. In this regard, Ang-(1-7) has been described as the main counter-regulatory component of Ang II/AT_1 receptor effects, attenuating pressor and tachycardic responses, exerting anxiolytic and antidepressant actions, and improving cognition. Despite some studies indicating that Ang II effects at the AT_1 receptor are opposed by actions at the AT_2 receptor, a deeper understanding of this interaction in stress responses remains to be determined.

Blockade of the classical RAS axis and activation of the counter-regulatory RAS axis can be an additional strategy for the treatment of stress-associated disorders, as summarizes (Fig. **3**). In this regard, ARBs and ACEi are potential candidates already available because they block the classical axis, activate the counter-regulatory axis, and are safe and efficient drugs.

LIST OF ABBREVIATIONS

ACE	=	Angiotensin-converting Enzyme
ACE2	=	Angiotensin-converting Enzyme 2
ACEi	=	Angiotensin-converting Enzyme Inhibitor
AD	=	Alzheimer's Disease
Ang I	=	Angiotensin I
Ang II	=	Angiotensin II
Ang III	=	Angiotensin III
Ang IV	=	Angiotensin IV
Ang-(1-7)	=	Angiotensin-(1-7)
Ang-(1-9)	=	Angiotensin-(1-9)
Ang A	=	Angiotensin A
ARBs	=	Angiotensin Receptor Blockers
ARS	=	Acute Restraint Stress
AT_1	=	Angiotensin II Type 1 Receptor
AT_2	=	Angiotensin II Type 2 Receptor
AT_4	=	Angiotensin Type 4 Receptor
BDNF	=	Brain-derived Neurotrophic Factor
BK	=	Bradykinin
BLA	=	Basolateral Amygdala
B2R	=	B2 Receptor
CAT	=	Catalase
Cdc42	=	Cell Division Control Protein 42
CNS	=	Central Nervous System
CRF	=	Corticotropin-releasing Factor
CUS	=	Chronic Unpredictable Stress

DMH	=	Dorsomedial Hypothalamus
GSH	=	Glutathione
HPA	=	Hypothalamus-pituitary-adrenal
ICV	=	Intracerebroventricular
MrgD	=	Mas Related G-protein Coupled Receptor
TORC1	=	Mammalian Target of Rapamycin Complex
NEP	=	Neutral Endopeptidase
PCP	=	Prolyl Carboxipeptidase
PEP	=	Prolyl Endopeptidase
PFC	=	Prefrontal Cortex
PL	=	Prelimbic Cortex
PTSD	=	Post-traumatic Stress Disorder
PVN	=	Paraventricular Nucleus of the Hypothalamus
RAS	=	Renin-angiotensin System
RSNA	=	Renal Sympathetic Nerve Activity
SAM	=	Sympathetic-adrenal-medullary
TBARS	=	Thiobarbituric Acid Reactive Substance

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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