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REVIEW ARTICLE

Brain Angiotensinergic Regulation of the Immune System: Implications for Cardiovascular and Neuroendocrine Responses

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Abstract: ***Objective:*** The Renin-Angiotensin-Aldosterone System (RAAS) plays a major role in the regulation of cardiovascular functions, water and electrolytic balance, and hormonal responses. We perform a review of the literature, aiming at providing the current concepts regarding the angiotensin interaction with the immune system in the brain and the related implications for cardiovascular and neuroendocrine responses.

Methods: **A**ppropriate keywords and MeSH terms were identified and searched in Pubmed. Finally, references of original articles and reviews were examined.

Results: Angiotensin II (ANG II), beside stimulating aldosterone, vasopressin and CRH-ACTH release, sodium and water retention, thirst, and sympathetic nerve activity, exerts its effects on the immune system *via* the Angiotensin Type 1 Receptor (AT 1R) that is located in the brain, pituitary adrenal gland, and kidney. Several actions are triggered by the binding of circulating ANG II to AT 1R into the circumventricular organs that lack the Blood-Brain-Barrier (BBB). Furthermore, the BBB becomes permeable during chronic hypertension thereby ANG II may also access brain nuclei controlling cardiovascular functions. Subfornical organ, organum vasculosum lamina terminalis, area postrema, paraventricular nucleus, septal nuclei, amygdala, nucleus of the solitary tract and retroventral lateral medulla oblongata are the brain structures that mediate the actions of ANG II since they are provided with a high concentration of AT 1R. ANG II induces also T-lymphocyte activation and vascular infiltration of leukocytes and, moreover, oxidative stress stimulating inflammatory responses *via* inhibition of endothelial progenitor cells and stimulation of inflammatory and microglial cells facilitating the development of hypertension.

Conclusion: Besides the well-known mechanisms by which RAAS activation can lead to the development of hypertension, the interactions between ANG II and the immune system at the brain level can play a significant role.

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1. INTRODUCTION

The Renin-Angiotensin System (RAS) is the major physiological regulator of blood pressure and body fluid homeostasis. Aldosterone releases from the adrenal glands, Vasopressin (VP) secretion from VPergic neurons of hypothalamic Supraoptic (SON) and Paraventricular Nuclei (PVN), central stimulation of thirst induced *via* Circumventricular Organs (CVOs) as Organum Vasculosum Of The Lamina Terminalis (OVLT) and Subfornical Organ (SFO), sodium and water retention from the kidney, vasoconstriction and sympathetic stimulation, activation of the immune system, in particular at the Bone Marrow (BM) level, and are mainly due to the stimulation of type 1 receptor (AT 1R) by circulating Angiotensin II (ANG II) [1-3].

The enzymatic cascade leading to the synthesis of ANG II starts from the renin, an aspartyl protease synthetized in the juxtaglomerular apparatus of the kidney, which cleaves angiotensinogen, an α-2-globulin released into the circulation by the liver, to form the decapeptide Angiotensin I (ANG I). Once formed, ANG I is cleaved by the Angio-

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tensin-Converting Enzyme (ACE), a dipeptidyl carboxypeptidase located into the capillaries of the lungs and kidney epithelial cells, to produce the octapeptide ANG II. Further enzymatic processes by aminopeptidase A and N removing the amino-terminal aspartic acid produce, respectively, ANG III and ANG IV.

ANG II acts by stimulation of tissue-specific G-Protein-Coupled Receptors (GPCRs) classified into AT 1R and AT 2R. GPCRs are signal transducers, by their binding to cell surface membrane, that connect receptors to effectors and thus to intracellular signaling pathways [4, 5].

AT 1R and AT 2R are located in the brain, pituitary and adrenal gland, and kidney. Several studies indicate a key role of AT 1R in the physiological mechanisms of ANG II. It has been identified that two subtypes of AT 1R: the AT 1aR and the AT 1bR [6-8], synthesized from different genes, namely Agtr 1a and Agtr 1b, which activation by the ligand, however, leads to similar effects [1, 9-11]. More specifically, AT 1aRs are predominantly involved in aldosterone and VP release, sodium and water retention, vasoconstriction and sympathetic activation, while AT 1bRs mediate drinking behavior induced by ANG II.

Mice Knockout (KO) for the gene of AT1 receptor showed impaired water intake response to ANG II [12]. Moreover, water intake and sodium appetite elicited by central administration of ANG II is completely inhibited by the AT 1R antagonist losartan, but not by AT 2R antagonists [13, 14]. It has been postulated that ANG II, by binding to AT 1R, induces water intake and sodium appetite by separate intracellular signaling pathways: 1) activation of Protein Kinase C (PKC), the G protein-dependent pathway, and 2) activation of Mitogen-Activated Protein (MAP) kinase, the G protein-independent pathway. It has been reported that PKC is involved in water intake but not in NaCl intake induced by ANG II, and conversely MAP kinase is involved in NaCl intake but not in water intake after ANG II administration. In fact, the PKC inhibitor chelerythrine reduced water intake induced by ANG II, but it did not affect NaCl intake. On the other hand, a MAP kinase inhibitor reduced NaCl intake, but it did not affect water intake induced by ANG II, thus showing the existence of separate intracellular signaling pathways coming to divergent behavioral responses of AT 1R activation [15].

Circulating ANG II is a peptide too large and hence it is not able to cross the Blood-Brain Barrier (BBB); therefore, its action is mediated by activation of receptors located within the CVOs that lack the BBB. CVOs receive the signal of peripheral ANG II and *via* efferent pathways transmit it to hypothalamic and brainstem nuclei controlling cardiovascular system [16]. Moreover, it has been observed that an increased BBB permeability during hypertension allows access of circulating ANG II to brain areas that are normally excluded as the PVN, the Nucleus of the Solitary Tract (NTS) and Rostral Ventral Lateral Medulla (RVLM) oblongata [17, 18]. Chronic treatment with the AT 1R antagonist losartan prevented the breakdown of the BBB thus showing that peripheral ANG II *via* AT 1R, in addition to acting at CVOs, increases BBB permeability and consequently is able to reach brain cardiovascular-regulating nuclei [18].

A relationship between circulating levels of ANG II and dietary salt intake has been reported. When sodium intake increases, plasma ANG II levels decrease and, consequently, the sympatho-excitatory effects of ANG II decrease. On the other hand, reduced dietary salt intake increased ANG II and aldosterone levels stimulating sympatho-excitatory pathway, thus showing that arterial pressure maintenance is the result of the balance between sympatho-inhibitory and sympatho-excitatory mechanisms [19].

AT 2Rs seem to play opposite effects to AT 1Rs, as they induce vasodilator responses and a decrease in renal tubular sodium retention [20, 21].

In addition to circulating ANG II acting on target tissues, a local RAS synthesis is also present in several tissues with the role of autocrine or paracrine function. Tissue RAS has been found in the brain [22], heart, vessel wall and adrenal gland [23], adipose tissue [24], pancreas [25], uterine tissue and placenta [26] and kidney [23, 27]. All components of the RAS are present in the brain and local synthesis of ANG II contributes to hypertension development. The (pro)renin receptor, a transmembrane receptor that binds renin and prorenin, is upregulated in the brain of hypertensive animals [28] and transgenic hypertensive mice with selective knockdown of the (pro)renin receptor in SFO showed reduced hypertension, sympathetic tone and VP release. Deoxycorticosterone acetate (DOCA)-salt, inducing brain increase of (pro)renin expression and angiotensin synthesis, provokes hypertension and sympathetic activation. These effects are attenuated in neuron-specific (pro)renin receptor KO mice [29] and following intracerebroventricular administration of a (pro)renin receptor antagonist [30]. In addition, transgenic mice carrying a conditional allele of the endogenous AT 1R in the SFO were unable to increase arterial blood pressure, sympathetic cardiac activity, VP release, water and salt intake in response to DOCA-salt [31].

2. BRAIN ANGIOTENSIN RECEPTORS IN THE ACTIVATION OF THE IMMUNE SYSTEM

Among the various actions of ANG II in the brain, the activation of immune responses has been highlighted thus suggesting a role of immune system in the pathogenesis of hypertension [32]. It has been observed that lesions of the Anteroventral Third Ventricle (AV3V) region, where SFO and OVLT are located, prevent central actions of ANG II as T-lymphocyte activation and vascular infiltration of leukocytes thus showing that hypertension induced by ANG II is mediated, at least in part, by T-lymphocyte activation and vascular inflammation [33]. An important role is played by the oxidative stress. In fact, it has been reported that the reduction in the SFO of the extracellular antioxidant enzyme superoxide dismutase, that catalyzes dismutation of superoxide anion into hydrogen peroxide and oxygen, induced a significant increase in T-lymphocyte and vascular infiltration of leukocytes following ANG II administration [34]. In addition, deletion of NADPH oxidase in the SFO eliminated hypertension and vascular inflammatory responses to ANG II [35].

Several mechanisms may be involved in the regulation of immune system and hence in immune responses to brain

ANG II actions, as stimulation of sympathetic nerve activity, inhibition of parasympathetic tone, and activation of immune cells of lymphoid organs, mainly the BM, the primary site of hematopoietic cell production in the body [3, 32, 36]. Indeed, it has been reported that ANG II, centrally administered, modulates the immune system increasing splenic cytokine gene expression *via* sympathetic nervous system [37]. These data indicate a relationship between ANG II, autonomic inputs to the BM and inflammatory status [3]. It has been observed that elevated oxidative stress in brain cardiovascular-regulating nuclei causes an increase in Inflammatory Cells (ICs) and a decrease in Endothelial Progenitor Cells (EPC), that play an important role in the repair and maintenance of vascular endothelium, favoring thereby the development of hypertension. Administration of ANG II induces a decrease in EPCs and an increase in ICs in BM. This dysregulation of EPCs/ICs was blunted by an antioxidant dismutase-mimetic, centrally administered, normalizing EPCs/ICs ratio and blood pressure [38]. Similar data have been observed in Spontaneously Hypertensive Rats (SHR), where a dysfunctional relationship between BM and sympathetic nerve activity is associated with decreased EPCs and increased ICs [3]. These results indicate that ANG II-induced oxidative stress in brain cardiovascular centers, as PVN, SFO, RVLM and NTS, leads to inflammatory responses by inhibiting EPCs and hence vascular reparative mechanisms *via* inputs to the BM. Moreover, ANG II causes activation of microglial cells, that play an important role in the brain autoimmunity [39], inducing an increase in the mRNA for inflammatory cytokines as Interleukin (IL) 1β, IL-6 and Tumor Necrosis Factor (TFN)α in PVN. Minocycline, as anti-inflammatory antibiotic, reduces significantly hypertension, cardiac hypertrophy and sympathetic nerve activity following ANG II infusion *via* reduction of inflammatory cytokines, thus suggesting that hypertension induced by ANG II is dependent to microglia activation that increases pro-inflammatory cytokines in the PVN [40]. Microglial cells express AT 1R, and inhibition of PVN AT 1R causes a significant decrease of high blood pressure in SHR [40]. In addition, pro-inflammatory molecules as junctional adhesion molecules, that regulate leukocyte-platelet-endothelial cell interactions, were over-expressed in endothelial cells of NTS as well as vascular infiltration of leukocytes was observed in SHR as compared to normotensive rats. This vascular leukocyte accumulation increases hypoperfusion in the NTS inducing the secretion of pro-inflammatory molecules that modifying molecular mechanisms of NTS, one of the principal brainstem nuclei controlling arterial pressure [41].

Therefore, ANG II by promoting activation of the immune system increases inflammatory cells and their transport to the brain where vascular infiltration of leukocytes and reduction of EPCs facilitate the hypertensive action of brain ANG II (Fig. **1**).

3. BRAIN ANGIOTENSIN RECEPTORS IN THE CONTROL OF DRINKING BEHAVIOR, BLOOD PRESSURE AND HORMONE RELEASE

CVOs, mainly SFO and OVLT, localized in the periventricular tissue of the Anteroventral Third Ventricle (AV3V region), and AP, localized at the transition of 4th ventricle to the central canal, contain specific ANG II binding sites and are involved in the control of drinking behavior, salt appetite, blood pressure and hormonal outputs [42-45]. The capillaries of CVOs are fenestrated and therefore the Blood Brain Barrier (BBB) is missing. This lack of BBB allows the brain to receive peripheral signals concerning modifications of circulating ions, hormones and related molecules, therefore, the anatomical position of CVOs is strategic in the control of homeostatic functions [46-48].

4. SUBFORNICAL ORGAN (SFO) AND ORGANUM VASCULOSUM LAMINA TERMINALIS (OVLT)

The SFO and OVLT function as central receptor sites for peripherally circulating ANG II [46, 49, 50]. Ablation of the SFO and OVLT reduces water or NaCl intake induced by ANG II systemically administered [46, 51, 52]. On the other hand, ANG II directly injected into the SFO or OVLT increased water or NaCl intake [53-55]. High levels of AT1 receptors expression have been localized in CVOs [56], as well as neurons activation [57] and c-Fos expression [58] have been observed in SFO and OVLT during ANG II administration. Also, electrophysiological studies showed ANG II responsiveness of SFO neurons *via* the inhibitory role of ANG II on transient outward K+ currents [59].

SFO and OVLT angiotensin receptors play a role also in the control of blood pressure *via* stimulation of VP and renal sympathetic nerve activity. It has been reported that a significant reduction of hypertension induced by peripheral administration of ANG II in rats with electrolytic lesions of SFO or OVLT [54, 60-63]. Furthermore, ANG II injected directly into the SFO elicits pressor effects that are blocked by the AT 1 receptor antagonist saralasin thus showing SFO is a site of ANG II pressor action in addition to that of thirst [54].

However, these actions of SFO may be mediated by median preoptic nucleus since destruction of this nucleus blocked thirst induced by ANG II, thus suggesting synaptic inputs arising from the SFO are carried to median preoptic nucleus for the stimulation of thirst [64]. Moreover, SFO-median preoptic connections are not involved in pressor effects of ANG II peripherally or centrally administered [64], thus showing a functional separation between brain nuclei involved in drinking behavior and brain nuclei involved in the control of blood pressure.

The development of hypertension induced by ANG II is related to increased intracellular $\cdot O_2^-$ synthesis in the SFO. This increase is observed both following acute injection of ANG II into the brain than by chronic systemic infusion. In fact, ANG II administered over a 2-week period in mice caused the development of hypertension and increased levels of intracellular $\cdot O_2^-$ in the SFO. The antioxidant enzyme superoxide dismutase, intra-cerebro-ventricularly injected, was able to inhibit the hypertension and the increase of intracellular $\cdot O_2^-$ in SFO induced by ANG II [65]. *In vitro* data suggest that ANG II *via* AT 1R promotes in SFO phospholipase A2-induced synthesis of arachidonic acid [66]. Once formed, arachidonic acid is metabolized to Prostaglandin E2 (PGE2) by Cyclooxygenase-1 (COX-1) and acts on EP1, the receptor of PGE2, that increases intracellular Ca++ levels.

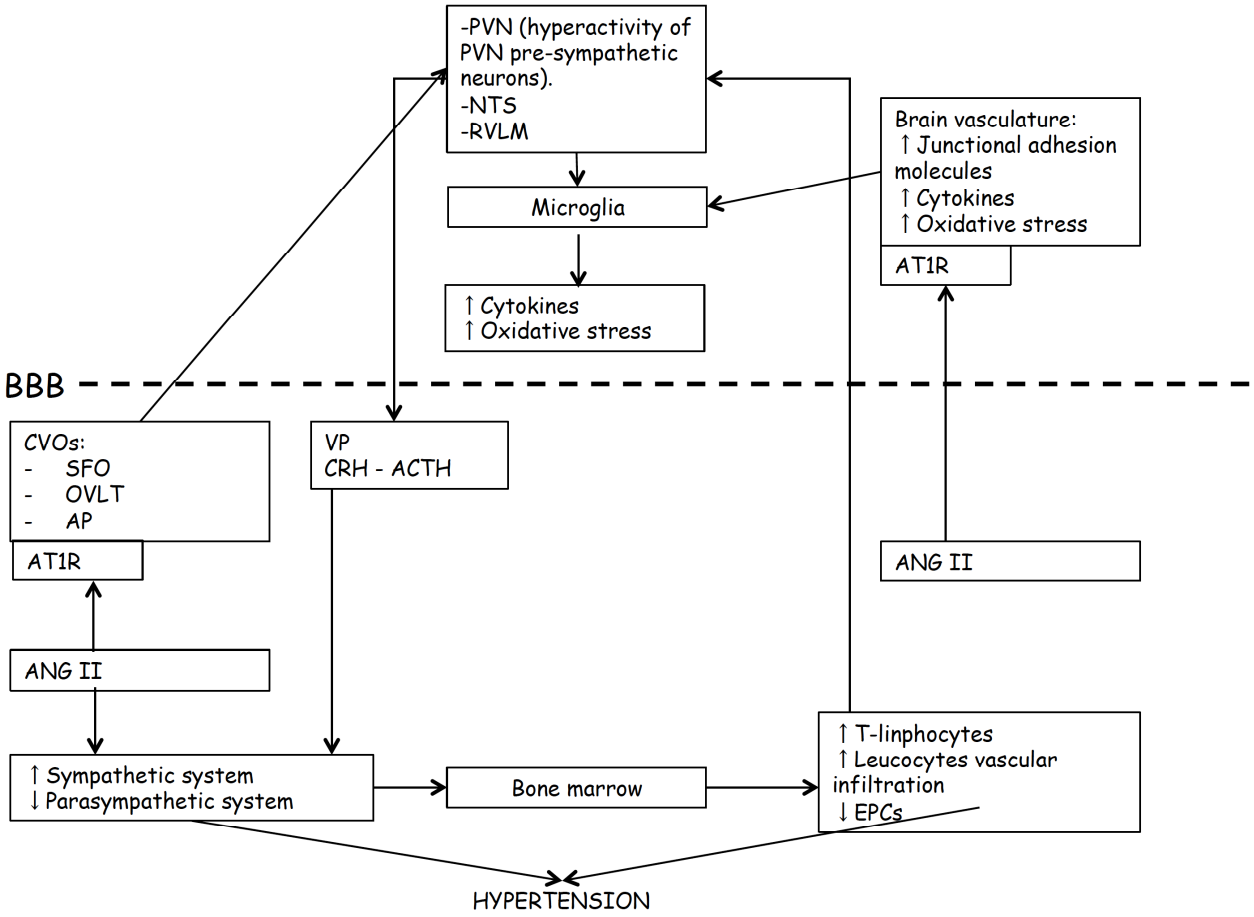

Fig. (1). anatomical, immunological and neuroendocrine pathways involved in angiotensin II-induced hypertension.
ANG II stimulates CVOs *via* AT 1R that transmits the signal to brain nuclei controlling the synthesis and release of hypertensive hormones, as VP and CRH-ACTH, and cardiovascular function. PVN, NTS and RVLM induce the activation of microglia with the increase of cytokines and oxidative stress. The hyperactivity of PVN pre-sympathetic neurons by increasing sympathetic vasomotor tone contributes to hypertension. In addition, ANG II stimulates sympathetic nerve activity inducing bone marrow to increase the synthesis of pro-inflammatory cells, that determines vascular inflammation, and to reduce the production of endothelial progenitor cells, that play a role in vascular repair, thereby the final step is the hypertension. Circulating ANG II, immune cells and cytokines may cross directly the BBB, during chronic hypertension, because the permeability is increased thus showing an additional pathway to brain vascular inflammation.
PVN: paraventricular nucleus; NTS: nucleus of the solitary tract; RVLM: rostral ventrolateral medulla oblongata; SFO: subfornical organ; OVLT: organum vasculosum lamina terminalis; BBB: blood brain barrier; VP: vasopressin; CRH: corticotropin releasing hormone; ACTH: adrenocorticotropin hormone; EPCs: endothelial progenitor cells.

This increase induces the production of NADPH oxidase, the major enzymatic source of brain Reactive Oxygen Species (ROS) [67], with stimulation of voltage-gated Ca++ channels inducing activation of SFO neurons [66]. In a murine model, mice with deletion of coding region of the NADPH oxidase in the SFO show hypertension and vascular inflammation to ANG II infusion compared with control mice [35] thus suggesting the crucial role of NADPH oxidases in the SFO in the control of blood pressure and vascular inflammation to ANG II, supporting the role of oxidative stress promoted by ANG II in the development of hypertension [35]. ANG II may induce cellular stress, *via* alterations in cellular redox status and Ca++ levels, determining an accumulation of unfolded proteins in the Endoplasmic Reticulum (ER) of SFO neurons [68] and, hence, the development of ANG II-dependent hypertension [68]. Indeed, ANG II infusion induces upregulation of unfolded protein response and morphological alterations of ER in SFO neurons [68]. The ER stress inhibitor tauroursodeoxycholic acid and the selective genetic supplementation of the ER chaperone within the SFO reduces significantly ANG II-dependent hypertension thus suggesting that increased blood pressure induced by ANG II is mediated *via* ER oxidative stress in SFO neurons [68].

ANG II increases Adrenocorticotrophin Hormone (ACTH) release by stimulating Corticotrophin-Releasing Hormone (CRH) secretion *via* CVOs. Indeed, the ANG II antagonist saralasin is able to prevent the binding of peripheral circulating ANG II to CVOs. It has been reported that central and peripheral administration of ANG II increased plasma ACTH levels and CRH content of the median eminence in a dose-depended manner and saralasin prevented these effects indicating AT 1R were required for the biologic response [45,69, 70].

ANG II stimulates VP release by acting on SFO and OVLT AT 1R [71, 72]. Indeed, electrolytic lesions of SFO

inhibit VP release to ANG II [73, 74]. Similar effects have been observed following OVLT lesion [72].

5. AREA POSTREMA (AP)

The demonstration of high affinity ANG II binding sites within the AP by autoradiographic methods [75], showed the involvement of the AP in several actions of ANG II as the control of drinking behavior and blood pressure.

Rats with electrolytic lesions of the AP drink more water and show increased urine output, decreased urine osmolality and VP release, than control rats to various thirst stimuli as subcutaneous administration of ANG II, polyethylene glycol, isoproterenol and hypertonic NaCl load, thus suggesting that AP plays with SFO and OVLT an important role in thirst, fluid intake and VP release [76-80].

AP plays a critical role for ANG II-induced neurogenic hypertension. It has been observed that ANG II infusion for 24 hours does not induce mean arterial pressure differences between normal and AP-lesioned rats. On the other hand, when ANG II was infused for 10 days, a significant increase of mean arterial pressure was observed in normal but not in AP-lesioned animals, thus showing that the development of chronic, but not acute, hypertension induced by ANG II requires an intact AP [81]. In addition, there is evidence showing the role played by circulating ANG II in the control of blood pressure in animals submitted to a normal dietary salt by acting on the AP. In fact, the long-term hypotensive response of losartan, the AT 1 receptor antagonist, is significantly reduced in AP-lesioned rats [82]. However, although elevated plasma sodium levels can worsen the hypertensive effects of ANG II, the AP is not involved in the development of hypertension during elevated dietary sodium [83].

6. MEDIO-VENTRAL SEPTAL (MVS) NUCLEUS

The MVS nucleus contains a high concentration of angiotensin receptors [48, 84] and neurons in the MVS nucleus are excited by ANG II iontophoretically applied [85-87]. The MVS nucleus plays an important role in drinking behavior and has been recognized as a brain site for thirst and salt-water balance. It has been observed that electrolytic ablation of MVS nucleus causes a sustained increase of daily water intake and diuresis [88-94] and similar results has been shown after selective damage of MVS nucleus neuron perikaria with kainic acid [95]. No difference has been observed in the dipsogenic effect induced by ANG II, centrally administered, between normal, sham- and MVS-lesioned rats [92, 93]. The polyuro-polydipsic syndrome induced by lesions of MVS nucleus is associated to decreased levels of VP and the stimulatory effect induced by dipsogenic stimuli or ANG II, centrally injected, on VP release is significantly attenuated in rats with lesion of the MVS nucleus thus showing that VP secretion rests upon the integrity of the MVS nucleus [91-93].

However, the dipsogenic responses to intracerebroventricular injection of ANG II may be mediated by α1 and α2 adrenergic receptors. In fact, the presynaptic α2-adrenergic agonist clonidine injected into the MVS nucleus inhibit water intake induced by ANG II and similar responses has been observed following the administration of the α1-adrenergic antagonist prazosin thus showing septal α1 and α2-adrenergic receptors are involved in dipsogenic responses induced by ANG II [96]. Angiotensinergic stimulation of MVS nucleus elicits hypertension and bradycardia [97]. These effects might be mediated *via* efferent pathways between MVS nucleus and SFO. In fact, activation of the SFO by ANG II determines pressor and dipsogenic responses. While electrolytic lesion of the MVS nucleus reduces significantly the pressor and dipsogenic effects of ANG II into the SFO thus showing that MVS nucleus plays an important role in the regulation of cardiovascular and fluid intake responses [98].

7. AMYGDALA

Electrolytic lesions of the Central Nucleus of the Amygdala (CNA) inhibit daily intake of hypertonic NaCl (3%). ANG II is unable to stimulate sodium appetite in CNA-lesioned rats also after postoperative sodium depletion sessions. Other ingestive behaviors, as intake of water, food and 5% sucrose, however, were in normal range [99, 100], thus showing that CNA plays a role in central mechanisms controlling the salt taste signal.

CNA GABA-A receptors reduce significantly the intake of water and salt appetite. The AT 1 receptor antagonist losartan injected into the CNA reversed the inhibitory effect induced by the GABA-A receptor agonist muscimol on sodium and water intake. These data indicate that activation of GABA-A receptors into the CNA are mediated by endogenous ANG II acting on AT 1 receptors of the CNA [101].

The role of CNA opioid receptors in the control of drinking behavior has also been demonstrated. CNA μ-opioid agonists stimulate salt appetite *via* angiotensinergic neurons. In fact, the AT1 antagonist losartan reduces sodium and water intake significantly induced by μ-opioid receptor activation into the CNA, thus suggesting that opioid mechanisms are facilitated by endogenous ANG II acting on AT 1 receptors in the CNA [102].

AT 1 receptors and the presence of ACE activity have been detected within the amygdala [103, 104].

The CNA is involved in the control of blood pressure and sympathetic nerve activity *via* connections with brain areas as hypothalamus and the medulla oblongata that play an important role in the control of cardiovascular system. Efferent projections from CNA synapse on medullary nuclei as the Nucleus of the Solitary Tract (NTS) receives peripheral signals from cardiac and aortic baroreceptors *via* the glossopharyngeal and vagus nerves and the retrotrapezoid nucleus of the Rostral Ventrolateral Medulla (RVLM) receives signals from carotid, aortic and renal chemoreceptors [105]. ANG II activating AT 1 receptors into CNA influences blood pressure *via* this neural network [106].

Sodium appetite induced by aldosterone is inhibited following lesion of the CNA thus showing a major role of this limbic area in the control of salt appetite by aldosterone and ANG II [107-109].

8. NUCLEUS OF THE SOLITARY TRACT (NTS)

The NTS of the dorsal medulla oblongata is the site of autonomic afferents of carotid and aortic baroreceptors *via* the glossopharyngeal (IX) and vagus (X) nerves [110] and is

an important site of ANG II actions. A high concentration of ANG II binding sites within the NTS has been showed [111, 112]. Bilateral electrolytic lesions of the NTS increase significantly blood pressure and VP release removing sympathoinhibitory mechanisms played by baroreceptors [113]. In addition, pharmacological activation of α2-adrenergic presynaptic receptors with clonidine, injected into the NTS, attenuates VP release induced by hypovolemia [114], thus showing the critical role of NTS in the regulation of VP secretion (Fig. **1**). It has been also reported that ANG II injected into the NTS induces an increase in the arterial pressure by stimulation of efferent sympathetic fibers [115] and inhibits the function of baroreceptor reflexes [116].

NADPH oxidase is observed in astrocytes and axons of NTS neurons containing AT 1R. ANG II increases Ca(2+) currents *via* AT 1R showing that NADPH oxidase contributes to the effects of ANG II on Ca(2+) influx in NTS neurons receiving signals from cardiac and carotid baroreceptors *via* the IX and X nerves [117]. In addition, Nox2-containing NADPH oxidase contributes to increased effects of ANG II on Ca(2+) currents in NTS neurons thus demonstrating that the effects of ANG II on autonomic nervous system is mediated by Nox 2-containing NADPH oxidase in NTS neurons [118].

9. DISCUSSION AND CONCLUSION

ANG II plays a major role in the regulation of arterial blood pressure and fluid, electrolytic and hormonal responses interacting not only with VP [119-121], ACTH and autonomic system, but also with the immune system in the brain. Brain angiotensinergic control is mediated mainly by AT 1R located in CVOs. The high permeability and fenestrated capillaries of CVOs permits ANG II and other peptides the transmission of signals generated into the peripheral circulation to brain areas. However, an emerging ANG II mechanism of action has been postulated on the basis of interaction with the immune, autonomic and vascular system. Three observations may be taken into account. (1) hypertension-induced by ANG II is dependent from the elevated oxidative stress in brain cardiovascular-regulating nuclei as PVN, SFO, RVLM and NTS, that produces increased ICs and decreased EPCs, and morphological alterations of ER. Indeed, the antioxidant dismutase, centrally injected, is able to normalize arterial blood pressure *via* normalization of ICs and EPCs levels. (2) ANG II actives microglial cells that stimulates in the brain the secretion of pro-inflammatory cytokines inducing vascular inflammation, and the anti-inflammatory antibiotic minocycline reduces hypertension by reduction of inflammatory cytokines in PVN. (3) ANG II induces vascular infiltration of leukocytes in NTS causing hypoperfusion and consequently secretion of cytokines. These data indicate the pivotal role of oxidative stress in brain nuclei controlling blood arterial pressure and the development of antioxidant drugs in the treatment of hypertension.

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CONFLICT OF INTEREST

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