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Stechnolock: Brain and Neurological Disorders
Published Date: 10 March 2024
RESEARCH ARTICLE

Neurophysiological Regulation of Cardiovascular Parameters by the Renin-Angiotensin System: A Review

Mahmoud Mahmoud*, Nissrine Ballout, Ali Al Arab

[1]*Neuroscience Research Center, Faculty of Medicine, Lebanese University*

***Corresponding author:** Mahmoud Mahmoud, Neuroscience Research Center, Faculty of Medicine, Lebanese University, Tel: +96178876601, E-mail: mahmoud.mhd1@outlook.com

Citation: Mahmoud Mahmoud*, Nissrine Ballout, Ali Al Arab (2024) Neurophysiological Regulation of Cardiovascular Parameters by the ReninAngiotensin System: A Review. Stech: Brain and Neuro Disord 1: 104

ABSTRACT

Cardiovascular diseases and complications form the primary source of deaths globally.The renin-angiotensin system is a ubiquitous system of neuropeptides best known for controlling cardiovascular parameters. This review aims to collect all recent updates on this system in control of heart rate and blood pressure, more specifically, it will tackle the classicaland the non-classical renin-angiotensin system and their clinical relevance. To do this, a precisesearch strategy on the topic will be held on certain databases to find relatable articles and collectthe updates. These cardiovascular parameters were found to be controlled by autonomic and neuroendocrine pathways, both of which are initiated from the paraventricular nucleus. The paraventricular nucleus is the site of integration of all peripheral signals from angiotensin II andits further catalytic products. These signals are perceived by the circumventricular organs and the hypothalamic arcuate nucleus through certain receptors and signaling cascades. This systemhas shown a presence in several diseases and represents a remarkable therapeutical target.

Keywords: Renin-Angiotensin System; Heart Rate; Blood Pressure; Circumventricular Organs; Paraventricular Nucleus; Cardiovascular Neurophysiology

Introduction

The cardiovascular system is a highly regulated blood-pumping heart and vessels. Dysregulation in its functioning is frequent and would lead to many cardiovascular diseases (CVDs). According to the world health organization (WHO), CVDs are the leading cause of death globally, forming up to 32% of all global deaths [1]. Among CVDs, unachieved homeostasis of cardiovascular parameters is an uprising issue to be addressed. Studies have linked the control of cardiovascular parameters to the autonomic nervous system(ANS) and several neuropeptides, among which the renin-angiotensin-aldosterone system (RAAS or RAS) provides many neuroactive forms of angiotensin peptides involved in controlling the ANS and peripheral neurotransmission [2]. RAS has been recognized for its importance in regulating blood pressure homeostasis, extracellular fluid volume, and the neural and endocrine functions in cardiovascular control, hence its role in manypathophysiological CVDs including hypertension, heart failure, coronary artery disease, strokes, and cardiovascular-related diseases as obesity and chronic kidney disease [3].

The RAS is a ubiquitous hormonal system that includes a series of enzymatic reactions,peptide hormones, and byproducts. The classic RAS is a systemically acting system in the bloodstream. Other renin-angiotensin systems are tissue-specific in the brain, kidney, heart, blood vessels, adipocytes, and adrenal glands; they operate completely independent of the

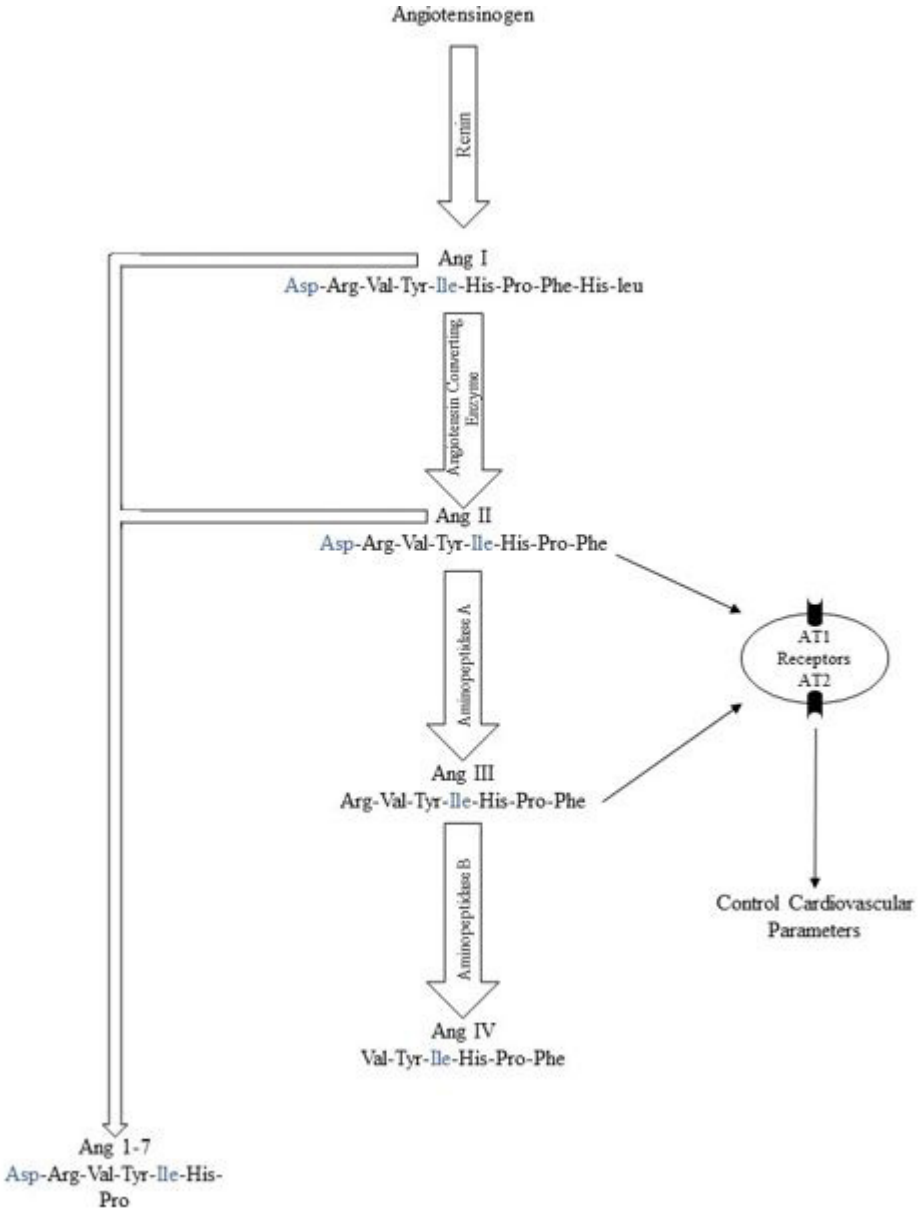

Figure 1: Illustration on the enzymatic and peptide series of the renin-angiotensin system. Angiotensinogen is catalyzed by renin into Ang I, which is then catalyzed into Ang II by angiotenin converting enzyme. Ang II can be further catalyzed into Ang III and Ang IV by aminopeptidase A andB, respectively. Ang 1-7 is a product of catalysis of Ang I and Ang II. Ang II and Ang III have the samefunctions and act on the same receptors AT1 and AT2. Ang: angiotensin, AT1/2: angiotensin II receptortype 1/2. (Arab, 2013)

classic RAS except for renin and angiotensinogen, which can only be obtained from the bloodstream [4]. Other RAS can also be intracellular as in cardiac myocytes,vascular smooth muscle cells, renal proximal tubule cells, and neurons; in these systems, angiotensin II, the representative neuropeptide of RAS, can either be synthesized or internalized [5]. Generally, this series of enzymatic starts withangiotensinogen cleavage into angiotensin I by renin, then into angiotensin II (Ang II) by angiotensin-converting enzyme. Furthermore, Ang II is cleaved into angiotensin III (Ang III) by aminopeptidase A and then angiotensin IV (Ang IV) by aminopeptidase N. Another cleavageseries of Ang II involves the production of angiotensin 1-7 (Ang 1-7), which can be further cleaved into alamandine [6-7] Ang II exerts its activity through interactions with its receptors angiotensin II receptor types 1 and 2 (AT1R/AT2R), Ang III has the same effects and same receptor compatibility to Ang II (Figure1) but it is five times faster cleared from the circulation [8]. AngIV, however, interacts with angiotensin II receptor type 4 (AT4R) but has rather far roles fromthe regulation of blood pressure and heart rate [9].

The research on RAS and its link to heart rate and blood pressure control are intensive and only a few reviews have considered covering this topic, or at least parts of it. This review will tackle most of the details related to this topic and provide an in-depth collection of recent advances in this field. Hence, RAS, here, will be classified into:

Classical RAS: this involves a brief introduction to Ang II production and its activity on thelamina terminalis in the brain, and how recent studies have tackled them.

Another part of this classification in the non-classical RAS: it involves the novel Ang 1-7, alamandine, and the prorenin receptor – a receptor for prorenin and/or renin that is known to non-proteolytically cleave angiotensinogen to produce angiotensin I -, in addition to proinflammatory molecules as tumor necrosis factor α and the interleukins.

Finally, RAS is to be applied in the clinical field of research.

Classical Renin-Angiotensin System and the Brain

The classic RAS acts systemically and begins in the juxtaglomerular cells of the renal afferent arteriole of the kidney. These cells synthesize preprorenin that is cleaved to prorenin in the endoplasmic reticulum and packaged into secretory granules in the Golgi apparatus [10]. While prorenin is constitutively secreted across the cell membrane, mature renin is only released upon a stimulus by the afferent arteriolar baroreceptor when arterial perfusion pressure decreases or when the sympathetic nervous system is activated and stimulates norepinephrine release and activity on beta-1 adrenergic receptors [11]. Renin is responsible for the cleavage of angiotensinogen, a precursor majorly producedby the liver and secreted into the bloodstream, into angiotensin I (Ang I). Ang I fate is to be converted by the angiotensin-converting enzyme (ACE) into angiotensin II (Ang II), the representative active neuropeptide of RAS [12].

Central angiotensin II (Ang II) has been known to elevate blood pressure as early as 1963 [13]. It interacts with angiotensin II type 1 receptor (AT1R) onthe circumventricular organs (CVOs): the subfornical organ (SFO), the median preoptic nucleus(MnPO), and the organ vasculosum of the lamina terminalis (OVLT). These CVOs are blood- brain barrier deficit and act as the interface between blood and its signals to the brain, hence the role as sensory organs. They receive the signal and transduce it to excitatory - through glutamate neurotransmitter - or inhibitory - through γ-aminobutyric acid (GABA) - projectionstowards the hypothalamic paraventricular nucleus (PVN) either directly or indirectly through the MnPO [14-15-16].

Subfornical Organ (SFO)

A 40-year-old notable study on the SFO has reported it as a source of producing Ang IIin addition to a sensory organ [16-17-18]. Later in 2017, this was addressed again. The 2017 study has characterized a superficial population of secretory cells on the SFO that are similar to other SFO neurons exceptfor the secretory vesicles within. Real-life monitoring of Vesicle Associated Membrane Protein2 (VAMP2) confirmed their exocytosis and uncovered their route into the ventricles. This SFOsecretory role may be providing a direct route for the effects mediated by SFO on blood pressureand heart rate [19].

Paraventricular Nucleus (PVN)

The PVN is of major interest to the researchers in this field for it acts as an integrative center, receiving projections from different brain regions including the CVOs and arcuate nucleus, and sending projections to the hypothalamus-pituitary-adrenal (HPA) axis and pre- sympathetic projections to the rostral ventrolateral medulla (RVLM) [20].

The paraventricular nucleus is functionally divided into two parts: the magnocellular PVN (PVNm) and the parvocellular PVN (PVNp). Afferent Glutamatergic projections increasing the firing of neurons within the PVN is the basic knowledge, however, several recentfindings were reported in the last 5 years [21].

Parvocellular Paraventricular Nucleus

PVNp neurons are presympathetic projections towards the RVLM responsible for adjusting the autonomic nervous messages towards the heart, vessels, and kidneys to achieve homeostasis [22].

Within the PVNp, a mutual activating system between several angiotensinergic (Ang) neurons and vasopressinergic (VP) neurons functions to deliver these adjustments [23]. The latter responds to excitatory signals from the former through AT1R and angiotensin II type 2 receptor (AT2R), though AT2R accounts for the main receptor [24]. Now that VP neurons are activated, they secrete vasopressin to Ang neurons, which, in turn, respond through their V1a receptor. However, the mutual activating system might cause an over-activation, this requires GABAergic interneurons activation; Ang neurons send excitatory projections to GABAergic interneurons soma and presynaptic terminals acting on AT2R and AT1R, respectively, and these neurons send inhibitory projections to the VP neurons. Moreover, activated VP neurons send the pre-sympathetic projections to the RVLM [25] (Figure 2).

Magnocellular Paraventricular Nucleus

The PVNm are involved in the neuroendocrine pathway, extending their projections tothe pituitary gland. Angiotensin II signals received by the CVOs activate the vasopressingeric neurons within, which then act to activate the pituitary gland [26] (Figure 2).

A Cross-Talk between the Autonomic and Neuroendocrine Control of CardiovascularParameters

Within the PVN, some neurons have been reported to express AT1aR. Selectiveoptogenetic activation or inhibition of these neurons, respectively, activate or inhibit the HPA axis; these neurons control the neuroendocrine pathway of cardiovascular parameter control [27]. In a subsequent study, it was detected that these neurons express corticosteroid-releasing hormone (CRH) and make appositions with the presympathetic neurons sent from the PVN to the RVLM and control the sympathetic activity. The former neurons respond to CRH secretion through the CRH type 1 receptor (CRHR1) and transducethe signal as an excitatory message [28] (Figure 2)

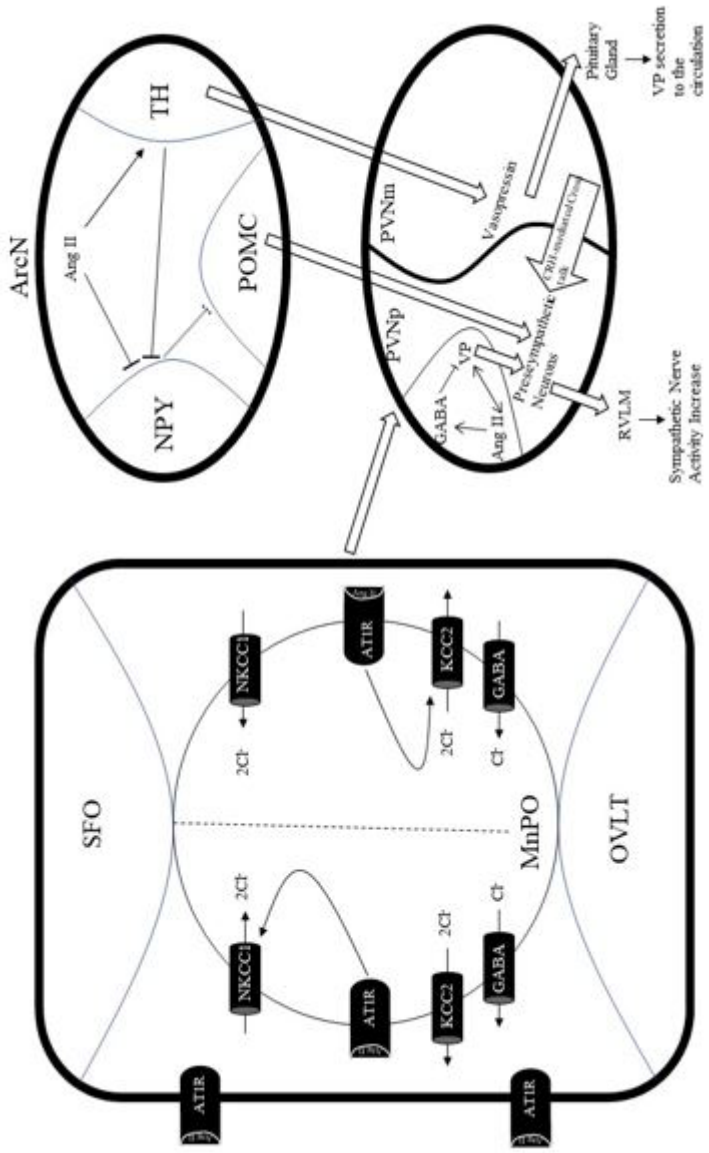

Figure 2: An illustration on the molecular mechanisms that occur within the brain regions involved in RAS signaling. Within the MnPO, depending on AT1R signal, it favors NKCC1 in normal conditions or KCC2 in dysregulations, which only causes the projections towards the PVN to be inhibitory or lessinhibitory, respectively. Within ArcN, Ang II causes a disinhibition of the POMC either through directactions on NPY neurons on indirectly through TH neurons; thence, POMC activates presympathetic neurons of the PVNp and TH neurons activate vasopressin neurons in the PVNm. Within the PVP, a mutual activating system between angiotensinergic and vasopressinergic neurons in the PVNp activatesthe presympathetic neurons, activated neurons in the PVNm activates the pituitary through vasopressinand the presympathetic neurons through CRH as means of cross-talking. Ang II: angiotensin II, AT1R: angiotensin II receptor type 1, NKCC1: Na-K-Cl cotransporter isoform 1, KCC2: -Cl cotransporter, isoform 2, GABA: γ-aminobutyric acid, SFO: subfornical organ, MnPO: median preoptic nucleus, OVLT: organ vasculosum of the lamina terminalis, ArcN: arcuate nucleus, POMC: proopiomelanocortin, TH: tyrosine hydrolase, NPY: neuropeptide Y, PVNp: parvocellular paraventricular nucleus, PVNm: magnocellular paraventricular nucleus, VP: vasopressin, CRH: corticosteroid-releasing hormone, RVLM: rostral ventrolatermal medulla. (Elsaafien et al., 2021;Farmer, Little, Marciante, & Cunningham, 2021; Frazier et al., 2021; Nasimi, Haddad, Mirzaei-Damabi,Rostami, & Hatam, 2021; Shi, Stornetta, Stornetta, & Brooks, 2022)

Arcuate Nucleus and RAS

Studies on Ang II and the arcuate nucleus (ArcN) first come up in 2007, this study showed increased activity of the ArcN in response to Ang II [29]. Later in 2011, the ArcN has shown to elevate the arterial blood pressure in response to Ang II, and hence, its increased activity [30]. Only recently, the mechanism of action of Ang II on the ArcN has been deciphered. The arcuate nucleus has several populations of neurons, some of our interests here are the proopiomelanocortin (POMC) -expressing neurons, tyrosine hydrolase (TH) - expressing interneurons, and neuropeptide Y (NPY) - expressing neurons [31].

In the absence of the Ang II signal, NPY neurons send inhibiting projections to POMCand PVN neurons acting through Y1 receptors. Ang II inhibits NPY neurons either directly through inhibitory AT1aR on NPY neurons or indirectly through activating AT1aR receptors on TH neurons that send GABAergic projections to NPY neurons. This causes disinhibition onthe POMC neurons in particular, which, then, activates PVN neurons expressing melanocortin-4-receptor (MC4R) through secreting α-Melanocyte-stimulating hormone (α-MSH). TH neurons might also activate the pituitary gland either directly or indirectly through activating projections to vasopressinergic neurons in the PVN. This works as a 2-phase response to the Ang II signal in the arcuate nucleus: it first starts with increased vasopressin secretion to the circulation and ends with increased sympathetic activity from the PVN [32] (Figure 2).

Median Preoptic Nucleus

Researchers have been studying MnPO as a site of dysregulation in RAS signaling. Early studies have only linked MnPO to ACE to dysregulations of RAS signaling [33-34-35] Putting pieces together, subsequent studies started linking it to Ang II and glutamate signaling[36]. And, only recently, a decisive mechanism was established. This dysregulation is due to an imbalance between excitatory and inhibitory messages; the former increase and the latter decreases. The increased activation of AT1aR causes a functional shift in the activity of chloride channels - Na-K-2Cl cotransporter isoform 1 (NKCC1) influx ion channels and K-Cl cotransporter isoform 2 (KCC2) outflux ion channels. Initially, normal AT1aR activity maintains a low level of chloride ions within the neurons as it favors the activityof KCC2, hence GABA receptors are activated and transport chloride ions into the neurons leading to the formation of an inhibitory message. However, increased activity of AT1aR favorsNKCC1 leading to high levels of intracellular chloride ions, and, eventually, GABA receptors act to expel chloride ions leading to less inhibition or even excitation in some cases [37] (Figure 2).

Central RAS at the Molecular Level

The interaction of Ang II with its receptor AT1R leads to a glutamatergic message. Glutamate interacts with either alpha-amino-3-hydroxy-5-methyl4-isoxazole propionic acid (AMPA) GluA1 receptor [38] or N-methyl-D-aspartate (NMDA) receptor [38]. This interaction either causes an influx of calcium ions into the neuron [39] or activates protein kinase C δ (PKCδ) [40]. which, in both cases, interacts with nicotinamide adenine dinucleotide phosphate (NADPH) oxidases [41], specifically through Ras-related C3 botulinum toxin substrate 1 (Rac1) in case of PKCδ [42]. This only leads to the production of reactive oxygen species(ROS), especially superoxides [43]. Potassium channels might beregulated by superoxides mediated by calcium/calmodulin (CaM)-dependent kinase II α (CaMKIIα) as a redox-sensitive signaling protein [44] (Figure 3).

In another study, Ang II response was reported to be related to brain cytosolic phospholipase alpha 2 (cPLA2). Activated cPLA2 leads to the production of arachidonic acid that is catalyzed by cyclooxygenase 2 into prostaglandin E2 (PGE2). PGE2 binds its receptorsProstaglandin E2 receptor 2/4 (EP2/4) to mediate RAS effects [45] (Figure 3).

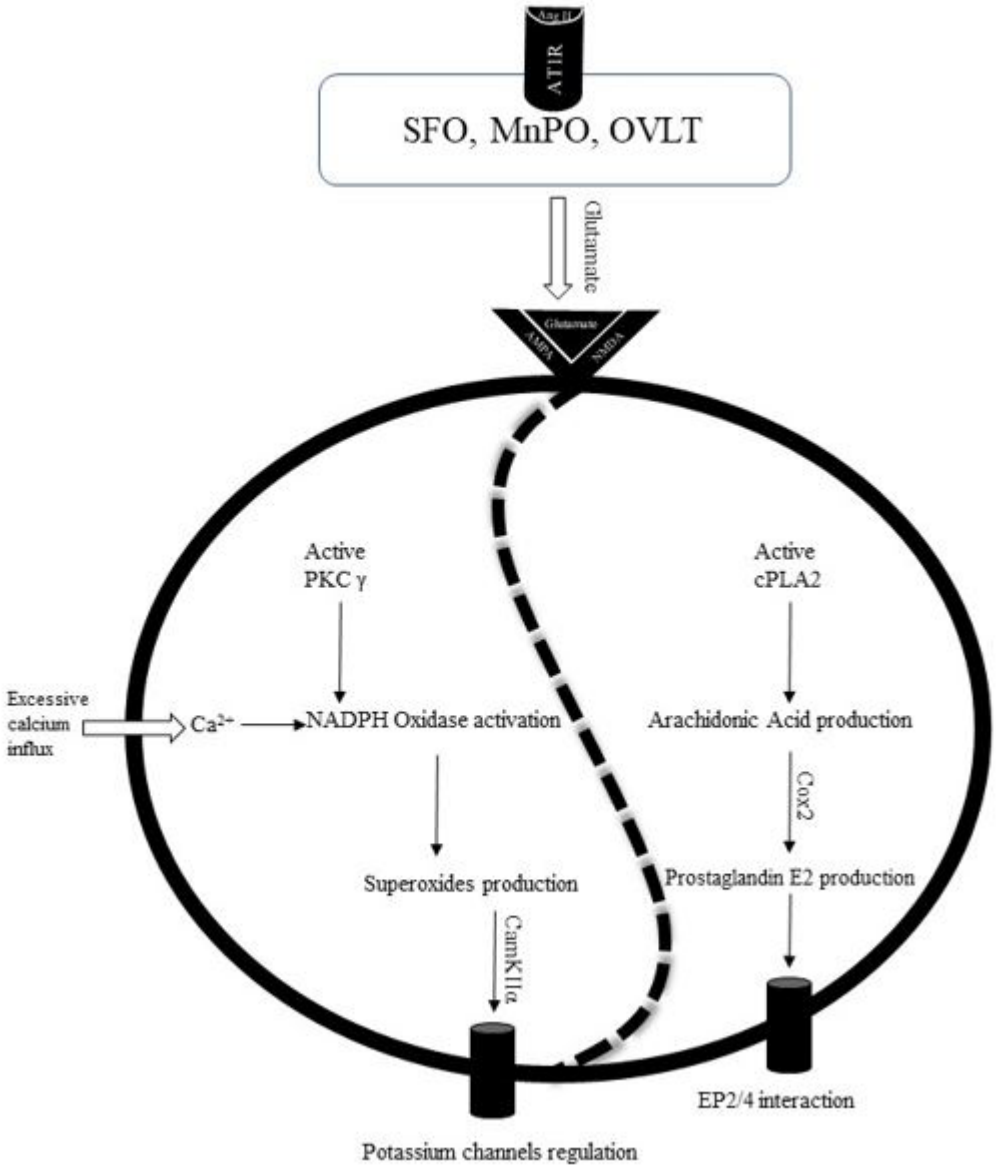

Figure 3: An illustration on the two molecular pathways of Ang II signaling. Ang II-AT1R interaction in SFO, OVLT, and MnPO induces glutamate signaling that acts on both AMPA and NMDA receptorsof glutamate leading to molecular mechanisms within the cells of the paraventricular nucleus. The firstscenario shows excessive calcium influx and active PKC gamma that activate NADPH oxidation further leading to superoxide production and regulating potassium channels through CamKII alpha. A second scenario shows active cPLA2 producing arachidonic acid, which is catalyzed into prostaglandin E2 by Cox2, and the latter interacts with EP2/4 for further responses. Ang II: angiotensin II, AT1R: angiotensinII receptor type 1, SFO: subfornical organ, MnPO: median preoptic nucleus, OVLT: organ vasculosumof the lamina terminalis, PKC: protein kinase C, NADPH: reduced nicotinamide adenine dinucleotide phosphate, CamKII alpha: calcium/calmodulin (CaM)-dependent kinase II α, cPLA2: brain cytosolic phospholipase alpha 2, Cox2: cyclooxygenase 2, EP2/4: prostaglandin E2 receptor 2/4. (Basu et al., 2019; Song et al., 2018; Su et al., 2017)

Non-classical Renin-Angiotensin System and the Brain

For many years, Ang II was thought to be the only active neuropeptide in RAS. However, two decades earlier, angiotensin-converting enzyme 2 (ACE2) was discovered [46]. ACE2 is an enzyme that further catalyzes Ang II into angiotensin 1-7 (Ang 1-7), which can be further decarboxylated into alamandine. These relatively new components of RAS along with angiotensin II type 2 receptor (AT2R) fall in theprotective arm of RAS considered to be vasodilators and lower the cardiovascular parameters [47]. However, these components have arisen many controversies about theiractions.

Angiotensin 1-7 and Alamandine

Most of the functions of Ang 1-7 are mediated through its interaction with mitochondrialassembly protein 1 receptor (MasR) and those of alamandine are mediated through Mas-relatedreceptor member D (MrgD) [48]. The controversy with these RAS components revolves around their position: In the periphery and caudal ventrolateral medulla, they act as a vasodilator – counter-regulating Ang II. However, in RVLM and PVN, they act as vasoconstrictors [49].

Another controversy related to Ang 1-7 is about is the molecular pathway. In an earlierstudy in 2005, Ang 1-7, through its interaction with MasR, was thought to activate the NO pathway [50]. Later in 2017, in a study that showed a depressor effect of Ang 1-7 on the PVN, it was reported that Ang 1-7 exerts its effects through the cyclic adenosinemonophosphate (cAMP)-protein kinase A (PKA) pathway [51] and through reduced nicotinamide adenine dinucleotide phosphate (NADPH)oxidase-derived superoxide anions and not through NO pathway [52].

Tumor Necrosis Factor α and RAS

As a pro-inflammatory cytokine, tumor necrosis factor α or TNFα can exist in two forms: a benign and rather beneficial transmembrane TNFα (trTNFα) and a soluble form (sTNFα) [53] known for its inflammatory effects and involved in blood pressurecontrol in some conditions through epidermal growth factor receptor (EGFR) and extracellularsignal-regulated kinase (ERK) 1/2 signaling molecules [54]. Thissignaling cascade starts with TNFα receptor 1 (TNFaR1) [55].

Tumor Necrosis Factor α Receptor 1 and AT1R

TNFaR1 colocalizes with AT1R in SFO neurons [55] andits interaction with its ligand TNFα shifts the activation threshold of voltage-gated sodium channels to a hyperpolarized state rendering the depolarization of these neurons more robust; their excitability increases [56]. This concludes with TNFα potentiating the induced calcium rise in response to Ang II in SFO [57].

ADAM Metallopeptidase Domain 17, AT1R, and ACE2

The molecule responsible for catalyzing the reaction from trTNFα to sTNFα is called TNFα converting enzyme (TACE), also known as ADAM Metallopeptidase Domain 17(ADAM17). ADAM17 has a rather noteworthy involvement in RAS. It is expressed in the periphery and brain regions as SFO and PVN on neurons and glial cells [58].

While, at first sight, ADAM17 does not show any direct relevance to RAS components,ADAM17 co-exists with AT1R in many cells and can be activated and upregulated by AT1R activation; Once AT1R is activated, both molecules are brought into a closer proximity for downstream signals to activate ADAM17 through intracellular signals from G-protein coupled receptors or oxidative stress that phosphorylate its cytoplasmic domain or upregulate its availability due to translocation in acute stimulations or upregulate its availability through the involvement of transcription factors in chronic stimulations [59].

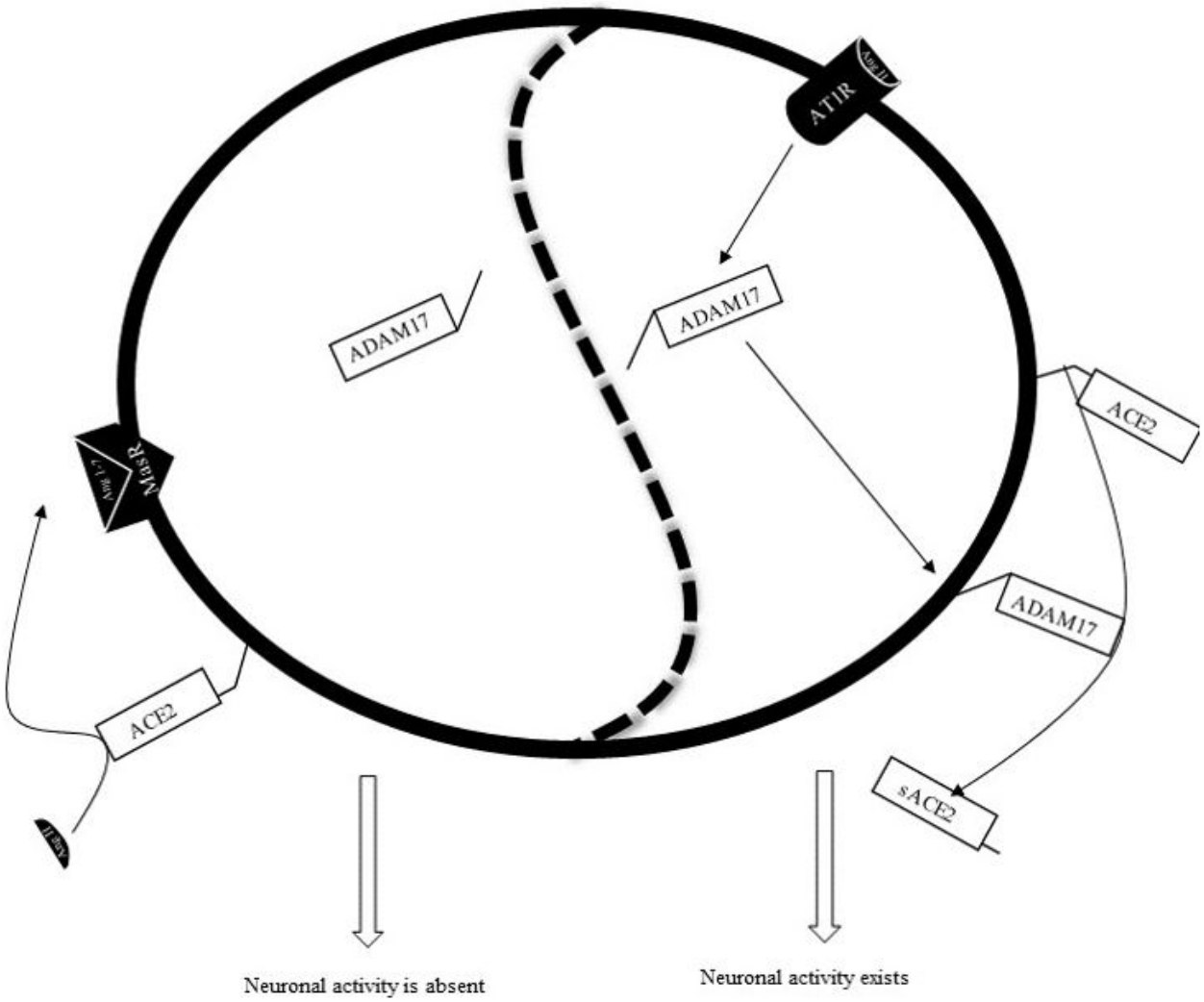

Figure 4: An illustration on how AT1R overactivation modulates ADAM17 activity leading to a neuronal activity and how ACE2 can have a compensatory role in normal conditions. ACE2 converts Ang II into Ang 1-7, which interactrs with MasR to produce compensatory effects. In overactive Ang II, AT1R induces colocalization of ADAM17 into the the membrane, which then converts ACE2 into sACE2 leading to an active neuronal response. Ang: angiotensin , ACE2: angiotensin converting enzyme 2, MasR: mitochondrial assembly protein 1 receptor, ADAM17: ADAM Metallopeptidase Domain 17, sACE2: soluble ACE2. (Mukerjee et al., 2019; Xu et al., 2017)

An interesting ligand of ADAM17 is ACE2, in which they interact in a process called ADAM17-mediated shedding of ACE2. This interaction regulates the activity of presympathetic neurons of the PVN: neuronal ACE2 supports an inhibitory input to the PVN, ADAM17 cleaves ACE2 membrane proteins reducing its compensatory effects [60], and assists glutamatergic neurons that induce sympathoexcitation at some point [61]. A controversy, here, lies in the activity of the shed, now soluble, ACE2 in whetherit has a therapeutic benefit or it is merely a degradation product [62] (Figure 4).

Interleukins and RAS

Low-grade inflammation is detected in hypertension in the peripheral tissues, blood [63-64], and the cardiovascular centers in the brain [65-66-67-68]. Studies relating proinflammatorycytokines and hypertension has come to mention three main cytokines: Interleukin 1β, Interleukin 17A, and Interleukin 10.

As for interleukins that induce hypertension, microinjection studies of Interleukin 1β inthe SFO induces hypertension [69]. In a subsequent study, interleukin 1β in the circulation showed an interaction with the SFO to produce hypertension through inflammation and increasing RAS activity [70]. Moreover, Interleukin 17A is involvedin neuroinflammation and sympathetic activation during hypertension. In fact, Interleukin 17Areadily crosses the blood-brain barrier to boost inflammation in the brain through various inflammatory mediators in the PVN [71].

Regarding protective interleukins, alterations of the expression of interleukin 10 and itsreceptor takes place in hypertension [72],suggesting their involvement. In fact, interleukin 10 has a rather protective effect by lowering the low-grade inflammation [73].

Brain Local RAS and the (Pro) renin Receptor

RAS components also exist in tissues. One of the most remarkable components in localRAS is the (pro)renin receptor ((P)RR or PRR). PRR binds to prorenin, the inactive form of renin, and/or renin to catalyze a fourfold increased production of Ang I [74] or a non-proteolytic production of Ang II [75] in response to specific signals as high salt intake [76], directly affect Ang II signaling [77], or increase in the excitability ofmagnocellular neurons, through increasing intracellular calcium and inhibition A-type potassium channels, leading to an increase in vasopressin secretion in an Ang II-independent pathway [78]. Within the brain, local RAS components have autocrine or paracrine effects [79].

Clinical Relevance of RAS

In context of diseases, RAS has been linked to hypertension as a disease and acomplication in many diseases. Hypertension has been linked to overactive Ang II -especially since the blood-brain barrier shows a higher permeability in hypertension [80] in the PVN [81] and ArcN [82], Ang 1-7 [83] and alamandine in the PVN [84], and to the action ofADAM17 corresponding to ACE2 activity [85]. Other brain regions and other related molecules have also been linked to hypertension due to elevated sympathetic activity and excitatory nerve messages in the OVLT and MnPO and the RVLM [86]. Some remarkable molecules are TNFα[87], ADAM17 [88], and PRR [89]. This also falls for hypertension which is a complication of other diseases, specifically talking about chronic intermittent hypoxia (CIH) [90], obesity polycystic kidney disease (Underwood, McMullan, Goodchild, Phillips, & Hildreth, 2022), and stress-related anxiety .

As for treatments that relate to RAS, lesions of MnPO neurons that project to the PVNhave been reported viable for treating CIH. Several other less invasivetreatments have also been studied; any of the involved molecules in hypertension is likely to bea target: AT1R antagonist losartan has shown to lower blood pressure and heart rate , Ang 1-7 can be selectively blocked by D-Alanine-Ang-1-7 (A-779) , in addition to PRR antagonists as PRR knockdown was proven efficient to reduce hypertension. Following the cascade that Ang II receptors activate, the cascade can be a viable therapeutical target antioxidants have, though, proven insufficient for the treatment of hypertension due to reasons related to sublocalization and specificity of ROS type;more specific antioxidants should be directed against superoxides as they have been reported to be elevated during hypertension. Studies on Metformin have also linked it to reducing the oxidative stress related to hypertension.

Conclusion and Future Perspectives

The renin-angiotensin system is a ubiquitous hormonal system with severalneuropeptide components acting on numerous targets through various receptors. It has been assigned to several functions; one of our interests is its effect on the cardiovascular parameters: heart rate and blood pressure. This area of research is intensive andmost of the reviews on it are rather considering parts of the system as to how massive this system is. In this review, RAS has been briefly described, the recent advances in this field werein-depth collected, and a clinical significance to what RAS can help with was provided.

Studies have shown its involvement in controlling heart rate and blood pressure via theautonomic and neuroendocrine systems, ultimately, increasing the sympathetic nerve activity and activating the pituitary, however, signals are first integrated within the PVN. Signals towards the PVN are initiated within the CVOs, where SFO not only responds to Ang II but also can be its source into the ventricles, and where MnPOutilizes two channels in order to either activate GABA receptor chloride ion channels and, hence, send inhibitory messages to the PVN in case of low Ang II signal or rather be less inhibitory in case of high Ang II signaling. The ArcN also receives Ang II signals and, ultimately, sends excitatory projections to the PVN presympathetic neurons or to vasopressinergic neurons, both of which cross-talk through CRH. The PVN, itself, has a mutual activating system between angiotensinergic and vasopressinergic neurons that ultimately activates the presympathetic neurons. All of this shows how Ang II ultimately increases heart rate and blood pressure throughactivating the sympathetic nervous and neuroendocrine systems. Ang II metabolites are still controversial

in terms of periphery versus central actions. Moreover, the proinflammatory cytokines and TNFα convertase have shown to be involved in the dysregulations during hypertension.

This collection of RAS updates pinpoints not only how intensive the research is, but also how redundant it is in the case of the PVN especially since it is the site of integratio nof these peripheral signals. Studies on non-classical RAS have not shown any in-depth results andare still on the margins. In conclusion, RAS is a broad source of neuropeptides acting on manyreceptors in various regions of the body, and understanding its exhaustive list of activities is a step toward treating many disease-related complications.

With the drugs utilizing RAS in the market: angiotensin-receptor blockers (ARBs or sartans), angiotensin-converting enzyme inhibitors, and direct renin inhibitors (aliskiren), RAShas not been in the clinical field for some time now; in a span of 27 years starting from 1986, only 3 clinical trials were reported related to either brain regions involved of RAS signaling orRAS component Ang II. While current studies still aim to understand the renin-angiotensin system furthermore, future studies should utilize this knowledge and push RAS metabolites andneuropeptides into the clinical field.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This work was not funded.

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