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The Renin-Angiotensin System in Cardiovascular Autonomic Control: Recent Developments and Clinical Implications

Amanda J. Miller and **Amy C. Arnold**

Department of Neural and Behavioral Sciences, Pennsylvania State University College of Medicine, Hershey, PA, USA

Abstract

Complex and bidirectional interactions between the renin-angiotensin system (RAS) and autonomic nervous system have been well established for cardiovascular regulation under both physiological and pathophysiological conditions. Most research to date has focused on deleterious effects of components of the vasoconstrictor arm of the RAS on cardiovascular autonomic control such as renin, angiotensin II, and aldosterone. The recent discovery of prorenin and the prorenin receptor have further increased our understanding of RAS interactions in autonomic brain regions. Therapies targeting these RAS components, such as angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers, are commonly used for treatment of hypertension and cardiovascular diseases, with blood pressure lowering effects attributed in part to sympathetic inhibition and parasympathetic facilitation. In addition, a vasodilatory arm of the RAS has emerged that includes angiotensin-(1-7), ACE2, and alamandine and promotes beneficial effects on blood pressure in part by reducing sympathetic activity and improving arterial baroreceptor reflex function in animal models. The role of the vasodilatory arm of the RAS to cardiovascular autonomic regulation in clinical populations, however, has yet to be determined. This review will summarize recent developments in autonomic mechanisms involved in effects of the RAS on cardiovascular regulation, with a focus on newly discovered pathways and therapeutic targets for this hormonal system.

Keywords

renin angiotensin system; autonomic nervous system; blood pressure; baroreflex

Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality in the United States, despite decades of research into underlying mechanisms and optimal treatment approaches. In this regard, the renin-angiotensin system (RAS) has remained a focus of cardiovascular research for over a century. The RAS is well recognized for its importance in physiological regulation of blood pressure, extracellular volume, and cardiovascular control

Address for Correspondence: Amy C. Arnold, PhD, MSCI, Department of Neural and Behavioral Sciences, Pennsylvania State University, College of Medicine, 500 University Drive, Mail Code H109, Hershey, PA 17033, Phone: (717) 531-3674; Fax: (717) 531-5184, aarnold5@pennstatehealth.psu.edu.

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of neural and endocrine functions. In addition, the RAS has been shown to play a pathophysiological role in the development and progression of numerous cardiovascular-related diseases including hypertension, heart failure, obesity, chronic kidney disease, coronary artery disease, and stroke. As a result, pharmacological agents targeting the RAS are increasingly used in these clinical populations. At a mechanistic level, the cardiovascular regulatory actions of the RAS involve extensive interactions with the autonomic nervous system. This review will highlight recent developments in our understanding of these RAS: autonomic interactions for cardiovascular control, as well as discuss potential implications for targeting the RAS to improve cardiovascular autonomic regulation in clinical populations.

RAS Pathways for Cardiovascular Regulation

The RAS is a series of enzyme-substrate interactions that generates functional peptide hormones critical to physiological and pathophysiological regulation of cardiovascular function. The enzyme renin, an aspartyl protease, is synthesized and released from the juxtaglomerular cells of the kidneys in response to various stimuli including increased sympathetic nervous system (SNS) activity, decreased perfusion pressure in the renal afferent arterioles, decreased sodium chloride content in the macula densa segment of the renal distal tubules, and local actions of nitric oxide and prostanoids [1]. As shown in Figure 1, renin catalyzes the conversion of angiotensinogen to the decapeptide angiotensin (Ang) I, which is subsequently cleaved by Ang converting enzyme (ACE) to form the octapeptide Ang II [2]. In addition to this classical circulating system, components of the RAS are found locally within tissue systems such as brain, heart, kidney, adipose, skeletal muscle, and adrenal gland [2]. The existence and independence of these local RAS from the circulating system, however, has been challenged with studies showing that while tissue Ang II generation does occur via actions of membrane-bound ACE, this process requires uptake of renin and angiotensinogen from the circulation [3]. The presence of an intracellular RAS has also been described in cardiac myocytes, vascular smooth muscle cells, renal proximal tubule cells, and neurons [4,5]. In this intracellular RAS, Ang II can be generated within cells or internalized by cells following activation of cell surface receptors to elicit intracrine effects via AT_1-like nuclear receptors. Finally, ACE-independent pathways can contribute to Ang II generation, particularly within tissues, and involve actions of proteinases such as chymase, kallikrein, and cathepsin G [6].

Ang II has primary actions at cell surface type I (AT_1) g-protein coupled receptors to elevate blood pressure via numerous mechanisms including vasoconstriction, cellular proliferation, aldosterone and vasopressin release, oxidative stress, inflammation, immune activation, sympathetic activation, and baroreflex dysfunction [2]. While this is an understudied area of research, a handful of studies have also shown a role for intracellular Ang II to induce cardiac hypertrophy and pressor responses via actions at nuclear AT_1 receptors in rodents [7]. Ang II can also bind type II (AT_2) receptors to counteract AT_1 receptor-mediated vasoconstrictor and proliferative actions, although these receptors are more limited in terms of affinity and tissue expression [8]. Ang II is degraded by aminopeptidase A and N to form the active metabolites Ang III and Ang IV, respectively. Most biological actions of Ang III are mediated by AT_1 receptors and include promotion of cellular proliferation, vasopressin

release, thirst and sodium appetite, inflammation, and aldosterone release [9]. Ang III is reported to have similar affinity for AT_1 receptors and to produce equipotent pressor responses compared with Ang II, although this remains an area of active debate [9,10]. While less studied, Ang IV can also activate AT_1 receptors centrally to induce hypertension in animal models [10] as well as Ang type 4 (AT_4) receptors to modulate learning and memory functions.

The complexity of the Ang II-ACE-AT_1 receptor vasoconstrictor arm of the RAS is further increased by recent discovery of additional biologically active components including Ang-(1-12), prorenin, and the prorenin receptor (Figure 1). Ang-(1-12) is a C-terminally extended form of Ang I that is found in plasma and peripheral tissues, formed independent of renin, and processed to Ang II for cardiovascular actions [11]. Prorenin is an inactive precursor of renin, which contains a 43-amino acid prosegment covering the active cleft, and is found in the circulation at concentrations at least 10-fold higher than renin. Renin and prorenin can both bind the prorenin receptor (PRR). Binding of prorenin to the PRR induces non-proteolytic activation to contribute to Ang II production in tissues as well as initiates intracellular signaling independent of Ang II actions [12].

Finally, a vasodilatory arm of the RAS has emerged, which is characterized by the heptapeptide Ang-(1-7) and generally opposes the deleterious cardiovascular actions of Ang II. Ang-(1-7) is formed from Ang II degradation by ACE2 or from cleavage of Ang I by various endopeptidases such as neutral endopeptidase (NEP), prolyl oligopeptidase, and thimet oligopeptidase. In addition, Ang I can be converted by ACE2 to Ang-(1-9), which in turn can be cleaved by NEP or ACE to form Ang-(1-7). In animal models, Ang-(1-7) lowers blood pressure and induces cardioprotective effects through vascular, cardiac, renal, and neural mechanisms [13], The literature suggests that most, if not all, of the physiological cardiovascular actions of Ang-(1-7) are mediated through *mas* g-protein coupled receptors [13], A few recent studies, however, provide evidence for potential heterodimerization and functional interactions between *mas* and AT_2 receptors, as well as a role for Ang-(1-7) to antagonize AT_1-receptor mediated signaling [14,15], More recently, the endogenous heptapeptide alamandine was identified in human blood [16], Alamandine is primarily formed from cleavage of Ang A via ACE2, but also from decarboxylation of Ang-(1-7) [Figure 1], Alamandine differs from Ang-(1-7) only in its N-terminal amino acid [Ala^1 versus Asp^1 for Ang-(1-7)], and binds mas-related g-protein coupled receptor D (MrgD) to elicit vasodilatory and anti-hypertensive actions, similar to Ang-(1-7) [17].

RAS and Autonomic Interactions in Cardiovascular Control Ang II Pathways

In addition to actions on the vasculature, kidneys, adrenal glands, and heart, an important mechanism by which the RAS contributes to cardiovascular regulation is through modulation of the autonomic nervous system. The autonomic nervous system regulates cardiovascular function via coordinated actions of: (1) afferent autonomic neural pathways signaling distension of the great vessels and cardiac chambers; and (2) efferent pathways transmitting sympathetic and parasympathetic outflow to cardiovascular end organs such as heart and vasculature. Most research to date has focused on the bidirectional stimulatory interactions between Ang II and the SNS. Renal sympathetic innervation is a major

determinant of β1-adrenergic receptor-mediated renin release, thus contributing to control of circulating Ang II levels (Table 1; Figure 2). Consistent with this, renal denervation or electrical activation of the carotid baroreflex activation to suppress efferent sympathetic outflow reduces circulating renin activity, Ang II, and aldosterone in experimental animal models and patients with resistant hypertension [18,19].

Conversely, Ang II AT_1 receptors are abundant at each synaptic relay of the autonomic nervous system (e.g. preganglionic neurons, ganglia, nerve terminals, regulatory brain regions), to influence sympathetic and parasympathetic neurotransmission (Figure 2) [20]. Ang II enhances SNS neurotransmission by stimulating presynaptic release of norepinephrine and epinephrine from sympathetic nerves, facilitating sympathetic ganglionic transmission, inhibiting norepinephrine reuptake in nerve terminals, increasing the density of sympathetic innervation in cardiovascular end organs, and enhancing vasoconstrictor responses to norepinephrine (Table 1; Figure 2) [21]. The physiological importance of this sympathetic activation to the pressor effects of exogenous Ang II, however, remains controversial [21,22]. This may reflect differences in the animal models used, sites and routes of administration, rates of infusion, and time course of studies. In particular, higher pharmacological doses of Ang II are often required to increase sympathetic outflow [21]. Despite this, emerging evidence suggests that activation of endogenous central angiotensinergic pathways (either through increased Ang II production or enhanced AT_1 receptor expression and signaling) contributes to sympathetic hyperactivity and hypertension induced by high salt diet, obesity, cold exposure, and heart failure [23].

While Ang II does not readily cross the blood-brain barrier, it can be formed directly within brain or can access the central nervous system via AT_1 receptors distributed to circumventricular organs including the subfornical organ (SFO), area postrema, median eminence, and organum vasculosum of the lamina terminalis (OVLT) [24]. These circumventricular organs send efferent projections to brain regions implicated in the cardiovascular autonomic actions of Ang II including the arcuate (ARC) and paraventricular (PVN) nuclei of the hypothalamus, as well as the solitary tract nucleus (NTS), caudal ventrolateral medulla (CVLM), and rostral ventrolateral medulla (RVLM) of the brainstem. The RVLM contains sympathetic premotor neurons that project to the intermediolateral column of the spinal cord, to influence sympathetic vasomotor tone. Ang II AT_1 receptor-mediated activation of SFO/OVLT-PVN-RVLM pathways has been widely implicated in animal models of hypertension [25]. The actions of Ang II at AT_1 receptors in the PVN and RVLM rapidly contribute to sympathoexcitation and hypertension in rats, in part by stimulating oxidative stress and immune pathways [25]. As recently reviewed, Ang II stimulates AT_1 receptor-mediated oxidative stress to increase intracellular calcium, which inhibits voltage-gated potassium channels to increase spontaneous neuronal action potentials and firing [23]. This results in activation of glutamatergic and inhibition of GABAergic interneurons contributing to presympathetic neuron activation to increase SNS activity and elevate blood pressure. Similar to Ang II, Ang-(1-12) administration in the ARC, PVN, or RVLM increases blood pressure, heart rate, and sympathetic nerve activity [26]. The blood pressure and sympathetic effects of both Ang II and Ang-(1-12) are prevented by central administration of ACE inhibitors or AT_1 receptor blockers (ARBs).

Ang II also impairs arterial baroreceptor reflex function in animal models, to allow for unrestrained sympathetic activation, by resetting the set point to higher levels of pressure as well as decreasing the baroreflex sensitivity [21,26]. These baroreflex inhibitory effects are primarily mediated by actions of Ang II on the brain to reduce efferent vagal tone to the heart, although a few reports have suggested direct actions of Ang II to inhibit firing of aortic arch baroreceptors or the vagus nerve [21]. The effects of Ang II on baroreflex function involve the NTS, a brainstem region that is the first central locus receiving afferent baroreceptor input. Several neuropeptide or intracellular mediators are implicated in the ability of Ang II to suppress baroreflex function including substance P, nitric oxide pathways, GABA release, the Rho kinase pathway, and endocannabinoids [20,27–29]. Ang-(1-12) also impairs baroreflex sensitivity for control of heart rate and sympathetic activity when given in the NTS and CVLM, respectively, with effects requiring conversion to Ang II by ACE or chymase and subsequent binding to AT_1 receptors [30,26].

Similar to Ang II, Ang III can act at AT_1 receptors distributed to autonomic nervous system pathways to facilitate post-synaptic noradrenergic neurotransmission, and inhibit the parasympathetic component of the arterial baroreceptor reflex [10,9]. When administered directly into brain, Ang III increases blood pressure and renal sympathetic nerve activity in anesthetized rats, to a similar magnitude as Ang II and with responses exacerbated under high sodium conditions [31]. The duration of pressor and sympathoexcitatory responses elicited by Ang III is shorter compared to Ang II, however, due to a reduced half-life. Central Ang III also exerts tonic stimulatory control of blood pressure in hypertensive rats, and contributes to sympathetic hyperactivity and cardiac dysfunction in a rat model of myocardial infarction [32,33]. Interestingly, it has been proposed Ang III is the major bioactive peptide of the brain RAS, and that Ang II requires conversion to Ang III to elicit AT_1 receptor-mediated pressor and dipsogenic responses. This hypothesis is primarily based on findings that aminopeptidase inhibitors attenuate pressor responses to Ang II; however, this remains controversial [34].

The evidence for RAS: autonomic interactions in humans is more tenuous with acute Ang II administration producing inconsistent effects on sympathetic neural outflow and adrenal medullary catecholamine secretion in healthy subjects and patients with essential hypertension [35,21,36,37]. This may reflect a reflexive decrease in sympathetic activity in response to the pressor response produced by peripheral Ang II administration, regional differences in changes in sympathetic outflow, limitations in the route and duration of administration in humans, and difficulties with quantitatively assessing cardiovascular autonomic activity in humans. Despite conflicting findings for sympathetic tone, Ang II alters the operating point and sensitivity of the arterial baroreceptor reflex in clinical populations [35,38,39,36]. There is currently no information on the role of other components of Ang II pathways, such as Ang-(1-12) or Ang III, in cardiovascular control in humans.

Aldosterone

Ang II is a major stimulus for secretion of aldosterone, a steroid hormone produced by the zona glomerulosa of the adrenal cortex. Classically, aldosterone activates nuclear mineralocorticoid receptors (MR) in the distal tubules and collecting ducts of the nephron to

promote sodium retention and elevate blood pressure via genomic mechanisms. Aldosterone can also activate cell surface MR to promote vasoconstriction via more rapid non-genomic mechanisms [40]. In addition to direct renal and vascular actions, emerging evidence suggests that aldosterone activates brain MR to contribute to sympathetic activation, blood pressure elevation, and augmentation of the exercise pressor reflex in animal models of hypertension and heart failure [23,25,41]. Circulating aldosterone accesses neurons in the brain via MR distributed to circumventricular organs such as the SFO and OVLT, and the hypertensive effects of systemic aldosterone administration are attenuated by lesion of the SFO [23]. Aldosterone is also produced locally in the brain and can activate central MR to induce slower neuromodulatory effects to increase activity of epithelial sodium channels, resulting in release of endogenous ouabain from magnocellular neurons in the PVN. In addition, aldosterone increases expression of Ang II pathway components (e.g. ACE, AT_1 receptors) and oxidative stress, to enhance angiotensinergic signaling and elevate blood pressure and sympathetic activity via an AT_1 receptor-mediated mechanism [23]. Few studies have examined effects of aldosterone administration on cardiovascular autonomic regulation in clinical populations. A handful of studies have shown no effect of acute intravenous aldosterone infusion on muscle SNS activity, with either impairment or improvement of cardiac vagal tone, in healthy subjects [42–45]. Patients with aldosterone-producing adenoma, however, have increased muscle sympathetic nerve activity that is normalized following unilateral adrenalectomy suggesting central sites of action for circulating aldosterone in humans [23]. The effects of blocking endogenous aldosterone actions with MR antagonists on cardiovascular autonomic control are discussed in the clinical implications section of this review.

Prorenin and Prorenin Receptor

While the importance of the brain RAS to hypertension is well recognized, there is low renin expression within the central nervous system for local Ang II formation. PRR is highly expressed in brain and can bind renin and prorenin to increase catalytic efficiency for Ang II biosynthesis as well as initiate intracellular signaling independent of Ang II [46]. Recent studies have begun to elucidate the role of the PRR in neural control of cardiovascular function, particularly related to the pathogenesis of neurogenic hypertension. In hypertensive rodents, PRR gene expression is upregulated in neurons in cardiovascular autonomic regulatory brain regions including supraoptic nucleus, SFO, and PVN [47,48]. In anesthetized rats, microinjection of human prorenin in the PVN increases splanchnic sympathetic nerve activity via direct PRR signaling [49]. Conversely, in hypertensive rodents, brain-targeted PRR inhibition attenuates hypertension, cardiac and vasomotor sympathetic tone, vasopressin release, and baroreflex dysfunction [50,51], Deleterious effects of prorenin on cardiovascular autonomic regulation involve increased Ang II formation, and potential direct effects to stimulate proinflammatory cytokines, reactive oxygen species, and microglia [52,49], In addition, prorenin increases firing activity of magnocellular and parvocellular neurons in the PVN via Ang II-dependent and –independent mechanisms, respectively, by increasing intracellular calcium to inhibit voltage-gated potassium currents [53].

Ang-(1-7) Pathways

The understanding of potential interactions between Ang-(1-7) and the autonomic nervous system has emerged as an important, yet understudied, area of research. Similar to Ang II AT_1 receptors, Ang-(1-7) *mas* receptors are distributed to all pathways of the autonomic nervous system including preganglionic neurons, ganglia, nerve terminals, and in circumventricular organs and regulatory brain regions including the NTS, PVN, and RVLM [20,54], In terms of interactions with the SNS, Ang-(1-7) enhances norepinephrine reuptake and reduces evoked norepinephrine release from hypothalamus and mesenteric arteries of hypertensive rats [55], In addition, Ang-(1-7) reduces sympathetic nerve proliferation in the atria in a canine model of chronic atrial tachycardia [56], While producing no effect on blood pressure in normal rodents, perhaps due to restraint of vasodilatory actions by arterial baroreflex buffering, chronic central Ang-(1-7) infusion lowers blood pressure in hypertensive animal models [55], These blood pressure lowering effects are associated with reductions in cardiac and renal sympathetic nerve activity and improvements in heart rate variability and the arterial baroreflex sensitivity for control of both heart rate and renal sympathetic nerve activity [26,55], Similarly, the nonpeptide Ang-(1-7) receptor agonist AVE0991 lowers blood pressure and improves baroreflex sensitivity in hypertensive rats [55]. Ang-(1-7) also attenuates cardiac and renal sympathetic responses to an acute emotional stressor in rats [57]. Conversely, global *mas* receptor knockout in mice reduces baroreflex sensitivity, implicating a protective role for endogenous Ang-(1-7) actions in cardiac autonomic tone [58]. Discordant effects can be observed, however, when Ang-(1-7) is administered directly into cardiovascular regulatory brain regions [26]. Similar to Ang II, microinjection of Ang-(1-7) in the NTS and CVLM produces depressor and bradycardic effects, whereas administration in the PVN and RVLM increases blood pressure, renal and splanchnic nerve activity, and cardiac sympathetic afferent reflex [59,60]. The hypertensive and sympathoexcitatory effects of Ang-(1-7) in the RVLM are reported to involve activation of *mas* receptors on glial cells to engage glutamatergic- and adenosine triphosphate-mediated mechanisms [59].

Another component of the Ang-(1-7)-forming axis, ACE2, is found in neurons and astroglial cells in cardiovascular brain regions including the OVLT, SFO, PVN, RVLM and NTS [54]. ACE2 expression is reduced in these brain regions in animal models of hypertension and heart failure. ACE2 overexpression in the brain lowers blood pressure and reduces urinary norepinephrine excretion and renal sympathetic nerve activity in these models [61]. In addition, either ACE2 overexpression or the small molecule ACE2 activator XNT improves cardiac autonomic balance in response to diabetes and emotional stressors in animals [61]. Conversely, ACE2 genetic deletion or pharmacological inhibition elevates blood pressure, increases cardiac sympathetic tone, and reduces the baroreflex sensitivity. While the beneficial effects of ACE2 on cardiovascular autonomic tone could be due to either reduced Ang II or increased Ang-(1-7) formation, most of these effects are blocked by the *mas* receptor antagonist A779 suggesting Ang-(1-7)-mediated mechanisms [61]. Similar to Ang-(1-7), central alamandine infusion improves baroreflex sensitivity for control of heart rate [17]. Alamandine, however, also has site-specific cardiovascular actions by acting at MrgD

within the CVLM and RVLM to produce vasodilation and decrease blood pressure [16], and by acting in the PVN to increase blood pressure and renal sympathetic nerve activity [62].

Taken together, the cardiovascular actions of Ang-(1-7) and components of the protective counter-regulatory arm of the RAS, appear to involve modulation of sympathetic and parasympathetic tone. Additional research is needed, however, to better understand site-specific actions of Ang-(1-7) in autonomic brain regions as well as the magnitude and relative importance of autonomic mechanisms to cardiovascular effects of this hormone, particularly in the context of cardiovascular pathophysiology.

Clinical Implications of Targeting the RAS

The literature provides strong evidence for facilitatory RAS: autonomic interactions in cardiovascular pathophysiology in animal models; however, these findings do not always translate to clinical studies. While there is general consensus that the blood pressure lowering effects of RAS blockers involve modulation of the autonomic nervous system, the magnitude of this mechanism remains unclear due to heterogeneity of responses among clinical trials. This may reflect differences in the route, dose and duration of treatment, limitations of current methods to quantitatively measure cardiovascular autonomic activity in humans, as well as incomplete RAS inhibition resulting from the lower clinically used doses, low brain or tissue penetrance, an inability to enter the cell due to low lipophilicity to modulate intracellular RAS activity, or reactive rises in plasma renin activity or Ang I to activate non-canonical and/or tissue RAS pathways.[63,64] Of interest, RAS blockers attenuate but often fail to normalize sympathetic overactivity and blood pressure in essential hypertension, potentially placing patients at residual risk for major cardiovascular events [65]. Additionally, sympathetic and RAS overactivity are exacerbated in patients with comorbid risk factors (e.g. cardiac hypertrophy, obesity, metabolic syndrome, renal failure, chronic heart failure), with beneficial cardiovascular effects of RAS blockade often magnified under these conditions.

ACE Inhibitors and Angiotensin Receptor Blockers

Pharmacological therapies blocking Ang II activity are widely used in the treatment of essential hypertension and cardiovascular-related diseases due to their protective effects on blood pressure and cardiovascular end organs. These therapies are often also used in obese and type II diabetic patients due to their beneficial metabolic profile, including the ability to improve insulin sensitivity and reduce incidence of new-onset diabetes in controlled clinical trials [66,67]. The two main classes of drugs clinically used for inhibiting Ang II activity are ARBs and ACE inhibitors [68]. ARBs prevent the ability of Ang II to bind AT_1 receptors and initiate intracellular signaling, while ACE inhibitors competitively block ACE to prevent Ang II formation from Ang I. These therapies also shift the balance of the RAS to increase circulating levels of Ang-(1-7), which may contribute to their beneficial cardiovascular effects [69–71]. ACE inhibitors block Ang II formation and Ang-(1-7) degradation by ACE to shunt metabolism towards Ang-(1-7) production. ARBs produce reflexive increases in plasma renin activity and ineffective Ang II, resulting in increased Ang-(1-7) formation. Some studies have shown neutral effects of ACE inhibitors and ARBs on measures of

sympathetic tone such as plasma norepinephrine and muscle sympathetic nerve activity in clinical populations [72,73,37,74–76]. The collective literature, however, suggests that the beneficial effects of these therapies on blood pressure are, at least in part, due to cardiovascular autonomic mechanisms (Table 2) [62]. ACE inhibitors and ARBs reduce central sympathetic neural discharge as well as reduce norepinephrine spillover rates and improve tissue clearance at peripheral nerve terminals in essential hypertension [65]. These therapies also improve the gain and set point of the arterial baroreflex for control of heart rate and sympathetic activity to preserve autonomic reflex control.

The beneficial cardiovascular autonomic effects of ACE inhibitors and ARBs appear magnified in conditions with exaggerated sympathetic overactivity or baroreflex dysfunction such as obesity, congestive heart failure, chronic renal disease, and primary autonomic failure [65,77,78]. Obesity is associated with sympathetic and RAS overactivity, both of which can be attenuated by lifestyle modifications such as weight loss or by pharmacological RAS blockade [79–81]. Interestingly, depressor and sympathoinhibitory effects of weight loss are amplified in obese hypertensive subjects when combined with ACE inhibition, by reducing circulating RAS overactivation as well as hyperleptinemia [81]. In heart failure, ACE inhibitors and ARBs reduce muscle SNS activity (measured by microneurography) and improve cardiac SNS activity (measured by ^{123}I-*meta*-iodobenzylguanidine scintigraphy) and enhance the baroreflex sensitivity for control of heart rate [82]. In chronic kidney disease, these therapies reduce, but do not normalize, blood pressure and sympathetic activity [83]. Based on this, recent studies have examined combination ARB and sympatholytic treatment, and have shown greater sympathoinhibitory effects compared with either drug alone in selected patients with chronic renal disease [77]. Finally, acute administration of the ARB losartan reduces nocturnal blood pressure and pressure natriuresis in patients with primary autonomic failure, without worsening morning orthostatic tolerance [78]. Of interest, primary autonomic failure is often associated with undetectable plasma renin activity due to loss of renal sympathetic innervation, suggesting non-canonical and renin-independent pathways for Ang II formation in these patients.

Direct Renin Inhibitors

Direct renin inhibitors offer a therapeutic approach to potentially achieve more complete RAS inhibition. Aliskiren is a first-in-class nonpeptide orally active renin inhibitor that binds renin and non-proteolytically activated prorenin to prevent cleavage of angiotensinogen to Ang I, to ultimately reduce Ang II formation. Aliskiren elicits sustained antihypertensive effects in clinical populations [84]; however, this drug has increased side effects compared with ACE inhibitors and ARBs as well as contraindications in patients with diabetes or moderate to severe renal impairment. In hypertensive rats, centrally administered aliskiren lowers blood pressure, in part by reducing renal sympathetic nerve activity and restoring arterial baroreflex function (Table 2) [85], The ability of aliskiren to inhibit sympathetic tone in patients with hypertension remains controversial. While a few studies provide evidence aliskiren reduces resting and upright muscle sympathetic nerve activity in hypertensive subjects [86,87], others show no effect to attenuate sympathetic activation produced by amlodipine or cold pressor test [88,89], In terms of parasympathetic function, aliskiren restores the arterial baroreflex sensitivity in rats with renovascular hypertension, and

improves heart rate responses to deep breathing (sinus arrhythmia) in patients with diabetes [90,91], These limited studies suggest that the blood pressure-lowering effects of renin inhibition involve improved cardiovascular autonomic tone (Table 2); however, further research is needed. In this regard, an active clinical trial is examining effects of aliskiren versus the centrally acting α2-adrenergic agonist clonidine on endothelial function and muscle sympathetic nerve activity in obesity hypertension (NCTO1983462).

Mineralocorticoid Receptor Antagonists

The MR is a steroid hormone receptor that can bind aldosterone, Ang II, cortisol or other hormone-independent ligands to promote hypertension via genomic and non-genomic mechanisms [92]. Spironolactone is a first generation nonselective MR antagonist limited by anti-androgenic side effects including gynecomastia, breast tenderness, and erectile dysfunction. Eplerenone is a second generation highly selective competitive MR antagonist with a more rapid time course to reach peak plasma concentrations and reduced side effects compared with spironolactone [93]. These MR antagonists effectively lower blood pressure and improve vascular function, particularly in drug resistant and low renin forms of essential hypertension [94]. Acute eplerenone also reduces nocturnal blood pressure in primary autonomic failure, implicating a role for MR activation in supine hypertension in these patients [95]. Chronic central MR antagonism lowers blood pressure, reduces efferent sympathetic discharge, and attenuates exaggerated exercise pressor reflex responses in rodent models of hypertension, myocardial infarction, and heart failure (Table 2) [23,41]. Furthermore, spironolactone enhances cardiac vagal tone and renal baroreceptor reflex sensitivity in rodent models, suggesting improved parasympathetic function.[96,97] In patients with hypertension, spironolactone lowers blood pressure, reduces plasma norepinephrine levels and attenuates diuretic-induced sympathetic activation, with neutral effects on muscle sympathetic nerve activity (Table 2) [23]. Spironolactone also improves heart rate variability and blunts the morning surge in heart rate associated with sympathetic reactivity in patients with heart failure suggesting improved cardiac sympathovagal balance [98,82]. Current clinical trials are investigating effects of eplerenone on exercise-induced sympathetic and pressor responses in essential hypertension and primary aldosteronism (NCT01996449), as well as effects of spironolactone on baroreflex sensitivity and muscle sympathetic nerve activity during controlled hypoglycemia in healthy subjects (NCT03429946). While third generation non-steroidal selective MR antagonists have been developed, they have not yet been marketed. It has been suggested that newer MR antagonists are needed that preferentially target inflammatory, profibrotic, and potentially sympathoexcitatory effects of MR activation, without effects on renal potassium excretion or brain centers involved in normal physiological regulation of affect, stress, learning and memory (e.g. cortical and hippocampal neurons) [99].

Dual Neprilysin and Angiotensin Receptor Inhibitor

NEP is an enzyme that degrades numerous vasodilatory and natriuretic hormones (e.g. natriuretic peptides, bradykinin, substance P) as well as reduces Ang II and increases Ang-(1-7) formation. While NEP inhibition increases the bioavailability of these circulating vasodilatory and natriuretic mediators, clinical studies have not shown blood pressure

lowering effects of neprilysin inhibitors when administered alone, in part due to the increase in Ang II levels produced by these therapies. Therefore, combination therapies were developed to enhance the endogenous natriuretic peptide system to promote vasodilation, while reducing Ang II and increasing Ang-(1-7) levels, to improve overall neurohormonal balance. Sacubitril/valsartan (LCZ696) is a first-in-class dual NEP inhibitor and ARB approved to reduce risk of cardiovascular death and hospitalizations in heart failure [100]. Sacubitril/valsartan produces greater blood pressure-lowering effects when compared with an ARB alone or placebo in controlled trials in essential hypertension [101], and may produce insulin-sensitizing effects in obesity hypertension [102]. The specific mechanisms underlying beneficial effects of this combination drug remain unclear but may include sympathoinhibition, improved endothelial and cardiac function, and anti-arrhythmic, anti-atherosclerotic, and anti-thrombotic effects [103]. In support of a contribution of autonomic mechanisms, sacubitril/valsartan lowers blood pressure, reduces sympathetic vasomotor tone, and improves spontaneous baroreflex gain under low-salt conditions in hypertensive rats (Table 2) [104]; however, this finding has not been validated in clinical populations, with effects on sympathetic activity in heart failure currently under investigation (NCT02787798, NCT03415906).

Angiotensin-(1-7)

Ang-(1-7) has emerged as an attractive potential therapy for cardiovascular diseases based on its ability to produce vasodilatory, antihypertensive, anti-inflammatory, anti-atherosclerotic, and anti-thrombotic effects in experimental animal models. These antihypertensive effects appear to involve inhibition of sympathetic tone and facilitation of parasympathetic tone (Table 2). There are, however, limited clinical trials with Ang-(1-7) and its therapeutic potential is limited by short half-life and rapid turnover. Similar to findings in animal models, urinary Ang-(1-7) levels are reduced and inversely correlated with blood pressure in patients with untreated essential hypertension, suggesting an association of Ang-(1-7) deficiency with hypertension.[105] The majority of clinical trials with Ang-(1-7), to date, have examined effects of acute intra-arterial administration on forearm or renal vasodilation. These studies have shown vasodilation in patients with essential and obesity hypertension, no effect in patients with heart failure treated with ACE inhibitors, and inconsistent effects in healthy subjects [106]. Ongoing controlled trials are examining effects of acute intravenous Ang-(1-7) infusion on blood pressure, and interactions with the autonomic nervous system, in healthy subjects, essential hypertension, obesity hypertension, and primary autonomic failure (NCT02245230, NCT02591173, NCT03001271, NCT03604289). Methods to more chronically increase Ang-(1-7) levels or its actions are currently in development including oral formulations, stable analogues, *mas* receptor agonists, ACE2 activators, and recombinant human ACE2 [64]. Clinical targeting of Ang-(1-7) has also been explored for cancer, improving cognition following coronary artery bypass grafting, and hematological applications [107,108].

Conclusions

The identification of autonomic mechanisms underlying cardiovascular effects of the RAS, as well as the beneficial effects of RAS inhibition, remains an active area of research.

Studies in experimental animal models show extensive and reciprocal interactions between the RAS and autonomic nervous system for cardiovascular regulation, with an important role for activation of central angiotensinergic-sympathetic pathways in the development of hypertension and other cardiovascular diseases. These findings, however, do not always readily translate to clinical studies examining pharmacological targeting of the RAS. Regardless, there remains considerable evidence that cardiovascular effects of therapies targeting the RAS involve, at least in part, sympathetic inhibition and/or parasympathetic facilitation. The development of pharmacotherapies to provide more complete RAS inhibition or to activate Ang-(1-7) pathways may broaden the therapeutic potential for targeting the RAS, as well as provide new insights into mechanistic interactions of this hormone system with the autonomic nervous system.

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Abbreviations:

Ang	Angiotensin
ACE	Angiotensin converting enzyme
AT_1	Angiotensin type I
ARBs	Angiotensin receptor blockers
AT_2	Angiotensin type 2
ARC	Arcuate nucleus
CVLM	Caudal ventrolateral medulla
MrgD	Mas-related g-protein coupled receptor D
MR	Mineralocorticoid receptors
NEP	Neutral endopeptidase
OVLT	Organum vasculosum of the lamina terminalis
PRR	Prorenin receptor
PVN	Paraventricular nucleus
RAS	Renin-angiotensin system
RVLM	Rostral ventrolateral medulla
NTS	Solitary tract nucleus
SFO	Subfornical organ
SNS	Sympathetic nervous system

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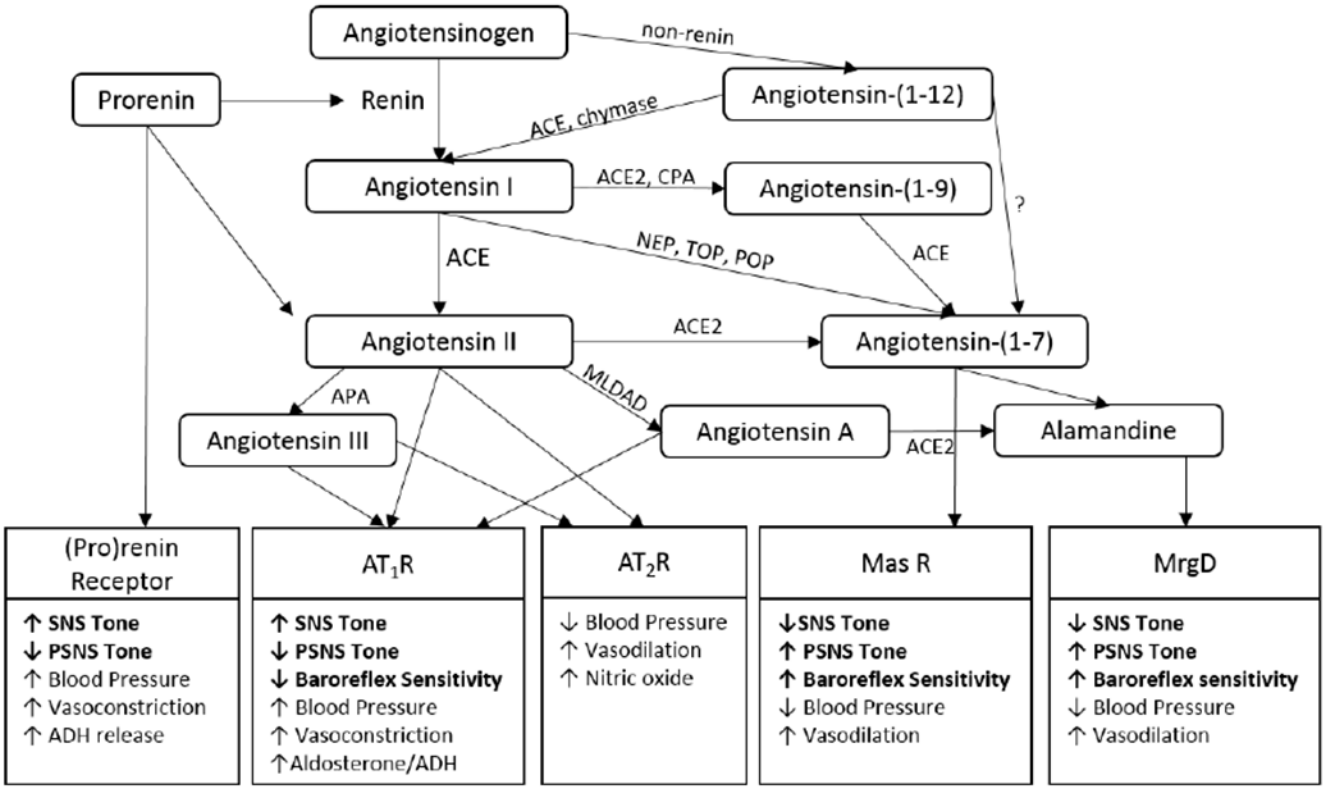

Figure 1. Overview of renin angiotensin system formation and degradation pathways showing primary receptor-mediated cardiovascular and autonomic effects.

Angiotensin converting enzyme (ACE), Neprilysin (NEP), propyl oligopeptidase (POP), thimet oligopeptidase (TOP), mononuclear leukocyte-derived aspartate decarboxylase (MLDAD), angiotensin type 1 receptor (AT1R), angiotensin type 2 receptor (AT2R), aminopeptidase A (APA), *mas* receptor (MasR), *mas* related g-protein couple receptor member D (MrgD), parasympathetic nervous system (PSNS), sympathetic nervous system (SNS), and anti-diuretic hormone (ADH).

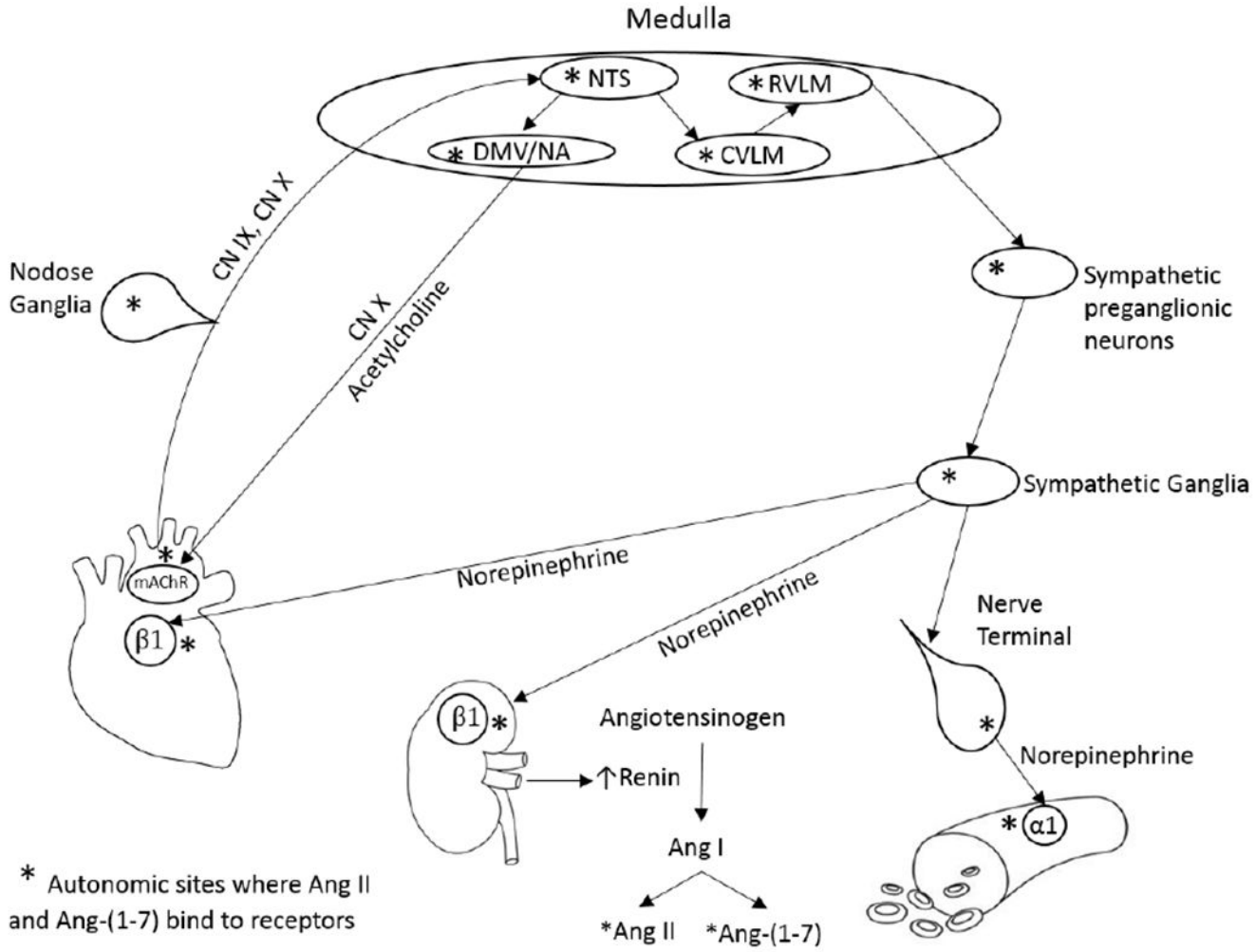

Figure 2. Bidirectional interactions between the renin-angiotensin and autonomic nervous systems.

The sympathetic nervous system is a major determinant of renin release from the kidneys via norepinephrine actions on beta-1 adrenergic receptors in juxtaglomerular cells. Renin is a key enzyme catalyzing formation of angiotensin I from angiotensinogen, which is subsequently cleaved to form angiotensin II and angiotensin-(1-7). These angiotensin peptides can act at AT_1 and *mas* receptors distributed throughout autonomic nervous system pathways (e.g. vagal afferents, nodose ganglion, regulatory brain regions, and sympathetic preganglionic neurons, ganglia, and nerve terminals) to influence sympathetic noradrenergic and parasympathetic cholinergic neurotransmission to cardiovascular end organs such as the heart, kidneys, and vasculature. Nucleus of the solitary tract (NTS), rostral ventrolateral medulla (RVLM), caudal ventrolateral medulla (CVLM), dorsal motor vagus (DMV), nucleus ambiguous (NA), glossopharyngeal nerve (CNIX), vagus nerve (CNX), beta 1 adrenergic receptor (β1), alpha 1 adrenergic receptor (α1), and muscarinic acetylcholine receptor (mAChR).

Table 1.

Summary of Interactions between Renin-Angiotensin and Autonomic Nervous Systems for Cardiovascular Control

Interaction	Site	Action
Ang II and ANS	Brain	• Increases sympathetic neural discharge.
	Sympathetic ganglia	• Facilitates sympathetic ganglionic transmission and inhibts norepinephrine reuptake in sympathetic nerve terminals.
	Adrenal Medulla	• Stimulates presynaptic norepinephrine and epinephrine release.
	Heart	• Inhibits firing of aortoic arch baroreceptors or vagal afferents to impair arterial baroreceptor reflex function. Decreases efferent parasympathetic tone to the heart to increase cardiac output.
	Blood Vessels	• Increases the density of sympathetic innervation and enhances α1 adrenergic receptor-mediated vasoconstrictor responses to norepinephrine.
Ang-(1-7) and ANS	Brain	• Descreases sympathetic neural discharge. Reduces norepinephrine release from hypothalamus.
	Sympathetic ganglia	• Attenuates sympathetic ganglionic transmission and enhances norepinephrine reuptake in sympathetic nerve terminals.
	Heart	• Improves arterial baroreceptor reflex function and reduces cardiac efferent sympathetic nerve activity to decrease cardiac output. Reduces sympathetic nerve proliferation in atria.
ANS and RAS	Kidney	• Sympathetic nerves release norepinephrine to stimulate β1 adrenergic receptors in renal juxtaglomerular cells to increase renin release, and thus circulating RAS hormone levels.

ANS, autonomic nervous system; Ang, angiotensin; RAS, renin-angiotensin system.

Table 2.

Autonomic Mechanisms of Therapies Targeting the Renin-Angiotensin System

Type of Drug	Plasma Norepinephrine	Sympathetic Nerve Activity	Vagal Tone/HRV	Baroreflex Sensitivity
ACE inhibitors				
Pre-clinical	↓	↓	↑	↑
Clinical	↓	↓	↑	↑
ARBs				
Pre-clinical	↓	↓	↑	↑
Clinical	−,↓	−,↓	↓	↑
MR Antagonist				
Pre-clinical	↓	↓	↑	↑
Clinical	↓	−,↓	↑	−,↑
Renin Inhibitors				
Pre-clinical	NA	↓	NA	↑
Clinical	−,↓	−,↓	↑	NA
Neprilysin Inhibitor/ARB				
Pre-clinical	NA	↓	NA	↑
Clinical	NA	NA	NA	NA
Angiotensin-(1-7)				
Pre-clinical	↓	↓	↑	↑
Clinical	NA	NA	NA	NA

Angiotensin converting enzyme (ACE), angiotensin receptor blocker (ARB), mineralocorticoid receptor (MR), and heart rate variability (HRV). ↓, decreases; ↑, increases; −, neutral effects; NA, information not currently available.