Role of the central renin-angiotensin system in hypertension (Review)

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Abstract. Present in more than one billion adults, hypertension is the most significant modifiable risk factor for mortality resulting from cardiovascular disease. Although its pathogenesis is not yet fully understood, the disruption of the renin-angiotensin system (RAS), consisting of the systemic and brain RAS, has been recognized as one of the primary reasons for several types of hypertension. Therefore, acquiring sound knowledge of the basic science of RAS and the underlying mechanisms of the signaling pathways associated with RAS may facilitate the discovery of novel therapeutic targets with which to promote the management of patients with cardiovascular and kidney disease. In total, 4 types of angiotensin II receptors have been identified (AT1R-AT4R), of which AT1R plays the most important role in vasoconstriction and has been most extensively studied. It has been found in several regions of the brain, and its distribution is highly associated with that of angiotensin-like immunoreactivity in nerve terminals. The effect of AT1R involves the activation of multiple media and signaling pathways, among which the most important signaling pathways are considered to be AT1R/JAK/STAT and Ras/Raf/MAPK pathways. In addition, the regulation of the nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and cyclic AMP response element-binding (CREB) pathways is also closely related to the effect of ATR1. Their mechanisms of action are related to pro-inflammatory and sympathetic excitatory effects. Central AT1R is involved in almost all types of hypertension, including spontaneous hypertension, salt-sensitive hypertension, obesity-induced hypertension, renovascular hypertension, diabetic hypertension, L-NAME-induced hypertension, stress-induced hypertension, angiotensin II-induced hypertension and aldosterone-induced hypertension. There are 2 types of central AT1R blockade, acute blockade and chronic blockade. The latter can be achieved by chemical blockade or genetic engineering. The present review article aimed to highlight the prevalence, functions, interactions and modulation means of central AT-1R in an effort to assist in the treatment of several pathological conditions. The identification of angiotensin-derived peptides and the development of AT-2R agonists may provide a wider perspective on RAS, as well as novel therapeutic strategies.

Contents

1. Introduction

Hypertension affects over a quarter of the adult population in developed countries, which poses a significant health concern (1). Hypertension leads to several pathological conditions, including renal failure, congestive heart failure, stroke and myocardial infarction (2). Additionally, its pathogenesis is not yet fully understood. Previous research has indicated that genetics could help alter arterial blood pressure via molecular pathways, and identify potential therapeutic targets for the treatment of hypertension (3). A disruption in the renin-angiotensin system (RAS), including the systemic and

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brain RAS, has been recognized as one of the primary reasons for several types of hypertension.

RAS is a hormonal system which regulates fluid balance and blood pressure. As a hormone, renin is secreted by granular cells in the juxtaglomerular apparatus of kidneys (4). It is a medium used for the conversion of angiotensinogen released from the liver to angiotensin I. The angiotensin-converting enzyme (ACE) then mediates the conversion to angiotensin II (ANG II). ANG II is a vasoactive peptide, which causes blood vessel constriction by activating G-proteins in the vessels, leading to blood pressure elevation. In addition, ANG II induces the secretion of aldosterone from the adrenal cortex, which leads to sodium and water retention in the kidneys, and in turn causes an elevation in blood pressure. Angiotensin receptors are a type of G protein-coupled receptors that require ANG II binding for their activation (5). In total, 4 types of ANG II receptors have been identified (AT1R-AT4R). Among these, AT1R, the most well-studied receptor, has been found in the heart, lungs, kidneys, brain, blood vessels and adrenal cortex, and AT2R has been considered to be involved in vascular growth. When first identified, peripheral RAS was considered to be simple as described above. However, recent studies have demonstrated that RAS is much more complex (6,7). Some new pathways that regulate the function of AT-1R have been identified, one of which is the function of AT-2R following ANG II binding. It is believed that AT-2R activation may counteract the function of AT-1R following ANG II binding and protect against brain injury (8). In addition to RAS, all the components of brain RAS have been identified over the past 30 years, and the functions of brain RAS have been extensively studied.

AT1R and AT2R are found in several regions of the brain, and their distributions are associated with angiotensin-like immunoreactivity in nerve terminals. ANG II functions through AT1R in the brain to control fluid homeostasis and autonomic pathways regulating the cardiovascular system and neuroendocrine system. AT-2R in the brain is involved in cardiovascular and behavioral function (9). Unlike AT1R and AT2R, AT4 receptors are not widely distributed in the brain (10,11). The presence of angiotensin receptors in the brain indicates that they have diverse and significant physiological functions. The present review article focuses on the distribution and function of AT1 receptors, in aim to help determine the pathways involved in their function.

2. Local AT1R in the central nervous system

The hypothalamic paraventricular nucleus (PVN). The PVN is connected reciprocally with other regions of the brain, which are involved in regulating cardiovascular function (12). PVN acts as a central location for the integration of sympathetic nerve activity and cardiovascular function (13). The functions of the PVN are controlled by neurotransmitters, such as norepinephrine and glutamate, pro-inflammatory cytokines and RAS. Previous studies have indicated that blocking cytokines in the brain leads to a decrease in RAS components (14,15). RAS blockade causes the increased production of pro-inflammatory cytokines in the brain, and blocking these cytokines without influencing their plasma levels leads to decreases in the levels of brain renin, ACE and AT1R expression. This indicates that pro-inflammatory cytokines can regulate brain RAS and in turn, influence sympathetic nervous system and extracellular fluid volume, which is involved in heart failure. Zhu *et al* demonstrated that the administration of intracerebroventricular AT1R antagonist helped to normalize cardiac sympathetic afferent reflex (CSAR) and reduced renal sympathetic nerve activity (RSNA) and mean arterial pressure (16). This finding suggests that AT1 receptors are involved in increased CSAR among rats with renovascular hypertension. The study by Zhong *et al* demonstrated that the inhibition or lesion of the PVN inhibits CSAR, while the excitation of the PVN induces CSAR, indicating that PVN is an essential component in the central neuroregulation of CSAR (17). It is well known that the PVN is rich in AT1 receptors. It has been reported that the microinjection of ANG II into the PVN increases CSAR and RSNA, which is mediated by AT1 receptors (18). The above-mentioned evidence indicates that the elevated activity of AT1 in the PVN increases CSAR and stimulates the nervous system, which is involved in renovascular hypertension.

Subfornical organ. RAS components in the brain regulate blood pressure by modulating sympathetic nerve activity. Notably, there are 2 significant areas of the brain that mediate the sympathoexcitatory actions of ANG II, the subfornical organ (SFO) and the rostral ventrolateral medulla (RVLM) (19,20). SFO is a circumventricular organ, which lies outside the blood-brain barrier (BBB), thereby having access to both intraventricular and circulating ANG II. A previous study illustrated an association between SFO and the hypothalamic nucleus, both of which regulate drinking and sympathetic nerve activity (21). Nunes and Braga demonstrated that chronically ANG II-infused (subcutaneous pump) rats had sympathetically mediated hypertension, which was associated with increased AT1 receptor mRNA levels in the RVLM and decreased levels in the SFO (22). That study suggested that the differential AT-1R expression in the SFO and RVLM was a crucial mechanism for the sympathoexcitatory and pressor effects that resulted from the increased plasma levels of ANG II. However, earlier research demonstrated that the direct administration of ANG II in the SFO induced a pressor response, which could either be blocked by the prior administration of an ANG II antagonist or a lesion in the SFO (23,24). The SFO extends to the median preoptic nucleus (MnPO), the organum vasculosum of the lamina terminalis (OVLT), nucleus tractus solitarius, as well as both the PVN and the supraoptic nuclei (SON) of the hypothalamus (25). SFO neurons that extend into the PVN are excited by ANG II administration, and an ANG II antagonist or a lesion in the PVN leads to a decrease in the pressor responses to SFO stimulation (26). These findings suggest that basal ANG II can act in the SFO to stimulate sympathetic nerve activity as well as maintain basal arterial pressure.

Systemic ANG II has been found to influence drinking, which is mediated through the SFO and angiotensin has been observed to be abundantly expressed in the SFO, suggesting that the source of SFO ANG II may be the circulation of cerebrospinal fluid (CSF) or the synthesis by SFO from angiotensin (27). Both angiotensin and renin are available at the SFO, indicating that there is a *de novo* synthesis of ANG II at the SFO. These findings suggest that ANG II may be a

neurotransmitter that originates from neuron cell bodies in the SFO.

Supraoptic nuclei. The supraoptic nucleus (SON) is a magnocellular neurosecretory nucleus from the hypothalamus. It is located at the base of the brain next to the optic chiasm and it consists of 3,000 neurons. There is ample evidence to infer that ANG II plays a critical role in the function of magnocellular neurons in the SON and PVN. AT1 receptors have been identified in some areas of the brain, including the SON neurons (28). Studies have demonstrated that ANG II enhances the firing rate of SON neurons, which is partly mediated by the suppression of the transient outward current (29,30). Yang *et al* demonstrated that ANG II induced the depolarization of SON neurons, which could be reversed by AT1 receptor antagonists (31). Excitatory synaptic inputs are potentiated by ANG II into the SON neurons through AT1 receptors (32). Moellenhoff *et al* demonstrated that the repetitive intracerebroventricular injection of ANG II led to an expression pattern of transcription factors, which was significantly different from the observation following acute ANG II injection (33). The chronic ANG II injection induces c-Jun, reduces the expression of c-Fos mRNA in the SON, and increases the expression of AT1 receptors. Antunes *et al* demonstrated that AT1 receptors in the SON participated in water and sodium intake following activation by ANG II within the medial septal area and also helped to prove that AT2 is not involved in this process (34).

MnPO. Research has demonstrated that the integrity of the anteroventral third ventricular (AV3V) region of the anterior hypothalamus, where the MnPO is located, is essential to the development of experimental hypertension (35,36). The MnPO has been reported to be rich in both AT1 and *N*-methyl-D-aspartate (NMDA) receptors (37,38). The MnPO is activated during stress and activated MnPO in turn leads to the stimulation of AT1 and NR1 receptors, which are the processes involved in cardiovascular homeostasis. Lesion and microinjection studies on the MnPO have demonstrated its importance in pressor and behavioral responses to the hyperosmotic stimulus or circulating ANG II (39), suggesting that the MnPO is the main site for neural integration of sensory, osmotic and circulating signals, as well as signal transduction into cardiovascular, hormonal or behavioral responses. Henry *et al* demonstrated that a large number of MnPO neurons responded to the activation of postsynaptic AT1 type receptors with extended inward current and membrane depolarization, as well as decreased membrane potassium conductance (40). However, Schwartz *et al* demonstrated that the administration of an AT1 receptor antagonist into the MnPO of rats selectively increased the hemodynamic response of vascular responders to pharmacological (cocaine) or behavioral (startle with cold water) stressors (37). Their results demonstrated that the the elevation of systemic vascular resistance in vascular responders rather than the pressor response, was mediated by the angiotensinergic conduction in the MnPO. The MnPO has been considered the target for central angiotensinergic input from neurons in the SFO.

RVLM. The RVLM is a portion of the brain stem that controls the heart, blood vessels, swallowing, breathing and several other functions that are part of the autonomic nervous system. It has been well established that RVLM cells play a critical role in toning and physically regulating blood pressure. Guertzenstein and Silver demonstrated that a bilateral lesion of these neurons in anesthetized mice caused a marked decrease in blood pressure similar to that of the spinal transaction (41). The excitation of cells in the RVLM by the local microinjection of excitatory amino acids leads to elevated blood pressure, which could be explained by the action of sympathetic vasoconstrictor nerves (42,43). The stimulation of these cells also leads to a higher heart rate and the release of adrenomedullary catecholamines. However, the experiments mentioned above were all performed among anesthetized animals. An experiment where excitatory amino acids were injected into the RVLM of conscious unrestricted rats demonstrated a significant pressor response (44). An interesting feature of the RVLM cells is that they do not exert control of sympathetic outflow in a uniform manner. A previous study demonstrated that the activity of single RVLM sympathetic neurons was related to the firing pattern of sympathetic nerves supplying different vascular beds. It was also shown that following the bilateral application of glycine in the RVLM, different RVLM regions displayed different time frames of sympathetic nerves supplying skeletal muscle and renal vascular beds, suggesting that cells in different RVLM regions exert differential effects (45). The stimulation of cells in various RVLM regions by local excitatory amino acid microinjection leads to different patterns of regional vasomotor responses, depending on the area that is stimulated. Another study demonstrated that an increase in the activity of vasoconstrictor nerves supplying blood vessels in the skin and skeletal muscles was observed when medial and lateral regions within the RVLM were stimulated (46). Moreover, other studies have indicated that RVLM neurons can not only control the renal bed, but also control the hind limb and the mesenteric bed (47,48). Therefore, the possibility that RVLM neurons that are both specific and non-specific was suggested by Barman and Gebber (49). *In vitro* autoradiographic studies have demonstrated that the RVLM of the majority of species, including human beings has a high density of AT1 receptors (50). AT_1 receptor blockade by the administration of a selective AT_1 receptor antagonist into the RVLM among anesthetized normotensive rats or rabbits exerts no effect on sympathetic nerve activity and resting arterial pressure (51,52). This suggests that endogenous ANG II does not affect the firing rate of presympathetic neurons in the RVLM under normal conditions. However, the bilateral blockade of AT_1 receptors in the RVLM does lead to low arterial pressure and reduced sympathetic activity among Dahl salt-sensitive (DS) hypertensive rats and spontaneously hypertensive rats (SHRs) (52,53). Though under normal conditions blockade of AT_1 receptors in the RVLM of normotensive rats does not change arterial pressure, we have shown that bilateral injections of $GABA_A$ receptor antagonists in the RVLM of normotensive anesthetized rats followed by bilateral microinjections of the selective AT_1 receptor antagonists in the RVLM reduces both arterial pressure and renal sympathetic nerve activity (54). Therefore, it is possible that the endogenous tonic excitatory effect of ANG II on sympathoexcitatory RVLM neurons can be counteracted by a tonic inhibitory action, which relies on GABAergic synaptic transmission in normal conditions.

Sheriff *et al* demonstrated that bilateral microinjections of the AT_1 receptor antagonist in the RVLM led to markedly increased arterial pressure under conditions of hypoxia rather than normoxia (55). The finding indicates that endogenous ANG II in the RVLM inhibits the activity of RVLM presympathetic neurons under conditions of hypoxia. All the above evidence, combined with results from prior studies, suggests that the effect of endogenous ANG II in the RVLM on the firing rate of sympathoexcitatory neurons is determined by their physiological and pathophysiological states.

Nucleus tractus solitarius (NTS). The NTS is situated along the medulla oblongata, and it is divided into a rostral gustatory nucleus and a caudal region of neurons. The cardiovascular neurons are located near the midline of the nucleus, while the respiratory neurons are located laterally. The NTS is a pivotal region of the brainstem, which mediates baroreflex and is also a region where ANG peptides modulate autonomic balance (56,57). Baroreflex has been shown to play a critical role in cardiovascular function in both normal and disease states (58). Central ANG II mechanisms have been shown to modulate the interaction between baroreflex and CSAR (59,60). Wang *et al* demonstrated that the local blockade of AT1 receptors in the NTS attenuated the blunting of the baroreflex by increased sympathetic activity (61). That study also demonstrated that CSAR activation at the NTS neuronal level led to decreases in barosensitivity and baseline discharge, which could be reversed by AT1 receptor antagonists. ANG-(1-12) is a C-terminally extended peptide which is longer than ANG I. It has been observed in peripheral tissues and plasma. It induced systemic dose-dependent vasoconstriction and pressor responses in isolated aortas of Wistar rats (62). ACE enzymatic activity has been detected in the dorsal medulla of Sprague-Dawley rats, indicating that ANG-(1-12) can be converted into ANG-(1-7) or ANG II within the NTS to regulate cardiovascular function (63). Arnold *et al* demonstrated that within the NTS of normotensive Sprague-Dawley rats, exogenous ANG-(1-12) elicited transiently decreased action potential (AP) without any change in heart rate (HR) (64). They also demonstrated that HR variability was reduced and the overall sympathovagal balance was shifted toward sympathetic dominance. It has been shown that low-dose injections of ANG (1-7) or ANG II within the NTS lead to transient depressor responses that are modulated by substance P and glutamate (65). The study by Arnold *et al* demonstrated that exogenous ANG-(1-12) was converted into ANG II to modulate baroreflex and cardiovascular function via the AT_1 receptors within the NTS of normotensive rats (64).

OVLT. The OVLT is one of the circumventricular organs of the brain. Both the SFO and the OVLT are closely interconnected with the MnPO of the hypothalamus (the nucleus medianus). The 3 structures constitute the AV3V region, which plays a vital role in regulating electrolyte balance by controlling thirst, vasopressin secretion, sodium excretion, and the regulation of blood volume. Cheung *et al* found that the administration of Ouabain for 2 weeks increased the levels of ANG II in the hypothalamus by several folds without affecting the ANG I levels (66). Increased levels of ANG II have been shown to be associated with significant decreases in AT_1 receptor densities in some nuclei. That study also demonstrated that ACE densities in the brain decreased, particularly in the OVLT and SFO (66).

3. Central AT1R pathway

AT1R/Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. The JAK/STAT signaling pathway transmits chemical signals from outside the cell through the cell membrane to the gene promoters on the DNA in the nucleus, leading to DNA transcription and activity inside the cell. The pathway is a main signaling alternative to the second messenger system. The JAK/STAT signaling system has 3 major parts, including a receptor, JAK, as well as STAT. There is abundant evidence to indicate that ANG II plays a critical part in the development of cardiac hypertrophy through AT-1 receptors. Cardiac hypertrophy has been shown to be an independent risk factor for cardiac morbidity and mortality (67). Cardiac hypertrophy can be triggered by mechanical and neurohumoral factors, among which ANG II has garnered interest in recent years due to its established importance *in vivo,* as well as *in vitro* (68). ANG II functions through the AT1 receptors. AT1-R activates the specific tyrosine kinase pathway and leads to tyrosine phosphorylation, subsequently activating ERK1/2, JNK and JAK. Previous research has demonstrated that JNK could be activated by ANG II via AT1-R in cardiomyocytes cultured from neonatal rats (69). Unlike the mitogen activated protein kinase family, the JAK/STAT pathway is closely associated with ANG II-induced cardiac hypertrophy. JAK/STAT signaling is a part of an autocrine loop for ANG II generation, which acts to reinforce the action of ANG II in cardiomyocytes (70). Chang *et al* demonstrated that the expression of visfatin, an adipocytokine present in cardiomyocytes and known to be involved in cardiomyopathy, was elevated in AT-1R mediated cardiomyopathy via JAK/STAT pathway (71).

Moreover, JAK-STAT activation provides a positive feedback pathway via the upregulation of angiotensinogen formation, resulting in elevated production of ANG II (72). The effect of cyclical stretch on the expression of matrix metalloproteinase in cardiac myocytes is also mediated by the ANG II-JAK-STAT pathway (73). ANG II has both direct and indirect effects on the JAK/STAT pathway, since AT-1R activation also leads to the release of interleukin (IL)-6 and other cytokines which stimulate the JAK/STAT pathway. Although ANG II serves as a pro-inflammatory mediator by directly activating macrophages and other immune cells, as well as by acting on endothelial cells, its exact role in the activation of the JAK/STAT pathway in immune cells remains unclear. AT-1R has been shown to activate JAK2 via its association with a YIPP motif in the C-terminal tail of the receptor (74). The ANG II-induced tyrosine phosphorylation of Jak2 is mediated by G proteins, since it is dependent on the activation of PKCδ and elevated cytoplasmic Ca^{2+} concentration (75). Furthermore, other researchers have indicated that the mediation of JAK/STAT activation by AT-1R can be independent of G protein-coupled mechanisms (76).

AT-1R Ras/Raf/ mitogen activated protein kinase (MAPK) pathway. The MAPK/ERK pathway is a chain of proteins

which communicate signals from a receptor on the surface of the cell to the DNA in the nucleus. Among these proteins, MAPK communicates by adding phosphate groups to a neighborinG protein, which serves as an 'on' or 'off' switch. Ras induces the protein kinase activity of RAF kinase, which in turn phosphorylates and activates MEK (77). MEK then phosphorylates and activates MAPK. RAF and MAPK belong to the serine/threonine-selective protein kinase family, while MEK is a tyrosine/threonine protein kinase.

Agonist-induced AT_1R could stimulate G-protein-independent signal transduction mechanisms via the direct activation of signaling molecules, such as tyrosine kinases and β-arrestins. It has been demonstrated that β-arrestins can also act as scaffold proteins which organize signaling complexes to activate MAPKs (78). β-arrestins serve as scaffolds in organizing signaling complexes which regulate AT1R-mediated activation of ERK and JNK3 MAPKs (79,80). Wei *et al* demonstrated that β-arrestin2-mediated ERK activation occurred happen in the absence of G protein activation, using a mutant AT1R which could not couple to G proteins (81). It is believed that the coupling process can facilitate phosphorylating cytosolic targets by ERK. The targets that are activated through this mechanism could not enter the nucleus for their association with the receptor, and they are mostly situated on the surface of endosomes (79). Another study suggested that ANG II could also induce chemotaxis via a β-arrestin-mediated, G-protein-independent pathway (82).

The study by Wei *et al* demonstrated that MAPK signaling pathways are involved in upregulating AT1R in the hypothalamus of rats with heart failure. Wei *et al* have further demonstrated that ANG II upregulated AT1R in the SFO and PVN regions of the brain which control cardiovascular functions (83). They demonstrated that phosphorylating p44/42 MAPK and JNK is a vital process for the ANG II-induced upregulation of AT_1R in the brain, whereas p38 was not involved. Low-dose chronic ANG II infusion caused increases in AT_1R mRNA and protein expression in the SFO and PVN to the levels similar to those in rats with heart failure. Aldosterone can activate MAPK signaling pathways in peripheral tissues, and can also enhance AT_1R expression in the brain of normal rats, as well as rats with heart failure (84,85). MAPK signaling is redox-dependent, and NAD(P)H oxidase is another crucial element in the ANG II-induced expression of AT_1R. Therefore, the activation of p44/42 MAPK and JNK is one of the signaling cascades which are essential to ANG II-induced expression of AT_1R.

AT1R-nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) and cyclic AMP response element-binding (CREB) pathway. NF-κB is a protein complex which controls DNA transcription. NF-κB can be detected in almost all cell types and it participates in cellular responses to stimuli, such as free radicals, cytokines, oxidized LDL, bacterial or viral antigens, stress and ultraviolet irradiation (86). Recent research has suggested that hypertension is an inflammatory state, where pro-inflammatory cytokines, such as TNF-α and IL-6 play a role in the hypertensive effect (87). *In vivo* research has suggested that ANG II infusion elevates the levels of proinflammatory cytokines both in circulation and tissues, which can be reversed by blockade of RAS (88). It has been demonstrated that pro-inflammatory cytokines, generated in the PVN of rats with heart failure, contribute to sympathoexcitation (89). NF-κB is an important downstream molecule that is involved in the activation of proinflammatory cytokines. NF-κB promotes the production of pro-inflammatory cytokines and induces oxidative stress. A previous study by Kang *et al* demonstrated that ANG II infusion stimulated NF-κB activation in the PVN and enhanced hypertensive responses via sympathoexcitation (90). They also demonstrated that the central blockade of AT-1R or NF-κB attenuated sympathoexcitation, and decreased blood pressure and pro-inflammatory cytokine levels in the PVN of ANG II-infused rats. The central blockade of both AT-1R and NF-κB normalized blood pressure, pro-inflammatory cytokines in the PVN, as well as sympathetic activity in ANG II infused rats. CREB protein, a cellular transcription factor, binds to specific DNA sequences termed cAMP response elements (CRE), thereby regulating the transcription of downstream genes. Du *et al* demonstrated that an AT-1R blocker, irbesartan, effectively attenuated the effect of ANG II on cell cycle development, cell proliferation and downstream AT-1R signaling events, including the activation of Ras/Raf/MAPK pathway and the transcription factors CREB and NF-κB (91). Another study using peroxisome proliferator-activated receptor γ (PPARγ) agonists in vascular smooth muscle cells reported that vascular PARγ function may be attenuated by MAPK-mediated phosphorylation in patients with atherosclerosis, hypertension, obesity or hyperinsulinemia (92). PPARγ phosphorylation by the MAPK pathway may attenuate PPARγ-mediated AT1R gene transcription suppression by inhibiting PARγ activity. Co-activator CREB/p300 is known to interact with PARγ through its LXXLL motif, and modulate PPARγ function (93). That study demonstrated (93) that CREB overexpression could abrogate PPARγ-mediated AT1R gene transcription suppression, suggesting that the MAPK pathway and CREB may antagonize PPARγ in AT1R gene transcription, leading to the progression of atherosclerosis.

4. Central AT1R in different types of hypertension

Spontaneous hypertension. The cardiovascular effects of ANG II in the brain include the increased release of vasopressin, the dampening of baroreflex sensitivity and stimulating sympathetic pathways through AT-1R activation in cardioregulatory hypothalamic and brain stem nuclei (94). SHRs exhibited an elevated expression and activity of AT1R in several hypothalamic and brain stem nuclei, such as subfornical organ, nucleus tractus solitarius, median preoptic nucleus, dorsal motor nucleus of the vagus, and the paraventricular nucleus (95). Notably, blocking brain AT-1R functions using pharmacological or genetic means helps to lower blood pressure in SHRs (96). The intracerebroventricular injection of antagonists of either AT-1R or angiotensin-converting enzyme decreases arterial pressure in SHRs (97). Moreover, the central injection of AT1R or angiotensinogen antisense oligonucleotides also lowers arterial pressure in SHRs, but not in normotensive controls (98). Sun *et al* developed an *in vitro* neuronal cell culture model from prehypertensive SHRs to explore the mechanisms underlying AT-1R-mediated elevations in ANG II actions in the SHRs brain (99). An earlier study demonstrated that the physiological response induced

by ANG II acting in the brain involved moderating specific neuronal pathways (100). The study by Sun *et al* demonstrated that the increased chronotropic effect of ANG II in SHR neurons was blocked by the inhibition of PI3 kinase, suggesting that PI3 kinase may participate exclusively in the chronotropic actions of ANG II (99). ANG II acts on AT-1R in SHR neurons to generate an increased firing rate through the signaling pathway, which involves the parallel activation of CaMKII and PKCα (101). AT1R in SHR neurons may be associated with the PI3 kinase signaling pathway, which is a cause for the increased chronotropic response to ANG II in SHRs. The expression of AT-1R is 2- to 4-fold greater in neuronal cultures from the SHR hypothalamus or brain stem compared to equivalent cultures from normotensive rats (102), which is consistent with an elevation in ANG II-mediated neuromodulatory effects in SHR neurons, including a Ras/Raf/MAPK pathway (103). The study by Sun *et al* illustrated that the presence of another PI3 kinase signaling system may be associated with the increased chronotropic response to ANG II in the SHR (99). That study also demonstrated that the PI3-kinase signaling was unique in SHR neurons and it can be associated with the hyperactive brain angiotensin system. *In vivo* studies have also demonstrated that ANG II increases PI3-kinase activity in the brain stem and hypothalamus, two cardio-regulatory relevant brain regions (104). The inhibition of PI3 kinase in the RVLM elevates neuronal excitation, lowers basal arterial blood pressure, and attenuates the ANG-II-induced elevations in BP exclusively in SHRs *in vivo* (105). Gene profiling data also have indicated a significantly lowered expression of the regulatory subunit (p85) of PI3 kinase in the brain of SHRs, which could lead to increased activity of the catalytic subunit of PI3-kinase (106).

Salt-sensitive hypertension. Decreased arterial pressure following the blockade of brain AT-1Rs has been reported for several models of hypertension; for example, the DS rat model (107,108). The DS model is of great interest as it can be used to study salt-dependent hypertension in comparison to normotensive rats that have a similar genetic makeup. Among the regions of the brain participating in the regulation of arterial pressure, the RVLM is known to contain the majority of ANG II receptors, which are mainly AT1 type (50). In SHRs and TGR(mREN2)27 transgenic rat models of renin-dependent hypertension, the microinjection of an AT_1R antagonist into the RVLM has been shown to lower AP, while this drug exerts no effect on AP among normotensive rats (53,109). Ito *et al* demonstrated that not only RVLM AT-1Rs were activated in hypertensive rats, evidenced by a decrease in blood pressure following the administration of an AT-1R antagonist into this region, but also the response to stimulation of these receptors was enhanced (53). Following the injection of 100 pmol ANG II (the dose exhibiting the greatest effect) into the RVLM, the MAP of hypertensive DS-HNa rats increased compared with normal blood pressure DS-Lna (low Na CL) or DR (Dahl >50%-salt-tolerant) rats. A similar phenomenon of the response of DS-HNa (a diet containing high Na Cl- HNa) rats was also observed with a submaximal dose of ANG II. In particular, hypertensive DS-HNa rats responded gradually to RVLM AT1Rs block or neuron activity near PVN, and a similar reaction process was also observed in SHRs (53), indicating that SHR neutralizes DS-HNa hypertensive rats. Removing the excitement of AT-1R in the RVLM will cause RVLM sympathetic excitatory neurons to slowly disappear. It was also observed that a shift in NaCl intake in the diet of DR rats did not affect the baseline MAP, but it did affect the response to injection of test drugs into RVLM and PVN. Compared with the response caused by glutamate, the pressure response of DR-HNa rats to RVLM-injected ANG II was not enhanced, and the response of DR-HNa rats to ANG II was actually reduced compared to DR-LNa rats. Notably, it has been shown that increasing the intake of NaCl in the diet can enhance certain boosting responses caused by RVLM. It has also been suggested that changing the salt intake in the diet will selectively alter the ANG II-mediated response in RVLM (110). DiBona and Jones demonstrated that, compared with the high-salt diet group, rats in the low-salt diet group injected AT1R antagonists candesartan and losartan into the LMLM to reduced renal sympathetic nerve activity and AP to a certain extent (110). The study by Ito *et al* demonstrated that compared with in rats, the pressure response of injecting bicoulomb into the PVN was significantly higher in rats fed a LNa diet than in rats fed a HNa diet (52). An earlier study by DiBona and Jones suggested that a low sodium intake activated the brain renin-angiotensin system, resulting in the increased reactivity of the RLVM to drugs acting on the renin-angiotensin system (111). According to the reports of DR rats, the increase of AT-1Rs in the brain of DS-HNa rats is greater than that of DR-HNa rats, which suggests that DS-HNa rats have a greater response to the injection of ANG II into the RVLM (112). DS-HNa rats also seem to have an enhanced ACE activity in the hypothalamus and pons, but ANG II has no detectable changes (113). The above-mentioned evidence indicates that the tonic activation of RVLM AT-1Rs seems to help maintain arterial pressure elevation in the Dahl salt-sensitive rat hypertension model. It has been observed that the inhibition of neuronal function near PVN also reduces AP in hypertensive DS rats, which is consistent with the view that the increased activity of RVLM vasomotor neurons is driven by the pathway from PVN to RVLM. Therefore, the activation of RVLM vasomotor neurons by activating AT1Rs may play an important role in salt-sensitive hypertension. Furthermore, observations in DR rats with normal blood pressure indicate that changes in dietary salt intake may selectively alter the responsiveness of RVLM neurons to angiotensin.

Obesity-induced hypertension. Obesity is a metabolic disease characterized by chronic inflammation and dyslipidemia, and is a potent predictor of the development of hypertension, diabetes and cardiovascular disease. A potential pharmacological target for treating obesity-related metabolic disorders is ANG II, which is a regulator of cardiovascular homeostasis (114). When challenged by a high-fat diet, fat cells and inflammatory stromal cells in adipose tissue secrete free fatty acids and inflammatory mediators. These factors are released into the circulation to exert a systemic effect (115). Central obesity is associated with an increased risk of type 2 diabetes. Adipose tissue dysfunction leads to increased release of pro-inflammatory mediators, which in turn impairs insulin signaling and pancreatic β-cell function. The study by Cole *et al* demonstrated that treatment of Western diet-fed

mice with the AT1R blocker valsartan significantly reduced the harmful effects of a high-fat intake (116). Monocyte chemoattractant protein-1 (MCP-1), interferon-γ (IFN-γ), IL-6, IL-12 and inducible nitric oxide synthase (iNOS) systemically impair systemic insulin sensitivity, and dominate MCP-1 negative expression in wild-type C57BL/6J mice or db/db mice (117). The study by Cole *et al* demonstrated that the expression of MCP-1, IFN-γ, IL-12 and iNOS in the serum and adipose tissue of mice fed a Western diet increased, and impaired glucose tolerance and insulin sensitivity, and these changes were normalized by valsartan treatment (116). That study found that the expression of AT1R in the fat cells of rats fed a Western-style diet was significantly upregulated, which was reversed by valsartan administration. It also observed that mice fed Western diets had reduced fat cell size following treatment with valsartan, which is consistent with previous findings that AT1R improves fat cell function by promoting the development of smaller and more metabolically efficient fat cells. Angiotensin receptor blockers may target members of the 12-lipoxygenase (12-LO) family of fatty acid metabolism, which is related to the reduced expression of 12-LO platelets in fat cells of valsartan-treated mice.

Renovascular hypertension. Renal vascular hypertension is a syndrome characterized by hypertension, which is caused by the narrowing of the blood supply artery of the kidney. Macular dentin cells detect low perfusion pressure through the glomerular device, which leads to the secretion of renin, which leads to the conversion of ANG to angiotensin I. Angiotensin I then enters the lungs, where it is converted to ANG II by ACE. ANG II causes the release of aldosterone, resulting in the retention of water and sodium retention and potassium depletion. An increase in blood volume causes an increase in blood pressure, which leads to the development of hypertension. RAS blockers are widely used to treat ANG-dependent hypertension and congestive heart failure (118). ACE inhibition and AT-1R blockade are standard methods of treating hypertension. Since polymorphisms in the AT-1R-encoding gene are associated with hypertension in human and hypertension animal models, it is logically believed that AT1R is an important target for controlling hypertension (119). As ACE inhibitors can attenuate the progression of kidney disease, the use of ACE inhibitors has increased in patients with hypertension and renal insufficiency to prevent progression to end-stage renal failure requiring dialysis or kidney transplantation. Studies have also demonstrated that AT-1R antagonists are as effective as ACE inhibitors in preventing the progression of kidney disease. Nakaya *et al* studied the structural/ultrastructural changes of the rat kidney in the early stage of hypertension, and the effects of ACE inhibitors and AT-1R antagonists were compared (120). They also examined the effects of these drugs on mRNA expression of AT receptor subtypes in the kidney. They found that ACEI inhibitors and AT-1R antagonists had no significant difference in kidney changes in hypertensive rats. Notably, treatment with both ACE inhibitors and AT-1R antagonists will cause a transient decrease in kidney AT 2 mRNA expression. The study by Katovich *et al* demonstrated that the use of AT-1R antisense (AT-1R AS) in adult hypertensive rats effectively reduced BP to control levels and reversed the pathophysiological effect of hypertension on renal blood vessels (121). In addition to its role in the normalization of hypertension and vascular pathophysiology, this gene therapy method can also greatly reduce the non-compliance of patients with hypertension with conventional treatment. The study by Zhi *et al* demonstrated that the treatment of rats with renal vascular hypertension with AT-1R antagonist losartan not only prevented changes in kidney structure and function, but also significantly reduced the frequency and titer of AT-1R autoantibodies (122).

Diabetic hypertension. Diabetes increases the risk of high blood pressure and other cardiovascular problems because it makes arteries susceptible to atherosclerosis. In turn, hypertension is a risk factor for the development and severity of a number of complications of diabetes, including diabetic eye disease and kidney disease. An important mechanism that causes poor vasodilation in diabetes is related to insulin-mediated vasodilation (123). The expression level of AT-1R determines the biological efficacy of ANG II, which has been regulated by various factors, such as ANG II, glucose, insulin, ROS, low-density lipoprotein (LDL) and diabetes (124). It has been reported that ANG II inhibits insulin signaling through AT-1 and AT-2 receptors, induces insulin resistance and mediates the pathophysiology of diabetic complications (125). The study by Van Linthout *et al* reported that high-density lipoprotein (HDL) downregulated the expression of AT-1R and exerted a vascular protective effect on the aorta of STZ-induced diabetic rats *in vivo* and HAECs *in vitro* (126). AT-2R has been reported to be upregulated under certain pathological conditions (such as hypertension, vascular injury and inflammation), and studies have demonstrated that AT-2R is involved in the regulation of certain cardiovascular functions, such as vasodilation and diuresis (127,128). AT-2R mediates cell differentiation and growth, and opposes the role of AT-1R; thus, it is plays a crucial role in preventing tissue remodeling and disease progression (129). Lee *et al* confirmed that the normal blood pressure of non-insulin-dependent diabetes mellitus (NIDDM) was accompanied by abnormal AT2R levels and iNOS upregulation at the early stage, as it simultaneously stimulates AT-2R and inhibits NO-induced ANG-II-induced contraction, and causes vasodilation through NO (130).

L-NAME-induced hypertension. L-arginine analogues serve as NOS inhibitors by virtue of their substitution of one or both of the terminal guanidino (G or *w*) nitrogen(s) (131). One of the most commonly used L-arginine substituents, Nw-nitro-L-arginine (L-NA) or its esterified form, Nw-nitro-L-arginine methyl ester (L-NAME), is a non-selective inhibitor (132). L-NAME has a variety of effects on the cardiovascular system, including the inhibition of acetylcholine-induced relaxation and induced arterial blood pressure increase. Miguel-Carrasco *et al* demonstrated that L-carnitine (LC) produced a significant, but not complete, reduction in the blood pressure of L-NAME-treated rats (133). In L-NAME-treated rats, the plasma levels and gene expression of IL-1β, IL-6 and TNF-α hearts increased, while LC treatment was reversible (133). Hypertension did not alter plasma ACE activity, although LC treatment reduced IL-1β, IL-6 and TNF-α in hypertensive rats. Finally, in the heart of rats treated with L-NAME, protein and mRNA

expression of ACE and AT-1R increased, and LC reversed this situation. Thus, it was concluded that LC may produce partial inactivation in RAS, resulting in the reduced production and effect of ANG II. When AT-1R inhibitor and AT-2R are upregulated, AT-2R mediates ANG II-induced vasodilation (134). ANG II/AT-2R-induced vasodilation involves nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) dependent processes. The study by Savoia *et al* confirmed that ANG II caused vasodilation in valsartan-treated stroke-prone spontaneously hypertensive rats (SHRSP), which was reversed by L-NAME, indicating the role of nitric oxide (NO) in this process (135). Their experiments revealed that eNOS expression and NO concentration were increased 2-fold by valsartan in SHRSP and they concluded that ANG II facilitates vasodialation through NOS/NO-mediated pathways, via AT-2R, in the presence of AT-1R antagonists. Another study demonstrated that when norepinephrine causes contraction, ANG II induces concentration-dependent relaxation only in the aorta isolated from SHR who has been receiving losartan for a long time (136). Selective AT-2R blockers PD123319 and L-NAME inhibit relaxation. ANG II only increased NO production in the treated SHR aorta, and AT-2R mRNA increased significantly after AT-1R blockade. These findings indicate that in hypertensive rats, chronic AT-1R blockade is related to the reverse vasomotor response of ANG II to NO production mediated by AT-2R.

Stress-induced hypertension. It is well known that repeated exposure to a stress state or a chronic stress state with increased blood pressure may lead to persistent hypertension (137). Genetic susceptibility may play a major role in the hypertensive response to emotional stress. In order to study the underlying genetic and physiological mechanisms, a strain of rat stress arterial hypertension (NISAG) was developed. Epstein *et al* studied the effects of ultra-low dose antibodies against ANG II and their receptors on genetic stress-induced arterial hypertension in adult rats (NISAG rats) (138). They found that antibodies against the C-terminal fragment of the angiotensin II receptor produced the most significant blood pressure lowering effect and reduced systolic blood pressure by 16.40±0.62 mm Hg. The most rapid anti-hypertensive effect is produced by affinity purified antibodies against ANG II. At 2 h following the administration of these antibodies, the systolic blood pressure decreased by 12.80±5.49 mm Hg (138). There are few reports on the effects of AT-1R and ANG II on hereditary stress-induced hypertension; thus, further studies are warranted to confirm these effects in the future.

Angiotensin II-induced hypertension. ANG II is the main effector molecule of RAS, and through its boosting properties and the resulting increase in blood pressure, it exerts a harmful effect on the vasculature of different organ systems. ANG II-mediated vascular dysfunction and tissue damage response may be attributed to the ability of the peptide to induce pro-inflammatory, pro-thrombotic, and pro-oxidative phenotypes in large and microvascular vessels (139). The vasomotor and inflammatory response of ANG II is mediated by AT-1R activation expressed on white blood cells, platelets, endothelial cells and vascular smooth muscle. ANG II is also associated with the pathogenesis of ischemic and hemorrhagic strokes. Animal experiments have demonstrated that AT-1R blockers can inactivate brain inflammation and tissue damage response to ischemia and reperfusion (I/R) (140). In mice genetically deficient in AT-1R or angiotensinogen, a decrease in the area of ischemic lesions after cerebral I/R was also found, while in renin/angiotensinogen transgenic mice, excessively large Brain injury response (mediated by AT-1R) (141-143). Research on ANG II-induced hypertension and ANG II accelerated atherosclerosis has indicated that in these human disease models, blood cell-related AT1R plays a role in mediating inflammation and vascular dysfunction/injury (144). The study by Nagai *et al* demonstrated that long-term elevated ANG II levels can cause overreaction to I/R brain damage, and genetic defects in $AT1aR^{-/-}$ can protect normal-blood pressure and ANG II hypertensive mice from I/R-induced brain damage microvascular inflammation and tissue damage (145). The comparison of results from $AT1aR^{-/-}$ mice with WT BM chimera revealed the unique role of blood vessel wall and blood cell-associated AT1aR in blood cell recruitment and brain injury response to I/R (145). In normal blood pressure and ANG II hypertensive mice, AT1aR, which is associated with the blood vessel wall, appears to be mainly responsible for promoting the recruitment of leukocytes and platelets in the cerebral microvasculature. Previous research on the brain and other vascular beds have indicated that acute exposure (≤24 h) through elevated ANGII levels can promote the adhesion of leukocytes and platelets in the capillary venules through AT1R-dependent P-selectin-mediated mechanisms (146). The administration of ANGII can cause a rapid increase in blood pressure, BBB failure and cerebral edema, all of which can be prevented by pre-treatment with AT1r antagonists (147). The BBB failure induced by ANG II is usually attributed to mechanical pressure on endothelial cells, resulting in an increase in blood pressure, which is then directly dependent on the endothelial cell function of AT-1R (148). Vital *et al* demonstrated that ANGII induced an inflammatory and prothrombogenic phenotype in the cerebral microcirculation, which was accompanied by impaired BBB function (149). They also demonstrated that AT1R participated in the ANGII-mediated microvascular response and involved immune cells, RANTES and P-selectin in the blood cell recruitment reaction. These findings may explain why ANG II-mediated hypertension seems to be related to the increased incidence and severity of ischemic stroke. They concluded that chronic ANG II infusion affected cerebral microcirculation by promoting the recruitment of leukocytes and platelets in the small veins behind the capillaries and increasing the permeability of the BBB (149). Blood cell-related AT-1R contributes to ANG II-induced blood cell recruitment reaction and increased blood pressure, while blood vessel wall-related AT-1R is involved in BBB failure.

ANG II-induced hypertension. One of the basic effector molecules in RAS is ANG II. It influences different organ systems through some deleterious effects on the vasculature and its pressor properties and increasing blood pressure. ANG II-mediated vascular dysfunction and tissue injury response can be classified as the capacity of the peptide to induce a pro-inflammatory, pro-thrombogenic and pro-oxidative phenotype in both large and microscopic blood vessels (139). The vasomotor and inflammatory responses

of ANG II are adjusted by the stimulation of AT-1R that are influenced on leukocytes, platelets, endothelial cells and vascular smooth muscle. In addition, ANG II are bound in the pathogenesis of ischemic and hemorrhagic stroke. Research has indicated that AT-1R blockers blunt brain inflammation, as well as tissue injury response to ischemia and reperfusion (I/R) (140). Decreased ischemic lesion areas following brain I/R have also been found in mice with genetically deficient in either AT-1R or angiotensinogen, while an exaggerated brain injury response (mediated through AT-1R) has been observed in renin/angiotensinogen transgenic mice (141-143). Another study on ANG II-induced hypertension and ANG II-accelerated atherogenesis expressed the status of blood cell-associated AT1R in mediating inflammation and vascular dysfunction/injury in human disease models (144). The study by Nagai *et al* revealed that chronically elevated ANG II levels resulted in the marked influence of brain injury response to I/R and that genetic deficiency of $AT1aR^{-/-}$ protected both normotensive and ANG II-hypertensive mice against cerebral microvascular inflammation and tissue damage elicited by I/R (145). The comparison of $AT1aR^{-/-}$ mice with WT BM chimeras revealed the clear status of vessel wall and blood cell-associated AT1aR in blood cell recruitment and brain injury responses to I/R. In both normotensive, as well as ANG II-hypertensive mice, vessel wall-associated AT1aR seems less effective in promoting recruitment of leukocytes and platelets in cerebral microvessels.

Research on brain and other vascular beds has indicated that acute exposure (≤24 h) to increased ANGII levels advances the adhesion of leukocytes and platelets in postcapillary venules via an AT1R-dependent, P-selectin-mediated mechanism (146). ANGII administration can induce rapid increases in blood pressure, BBB failure and brain edema; all these could be prevented through prior treatment with AT1r antagonist (147). ANG II-induced BBB failure is mainly from stresses of endothelial cells, and increases blood pressure, subsequently exerting a direct AT-1R-dependent effect on endothelial cells (148). Vital *et al* demonstrated that ANGII led an inflammatory and prothrombogenic phenotype in the cerebral microcirculation, which was associated with impaired BBB function (149). They also demonstrated that AT-1R ws involved in the ANG II-mediated microvascular responses and implicates the status of immune cells, RANTES and P-selectin in the blood cell recruitment responses. The findings may answer the question why ANG II-mediated hypertension appears to be associated with the increased incidence and severity of ischemic stroke. They concluded that chronic ANG II infusion affected the cerebral microcirculation through advanced the recruitment of leukocytes and platelets in postcapillary venules, and by increasing BBB permeability. Blood cell-associated AT-1R contributed to the blood cell recruitment response and increased blood pressure elicited by ANG II, while vessel wall-associated AT-1R was involved in the BBB failure (149).

Aldosterone-induced hypertension. The rennin-angiotensin-aldosterone system (RAAS) is a significant part of regulation for sodium and potassium balance, blood volume, and blood pressure (150). Aldosterone is defined as the essential constitute and mediator of the RAAS. This steroid is vital in pathophysiology, particularly for cardiovascular disease. On the other hand, the mineralocorticoid receptor (MR) antagonists in conjunction with ANG II therapies emphasize the clinical relevance of an ANG II/aldosterone-interdependent humoral network (151). Although ANG II is known to induce aldosterone production in the adrenal cortex, a reciprocal interaction was recently reported between hormones in extra-adrenal tissues. Aldosterone has been shown to increase ANG II relation, upregulate the expression of AT-1R and ACE, as well as potentiate the ANG II-stimulated intracellular signaling and proliferation in peripheral cardiovascular tissues (152,153). I was also revealed that aldosterone was vital for enhancing the action of AT-1Rs and ACEs in the brain (154). Xue *et al* demonstrated that the central blockade of MRs or the generation of ROS suppressed aldosterone/NaCl-induced hypertension (155). They have also demonstrated that the central antagonism of AT-1R attenuates aldosterone/NaCl-induced hypertension and central antagonism of MR attenuates ANG II-induced hypertension (151,155). In addition, the attenuated effect of blood pressure on aldosterone/NaCl- or ANG II-induced hypertension in rats, which was produced by the central blockade of AT-1R, MR, or ROaS, was found to be related to a reduced sympathetic outflow. Those outcomes indicated that there was an interaction in the brain between ANG II and aldosterone in a cooperative manner, so that the destruction of the functional integrity of either AT-1R or MR may close hypertension development produced by systemic treatment with either ANG II or aldosterone.

Although ACE inhibitors and AT-1R antagonists are well known agents for the treatment of hypertension, the long-term use of these drugs can lead to an increase in the plasma aldosterone level in some patients (156). Aldosterone may stimulate fibrosis and chronic damage in several organ systems (157,158). The production from ANG II and other angiotensin metabolites exist through non-ACE pathways, although metabolites are usually produced by aldosterone secretion after the administration of ACE inhibitors. Although the AT1R ($AT1_A$ and $AT1_B$ in rat) and the AT2R subtypes have been shown in the adrenal glands, there is still a question over how much of the aldosterone release induced by various angiotensin peptides is mediated by each receptor subtype (159). Yatabe *et al* examined the hypothesis that the unfettered AT2R during AT1R blockade may be responsible for increased aldosterone secretion (160). Their study revealed that aldosterone secretion was activated by ANG II in a concentration- and incubation time-dependent manner, which was mainly prevented by the conjunct pretreatment of candesartan and PD123319. In order to verify whether AT2R activation influences aldosterone secretion, they used CGP42112 a selective AT-2R agonist. They found that CGP42112 dose-dependently enhanced aldosterone secretion through adrenal glomerulosa cells, which was prevented by PD123319. In addition, ANG III was found to activate aldosterone release *in vitro* and enhance circulating aldosterone levels *in vivo* (161,162). Based on these findings, their study suggests that ANG III activated aldosterone secretion from adrenal grand, and AT-2R is partly adjusted the ANG III-induced aldosterone release not AT-1R (160,161). Since the *in vivo* infusion of ANG III increased plasma

aldosterone concentration without increasing blood pressure, ANG III may be significant for the pathophysiological part of aldosterone breakthrough through the induction of aldosterone release.

5. Central AT1R blockade

Acute blockade. In the brain, there are neuromodulatory actions influenced by ANG II through the regulation of the actions of neuronal enzymes concluding the catecholamines's turnover. ANG II binds to the AT-1R and stimulates the activity of tyrosine hydroxylase (TH), dopamine β-hydroxylase (DβH) and norepinephrine transporter (NET) (163). Signaling through both AT1 receptors and dopamine D1 receptors (D1R) modulates renal sodium excretion and arterial BP (164). Angiotensin, exerting on AT1 receptor, and dopamine, exerting on the dopamine D1 family receptors, and there are contrary influence on sodium excretion (165). Li *et al* demonstrated that AT1R and D1R formed a heteromeric signaling composite and identified losartan, an AT1R antagonist and the well-known anti-hypertensive drug, as an allosteric modifier of this complex (166). Another study using SHRs explained that the treatment of prepubescent rats with both ACE inhibitors and AT-1R antagonists during the developmental stage (3-10 weeks old) led to a decrease in the blood pressure plateau, which was reached after 14 weeks (167), indicating that the effects were due to angiotensin actions's inhibition at the AT1 receptor. Iwasaki *et al* demonstrated that olmesartan, an AT-1R antagonist, reduced spinal motor neuron death in the spinal nerve injury model of rats (168). Another study using an ischemia-reperfusion injury model reported that pre-treatment with candesartan for 40 min prior to injury leaded to improvement in peak systolic pressure and increased AT-2R protein compared to the controls (169). Lacourcière *et al* demonstrated that AT-1R blockers caused lasting AT1-receptor binding produced adequate 24-h ambulatory blood pressure control (170). A human study revealed that in gently sodium-depleted normotensive individuals, RAS blockade, which was stimulated by the acute administration of low doses of valsartan, increased by inhibiting renin activity, via the co-administration of a potent, orally active, long-lasting renin inhibitor (171). The acute administration of losartan *in vitro* in ventral mesencephalic neurons along with rotenone (a compound known to induce neuronal death) provided neuronal protection (172). However, the administration of an AT-2R antagonist led to neuronal death. de Oliveira-Sales *et al* indicated that losartan with the direct injection into the RVLM of hypertensive rats led to a 11% decrease in mean arterial pressure and an 18% decrease in renal sympathetic nerve activity (173).

Chronic blockade. *In vivo*, AT-1R antagonists are related to an increase in the plasma ANG II concentration via their inhibition of the AT-1R-mediated passive respond on renin release. Thus, when the therapeutic doses of AT-1R antagonists are used, endogenic ANG II can excite unopposed AT-2R, therefore reducing blood pressure. Widdop *et al* demonstrated that long-term AT-1R blockade using candesartan led to AT2R-mediated vasorelaxation (174). Moudgil *et al* indicated that ischemia reperfusion was related to LV dysfunction and cardiomyocyte apoptosis, and chronic AT1R blockade inhibited apoptosis without improving functional recovery (175). The study by Kumagai *et al* reported that the chronic administration of candesartan (6 weeks) in dogs with sustained atrial fibrillation prevented disease progression by suppressing structural remodeling (176). β-adrenergic receptors (βARs) and AT-1Rs are 2 parts of the superfamily of G-protein-coupled receptors. When excited, there are interactions between it and effector molecules through coupling to G proteins. The study by Barki-Harrington *et al* demonstrated that AT-1Rs may exert a mutual effect with both βAR subtypes and that the interaction elicits a phenomenon immediately where selective βAR blockade inhibits the signaling of AT-1Rs, whereas selective AT-1R blockade inhibits downstream signaling of βARs (177). That study concluded that β-blockers in combination with valsartan may offer near-complete inhibition of both receptor signaling pathways (177). This antagonist blocks its own receptor and at the same time the signaling of the reciprocal receptor occurs via a mechanism of trans-inhibition. The control of the ACE inhibitor would reduce circulating ANG II levels and norepinephrine through the inhibition of the renin-angiotensin and sympathetic nervous system. Two examples of chronic blockade are as follows:

i) Chemical blockade. Highly sensitive chemical angiotensin receptor blockers (ARBs) have been developed over the past few decades that can offer a particular blockade of the RAS. They have no agonist effects and thus they are safer, compared with ACE inhibitors (177). Several potent orally active ARBs have been developed, including losartan, eprosartan, candesartan, valsartan, irbesartan, telmisartan, tasosartan and olmesartan, to name a few. The main selective ARBs are influenced by the alteration or replacement of some pharmacophore groups of losartan. Structure-activity relationship (SAR) studies have demonstrated that the structural requirements of ARBs to be potentially practical anti-hypertensive agents are a biphenyl moiety at the *N*-1 position of a heterocyclic ring 11, and acidic functionality, such as a tetrazole group and a short lipophilic alkyl chain substituted in heterocyclic ring for efficient binding to the receptor (178,179). There are also studies using synthetic and cyclic peptide antagonists of AT-1R, such as sarilesin, sarmesin, etc. which are as effective as other chemical AT-1 antagonists (180,181). Zoumpoulakis *et al* also developed synthetic non-peptide antagonists of AT-1R and compared them with losartan, and found they were also effective with an advantage of not requiring a lipophilic moiety for binding (182).

ii) Gene knockdown. The study by Katovich *et al* revealed that AT-1R antisense administration, over a period of 6 days in SHRs, by a retroviral gene delivery vector was efficacious in decreasing blood pressure and changing some renovascular pathophysiological conditions related to hypertension. A decrease of 30 mmHg in BP observed was with this method, which was similar to the reduction in BP observed with acute losartan treatment (121). A similar study demonstrated the antisense oligonucleotide inhibition of angiotensinogen, ACE or AT-1R genes components of the renin-angiotensin system. Its substantially reduced blood pressure with high pressure laboratory animal subject of hypertension including genetic subject (SHR), surgical subject (2KIC), and environmental subject(cold-induced hypertension) (183). This study reported that the sole systemic control of antisense

reduced blood pressure approximately 25 mmHg, which was sustained for 1 month, and no toxic side-effects of repeated antisense administration were observed (183). Another study investigated the influence of double-stranded, recombinant adeno-associated virus vector (rAAV)-mediated antisense AT-1R gene efficiency and found that it attenuated the hypertension also resisted renal injury and cardiac remodeling (184).

6. Conclusion and future perspectives

RAS plays a significant role in the pathophysiology of clinical hypertension, diabetes, chronic kidney disease and heart failure, which is reflected by the ANG II-mediated reaction of AT-1R via its diverse repertoire of signaling pathways also the signaling mechanisms. Several pharmacological agents that block ANG II, including ACE inhibitors and ARBs have gained extensive clinical use for treating several related diseases. It has been well-established that the function of these blockers extends blood pressure control, decreasing mortality from myocardial infarction, heart failure, atherosclerosis, stroke, diabetes, peripheral vascular disease, chronic renal disease and stroke. Even though the knowledge of ANG II and AT-1R signaling networks is extensive, there are still novel avenues to explore for the molecular mechanisms of ANG II-mediated influence in physiological and pathological conditions. The present review may have helped to highlight the central AT-1R prevalence, functions, interactions and means of modulation to aid in treating several pathological conditions. The identification of angiotensin-derived peptides and the development of AT-2R agonists have provided a wider perspective on RAS, as well as new therapeutic strategies. Getting a grasp of the basic science of the RAS and the underlying mechanisms of the signaling pathways associated with RAS, particularly in human beings rather than animal models, will facilitate the discovery of novel therapeutic targets to promote the management of patients with cardiovascular and kidney disease.

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Authors' contributions

CS, JX and CY were involved in the writing of the manuscript and in the literature search. AC was involved in the critical revision of the manuscript for intellectual content. CS and JX confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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