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Review

Aldosterone and angiotensin: Role in diabetes and cardiovascular diseases

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ABSTRACT

The present review shall familiarize the readers with the role of renin–angiotensin aldosterone system (RAAS), which regulates blood pressure, electrolyte and fluid homeostasis. The local RAAS operates in an autocrine, paracrine and/or intracrine manner and exhibits multiple physiological effects at the cellular level. In addition to local RAAS, there exists a complete pancreatic RAAS which has multi-facet role in diabetes and cardiovascular diseases. Aldosterone is known to mediate hyperinsulinemia, hypertension, cardiac failure and myocardial fibrosis while angiotensin II mediates diabetes, endothelial dysfunction, vascular inflammation, hypertrophy and remodeling. As the understanding of this biology of RAAS increases, it serves to exploit this for the pharmacotherapy of diabetes and cardiovascular diseases.

Contents

1. Introduction

The renin–angiotensin aldosterone system (RAAS) is classically known as a circulating or hormonal system regulating blood pressure, electrolyte and fluid homeostasis (Peach, 1977) largely mediated by its potent effects on vascular smooth muscle, renal

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re-absorption of electrolytes and water and via stimulation of aldosterone and vasopressin (Matsusaka and Ichikawa, 1997). The major key components of RAAS are the hepatic derived precursor angiotensinogen, the renal synthesized renin and pulmonary-bound angiotensin-converting enzyme (ACE), and the physiologically active peptide, angiotensin II, as well as its receptors. In addition, alternative enzymes to renin and ACE generate a number of bioactive peptides from angiotensin I and/or angiotensin II, such as angiotensin III, angiotensin IV and angiotensin (1–7). Such angiotensin-processing peptidases include, to name but a few, chymase, chymotrypsin, tonin, ACE2 (a homolog of ACE) and aminopeptidase A, as well as the aminopeptidase *B*/*N*. Angiotensin II, together with these bioactive peptides, mediates their specific functions via the respective cellular receptors of target tissue organs (Lavoie and Sigmund, 2003).

Aldosterone is another component of RAAS which was isolated 50 years ago. The physiologic importance of aldosterone in preventing the loss of salt and water during periods of dietary sodium deprivation is now clear (Weber, 2001). Aldosterone is synthesized from cholesterol in the zona glomerulosa of the adrenal cortex by a series of locus- and orientation-specific enzymatic reactions. Moreover, extra-adrenal sites of aldosterone synthesis (Casey and MacDonald, 1982), including the brain, vascular tissue, and the myocardium (Silvestre et al., 1998, Takeda et al., 1996) have been identified. Aldosterone activates mineralocorticoid receptors present in brain, vascular tissue, and the myocardium (Shah et al., 2006).

The generation of angiotensin I and II is not restricted to the systemic circulation but production also takes place in vascular and other tissues (Admiraal et al., 1990). The presence of local tissue RAAS has been increasingly recognized over the last 20 years, with mounting recognition of their clinical importance (Montgomery et al., 2003). These functional local RAAS have been found in diverse organ systems as the pancreas, heart, kidney, vasculature and adipose tissue as well as the nervous, reproductive and digestive systems (Paul et al., 2006). The local RAAS operates in an autocrine, paracrine and/or intracrine manner and exhibits multiple and novel functions including the regulation of reactive oxygen species generation, cell growth, differentiation, proliferation and apoptosis, tissue inflammation, fibrosis and hormonal secretion (Leung, 2004).

In addition to local RAAS, there exists a complete pancreatic RAAS. Neither angiotensin I nor renin activity has been identified in the dog pancreas (Chappell et al., 1991) but other scientists report that angiotensinogen and renin are expressed in rat pancreas (Leung et al., 1999). On the other hand, binding sites for angiotensin II receptors have been characterized in the endocrine and exocrine cells of pancreas (Chappell et al., 1992, 1995, Ghiani and Masini, 1995). Similarly, AT_1 and AT_2 receptors and angiotensin II have been specifically localized to different cell types of the pancreas including endothelial, ductal, acinar and islet cells (Leung et al., 1997, 1999). In the human pancreas, AT_1 receptors and (pro)renin have been shown to be localized not only in exocrine cells but also the beta cells of the endocrine pancreas (Tahmasebi et al., 1999). The presence of a pancreatic RAAS in the human pancreas is further substantiated by the expression and localization of angiotensinogen and AT_1 receptors, notably in pancreatic islets and ducts (Lam and Leung, 2002). Accumulating evidence also indicates that angiotensins produced locally in various brain nuclei is involved in homeostasis control to regulate cardiovascular and fluid–electrolyte homeostasis and chronic over activation of the brain RAS is responsible for the development and maintenance of hypertension in several animal models of disease (Baltatu et al., 2011; Diz et al., 2011). Such a diversity of roles makes tissue RAAS attractive therapeutic targets in diverse disease states. The present review aims to put forth the involvement of RAAS in diabetes and cardiovascular diseases.

2. Angiotensin II

Angiotensins are peptide hormones derived from the protein precursor angiotensinogen by the sequential actions of proteolytic enzymes. Ang II has emerged as a critical hormone that affects the function of virtually all organs, including heart, kidney, vasculature and brain, possessing both beneficial and pathological effects. Acute stimulation with Ang II regulates salt/water homeostasis and vasoconstriction, modulating blood pressure, while chronic stimulation promotes hyperplasia and hypertrophy of vascular smooth muscle cells (VSMCs) (Geisterfer et al., 1988, Xi et al., 1999). In addition, long-term exposure to Ang II also plays a vital role in cardiac hypertrophy and remodeling, in-stent restenosis, reduced fibrinolysis, and renal fibrosis (Mehta and Griendling, 2007) (Table 1).

The mechanisms controlling the formation and degradation of Ang II are important in determining its final physiological effect. An octapeptide, Ang II is formed from enzymatic cleavage of angiotensinogen to angiotensin I (Ang I) by the aspartyl protease renin, with subsequent conversion of Ang I to Ang II by (ACE). This classic pathway of angiotensin synthesis occurs not only in plasma but also in the kidneys, brain, adrenal glands, ovaries, and possibly other tissues (Johnston, 1992). The intrarenal renin–angiotensin system affects glomerular filtration. Angiotensin II (Ang II), the principal effector of the renin–angiotensin cascade, can also be synthesized by a pathway that does not require ACE (Liao and Husain, 1995). A recently identified carboxypeptidase, ACE2, cleaves one amino acid from either Ang I or Ang II (Cui et al., 2001), decreasing Ang II levels and increasing the metabolite Ang 1–7, which has vasodilator properties. Thus the balance between ACE and ACE2 is an important factor controlling Ang II levels (Danilczyk and Penninger, 2006). Even though ACE is the primary enzyme leading to Ang II generation, in the heart the majority of Ang I is converted by chymase (Wolny et al., 1997).

Table 1
Pharmacological effects of angiotensin II.

Organ/tissue	Actions	
	AT_1 receptor	AT_2 receptor
Kidney	Na^+ and water retention	Natriuresis
Adrenal gland	Increase in aldosterone	No change in aldosterone levels
Cardiovascular system	Increased contractility, cardiac hypertrophy	Inhibit cardiac hypertrophy
Vascular smooth muscle	Vasoconstriction, atherogenesis	Vasodilation prevention of atherogenesis
Blood	Platelet aggregation, thrombogenicity, fibrinolysis	Anti-thrombotic effects
Endocrine	Glucose intolerance insulin resistance	Maintenance of glucose homeostasis improvement in insulin sensitivity
Brain	Ischemic brain damage cognitive impairment	Increase in cerebral blood flow

2.1. Angiotensin II receptors

Ang II acts mainly via two receptors viz. Ang II type 1 receptors and Ang II type 2 receptors (de Gasparo et al., 2000). The receptor subtypes AT_1 and AT_2 are polypeptides containing approximately 360 amino acids that span the cell membrane seven times (Mukoyama et al., 1993, Murphy et al., 1991, Sasaki et al., 1991). Despite their similar affinities for angiotensin II, AT_1 and AT_2 receptors are functionally distinct, with a sequence homology of only 30 percent. Much less is known about the other subtypes.

Most of the known physiological effects of Ang II are mediated by AT_1 receptors, which are widely distributed in all organs, including liver, adrenals, brain, lung, kidney, heart, and vasculature. Composed of 359 amino acids, the AT_1 receptor (40 kDa) belongs to the seven-membrane superfamily of *G* protein-coupled receptors. Angiotensin receptors of the AT_1 subtype bind angiotensin II in ways characteristic of other hormone receptors on the cell surface. They have high structural specificity and limited binding capacity (saturability). They bind angiotensin II with an affinity similar to its circulating concentration, about 10–10 M (high affinity); they convert the interaction with angiotensin II into cellular responses (signal transduction); and they are regulated by their rates of biosynthesis and recycling (up-regulation and down-regulation).

Three of these characteristics – specificity, saturability, and high affinity – are the basis of radioligand-binding assays that helped characterize angiotensin receptors and identify candidate antagonist compounds for drug development (Carini et al., 1991, Goodfriend et al., 1971, Lin and Goodfriend, 1970). The human AT_1 receptor gene has been mapped to chromosome 3. In rats, two isoforms that share 95% amino acid sequence identity have been identified: the AT_{1A} receptor on chromosome 17 and the AT_{1B} receptor on chromosome 2 (Griendling et al., 1996). The two receptor subtypes are indistinguishable functionally and pharmacologically (Gasc et al., 1994). However, AT_{1A} receptor isoform has shown to be more important than AT_{1B} receptor in regulation of blood pressure by in vivo experiments (Chen et al., 1997). The extracellular domain of the receptor is characterized by three glycosylation sites, and mutation of these sites has no effect on agonist binding. *G* protein interactions occur on the transmembrane domain at the NH_2 terminus and the first and the third extracellular loops (Bumpus et al., 1991). Four cysteine residues of AT_1 receptor form disulfide bridges along with several residues located on the extracellular region of the receptor and are essential for Ang II binding (Ohyama et al., 1995). Similar to other receptors like muscarinic and adrenergic receptors, the AT_1 receptor's cytoplasmic tail contains many serine/threonine residues, which are phosphorylated by *G* protein receptor kinases. Modifications within these functional sites may be responsible for the altered receptor function in cardiovascular disease.

Even though most of the vasoactive effects of Ang II occur via AT_1 receptors, AT_2 receptors have been shown to exert antiproliferative and pro-apoptotic changes in vascular smooth muscle cells, mainly by antagonizing AT_1 receptors (Griendling et al., 1996). AT_2 receptor is highly expressed in fetal tissue, including fetal aorta, gastrointestinal mesenchyme, connective tissue, skeletal system, brain, and adrenal medulla. Similar to the AT_1 receptor, the AT_2 receptor (MW 41 kDa) is a seven transmembrane domain receptor, but is only 34% identical to AT_1 receptor (Mukoyama et al., 1993). The gene for the AT_2 receptor is on chromosome *X* (Szpirer et al., 1993). AT_2 receptor consists of 363 amino acids. It is reported that AT_2 receptor expression declines after birth, suggesting that it may play an important role in fetal development (Shanmugam et al., 1996), and can be induced later in adult life under pathological conditions. Autopsy results of non-failing human hearts show that the heart has approximately 50% AT_2 receptors; in chronic heart failure, AT_1 receptors are downregulated compared with AT_2 receptors (Tsutsumi et al., 1998). AT_2 receptors are also expressed at low levels in kidney, lung, and liver. Over-expression of AT_2 receptor in mouse coronary artery endothelial cells increases expression of prolylcarboxypeptidase, which may contribute to kinin release, producing beneficial effects on the cardiovascular system (Zhu et al., 2010). Studies have shown that AT_2 receptor antagonizes AT_1 receptor by inhibiting its signaling pathways via activation of tyrosine or serine/threonine phosphatases (Bedecs et al., 1997, Munzenmaier and Greene, 1996). However, it is recently found that AT_2 receptors cause hypertrophy in cardiomyocytes, independent of Ang II, and does not block AT_1 receptor-mediated hypertrophy (D'Amore et al., 2005). This hypertrophic response is mediated by direct binding of the transcription factor promyelocytic leukemia zinc finger protein to the tail of the AT_2 receptor, leading to nuclear translocation and enhanced transcription of the p85 subunit of phosphatidylinositol 3-kinase (Landon and Inagami, 2005; Senbonmatsu et al., 2003). In contrast, consistent with its antagonistic effects on AT_1 receptor, in a mouse model of inflammation-dependent vascular disease, deletion of AT_2 receptors enhanced neointimal formation and inflammation (Bumpus et al., 1991). Furthermore, dimerization of the two receptor types also causes an interruption in AT_1 receptor signaling (AbdAlla et al., 2001). Some beneficial effects of AT_2 receptor are reported to be mediated by the bradykinin/NO system (Gohlke et al., 1998; Liu et al., 1997). Hence, the absence of constitutively expressed bradykinin B2 receptor should be leading to prothrombotic states. However, it is reported that in the absence of the bradykinin B2 receptor in mice, there is probable reduced bradykinin uptake into cells and increased plasma prekallikrein and Ang II. The elevated Ang II probably binds to an overexpressed AT_2 receptor to contribute to thrombosis protection (Shariat-Madar et al., 2006).

2.1.1. Signal transduction

The binding of angiotensin II to the AT_1 receptor leads to the dissociation of subunits of a guanine-nucleotide-binding protein ($G_{q/11}$), which then activates phospholipase C to generate diacylglycerol and inositol trisphosphate (Catt et al., 1993; Ohyama et al., 1992). The calcium is then released from intracellular stores due to inositol trisphosphate. Angiotensin II also increases the entry of calcium into the cell through channels in the cell membrane (Spät et al., 1991). Calcium and diacylglycerol activate various enzymes viz. protein kinase C and calcium–calmodulin kinases that catalyze the phosphorylation of protein, and this ultimately regulates the cell functions affected by angiotensins (Tsuda et al., 1993). These signal-transduction events are majorly completed within seconds or minutes. However, they also initiate the slower responses to angiotensin—including vascular growth and ventricular hypertrophy. The stimulation of growth by angiotensin II also involves other processes common to growth factors in general, such as the phosphorylation of tyrosine, and the activation of mitogen-activated protein kinase and Stat 91, proteins that affect the cell nucleus and activate DNA transcription (Bhat et al., 1994). Signal transduction by the AT_2 receptor differs from transduction by AT_1; it does not involve phosphoinositides, and it leads to the dephosphorylation of tyrosine (Nahmias and Strosberg, 1995). Despite the structural resemblance of AT_2 receptor with G-protein coupled receptors, the signal transduction is atypical (Nahmias and Strosberg, 1995). AT_2 receptor produces activation of protein phosphatases and protein dephosphorylation regulates nitric oxide (NO)–cGMP system and stimulates phospholipase A2 producing release of arachidonic acid (Nouet and Nahmias, 2000). AT_2 may couple to Gi (Horiuchi

et al., 1997; Zhu et al., 1998) or to still unknown *G* proteins (Bedecs et al., 1997; Buisson et al., 1995) producing cellular responses or functions in corresponding target organs.

2.1.2. Regulation of angiotensin receptors and their actions

The rates, at which receptors are biosynthesized and inserted into the membrane and the competing rates of internalization and degradation, govern the number of unoccupied receptors on the cell membrane. The internalization of receptors is initiated by binding to hormone and is one mechanism by which target cells can become desensitized during prolonged exposure to agonists. Angiotensin receptors are subject to phosphorylation. The phosphorylation does not affect the binding of angiotensin but uncouples the receptors from their signal-transduction apparatus (Kai et al., 1994). This is one way in which cells become desensitized to angiotensin without internalizing its receptors. In addition, the binding of angiotensin by receptors is inhibited by several endogenous compounds, such as unesterified fatty acids, which may explain the reduced responsiveness to angiotensin seen in some seriously ill patients (Goodfriend et al., 1991).

A region rich in serine and threonine in the carboxy-terminal cytoplasmic tail is essential for internalization in the AT_1 receptor (Hunyady et al., 1994). The internalization of angiotensin receptors is not stimulated when an antagonist is bound; the process requires an active hormone agonist (Hunyady et al., 1994). Thus, receptor antagonists remain potent during long-term administration, whereas agonists tend to lose potency (i.e., to show tachyphylaxis). The activation of some tissues by angiotensins directly stimulates the formation of counter regulatory substances, including vasodilating prostaglandins and nitric oxide (McGiff et al., 1970, Seyedi et al., 1995). In contrast to this, amplification of the actions of angiotensin II by target organs can occur by releasing substances with angiotensin-like effects, such as catecholamines, endothelin and growth factors (Berk and Rao, 1993; Chen et al., 1995; Lin and Nasjletti, 1991; Reid, 1992; Stern et al., 1993). The balance between vasodilators and vasoconstrictors helps to determine the response of blood vessels to angiotensin II. Vasodilators appear to predominate during a normal pregnancy, whereas disturbances favoring vasoconstrictors may contribute to the increased sensitivity to angiotensin in women with certain forms of pregnancy-induced hypertension (Brown et al., 1990). Although patients with hypertension have increased responsiveness to pressor hormones, including angiotensin, there is no evidence that hypertension is caused by structural abnormalities in AT_1 receptors (Bonnardeaux et al., 1994). The mechanism of increased sensitivity to angiotensin in essential hypertension is probably extrinsic to the receptor itself (Williams, 1994).

2.2. Angiotensin II in diabetes

The generalized pathogenesis of cardiovascular disease involves cellular oxidative metabolic stress and endothelial dysfunction, which are closely linked to circulating and tissue levels of Ang II (Dzau, 2001). This finding is based on experimental studies and clinical observations demonstrating RAS stimulation and simultaneous activation of nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate oxidase in the arterial wall (Laursen et al., 1997; Munzel and Keaney, 2001; Warnholtz et al., 1999). There is an increase in plasma renin activity, mean arterial pressure, and renal vascular resistance (Miller et al., 1996), with the activation of circulating and local (intrarenal) RAS in short-term moderate hyperglycemia without glycosuria during the early stages of diabetes mellitus. It has been demonstrated that an enhanced renal vasodilator response occurs to captopril and eprosartan use during hyperglycemia, suggesting that hyperglycemia leads to an increase in Ang II-mediated renal vascular tone (Osei et al., 2000). This may occur through increased responsiveness, which can be direct or indirect depending on the input of other systems, such as the autonomic nervous system and the baroreflex arc, which are also abnormal in diabetes. In the study by Miller (1999), the mean arterial pressure was significantly higher during hyperglycemic than euglycemic conditions, and arterial pressure responded well to losartan potassium therapy, whereas the response to losartan therapy during euglycemia was minimal. Hyperglycemia results in p53 glycosylation, which has been linked to the transcription of angiotensinogen and the subsequent production of Ang II from the local RAAS (Leri et al., 1998, 2000). Further, a direct correlation among glucose levels, p53 expression, and the quantity of Ang II has been reported by Fiordaliso et al. (2001). Angiotensin II synthesis increased with the degree of glycemia, and this was attenuated by the inhibition of p53 glycosylation. Angiotensin II is recognized to have pro-apoptotic properties (Horiuchi et al., 1999) and thus presents a plausible role for the RAAS in the pathogenesis of diabetic heart disease. Specific blockade of the RAAS with ACEIs and angiotensin receptor blockers (ARBs), for example, may attenuate some of these effects.

Various clinical outcome studies, such as the Heart Outcomes Prevention Evaluation (HOPE) study, the Captopril Prevention Project (CAPPP), and Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, have consistently and unexpectedly suggested a reduction in the incidence of new-onset diabetes. However, in the HOPE study (Heart Outcomes Prevention Evaluation (HOPE) Study Investigators, 2000; Yusuf et al., 2001), the diagnosis of diabetes was self-reported by the trial participants and was not verified by glucose measurements and this could undermine any firm conclusions. In the CAPPP study, the diagnosis was confirmed according to 1985 World Health Organization criteria. This trial reported an 11% lower risk (337 of 5183 patients in the captopril group vs 380 of 5230 patients in the conventional treatment group) of developing diabetes in the captopril-treated group (Hansson et al., 1999). The LIFE study demonstrated a significant 25% reduction in new-onset diabetes, which, again, was a prespecified secondary end point. This latter study, however, used atenolol as a comparator (Lindholm et al., 2002). These studies thus support the link of RAAS to diabetes mellitus.

RAAS blockade is reported to reduce insulin resistance, which is the pathophysiological hallmark of the metabolic syndrome and type 2 diabetes (Jandeleit-Dahm et al., 2005). Better skeletal muscle perfusion, improvement of microvascular changes, and increased perfusion of the pancreatic islet cell are some of the proposed mechanisms by which insulin sensitivity is increased. Additionally, direct effects of angiotensin II on the pancreatic β cells from a local renin–angiotensin system in the islet might contribute to a loss of β cell function. Activation of renin–angiotensin system is associated with fibrosis of pancreatic islets in animals with type 2 diabetes (Jandeleit-Dahm et al., 2005). Acute angiotensin II infusion in rats hinders the early phase of insulin secretion (Carlsson et al., 1998) and treatment with losartan stimulates the early phase of insulin secretion in transplanted islets in mice (Kampf et al., 2005). In experimental models, specific ARBs have modulated peroxisome proliferator-activated receptor γ (PPARγ) activity and thereby reduce insulin resistance, with the highest activity found with telmisartan (Benson et al., 2004; Schupp et al., 2006).

Several clinical trials have shown that the frequency of new onset of type 2 diabetes can be reduced by ACE inhibitors and ARBs (as opposed to β blockers and diuretics) (Abuissa et al., 2005; Gillespie et al., 2005). In patients with high cardiovascular risk, the Valsartan Antihypertensive Long-Term Use Evaluation

(VALUE) study showed that renin–angiotensin system blockade with valsartan was better than amlodipine besilate with respect to prevention of new onset of diabetes (13% versus 16·4%) (Kjeldsen et al., 2006). In the ALLHAT trial of 33,357 hypertensive patients, the rate of new onset of diabetes over 4 years was 8.1% with lisinopril, 9.8% with amlodipine besilate, and 11.6% with chlortalidone (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002). These data support that diuretics stimulating the renin–angiotensin system are harmful, ACE inhibitors or ARBs that block the system are beneficial, and calcium antagonists that do not affect the system seems to be neutral. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication trial produced mixed results in 5269 patients without cardiovascular disease but with impaired fasting glucose (DREAM Trial Investigators, 2006). Ramipril did not reduce the development of diabetes (primary endpoint) compared with placebo within the first 3 years. However, regression to normoglycaemia was increased and glucose concentrations in plasma 2 h after an oral glucose load were lower in the ramipril group than in placebo group. Therefore, in hypertensive patients at risk of developing type 2 diabetes—namely patients who have a family history of type 2 diabetes, have a body-mass index greater than 30 kg/m^2, have impaired glucose tolerance (fasting plasma glucose 6·5 mmol/L or greater), or are of southeast Asian or African descent—ACE inhibitors or ARBs should be the first choice of antihypertensive therapy, with calcium antagonists being second-line treatments (Schmieder et al., 2007).

2.3. Cardiovascular effects of angiotensin II

Ang II, within seconds to minutes of binding to AT_1 receptors, activates signaling pathways leading to vascular smooth muscle cell contraction, maintaining vascular tone. In addition to stimulating the synthesis and release of aldosterone and increasing renal Na^+ absorption, Ang II's actions on the central nervous system are critical in maintaining sympathetic outflow to the vasculature and in autoregulating cerebral blood flow. Ang II serves as a focal point in integration of all these complex processes to help to maintain blood pressure and perfuse vital organs. Ang II is extremely important in modulating minute to minute changes that occur in spatial adaptation. For example, when we stand up from a supine position, the endocrine function of Ang II allows for increased myocardial activity (via enhanced inotropy and chronotropy) that appears to occur via augmentation of inward Ca^{2+} current through L-type channels (Baker et al., 1992). In atherosclerotic plaques, the local RAAS system is active, with high levels of ACE, Ang II, and AT_1 receptor (Schieffer et al., 2000). Antagonism of actions of Ang II may slow atherosclerotic disease progression and stabilize vulnerable plaques, partially explaining the benefits seen with ACE-I and ARB therapy. Ang II's cytokine-like effects usually occur with longer exposure, and promote cell growth and migration, extracellular matrix deposition, and vascular and electrical remodeling. Pathological effects of Ang II develop, when the balance of the RAAS is perturbed (due to genetic, environmental, and lifestyle factors) (Mehta and Griendling, 2007). RAAS plays a key role in heat acclimation mediated myocardial adaptation. This effect is mediated at least partially by changes in thyroxine levels and is associated with a change in angiotensin II receptor compartmentalization (Durst et al., 2010).

2.3.1. Ang II and endothelial dysfunction

The principal targets of Ang II are VSMC. However, it has multiple effects on endothelial cells (ECs), such as producing reactive oxygen species, activating apoptotic signaling pathways, and promoting thrombosis. In people with enhanced RAS activity, reactive oxygen species-mediated endothelial dysfunction combined with vascular growth and inflammation has been implicated in atheroma formation. The increase in oxidative stress caused by Ang II leads to impaired endothelial relaxation and endothelial dysfunction (Rajagopalan et al., 1996). In endothelial cells, Ang II regulates the production of NO, formed by nitric oxide synthase (NOS). Exposure to Ang II increases eNOS mRNA and NO production in human endothelial cells (Schena et al., 1999). In the vessel wall, homeostatic mechanisms balance thrombosis with fibrinolysis. Plasminogen-activator inhibitor type 1 (PAI-1) inhibits tissue plasminogen activator (t-PA) and urokinase, tipping the balance in favor of thrombosis. Exposure to Ang II in VSMCs and ECs, leads to increased levels of PAI-1 mRNA (Feener et al., 1995). Ang II-mediated inhibition of fibrinolysis and its induction of cell adhesion molecules such as VCAM-1 and ICAM-1 (via NF-κB activation) provide for further mechanisms by which Ang II initiates and causes progression of atherosclerosis. In endothelial cells, Ang II has been shown to induce the LDL receptor (Li et al., 1999), which is critical in atherosclerotic lesion formation. TNF-α is also an important contributor to vascular inflammation, and its levels are elevated in vascular disorders. Many of the effects of TNF-α are similar to effects of Ang II; indeed, Ang II has been shown to stimulate the production of TNF-α through a protein kinase C dependent pathway in adult mammalian heart (Kalra et al., 2002). The intracellular reactive oxygen species have been shown to activate transcription of nuclear factor κB (NF-κB) and stimulate degradation of its cytoplasmic inhibitor, IκB (Pueyo et al., 2000). NF-κB gene expression results in increased levels of VCAM-1, an important factor in endothelial cell adhesion. This observation is concordant with the report from Arenas et al. (2004), who showed that Ang II modulates the secretion of inflammatory cytokines TNF-α and matrix metalloproteinase (MMP)-2 from ECs. Thus, Ang II plays a key role in modulating endothelial function, and its enhanced presence contributes to endothelial dysfunction and inflammation.

2.3.2. Ang II and vascular inflammation

Ang II plays a role in atherosclerosis. Cytokines have been shown to play a major part in development and progression of atherosclerotic lesion formation. For example, elevated levels of the inflammatory cytokine interleukin-18 (IL-18) are expressed in human atherosclerotic plaques compared to normal arterial tissue (Gerdes et al., 2002). In a series of experiments, it is demonstrated that IL-18 activates Src, Protein kinase *C*, and MAPK (Sahar et al., 2005). In Ang II-stimulated VSMCs, the effects of IL-18 were enhanced via activation of NF-κB; Ang II also induced mRNA expression of IL-18α receptors via STAT 3. The cross-talk with IL-18 signaling pathways may prove to be one of the mechanisms by which Ang II mediates its local proatherogenic effects in VSMCs (Mehta and Griendling, 2007). In apolipoprotein E-deficient mice, infusion of Ang II causes accelerated atherosclerosis and aneurysm formation (AbdAlla et al., 2001; Ushio-Fukai et al., 1999). Ang II activates NF-κB in monocytes, macrophages, VSMCs and endothelial cells, which induces the production of cell adhesion molecules such as VCAM-1, ICAM-1, and E-selectin, and chemokines such as monocyte chemoattractant protein (MCP-1), IL-6, and IL-8 (Ruiz-Ortega et al., 2000, 2001; Schieffer et al., 2000). In VSMCs, the induction of MCP-1 and IL-6 by Ang II is dependent on the activation of NAD(P)H oxidase (Chen et al., 1998; Kranzhofer et al., 1999; Marui et al., 1993).

2.3.3. Ang II and vascular hypertrophy and remodeling

Various in vitro and in vivo experiments have shown that Ang II is an important growth factor, causing cell proliferation, VSMC

hypertrophy, cell differentiation, and apoptosis (Dzau, 2001). Elevation in blood pressure affects cell growth which is one of the mechanisms implicating Ang II in cell growth. In rats, Ang II infusion for 2 wk leads to hypertension and VSMC hypertrophy (Lombardi et al., 1999). Shear stress from elevated blood pressure has been shown to upregulate Ang II receptors (Ruiz-Ortega et al., 2001), linking hypertension to vascular remodeling. Ang II also stimulates the production of matrix metalloproteinases, which are necessary for vascular remodeling (Dzau et al., 1991). Ang II also has direct effects on myocardial cells, including hypertrophy (Dorn and Force, 2005; Lips et al., 2003; Pfeffer and Braunwald, 1990), mediated by AT_1 receptors. Kim et al. (1995) carried out in vivo experiments in rats and reported that AT_1 receptor antagonists prevent Ang II-induced cardiac hypertrophy. The AT_1 receptor also has been shown to play a role in neointima formation via proliferation of VSMCs after balloon injury (Kim et al., 1998). Ang II has different growth effects (proliferation vs. hypertrophy). These differential growth effects are in part regulated by p27 kip1, a cyclin-dependent kinase (CDK) inhibitor; CDKs are suppressed in the presence of high levels of p27 kip1, preventing cells from progressing in the cell cycle. Braun-Dullaeus et al. (1999) showed that in Ang II-treated VSMCs, CDK2 activity was suppressed, leading to G1-phase arrest and cell hypertrophy.

2.3.4. Ang II and extracellular matrix

Accumulation of ECM and reduced ECM turnover play a role in the development of vascular restenosis, hypertrophy, and heart failure after an ischemic insult to the myocardium. Ang II has been implicated in synthesis of the extracellular matrix protein collagen via both AT_1 receptors and AT_2 receptors (Kato et al., 1991; Mifune et al., 2000). Fibroblast-derived Ang II exerts its local paracrine effects by stimulating the production of collagen (Ju and Dixon, 1996). Ang II-induced EGFR- and MAPK-dependent pathways may participate in the matrix formation and regulation (Matsubara et al., 2000; Touyz et al., 2001). Abnormal accumulation of proteoglycans has been noted in atherosclerotic lesions (Evanko et al., 1998; Iozzo, 1998). AT_1 receptor antagonists cause proteoglycan changes that control cell adhesion, migration, and differentiation in hypertensive rats (Iozzo, 1998; Sasamura et al., 2001). It has been reported that the Ang II-induced increase in proteoglycan synthesis was attenuated by the EGFR inhibitor AG1478 and by the MEK inhibitor PD98059 (Shimizu-Hirota et al., 2001). Besides regulating structural components such as collagen, Ang II has also been implicated in adhesive remodeling. Ang II-mediated EGFR transactivation regulates fibronectin and TGF-β synthesis (Moriguchi et al., 1999). Additionally, production of matrix metalloproteinases (like MMP-2) and breakdown of collagen IV is also modulated by Ang II (Libby and Lee, 2000). Thus, Ang II acts on several different components of ECM formation and deposition to influence matrix turnover, and many of the mechanisms and pathways that integrate ECM formation and deposition with Ang II signaling are still being discovered.

3. Aldosterone

Nearly 50 years ago, aldosterone was isolated from blood and urine, its adrenal origin elucidated, and its steroid structure was identified. Actions involving the reabsorption of sodium and the release of potassium by epithelial cells in the kidneys, intestine, and sweat and salivary glands led to its designation as a mineralocorticoid. The physiologic importance of aldosterone in preventing the loss of salt and water during periods of dietary sodium deprivation is now clear (Weber, 2001). Its contribution to the retention of sodium in patients with congestive heart failure, cirrhosis, and the nephrotic syndrome has also been established (Coppage et al., 1962, Luetscher and Johnson, 1954).

3.1. Biosynthesis of aldosterone

Aldosterone is synthesized from cholesterol in the zona glomerulosa (ZG) of the adrenal cortex by a series of locus- and orientation-specific enzymatic reactions. First, cholesterol must cross the outer mitochondrial membrane to the inner membrane where the first enzyme in the steroidogenic pathway is located. A number of cholesterol-carrier/-translocation systems have been identified including sterol carrier protein and peripheral benzodiazepine receptors. However, the process is now known to be mediated by steroidogenic acute regulatory protein (StAR), which forms a core through the membrane. StAR is present in all steroidogenic tissue (Stocco, 2001a) and evidence that it plays a key role in steroidogeneis came from studies of patients with congenital lipoid adrenal hyperplasia, whereby mutations of StAR gene resulted in an inability to make steroids and accumulation of cholesterol in the adrenal glands (Lin et al., 1995). Similarly, the StAR-knockout mouse has elevated lipid deposits in the adrenal cortex and extremely low levels of steroid despite elevated levels of adrenocorticotrophic hormone and corticotrophin-releasing hormone (CRH) (Caron et al., 1997). StAR gene expression is increased by most agents known to stimulate steroid biosynthesis and the translocation of cholesterol to the inner mitochondrial matrix is now considered to be the rate-limiting step in steroidogenesis (Stocco, 2001b).

The RAAS majorly regulates the aldosterone biosynthesis. Ang II acts on vascular smooth muscle to cause vaso-constriction, and on the adrenal ZG to stimulate aldosterone production. The adrenal response to Ang II occurs within minutes, a time course that implies that no new protein synthesis is required. This acute, Ang II-mediated release of aldosterone may involve rapid synthesis from intermediate compounds in the steroidogenic pathway or de novo synthesis from cholesterol, possibly as a consequence of StAR protein activation, leading to increased transport of cholesterol to the inner mitochondrial membrane. Chronic stimulation by Ang II results in ZG hypertrophy and hyperplasia, increased CYP11B2 expression and subsequent aldosterone secretion (Connell and Davies, 2005). And II acts on specific G-protein-coupled receptors (AT_1 receptors) which cause phospholipase C to stimulate intracellular production of inositol 1,4,5-trisphosphate (IP_3) and 1,2-diacylglycerol (DAG), which then activate protein kinase C. IP_3 also increases the concentration of intracellular free calcium ($[Ca^{2+}]_i$), causing several Ca^{2+}/calmodulin-dependent protein kinases (CaM kinases) to phosphorylate and activate such transcription factors as activating transcription factor (ATF)-1, ATF-2 and cAMP-response-element binding protein (Spat and Hunyady, 2004). These bind cAMP-response-element and other *cis*-acting elements (e.g. Ad-5 and NBRE-1) which are unique to the 5' untranslated region of the CYP11B2 gene. The Ad-5 *cis*-element binds members of the NGFIB family as well as steroidogenic factor 1 (SF-1) and chicken ovalbumin upstream promoter-transcription factor (Connell and Davies, 2005). This is the probable mechanism by which Ang II stimulates aldosterone. Studies have identified the transcription factor NURR-1 as a key regulator of CYP11B2 transcription that responds to Ang II; its expression is upregulated in aldosterone-secreting tumors (Bassett et al., 2004).

3.1.1. Extra-adrenal biosynthesis of aldosterone

Since the 1990s, there has been a revolution in our understanding of the physiology and biology of aldosterone. The first novel finding was the discovery of extra-adrenal sites of aldosterone

synthesis (Casey and MacDonald, 1982), including the brain, vascular tissue, and the myocardium (Silvestre et al., 1998; Takeda et al., 1996). Apart from this, it was also reported that mineralocorticoid receptors, which are activated by aldosterone, are widespread in the body including the brain, vascular tissue, and the myocardium (Shah et al., 2006). Human aorta and pulmonary artery endothelial and smooth muscle cells were found to express the genes encoding P450 scc, 3β-HSD (types 1 and 2), 21-hydroxylase and aldosterone synthase, in addition to mineralocorticoid receptors (Takeda et al., 1994). Transcripts for the cofactors StAR and adrenodoxin have also been detected, suggesting that all of the components necessary for local de novo biosynthesis from cholesterol are present (Takeda et al., 1996). Silvestre et al. (1998) first described CYP11B2 expression in the four cardiac chambers of the adult Wistar rat; this was upregulated in response to Ang II or sodium restriction. The genes for P450 scc, P450c21 and type 2 3β-HSD and mineralocorticoid receptors are also transcribed in all chambers of the normal human adult heart and fetal heart (Kayes-Wandover and White, 2000). Cardiac aldosterone expression may only be of significance under pathological conditions since CYP11B2 transcription was detected in the fetal heart but not in normal adult cardiac chambers. Further, during heart failure, cardiac levels of CYP11B2 transcripts are reported to be raised and there exists a direct correlation between myocardial CYP11B2 mRNA expression and collagen volume in the failing human heart (Satoh et al., 2002; Young et al., 2001). After myocardial infarction, Wistar rats had increased cardiac levels of CYP11B2 transcripts and aldosterone in the non-infarcted areas of their left ventricles, although CYP11B1 mRNA and corticosterone levels actually fell in these areas (Silvestre et al., 1999).

3.2. Aldosterone in diabetes

Patients with obesity, essential hypertension or type 2 diabetes are insulin resistant. It is possible that early compensatory hyperinsulinaemia might contribute to some of the phenotypic changes that lead to cardiovascular dysfunction (Goodfriend et al., 1999). It has been reported that insulin increases adrenal aldosterone release in response to a range of agonists, and the hyperinsulinaemia associated with essential hypertension and type 2 diabetes may stimulate aldosterone secretion for this reason. Further, persons with insulin resistance are particularly likely to develop hypertension associated with a raised aldosterone to renin ratio (Epstein et al., 2002) and it may be that aldosterone receptor antagonism is particularly appropriate in this circumstance. There are relatively few data in patients with insulin resistant syndromes or type 2 diabetes treated with aldosterone receptor antagonists. However, recent studies with eplerenone in patients who had diabetes showed that the agent was well tolerated, and was effective in lowering BP (White et al., 2003). Additionally, when compared with amlodipine, eplerenone reduced urinary albumin excretion to creatinine ratio to a significantly greater extent (White et al., 2003). Thus, more extensive studies of the effect of aldosterone receptor antagonism in patients with the insulin resistance syndrome or type 2 diabetes and its complications are now indicated (Connell, 2004).

3.3. Aldosterone in cardiovascular diseases

3.3.1. Aldosterone in hypertension

There is increasing evidence of the importance of aldosterone as a key target hormone in hypertension. Excess aldosterone secretion results in hypertension, which may be due in part to its direct actions on the cardiovascular system and vascular effects (Fig. 1). In the vascular system, aldosterone is known to modulate vascular tone, possibly by increasing the pressor response to catecholamines and impairing the vasodilatory response to acetylcholine or by upregulation of Ang II receptors (Jazayeri and Meyer, 1989; Schiffrin et al., 1985; Taddei et al., 1993; Wang et al., 1992). Aldosterone to renin ratio can be used in the detection of primary aldosteronism (Hiramatsu et al., 1981).

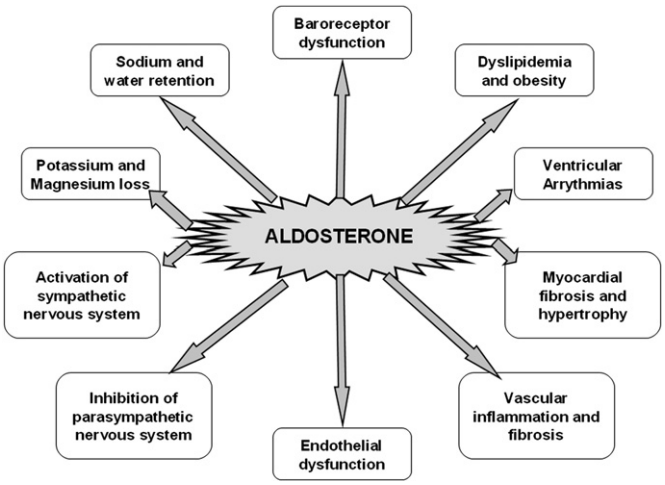

Fig. 1. Vascular effects of aldosterone.

Furthermore, measurement of the aldosterone to renin ratio in patients with apparent essential hypertension has identified an elevated ratio in approximately 10% of unselected cases (Lim et al., 2002). Abnormal ratio identifies patients who have inappropriate production of aldosterone and have 'aldosterone-associated hypertension' (Connell et al., 2003). The importance of the rediscovery of aldosterone in patients with hypertension is the potential that this offers for specific therapy, particularly where the ratio of aldosterone to renin is elevated (Lim et al., 1999).

3.3.2. Aldosterone in cardiac failure

At a very early stage in the development of cardiac failure, individuals exhibit activation of the neurohumoral compensatory mechanisms. A key component of the hormonal response to cardiac dysfunction is increased generation of angiotensin II and, as a consequence, secretion of aldosterone. Yamamoto et al. (1996) stated that measurement of cardiac B-type natriuretic peptide is a sensitive marker for the presence of left ventricular dysfunction. For many years patients with cardiac failure have been known to have sustained aldosterone excess, and this leads to sodium retention, hypokalemia and the other adverse effects (Weber and Villarreal, 1993). Some biochemical anomalies persist despite the fact that effective blockade of ACE activity is of benefit in these circumstances (Cleland et al., 1984). In particular, aldosterone concentrations are not reduced significantly during chronic therapy with ACE inhibitors in patients with cardiac failure (Staessen et al., 1981) (a phenomenon known as aldosterone escape), and the same situation is seen during treatment with angiotensin II receptor blockers (McKelvie et al., 1999). This inability to effectively inhibit aldosterone production may contribute to the failure of conventional cardiovascular therapy to make a greater impact on the morbidity and mortality of the disease.

The major interest in the pathophysiological role of aldosterone in development and progression of heart disease was emphasized by several clinical studies which have provided evidence for a positive correlation between primary aldosteronism and modification of the left ventricle tissue structure and function in humans (Rossi et al., 1996, 1997, 2002). In normal subjects whose diet contains a normal amount of sodium, the aldosterone secretion rate is 100–175 μg

(277–485 nmol) per day; in patients with congestive heart failure, the aldosterone secretion rate may be as high as 400–500 μg (1100–1400 nmol) per day) (Laragh, 1962). In patients with congestive heart failure, decreased metabolic clearance of aldosterone by the liver further contributes to increased plasma concentrations of aldosterone. In normal subjects, hepatic aldosterone clearance is complete within one passage through the liver, so that little or no aldosterone is found in hepatic venous plasma. However, in patients with congestive heart failure, there is reduced hepatic perfusion in patients resulting into reduced aldosterone clearance and this reduction can account for a several fold increase in plasma aldosterone concentrations (Tait et al., 1965). The importance of aldosterone in the pathophysiology of congestive heart failure and other edematous states is supported by the efficacy of aldosterone-receptor–antagonist drugs to ameliorate edema in patients with these conditions (Coppage and Liddle, 1960; Kagawa et al., 1957; Liddle, 1958).

Aldosterone, in addition to its classic mineralocorticoid properties, which can lead to hypokalemia and hypomagnesemia, has other adverse effects that can contribute to the pathophysiology of congestive heart failure. These effects include coronary and renovascular remodeling, endothelial-cell and baroreceptor dysfunction, and inhibition of myocardial norepinephrine uptake, together with reduced heart-rate variability (Barr et al., 1995; Farquharson and Struthers, 2000; Zucker et al., 1995).

3.3.3. *Aldosterone in myocardial fibrosis*

Aldosterone produces perivascular fibrosis of small arteries and arterioles with associated interstitial fibrosis. Additionally, other effects such as myocardial necrosis, vascular stiffening and injury, and production of cardiac arrhythmias were also attributed to aldosterone (Stier et al., 2002). Using different models of rats with increased circulating aldosterone levels various scientists provided evidence for the direct role of aldosterone in the development of cardiac fibrosis in vivo (Brilla et al., 1992, 1993a, 1993b; Robert et al., 1994; Young et al., 1994, 1995). Importantly, aldosterone effect on cardiac fibrosis was dependent on sodium load, thus indicating that aldosterone may promote the entry of sodium into cardiac cells. Aldosterone exerts hemodynamic independent effects and this was confirmed since in a rat model, the aldosterone infusion resulted in the fibrosis of left and right ventricles with constant blood pressure (Robert et al., 1994; Young et al., 1995). Further, induction of cardiac fibrosis was reversible upon concomitant infusion of a mineralocorticoid antagonist (spironolactone), thus demonstrating that aldosterone acts via its classical nuclear receptor (Brilla et al., 1993a). It was important to establish whether the cardiac effects of aldosterone were dependent on the activation of the RAAS, since aldosterone production is regulated by angiotensin II and angiotensin II itself has a stimulatory effect on cardiac fibrosis. Clinically, this question is of special relevance, because of the "aldosterone escape" phenomenon in which plasma aldosterone levels in patients treated with ACE inhibitors have been observed to rise after several months of treatment (Staessen et al., 1981). It has been reported that aldosterone infusion stimulates cardiac fibrosis in rats with suppressed activity of the ACE (Rocha et al., 1999).

Aldosterone can also induce cardiac fibrosis without involvement of the RAAS. Aldosterone is mostly involved in the modulation of activity and/or expression of proteins related to the transepithelial sodium transport process in the kidney epithelial cells (Na,K-ATPase, ENaC, Sgk-1). Similarly, Ikeda et al. (1991), using rat neonatal and adult cardiomyocytes, have demonstrated a significant increase in the α1 subunit of the Na,K-ATPase mRNA content after 6 h of stimulation with aldosterone; however, this effect was not confirmed in two other studies (Ramirez-Gil et al., 1998; Robert et al., 1995). Studies have shown that long-term (24 h) treatment with aldosterone upregulates Ca^{2+} currents in adult rat cardiomyocytes, probably through the activation of L-type Ca^{2+} channels (Benitah and Vassort, 1999). Secondary to the increase in L-type Ca^{2+} channels activity, Benitah et al. (2001) have also demonstrated a decrease in outward K^+ current in rat cardiomyocytes. All these effects were blocked by RU28318, a specific mineralocorticoid receptor antagonist, thus indicating a mineralocorticoid receptor mediated mechanism. Wang et al. (1999) have recently shown that in neonatal mouse cardiomyocytes the L-type Ca^{2+} channels are also activated by glucocorticoids. Aldosterone is also known to participate in the regulation of the acid base balance in rat neonatal cardiomyocytes via the regulation of activity of $Cl^-/HCO3^-$ and of Na^+/H^+ exchangers after 24 h of treatment with the hormone (Korichneva et al., 1995). Mihailidou et al. (2000) have demonstrated that the activity of $Na^+K^+Cl_2$–co-transporter is regulated by aldosterone in rabbit cardiomyocytes. Several transgenic mouse models with a cardiac expression of mineralocorticoid receptors or 11-b-HSD2 have been generated (Ouvrard-Pascaud and Jaisser, 2003). A mice line over-expressing the human mineralocorticoid receptor in many tissues, including the heart, was obtained using a promoter with a widespread tissue activity (Le Menuet et al., 2001). Mild dilated cardiomyopathy, increased heart rate and increased frequency of dysrhythmia were the major cardiac phenotypes observed in this study. These changes were observed without a significant increase in blood pressure and no cardiac fibrosis was observed in this model. An original protocol for cardiac-specific decrease of mineralocorticoid receptor expression has been chosen by conditional overexpression of an antisense mineralocorticoid receptor mRNA, specifically in cardiomyocytes (Beggah et al., 2002). In this model, mice with reduced mineralocorticoid receptor expression developed within 2–3 months a severe heart failure and cardiac fibrosis without an increase in blood pressure. A transgenic mouse model with cardiomyocyte restricted 11-b-HSD2 overexpression was developed by Wang et al. (2004) and three independent lines of mice have been studied which showed a severe myocardial hypertrophy and left ventricular interstitial fibrosis in the absence of an increased blood pressure. In this model, the hearts are severely dilated and the cardiomyocyte size is increased indicating a role of aldosterone in remodeling cardiac tissue (Firsov and Muller, 2003). In the aldosterone-signaling pathway, several advances have been made in the identification of downstream renal targets (Sgk1, GILZ, KRAAS, Nedd4-2, ENAC, Na,K-ATPase) using differential display or serial analysis of gene expression (Loffing et al., 2001; Robert-Nicoud et al., 2001; Spindler et al., 1997).

4. Conclusions

With the isolation of aldosterone five decades ago, many developments have taken place; however in last two decades the developments in RAAS have been remarkable and have revolutionized the research. Moreover, in addition to local RAAS, the discovery of the pancreatic RAAS has led to development of more detailed understanding of RAAS. Ongoing research worldwide has provided valuable clues regarding the precise mechanism of RAAS and its role in metabolic and cardiovascular diseases thus suggesting that RAAS has a multi-facet role to play. Currently, diabetes and cardiovascular diseases remain as areas of concern, globally. Various experimental and clinical studies have reported the effects of drugs manipulating with the RAAS. With the advancements in the technologies, it is now possible to co-relate aldosterone and angiotensin II with diabetes and cardiovascular disease. Thus, with these co-relations and more ongoing

research, it is possible that in future RAAS may become as the main target for curbing these culminating diseases of diabetes and cardiovascular system.

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