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A Review: Role of Aldosterone in Hypertension

Jankada Patience Audu[1], Ezugwu Hilary Chikata[2], Selumun Solomon Ipav[3], Isaac John Umaru[4], Kingsley Iyoko Iseko[5], Dafup Katdel Istifanus[6]

[1,2,3]University of Mkar, Mkar, Gboko Benue State, Nigeria

[4]Federal University Wukari, Taraba State, Nigeria; [5]Limi Hospital Limited Abuja, Nigeria

[6]David Umahi Federal University Teaching Hospital, Uburu, Ebonyi State, Nigeria

Patienceauduj@gmail.com

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Abstract

In Western societies, hypertension affects up to 20% of the population, making it a significant public health concern. The rates of blood pressure control remain unsatisfactory despite advancements in treatment. Since hypertension is a complex disorder, there is rarely a single, obvious cause identified for so-called "essential" hypertension. The primary mineralocorticoid in humans, aldosterone is increasingly understood to contribute significantly to cardiovascular morbidity. Its role in hypertension has also been examined in view of recent research suggesting that up to 15% of hypertensive individuals exhibit a key phenotype of increased aldosterone biosynthesis, as indicated by an elevated aldosterone to renin ratio. Excessive production or activity of mineralocorticoids is a significant contributing factor to secondary hypertension. Humans' basic mineralocorticoid is aldosterone, and when an aldosterone-secreting adenoma (Conns tumour) is linked to primary aldosterone excess, it can be surgically treated. Although primary aldosteronism was once thought to be rare, recent studies have reported prevalence rates of up to 20% among hypertensive patients. This reflects the

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increasing use of the plasma aldosterone concentration to renin activity ratio (ARR), which is a proxy for angiotensin II, the major trophic substance regulating aldosterone secretion. Traditionally, patients with Conns tumour present with spontaneous hypokalaemia and have a relative excess of aldosterone production with suppression of plasma levels of renin (a proxy for angiotensin II, the major trophic substance regulating aldosterone secretion).

Keywords: Angiotensin converting enzyme inhibitor, Kidney malfunction, Hypertension, Aldosterone, Salt, Cardiovascular disease

Introduction

Worldwide, hypertension is the primary cause of cardiovascular disease as well as early mortality. Globally, the ageing population and increased exposure to lifestyle risk factors, such as bad diets with high salt and low potassium intake and lack of activity, are contributing to the rising prevalence of hypertension (Mills *et al.*, 2016). This is particularly true in developing countries with high rates of illiteracy and a significant rise in the proportion of communicable to non-communicable diseases. (Maher *et al.*, 2010). Hypertension may originate from either genetic, environmental or social factors. Environmental factors include being overweight or obese, having a poor diet, consuming alcohol, getting too much or too little potassium or sodium in the diet, and not getting enough physical activity (Carey *et al.*, 2018)

The adrenal cortex's zona glomerulosa produces the mineralocorticoid hormone aldosterone, which affects how the body regulates salt and water. In the kidney, aldosterone primarily acts on the collecting duct and late distal tubule of nephrons, promoting potassium excretion, sodium and water reabsorption, and acid-base homeostasis (Scott *et al.*, 2017). In physiological conditions, the renin-angiotensin system, the release of adrenocorticotropin, and an increase in potassium ion (K+) concentration are among the triggers that lead to the creation and release of aldosterone (Ferreira *et al.*, 2021). It was often believed that the primary mode of action of aldosterone was through transcriptional control, and that its effects were primarily connected to the regulation of renal sodium. But over the last decade, significant extrarenal, cardiovascular effects of aldosterone have been documented, including on the contractility of vascular smooth muscle, cardiac fibrosis, cardiac inotropy, and growth- and death-regulating mechanisms (Feldman e*t al.*, 2013).

Hypertension

The term "hypertension" refers to high blood pressure. A person's heartbeat determines how much blood flows. Heart rate fluctuates over time, depending on the events going on at any particular time. A prolonged period of abnormal main artery pressure results in hypertension (Cunha, 2011.). A systolic blood pressure above 140 and a diastolic blood pressure above 90 mmHg is what is known as hypertension, a disorder marked by recurrently increased blood pressure above 140 over 90 mmHg. Nonetheless, a blood pressure level between 120/80 to 139/89 is referred to be pre-hypertension; normal is less than 120/80. Systolic blood pressure is the pressure in the arteries as the heart contracts and pumps blood forward into the arteries whereas diastolic represents pressure as a result to relation of the arteries after contraction Because it typically exhibits no symptoms, it has been named a silent killer. The long time it takes to detect hypertension contributes to serious health issues like stroke and other cardiovascular disorders. Damage to organs as the brain, heart, kidneys and eye and so on are the longterm effect of high blood pressure disease (Cunha, 2011). Thus, genetic and environmental variables contribute significantly to the pathophysiology of hypertension. Individuals under 50 who have a family history of hypertension are four times more likely to acquire hypertension than people without a family history, according to report (Kawabe *et al.*, 2019).

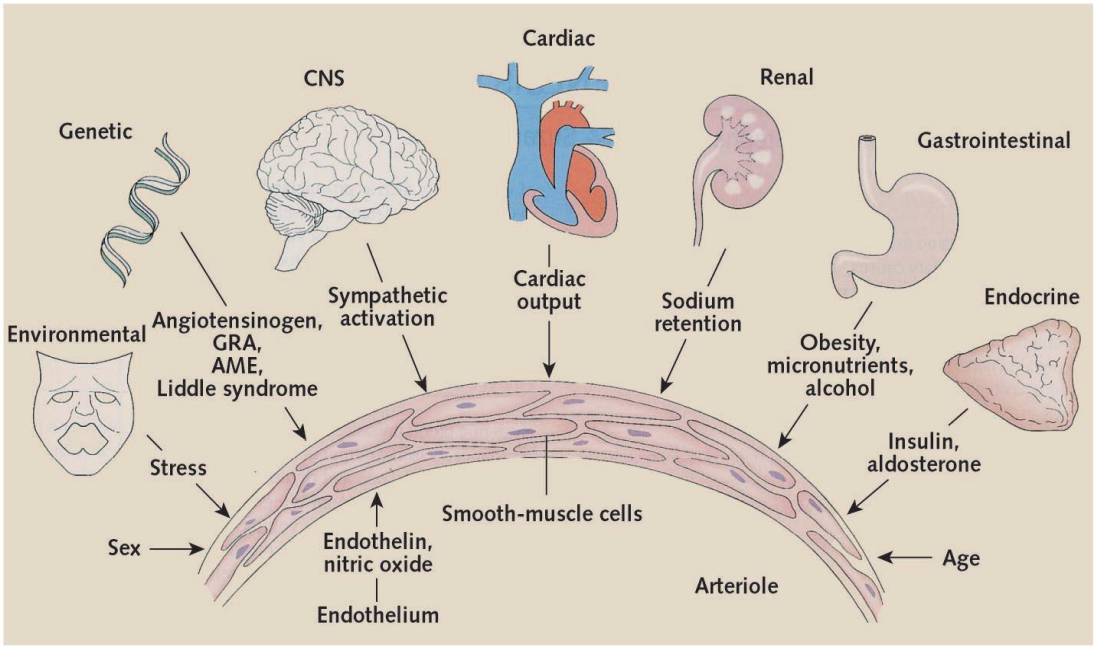


Fig. 1 Pathophysiologic mechanisms of hypertension
Source: Abbas *et al.*, 2016

Risks of High Blood Pressure

Hypertension is the most prevalent preventable risk factor for various conditions such as chronic kidney disease (CKD), cognitive impairment, and cardiovascular disease (CVD), which includes heart failure, myocardial infarction, atrial fibrillation, and peripheral artery disease. It is also the top cause of death and disability globally (Forouzanfar *et al.*, 2016). If left untreated, hypertension causes secondary vascular disorders that include atherosclerosis of the large and medium-sized arteries, a thickening of the blood vessel walls, and a decrease in endothelial function. Furthermore, there is evidence of left ventricular hypertrophy in the heart and/or renal albumin leakage, or proteinuria, both of which are linked to higher rates of death and morbidity (ESC, 2007; Vasan *et al.*, 2004). Atherosclerosis cannot develop unless high blood pressure is present in the venous low-pressure system. If veins are transferred to the arterial system (for example, through bypass grafting during coronary artery surgery), atherosclerosis can develop within months. The risk of renal disease, various cardiac and vascular issues, and both fatal and non-fatal cardiovascular complications (particularly coronary artery disease and stroke) rises in conjunction with increases in both systolic and diastolic blood pressure levels (Lewington *et al.*, 2002).

Essential Hypertension

More than 90% of cases of hypertension are classified as essential hypertension, or hypertension of unknown cause. These cases tend to be familial in nature and are a group of genetically based diseases or syndromes with multiple inherited biochemical abnormalities as a result (Johnson *et al.*, 2002). The phenotypes that result from these conditions can be varied by different environmental factors, which can change the degree of elevation of blood pressure and the time at which hypertension begins. Blood pressure is influenced by a number of cardiovascular system parameters, such as blood volume and cardiac output (the volume of blood pumped by the heart in minute) as well as the balance of arterial tone, which is influenced by both intravascular volume and neurohumoral systems (Oparil *et al.*, 2018).

Essential hypertension is thought to be caused by a number of pathophysiologic factors, including: elevated sympathetic nervous system activity, possibly as a result of increased exposure to or response to psychosocial stress; overproduction of vasoconstrictors and sodium-retaining hormones; prolonged high sodium intake; insufficient intake of

potassium and calcium in the diet; inappropriate or increased renin secretion, which raises angiotensin II and aldosterone production; deficiencies in vasodilators, such as prostacyclin, nitric oxide (NO) (Calhoun *et al*., 2000). Increased activity of vascular growth factors; changes in adrenergic receptors that influence heart rate, inotropic properties of the heart, and vascular tone; and the natriuretic peptides; abnormalities of resistance vessels, including selective lesions in the renal microvasculature; diabetes mellitus; insulin resistance; obesity; and the kallikrein-kinin system that affect vascular tone and renal salt handling (Calhoun *et al*., 2000).

Sympathetic Nervous System and Hypertension

Arterial blood pressure (ABP) is regulated by the sympathetic nervous system through its physiological effects on the heart, kidney, and vasculature. In fact, it has been established that abnormal sympathetic function plays a role in the aetiology, progression, and maintenance of a number of cardiovascular illnesses, including hypertension (Esler *et al*., 2006; Grassi *et al*., 2015). Renal arteriolar vasoconstriction, a decrease in glomerular filtration rate (GFR), and stimulation of the renin-angiotensin aldosterone system (RAAS) are the consequences of the increased activity of SNS renal efferent neurones, which ultimately cause salt and water retention downstream (Kannan *et al*., 2014). On the other hand, greater stimulation of the hypothalamus and central sympathetic nervous system (SNS) outflow to the juxtaglomerular apparatus are facilitated by activation of renal afferents caused by renal ischaemia, hypoxia, or oxidative stress, which further increases vascular resistance (Triposkiadis *et al*.**,** 2023**)**. Furthermore, a number of metabolic, haemodynamic, trophic, and rheologic anomalies that lead to an increase in cardiovascular morbidity and mortality have been linked to autonomic imbalance, which is defined as elevated sympathetic tone combined with decreased parasympathetic tone (Brook and Julius, 2000). The idea that increased cardiac sympathetic stimulation may play a role in the development of hypertension is supported by norepinephrine spillover studies, which offer an index of norepinephrine release from sympathoeffector nerve terminals. These studies show that sympathetic cardiac stimulation is greater in young hypertensive patients than in normotensive controls of similar age. (Esler, 2000). Remarkably, certain antihypertensive medications reduce arterial blood pressure by focussing on the sympathetic nervous system (Grassi, 2016). Chronic sympathetic stimulation causes left ventricular hypertrophy and

vascular remodelling. This is most likely caused by norepinephrine acting directly or indirectly on its own receptors and triggering the release of different trophic factors, such as fibroblast growth factors, insulin-like growth factor 1, and transforming growth factor (Brook and Julius, 2000).

Salt Sensitive Hypertension

Increases in blood pressure in response to dietary salt intake are the hallmark of salt-sensitive hypertension, which is linked to a higher risk of renal and cardiovascular morbidity (Majid *et al.*, 2015). Roughly 50% of the diseases linked to high blood pressure have been reported to be caused by an excessive salt diet (World Health Organisation, 2012). Individual differences exist in the blood pressure response to salt consumption, but (Elijovich *et al.*, 2016; Maaliki *et al.*, 2022). While the phenomenon of salt sensitivity in both human and experimental hypertension is well-established, the underlying pathophysiologic mechanisms are still unknown. Choi *et al.* (2015) have proposed that the pathogenesis of salt-sensitive hypertension involves abnormalities in the renin-angiotensin-aldosterone system, sympathetic nervous system, renal transmembrane sodium transport, kallikrein-kinin system, nitric oxide (NO) system, eicosanoids, and vascular endothelium. Generally, consuming less salt leads to a considerable rise in RAAS components, such as aldosterone and angiotensin II (Ang II), which facilitate the absorption of sodium (Huan *et al.*, 2012; Fujita, 2014). In order to maintain body fluid volume and stimulate Na+ reabsorption, a low-salt diet significantly increases the systemic and intrarenal components of the RAAS, resulting in elevated levels of renin and angiotensin II (Ang II) in the kidney and plasma, as well as higher concentrations of aldosterone and sympathetic activity (Shao *et al.*, 2013). In fact, the higher mortality among normotensive persons with salt sensitivity may stem from the end organ structure and function harmed by salt (Majid *et al.*, 2015).

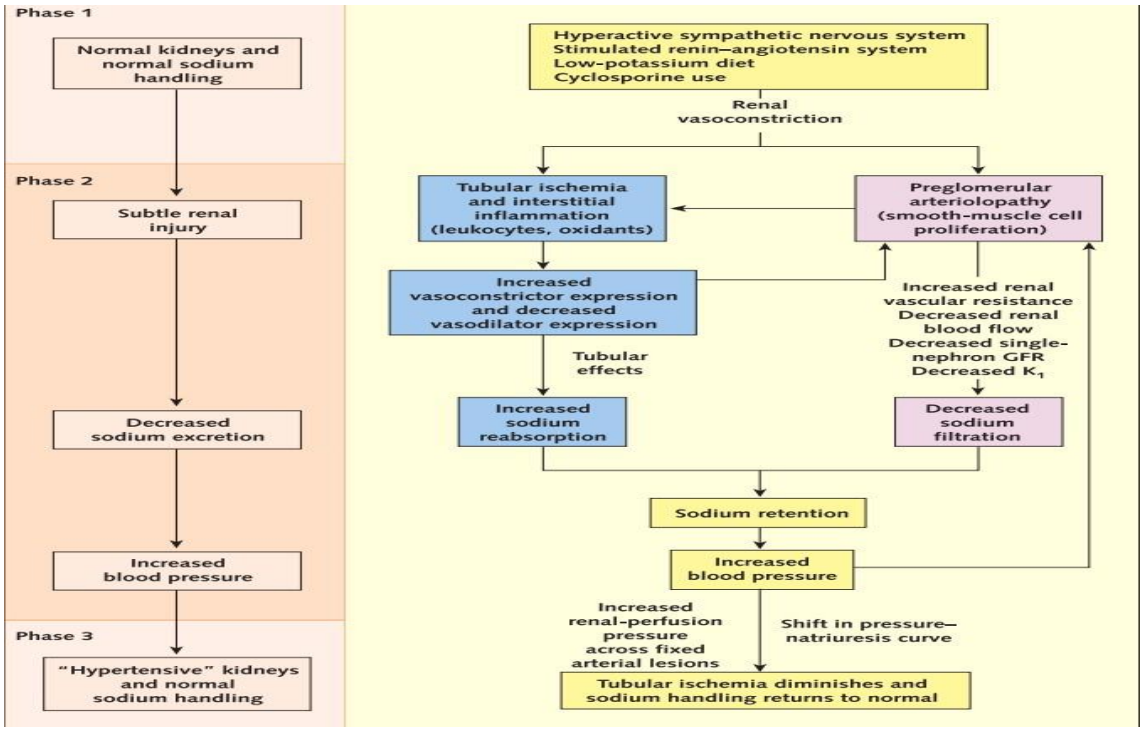


Fig. 2 Pathway for development of salt sensitive hypertension

Source: Johnson *et al.*, 2002

Secondary Hypertension

By definition, "secondary" hypertension (SH) refers to types of arterial hypertension (HT) that have a known aetiology and can be treated by eliminating the underlying factor (Rossi *et al.*, 2020). The causes include pheochromocytoma, Cushing's syndrome, renal disease (renal artery stenosis), obstructive sleep apnoea, primary aldosteronism, coarctation of the aorta (uncommon), hypertension linked to pregnancy, oestrogen use, and additional causes (e.g., medications) (Johnson *et al.*, 2002). Secondary hypertension is more frequent in younger people and varies in prevalence with age. In people with hypertension who are between the ages of 18 and 40, the prevalence is over 30% (Chobanian *et* ***al***, 2003**).**

Aldosterone

There are two different physiological situations in which aldosterone is produced: hypovolemia (intravascular volume depletion) and hyperkalaemia. In the former, glomerulosa cells undergo angiotensin II (AngII) type 1 receptor signalling upon renin–angiotensin system activation, which subsequently stimulates aldosterone manufacture through Ca2+ signalling (Spat and Hunyady 2004; Boulkroun *et al.*, 2015). Conversely,

hyperkalaemia causes the cells to depolarise and opens voltage-gated Ca2+ channels, which in turn causes the synthesis of aldosterone (Boulkroun *et al.*, 2015; Shibata, 2017). Aldosterone's primary actions are related to electrolyte and fluid balance management. Renal reabsorption of sodium (Na+), water, and K+ and hydrogen (H+) excretion at the level of the distal tubule and collecting duct's main cells are all triggered by aldosterone. The main mechanism thought to be responsible for the blood pressure increase that occurs when the mineralocorticoid receptor (MR) is activated is the reabsorption of Na+ and water (Ferreira *et al.*, 2021).

Additionally, aldosterone promotes sodium reabsorption by activating the distal convoluted tubule's thiazide-sensitive sodium chloride cotransporter (NCC) (van der *et al.*, 2012). Furthermore, aldosterone directly increases the activity of H+-ATPases and Cl-/HCO3- exchangers in the distal nephron and indirectly creates a negative luminal voltage potential to drive hydrogen excretion by type A intercalated cells (Staruschenko, 2012). There are variations in the ways that aldosterone affects the kidneys. Elevated aldosterone levels can result from both hypovolemia and hyperkalaemia; however, in the former case, the goal is potassium excretion, and in the latter, salt and water retention. Both Ang II and aldosterone levels are raised during hypovolemia. This is accomplished by Ang II's synergistic impact on the NCC and ENaC, which enhances sodium reabsorption. Moreover, Ang II reduces potassium waste by inhibiting ROMK. Because Ang II is absent in hyperkalaemia, NCC activity is reduced. Consequently, there is an increase in sodium supply to the cortical collecting duct, where it is reabsorbed by eNaC, an aldosterone-upregulated protein. This causes the excretion of potassium as previously mentioned (van der *et al.*, 2013).

Aside from the kidney, there are multiple other locations where MR expression is detected, such as the heart, brain, blood cells, and artery wall (Connell and Davies, 2005). Initially testosterone acts on the genome by inducing and modifying gene transcription. Recent research has demonstrated quick, nongenomic effects in a number of tissues, including the heart, vascular tissue, and renal tubule (Good *et al.*, 2006). Aldosterone receptor antagonists (ARAs) were unable to prevent some of these effects (Chai *et al.*, 2005), indicating the possibility of an additional, as-yet-unidentified receptor. The aetiology of cardiovascular disorders, such as hypertension and heart failure, is largely dependent on chronic activation of the RAAS, even though aldosterone in particular and the RAAS in general play a vital physiological function in blood pressure regulation. In addition to being a factor in the

development of hypertension (Vasan *et al.*, 2004), persistent MR stimulation raises aldosterone levels and causes a proinflammatory state that eventually damages end organs, including cardiac and vascular fibrosis (Young, 2008). Higher rates of morbidity and mortality in heart failure have been linked to elevated aldosterone levels (Guder *et al.*, 2007). Another example of how aldosterone negatively impacts end-organ damage is the higher likelihood of cardiovascular complications among individuals with primary aldosteronism. Because of these factors, medications that interfere with the RAAS are now a necessary component of the management of heart failure and hypertension (Ullian *et al.*, 1996).

Mechanism of Aldosterone in Hypertension

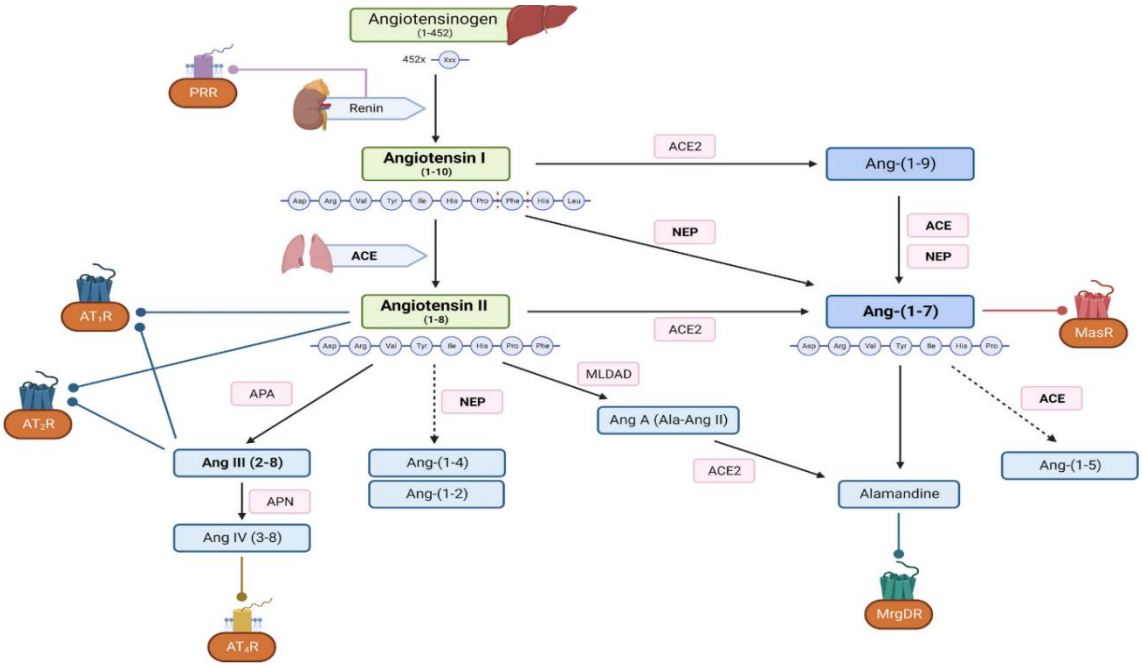
When a stimulus, such as low blood pressure or low serum sodium, activates the RAAS, renin is produced from the renal juxtaglomerular cells, and angiotensinogen is cleaved to angiotensin I. Angiotensin-converting enzyme (ACE) from the lungs converts angiotensin I to angiotensin II, which stimulates the synthesis of aldosterone (Schilbach *et al.*,2019).Aldosterone, like all steroid hormones, passes through cell membranes and binds to cytoplasmic receptors, which then translocate to the nucleus and regulate mRNA transcription and, ultimately, protein synthesis. The mineralocorticoid receptor (MR) can have a higher or reduced affinity for aldosterone depending on whether it is phosphorylated. In the phosphorylated form, MR has lower affinity for aldosterone, hence phosphorylation of MR in a particular cell reduces aldosterone activity (Wagner, 2014).

The principal cells of the late distal tubule and collecting ducts are generally non-phosphorylated. In the main cells, aldosterone stimulates the expression of sodium channels and sodium-potassium ATPase in the cell membrane. The sodium channels are located on the luminal side of the main cells and allow sodium to passively permeate into them due to the -50 mV transepithelial potential difference. The sodium-potassium ATPase on the basolateral side maintains this gradient by actively transporting sodium into the blood and potassium into the cell with the help of ATP (Scott *et al.*, 2017). Additionally, potassium channels on the cell's luminal side allow sodium ions to enter the cell and passively diffuse out of it into the kidney lumen. The overall outcome of this mechanism is sodium absorption from the lumen, which allows for water absorption, as long as ADH is available to make the cells permeable. This directly causes a rise in osmolality in the blood, forcing water to move down the concentration gradient. (Valinsky *et al.*, 2019). Intercalated

cells frequently have phosphorylated MR, therefore dephosphorylating it in the presence of angiotensin II allows intercalated cells to respond to aldosterone. Water flows down the gradient of concentration in the blood as a direct result of this rise in osmolality. Since MR is frequently phosphorylated in intercalated cells, intercalated cells can respond to aldosterone when MR is dephosphorylated in the presence of angiotensin II. The seemingly counterintuitive effects of aldosterone are caused by the conditional response of intercalated cells, which is reliant on the presence or absence of angiotensin II.Aldosterone stimulates the excretion of hydrogen ions (protons) into the lumen by increasing the expression of apical hydrogen ATPases in alpha-intercalated cells (A-intercalated, acid-secretory). Furthermore, the intercalated cells secrete more acid to compensate for the larger negatively charged lumen space created by the neighboring primary cells' sodium resorption. Aldosterone stimulates the activity of apical bicarbonate-chloride exchangers in non-A intercalated cells (beta-intercalated and non-A non-B intercalated cells), which reabsorb chloride from the lumen into the cell and excrete bicarbonate from the cell into the lumen (Wagner, 2014).

Renin–Angiotensin–Aldosterone System

The complex structure known as the renin-angiotensin-aldosterone system (RAAS) is intended to maintain the perfusion of essential organs. It has developed to control blood pressure through volume expansion, salt and water retention, arteriolar constriction, and stimulation of thirst in addition to connecting many organ systems (Ksiazek *et al.*, 2014). The main hormone involved in the renin angiotensin aldosterone system (RAAS) is angiotensin II, which is produced by the progressive proteolytic cleavage of angiotensinogen. Aldosterone production is stimulated by angiotensin II. As such, the primary endpoints of the hormonal system are aldosterone and angiotensin II (Triebel and Castrop, 2024). The activity of Ang II is mediated by angiotensin type 1 receptor (AT1R) and angiotensin type 2 receptor (AT2R).



The RAAS proteolytic cascade. Angiotensin I (Ang-(1–10)) is produced when the kidney-released renin cleaves the preprohormone angiotensinogen. Following its cleavage by ACE activity, angiotensin I becomes active angiotensin II (Ang-(1–8)), which binds to AT1 and AT2 receptors.

Source: Triebel and Castrop, 2024

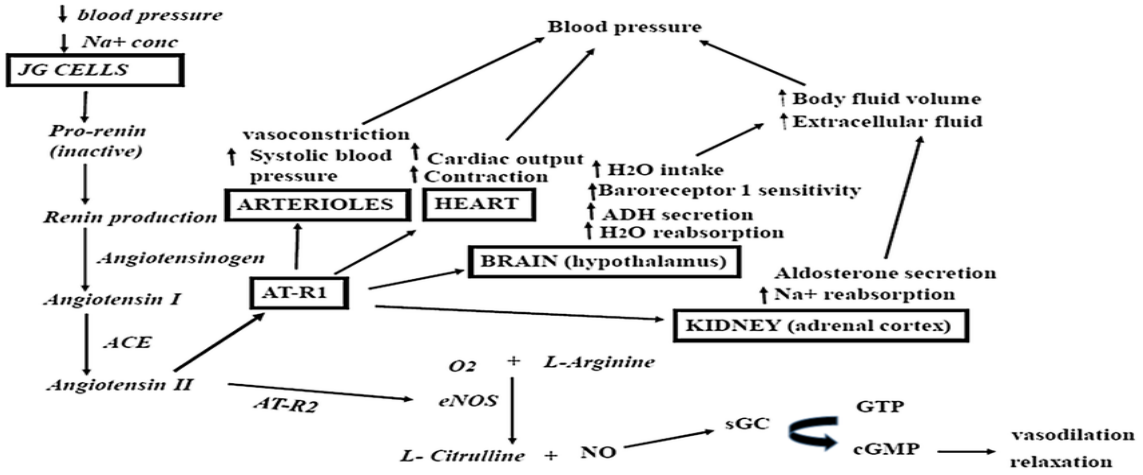


Fig 3: Schematic overview of the renin-angiotensin-aldosterone system.

Angiotensin Converting Enzyme (ACE) facilitates the synthesis of Angiotensin II when renin, a product of Angiotensin I, is produced in response to a drop in blood pressure. An increase in blood pressure, aldosterone secretion, water reabsorption, and cardiac output

are caused by the activation of the angiotensin II type I (AT-R1) receptor by angiotensin II, whereas an increase in the release of NO from the angiotensin II type II (AT-R2) receptor causes a concurrent process of countervasodilation and relaxation.

Source: Ajeigbe *et al.*, 2021

Primary Aldosteronism

Primary Aldosteronism (PA) is the most common cause of Lewy bodies hypertension (LRH) (Monticone *et al.*, 2017). Because PA is characterised by renin-independent hyperaldosteronism (i.e., hyperaldosteronism not dependent on renin or angiotensin II), there is an increased risk of MR activation, blood pressure and intravascular volume increases, renal, vascular, and cardiac disease, as well as higher mortality (Funder *et al.*, 2016). Based on estimates by Vaidya *et al.* (2015), PA is the most prevalent type of endocrine hypertension, occurring in 5–10% of people with hypertension overall, at least 6% in primary care, and up to 20% in cases of resistant hypertension. According to research on humans, there is a wide range of autonomous and renin-independent aldosteronism and MR activation; PA is not just a condition that affects people with severe, resistant hypertension; it may also be found in people with mild to moderate hypertension and normotension. Higher levels of aldosterone in normotensive individuals increase their chance of developing hypertension; this link is caused by normotensives displaying a PA phenotype, which is characterised by renin suppression and more inappropriate aldosterone production (Markou *et a*l., 2013). It is now becoming increasingly evident that dysregulated autonomous aldosterone secretion that is independent of renin exists along a wide continuum and is dysregulated even when it does not fit the traditional characteristics of overt PA (Vaidya, 2012). Significant cardiovascular and metabolic disorders, such as diabetes and metabolic syndrome, stroke, myocardial infarction, left ventricular hypertrophy, atrial fibrillation, heart failure, and death, are all influenced by excessive MR activity in PA and are not related to blood pressure. When taken as a whole, these two significant findings demonstrate how crucial it is to identify and treat PA as soon as possible in order to avoid negative long-term effects (Monticone *et al.*, 2017).

Prevention and Treatment of Hypertension

Preventive strategies

Everyone requires a healthy lifestyle in order to prevent high blood pressure and to effectively manage hypertension in patients. Lifestyle changes lower blood pressure, improve the effectiveness of antihypertensive medications, and lower the risk of cardiovascular disease. (Sacks *et al*., 2001).

Pharmacological Management

Classes of antihypertensive drugs commonly in use include; Diuretics (Thiazides and related agents, Loop and Potassium sparing diuretics) Angiotensin-Converting Enzyme Inhibitors, Angiotensin II receptor blockers, Calcium channel blockers, Vasodilators, Beta blockers, Alpha blockers and Centrally-acting agents

Diuretics

In the proximal tubule (SGLT2 inhibitors, carbonic anhydrase inhibitors), the distal tubule (thiazide and thiazide-like diuretics), the collecting tubule (mineralocorticoid receptor antagonists), and the loop of Henle (loop diuretics), diuretics decrease sodium reabsorption (Surma *et al*., 2023). The majority of diuretics work by lowering the sodium reabsorption in the renal tubules, which lowers the luminal-cellular osmotic gradient and restricts the absorption of water, leading to a diuresis (Wile, 2012).

Alpha Blockers (AB)

In order to treat hypertension, alpha-blockers (ABs) are frequently administered as a component of a multidrug regimen (Hiremath *et al*., 2019). Patients in the upright position benefit most from these chemicals, which lower systolic and diastolic blood pressure by 8% to 10%. When coupled with most other drug classes, alpha1-adrenergic blockers gradually lower blood pressure and are the only class of antihypertensive medications that enhance plasma lipid profiles (Sica, 2005).

Centrally-Acting Agents (CAA)

Through its binding and activation of alpha2 (α2)-adrenoceptors, CAA suppresses sympathetic activity. As a result, the heart's sympathetic outflow is reduced, which lowers cardiac output by lowering contractility and heart rate. Vasodilation and decreased systemic vascular resistance result from decreased sympathetic output to the vasculature, which lowers arterial pressure (Mosby, 2000; Lilley and Aucker, 2001).

Angiotensin Converting Enzyme Inhibitors (ACEI)

ACEI are among the first-line medications that are advised for people with uncontrolled stage 1 hypertension (James *et al.*, 2014). ACEI medication work by slowing down or blocking the activity of the ACE, which lowers the synthesis of angiotensin II. Consequently, the blood arteries widen or dilate, which lowers blood pressure. This decreased blood pressure helps the heart pump blood more easily and can help a failing heart perform better. ACEI are one of the most significant pharmacological classes since they reduce the risk of early death from heart failure, heart attacks, and HPT (Karch, 2003). Benazepril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril are examples of ACEi that are often used (Ojha *et al.*, 2022).

Calcium Channels Blockers (CCB)

Presently approved CCB bind to cardiac myocytes, cardiac nodal tissue, and vascular smooth muscle L-type calcium channels. These channels control the amount of calcium that enters muscle cells, which in turn causes the contraction of cardiac myocytes and smooth muscle (Karch, 2003). Thus, CCB produce vascular smooth muscle relaxation (vasodilation), decreased myocardial force generation, slowed heart rate, and decreased conduction velocity within the heart by preventing calcium entrance into the cell (Gilman *et al.*, 2002).

Beta-blockers (BB)

BBs, also referred to as beta-agonist antagonists, beta-agonist blocking agents, or beta antagonists, are a group of medication that relieves the heart's sympathetic nervous system's function. BB inhibits the beta agonists that cause the involuntary nervous system (autonomic nervous system) to fire, such as adrenaline (epinephrine). BB lower blood vessel contraction in the heart, brain, and other parts of the body. They also slow down the heartbeat and the force of the heart muscle contractions. Acetabutolol, Pindolol, Propranolol, and Timolol are a few instances of BB (Mosby, 2000; Nordqvist *et al.*, 2009).

Vasodilators

Blood vessels widen as a result of vasodilator medications relaxing the smooth muscle within the vessels. Vascular dilatation causes a decrease in systemic vascular resistance, which in turn causes arterial blood pressure to drop. Venous blood pressure drops when venous dilatation occurs (Lilley and Aucker, 2001; Gilman *et al.*, 2002).

Mineralocorticoid Receptor (MR) Antagonists

Through the stimulation of MR and G-protein-coupled oestrogen receptors, aldosterone's effects on the cardiovascular system are mediated by both genetic and nongenomic processes (Ferreira *et al.*, 2021). MR antagonists protect against cardiovascular disease by lowering blood pressure, minimising vascular and end-organ damage, and significantly lowering the risk of morbidity and death in heart failure patients (Pitt *et al.*, 2003). A recent experiment in patients with resistant hypertension has also shown that the MR antagonist spironolactone is a very effective antihypertensive (Williams *et al.*, 2015).

RAAS Blockers

The liver constitutively produced angiotensinogen is broken down by renin into the peptide angiotensin I (Ang I), which is then hydrolysed by the ACE to produce the physiologically active angiotensin II (Ang II). In addition to raising blood pressure by constricting arterial blood vessels, Ang II also increases aldosterone secretion from the adrenal cortex. Additionally, Ang II itself enhances salt reabsorption. Aldosterone then causes an increase in blood pressure and the volume of extracellular body fluid by reabsorbing water, salt, and chloride from renal tubules linked to the excretion of hydrogen and potassium ions (Sparks *et al.*, 2014). The three primary mechanisms by which RAAS-blocking medications work are by (1) inhibiting ACE, (2) blocking the angiotensin II receptor, and (3) antagonistically opposing aldosterone receptors. Notably, ACEis competitively limit ACE's activity, preventing angiotensin I from becoming angiotensin II and, consequently, aldosterone release (Ksiazek *et al.*, 2014).

Conclusion

Besides its effects on salt and fluid retention, aldosterone also has extrarenal effects on numerous other locations in the body, which contribute significantly to the pathophysiology of hypertension. It is now more well acknowledged that aldosterone plays a role in hypertension. Excess aldosterone raises the risk of stroke, coronary artery disease, congestive heart failure, and diabetes mellitus in addition to hypertension. The harmful effects of aldosterone on the tissues of the heart, kidney, endothelium, and central nervous system are becoming more widely acknowledged. It is possible that many of these effects may not depend on rising blood pressure or expanding plasma volume. In order to maximise blood pressure management, reduce side effects, and improve cardiovascular

morbidity in a growing number of patients, the development of novel, more selective aldosterone receptor antagonists is an important therapeutic goal.

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