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Hypertension Manual



A Muruganathan

Foreword
Gurpreet S Wander

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CHAPTER 3

Renin-Angiotensin-Aldosterone System in Hypertension

Rubi Dey, Bidita Khandelwal

INTRODUCTION

Kidneys are one of the major organs that are instrumental in providing the physiological means for the maintenance of blood pressure and electrolyte homeostasis. Blood pressure has a direct relation to the body's tissue perfusion. The two most important etiologic factors of BP include sodium-volume factor and vascular tonality. These factors reside in the kidney and therefore kidney plays an important role in the regulation of BP. The kidney has the capability of controlling arterial BP mainly through the various changes in the extracellular fluid and by the renin-angiotensin-aldosterone system (RAAS).

Tigerstedt and Bergman in the year 1889 reported the vasopressor effect of renal extract—Renin—which was found to cause a sustained rise in arterial pressure.[1] This formed the stepping stone in the discovery of the RAAS, although this finding was criticized for quite a long period before it got recognition. Goldbaltt et al. validated the rise in arterial pressure following renal ischemia.[2] Within a short period after this, it was found that along with renin, the ischemic kidney also released a short-lived pressor substance called angiotensinogen.

The RAAS is a complex multiorgan hormonal cascade that plays an important role as a critical regulator of BP, vascular resistance, and tone. The RAAS has a direct impact on systemic BP by regulating sodium concentration and water absorption in the kidney. The monitoring and controlling of the arterial tone by RAAS helps in maintaining the physiological perfusion, in spite of the constantly changing internal and external influences on the BP. A short-term decrease in arterial pressure is a function of the baroreceptor reflex whereas the RAAS is responsible for chronic alterations in arterial pressure. Long-term activation of RAAS is maladaptive and adversely affects the heart, vessels, and kidneys. The RAAS activation affects every organ along with the resultant hypertension, cell proliferation, inflammation, and fibrosis. An overwhelming number of chronic and acute diseases are because of the imbalance of renin and angiotensin II.

The primary function of RAAS is the regulation of BP by modulating blood volume, sodium reabsorption, potassium secretion, water reabsorption, and vascular tone. Apart from this, other functions of RAAS include inflammation, apoptosis, and fibrosis.[3] The various organs involved in RAAS include the kidneys, lungs, systemic vasculature, and brain.[4] The main players in the RAAS are renin, angiotensin II, and aldosterone which act as a series of designed reactions. They are responsible for elevation of the arterial BP in response to a decrease in renal BP, a decrease in salt delivery to the distal convoluted tubule, and β-agonism.[5-7]

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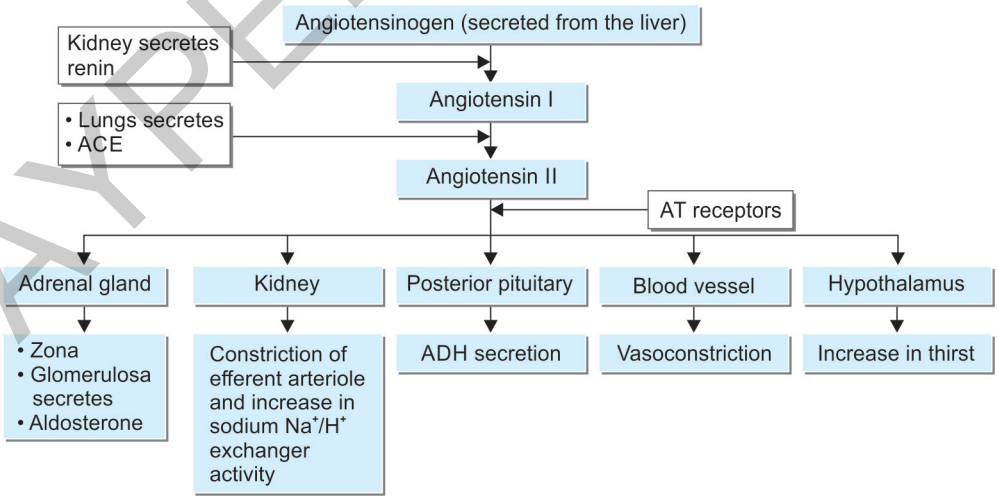
MECHANISM OF RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Juxtaglomerular (JG) cells, present within the afferent arterioles of the kidney, contain prorenin. Prorenin is in its inactive form and activation of JG cells causes the cleavage of prorenin to renin which is the active form and is released into the blood. The JG cell activation occurs in response to decreased BP, β-activation, or activation by macula densa cells in response to a decreased sodium load in the distal convoluted tubule.[8,9]

Renin released into the blood acts on the target angiotensinogen which is produced by the liver and is present continuously circulating in the blood. Renin then causes the cleaving of angiotensinogen into angiotensin I **(Flowchart 1)**. Angiotensin I which is physiologically inactive is the precursor for the active form—angiotensin II.[4] The angiotensin-converting enzyme (ACE) is found primarily in the vascular endothelium of the lungs and kidneys and catalyzes the conversion of angiotensin I to angiotensin II. Angiotensin II causes a diverse set of RAAS-induced physiological and pathophysiological actions by acting on its target organs. So far, four subsets of angiotensin receptors have been described.[10] Type 1 angiotensin (AT1) receptor—most of the physiological function of angiotensin II is mediated by the AT1 receptor widely distributed in many cells of the target organs. The main physiological actions mediated by the AT1 receptor include vasoconstriction; a rise in BP, increased cardiac contractility; vascular and cardiac hypertrophy; Na^+ reabsorption by renal tubules; and stimulation of aldosterone synthesis. Other actions mediated by the AT1 receptor are cell growth and proliferation, inflammatory responses, and oxidative stress. (2) Type 2 angiotensin (AT2) receptor are more present abundantly during fetal life mainly in the kidneys and brain and the levels of the same decreases markedly in the postnatal period. The actions mediated by the AT2 receptor in adults are uncertain but it is thought to cause vasodilation, antiproliferative, and apoptotic

Flowchart 1: Renin-angiotensin-aldosterone system.



(ACE: angiotensin-converting enzyme; AT: angiotensin; ADH: antidiuretic hormone)

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effects in the vascular smooth muscles. (3) Type 3 angiotensin (AT3) receptor action is still not fully ascertained. (4) Type 4 angiotensin (AT4) receptor is to be instrumental in mediating the release of plasminogen inhibitor I. Angiotensin II then has its effects on the kidney, adrenal cortex, arterioles, and brain by binding to angiotensin II type 1 (AT1) and type 2 (AT2) receptors.[11] Angiotensin II has a half-life of 1–2 min and at this point, the peptidases in the plasma degrades it to angiotensin III and IV. Angiotensin III has been found to have 100% of the aldosterone stimulating effect as angiotensin II but it has only 40% of the pressor effects. Angiotensin IV further decreases the systemic effect **(Flowchart 1)**.

Angiotensin II acts in the proximal convoluted tubule of the kidney to increase sodium–hydrogen (Na^+/H^+) exchange and to increase sodium reabsorption. Increased levels of Na in the body lead to an increase in the osmolarity of the blood which causes a shift of fluid into the blood volume and extracellular space (ECF) thereby increasing the arterial pressure.

Angiotensin II also acts specifically on the zona glomerulosa of the adrenal cortex and stimulates the release of aldosterone. Aldosterone being a steroid hormone enacts change by binding to nuclear receptors and altering gene transcription as a result of which the effect of aldosterone takes hours to days to begin. Effects of aldosterone include sodium reabsorption and potassium excretion at the distal tubule and collecting duct of the nephron by stimulating the insertion of luminal Na channels and basolateral sodium–potassium (Na^+/K^+) adenosine triphosphatase (ATPase) proteins.

Angiotensin II has influences on renal epithelial cells, phosphorylation of mineralocorticoid receptors (MRs) in the intercalated cells of the distal nephron, and inhibition of potassium secretion by altering kinase activity, specifically WNK family kinases.[12] The vasoconstrictive effect of angiotensin II takes place in systemic arterioles. Angiotensin II binds to G protein-coupled receptors which causes a secondary messenger cascade that results in potent arteriolar vasoconstriction leading to an increase in the total peripheral resistance and a subsequent increase in BP.

The final effect of angiotensin II is on the brain; initially, it binds to the hypothalamus, stimulating thirst and increasing water intake. Subsequently, it stimulates the release of antidiuretic hormone (ADH) by the posterior pituitary which thereafter acts to increase water reabsorption in the kidney by inserting aquaporin channels at the collecting duct. Angiotensin II also decreases the sensitivity of the baroreceptor reflex thus diminishing the baroreceptor response to an increase in BP. The net effect of these interactions is an increase in total body sodium, total body water, and vascular tone causing an increase in BP.

DYSREGULATED RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM: EFFECTS AND MANAGEMENT (FLOWCHART 2)

The RAAS helps to manage long-term basis of blood volume and arteriolar tone. Inappropriate activation of the RAAS in various conditions causes the development of hypertension and cardiovascular disorders. The baroreceptor reflex manages minor and rapid shifts whereas the RAAS has the capability to alter blood volume chronically. Dysregulated RAAS is an essential factor in essential hypertension.[13] In young male patients with essential hypertension around

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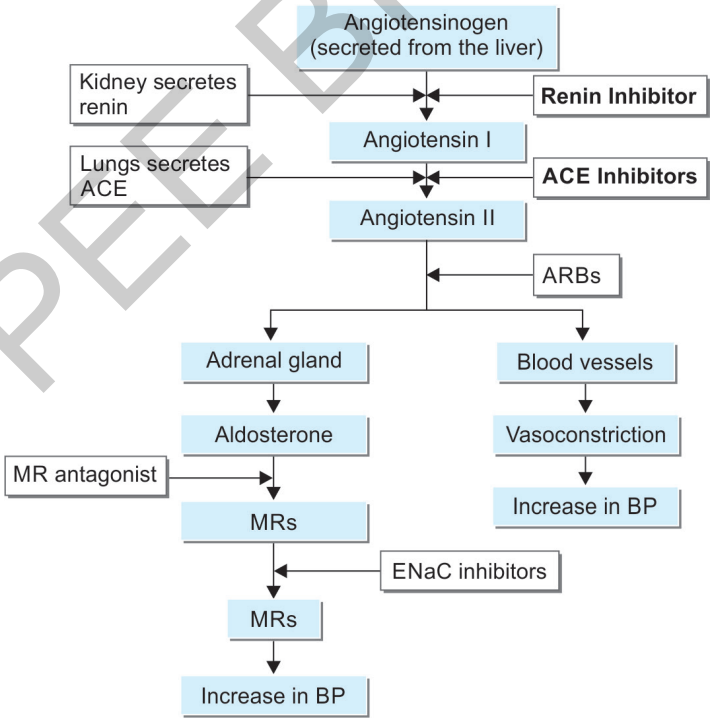
15% have mild-to-moderate rise in plasma renin activity which can be due to sympathetic overactivity and mild volume depletion. Apart from hypertension, RAAS plays a pivotal role in several nonhypertensive conditions, especially in congestive heart failure (CHF) **(Flowchart 2)**.

The RAAS is a frequently manipulated system in the management of several diseases like heart failure, hypertension, diabetes mellitus, and acute myocardial infarction. Renin is the first step in the RAAS cascade and the inhibition of renin decreases the levels of renin, angiotensin I, angiotensin II, aldosterone, and subsequent decrease in BP. This can be thought to be a logical therapeutic target for RAAS blockade. Aliskiren—a renin inhibitor is available for use but because of its side effects especially in combination with ACE inhibitors or ARBs it is not advocated.[14] Drugs such as ACE inhibitors (e.g., enalapril) inhibit the action of ACEs, thus decreasing the production of angiotensin II and inhibiting the progression of the RAAS cascade and the physiological effects of angiotensin II. The physiological actions of angiotensin II are mediated by its receptors present in target organs. Angiotensin receptor blockers (ARBs; e.g., losartan) inhibit the action of ARBs to block AT receptors, thus inhibiting angiotensin's effect while maintaining normal levels of the compound. Aldosterone antagonists have two specific varieties. The first (e.g., spironolactone or eplerenone) group acts as an aldosterone antagonist by preventing the binding of aldosterone to binding sites in the kidney thus preventing insertion of Na channels and the second

Flowchart 2: Pharmacological modulation of dysregulated RAAS.



(ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; MRs: mineralocorticoid receptors)

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(e.g., amiloride or triamterene) group acts by blocking the inserted Na channels in the distal convoluted tubule. These drugs act by decreasing the effect of the RAAS. The ACE inhibitors or ARBs are commonly used in the management of hypertension by decreasing sodium and water reabsorption, leading to a reduction in blood volume, and decreasing arteriolar tone.

The renin-angiotensin-aldosterone pathway is mainly regulated by the mechanisms that stimulate renin release. However, it is also found to be modulated by natriuretic peptides released by the heart and acts as an important counterregulatory system.

FUTURE PROSPECTS

The ACE inhibitors and the ARBs have shown promising results in improving the survival of the high-risk group of patients. They are currently advocated in the management of hypertension, diabetic nephropathy, left ventricular dysfunction, and chronic cardiac failure. Though treatment modalities with the present drugs have shown promising results, more targeted therapies including molecular approaches like antisense gene therapy, and parallel intervention at various sites of the RAAS cascade could help slow the progression of cardiovascular and renal diseases.

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Hypertension Manual

Key Features

- *Comprehensive Update:* Provides a comprehensive update on the current understanding of hypertension.
- *Highly Experienced Authors:* Authored and compiled by highly experienced professionals, offering deep insights into the latest hypertension management modalities.
- *Sectional Organization:* Divided into 13 sections for easy navigation and focused exploration.
- *Coverage of History and Epidemiology:* Begins with a section covering the history and epidemiology of hypertension.
- *In-depth Coverage of Etiopathogenesis*: Provides in-depth coverage of risk factors and etiopathogenesis of hypertension.
- *Focus on Secondary Hypertension:* Includes a dedicated section on secondary hypertension, addressing damage, and evaluation.
- *Target Organ Management:* Explores target organ management in hypertension cases.
- *Special Considerations:* Covers hypertension in different life conditions and diverse populations.
- *Holistic Management Approach:* Addresses management strategies for hypertension, encompassing both pharmacological and non-pharmacological therapies.
- *Valuable Resource:* Serves as a valuable resource for cardiologists, physicians, general practitioners, and postgraduate students.

This edition is a comprehensive guide that combines the expertise of experienced authors, revised content, and chapters to present the most up-to-date information on hypertension. It caters to a diverse audience, offering insights and guidance for effective management in various medical settings.

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