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Renin-Angiotensin-Aldosterone System (RAAS)

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ABSTRACT

Renin angiotensin aldosterone system is an important regulator of blood volume, electrolyte balance and systemic vascular resistance. The RAAS system maintains cardiac, vascular and renal physiology through the regulation of vascular tone and water homeostasis. In addition to physiological function RAAS system has a significant role in pathophysiological conditions like hypertension, other cardiovascular and renal diseases. So, the medications which block RAAS system produce favorable outcomes in these conditions.

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INTRODUCTION

The renin-angiotensin-aldosterone system (RAAS) is a critical regulator of blood volume and systemic vascular resistance. It is composed of three major compounds: renin, angiotensin II, and aldosterone. These three act to elevate arterial pressure in response to decreased renal blood pressure, decreased salt delivery to the distal convoluted tubule, and/or beta-agonism. Through these mechanisms, the body can elevate blood pressure in a prolonged manner.[1][2][3].

Aldosterone is a mineralocorticoid hormone produced in the zona glomerulosa of the adrenal cortex that influences water and salt regulation in the body. Aldosterone's primary function is to act on the late distal tubule and collecting duct of nephrons in the kidney, favoring sodium and water reabsorption and potassium excretion while also contributing to acid-base balance. Aldosterone affects blood pressure by regulating the sodium gradient in the nephron to either increase or decrease the water reabsorbed to contribute to the volume of the extracellular fluid (ECF). aldosterone is a key player in the multi-factorial regulation of salt, potassium, blood pressure, and acid-base balance.

Function

The renin-angiotensin-aldosterone system is primarily associated with blood pressure regulation by modulating blood volume, sodium reabsorption, potassium secretion, water reabsorption, and vascular tone. Other described functions of the RAAS include inflammation, apoptosis, and fibrosis.[4]

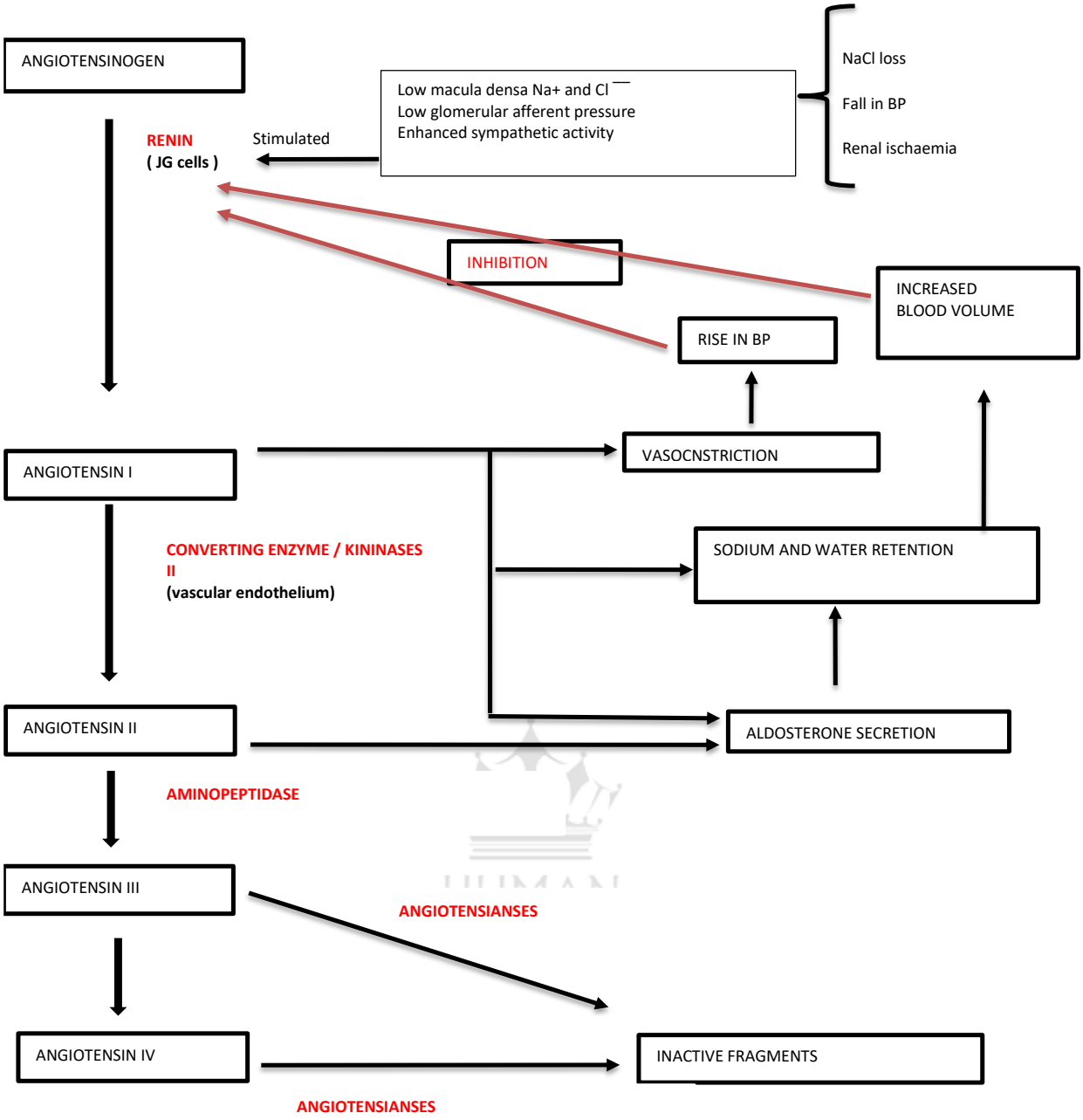
Mechanism

Renin has been released into the blood, it can act on its target, angiotensinogen. Renin then acts to cleave angiotensinogen into angiotensin I. Angiotensin I is physiologically inactive but acts as a precursor for angiotensin II.[4] ATI is converted to angiotensin II (ATII) by angiotensin- converting enzyme (ACE) and other non-ACE pathways.[5] The conversion of angiotensin I to angiotensin II is catalyzed by an enzyme called angiotensin-converting enzyme (ACE).[6] ATII is the principal vasoactive peptide in the RAAS and acts on two receptors, AT1 and AT2. ATII activation of AT1 receptors causes increased blood pressure due to contraction of vascular smooth muscle, increased systemic vascular resistance, increased sympathetic activity, sodium (Na), and water retention due to increased Na

reabsorption in the proximal convoluted tubule.[7] After angiotensin I is converted to angiotensin II, it has effects on the kidney, adrenal cortex, arterioles, and brain by binding to angiotensin II type I (AT1) and type II (AT2) receptors.[6]

In the proximal convoluted tubule of the kidney, angiotensin II acts to increase Na^+-H^+ exchange, increasing sodium reabsorption. Increased levels of Na in the body act to increase the osmolarityof the blood, leading to a shift of fluid into the blood volume and extracellular space (ECF). This increases the arterial pressure of the patient. The net effect of these interactions is an increase in total body sodium, total body water, and vascular tone.

RAAS system blockade can take place at several levels. RAAS-blockers include direct renin inhibitors (DRIs), which block the production of renin, ACEIs block conversion of AT1 to AT2by blocking the angiotensin-converting enzyme, ARBs antagonize the effect of AII on AT1 receptors, and aldosterone antagonists block the effect of aldosterone.[8][9] increased Na reabsorption in the proximal convoluted tubule.[7] After angiotensin I is converted to angiotensin II, it has effects on the kidney, adrenal cortex, arterioles, and brain by binding to angiotensin II type I (AT1) and type II (AT2) receptors.[6]



Angiotensin II Receptor Blockers

The angiotensin II receptor blockers (ARBs) represent a newer class of antihypertensive agents. Their mechanism of action differs from that of the angiotensin-converting enzyme (ACE) inhibitors, which also affect the renin angiotensin system. The ARBs were developed to overcome several of the deficiencies of ACE inhibitors: competitive inhibition of ACE results in a reactive increase in renin and angiotensin I levels, which may overcome the blockade effect; ACE is a relatively nonspecific enzyme that has substrates in addition to angiotensin I, including bradykinin and other tachykinins, and thus, inhibition of ACE may result in accumulation of these substrates; production of angiotensin II can occur through

non-ACE pathways as well as through the primary ACE pathway, and these alternative pathways are unaffected by ACE inhibition; specific adverse effects are associated with ACE inhibitor effects on the enzyme; andARBs may offer more complete angiotensin II inhibition by interacting selectively with the receptor site.[10]

Examples of angiotensin receptor blocker is Losartan, Valsartan, Candesartan, Olmesartan etc.

Drugs	**Mechanism ofAction**	**Uses**	**Adverse Effects**
Losartan	Hepatic P450 enzyme CYP2C9 metabolizes losartan to a more potent 5- carboxylic acid metabolite, EXP 3174. The onset of action of losartan is 6 hours, lasting for 24 hours, and the half-lives of losartan and EXP 3174 are 1.5 to 2 hours and 6 to 9 respectively.	• Losartan is used alone or in combination with other medications to treat high blood pressure. • Losartan is also used to decrease the risk of stroke in people who have high blood pressureand a heart condition	• Blurred vision. • Difficult breathing. • Dizziness, faintness, or lightheadednesswhen getting up suddenly from a lying or sitting position. • Fast or irregularheartbeat. • Numbness or tingling in thehands, feet, orlip
		called left ventricular hypertrophy.	• A skin rash that may include itchy, red, swollen, blistered or peeling skin.
Valsartan	It blocks the vasoconstrictor and aldosterone- secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.	• It is used to treat high blood pressure and heart failure. • It is also used to improve the chance of living longer after a heart attack. In people with heart failure, it may also lower the chance of having to go to the hospital for heart failure.	• Dizziness or lightheadedness may occur as your body adjusts to the medication. If any of these effects last or get worse, tell your doctor or pharmacist promptly.
Candesartan	It blocks the vasoconstrictor and aldosterone- secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland.	• It is used to treat high blood pressure. • Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. It works by relaxing blood vessels	• Arm, back, or jaw pain. • chest pain or discomfort. • chest tightness or heaviness. • cough or hoarseness. • fast or irregular heartbeat. • joint pain. • large, hive-like swelling on the face, eyelids, lips, tongue,
		so, blood can flow more easily. This medication is not recommended for use in children younger than 1 year due to increased risk of side effects.	throat, hands, legs, feet, or sex organs. • Light headedness.

Olmesartan	It functions as an angiotensin-II receptor blocker to undermine the renin- angiotensin- aldosterone system. Olmesartan is an antagonistic molecule that binds to angiotensin type I receptors (AT-I) and angiotensin type II receptors (AT-II	• IT is used to treat high blood pressure . • Lowering high blood pressure helps prevent strokes, heart attacks, and kidney problems. •	• Feeling dizzy or tired. • Headaches, flu- like symptoms, runny or stuffy nose, cough or bronchitis. • Pain in your back, bones or joints. • Feeling sick (nausea) or indigestion. • Stomach ache. • Swollen feet, ankles, legs or hands (oedema) • Urinary tract infection (UTI)
Telmisartan	It is an angiotensin II receptor blocker. It work by blocking a substance in the body that cause blood vessel to tighten	• To treat high blood pressure • Lowering high blood vessel helps to prevent strokes, heart attacks, and	• Changes vision • Dizziness, lightheadedness, fainting • Fast heartbeat • Large hives • Painful urination • Swelling in the hand, lower legs and feet.
		kidney problems.	
Irbesartan	It blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor.	• To treat high blood pressure • Lowering high blood vessel helps to prevent stokes, heart attack, and kidney Problems.	• Feeling dizzy • Headache • Nausea • Vomiting diarrhoea • Pain in your joints or muscles

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