

**CHAPTER 21**  
**MAIN COMPONENTS OF THE RAS AND ACTIONS**  
**OF ANGIOTENSIN-II**

- Main Components of the RAS
  - Renin
  - Angiotensinogen
  - ACE
  - Angiotensin II (AII)
  - Angiotensin II receptors
  
- Actions of Angiotensin II
  - Actions related to blood pressure and blood volume control.
  - Actions related to inflammation and repair.

## MAIN COMPONENTS OF THE RAS

- Renin.
- Angiotensinogen.
- ACE.
- Angiotensin-II (All).
- Angiotensin-II receptors.
  
- Renin
  - Renin is proteolytic enzyme whose substrate is angiotensinogen.
  - It is produced chiefly by the juxtaglomerular (JG) cells in the kidney which are the main site for its synthesis, storage and release.
  - Other sites for the production of renin outside the kidneys include the brain, pituitary gland, blood vessels, adrenal glands and the heart.
  - Secretion of active renin occurs in response to four regulatory mechanisms:
    1. Renal baroreceptor.
    2. Macula densa.
    3. Renal nerves.
    4. Humoral factors.
    1. *Renal baroreceptor* is an intrarenal vascular receptor in the afferent arteriole that stimulates renin secretion in response to reduced renal perfusion pressure. It is the most powerful regulator of renin release.
    2. *The macula densa* is a modified group of cells in the distal tubules of the nephron, at the end of the loop of Henle and adjacent to the efferent arteriole, the JG cells, and the extraglomerular mesangium. When the macula densa senses a decrease in distal tubular salt delivery, it sends signals that stimulate renin secretion.
    3. *The renal sympathetic nerve* stimulation increases renin secretion from the JG cells through a B<sub>1</sub>-adrenergic-mediated mechanism. Activation of renal nerves is provoked by stress and posture.
    4. Humoral factors such as All,  $\alpha$ -adrenergic agonists, atrial natriuretic peptide and endothelin inhibit renin release.
  
- Angiotensinogen
  - Angiotensinogen is a protein that is synthesized mainly by the liver hepatocytes and also in the central nervous system, heart, vessel wall, kidney and fat cells.

- The plasma level of systemic angiotensinogen is determined by its rate of synthesis and secretion from liver cells.
  - It is constitutively secreted with little or no intracellular storage.
  - There is an association between angiotensinogen levels with arterial pressure.
  - Angiotensinogen is the renin substrate and as a result of renin action. It is broken down to a decapeptide (made of 10 amino acids) known as angiotensin-I which in turn is changed by ACE into the potent hormone angiotensin II (A-II).
- Angiotensin- Converting Enzyme (ACE)
    - ACE converts the inactive decapeptide angiotensin I to the active octapeptide (8 amino acids) angiotensin II (AII).
    - ACE is not specific for angiotensin because it cleaves and inactivates other peptides such as bradykinin.
    - ACE is bound to the plasma membrane of endothelial cells. Vessel in the lungs and brain are rich in ACE. Epithelial cells have high concentration of ACE particularly the proximal tubular cells of the kidney (brush border), small intestine and placenta.
    - Genetic polymorphism of the ACE gene (noncoding region) have been identified (presence or absence of certain nucleotide sequence- insertion/deletion). Individuals homozygous for the insertion polymorphism (II) have lower levels of ACE in plasma than those with deletion (DD) genotype. Suggestion of association between the D allele and the increased risk for myocardial infarction or diabetic nephropathy.
    - Only 10% of body ACE is in circulating plasma while 90% is present in tissues.
- Angiotensin-II (AII).
    - AII is the major pressor and trophic factor of the RAS.
    - It is formed through enzymatic degradation of AI by ACE.
    - Other enzyme systems including chymase, tonin and cathepsin provide an alternative pathway for AII formation in addition to ACE.
    - There are independent AII generating systems in the brain, aorta, arteries, ventricles, kidneys, adrenal glands, adipocytes, leukocytes, uterus, skin, ovaries, testes and spleen.
- Angiotensin-II receptors.
    - AII, like other peptide hormones, interact with receptors at the surface of its target cells. Three subtypes of receptors have been described designated AT<sub>1</sub>, AT<sub>2</sub>, and AT<sub>4</sub>.
    - All of the well known actions of AII are mediated by AT<sub>1</sub> receptors.

- AT<sub>2</sub> subtype is much more prevalent in fetuses than in adults. It affects growth and remodeling of organs. AT<sub>2</sub> receptor activation attenuates all actions (vasoconstriction, hypertrophy, proliferation).

## ACTIONS OF ANGIOTENSIN II

1. *Actions related to blood pressure and blood volume control.*
2. *Actions related to inflammation and repair.*

- Target tissues:
  - All acts on the following organs and cells
    - \* Blood vessels.
    - \* Kidneys.
    - \* Myocardium.
    - \* Sympathetic neurones.
    - \* Adrenal gland (cortex and medulla).
- \* Brain.
- \* Pituitary gland.
- \* Endothelial cells, platelets and monocytes.
- \* Intestines and liver.

### ***All Actions Leading To Increase in Blood Pressure and Blood Volume***

The main function of the RAS is blood pressure and blood volume hemostasis. RAS is activated when blood pressure is lowered or there is a decrease in blood volume.

- All through its actions on a number of tissues and organs produce rise in blood pressure, salt and water retention and increase in blood volume.
- *Blood vessels*: acting on vascular smooth muscle cells, All produces vasoconstriction and increase in systemic vascular resistance.
- *Myocardium*: increases strength of contraction (inotropy) and cardiac myocyte hypertrophy.
- *Adrenal cortex (zona glomerulosa)*: stimulates aldosterone production which causes sodium retention and expansion of blood volume.
- *Adrenal medulla*: stimulates catecholamine release.
- *Posterior pituitary*: ADH release leading to water retention.
- *Kidney*: stimulates sodium reabsorption from the proximal tubules.
- *Sympathetic neurons*: stimulates norepinephrine release.
- *Brain*: stimulates thirst center, ADH synthesis, pressor center activation, and baroreceptor blunting.

### ***All Actions Not Related To Blood Pressure and Blood Volume Hemostasis***

- All is involved in a number of proinflammatory and repair processes which are responsible when excessive or maladaptive, to many of the harmful effects of RAS activation.

### ***Vascular Endothelial and Smooth Muscle Cells***

- **All induces endothelial cell dysfunction and VSM cell activation. These actions results in:**
  1. Decreased production of *nitric oxide* (NO). NO has a number of antiatherogenic, antiinflammatory and antithrombotic actions. NO produces vasodilatation through VSMC relaxation, it inhibits platelet aggregation and decreases production of adhesion molecules, inflammatory cytokines and growth factors.
  2. Increase the expression of *adhesion molecules* (ICAM-I and VCAM-I) which help endothelial monocyte binding; an initial step in inflammation.
  3. Increased *endothelin* production. Endothelin is a very potent vasoconstrictor peptide with cellular trophic and proliferative actions.
  4. Increased production of *plasminogen activator inhibitor* (PAI-1) which shifts the fibronolytic equilibrium in favour of fibrin thrombi formation, impaired fibrinolysis, failure of lysis of fibrin clots and hypercoagulability.

5. Stimulates the production of *chemoattractant proteins* e.g. monocyte chemoattract protein-1 (MCP-1) which stimulate monocyte and macrophage recruitment and infiltration of the vessel wall.
6. Increased *endothelial permeability*, an action that helps the passage of macromolecules such as LDL-cholesterol and inflammatory cells to the subendothelial space.
7. Increased production of *superoxide anions* (reactive oxygen species).
  - All through its action on an enzymatic oxidase system on the endothelial cell membrane utilizing a substrate as NADH/NADPH leads to generation of excess of superoxide ( $O_2^-$ ) anions which increases vascular oxidative stress. Increased oxidative stress leads to further dysfunction and activation of endothelial and vascular smooth muscle cells. Furthermore, superoxide combines with NO, shunting NO away and limiting its availability. Superoxide will favour lipoprotein oxidation within the subendothelial space.
  - Increased superoxide in the cytoplasm of endothelial and VSMCs will activate transcription factor (a peptide or protein that regulates gene transcription by binding to its regulatory region) known as nuclear factor kappa-beta (NF- $K\beta$ ). NF- $K\beta$  when activated translocates from the cytoplasm to the nucleus to induce transcription of genes coding for proinflammatory proteins, namely cytokines (IL-6), growth factors (PDGF), adhesion molecules (ICAM-1, VCAM-1) and chemotactic proteins (MCP-1, GSM-CSF).
8. Stimulation of VSMC growth, proliferation and migration. VSMCs migrate from the media of the vessel wall to the subintimal region, where they proliferate, change their shape and phenotype from the contractile form to secretory form. They are the chief source of extracellular matrix proteins namely collagen.

#### *Monocyte and Macrophages*

All has a proatherogenic potential through the following actions:

- All stimulates monocyte adhesion to vessel wall, migration through the endothelium, and transformation into active macrophages. These processes are stimulated by the large number of proinflammatory molecules described in the previous section.
- All enhances lipid peroxidation in macrophages and upregulates the oxidized LDL-receptors.
- It stimulates NF- $K\beta$  in monocytes.

#### *Blood Platelets*

All stimulates platelet activation. This action results in an increased tendency to platelet adhesion and aggregation resulting in formation of platelet thrombi.

#### *Coagulation Factors*

- All increases plasma fibrinogen level and tissue factor activity.
- Tissue factor is a glycoprotein expressed by plasma membrane of activated endothelial cells, macrophages and fibroblasts. It is present in very small amount in blood. When released from

endothelial cells it interacts with coagulation factor VIIa increasing its procoagulant activity. This combination of tissue factor with activated factor VII will act as a spark plug that initiates the extrinsic pathway of blood coagulation by activating factors IX and X ending finally in thrombin and fibrin formation (see section on anticoagulants).

- ACE inhibitors attenuate the hypercoagulable state after MI by reducing PAI-1 and tissue factor levels and increasing the release of tissue plasminogen activator (TPA) by the endothelial cells within the coronary artery.
- Bradykinin stimulates the release of TPA.