BLOOD PRESSURE REGULATION

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NORMAL BLOOD PRESSURE

The normal blood pressure is **120/80** mmHg

Here Systolic pressure = 120mmHg

Diastolic pressure = 80mmHg

Hence we can say that 80mmHg is maintained throughout the cardiac cycle but during systole additional 40mmHg pressure builds up.

Systolic pressure mainly depends on cardiac output.

Diastolic pressure mainly depends on total peripheral resistance.

SYSTOLIC PRESSURE AND CARDIAC OUTPUT

After isovolumetric contraction of ventricles, aortic valve open and push the blood into aorta. This is called the cardiac output of the heart.

The blood comes into aorta with pressure and this pressure stretches the aorta. Hence whenever cardiac output is increased, the pressure in major arteries thereby increase and systolic pressure goes up.

If cardiac output drops, the amount of blood per systole pumped into major arteries falls and systolic pressure goes down.

So if cardiac output increase, systolic pressure increase

If cardiac output decrease, systolic pressure decrease

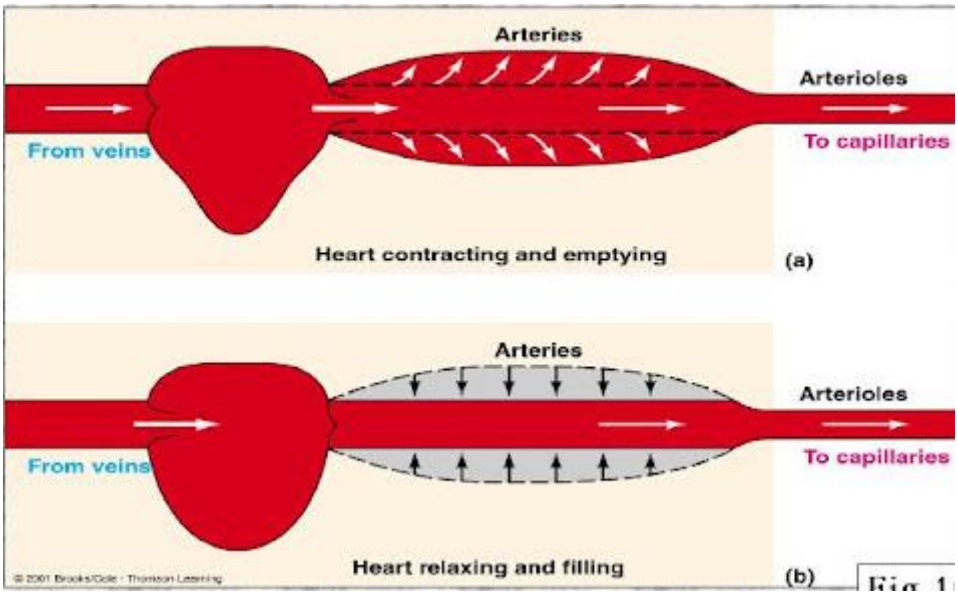
DIASTOLIC PRESSURE AND TOTAL PERIPHERAL RESISTANCE

Diastolic pressure is the pressure in major arteries during diastole. Its value is around 80mmHg.

In the beginning of diastole i.e. ventricular relaxation, intraventricular pressure drops and aortic valves close. The connection between ventricles and major arteries is closed so intraventricular pressure variations do not affect pressure changes in major arteries. During diastole, the major vessels e.g. aorta recoils and squeezes the blood allowing blood to move forward.

In arteriolar constriction, total peripheral resistance to forward flow increases which slows down the forward motion of blood and thereby increase total diastolic pressure.

In arteriolar dilation, total peripheral resistance decrease and blood rapidly flows forward hence diastolic pressure decrease as volume in major arteries decrease.



MEAN ARTERIAL PRESSURE

Difference between systolic pressure and diastolic pressure is called **pulse pressure**.

Mean Arterial Pressure = Diastolic Pressure + 1/3 of pulse pressure

= 80 + 1/3 (120 – 80)

= 80 + 140/3

= 80 + 13

Mean Arterial Pressure = 93 mmHg

So mean arterial pressure is approximately equal to **100 mmHg**

Normal range of mean arterial pressure = 90 – 100 mmHg

Mean Arterial pressure = Cardiac output x Total peripheral resistance

Cardiac output and total peripheral resistance are not independent variables. They are rather inter-dependent variable. Usually if one is increased, the other is decreased to maintain the set point e.g if cardiac output increases, total peripheral resistance decreases.

MEAN SYSTEMIC PRESSURE

Mean systemic pressure is the pressure maintained in systemic circulation when cardiac output stops.

Mean systemic pressure is far less than mean arterial pressure. Its value is 6.5 mmHg. This is the pressure which maintains the venous return.

Mean arterial pressure maintains blood flow to the tissues.

Mean systemic pressure maintains blood flow from the tissues to the heart.

FACTORS AFFECTING CARDIAC OUTPUT

Cardiac output depends on

1. Stroke volume
2. Heart Rate

1. STROKE VOLUME

Stroke Volume (SV) is **the volume of blood in millilitres ejected from the each ventricle** due to the contraction of the heart muscle which compresses these ventricles. SV is the difference between end diastolic volume (EDV) and end systolic volume (ESV).

Stroke volume depends on

1. Preload
2. Contractility
3. Afterload

• PRELOAD

Preload is the **end-diastolic volume** of ventricles and is the amount of blood present in blood just before contraction of ventricles.

End Diastolic volume depends on venous return. Venous return further depends on:

1. Right atrial pressure
2. Filling time i.e. time allotted for filling of ventricles (Diastolic interval)

Right atrial pressure depends on venomotor tone and blood volume. Hence when blood volume is increased, blood pressure eventually increases.

If venomotor tone is greater (i.e. veins constrict), blood pressure will increase

Venodilation will decrease blood pressure

The **normal diastolic interval** is 0.5s. If filling time is increased, the ventricles will be appropriately filled. But if heart rate is increased, diastolic interval decreases and hence end diastolic volume decreases. In this case in spite of high heart rate, stroke volume decrease and blood pressure falls.

- ### CONTRACTILITY

Blood pressure increase with increase in contractility

Blood pressure decrease with decrease in contractility

- ### AFTERLOAD

Afterload is the pressure that the heart must work against to eject blood during systole.

In arterial dilation, afterload decrease. Due to arterial dilation, total peripheral resistance decrease and stroke volume increase which increase cardiac output and hence blood pressure increase.

2. HEART RATE

Within a certain limit, increase in heart rate increases cardiac output.

In dangerous tachy arrythmia, blood pressure falls down.

TOTAL PERIPHERAL RESISTANCE AND BLOOD PRESSURE

Stressed volume – volume in arteries

Unstressed volume – volume in veins

Pressure in cardiovascular system is maintained by stress volume and blood pressure rise.

As stressed volume increase, blood pressure increase

As stress volume decrease, blood pressure decrease

During venoconstriction, a part of unstressed volume shifts to stressed volume and blood pressure rises.

During vasodilation, more blood coming from stressed volume to unstressed volume so blood pressure falls.

Similarly during arterial constriction, stress volume increases. As stressed volume cannot flow to unstressed volume easily so blood pressure rises.

During arterial dilation, stress volume decrease and blood pressure falls.

REGULATION OF BLOOD PRESSURE

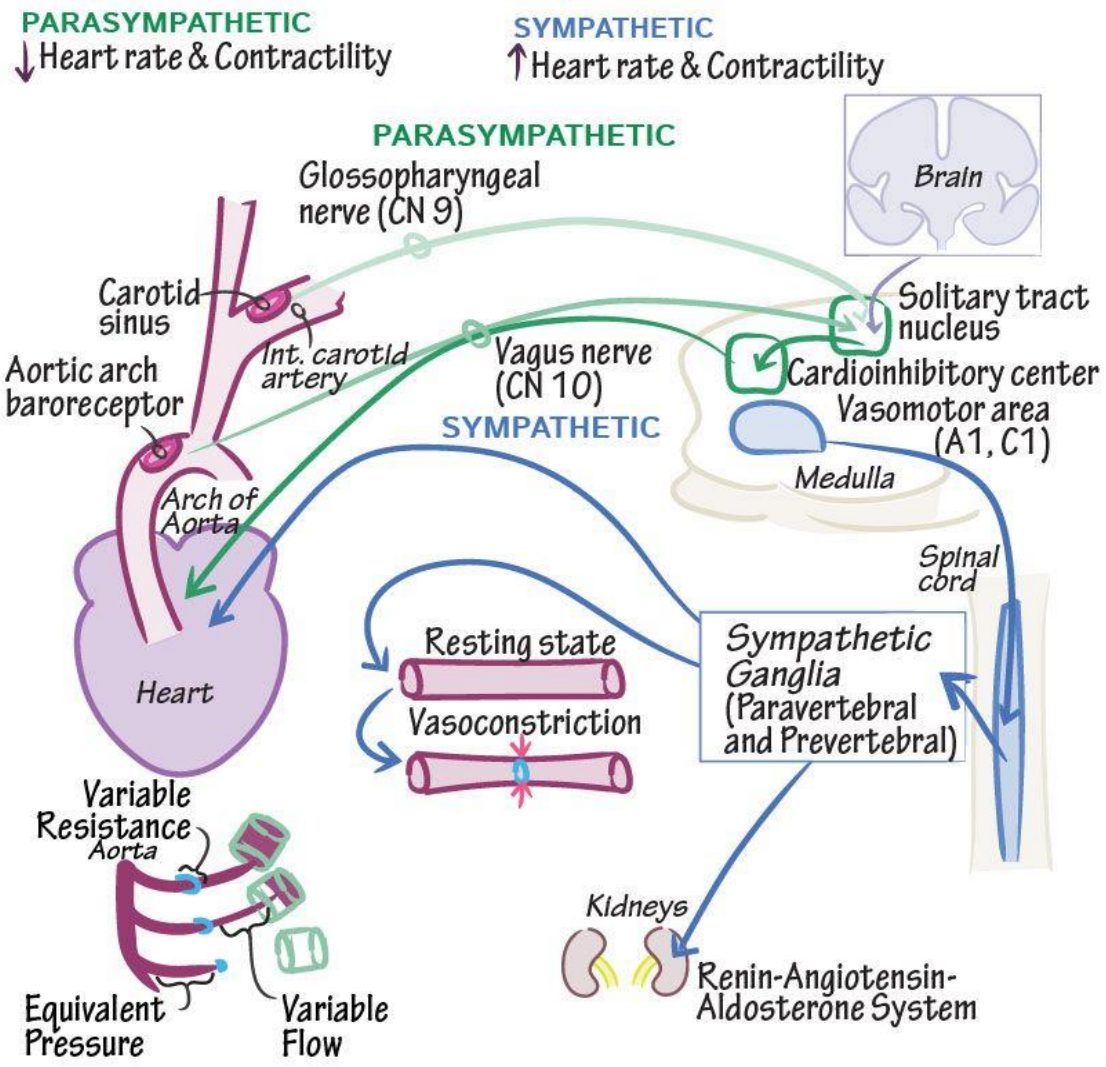
1. Short-term regulation
2. Long-term regulation

Short term regulation is mainly neurological regulation.

Long term regulation is mainly Renin-Angiotensin-Aldosterone system.

These regulatory mechanisms bring blood pressure back to the setpoint (i.e. mean arterial pressure), if blood pressure rises or falls due to some reasons.

SHORT TERM REGULATION OF BLOOD PRESSURE



Blood pressure sensors are present in cardiovascular system. Volume sensors are present in veins while pressure sensors are present in arteries.

In the adventitia of carotid sinus there are nerve endings which act as baroreceptors. These baroreceptors are connected to the 9th cranial nerve (glossopharyngeal nerve) through carotid sinus branch. This 9th cranial nerve takes information to the medulla oblongata.

The baroreceptors in the aorta are connected to the 10th cranial nerve (vagus nerve) which also transmit impulses to the medulla.

The 9th and 10th cranial nerves are also called **buffer nerves** as they buffer the blood pressure.

REGULATION OF INCREASED BLOOD PRESSURE

With increase in blood pressure, walls of aorta and carotid sinus are stretched. The nerve endings in these vessels also stretches and stretch-regulated sodium channels open due to which sodium influx

increase and RMP goes towards threshold which produces action potential. This action potential travels to the medulla through afferent pathway towards the **nucleus of tractus solitarius** located in the medulla oblongata.

The nerve endings in aorta and carotid sinus are very sensitive to rate of change of blood pressure and they stabilize the blood pressure around set point. (In patients with hypertension, these nerve endings become adjusted at high set point).

The nerve endings in carotid sinus are sensitive to both increasing and decreasing blood pressure while the nerve endings in aorta are more sensitive to increasing pressure and show no significant response to decreasing blood pressure.

The nucleus of tractus solitarius coordinates the response to increased blood pressure in following way

1. Cardio-inhibitory center stimulated
2. Cardio-accelerator area inhibited
3. Vasomotor center inhibited

STIMULATION OF CARDIO-INHIBITORY CENTER

The nucleus of tractus solitarius stimulates cardio-inhibitory center by buffer nerves which thereby inhibit the SA node by releasing acetylcholine on SA node.

INHIBITION OF CARDIO-ACCELERATOR AREA

The nucleus of tractus solitarius inhibits cardio-accelerator area.

Under normal conditions, cardio-accelerator gives descending pathway fiber and are connected with lateral horn of spinal cord. From the lateral horn, post ganglionic fibers move to sympathetic ganglion. From sympathetic ganglion, post ganglionic fibers move to SA node.

When cardio-accelerator area is inhibited in response to high blood pressure, the pathway to SA node is inhibited and norepinephrine release on SA node is reduced and heart rate is reduced due to which cardiac output is decreased and blood pressure drops.

INHIBITION OF VASOMOTOR CENTER

The nucleus of tractus solitarius inhibit vasomotor center in the medulla oblongata. With inhibition of vasomotor center, sympathetic outflow is inhibited and cause venodilation, arteriodilation and decreased sympathetic stimulation.

- With increase in venodilation, venous return decrease and cardiac output decrease due to which blood pressure drops.
- With increase in arteriodilation, total peripheral resistance decrease, blood from arteries can easily go to veins and blood pressure drops.
- Epinephrine induced cardiac stimulation is reduced.

Epinephrine induced positive ionotropic action is reduced
Epinephrine induced venoconstriction is reduced
Epinephrine induced arterioconstriction is reduced
Due to above changes, cardiac output is reduced and blood pressure falls

- Sympathetic outflow to kidney also reduce. In the kidney there is juxtaglomerular apparatus which have β-1 receptors.
  Normally under sympathetic stimulation, juxtaglomerular apparatus secretes renin but due to reduced sympathetic outflow renin is not secreted.

REGULATION OF DECREASED BLOOD PRESSURE

When blood pressure falls, vessels are not stretched. Less sodium channels open and less frequency of action potential moves to nucleus of tractus solitarius.

The nucleus of tractus solitarius acts to increase blood pressure by:

1. Inhibiting cardio-inhibitory center
2. Stimulating cardio-accelerator center
3. Stimulating vasomotor center

	Afferent nerves response	PNS response	SNS response
Increasing BP	increase	increase	Decrease
Decreasing BP	decrease	decrease	increase

CAROTID SINUS MASSAGE

By carotid sinus massage, vagus nerve is stimulated due to increase in pressure in the sinus. The strong vagal outflow reaches the SA node and inhibits SA node. To regulate this pressure

- Afferent nerves response increase
- PNS response increase
- SNS response decrease
- Blood pressure goes down

When afferent nerves are cut down

When afferent nerves are cut down, the afferent nerve response to the nucleus of tractus solitarius decrease due to which

- PNS response decrease
- SNS response increase
- Heart rate increase

- Blood pressure rises

SUDDEN STANDING UP FROM LYING POSITION

Normally when a person suddenly stands up from lying position, blood tends to gravitate down into lower part of the body and venous return from lower part of the body is decreased as gravity is antagonizing venous return. Cardiac output is reduced and blood pressure drops. To regulate this drop of blood pressure

- Afferent nerve response decrease
- PNS response decrease
- SNS response increase
- Heart rate increase
- Blood pressure rises and hence BP is maintained

ORTHOSTATIC HYPOTENSION

Orthostatic hypotension is a condition in which the blood pressure quickly drops as a person stands up from sitting or lying position. This low blood pressure can cause dizziness or fainting.

In case of severe dehydration or loss of fluids, if a person stands suddenly from lying position, the person will feel black out and vertigo.

- Due to standing up, blood pressure drops.
- Afferent system report to CNS of low blood pressure
- CNS gives sympathetic outflow
- Veins constrict but as volume is reduced due to diarrhea, the constricted veins cannot squeeze enough venous return and hence cardiac output decrease and the patient experiences blackout and vertigo.
- Blood pressure decrease and this condition is called orthostatic hypotension

Orthostatic hypotension may be due to:

1. Volume depletion
2. Strong toxicity of arterio-dilator or venodilator drugs
3. Sympathetic receptor blockers
4. Reduced sympathetic activity

If a patient taking antihypertensive drugs experiences vertigo, the dose of the drug is lowered.

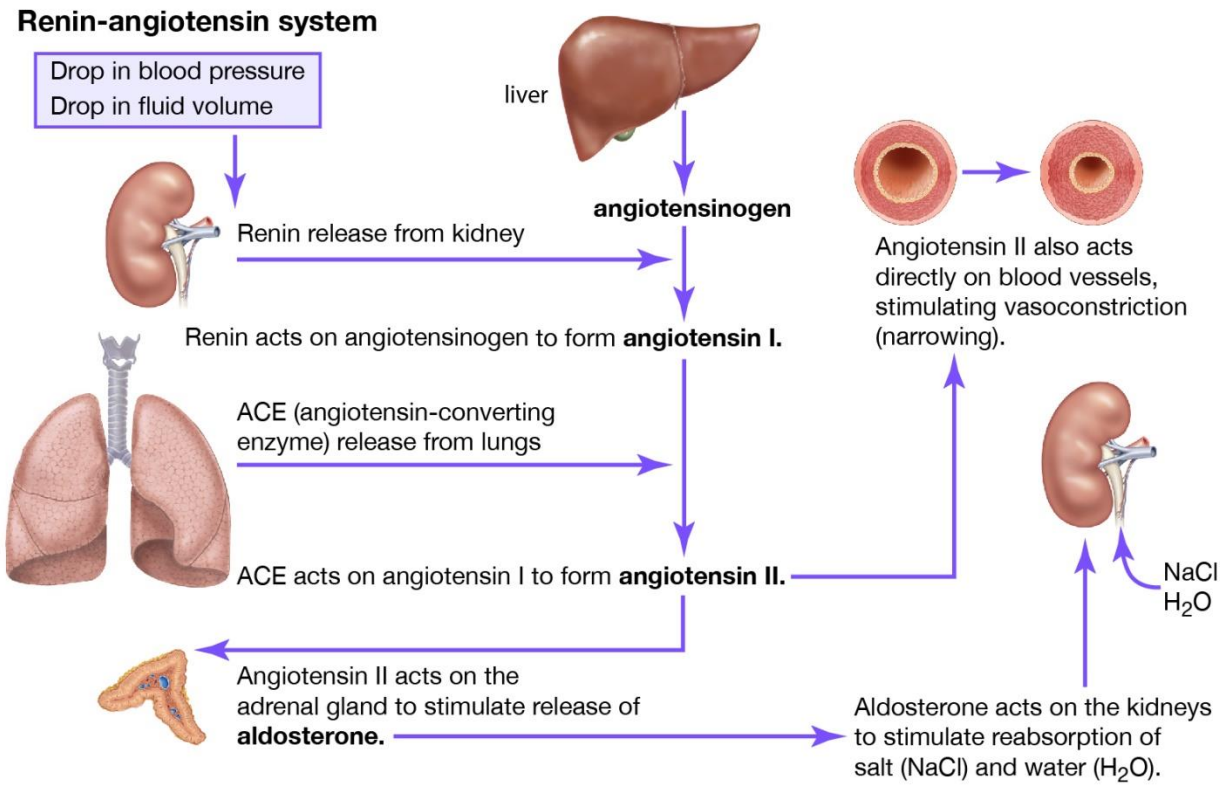
INCREASE IN BLOOD VOLUME

If blood volume increases e.g. when saline water is given to a patient, the blood volume increase, venous return increase, cardiac output is increased causing rise in blood pressure. This rise in pressure is regulated by:

- Increasing afferent response
- Increasing PNS response
- Decreasing SNS response

LONG TERM REGULATION OF BLOOD PRESSURE BY RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Renin-Angiotensin-Aldosterone system regulates blood pressure by handling blood volume and body sodium concentration.



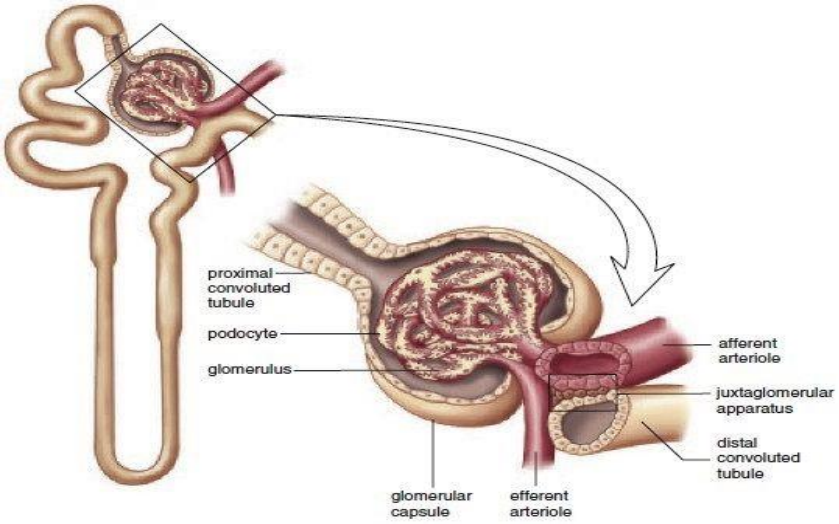
JUXTAGLOMERULAR APPARATUS

A drop in blood pressure causes reduced renal perfusion i.e. blood flow to kidney is reduced. In its response, **juxtaglomerular apparatus** forms. Juxtaglomerular apparatus is a specialized structure formed by **macula densa** in distal convoluted tubule and **Polkissen cells** in glomerular afferent arteriole. **Lacis cells** connect the macula densa and Polkissen cells. The main function of juxtaglomerular apparatus is to regulate blood pressure and filtration rate of glomerulus.

As blood pressure reduces, the Polkissen cells become less stretched. These cells are very sensitive to stretch and blood pressure is determined through their stretch. In response to low blood pressure, juxtaglomerular cells secrete **renin** enzyme. Renin increase blood pressure via the Renin-Angiotensin-Aldosterone system.

As renal perfusion is reduced due to low BP, glomerular filtration pressure in glomerulus is also reduced. As there is less lumen fluid so cells of nephron can work on less fluid more efficiently and sodium is absorbed more and very little sodium reaches distal convoluted tubule. So when blood pressure drops, amount of filtered sodium also drops. The macula densa is a collection of specialized cells in the distal

convoluted tubule that detect sodium concentration of the fluid in the tubule. In response to low sodium concentration in urinary flitrate, macula densa cells stimulate juxtaglomerular cells and renin is released.



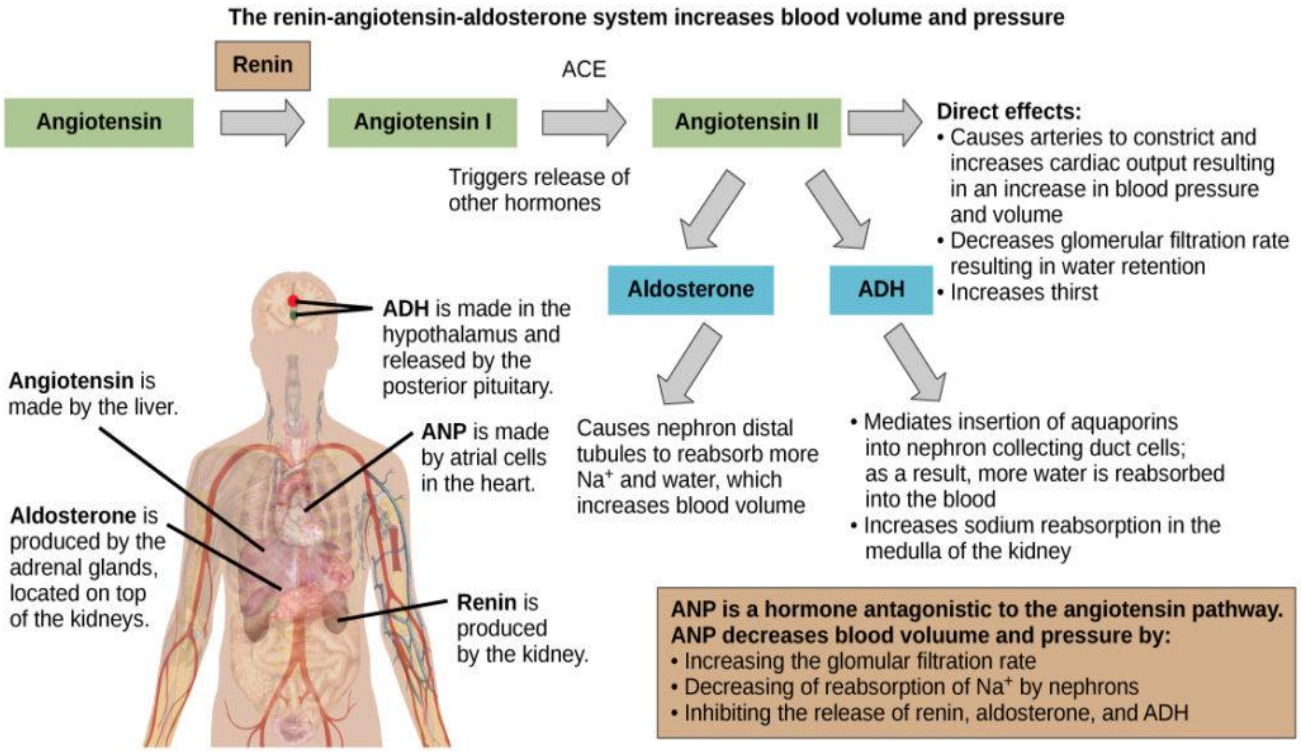
Above Figure showing Juxtaglomerular apparatus

Juxtaglomerular apparatus have β-1 adrenergic receptors. Drop in blood pressure activate sympathetic outflow from CNS and release of epinephrine from adrenal medulla through baroreceptor system. So epinephrine and nor-epinephrine works on juxtaglomerular apparatus under the influence of sympathetic stimulation through β-1 adrenergic receptors and further release of renin is stimulated.

RENIN

Renin moves to blood and works on **angiotensinogen** in the blood. Angiotensinogen is released by hepatocytes into the bloodstream. Renin coverts the inactive angiotensinogen into **Angiotensin-I** (decapeptide). Angiotensin-I pass through the right heart and into the pulmonary circulation. The endothelial cells of pulmonary capillaries in lungs are loaded with special enzymes, **angiotensin converting enzyme**. These enzymes work on Angiotensin-I and remove two amino acids and convert it into **Angiotensin-II** (octapeptide). Angiotensin-II moves to systemic circulation.

FUNCTIONS OF ANGIOTENSIN-II



1. VASOCONSTRICTION

Angiotensin-II have 7-path receptors on blood vessels. These receptors are coupled with Gq on inside of cell. Angiotensin-II binds with its receptor. Gq stimulate phospholipase-C (PLC). PLC breaks down PIP_2 into IP_3 and DAG (Diacetyl glycerol).

IP_3 acts on endoplasmic reticulum to release Ca^{+2} ions and induce vasoconstriction.

When Ca^{+2} level increases in venous smooth muscle, veins will constrict (**venoconstriction**). Venous constriction leads to increased venous return of heart which leads to increased EDV (End Diastolic Volume) and increased stroke volume. Cardiac output increases and systolic blood pressure increases.

When Ca^{+2} level increase in arterioles, arterioles will constrict (arterioconstriction). Arterioconstriction leads to increased total peripheral resistance due to which diastolic blood pressure increases.

2. INCREASE THIRST

Angiotensin-II have receptors on hypothalamus of brain. Thirst center of hypothalamus is stimulated. More fluid is taken and blood volume increases. Venous return increases, cardiac output increases and in turn systolic blood pressure increases.

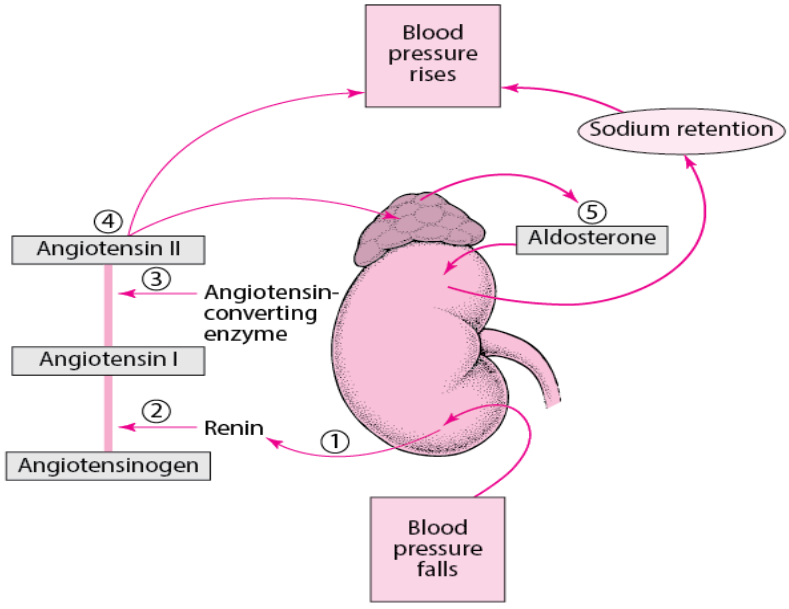
3. RELEASE OF NOR-EPINEPHRINE FROM POST-GANGLIONIC SYMPATHETIC FIBERS

Post Ganglionic sympathetic fibers release nor-epinephrine. All sympathetic nerve endings have Angiotensin-II receptors. When these receptors are stimulated by Angiotensin-II, excessive amount of nor-epinephrine is released.

Nor-epinephrine:

- Acts as cardiac stimulant and increase cardiac output to stabilize blood pressure
- Acts as venoconstrictor
- Acts as arterioconstrictor

4. ALDOSTERONE PRODUCTION



Angiotensin-II acts on zona glomerulosa cells in cortex of adrenal gland.

Adrenal cortex has three types of cells

i. Zona glomerulosa cells produce aldosterone
ii. Zona fasciculata cells synthesize glucocorticois
iii. Zona reticularis cells produce androgens

Zona glomerulosa cells have receptors for Angiotensin-II. When these receptors are stimulated, aldosterone hormone is released. Aldosterone is a steroid hormone i.e. lipid soluble and is distributed all over the body. Aldosterone move to blood and reach kidney. In kidneys, aldosterone works on cells called **principal cells** present in distal convoluted tubules and collecting tubules.

Aldosterone binds with its receptors in principal cells. These receptors acts as transcription factor i.e. it stimulates certain genes. This transcription factor stimulates three genes:

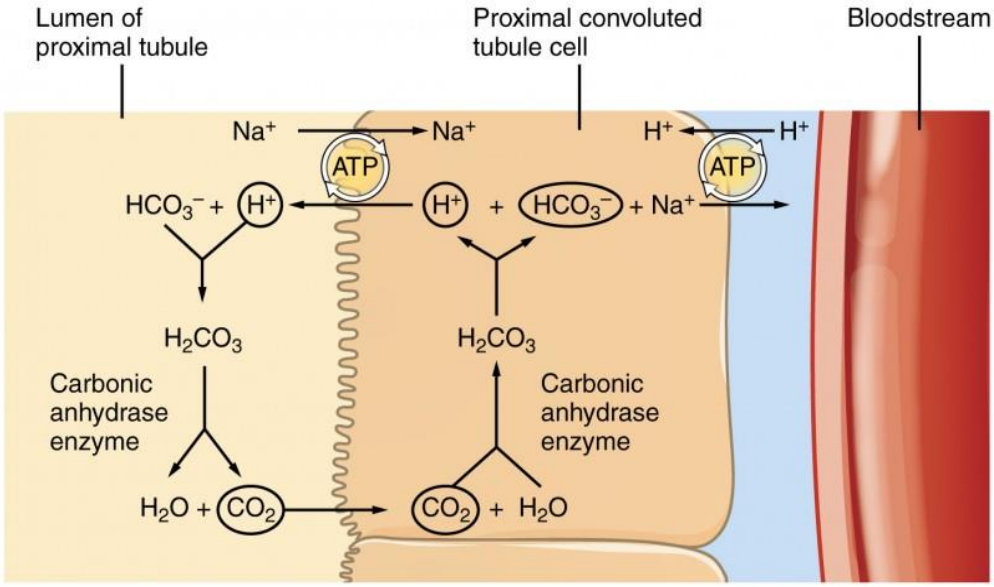
i. Gene for sodium-potassium ATPases

ii. Gene for sodium channels
iii. Gene for potassium channels

After stimulation of these genes, Na-K ATPases concentration increase in basolateral membrane while concentration of sodium and potassium channels increase in membrane of cell towards the lumen. Na^+ ions move out of cell while K^+ ions move inside cell through Na-K ATPases. As sodium concentration decreases inside cell, sodium moves from lumen to inside cells through sodium channels. As potassium concentration increase inside cell (due to Na-K ATPases), K^+ ions move out of cell into the lumen through K^+ channels. So concentration of sodium and water decrease in urine while concentration of potassium increase in urine.

The absorbed salt and water moves to blood and blood volume increases, venous return increase, cardiac output increase due to which blood pressure is increased and stabilized.

5. EFFECT ON PROXIMAL CONVOLUTED TUBULE



Angiotensin-II receptors are present in proximal convoluted tubules. Angiotensin-II stimulates these receptors and these cells take up more sodium from lumen to the cell and this sodium moves to blood.

For every Na^+ ion coming from lumen, a H^+ ion is secreted into the lumen. This exchange of ions takes place through Sodium-proton counter transporter.

The H^+ ion which comes to lumen binds with already present HCO_3^- and form H_2CO_3. Carbonic anhydrase enzyme breaks down H_2CO_3 into H_2O and CO_2.

CO_2 moves to cells of proximal convoluted tubule and combine with H_2O to form H_2CO_3. H_2CO_3 further splits into H^+ and HCO_3^-. The HCO_3^- moves to blood along with Na^+.

Angiotensin-II by stimulating the system increases re-absorption of Na^+ and HCO_3^- from proximal convoluted tubule into blood.

6. EFFECT ON EFFERENT ARTERIOLES

Angiotensin-II receptors are present in efferent arteriolar smooth muscles in high concentration. Angiotensin-II stimulate these receptors and induce efferent arteriolar constriction. By constricting the efferent arteriole, glomerular filtration is maintained.

DRUGS ACTING ON RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

1. ANGIOTENSIN CONVERTING ENZYME INHIBITOR

These drugs act on angiotensin converting enzymes present in pulmonary capillaries. These drugs are commonly used as antihypertensive. Angiotensin I cannot be converted into Angiotensin II.

As Angiotensin II level goes down:

i. Veins dilate which causes reduced venous return to heart. Cardiac output drops and blood pressure drops
ii. Arterioles dilate which reduces total peripheral resistance so diastolic blood pressure drops
iii. Proximal part of nephron does not retain sodium and bicarbonate additionally. Loss of Na and HCO_3^- helps get rid of extra volume. Reduced volume help stabilize elevated blood pressure.
iv. Adrenal gland cannot be stimulated to release aldosterone. Aldosterone cannot work on principal cells. Principal cells have reduced capacity to retain salt and water. So salt and water goes into urine, blood volume decrease and systolic blood pressure goes down. The principal cells cannot throw potassium from body to urine so there is risk of hyperkalemia with these drugs.

Never give Angiotensin converting enzyme inhibitor to a patient who have renal artery stenosis. If renal artery is narrow, blood flow to corresponding kidney is reduced. Glomerular filtrate pressure is reduced and as glomerular filtrate is less, the kidney has a risk of failure. The defense mechanism of kidney in turn is to release a lot of renin. Extra Angiotensin II is produced and this Angiotensin II constrict efferent arteriole to maintain glomerular filtrate pressure.

When Angiotensin converting enzyme inhibitor are given to such patients, Angiotensin II level decrease in blood and efferent arteriolar constriction cannot be maintained and renal failure can take place.

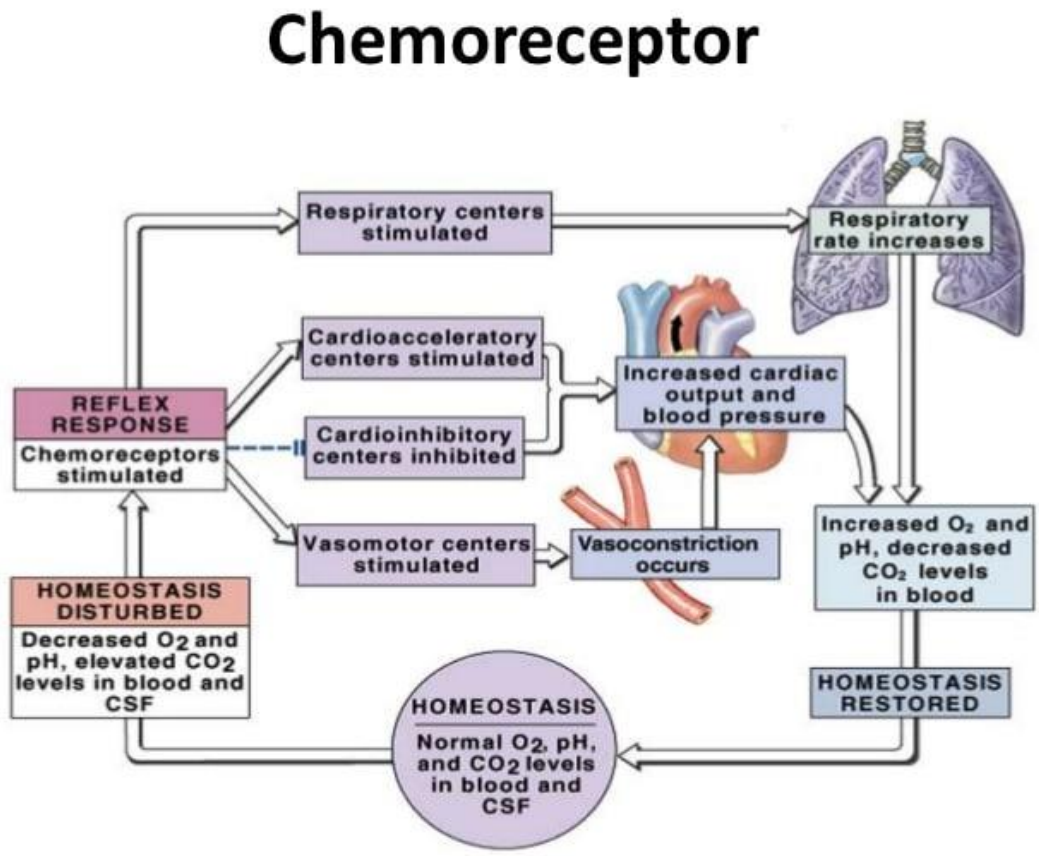
2. SPIRONOLACTONE

Spironolactone is structurally similar to aldosterone. Spironolactone binds to aldosterone receptors, thus prevent binding of aldosterone. Aldosterone mediated actions on the principal cells are lost. Principal cells cannot retain salt and water. Salt and water is excreted and blood pressure goes down.

3. ANGIOTENSIN II RECEPTOR BLOCKERS

The drugs Losartan are used as Angiotensin II receptor blockers. Angiotensin II cannot mediate its action and blood pressure is regulated.

CHEMORECEPTORS AND BLOOD PRESSURE REGULATION



Two types of chemoreceptors are present

i. Peripheral chemoreceptors
ii. Central chemoreceptors

Peripheral chemoreceptors are present in carotid body and aortic body while central chemoreceptors are present in medulla.

Peripheral chemoreceptors are sensitive to partial pressure of oxygen (PO_2) while central chemoreceptors are sensitive to PCO_2 and pH.

As PCO_2 in blood drops, peripheral chemoreceptors fires through 9^{th} and 10^{th} nerve. These neurons take information to tractus solitarius in CNS. Tractus solitarius inhibit vagal outflow while stimulate vasomotor center and cardio stimulation. Sympathetic outflow is increased and blood pressure goes up.

If in CNS PCO_2 goes up, CO_2 fuses with H_2O and H_2CO_3 level goes up. H_2CO_3 converts into HCO_3^- and H^+

$CO_2 + H_2O \rightarrow H_2CO_3$

$H_2CO_3 \rightarrow HCO_3^- + H^+$

It is these H^+ ions that stimulate central chemoreceptors. These chemoreceptors lead to increased sympathetic as well parasympathetic activity. Increased parasympathetic activity stimulation leads to negative coronotropic action and heart rate goes down. If sympathetic activity is too much, the sympathetic activity on heart is nullified by the action of vagus but sympathetic activity on veins and arteries takes the blood pressure up.

The patients with severe stimulation of central chemoreceptors can develop rising blood pressure and falling pulse rate. This effect is called Cushing reaction. Cushing reaction is seen in patients having rising intracranial pressure e.g. in case of tumor. When intracranial pressure becomes very high, cerebral circulation is impaired because cerebral vasculature is compressed with high pressure due to which oxygen becomes low in CNS while CO_2 accumulates. CO_2 fuse with water

$CO_2 + H_2O \rightarrow H_2CO_3$

$H_2CO_3 \rightarrow HCO_3^- + H^+$

These protons (H^+) stimulate central chemoreceptors. These chemoreceptors lead to increased powerful vagal output and increased sympathetic output. Sympathetic and parasympathetic activity is simultaneously over stimulated. Vagal activity has negative coronotropic effect on heart and heart rate goes down so a fall in pulse rate is observed. At the same time, increased sympathetic activity on veins and arterioles lead to increased blood pressure.

Severe parasympathetic activity in such patients also produce projectile vomiting.

When intracranial pressure becomes very high, retinal veins are compressed. Retinal artery keeps taking blood to retina but retinal veins cannot drain the blood out of retina. So optic disc becomes swollen and edematous and this condition is called papilledema.

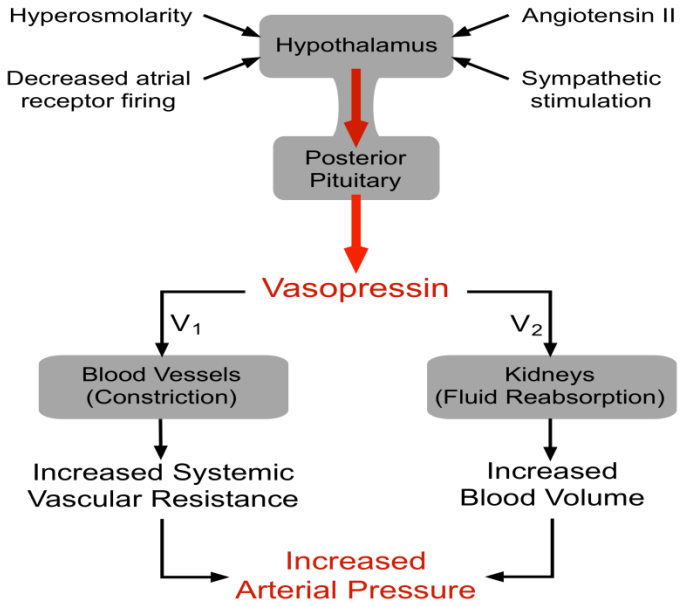
ADH AND BLOOD PRESSURE REGULATION

If blood volume becomes significantly low e.g. in case of severe hemorrhage, then posterior pituitary release ADH.

ADH functions include:

i. ADH works on v_2 receptors on distal convoluted tubules and collecting ducts to open water channels. More water is re-absorbed from lumen of nephron to the interstitium. Retention of water helps maintain blood volume

ii. ADH can also induce arterioconstriction and venoconstriction which help regulate blood pressure.



ANP AND BLOOD PRESSURE REGULATION

Atrial natriuretic peptide (ANP) is released when body has excessive volume. ANP act on kidney and induce natriuresis (loss of sodium). With loss of sodium, water is also lost. ANP also help in vasodilation to help bring blood pressure down.