ANTIHYPERTENSIVE DRUGS

BY

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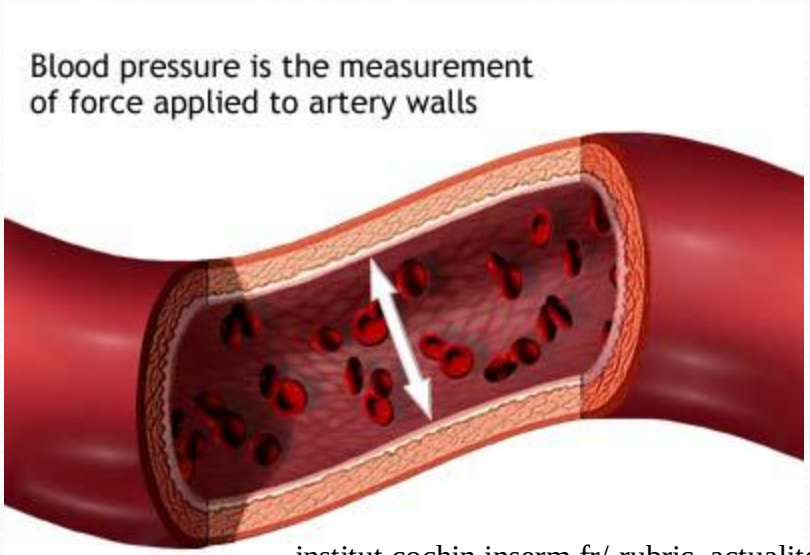
BLOOD PRESSURE:

It is defined as "**hydrostatic pressure exerted by blood on the walls of blood vessels.**"

Blood pressure is measured in terms of systolic/diastolic pressure.

The blood pressure of **120/80mmHg** is considered to be normal.



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PULSE PRESSURE:

Pulse pressure is the **difference between systolic and diastolic BP.**

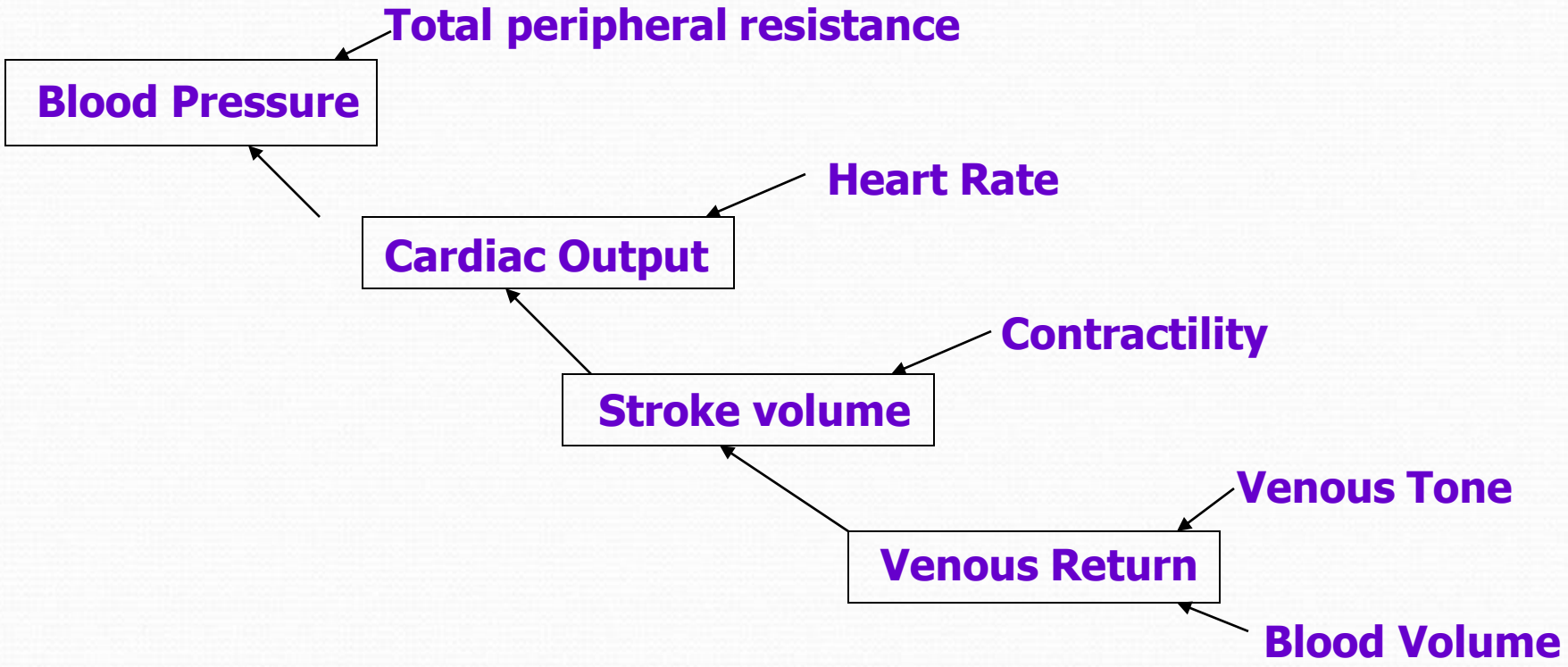


Fig: Scheme for Physiological Maintenance of BP.

HYPERTENSION

It is defined as systolic blood pressure of **140mmHg or greater** and diastolic BP of **90mmHg or greater.**

Clinical classification of hypertension :

Sr. no.	Category	Systolic (mmHg)	Diastolic (mmHg)
1.	**Normal**	< 130	<85
2.	**High normal**	130-139	85-89
3.	**Hypertension**		
I.	Mild (stage 1)	140-159	90-99
II.	Moderate(stage2)	160-179	100-109
III.	Severe(stage3)	180-209	110-119
IV	Very severe(stage4)	**≥**210	≥120
4.	**Malignant hypertension**	≥200	≥140

Regulation of blood pressure:

Blood pressure is regulated through following factors:

1. **Cardiovascular centre:**

   Cardiovascular centre in medulla oblongata helps to regulate HR & stroke volume.

2. **Neural regulation:**

   a) Baroreceptor reflex

   b) chemoreceptor reflex

3. **Hormonal regulation:**

   a) Renin-Angiotensin-Aldosterone system(RAAS)

   b) Epinephrine & norepinephrine

   c) Antidiuretic hormone(ADH)

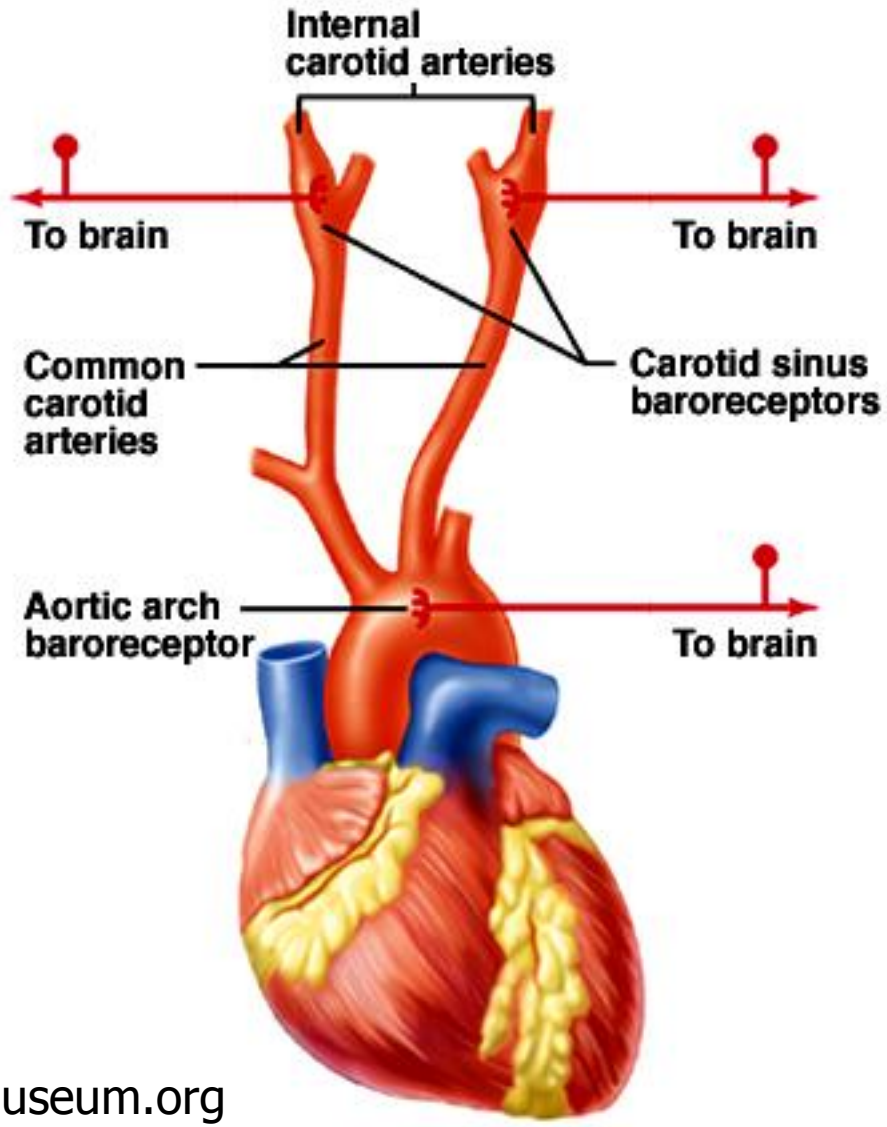
   d) Atrial natriuretic peptide(ANP)

4. **Auto regulation:**

   a) Physical changes

   b) vasodilating or vasoconstricting chemicals

Arterial baroreceptors



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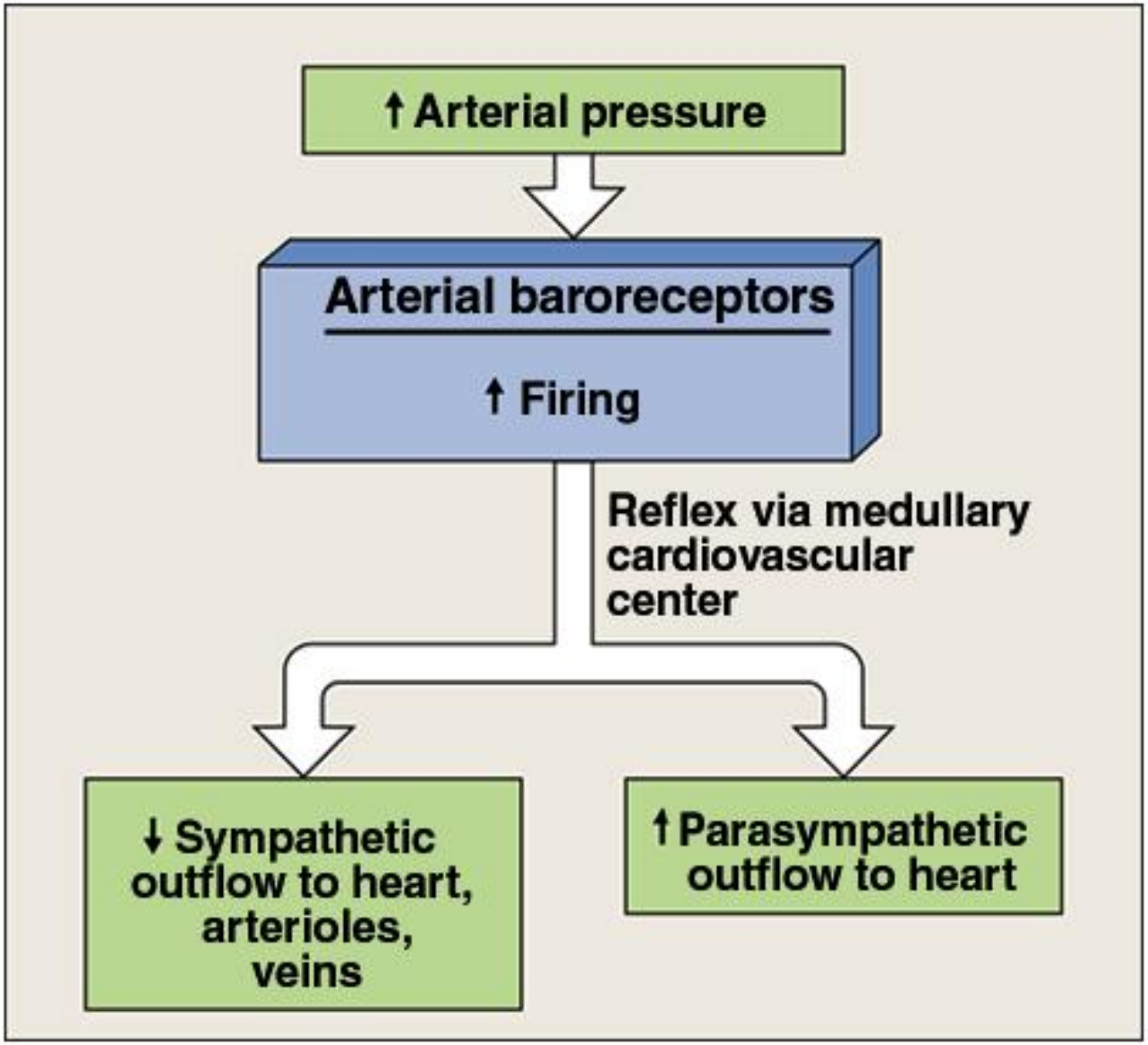
Arterial baroreceptor reflex



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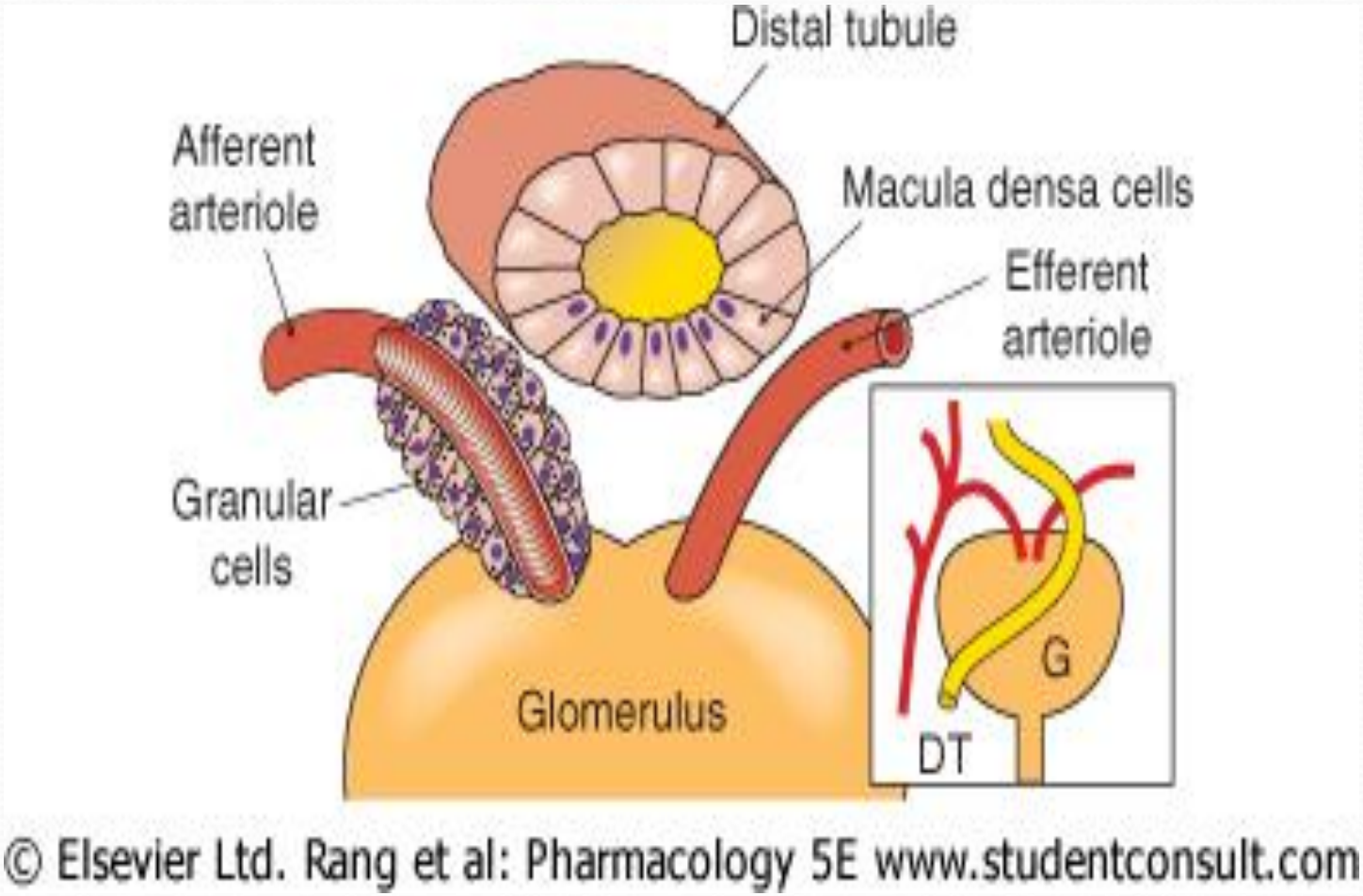
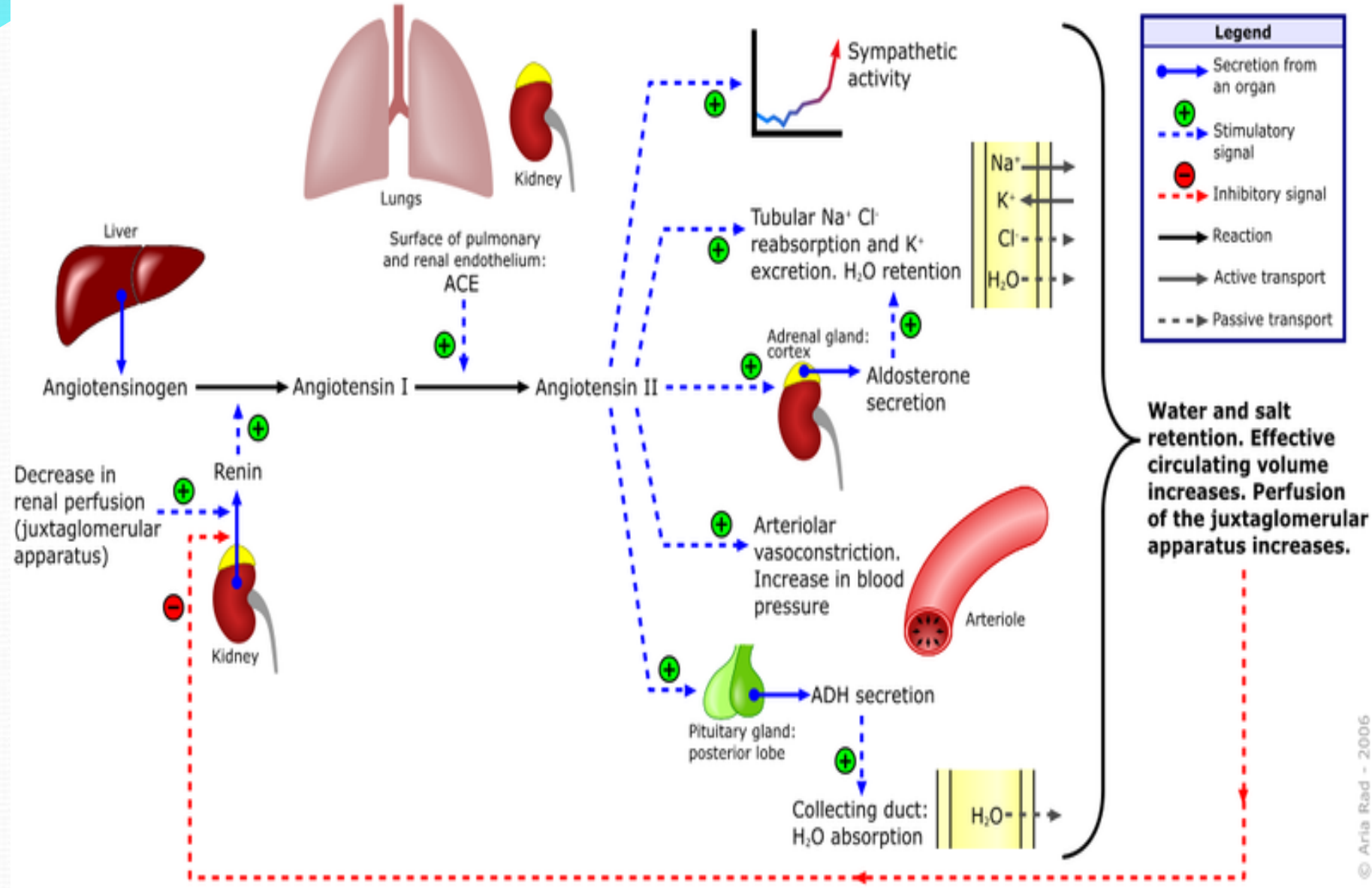


Fig: Juxtaglomerular Apparatus

Renin-angiotensin-aldosterone system



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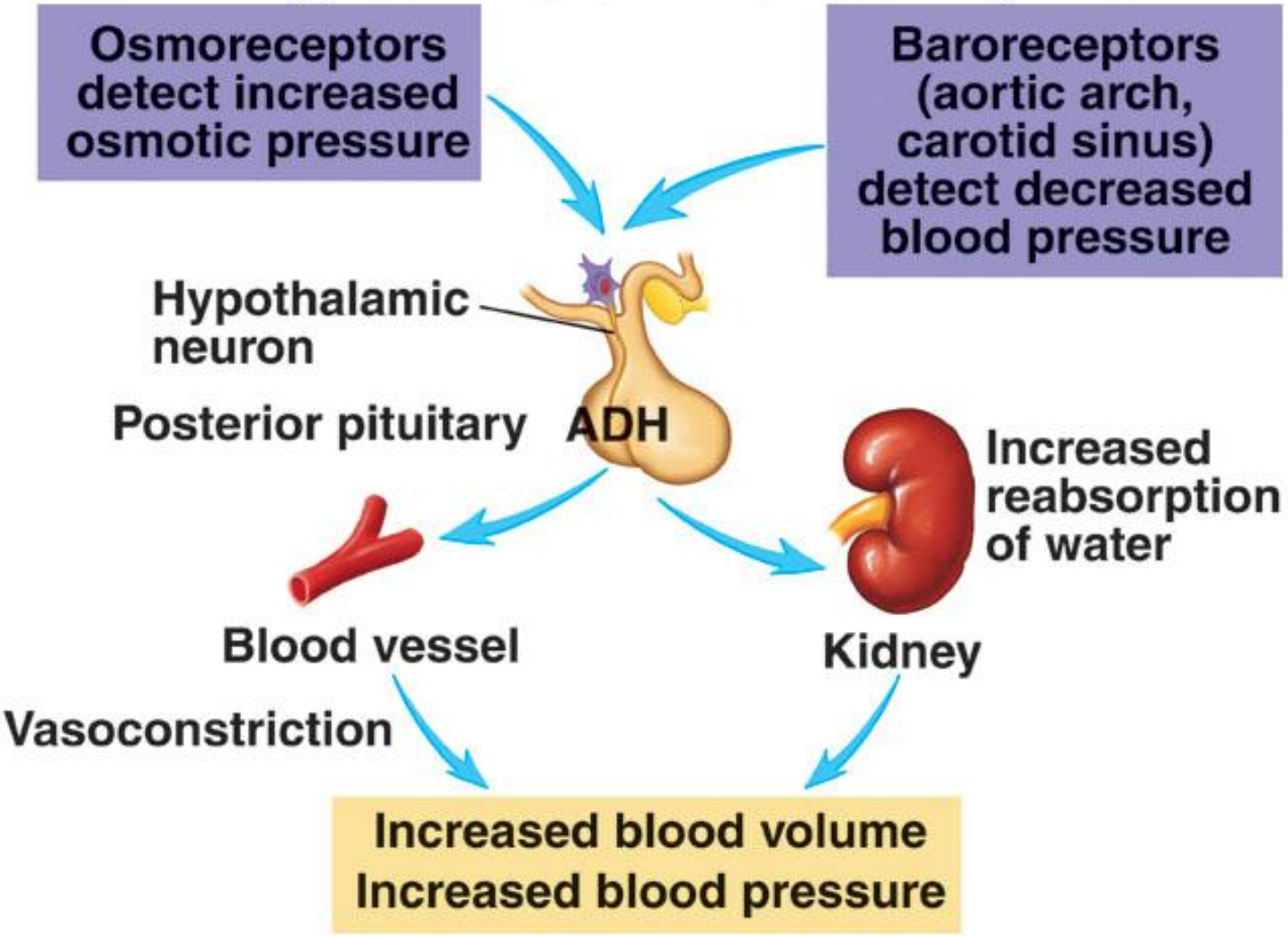

Fig: Secretion of Vasopressin

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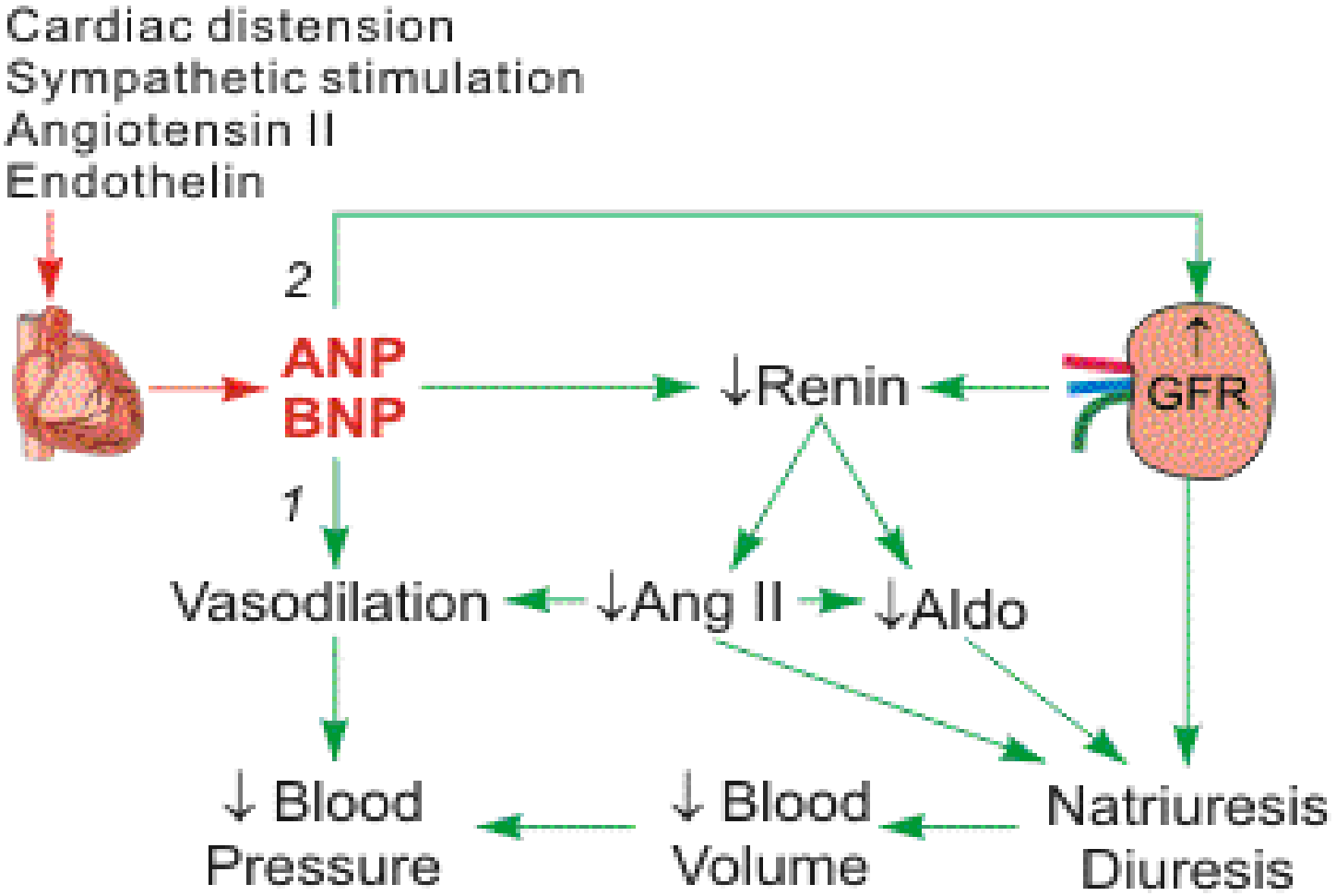

Fig: Atrial and Brain Natriuretic Peptides

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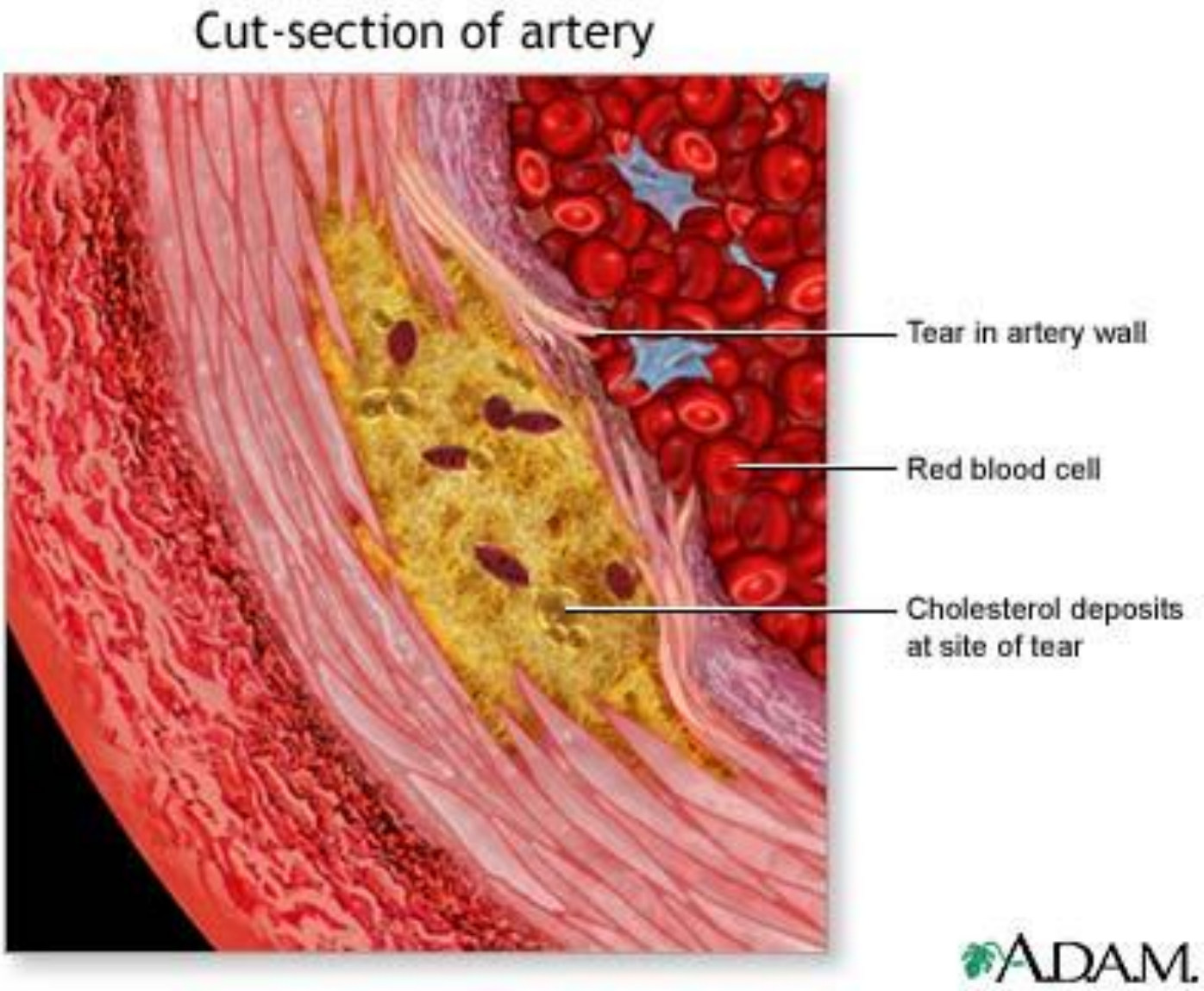

Fig: Arterial damage

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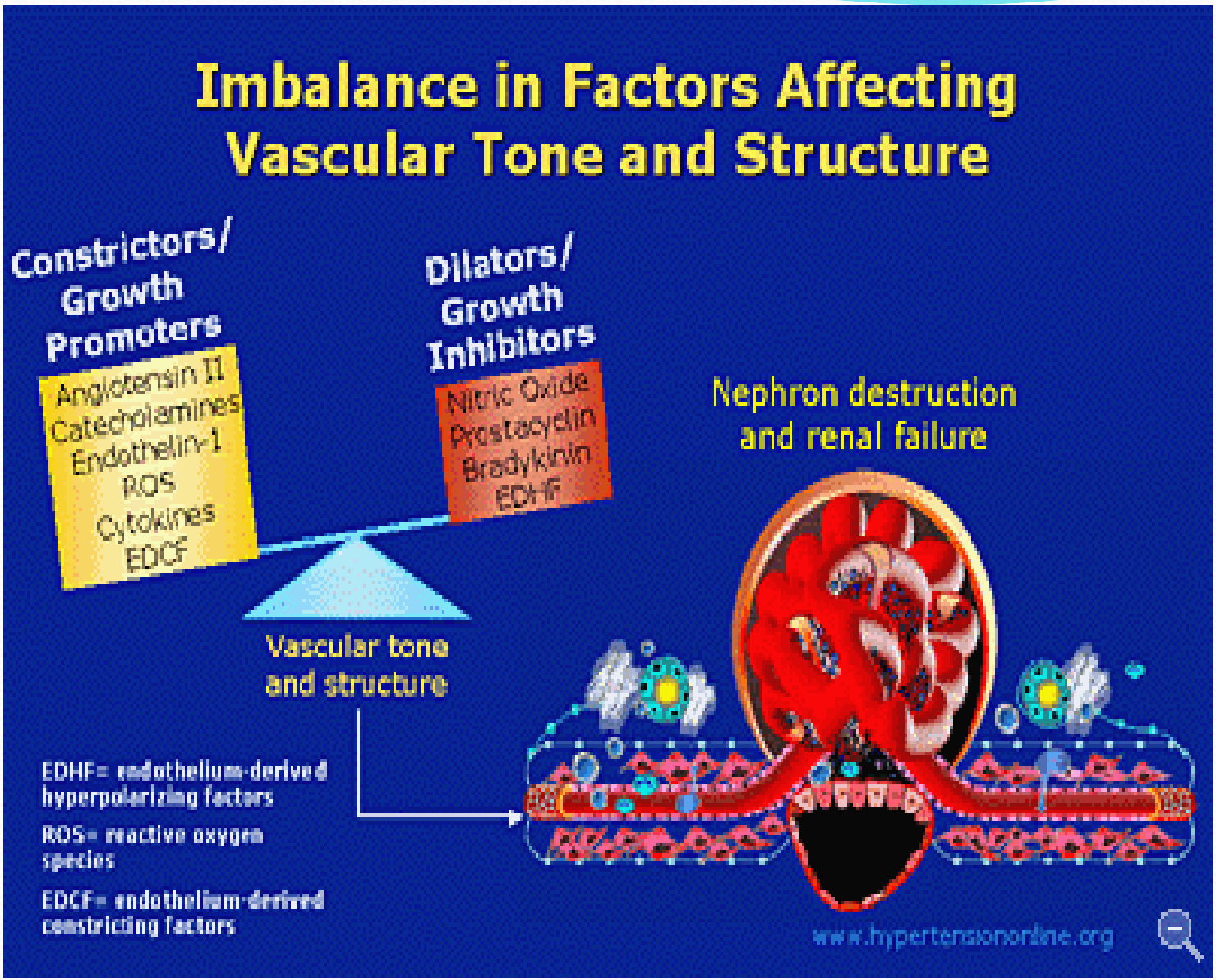

Imbalance in Factors Affecting Vascular Tone and Structure
Constrictors/ Growth Promoters
Angiotensin II
Catecholamines
Endothelin-1
ROS
Cytokines
EDCF
Dilators/ Growth Inhibitors
Nitric Oxide
Prostacyclin
Bradykinin
EDHF
Vascular tone and structure
Nephron destruction and renal failure
EDHF= endothelium-derived hyperpolarizing factors
ROS= reactive oxygen species
EDCF= endothelium-derived constricting factors
www.hypertensiononline.org

Types of hypertension:

1. **Primary or essential hypertension:**

- Cause is unknown.
- Constitutes about 90-95% patients of HT.
- Average age of onset about 35 yrs.

2. **Secondary hypertension:**

- Increase in BP due to several disorders like hyperaldosteronism, Pheochromocytoma.
- Develops between 30-50 yrs.

Etiology of Hypertension

1. Primary hypertension:

Number of factors related to its development are;

i) Genetic factors

ii) Racial & environmental factors

iii) Risk factors modifying the course of essential hypertension:

a) Age

b) Atherosclerosis

c) Smoking

d) Excess alcohol intake

e) Diabetes mellitus

2. Secondary hypertension

1. Renal hypertension:

Hypertension produced by renal diseases

Renal hypertension can be produced by one of the following mechanisms:

i) Activation of RAAS

ii) Sodium & water retention

iii) Decrease in vasopressor material

e.g. PAF, prostaglandins

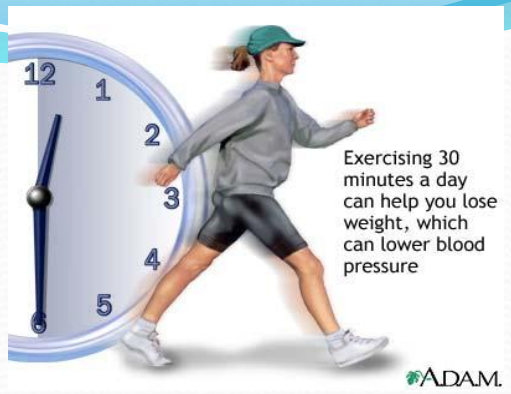
2. Endocrine hypertension:

i) Adrenal gland: Pheochromocytoma

ii) Oral contraceptives

3. Rebound hypertension

Treatment of hypertension



1) Lifestyle changes:
   a) Lose weight, exercise & stress management.
   b) Limit alcohol intake & avoid smoking.
   c) Diet:DASH diet.

2) Drug treatment:
   They can be classified according to their site of action:
   I. Diuretics:
      a) Thiazides & related agents(chlorthiazide)
      b) Loop diuretics (frusemide, Bumetanide)
      c) Potassium sparing diuretics (spironolactone)
   II. Sympatholytic drugs:
      a) Centrally acting agents (clonidine, methyldopa
      b) Beta adrenoceptor blockers (propranolol)
      c) Adrenergic neuron blocking (guanethidine, res

III. Vasodilators:

a) Arterial (minoxidil, diazoxide)

b) Arterial & venous (nitroprusside)

IV. Calcium channel blockers:

verapamil, diltiazem, nifedipine, amlodipine

V. ACE inhibitors:

captopril, enalapril, lisinopril

VI. Angiotensin -II receptor blockers:

losartan, valsartan

VII. Potassium channel openers:

pinacidil

1. DIURETICS

Diuretics are drugs which cause a net loss of Na^+ and water in urine.
Diuretics have been the standard antihypertensive drugs over the past 4 decades, though they do not lower BP in normotensives.

Thiazides

Thiazides and related drugs (chlorthalidone, etc.) are the diuretic of choice in uncomplicated hypertension. The proposed mechanism of antihypertensive action is:

1. Initially, the diuresis reduces plasma and e.c.f. volume by 5–15% → decreased c.o.
2. Subsequently, compensatory mechanisms operate to almost regain Na^+ balance and plasma volume; c.o. is restored, but the fall in BP is maintained by a slowly developing reduction in t.p.r.
3. The reduction in t.p.r. is most probably an indirect consequence of a small (~5%) persisting Na and volume deficit. Decrease in intracellular Na+ concentration in the vascular smooth muscle may decrease stiffness of vessel wall, increase their compliance and dampen responsiveness to constrictor stimuli (NA, AII).

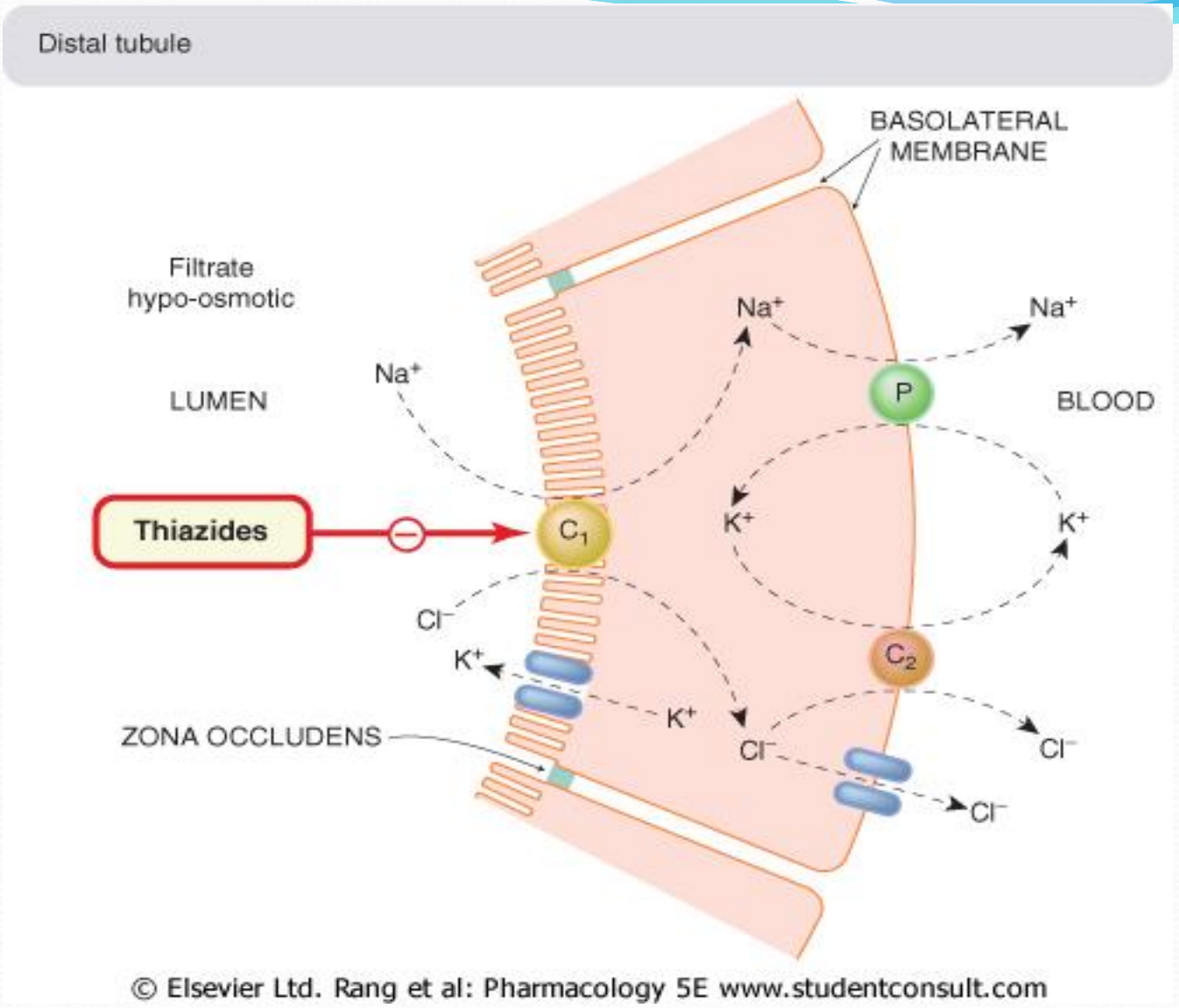


Fig: Site of action of thiazide diuretics

Desirable properties of diuretics as antihypertensives are:

1. Once a day dosing and flat dose-response curve permitting simple standardized regimens.
2. No fluid retention, no tolerance.
3. Low incidence of postural hypotension and relative freedom from side effects, especially CNS, compared to sympatholytics.
4. Effective in isolated systolic hypertension (ISH).
5. Lessened risk of hip fracture in the elderly due to hypocalciuric action of thiazides.
6. Low cost.

2. Angiotensin Receptor Blockers (AT1 blockers)

Over the past 2 decades, several nonpeptide orally active AT receptor antagonists have been developed as alternatives to ACE inhibitors. These include losartan, candesartan, valsartan, telmisartan and irbesartan.

Losartan: It blocks all overt actions of A-II, viz. vasoconstriction, central and peripheral sympathetic stimulation, release of aldosterone and Adr from adrenals, renal actions promoting salt and water reabsorption.

Pharmacokinetics

Oral absorption is not affected by food, but bioavailability is 33% due to first pass metabolism. It is partially carboxylated in liver to an active metabolite (E3174). After oral ingestion peak plasma levels are attained at 1 hr for losartan and at 3-4 hours for E3174. Both compounds are 98% plasma protein bound, do not enter brain and are excreted by the kidney. The plasma t½ of losartan is 2 hr, but that of E3174 is 6–9 hr. No dose adjustment is required in renal insufficiency, but dose should be reduced in presence of hepatic dysfunction.

Adverse effects: It is well tolerated, it can cause hypotension and hyperkalemia, dry cough, Angioedema is reported in fewer cases. Headache, dizziness, weakness and upper g.i. side effects are mild and occasional. However, losartan has fetopathic.

3. Calcium Channel Blockers (CCBs)

CCBs are another class of first line antihypertensive drugs. All 3 subgroups of CCBs, *viz. dihydropyridines (DHPs*, e.g. amlodipine), phenylalkylamine (verapamil) and benzothiazepine (diltiazem) are equally efficacious antihypertensives. They lower BP by decreasing peripheral resistance without compromising c.o. Despite vasodilatation, fluid retention is insignificant.

- The common property of all three subclasses of CCBs is to inhibit Ca^{2+} mediated slow channel component of action potential (AP) in smooth/cardiac muscle cell. The two most important actions of CCBs are:
  (i) Smooth muscle (especially vascular) relaxation.
  (ii) Negative chronotropic, inotropic and dromotropic action on heart.

The onset of antihypertensive action is quick. With the availability of long acting preparations, most agents can be administered once a day.

Monotherapy with CCBs is effective in ~ 50% hypertensives; their action is independent of patient's renin status, and they may improve arterial compliance.

Other advantages of CCBs are:

1. **No impairment of physical work capacity.**
2. **No sedation or other CNS effects; cerebral perfusion is maintained.**
3. **Not contraindicated in asthma, angina (especially variant) and PVD patients: may benefit these conditions.**
4. **Do not impair renal perfusion.**
5. **Do not affect male sexual function. No fetopethic effect.**
6. **No deleterious effect on plasma lipid profile, uric acid level and electrolyte balance.**

Adverse effects

- *Nausea*, *constipation and* bradycardia are more common than other CCBs, while flushing, headache and ankle edema are less common. Hypotension is occasional and tachycardia (common with DHPs) is absent. It can accentuate conduction defects (contraindicated in 2nd and 3rd degree A-V block) and precipitate CHF in patients with preexisting disease. Cardiac arrest has occurred on i.v. injection and when it is given to patients with sick sinus.

Interactions: **Verapamil should not be given** with ß blockers-additive sinus depression, conduction defects or asystole may occur.

- It increases plasma digoxin level by decreasing its excretion: toxicity can develop. It should not be used with other cardiac depressants like quinidine and disopyramide.

4. β ADRENERGIC BLOCKING DRUGS

These drugs inhibit adrenergic responses mediated through the ß receptors.

Propranolol: It decreases heart rate, force of contraction (higher doses) and cardiac output (c.o.). Cardiac work and oxygen consumption are reduced as the product of heart rate and aortic pressure decreases.

Other mechanisms that may contribute for antihypertensive action are:

(i) Reduced NA release from sympathetic terminals due to blockade of ß receptor mediated facilitation of the release process.

(ii) Decreased renin release from kidney (ß mediated): Propranolol causes a more marked fall in BP in hypertensives. However, pindolol does not decrease plasma renin activity but is an effective antihypertensive.

(iii) Central action reducing sympathetic outflow. However, ß blockers which penetrate brain poorly are also effective antihypertensives.

Pharmacokinetics: Propranolol is well absorbed after orally but low bioavailability due to high first pass in liver. It is lipophilic and penetrates into brain easily. The metabolites are excreted in urine, mostly as glucuronides. More than 90% of propranolol is bound to plasma proteins.

Contraindication: There are several contraindications to ß blockers, including cardiac, pulmonary and peripheral vascular disease. The nonselective ß blockers have an unfavourable effect on lipid profile (raise triglyceride level and LDL/HDL ratio).

Advantage: Because of absence of postural hypotension, bowel alteration, salt and water retention; a low incidence of side effects, low cost; once a day regimen and cardioprotective potential, ß blockers continue to be among the first choice drugs recommended by JNC 7 and WHO-ISH, especially for relatively young nonobese hypertensives.

5. Central Sympatholytics

Clonidine It is an imidazoline derivative having complex actions. Clonidine is a partial agonist with high affinity and high intrinsic activity at a α_2 receptors, especially α_{2A} subtype in brainstem. The major haemodynamic effects result from stimulation of α_{2A} receptors present mainly postjunctionally in medulla (vasomotor centre)→ decrease sympathetic out flow → fall in BP and bradycardia (also due to enhanced vagal tone). Plasma NA declines. Though clonidine is capable of reducing NA release from peripheral adrenergic nerve endings (release inhibitory prejunctional a action), this is not manifest at clinically used doses. Clonidine is a moderately **potent antihypertensive.**

Pharmacokinetics: Clonidine is well absorbed orally; peak occurs in 2–4 hours; 1/2 to 2/3 of an oral dose is excreted unchanged in urine, the rest as metabolites. Plasma t½ is 8–12 hours. Effect of a single dose lasts for 6–24 hours.

Adverse effect: Sedation, mental depression, disturbed sleep; dryness of mouth, nose and eyes, constipation. Impotence, salt and water retention, bradycardia (due to reduced sympathetic tone). Postural hypotension occurs, but is mostly asymptomatic.

Thank You