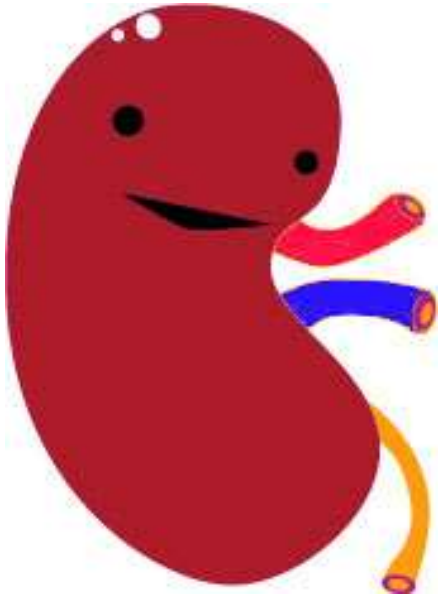
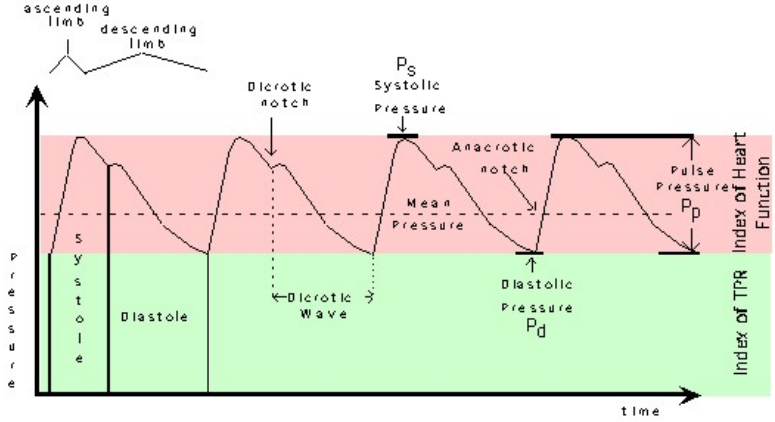
# Secondary hypertension

Exp. induced stenosis of renal artery as a model of renovascular hypertension



# Arterial blood pressure - definition

- $P = Q \times R$
- Analogous to Ohm's law defining voltage
- Tensor in moving viscous fluid
- Vessel wall is challenged by its radial member (i.e. pointing towards the endothelium)
  - Systolic – on the top of the pulse curve
  - Diastolic – on the bottom of the pulse curve
  - Pulse – pulse curve amplitude
  - Mean – average pressure during the cycle



# Cardiac output

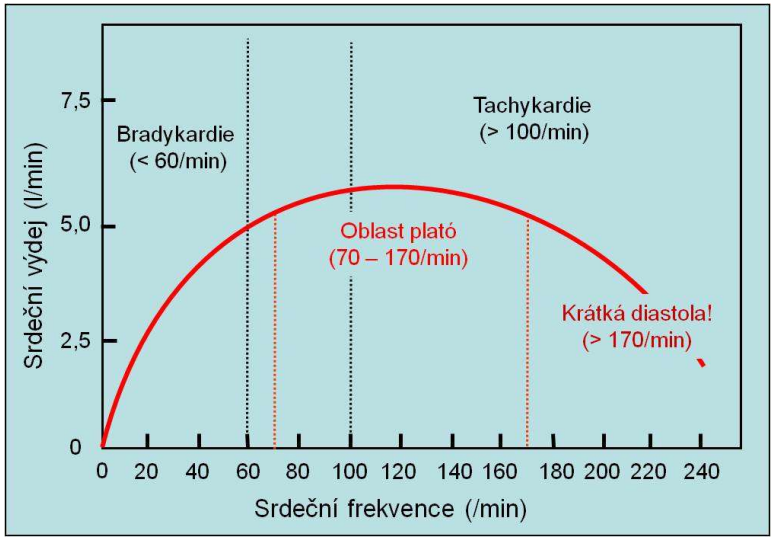
- Q: is equal to cardiac output (CO) – anatomic shunts

  CO = SV (stroke volume) × f

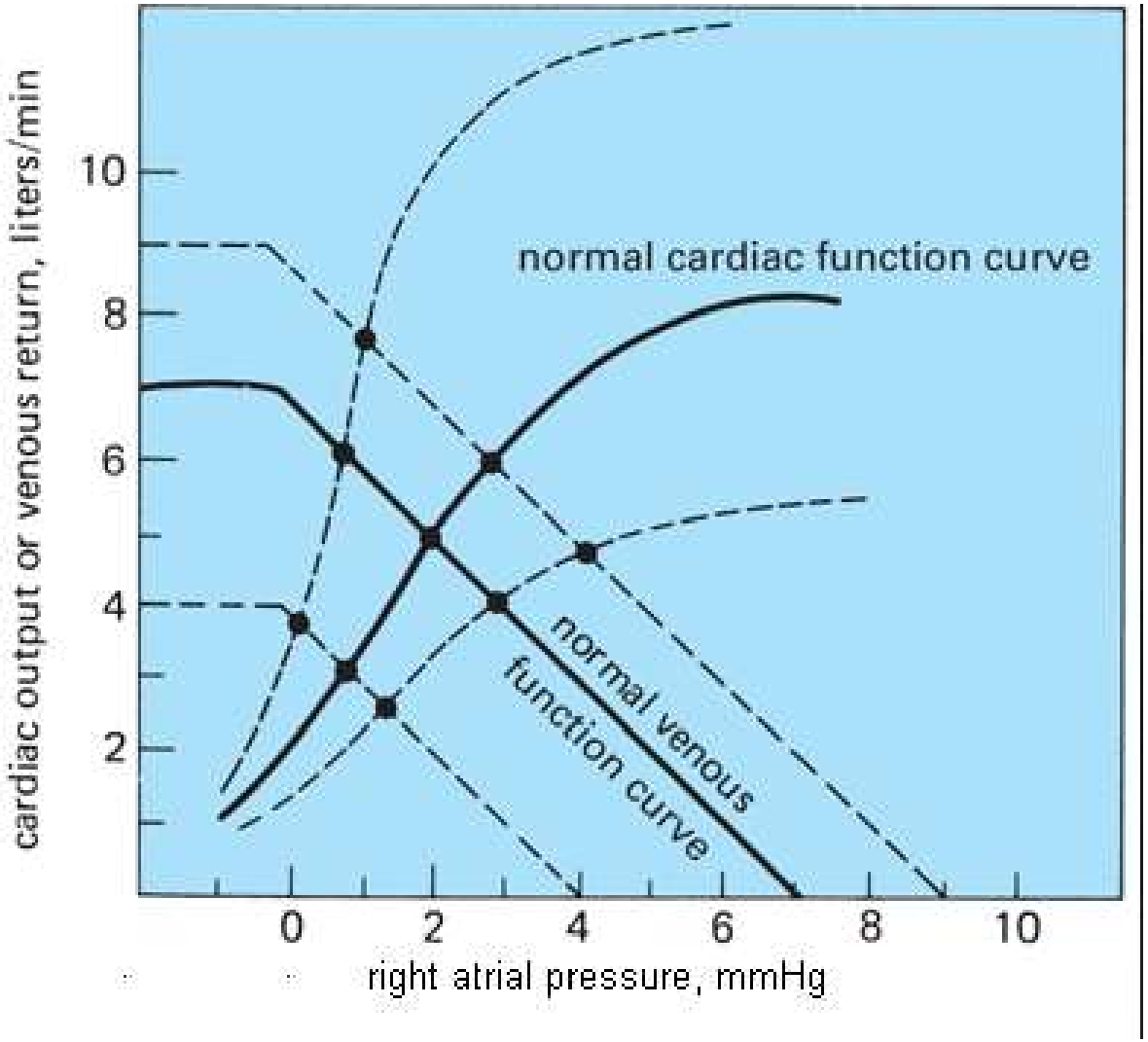
  SV = EDV (enddiastolic volume) – ESV (endsystolic volume)

  EF [%] = SV/EDV

- CO is physiologically equal to venous return (depends on circulating volume)
- In very high HR the CO paradoxically decreases (the ventricles are not filled effectively)

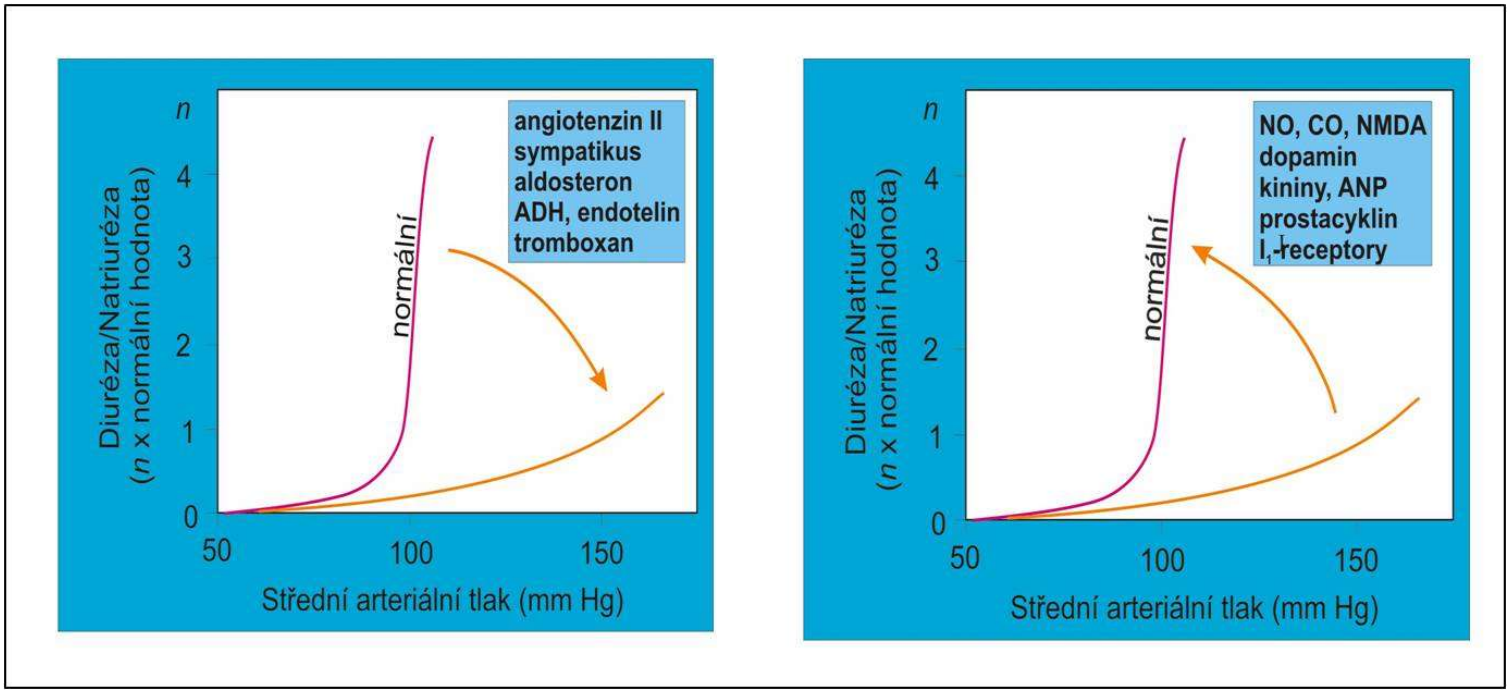


# Cardiac and venous function curve



# Renal function curve

- Provided the renal functions are untouched, the increase in CO or resistance can be compensated by lowering of circulating volume




- This can be disturbed under pathological conditions - hypervolemia

# Circulating volume

| Part of circulatory system | % | ml |
|---|---|---|
| Pulmonary circulation | 9 % | 450 |
| Heart | 7 % | 350 |
| Arteries | 13 % | 650 |
| Arterioles and capillaries | 7 % | 350 |
| Venules, veins and venous sinuses | 64 % | 3200 |

# Resistance

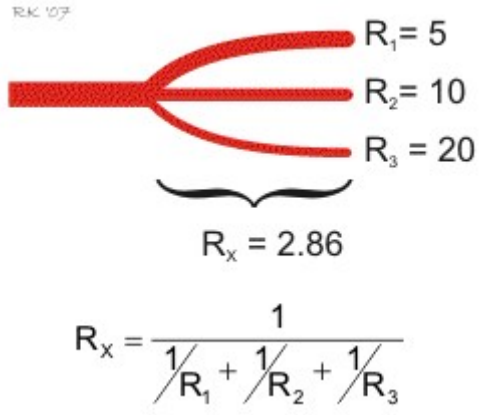
- R [$kg.s^{-1}.m^{-4}$]: can be obtained from Hagen-Poiseuill law:

$$R = 8 \times \eta \times d / \pi \times r^4, \text{where:}$$

$\eta$ = viscosity

d = lenght of the segment

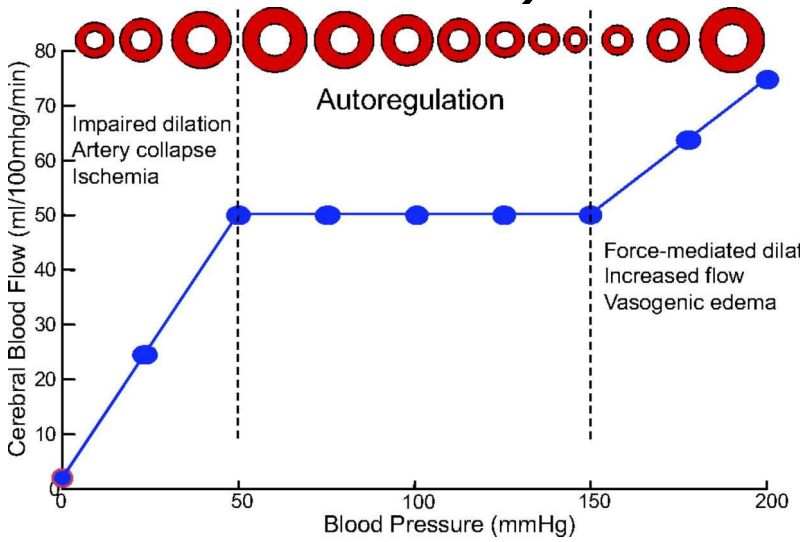
r = radius

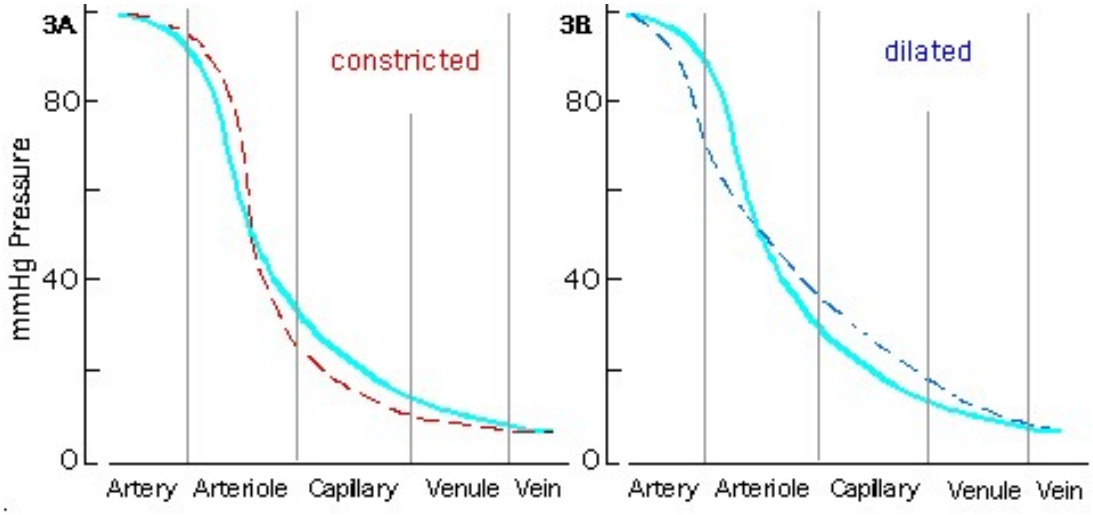



$$R_X = \frac{1}{1/R_1 + 1/R_2 + 1/R_3}$$

# Peripheral resistance

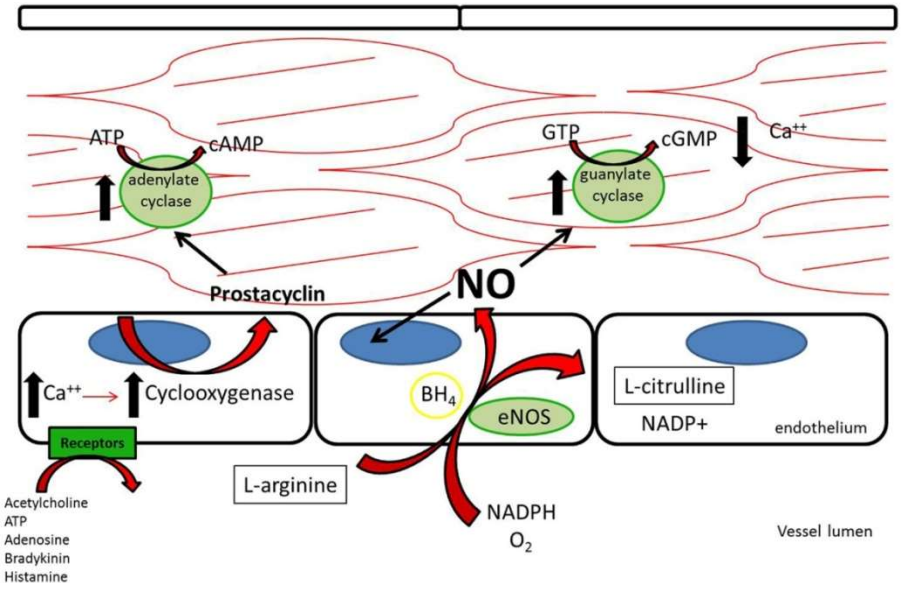
- The resistance increases inversely to the radius at the power of 4
- The decrease in radius is most evident in arterioles
- The smooth muscle tone in the wall of arterioles changes depending on many factors – this controls peripheral resistance („resistance arterioles“)



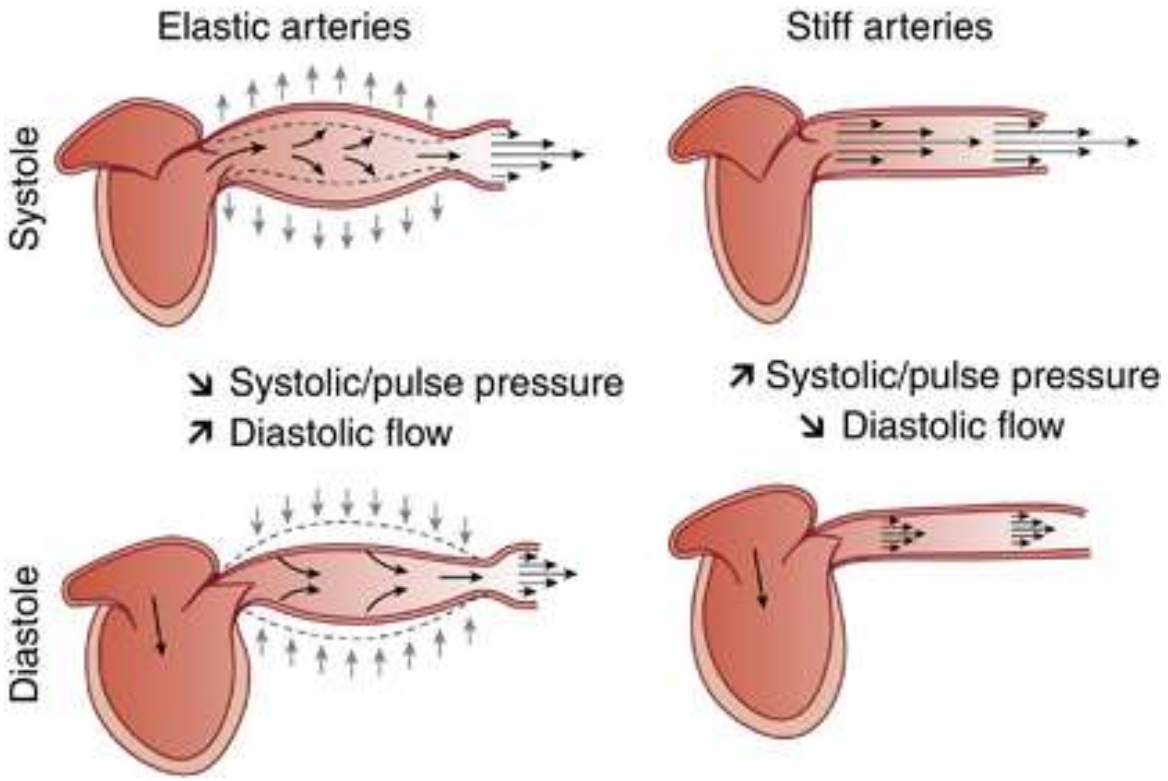



# Vascular smooth muscle

- Vasodilatation
  - NO – produced in the endothelium by constitutive (eNOS) and inducible (iNOS) synthase
  - prostacyclins
  - histamine
  - bradykinin
  - $pO_2$, $pCO_2$ ,pH
  - adenosine
  - catecholamines
  - cGMP, cAMP
- Vasoconstriction
  - endothelin
  - ATII
  - ADH
  - catecholamines
  - $Ca^{2+}$



# Arterial wall elasticity (elastic arteries)




- Worsens with age
- Loss of elasticity (arterial stiffness) leads to isolated systolic hypertension

# Blood pressure regulation

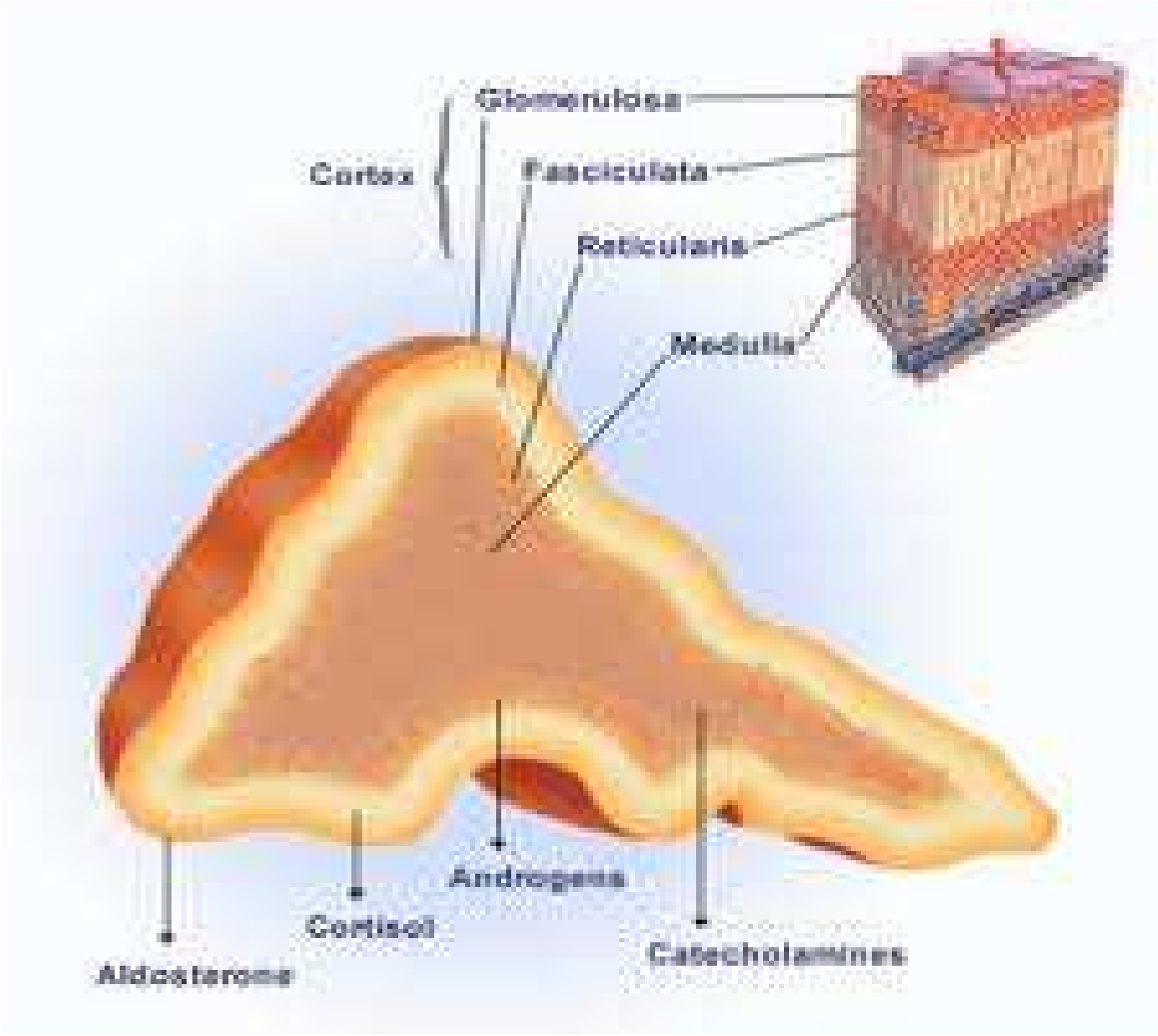
- Several interconnected systems
- Regulation of:
  - heart rate
  - cardiac contractility
  - peripheral resistance
  - circulating volume

# Hypertension (BP = CO × R)

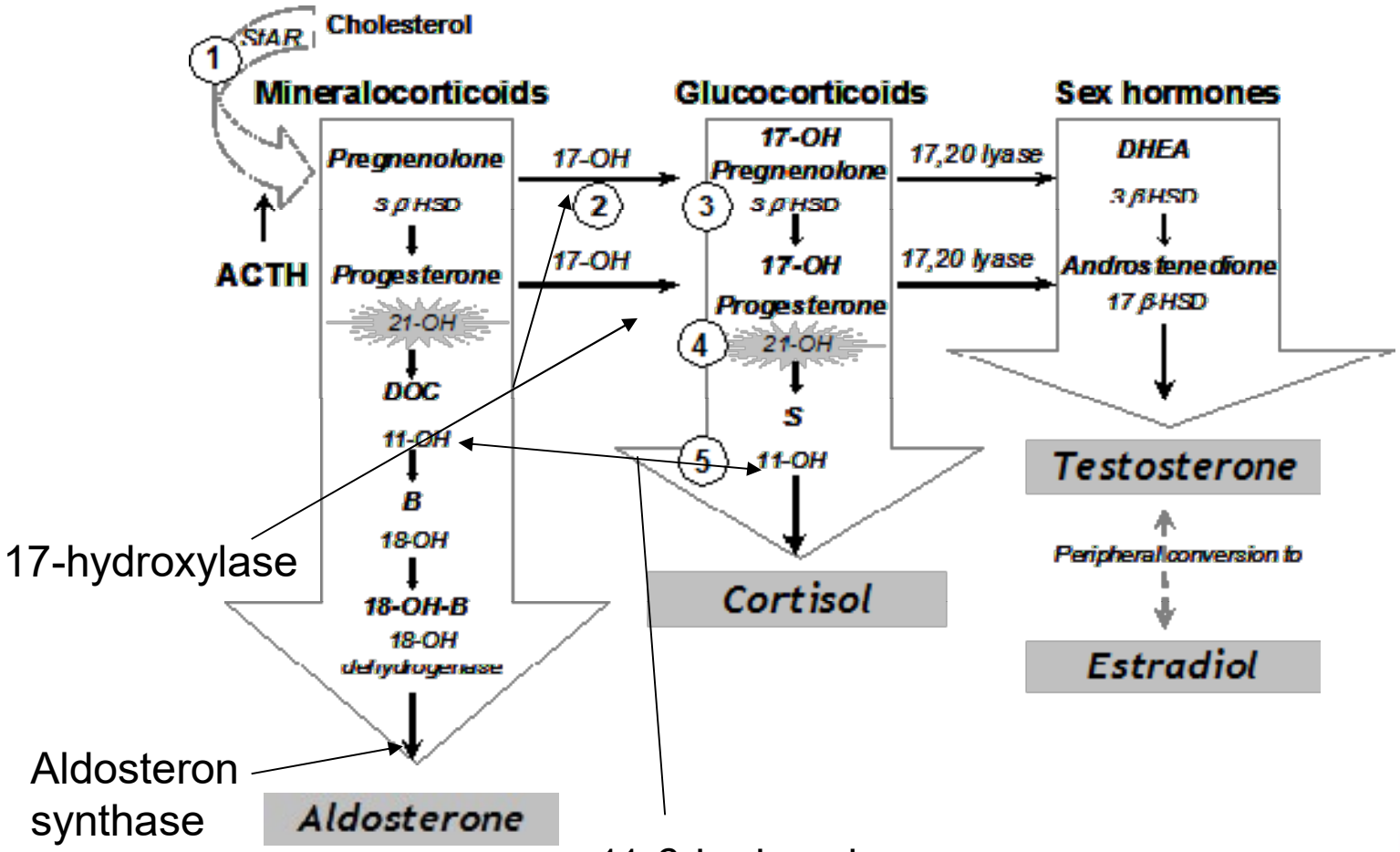
- essential – 90-95%

- secondary – 5-10%
  - renal
    - renovascular
    - renoparenchymatous
  - endocrine
    - adrenal gland
      - prim. Hyperaldosteronism
      - Cushing syndrome
      - feochromocytome
    - others
      - Akromegalia
      - Hyperthyreosis
  - Other causes
    - Aortic coarctation

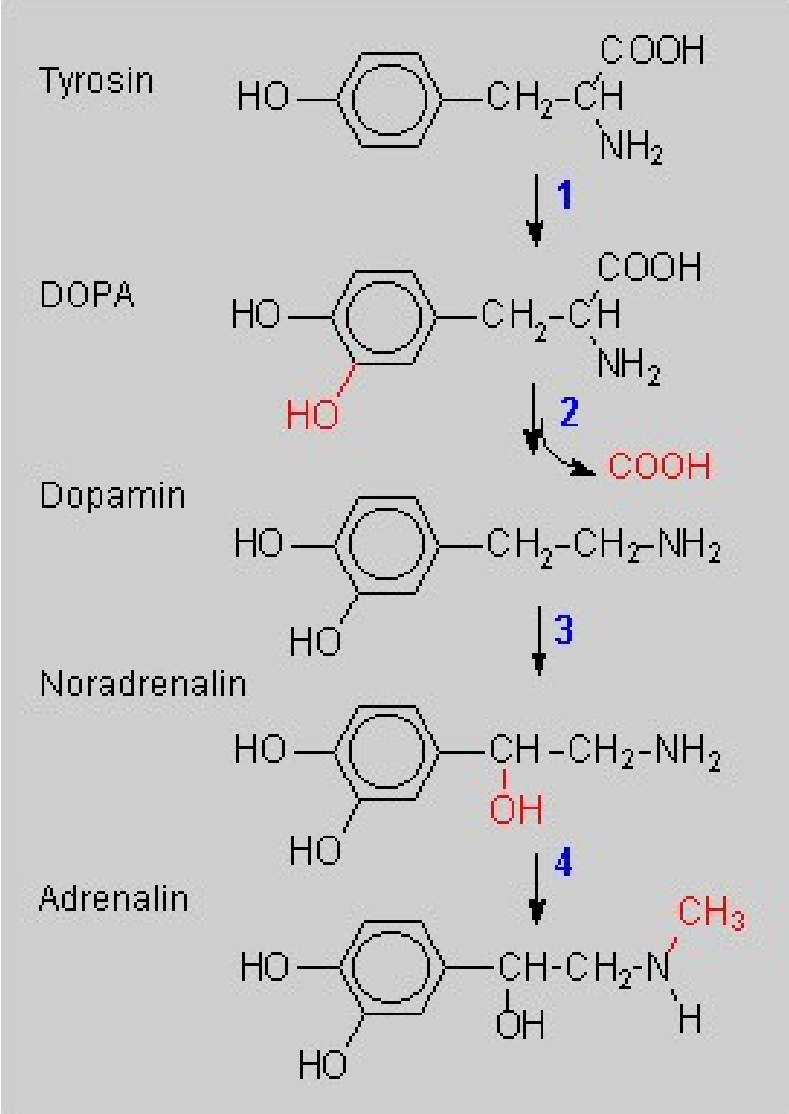
# Adrenal gland



# adrenal cortex



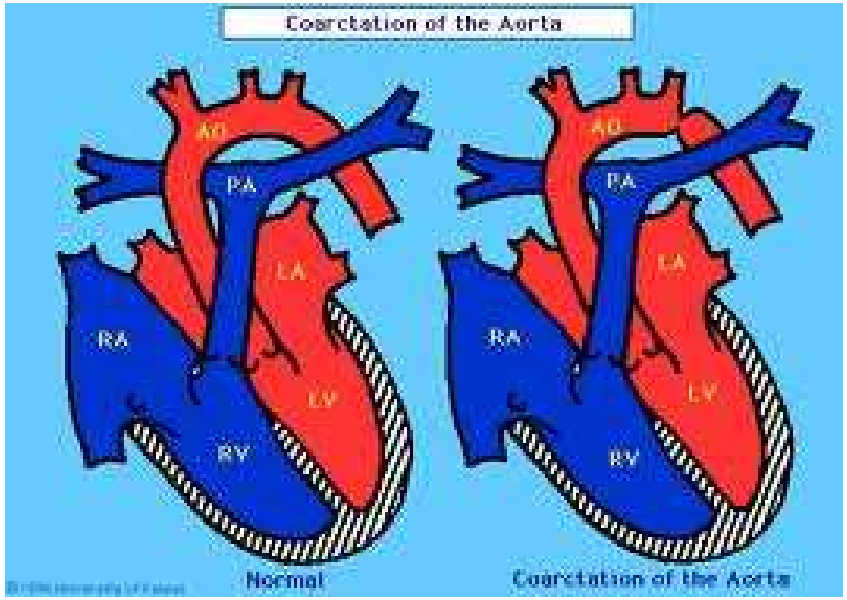
# Adrenal medulla




- pheochromocytoma
- Paroxysmal hypertension
- 90% in the adrenal gland, 10% outside
- They produce norepinephrine, epinephrine, dopamine

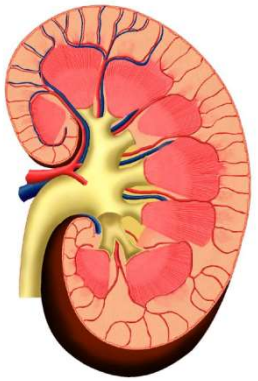
# Aortic coarctation

- Stenosis of aortic lumen, usually behind a. subclavia sinistra



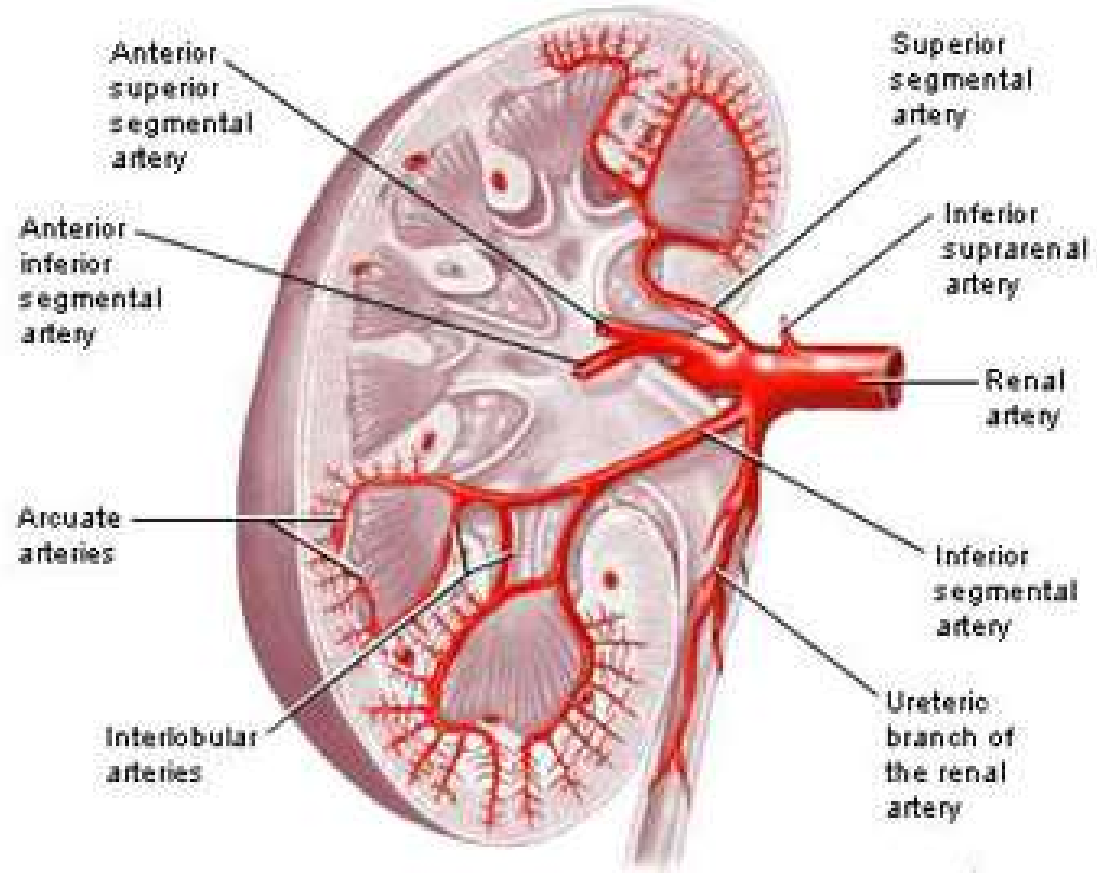

- Hypertension od the upper part, hypotension of the lower part

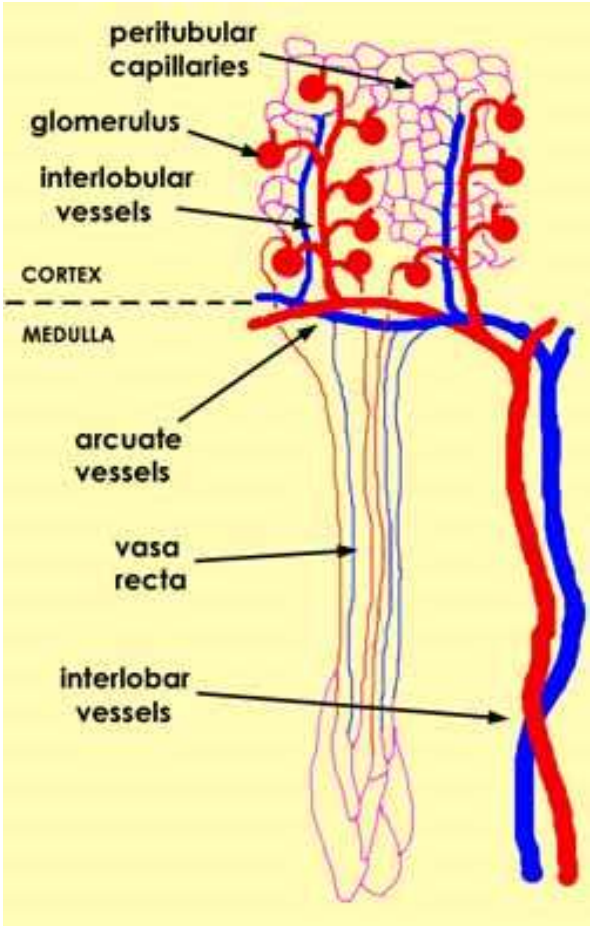
# Renal functions



- Regulation of
  - extracelular volume
  - tonicity and osmolarity
  - acid-base equilibrium
  - nitrogene metabolism
  - calcium and phosphate homeostasis
  - hematocrite
  - lipid metabolism, low molecular weight substances
- Total flow through the kidney is cca 1200 ml/min, which corresponds with ~20-25% of cardiac output
  - cortex >>> medulla
- Renal plasma flow, RPF) ~600-700 ml/min
  - with hematocrite ~0.50
- glom. filtration ~20% → glomerular filtration rate (GFR) ~100-120ml/min
  - ~144 – 170 l daily, but 99% reabsorption → i.e. 1.5 – 1.7 l urine daily
- The difference in hemoglobin saturation between arteries and veins is very small
  - given 100% saturation Hb $O_2$ in arterial blood, the saturation of Hb in venous blood coming out of following organs is:
    - heart - 35%
    - brain - 50%
    - kidney - 90%
  - The main physiological function of high perfusion through the kidney is thus regulation (see above) and not nutrition.

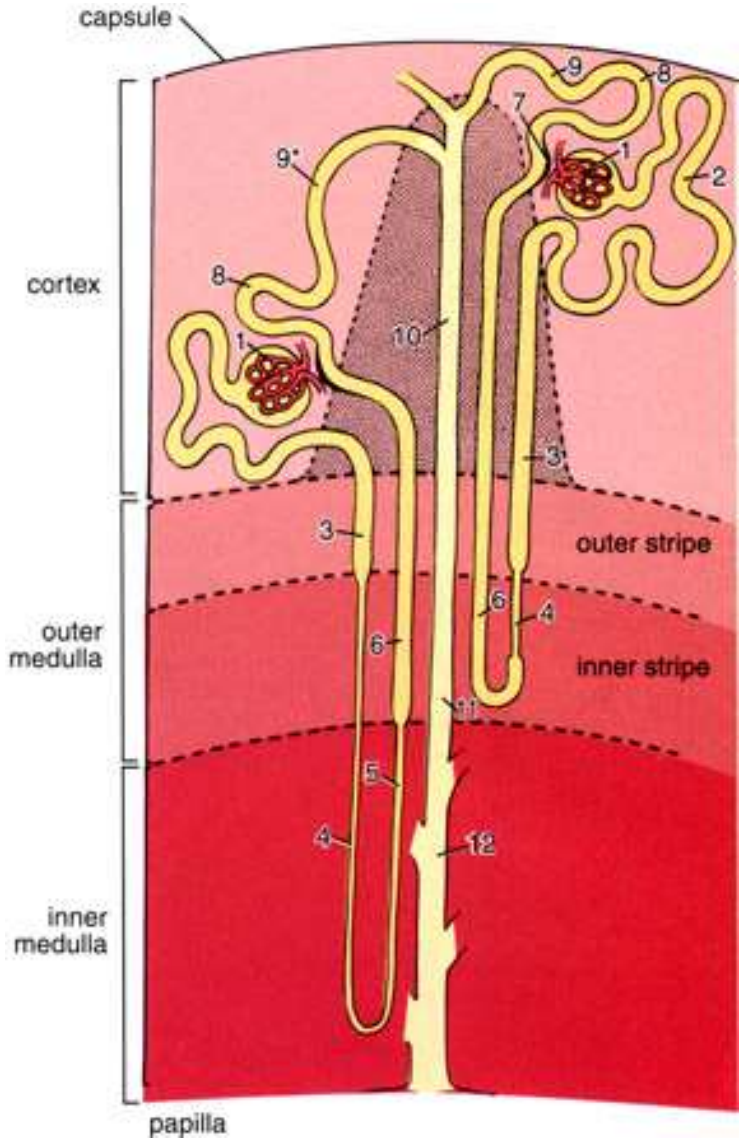
# Blood supply in the kidney

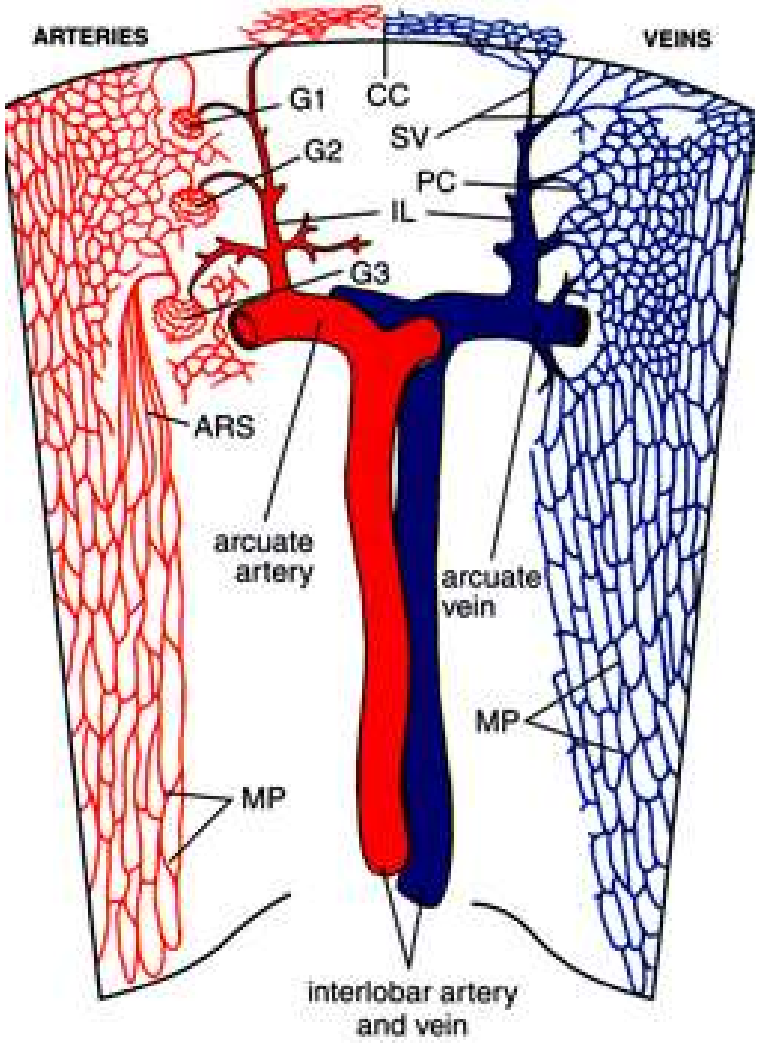



- a. renalis → aa. interlobares → aa. arcuates → aa. interlobulares → afferent arterioles → glomerular capillaries → efferent arterioles
  - → peritubular capillaries (in cortical nephrones)
  - → vasa recta (in juxtamedullar nephrones)

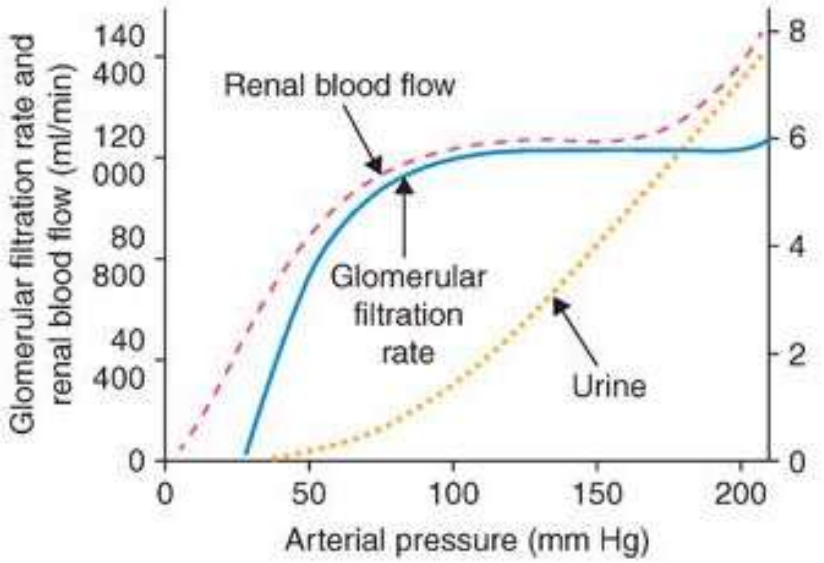
# Two kinds of nephrones

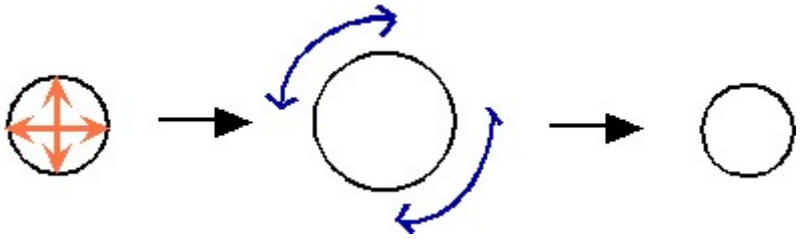


# Regulation of blood pression in the kidney

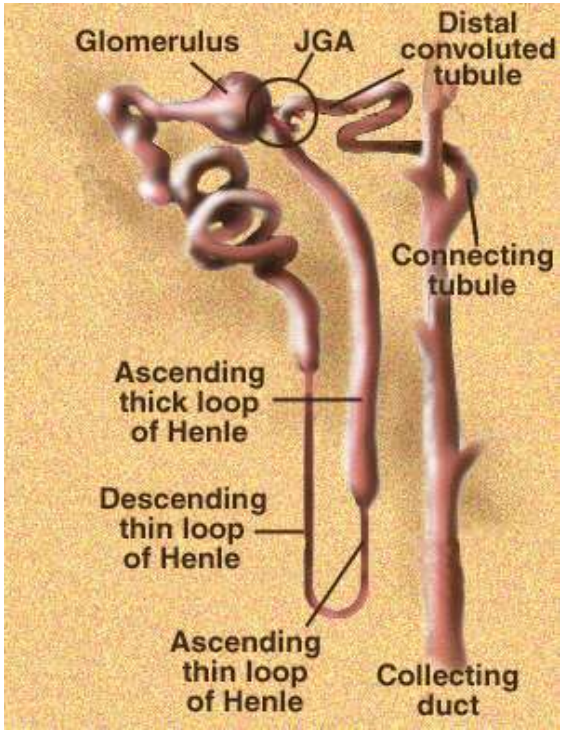
- Systemic blood pressure
  - between 80-160mmHg, RBF is quite stable thanks to the autoregulation
  - In case of significant decrease of BP, renal perfusion is impaired(→ ischemia, necrosis)
- Autoregulation of RBF
  - (1) myogennic regulation
    - SMC of afferent and efferent arterioles detect the tension and react by their contraction
  - (2) tubuloglomerular feedback
    - juxtaglomerular apparatus detects eventual changes of NaCl concentration and releases renin
    - activation of **local RAS** ensures the contraction of efferent arteriole (in higher concentrations of ATII also the afferent arteriole)
- other paracrinne factors
  - prostaglandins, adenosine and NO
- sympaticus
  - noradrenaline from adrenergic terminal endings and circulating adrenaline from adrenal medula lead into vasoconstriction of both afferent and efferent arteriole ($\alpha$1-receptors)
    - Lowering of RBF and GFR
  - noradrenaline stimulates renin release from granular JG-cells ($\beta$1-receptors) and subsequent systemic RAS activation
  - noradrenaline increase $Na^+$-reabsorption of prox. tubulus
- **systemic RAS**



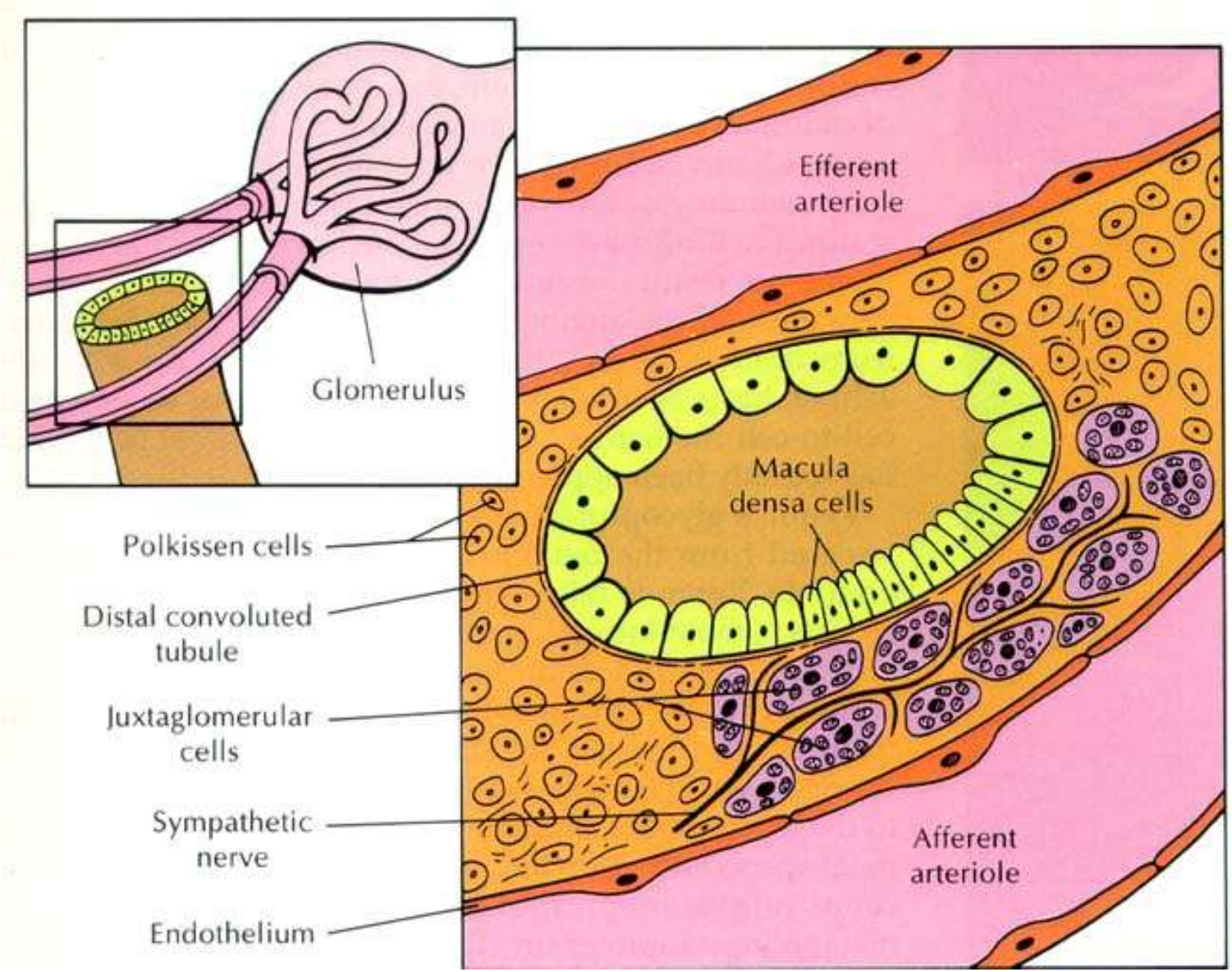



# Juxtaglomerular apparatus

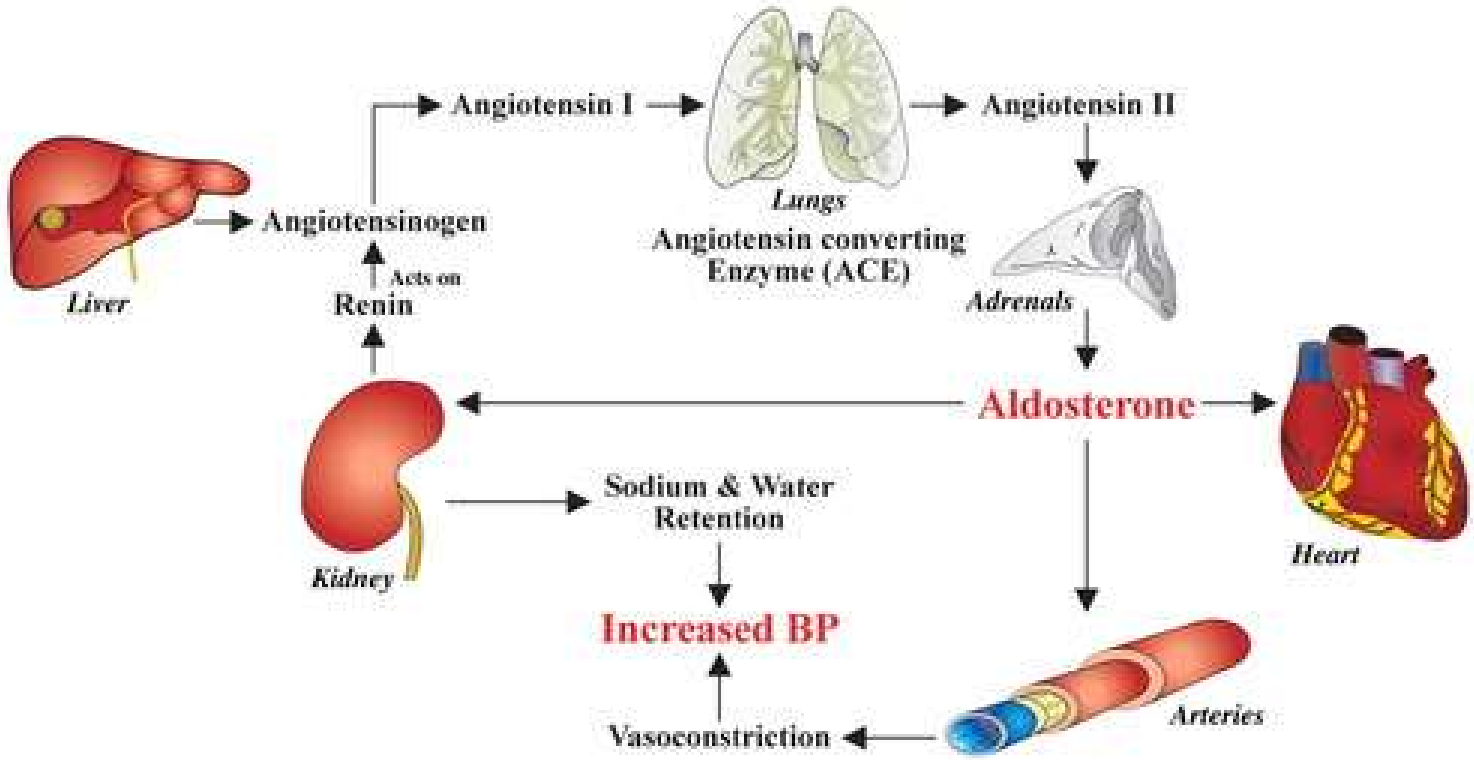
- tubular and vascular component
  - (1) tubular component
    - specialized area of the distal tubule near to afferent and efferent arteriole (macula densa)
    - cells of macula densa are sensitive to NaCl and control the production of **renin** in **juxtaglomerular cells (JG-cells)** – increase of tubular salinity -> increase in renin
  - (2) vascular component
    - afferent and efferent arterioles
    - extra-glomerular mesangium
- JG-cells (granular cells) are specialized smooth muscle cells that produce and store the renin
- the cells of macula densa do not have a basal membrane, which enables close contact with JG-cells.
- JG-cells also contain baroreceptors; when perfusion pression is lower, they start producing renin
- Both vascular and tubular components are innervated by the sympaticus



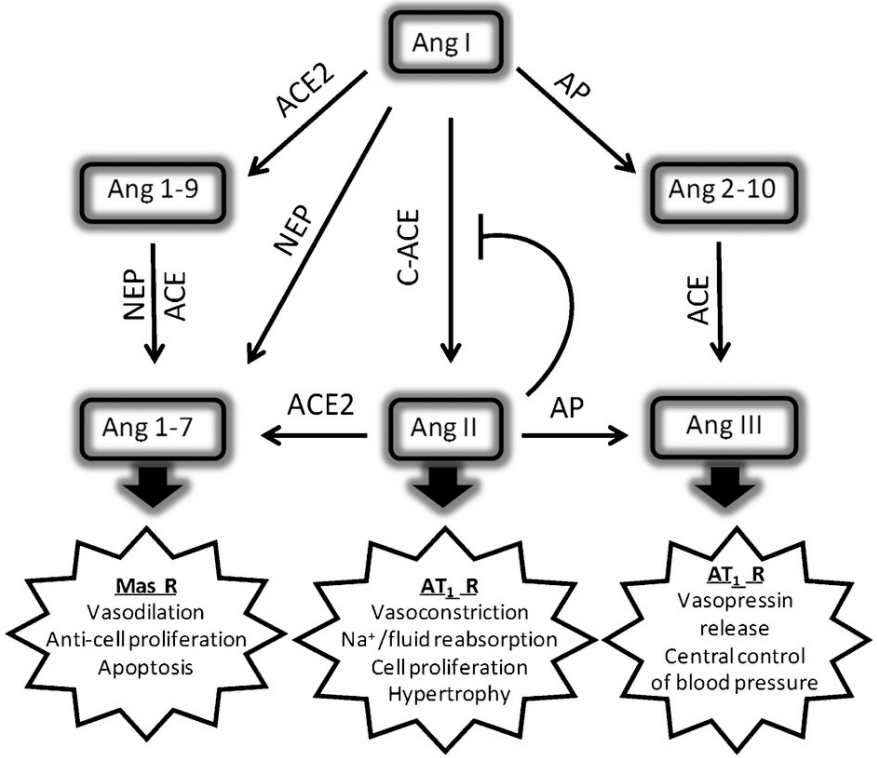
# Juxtaglomerular apparatus



# Renin-angiotensin-aldosterone

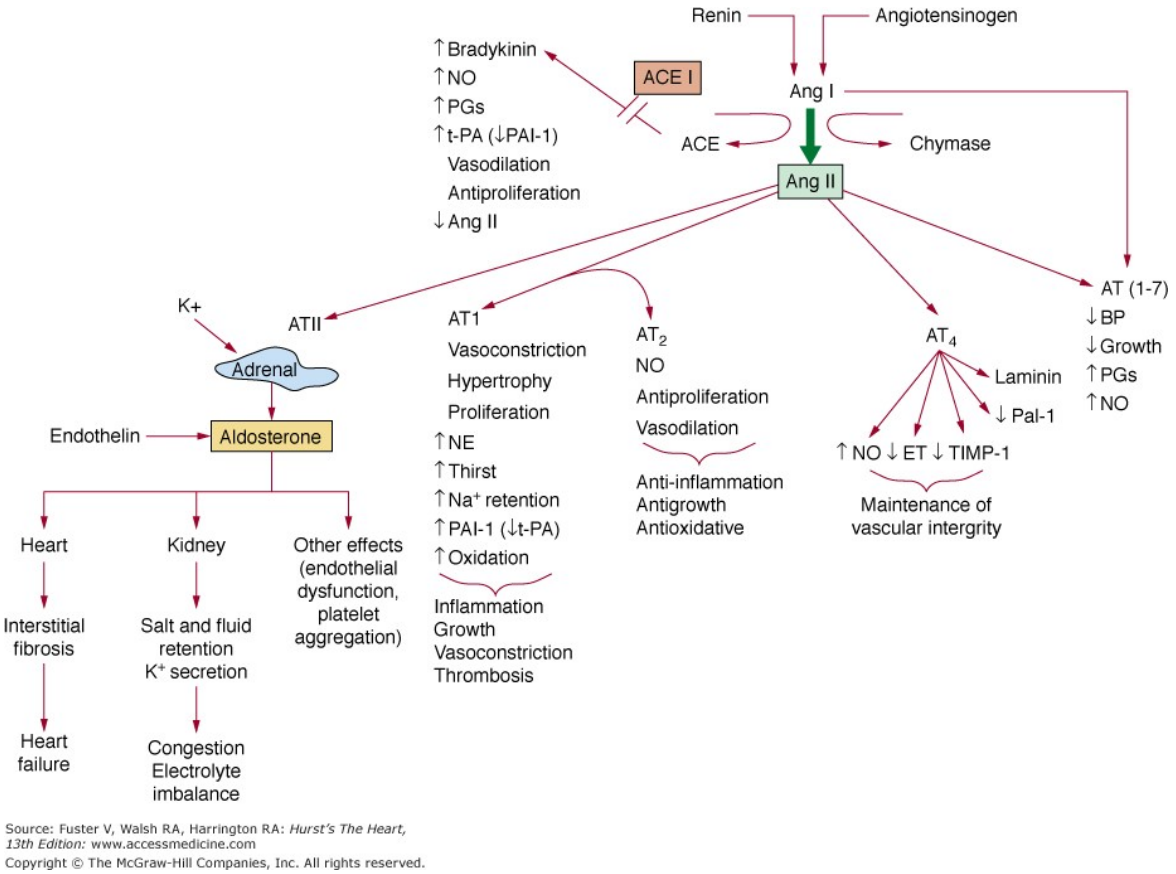


# ACE and ACE 2




- Angiotensin I (Ang I) can be then transformed into several products
- Through ACE action, Ang II and Ang III with vasoconstriction effects are formed
- ACE also degrades bradykinin (pharmacologic inhibition of ACE leads to angioedema)
- Through the action of ACE 2, angiotensin 1-7 is formed, having vasodilatation and antiproliferation effect on vessel wall (contributing to the decrease of peripheral resistance – Mas receptors

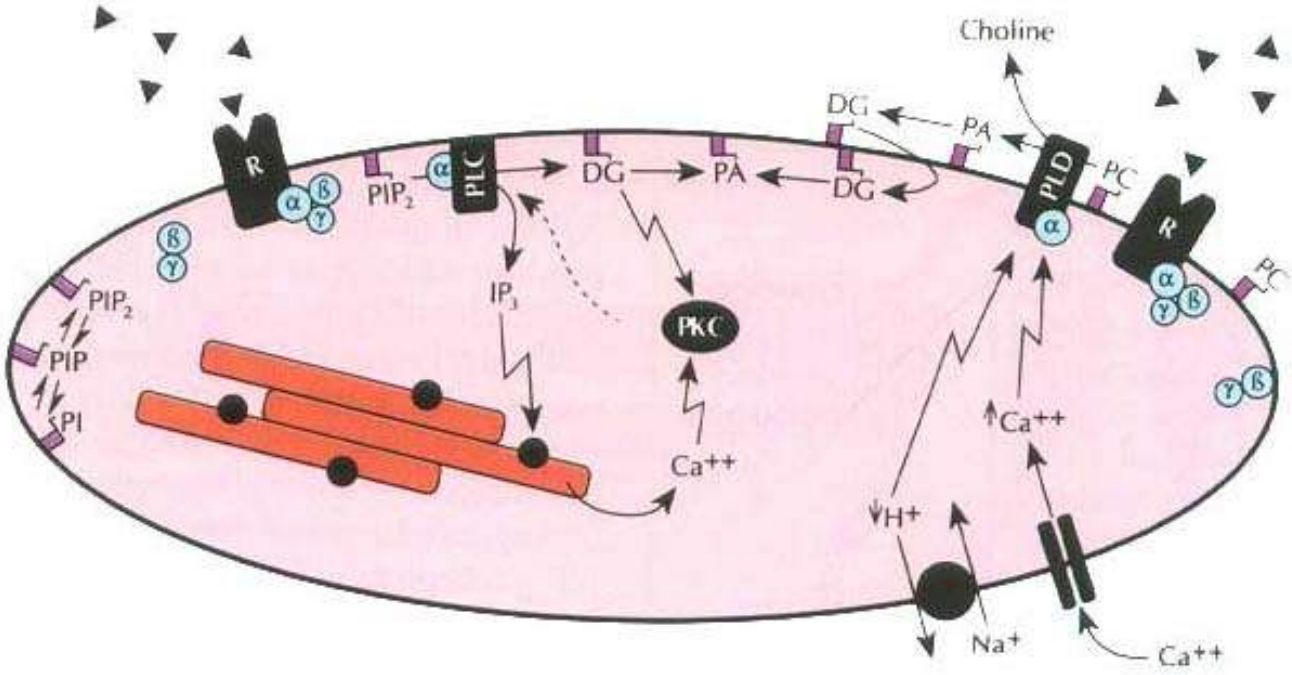
# angiotensin II receptors and systemic effects of aldosterone





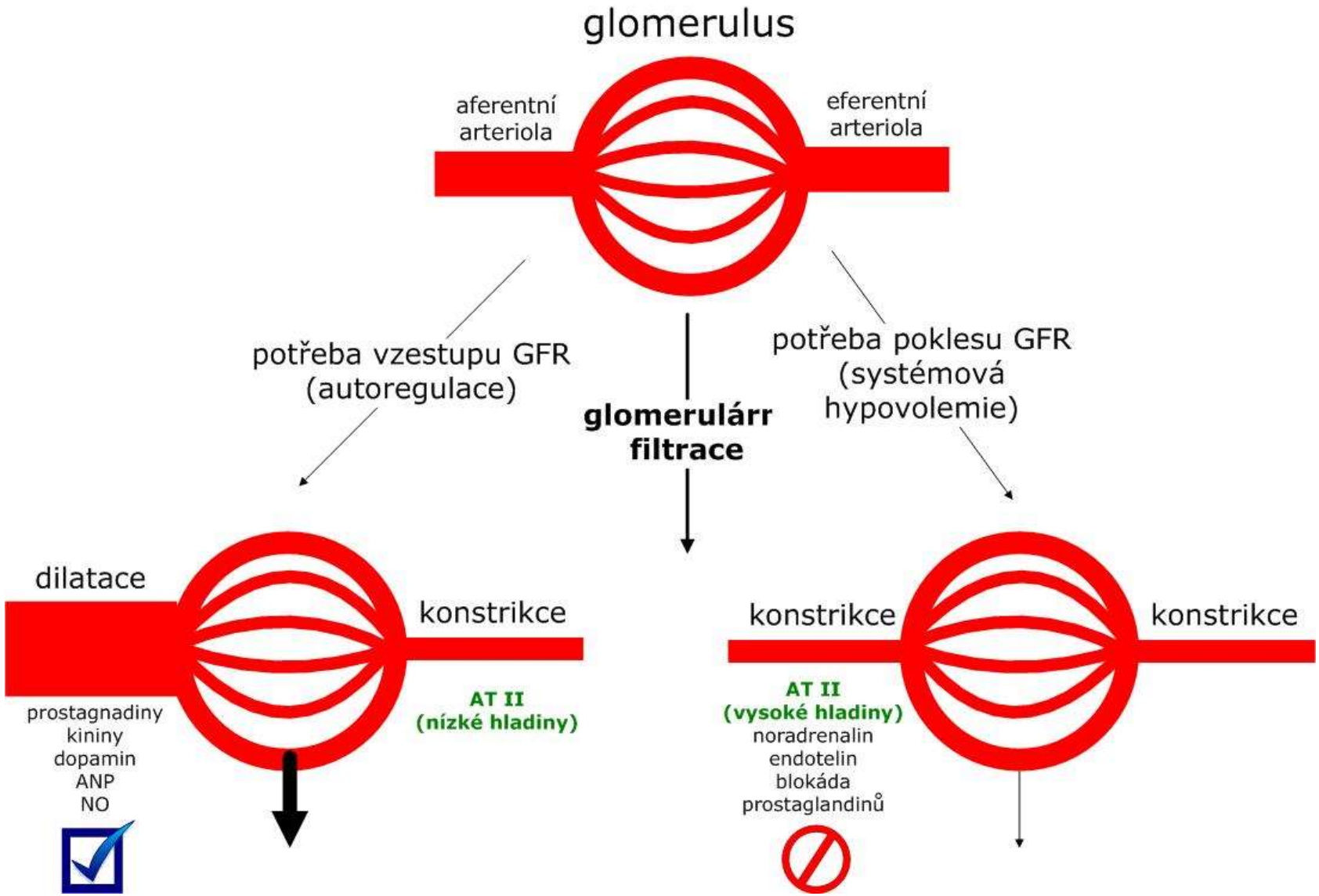
- AT 2 receptors are mostly involved in fetal development
- Ang III is mostly involved in aldosterone secretion and in the CNS

# Signal cascade AT II

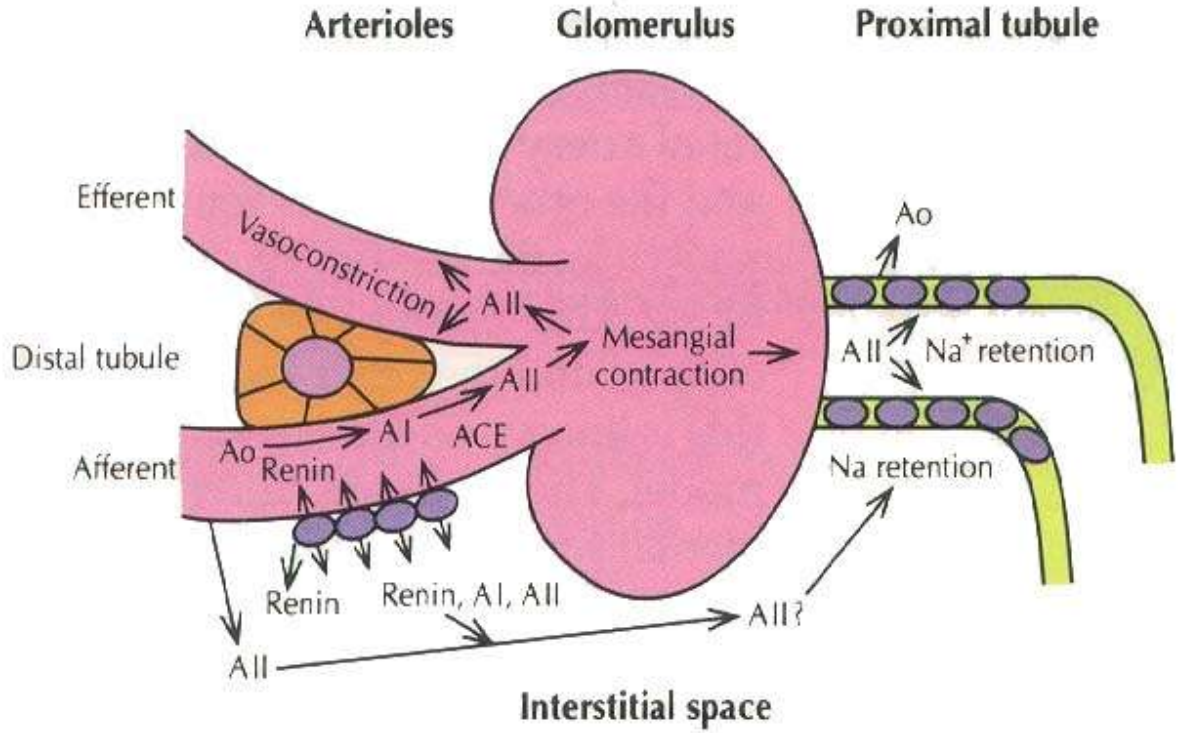



- AT II receptors use 2 secondary messengers:
  - activation of phospholipase C (PLC)
    - PIP2 is cleaved into IP3 (intracelular Ca mobilization) and DAG
    - DAG activates proteinkinase C (PKC), hydrolyses fosfatidylcholin through the activation of fosfolipase D (PLD) and alkalizes intracelular environment

# ATII effect on GFR is dose-dependent (biphasic response)

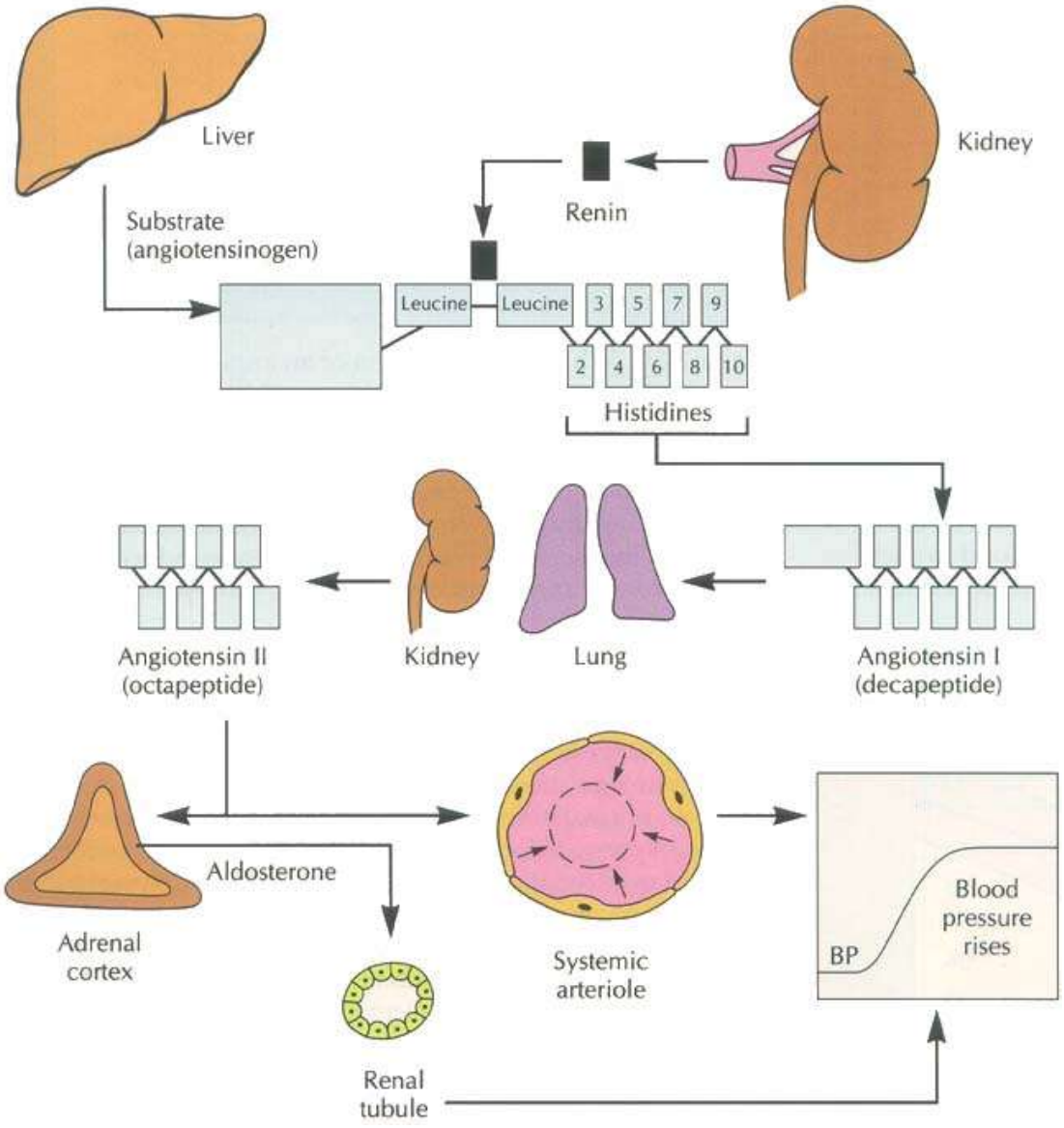


# Local RAAS - paracrine effects of AT II

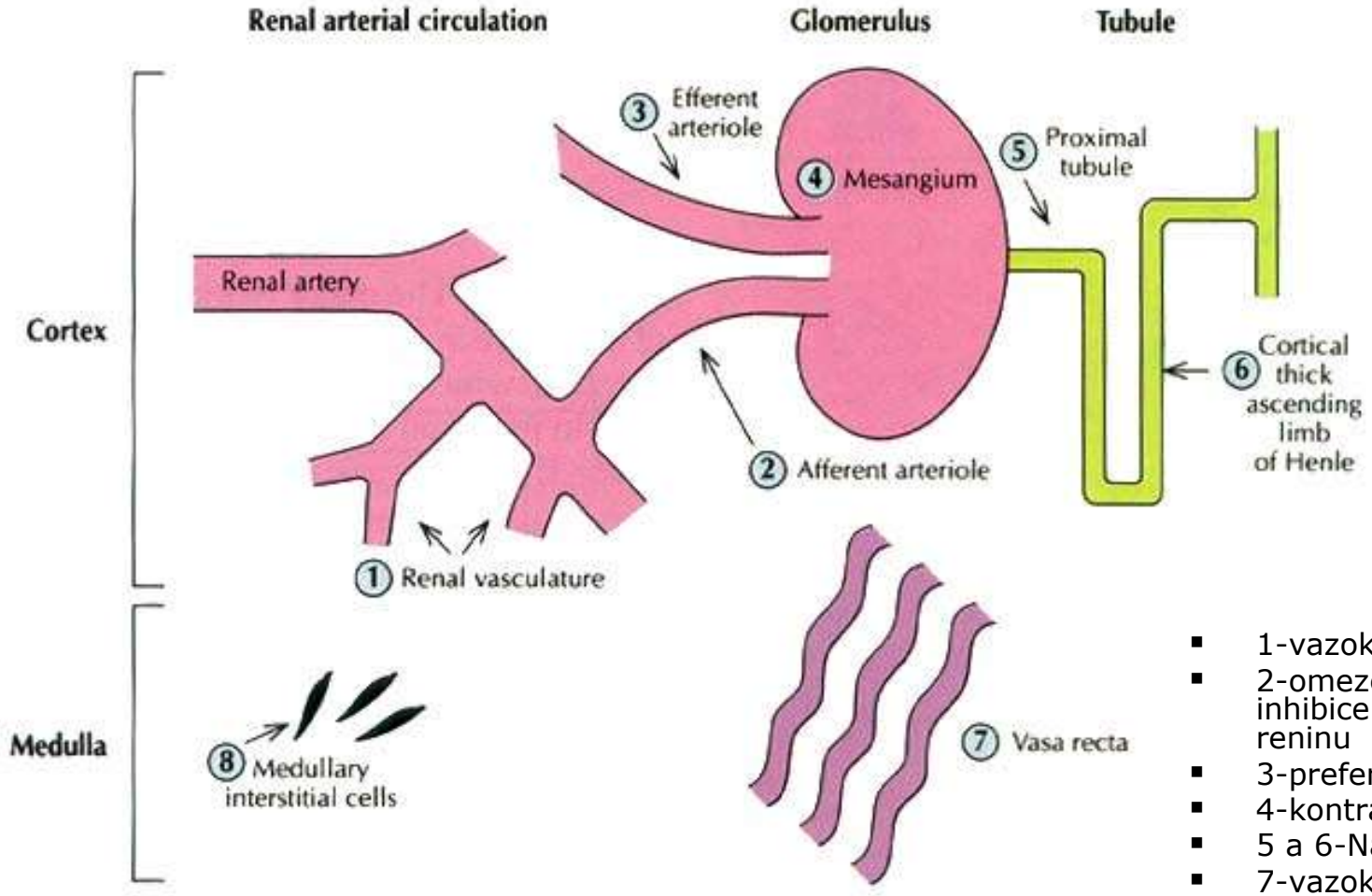



- angiotensinogen in the kidney is synthethized in the liver and locally in the kidney (proximal tubular cells)
  - renin is released from JG-cells to afferent arteriole and renal interstitium, where it converts circulating angiotensinogen into AT I, which is further converted into AT II through circulating ACE
  - parakrine effects
    - mesangial contraction
    - contraction of eferent arteriole
    - Sodium reabsorption in proximal tubule

# Systemic RAAS

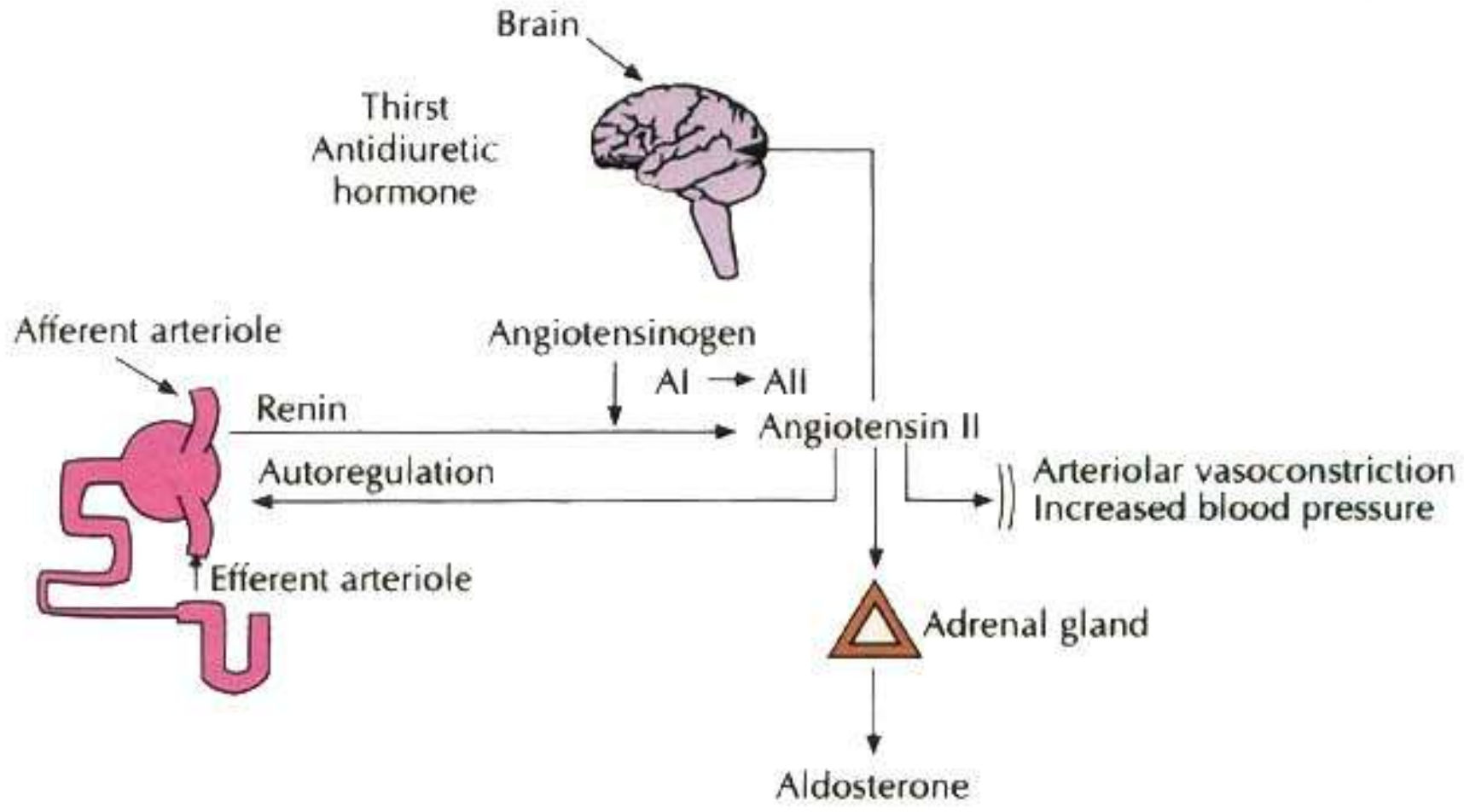


# Localization of AT II receptors and their main effects in the kidney

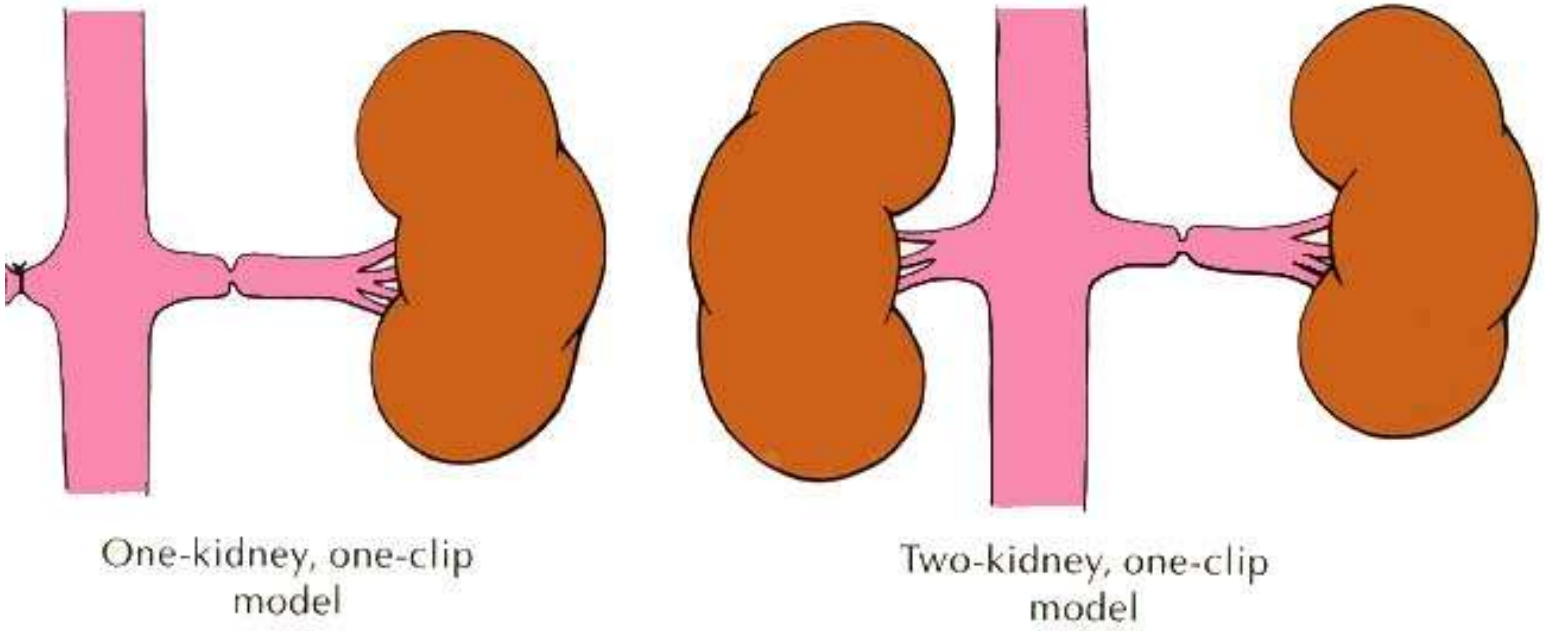



- 1-vazokonstrikce
- 2-omezeně vazokonstrikce a inhibice tvorby a uvolňování reninu
- 3-preferenční vazokonstrikce
- 4-kontrakce
- 5 a 6-$Na^+$ reabsorpce
- 7-vazokonstrikce
- 8 –efekt neznámý

# Systemic RAAS



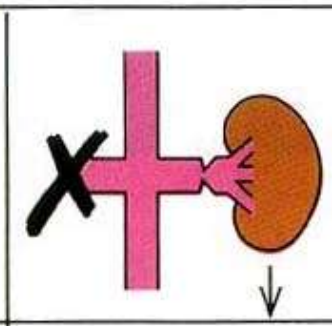
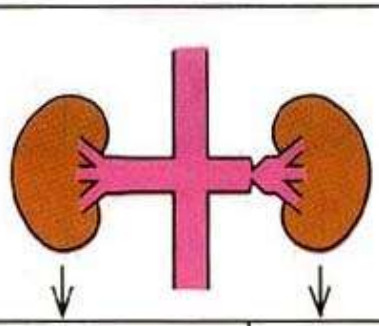
# Goldblatt's model of renovascular hypertension



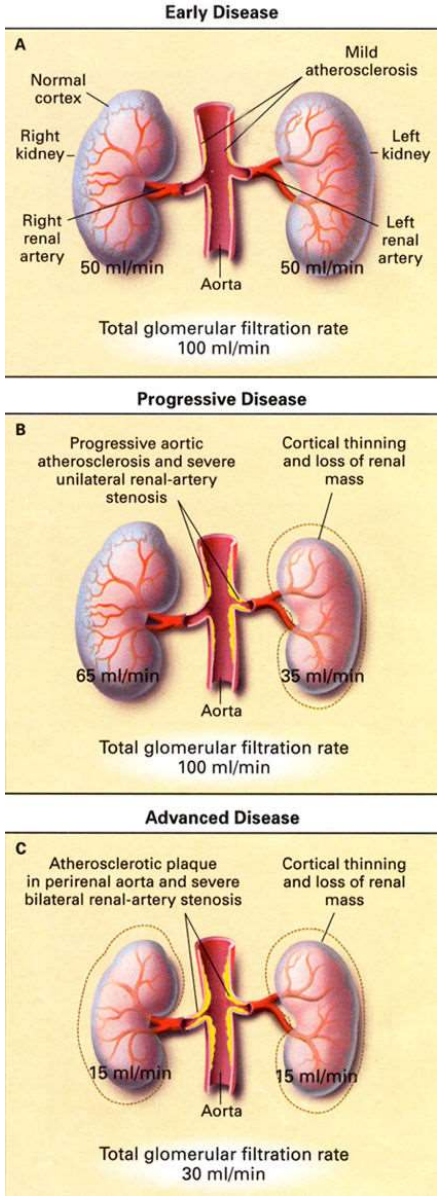

- 2 kidneys / 1 clip
  - hypertension (pressure effect of ATII), but maintained regulation of ECV and plasma composition (pressure natriuresis in the contralateral kidney)
- 1 kidney / 1 clip (=2 kidney / 2 clips)
  - hypertension (pressure effect of ATII, hypervolemia) + dysregulation of ECV and plasmatic composition
- 1 kidney / 0 clips
  - normal BP + regulation of ECV and composition

# Pathophysiology

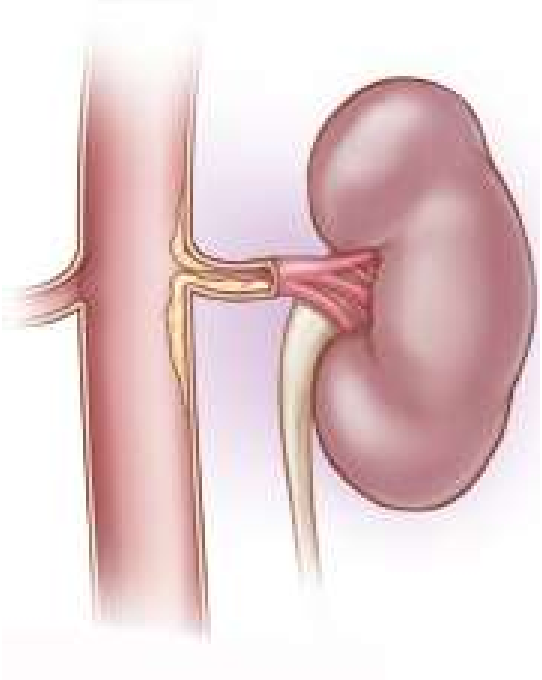
- While the hypertension is present in both cases (see the picture below), they differ in other parameters
  - in "1 kidneys/1 clip", the plasmatic level of renin is normal or lower and hypervolemia is present (renin dilution)
    - **Higher perfusion pressure of the kidney**
  - in "2 kidneys/1 clip", the plasmatic level of renin is high together with normal plasmatic volume (eventual volume expansion is compensated by the other kidney, but there is still the pressure effect of AT II)

| |  |  | |
|---|---|---|---|
| Renin content of kidney | No change | Decreases on contralateral side | Increases on stenotic side |
| Blood pressure | Significantly increases | Significantly increases | |
| Plasma renin activity | No change or decreases | Significantly increases | |
| Plasma volume | Increases | No change | |
| Blood pressure after block of angiotensin II | No change | Decreases | |

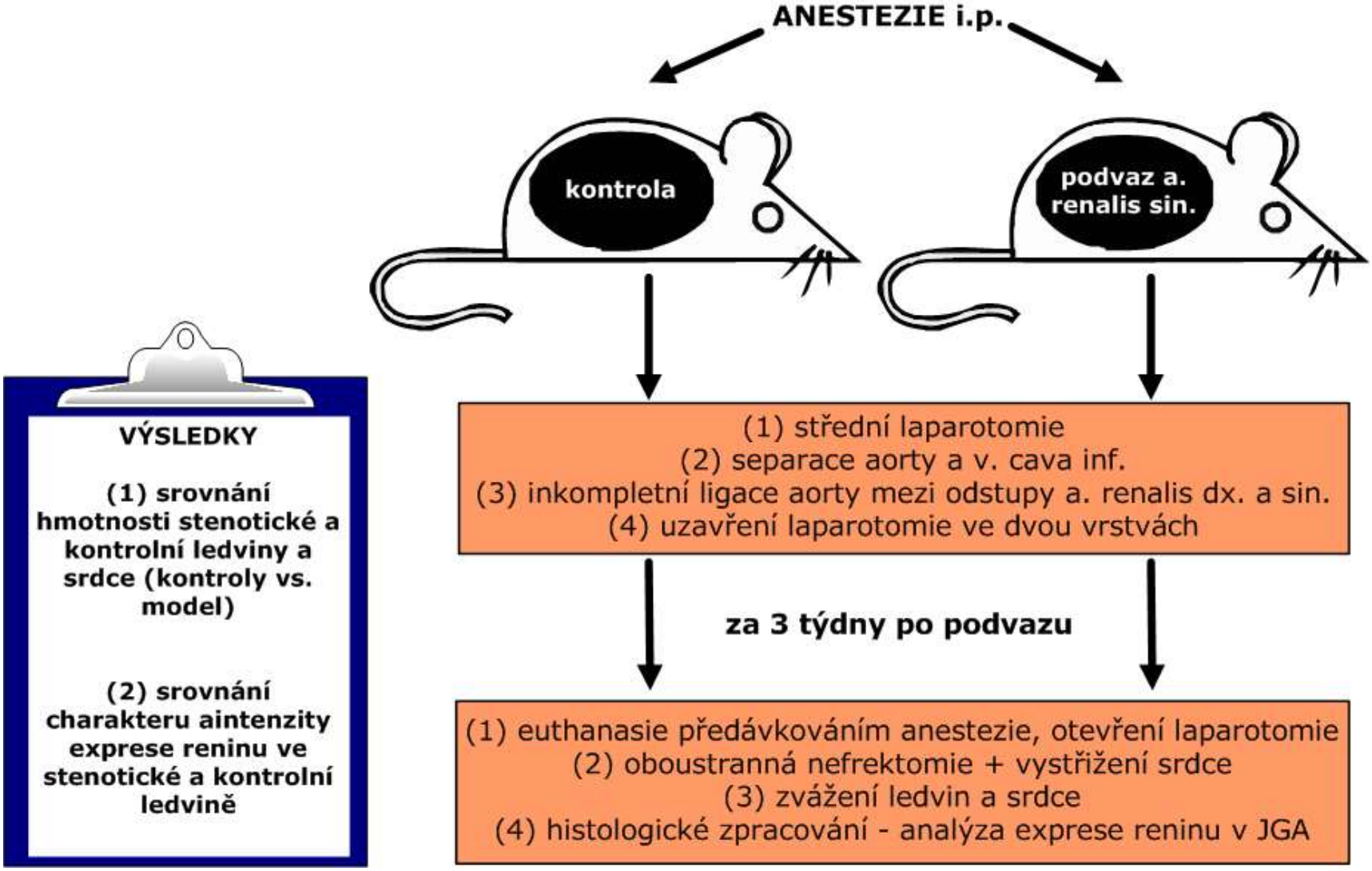
# Stenosis of the renal artery




- typical causes of renovascular hypertension:
  - atherosclerosis
    - Frequent, usually older people
    - Cca 30% of patients with other form of atherosclerosis have also atherosclerosis of renal artery (usually insignificant)
  - fibromuscular hyperplasia
    - younger women



# Practical


ANESTEZIE i.p.
kontrola
podvaz a. renalis sin.
(1) střední laparotomie
(2) separace aorty a v. cava inf.
(3) inkompletní ligace aorty mezi odstupy a. renalis dx. a sin.
(4) uzavření laparotomie ve dvou vrstvách
za 3 týdny po podvazu
(1) euthanasie předávkováním anestezie, otevření laparotomie
(2) oboustranná nefrektomie + vystřižení srdce
(3) zvážení ledvin a srdce
(4) histologické zpracování - analýza exprese reninu v JGA
VÝSLEDKY
(1) srovnání hmotnosti stenotické a kontrolní ledviny a srdce (kontroly vs. model)
(2) srovnání charakteru aintenzity exprese reninu ve stenotické a kontrolní ledvině

# Practical – operation