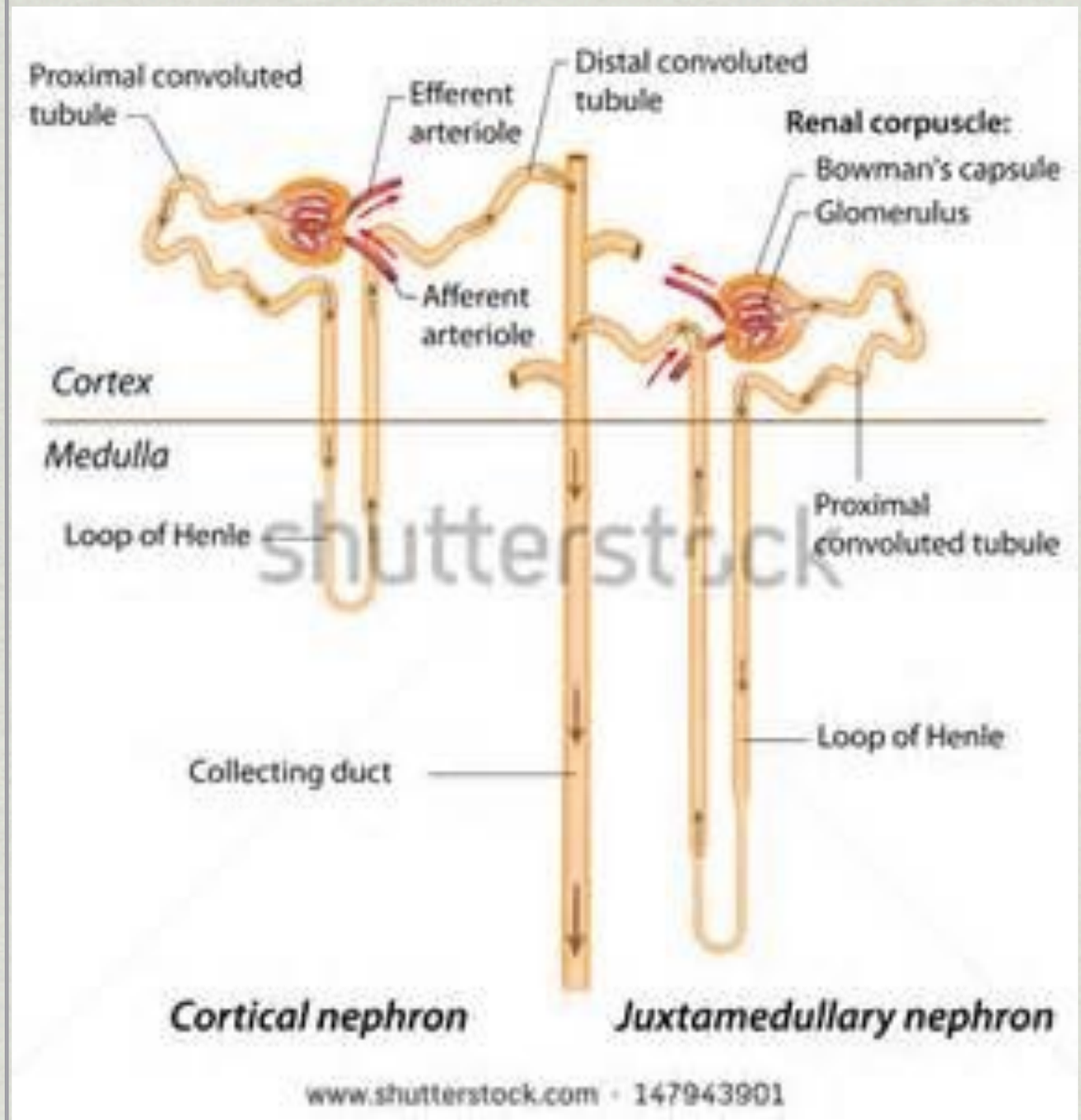
Renal Basics

Short Notes

Renal basics

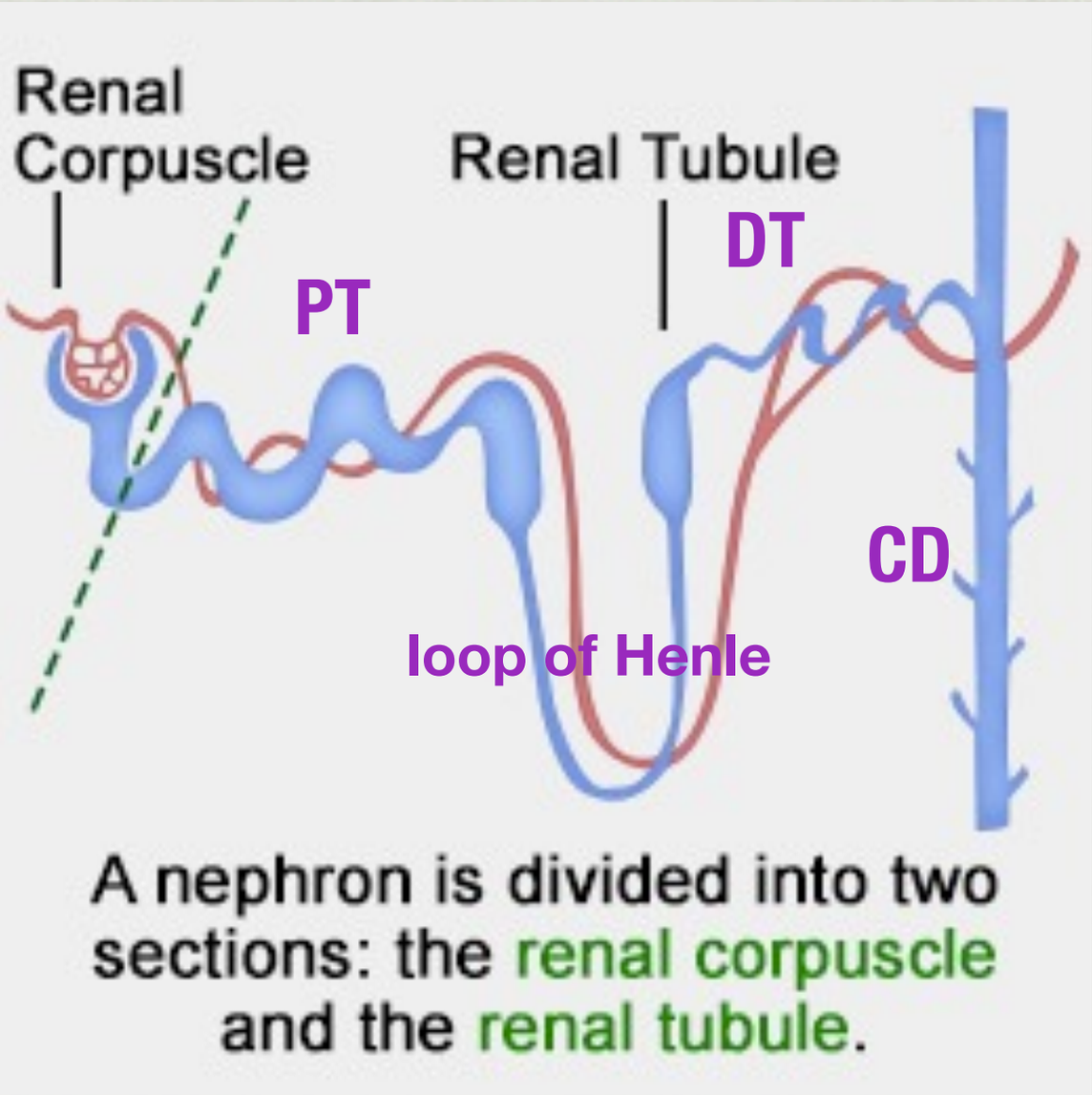
- Nephron: structure, function, cortical vs juxtamedullary
- Filtration membrane: electron microscopy view
- Estimating renal function: GFR,Clearance, RPF, RBF, FF, FE, FR
- Juxtaglomerular apparatus
- Renin-Angiotensin-Aldosterone System (RAAS) regulation
- RAA synthesis
- Angiotensin II function
- New paradigms in RAAS
- ACEIs and ARBs
- ACEIs and bradykinin
- Renal prostaglandins
- NSAIDs and renal function
- NSAIDs and ACEIs/ARBs and renal function
- Aldosterone regulation

Nephron: cortical vs juxtamedullary



- Nephron (from Greek nephros=kidney) is the smallest functional unit of the kidney.
- Function: regulate the concentration of water and Na salts (and other) by filtering the blood, reabsorbing what is needed and excreting the rest in the urine. Thus regulates: BP, blood volume, controls levels of electrolytes and metabolites and regulates blood pH.
- normal kidneys contain 800K-1.5mil.nephrons
- There are 2 types of nephrons: cortical (most of them) and juxtamedullary. Both have corpuscles in the renal cortex and tubules in medulla but juxtamedullary run deep in medulla and have a main role in urine concentration.

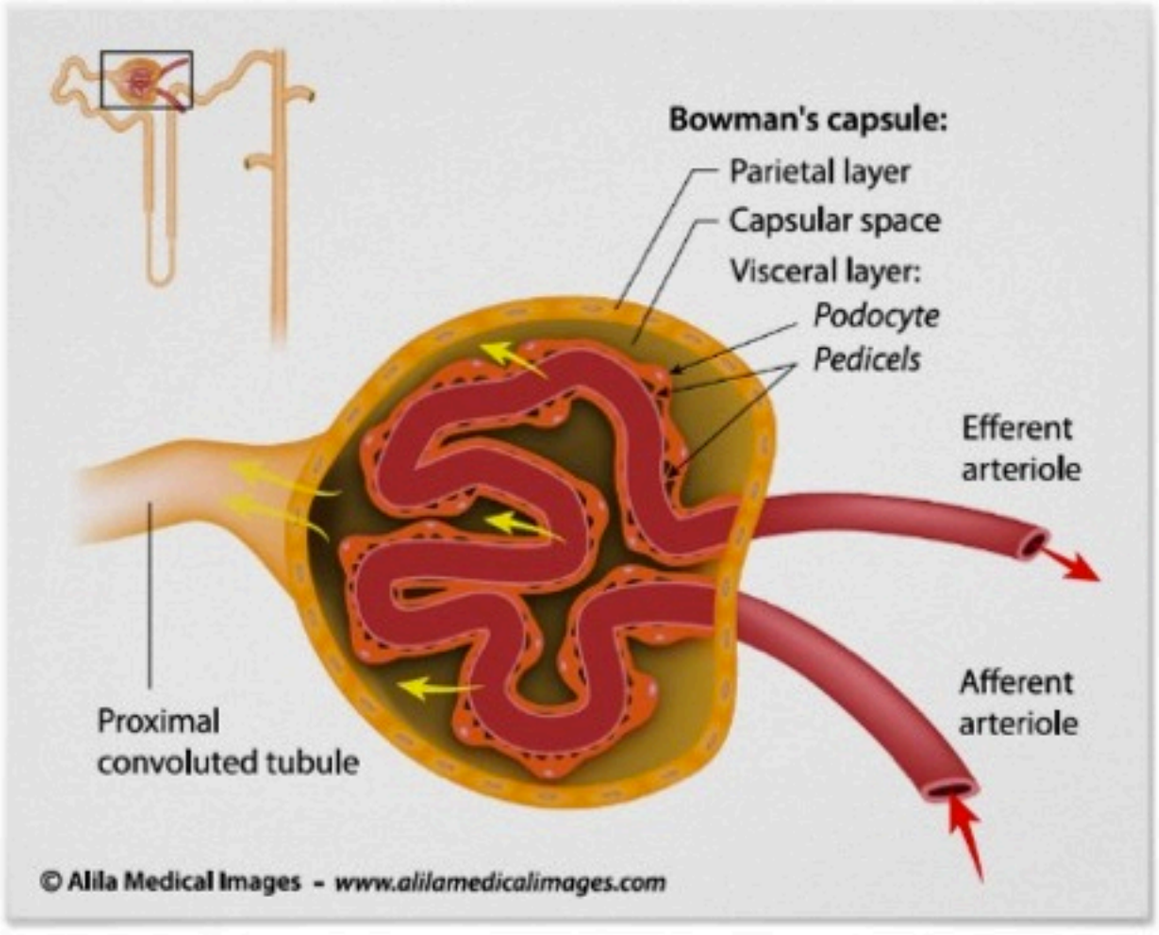
Nephron anatomy



A nephron is divided into two sections: the renal corpuscle and the renal tubule.

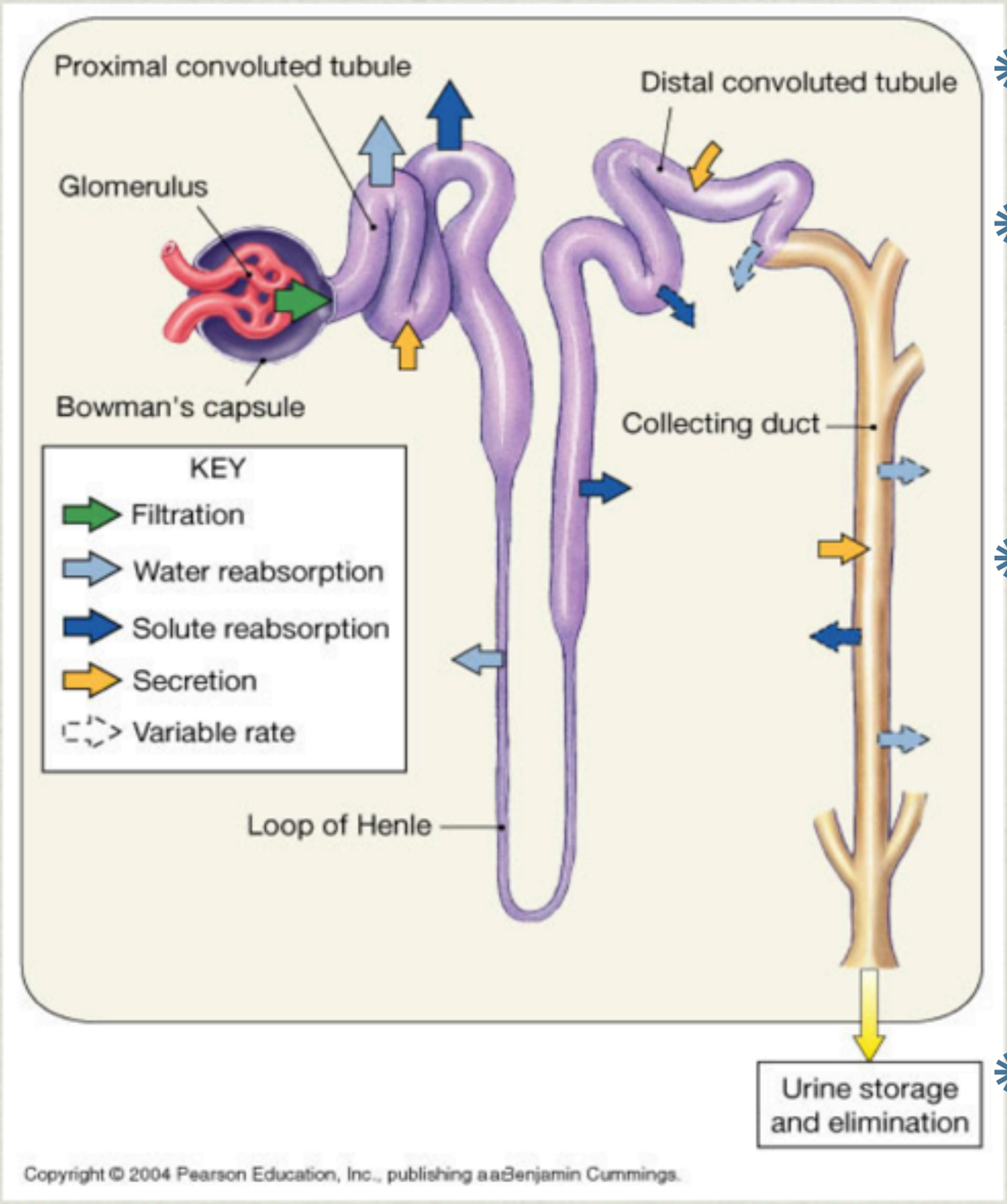
- **Renal corpuscle:**
  - Bowman capsule
  - glomerulus
- **Renal tubule:**
  - proximal PT
  - loop of Henle with 2 limbs: thin and thick ascending
  - distal DT
  - collecting duct CD

Renal corpuscle anatomy



Bowman's capsule:	1, 2 and 3
1.Parietal layer	epithelial cells continue on PT
2.Capsular space	btw 1 and 3
3.Visceral layer (podocytes)	epithelial cells with foot processes (pedicels)
Glomerulus	endothelial capillary fenestrated cells
Arterioles aff.& eff.	in & out capsule
Renin releasing (JG cells)	modified muscular cells on aff. art.
Macula densa	cells on DT sensitive to Na conc.

Nephron physiology



- **Main nephron functions:**
- **Renal corpuscle: Filtration of plasma through filtration membrane**
- **Renal tubule: Reabsorption* from tubule in interstitium->blood Secretion (excretion)* from interstitium into the tubule**
- **Final product: urine**

***of water and solutes**

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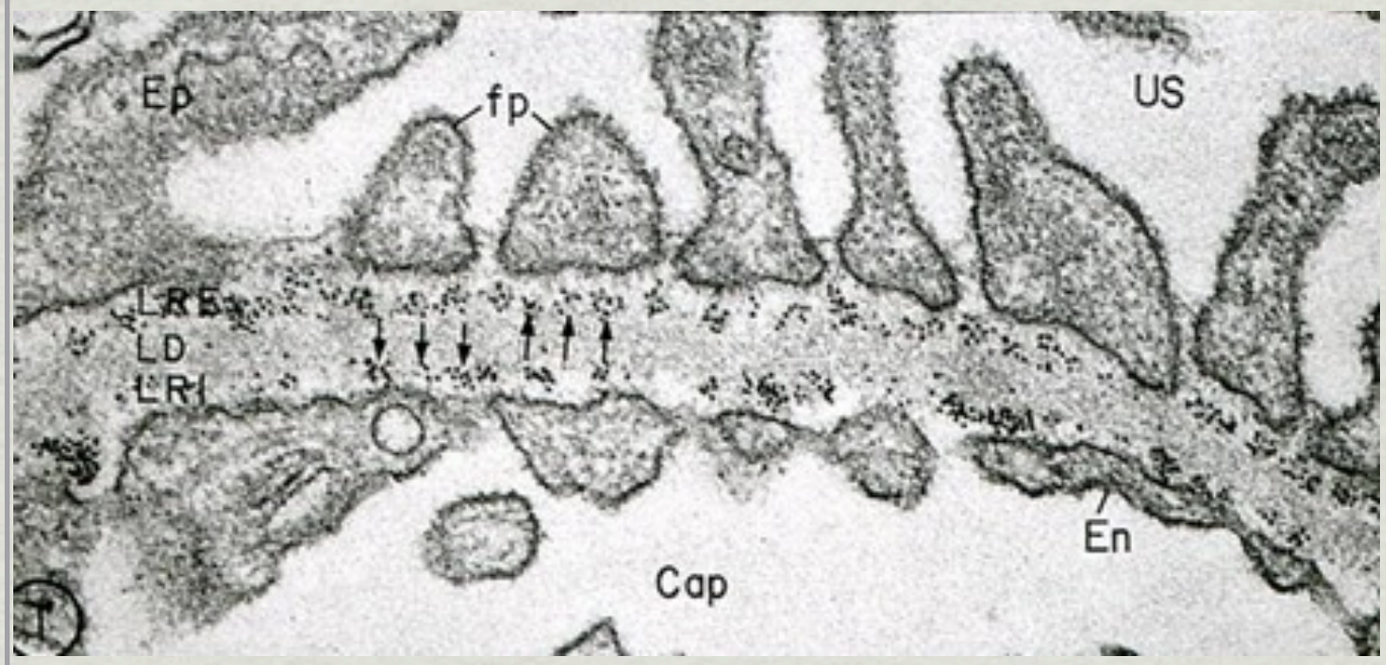
EM view of filtration membrane

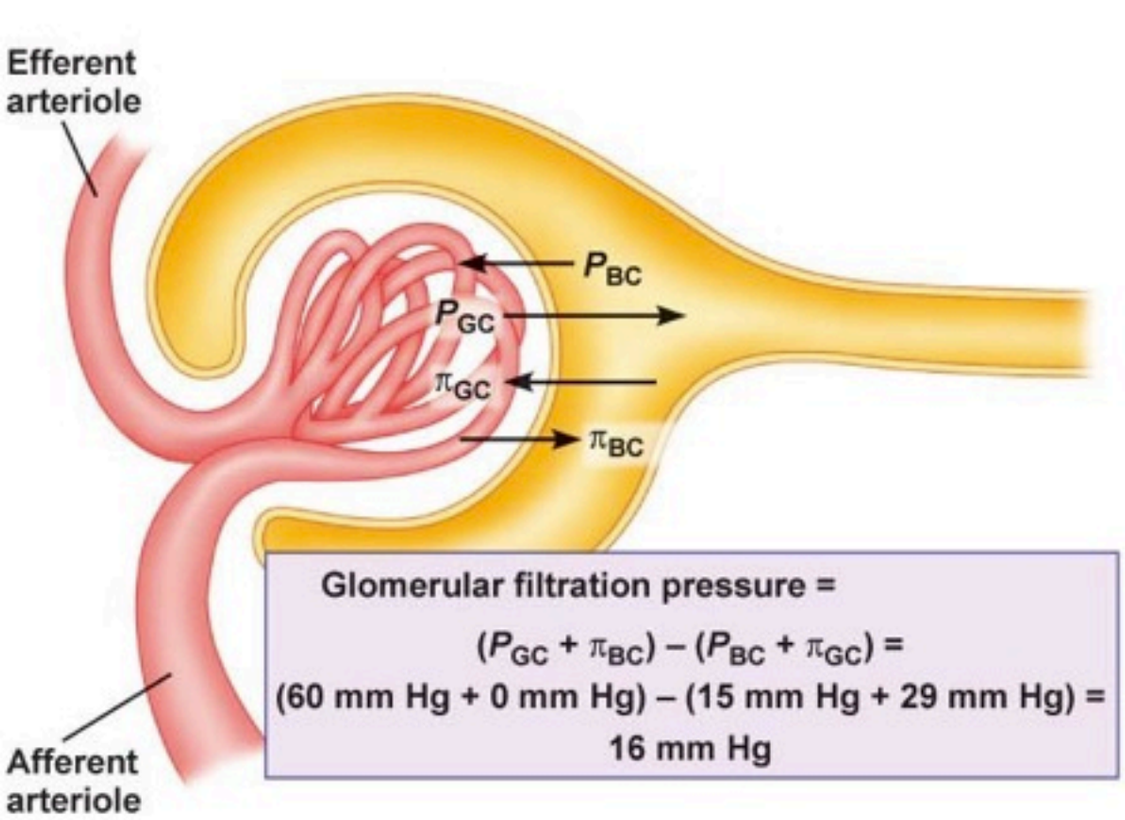


- **Filtration membrane:**
- **epithelial cells (podocytes) with foot processes (fp, pedicels) and slits (spaces btw fp)**
- **endothelial (En) fenestrated capillary cells**
- **fused basal membrane (from epithelial and endothelial cells)**

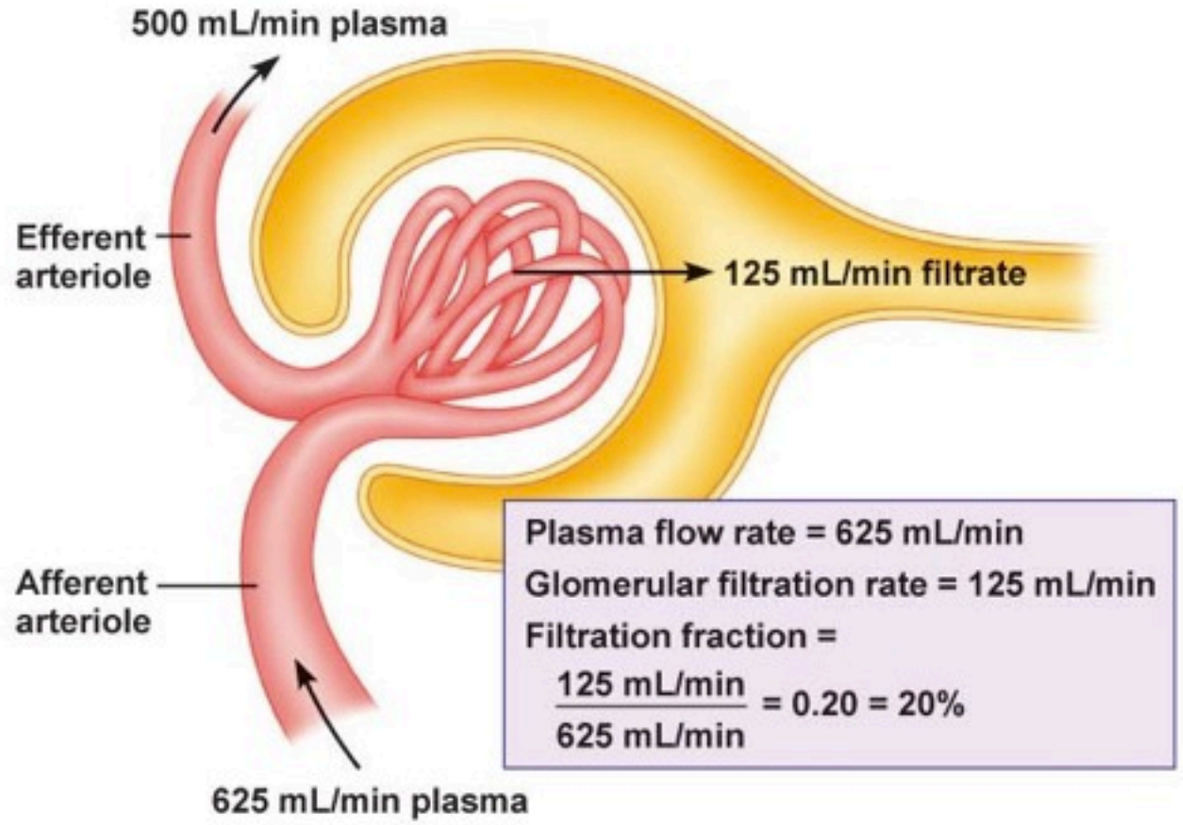
Estimating renal function

- GFR=total amount of plasma filtered at the glomerulus.This is a special clearance of a substance that is just filtered.
- Clearance= the volume of plasma cleared of a substance per min due to either filtration or secretion
- RPF=amount of plasma that flows through the kidneys per unit of time
- In practice, RPF is difficult to calculate. Instead it is estimated from ERPF which is calculated from Cl PAH which is mainly secreted (80%)
- RBF=measure of blood (plasma+RBC) that passes through kidneys per unit of time
- Filtered Fraction FF=ratio of plasma filtered to renal plasma flow. FF=GFR/RPF
- Fractional Excretion=the fraction of a substance that is filtered and excreted in the urine.
- Fractional Reabsorption=the fraction of a substance that was reabsorbed after filtration.

GFP, GFR, RPF and FF



(a) Glomerular filtration pressure



(b) Glomerular filtration rate and filtration fraction

- The Starling equation above illustrates the role of hydrostatic and oncotic forces (Starling forces) in the movement of fluids across the capillary membranes.
- Fluids movement across membrane other than capillary membrane is due to difference in tonicity (effective osmotic pressure- see plasma osmolality)
- GF pressure ↑ when aff.art. dilates or eff.art.constricts
- GF pressure ↓ when aff.art. constricts or eff. art. dilates

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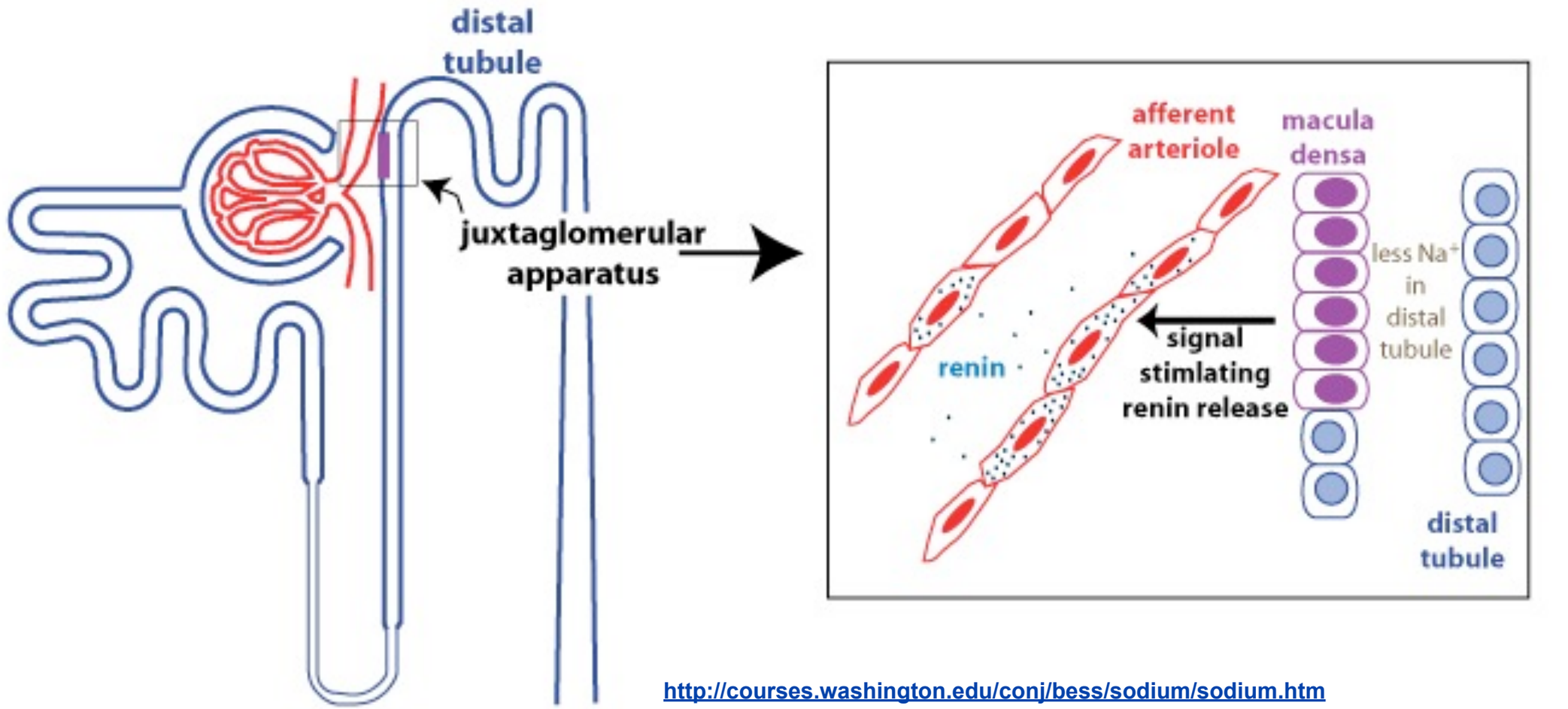
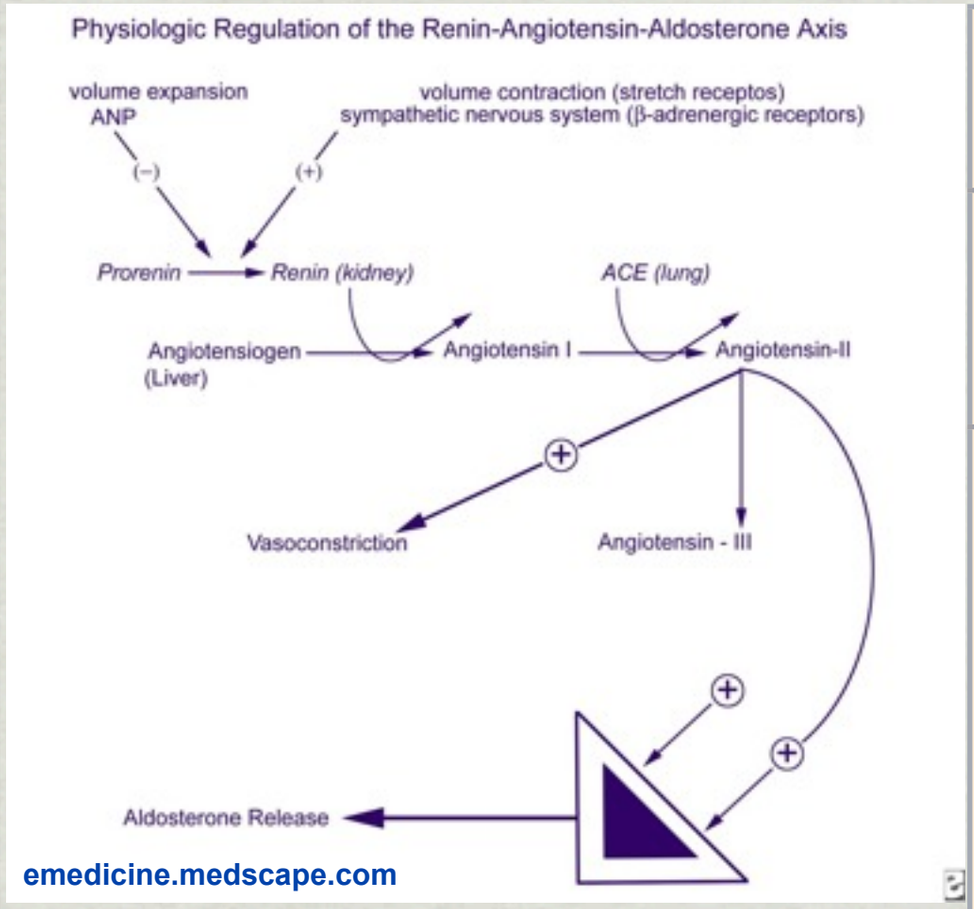
Juxtaglomerular apparatus

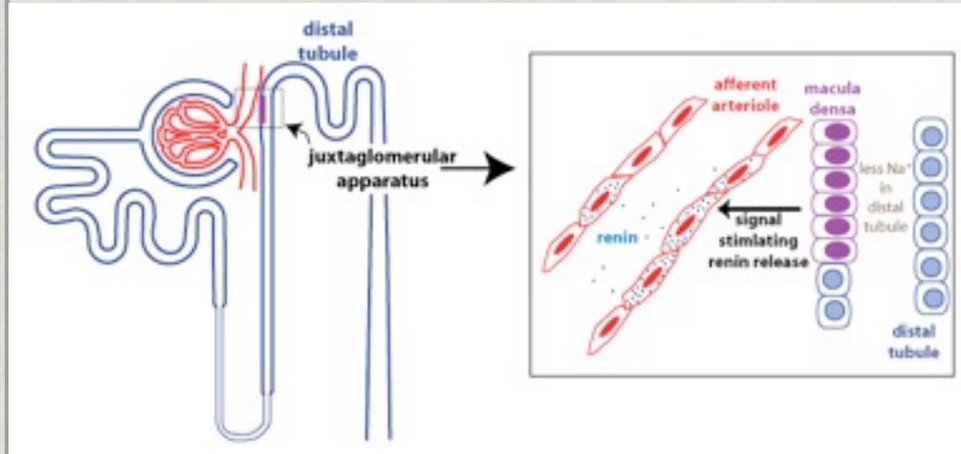


http://courses.washington.edu/conj/bess/sodium/sodium.htm

Juxtaglomerular apparatus	**1.JG cells**	cells on afferent arteriole produce RENIN (Renin-Angiotensin-Aldosterone system RAAS)
	2.Macula densa	cells on DT (next to JG cells) detect ↓ Na and stimulates renin release through prostaglandins
	3.Extraglomerular mesangial cells	cells btw afferent and efferent arterioles unknown significance. renin also found here

RAAS regulation



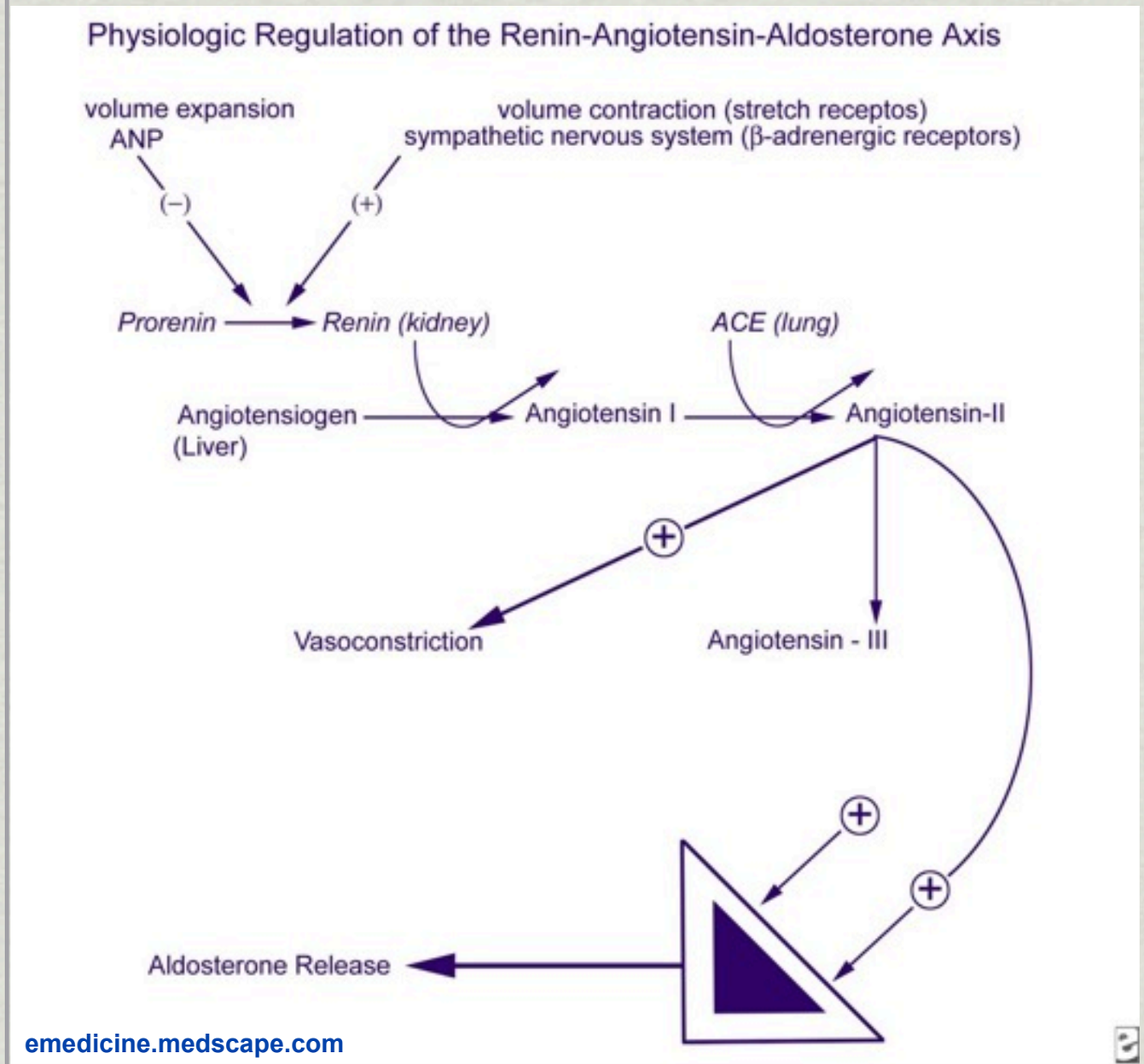


http://courses.washington.edu/conj/bess/sodium/sodium.htm

RAAS function	regulates blood volume -> cardiac output (CO) regulates systemic vascular resistance-> MAP
RAAS structure	the system has 3 important components: Renin Angiotensin Aldosterone
RAAS stimulation (Renin release)	1.SYMPATHETIC stimulation via beta1 receptors located on JG cells (↑intracellular Ca-> renin release)
	2. ↓ PRESSURE IN AFFERENT ARTERIOLE (due to ↓ pressure in systemic circulation or renal artery stenosis)
	3. ↓Na sensed by MACULA DENSA in DT (could be related to↓ pressure in afferent art.-> ↓GFR-> ↓Na in DT -> stim. PG E2 & I2 produce renin release
RAAS inhibition	1. ↑ PRESSURE IN AFFERENT ARTERIOLE 2. NATRIURETIC PEPTIDES (ANP&BNP) 3. ↑ in Na sensed by MACULA DENSA

http://cvphysiology.com/Blood%20Pressure/BP015.htm

RAA synthesis



- When renin is released into the blood it acts upon a circulating substrate angiotensinogen, a proenzyme produced in the liver that undergoes proteolytic cleavage to form angiotensin I, a decapeptide, which is then converted into an octapeptide, angiotensin II by angiotensin-converting enzyme (ACE) formed in the vascular endothelium particular in the lungs. Many other tissues in the body (heart, brain, vascular) can also form AII.
- Angiotensin II is metabolized to angiotensin III, a heptapeptide which is also a stimulator (as Angiotensin II) of aldosterone secretion.

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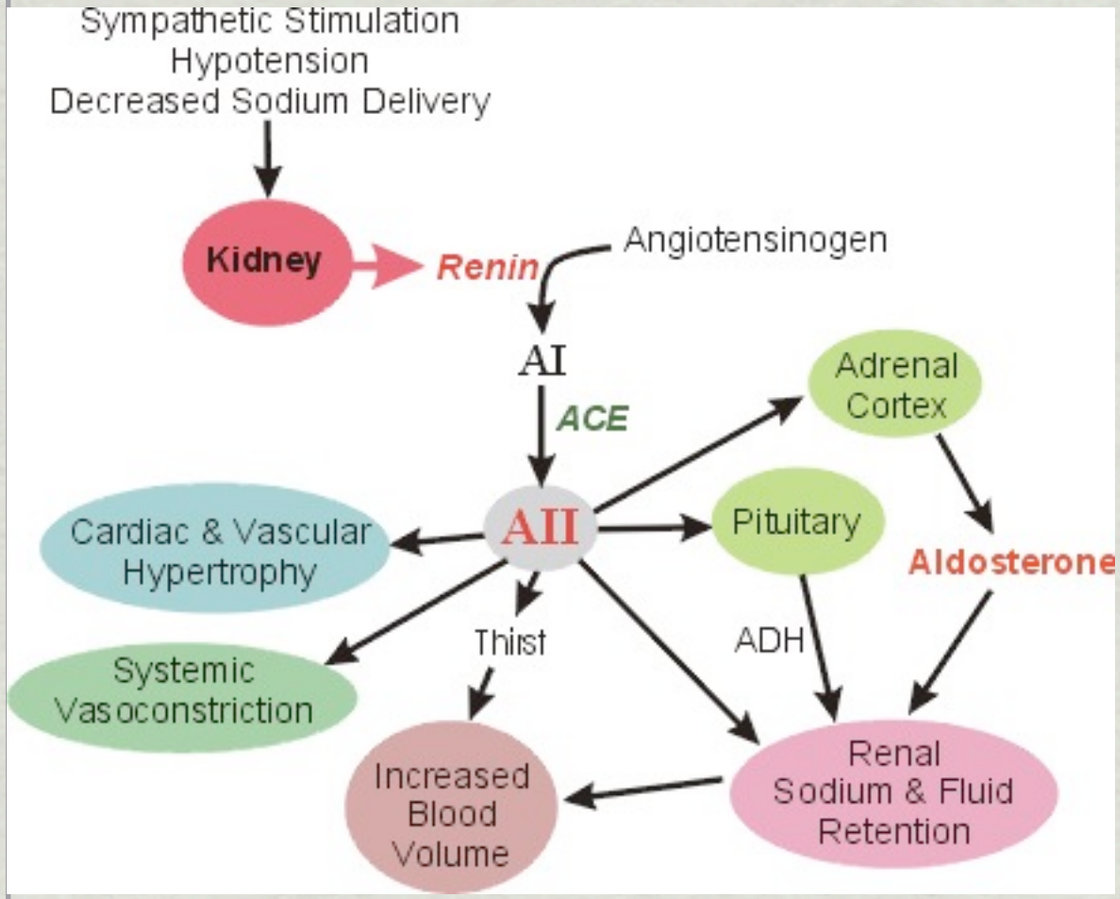
Angiotensin II functions via AT1 receptors



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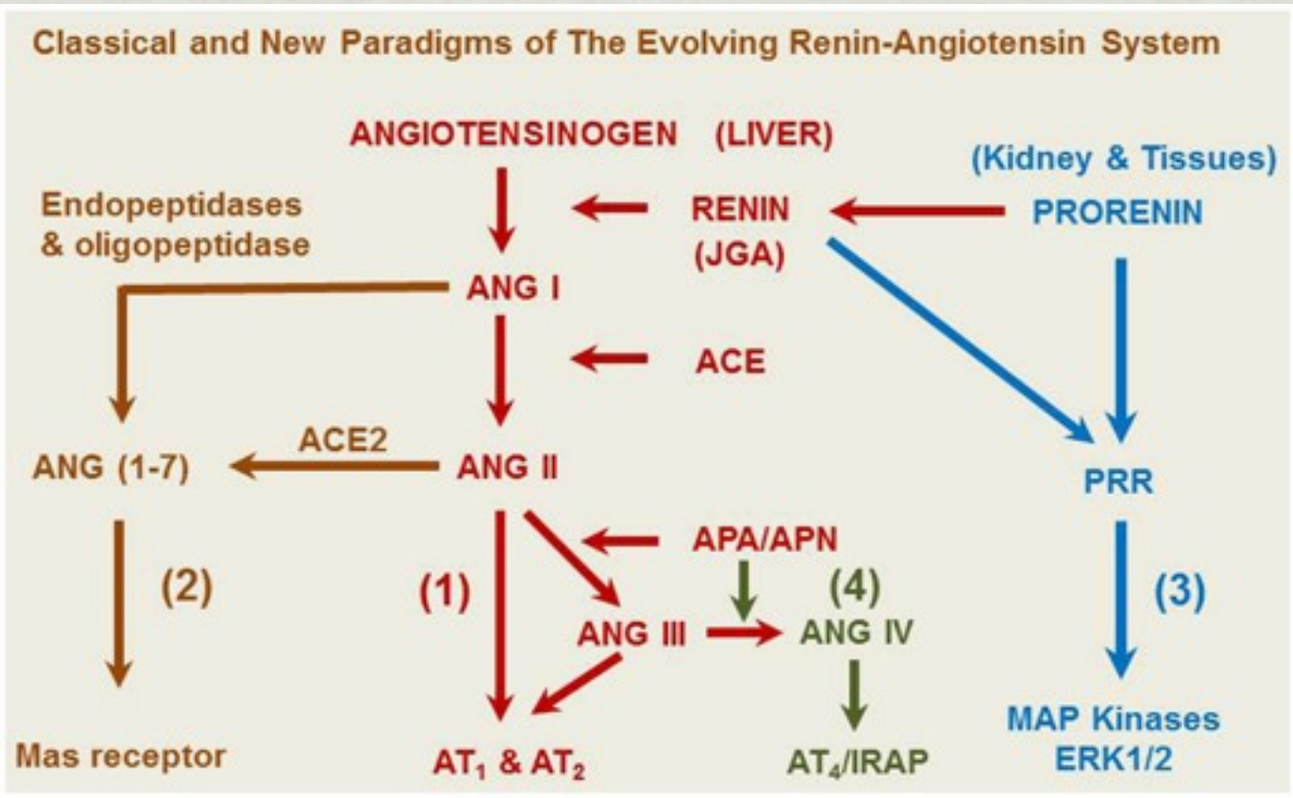
cardio-vascular	arteriolar and venous constriction via AT1 receptors-> ↑SVR and ↑MAP Renal: efferent art constriction >>> afferent art.
	cardiac (ventricular) hypertrophy &remodeling vascular hypertrophy
↑Na reabsorbtion	acts on adrenal cortex to release ALDOSTERONE -> ↑Na reabsorption
	stimulate Na reabsorption on several renal tubular sites
↑water retention	stimulate the release of ADH from posterior pituitary -> ↑water retention
	stimulate the thirst center in hypothalamus
↑sympathetic function	increase norepinephrine release from terminal endings and inhibits NE re-uptake

http://cvphysiology.com/Blood%20Pressure/BP015.htm

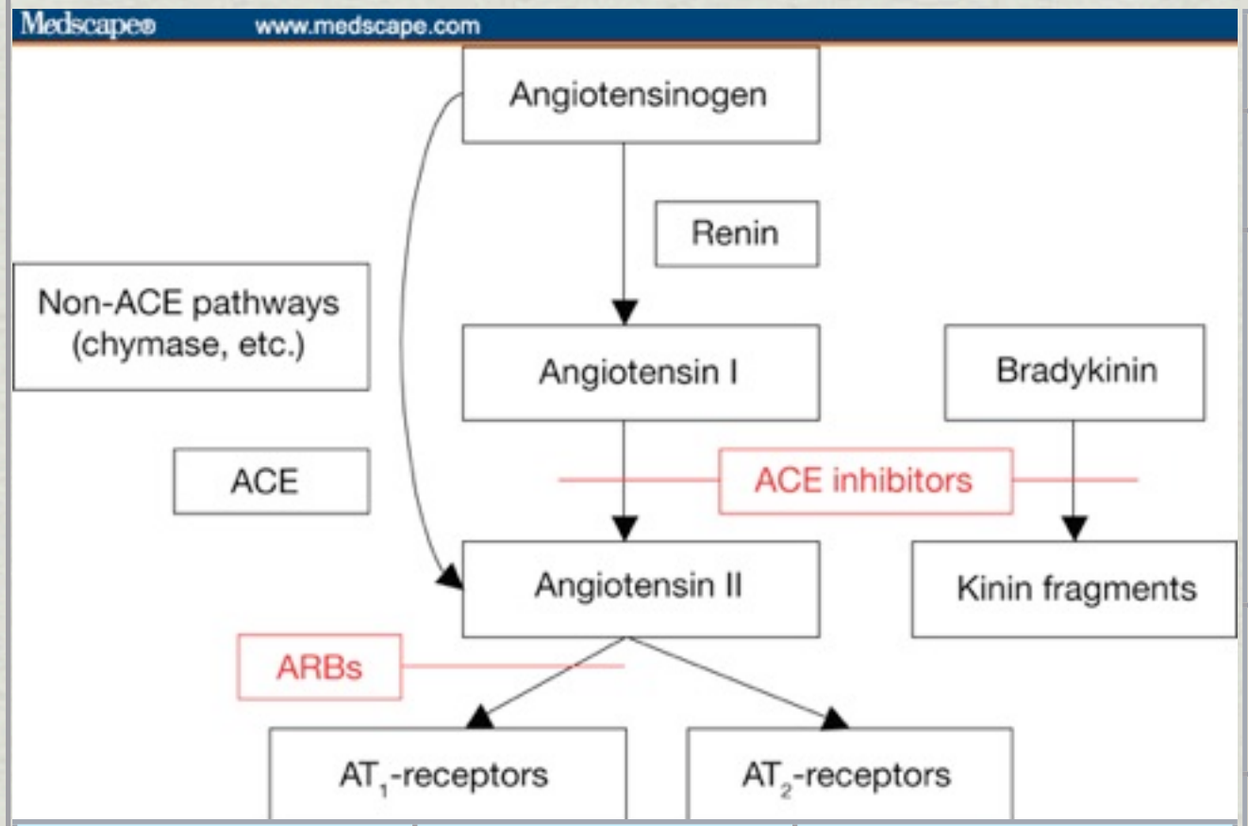
New paradigms in RAS



http://journal.frontiersin.org/article/10.3389/fendo.2013.00166/full

- Tigerstedt and Bergman discovered renin more than 115 years ago.
- Since then, our understanding evolved from the recognition of Renin/ACE/ANGII/AT1 and AT2 receptors as the exclusive pathway within the RAS for regulating BP and blood volume to the recognition of 3 new pathways (2,3,4 on the pic)
- ANG II can be hydrolyzed by various angiotensinases, ACE2 and neprilysin, to generate ANG (1-7), ANG III and ANG IV.
- appropriate concentrations of ANG (1-7), ANG III and ANG IV may activate their respective Mas receptors, AT2 receptors or AT4 receptors to oppose the known effects of ANG II.
- Conversely, high concentrations of ANG (1-7), ANG III and ANG IV may activate AT1 receptors to induce the effect of ANG II.
- the renin/ prorenin receptor PRR not only generates ANG II but also induces intracellular responses independent of ANG II (3)
- Finally, the RAS is no longer considered to act as an endocrine system but also as a paracrine, autocrine and intracrine system. It is likely that ANG II and its smaller peptides may both act as an endocrine, paracrine and intracrine peptides stimulating cell surface, cytoplasmatic and nuclear receptors to exert biological, physiological and nuclear effects.

ACEIs and ARBs



	ACEIs	ARBs
action	inhibit ACE	block AT1 receptor
cardivascular	**Vasodilator: ↓afterload &preload** by blocking arteriolar and venous constriction produced by ANG II **Inhibit cardiac &vascular remodeling** associated w/ HTN, CHF and MI	
↓sympathetic activity	by blocking the facilitating effects of ANG II on release and reuptake of norepinephrine	
↓blood volume	**natriuretic and diuretic** by blocking the effects of ANG II in the kidney and on Aldosterone secretion.	

Indications:	**"prils" (ACEIs)**	**"sartans"(ARBs)**
HTN	**Captopril** **Lisinopril** **Enalapril** **Benazepril** **Fosinopril** **Moexipril** **Quinapril** **Ramipril**	**Losartan** **Valsartan** **Olmesartan** **Telmisartan** **Candesartan** **Eprosartan** **Irbesartan**
dilative CHF		
post MI (ACEIs only)		

USING in	ACEIs	ARBs
dry cough/ angioedema after ACEIs	STOP ACEIs (side effects of bradykinin)	replace ACEIs w/ ARBs
Pregnancy	NO (teratogenic)	NO (teratogenic)
renal perfusion low bilateral	NO (renal failure)	NO (renal failure)

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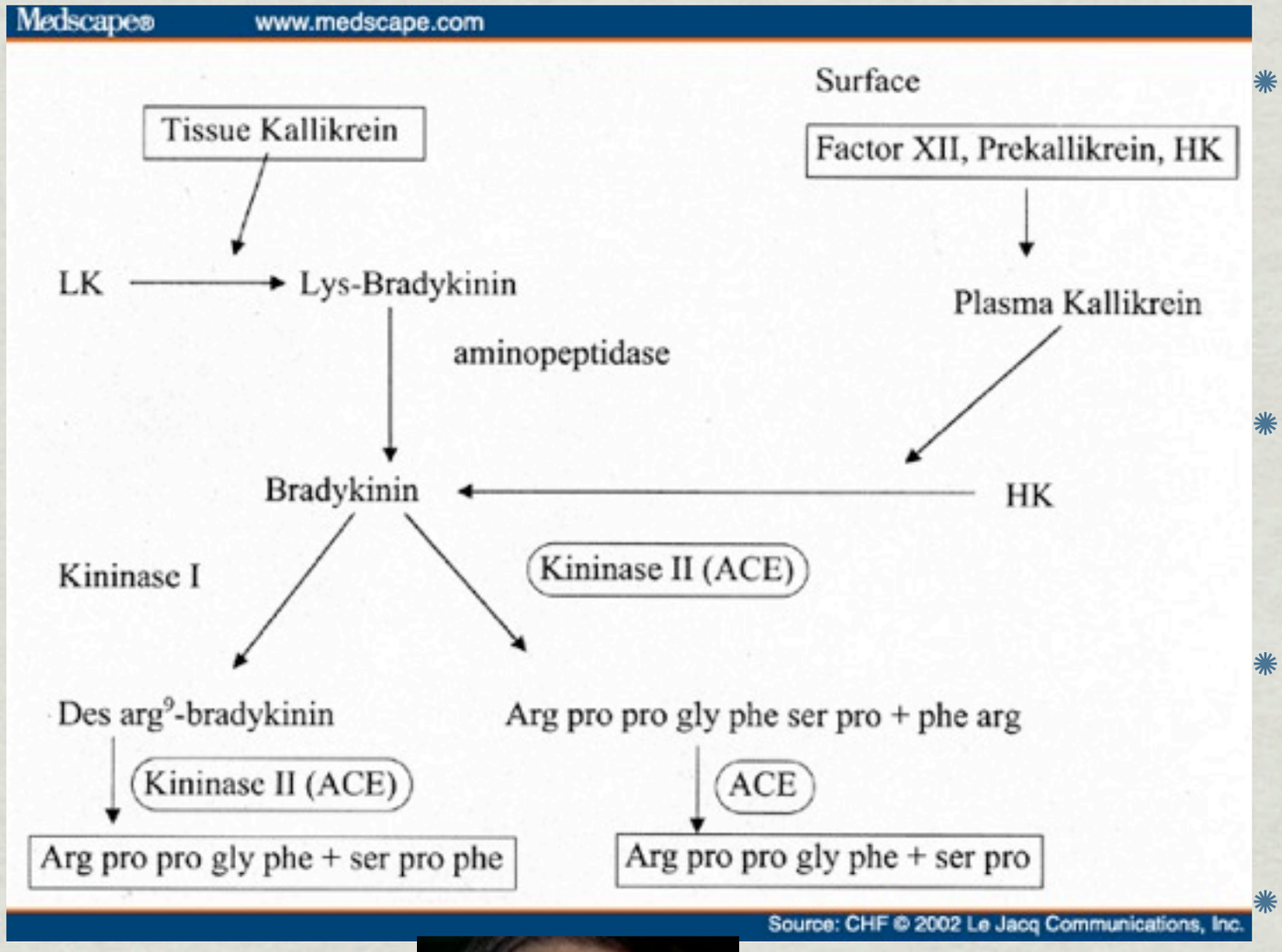
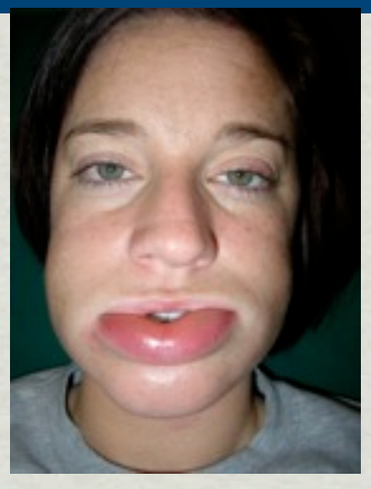
ACEIs and bradykinin

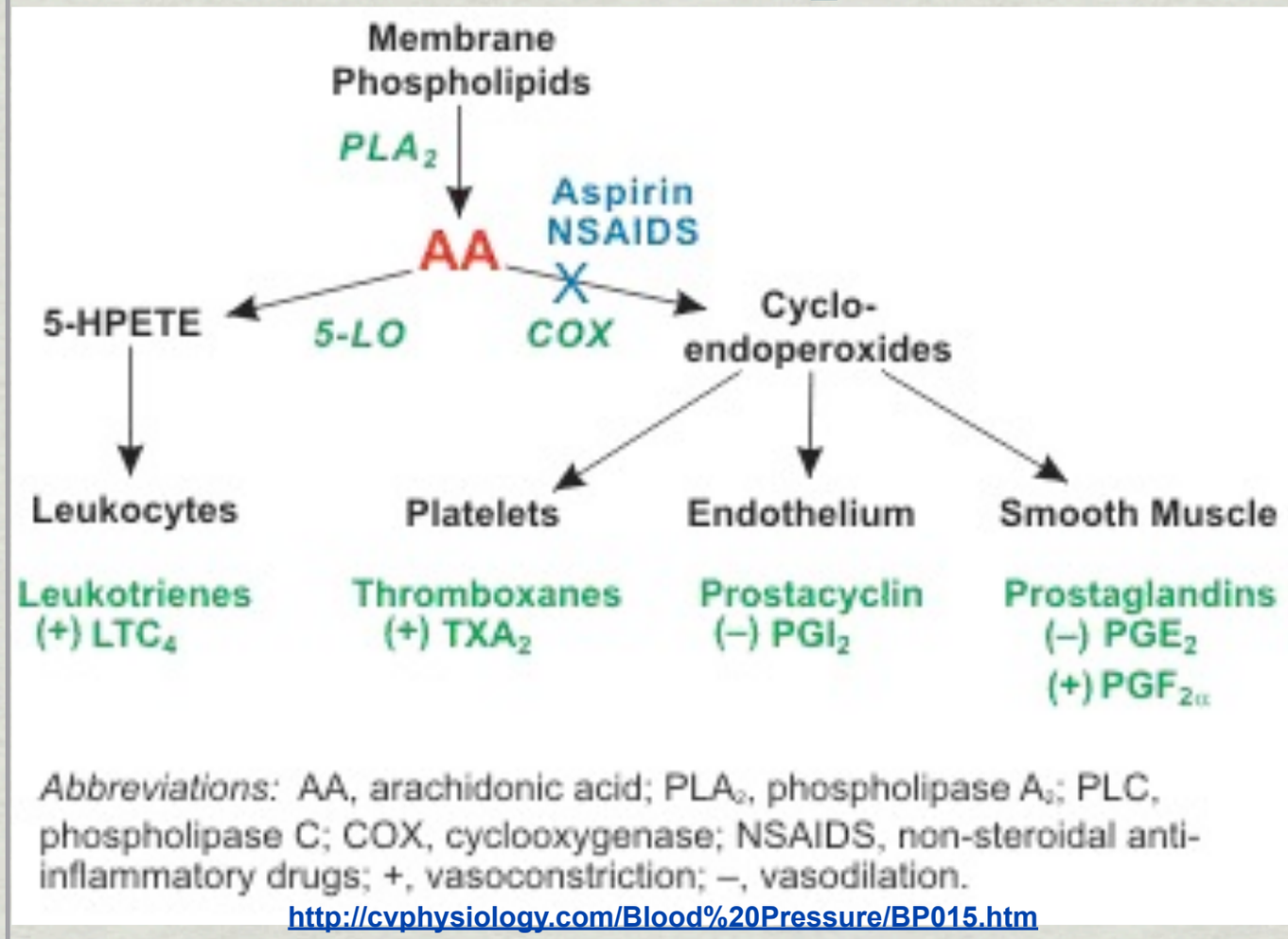




http://diseaseslab.com/angioedema-causes-pictures-symptoms-treatment/

- Bradykinin is a potent vascular endothelial peptide that produces vasodilation through NO and PG I2, contraction of smooth muscle in the bronchus and gut, increase vascular permeability, and is also involved in pain mechanism and natriuresis etc.
- Bradykinin is formed from a substrate called kininogen by tissue and plasma activators .The activation is particularly important in blood pressure regulation and inflammation.
- ACE breaks down bradykinin. Therefore ACEIs by blocking the breakdown of bradykinin increase its levels which contributes to increased vasodilator action of ACEIs.
- Elevated levels of bradykinin produce a dry cough in 10% of patients.
- Hypotension can also be a problem especially in CHF patients
- Angioedema (pic on left) appears in 0.1-0.2% patients but incidence is 2-4 times higher in African Americans compared to Caucasians .

Renal prostaglandins



Abbreviations: AA, arachidonic acid; PLA_2, phospholipase A_2; PLC, phospholipase C; COX, cyclooxygenase; NSAIDS, non-steroidal anti-inflammatory drugs; +, vasoconstriction; –, vasodilation.

http://cvphysiology.com/Blood%20Pressure/BP015.htm

	E2	F2@	I2	TXA2
Location	arteriolar smooth muscle	arteriolar smooth muscle	endothelium	platelet
Action	vasodilation	vasoconstriction	vasodil.	vasoconstr.
Pathway	Gs coupling	Gq coupling	Gs coupling	Gq coupl.
Special note			antithrombo-tic	thrombotic

- Prostaglandins and related compounds (AKA prostanoids or eicosanoids) such as prostacyclin (PGI2), leukotrienes (LTs) and thromboxanes (TXs) are produced by many different cells in the body from membrane phospholipids.
- Although their primary physiological actions are generally related to inflammation and hemostasis, by nature they all are vasoactive and can modulate cardiovascular function, particularly vascular tone.
- Their effects are very localized because they are paracrine hormones; that is, they are released by one cell and act on nearby cells.
- There are many different classes of prostaglandin present in the kidney, but PGE2 and PGI2 are the most known ; part responsible for the vasodilatation of the afferent arteriole which increases blood flow to the glomerulus
- PGE2 also is known to inhibit ADH-stimulated water permeability in the cortical collecting duct.
- *Leukocytes* produce leukotrienes such as LTC_4 in response to inflammation and tissue injury. Like TXA_2, it is a potent vasoconstrictor and acts through the Gq-protein pathway.
- Leukotrienes (and prostaglandins) can also make the vascular endothelium more "leaky" thereby promoting *edema* formation during inflammation.

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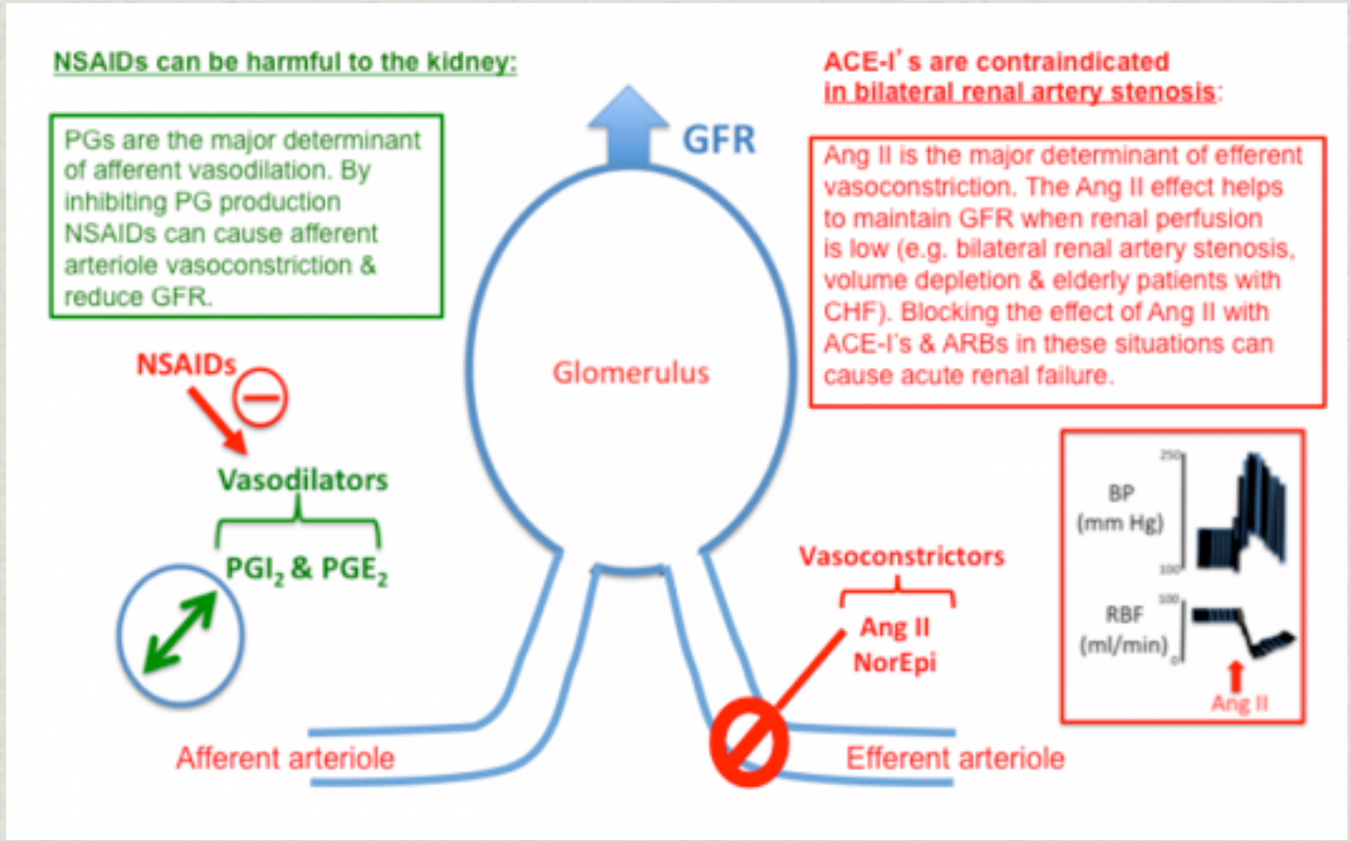
NSAIDs and renal function



http://tmedweb.tulane.edu/pharmwiki/doku.php/ace_inhibitor_pharmacology

	COX-1	COX-2
expression induced by	constitutive	inflammation
RENAL expression*	constitutive	constitutive
NSAIDs side effects	GI bleeding & ulcer ↓ GFR	↓ GFR

- Traditional nonsteroidal antiinflammatory drugs (NSAIDs) inhibit both isoforms of the enzyme cyclooxygenase (COX). The first, **COX-1**, is **constitutively expressed** in most cells throughout the body, and its inhibition has been associated with **gastrointestinal bleeding** and **ulceration**.

- In contrast, **COX-2 expression** is induced in the presence of **inflammation** and its inhibition results in the therapeutic effects of NSAIDs. Thus, the development of selective COX-2 inhibitors brought about a new way to produce potent antiinflammatory actions with a decreased risk of significant gastrointestinal adverse effects

- NSAIDs (which also **inhibit renal prostaglandin synthesis**) result in **afferent arteriole vasoconstriction** and that's why NSAIDs can cause a **reduced GFR** in patients who rely heavily on prostaglandin synthesis to maintain renal blood flow.

- Interestingly, however, the **kidney constitutively expresses COX-2,** and therefore **COX-2 inhibitors can lead to alterations in renal hemodynamics** similar to the NSAIDs **(reduced GFR)**

http://renalfellow.blogspot.com/2009/04/prostaglandin-basics.html

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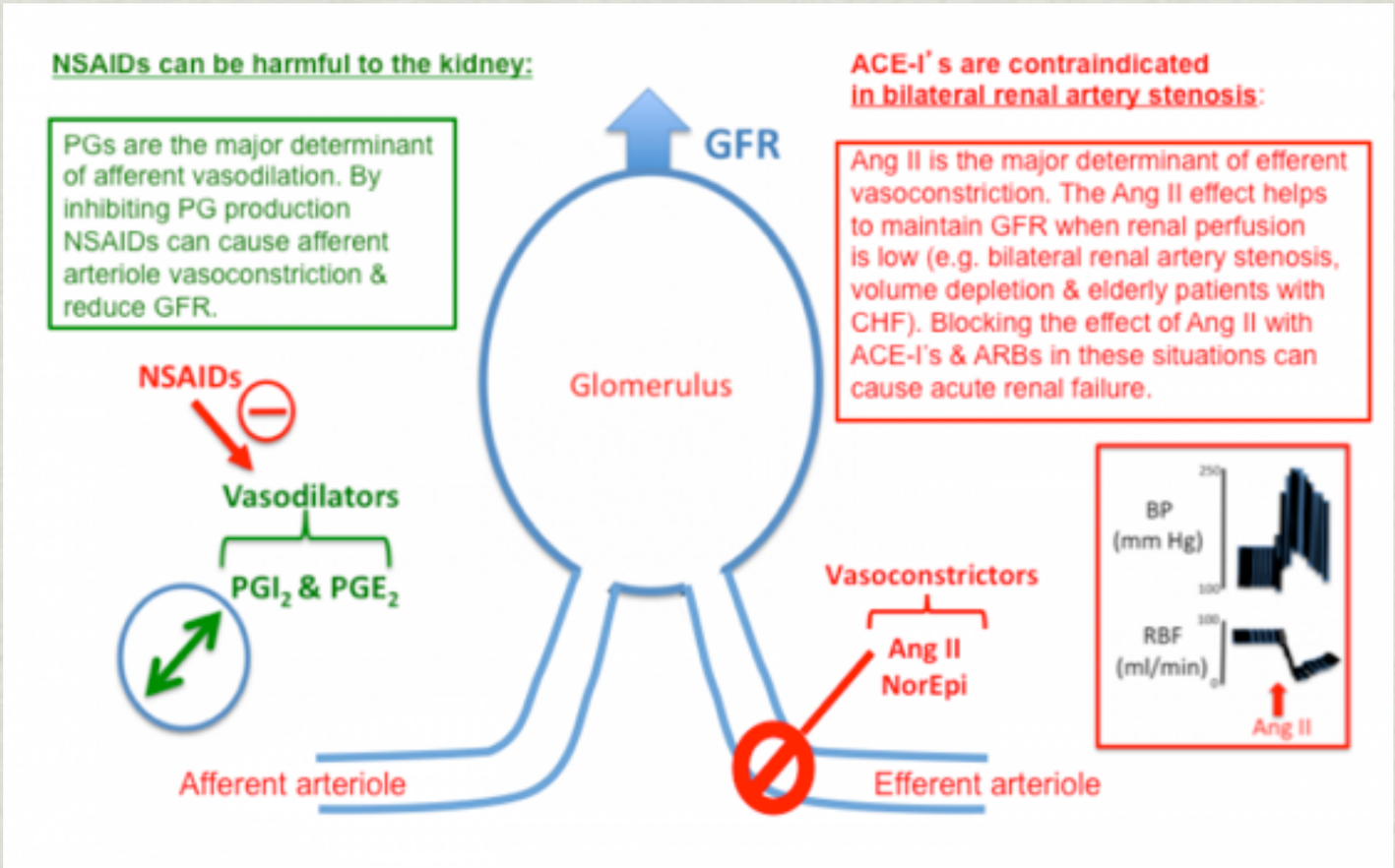
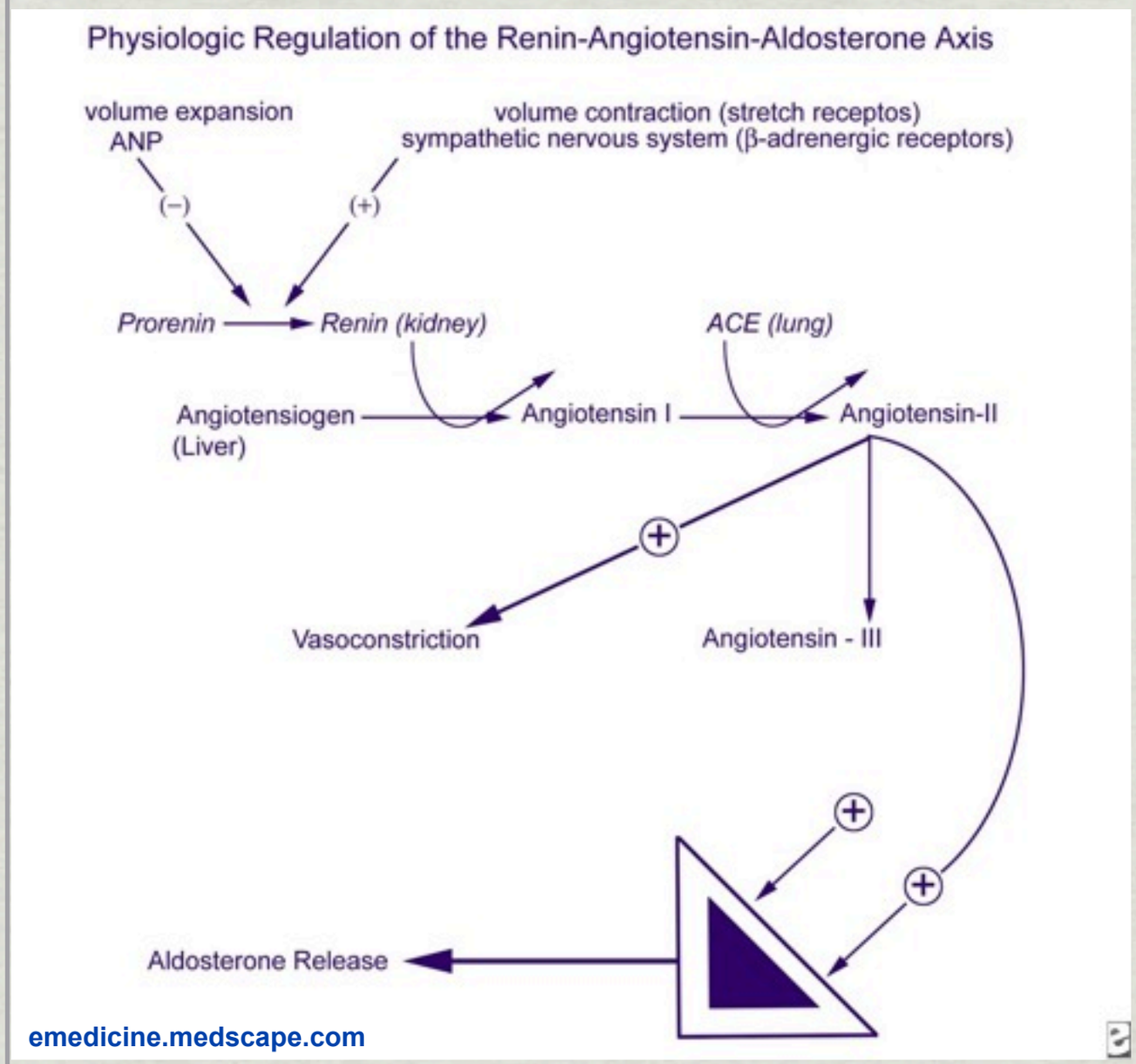
NSAIDs and ACEIs/ARBs in renal function



http://tmedweb.tulane.edu/pharmwiki/doku.php/ace_inhibitor_pharmacology

- **NSAIDs produce ↓GFR (both non-selective and COX2 selective) by inhibiting vasodilator action of PGE2 and PGI2 on the afferent arteriole.**
- **At renal level, ANG II constricts the efferent arteriole more than the afferent resulting an increased perfusion pressure (↑GFR). ANG II also stimulates PG E2 and I2 which dilates afferent arteriole and also ↓GFR.**
- **ACEIs/ARBs blocks ANG II effect --->> ↓ GFR. So pay attention when ↓GFR like : bilateral renal stenosis, volume depletion or elderly patients (GFR ↓ since only 1/3 of the nephrons are functional) since it may cause acute renal failure.**

Aldosterone regulation



- **Main regulators:**
- **1. RAAS**
- **2. plasma K as is sensed through receptors in the carotid artery. Increased serum K determines ↑ in Aldosterone which ↑ Na reabsorption in exchange w/ K and H+**
- **Minor regulator: ACTH producing deoxycorticosterone, a precursor of aldosterone**

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