## Integrative Sciences 2011

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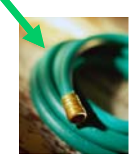
Regulation of Glomerular Filtration Rate and Renal Blood Flow – 2 Hrs
Chapters 3 Koeppen & Stanton Renal Physiology

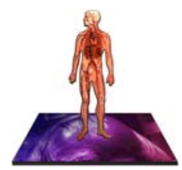
1. Starling Forces
2. Control of GFR
3. Oxygen Consumption
4. Autoregulation
   - Myogenic
   - Tubuloglomerular Feedback
5. Control of Renal Circulation
   - AngII, ANP, SNS, AVP

## Terminology



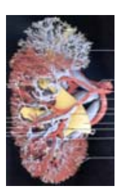
- Oncotic pressure – pressure generated by large molecules (especially proteins) in solutions
- Hydrostatic pressure – pressure exerted by liquids
- Renal artery pressure - **RAP**
- Renal plasma flow - **RPF**

## Which of the following is the most important in regulating water balance in the body?

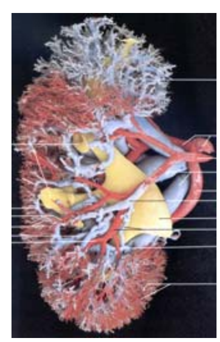


a) Water lost through skin and lungs
b) Water lost in feces
c) Water lost in sweat
d) Urine production

## What are some of the functions of the kidney???



## Functions of the Kidney



Kidneys - major regulation of body water and inorganic ions = extracellular fluid (**ECF**)

Body fluid
- osmolality
- volume

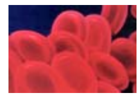
## Functions of the Kidney

- Regulate water & inorganic-ion balance ≡ BP
  - $H_2O$, $Na^+$, $K^+$, $Ca^{2+}$, $Cl^-$, $Mg^{2+}$, etc.

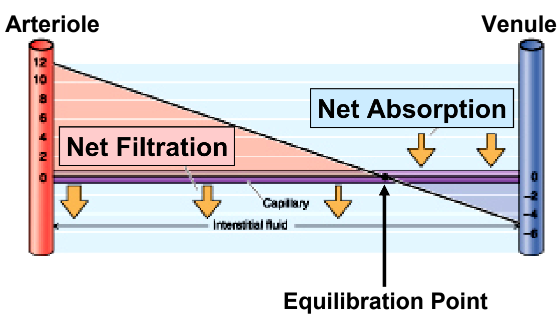
- Acid-base balance
- Remove metabolic waste products
  - Urea, uric acid, creatinine

## Functions of the Kidney

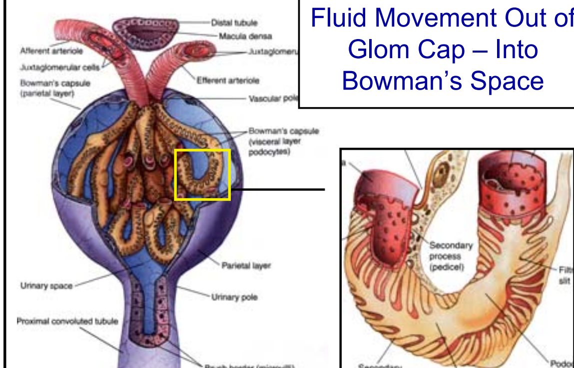
- Remove foreign chemicals
  - Drugs, toxins, pesticides
- Secrete hormones
  - Erythropoietin
  - Renin
  - Vitamin D



## Starling Forces Change Along the Length of Capillaries: Skeletal Muscle




## Fluid Movement Out of Glom Cap – Into Bowman's Space

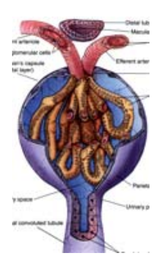



## Filtration

- Net filtration of fluid across all capillaries (*except* kidney)
  - = **4** L/d
- Glomerular Filtration Rate - **GFR**
  - = **125 ml/min** (both kidneys)
  - = 180 L/day
- Plasma volume - **PV**
  - = 3L = filtered **60**X /d
- **ECFV**
  - = 17L = filtered **10X** /d

## Glomerular Filtration

- 1st step in urine formation
- Ultrafiltration of plasma by glomerulus
- *Devoid* of cellular elements
- Essentially *protein free*
- Conc salts, glucose, amino acids = *plasma*
- Driven by *Starling* forces



### Glomerular Ultrafiltration - Eq 3-10

$$GFR = K_f\,[(P_{GC}-P_{BS}) - \sigma(\pi_{GC}-\pi_{BS})]$$

**σ – reflection coefficient for protein**
**= 1**
**protein *cannot* cross glomerular membrane**

### Glomerular Ultrafiltration - Eq 3-10

$$GFR = K_f\,\underbrace{[(P_{GC}-P_{BS}) - (\pi_{GC}-\pi_{BS})]}_{P_{UF}}$$

Rate of glomerular ultrafiltration = product of *ultrafiltration coefficient* (**$K_f$**) and <u>net</u> *Starling forces* (**$P_{UF}$**)

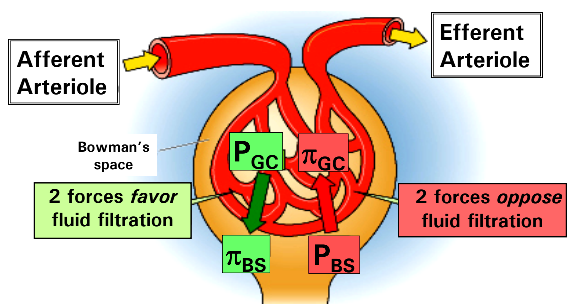
### Ultrafiltration Coefficient

$$GFR = K_f\,[(P_{GC}-P_{BS}) - (\pi_{GC}-\pi_{BS})]$$

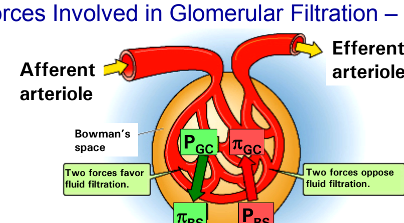
**$K_f$** ml/min/mmHg

- Intrinsic *permeability* of glom capillary
- Product of *hydraulic conductivity* & *surface area*
- *10-100X > other beds*

### Forces Involved in Glomerular Filtration – Fig 3-6




### Forces Involved in Glomerular Filtration – Fig 3-6

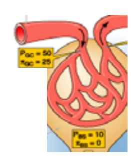



$P_{GC}$ = Glomerular capillary hydrostatic pressure
$\pi_{BS}$ = Bowman's space oncotic pressure
$P_{BS}$ = Bowman's space hydrostatic pressure
$\pi_{GC}$ = Glomerular capillary oncotic pressure

**Net Filtration Pressure = $P_{GC} - P_{BS} - \pi_{GC} + \pi_{BS}$**

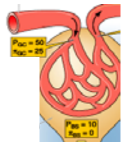
### Forces Involved in Glomerular Filtration

<u>Net glomerular filtration pressure - beginning of capillary</u>



$$= P_{GC} - P_{BS} - \pi_{GC} + \pi_{BS}$$

## Forces Involved in Glomerular Filtration




Net glomerular filtration pressure-
beginning of capillary

$$= P_{GC} - P_{BS} - \pi_{GC} + \pi_{BS}$$

$P_{GC}$= 50, $P_{BS}$= 10, $\pi_{GC}$= 25, $\pi_{BS}$= 0 mmHg

50 - 10 - 25 + 0 mmHg = **15 mmHg**

**$P_{GC}$ – only force that favors filtration**
**2X > most capillaries**

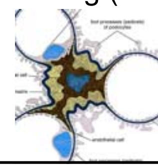
## Ultrafiltration Coefficient

**GFR = $K_f$ ($P_{UF}$)**

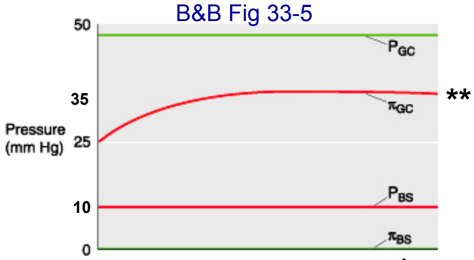
**$K_f$** ml/min/mmHg

125 ml/min =

**8.3** ml/min/mmHg (15 mmHg)

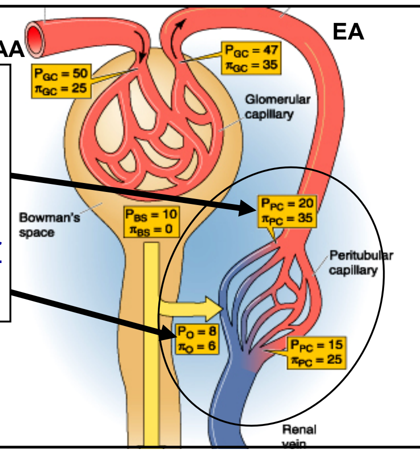


## Starling Forces Along Glomerular Capillaries
B&B Fig 33-5

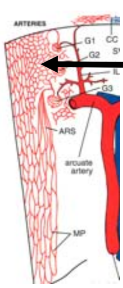



$\pi_{GC}$ increases along glom capillary

## Forces Involved in Absorption by Peritubular Capillaries

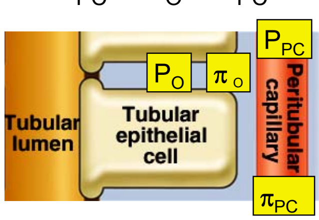



## Forces Involved in Absorption by Peritubular Capillaries



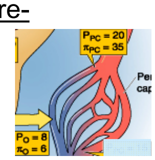
Net peritubular
capillary pressure –

$$= P_{PC} - P_O - \pi_{PC} + \pi_O$$




## Forces Involved in Absorption by Peritubular Capillaries

Net peritubular capillary pressure-
beginning of the capillary



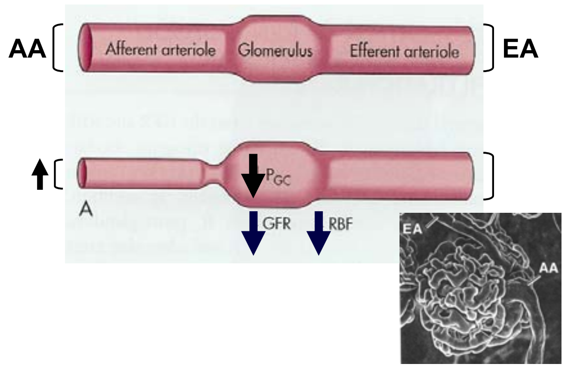

$$= P_{PC} - P_O - \pi_{PC} + \pi_O$$

$P_{PC}$=20, $P_O$=8, $\pi_{PC}$=35, $\pi_O$=6mmHg

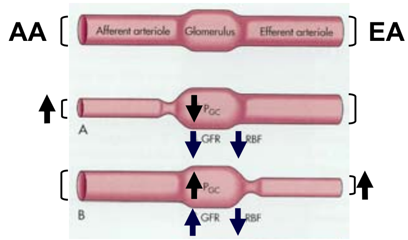
20 - 8 – 35 + 6mmHg = **minus 17mmHg**

**Negative filtration ≡ absorption**
**Forces favors reabsorption of fluid**

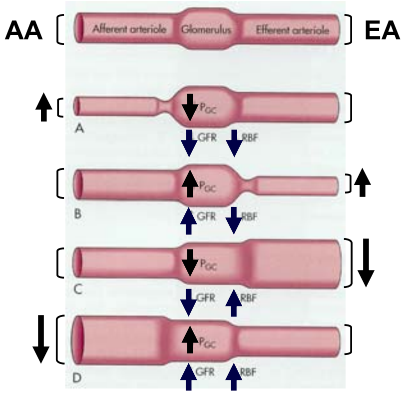
## CHANGING RESISTANCE Fig 3-9




## CHANGING RESISTANCE Fig 3-9




## CHANGING RESISTANCE Fig 3-9

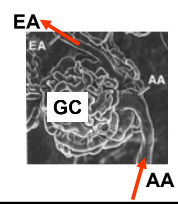



## Control of GFR

$P_{UF} = P_{GC} - P_{BS} - (\pi_{GC} - \pi_{BS})$

$GFR = K_f\ (P_{UF})$

- ⇑ Renal Artery Pressure (RAP) = ⇑ $P_{GC}$ = ⇑ GFR
- ⇑ AA resistance
  ⇓ $P_{GC}$ = ⇓ GFR




## Control of GFR

$P_{UF} = P_{GC} - P_{BS} - (\pi_{GC} - \pi_{BS})$

$GFR = K_f\ (P_{UF})$

- ⇓ AA resistance
  ⇑ $P_{GC}$ = ⇑ GFR
- ⇓ EA resistance
  ⇓ $P_{GC}$ = ⇓ GFR


## Control of GFR

$P_{UF} = P_{GC} - P_{BS} - (\pi_{GC} - \pi_{BS})$

$GFR = K_f\ (P_{UF})$

- ⇓ $\pi_{GC}$ - ⇑ GFR
  Δ protein metabolism,
  protein loss in urine

## Control of GFR

$P_{UF} = P_{GC} - P_{BS} - (\pi_{GC} - \pi_{BS})$

$GFR = K_f \ (P_{UF})$

- $\Uparrow P_{BS}$ - $\Downarrow$ GFR
  acute obstruction – stone, enlarged prostate
- $\Uparrow \pi_{BS}$ - $\Uparrow$ GFR
  filter protein - proteinuria

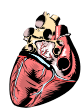
## Control of GFR

$P_{UF} = P_{GC} - P_{BS} - (\pi_{GC} - \pi_{BS})$

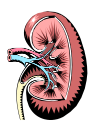
$GFR = K_f \ (P_{UF})$

- $\Downarrow K_f$
  – hypertension
  – diabetes
  – glomerulosclerosis

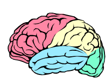
## Renal Parameters



- Cardiac Output (CO) = 5,000 ml/min
- Renal Blood Flow (RBF) =
  - 1,000 ml/min
  - 350 ml/min/100gKW
  - 4 ml/min/g (1% BW)

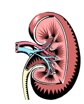


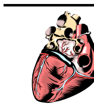
- Brain = 50 ml/min/100g
- Skeletal muscle = 0.08 ml/min/g



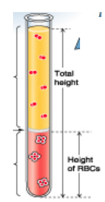
## Renal Parameters

- Renal Fraction (**RF**) = RBF/CO
  - 1,000 ml/min ÷ 5,000 ml/min
    = 0.20 = 20%



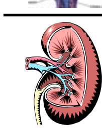


- Hematocrit (**Hct**) = 0.40
  - 40% BV = **RBC**



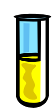

## Renal Parameters

- Renal Plasma Flow (**RPF**) =
  - **RBF** x (1 – Hct)
  - 1,000 ml/min x (1 – 0.40) = 600 ml/min
- Filtration Fraction (**FF**) =
  **GFR** ÷ **RPF** =
  125 ml/min ÷ 600 ml/min = 0.20



## Renal Parameters

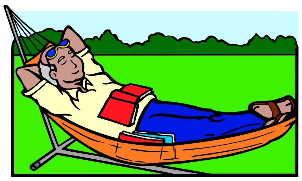
- Urine flow ($\dot{V}$) = 1 ml/min



- Fluid reabsorbed =
  - 125 ml/min – 1 ml/min =
    124 ml/min > 99%

* Filtration **>>>** Urine Output *

# Time for a Break

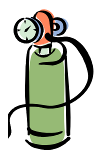


Regulation of Renal Blood Flow and Glomerular Filtration Rate
Chapters 3 Koeppen & Stanton Renal Physiology

3. Oxygen Consumption
4. Autoregulation
   - Myogenic
   - TGF
5. Control of Renal Circulation
   - AngII, ANP, SNS, AVP

## $O_2$ Consumption by Kidneys

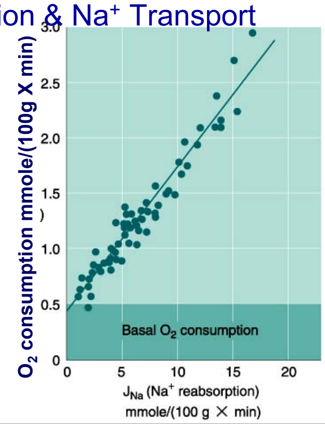
- $O_2$ consumption/g tissue > any organ except heart
- Arterial - Venous $O_2$ difference lowest
- $O_2$ consumption relative to RBF is not very high
- $O_2$ is not the critical factor for RBF



## $O_2$ Consumption & $Na^+$ Transport

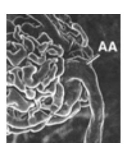
- $O_2$ consumption is **LARGE** and parallels $Na^+$ reabsorption
- RBF large –

  Arterial - Venous $PO_2$ difference is **SMALL**

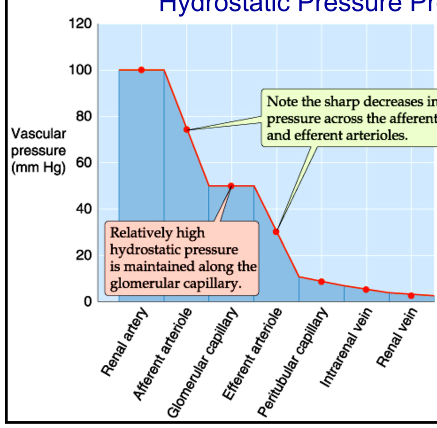


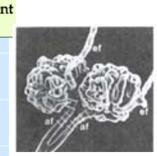

## Regulation of RBF

- Intrinsic mechanisms
  - Renal autoregulation
    - Myogenic mechanism
    - Tubuloglomerular feedback mechanism (TGF)
- Extrinsic control mechanisms
  - Role of renal nerves
  - Circulating vasoactive hormones – ANP, AVP, RAS




## Hydrostatic Pressure Profile



## Renal Blood Flow Autoregulation

- Autoregulation – vascular bed maintains BF with Δ Blood Pressure

- RAP ~ 80 – 170 mmHg

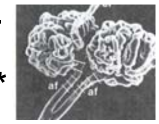
(posture, exercise, sleep)

RBF & GFR constant

* *Intrinsic phenomenon* *

## Renal Blood Flow Autoregulation

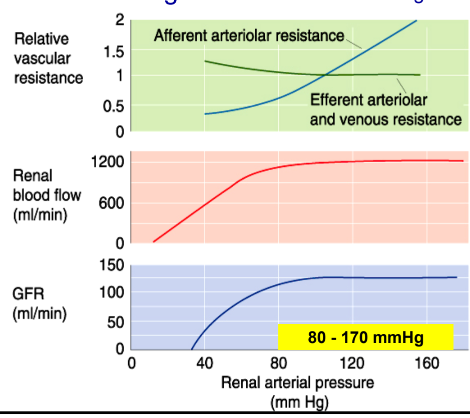
* **Δ AFFERENT ARTERIOLE RESISTANCE** *



- w/o renal nerves or circulating hormones, occurs isolated kidney perfused *in vitro*

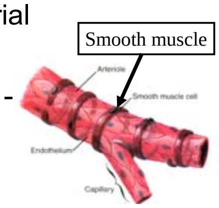
* *Intrinsic phenomenon* *

## Autoregulation of RBF K&S Fig 3-7




## Myogenic Mechanism
### Responds to Change AP

- *Intrinsic property* of arterial smooth muscle



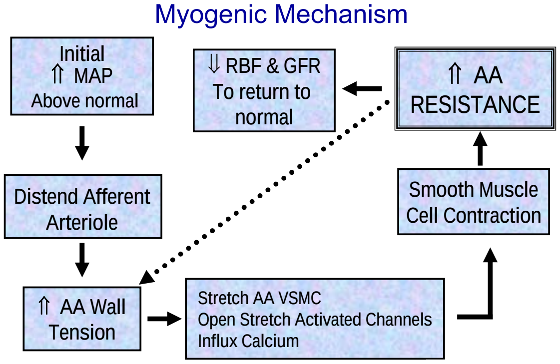

⇑ vascular wall tension - contract

or

⇓ vascular wall tension - relax

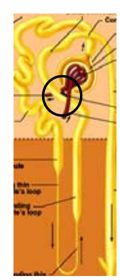
* Renal Blood Flow Autoregulation *

## The Mechanism of Autoregulation
### Myogenic Mechanism



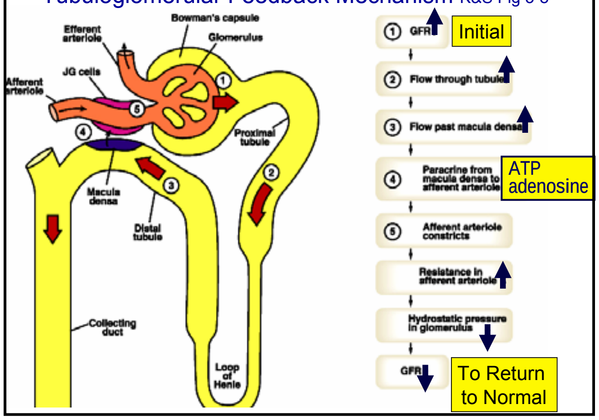

## Tubuloglomerular Feedback (TGF)

- Balance filtration (hemodynamic) & reabsorption (metabolic)
- Tubulo-vascular crosstalk preservation of electrolyte balance
  - Limits $U_{Na}V$



* Renal Blood Flow Autoregulation *

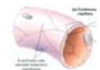
## Tubuloglomerular Feedback Mechanism K&S Fig 3-8




## Control of Renal Circulation

- Sympathetic nervous system

- Hormones
- Endothelial factors



Affect AA & EA resistance

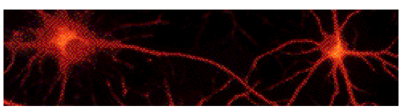
Alter RBF & GFR

Autoregulation RBF & GFR can be overridden

## Sympathetic Nervous System

- AA & EA
- Juxtaglomerular cell
- Tubule
- ⇑ firing rate = vasoconstriction
- Trauma/shock – strong SNS output

  ⇓ RBF cease GFR

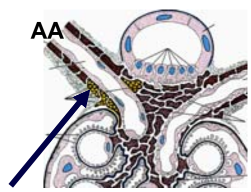


## Renin-Angiotensin System - RAS

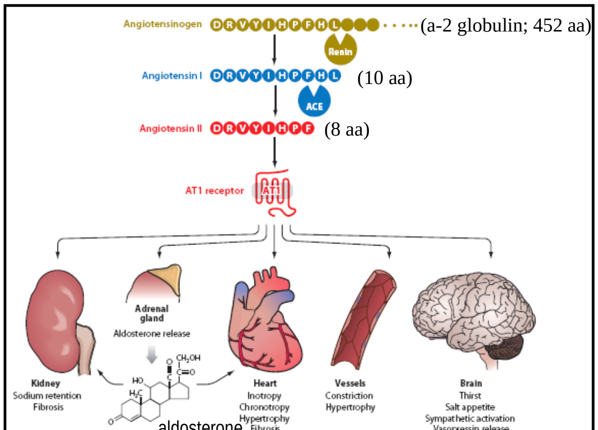
- RAS regulates $Na^+$ balance, plasma volume

  control of arterial blood pressure

- Renin - rate limiting step AngII formation




*** Major concern = ⇑ ECFV ⇑ BP ***




## HEMODYNAMIC Actions of Angiotensin II

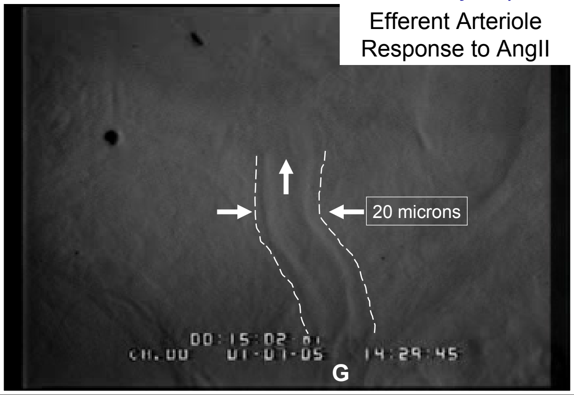
- vasoconstriction ⇑ TPR
  ⇑ BP
- constrict afferent & efferent arterioles

  ⇓ RBF


- contract mesangial cells - ⇓ $K_f$ ⇓ GFR

*** Reduce RBF & GFR ***

*Mouse In Vitro Blood Perfused Juxtamedullary Nephron*




**AVP** – **A**rginine **V**aso**P**ressin

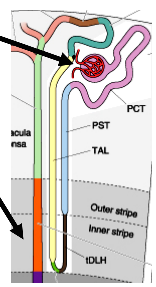
=

**ADH** – **A**nti**D**iuretic **H**ormone

Identical Peptide

## Actions of AVP (ADH)

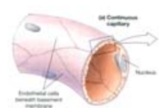
- Constriction of afferent and efferent arterioles
- ⇓ BF to renal medulla
- Systemic vasoconstriction ⇑ BP




*** Reduce $H_2O$ Excretion ⇑ BP ***

## Nitric Oxide

- Endothelia generate <u>nitric oxide</u> – acetylcholine, histamine, bradykinin
- <u>Relax</u> vascular smooth muscle
  - ✓afferent & efferent arterioles
- <u>Buffer</u> excessive vasoconstriction of AngII & NE



## Atrial Natriuretic Peptide (ANP)

- Synthesized, secreted - <u>cardiac atria</u>

  Stimulus
  - ✓↑ atrial distention
  - ✓↑ plasma volume
  - ✓Severe volume expansion

## Atrial Natriuretic Peptide (ANP)

- Dilates afferent arteriole ↑ GFR

**⇓ Plasma $Na^+$ & Volume**

## Renal Prostaglandins

- VSMC, endothelial cells, mesangial cells, tubule, interstitial cells synthesize PG
- vasodilate afferent & efferent arteriole

  ↑ RBF and ↑ GFR

## Renal Prostaglandins

↑ Severe volume depletion (dehydration), salt depletion, blood loss (hemorrhage), low BP, surgery, anesthesia, stress, SNS, RAS

Prevents severe and potential harmful vasoconstriction and renal ischemia

NSAIDs

**Buffer Excessive Vasocontriction**

## Summary Major Renal Hormones

| Vasoconstrictors | ⇓ RBF ⇓ GFR |
|---|---|
| Sympathetic nerves | |
| Angiotensin II | |
| Endothelin | |
| AVP | |
| Norepinephrine | |
| **Vasodilators** | **⇑ RBF ⇑ GFR** |
| Prostaglandins | |
| Nitric Oxide | |
| Bradykinin | |
| ANP | |

## Summary

1. Glomerular filtrate formation - dependent on filtration barrier & Starling forces
2. $O_2$ consumption is NOT regulator of RBF
3. RBF autoregulation – AFFERENT ARTERIOLE RESISTANCE
   - TGF & Myogenic
4. Hormonal regulation of RBF and GFR to maintain BV & BP

# Time for Questions