Primary Cast Episode 9 - Renal Physiology

Host - Dr. Charlotte Durand
Guest - Dr. Josh Monester

1. **Micturition**

Describe the neurological pathways involved in normal micturition

- Sacral spinal reflex Mediated by S2, S3 and S4 nerve roots facilitated and inhibited by hire centres, subject to voluntary control.
- First urge to void at 150ml.
- Marked fullness at 400 ml – sudden rise in intravesical pressure triggers reflex contraction.
- Micturition reflex:
    - Stretch receptors in the bladder wall.
    - Afferent limb in pelvic nerves
    - Parasympathetic efferent fibres (via same pelvic nerves) mediate contraction of detrusor muscle.
    - Pudendal nerve (S2, S3 and S4) permits voluntary contraction of perineal muscles/external urethral sphincter, to slow or halt flow.
- Sympathetic nerves to the bladder play no role in micturition.

Describe the muscles involved in micturition

- Bladder- smooth muscle arranged in spiral, longitudinal and circular bundles. Circular bundle is called the detrusor muscle period contraction of detrusor is responsible for involuntary emptying.
- External urethral sphincter - skeletal muscles of the membranous urethra. Relaxes during micturition. This is voluntarily controlled
- Perineal muscles. Relaxes during nutrition. Also voluntarily controlled.
- In males, urine left in the urethra is expelled by several contractions of bulbocavernosus muscle.
- Contraction of abdominal wall muscles aids expulsion of urine.

List other factors that stimulate and inhibit micturition

Stimulants

- Stretch/pressure
- Higher centre input
- Parasympathetics
- Sympathetic inhibiting drug (Alpha blockers)
- Voluntary abdominal muscle contraction augments stream but does not initiate micturition per se

Inhibitors

- Parasympathetic inhibitors (atropine)
- Higher centres
- Sympathomimetics

2. **Glucose handling**

Describe how the kidney handles glucose

- Freely filtered in the glomerulus
- Reabsorbed in the early part of the PCT by secondary active transport
- Na dependent co transport via SGLT2 into cells then GLUT2 facilitated diffusion into the interstitium
- Excreted in the urine if the renal threshold is exceeded

What are the clinical consequences of glycosuria

- Osmotic diuresis
- Dehydration
- Electrolyte loss (Na, K)

3. **Sodium handling**

Where does sodium reabsorption occur in the nephron?

- Filtered by the glomerulus, 99% reabsorbed overall
- 60% reabsorbed in the PCT by Na-H exchange but also a range of co-transporters (with glucose, AAs, lactate)
- 30% thick ascending limb of the loop of henle
- 7% in the DCT via NaCl cotransporter
- 3% via ENac channels in collecting ducts

How is Na transported from the tubular cell into the interstitium?

By the Na/K ATPase active transport pump
Moves 3Na and 2K across the basolateral memnrabe

Following high Na intake, what mechanisms are there to enhance Na excretion?

High Na intake causes ECF expansion (Na is the prime determinant of ECF volume)
This increase triggers various response mechanisms

- Stretch receptors in pulmonary veins inhibit sympathetic outflow to the kidneys and decreased Na reabsorption
- Small increase in arterial pressure can cause pressure natriuresis
- Suppression of AT II formation, thereby reducing aldosterone activity
- Stimulation of atrial natriuretic peptide.

How does the kidney reduce Na secretion?

By reducing the GFR to reduce the amount filtered
Increasing tubular reabsorption via increase in adrenocortical hormones such as aldosterone.

How does aldosterone influence sodium handling?

- Aldosterone acts on principal cells in collecting ducts to increase the number of active epithelial sodium channels (ENaC)
- Upregulates and activated basolateral Na/K ATPase
- Increased tubular reabsorption of Na, and Cl follows.
- Secretion of K into lumen via exchange with Na
- Latent period of 10-30 minutes before the effect

4. **Hydrogen handling**

Where does acidification of the urine occur?

Proximal and distal tubules and collecting ducts

How is H+ secreted in each of those areas?

- *PCT -* Na/H exchange transporter. This pathway also involves the action of carbonic anhydrase, which allows the recycling of H+ and absorption of one Na and one HCO3 for every H+ secreted.
- *DCT/CD -* secretion of H+ is independent of Na.
    - ATP driven pump
    - Also H-K ATPase pump an anion exchanger.

What is the limiting pH and where does it occur?

The limiting pH is 4.5 because this is the maximal gradient that can be achieved across the tubules. It occurs in the collecting duct. Possible due to buffers (bicarb, phosphate, ammonia)

In metabolic acidosis, describe the buffer systems in the urine that allow excretion of large amounts of H+

BICARB: HCO_3^- forms CO_2 and H_2O
PHOSPHATE: HPO_4^{2-} forms $H_2PO_4^-$
AMMONIA: NH_3 forms NH_4^+ (ammoniA = A goes first, then AmmoniUM)

What happens to glutamine synthesis in chronic metabolic acidosis?

Glutamine synthesis increased in the liver to provide the kidneys with enough ammonia to form buffer

5. **K handling**

How do the kidneys deal with potassium?

- Freely filtered at the glomerulus (600mmol/day)
- Actively reabsorbed in the PCT (over 90% resorbed)
- Also reabsorbed in the Na/K/2Cl co-transporter
- Secreted in the DCT - rate proportional to flow
- Secreted in CD in response to aldosterone, which increased K secretion
- Total secretion is low (approx 90mmol per 24hrs) but varies with flow and aldosterone

Explain K transport in the collecting duct

- H-K ATPase in the cells of collecting ducts reabsorbs K in exchange for H
- So, if H secretion is increased, K excretion is decreased.

How does aldosterone increase potassium secretion in the urine?

- Aldosterone secretion is triggered by hyperkalaemia
- Acts at the DCT and collecting ducts
- Stimulates the Na/K APT pump at the basolateral surface of the principle cells.
- 2K enters in exchange for 3 Na into the bloodstream
- Causes K channels to form at the apical surface of the principle cells
- Higher intracellular K concentration means that K enters the tubular lumen
- This causes Na channels to form at the apical surface of the principle cells
- Na enters the principal cells from the tubular lumen and gets to the bloodstream via Na/K ATP pump.

How do hydrogen ions influence K transport in the nephron?

It is coupled. If H secretion is increased then K excretion is decreased as K is reabsorbed in exchange for H+

6. **Urea handling**

What is the role of urea in the countercurrent mechanism?

- Contributes to the osmotic gradient in the medullary pyramids
- Enhances the ability of the kidney to concentrate urine

How does the kidney handle urea?

- Facilitated diffusion out of the late PCT
- Secreted in the loop of henle
- Reabsorbed in the collecting ducts
- 40% of filtered urea can be found in the urine
- The amount of urea depends on the amount filtered, which is influenced by dietary protein

How does urea reach the interstitium?

Transported via 4 different urea transporters (facilitated diffusion)

7. **Renal blood flow**

What is the normal renal blood flow?

1.2 - 1.3 litres per minute or 25% of cardiac output.

Describe the factors which determine renal blood flow

- Perfusion pressure (systemic MAP)
- Renal arterial effects
    - local constriction from Na, Ang II
    - dilation from ACh, PGs, dopamine

- Renal nerves (sympathetic nerves constrict and decrease RBF)
- Autoregulation (myogenic, NO, Ang II)
- Regional differences between the cortex and medulla

How can renal blood flow be measured?
Short answer from ED Vivas below, long answer below with a transcription of my explanation on the show.

What is normal renal blood flow and how can it be measured?
1. **Fick principle** (amount of a substance taken up per unit time divided by arterio-venous concentration difference)
2. **PAH (excreted, not metabolised or stored, doesn't affect flow) is used to measure effective renal plasma flow (90% cleared)** ERPF = Clearance of PAH = UV/P = 630 mL/min
3. Actual renal plasma flow = ERPF/0.9 = 700 mL/min
4. Renal blood flow = RPF x 1/1-Hct (Hct = 0.45)
5. **Renal blood flow = approx 1250 mL/min**

- Fick Principle (the amount of a substance taken up per unit time divided by arterio-venous concentration difference)
- Para-amino hippuric acid (PAH) is used to measure renal blood flow. It is both filtered and secreted, meaning 90% of it is cleared from circulation by the kidney and only small amounts remain in the renal vein.
- So, if we know the concentration in the plasma, and concentration in the urine and the urine flow rate we can use that to calculate the renal blood flow.
- This is done by using the formula for clearance - UV/P - U is the Urine concentration, V is the volume of urine collected in minutes and P is the plasma concentration.
- The clearance of PAH from the circulation is equal to the effective renal plasma flow. The ERPF from the calculation is only 90% of the actual flow, because we know that when we measure the PAH in the urine, we are only getting 90% of it, because 10% flows back out into the renal vein.
- The actual renal plasma flow is calculated by dividing the effective renal plasma flow by 0.9 to reflect the fact that what we have calculated is only 90%
- In order to calculate whole blood flow we need to think about what else is in blood aside from the plasma, particularly RBCs. So, the renal whole blood flow is the actual renal plasma flow divided by 1-HCT.

How do blood flow and oxygen extraction vary in different parts of the kidney?

- Cortical flow is high and oxygen extraction is low
- Medullary blood flow is low and oxygen extraction is high because there is a lot of metabolic work done.
- This means the medulla is more vulnerable to hypoxic damage if flow is compromised.

8. **Counter current mechanism**

How does the countercurrent mechanism enable the kidney to concentrate urine?

- The "countercurrent mechanism" refers to a system in which the inflow runs parallel to, counter to and in close proximity to the outflow for some distance.
- Concentrating mechanism depends on maintaining a gradient of increasing osmolality along medullary pyramids
- 2 parts in this system:
    - Gradient is produced by the countercurrent ***multipliers*** in the loop of Henle
    - and maintained by the vasa recta acting as countercurrent ***exchangers***
- Countercurrent Multiplier:
    - Isotonic fluid flows from the PCT and enters the medulla in the lumen of tubules.
    - Water moves out of the thin descending limb of the LoH (highly permeable to water via aquaporin 1)
    - The luminal fluid becomes hypertonic, to equilibrate with the interstitium
    - When flowing back up the thick ascending limb of the loop of Henle, there is active transport of Na and Cl out of the lumen which is not permeable to water
    - The fluid flowing into the DCT is hypotonic
    - Water moves out of collecting duct (into the hypertonic interstitium of the medullary pyramids) under the influence of ADH
- The vasa recta acts as a countercurrent exchanger
    - Water diffuses out of the descending limb and into the ascending limb of the vascular loop.
    - Na, Cl and urea diffuse out of the ascending limb and into the descending limb.
    - As a result, the solute remains in the medullary pyramid, maintaining the interstitial concentration.

Youtube - *Professor Wendy Riggs covering the countercurrent mechanism as recommended by Josh:* **https://www.youtube.com/watch?v=UCfaca-92rY**

9. **GFR**

What is the definition of glomerular filtration rate

Amount of fluid (plasma filtrate) filtered by the glomerulus per unit time

What is the normal GFR?

125ml/minute or 180L in 24 hours in a normal adult

List some factors that affect GFR

- Overall surface of the capillary bed within the glomerulus - Regulated by mesangial cells that can contract, located between the basal lamina and endothelium.
- Permeability of glomerular capillaries
    - More permeable than those found elsewhere in the circulation
- Hydrostatic pressure gradients
    - Afferent arterial pressure (renal artery blood flow) This is kept stable through autoregulation between 90-220mmHg
    - Systemic BP may be proportional to GFR if outside autoregulation range
    - Afferent or efferent arteriolar constriction and the resulting renal blood flow
    - Hydrostatic pressure in Bowman's capsule (i.e. ureteric obstruction)
- Osmotic pressure gradients
    - oncotic from plasma protein concentration
    - Intrarenal interstitial pressure from obstruction or oedema
- Number of functioning renal corpuscles
    - Age
    - Atrophy
    - Nephrectomy
    - Parenchymal disease

Describe a method for measuring the GFR

Measure the excretion of a substance which is freely filtered through the glomerulus and neither secreted nor absorbed by the tubules. Must also be non toxic and not metabolised. Example: Inulin.

Again, we can use the clearance equation UV/P
Where;
U is the urine concentration of inulin
V is the urine flow in ml/min
P is the arterial plasma level of inulin
The resulting value or the “clearance” rate is the GFR
It can be easy to confuse PAH and Inulin calculations and what you use for which equation but if you remember that only about 20% of plasma inulin is filtered by the kidney then you know that concentration in the renal vein will still be pretty high so it’s not useful for calculating renal blood flow. Whereas, PAH is almost completely eliminated by the kidney through filtration and secretion, so the AV difference will be high, and the fact that it’s secreted by the kidney makes PAH unsuitable to be used to calculate GFR.

10. Water Handling & Thirst

Describe how water is reabsorbed in the different parts of the nephron

- 60-70% in the proximal tubule
- 15% in the loop of henle
- 5% in the distal tubule
- Up to 10% in the collecting duct depending on the presence of ADH or vasopressin

What is thirst, what causes it?

- An appetite, under hypothalamic control
- Increased plasma osmolarity
- Hypovolaemia
- Prandial response - habitual
- Psychogenic
- Response to dry mucous membranes

What are the physiological effects of dehydration?

Water loss lowers the ECF and ICF leading to low BP, tachycardia, increased ADH, decreased urine output, decreased GFR, activation of the renin-angiotensin system, increase in thirst.

Explain how thirst works to restore fluid status

- As plasma oncotic pressure rises, it is sensed by the osmoreceptors in the anterior hypothalamus.
- This triggers a release of vasopressin (ADH) from the posterior pituitary
- Vasopressin acts on the V2 receptor to trigger insertion of aquaporin channels into the luminal membrane of the renal collecting tubules. Aquaporins are usually stored in the cytoplasm of principal cells.
- Insertion of these allows more water to return to the body

What factors other than rising osmotic pressure increase vasopressin secretion?

Decreased ECF volume, emotion, surgical stress, nausea, vomiting, standing, angiotensin II, medications.

Describe the effects of a rapid infusion of 1000ml of normal saline to a dehydrated person (2016)

- Increased Cl and acidosis
- Increased baroreceptor firing
- Decreased HR
- Increased BP
- Increased urine output
- Decreased RAAS

What is an alternative physiological fluid?

Hartmanns or plasmalyte

11. RAAS

What conditions lead to activation of the renin-angiotensin system?

Activated in response to a decrease in BP/ECF or increased sympathetic activity. I.e. hypotension, haemorrhage, dehydration, cardiac failure, cirrhosis, Na depression, diuretics, pain, fear

Explain how hypotension activates the renin-angiotensin system

- Hypotension leads to reduced perfusion pressure of the afferent glomerular arteriole, stimulating release of renin by the juxtaglomerular cells.
- Renin converts angiotensinogen to angiotensin I.
- Angiotensin-converting enzyme converts angiotensin I to angiotensin II.
- Angiotensin II acts on the adrenal cortex's zona glomerulosa cells to release aldosterone.
- Aldosterone acts on the renal distal tubules to retain Na+ and water, thus in intravascular volume.
- Angiotensin II is also a potent arteriolar constrictor and contributes to a rise in blood pressure.

What physiological factors are involved in regulating renin secretion?

- Intrarenal baroreceptors - an increase of afferent arteriolar pressure at the JG cells causes a decrease in renin secretion and vise versa.
- The amount of Na and Cl entering the distal tubules in the macula densa - increased resorption causes a decrease in renin secretion.
- Increase in sympathetic nervous system - stimulates renin
- Vasopressin can decrease renin
- Angiotensin II provides inhibitory feedback to JG cells

12. Angiotensin

Describe the factors influencing angiotensin II production

Angiotensin II is the effector protein in the renin-angiotensin system
So, the factors which increase renin secretion also increase the activity of angiotensin II
These are:

- Increased sympathetic activity
- Increased circulating catecholamines
- Prostaglandins

Factors which decrease renin and therefore decrease ATII

- Increased Na and Cl reabsorption across macula densa
- Increased afferent arteriolar pressure
- Vasopressin

What are the physiological effects of angiotensin II?

- Arteriolar constriction
- Direct effects on the adrenal cortex to increase aldosterone
- Can enhance noradrenaline release
- Contraction of mesangial cells

- Direct action on renal tubules to reabsorb Na+
- Acts on the brain to decrease sensitivity of baroreceptor reflex
- Acts on the brain to increase water intake and increase release of vasopressin and ACTH

13. Impaired renal function (yes this is a physiology question!)

What are the physiological consequences of impaired renal function?

- Proteinuria (predominantly albuminuria) due to the increased permeability of glomerular capillaries
- Uremia - the accumulation of breakdown products of protein metabolism resulting in symptoms of uremia
- Acidosis - failure to excrete products of digestion and metabolism with the urine maximally acidified. The total amount of H+ that can be secreted can be reduced do to impaired renal tubular production of ammonium (NH4). The exception to this is renal tubular acidosis where there is an impaiored ability to acidify the urine.
- Hyperkalaemia from H+/K+ exchange.
- Abnormal handling and excess retention of Na - 3 mechanisms
    - Acute GN - reduction in the amount of Na filtered
    - Nephrotic syndrome - increased aldosterone causing salt retention. Low plasma proteins cause fluid shift from plasma to interstitium.
    - Volume overload

Why does the kidney lose the ability to concentrate urine in a patient with impaired renal function?

In advanced kidney disease osmolality is fixed at pasma level indicating loss of ability to concentrate or dilute the urine

This is due to

- Disruption of countercurrent mechanism
- Loss of functioning nephrons causing positive feedback that increases filtration on the remaining nephrons, which eventually causes more damage to remaining nephrons