Renin Angiotensin Aldosterone System

- Powerful mechanism for controlling pressure
- Renin – small protein enzyme released by the kidneys when the arterial pressure falls too low
  - Synthesized and stored in an inactive form called prorenin in the JG cells of the kidneys
  - JG cells are modified smooth muscle cells located in the walls of the afferent arterioles immediately proximal to the glomeruli
**RAAS**

Decreased Arterial Pressure

- Renin (Kidney)
- Renal substrate/Angiotensinogen (plasma protein)
  - A1
  - A2
- Renal retention of salt and water
- VC
- Inactivation
- Increased AP

**Two principal effects of Angiotensin II that can elevate AP**

- Vasoconstriction – occurs rapidly
  - Intense in the arterioles and less extent in the veins
  - Constriction of the arterioles increases peripheral resistance, raising AP
  - Mild constriction in veins promotes increased venous return of blood to the heart, helping the heart pump against the increasing pressure
Decreased excretion of both salt and water – slowly increases the ECF volume, increases the AP over a period of hours and days

- Even more powerful than the acute vasoconstrictor mechanism in eventually returning the AP back to normal

---

Two ways by which Angiotensin causes water and salt retention

- 1. angiotensin acts directly on the kidneys to cause salt and water retention
- 2. angiotensin causes the adrenal glands to secrete aldosterone, and the aldosterone in turn increases salt and water reabsorption by the kidney tubules
The AP must rise to a considerably increased level to overcome the two fluid retaining effects of angiotensin.

Whenever excess amounts of angiotensin circulate in the blood, the entire long-term renal-body fluid mechanism for AP control automatically becomes set to a higher than normal AP level.

Intrarenal effects of angiotensin that make kidneys retain salt and water:

- Constriction of renal blood vessel
  - diminished blood flow through the kidneys → less fluid filters through the glomeruli into the tubules → less urine excretion
- Slow blood flow in the peritubular capillaries
  - reduces their pressure which allows rapid osmotic reabsorption of fluid from the tubules → less urine excretion
- Increase tubular reabsorption of salt and water in the tubular cells
Aldosterone

- Marked increase in sodium reabsorption by the kidney tubules
- Water retention

Use of Clearance Methods to Quantify Kidney Function

- The rates at which different substances are cleared from the plasma provide a useful way of quantifying the effectiveness by which the kidneys excrete various substances
Renal Clearance of a substance

- The volume of plasma that is completely cleared of the substance by the kidneys per unit time
- There is no single volume of plasma that is completely cleared of a substance
- Provides a useful way of quantifying the excretory function of the kidneys
- Can be used to quantify the rate at which blood flows through the kidneys as well as the basic functions of the kidney: glomerular filtration, tubular reabsorption, and tubular secretion

If the plasma passing through the kidneys contains 1 mg of a substance in each ml and 1 mg of this substance is also excreted into the urine each minute, then 1 ml/min of the plasma is cleared of the substance

Clearance refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit time
\[ \text{Cs} \times \text{Ps} = \text{Us} \times \text{Vs} \]

where

\( \text{Cs} \) = clearance rate of a substance \( s \)
\( \text{Ps} \) = plasma concentration of the substance
\( \text{V} \) = urine flow rate
\( \text{Us} \) = urine concentration of the substance

Thus, renal clearance of a substance is calculated from the urinary excretion rate \((\text{Us} \times \text{V})\) of that substance divided by its plasma concentration.
Inulin Clearance

- Can be used to estimate GFR
- If a substance existed that was freely filtered (filtered as freely as water) and if it was not reabsorbed or secreted by the renal tubules, then the rate at which that substance was excreted in the urine \((U_s \times V)\) would be equal to the rate at which the substance was filtered by the kidneys \((GFR \times P_s)\)
- \(GFR \times P_s = U_s \times V\)

- \(GFR = U_s \times V = \frac{C_s}{P_s}\)
- Inulin – a polysaccharide molecule with a molecular weight of about 5200
  - Not produced in the body
  - Found in the roots of certain plants and must be administered IV into a patient to measure GFR
Renal handling of Inulin

- Plasma concentration = 1 mg/ml
- Urine concentration = 125 mg/ml
- Urine flow rate = 1 ml/min
- Inulin clearance = \( \frac{U_s \times V}{P_s} \)
  - \( = \frac{125 \times 1}{1} \)
  - \( = 125 \text{ ml/min} \)

Thus, 125 ml of plasma flowing through the kidneys must be filtered to deliver the inulin that appears in the urine.

Other substances used to estimate GFR:

- 1. radioactive iothalamate
- 2. creatinine – by product of skeletal muscle metabolism
  - Present in the plasma at a relatively constant concentration
  - Does not require IV infusion into the patient
Creatinine Clearance

- The most widely used method of estimating GFR clinically
- Creatinine is not a perfect marker for GFR
  - A small amount is secreted by the tubules
  - The amount of creatinine excreted in the urine slightly exceeds the amount filtered
  - Overestimate of the plasma concentration
- The creatinine clearance provides a reasonable estimate of GFR

Renal Circulation

- Renal Blood Flow
  - The 2 kidneys are perfused with 1/5 to ¼ of cardiac output per minute
  - This high BF is more of an expression of the renal processes involved in regulating the composition of the ECF than of excessive metabolic demands
  - Measurement:
    - Direct method – use of magnetic flow meters
    - Indirect method – application of clearance principles
Requirements for PAH Clearance test:

- In small amounts or plasma concentration, the extraction (combined filtration and secretion) is almost complete.
- It is not synthesized, destroyed, or altered in any way by the kidneys.
- The amount removed from the plasma by the kidneys is excreted in the urine (not reabsorbed).
- It does not by itself alter renal hemodynamics.
- The chemical detection or analysis of both substances in both urine and plasma is easy.

PAH Clearance

- Can be used to estimate renal plasma flow.
- If a substance is completely cleared from the plasma, the clearance rate of that substance is equal to the renal plasma flow.
- The amount of the substance delivered to the kidneys in the blood (renal plasma flow x Ps) would be equal to the amount excreted in the urine (Us x V).
RPF = \frac{U_s \times V}{P_s} = C_s

- GFR is only 20% of the total plasma flow
- A substance that is completely cleared from the plasma must be excreted by tubular secretion as well as glomerular filtration
- PAH 90% cleared from plasma, therefore can be used as an approximation of RPF

**Extraction ratio of PAH**

- The % of substance removed from the blood
- Averages 90% in normal kidneys
- Maybe reduced in diseased kidneys because of inability of damaged tubules to secrete PAH into the tubular fluid
- EPAH is calculated as the difference between the renal arterial (P PAH) and renal venous (V PAH) PAH concentration, divided by the renal arterial PAH concentration

\[ E_{PAH} = \frac{P_{PAH} - V_{PAH}}{P_{PAH}} \]
Calculation of RPF

- Plasma concentration of PAH = 0.01 mg/ml
- Urine concentration = 5.85 mg/ml
- Urine flow rate = 1 ml/min
- CPAH = \( \frac{5.85 \times 1}{0.01} = 585 \) ml/min RPF

Total Renal Plasma Flow

- TRPF = \( \frac{\text{Clearance of PAH}}{\text{Extraction Ratio of PAH}} \)
  = \( \frac{585}{0.9} = 650 \) ml/min
Total Blood Flow

- RPF = 650 ml/min
- Hematocrit = 0.45
  - % of RBC in the blood
- TBF = \[ \frac{650}{1 - 0.45} \] = 1182 ml/min

Filtration Fraction

- Calculated from GFR divided by RPF
- Fraction of plasma that filters through the glomerular membrane
- If RPF = 650 ml/min, GFR = 125 ml/min
- FF = 0.19
Calculation of Tubular Reabsorption or Secretion from Renal Clearances

- If the rates of GF and renal excretion of a substance are known, one can calculate whether there is a net reabsorption or a net secretion of that substance by the renal tubules.
- If the rate of excretion of the substance is less than the filtered load of the substance, then some of the substance must have been reabsorbed from the renal tubules.
- If the excretion rate is more than the filtered load, then the rate at which it appears in the urine represents the sum of the rate of GF plus tubular secretion.

Urine flow rate = 1 ml/min
Urine conc of sodium = 70 uEq/L
Plasma sodium conc = 140 uEq/L
GFR (inulin clearance) = 100 ml/min

Filtered sodium load = GFR x P Na = 100 x 140 = 14,000 uEq/min
Urinary sodium excretion = U Na x Urine flow rate = 70 uEq/min
Tubular reabsorption of sodium = 14,000 – 70 = 13,930 uEq/min
Comparisons of Inulin Clearance with Clearances of Different Solutes

- If the clearance rate of the substance equals that of inulin, the substance is only filtered and not reabsorbed or secreted.
- If the clearance rate of a substance is less than inulin clearance, the substance must have been reabsorbed by the nephron tubules.
- If the clearance rate of a substance is more than that of inulin, the substance must be secreted by the nephron tubules.

Renal Handling of Organic Substances

- GLUCOSE
  - Reabsorption involves an active process and the expenditure of energy.
  - A carrier substance is present in the luminal membrane of proximal tubular cells in fixed and limited amount.
    - The carrier combines reversibly with glucose from the tubular fluid to form the complex within the membrane, where it is split.
    - Glucose is delivered to the cytoplasm, and the membrane carrier returns to the luminal surface to accept another glucose molecule.
Glucose

- Normally, amount of glucose filtered per minute is totally reabsorbed
- Increase plasma glu conc $\rightarrow$ transport system becomes saturated (Tm glu) $\rightarrow$ glucose not reabsorbed is spilled in the urine
  - This limitation is due to:
    - Carrier shortage
    - Lack of metabolic energy for the transport system
- Renal threshold of glucose = 160 to 200 mg%
  - Tm G = 340 mg/min

Amino Acids

- There are probably no less than three renal tubular mechanisms for reabsorption of amino acids
  - One transports lysine, arginine, ornithine, cystine, and possibly histidine
  - A second handles aspartic and glutamic acids
  - A third involves proline, hydroxyproline, and glycine
- Amino acid transport mechanism displays saturability and substance specificity
Amino Acids

- AA that demonstrate relatively poor reabsorption with small Tm:
  - Glycine, arginine, proline, and hydroxyproline
- AA that are so effectively reabsorbed that saturation is not achieved by plasma concentrations which do not cause severe nausea and other physiological disturbances
  - Histidine, methionine, leucine, isoleucine, tryptophan, valine, threonine, and phenylalanine

Amino Acids

- One major role of the kidneys is to conserve amino acids as they pass through the tubules
- Inborn errors of membrane transport is manifested by some of the amino acids – cystinuria, hyperprolinemia
  - The third is associated with mental deficiency
Ascorbic Acid

- $T_m = 2 \text{ mg/min}$
  - Represents the net activity of a three component system (filtration, proximal tubular reabsorption, and distal tubular secretion)
- Distal secretion – promoted by adrenal steroid and increased filtered load of sodium

Urea

- Major product of protein metabolism; is filtered and reabsorbed to varying degrees (40-70% throughout the nephron)
- Reabsorptive mechanism is by passive diffusion
Uric acid

- Appears as a consequence of metabolism of purine bases
- Tm limited
- More or less completely reabsorbed by the renal tubules of both normal and gouty individuals

Creatine

- Product of muscle metabolism which disappears from the urine after adolescence
- Filtered and reabsorbed in concentrations below 0.5 mg%
  - At higher concentrations, reabsorption is incomplete and excretion is enhanced
- No Tm has been demonstrated
Creatinine

- Derived from creatine in muscles
- Clearance is by glomerular filtration and tubular secretion
- Tm is small – about 16 mg/min

It is a function of the tubules to reabsorb selectively the necessary substances and to reject undesirable excesses of anything taken into the body.

---

Post test

1. Effects of aldosterone
   A) increase sodium reabsorption
   B) increase water reabsorption
   C) affects principal cells in the collecting ducts
   D) A and B
   E) all of the above
2. True about renin
   A) converts angiotensinogen to angiotensin I
   B) synthesized as prorenin
   C) it is a protein enzyme
   D) all of the above
   E) none of the above
   F) B and C

3. The most powerful vasoconstrictor agent in the human body
   A) aldosterone
   B) angiotensinogen
   C) renin
   D) vasopressin
   E) none of the above
4. The conversion of angiotensin I to angiotensin II takes place in the
   A) adrenals
   B) kidneys
   C) pancreas
   D) uterus
   E) none of the above

5. The expected renal plasma flow is equal to the clearance of
   A) PAH
   B) creatinine
   C) inulin
   D) A and B
   E) none of the above