URINARY SYSTEM, GLOMERULAR FILTRATION

I Overview

A Function of Urinary System

1 Maintaining water balance/osmotic balance in the body
2 Regulating quantity and concentration of most ions (e.g. Na^+, K^+, HCO_3^-)
3 Maintaining plasma volume
4 Maintaining acid-base balance
5 Excreting end products of bodily metabolism and foreign compounds
6 Endocrine function: Secreting erythropoietin and renin (hormone involved in salt regulation)

B Kidney Structure

1 each kidney is composed of about 1 million microscopic *functional units* called **nephrons**
2 Arrangements of nephrons give rise to two distinct regions
a outer region: **renal cortex**
b inner region: **renal medulla**

C Nephron structure: Can be broken into two major parts

1 Vascular component
a **renal artery**
b **afferent arterioles**, one of which supplies each nephron
c **glomerular capillaries**. The **glomerulus** of each nephron is a ball-like tuft of these capillaries, and

is where filtration occurs (fenestrations)

d **efferent arteriole**, which leaves the glomerulus

e **peritubular capillaries**, which supply the renal tissue with blood, and are important in exchanges between the tubular system and the blood during urine production

2 Tubular component B where urine is processed

a Hollow fluid filled tube formed by a single layer of epithelial cells.

b **Bowman=s capsule** begins the tubular component, and is a doubled wall cup that surrounds the glomerulus and collects the fluid filtered from the glomerular capillaries

c **proximal tubule**

d **loop of Henle**, which forms a U-shaped loop that descends into the renal medulla, then ascends back into cortex

e The **juxtaglomerular apparatus** lies next to the glomerulus, is composed of both tubular and vascular components

f **distal tubule**

g **collecting duct**

D The Three Basic Renal Processes

1 **Glomerular filtration** B in glomerulus (material passes from blood to tubules)

2 **Tubular reabsorption** B primarily in proximal tubule (material passes back from tubules to blood)

3 **Tubular secretion** B primarily in distal tubule (material

selectively transferred from blood to tubules)

II Glomerular Filtration

A Process of filtration
1 Glomerular membrane allows passage of plasma and plasma ions
2 Glomerular membrane excludes all cellular components, and more than 99% of all proteins in blood from Bowman=s capsule

B Physics of filtration
1 Glomerular capillary blood pressure is driving force for filtration. Opposed by osmotic and hydrostatic pressures. Yields Net Driving Force
2 Glomerular filtration rate (GFR) = **net pressure** x **filtration coefficient**
a net pressure = 10 mm Hg
b filtration coefficient is determined by surface area and permeability of glomerular membrane

C Regulation of GFR
1 General considerations
a Plasma colloid osmotic pressure and hydrostatic pressure in Bowman=s capsule are constant
b The glomerular capillary blood pressure can be changed to regulate GFR
2 Alteration in glomerular capillary blood pressure
a Autoregulation
i when arterial blood pressure increases: reduced blood flow
ii when arterial pressure declines: increase in blood flow.

iii How it works: * tubuloglomerular feedback mechanism:
juxtaglomerular apparatus (JGA) detects changes in fluid flow rate. JGA releases a vasoconstrictor or vasodilator.

b Extrinsic regulation

i Baroreceptors sense changes in mean arterial blood pressure, which leads to stimulation of autonomic nervous system to either vasoconstrict or vasodilate blood vessels.

ii Kidneys participate in this response if large drop in blood pressure:
*In kidneys, afferent arterioles carrying blood to the glomeruli vasoconstrict, which results in less glomerular filtration, and hence reduces urine output. This reduces fluid loss which helps to stabilize mean arterial blood pressure.

TUBULAR REABSORPTION AND TUBULAR SECRETION

Tubular Reabsorption (from tubules to blood)

A General: selective reabsorption of essential materials out of tubules and back into the blood

B Transepithelial Transport
- 1 Reabsorption occurs by transepithelial transport, which occurs in 5 steps
  - a substance leaves the tubular fluid by crossing the luminal side of membrane of the tubular epithelial cell
  - b it crosses the cytosol of the tubular epithelial cell
  - c it crosses the basolateral side of the tubular epithelial cell membrane
  - d it diffuses through the interstitial fluid
  - e it crosses the peritubular capillary wall and enters the plasma
- 2 Two types of reabsorption
  - a active: at least one of the 5 steps requires energy
  - b passive: none of the 5 steps requires energy

C Reabsorption of Na^+ is Active
- 1 Na+/K+ ATPase pump generates a concentration gradient
- 2 Na+ in epithelial cell is low; Na+ in interstitial fluid is high
- 3 Na+ diffuses from tubule lumen to epithelial cell
- 4 Na+ is pumped (by Na+/K+ ATPase) into interstitial fluid (this is the active step)
- 4 Na+ diffuses from interstitial fluid to capillary

D Na^+ Dependent Secondary Active Transport

1 Glucose, amino acids and other nutritionally important compounds are moved against their concentration gradients by secondary active transport

2 These substances are co-transported (from the tubule lumen to the tubule cell) along with the Na+; they get a 'free' ride.

E Na^+ Dependent Passive Reabsorption

1 Na+ movement makes an electrical gradient

2 Cl- follows (opposite charges attract)

3 Na+ Cl- movement makes an osmotic gradient

4 ***Water follows***

5 Water movement makes a concentration gradient for remaining substances, especially urea

6 Urea follows

a about half of the urea is reabsorbed, the other half is excreted

F Regulation of Na+ reabsorption

1 Amount of Na^+ in the body affects blood pressure

a Increases in Na^+ lead to increases in ECF volume (because of osmotic forces) and therefore increases blood pressure.

2 Na^+ reabsorption is regulated in the distal tubule & collecting ducts.

3 Primary positive regulation system is the renin-angiotensin-aldosterone system (positive regulation means it promotes Na^+ retention and increases in blood volume)

a If Na^+ /ECF volume/blood pressure falls, the juxtaglomerular apparatus secretes the enzyme

renin into the blood.

b Renin converts **angiotensinogen** to angiotensin I, which is then converted to

c angiotensin II by angiotensin converting enzyme **(ACE)** in the lungs.

d **Angiotensin II** then stimulates the adrenal cortex to secrete **aldosterone**;

e **aldosterone** increases Na^+ reabsorption in the distal and collecting tubules by **adding** more Na^+/K^+ ATPase pumps to the basolateral membranes & increasing apical membrane permeability of Na^+ and (K^+).

f This promotes **Na^+ retention**, and so, indirectly, increases ECF volume and arterial blood pressure

5 Primary negative system is the **atrial natriuretic peptide (ANP)** system

a the heart produces ANP

b when ECF volume increases too much (↑BP), cardiac cells are stretched and ANP is released.

c ANP inhibits Na^+ retention in the distal parts of the nephron, inhibits renin and aldosterone secretion, and increases GFR by changing the filtration coefficient.

d These actions <u>decrease</u> Na^+ retention, and lower ECF volume and arterial <u>blood pressure</u>.

II Tubular Secretion (from blood to tubules)

A General: supplemental mechanism for getting rid of substances (filtration takes care of most of it) B is the reverse of tubular reabsorption

B H^+: when ECF is too acidic, H^+ is secreted. (Mechanisms will be discussed later)

C K^+

1 Is both reabsorbed and secreted

2 K^+ secretion (not K^+ filtration or reabsorption) is the process regulated by the kidneys

a active transport of Na^+ during Na^+ reabsorption results in the secretion of K, since the Na^+-K^+-ATPase pump moves Na^+ and K^+ in opposite directions

b If K^+ is too high

i High K^+ directly increases aldosterone production

ii more Na^+/K^+ pumps added at basal membrane; more K^+ channels added to apical membrane

iii which increases K^+ secretion

D Organic Ions

1 Separate secretory carriers for (+) ions and (-) ions

2 Involved in removal of:

a unwanted endogenous substance, such as prostaglandins

b foreign inorganic chemicals, such as pesticides and drugs

URINE CONCENTRATION AND FLUID BALANCE

I Urine Concentration

A Overview

1 Need to be able to produce urine of varying concentrations.

2 The way this is accomplished

a is by using the loop of Henle to set up a concentration gradient within the interstitial fluid of the renal medulla

b The collecting tubule passes through this concentration gradient. The collecting tubule is selective permeably to water. Control of this permeability is the basis for generating a concentrated urine = water recovery.

B Countercurrent Multiplication (to set up the concentration gradient)

1 The descending loop of Henle is permeable to water, and does not transport Na^+

2 The ascending loop of Henle is not permeable to water, but has active Na^+ transport systems that can pump out Na^+

3 Na^+ is pumped out of the ascending loop, which increases the osmolarity of the interstitial fluid, which causes water to leave the descending loop.

4 The water leaving the deciding loop causes the fluid in the loop to increase in osmotic pressure.

5 Net result: the **fluid leaving the loop has an osmotic pressure of 100** (is dilute), and a concentration gradient from 300 to 1200 mosm/liter exists in the interstitial

fluid of the renal medulla.

C Controlling Urine Concentration
  1 The collecting tubule runs through the concentration gradient as it heads toward renal pelvis
  2 Urine in collecting tubule is dilute with an osmotic pressure of 100 mosm/liter. HOWEVER, in the presence of vasopressin (also called Anti-Diuretic Hormone = ADH) the collecting tubules become permeable to water & water recovery.
  3 Vasopressin is produced/released by the hypothalamus/posterior pituitary
    a If ECF is too concentrated (too many solutes and not enough water), vasopressin is released, and water is allowed to diffuse out of distal and collecting tubules, which makes the urine more concentrated (= increased recovery of water)
    b If ECF is too dilute (too much water), vasopressin is not released, water is not reabsorbed in the distal and collecting tubules, and the urine is dilute (= decreased recovery of water).
    c Range of urine concentration is 100 to 1200 mosm/liter
    d vasopressin also stimulates thirst

II Fluid Balance

A Mass balance
  1 Input must equal output.
  2 most fluid input pathways are poorly regulated
  3 some fluid output poorly regulated

B Fluid Distribution in the Body
  1 40 to 80% of body mass is water

2 Specific individual=s water content stays constant over long periods of time, but can vary a lot from individual to individual

3 Fat content is the major factor that influences water composition of body

C Ion Distribution in the body

1 Plasma and Interstitial fluid

a Essentially the same. Together plasma and interstitial fluid make up the ECF. Any change in one of the components of the ECF is quickly reflected in the other component.

2 ECF vs. ICF

a Cellular membranes are more selective than capillary walls, so materials don=t move as freely across cellular membranes as across the capillary membranes

b Cellular proteins in the ICF cannot leave cells very easily.

c Na^+ and K^+ and their associated anions are unequally distributed between ECF and ICF; this is maintained in large part by the Na^+ K^+ ATPase pump.

d **Water moves freely** between ECF and ICF: this movement is determined by osmotic effects alone

D Regulation

1 The ECF is intermediate between the cells (ICF) and the external environment; all exchanges of water and solutes between the ICF and the external environment must go through the ECF.

2 **Plasma is the only** fluid that can have its volume and composition regulated. However, if plasma volume or composition changed

a the interstital fluid also changes
b the ICF changes to the extent allowed by cell membrane permeability

3 Two methods of control:

a ECF volume is regulated to maintain blood pressure. Maintenance of salt (Na^+) balance is the primary way that ECF volume is regulated over the long term

b ECF osmolarity (all solutes) must be regulated to prevent shrinking or swelling of cells. Maintenance of water balance is the primary way this is accomplished.

c ECF volume and ECF osmolarity are related to each other!

III Regulation of ECF Volume: Controlling the Na^+ load.

A Overview/purpose: **Long term regulation of blood pressure** by regulating plasma volume, which is accomplished by regulating the **total quantity of Na^+.**

B Mechanisms regulating Na^+ in urine

1 Control of GFR by extension of baroreceptor reflex
2 Control of Na^+ reabsorption in kidneys using the renin-angiotensin-aldosterone system
3 Control of Na^+ retention using atrial natriuretic peptide

IV Regulation of ECF Osmolarity B by regulating conservation of H2O

A Overview/purpose

1 ECF osmolarity affects ICF osmolarity.
2 ECF hypertonicity (usually by dehydration) leads to

ICF hypertonicity which causes cells to shrink which can lead to mental impairment and circulatory shock.

3 ECF hypotonicity (usually overhydration) leads to ICF hypotonicity which can lead to brain dysfunction and muscle weakness.

B Mechanisms of water regulation

1 Hypothalamic osmoreceptors monitor ECF osmolarity and initiate responses.

2 High osmolarity (too little water): vasopressin released.

3 Low osmolarity (too much water): vasopressin release inhibited

ACID/BASE BALANCE

I Acid Base Chemistry

A Acids
1 Hydrogen-containing substances that dissociate in solution to produce
a free H^+
b anions (negatively charged ions)
2 Strong acid has a greater tendency to dissociate in solution than does a weak acid.
a Strong acid: for example, HCl: every molecule dissociates into H^+ and Cl^-
b Weak acid: for example, H_2CO_3 (carbonic acid): only a portion dissociate into H^+ and HCO_3^-

B Bases
1 A base is a substance that can bind with a free H^+ and remove it from solution
2 A strong base can bind H^+ more readily than can a weak base.

C pH
1 $pH = \log 1/[H^+]$
2 low pH = high acid
3 Every unit change in pH = tenfold change in $[H^+]$ because of log

D Buffers
1 Mixture of compounds that minimize pH changes when either an acid or a base is added or removed from the solution
a When a buffer is present, the addition of a HCl causes less of a change in pH than it would have if

the buffer were not present.

E Effects of pH fluctuations on the body
  1 Only a narrow pH range is compatible with life
  2 Effects of pH fluctuations
    a changes in muscle and nerve excitability
      i acidosis (more free H^+) depresses CNS and muscle
      ii alkalosis (less free H^+) causes overexcitability of neurons
    b change enzyme activities profoundly

II Chemical buffer systems are first line of defense

A Buffers respond within fractions of a second to changes in $[H^+]$. Although buffers pick up H^+ very rapidly, they do not eliminate them from the body.

B H_2CO_3 / HCO_3^- buffer pair
  1 Very effective buffer & is **most important in body** for buffering pH changes caused by anything other than fluctuations in CO_2 generated H_2CO_3
  2 $H^+ + HCO_3^- \approx\equiv H_2CO_3 \approx\equiv H_2O + CO_2$ (H_2CO_3 = carbonic acid)
  3 When H^+ is added from any source other than CO_2, drives above reaction to right; H^+ ions are absorbed, and CO_2 is produced.
  4 When H^+ falls, above reaction is driven to the left, and CO_2 and water combine to produce H^+ and HCO_3^-

C Protein buffers
  1 proteins contain both acidic and basic groups that can accept or give up H^+
  2 Most important in ICF, where most of proteins exist

3 Hemoglobin is an important buffer in the blood

D Phosphate buffers
1 Important buffer in the ICF (secondary to proteins)
2 Only buffer in urine
a Humans usually consume excess phosphates which are excreted in urine

III Pulmonary ventilation is the second line of defense.

A The respiratory system can respond to increases in arterial $[H^+]$ within a few minutes (peripheral chemoreceptors).

B When $[H^+]$ increases, ventilation rates increase.

C Increase in ventilation rate results in more CO_2 than usual being expired

D This drives the following reaction to the right

$$H^+ + HCO_3^- \approx\equiv H_2CO_3 \approx\equiv H_2O + CO_2$$

E Conversely, when $[H^+]$ falls, ventilation is reduced, which results in a buildup of $[H^+]$ in the plasma by reversing the reaction above.

F Lungs rid the body fluids of 100 times more H^+ (derived from carbonic acid) than the kidneys remove from non-carbonic acid sources.

IV Kidneys are third line of defense B slowest but most effective in the long term

A Mechanisms of Acid Base Regulation to eliminate H^+ when

H^+ too high

1 Small amounts of H^+ filtered into tubules through Bowman=s capsule
   a Small amount because very little H^+ in plasma

2 Secretion of H^+ into tubules -- how it works:
   a In tubule cells: $H_2O + CO_2 \equiv H_2CO_3 \equiv H^+ + HCO_3^-$
   b H^+ then actively transported into tubular lumen
      i There it combines with FILTERED HCO_3^- to form H_2O and CO_2
      ii CO_2 diffuses back into tubular cell, where it can combine with water; back to a) above
   d HCO_3^- diffuses back into plasma to act as buffer
   e This process continues until all filtered HCO_3^- is used up.

3 Production of Anew@ HCO_3^- once all filtered HCO_3^- used up
   a CO_2 diffuses into tubular cells from plasma
   b $H_2O + CO_2 \; 6 \; H_2CO_3 \; 6 \; H^+ + HCO_3^-$
   c H^+ then actively transported into tubular lumen
      i There it combines with filtered phosphate ($HPO_4^=$)
      ii The HCO_3^- produced in b) above diffuses into plasma; this is Anew@ in the sense that it=s production is not matched by a concurrent disappearance of an HCO_3^- in the tubular lumen. This adds to plasma buffering capacity.

4 Once all phosphate buffer in urine used up:
   a NH_3 produced from amino acid glutamine
   b Acts as a buffer for H^+ & is excreted in urine

i $NH_3 + H^+ \equiv NH_4^+$

B Mechanisms of Acid Base Balance when H+ is low
1 Rate of H^+ secretion reduced
2 Rate of HCO_3^- filtration increased
3 Result: less H^+ in urine, more HCO_3^- in urine, urine becomes alkaline. Continues till acid base balance restored.

VI Acid/Base Imbalances

A Respiratory acidosis: hypoventilation
1 Causes: lung disease, depression of respiratory center by drugs or disease, nerve or muscle disorders that reduce respiratory capability, or holding your breath
2 Results: CO_2 elevated, H+ elevated
3 Compensation
a Chemical buffers take up extra H^+
b Lungs can NOT get rid of extra H^+ since they are the problem in the first place
c Kidneys compensate in the long term

B Respiratory alkalosis: hyperventilation
1 Causes: fever, anxiety, exposure to high altitude
2 Results
a Excessive loss of CO_2, so too little H^+ in ECF
3 Compensation
a Chemical buffers release H^+ -- this tends to reduce the hyperventilation quickly
b If alkalosis persists for hours/days, kidneys respond as described previously

C Metabolic acidosis

1. Causes: severe diarrhea (HCO_3^- lost from GI tract), diabetes, strenuous exercise, severe renal failure
2. Results: reduced HCO_3^- & increased H+

3. Compensation
    a. buffers take up extra H^+
    b. lungs blow off additional CO_2
    c. kidneys excrete more H^+ and conserve more HCO_3^-
        i. note: if renal failure is the cause, this will not occur, and complete restoration of acid base balance not possible

D. Metabolic alkalosis
1. Causes: vomiting (loss of non-carbonic acid H^+ from GI tract)
2. Results: Increase in blood HCO_3^- , decrease in blood H^+
3. Compensation
    a. chemical buffers liberate H^+
    b. ventilation reduced
    c. after several days, kidneys conserve H^+ and excrete more HCO_3^-