Regulation of Body Fluid Compartments: Extracellular and Intracellular Fluids; Edema

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The maintenance of a relatively constant volume and stable composition of the body fluids is essential for homeostasis.

STEADY-STATE CONDITIONS

Fluid (water) added to the body is highly variable and must be carefully matched by an equal output of water from the body to prevent body fluid volumes from increasing or decreasing.

DAILY INTAKE OF WATER

(1) it is ingested in the form of liquids or water in food, which together normally add about 2100 ml/day to the body fluids;

(2) it is synthesized in the body by oxidation of carbohydrates, adding about 200 ml/day.

These mechanisms provide a total water intake of about 2300 ml/day

DAILY LOSS OF BODY WATER

- Insensible water loss.
  - Cannot be precisely regulated
  - We are not consciously aware of it
  - Water loss by evaporation from:
  - The respiratory tract:
    - Averages about 300 to 400 ml/day
  - Diffusion through the skin:
    - Independent of sweating
    - Average 300 to 400 ml/day.
    - Minimized by the cholesterol-filled, cornified layer of the skin
    - With extensive burns, the rate of evaporation can increase as much as 10-fold, to 3 to 5 L
- Fluid loss in sweat.
  - Highly variable, depending on physical activity and environmental temperature.
  - Average 100 ml/day
  - Increases to 1 to 2 L/hour in very hot whether.
- Water loss in feces.
  - Small amount of water (100 ml/day) normally is lost in the feces.
  - Can increase to several liters a day in people with severe diarrhea
- Water loss by the kidneys
  - The most important means whereby the body maintains balance between water intake and output as well as most electrolytes.
  - urine volume can be as low as 0.5 L/day or as high as 20 L/day.

BODY FLUID COMPARTMENTS

- The total body fluid is distributed mainly between two compartments, the extracellular fluid and the intracellular Fluid
- The extracellular fluid is divided into the interstitial fluid and the blood plasma.
- another small compartment of fluid that is referred to as transcellular fluid.
  - includes fluid in the synovial, peritoneal, pericardial, and intraocular spaces, as well as the cerebrospinal fluid
  - specialized type of extracellular fluid
  - about 1 to 2 liters.
- total body water is about 60% of the body weight
- Women and elderly has high percentage of body fat and lower percentage of body water

INTRACELLULAR FLUID COMPARTMENT

- the intracellular fluid constitutes about 40% of the total body weight (2/3 Total body water)
- the composition of cell fluids is remarkably similar between cells.

EXTRACELLULAR FLUID COMPARTMENT

account for about 20% of the body weight (1/3 of total body water)

Divided into two largest compartments

the interstitial fluid, which makes up more than three-fourths

The plasma, which makes up almost one-fourth of the extracellular fluid,

The plasma:

- Noncellular part of the blood;
- exchanges substances continuously with the interstitial fluid through pores impermeable to proteins

BLOOD VOLUME

The average blood volume of adults is about 7% of body weight, or about 5 liters.

60% of the blood is plasma and 40% is red blood cells.

Hematocrit (Packed Red Blood Cell Volume):

The hematocrit is the fraction of the blood composed of red blood cells

In men, the measured hematocrit is normally about 0.40, and in women, it is about 0.36.

CONSTITUENTS OF EXTRACELLULAR

- Similar Ionic Composition of Plasma and Interstitial Fluid is similar.
- The most important difference between these two compartments is the higher concentration of protein in the plasma
- Donnan effect:
  - the concentration of positively charged ions (cations) is slightly greater (~2%) in plasma.
  - Plasma proteins have a net negative charge and therefore tend to bind cations
  - Negatively charged ions (anions) tend to have a slightly higher concentration in interstitial fluid the plasma proteins repel the negatively charged anions.
- The extracellular fluid, including the plasma and interstitial fluid, contains large amounts of sodium and chloride ions and reasonably large amounts of bicarbonate ions but only small quantities of potassium, calcium, magnesium, phosphate, and organic acid ions.

INTRACELLULAR FLUID CONSTITUENTS

In contrast to the extracellular fluid, the intracellular fluid contains only small quantities of sodium and chloride ions and almost no calcium ions.

Instead, it contains large amounts of potassium and phosphate ions plus moderate quantities of magnesium and sulfate ions,

Also, cells contain large amounts of protein—almost four times as much as in the plasma.

FLUID EXCHANGE AND OSMOTIC EQUILIBRIUM BETWEEN INTRACELLULAR AND EXTRACELLULAR FLUID

The distribution of fluid between intracellular and extracellular compartments is determined mainly by the osmotic effect of smaller solutes acting across the cell membrane

That’s because cell membranes are relatively impermeable to most solutes but are highly permeable to water

Water diffuses across the membrane toward the region of higher solute concentration.

The pressure that makes water moves called the osmotic pressure.

osmolality is the concentration is expressed as osmoles per kilogram of water

osmolarity is expressed as osmoles per liter of solution.

Calculation of the Osmolarity and Osmotic Pressure of a Solution

the osmotic pressure of a 0.9% sodium chloride

solution is calculated as follows.

A 0.9% solution= 0.9 gram of sodium chloride per 100 milliliters of solution, or 9 g/L.

molecular weight of sodium chloride is 58.5 g/mol

molarity of the solution is 9 g/L divided by 58.5 g/mol = 0.154 mol/L.

Because each molecule of sodium chloride is equal to 2 osmoles

osmolarity of the solution is 0.154 × 2, = 0.308 Osm/L.

potential osmotic pressure of this solution would therefore be 308 mOsm/L × 19.3 mm Hg/ mOsm/L, or 5944 mm Hg.

osmotic coefficient for sodium chloride is 0.93

So actual osmolarity is 308 × 0.93, or about 286

Isotonic, Hypotonic, and Hypertonic Fluids

- osmolarity of intracellular fluid is 282 mOsm/L
- The terms isotonic, hypotonic, and hypertonic refer to whether solutions will cause a change in cell volume.
- The tonicity of solutions depends on the concentration of impermeant solutes.
- The solution is said to be isotonic because it neither shrinks nor swells the cells.
- Examples of isotonic solutions include a 0.9% solution of sodium chloride or a 5% glucose solution.

Isosmotic, Hyperosmotic, and Hypo-Osmotic Fluids

Some solutes can permeate the cell membrane.

Solutions with an osmolarity the same as the cell are called isosmotic, regardless of whether the solute can penetrate the cell membrane.

The terms hyperosmotic and hypo-osmotic refer to solutions that have a higher or lower osmolarity, respectively, without regard for whether the solute permeates the cell membrane.

Highly permeating substances, such as urea, can cause transient shifts in fluid volume between the intracellular and extracellular fluids.

given enough time, the concentrations of these substances eventually becomes equal.

Physiological anatomy of the renal system, general mechanism of homeostasis and excretion.

Multiple functions of the kidney:

First to rid the body of waste materials that are ingested or produced by metabolism.

A second function that is especially critical is to control the volume and electrolyte composition of the body fluids.

And many other important homeostatic functions.

Excretion of Metabolic Waste Products, Foreign Chemicals, Drugs, and Hormone Metabolites

- Urea (from the metabolism of amino acids),
- Creatinine (from muscle creatine),
- Uric acid (from nucleic acids),
- End products of hemoglobin breakdown (e.g., bilirubin),
- Most toxins and other foreign substances that are produced by the body or ingested
- These waste products must be eliminated from the body as rapidly as they are produced.

Regulation of Water and Electrolyte Balances

Excretion of water and electrolytes must match intake precisely.

Although temporary (or cyclic) imbalances occurs but maintenance of life depends on restoration of water and electrolyte balance.

Experimental studies have shown that in many people, sodium intake can be increased to 1500 mEq/day (more than 10 times normal) or decreased to 10 mEq/ day (<0.1 of normal), with relatively small changes in extracellular fluid volume or plasma sodium concentration.

Sudden 10-fold increase in sodium intake from a low level of 30 mEq/day to a high level of 300 mEq/day.
Within 2 to 3 days after raising the sodium intake, renal excretion also increases to about 300 mEq/day so that the balance between intake and output is rapidly re-established.
The shaded areas represent the net sodium retention or net sodium loss

Other functions:

- Regulation of arterial pressure:
  - Excreting variable amounts of sodium and water.
  - Secreting hormones and vasoactive factors or substances
- Regulation of acid–base balance
  - Excreting acids and by regulating the body fluid buffer stores.
- Regulation of erythrocyte production
  - Produces erythropoietin in response to hypoxia.
- Regulation of 1,25-dihydroxyvitamin d3 production
- Glucose synthesis
  - During prolonged fasting, through a process referred to as gluconeogenesis.

PHYSIOLOGIC ANATOMY OF THE KIDNEYS

The two kidneys lie on the posterior wall of the abdomen, outside the peritoneal cavity

weighs about 150 grams

contains an indented region called the hilum through which pass the renal artery and vein, lymphatics, nerve supply, and ureter

Surrounded by a tough fibrous capsule

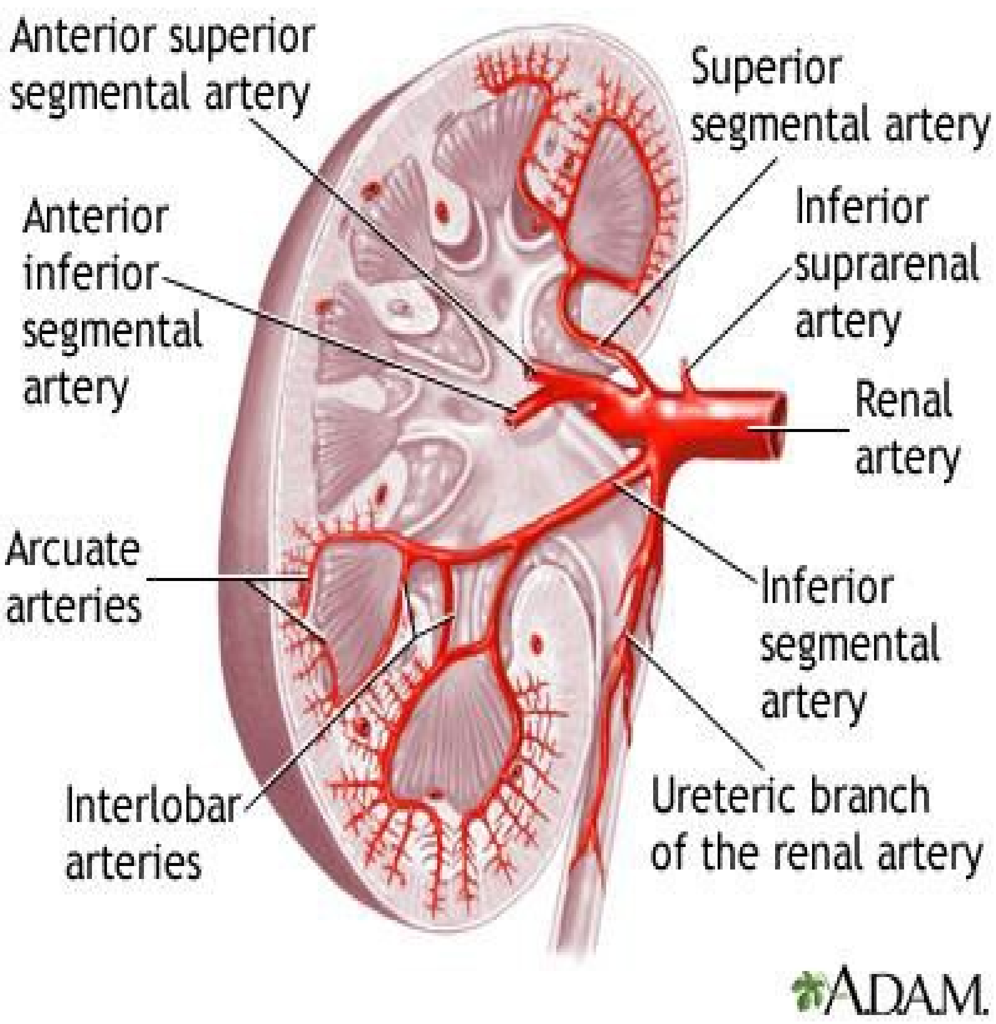
On sectioning, outer cortex and the inner medulla regions.

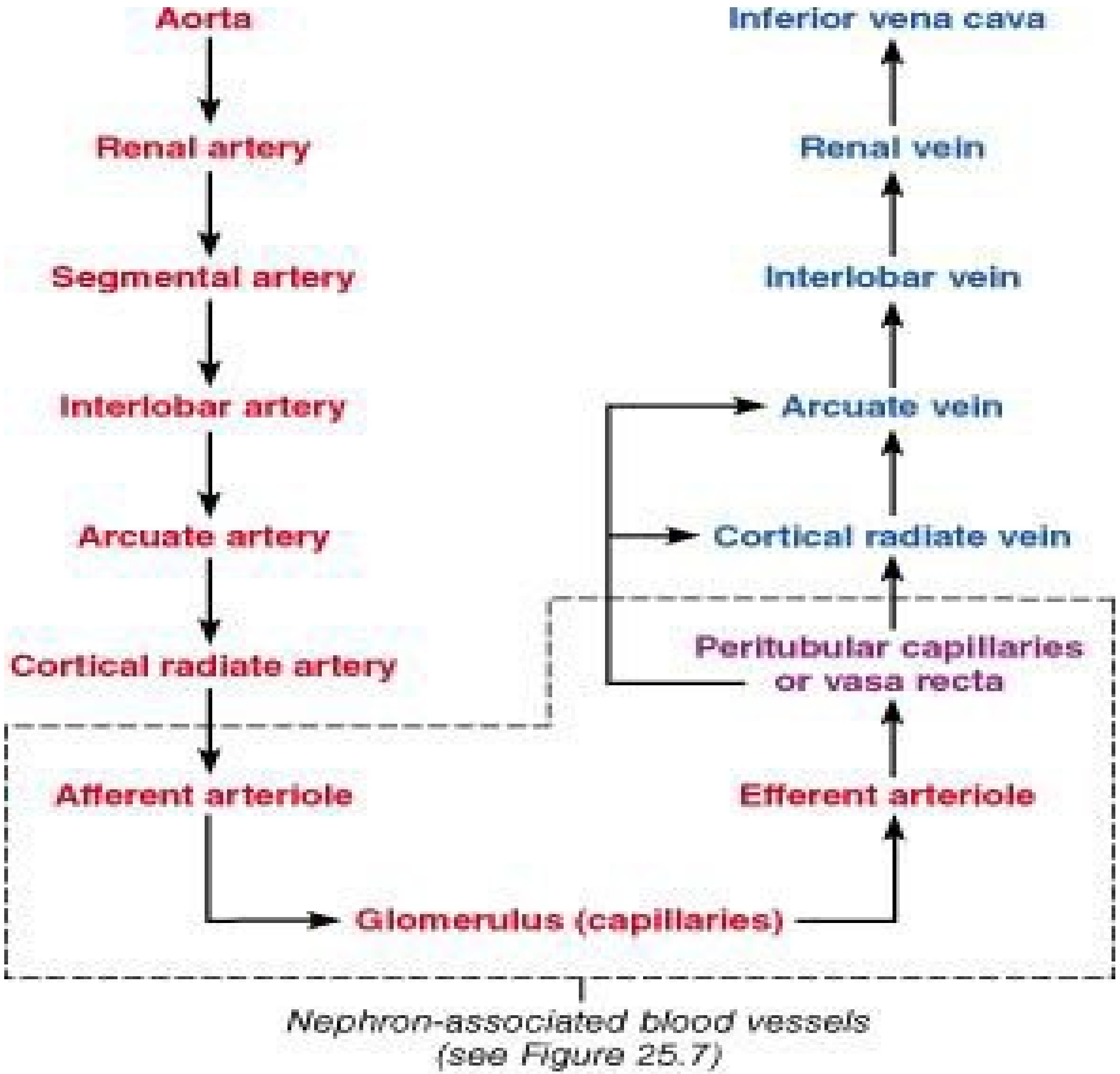
medulla is divided into 8 to 10 cone-shaped masses of tissue called renal pyramids, terminates in the papilla,

the renal pelvis, a funnel-shaped continuation of the upper end of the ureter divided into major calyces that extend downward and divide into minor calyces.

RENAL BLOOD SUPPLY

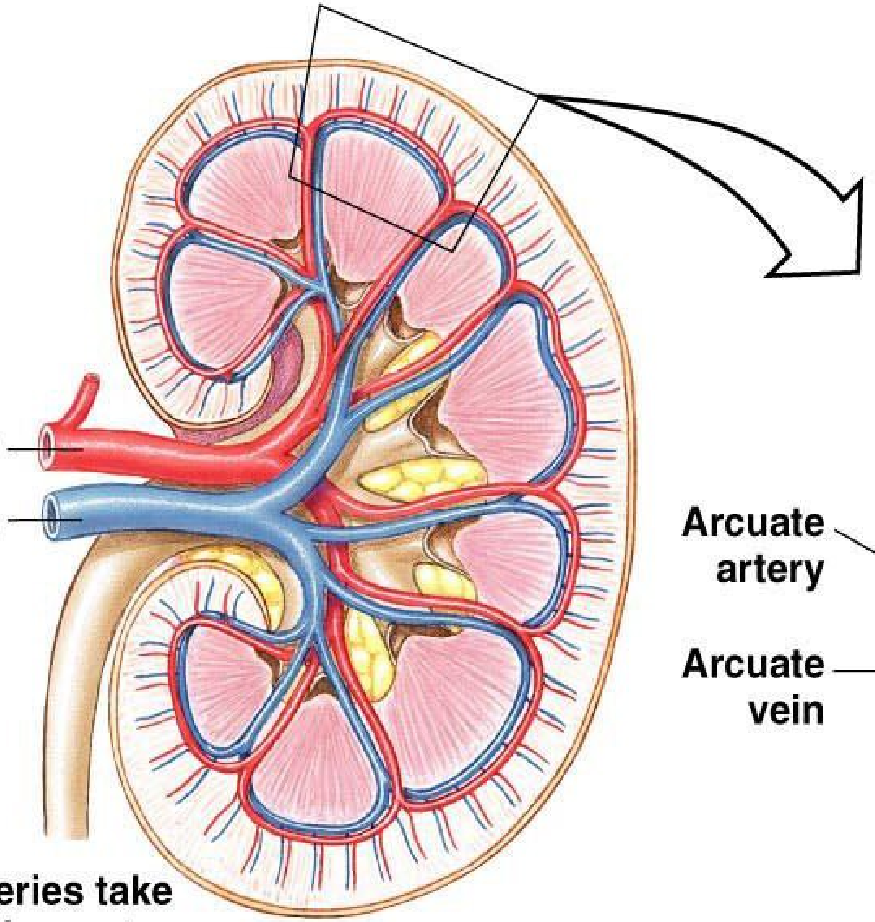
Blood flow to the two kidneys is normally about 22% of the cardiac output, or 1100 ml/min.



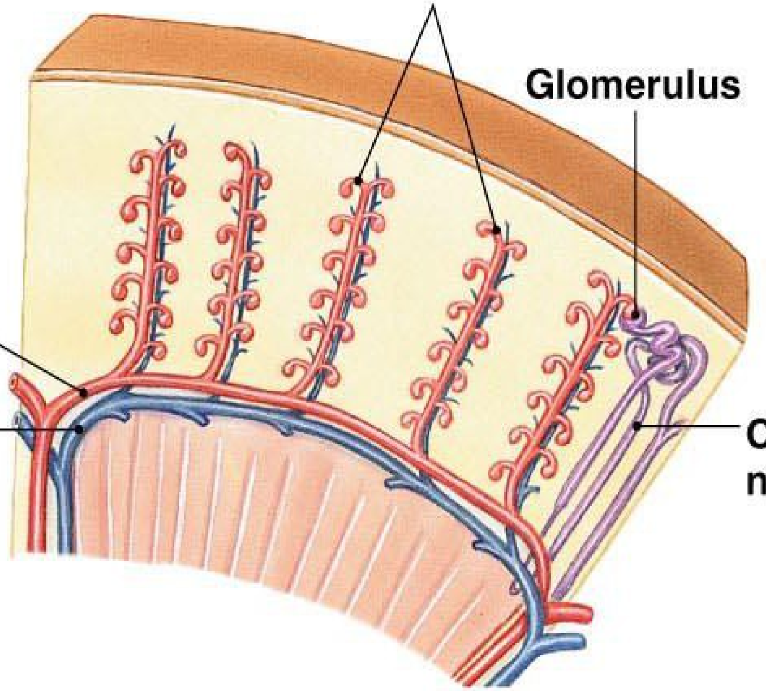


(b) Path of blood flow through renal blood vessels

STRUCTURE OF THE KIDNEY



(d) Renal arteries take blood to the cortex.



(e) Afferent arterioles and glomeruli are all found in the cortex.

Figure 19-1d–e

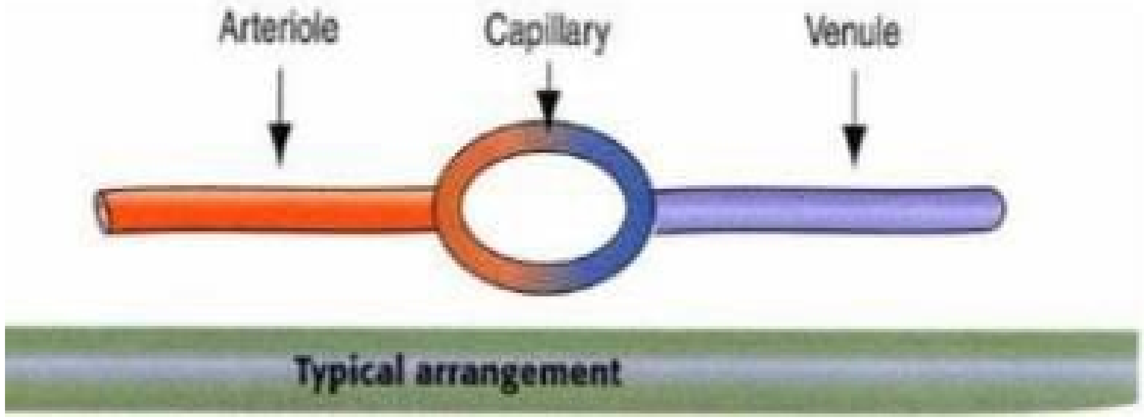
Special arrangement.

The renal circulation is unique in having two capillary beds, the glomerular and peritubular capillaries.

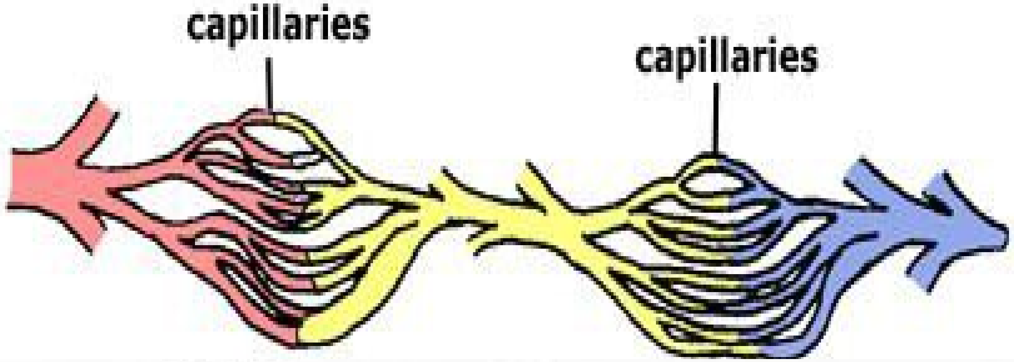
High hydrostatic pressure in the glomerular capillaries (≈60 mm Hg) causes rapid fluid filtration,

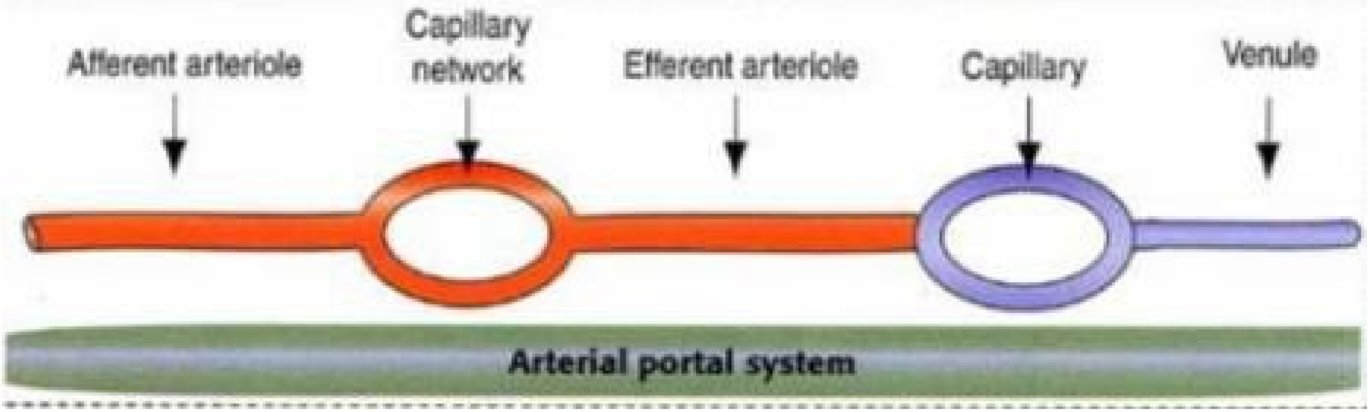
whereas a much lower hydrostatic pressure in the peritubular capillaries (≈13 mm Hg) permits rapid fluid reabsorption.

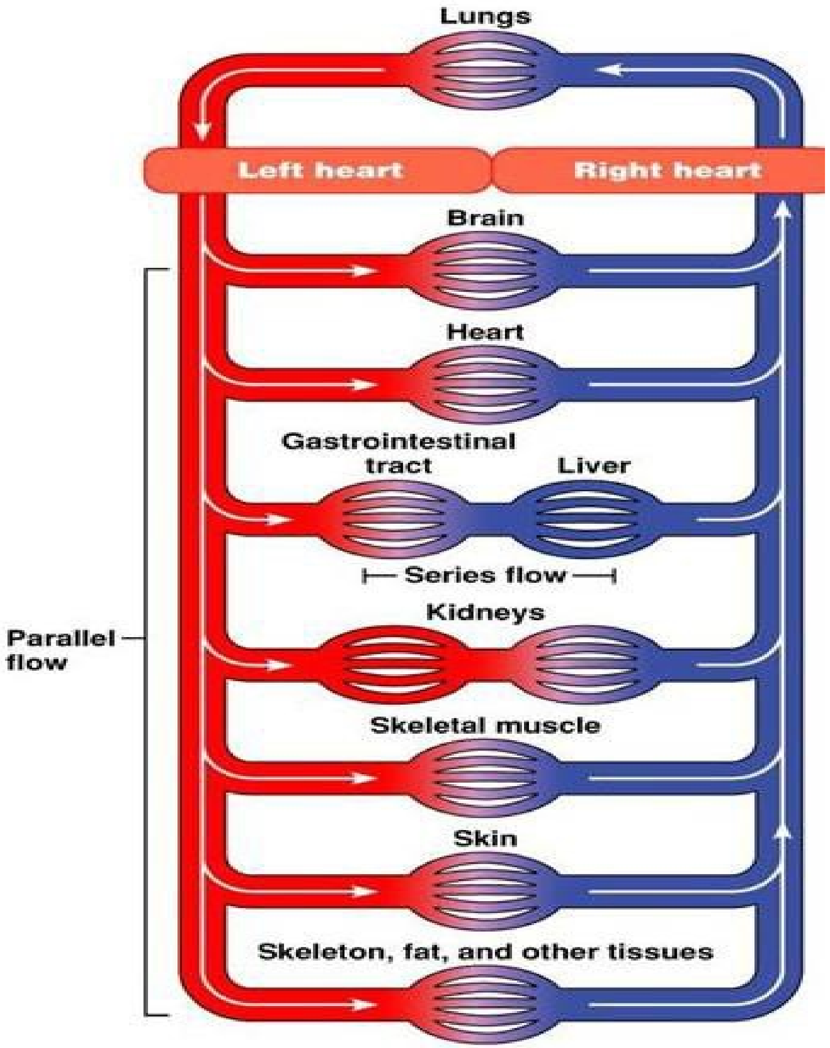
Circulation



Portal circulatory route







THE NEPHRON

Each human kidney contains about 800,000 to 1,000,000 nephrons.

The kidney cannot regenerate new nephrons.

Therefore, with renal injury, disease, or normal aging, the number of nephrons gradually decreases.

After age 40 years, the number of functioning nephrons usually decreases about 10% every 10 years

Each nephron contains:

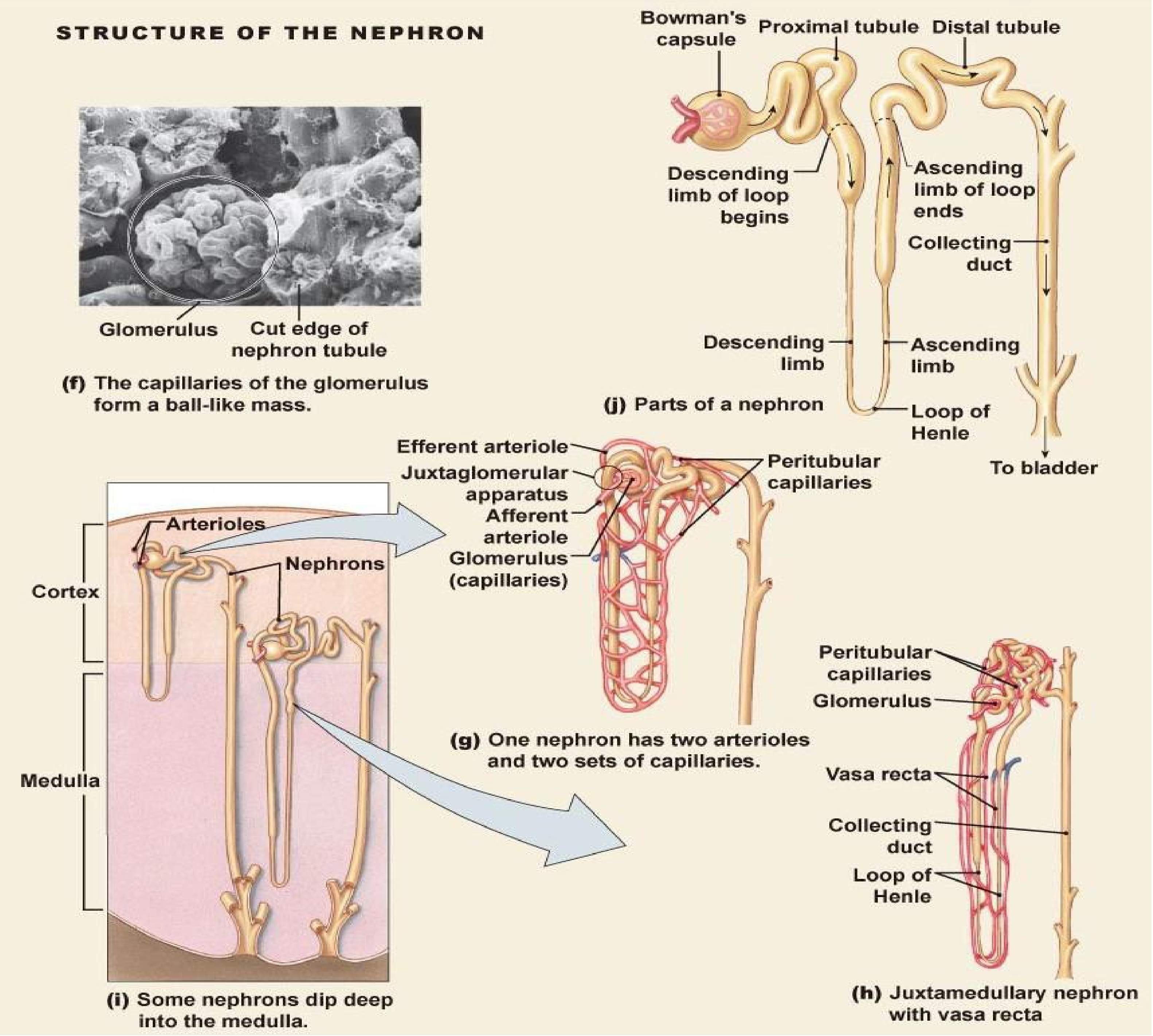
- (1) a tuft of glomerular capillaries called the glomerulus, through which large amounts of fluid are filtered from the blood
- (2) a long tubule in which the filtered fluid is converted into urine on its way to the pelvis of the kidney

The glomerular capillaries are covered by epithelial cells, and the total glomerulus is encased in Bowman’s capsule.

Nephron

The nephron consists of:

- **Vascular components**
  - Afferent & efferent arterioles
  - Glomerulus
  - Peritubular capillaries
  - Vasa recta
- **Tubular components**
  - Proximal convoluted tubule
  - Distal convoluted tubule
  - Nephron loop (loop of Henle)
  - Collecting duct
- **Tubovascular component**
  - Juxtaglomerular



Flow of filtrate

From the glomerular capillaries > bowman’s capsule > proximal tubule (lies in the cortex) > loop of henle (dips into the renal medulla) > macula densa > distal tubule (lies in cortex)> connecting tubule and cortical collecting tubule > cortical collecting duct.

Loop of henle consists of descending and an ascending limb, there is thin segment and thick segment.

8 to 10 cortical collecting ducts join to form a single, larger collecting duct which runs downward into the medulla and becomes the medullary collecting duct which empties through renal papillae.

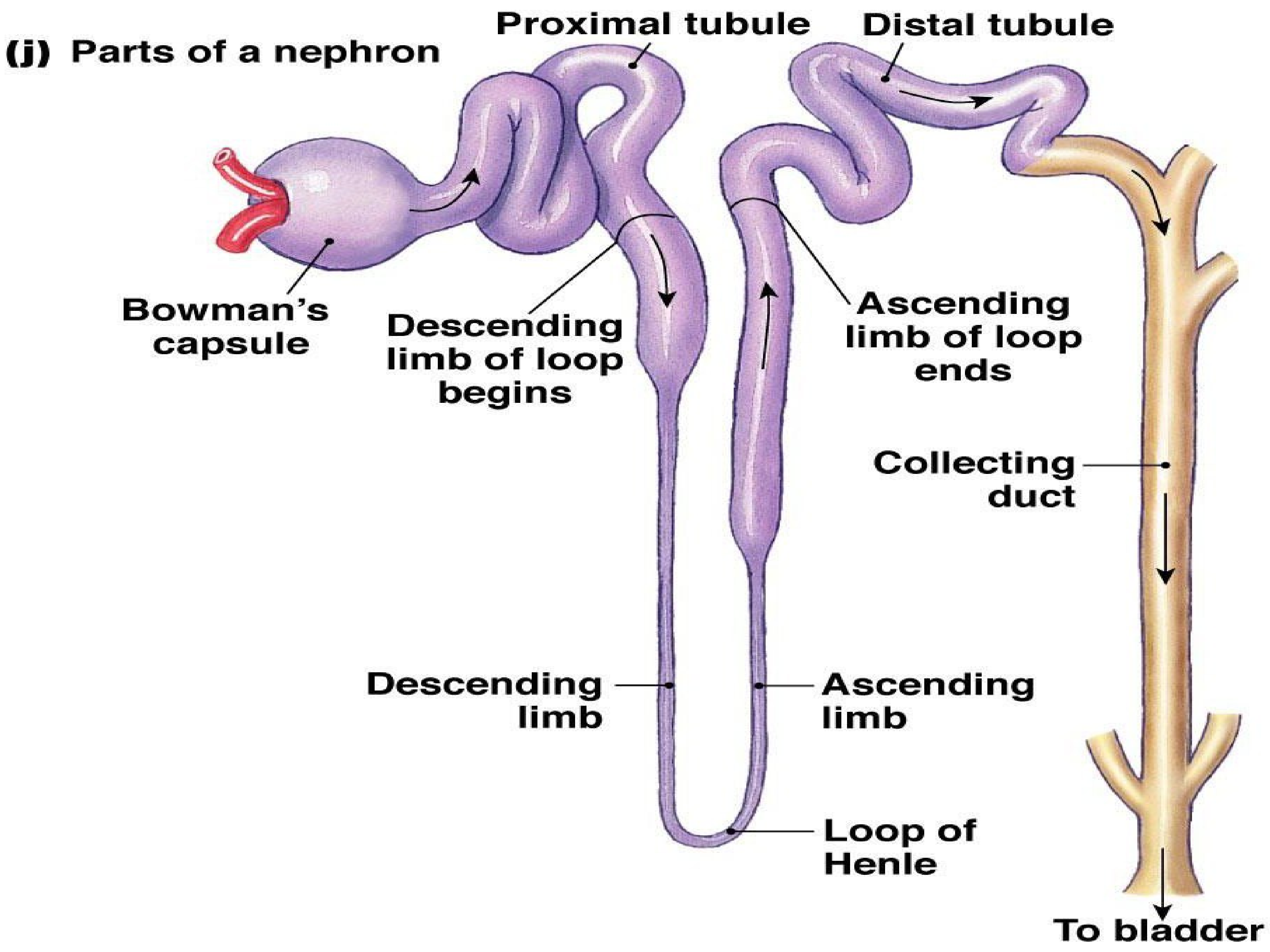

(j) Parts of a nephron
Proximal tubule
Distal tubule
Bowman's capsule
Descending limb of loop begins
Ascending limb of loop ends
Collecting duct
Descending limb
Ascending limb
Loop of Henle
To bladder

Figure 19-1j

Regional Differences in Nephron Structure:

Cortical and juxtamedullary nephrons.

Cortical nephrons:

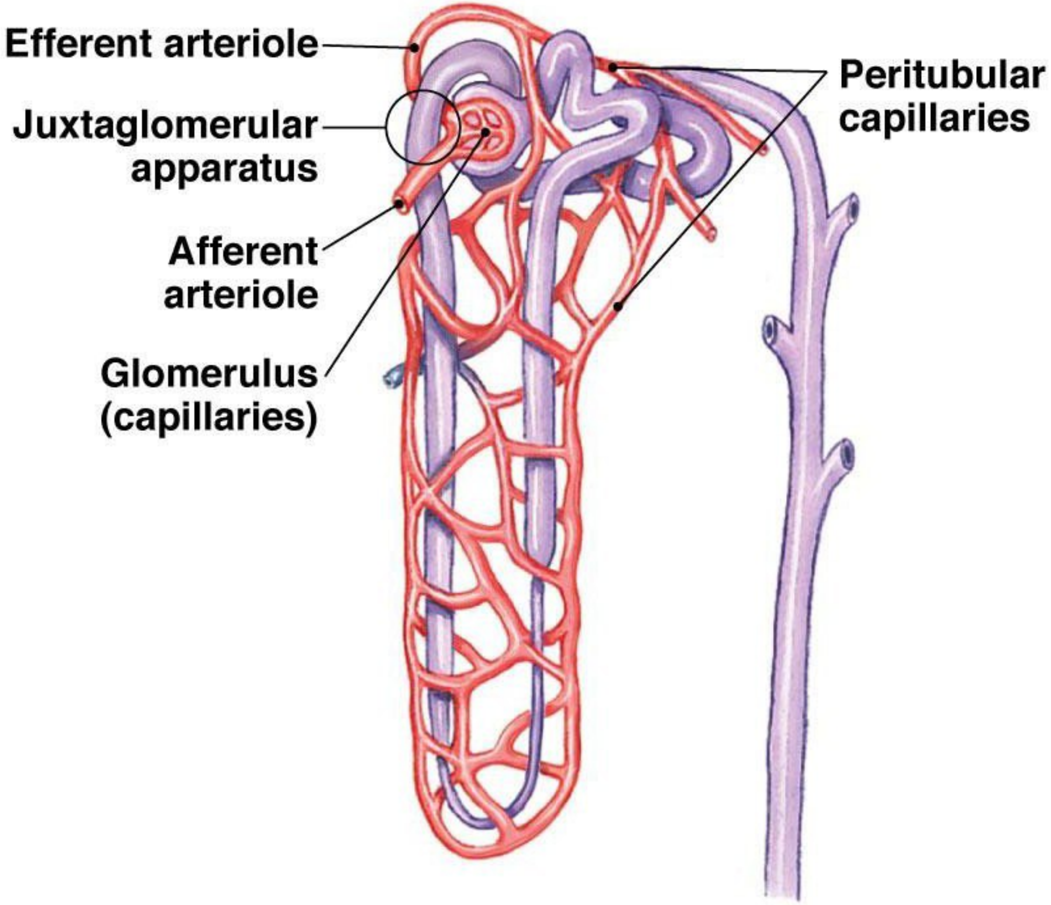
- Glomeruli located in the outer cortex
- Have short loops of henle that penetrate only a short distance into the medulla
- The entire tubular system is surrounded by an extensive network of peritubular capillaries.

Juxtamedullary nephrons:

- 20% to 30% of the nephrons
- Glomeruli lie deep in the renal cortex near the medulla
- Loops of henle that dip deeply into the medulla
- Specialized peritubular capillaries called vasa recta extend downward into the medulla, lying side by side with the loops of henle and return toward the cortex and empty into the cortical veins

Cortical nephrons

(g) Each nephron has two arterioles and two sets of capillaries associated with it.



(h) Juxtamedullary nephron with vasa recta

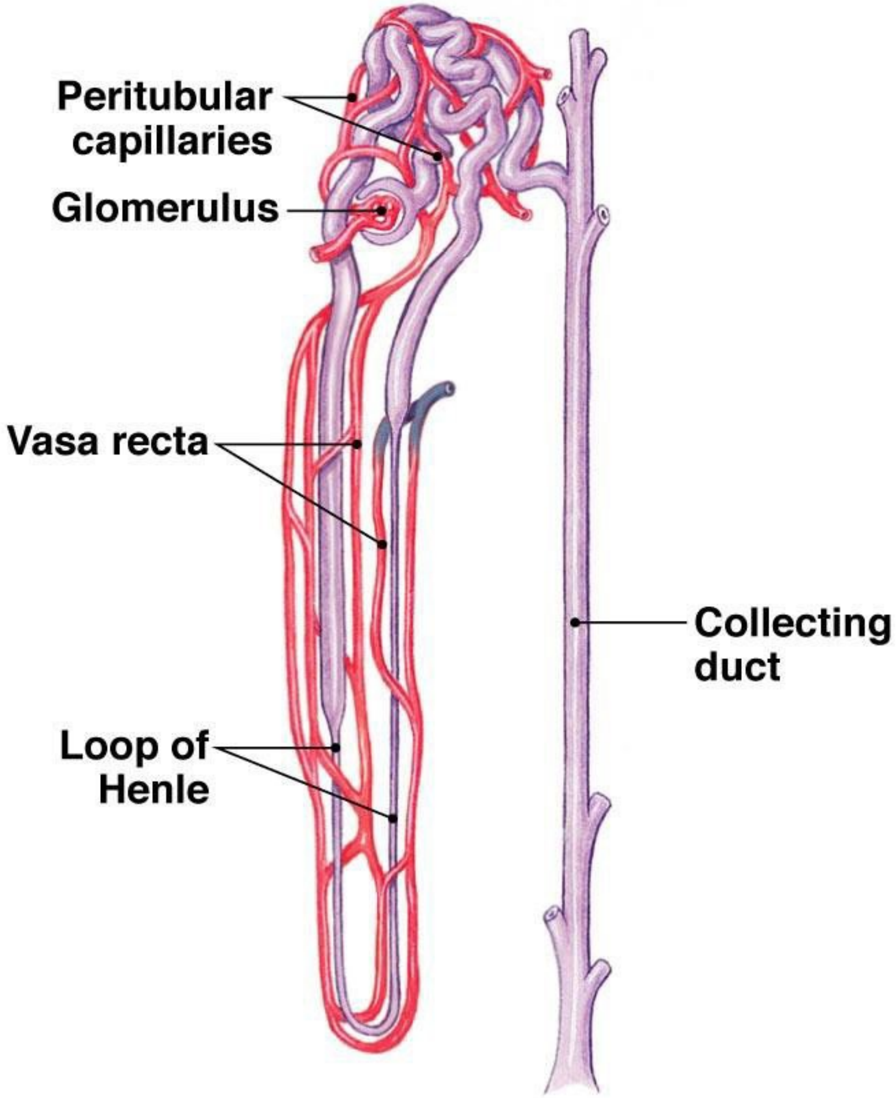


Figure 19-1g

Urine formation

Excretion is the end result of 3 processes:

1) glomerular filtration of substances in the blood;

(2) reabsorption of substances from the renal tubules into the blood;

(3) secretion of substances from the blood into the renal tubules

Renal handling of substances

excretion rate is equal to the rate of filtration

Certain waste products in the body, such as creatinine,

rate of urinary excretion is less than the
rate of filtration

typical for many of
the electrolytes of the
body, such as sodium
and chloride
ions.

filtered substance is
reabsorbed from the
tubules back into
the blood.

This pattern occurs for some of the nutritional substances in the blood, such as amino acids and glucose

additional quantities
of this substance are
secreted

This pattern often
occurs for organic acids
and bases, permitting
them to
be cleared from the
blood rapidly and
excreted in large
amounts in the urine.

For most substances, the rates of filtration and reabsorption are extremely large relative to the rates of excretion.

Why Are Large Amounts of Solutes Filtered and Then Reabsorbed by the Kidneys?

Allows the kidneys to remove waste products rapidly from the body that depend mainly on glomerular filtration for their excretion.
Most waste products are poorly reabsorbed by the tubules

Allows all the body fluids to be filtered and processed by the kidneys many times each day.

Entire plasma volume is only about 3 liters, whereas the GFR is about 180 L/ day, the entire plasma can be filtered and processed about 60 times each day.

Glomerular Filtration

Filtration is the mass movement of water and solutes from plasma to the renal tubule that occurs in the renal corpuscle.

First step in urine formation

filtered fluid (called the glomerular filtrate) is essentially protein-free and devoid of cellular elements, including red blood cells.

concentrations of other constituents of the glomerular filtrate, including most salts and organic molecules, are similar to the concentrations in the plasma.

Exceptions include those substances that partially bound to the plasma proteins.

Filtration fraction

Glomerular capillaries filter fluid at a rate that is determined by:

(1) the balance of hydrostatic and colloid osmotic forces acting across the capillary membrane;

(2) the capillary filtration coefficient (kf), the product of the permeability and filtering surface area of the capillaries.

The glomerular capillaries have a much higher rate of filtration than most other capillaries because of a high glomerular hydrostatic pressure and a large kf.

The filtration fraction:

The fraction of the renal plasma flow that is filtered

Filtration fraction = GFR /renal plasma flow

About 20%.

GLOMERULAR CAPILLARY MEMBRANE

Filtration barrier:

Three major layers:

- (1) the endothelium of the capillary;
- (2) a basement membrane;
- (3) a layer of epithelial cells (podocytes)

Special characteristics permit high filtration of water and solute and low filtration of proteins.

- Capillary endothelium is perforated - small holes called fenestrae
- Endothelial cell proteins are richly endowed with fixed negative charges
- Basement membrane, which consists of a meshwork of collagen and proteoglycan fibrillae which have strong negative electrical charges
- Epithelial cells (podocytes) are not continuous but have long footlike processes (pedicels) that encircle the outer surface of the capillaries.
- The foot processes are separated by gaps called slit pores

Filterability of Solutes Inversely Related to Their Size.

- Despite the high filtration rate, the glomerular filtration barrier is selective in determining which molecules will be filtered, based on their size and electrical charge.
- As the molecular weight of the molecule increases its filterability decreases.
- Negatively charged large molecules are filtered less easily than positively charged molecules of equal molecular size.
- The pores of the glomerular membrane are thought to be about 8 nanometers
- Plasma protein albumin is only about 6 nanometers but albumin is restricted from filtration
- The electrostatic repulsion exerted by negative charges of the glomerular capillary wall proteoglycans.

DETERMINANTS OF THE GLOMERULAR FILTRATION RATE

GFR = Kf × Net filtration pressure

The net filtration pressure:

the sum of the hydrostatic and colloid osmotic forces across the glomerular membrane.

Factors promotes filtration:

(1) hydrostatic pressure inside the glomerular capillaries (glomerular hydrostatic pressure, PG)

(2) the colloid osmotic pressure of the proteins in Bowman's capsule (πB) nearly zero.

Factors opposes filtration:

(1) the hydrostatic pressure in Bowman's capsule (PB) outside the capillaries

(2) the colloid osmotic pressure of the glomerular capillary plasma proteins (πG)

The GFR can therefore be expressed as follows:

$$GFR = K_f \times (PG - PB - \pi G)$$

DETERMINANTS OF THE GLOMERULAR FILTRATION RATE

Forces Favoring Filtration (mm Hg)

Glomerular hydrostatic pressure 60

Bowman’s capsule colloid osmotic pressure 0

Forces Opposing Filtration (mm Hg)

Bowman’s capsule hydrostatic pressure 18

Glomerular capillary colloid osmotic pressure 32

Thus, the net filtration pressure = 60 − 18 − 32 = +10 mm Hg.

INCREASED GLOMERULAR CAPILLARY FILTRATION COEFFICIENT INCREASES GLOMERULAR FILTRATE RATE

product of the hydraulic conductivity and surface area of the glomerular capillaries

The Kf cannot be measured directly but can be estimated.

Kf = GFR/Net filtration pres sure

It is not the primary mechanism for the normal daily regulation of GFR.

Some diseases, however, lower Kf

HTN...

BOWMAN’S CAPSULE HYDROSTATIC PRESSURE

Bowman’s capsule pressure in humans is about 18 mm Hg under normal conditions.

Increasing the hydrostatic pressure in Bowman’s capsule reduces GFR, whereas decreasing this pressure raises GFR.

It is not primary means for regulating GFR.

In certain pathological states associated with obstruction of the urinary tract, Bowman’s capsule pressure can increase markedly

This situation reduces GFR and eventually can cause hydronephrosis (distention and dilation of the renal pelvis and calyces)

GLOMERULAR CAPILLARY COLLOID OSMOTIC PRESSURE

As blood passes from the afferent arteriole through the glomerular capillaries to the efferent arterioles one-fifth of the fluid in the capillaries filters into bowman’s capsule

Concentrating the glomerular plasma proteins that are not filtered

Raising plasma protein concentration increases about 20%.

Normal colloid osmotic pressure of plasma entering the glomerular capillaries is 28 mm hg,

This value usually rises to about 36 mm hg by the time the blood reaches the efferent end of the capillaries.

The average is about 32 mm hg.

GLOMERULAR CAPILLARY COLLOID OSMOTIC PRESSURE

About 32 mm hg.

Two factors that influence the glomerular capillary colloid osmotic pressure are the following:

(1) the arterial plasma colloid osmotic pressure;

(2) the fraction of plasma filtered by the glomerular capillaries (filtration fraction).

Increasing the filtration fraction concentrates the plasma proteins and raises the glomerular colloid osmotic pressure

$$\text{Filtration fraction} = \frac{\text{GFR}}{\text{The renal plasma flow}}$$

With constant GFR decrease in renal plasma flow increase the filtration fraction which leads to more elevation in glomerular colloid pressure and more reduction in GFR

Consequently, even with a constant glomerular hydrostatic pressure, a greater rate of blood flow into the glomerulus tends to increase the GFR and a lower rate of blood flow into the glomerulus tends to decrease the GFR.

GLOMERULAR CAPILLARY HYDROSTATIC PRESSURE

Estimated to be about 60 mm Hg under normal conditions.

primary means for physiological regulation of GFR.

determined by three variables:

1) arterial pressure;

(2) afferent arteriolar resistance;

(3) efferent arteriolar resistance.

Increased arterial pressure tends to raise glomerular hydrostatic pressure and, therefore, to increase the GFR.

this effect is buffered by autoregulatory mechanisms that maintain a relatively constant glomerular pressure as arterial pressure fluctuates.

Afferent arteriolar resistance

Increased resistance of afferent arterioles reduces glomerular hydrostatic pressure and decreases the GFR

dilation of the afferent arterioles increases glomerular hydrostatic pressure and GFR.

Efferent arteriolar resistance

Constriction of the efferent arterioles increases the resistance to outflow from the glomerular capillaries

as long as the increase in efferent resistance does not reduce renal blood flow too much, GFR increases slightly

Efferent arteriolar resistance

Efferent arteriolar constriction also reduces renal blood flow,

Filtration fraction and glomerular colloid osmotic pressure increase therefore, if constriction

Of efferent arterioles is severe (more than about a threefold increase in efferent arteriolar resistance), the rise in colloid osmotic pressure exceeds the increase in glomerular capillary hydrostatic pressure

When this situation occurs, the net force for filtration actually decreases, causing a reduction in GFR.

Clearance and clearance ratio and renal blood flow

What is clearance?

The renal clearance of a substance is the volume of plasma that is completely cleared of the substance by the kidneys per unit of time.

No single volume of plasma that is completely cleared of a substance

We can use renal clearance to quantify renal blood flow, GFR, tubular reabsorption, and tubular secretion.

Clearance rate refers to the volume of plasma that would be necessary to supply the amount of substance excreted in the urine per unit of time.

$C_s \times P_s = U_s \times V$

Where C_s is the clearance rate of a substance s, P_s is the plasma concentration of the substance, U_s is the urine concentration of that substance, and V is the urine flow rate.

INULIN CLEARANCE CAN BE USED TO ESTIMATE GLOMERULAR FILTRATION RATE

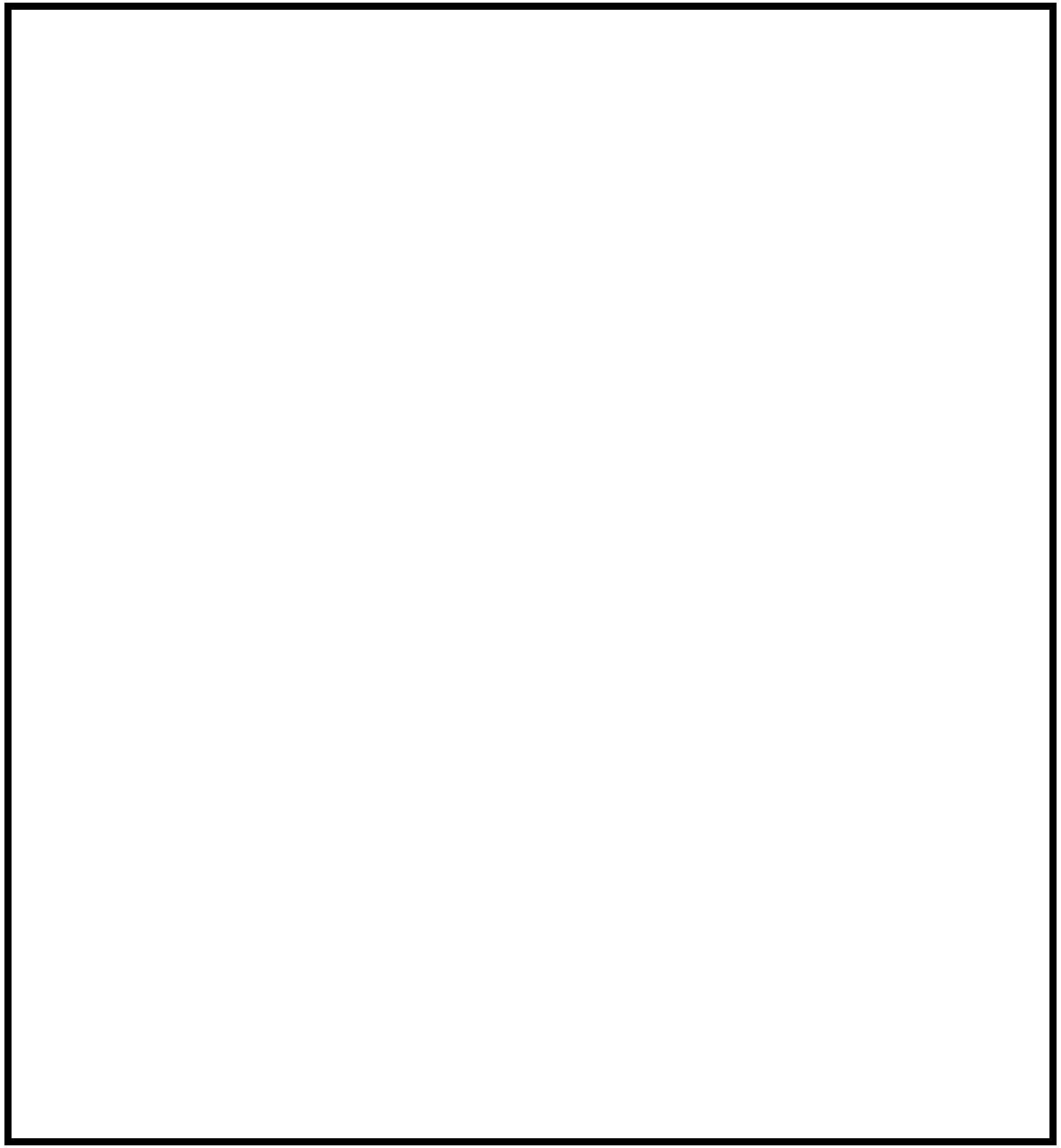
If a substance is freely filtered and is not reabsorbed or secreted by the renal tubules then the rate at which that substance is excreted in the urine ($U_s \times V$) is equal to the filtration rate of the substance by the kidneys ($GFR \times P_s$).

$$GFR \times P_s = U_s \times V$$

$$GFR = \frac{U_s \times V}{P_s} = C_2$$

substance that fits these criteria is inulin
Polysaccharide
molecular weight of about 5200
not produced in the body
found in the roots of certain plants
must be administered intravenously to a patient to measure GFR.

Other substances include iothalamate, chromium ethylenediaminetetraacetic acid (EDTA), cystatin C, and creatinine.



CREATININE CLEARANCE AND PLASMA CREATININE CONCENTRATION CAN BE USED TO ESTIMATE GLOMERULAR FILTRATION RATE

- creatinine is cleared from the body fluids almost entirely by glomerular filtration.
- creatinine clearance can also be used to assess GFR.
- does not require intravenous infusion
- creatinine clearance is not a perfect marker of GFR:
  - small amount of it is secreted by the tubules
  - the amount of creatinine excreted slightly exceeds the amount filtered.
  - There is normally a slight error in measuring plasma creatinine that leads to an overestimation
- An approximation of changes in GFR can be obtained by simply measuring the plasma creatinine concentration (PCr), which is inversely proportional to the GFR

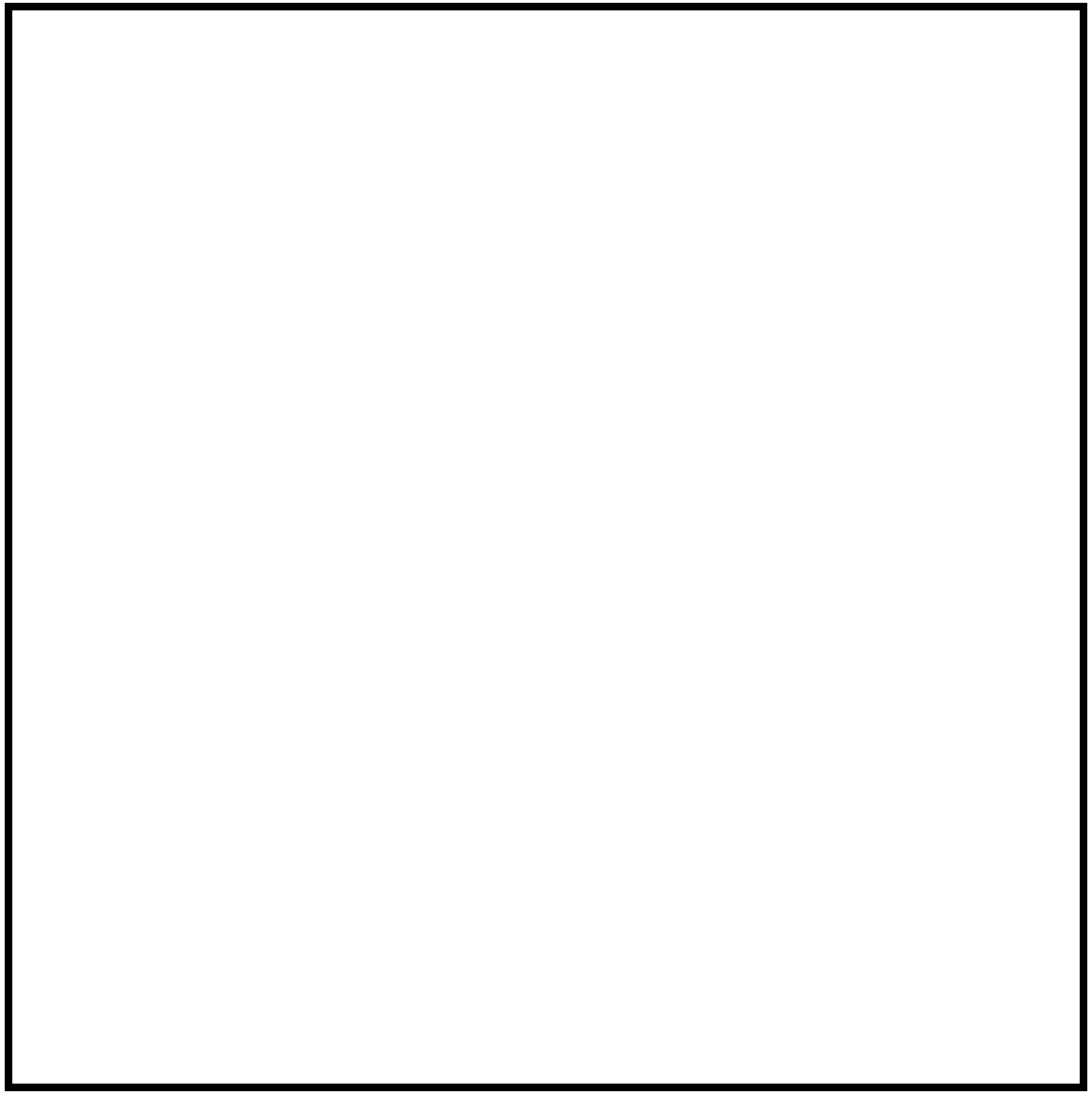
If GFR suddenly decreases by 50% the kidney will filter and excrete only half as much creatinine causing the accumulation of creatinine and raising plasma concentration.

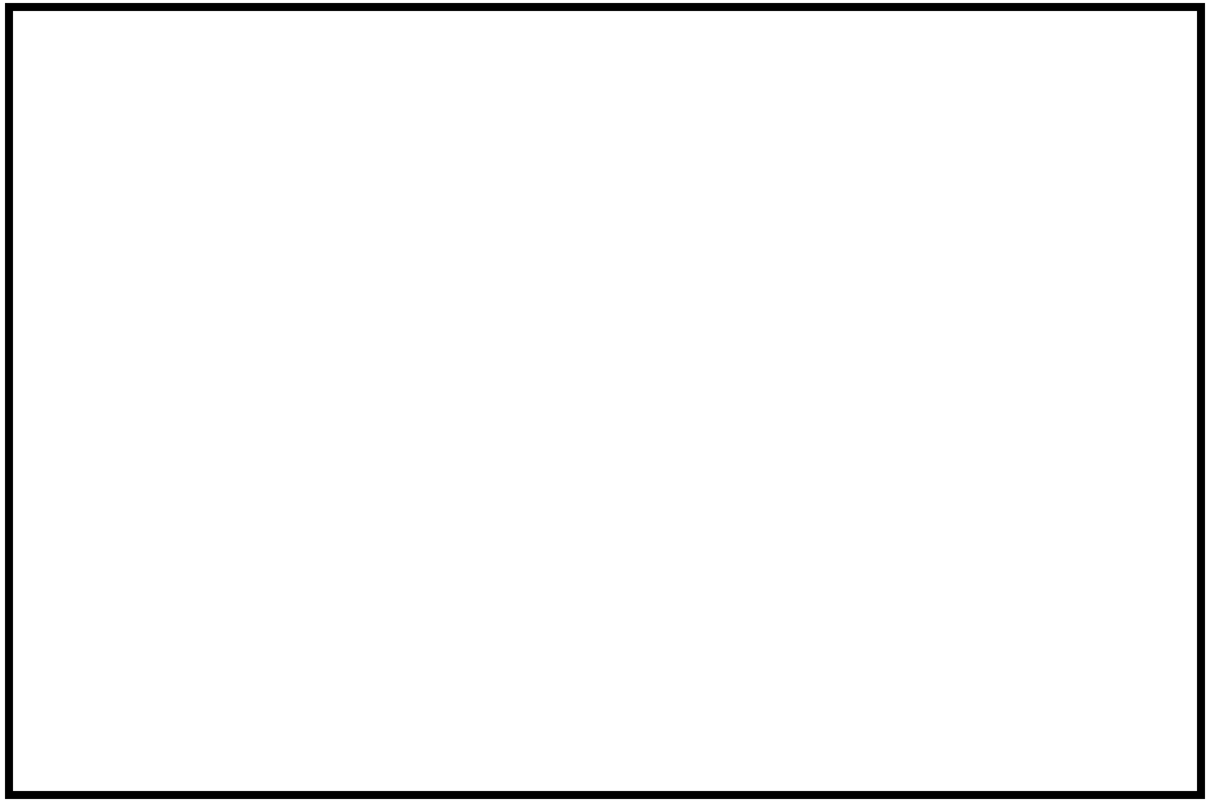
As the plasma concentration rises the filtered load of creatinine (PCr × GFR) and creatinine excretion (UCr × V) will rise, until the balance between creatinine production and creatinine excretion is re-established.

This response will occur when the plasma creatinine level increases to approximately twice normal.

If GFR falls to one-fourth normal, plasma creatinine level would increase to about four times normal

Thus, under steady-state conditions, creatinine excretion rate equals the rate of creatinine production, despite reductions in GFR. However, this normal rate of creatinine excretion occurs at the expense of an elevated plasma creatinine concentration





PARA-AMINOHIPPURIC ACID 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 total RPF.

Because the GFR is only about 20% of the total plasma flow, a substance that is completely cleared from the plasma must be excreted by tubular secretion

Therefore, clearance of PAH can be used to approximate RPF.
Correction formula (extraction ratio) can be used to increase accuracy.
Extraction ratio of PAH : The percentage of PAH removed from the blood it averages about 90% in normal kidneys.

Example:

Assume that the plasma concentration of PAH is 0.01 mg/ml, urine concentration is 5.85 mg/ml, and urine flow rate is 1 ml/min.

the clearance of PAH = 1 * 5.85 / 0.01 = 585 ml/min.

the actual RPF = 585 /0.9 = 650 ml/min

CALCULATION OF TUBULAR REABSORPTION OR SECRETION FROM RENAL CLEARANCES

If the rates of glomerular filtration and renal excretion of a substance are known can calculate whether there is a net reabsorption or net secretion of that substance.

If excretion of the substance (Us × V) is less than the filtered load of the substance (GFR × Ps) then there is net reabsorption.

If excretion of the substance (Us × V) is more than the filtered load of the substance (GFR × Ps) then there is net secretion.

Example :

- Urine flow rate = 1 ml/min
- Urine concentration of sodium (UNa) = 70 mEq/L = 70 µEq/ml
- Plasma sodium concentration = 140 mEq/L = 140 µEq/ml
- GFR (inulin clearance) = 100 ml/min`

Filtered load = 140 * 100 = 14000 mEq/min

Excretion = 1 * 70 = 70 mEq/min

Net reabsorption = 14000- 70 = 13,930 µEq/min

(1) if the clearance rate of the substance equals that of inulin, the substance is only filtered and not reabsorbed or secreted;

(2) if the clearance rate of a substance is less than inulin clearance, the substance must have been reabsorbed by the nephron tubules;

(3) if the clearance rate of a substance is greater than that of inulin, the substance must be secreted by the nephron tubules.

Hormonal and neuronal control of renal system

DR. Khaled A Shaheen

PHYSIOLOGICAL CONTROL OF GLOMERULAR FILTRATION AND RENAL BLOOD FLOW

The determinant of GFR that is most variable and subject to physiological control is the glomerular hydrostatic pressure.

STRONG SYMPATHETIC NERVOUS SYSTEM ACTIVATION DECREASES GLOMERULAR FILTRATION RATE

- Essentially all the blood vessels of the kidneys are richly innervated by sympathetic nerve fibers.
- Strong activation
  - Example: reflex elicited by the defense reaction, brain ischemia, or severe hemorrhage.
  - Last few minutes to a few hours
  - Can reducing GFR RBF.
- Moderate or mild sympathetic stimulation
  - Examples: moderate decreases in pressure at the carotid sinus baroreceptors or cardiopulmonary receptors
  - Has little influence on renal blood flow or GFR.

HORMONAL AND AUTACOID CONTROL OF RENAL CIRCULATION

Role of Norepinephrine, Epinephrine, and Endothelin

Role of Angiotensin II

Role of Endothelial-Derived Nitric Oxide

Role of Prostaglandins and Bradykinin

Role of Norepinephrine, Epinephrine, and Endothelin

- Norepinephrine and epinephrine:
  - Released from the adrenal medulla.
  - Constrict afferent and efferent arterioles, causing reductions in GFR and renal blood flow.
  - Parallel the activity of the sympathetic nervous system
  - Significant influence under strong activation of the sympathetic nervous system.
- Endothelin:
  - Peptide released by damaged vascular endothelial cells
  - Powerful vasoconstrictor.
  - Physiological role is not completely understood.
  - Plasma levels increased in toxemia of pregnancy, acute renal failure, and chronic uremia
    - May contribute to renal vasoconstriction and decreased GFR

Role of Angiotensin II

Powerful renal vasoconstrictor

Circulating hormone and a locally produced autacoid or paracrine hormone formed in the kidneys and in the systemic circulation.

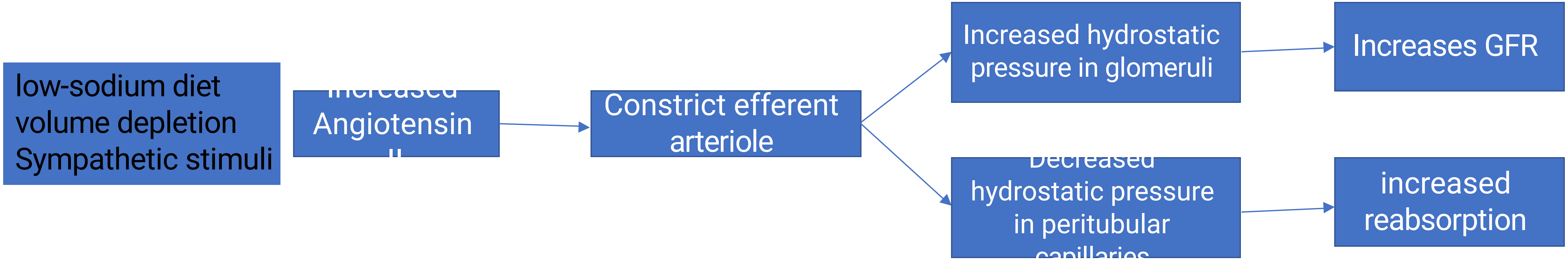
Its receptors present in virtually all blood vessels of the kidneys.

Effects on afferent arterioles,

- Minimal in most physiological conditions,
- Due to release of vasodilators, especially nitric oxide and prostaglandins

Effects on efferent arterioles:

Angiotensin II preferentially constricts efferent arterioles in most physiological conditions.



The net effect is enhanced excretion of metabolic waste products , maintain GFR , increases tubular reabsorption of sodium and water

Role of Endothelial-Derived Nitric Oxide

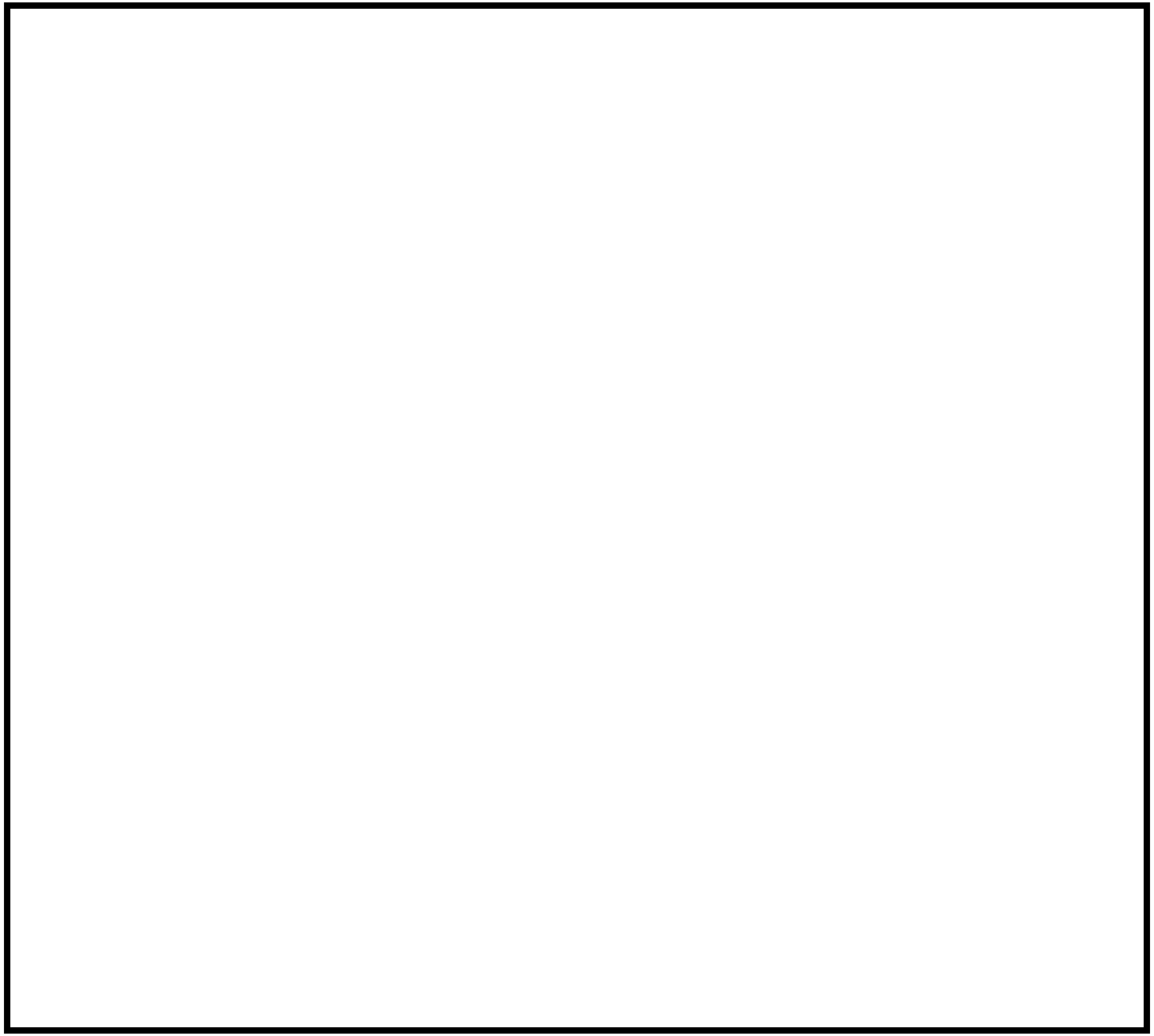
- Released by the vascular endothelium
- A basal level of nitric oxide production appears to be important for maintaining vasodilation of the kidneys
- It is reduced in:
  - Drugs that inhibit its production
  - In some hypertensive patients or in patients with atherosclerosis
    - The net effect is contribute to increased renal vasoconstriction and elevated blood pressure.

Role of Prostaglandins (PGE2 and PGI2) and Bradykinin

- Cause vasodilation, increased renal blood flow, and increased GFR.
- Do not appear to be of major importance in normal conditions.
- Dampen the renal vasoconstrictor effects of the sympathetic nerves or angiotensin 2, especially their effects to constrict the afferent arterioles.
  - Prevent excessive reductions in GFR and renal blood flow.
- In stressful condition or in pt. using NSAIDS and aspirin inhibition prostaglandin synthesis may cause significant reductions in GFR.

AUTOREGULATION OF GLOMERULAR FILTRATION RATE AND RENAL BLOOD FLOW

- Autoregulation: relative constancy of GFR and renal blood flow despite marked changes in arterial blood pressure.
- Feedback mechanisms
- Intrinsic to the kidneys
    - Function in blood-perfused kidneys that have been removed from the body.
    - Independent of systemic influences.
- Autoregulation in all body tissue maintains blood flow enough for delivery of oxygen and nutrients at a normal level and remove the waste products of metabolism.
- In kidneys, blood flow is much higher than that required for these functions.
- The major function of autoregulation in the kidneys is to maintain a relatively constant the GFR.
- In general, renal blood flow is autoregulated in parallel with GFR, but GFR is

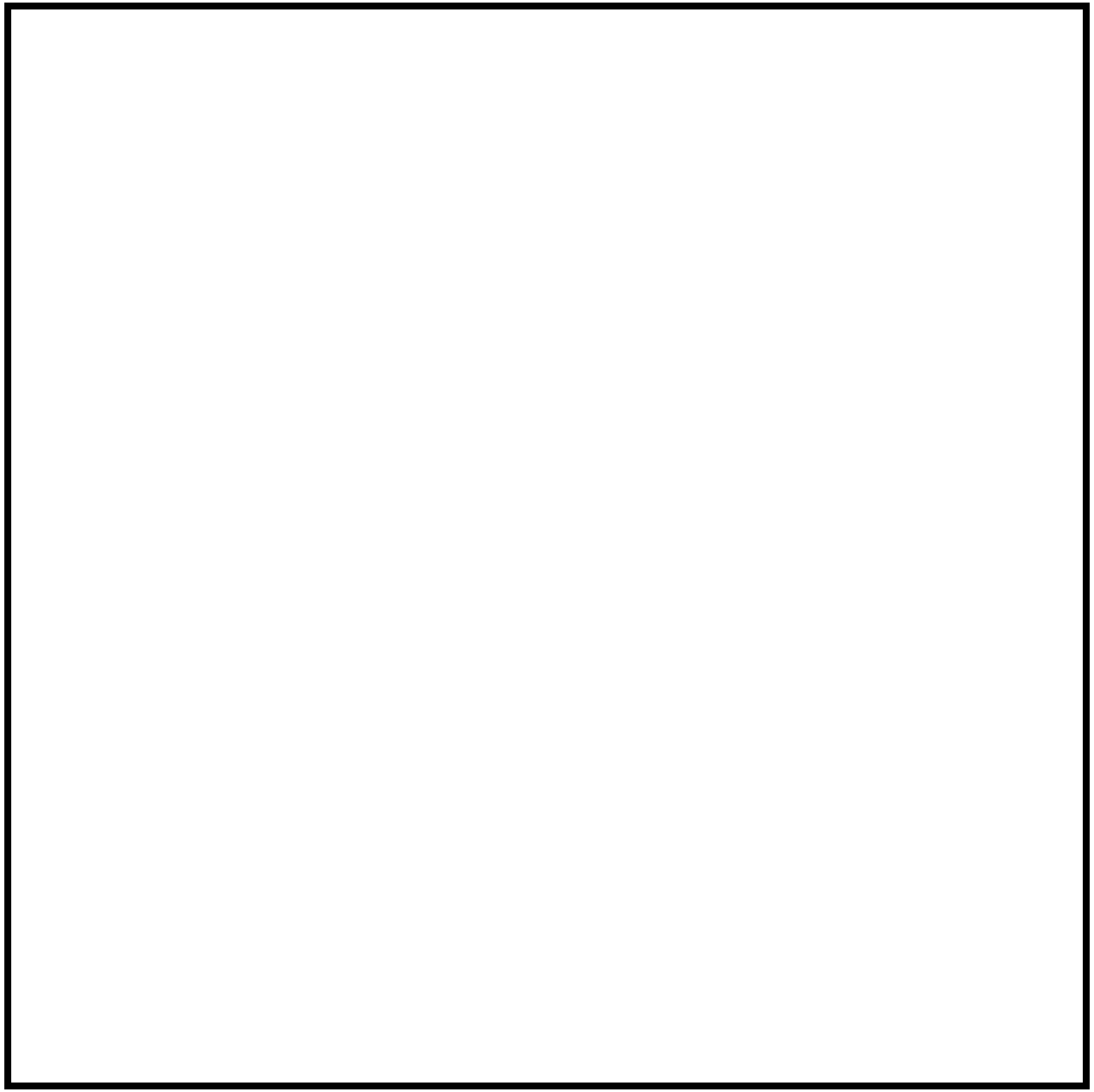


Importance of Glomerular Filtration Rate Autoregulation

- To appreciate the quantitative importance of autoregulation
  - Consider the relative magnitudes of glomerular filtration, tubular reabsorption, and renal excretion without autoregulatory mechanisms.
- Normally:
  - GFR is about 180 L/day, and tubular reabsorption is 178.5 L/day, leaving 1.5 L/day of fluid to be excreted in the urine.
  - In the absence of autoregulation:
  - Small increase in blood pressure (from 100 to 125 mm Hg) would cause a similar 25% increase in GFR (from about 180 to 225 L/day).
  - If tubular reabsorption remained constant at 178.5 L/day, the urine flow would increase to 46.5 L/day

TUBULOGLOMERULAR FEEDBACK

- Special feedback mechanism
- Depend on special anatomical arrangements of the juxtaglomerular complex
- Autoregulates renal blood flow and GFR in parallel In many circumstances
  - However, instances Occur when GFR is autoregulated at the expense of changes in renal blood flow.
- The tubuloglomerular feedback mechanism has two components that act together to control GFR:
  - (1) An afferent arteriolar feedback mechanism;
  - (2) An efferent arteriolar feedback mechanism.
- The juxtaglomerular complex:
  - Macula densa cells in the initial portion of the distal tubule
  - Juxtaglomerular cells in the walls of the afferent and efferent arterioles.



Decreased Macula Densa Sodium Chloride Causes Dilation of Afferent Arterioles and Increased Renin Release.

The macula densa cells sense changes in sodium chloride delivery to the distal tubule.

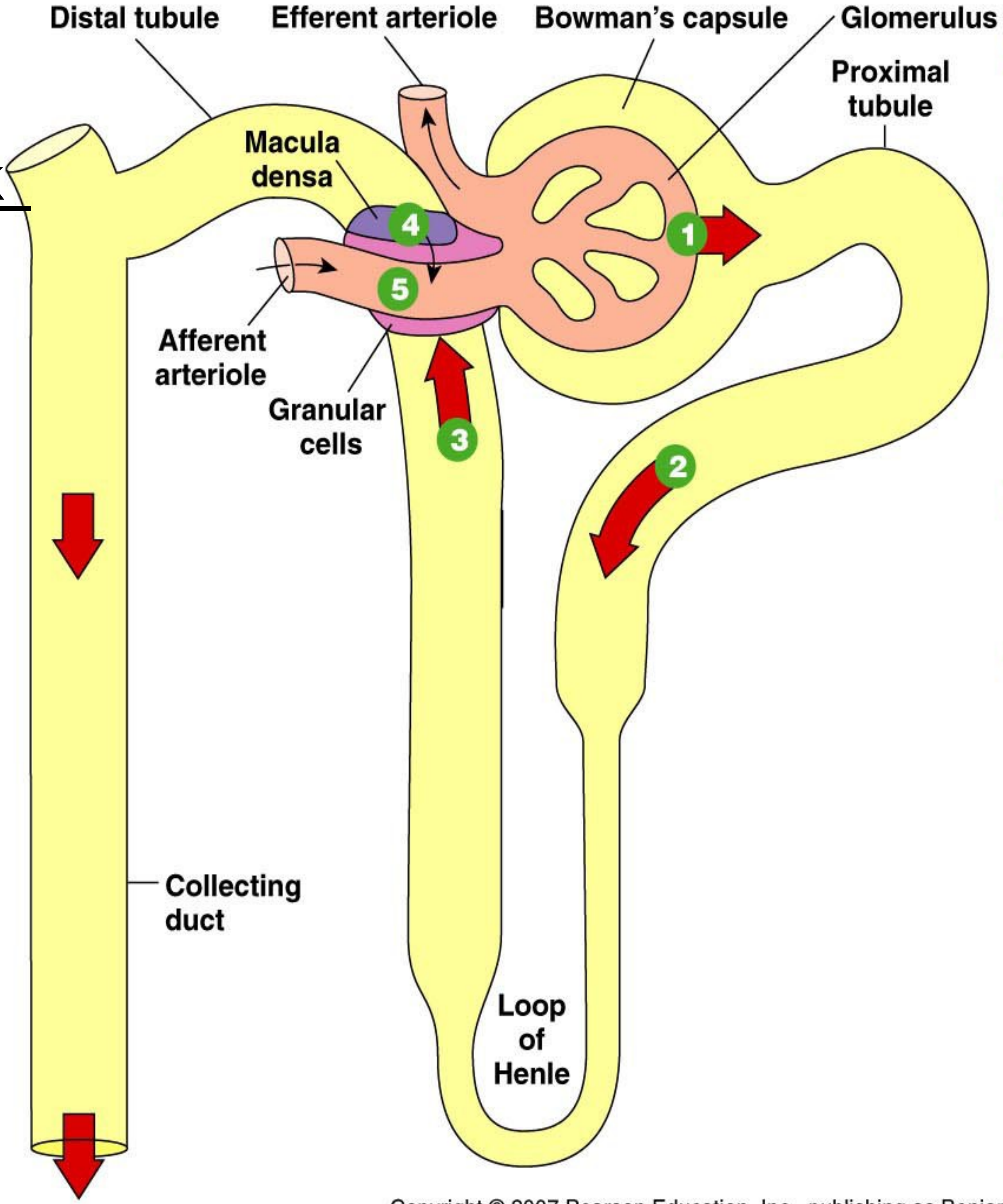
Initiates a signal from the macula densa that has two effects:

(1) It decreases resistance to blood flow in the afferent arterioles, which raises glomerular hydrostatic pressure and helps return GFR toward normal;

(2) It increases renin release from the juxtaglomerular cells of the afferent and efferent arterioles, which are the major storage sites for renin.

Renin increase the formation of angiotensin I an II increasing glomerular hydrostatic pressure and helping return GFR toward normal.

Tubuloglomerular feedback helps GFR autoregulation.



1. GFR increases.

↓

2. Flow through tubule increases.

↓

3. Flow past macula densa increases.

↓

4. Paracrine diffuses from macula densa to afferent arteriole.

↓ ATP

5. Afferent arteriole constricts.

↓

Resistance in afferent arteriole increases.

↓

Hydrostatic pressure in glomerulus decreases.

↓

GFR decreases.

MYOGENIC AUTOREGULATION OF RENAL BLOOD FLOW AND GLOMERULAR FILTRATION RATE

- Ability of individual blood vessels to resist stretching during increased arterial pressure, referred to as the myogenic mechanism.
- Increase blood pressure :
  - Stretch of the vascular wall allows increased movement of calcium ions from the extracellular fluid into the cells, causing them to Contract
  - Raising vascular resistance
  - Prevent excessive increases in renal blood flow and the GFR when arterial pressure increases
  - Help protecting the kidney from hypertension-induced injury.
- If arteriole blood pressure decreases slightly, GFR only increases slightly as arterioles dilate
  - Due to the fact that the arterioles are normally close to maximal dilation
  - Further drop in bp (below 80mmHg) reduced GFR and conserves plasma volume

REGULATION OF TUBULAR REABSORPTION

- GLOMERULOTUBULAR BALANCE— REABSORPTION RATE INCREASES IN RESPONSE TO INCREASED TUBULAR LOAD.
- EFFECT OF ARTERIAL PRESSURE ON URINE OUTPUT— PRESSURE NATRIURESIS AND PRESSURE DIURESIS

HORMONAL CONTROL OF TUBULAR REABSORPTION

Precise regulation of body fluid volumes and solute concentrations requires the kidneys to excrete different solutes and water at variable rates, independent from each other.

Several hormones in the body provide this specificity of tubular reabsorption for different electrolytes and water.

Aldosterone

Secreted by the zona glomerulosa cells of the adrenal cortex

A major renal tubular site of aldosterone action is on the principal cells of the cortical collecting tubule.

Stimulating the Na+-K+ ATPase pump on the basolateral

Increases the sodium permeability of the luminal side of the membrane by the insertion of epithelial sodium channels

Stimuli for aldosterone:

1. increased extracellular potassium concentration
2. increased angiotensin II levels
3. low extracellular Na+ concentration (hyponatremia)
4. ACTH – causes small increases of aldosterone during stress
5. Atrial natriuretic peptide (ANP) inhibits activity of the zona glomerulosa

The net effect is:

Renal sodium and water retention

Elevation of blood pressure

Addison disease and Conn syndrome

Major Mechanisms of Aldosterone Secretion

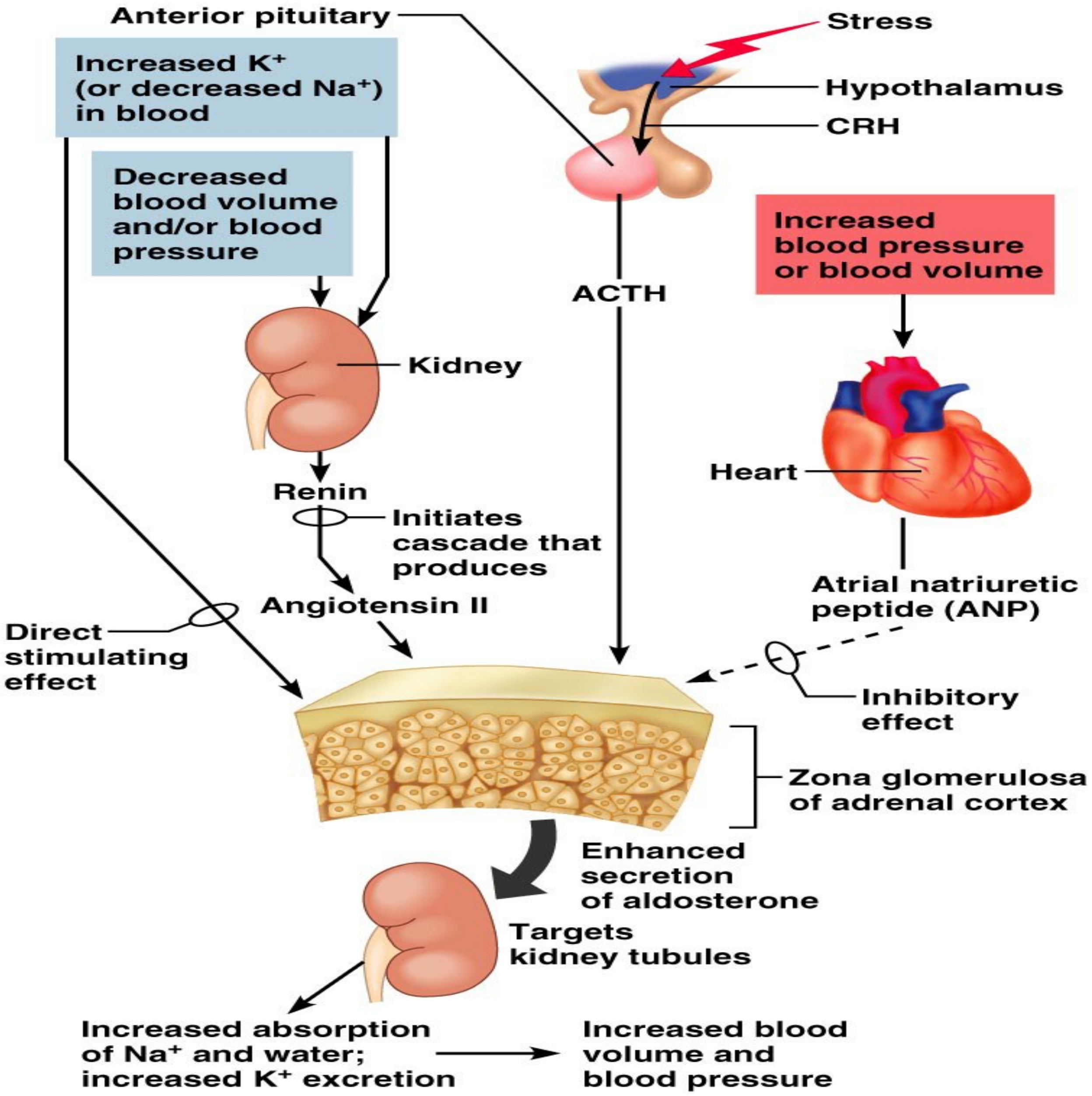
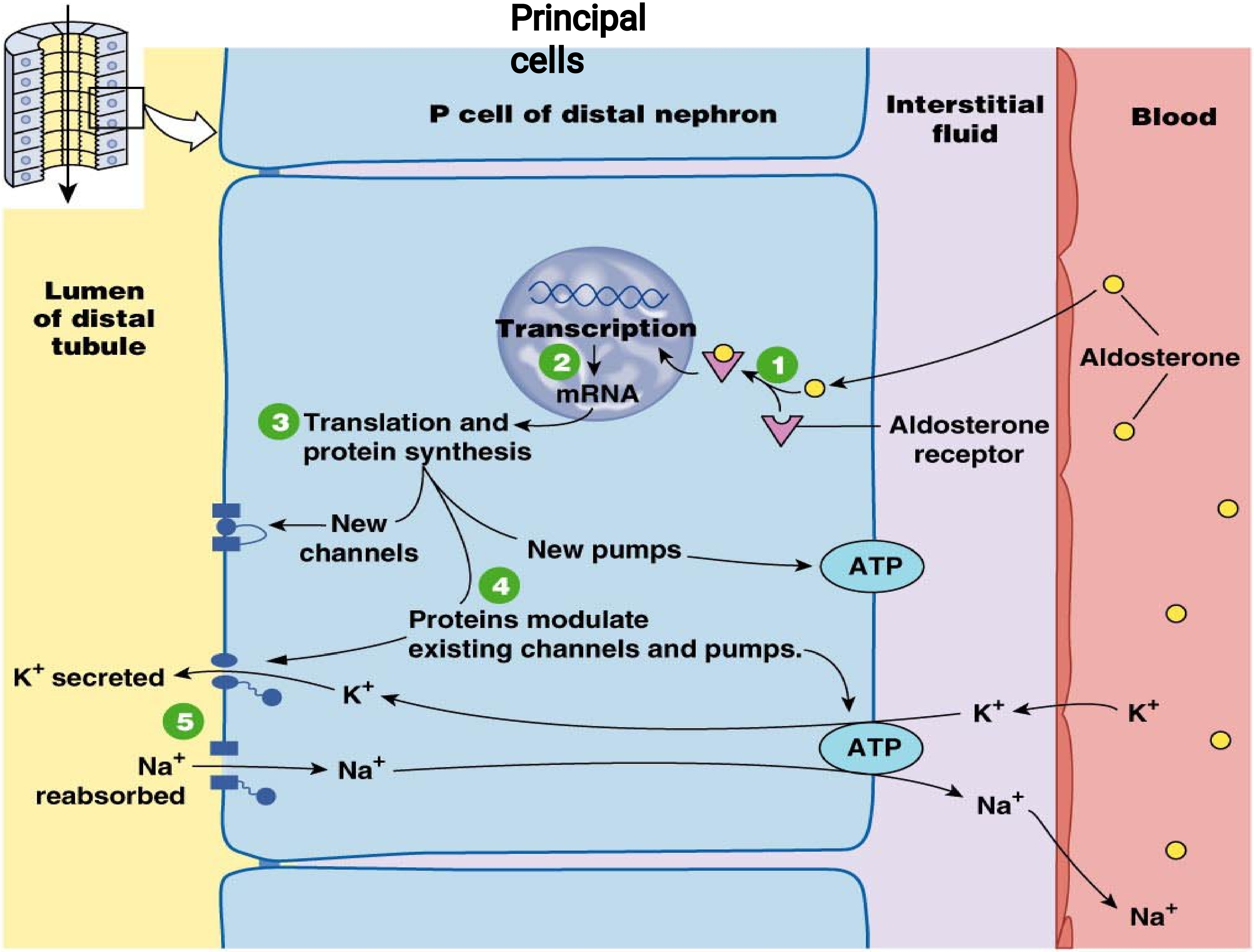


Figure 16.14

Principal cells



1. Aldosterone combines with a cytoplasmic receptor.
2. Hormone-receptor complex initiates transcription in the nucleus.
3. New protein channels and pumps are made.
4. Aldosterone-induced proteins modify existing proteins.
5. Result is increased Na^+ reabsorption and K^+ secretion.

Figure 20-13

Several factors trigger renin release:

1. **Reduced stretch of the granular cells** . A drop in mean systemic blood pressure below 80 mm Hg (as might be due to hemorrhage, dehydration, etc.) reduces the stretch of the granular cells and stimulates them to release more renin.
2. **Stimulation of the granular cells by input from activated macula densa cells**. When macula densa cells sense low NaCl concentration (slowly moving filtrate), they signal the granular cells to release renin. This signal may be decreased release of ATP (tubuloglomerular feedback messenger), increased release of the prostaglandin PGE2 (vasodilator), or both.
3. **Direct stimulation of granular cells via β1-adrenergic** receptors by renal sympathetic nerves.

Angiotensin II Increases Sodium and Water Reabsorption

Powerful sodium-retaining hormone.

Effects on tubular reabsorption:

1. Angiotensin II stimulates aldosterone secretion
2. Angiotensin II constricts the efferent arterioles
    - Reduces peritubular capillary hydrostatic pressure
    - Reducing renal blood flow, raises filtration fraction increases the concentration of proteins and colloid osmotic pressure in the peritubular capillaries.
    - Increases the reabsorptive force at the peritubular capillaries
3. Angiotensin II directly stimulates sodium reabsorption in the proximal tubules, the loops of Henle, the distal tubules, and the collecting tubules
    - Stimulate the Na+-K+ ATPase pump at basolateral membrane.
    - Stimulate sodium-hydrogen exchange in the luminal membrane
    - Stimulate sodium-bicarbonate co-transport in the basolateral membrane

Stimulates the hypothalamus to release antidiuretic hormone and activates the hypothalamic thirst center, both of which increase blood volume

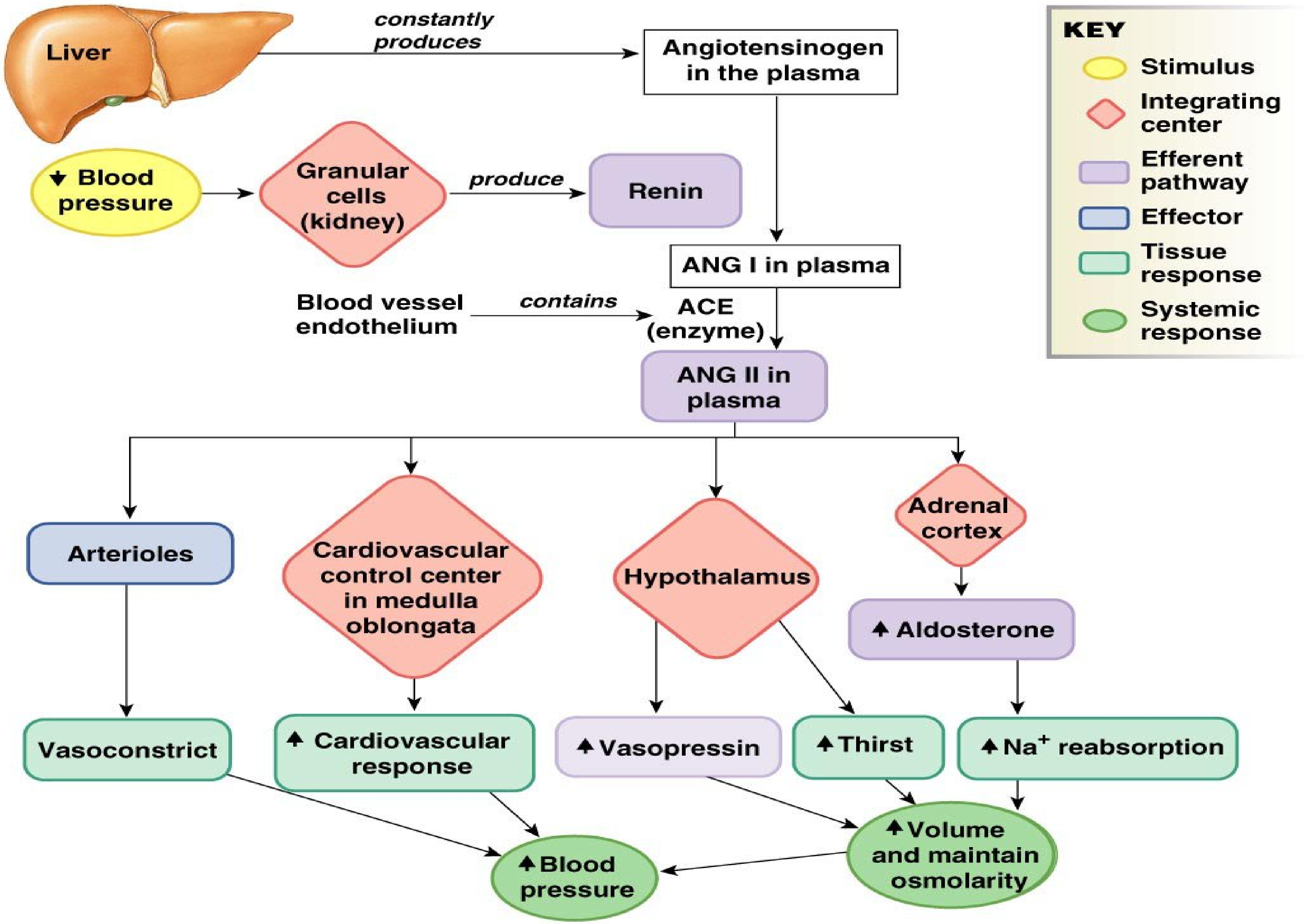

Liver
constantly produces
Angiotensinogen in the plasma
↓ Blood pressure
Granular cells (kidney)
produce
Renin
ANG I in plasma
Blood vessel endothelium
contains
ACE (enzyme)
ANG II in plasma
Arterioles
Cardiovascular control center in medulla oblongata
Hypothalamus
Adrenal cortex
↑ Aldosterone
Vasoconstrict
↑ Cardiovascular response
↑ Vasopressin
↑ Thirst
↑ Na^+ reabsorption
↑ Volume and maintain osmolarity
↑ Blood pressure
KEY
Stimulus
Integrating center
Efferent pathway
Effector
Tissue response
Systemic response

Figure 20-14

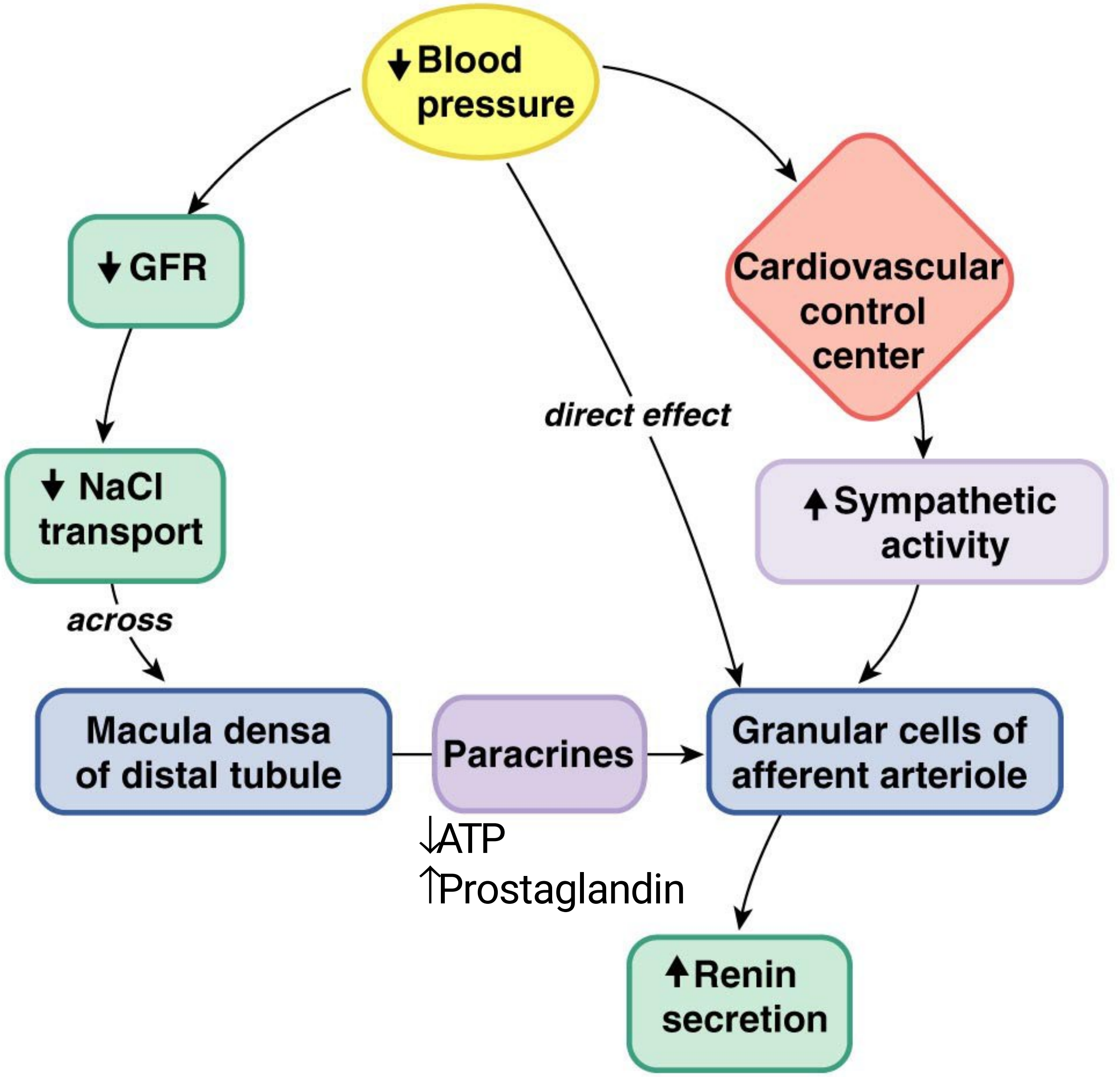
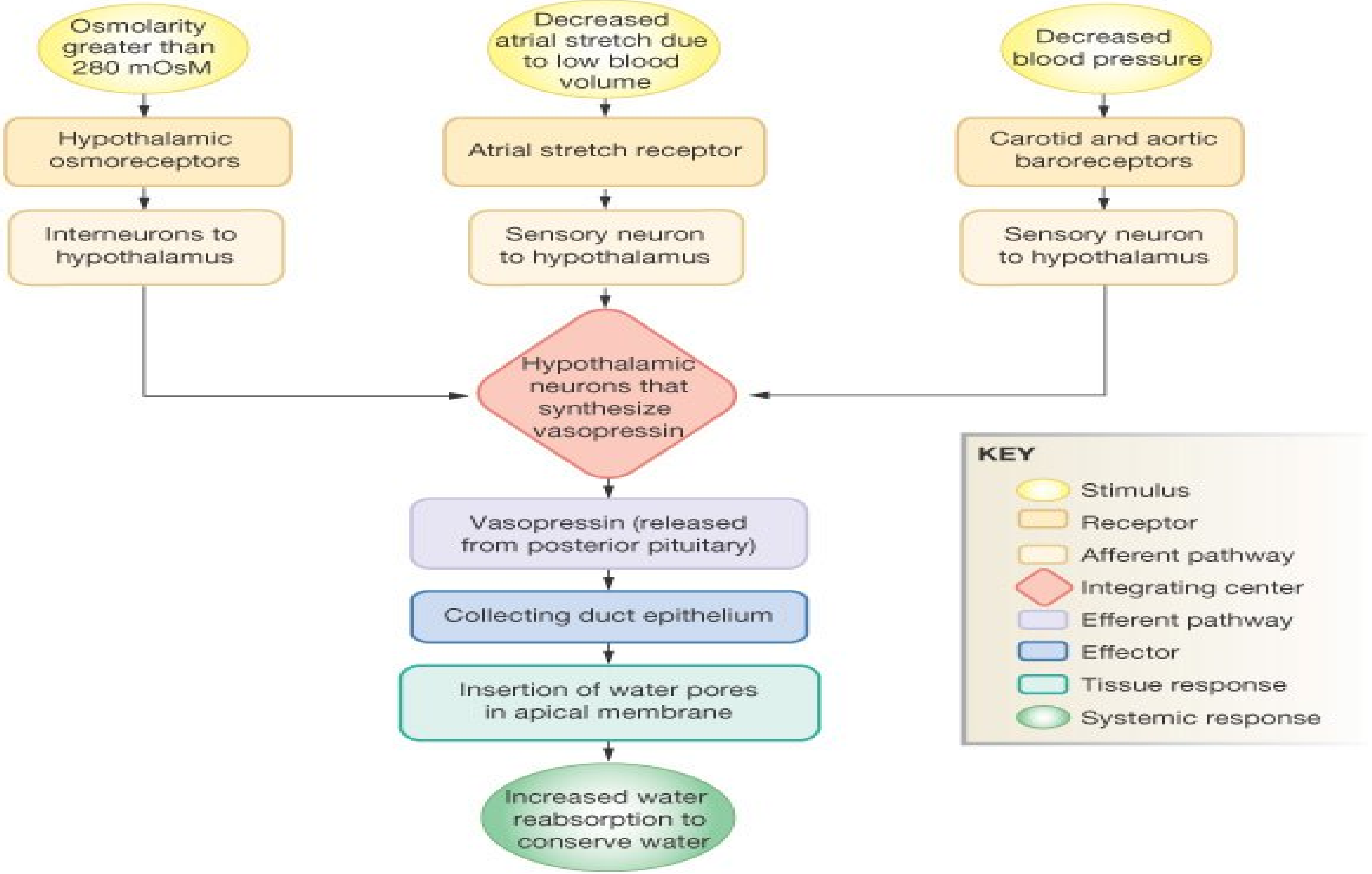

↓Blood pressure
↓GFR
↓NaCl transport
across
direct effect
Cardiovascular control center
↑Sympathetic activity
Macula densa of distal tubule
Paracrines
Granular cells of afferent arteriole
↓ATP
↑Prostaglandin
↑Renin secretion

Figure 20-15

Antidiuretic Hormone Increases Water Reabsorption

- ADH is to increase the water permeability of the distal tubule, collecting tubule, and collecting duct epithelia.
- Stimuli:
  - Increased plasma osmolarity.
  - Drop in blood pressure.
  - Decreased stretch of atrial wall.
- Mechanism:
  - ADH binds to specific V2 receptors >> increase in cAMP and >> activating protein kinases >>stimulates movement of an intracellular protein, called aquaporin-2 (AQP-2), to the luminal side of the cell membranes.
  - This form water channels that permit rapid diffusion of water.
  - There are other aquaporins, AQP-3 and AQP-4, in the basolateral side of the cell membrane.
  - When the concentration of ADH decreases, the molecules of AQP-2 are shuttled back to the cell cytoplasm

Water Balance Reflex: Regulators of Vasopressin Release



Atrial Natriuretic Peptide Decreases Sodium and Water Reabsorption

- Stimuli:
  - Cardiac atrial cells are stretched because of plasma volume expansion.
- Effect:
  - Directly inhibit reabsorption of sodium and water by the renal tubules, especially in the collecting ducts.
  - Inhibits renin secretion
- Result:
  - Decreased sodium and water reabsorption increases urinary excretion which helps return the blood volume back toward normal.

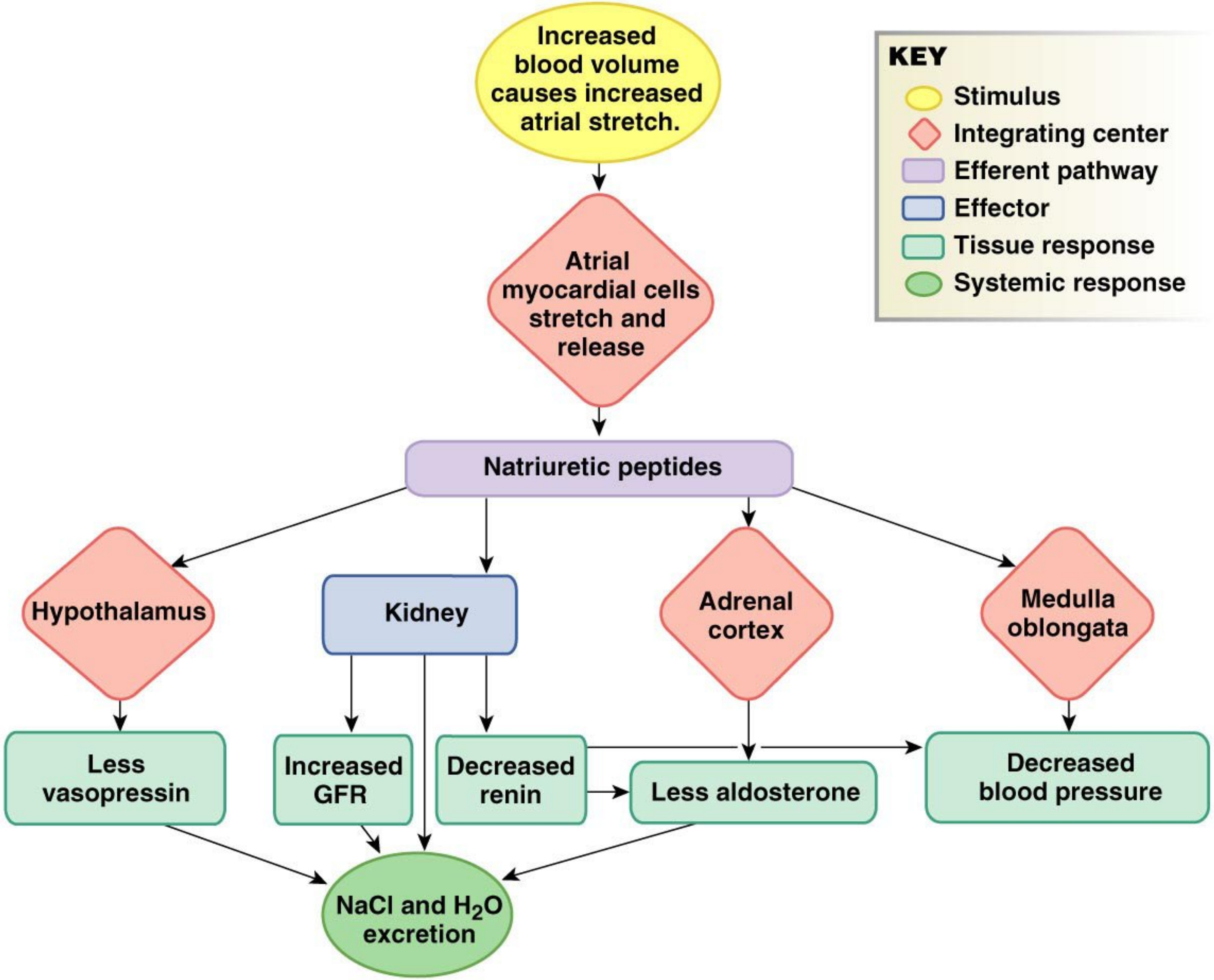

Increased blood volume causes increased atrial stretch.
Atrial myocardial cells stretch and release
Natriuretic peptides
Hypothalamus
Kidney
Adrenal cortex
Medulla oblongata
Less vasopressin
Increased GFR
Decreased renin
Less aldosterone
Decreased blood pressure
NaCl and H_2O excretion
KEY
Stimulus
Integrating center
Efferent pathway
Effector
Tissue response
Systemic response

Figure 20-16

Parathyroid Hormone Increases Calcium Reabsorption

- Increase tubular reabsorption of calcium, by distal tubules and connecting tubules.
- Inhibition of phosphate reabsorption by the proximal tubule
- Stimulation of magnesium reabsorption by the loop of henle

Hormonal control of tubular mechanism

1. **Aldosterone** ------> increase Na^+ re-absorption shifted by K^+,H^+
2. **ADH (vasopressin)** ------> increase water re-absoption
3. **Angiotensin II** ------> increase NaCl and water re-absorption
4. **Parathyroid hormone** ------> increase Ca_{++}, Mg_{++} re-absorption

   decrease PO_{4---} re-absoption