Physiology of Urine Formation

FNTA SEM II

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Introduction

Formation of urine is a process important for the whole organism. Not only **acid-base balance** is modulated by it, but also **blood osmolarity**, **plasma composition** and **fluid volume**, and thus it influences all cells in our body.

A healthy adult person produces **1.5-2 liters of urine per day** and this process involves **three basic mechanisms**:

1) Glomerular filtration

2) Tubular reabsorption

3) Tubular secretion

1) Glomerular filtration

The volume of liquid filtered per unit time in all glomeruli can be expressed as the **glomerular filtration rate** (**GFR**). Its physiological value is **120 ml/min/1,73m^2 body surface area**, thus **180 l/day**. About **99 % of the filtrate gets reabsorbed by the tubular resorption** to the extracellular fluid (back into the body), leaving only 1.5-2 l of urine per day. Movement of the fluid through the filtration membrane is controlled and determined by the ratio of the hydrostatic pressure in the capillaries and oncotic pressure of plasma proteins (less by the hydrostatic pressure of the interstitial fluid and oncotic pressure in the filtrate). These forces are called **Starling´s forces** and there are a few differences from the general principles:

1) Fluid is not exchanged between the capillary and the interstitium, but between the capillary and the fluid of Bowman's capsule

2) Hydrostatic pressure in the capillaries is different, the movement is thus only one-sided (in the direction of filtration)

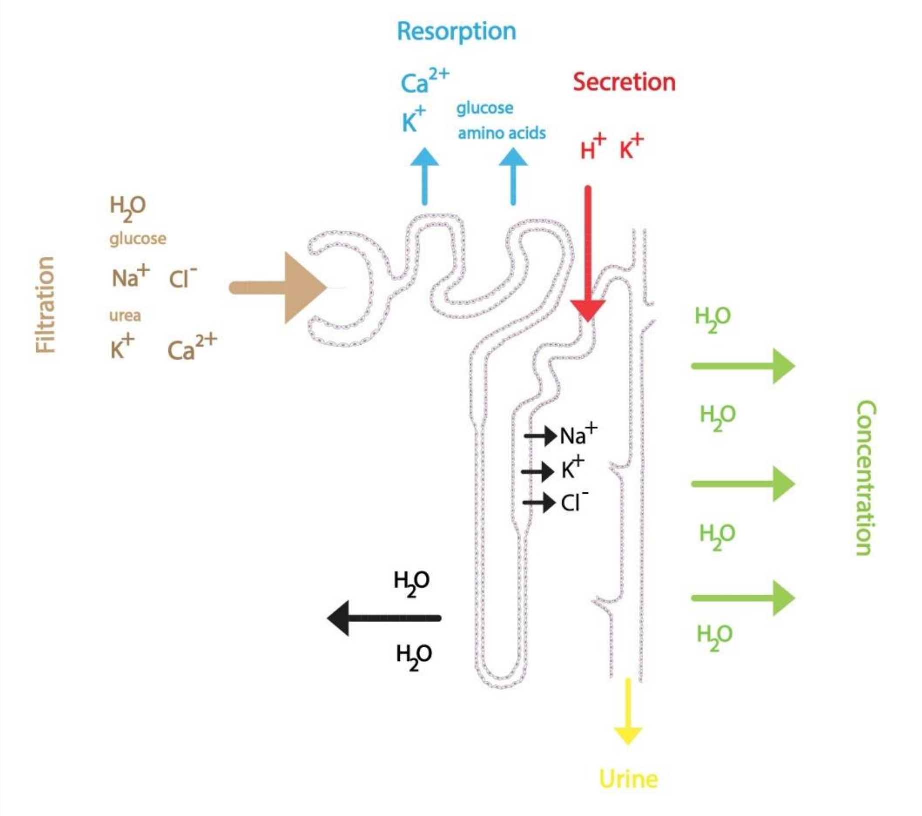
3) Filtration barrier (see above) has a unique structure and properties which do not allow passage of proteins into the filtrate (primary urine)

GFR is therefore dependent on the **renal blood flow**, the **filtration pressure**, the **plasma oncotic pressure**, and the **size of the filtration area**.

2&3) Tubular reabsorption and secretion

As it is already mentioned above, about **99 % of the filtrate gets reabsorbed by the tubular resorption** to the extracellular fluid (back into the body), leaving only 1.5-2 l of urine per day. The main task for renal tubules is therefore an isosmotic tubular reabsorption of primary urine. They absorb water, ions (sodium, chlorides, potassium, calcium, magnesium, bicarbonate or phosphate), urea, glucose and amino acids. All of this is independent on the extracellular fluid volume in the body in case of **obligatory resorption**. Its primary role is to **maintain fluid volume in the body** under normal conditions.

Transport can be carried by **passive diffusion** (in the direction of the concentration or electrical gradient), **primary active transport** against gradient (needs energy – ATP) or **secondary active transport** (transport protein uses the concentration gradient created by a primary active transport realized by other transport protein). Substances can be transported by **paracellular** or **transcellular** routes. Transport of water is always passive. **Na^+/K^+-ATPase** located on the basolateral membrane plays important role in the secondary active transport. It creates a concentration gradient for Na^+. Transport proteins act as symporters (transport of compound is coupled to the transport of Na^+ in the same direction) or antiporters (transport of compound is coupled to the transport of Na^+ in the opposite direction). To understand the processes in the tubular system, it must be imagined tubular epithelial cells, their **apical membrane** facing the **tubular fluid** (primary urine), basolateral membrane, on the other hand, is in contact with the **peritubular fluid** (here is located the Na^+/K^+-ATPase).



Tubular reabsorption process

The proximal tubule

Reabsorption of sodium ions is in the **first half of the proximal tubule** coupled with the reabsorption of bicarbonate, glucose, amino acids, lactate, urea and phosphate. Absorbed compounds are osmotically active, thereby **draining water from tubules**. This leads to an increased concentration of chloride ions in the tubular fluid that is very important for a resorption in other parts of the proximal tubule.

Reabsorption of bicarbonate ions in the proximal tubule

Movement of **bicarbonate** and **hydrogen ions** depends on the transport sodium ions. This process is catalyzed by enzyme **carbonic anhydrase** (located in the apical membrane and in the intracellular part of the epithelial cells). The first step is the secretion of H^+ into the tubular fluid through the **Na^+/H^+ antiport**, located at the luminal (apical) membrane of proximal tubule cells. Transferred H^+ may in the tubular fluid react with filtered bicarbonate ions to form carbonic acid. **Carbonic anhydrase** facilitates the decomposition of carbonic acid in the tubular fluid to water and carbon dioxide. Both compounds can freely **diffuse** into the tubule epithelial cells, where carbonic acid is restored by the carbonic anhydrase. Molecules of carbonic acid **dissociates** into hydrogen and bicarbonate ions. Bicarbonate ions then pass through the basolateral membrane into the interstitial fluid through **$Na^+/3HCO_3^-$-cotransporter** or **anion exchanger** (Cl^-/HCO_3^-). H^+ returns via antiport with Na^+ into the tubular fluid. For each secreted H^+, Na^+ and HCO_3^- is absorbed (Na^+ is returned to the blood by active transport in exchange for K^+ – **Na^+/K^+-ATPase**).

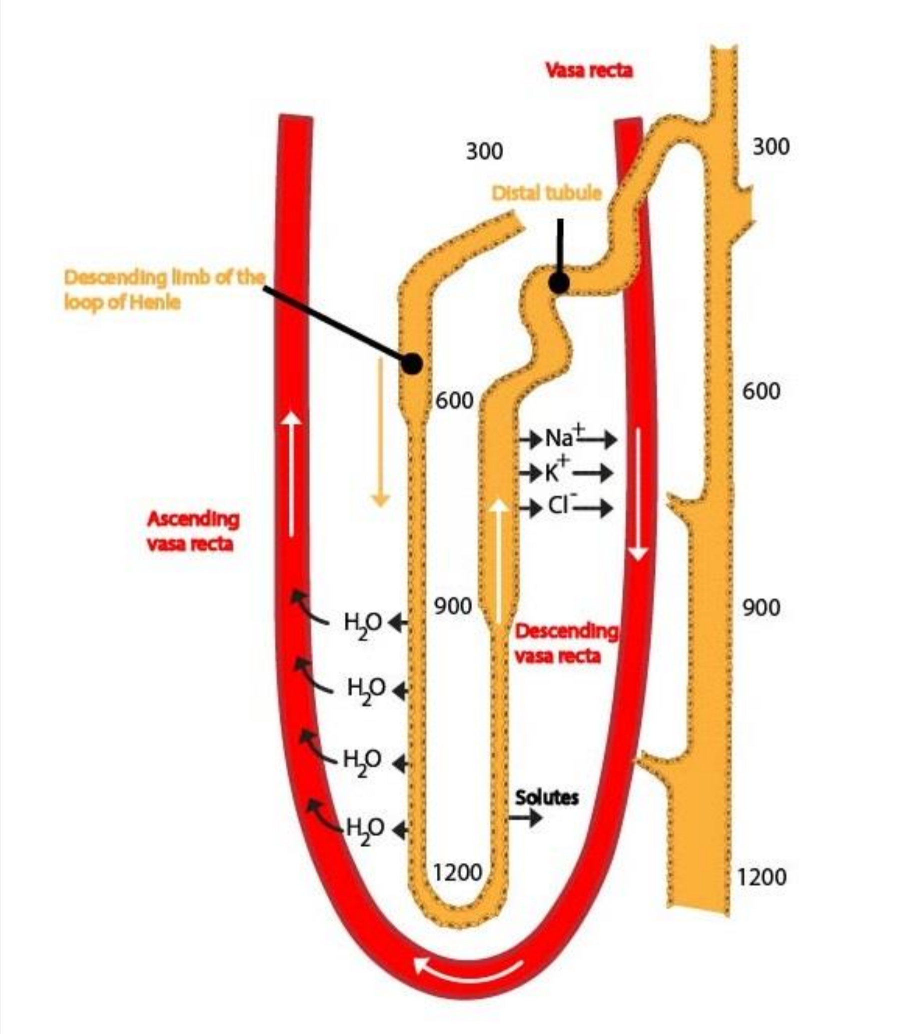
Renal (tubular) threshold

Glucose, amino acid and many other organic compounds are in this part of the tubule **completely resorbed** under physiological conditions. This transport has some **maximum value** – so-called **renal/tubular threshold**. As an example the **renal threshold for glucose** can be mentioned. When this renal threshold is exceeded (due to **too high plasma concentration** – such as **10 mmol/l for glucose**), glucose reabsorption in the proximal tubule is incomplete and some amount of glucose remains in the final urine. Unabsorbed **osmotically active** molecules drain water molecules to renal tubules, thereby increasing diuresis (**osmotic polyuria**).

Reabsorption of sodium ions is in the **second half of the proximal tubule** coupled with the transport of chloride ions, used are both transcellular (on basolateral membrane helps K^+/Cl^--symport) and paracellular routes. Relatively abundant positively charged ions (sodium, potassium, calcium, magnesium) in the tubular fluid accompany chloride ions in paracellular transport. Transport of ions is followed by passive reabsorption of water.

Loop of Henle

Henle's loop absorbs about 25 % of the solutes (thick segment of the ascending limb), but only about 15 % water (descending limb). Its proper function (thick part of the ascending limb is impermeable to water and has active transport of Na^+ and Cl^-) is essential for the **formation of a high osmotic pressure** (**hyperosmolarity**) **in the renal medulla** that ensures a production of highly concentrated urine. Some mechanisms of reabsorption of ions are similar to those in the proximal tubule. Very important is the specific symport of Na^+, K^+ and 2 Cl^- across the apical membrane. This symport uses energy derived from the transport of sodium and chloride ions in the direction of their concentration gradient for the transport of potassium ions into the cell (against their concentration gradient). Some of these ions leave cells on the basolateral membrane (together with Cl^-), some return back into the tubular fluid, thereby creating an electrical imbalance. Due to this, positively charged ions (Na^+, K^+, Ca^{2+}, Mg^{2+}) are resorbed by paracellular route (very important mechanism for resorption of solutes). This is especially significant for formation of a hypertonic renal medulla. Hypotonic fluid leaves the loop of Henle and enters the distal tubule.



Reabsorption of ions and water in the loop of Henle

Clinical correlation:

Substances that block the symport (e.g. furosemide) are used as very effective diuretic drugs – loop diuretics.

Distal convoluted tubule and collecting duct

Distal convoluted tubule and collecting duct resorbe about **7% of solutes** (mainly Na^+ and $Cl^–$) and approximately **17% water**. Their resorption is **affected by hormones** (e.g. ADH) – **facultative resorption**. Hydrogen and potassium ions are secreted here. The distal convoluted tubule and the collecting duct thus play an important role in the formation of the final urine and in the regulation of osmolarity and pH. Sodium and chloride ions are absorbed in the first part of the distal convoluted tubule. The distal part of the distal convoluted tubule and the collecting duct consist of two cell types:

1) Principal cells responsible for the resorption of sodium ions and water (dependent on ADH) and secretion of K^+ ions

2) Intercalated cells containing carbonic anhydrase. They are involved in acid-base balance, because they can secrete both hydrogen and bicarbonate ions

Calcium and phosphate reabsorption and secretion

Plasma concentration of total calcium is **2.25-2.75 mmol/l** and for ionized calcium **1.1-1.4 mmol/l**. Only ionized calcium (about 48 % of total) is filterable by kidneys. Resorption takes place by both **active** (15-20 %) and **passive paracellular** (80 %) mechanisms. It is localized in the **proximal tubule**, the **ascending part of Henle's loop** and partially in the **distal convoluted tubule**. **Parathyroid hormone stimulates the reabsorption by transcellular route** in this segment. Calcitriol acts the same way, just mostly in the distal convoluted tubule. In contrast, **calcitonin increases the excretion of calcium ions** by inhibition of tubular reabsorption.

Serum phosphate concentration is 0.7-1.5 mmol/l, **urine concentration is 15-90 mmol/l**. Phosphates are also influenced by the **parathyroid hormone** (**inhibits the resorption of phosphates**) and by the **calcitonin** (also reduces the resorption of phosphates).

Control of tubular processes

The tubular processes can be distinguished as **local** and **central regulatory mechanisms**.

Local mechanisms

Local mechanisms are represented mainly by **Starling´s forces** (increased plasma oncotic pressure leads to an increased reabsorption of water and solutes from the interstitium into the capillaries, thereby supporting the tubular resorption) and **glomerulotubular balance** (increased GFR leads to an increase in glucose, amino acids and sodium ions resorption, these are followed by water – volume of resorbed fluid increases proportionally with increased GFR).

Central mechanisms

Central mechanisms are represented by many **hormones** – such as **ADH**, **aldosterone**, **angiotensin II**, **epinephrine**, **natriuretic peptides** (**ANP** and **BNP**) or **parathyroid hormone**. **Sympathetic nervous system** has a role also.

ADH (antidiuretic hormone, vasopressin) is produced in the **hypothalamus** and secreted by the **posterior pituitary gland** in a response to an **increased osmolarity of extracellular fluid** (to a lesser extent as an answer to a decrease of extracellular fluid volume). ADH binds to the **V_2-receptor** located on collecting duct cells (partly on distal tubule cells). Its effect increases the number of **aquaporins** in cell membranes and water molecules can pass along the osmotic gradient into peritubular fluid (ECF). ADH acts also on a **transport of urea** in the collecting duct and on a transport of Na^+ and Cl^- in the thick segment of the ascending limb of the loop of Henle.

Aldosterone is secreted by the **zona glomerulosa** of the **adrenal cortex** in response to increasing plasma concentrations of **angiotensin II** and **potassium ions**. It plays therefore an important role in maintaining of constant level of potassium ions (**accelerates secretion** of potassium ions in the thick segment of the loop of Henle and in the distal tubule) and in **regulation of volume of ECF**. As the part of the **renin-angiotensin-aldosterone system**, it **stimulates reabsorption of sodium ions**, accompanied by **passive water resorption** (distal tubule and collecting ducts). This system is activated by decrease in the plasma volume.

Angiotensin II stimulates aldosterone secretion and resorption of sodium ions (and consequently resorption of water molecules) in the proximal tubule.

Sympathetic nervous system and **epinephrine** stimulate reabsorption of sodium ions and water molecules in the proximal tubule and in the thick segment of the loop of Henle.

As the name suggests, **natriuretic peptides** (ANP – atrial natriuretic peptide and BNP – brain natriuretic peptide) **increase natriuresis**. They **inhibit Na^+ reabsorption** in the distal tubule, thereby increasing its loss in urine. Sodium ions drain water molecules, result is **increased diuresis**. Both peptides are secreted by our **heart**. ANP is secreted by **atrial cardiomyocytes**, the stimulus for its secretion is an **increased wall stress** (**increased venous return** causes dilation of heart). BNP is secreted by **ventricular cardiomyocytes**, the signal is **increased tension in the ventricular wall**. Natriuretic peptides thus mediate response of our organism to an excess of Na^+ and increased blood volume. Only natriuretic peptides (together with **dopamine**) increase diuresis.

Parathyroid hormone reduces Ca^{2+} excretion (stimulates reabsorption of Ca^{2+} from the primary urine) and **increases excretion of phosphates** in our kidneys. In result, it **increases calcaemia** and **decreases phosphatemia**.

Control of urine osmolarity

There are several processes controlling the urine osmolarity. **Excretion of excess water** leads to a formation of hypotonic urine, **excretion of excess solutes** results in a formation of hypertonic urine.

1) Dilution of urine

a) The loop of Henle creates an osmotic gradient from the cortex to the hypertonic medulla (due to impermeability of the thick segment to water molecules and high reabsorption of solutes)

b) Production of ADH is reduced

c) Urea passes from the medulla into the tubular system, thereby reducing hypertonicity of the medulla

2) Production of hypertonic urine

a) The loop of Henle creates an osmotic gradient (hypertonic medulla); Na^+, Cl^- (see above) and **urea** play an important role – hypertonicity of the renal medulla reaches its maximum
b) Production of ADH is increased

c) Urea circulates in the renal medulla – increased hypertonicity of the medulla

Final urine

Final urine is characteristically malodorous, clear, golden yellow liquid. Its specific gravity varies between **1 003-1 038 kg/m^3** and its pH between **4.4-8.0**. It contains Na^+ (100-250 mmol/l), K^+ (25-100 mmol/l), Cl^- (about 135 mmol/l), Ca^{2+}, creatinine, vanillylmandelic acid (degradation product of catecholamines), uric acid, urea, etc. Healthy kidneys do not allow a significant amount of proteins and glucose to reach the final urine (they are almost completely reabsorbed). **Presence of high amount of proteins and glucose in the final urine is a pathological finding**. **Normal diuresis** is **1.5-2 l/day**. **Polyuria** is diuresis **higher than 2 l/day**, **oliguria lower than 0.5 l/day** and **anuria lower than 0.1 l/day**.