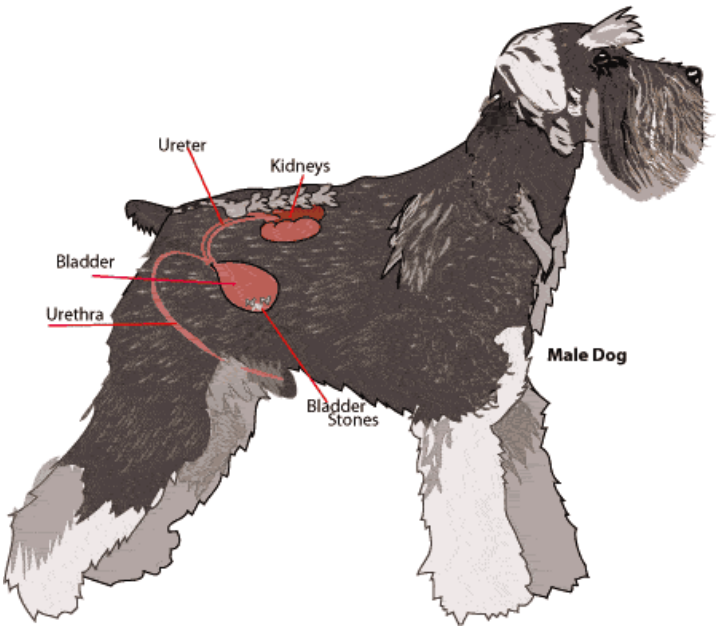
THE UNIVERSITY OF MELBOURNE
FACULTY OF VETERINARY & AGRICULTURAL SCIENCES

STRUCTURE AND FUNCTION OF THE KIDNEY 4

Regulation of effective circulating volume and NaCl balance

Veterinary Bioscience: Metabolism and Excretion



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REGULATION OF EFFECTIVE CIRCULATING VOLUME AND NaCl BALANCE

Learning objectives:

1. Explain why changes in effective circulating volume are linked to Na+ (and water) levels
2. Describe the renin angiotensin aldosterone system and how it is regulated.
3. Discuss how sympathetic nerves, angiotensin II, aldosterone and naturietic peptides regulate Na excretion and reabsorption
4. Describe both the mechanism and regulation of K^+ reabsorption and secretion by the kidney

Major solute of the ECF is NaCl . Changes in NaCl is a major determinant in changes to ECF and effective circulating volume (ECV).

Under normal conditions alterations in Na+ balance do not alter the ECF osmolality because water and Na regulation are closely linked. Body fluid osmolality is tightly regulated by ADH and thirst systems. If NaCl is added to the ECF without H2O it leads to an increase in osmolality which leads to water moving out of the intracellular compartment of cells and to an increase in ADH secretion Ultimately causing a return to normal osmolality concentrations.

The amount of NaCl in the ECF determines the volume of this body fluid compartment.
The kidneys regulate excretion of NaCl so they are important in regulating the volume of the ECF. The ECV which is the volume of blood in the vascular space perfusing tissues and a major determinant of blood pressure is part of the ECF . In normal animals ECV varies according to volume of the ECF and is proportional to NaCl.

Kidneys alter their excretion of Na^+ in responses to ECV rather than ECF. When ECV is reduced Na^+ excretion by the kidney is reduced restoring ECV back to normal. In some pathological states however this relationship is not maintained. For example, animals with cardiac failure can have a low ECV yet expanded ECF (oedema).

Regulation of effective circulating volume

1. Change to ECV is detected by volume receptors that detect vascular stretch (carotid sinuses, aortic arch and afferent glomerular arterioles).
2. These receotors in turn activate a series of effectors such as sympathetic nerves, angiotensin II, ANP, ADH which restore normovolemia by varying, Na+ and water excretion by the kidneys.

Renin-Angiotensin-Aldosterone system.

Aldosterone
Aldosterone is a steroid hormone produced in the zona glomerulosa of the adrenal cortex. It stimulates Na+ reabsorption & K+ secretion in the principal cells of the collecting ducts. Aldosterone increases Na/K ATP pump activity and sodium permeability of the luminal membrane by increasing the number of ENa channels.

Angiotensin II

Major actions include increasing blood volume by retaining body Na & water.

1. Raises blood pressure via arterial vasoconstriction via activation of specific receptors termed AT1 or AT2.
2. Stimulates aldosterone secretion by the adrenal cortex, which increases Na reabsorption in collecting duct.
3. Enhances of NaCl reabsorption by proximal tubule by activating Na+-H+ antiporter via stimulation of an inhibitory G protein pathway that decreases cAMP, which normally acts to inhibit this antiporter. Also enhances DT Na reabsorption
4. Direct renal vasoconstriction afferent and efferent arterioles and mesangial and podocyte contraction dropping GFR
5. Stimulation of ADH secretion and thirst.

Sympathetic Nerves

Fibres innervate the afferent and efferent arterioles as well as cells of the renal tubule. These fibres are stimulated by a decrease in the ECV and which results in activation of β-adrenergic receptors.
Sympathetic nerves cause

1. Constriction of afferent arterioles which decreases the glomerular filtration rate. α-adrenergic
2. Renin secretion by juxtaglomerular cells β-adrenergic.
3. NaCl reabsorption by the proximal tubule and ascending loop of Henle's loop is increased by α-adrenergic receptors
4. Increases cardiac contractility and increases heart rate which increase cardiac output and helps to restore blood pressure.

Renin

Renin is secreted by juxtaglomerular cells of the afferent arteriole and is an aspartyl protease cleaving enzyme that cleaves **angiotensin I** (10 aa**)**, from the larger plasma protein **angiotensinogen**.
Angiotensin I then undergoes further cleavage by **angiotensin converting enzyme** (ACE) which is produced by endothelial cells (particularly in lung) to form **angiotensin II** (8 aa**)**. Angiotensin II has its own effector functions on the kidney (GFR and tubular reabsorption) but also stimulates the adrenal cortex to release aldosterone.

The rate limiting step in this pathway is the formation of renin.

Control of Renin Secretion

There are at least three distinct inputs to the juxtaglomerular cells that control renin release:

1. Renal sympathetic nerves: Baroreceptors external to the kidneys detect a drop in ECV (and blood pressure) and stimulate β–adrenergic receptors on juxtaglomerular cells to release renin
2. Intrarenal baroreceptors:- juxtaglomerular cells in afferent arteriole can sense a drop in blood pressure and function as intrarenal baroreceptors. When renal arteriolar pressure decreases as a consequence of a drop in ECV and systemic drop in blood pressure these cells secrete more renin.
3. Macula densa detects an increased concentration and delivery of Na+ and/or Cl- in the tubular fluid. . With a decrease in GFR and hence delivery, macula densa sodium and chloride concentrations tend to decrease when arterial pressure is decreased. A decreased NaCl (reflecting drop ECV) here causes increased renin secretion to promote increased reabsorption of Na and drop in GFR via renin AII and aldosterone.

Natriuretic peptides

Atrial Natriuretic Peptide (ANP) and Brain Natriuretic Peptide (BNP

1. ANP Synthesised and secreted by cardiac atrial myocytes when heart dilates (volume expansion) or via ventricle (BNP)
   a. They promotes water and sodium excretion by the kidneys.
   b. They are released in response to atrial or ventricle stretch (ECV increase) and antagonizes the effects of the angiotensin/aldosterone system.
2. Effector actions
   a. ANP dilates afferent and constricts efferent arterioles increasing GFR.
   b. ANP directly inhibits NaCl reabsorption by the collecting duct.
   c. Inhibits renin release
   d. Inhibits the action of ADH on collecting duct
   e. ANP inhibits aldosterone release both directly at the zona glomerulosa and indirectly via renin inhibition

Urodilatin produced by tubular epitheial cells also acts in a similar manner to ANP but its actions are limited to the kidney

Control of GFR

Control of GFR is a major mechanism by which Na+ levels are regulated as increased GFR leads to **more** Na+ being filtered and ultimately being removed from the body. Decreased GFR results in **less** Na+ filtered and removed from the body. Both sympathetic nerves and AII reduce GFR

Increased total-body Na+ levels increases ECV (after osmo regulation occurs) and results in **Natriuretic peptides** being released that can increased GFR via afferent arteriole vasodilation and block renin production. This helps correct expanded ECV back to normal by increasing renal Na+ excretion

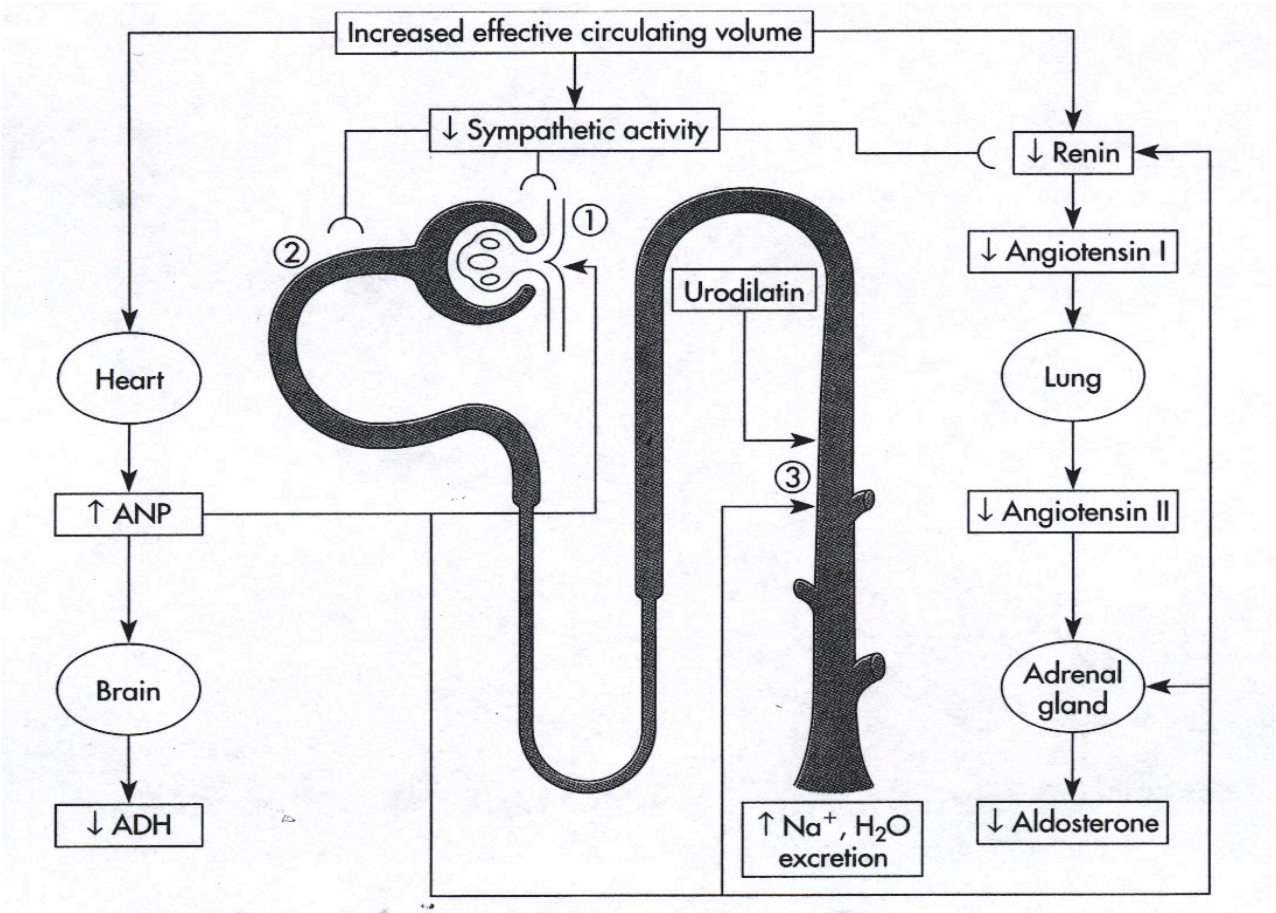

Figure Regulation of Na by the kidneys Koeppen, B.M. and Stanton, B.A. (2007)

6. POTASSIUM, REGULATION

The concentration of K+ in the body is tightly regulated by the kidney. [K+] is high inside cells (150 mmol/L) compared with ECF (4 mmol/L) and contributes to the electrical potential across the plasma membrane of cells.

Hyperkalemia [K+] > 5mEq/L in ECF.
Hypokalemia [K+]< 3.5 mEq/L in ECF.

K+ is freely filtered in the glomerulus but most filtered K+ is reabsorbed before it reaches the distal tubules. K+ that is to be excreted secreted by the distal tubule and cortical collecting duct.

Proximal tubule
65% of K+ reabsorbed in proximal tubule via paracellular route. Na/K ATPase pump establishes a concentration gradient across the epithelial cells that favour Na+ movement which is followed by Cl- This facilitates the reabsorption by K+ in mid to late proximal tubule.

Loop of Henle

The thick ascending limb reabsorbs 20-30% of the filtered K+. Mediated by a Na/K/Cl transporter in apical membrane and K/Cl cotransporter in basolateral membrane. Use a pump-leak mechanism relying on Na/K ATPase pump and K+ ion channels to transport K+. Some paracellular movement as well encouraged by positive potential in tubular lumen

Collecting tubule & ducts

Principal cells in the late segment of the distal tubule and collecting duct secrete K+ whereas the intercalated cells reabsorb K+.

The Na-K-ATPase pump drives K+ secretion in principal cells by increasing intracellular K+ concentrations and K channels on luminal surface permit K+ to be secreted via electrochemical gradient into tubular fluid.

When K+ is low in body intercalated cells have a K+/H+ ATPase antiporter that actively pumps K+ into the cell and it exits via a K+ ion channel in the basolateral membrane.

Renal regulation of K+ excretion occurs by altering K+ secretion by principal cells.

1. K+ secretion is regulated by altering K+ channels in luminal membrane and by in basolateral membrane of principal cells in distal tubule and collecting duct.
2. Factors which increase K+ secretion:
    a. Aldosterone
    b. Aldosterone released by adrenal cortex with increased K+ concentration of the extracellular fluid. Aldosterone increases K+ secretion by stimulating the production of Na+,K+-ATPase pumps and K+ channels.
3. [K+] inside cells
    a. Increases concentration gradient
4. Tubular flow rates
    a. Increases local gradient for K+
    b. Increased delivery of Na+ to collecting duct & its reabsorption leaves Cl- behind favouring electrochemical gradient for K+
    c. Increased flow bends cilium in principal cells which activates a PKD1 Ca^{2+} channel complex. Increased Ca^{2+} activates a K+ channel in apical membrane promoting K+ secretion from the cell into tubular fluid.
5. Acidosis K+ secretion decreased
    a. pH alters K+ channels & Na+,K+-ATPase pumps
    b. Possible that K+/H+ ATPase (intercalating cells) pumps increase.

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