PHYSIOLOGY OF POTASSIUM HOMEOSTASIS

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Disclosure

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Physiology of Potassium Homeostasis - Question 1

What determines the internal distribution of potassium and internal potassium homeostasis?

What is the role of aldosterone in mediating potassium uptake by extra-renal tissues?

What is the role of aldosterone in determining systemic potassium homeostasis? Is it primarily to regulate internal balance?
“The rate of excretion of potassium is not directly related to either the glomerular filtration rate or to the plasma potassium concentration; nor is it directly related to the product of these two quantities, the amount of potassium filtered.”
K Transport beyond the Macula Densa Largely Dictates K Excretion

Fig from: Giebisch & Wingo Semin Nephrol 2013; 33(3):209-14
Data from Malnic, Klose, & Giebisch Am J Physiol 1964;206:674-86

Adapted From Vallon, Pflugers Arch 2009;458:189-201
QUESTIONS

WHAT DETERMINES THE INTERNAL DISTRIBUTION OF POTASSIUM AND INTERNAL POTASSIUM HOMEOSTASIS?
WHAT IS THE ROLE OF ALDOSTERONE IN MEDIATING POTASSIUM UPTAKE BY EXTRA-RENAL TISSUES?
WHAT IS THE ROLE OF ALDOSTERONE IN DETERMINING SYSTEMIC POTASSIUM HOMEOSTASIS? IS IT PRIMARILY TO REGULATE INTERNAL BALANCE?
Serum Potassium Concentration in 38,689 Admissions

Figure 1. Distribution of Serum Potassium Levels at Admission in the Overall Population (N=38689)

Median potassium level at admission was 4.1 mEq/L (vertical dotted line). Each x-axis interval is equal to or greater than the lower limit of the interval and less than the upper limit. The first interval includes all serum potassium levels less than 2.0 mEq/L and the last interval includes all that are 8.0 mEq/L or greater.

Goyal et al. JAMA 307:(2) 157-164, 2012
Plasma Membrane Potassium Distribution Controls Resting Membrane Potential ($V_m$) & Repolarization of Nerves and Muscles
Cause-Specific Mortality in Peritoneal Dialysis Patients

Figure 3. Association of serum potassium, use as a time-varying covariate, with mortality in patients undergoing peritoneal dialysis \((n=10,454)\). Error bars represent 95% confidence intervals.

Plasma Potassium Ranges Associated with Mortality Across Stages of Chronic Kidney Disease

Gasparini et al-Nephrol Dial Transplant (2018, Aug 06)
A High Potassium Intake slows the progression of Renal and CV Disease

Araki et al.-Urinary K Excretion & Renal CV Complications in Diabetic Patients with normal Renal Function-CJASN (2015);10(12):2152
Benefit and Risk of a High Potassium Diet

Risk of Hyperkalemia

GFR

KDIGO
Renal & Extra-Renal Potassium Balance - Kinetics

98 % Total Body Potassium

Cellular Stores
~3300 mEq K+

ECF 65 mEq

GI Intake (~100 mEq/day)

Renal Excretion (90-95 mEq/day)

GI Excretion (~10 mEq/day)

~130 mEq/min into skeletal muscle

Cheng et al. Sem Nephrol 2013 May;33:237–
Renal & Extra-Renal Potassium Balance - Kinetics

- GI Intake: (~100 mEq/day)
- Renal Excretion: (90-95 mEq/day)
- Cellular Stores: ~3300 mEq K+
- ECF: 65 mEq

What Stabilizes Plasma Potassium?

- Renal Potassium Excretion
- Enhanced Cellular Potassium uptake
  - Insulin, β₂ catecholamines, aldosterone
- Gut Sensors
- Circadian Rhythm
Overview of Potassium Homeostasis: Meal-Driven Potassium Excretion

Overview of Potassium Homeostasis: Fasting Potassium Excretion

Potassium Adaptation: Renal and Extra-Renal Mechanisms

High dietary K⁺ adaptation: less of an increase in [K⁺]ₚ when given an acute KCl load

**Figure 1** Effect of an acute potassium load on plasma potassium in rats fed a regular or a high K diet. Points are means; vertical lines show ±SE in this and all subsequent figures.

Alexander and Levinsky  J Clin Invest (1968) 47:(4) 740-48
Potassium Adaptation: Renal and Extra-Renal Mechanisms

Renal $K^+$ excretion did not explain the protective effect of high dietary $K^+$ adaptation.

Animals adapted to a high $K^+$ diet excreted less $K^+$ in the urine.

**Figure 2** Cumulative urinary potassium excretion. The solid lines in the upper section show excretion after an acute KCl load. The broken lines in the lower section show the basal excretion when an acute load was not given. All rats were fasting for 16–20 hr before each study.

Alexander and Levinsky J Clin Invest (1968) 47:(4) 740-48
Potassium Adaptation: Renal and Extra-Renal Mechanisms

Acute nephrectomy did not alter the ability to tolerate an acute KCl load.

Adapted animals still had a smaller change in $[K^+]_p$.

Figure 3: Response of nephrectomized rats to an acute potassium load.

Alexander and Levinsky J Clin Invest (1968) 47:(4) 740-48
Potassium Adaptation: Renal and Extra-Renal Mechanisms

Adrenalectomy *abolished* the protective effect of $K^+$ adaptation.

*Figure 4* Effect of adrenalectomy on the response of nephrectomized rats to an acute potassium load. The rats had been adrenalectomized 2 wk before study and were maintained on 0.15–0.20 mg of deoxycorticosterone acetate (DOCA) daily.

Alexander and Levinsky  J Clin Invest (1968) 47:(4) 740-48
Potassium Adaptation: Renal and Extra-Renal Mechanisms

Chronic mineralocorticoid stimulation resulted in a smaller rise in $[K^+]_p$ to an IV load of KCl.

*Figure 7* Effect of high (5-7.5 mg/day) and low (0.75-1.25 mg/day) doses of DOCA on the response of nephrectomized rats to an acute potassium load. The rats had been on DOCA for 4 days before the experiment. All rats were on a low sodium diet to prevent potassium depletion.

Alexander and Levinsky J Clin Invest (1968) 47:(4) 740-4
Mineralocorticoid activity & excretion oral potassium load in normal man

Mineralocorticoid treatment stabilized $[K^+]_p$ but renal K excretion was less.

By 5 hours 85±4% of the K load was excreted without drug treatment.

With fludrocortisone only 37±5% of the K load was excreted in 5 hours (P<0.001).

Hene et al.-Kid Int 1988;34:697-703
Mineralocorticoid activity & excretion oral potassium load in normal man

Mineralocorticoid stimulation resulted in significantly less urinary potassium excretion of an oral potassium load during the following 5 hours.

Hene et al.-Kid Int 1988;34:697-703
Effects of Aldosterone on Potassium Distribution

• “Data from the two groups of experiments are consistent with the hypothesis that aldosterone alters the distribution of potassium between the intra- and extracellular spaces, a greater portion of total potassium being intracellular at higher levels of aldosterone.”

Effect of Aldosterone on Blood Pressure
Pan & Young

Pan & Young, Hypertension 4:279-287, 1982
Effect of Aldosterone on Potassium Balance -
Pan & Young

Pan & Young, Hypertension 4:279-287, 1982
Effect of Aldosterone on Plasma Electrolytes - Pan & Young

Pan & Young, Hypertension 4:279-287, 1982
Summary of Pan & Young Study

- Aldosterone increased systemic blood pressure and mean circulatory filling pressure.
- Aldosterone stimulated transient sodium retention before animals went into “aldosterone escape”.
- Aldosterone did not increase the absolute rate of renal potassium excretion.
- Aldosterone reduced steady-state plasma potassium concentration.
- Aldosterone increased renal potassium clearance.

\[ C_k = \frac{U_K \times V}{P_K} \]
In vitro Effect of Aldosterone

Effect of Mineralocorticoids on K secretion at basolateral membrane


FIG. 3. Graph showing differences in driving forces between CCDs from control \( (n = 9) \) and DOCA-treated \( (n = 6) \) rabbits across apical \( (V_a-E_K) \), basolateral \( (V_b-E_K) \), and transepithelial \( (V_T) \) membranes. DOCA significantly increased driving force for K secretion (negative direction) across basolateral membrane. Error bars are SE. * \( P < 0.05 \) using t test for unpaired data. See text for definitions of abbreviations.
Metabolic Balance studies that Examine the Effect of Aldosterone or DOC Stimulation

Mineralocorticoids stimulate the activity and expression of renal H^+\text,/K^+-ATPases

Mineralocorticoids stimulate the activity and expression of renal H⁺,K⁺-ATPases


In normal mice K balance did not decrease.
Aldosterone Stimulation of Ion Transport in the Aldosterone-Sensitive Distal Nephron & Collecting Duct

QUESTIONS

What is known about gastric renal signaling with regards to potassium homeostasis? What is the evidence favoring a 'feed forward' versus a 'feedback' system for potassium homeostasis?
QUESTIONS

WHAT IS KNOWN ABOUT THE DIURNAL VARIABILITY IN POTASSIUM HOMEOSTASIS? WHAT IS THE KNOWN ABOUT CLOCK GENES AND HOW THEY MIGHT BE INVOLVED IN POTASSIUM SECRETION AT THE TUBULAR LEVEL AND IN REGULATING ALDOSTERONE SECRETION?
What Stabilizes Plasma Potassium?
-Both with meals and between meals-
  • Renal Potassium Excretion
  • Potassium Redistribution into Cells:
    • Insulin, $\beta_2$ catecholamines, aldosterone
  • Potassium Sensors (Independent of $P_K$)
  • Potassium Regulation by Circadian Clock
Westward or Eastward Travel on Urinary Potassium Circadian Rhythm

Circadian Rhythm of Urinary Potassium Excretion in Humans during Two Levels of Potassium Intake on Constant Liquid Diet

Early and late adjustment to potassium loading in humans


Data from: Rabelink et al. - Kidney Int. 1990; 38:942-7
Serum Potassium Exhibits a Small Circadian Variation Throughout the Day

- The nadir of serum [K+] occurs just before bedtime, slowly increasing by morning\(^1\)
- Urinary K\(^+\) excretion varies throughout the day due to an individual’s activity, circadian rhythm, and dietary K\(^+\) intake\(^2\)


Urinary Potassium Excretion Exhibits a Diurnal Variation that is Reversed in CKD

• In healthy individuals, much more K⁺ excretion occurs during the day than during the night.¹

• In patients with CKD, circadian patterns reverse, with more urinary K⁺ excretion during the night than during the day.²

Sgk1 and Sgk2 Exhibit Circadian Changes in mRNA in the Mouse Kidney
SPAK (Stk39) and Wnk1 Exhibit Circadian Changes in mRNA in the Mouse Kidney
Hypothetical Model of the Aldosterone-Sensitive Distal Nephron and Collecting Duct
Hypothetical Model of the Aldosterone-Sensitive Distal Nephron and Collecting Duct

McDonough & Youn-Physiology(Bethesda) 2017; 32:100-11
SUMMARY

Multiple hormones determine the distribution of potassium.

Aldosterone’s main role is to increase sodium conservation.

Aldosterone also mediates potassium uptake by extra-renal tissues & increases potassium clearance.

By this action, aldosterone serves to stabilize internal potassium balance.
Questions?
“Normally, and in the state of dietary Na depletion, net sodium reabsorption along the distal tubule exceeds simultaneous potassium secretion by an order of magnitude or more.”

“Neither the amount of sodium entering the distal tubule nor the intratubular sodium concentration were found rate limiting if a one-to-one exchange of cellular potassium for intratubular sodium were the sole mode of potassium secretion across the distal tubular epithelium.”
In vivo Effect of Aldosterone

Fig. 1. Results of a single clearance experiment. Urine sodium excretion (U_{Na}V), urinary Na:K concentration ratio (U_{Na}/U_{K}), and glomerular filtration rate (GFR) are graphed over time before and after intravenous aldosterone (arrow).

Differential Acute Effects of Aldosterone and Hyperkalemia on Distal Tubular Potassium Secretion in the Rat Kidney

Field, Stanton, Giebisch – J Clin Invest 1984;74:1792-802
Acute effects of aldosterone on Epithelial Na channel in the rat kidney

Effect of Mineralocorticoids on apical and basolateral membrane conductances

FIG. 13. Cellular model for Na\(^+\) and K\(^+\) transport by the cortical collecting duct. The coupling ratio of Na\(^+\)-K\(^+\)-ATPase may be different from unity so that the pump is electrogenic. Depending on the magnitude of basolateral membrane potential, K\(^+\) may move passively into or out of the cell across this membrane.

Koeppen, Biagi, and Giebisch-Am J Physiol 1983; 244:F35-F47

FIG. 6. Distribution of \(V_{bl}\) in control and DOCA-treated (shaded area) tubules.
K Homeostasis - I

- Berliner – Harvey Lectures, Acad. Press 1961 Ser. 55 p141-71
- Malnic, Klose, Giebisch – Am. J. Physiol. 1966;211:529-547
- Good & Wright – Am J Physiol 1979; 236:F192-205
K Homeostasis - II

- Stanton & Giebisch – Am J Physiol 1982;242:F544-51
- Pan & Young – Hypertension 1982;4:279-87
- Field, Stanton, Giebisch – J Clin Invest 1984;74:1792-802
- Hene et al.-Kidney Int 1988;34:697-703
- Park et al. – Histol Histopathol 2012; 27:1559-77
Effect of Mineralocorticoid Stimulation [Aldosterone/DOC] on K Balance

Circadian

- Zuber et al. Proc Natl Acad Sci USA 2009; 106:16523-16528
- Salhi et al. FASEB J 2012; 26(7):2859-2867
- Stow et al. Hypertension 59(6):1151-6, 2012
Additional Reading