Physiology of Potassium Homeostasis

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Disclosure

- Consultant and Speaker for AstraZeneca

Physiology of Potassium Homeostasis-Question1

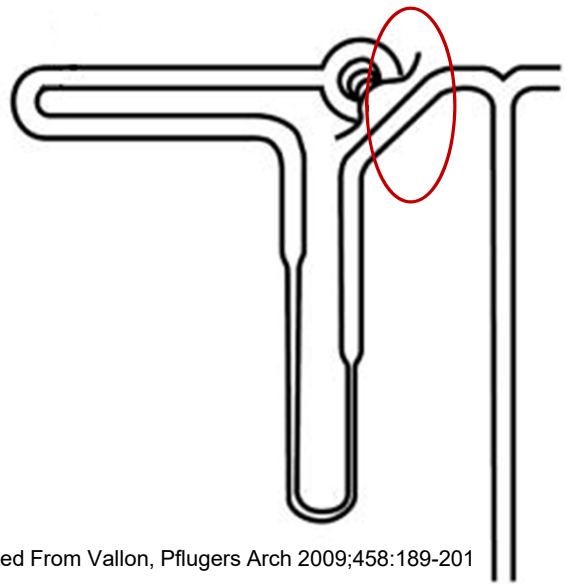
What determines the internal distribution of potassium and internal potassium homeostasis?

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?

Robert Berliner – Harvey Lectures - 1961

"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."



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

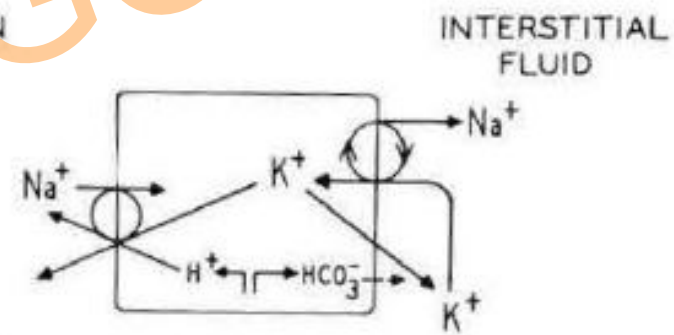


FIG. 8. Hypothetical model of distal tubule electrolyte transport involving specific exchange mechanisms at both surfaces of the tubule cell.

Berliner, Harvey Lectures, Acad. Press 1961 Ser. 55, pp 141-71

K Transport beyond the Macula Densa Largely Dictates K Excretion

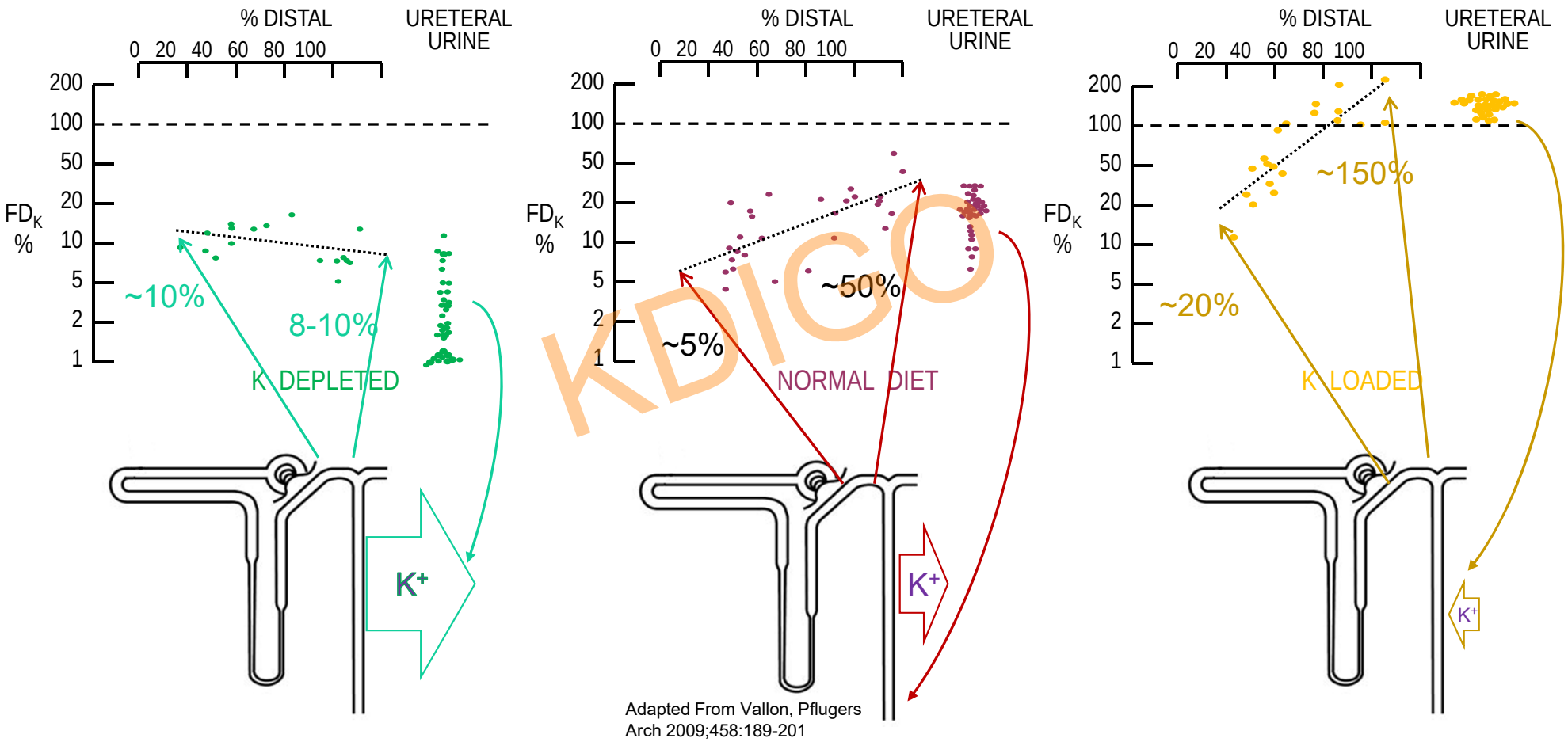


Fig from: Giebisch & Wingo Semin Nephrol 2013; 33(3):209-14

Data from Malnic, Klose, & Giebisch Am J Physiol 1964;206:674-86

Questions

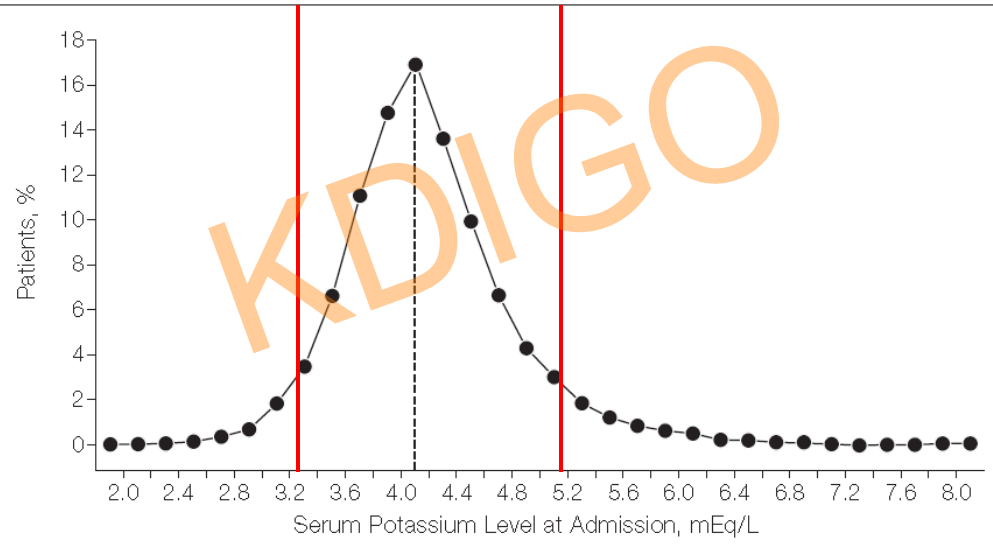
What determines the internal distribution of potassium and internal potassium homeostasis?

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

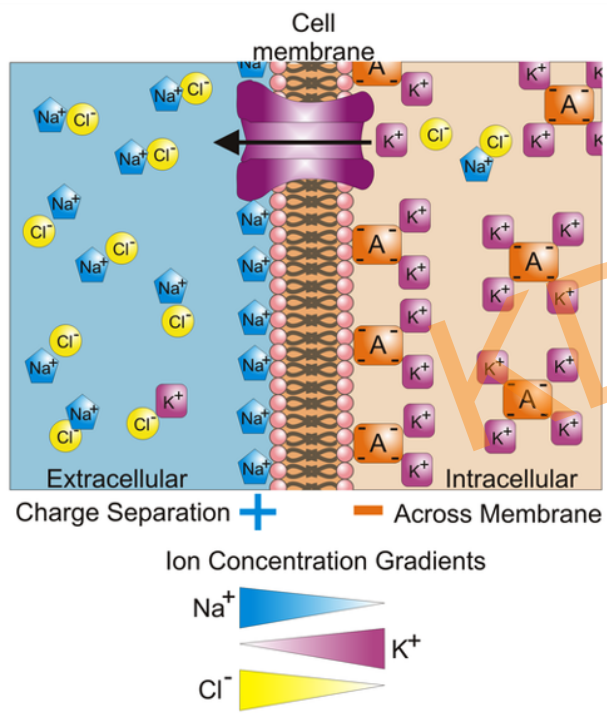
Figure 1. Distribution of Serum Potassium Levels at Admission in the Overall Population (N=38 689)

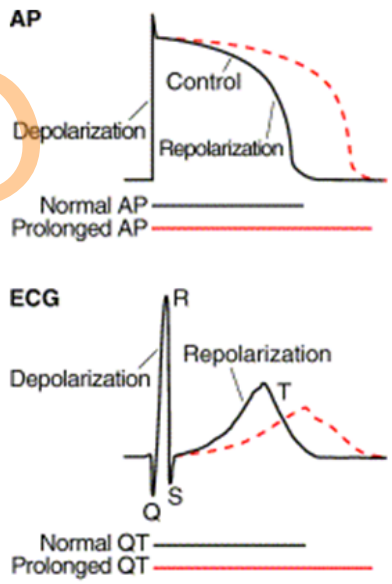


Median potassium level at admission was 4.1 mEq/L (vertical dotted line). Each x-axis interval is equal to or greater than the lower limit of the interval and less than the upper limit. The first interval includes all serum potassium levels less than 2.0 mEq/L and the last interval includes all that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

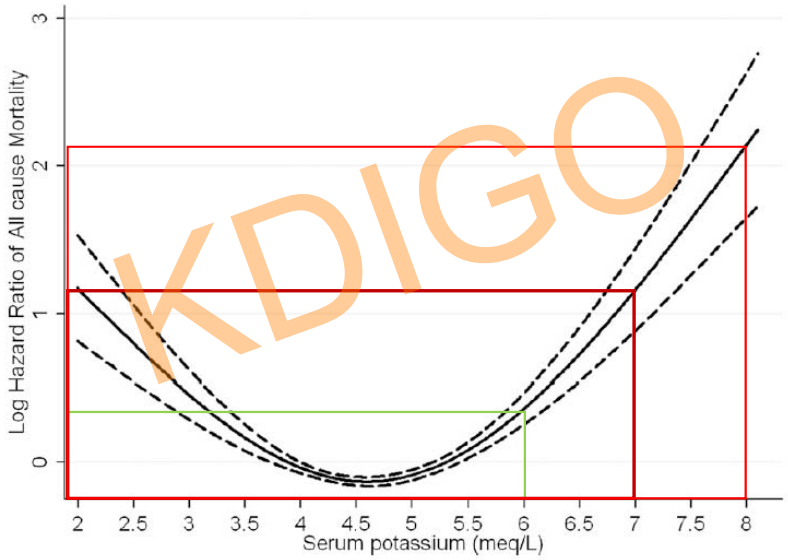
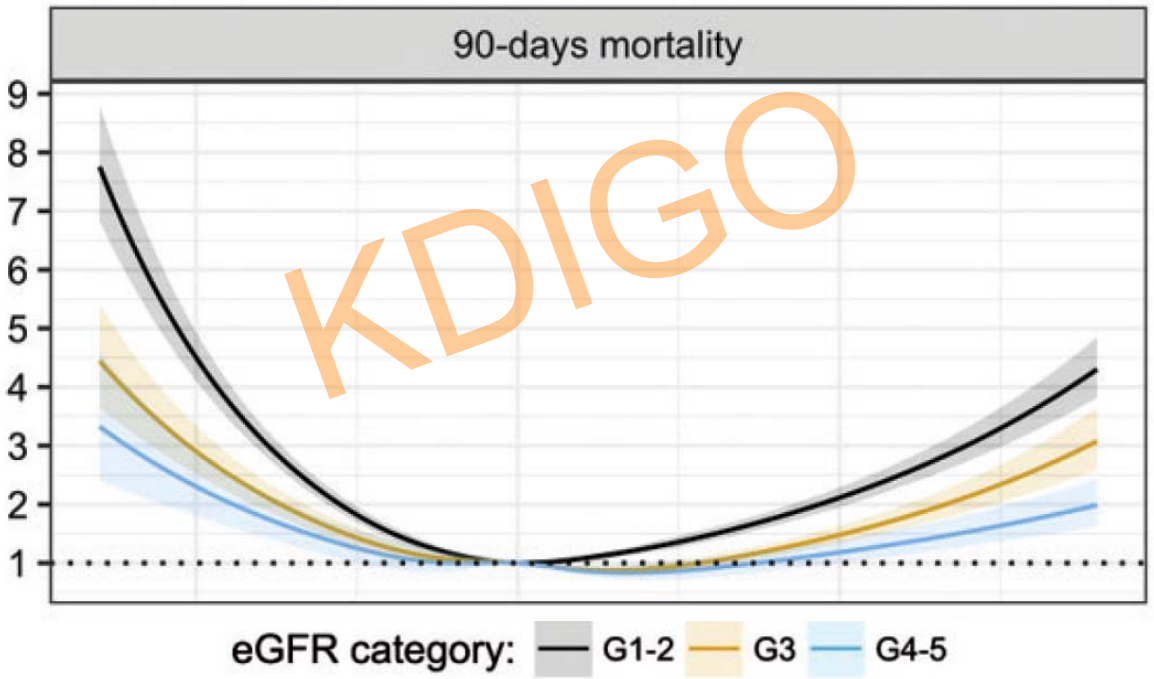


Figure 3. | Association of serum potassium, use as a time-varying covariate, with mortality in patients undergoing peritoneal dialysis (*n*=10,454). Error bars represent 95% confidence intervals.

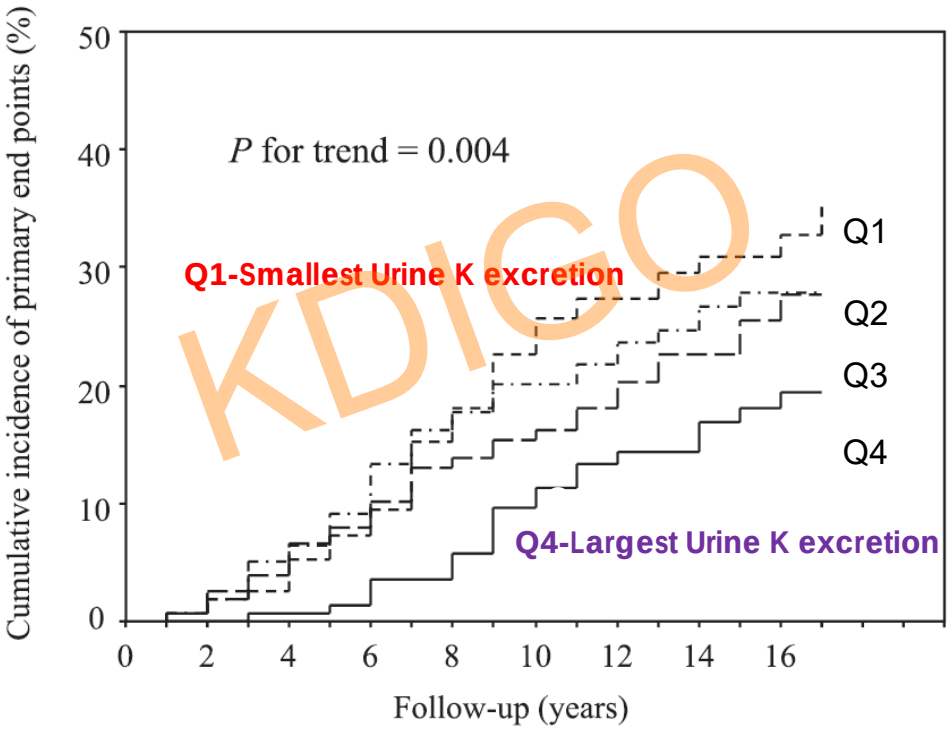
Torlen et al. Serum Potassium and Cause-Specific Mortality in a Large Peritoneal Dialysis Cohort - Clin J Am Soc Nephrol(2012);7(8)p1272-84

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



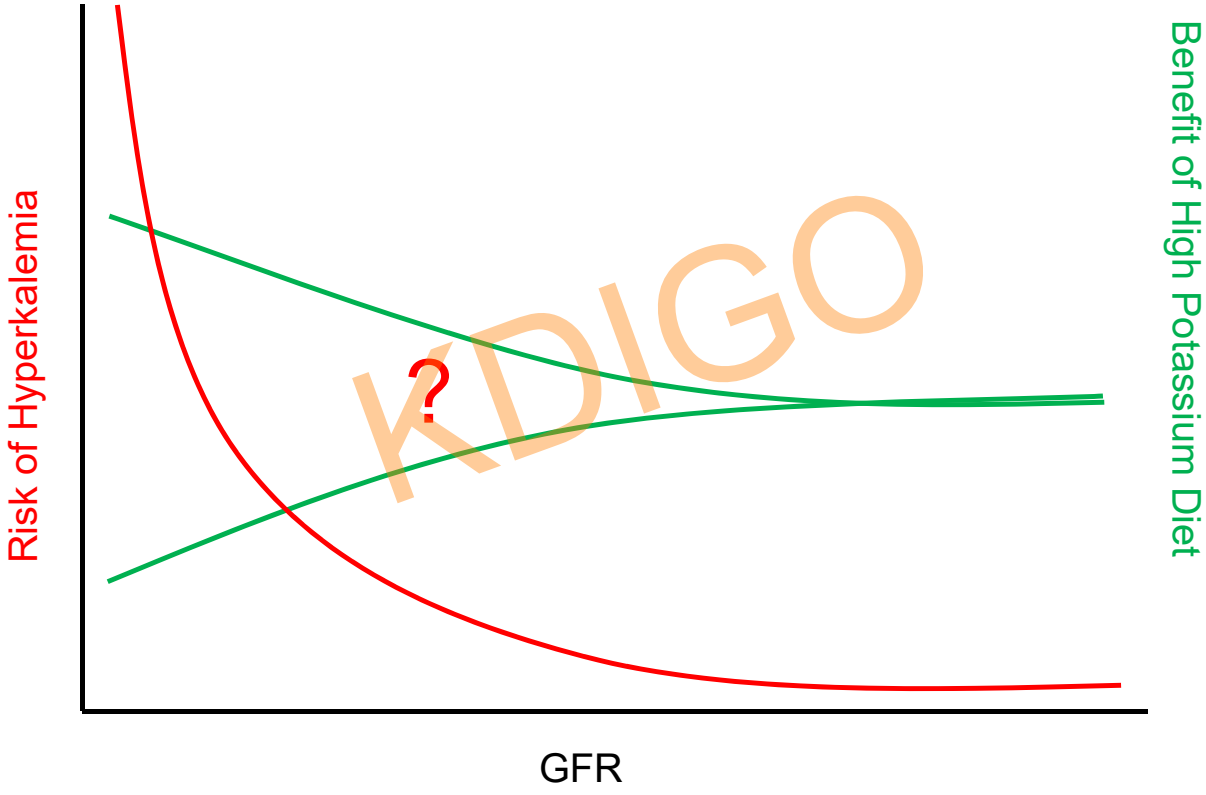
Gasparini et al-Nephrol Dial Transplant (2018, Aug 06)

A High Potassium Intake slows the progression of Renal and CV Disease

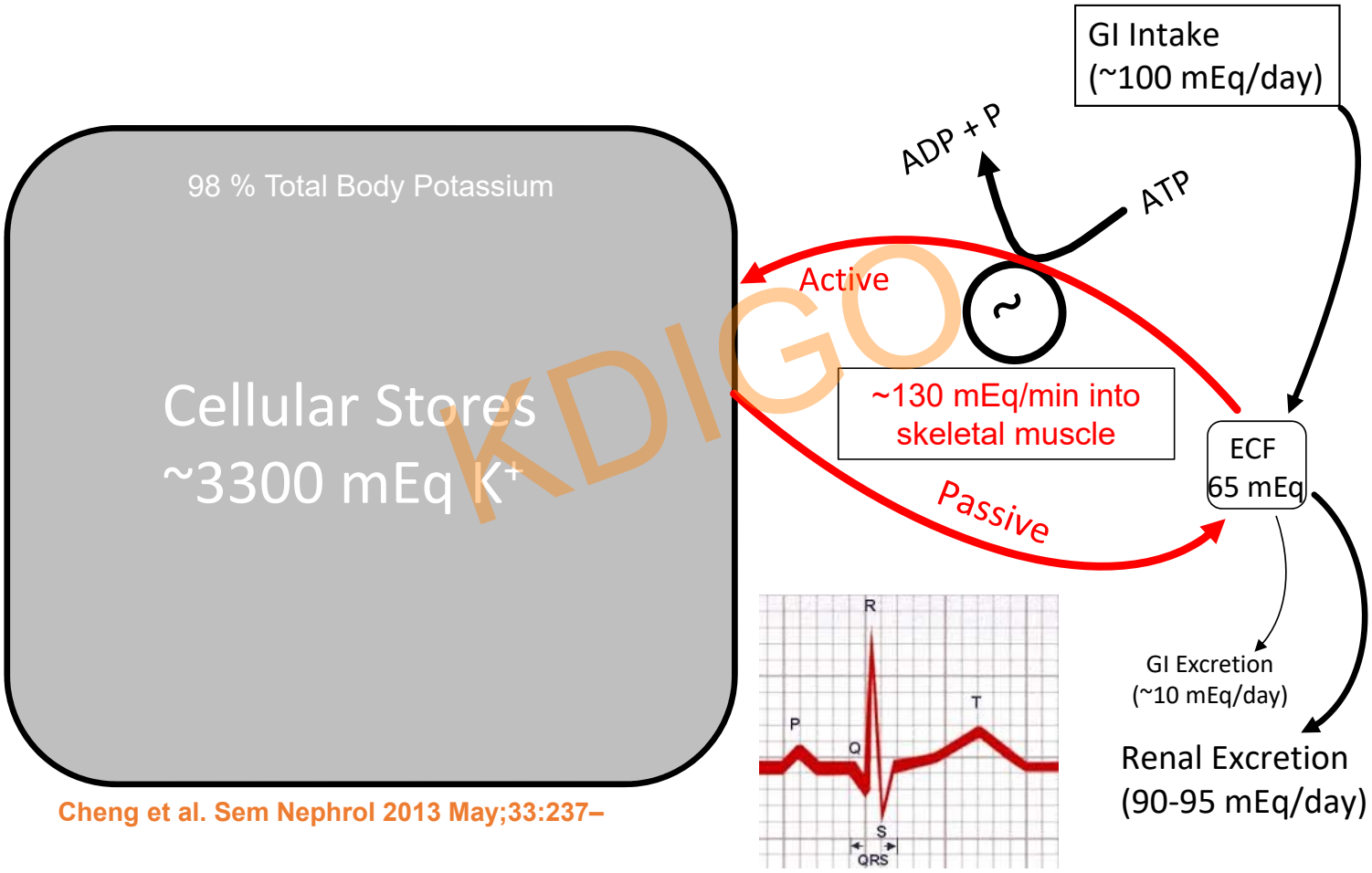


Araki et al.-Urinary K Excretion & Renal CV Complications in Diabetic Patients with normal Renal Function-CJASN (2015);10(12):2152

Benefit and Risk of a High Potassium Diet

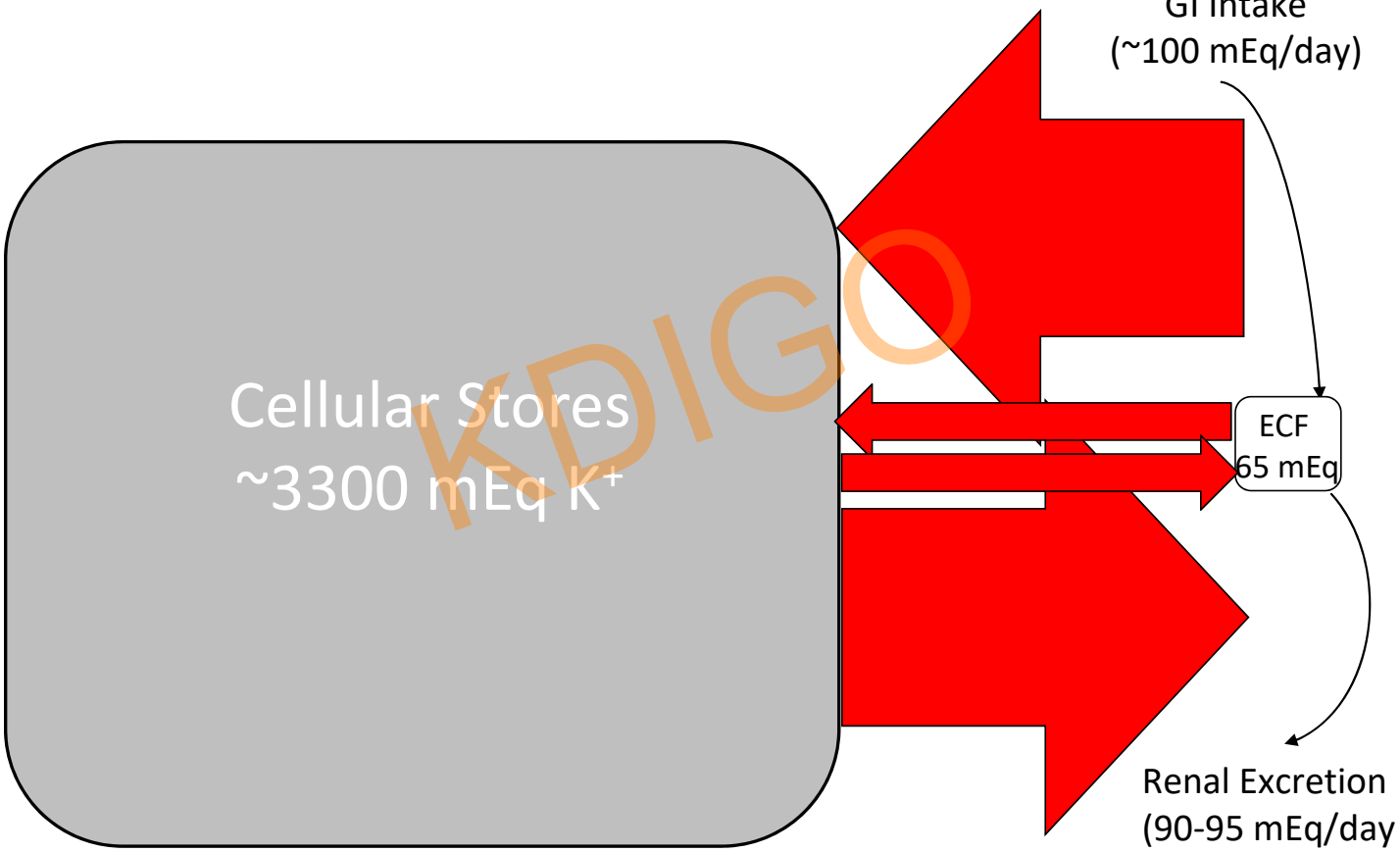


Renal & Extra-Renal Potassium Balance - Kinetics



Cheng et al. Sem Nephrol 2013 May;33:237–

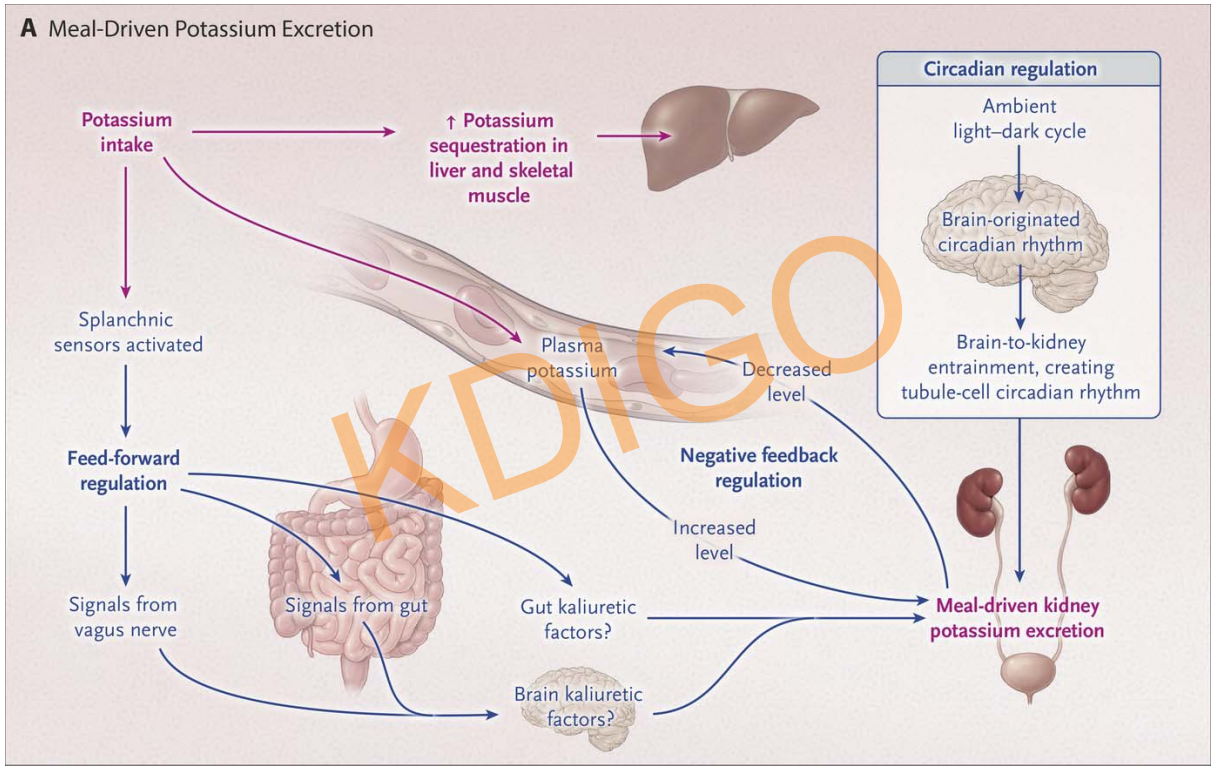
Renal & Extra-Renal Potassium Balance - Kinetics



What Stabilizes Plasma Potassium?

- Renal Potassium Excretion
- Enhanced Cellular Potassium uptake
  - Insulin, $ß_2$ catecholamines, aldosterone
- Gut Sensors
- Circadian Rhythm

Overview of Potassium Homeostasis: Meal-Driven Potassium Excretion



Gumz, Rabinowitz, & Wingo - An Integrated View of Potassium Homeostasis N Engl J Med (2015) 373:60-72

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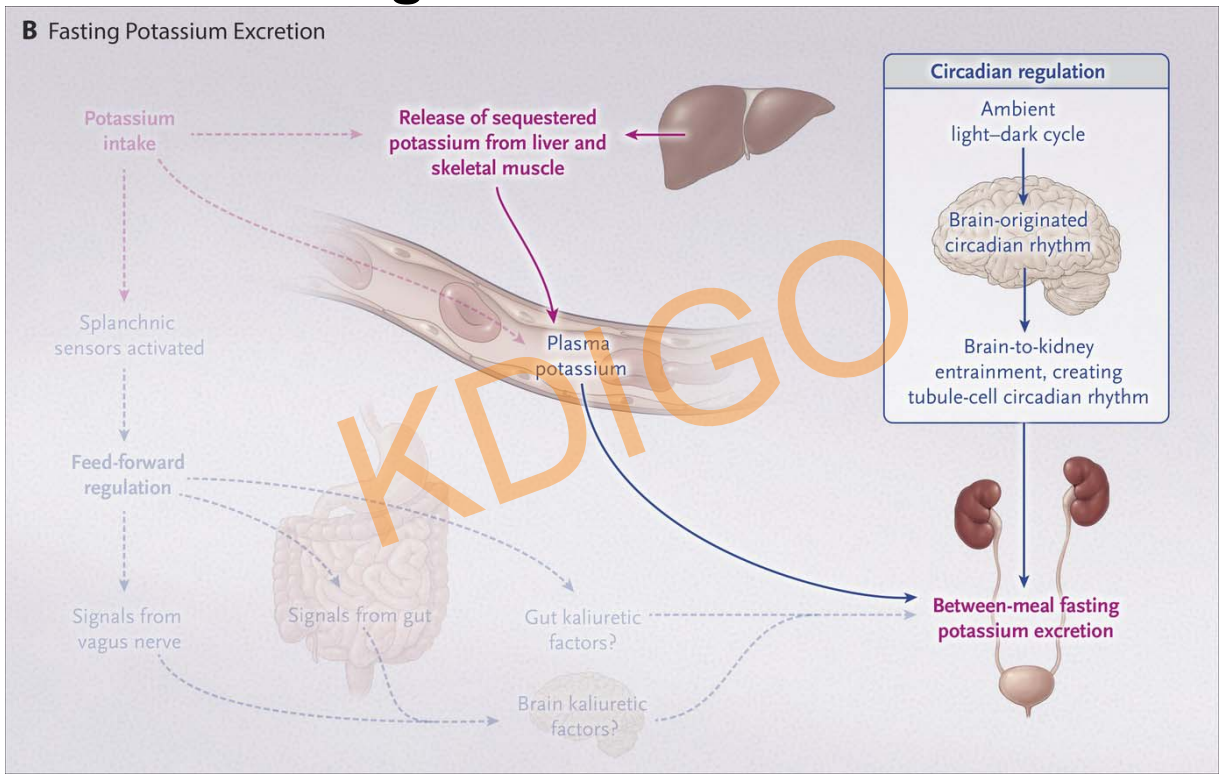
Overview of Potassium Homeostasis: Fasting Potassium Excretion



Gumz, Rabinowitz, & Wingo - An Integrated View of Potassium Homeostasis N Engl J Med (2015) 373:60-72

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Potassium Adaptation: Renal and Extra-Renal Mechanisms

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

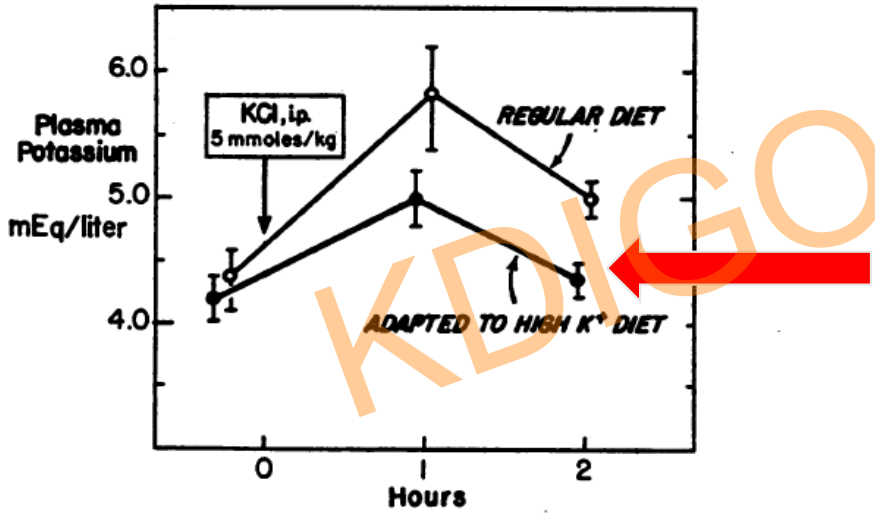


FIGURE 1 Effect of an acute potassium load on plasma potassium in rats fed a regular or a high K diet. Points are means; vertical lines show ± SE in this and all subsequent figures.

Adaptation to a high K^+ diet blunted the increase in $[K^+]_p$ to a KCl load .

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.

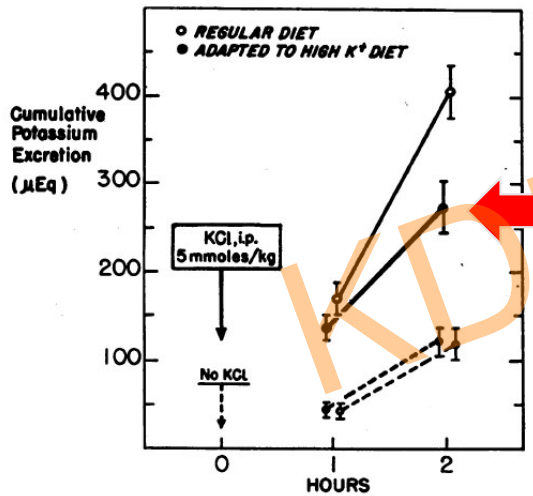


FIGURE 2 Cumulative urinary potassium excretion. The solid lines in the upper section show excretion after an acute KCl load. The broken lines in the lower section show the basal excretion when an acute load was not given. All rats were fasting for 16–20 hr before each study.

Animals adapted to a high K^+ diet excreted <u>less</u> K^+ in the urine.

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.

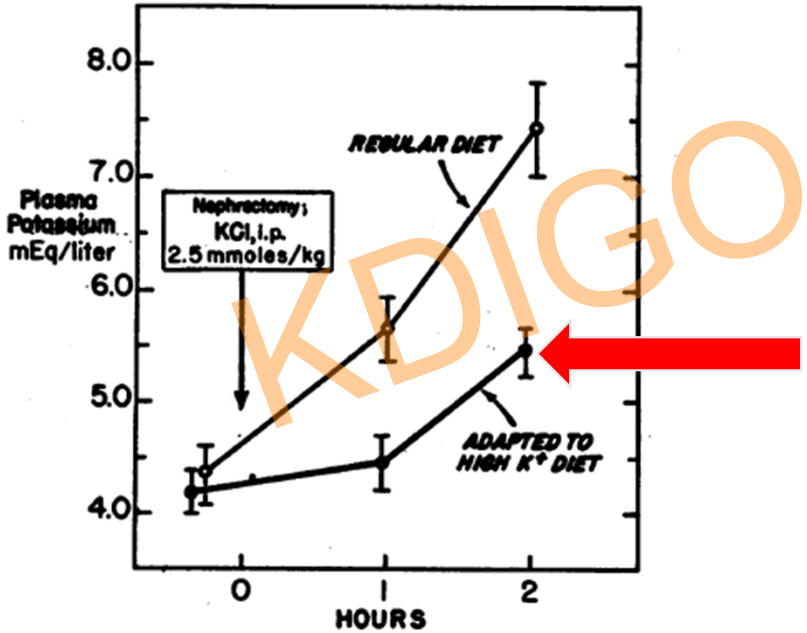


FIGURE 3 Response of nephrectomized rats to an acute potassium load.

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

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.

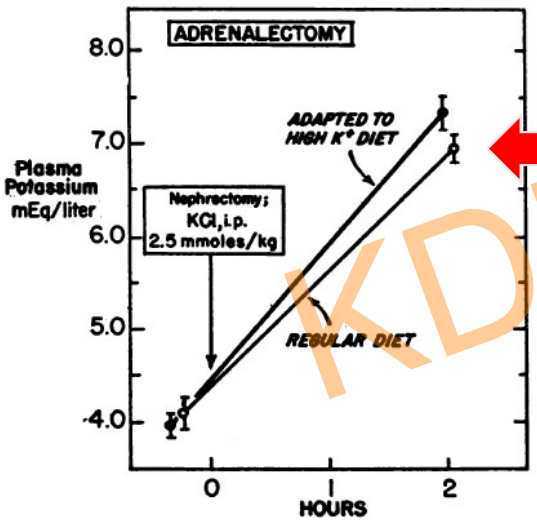


FIGURE 4 Effect of adrenalectomy on the response of nephrectomized rats to an acute potassium load. The rats had been adrenalectomized 2 wk before study and were maintained on 0.15–0.20 mg of deoxycorticosterone acetate (DOCA) daily.

Adrenalectomy abolished the effect of K^+ adaptation.

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.

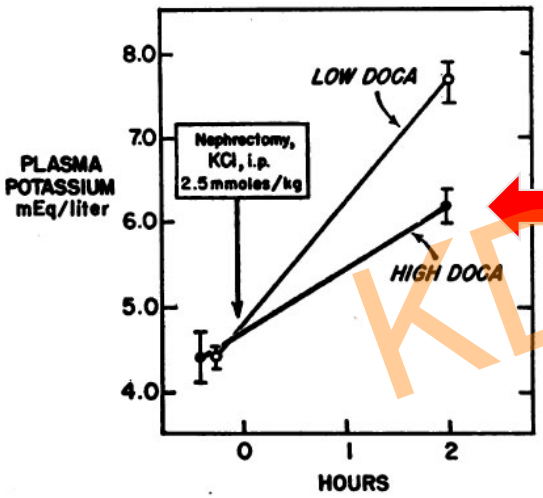


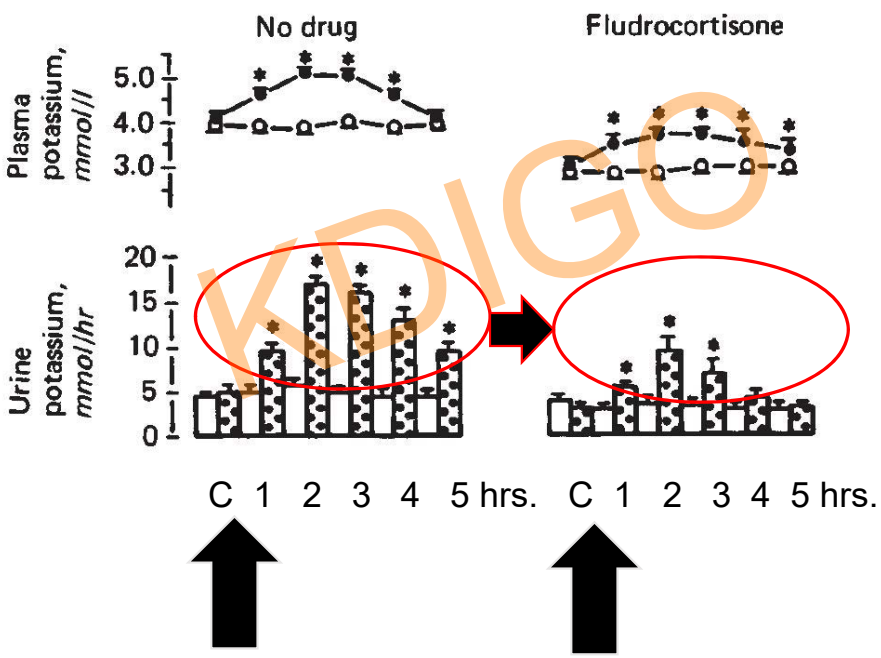
FIGURE 7 Effect of high (5–7.5 mg/day) and low (0.75–1.25 mg/day) doses of DOCA on the response of nephrectomized rats to an acute potassium load. The rats had been on DOCA for 4 days before the experiment. All rats were on a low sodium diet to prevent potassium depletion.

High dose desoxycorticosterone acetate (DOCA) treatment blunted the increase in $[K^+]_p$ to a KCl load.

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.

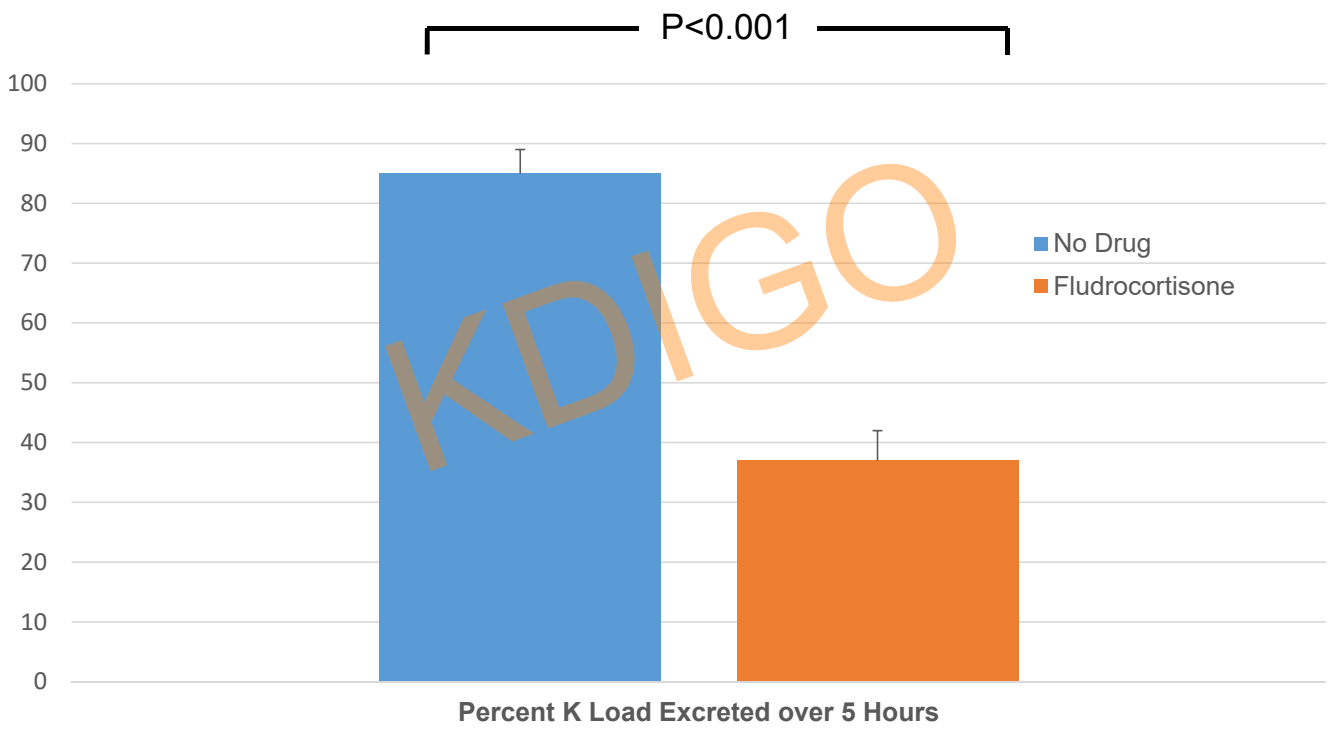


By 5 hours 85±4% of the K load was excreted without drug treatment.

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

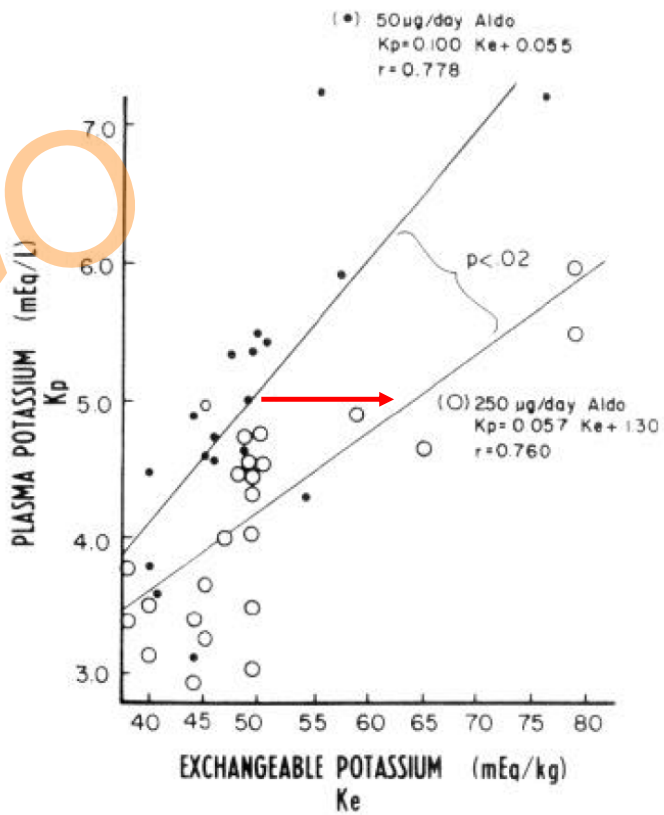


Mineralocorticoid stimulation resulted in significantly less urinary potassium excretion of a oral potassium load during the following 5 hours.

Hene et al.-Kid Int 1988;34:697-703

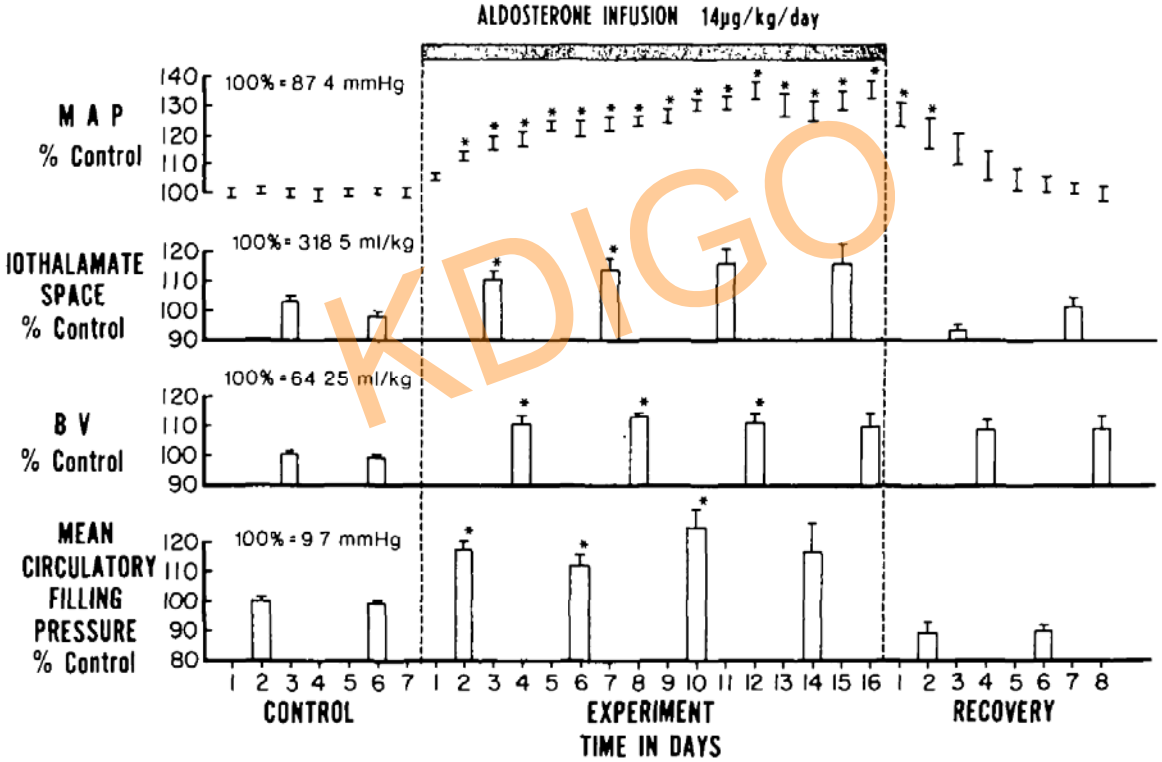
Effects of Aldosterone on Potassium Distribution

- "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."



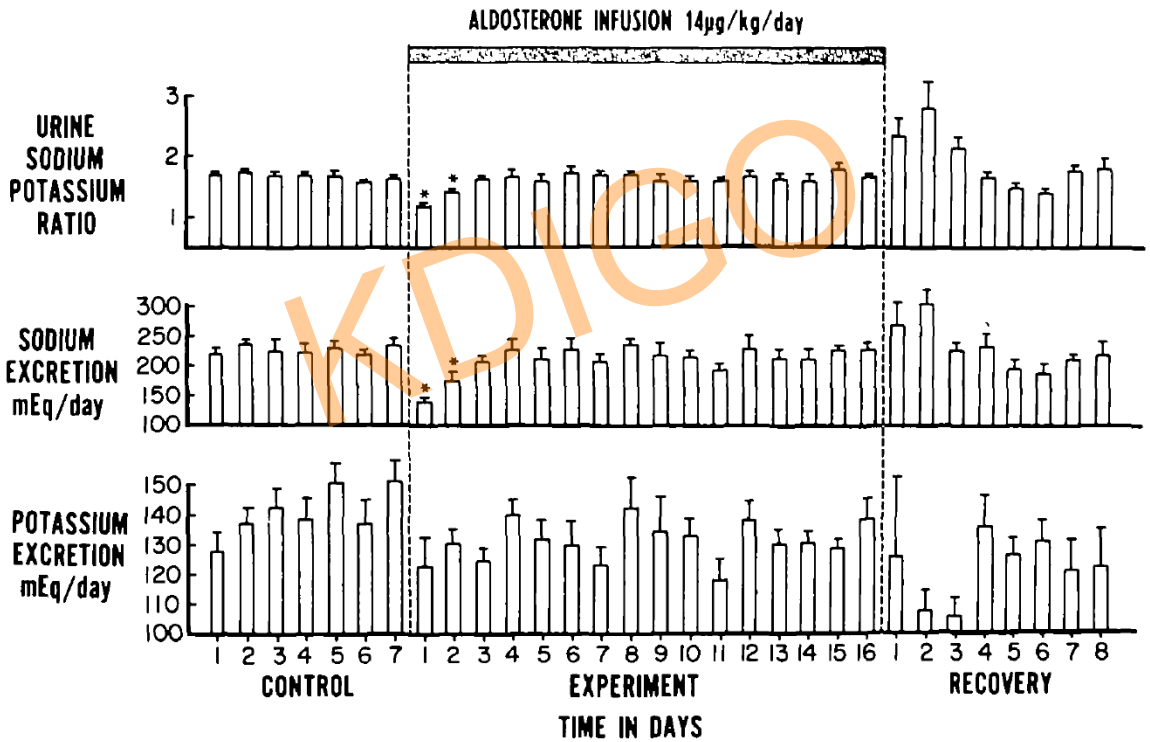
Young & Jackson – Am J Physiol 1982; 243:R526-30

Effect of Aldosterone on Blood Pressure Pan & Young



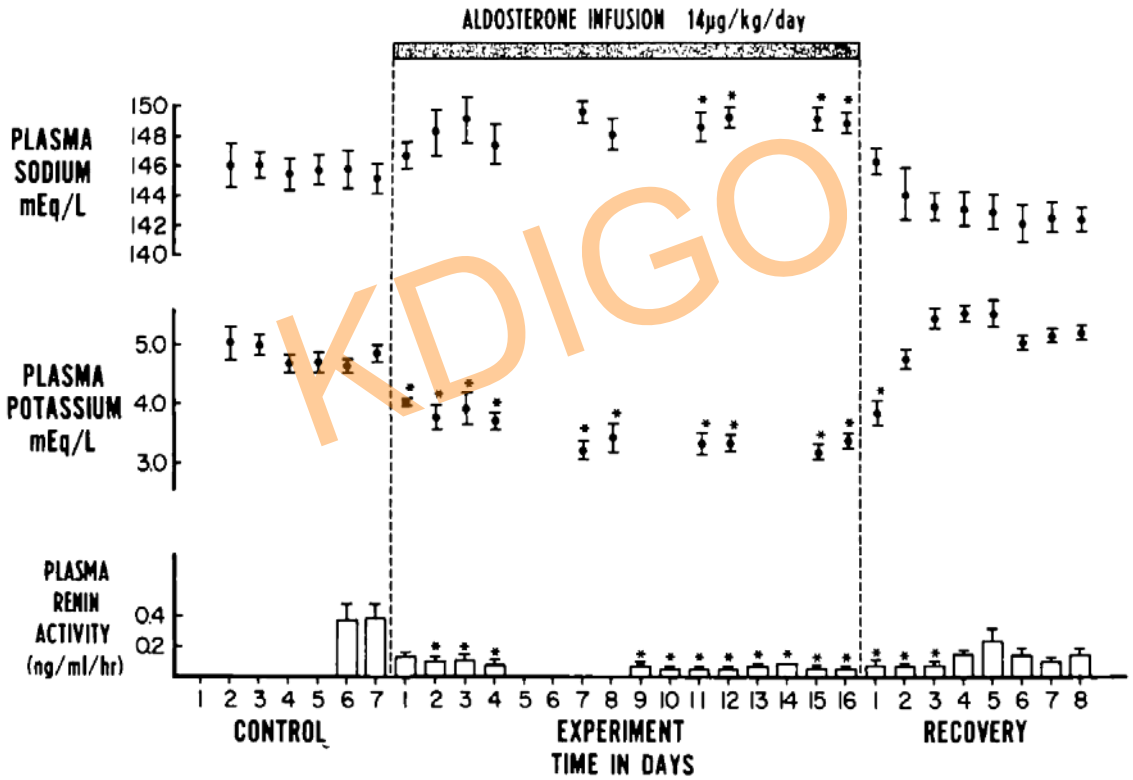
Pan & Young, Hypertension 4:279-287,1982

Effect of Aldosterone on Potassium Balance - Pan & Young



Pan & Young, Hypertension 4:279-287,1982

Effect of Aldosterone on Plasma Electrolytes - Pan & Young



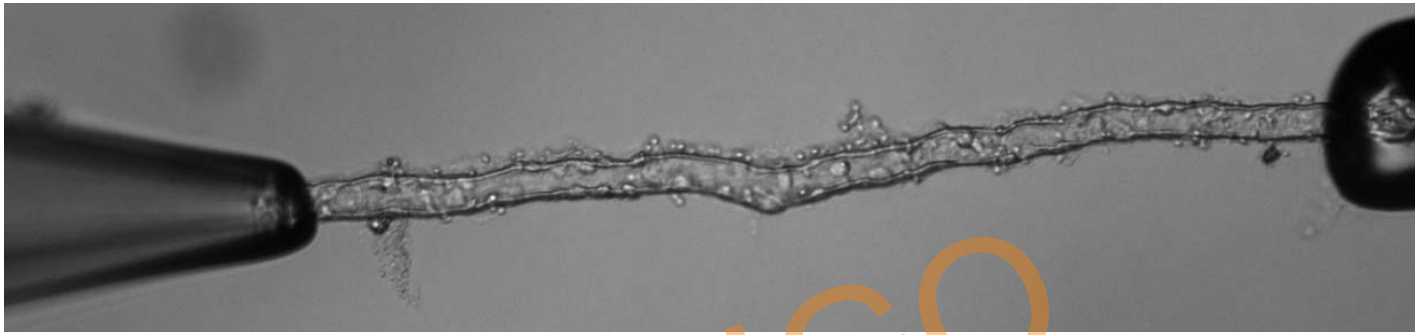
Pan & Young, Hypertension 4:279-287,1982

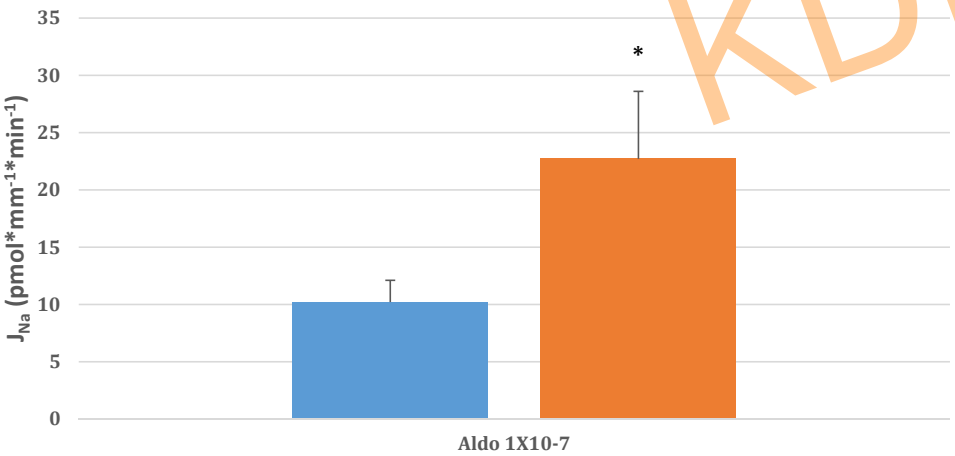
Summary of Pan & Young Study

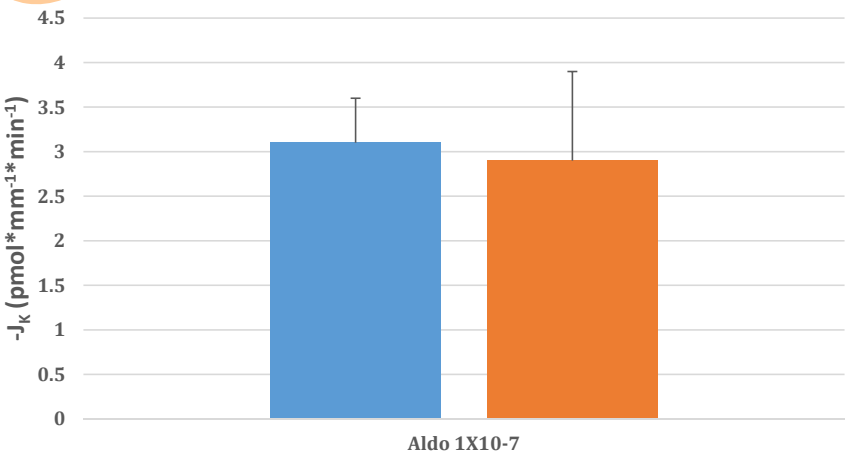
- Aldosterone increased systemic blood pressure and mean circulatory filling pressure.
- Aldosterone stimulated transient sodium retention before animals went into “aldosterone escape”.
- Aldosterone did not increase the absolute rate of renal potassium excretion.
- Aldosterone reduced steady-state plasma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

$$C_K = \frac{U_K \times V}{P_K}$$

In vitro Effect of Aldosterone

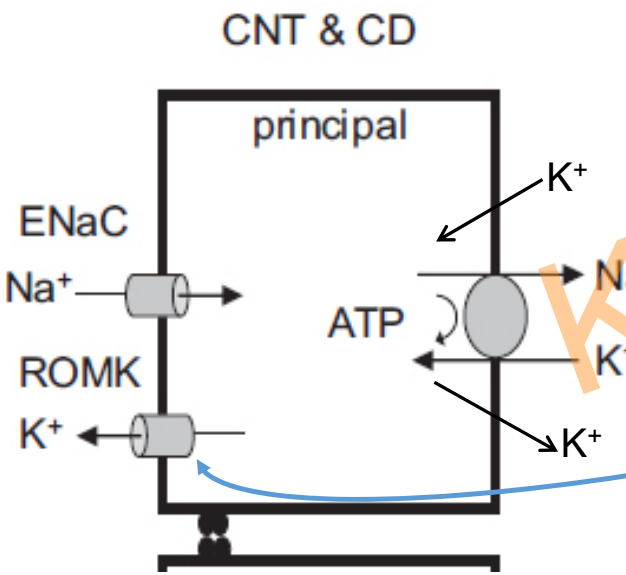






Wingo, Kokko, Jacobson -Kidney Int 1985; 28:51-7

Effect of Mineralocorticoids on K secretion at basolateral membrane



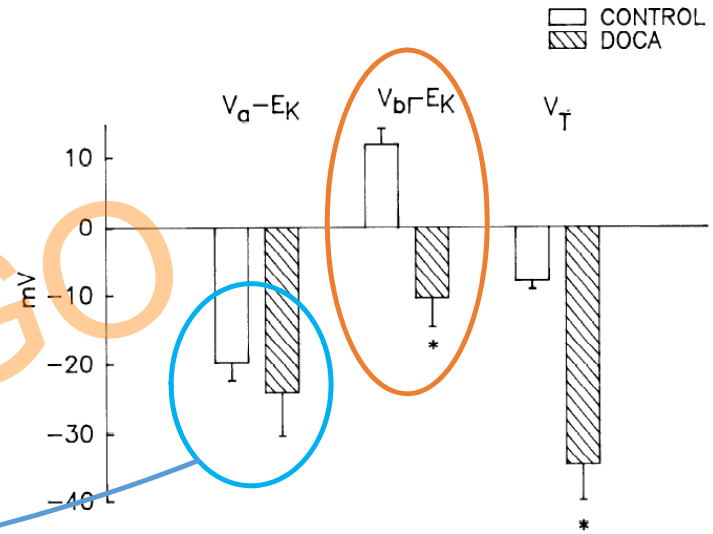


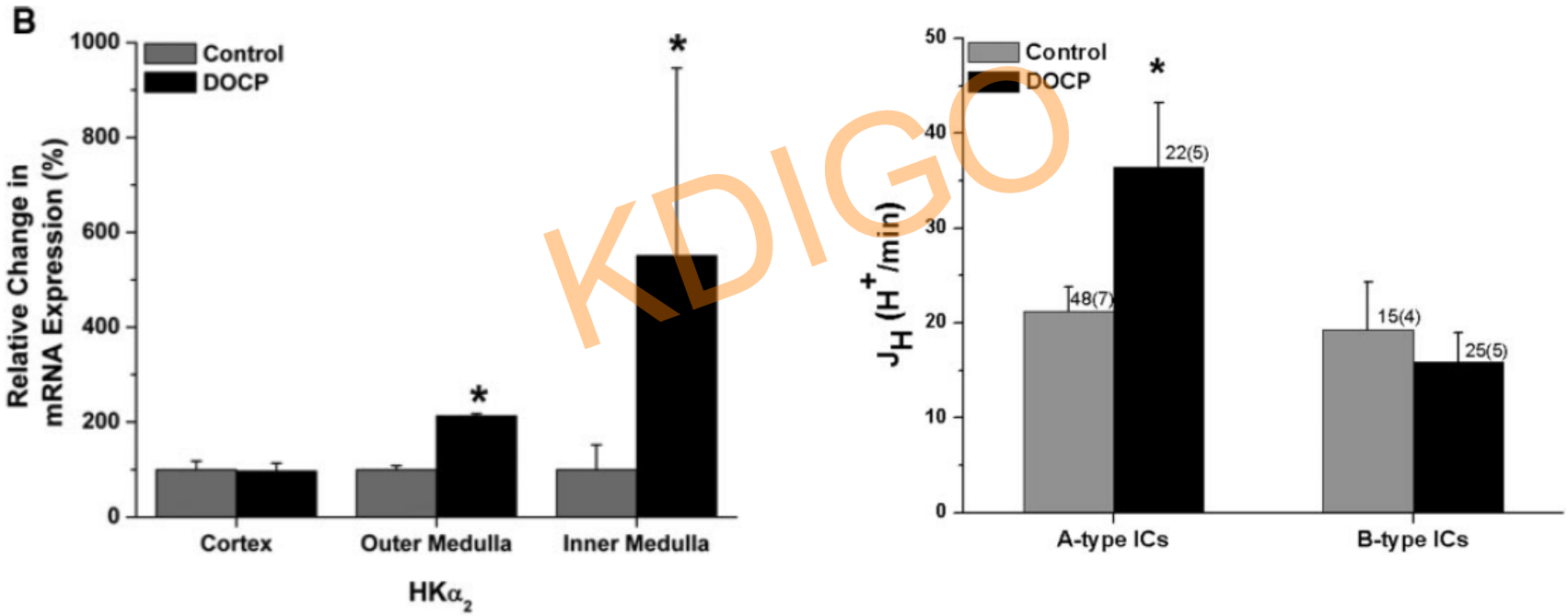
FIG. 3. Graph showing differences in driving forces between CCDs from control ($n = 9$) and DOCA-treated ($n = 6$) rabbits across apical (V_a-E_K), basolateral (V_{bl}-E_K), and transepithelial (V_T) membranes. DOCA significantly increased driving force for K secretion (negative direction) across basolateral membrane. Error bars are SE. * $P < 0.05$ using t test for unpaired data. See text for definitions of abbreviations.

Sansom Muto Giebisch – Am J Physiol 1989; 256:F136-42

Metabolic Balance studies that Examine the Effect of Aldosterone or DOC Stimulation

1. Dawborn & Ross - Clin Sci 1967; 32:559-70
2. Hulter et al. -Am J Physiol 1978;235:F298-309
3. Hulter et al. -Am J Physiol 1979;236:F48-57
4. Grekin et al. Hypertension 1980; 2:326-32
5. Greenlee et al. – J Am Soc Nephrol 2011; 22:49-58
6. Lynch et al. – Am J Physiol 2015; 309:F1026-34

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



Greenlee et al. – Mineralocorticoids stimulate the activity and expression of renal H^+,K^+-ATPases-J Am Soc Nephrol 2011; 22:49-58

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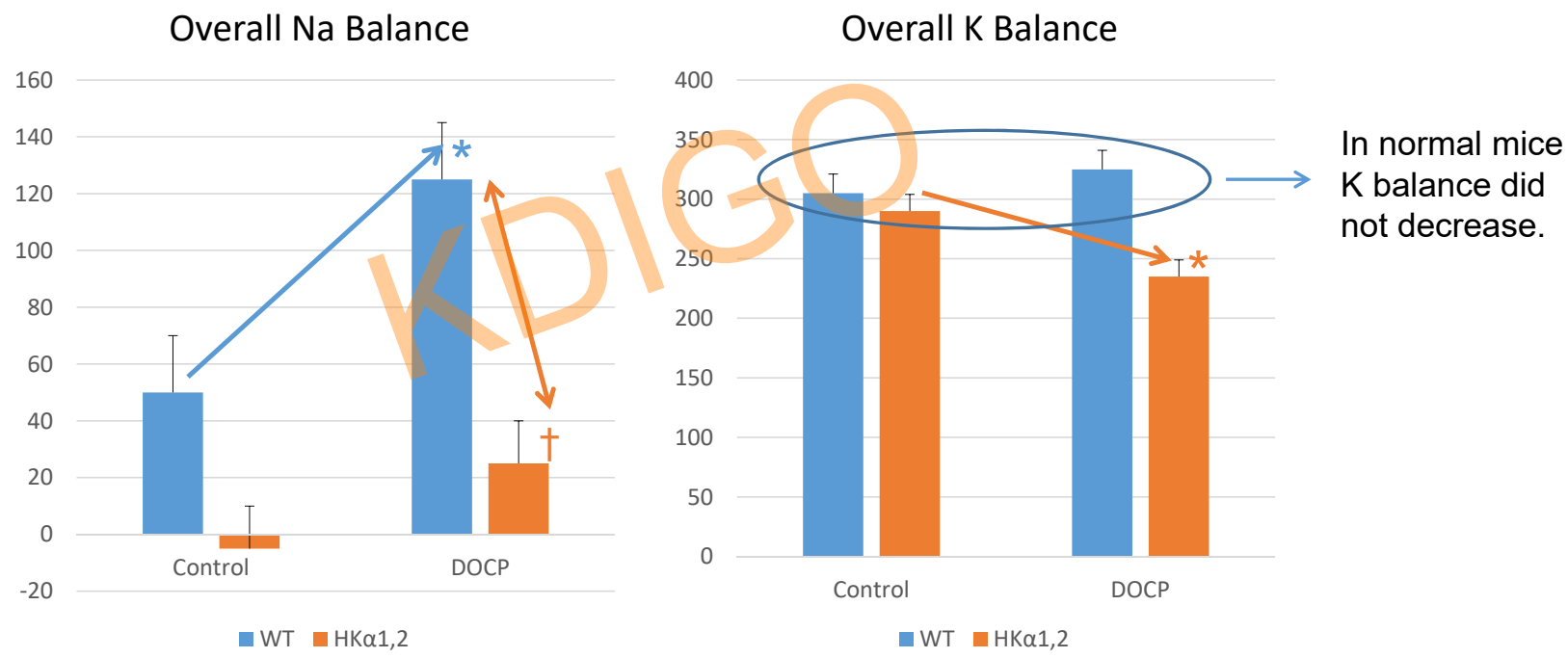
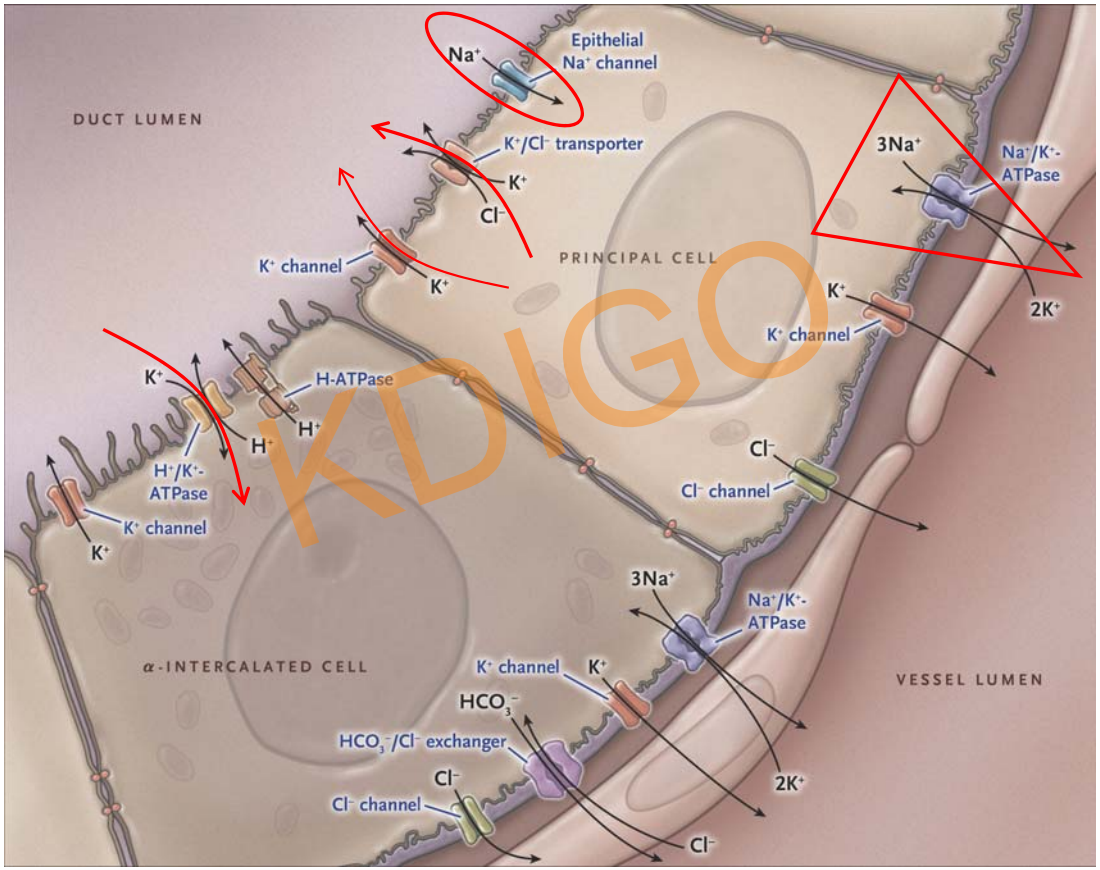


Greenlee et al. – Mineralocorticoids stimulate the activity and expression of renal H^+,K^+-ATPases-J Am Soc Nephrol 2011; 22:49-58

Aldosterone Stimulation of Ion Transport in the Aldosterone-Sensitive Distal Nephron & Collecting Duct



Gumz ML et al. N Engl J Med 2015;373:60-72

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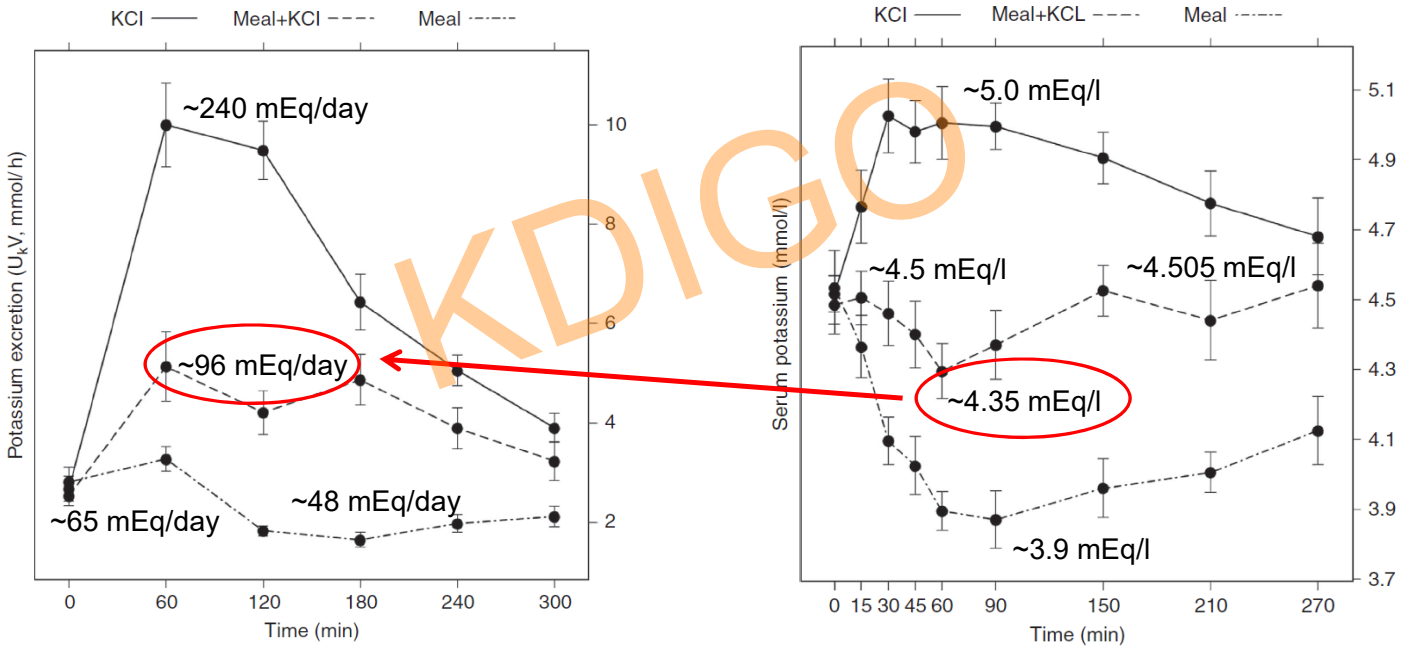
Questions

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?

Gastrointestinal-Renal Kaliuretic Signaling Axis



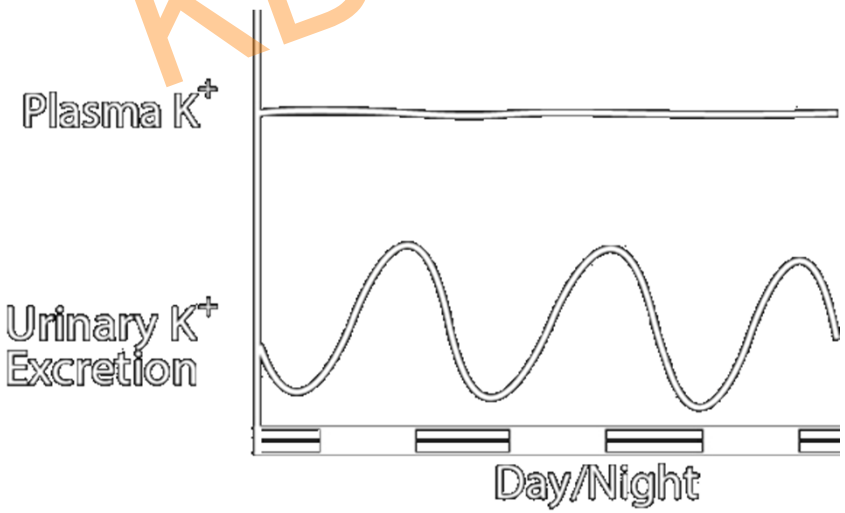
Preston RA et al.-Evidence for a gastrointestinal-renal kaliuretic signaling axis in humans-Kidney Int.(2015)V88(6)p1383-91

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-

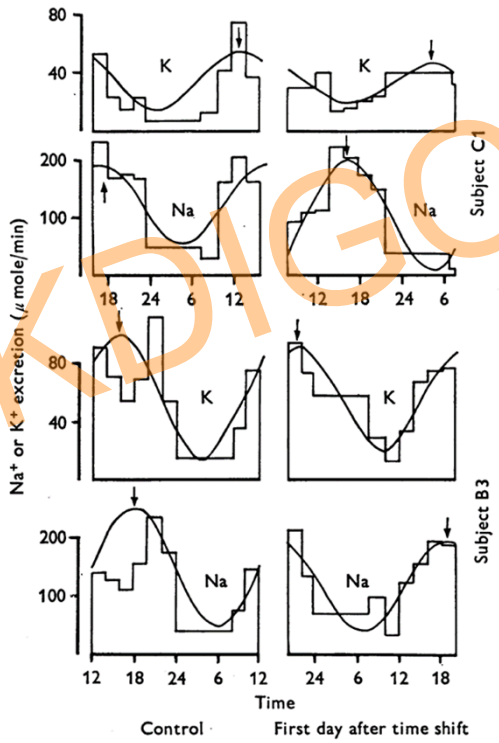
- Renal Potassium Excretion
- Potassium Redistribution into Cells:
  - Insulin, $ß_2$ catecholamines, aldosterone
- Potassium Sensors (Independent of P_K)
- Potassium Regulation by Circadian Clock



Westward or Eastward Travel on Urinary Potassium Circadian Rhythm

Westward Travel

Eastward Travel

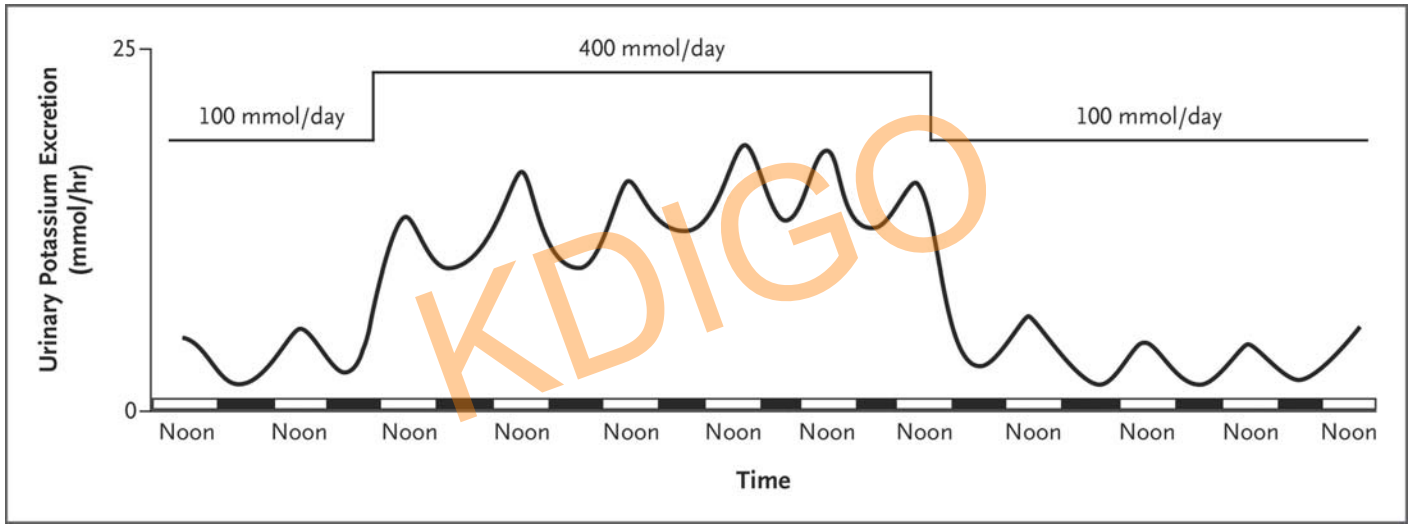


Urinary K excretion stays synced to previous time zone

Elliott et al. J Physiol 1972; 221(1): 227-57

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



Gumz ML et al. N Engl J Med 2015;373:60-72

Data from: Rabelink et al. - Kidney Int. 1990; 38:942-7

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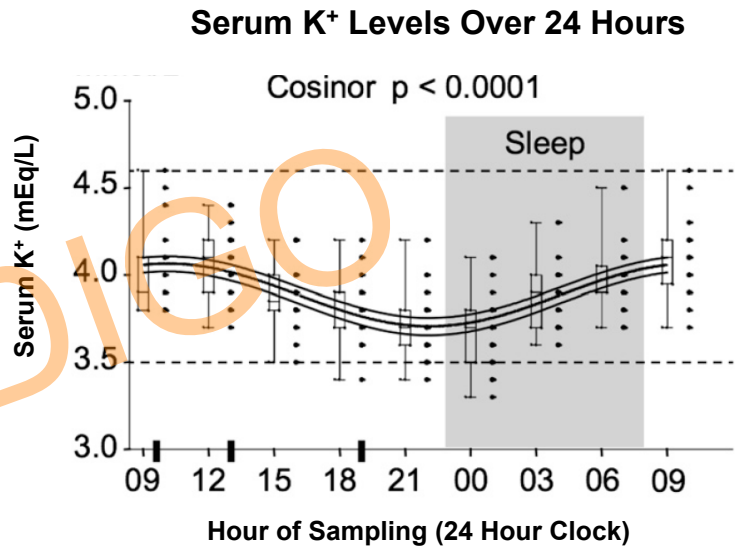
Serum Potassium Exhibits a Small Circadian Variation Throughout the Day

- 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]



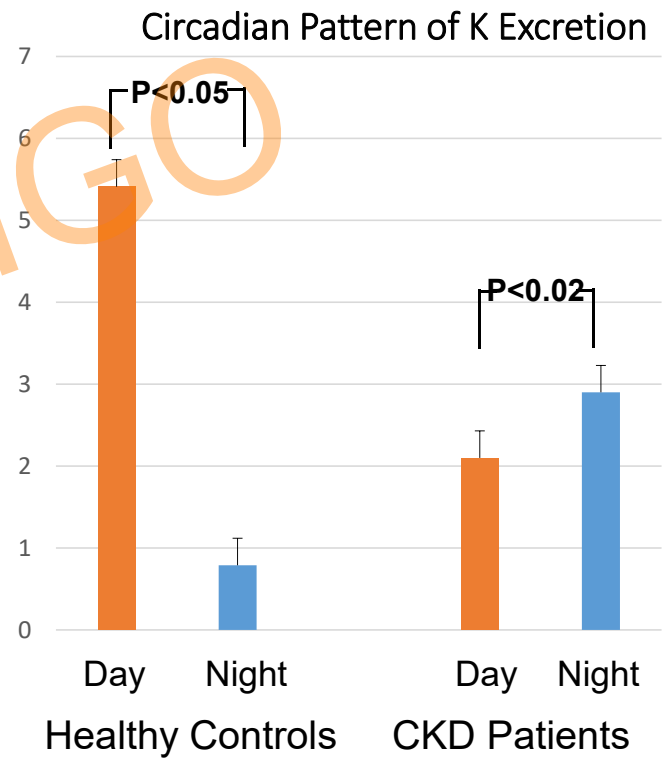
1. Sennels et al. *Scand J Clin Lab Invest.* 2012;72:287-295. Study of 24 healthy Danish males evaluated time of day effect on multiple clinical values.

2. Gumz et al. N Engl J Med (2015) 373:60-72 .

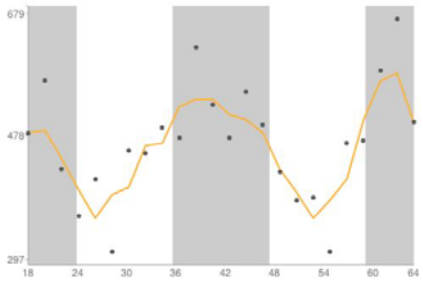
Urinary Potassium Excretion Exhibits a Diurnal Variation that is Reversed in CKD

- 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]

1. Koopman MG, et al. *Clin Sci*. 1989;77:105-111.
2. Agarwal R. *Am J Physiol.* 2007;293:F655-F659.



Sgk1 and Sgk2 Exhibit Circadian Changes in mRNA in the Mouse Kidney



Experiment Mouse 1.OST Kidney (Affymetrix)

UCSC RNAseq
RNAseq_NM_001161845

RNAseq_NM_001161850
RNAseq_NM_011361
RNAseq_NM_001161847

RNAseq_NM_001161848

RNAseq_NM_001161849

Probeset 10362073

Links Wikipedia
HomoloGene

Symbol Sgk1

Unigene Mm.28405

RefSeq Protein *None*

RefSeq DNA
NM_001161845
NM_001161850
NM_011361
NM_001161847
NM_001161848
NM_001161849

Description
serum/glucocorticoid regulated kinase 1

	p-Value	q-Value	period	phase
JTK	0.000125703	0.00560009	24.0	15.5
Lomb Scargle	0.0174	0.44864	23.892	15.95
DeLichtenberg	0.9206	1.0	24.0	*NA*

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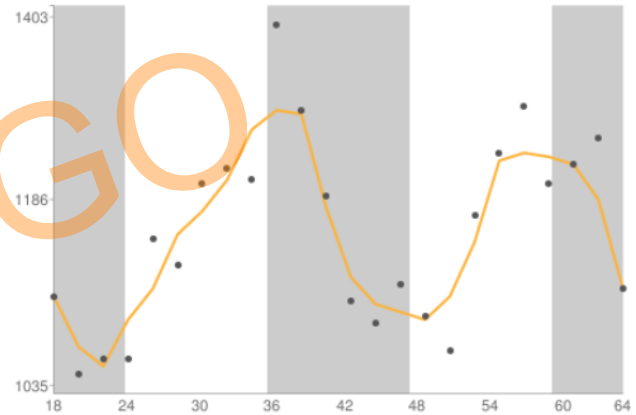


Experiment Mouse 1.OST Kidney (Affymetrix)

UCSC RNAseq
RNAseq_NM_013731

Probeset 10478326

Links Wikipedia
HomoloGene

Symbol Sgk2

Unigene Mm.26462

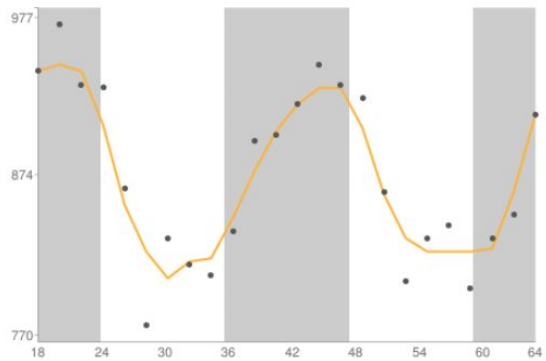
RefSeq Protein *None*

RefSeq DNA
NM_013731

Description
serum/glucocorticoid regulated kinase 2

	p-Value	q-Value	period	phase
JTK	0.000509591	0.014962	25.0	10.0
Lomb Scargle	0.0128	0.41187	23.064	10.29
DeLichtenberg	0.4823	1.0	24.0	*NA*

SPAK (Stk39) and Wnk1 Exhibit Circadian Changes in mRNA in the Mouse Kidney



Experiment Mouse 1.OST Kidney (Affymetrix)

UCSC RNAseq RNAseq_NM_016866

Probeset 10483381

Links Wikipedia HomoloGene

Symbol Stk39

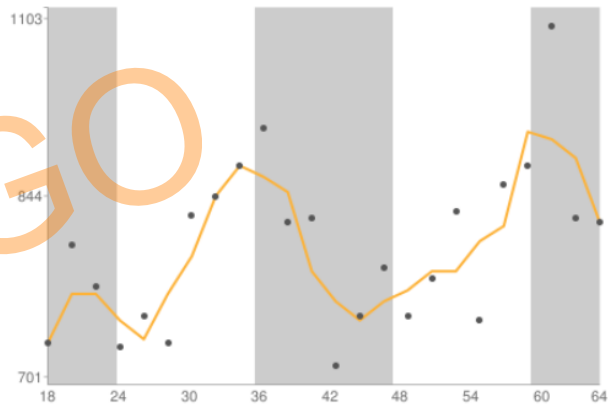
Unigene Mm.198414

RefSeq Protein *None*

RefSeq DNA NM_016866

Description serine/threonine kinase 39, STE20/SPS1 homolog (yeast)

?	p-Value	q-Value	period	phase
JTK	1.57188e-05	0.00132127	24.0	21.5
Lomb Scargle	0.00241	0.331718	23.892	21.08
DeLichtenberg	1.0	1.0	24.0	*NA*



Experiment Mouse 1.OST Kidney (Affymetrix)

UCSC RNAseq

Probeset 10547469

Links Wikipedia HomoloGene

Symbol Wnk1

Unigene Mm.333349

RefSeq Protein *None*

RefSeq DNA

Description WNK lysine deficient protein kinase 1

?	p-Value	q-Value	period	phase
JTK	0.00103343	0.0240791	24.0	12.0
Lomb Scargle	0.0251	0.499416	23.892	10.13
DeLichtenberg	0.9998	1.0	24.0	*NA*

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Hypothetical Model of the Aldosterone-Sensitive Distal Nephron and Collecting Duct

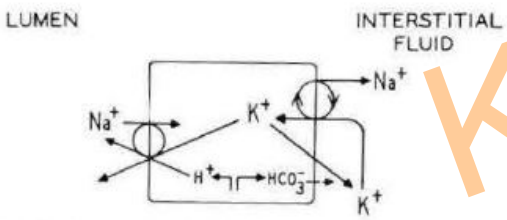
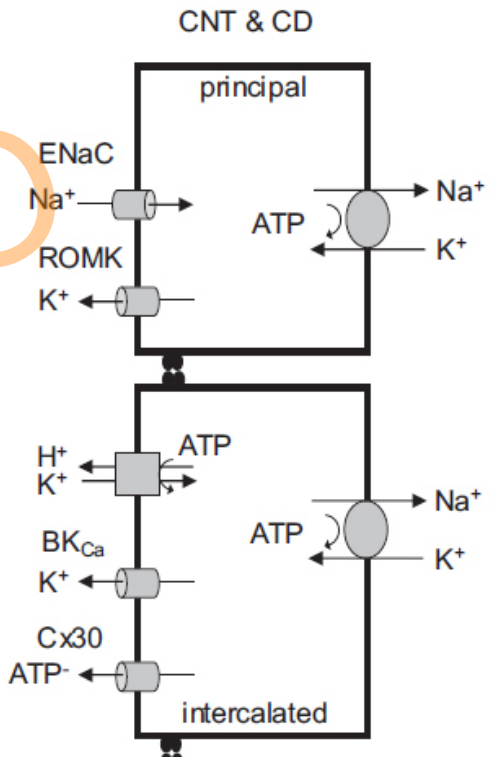
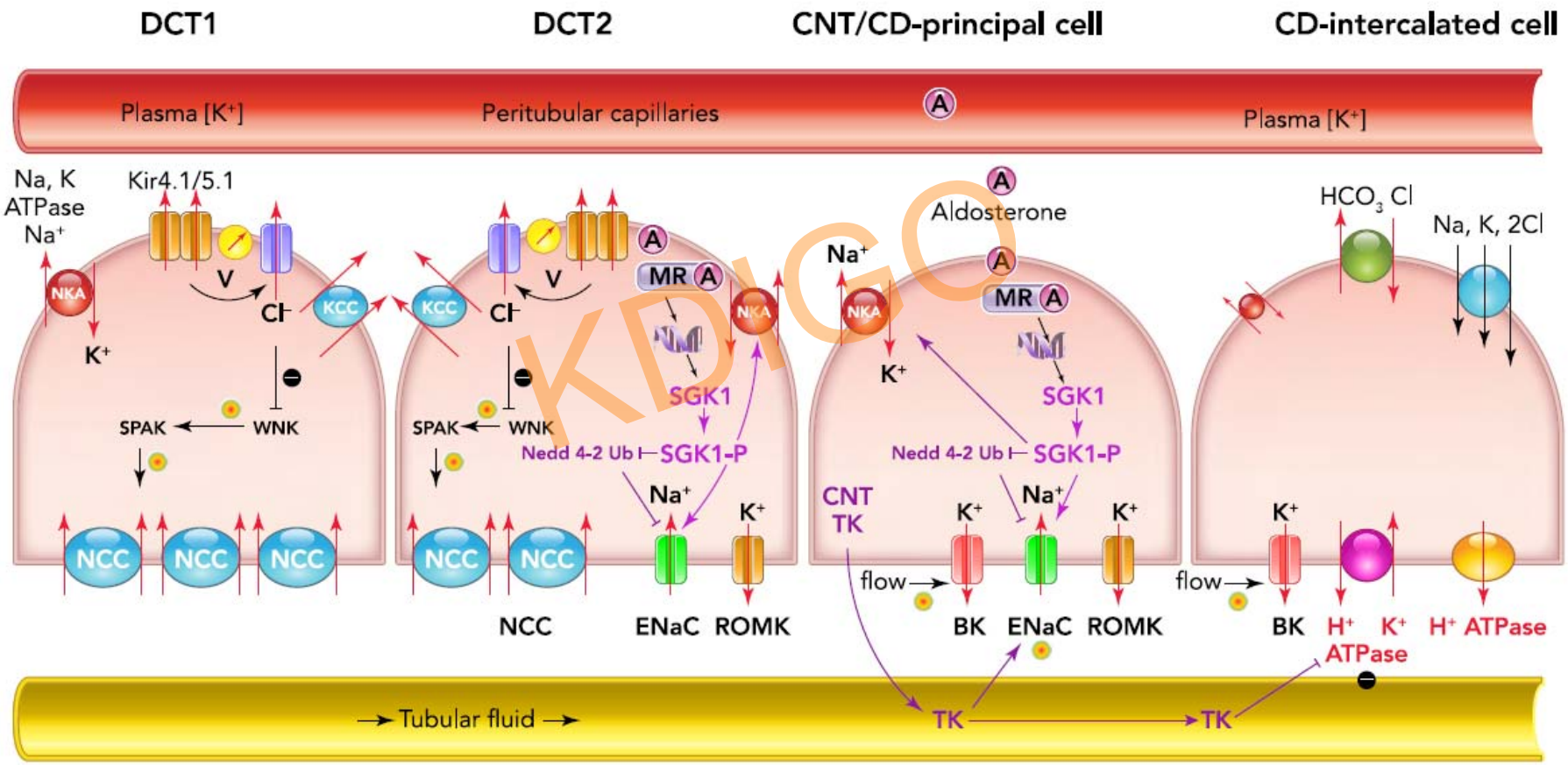


FIG. 8. Hypothetical model of distal tubule electrolyte transport involving specific exchange mechanisms at both surfaces of the tubule cell.



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?

Malnic Klose Giebisch– Am. J. Physiol. 1966;211:529-547

- “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

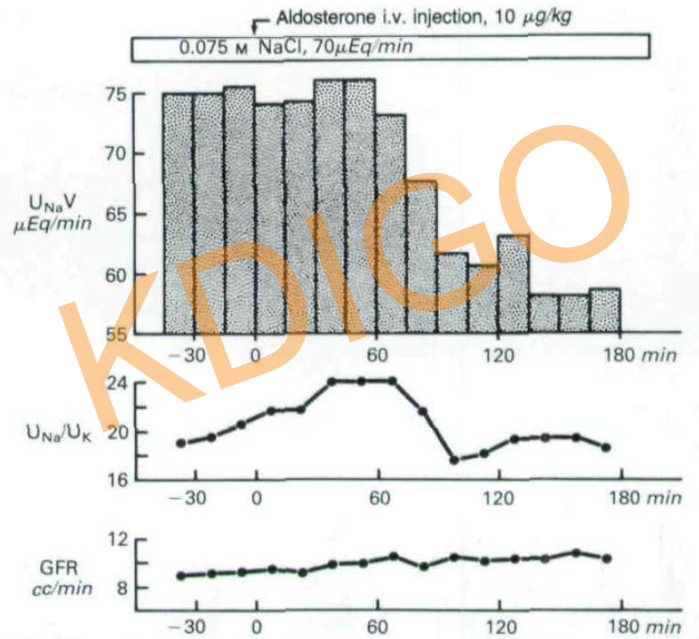
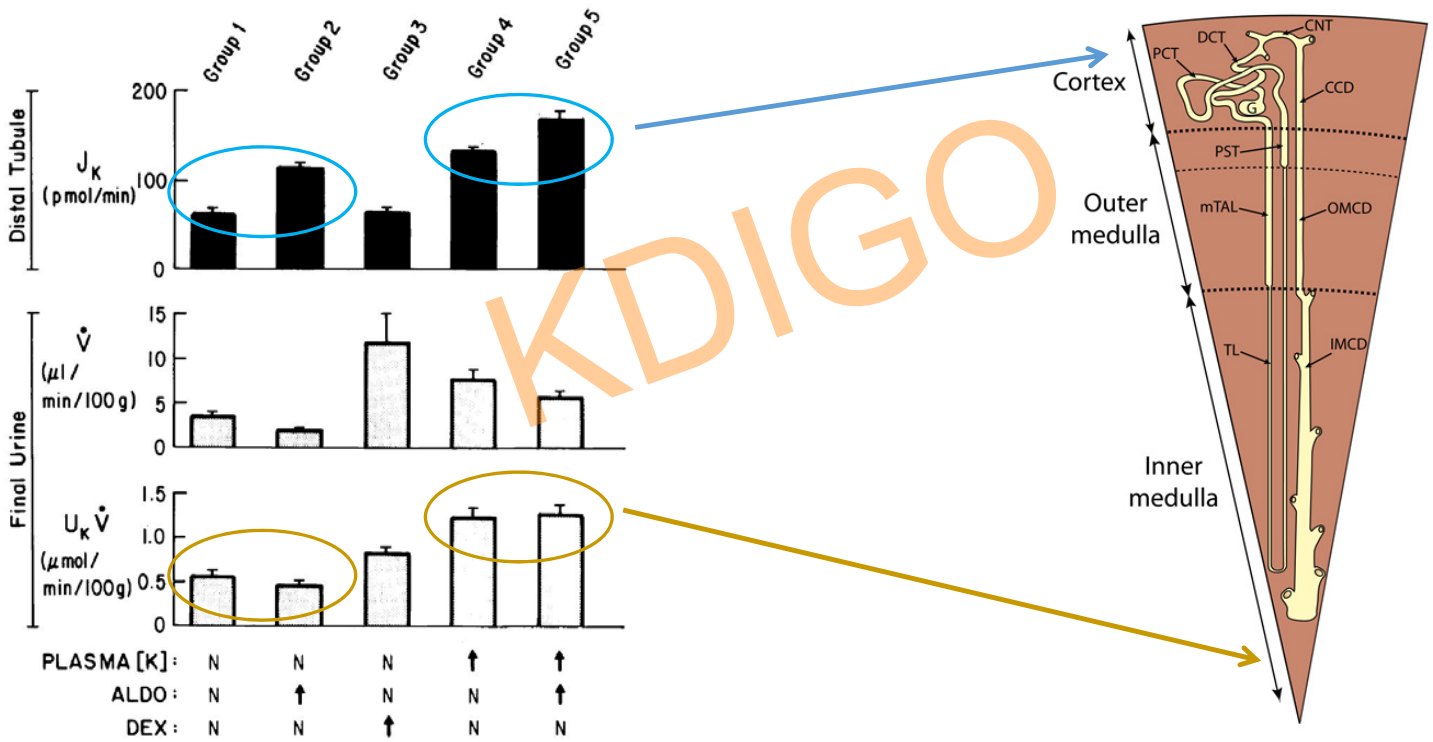


Fig. 1. *Results of a single clearance experiment.* Urine sodium excretion ($U_{Na}V$), urinary Na:K concentration ratio (U_{Na}/U_K), and glomerular filtration rate (GFR) are graphed over time before and after intravenous aldosterone *(arrow)*.

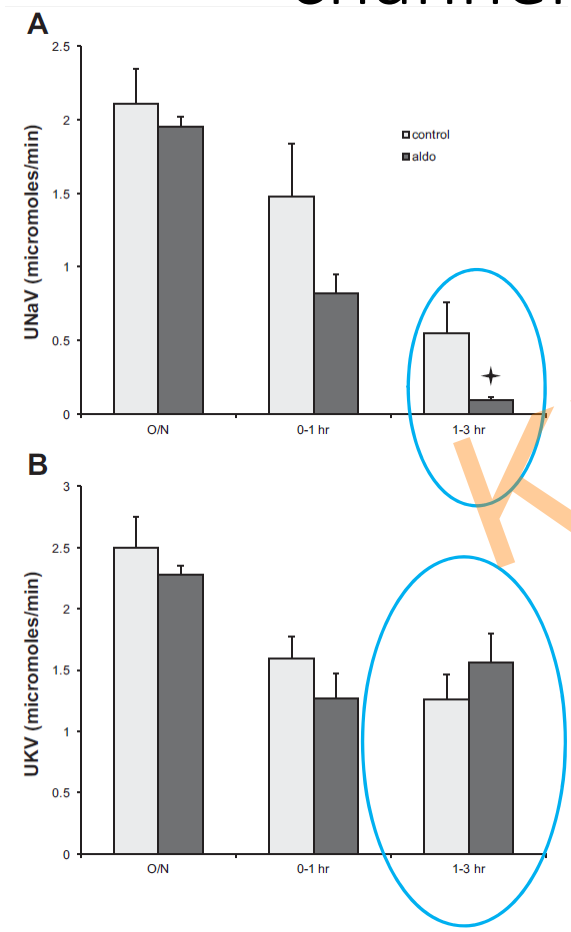
Wingo, Kokko, Jacobson -Kidney Int 1985; 28:51-7

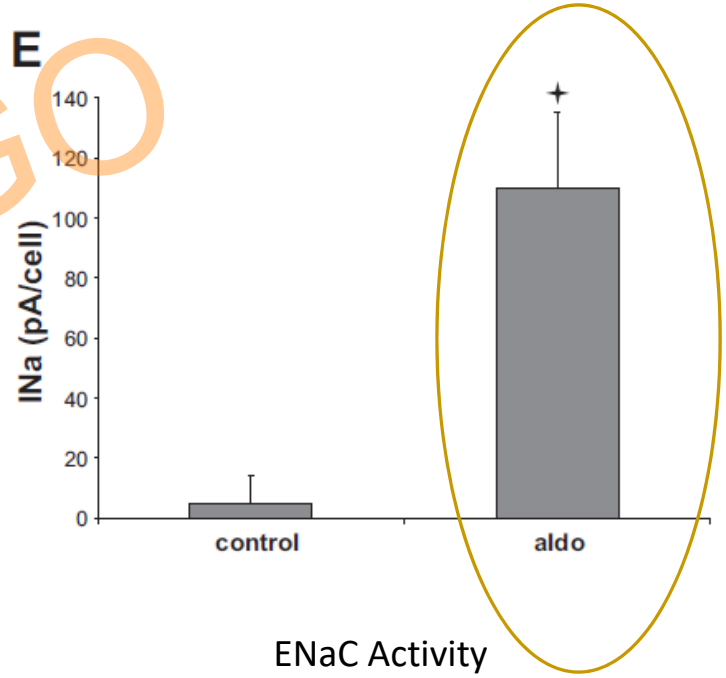
Differential Acute Effects of Aldosterone and Hyperkalemia on Distal Tubular Potassium Secretion in the Rat Kidney



Field, Stanton, Giebisch – J Clin Invest 1984;74:1792-802

Acute effects of aldosterone on Epithelial Na channel in the rat kidney





ENaC Activity

Frindt & Palmer – Am J Physiol 2014;308:F572-8

Effect of Mineralocorticoids on apical and basolateral membrane conductances

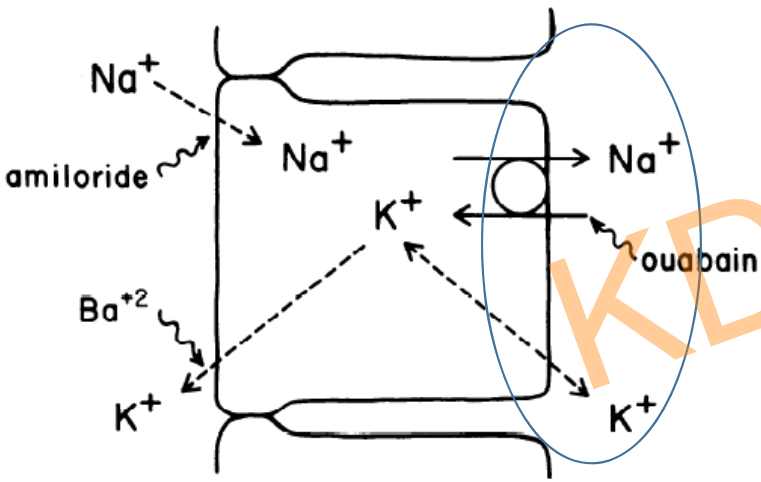


FIG. 13. Cellular model for Na^+ and K^+ transport by the cortical collecting duct. The coupling ratio of Na^+-K^+-ATPase may be different from unity so that the pump is electrogenic. Depending on the magnitude of basolateral membrane potential, K^+ may move passively into or out of the cell across this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

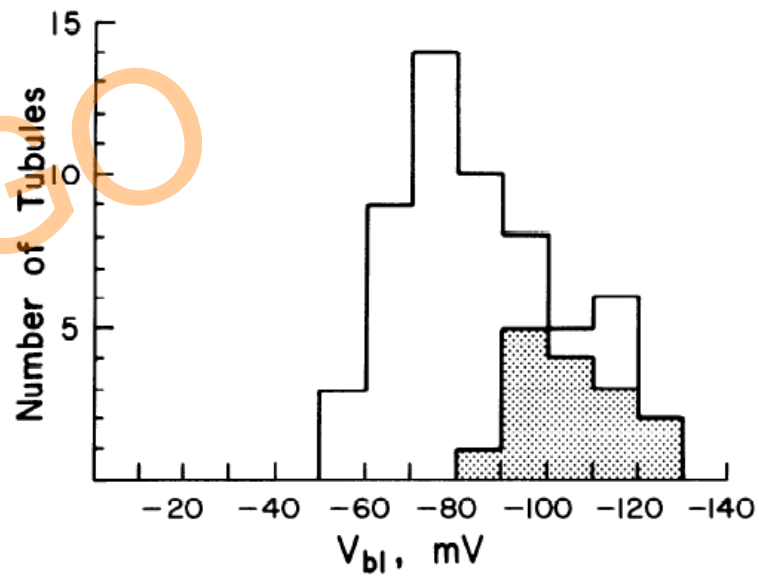


FIG. 6. Distribution of V_{bl} in control and DOCA-treated (shaded area) tubules.

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

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- Berliner – Harvey Lectures, Acad. Press 1961 Ser. 55 p141-71
- Chobanian et al. – J Clin. Invest. 1961;40:416-22
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- Hulter et al. – Am. J Physiol. 1978;235:F298-309
- Linas et al. – Kidney Int 1979;15:601-11
- Good & Wright – Am J Physiol 1979; 236:F192-205

K Homeostasis - II

- Stokes – Am J Physiol 1981; 241:F395-F402
- Stanton & Giebisch – Am J Physiol 1982;242:F544-51
- Pan & Young – Hypertension 1982;4:279-87
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- Park et al. – Histol Histopathol 2012; 27:1559-77
- Palmer & Frindt – Am J Physiol 2014;308:F572-8

Effect of Mineralocorticoid Stimulation [Aldosterone/DOC] on K Balance

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2. Hulter et al. -Am J Physiol 1978;235:F298-309
3. Hulter et al. -Am J Physiol 1979;236:F48-57
4. Grekin et al. Hypertension 1980; 2:326-32
5. Greenlee et al. – J Am Soc Nephrol 2011; 22:49-58
6. Lynch et al. – Am J Physiol 2015; 309:F1026-34

Circadian

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- Zuber et al. Proc Natl Acad Sci USA 2009;106:16523-16528
- Nikolaeva et al. J Am Soc Nephrol 2012; 23:1019-1026
- Salhi et al. FASEB J 2012; 26(7):2859-2867
- Tokonami et al. J Am Soc Nephrol 2014; 25(7):1430-1439
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Additional Reading

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2. Greenlee et al. – J Am Soc Nephrol 2011; 22:49-58
3. Palmer & Frindt – Am J Physiol 2014;308:F572-8
4. Gumz et al. J Clin Invest. 2009; 119(8): 2423-34
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6. Zuber et al. Proc Natl Acad Sci USA 2009;106:16523-16528
7. Nikolaeva et al. J Am Soc Nephrol 2012; 23:1019-1026
8. Salhi et al. FASEB J 2012; 26(7):2859-2867
9. Tokonami et al. J Am Soc Nephrol 2014; 25(7):1430-1439