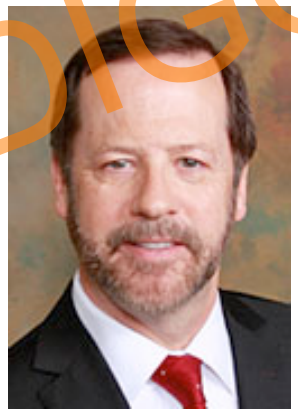
Disclosure statement

It is much ado about something, we know not what. We like it because without controversy we are out of jobs. A “hard-endpoint” trial seems unlikely. Thus, we can believe whatever we want!

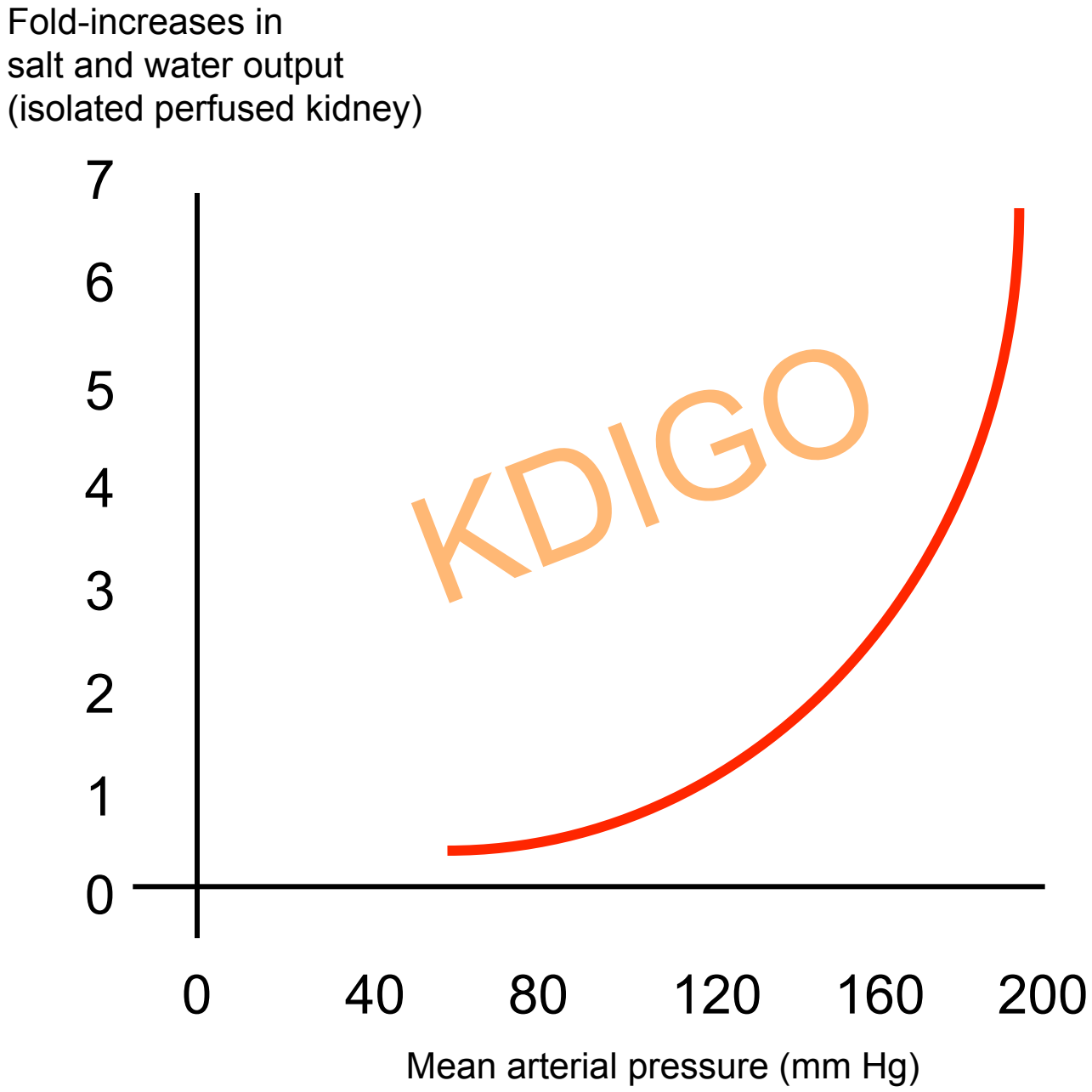
Arthur Clifton Guyton (September 8, 1919 – April 3, 2003) was an American physiologist



Theodore W. Kurtz, MD, Professor and Vice Chair of Laboratory Medicine, Chief of Clinical Chemistry

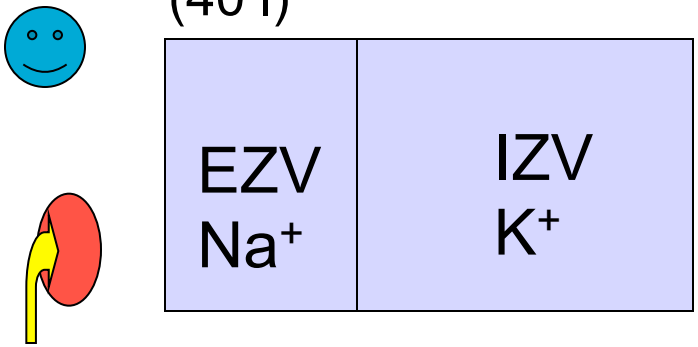
John E. Hall, Ph.D. Arthur C. Guyton Professor & Chair, Director, Mississippi Center for Obesity Research

Fig. 1. ***Renal-pressure natriuresis from the Selkurt data***

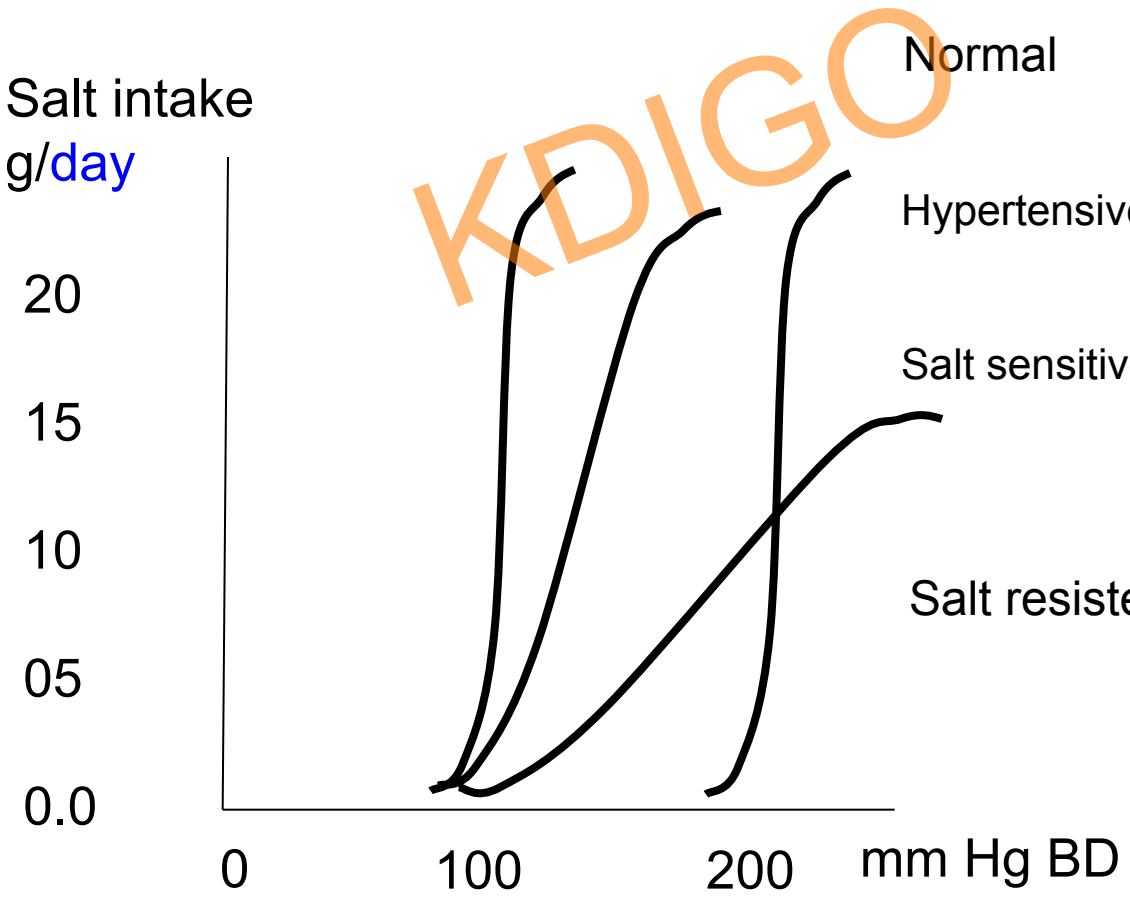


Variable renal-pressure natriuresis

Total body water
(40 l)



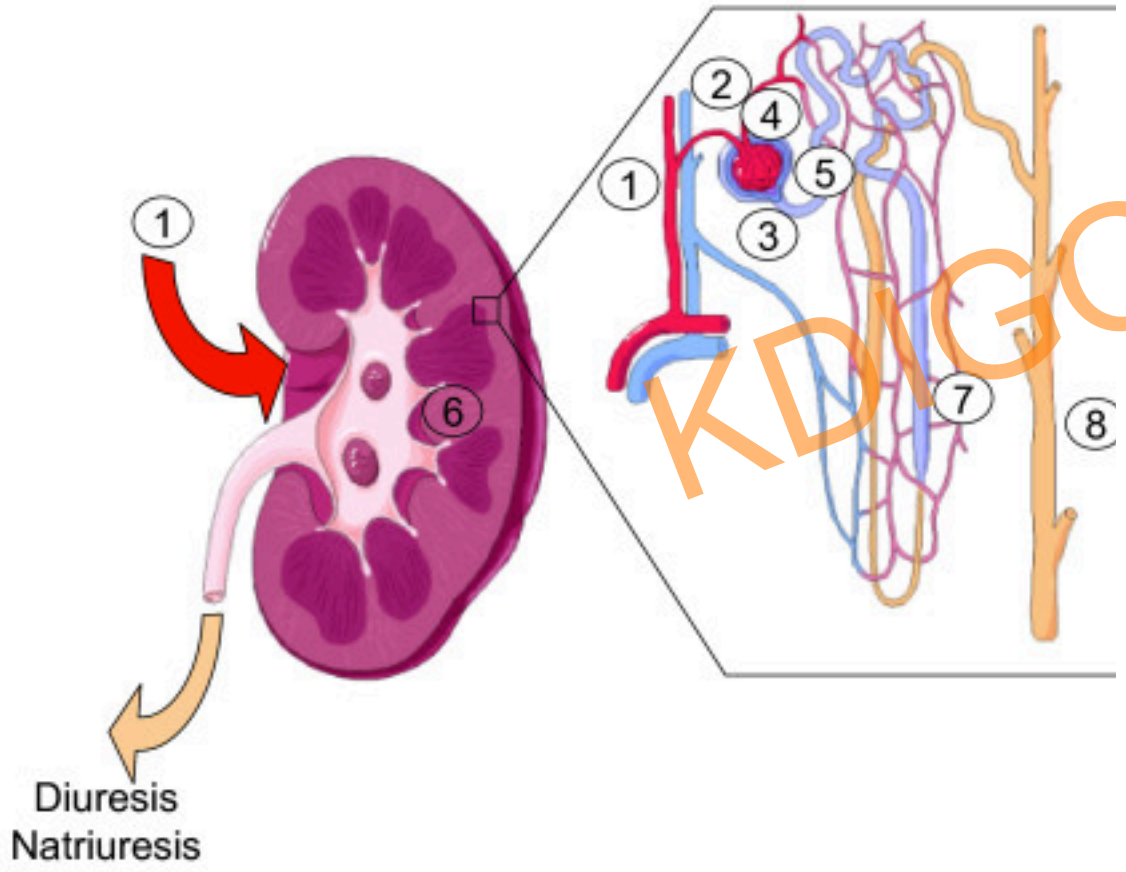
Sodium (Na^+) 1 g = 44 mmol
Sodium (Na^+) 1 mol = 23 g/l
Salt (NaCl) 1 g = 18 mmol/Na^+
Daily intake is about
NaCl 8-10 g (150-180 mmol/day)



Pressure-natriuresis Relationship

What raises the pressure?

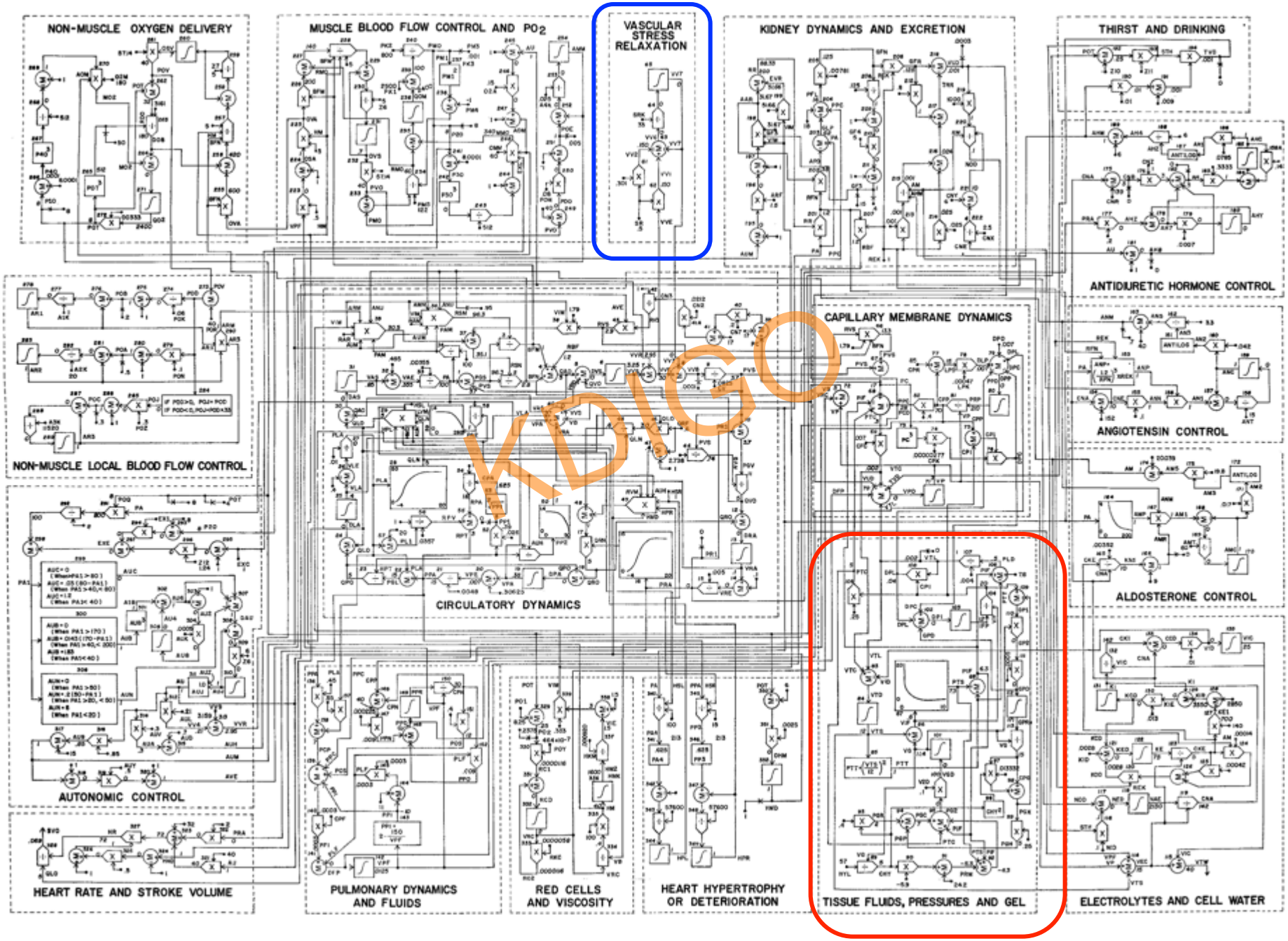
Does pressure natriuresis hold up?



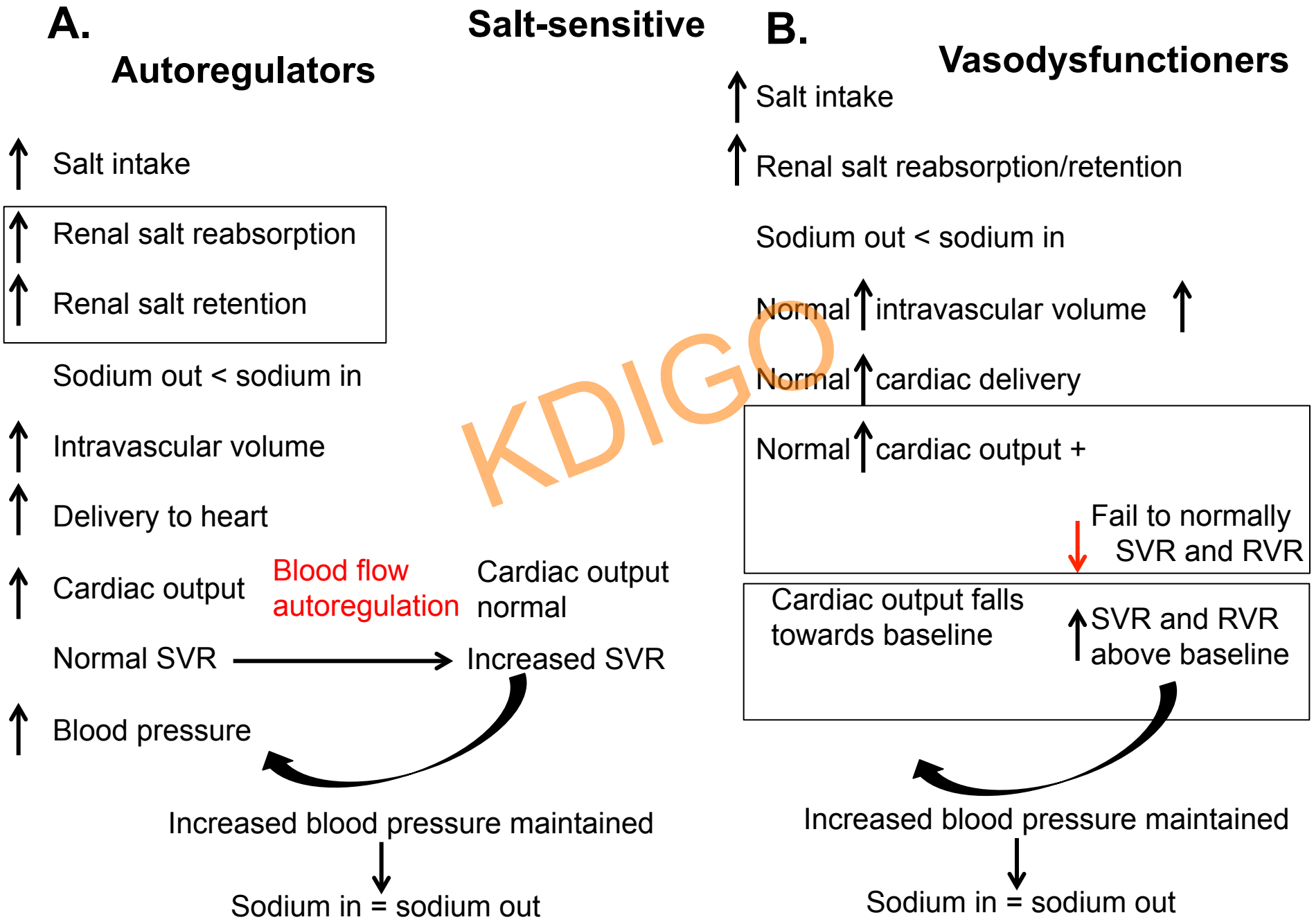
1. Renal blood flow and perfusion
2. Afferent and efferent tone
3. T-G feedback
4. Plasma oncotic pressure
5. Bowman's capsular pressure
6. Intra-renal blood flow distribution and pressure
7. Conformational changes in ion channels
8. Aquaporin-2 expression

(Blood vessels and interstitium receive little attention)

Supplemental Figure to everything



John Hall is on the left; Ted Kurtz is on the right.



John Hall is on the left; Ted Kurtz is on the right.

Salt-resistant

A. Autoregulators

↑ Salt intake

Minimal ↑ renal reabsorption

Minimal ↑ renal salt retention

Sodium out = sodium in

Minimal ↑ in intravascular volume

Minimal ↑ in volume cardiac delivery

Minimal ↑ in cardiac output

Minimal ↓ in SVR

Little or no increase in blood pressure

B. Vasodysfunctioners

↑ Salt intake

Normal ↑ Renal salt reabsorption

Sodium out < sodium in

Normal ↑ intravascular volume

Normal ↑ cardiac delivery

Normal ↑ cardiac output + normal ↓ SVR & RVR

Blood pressure does not increase

Cardiac output returns towards baseline

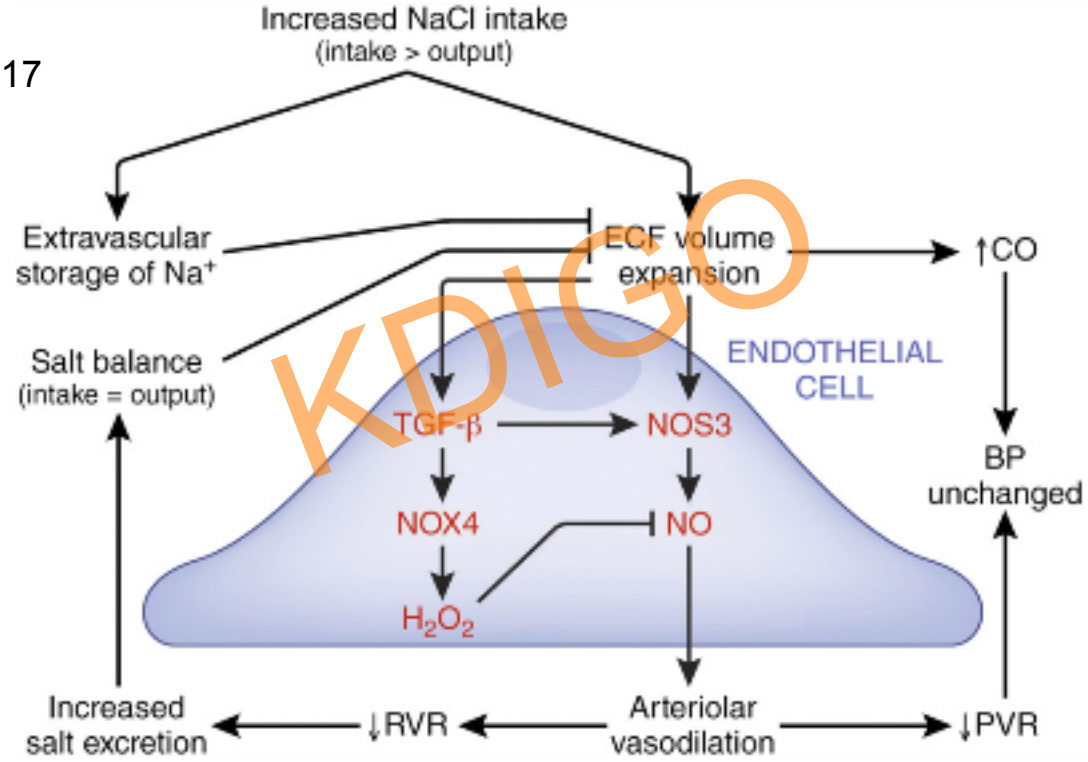
SVR & RVR increase to baseline

Normal blood pressure maintained

Sodium out = sodium in

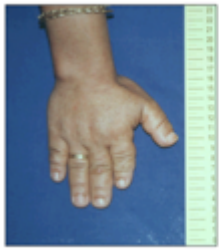
Recent support for the vasodysfunctioners from Hans Oberleithner and Paul Sanders

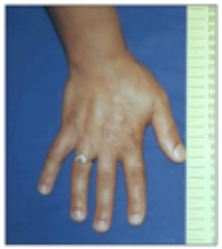
J Am Soc Nephrol 2017
Pflugers Arch 2015

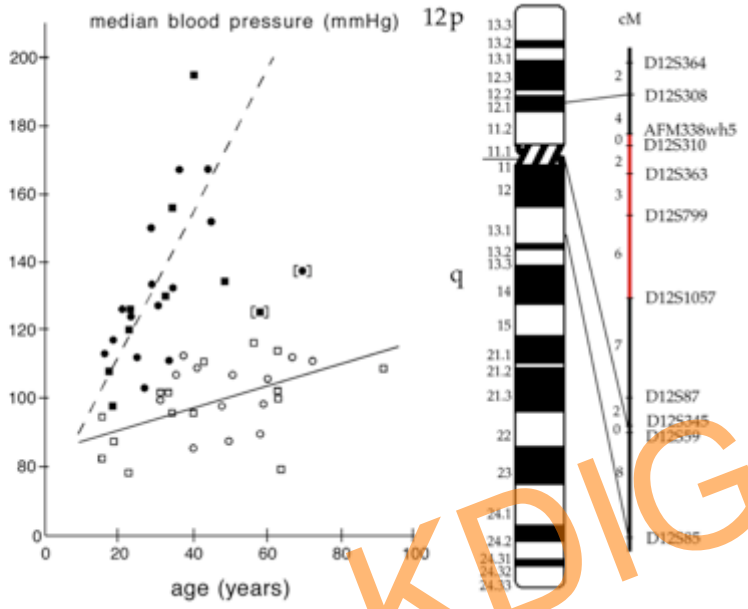


Glycocalyx, endothelium, NO dysfunction and no dilatation

A salt-independent Mendelian hypertension



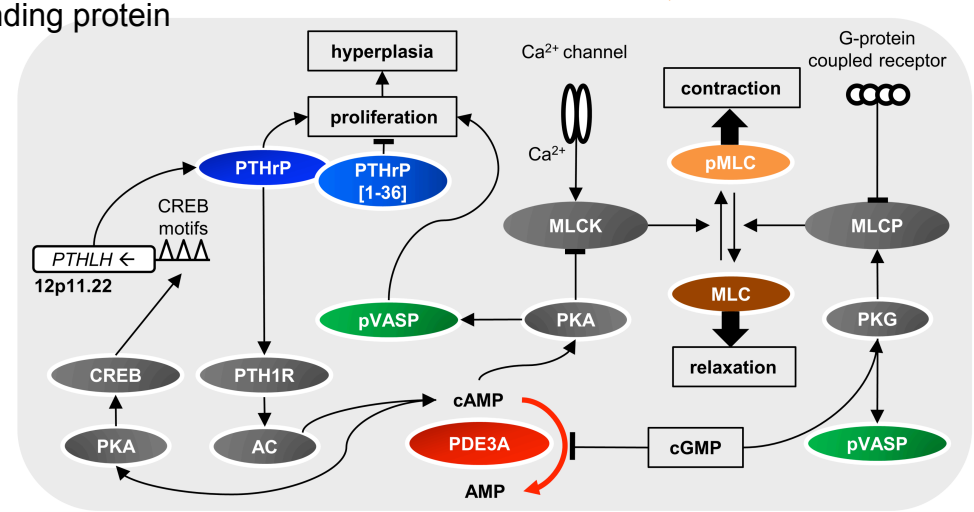




Schuster et al. Nat Genet 1996

How does mutated PDE3A work?

cAMP responsive element binding protein

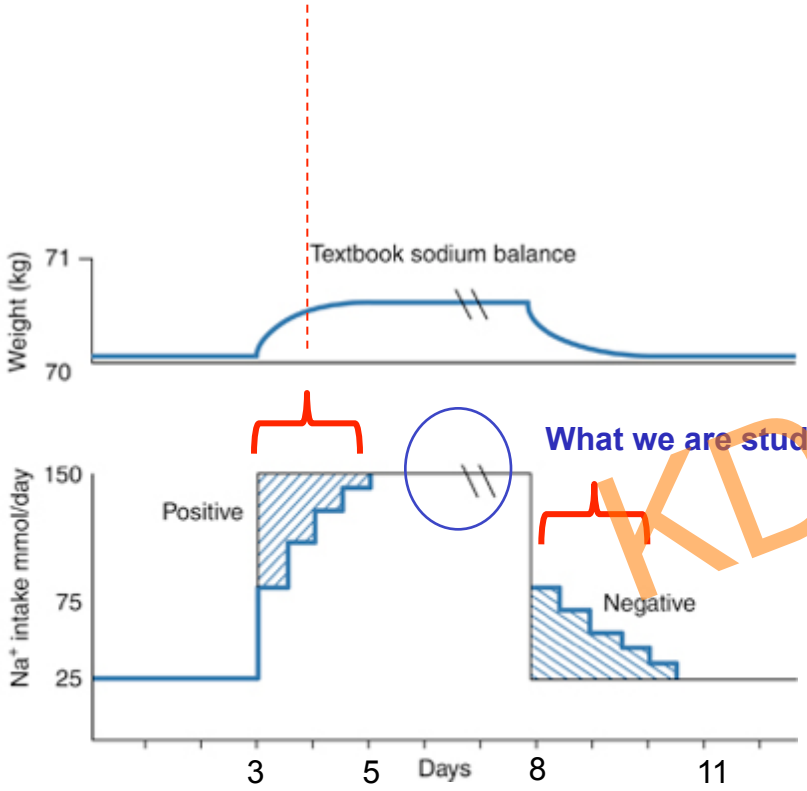


Vasodilator-stimulated phosphoprotein

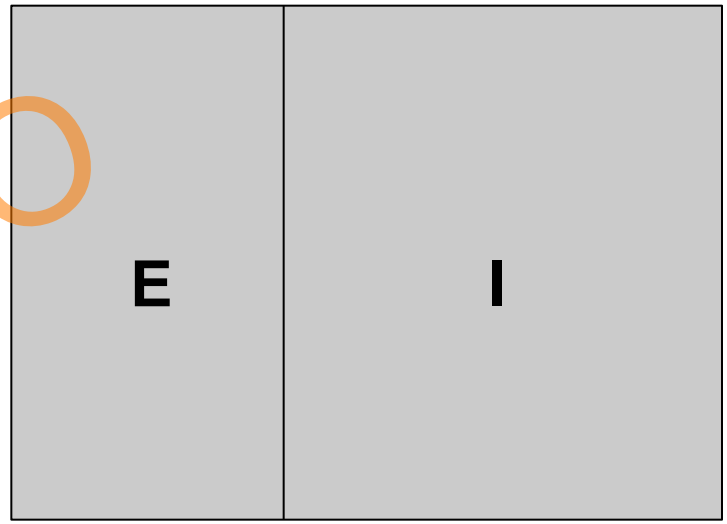
Maass et al. Nat Genet 2015

We teach this:

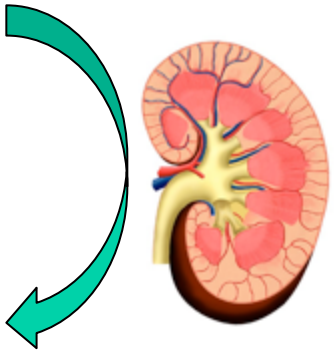
What we studied in 1979



What we are studying now



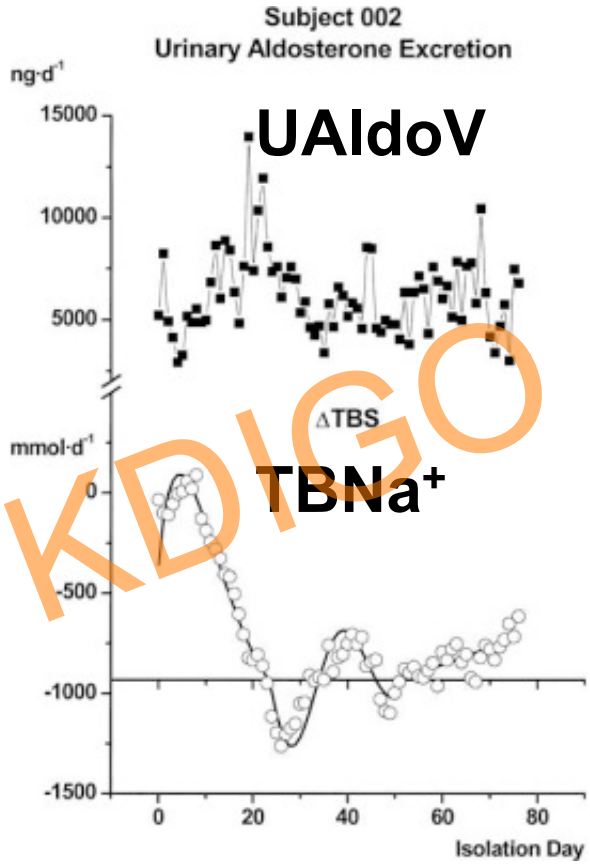
Studies lasted for about 1 week; however, life lasts longer than 1 week.

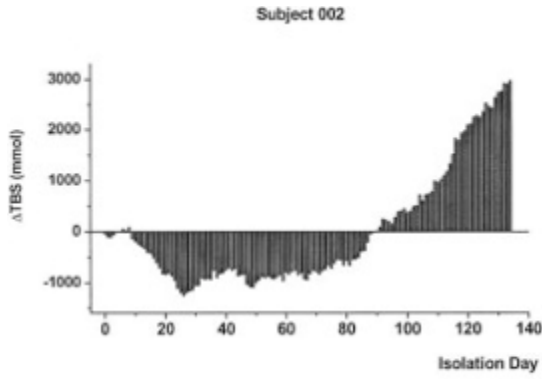


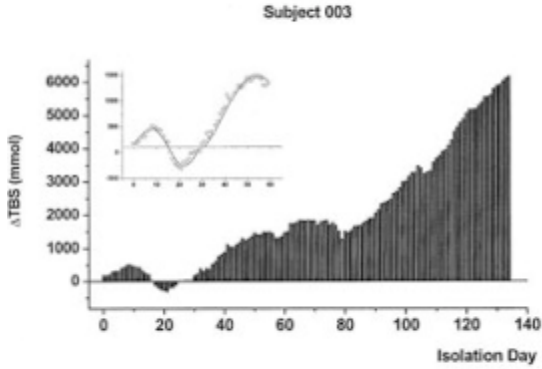
Rose. Regulation of water and electrolyte balance. 1994

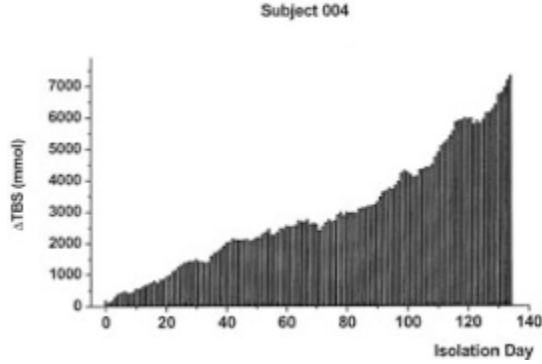
But, where is the salt? TBNa+

Titze et al. Am J Kidney Dis 2002







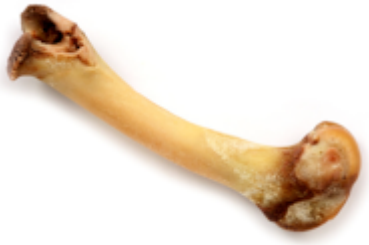


Abstract

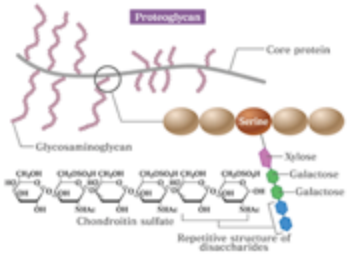
The finding of sodium gain without weight gain is in contradiction to the widely accepted theory that changes in TBNa+ levels are accompanied by changes in extracellular volume. We suggest the existence of a sodium reservoir with the ability to store significant amounts of sodium in an osmotically inactive form. This reservoir might be located in bone, dense connective tissue, or cartilage.

But not Bwt.

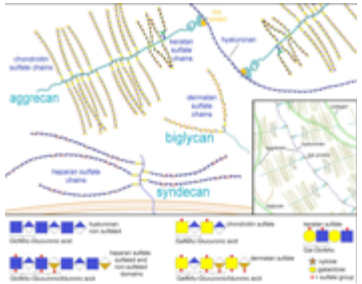
Mostly Skin



Not very exchangeable –
Titze et al. Am J Physiol 2002, 2003



Charged glycosaminoglycans



Synthesis is salt-dependent

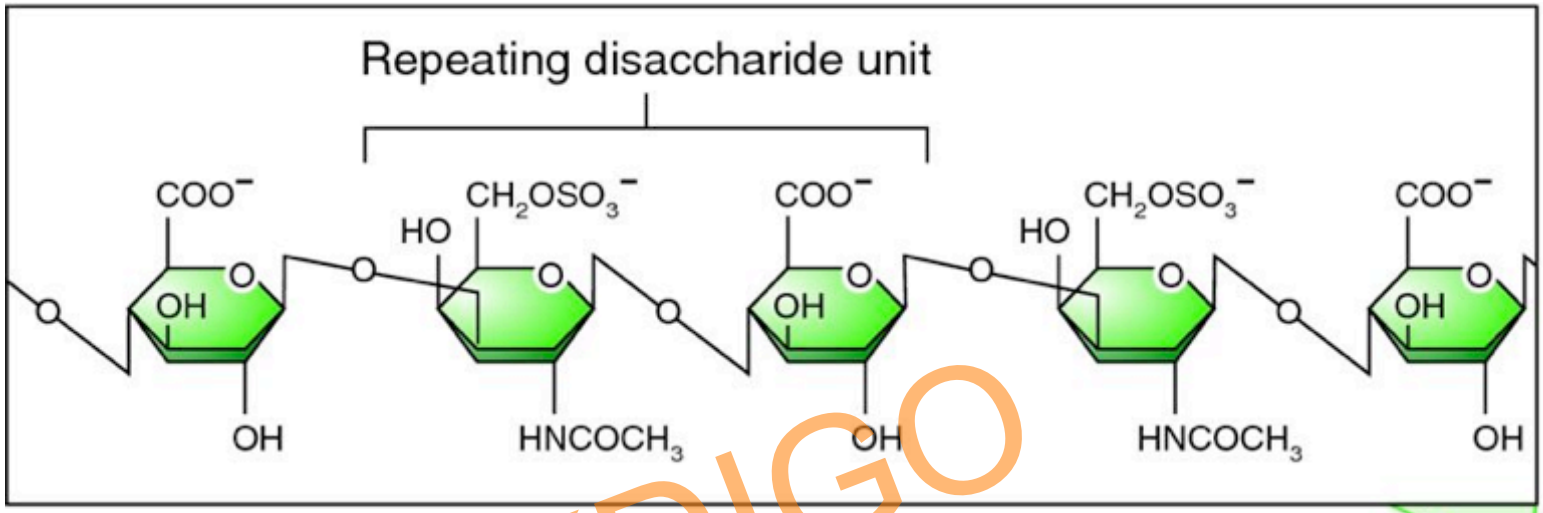
Complete ashing

Atomic absorption spectrometry

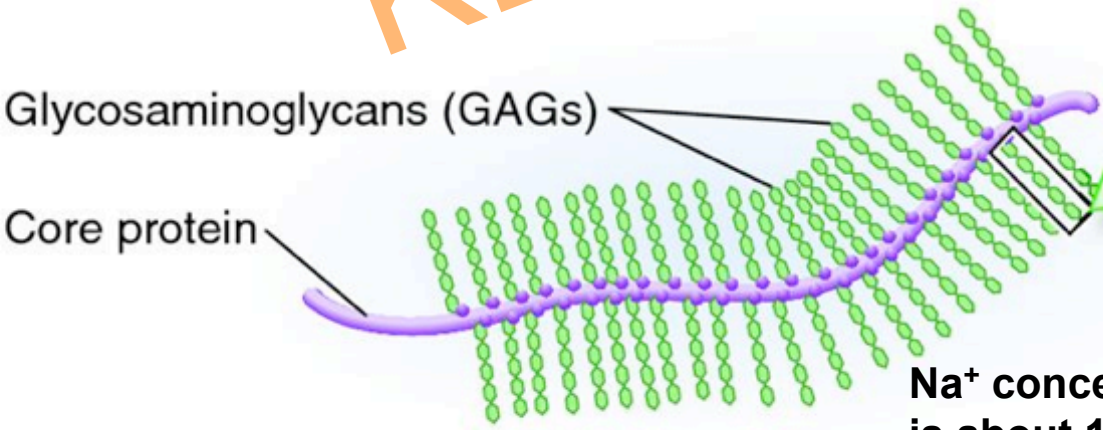
ECF = 13 L	ICF = 27 L
Na 140 K 5 Cl 100 HCO_3 25 etc	K 140 Na <5 Cl < 5 HCO_3 ? Phosphate & proteins

Totals 1820 mmol Na^+
(where is the rest?)

Envision it as a gel; the Na^+ content is higher



(a) Structure of chondroitin sulfate, a glycosaminoglycan



(b) General structure of a proteoglycan

Na^+ concentration here is about 170 mmol/L while plasma is 140 mmol/L

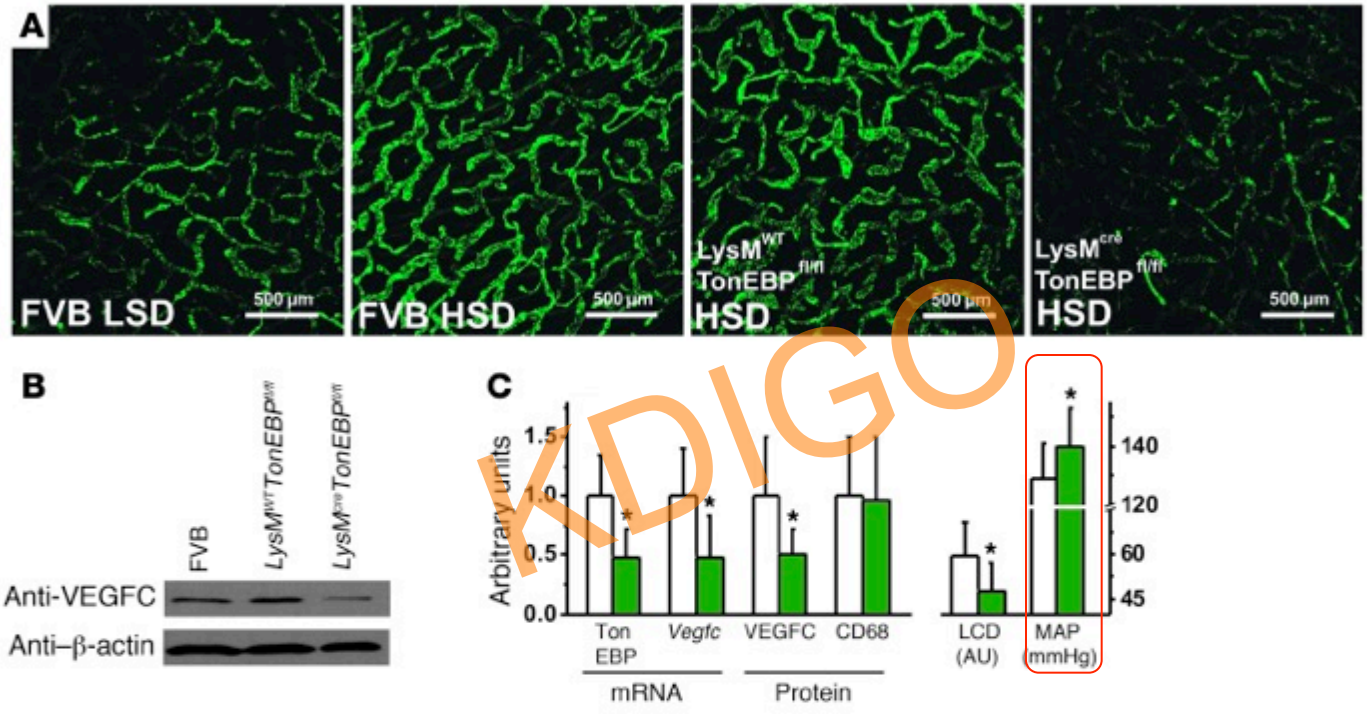
Tonicity-Responsive-Enhancer-Binding-Protein (NFAT5)

How could this work?

(anti–Lyve-1 antibody, green (Lymphatic endothelial cells)

(without MPS-specific TONEBP deletion)

with MPS-specific TONEBP deletion



Machnik et al. Nat Med 2009
Wiig et al. J Clin Invest 2013

We thought we were the first, but we were not!

Naunyn-Smiedeberg 1909

Über die Bedeutung der Gewebe als Chlordepots.

Von

Valdemar Wahlgren † aus Upsala.[1])

Herausgegeben von R. Magnus in Utrecht.

Organ	% des Körper-gewichts	Gewicht der Organe in g	Normaler Cl-Gehalt in g	Chlor-verteilung in %	Clorverteilung, berechnet nach Nencki in %
Haut	16.11	1611	6.064	**34.95**	32.60
Muskeln	42.84	4284	3.183	**18.33**	19.65
Skelett	17.39	1739	3.106	**17.87**	7.66
Blut	7.00	700	2.160	**12.44**	26.05
Darm	8.18	818	1.359	**7.82**	4.60
Lunge	2.36	236	0.569	**3.27**	4.87
Leber	3.60	360	0.453	**2.60**	1.25
Gehirn	1.37	137	0.253	**1.46**	1.95
Niere	0.85	85	0.219	**1.26**	1.39
Summe		9970	17.366	**100.00**	100.00

German: Over 1/3 Cl is in the skin

Archiv f. experiment. Pathol. u. Pharmakol. Bd. 61.

Zusammenfassung.

1. Haut, Blut, Niere und Lunge besitzen unter den Organen des Körpers den größten prozentischen Chlorgehalt, die Muskeln den niedersten.

2. Der Chlorgehalt der untersuchten Hunde betrug im Mittel 0,17 Proz.

3. Über ein Drittel des gesamten Körperchlors befindet sich in der Haut.

4. Das übrige befindet sich zum größten Teil in Blut, Muskeln, Skelett und Darm.

5. Nach intravenöser Chlorzufuhr wächst der prozentische Chlorgehalt am stärksten in der Lunge, danach in Darm, Blut, Haut und Niere.

6. Absolut wird die größte Menge des zugeführten Chlors in Muskel, Darm und Haut aufgenommen.

7. Nach intravenöser Infusion hypertonischer NaCl-Lösungen tritt Wasser zur Blutverdünnung hauptsächlich aus den Muskeln ins Blut über. Dagegen nimmt der Wassergehalt der Eingeweide zu. Dieses wurde mit der dort stattfindenden Lymphbildung in Beziehung gesetzt.

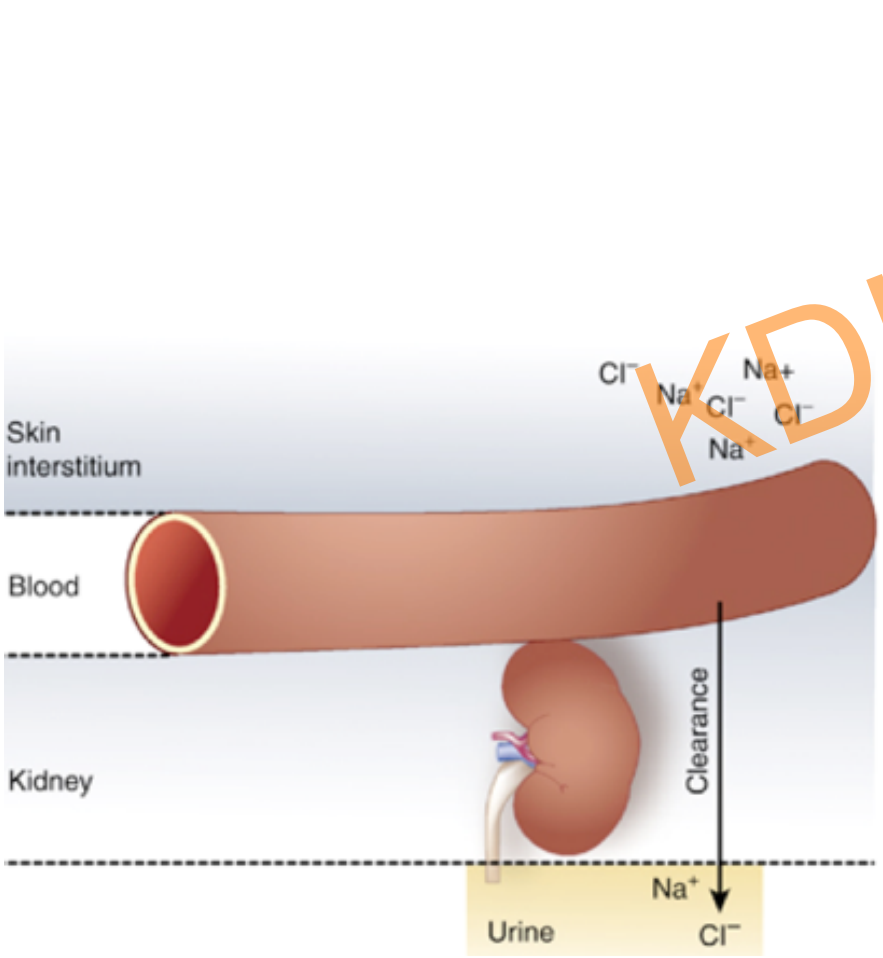
[Sodium-depositing function of the skin in white rats].

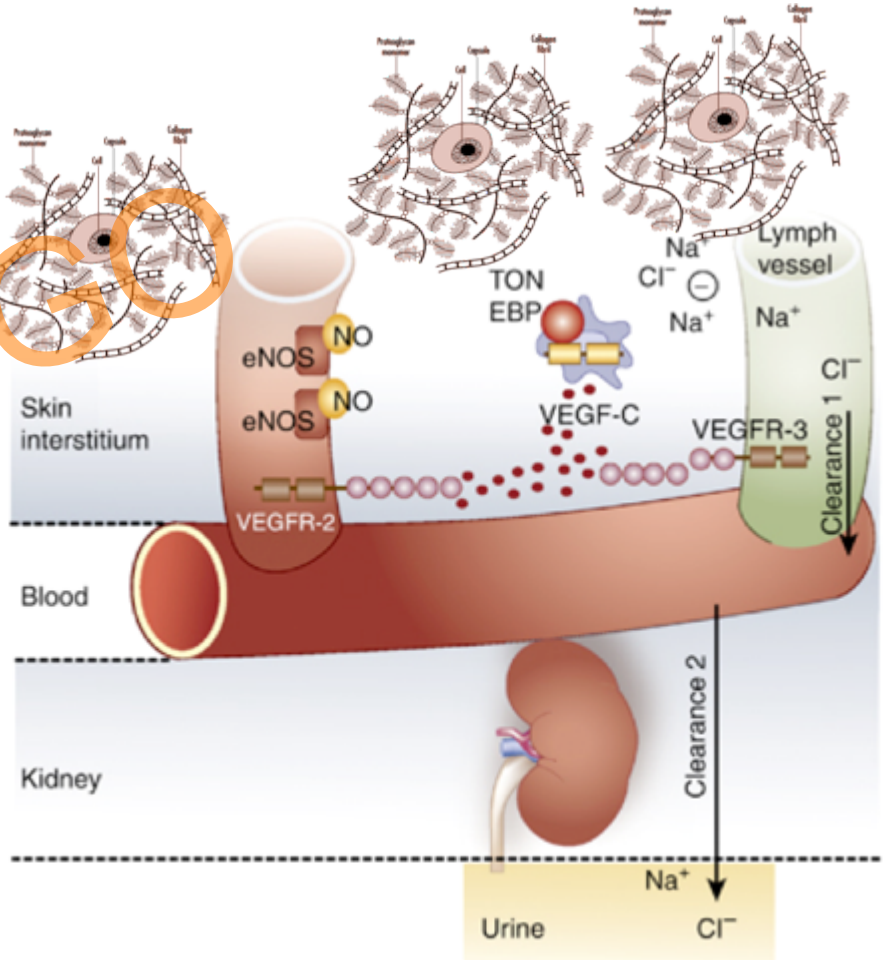
Ivanova LN, Archibasova VK, Shterental' ISh.

Fiziol Zh SSSR Im I M Sechenova. 1978 Mar;64(3):358-63. Russian.

Left - Then

Right - Now

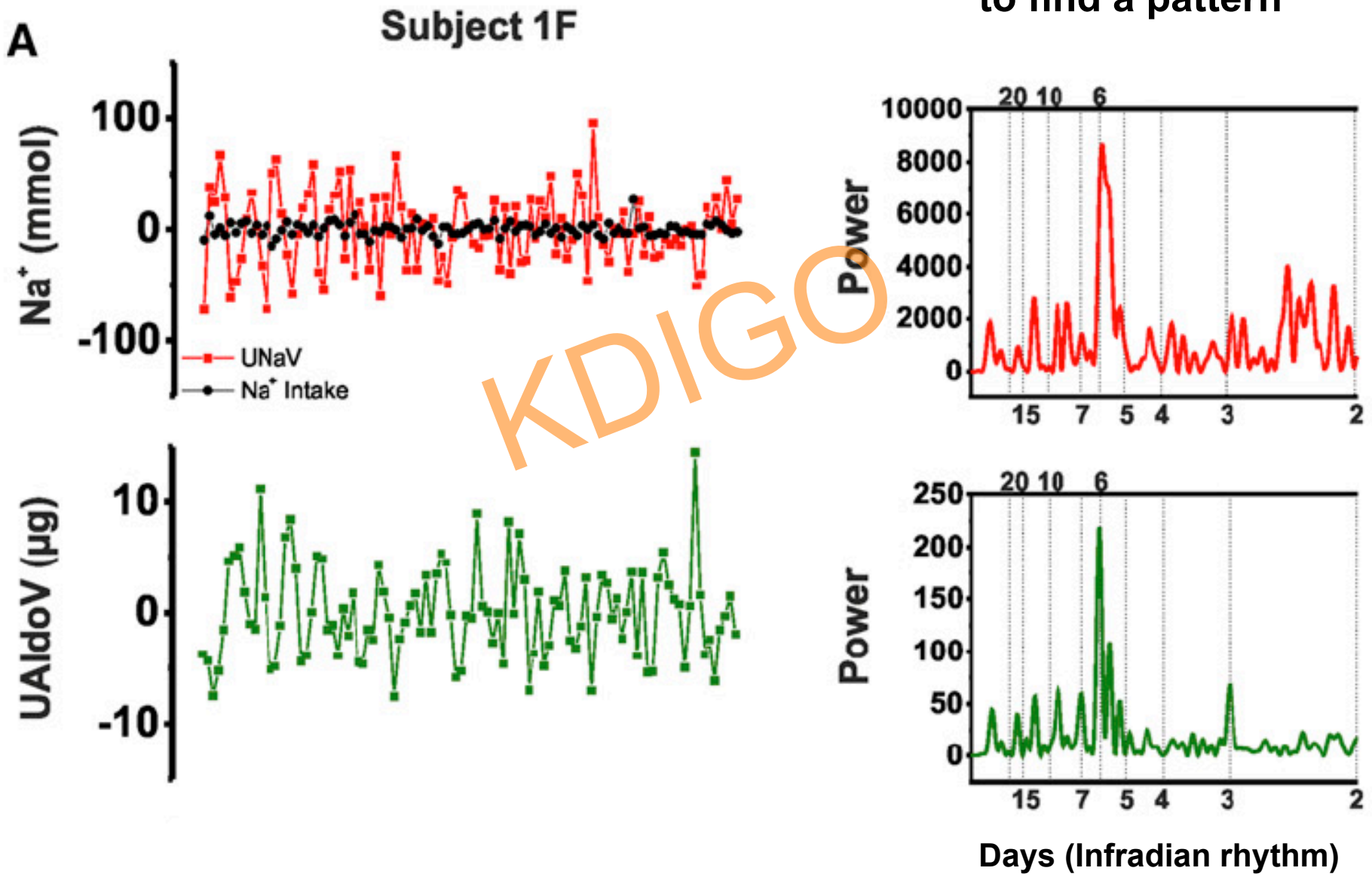




Movers and shakers

We „norm“ Na+ intake as constant across intakes

Fourier analysis to find a pattern



Data from all 10 subjects in two studies

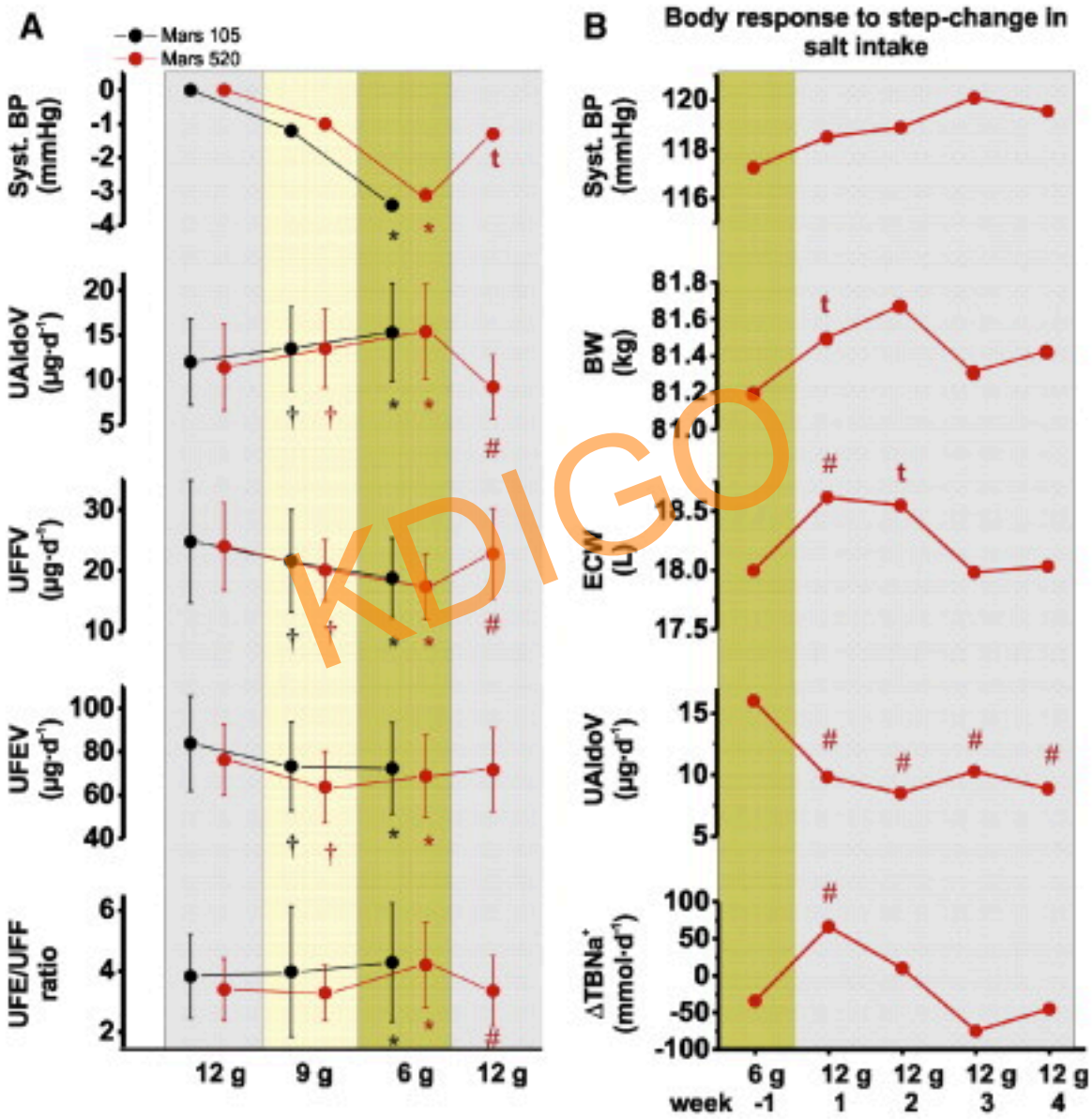
Blood pressure

Aldosterone

Cortisol

Cortisone perhaps the best Integrator

A relationship between cortisol/ and cortisone



Blood pressure

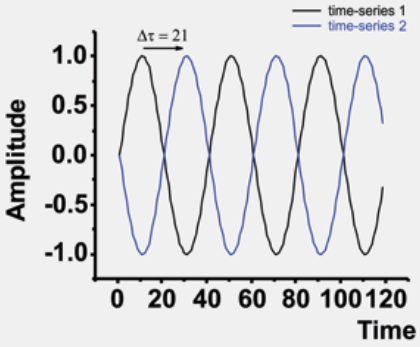
Body weight

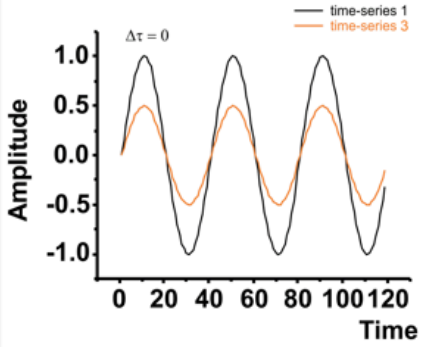
Impedance measurements

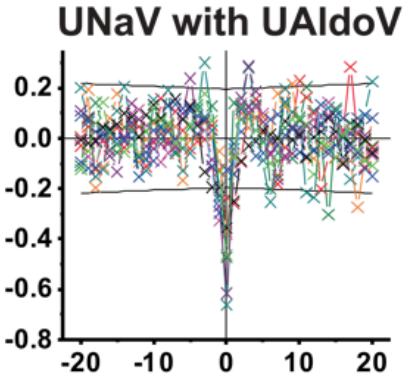
Aldosterone excretion

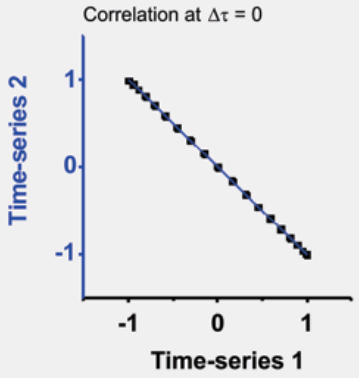
$TBNa^+$ wanders irrespective of salt intake

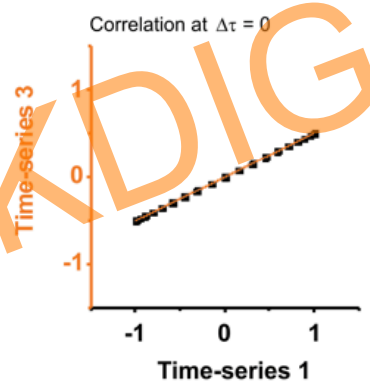
Rhythmic schematic of very-long-term balance studies

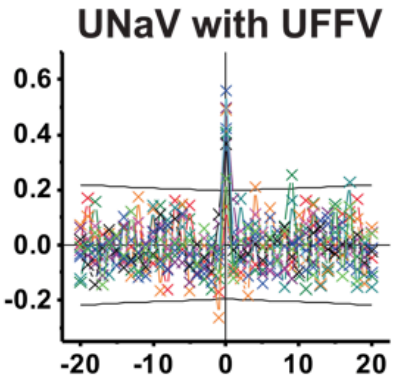


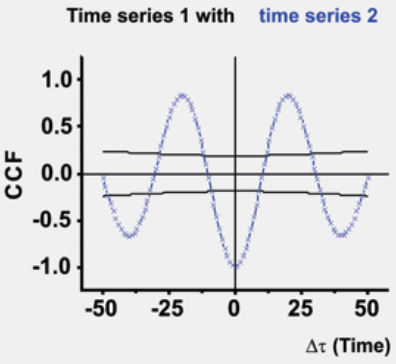


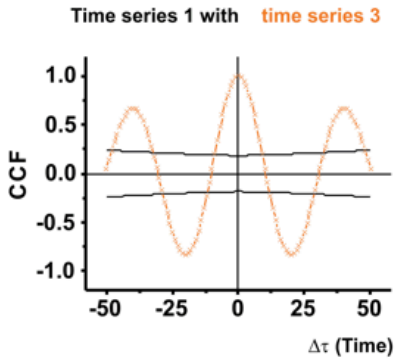


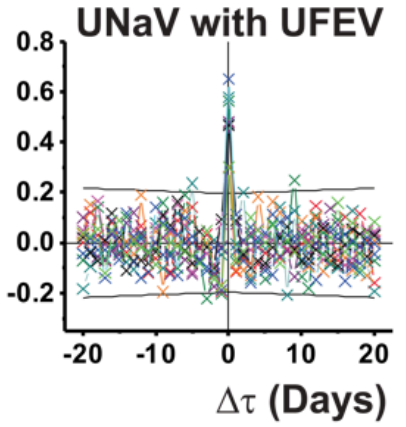




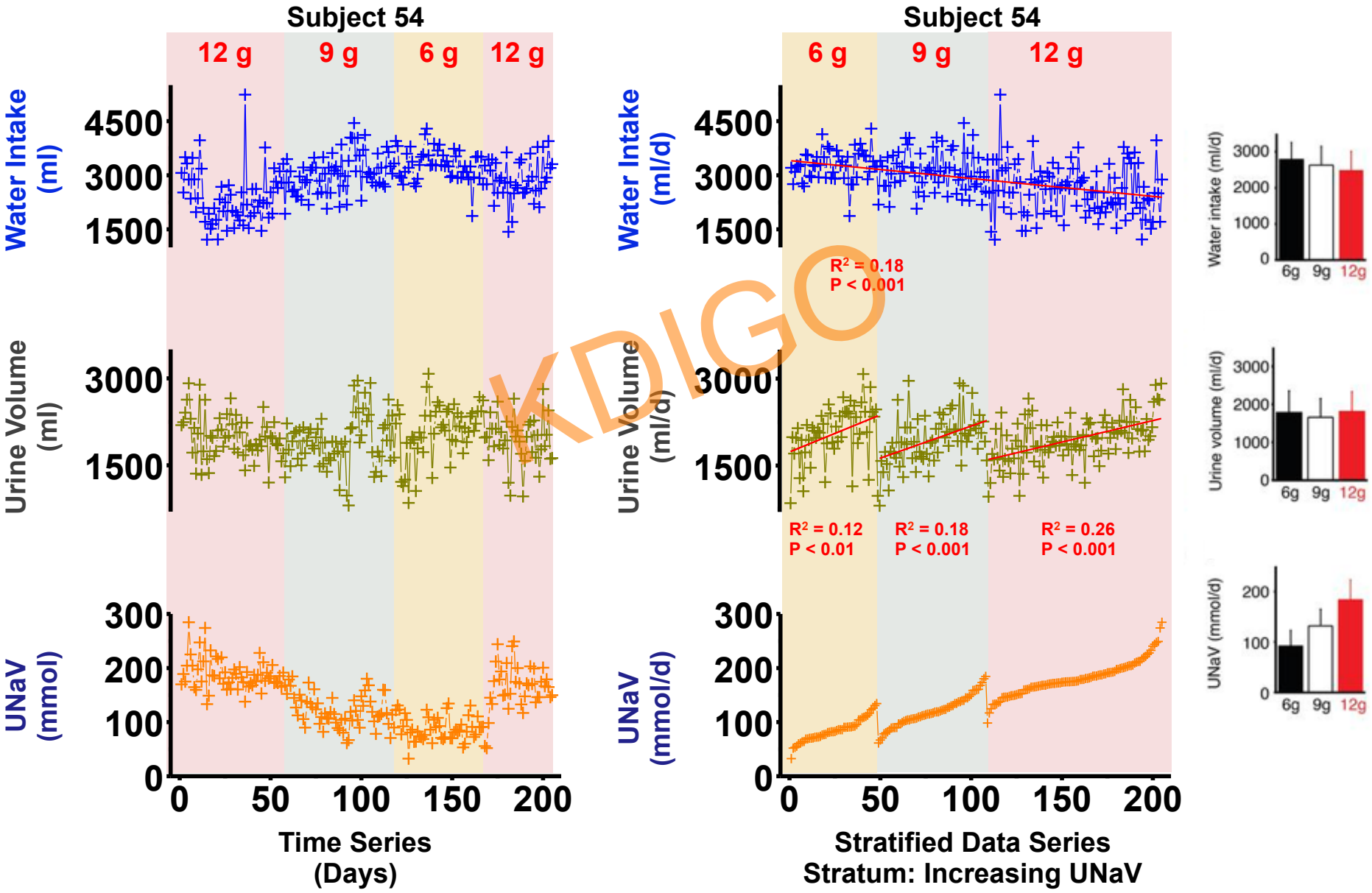






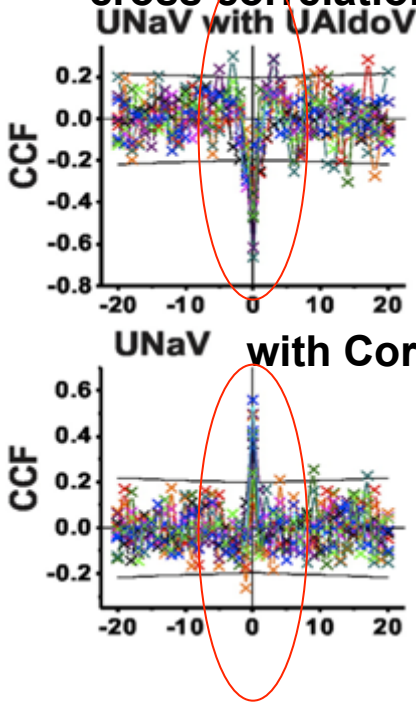


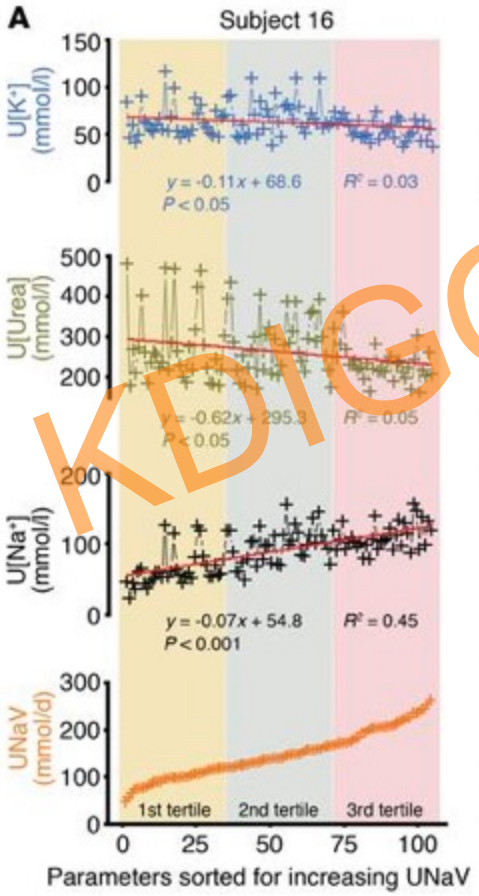
With increasing salt intake, drinking behavior goes down, not up.

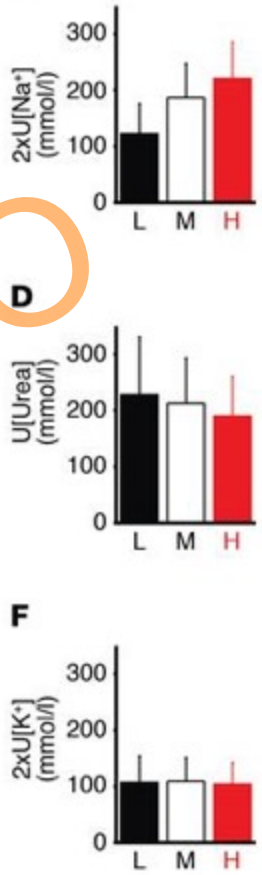


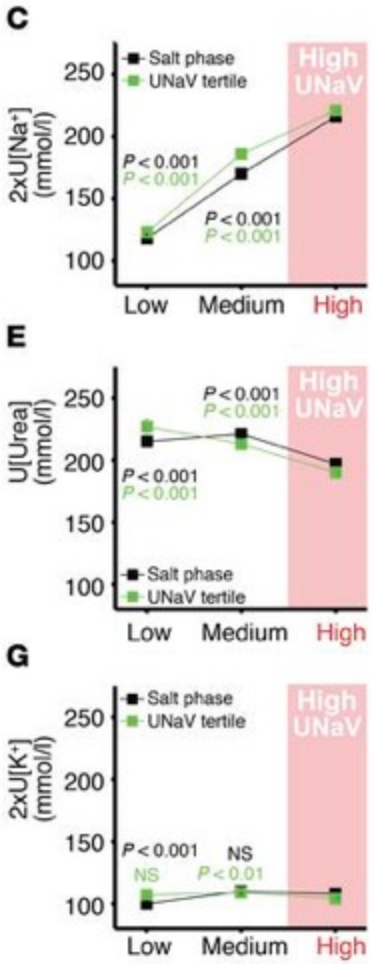
With increasing UNaV, UNa goes up while Uurea goes down.

Strong inverse (Aldo) and direct (Cortisol) cross correlation

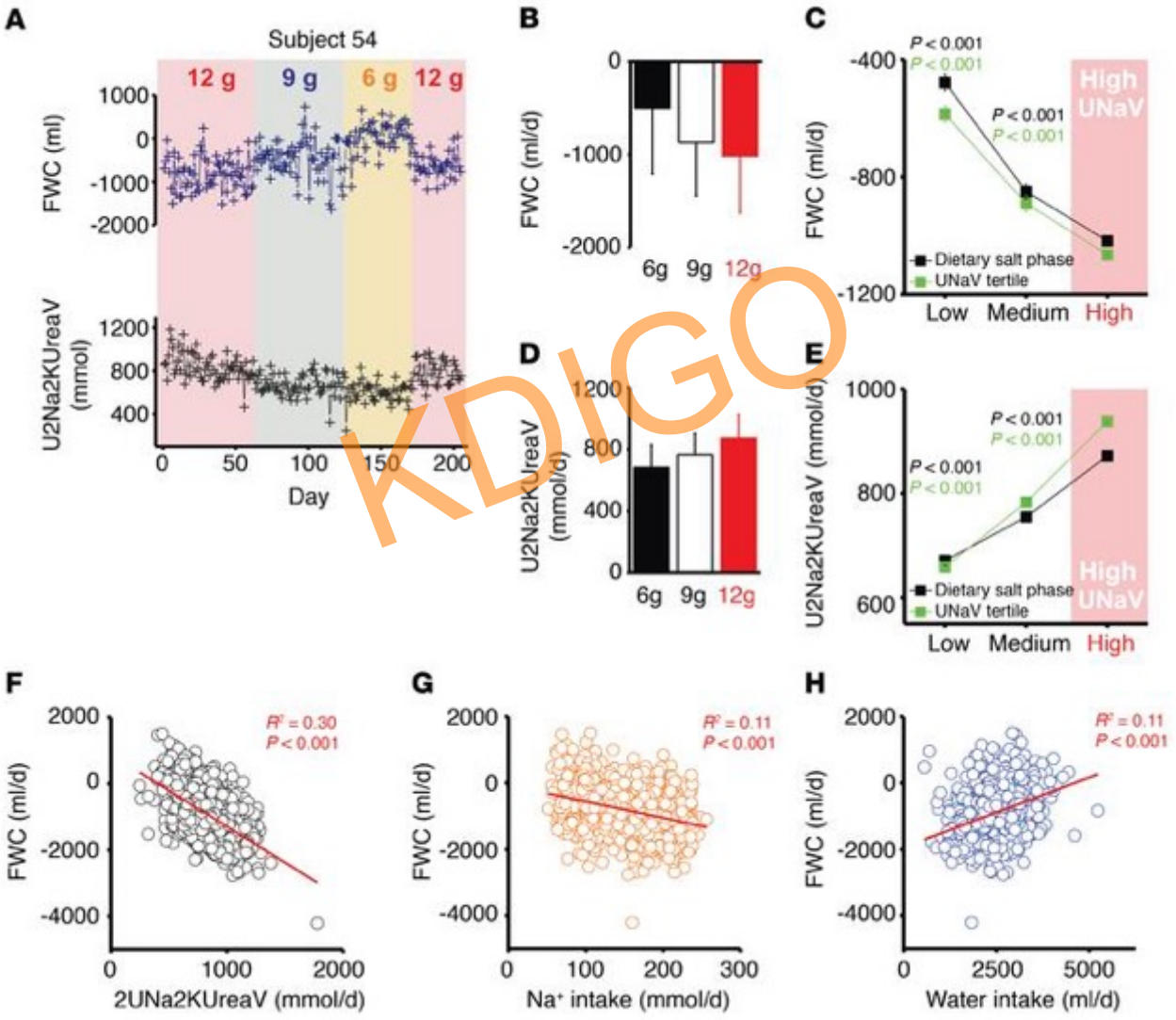








With increasing sodium intake, free-water clearance decreases. (aldosterone goes down, while glucocorticoids go up).



The mice with HSD became catabolic to produce urea and water.

Oxidative phosphorylation

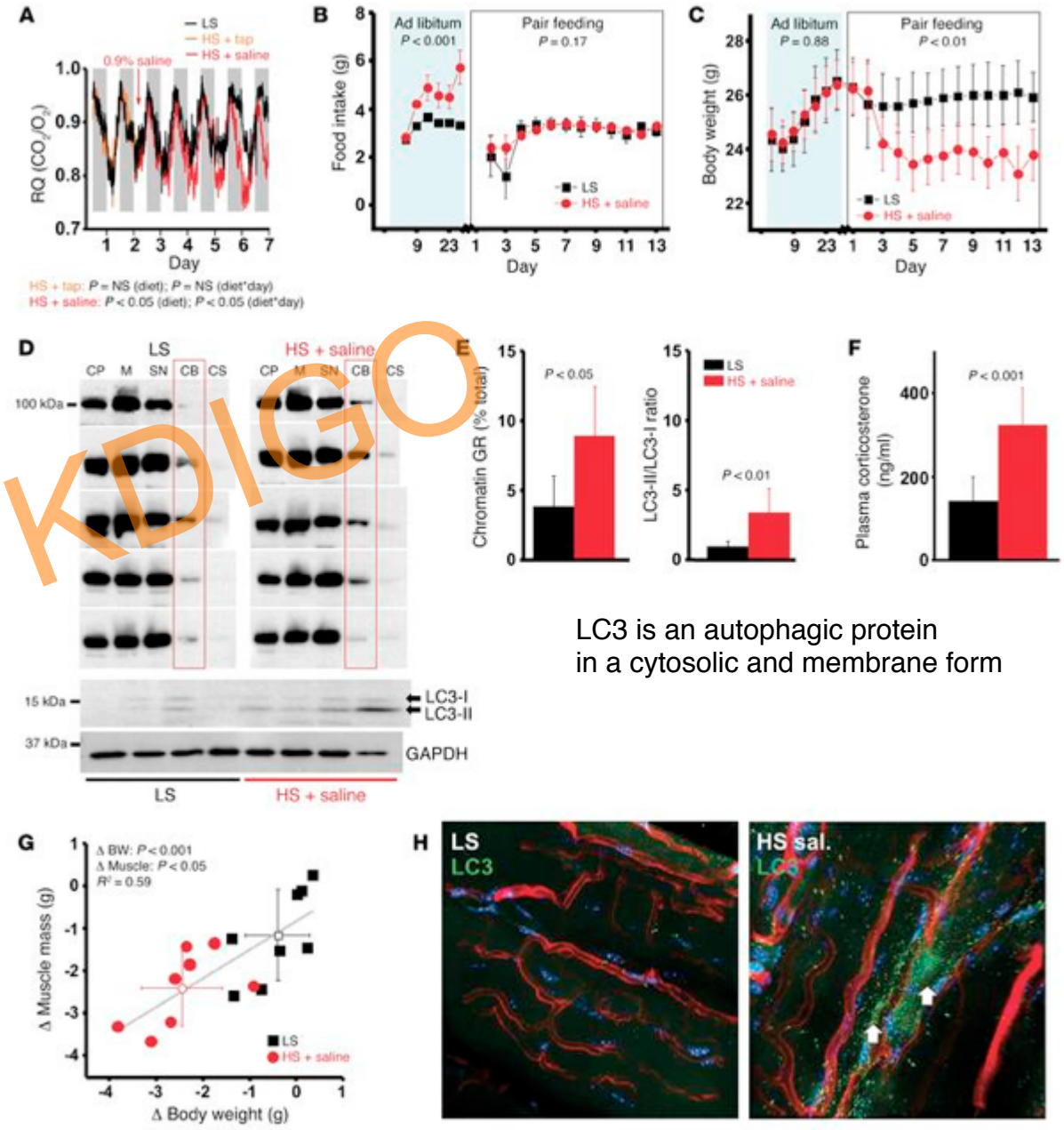
Option to increase food intake

Conversion to urea production

GR bound to cytoplasm (CP), membrane (M), soluble fraction (SN), chromatin-bound (CB), cytoskeletal (CS).

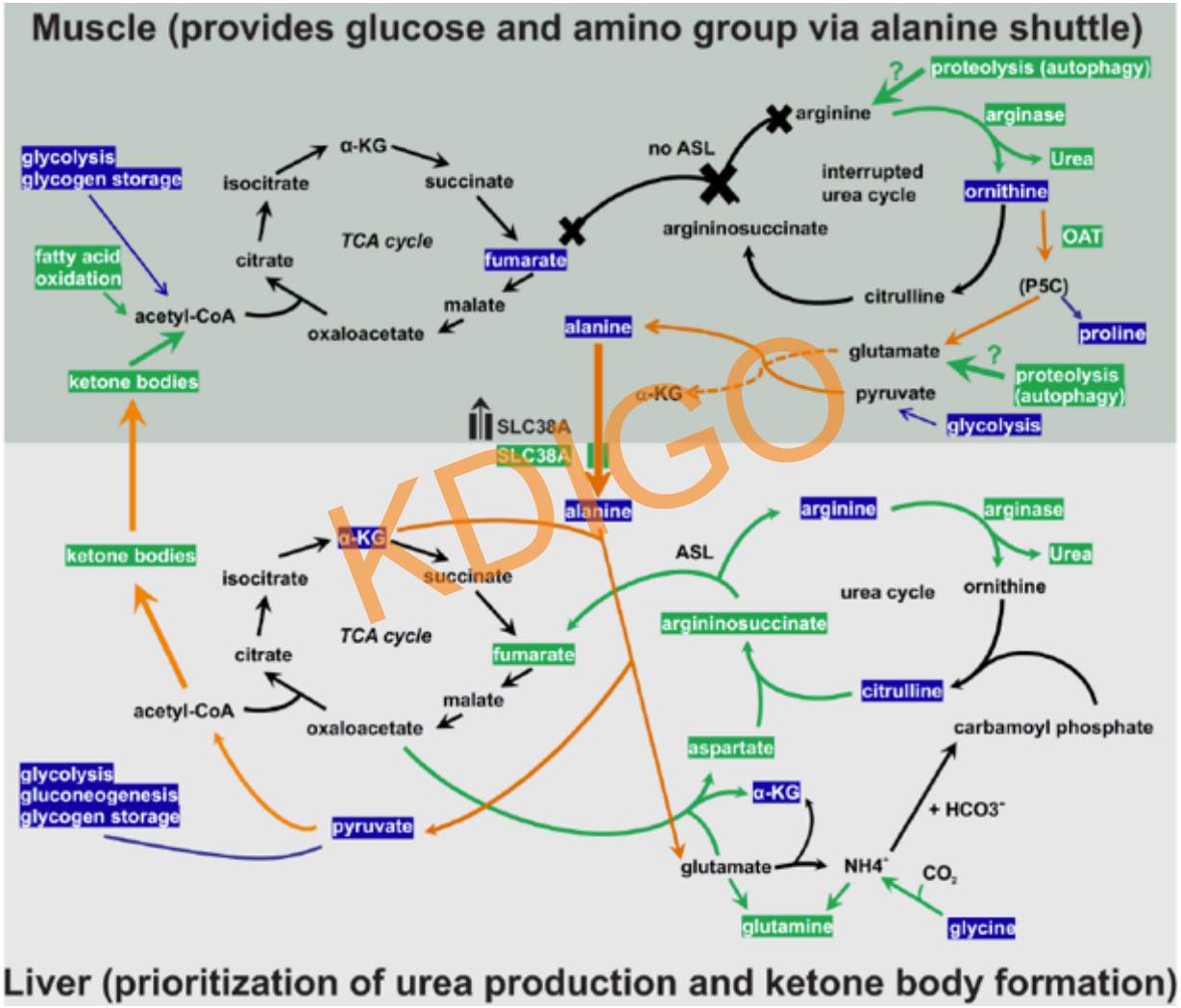
Apoptosis in framework of catabolism

Salt intake reprioritizes osmolyte and energy metabolism



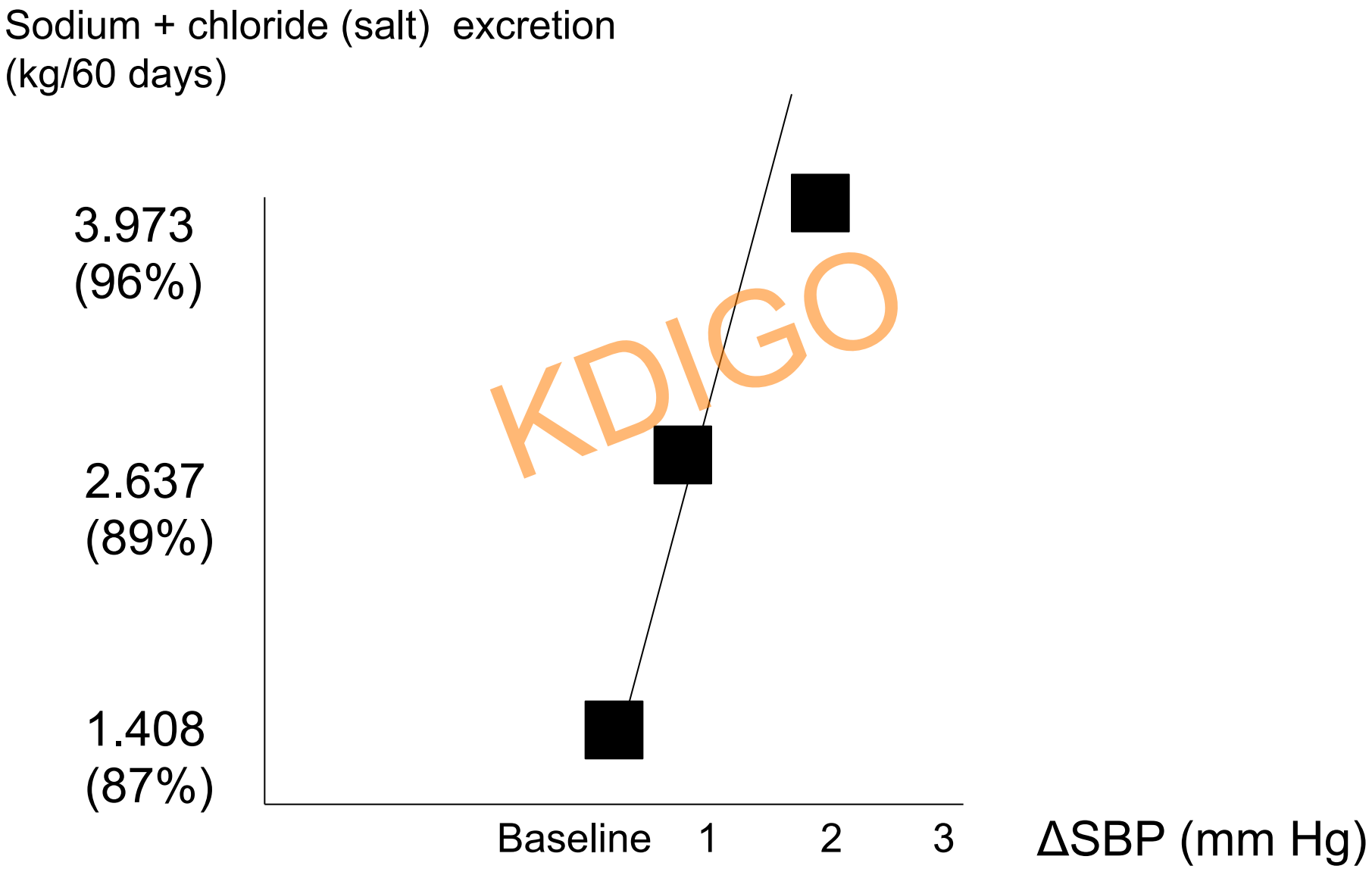
LC3 is an autophagic protein in a cytosolic and membrane form

HSD reprioritizes osmolyte and energy metabolism for body fluid conservation.

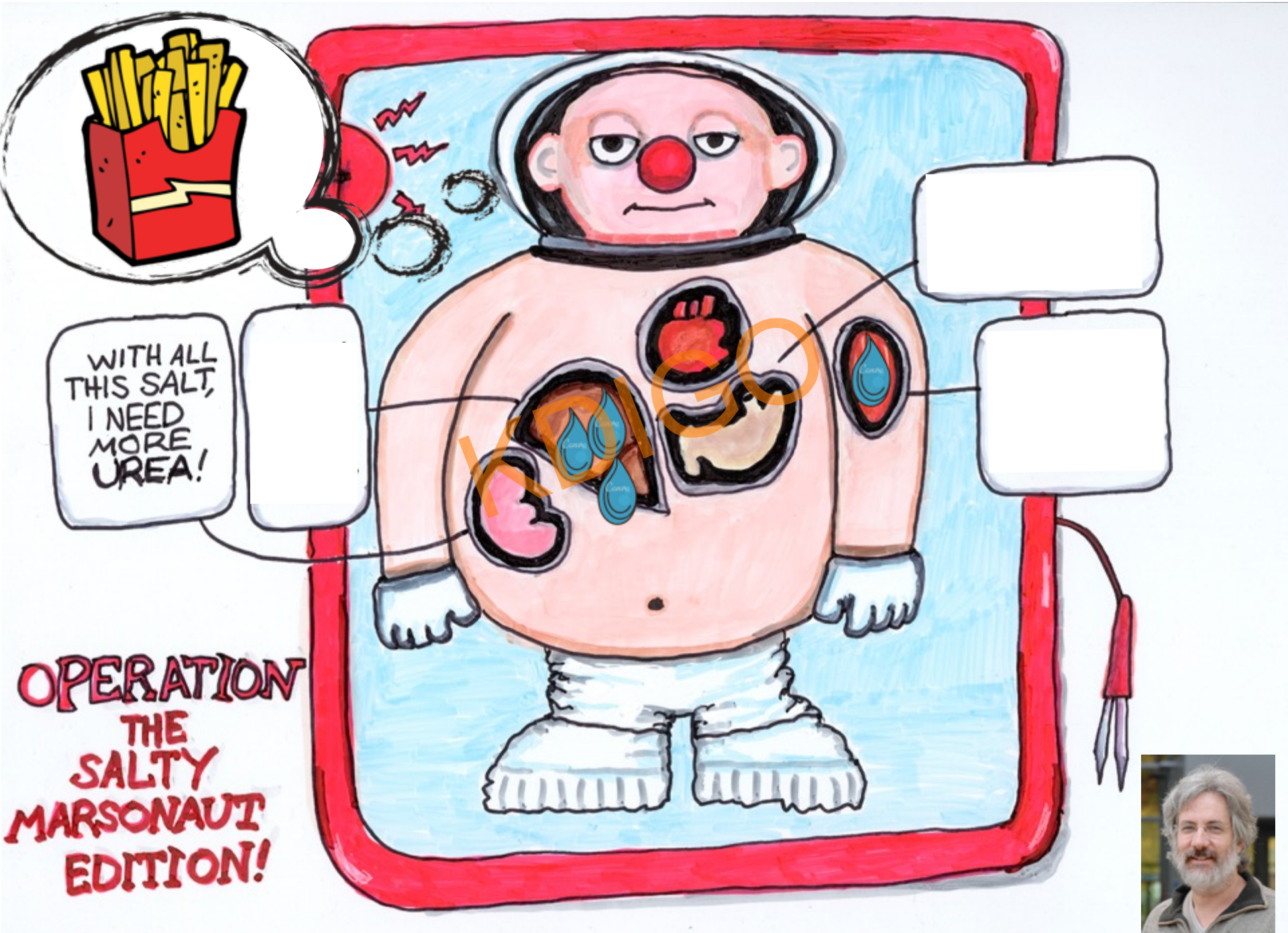


Muscle in HS+saline mice increases urea production and transfers nitrogen and glucose via the alanine-glucose-nitrogen shuttle to the liver, where alanine is taken up by increased active transport and preferentially metabolized to urea.

Renal-pressure natriuesis may take a very long time ∝




ALL YOU CAN EAT PEANUTS!!!
BEER = $50.00 a BOTTLE!
TOUCH THOSE AND YOU'LL BE ON A FAST TRACK TO ALCOHOLICS ANONYMOUS -AND A LONG TRACK TO WEIGHT WATCHERS!!
KDIGO


WITH ALL THIS SALT, I NEED MORE UREA!
OPERATION THE SALTY MARSONAUT EDITION!

Where do we go from here?

- On the Mars500 subjects we have AM and PM BPs every day (4000 BP measurements). These have not been evaluated. Is UNaV dominant or is it UNa alone, or free-water clearance?

- PDE3A mutations cause solely generalized vasoconstriction (salt-resistant hypertension).

- We have new patient mutations and other clinical data.

- Mouse and rat models are coming.

- We will re-define pressure natriuresis.