Ετήσιο μετεκπαιδευτικό σεμινάριο

Υγρών, Ηλεκτρολυτών & Οξεοβασικής Ισορροπίας

Επιπτώσεις της οξέωσης στους μύες, τα νεύρα και το έντερο

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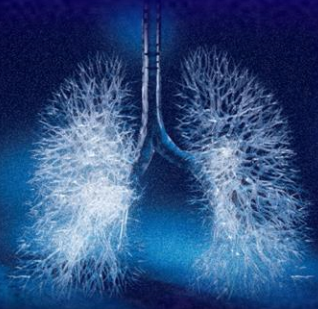
Νεφρολόγος
Γενικό Νοσοκομείο Χανίων


NO
CONFLICT OF
INTEREST

Μεταβολική οξέωση

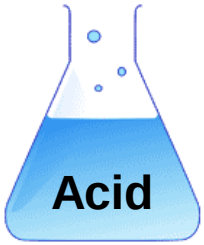
- Γαλακτική οξέωση
- Κετοξέωση
- Νεφρική ανεπάρκεια
- Διάρροια
- Νεφροσωληναριακές οξεώσεις
- Τοξίνες



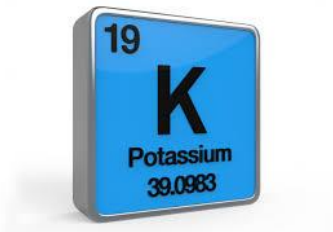

CO_2


O_2
Oxygen


KETONES
Do They Matter?


Acid


SPRING WATER
SPRING WATER
SPRING WATER


19
K
Potassium
39.0983


Acid

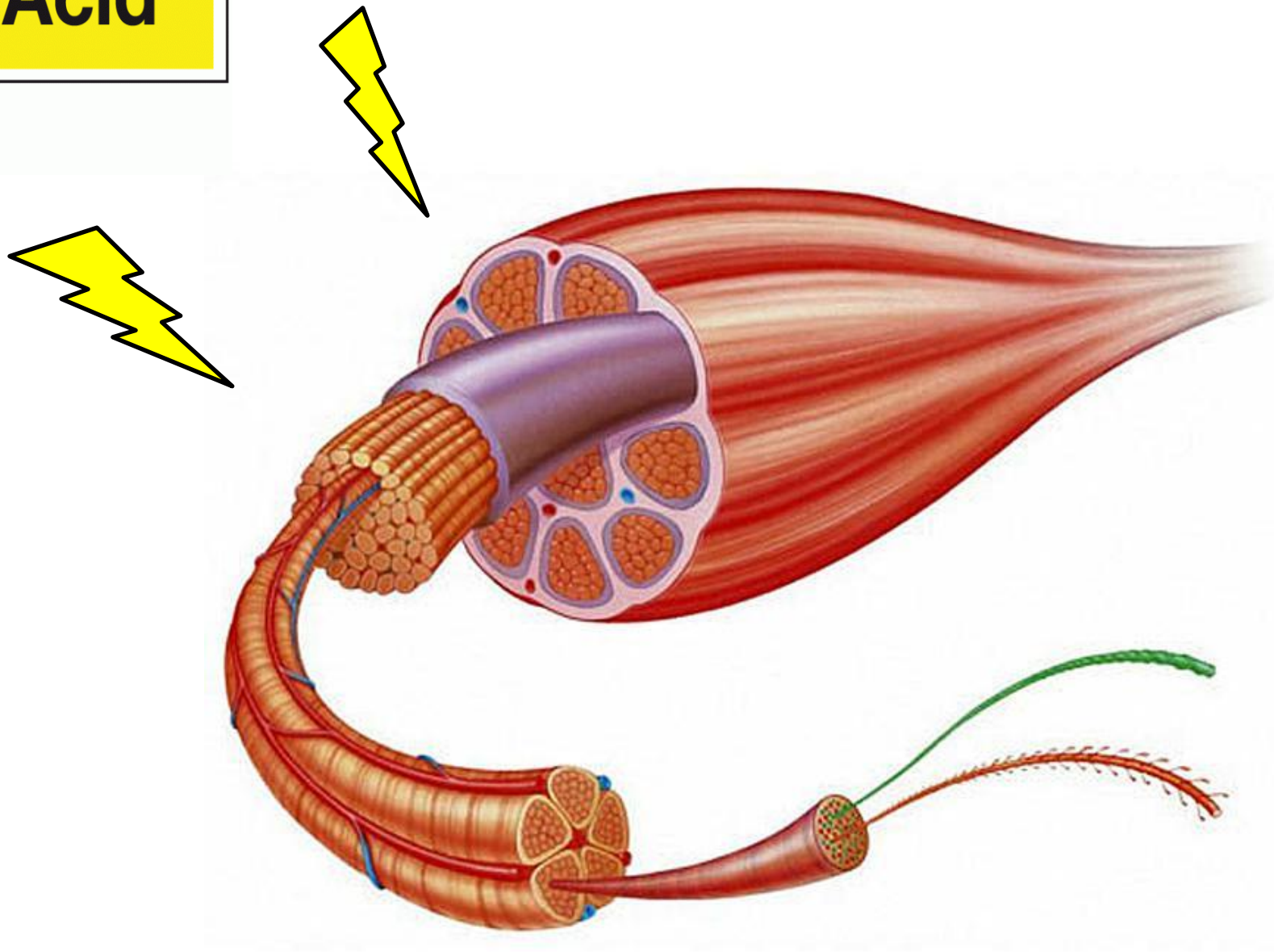


Table 3. Amino acid oxidation and protein turnover in adrenalectomized rats

	No supplements		Dexamethasone	
	Control	Acid	Control	Acid
Oxidation	6.2 ± 0.5	6.7 ± 0.7	7.4 ± 0.5	12.5 ± 0.8[a]
Protein degradation	37.7 ± 2.3	37.8 ± 3.9	34.6 ± 1.6	46.3 ± 3.3[a]
Protein synthesis	31.2 ± 2.0	31.1 ± 3.6	27.2 ± 1.2	33.8 ± 2.8

Components of leucine turnover are expressed as μmol leu/100 g wt/hr. Results (mean ± SEM) are from at least 7 animals in each group. All values were calculated based on plasma leucine specific activity.

May et al, Kidney Int 1996

Table 2. *FSR, RNA content, and K_{RNA} in different muscles of control and acidotic rats*

	FSR, %/day		RNA Content, mg/g		K_{RNA}, g·day^{-1}·g RNA^{-1}	
	Control	Acidosis	Control	Acidosis	Control	Acidosis
Gastrocnemius	4.34±0.16	3.10±0.22*	4.53±0.34	4.90±0.23	9.95±1.09	6.35±0.42*
Plantaris	5.04±0.13	3.86±0.19*	4.66±0.17	4.97±0.17	10.93±0.48	7.76±0.25*
Soleus	7.51±0.19	6.25±0.25*	7.67±0.18	7.57±0.29	9.72±0.16	8.24±0.31*

Values are means ± SE; $n = 8$. FSR, protein synthesis rates. RNA content is expressed as RNA-to-protein ratio; K_{RNA}, FSR per unit of RNA. Acidosis was induced by administration of NH_4Cl, and FSR were measured with the flooding method after 24 h (*experiment 2*). *Significantly different from control, $P < 0.01$.

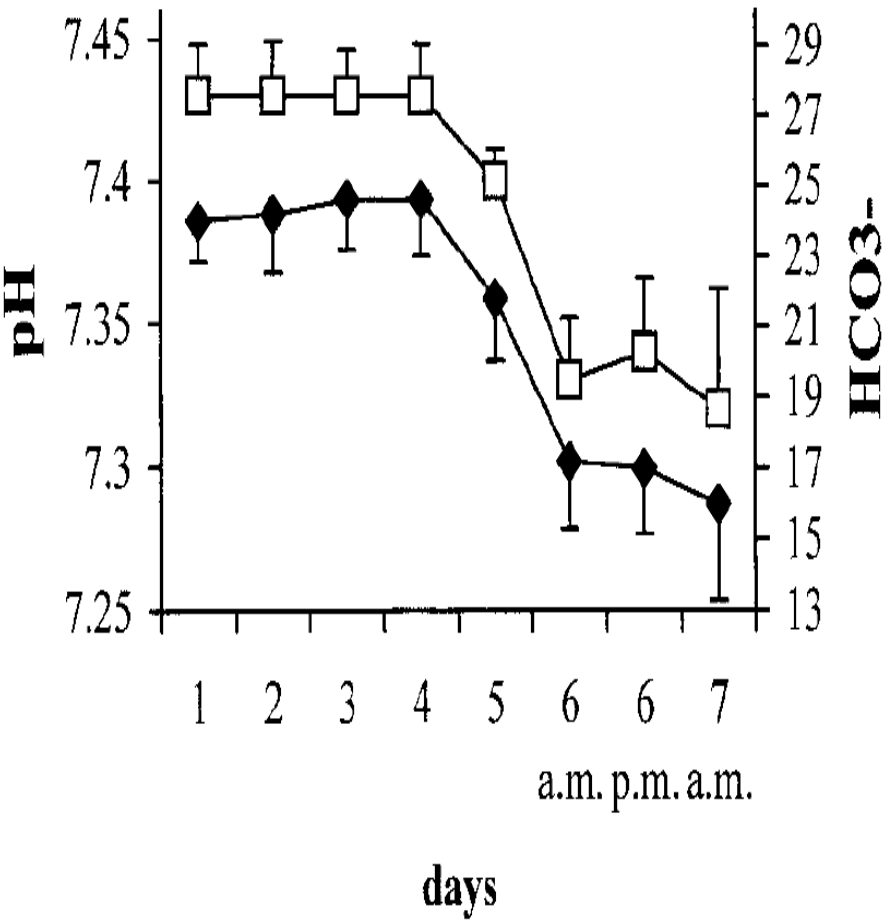
Table 3. *FSR in skeletal muscle, heart, and liver of control and acidotic rats*

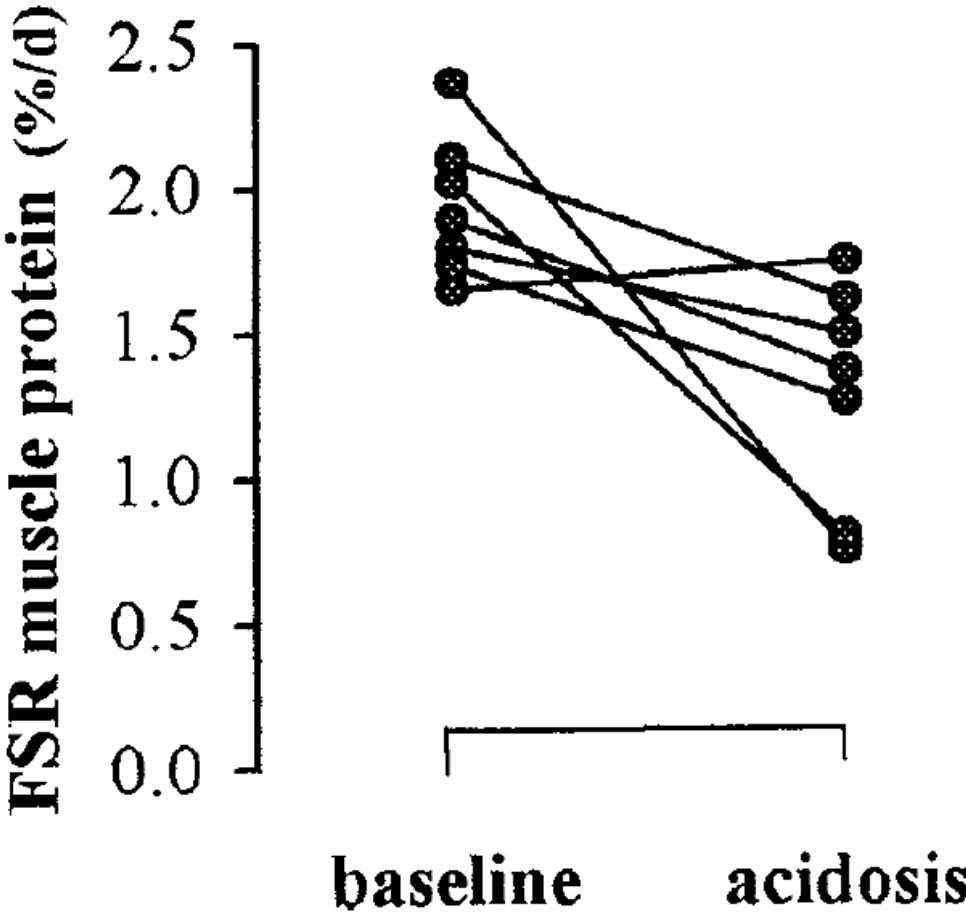
	FSR, %/day				
	Gastrocnemius	Plantaris	Soleus	Heart	Liver
Control	5.52±0.36	6.20±0.21	10.10±0.33	12.15±0.37	82.97±5.73
Acidosis	3.98±0.17*	5.05±0.21*	9.50±0.3	11.64±0.33	71.85±2.75

Values are means ± SE; $n = 6$. Acidosis was induced by administration of NH_4Cl, and FSR were measured with the constant infusion method after 24 h (*experiment 3*). *Significantly different from control, $P < 0.02$.

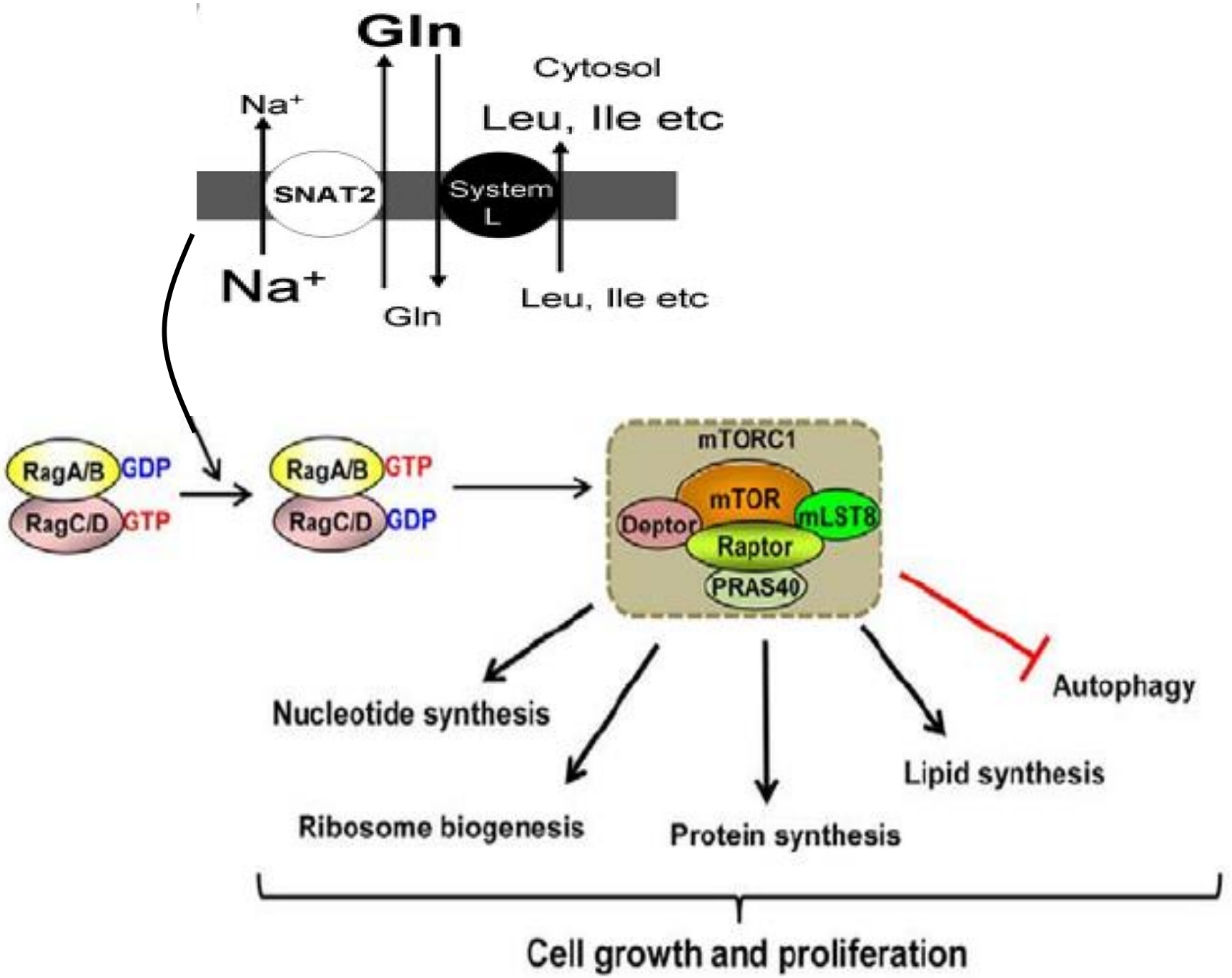
Caso et al, Am J Physiol Endocrinol Metab 2004

7 υγιείς εθελοντές





Kleger et al, Am J Kidney Dis 2001


Gln
Cytosol
Na+
Leu, Ile etc
SNAT2
System L
Na+
Gln
Leu, Ile etc
RagA/B GDP
RagC/D GTP
RagA/B GTP
RagC/D GDP
mTORC1
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Deptor
mLST8
Raptor
PRAS40
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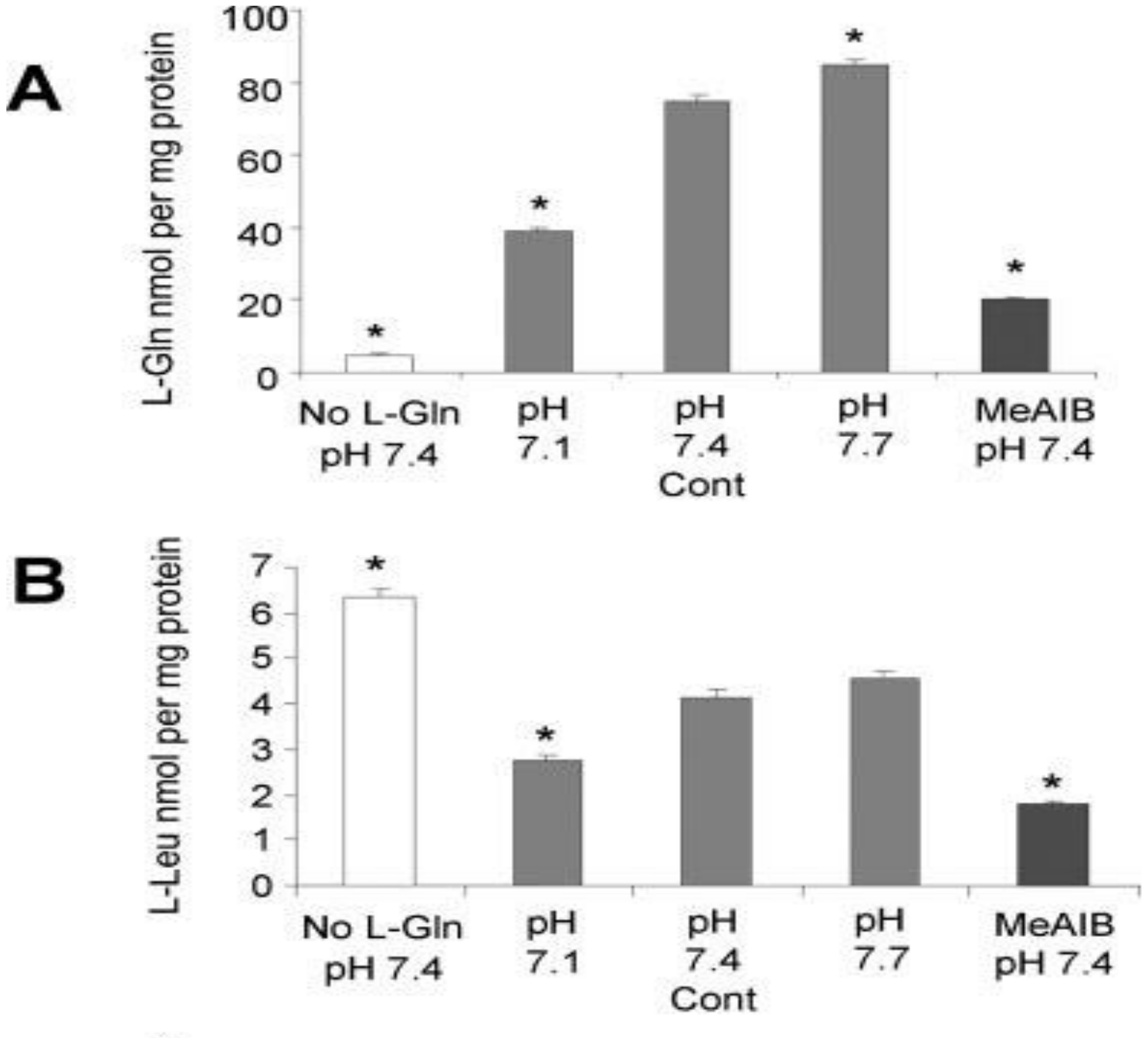
Lipid synthesis
Ribosome biogenesis
Protein synthesis
Cell growth and proliferation



Evans et al, J Am Soc Nephrol 2007

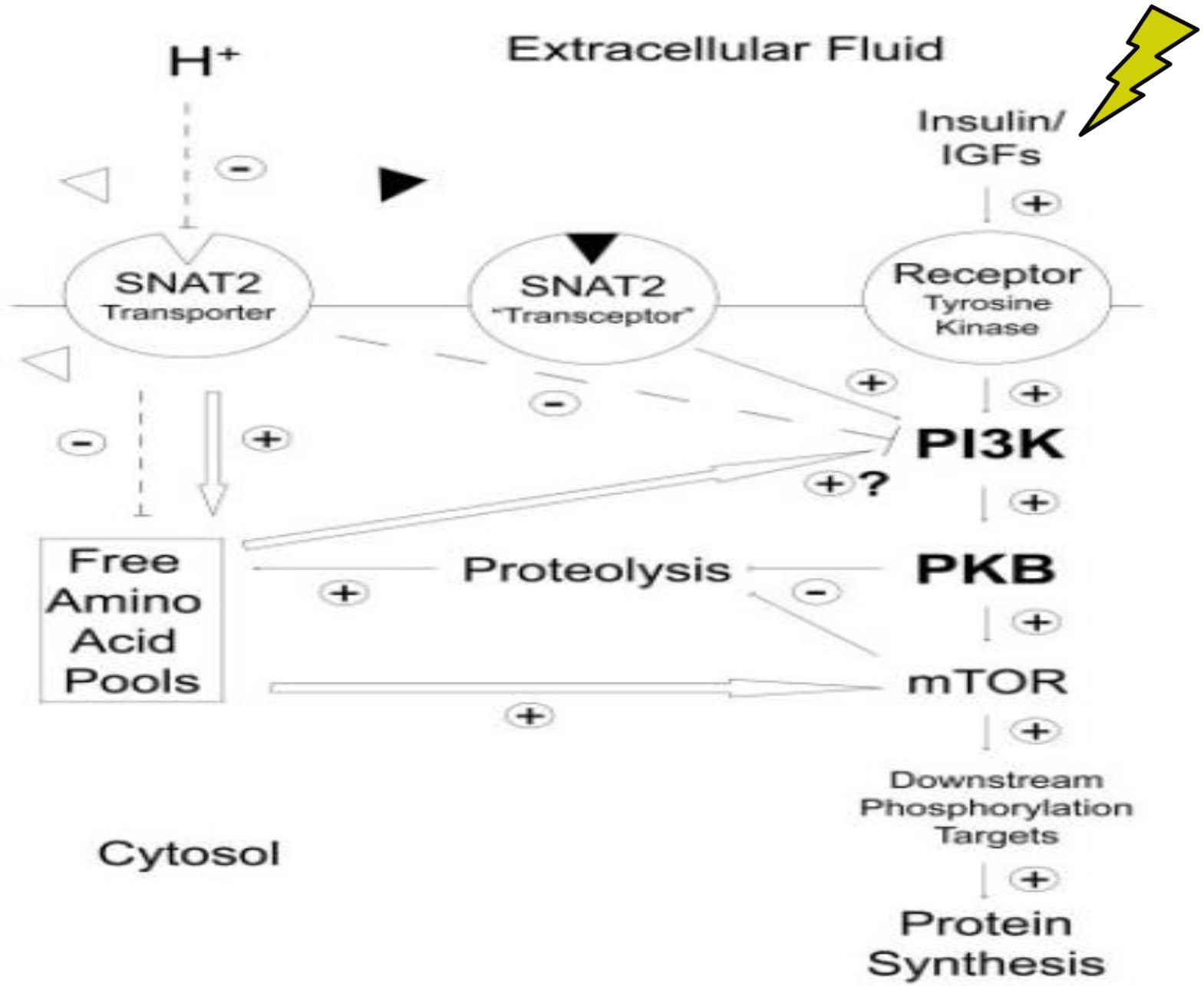
Parameter	Composition of the Experimental Medium (pH)			
	7.1	7.4 (Control)	7.7	7.4
L-Gln (mmol/L)	2	2	2	2
MeAIB (mmol/L)	0	0	0	10
Total protein t = 28 h				
μg/35-mm well	174 ± 17	212 ± 11	195 ± 15	165 ± 18[b]
% of pH 7.4 control value	81 ± 6[b]	100	92 ± 5	77 ± 7[b]
Protein synthesis rate t = 24 to 28 h				
nmol L-Phe/mg protein in 4 h	8.8 ± 0.3[c]	9.9 ± 0.5	10.3 ± 0.3	8.15 ± 0.12[b]
% of pH 7.4 control value	89 ± 3[b]	100	104 ± 3	82 ± 1[b]
Protein degradation rate t = 26 to 33 h				
$\log_{10}$%/h × 10^3	10.8 ± 0.9	10.5 ± 0.9	10.4 ± 1.1	13.6 ± 1.0
% of pH 7.4 control value	102 ± 2	100	98 ± 2	130 ± 2[b]
Intact protein leakage (cell damage indicator) t = 26 to 33 h				
% per h	0.13 ± 0.01	0.16 ± 0.01	0.17 ± 0.02	0.15 ± 0.02
% of pH 7.4 control value	80 ± 8	100	102 ± 8	94 ± 8

[a]Pooled data from three experiments are shown (with three replicate culture wells for each treatment). Cells were incubated in the experimental medium (MEM + 2% dialyzed FBS with the additions stated) for 24 h. All measurements were then made in parallel at the times (t) indicated using fresh samples of the same experimental medium.

[b]$P < 0.05$ *versus* pH 7.4 control.

[c]$P < 0.05$ *versus* pH 7.7.

Evans et al, J Am Soc Nephrol 2007



Evans et al, J Am Soc Nephrol 2008

Table 1. Characteristics of control and NH_4Cl-gavaged acidotic rats

	Control	Acidotic
Blood pH	7.36±0.00	6.93±0.04*
Blood bicarbonate, mmol/l	26.2±0.91	10.7±1.23*
Initial body weight, g	129±4	127±4
Body weight change, g	−1±1	−16±2*
Extensor digitorum longus w.t., mg	45±1	41±1*
Plantaris w.t., mg	224±7	198±6*

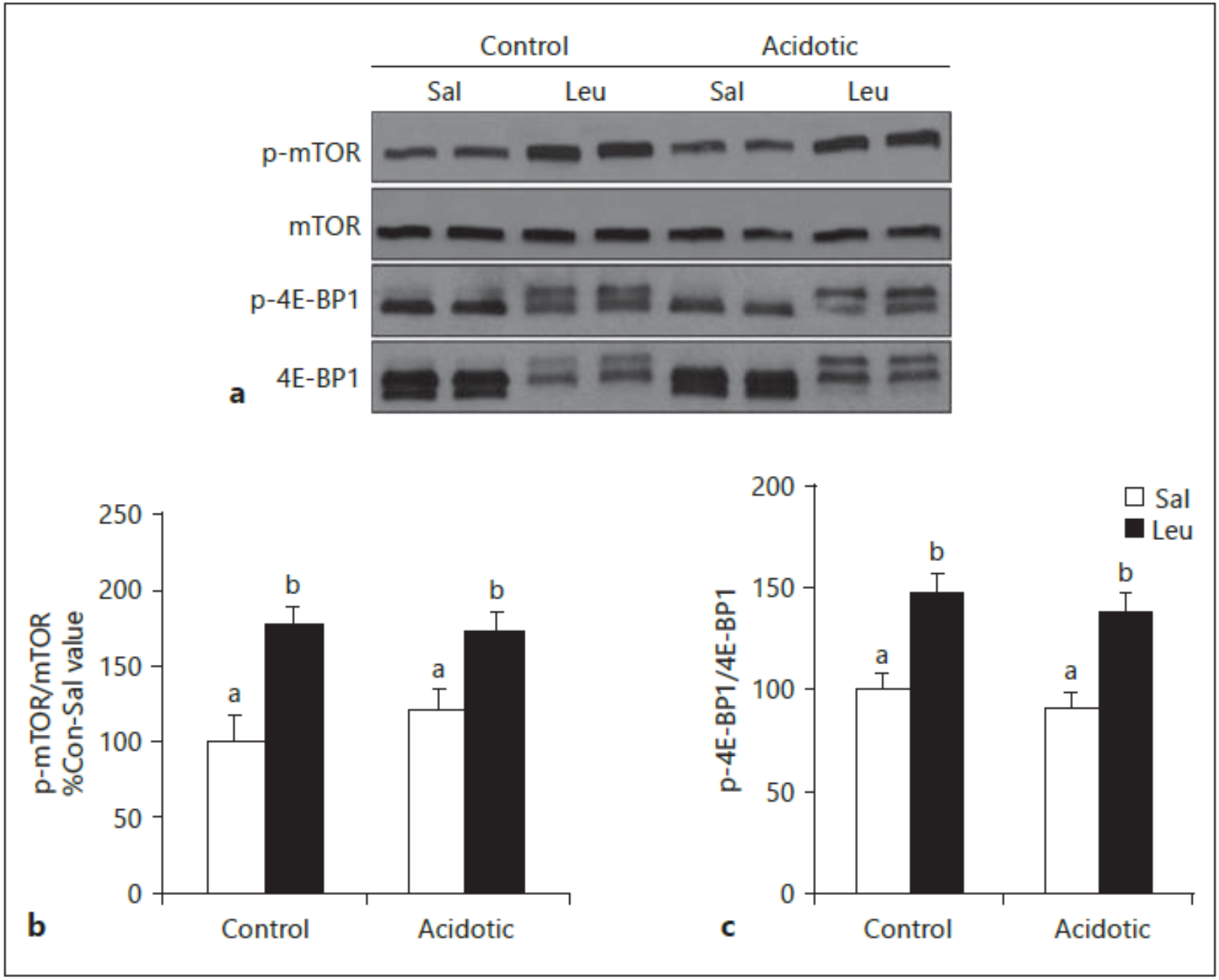
* $p < 0.01$, acidotic vs. control group. n = 7/group.

Table 2. Concentrations of leucine and insulin in plasma of control and acidotic rats gavaged with saline or leucine

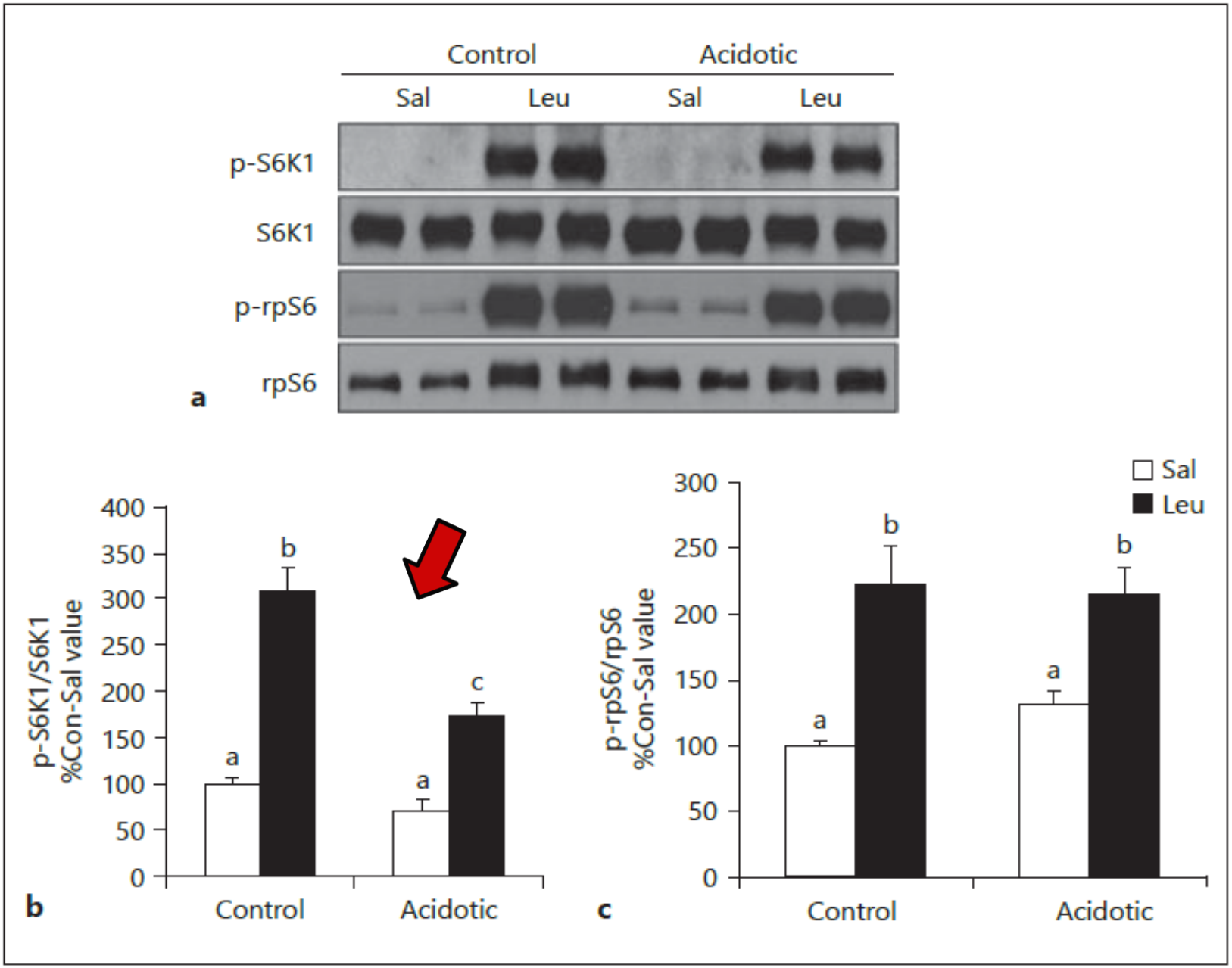
	Saline		Leucine	
	control	acidotic	control	acidotic
BCAA, nmol/ml	336±32[a]	426±71[a, c]	1,581±251[b]	1,011±90[d]
Insulin, pmol/l	26±7[a]	156±27[b]	87±25[b]	292±68[b]

Dissimilar superscript letters indicate a significant difference between groups ($p < 0.05$); groups with common letters are similar.

Sood et al, Am J Nephrol 2014

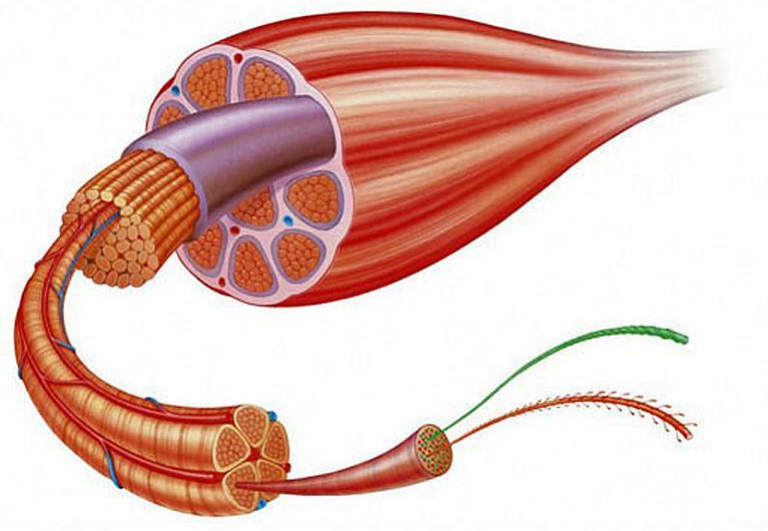


Sood et al, Am J Nephrol 2014



Sood et al, Am J Nephrol 2014

IN VITRO



IN VIVO

Table 1 | Arterial insulin concentrations (μU/ml) in patients with chronic kidney disease (CKD) and in controls in the baseline and during insulin infusion

	Insulin infusion rate (mU/kg per min)								
	0.01					0.035			
	0	80	100	120		0	80	100	120 min
Controls ($n=5$)	6±1	22±4[a]	28±3[a]	30±1[a]	Controls ($n=7$)	7±1	47±4[a]	60±4[a]	62±3[a]
CKD ($n=5$)	8±1	26±2[a]	26±2[a]	29±2[a]	CKD ($n=7$)	10±2	44±3[a]	56±3[a]	59±3[a]

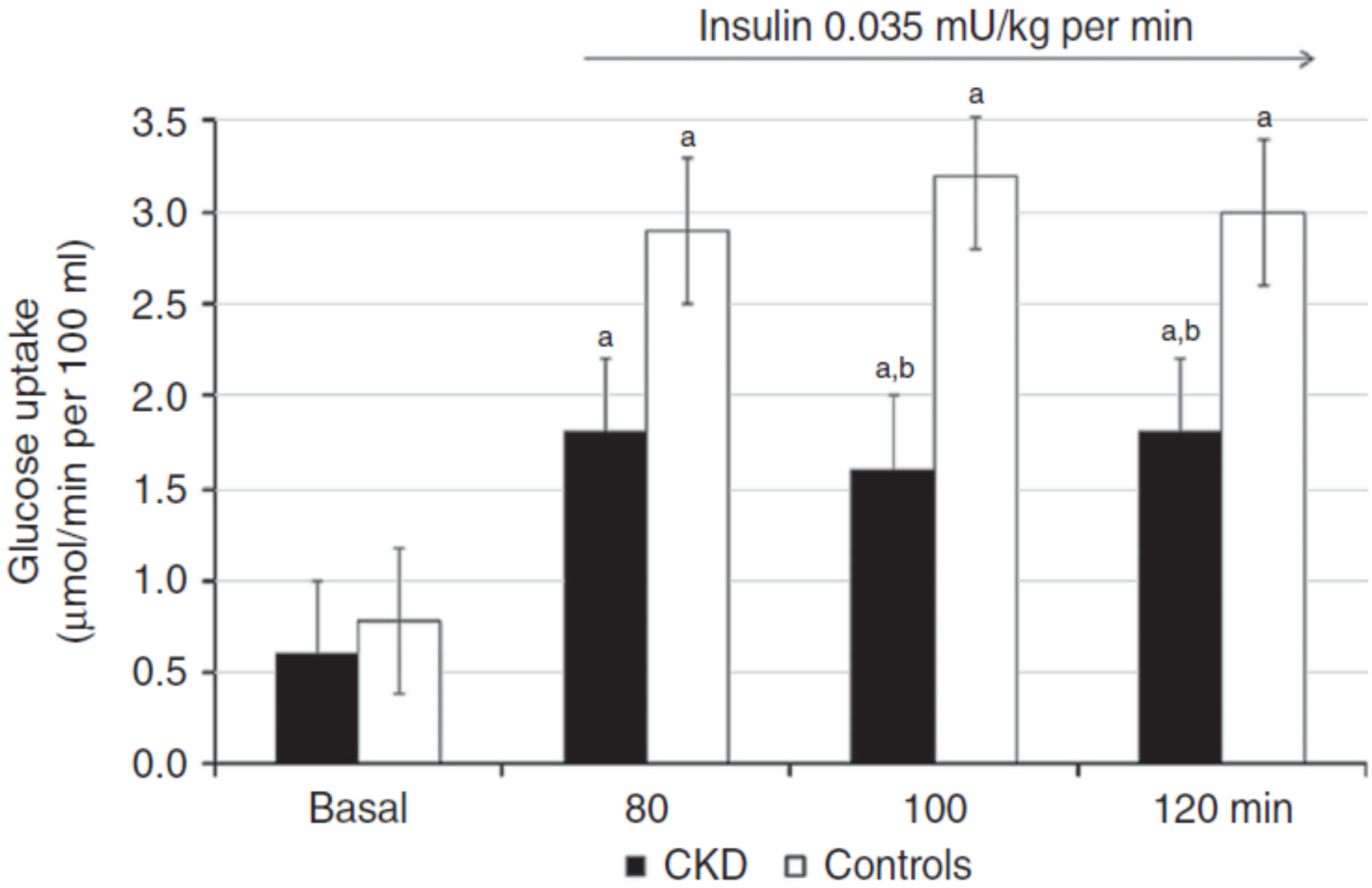
[a]$P \leqslant 0.05$ basal versus insulin-infused period.

Table 2 | Forearm blood flow (ml/min per 100 ml) in patients with chronic kidney disease (CKD) and in controls in the baseline and during insulin infusion

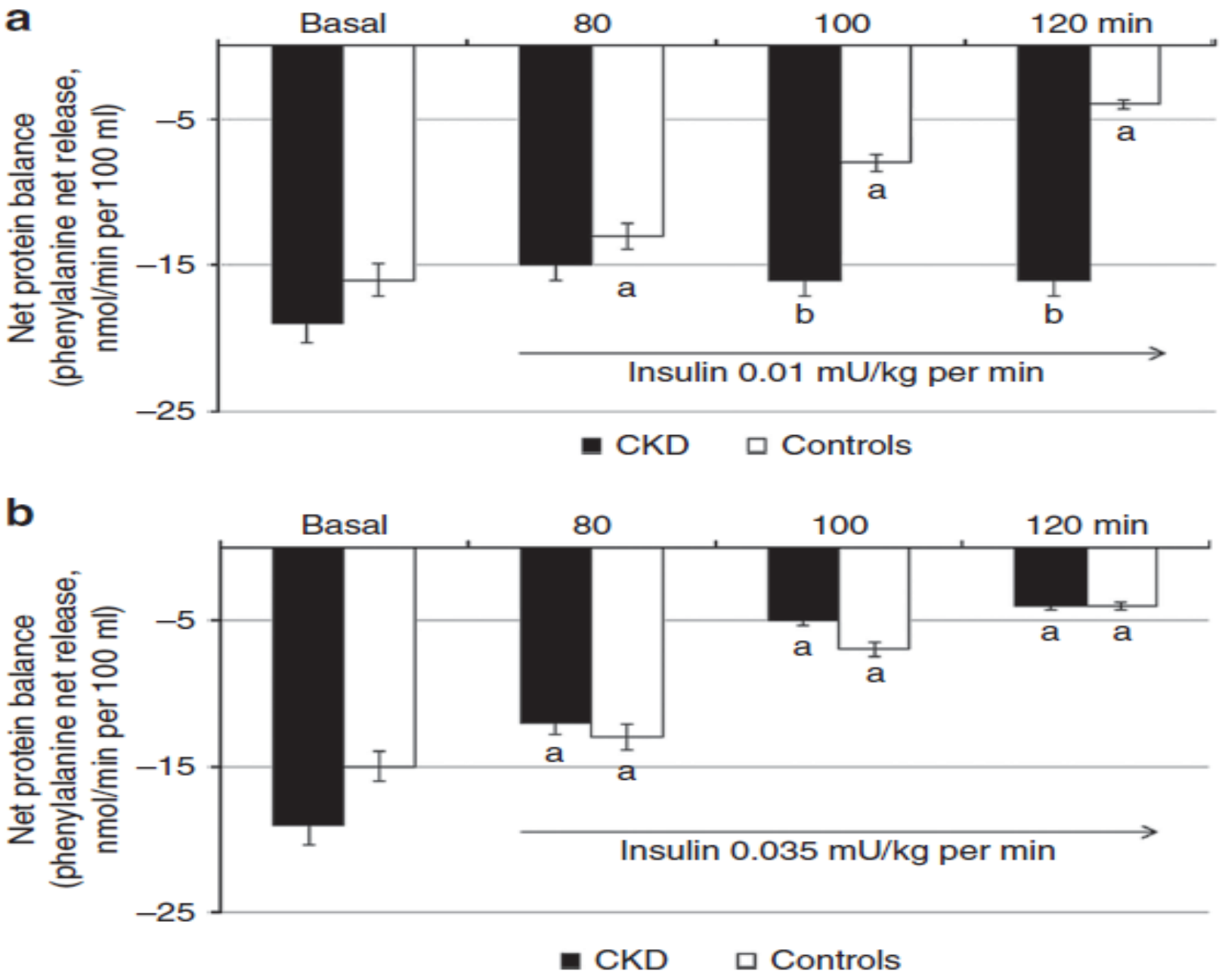
	Insulin infusion rate (mU/kg per min)								
	0.01					0.035			
	0	80	100	120		0	80	100	120 min
Controls ($n=5$)	3.5±0.2	3.7±0.1	3.6±0.2	3.7±0.2	Controls ($n=7$)	3.7±0.1	4.2±0.3	4.6±0.1[a]	4.7±0.2[a]
CKD ($n=5$)	4.1±0.2	4.0±0.2	3.8±0.26	4.0±0.3	CKD ($n=7$)	4.2±0.4	4.9±0.6	4.9±0.4[a]	5.1±0.4[a]

[a]$P \leqslant 0.05$ basal versus insulin-infused period.

Garibotto et al, Kidney Int 2015



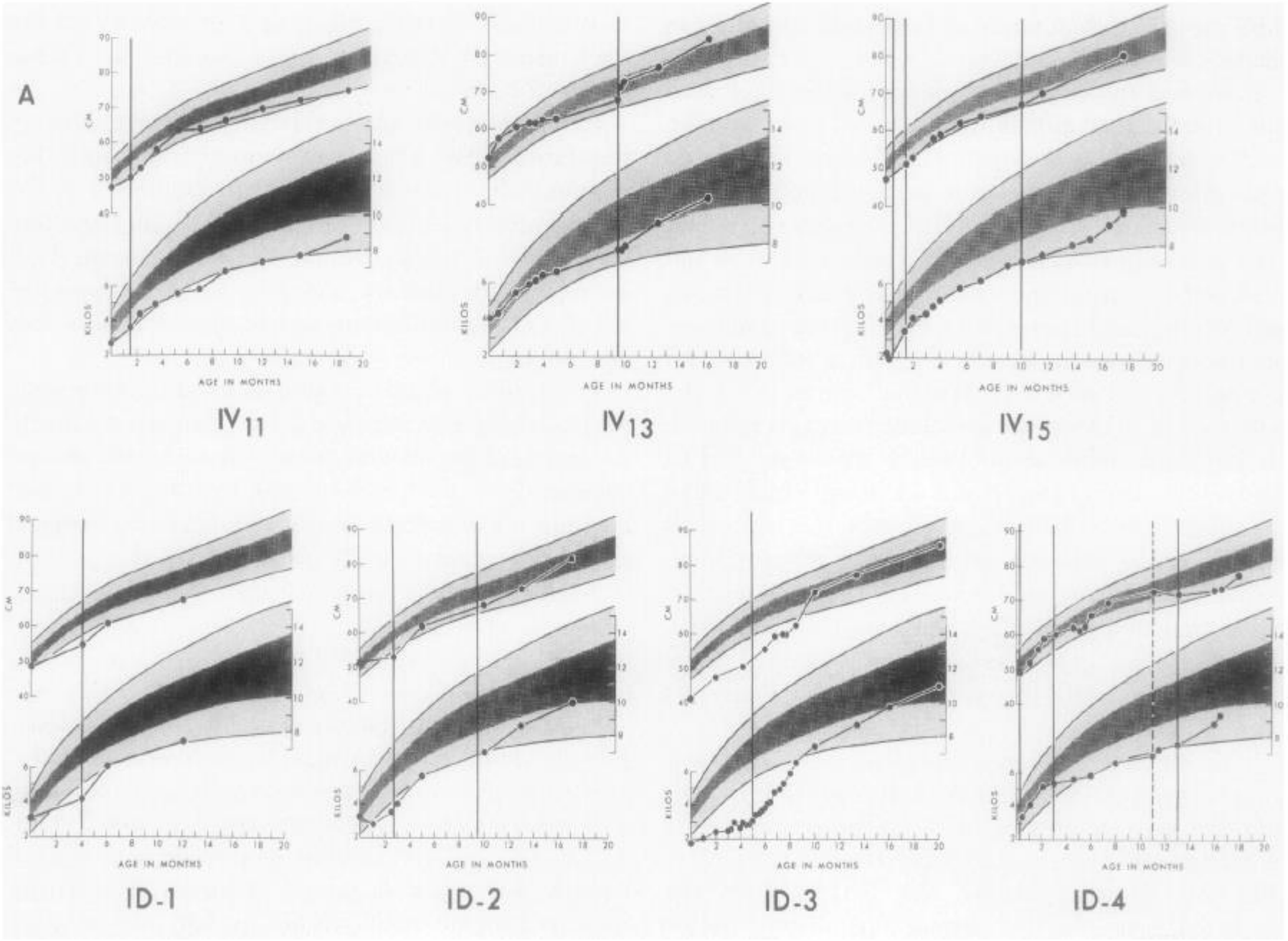
Garibotto et al, Kidney Int 2015



Garibotto et al, Kidney Int 2015

Attainment and Maintenance of Normal Stature with Alkali Therapy in Infants and Children with Classic Renal Tubular Acidosis

ELISABETH MCSHERRY and R. CURTIS MORRIS, JR., *Departments of Pediatrics and Medicine, University of California, San Francisco, California 94143*



McSherry & Morris, J Clin Invest 1978

CAPD

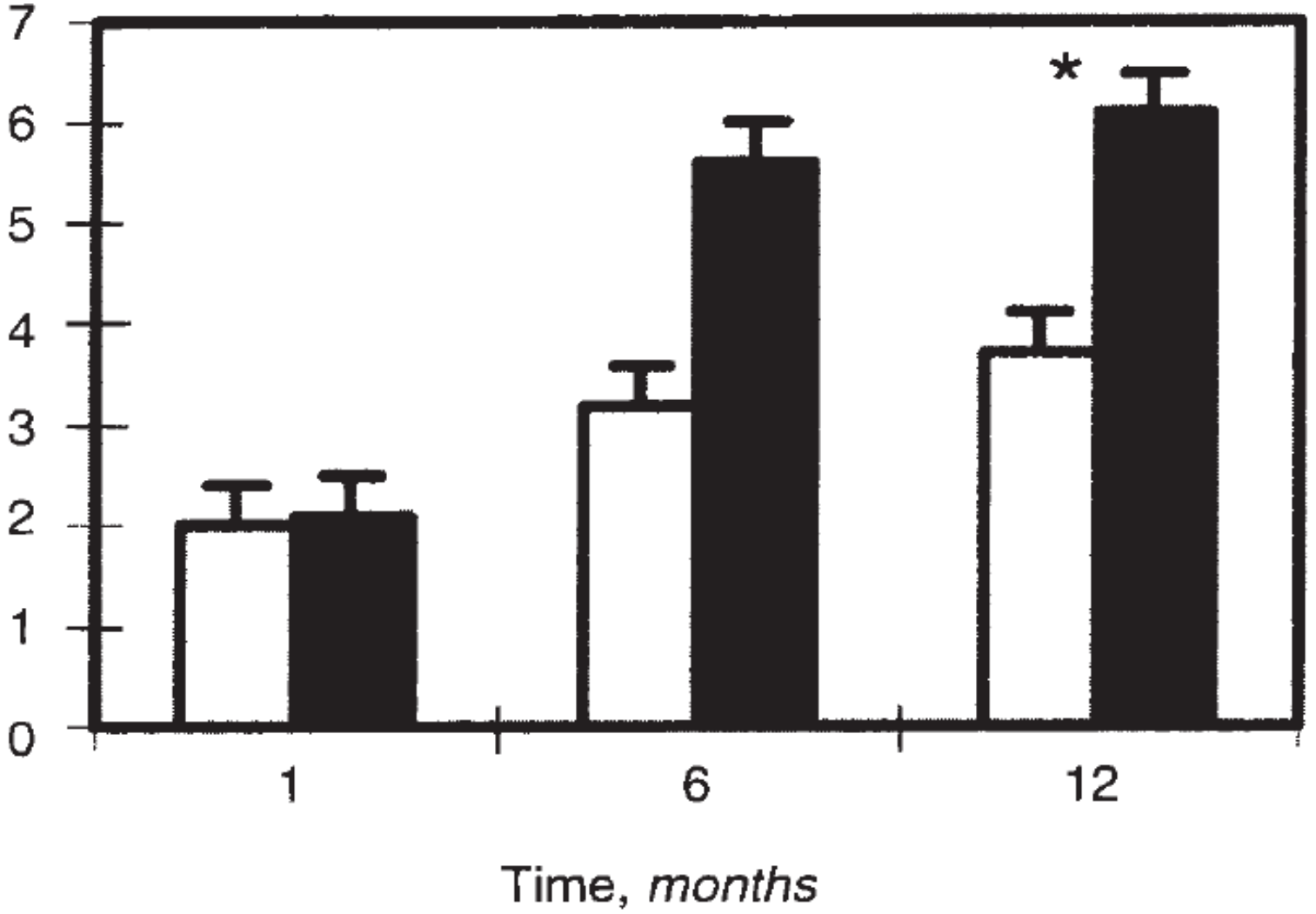


Fig. 2. Weight gain (kg) in high (■) and low (□) alkali groups (*$P < 0.05$).

Stein et al, Kidney Int 1997

CAPD

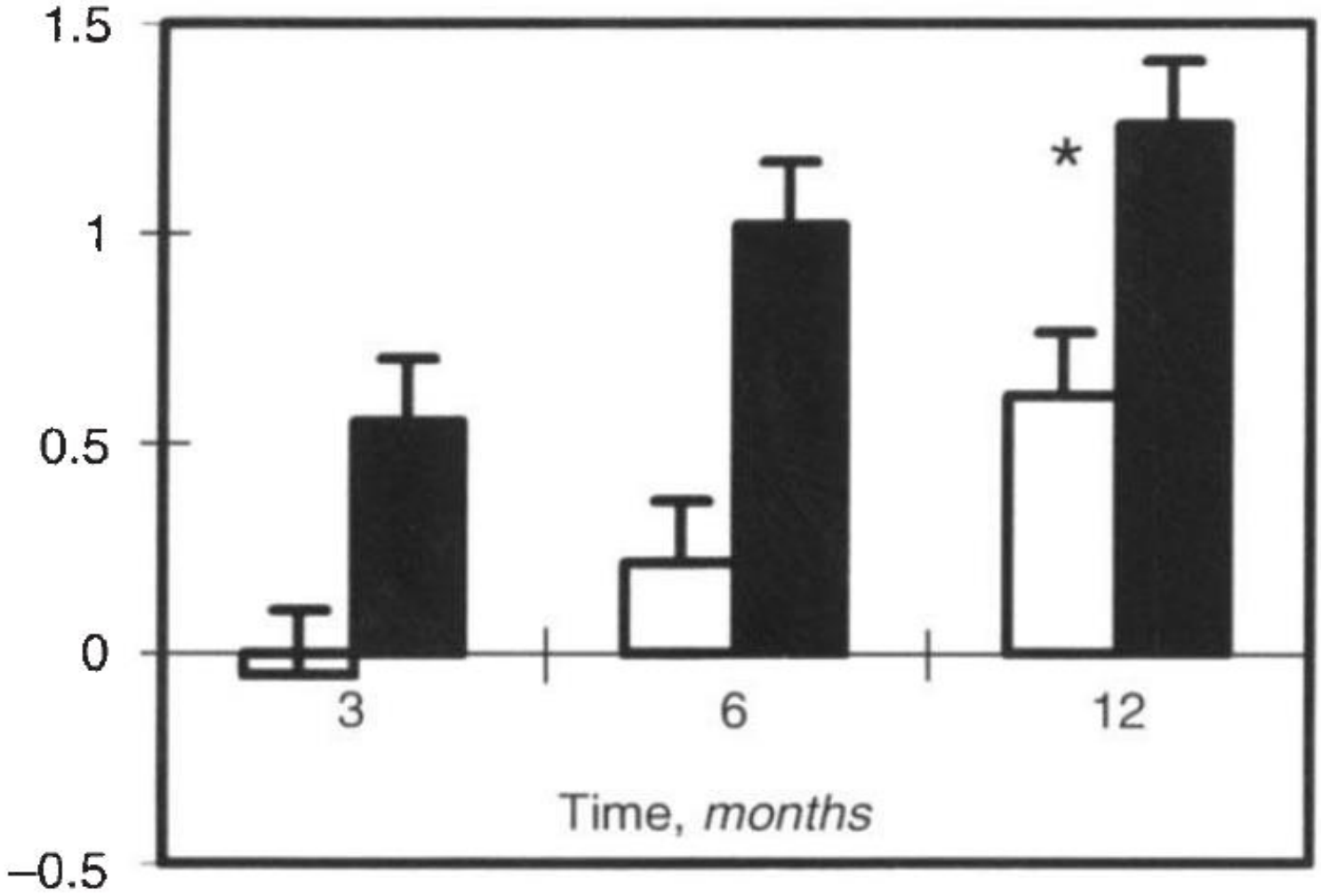
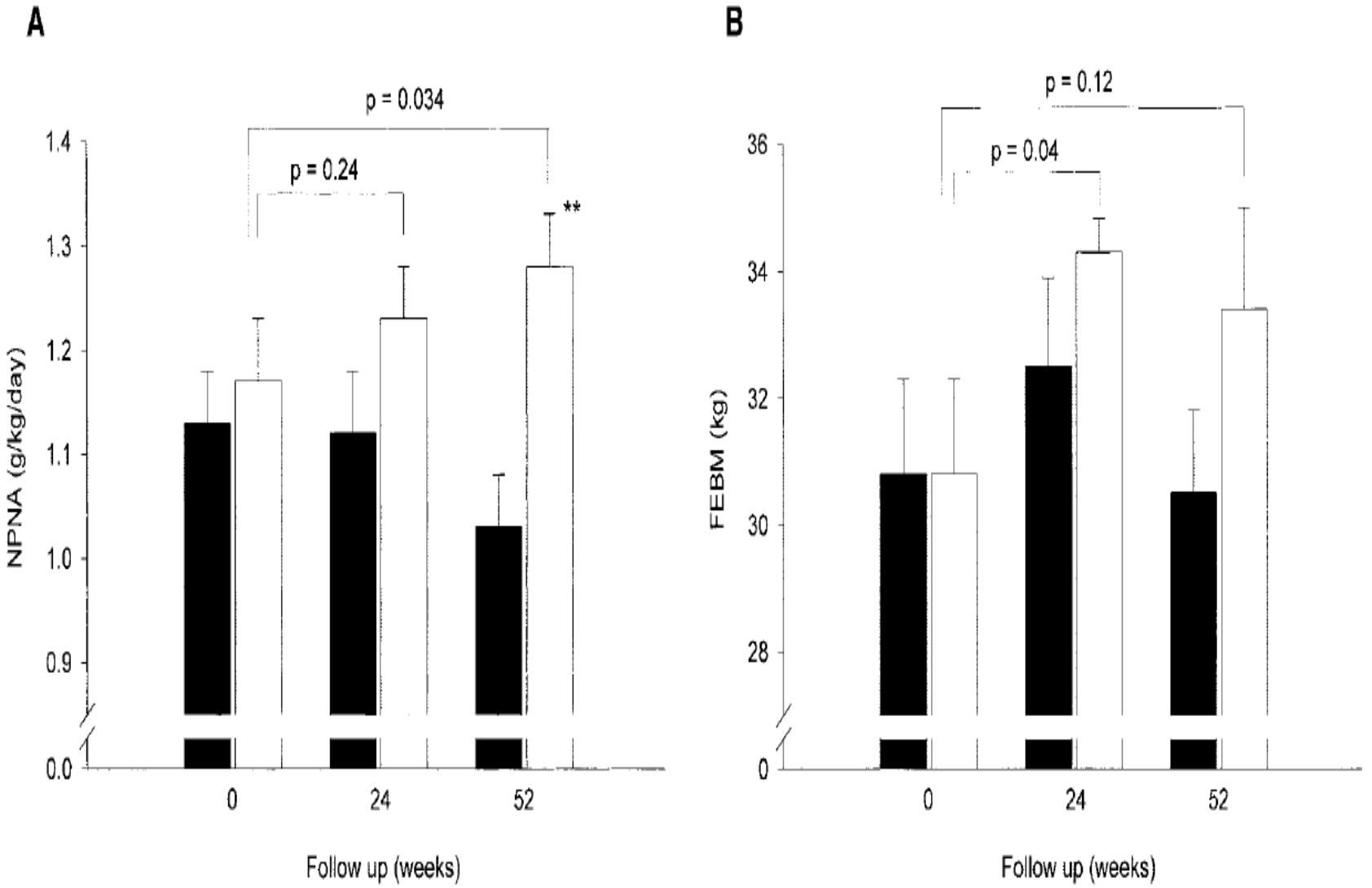


Fig. 3. Midarm circumference gain (cm) in high (■) and low (□) alkali groups (*$P < 0.05$).

Stein et al, Kidney Int 1997

CAPD

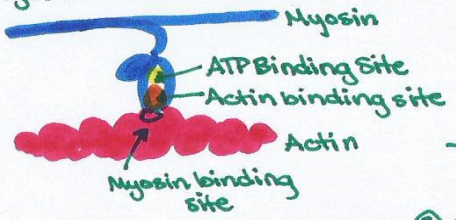


Szeto et al, J Am Soc Nephrol 2003

MUSCLE CONTRACTION

Calcium is the [illegible] ysiological trigger fo[illegible] a contraction

① Rigor Conformation
- Myosin head bound to actin w/o ATP



② ATP

in bind site
in bind site

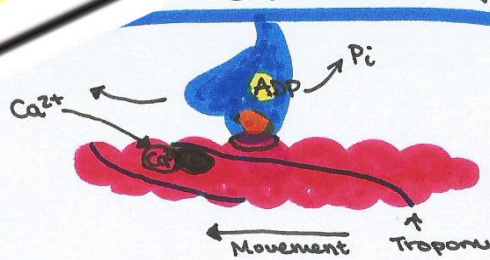
in
site)

[illegible] complex

⑥ ADP is released after the power stroke to put head back in rigor

⑤ Myosin binding to actin triggers Pi release and pow stroke of myosin head occurs

[illegible] used from the sarcoplasmic R.



[illegible] in

[illegible] drolyzes the ATP and Pi storing energy in myosin head

· Ca^{2+} binding to the troponin/tropomyosin complex causes a conformational change that reveals the actin binding site for the myosin head

* Many myosin [illegible] ads work together at once to move the muscle about 10nm at a time

AW 2013


Acid

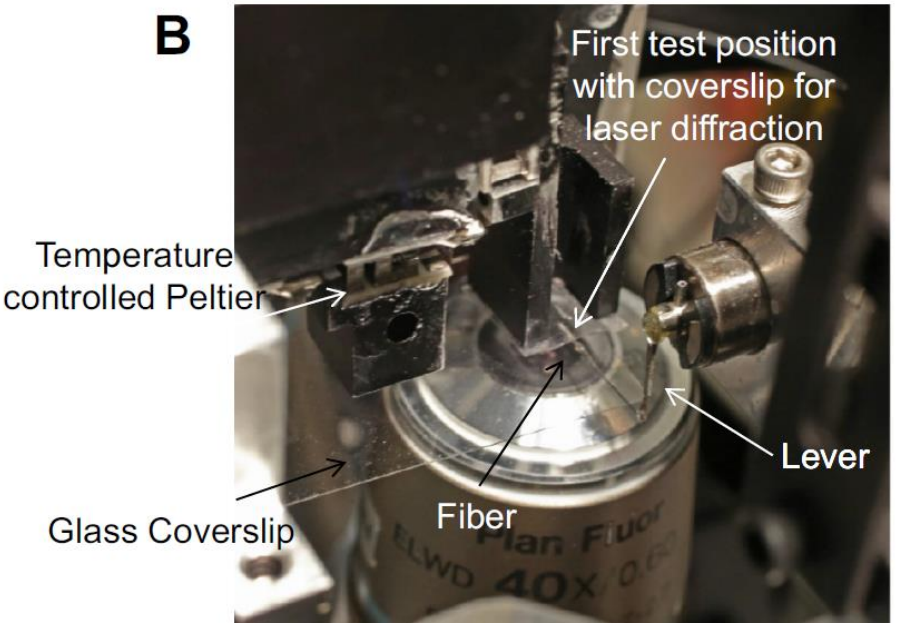
- **Μυϊκές συσπάσεις υψηλής έντασης οδηγούν σε μεγάλη πτώση του pH σε τιμές της τάξης του 6,2-6,3**

- **Η οξέωση συνέπεια έντονης μυϊκής δραστηριότητας δύναται να συσχετιστεί με το φαινόμενο του μυϊκού κάματου**

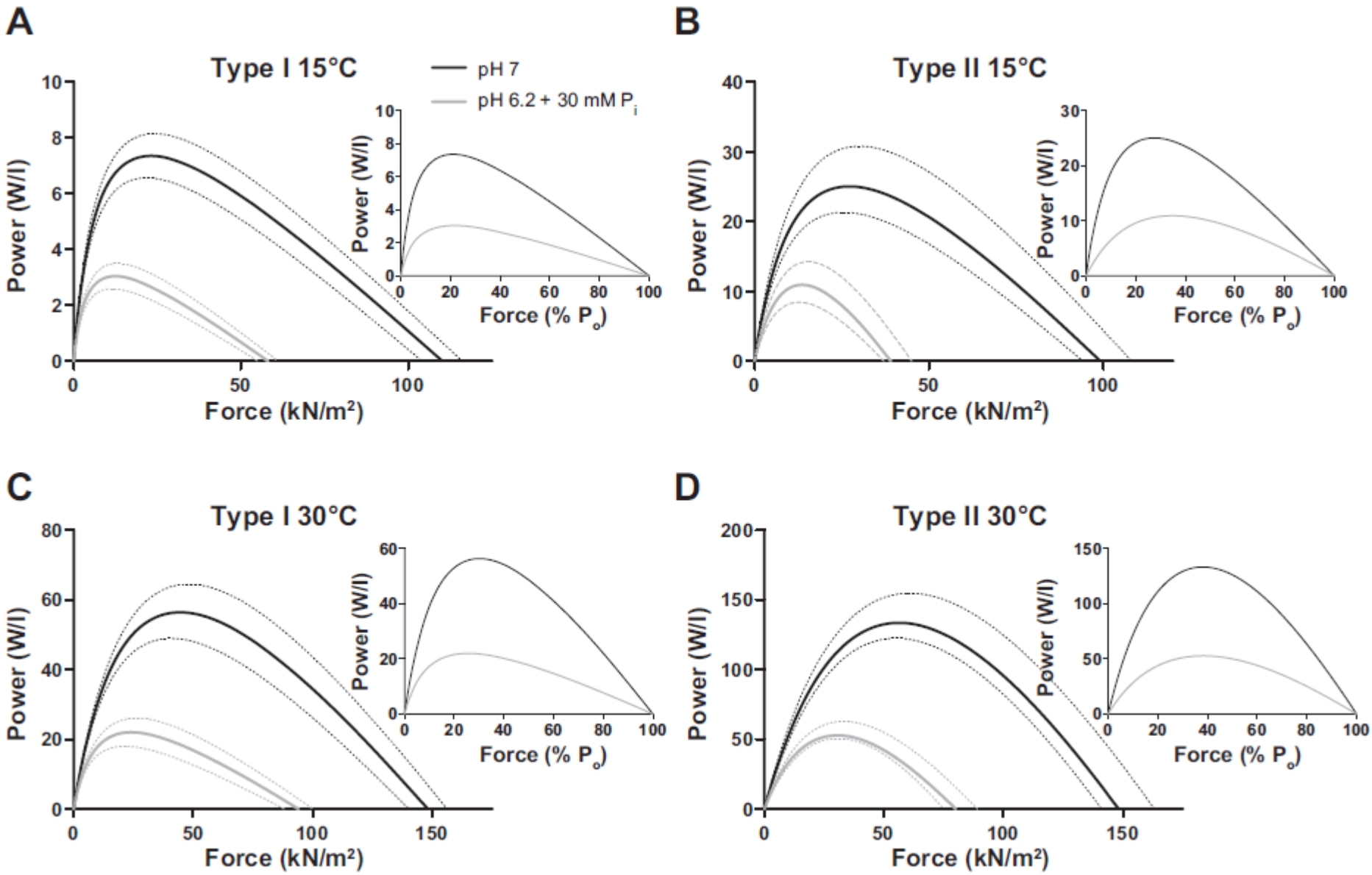
- **Η δυνατότητα του όξινου pH να προκαλεί μυϊκό κάματο επάγεται με τη συνδρομή άλλων παραγόντων, όπως η αυξημένη συγκέντρωση ανόργανου φωσφόρου και η ελαττωμένη ηλεκτροχημική κλίση του ασβεστίου**

Fitts, Med Sci Sports Exerc 2016

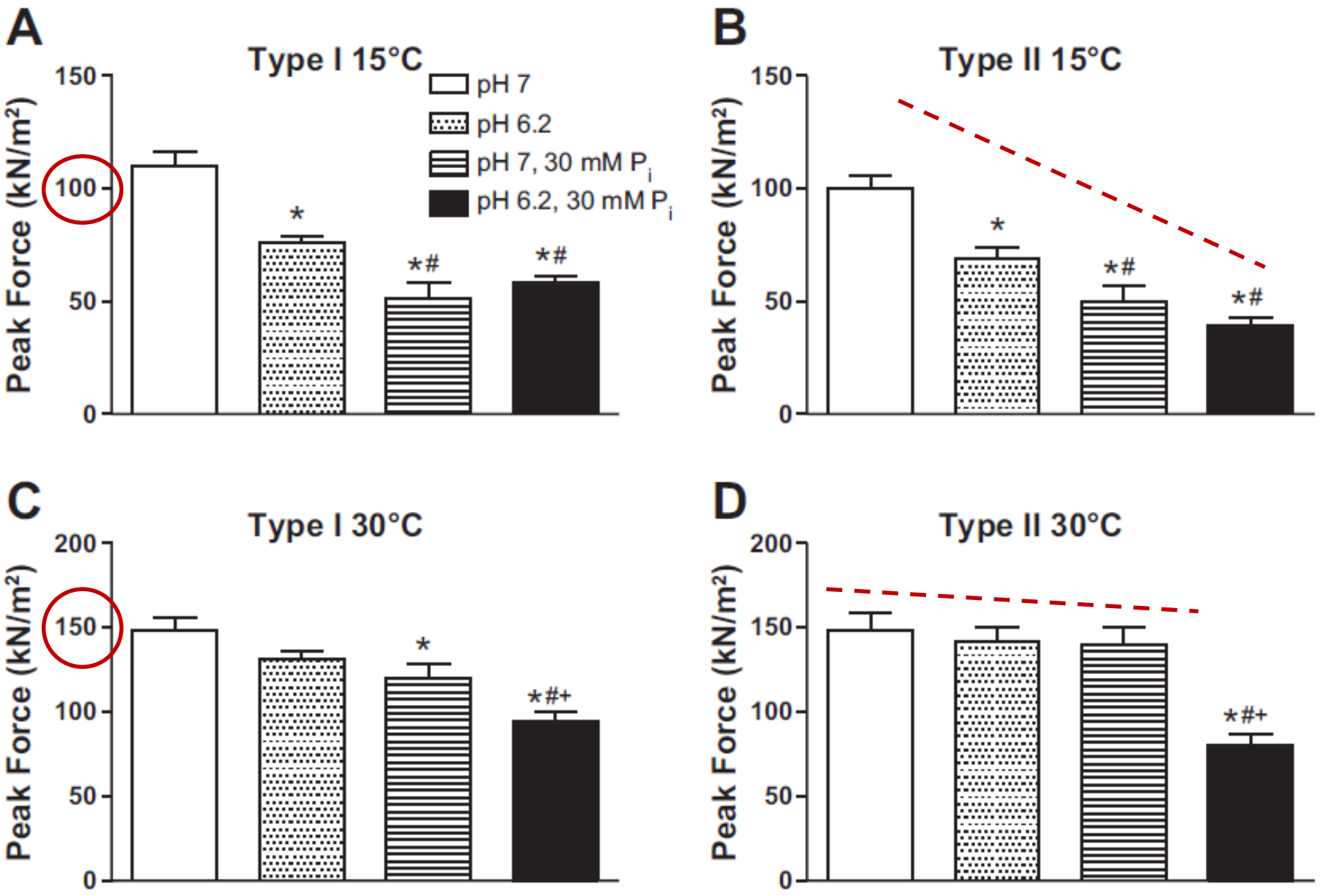
25



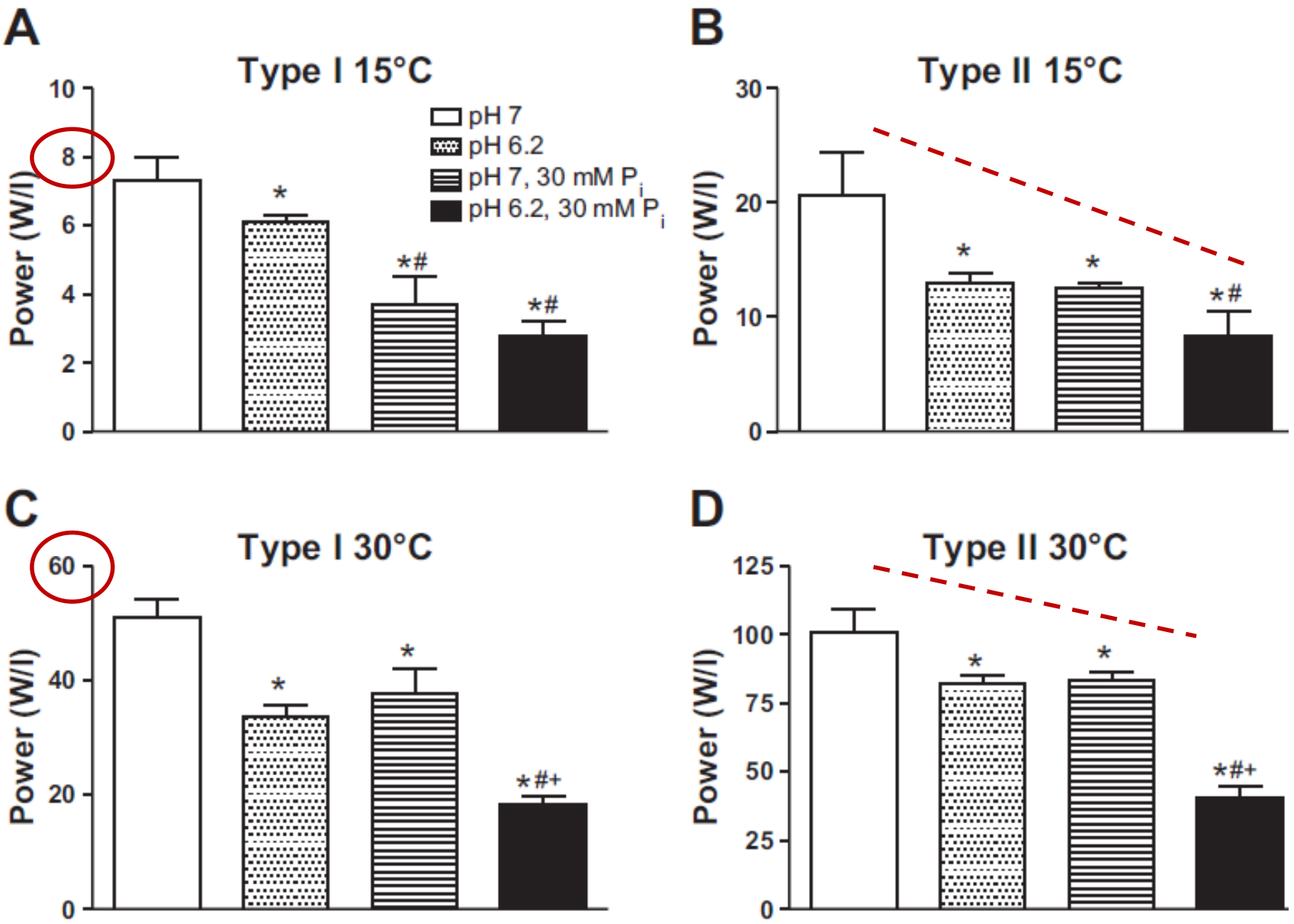
Nelson et al, Am J Physiol Cell Physiol 2014



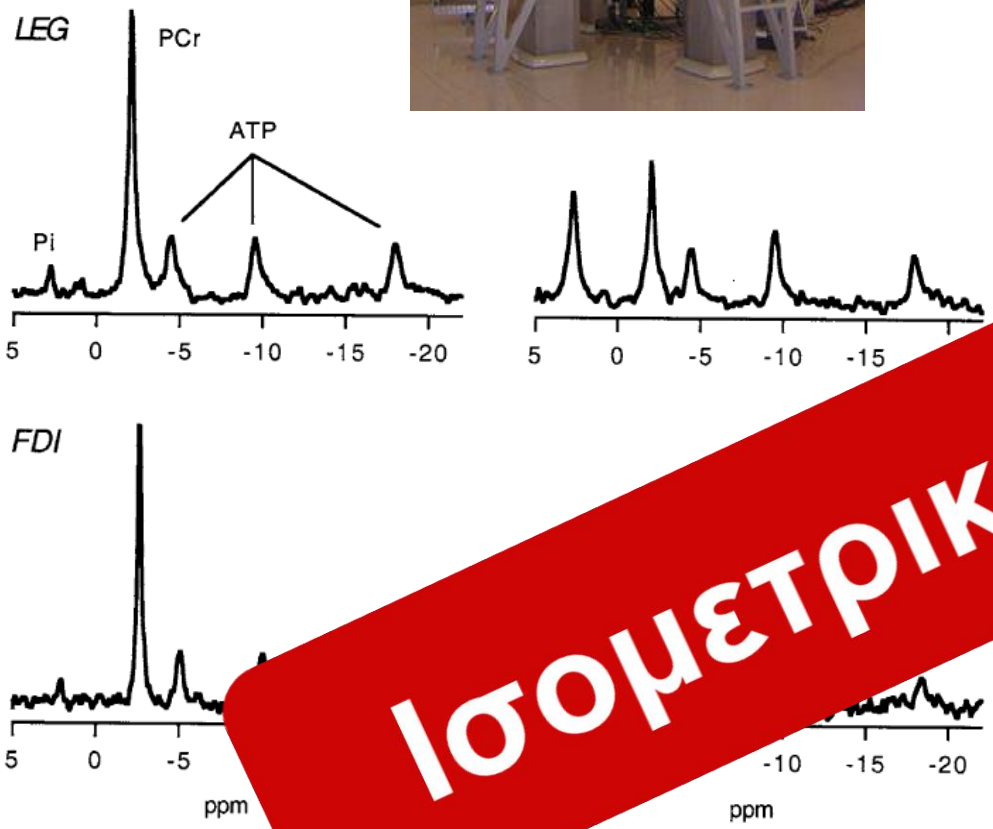
Nelson et al, Am J Physiol Cell Physiol 2014



Nelson et al, Am J Physiol Cell Physiol 2014

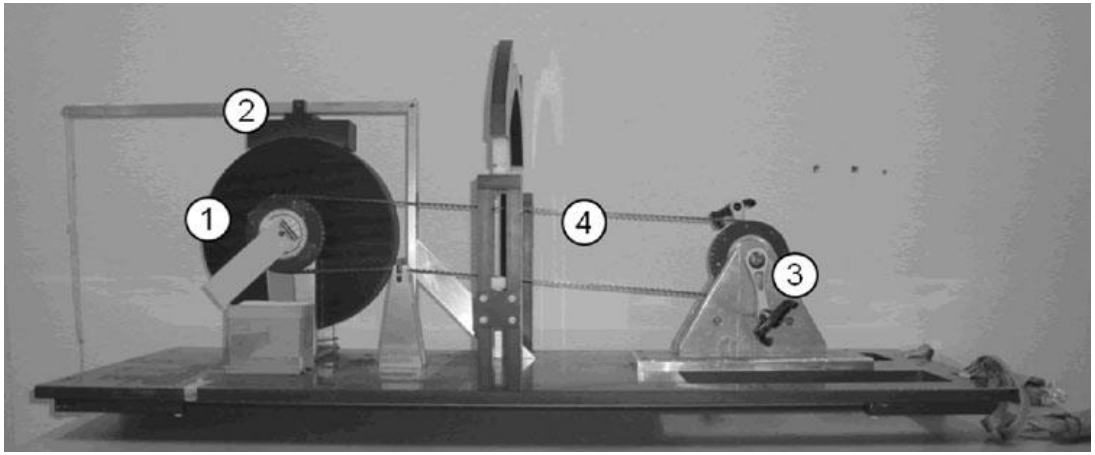


Nelson et al, Am J Physiol Cell Physiol 2014



Ισομετρική συστολή

Jubrias et al, J Physiol 2003



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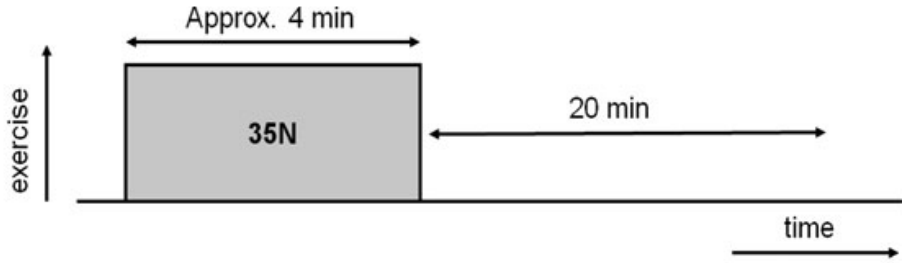

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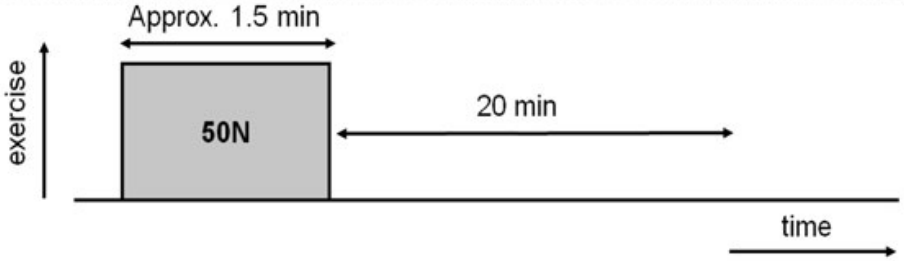

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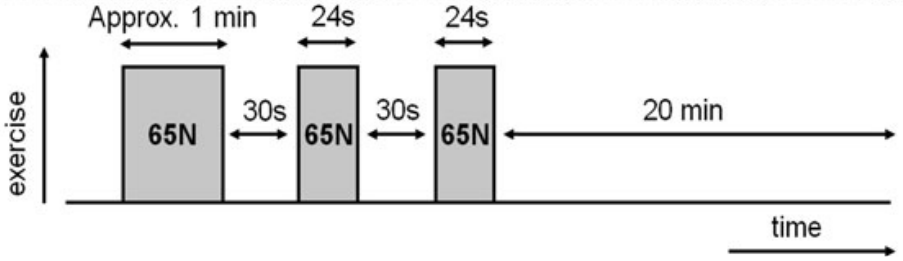
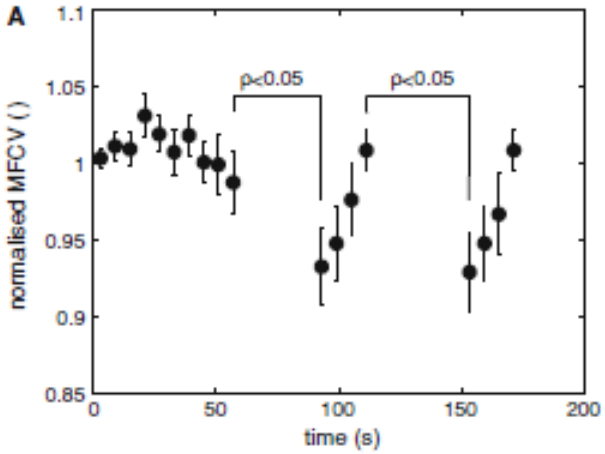
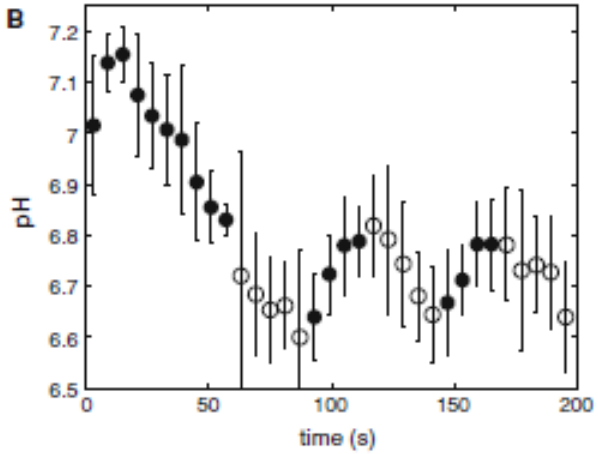
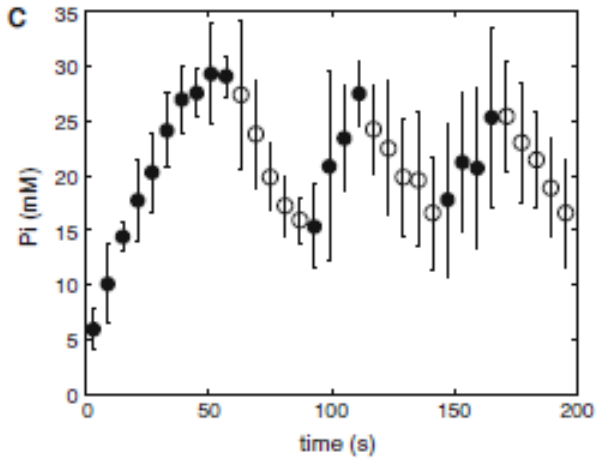








- **Σχέση MFCV και μυϊκού κάματου**
- **MFCV & pH**
- **Μικρές μεταβολές του pH και διατήρηση MFCV**

Schmitz et al, Eur J Appl Physiol 2012

Acidosis Is Not a Significant Cause of Skeletal Muscle Fatigue

SPECIAL COMMUNICATIONS

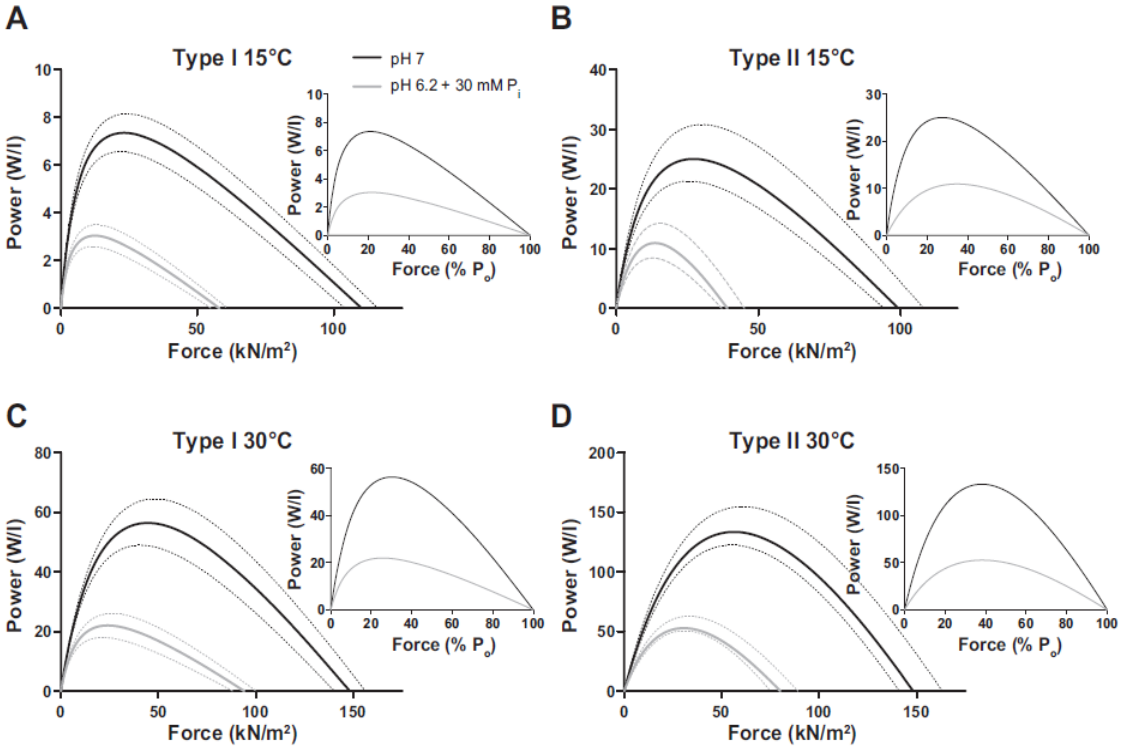
Acute skeletal muscle fatigue develops in situations with high energy demand and large dependency on anaerobic metabolism. When fatigued, muscles become weaker and slower, and two end products of anaerobic metabolism, H^+ and inorganic phosphate ions (P_i), have received most attention as causes of the impaired contractility in fatigue (1). In particular, the increase in H^+ (i.e., reduced intracellular pH [pH_i] or acidosis) is believed to play a central

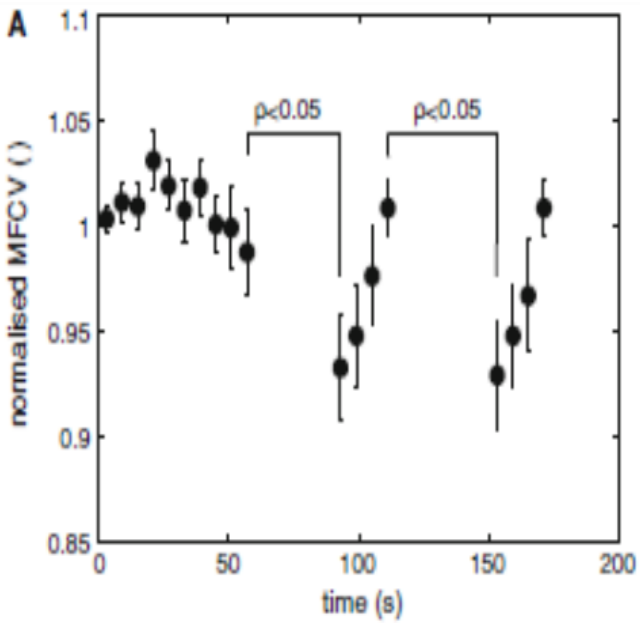
is no obvious causal relationship between an intracellular acidosis and a reduced force production in fatigue.

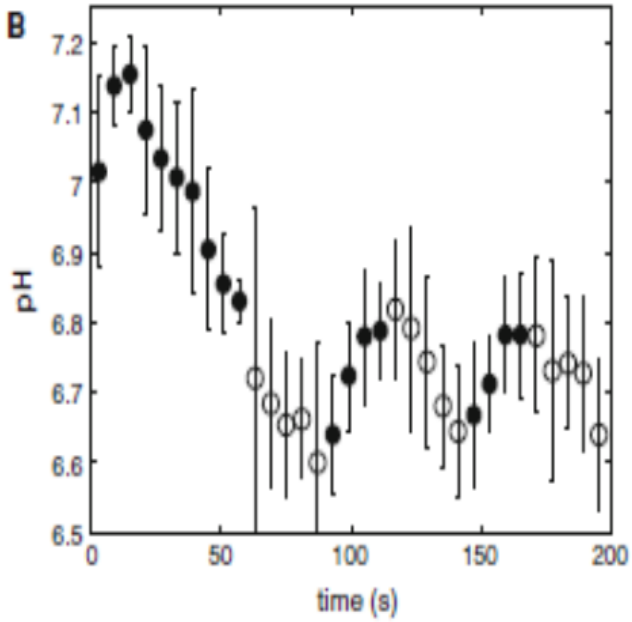
Experiments on skinned muscle fibers allow direct control of the solution surrounding the contractile proteins. Early skinned fiber experiments performed at low temperatures (≤15°C) showed a marked decrease of maximum force under acidic conditions and this was considered a fundamental proof of an important role of acidosis in fatigue. More re-

Westerblad, Med Sci Sports Exerc 2016

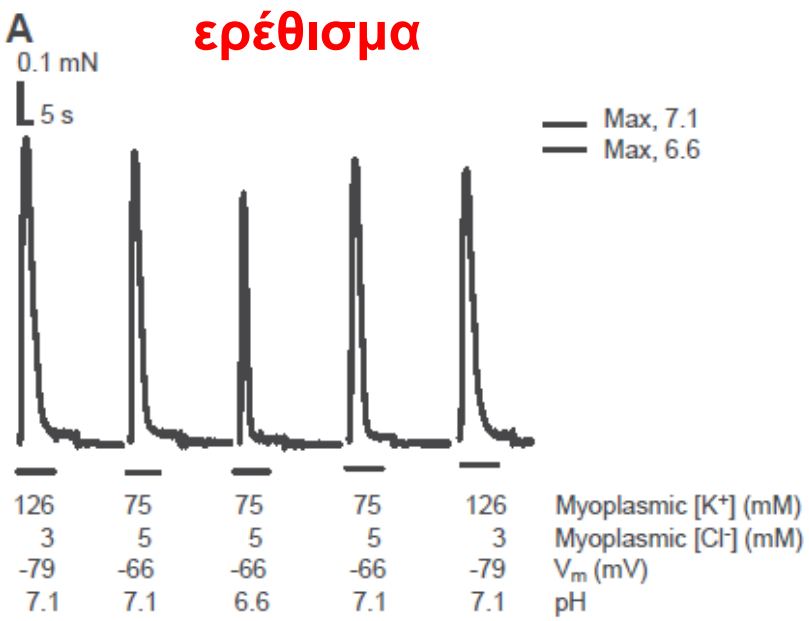
- **Έλλειψη αιτιολογικής συσχέτισης**
- **Κυρίως in vitro δεδομένα**
- **T ≠ 37 °C**
- **Προσομοίωση εξωκυττάριου περιβάλλοντος**

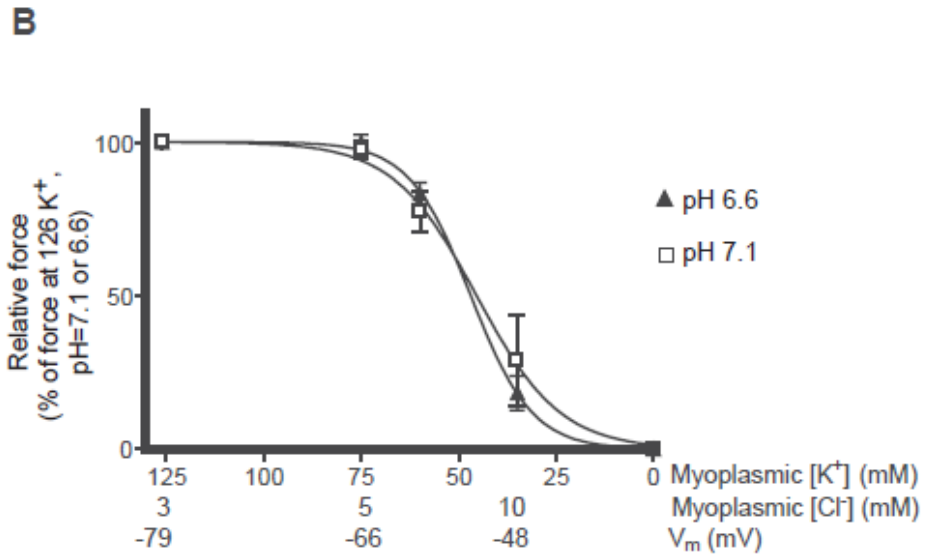

A
Type I 15°C
pH 7
pH 6.2 + 30 mM P$_i$
Power (W/l)
Force (kN/m²)
Force (% P$_o$)
B
Type II 15°C
C
Type I 30°C
D
Type II 30°C

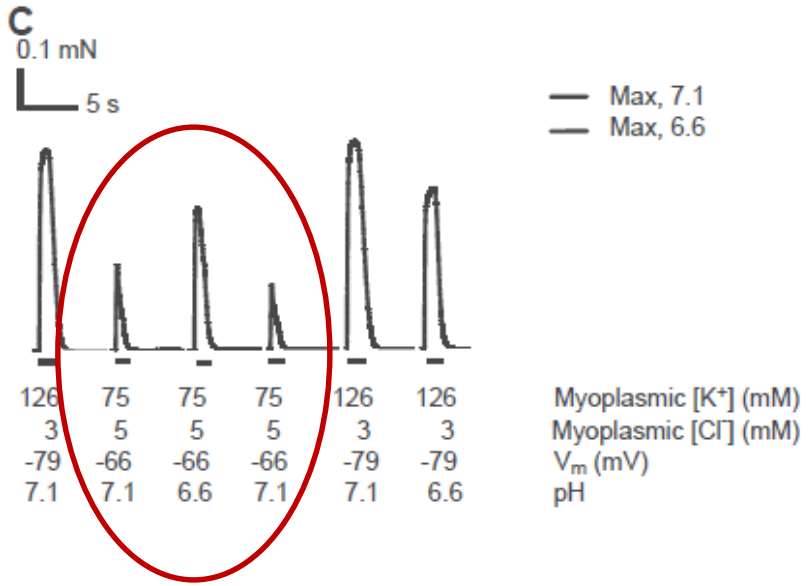

A
p<0.05
p<0.05
normalised MFCV ( )
time (s)

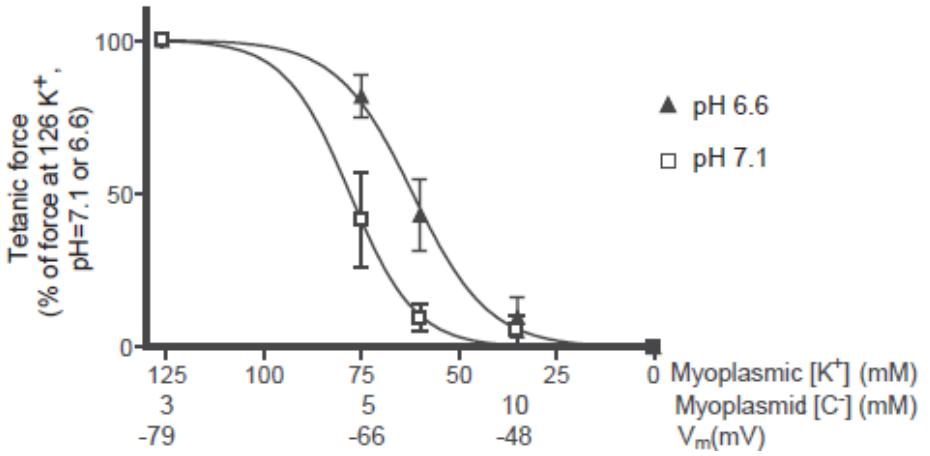

B
pH
time (s)

Μεμονωμένο ερέθισμα





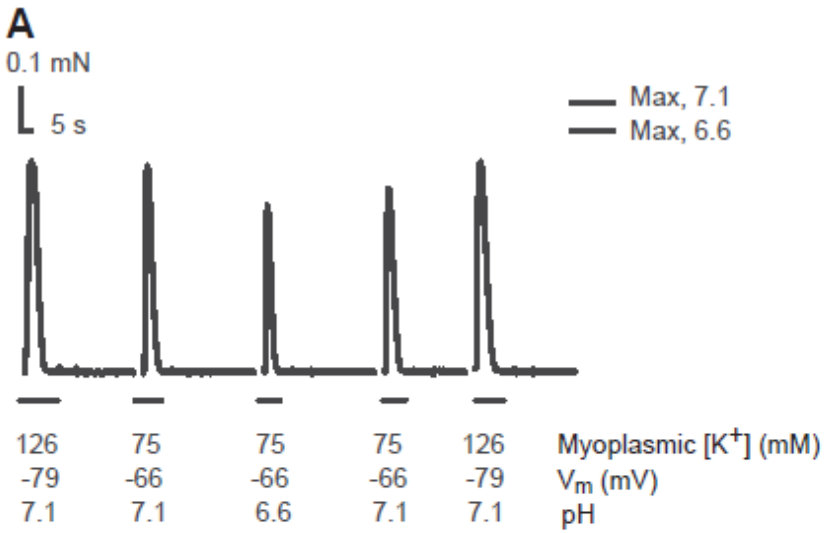


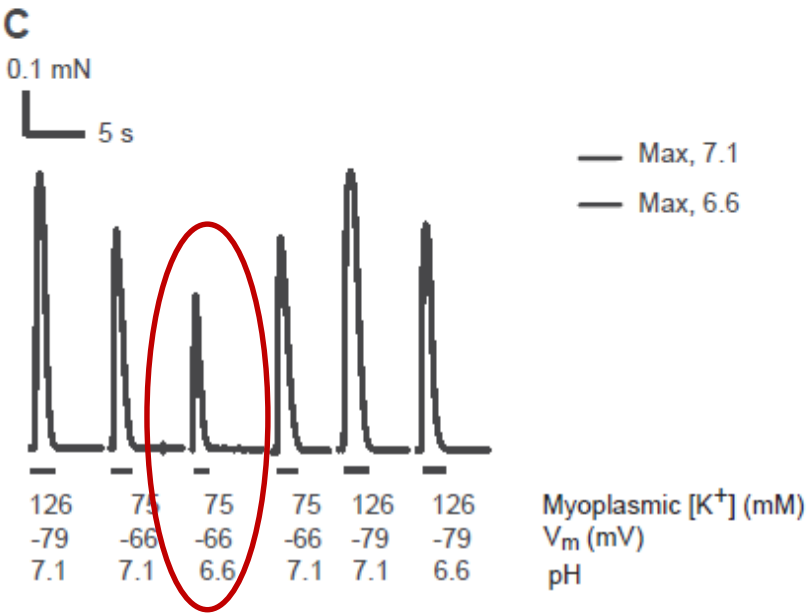


Τετανική συστολή

Pedersen et al, Science 2004

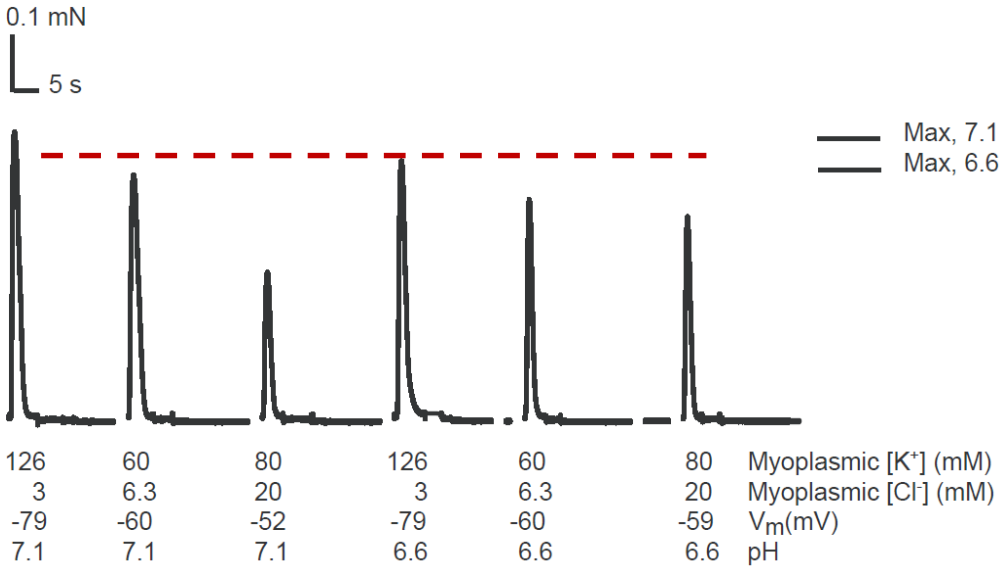
Άνευ χλωρίου



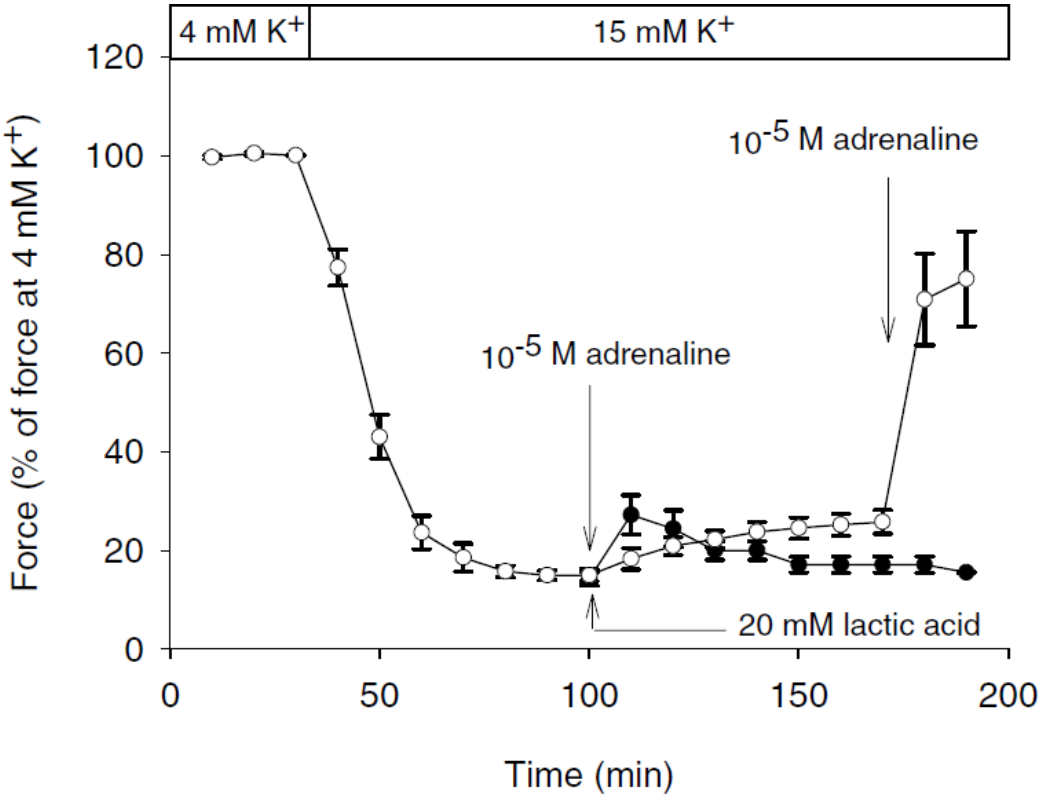


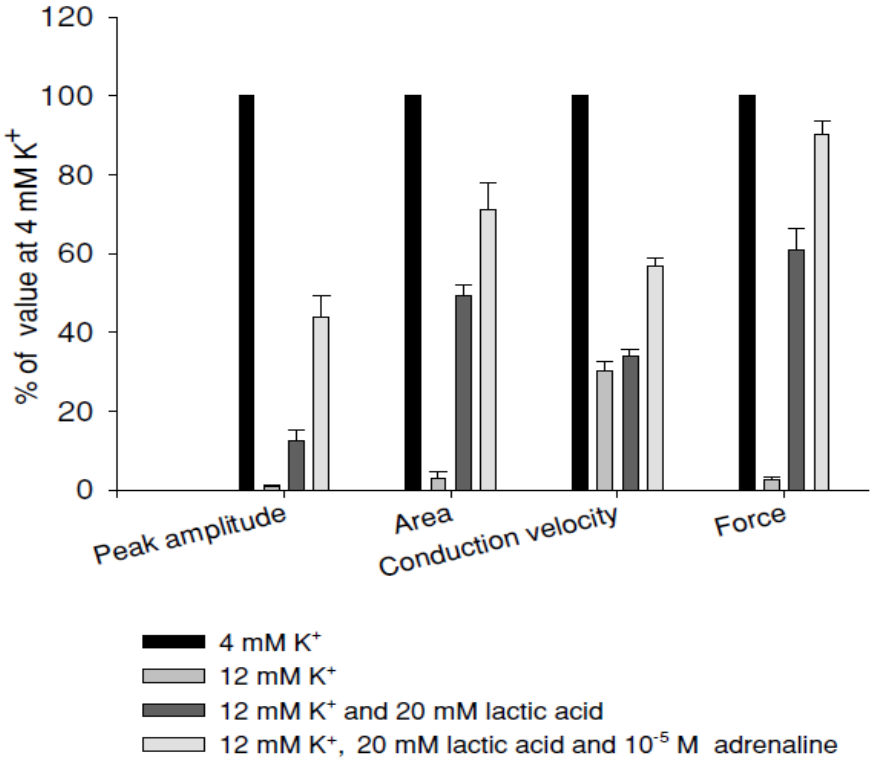
pH

Διαπερατότητα Cl



Pedersen et al, Science 2004





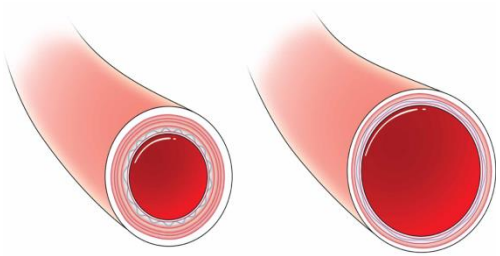
De Paoli F
Overgaard K
Pedersen T
Nielsen O

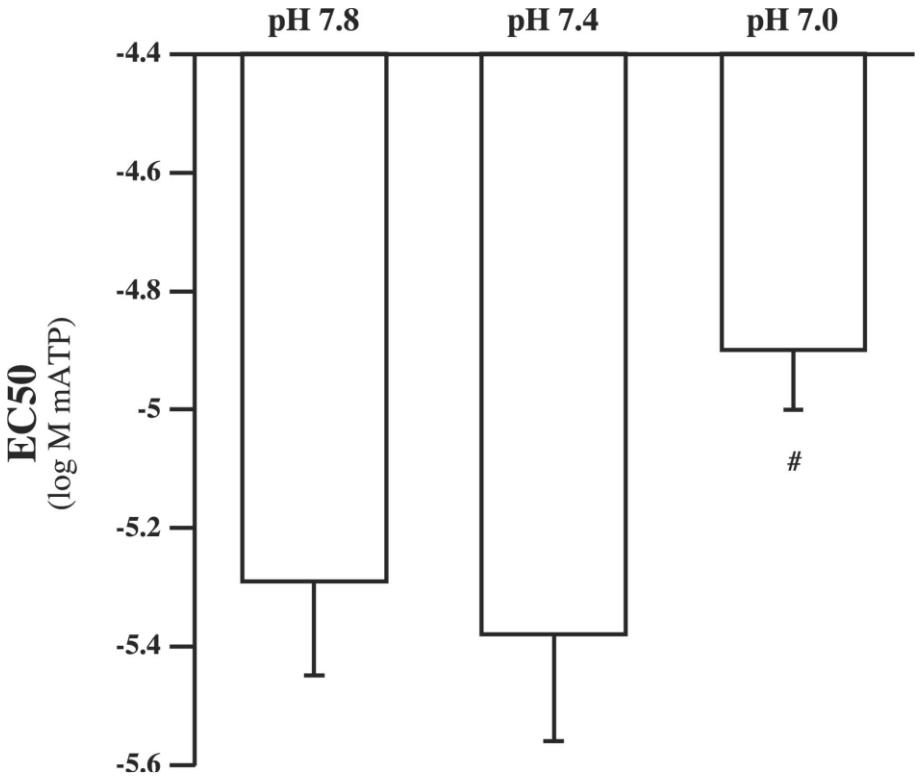
J Physiol 2007

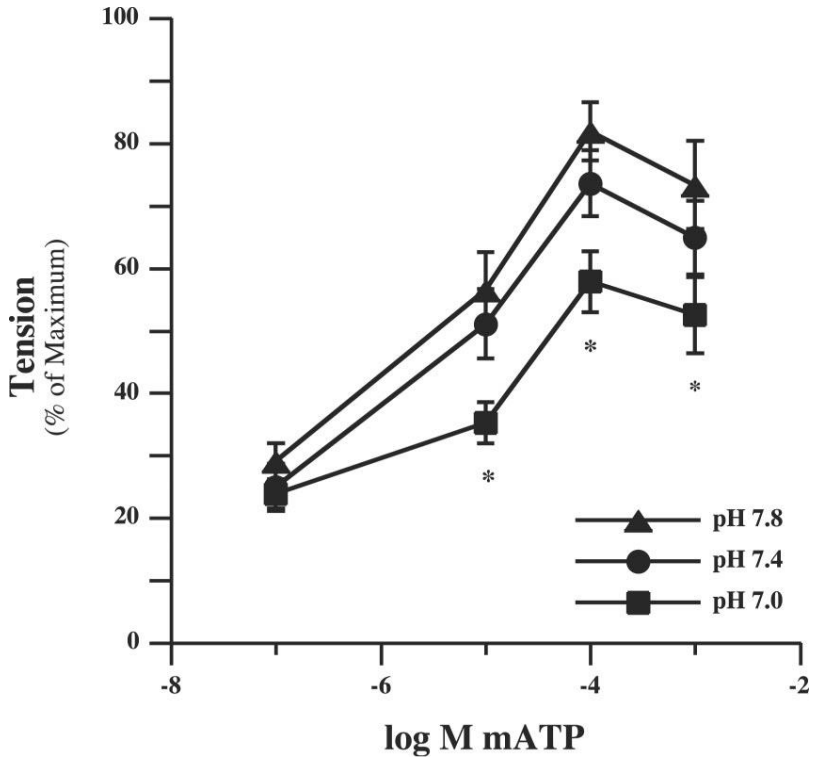
Λείες μυϊκές ίνες

Υποξία

⬇ ATP



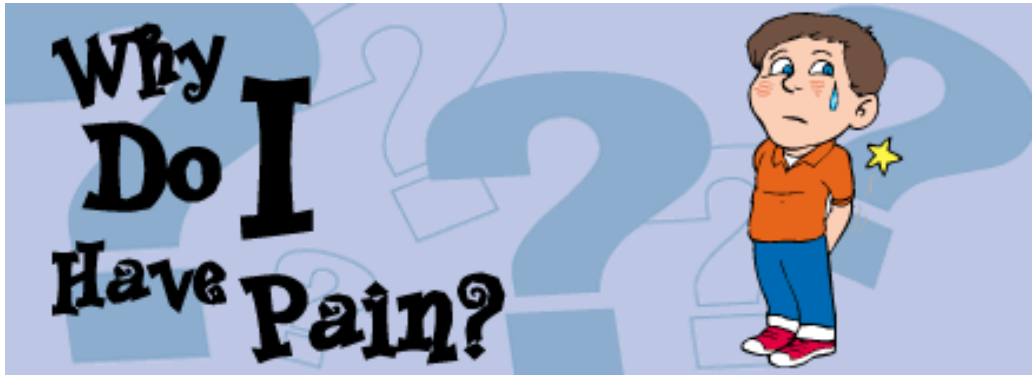


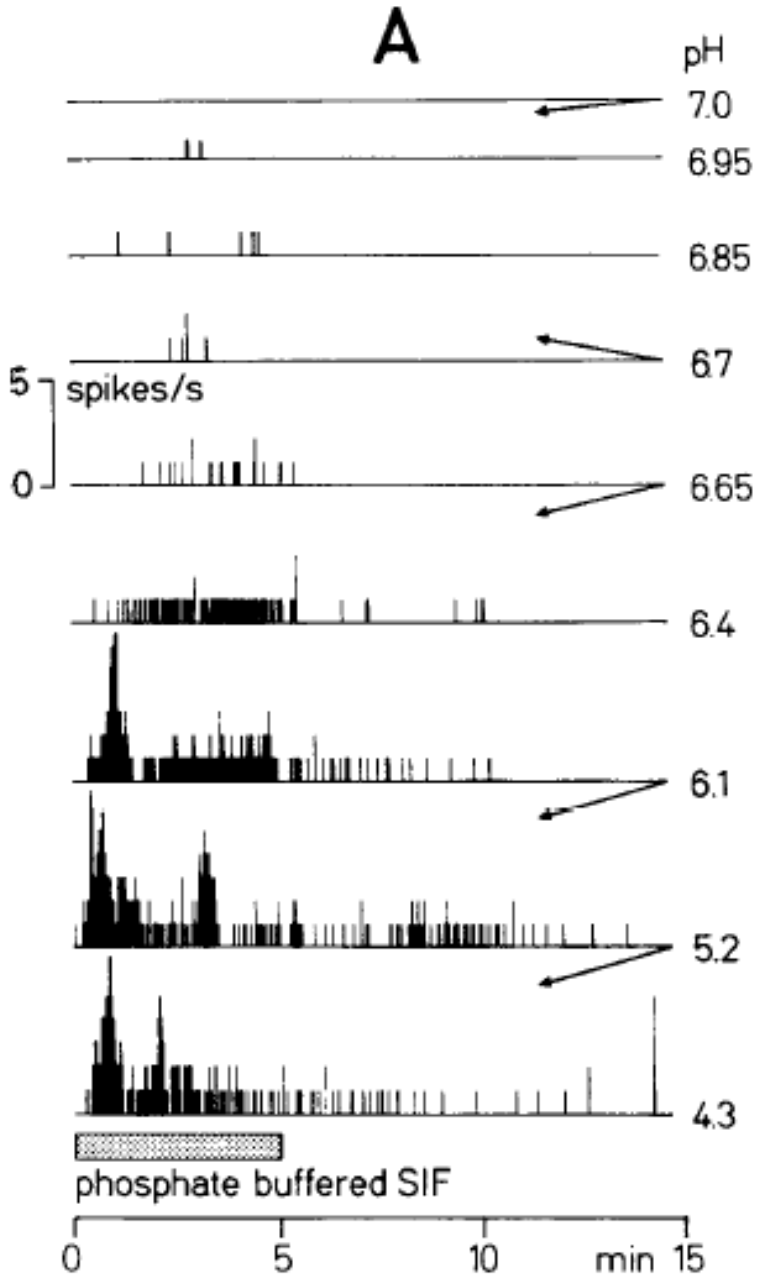


Kluess et al, Am J Physiol Heart Circ Physiol 2005

I Can't Keep Calm

Getting on my NERVES!!!



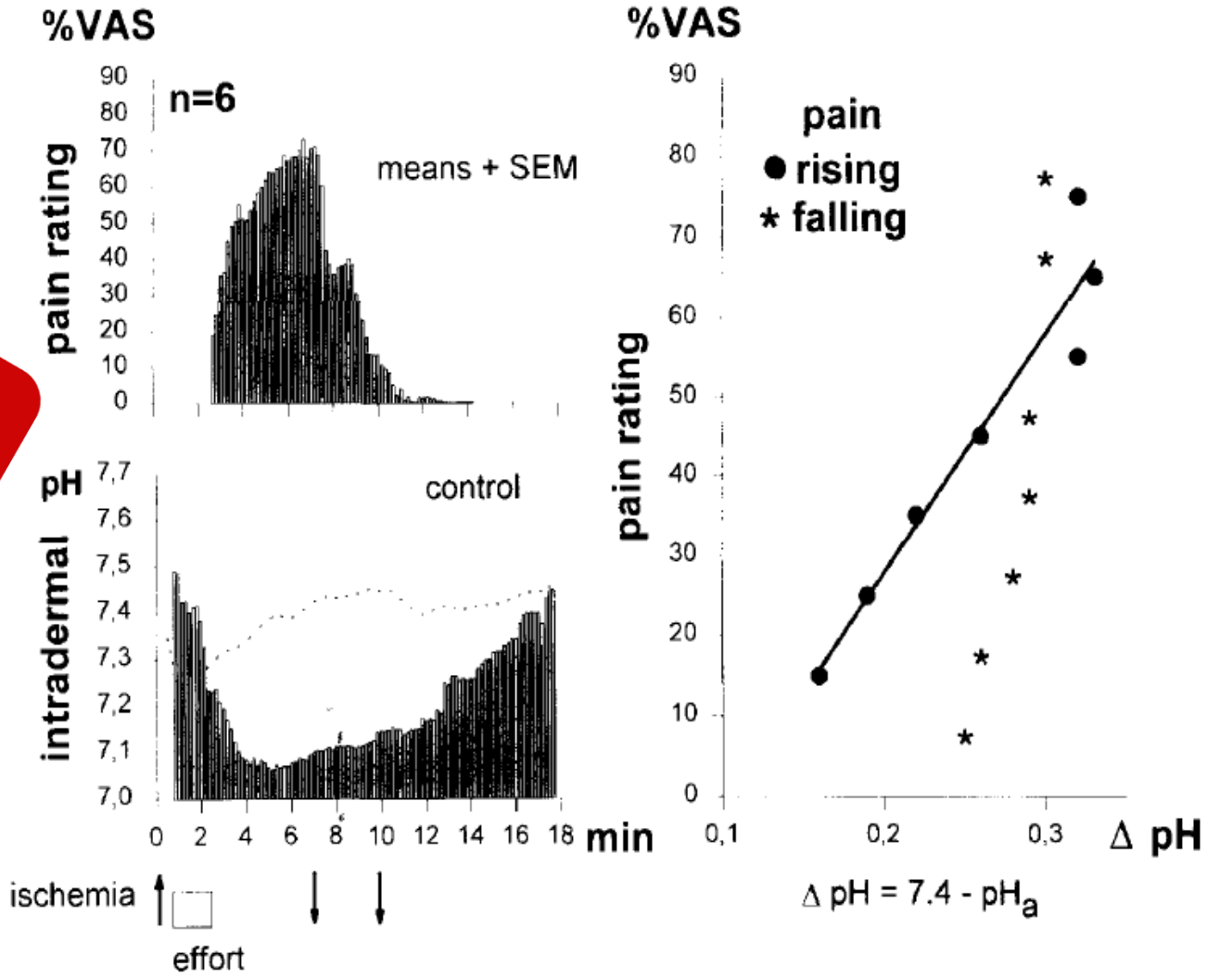


Steen et al, J Neurosci 1992

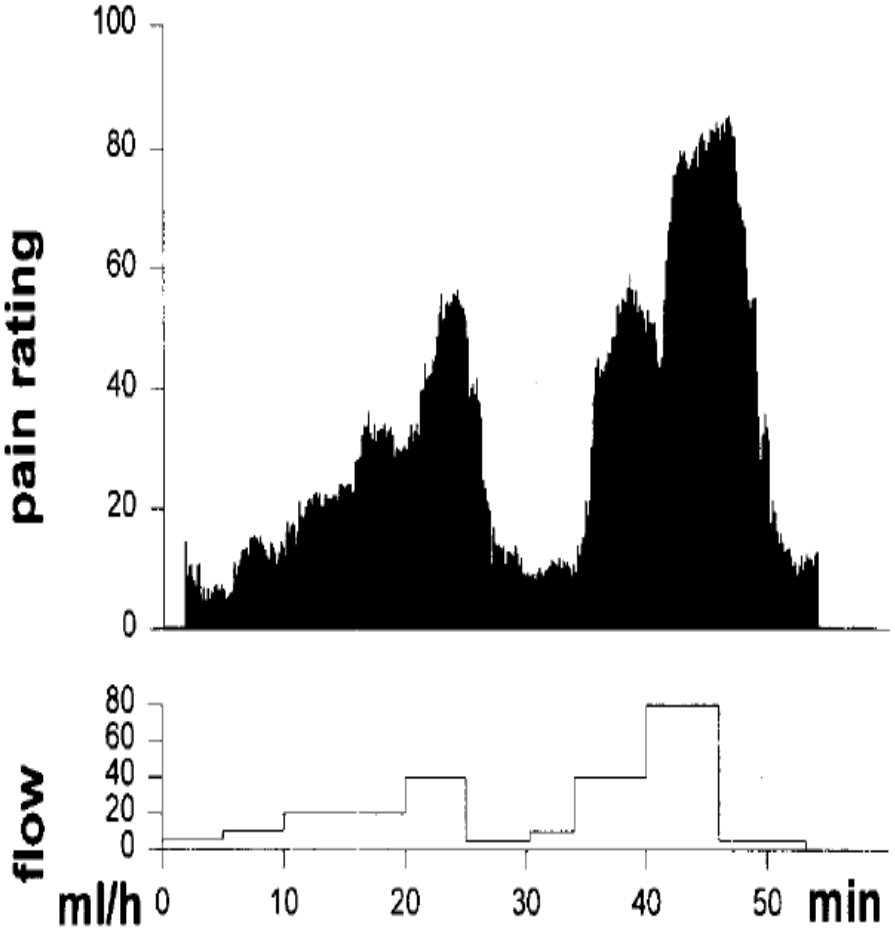
0 5 10 0 5 10 0 5 min 10

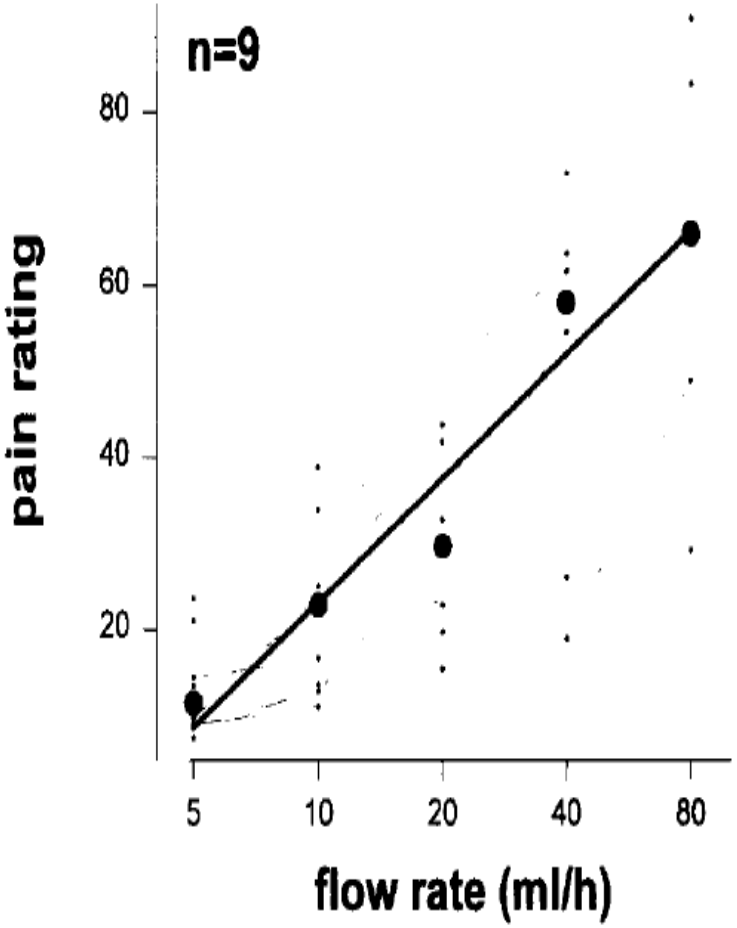
Steen et al, Pain 1996

Ισχαιμία



Issberner et al, Neurosci Lett 1996

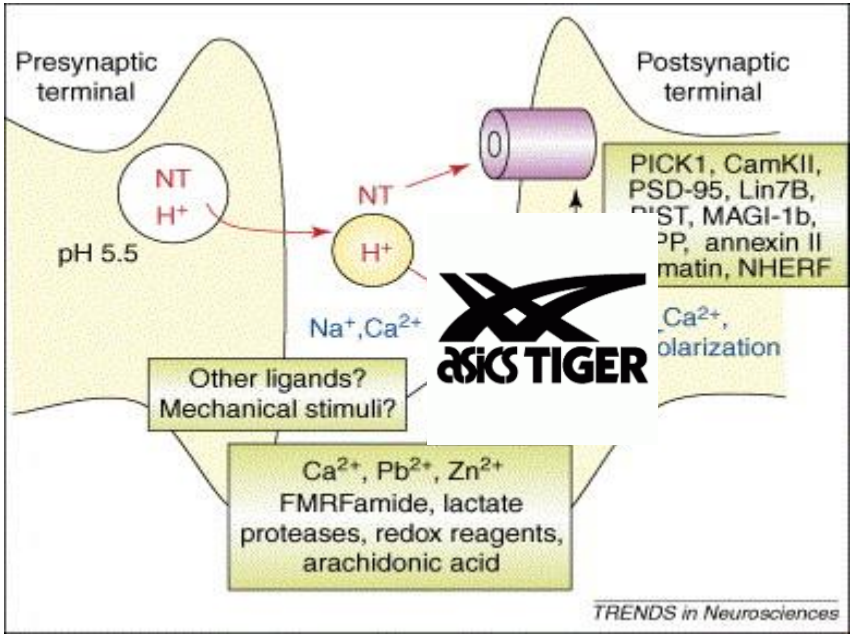


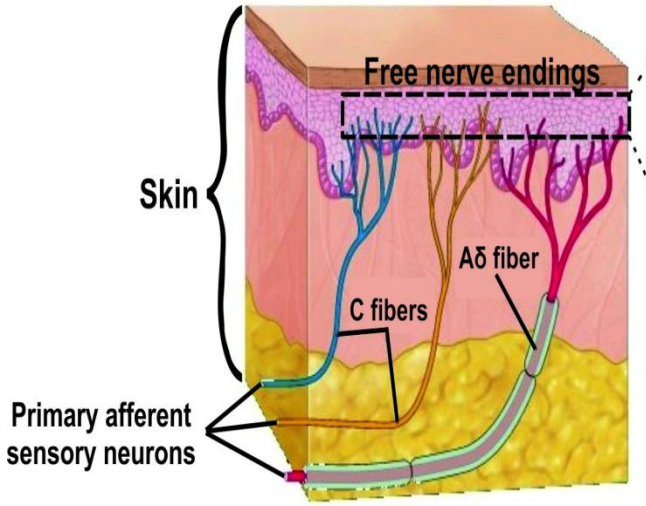


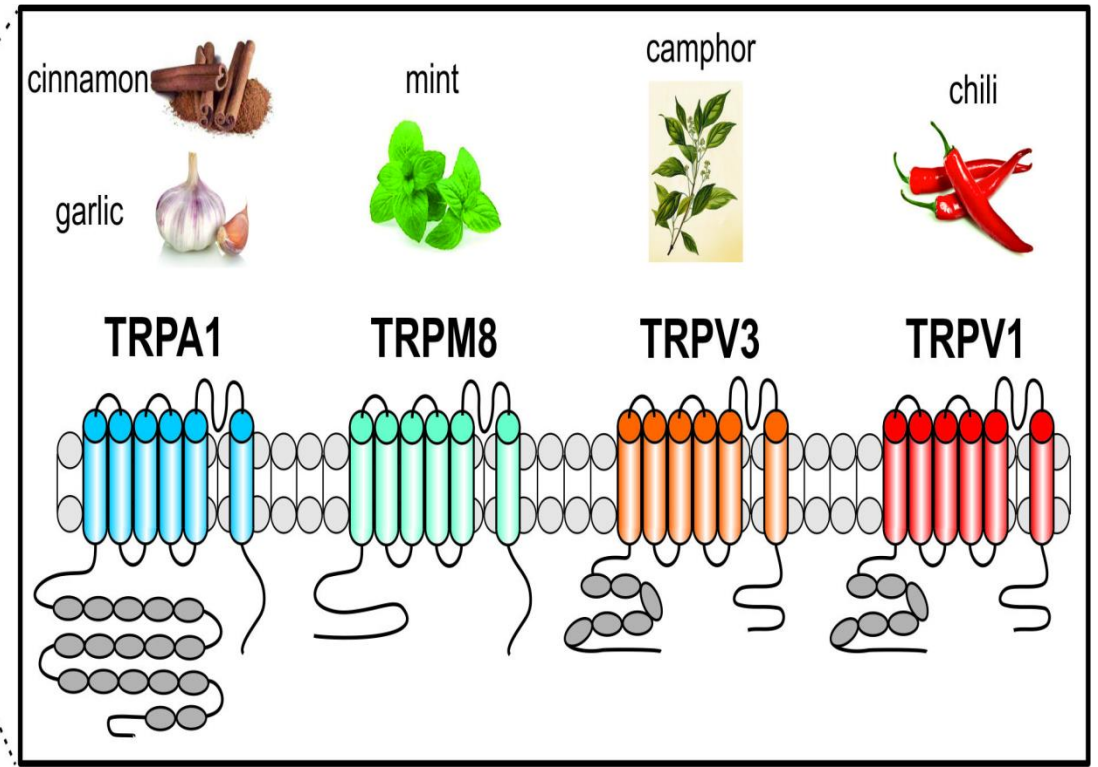
Phosphate buffer pH=5.2

Issberner et al, Neurosci Lett 1996

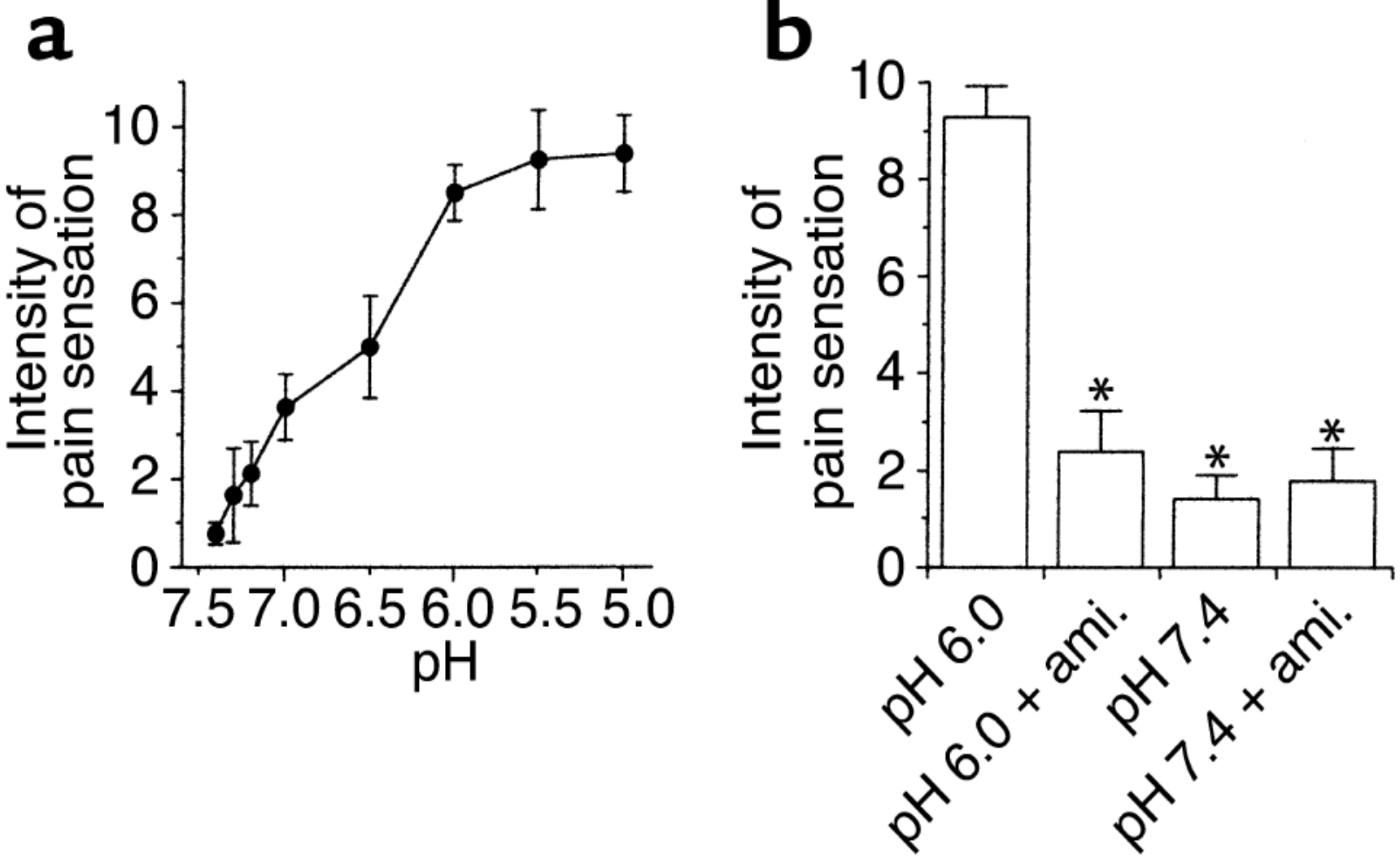
Ιοντικά κανάλια



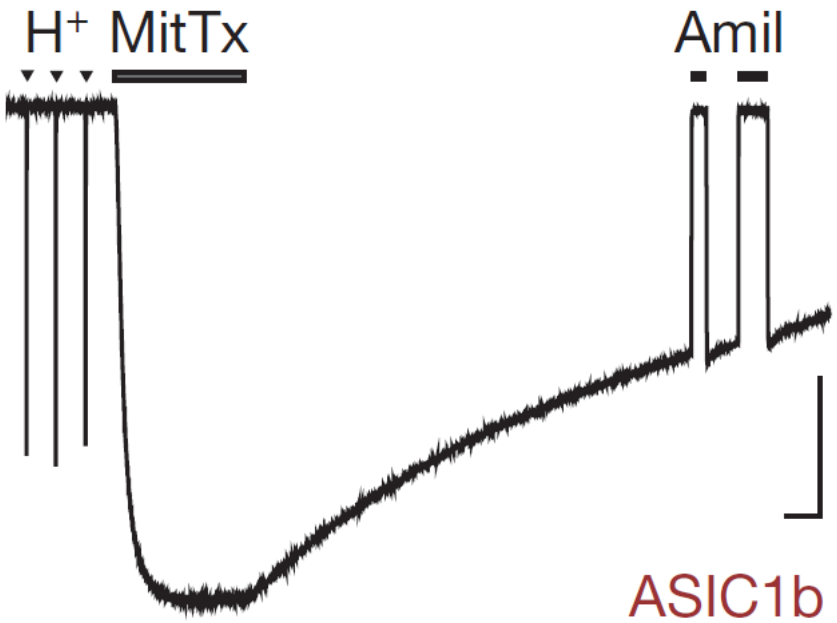


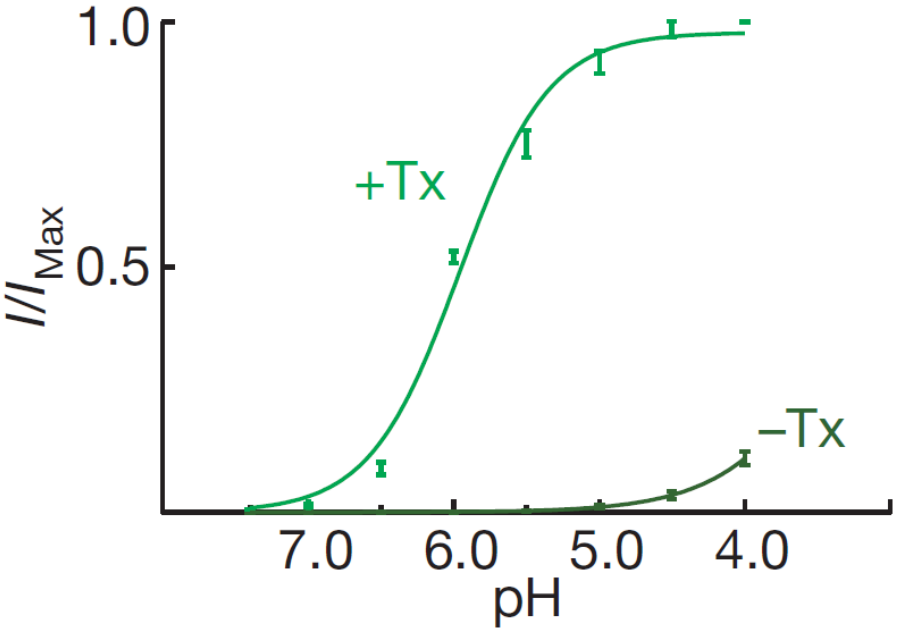


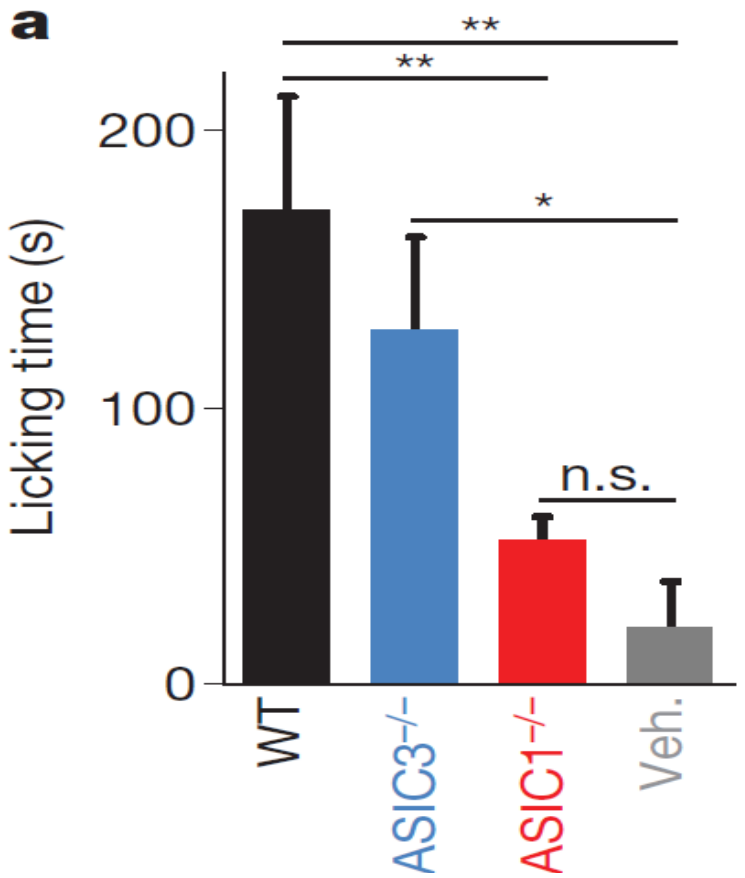
Amiloride **ASICs**



Ugawa et al, J Clin Invest 2002

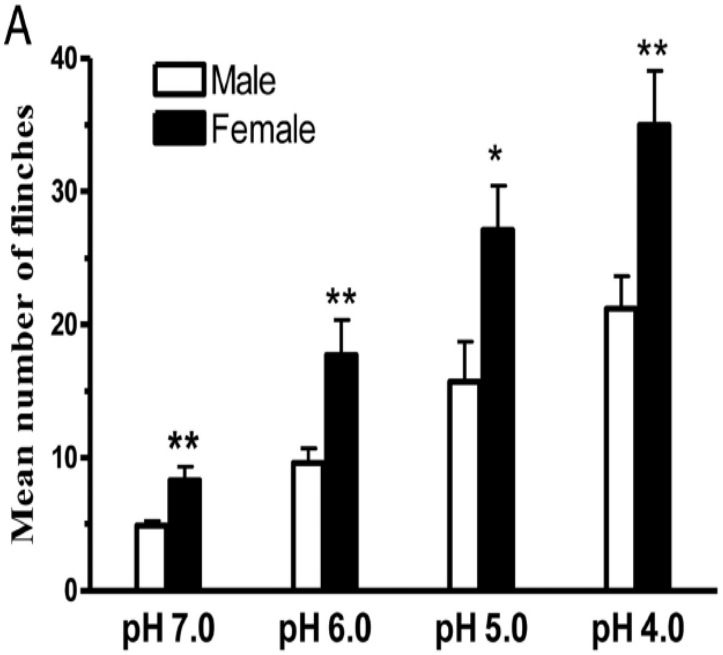


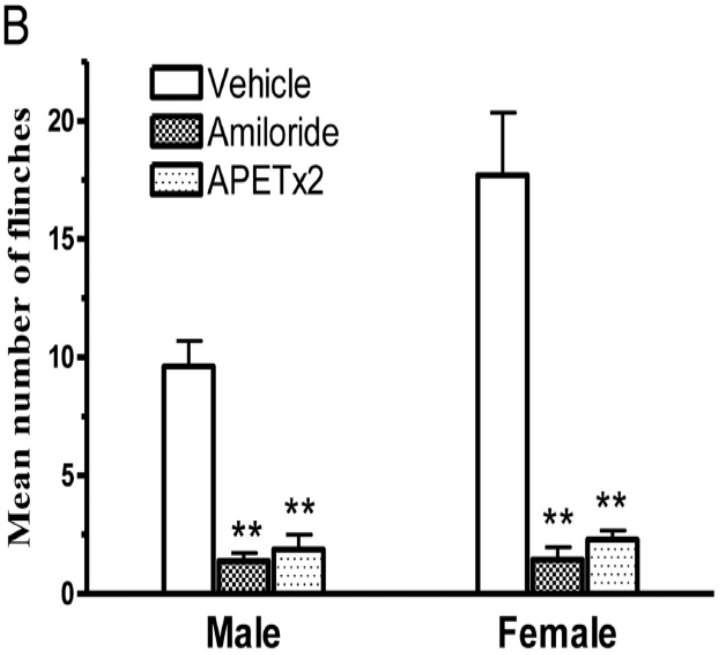




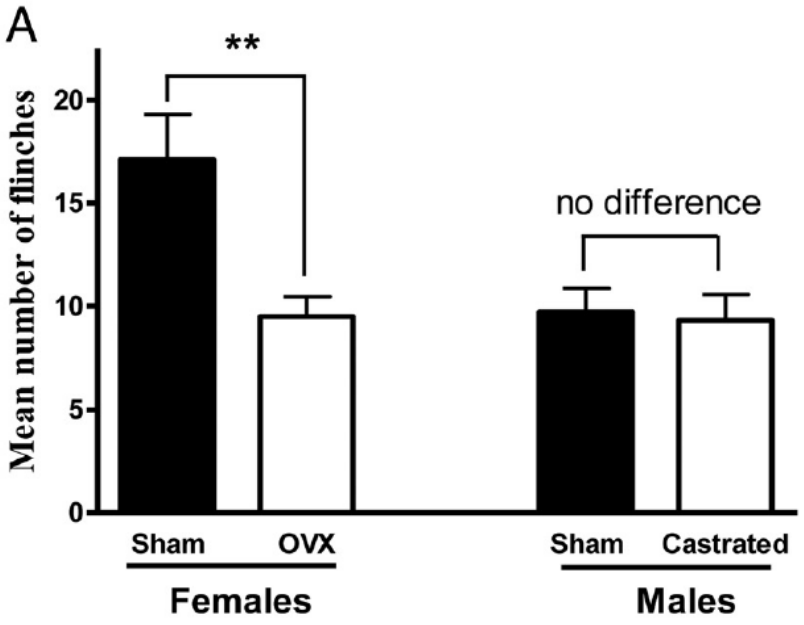
Bohlen et al, Nature 2011

+





Sex difference occurred in the acetic acid-evoked nociceptive response in rats. In the presence of the TRPV1 inhibitor capsazep



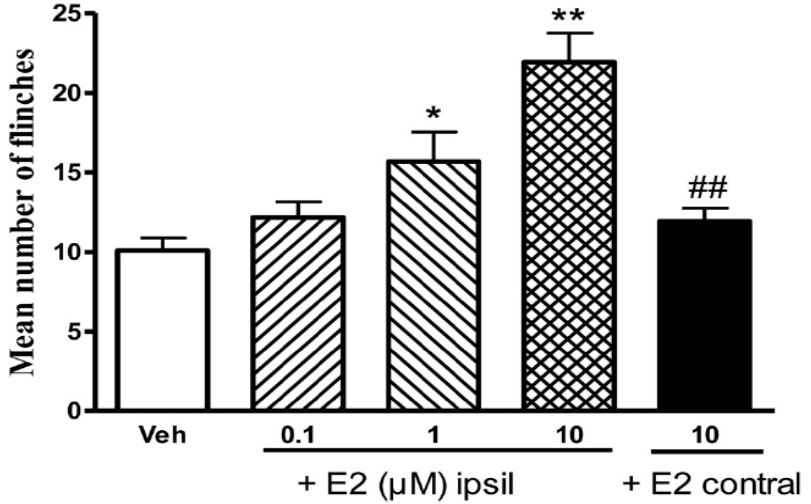
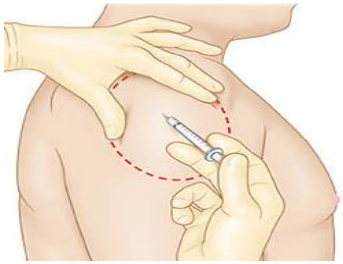


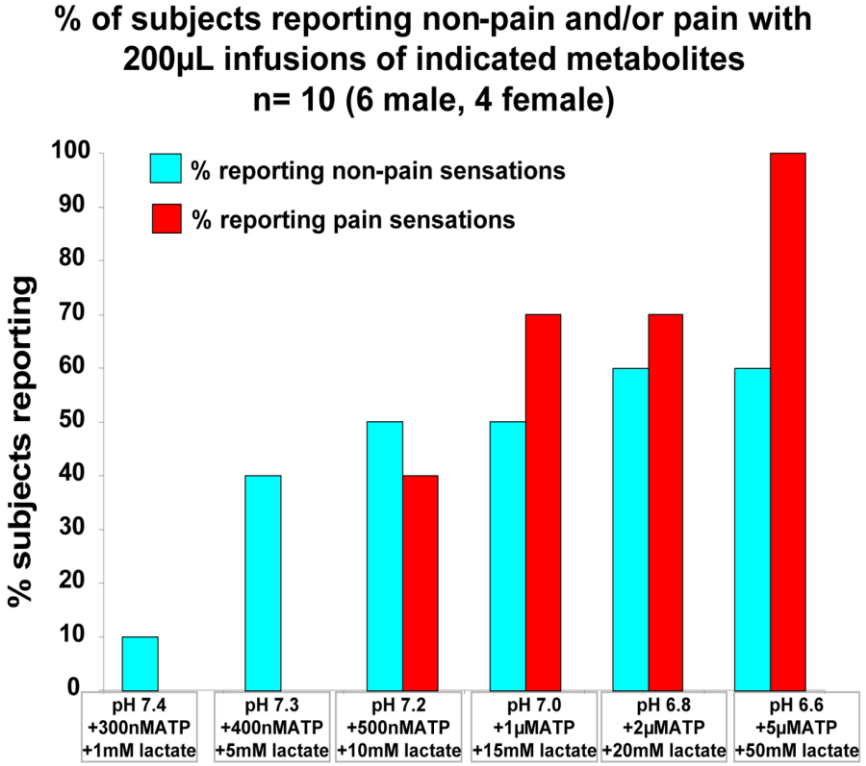
Figure 3. Effect of E2 on nociceptive responses to intraplantar injection of acetic acid in male rats. The pretreatment of E2 dose

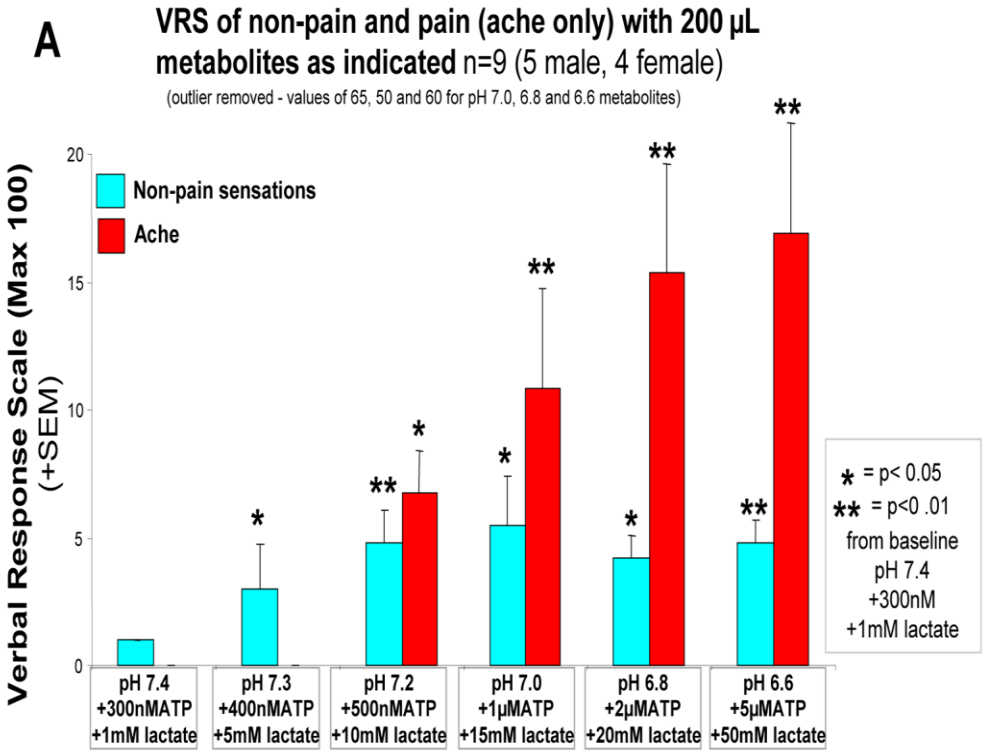
Qu et al, Endocrinology 2015

10 υγιείς εθελοντές

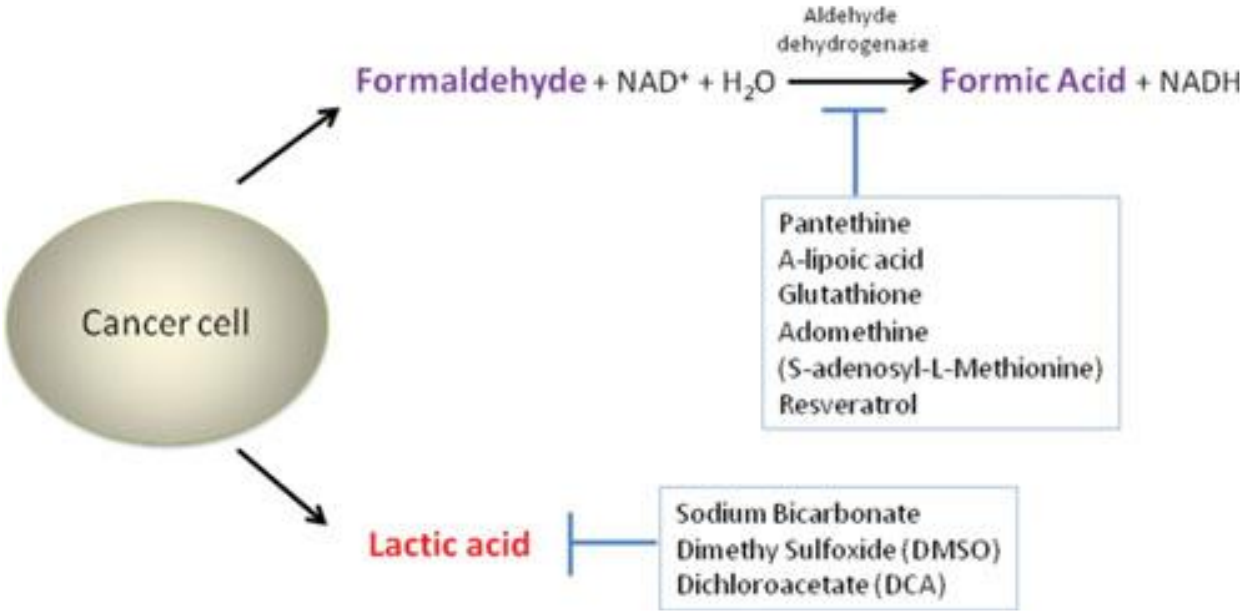


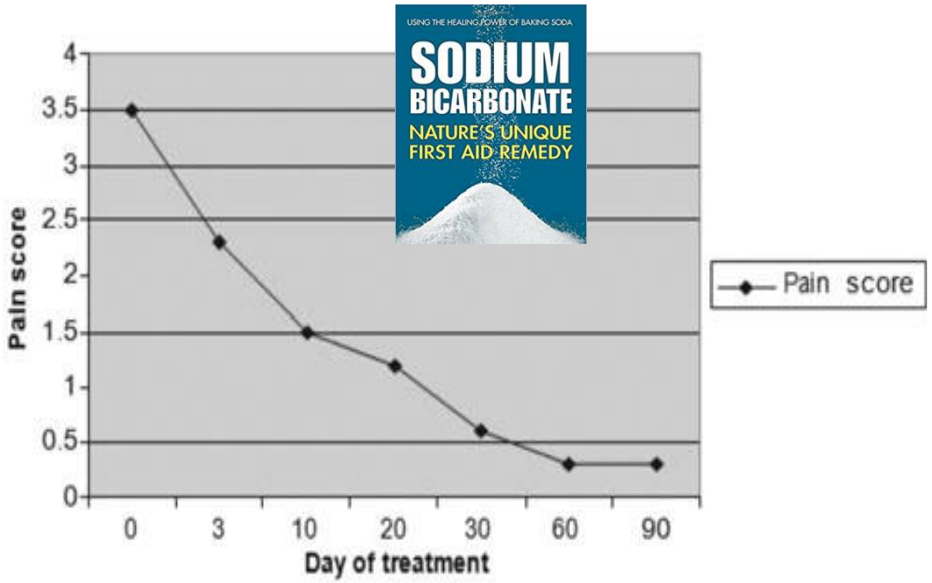
Κάματος
+
Πόνος



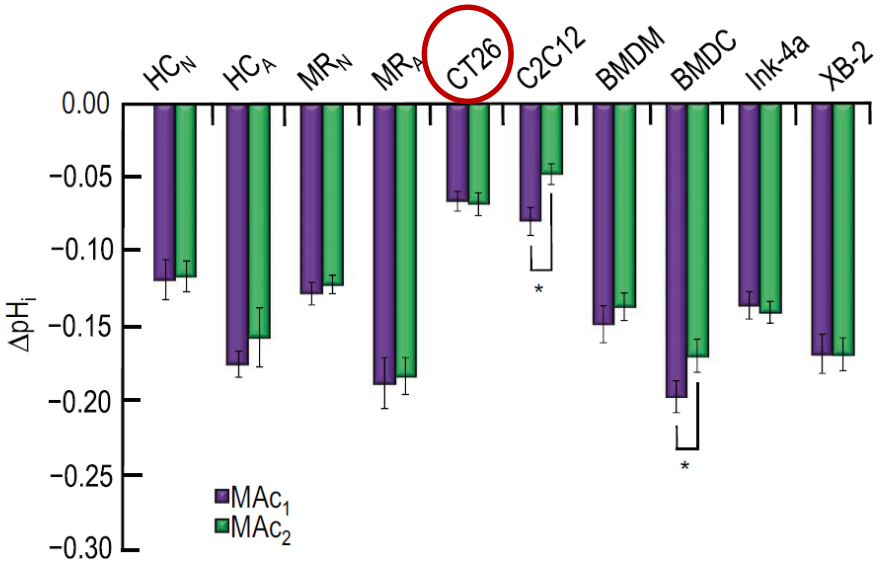


Pollak et al, Exp Physiol 2014



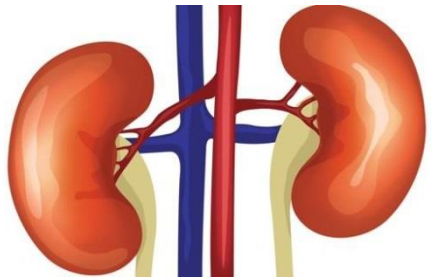


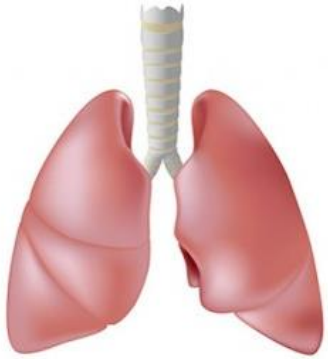
Hoang et al, J Pain 2015

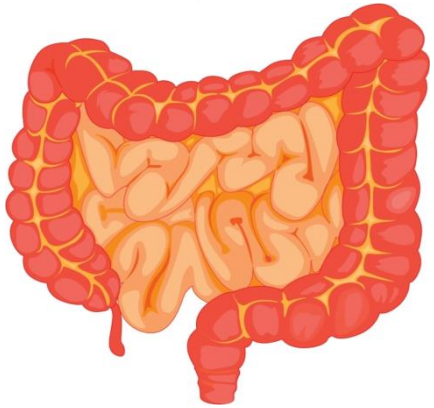


Salameh et al,
Am J Physiol Regul Integr Comp Physiol 2014


Acid







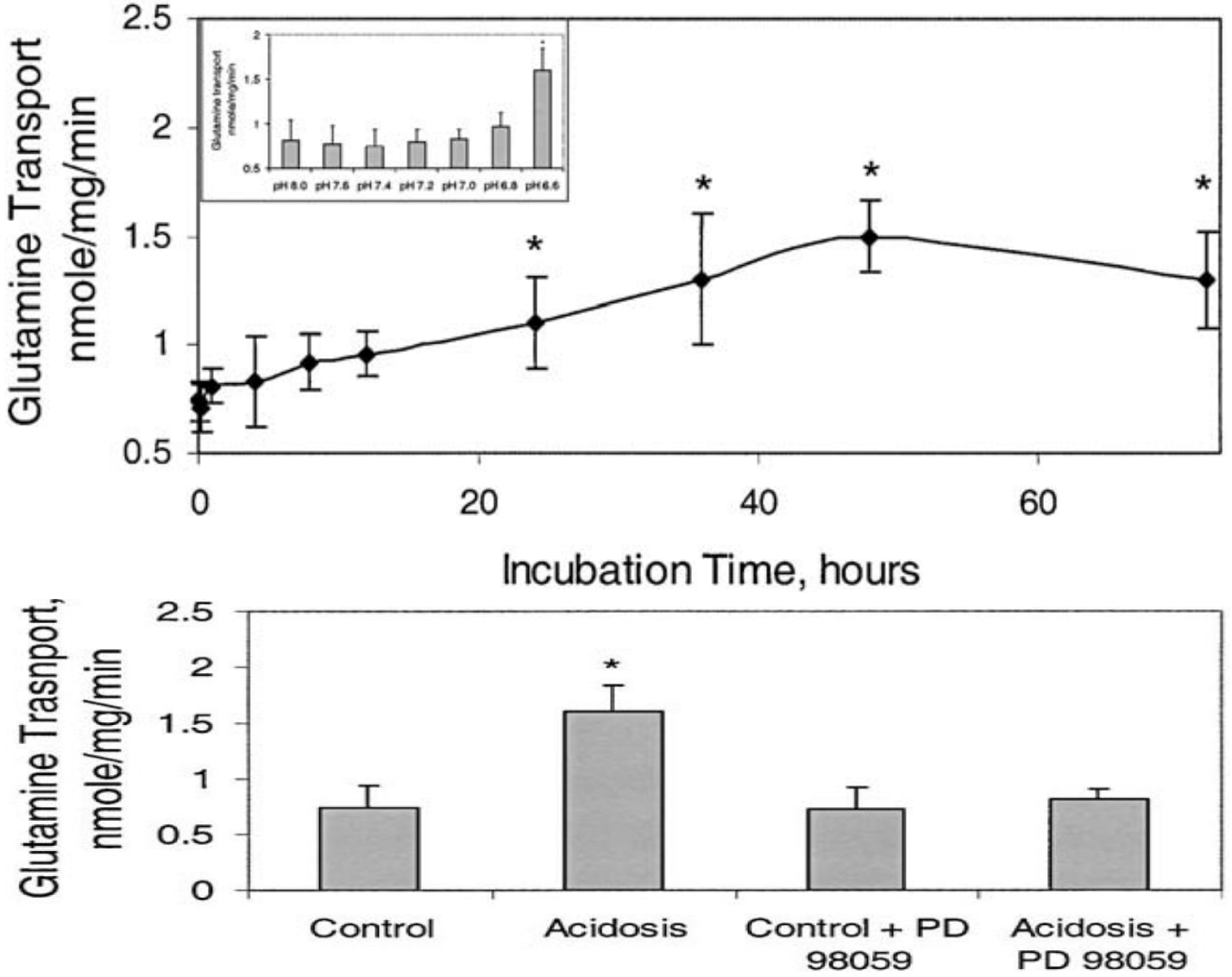
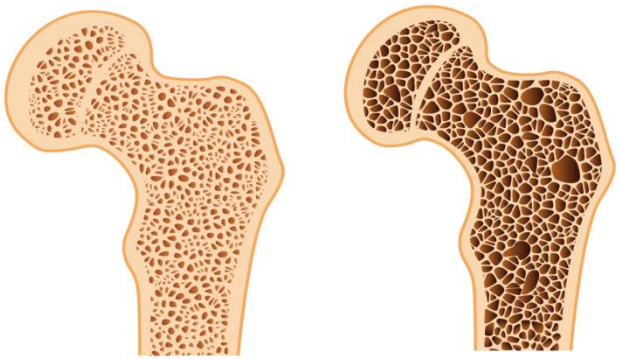
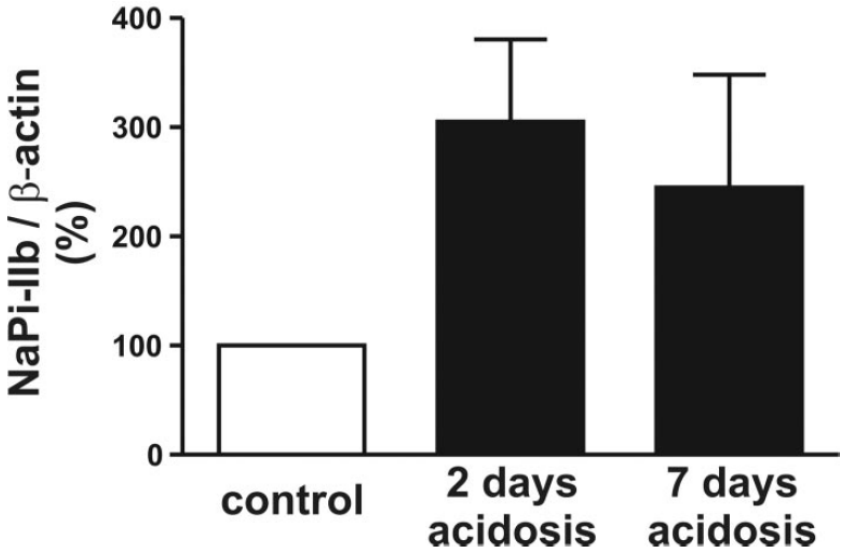


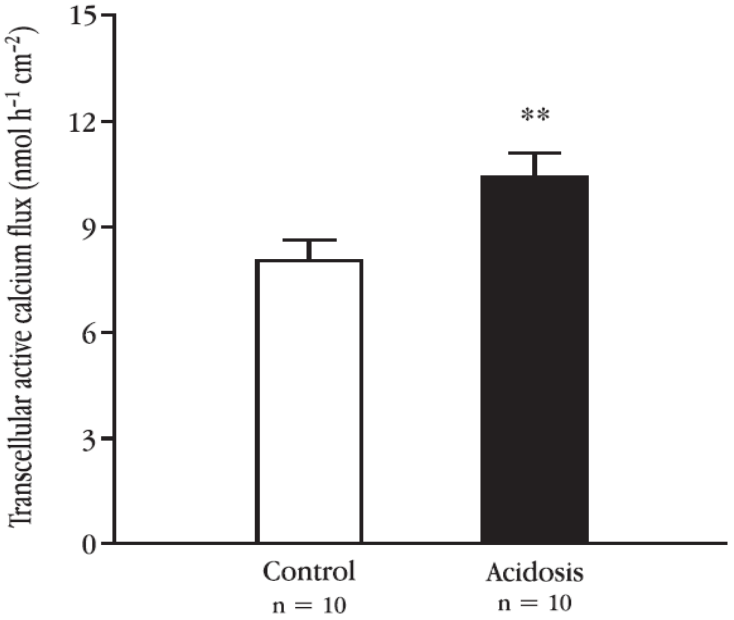
Fig. 6. Involvement of mitogen-activated protein kinase (MAPK) in acidosis stimulation of system B glutamine transport. Uptake of glutamine (50 μmol/L) was measured in

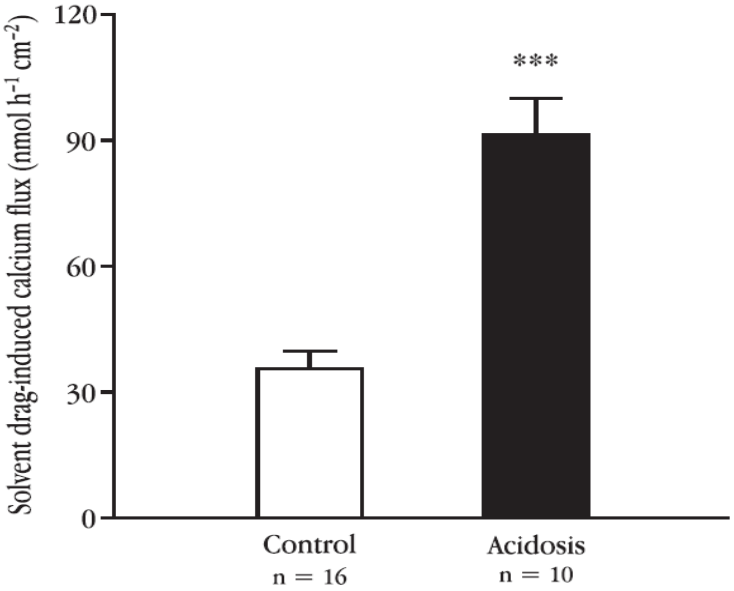
Epler et al J Gastrointest Surg 2003



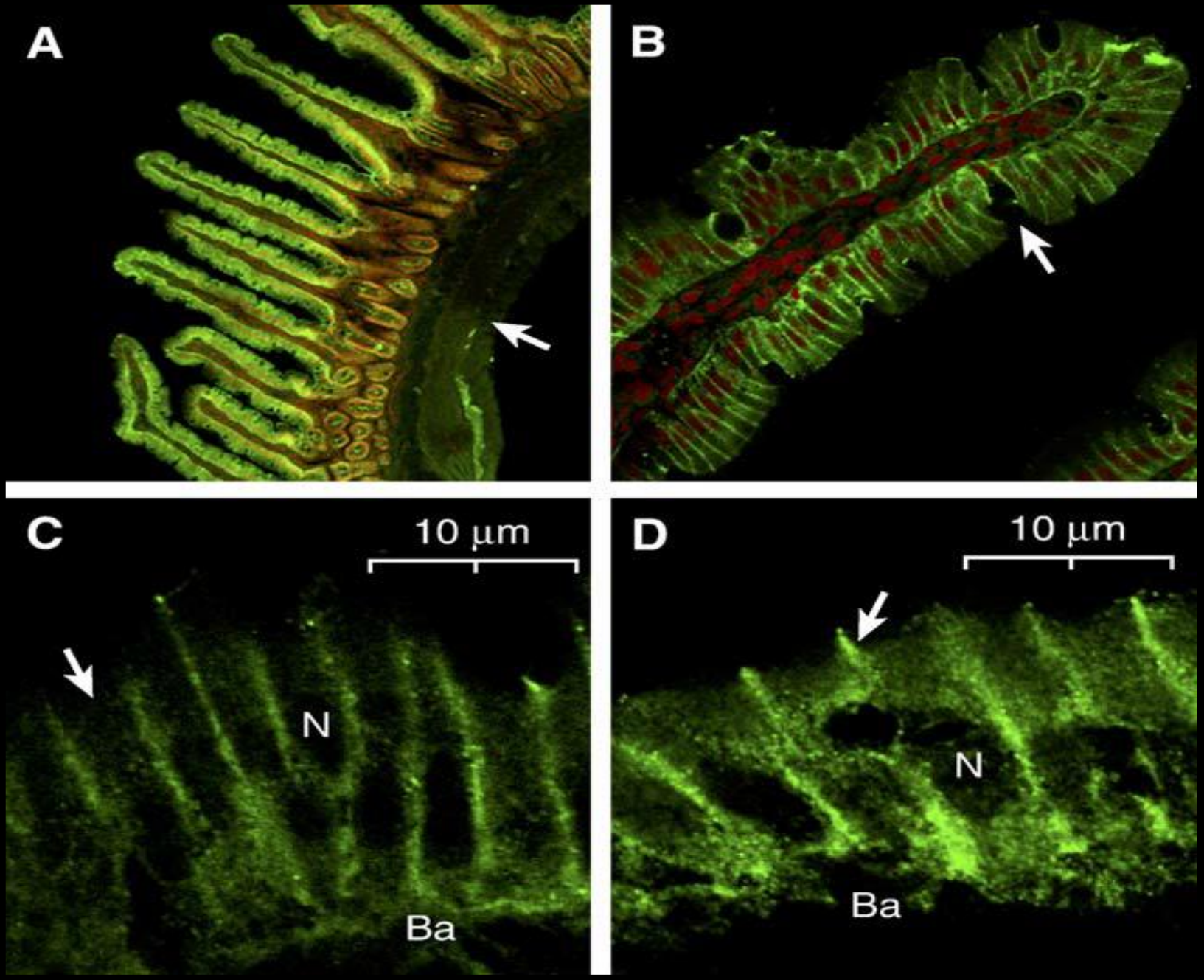


Stauber et al,
Am J Physiol Gastrointest Liver Physiol 2005

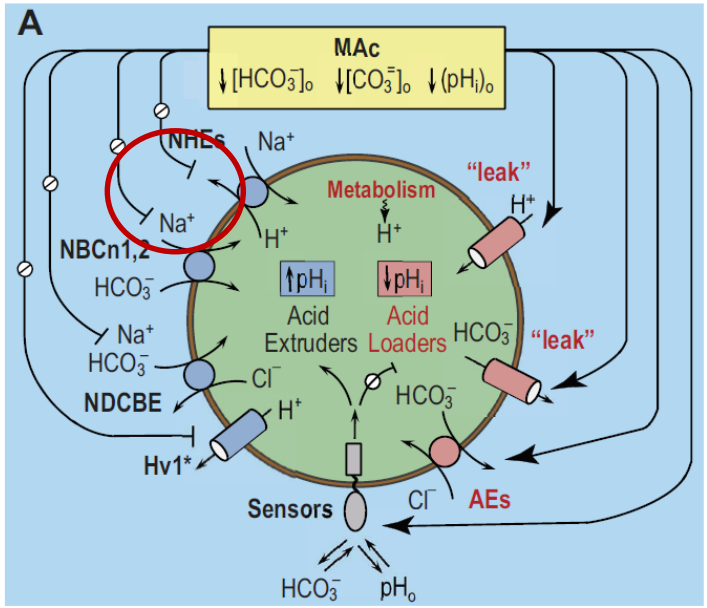


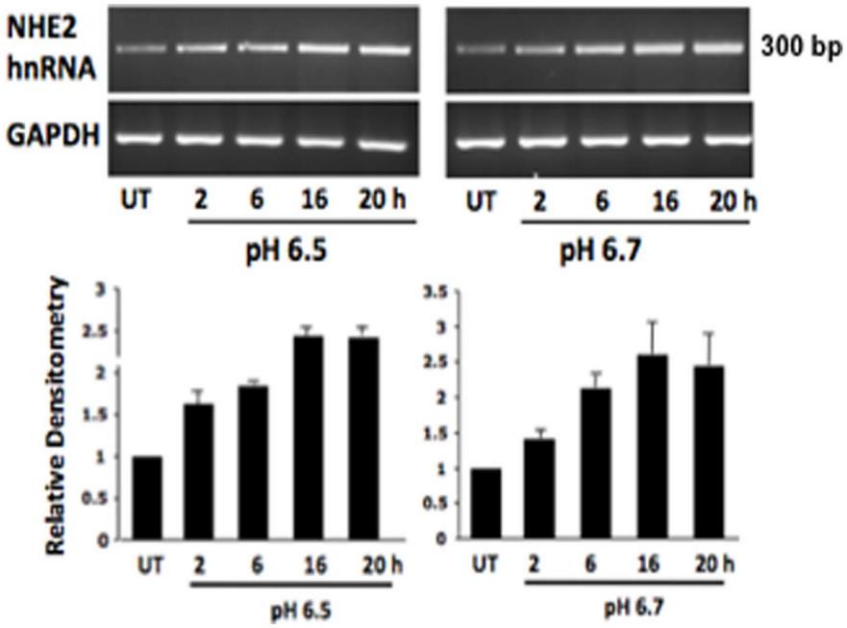


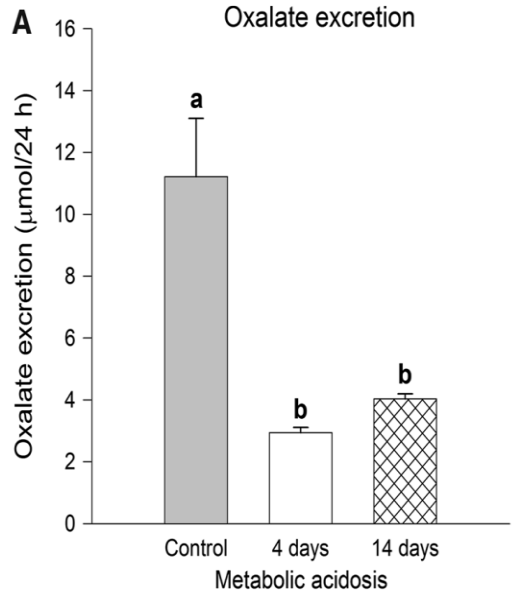
Charoenphandhu et al,
Am J Physiol Gastrointest Liver Physiol 2006

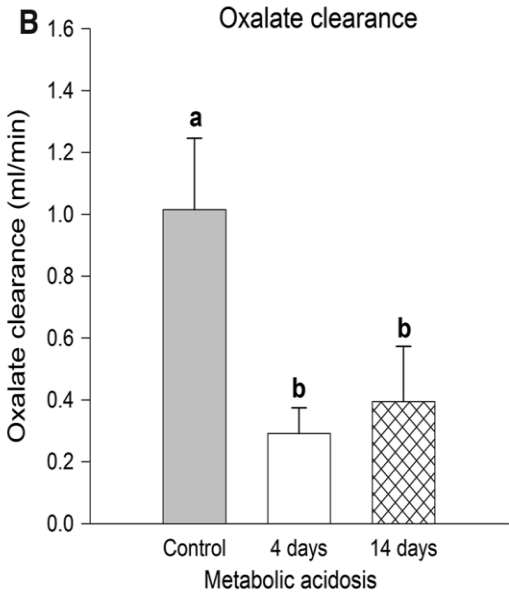


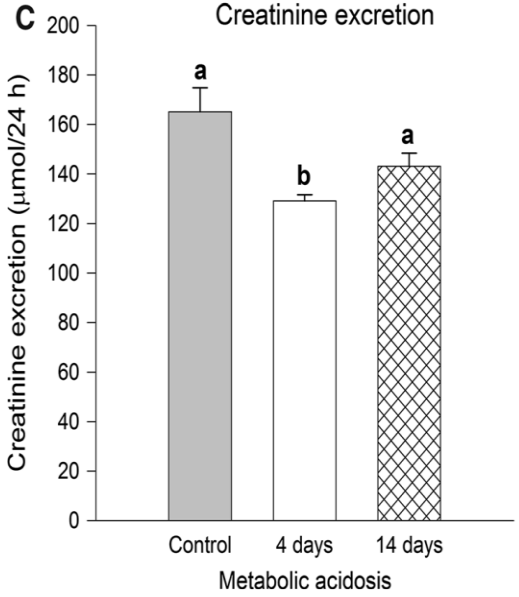
Charoenphandhu et al, Life Sci 2007

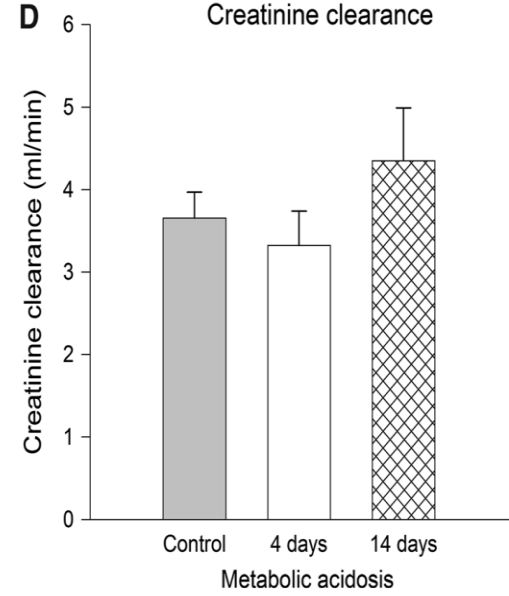












Muthusamy et al, PLoS One 2013

Whittamore & Hatch, Urolithiasis 2015

Table 2 Known genes upregulated in the duodenal epithelial cells of CMA rats

Gene name	
Chloride channel Kb	
Potassium voltage-gated channel, shaker-r	
Prolactin-like protein D	
Calyntenin 2	
CEA-related cell adhesion molecule 10	
Fatty acid binding protein 3	
Epimorphin	
Membrane-associated DHHC26 zinc finger	
Paraoxonase 1	
Synapsin II, transcript variant 2	
Inhibin beta-A	
FSH primary response 1	
Kinesin 13B	
Sex hormone binding globulin	
Toll-like receptor 4	
Sarcosine dehydrogenase	
Guanine nucleotide binding protein, alpha	
Mitochondrial hepatocellular carcinoma-de	
Synaptogyrin 1	
C1q and tumor necrosis factor related prot	
Gastrokine 1	
NHL repeat containing 1	
Ly6-C antigen	
Sterol O-acyltransferase 1	
Regulating synaptic membrane exocytosis	
Unc-5 homolog A (*C. elegans*)	
Dynein, axonemal, light intermediate poly	
GTP binding protein 3	
Calcium channel, voltage-dependent, beta	
Endothelial cell-specific molecule 1	
Synaptotagmin-like 1	
Tumor protein D52-like 2	
Corticotropin releasing hormone receptor 1	
ELAV (embryonic lethal, abnormal vision,	
Arginine vasopressin	
Solute carrier family 22 (organic cation tr	
Cadherin 13	
Complement component factor H	
Pregnancy upregulated non-ubiquitously e	
Fc receptor, IgE, high affinity I, alpha poly	
Guanylate cyclase 1, soluble, beta 3	
Phosphatidylinositol-specific phospholipase	
Zona pellucida glycoprotein 4	
Natriuretic peptide receptor 2	
Trefoil factor 1	
Mitogen-activated protein kinase 15	
Retinoic acid early transcript 1L	
Chemokine (C-X-C motif) receptor 4	
ST6 (alpha-*N*-acetyl-neuraminyl-2,3-beta-galactosyl-1, 3)-*N*-acetylgalactosaminide alpha-2,6-sialyltransferase 3	St6galnac3

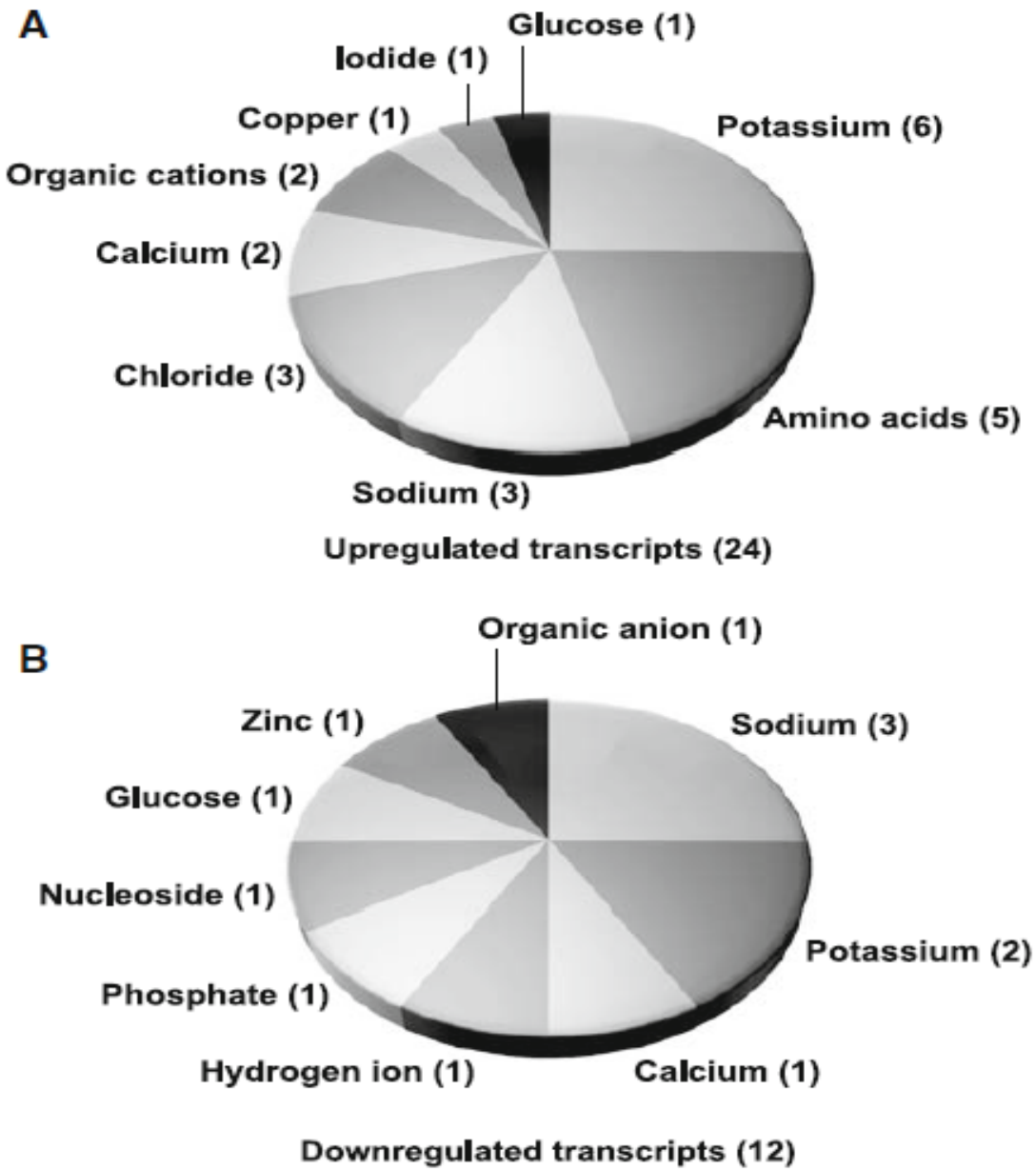


Table 3 Known genes downregulated in the duodenal epithelial cells of CMA rats

	Gene symbol
	Kynu
	Apoa2
	Rup2
	S100a9
	Mfap4
	Grik3
	Mcpt8
	Kremen1
	Taar6
	Dyx1c1
	P2ry6
	Pcyt1b
	V1rg6
	Cnksr2
	Tnfrsf8
	Tcp11
	Dbnl
	Gata3
	Atxn1
	Olr1687
	Ptgdr
	Neurod3
	Slc9a4
	Tas2r10
	Brinp2
yme	Gcnt2
ic	Myh3
ins, 1 (mapped)	Uhrf1_mapped
	Rax
	Prlpi
	Fxyd7
	VCS-beta1
	Ly49i5
	Sftpd
	tGapl
	RT1-M1-2
	Aldh6a1
	LOC306929
Gamma-aminobutyric acid (GABA-A) receptor, subunit alpha 4	Gabra4

Wongdee et al, Mol Cell Biochem 2009

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Metformin-associated Lactic Acidosis Masquerading as Ischemic Bowel

Correia & Bronander, Am J Med 2011

Συμπεράσματα

- Η συσχέτιση της οξέωσης με συγκεκριμένα κλινικά ευρήματα είναι δύσκολη
- Η οξέωση προκαλεί απώλεια μυϊκής μάζας
- Το όξινο περιβάλλον προκαλεί μυϊκό κάματο
- Το όξινο περιβάλλον δεν προκαλεί μυϊκό κάματο
- Η αλκαλοθεραπεία ίσως βελτιώνει το χρόνιο πόνο
- Το έντερο συμμετέχει ποικιλιτρόπως στην αντιρρόπηση των οξεοβασικών διαταραχών


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