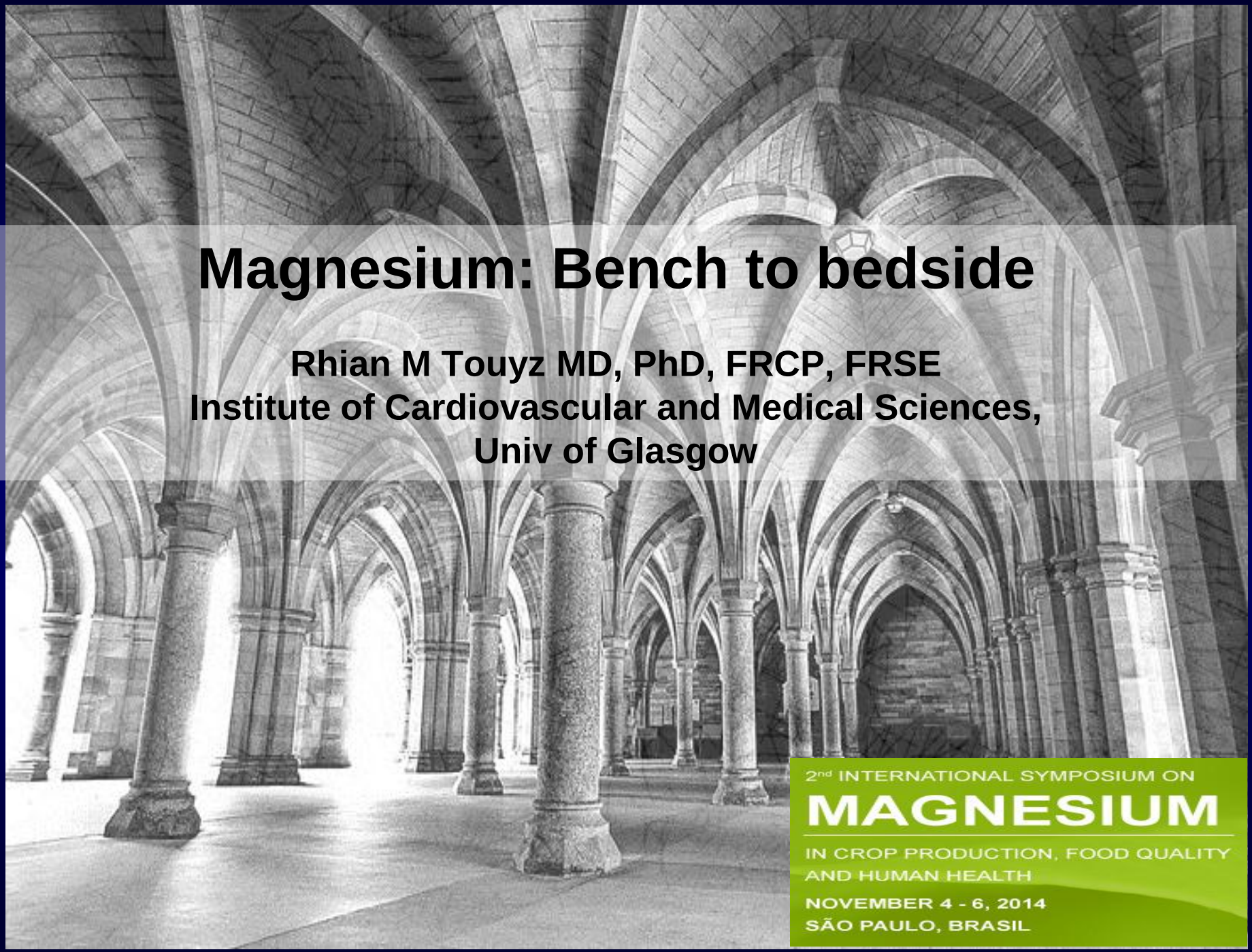


Magnesium: Bench to bedside

Rhian M Touyz MD, PhD, FRCP, FRSE
Institute of Cardiovascular and Medical Sciences,
Univ of Glasgow

2nd INTERNATIONAL SYMPOSIUM ON
MAGNESIUM
IN CROP PRODUCTION, FOOD QUALITY AND HUMAN HEALTH
NOVEMBER 4 - 6, 2014
SÃO PAULO, BRASIL

Joseph Black 1728 - 1799

Discoverer of magnesium as an element

- At the University of Glasgow, he discovered magnesium as an element in 1750-1755.
- Black found out that MgO was a compound of magnesia and that magnesia was not the same as calcium carbonate.
- He submitted this for his MD thesis

A history of magnesium in clinical research

Epson salts

elemental Mg^{2+}

Mg^{2+} Isolation

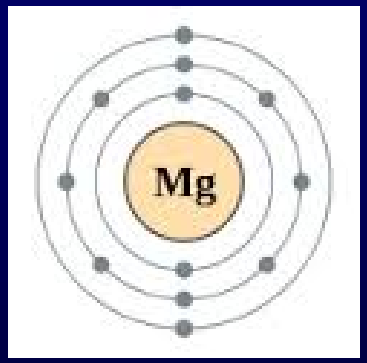
Mg^{2+} in plasma

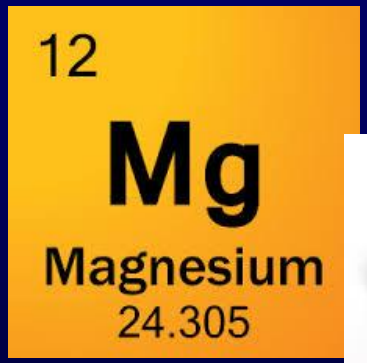
Mg^{2+} essential for life

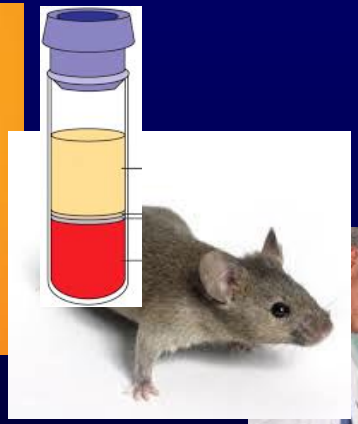
Hypomagnesemia in patients

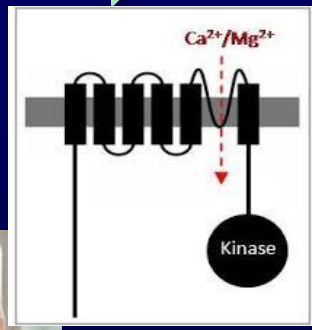
Mg^{2+} transporters

1600 1700 1800 1900 2000

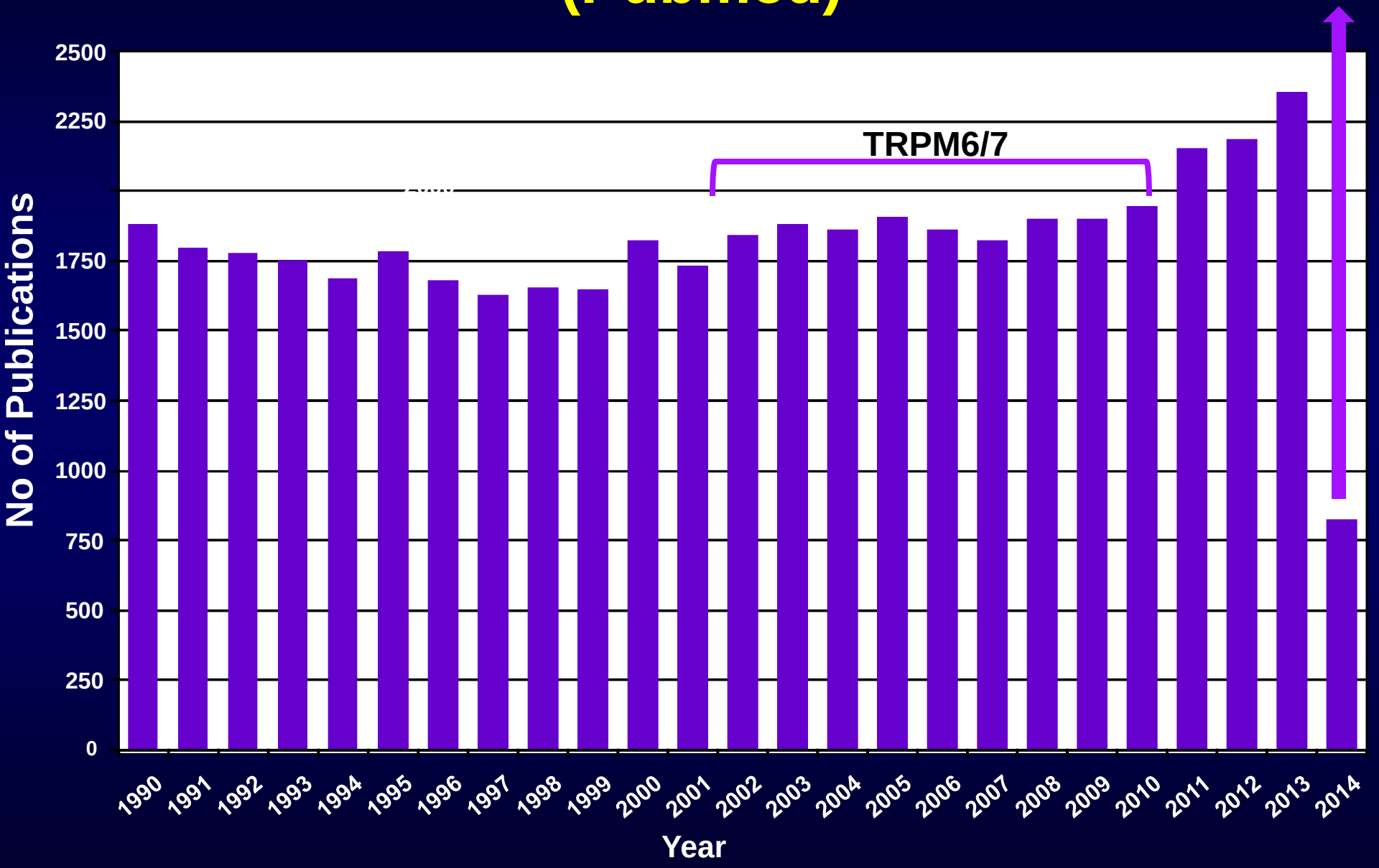






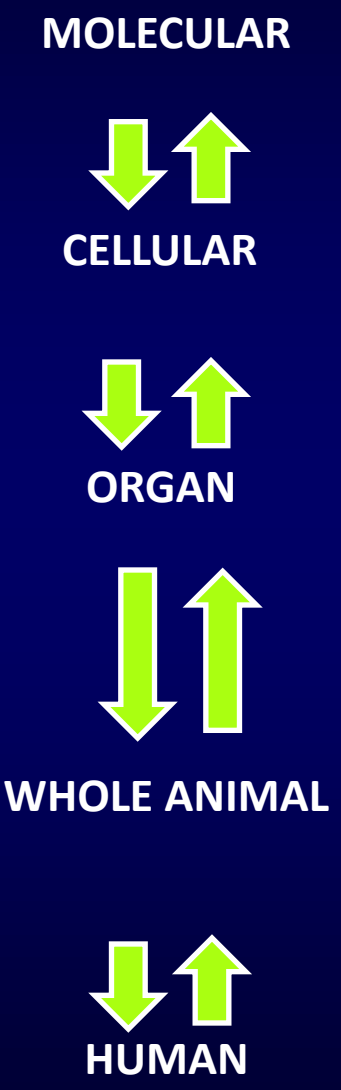


Magnesium Publications 1990-2014 (Pubmed)



Outline

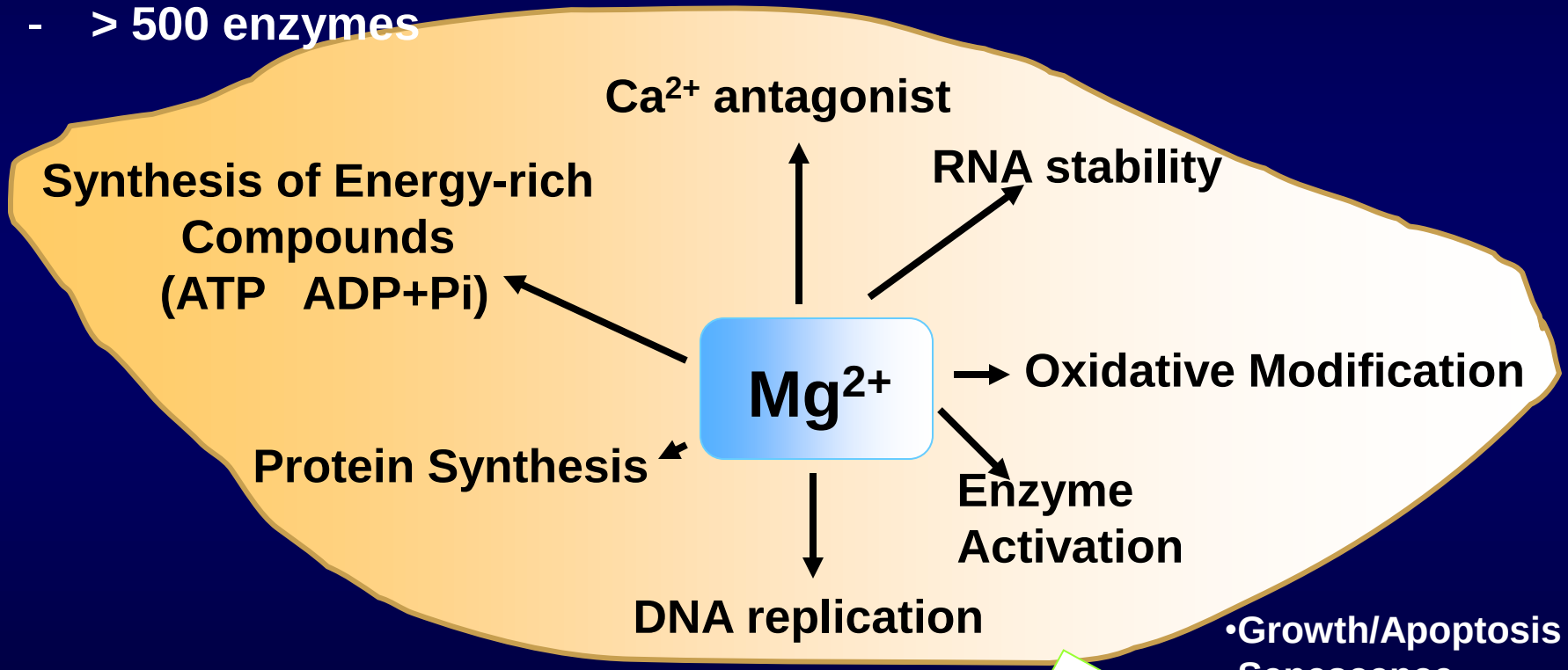
- Biochemistry and cell function
- Mg^{2+} and intracellular signaling
- Mg^{2+} transporters and cell biology
- Physiology of Mg^{2+}
- Mg^{2+} in the clinic



Major Biochemical Properties of Mg^{2+}

Magnesium:

- Second most abundant intracellular cation
- Most abundant cellular divalent cation
- > 500 enzymes



- Growth/Apoptosis
- Senescence
- Differentiation
- Contraction/dilation
- Inflammation, Fibrosis
- ……

$ATP + H_2O \xrightleftharpoons[Mg^{2+}]{ATPase} ADP + Pi$

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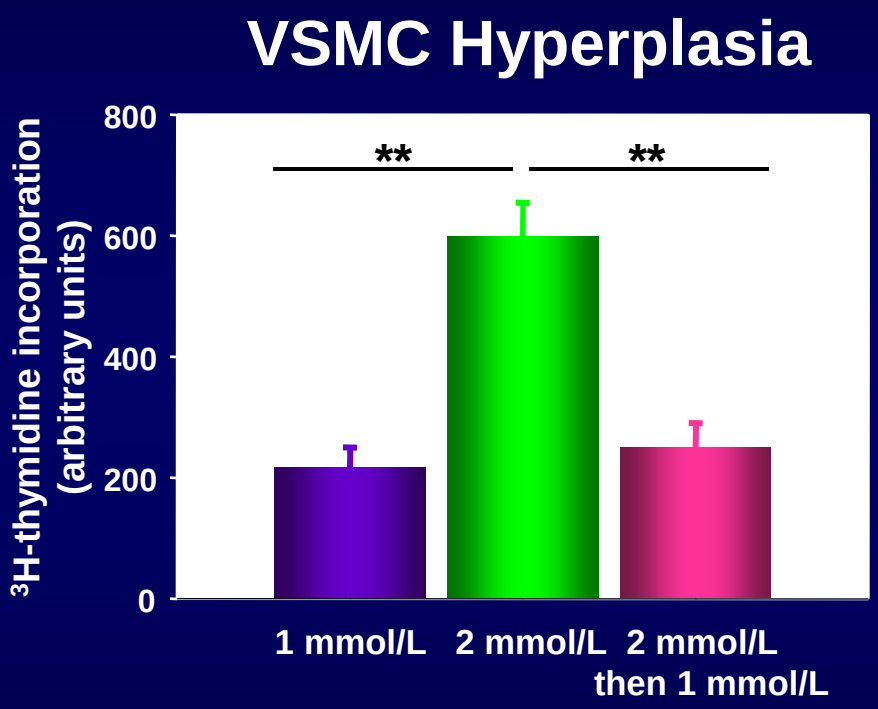
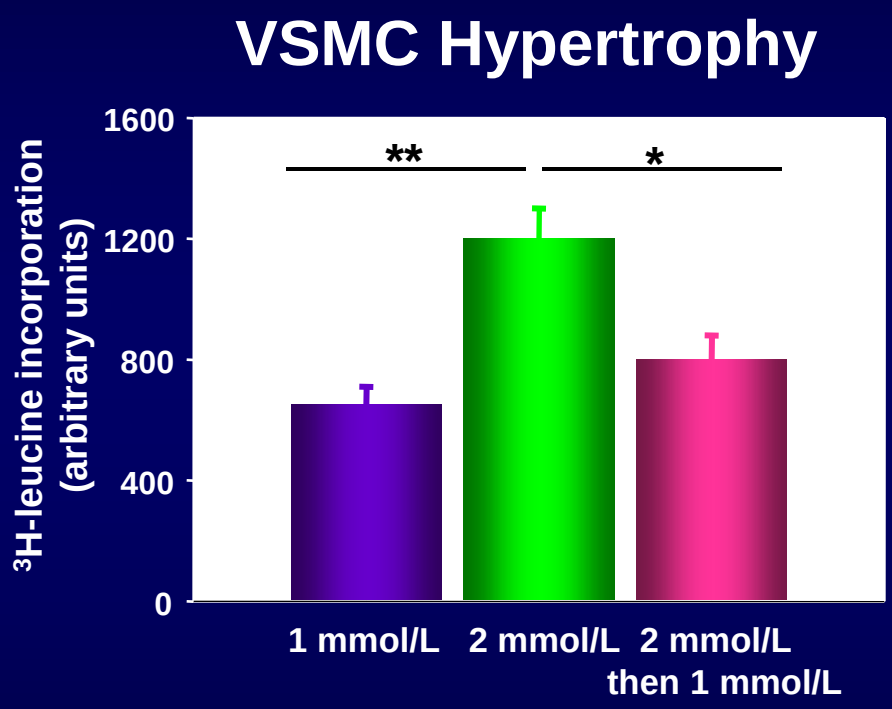
Mg^{2+} and cell function

- Survival
- Apoptosis
- Growth
- Proliferation
- Migration
- Differentiation
- Inflammation

Effects of Mg^{2+} on VSMC Growth

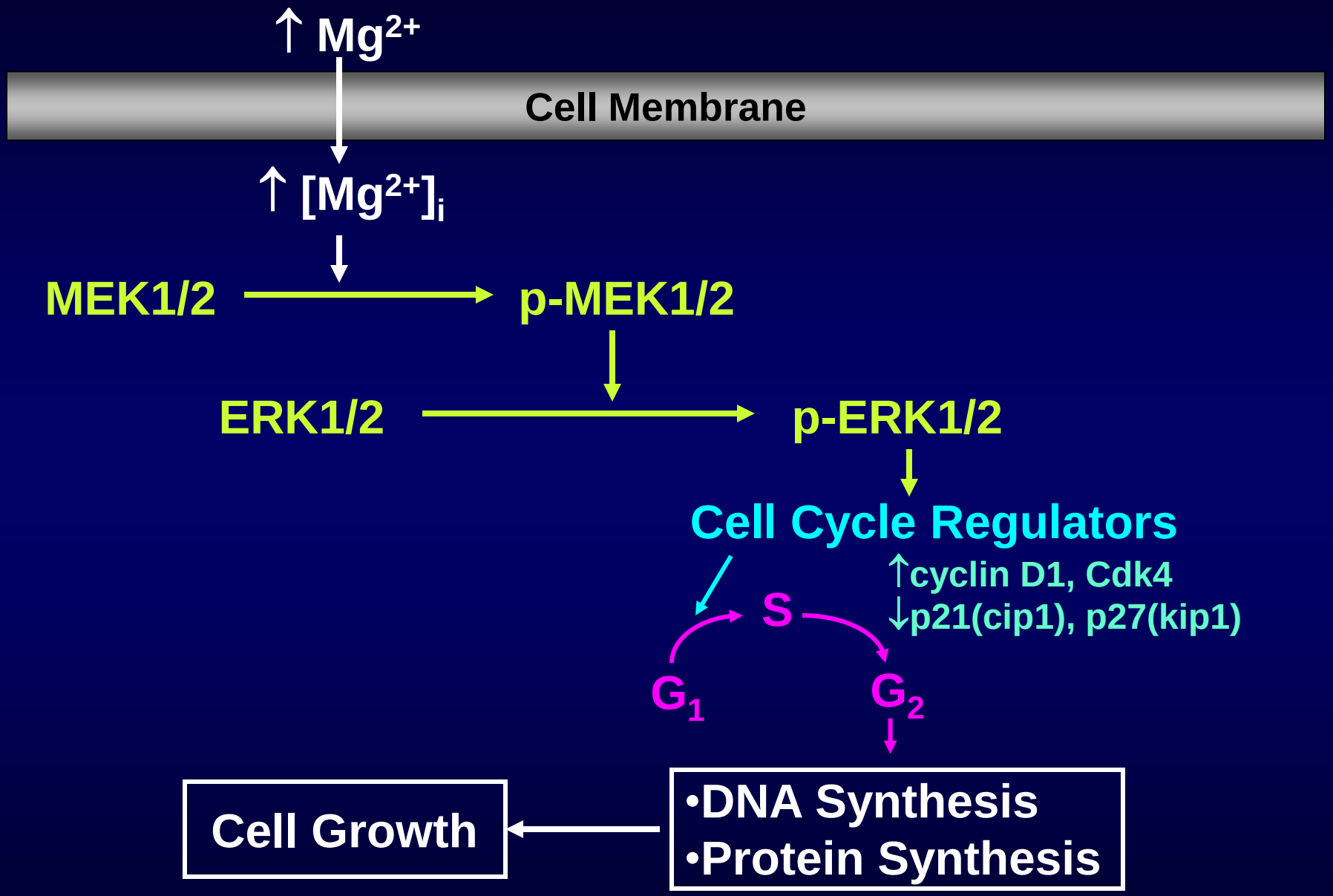




*p<0.05, **p<0.01

J Cell Physiol. 2003;197(3):326

Mechanisms Whereby $[Mg^{2+}]_i$ Influences Cell Growth



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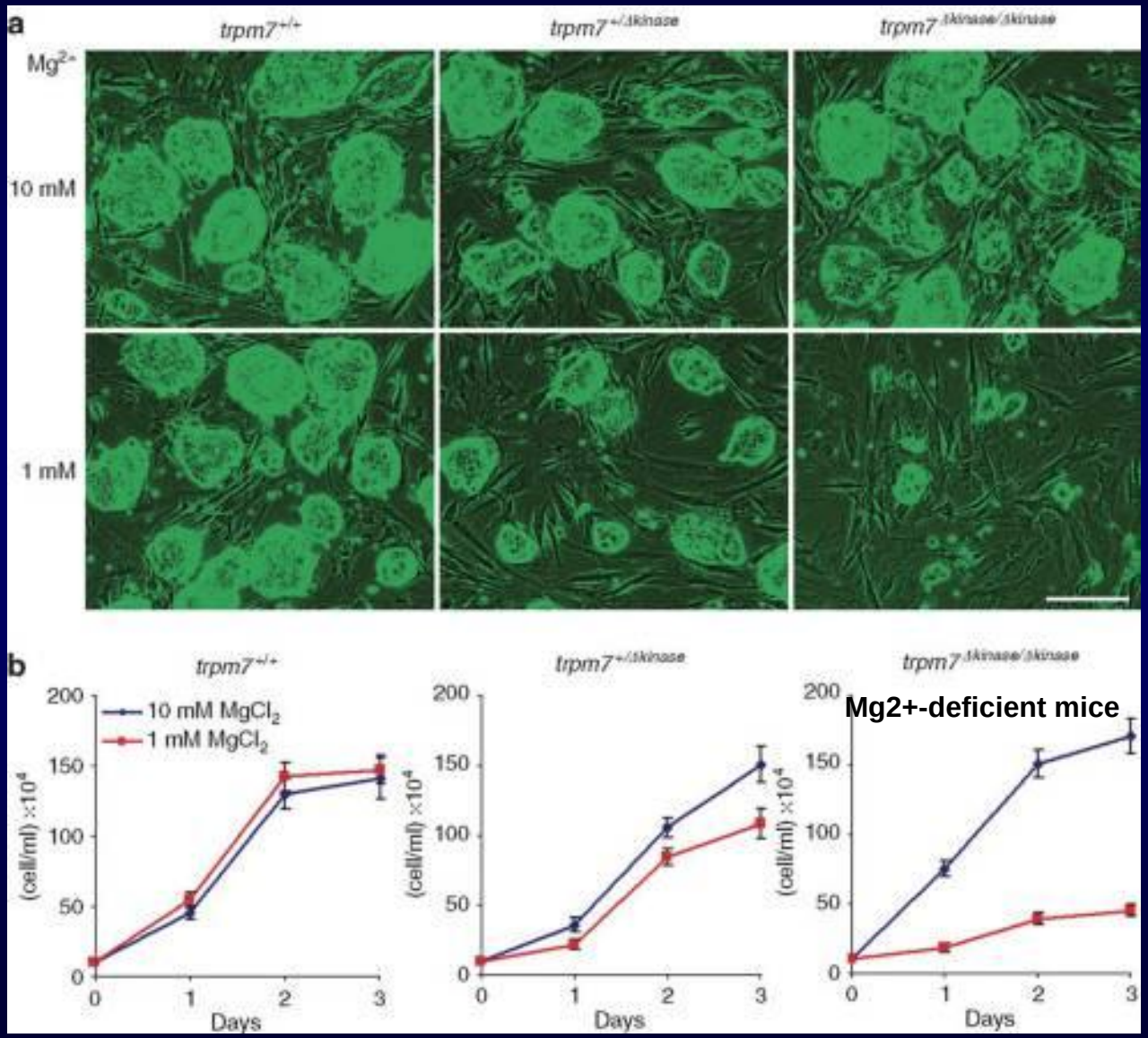
Mg^{2+} supplementation rescues the growth arrest phenotype of TRPM7-Mg2+ deficient ES cells



Ryazanov. Nature 2010:1109

Functions of cellular Mg^{2+}

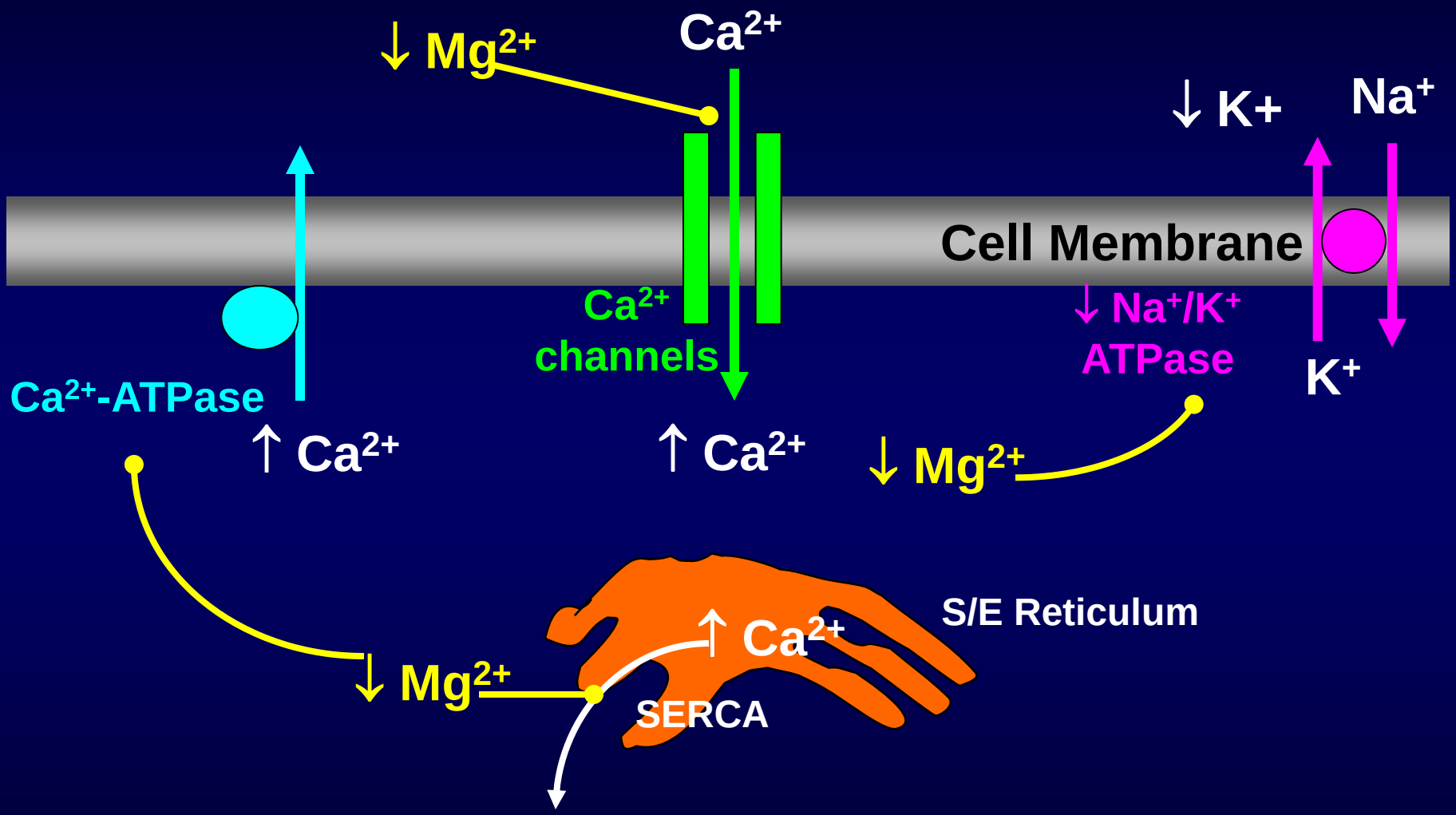
Mg++-induced endothelial cell **migration**: Substratum selectivity and receptor-involvement
Lapidos. Angiogenesis 2001;4.

Magnesium decreases **inflammatory** cytokine production.
Sugimoto. J Immunol 2012

Magnesium: The missing element in molecular views of cell **proliferation** control
Rubin. Bioessays. 2005

Vascular smooth muscle cell **differentiation** to an osteogenic phenotype involves TRPM7 modulation by Mg2+
Montezano Hypertension 2011

Mg^{2+} influences Ca^{2+} and K^{+} Homeostasis



- 40% patients with hypomagnesemia have hypokalemia.
- 60% patients with hypokalemia have hypomagnesemia.

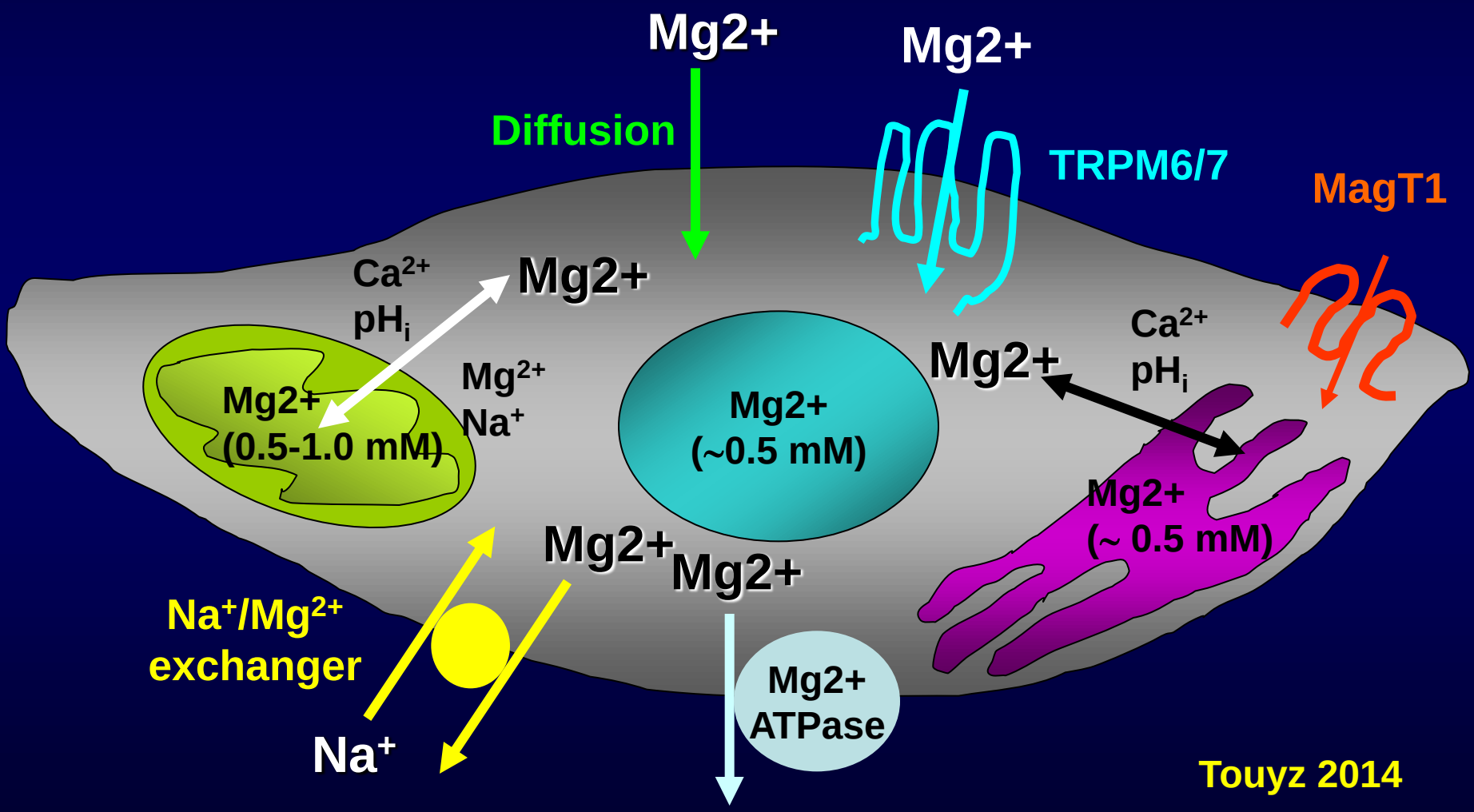
Mg^{2+} as a second messenger in immune cells

Second messenger role for Mg^{2+} revealed by human T-cell immunodeficiency

Li et al. Nature 2011:475:471–476

Immunology: Magnesium in a signaling role. Wu. Nature. 2011;475(7357)

For Mg^{2+} to Influence Cellular Events, Mg^{2+} itself needs to be Regulated: Cellular level



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Editorials

Mysteries of Magnesium Homeostasis

Elizabeth Murphy

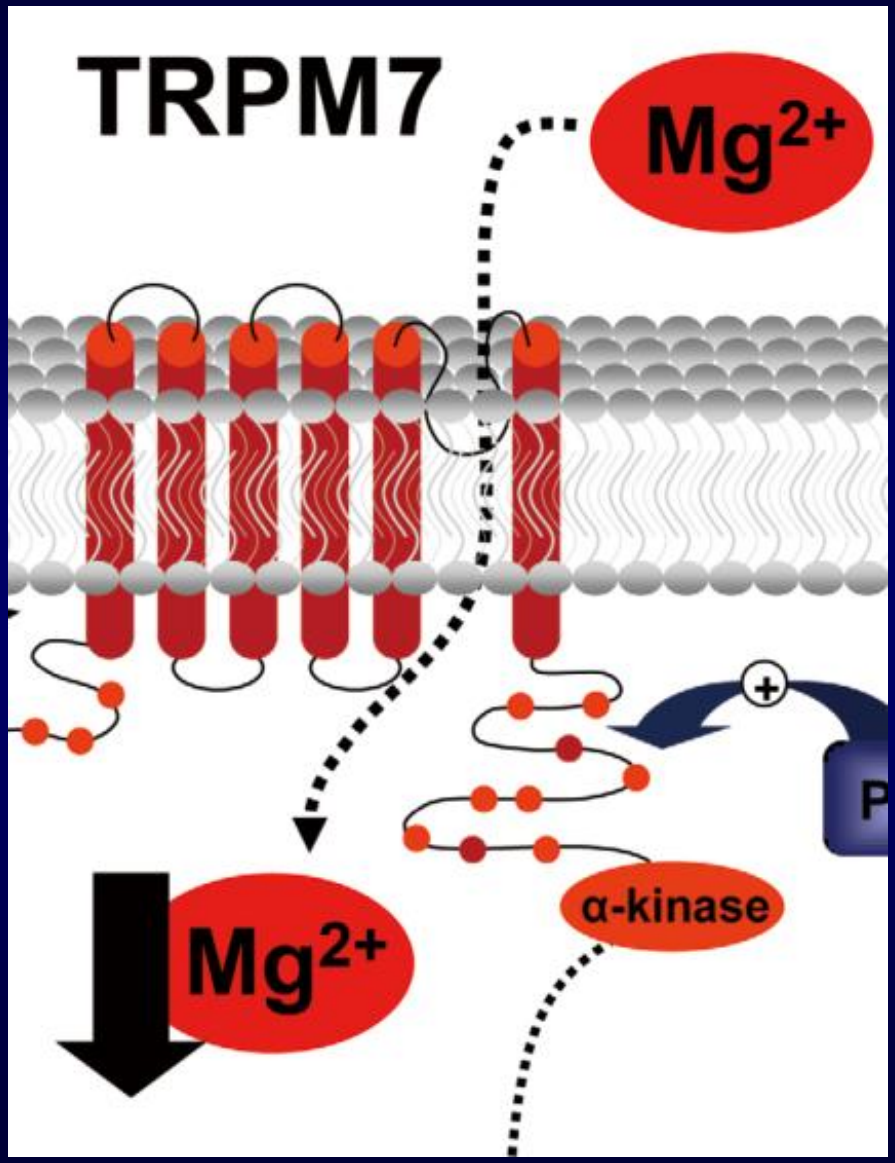
Circulation Research. 2000;86:245

Mg^{2+} transporters in mammalian cells

Transporter	Mutation/disease
TRPM6	Hypomagnesemia+hypocalcemia
TRPM7	
MagT1	X-MEN
SLC41A1	
SLC41A2	
CNNM3	
MRS2	

Transmembrane Mg^{2+} Transporter – TRPM6/7

(Ryazanova, Runnels, Nadler, Bindels, Fleig, Gudderman, Chubanov)



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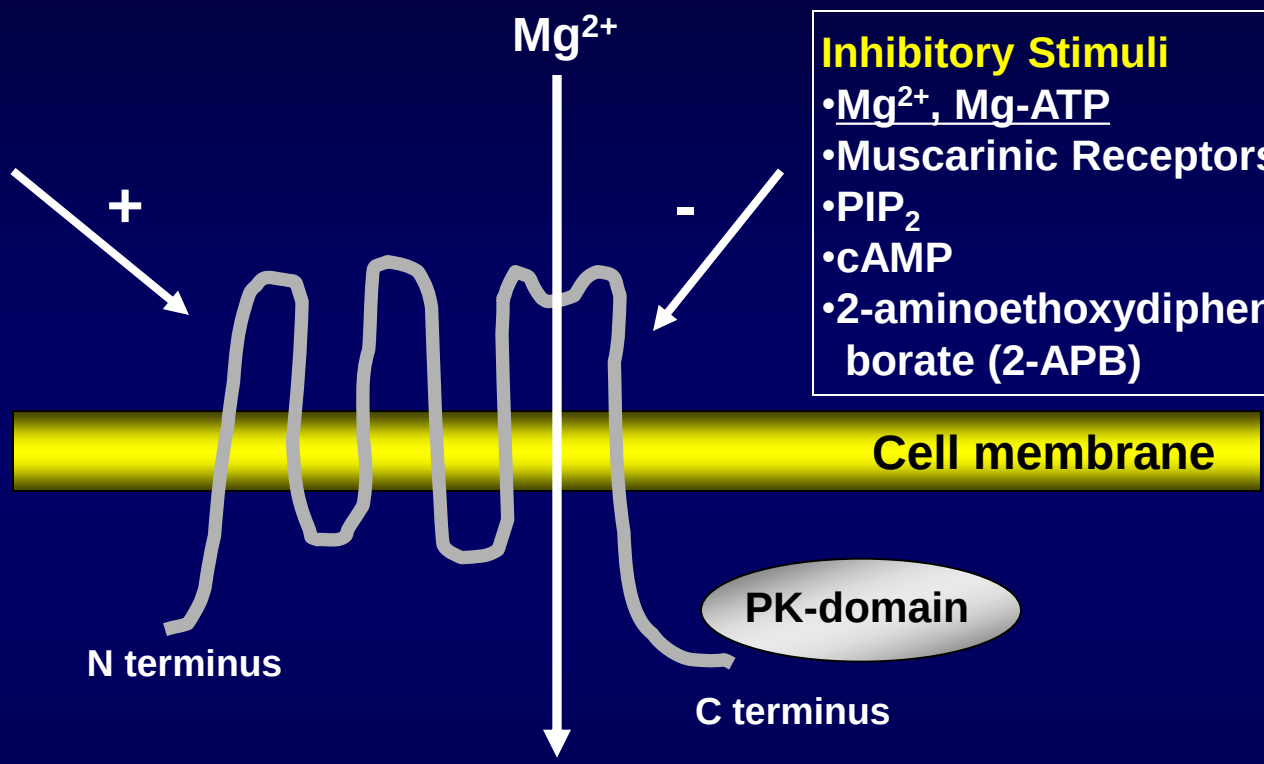
Regulation of TRPM7 (Cell lines)

Stimulatory Stimuli

Receptors
- Bradykinin
- Estrogen
- Muscarinic receptors
- EGFR

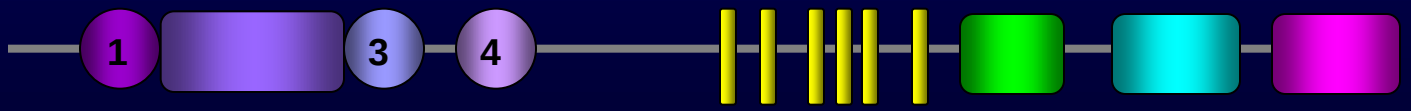
Mechanical factors
- Stretch, flow, pressure

Signaling molecules
- PLC, PKC, PKA
- cAMP
- Phosphatidylinositol bisphosphate (PIP_2)



Inhibitory Stimuli
- Mg^{2+}, Mg-ATP
- Muscarinic Receptors
- PIP_2
- cAMP
- 2-aminoethoxydiphenyl borate (2-APB)

Role of kinase domain is unclear



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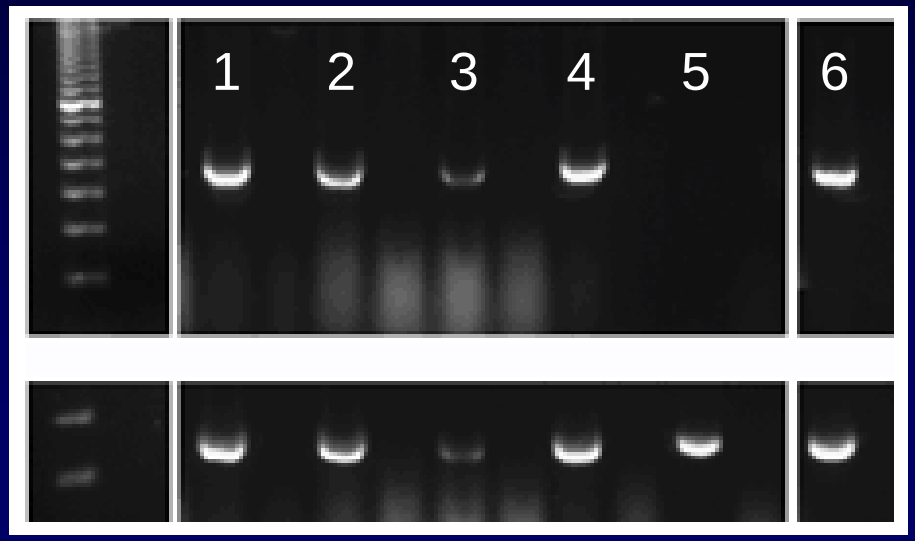
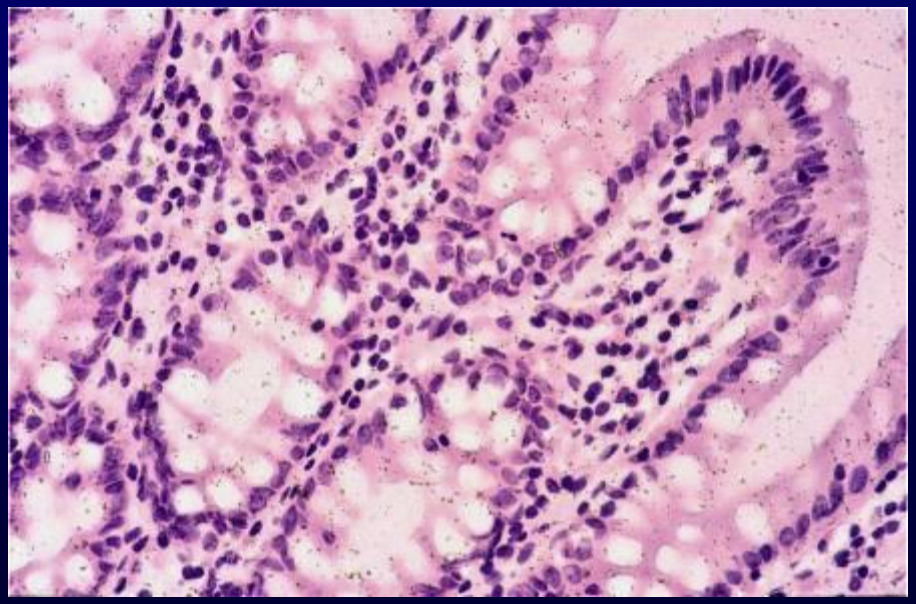
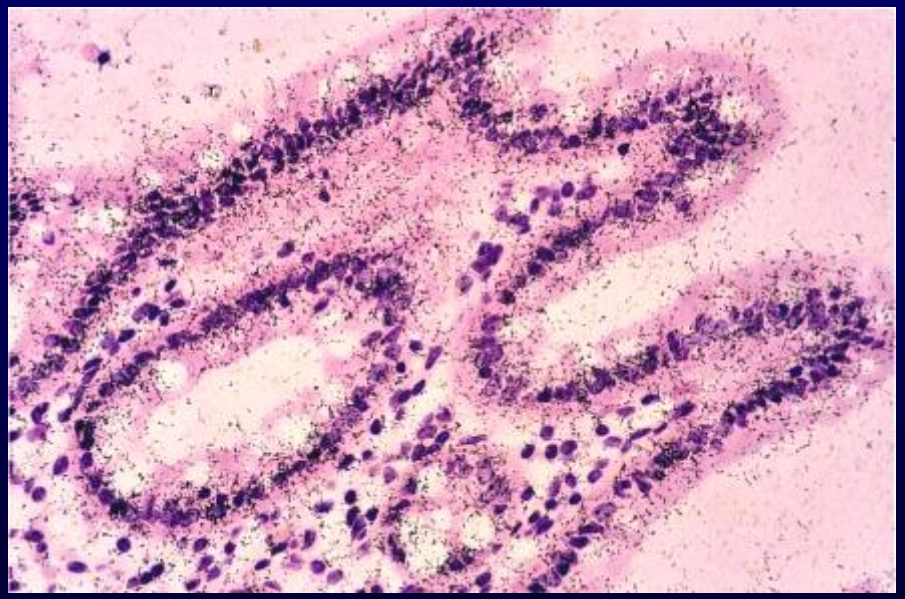
TRPM6 Expression in the Gastrointestinal Tract



1. Duodenum
2. Jejunum
3. Ileum
4. Colon
5. Liver
6. Kidney



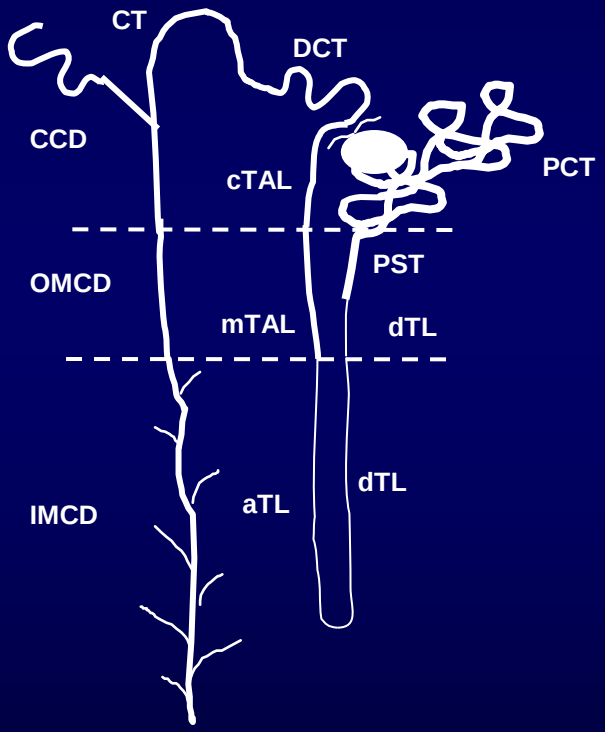
sense

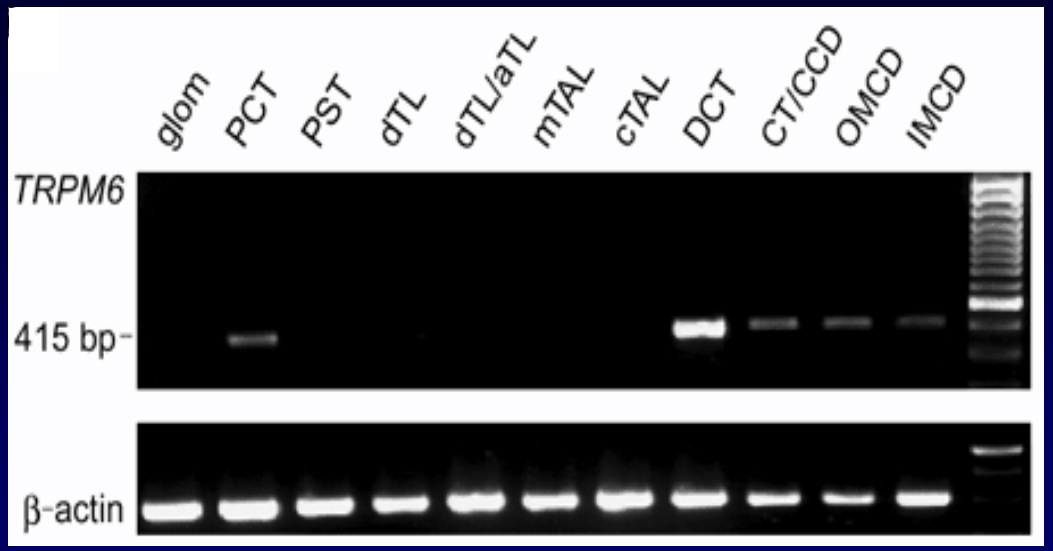


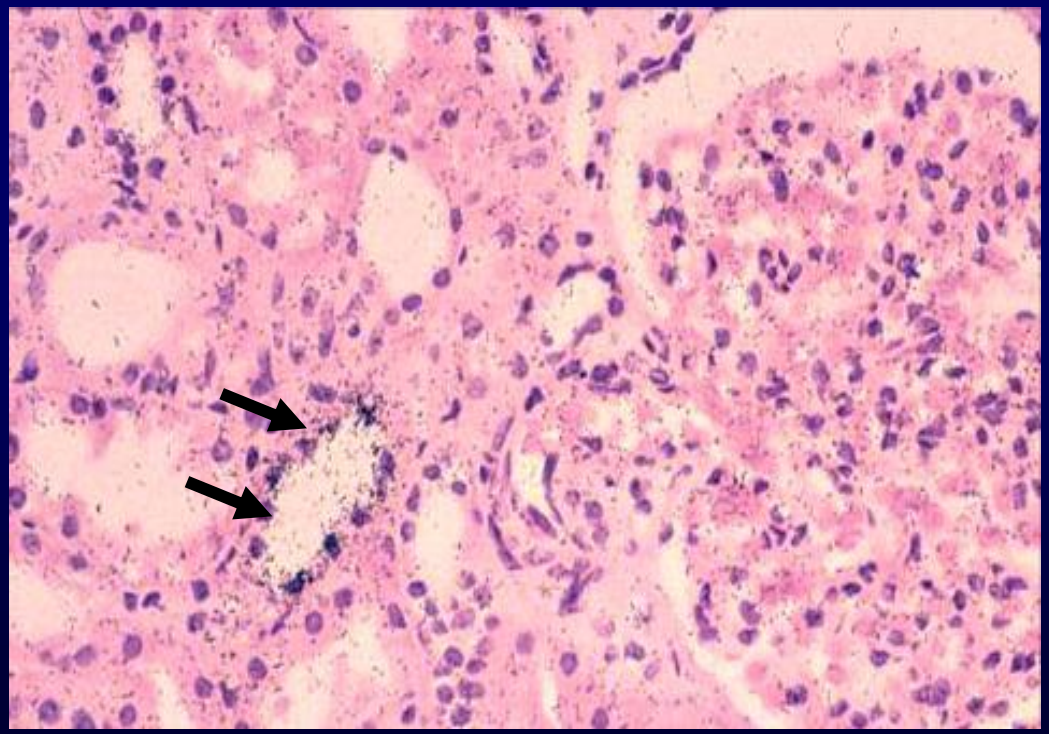
antisense

Schlingmann et al. Nat Genet 2002

TRPM6 expression along the nephron

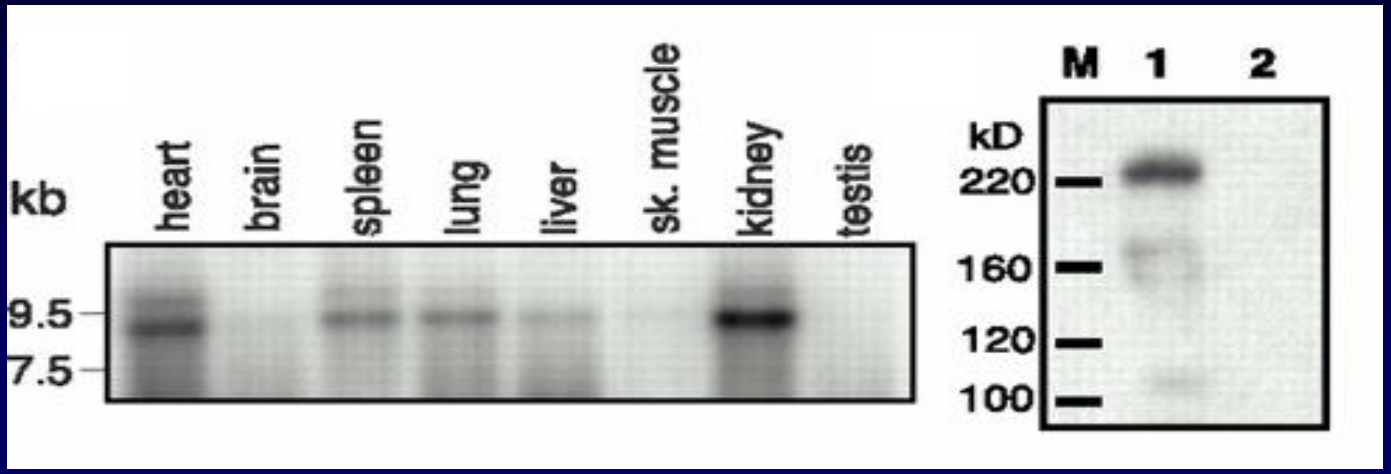






Schlingmann et al. Nat Genet 2002

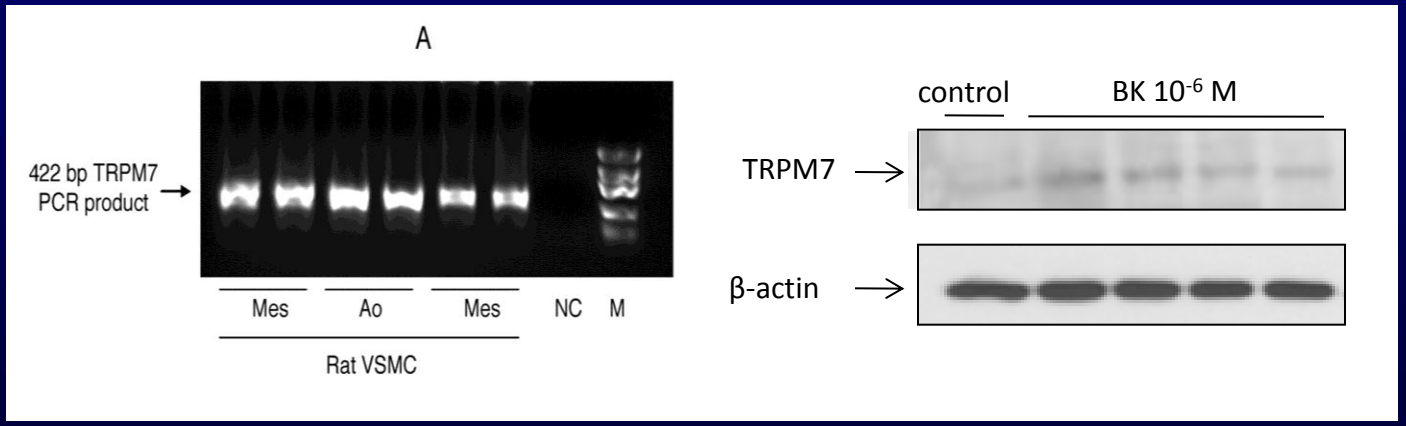
Expression of TRPM7



Northern blot analysis of TRPM7

Western blot of TRPM7

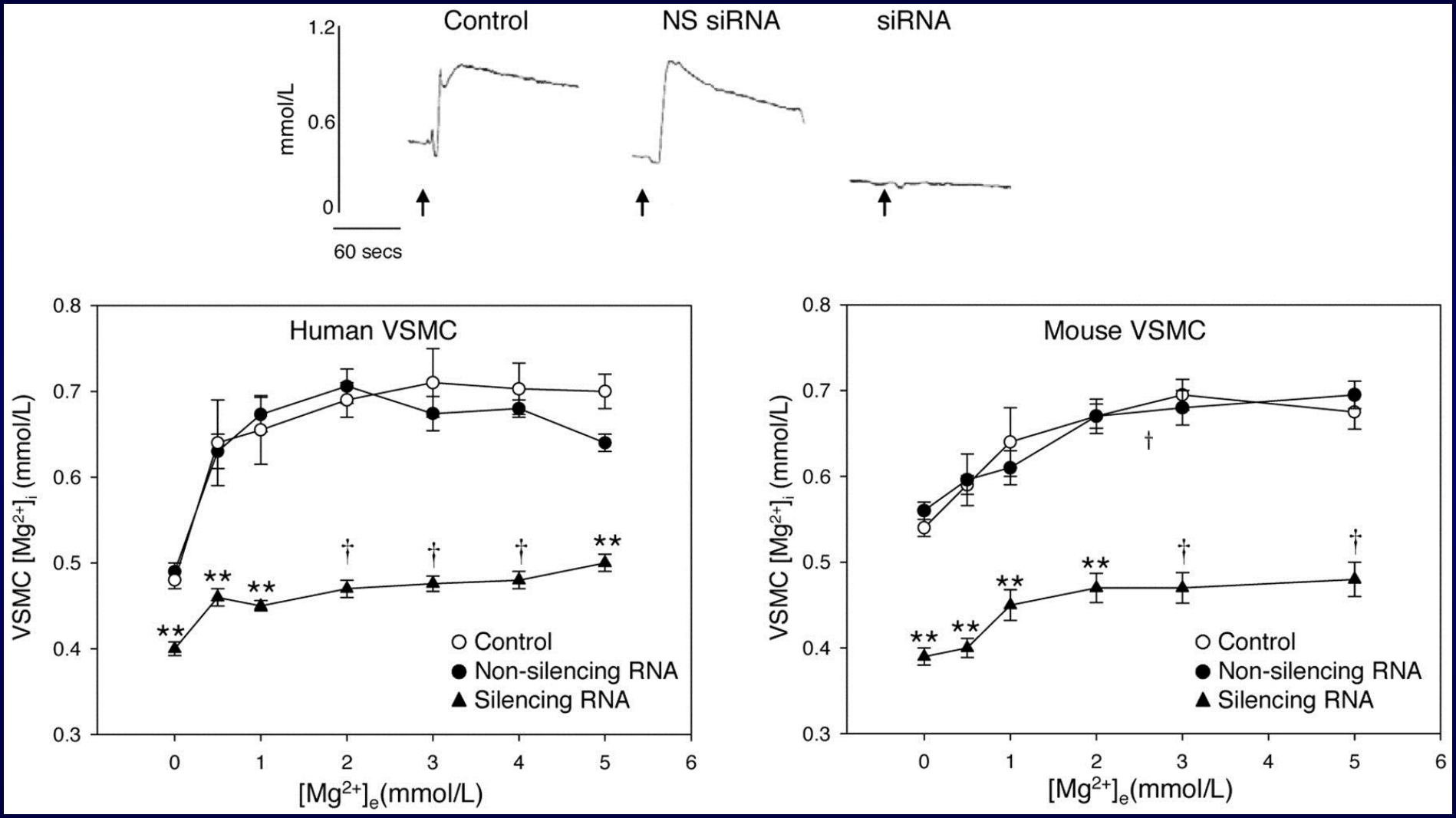
Science 2001;291:1043



Mouse VSMC

Circ Res 2010

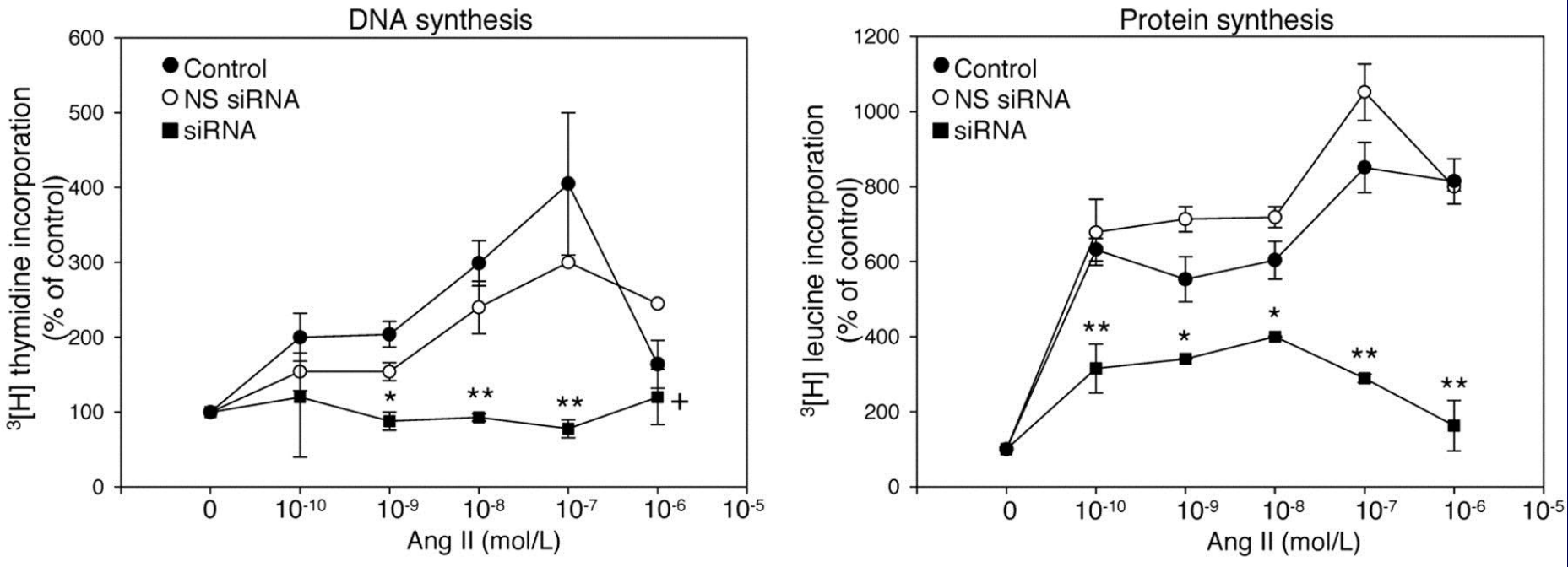
TRPM7 Regulates $[Mg^{2+}]_i$ in VSMCs



Effects of increasing $[Mg^{2+}]_e$ on $[Mg^{2+}]_i$ in TRPM7-deficient VSMCs.

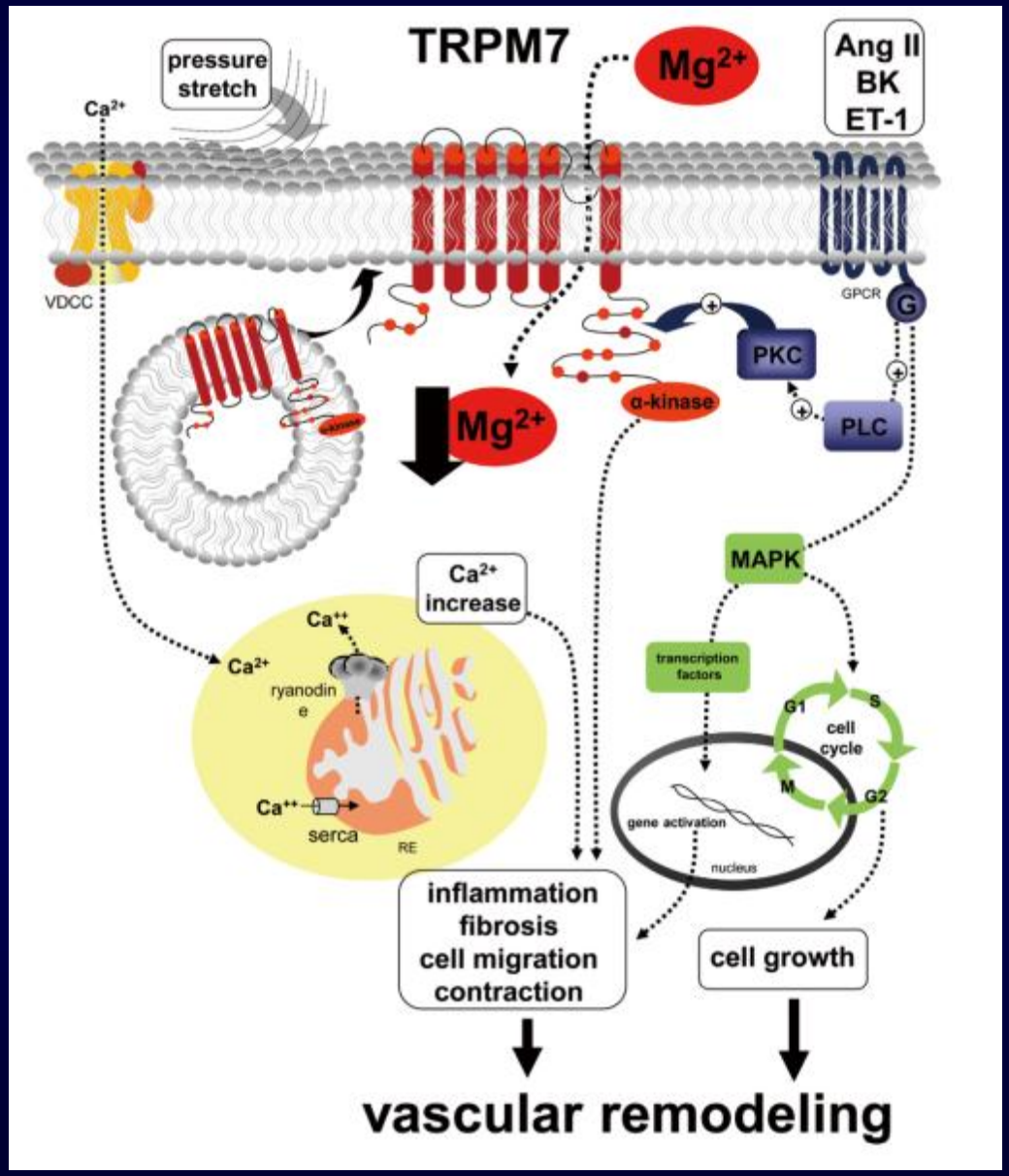
Touyz. Circ Res. 2005;96(2):207-15

TRPM7 Plays a Critical Role in Ang II-stimulated VSMC Growth



Touyz. Circ Res. 2005;96(2):207-15

TRPM7 and the cardiovascular system



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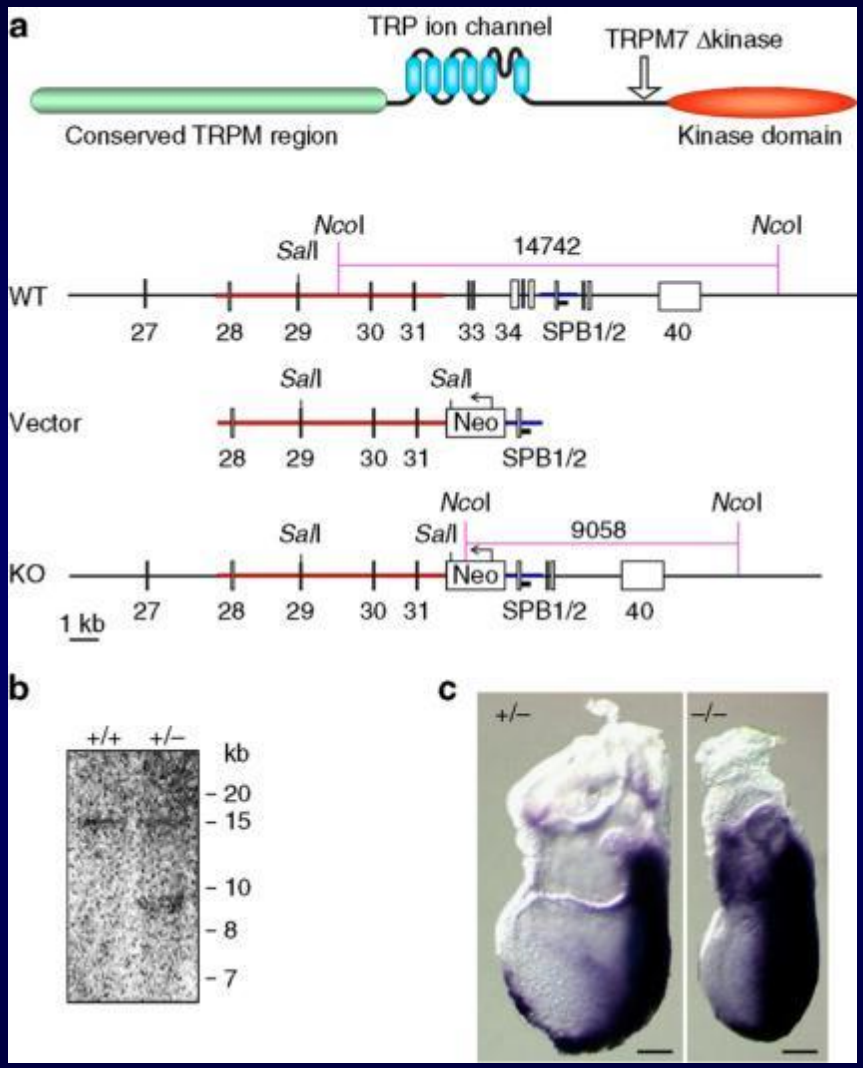
Generation of TRPM7-deficient mice

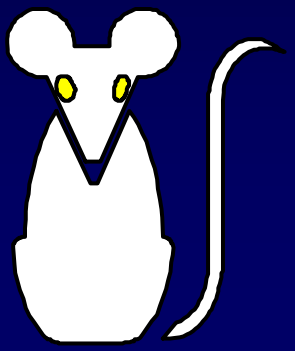


(a) A schematic representation of TRPM7 protein. Arrow indicates position of truncation in TRPM7$^{\Delta kinase}$ mice. (b) Southern blot analysis of genomic DNA from wild-type (+/+) or TRPM7$^{+/\Delta kinase}$ (+/−) mice (c) TRPM7$^{+/\Delta kinase}$ (+/−) and TRPM7$^{\Delta kinase/\Delta kinase}$ (−/−) embryos at 7.5 days Scale bar, 100 μm

Ryazanov. Nature 2010:1109

Cardiovascular phenotype in TRPM7+/- mice

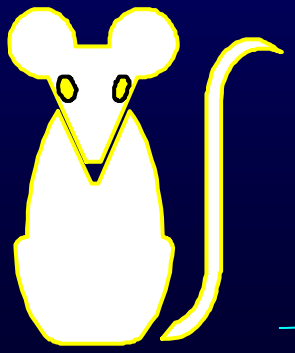
Control

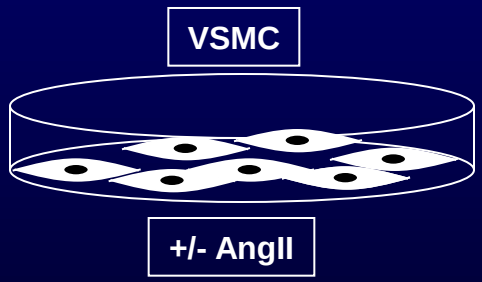


Angiotensin II infusion at 400 ng/kg/min, 2 wks

- Blood pressure
- Plasma and urine ions
- Cardiac, vascular and renal injury
- Inflammatory markers
- TRPM7 expression

TRPM7$^{+/\Delta kinase}$



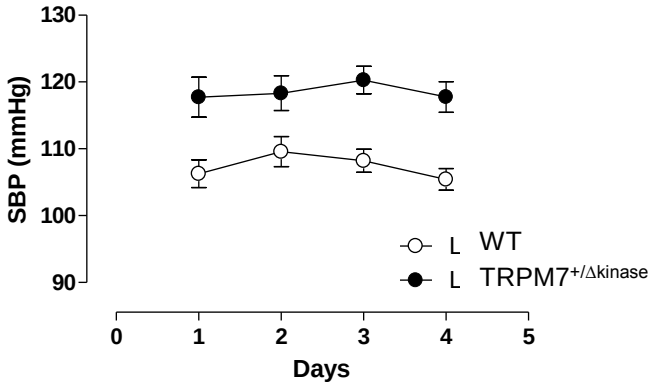


Western Blot

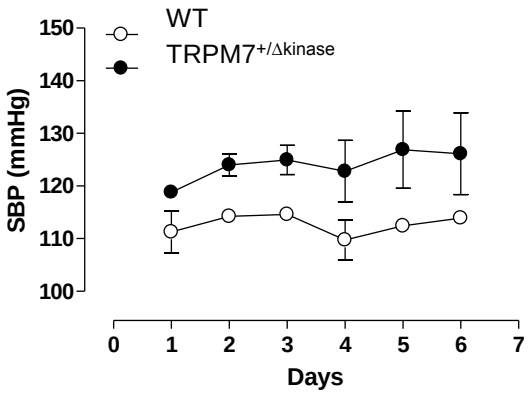
Phospho ERK 1/2
Phospho-JNK
Phospho-p38

Systolic blood pressure

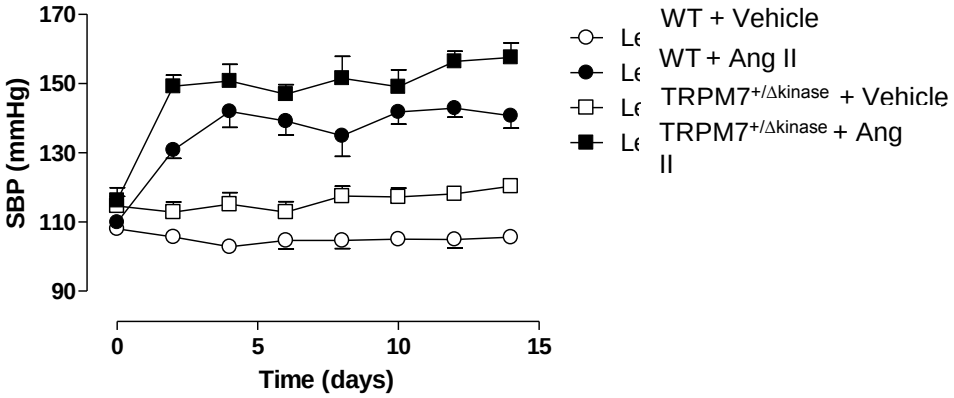
Baseline (Tail-Cuff)



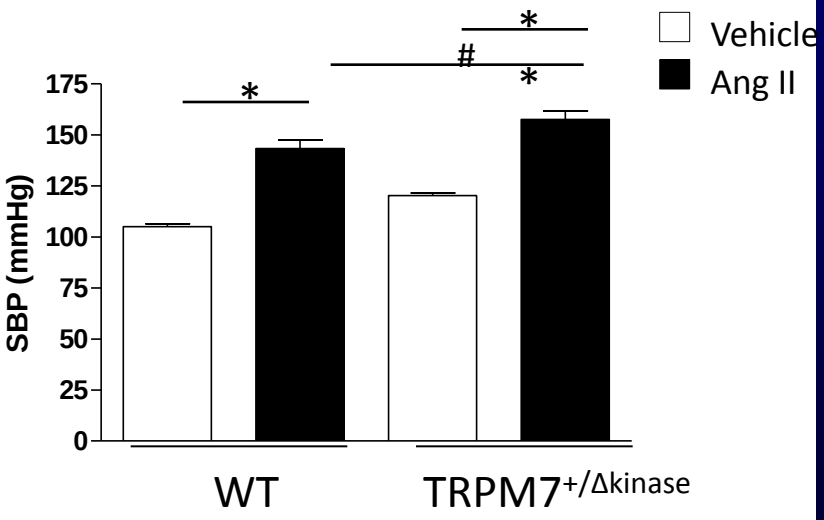
Baseline (Telemetry)



Ang II pump (Tail-Cuff)



Final SBP (Day 14)



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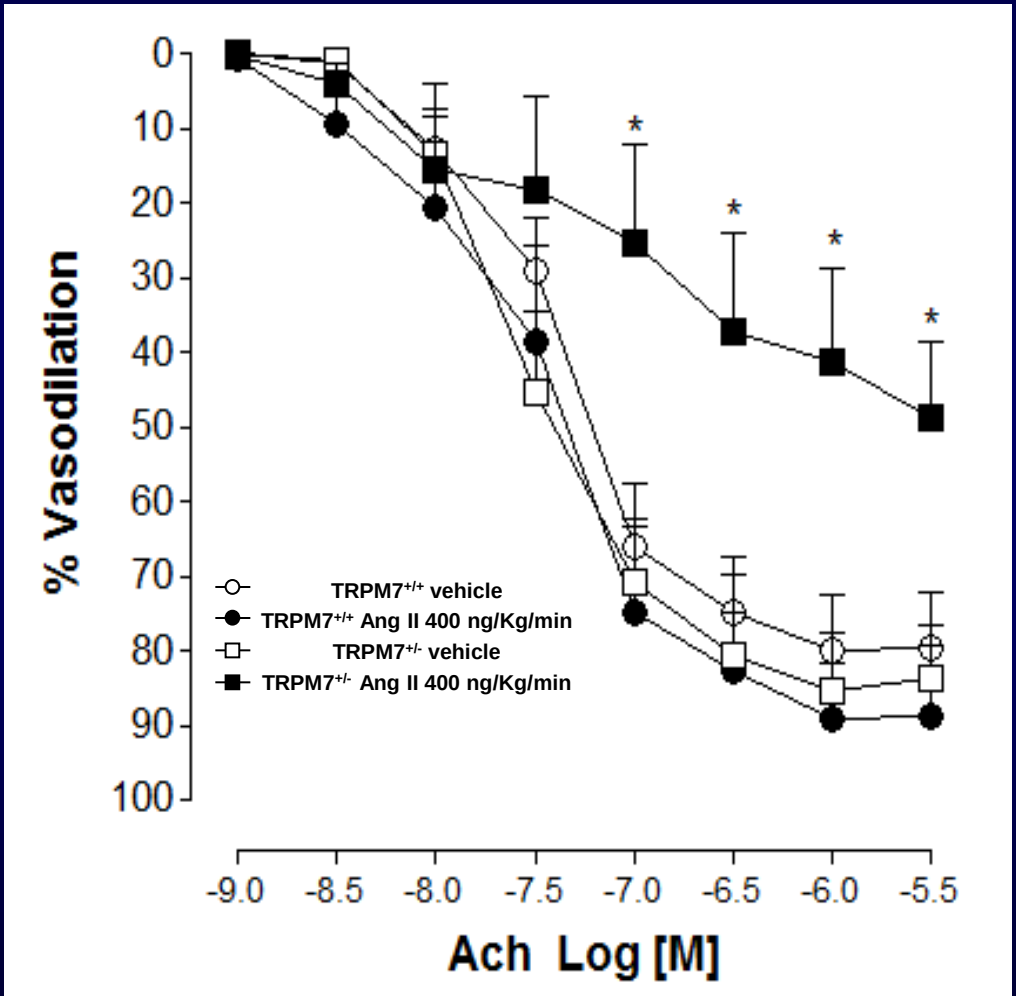
Impaired endothelial function in Ang II-infused TRPM7-deficient mice



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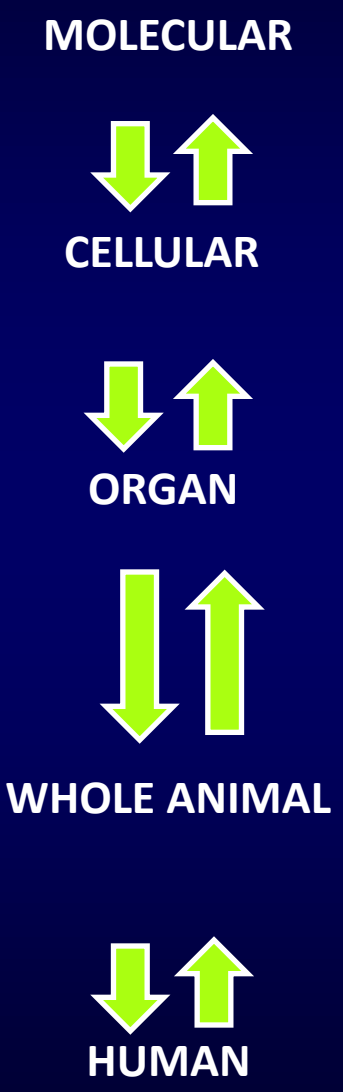
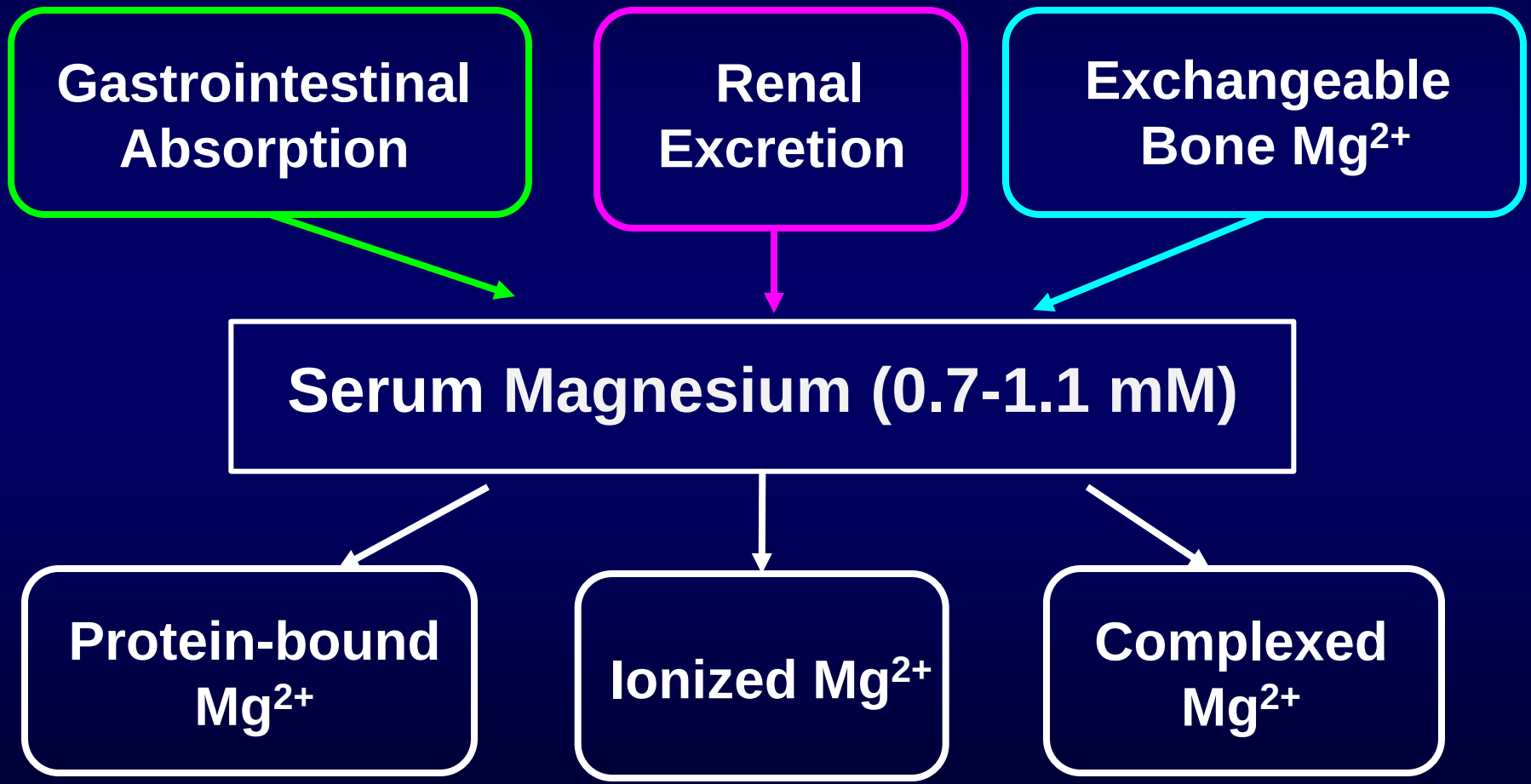
Insights from TRPM7-deficient mice

- Cell survival and viability
- Cardiac development
- Cardiac rhythmicity
- Vasodilation
- Renal function
- Blood pressure regulation

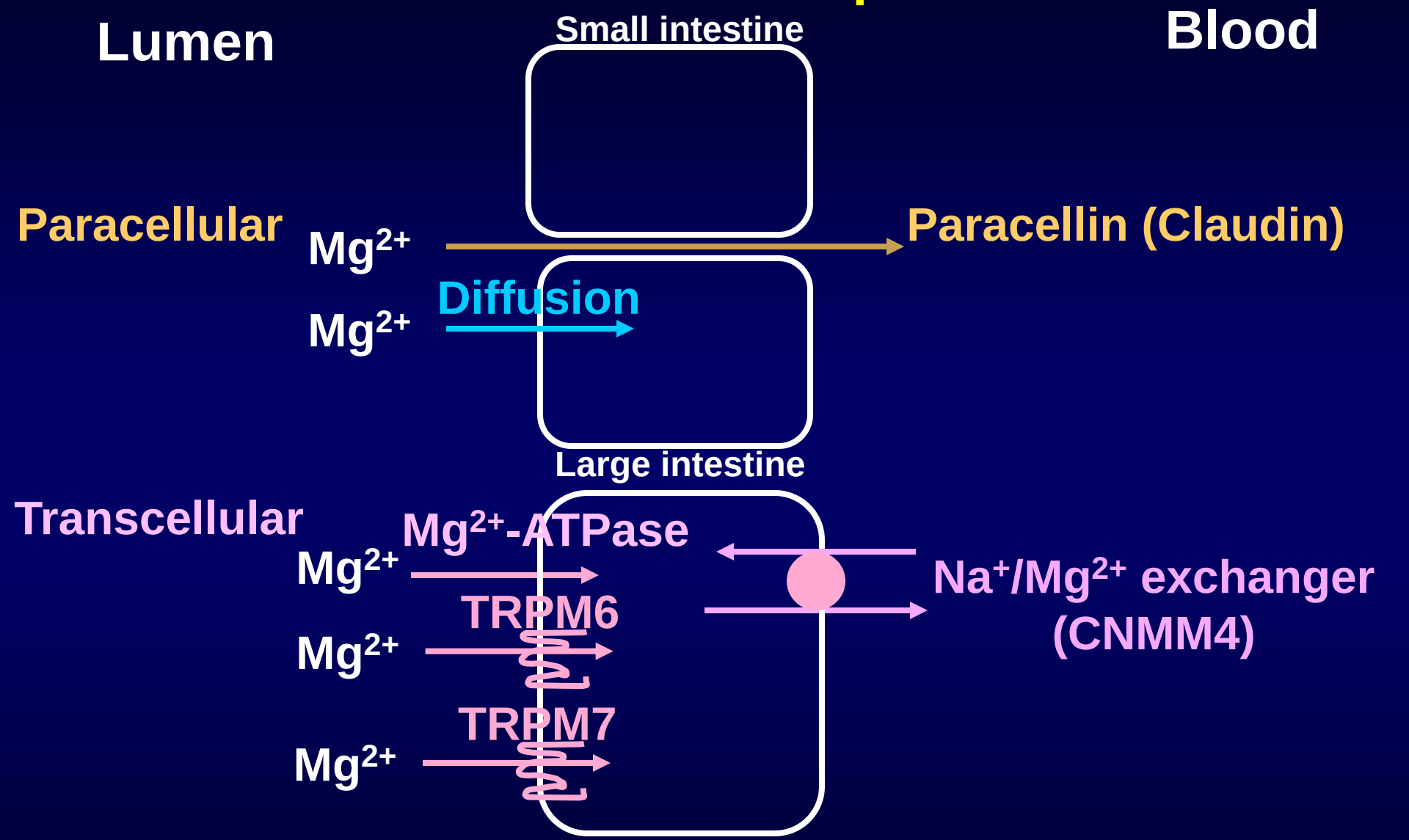
- Biochemistry of magnesium
- Mg^{2+} and intracellular signaling
- Mg^{2+} transporters and cell biology
- Physiology of Mg^{2+}
- Mg^{2+} in the clinic



Magnesium Homeostasis in man



Intestinal Absorption



- Mg^{2+}-rich food: vegetables, nuts, cocoa.
- Phytate, fibre, alcohol inhibit Mg^{2+} absorption.
- Daily Mg^{2+} intake = ~ 300 mg/day.

Renal Magnesium Handling

- **Kidney/Nephron - main regulator of Mg^{2+} homeostasis.**

  - 80% filtered through glomerulus

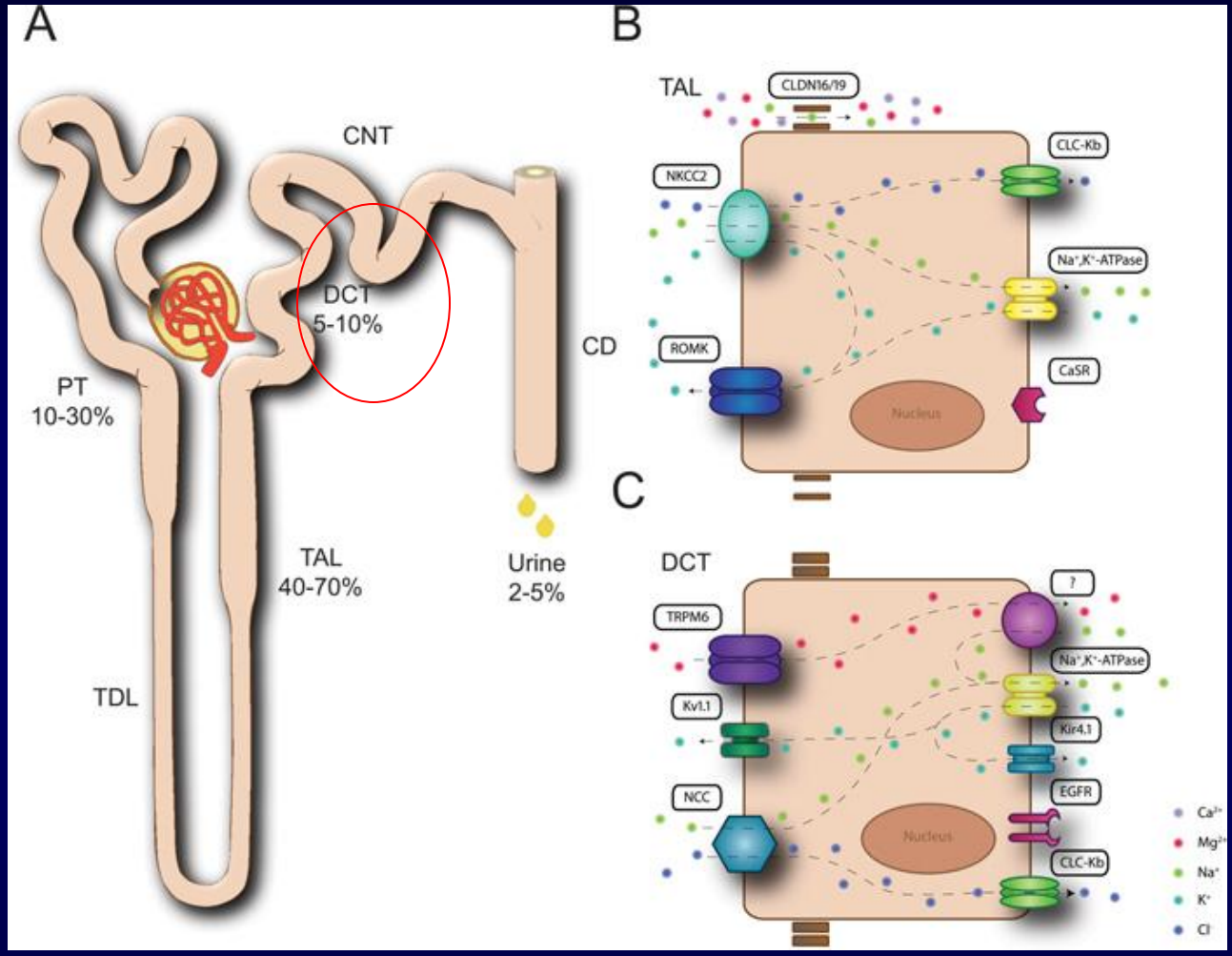
  - 15-20% reabsorbed in proximal tubule

  - 65-75% reabsorbed in TAL

  - 5-10% reabsorbed in distal convoluted tubule.

- **Drugs (diuretics) and hormones (PTH, insulin, aldosterone) influence Mg^{2+} excretion**

Nephron and electrolyte handling in the Thick Ascending Limb (TAL) of Henle and Distal Convoluted Tubule (DCT)



A) 95 % of Mg2+ filtered in the glomerulus is reabsorbed in the nephron: 10–30 % in the PT and 40–70 % in the TAL. The DCT is responsible for the final 5–10 % of Mg2+ back into blood.

(B) In the TAL, NKCC2 allows entry of Na+ , K+ and Cl− . ROMK2 recycles K+ back into the tubular lumen. Cl− exits via CLC-Kb. Na+ /K+ -ATPase constitutes the initial driving force for Na+ transport in the TAL. Paracellular Mg2+ absorption is facilitated by claudin-16 and claudin-19 (CLDN16/19).

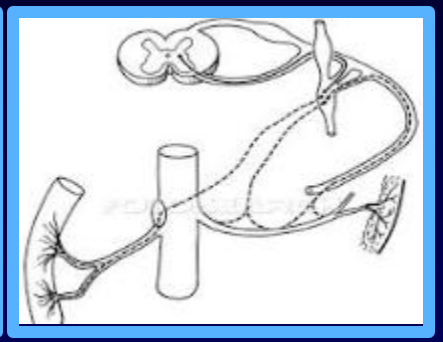
(C) In the DCT, Mg2+ absorption via TRPM6 depends on the membrane potential, which is set by Kv1.1 and can be stimulated via EGFR. Na+ /K+ -ATPase provides a Na+ gradient used by NCC. K+ that enters the cell in this process is recycled via Kir4.1.

Magnesium Metabolism – Bone

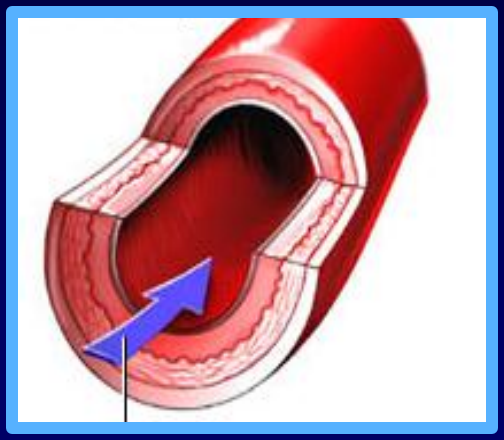
- Major Mg^{2+} reservoir is bone
- ↓ serum Mg^{2+} stimulates Mg^{2+} release from bone.
- 30% bone Mg^{2+} is exchangeable.
- Bone = buffer regulating serum Mg^{2+}.

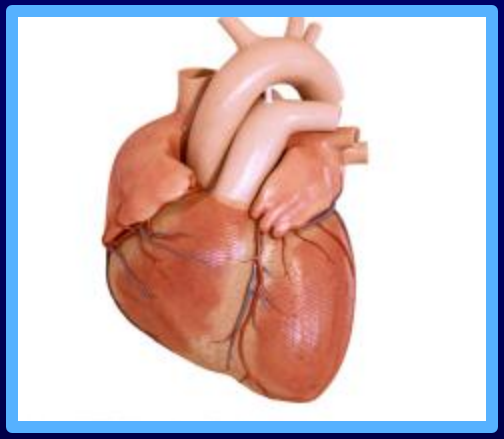
Mg^{2+} and organ function

Central and peripheral nervous system

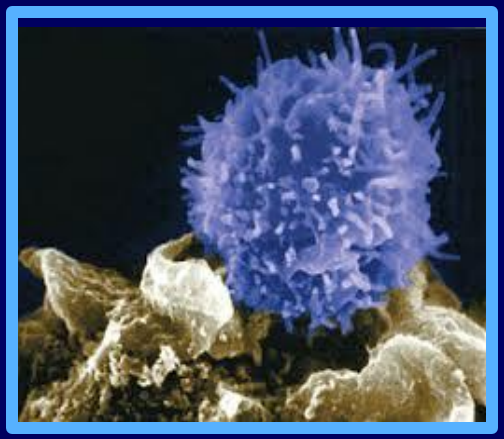


Cardiovascular system





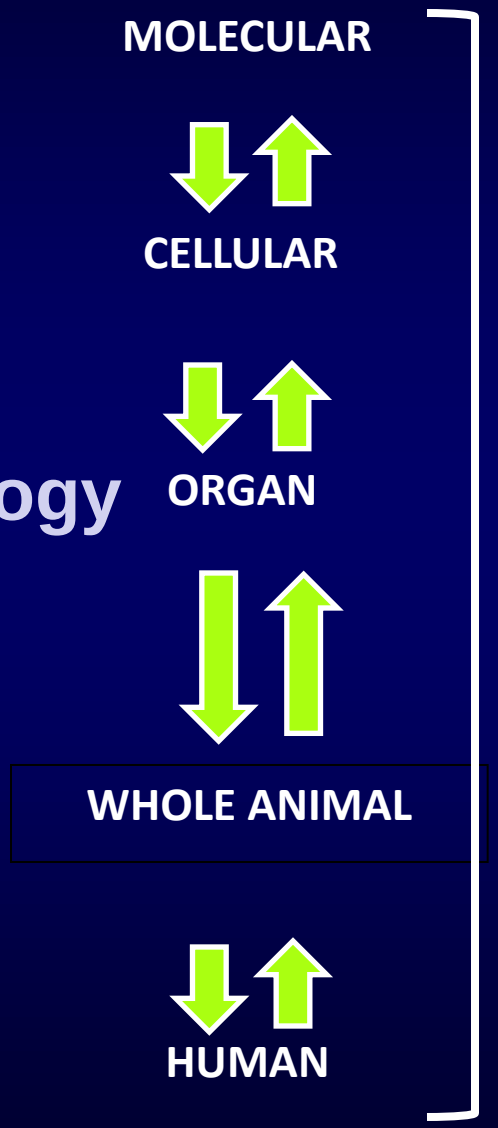
Immune system



Musculoskeletal system

Touyz 2014

- Biochemistry of magnesium
- Mg^{2+} and intracellular signaling
- Mg^{2+} transporters and cell biology
- Physiology of Mg^{2+}
- Mg^{2+} in the clinic
  - -hypomagnesemia
  - -hypermagnesemia



Manifestations of Magnesium Deficiency

Cardiac Manifestations

- atrial fibrillation
- ventricular arrhthmias
- Torsades de pointes
- Hypersensitivity to cardiac glycosides

Neurological Manifestations

- convulsions
- nystagmus
- athetoid movements
- apathy
- delirium, coma

Neuromuscular Manifestations

- positive Chvostek's sign
- positive Trousseau's sign
- tetany, muscle cramps
- muscle fasciculations and tremor
- muscle weakness

Electrolyte disturbances

- hypokalemia, hypocalcemia

Immunodeficiency

Causes of Mg^{2+} deficiency

1. Decreased dietary Mg^{2+} intake
2. Gastrointestinal malabsorption
3. Increased gastrointestinal loss
   - Diarrhoea
   - Vomiting
   - Laxative abuse

Gastrointestinal

4. Increased renal loss
5. Congenital or acquired tubular defects
6. Drug-induced

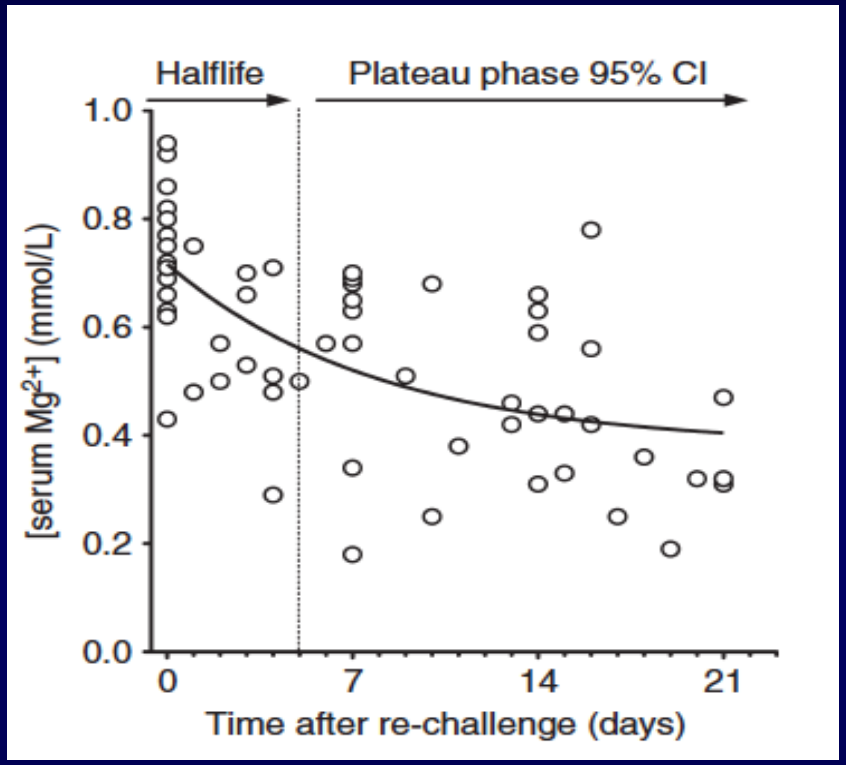
Renal

7. Endocrine causes
   - Hyperaldosteronism
   - Hyperparathyroidism
   - Hyperthyroidism
   - SIAD
   - Diabetes
8. Other causes
   - Alcoholism
   - Excessuive sweating
   - Severe burns

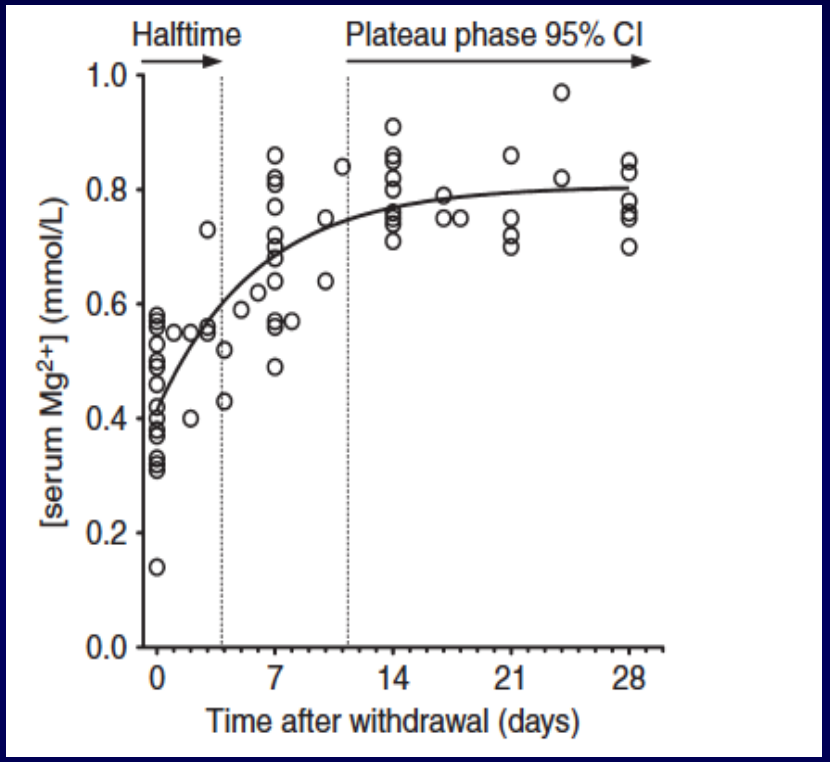
Magnesium:Drug Interactions

Drug	Interaction
• Diuretics	↑ renal Mg^{2+} loss
• Immunosupressants	Cyclosporine, tacrolimus ⬇ TRPM6
• Antibiotics • Tetracycline	Mg^{2+} binds tet in gut and ↓ absorption.
• Mg^{2+}-containing laxatives/antacids	Chronic use leads to hypermagnesemia
• Tyrosine kinase inhibitors EGF, VEGF, c-Src inhibitors (anti-cancer drugs)	TRPM6/7
• Chemotherapy: cisplatin	
• Proton pump inhibitors	

Effects of proton pump inhibitors on serum Mg^{2+} levels



PPI rechallenge effect on Mg^{2+}

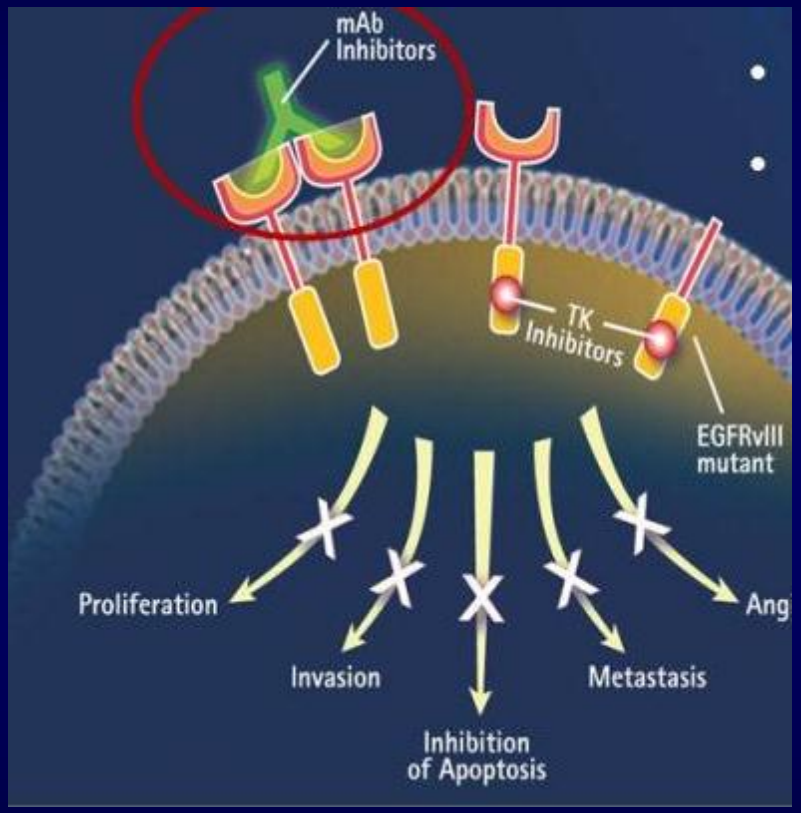


Effect of PPI withdrawal on Mg2+

Hess et al. Aliment Pharmacol Ther 2012:36

Cetuximab

- Monoclonal anti-EGRF antibody
- FDA approved for metastatic colorectal cancer.
- Adverse events:
- rash, diarrhoea, fatigue, neutropenia, hypertension, severe hypomagnesemia
- Meta-analysis: hypomagnesemia in 97% patients.

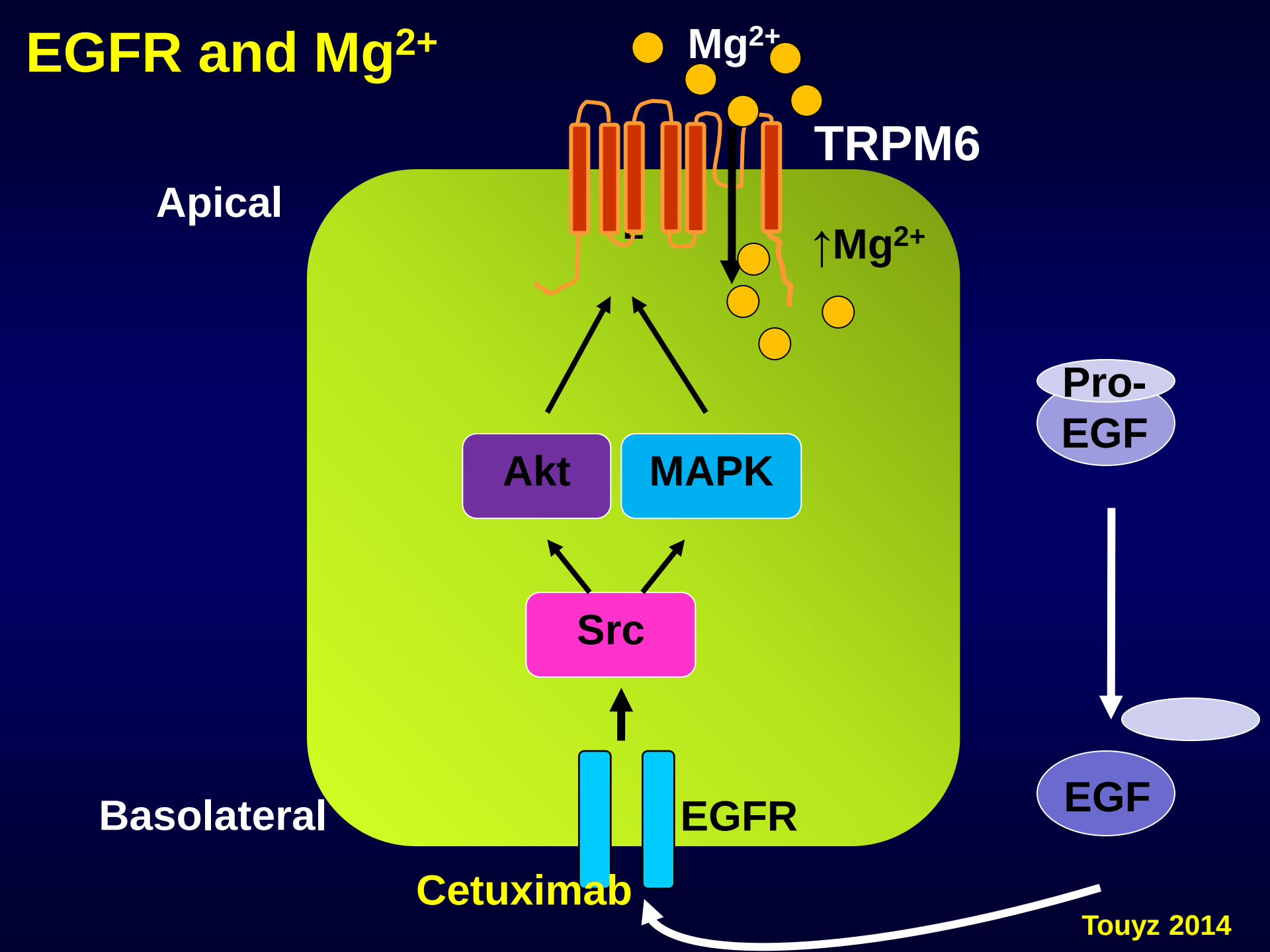


Cetuximab-induced hypomagnesemia

- Due to renal Mg^{2+} wasting
- Class effect – all EGFR monoclonal Abs .
- Normalization when cetuximab stopped.
- Rx – daily IV Mg^{2+} (weekly Rx ineffective).
- Monitor serum Mg^{2+}
- Early hypomagnesemia = surrogate marker of cetuximab efficacy. (Vincenzi. Ann Oncol 2011;22)

Molecular Mechanisms

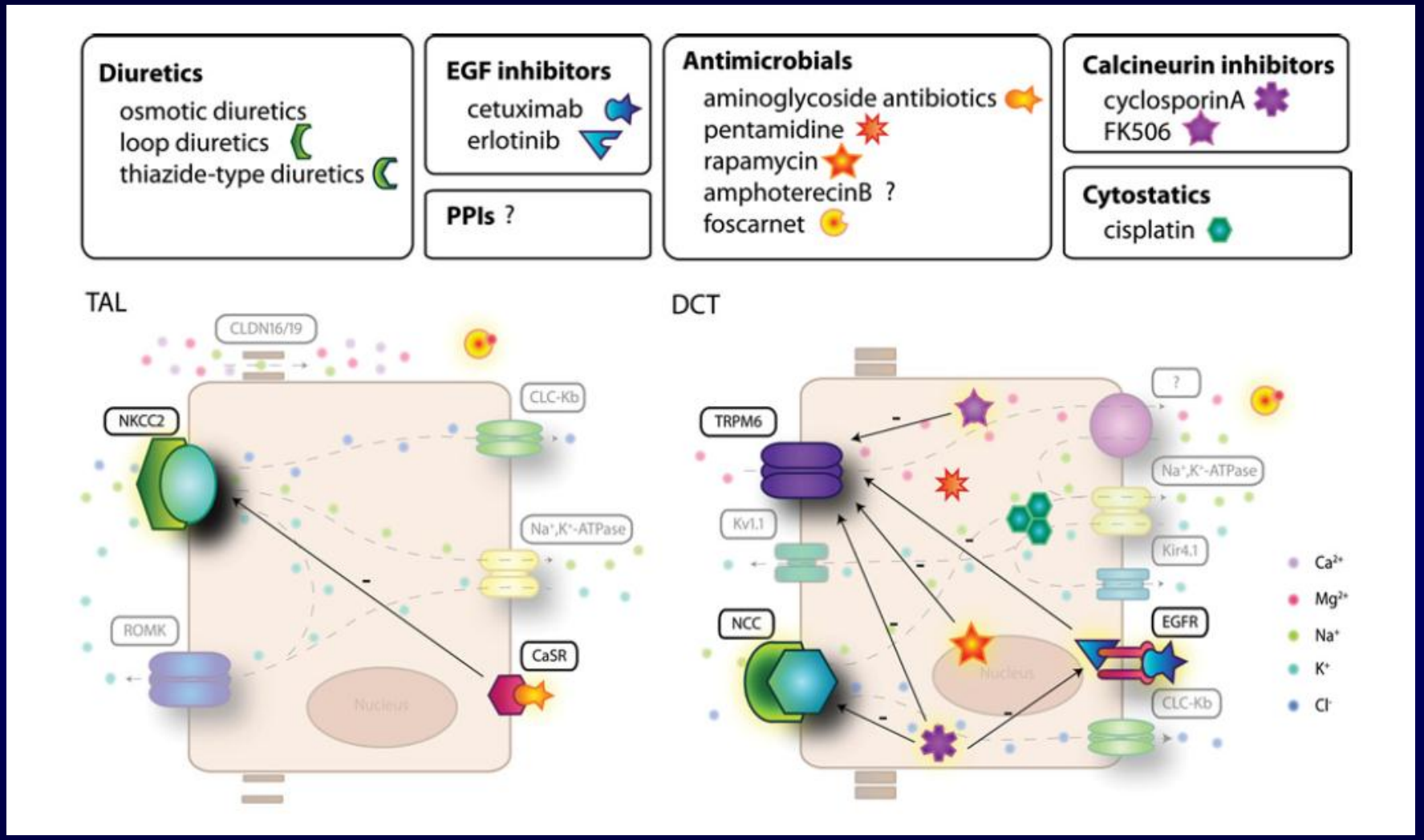
- Isolated autosomal recessive renal hypomagnesemia due to **EGF gene mutation**. (Groenestege 2007)
- Mutation causes impaired basolateral sorting of pro-EGF and reduced activation of EGFR (~ EGFR inhibition by cetuximab).
- So what is the relationship between EGFR, cetuximab and Mg^{2+}?.


EGFR and Mg2+
Mg2+
TRPM6
Apical
↑Mg2+
Pro-
EGF
Akt
MAPK
Src
EGF
Basolateral
EGFR
Cetuximab
Touyz 2014

TRPM6 and Cetuximab

- EGFR inhibition by cetuximab leads to decreased activation of TRPM6.
- ↓TRPM6 activation leads to ↓ Mg^{2+} reabsorption and consequent hypomagnesemia.
- Other tyrosine kinase inhibitors????

Overview of drugs causing hypomagnesaemia



Drug effects on key players in Mg2+ homoeostasis in cells of the TAL and DCT. Pentamidine and cisplatin do not influence specific Mg2+ transporters, but are toxic to/accumulate in DCT cells respectively.

Lameris et al. Clin Sci. 2012;123

Clinical Conditions and Hypomagnesemia

- Chronic diseases: Hypertension, diabetes, metabolic syndrome
- Stroke
- Cardiac disease (IHD, arrhythmias)
- Pre-eclampsia/eclampsia
- Neurodegenerative disorders
- Cancer
- Drug-induced: Cetuximab, PPI, anti-angiogenic drugs

Paucity of information on hypomagnesemia in the clinic

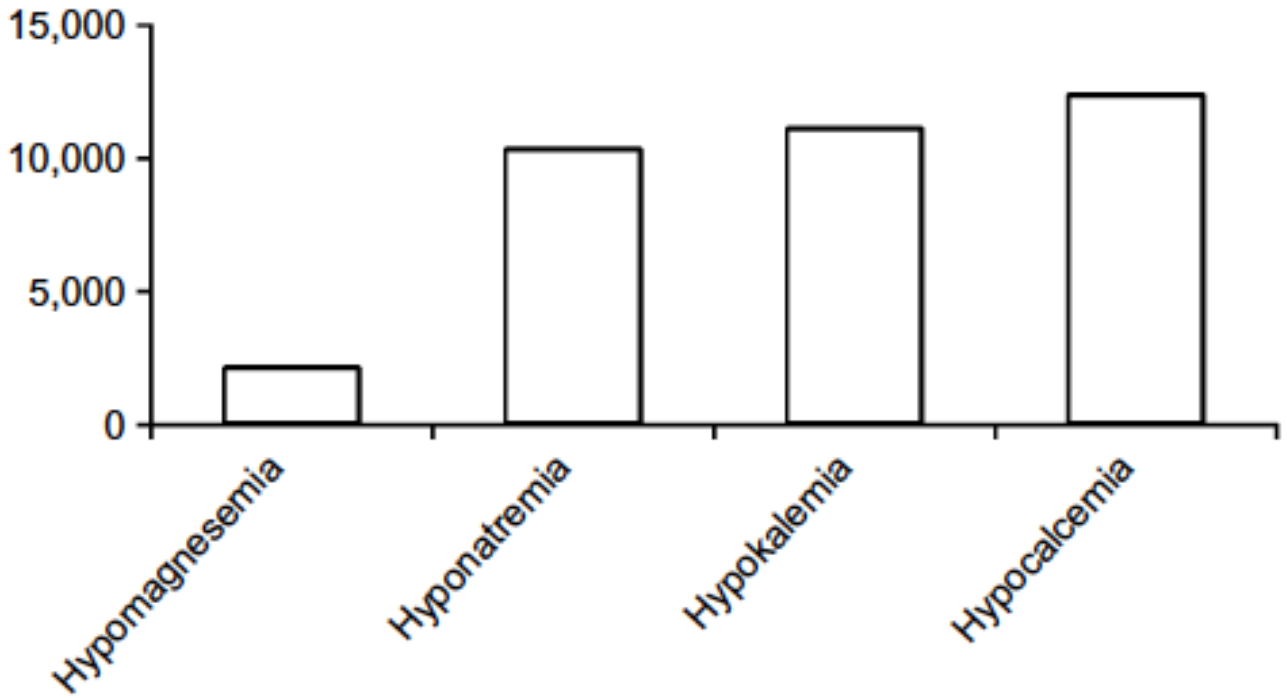
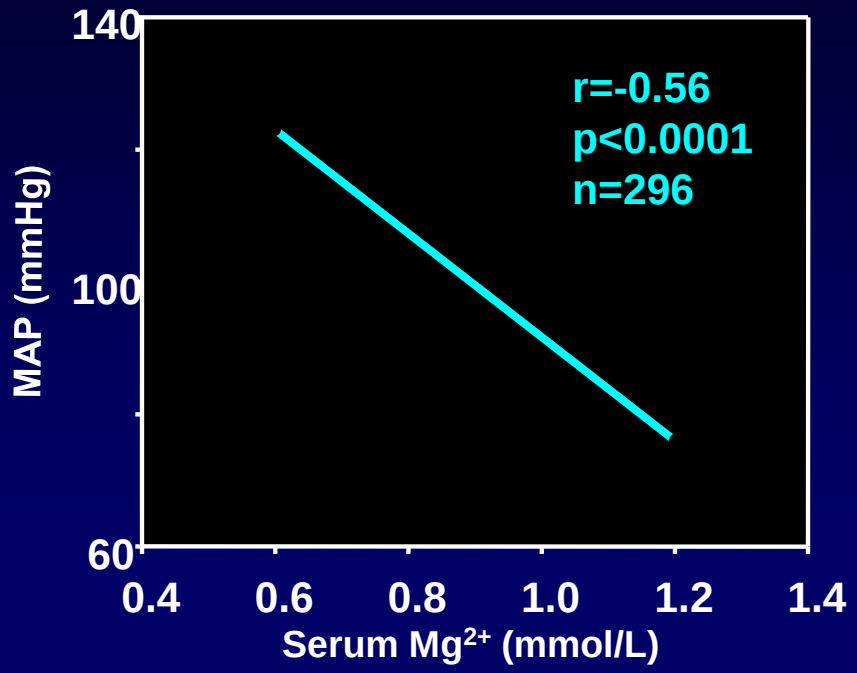
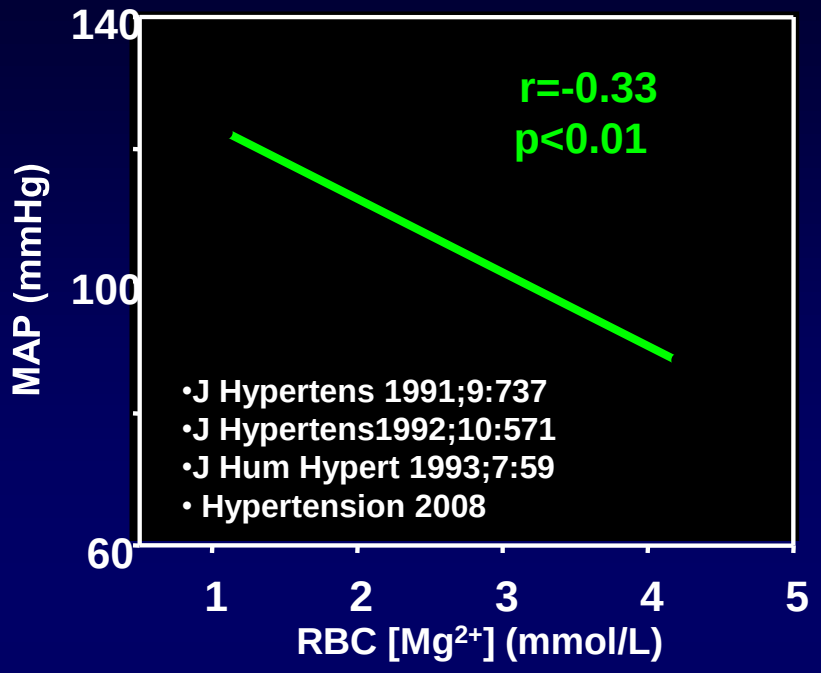


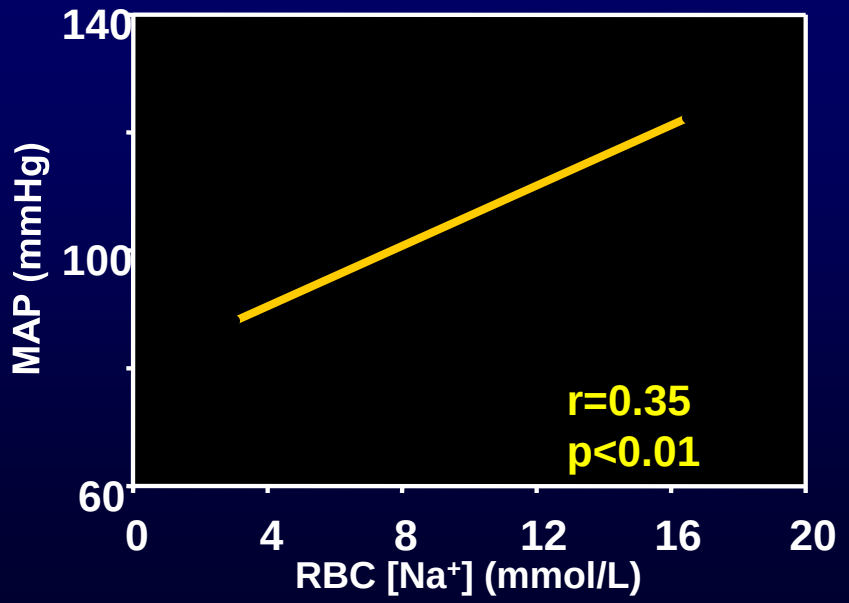
Figure 1 Number of PubMed citations (November 2013).

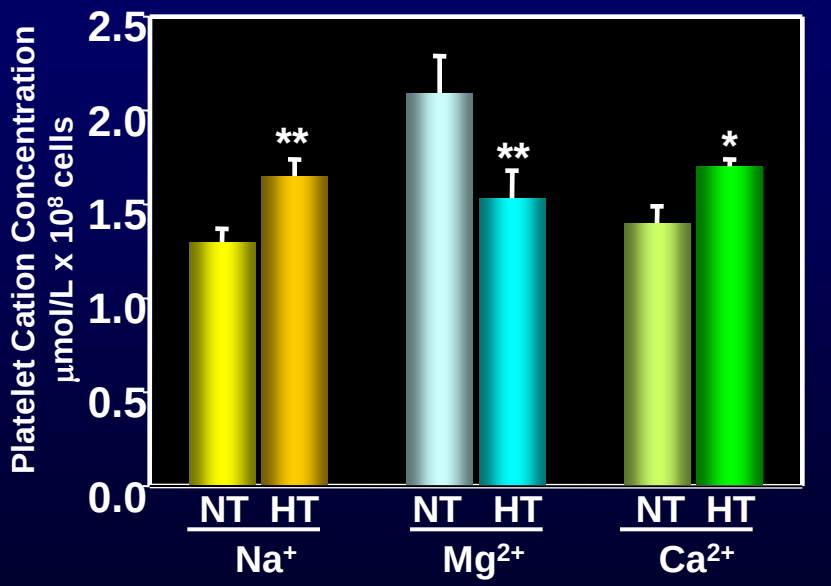
Pham et al. Int J Neph Renovasc Dis 2014;7

Hypertension. Relationship Between BP and Cations









Mg^{2+} and clinical hypertension: Conflicting data

- Lack of association between serum Mg^{2+} and risks of HT and CVD. Framingham study. *(Khan. Am Heart J. 2010;160)*
- Hypomagnesemia is one of the strongest predictors of gain in LVM over 5 years. *(Reffelmann. Atherosclerosis. 2010. 213).*
- Most clinical studies fail to demonstrate BP-lowering effects of Mg^{2+}.
- Intravenous $MgSO_4$ vs. inhaled NO for moderate, persistent pulmonary hypertension of the newborn. *(Raimondi J Trop Pediatr. 2008;54)*
- *BP lowering in mild HT with Mg- salt replacement (Sarkkinen, Nut J 2011l10)*
- *BP lowering in HT (Kisters)*

Subgroup of Patients who may Benefit from Mg^{2+} Supplementation

- African Americans
- Elderly
- Insulin resistance/metablic syndrome
- Patients on diuretics
- Hypomagnesemic patients
- Patients resistant to therapy
- Severe or malignant hypertension
- Pre-eclampsia.

Clinical Trials: IHD and Mg^{2+}

- **Second Leicester Intravenous Magnesium Intervention Trial (LIMIT2).** Randomized, DB, PC, n=2316, Mg2+ 8 mmol/L/5 mins, then 65 mmol/24 hours. Follow up, 2.7 years

  Findings - IV Mg2+ protective against complications of acute MI.

- **Fourth International Study of Infarct Survival (ISIS 4).**

  n=58 050, IV $MgSO_4$ acutely. Findings – no benefit, trend of ↑ mortality at 35 days.

- **Magnesium in Coronaries Trial (MAGIC).**

  n=6213, IV MgSO4 2g (8 mmol)/15 mins, then 17 g (68 mmol)/24 hours (n=3113).

  Findings, at 30 days 15 placebo and 15 treated patients had died. No benefit of treatment. MAGIC 2 – no benefit

- Meta-analysis of all randomized controlled studies (n=68 684) showed patients at low risk of mortality from MI gain little benefit from Mg2+, whereas high risk patients, especially if unsuitable for thrombolysis, may have some benefit.

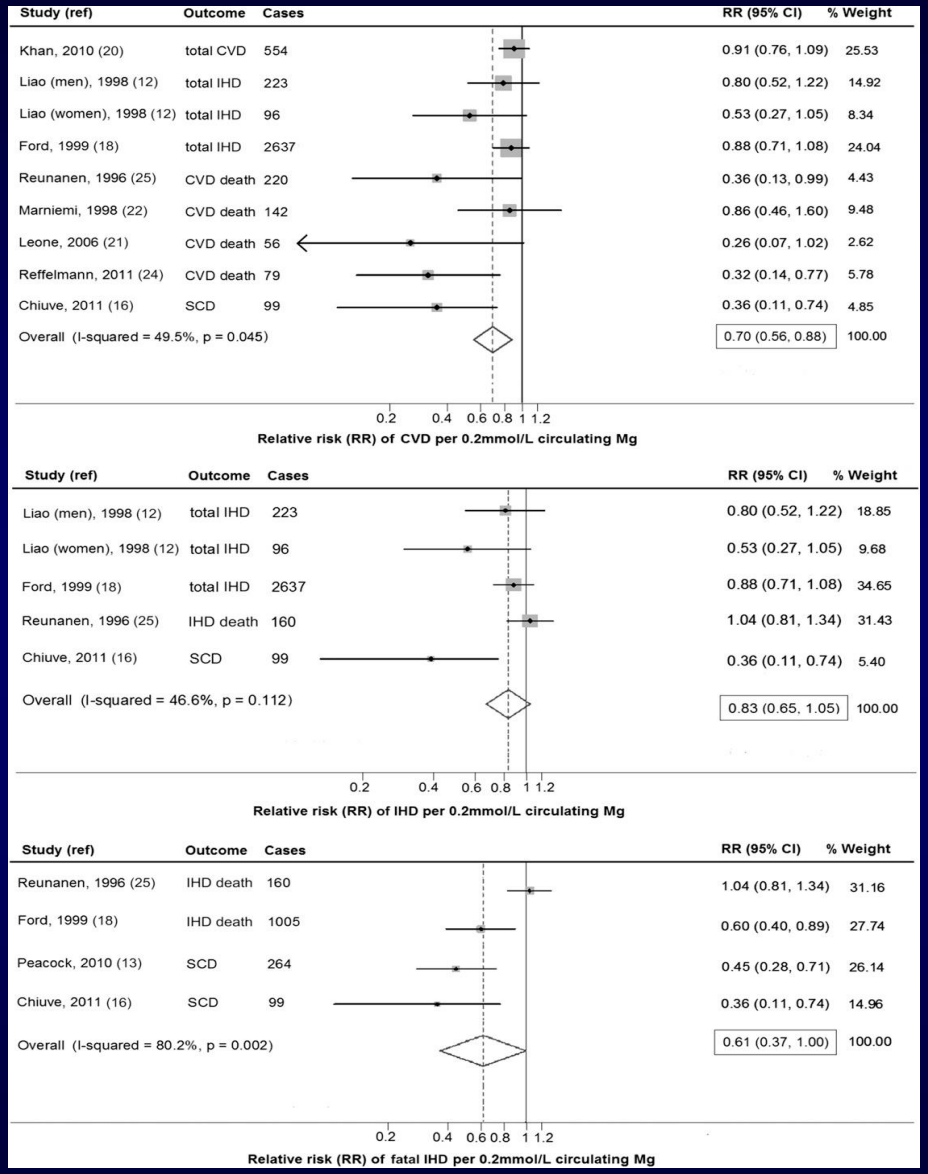
- Clinical studies - Magnesium sulfate as an adjunct to primary coronary intervention shows favorable functional outcomes in patients with AMI.

Magnesium and Ventricular Arrhythmias

- **Torsades de Pointes.** Ventricular arrhythmia associated with prolonged QT syndrome

- Mg^{2+} is the treatment of choice (AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiac Care).
- Recommended dose: 2 g $MgSO_4$ (8 mmol)/10 mins, repeated if necessary.

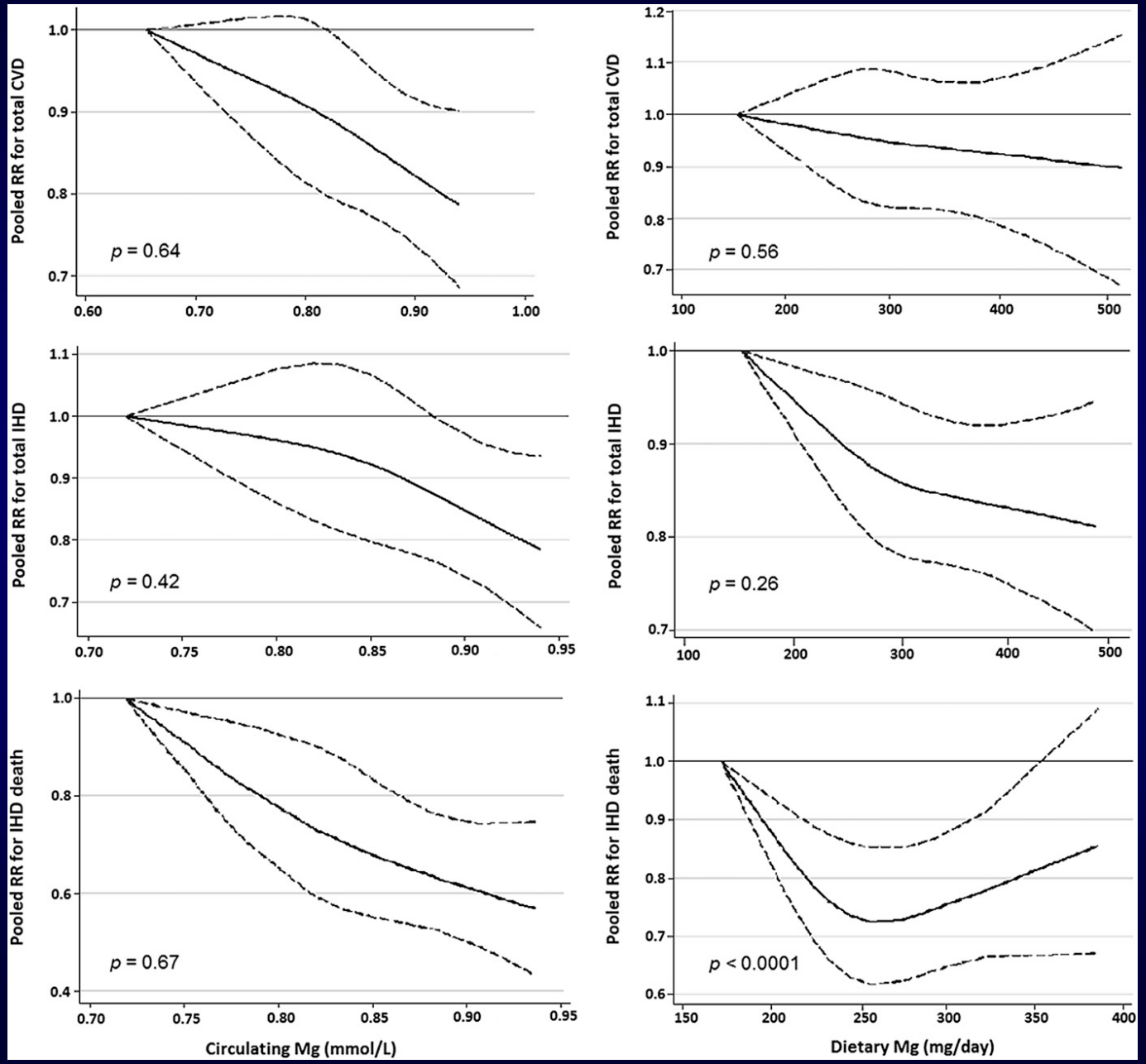
Mg and risk of Cardiovascular Disease



RR of CVD, IHD, and fatal IHD associated with a 0.2-mmol/L higher circulating Mg concentration.

Del Gobbo. Am J Clin Nutr 2013;98

Prospective associations between circulating and dietary Mg and RR of CVD, IHD, and fatal IHD estimated



Magnesium and Pre-eclampsia/Eclampsia

- **Mg^{2+} improves endothelial function in pre-eclampsia: ↑prostacyclins, EDRF and ↓platelet activation.**
- **Mg^{2+} infusion ↓ BP, ↑ renal blood flow and reduces peripheral resistance.**

Magpie Trial

10,141 women with pre-eclampsia in 175 hospitals, in 33 countries, showed Mg^{2+} sulphate decreased BP and significantly reduced risk of eclampsia.

(Lancet 2002;359:1877-1890).

Stroke

- **Health professional Follow-Up Study: inverse association between Mg^{2+} intake and stroke.**

- **Mg^{2+} is neuroprotective:**
  - **blockade of NMDA receptors**
  - **enhanced cerebral blood flow**
  - **inhibition of Ca^{2+} influx.**

Stroke Trials

- **Intravenous Magnesium Efficacy in Stroke trial (IMAGES) (Lancet 2004;363)**

  Results: Mg^{2+} given within 12 h of acute stroke does not reduce chances of death or disability significantly, although it may be of benefit in lacunar strokes.

- **Intravenous MgSO4 for aneurysmal subarachnoid hemorrhage (IMASH) trial.**

  (Wong. Stroke 2010;41)

  Results: No clinical benefit.

Clinical trials and magnesium

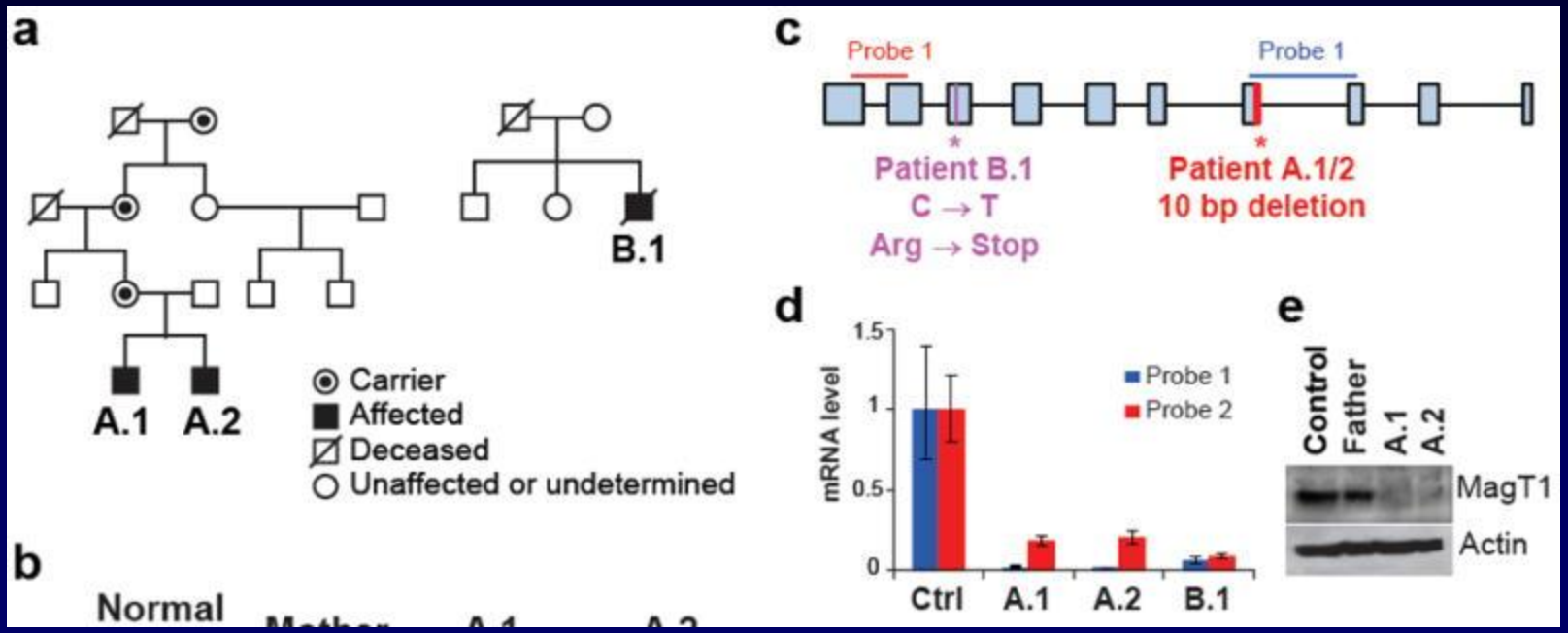
• Preeclampsia	MAGPIE*
• Asthma	MAGNETIC
• Stroke	FAST-MAG, IMAGES
• MI	MAGIC, LIMIT-2, ISIS-2
• Subarrachnoid hemorrhage	IMASH, MASH II

*Mg^{2+} showed benefit

MagT1

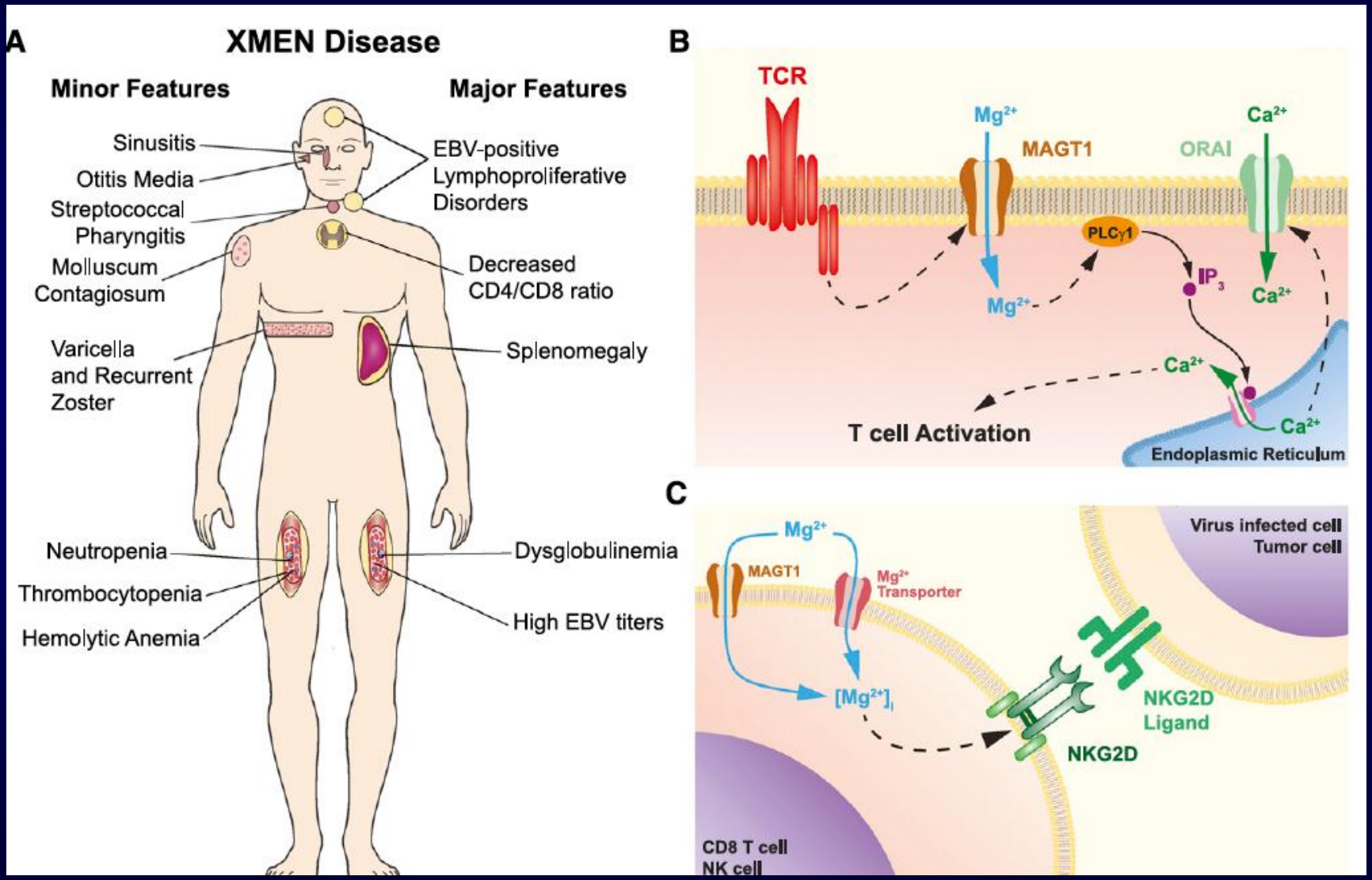
- Membrane protein with 5 transmembrane domains
- Contains a N-linked glycosylation site
- N-terminal region contains 4 cAMP-dependent protein kinase phosphorylation sites.
- Gene located on X chromosome
- Regulated by extracellular Mg^{2+}
- Selective Mg^{2+} transporter

  – Goytain and Quamme. BMC Genomics. 2005:6:48



- **Mutations in MAGT1, in a novel X-linked human immunodeficiency characterized by CD4 lymphopenia, viral infections and defective T-lymphocyte activation.**
- **Transient Mg^{2+} influx is induced by antigen receptor stimulation in normal T cells and by growth factor stimulation in non-lymphoid cells.**
- **MAGT1 deficiency abrogates the Mg^{2+} influx, leading to impaired responses to antigen receptor engagement.**

X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia (XMEN) disease



Li et al. Blood 2014;123

Clinical Assessment of Mg^{2+} Status

Clinical challenges

- Mg^{2+} is an intracellular cation
- No lab test tracks total body Mg^{2+} levels.
- Changes in serum Mg^{2+} do not reflect intracellular levels.

Clinical assessment

- Serum Mg (total vs ionized) (photometry, atomic absorption spectroscopy).
- Metabolic studies: Mg^{2+} loading
- Probes, fluorescence markers - research

Treatment of Magnesium Deficiency

- **Emergency conditions – intravenous**
  - **8-16 mmol magnesium over 1-2 minutes**
  - **40 mmol magnesium over the next 5 hours**
- **Severe illness – intravenous or intramuscular**
  - **40-48 mmol magnesium on the first day**
  - **16-25 mmol magnesium on days 2-5**
- **Oral maintenance**
  - **15-24 mmol magnesium/day**

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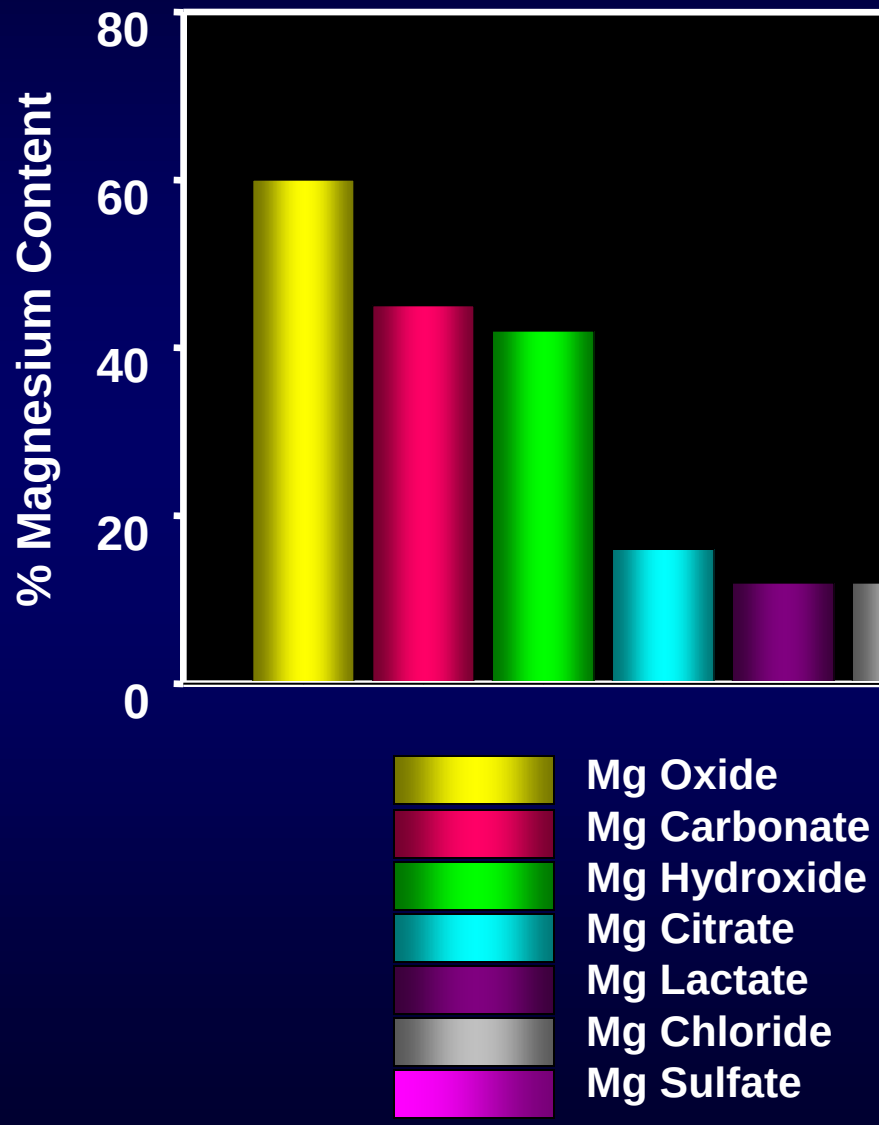
Dose-related Effects of Magnesium

Serum Magnesium mg/dL	Serum Magnesium mmol/L	Clinical Manifestation
1.7-2.4	0.7-1.05	Normal serum level.
5-8	2-3.5	Nausea, flushing, headache, hyporeflexia, lethargy.
9-12	4-5	Somnolence, loss of deep tendon reflexes, hypotension, prolongation of QRS, PR, QT intervals, bradycardia.
>15	>6	Complete heart block, respiratory paralysis, coma, shock.
>20	>8	Asystole, death.

Magnesium Content of Oral Supplements



Hypermagnesemia

- Most patients have impaired renal function.
- Most common causes of hypermagnesemia:
  - therapeutic administration of Mg^{2+} in patients with renal failure,
  - elderly who overuse laxatives and antacids
  - treatment of eclampsia.

Food content of magnesium

Food	mg per serving	Percent daily value
Almonds, dry roasted, 1 ounce	80	20
Spinach, boiled, ½ cup	78	20
Cashews, dry roasted, 1 ounce	74	19
Peanuts, oil roasted, ¼ cup	63	16
Cereal, shredded wheat, 2 large biscuits	61	15
Soymilk, plain or vanilla, 1 cup	61	15
Black beans, cooked, ½ cup	60	15
Edamame, shelled, cooked, ½ cup	50	13
Peanut butter, smooth, 2 tablespoons	49	12
Bread, whole wheat, 2 slices	46	12
Avocado, cubed, 1 cup	44	15
Potato, baked with skin, 3.5 ounces	43	11
Rice, brown, cooked, ½ cup	42	11
Yogurt, plain, low fat, 8 ounces	42	11
Breakfast cereals, fortified with magnesium	40	10

Note: Adapted from US Department of Health and Human Services. National Institutes of Health. *Magnesium fact sheet for health professionals*. Available from ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/#h3.[83]

Management of Hypermagnesemia

1. Enhance elimination of Mg^{2+} by forced diuresis and removal of exogenous Mg^{2+}-containing drugs, supplements, food.
2. General supportive care.
3. Renal dialysis, using Mg^{2+}- free dialysate, in the presence of renal impairment.
4. Calcium, reverses antagonistic actions of magnesium.

Dose for treatment: 100-200 mg elemental calcium IV over 5-10 mins (+/- diuretics).

Oxidative stress, antioxidants and clinical research, a similar paradigm to Mg^{2+} and clinical research

- Unambiguous data that oxidative stress causes cell damage
- Experimental evidence that oxidative stress causes CVD, neurodegenerative disease, cancer, diabetes…..
- Measuring ROS in the clinic is challenging
- Clinical trials have been negative.

Current research: targeting sources of ROS

Conclusions

- Mg2+ is essential for cell growth/survival.
- Mg2+ is a second messenger
- Body Mg2+ is regulated by kidneys, gut, bone.
- Cellular Mg^{2+} is regulated by Mg2+ transporters.
- Hypomagnesemia - underdiagnosed
- Mg^{2+} is not recommended in routine treatment of hypertension, IHD, stroke, diabetes.
- Conditions in which Mg^{2+} is recommended:

  - Torsades de Pointes; Eclampsia.

- Assessment of Mg^{2+} in the clinic is challenging

Moving forward in Mg^{2+} research

- Better understanding of basic mechanisms of cell biology and signaling of Mg2+.
- Elucidate mechanisms of Mg2+ regulation.
- Therapeutic targeting of Mg2+ transporters and regulators.
- Better tools to assess Mg2+ in basic and clinical research.

- Exciting time for Mg2+ research

Turkey
Brazil
USA
UK
Germany
India
Australia
Europe
Paraguay
……..

Mg^{2+}

2nd INTERNATIONAL SYMPOSIUM ON

MAGNESIUM

IN CROP PRODUCTION, FOOD QUALITY AND HUMAN HEALTH

NOVEMBER 4 - 6, 2014

SÃO PAULO, BRASIL

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