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OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

OMICS Group has organized 500 conferences, workshops and national symposiums across the major cities including San Francisco, Las Vegas, San Antonio, Omaha, Orlando, Raleigh, Santa Clara, Chicago, Philadelphia, Baltimore, United Kingdom, Valencia, Dubai, Beijing, Hyderabad, Bengaluru and Mumbai.

Myocardial TRPM7 channels:

Biophysical properties and involvement in cardiac diseases

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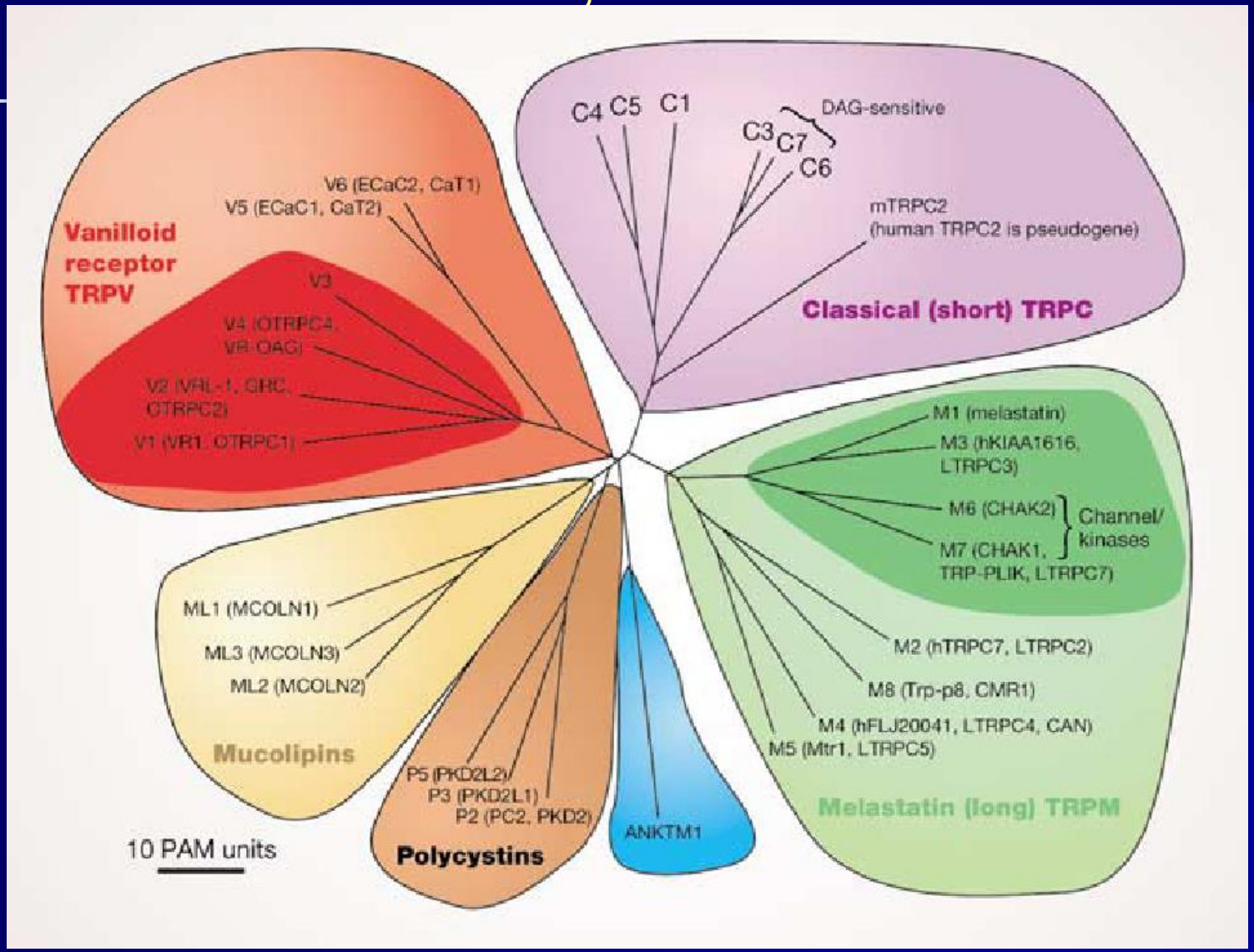
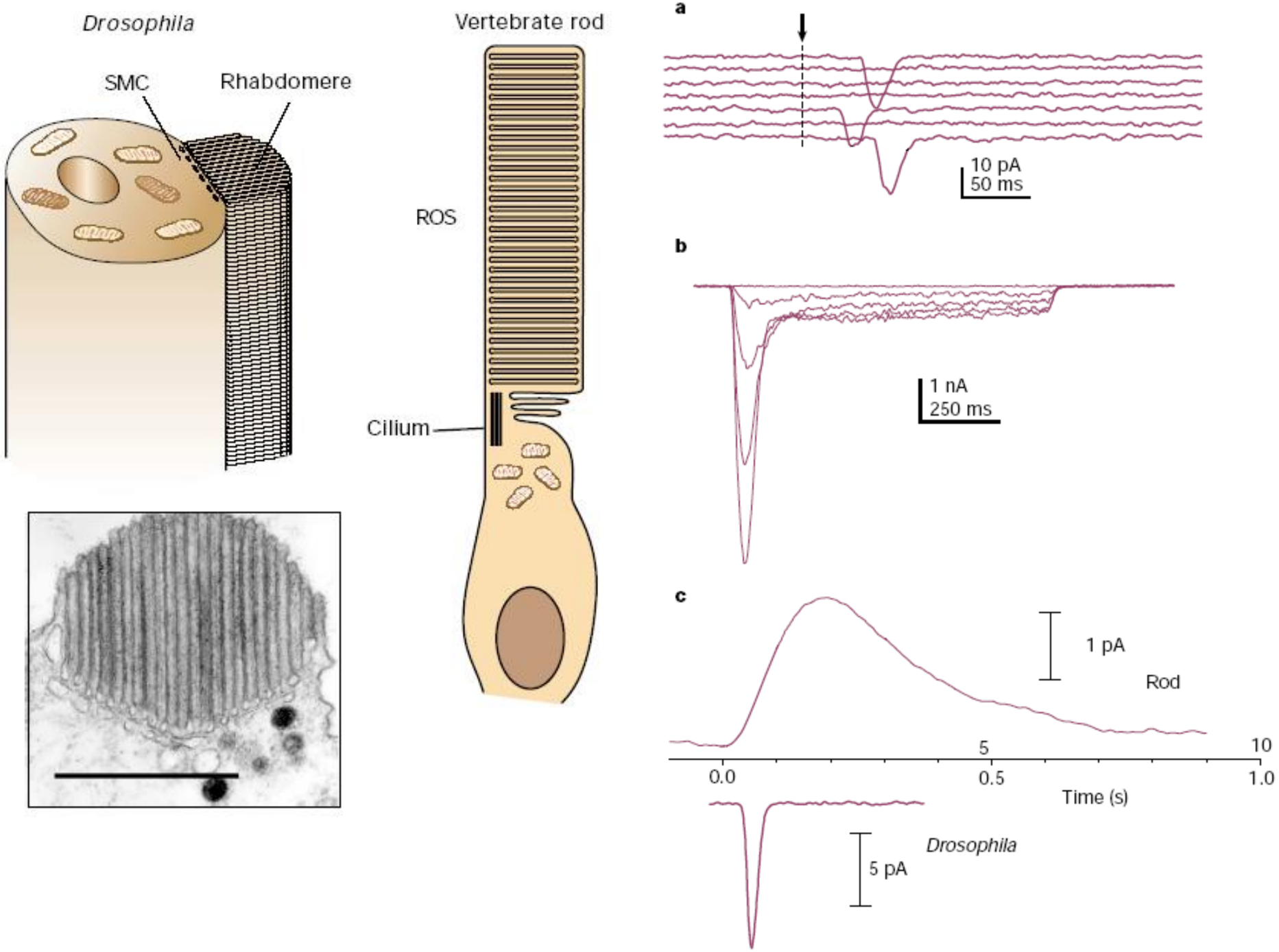
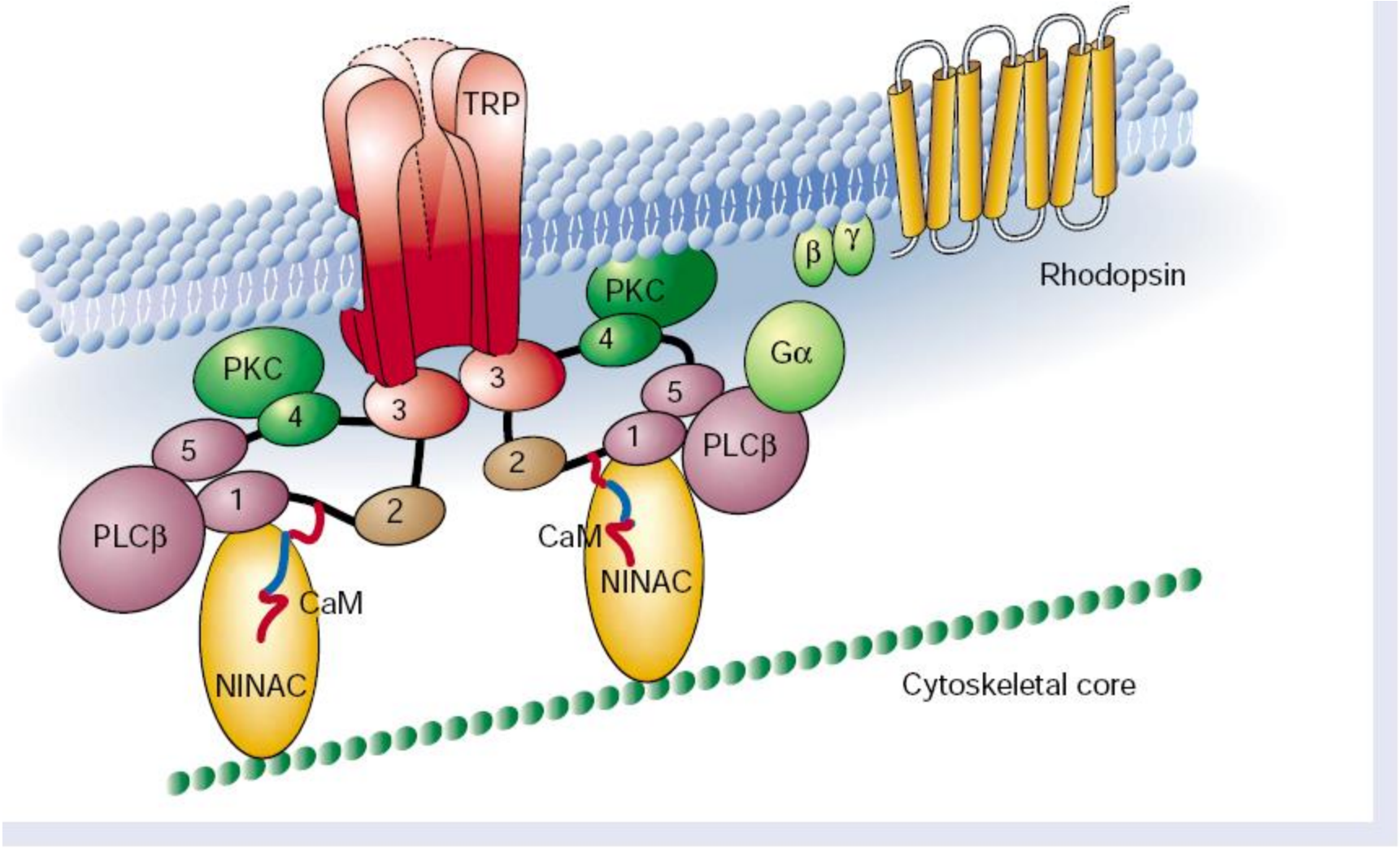
Dept. Biophysics & Physiology
Faculty of Biology
University of Bucharest

The TRP Family of Ion Channels

from Clapham D.: TRP Channels as Cellular Sensors, ***Nature* 426:517–524, December 4, 2003**




Drosophila
SMC
Rhabdomere
Vertebrate rod
ROS
Cilium
a
10 pA
50 ms
b
1 nA
250 ms
c
1 pA
Rod
5
10
0.0
0.5
1.0
Time (s)
5 pA
Drosophila



Brief history

- 1986 – Putney: store-operated Ca^{2+} channels (SOCC)
- 1992 – Hoth & Penner: I_{CRAC} (Ca^{2+} release-activated Ca^{2+} current)

  activated upon divalent cation removal

  carried by monovalent cations
- 1996 – Lepple-Wienhues & Cahalan recorded a similar CRAC current
- 1998 – Kerschbaum & Cahalan recorded a much larger and non-inactivating monovalent current when internal Mg^{2+} was also omitted

Journal of Physiology (1997), **502.2**, *pp.*235–247

Extracellular divalent cations block a cation non-selective conductance unrelated to calcium channels in rat cardiac muscle

Kanigula Mubagwa, Milan Stengl and Willem Flameng

Centrum voor Experimentele Heelkunde en Anesthesiologie, University of Leuven, 3000 Leuven, Belgium

1. The effect of removing extracellular divalent cations on resting potential (V_{rest}) and background conductance of rat cardiac muscle was studied. V_{rest} was measured with 3 M KCl-filled microelectrodes in papillary muscles, or with a patch electrode in ventricular myocytes. Whole-cell membrane currents were measured in myocytes using step or ramp voltage commands.

2. In both muscles and single cells, decrease or removal of Ca_o^{2+} and Mg_o^{2+} caused a nifedipine-resistant depolarization, which was reversed upon readmission of Ca_o^{2+} or Mg_o^{2+} (half-maximal effect at 0·8 mM Ca_o^{2+} or 3 mM Mg_o^{2+} in muscles).

3. In single myocytes, removal of Ca_o^{2+} and Mg_o^{2+} had no effect on the seal resistance in non-ruptured cell-attached recordings, but reversibly induced a current with a reversal potential (V_{rev}) of $-8 \pm 3{\cdot}4$ mV (with internal Cs^+; mean ± S.E.M., $n = 23$) during whole-cell recordings. The current was insensitive to nifedipine (3–100 μM) or amiloride (1 mM). V_{rev} was insensitive to changes in the equilibrium potential for chloride ions (E_{Cl}).

4. The current induced in the absence of extracellular divalent cations was blocked in a concentration-dependent manner by Ca_o^{2+}. (At −80 mV, the affinity constant K_{Ca} was 60 μM with a Hill coefficient of 0·9.) K_{Ca} was voltage dependent at positive but not negative potentials. Mg_o^{2+}, Ni_o^{2+}, Sr_o^{2+}, Ba_o^{2+}, Cd_o^{2+} and Gd_o^{3+} also blocked the current.

5. In 0 mM Na^+ (145 mM $NMDG^+$), the inward component of the divalent cation-sensitive current was decreased and V_{rev} shifted to more negative potentials.

6. These results suggest that a novel conductance pathway, permeable to monovalent cations but not to Cl^- and blocked by divalent cations, exists in ventricular myocytes.

LIETUVOS SVEIKATOS MOKSLŲ UNIVERSITETAS
KARDIOLOGIJOS INSTITUTAS
Membranų biofizikos laboratorija

Aims of study

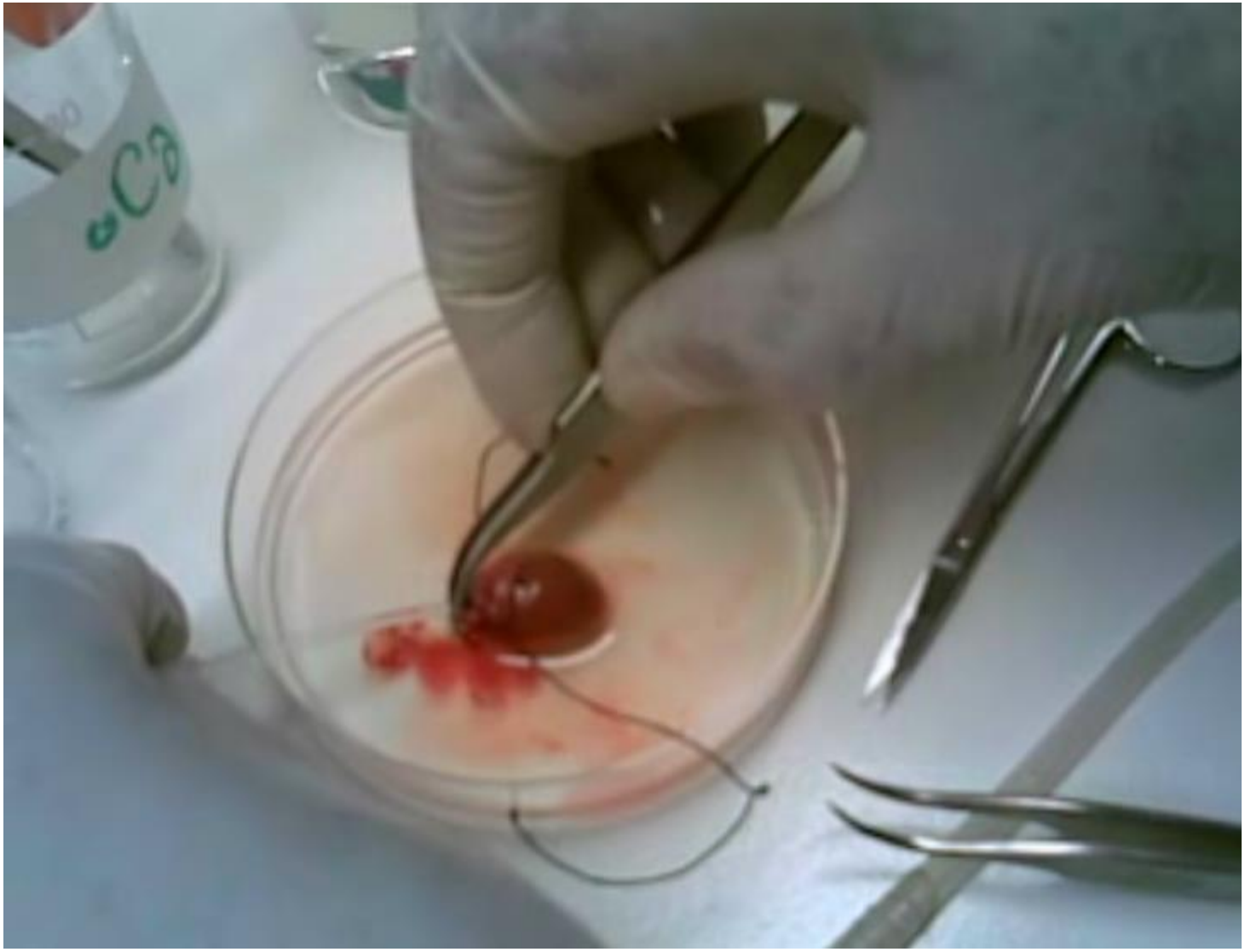
To characterise cardiac MIC channels

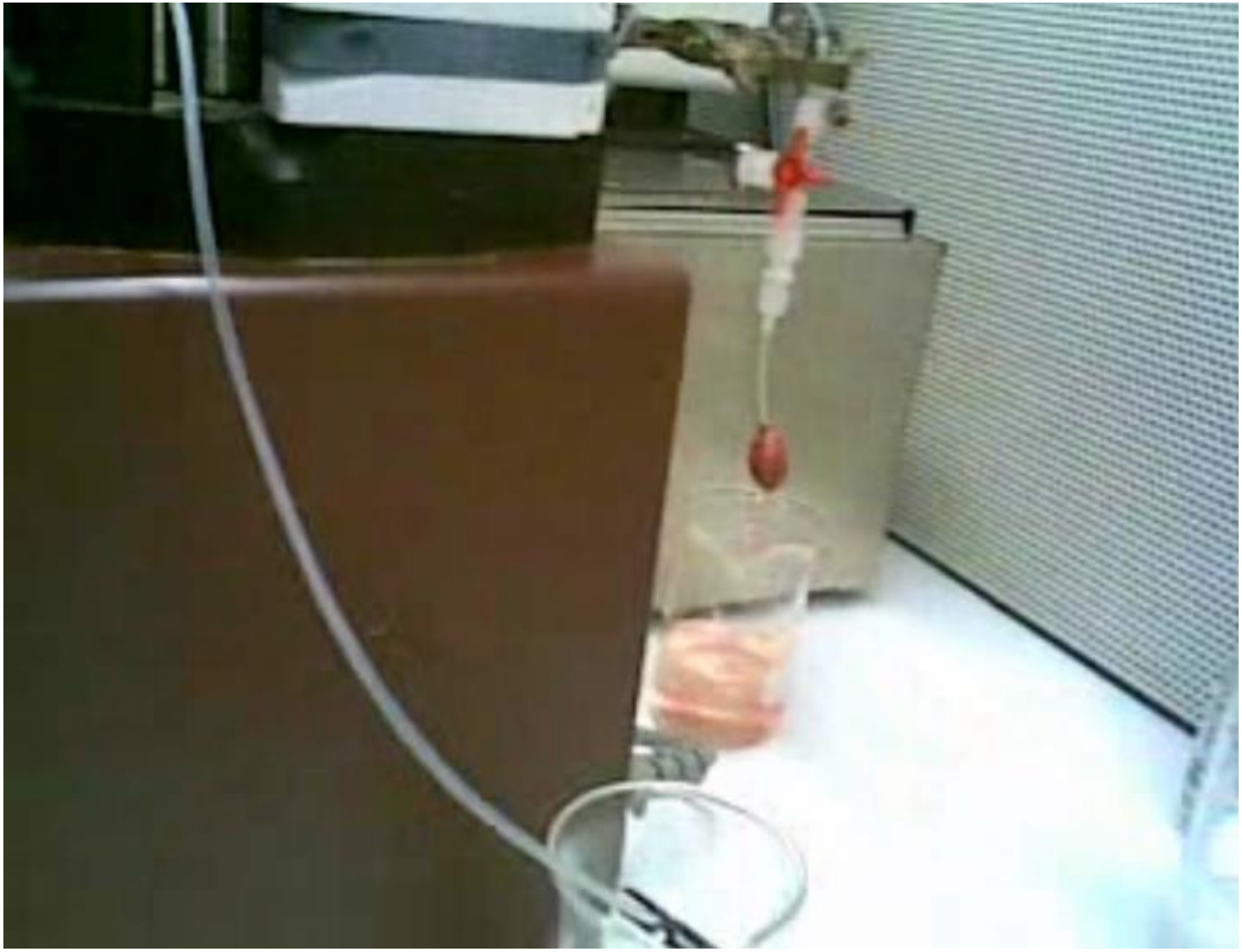
- ***permeation***
- ***blockade***
- ***regulation***

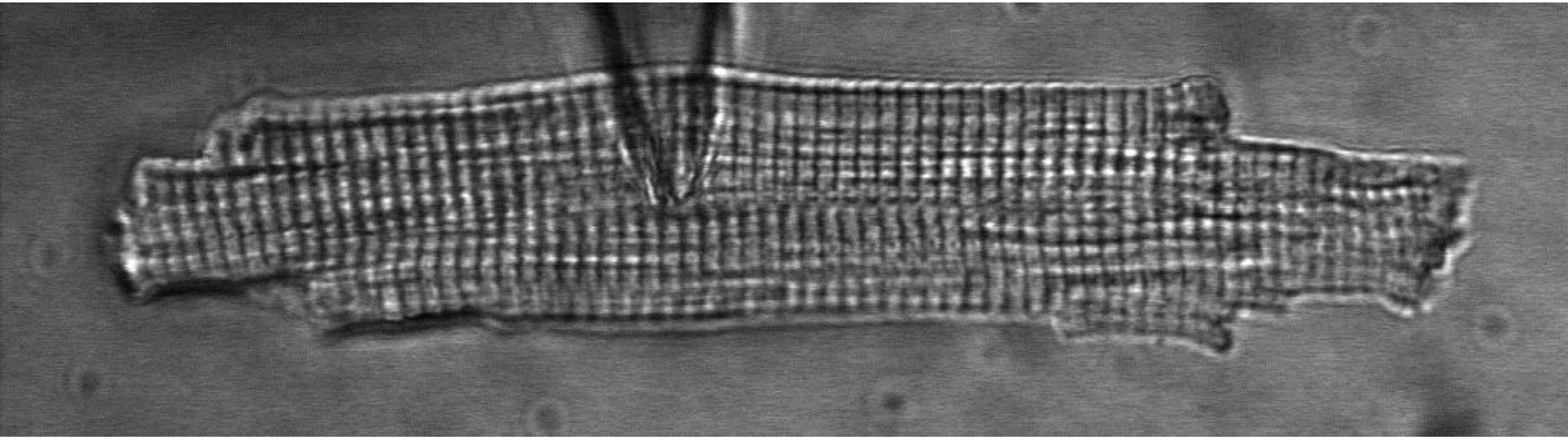
in order to compare them with TRPM6 and TRPM7.

Materials and Methods

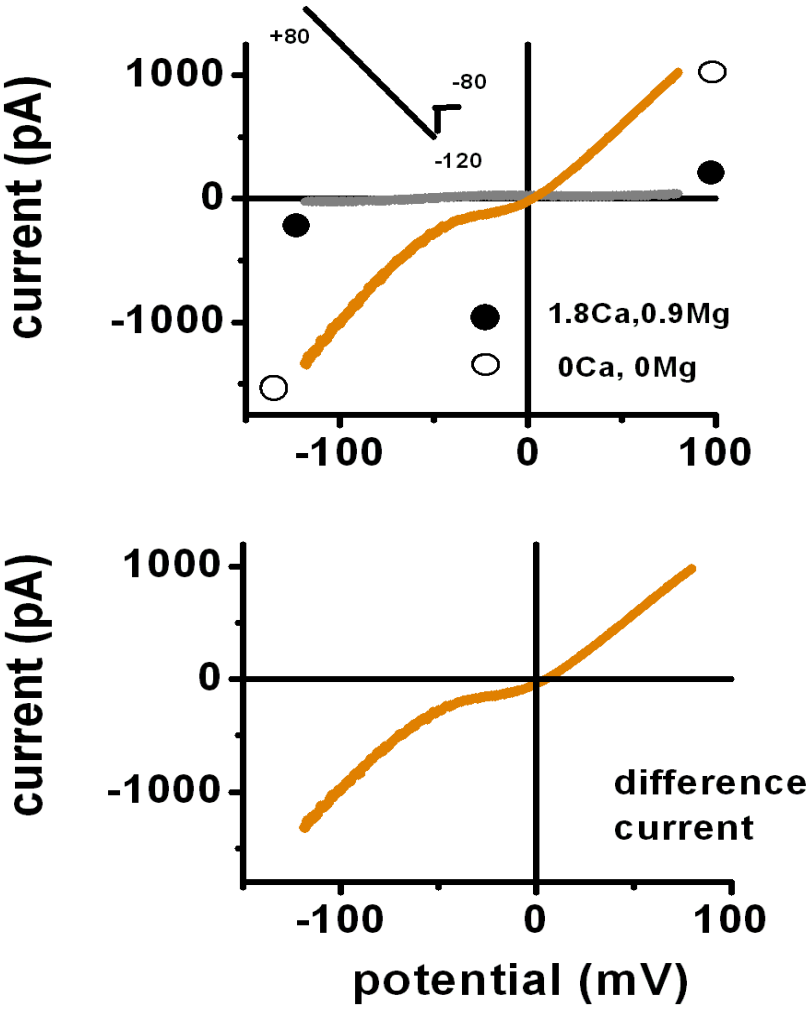
- ***isolated single cardiac myocytes***
- ***whole-cell patch clamp***
- ***solutions, drugs and protocols designed to block K^+ and voltage-gated channels***



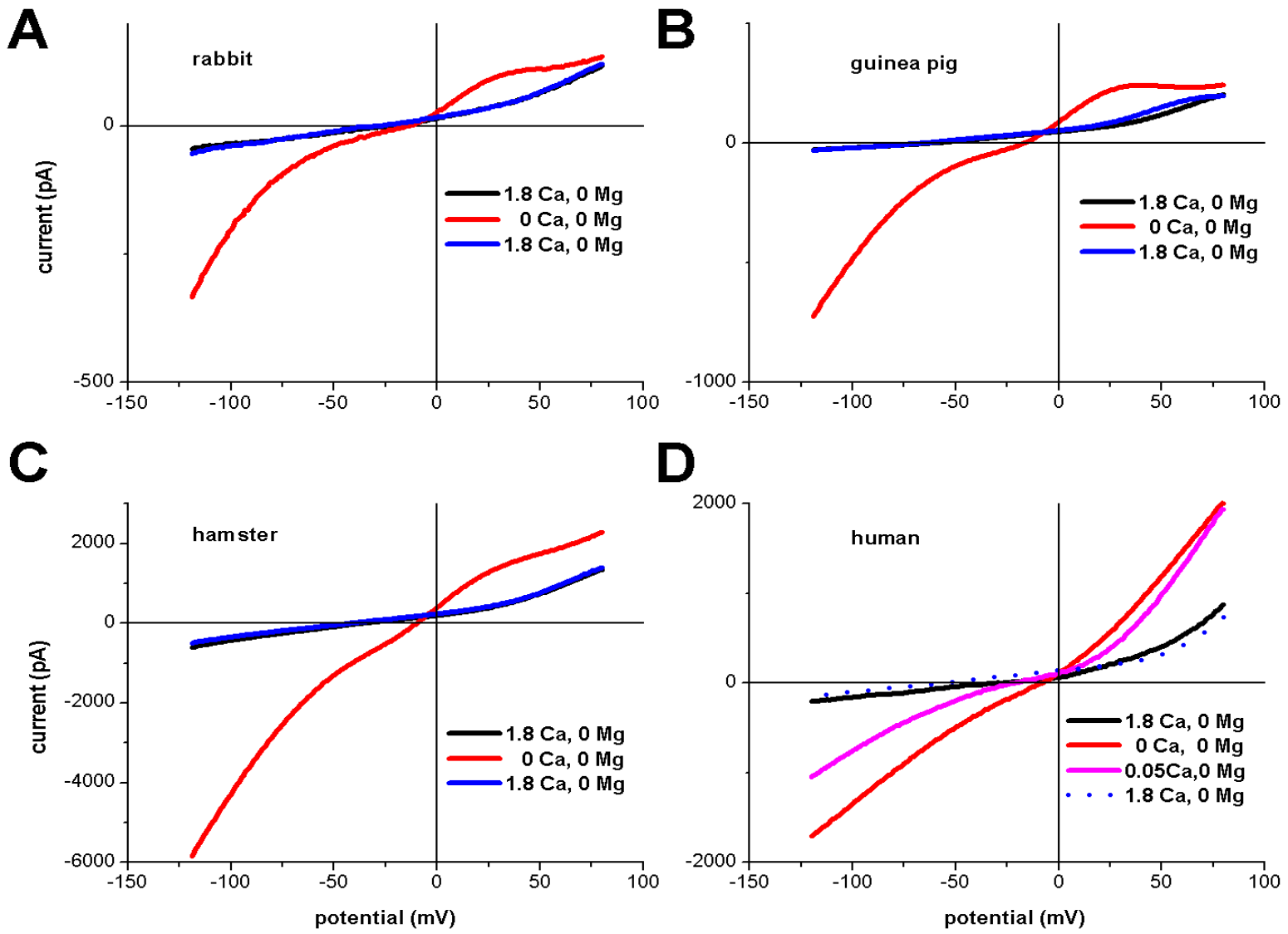




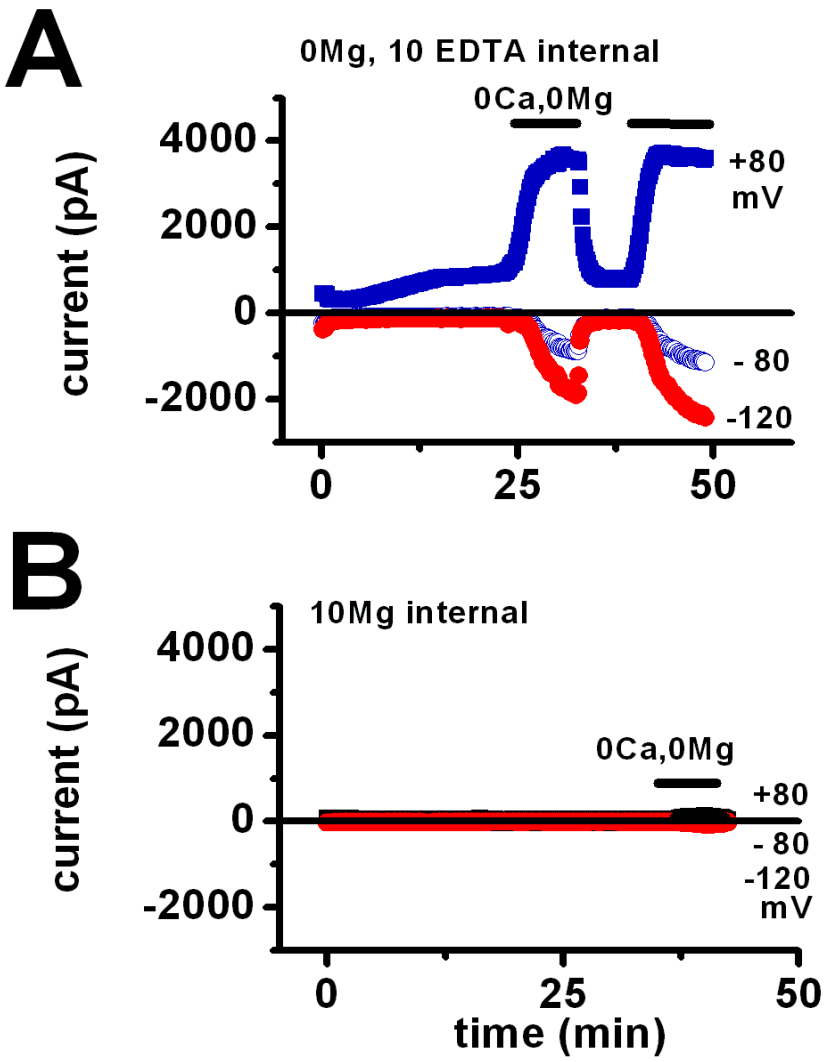
I_{MIC} in cardiomyocytes



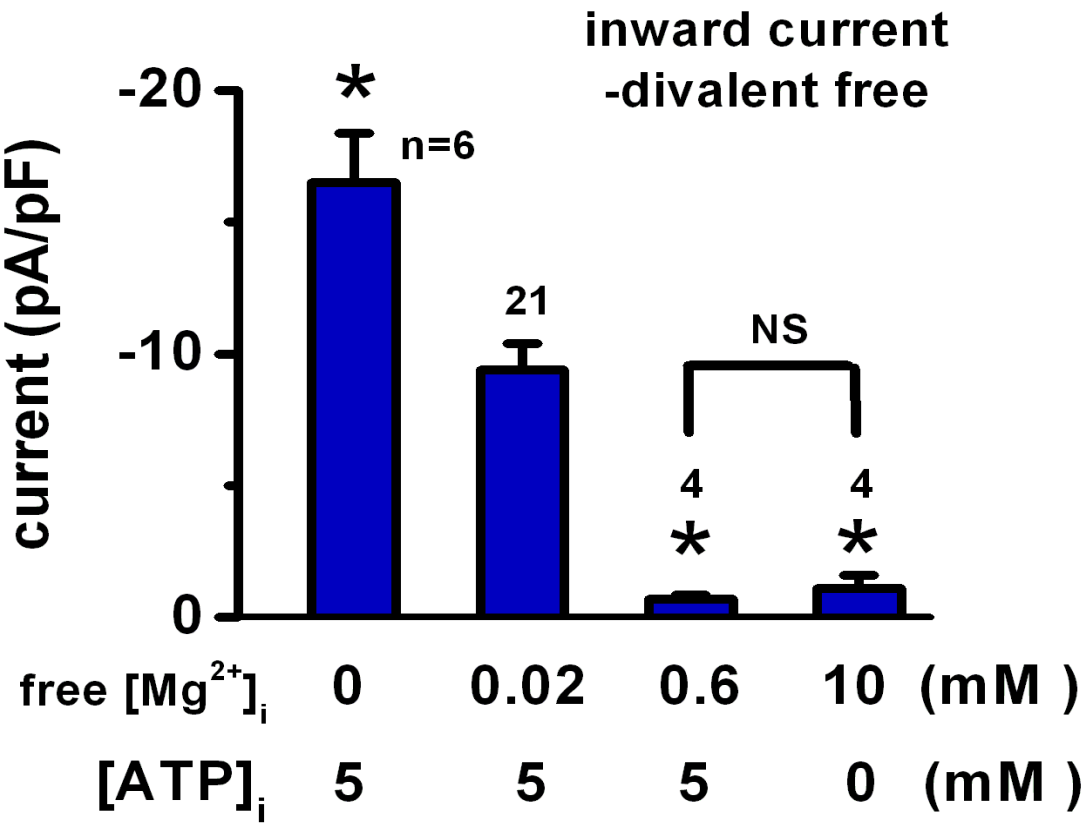
I_{MIC} present in various species



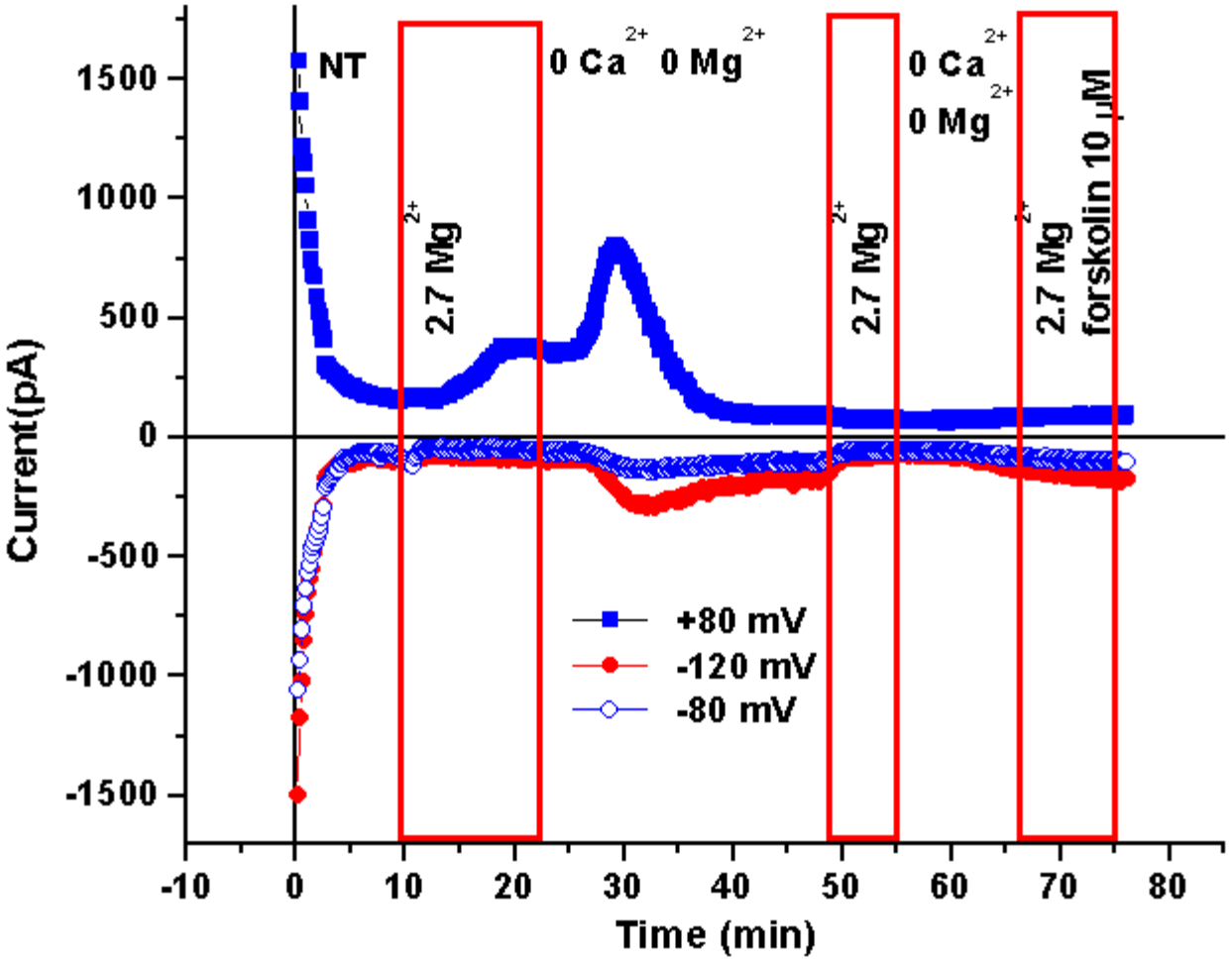
Internal Mg^{2+} sensitivity



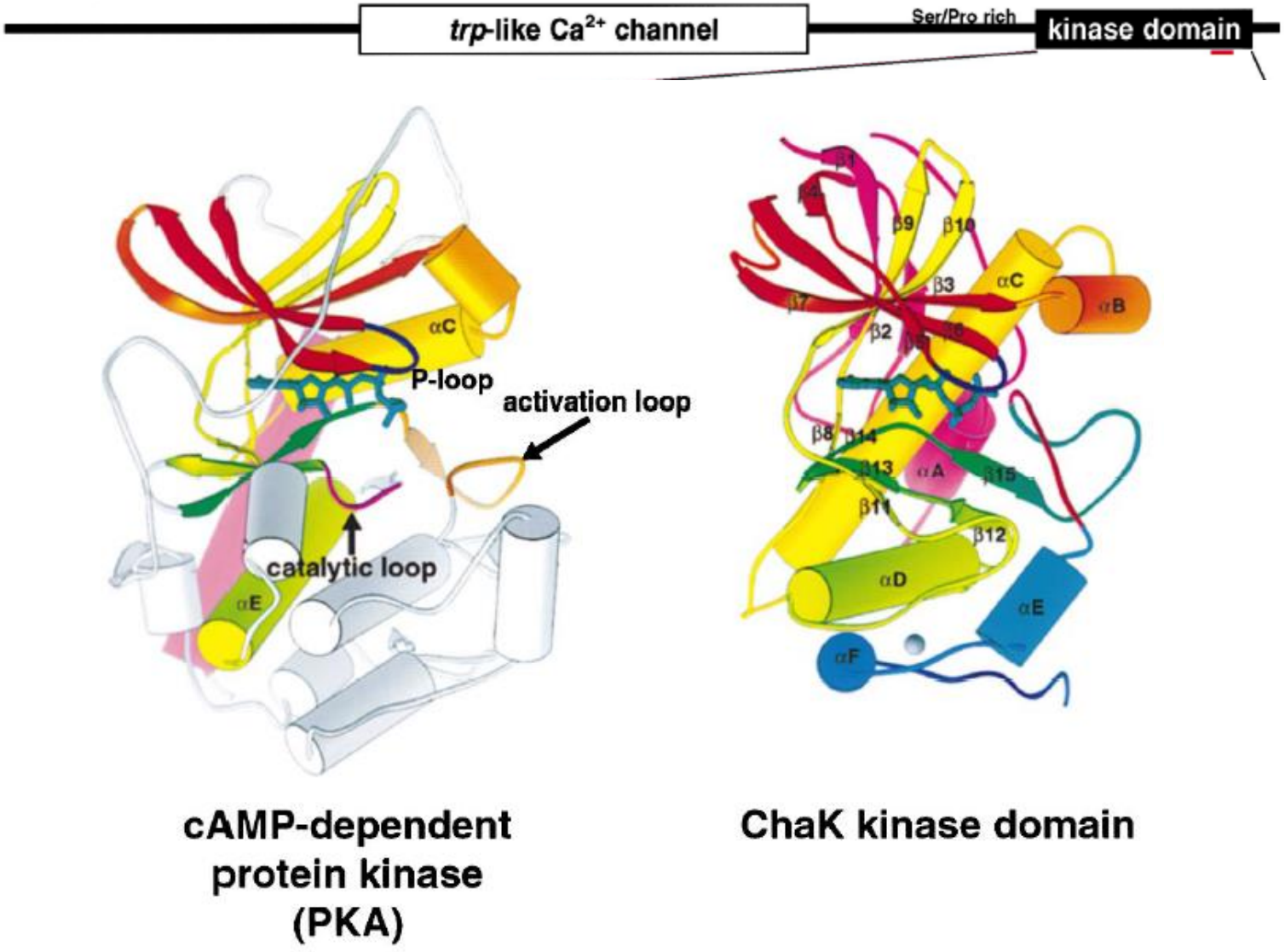
Internal Mg^{2+} sensitivity



Transient I_{MIC} activation in ATP and Mg^{2+} - free pipette solution + glucose-free Tyrode

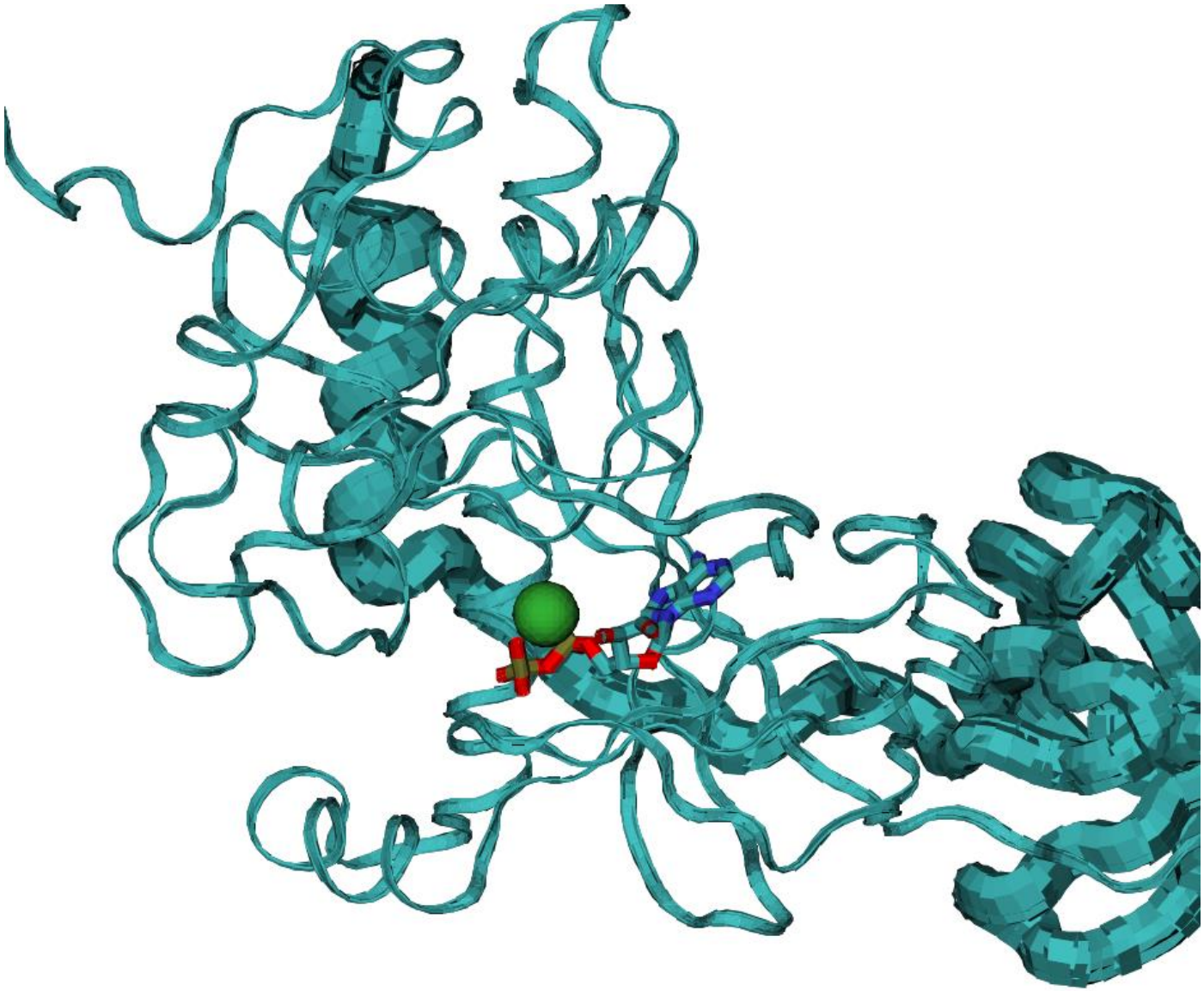


The α - kinase domain of TRP M7

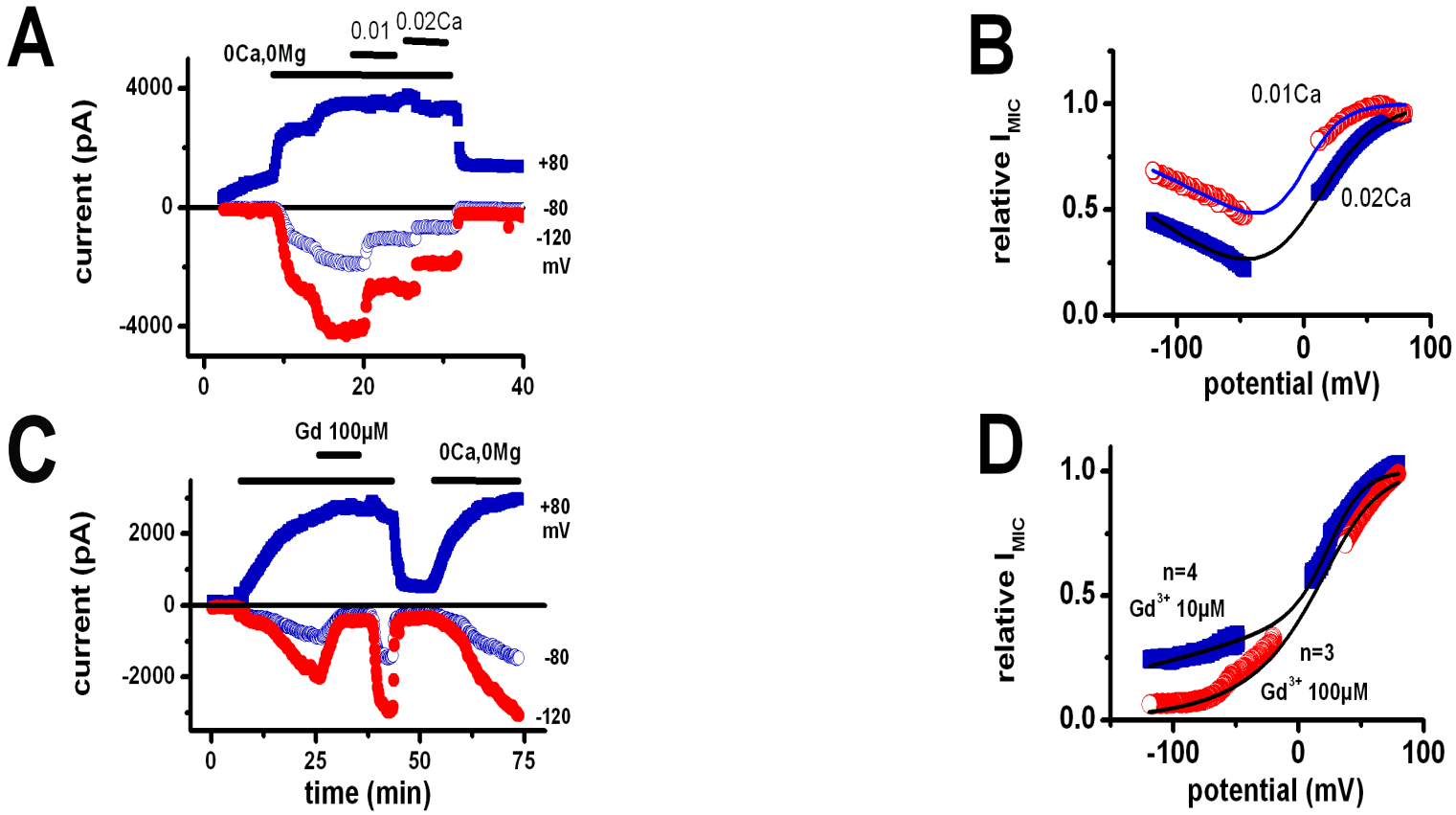


from H. Yamaguchi *et al.*: Crystal Structure of the Atypical Protein Kinase Domain of a TRP Channel with Phosphotransferase Activity, *Molecular Cell* **7**:1047-1057 (2001)

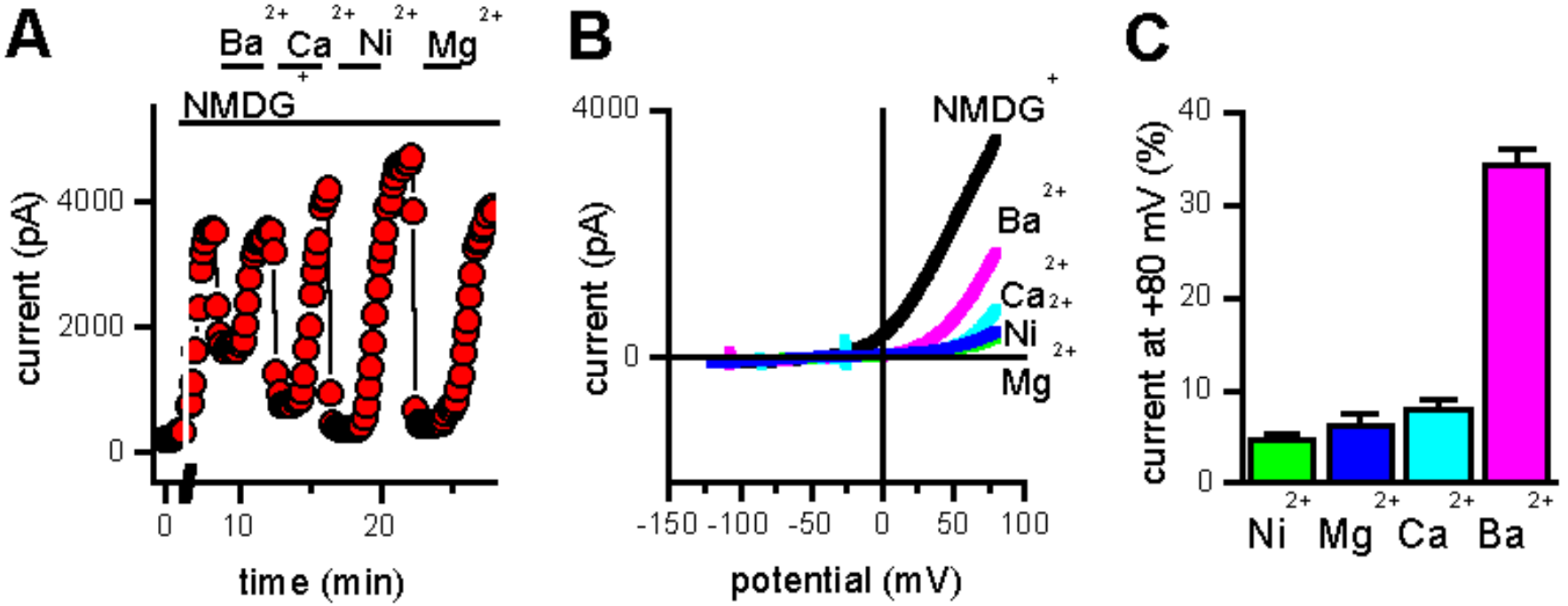
Mg^{2+} or Mn^{2+} binding in the catalytic pocket of ChaK stimulates α - kinase activity



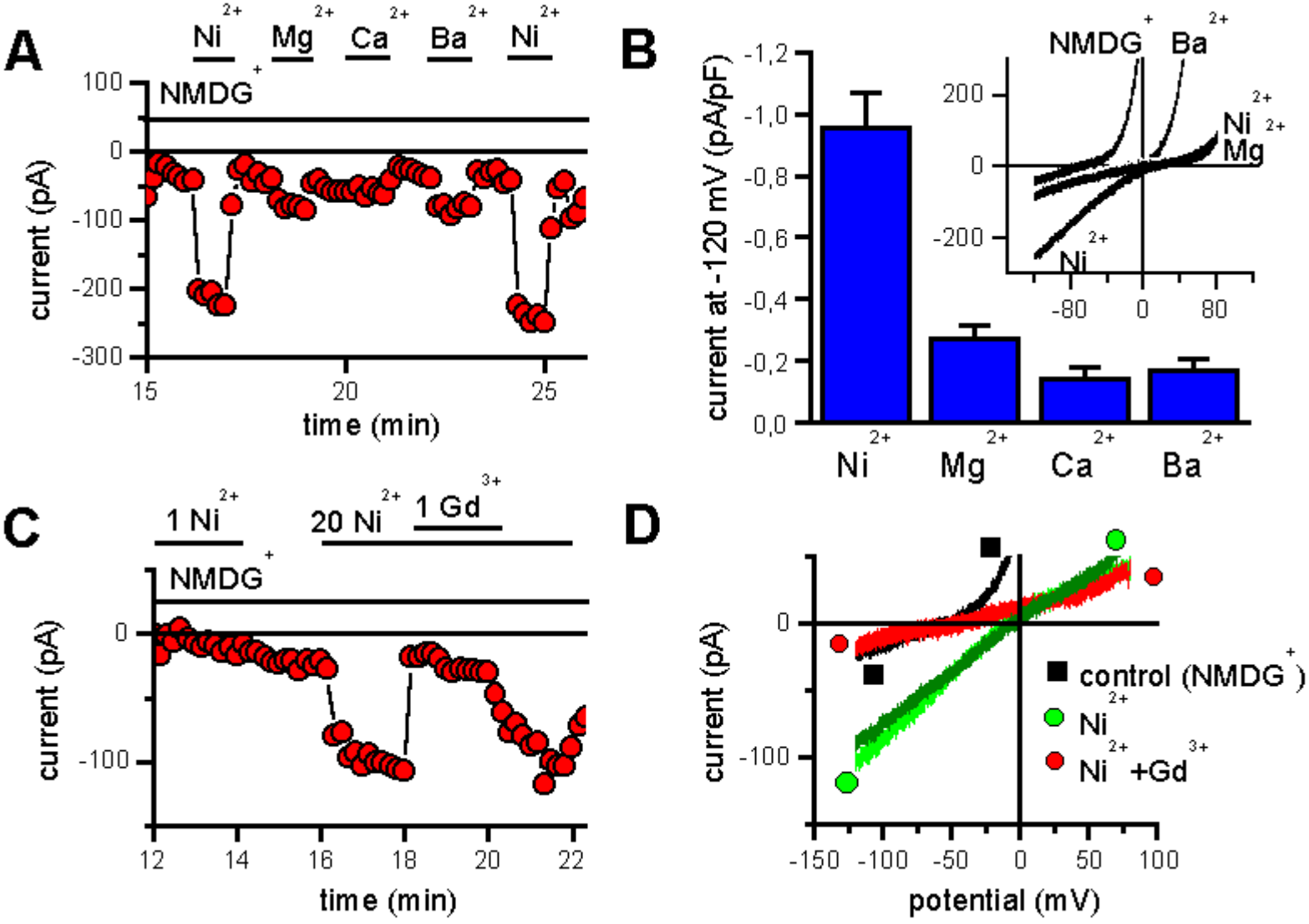
Block by di- and trivalent cations



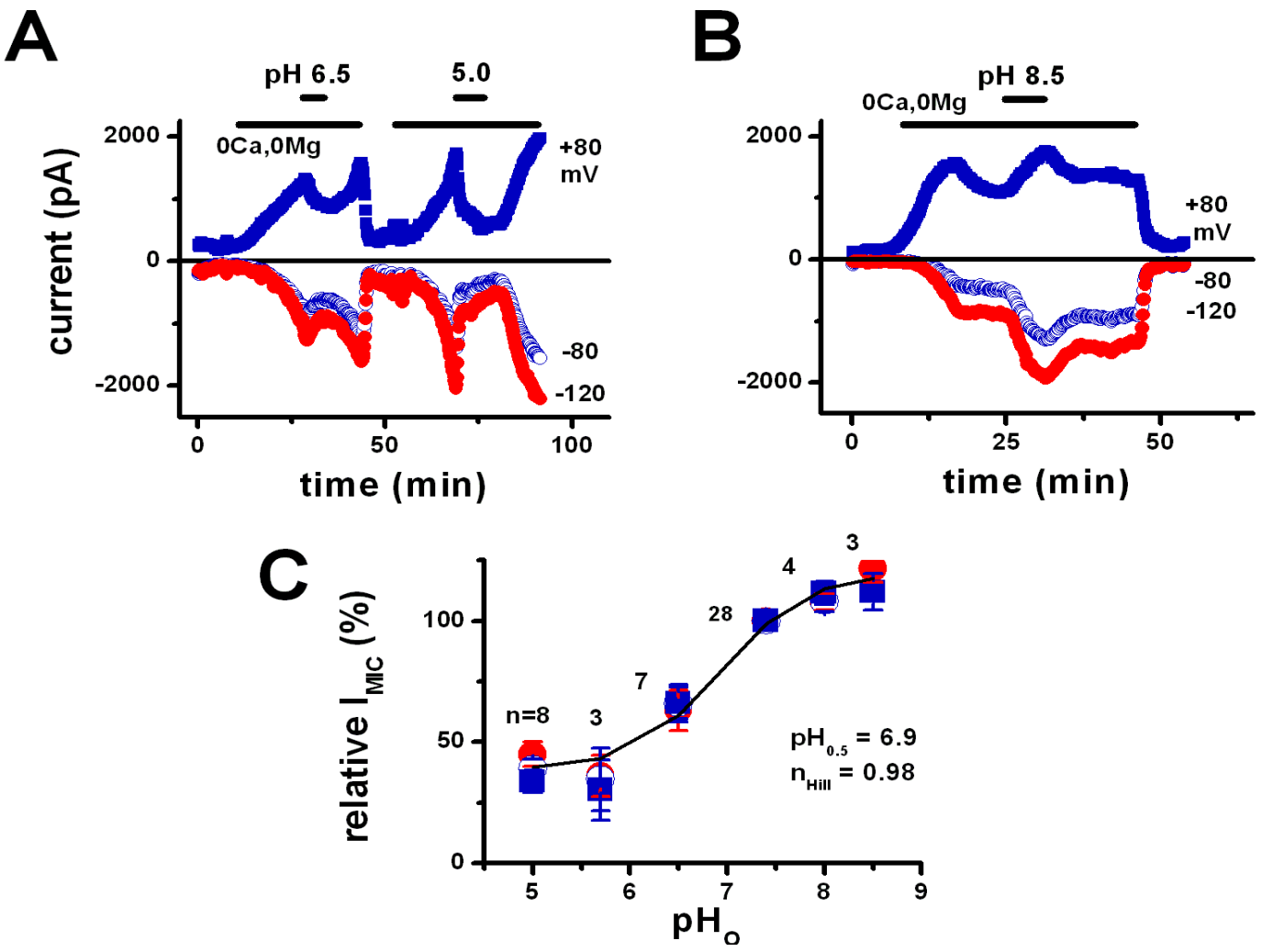
Outward current block by divalent cations



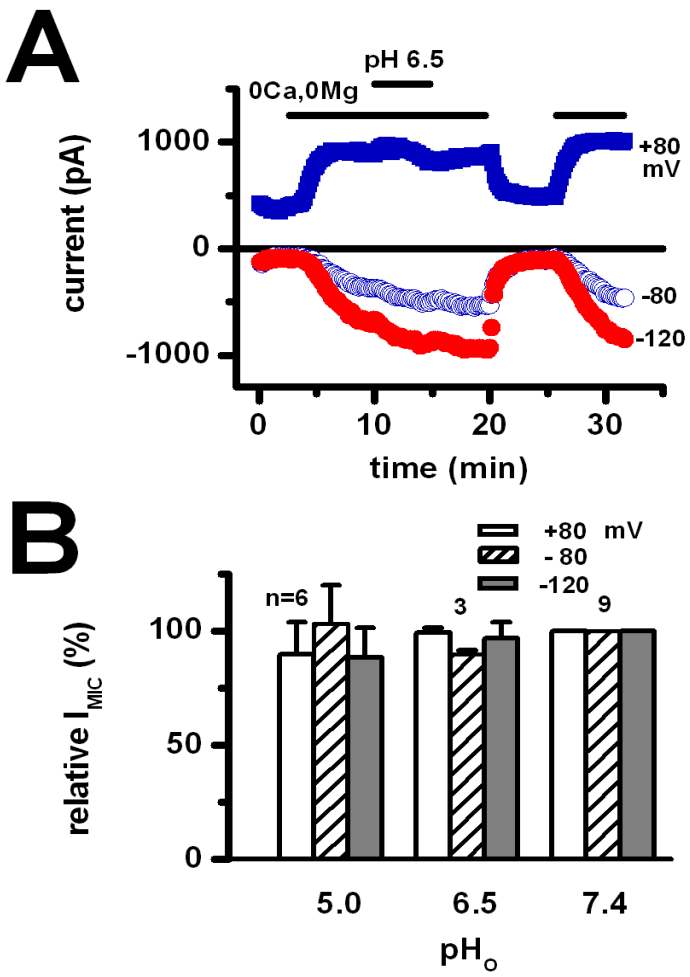
Divalent cation permeability



pH sensitivity



High internal buffering (HEPES 40 mM) prevents the effect of pH



Roles of TRPM7 (and TRPM6)

- ***in Mg^{2+} homeostasis and cell growth***

• TRPM6: autosomal hypomagnesemia with secondary hypocalcemia (HSH) – 9q – frameshift / nonsense mutations

Chubanov et al. (2004): S141L mutation in HSH impairs TRPM6/M7 multimer formation and membrane trafficking

• chicken DT40 B cells with Cre/loxP TRPM7 KO show growth arrest

• TRPM7 RNAi inhibits cell proliferation in gastric ADK & human retinoblastoma

• TRPM7 overexpressed in breast ADK – expression correlates with tumor size, grade, and Ki67 proliferative index

Roles of TRPM7

- ***in embryonic development***

- ***TRPM7 deletion in mice: embryonic lethality before day 7.5***
- ***tissue-specific TRPM7 deletion in T cells (lck-Cre) disrupts thymopoiesis***
- ***TRPM7 disruption in zebrafish (Robert Cornell et al., U Iowa):***

nutria^{j124e2} : mineralization of mesonephric tubules

severe growth deficit

skeletal deformities by accelerated endochondral and delayed intramembranous ossification

touchstone tct^{j124e1} (premature stop codon at res. 1545)

Both mutants: melanophore deficiencies and touch unresponsiveness

Roles of TRPM7

- ***in neurological pathology***

- ***Hermosura et al. (2005): TRPM7 SNP T1482I (missense) linked to Guam amyotrophic lateral sclerosis (ALS-G) or Parkinson dementia (PD-G), and associated with elevated risk for both adenomatous and hyperplastic polyps***
- ***Krapivinsky et al. (2006, 2008): TRPM7 resides in synaptic vesicles of sympathetic neurons, where it forms complexes with synapsin I, synaptotagmin I, and directly interacts with snapin***

RNAi /targeted peptide interference with TRPM7/snapin interaction reduces quantal neurotransmitter release

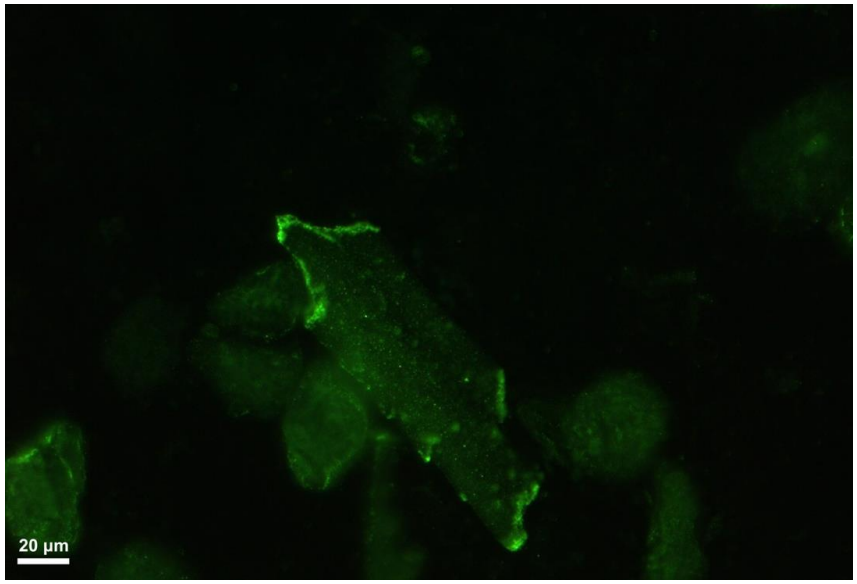
Roles of TRPM7

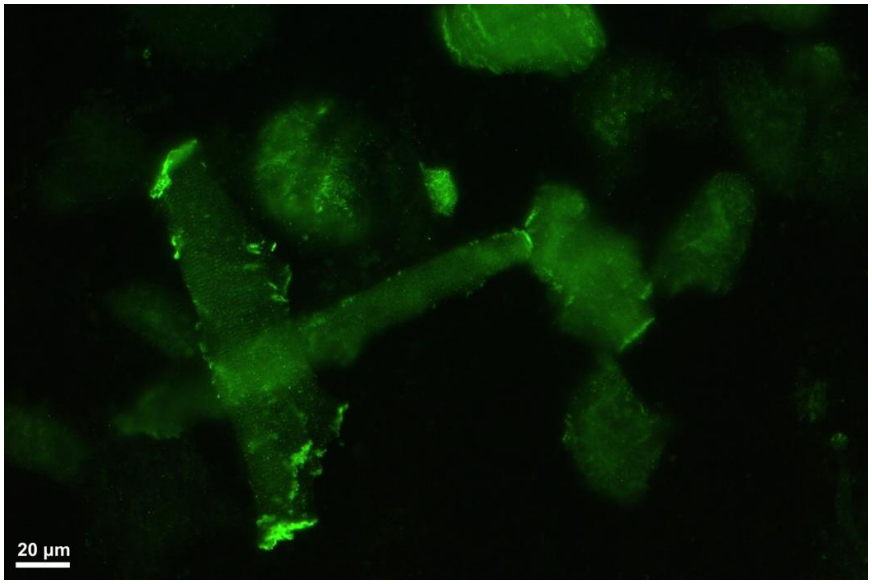
- ***in cell motility and adhesion***

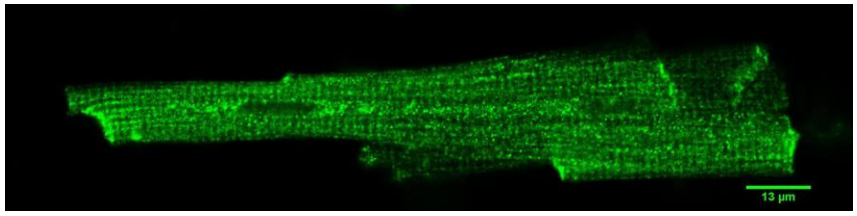
- ***Su et al. (2006): TRPM7 overexpression in HEK293 cells produces cell rounding by stimulating m-calpain Ca2+ protease***
- ***TRPM7 depletion by RNAi: opposite effects, increased cell adhesion***
- ***M-calpain activation dependent on production of reactive oxygen/nitrogen species, stimulation of p38 MAPK and c-Jun N-terminal kinase (JNK)***
- ***Clark et al. (2006): TRPM7 overexpression in BK-treated N1E-115 neuroblastoma induces podosome-like adhesive structures***
- ***TRPM7 α kinase ~ myosin heavy chain kinase: it may interact with the actomyosin cytoskeleton – coimmunoprecipitation with β-actin and myosin IIA heavy chain***

Nonhomogeneous TRPM7 distribution in ventricular cardiomyocytes

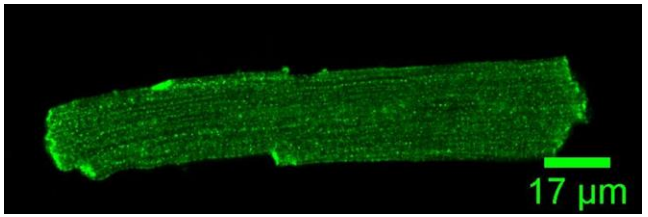
B Istrate, A Gwanyanya, R Driessen, V Bito, K Mubagwa (2012)







pig cm

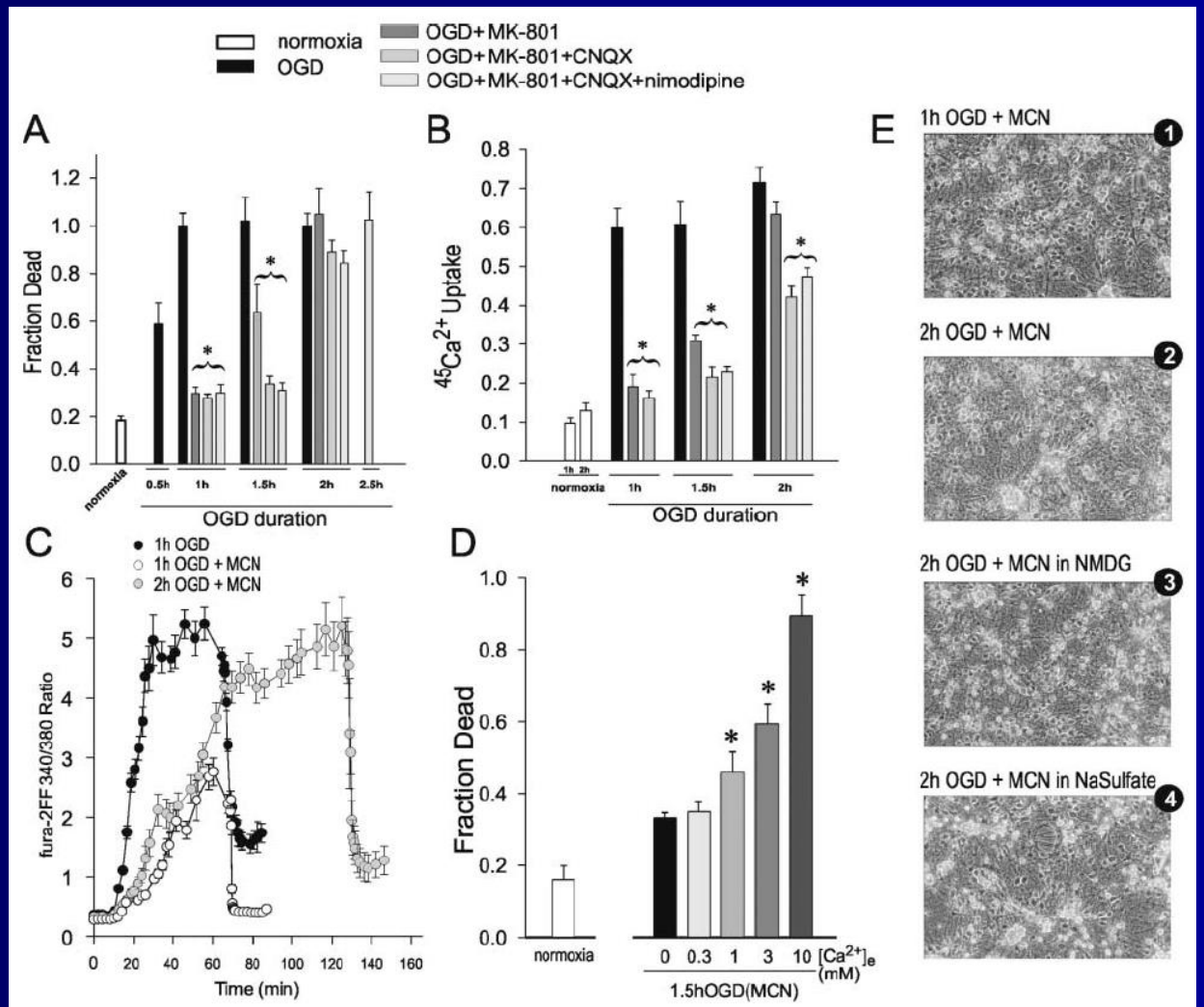


rat cm

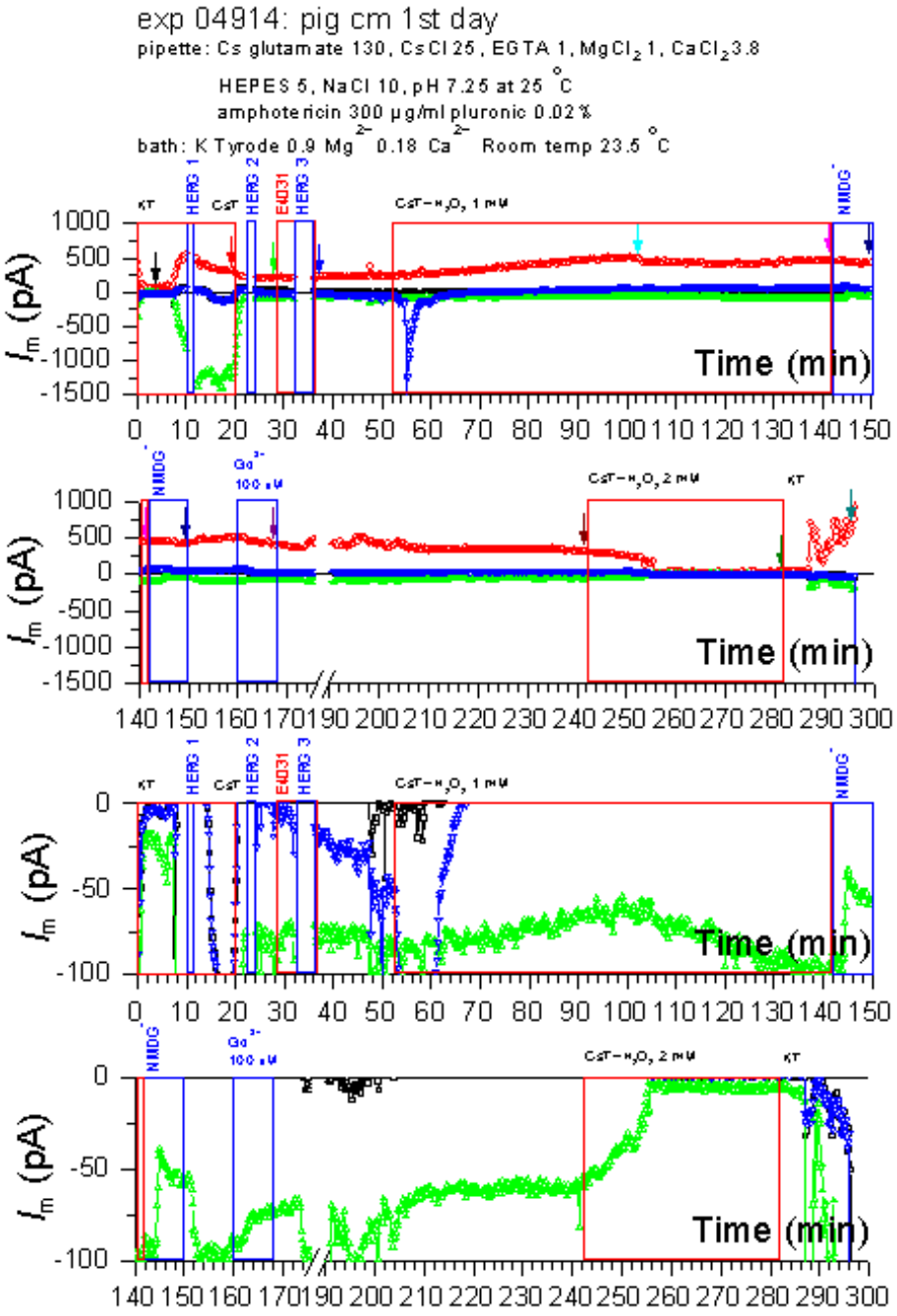
Michelle Aarts, Koji Iihara, Wen-Li Wei, Zhi-Gang Xiong, Mark Arundine, Waldy Cerwinski, John F. MacDonald, and Michael Tymianski

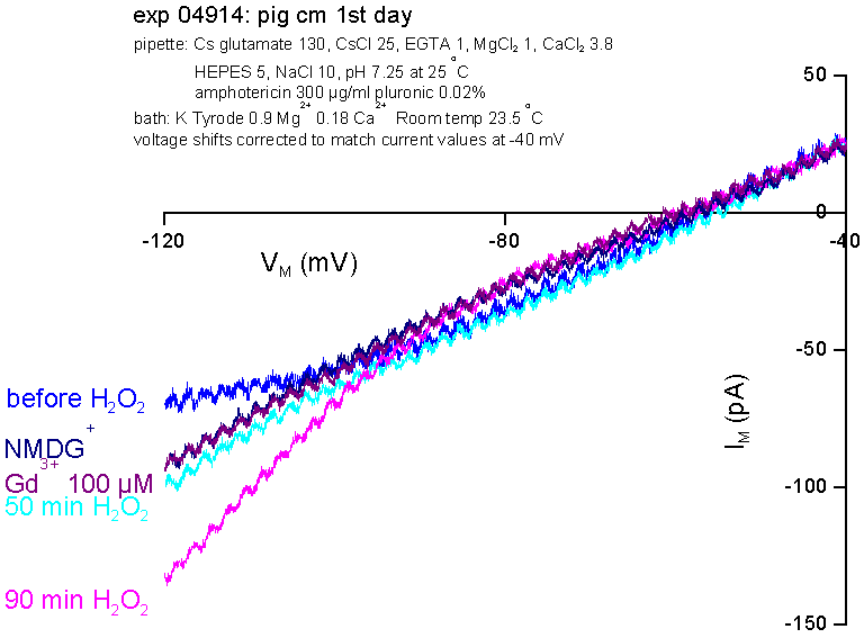
A Key Role for TRPM7 Channels in Anoxic Neuronal Death

Cell 115:863–877, December 26, 2003



Prolonged exposure to H_2O_2 0.1 mM activates an inward current





Macianskiene et al. Journal of Biomedical Science 2012, 19:75
http://www.jbiomedsci.com/content/19/1/75

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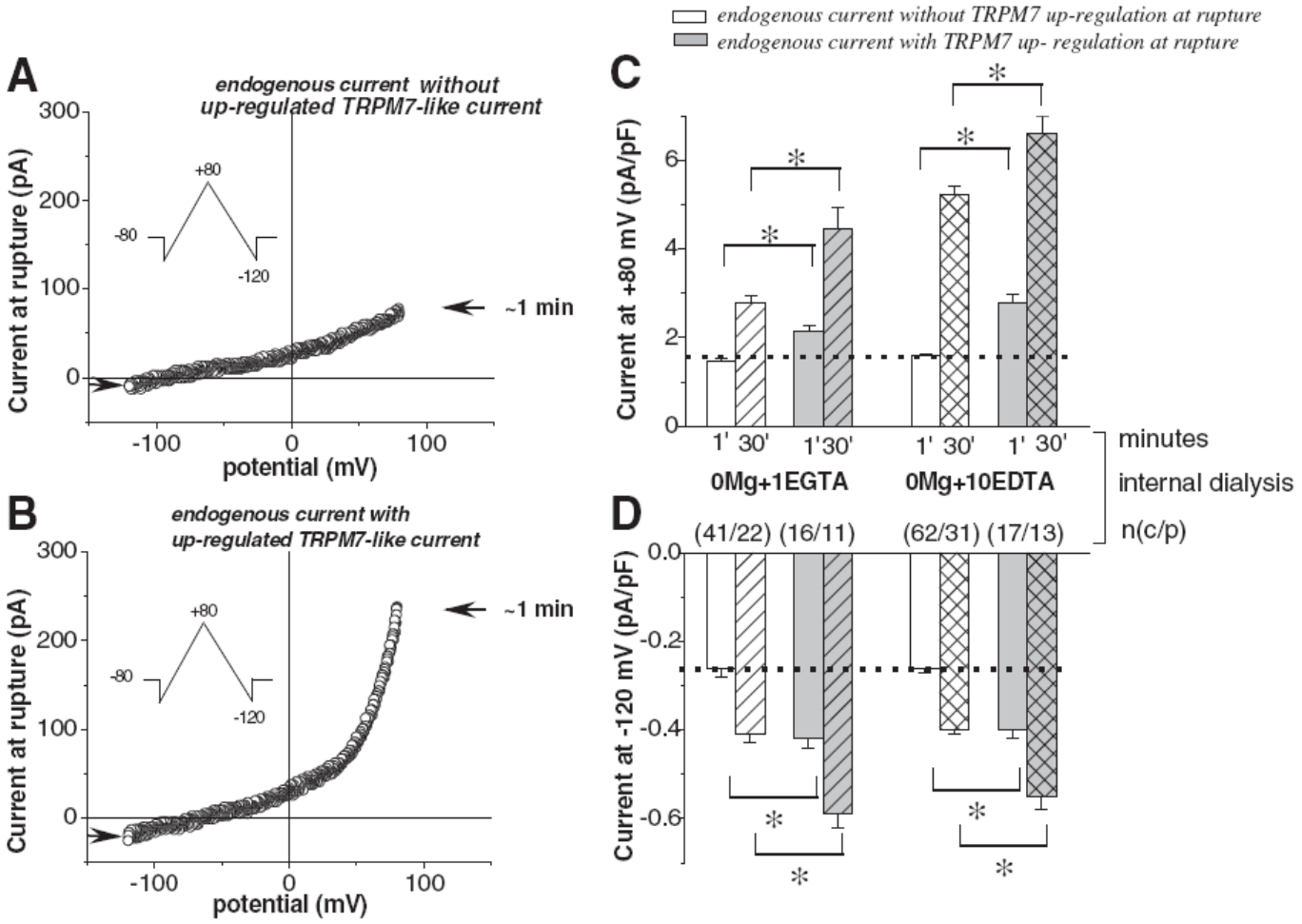
RESEARCH Open Access

Characterization of Mg^{2+}-regulated TRPM7-like current in human atrial myocytes

Regina Macianskiene*, Irma Martisiene, Danguole Zablockaite and Vida Gendviliene



Macianskiene et al. Journal of Biomedical Science 2012, 19:75
http://www.jbiomedsci.com/content/19/1/75

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RESEARCH Open Access

Characterization of Mg^{2+}-regulated TRPM7-like current in human atrial myocytes

Regina Macianskiene*, Irma Martisiene, Danguole Zablockaite and Vida Gendviliene

Table 1 Patients' preoperative clinical characteristics

Characteristic	Total n = 116; n and (%)	free-Mg_i^{2+} (all) n = 77; n and (%)	free-Mg_i^{2+} Without up-regulated TRPM7 at rupture n = 53; n and (%)	free-Mg_i^{2+} With up-regulated TRPM7 at rupture n = 24; n and (%)
Age (years)	65.6±1.02	65.7±1.09	65.3±1.43	66.3±1.59
Gender (male/female)	73/43	49/28	30/23	19/5
Ischaemic heart disease	98(84.5)	68(88.3)	45(84.9)	23(95.8)
Myocardial infarction	47(40.5)	37(48.1)	25(47.2)	12(50.0)
Hypertension	97(83.6)	67(87.0)	43(81.1)	24(100.0)
Heart failure	54(46.6)	36(46.8)	21(39.6)	15(62.5)
Diabetes mellitus	15(12.9)	9(11.7)	0(0.0)	9(37.5)
Rheumatic heart disease	6(5.2)	6(7.8)	5(9.4)	1(4.2)
Type of heart surgery:				
coronary bypasses	63(54.3)	41(53.2)	32(60.4)	9(37.5)
valve repair/replacement	28(24.1)	16(20.8)	10(18.9)	6(18.9)
both (valves and bypasses)	25(21.6)	20(26.0)	11(20.8)	9(37.5)

Values are given as numbers of patients (n and %) with indicated clinical characteristics, except for age (MEAN±S.E.M.) and gender (numbers of male/female).

Thanks' for your kind attention!!!!!

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