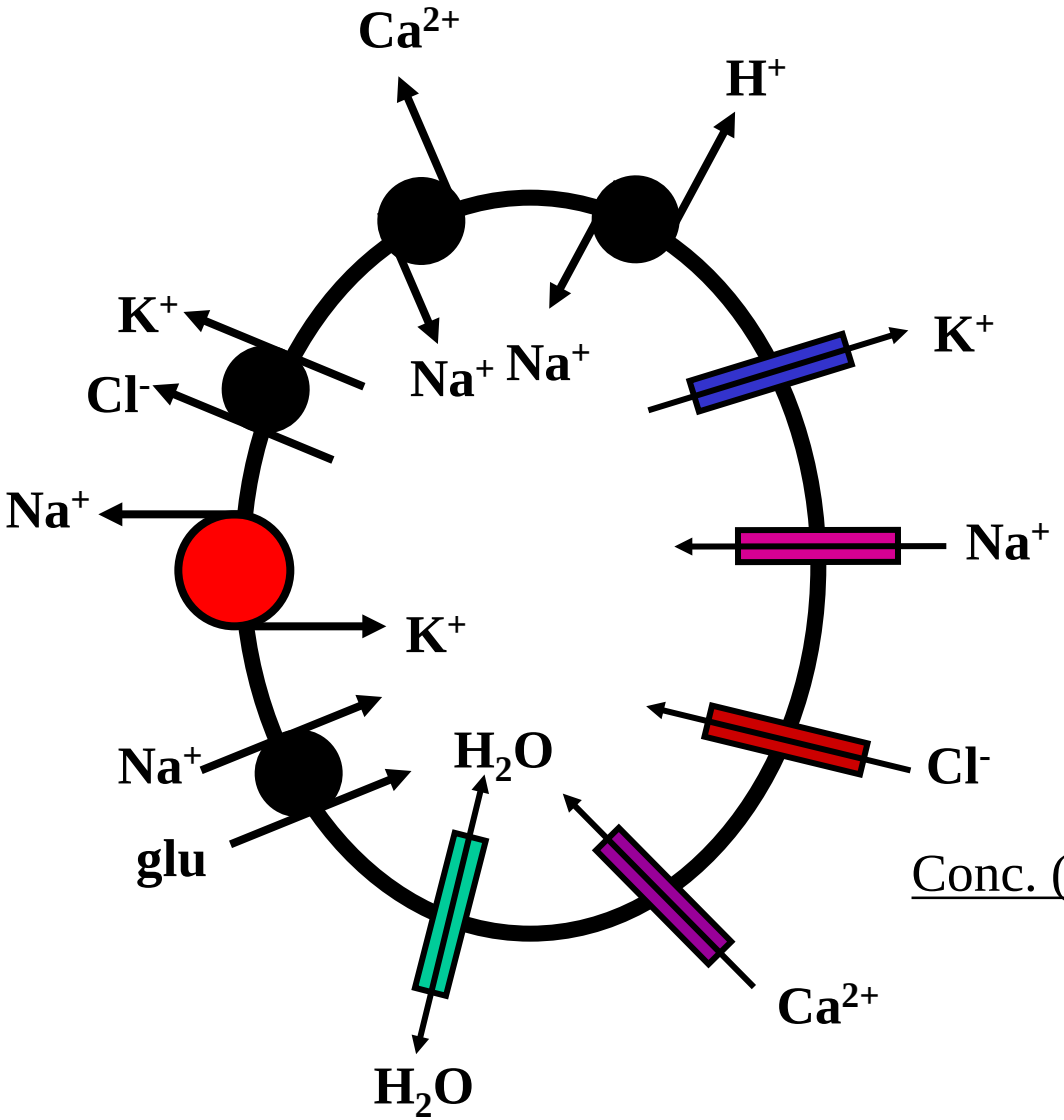
New developments in membrane channel physiology

-with focus on ion and water flux

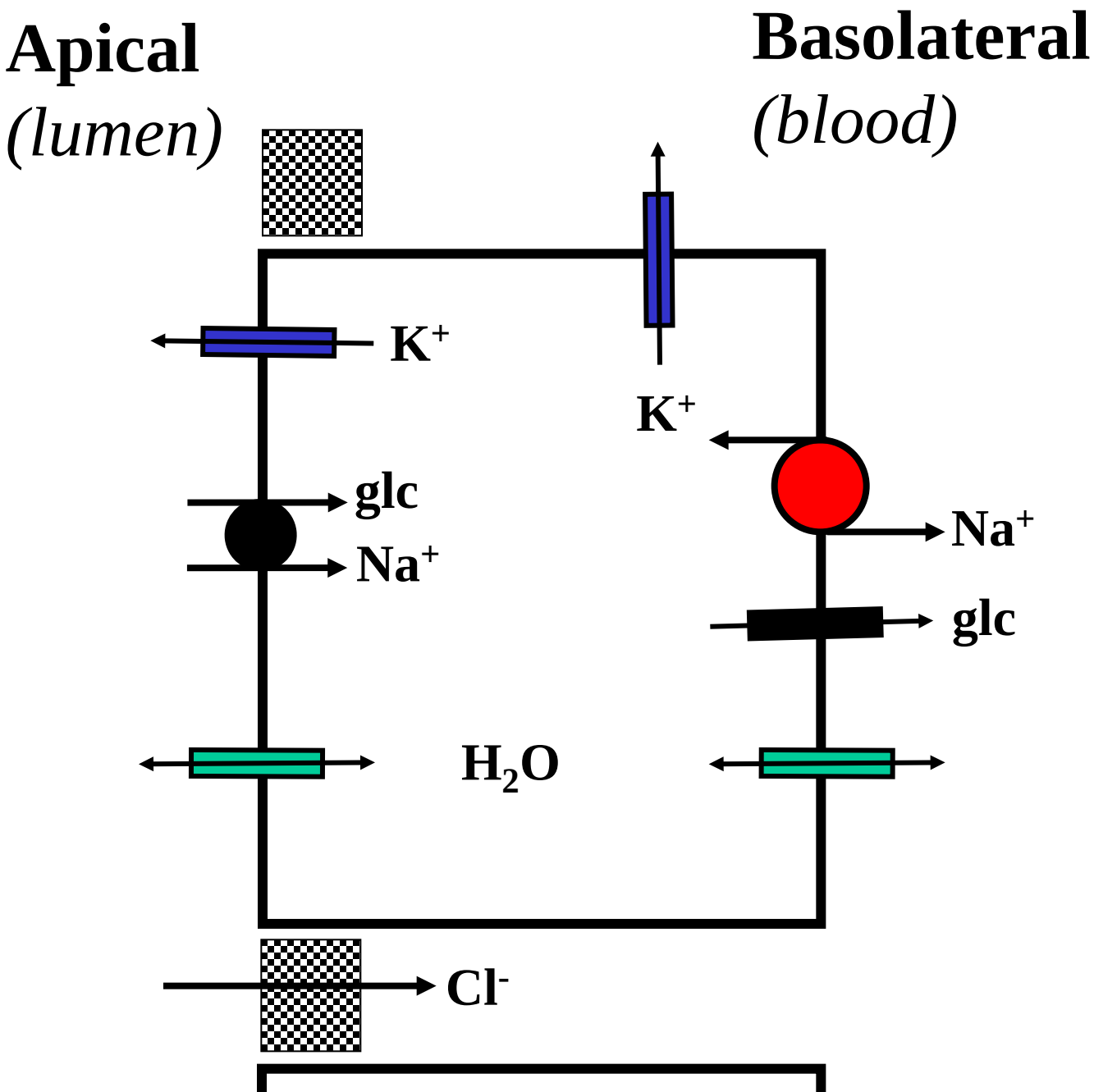
Dan A. Klærke
Professor, MD
University of Copenhagen

The cell

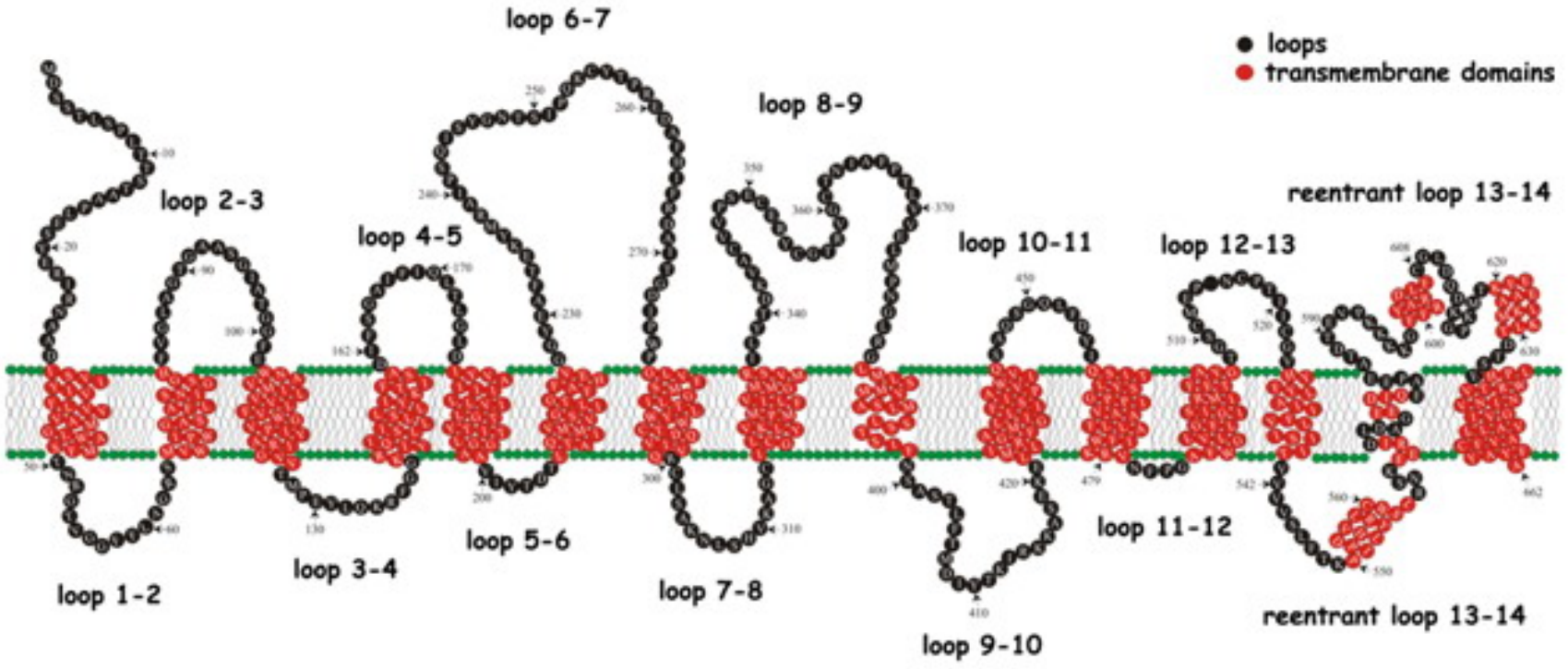


Conc. (mM)	intracellular	extracellular
Na^+	14	140
K^+	150	4
Cl^-	4	110
Ca^{2+}	0.0001 (100 nM)	2.5

Absorptive cell:



Na^+-glucose co-transporter



Water pump

Journal of Physiology (1998), **508.1**, *pp.*15–21

Rapid Report

The human Na^+–glucose cotransporter is a molecular water pump

A.-K. Meinild, D. A. Klaerke , D. D. F. Loo*, E. M. Wright* and T. Zeuthen

*The Panum Institute, University of Copenhagen, Department of Medical Physiology, Blegdamsvej 3, DK-2200N Copenhagen, Denmark and *Department of Physiology, University of California School of Medicine, Los Angeles, CA 90095-1751, USA*

Water pump

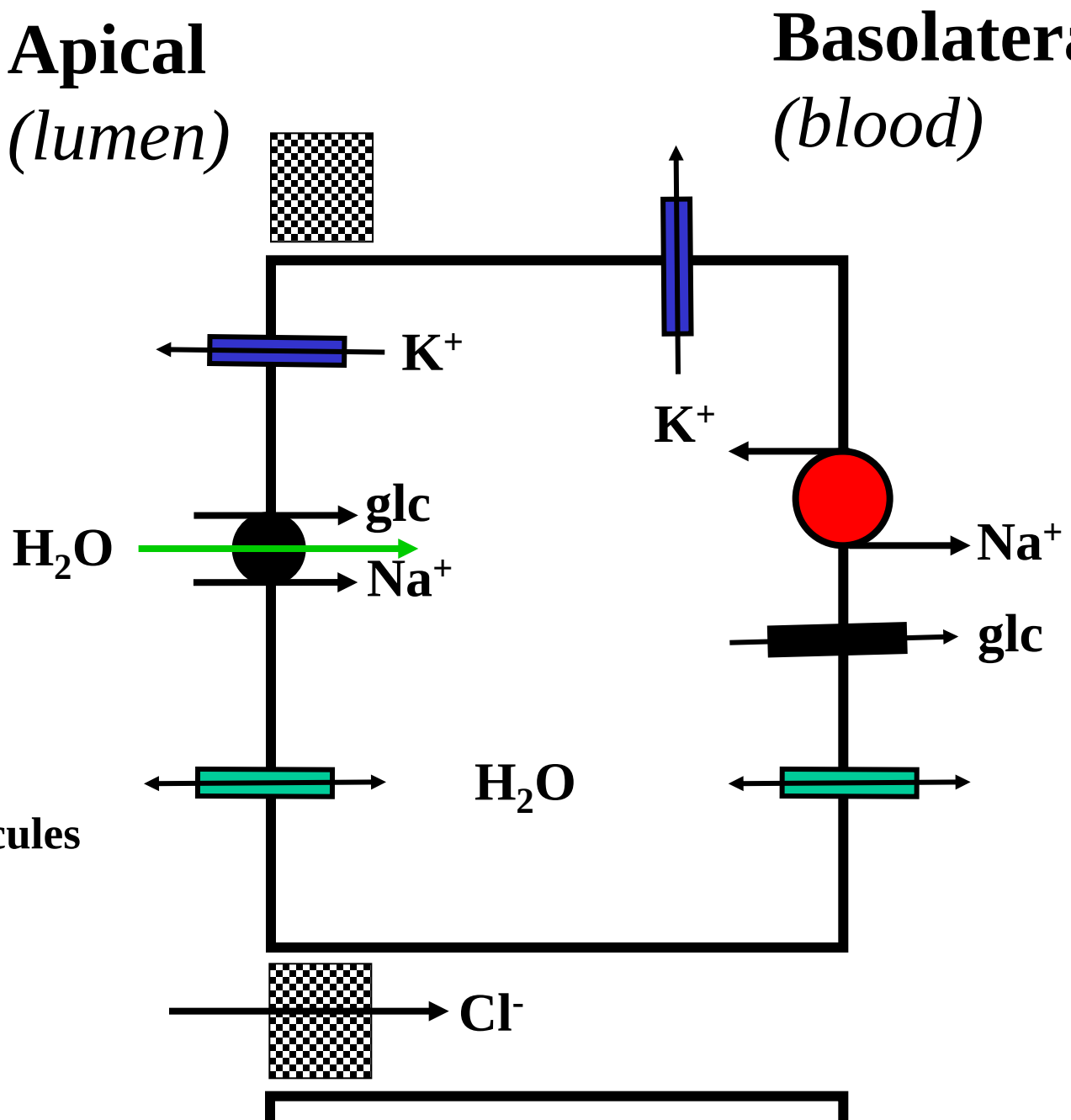
Journal of Physiology (2001), 531.3, *pp.*631–644

Isotonic transport by the Na^+–glucose cotransporter SGLT1 from humans and rabbit

T. Zeuthen, A.-K. Meinild*, D. D. F. Loo*, E. M. Wright* and D. A. Klaerke

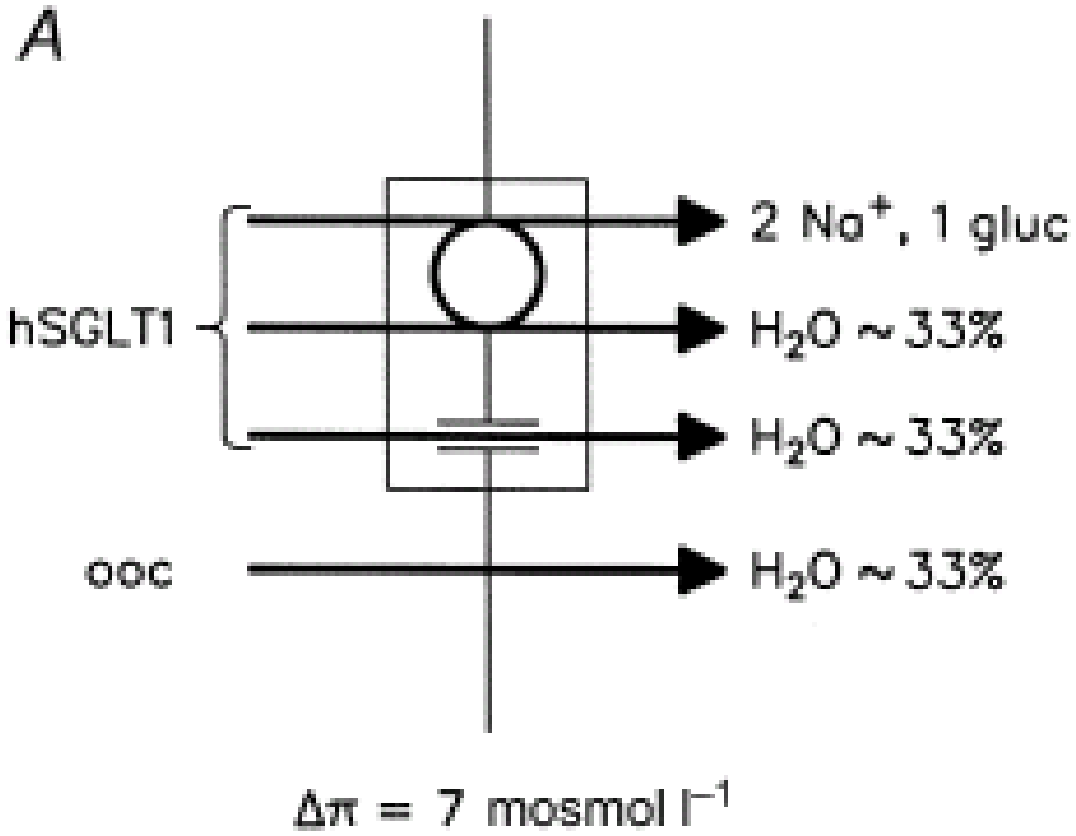
*The Panum Institute, Blegdamsvej 3C, DK-2200 Copenhagen N, Denmark and *Department of Physiology, University of California Los Angeles School of Medicine, Los Angeles, CA 90095-1751, USA*

Absorptive cell:

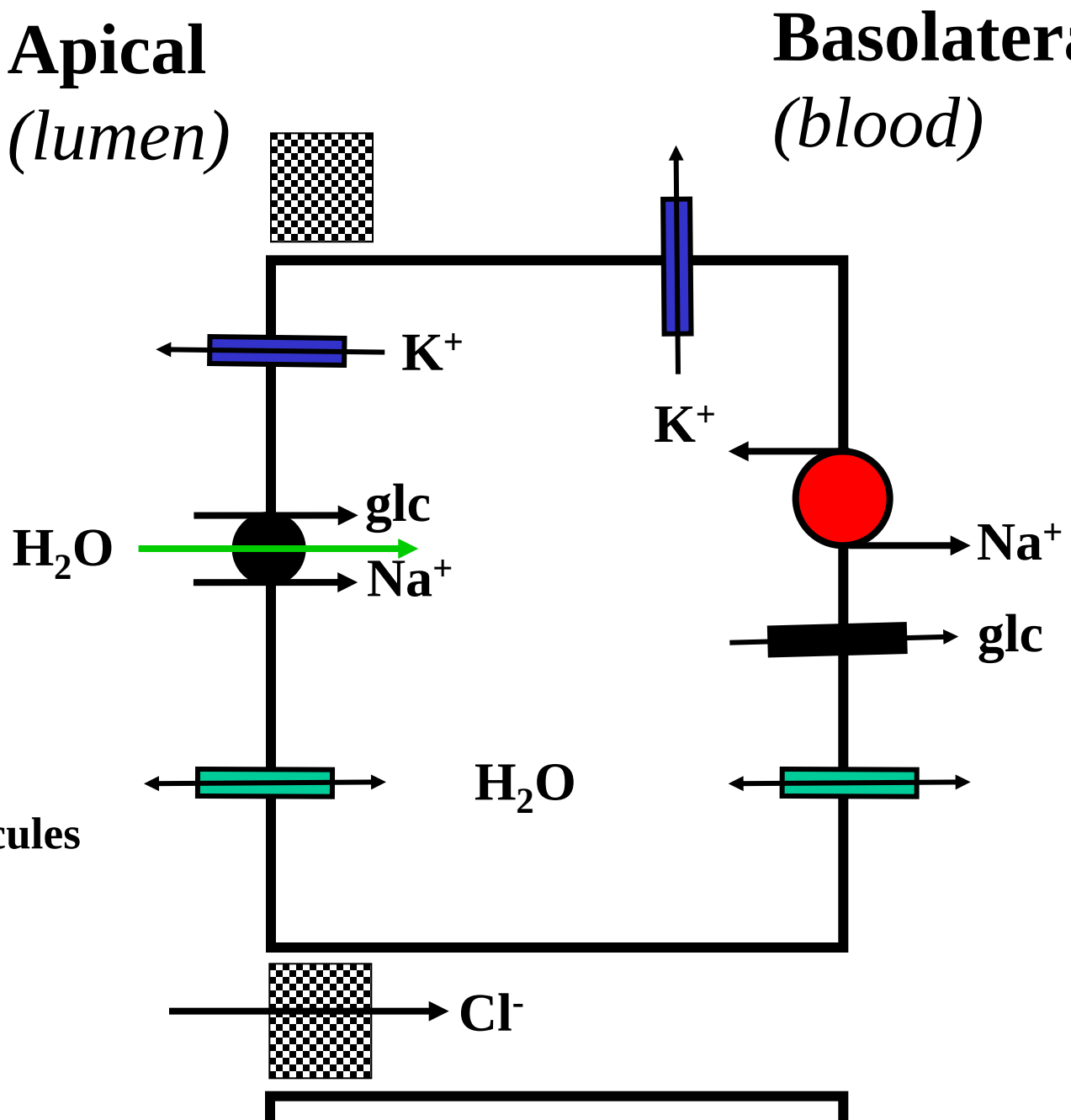


SGLT1:
230-380 water molecules per turnover

Water pump



Absorptive cell:



SGLT1:
230-380 water molecules per turnover

Water transport by GLUT

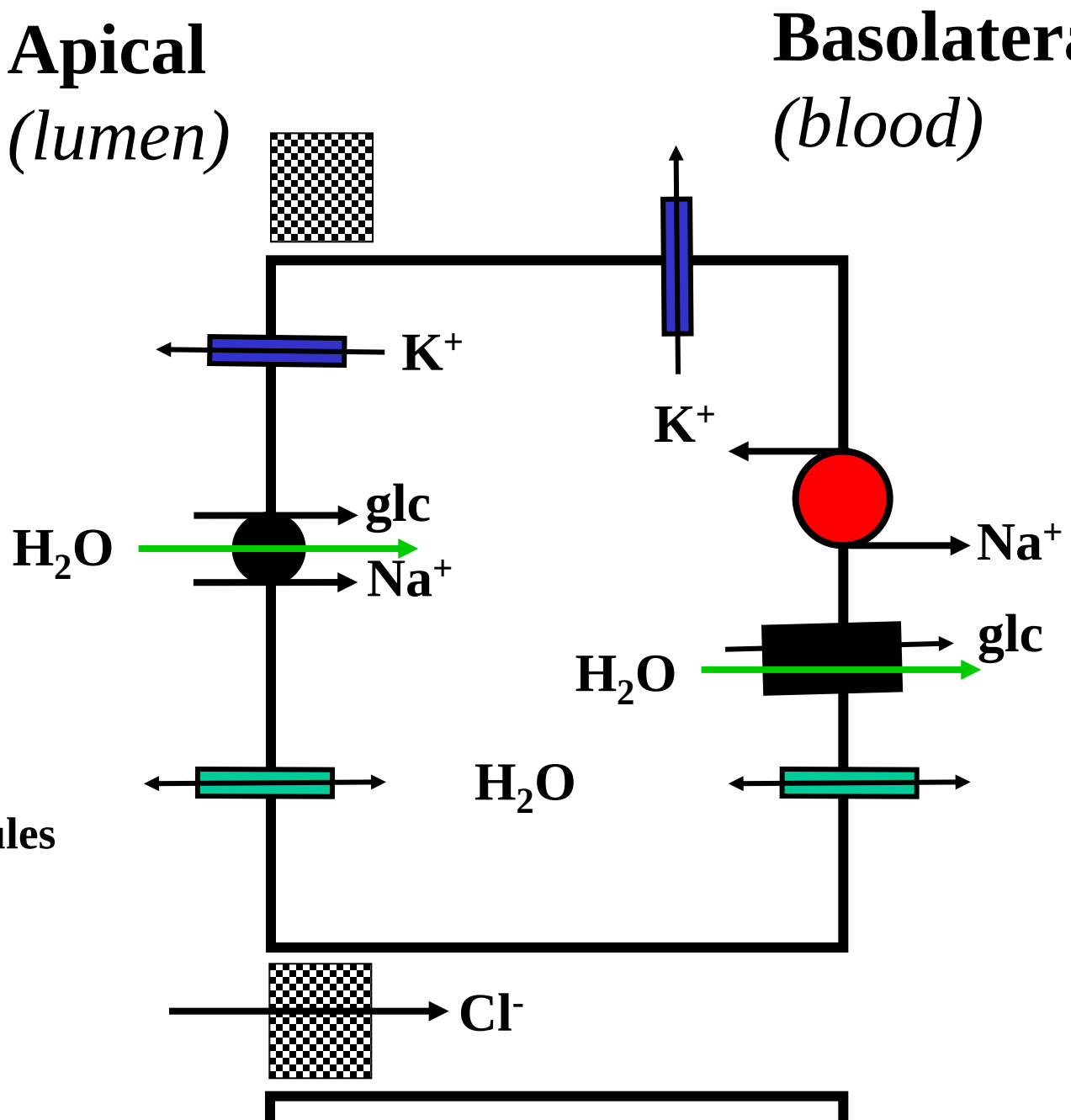
J Physiol 579.2 (2007) pp 345–361

Water transport by GLUT2 expressed in *Xenopus laevis* oocytes

Thomas Zeuthen, Emil Zeuthen and Nanna MacAulay

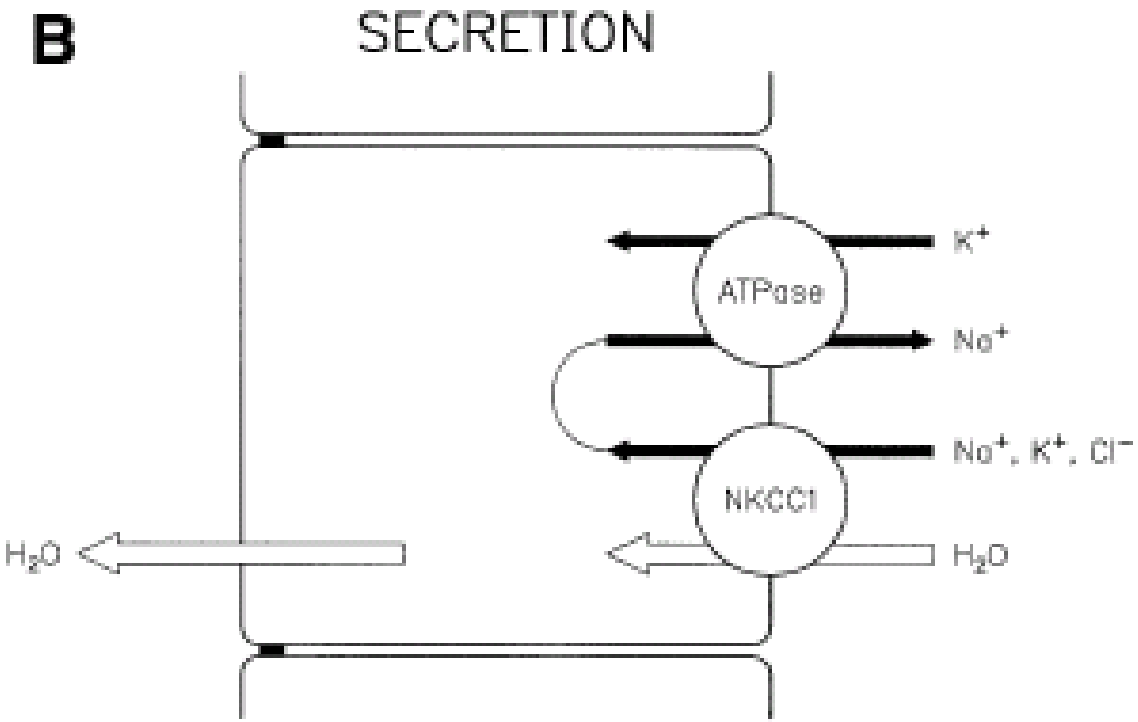
Nordic Centre for Water Imbalance Related Disorders, Department of Medical Physiology, The Panum Institute, Blegdamsvej 3C, University of Copenhagen DK-2200 N, Denmark

Absorptive cell:



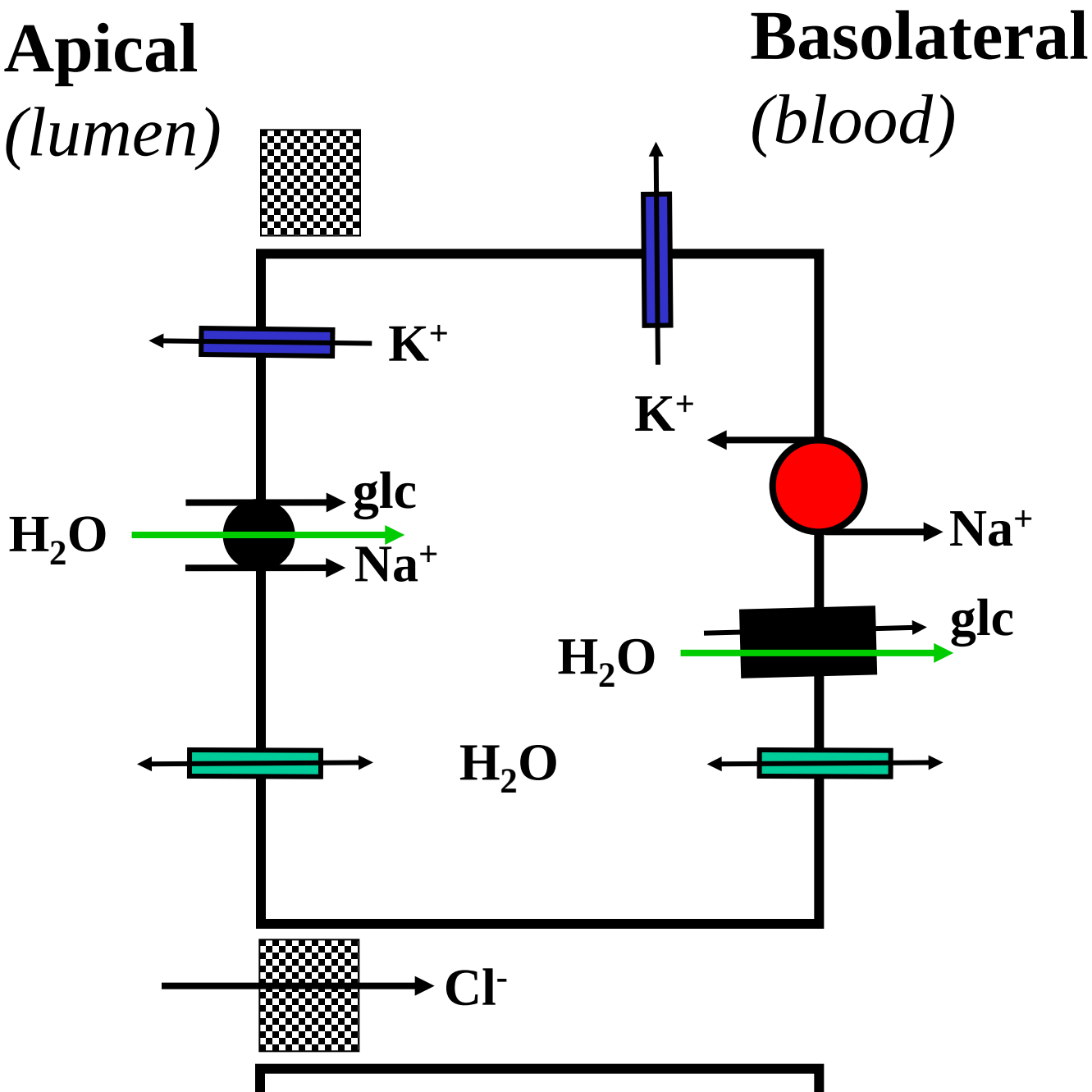
GLUT:
40-110 water molecules per turnover

Secretory cell

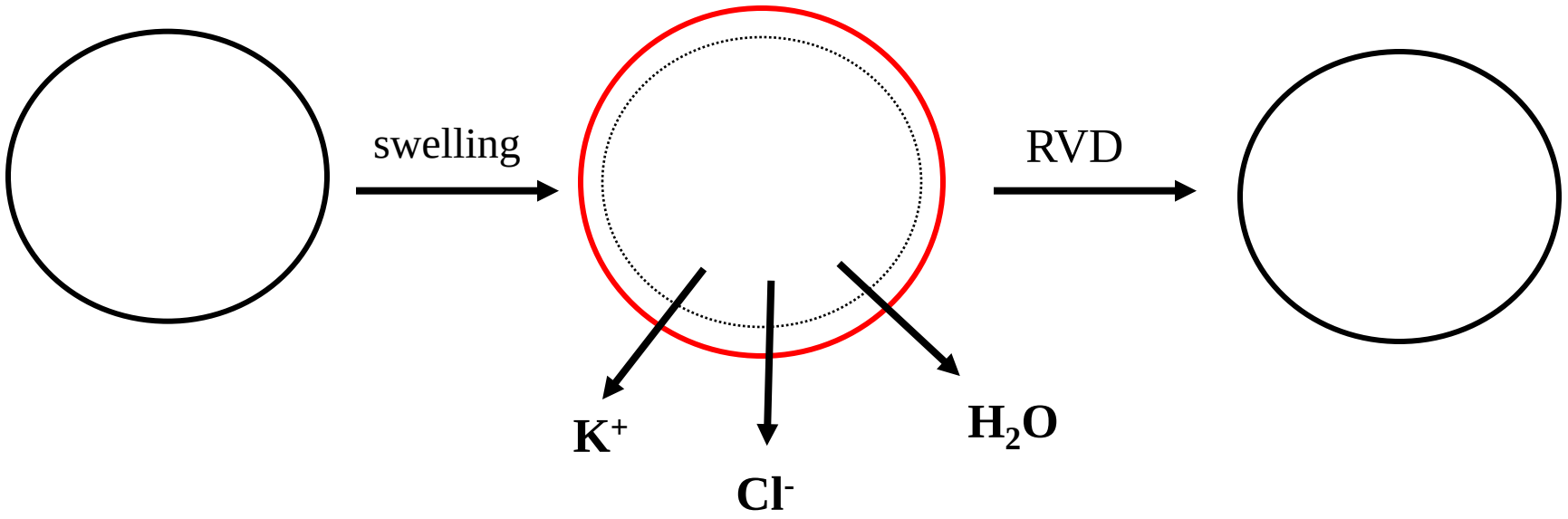


Zeuthen et al., J. Membrane Biol., 2010

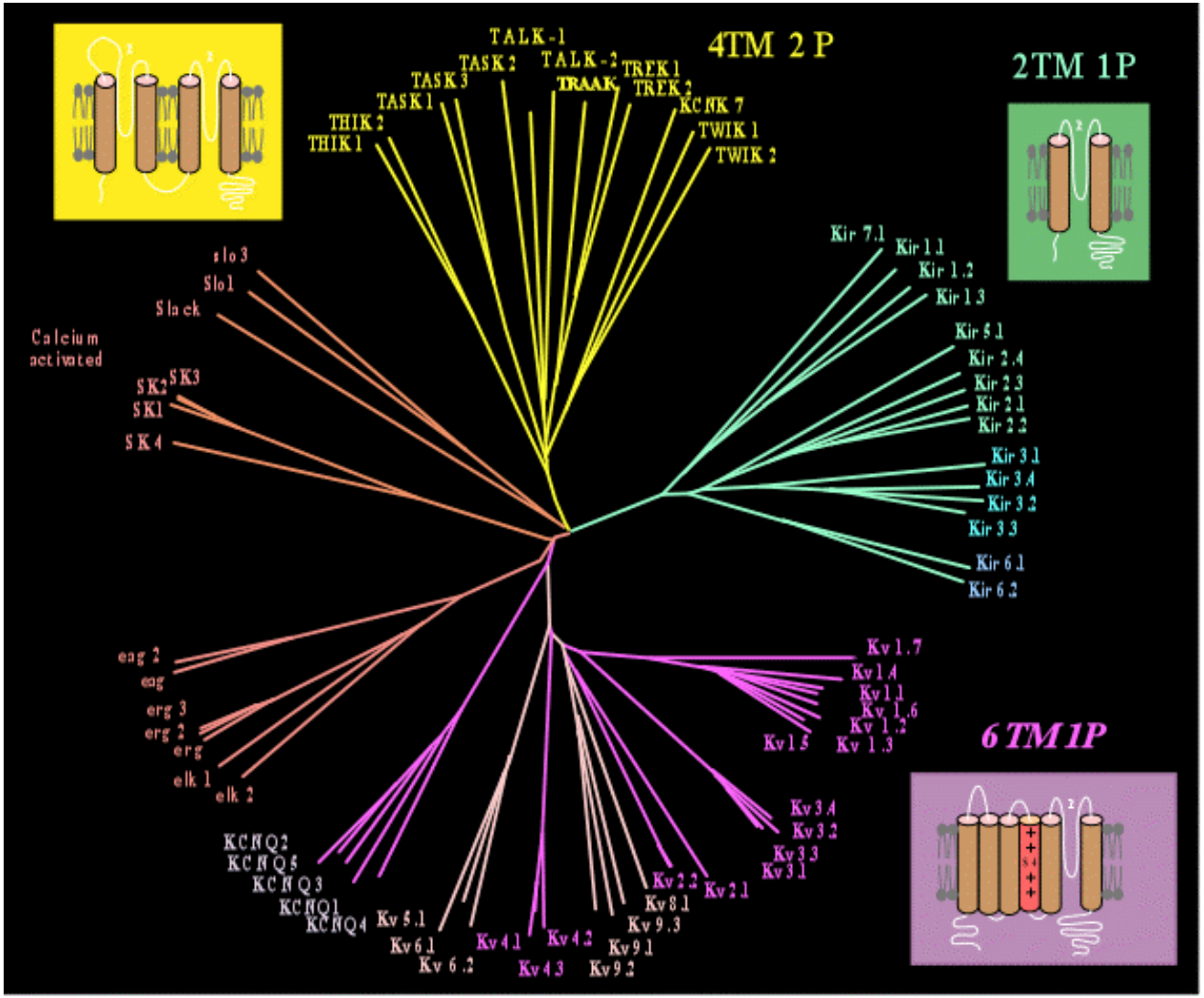
Absorptive cell:



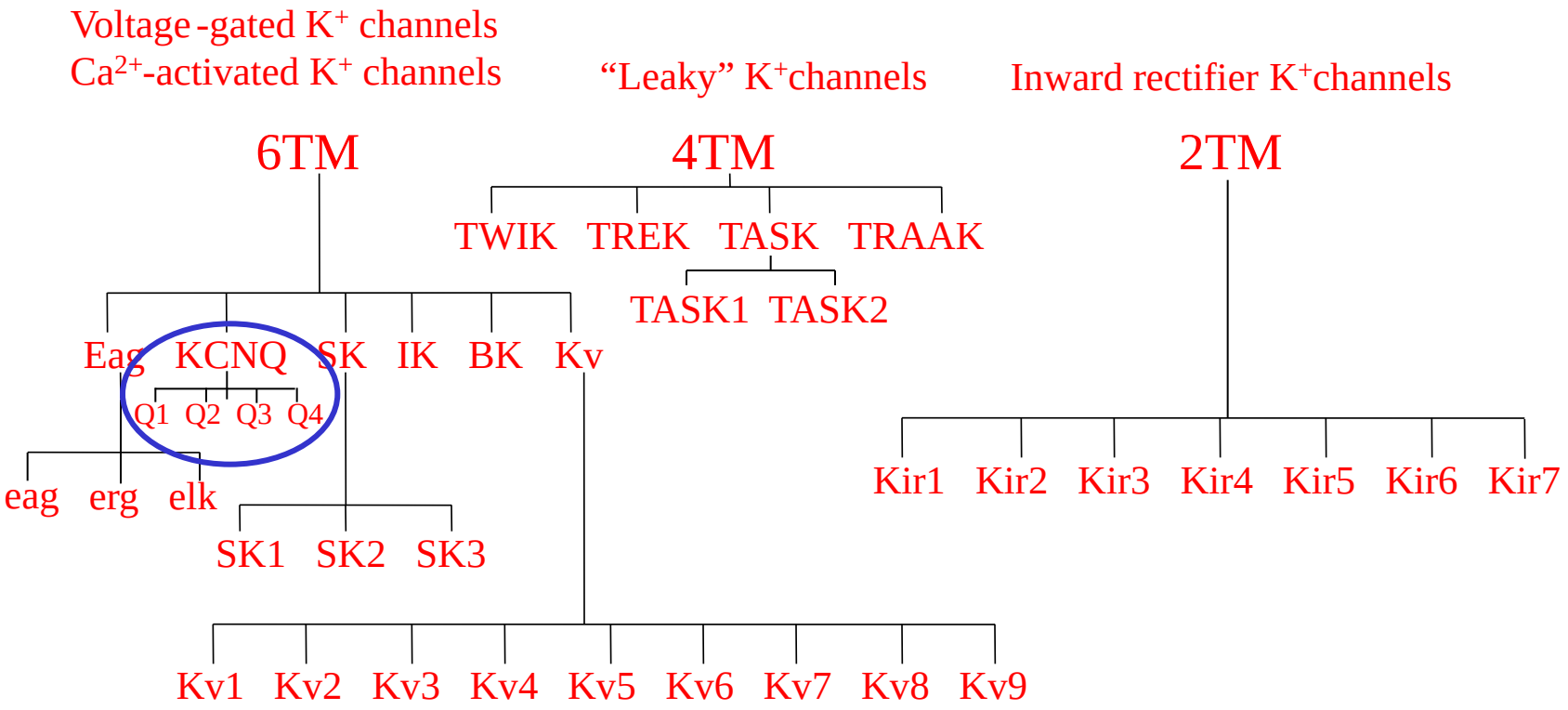
Regulatory volume decrease



K^+ channels

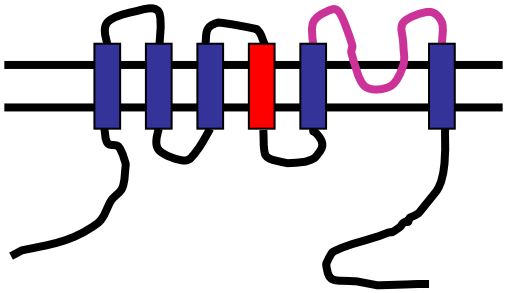

4TM 2 P
2TM 1P
6TM1P
TALK-1
TASK 2
TALK-2
TREK 1
TASK 3
TRAAK
TREK 2
TASK 1
KCNK 7
THIK 2
TWIK 1
THIK 1
TWIK 2
Kir 7.1
Kir 1.1
Kir 1.2
Kir 1.3
Kir 5.1
Kir 2.4
Kir 2.3
Kir 2.1
Kir 2.2
Kir 3.1
Kir 3.4
Kir 3.2
Kir 3.3
Kir 6.1
Kir 6.2
slo 3
Slo1
Slack
Calcium activated
SK2
SK3
SK1
SK4
eag 2
eag
erg 3
erg 2
erg
elk 1
elk 2
KCNQ2
KCNQ5
KCNQ3
KCNQ1
KCNQ4
Kv 5.1
Kv 6.1
Kv 6.2
Kv 4.1
Kv 4.2
Kv 4.3
Kv 9.3
Kv 9.1
Kv 9.2
Kv 8.1
Kv 2.2
Kv 2.1
Kv 3.4
Kv 3.2
Kv 3.3
Kv 3.1
Kv 1.7
Kv 1.4
Kv 1.1
Kv 1.6
Kv 1.2
Kv 1.5
Kv 1.3

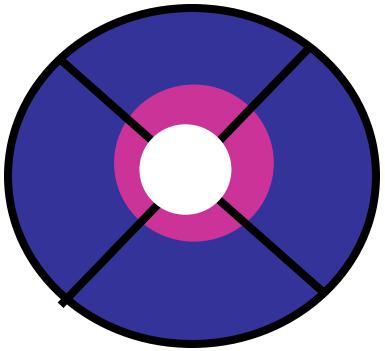
K^+ channels

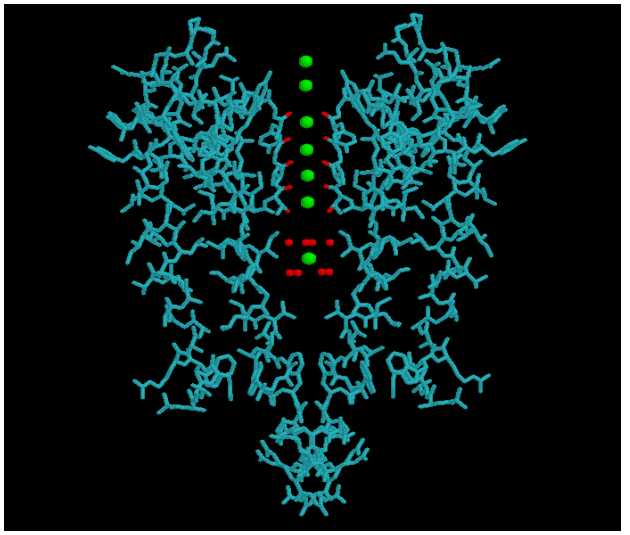

Voltage-gated K+ channels
Ca2+-activated K+ channels
“Leaky” K+channels
Inward rectifier K+channels
6TM
4TM
2TM
TWIK
TREK
TASK
TRAAK
TASK1
TASK2
Eag
KCNQ
SK
IK
BK
Kv
Q1
Q2
Q3
Q4
eag
erg
elk
SK1
SK2
SK3
Kv1
Kv2
Kv3
Kv4
Kv5
Kv6
Kv7
Kv8
Kv9
Kir1
Kir2
Kir3
Kir4
Kir5
Kir6
Kir7

K^+ channel structure

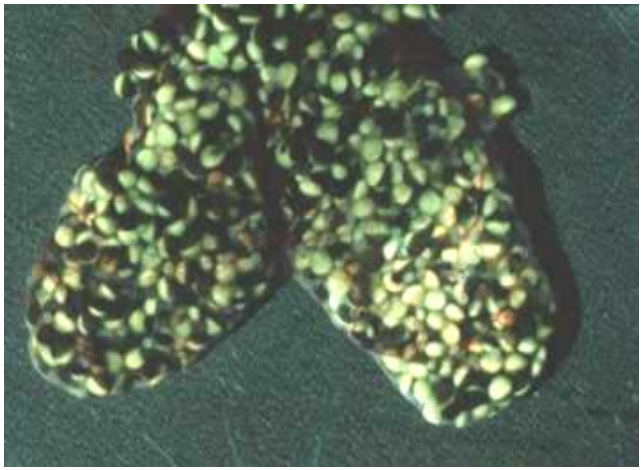
6 TM



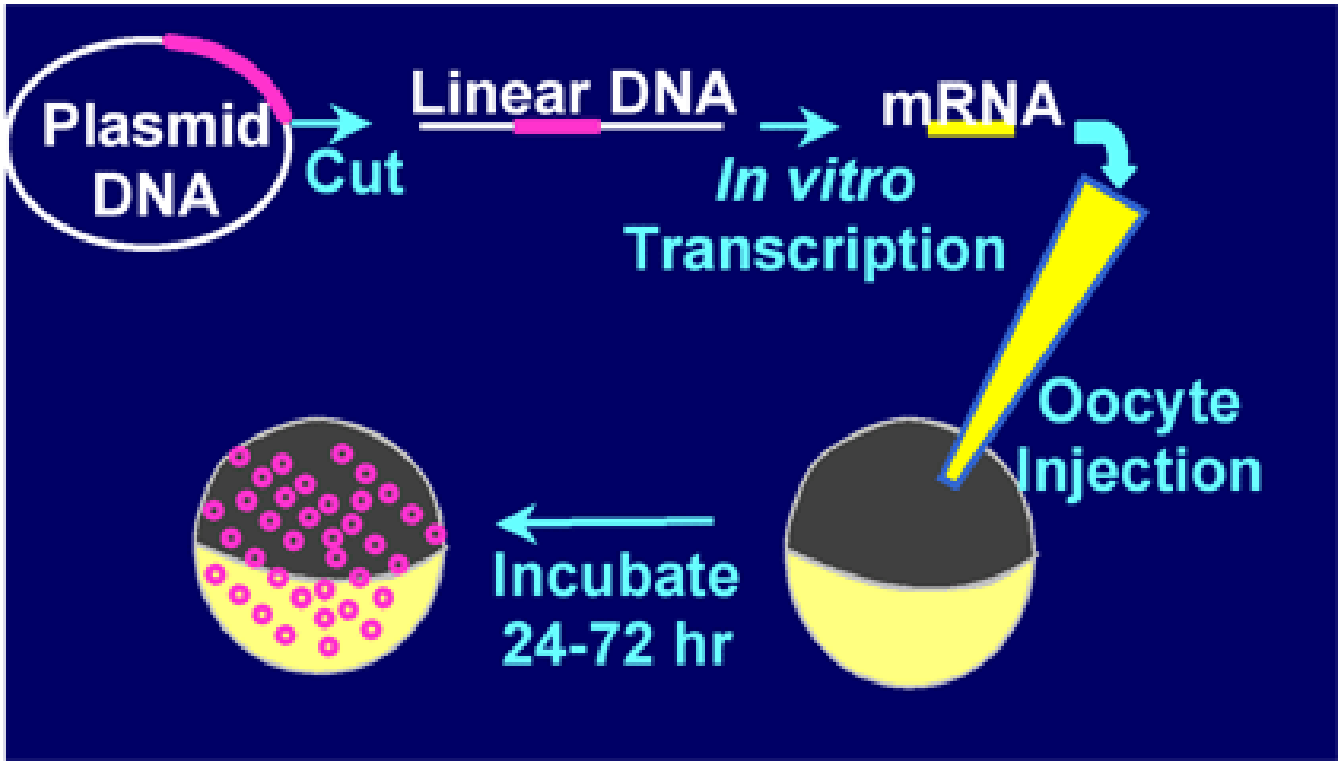




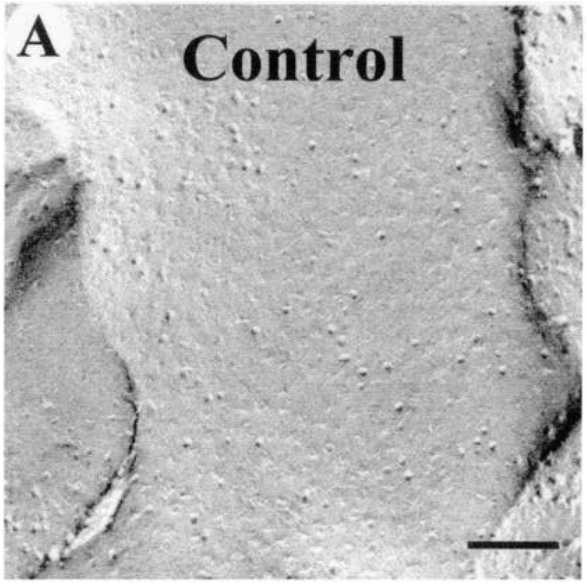
Xenopus laevis oocytes

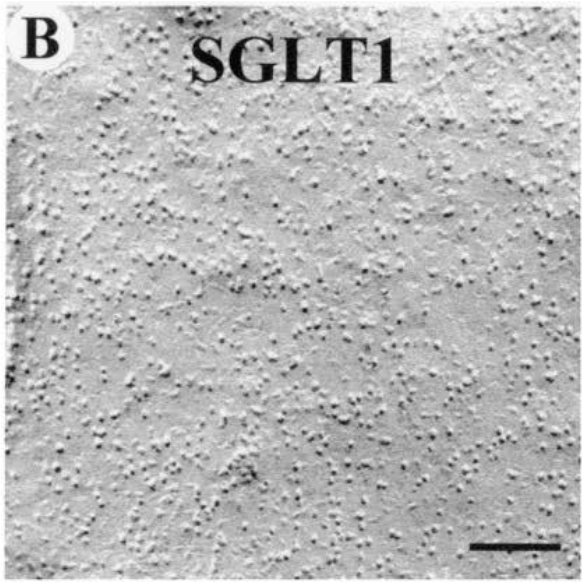


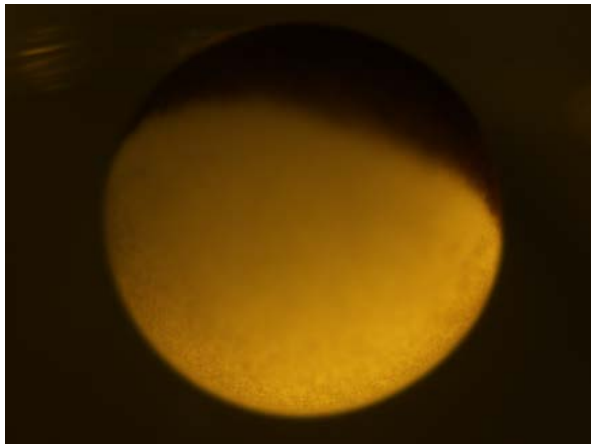
Expression in *Xenopus laevis* oocytes

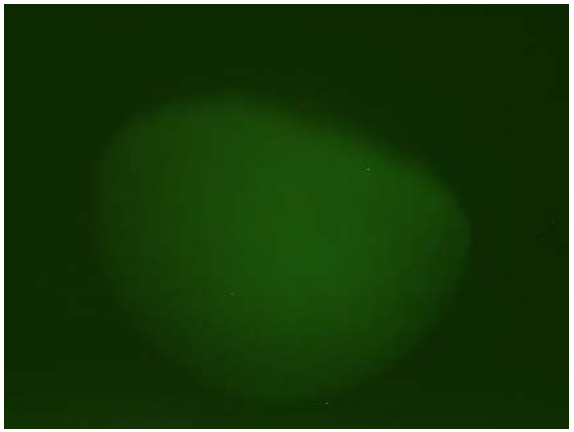


Expression in *Xenopus laevis* oocytes

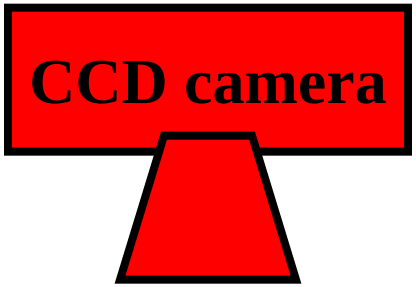


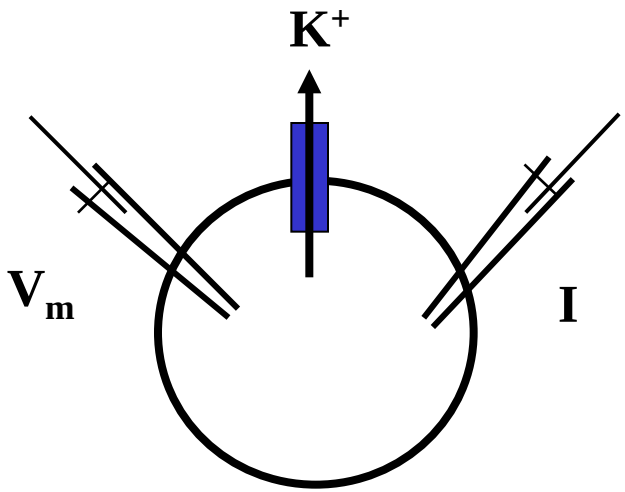


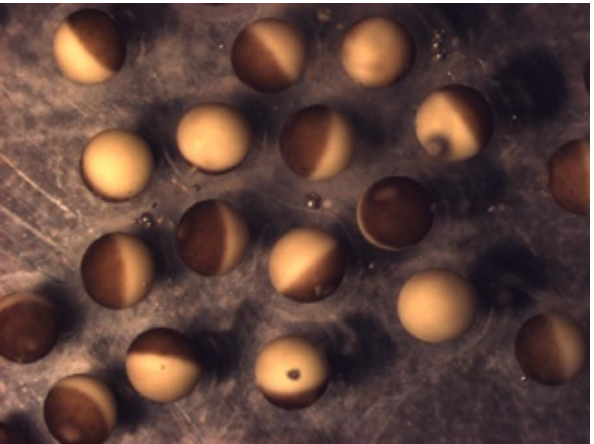




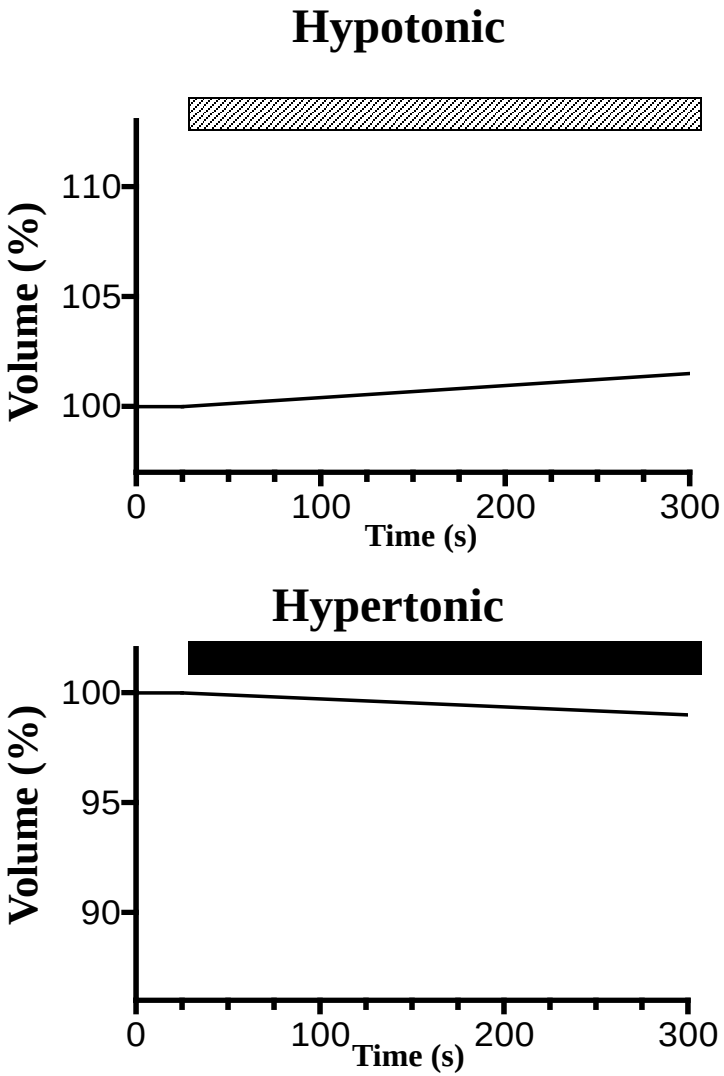
Two-electrode-voltage-clamp setup

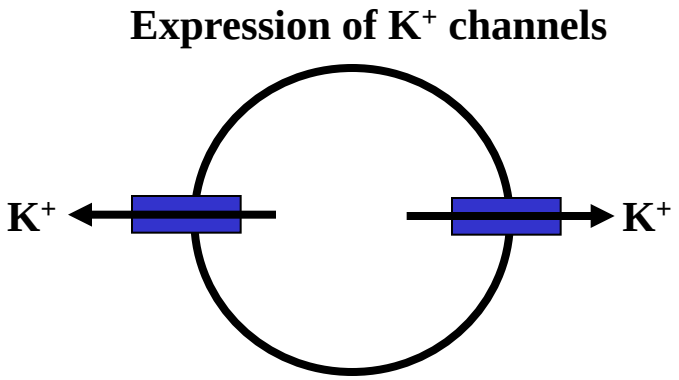




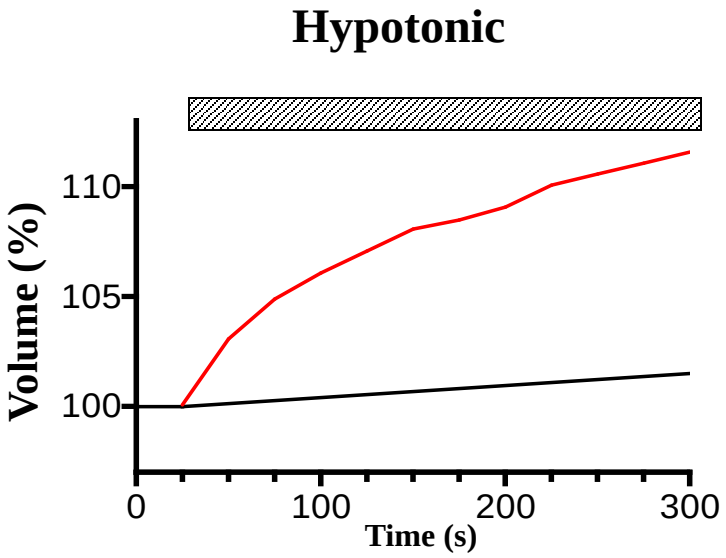


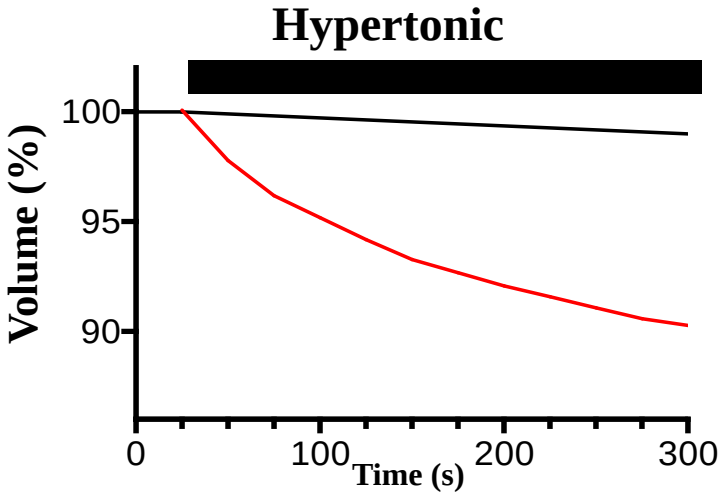
Volume changes of *Xenopus laevis* oocytes.

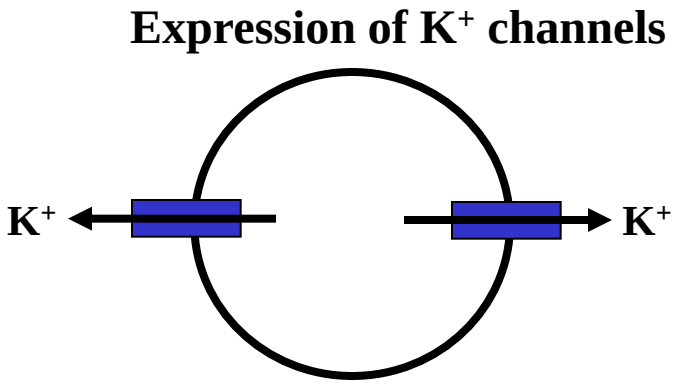


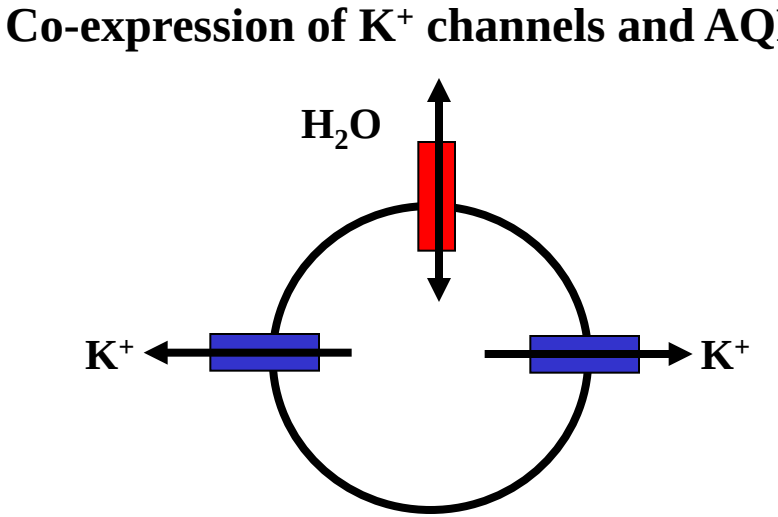


Volume changes of *Xenopus laevis* oocytes.

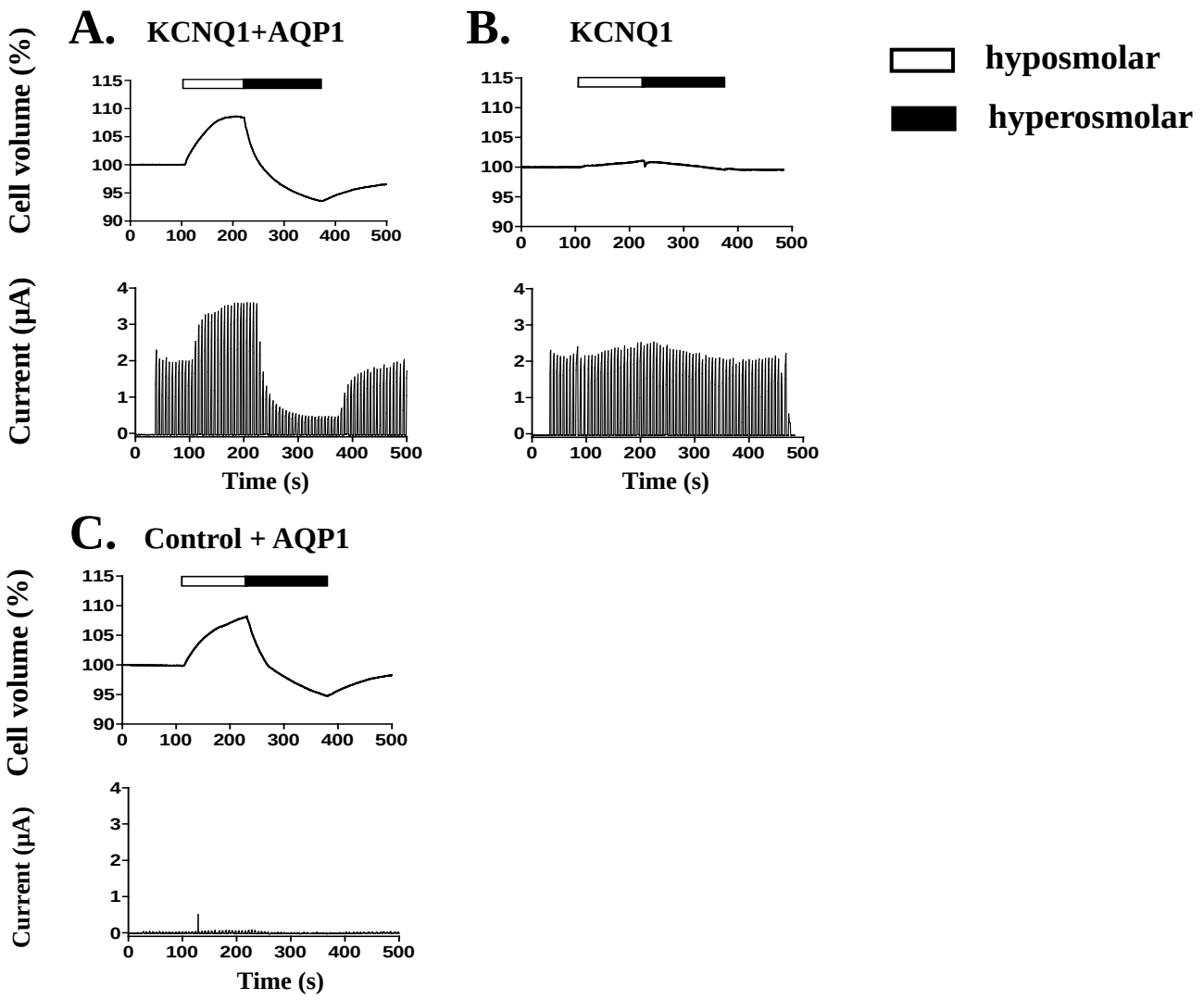




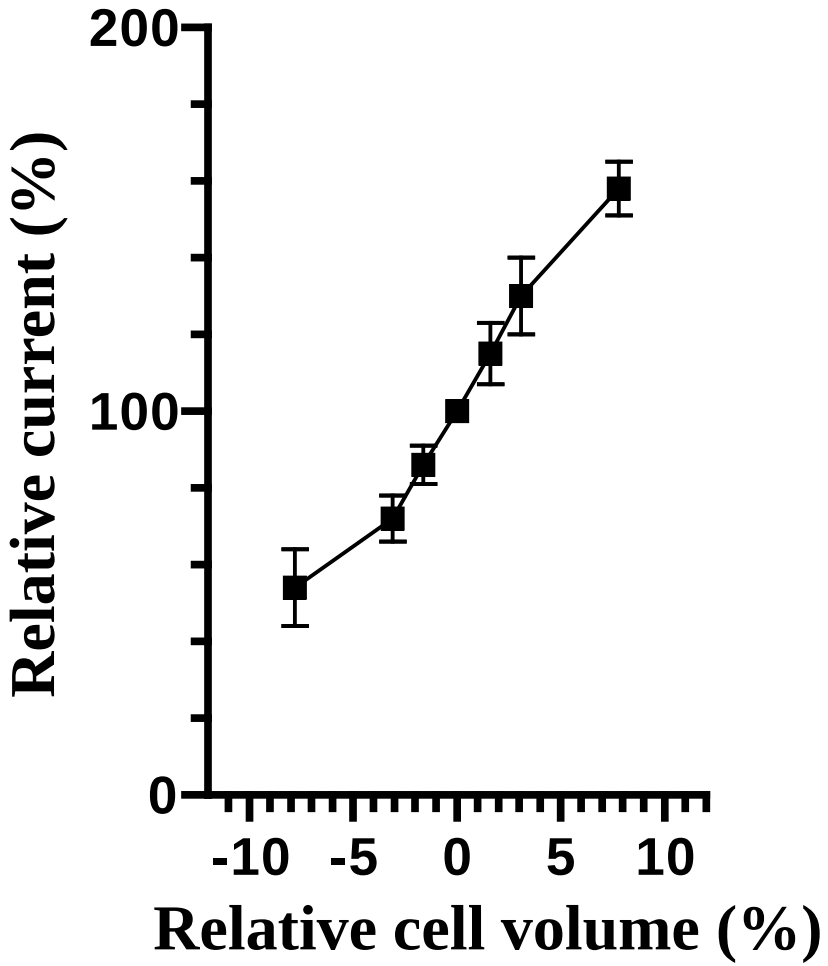


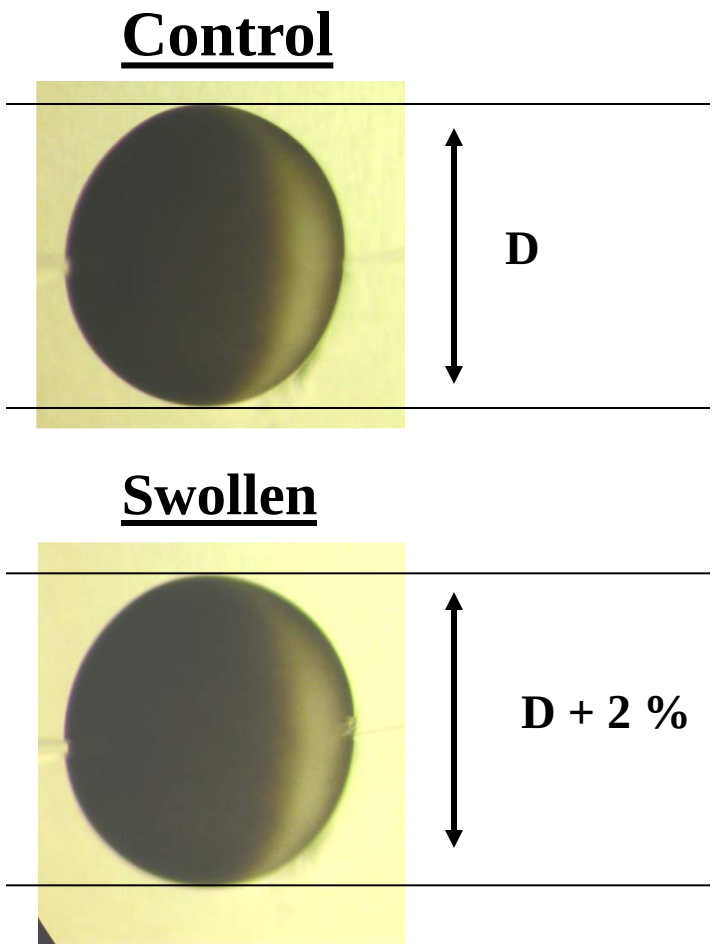


Effect of volume changes on KCNQ1 channels

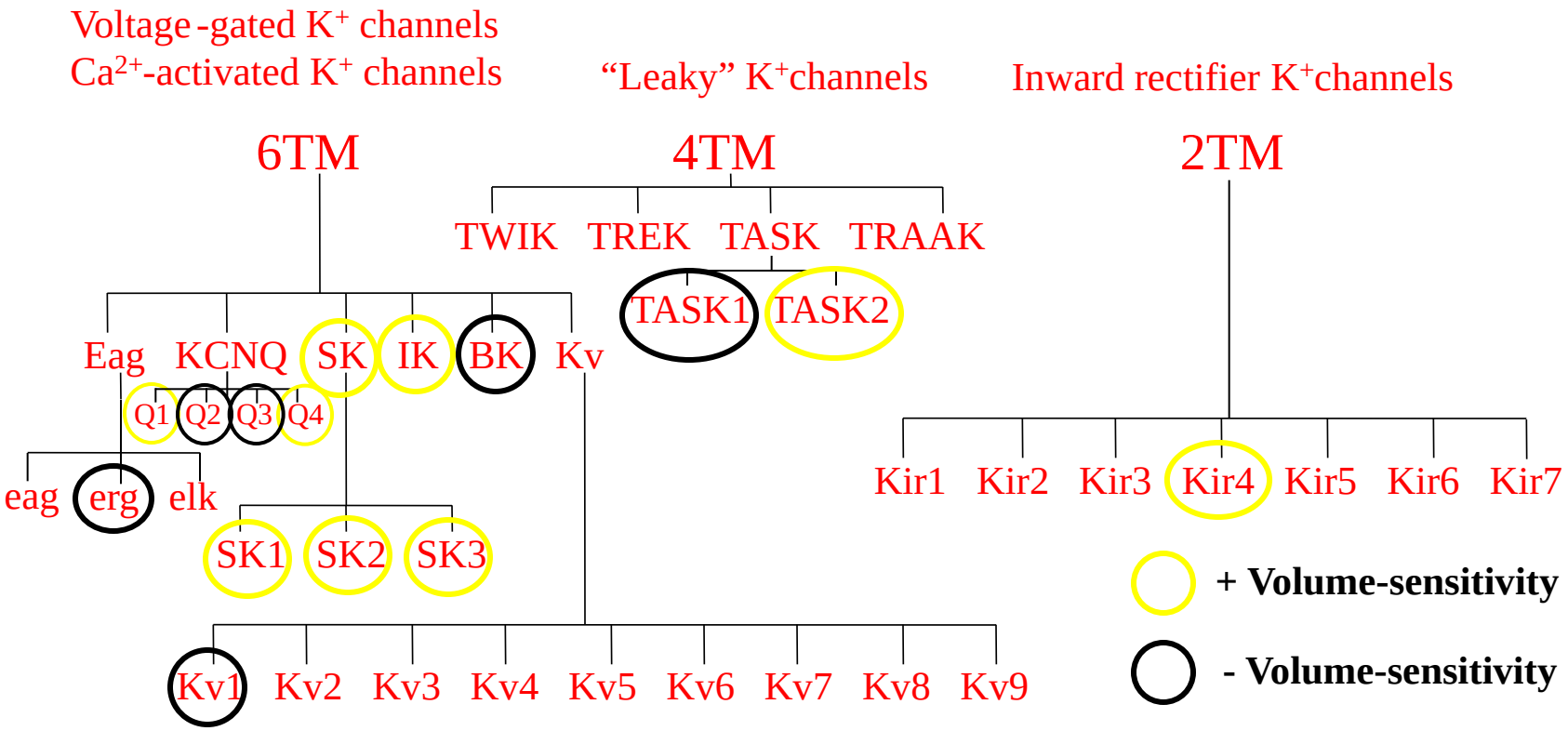


Effect of gradual cell volume changes

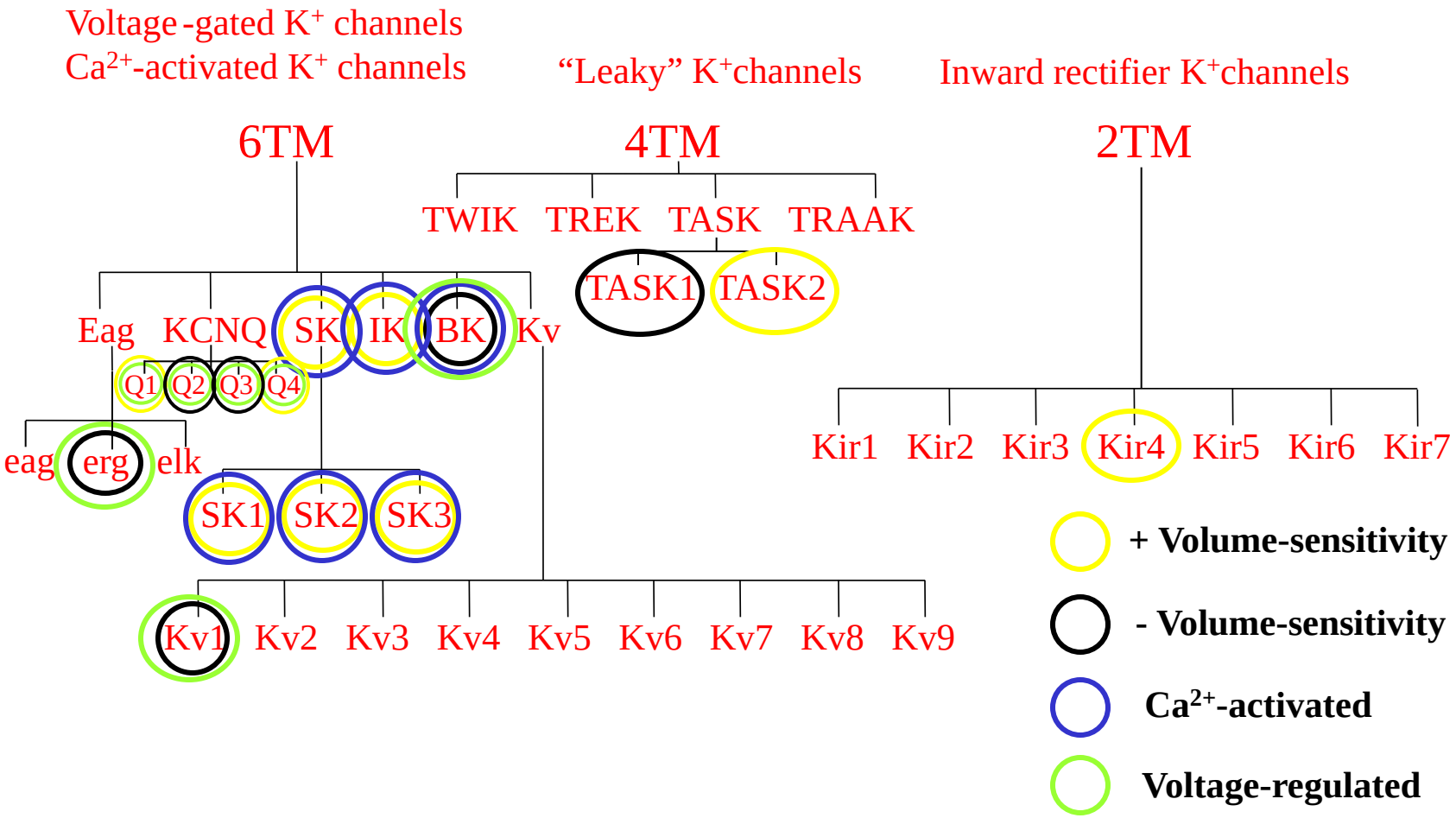




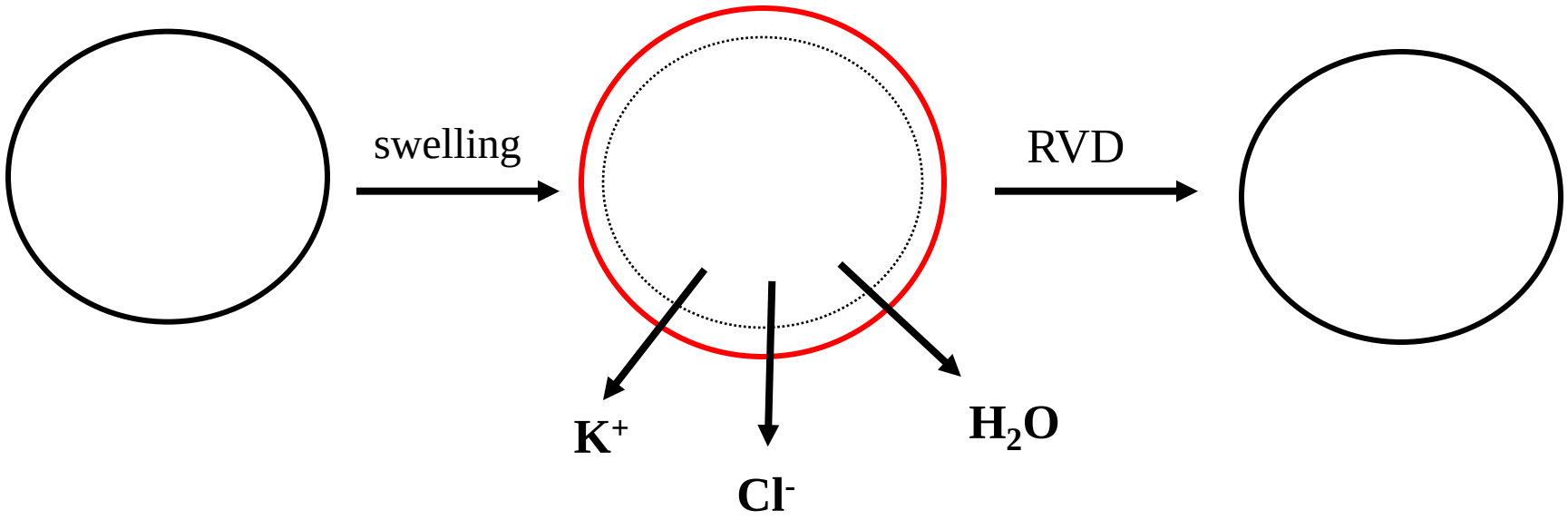
K^+ channels


Voltage-gated K+ channels
Ca2+-activated K+ channels
"Leaky" K+channels
Inward rectifier K+channels
6TM
4TM
2TM
TWIK
TREK
TASK
TRAAK
TASK1
TASK2
Eag
KCNQ
SK
IK
BK
Kv
Q1
Q2
Q3
Q4
eag
erg
elk
SK1
SK2
SK3
Kv1
Kv2
Kv3
Kv4
Kv5
Kv6
Kv7
Kv8
Kv9
Kir1
Kir2
Kir3
Kir4
Kir5
Kir6
Kir7
+ Volume-sensitivity
- Volume-sensitivity

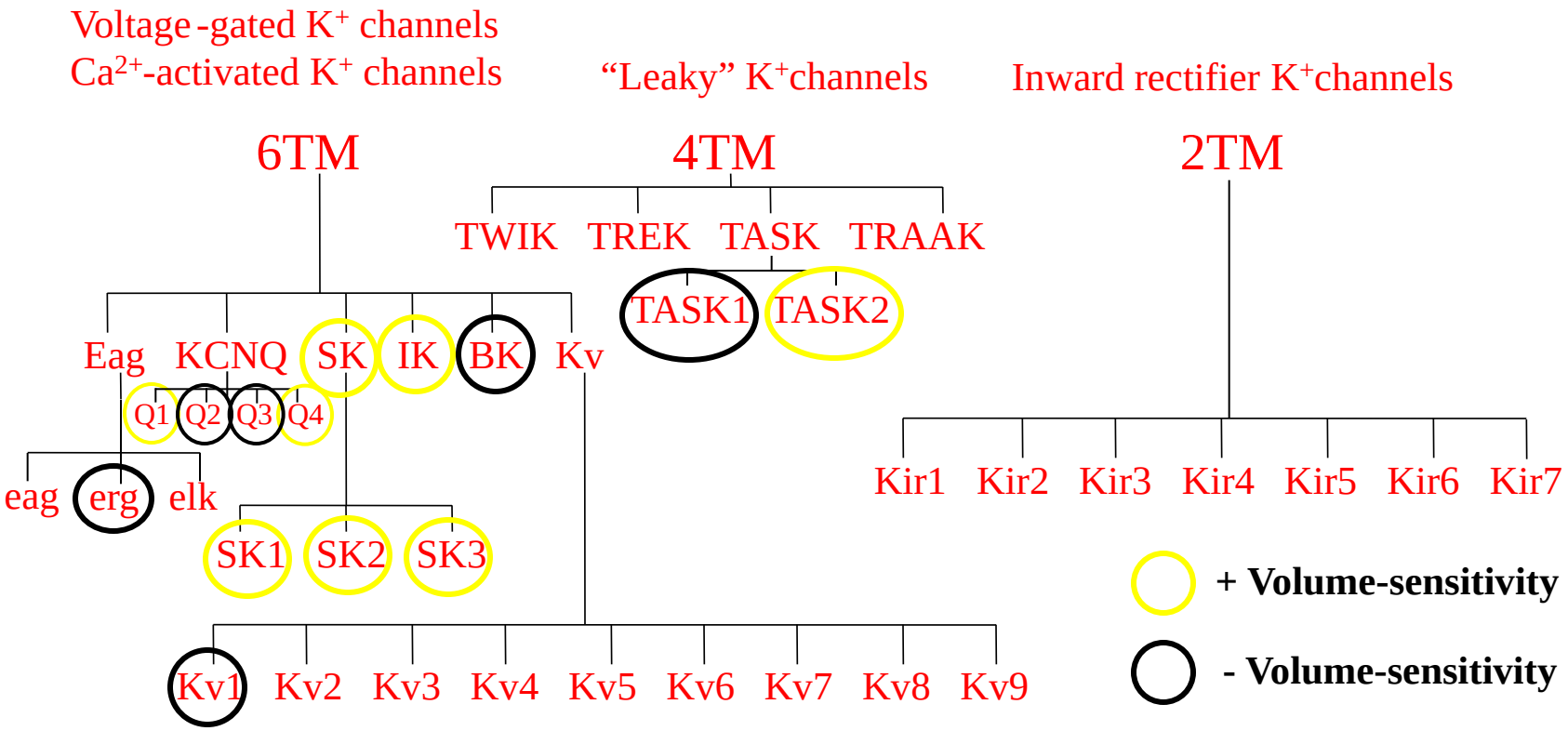
K^+ channels


Voltage-gated K+ channels
Ca2+-activated K+ channels
"Leaky" K+channels
Inward rectifier K+channels
6TM
4TM
2TM
TWIK
TREK
TASK
TRAAK
TASK1
TASK2
Eag
KCNQ
SK
IK
BK
Kv
Q1
Q2
Q3
Q4
eag
erg
elk
SK1
SK2
SK3
Kv1
Kv2
Kv3
Kv4
Kv5
Kv6
Kv7
Kv8
Kv9
Kir1
Kir2
Kir3
Kir4
Kir5
Kir6
Kir7
+ Volume-sensitivity
- Volume-sensitivity
Ca2+-activated
Voltage-regulated

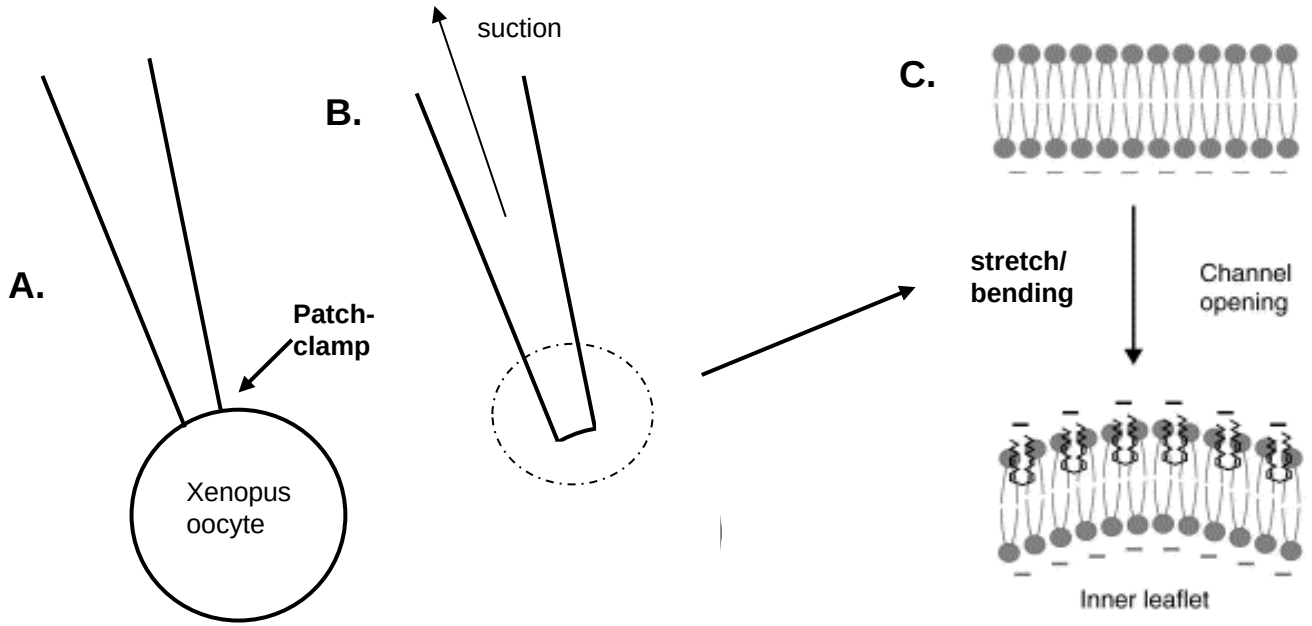
What about stretch ?



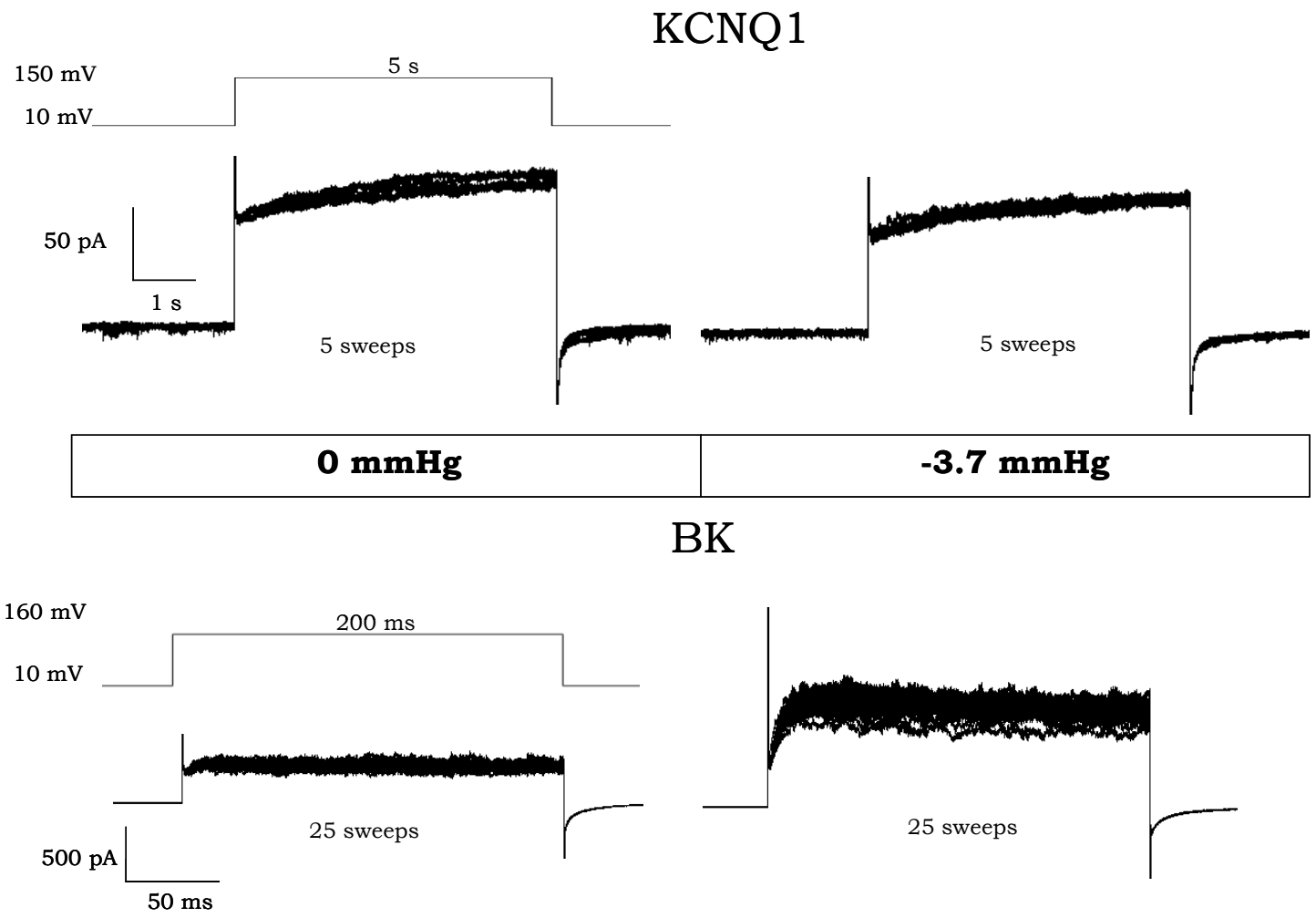
K^+ channels


Voltage-gated K+ channels
Ca2+-activated K+ channels
“Leaky” K+channels
Inward rectifier K+channels
6TM
4TM
2TM
TWIK
TREK
TASK
TRAAK
TASK1
TASK2
Eag
KCNQ
SK
IK
BK
Kv
Q1
Q2
Q3
Q4
eag
erg
elk
SK1
SK2
SK3
Kv1
Kv2
Kv3
Kv4
Kv5
Kv6
Kv7
Kv8
Kv9
Kir1
Kir2
Kir3
Kir4
Kir5
Kir6
Kir7
+ Volume-sensitivity
- Volume-sensitivity

Stretch in a patch-pipette

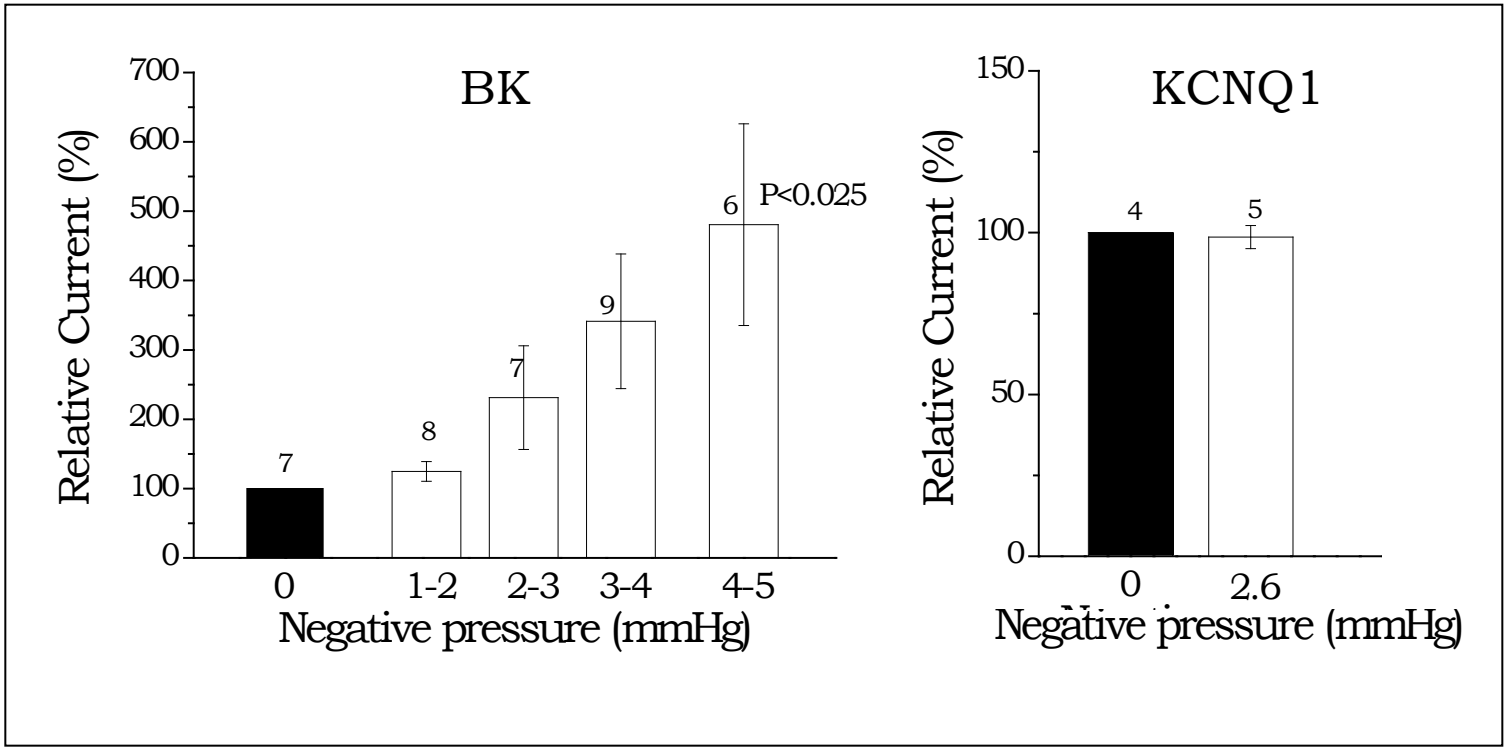


Stretch: BK vs. KCNQ1



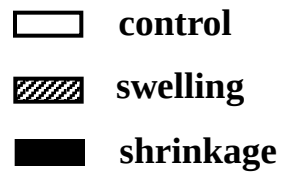
Stretch: BK vs. KCNQ1

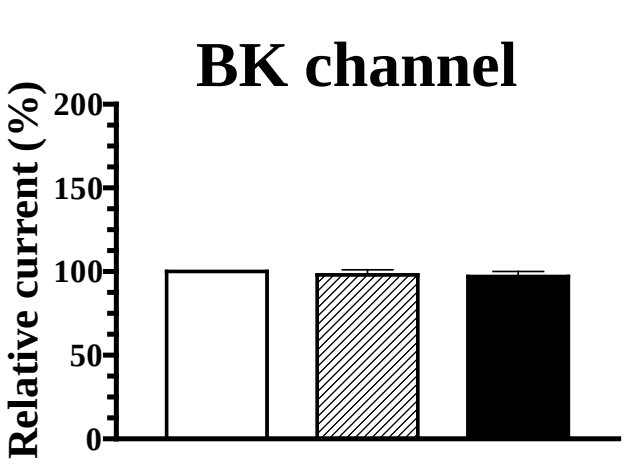
BK is stretch activated, KCNQ1 is not

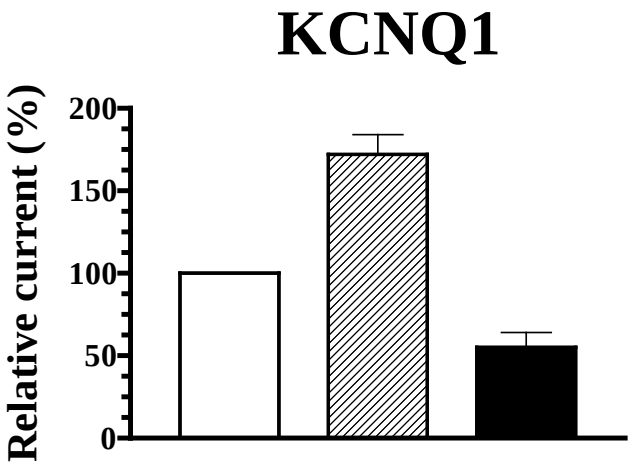


Volume: BK vs. KCNQ1

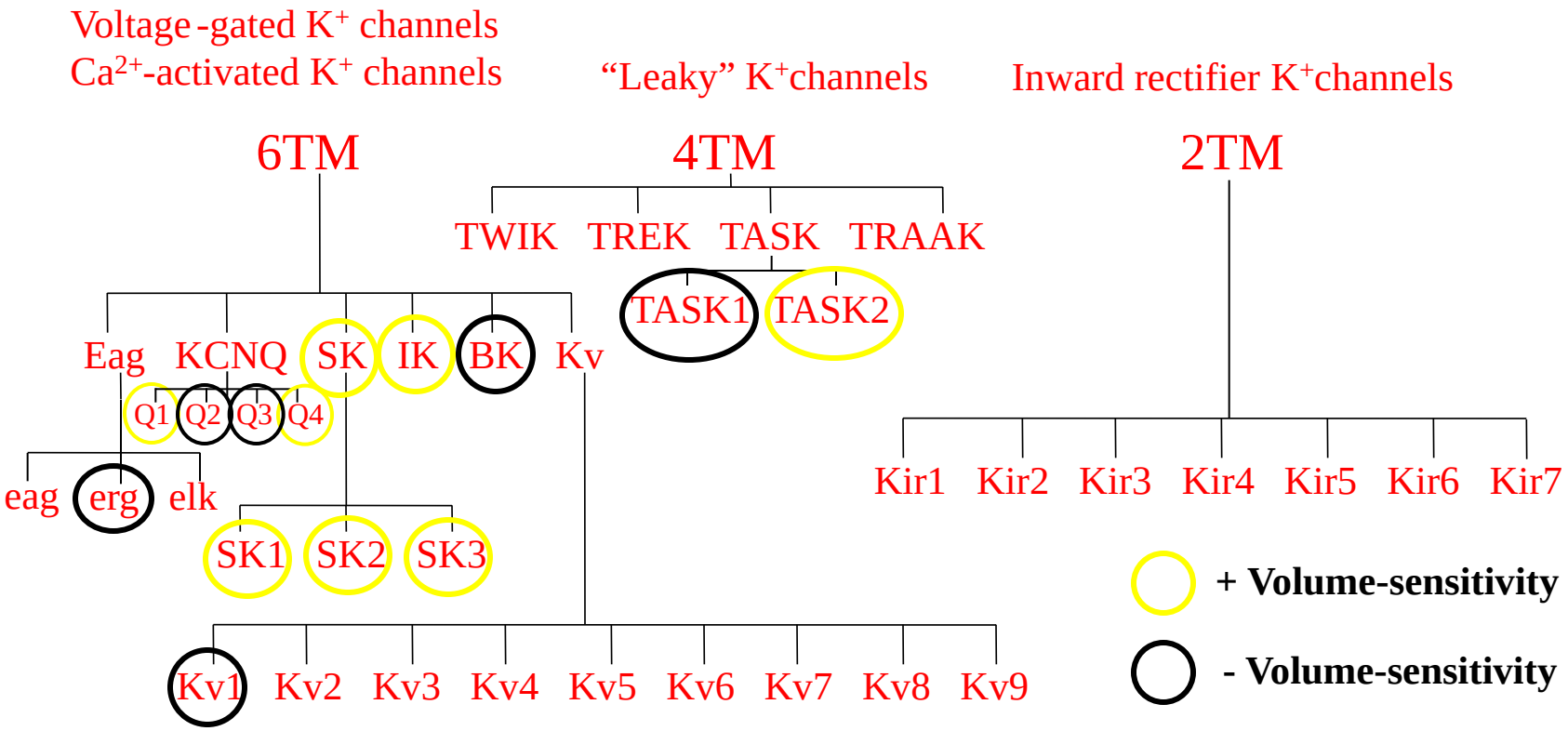
KCNQ1 is volume activated, BK is not





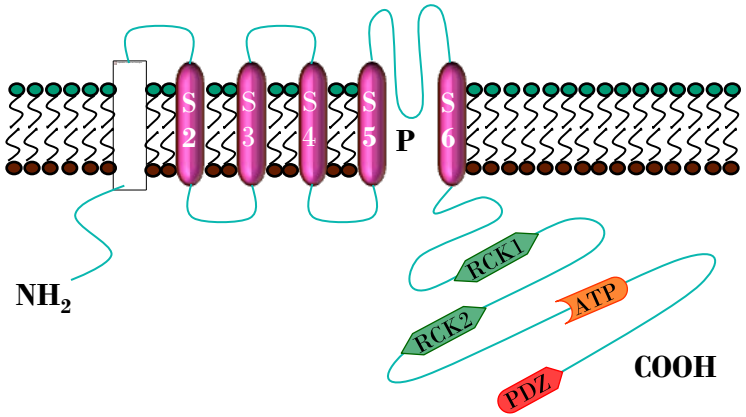


K^+ channels

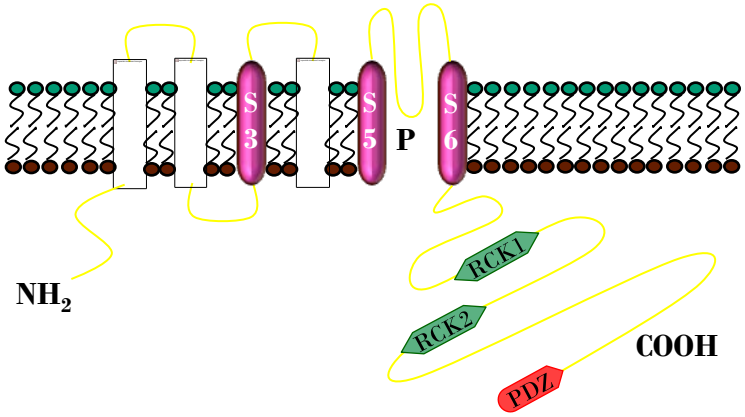

Voltage-gated K+ channels
Ca2+-activated K+ channels
“Leaky” K+channels
Inward rectifier K+channels
6TM
4TM
2TM
TWIK
TREK
TASK
TRAAK
TASK1
TASK2
Eag
KCNQ
SK
IK
BK
Kv
Q1
Q2
Q3
Q4
eag
erg
elk
SK1
SK2
SK3
Kv1
Kv2
Kv3
Kv4
Kv5
Kv6
Kv7
Kv8
Kv9
Kir1
Kir2
Kir3
Kir4
Kir5
Kir6
Kir7
+ Volume-sensitivity
- Volume-sensitivity

Slick (slo2.1) and slack (slo2.2)

Slick

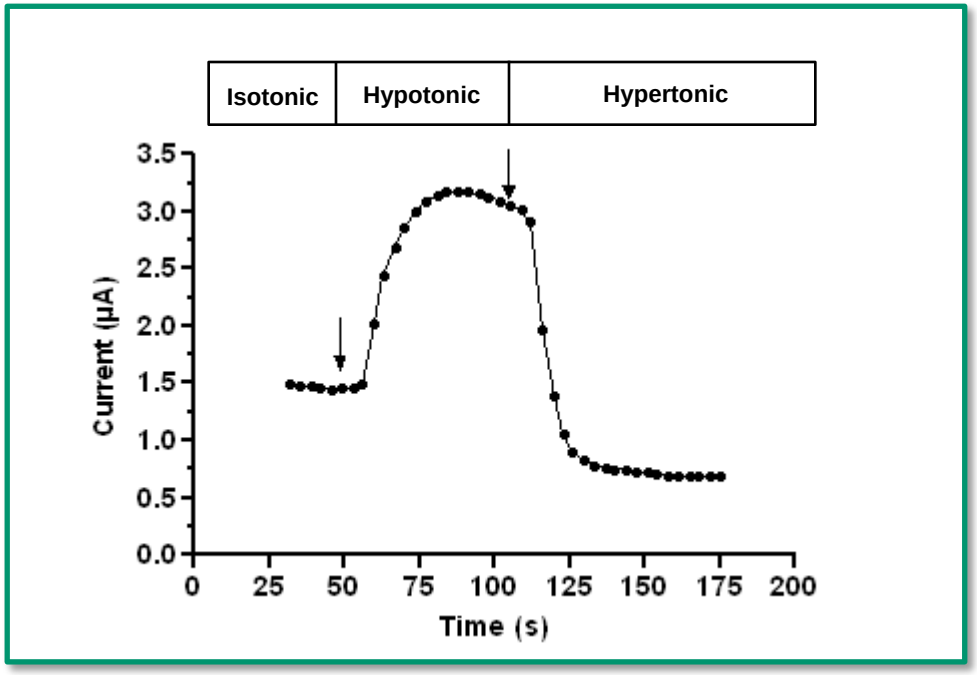


Slack

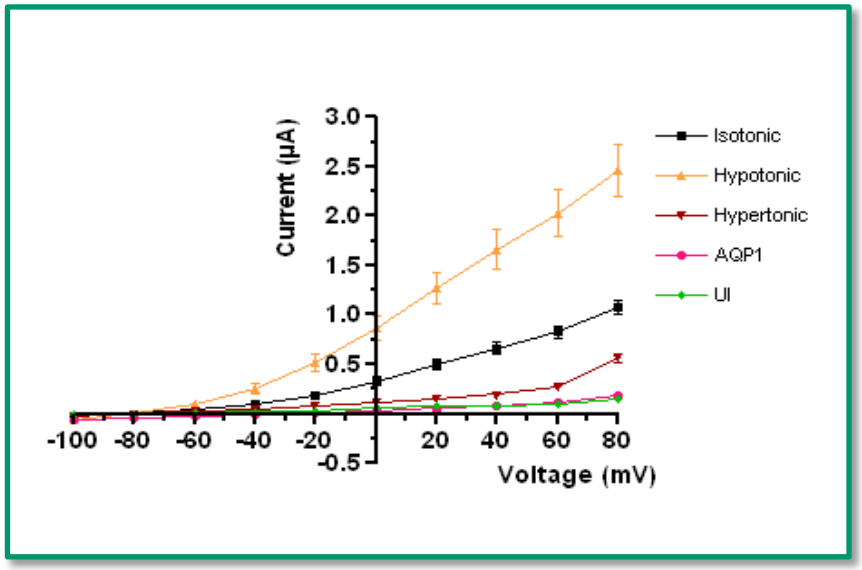


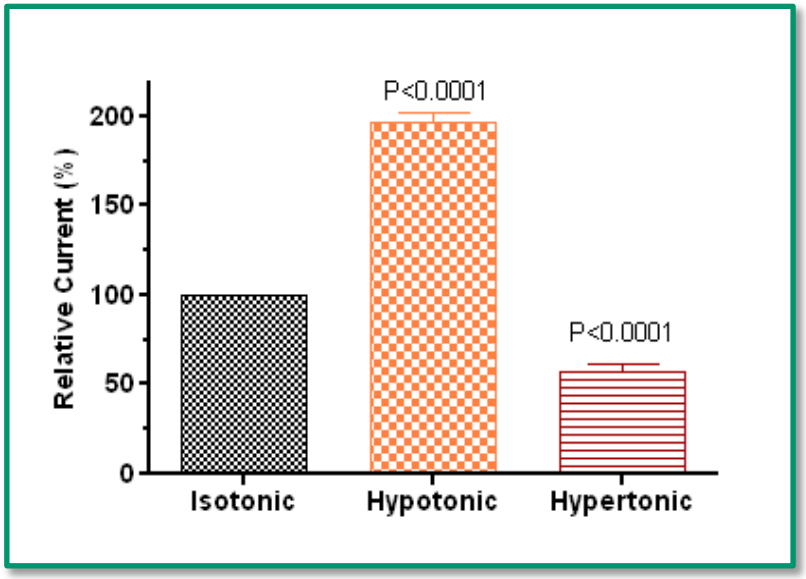
- High conductance K channels
- Activation: Na and Cl (slick and slack)
- Inhibition: ATP (slick)
- Expression: CNS, heart (?), other (?)

Slick is sensitive to cell volume

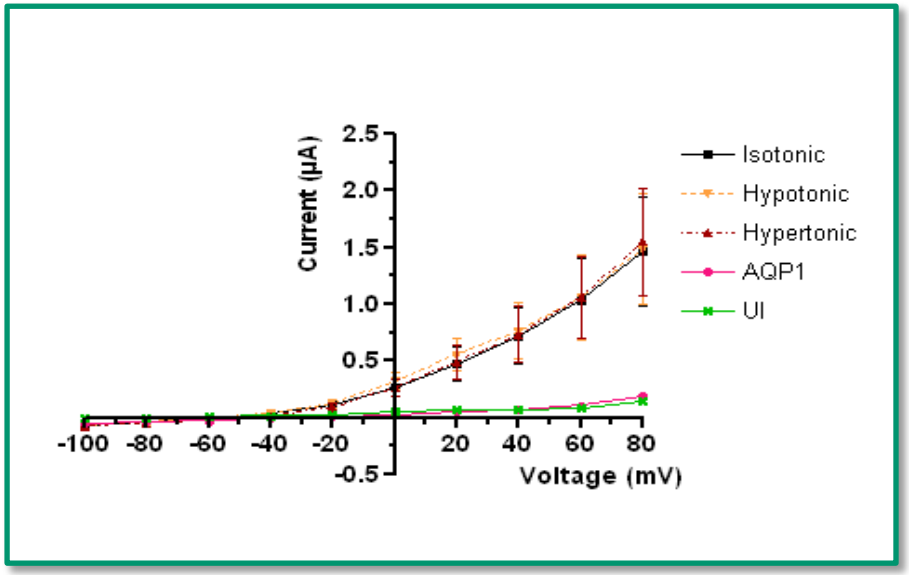


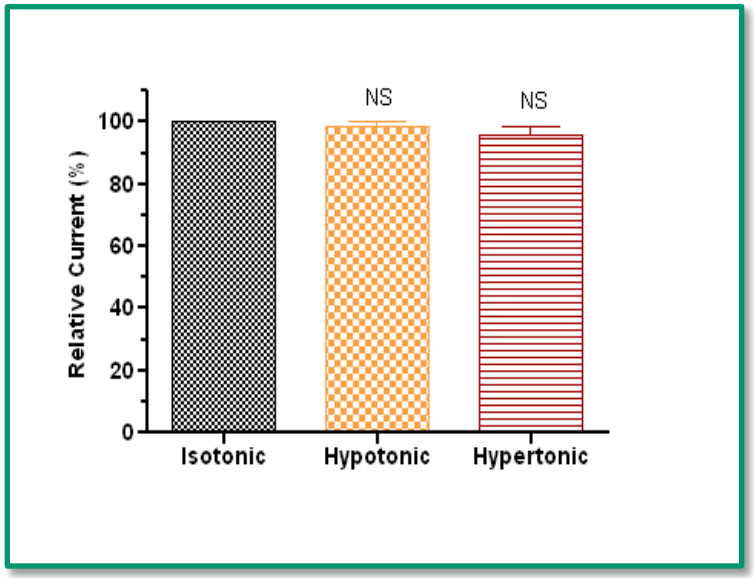
Slick is sensitive to cell volume



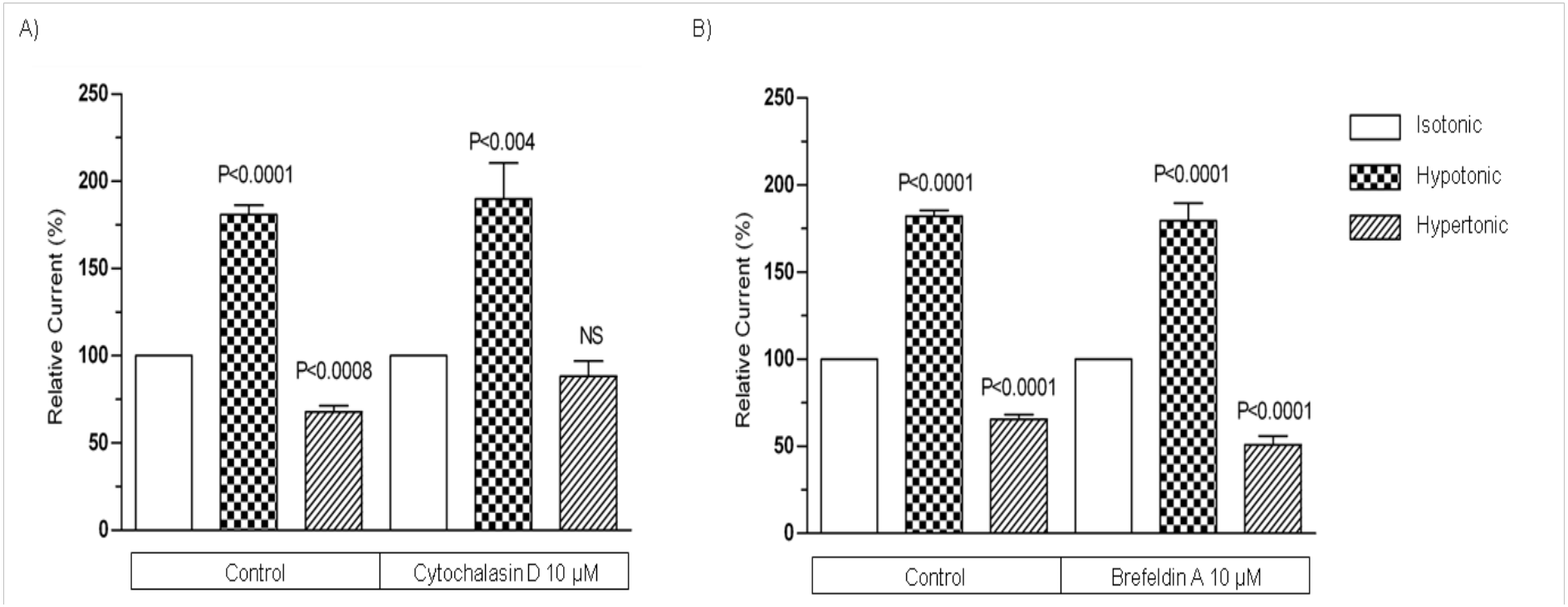


Slack is insensitive to cell volume

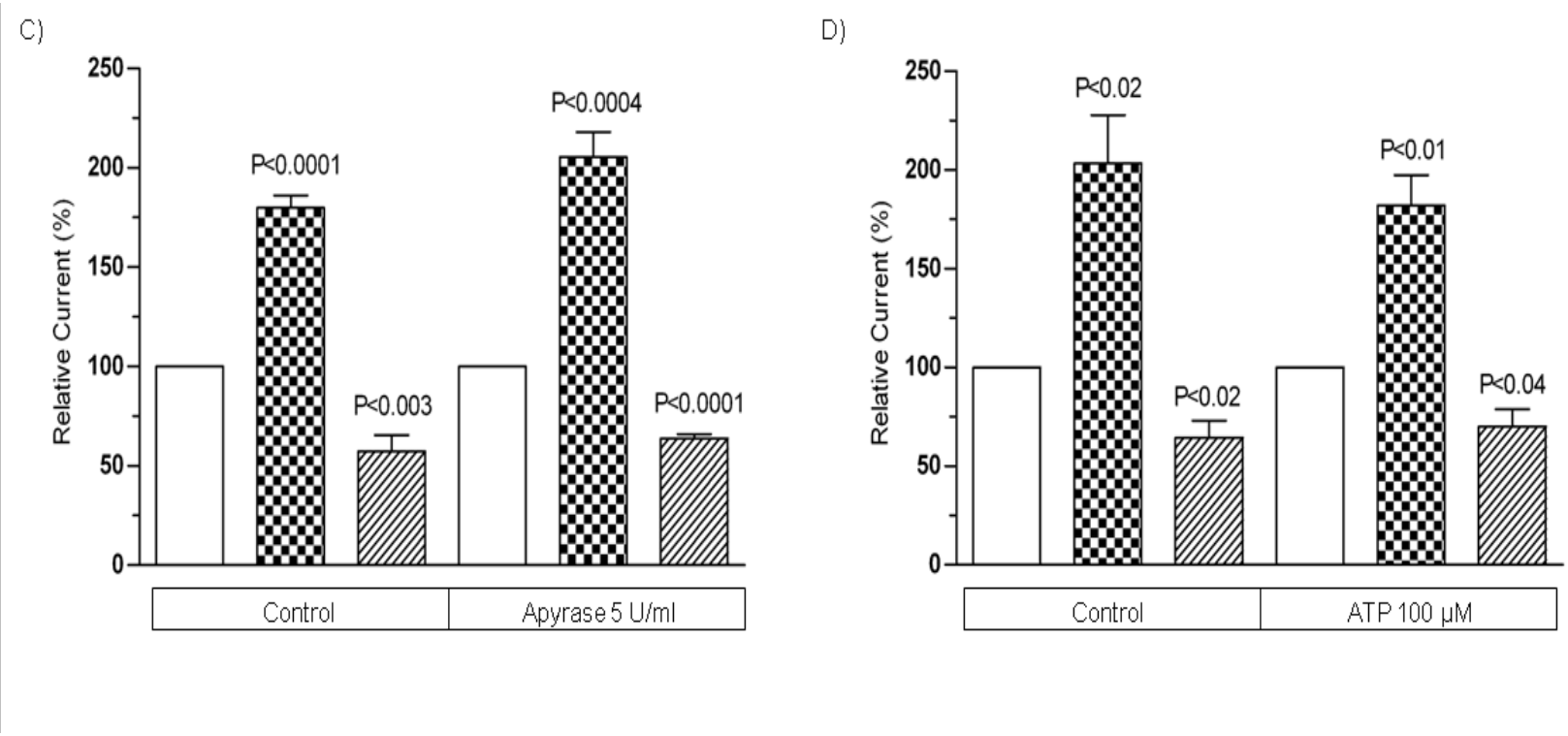




Mechanism ?


A)
Relative Current (%)
250
200
150
100
50
0
P<0.0001
P<0.0008
P<0.004
NS
Control
Cytochalasin D 10 µM
B)
Relative Current (%)
250
200
150
100
50
0
P<0.0001
P<0.0001
P<0.0001
P<0.0001
Isotonic
Hypotonic
Hypertonic
Control
Brefeldin A 10 µM

Extracellular ATP?



Is PIP2 the answer ?

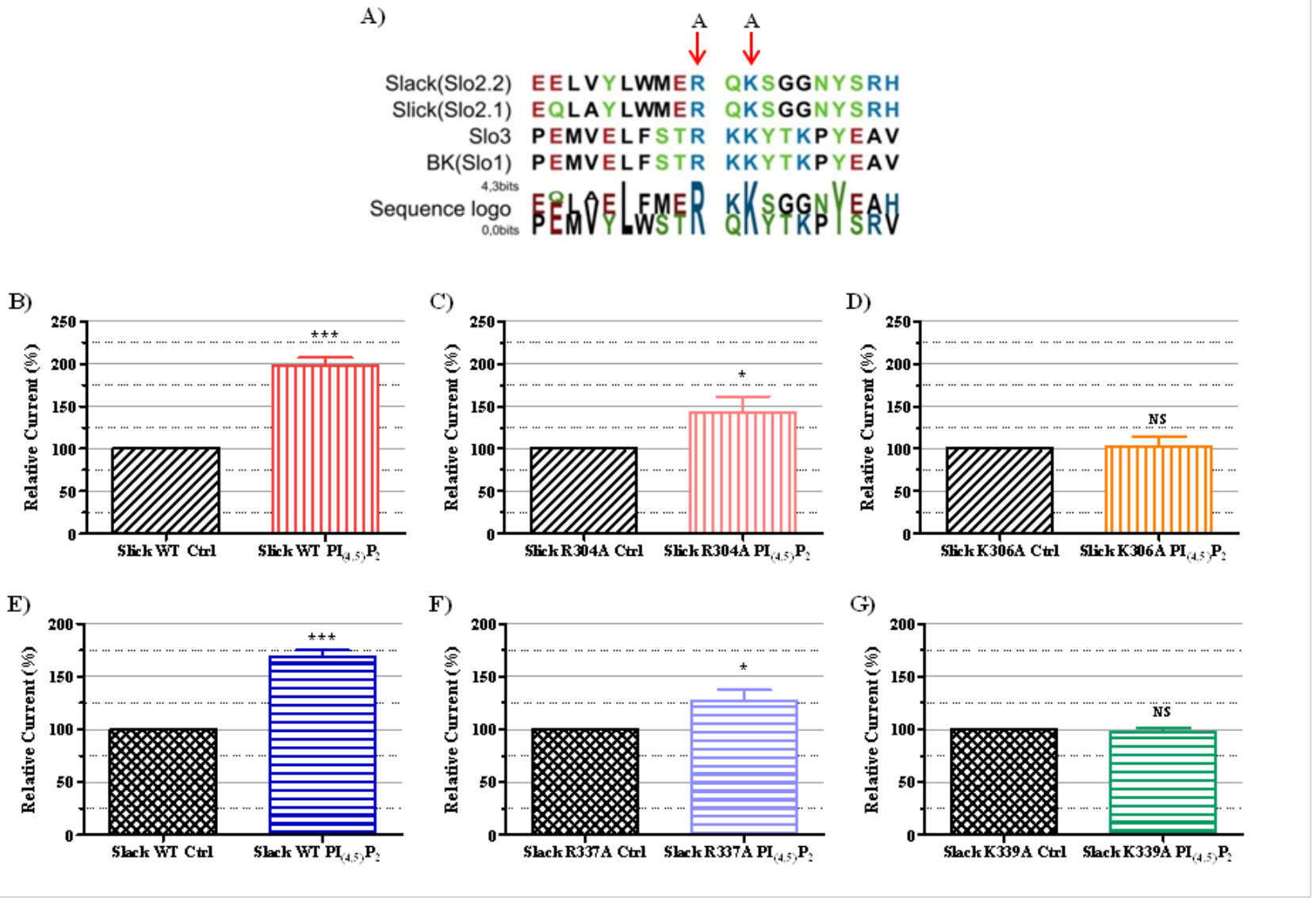
J Physiol 588.18 (2010) pp 3471–3483

KCNE1–KCNQ1 osmoregulation by interaction of phosphatidylinositol-4,5-bisphosphate with Mg^{2+} and polyamines

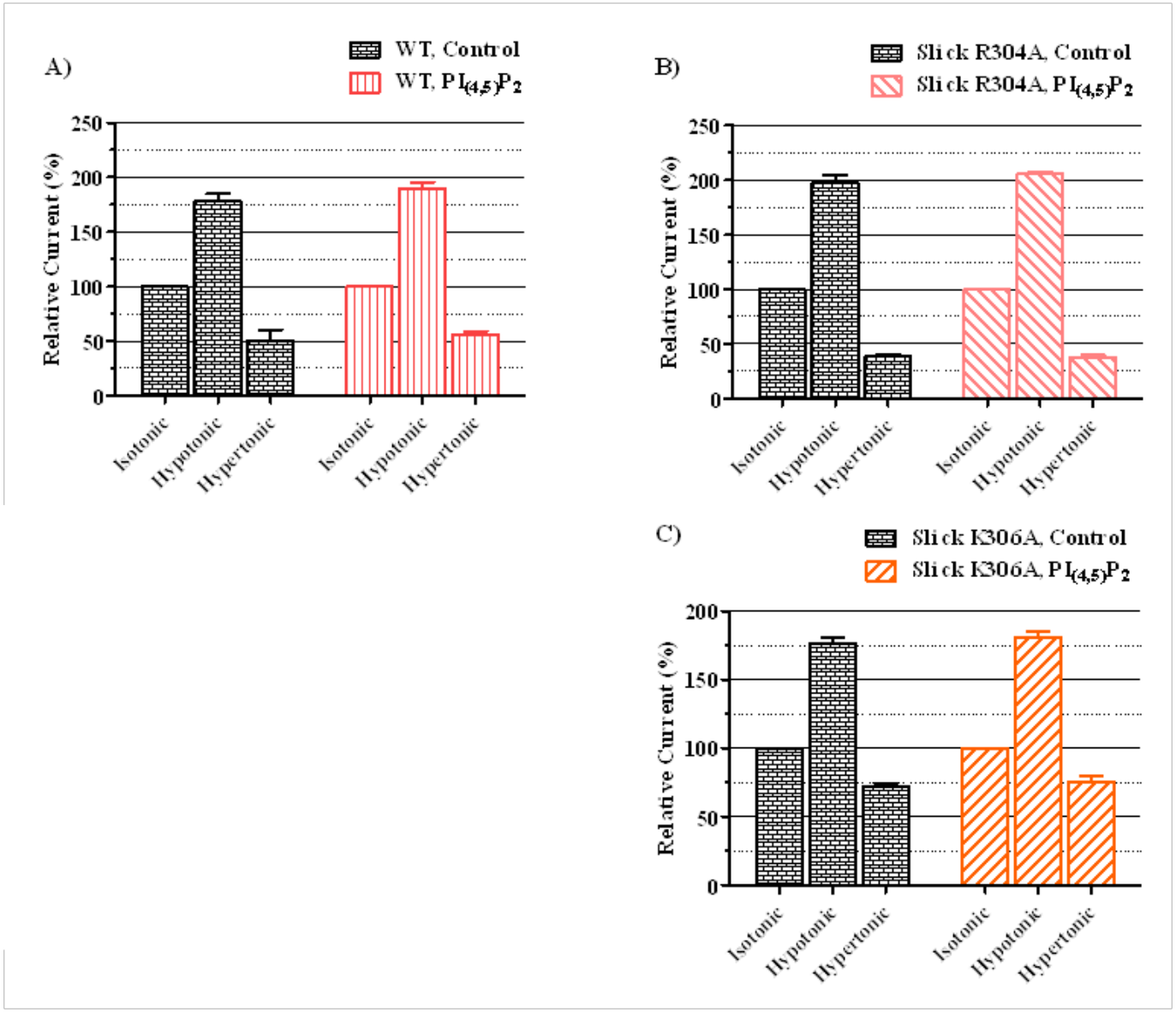
Julien Piron[1,2,3], Frank S. Choveau[1,2,3], Mohammed Yassine Amarouch[1,2,3], Nicolas Rodriguez[1,2,3], Flavien Charpentier[1,2,3,4], Jean Mérot[1,2,3], Isabelle Baró[1,2,3] and Gildas Loussouarn[1,2,3]

[1] *INSERM, UMR 915, l'institut du thorax, Nantes, France*
[2] *CNRS, ERL 3147, Nantes, France*
[3] *Université de Nantes, UFR de Médecine, Nantes, France*
[4] *CHU Nantes, l'institut du thorax, Nantes, France*

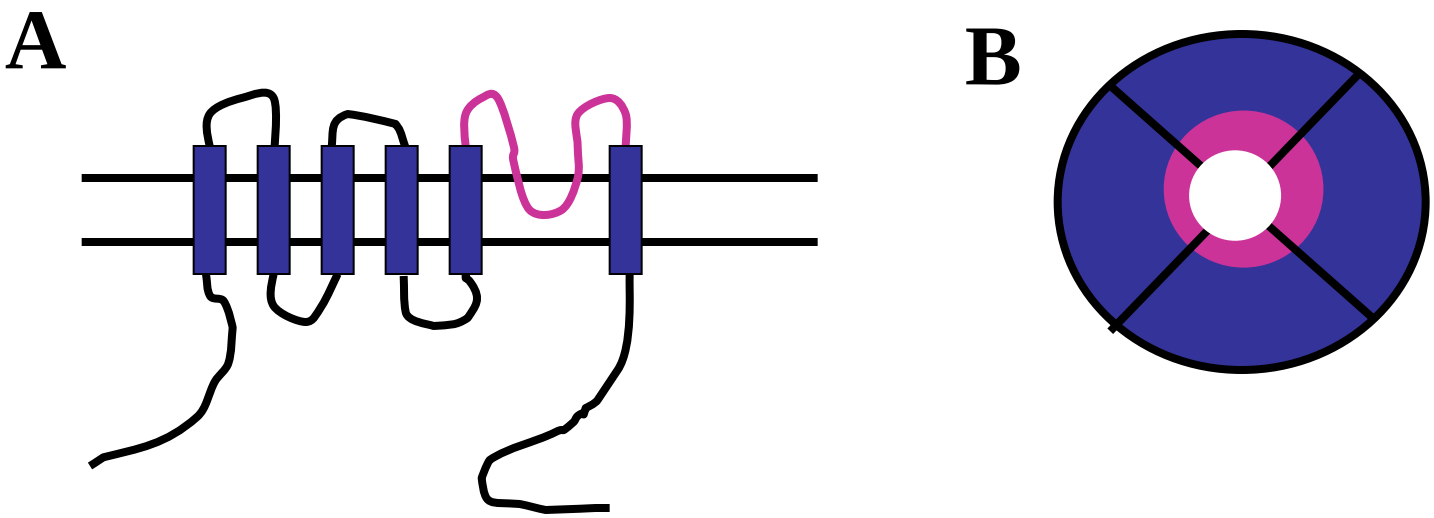
Slick and Slack are sensitive to PIP2



PIP2 does not affect sensitivity to cell volume

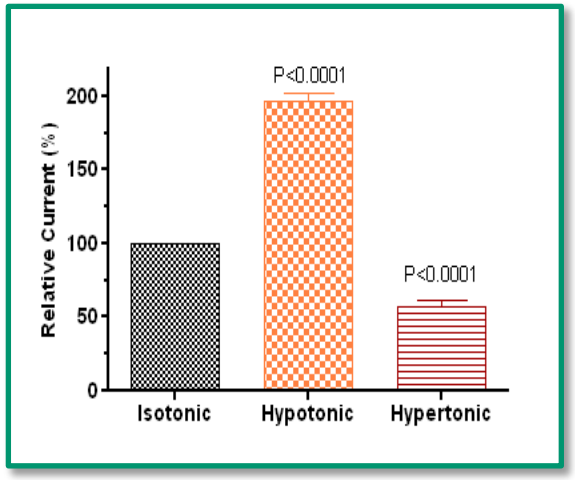


Slick/Slack channels

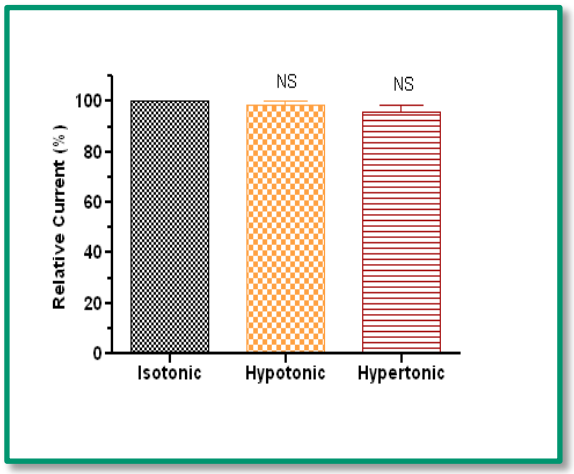


Heteromers show graded sensitivity

Slick

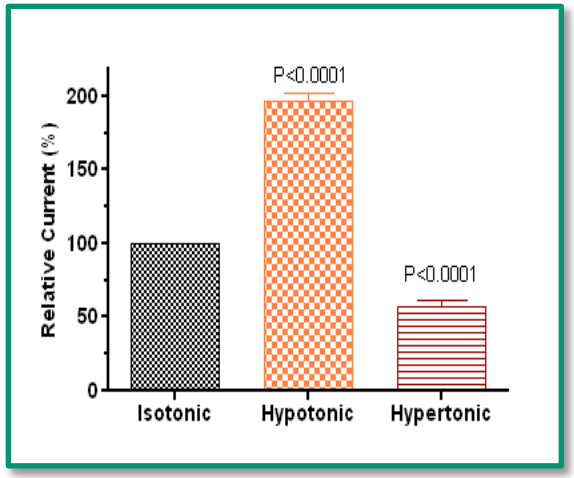


Slack

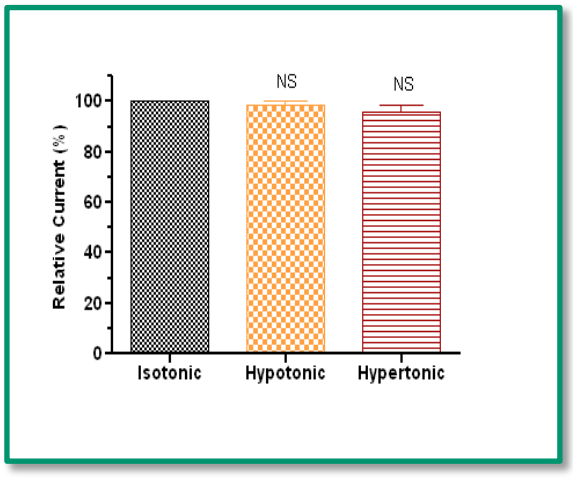


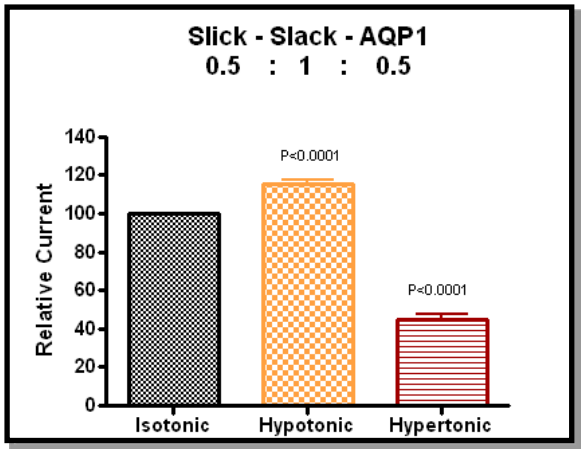
Heteromers show graded sensitivity

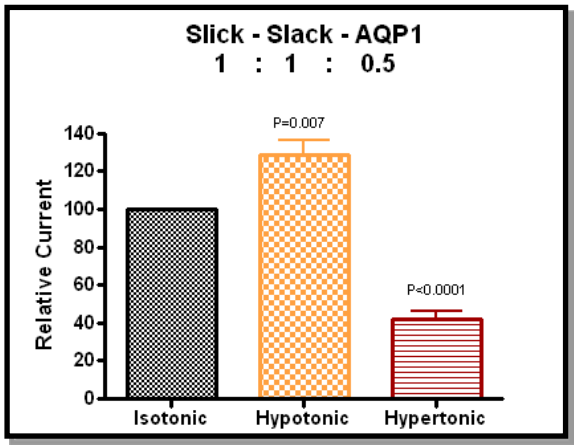
Slick

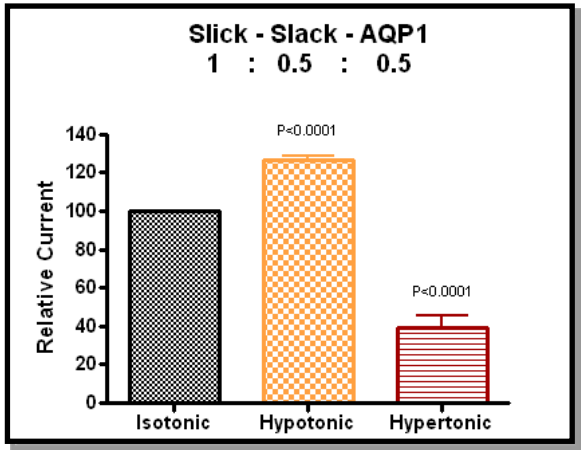


Slack

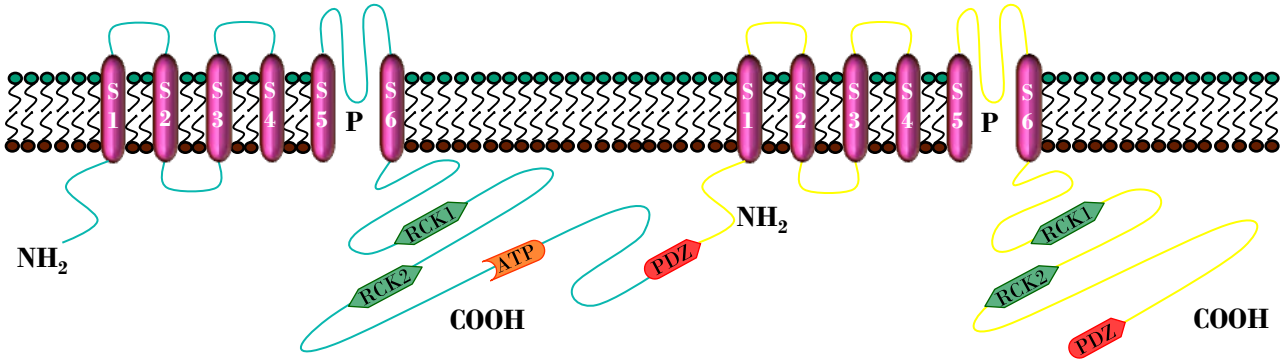




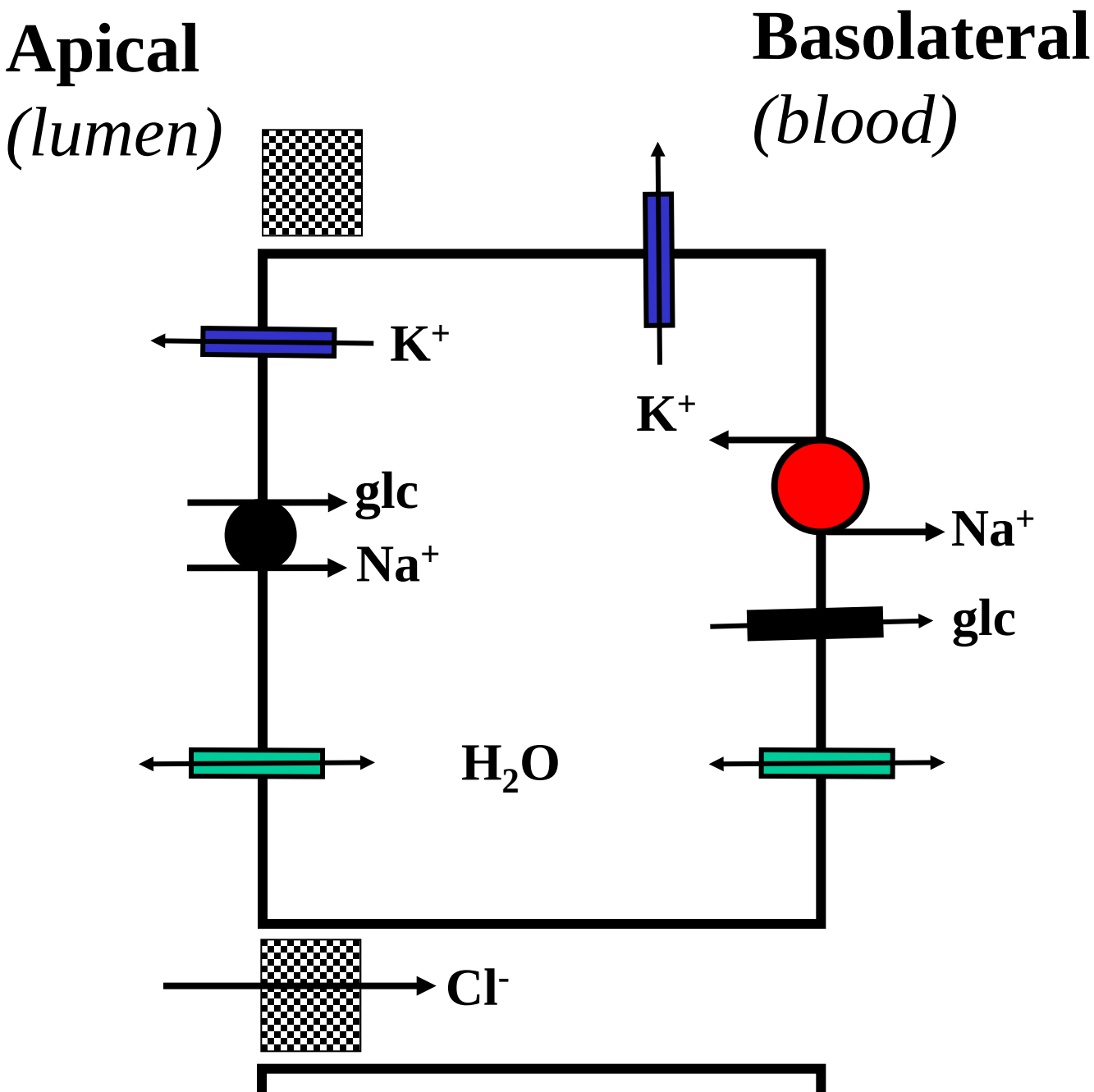




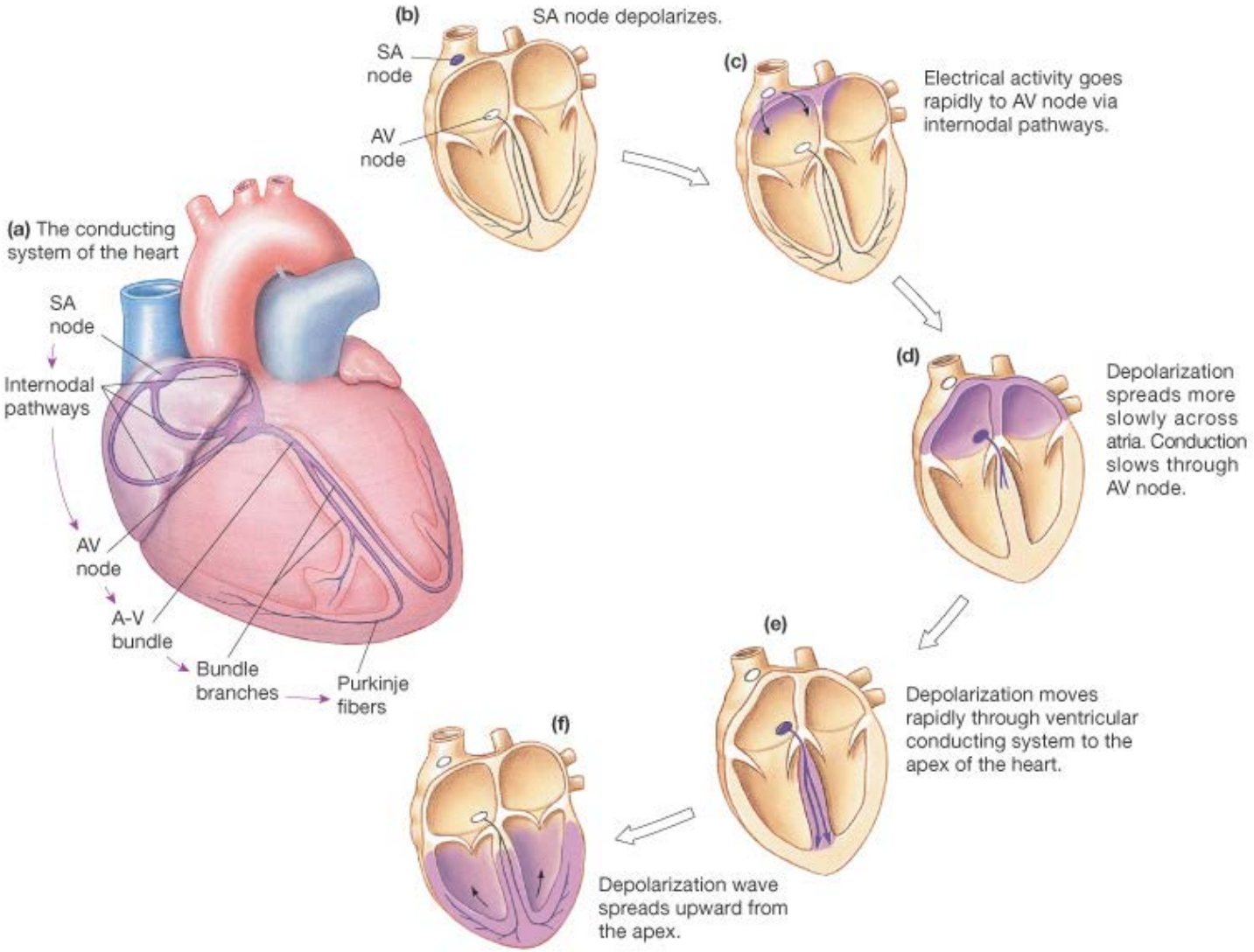
Slick and slack are well behaved



Absorptive cell:



The heart

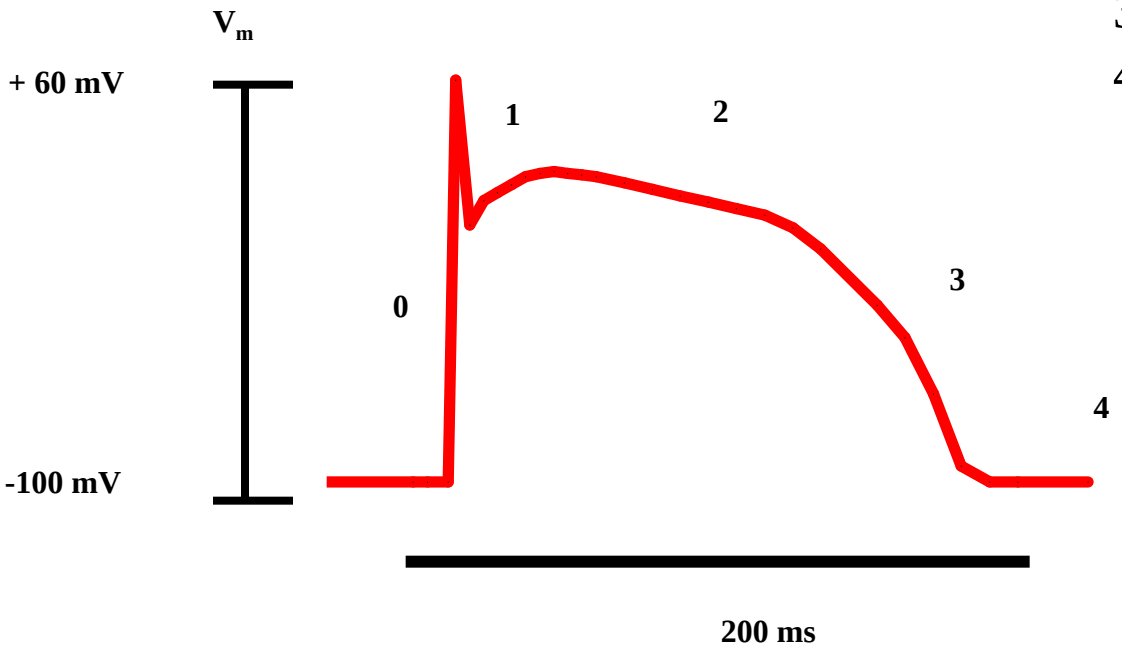

(a) The conducting system of the heart
SA node
Internodal pathways
AV node
A-V bundle
Bundle branches
Purkinje fibers
(b)
SA node depolarizes.
SA node
AV node
(c)
Electrical activity goes rapidly to AV node via internodal pathways.
(d)
Depolarization spreads more slowly across atria. Conduction slows through AV node.
(e)
Depolarization moves rapidly through ventricular conducting system to the apex of the heart.
(f)
Depolarization wave spreads upward from the apex.

Cardiac actionspotential

Depolarisation

0: Na^+-channel, SCN5A

2: Ca^{2+}-channel, L-type



Repolarisation

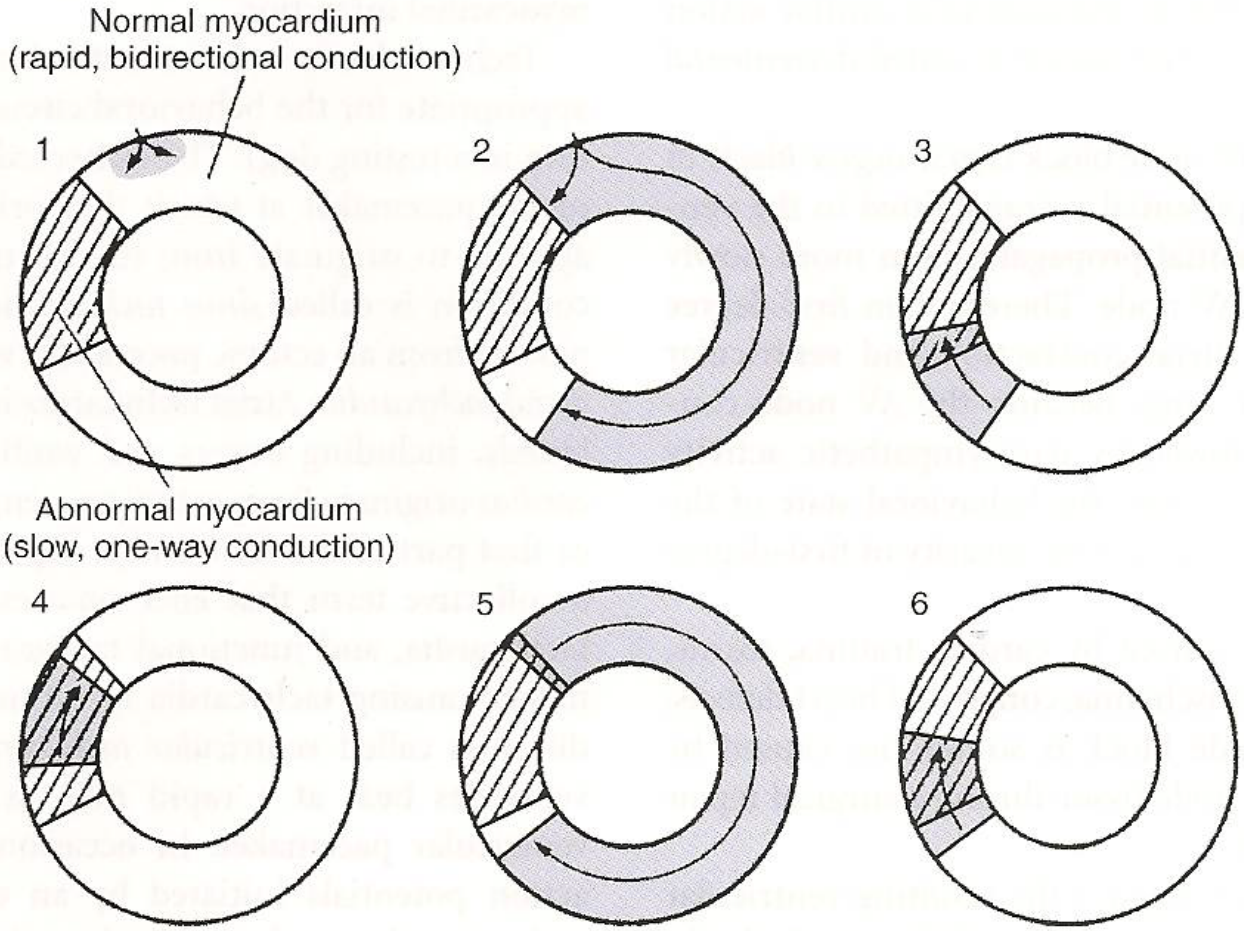
1: K_v4.2, K_v4.3, K_v1.4

2: HERG, KCNQ, K_v1.5

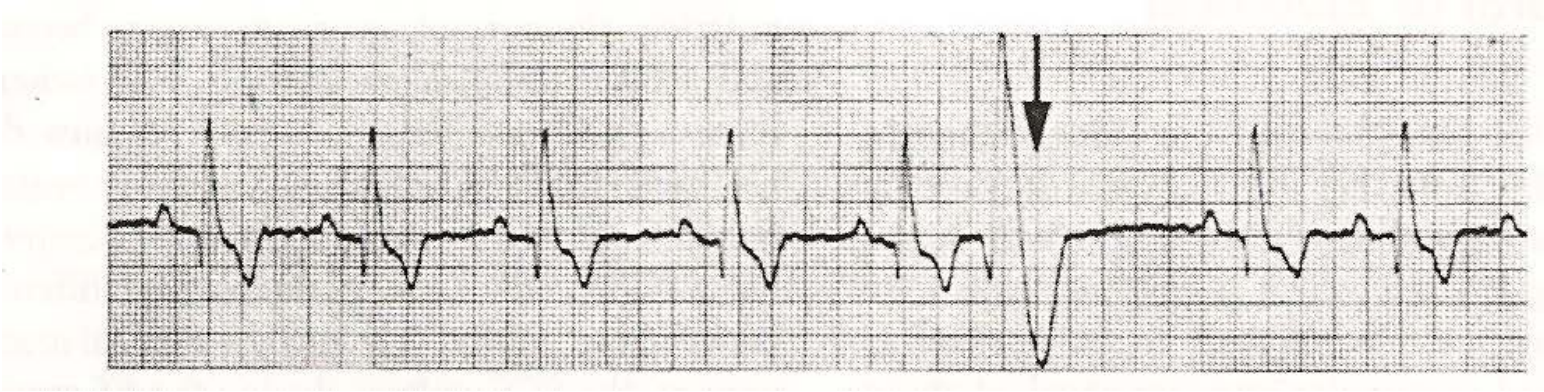
3: HERG, KCNQ, Kir6.2

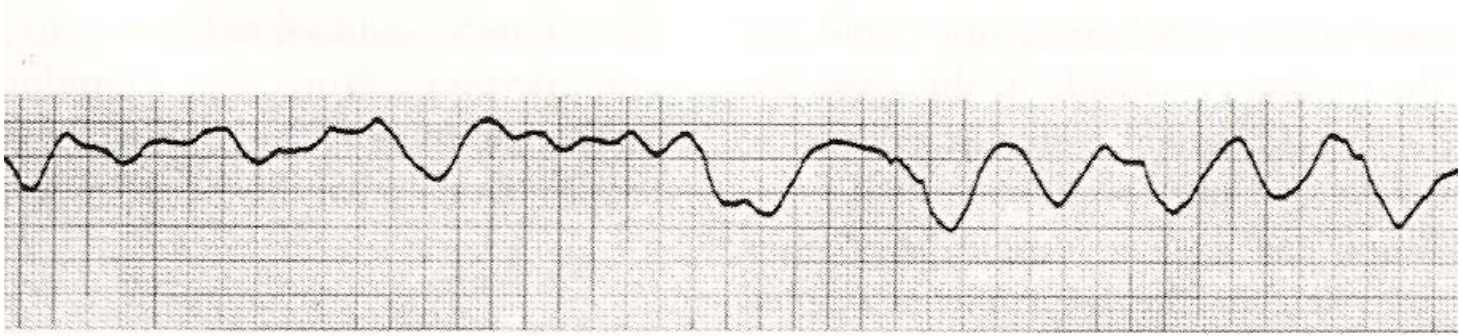
4: ”Leak”: 4TM K^+ channels

Heart

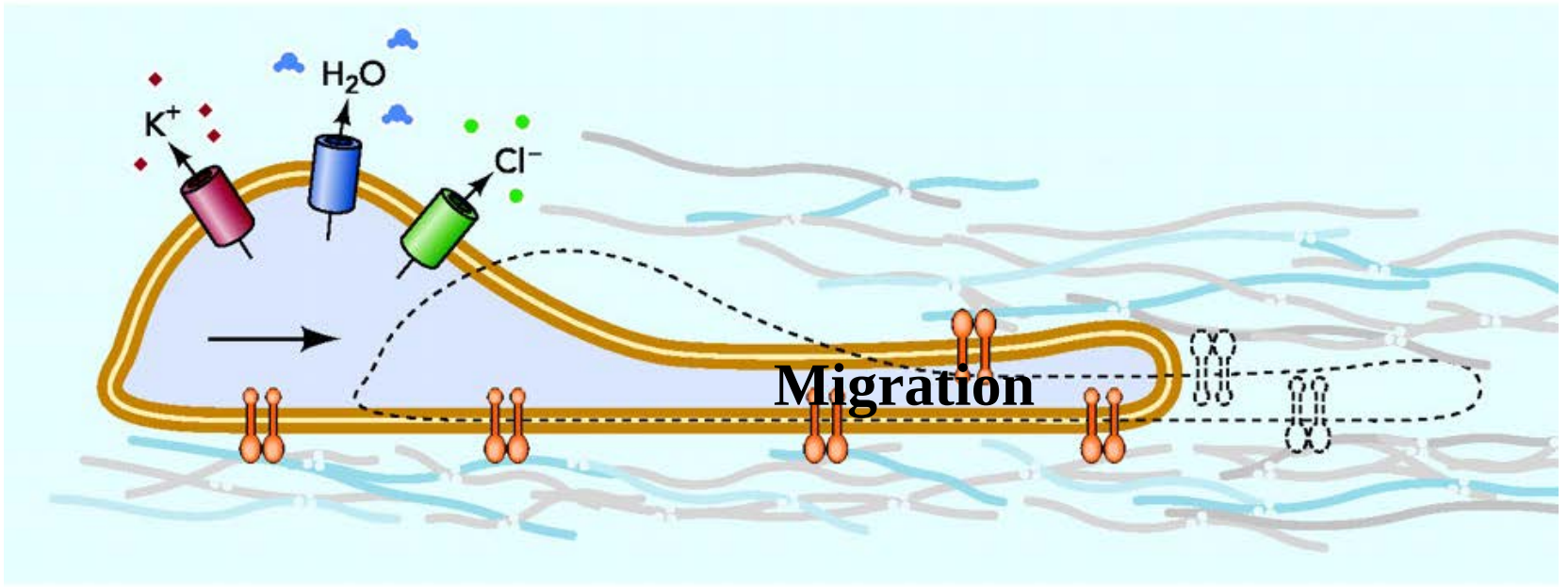

Normal myocardium
(rapid, bidirectional conduction)
1
2
3
Abnormal myocardium
(slow, one-way conduction)
4
5
6

EKG





Functional interaction: AQP – K^+ channels



Other

Other


Hydra IQ is a unique ingredient that stimulates the creation of new aquaporins*, the skin cell's own hydration channels, which improve the moisture flow from cell to cell. This leads to optimal moisture distribution - even in deeper skin layers.
Hydra IQ هو مكون فريد ينشّط إنتاج Aquaporin* جديدة، وهي قنوات الترطيب التي تحتويها البشرة طبيعياً، ما يحسّن انسياب الترطيب من خلية إلى أخرى، ويؤدي إلى توزيع مثالي للترطيب، حتى في طبقات البشرة العميقة.
before Hydra IQ application
Hydra IQ قبل استعمال
after Hydra IQ application
Hydra IQ بعد استعمال
* in vitro data/ *بيانات من المختبر
Recommended Age Group:

Conclusion: a new regulatory mechanism

1. A number of transporters cotransport solutes and water.

2. A number of K channels are precisely regulated by small changes in cell volume through ”functional interaction” with aquaporins.

3. This may be an important regulatory mechanism in cardiac myocytes and epithelial cells.

4. The regulation is not mediated through membrane stretch, phosphorylation, pH, Ca, ATP or PIP2

5. Slick and slack may provide insight …….

University of Copenhagen, Health and Medical Sci.

- Maria Tejada
- Sofia Hammami
- Kathleen Stolpe
- Asser Nyander Poulsen
- Lars Jørn Jensen
- Rikke Søe
- Morten Grunnet
- Nanna MacAulay

University of Copenhagen Science

-Ivana Novak
-Niels Willumsen

University of Zürich Schwitzerland

Stine Meinild

University of Hamburg

ZMNH, Germany

- Olaf Pongs

University of Valparaiso

Chile

- Ramon Latorre