

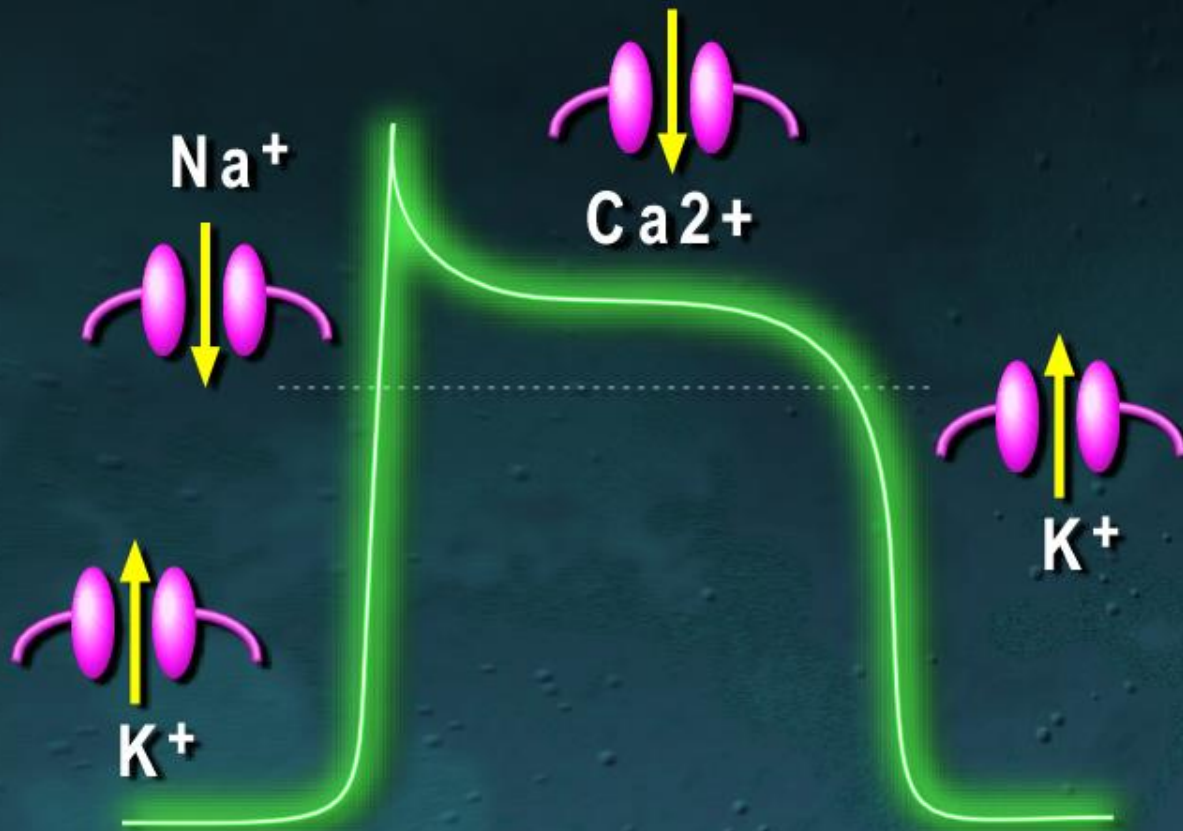
Marine lipids and cellular excitability



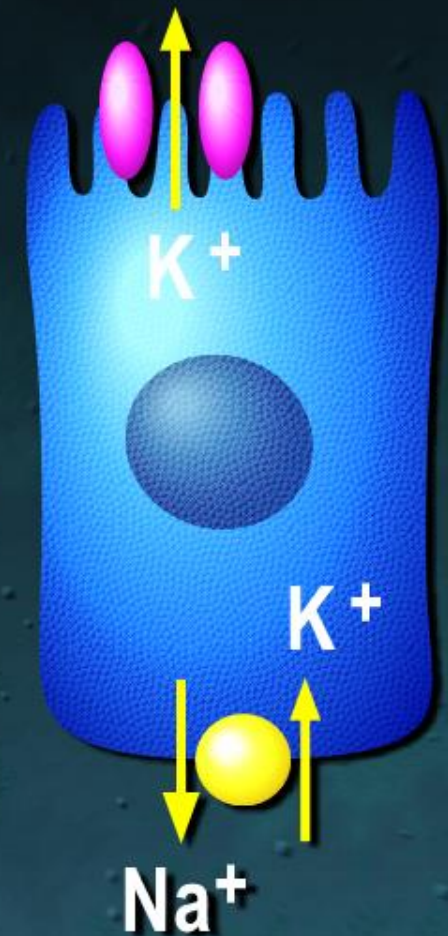
IPMC-CNRS
Nice-Sophia Antipolis, France

Functional diversity of ion channels

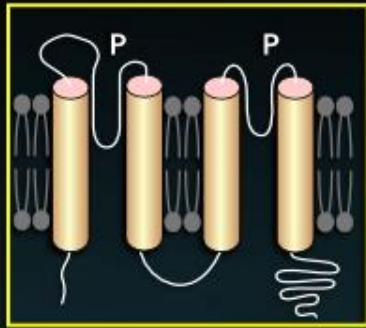
Cell electrogenesis



Ionic transport



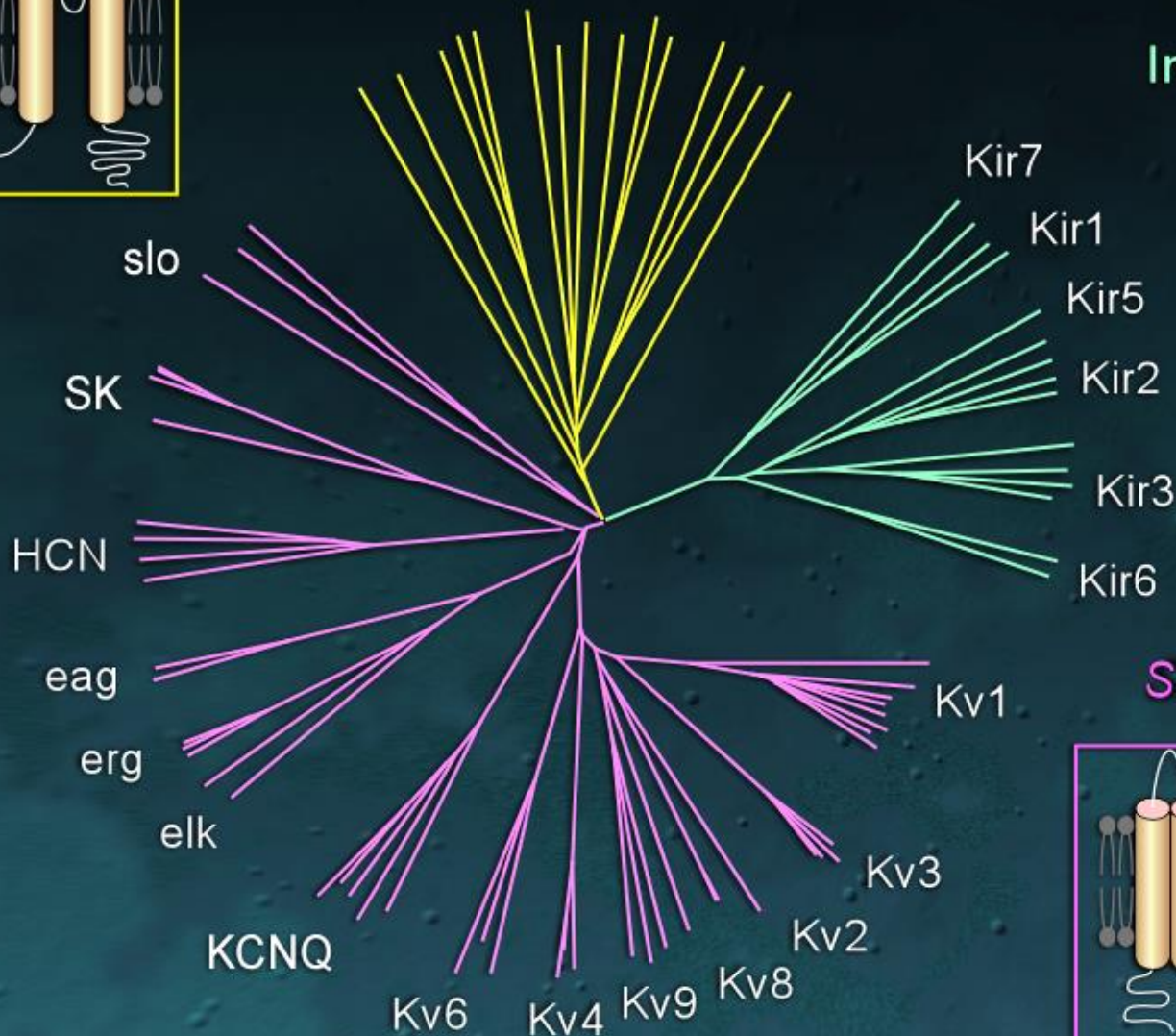
twik-related



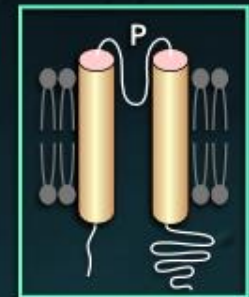
Mammalian K⁺ channels

78 genes

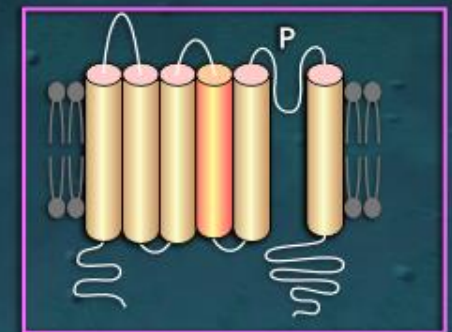
KCNK



Inward rectifiers

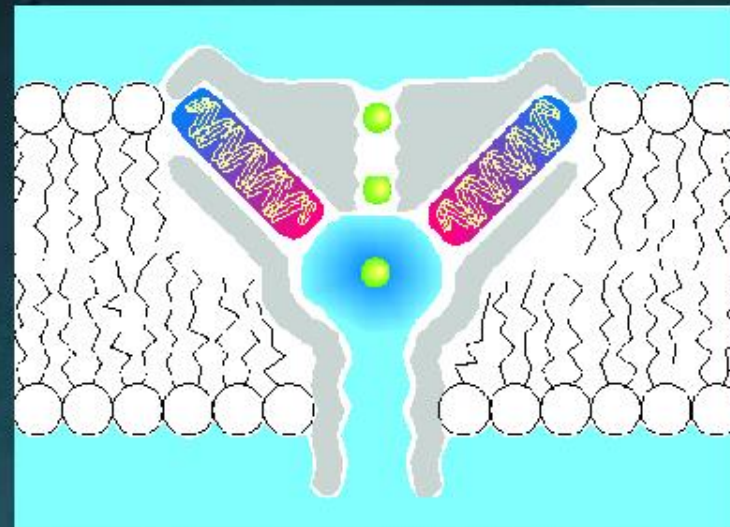
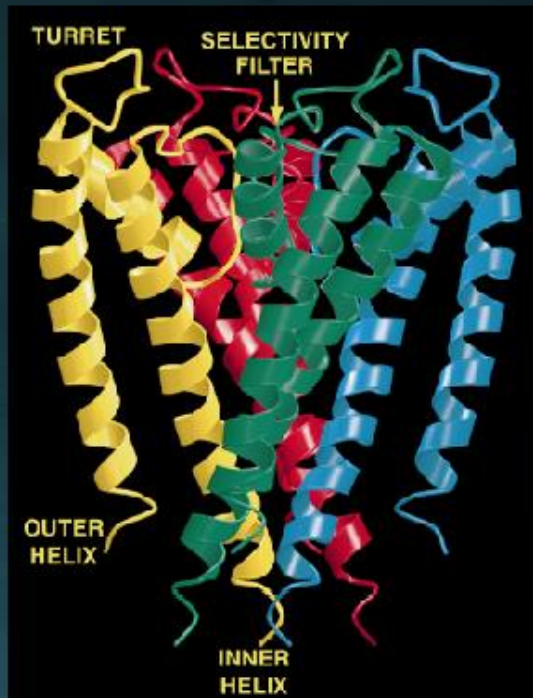
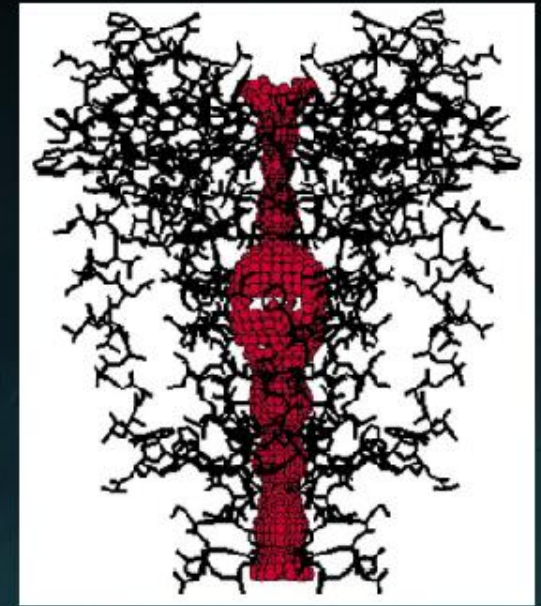
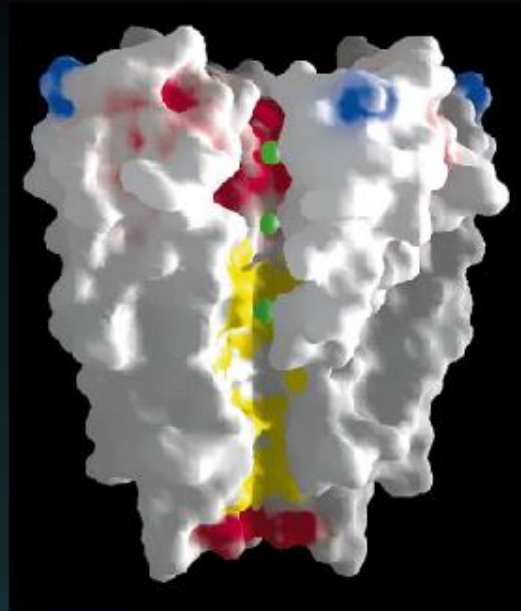


Shaker type

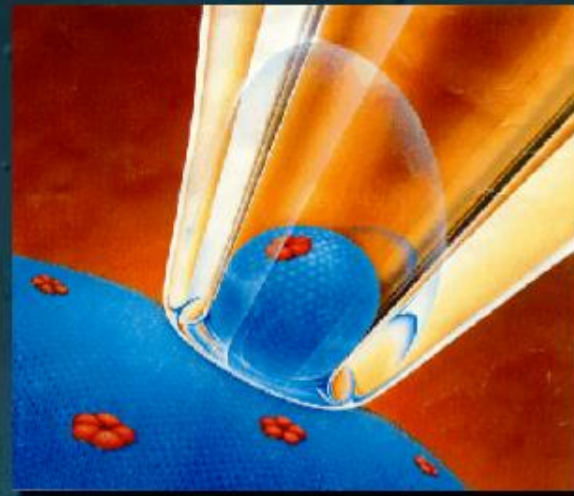
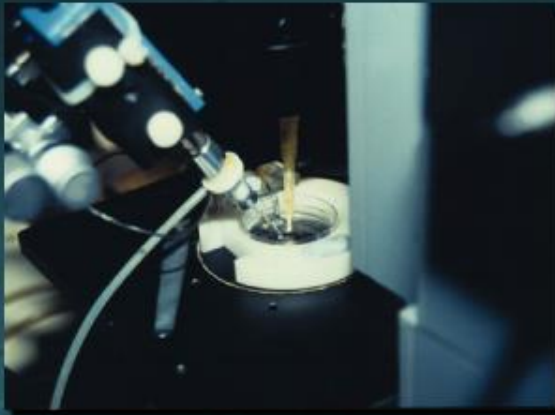
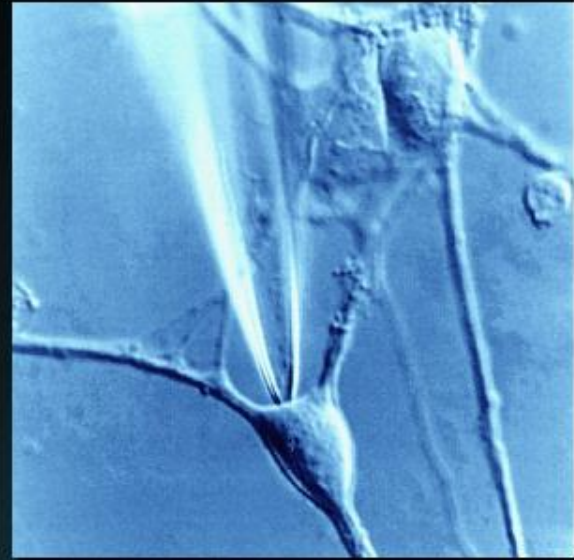


3D structure of the bacterial K^+ channel KcsA

Doyle et al., (1998) Science

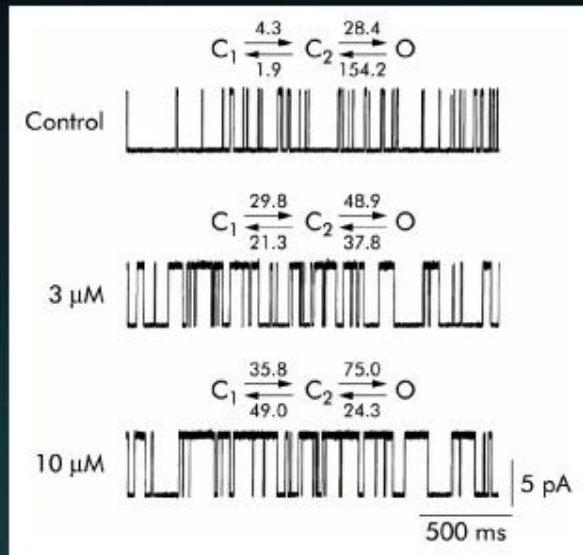


The patch clamp technique

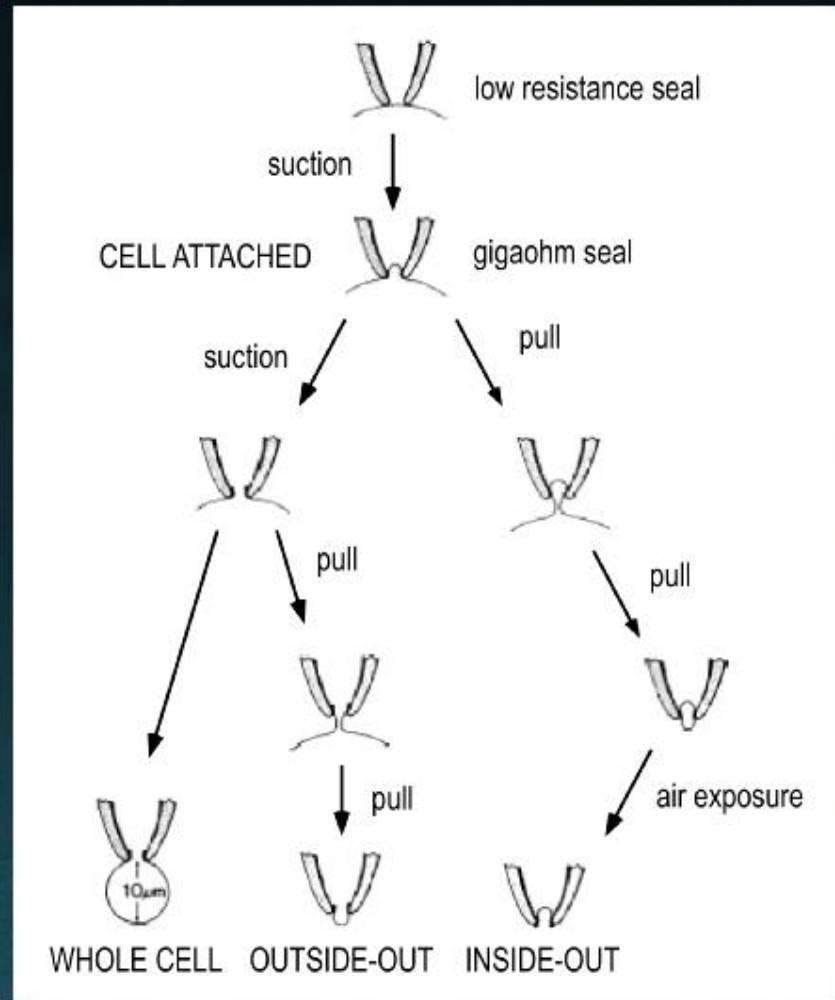
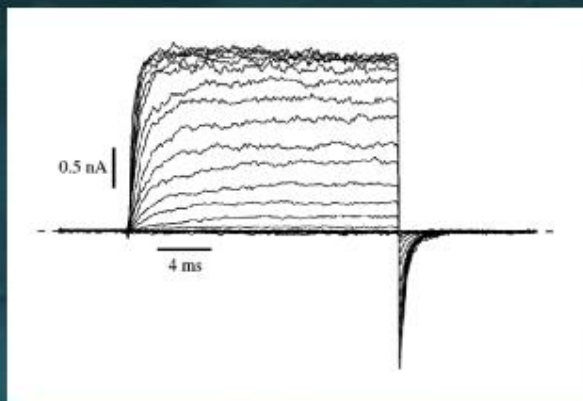


Patch clamp configurations

INSIDE-OUT

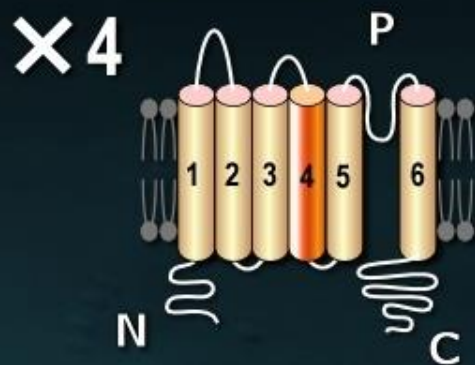


WHOLE CELL

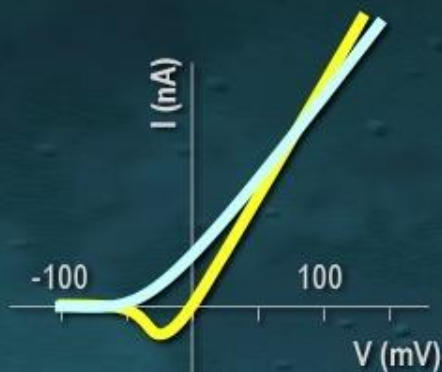


Molecular and functional diversity of K^+ channels

78 human genes



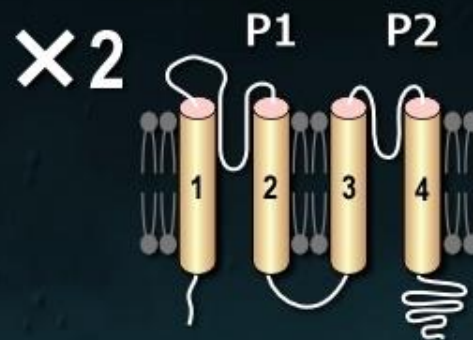
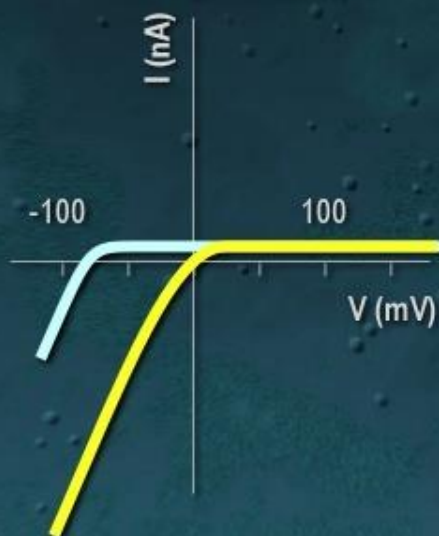
Voltage- and Ca^{2+} -gated



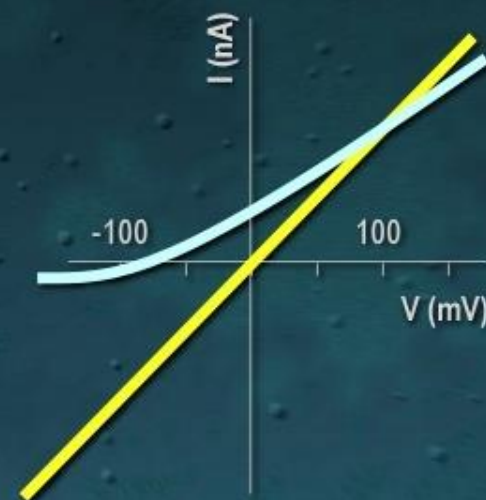
Phys K^+
Sym K^+



Inward rectifier



Background



The marine omega-3 polyunsaturated fatty acids (n-3 PUFAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DOHA) are present mainly in oily fish.



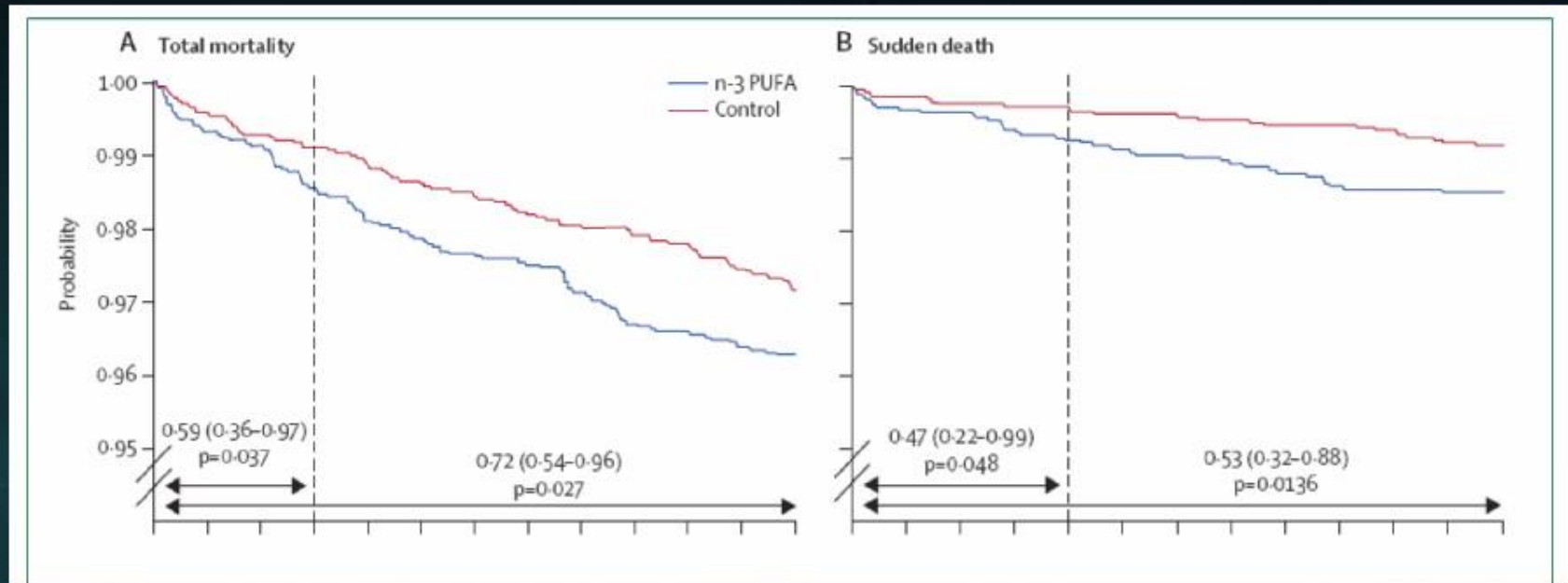
Greenland Inuit population is reported is at low risk of death from coronary artery disease and this resistance has been related to an abundance of n-3 PUFAs in their diet.



Early protection from mortality with n-3 PUFA supplementation after myocardial infarction

11323 patients with recent myocardial infarction (median: 16 days)

GISSI-Prevenzione study



Incidence of sudden cardiac death was significantly reduced within 4 months of treatment with n-3 PUFAs (1g / day).

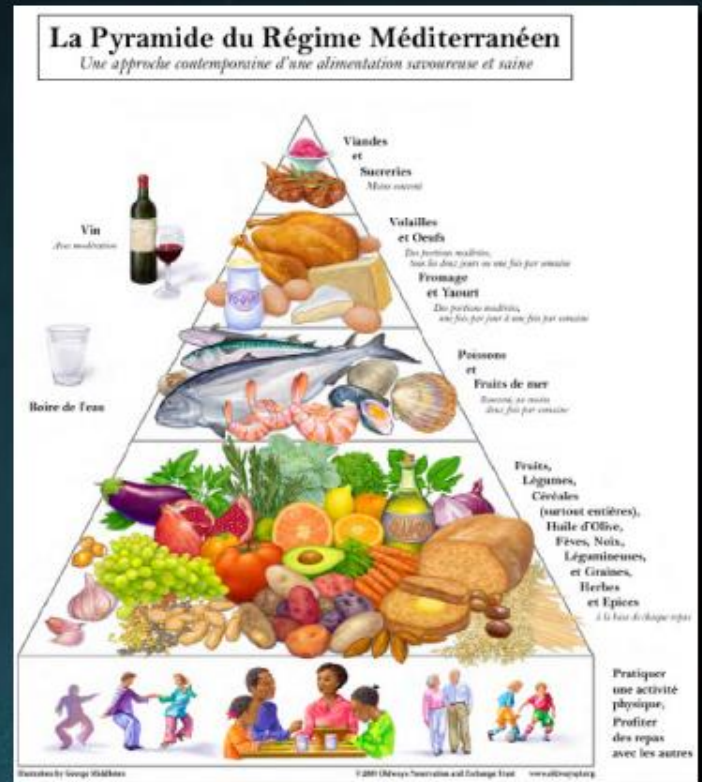
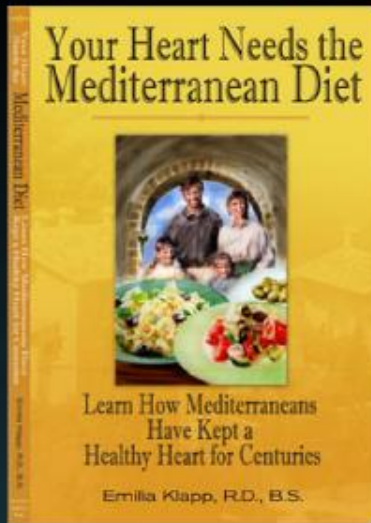
These results suggest an antiarrhythmic effect of n-3 PUFAs. The presumed mechanism of such benefit would be a reduction in life-threatening ventricular arrhythmias, the most common cause of sudden cardiac death in the early stages after a myocardial infarction.

The most important cardio-protective effect is related to a reduction in mortality after infarction

The joint American College of Cardiology and American Heart Association statement on n-3 PUFA use recommends an intake of at least two fish meals per week in patients with coronary artery disease, and supplemental therapy for 1 year with 1 g per day of n-3 PUFA ethyl esters for those who have had a myocardial infarction



What is the molecular basis for the anti-arrhythmic action of n-3 fish oil PUFAs?



**OMEGA
BRAIN FUEL**

**100%
NATURAL OMEGA 3 OILS**

NOVEL WAY TO SUPPRESS EMOTIONAL EATING

LifeExtension
MAGAZINE

Omega-3 Fatty Acids Increase Brain Volume

Protect Your DNA Against CT Scan Radiation

Hidden Link Between Obesity and Diabetes

Drugs That Deplete Vital Nutrients

Plus: Vitamin K Lowers Diabetes Risk
New Study Shows Blood Flow to Brain
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New!

Smart!
with **DHA** and **OMEGA-3**

Boost Your Brain with...

New Breyers Smart! All Natural Lowfat Yogurt.

Dietary Supplement

Omega 3 Mood

THIRD PARTY TESTED

FISH

High EPA Mood Balancing Formula***

GF

Country Life

180 Softgels

NATURE'S WAY

Omega³ Fish Oil

Brain & Memory

Fish Oil & Ginkgo for Memory & Concentration

60 Capsules

COMING THIS SUMMER!

ADD to your FAVORITE FOODS

Omega 3 Brain Booster

AGES 2 to 102

Dietary Supplement for Mind, Heart & Body!

◆ Omega 3: DHA + EPA ◆ Rice Protein

Net Wt. 12 oz. (340 grams)

n-3 fish oil PUFAs and the brain

Development and maintenance of learning memory performance

Epilepsy: antiseizure effects

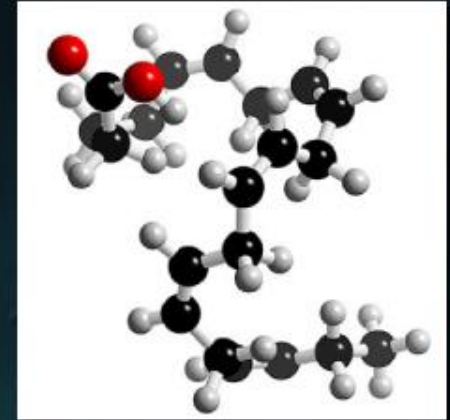
Treatment of depression

Ischemic neuroprotection

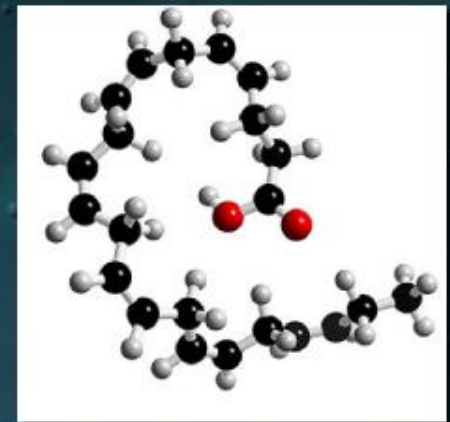
Initiation and progression of neurodegenerative diseases including Alzheimer's disease

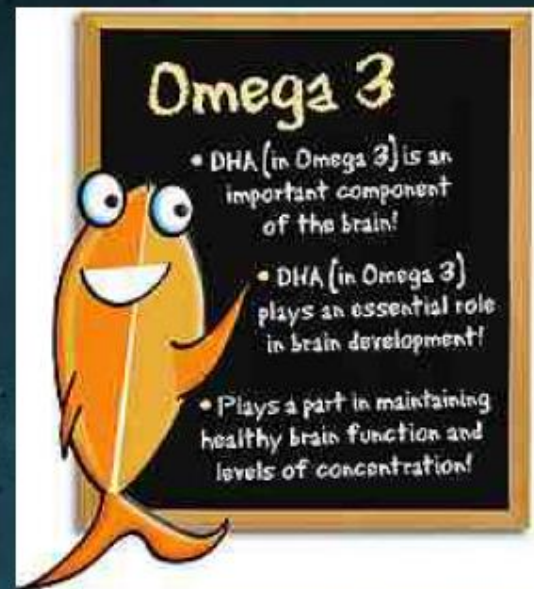


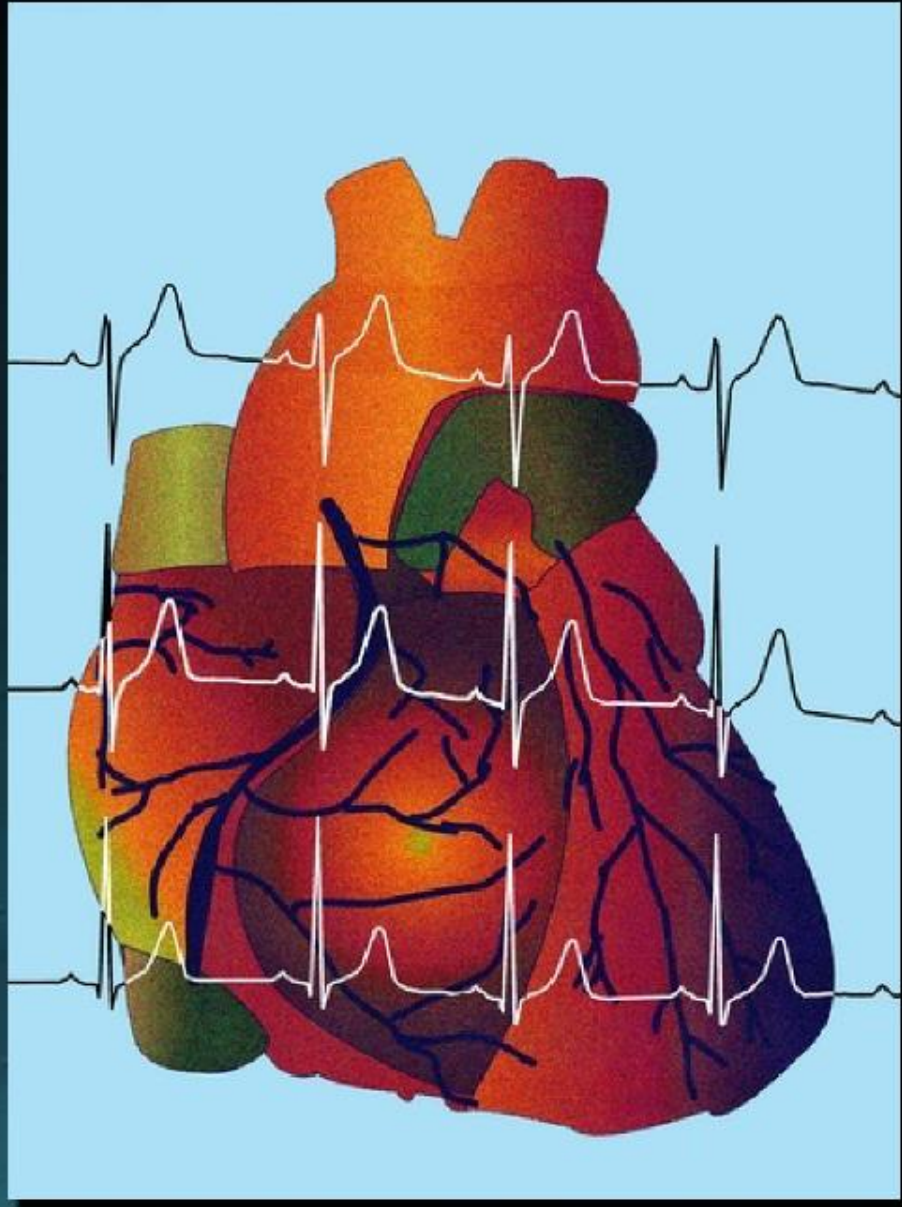
EPA



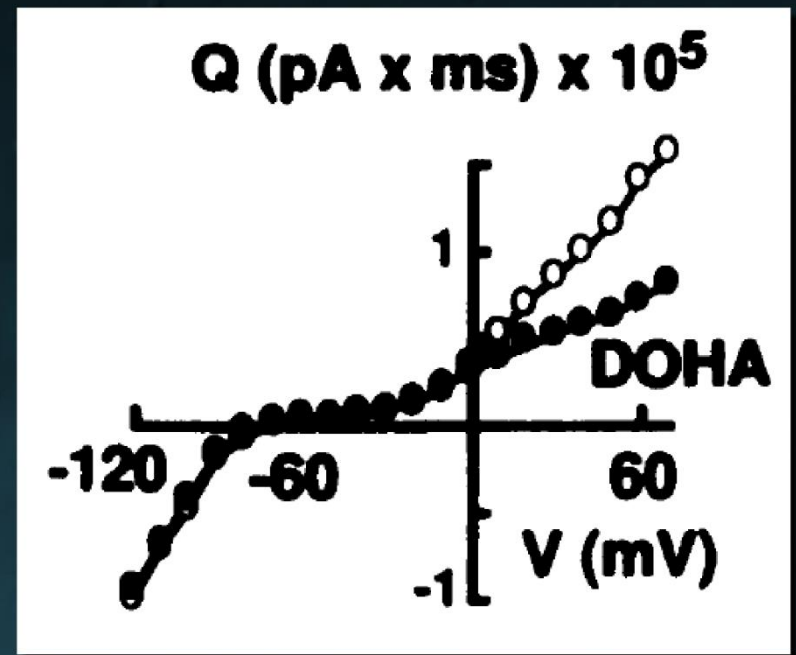
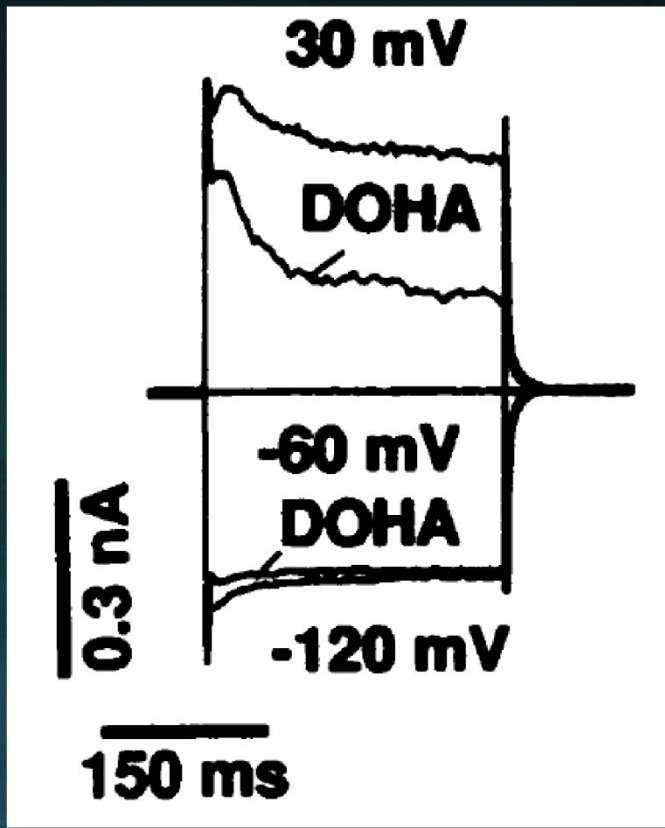
DOHA



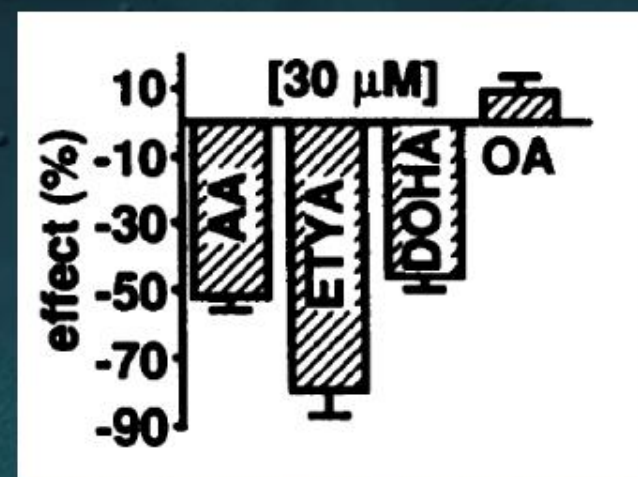
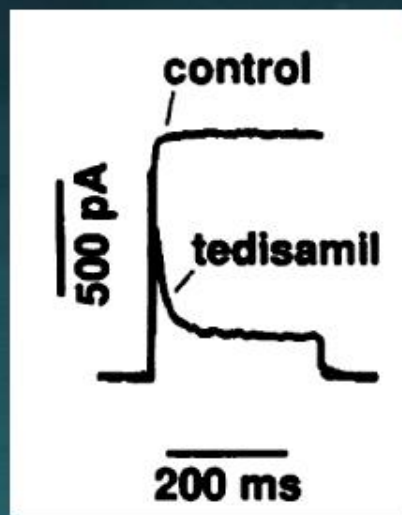
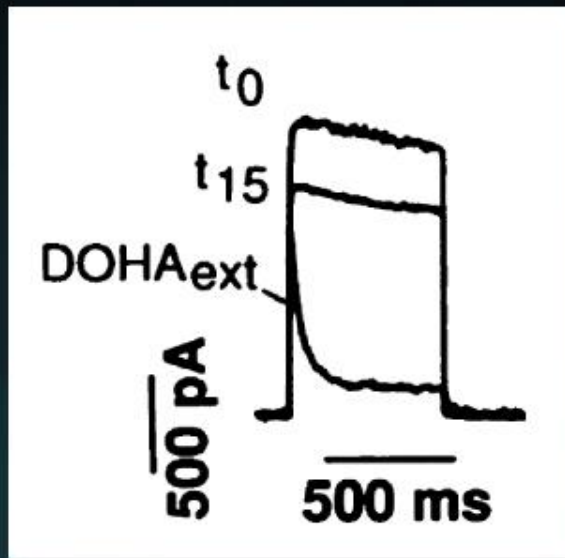




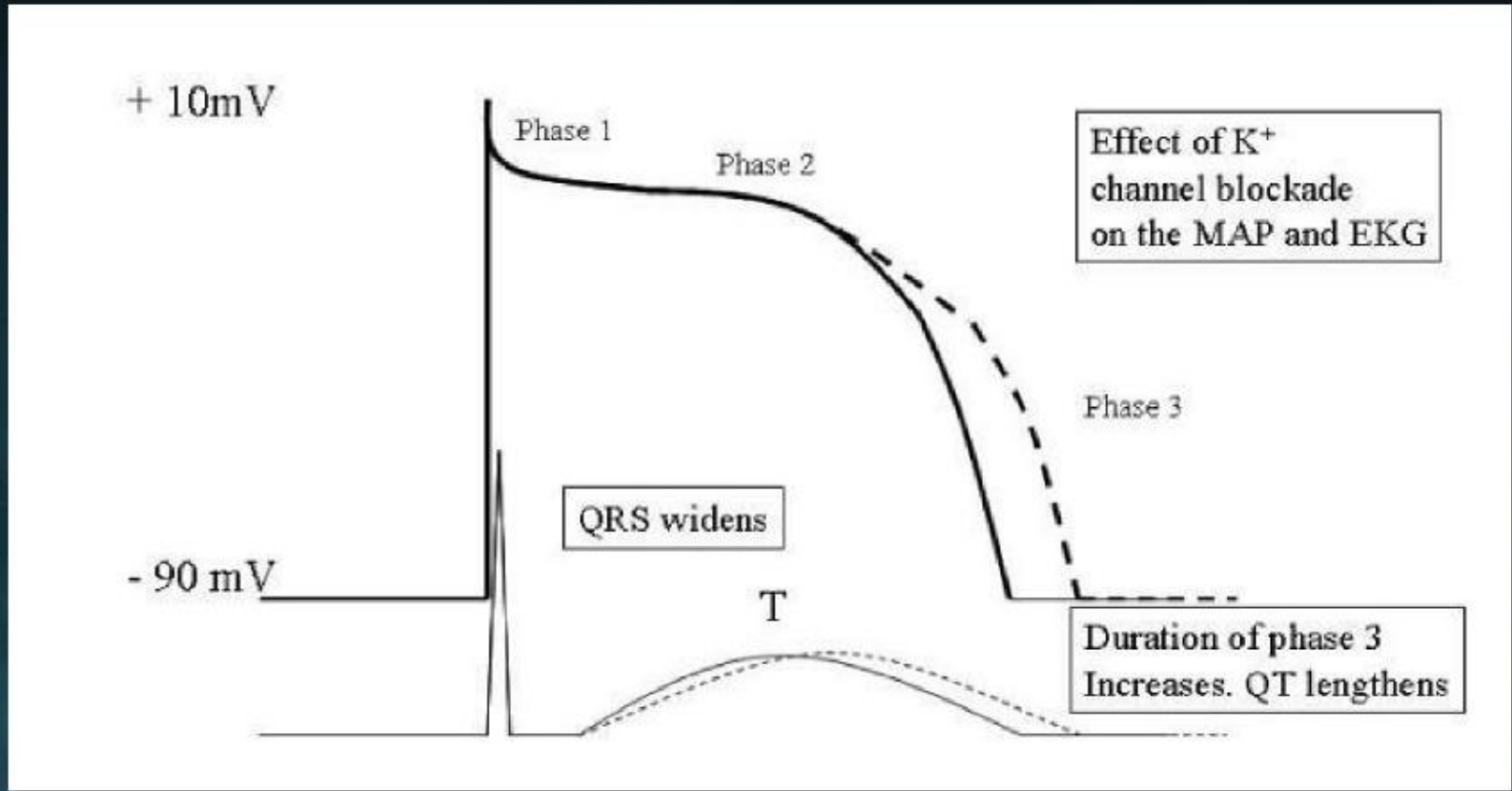
DOHA inhibits voltage-gated K^+ channels in cardiomyocytes



DOHA inhibits Kv1.5 channels

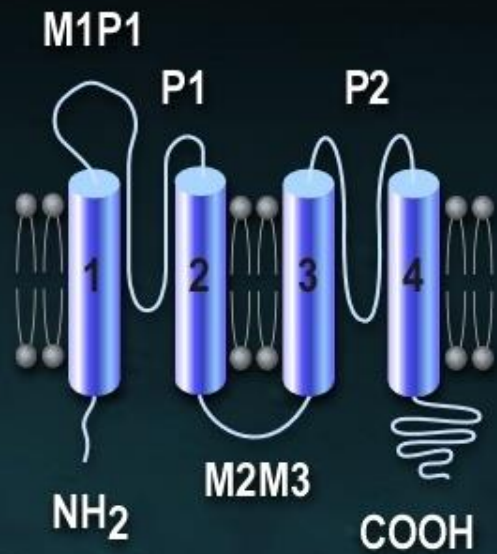


Class III antiarrhythmic agents enhance action potential duration





The human 2P domain K⁺ channels



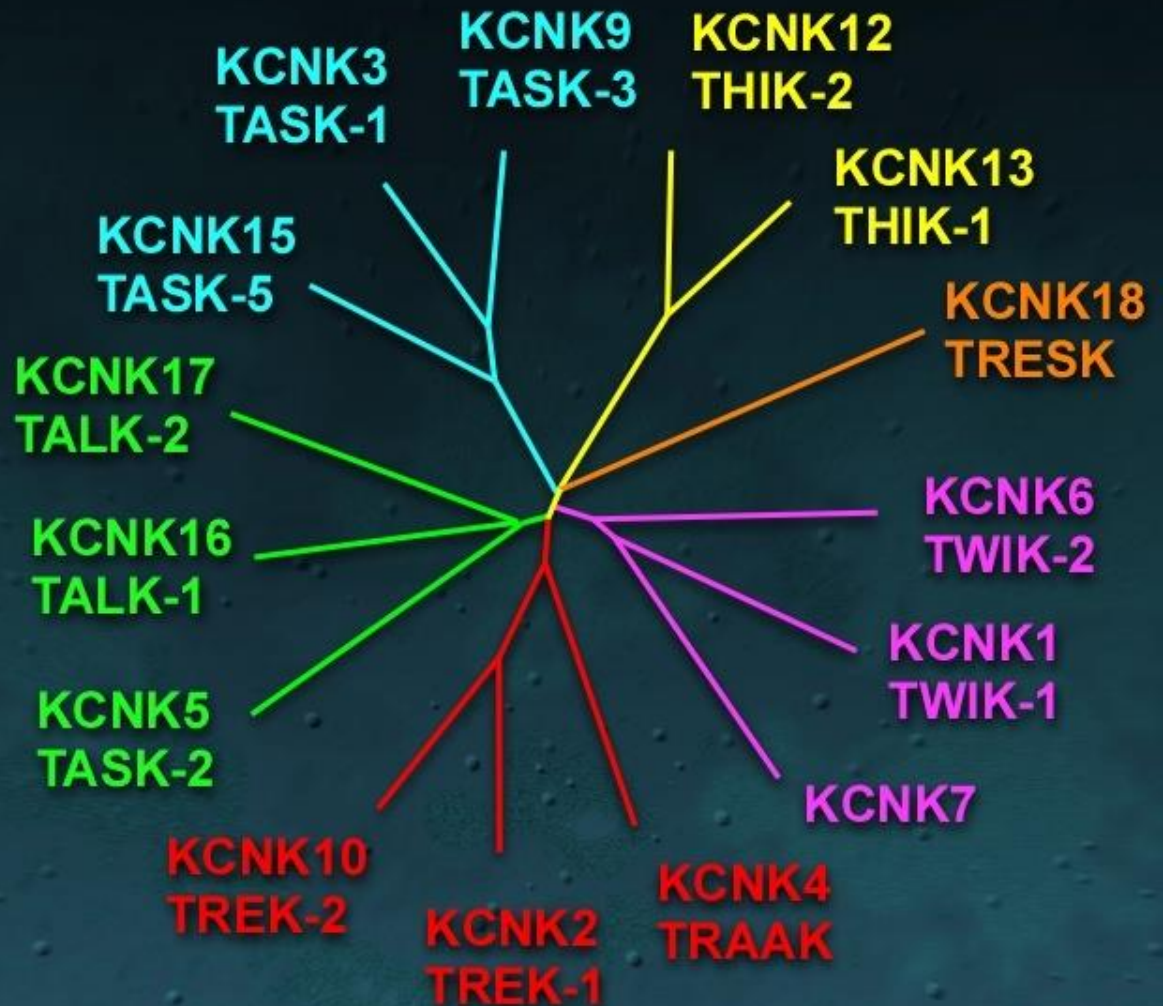
X2

Heteromultimers

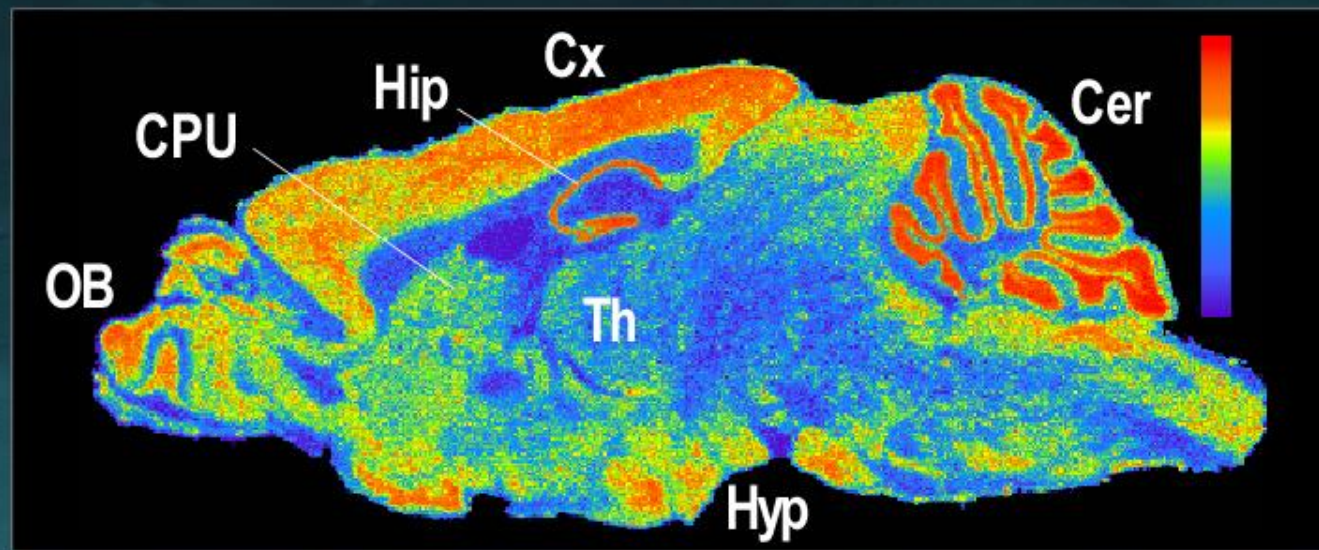
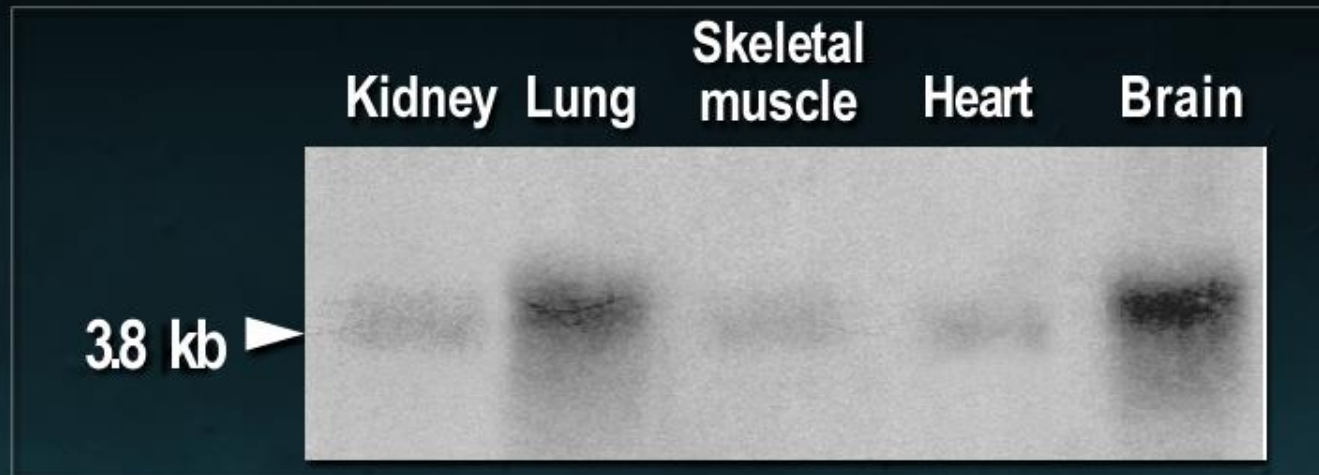
C. elegans : 50/80

Drosophila : 11/30

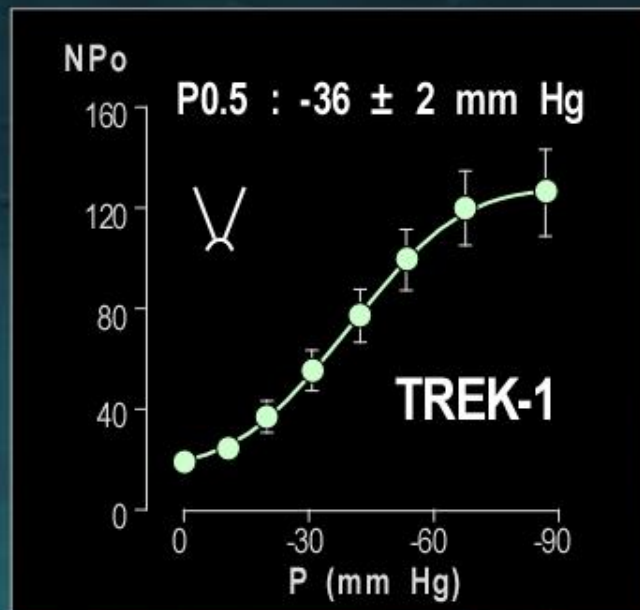
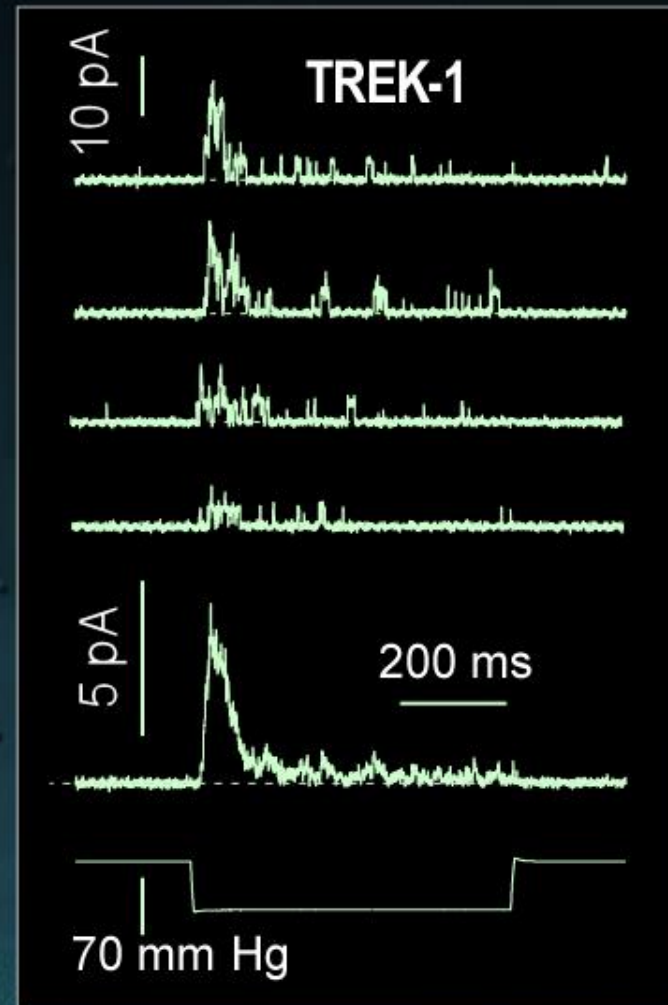
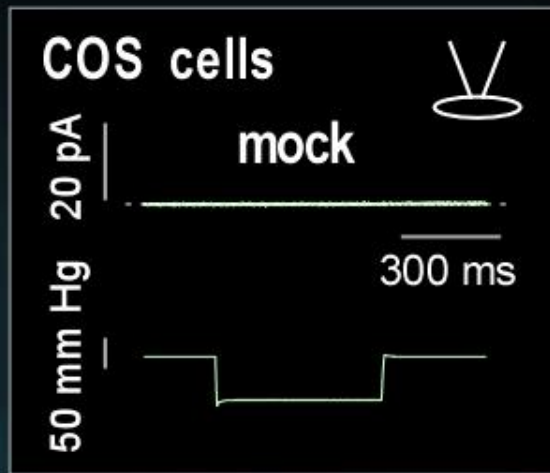
Human : 15/78



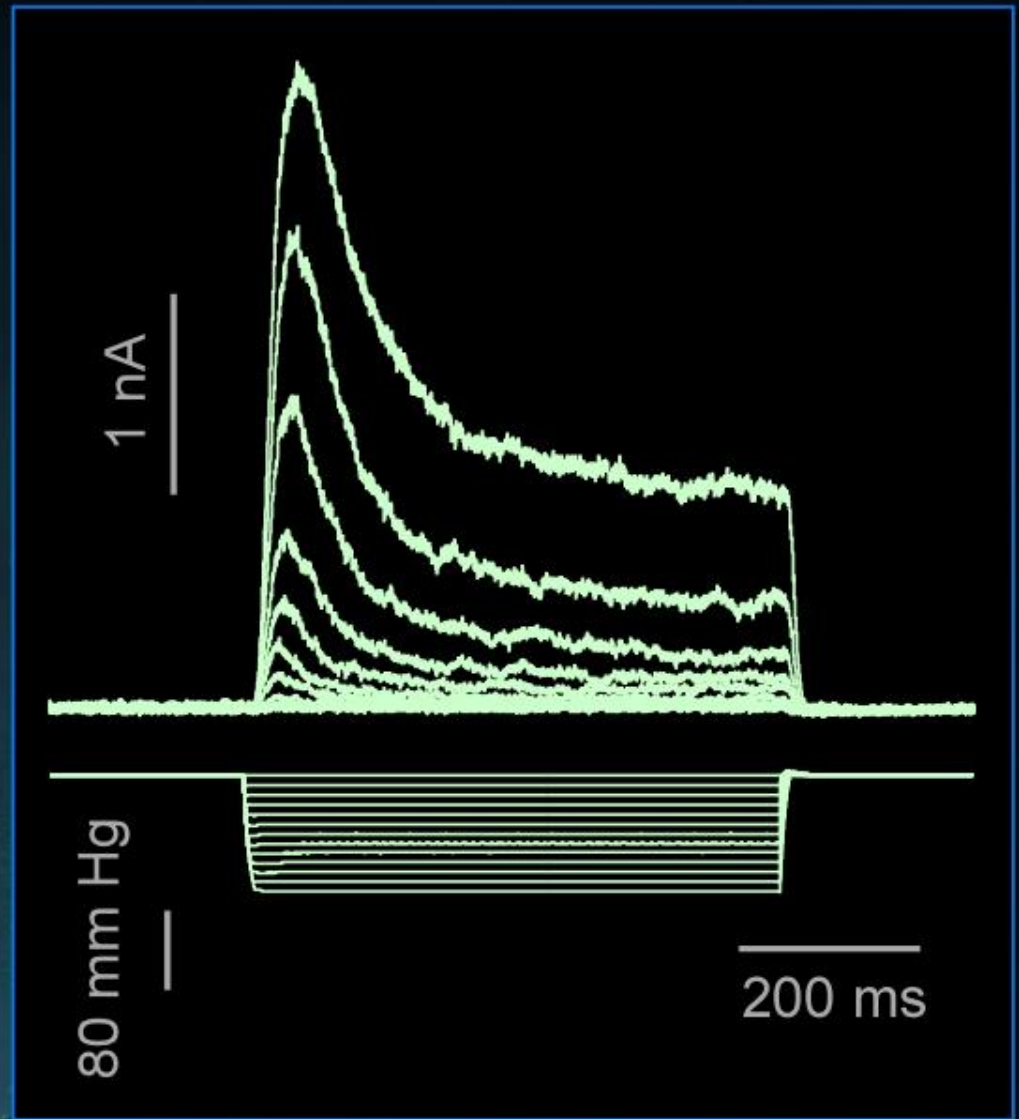
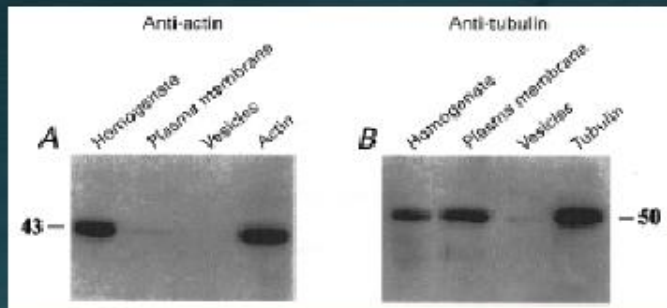
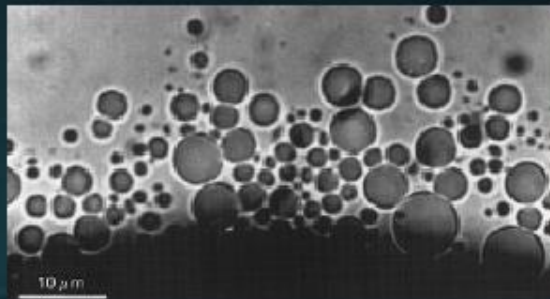
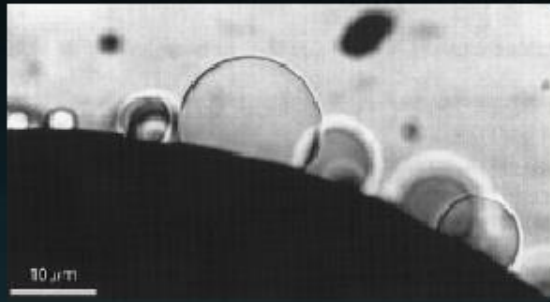
Pattern of expression of mouse TREK-1



TREK-1 is a mechano-gated K^+ channel

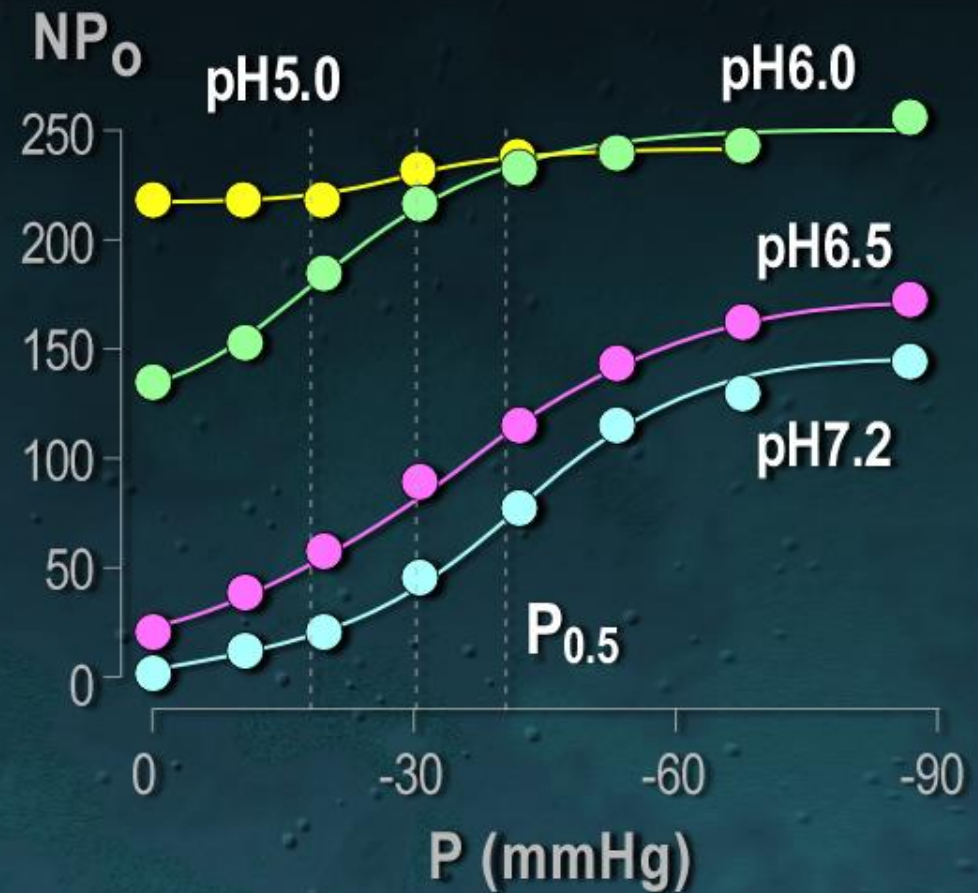
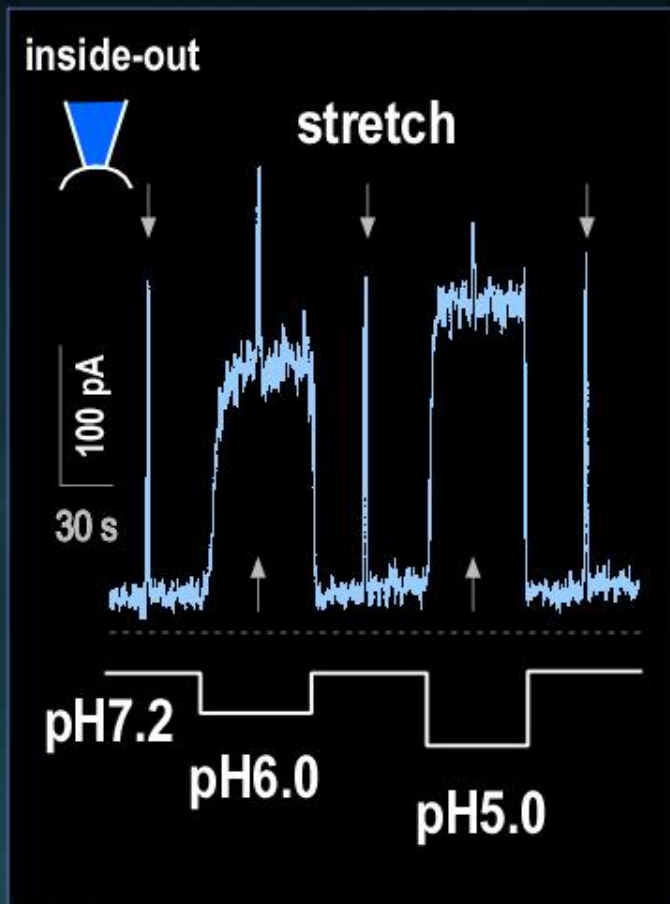


TREK-1 in cytoskeleton less vesicles

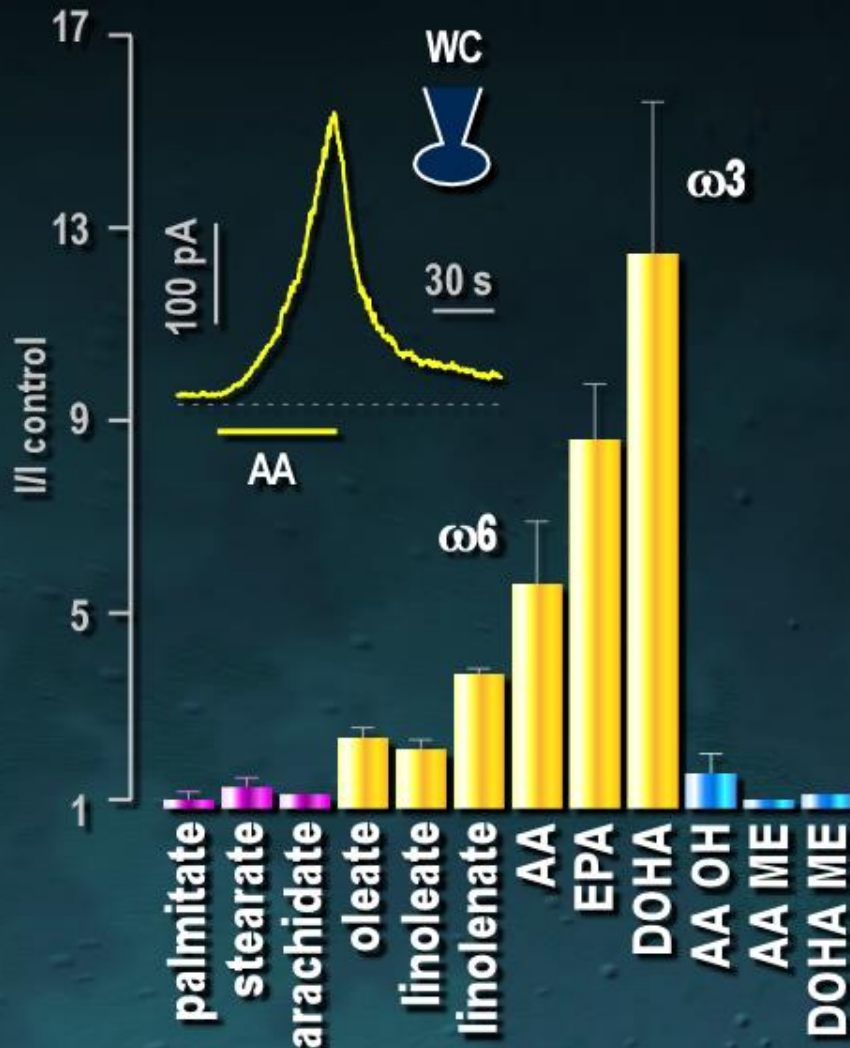


Zhang et al., 2000

Internal acidification removes the requirement for mechanical activation of TREK-1



Fish oil fatty acids open TREK-1



arachidic acid



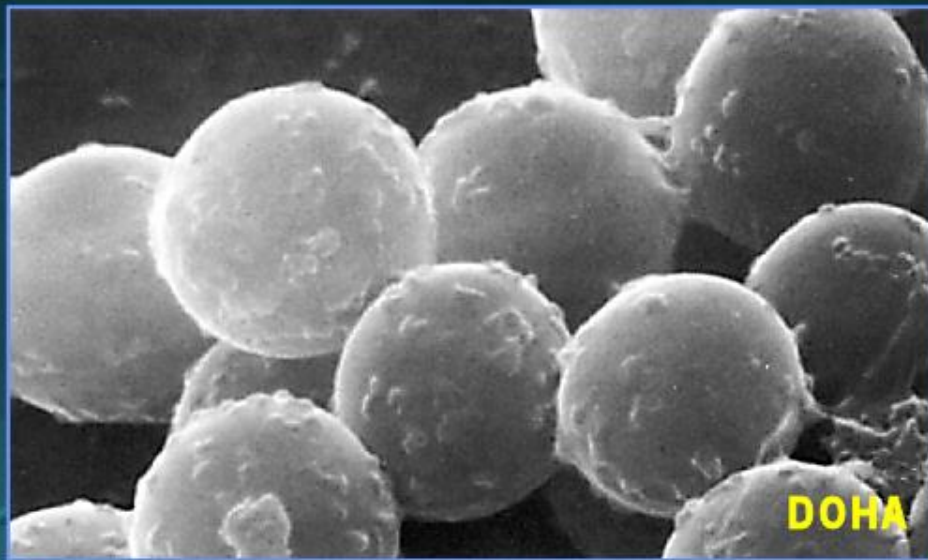
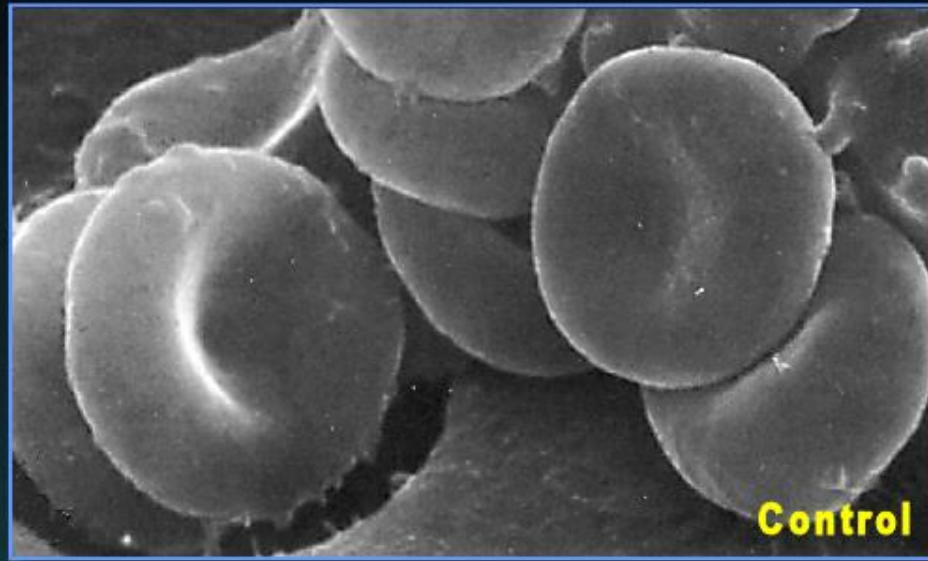
docosahexaenoic acid



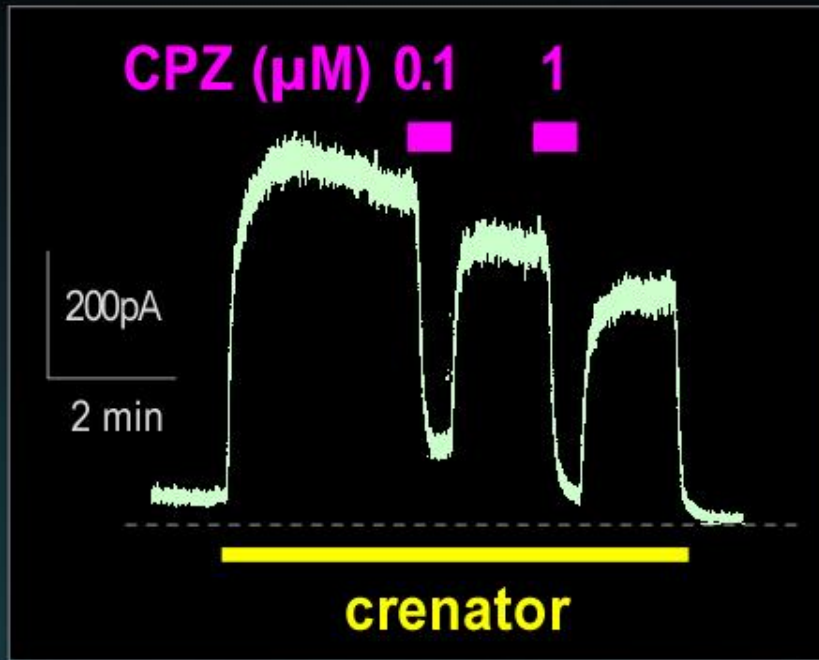
docosahexaenoic acid methyl ester



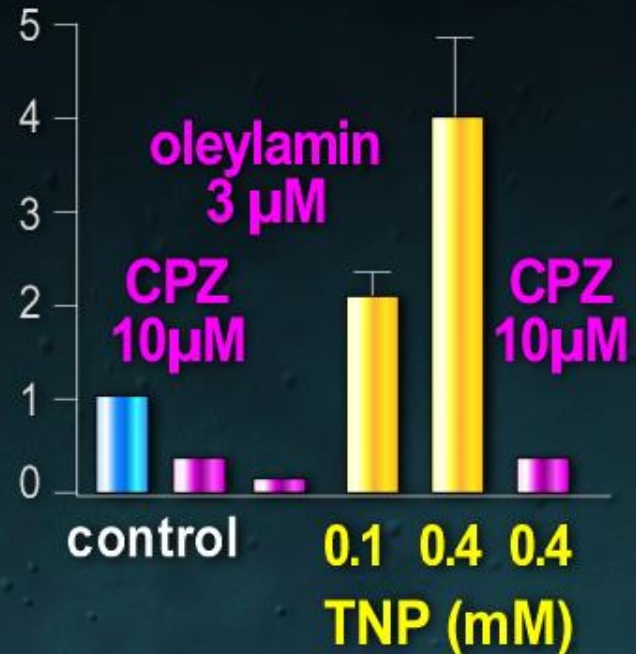
Erythrocyte crenation by PUFAs



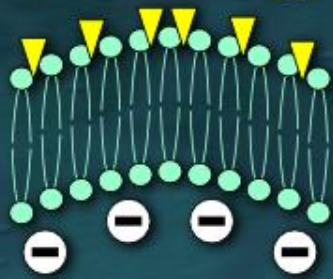
Anionic amphipaths open TREK-1



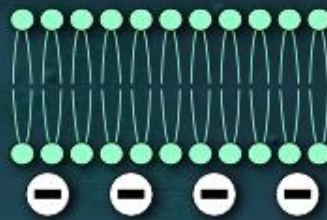
I/I control



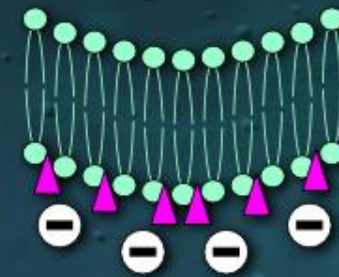
crenator \ominus



outside



inside

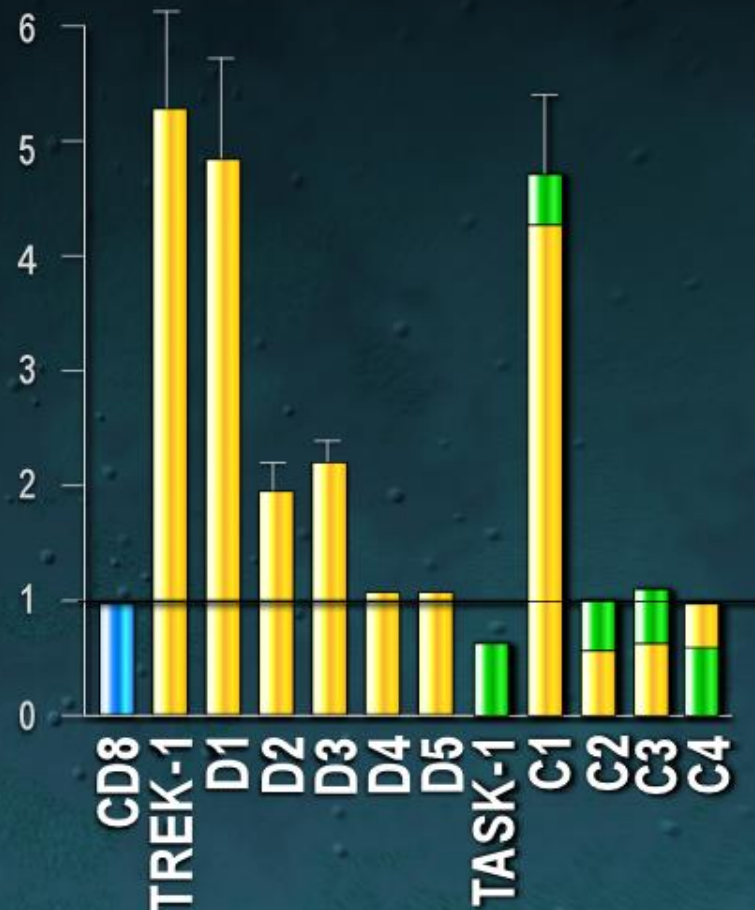


cup-former \oplus

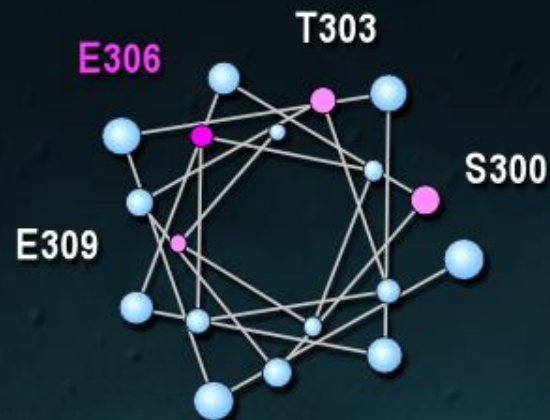
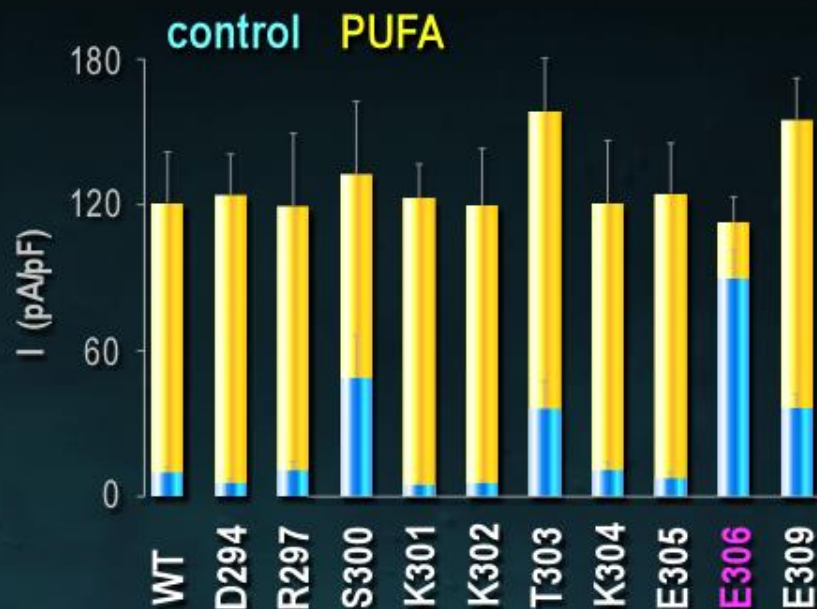
The carboxy-terminus of TREK-1 is critical for PUFA activation



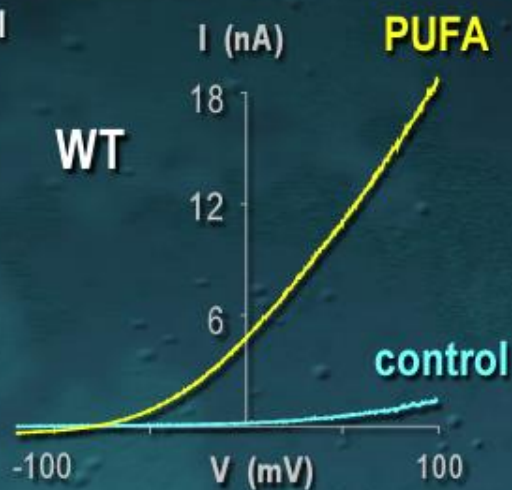
Fold increase PUFA



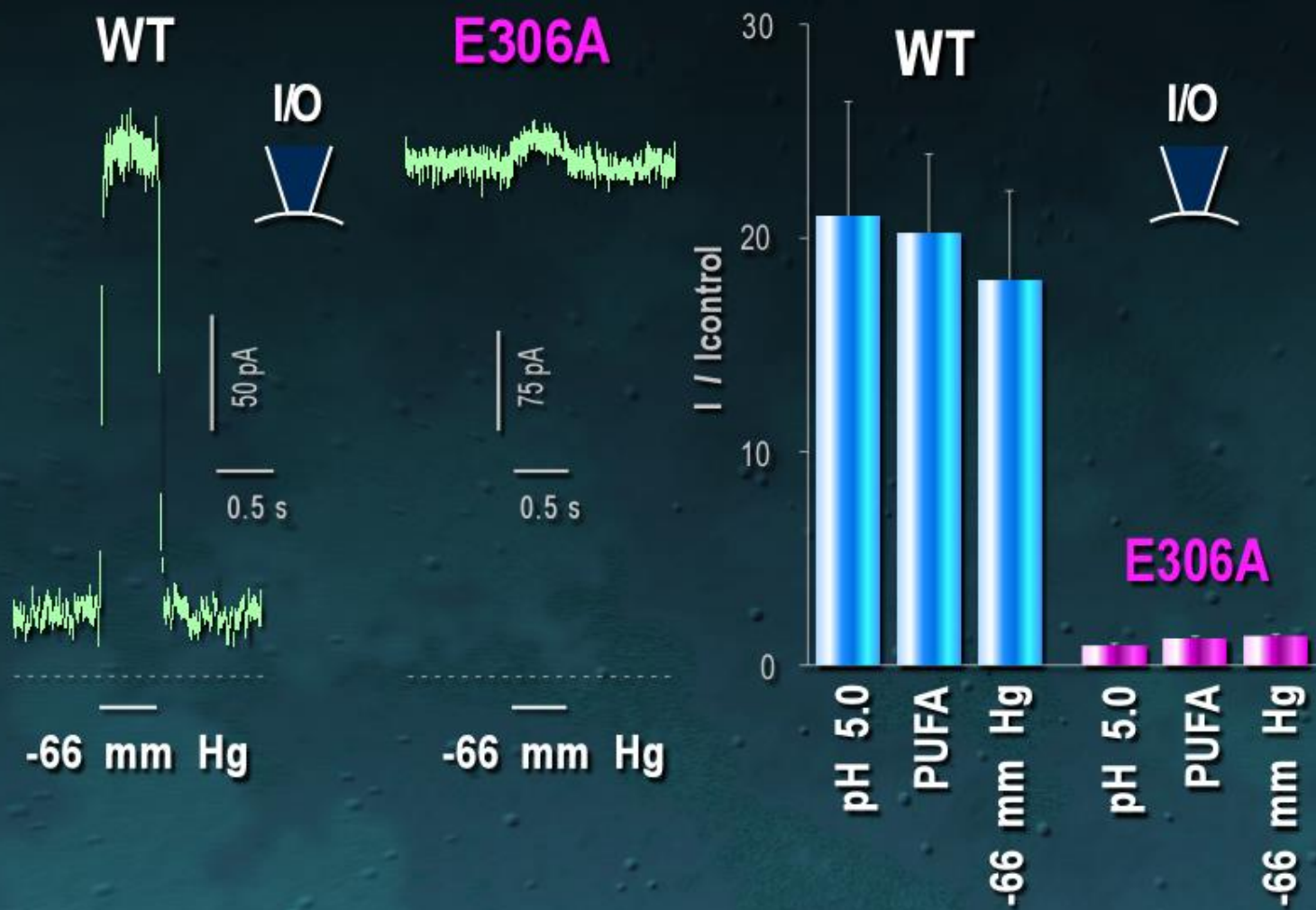
Alanine scanning of the charged region



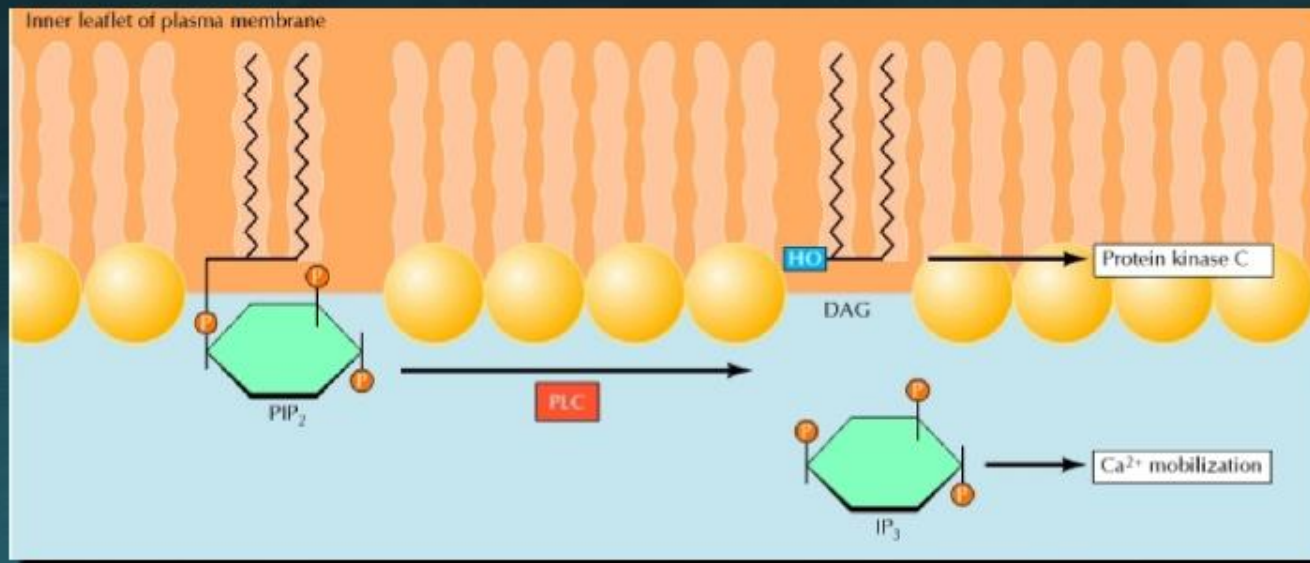
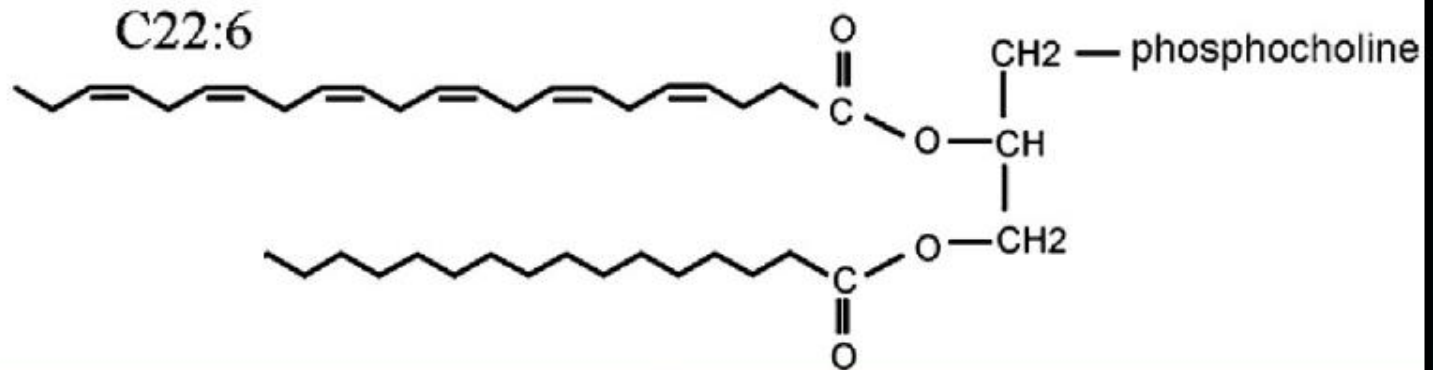
Whole Cell



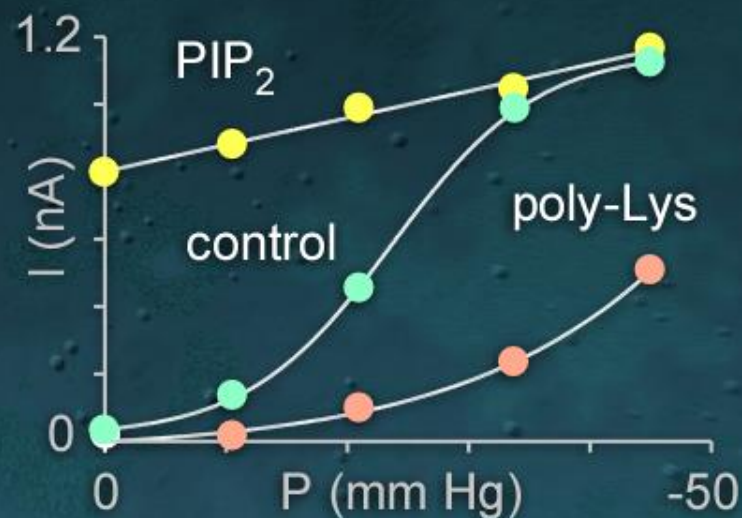
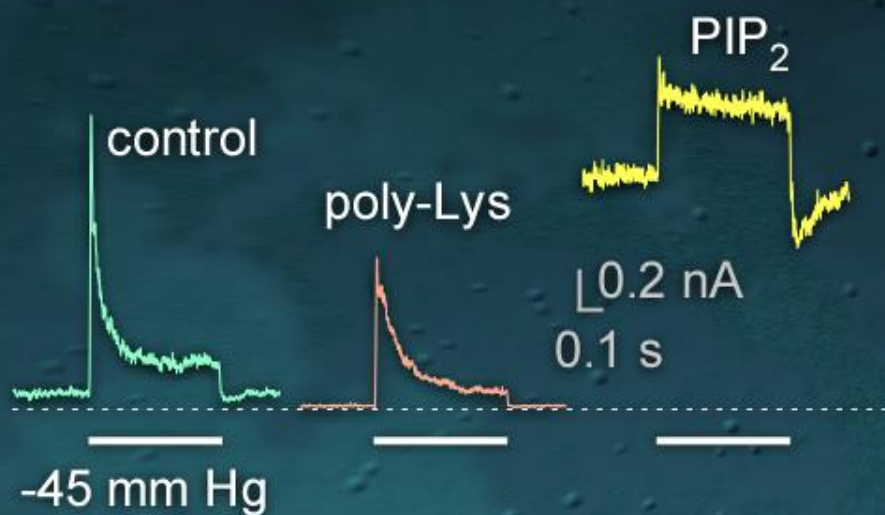
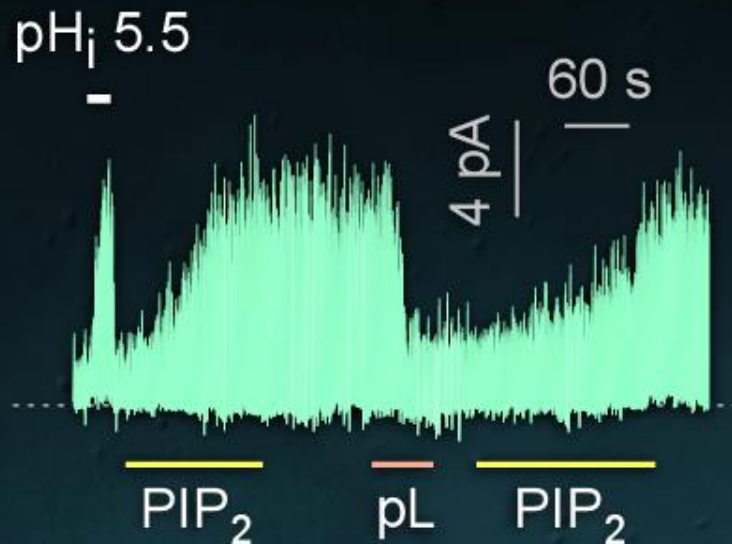
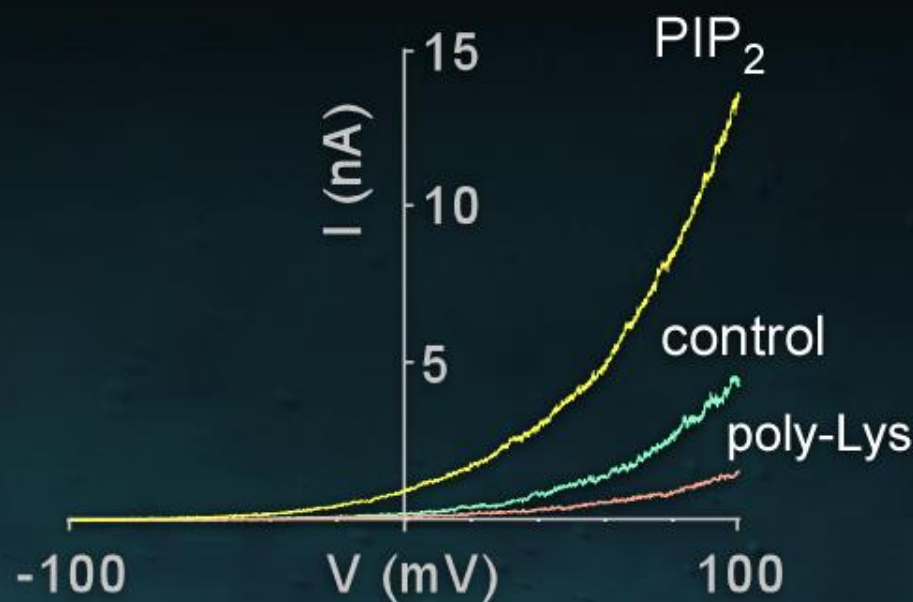
The E306A mutation locks TREK-1 open



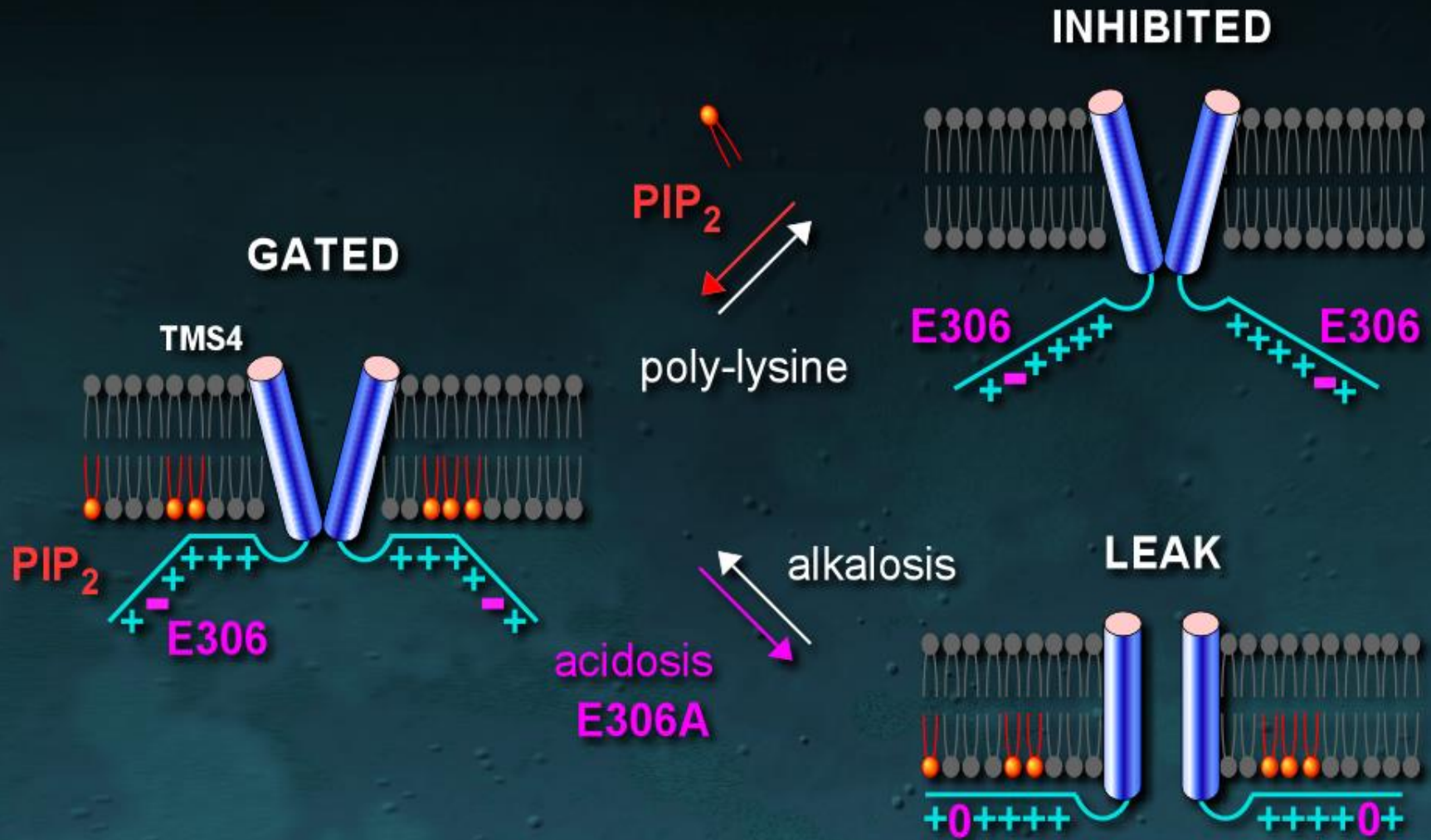
Phospholipids and cellular signaling



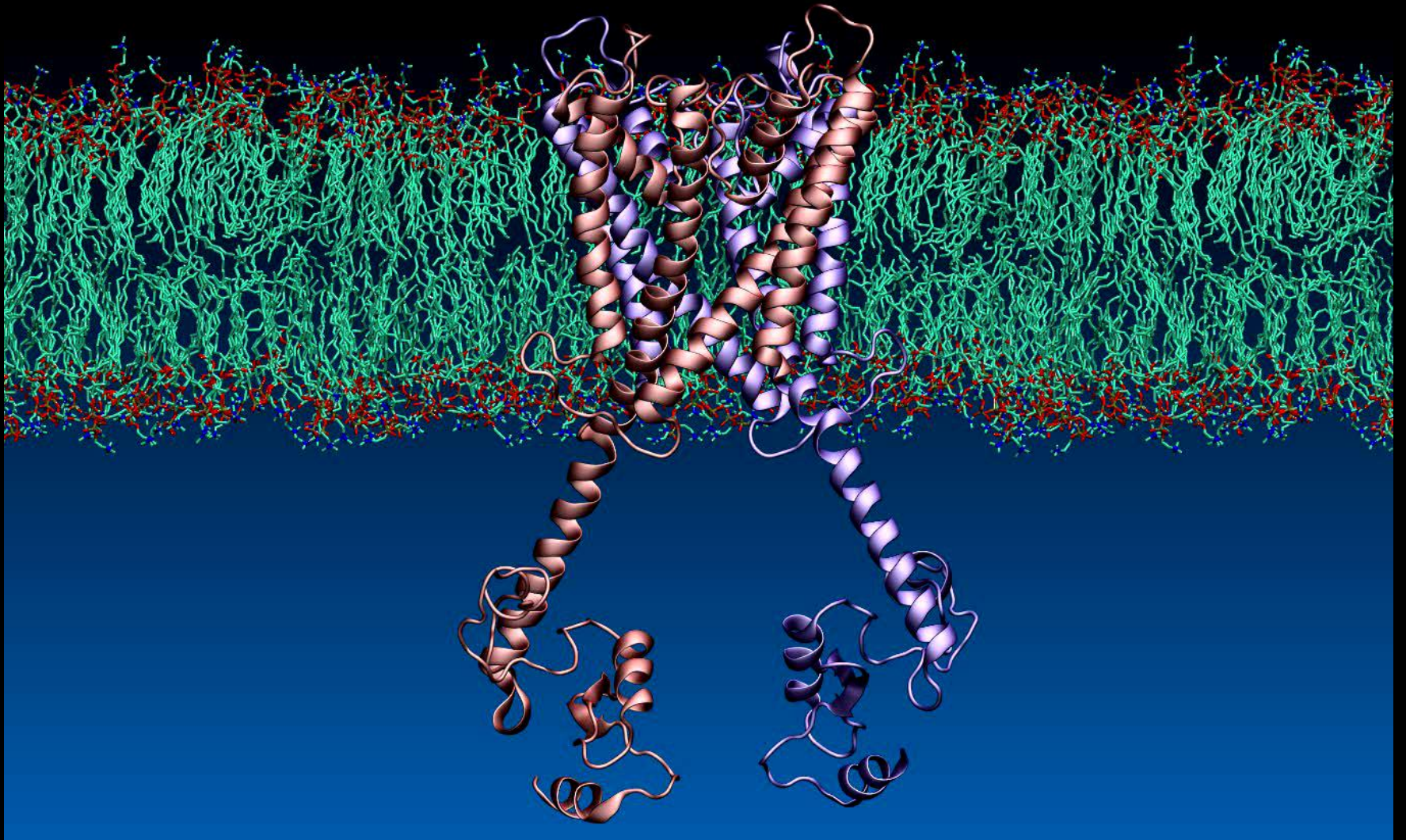
Regulation of TREK-1 by PIP₂



PIP₂ and TREK-1 gating

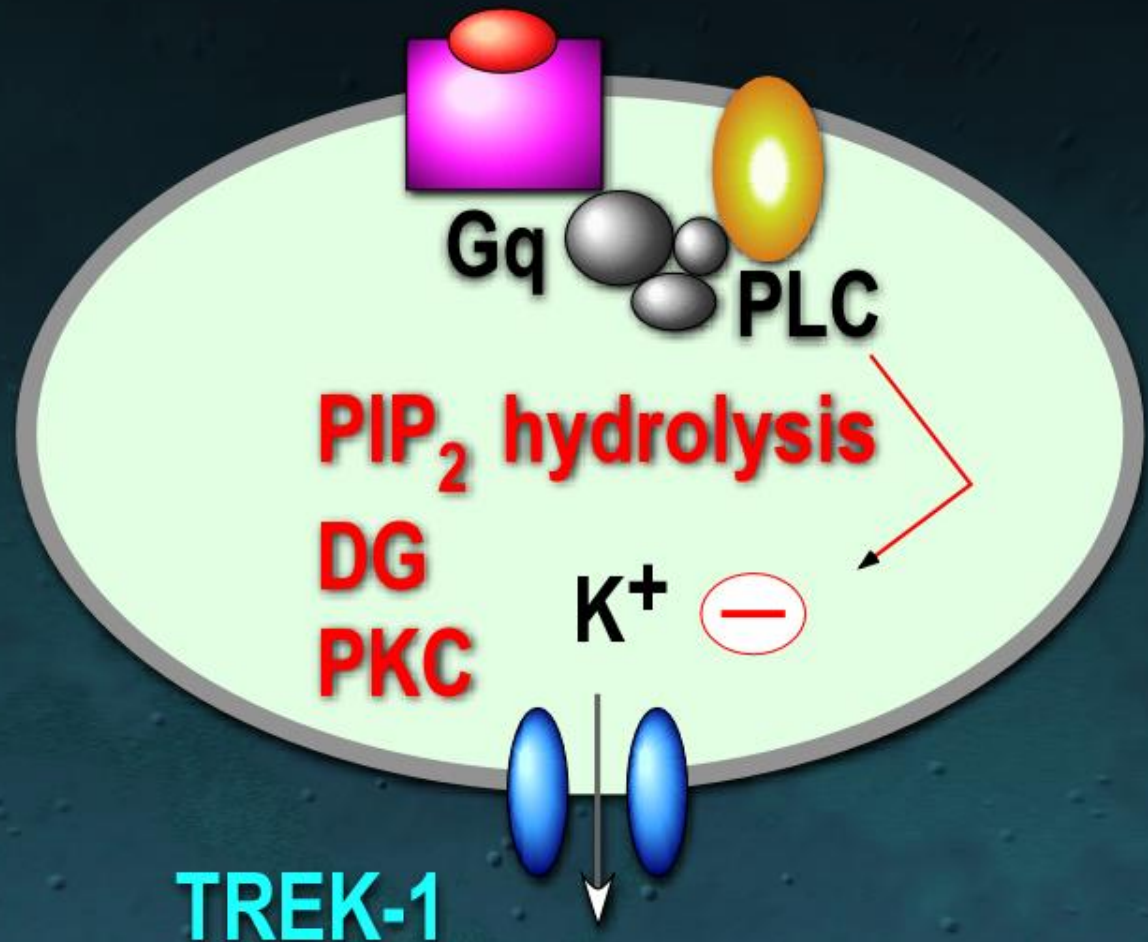


Produced by Werner Treptow & Michael Klein 2010



Stimulation of G α q-coupled receptors inhibits TREK-1

5-HT/5-HT₂
SP/NK1
TRH/TRH-R1
NE/ α 1
glu/mGluR1-5
ACh/M3



Inhibition of TREK-1 by PKA phosphorylation

M4



VLSMGDWLRVISKKTKEEVGEFRAHAAEWTANVTAEFKETRRRLSVEIYDKFQRATSVKRKL



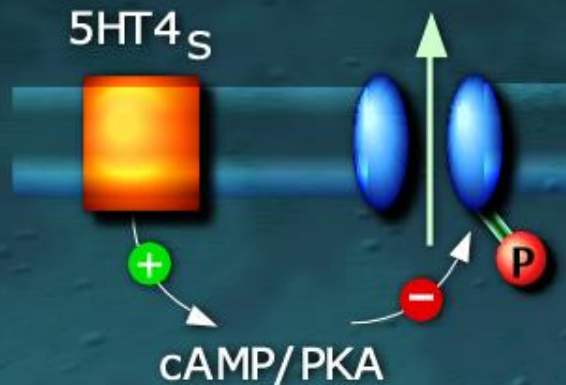
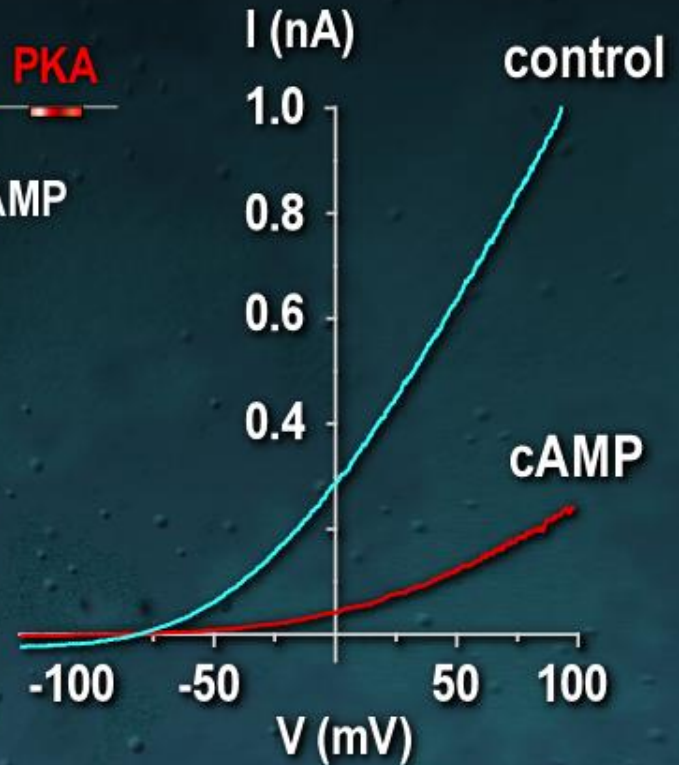
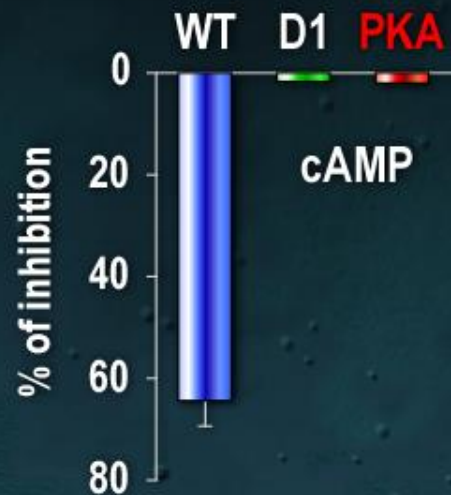
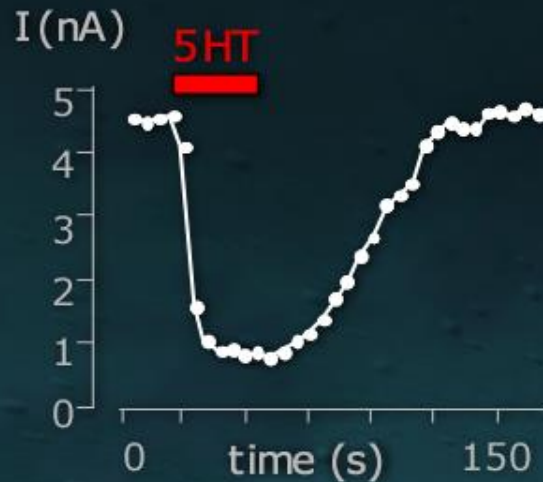
D1

PKA

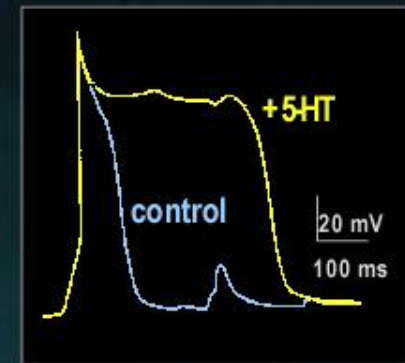
S333

PKA2

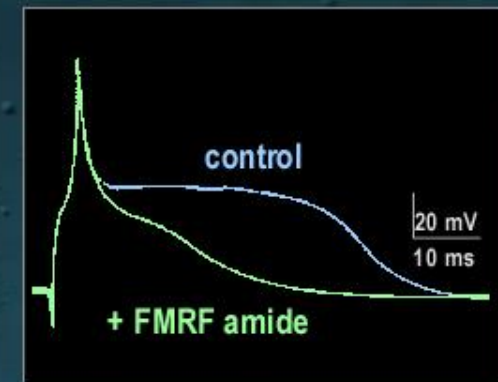
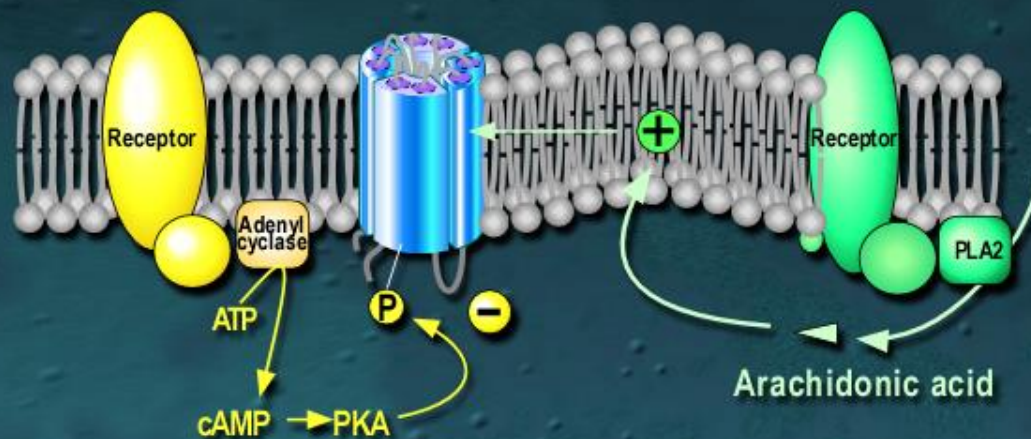
VLSMGDWLRVISKKTKEEVGEFRAHAAEWTANVTAEFKETRRRLSVEIYDKFQRATSVKRKL



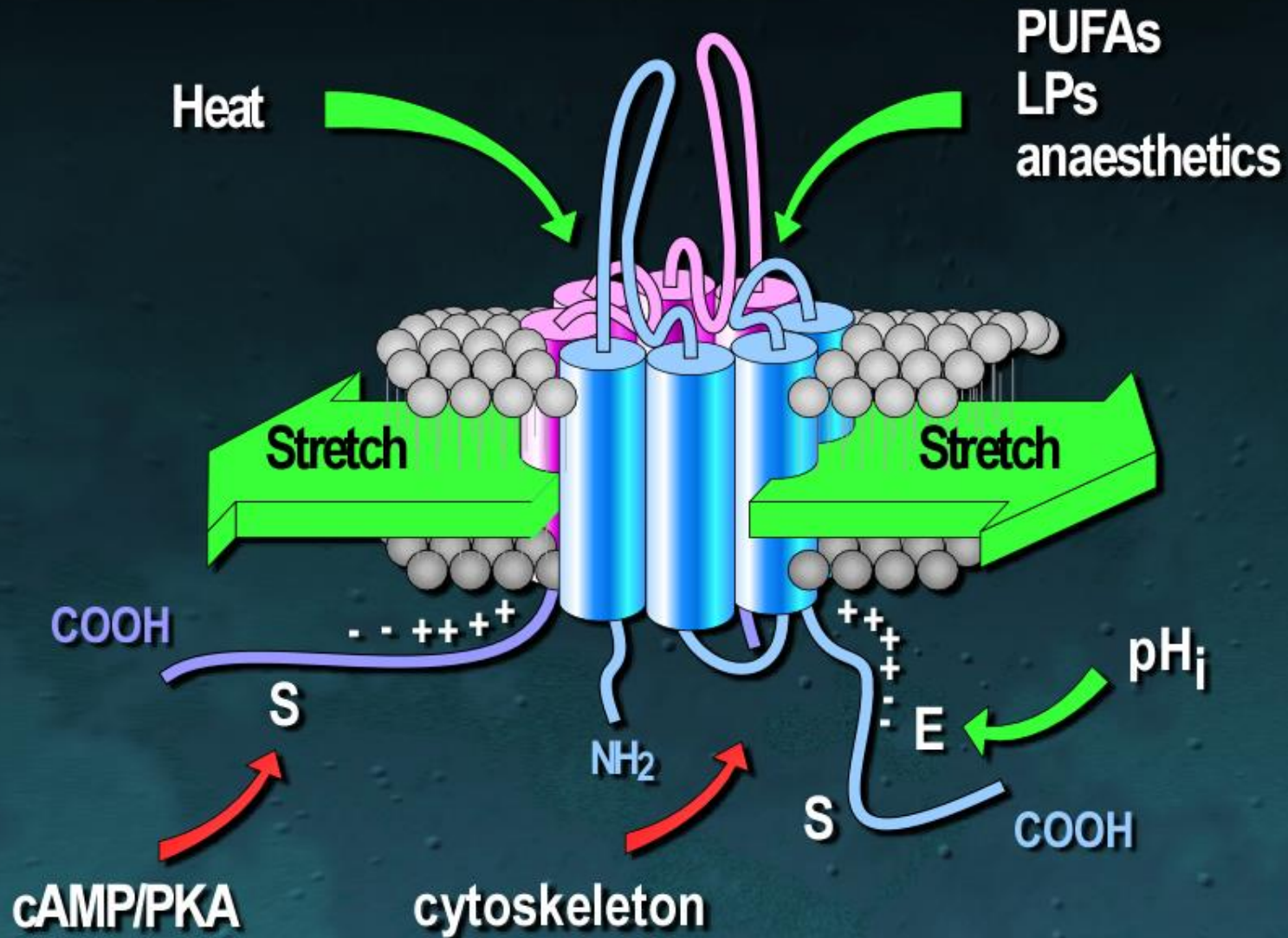
Presynaptic sensitization in *Aplysia* : role of the S-type K^+ channel



5HT S channel **FMRF amide**



TREK-1 is a polymodal K⁺ channel



Institut de Pharmacologie Moléculaire et Cellulaire

CNRS



Malika Arhatte
Charbel El Boustany
Anaïs Couvreur
Fabrice Duprat
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Université de Nice - Sophia Antipolis, FRANCE