Biochemical messengers: why calcium?

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THE BEGINNINGS

At the beginning, life on earth was made of single cells capable of carrying out all vital functions: the interplay with other cells was limited to the competition for nutrients Unicellular life was successful, as shown by the fact that unicellular organisms are still predominant today.

Nevertheless, for reasons that are not understood, 600 to 700 million years ago multicellular life appeared, in which cooperation replaced competition.

Cooperation soon led to the division of labor among cells, and naturally demanded the comunication of cells with each other: agents had to be developed that exchanged messages between cells.

All vital functions of cell are regulated: thus, the agents that exchanged messages from cell to cell had to be able to perform this regulatory function.

Calcium, the third most abundant metal in nature, was amply available to cells from the beginning. It was chosen as a regulatory messenger at an early evolutionary stage.

Why was calcium chosen ?

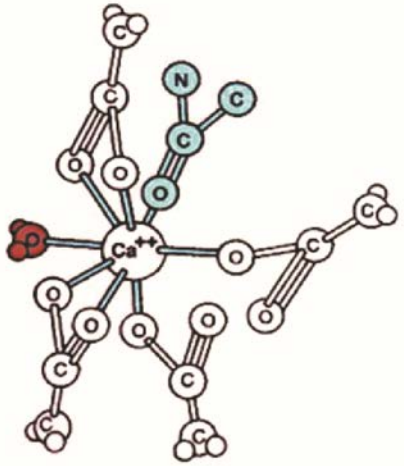
Because it is a very flexible ligand compared to the other three abundant cations of the environment: sodium, potassium, magnesium.

COORDINATION CHEMISTRY OF CALCIUM

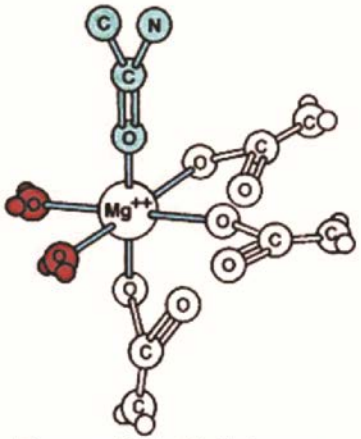
- The valency (i.e. its charge)
- The ionic radius, which determines its charge density
- The "*polarizability*", which defines the aptitude of its electron cloud to be distorted by external electrical forces
- The hydration energy, i.e., the easiness with which water molecules can be stripped off it
- Its hydrated radius, which determines its charge density

Properties of un-hydrated and hydrated Ca^{2+} and Mg^{2+}.

	Ionic radius	Polarizability	Hydration energy	Hydrated ions
	Å	$\alpha_0 \times 10^{24}$ cm^3	kcal/g ion	Å
Ca^{2+}	0.99	0.531	410	4.5
Mg^{2+}	0.65	0.012	495	5.9



Range of Ca-O distances
0.230-0.282 nm

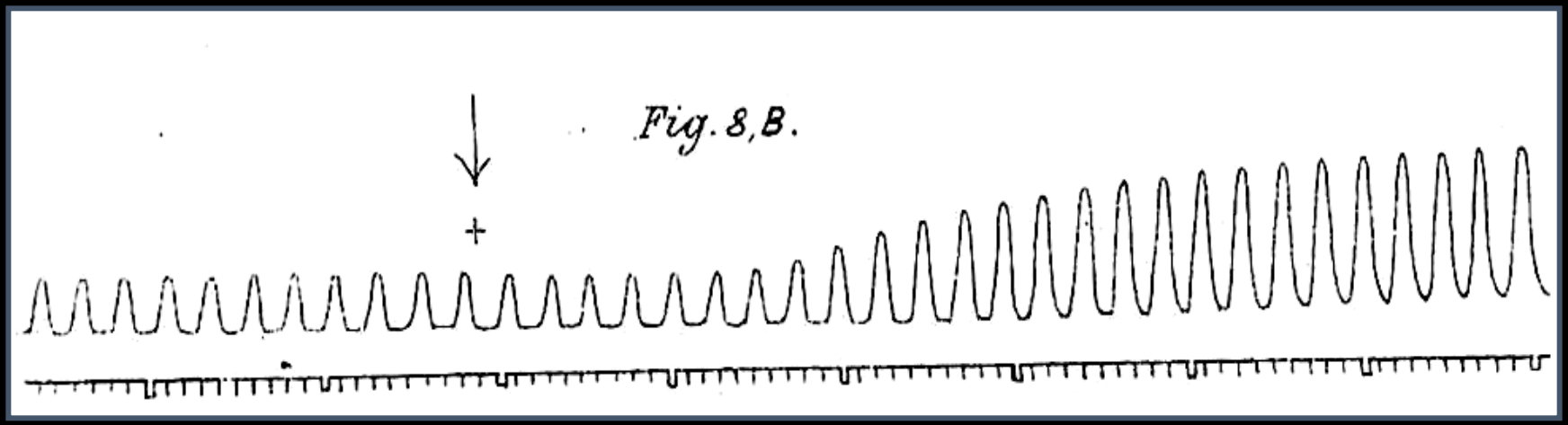


Range of Mg-O distances
0.200- 0.212 nm

Sidney Ringer

Born 1835, Norwich; died October 14, 1910, Lastingham, Yorkshire

...The heart contractility can not be sustained by saline solution nor by saline containing potassium chloride, nor with saline solution containing bicarbonate of soda, nor by saline solution containing bicarbonate of soda and potassium chloride....
.... A small quantity of calcium bicarbonate or calcium chloride added to saline solution..... makes a good artificial circulating fluid and the ventricle will continue beating perfectly for more than four hours....



Agents that transmit messages must be present within cells at very low levels. Their concentrations must be changed significantly and rapidly around the targets they regulate .This would demand unacceptable investments of energy if they were present within cells in high concentrations

INTRACELLULAR CALCIUM COMPLEXATION

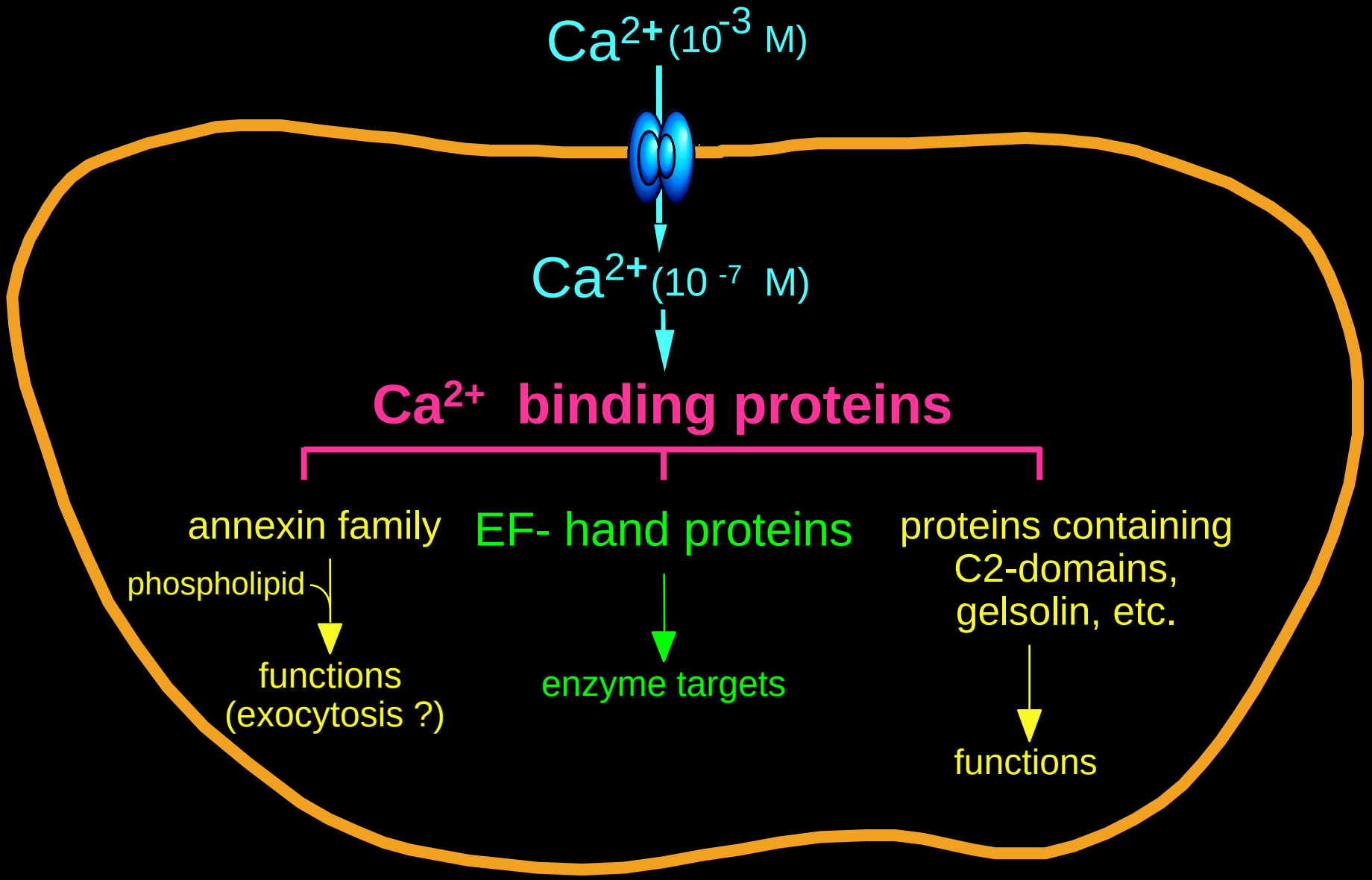
- Evolution has exploited the special coordination chemistry of calcium to develop complexing systems that would keep its intracellular concentration very low. Since the complexation had to occur in the presence of large excesses of other possibly competing ions, it had to be performed with high affinity and specificity: this demanded molecules of high structural complexity: i.e. it demanded proteins: they complex calcium to (reversibly) maintain its free concentration orders of magnitud lower than outside cells.

Cells live in an ambient in which calcium is far more concentrated that in their interior: mM versus nM. They are insulated from calcium in the environment, as their plasma membrane is impermeable to charged species. They only admit it to their interior under careful control through proteinaceous channels, in response to the demands of their calcium regulated systems. This inwardly directed high ”calcium pressure” is dynamically favourable, as it allows the rapid admittance of calcium to cells whenever regulation demands it

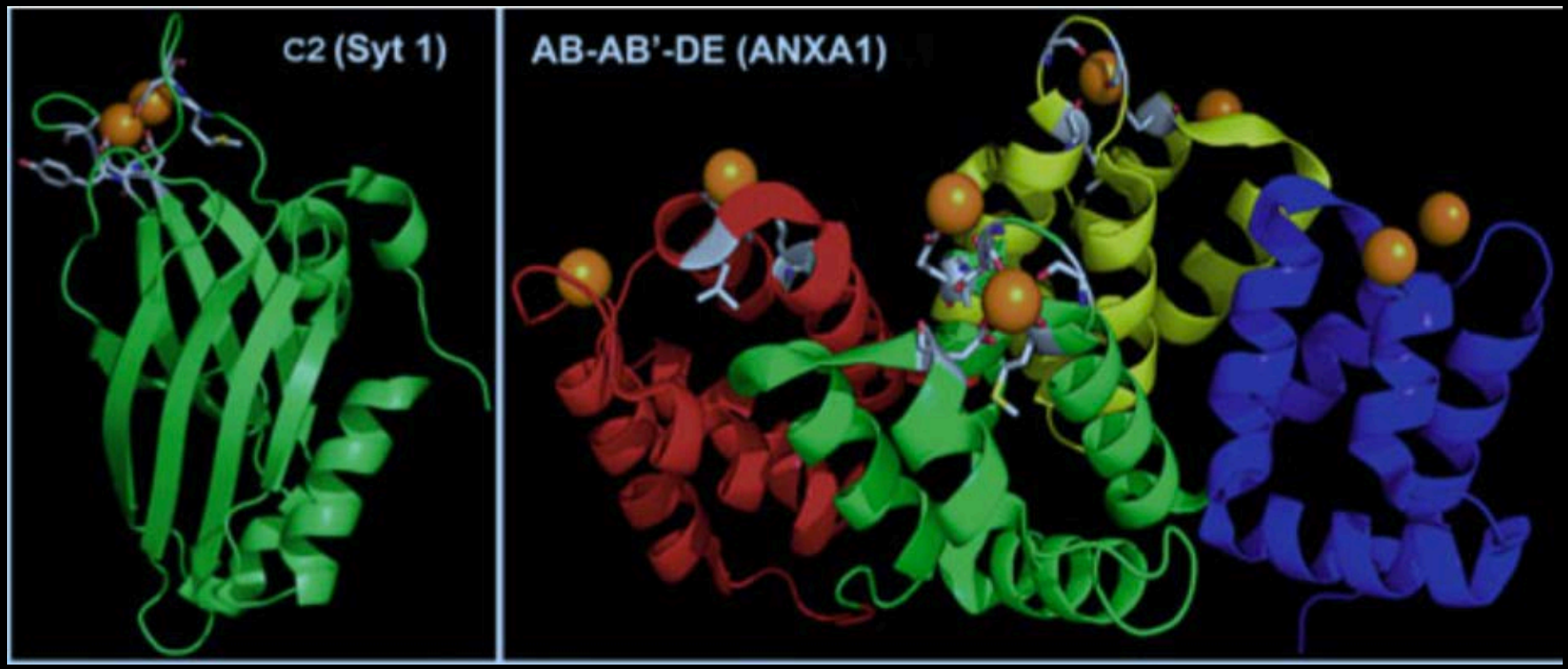
There was another important advantage in the choice of calcium as an intracellular carrier of signals.The energetic metabolism of cells is phosphate-oriented. The poor solubility of calcium phosphate salts demanded that calcium be kept very low inside cells, if phosphate was to be used as the energetic currency. Systems were thus developed which maintained intracellular calcium very low.

When this was accomplished, calcium had become an ideal carrier of signals

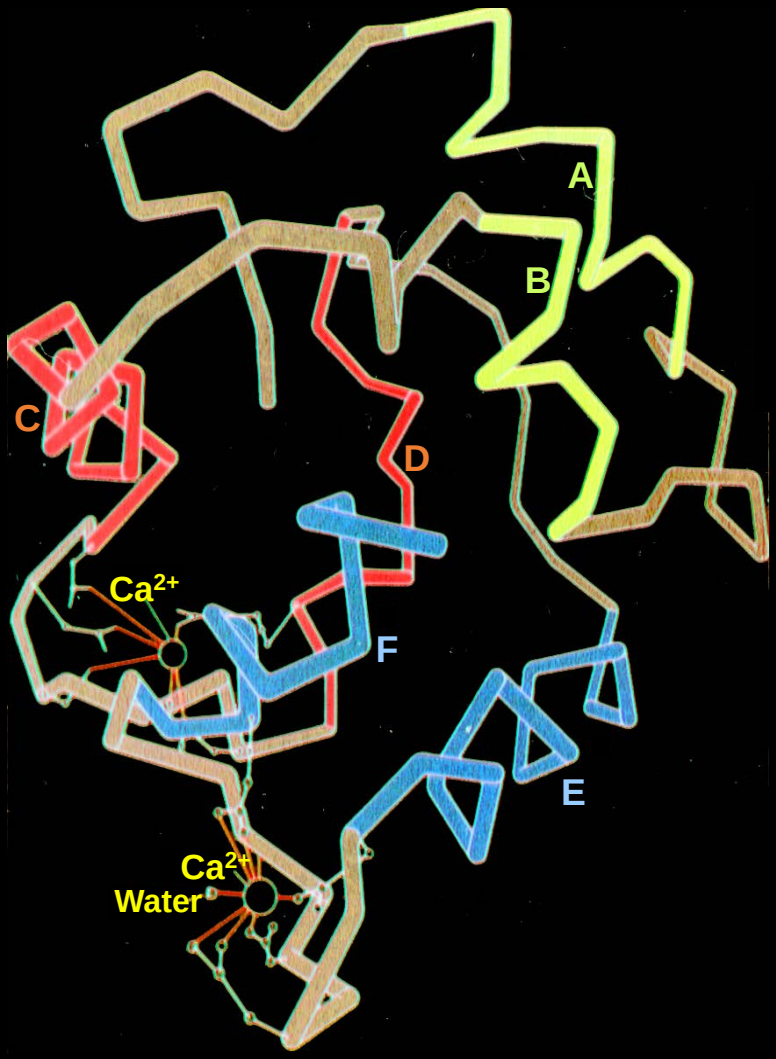
Proteins that bind Ca may simply buffer its concentration or may also decode its signal. The latter are called Ca-sensor proteins. They belong to several families



CRYSTAL STRUCTURE OF C2 DOMAINS AND OF ANNEXINS



CRYSTAL STRUCTURE OF PARVALBUMIN



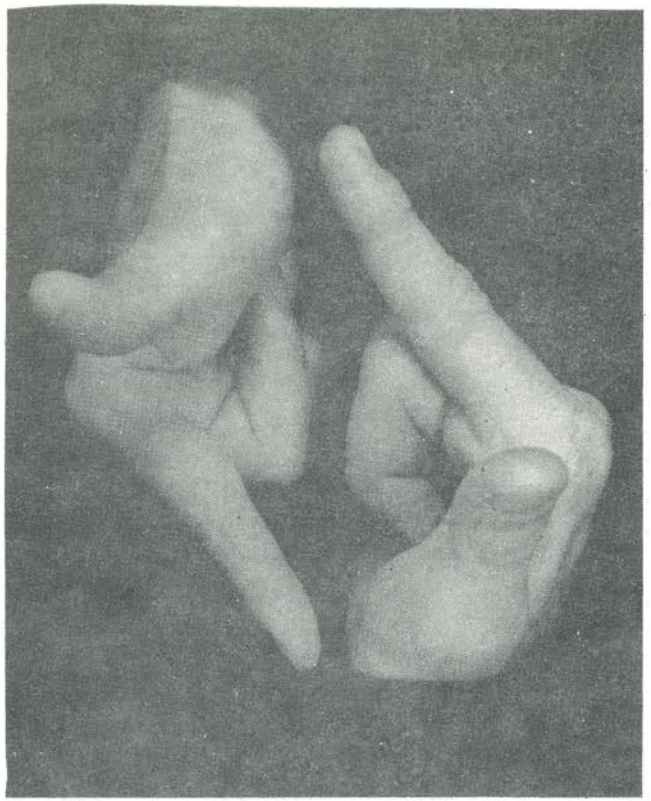
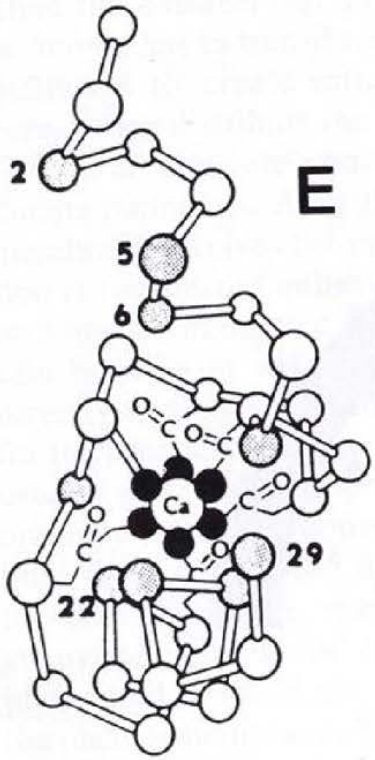
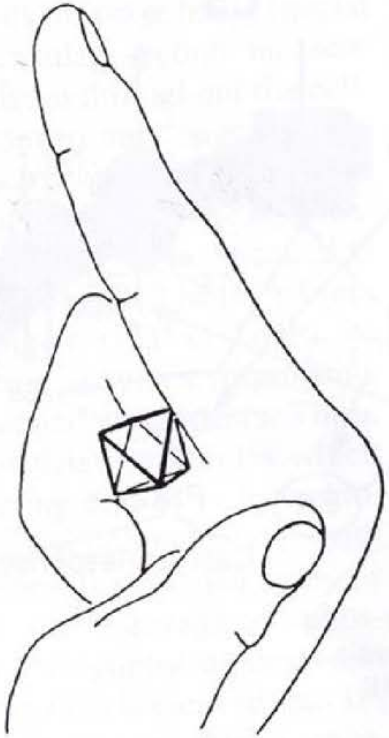


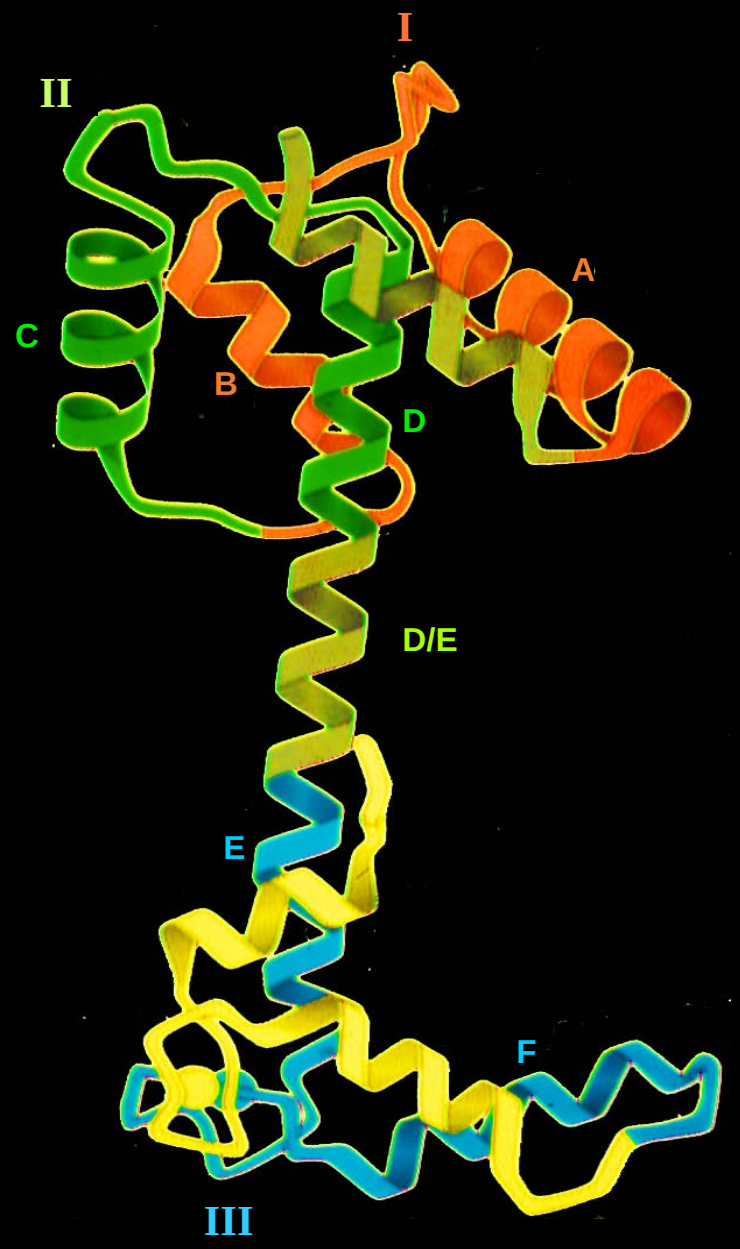
Fig. 2. The CD and EF regions are symbolized by a pair of right hands. Helix C (and helix E) runs from the tip to the base of the forefinger. The flexed middle finger corresponds to the CD (and to the EF) calcium binding loop. Helix D (and helix F) runs to the end of the thumb. The thumb representing helix D is tilted outward, representing the kink at leucine 65. In both Fig. 1 and 2 the loops are viewed from the interior of the protein looking outward



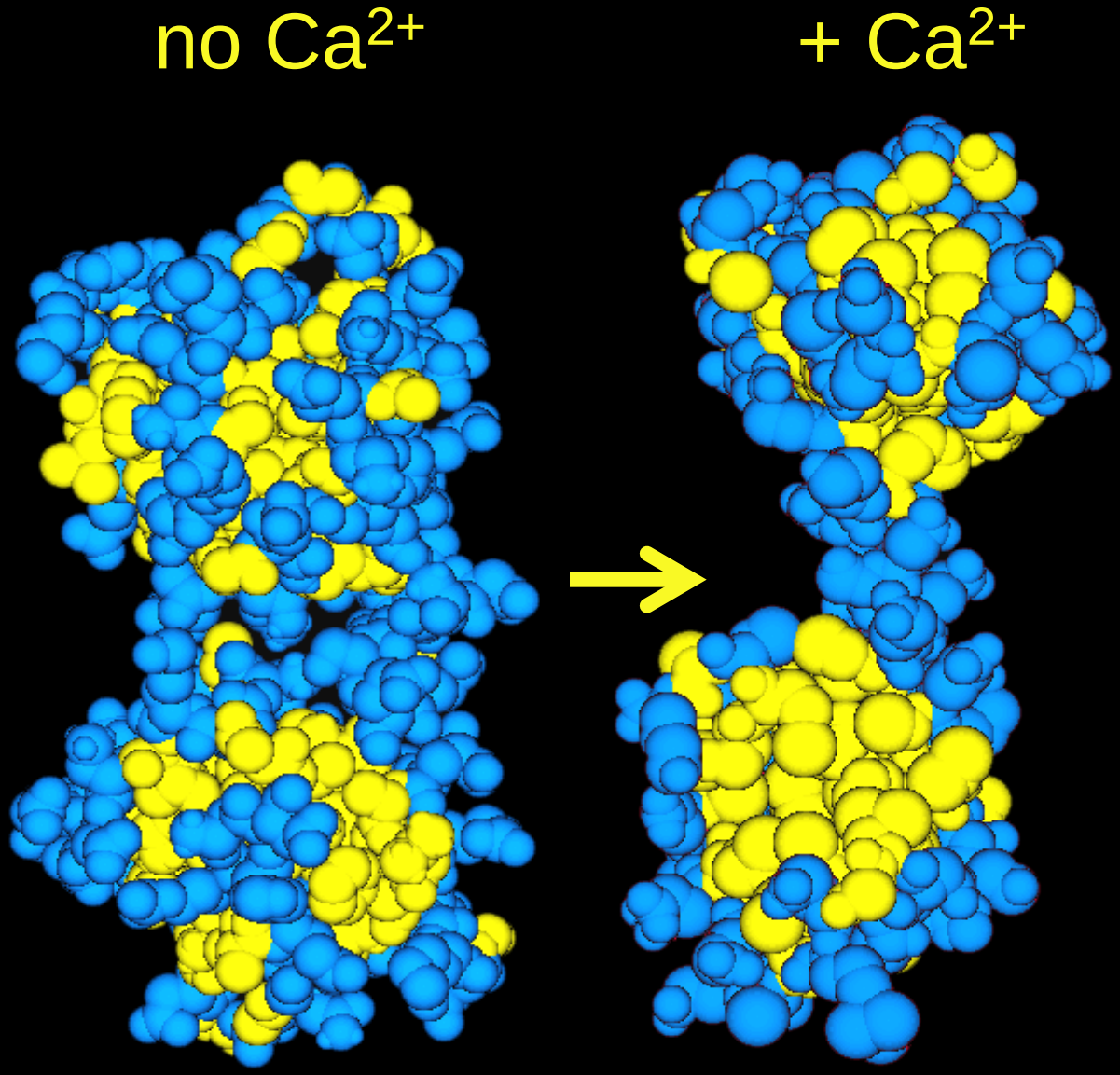
E



F



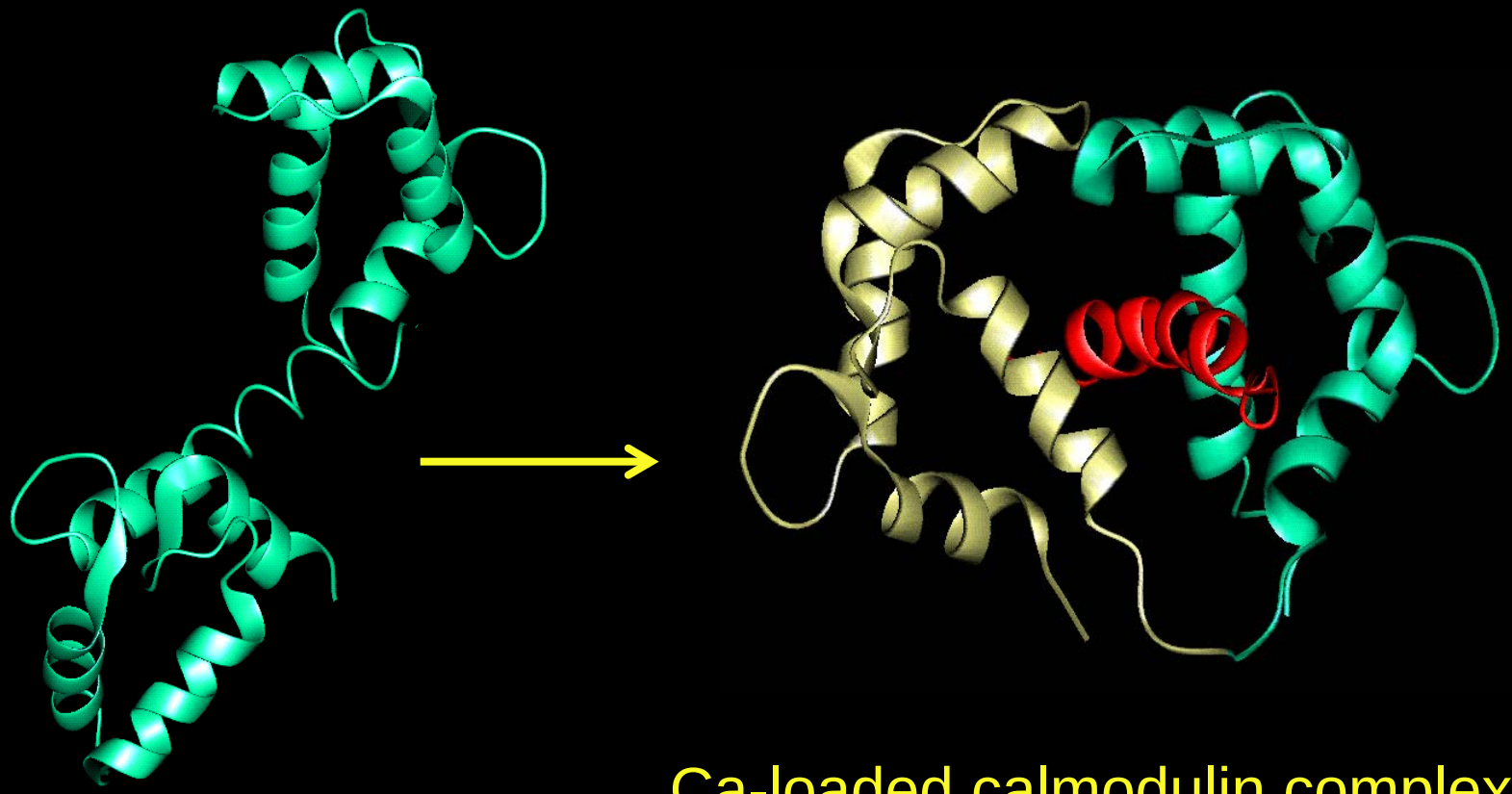
Troponin C, the calcium receptor in skeletal and heart muscles, is a very important EF-hand protein. It has two peripheral Ca-binding lobes, which bind two Ca^{2+} each, and a long central α-helix.



yellow = hydrophobic residues

The decoding of the calcium signal by EF-hand proteins has been best studied in calmodulin, which is an elongated molecule, with a long central helix connecting the two Ca-binding lobes.

The decoding occurs by two sequential changes of conformation: the first is the expression of hydrophobicity on the surface of the protein upon calcium binding.

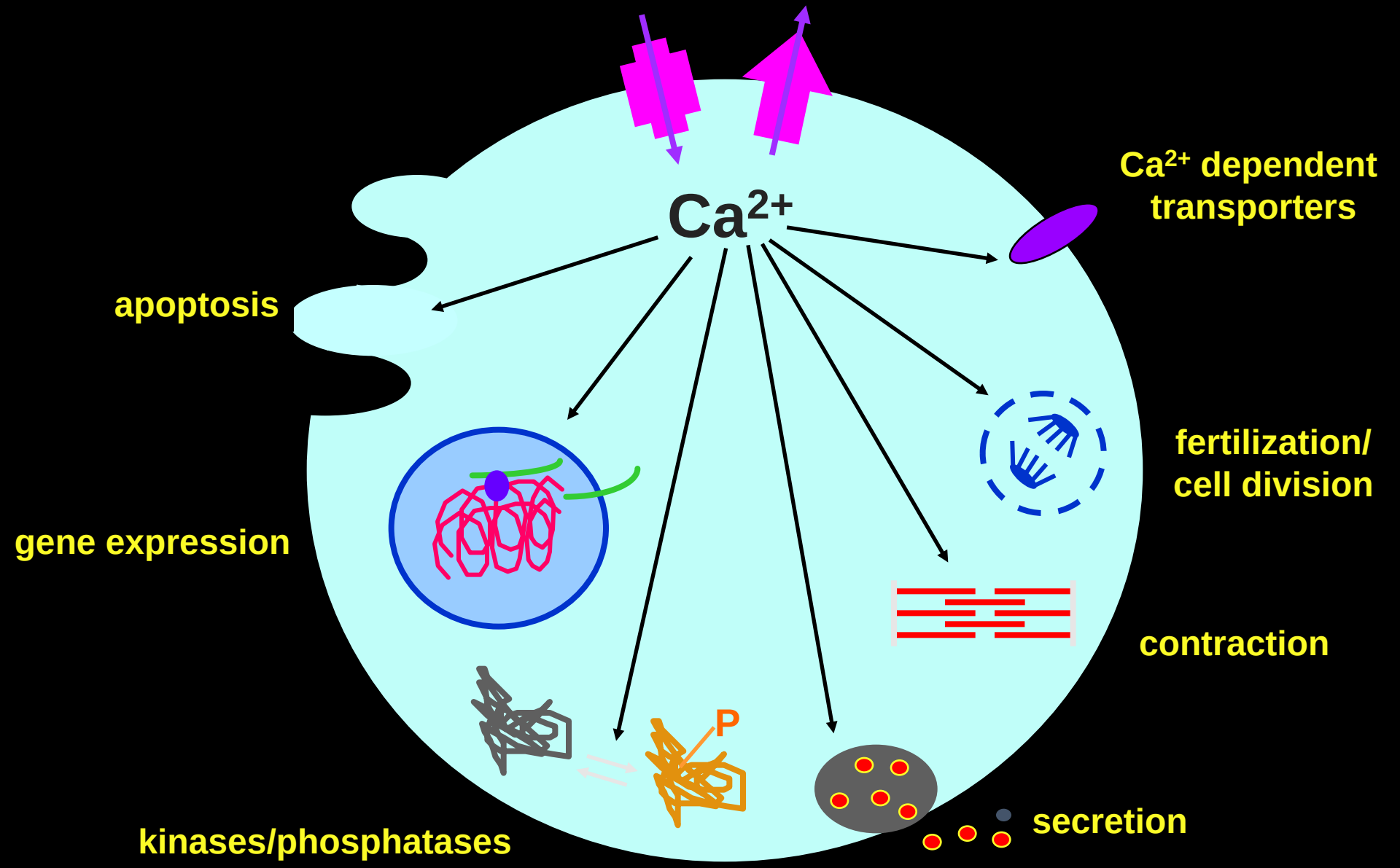


Ca-loaded calmodulin

Ca-loaded calmodulin complexed with a binding domain

The second conformational change in the decoding process is the collapse of the central helix of calmodulin to form an hairpin structure wrapped around the specific “binding”domain of target enzymes

Ca^{2+}- modulated functions in mammalian cells



CALCIUM-MODULATED FUNCTIONS

Metabolism: generation of fuels
Glycogenolysis (phosphorylase b kinase)
Glycerophosphate dehydrogenase
Pyruvate dehydrogenase phosphate phosphatase
NAD-dependent isocitric dehydrogenase
Ketoglutarate dehydrogenase
NADH dehydrogenase (plant mitochondria)
Hydroxybutyrate dehydrogenase
Lipases and phospholipases

Membrane-linked functions
Excitation-contraction coupling
Excitation-secretion coupling (*e.g.* neurotransmitter release)
Action potentials
Tight junctions
Cell contact
Calcium-transporting ATPases
Channels in the plasma membrane and organelles
Plasma membrane-vesicles fusion

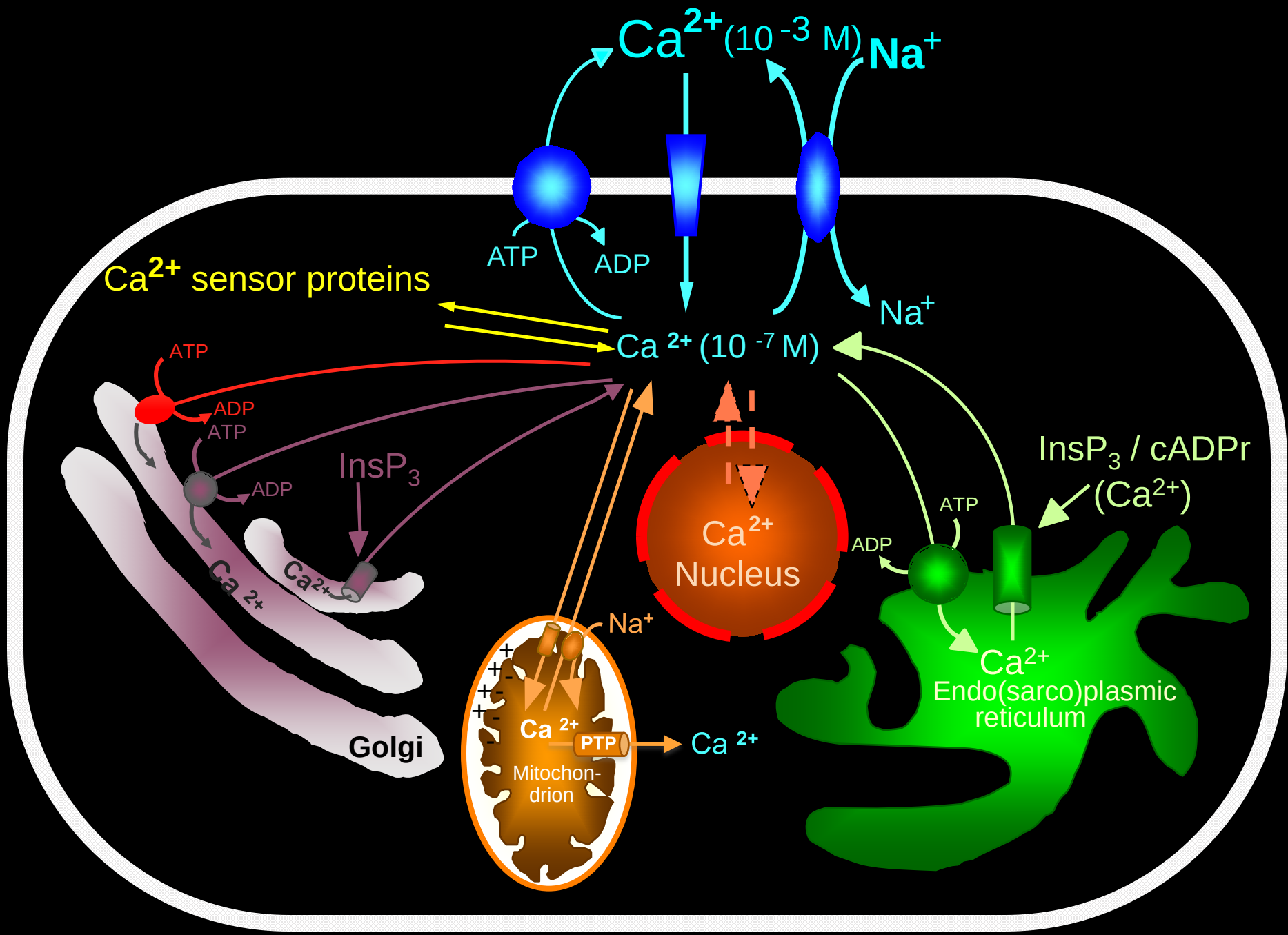
Hormonal regulation
Formation/degradation of cyclic AMP and GMP
Release of several hormones

Contractile and motile systems
Muscle myofibrils
Cilia and flagella
Microtubules and microfilaments
Cytoplasmic streaming
Pseudopod formation

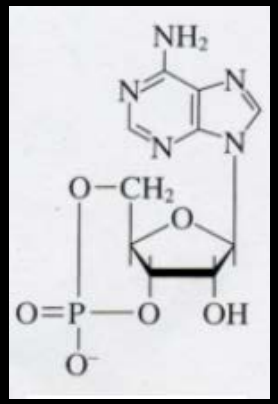
Miscellaneous functions
Fertilization
Bone metabolism
Proteases
Protein kinases
Protein phosphatase (calcineurin) Production of messengers (*e.g.* NO)
Gene expression
Neurogenesis and memory
Vision
Apoptosis

The Ca-buffering capacity of the Ca-sensor proteins is limited by their total intracellular concentration. Situations may arise in which the amount of Ca to be buffered exceeds the total capacity of Ca-decoding proteins.

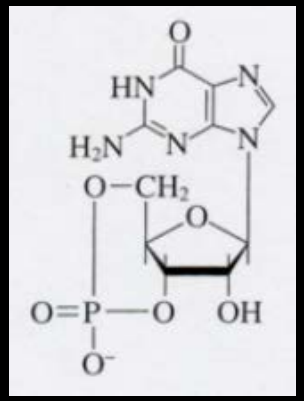
To overcome the quantitative Ca-buffering limitations of Ca-processing intracellular proteins, which are mostly present in the cystosol, evolution has developed other classes of Ca-binding proteins which are intrinsic to membranes. Their Ca buffering capacity has no quantitative limitations. They buffer very large amounts of Ca even if present in minute amounts: they pick up Ca at one side of a membrane, discharge it to the other side, and "return" uncomplexed for the next binding and transport cycle. Thus, the buffering of intracellular Ca is performed essentially by membrane-intrinsic Ca-binding proteins.


Ca2+ (10 -3 M)
Na+
ATP
ADP
Ca2+ sensor proteins
Na+
Ca 2+ (10 -7 M)
ATP
ADP
ATP
ADP
InsP3
Ca2+
Ca2+
Golgi
Ca2+
Nucleus
InsP3 / cADPr
(Ca2+)
ATP
ADP
Ca2+
Endo(sarco)plasmic
reticulum
Na+
Ca 2+
PTP
Ca 2+
Mitochon-
drion

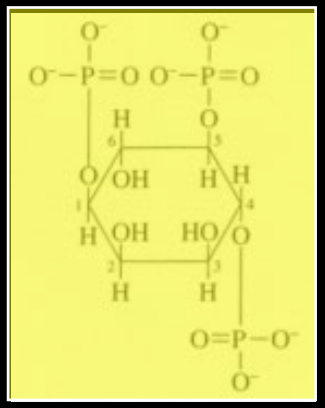
The “second messengers” that regulate the cellular homeostasis of calcium



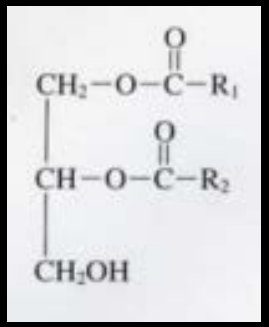
Cyclic AMP



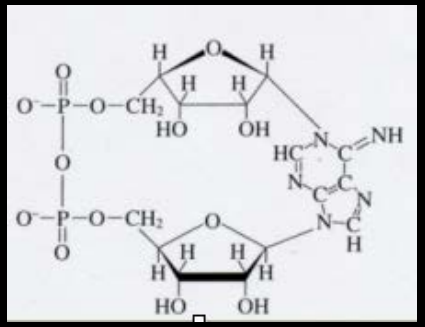
Cyclic GMP



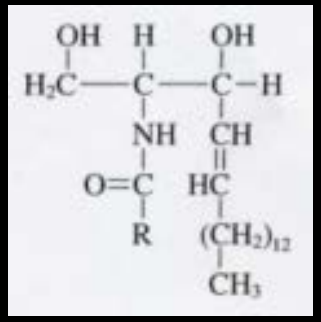
1,4,5 Inositol tris-phosphate



Diacylglycerol



Cyclic ADP ribose



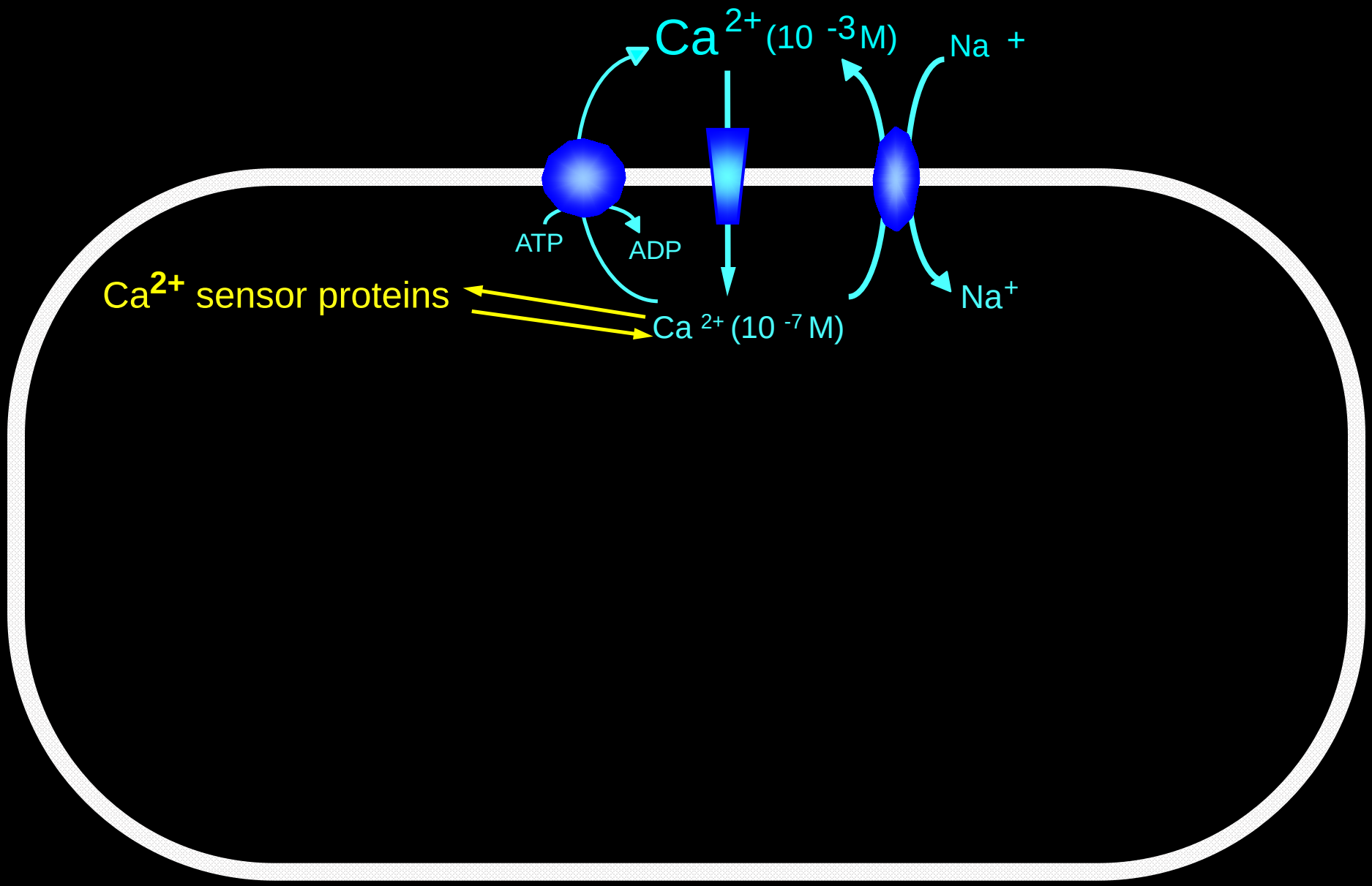
Ceramide

Ca^{2+}

Calcium

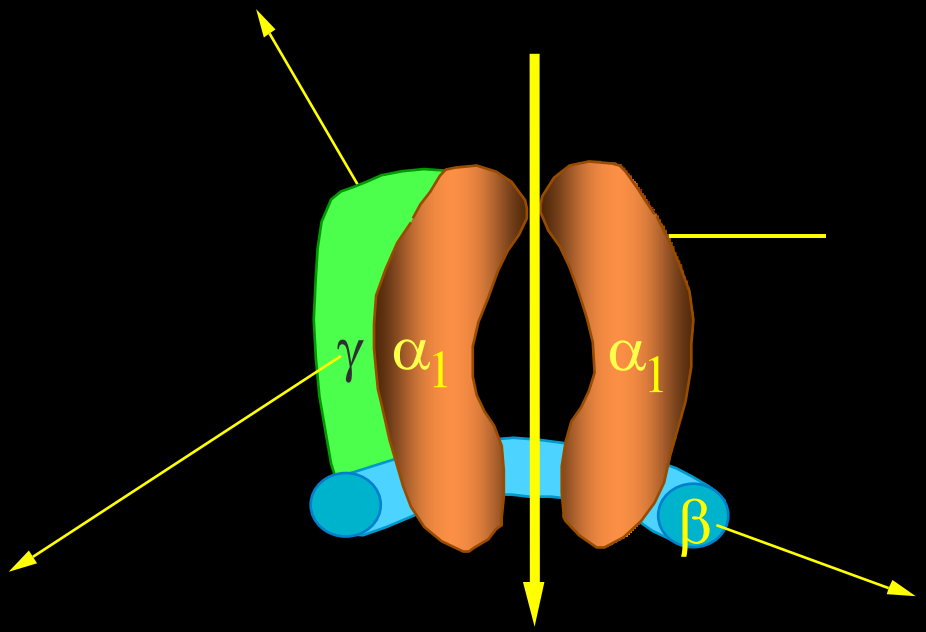
N=O •

Nitrogen monoxide


Ca 2+ (10 -3 M)
Na +
ATP
ADP
Ca2+ sensor proteins
Ca 2+ (10 -7 M)
Na+

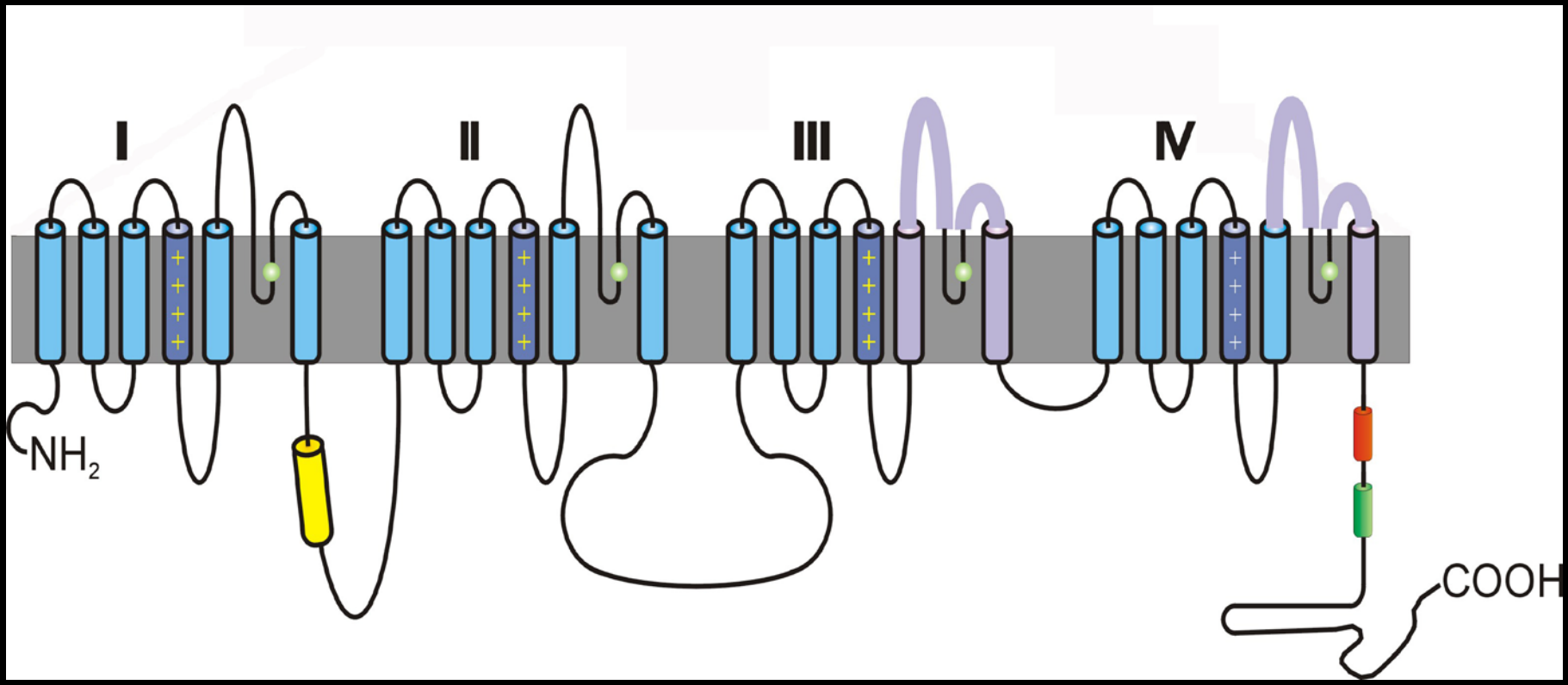
Plasma membrane Ca^{2+}-channels

voltage-gated (L type)



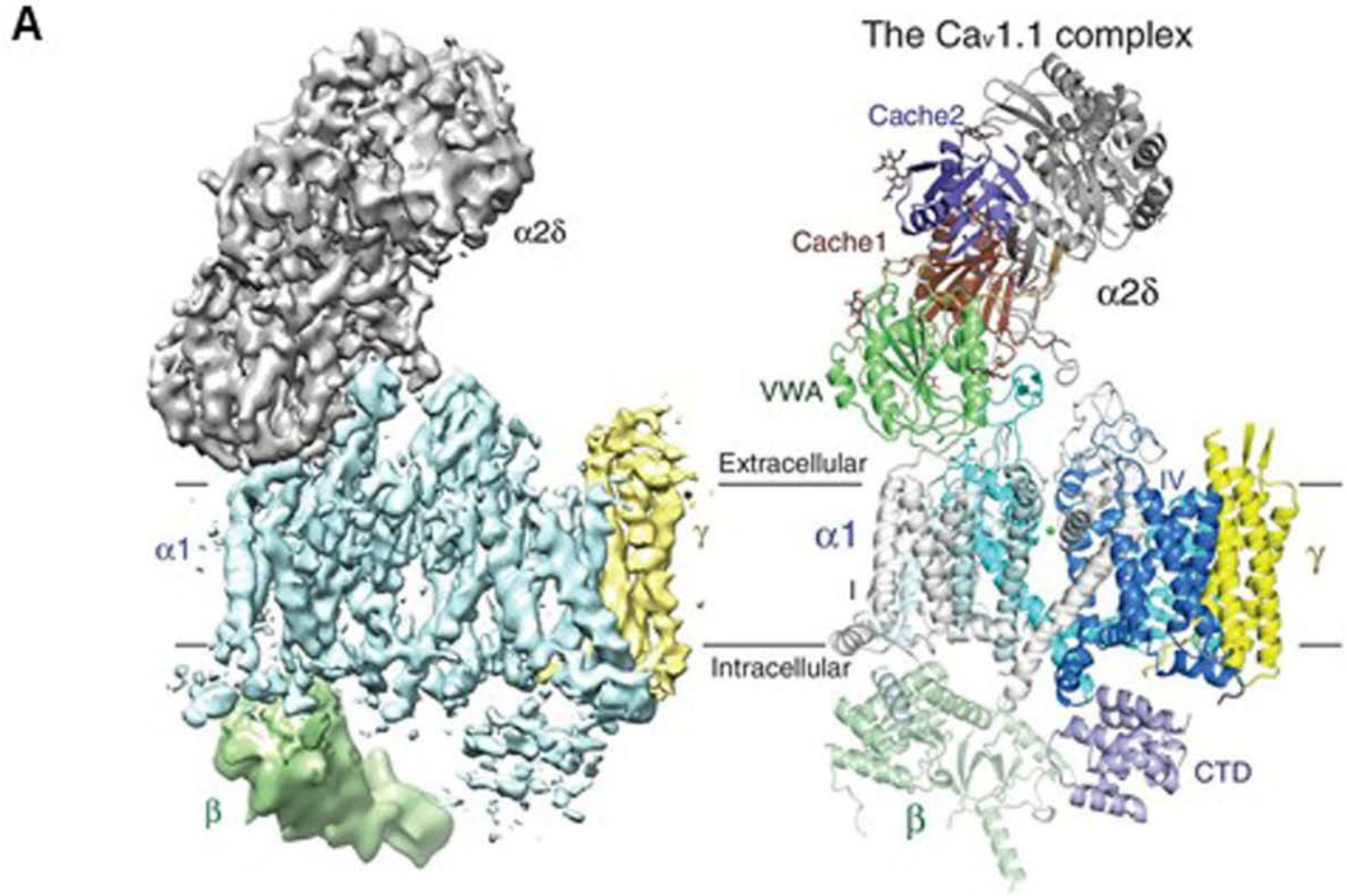
(N, T, P/Q, R channels are also known)

The α subunit of the L-type calcium channels

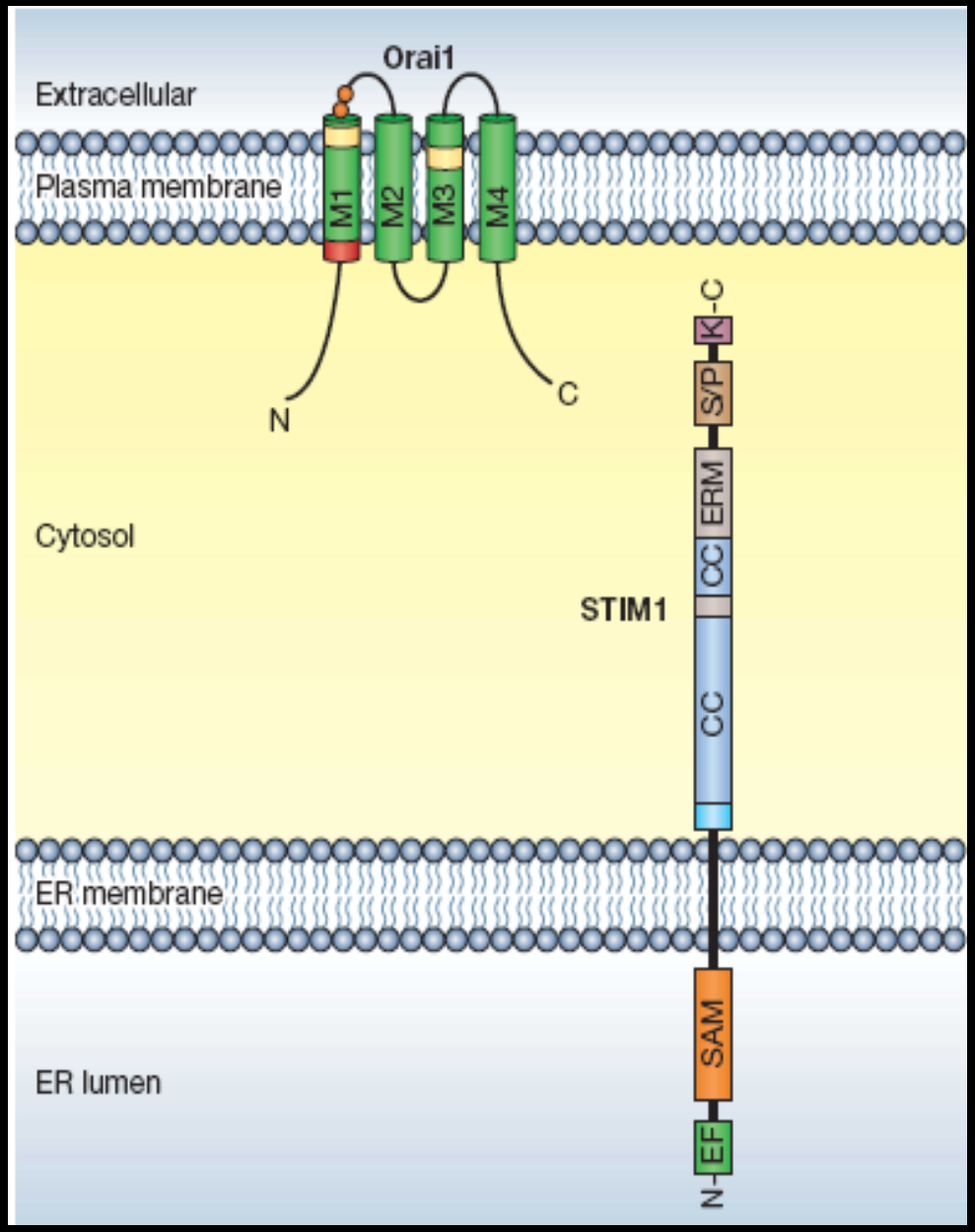


The **yellow** cylinder is the binding site for β-γ subunit of G-proteins (only present in some α subunit families)
The **red** cylinder is a EF-hand motif
The **green** cylinder is an IQ calmodulin binding domain
The sphere in the folded in loops is a conserved glutamate residue

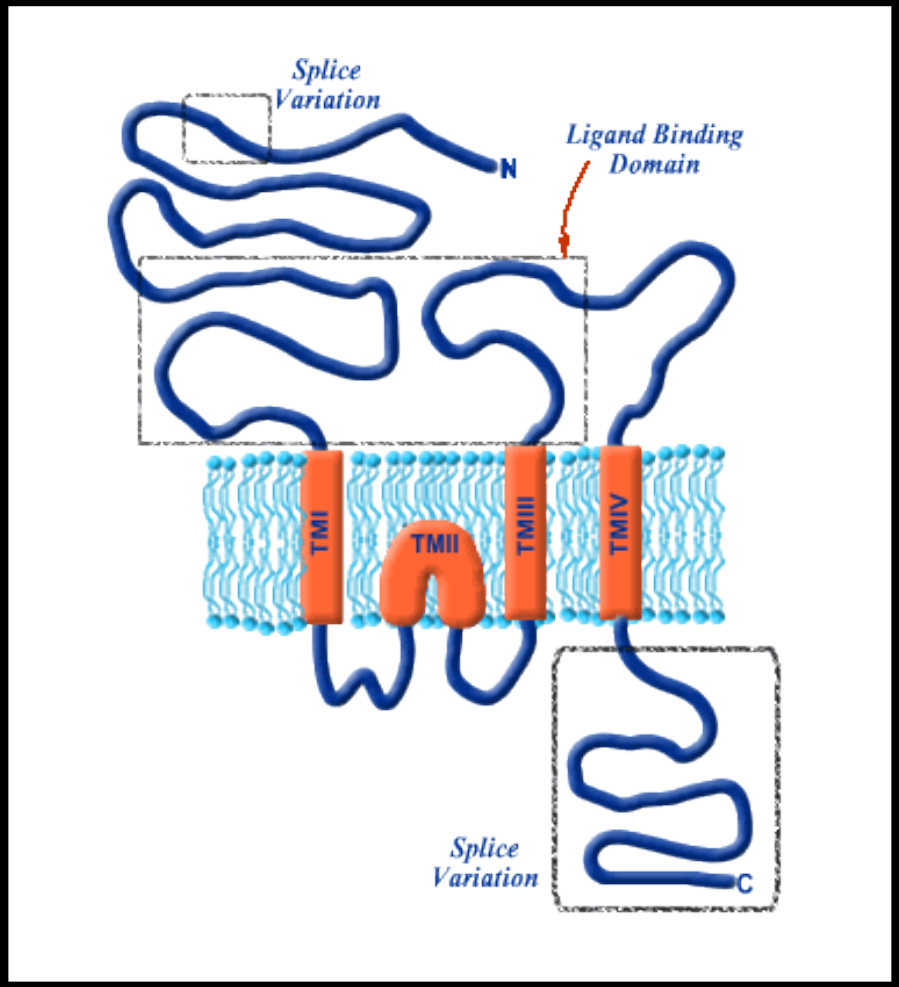
3D structure of the L-type calcium channel



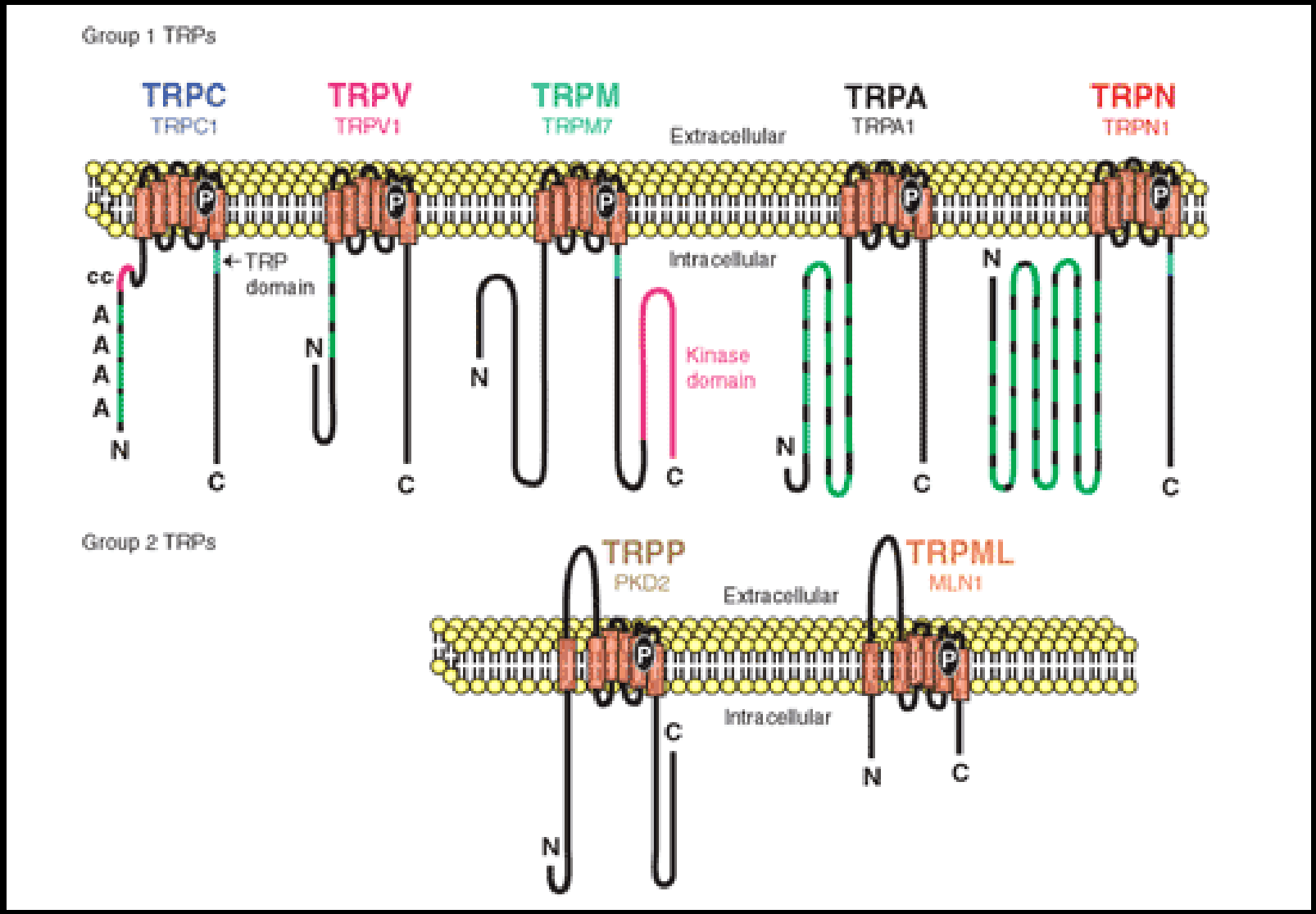
Store Operated plasma membrane Calcium Channels (SOC)



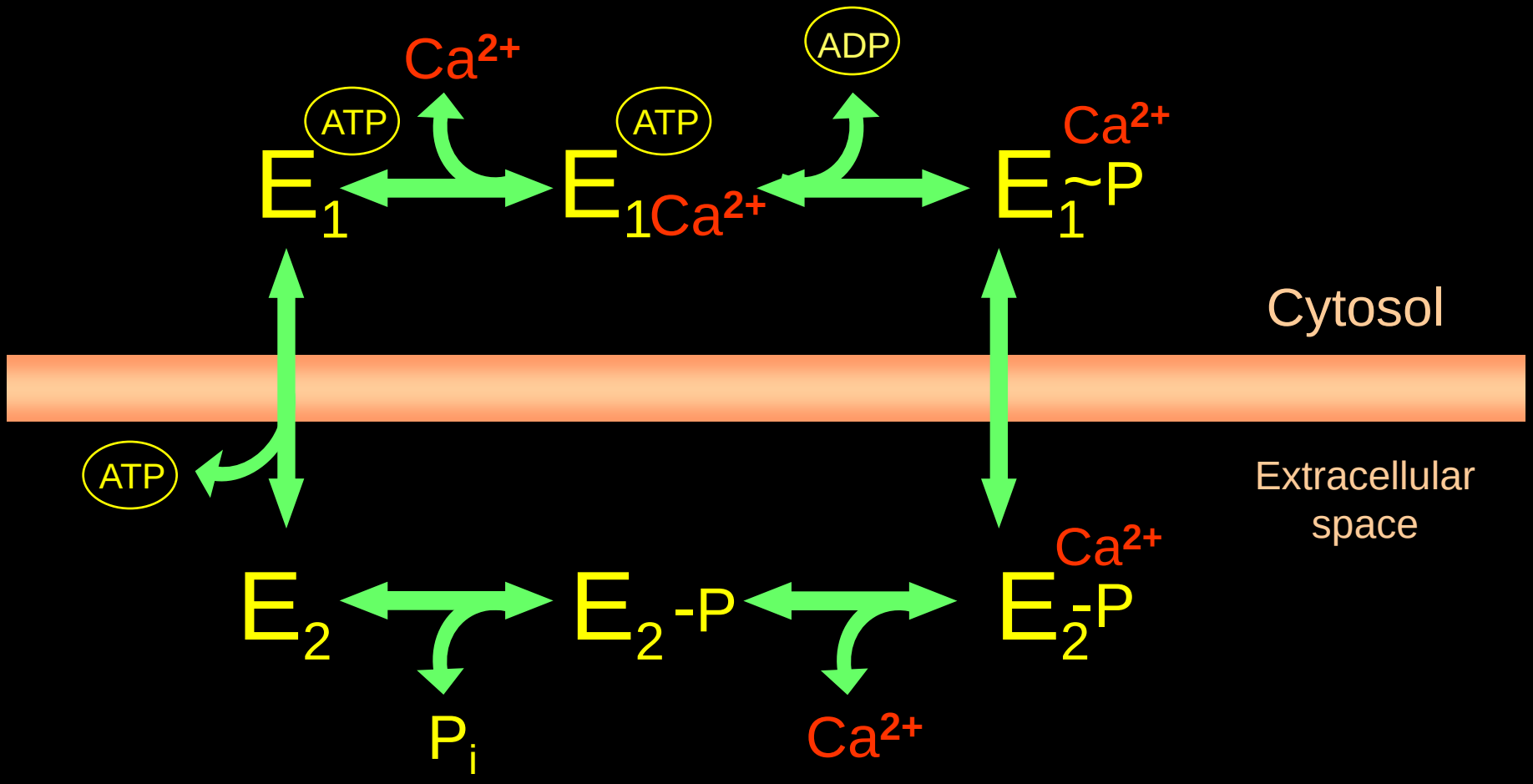
The ligand-gated plasma membrane calcium channels (the neuronal NMDA receptor)



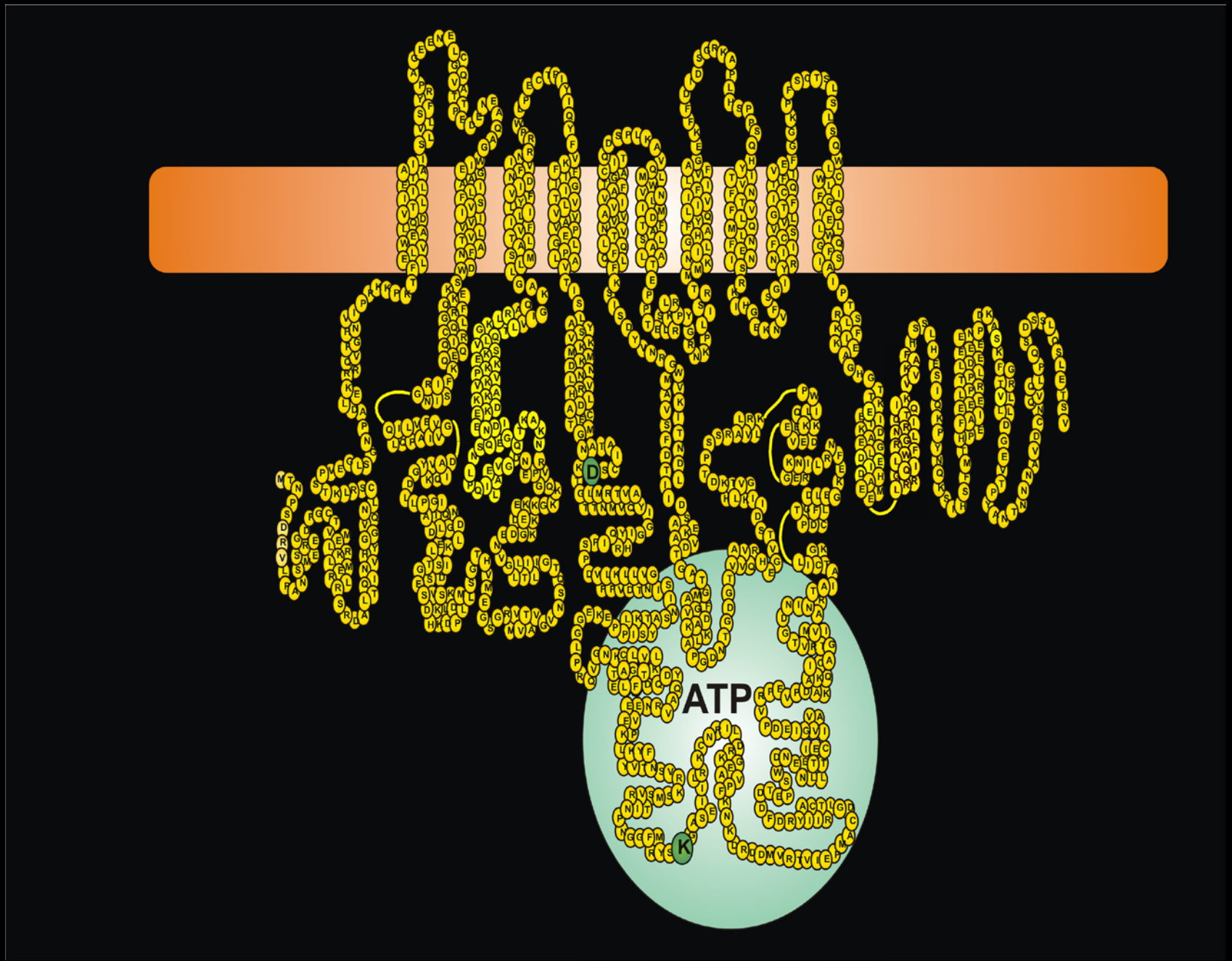
TRP (Transient Receptor Potential) plasma membrane channels



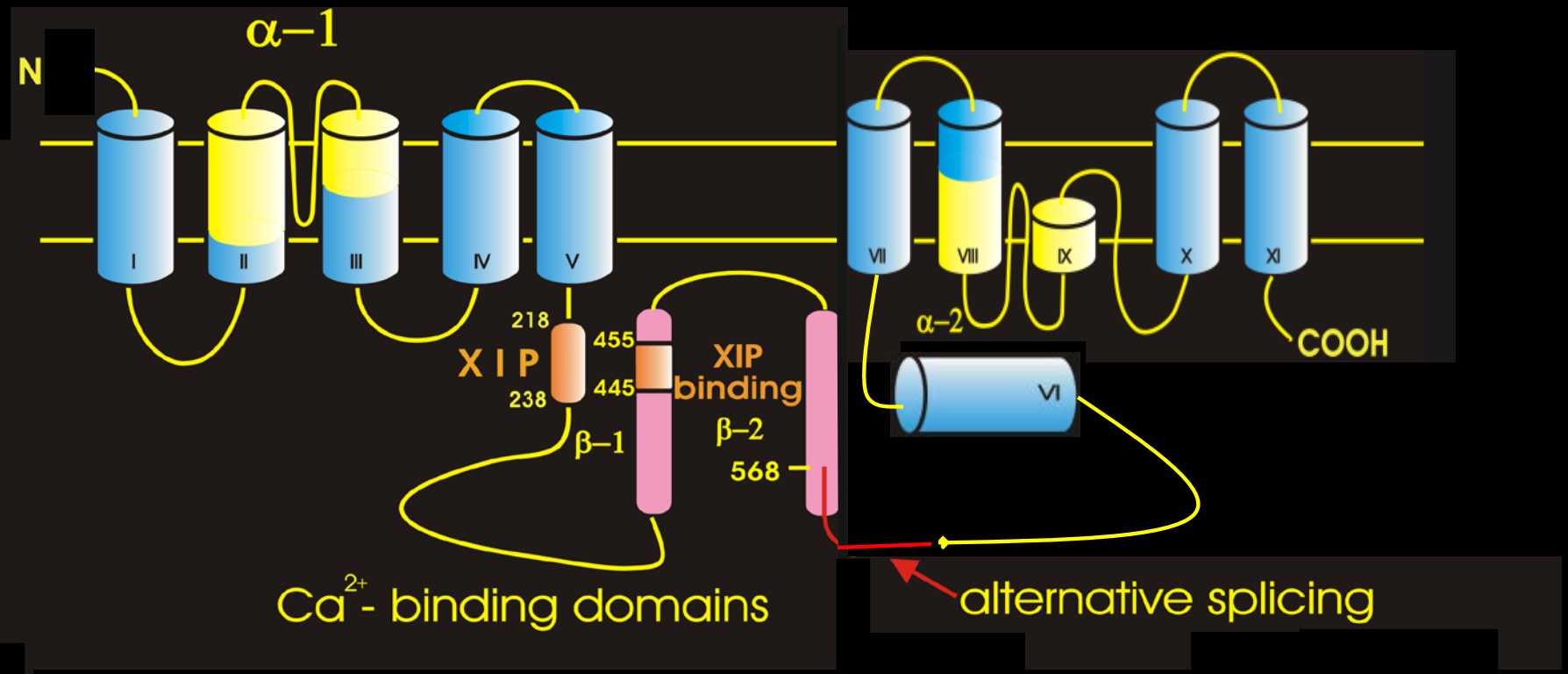
Catalytic cycle of calcium ATPases (calcium pumps)

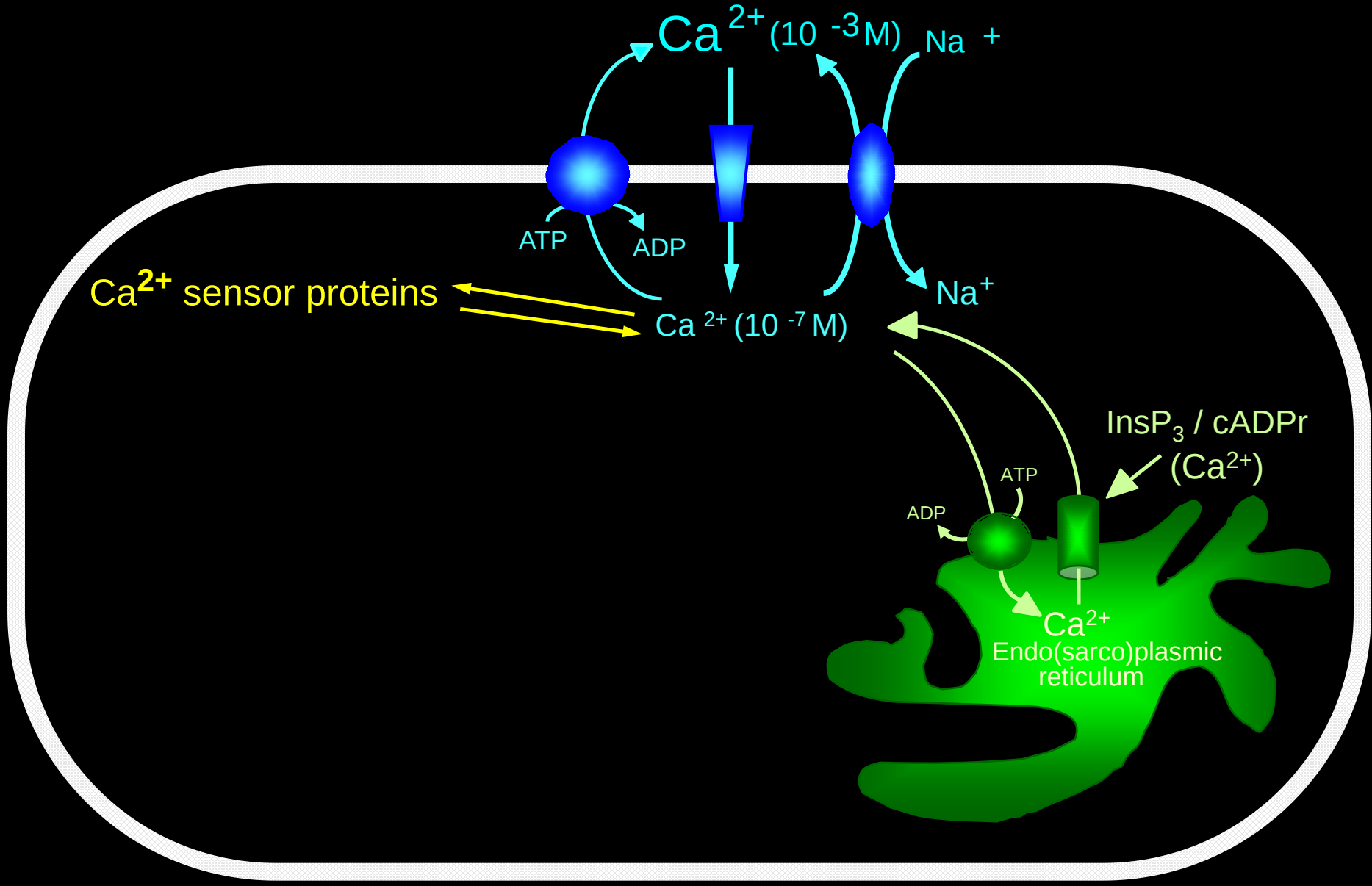


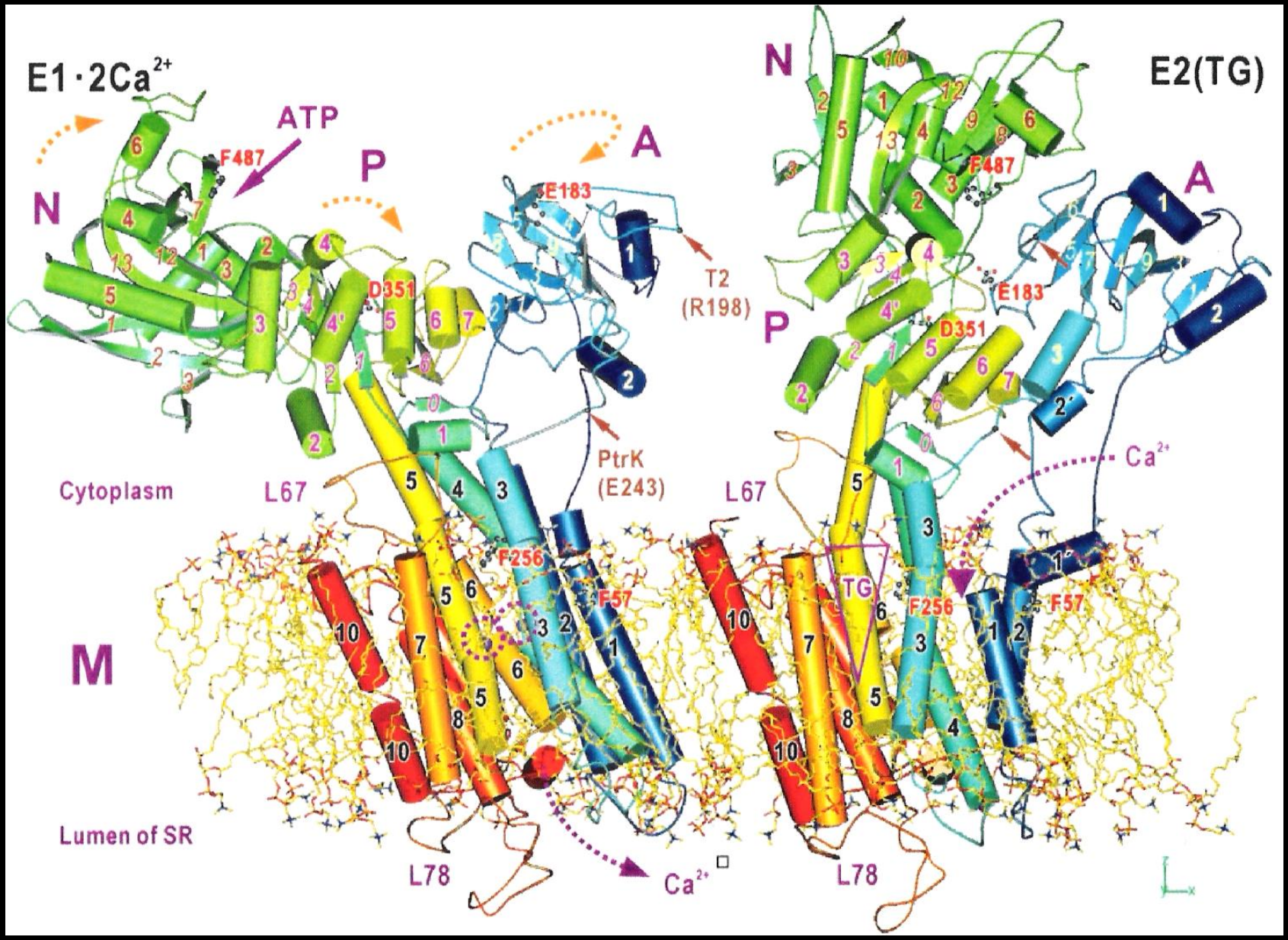
The plasma membrane calcium ATPase

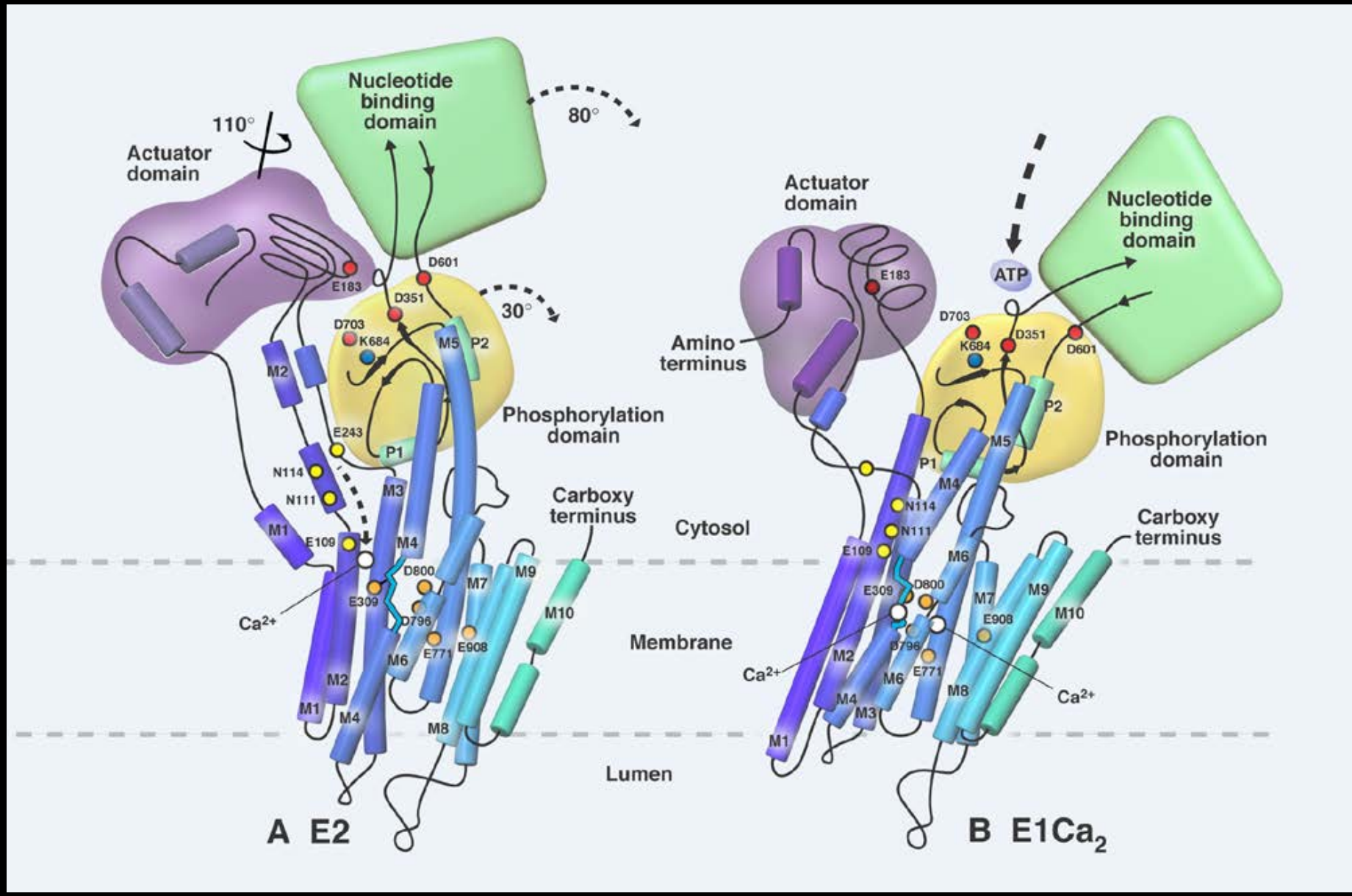


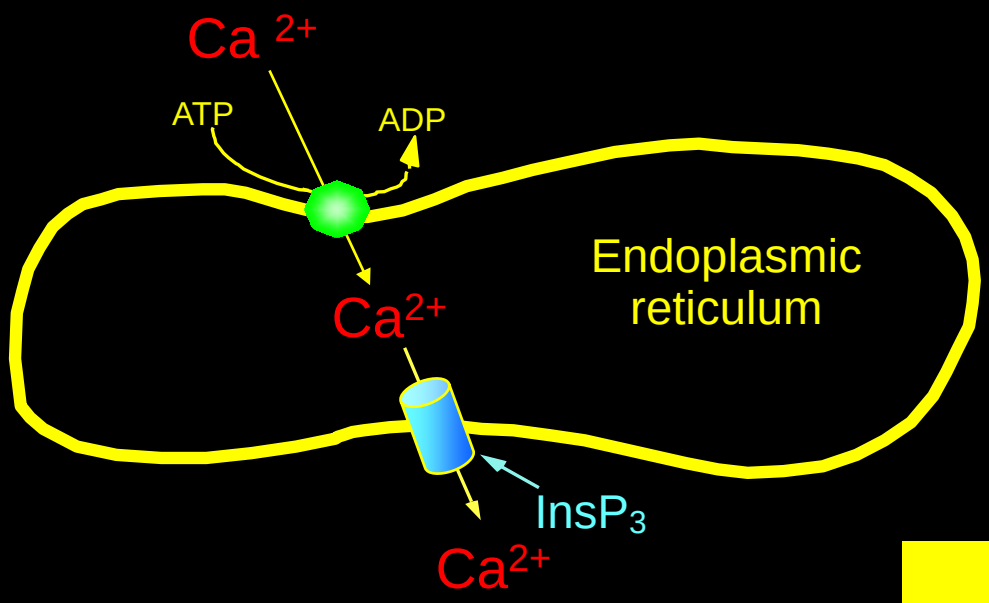
The Na/Ca exchanger of the plasma membrane

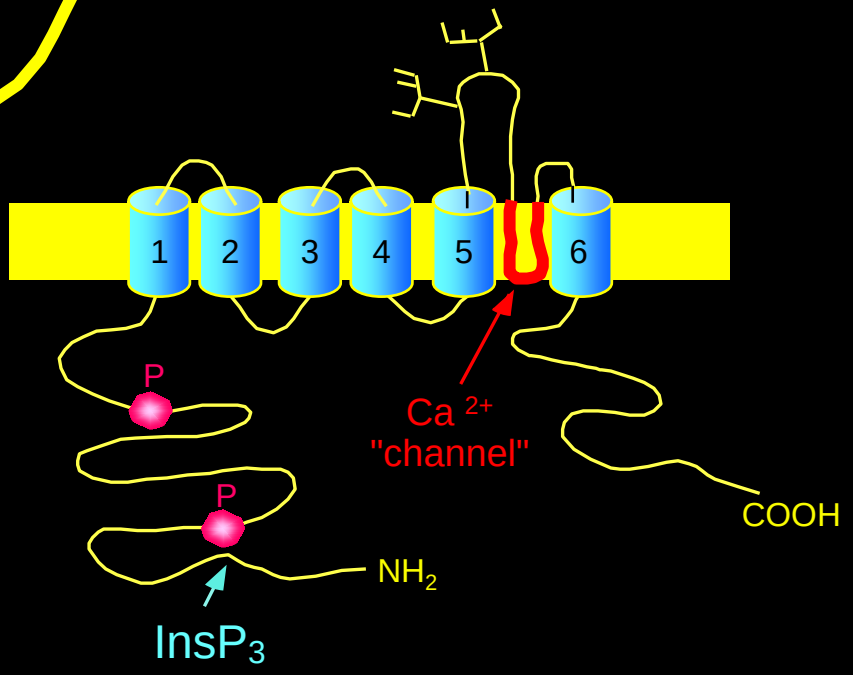



Ca 2+ (10 -3 M)
Na +
ATP
ADP
Ca2+ sensor proteins
Ca 2+ (10 -7 M)
Na+
InsP3 / cADPr
(Ca2+)
ATP
ADP
Ca2+
Endo(sarco)plasmic
reticulum


E1·2Ca2+
ATP
F487
N
P
A
E183
T2
(R198)
D351
PtrK
(E243)
Cytoplasm
L67
F256
F57
M
Lumen of SR
L78
Ca2+
E2(TG)
TG

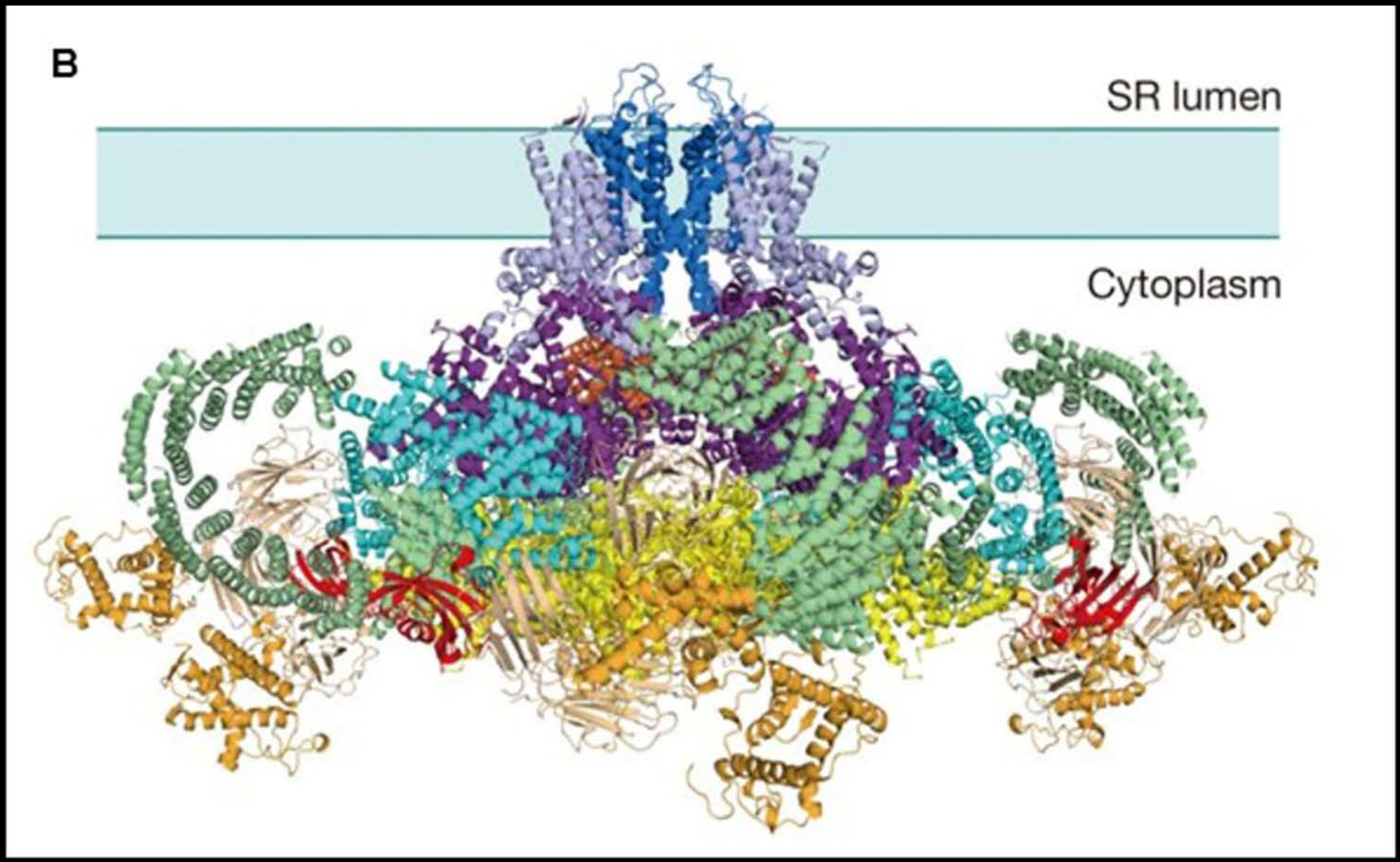

Nucleotide binding domain
110°
80°
Actuator domain
D601
E183
D351
30°
D703
K684
M5
P2
M2
Phosphorylation domain
E243
P1
N114
N111
M3
Carboxy terminus
M1
E109
M4
D800
M7
M9
E309
D796
M10
Ca2+
E908
E771
M6
M2
M1
M4
M8
Cytosol
Membrane
Lumen
A E2
Actuator domain
Nucleotide binding domain
ATP
E183
Amino terminus
D703
D351
D601
K684
P2
M5
Phosphorylation domain
P1
M4
N114
N111
Carboxy terminus
E109
M6
D800
E309
M7
M9
E908
M10
D796
M2
E771
Ca2+
M6
M8
M4
M3
M1
Ca2+
B E1Ca2

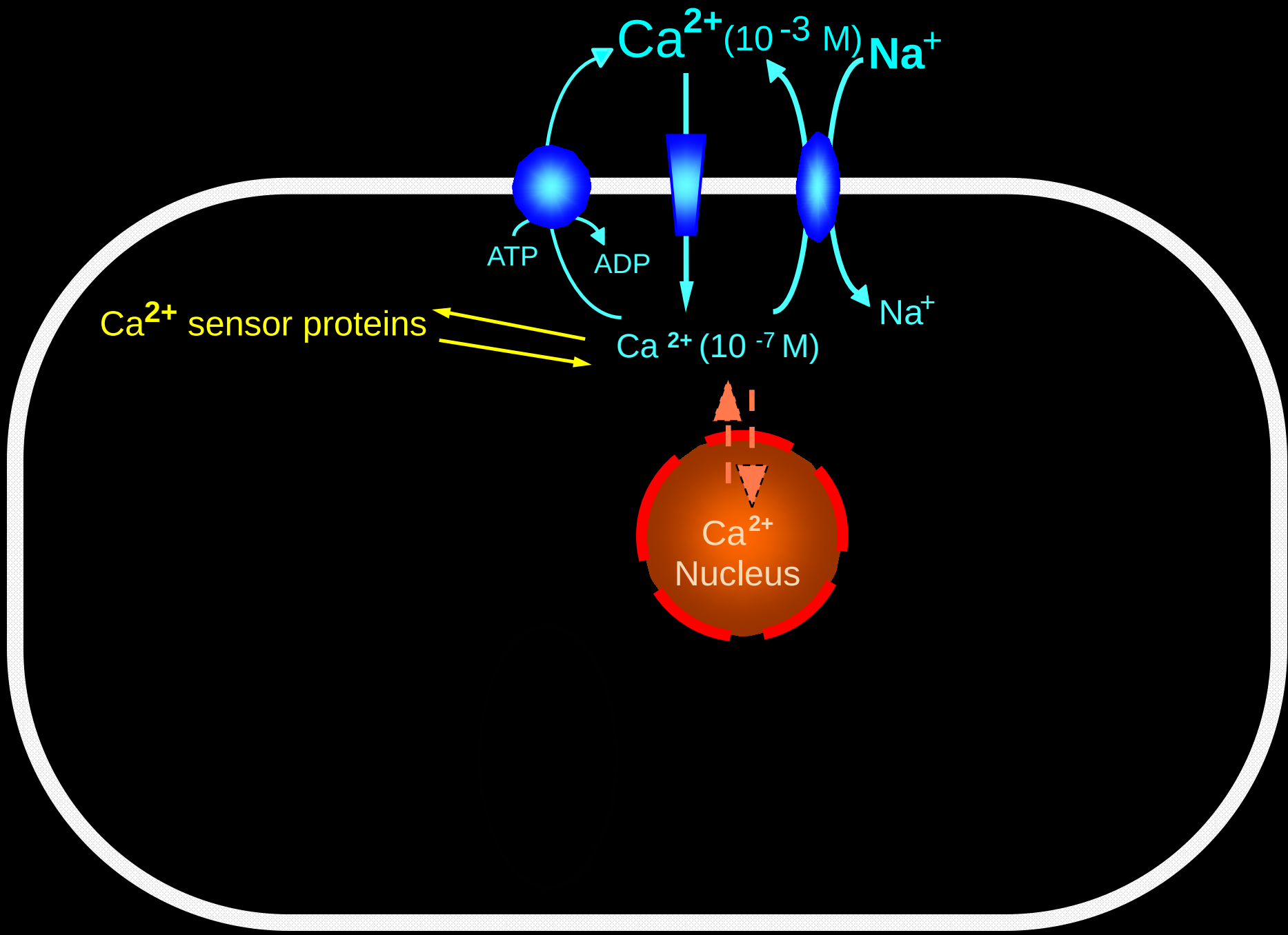




Ca is released from endoplasmic reticulum via a tetrameric channel which is gated by Ca itself, but requires the presence of the second messenger inositol-tris-phosphate ($InsP_3$)

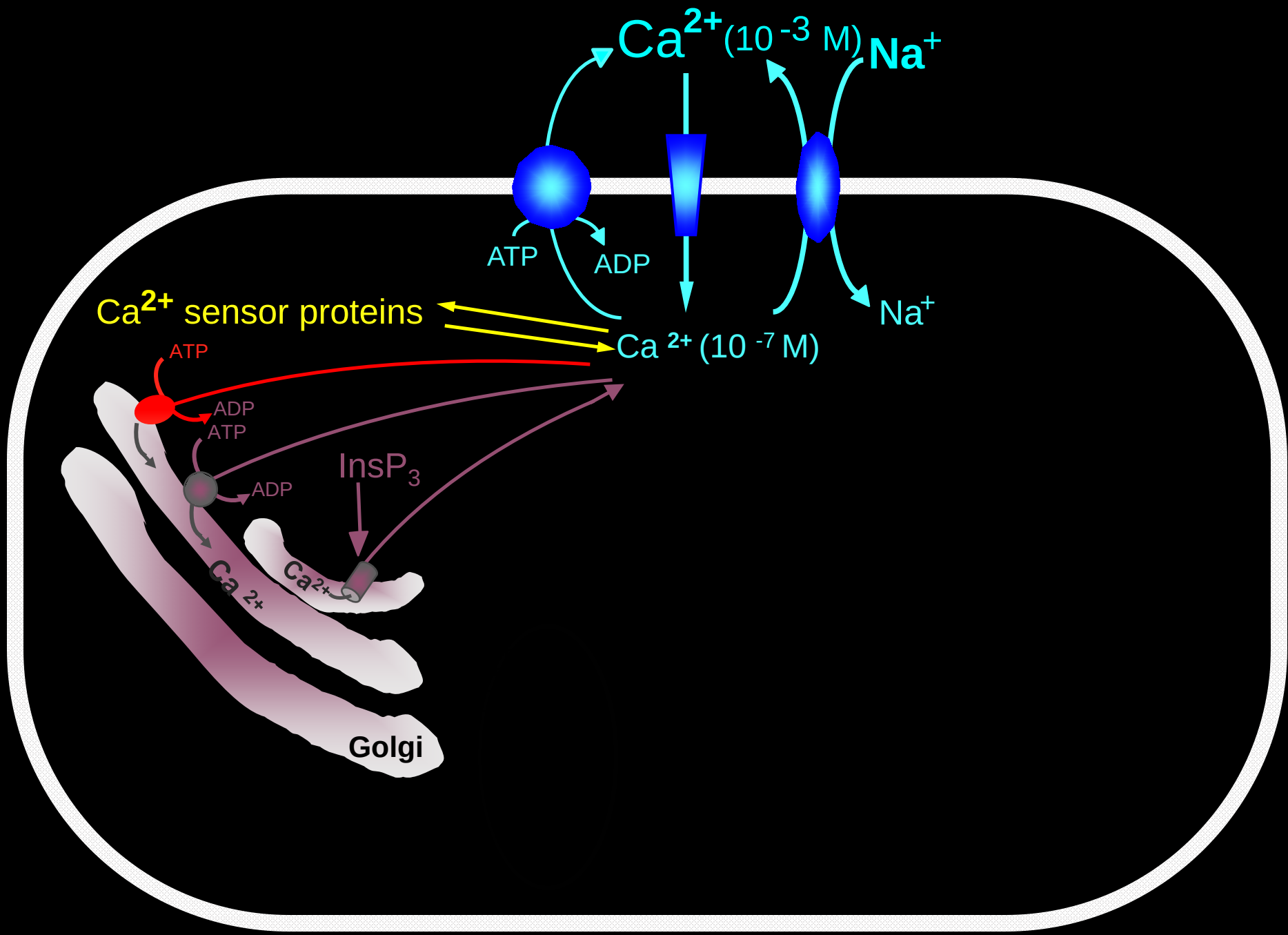
3D structure of the ryanodine receptor of the SR




Ca2+ (10 -3 M)
Na+
ATP
ADP
Na+
Ca2+ sensor proteins
Ca 2+ (10 -7 M)
Ca2+
Nucleus

Calcium in the nucleus

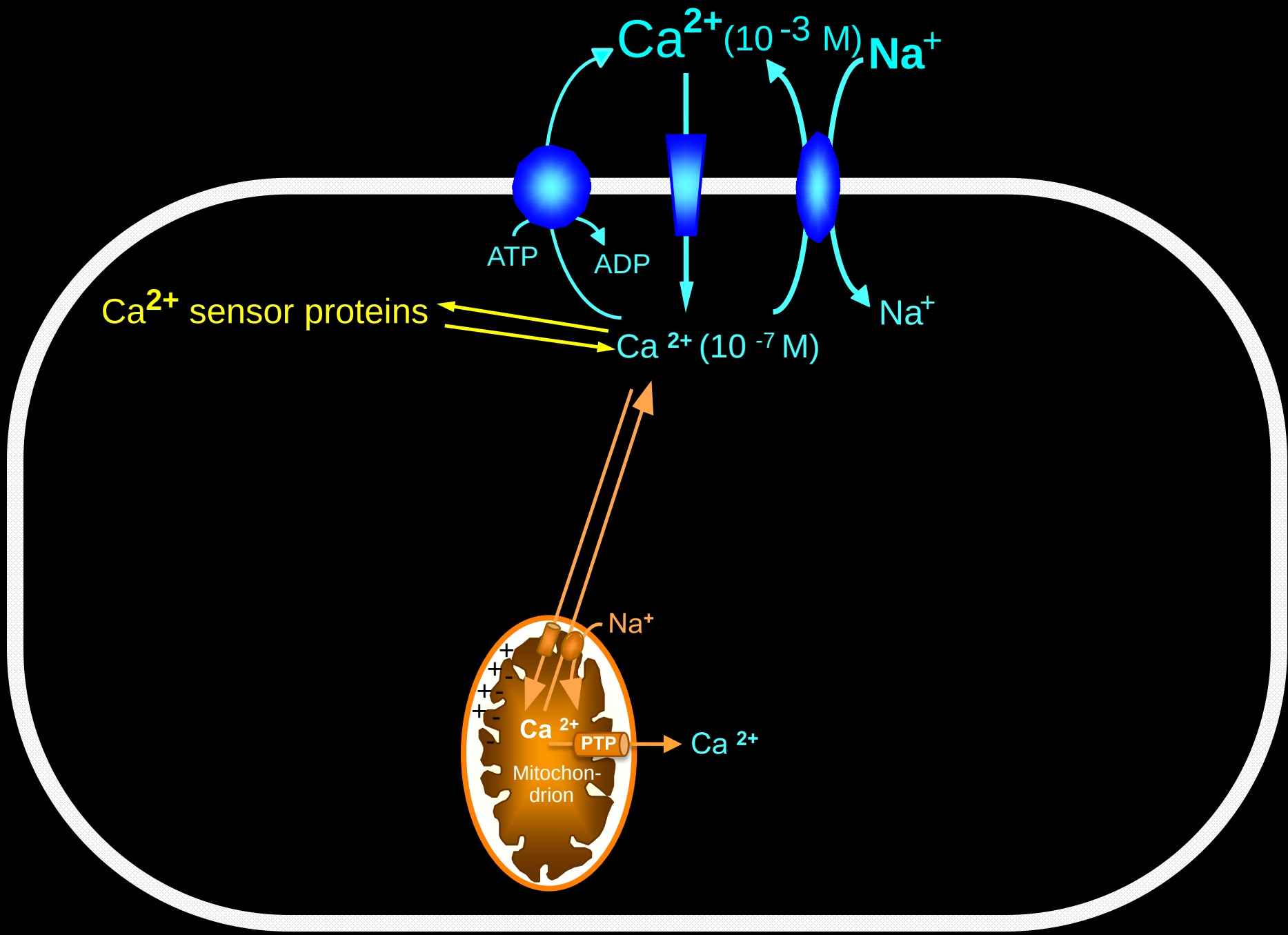
The nucleus contains a number of specific processes that are calcium regulated, beginning with the transcription of numerous genes. The nuclear envelope, which is an extension of the endoplasmic reticulum, contains the components of calcium regulatory pathways, e.g., that which produces inositol-*tris*-phosphate. It would thus be logical to expect that the homeostasis of calcium in the nucleoplasm would be independent from that in the cytosol. However, the nuclear envelope contains numerous large pores, that would freely permit the passive passage of calcium: most calcium imaging experiments have indeed shown no delays in the transmission of calcium increases from the cytosol to the nucleoplasm.In some cell types, for instance oocytes, significant delays have instead been observed , and evidence has been provided that the envelope pores are not permanently open, but could be “gated”. Whether the homeostasis of calcium in the nucleoplasm is, or is not, independent from that in the nucleoplasm is not yet conclusively established.


Ca2+ (10 -3 M)
Na+
ATP
ADP
Na+
Ca2+ sensor proteins
Ca 2+ (10 -7 M)
ATP
ADP
ATP
ADP
InsP3
Ca 2+
Ca2+
Golgi

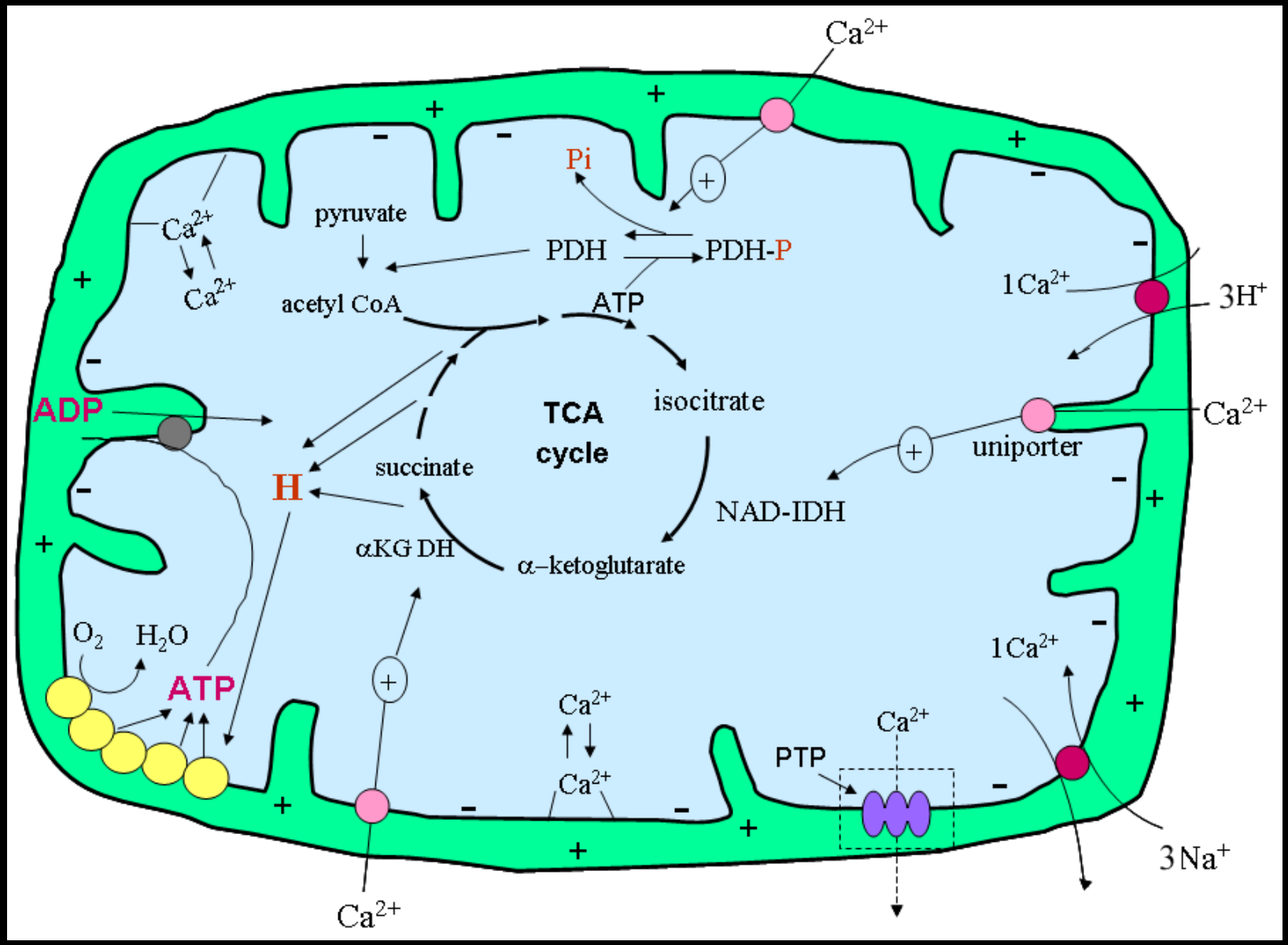
Calcium in the Golgi System

The vesicles of the Golgi systems contain two calcium ATPases that transport calcium into its vesicles. One is identical to that of the reticulum (the SERCA pump) the other (the SPCA pump) is essentially a variant of the SERCA pump but also has differences from it . The most important functional difference is the ability of the SPCA ATPase to also transport manganese, which the SERCA ATPase does not. Two SPCA gene products have been described in humans, SPCA 1 and SPCA 2. The SPCA pumps contribute to the cytosolic calcium homeostasis, but also have a role, thanks to their ability to transport manganese, in preventing manganese cell toxicity. A genetic mutation of the SPCA ATPase is responsible for a serious skin disease, the Hailey-Hailey disease.

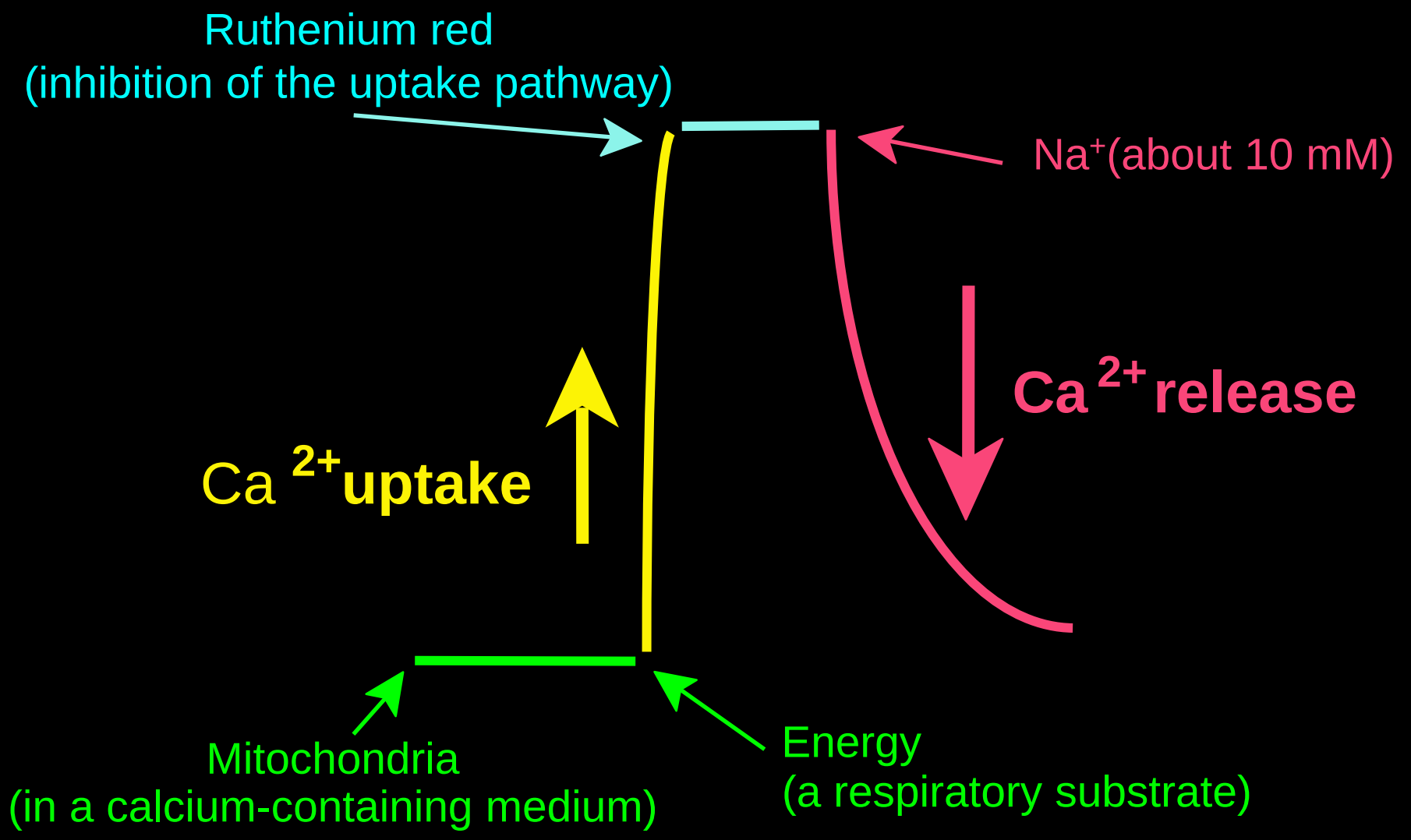
Calcium is ejected fron the Golgi vesicles through the same ligand gated channels that release calcium from the reticulum


Ca2+ (10 -3 M)
Na+
ATP
ADP
Ca2+ sensor proteins
Ca 2+ (10 -7 M)
Na+
Na+
Ca 2+
PTP
Ca 2+
Mitochon-
drion

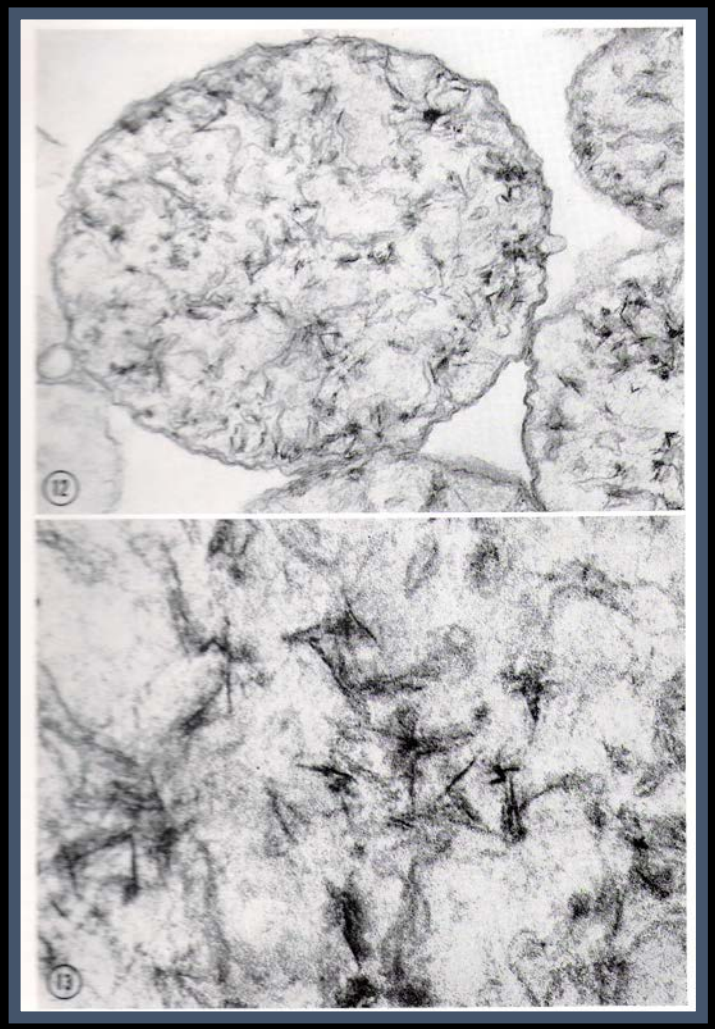
The mitochondrion is a low-affinity, large-capacity system which takes up Ca very inefficiently at the physiological concentrations of the cytosol at rest. If cytosolic Ca increases to the µM level, the mitochondrial uptake system becomes activated. This occurs whenever the release of Ca by neighbouring endoplasmic reticulum creates Ca hotspots of short duration in the vicinity of mitochondria. When the hotspots become dissipated mitochondria cease to take up Ca. This time-limited transporting ability is sufficient for the activation of three Ca-dependent matrix dehydrogenases which are essential for the operation of the TCA cycle

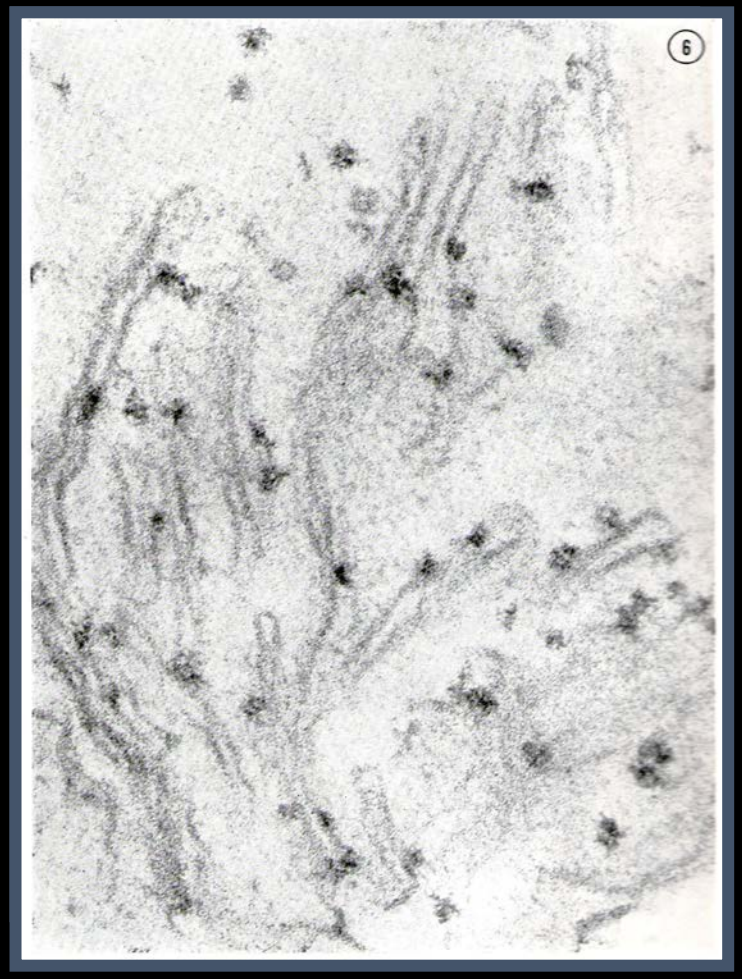

Ca2+
Pi
pyruvate
PDH
PDH-P
Ca2+
Ca2+
acetyl CoA
ATP
1Ca2+
3H+
ADP
TCA
cycle
isocitrate
Ca2+
uniporter
H
succinate
NAD-IDH
αKG DH
α–ketoglutarate
O2
H2O
ATP
1Ca2+
Ca2+
Ca2+
PTP
Ca2+
3Na+
Ca2+

Calcium movements in isolated mitochondria

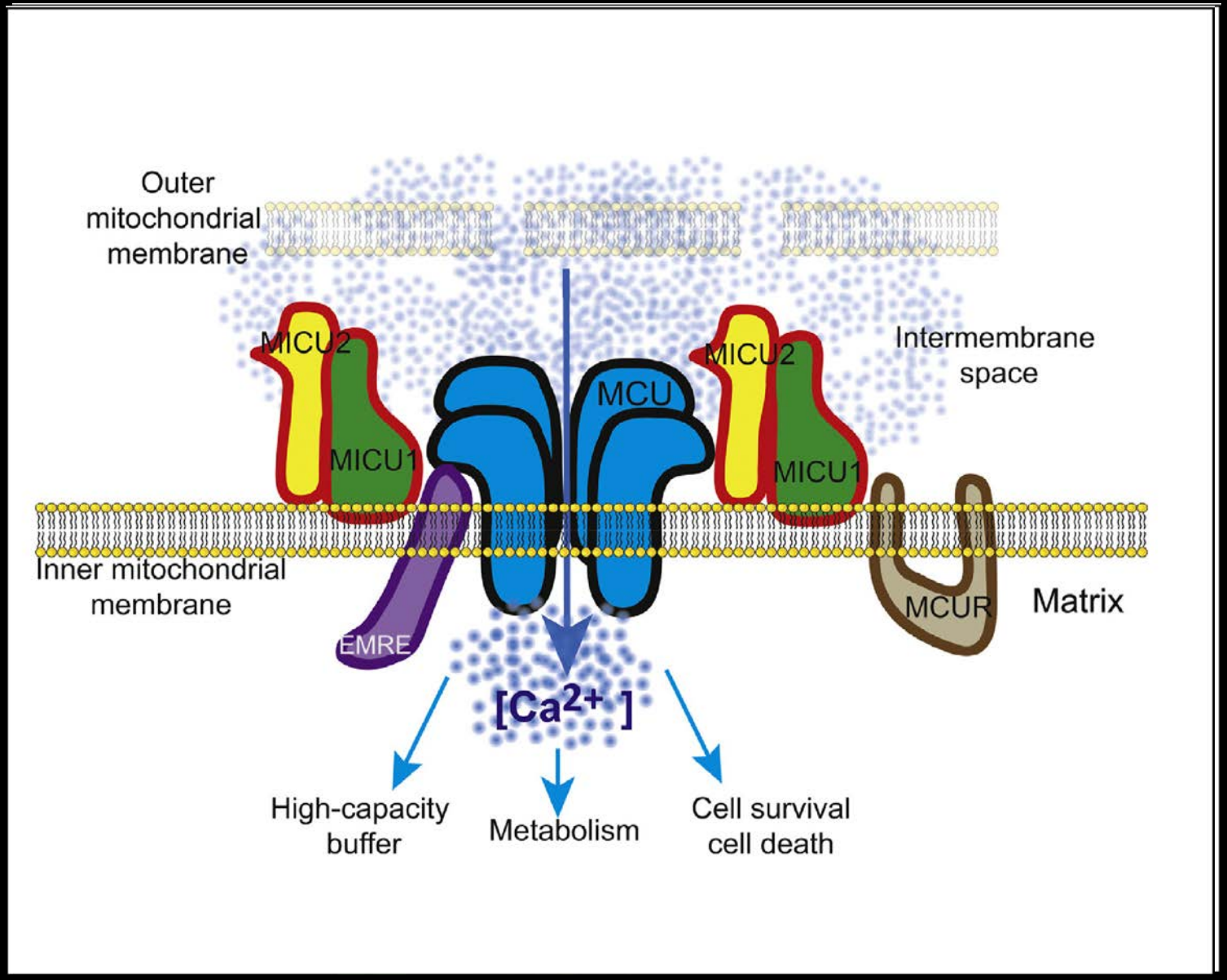


Phosphate is taken up together with calcium and precipitates it in the mitochondrial matrix as an insoluble salt (strontium was used in this experiment as a calcium analogue)

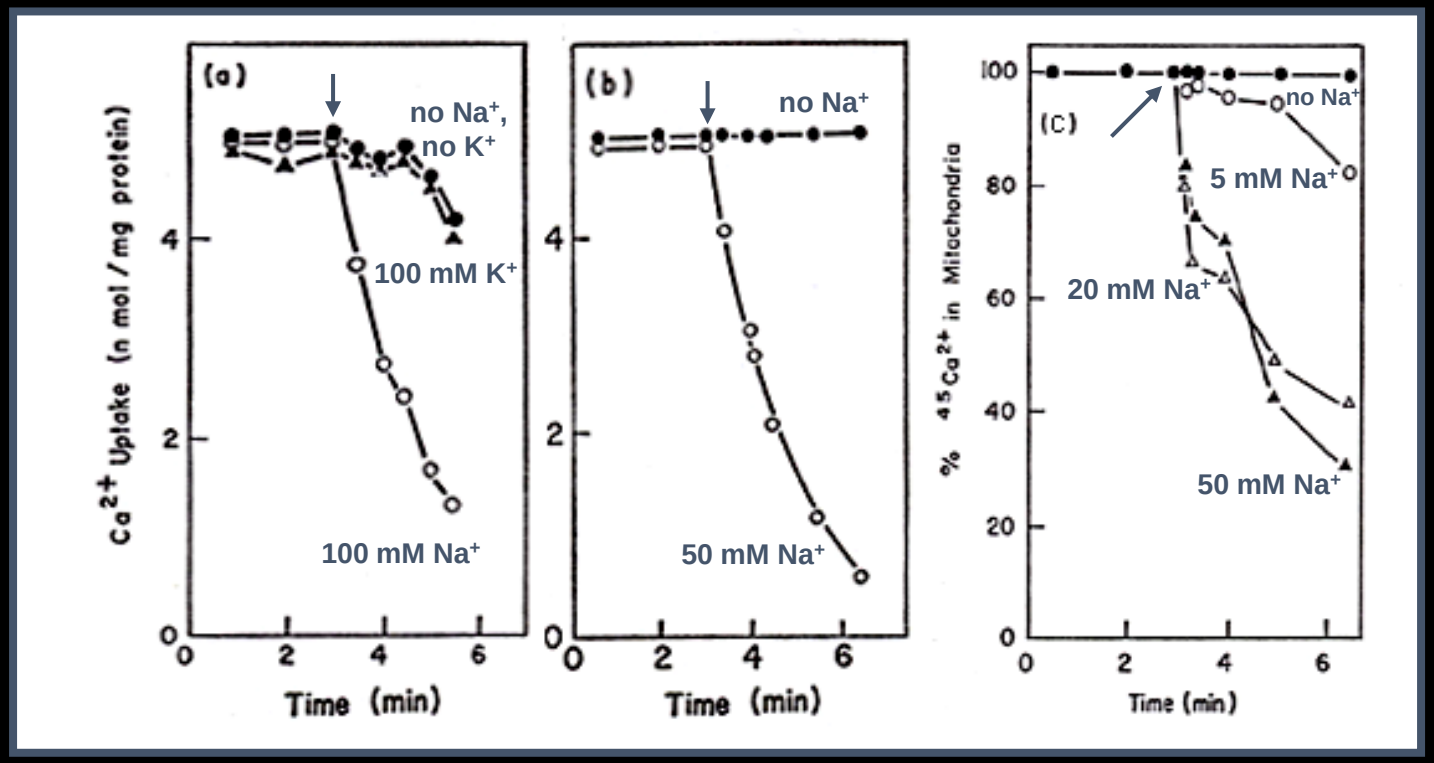




The mitochondrial calcium uptake complex

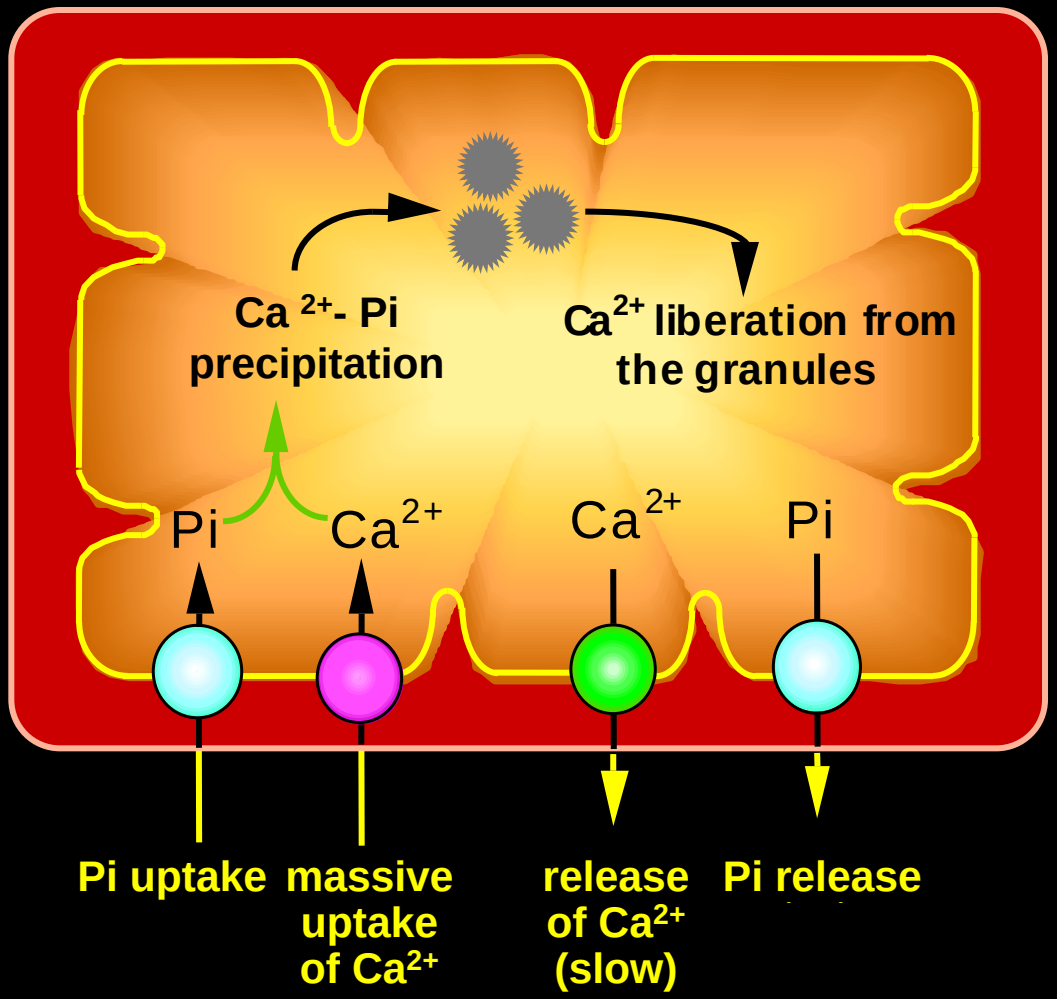


Na^+-induced release of Ca^{2+} from heart mitochondria



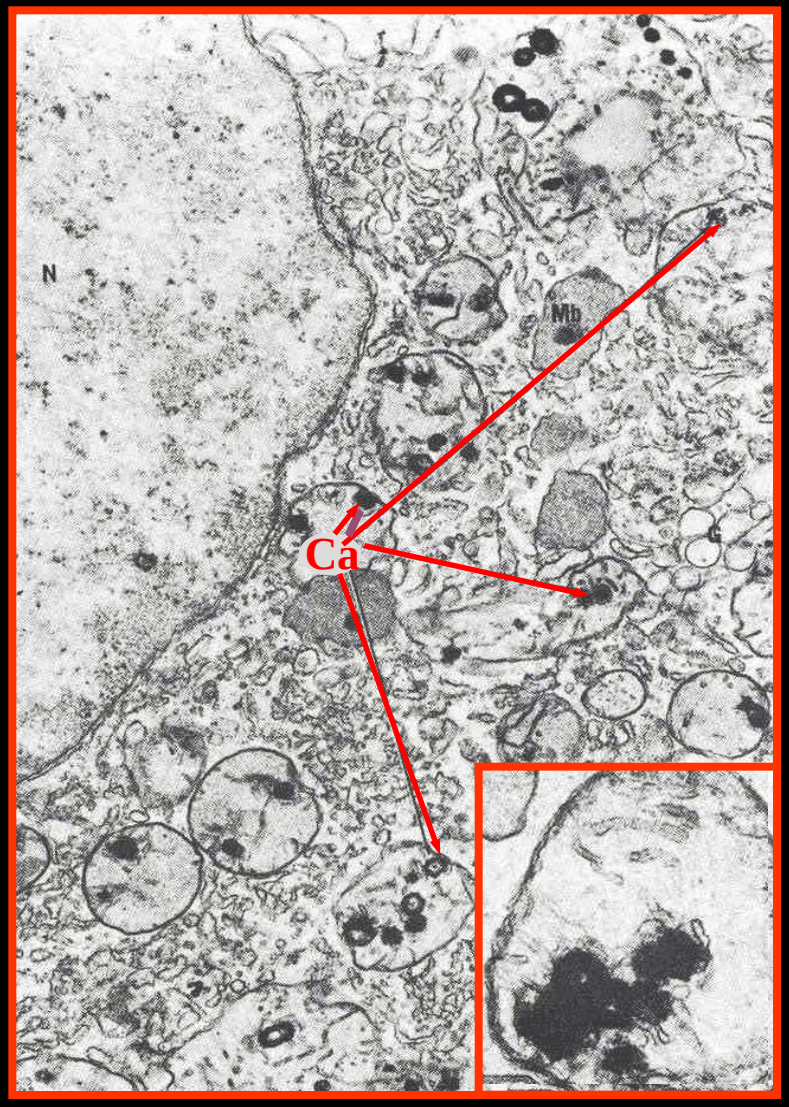
The mitochondrial uptake system also becomes activated when injuring conditions increase the Ca permeability of the plasma membrane and produce persistent cytosolic Ca overload. When this happens mitochondria react by accumulating inorganic phosphate together with Ca and by storing large amounts of precipitated hydroxyapatite in the matrix. In this way the free Ca concentration in the matrix remains essentially unchanged, thus leaving the activity of the three dehydrogenases unaffected. If the injuring condition is removed in time, Ca is slowly released and then ejected from the cell. The precipitated hydroxyapatite is amorphous, not crystalline, presumably making the release easier.

Cytosolic Ca-overload

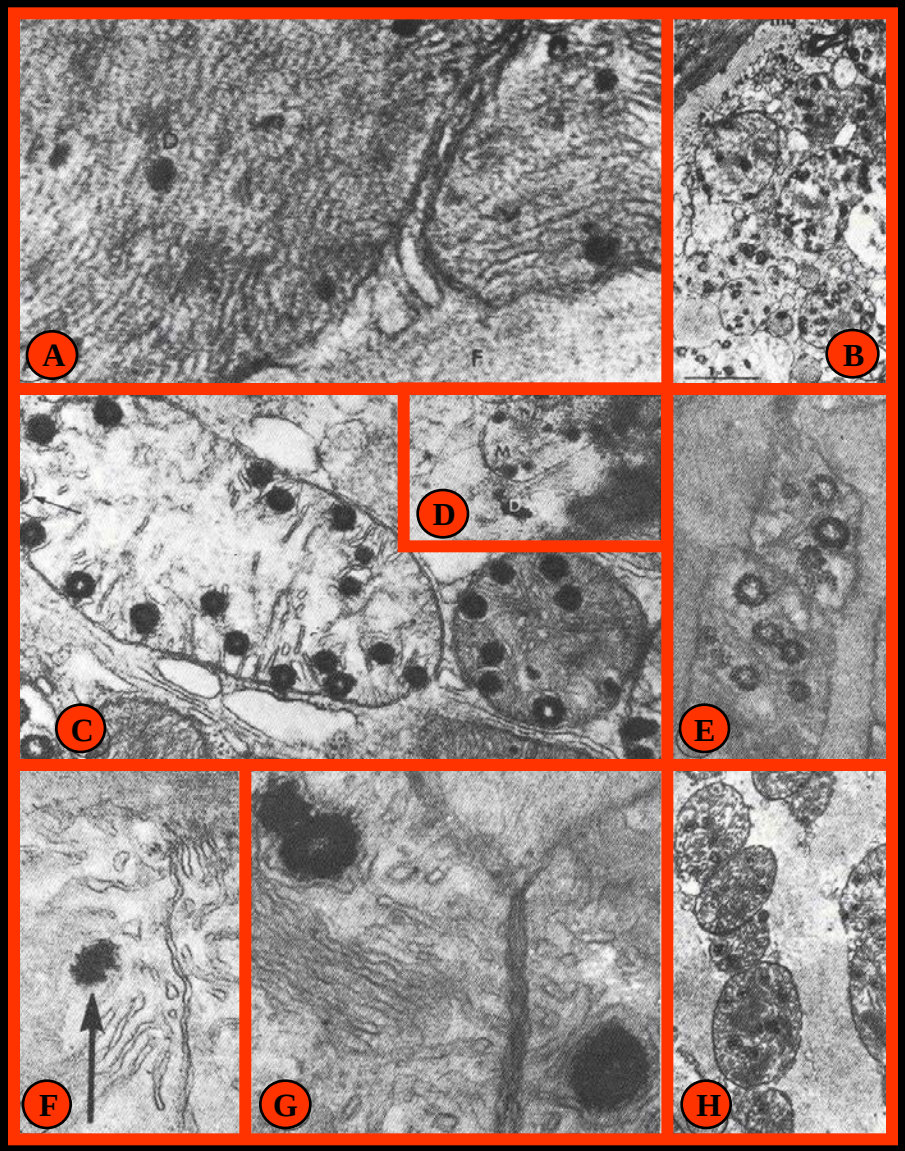


Ca and Pi precipitate as amorphous hydroxyapatite. When the Ca emergency is over, the granules dissolve slowly and Ca is released to the cytosol at a rate compatible with the transport capacity of the plasma membrane exporting systems.

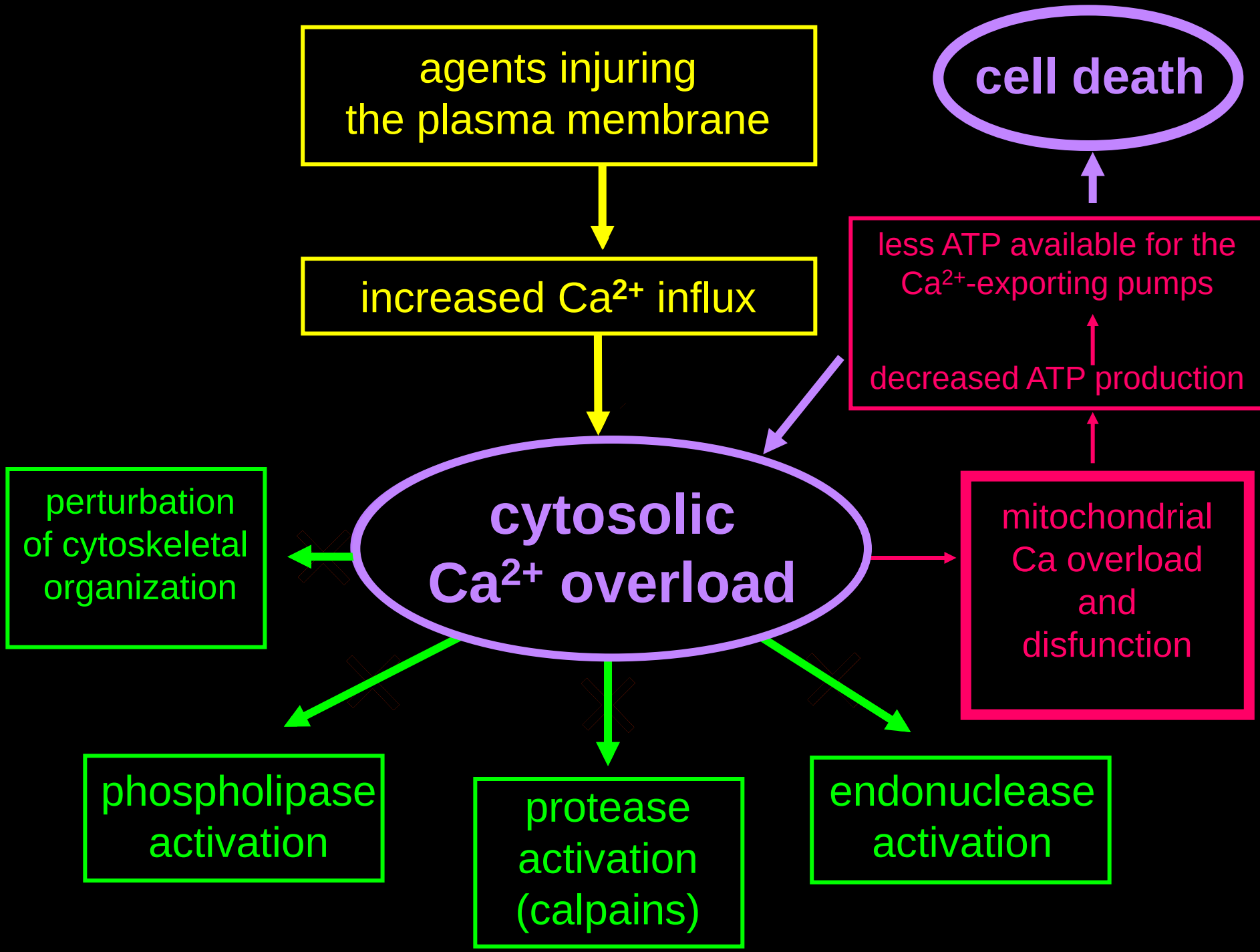
Dense (Ca-phosphate) mitochondrial granules in the liver of a rat intoxicated with CCl_4



Electron-opaque (Ca-phosphate) granules in mitochondria of variously injured cells



A : muscle (mouse poisoned with tetanus toxin)
B : kidney tubule (rat poisoned with sublimate)
C : kidney tubule (mouse treated with PTH)
D : ischemic dog myocardium
E : myocardium of a Mg-deficient, cold-stressed rat
F : ischemic dog myocardium
G : ischemic, reperfused dog myocardium
H : myocardium (rat poisoned with isoproterenol)


agents injuring
the plasma membrane
cell death
increased Ca^{2+} influx
less ATP available for the
Ca^{2+}-exporting pumps
decreased ATP production
perturbation
of cytoskeletal
organization
cytosolic
Ca^{2+} overload
mitochondrial
Ca overload
and
disfunction
phospholipase
activation
protease
activation
(calpains)
endonuclease
activation

Properties that make the calcium signal unique

1. Autoregulation

2. Ability to act both as first and as second messenger

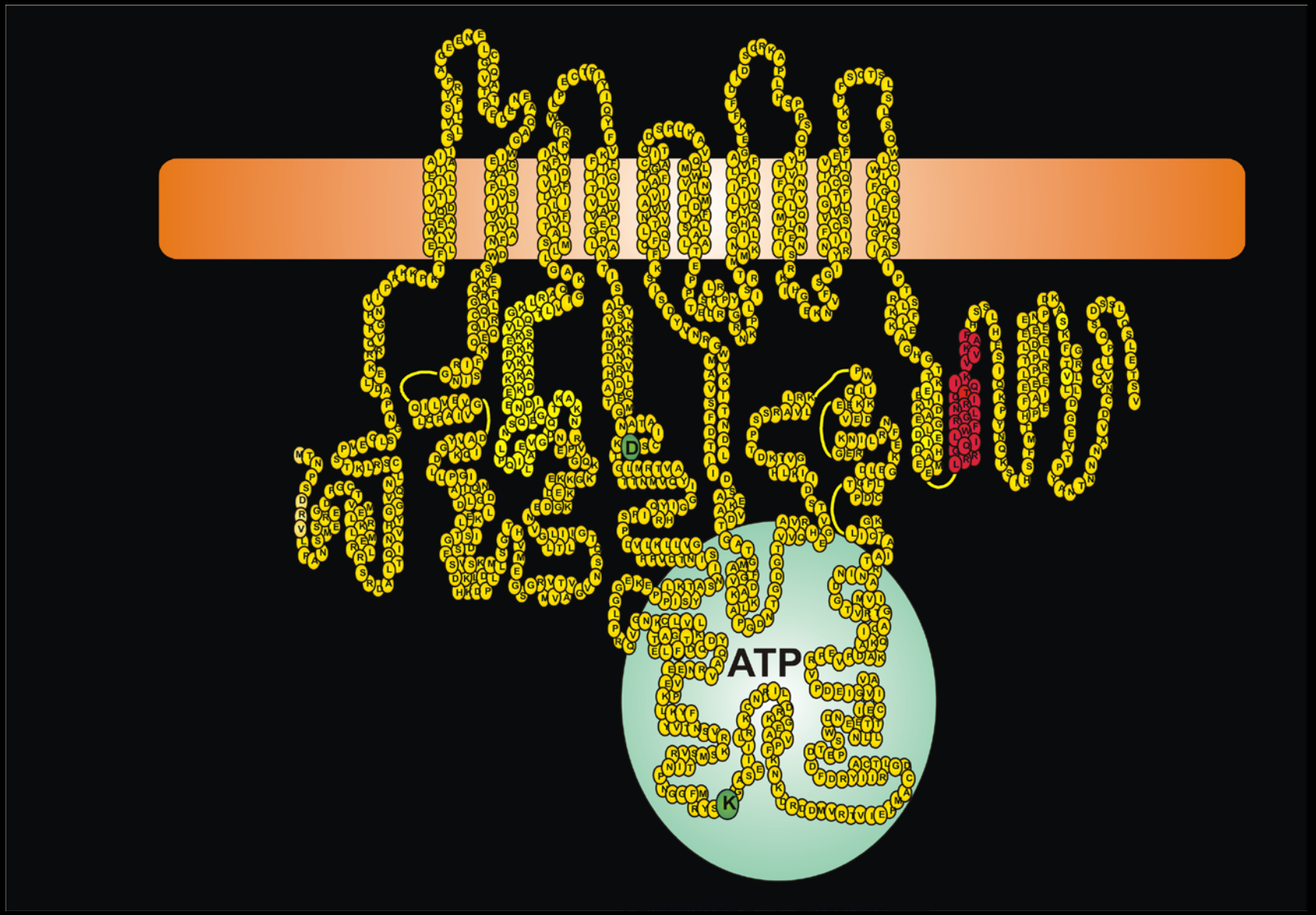
3. Ambivalence

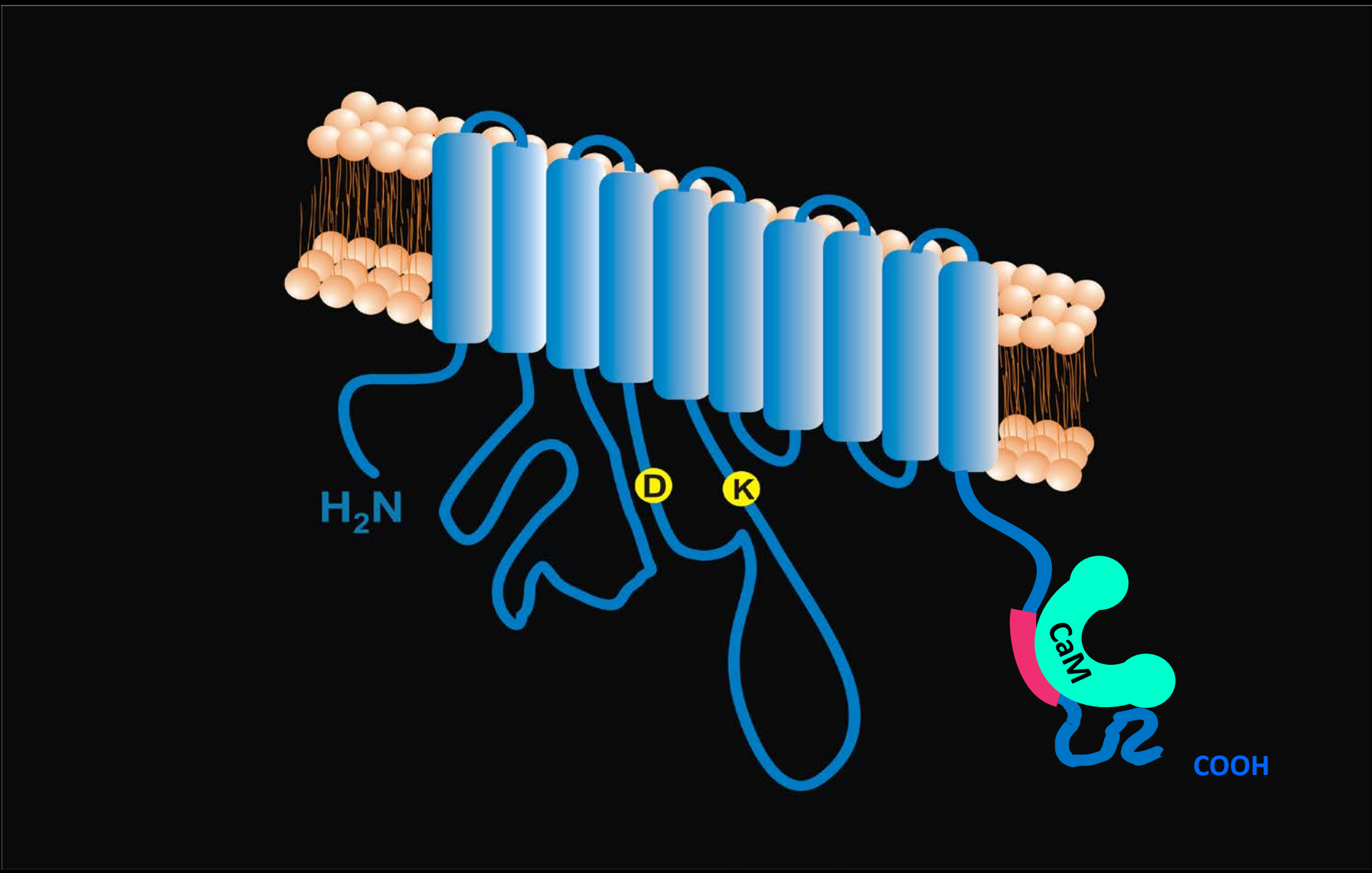
Autoregulation of the Ca^{2+} signal

Membrane transporters of Ca^{2+} may be regulated by Ca^{2+} itself. For instance, the plasma membrane Ca^{2+} pump is regulated by Ca^{2+}-calmodulin.

Another interesting Ca^{2+}-mediated regulation of calcium transporters is transcriptional. It affects not only the plasma membrane Ca^{2+} pumps, but also the plasma membrane Na/Ca exchangers and some intracellular Ca^{2+} channels.

The plasma membrane calcium ATPase




H_2N
D
K
CaM
COOH

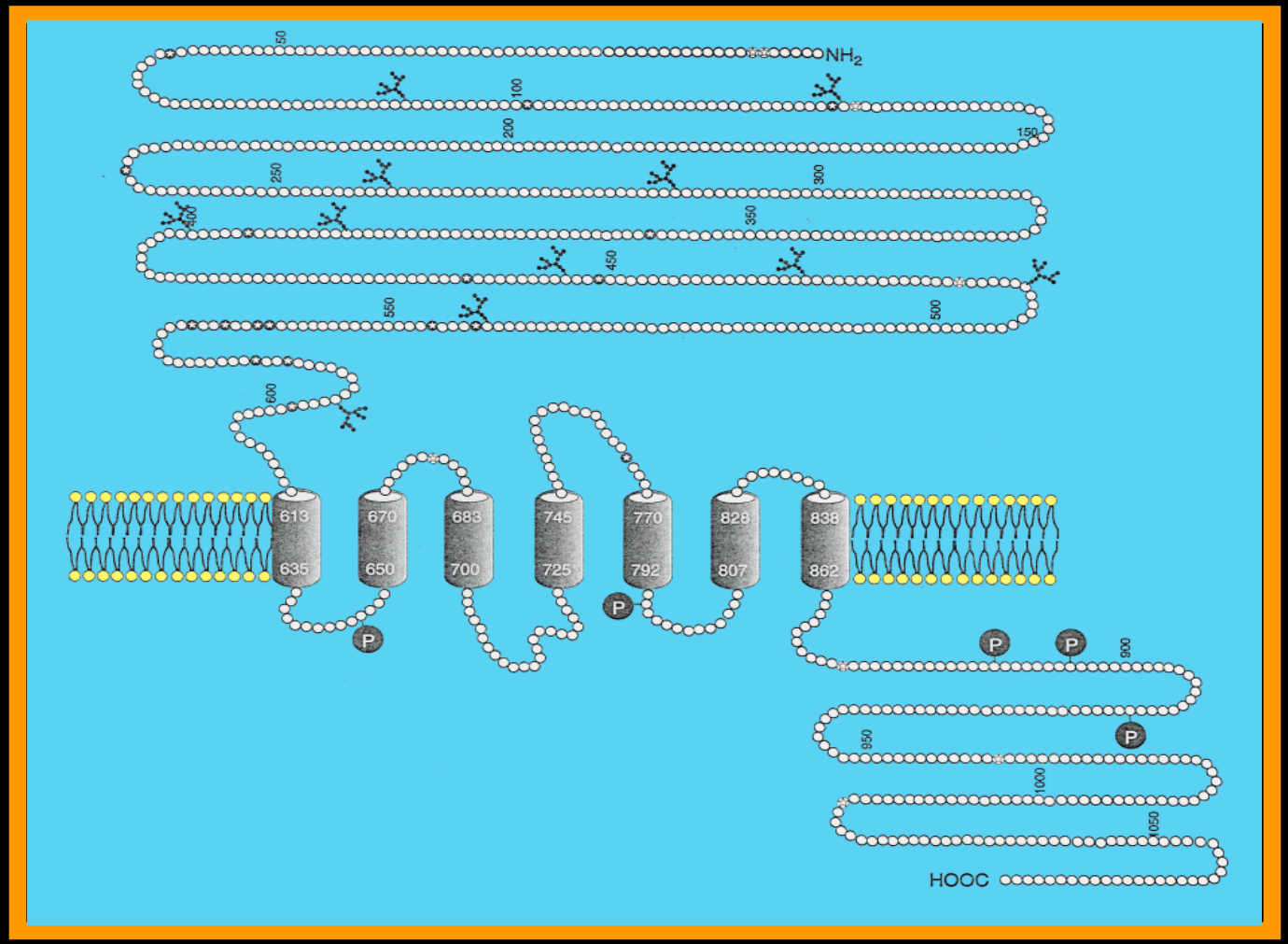
Properties that make the calcium signal unique

1. Autoregulation

2. Ability to act both as first and as second messenger

3. Ambivalence

The plasma membrane calcium sensor



Properties that make the calcium signal unique

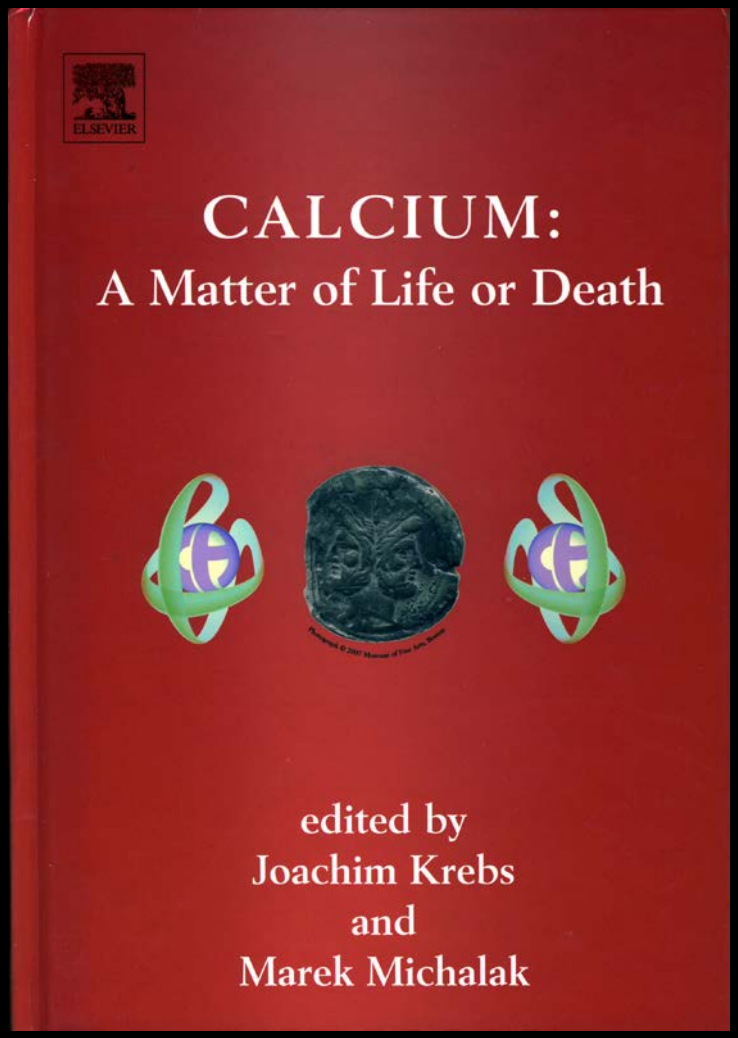
1. Autoregulation

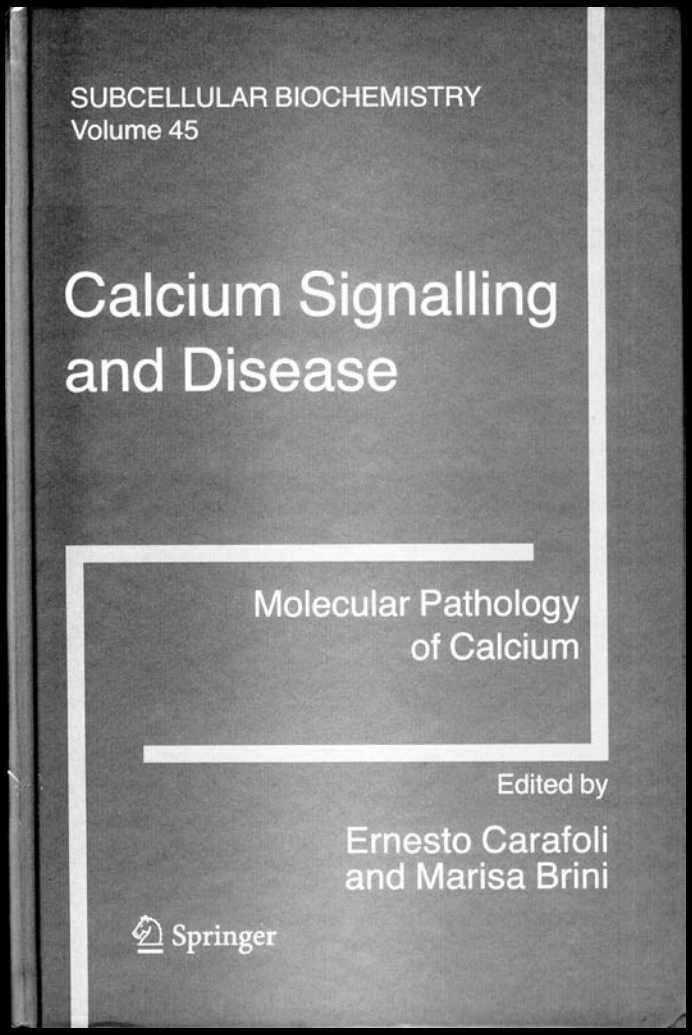
2. Ability to act both as first and as second messenger

3. Ambivalence

The ambivalent nature of the calcium signal

Free cytosolic calcium must be maintained in the low nM concentration range demanded by the affinity of the calcium sensor proteins, e.g., calmodulin, that bind it reversibly to process its signal for the benefit of the target proteins (enzymes). Deviations from this range in either direction are incompatible with the correct functioning of cell life. The choice of calcium as a determinant for function has thus led to the development of a large number of systems that keep it under very precise control. Their failure transforms calcium into a conveyor of doom.


ELSEVIER
CALCIUM:
A Matter of Life or Death
edited by
Joachim Krebs
and
Marek Michalak


SUBCELLULAR BIOCHEMISTRY
Volume 45
Calcium Signalling
and Disease
Molecular Pathology
of Calcium
Edited by
Ernesto Carafoli
and Marisa Brini
Springer

Massive and global Ca^{2+} increases in the cytosol are incompatible with cell live and inevitably induce toxic cell death due to the permanent activation of deleterious hydrolytic activities (proteases, phospholipases, nucleases).

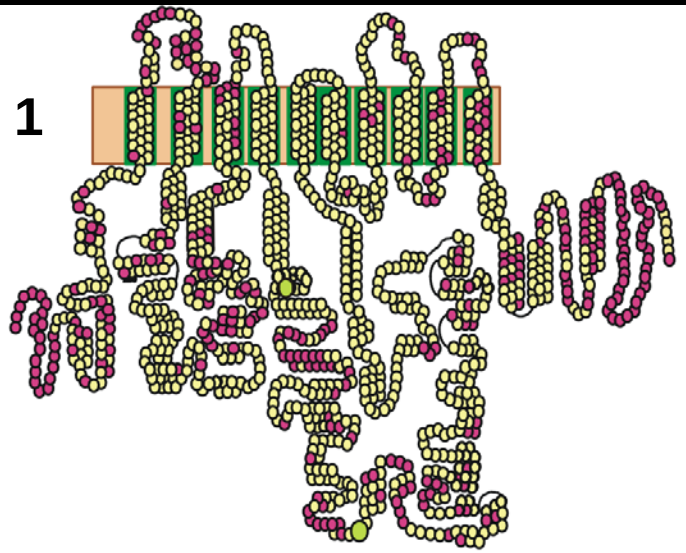
However, Ca^{2+} signaling may also be disturbed in subtler, more specific ways, due to alterations (mostly genetic) of individual components of the Ca^{2+}-decoding and/or Ca^{2+}-controlling systems. These alterations do not immediately terminate cell life. They permit it to go on, albeit with various degrees of dyscomfort.

Calcium signaling and disease

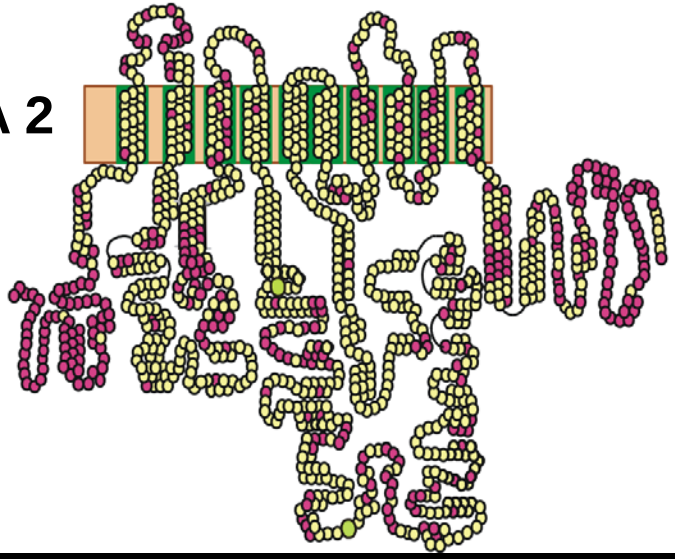
A – Calcium sensor proteins	gelsolin, annexins, calpains, neuronal Ca sensors, S-100
B – Calcium channels	plasma membrane voltage-gated and other types of Ca channels, internal ligand gated Ca channels
C – Calcium transporters	plasma membrane Ca pump, endo(sarco)plasmic reticulum Ca pump, Golgi-membranes Ca pump, plasma membrane Na/Ca exchanger

PMCA 4

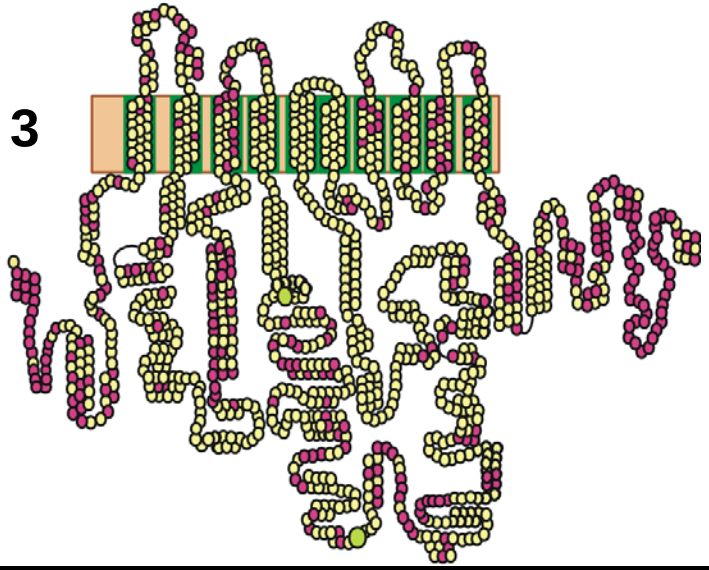
PMCA 1



PMCA 2



PMCA 3



Purple : the residues that are different with respect to isoform 4 (taken as reference)

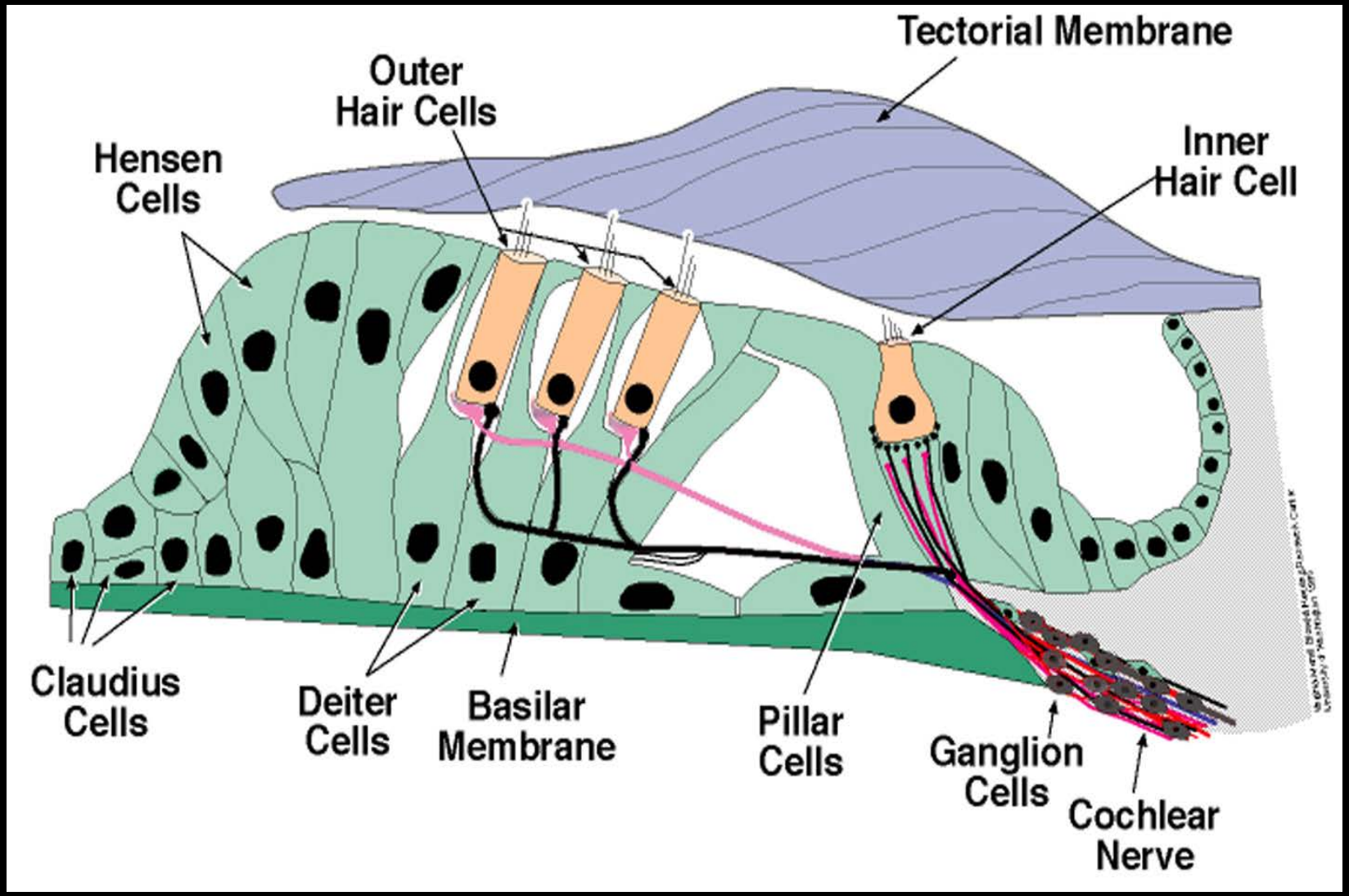
Main properties of the four basic isoforms of the PMCA pump

	PMCA1	PMCA2	PMCA3	PMCA4
Tissue distribution	UBIQUITOUS	RESTRICTED (BRAIN)	RESTRICTED (BRAIN)	UBIQUITOUS
K_d CaM	40-50 nM	2-4 nM	8 nM	30-40 nM
K_d ATP	100 nM	200-300 nM	ND	700 nM
Calpain sensitivity	HIGH	LOW	LOW	HIGH

Genetic pathology of PMCAs

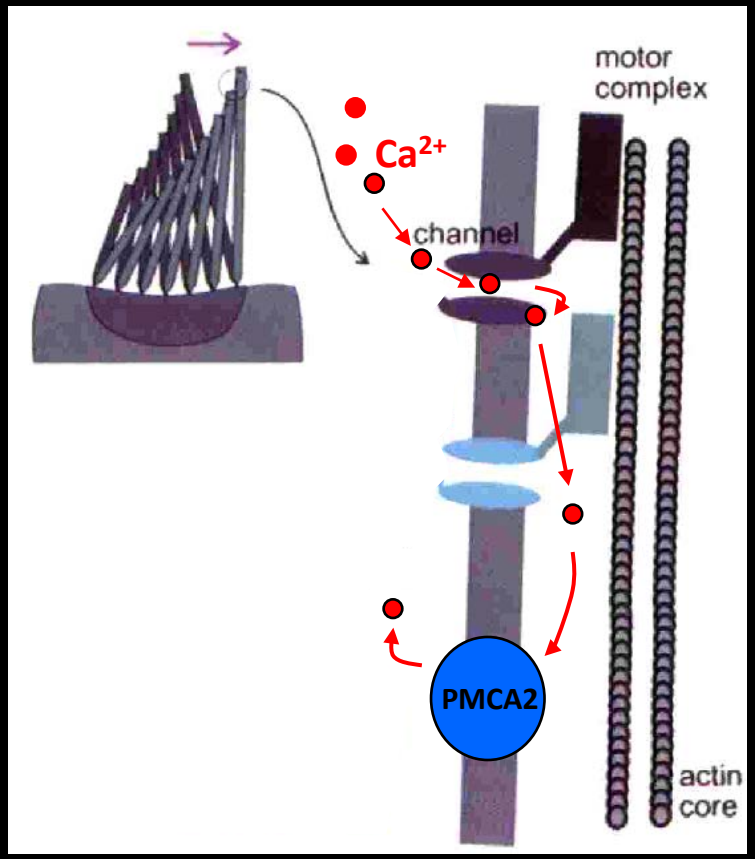
Gene	Pump	Tissue	Phenotype
ATP2B1	PMCA1	All tissues	Systolic hypertension
ATP2B2	PMCA2	Brain Mammary gland	Hereditary deafness Breast cancer
ATP2B3	PMCA3	Brain, Spinal Cord, Skeletal muscle	Familial hypercalcemia? Pancreatic cancer? Ataxias
ATP2B4	PMCA4	All tissues	Breast cancer Spastic paraplegia

The Organ of Corti

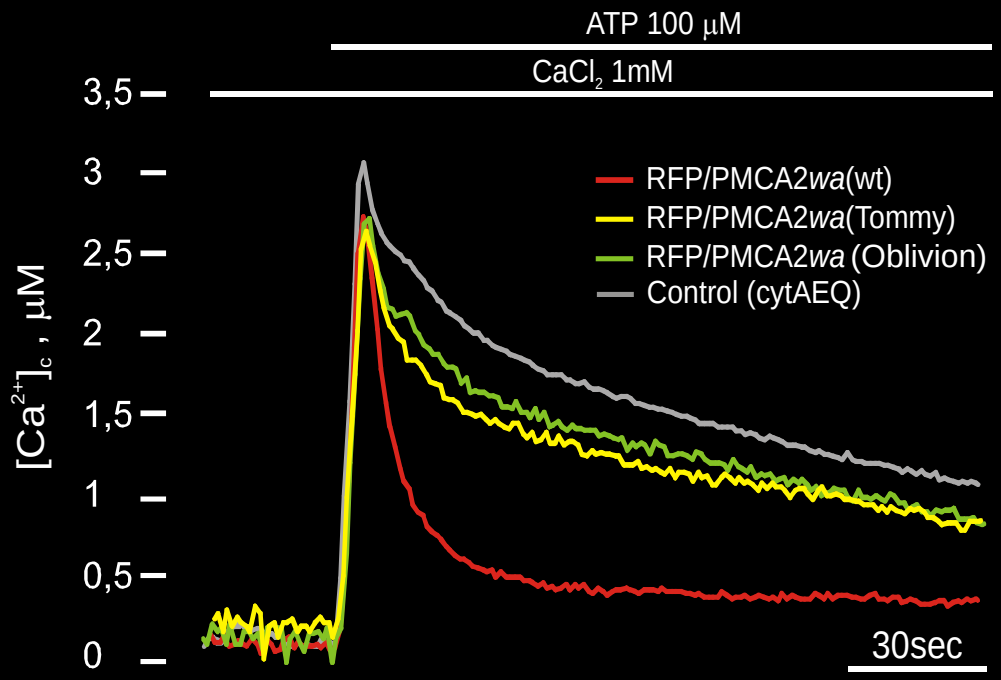


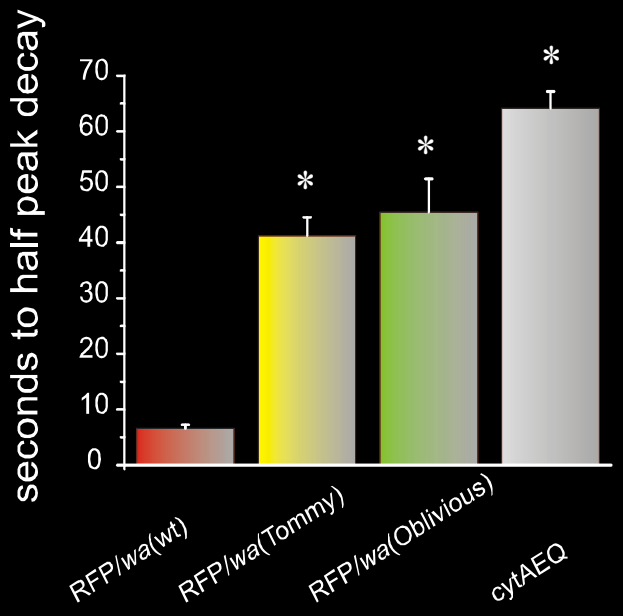
Hair cells generate a mechano-electrical transduction current which is modulated by Ca^{2+}

Hair cells are patch-clamped and the stereociliary bundle is mechanically stimulated and opens the "transduction channel". Ca^{2+} enters through the open channel.

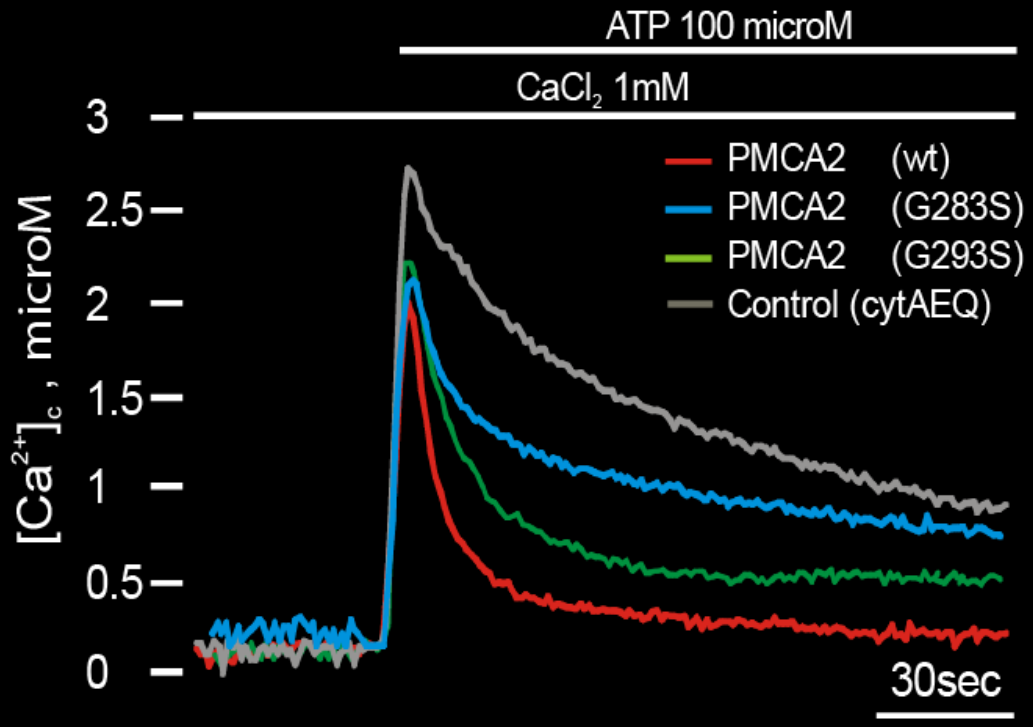


A comparison of the activity of the spliced, mutated isoforms of the PMCA2 pump

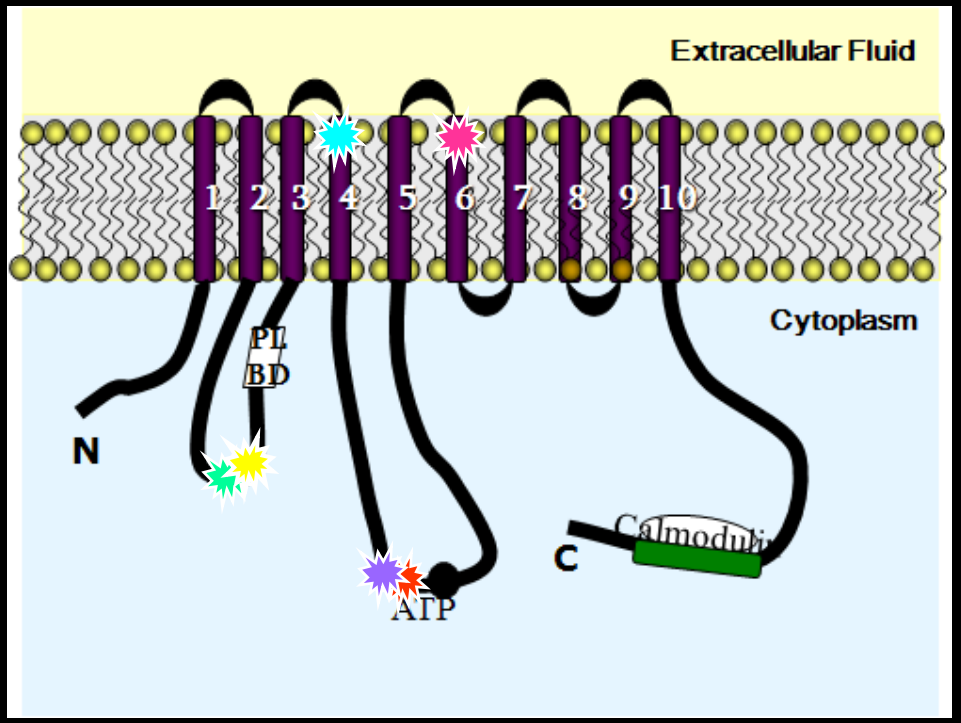




A comparison of the activity
of the mutated isoforms of the PMCA2 pump



Mutations in PMCA2 that cause hereditary deafness



Knock out mice: Mice are deaf and present vestibular/motor imbalance. Abnormalities of the organ of Corti are also present. *(Kozel et al. J Biol Chem 273,18693, 1998)*

Deafwaddler mice: G283S *(dfw1)* or two different frame shift mutations *(dfw2j,dfw3j)*. Mice are deaf and present vestibular/motor imbalance. *(Street et al. Nature Genetics 19,390, 1998).*

Wriggle Mouse Sagami (E412K). The level of PMCA2 expression may be reduced and mice present hearing loss.*(Takahashi et al Biochem Biophys Res Commun 261, 773,1999)*

TOMMY (E584K): Mice are deaf as judged by the lack of Preyer reflex and present ataxia. *(Bortolozzi et al. J. Biol. Chem.285, 37693, 2010)*

OBLIVION (S877F): Mice presents ataxia, loss of balance, progressive loss of auditory function. *(Spiden et al. PLoS Genetics, 4 (2008) e 1000238*

Human mutation V586M increases the severity of hearing loss in a deafness family with a mutation in the cdh23 (*Schultz* et al. N Engl J Med 352,1557, 2005)

Human mutation G293S creates hearing loss by a digenic mechanism involving the CDH23 gene in a human family (Ficarella et al, Proc. Natl. Acad. Sci., USA,104,1516, 2007)

PERIODIC TABLE OF THE ELEMENTS

Table of Radioactive Isotopes

Naturally occurring radioactive isotopes are indicated by a blue mass number. Half lives are in parentheses where s, m, h, d and y stand for seconds, minutes, hours, days and years respectively. The symbols describing the mode of decay and resulting radiation are defined as follows:

α	alpha particle	L	L-electron capture
β^-	beta particle	SF	spontaneous fission
β^+	positron	γ	gamma ray
K	K-electron capture	e^-	internal electron conversion

Ca 227(22y)β^-,α
Ca 110(24s)β^-,γ 111(7.5d)β^-,γ
Ca 241(458y)α,γ,e^- 242(16.0h)β^-,K,α,γ 243(8000y)α,γ
Ca 76(26.7h)β^-,γ 77(39h)β^-,γ
Ca 210(8.3h)K,α,γ 211(7.2h),Kα,γ
Ca 198(2.69d)β^-,γ
Ca 131(12d)K,γ 133(7.2y)K,γ,e^-
Ca 210(5d)β^-,α
Ca 245(4.9d)K,α,γ 249(314d)β^-,α,SF
Ca 82(36h)β^-,γ
Ca 14(5700 y)β^-
? 41(8x10^{4}y)K 45(165d)β^- 47(4.5d)β^-,γ

Ca 115(43d)β^-,γ
Ca 141(32d)β^-,γ 143(33h)β^-,γ 144(285d)β^-,γ
Ca 246(3.5h)α,γ,SF 249(360 y)α,γ,SF 251(800 y)γ
Ca 36(3x10^{5}y)β^-
Ca 243(35y)$,\alpha,\gamma$ 245(9300y)α,γ 247(10^{7}y)
Ca 58(71d),K,β^+,γ 60(5.27y)β^-,γ
Ca 51(27d),K,γ
Ca 134(2.0y)β^-,γ 135(3x10^{6}y)β^- 137(30y)β^-,γ
Ca 64(12.8h)K,β^-,β^+,γ
Ca 253(20d)α,γ,SF 254(1y)α,SF
Ca 154(16y)β^-,γ 155(1.8y)β^-,γ

Ca 55(2.6y)K 59(45d)β^-,γ
Ca 255(20h)α
Ca 223(22m)β^-,γ,α
Ca 72(14.1h),β^-,γ
Ca 153(236d)K,γ,e^- 159(18h)β^-,γ
Ca 71(11d)K
Ca 3(12.3y)β^-
Ca 181(45d)β^-,γ,e^-
Ca 197(65h)K,γ,e^- 203(47d)β^-,γ,e^-
Ca 166(27.3h)β^-,γ
Ca 129(10^{7}y)β^+,γ,e 131(8.05d)β^-,γ
Ca 114(50d)γ
Ca 192(74.4d)β^-,γ
Ca 40(10^{9}y)β^+,K,γ 42(12.4h),β^-,γ

Ca 140(40.2h)β^-,γ
Ca 176(10^{10}y)β^-,K,γ 177(6.8d)β^-,γ
Ca 256(90m)K,SF
Ca 99(67h)β^-,γ
Ca 22(2.6y)β^+,K,γ 24(15h)β^-,γ
Ca 147(11.1d)β^-,γ
Ca 63(125y)β^- 59(8x10^{4}y),K
Ca 237(2.2x10^{4}y)α,γ 239(2.33d)β^-,γ
Ca 191(15d)β^-,γ,e^-
Ca 32(14.2d)β^-
Ca 231(34000y)α,γ
Ca 210(19.4y)β^-,γ,e^- 202(10^{5}y)L
Ca 103(17d)K,γ
Ca 147(2.6y)β^-

Ca 210(138.4d)α,γ 209(103y)α,K,γ
Ca 143(13.8d)β^-
Ca 197(18h)β^-,γ
Ca 242(3.8 x 10^{5}y)α,SF 241(13y)β^-,α,γ 239(24300y)α,γ,SF
Ca 226(1620y)α,γ
Ca 86(18.6d)β^-,γ
Ca 188(16.7h)β^-,γ 186(3.7d)β^-,γ
Ca 222(3.82d)α
Ca 103(40d)β^-,γ 97(2.9d),K,γ,e^-
Ca 35(88d)β^-
Ca 122(2.8d)β^-,K,β^+,γ 124(60d)β^-,γ
Ca 46(84d)β^-,γ
Ca 75(120 d)K,γ
Ca 153(47h)β^-,γ 145(340d)K,γ
Ca 113(119d)K,L,γ,e^-

Ca 90(28y)β^- 89(51d)β^-,γ 85(64d)K,γ
Ca 182(115d)β^-,γ
Ca 160(73d)$\beta^-\gamma$
Ca 99(2x10^{5}y)β^- 97(10^{6}y)K
Ca 127(9.3h)β^-
Ca 232(1.4x10^{10}y)α,γ,SF 228(1.91y)β^-
Ca 204(3.81y)β^-,K
Ca 170(134d)β^-,γ,e^-
Ca 238(4.5x10^{9}y)α,γ,SF 234(2.5x10^{5}y)α,γ,SF 235(7.1x10^{8}y)α,γ,SF 233(1.6x10^{5}y)α,γ
Ca 185(75d)β^-
Ca 90(64h)β^-,e^-
Ca 175(4.2d)β^-,γ 169(31d)K,γ,e^-
Ca 65(245d)K,β^+,γ
Ca 95(65d)β^-,γ,e^- 93(9x10^{5}y)β^-,γ

GROUP IA | IIA | IIIB | IVB | VB | VIB | VIIB | VIII | IB | IIB | IIIA | IVA | VA | VIA | VIIA | VIIIA

1 1.00797 1 −252.7 −259.2 0.071 Ca															2 4.0026 −268.9 −269.7 0.126 Ca
3 6.939 1330 180.5 0.53 Ca	4 9.0122 2770 1277 1.85 Ca									5 10.811 — (2030) 2.34 Ca	6 12.01115 4830 3727^g 2.26 Ca ±4,2	7 14.0067 −195.8 −210 0.81 Ca ±3,5,4,2	8 15.9994 −183 −218.8 1.14 Ca −2	9 18.9984 −188.2 −219.6 1.505 Ca −1	10 20.183 −246 −248.6 1.20 Ca
11 22.9898 892 97.8 0.97 Ca	12 24.312 1107 650 1.74 Ca									13 26.9815 2450 660 2.70 Ca	14 28.086 2680 1410 2.33 Ca	15 30.9738 280^w 44.2^w 1.82^w Ca ±3,5,4	16 32.064 444.6 119.0 2.07 Ca ±2,4,6	17 35.453 −34.7 −101.0 1.56 Ca ±1,3,5,7	18 39.948 −185.8 −189.4 1.40 Ca
19 39.102 760 63.7 0.86 Ca	20 40.08 1440 838 1.55 ?	21 44.956 2730 1539 3.0 Ca 3	22 47.90 3260 1668 4.51 Ca 4,3	23 50.942 3450 1900 6.1 Ca 5,4,3,2,	24 51.996 2665 1875 7.19 Ca 6,3,2	25 54.938 2150 1245 7.43 Ca 7,6,4,2,3	26 55.847 3000 1536 7.86 Ca 2, 3	27 58.933 2900 1495 8.9 Ca 2, 3	28 58.71 2730 1453 8.9 Ca 2,3	29 63.54 2595 1083 8.96 Ca 2,1	30 65.37 906 419.5 7.14 Ca 2	31 69.72 2237 29.8 5.91 Ca 3	32 72.59 2830 937.4 5.32 Ca 4	33 74.922 613* 817 5.72 Ca ±3,5	34 78.96 685 217 4.79 Ca −2,4,6	35 79.909 58 −7.2 3.12 Ca ±1,5	36 83.80 −152 −157.3 2.6 Ca
37 85.47 688 38.9 1.53 Ca	38 87.62 1380 768 2.6 Ca 2	39 88.905 2927 1509 4.47 Ca 3	40 91.22 3580 1852 6.49 Ca 4	41 92.906 3300 2468 8.4 Ca 5,3	42 95.94 5560 2610 10.2 Ca 6,5,4,3,2	43 (98) — 2140 11.5 Ca 7	44 101.07 4900 2500 12.2 Ca 2,3,4,6,8	45 102.905 4500 1966 12.4 Ca 2,3,4	46 106.4 3980 1552 12.0 Ca 2,4	47 107.870 2210 960.8 10.5 Ca 1	48 112.40 765 320.9 8.65 Ca 2	49 114.82 2000 156.2 7.31 Ca 3	50 118.69 2270 231.9 7.30 Ca 4,2	51 121.75 1380 630.5 6.62 Ca ±3,5	52 127.60 989.8 449.5 6.24 Ca −2,4,6	53 126.904 183 113.7 4.94 Ca ±1,5,7	54 131.30 −108.0 −111.9 3.06 Ca
55 132.905 690 28.7 1.90 Ca	56 137.34 1640 714 3.5 Ca 2	57 138.91 3470 920 6.17 Ca 3 ★	72 178.49 5400 2222 13.1 Ca 4	73 180.948 5425 2996 16.6 Ca 5	74 183.85 5930 3410 19.3 Ca 6,5,4,3,2	75 186.2 5900 3180 21.0 Ca 7,6,4,2,−1	76 190.2 5500 3000 22.6 Ca 2,3,4,6,8	77 192.2 5300 2454 22.5 Ca 2,3,4,6	78 195.09 4530 1769 21.4 Ca 2, 4	79 196.967 2970 1063 19.3 Ca 3,1	80 200.59 357 −38.4 13.6 Ca 2,1	81 204.37 1457 303 11.85 Ca 3,1	82 207.19 1725 327.4 11.4 Ca 4, 2	83 208.980 1560 271.3 9.8 Ca 3,5	84 (210) — 254 (9.2) Ca 2,4	85 (210) — (302) — Ca ±1,3,5,7	86 (222) (−61.8) (−71) — Ca
87 (223) — (27) — Ca 1	88 (226) — 700 5.0 Ca 2	89 (227) — 1050 — Ca 3 ★★	104														

★	58 140.12 3468 795 6.67 Ca 3,4	59 140.907 3127 935 6.77 Ca 3,4	60 144.24 3027 1024 7.00 Ca 3	61 (147) — (1027) — Ca 3	62 150.35 1900 1072 7.54 Ca 3,2	63 151.96 1439 826 5.26 Ca 3,2	64 157.25 3000 1312 7.89 Ca 3	65 158.924 2800 1356 8.27 Ca 3,4	66 162.50 2600 1407 8.54 Ca 3	67 164.930 2600 1461 8.80 Ca 3	68 167.26 2900 1497 9.05 Ca 3	69 168.934 1727 1545 9.33 Ca 3,2	70 173.04 1427 824 6.98 Ca 3,2	71 174.97 3327 1652 9.84 Ca 3
★★	90 232.038 3850 1750 11.7 Ca 4	91 (231) — (1230) 15.4 Ca 5,4	92 238.03 3818 1132 19.07 Ca 6,5,4,3	93 (237) — 637 19.5 Ca 6,5,4,3	94 (242) 3235 640 — Ca 6,5,4,3	95 (243) — — 11.7 Ca 6,5,4, 3	96 (247) — — Ca 3	97 (247) — — Ca 4,3	98 (249) — — Ca 3	99 (254) — — Ca —	100 (253) — — Ca —	101 (256) — — Ca —	102 (254) — — Ca —	103 (257) — — Ca —