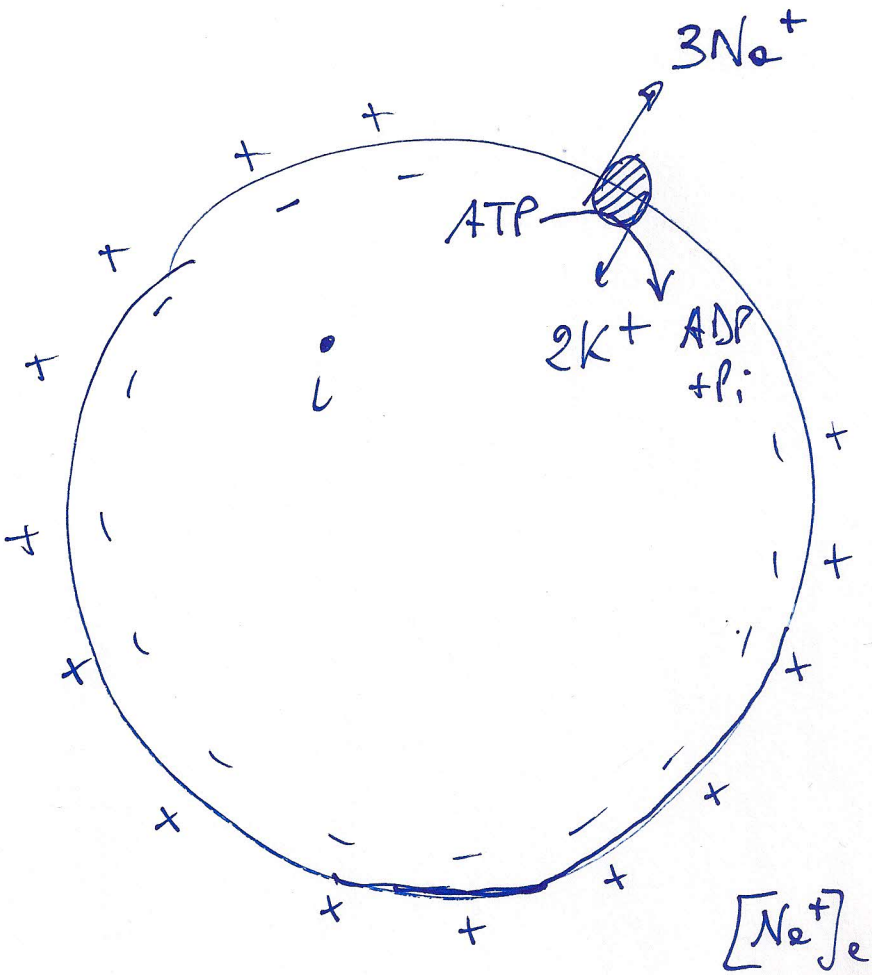
TRASPORTI ATTIVI

- PRIMARI (consumo diretto ATP)
  (pompe ioniche principalmente)

- SECONDARI
  (consumo indiretto di ATP)

ESTERNO



$[Na^+]_e \simeq 145\,mM$

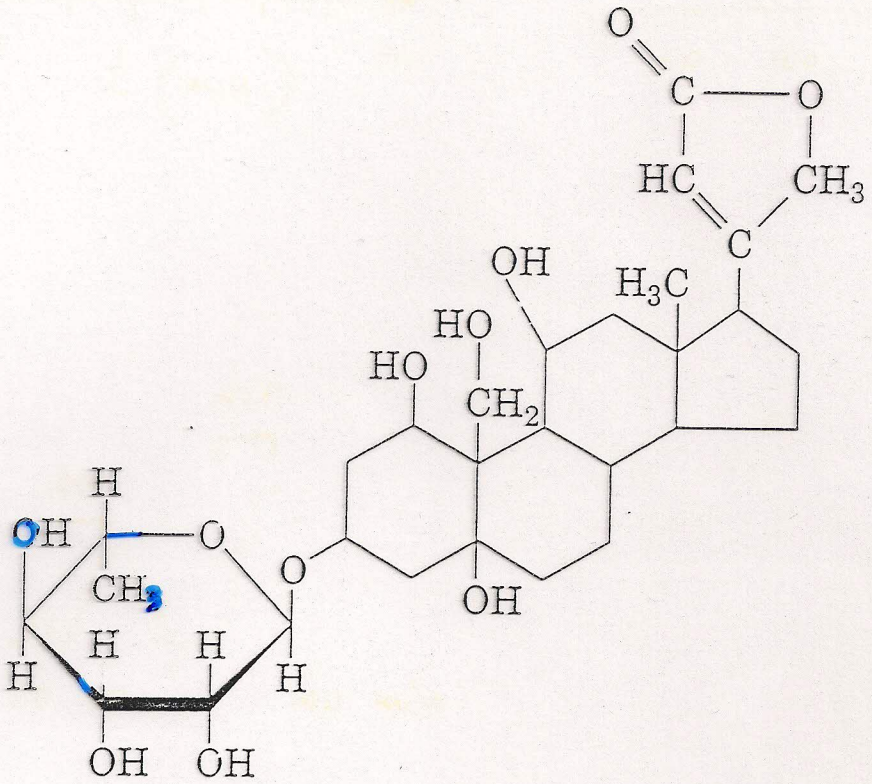
$[Na^+]_i \simeq 15\,mM$

$[K^+]_i \simeq 130\,mM$

$[K^+]_e \simeq 4\text{-}5\,mM$

GLICOSIDI CARDIACI (STEROIDI CARDIOTONICI)

$K_i \simeq 10\,nM$ per la pompa del Na^+
(bloccano la defosforilazione di E_2-P, se applicati extracell.)



Ouabaina

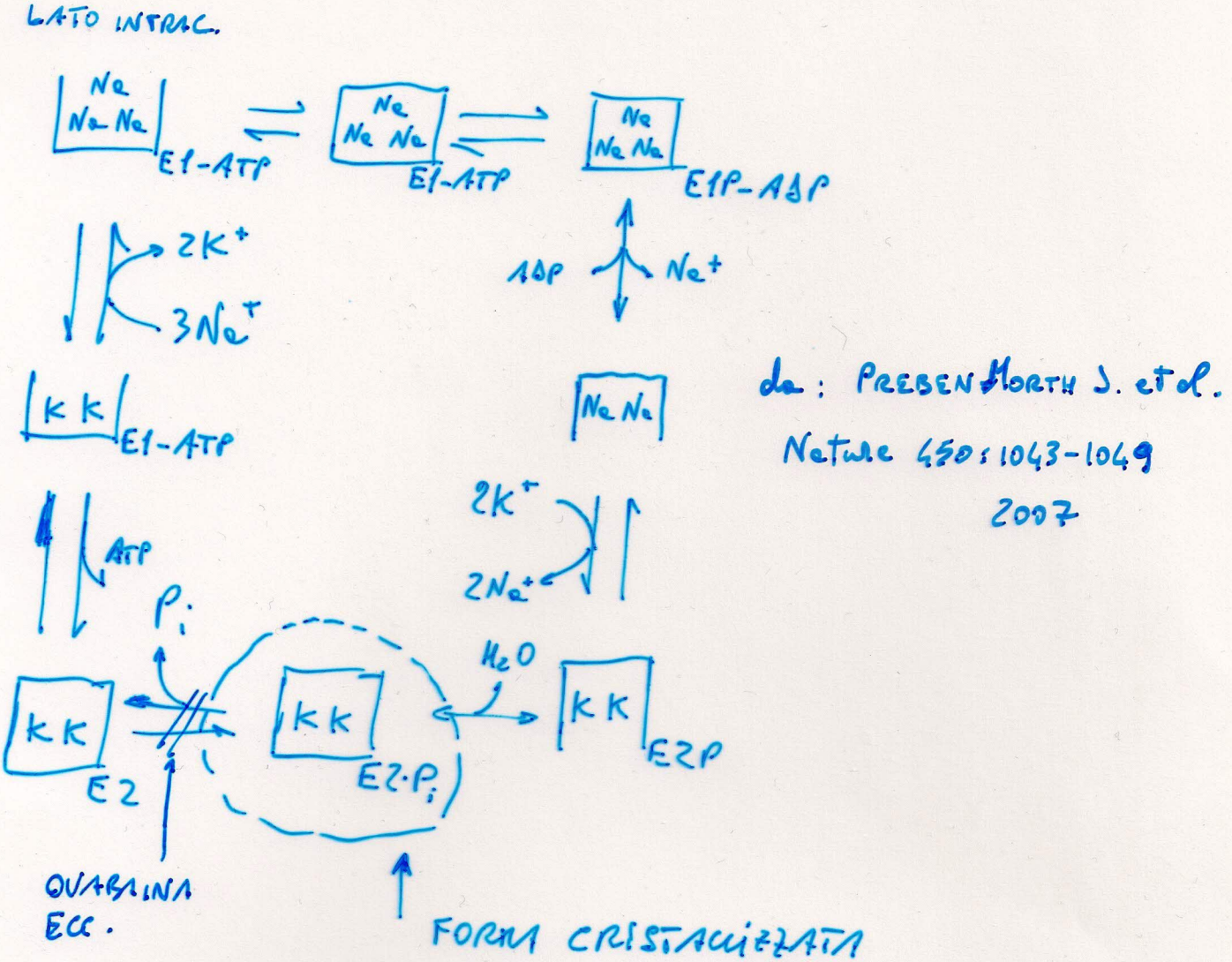
DIGITALE (Digitalis purpurea)

↓

FOGLIE SECCHE

→ OUABAINA
DIGITOSSIGENINA
STROFANTIDINA

CICLO DI POST



da: PREBEN MORTH J. et al.
Nature 450: 1043-1049
2007

ATPasi: di tipo P

- intermedio fosforilato
- bloccate da vanadato

MORTH J.P. et al.

CRYSTAL STRUCTURE OF THE SODIUM-POTASSIUM PUMP.

Nature 450: 1043-1049, 2007

MORTH J.P. et al.

A STRUCTURAL OVERVIEW OF THE PLASMA MEMBRANE Na^+, K^+-ATPase AND H^+-ATPase ION PUMPS.

Nat. Rev. Mol. Cell Biology

12: 60-70, 2011

two small helices connected by a loop, as a possible target for interaction with regulatory proteins (Fig. 5a).

The C-terminal extension is crucial for Na^+ binding

The αM10 helix ends with three arginines (1003–1005) followed by the PGG motif and an extension of eight residues relative to the C terminus of the Ca^{2+}-ATPase (SERCA1a isoform). The small α-helix formed by the first part of this extension is accommodated between βM, αM7 and αM10, and the two C-terminal tyrosine residues are recognized by a binding pocket between αM7, αM8 and αM5 (Figs 5b and 6a, b). The insertion of Tyr 1015 and Tyr 1016 in this pocket is made possible by the kink of αM7 at Gly 848. Tyr 1016 seems to interact with Lys 766 of αM5 and Arg 933 in the loop connecting αM8 and αM9. This loop also contains Ser 936, a controversial phosphorylation site proposed to be responsible for some of the cAMP-dependent kinase (PKA)-mediated effects on the Na^+,K^+-ATPase[9,38]. Ser 936 is located within interaction distance of Arg 1003 (Fig. 6b). The unexpected features of the C terminus prompted us to study its functional importance by deletion of the five most C-terminal residues (Fig. 6c). The truncated enzyme (ΔKETYY) exhibited an extraordinary 26-fold reduction of the Na^+ affinity, yet the affinity for activating K^+ was like wild-type (Fig. 6c, upper panels). This is a direct effect of the truncation on the Na^+-binding E1 conformation, and not caused by displacement of the E1–E2 conformational equilibrium toward E2. In fact, the conformational equilibrium of ΔKETYY seems to be slightly displaced in the opposite direction towards E1, because the apparent affinities for ATP (binding preferentially to E1) and vanadate (binding only to E2) were found slightly enhanced and reduced, respectively (Fig. 6c, lower panels). The conspicuous and highly Na^+-selective effect of the ΔKETYY truncation is reminiscent of the effects observed previously for mutation of Tyr 771 (αM5)[39] and Thr 807 (αM6)[18]. Together with Glu 954 (αM9) these residues have been suggested to make up a third Na^+-binding site (Na^+ sites 1 and 2 probably being formed by almost the same coordinating side chains as the two K^+/Rb^+ binding sites)[40–42]. We find these residues to cluster and to be lined by Asp 808 (αM6), bridging to K^+/Rb^+ site 2. In addition, Gln 923 (αM8) is found in the same cluster and could be involved with the

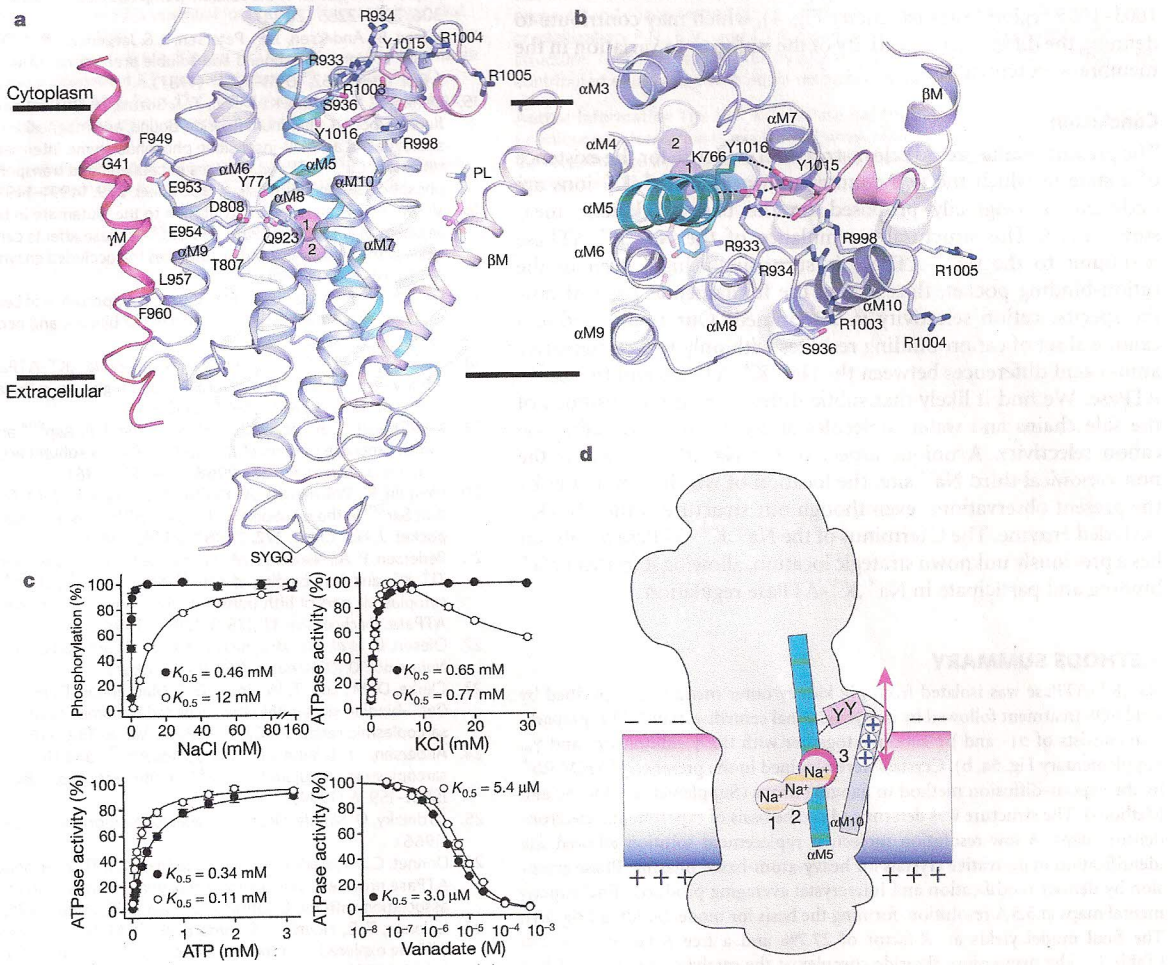


Figure 6 | The C-terminal switch. **a**, Side view of the transmembrane domain with the C-terminal switch region shown in the upper right part. In addition, residues of possible importance for interaction between α- and γ-subunits and between α- and β-subunits (SYGQ) and the third Na^+ site, as well as the modelled phosphatidylcholine head group (PL), are indicated. **b**, Top view from the cytoplasmic side of the C-terminal intrusion into the transmembrane region. Possible direct contacts between the tyrosine residues and Lys 766 and Arg 933 are represented by dashed lines. **c**, Functional analysis of the truncated enzyme ΔKETYY (open symbols) and the wild type (closed symbols). The apparent affinities for Na^+, K^+, ATP and vanadate are indicated as $K_{0.5}$ (the concentration giving half-maximum effect) values in the relevant panels. Error bars, s.e.m.; $n = 3$–6). The inhibition seen at high K^+ concentrations for ΔKETYY but not for the wild type, in the upper right panel, is a consequence of the reduced Na^+ affinity, allowing K^+ to compete efficiently with Na^+ at the sites of the E1 form[1]. **d**, Cartoon of the proposed functional elements of the C-terminal switch. The red double arrow indicates a change in membrane potential. The pull/push exerted by the switch on M5 may affect the affinity of the third electrogenic Na^+ site. The positive charges of the three arginines of αM10 at the membrane surface suggested to sense the membrane potential are indicated in blue. The interaction between the C-terminal tyrosine residue and M5 is indicated by lines.

PRINCIPALI TRASPORTI ATTIVI PRIMARI (ATPasi di trasporto).

ATPasi di trasporto	Localizzazione	Funzione
a) **Tipo P**		
Na^+/K^+	plasmalemma (tutte le cellule animali)	gradienti ionici controllo osmotico
H^+/K^+	plasmalemma (cell. parietali)	acidifica lo stomaco
H^+	plasmalemma (vegetali)	gradiente di H^+
Ca^{2+}	plasmalemma (tutte le cellule)	controlla $[Ca^{2+}]_i$
Ca^{2+}	reticolo endo/sarcoplasmico	controlla $[Ca^{2+}]_i$
Cu (ATP7A/B)		
b) **Tipo V**		
H^+	vacuoli, endosomi, lisosomi (animali, piante, funghi)	acidificano il compartimento
c) **Tipo F**		
H^+	mitocondri, cloroplasti plasmalemma di Procarioti	producono ATP
d) **ABC** (due **A**TP **B**inding **C**assettes)		
	plasmalemma ER epiteli	estrusione 'multidrug' assunzione di peptidi CFTR (canale)
	Procarioti	assorbimento

Physiol Rev 87: 1011–1046, 2007;
doi:10.1152/physrev.00004.2006.

Function and Regulation of Human Copper-Transporting ATPases

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Lutsenko S, Barnes NL, Bartee MY, Dmitriev OY. Function and Regulation of Human Copper-Transporting ATPases. *Physiol Rev* 87: 1011–1046, 2007; doi:10.1152/physrev.00004.2006.—Copper-transporting ATPases (Cu-ATPases) ATP7A and ATP7B are evolutionarily conserved polytopic membrane proteins with essential roles in human physiology. The Cu-ATPases are expressed in most tissues, and their transport activity is crucial for central nervous system development, liver function, connective tissue formation, and many other physiological processes. The loss of ATP7A or ATP7B function is associated with severe metabolic disorders, Menkes disease, and Wilson disease. In cells, the Cu-ATPases maintain intracellular copper concentration by transporting copper from the cytosol across cellular membranes. They also contribute to protein biosynthesis by delivering copper into the lumen of the secretory pathway where metal ion is incorporated into copper-dependent enzymes. The biosynthetic and homeostatic functions of Cu-ATPases are performed in different cell compartments; targeting to these compartments and the functional activity of Cu-ATPase are both regulated by copper. In recent years, significant progress has been made in understanding the structure, function, and regulation of these essential transporters. These studies raised many new questions related to specific physiological roles of Cu-ATPases in various tissues and complex mechanisms that control the Cu-ATPase function. This review summarizes current data on the structural organization and

ATP-asi di TIPO P

SERCA 1 subunità
H^+ ATPasi FUNGINA
] CRISTALLO N 2000

Na^+/K^+ ATPas: " 2007
2009

SUBUNITÀ PRINCIPALI:

10 SEGMENTI M (TM): M1-M10 (α-eliche)
3 ANSE CIRCONDANO UN CANALE CENTRALE

SERCA: SUBUNITÀ α

Na^+/K^+ ATPasi: $\alpha\beta(\gamma)$ x2 (?)
TIPICAMENTE $\alpha_1\beta_1$

α_1 URIDINA

α_2 MUSCOLO, CERVELLO, POLMONI, ADIPOCITI (TUTTI)

α_3 NEURONI e CELL. CARDIACHE

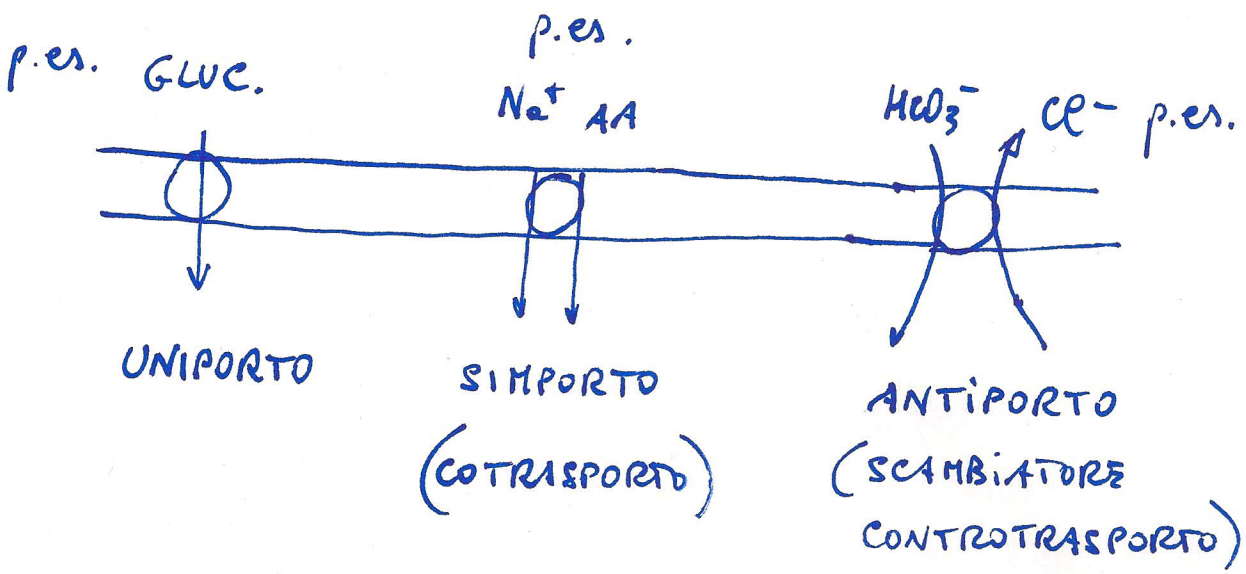
α_4 TESTICOLI

β_1 QUASI OVUNQUE

β_2 neuroni (cuore di certe specie, alveolo polmonare)

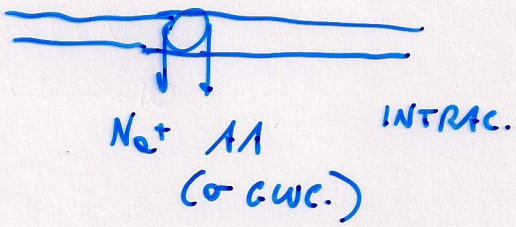
β_3 sviluppo CNS e Testicoli

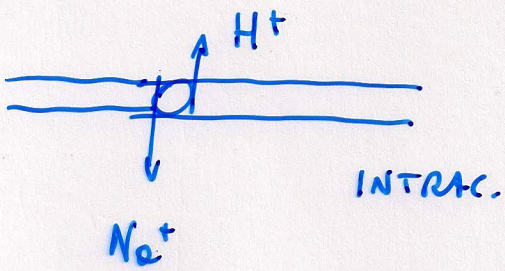
NOMENCLATURA DEI TRASPORTATORI

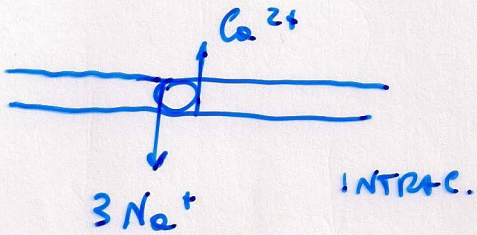


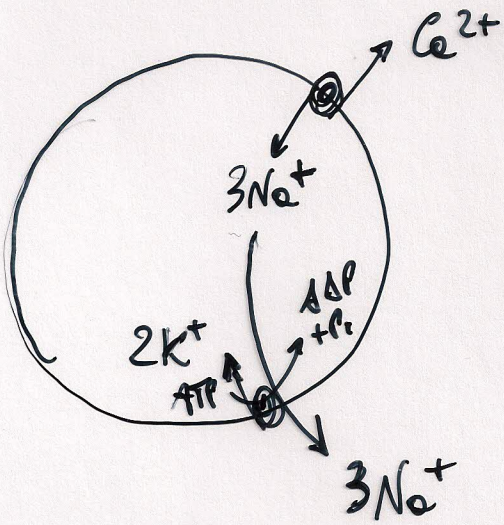
TRASPORTI ATTIVI SECONDARI

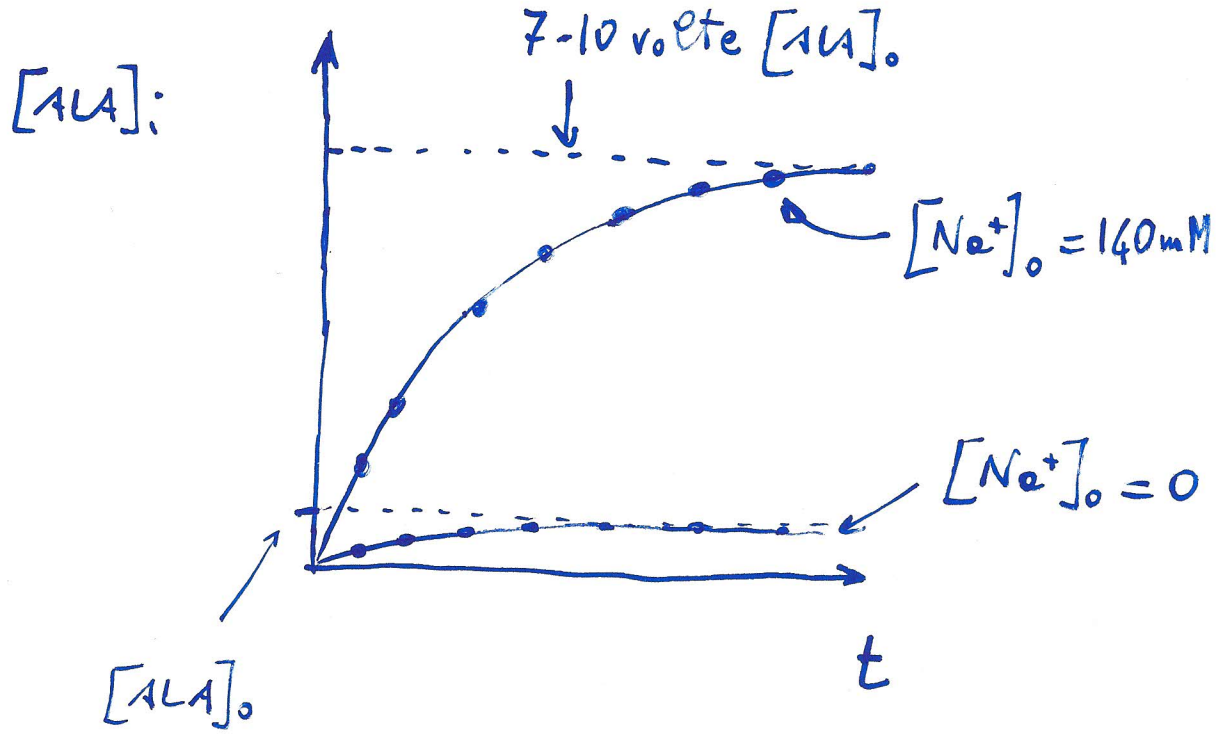
ESEMPI:











$[ALA]_i$ = conc. intracellulare di ALA

$[ALA]_0$ = conc. extracellulare " "

TRASPORTO ATTIVO SECONDARIO DI UN AMMINOACIDO

TRASPORTO TRANSEPITELIALE

Esempio del glucosio attraverso l'epitelio intestinale.