

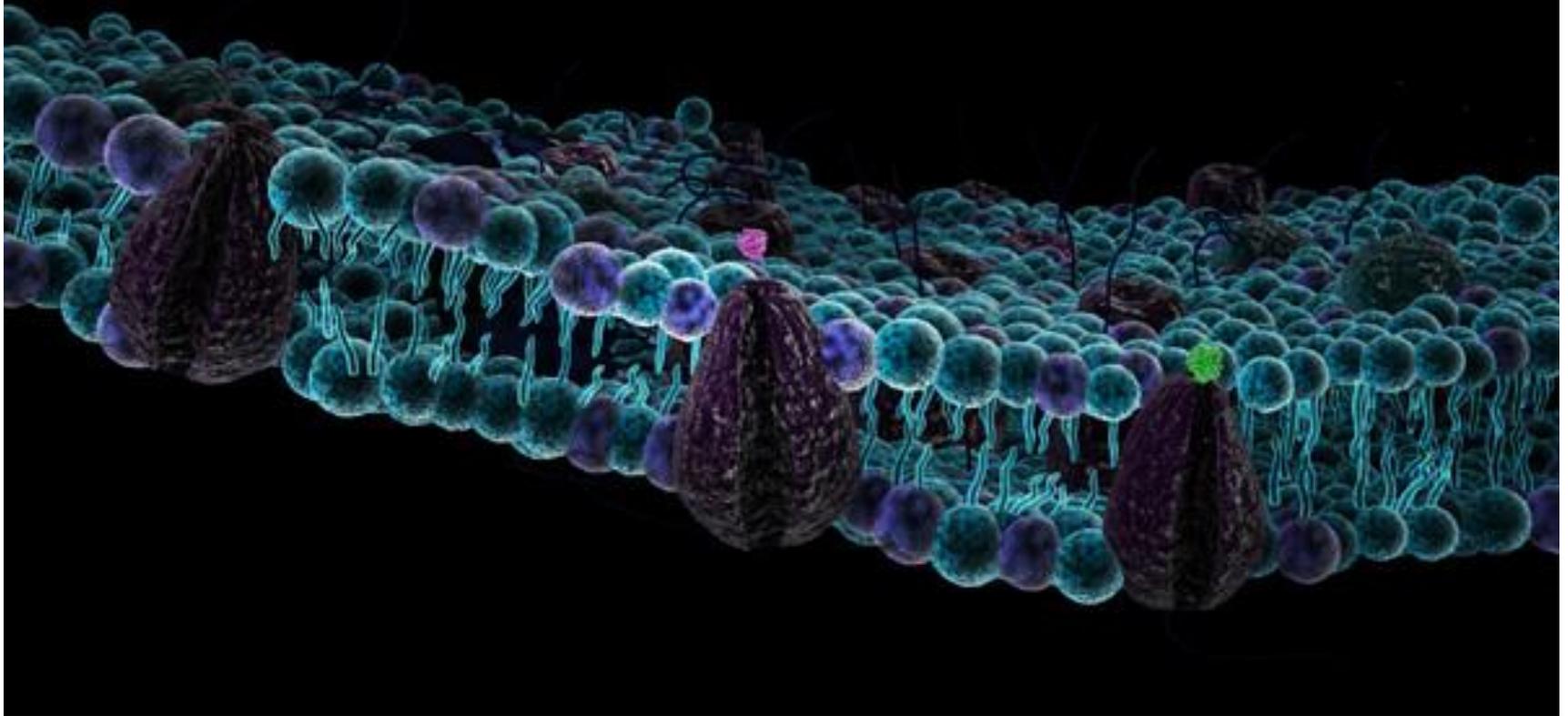


Transporte através da membrana

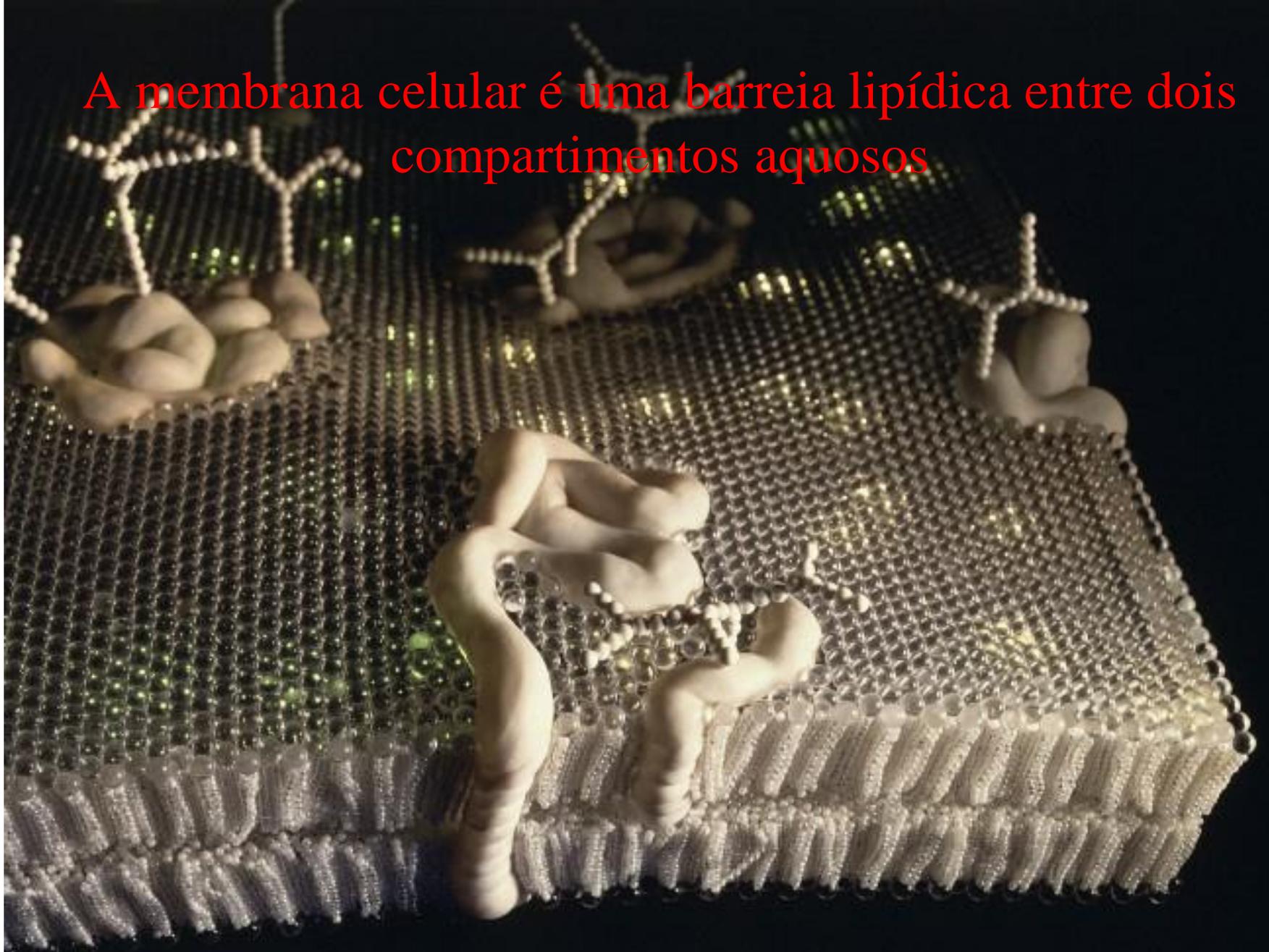
Fisiologia e Biofísica Celular - 2020

RFI5773

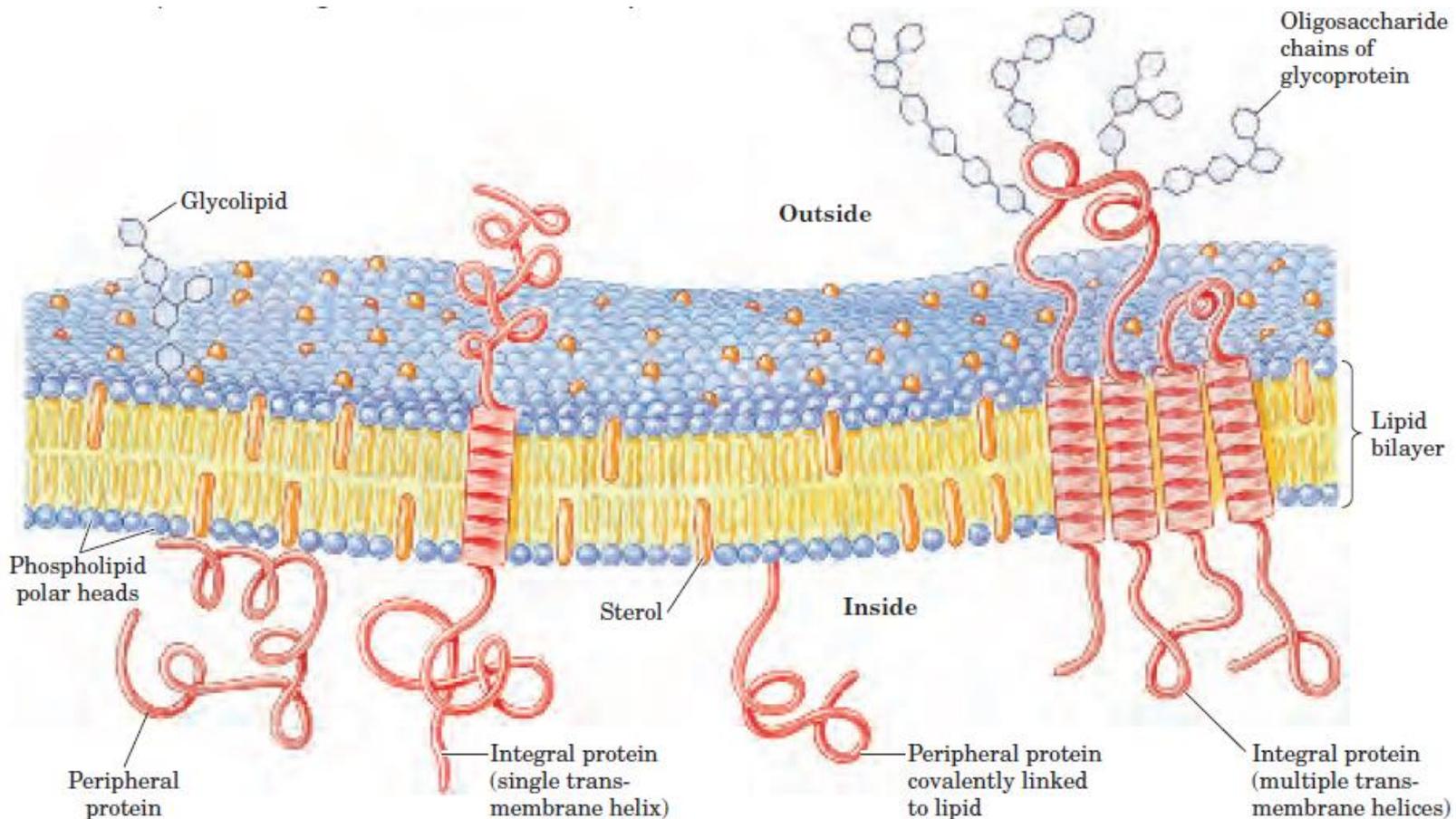
Prof. Ricardo Leão – Departamento de Fisiologia – FMRP-USP



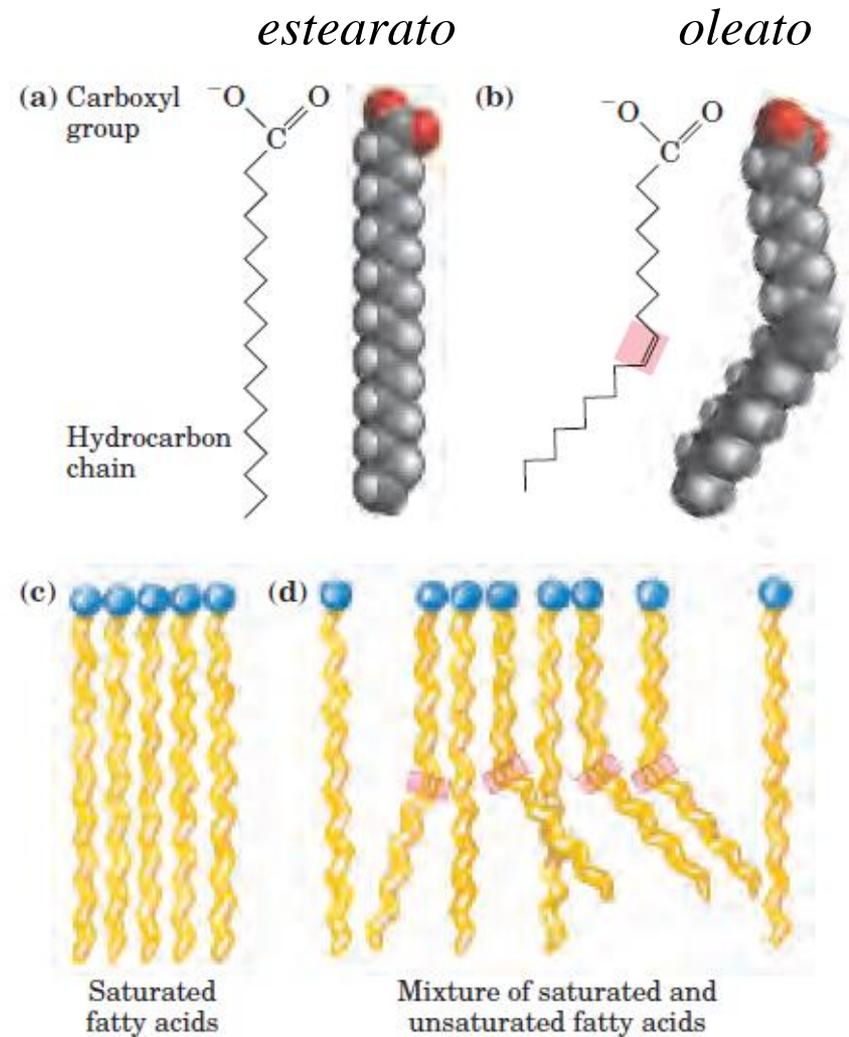
A membrana celular é uma barreira lipídica entre dois compartimentos aquosos



O modelo do mosaico fluido

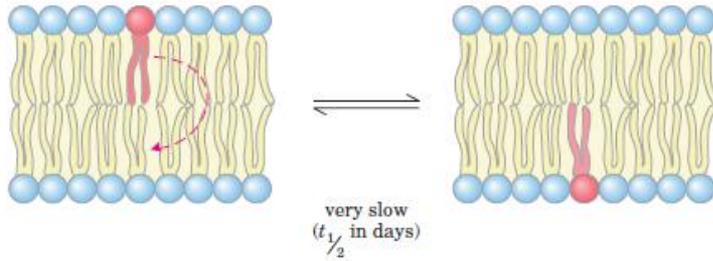


Ácidos graxos saturados e não saturados

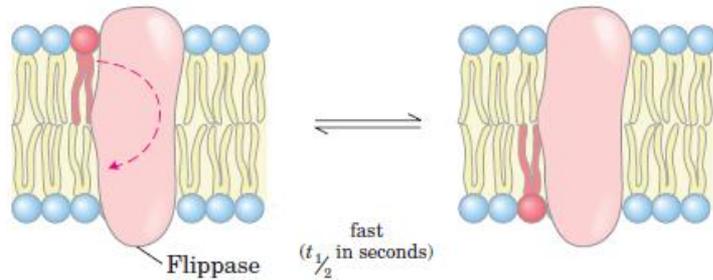


Translocação de lipídeos pela bicamada

(a) Uncatalyzed transverse ("flip-flop") diffusion



(b) Transverse diffusion catalyzed by flippase



(c) Uncatalyzed lateral diffusion

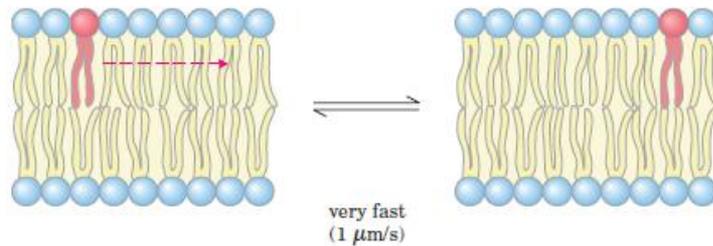
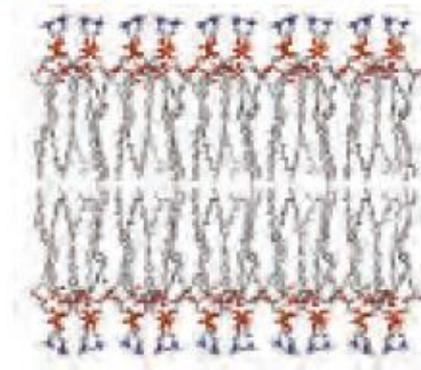


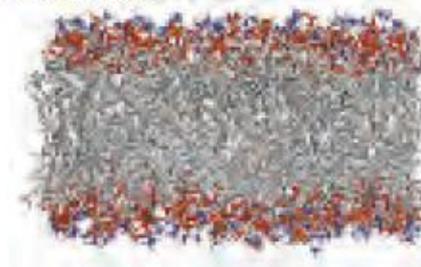
FIGURE 11-16 Motion of single phospholipids in a bilayer. (a) Movement from one leaflet to the other is very slow, unless (b) catalyzed by a flippase; in contrast, lateral diffusion within the leaflet (c) is very rapid and requires no protein catalysis.

Transição gel-sol

(a) Paracrystalline state (gel)



(b) Fluid state

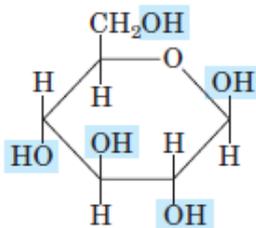


↑ Heat produces thermal motion of side chains (gel → fluid transition)

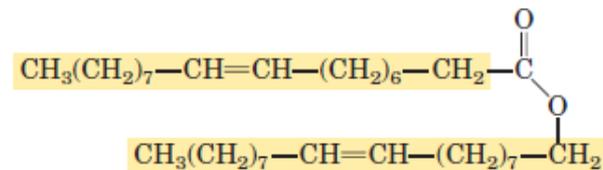
Substâncias polares, apolares e anfipáticas

TABLE 2-2 Some Examples of Polar, Nonpolar, and Amphipathic Biomolecules (Shown as Ionic Forms at pH 7)

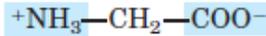
Polar
Glucose



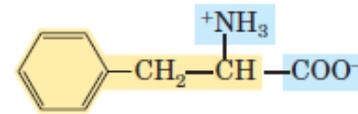
Nonpolar
Typical wax



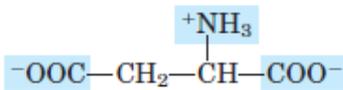
Glycine



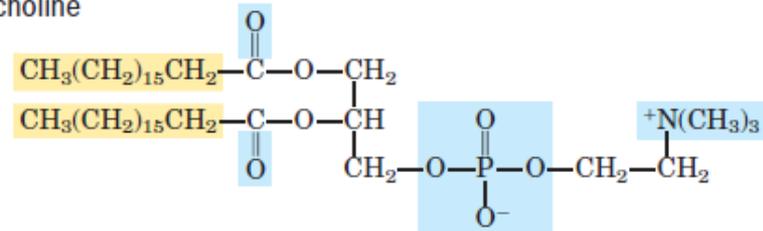
Amphipathic
Phenylalanine



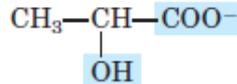
Aspartate



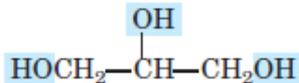
Phosphatidylcholine



Lactate



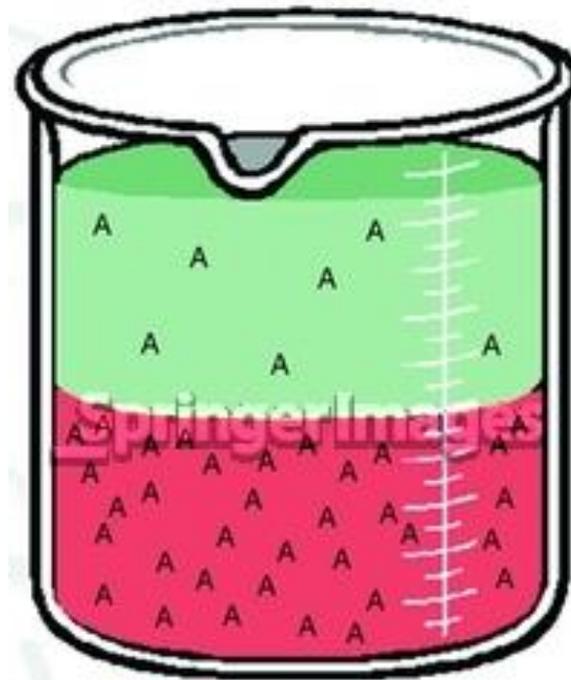
Glycerol



Polar groups Nonpolar groups

O coeficiente de partição óleo/água (β) reflete a solubilidade de uma substância em lipídeos e é proporcional a sua permeabilidade pela membrana

$$\beta = (C_{\text{lipídeo}}/C_{\text{água}}) \text{ no equilíbrio}$$

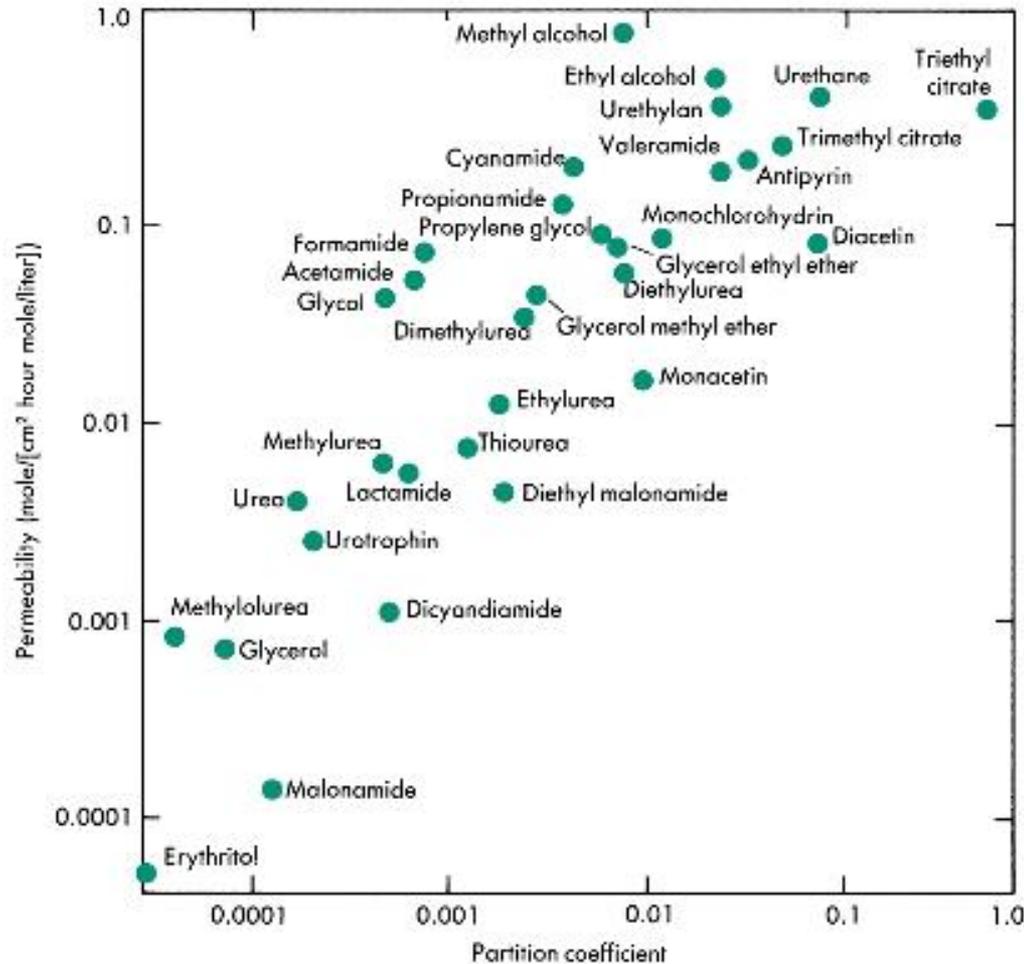


$$K_{ow} = 7/33$$

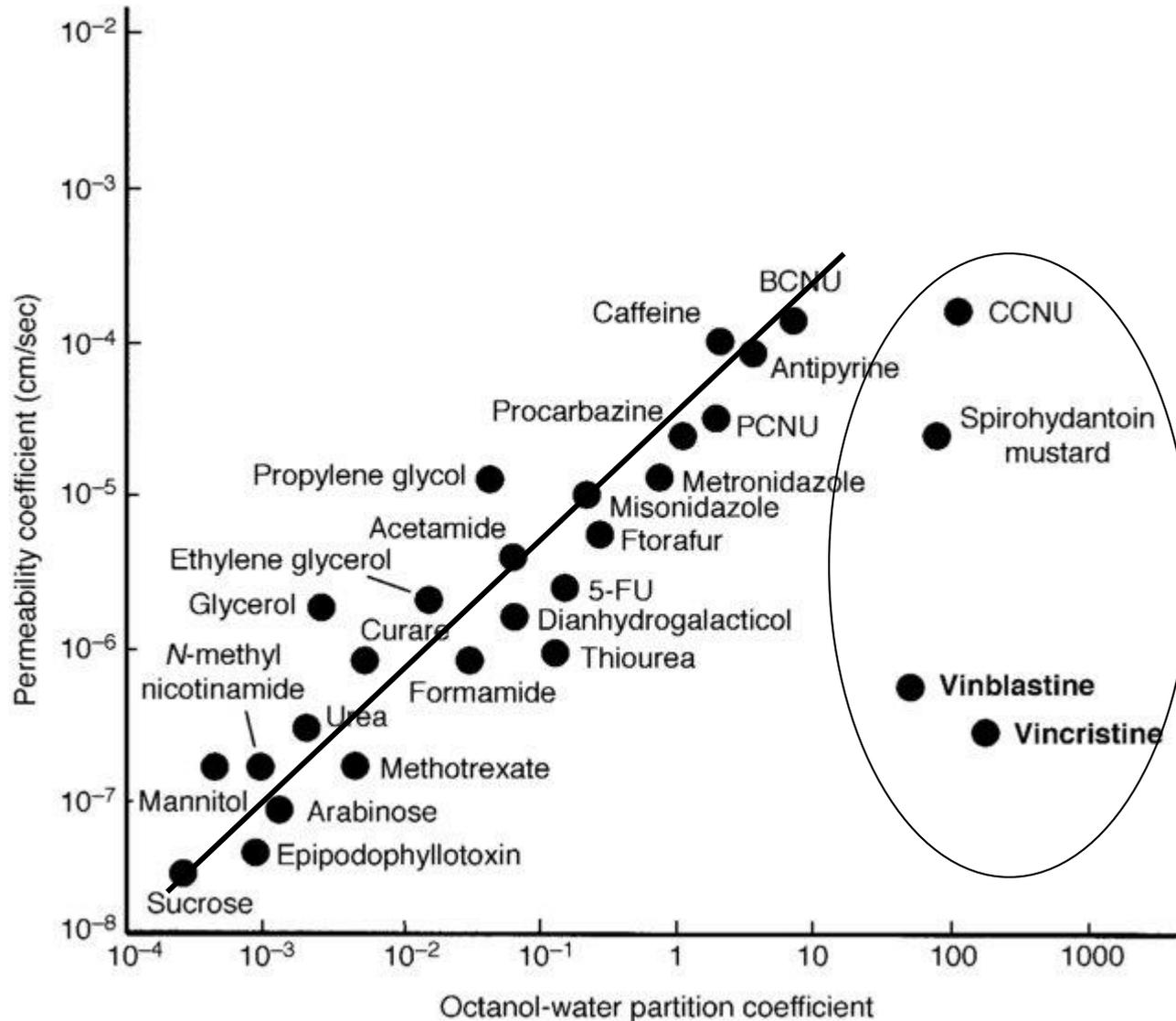


O coeficiente de partição óleo/água (β) reflete a solubilidade de uma substância em lipídeos e é proporcional a sua permeabilidade pela membrana

$$\beta = (C_{\text{lipídeo}}/C_{\text{água}}) \text{ no equilíbrio}$$



Relação coeficiente de partição vs. permeabilidade em capilares cerebrais



Difusão de soluto particionante

Coeficiente de permeabilidade (P)

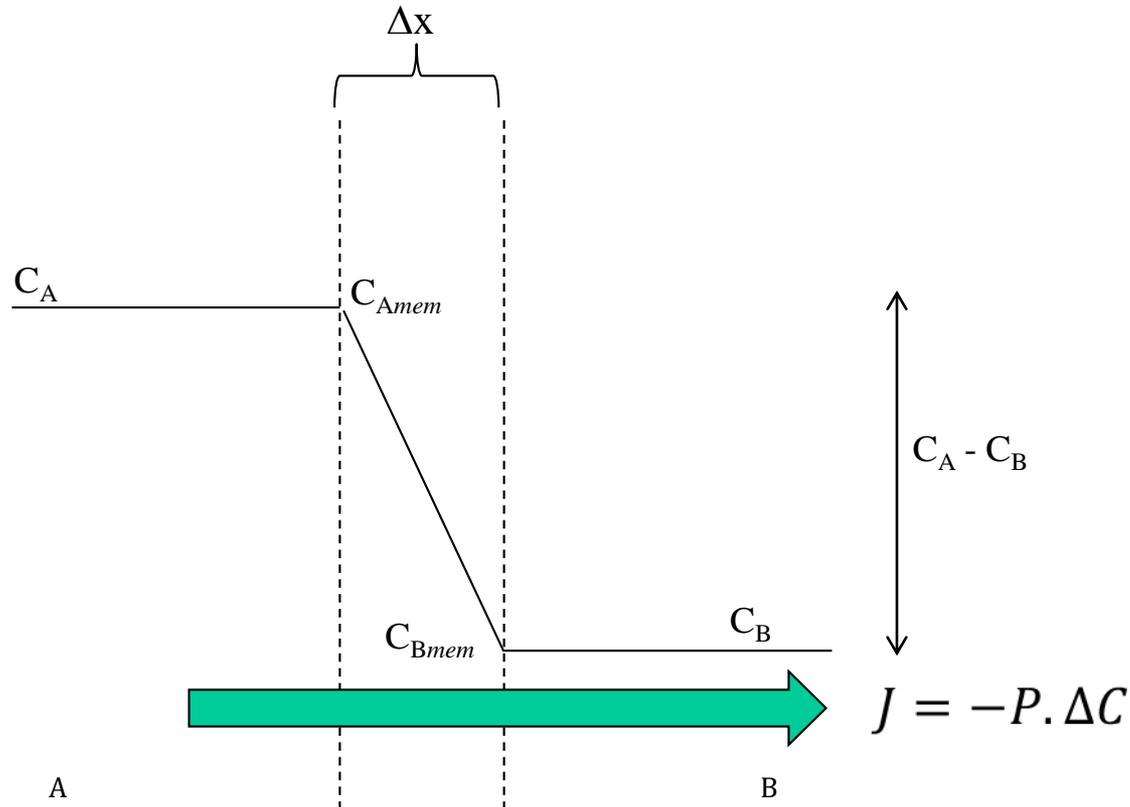
$$P = \frac{\beta D}{\Delta x}$$

Lei de Fick para solutos particionantes

$$J = -P \cdot \Delta C$$

Se $\beta = 0$ não há fluxo (soluto impermeável)

A permeabilidade modula o fluxo

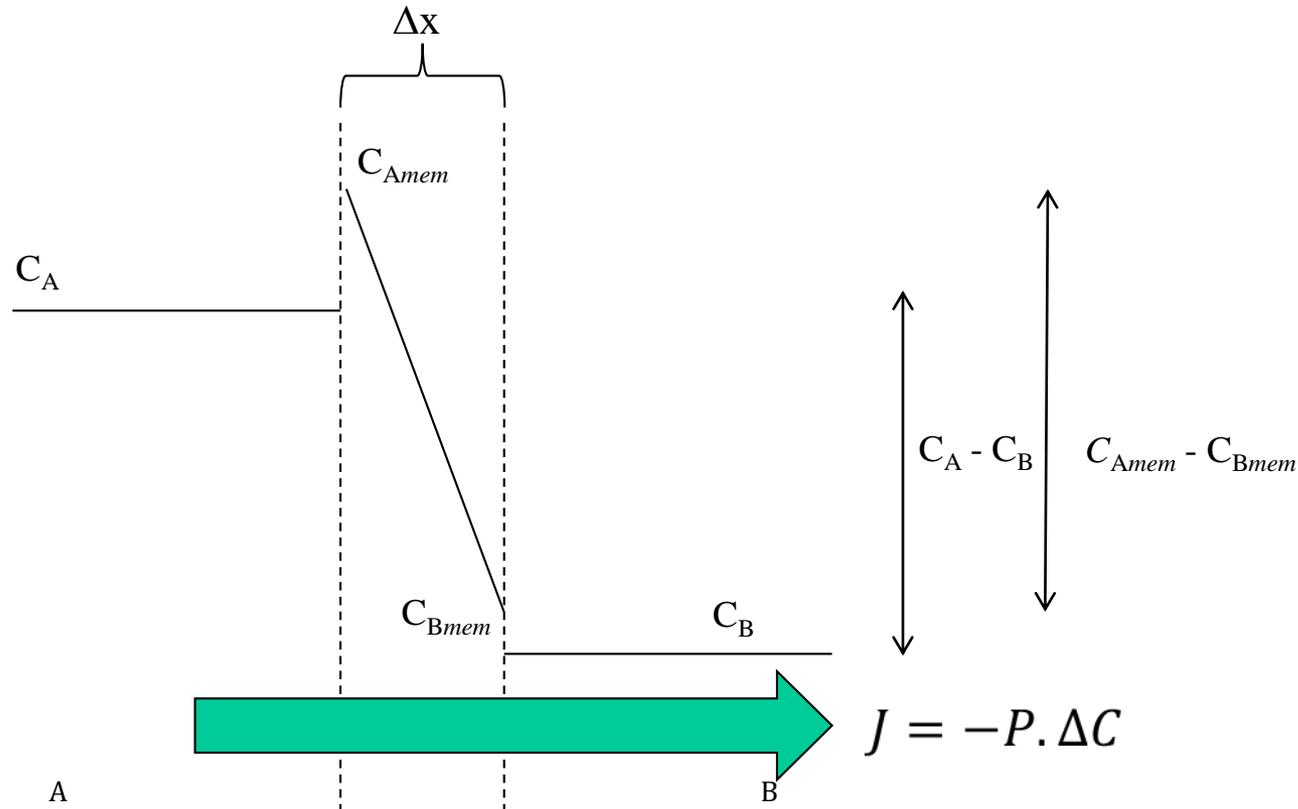


$\beta = 1$ (soluto igualmente solúvel na membrana e no citoplasma)

$$C_A = C_{A\text{mem}}$$

$$C_B = C_{B\text{mem}}$$

A permeabilidade modula o fluxo

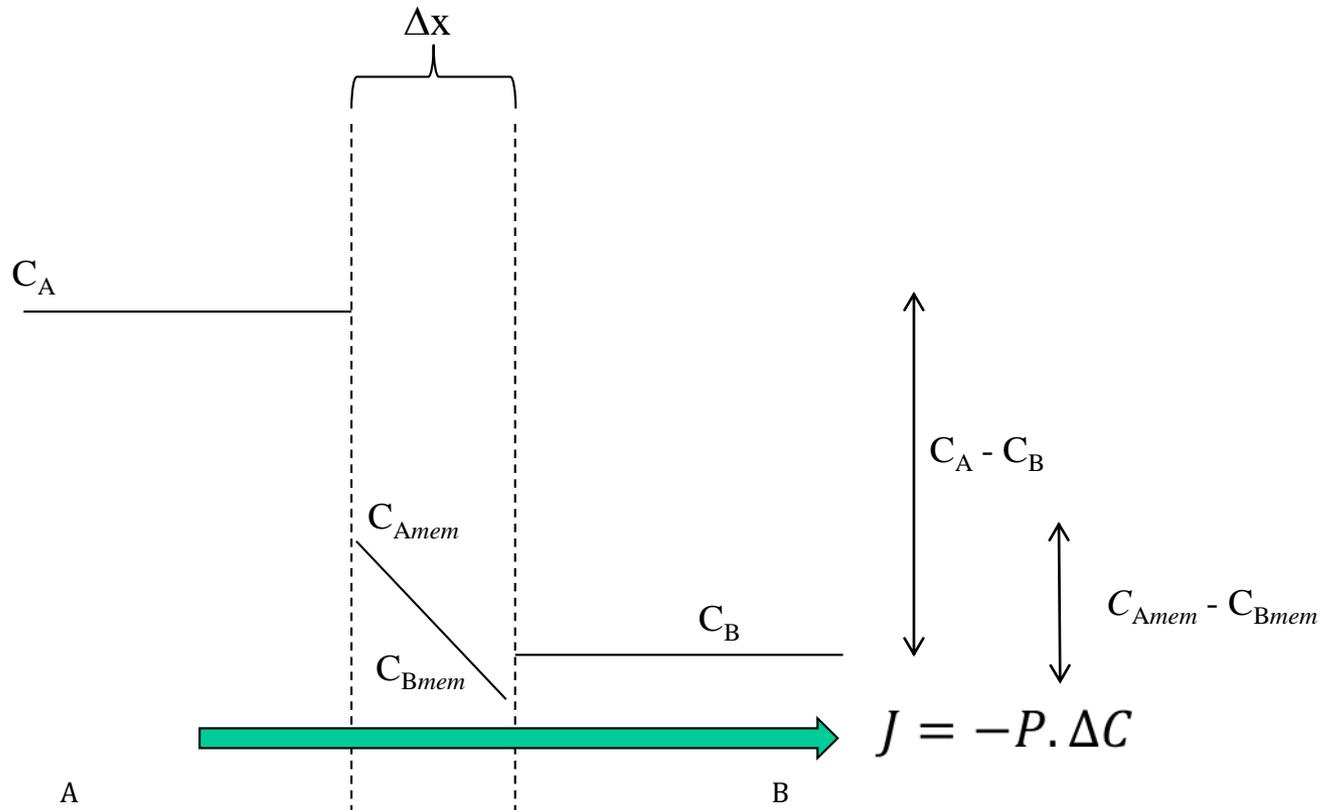


$\beta > 1$ (soluto mais solúvel na membrana do que no citoplasma)

$$C_A < C_{A_{mem}}$$

$$C_B < C_{B_{mem}}$$

A permeabilidade modula o fluxo

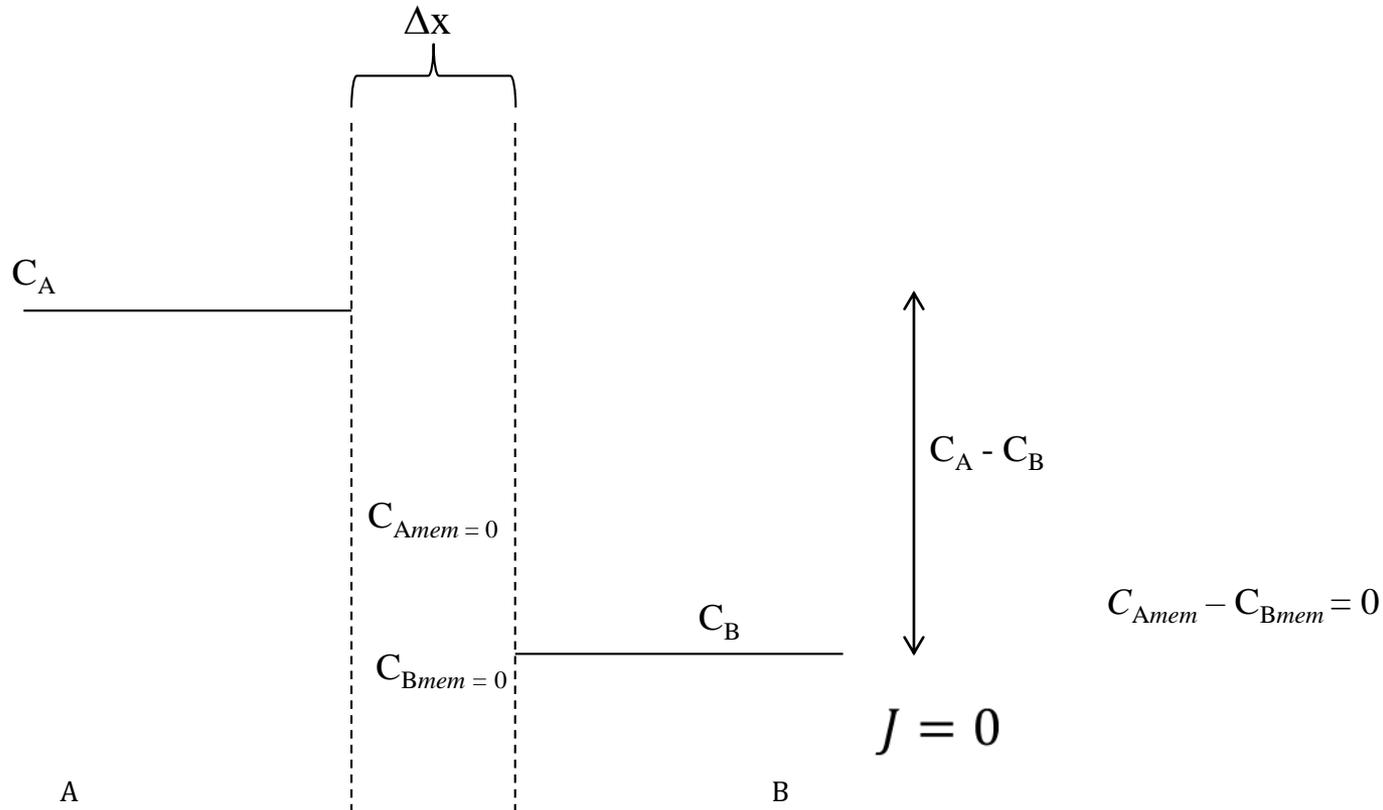


$\beta < 1$ (soluto menos solúvel na membrana do que no citoplasma)

$$C_A > C_{A_{mem}}$$

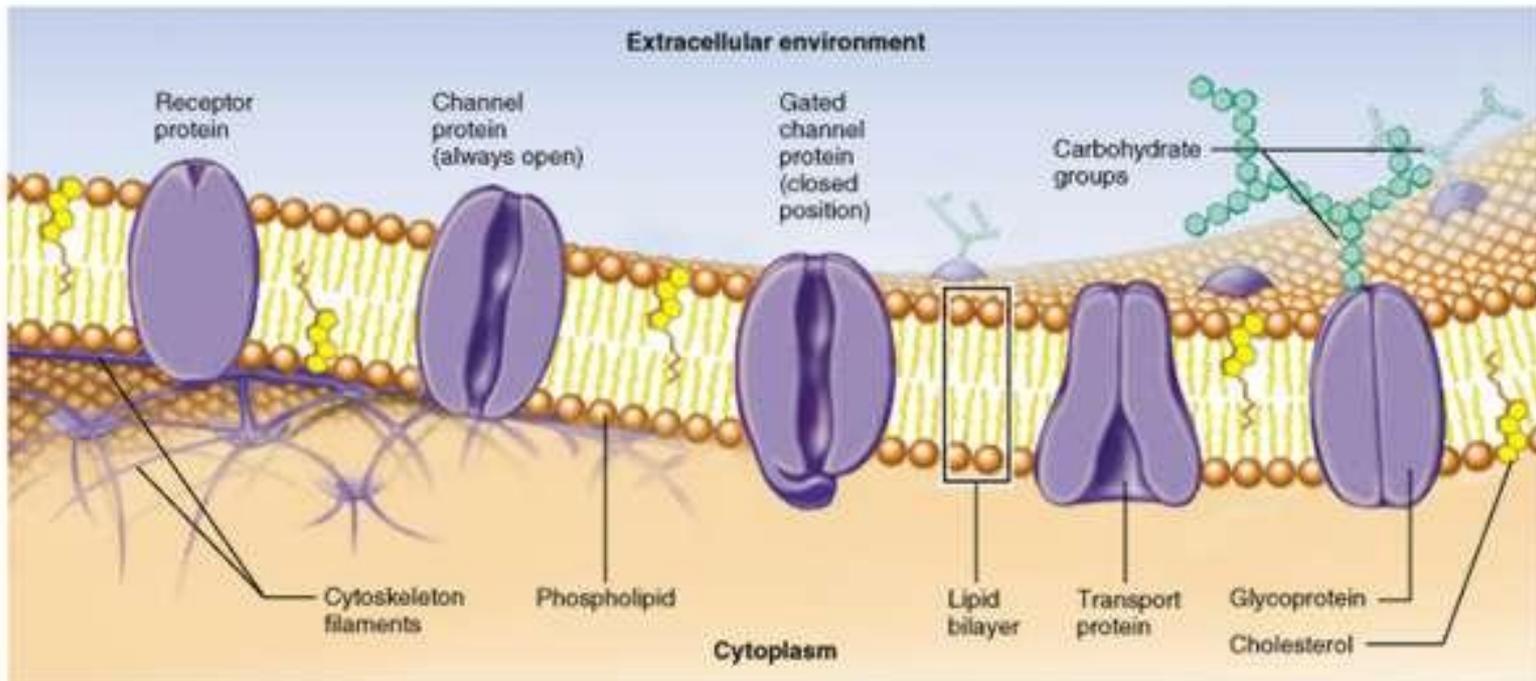
$$C_B > C_{B_{mem}}$$

A permeabilidade modula o fluxo



$\beta = 0$ (insolúvel na membrana)

A membrana celular é lipídica e possui proteínas integrais que a atravessam



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Substâncias hidrosolúveis maiores que a água necessitam de “caminhos” hidrofílicos para atravessar a membrana

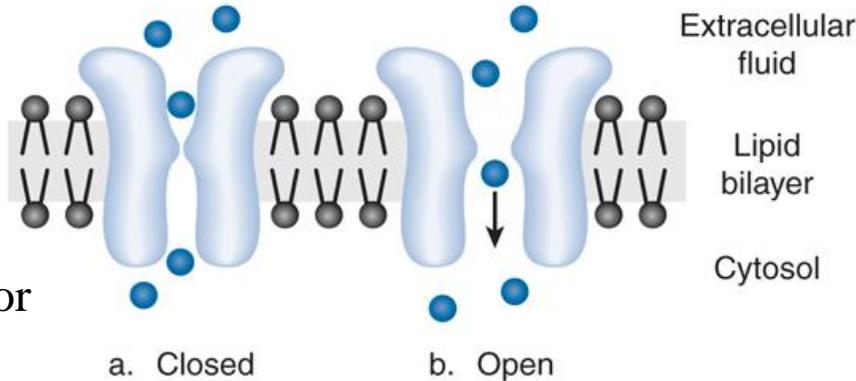
Difusão simples por poros/canais

A. Channel or pore

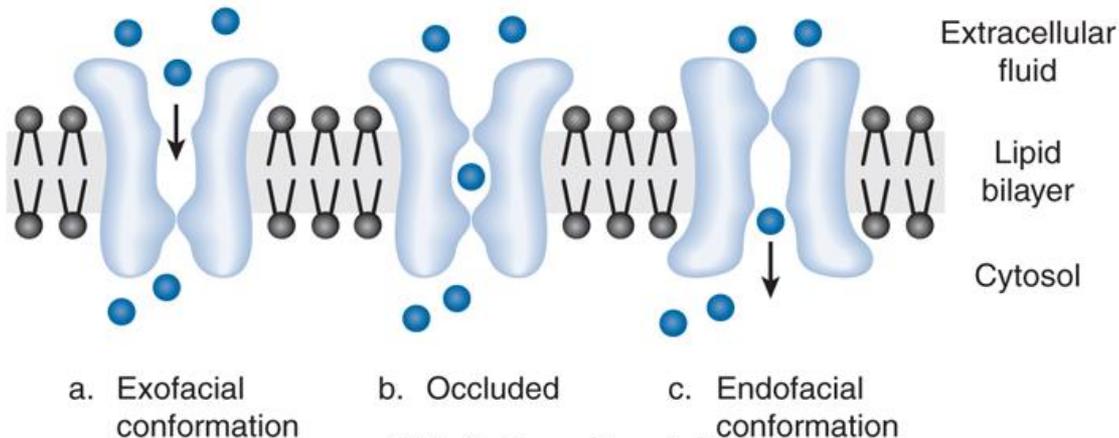


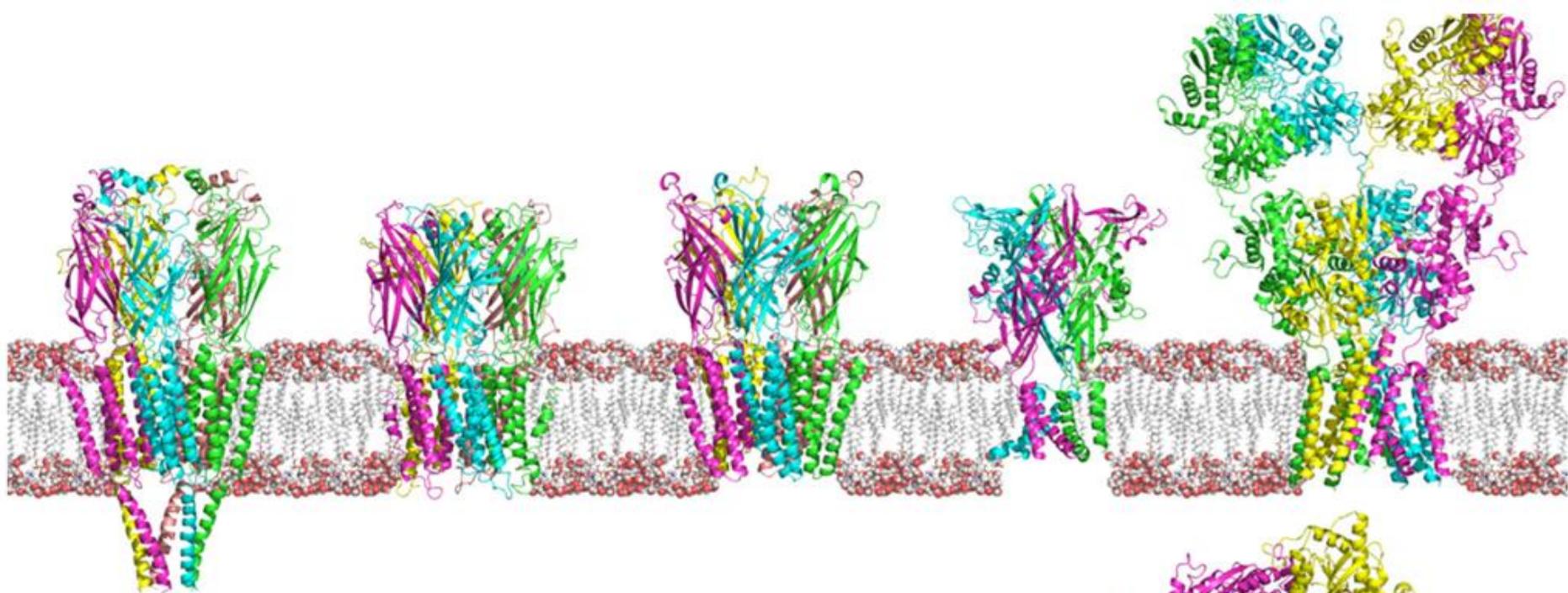
Difusão facilitada por transportadores

B. Gated channel



C. Carrier





8A

A

Receptor de
acetilcolina



7A

B

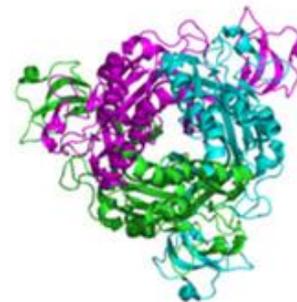
Canal iônico
bacteriano



5A

C

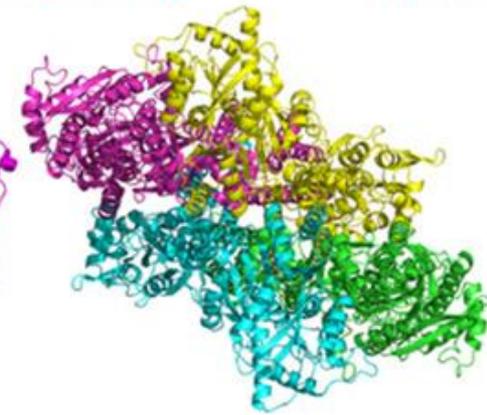
Canal iônico
bacteriano



7A

D

Receptor
purinérgico
(ATP)



Closed

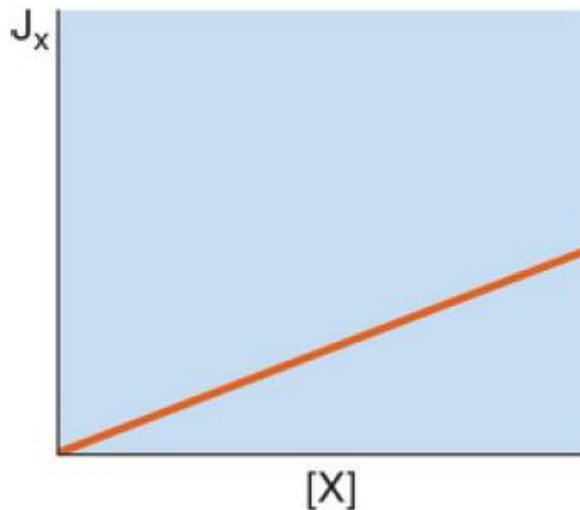
E

Receptor
glutamatérgico
(AMPA)

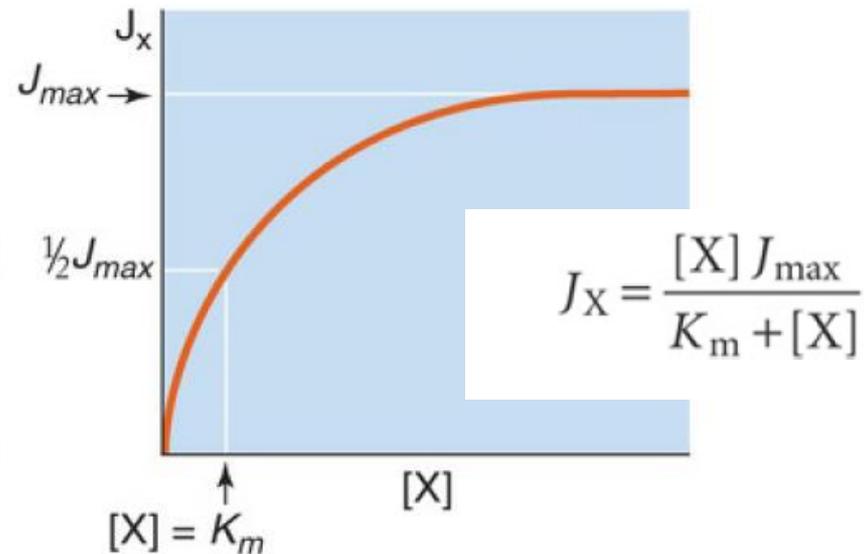
A difusão facilitada se caracteriza:

1. Pela saturação do transporte
2. Pela menor velocidade
3. Pela maior dependência da temperatura
4. Por competição com antagonistas

A SIMPLE DIFFUSION



B CARRIER-MEDIATED OR FACILITATED DIFFUSION

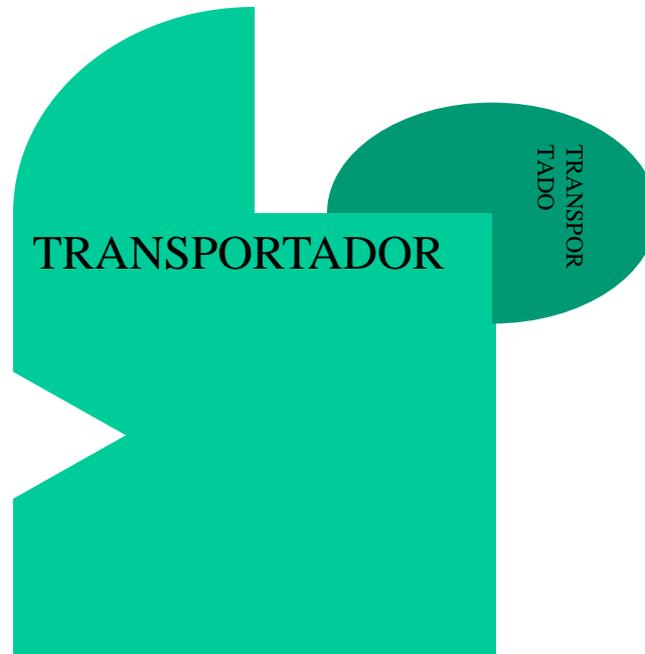
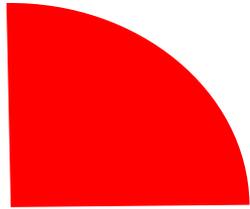


A difusão por canais é mais rápida

*Rate of cycling of the transporter molecule, except for ion channels such as the K⁺ channel, where the turnover number indicates the maximum number of ions transported in 1 second under physiological conditions. Thus each Na⁺ pump molecule cycles 150 times per second and transports 450 Na⁺ (and 300 K⁺) per second.

TRANSPORTER	TURNOVER NUMBER* (PER SEC)
K ⁺ channel	30,000,000
Valinomycin (carrier)	30,000
Glucose carrier (GLUT-1)	3,000
Na ⁺ /Ca ²⁺ exchanger	2,000
Ca ²⁺ pump (SERCA)	200
Na ⁺ pump	150

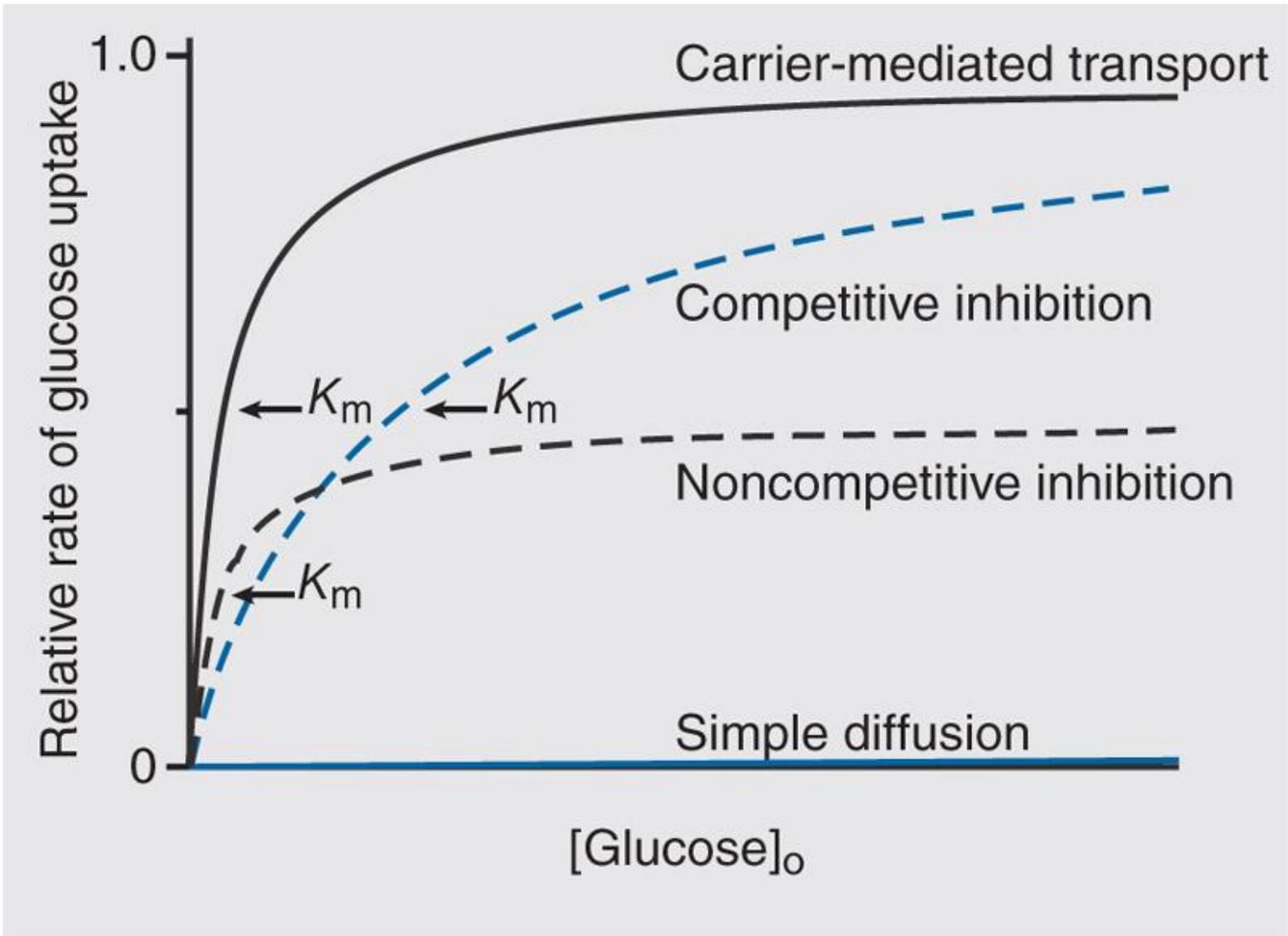
Transportadores podem ser antagonizados Competitivamente



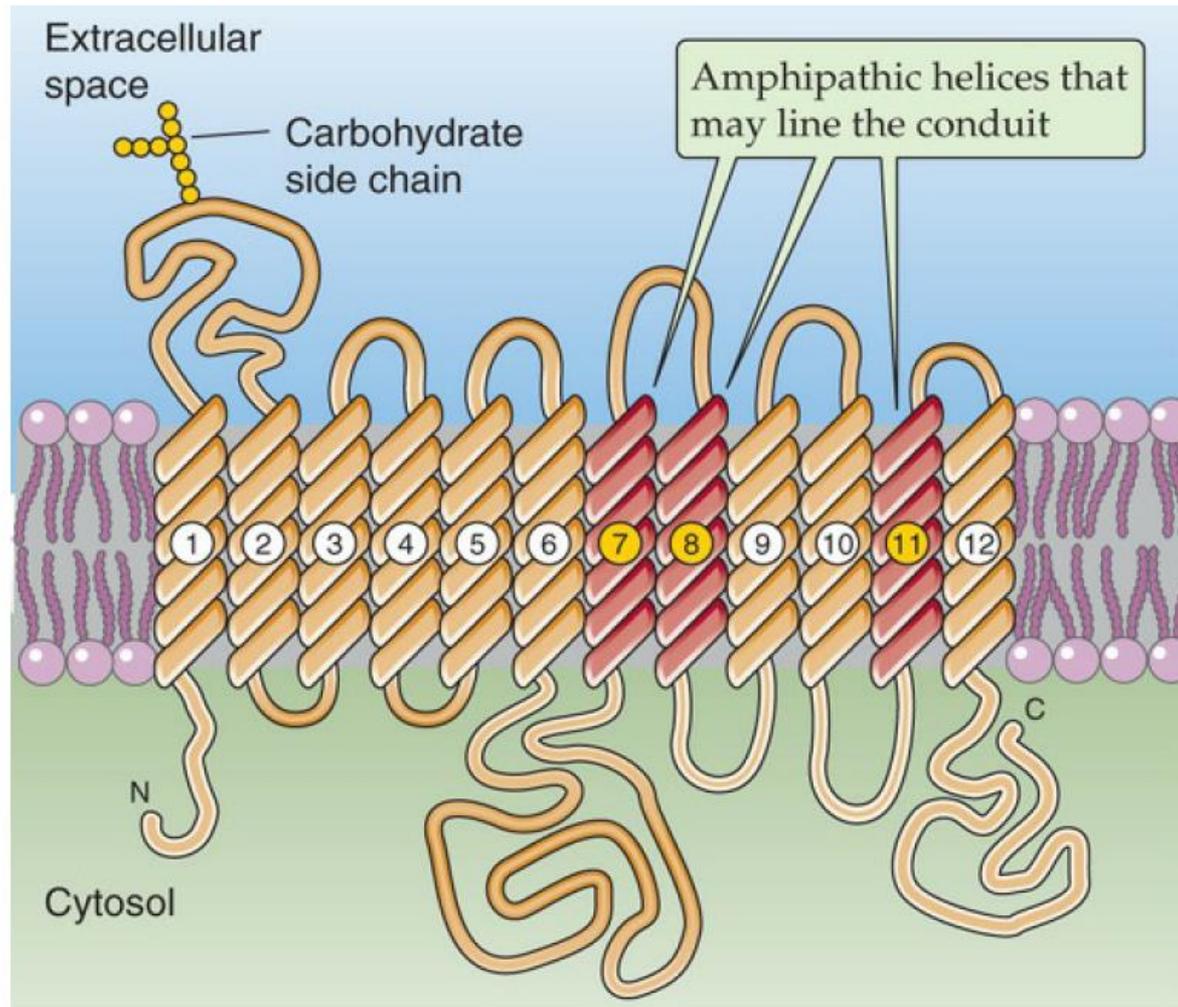
Transportadores podem ser antagonizados

Não-Competitivamente





Transportadores de glucose por difusão facilitada (GLUT)



Transportadores de glucose por difusão facilitada (GLUT)

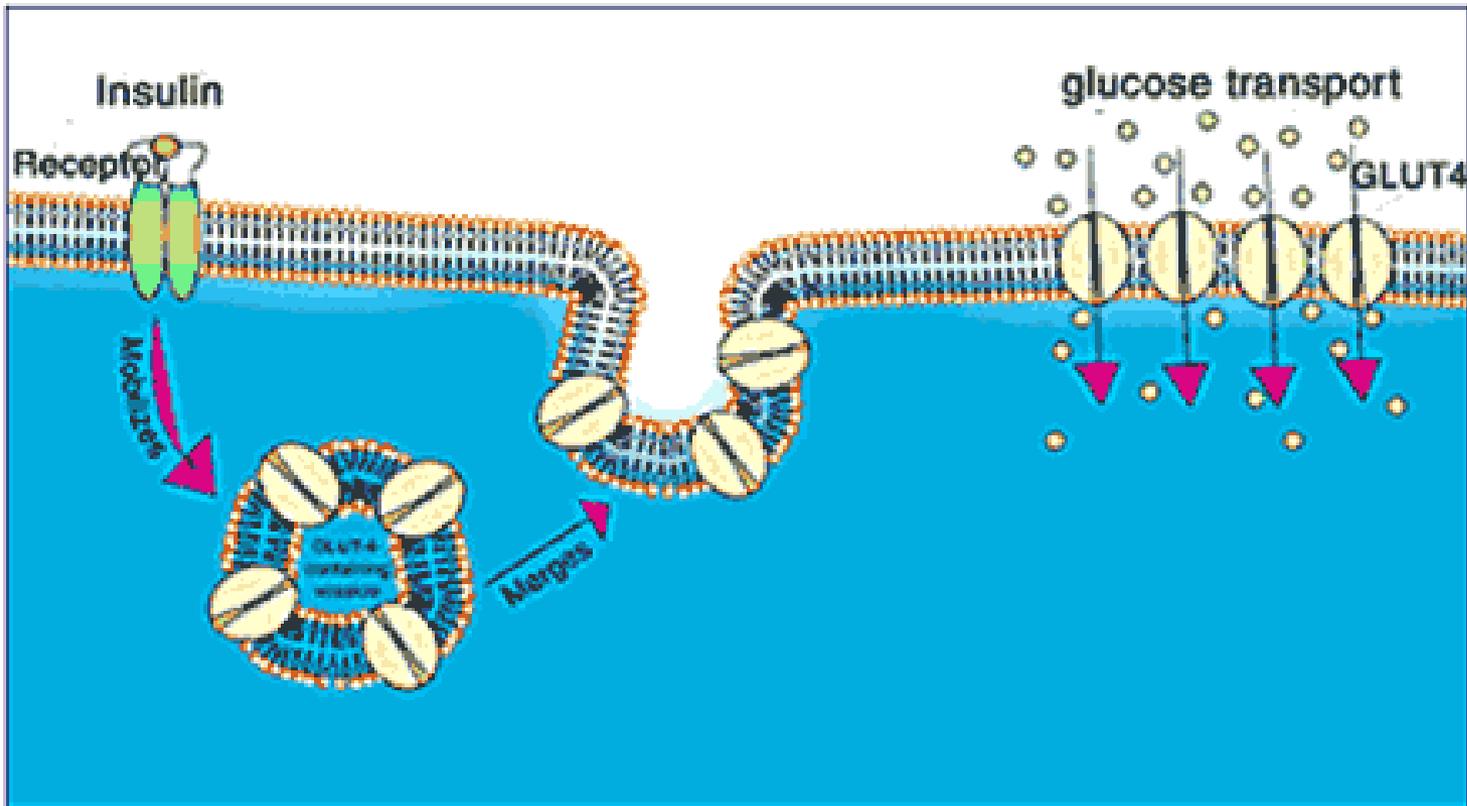
Table 16.4 Family of glucose transporters

Name	Tissue location	K_M	Comments
GLUT1	All mammalian tissues	1 mM	Basal glucose uptake
GLUT2	Liver and pancreatic β cells	15–20 mM	In the pancreas, plays a role in the regulation of insulin In the liver, removes excess glucose from the blood
GLUT3	All mammalian tissues	1 mM	Basal glucose uptake
GLUT4	Muscle and fat cells	5 mM	Amount in muscle plasma membrane increases with endurance training
GLUT5	Small intestine	—	Primarily a fructose transporter

Table 16.4

Biochemistry, Seventh Edition

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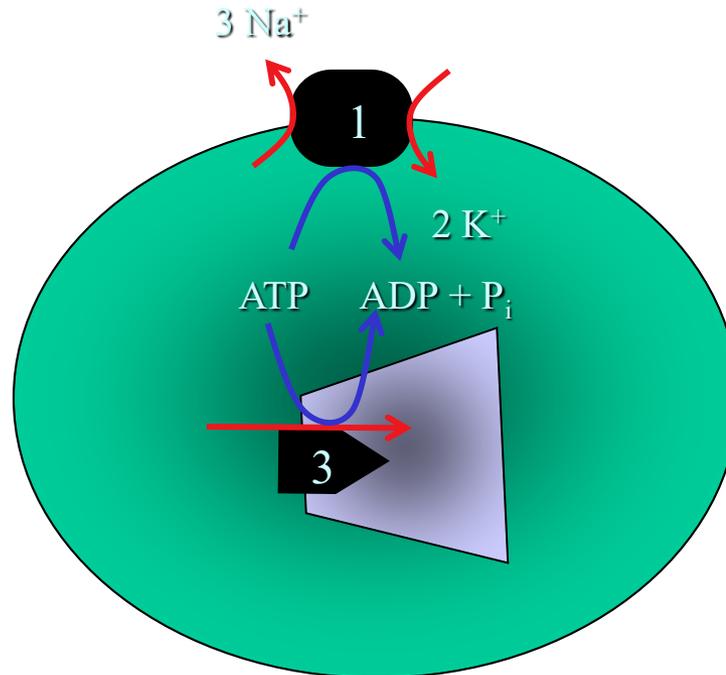
As concentrações iônicas são diferentes dentro e fora da célula

A tabela mostra os principais íons. As quantidades de cargas positivas e negativas são sempre iguais. Princípio da **eletroneutralidade**.

íon	$[\text{íon}]_{\text{externo}}$ (mM)	$[\text{íon}]_{\text{interno}}$ (mM)
Na^+	145	15
Cl^-	100	5
K^+	4,5	150
Ca^{++}	1,8	0,0001

Como esses gradientes químicos
são criados?

Os íons são segregados por transportadores presentes na membrana que realizam **transporte ativo primário**

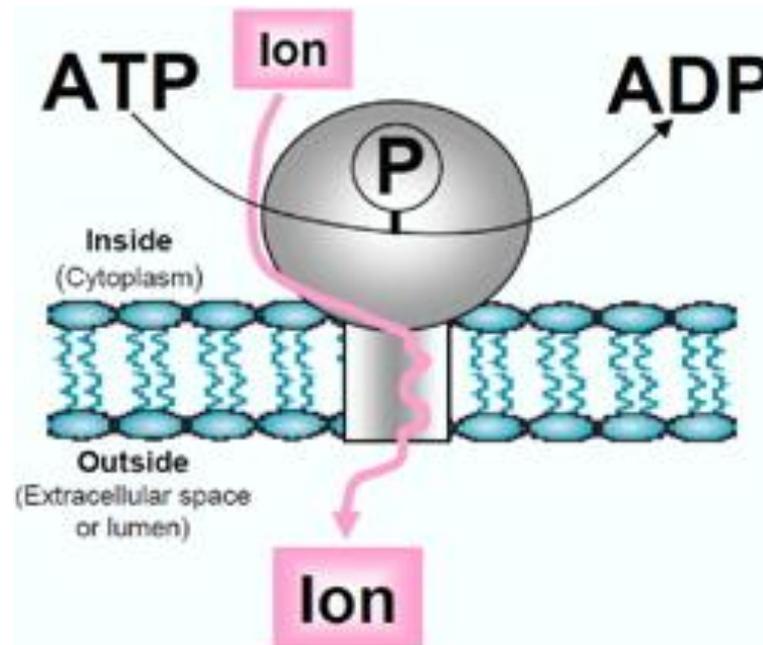


1 - Na/K ATPase

3 - Ca-ATPase reticular

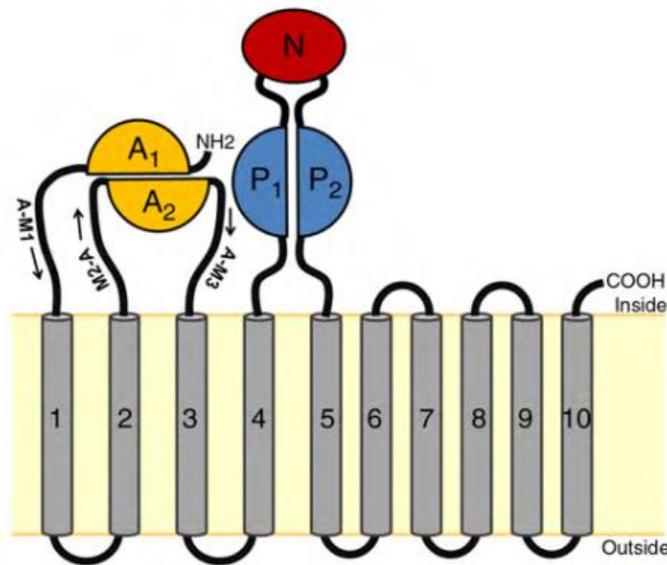
P-ATPases

- P-ATPases recebem esse nome porque são transitoriamente fosforiladas com o fosfato-gama do ATP durante o processo de transporte.
- Representam a grande maioria das ATPases transportadoras das células animais e vegetais.



Estrutura típica das P-ATPases

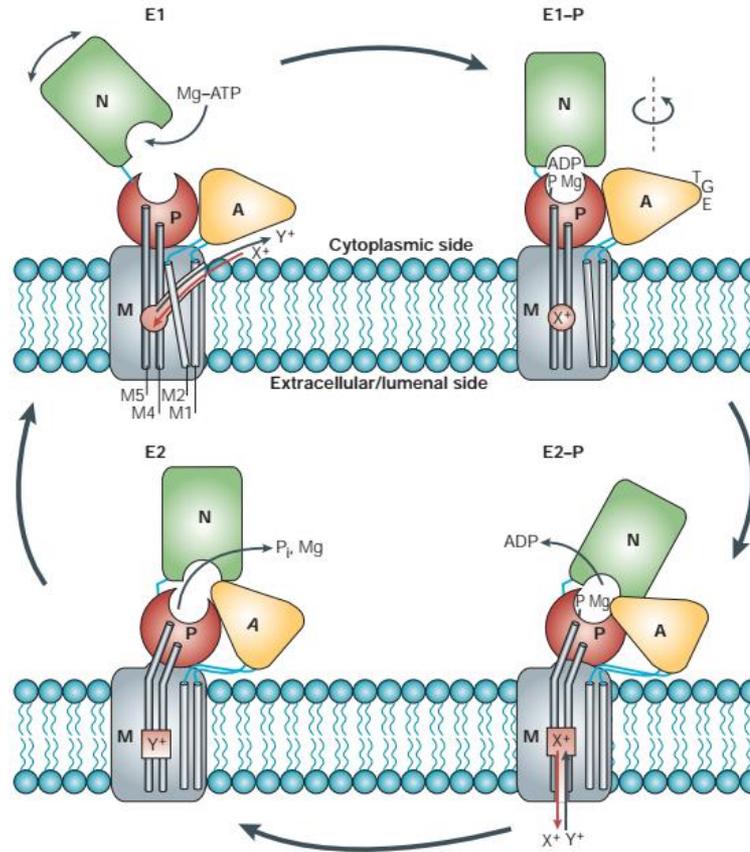
(a)



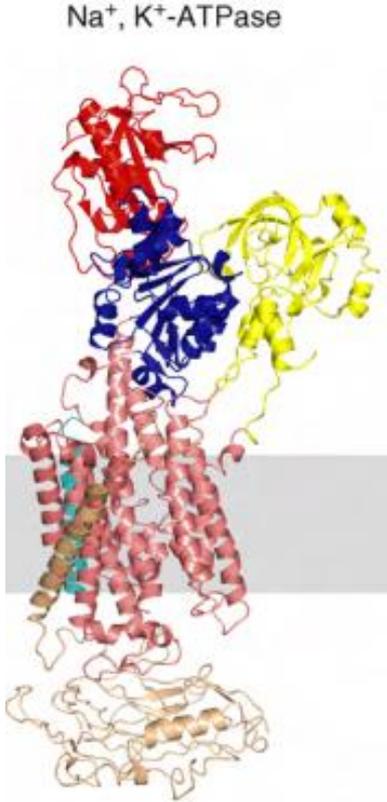
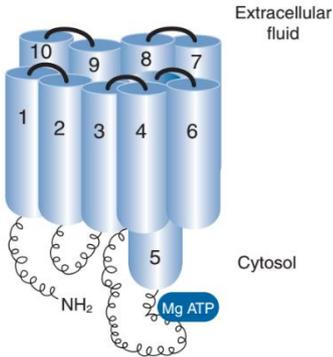
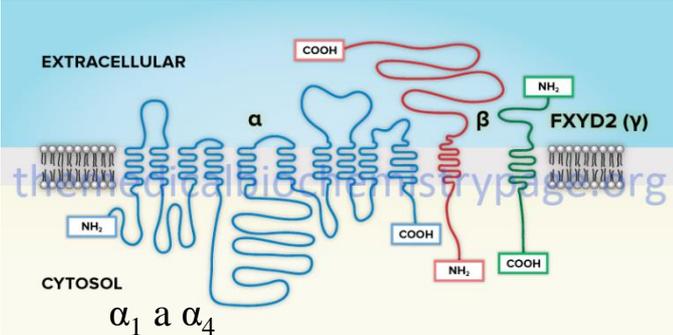
N = Nucleotide binding domain
P = Phosphorylation domain
A = Actuator domain

- Esferas = resíduos altamente conservados
- Rosa, vinho= resíduos medianamente conservados
- Amarelo, azul= resíduos pouco conservados

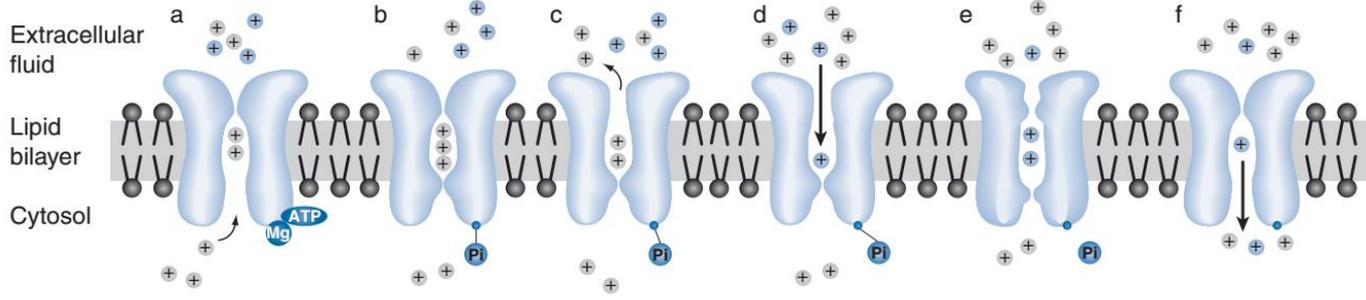
Mecanismo catalítico geral das P-ATPases



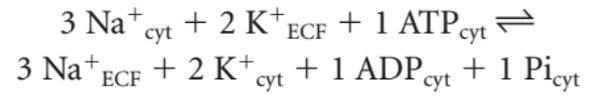
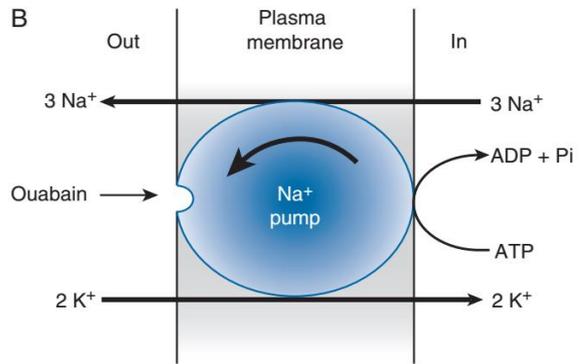
A Na/K-ATPase cria o gradiente de sódio e potássio através da membrana



A



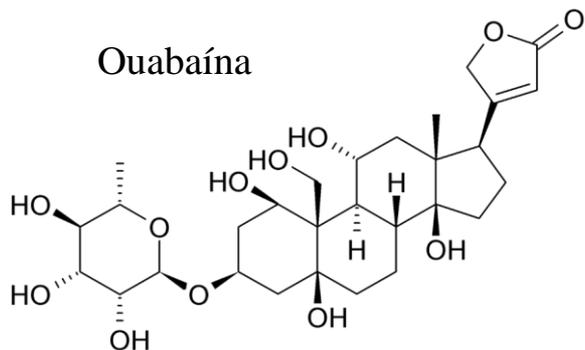
B



Glicosídeos cardíacos inibem a atividade da Na/K-ATPase

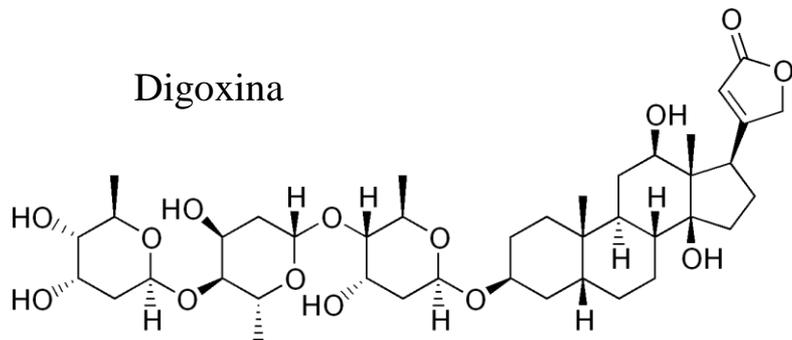
Acokanthera schimperi

Ouabaína



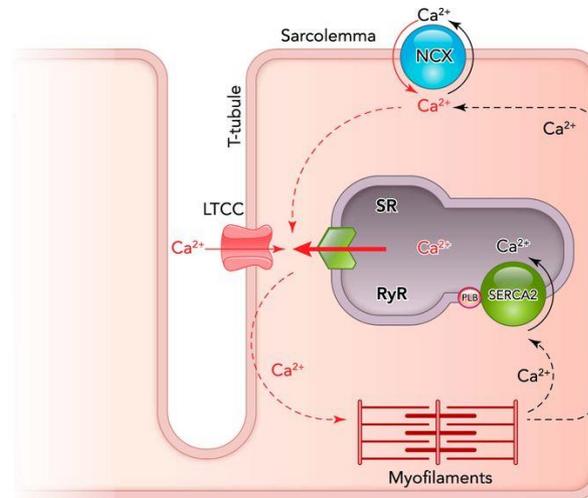
Digitalis purpúrea (dedaleira)

Digoxina



O cálcio intracelular é armazenado no retículo endoplasmático liso pelas ATPases reticulares

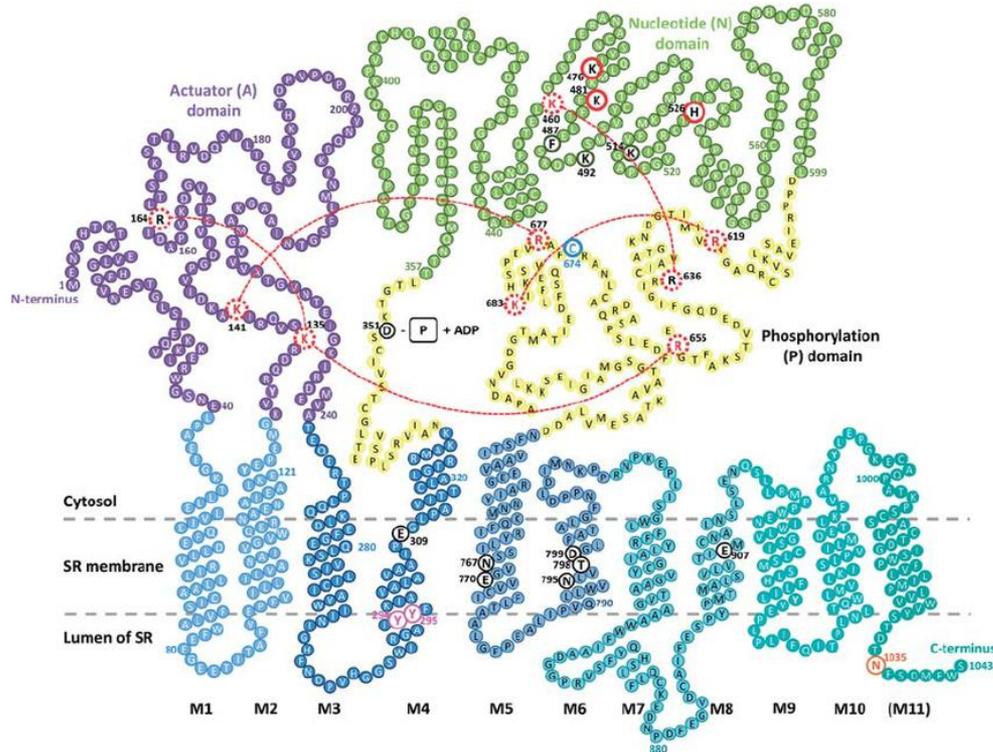
A mais estudada é a Ca-ATPase do retículo sarcoplasmático (musculo estriado), a **SERCA-ATPase**



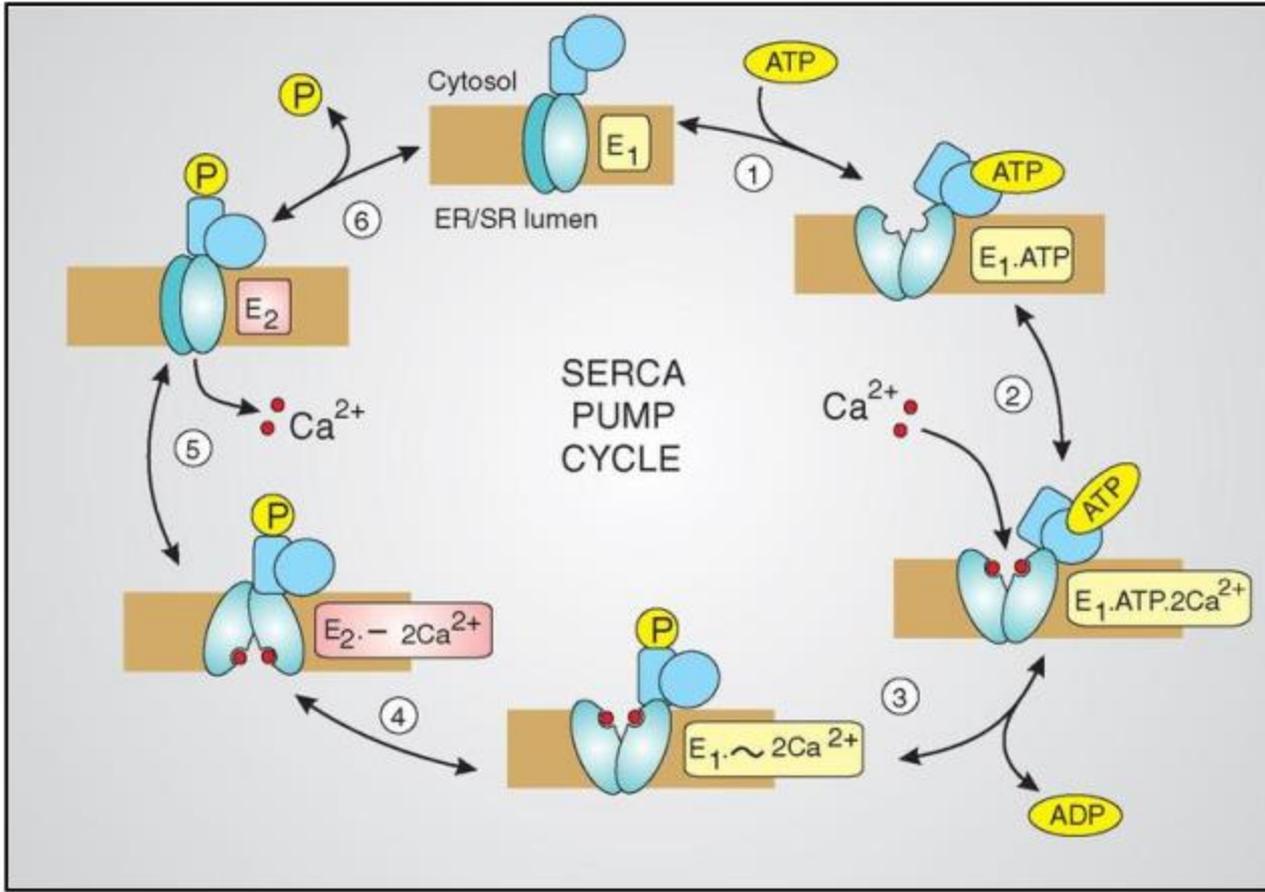
Holly A. Shiels, Gina L.J. Galli

Physiology Published 1 November 2014 Vol. 29 no. 6, 456-469 DOI: 10.1152/physiol.00015.2014

Estrutura da SERCA-ATPase

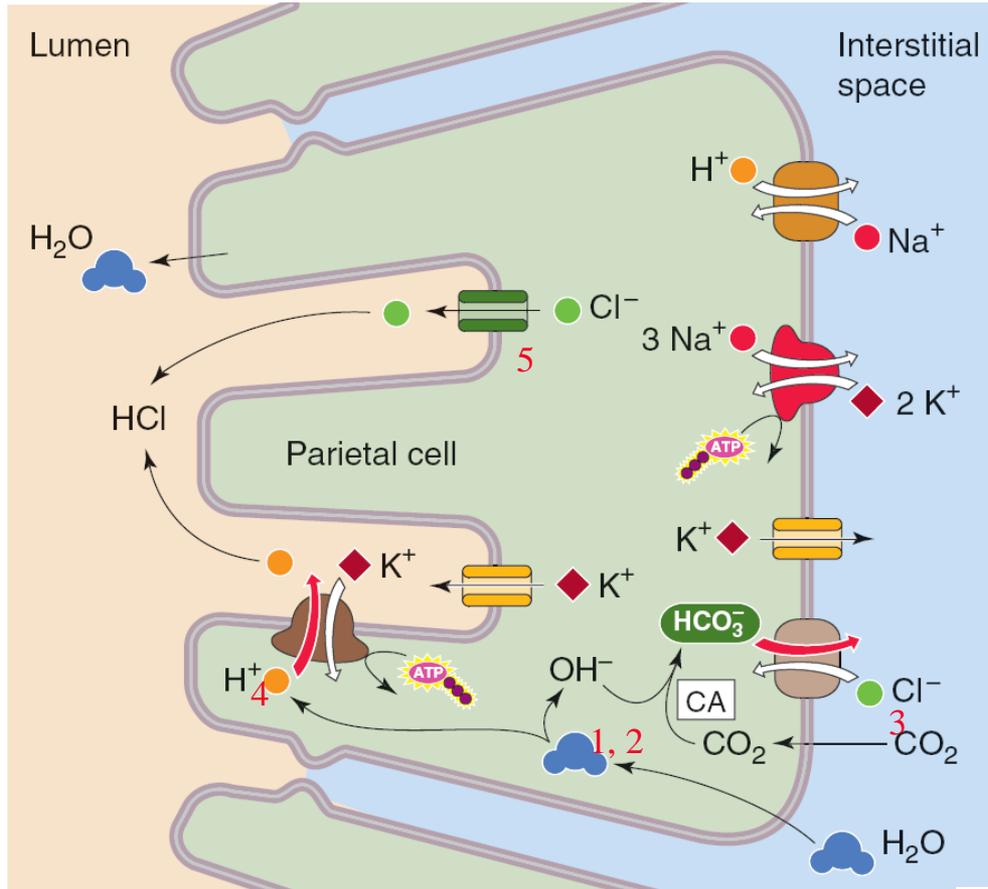


Mecanismo molecular de transporte da SERCA

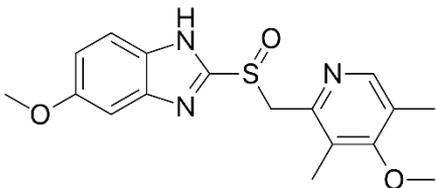


http://license.umn.edu/technologies/20130193-20140051_improved-serca-assay

A secreção de ácido pelo estômago se dá por transporte ativo primário



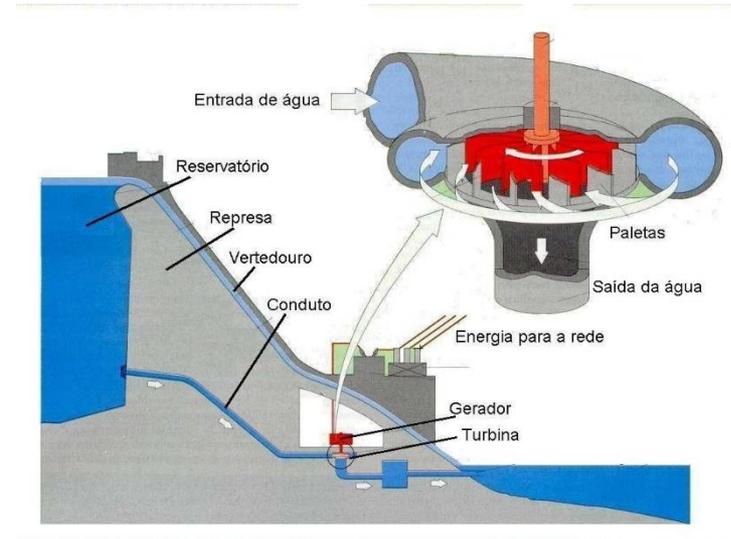
1. Conversão de CO_2 e H_2O em ácido carbônico pela anidrase carbônica (CA)
2. Dissociação do ácido carbônico em bicarbonato e próton
3. Troca do bicarbonato intracelular por um cloreto extracelular-alcalinização do meio intersticial (maré alcalina)
4. Os prótons são bombeados pela H^+/K^+ -ATPase da membrana apical
5. O cloreto flui eletrogenicamente para o lumen via canais de cloreto



Omeprazol, inibidor da H^+ ATPase, inibe a secreção ácida estomacal

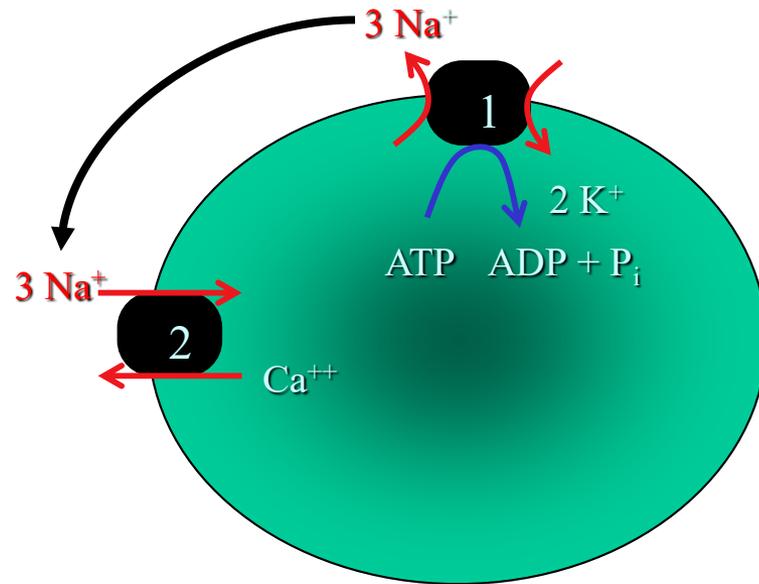


Como a água represada de uma queda de água pode ser usada como fonte de energia estocada para ser convertida a eletricidade.



O gradiente de sódio formado pelo transporte ativo primário da Na/K-ATPase acumula energia química do sódio que “alimenta” o co- transporte de outras substâncias contra seu gradient de concentração

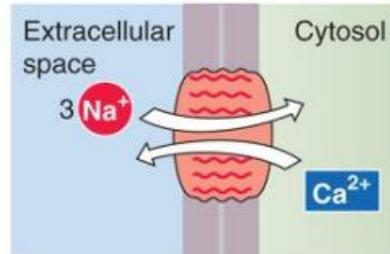
Transporte ativo secundário



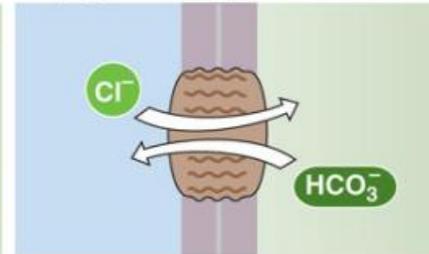
- 1 - Na/K ATPase
- 2 - Trocador Na/Ca

Trocadores

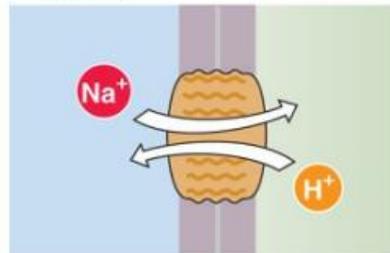
A Na-Ca EXCHANGER (NCX)



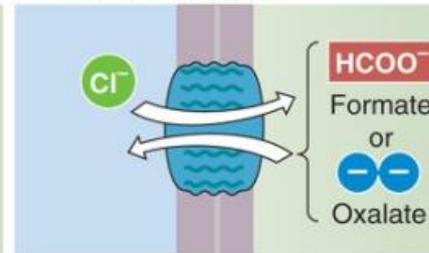
D Cl-HCO₃ EXCHANGER (e.g., AE, DRA)



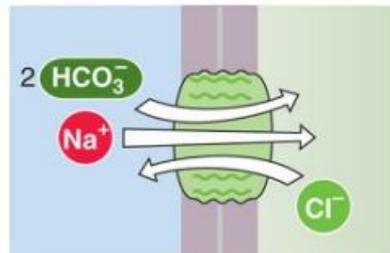
B Na-H EXCHANGER (NHE)



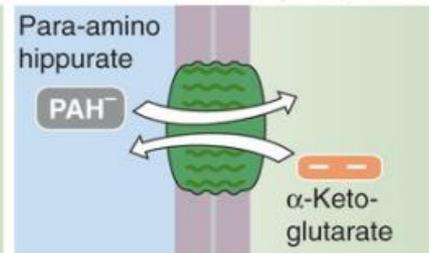
E Cl-FORMATE EXCHANGER (CFEX)



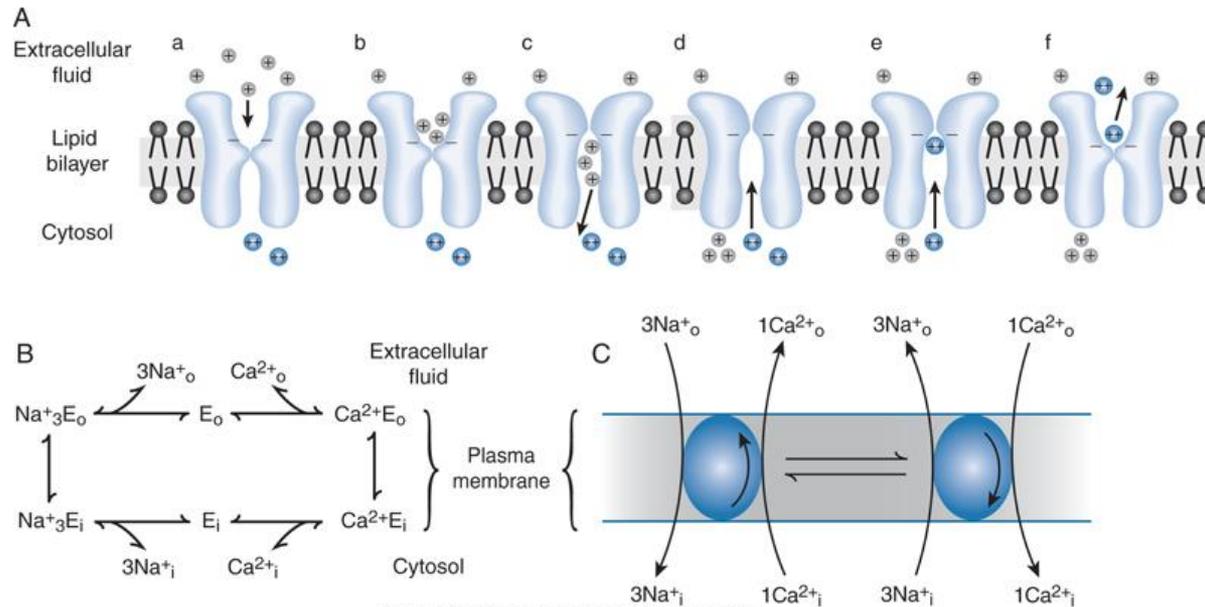
C Na-DRIVEN Cl-HCO₃ EXCHANGER (NDCBE)



F ORGANIC ANION TRANSPORTER (OAT)

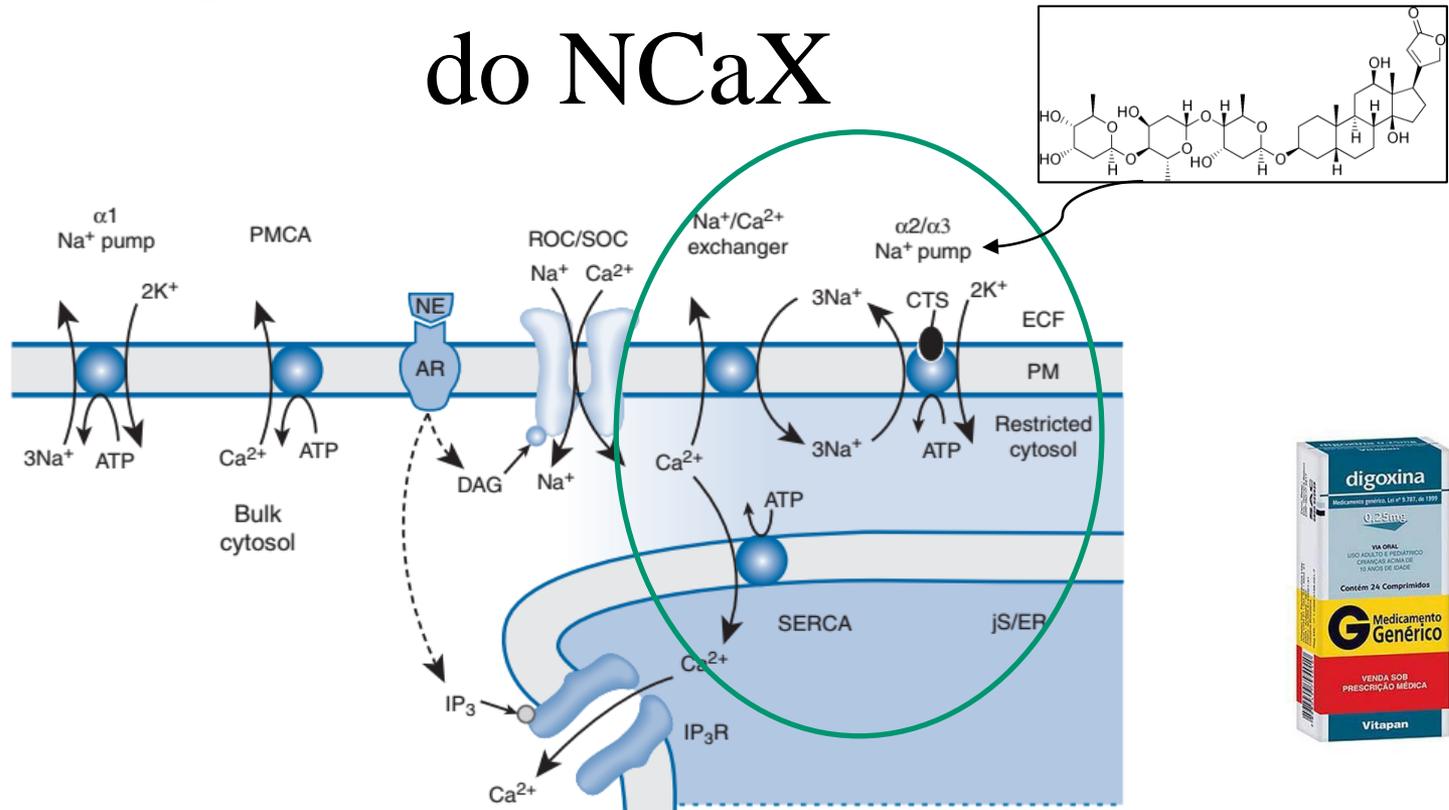


O trocador Na/Ca (NCaX) retira o excesso de cálcio da célula.



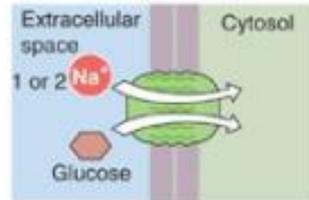
Cellular Physiology and Neurophysiology, 2e
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A localização subcelular da Na/K ATPase pode afetar o funcionamento do NCaX

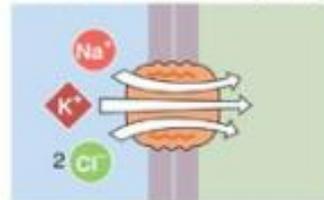


Co-transporte com o sódio

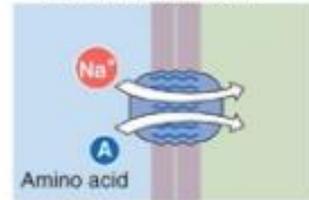
A Na/GLUCOSE COTRANS-
PORTER (SGLT1-3)



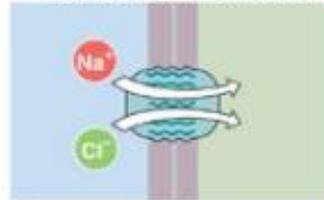
G Na/K/Cl
COTRANS-PORTER (NKCC)



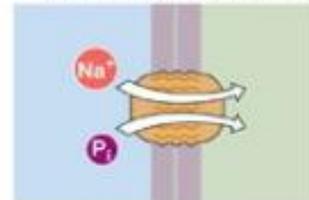
B Na/AMINO ACID
COTRANS-PORTER



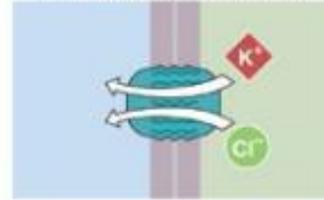
H Na/Cl
COTRANS-PORTER (NCC)



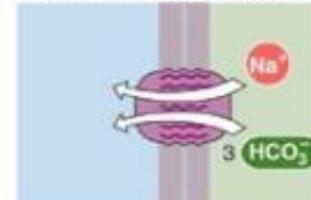
C Na/PHOSPHATE
COTRANS-PORTER (NaPi)



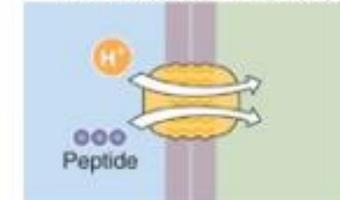
I K/Cl
COTRANS-PORTER (KCC)



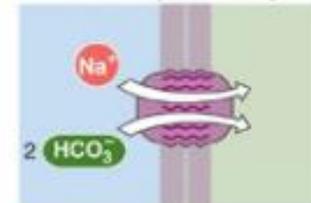
D Na/HCO₃ COTRANS-
PORTER (NBCe1, e2)



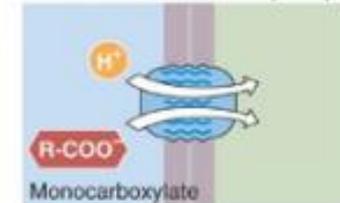
J H/OLIGOPEPTIDE
COTRANS-PORTER (PepT)



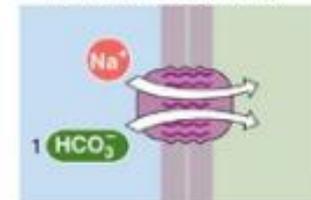
E Na/HCO₃ COTRANS-
PORTER (NBCe1, e2)



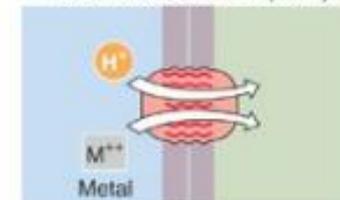
K H/MONOCARBOXYLATE
COTRANS-PORTER (MCT)



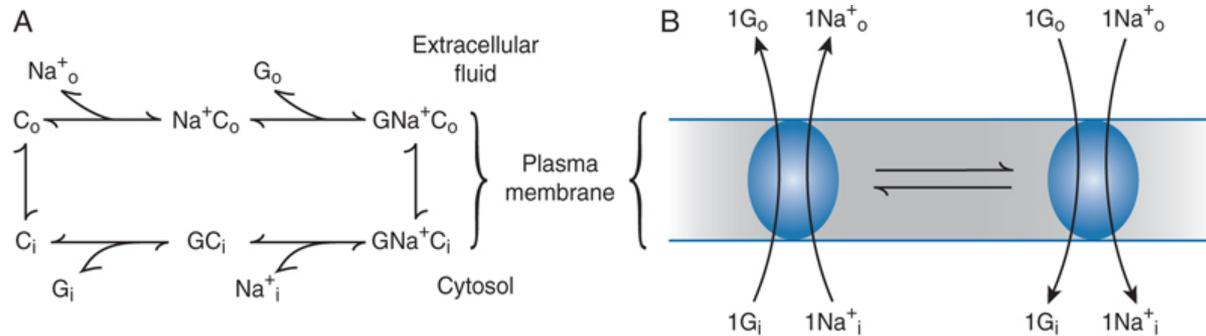
F Na/HCO₃ COTRANS-
PORTER (NBCn1, n2)



L H/DIVALENT METAL ION
COTRANS-PORTER (DMT)

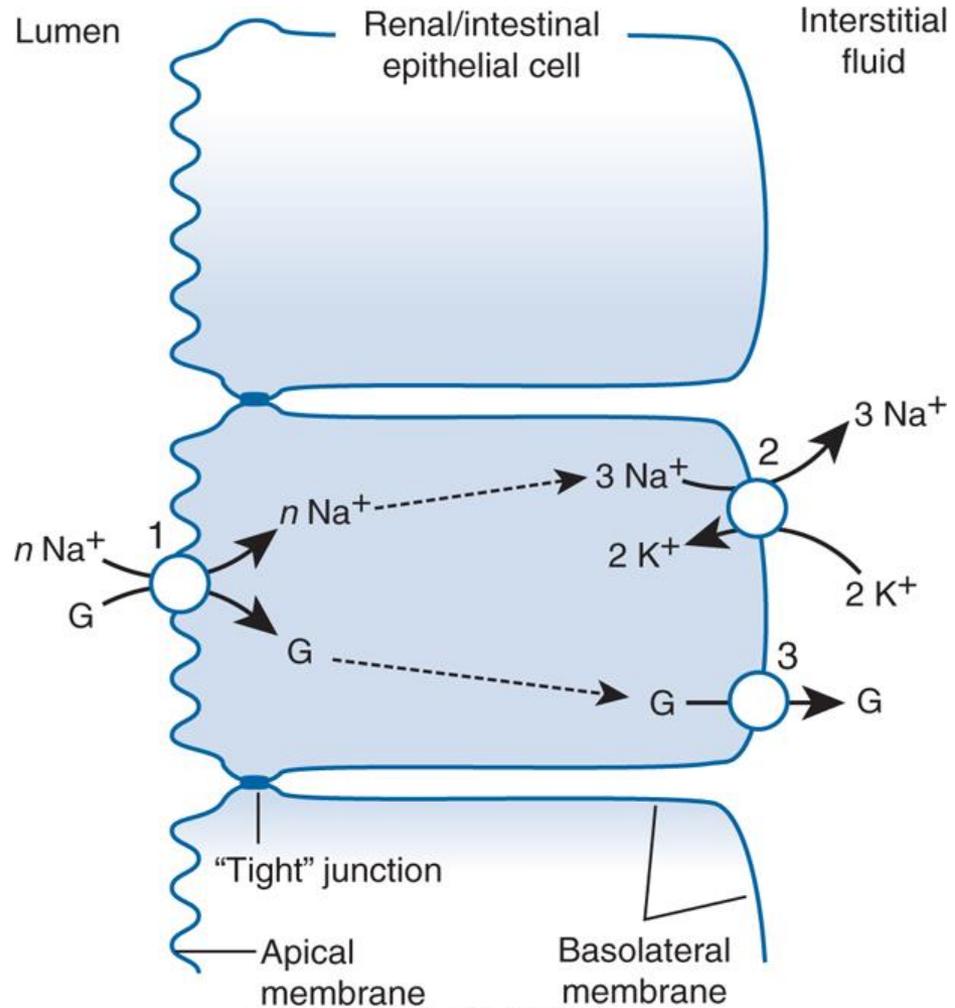


O gradiente de sódio formado pelo transporte ativo acumula energia química do sódio que “alimenta” o co- transporte de outras substâncias , como a glicose (G)



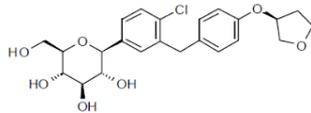
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Transporte/reabsorção de
de glicose
intestinal/tubular (*SGLT*)

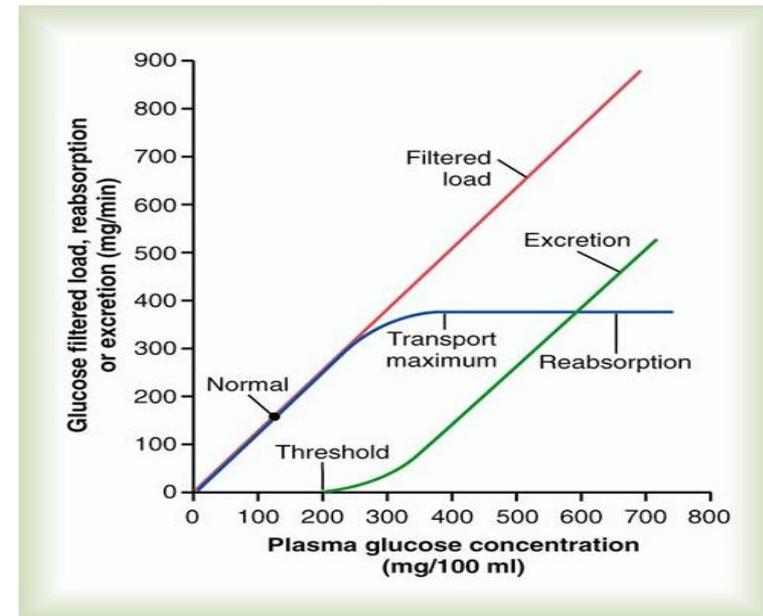
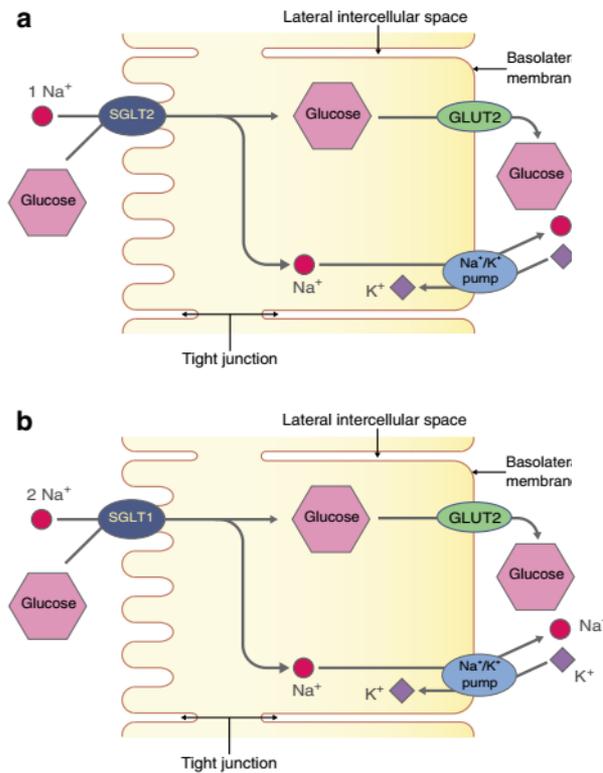
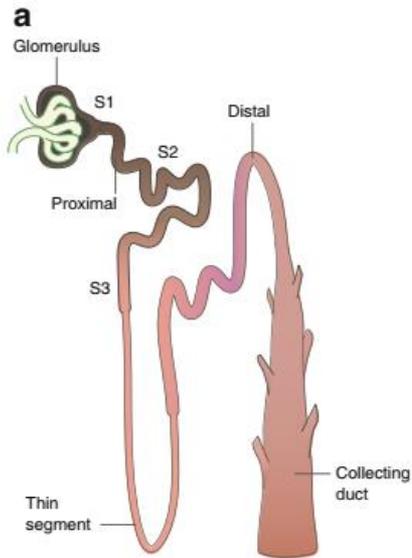


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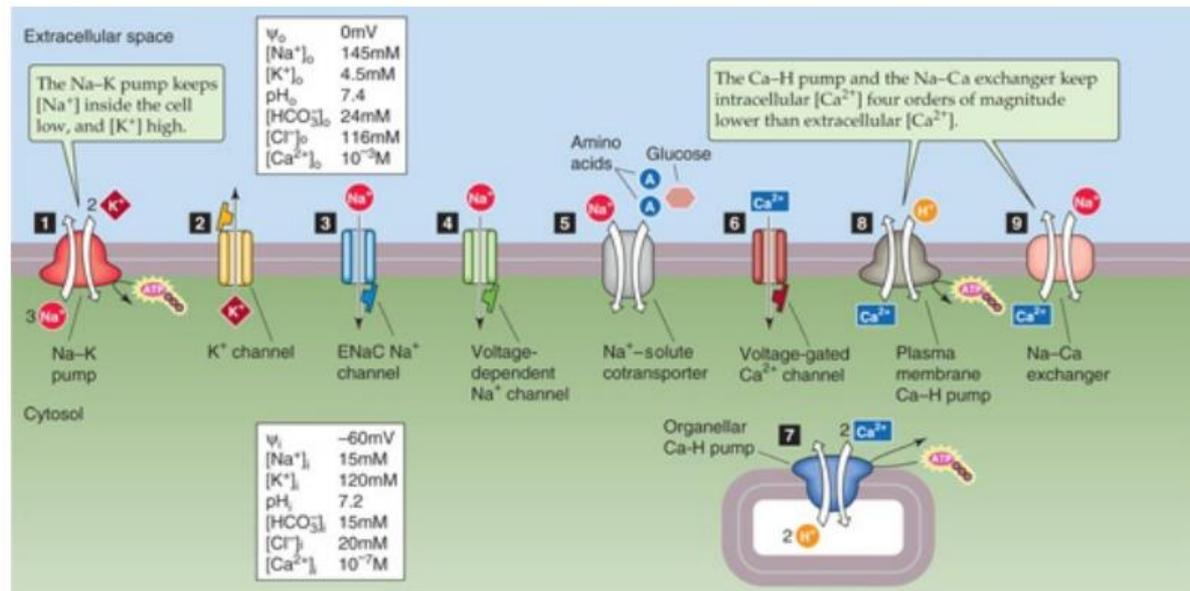
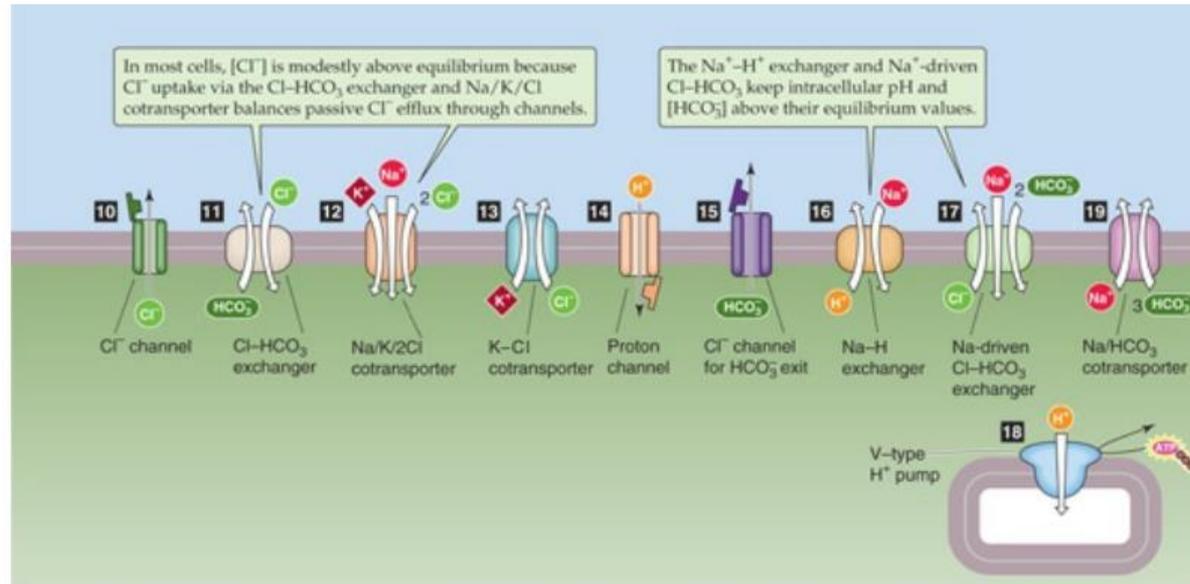
Saturação do transporte tubular renal de glicose nos diabéticos



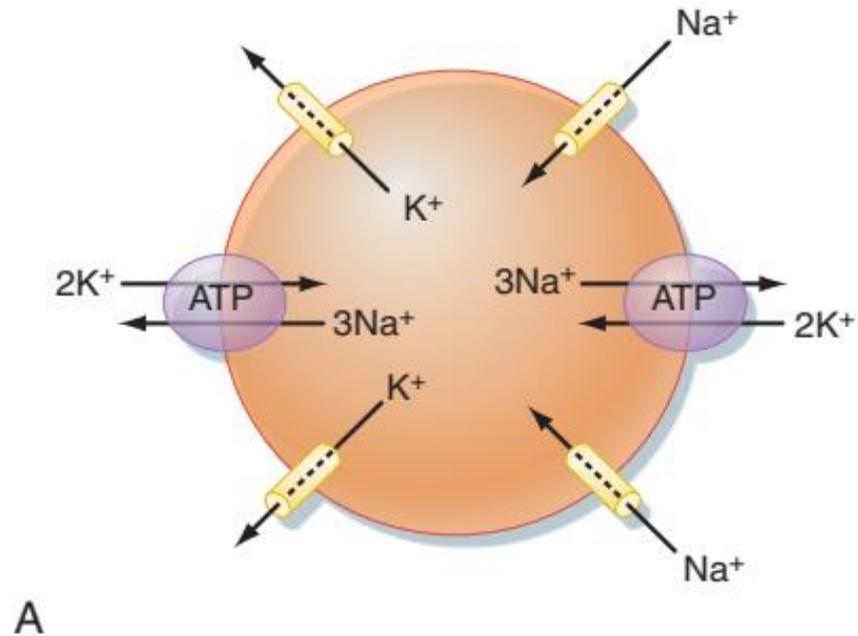
Empanglifozina (jardiance) inibidor de SGLT2, ação hipoglicemiante



Exemplos de canais e transportadores



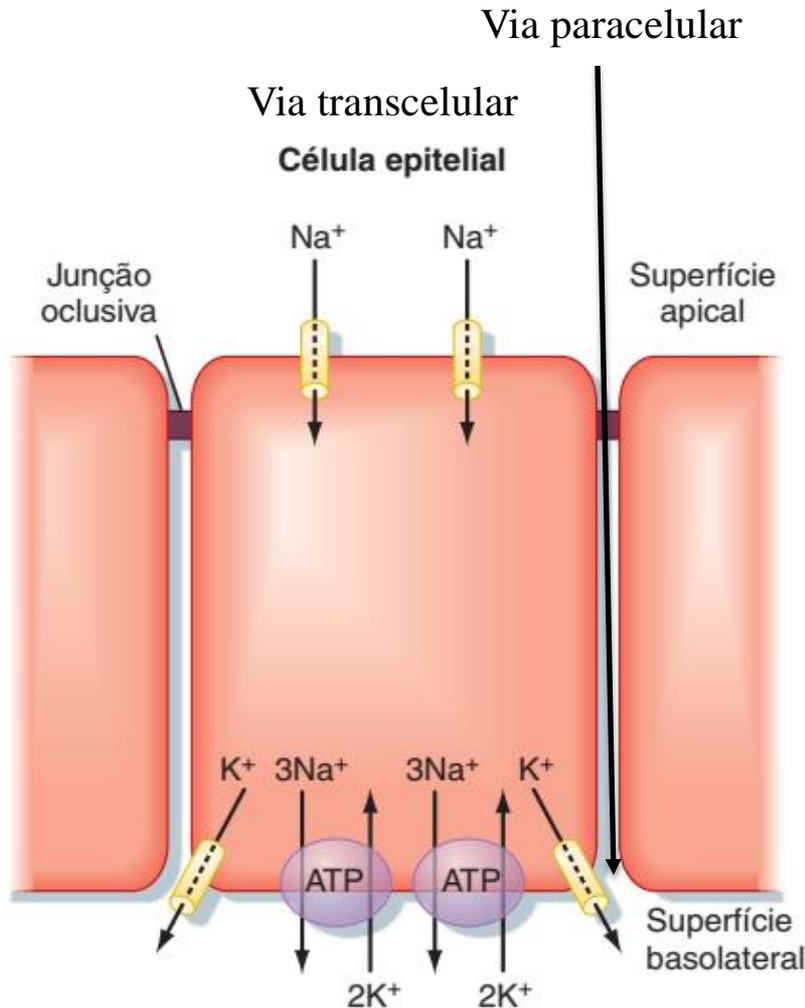
Célula simétrica



O transporte de íons através da membrana é sempre **ELETRONEUTRO**, ou seja uma saída de um íon é seguido pela entrada de um íon de carga igual ou saída de um íon de carga oposta

Como transportar um soluto através de um epitélio?

A localização subcelular de canais e transportadores é crucial para o transporte **vetorial** através de epitélios



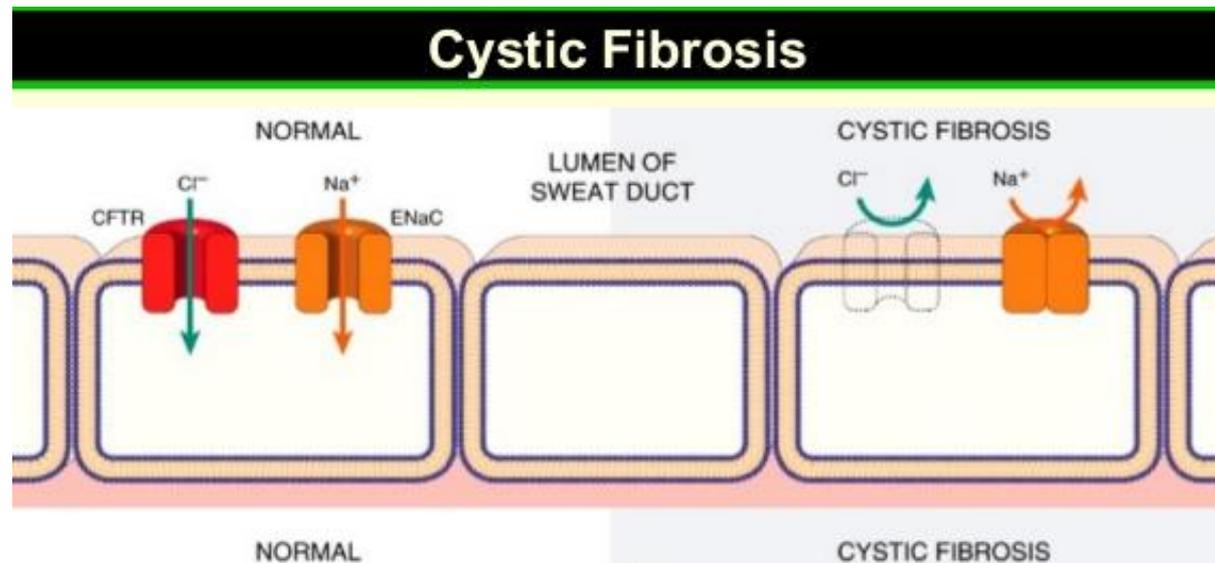
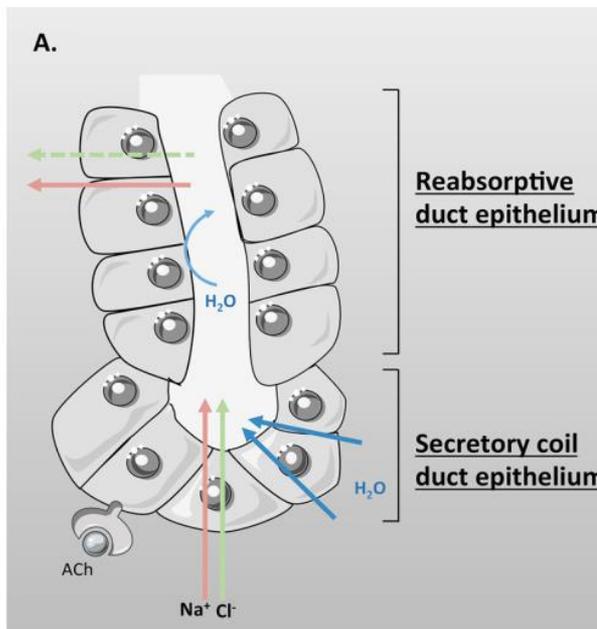
B

O impedimento do movimento de um íon pode influenciar o transporte de outro íon

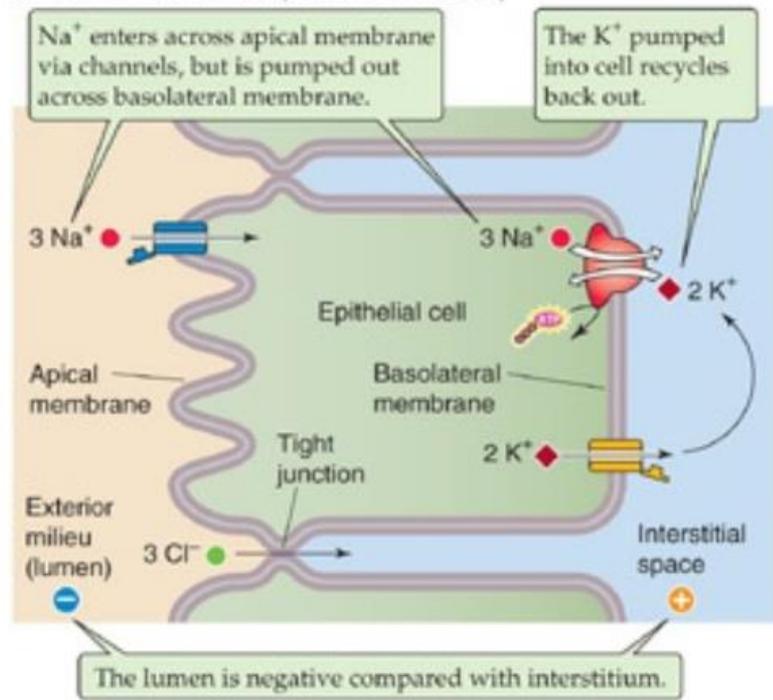
A fibrose cística é causada por um defeito em um canal para cloreto epitelial o *Cystic fibrosis transmembrane conductance regulator* (CFTR) – Canal de cloreto epitelial

Foi a primeira canalopatia de origem genética a ser identificada.

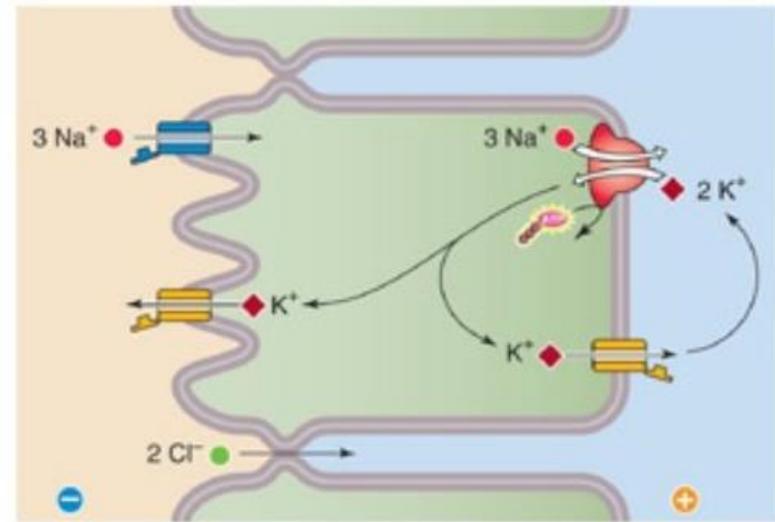
Diminuição da reabsorção de sódio pelo ducto das glândulas sudoríparas cria o suor salgado típico desses pacientes



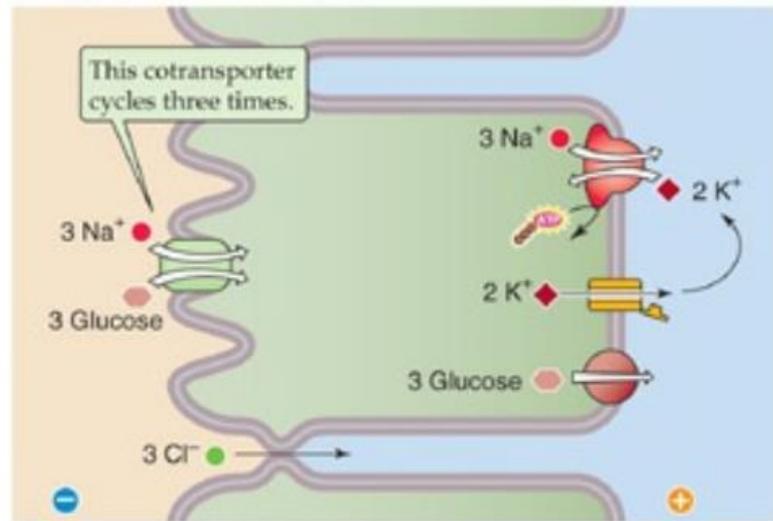
A Na⁺ ABSORPTION ("USSING MODEL")



B K⁺ SECRETION



C GLUCOSE ABSORPTION



D Cl⁻ SECRETION

