Intodução a Transporte e Sinalização Celular

Deborah Schechtman
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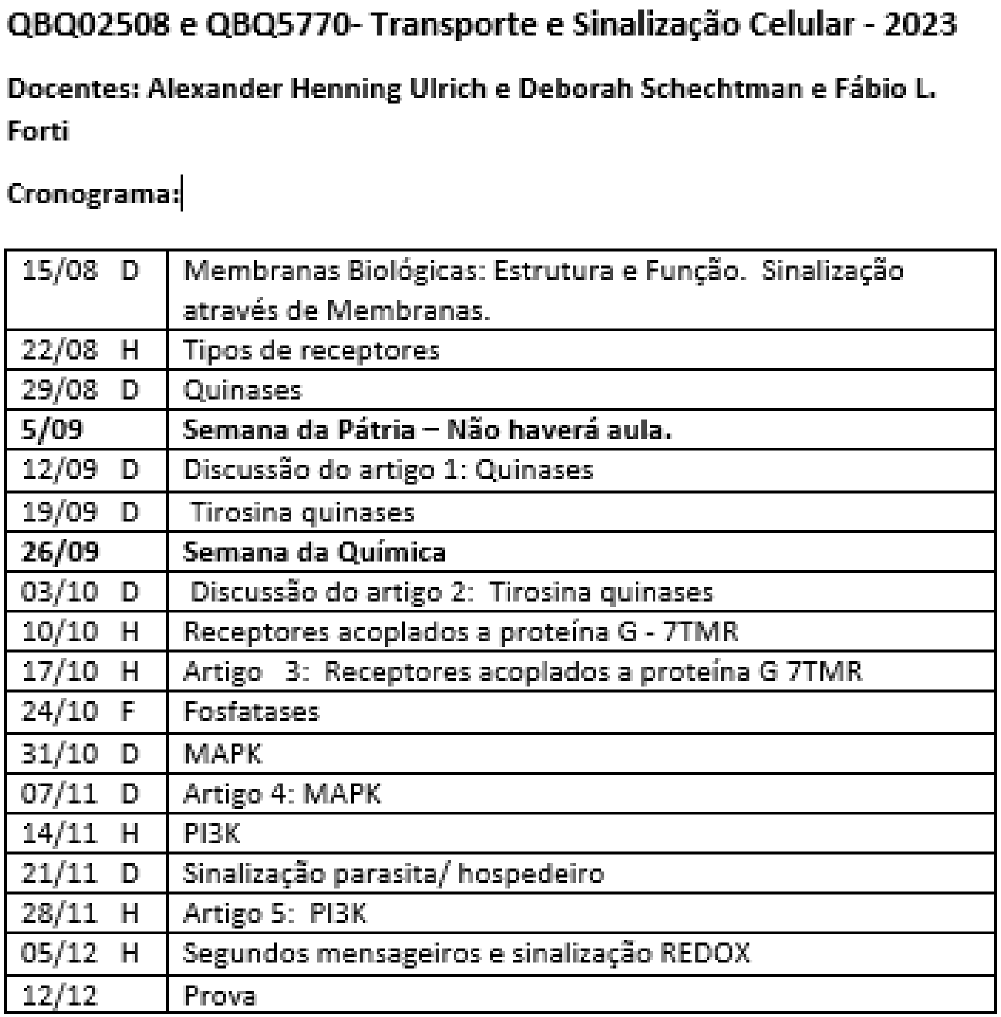
Cronograma



QBQ02508 e QBQ5770- Transporte e Sinalização Celular - 2023

Docentes: Alexander Henning Ulrich e Deborah Schechtman e Fábio L. Forti

Cronograma:

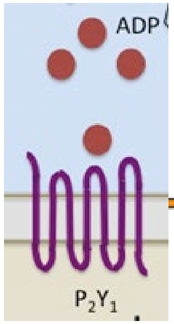
15/08	D	Membranas Biológicas: Estrutura e Função. Sinalização através de Membranas.
22/08	H	Tipos de receptores
29/08	D	Quinases
5/09		**Semana da Pátria – Não haverá aula.**
12/09	D	Discussão do artigo 1: Quinases
19/09	D	Tirosina quinases
26/09		**Semana da Química**
03/10	D	Discussão do artigo 2: Tirosina quinases
10/10	H	Receptores acoplados a proteína G - 7TMR
17/10	H	Artigo 3: Receptores acoplados a proteína G 7TMR
24/10	F	Fosfatases
31/10	D	MAPK
07/11	D	Artigo 4: MAPK
14/11	H	PI3K
21/11	D	Sinalização parasita/ hospedeiro
28/11	H	Artigo 5: PI3K
05/12	H	Segundos mensageiros e sinalização REDOX
12/12		Prova

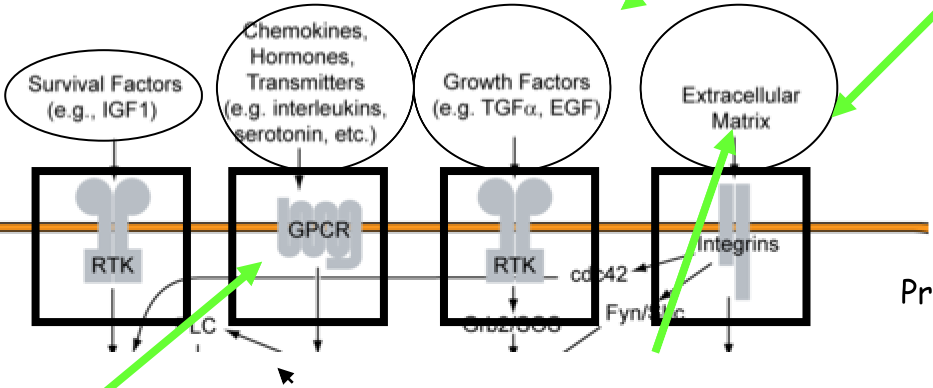
SINALIZAÇÃO NO IQ

Prof. Alexander
Henning Ulrich e
Profa. Claudiana
Lameu
Receptores
Purinérgicos

Profa. Deborah
Schechtman
NGF

Prof. Ricardo José Giordano
Angiogênese



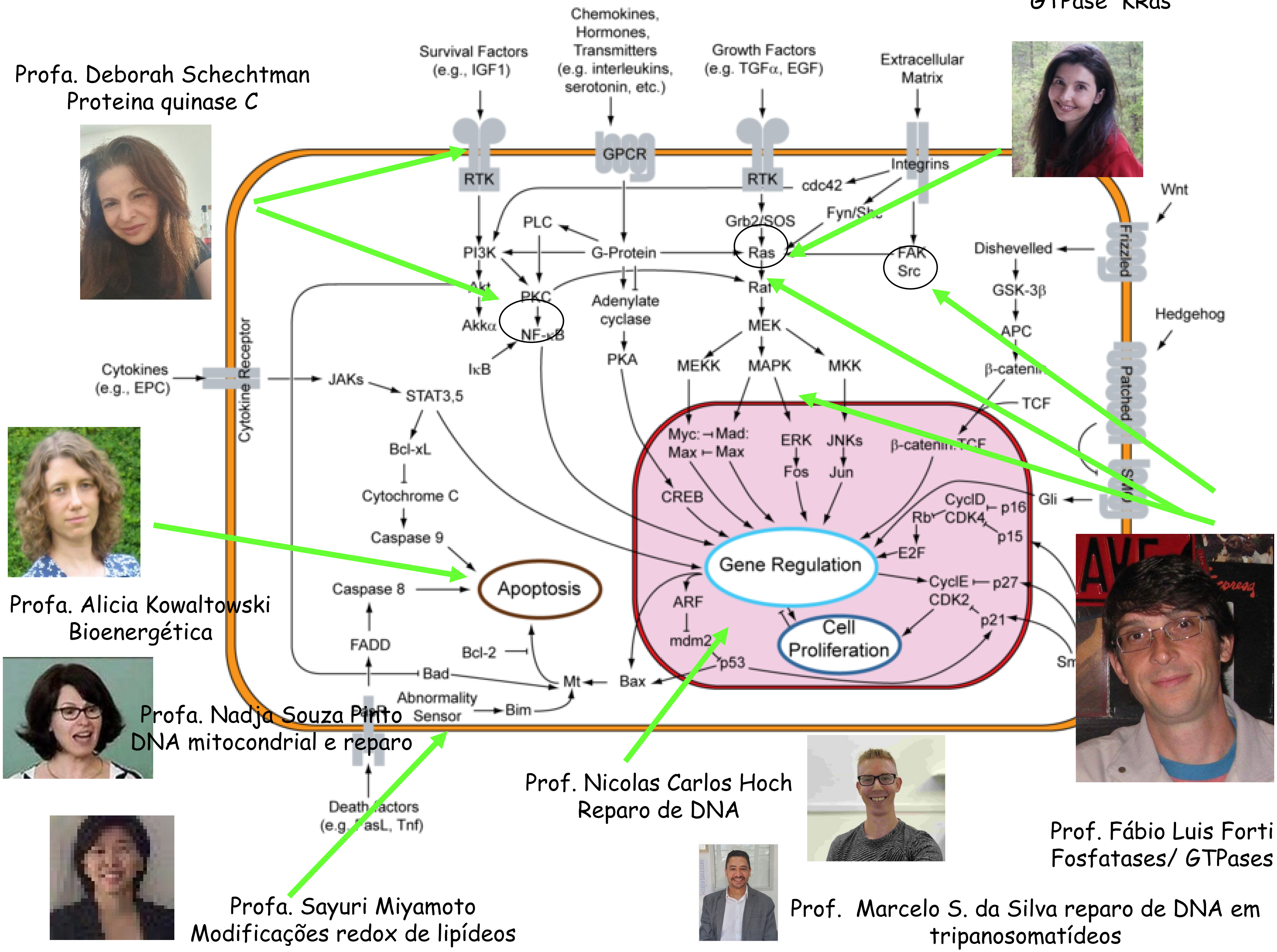


Survival Factors (e.g., IGF1)
Chemokines, Hormones, Transmitters (e.g. interleukins, serotonin, etc.)
Growth Factors (e.g. TGFα, EGF)
Extracellular Matrix
RTK
GPCR
RTK
Integrins
cdc42
Fyn/Shc
LC

Profa. Alexandre Bruni Cardoso
Interções células tumorais
com a matriz extracelular

Profa. Betina Malnic
Receptores olfatórios

SINALIZAÇÃO NO IQ



Survival Factors (e.g., IGF1)
Chemokines, Hormones, Transmitters (e.g. interleukins, serotonin, etc.)
Growth Factors (e.g. TGFα, EGF)
Extracellular Matrix
RTK
GPCR
RTK
Integrins
cdc42
Fyn/Shc
Grb2/SOS
Ras
FAK Src
Wnt
Frizzled
Dishevelled
GSK-3β
APC
β-catenin
TCF
Hedgehog
Patched
SMO
Gli
PLC
PI3K
G-Protein
PKC
Akt
Akkα
NF-κB
IκB
Adenylate cyclase
PKA
Raf
MEK
MEKK
MAPK
MKK
Cytokines (e.g., EPC)
Cytokine Receptor
JAKs
STAT3,5
Bcl-xL
Cytochrome C
Caspase 9
Caspase 8
Apoptosis
FADD
Bcl-2
Bad
Mt
Bax
Bim
Abnormality Sensor
FasR
Death Factors (e.g. FasL, Tnf)
Myc: Max
Mad: Max
ERK
Fos
JNKs
Jun
β-catenin:TCF
CREB
Gene Regulation
CycID
CDK4
Rb
p16
p15
E2F
CycIE
CDK2
p27
p21
ARF
mdm2
p53
Cell Proliferation
Smads

Profa. Deborah Schechtman
Proteina quinase C

Profa. Daniela Sanchez Basseres
GTPase KRas

Profa. Alicia Kowaltowski
Bioenergética

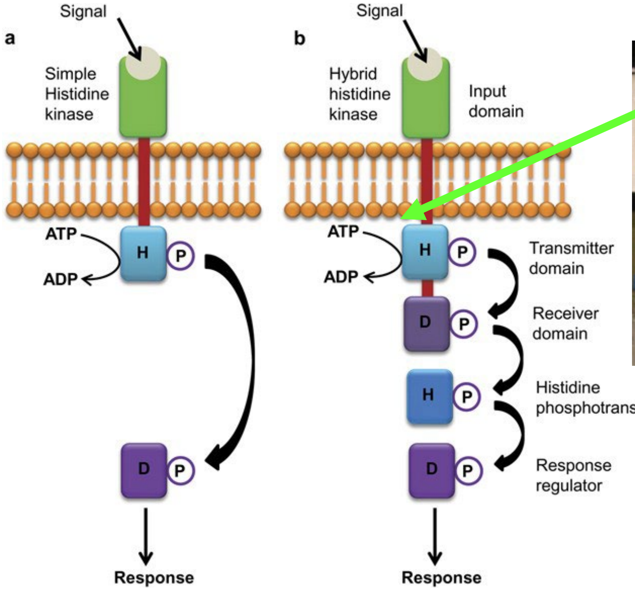
Profa. Nadja Souza Pinto
DNA mitocondrial e reparo

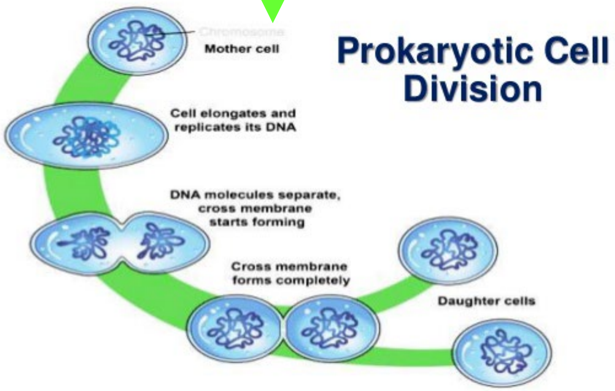
Profa. Sayuri Miyamoto
Modificações redox de lipídeos

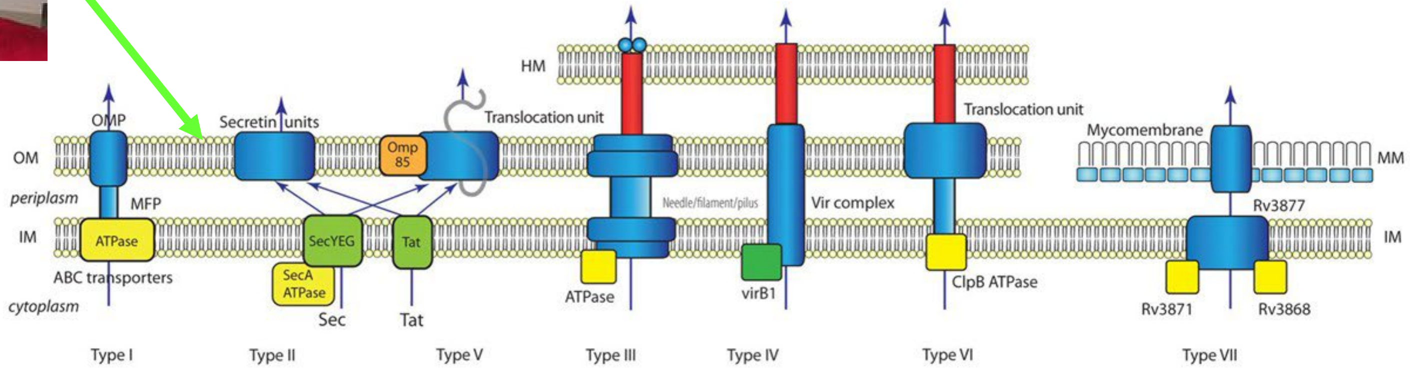
Prof. Nicolas Carlos Hoch
Reparo de DNA

Prof. Fábio Luis Forti
Fosfatases/ GTPases

Prof. Marcelo S. da Silva reparo de DNA em tripanosomatídeos

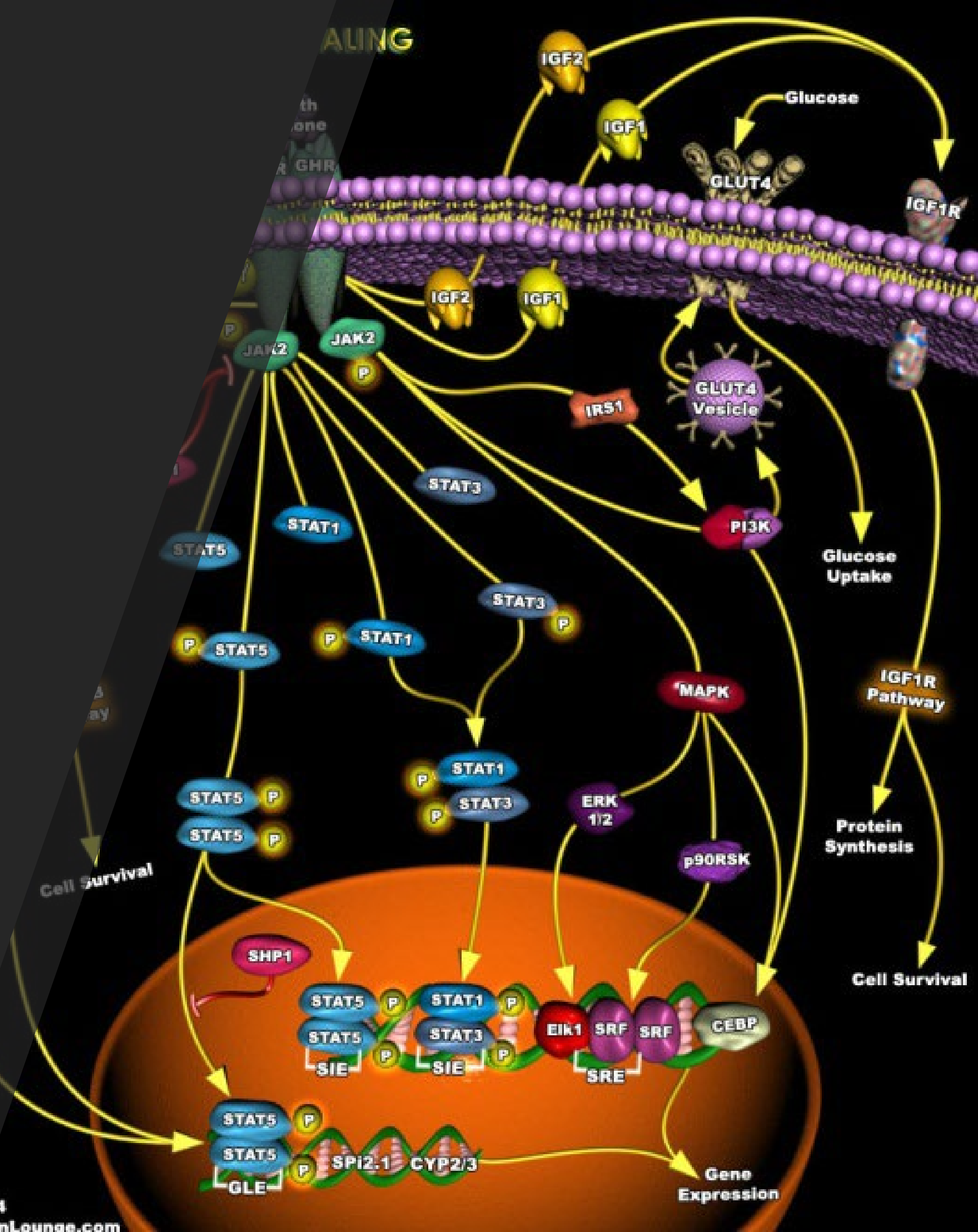

a
Signal
Simple Histidine kinase
ATP
ADP
H
P
D
P
Response
b
Signal
Hybrid histidine kinase
Input domain
ATP
ADP
H
P
Transmitter domain
D
P
Receiver domain
H
P
Histidine phosphotransferase
D
P
Response regulator
Response


Prokaryotic Cell Division
Chromosome
Mother cell
Cell elongates and replicates its DNA
DNA molecules separate, cross membrane starts forming
Cross membrane forms completely
Daughter cells

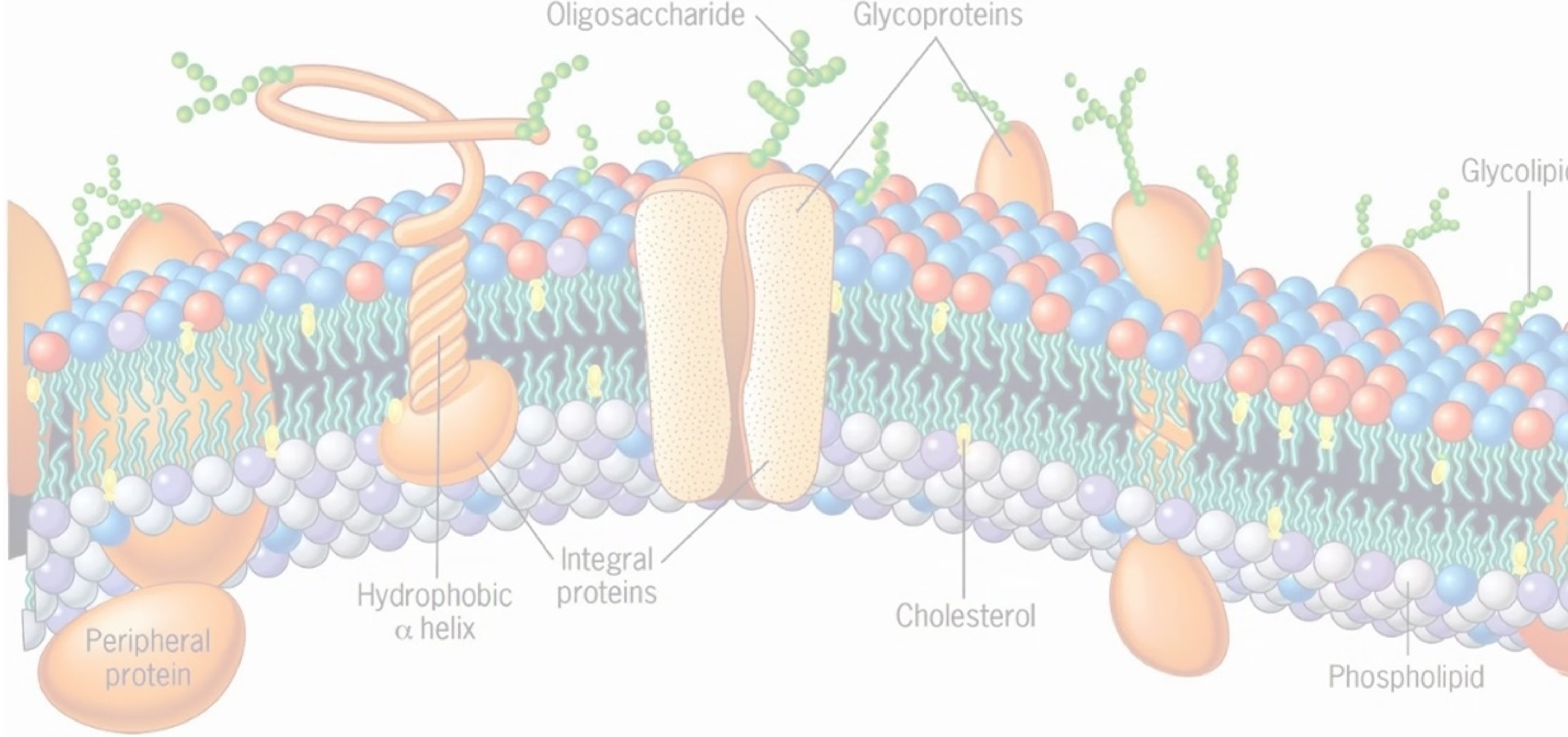

HM
OMP
Secretin units
Translocation unit
Translocation unit
Mycomembrane
OM
Omp 85
MM
periplasm
MFP
Needle/filament/pilus
Vir complex
Rv3877
IM
ATPase
SecYEG
Tat
IM
ABC transporters
SecA ATPase
ATPase
virB1
ClpB ATPase
Rv3871
Rv3868
cytoplasm
Sec
Tat
Type I
Type II
Type V
Type III
Type IV
Type VI
Type VII

O que é Transdução de sinal

- **Transdução de sinal** ”Processo pelo qual um sinal químico ou físico extracelular ativa um receptor ou uma alteração na membrana plasmática causando respostas intracelulares”

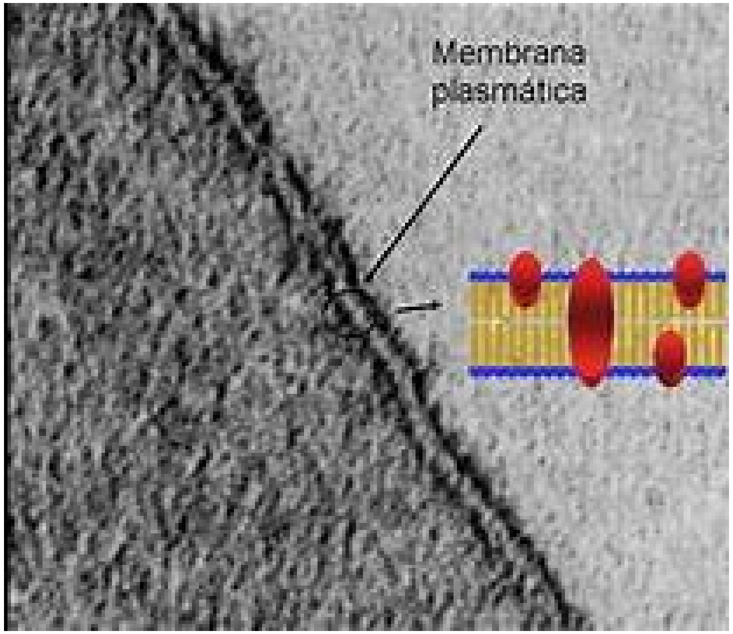

ALING
IGF2
IGF1
Glucose
GLUT4
IGF1R
GHR
IGF2
IGF1
JAK2
JAK2
P
IRS1
GLUT4 Vesicle
STAT3
STAT1
STAT5
PI3K
Glucose Uptake
STAT3
P
P
STAT5
P
STAT1
MAPK
IGF1R Pathway
Cell Survival
STAT1
STAT3
P
P
STAT5
P
STAT5
P
ERK 1/2
p90RSK
Protein Synthesis
Cell Survival
SHP1
STAT5
STAT5
SIE
STAT1
STAT3
SIE
P
Elk1
SRF
SRF
SRE
CEBP
STAT5
STAT5
P
SPi2.1
CYP2/3
GLE
Gene Expression
©2004 ProteinLounge.com

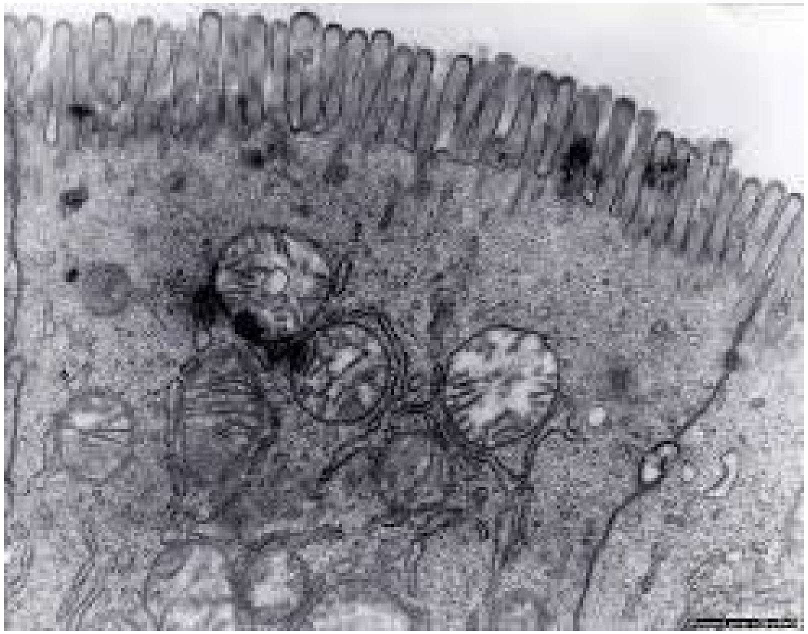
https://www.youtube.com/watch?v=tMMrTRnFdI4


Oligosaccharide
Glycoproteins
Glycolipi
Hydrophobic α helix
Integral proteins
Cholesterol
Peripheral protein
Phospholipid

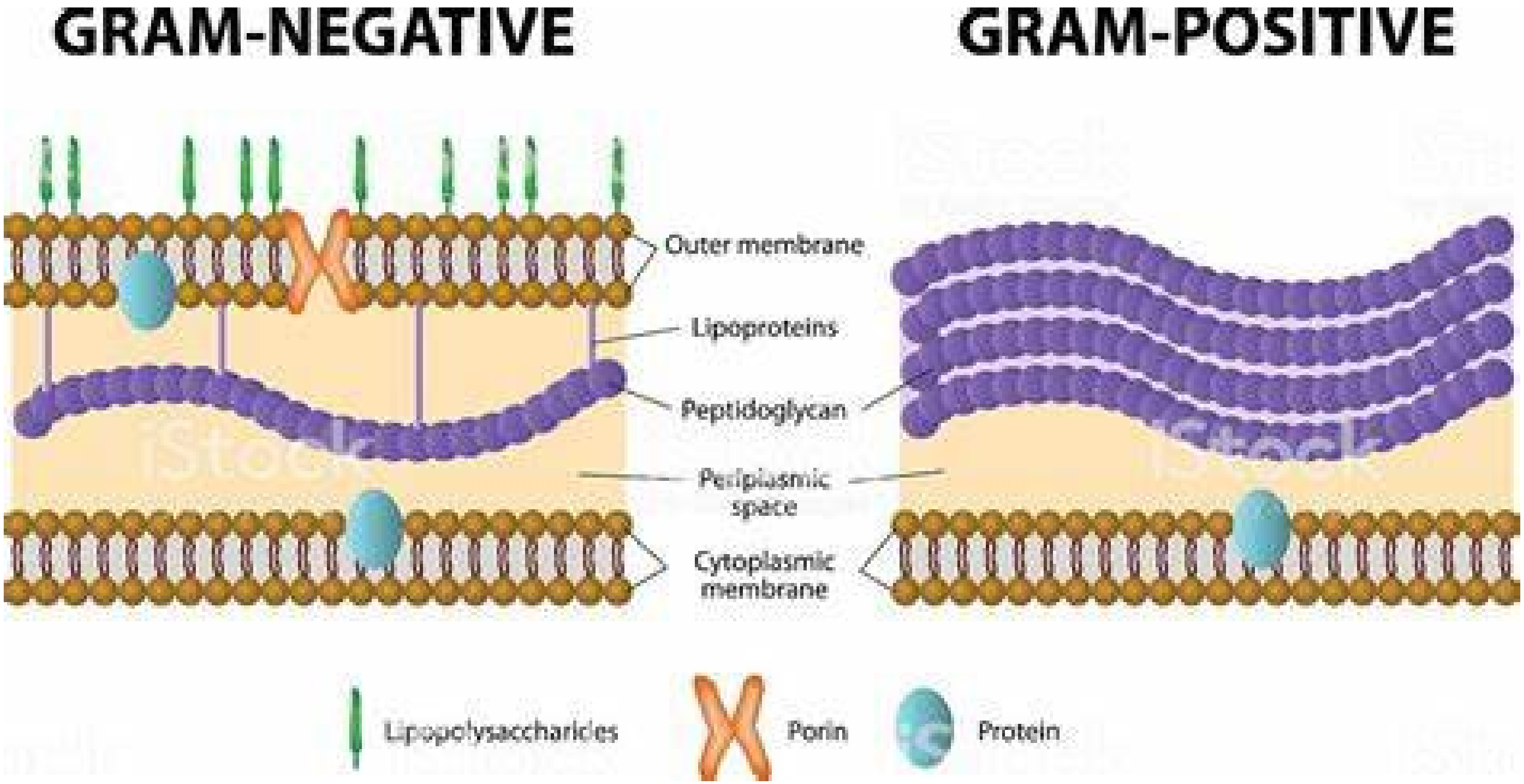
Membranas Biológicas
Definição características e funções

Membrana plasmática e de organelas


Membrana plasmática

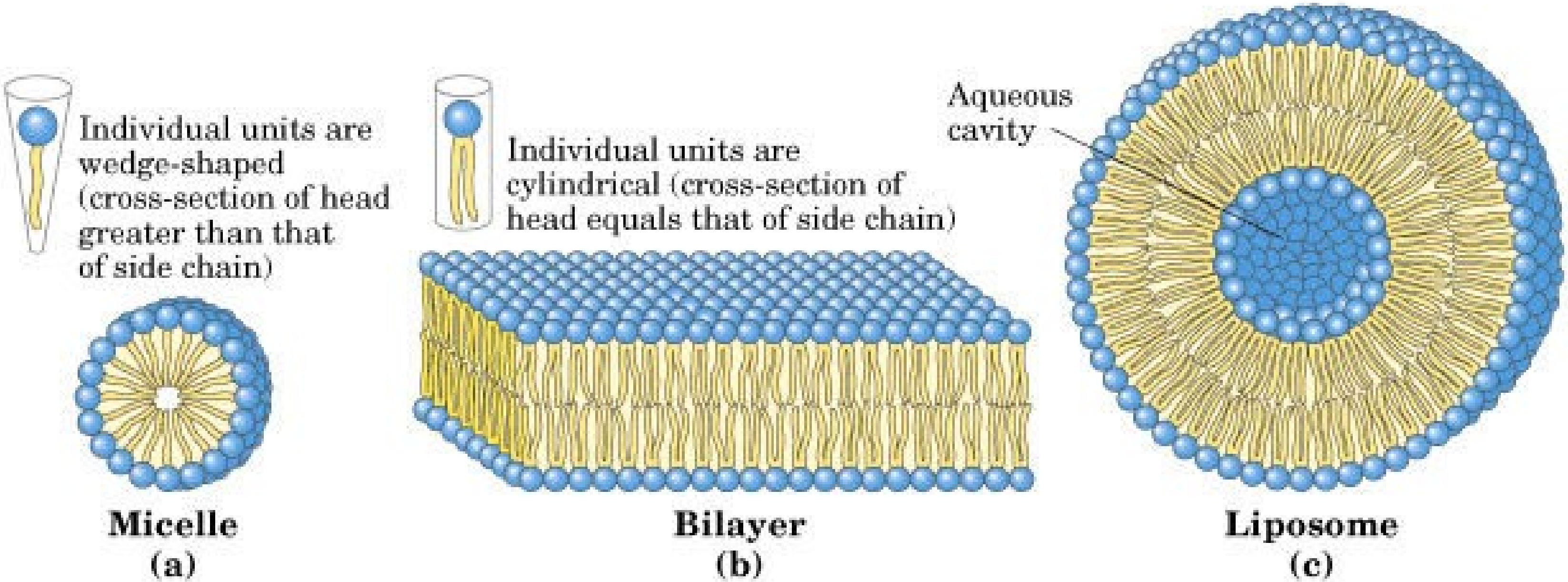


Parede celular



GRAM-NEGATIVE
GRAM-POSITIVE
Outer membrane
Lipoproteins
Peptidoglycan
Periplasmic space
Cytoplasmic membrane
Lipopolysaccharides
Porin
Protein

Estruturas lipídicas


Individual units are wedge-shaped (cross-section of head greater than that of side chain)
Individual units are cylindrical (cross-section of head equals that of side chain)
Aqueous cavity
Micelle
(a)
Bilayer
(b)
Liposome
(c)

Modelo do mosaico fluido

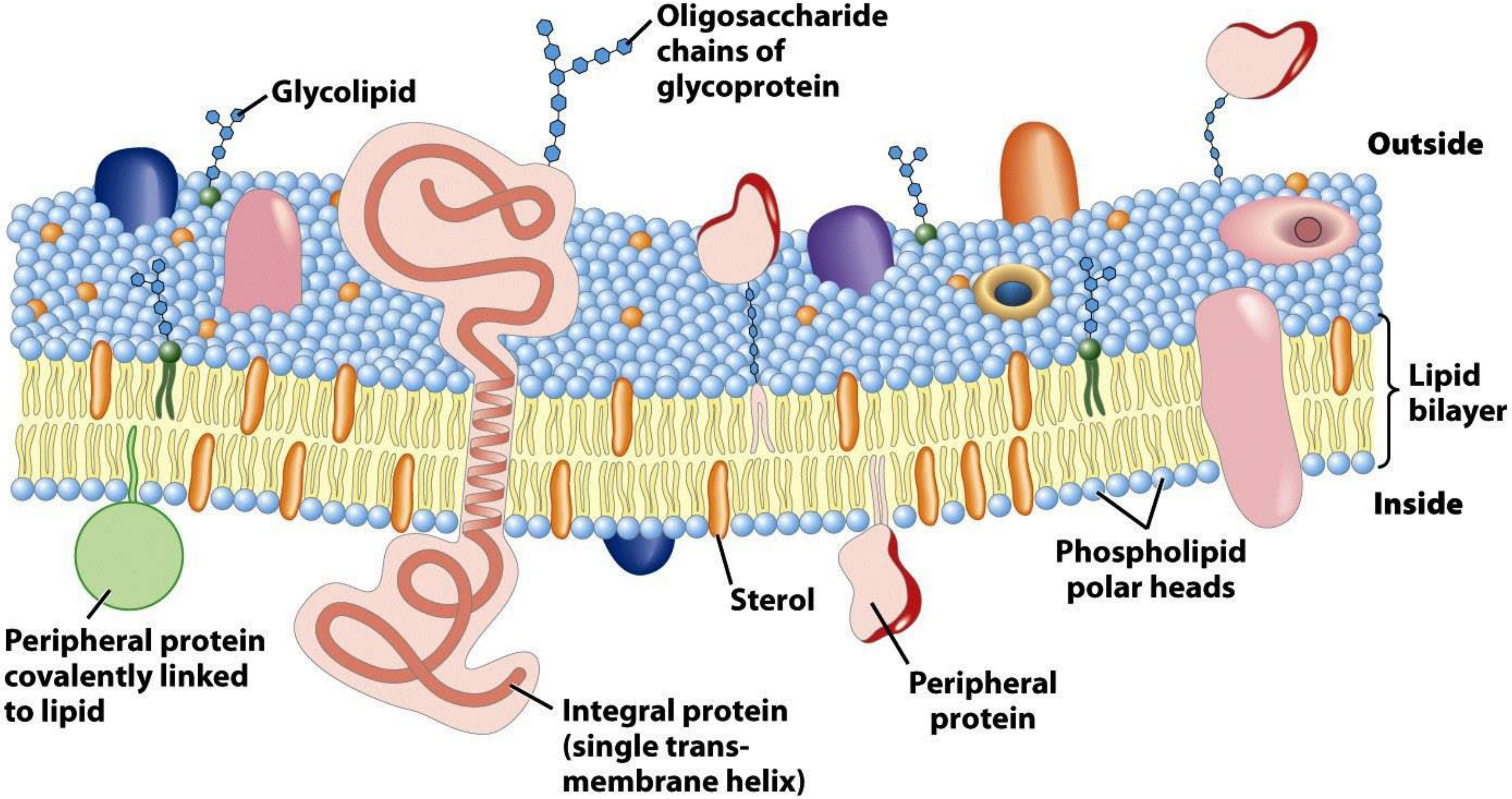

Oligosaccharide chains of glycoprotein
Glycolipid
Outside
Lipid bilayer
Inside
Phospholipid polar heads
Sterol
Peripheral protein covalently linked to lipid
Integral protein (single trans-membrane helix)
Peripheral protein

Figure 11-3
Lehninger Principles of Biochemistry, Fifth Edition
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Composição de lipídeos varia entre membranas de organismos diferentes

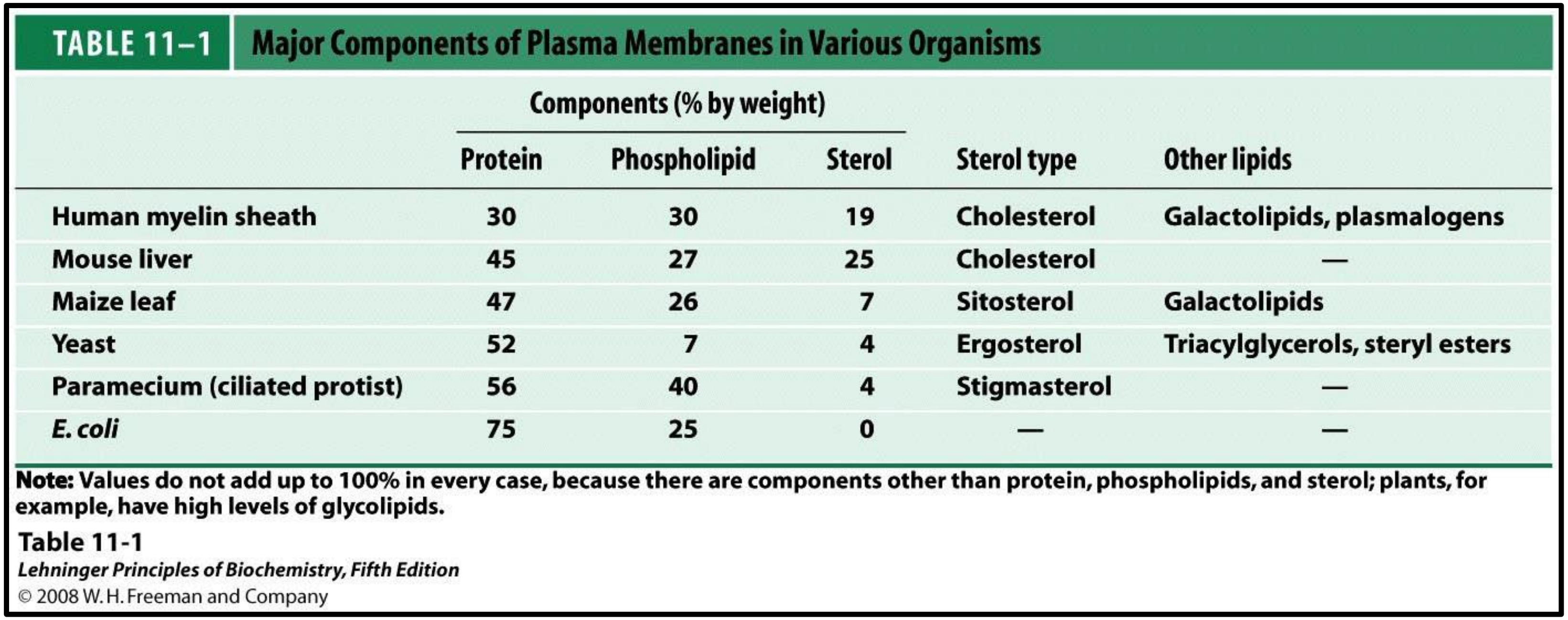

TABLE 11–1 **Major Components of Plasma Membranes in Various Organisms**

	Components (% by weight)				
	Protein	**Phospholipid**	**Sterol**	**Sterol type**	**Other lipids**
Human myelin sheath	30	30	19	Cholesterol	Galactolipids, plasmalogens
Mouse liver	45	27	25	Cholesterol	—
Maize leaf	47	26	7	Sitosterol	Galactolipids
Yeast	52	7	4	Ergosterol	Triacylglycerols, steryl esters
Paramecium (ciliated protist)	56	40	4	Stigmasterol	—
E. coli	75	25	0	—	—

Note: Values do not add up to 100% in every case, because there are components other than protein, phospholipids, and sterol; plants, for example, have high levels of glycolipids.

Table 11-1
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Composição de lipídios varia entre membranas das células

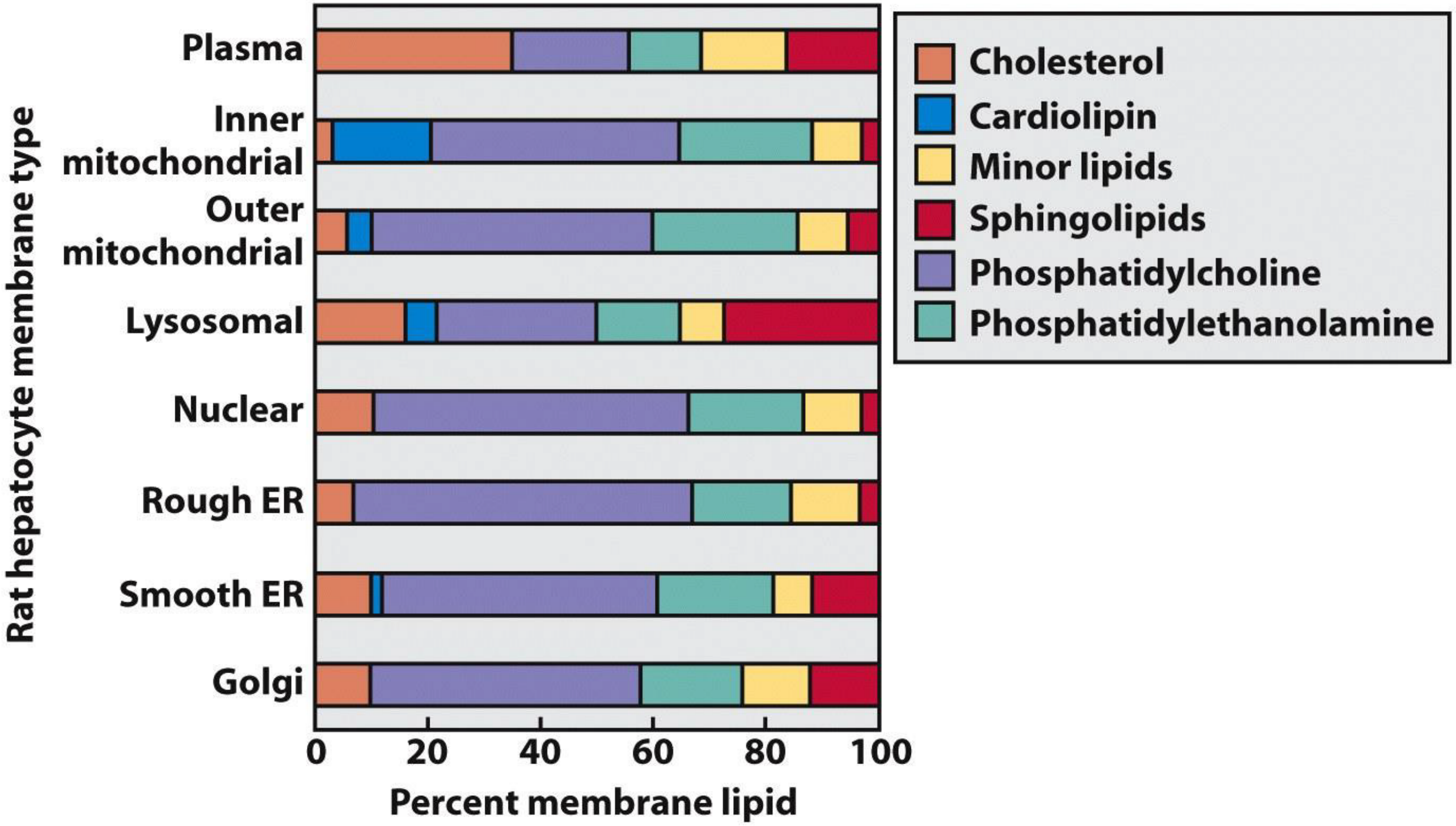

Figure 11-2
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Modelo do mosaico fluido revisitado

Assimetria

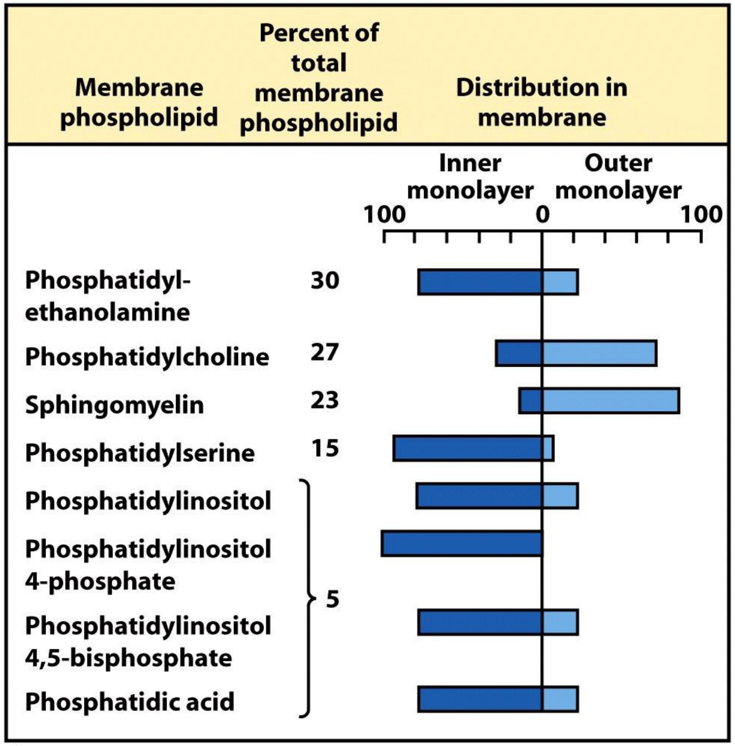

Figure 11-5
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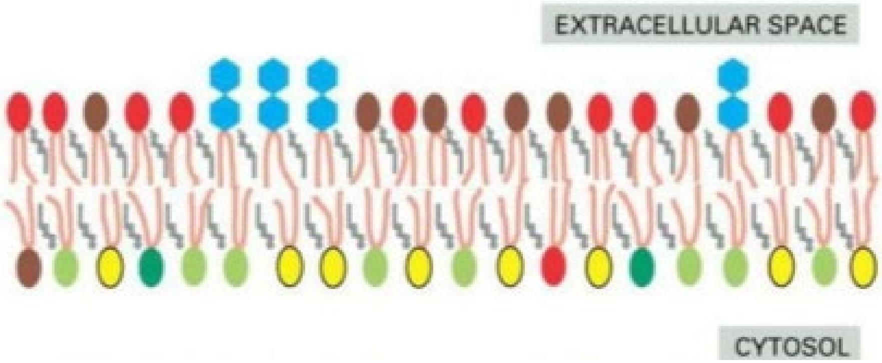
EXTRACELLULAR SPACE
CYTOSOL

Composição de lipídeos varia entre as faces de uma membrana

Movimento de “flip-flop” não é espontâneo

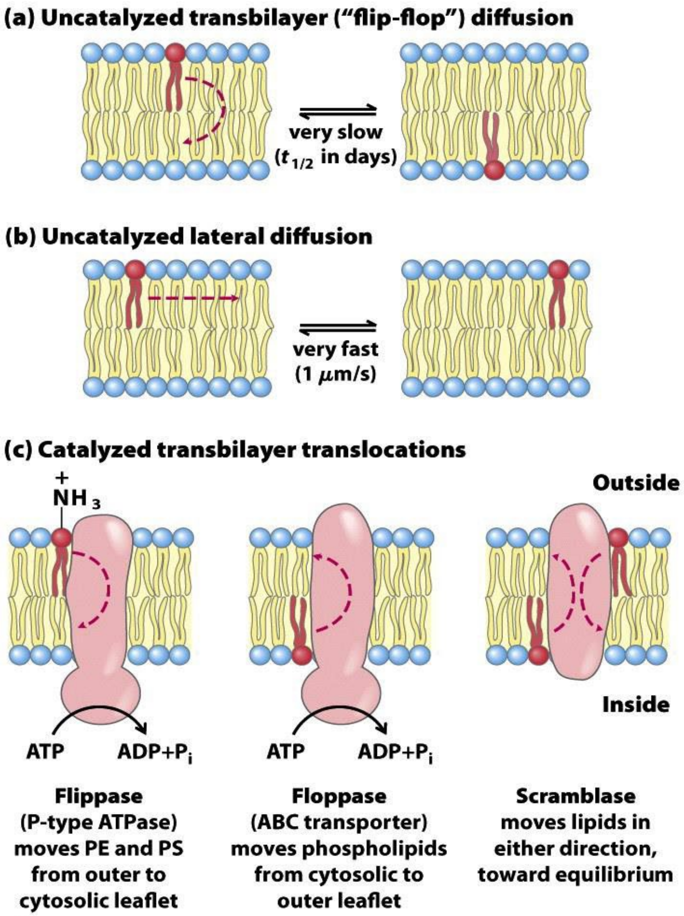
(a) Uncatalyzed transbilayer (“flip-flop”) diffusion
very slow
($t_{1/2}$ in days)
(b) Uncatalyzed lateral diffusion
very fast
(1 μm/s)
(c) Catalyzed transbilayer translocations
$\overset{+}{N}H_3$
Outside
Inside
ATP
$ADP+P_i$
ATP
$ADP+P_i$
Flippase
(P-type ATPase)
moves PE and PS
from outer to
cytosolic leaflet
Floppase
(ABC transporter)
moves phospholipids
from cytosolic to
outer leaflet
Scramblase
moves lipids in
either direction,
toward equilibrium

Figure 11-16

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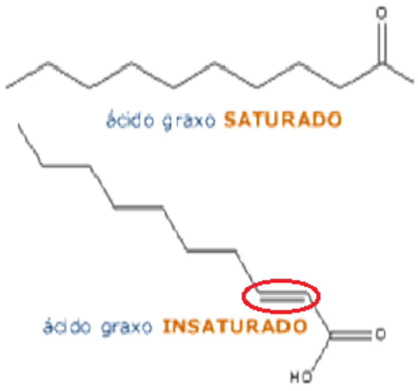
Composição de lipídeos e adaptação ao meio


O
OH
ácido graxo SATURADO
ácido graxo INSATURADO
O
HO

Observação: a instauração se deve à ocorrência de pelo menos uma dupla ligação entre os carbonos da molécula.

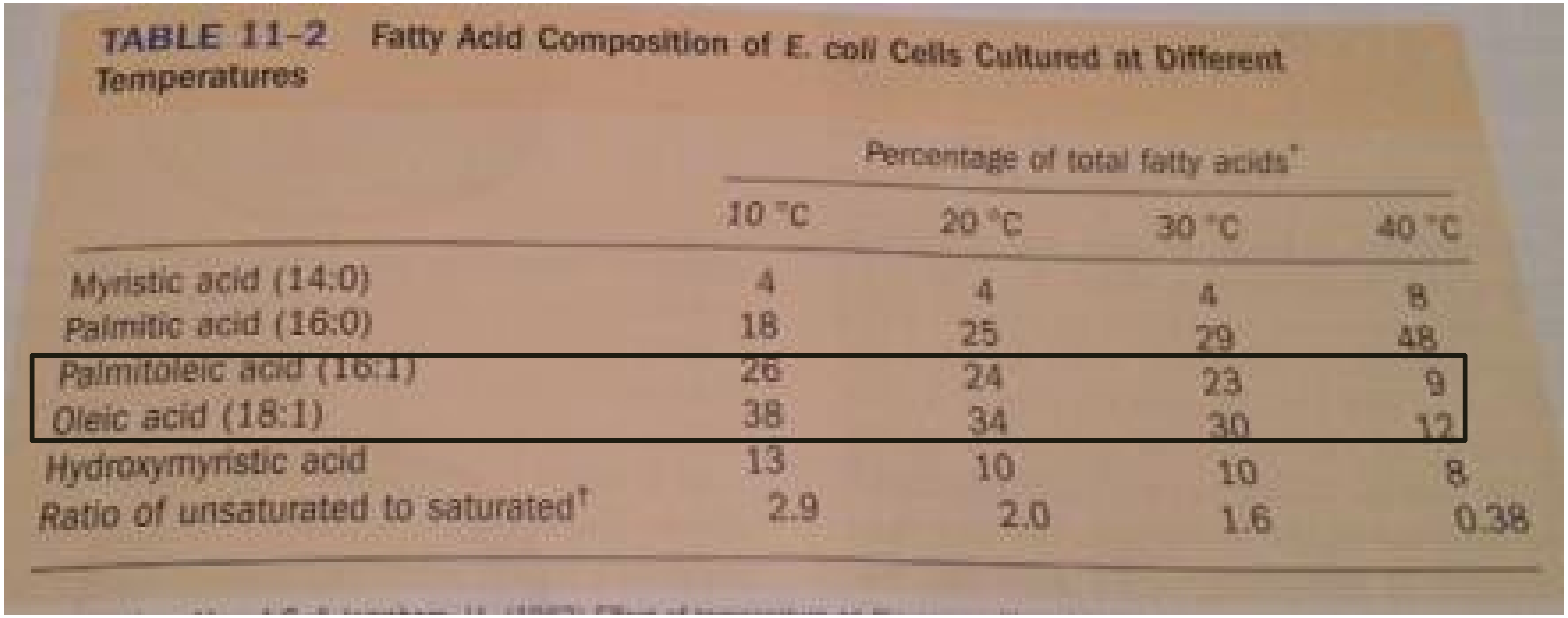
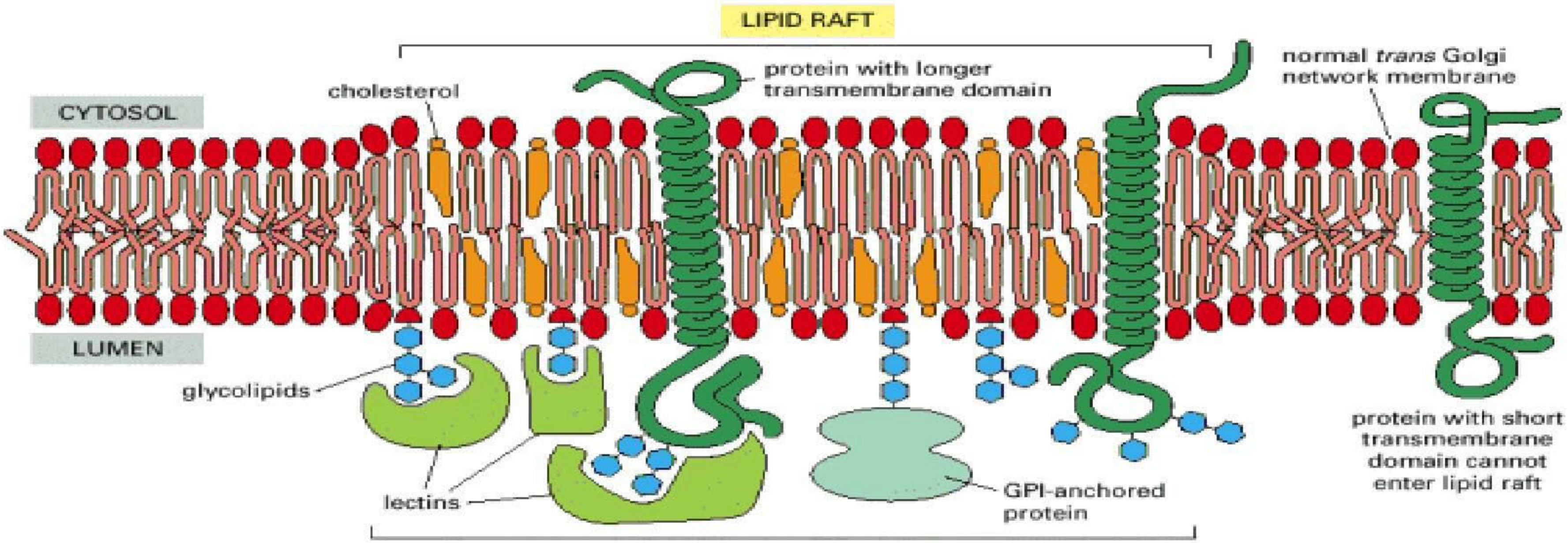


TABLE 11–2 Fatty Acid Composition of *E. coli* Cells Cultured at Different Temperatures

	Percentage of total fatty acids*			
	10 °C	20 °C	30 °C	40 °C
Myristic acid (14:0)	4	4	4	8
Palmitic acid (16:0)	18	25	29	48
Palmitoleic acid (16:1)	26	24	23	9
Oleic acid (18:1)	38	34	30	12
Hydroxymyristic acid	13	10	10	8
Ratio of unsaturated to saturated†	2.9	2.0	1.6	0.38

Modelo do mosaico fluido revisitado

Lipid rafts (balsas lipídicas)


LIPID RAFT
CYTOSOL
cholesterol
protein with longer transmembrane domain
normal *trans* Golgi network membrane
LUMEN
glycolipids
lectins
GPI-anchored protein
protein with short transmembrane domain cannot enter lipid raft

Membranas podem ter regiões mais ou menos definidas

Citoesqueleto limita movimento dos lipídeos e proteínas

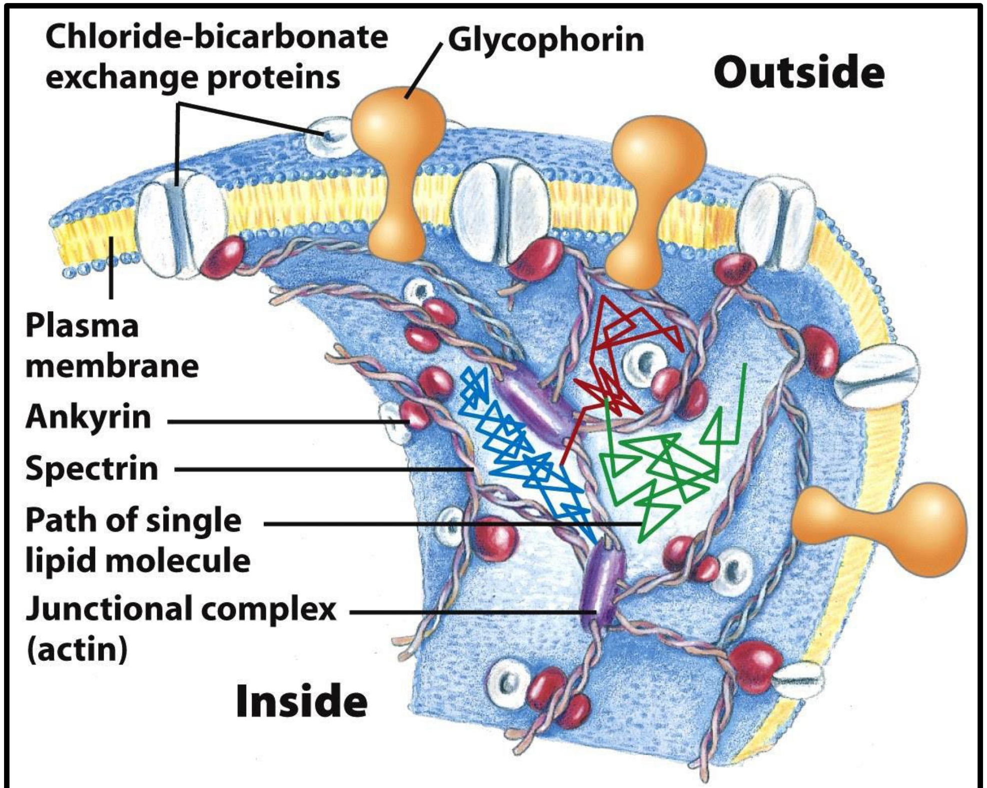

Chloride-bicarbonate exchange proteins
Glycophorin
Outside
Plasma membrane
Ankyrin
Spectrin
Path of single lipid molecule
Junctional complex (actin)
Inside

Figure 11-19
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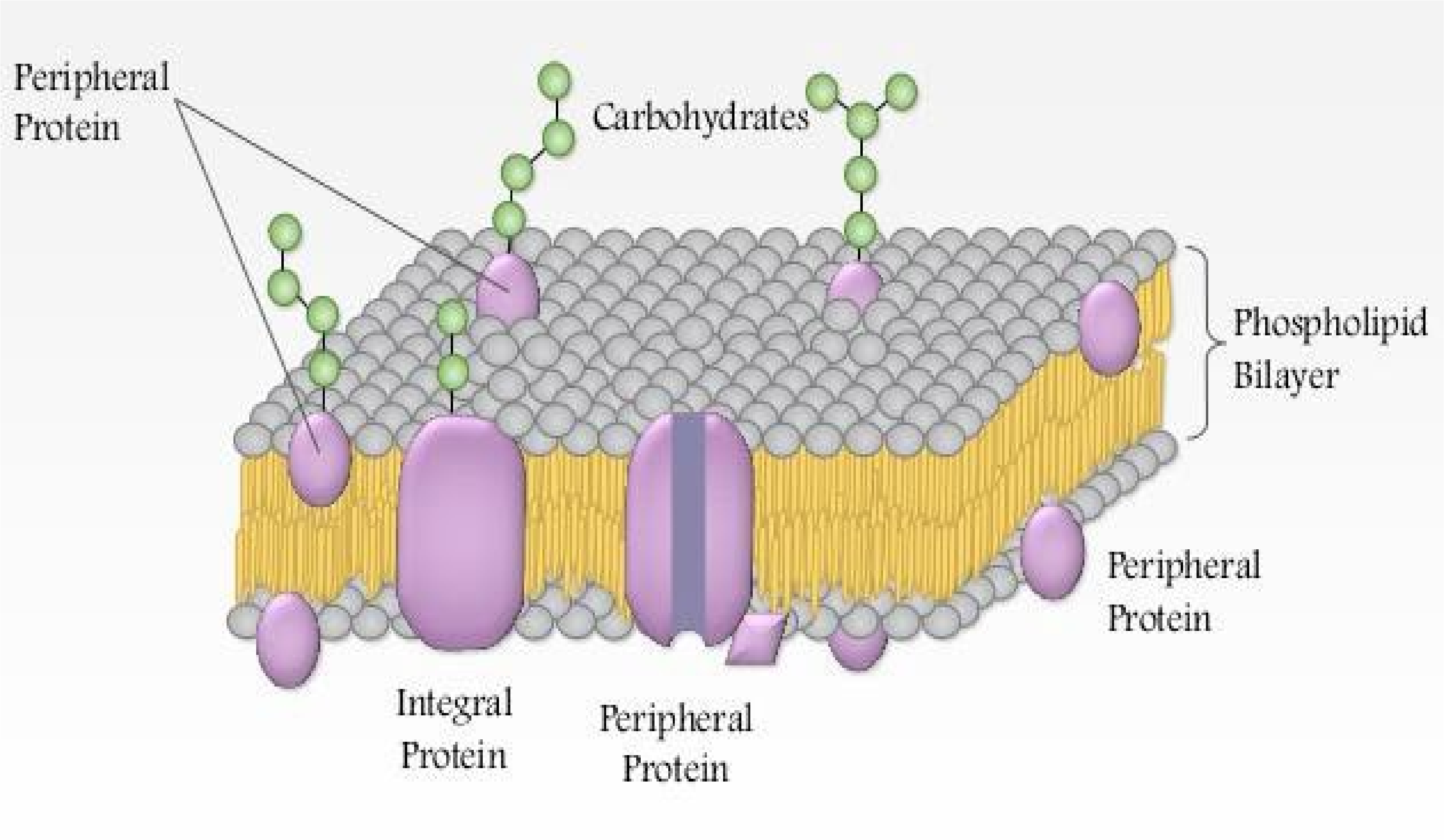
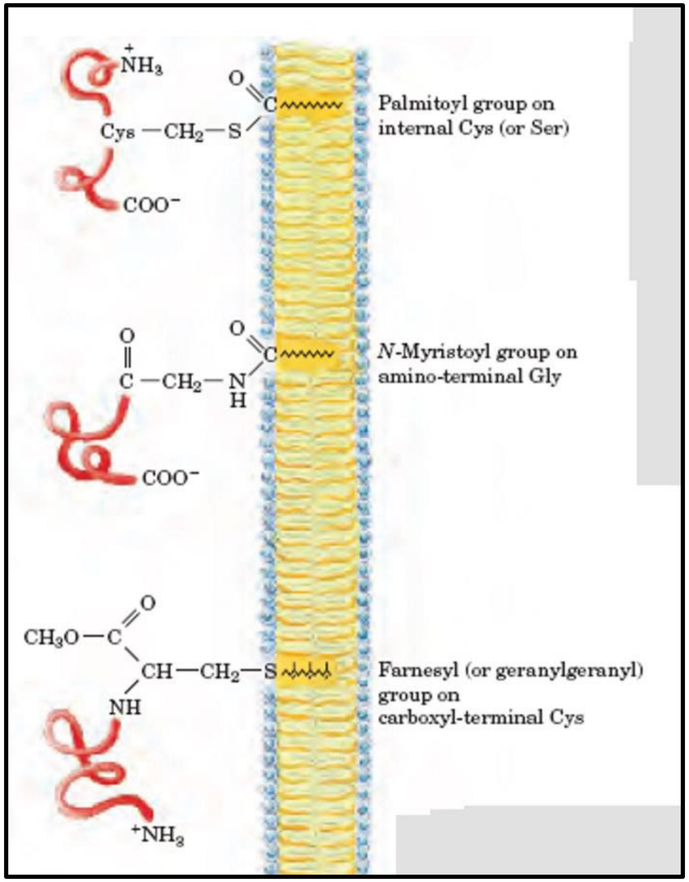
Proteínas de membranas

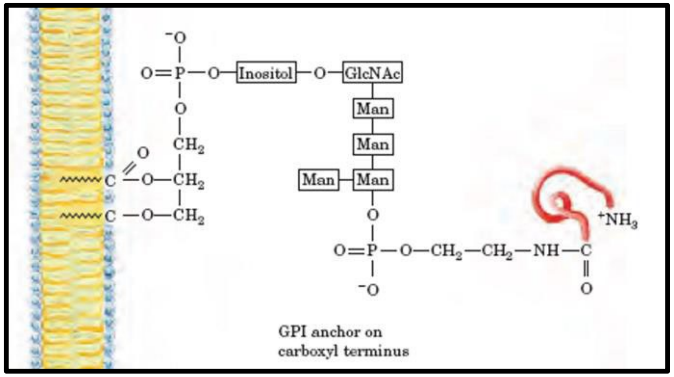

Peripheral Protein
Carbohydrates
Phospholipid Bilayer
Peripheral Protein
Integral Protein
Peripheral Protein

Proteínas periféricas – ancoradas na membrana

No lado interno da membrana plasmática são encontradas as proteínas ancoradas com ácidos palmítico e mirístico e com grupos farnesyl ou geranygeranyl



$^+NH_3$
O
Cys —CH₂—S
C
COO⁻
Palmitoyl group on internal Cys (or Ser)
O
C —CH₂— N H
O
C
COO⁻
N-Myristoyl group on amino-terminal Gly
CH₃O—C
O
CH—CH₂—S
NH
$^+NH_3$
Farnesyl (or geranylgeranyl) group on carboxyl-terminal Cys



⁻O
O=P—O—Inositol—O—GlcNAc
O
CH₂
O
C —O—CH₂
C —O—CH₂
Man
Man
Man
Man
O
O=P—O—CH₂—CH₂—NH—C
⁻O
O
$^+NH_3$
GPI anchor on carboxyl terminus

- No lado externo da membrana plasmática são encontradas as proteínas ancoradas com grupo glicosil-fosfatidilinositol

Proteínas integrais de membrana

- Alfa-hélices hidrofóbicas ou anfipáticas

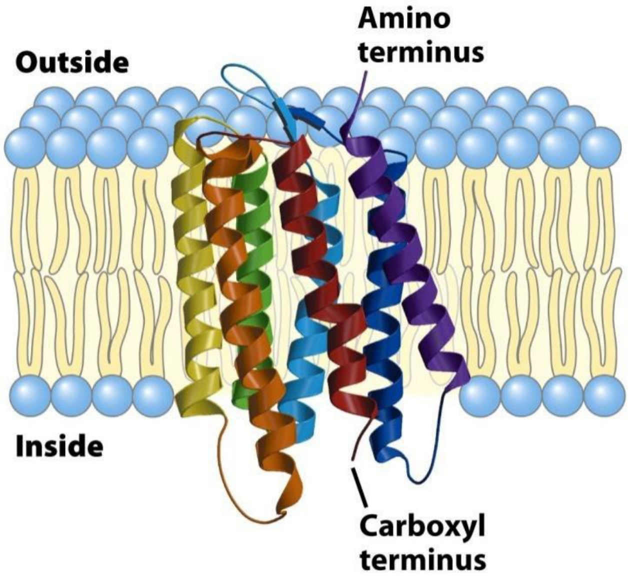

Outside
Amino terminus
Inside
Carboxyl terminus

Figure 11-9
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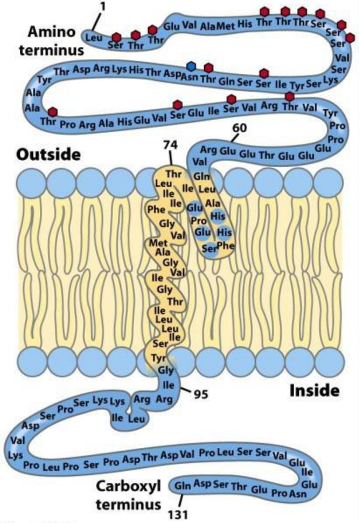
1
Amino terminus
Leu Ser Thr Thr Glu Val Ala Met His Thr Thr Thr Ser Ser Ser Val Ser Lys
Ser Tyr Ile Ser Ser Gln Thr Asn Asp Thr His Lys Arg Asp Thr Tyr Ala Ala
Thr Pro Arg Ala His Glu Val Ser Glu Ile Ser Val Arg Thr Val Tyr Pro Pro
60
Glu Glu Glu Thr Glu Glu Arg Val
74
Outside
Gln Ile Leu Ala Glu His Pro His Glu Ser Phe
Thr Leu Ile Ile Phe Gly Val Met Ala Gly Val Ile Gly Thr Ile Leu Leu Ile Ser Tyr Gly Ile
95
Inside
Arg Arg Leu Ile Lys Lys Ser Pro Ser Asp Val Lys
Pro Leu Pro Ser Pro Asp Thr Asp Val Pro Leu Ser Ser Val Glu Ile Glu
Asn Pro Glu Thr Ser Asp Gln
Carboxyl terminus
131

Figure 11-7
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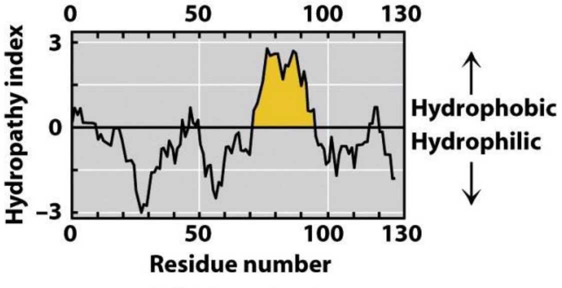
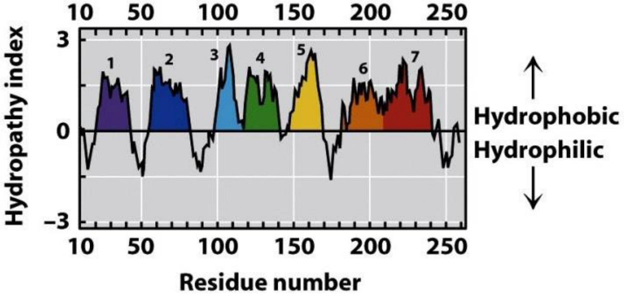


(a) Glycophorin



(b) Bacteriorhodopsin

Figure 11-11
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Barris β

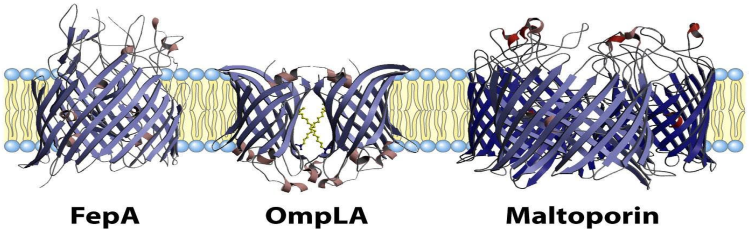
FepA
OmpLA
Maltoporin

Figure 11-13
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Fusão e fissão de membranas

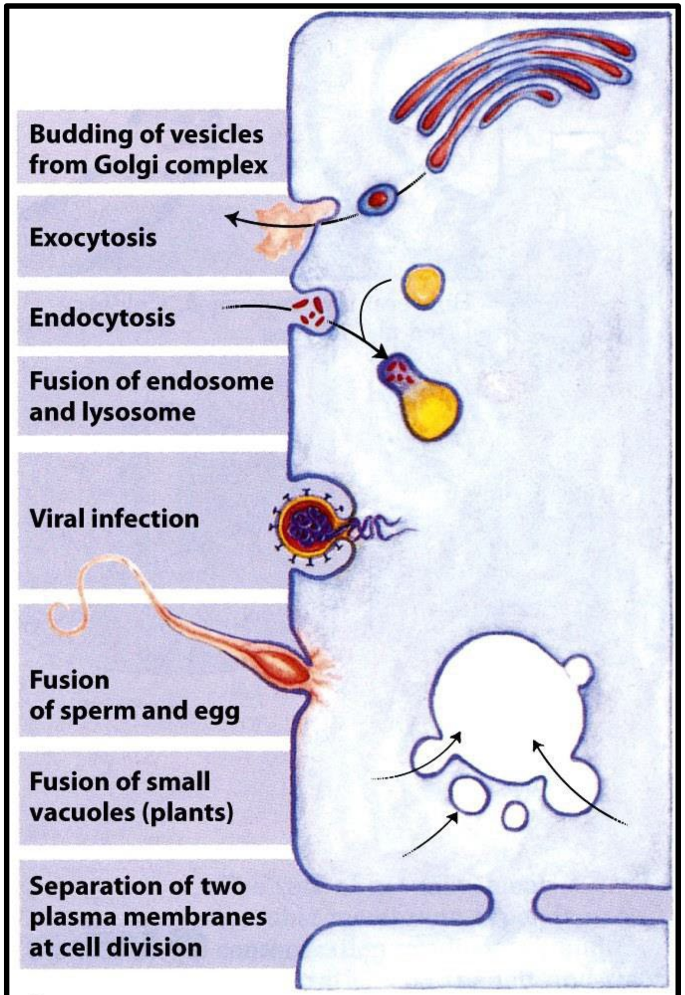
Budding of vesicles from Golgi complex
Exocytosis
Endocytosis
Fusion of endosome and lysosome
Viral infection
Fusion of sperm and egg
Fusion of small vacuoles (plants)
Separation of two plasma membranes at cell division

Figure 11-22
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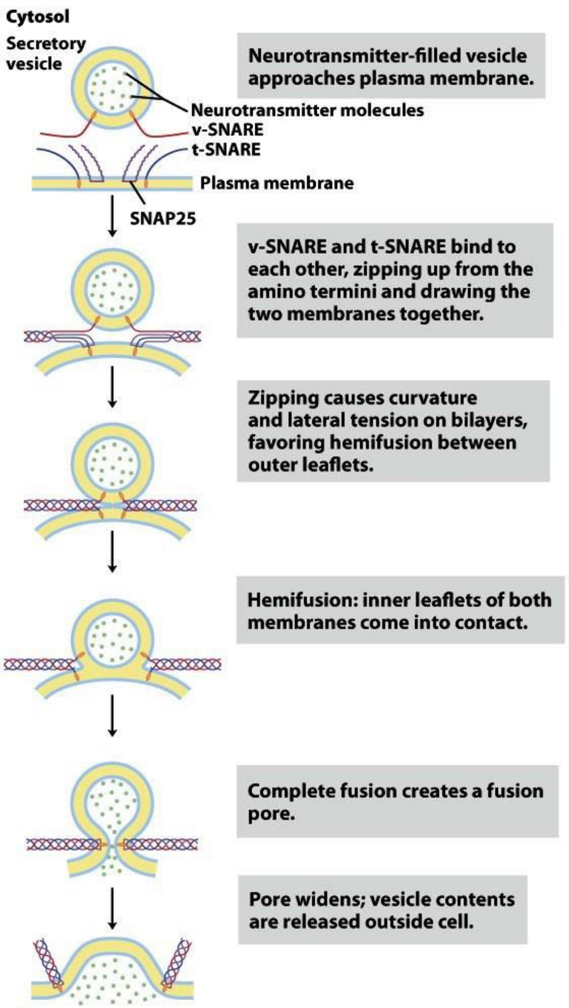
Fusão de membranas

- Mediada por proteínas
- SNARES (soluble NSF attachment receptor)
    - neurotransmissão
    - funcionam como “zíperes”


Cytosol
Secretory vesicle
Neurotransmitter molecules
v-SNARE
t-SNARE
Plasma membrane
SNAP25

Neurotransmitter-filled vesicle approaches plasma membrane.

v-SNARE and t-SNARE bind to each other, zipping up from the amino termini and drawing the two membranes together.

Zipping causes curvature and lateral tension on bilayers, favoring hemifusion between outer leaflets.

Hemifusion: inner leaflets of both membranes come into contact.

Complete fusion creates a fusion pore.

Pore widens; vesicle contents are released outside cell.

Figure 11-24
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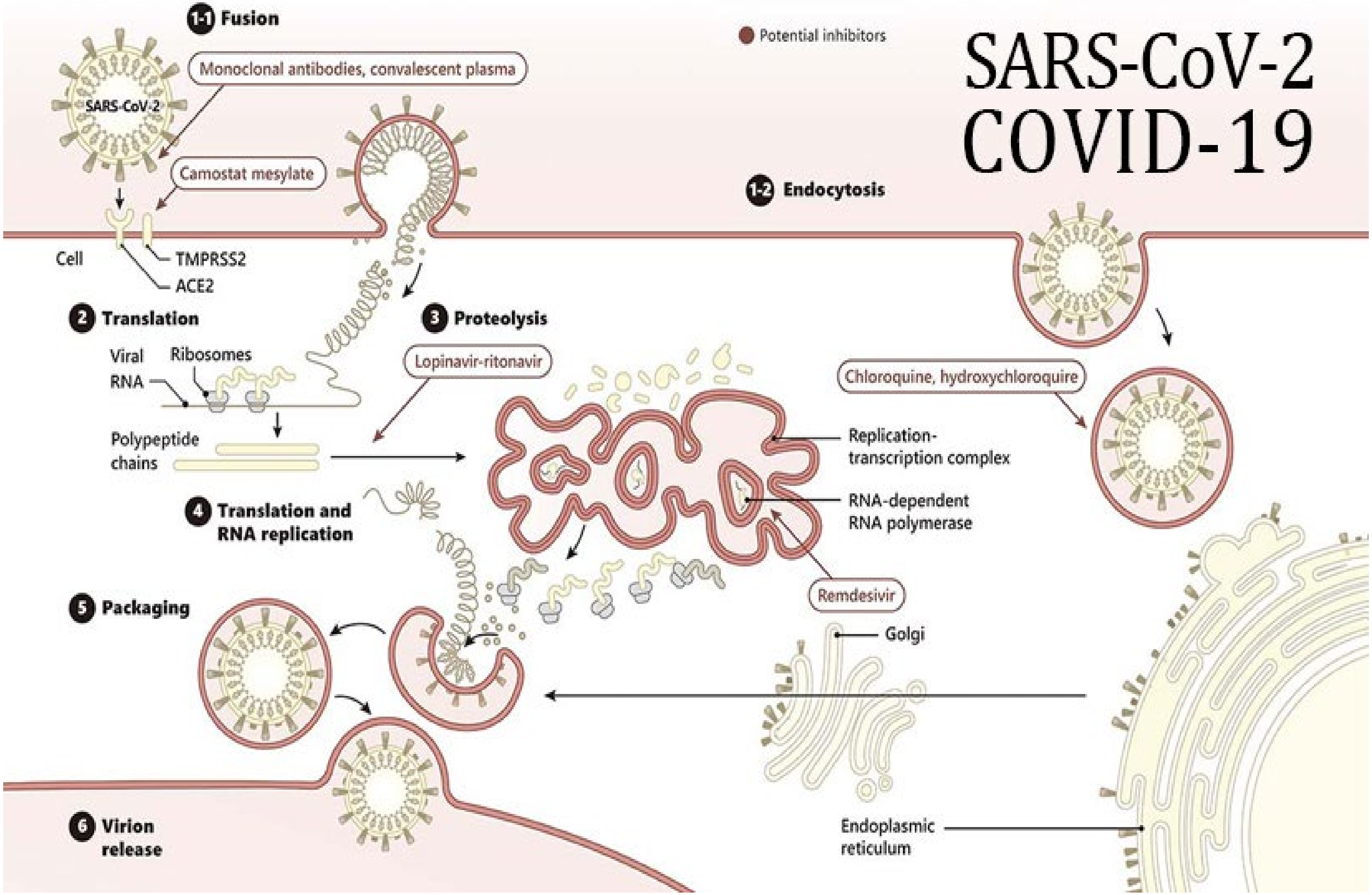
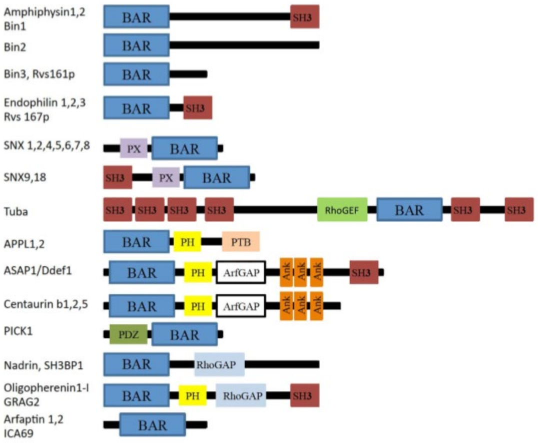
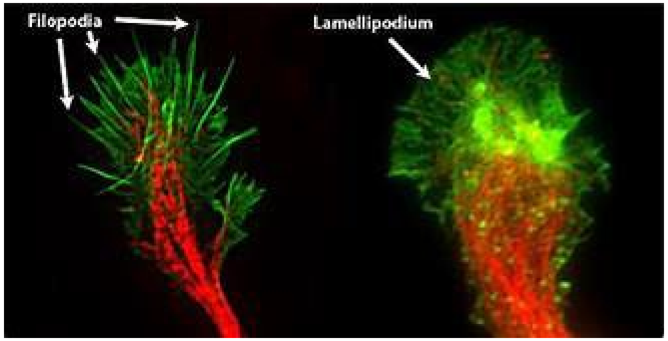
SARS-CoV-2
COVID-19

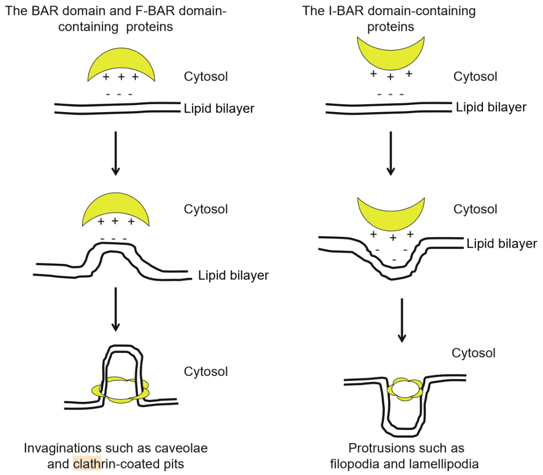

1-1 Fusion
● Potential inhibitors
SARS-CoV-2
Monoclonal antibodies, convalescent plasma
Camostat mesylate
1-2 Endocytosis
Cell
TMPRSS2
ACE2
2 Translation
Viral RNA
Ribosomes
Polypeptide chains
3 Proteolysis
Lopinavir-ritonavir
Chloroquine, hydroxychloroquire
Replication-transcription complex
RNA-dependent RNA polymerase
4 Translation and RNA replication
Remdesivir
5 Packaging
Golgi
6 Virion release
Endoplasmic reticulum

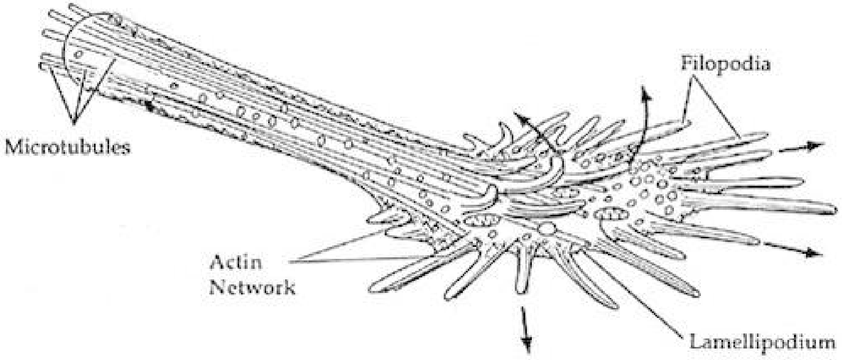
Membrane curvature
Filapodia e Lamellipodi

Bar domain containing proteins sense curvature


Amphiphysin1,2
Bin1
BAR
SH3
Bin2
BAR
Bin3, Rvs161p
BAR
Endophilin 1,2,3
Rvs 167p
BAR
SH3
SNX 1,2,4,5,6,7,8
PX
BAR
SNX9,18
SH3
PX
BAR
Tuba
SH3
SH3
SH3
SH3
RhoGEF
BAR
SH3
SH3
APPL1,2
BAR
PH
PTB
ASAP1/Ddef1
BAR
PH
ArfGAP
Ank
Ank
Ank
SH3
Centaurin b1,2,5
BAR
PH
ArfGAP
Ank
Ank
Ank
PICK1
PDZ
BAR
Nadrin, SH3BP1
BAR
RhoGAP
Oligopherenin1-I
GRAG2
BAR
PH
RhoGAP
SH3
Arfaptin 1,2
ICA69
BAR


Filopodia
Lamellipodium

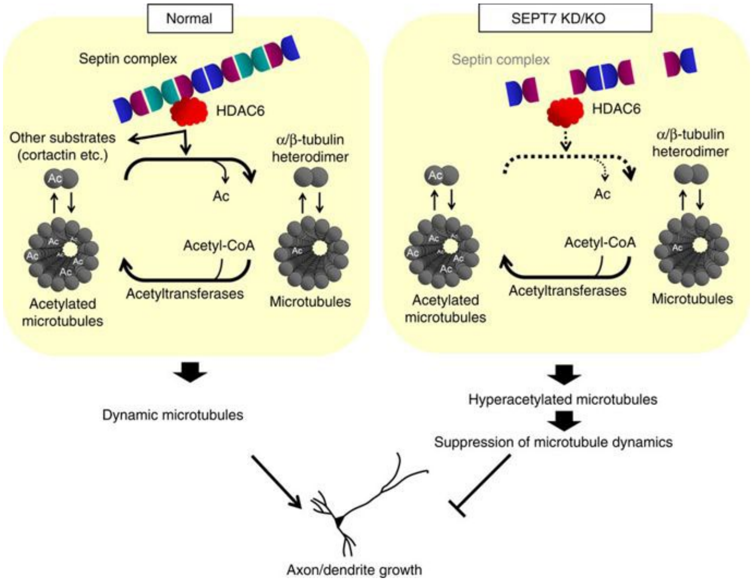

The BAR domain and F-BAR domain-containing proteins
The I-BAR domain-containing proteins
+ + +
- - -
Cytosol
Lipid bilayer
Cytosol
Lipid bilayer
Cytosol
Lipid bilayer
Cytosol
Lipid bilayer
Cytosol
Cytosol
Invaginations such as caveolae and clathrin-coated pits
Protrusions such as filopodia and lamellipodia

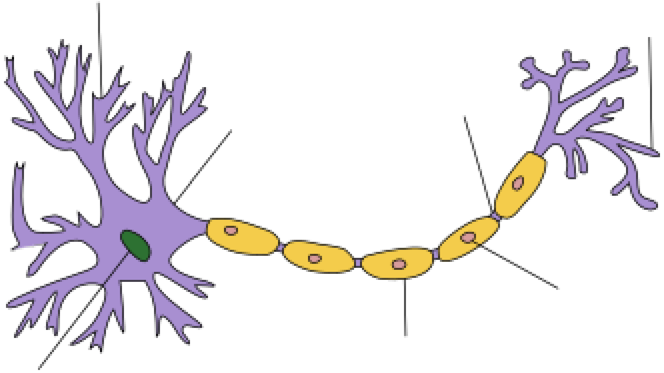

Filopodia
Microtubules
Actin Network
Lamellipodium

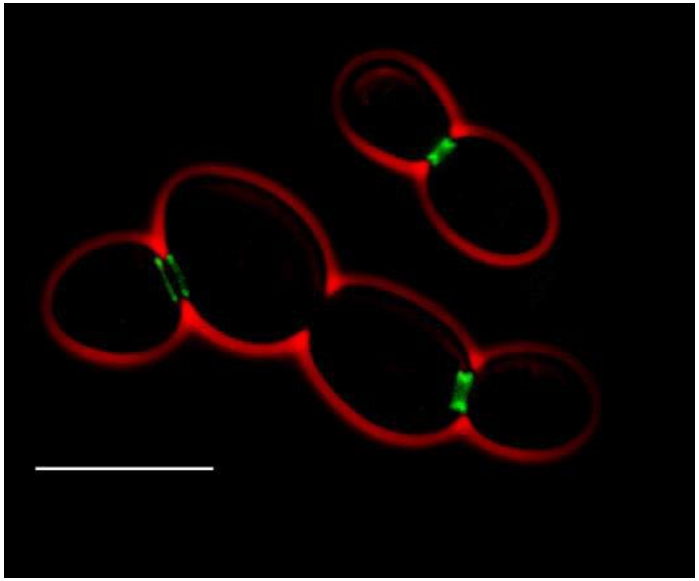
Membranes 2012, 2, 91-117; doi:10.3390/membranes2010091

Cytoskeletal fences

Septins are involved in the formation of structures such as, cilia and flagella, dendritic spines, and yeast buds. Limiting cell division.

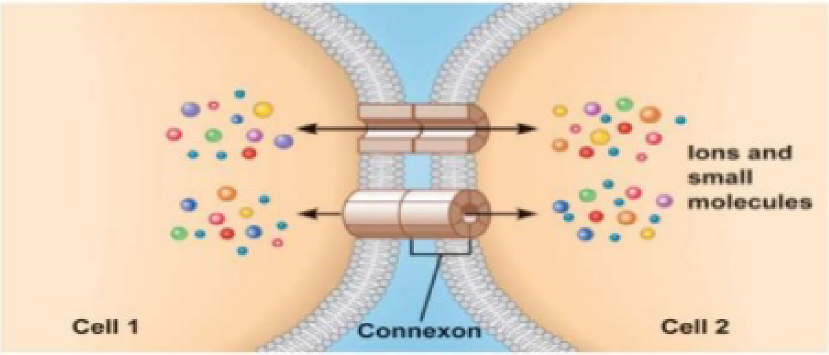

Normal
Septin complex
HDAC6
Other substrates (cortactin etc.)
α/β-tubulin heterodimer
Ac
Acetyl-CoA
Acetyltransferases
Acetylated microtubules
Microtubules
SEPT7 KD/KO
Septin complex
HDAC6
α/β-tubulin heterodimer
Ac
Acetyl-CoA
Acetyltransferases
Acetylated microtubules
Microtubules
Dynamic microtubules
Hyperacetylated microtubules
Suppression of microtubule dynamics
Axon/dendrite growth





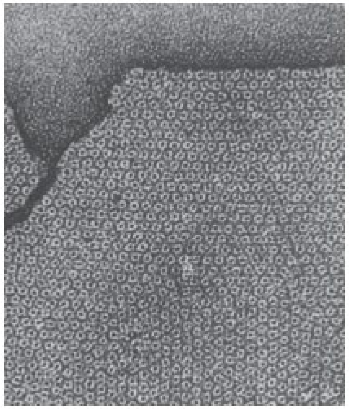
Gap junction

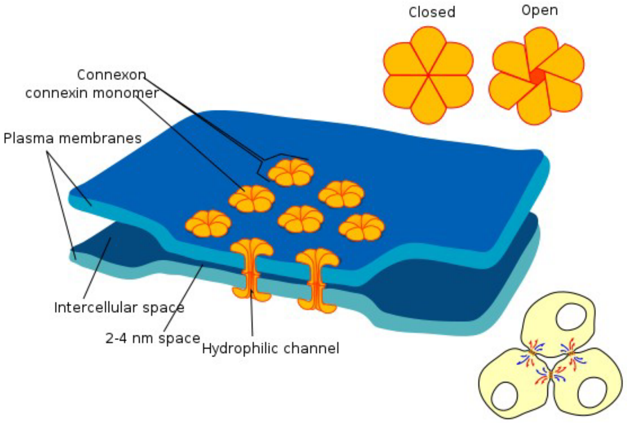
- Structure that permits direct transfer of small molecule(upto 1200Da).
- Composed of family of protein called connexins.
- Mutations in genes encoding connexins are associated with cardiovascular diseases and X-linked form of charcot-Marrie-tooth disease.


Ions and small molecules
Cell 1
Connexon
Cell 2

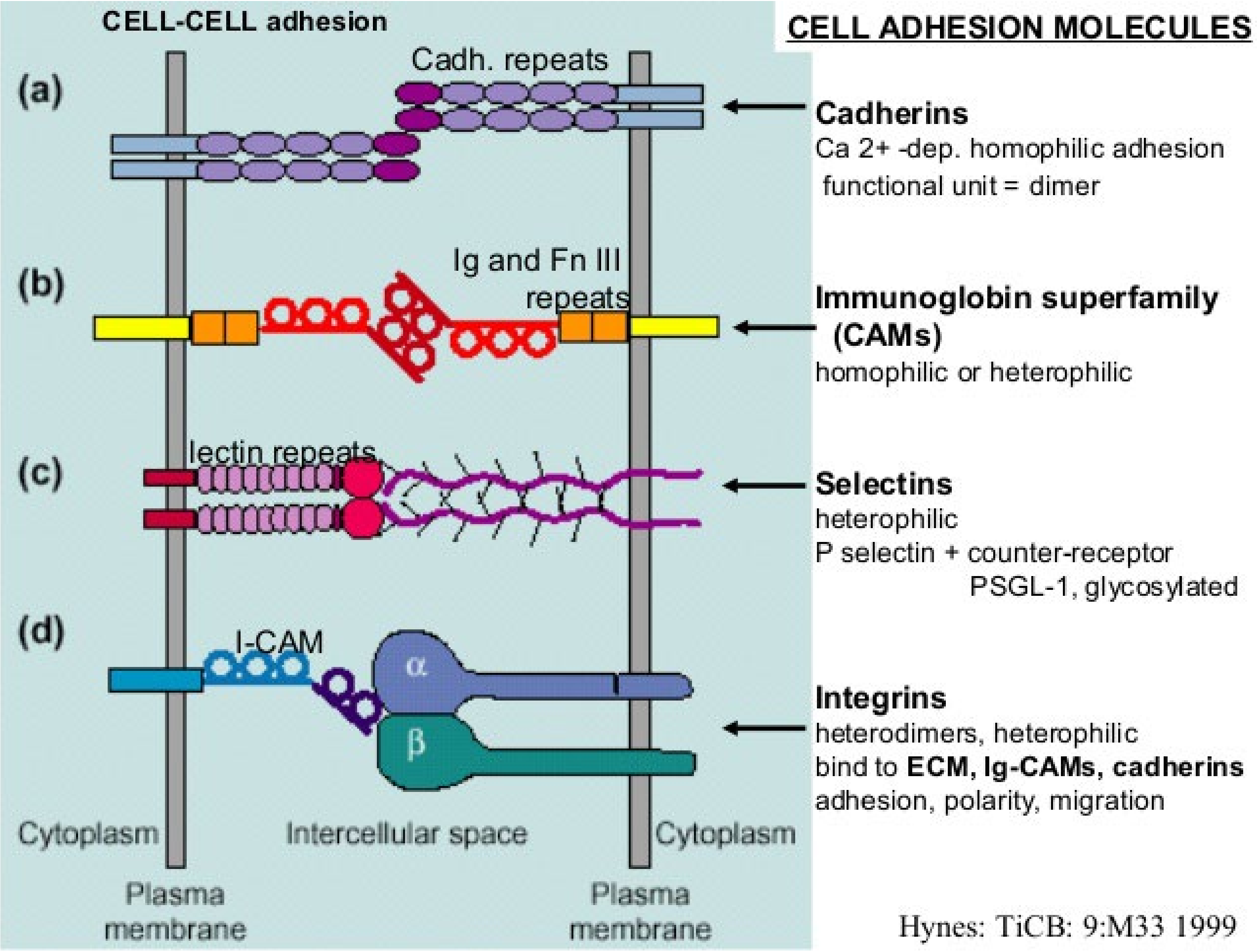
(a) Direct communication through gap junctions

© 2011 Pearson Education, Inc.




Closed
Open
Connexon
connexin monomer
Plasma membranes
Intercellular space
2-4 nm space
Hydrophilic channel

Comunicação celular adesão


CELL-CELL adhesion
(a)
Cadh. repeats
(b)
Ig and Fn III repeats
(c)
lectin repeats
(d)
I-CAM
α
β
Cytoplasm
Intercellular space
Cytoplasm
Plasma membrane
Plasma membrane

CELL ADHESION MOLECULES

Cadherins
Ca 2+ -dep. homophilic adhesion
functional unit = dimer

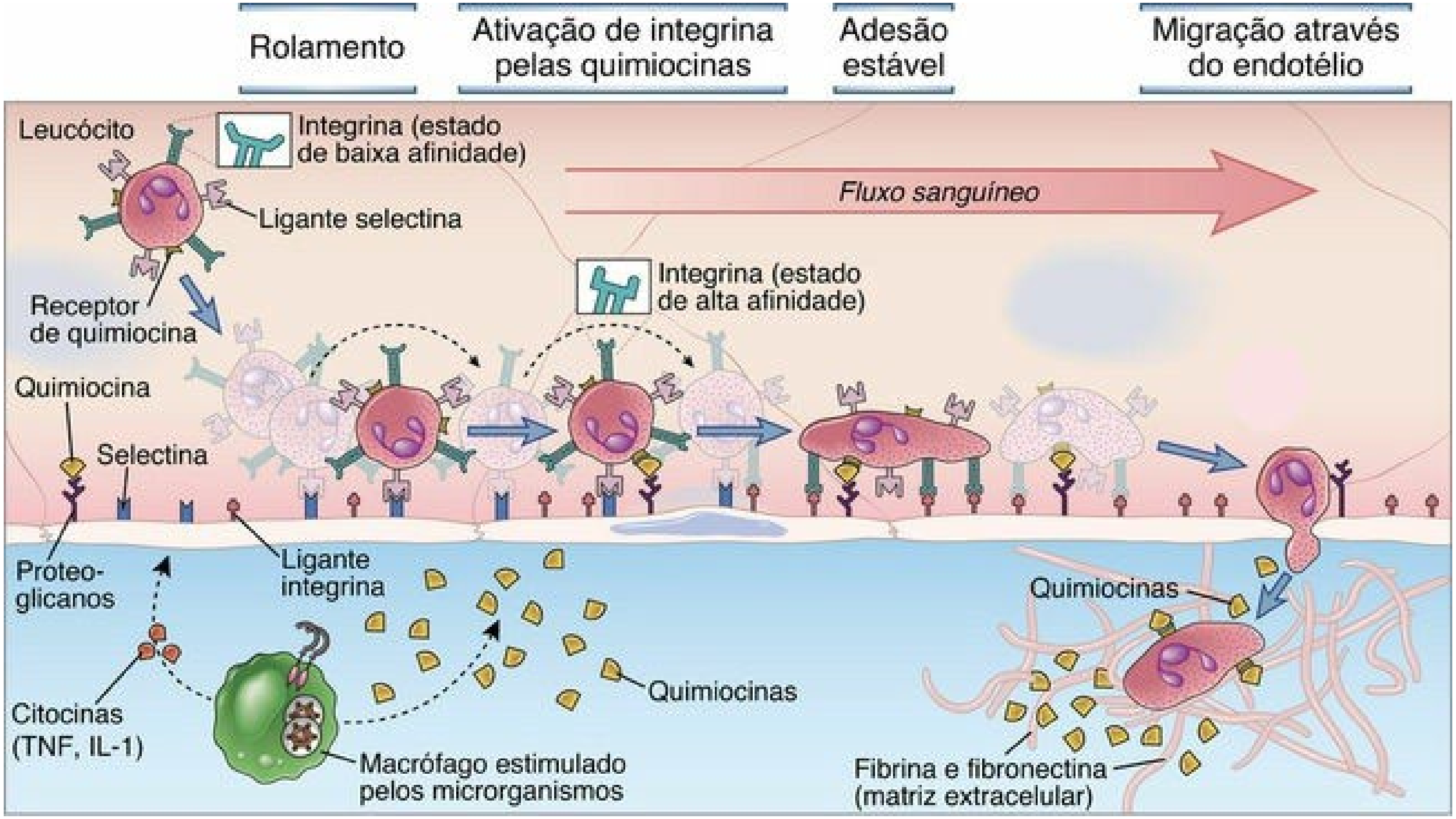
Immunoglobin superfamily (CAMs)
homophilic or heterophilic

Selectins
heterophilic
P selectin + counter-receptor PSGL-1, glycosylated

Integrins
heterodimers, heterophilic
bind to **ECM, Ig-CAMs, cadherins**
adhesion, polarity, migration

Hynes: TiCB: 9:M33 1999

Comunicação celular adesão
Migração de leucócitos

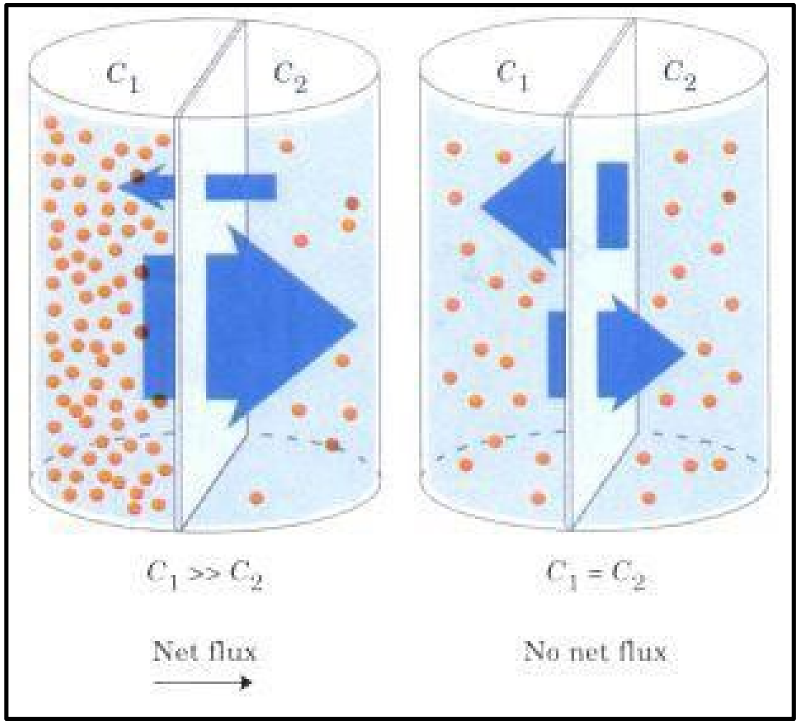

Rolamento
Ativação de integrina pelas quimiocinas
Adesão estável
Migração através do endotélio
Leucócito
Integrina (estado de baixa afinidade)
Ligante selectina
Fluxo sanguíneo
Receptor de quimiocina
Integrina (estado de alta afinidade)
Quimiocina
Selectina
Proteo-glicanos
Ligante integrina
Quimiocinas
Citocinas (TNF, IL-1)
Macrófago estimulado pelos microrganismos
Quimiocinas
Fibrina e fibronectina (matriz extracelular)

https://www.youtube.com/watch?v=B9Qi7we0Ynk

Transporte através de membranas

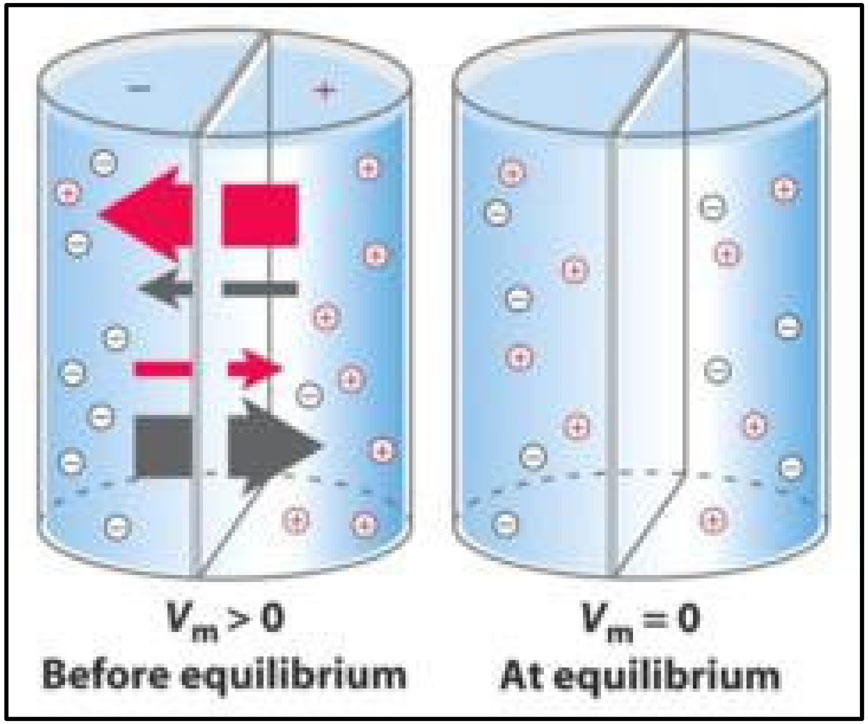
Movimento através de uma membrana permeável

Concentração



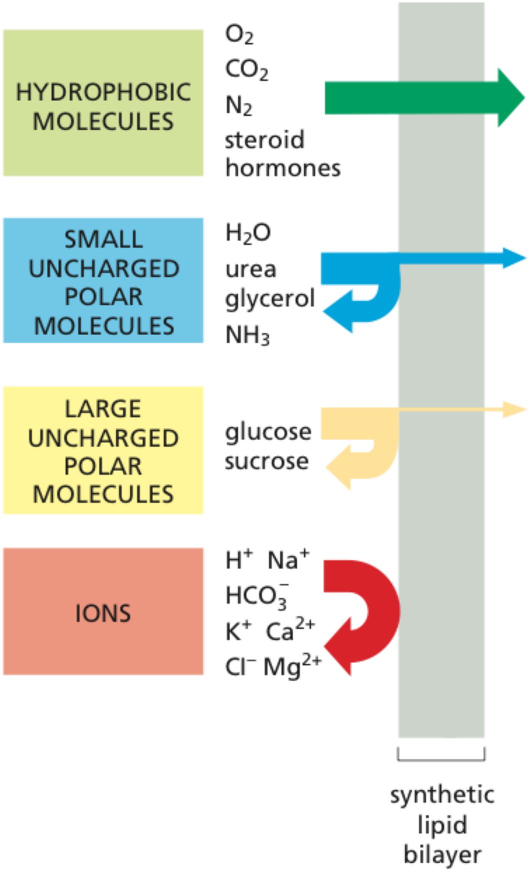
C_1
C_2
C_1
C_2
$C_1 >> C_2$
Net flux
$C_1 = C_2$
No net flux

Carga



−
+
$V_m > 0$
Before equilibrium
$V_m = 0$
At equilibrium

Permeabilidade das membranas biológicas


HYDROPHOBIC MOLECULES
O_2
CO_2
N_2
steroid hormones
SMALL UNCHARGED POLAR MOLECULES
H_2O
urea
glycerol
NH_3
LARGE UNCHARGED POLAR MOLECULES
glucose
sucrose
IONS
H^+ Na^+
HCO_3^-
K^+ Ca^{2+}
Cl^- Mg^{2+}
synthetic lipid bilayer

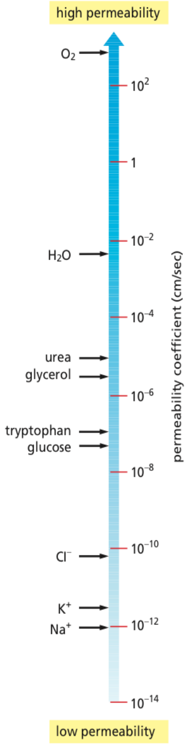
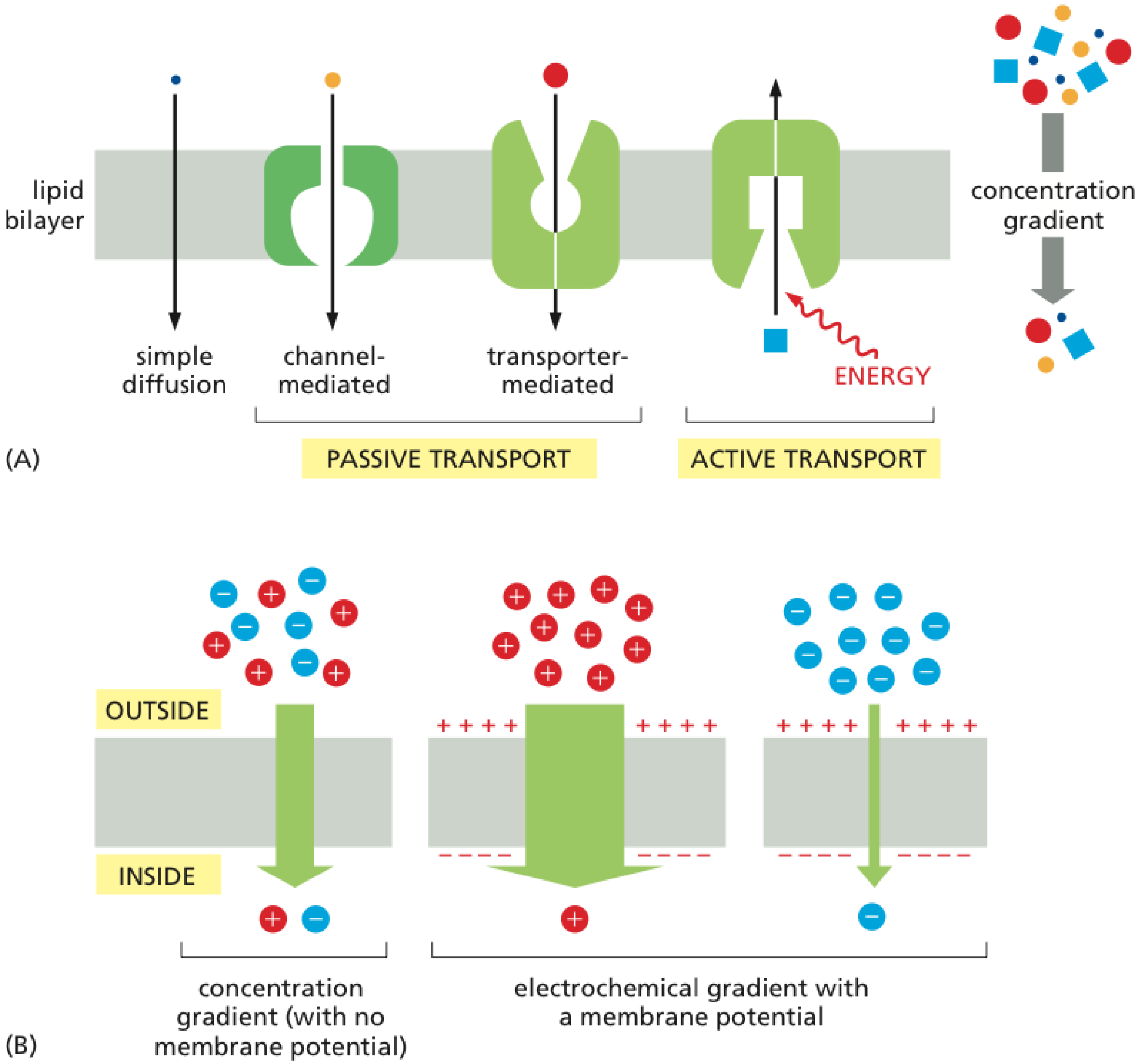


TABLE 11–1 A Comparison of Inorganic Ion Concentrations Inside and Outside a Typical Mammalian Cell*

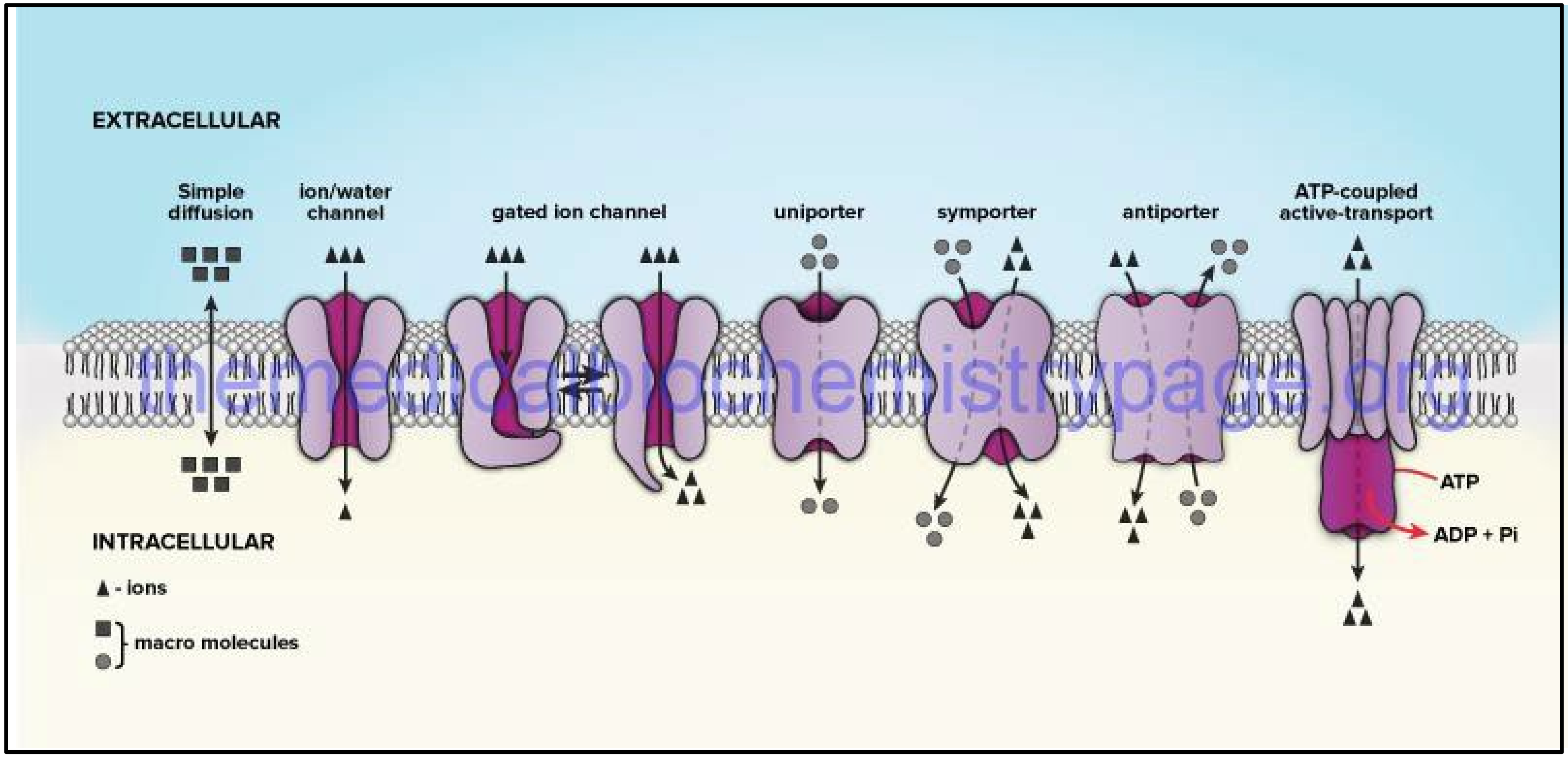
Component	Cytoplasmic concentration (mM)	Extracellular concentration (mM)
Cations		
Na^+	5–15	145
K^+	140	5
Mg^{2+}	0.5	1–2
Ca^{2+}	10^{-4}	1–2
H^+	7×10^{-5} ($10^{-7.2}$ M or pH 7.2)	4×10^{-5} ($10^{-7.4}$ M or pH 7.4)
Anions		
Cl^-	5–15	110

*The cell must contain equal quantities of positive and negative charges (that is, it must be electrically neutral). Thus, in addition to Cl^-, the cell contains many other anions not listed in this table; in fact, most cell constituents are negatively charged (HCO_3^-, PO_4^{3-}, nucleic acids, metabolites carrying phosphate and carboxyl groups, etc.). The concentrations of Ca^{2+} and Mg^{2+} given are for the free ions: although there is a total of about 20 mM Mg^{2+} and 1–2 mM Ca^{2+} in cells, both ions are mostly bound to other substances (such as proteins, free nucleotides, RNA, etc.) and, for Ca^{2+}, stored within various organelles.

Transporte

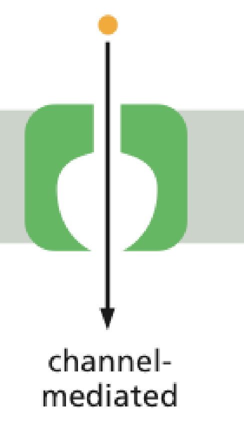

lipid bilayer
simple diffusion
channel-mediated
transporter-mediated
ENERGY
concentration gradient
PASSIVE TRANSPORT
ACTIVE TRANSPORT
(A)
OUTSIDE
INSIDE
+ + + +
– – – –
concentration gradient (with no membrane potential)
electrochemical gradient with a membrane potential
(B)

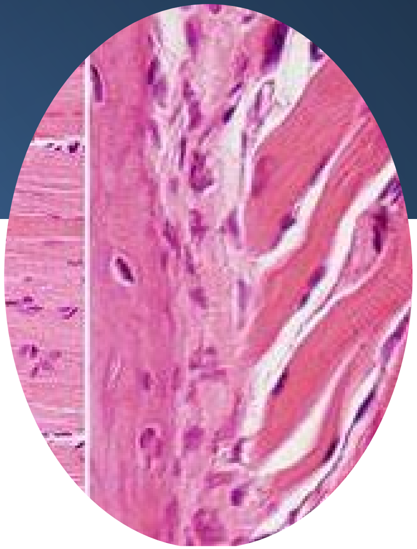
Transportadores e Canais

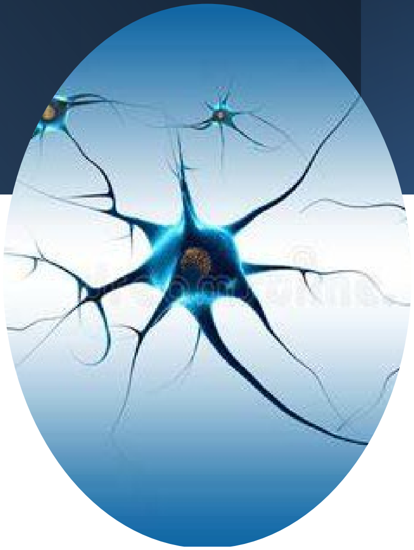

EXTRACELLULAR
Simple diffusion
ion/water channel
gated ion channel
uniporter
symporter
antiporter
ATP-coupled active-transport
ATP
ADP + Pi
INTRACELLULAR
▲ - ions
■ ● macro molecules

themedicalbiochemistrypage.org

Canais iônicos

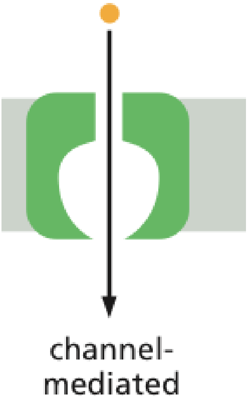

channel-
mediated





- -Movimentam íons inorgânicos.
- -Junto com os trocadores regulam a concentração citoplasmática de íons e o potencial de membrana.

Canais iônicos



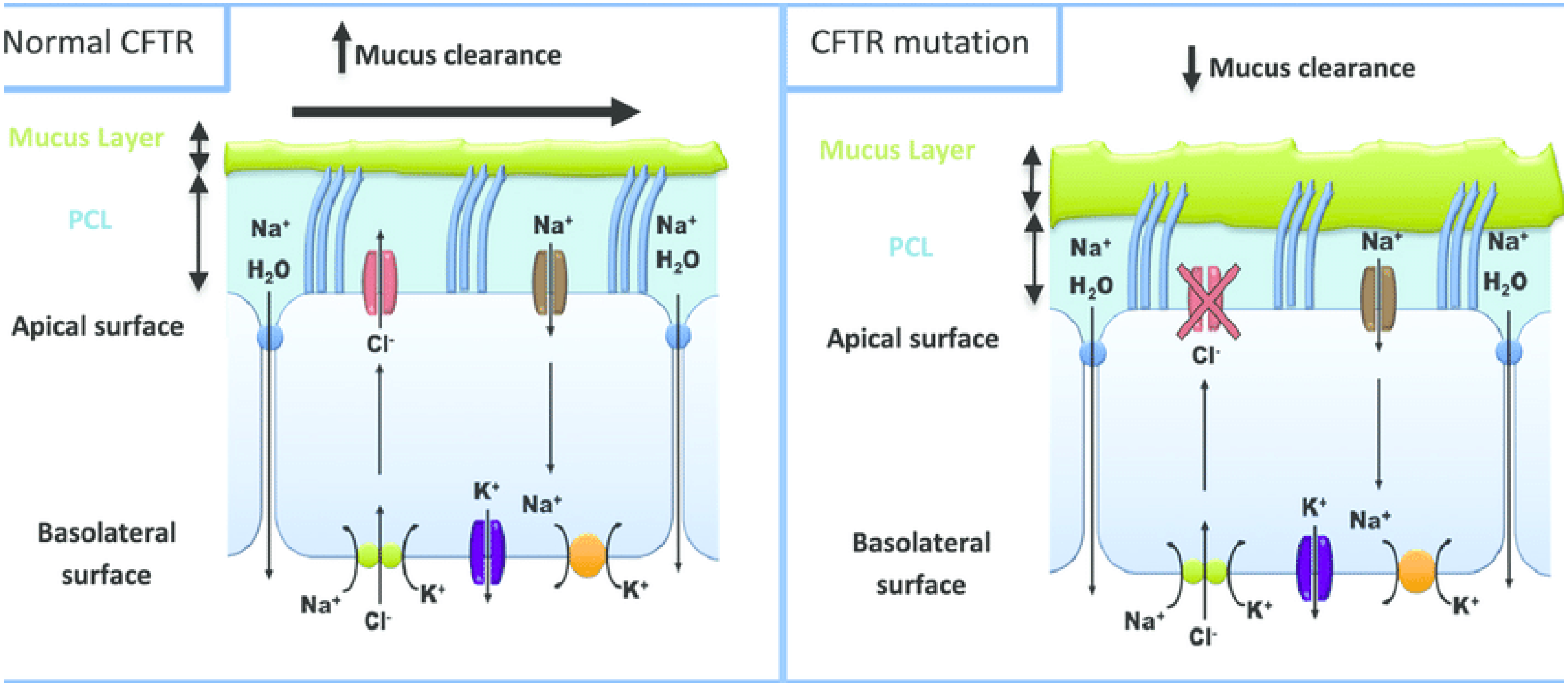
Canais iônicos diferem de transportadores de íons:
-Velocidade do fluxo de íons é maior nos canais.
- Canais não são saturáveis.
-"gated" controlados por algum estímulo.

Controlados por ligantes (geralmente oligoméricos).
- Mudança conformacional do canal que abre ou fecha com um ligante.

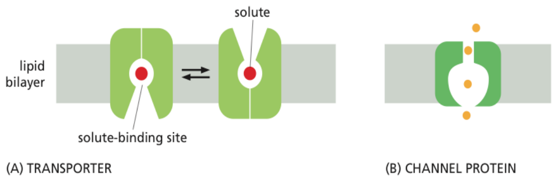
Controlados por voltagem
-Mudança no potencial transmembranar causa o movimento de uma proteína com carga relativo à membrana causando a abertura ou fechamento do canal

Cystic Fibrosis

https://youtu.be/eehsgyvm0SQ


Normal CFTR
Mucus clearance
Mucus Layer
PCL
Na+
H2O
Na+
Na+
H2O
Apical surface
Cl-
K+
Na+
Basolateral surface
Na+
Cl-
K+
K+
CFTR mutation
Mucus clearance
Mucus Layer
PCL
Na+
H2O
Na+
Na+
H2O
Apical surface
Cl-
K+
Na+
Basolateral surface
Na+
Cl-
K+
K+

Transportadores e Canais


lipid bilayer
solute
solute-binding site
(A) TRANSPORTER
(B) CHANNEL PROTEIN

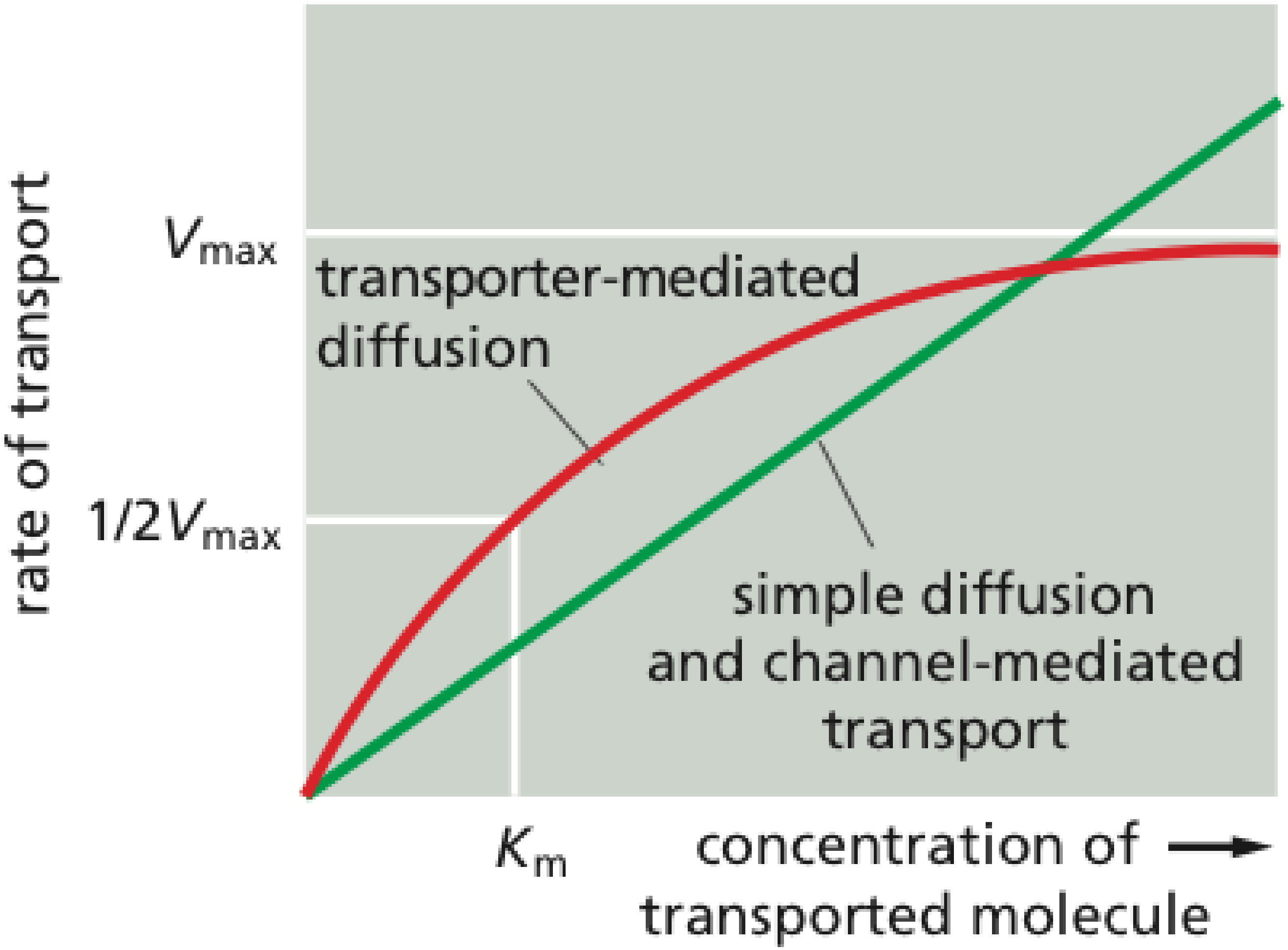
Transportadores

-Saturáveis
-Baixa velocidade de transporte
-Maioria proteínas monoméricas

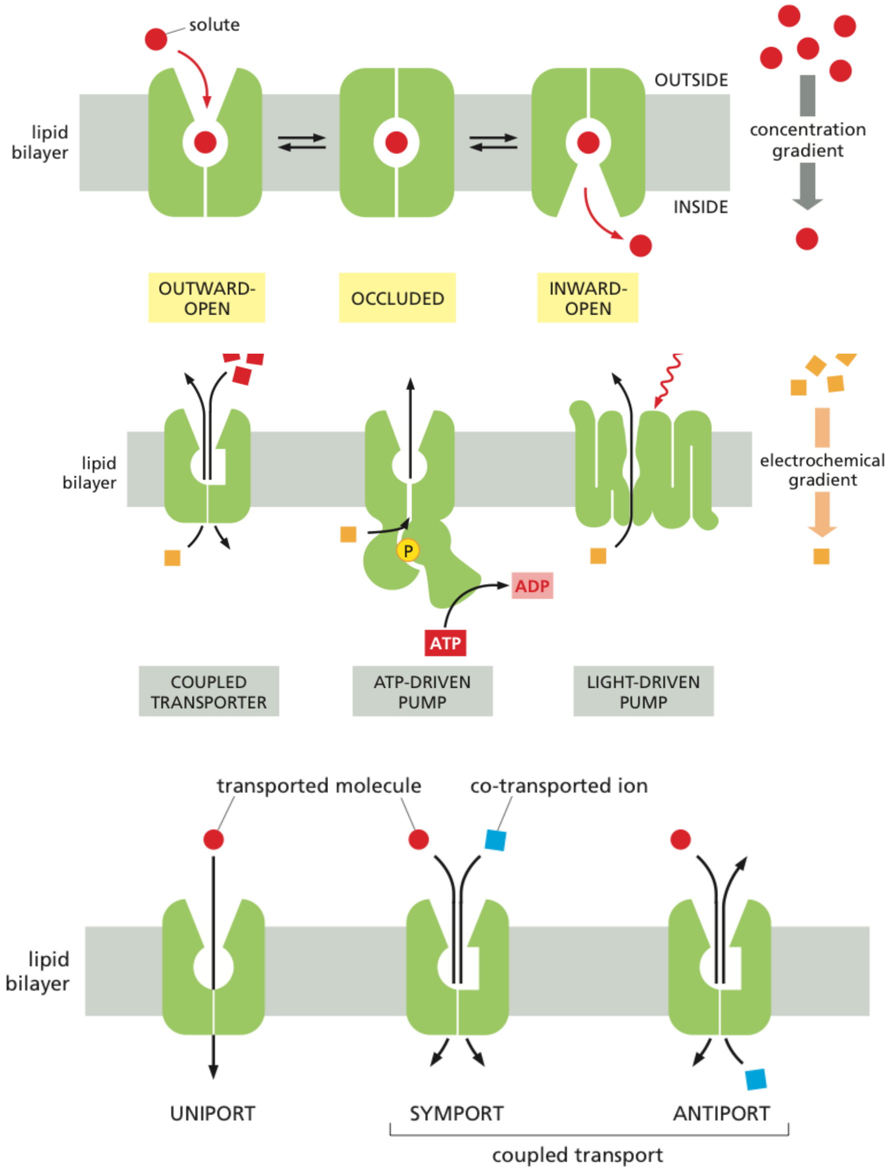
Canais

-Mais rápidos
-Insaturáveis
-Maioria proteínas oligoméricas

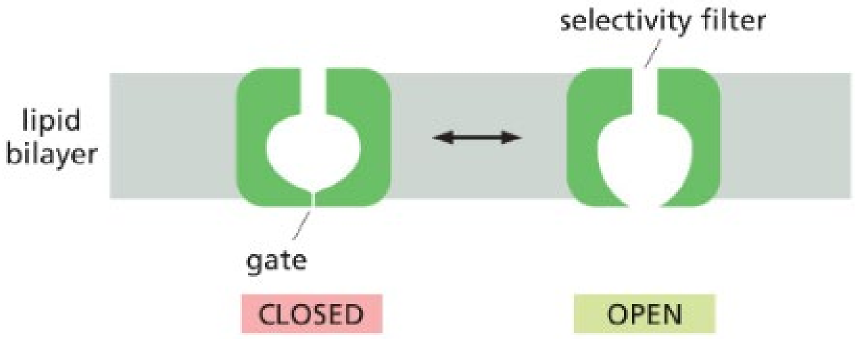
Transportadores e Canais



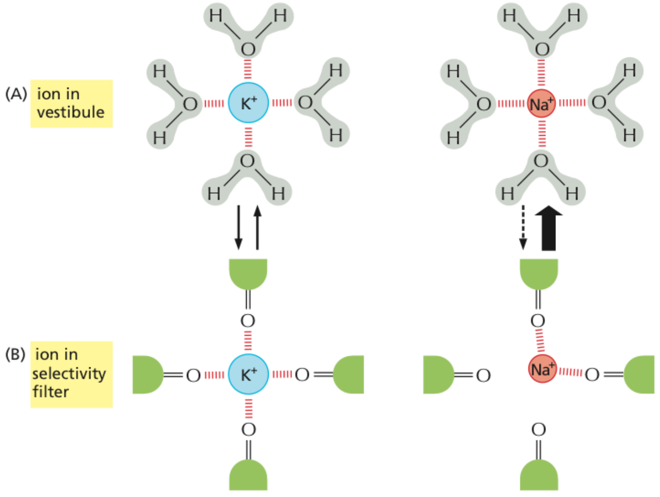
Transportadores

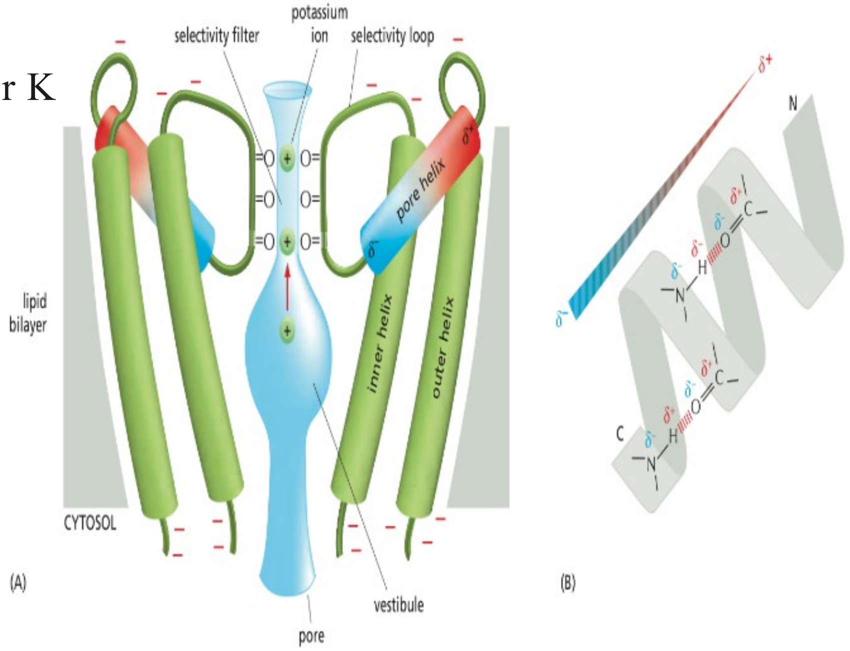

solute
lipid bilayer
OUTSIDE
INSIDE
concentration gradient
OUTWARD-OPEN
OCCLUDED
INWARD-OPEN
lipid bilayer
P
ADP
ATP
electrochemical gradient
COUPLED TRANSPORTER
ATP-DRIVEN PUMP
LIGHT-DRIVEN PUMP
transported molecule
co-transported ion
lipid bilayer
UNIPORT
SYMPORT
ANTIPORT
coupled transport

Transportadores de íons (transportador de K⁺/ filtro de seletividade)


selectivity filter
lipid bilayer
gate
CLOSED
OPEN

High selectivity needs tight binding site!
Easier to remove water more distant from nucleus !
Bond distance and backbone Carbonil oxigens = Water for K


(A) ion in vestibule
(B) ion in selectivity filter
K⁺
Na⁺
H
O


potassium ion
selectivity filter
selectivity loop
pore helix
inner helix
outer helix
lipid bilayer
CYTOSOL
vestibule
pore
(A)
(B)
N
C
δ+
δ-

https://www.youtube.com/watch?v=4l_OeDYbNVE

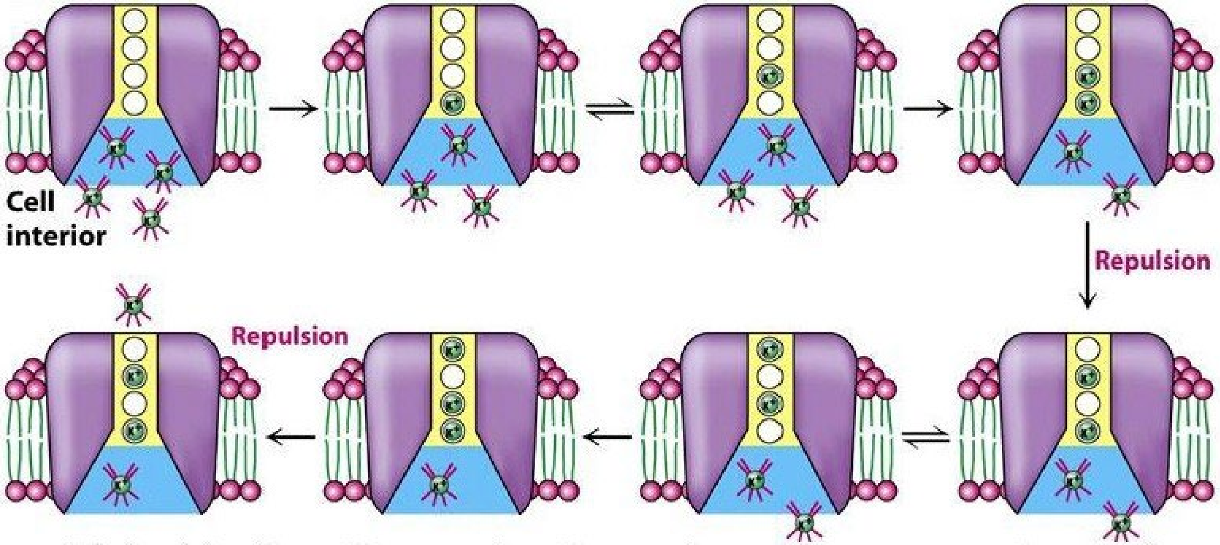
The structure of the potassium ion channel explains its rapid rate of transport

High selectivity needs tight binding site!
How to achieve fast transport of channels?

Hydrated K· ion proceeds into the channel.
Cell exterior

The ion then gives up its coordinated water molecules and binds to a site within the selectivity filter region

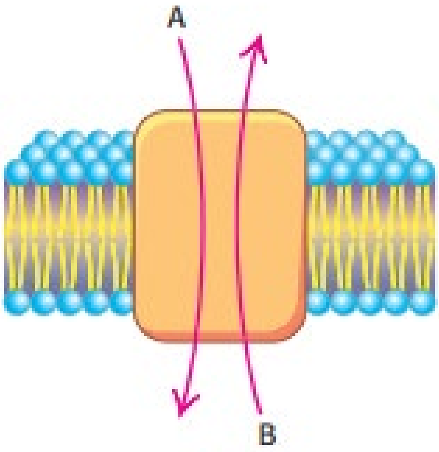
The ion can move between tthe four sites(tetramer, similar ion affinity).



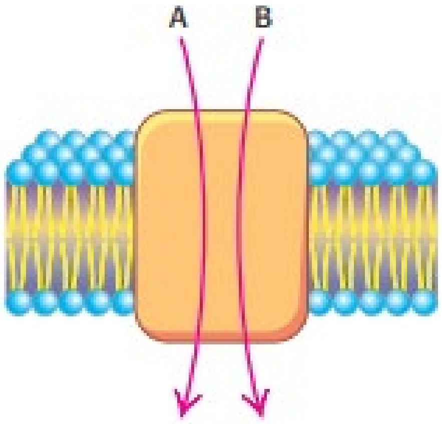
This multiple binding site mechanism solves the apparent paradox of **high ion selectivity** and **rapid flow**.

Transportadores

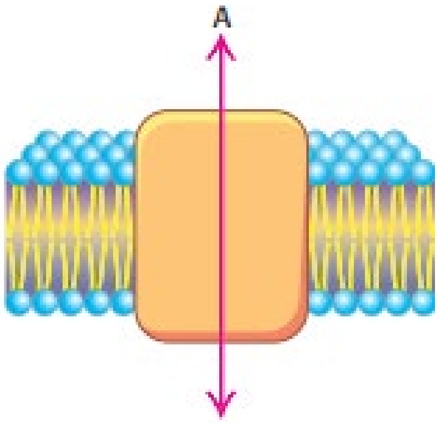
Antiporte



Simporte



Uniporte



Transportadores de Glicose

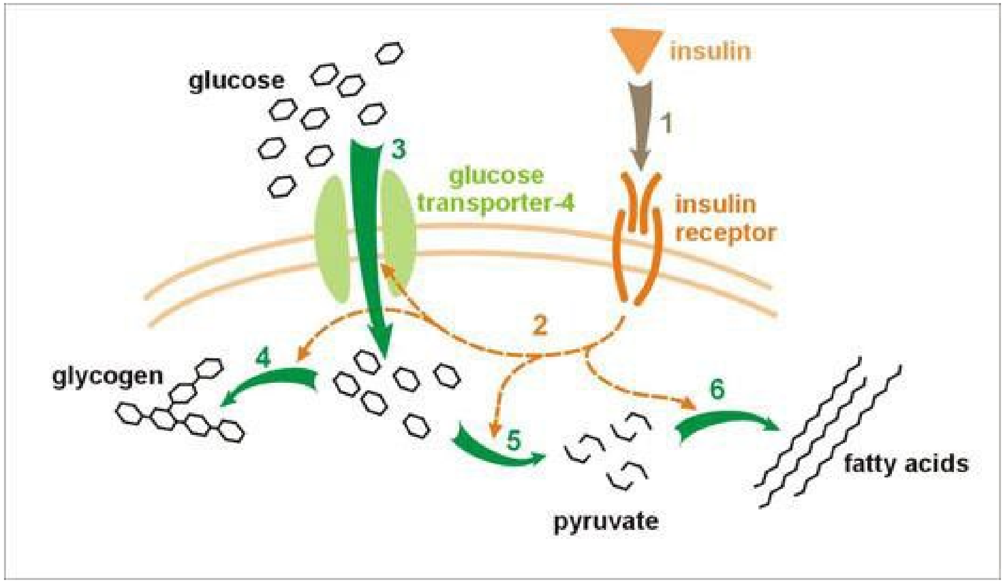
Glucose Transporters

- Tissue-specific expression pattern

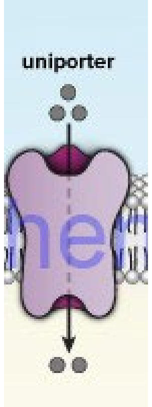
GLUT-1	RBCs and brain
GLUT-2	Liver, kidney & pancreas
GLUT-3	Neurons
GLUT-4	Adipose tissue & skeletal muscle
GLUT-5	Small intestine & testes
GLUT-7	Liver (ER-membrane)

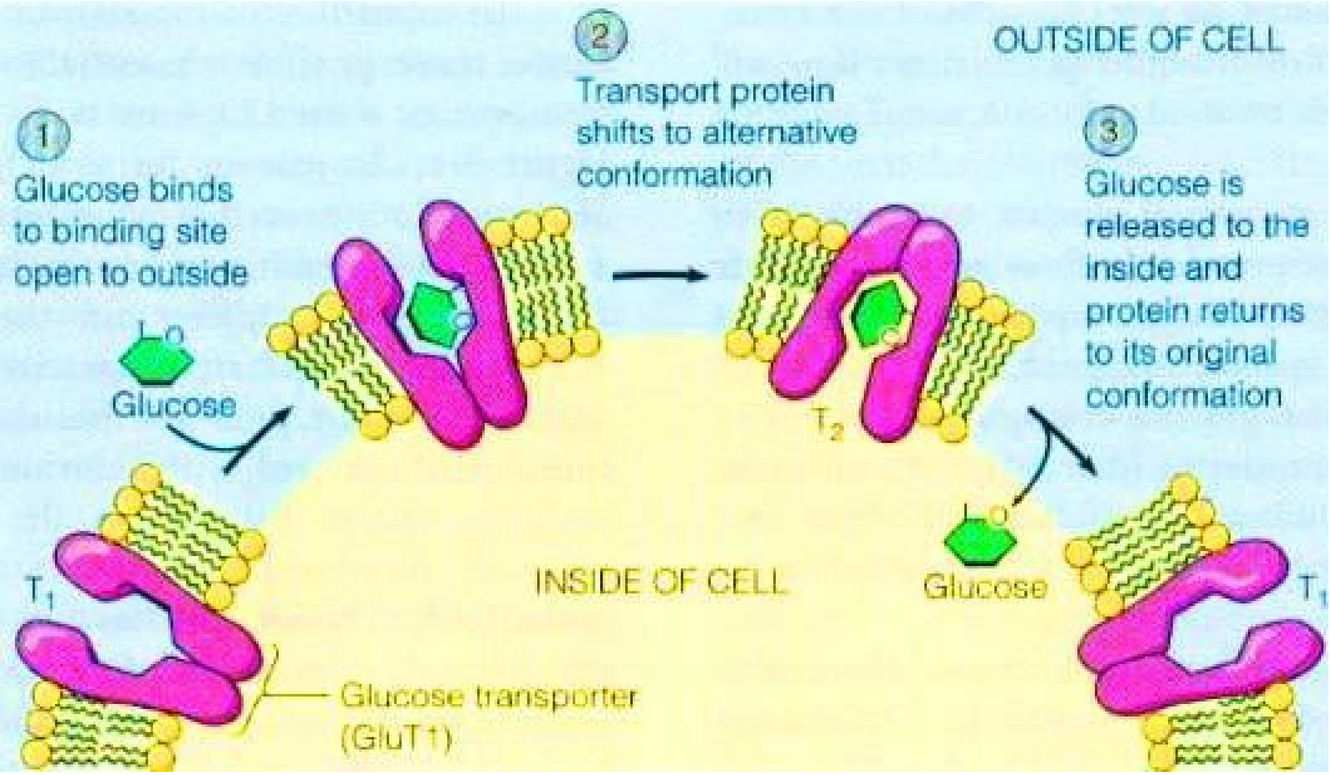
- Functions:

GLUT-1, 3 & 4	Glucose uptake from blood
GLUT-2	Blood & cells (either direction)
GLUT-5	Fructose transport


insulin
glucose
1
3
glucose transporter-4
insulin receptor
2
4
glycogen
6
5
fatty acids
pyruvate

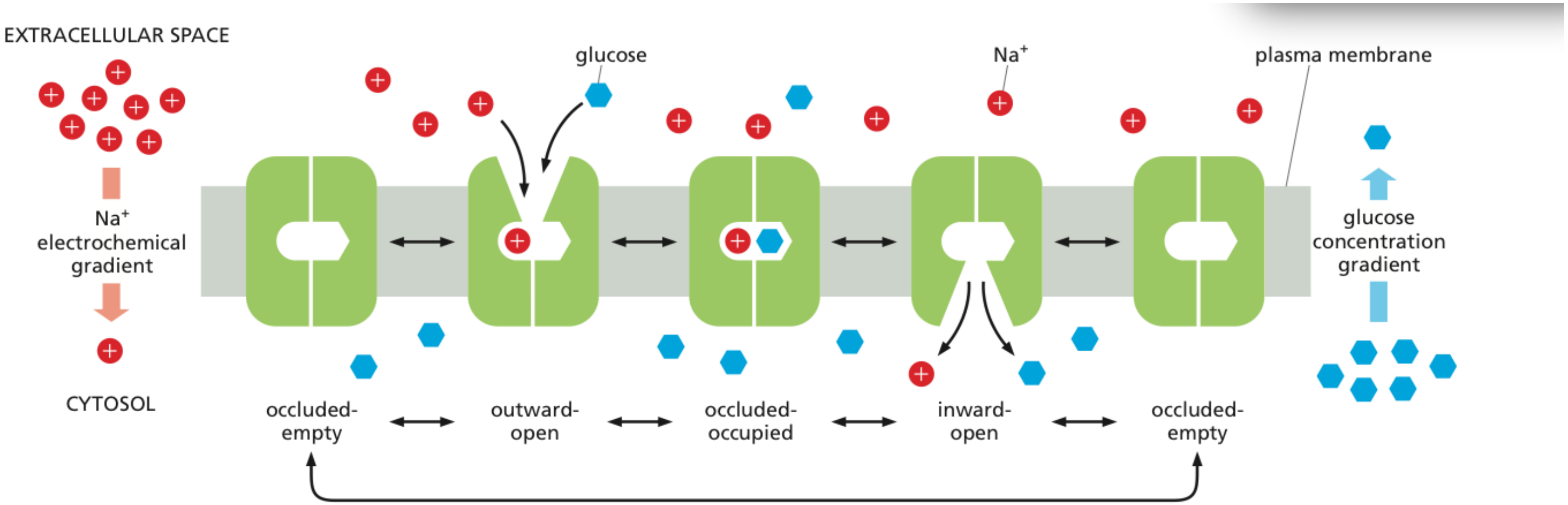
Transporte (Uniporter)




OUTSIDE OF CELL
①
Glucose binds to binding site open to outside
Glucose
②
Transport protein shifts to alternative conformation
③
Glucose is released to the inside and protein returns to its original conformation
T_1
T_2
T_1
INSIDE OF CELL
Glucose
Glucose transporter (GluT1)

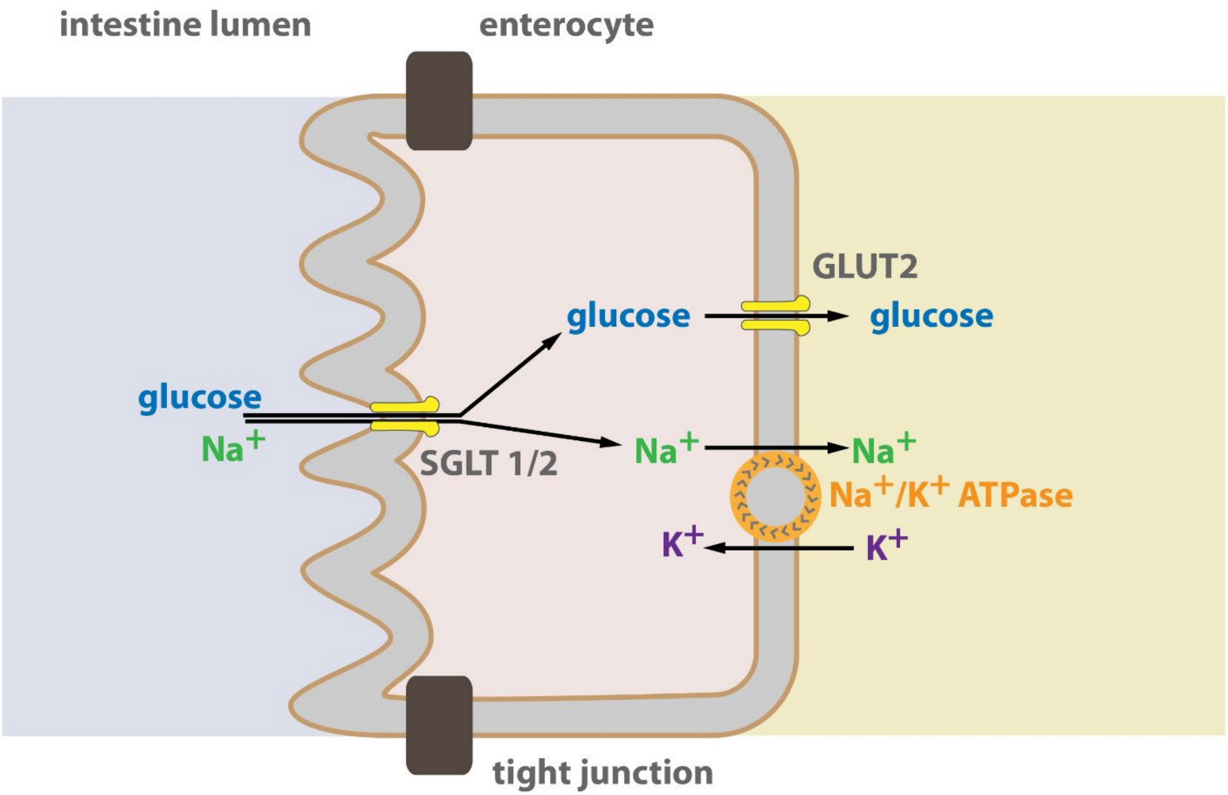
Transportadores

Sodium-dependent glucose co-transporters (symporter)


EXTRACELLULAR SPACE
glucose
Na⁺
plasma membrane
Na⁺ electrochemical gradient
glucose concentration gradient
CYTOSOL
occluded-empty
outward-open
occluded-occupied
inward-open
occluded-empty

Intestinal mucosa (enterocytes) of the small intestine and the proximal tubule of the nephron. They contribute to renal glucose reabsorption.

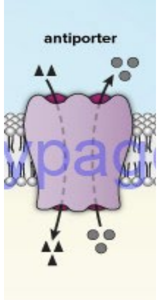
Sodium-dependent glucose co-transporters (symporter)

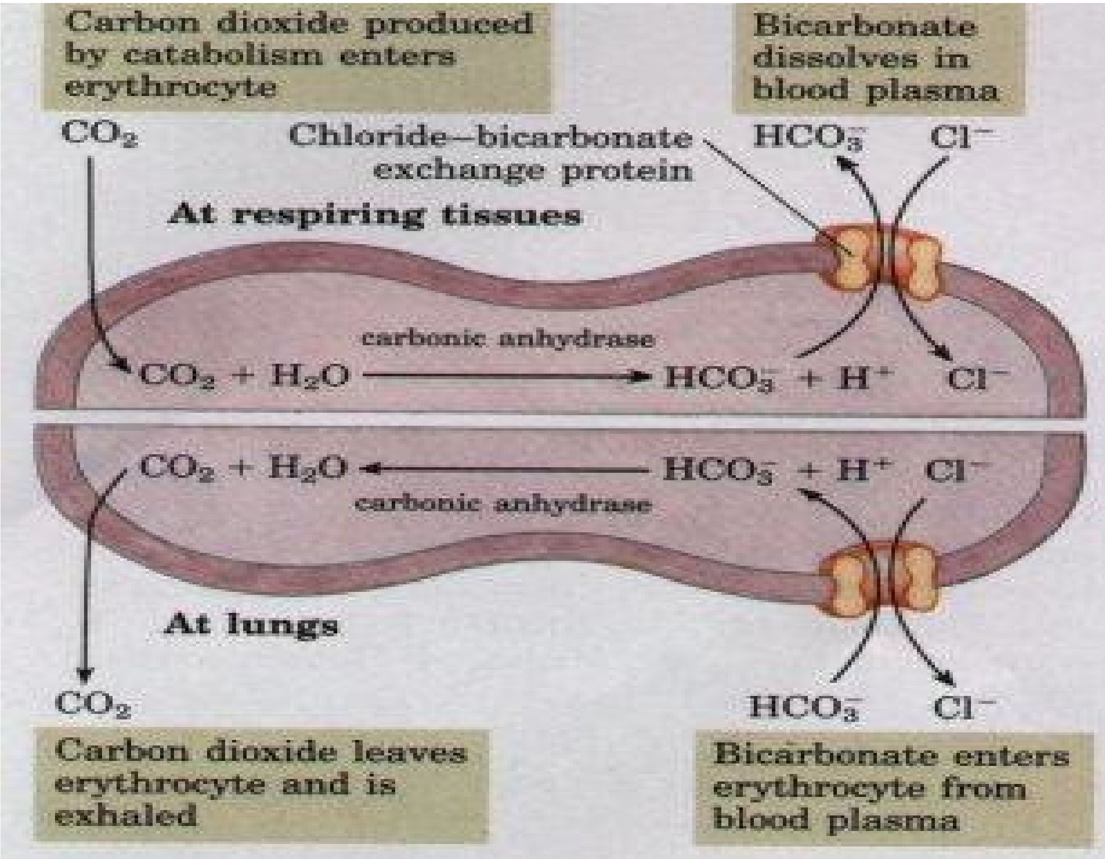

intestine lumen
enterocyte
GLUT2
glucose
glucose
glucose
Na+
SGLT 1/2
Na+
Na+
Na+/K+ ATPase
K+
K+
tight junction

Trocador de cloreto-bicarbonato (trocador aniônico)

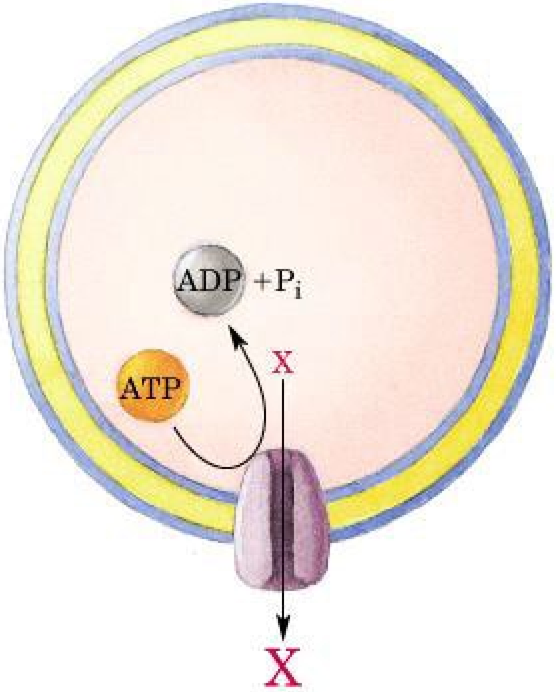
Co-transportador antiporte

O bicarbonato é mais solúvel no plasma do que o CO_2

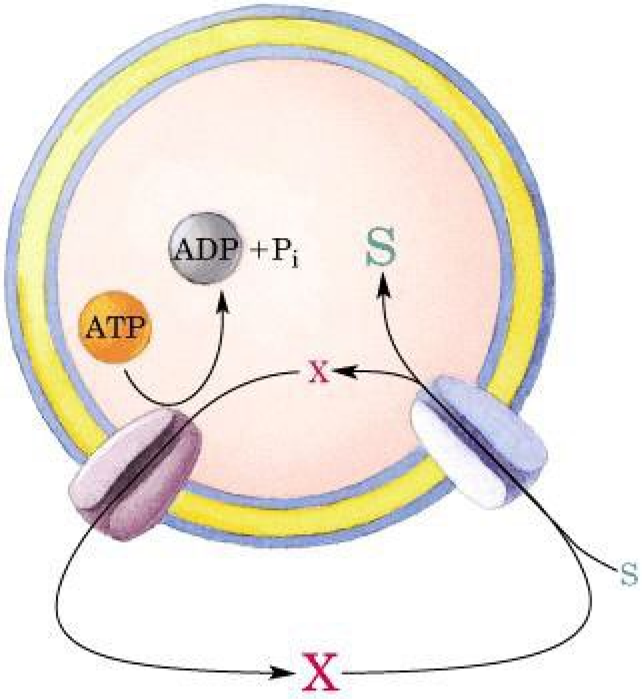

antiporter


Carbon dioxide produced by catabolism enters erythrocyte
Bicarbonate dissolves in blood plasma
CO_2
Chloride–bicarbonate exchange protein
HCO_3^-
Cl^-
At respiring tissues
carbonic anhydrase
$CO_2 + H_2O \longrightarrow HCO_3^- + H^+$
Cl^-
$CO_2 + H_2O \longleftarrow HCO_3^- + H^+$
Cl^-
carbonic anhydrase
At lungs
CO_2
HCO_3^-
Cl^-
Carbon dioxide leaves erythrocyte and is exhaled
Bicarbonate enters erythrocyte from blood plasma

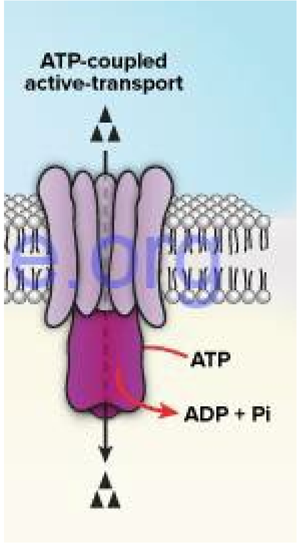
Transporte ativo resulta no acúmulo do soluto acima do ponto de equilíbrio termodinamicamente não é favorável e deve ser acoplado a um processo exergônico


ADP
+Pi
ATP
X
X

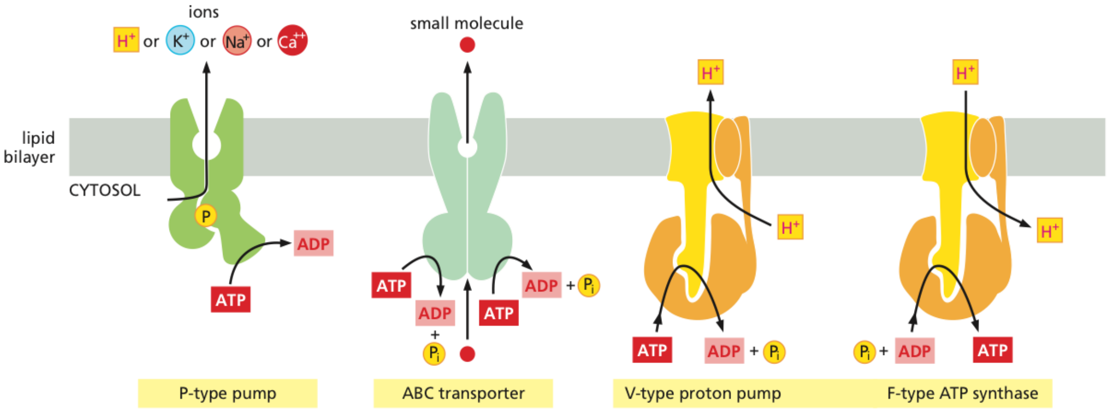
Primary active transport
(a)


ADP
+Pi
S
ATP
X
S
X

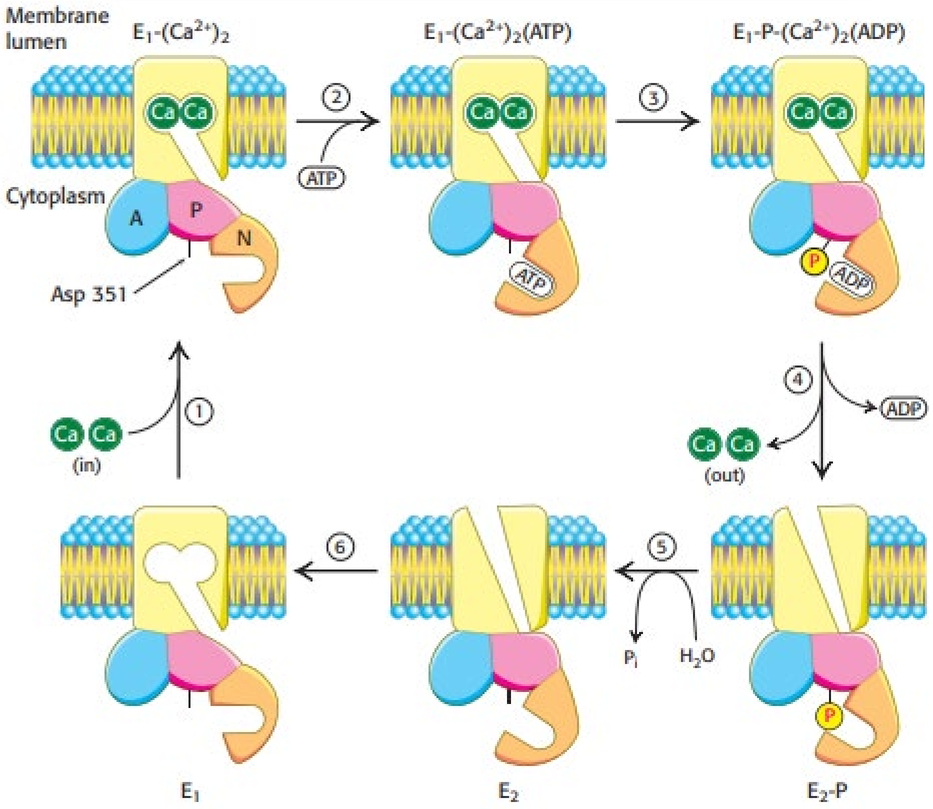
Secondary active transport
(b)

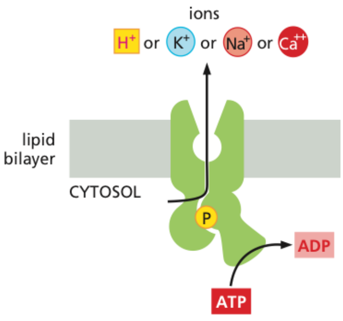

ATP-coupled
active-transport
ATP
ADP + Pi

Transportadores (ATP)


ions
H+ or K+ or Na+ or Ca++
small molecule
lipid bilayer
CYTOSOL
P
ADP
ATP
ATP
ADP
+
Pi
ATP
ADP + Pi
H+
H+
ATP
ADP + Pi
H+
H+
Pi + ADP
ATP
P-type pump
ABC transporter
V-type proton pump
F-type ATP synthase

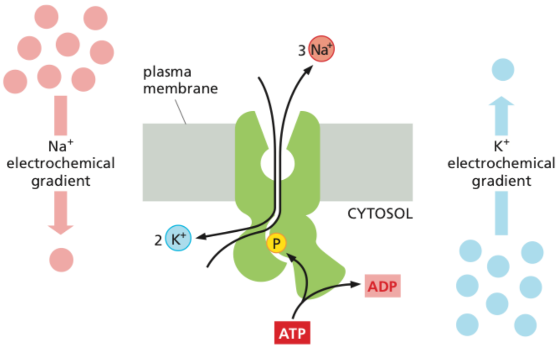
Transportador "bomba" tipo P

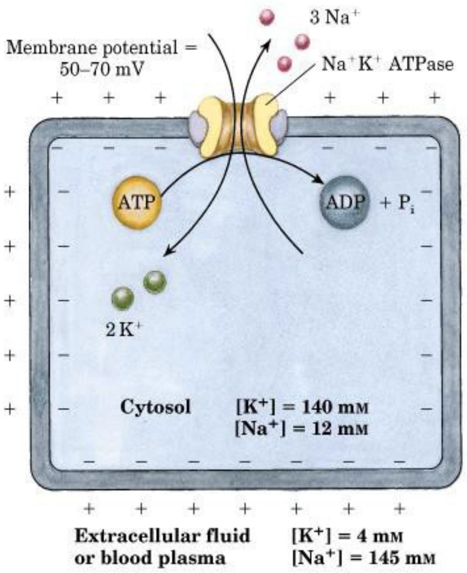

Membrane lumen
E₁-(Ca²⁺)₂
Cytoplasm
Ca Ca
A
P
N
Asp 351
②
ATP
E₁-(Ca²⁺)₂(ATP)
③
E₁-P-(Ca²⁺)₂(ADP)
P
ADP
④
ADP
Ca Ca
(out)
⑤
Pᵢ
H₂O
E₂-P
⑥
E₂
E₁
①
Ca Ca
(in)

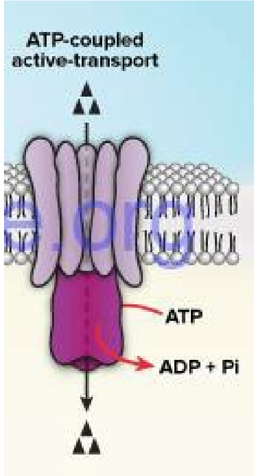

ions
H⁺ or K⁺ or Na⁺ or Ca⁺⁺
lipid bilayer
CYTOSOL
P
ADP
ATP

P-type pump

Na$^+$/K$^+$-ATPase

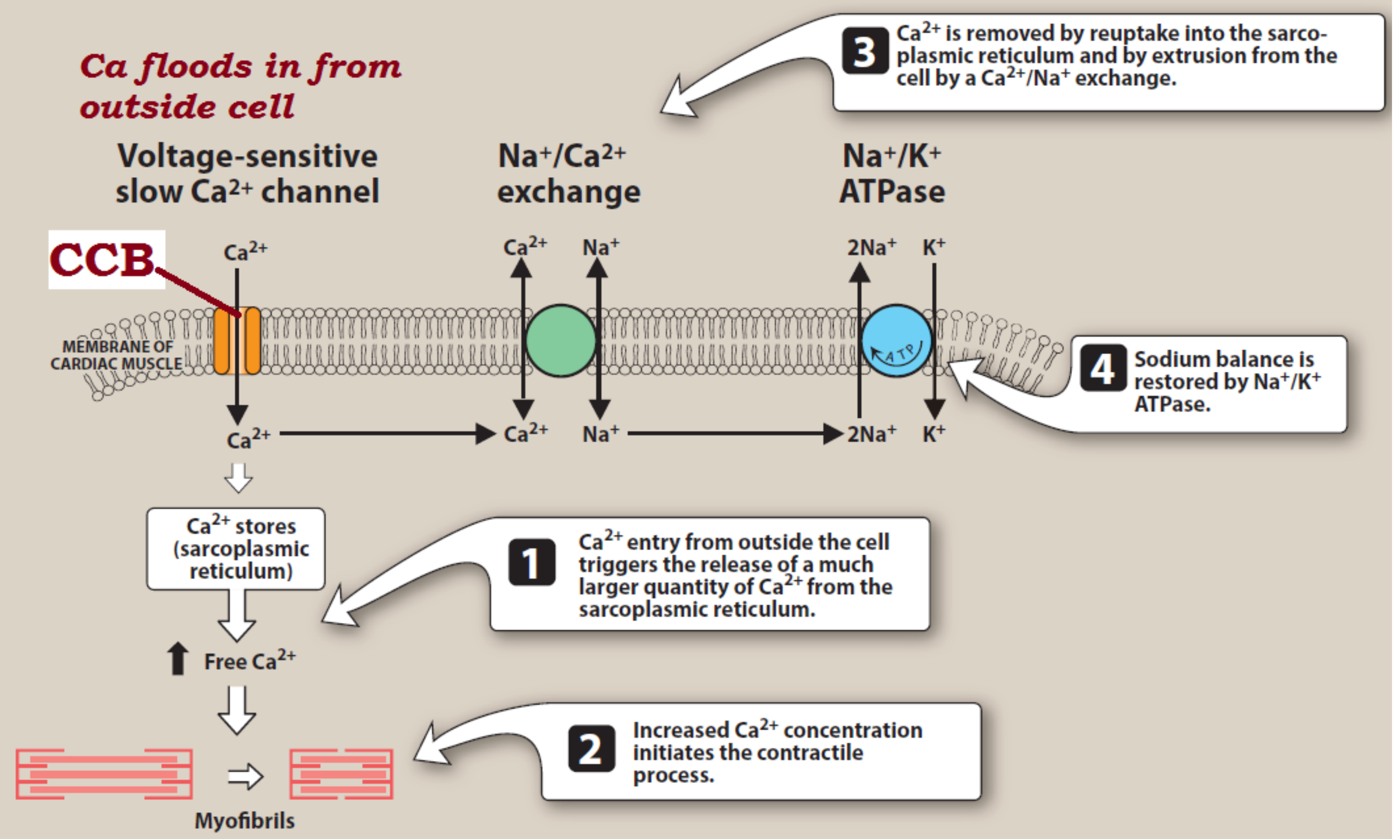

Na⁺ electrochemical gradient
plasma membrane
3 Na⁺
2 K⁺
P
CYTOSOL
ADP
ATP
K⁺ electrochemical gradient


3 Na⁺
Membrane potential = 50–70 mV
Na⁺K⁺ ATPase
ATP
ADP + Pᵢ
2 K⁺
Cytosol
[K⁺] = 140 mM
[Na⁺] = 12 mM
Extracellular fluid or blood plasma
[K⁺] = 4 mM
[Na⁺] = 145 mM


ATP-coupled active-transport
ATP
ADP + Pi

- Na$^+$/K$^+$-ATPase
  exporta 3 íons de Na$^+$ e importa 2 K$^+$ por ciclo
- O transporte ativo é acoplado com a hidrolise de 1 ATP

Digitalis
Digitalina (insuficiência cardíaca)

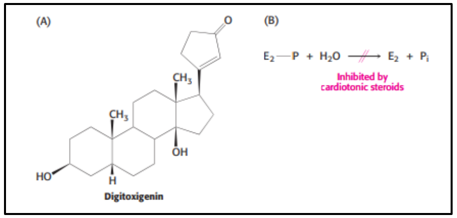

Ca floods in from outside cell
Voltage-sensitive slow Ca^{2+} channel
Na^+/Ca^{2+} exchange
Na^+/K^+ ATPase
CCB
Ca^{2+}
Ca^{2+}
Na^+
$2Na^+$
K^+
MEMBRANE OF CARDIAC MUSCLE
ATP
Ca^{2+}
Ca^{2+}
Na^+
$2Na^+$
K^+
Ca^{2+} stores (sarcoplasmic reticulum)
Free Ca^{2+}
Myofibrils

3 Ca^{2+} is removed by reuptake into the sarcoplasmic reticulum and by extrusion from the cell by a Ca^{2+}/Na^+ exchange.

4 Sodium balance is restored by Na^+/K^+ ATPase.

1 Ca^{2+} entry from outside the cell triggers the release of a much larger quantity of Ca^{2+} from the sarcoplasmic reticulum.

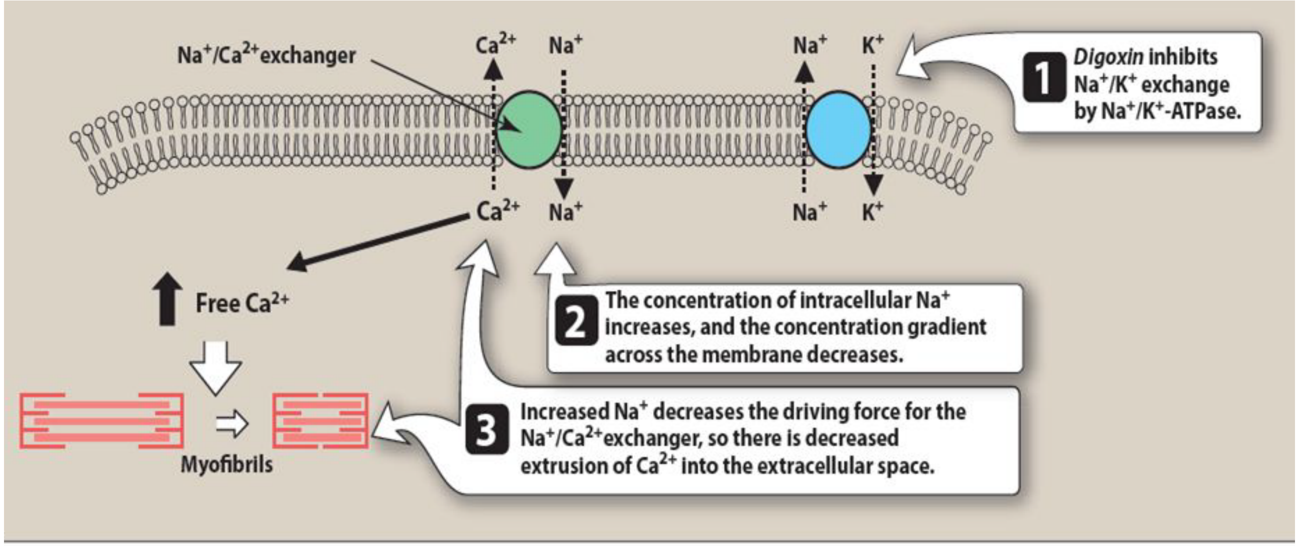
2 Increased Ca^{2+} concentration initiates the contractile process.



Digitoxigenin

$E_2{-}P + H_2O \not\longrightarrow E_2 + P_i$

Inhibited by cardiotonic steroids



1 *Digoxin* inhibits Na^+/K^+ exchange by Na^+/K^+-ATPase.

2 The concentration of intracellular Na^+ increases, and the concentration gradient across the membrane decreases.

3 Increased Na^+ decreases the driving force for the Na^+/Ca^{2+}exchanger, so there is decreased extrusion of Ca^{2+} into the extracellular space.

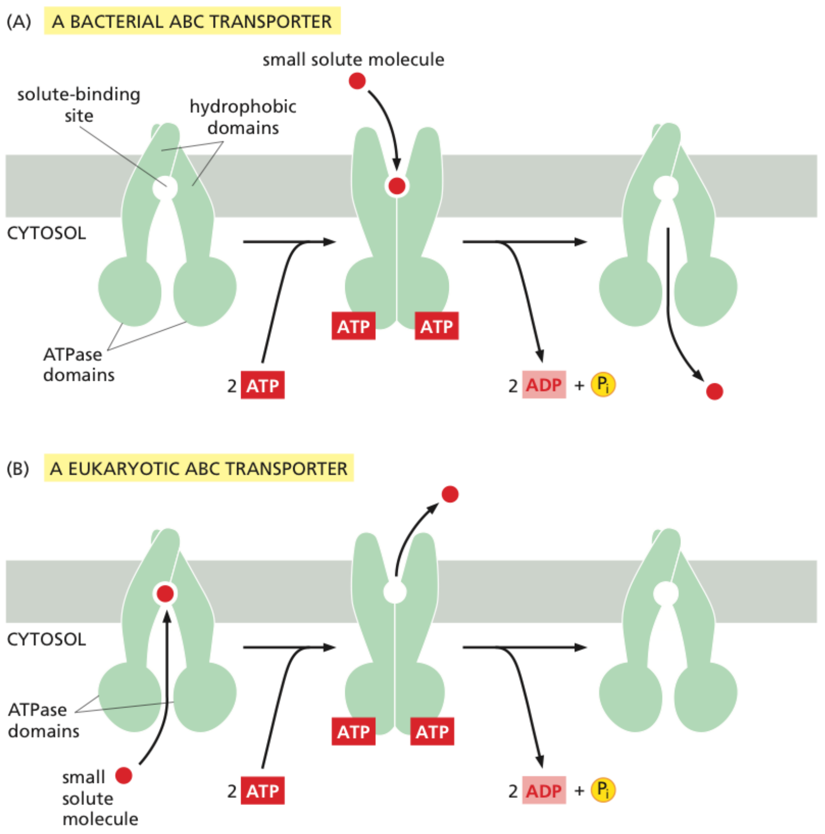
❖ Increases the force of cardiac contraction, causing the cardiac output.

❖ Improved circulation leads to reduced sympathetic activity, which then reduces peripheral resistance with reduction in heart rate.

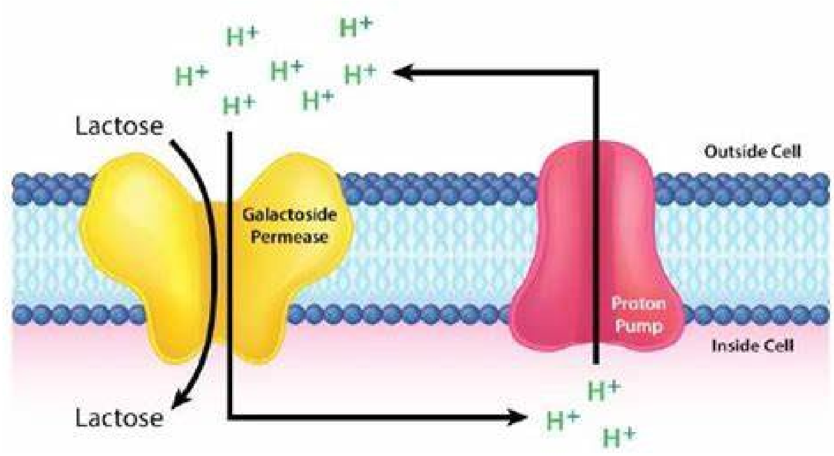
❖ Slows down conduction velocity through the AV node, which accounts for its use in atrial fibrillation.

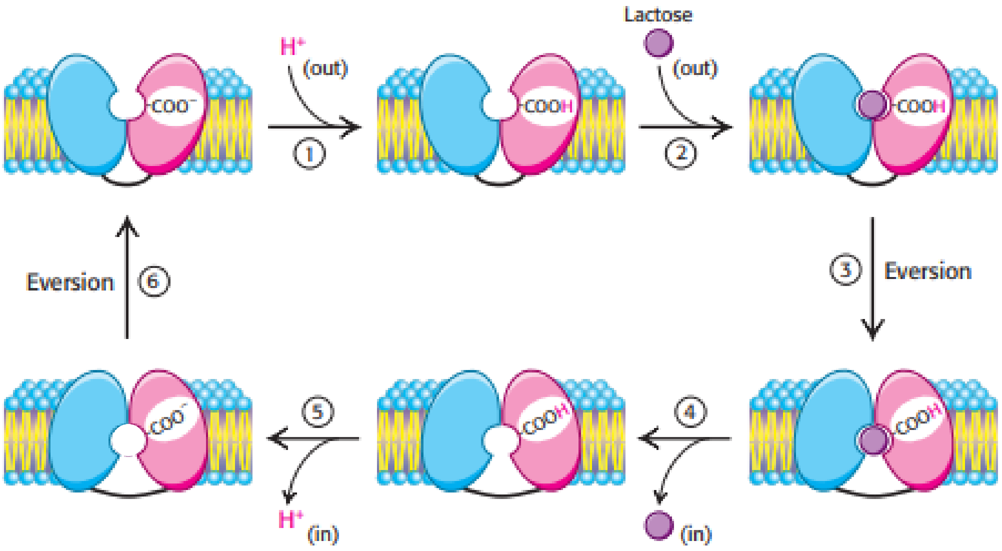
Transportadores (ABC)

(ABC –ATP binding Cassette)

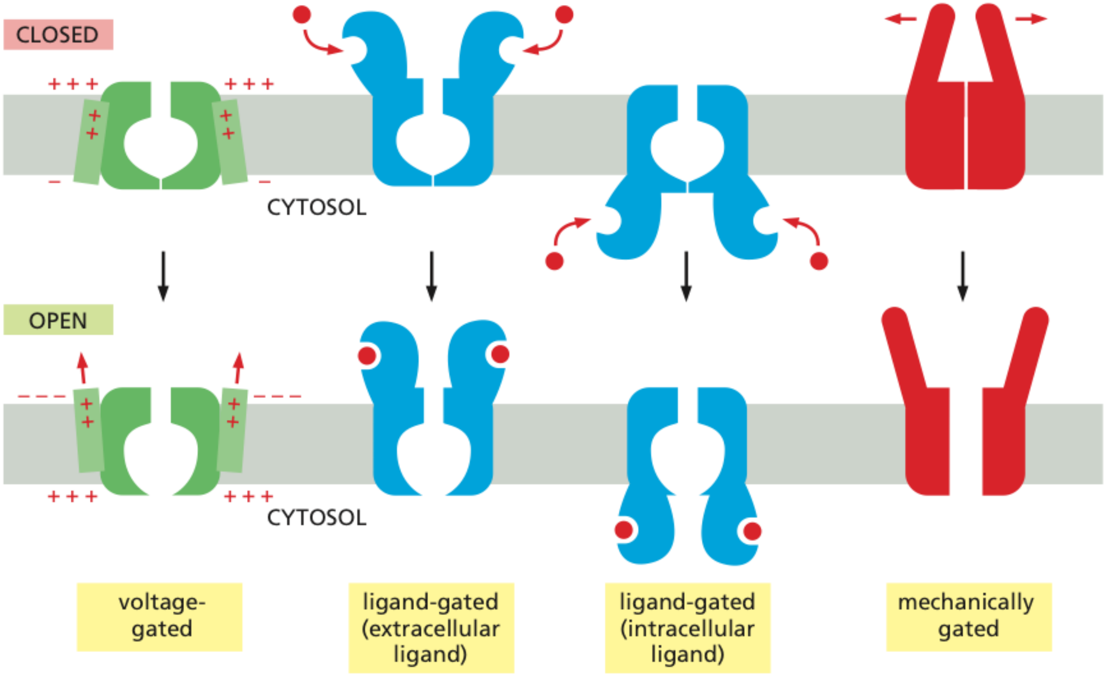

(A) A BACTERIAL ABC TRANSPORTER
small solute molecule
solute-binding site
hydrophobic domains
CYTOSOL
ATPase domains
2 ATP
ATP
ATP
2 ADP + P_i
(B) A EUKARYOTIC ABC TRANSPORTER
CYTOSOL
ATPase domains
small solute molecule
2 ATP
ATP
ATP
2 ADP + P_i

Transportador de lactose movido por um gradiente de H^+

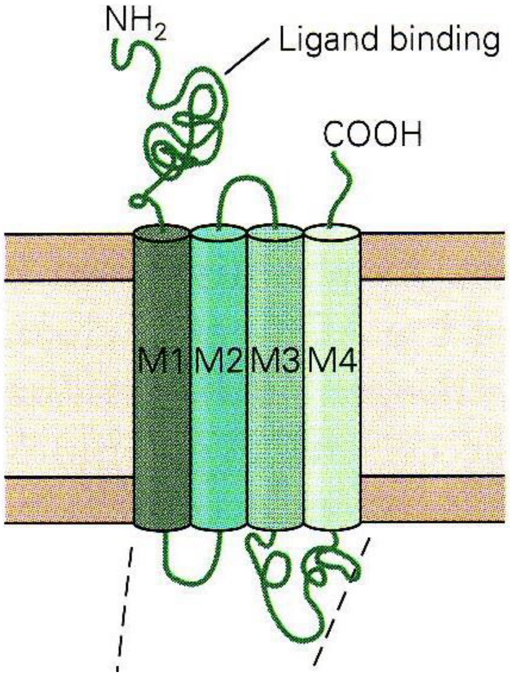

H+
H+
H+
H+
H+
H+
H+
Lactose
Galactoside Permease
Outside Cell
Proton Pump
Inside Cell
Lactose
H+
H+
H+


H+
(out)
①
COO−
COOH
Lactose
(out)
②
COOH
③
Eversion
④
COOH
(in)
⑤
COOH
COO−
H+
(in)
Eversion
⑥

Gated Channels

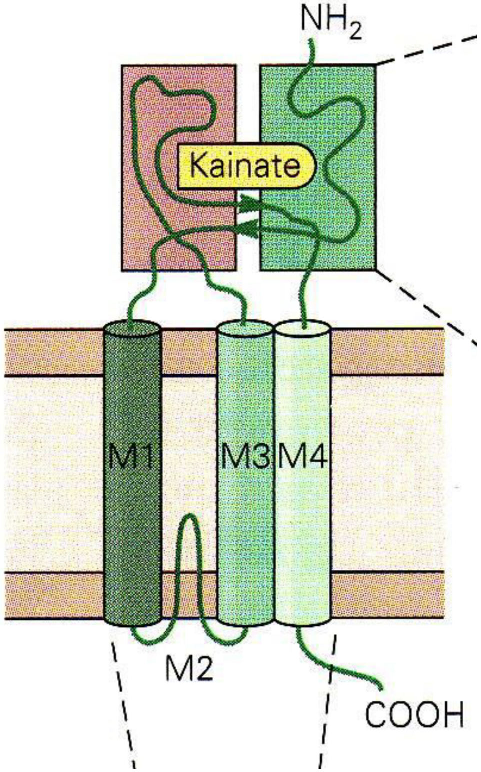

CLOSED
+ + +
+ + +
+
+
+
+
−
−
CYTOSOL
OPEN
− − −
− − −
+
+
+
+
+ + +
+ + +
CYTOSOL
voltage-gated
ligand-gated (extracellular ligand)
ligand-gated (intracellular ligand)
mechanically gated

Superfamilies of Ligand-Gated Ion Channels



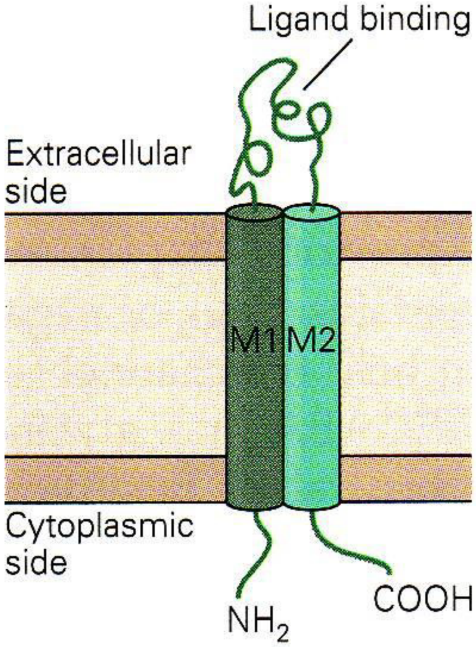
Cys-Loop Receptors

NH$_2$
Ligand binding
COOH
M1
M2
M3
M4



Glutamate receptors

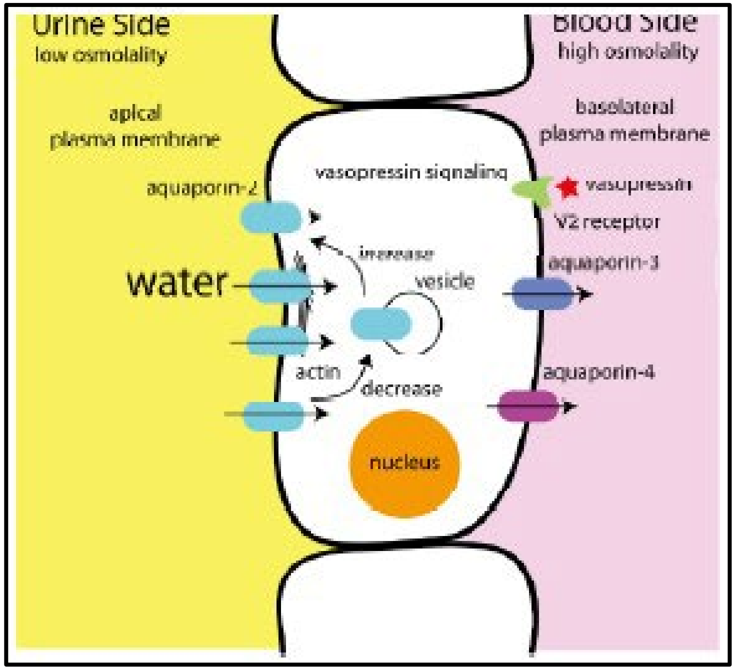
NH$_2$
Kainate
M1
M3
M4
M2
COOH

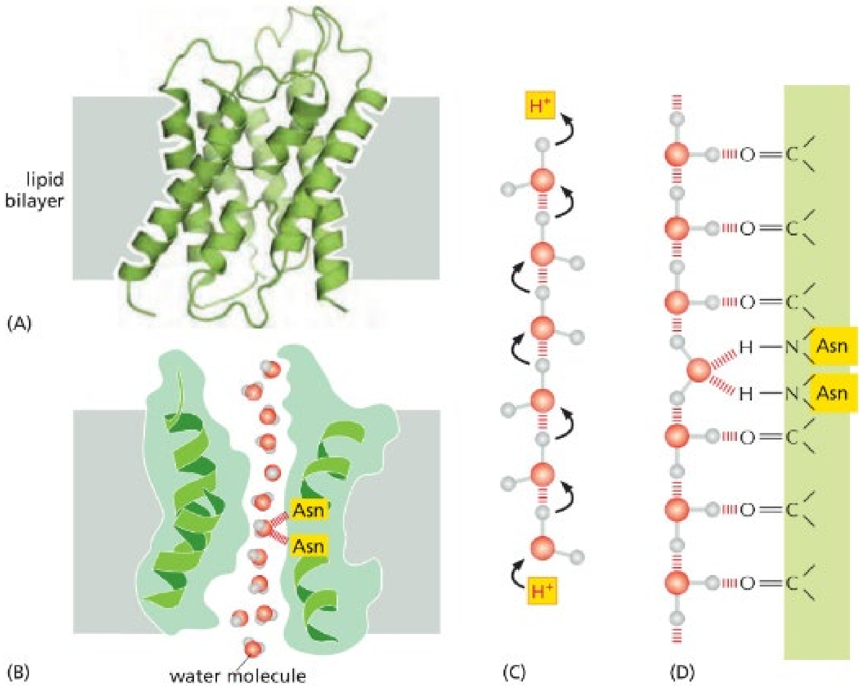


ATP receptors

Ligand binding
Extracellular side
M1
M2
Cytoplasmic side
NH$_2$
COOH

Aquaporina Transportador de água


Urine Side
low osmolality
aplcal
plasma membrane
aquaporin-2
water
actin
vasopressin signaling
increase
vesicle
decrease
nucleus
Blood Side
high osmolality
basolateral
plasma membrane
vasopressin
V2 receptor
aquaporin-3
aquaporin-4


lipid
bilayer
(A)
(B)
water molecule
Asn
Asn
(C)
H+
H+
(D)
O=C
H—N
Asn
H—N
Asn

- Mutations in the aquaporin-2 gene cause hereditary nephrogenic diabetes insipidus in humans.

- Mice homozygous for inactivating mutations in the aquaporin-0 gene develop congenital cataracts.

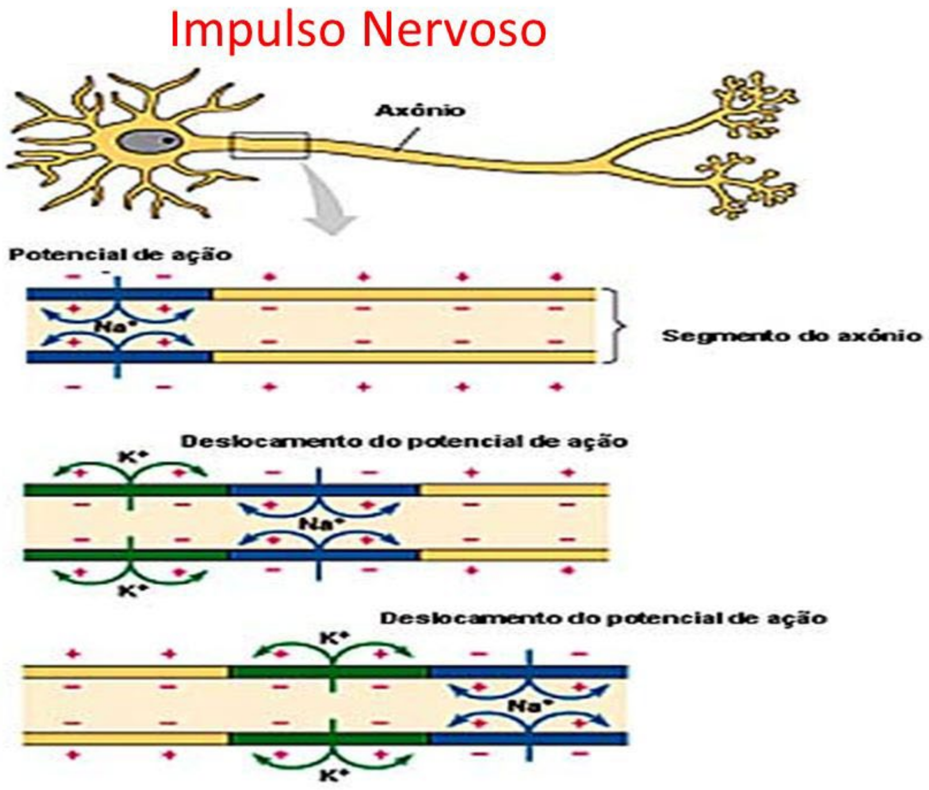
Potencial de ação

Um potencial de ação é uma inversão do potencial de membrana que percorre a membrana de uma célula. Potenciais de ação transportam rapidamente informações entre e dentro dos tecidos.

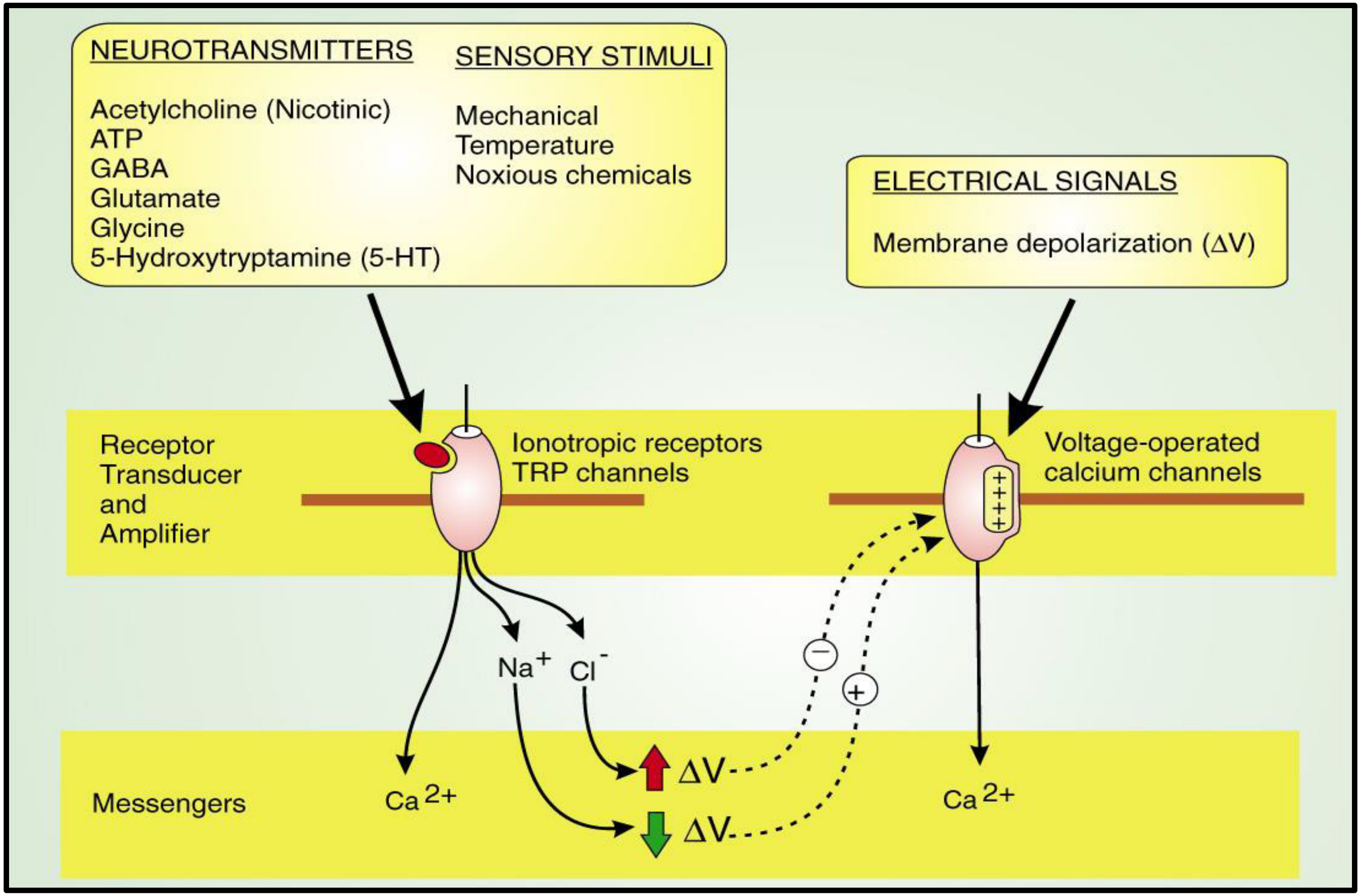
Utilizados mais intensamente pelo sistema nervoso, para comunicação entre neurônios e para transmitir informação dos neurônios para outro tecido do organismo, como os músculos ou as glândulas.

Despolarização neuronal

https://m.youtube.com/watch?v=fHRC8SlLcH0


Impulso Nervoso
Axônio
Potencial de ação
Na+
Segmento do axônio
Deslocamento do potencial de ação
K+
Na+
K+
Deslocamento do potencial de ação
K+
Na+
K+

Condução nervosa

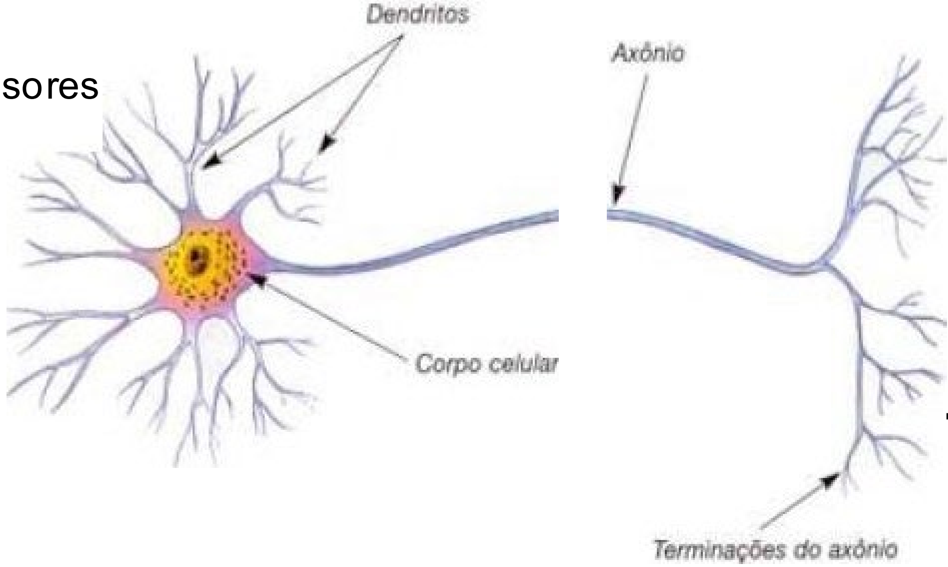

NEUROTRANSMITTERS
Acetylcholine (Nicotinic)
ATP
GABA
Glutamate
Glycine
5-Hydroxytryptamine (5-HT)
SENSORY STIMULI
Mechanical
Temperature
Noxious chemicals
ELECTRICAL SIGNALS
Membrane depolarization (ΔV)
Receptor
Transducer
and
Amplifier
Ionotropic receptors
TRP channels
Voltage-operated
calcium channels
+
+
+
+
Na+
Cl-
−
+
Messengers
Ca 2+
ΔV
ΔV
Ca 2+

Comunicação por meio de neurotransmissores

Constituição do Neurônio:

- corpo celular ou pericario
- prolongamento celulares: dendrites e ax6nio

Recepção de neurotransmissores

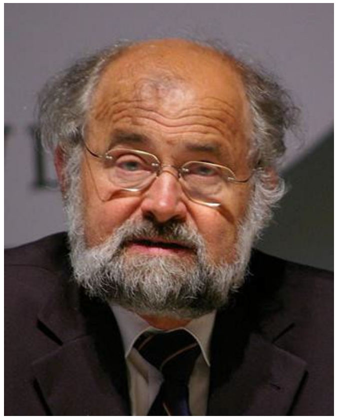

Dendritos
Axônio
Corpo celular
Terminações do axônio

Liberação de neurotransmissores

Recepção

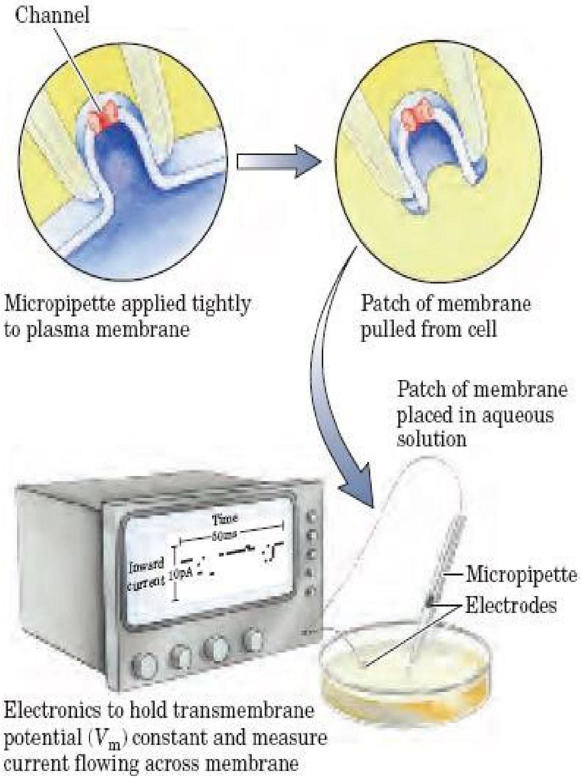
Transmissão

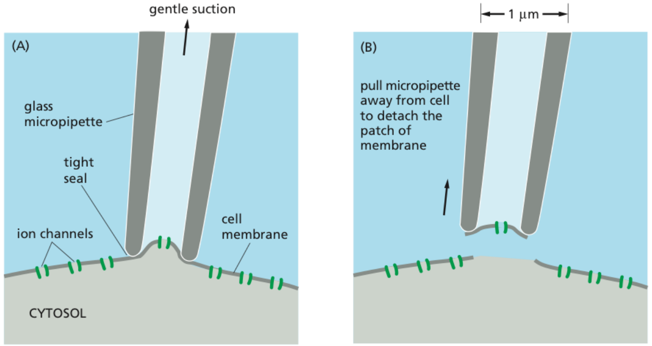
Método de medir os potenciais da membrana – *patch clamp*



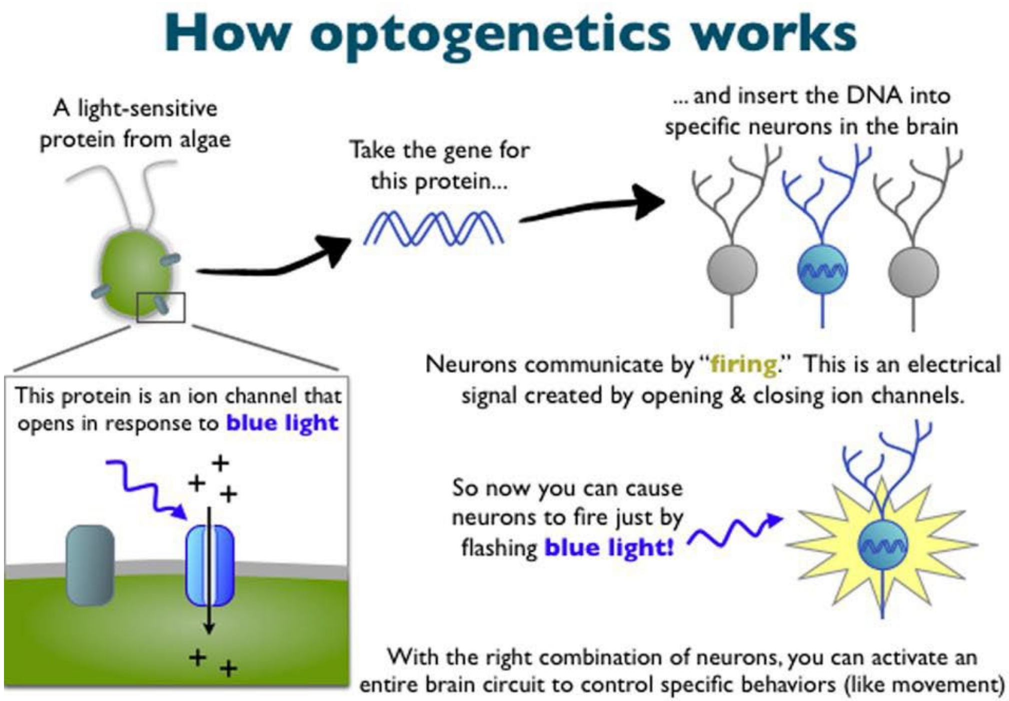
Erwin Neher

Bert Sakmann


Channel
Micropipette applied tightly to plasma membrane
Patch of membrane pulled from cell
Patch of membrane placed in aqueous solution
Time
50ms
Inward current
10pA
Micropipette
Electrodes
Electronics to hold transmembrane potential (V_m) constant and measure current flowing across membrane


gentle suction
(A)
glass micropipette
tight seal
ion channels
cell membrane
CYTOSOL
1 µm
(B)
pull micropipette away from cell to detach the patch of membrane

for their discoveries concerning the function of single ion channels in cells"



How optogenetics works

A light-sensitive protein from algae

Take the gene for this protein...

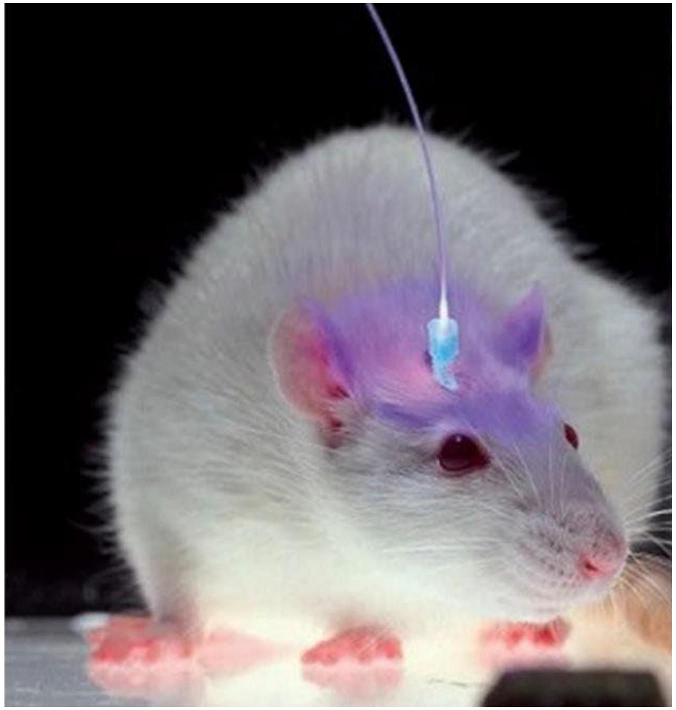
... and insert the DNA into specific neurons in the brain

This protein is an ion channel that opens in response to **blue light**

Neurons communicate by "**firing**." This is an electrical signal created by opening & closing ion channels.

So now you can cause neurons to fire just by flashing **blue light!**

With the right combination of neurons, you can activate an entire brain circuit to control specific behaviors (like movement)



https://www.youtube.com/watch?v=7Mmsah0v9Qc