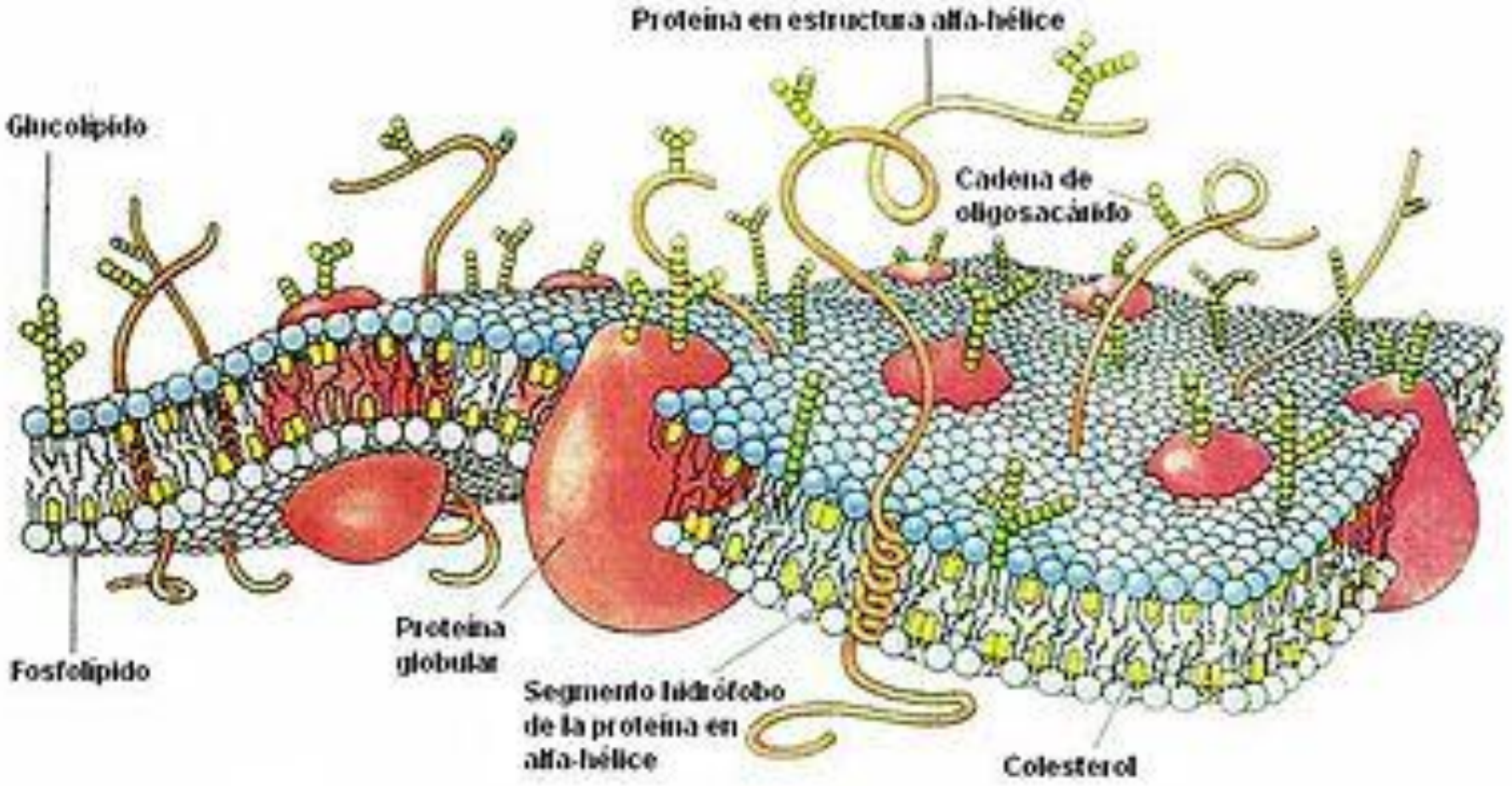
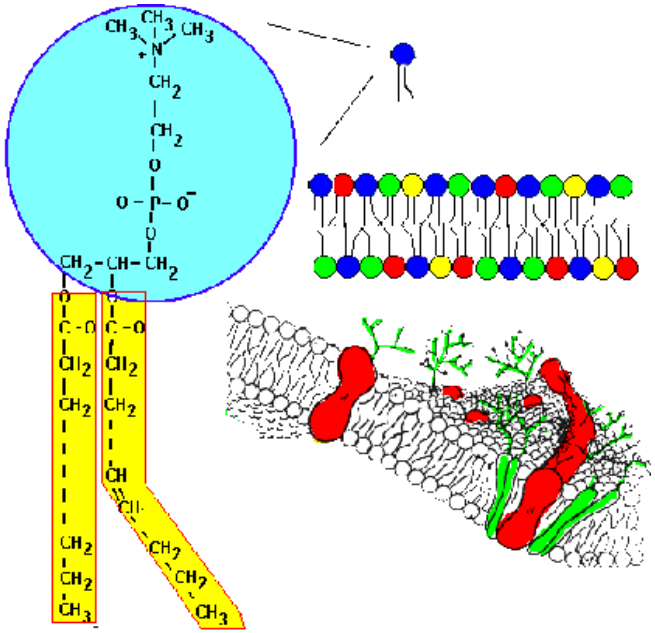
Membranas/ Transporte e Sinalização Celular



AULA 2: MEMBRANAS BIOLÓGICAS E SINALIZAÇÃO ATRAVÉS DE MEMBRANAS

Características dos lipídeos

Alta solubilidade em solventes orgânicos praticamente insolúveis em água

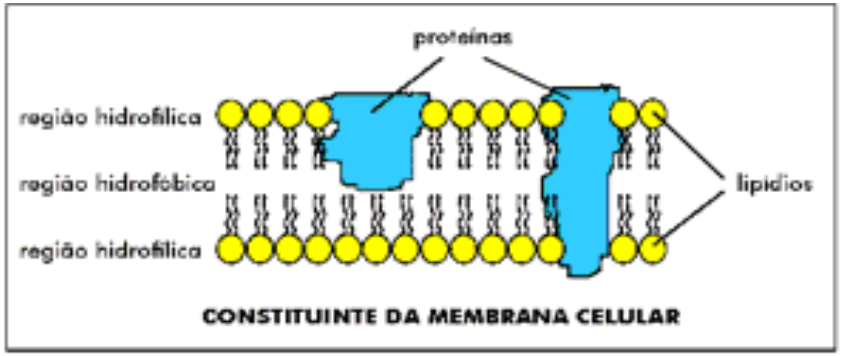


Anfipáticos (anfifílicos)

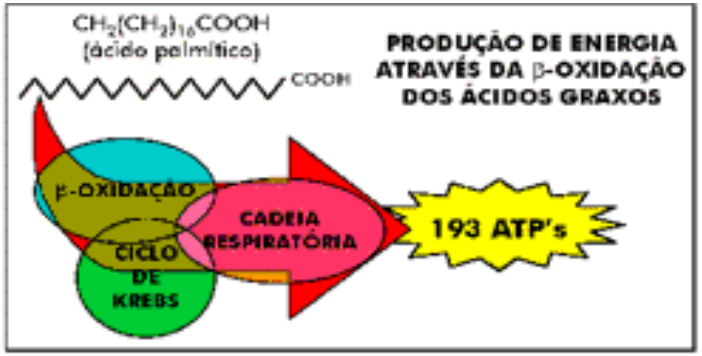
Porção polar hidrofílica e porção apolar hidrofóbica

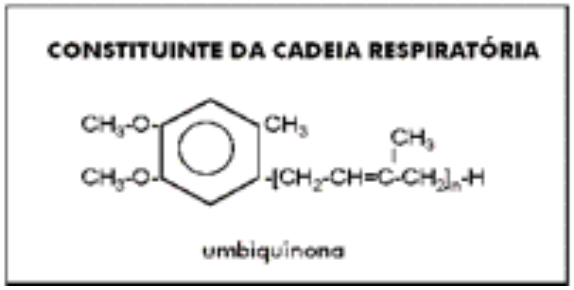
Funções biológicas

Componentes de membranas



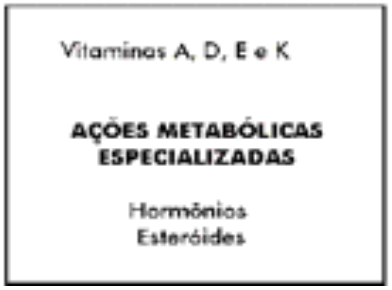
Reserva de energia





Constituintes da cadeia respiratória

Isolante térmico



Vitaminas
Hormônios

Tipos de lipídeos: para estoque e de membranas

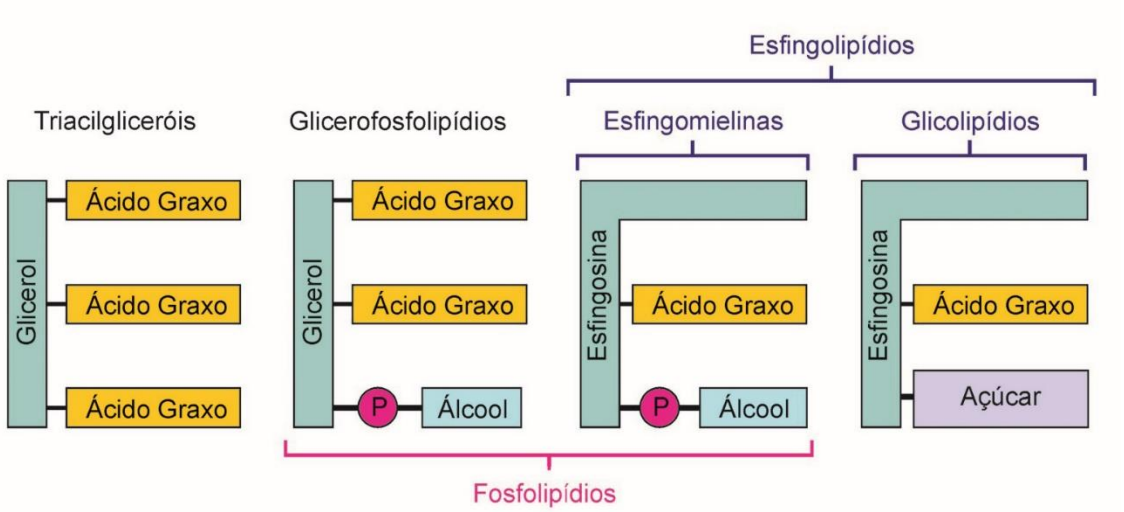
Triacilgliceróis (estoque)

Glicerofosfolípídios

Esfingolipídios

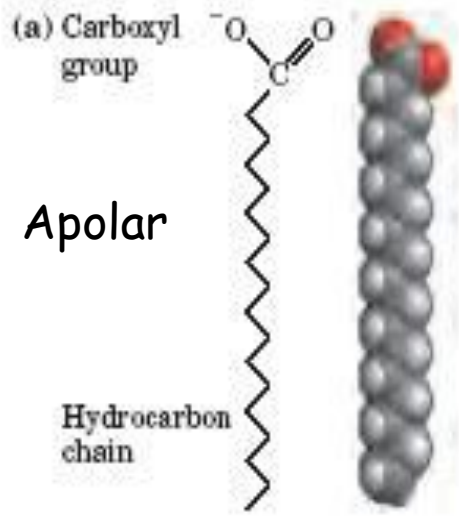
Esteróides

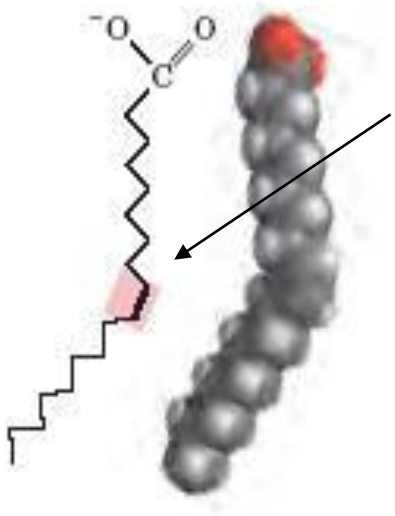
Colesterol



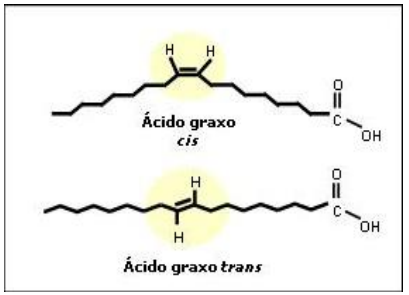
Ácidos Graxos

Polar



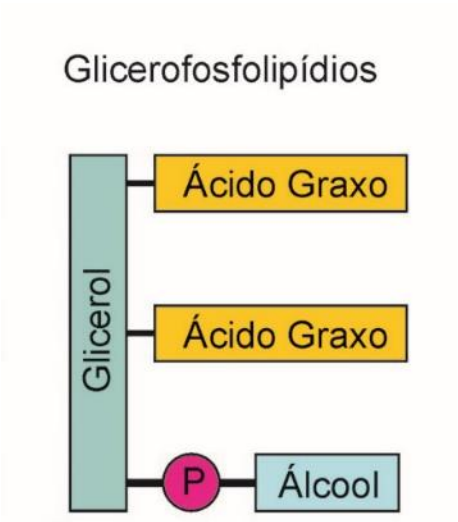


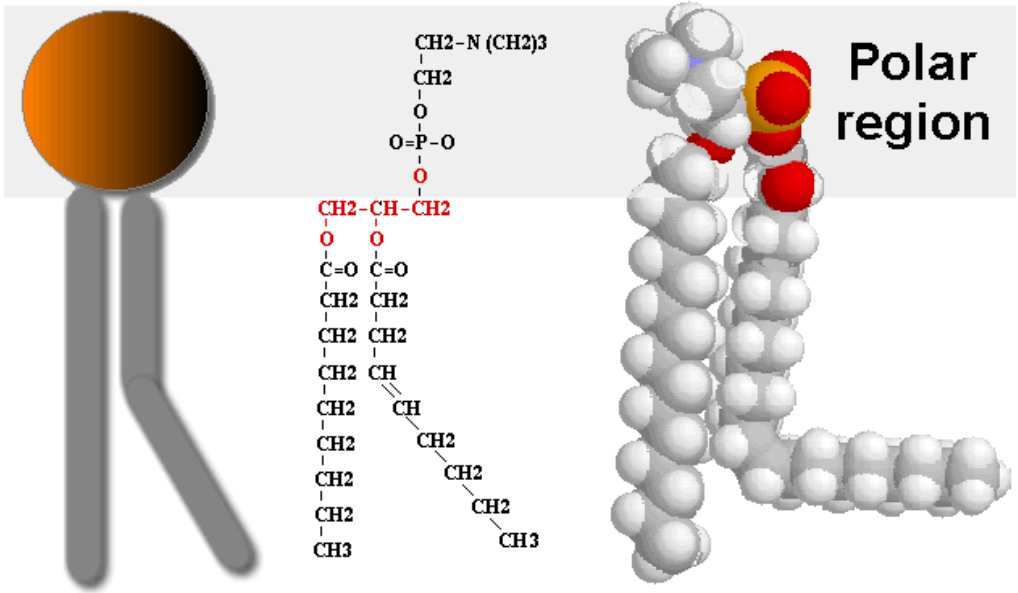
Dupla ligação em cis



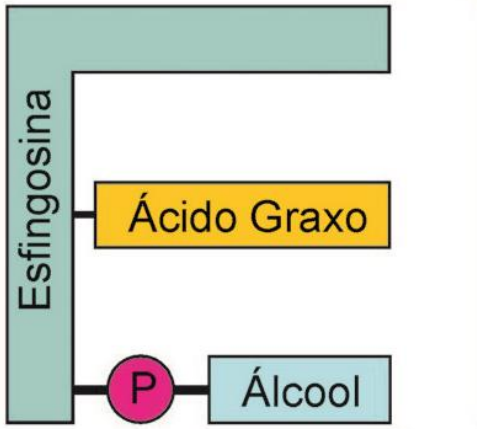
Saturado Insaturado

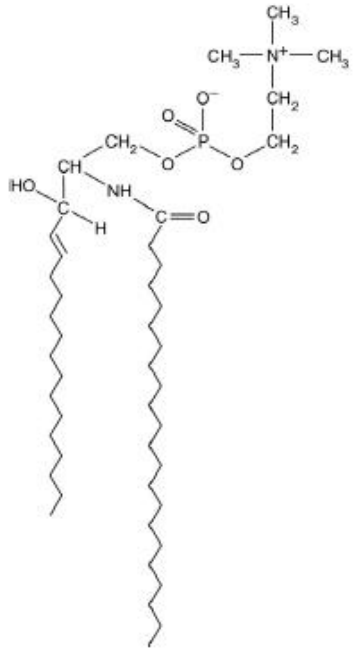
Fosfolipídeo

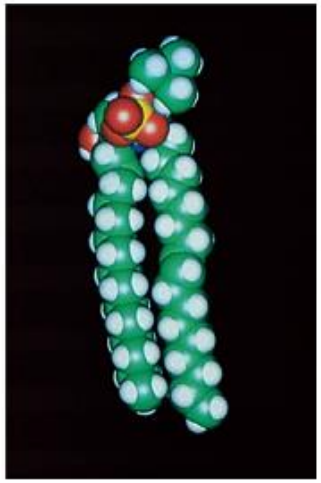




Esfingolipídeo (esfingomielina)



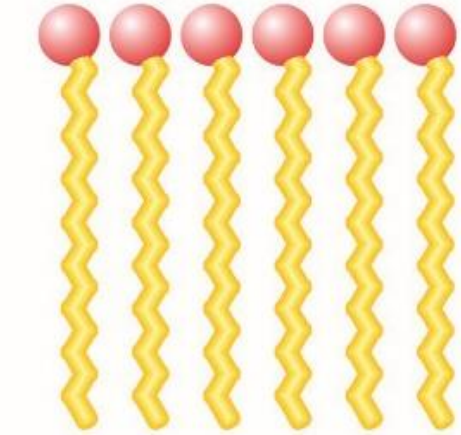




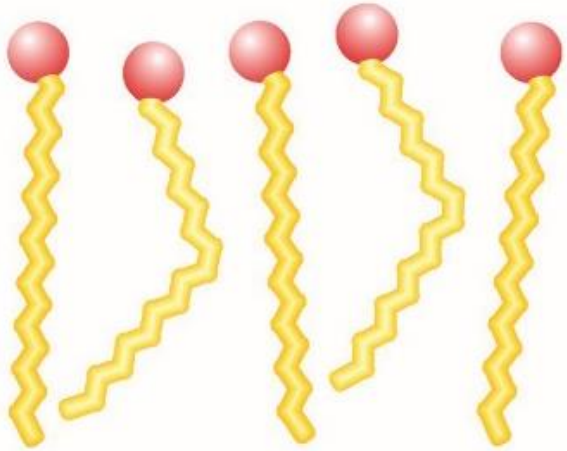
Propriedades físicas

Dependem das insaturações e do comprimento da cadeia de hidrocarboneto

Saturado



Insaturado

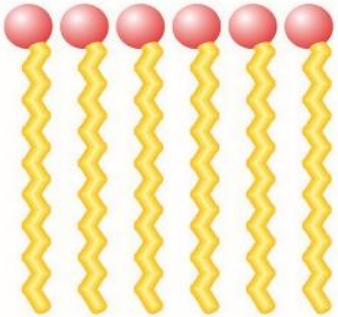


Temperatura de fusão

O **ponto de fusão** designa a temperatura nqa qual uma substância passa do estado sólido ao estado líquido.

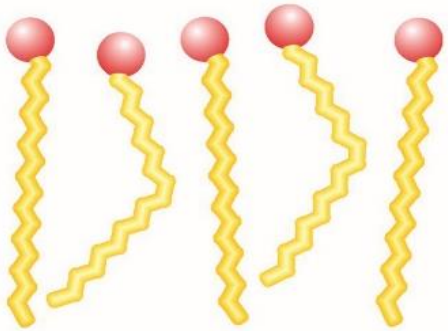
Propriedades físicas

Saturado



Cadeias flexíveis e distendidas
(interações hidrofóbicas)

Insaturado



Agregados menos compactos
mais instáveis

Temperatura de fusão: diminui com o número de insaturações e aumenta com o comprimento da cadeia.

Temperatura ambiente ácidos graxos saturados com mais de 14 carbonos são sólidos, possuíndo pelo menos uma dupla ligação são líquidos.

Grau de fluidez de membranas biológicas dependem da composição lipídica

Pontos de Fusão de Ácidos Graxos Saturados

Nome	*Nº de Carbonos*	*Ponto de Fusão (°C)*
Láurico	12	43,9
Mirístico	14	54,1
Palmítico	16	62,7
Esteárico	18	69,9
Araquídico	20	75,4

Pontos de Fusão de Ácidos Graxos Insaturados

Nome	*Nº de Carbonos*	*Nº de Ligas Duplas*	*Ponto de Fusão (°C)*
Palmitoléico	16	1	0,5
Oléico	18	1	13,4
Linoléico	18	2	-5,0
Linolênico	18	3	-10,0
Araquidônico	20	4	-49,5

(Blanco,A. Química Biológica,1991)

Esteróides (colesterol)

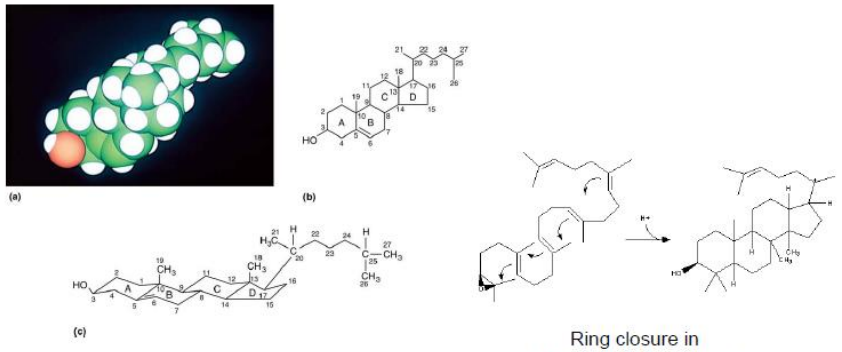
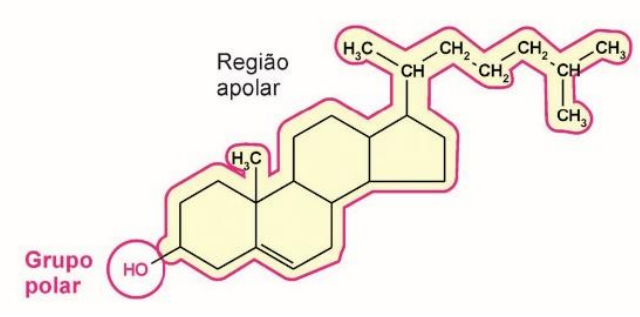
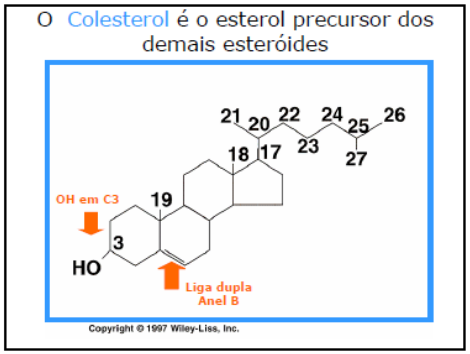


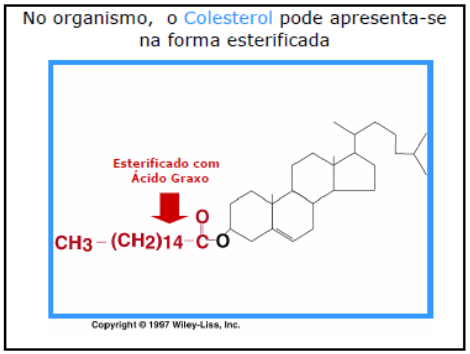
FIGURE 11.16
Structure of Cholesterol

Ring closure in
cholesterol biosynthesis

http://images.absoluteastronomy.com/images/encyclopediaimages/c/ch/cholesterol-synthesis-reaction12.png



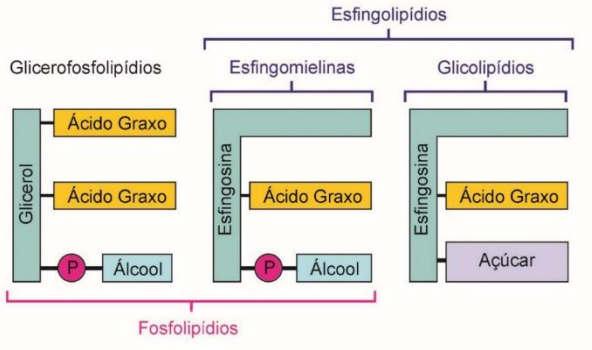




Pouco polar

Estrutura rígida influencia a fluidez das membranas

Lipídeos anfipáticos se organizam em solução2



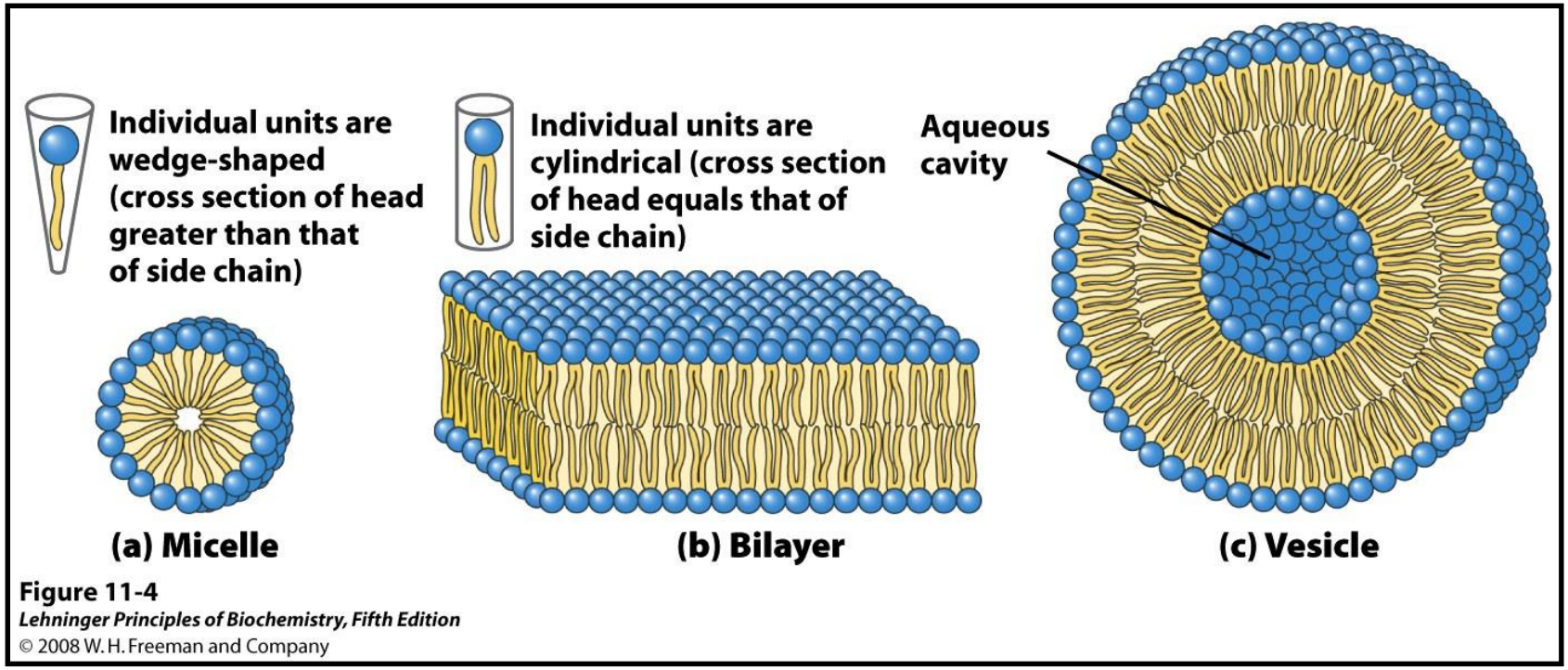


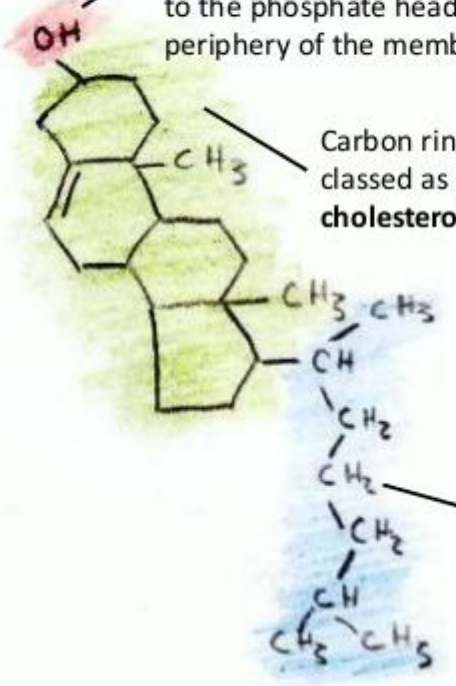
Figure 11-4
Lehninger Principles of Biochemistry, Fifth Edition

Colesterol afeta a fluidez da membrana

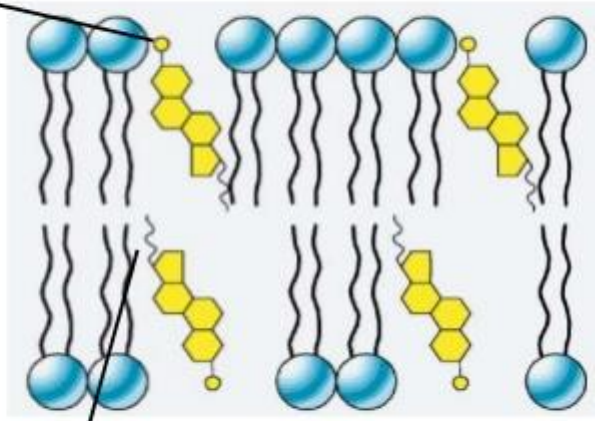
1.3.U3 Cholesterol is a component of animal cell membranes.

Cholesterol

Hydroxyl group makes the head polar and hydrophilic - attracted to the phosphate heads on the periphery of the membrane.



Carbon rings – it's not classed as a fat or an oil, **cholesterol is a steroid**



Non-polar (hydrophobic) tail –attracted to the hydrophobic tails of phospholipids in the centre of the membrane

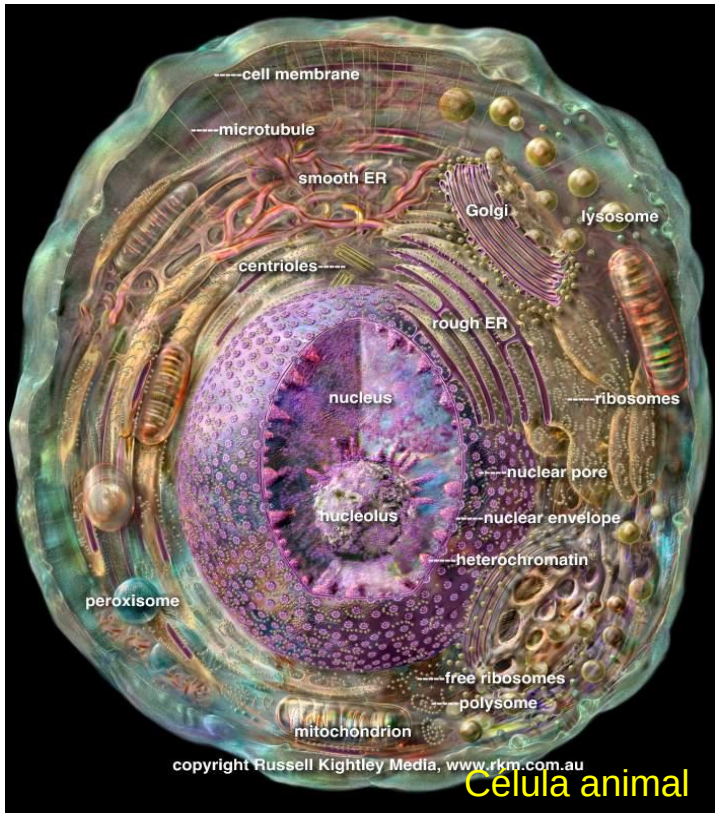
http://www.uic.edu/classes/bios/bios100/lectf03am/cholesterol.jpg

http://www.cholesterol-and-health.com/images/Cholesterol_Structure.jpg

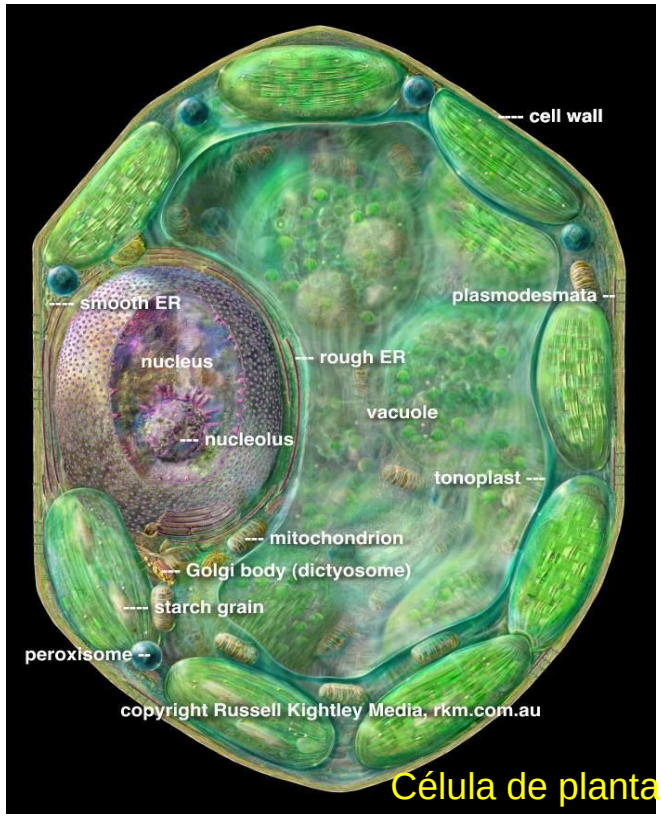
Membranas e paredes celulares

Diversos componentes celulares são separados pelas membranas.

Parede celular encontra-se somente nas células de planta, fungo e microorganismos como bactérias, algas etc.



Célula animal



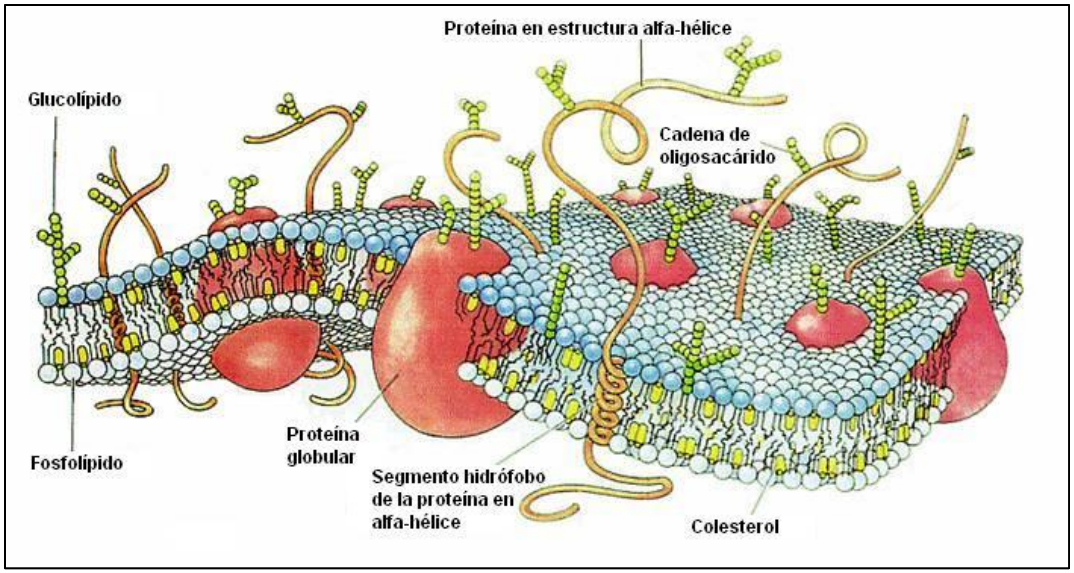
Célula de planta

Membranas Biológicas

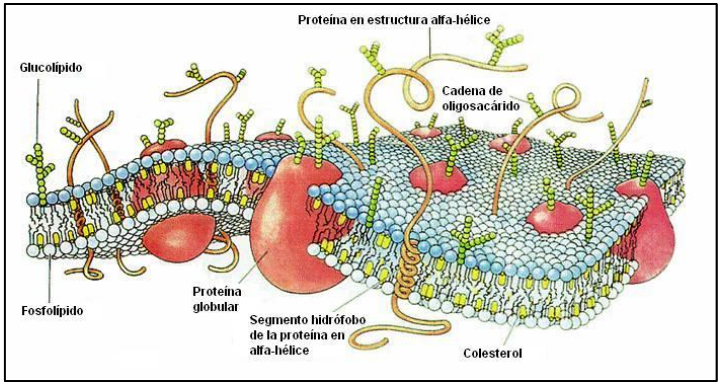
Os limites das células e de organelas são estabelecidos por membranas biológicas

Sistemas de transporte específicos mantém a permeabilidade seletiva

Estruturas dinâmicas formadas por lipídeos e proteínas



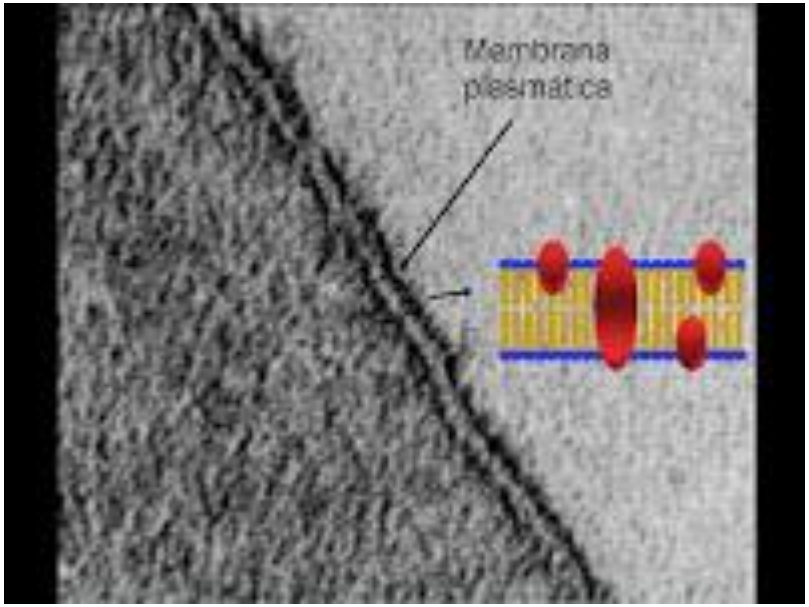
Membranas Biológicas

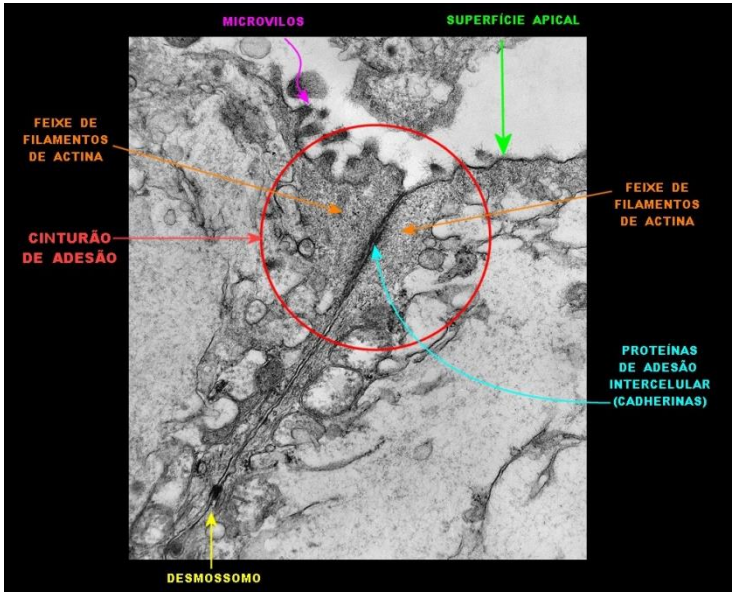


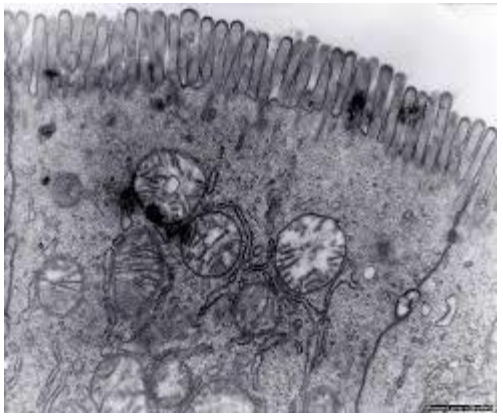
-Limites fechados
-contém carboidratos
-proteínas específicas medeiam diferentes funções das membranas
(bombas, canais, receptores, transdutores de energia, enzimas).
-Montagens não covalentes
-Assimétricas
-Estruturas fluidas
-Eletricamente polarizadas (lado interno negativo)

https://www.youtube.com/watch?v=y59P4P5d9VA

Membranas Biológicas







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

Lehninger Principles of Biochemistry, Fifth Edition

Composição de lipídeos varia entre membranas da célula

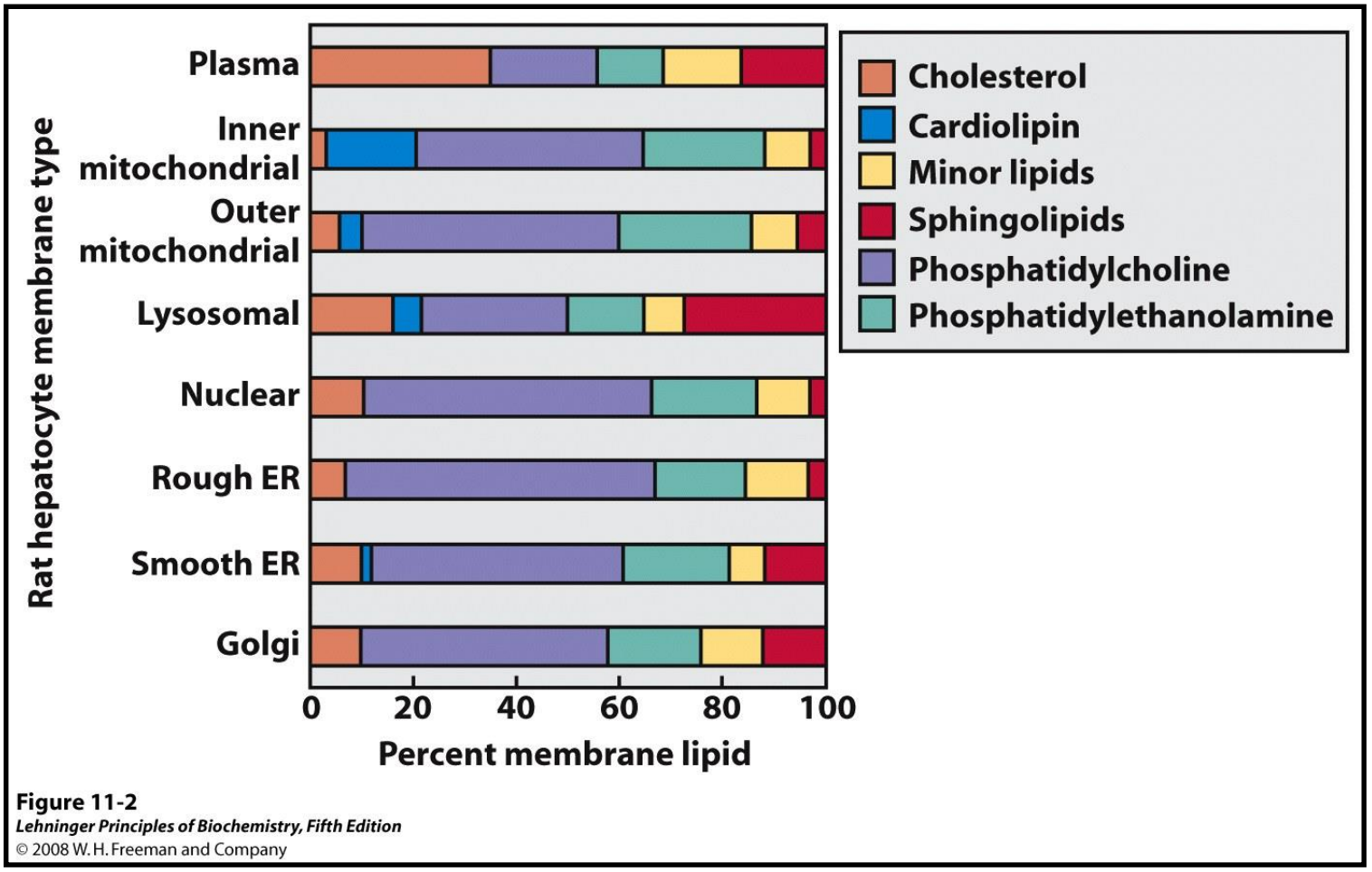


Figure 11-2
Lehninger Principles of Biochemistry, Fifth Edition

Modelo do mosaico fluido

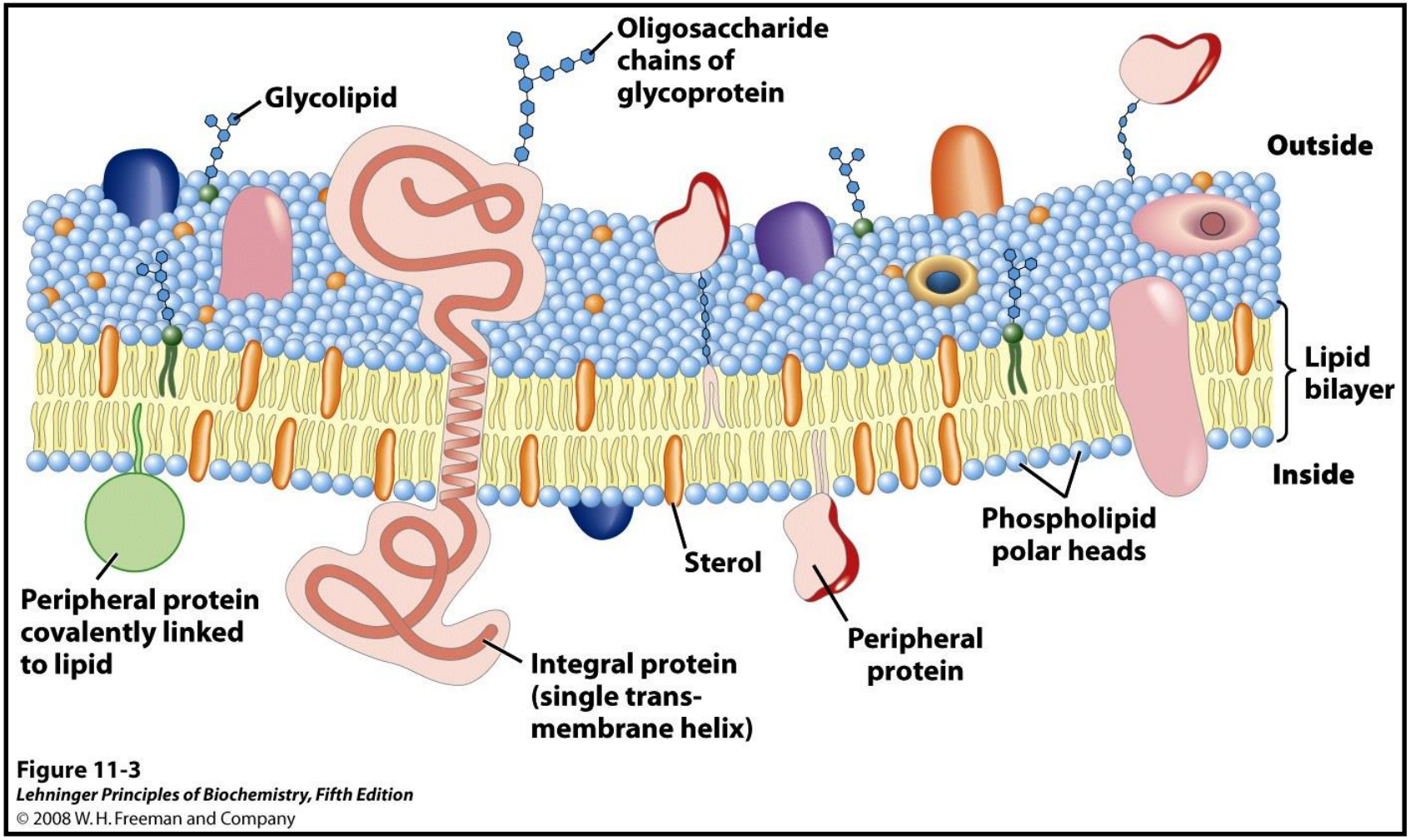


Figure 11-3
Lehninger Principles of Biochemistry, Fifth Edition

Modelo do mosaico fluido revisitado

Membrane asymmetry

Composição de lipídeos varia entre as faces de uma membrana

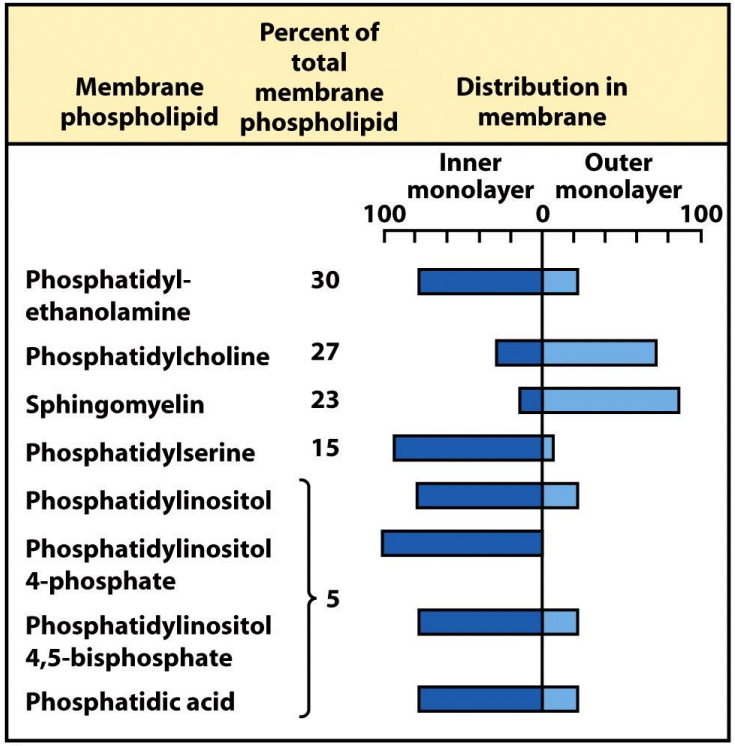


Figure 11-5
Lehninger Principles of Biochemistry, Fifth Edition

Modelo do mosaico fluido revisitado

Membrane asymmetry

Proteínas e lipídeos específicos permitem a segregação de processos biológicos.

Lipid Rafts concentração de colesterol e de proteínas que interagem com colesterol.

Translocação de fosfolipídeos de uma face da membrana para a outra feita por *flipases e scrambalases*

Mosaico fluido: movimento lateral das moléculas

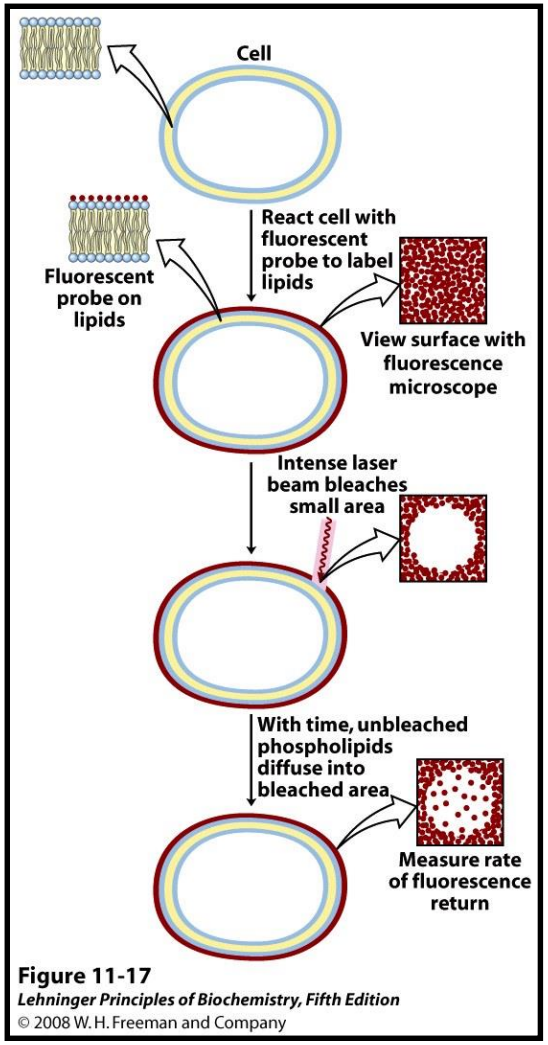


Figure 11-17
Lehninger Principles of Biochemistry, Fifth Edition

Movimento de "flip-flop" não é espontâneo

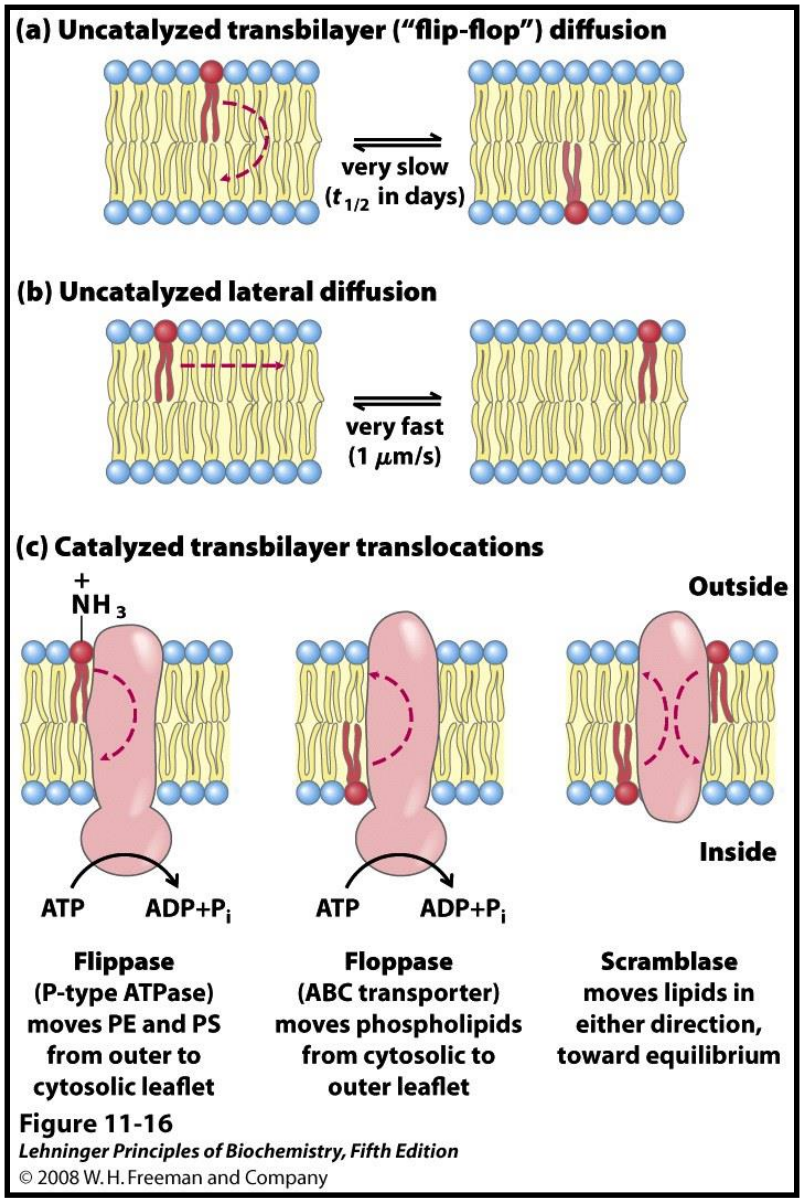


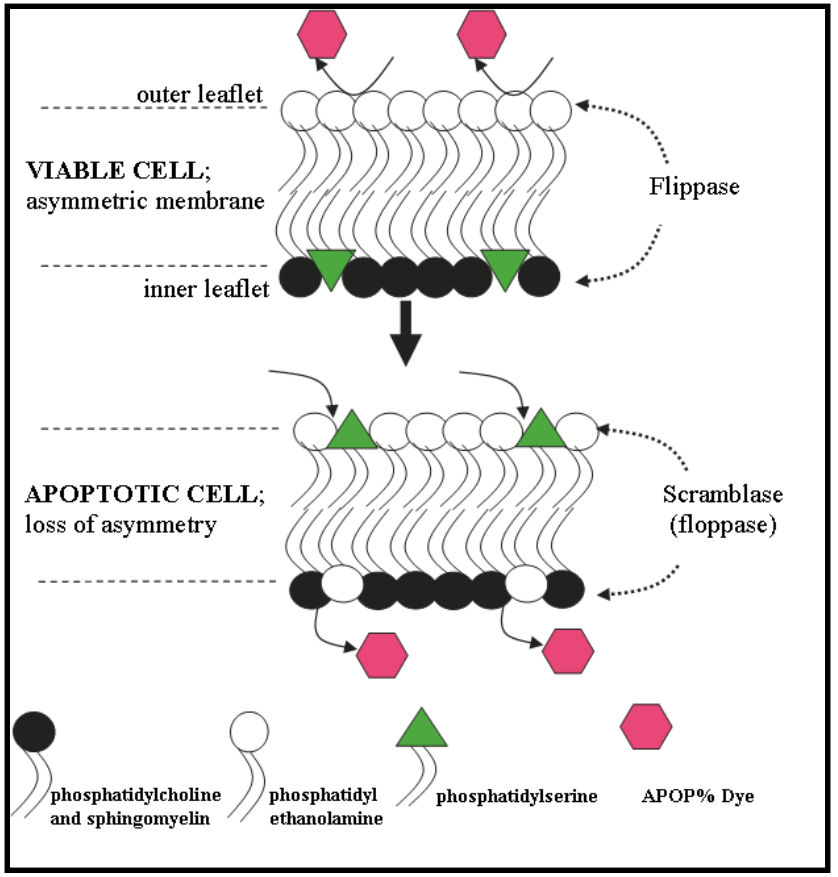
Figure 11-16

Lehninger Principles of Biochemistry, Fifth Edition

Apoptose

Apoptosis Greek"falling off"

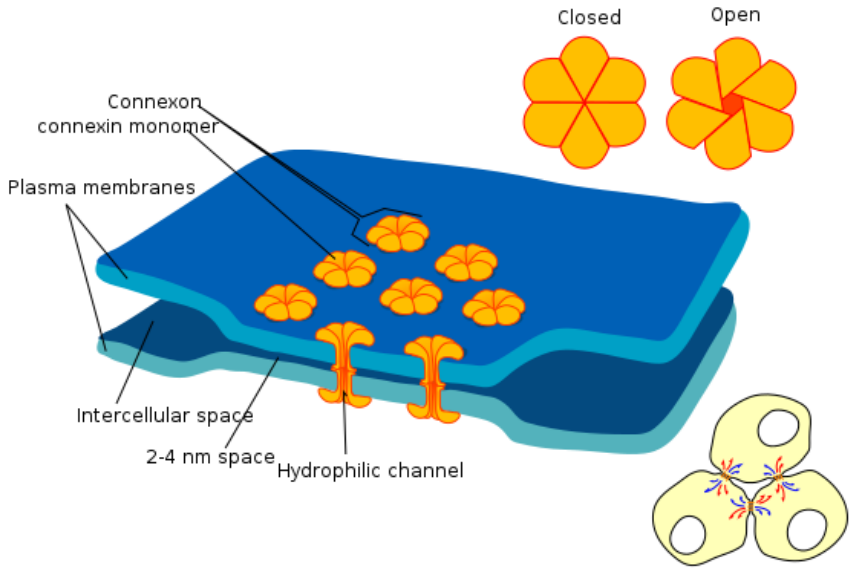
Programmed cell death



Modelo do mosaico fluido revisitado

Non-bilayer membranes

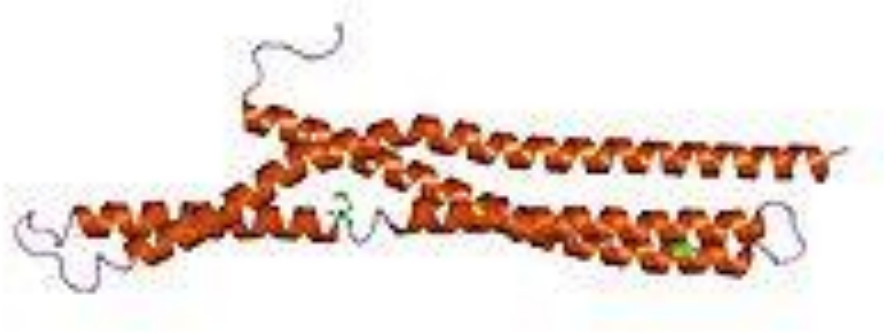
Gap junctions



Modelo do mosaico fluido revisitado

Membrane curvature

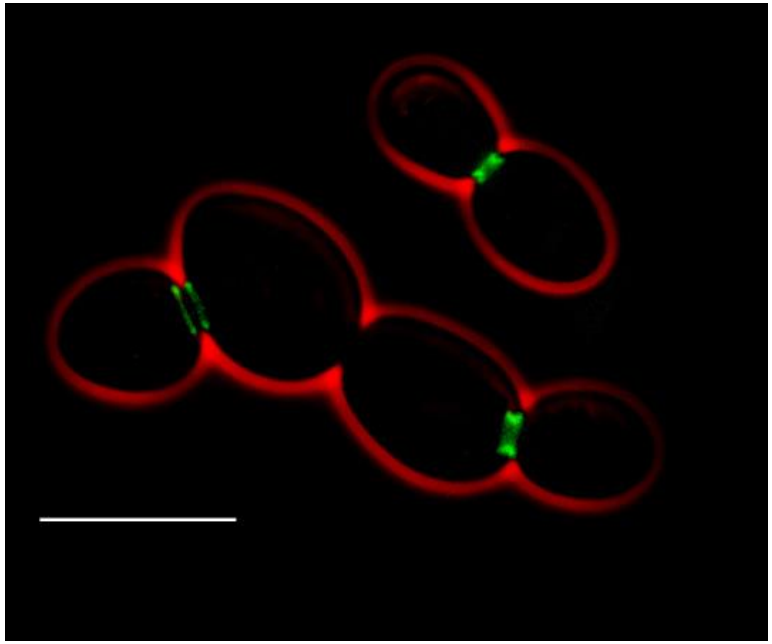
Bar domain containing proteins



Modelo do mosaico fluido revisitado

Cytoskeletal fences

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

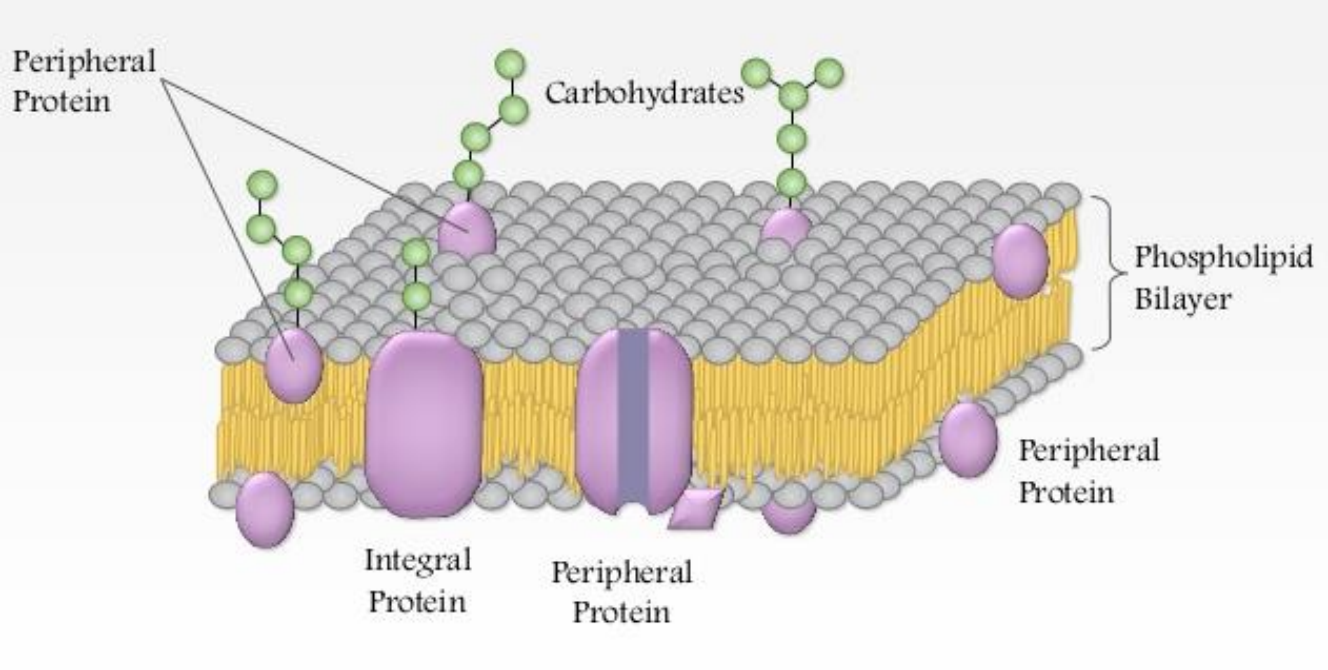


Adaptação ao meio

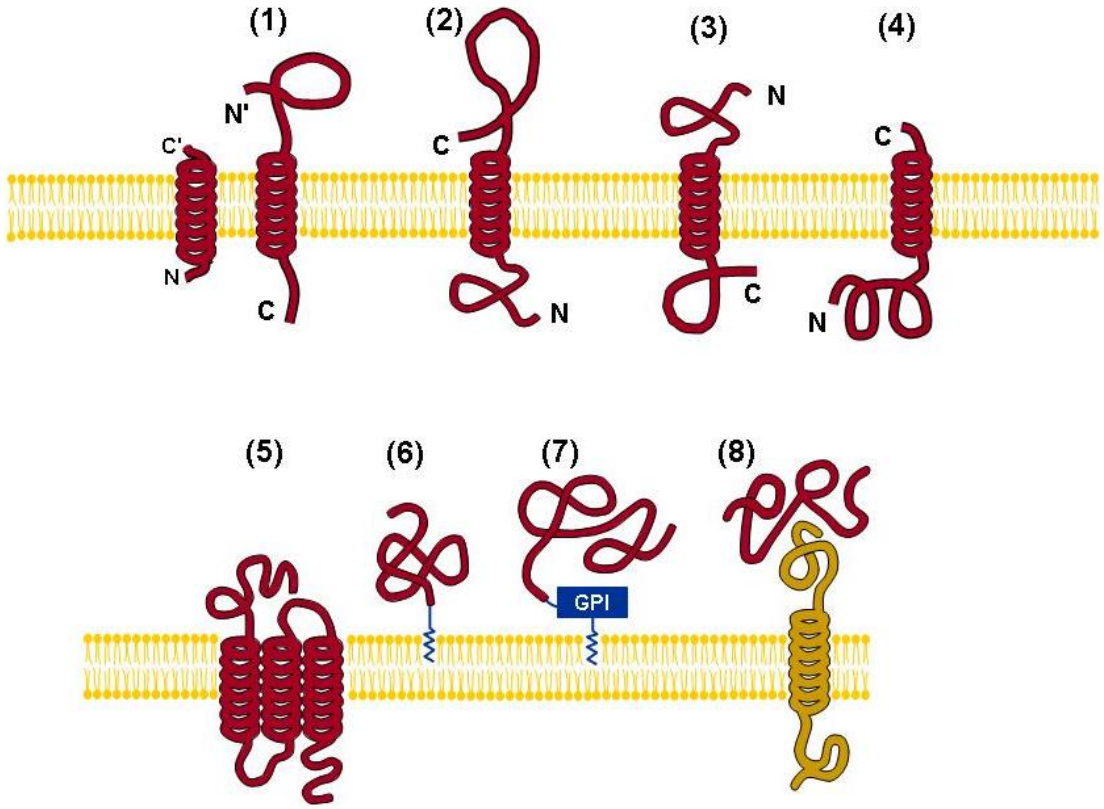
TABLE 11-2 Fatty Acid Composition of *E. coli* Cells Cultured at Different Temperatures

	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

Proteínas de membranas

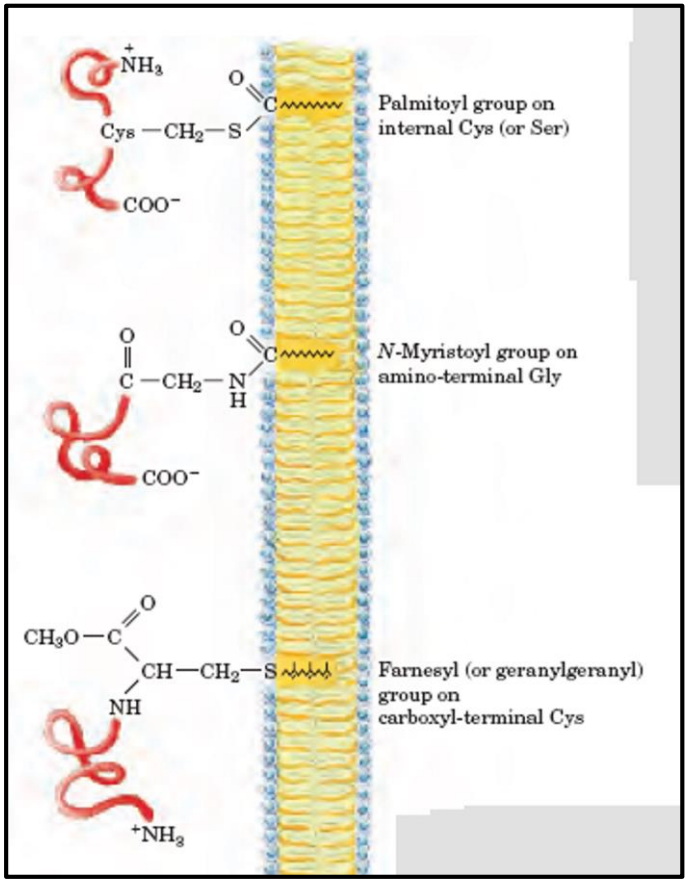


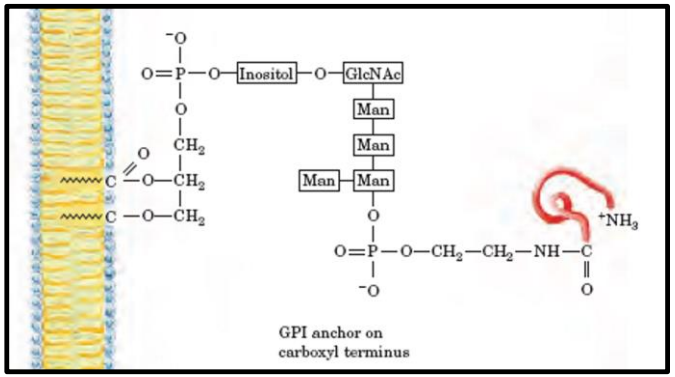
Proteínas de membranas



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





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

Proteínas integrais de membrana

- Alfa-hélices hidrofóbicas ou anfipáticas

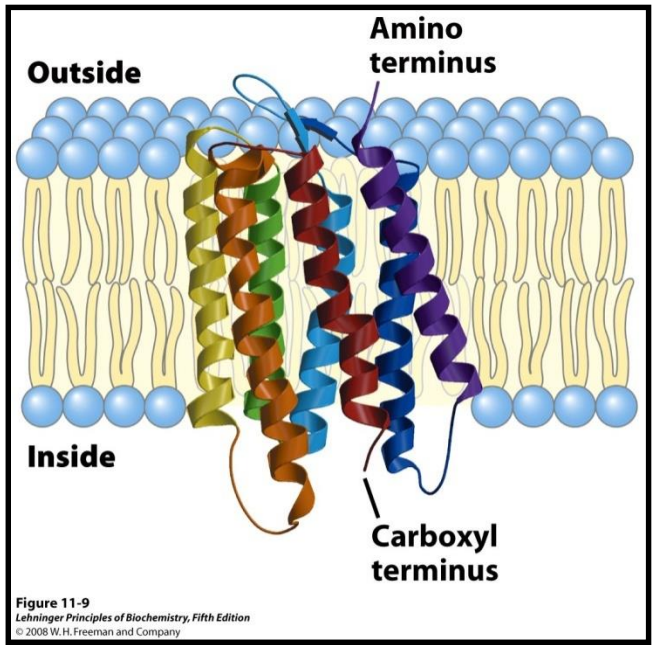


Figure 11-9
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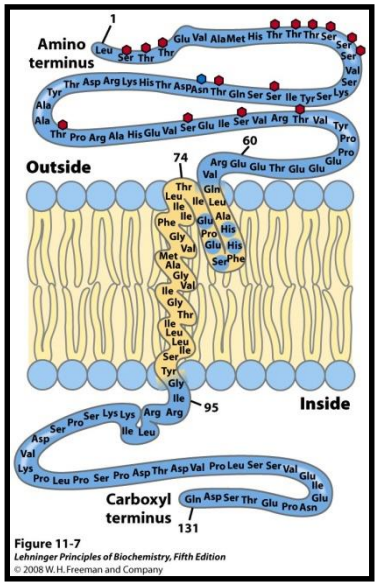

Figure 11-7
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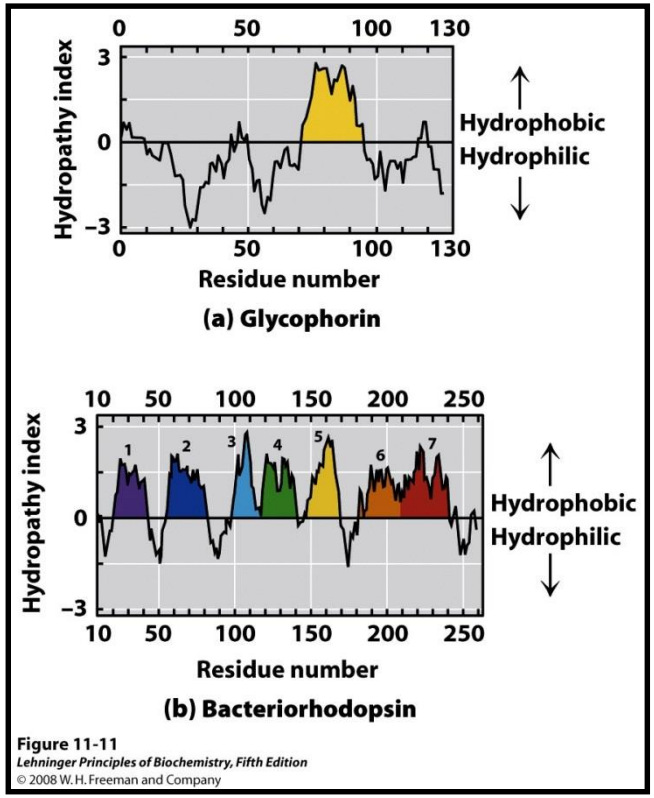

Figure 11-11
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Proteínas integrais de membrana

- Barris β

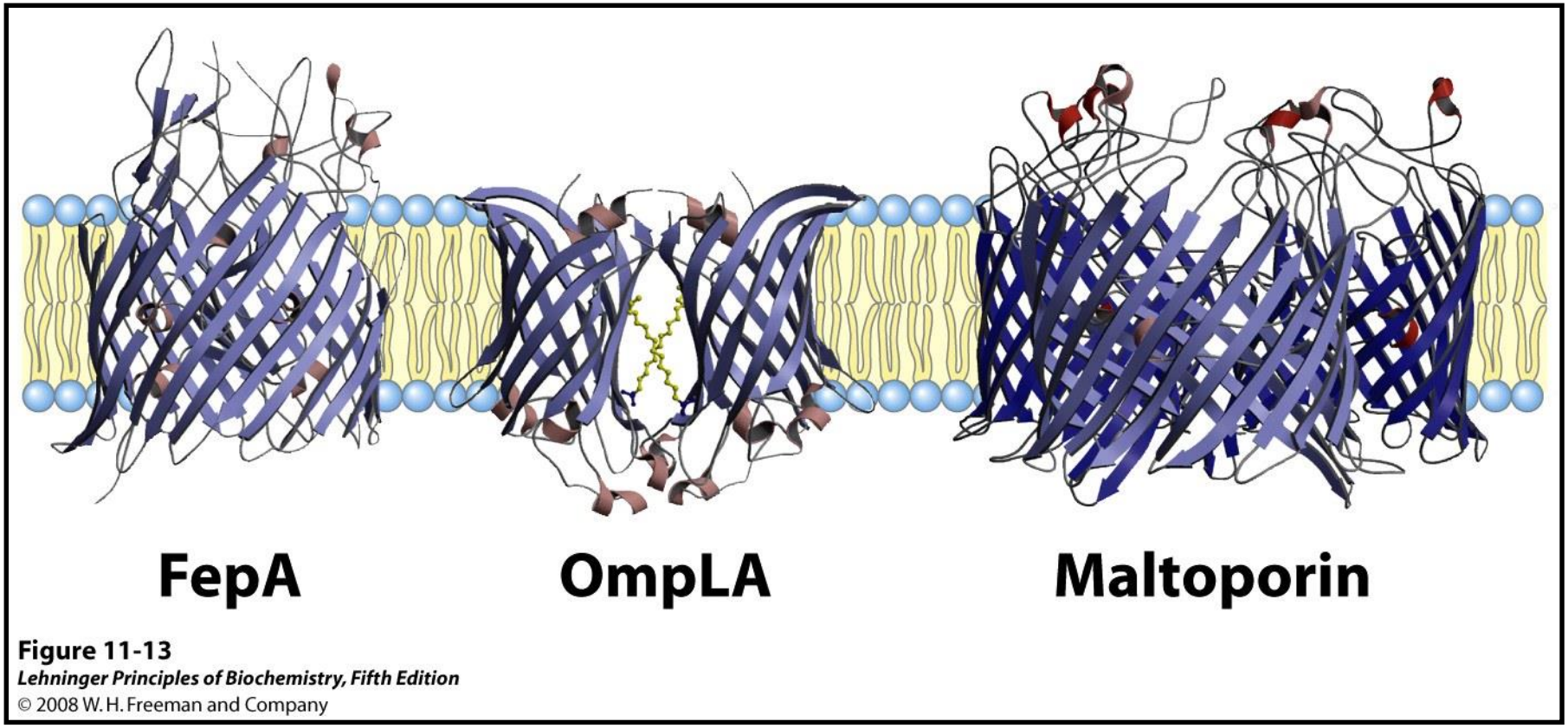

Figure 11-13
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Membrana podem ter regiões mais ou menos definidas

- Citoesqueleto limita movimento dos lipídeos e proteínas

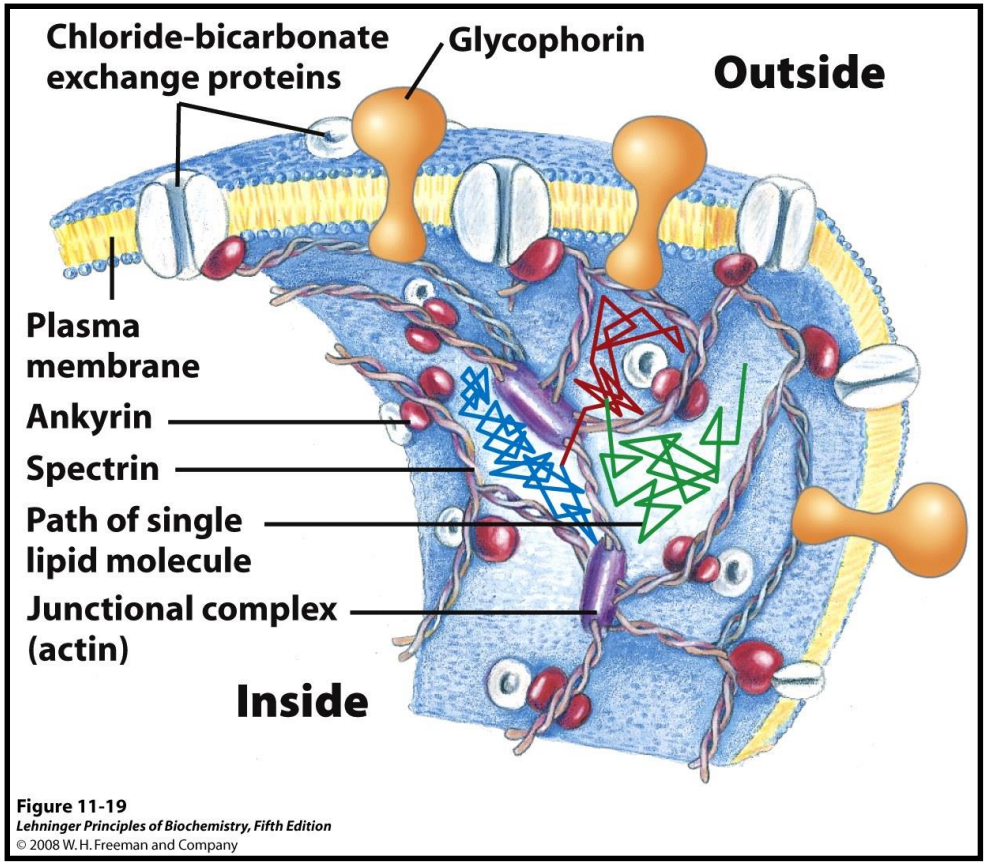

Figure 11-19
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Membranas podem ter regiões mais ou menos definidas

- "Rafts" (jangadas) concentram lipídeos de cadeias mais longas
- Maior concentração de lipoproteínas
- Facilita interação entre proteínas de vias de sinalização

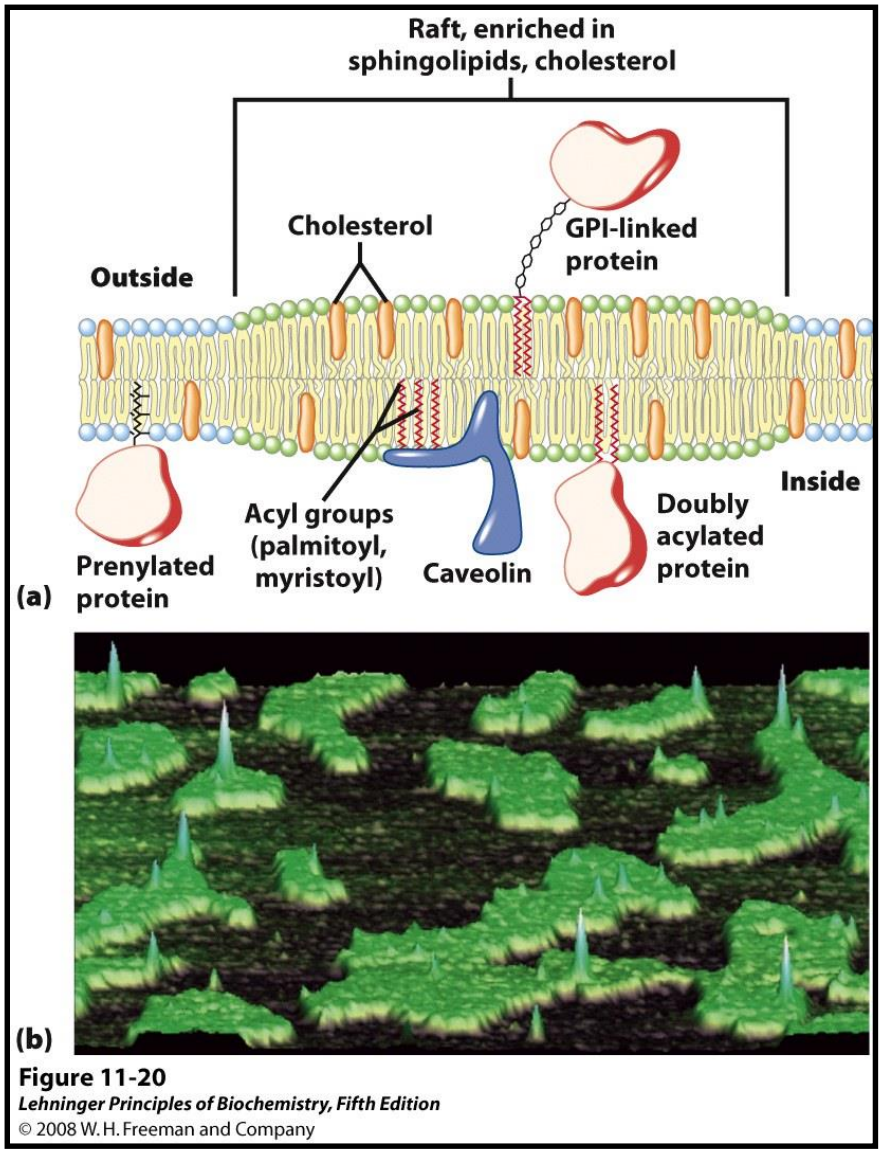

Figure 11-20
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Fusão de membranas (endocitose e exocitose)

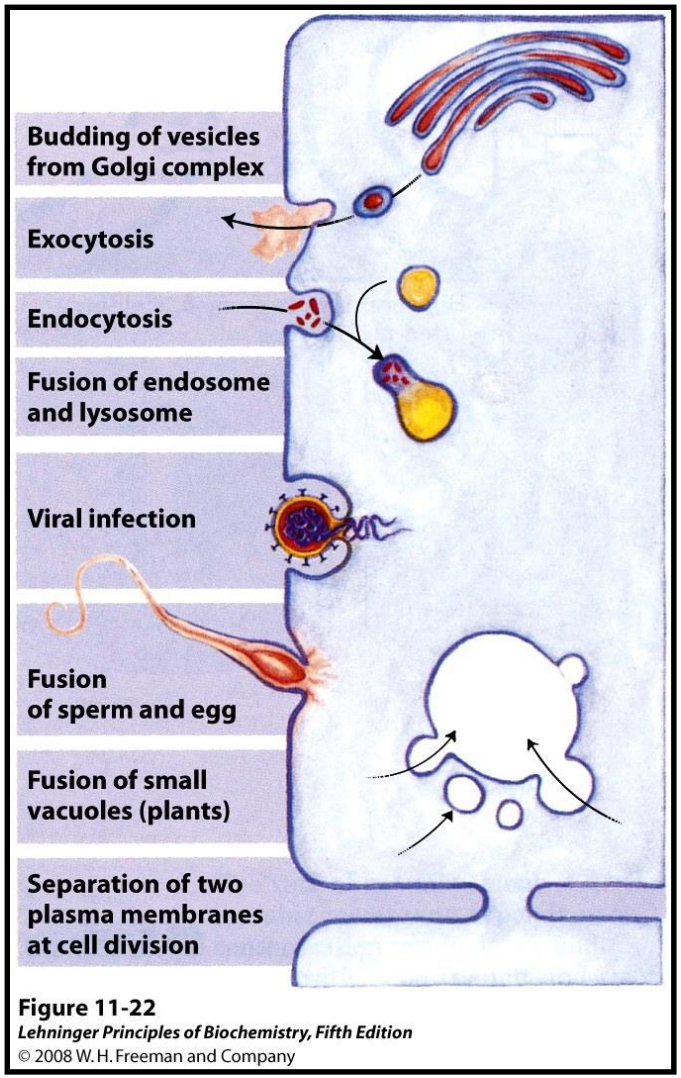

Figure 11-22
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Fusão de membranas

- Mediada por proteínas
- SNARES (soluble NSF attachment receptor)

  - neurotransmissão
  - funcionam como "zíperes"
  - inibidas por toxina botulínica

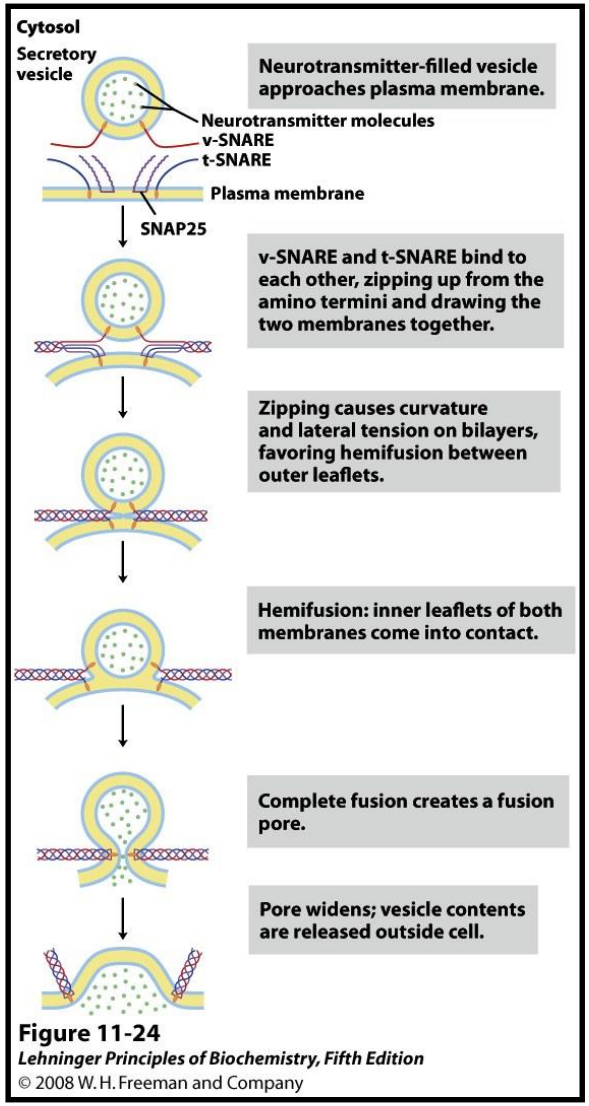

Figure 11-24
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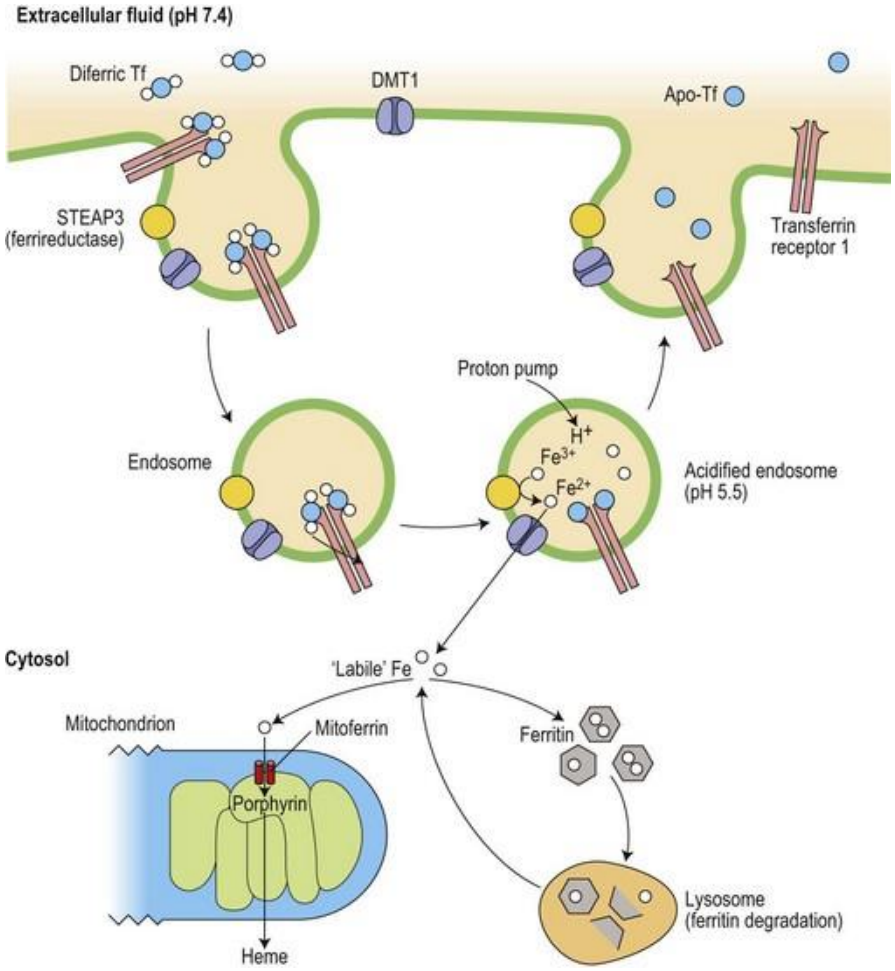
Receptor de transferrina

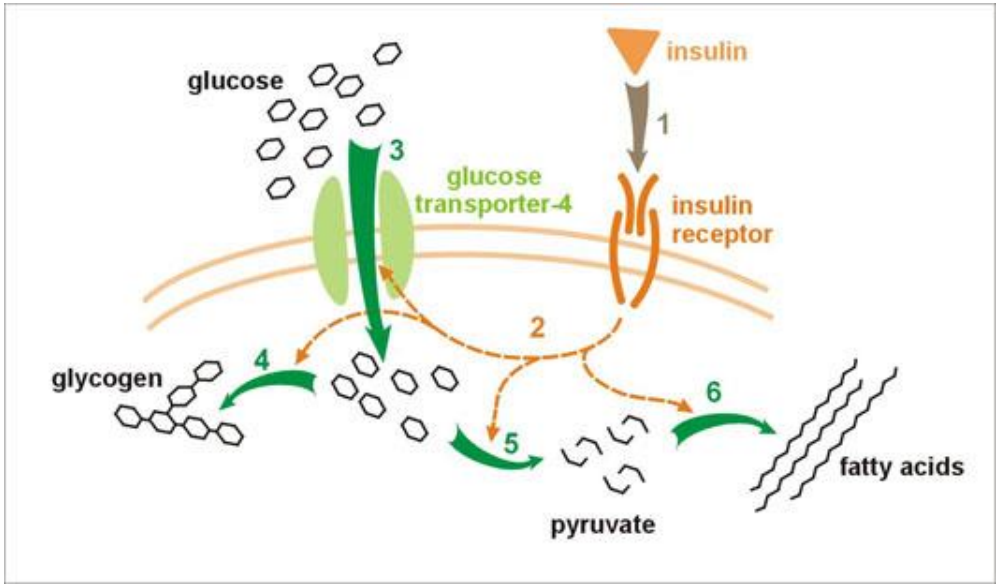


Transporte

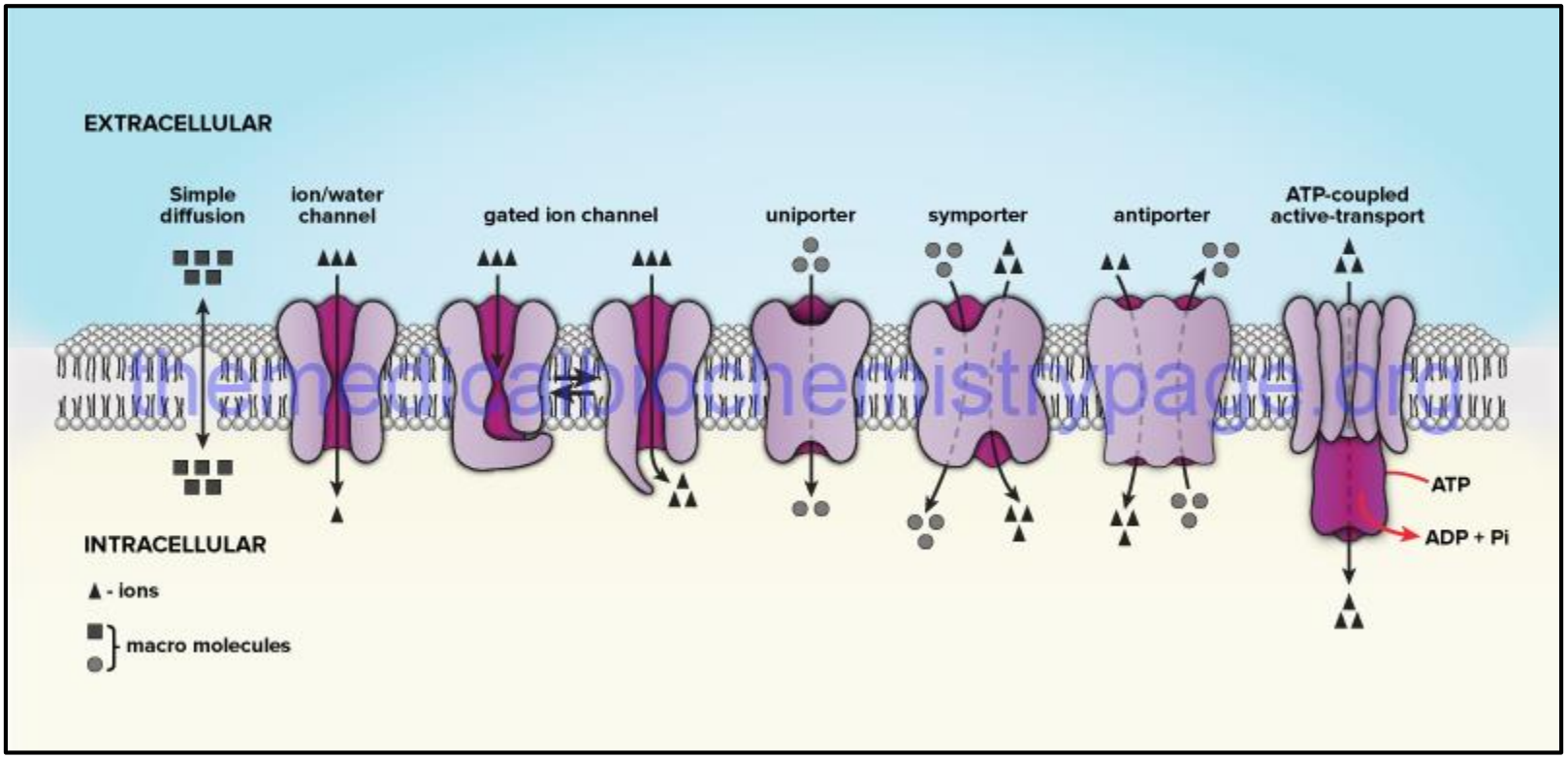
TRANSPORTE DE GLICOSE

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

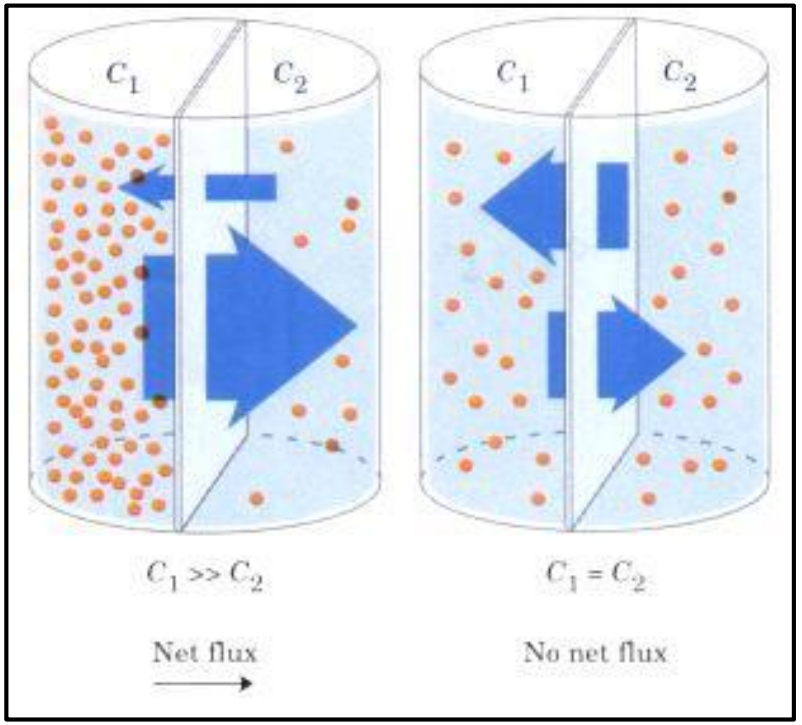


Tipos de transportadores

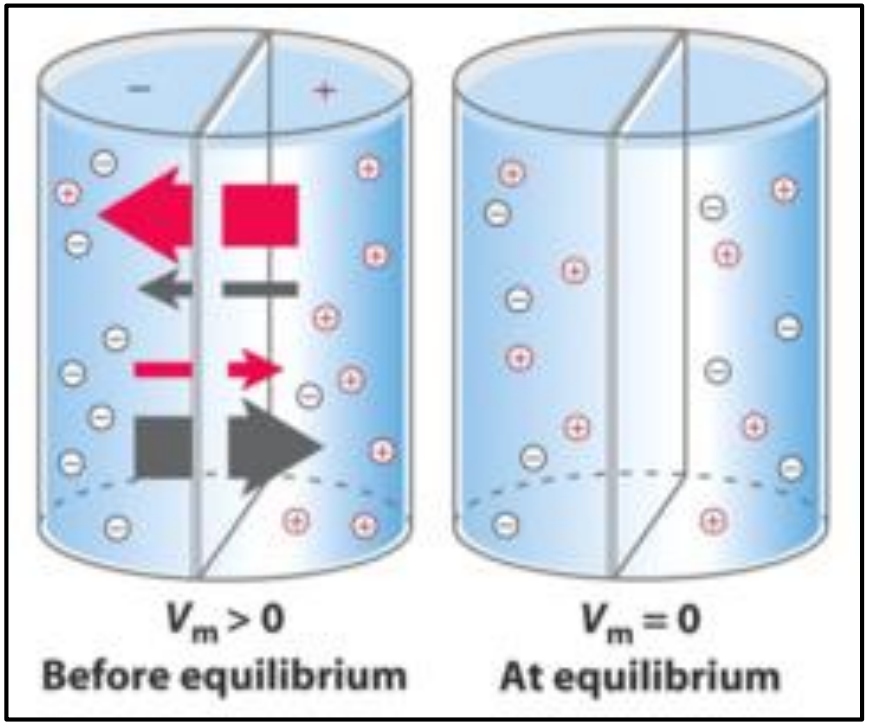


Movimento através de uma membrana permeável

Concentração



Carga



Transportadores e Canais

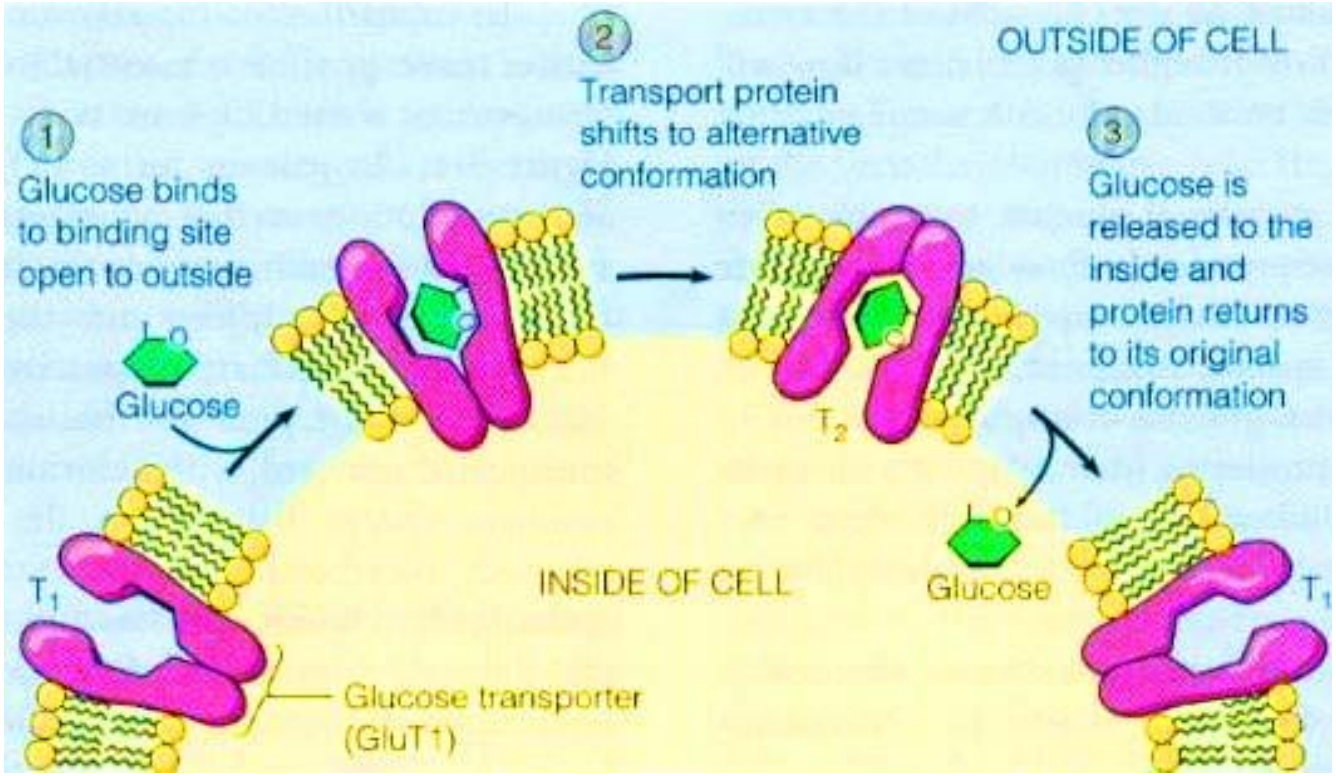
Transportadores

-Saturáveis
-Baixa velocidade de transporte
-Maioria proteínas monoméricas

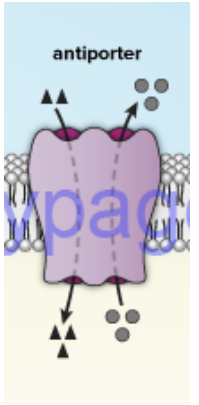
Canais

-Mais rápidos
-Insaturáveis
-Maioria proteínas oligoméricas

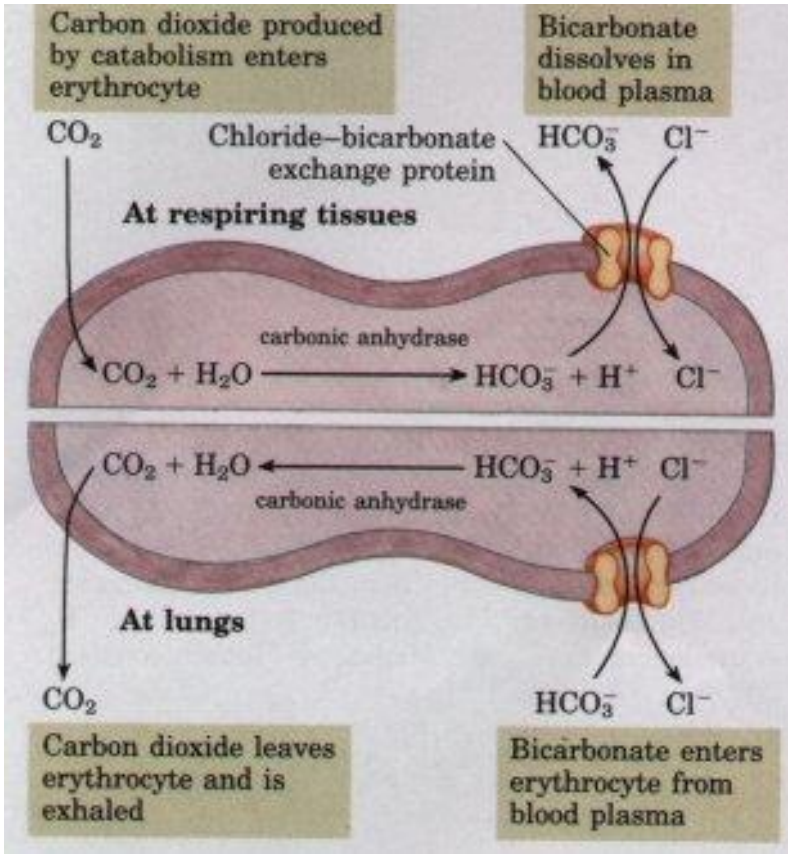
Transporte Uniporte



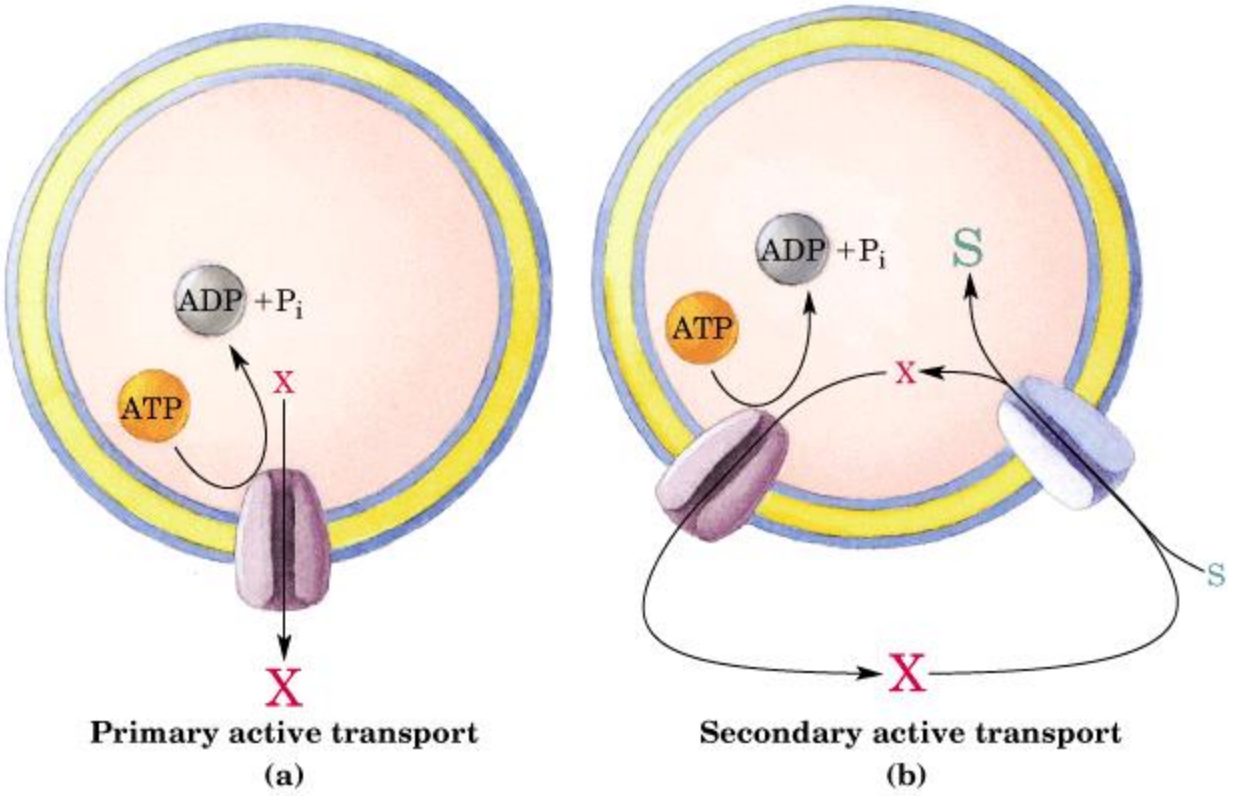
Trocador de cloreto-bicarbonato (trocador aniônico) Co-transportador antiporte

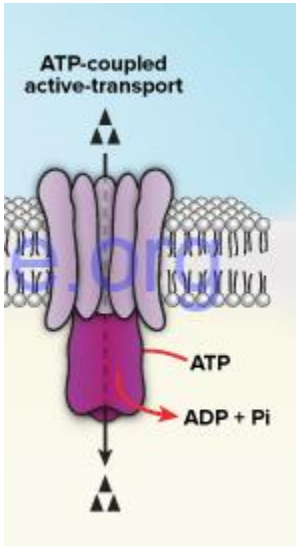


O bicarbonato é mais solúvel no plasma do que o CO_2

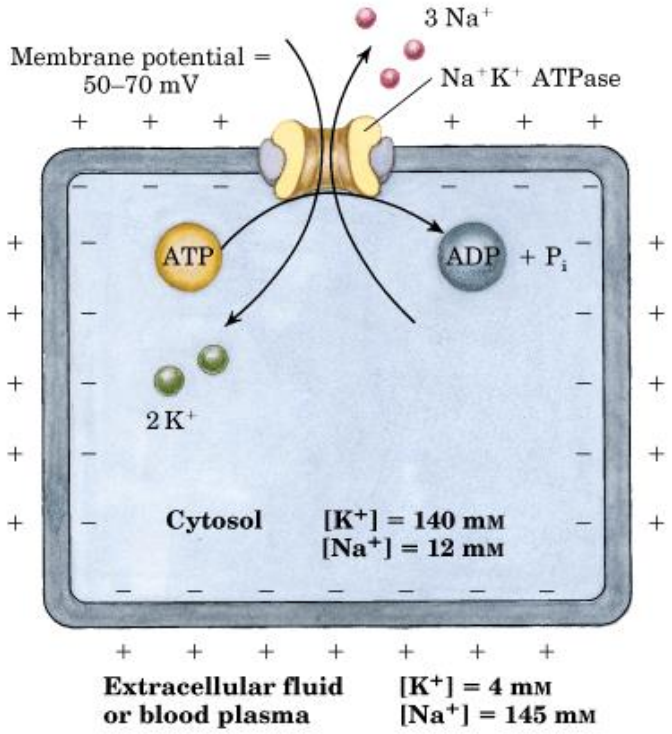


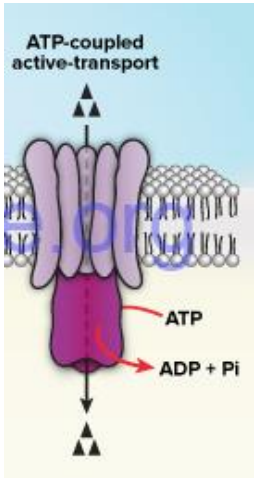
Transporte ativo resulta no acúmulo do soluto acima do ponto de equilíbrio termodinamicamente não é favorável e deve ser acoplado a um processo exergônico





Na^+/K^+-ATPase





- 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
- A atividade resulta em uma carga negativa por um ciclo de trabalho.

ATPase de cálcio

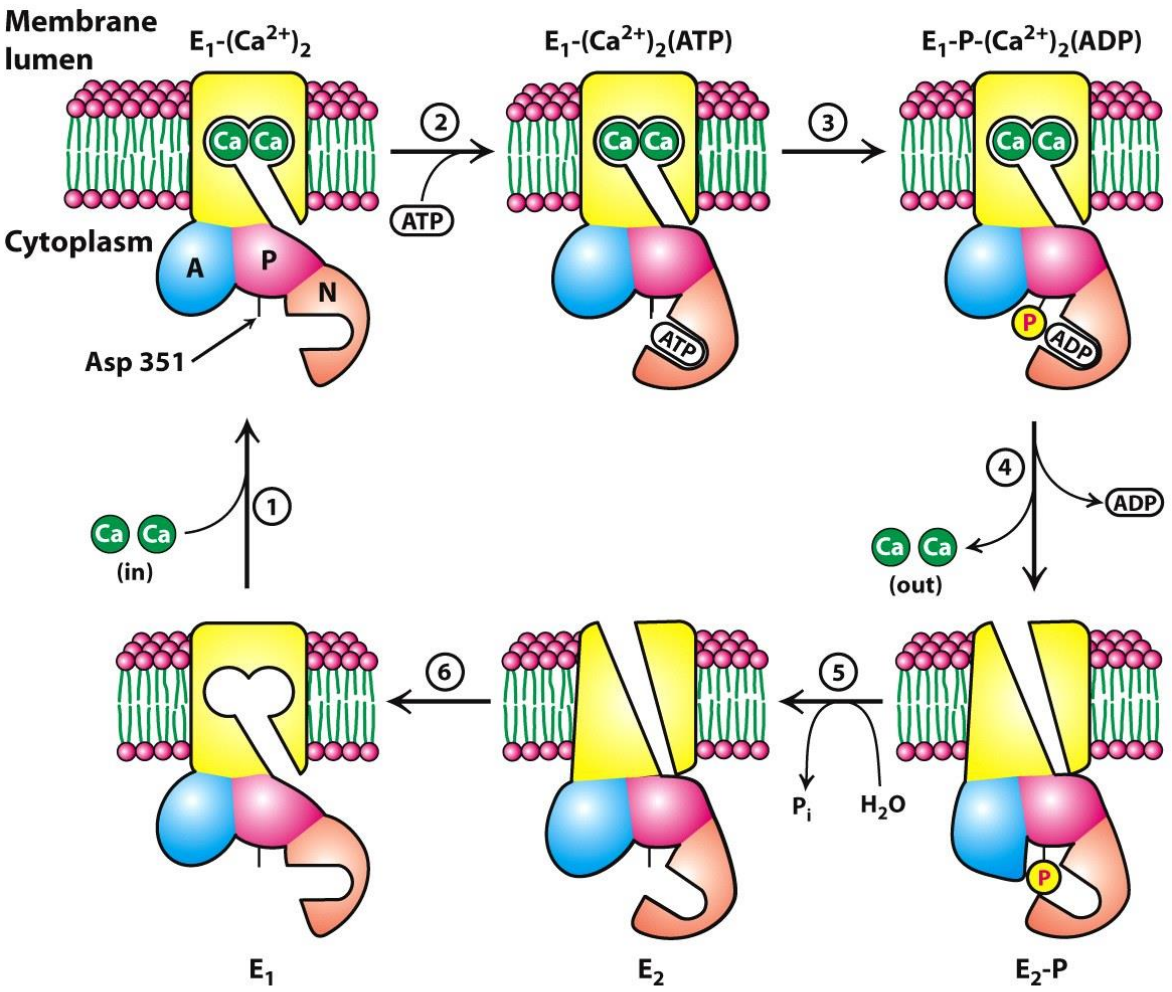
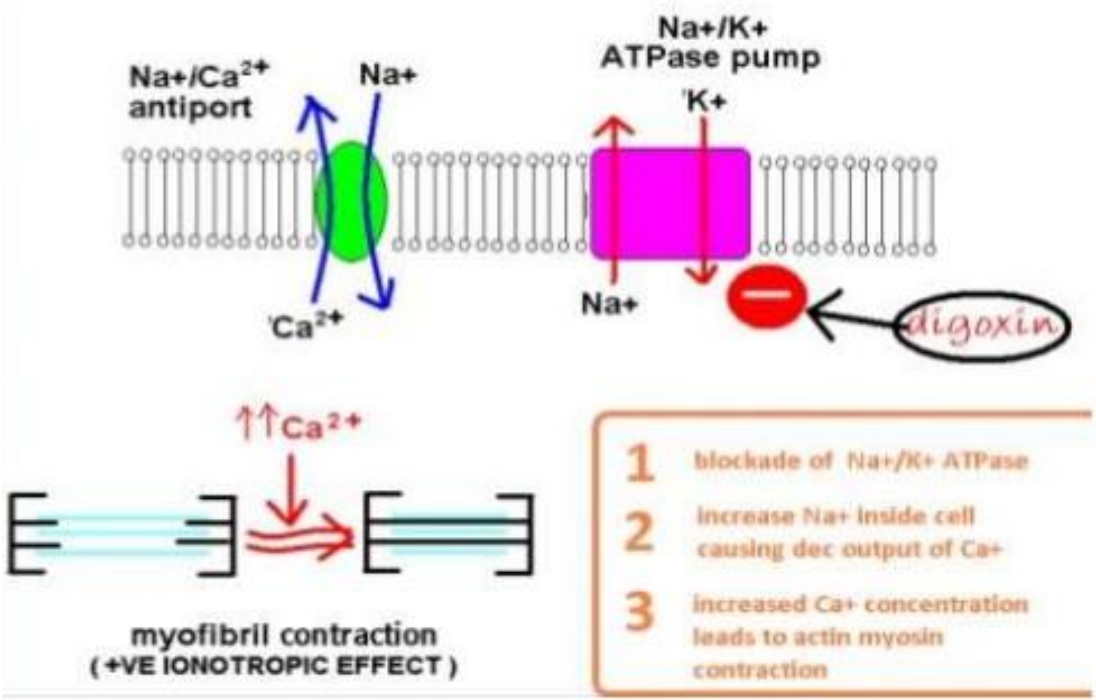


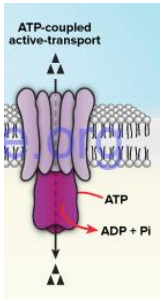
Figure 13.5
***Biochemistry*, Seventh Edition**

Digitalis

Digitalina (insuficiência cardíaca)



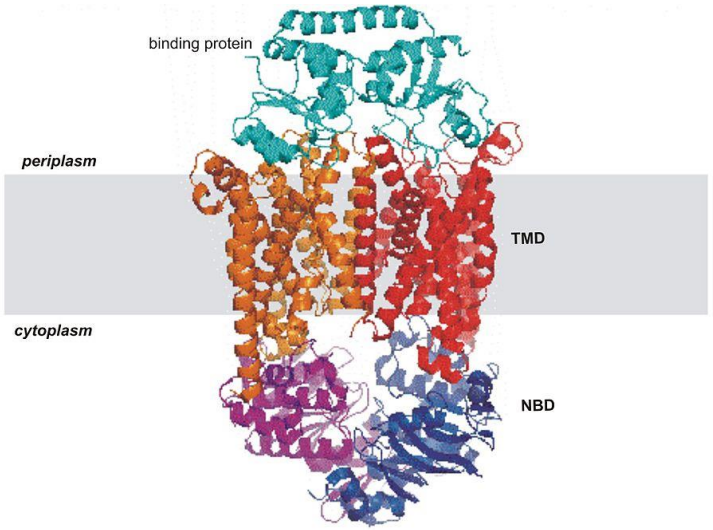
Transportadores ABC
ATP-binding cassette transporters
(MDR) Conferem resistência a drogas



ABC transporters utilize the energy of ATP binding and hydrolysis to transport various substrates across cellular membranes.

In prokaryotes, *importers* mediate the uptake of nutrients into the cell.

Eukaryotes do not possess any importers. *Exporters* or *effluxers*, which are present both in prokaryotes and eukaryotes, function as pumps that extrude toxins and drugs out of the cell.



Transportadores ABC

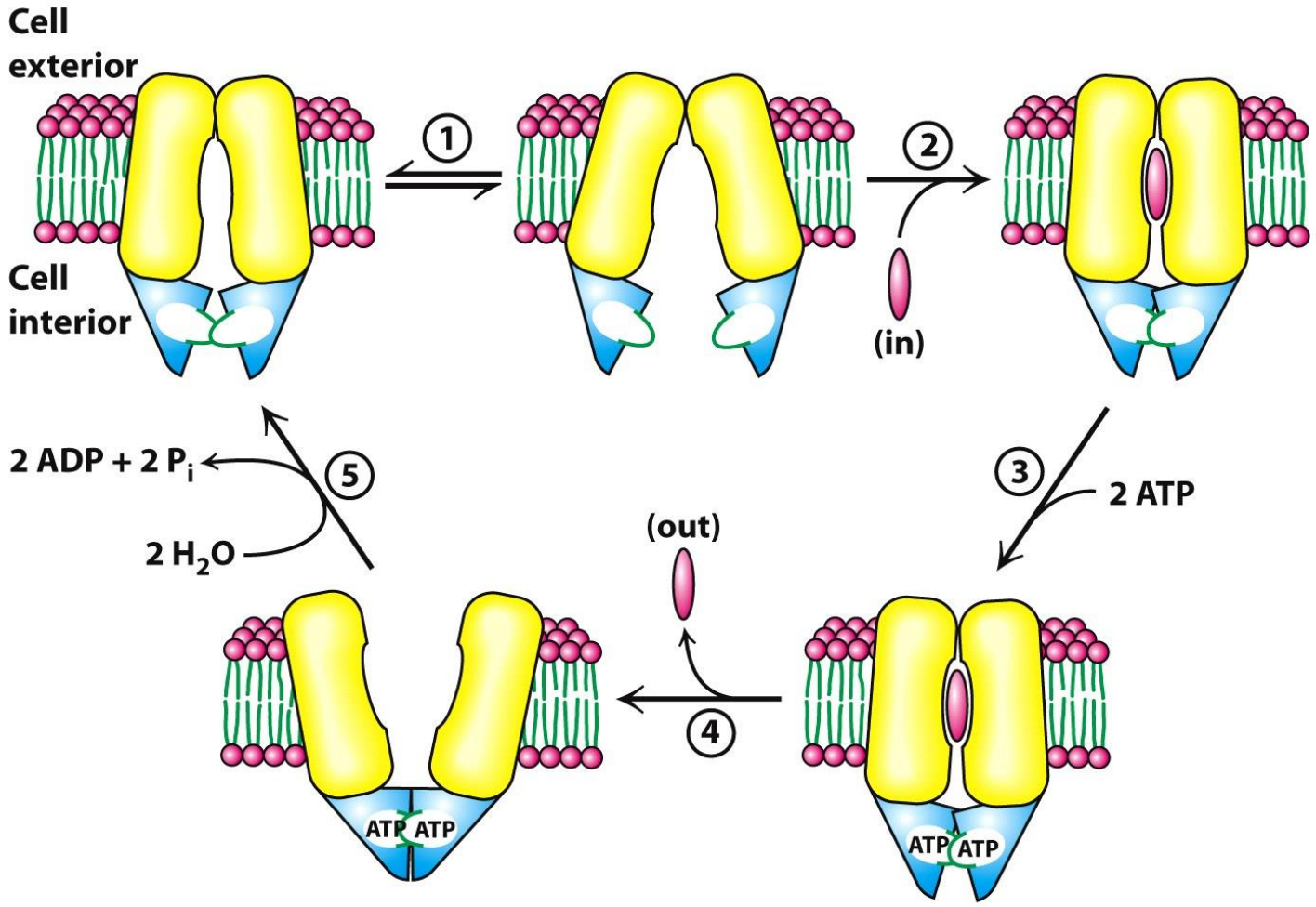


Figure 13.9
***Biochemistry*, Seventh Edition**

Transportador de lactose movido por um gradiente de H^+

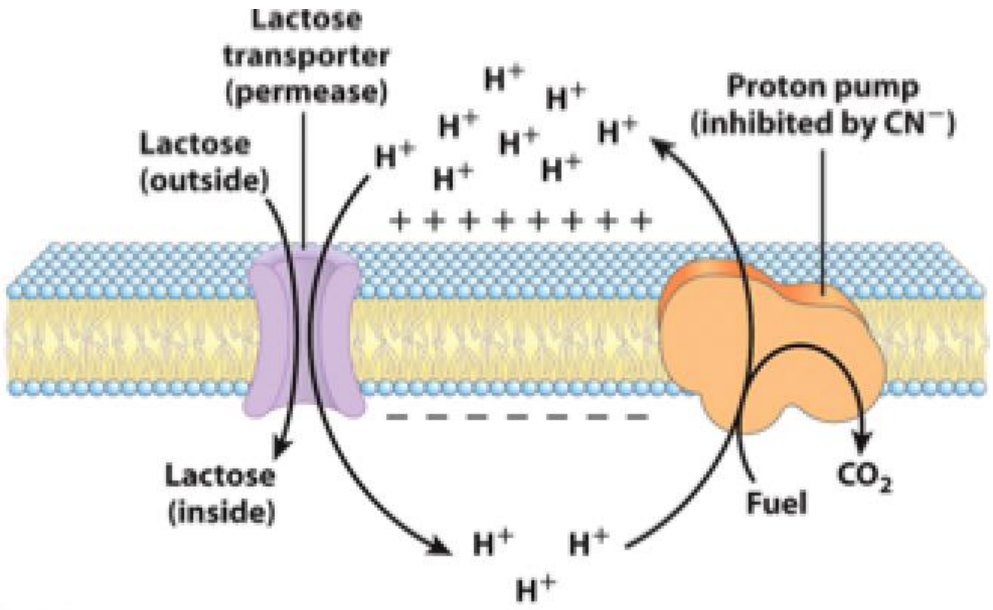


Figure 11-41
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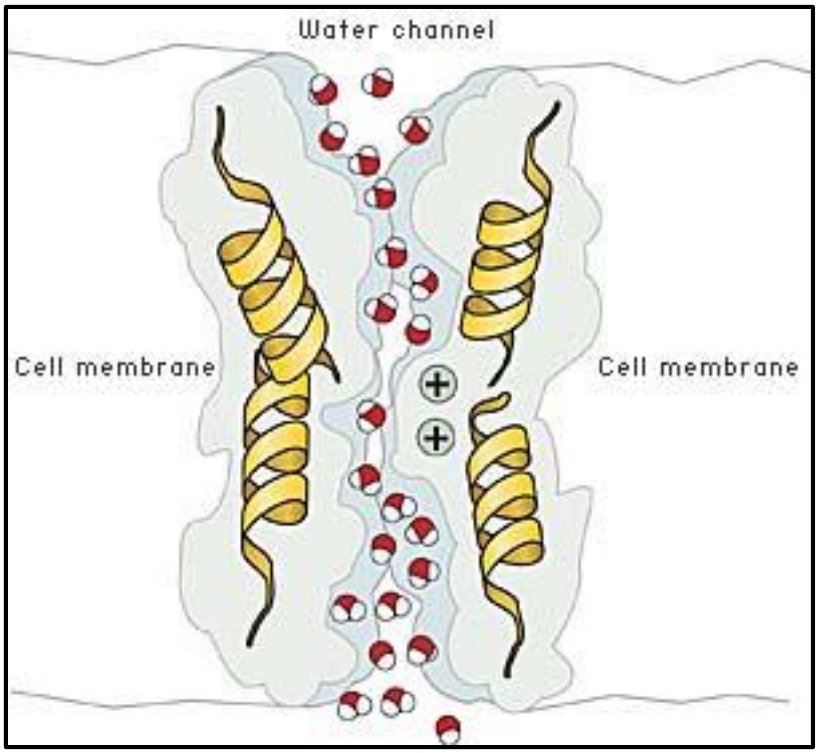
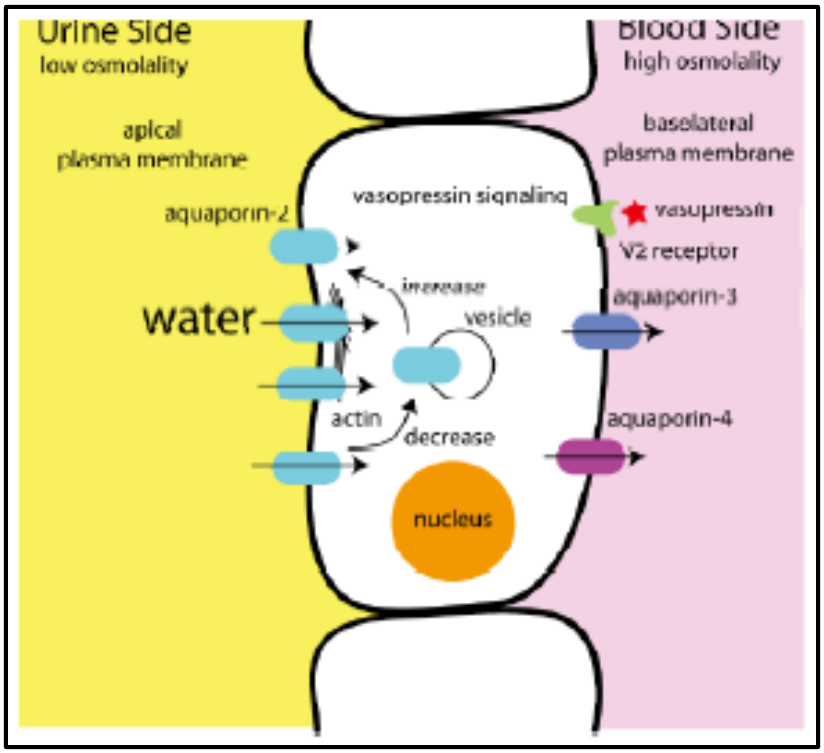
Aquaporina Transportador de água





•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.

Canais iônicos

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

-Em neurónios mudanças rápidas nos canais iônicos causam mudanças em potenciais de membrana (potencial de ação), que transmitem sinais no neurônio.

-Em miócitos a abertura de canais de cálcio no retículo sarcoplasmático libera o cálcio que ativa a contração muscular.

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.

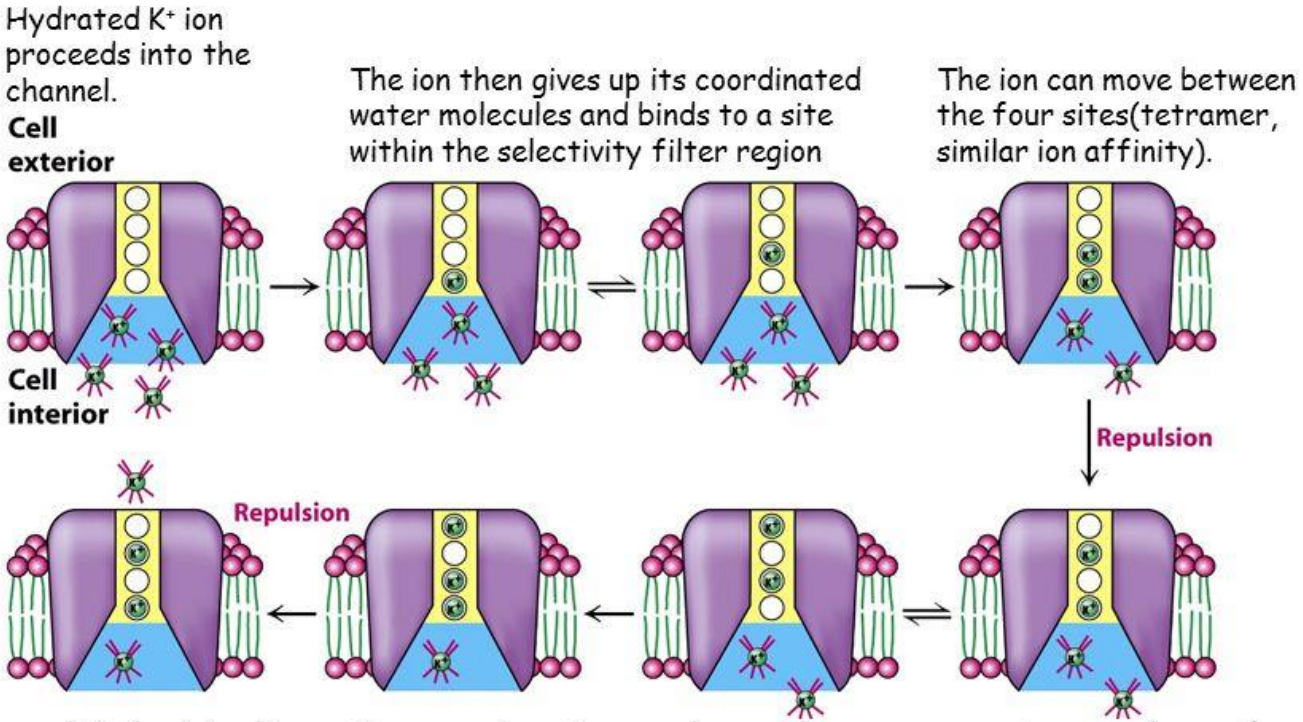
Controlados por ligantes (geralmente oligoméricos).
- Mudança conformacional do canal que abre ou fecha com um ligante.

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

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

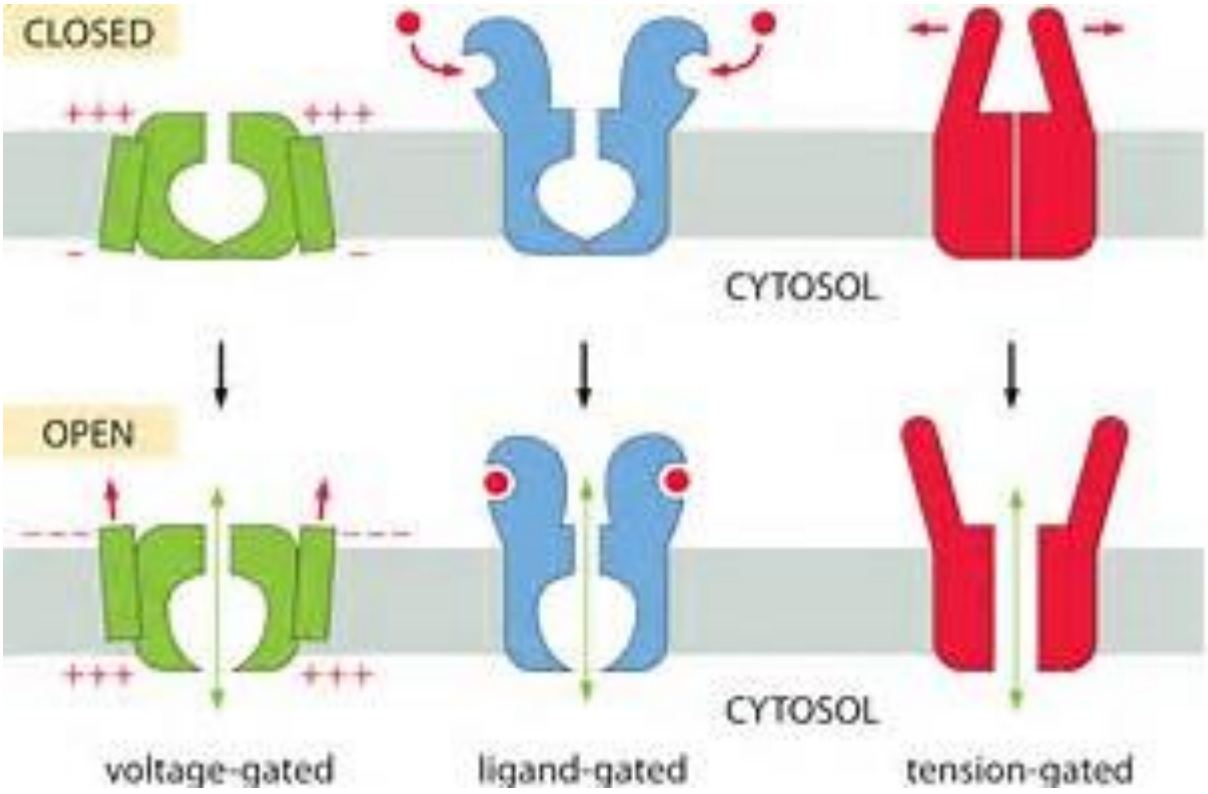
High selectivity needs tight binding site!

How to achieve fast transport of channels?

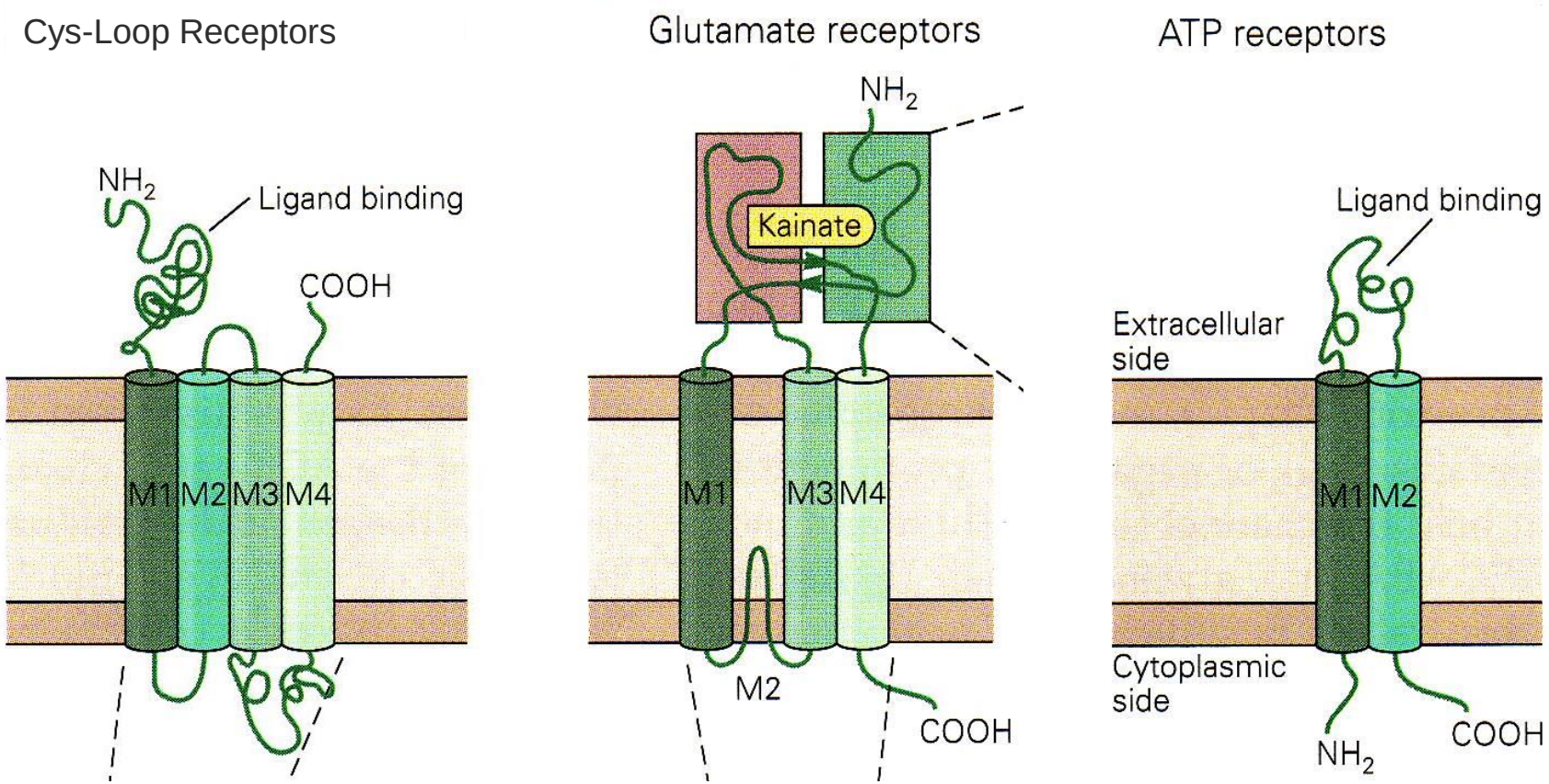


This multiple binding site mechanism solves the apparent paradox of **high ion selectivity** and **rapid flow**.

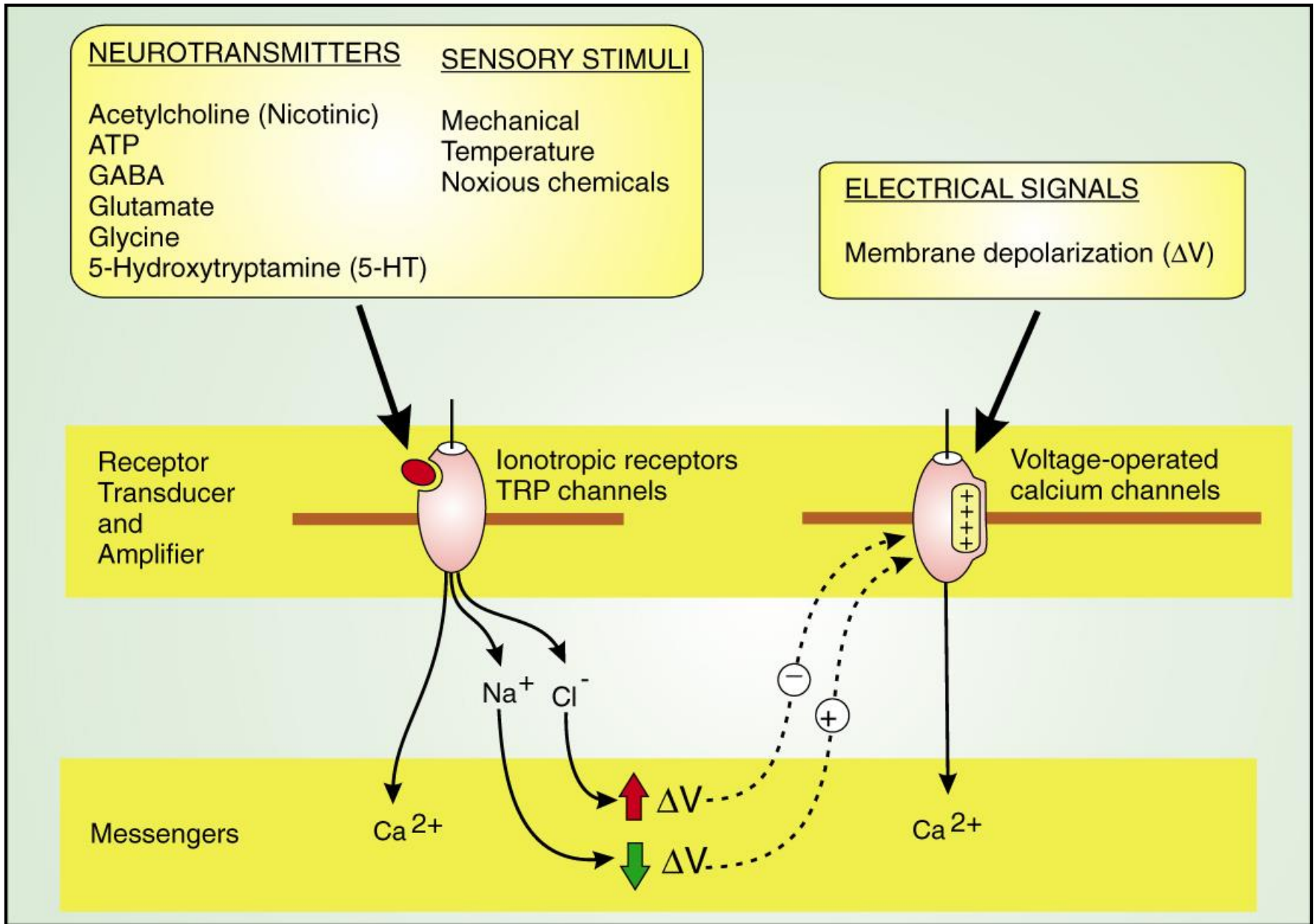
"Gated Ion Channels"



Superfamilies of Ligand-Gated Ion Channels



Estímulos por Canais Iônicos



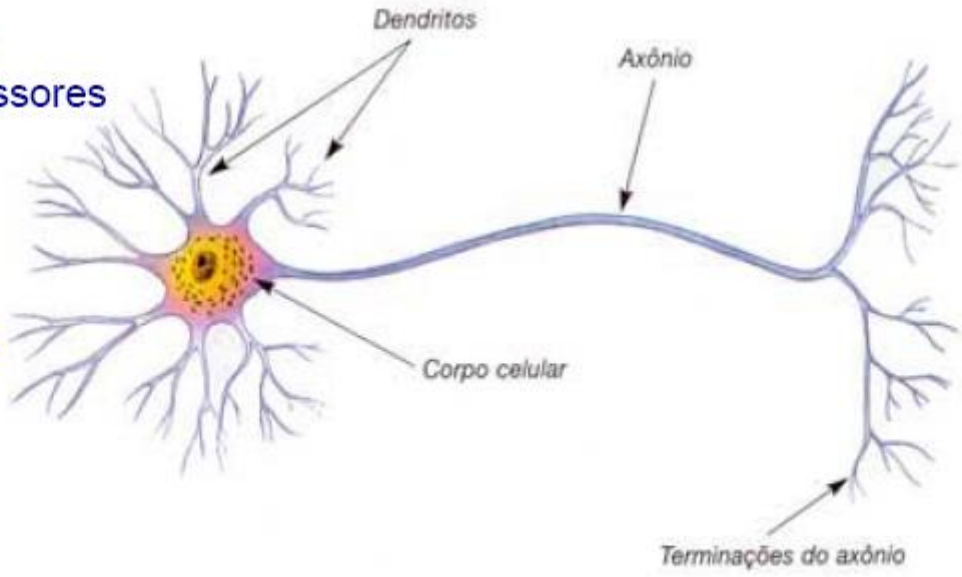
COMUNICAÇÃO POR MEIO DE NEUROTRANSMISSORES

Constituição do Neurónio:

- corpo celular ou pericário
- prolongamento celulares: dendritos e axónio

Recepção de neurotransmissores

Recepção



Libertação de neurotransmissores

Transmissão

Fases da transmissão sináptica

I. Síntese do neurotransmissor na terminação nervosa pré-sináptica.

II. Armazenamento dos neurotransmissores em vesículas secretoras.

III. Liberação regulada do neurotransmissor (exocitose) na fenda sináptica.

IV. Receptores específicos para os neurotransmissores estão presentes na membrana pós-sináptica.

V. Controle da ação do neurotransmissor na fenda e no receptor pós-sináptico.

Sinapse neuromuscular (placa motora)

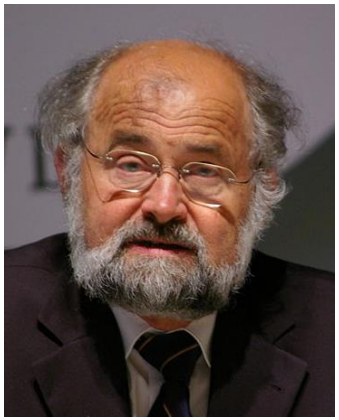
I. Despolarização e abertura de canais de cálcio com a liberação de cálcio para a membrana pré=sináptica.

II. Alta concentração de cálcio desencadeia a exocitose de Vesículas sinápticas que liberam acetilcolina.]

III. A acetilcolina liberada por exocitose atua sobre os receptores da membrana pós-sináptica, promovendo a contração da fibra muscular.

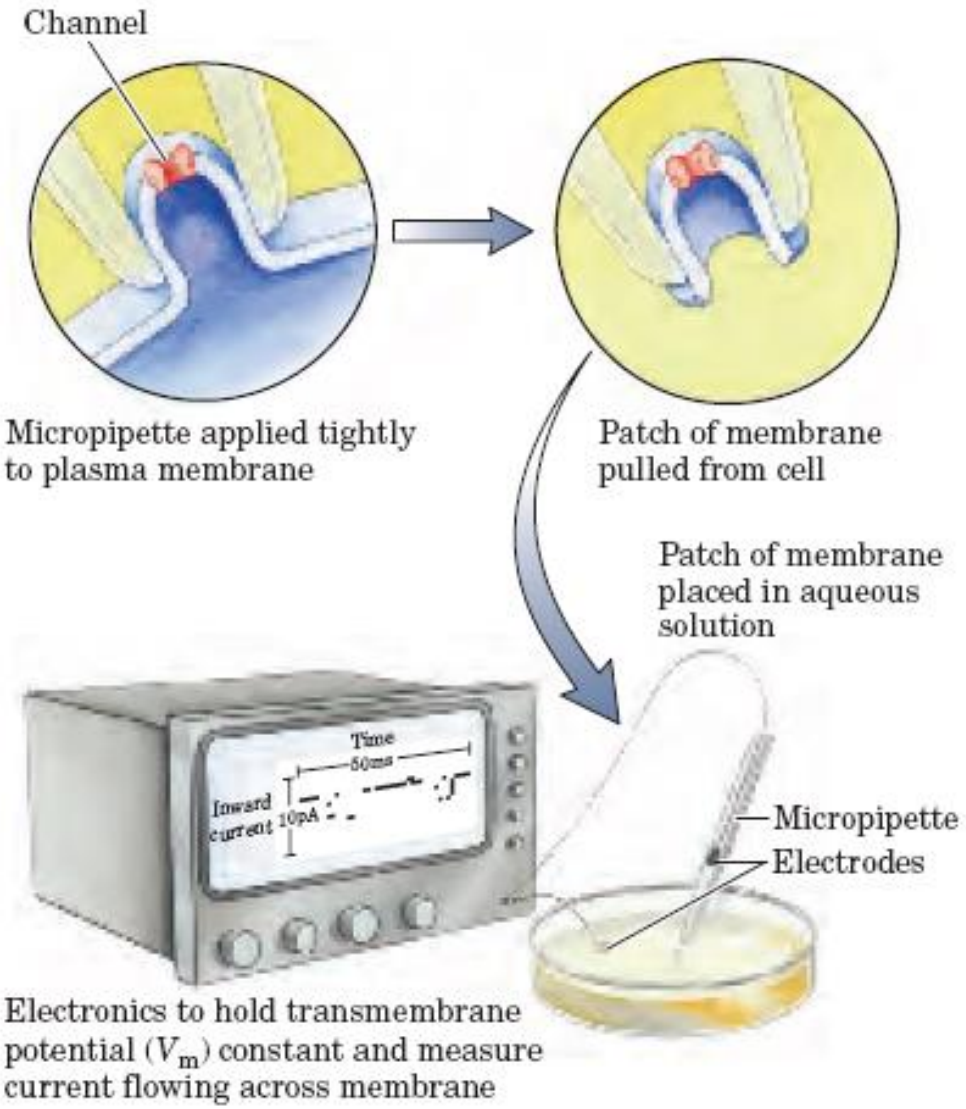
IV. A acetilcolina é inativada pela acetilcolinesterase.

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



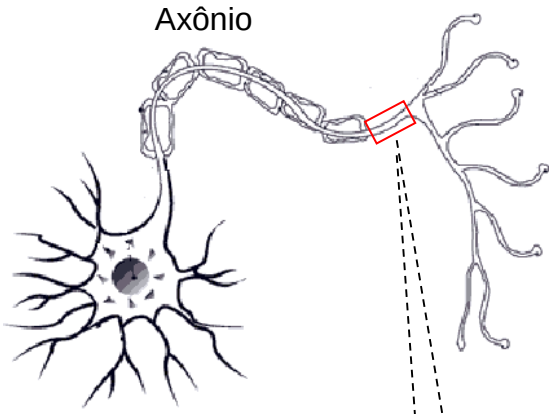
Erwin Neher

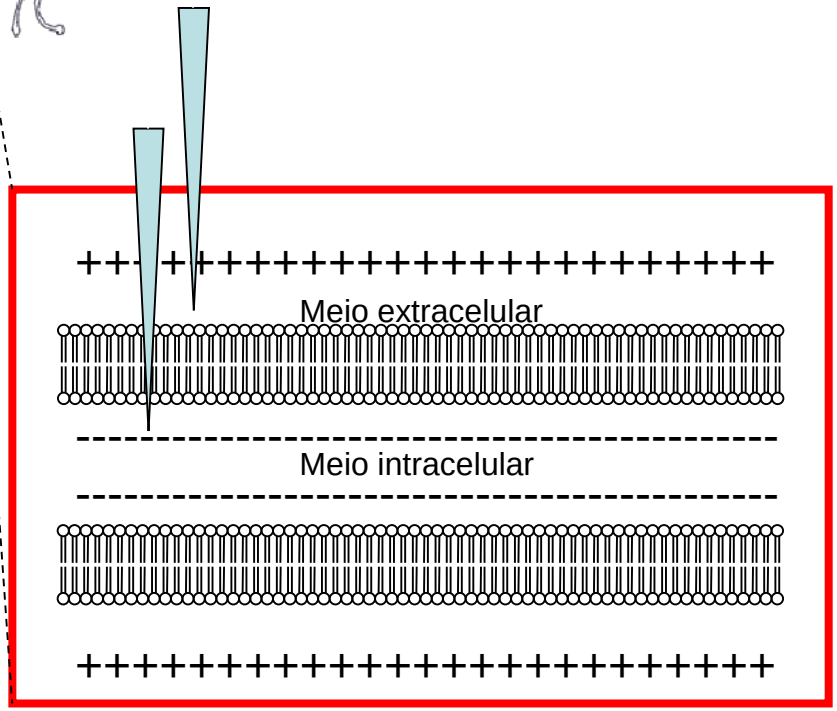
Bert Sakmann



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

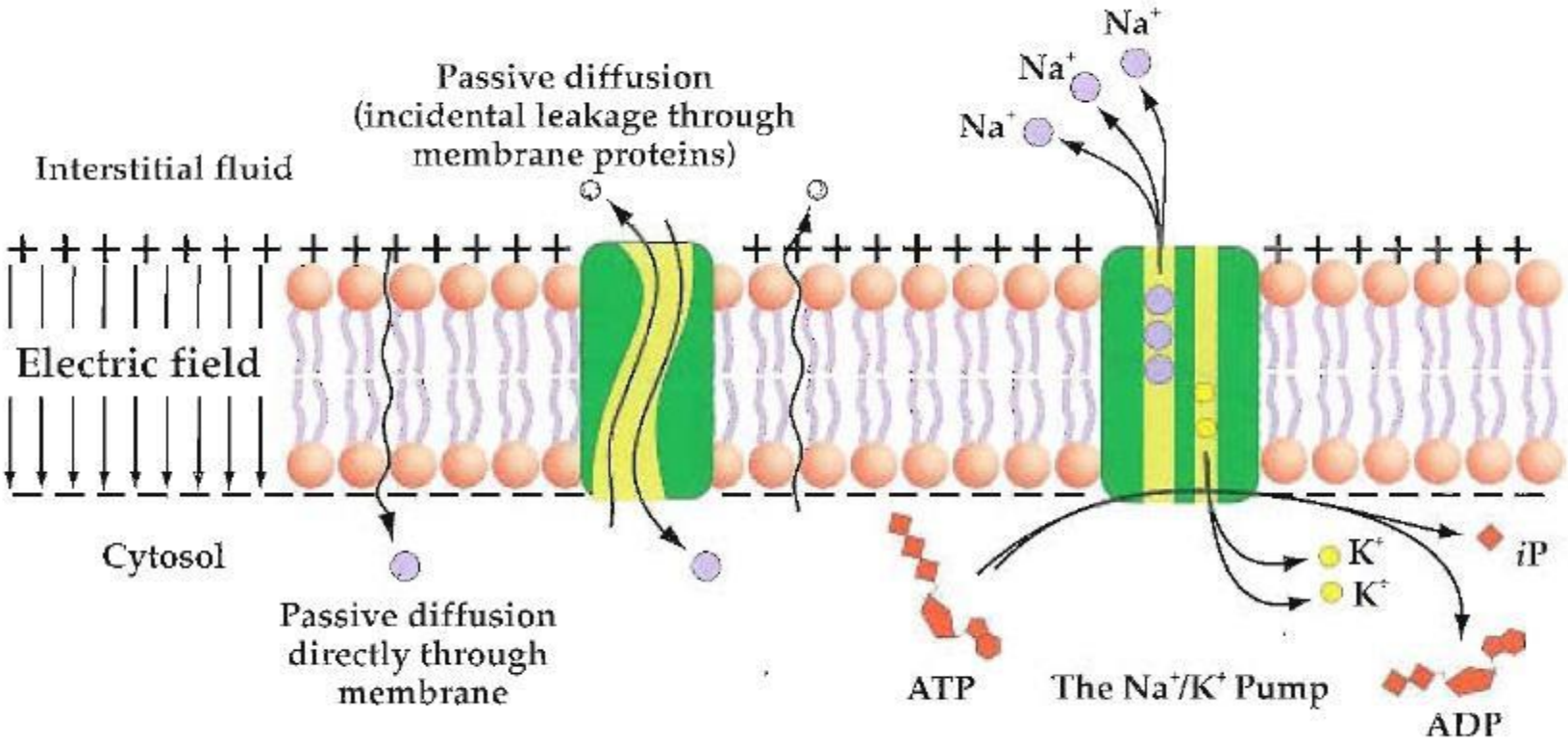
Método para Medir o Potencial de Repouso





Dois eletrodos, inseridos no axônio de um neurônio em repouso, detectam a pequena diferença de potencial, entre os meios extra e intra celular, esse sinal é amplificado e mostrado num osciloscópio.

Em repouso


Na+
Na+
Na+
Passive diffusion
(incidental leakage through
membrane proteins)
Interstitial fluid
Electric field
Cytosol
Passive diffusion
directly through
membrane
ATP
The Na+/K+ Pump
K+
K+
iP
ADP

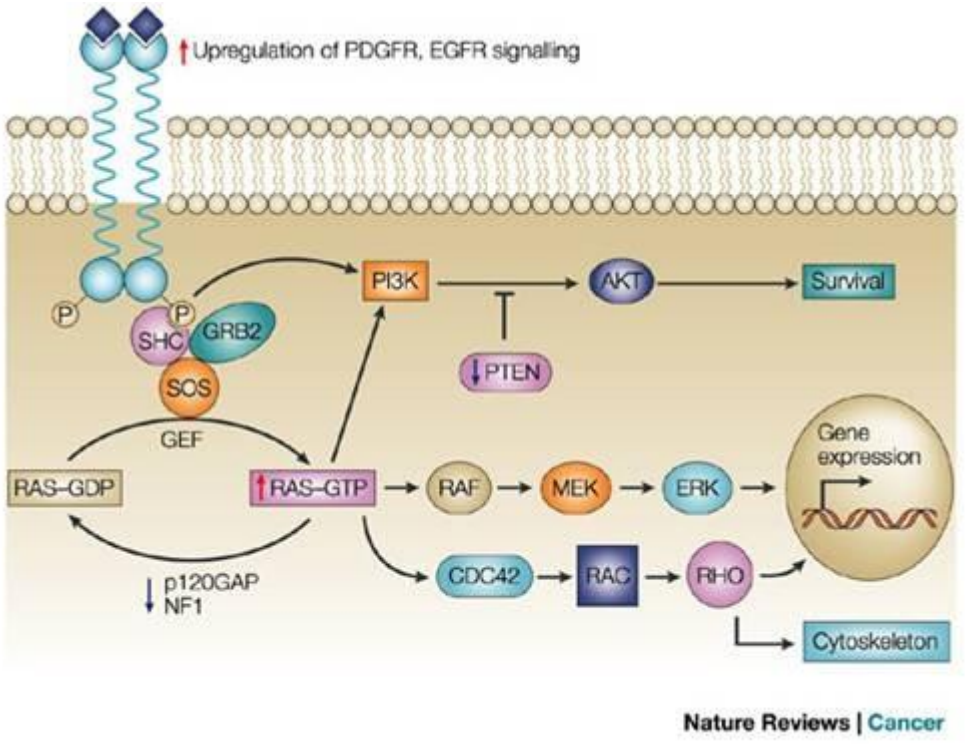
Potencial de ação

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.

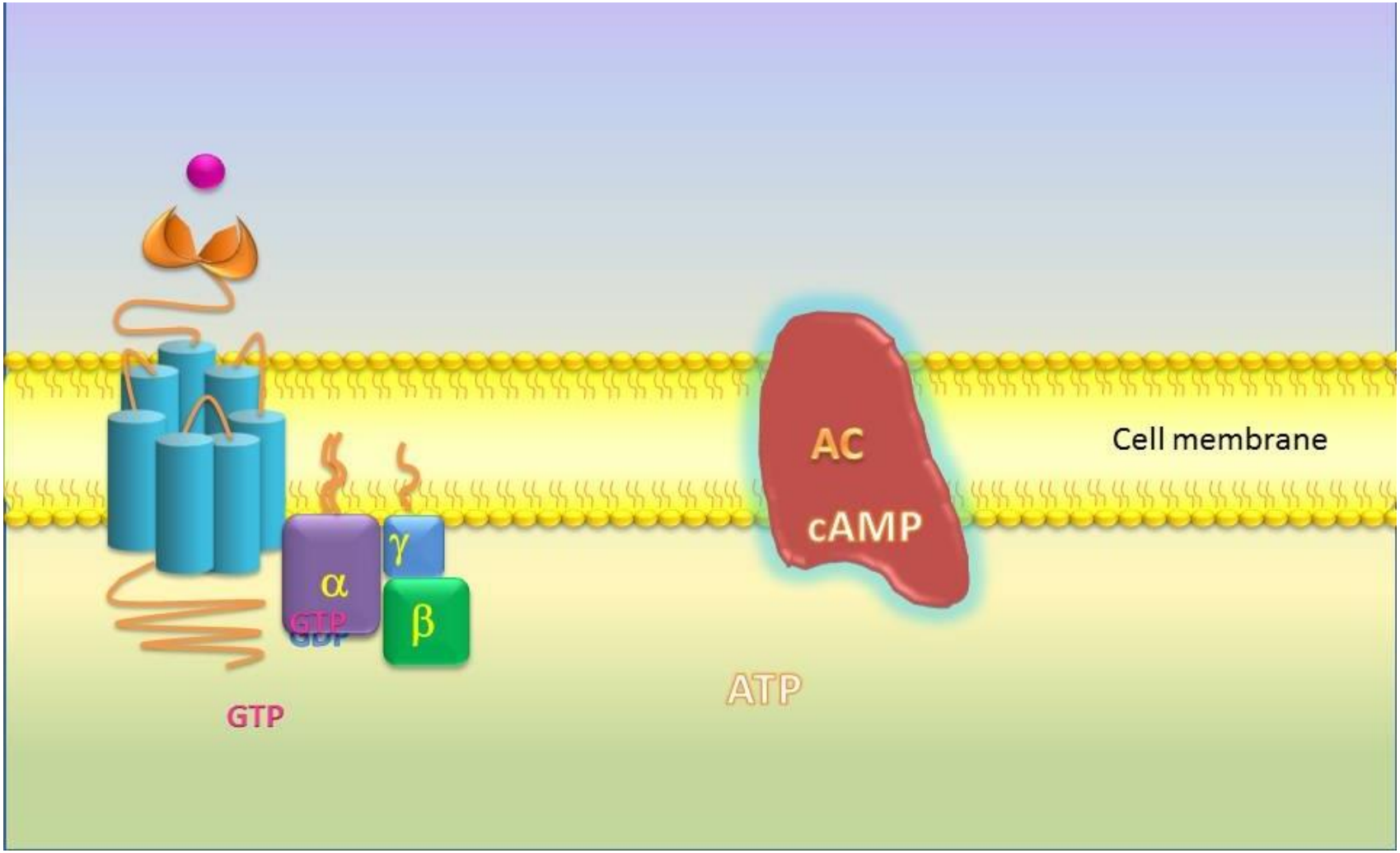
Utilizados mais intensamente pelo sistema nervoso, para comunicação entre neurônios e para transmitir informação dos neurônios para outro tecido do organismo, como os músculos ou as glândulas.

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

Receptores de fatores de crescimento



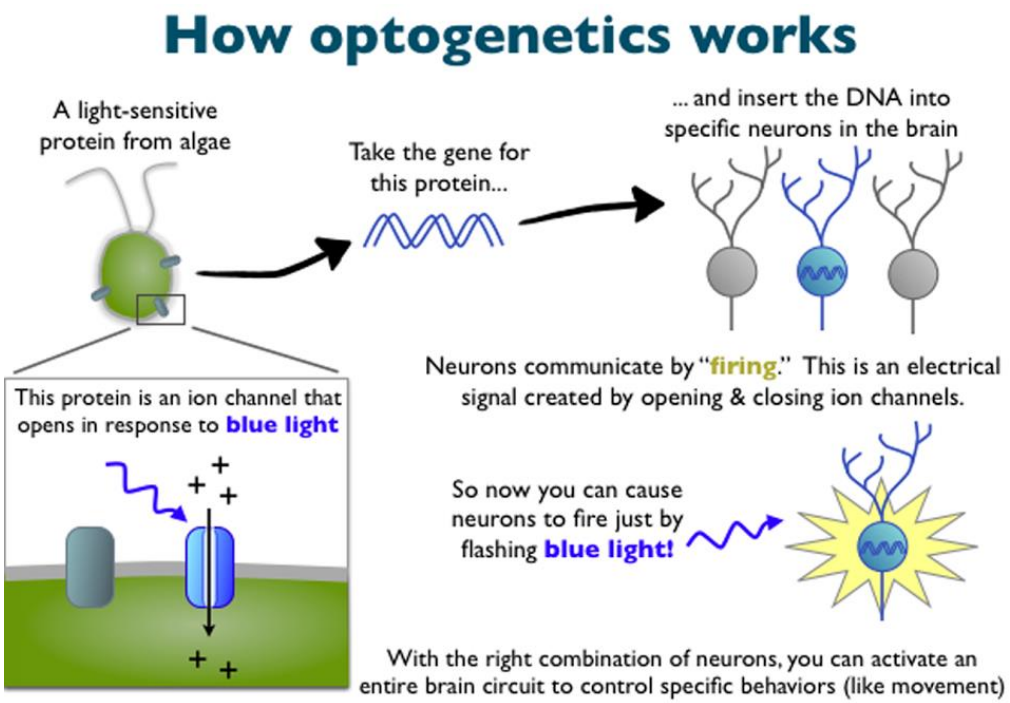
Receptores acoplados a proteína G

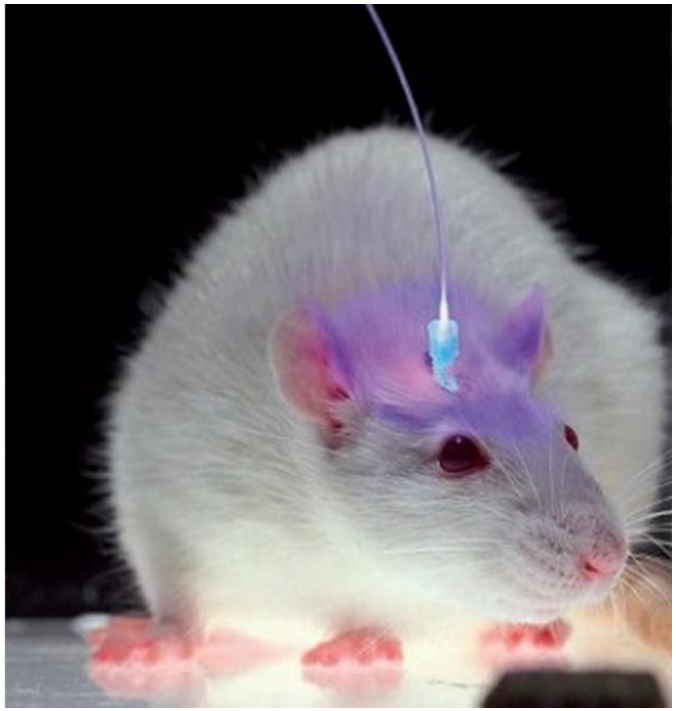


Disorders

Some disease resulting from or attributed to abnormalities of Membranes

Disease	Abnormality
Achondroplasia (MIM 100800)	Mutations in the gene encoding the fibroblast growth factor receptor 3
Familial hypercholesterolemia (MIM 143890)	Mutations in the gene encoding the LDL receptor
Cystic fibrosis (MIM 219700)	Mutations in the gene encoding the CFTR protein, a Cl^- transporter
Congenital long QT syndrome (MIM 192500)	Mutations in genes encoding ion channels in the heart
Wilson disease (MIM 277900)	Mutations in the gene encoding a copper-dependent ATPase
I-cell disease (MIM 252500)	Mutations in the gene encoding GlcNAc phosphotransferase, resulting in absence of the Man 6-P signal for lysosomal localization of certain hydrolases
Hereditary spherocytosis (MIM 182900)	Mutations in the genes encoding spectrin or other structural proteins in the red cell membrane
Metastasis	Abnormalities in the oligosaccharide chains of membrane glycoproteins and glycolipids are thought to be of importance
Paroxysmal nocturnal hemoglobinuria (MIM 311770)	Mutation resulting in deficient attachment of the GPI anchor to certain proteins of the red cell membrane





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