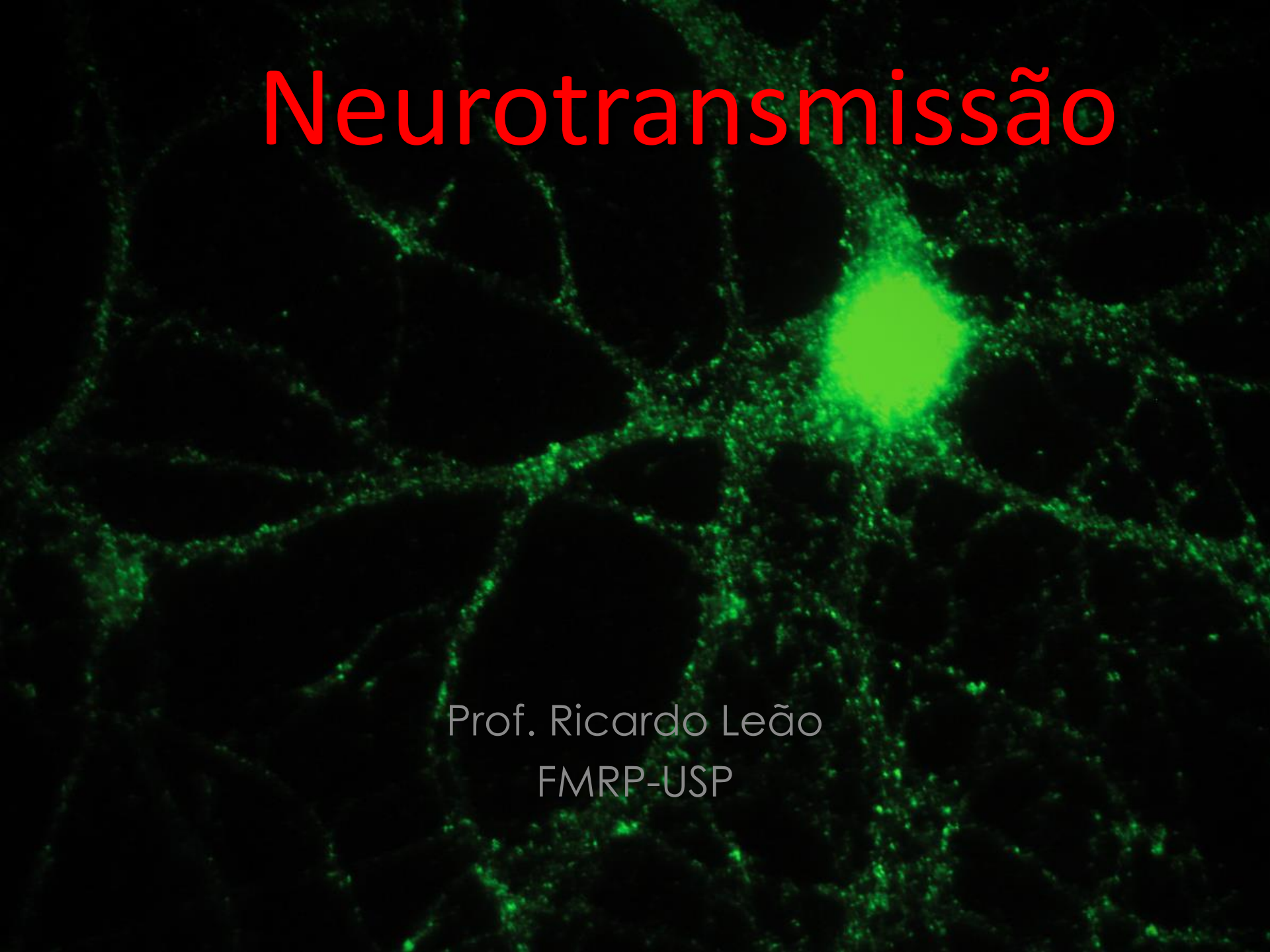
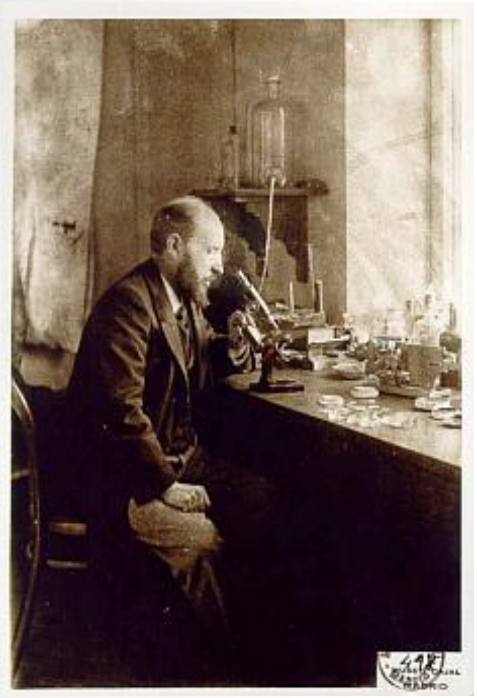
Neurotransmissão

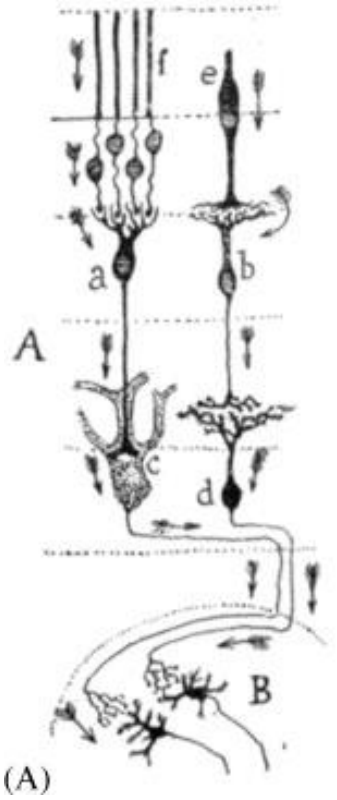


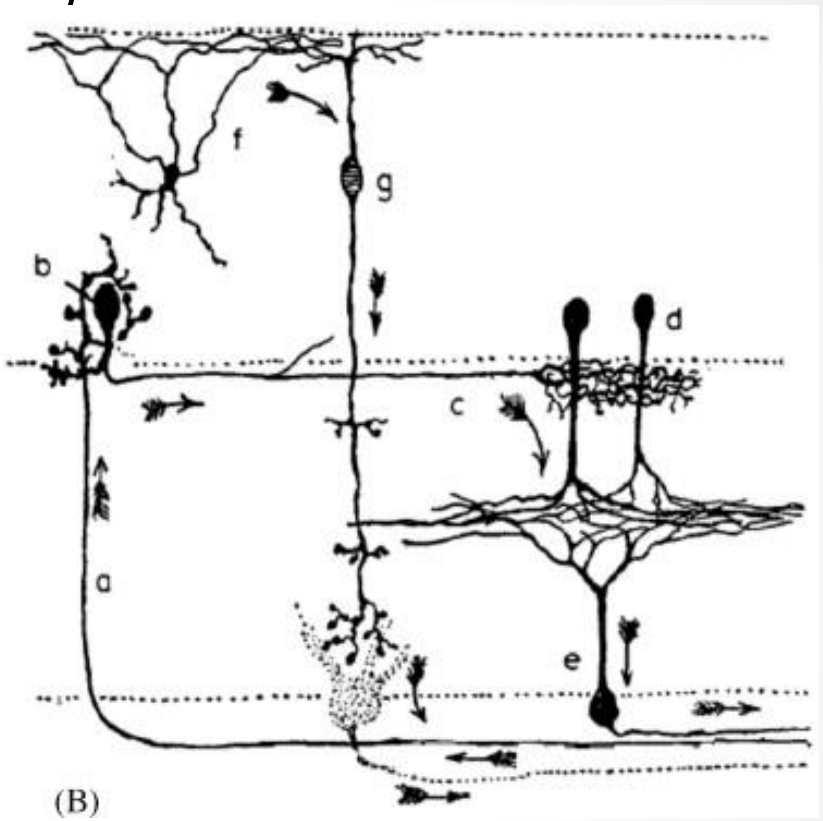
Prof. Ricardo Leão
FMRP-USP

Neurônios são células especializadas em se comunicarem com outras células

Santiago de Ramon y Cajal, o pai da doutrina neuronal



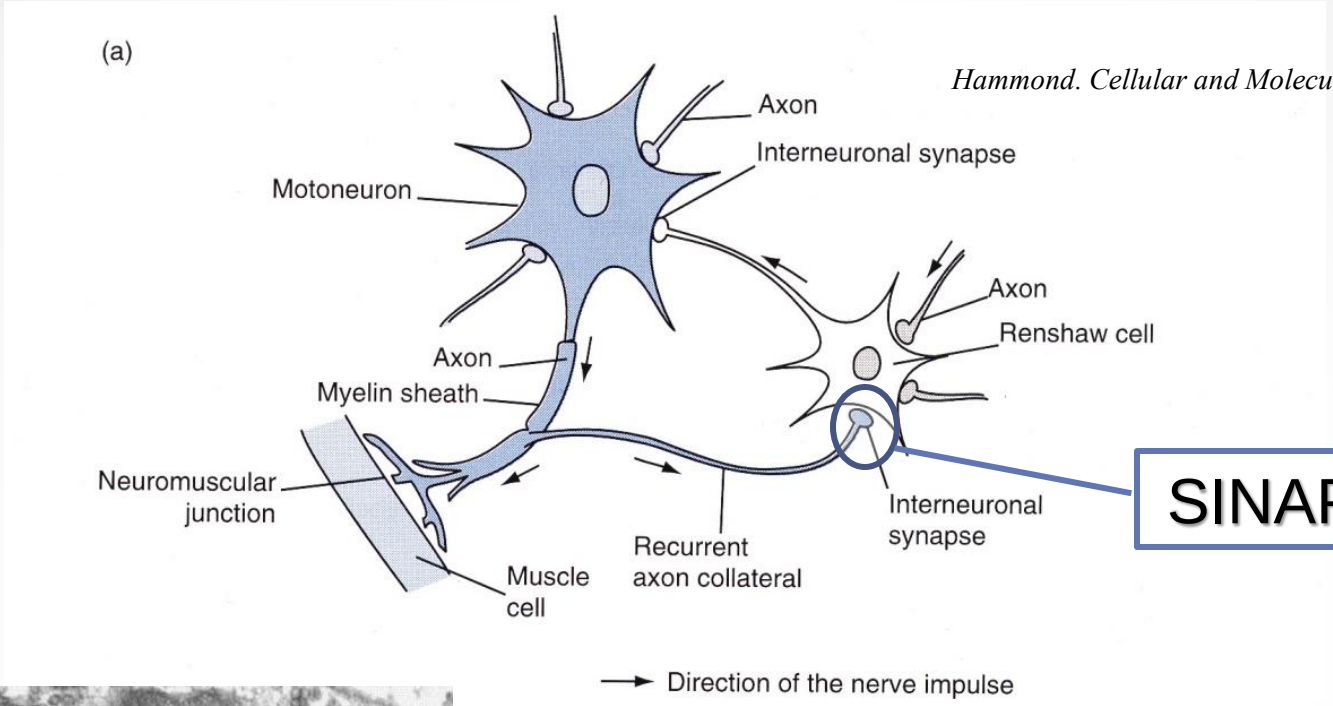




Lei da polarização dinâmica

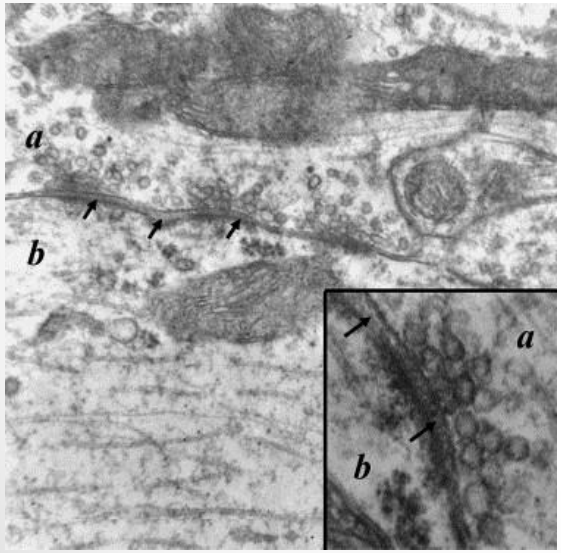
"*The facts remain and theories pass away*"
Santiago Ramón y Cajal, (1852–1934)

O fluxo de informação neuronal é dos dendritos para os terminais dos axônios

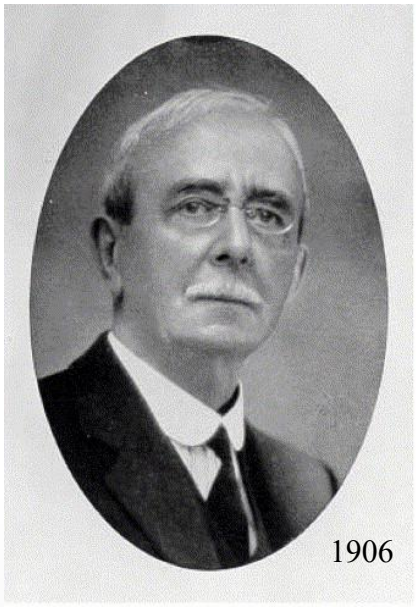


Hammond. Cellular and Molecular Neurophysiology.

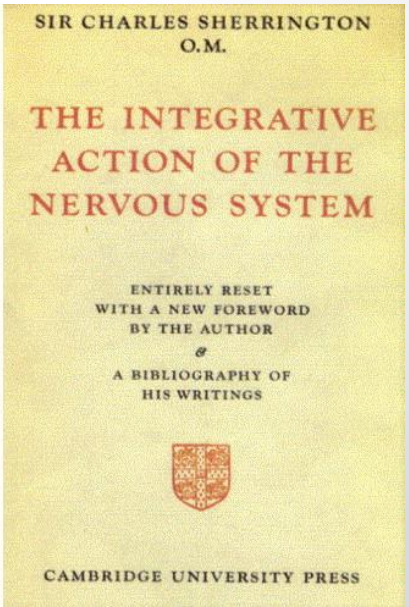
SINAPSE



- 1954 G. Palade, S. Palay



1906

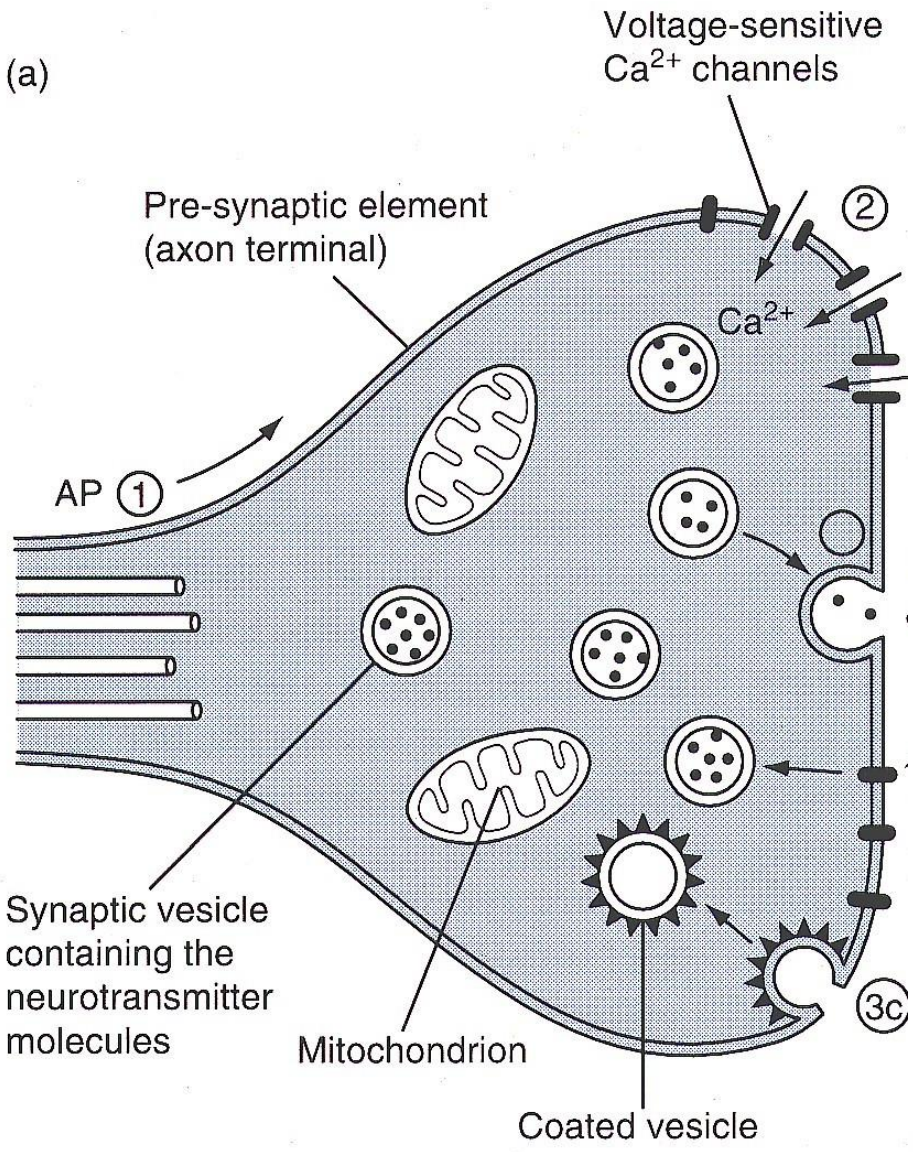


O que é a sinapse?

- **A estrutura responsável pela comunicação entre o neurônio e a sua célula alvo.**
- **É a estrutura mínima do sistema nervoso**
- **É composta de elementos de elementos de duas células:**
  - **pré-sináptico**
  - **pós-sináptico**

A Sinapse química

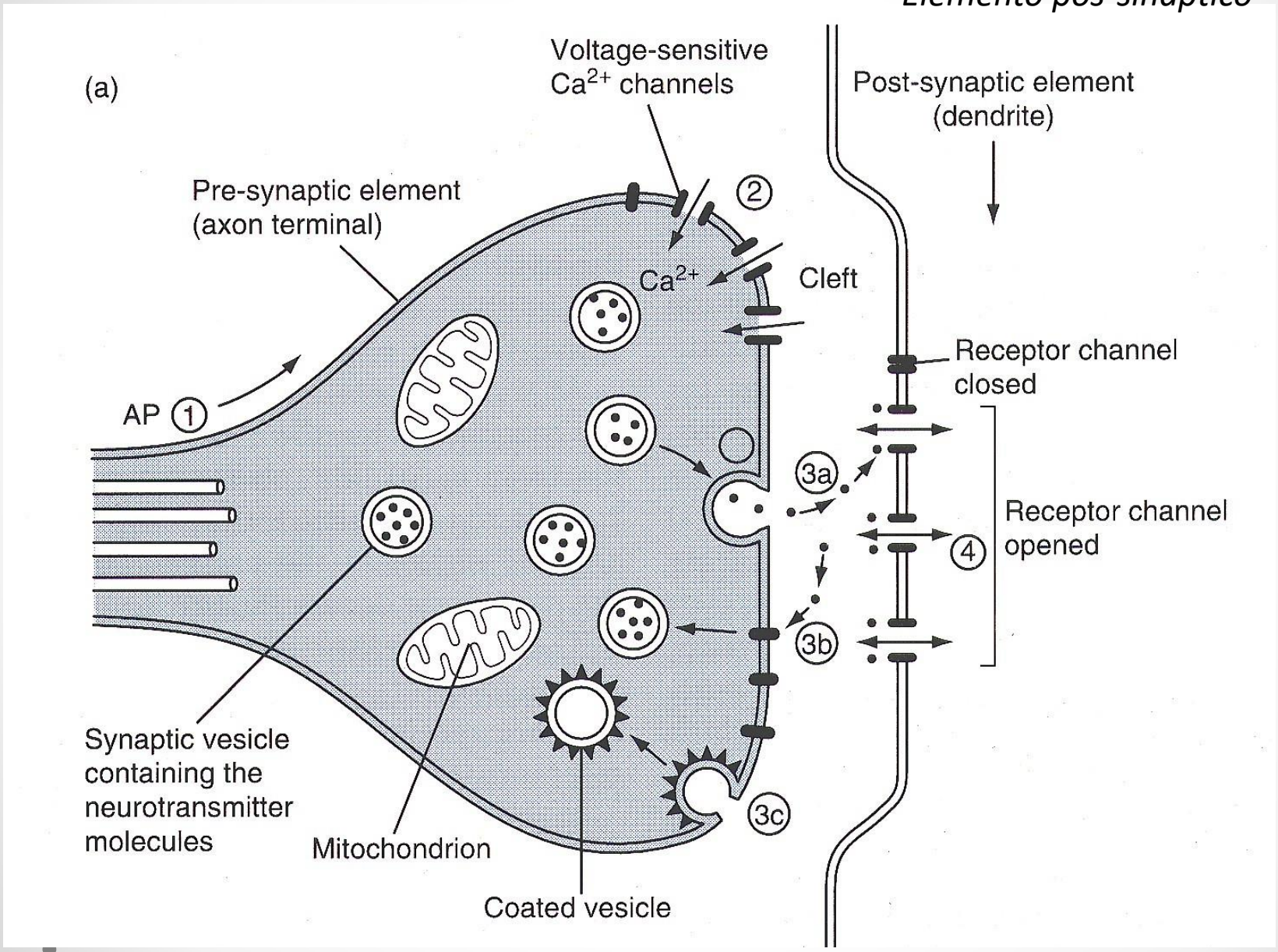
Elemento pré-sináptico



Hammond. Cellular and Molecular Neurophysiology.

A Sinapse química

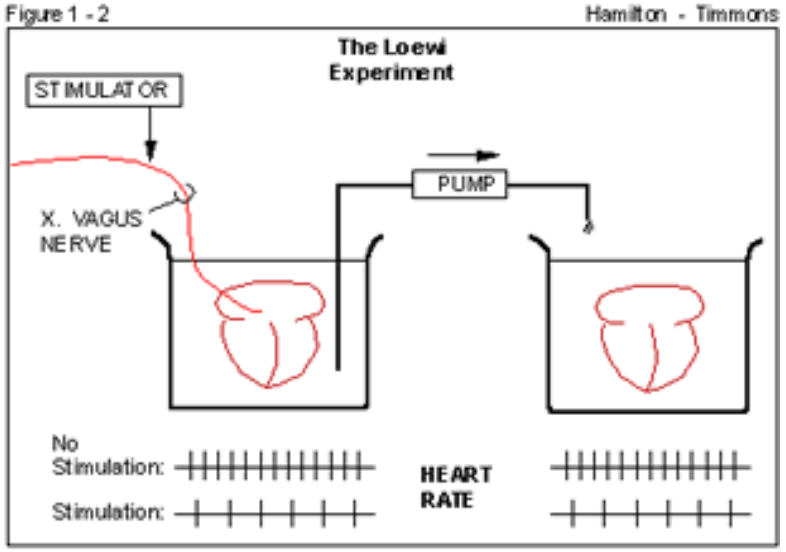
Elemento pós-sináptico



Hammond. Cellular and Molecular Neurophysiology.

A sinapse química usa um mediador químico: o **neurotransmissor**

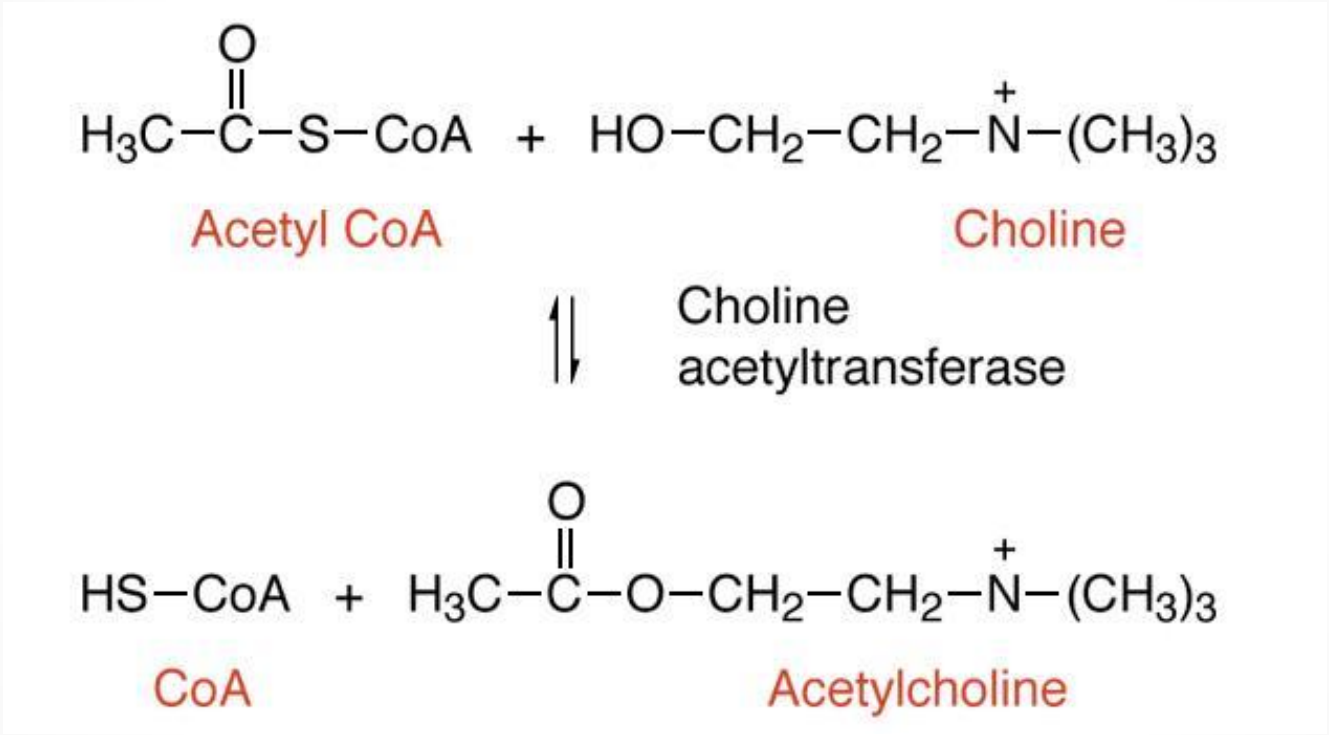
Otto Loewi, 1921

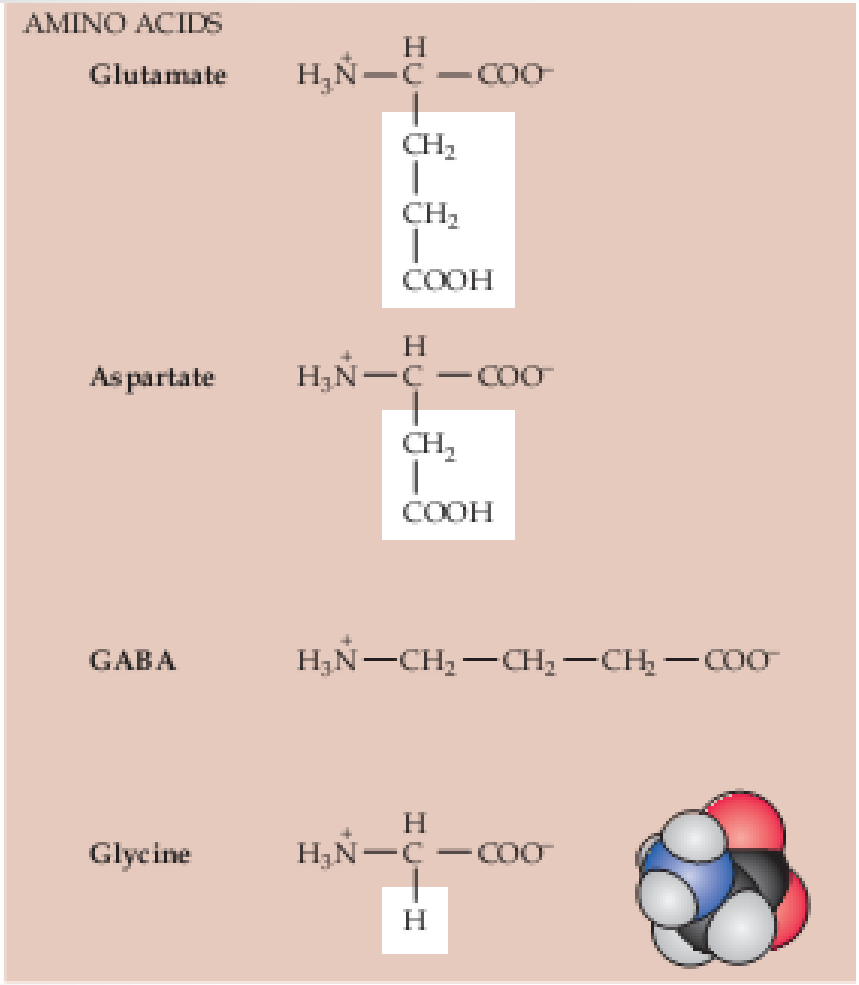


- Vagusstoff = **acetilcolina**

Neurônios **colinéricos** = sintetizam e secretam acetilcolina

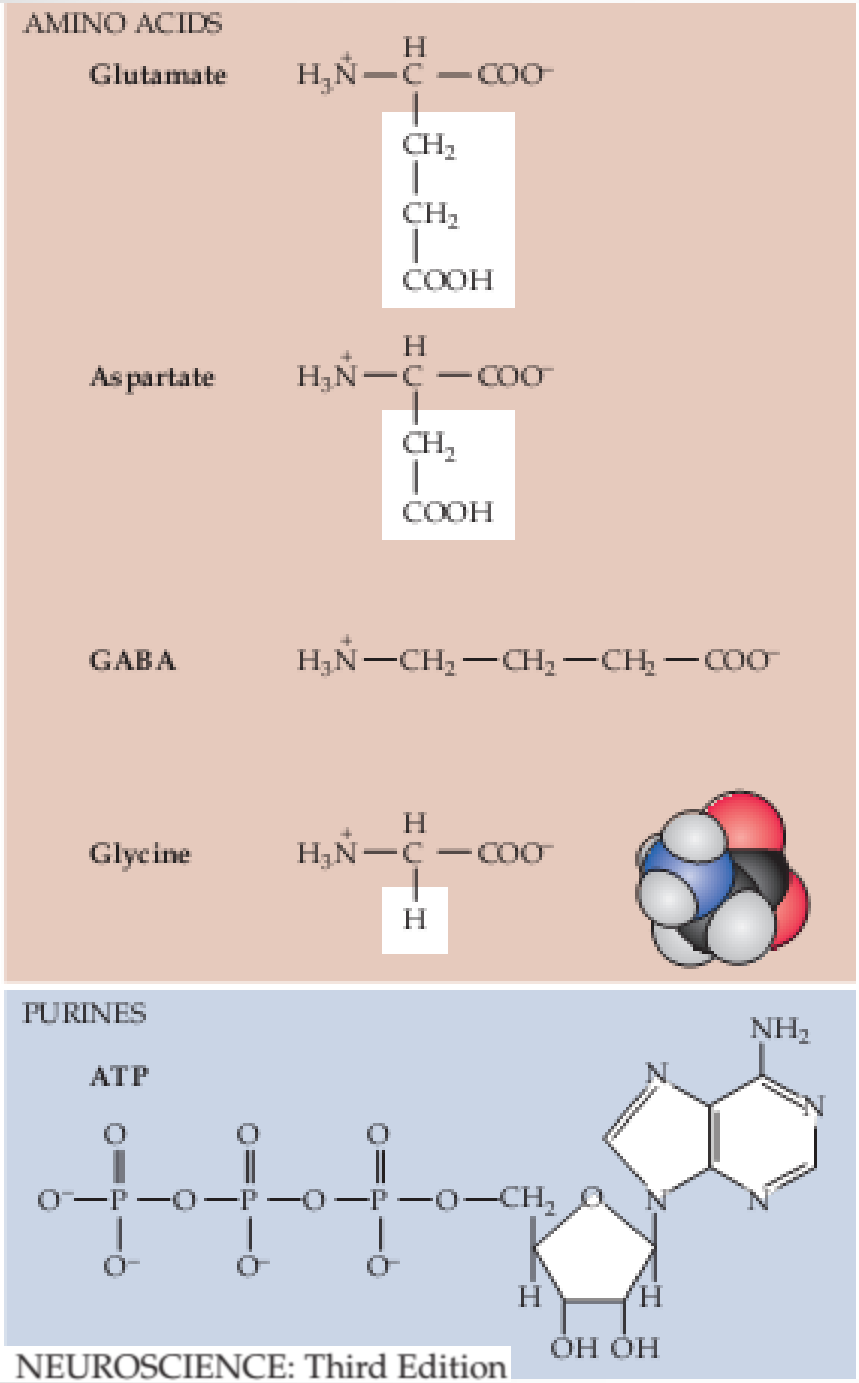
-Motoneuronios da Junção neuromuscular (mamiferos)
-Efetor parassimpático
-Neurônios específicos do SNC





excitatórios

inibitórios

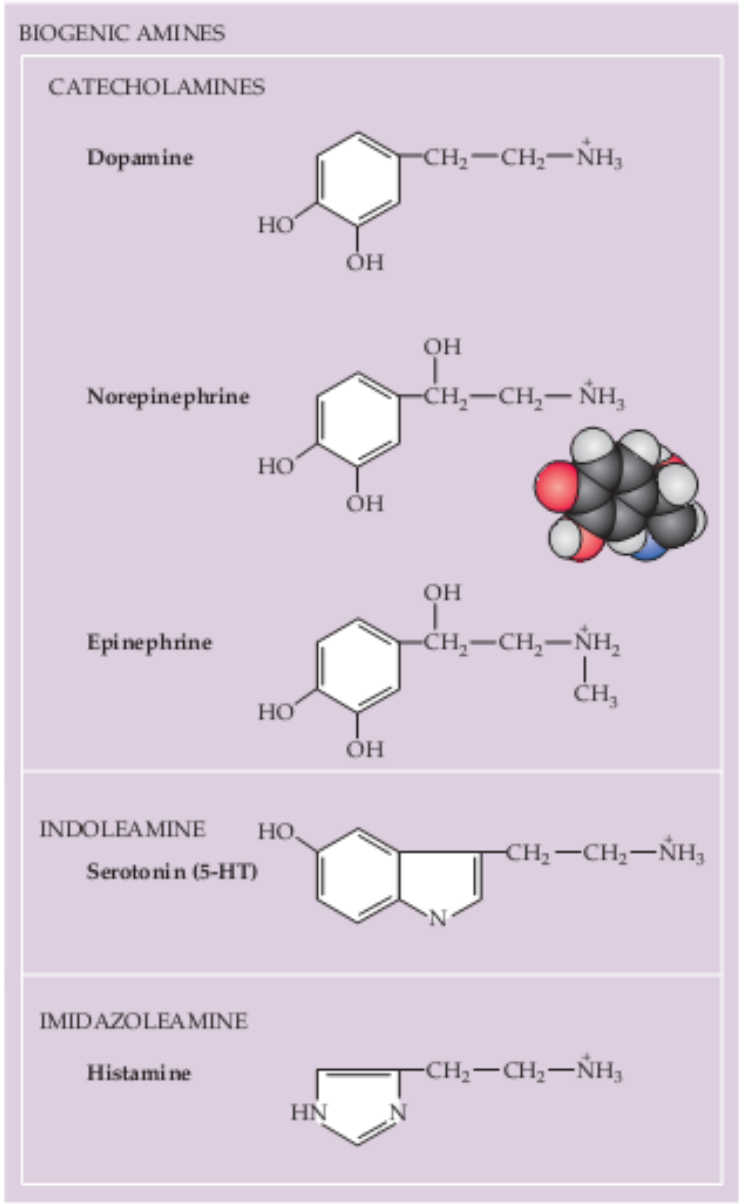


excitatórios

inibitórios

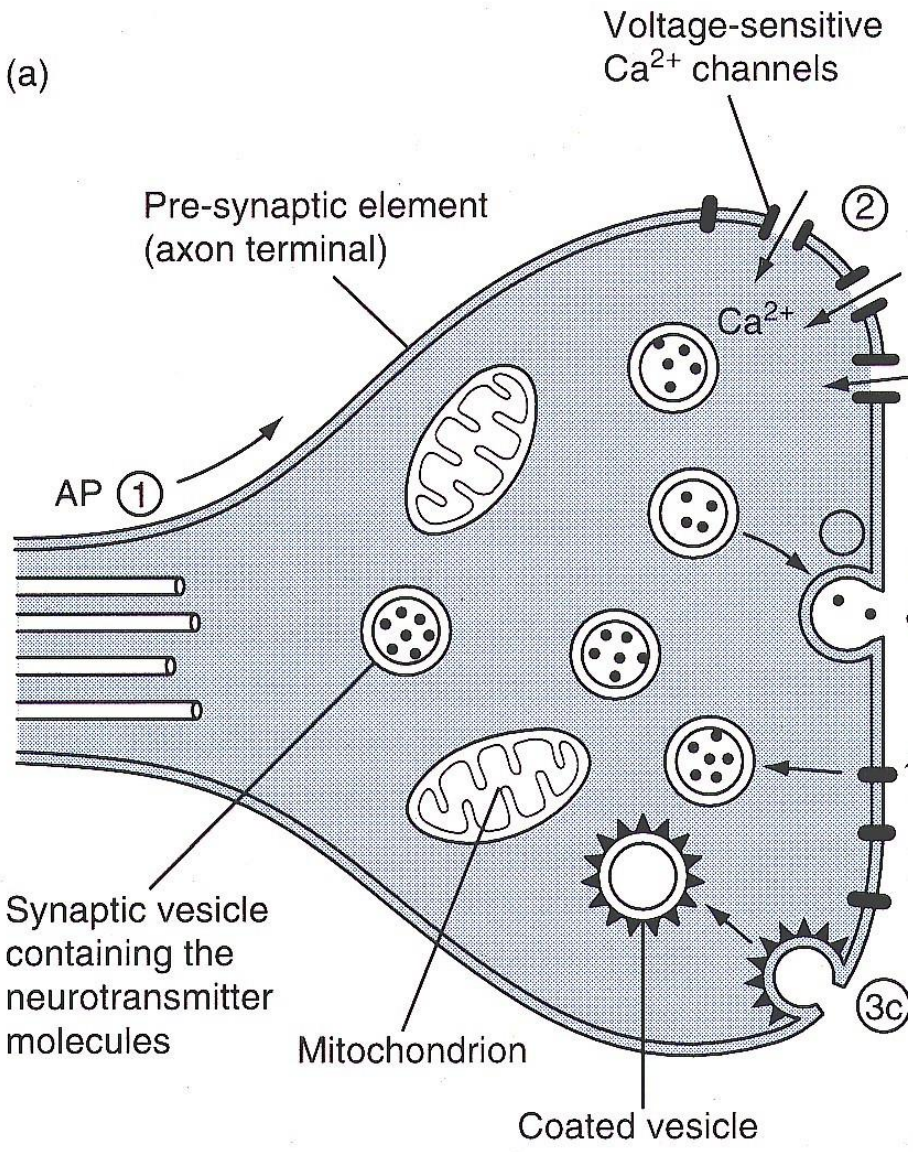
excitatório

Neurotransmisores “lentos” - ativam receptores ligados a proteínas G.
Efeitos modulatórios diversos da atividade neuronal



NEUROSCIENCE: Third Edition

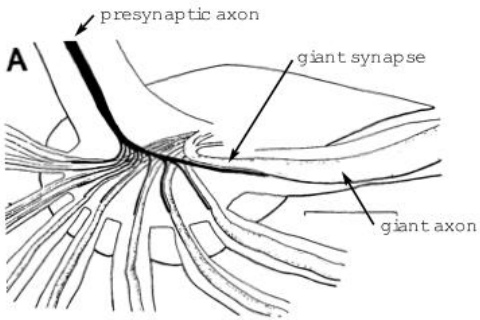
Fenômenos pré-sinápticos

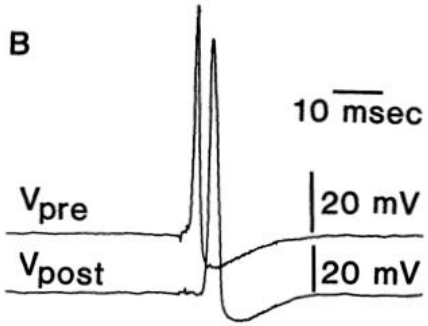


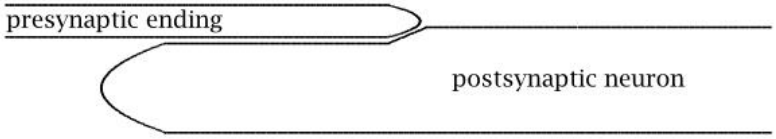
Hammond. Cellular and Molecular Neurophysiology.

A neurotransmissão é totalmente dependente da entrada de cálcio no terminal pré-sináptico por canais de cálcio dependentes de potencial.

Sinapse gigante da lula (gânglio estrelado) – década de 70/80



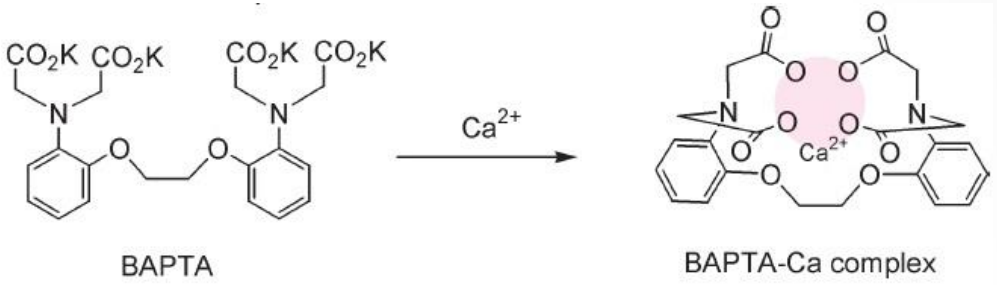


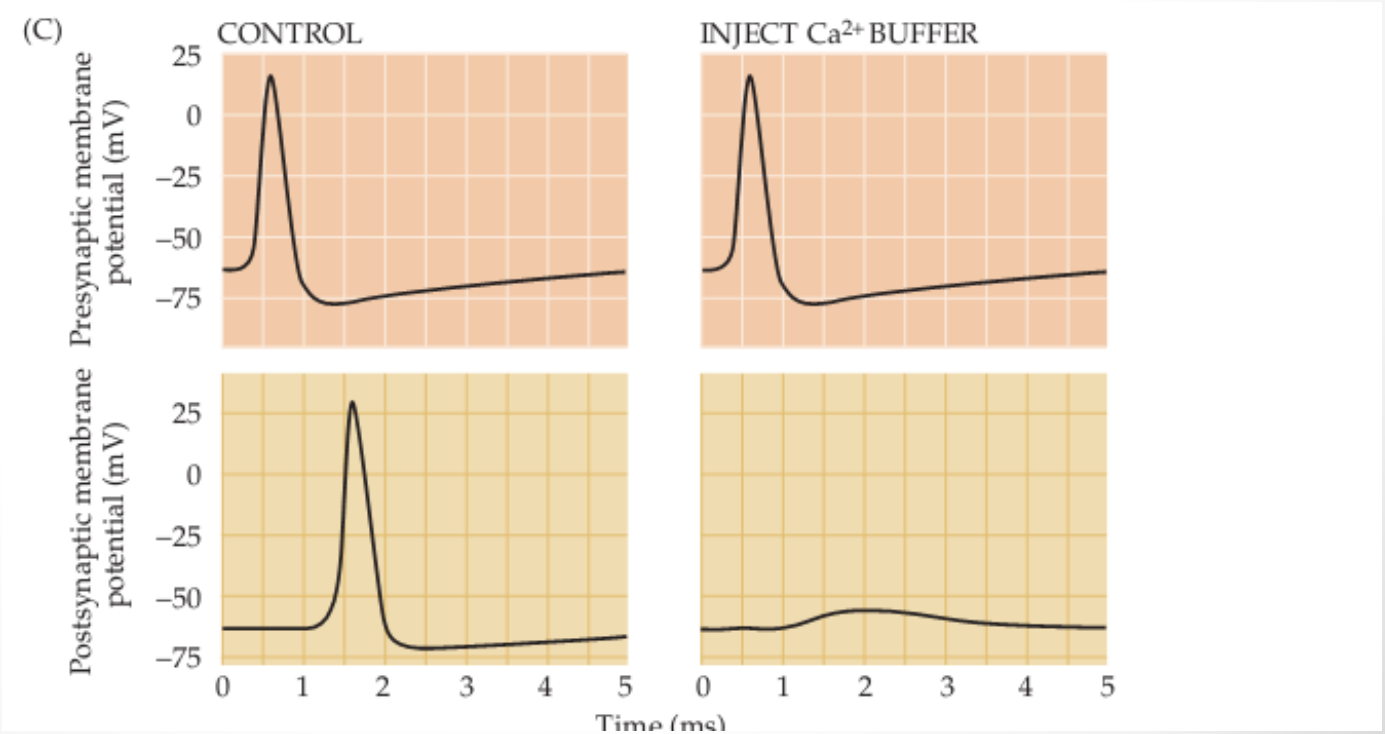


RODOLFO LLINÁS, IZCHAK Z. STEINBERG*, AND KERRY WALTON

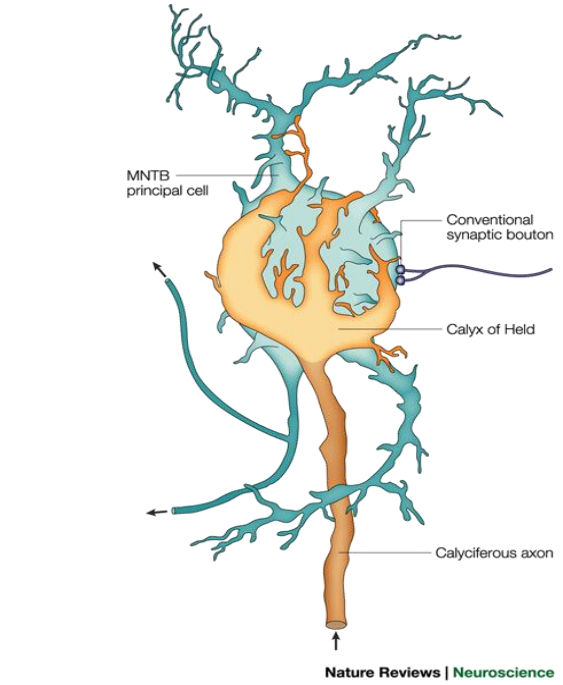
Division of Neurobiology, University of Iowa, Oakdale Iowa 52319, and Neurosciences Research Program, Massachusetts Institute of Technology, Boston, Mass. 02130

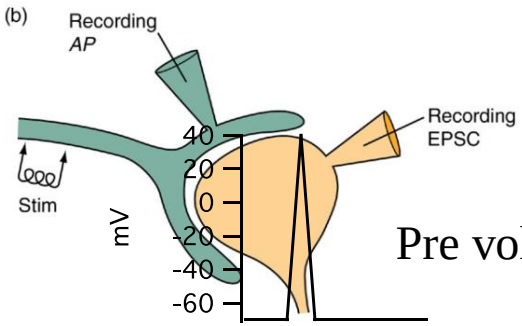
A neurotransmissão é dependente do cálcio

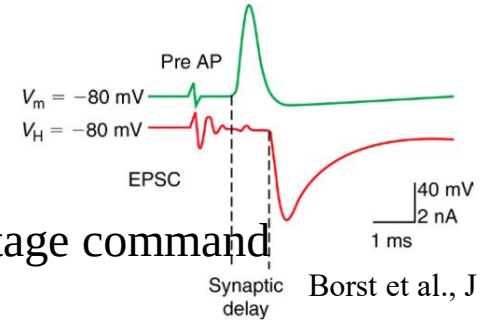




Registros duplos pré e pós-sinápticos na sinapse gigante "cálice de Held" (década de 90/2000)

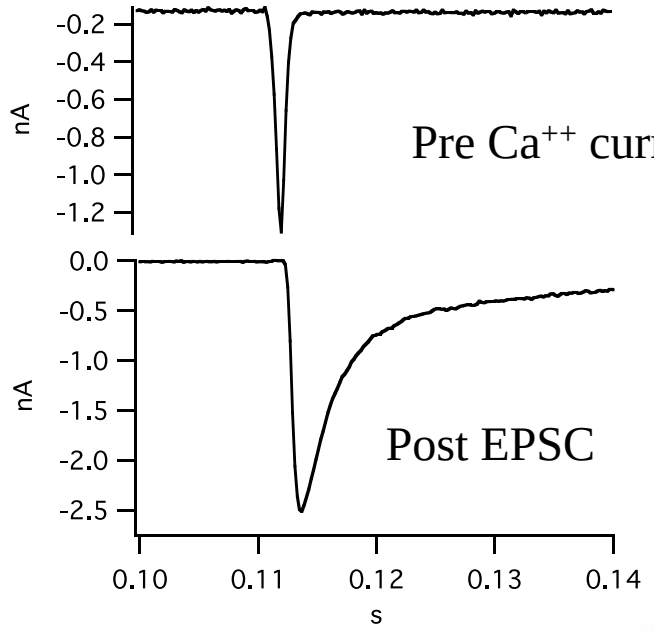






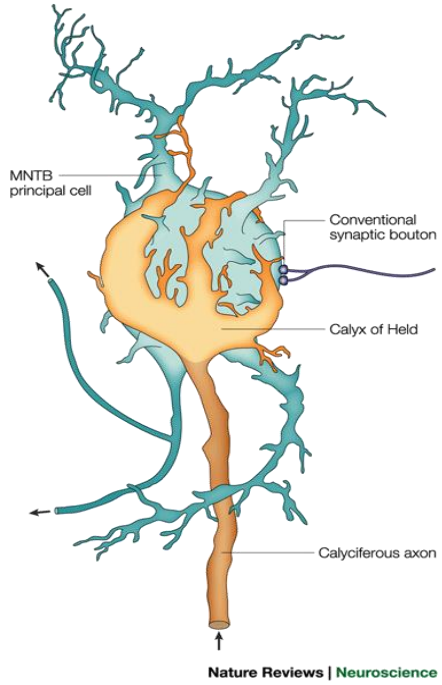
Pre voltage command

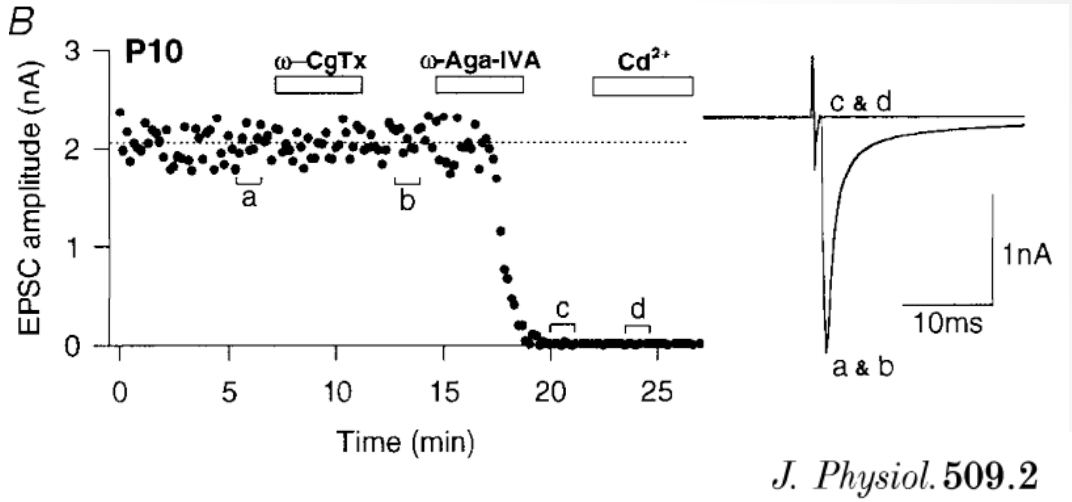
Borst et al., J Physiol. 1995



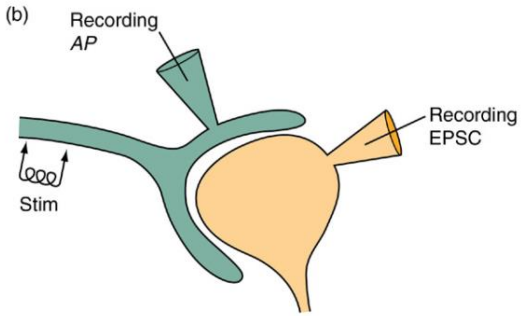
CANAIS DE SÓDIO E POTÁSSIO BLOQUEADOS
Registro pessoal

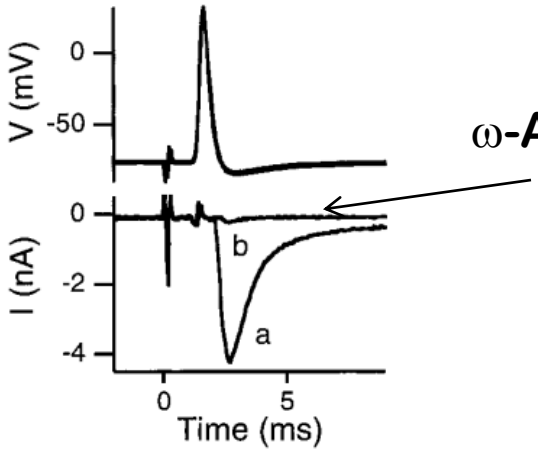
Inibição da neurotransmissão pelo bloqueio farmacológico dos canais de cálcio pré-sinápticos com ω-tonxinas





J. Physiol. **509.2**

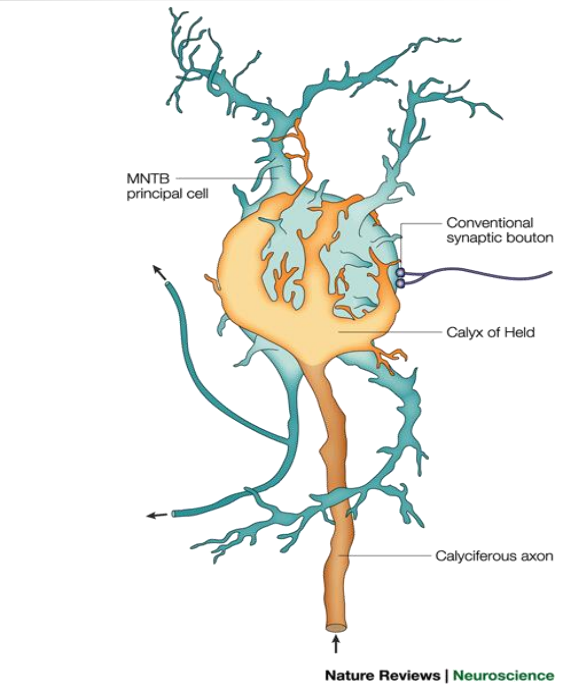


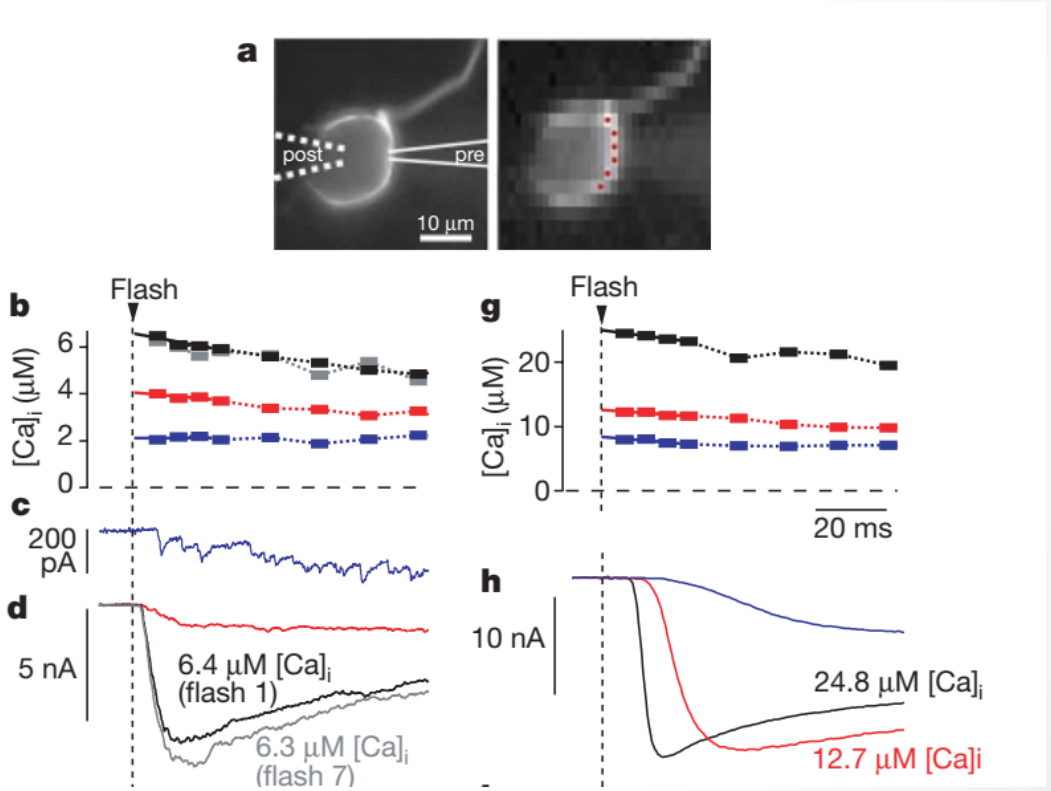


ω-Aga-IVA

J. Neurosci., January 15, 1999, *19*(2):726–736

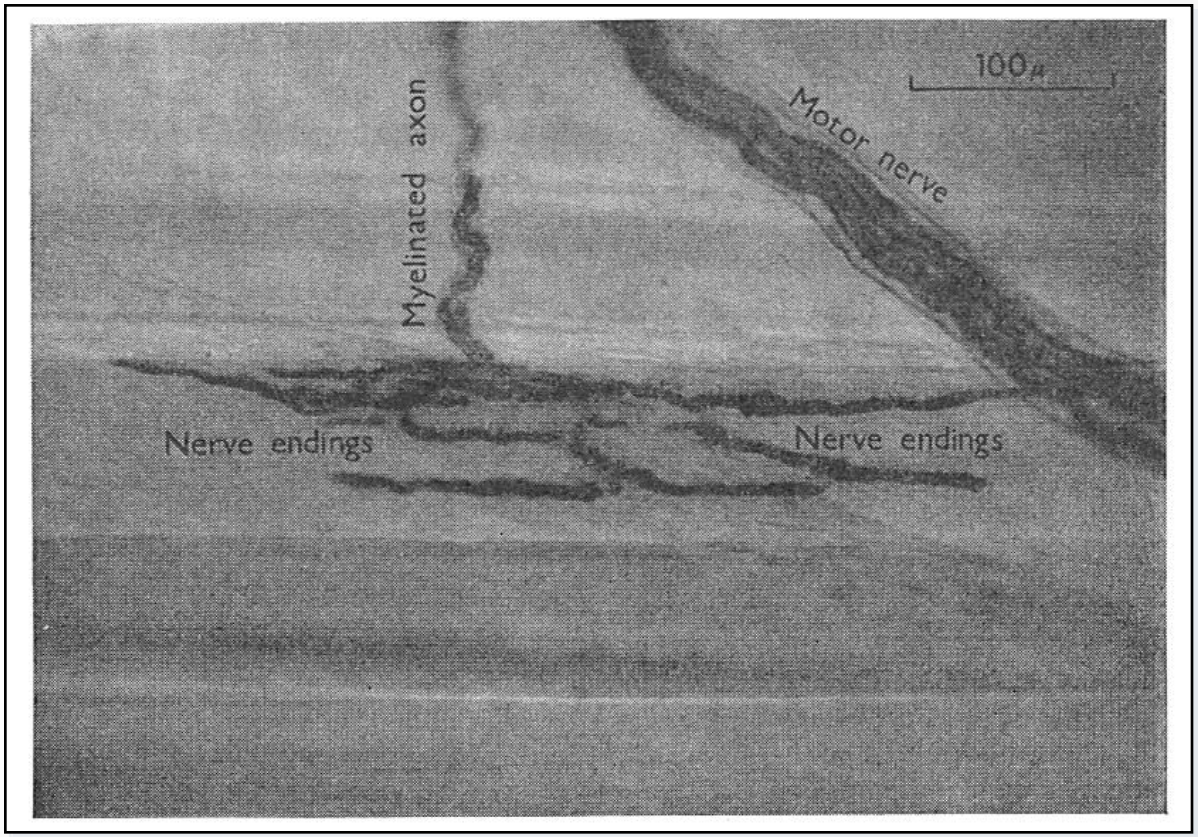
Aumento do cálcio intrasináptico por fotólise de cálcio "caged" estimula a liberação de neurotransmissores





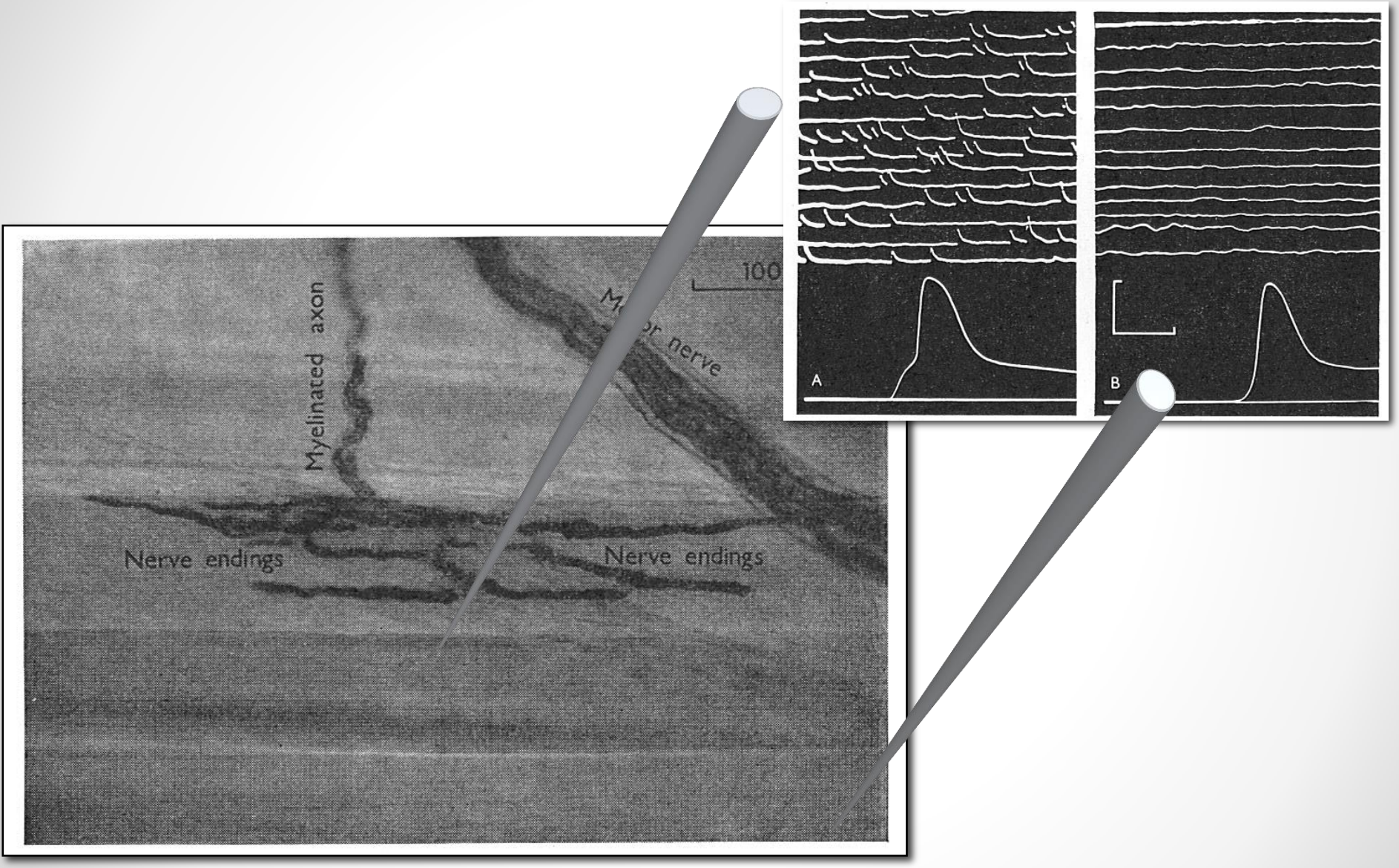
NATURE | VOL 406 | 24 AUGUST 2000 | www.nature.com

Bernard Katz e a neurotransmissão na junção neuromuscular da rã (1952)



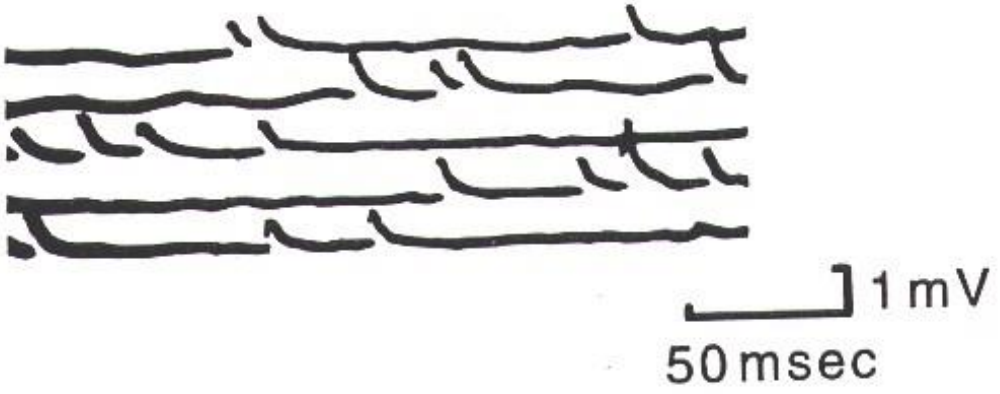
Katz, The release of neural transmitter substances, 1969.

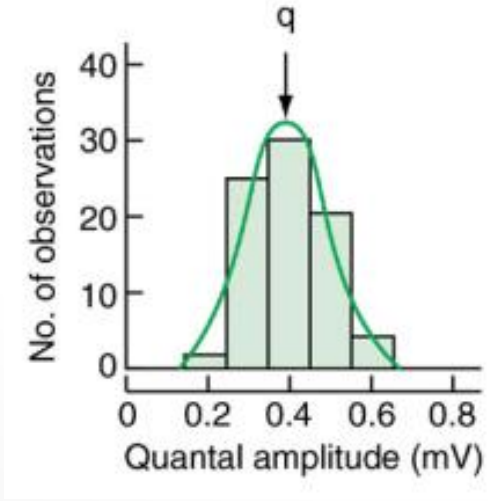
Bernard Katz e a neurotransmissão na junção neuromuscular da rã



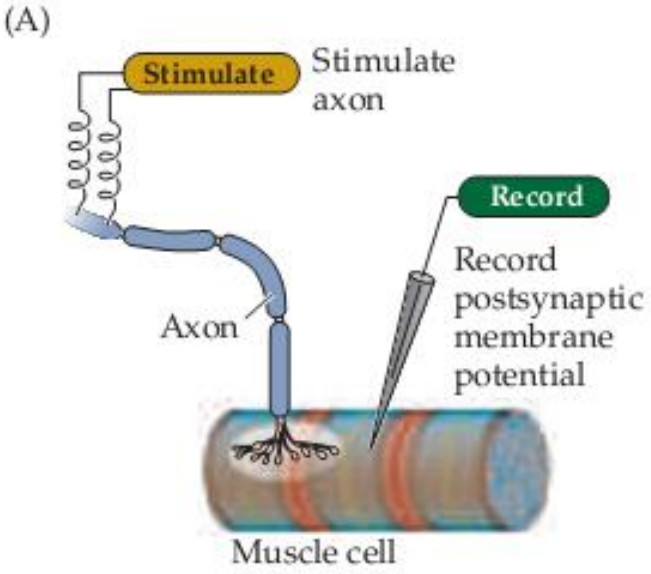
Katz, The release of neural transmitter substances, 1969.

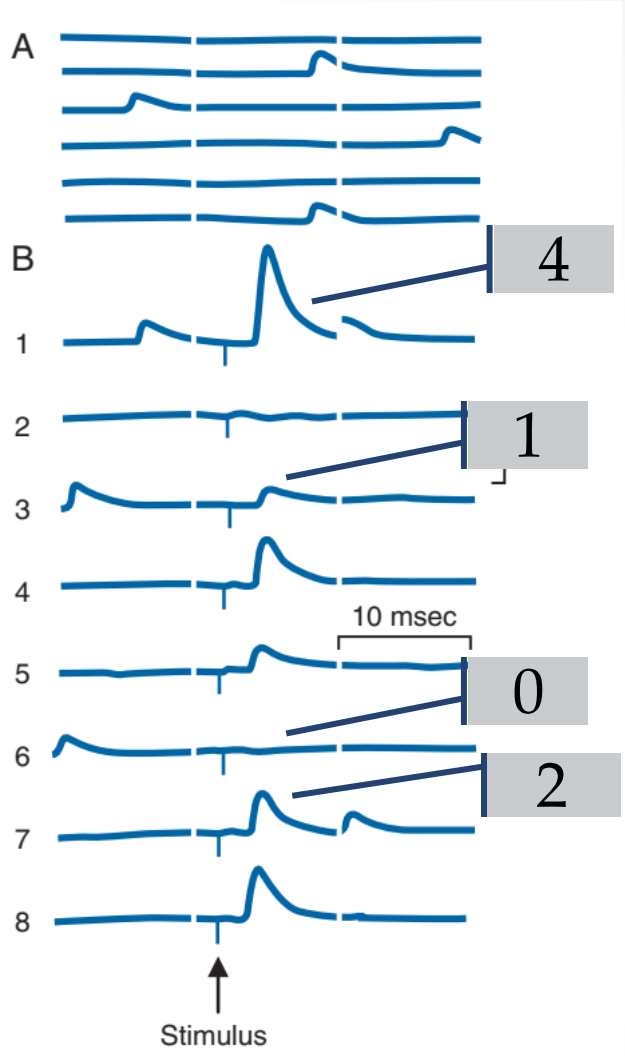
eventos miniatura = eventos sinápticos espontâneos





Katz, The release of neural transmitter substances, 1969.

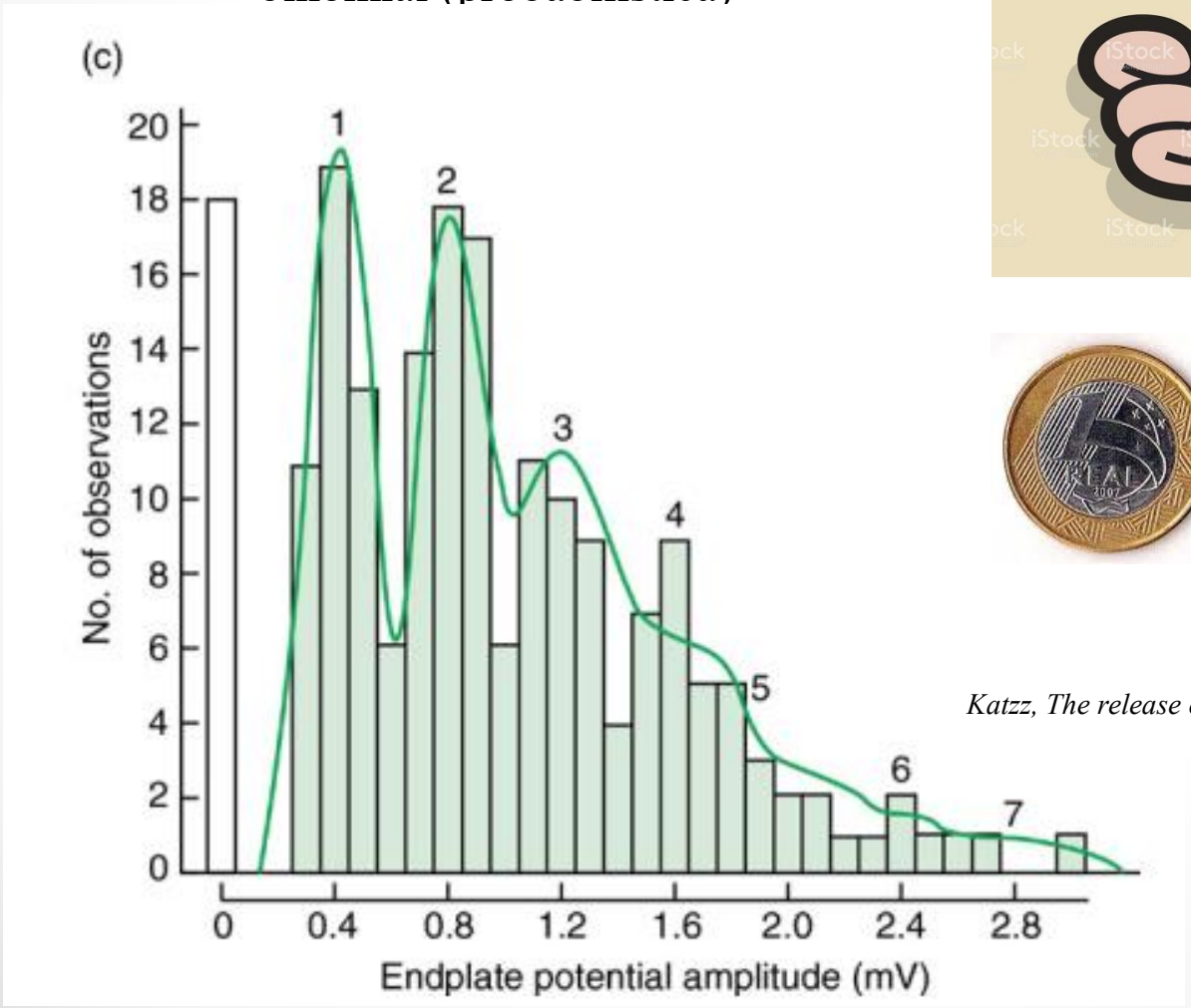




Estímulo em 0,2 Ca^{++} e 3 Mg^{++}

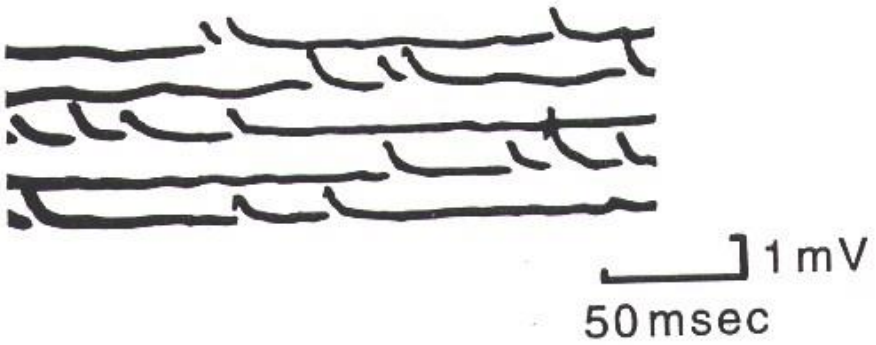
A natureza probabilística da neurotransmissão

A distribuição de amplitudes segue uma distribuição binomial (probabilística)

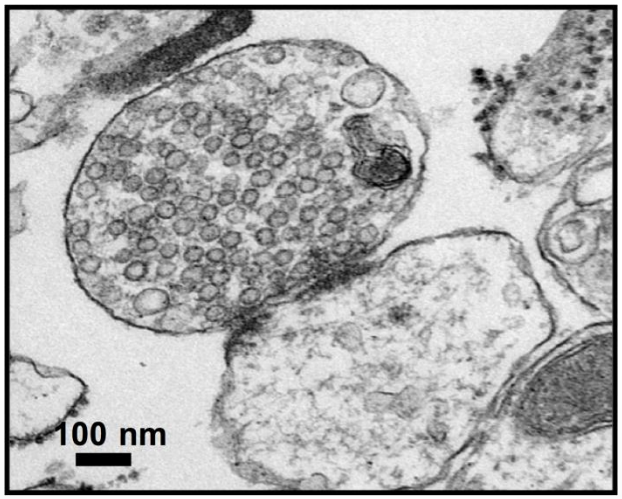


Katzz, The release of neural transmitter substances, 1969.

Katz postulou que a acetilcolina era liberada não continuamente, mas em "pacotes"que ele chamou de *quanta*



Hoje sabemos que 1 *quantum* corresponde ao conteúdo de acetilcolina de uma vesícula sináptica



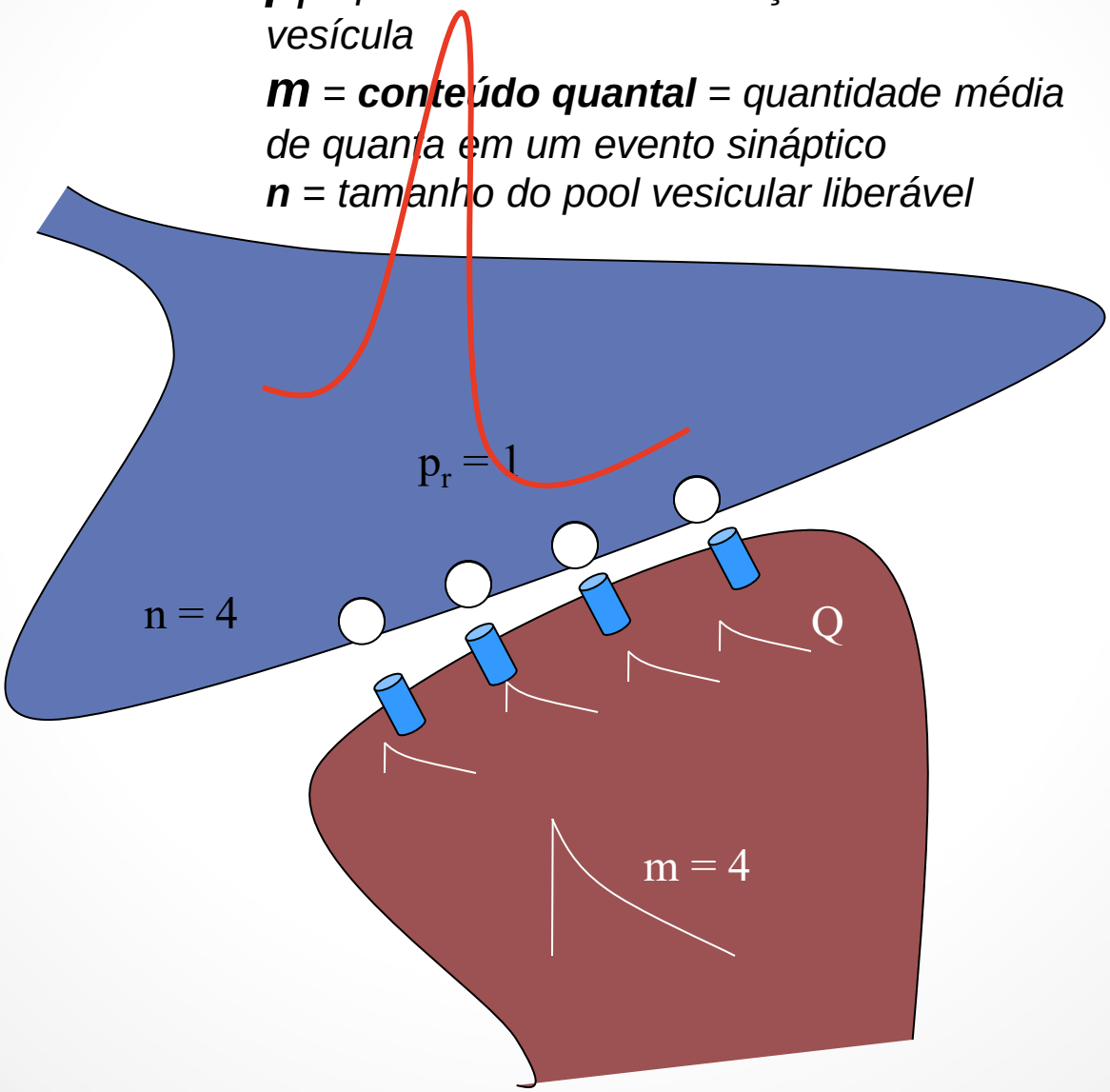
Parâmetros quantais

Q = ***tamanho quantal*** = *amplitude média dos eventos miniatura =quanta*

p_r = *probabilidade de liberação de uma vesícula*

m = ***conteúdo quantal*** = *quantidade média de quanta em um evento sináptico*

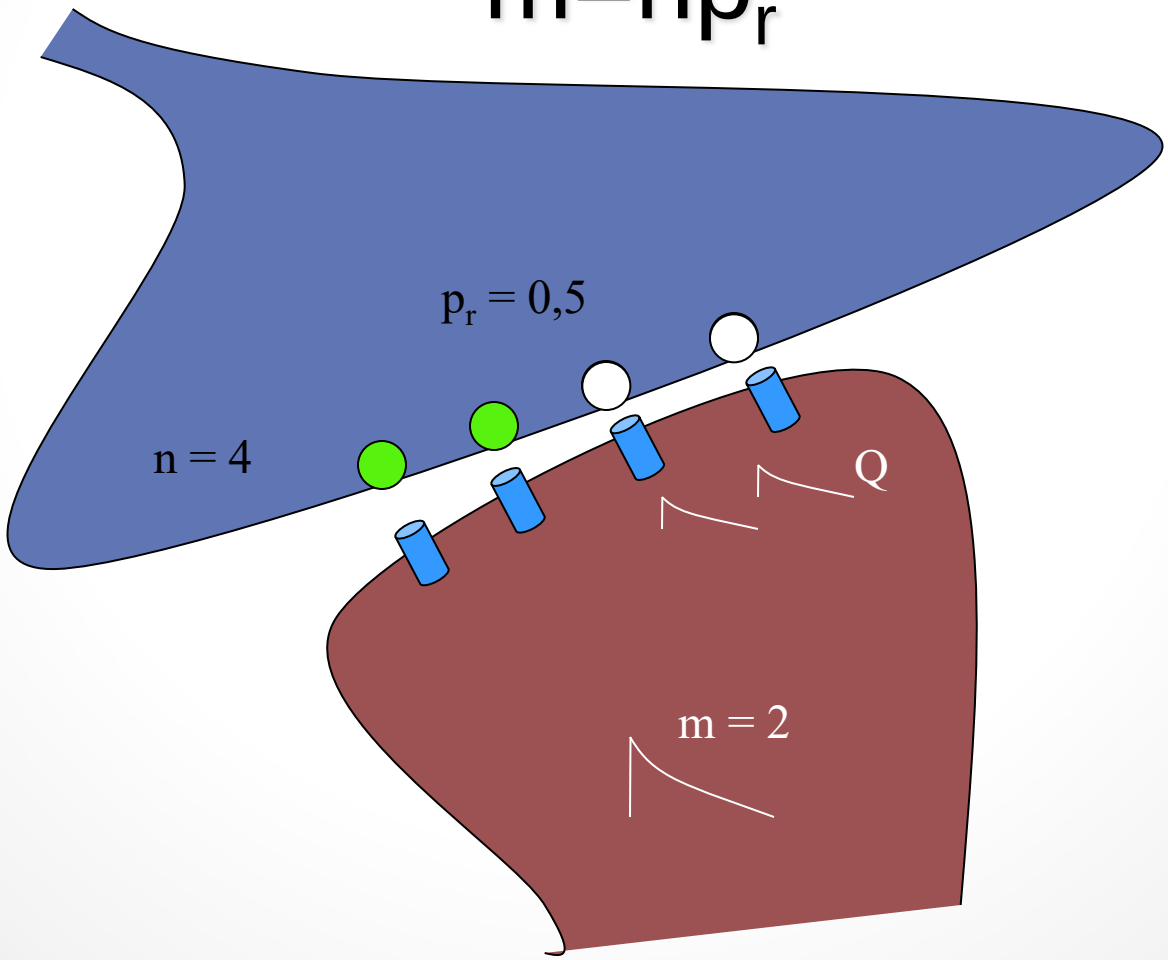
n = *tamanho do pool vesicular liberável*



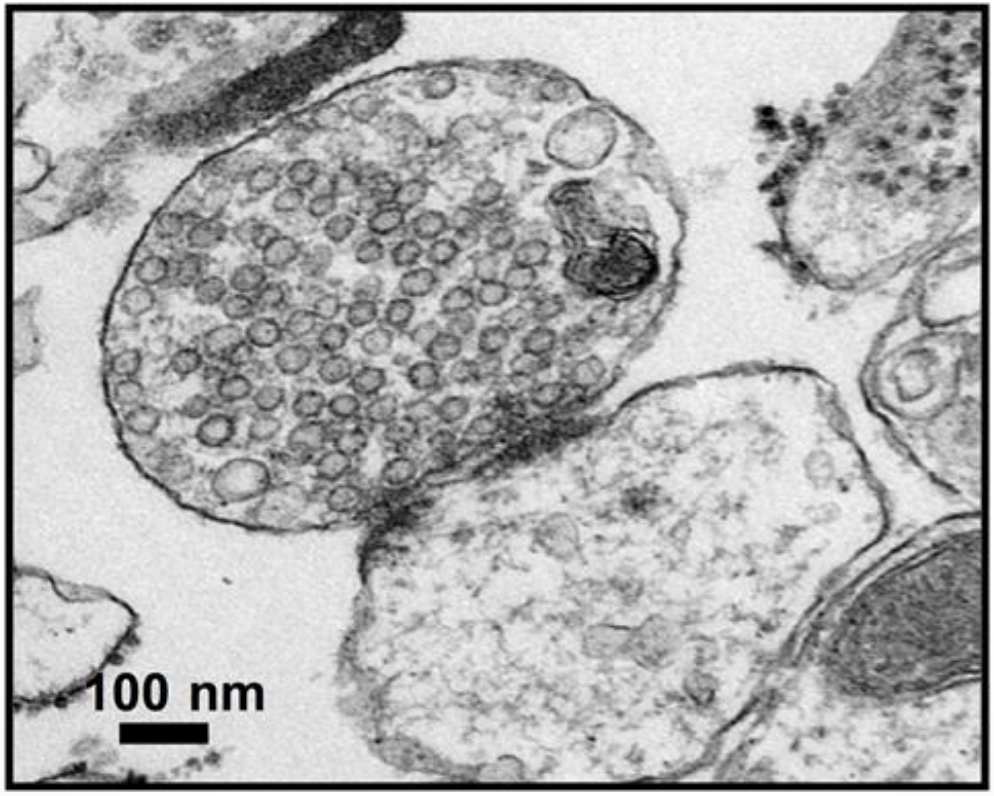
Conteúdo quantal de uma corrente sináptica

m = amplitude média do evento / Q (assumindo Q constante entre as zonas ativas)

$m=np_r$



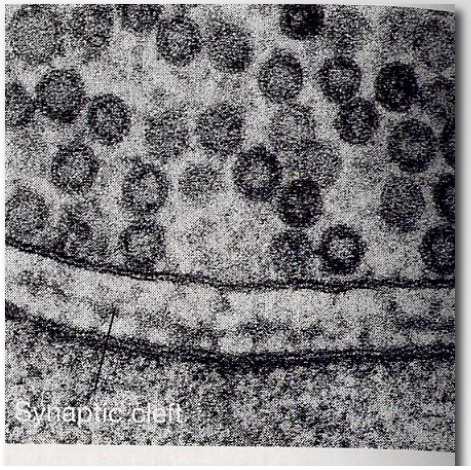
As vesículas sinápticas



As vesículas sinápticas são ancoradas, exocitadas e endocitadas nas zonas ativas

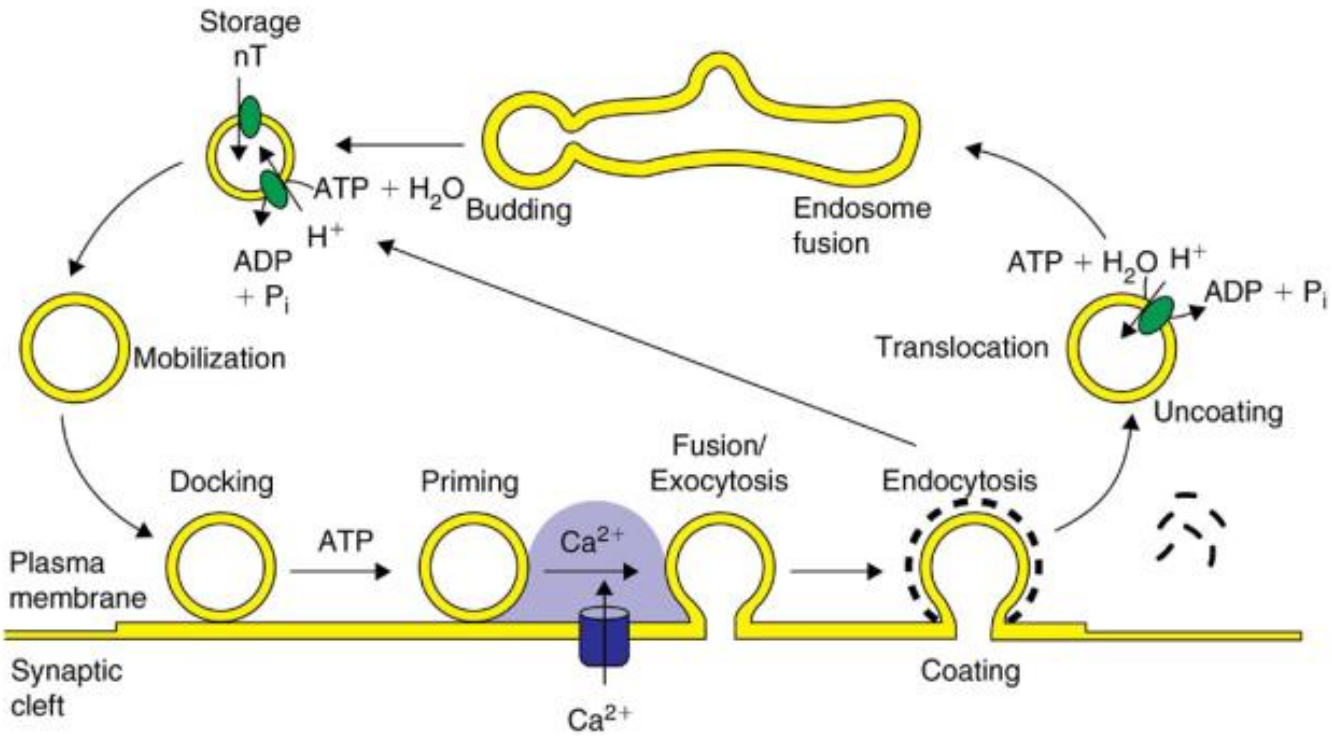
Taschemberger et al., Neuron, 2003

repouso



Heuser and Reese, J Cell Bio, 1981

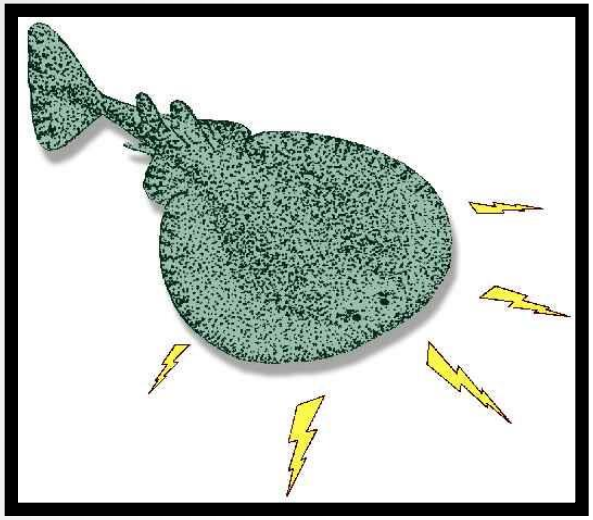
O Ciclo das vesículas sinápticas

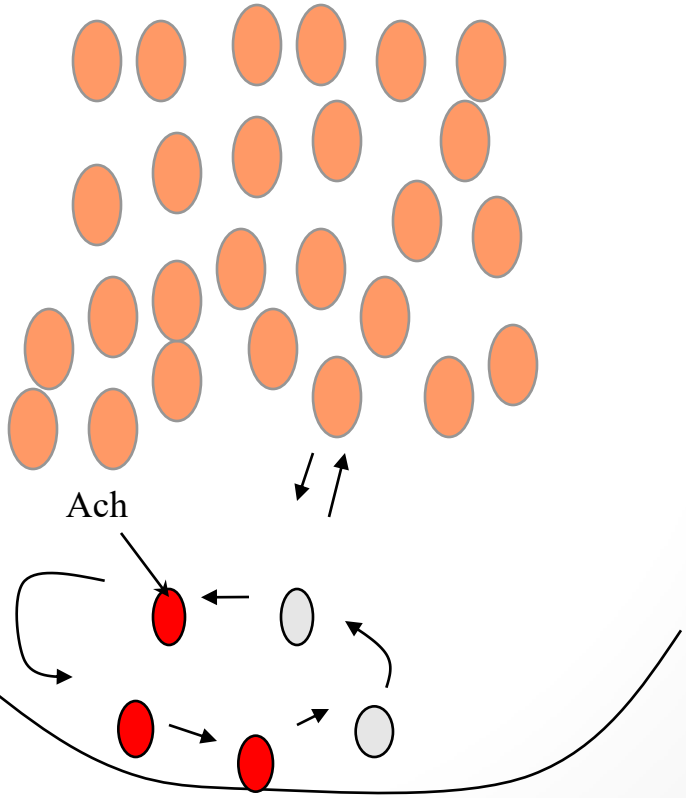


Südhof, Nature 1995

Apenas uma fração das vesículas participa na exocitose

"Pools" vesiculares na eletroplaca (1977)

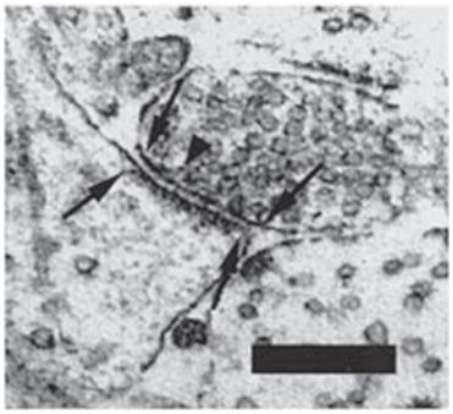


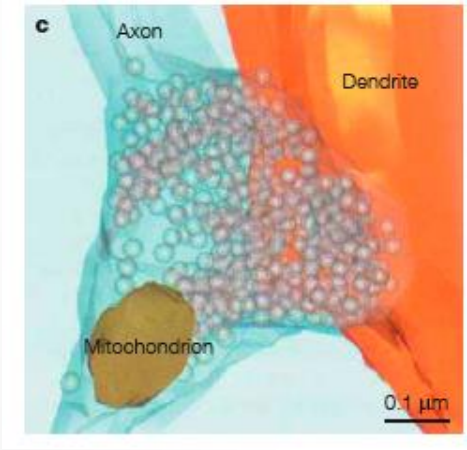


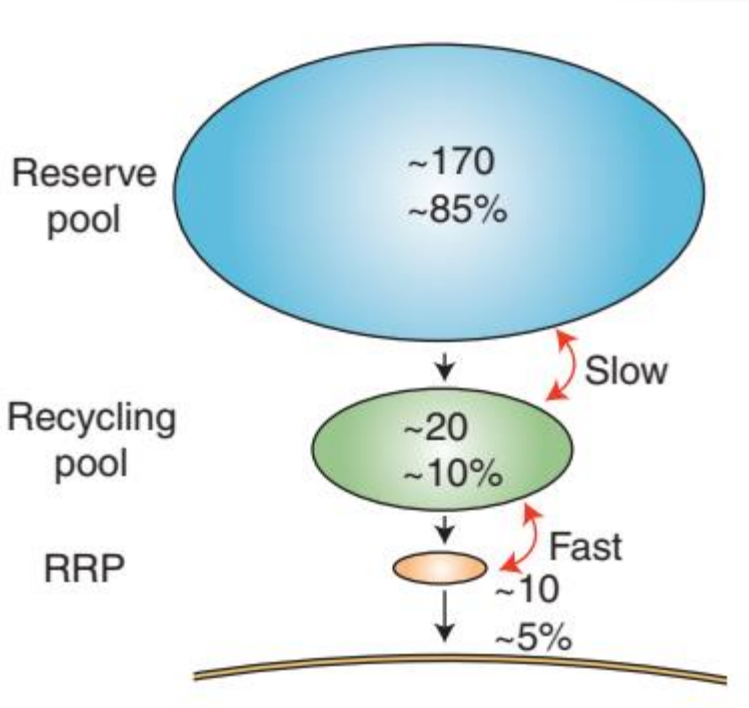
vesícula reciclante com Ach "quente"

vesícula não-reciclante com Ach "fria"

“Pools” vesiculares

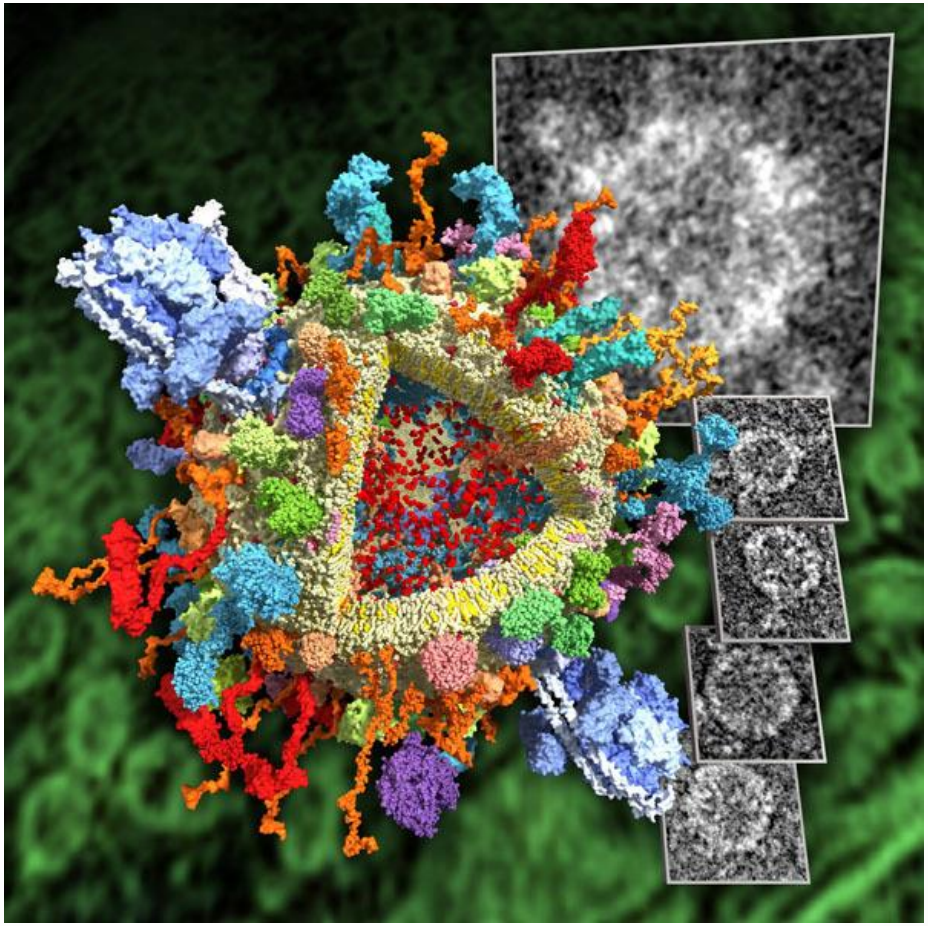






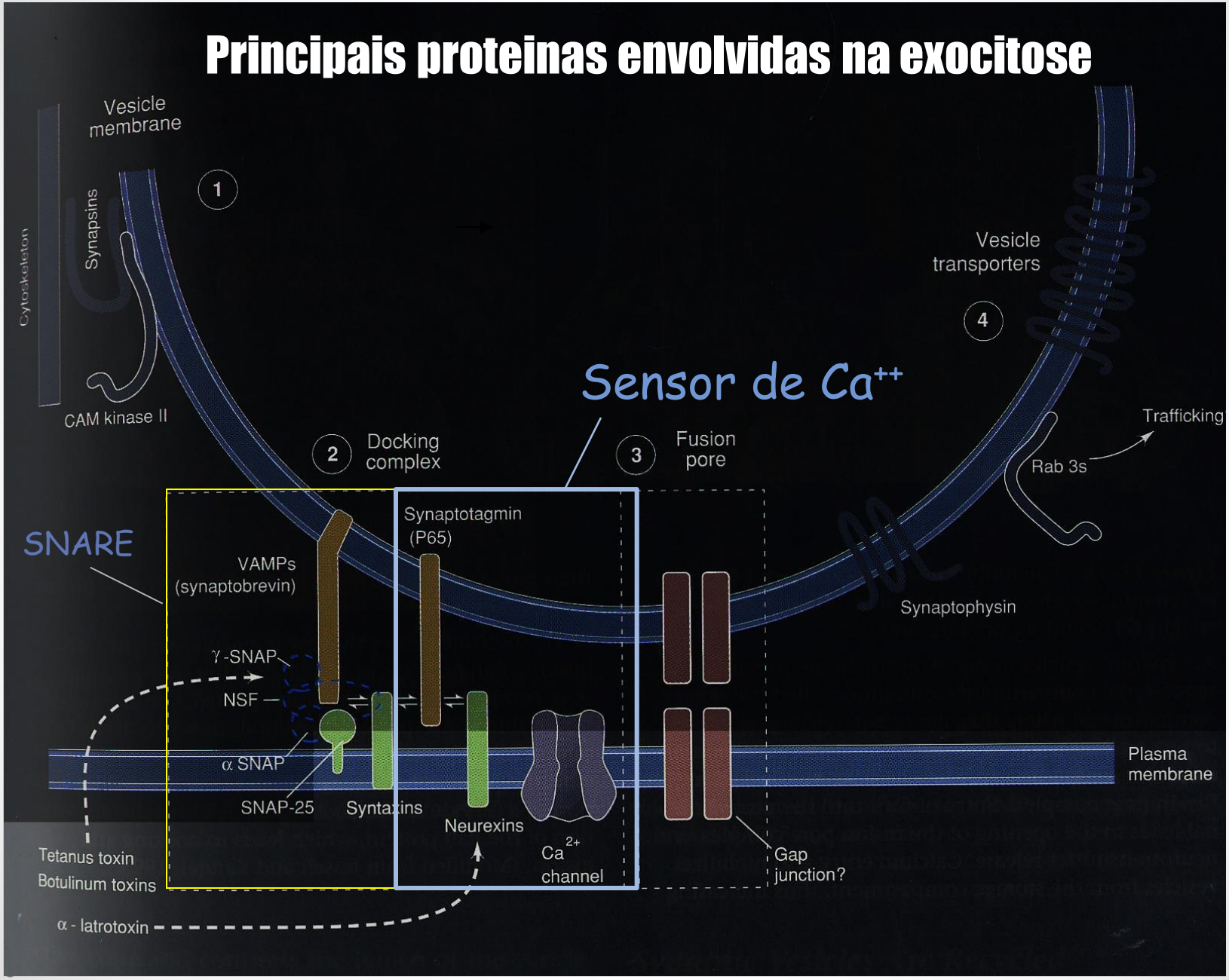
Rizzoli e Betz, Nature Reviews Neuroscience, 2005

As vesículas sinápticas expressam uma grande variedade de proteínas

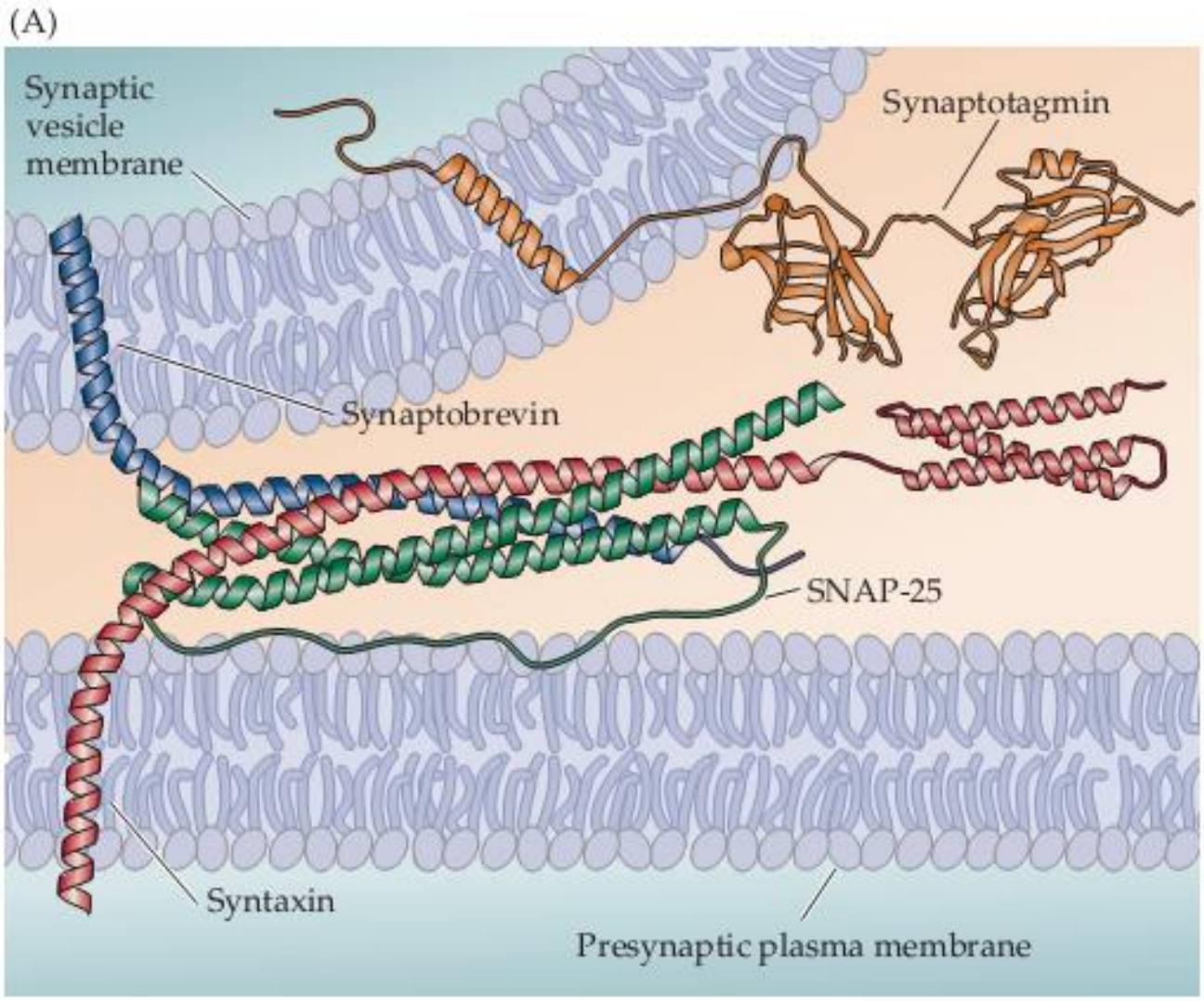


Helmut Grubmüller, Reinhard Jahn, Carsten Kutzner; Department of Theoretical and Computational Biophysics, Max-Planck Institute for Biophysical Chemistry

Principais proteinas envolvidas na exocitose

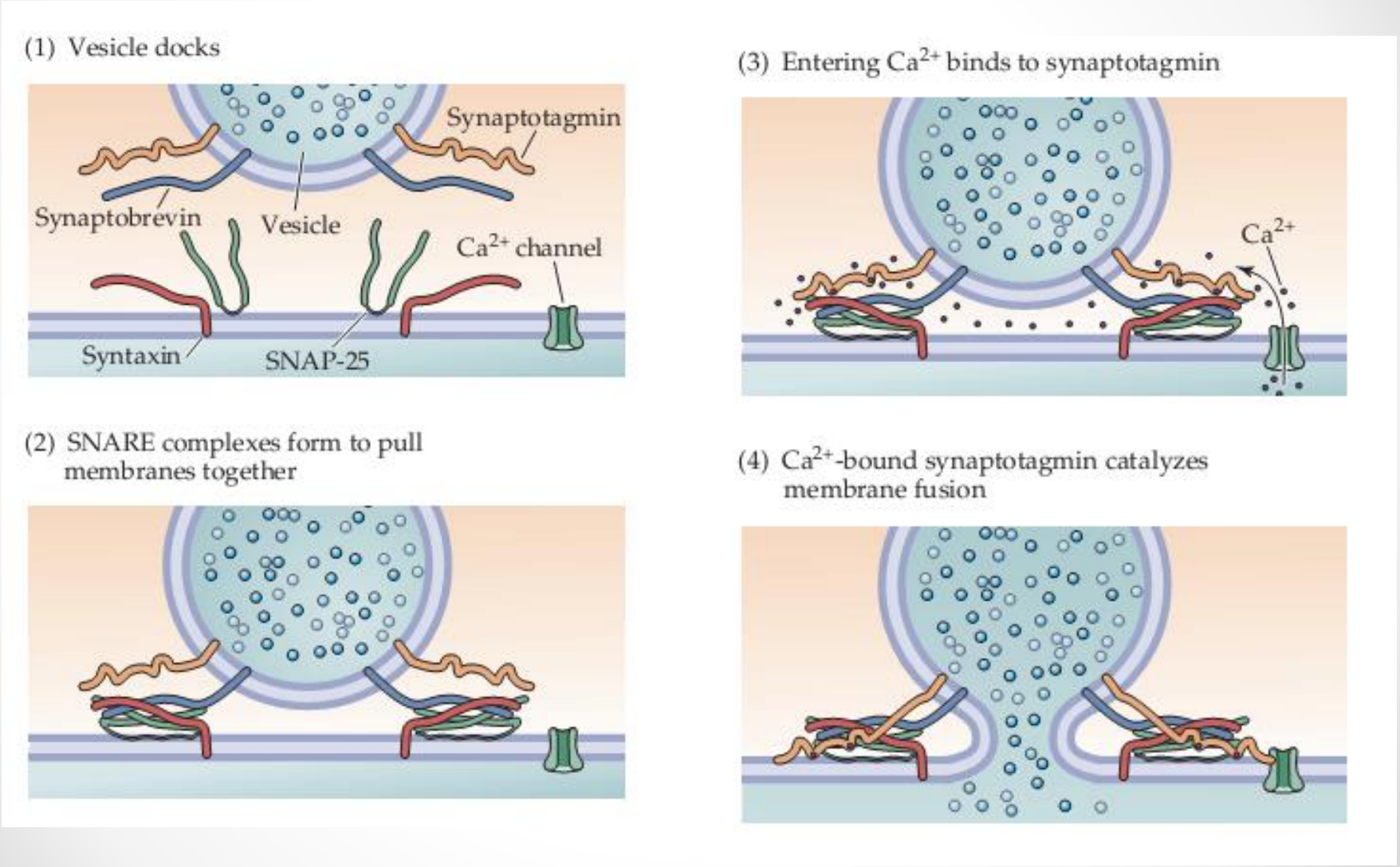


Principais proteinas envolvidas na exocitose



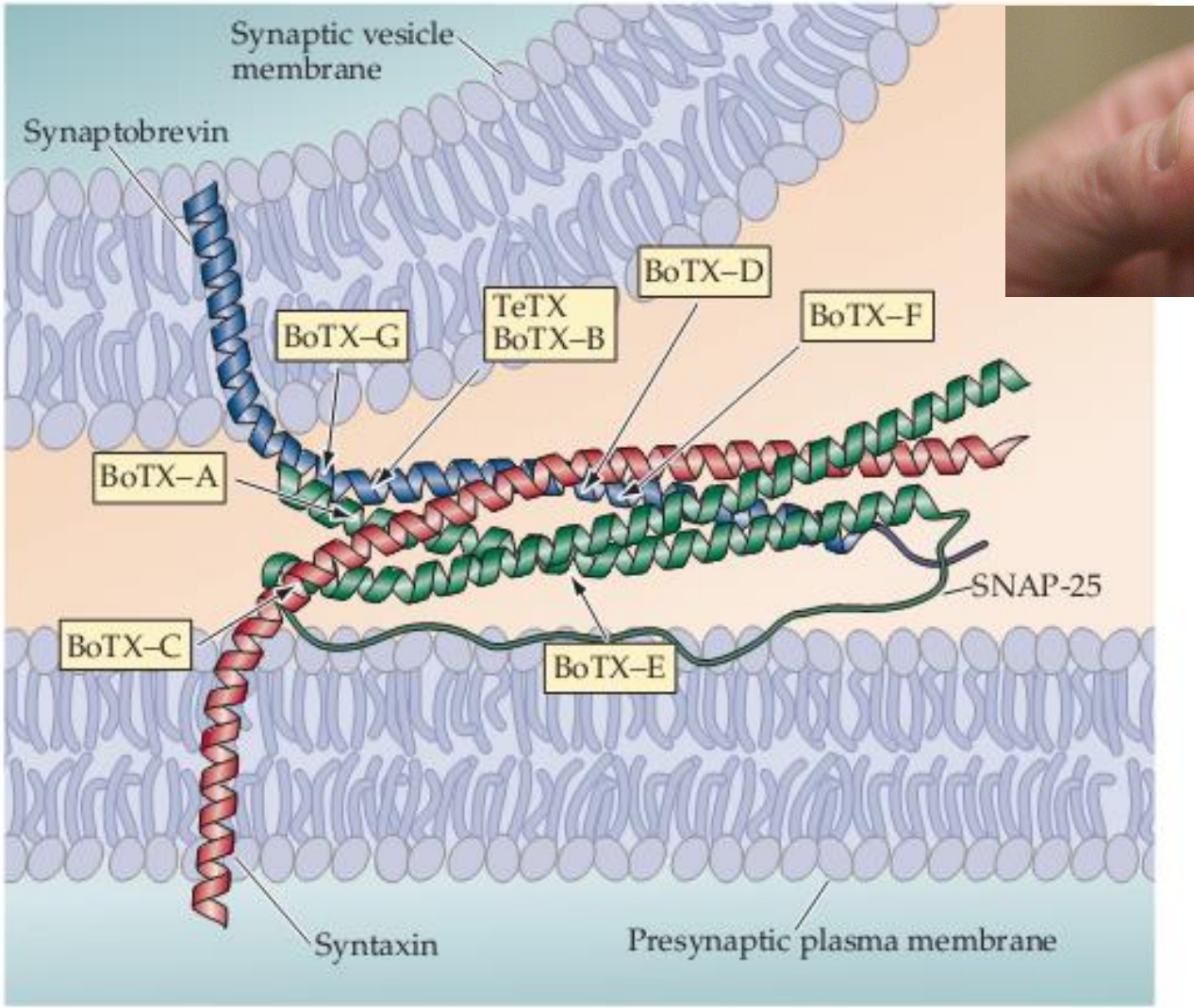
NEUROSCIENCE: Third Edition

O complexo SNARE ancora as vesículas na membrana e participa do processo de fusão



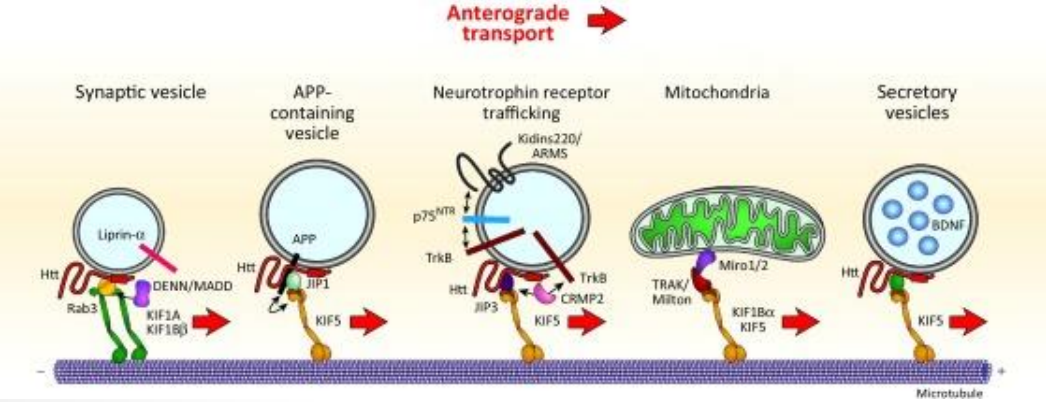
NEUROSCIENCE: Third Edition

As proteínas do complexo SNARE são alvos das **toxinas botulínicas**

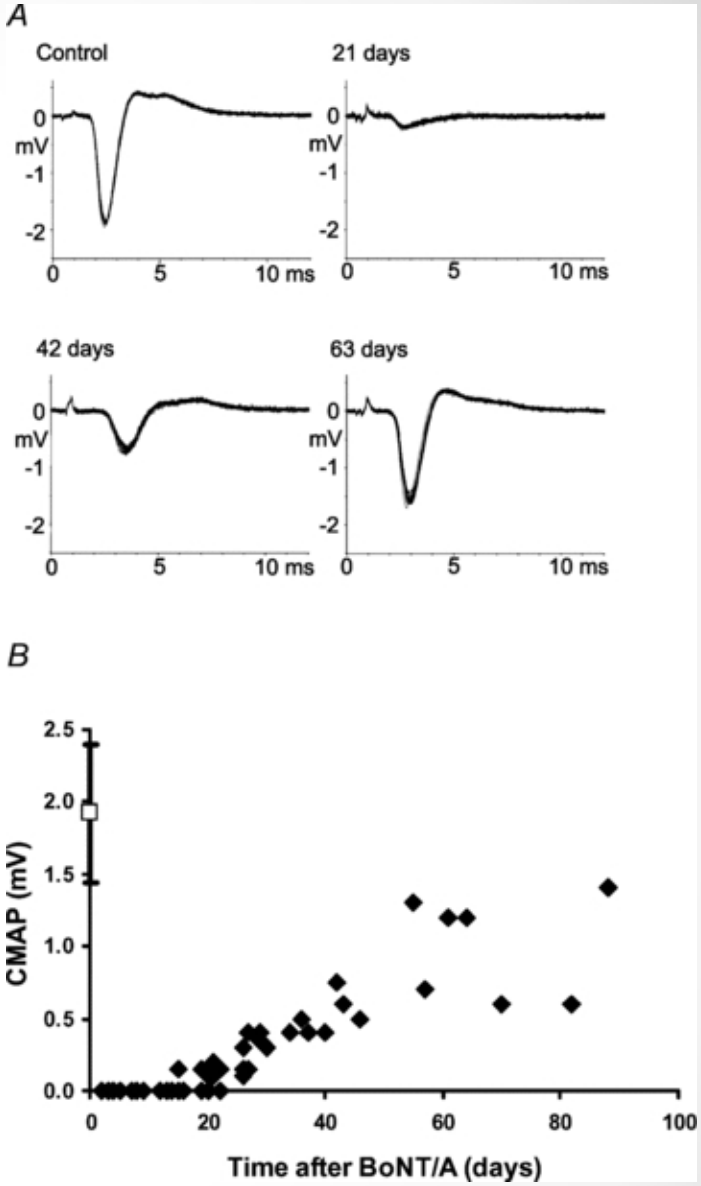


NEUROSCIENCE: Third Edition

Toxina botulinica inibe a neurotransmissão muscular por um longo prazo pois as novas vesículas com novas proteinas SNARE vem do corpo celular por **transporte axonal anterógrado**.

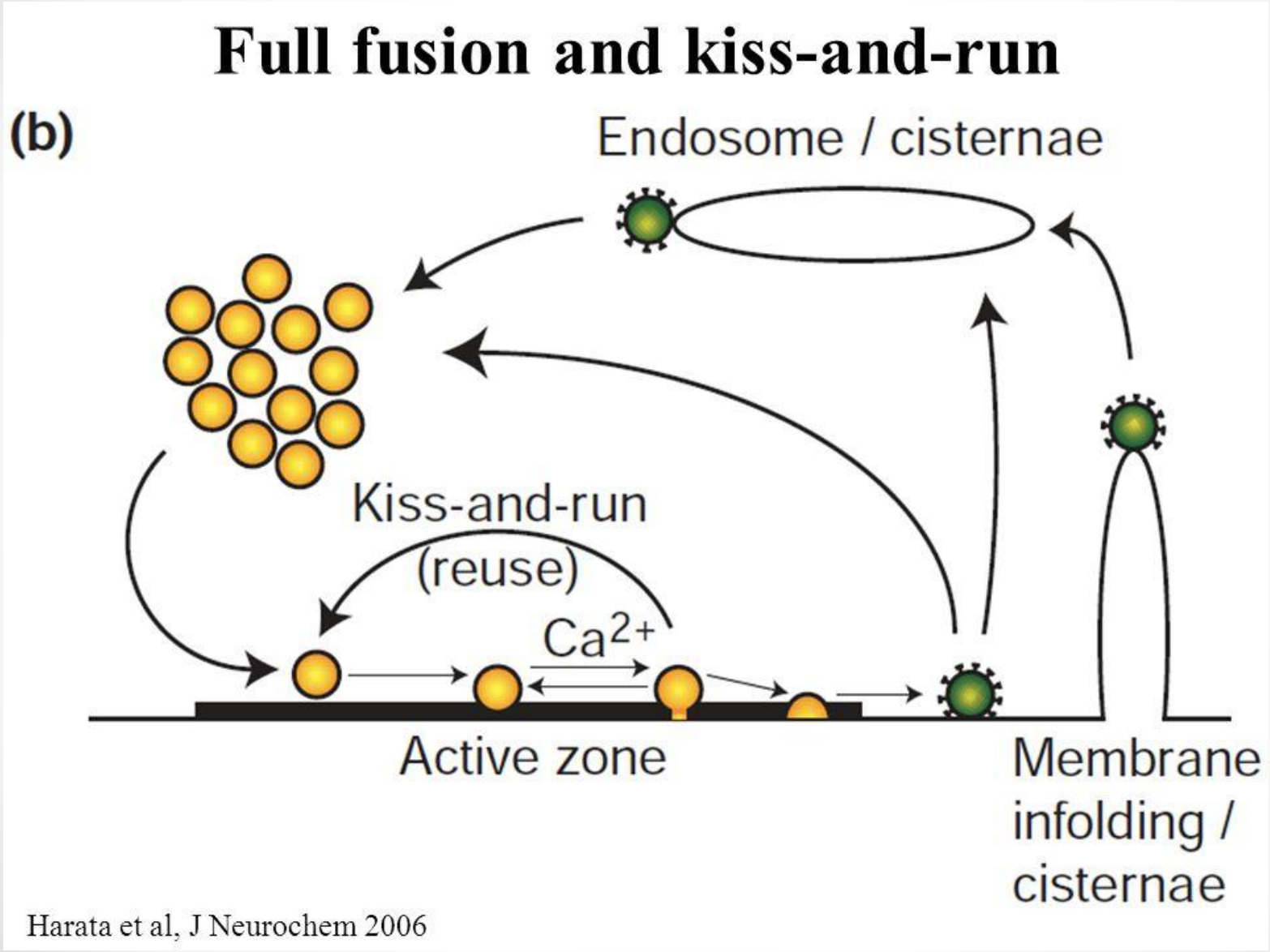


Trends in Biochemical Sciences 2015 40, 597-610DOI: (10.1016/j.tibs.2015.08.003)

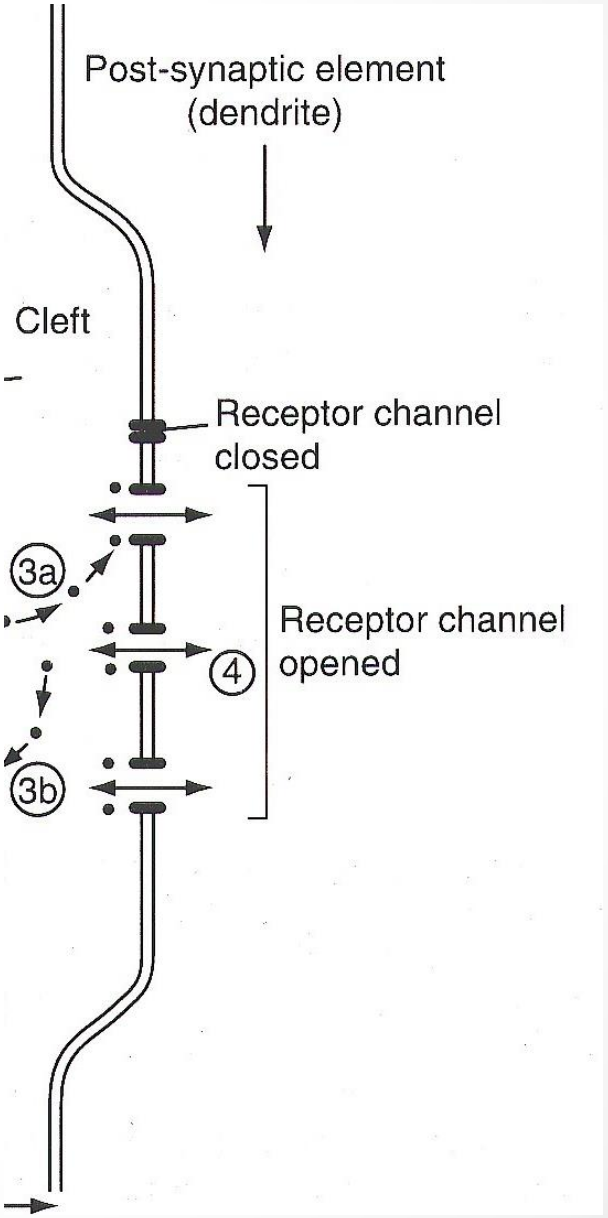


J Physiol 586.13 2008

E depois da exocitose?

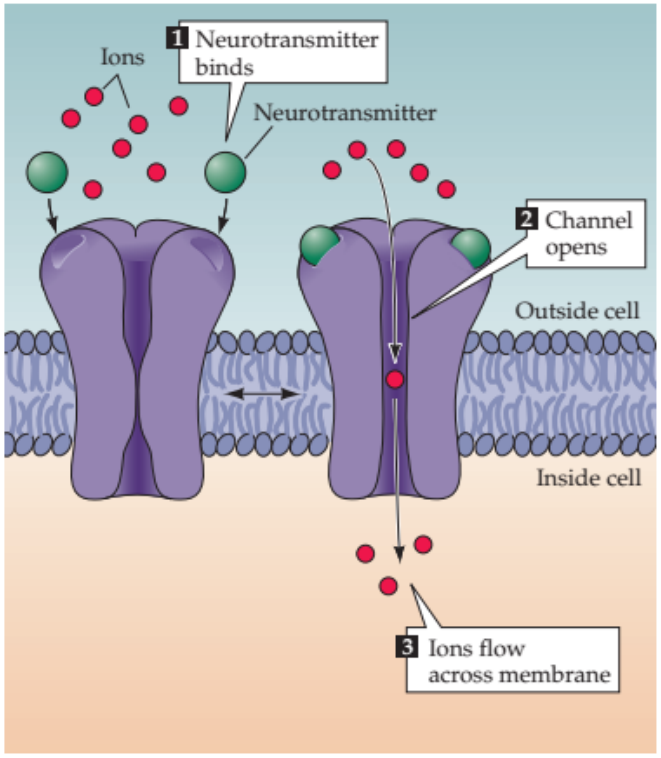


Fenômenos pós-sinápticos



Receptores de neurotransmissores podem ser classificados como ionotrópicos ou metabotrópicos, ligados a proteinas G

Receptores ionotrópicos



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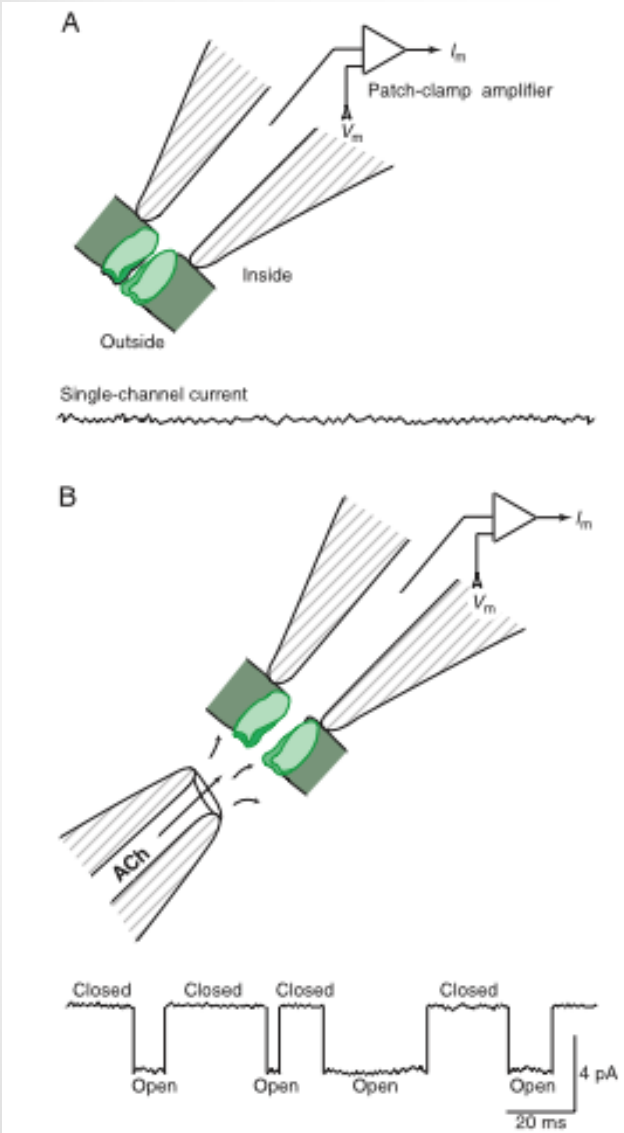
Receptores ionotrópicos são canais iônicos

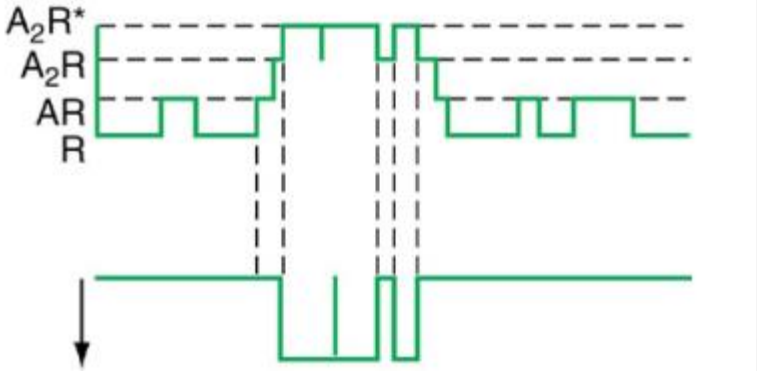


$$R \rightleftharpoons AR \rightleftharpoons A_2R \rightleftharpoons A_2R^*$$

closed channel states — open channel state

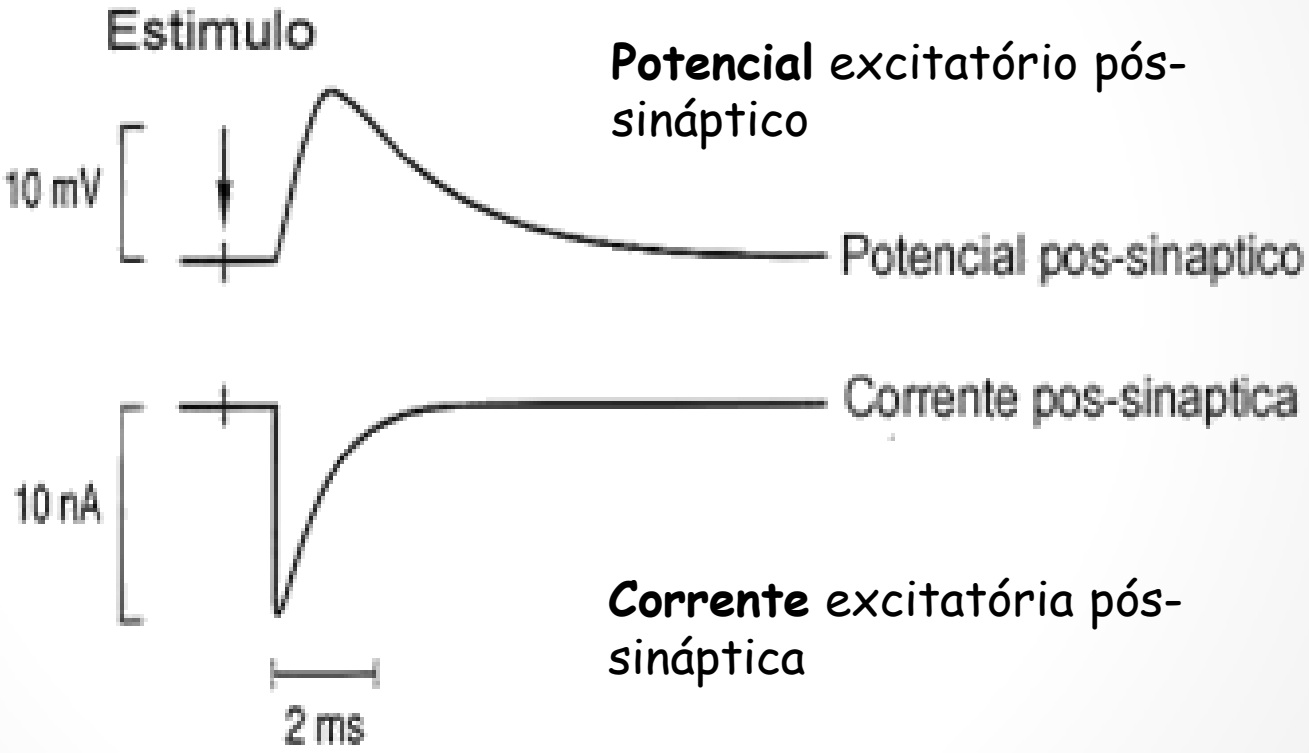
estados

corrente



Hammond. Cellular and Molecular Neurophysiology.

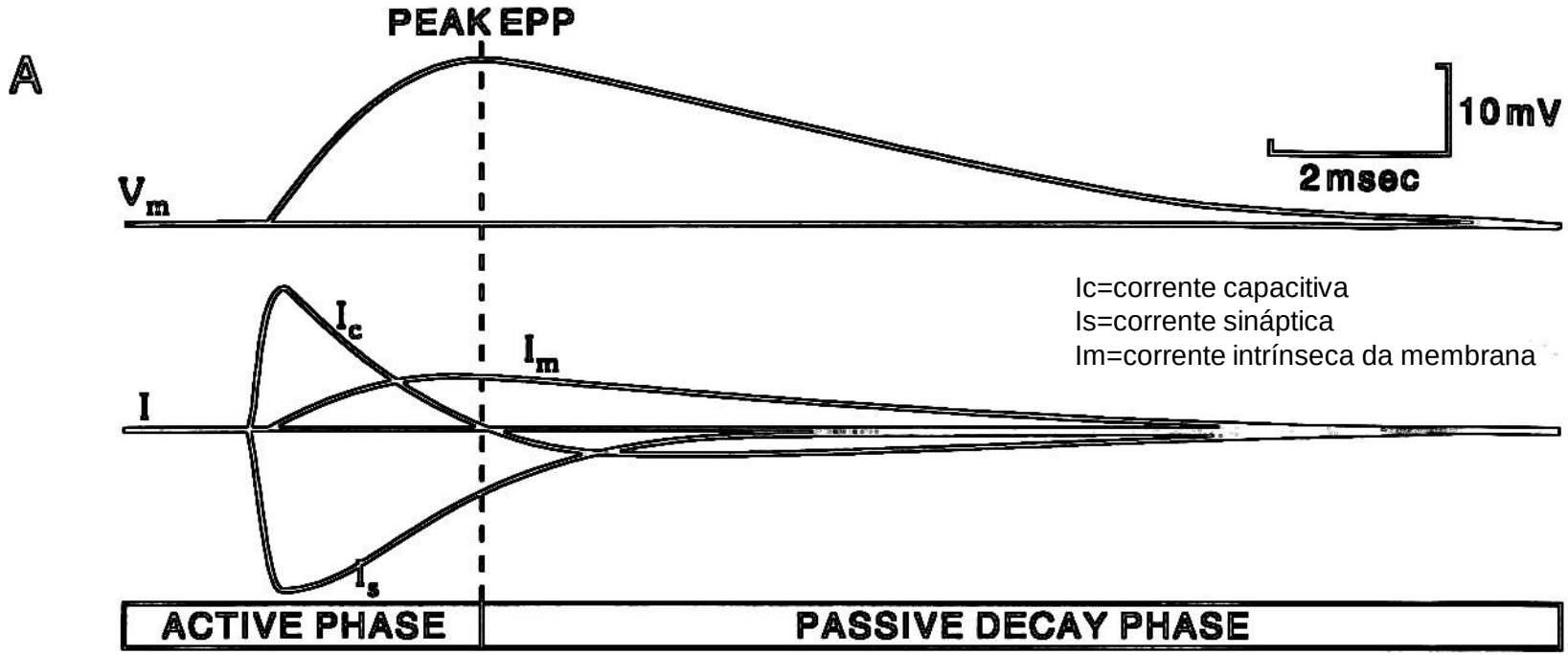
O fluxo iônico pelos receptores ionotrópicos (**corrente**) gera uma mudança de **potencial** da membrana



Potencial excitatório pós-sináptico

Corrente excitatória pós-sináptica

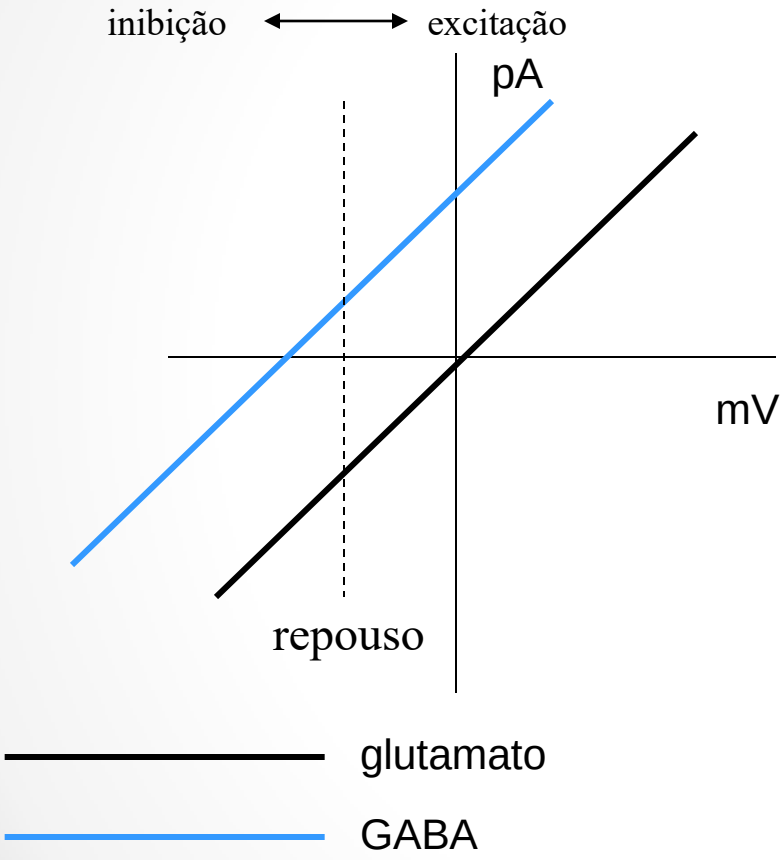
As correntes capacitivas e iônicas da membrana moldam os potenciais pós-sinápticos

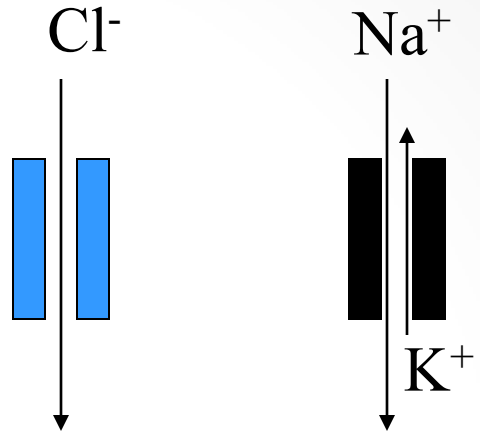


Sperelakis, Cell Physiology Sourcebook

Sinapses inibitórias e excitatórias

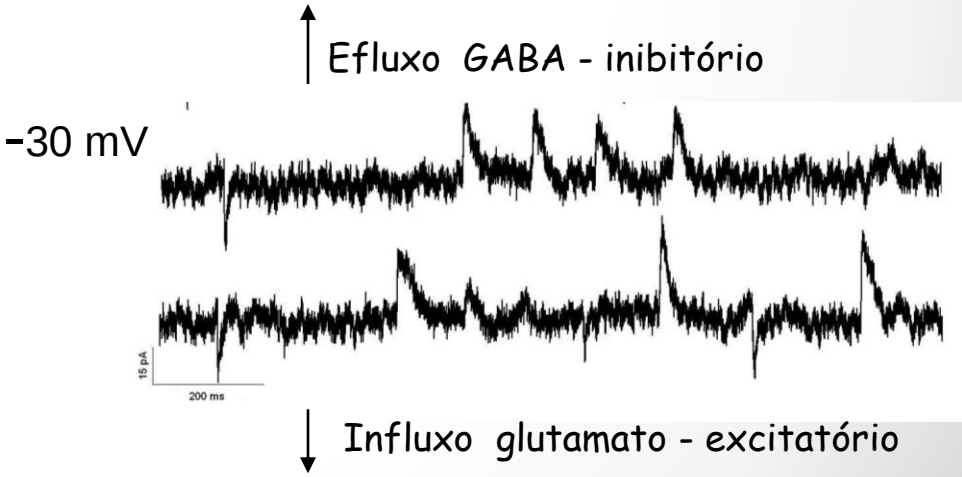
Polaridade/reversão





$E_{rev(GABAA)}=E_{revCl}$~-80 mV

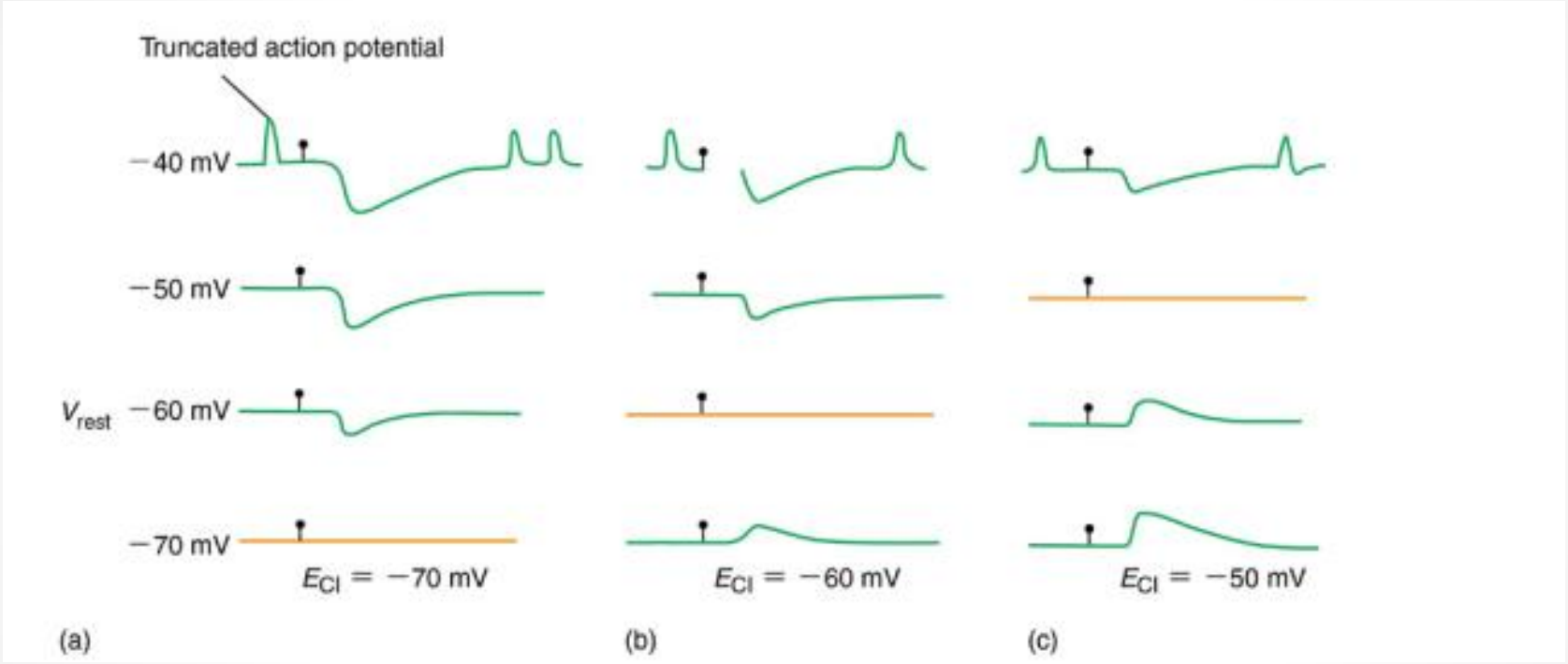
$E_{rev(AMPA)}$~0 mV



Registro pessoal

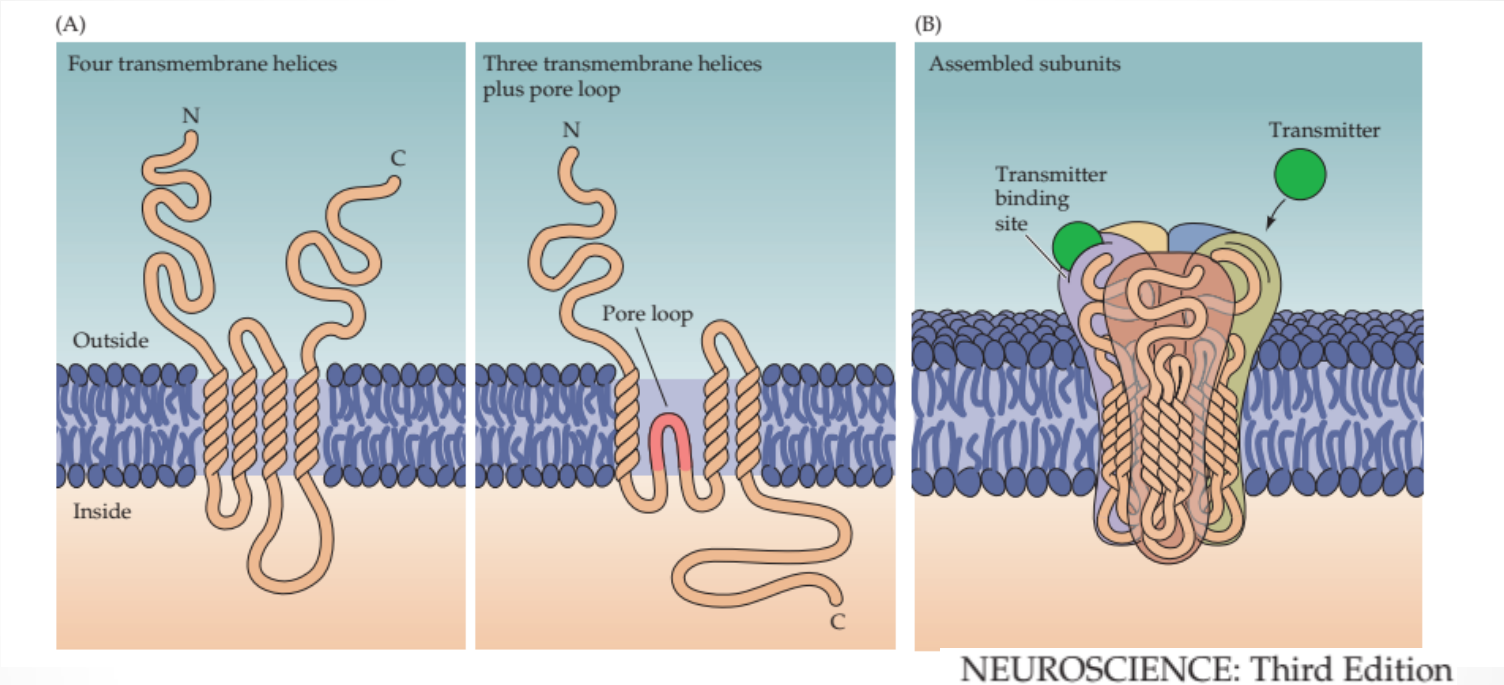
- Sinapses excitatórias levam o E_m próximo de 0 mV (despolarizam)
- Sinapses inibitórias hiperpolarizam ou estabilizam o E_m próximo de repouso

GABA pode ser excitatório dependendo da E_{Cl}

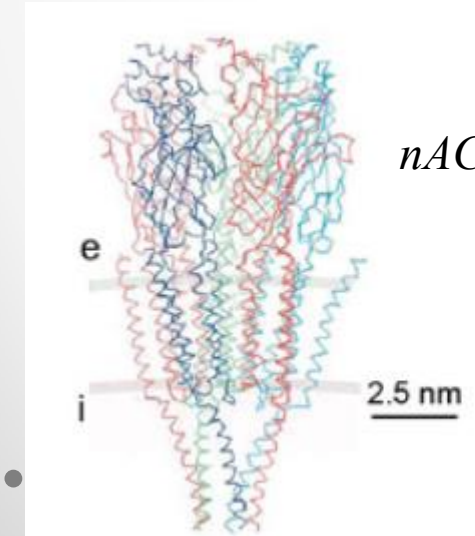


Hammond. Cellular and Molecular Neurophysiology.

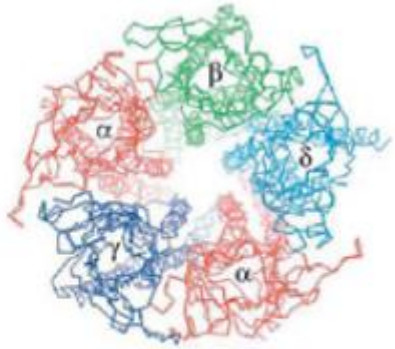
Estrutura geral dos receptores ionotrópicos



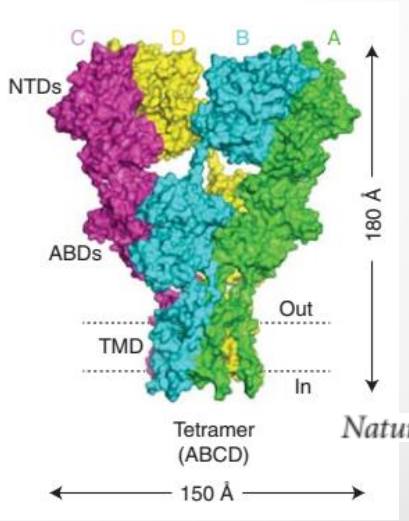
NEUROSCIENCE: Third Edition



nAChR



J. Mol. Biol. **346**, 967–989,



GluA2

Nature **462:** 745–756.

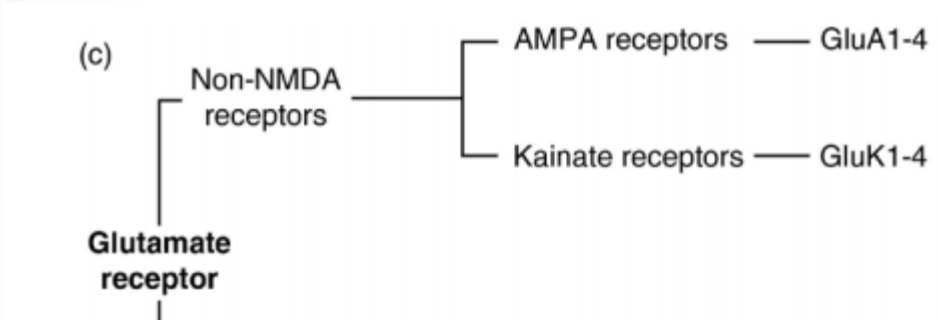
Várias subunidades compõem os receptores ionotrópicos

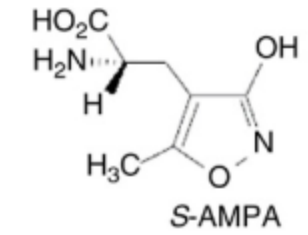
glutamato

Receptor	AMPA	NMDA	Kainate	GABA	Glycine	nACh	Serotonin	Purines
Subunits (combination of 4 or 5 required for each receptor type)	Glu R1	NR1	Glu R5	α_{1-7}	α1	α_{2-9}	5-HT_3	P_{2X1}
	Glu R2	NR2A	Glu R6	β_{1-4}	α2	β_{1-4}		P_{2X2}
	Glu R3	NR2B	Glu R7	γ_{1-4}	α3	γ		P_{2X3}
	Glu R4	NR2C	KA1	δ	α4	δ		P_{2X4}
		NR2D	KA2	ε	β			P_{2X5}
				ρ_{1-3}				P_{2X6}
								P_{2X7}

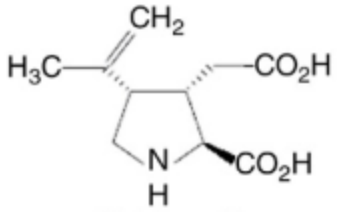
NEUROSCIENCE: Third Edition

Os receptores glutamatérgicos são divididos em 3 tipos de acordo com seus agonistas não-fisiológicos





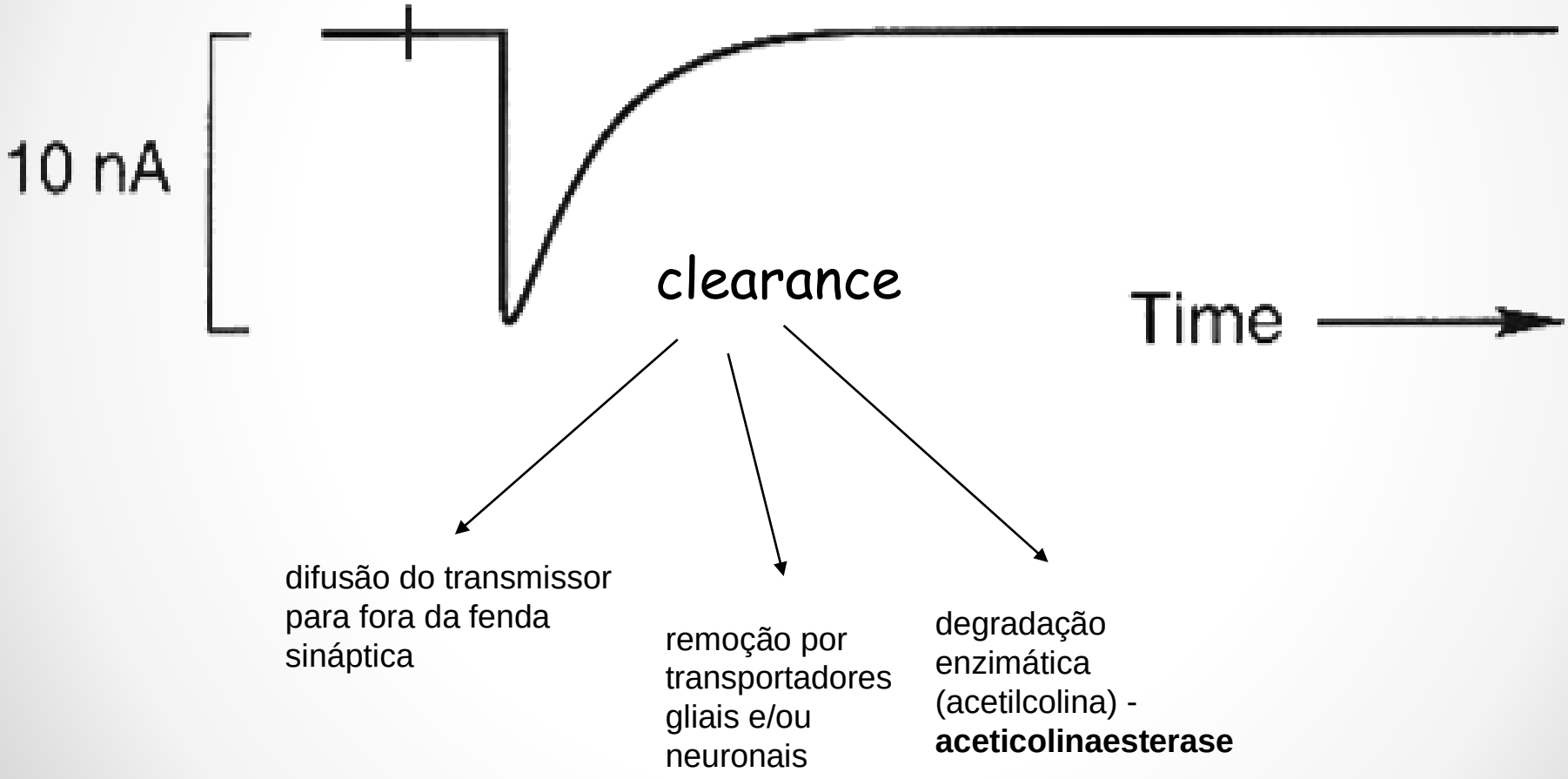
S-AMPA



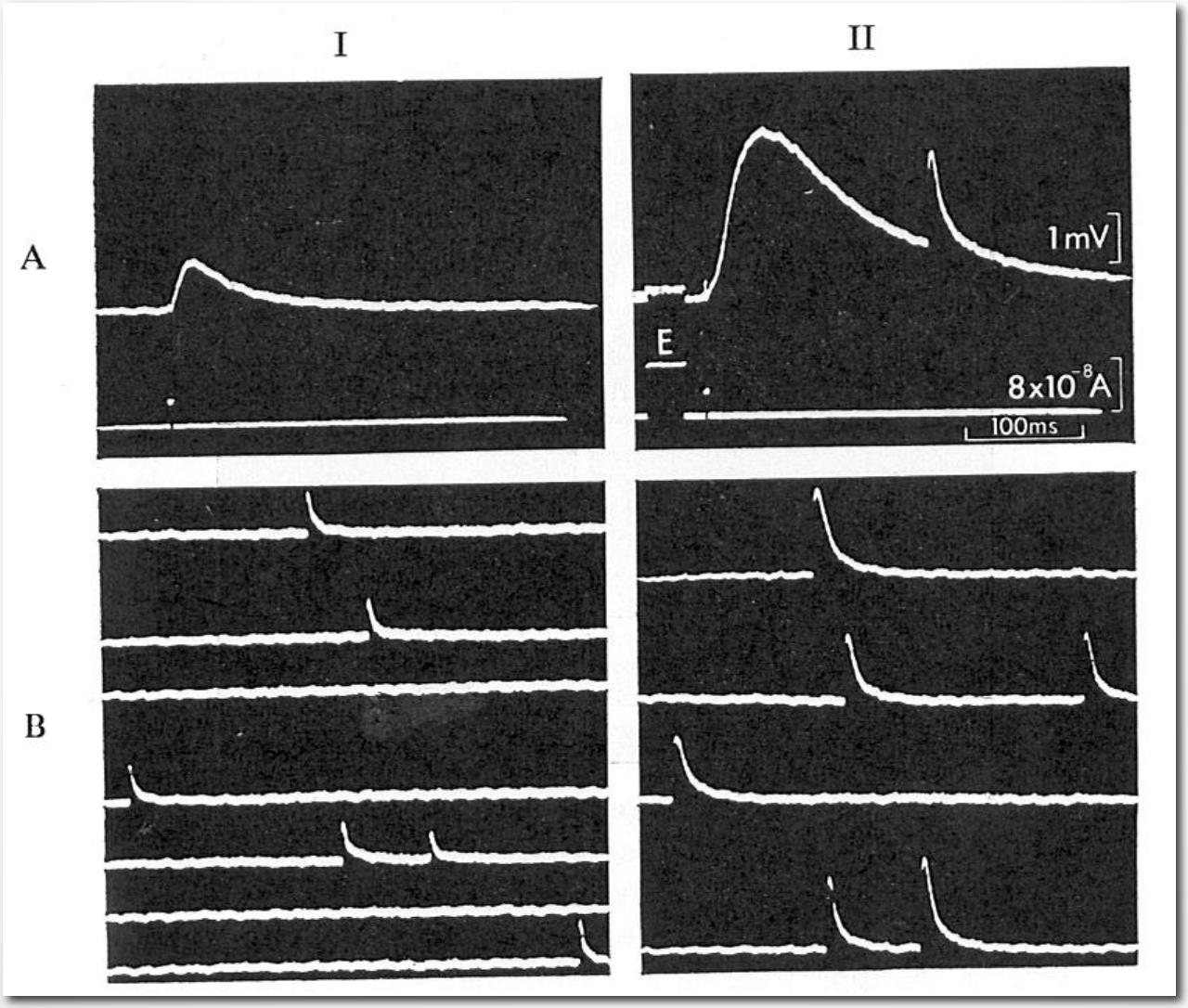
Kainic acid

Hammond. Cellular and Molecular Neurophysiology.

Decaimento das correntes sinápticas

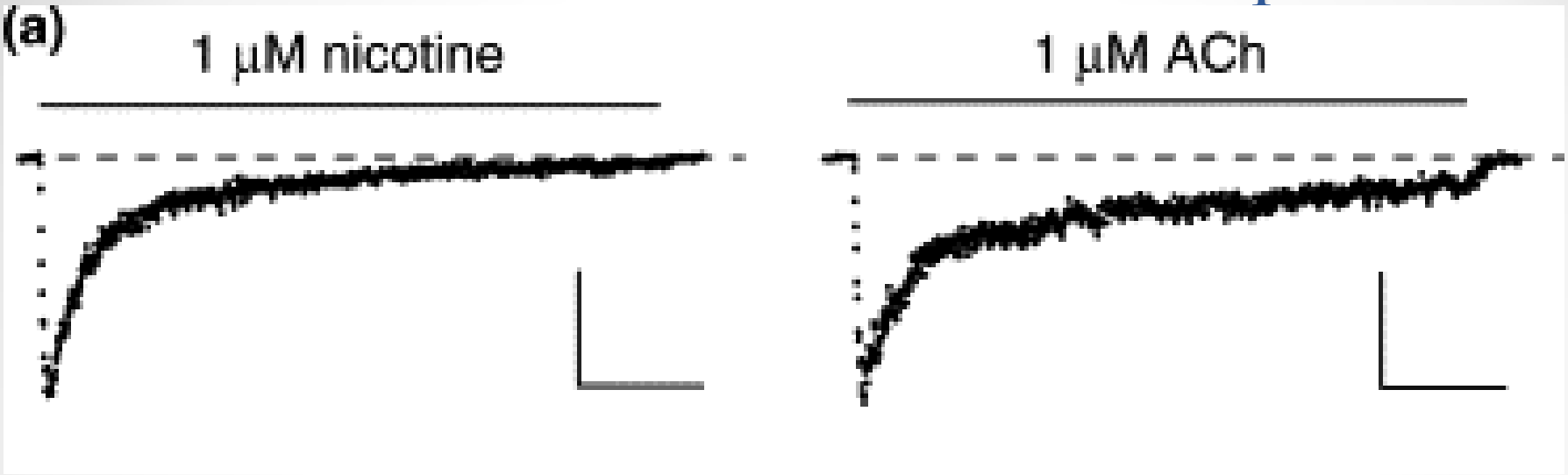


Inibição da acetilcolinaesterase por eserina (II) aumentou a amplitude e duração de tanto os EPSPs (A) quanto dos mEPSPs (B)

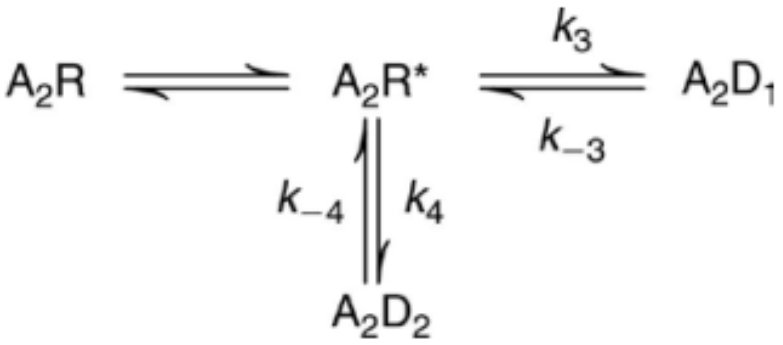


Katz, The release of neural transmitter substances, 1969.

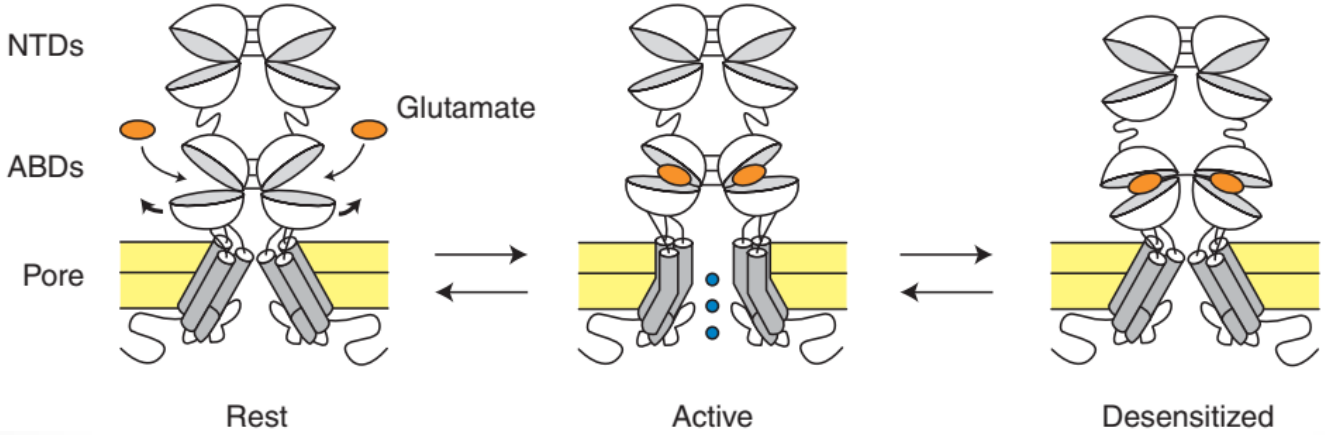
Decaimento das correntes sinápticas

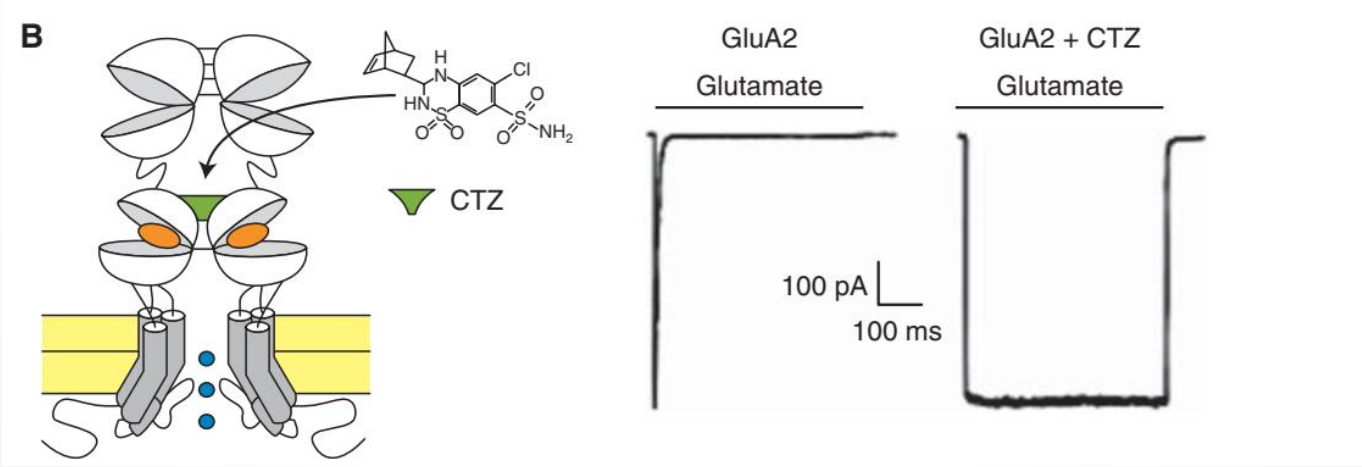


Dessensibilização = fechamento do canal na presença do agonista



Mecanismo de dessensibilização do receptor AMPA

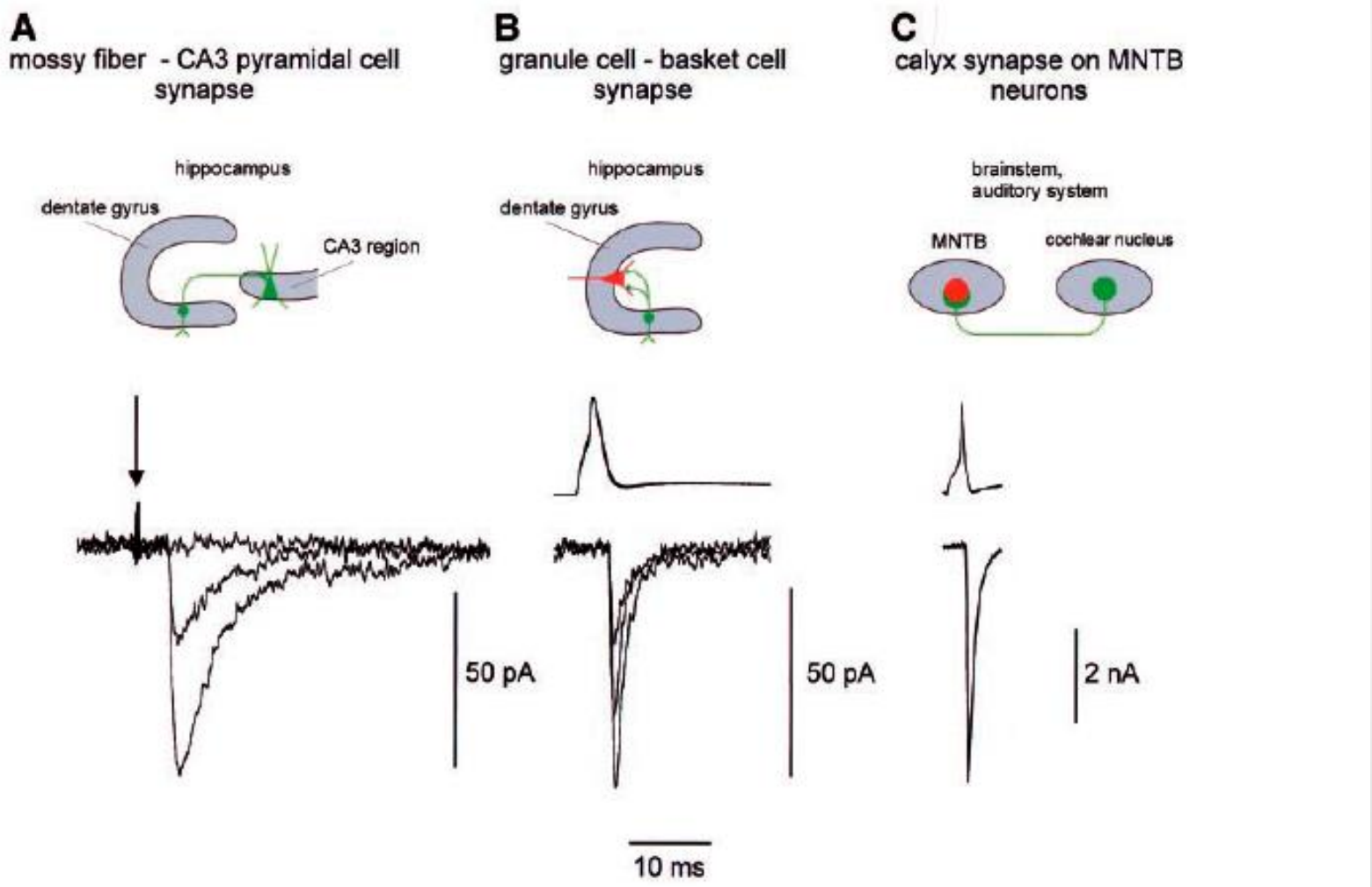




Cold Spring Harb Perspect Biol 2012;4:a009662

Diferentes sinapses possuem receptores com características diferentes

Correntes AMPA em diferentes sinapses centrais

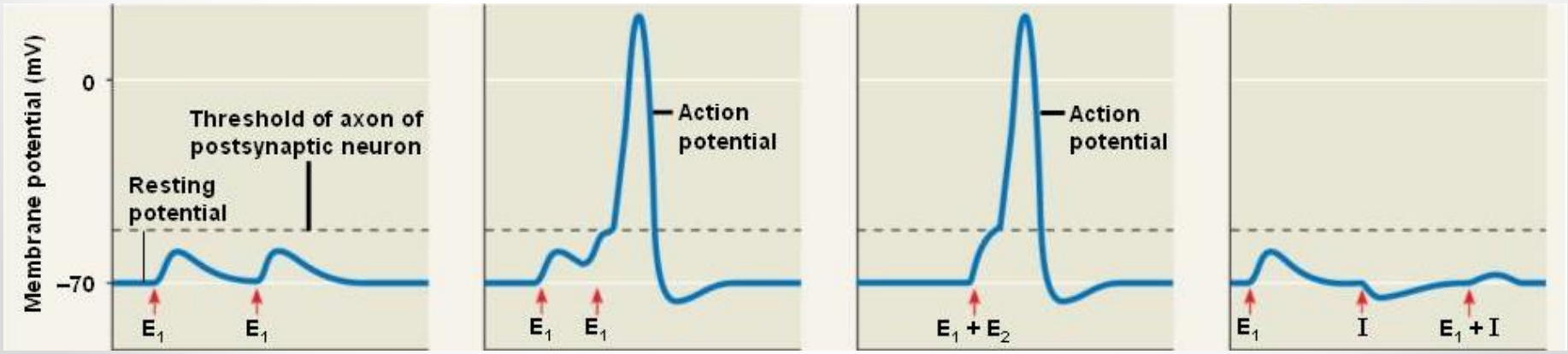


Peter Jonas, The Physiologist

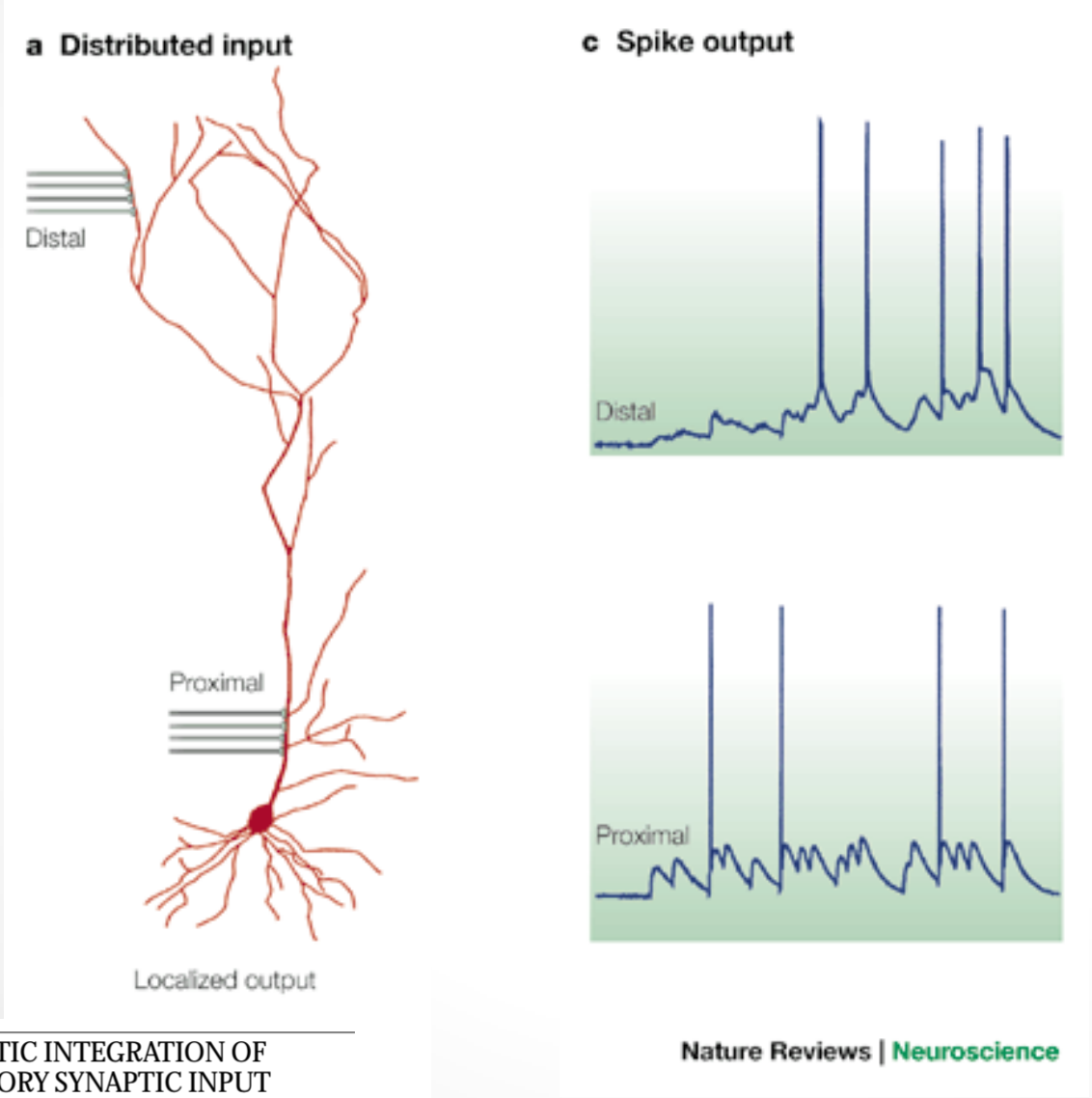
Integração sináptica

- Minúsculas
  - 0,5-2 μm de área de contato
  - Varicosidades, *bouton*
- Ação individual insignificante!
  - Cada sinapse em geral contém uma zona ativa que libera uma vesícula sináptica por vez

- Qual é o segredo?
- Numerosas
  - 1 neurônio de uma forma geral faz ~1.000 sinapses e recebe ~10.000 sinapses
  - Sinapses centrais são muitas para 1 (muitos potenciais de ação pré-sinápticos para gerar um PA pós sináptico).
  - **Somação temporal dos diferentes potenciais sinápticos**

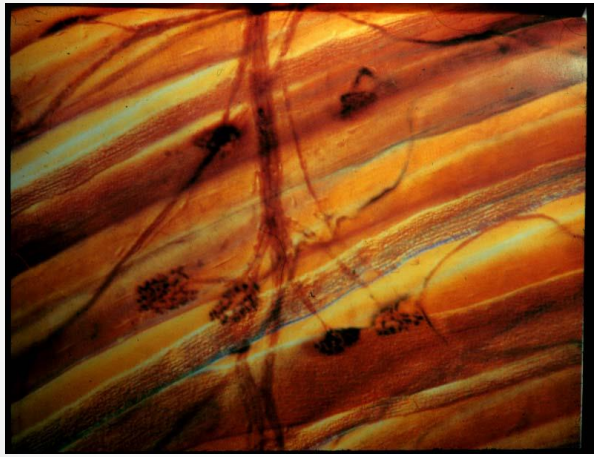


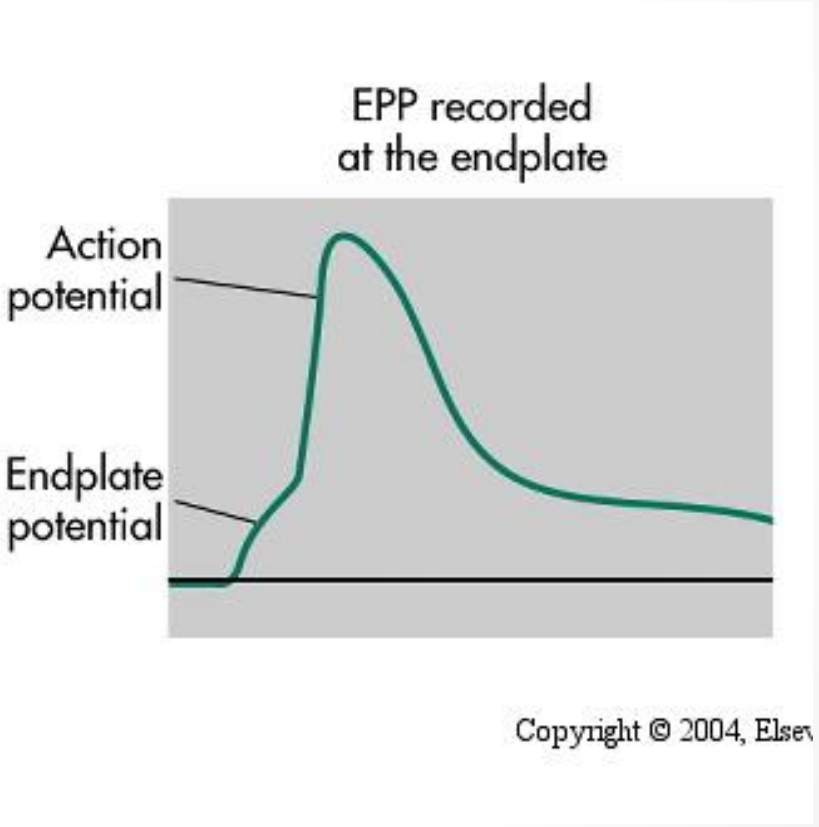
Integração dos potenciais sinápticos excitatórios dendríticos



A junção neuromuscular é uma sinapse do tipo 1 para 1

- ou seja: 1 potencial de ação pré-sináptico causa 1 potencial de ação muscular
- **Não há integração sináptica na JNM!**



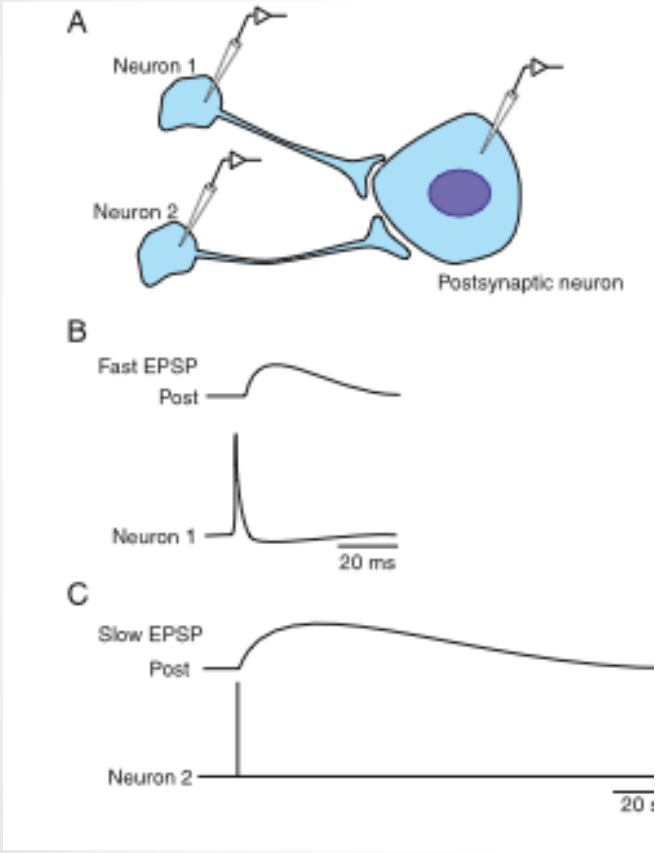


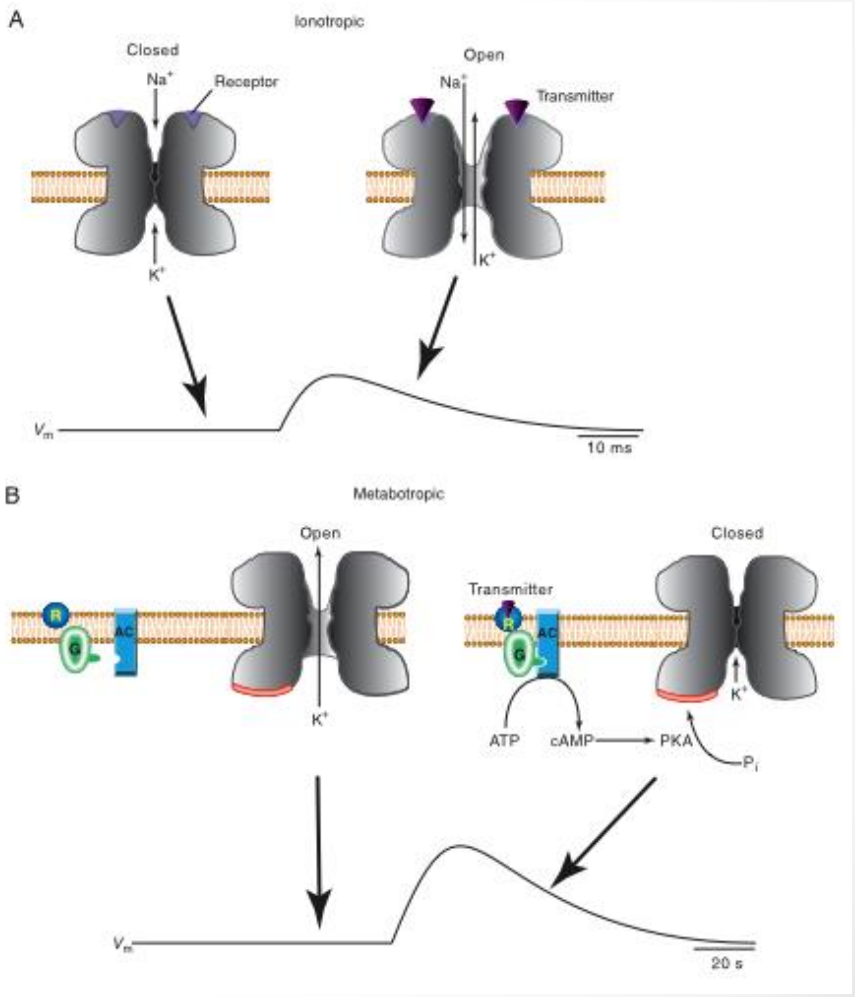
Receptores metabotrópicos

(B)

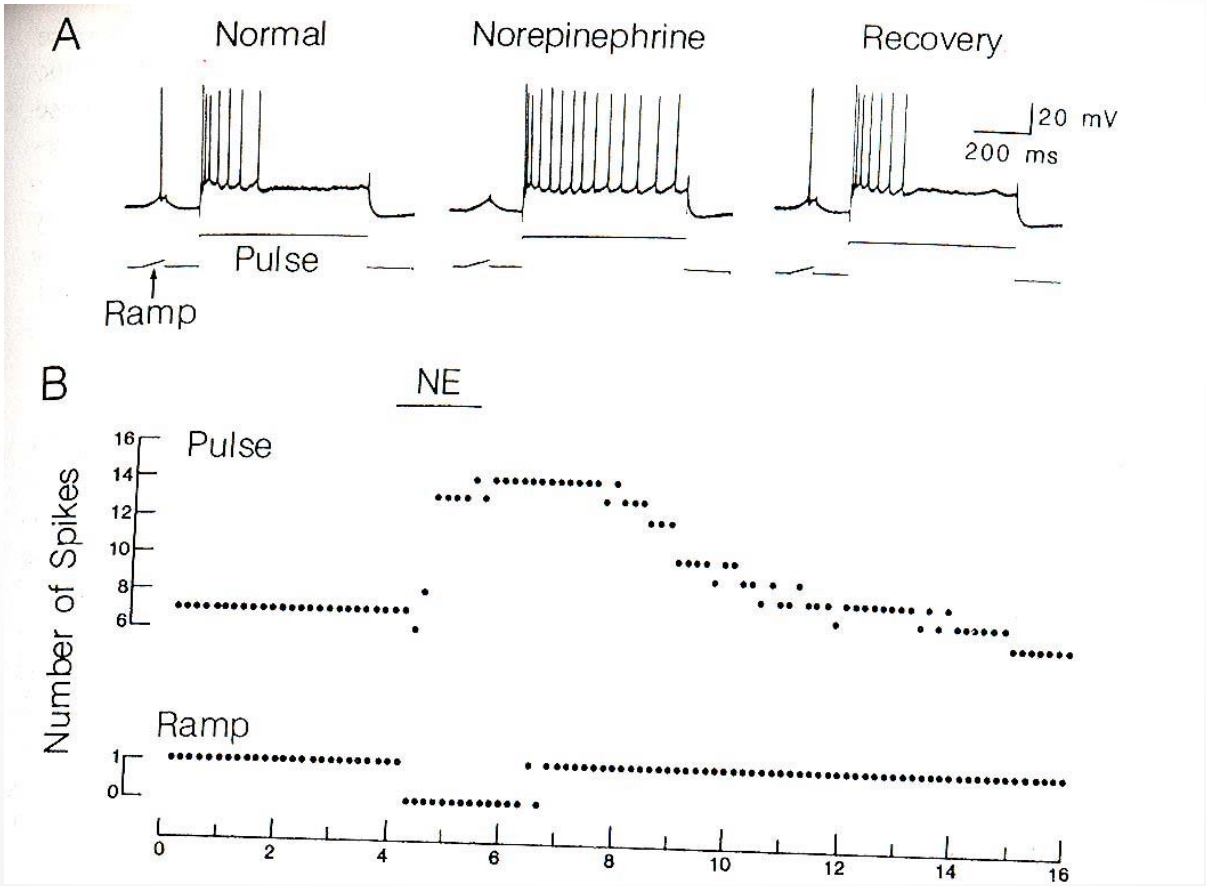
Receptor class	Glutamate	$GABA_B$	Dopamine	NE, Epi	Histamine	Serotonin	Purines	Muscarinic
Receptor subtype	Class I	$GABA_B$ R1	$D1_A$	α1	H1	5-HT 1	A type	M1
	mGlu R1	$GABA_B$ R2	$D1_B$	α2	H2	5-HT 2	A1	M2
	mGlu R5		D2	β1	H3	5-HT 3	A2a	M3
	Class II		D3	β2		5-HT 4	A2b	M4
	mGlu R2		D4	β3		5-HT 5	A3	M5
	mGlu R3					5-HT 6	P type	
	Class III					5-HT 7	P2x	
	mGlu R4						P2y	
	mGlu R6						P2z	
	mGlu R7						P2t	
	mGlu R8						P2u	

Receptores metabotrópicos produzem PPSs lentos





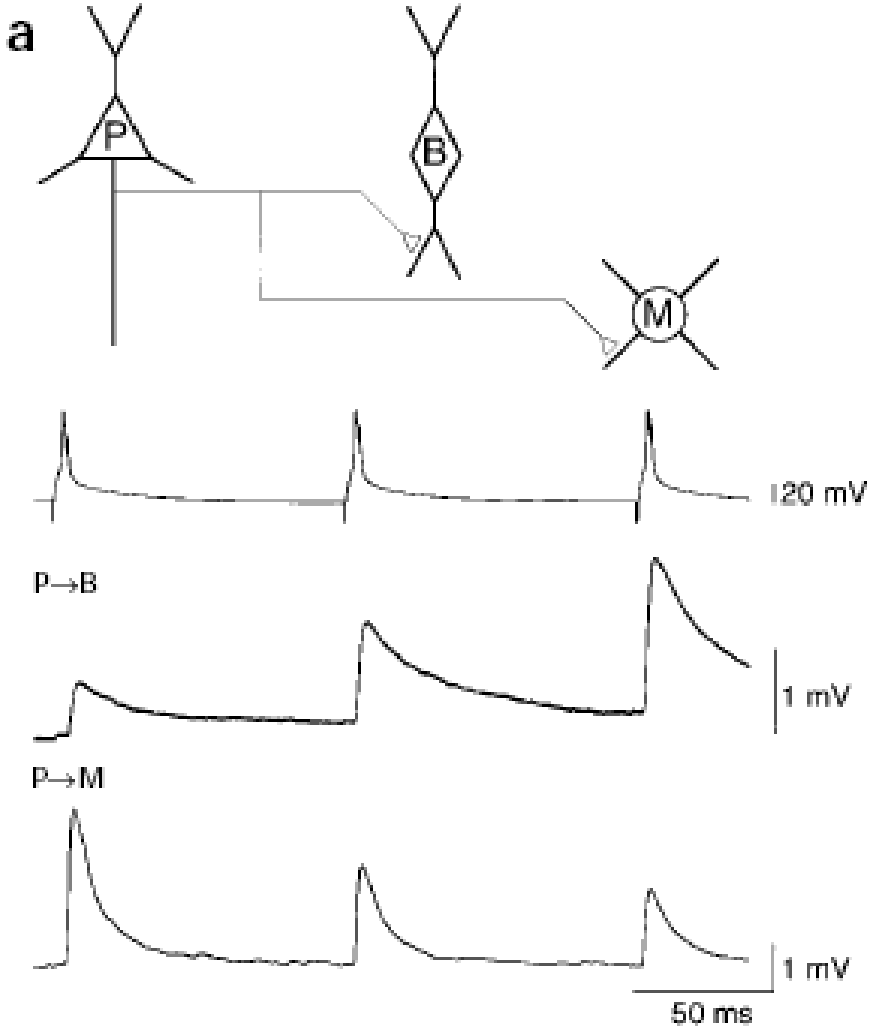
Neurotransmissores podem alterar a excitabilidade da membrana pós-sináptica via receptores metabotrópicos



Plasticidade sináptica

- Alterações da força sináptica em resposta a estimulação **repetitiva** das vias aferentes.
  - Curto prazo (milissegundos a segundos)
    - Observada em todas as sinapses
    - Reflete a fisiologia sináptica
  - Longo prazo (> 1 hora)
    - Específica de certas sinapses (ex. hipocampo, córtex)
    - Depende de mecanismos específicos

Plasticidade sináptica a curto prazo: Facilitação e depressão das correntes sinápticas em resposta a estímulos próximos.



Exemplo: neurônio **A** que excita os neurônios **B** e **M** a cada 100 ms

facilitação

depressão

Plasticidade sináptica a curto prazo

Mecanismos da depressão:

depleção vesicular (pré sináptico)
dessensibilização dos receptores (pós-sináptico

Mecanismos da facilitação:

acúmulo de cálcio no terminal (pré)
facilitação da mobilização de vesículas e/ou aumento da pr (pré)

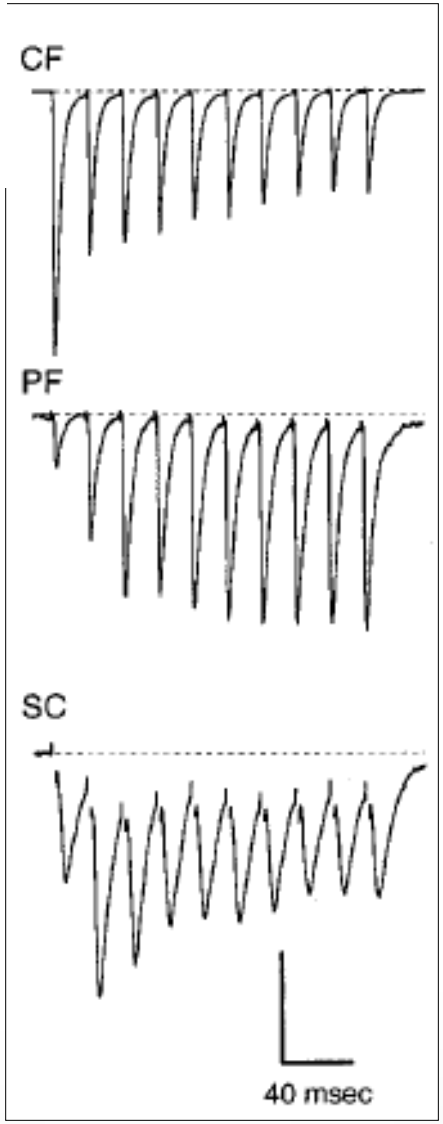
Pr determina se há depressão ou facilitação

Pr pode variar de 0.01 a 0.9

The Journal of Neuroscience, February 15, 2000, 20(4):1374–1385

Interplay between Facilitation, Depression, and Residual Calcium at Three Presynaptic Terminals

Jeremy S. Dittman, Anatol C. Kreitzer, and Wade G. Regehr
Department of Neurobiology, Harvard Medical School, Boston, Massachusetts 02115



Climbing fiber-Purkinje cell

Depressão

Alto pr

Parallel fiber-Purkinje cell

Facilitação

Baixo pr
n estável

CA3-CA1

Baixo pr
queda do n

Plasticidade a longo prazo

- Potenciação a longo prazo (LTP) e depressão a longo prazo (LTD)
- Dura horas ou dias (*in vivo*)
- Típico de sinapses hipocampais, cerebelares e corticais
- Plasticidade **associativa** significa que depende da despolarização simultânea do terminal pré-sináptico e do neurônio pós-sináptico.

J. Physiol. (1973), **232**, *pp.* 331–356
With 12 *text-figures*
Printed in Great Britain

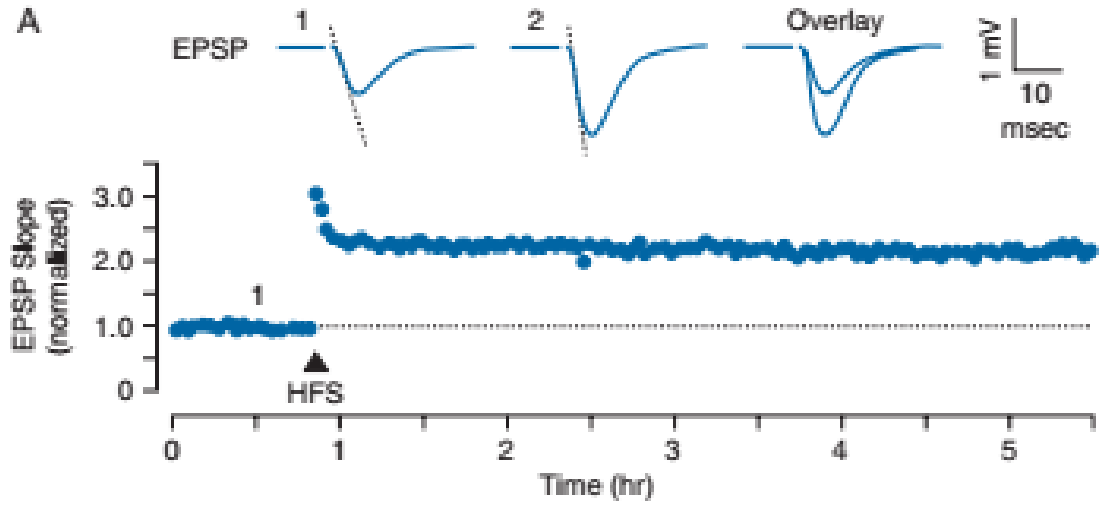
LONG-LASTING POTENTIATION OF SYNAPTIC TRANSMISSION IN THE DENTATE AREA OF THE ANAESTHETIZED RABBIT FOLLOWING STIMULATION OF THE PERFORANT PATH

BY T. V. P. BLISS AND T. LØMO

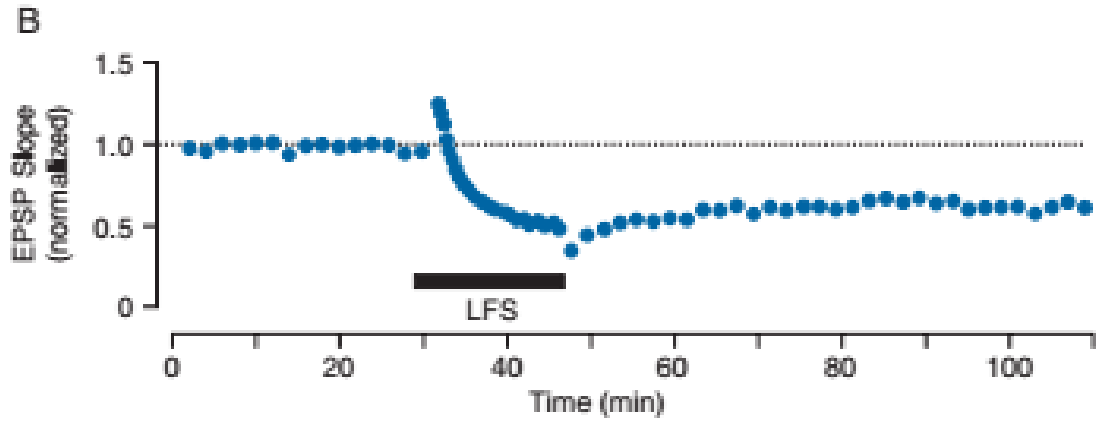
From the National Institute for Medical Research, Mill Hill, London NW7 1AA and the Institute of Neurophysiology, University of Oslo, Norway

(*Received 12 February 1973*)

Potenciação (LTP) vs. Depressão (LTD) a longo prazo



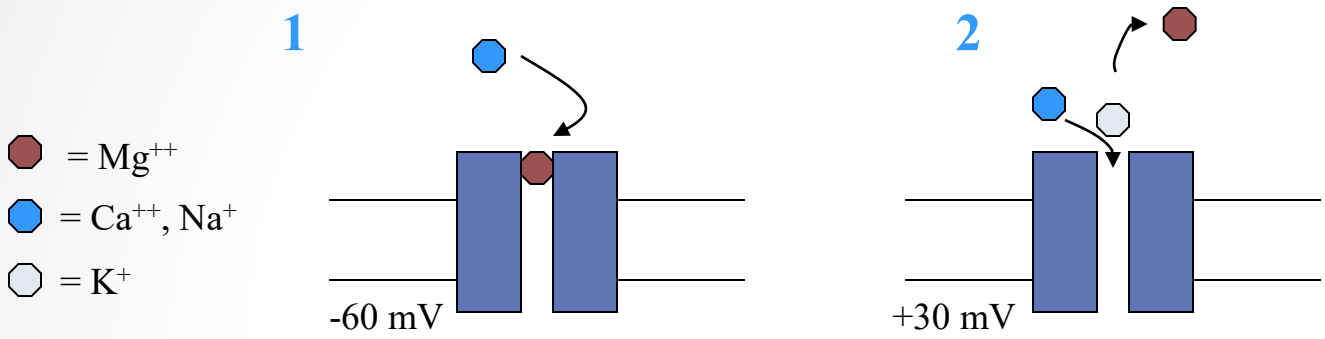
100 Hz; 3 segundos



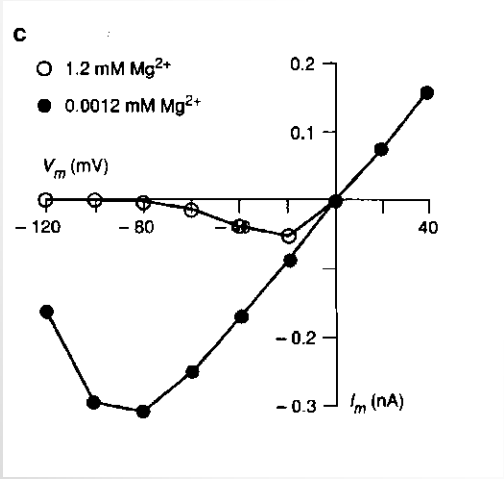
1 Hz; 90 segundos

Hammond. Cellular and Molecular Neurophysiology.

O LTP e LTD hippocampal dependem da entrada de cálcio pelo receptor NMDA durante as despolarizações

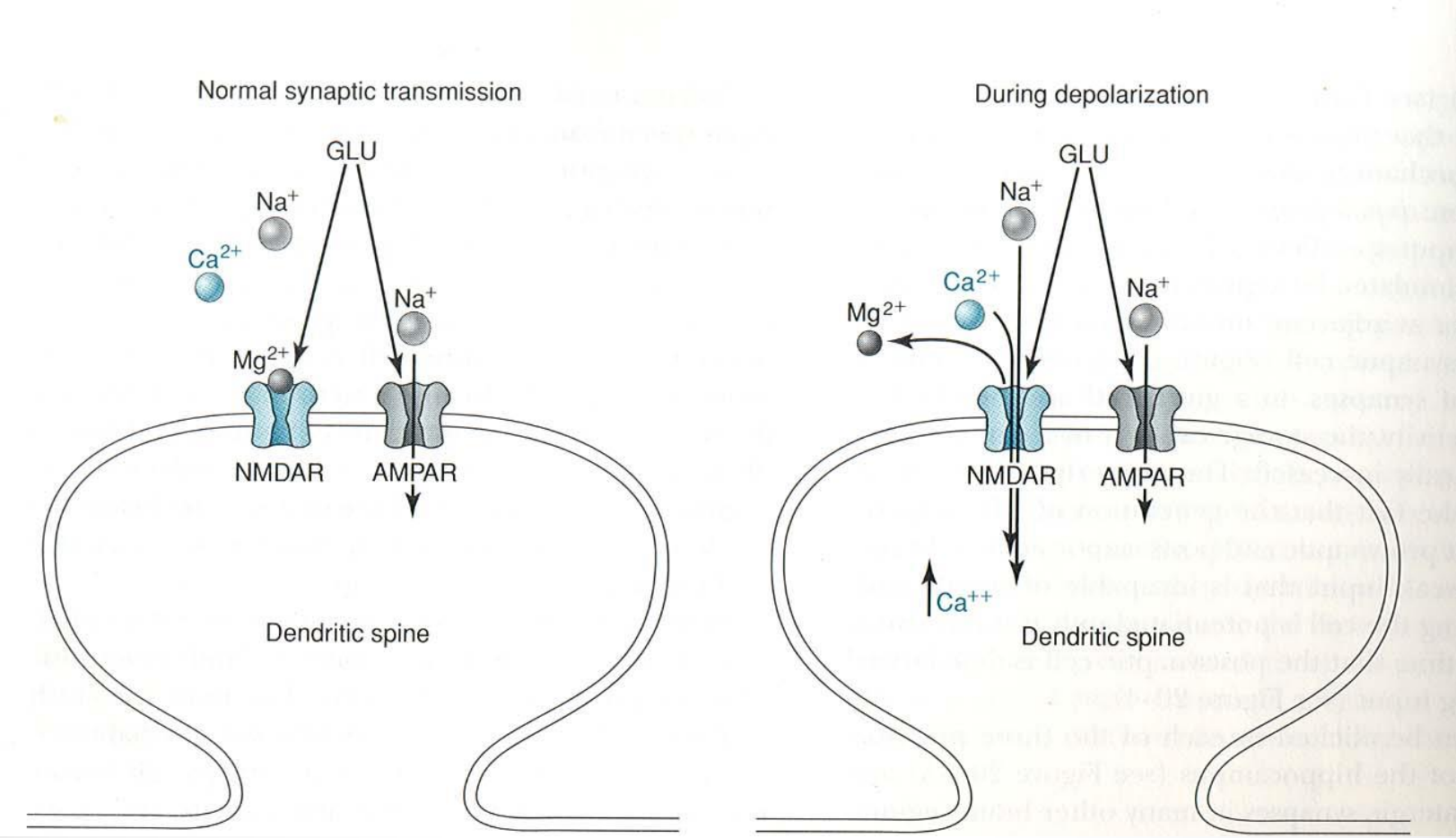


1. Bloqueio da entrada de cátios pelo magnésio externo no repouso
2. Em potenciais positivos a saída dos cátions expulsa o magnésio



Apenas quando a despolarização da célula pós-sináptica for grande o suficiente (>0 mV) é que o receptor NMDA se abre e permite o influxo de cálcio

O receptor NMDA funciona como um "detector de coincidência"



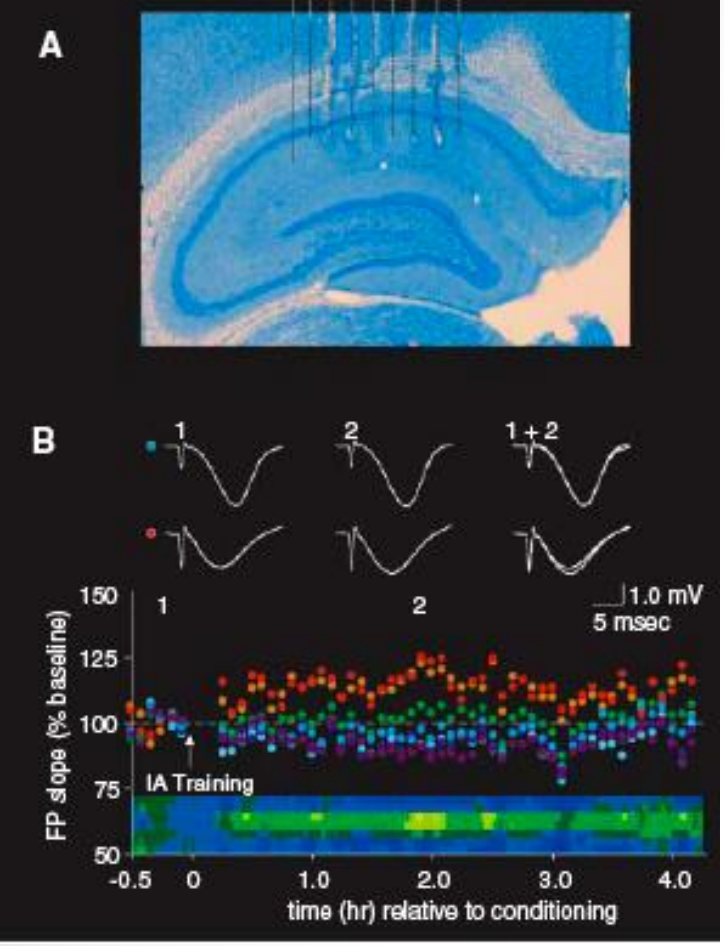
Hammond. Cellular and Molecular Neurophysiology.

- Mecanismos da LTP (hipocampo-CA1)
  - Aumento da condutância dos receptores AMPA
  - Incorporação de novos receptores AMPA en sinapses existentes
  - Incorporação de novos receptores AMPA em sinapses "silenciosas" (que contém apenas receptores NMDA)
  - Efetor: **CAM/kinase II**

- Mecanismos da LTD(hipocampo-CA1)
  - Reversão dos mecanismos da LTP pela **calcineurina (PP2B)**
    - "despontenciação"

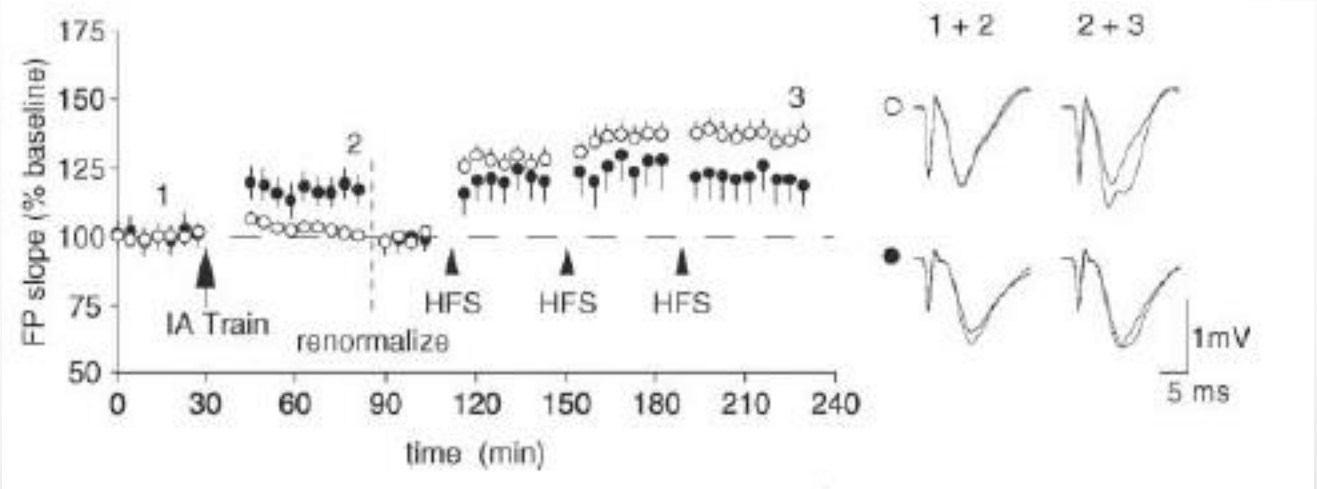
$$K_{dCa}\ PP2B < K_{dCa}\ CAMKII$$

LTP = memória?

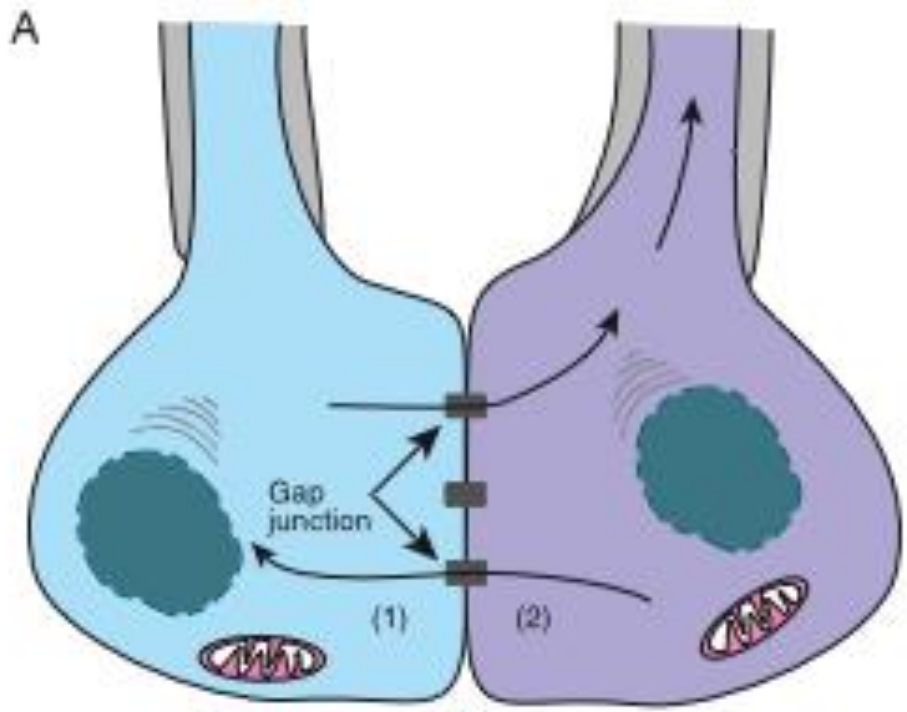


Science
AAAS

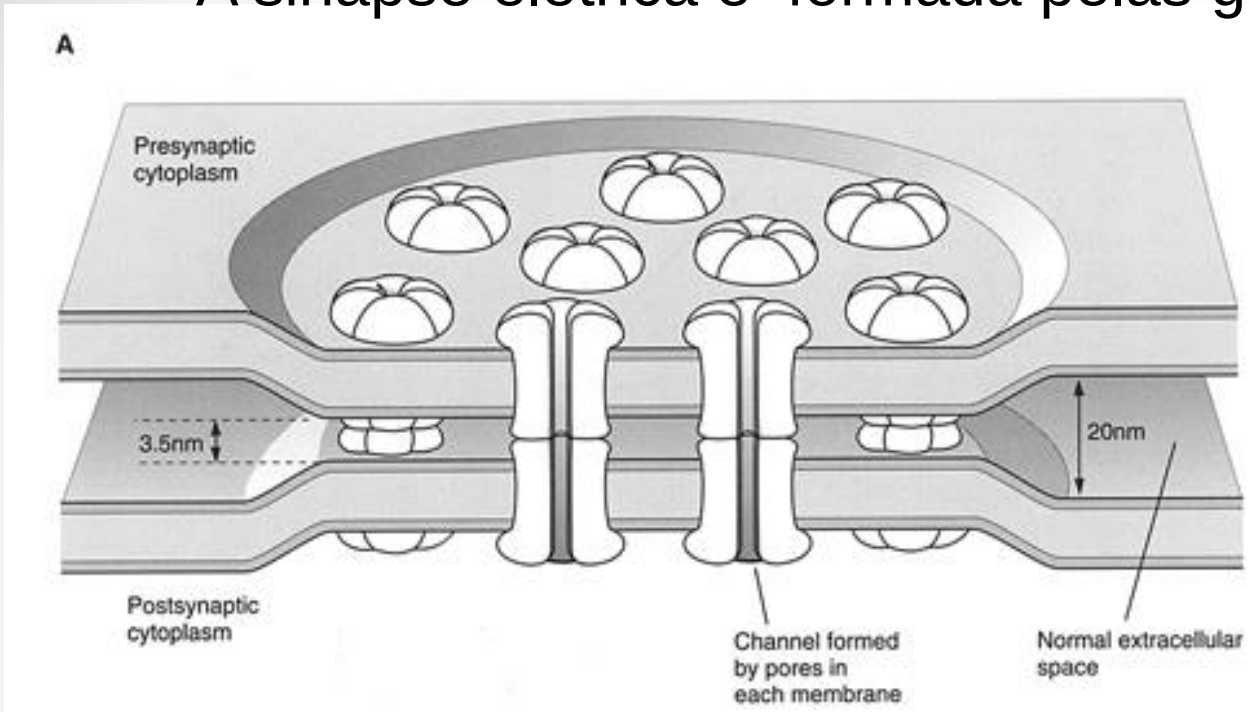
Learning Induces Long-Term Potentiation in the Hippocampus
Jonathan R. Whitlock, *et al.*
Science **313**, 1093 (2006);
DOI: 10.1126/science.1128134



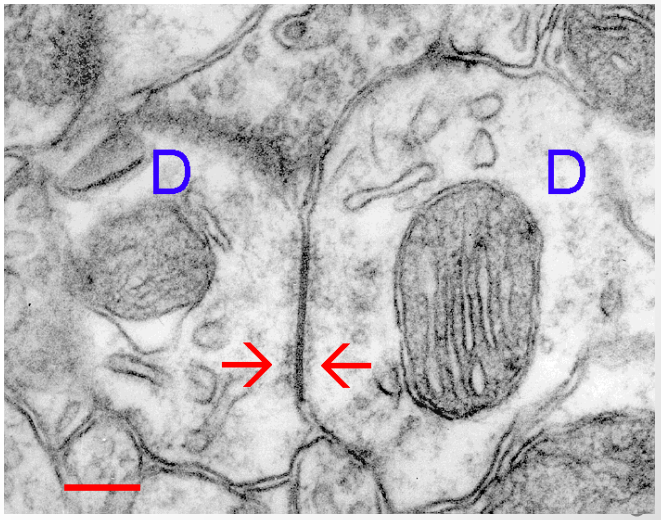
Sinapses elétricas independem de neurotransmissores



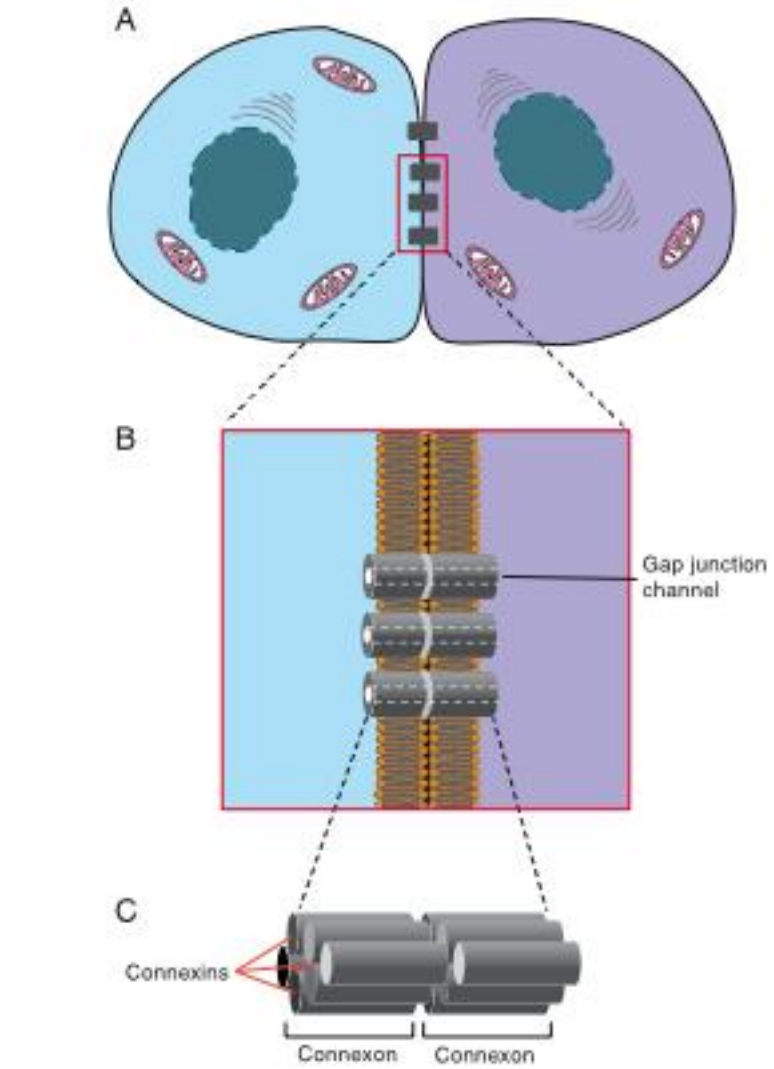
A sinapse elétrica é formada pelas gap-junctions

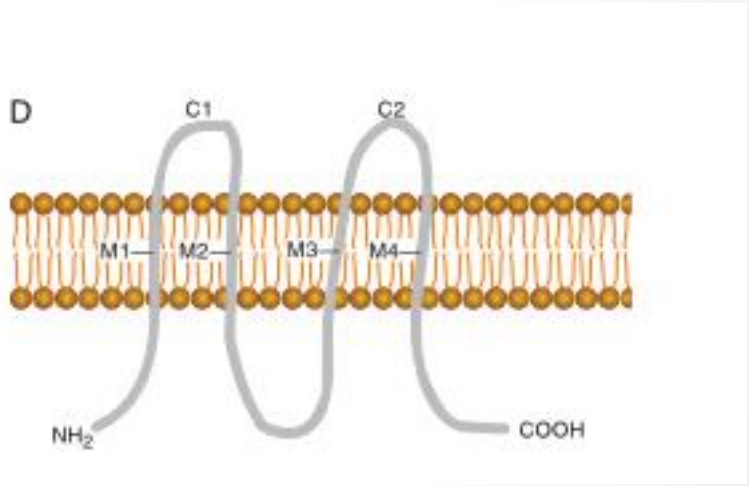


Gap-junctions podem serer aberas por cálcio e baixo pH por exemplo.
São importantes em arcos reflexos ou quando se requer sincronia de atividade.

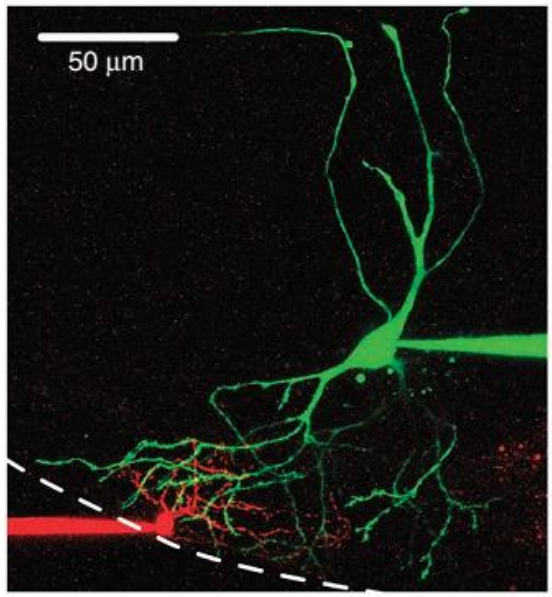


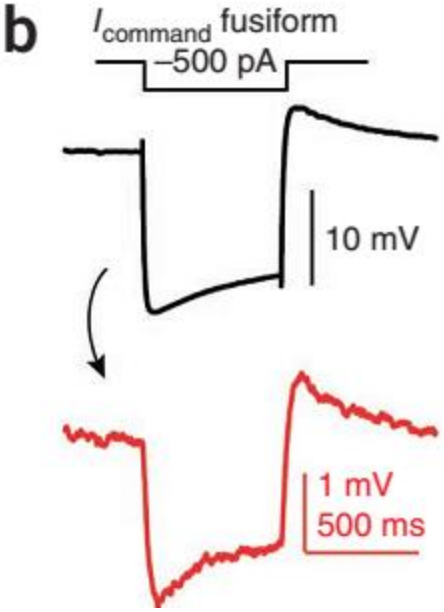
Os conexons (gap-junctions) são formados pelas conexinas (hemicanais)

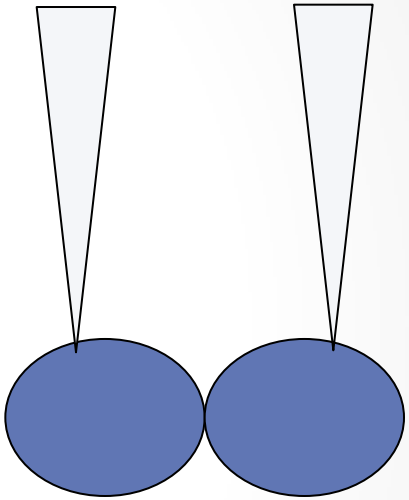


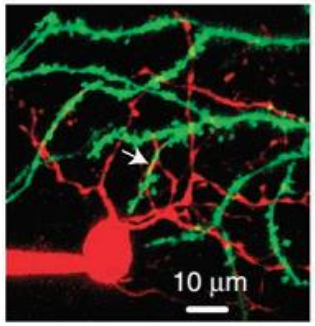


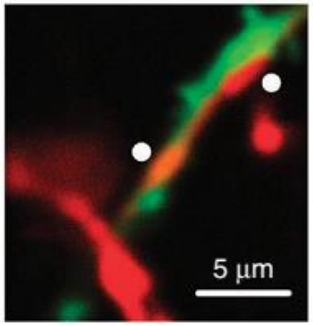
Neurônios acoplados eletricamente











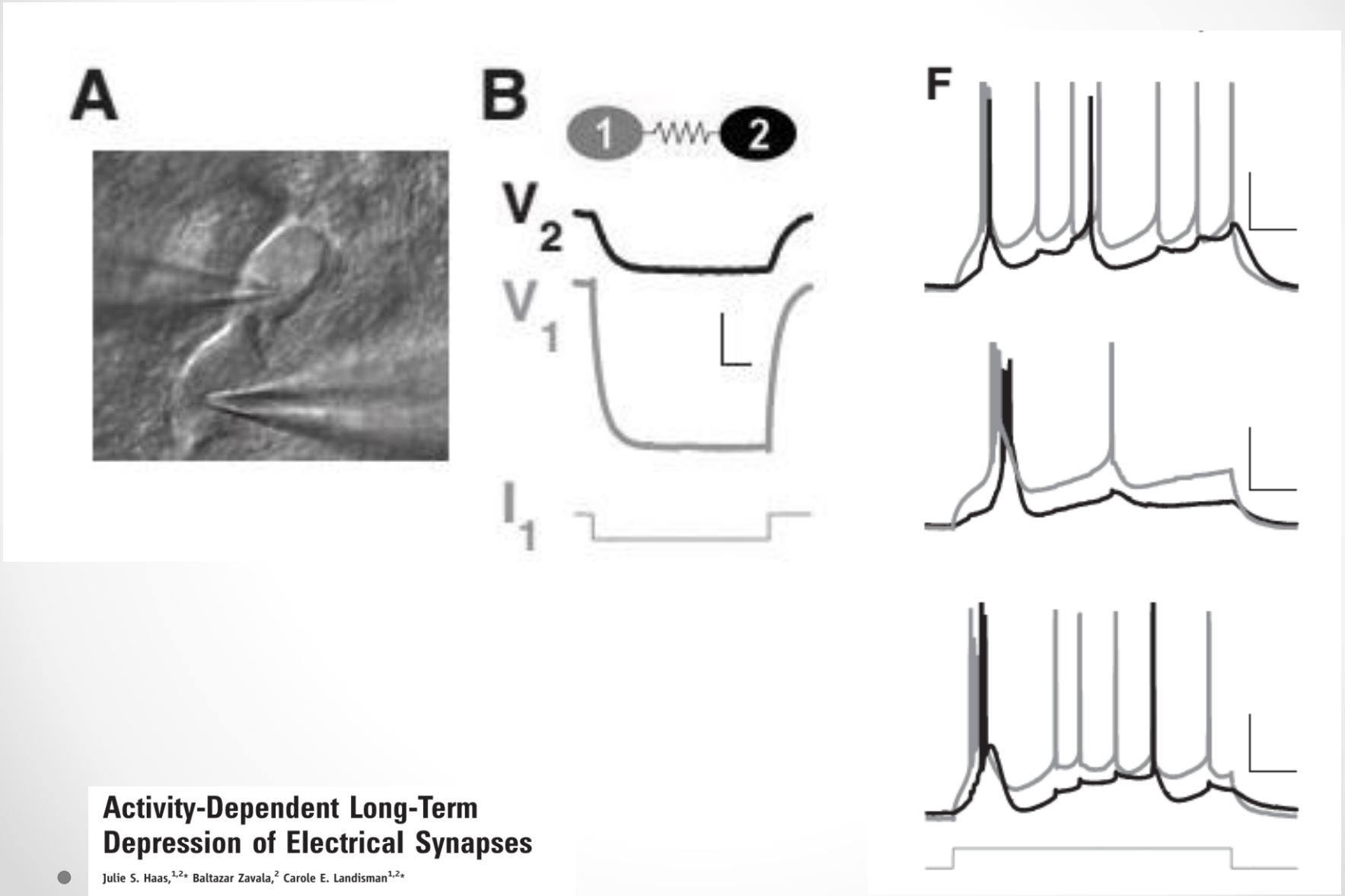
ARTICLES

nature neuroscience

Regulation of interneuron excitability by gap junction coupling with principal cells

Pierre F Apostolides[1,2] & Laurence O Trussell[2]

Sinapses elétricas talâmicas promovem sincronia



Activity-Dependent Long-Term Depression of Electrical Synapses

Julie S. Haas,[1,2]* Baltazar Zavala,[2] Carole E. Landisman[1,2]*

Obrigado pela atenção

Elk lake, Oregon, US – arquivo pessoal