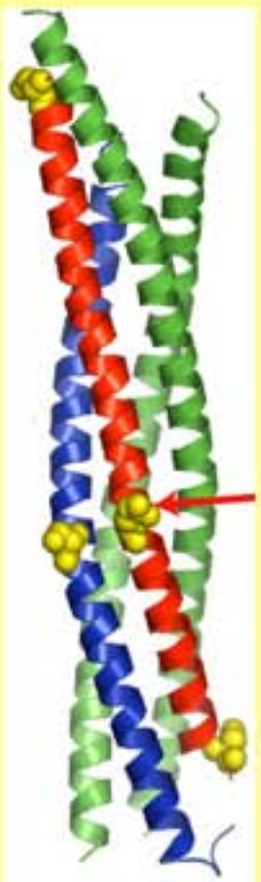
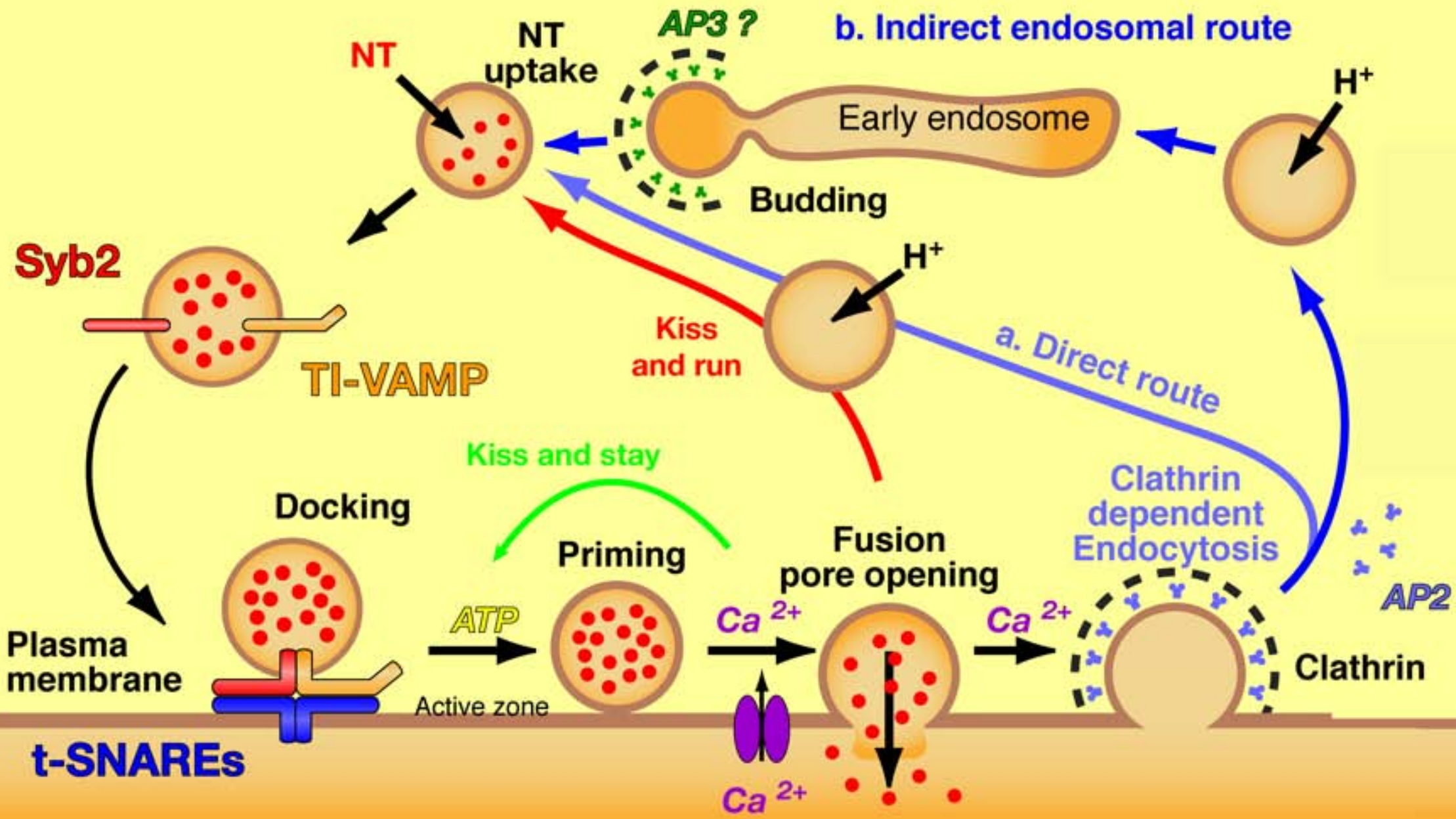
Complexe SNARE et communication cellulaire





Télécharger le cours sur http://lydia.danglot.free.fr

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Master de Neurosciences
Module « Communication cellulaire »
Université Pierre et Marie Curie (Paris 6)
20 octobre 2008

Le complexe SNARE et la communication cellulaire

1. **Exocytose et complexe SNARE**
   - Les voies d'exocytose régulée
   - Définition du complexe SNARE
   - Nomenclature v/t-SNARE et R/Q-SNARE
2. **Exemple de la synapse**
   - Découverte de NSF et SNAP
   - Isolement des SNARE
   - Rôle de NSF & SNAP dans la fusion
3. **Le cycle des vésicules synaptiques**
   - Voie lente: endocytose médiée par la clathrine
   - Voie courte: kiss and run
   - Les différents « pool » vésiculaires
4. **Comment mesurer l'exocytose ?**
   - Capacitance
   - Ampérométrie
   - GFP pH sensible: la Phluorin
   - Utilisation des SNARE inversée
5. **Comment mesurer le recyclage ?**
   - Utilisation des anti-synaptotagmine
   - Sondes fluorescentes de type FM
6. **Régulation de l'exocytose**
   - Munc-18 et les protéines SM
   - Munc 13, RIM et Rab3
   - Rôle de la complexine, synaptotagmine et du calcium
7. **Exemple de souris mutantes**
   - KO de la synaptobrevine
   - Mutants de l'adaptateur AP-3: les mocha

Master de Biologie
Module Neurbiologie n°2
Ecole Normale Supérieure

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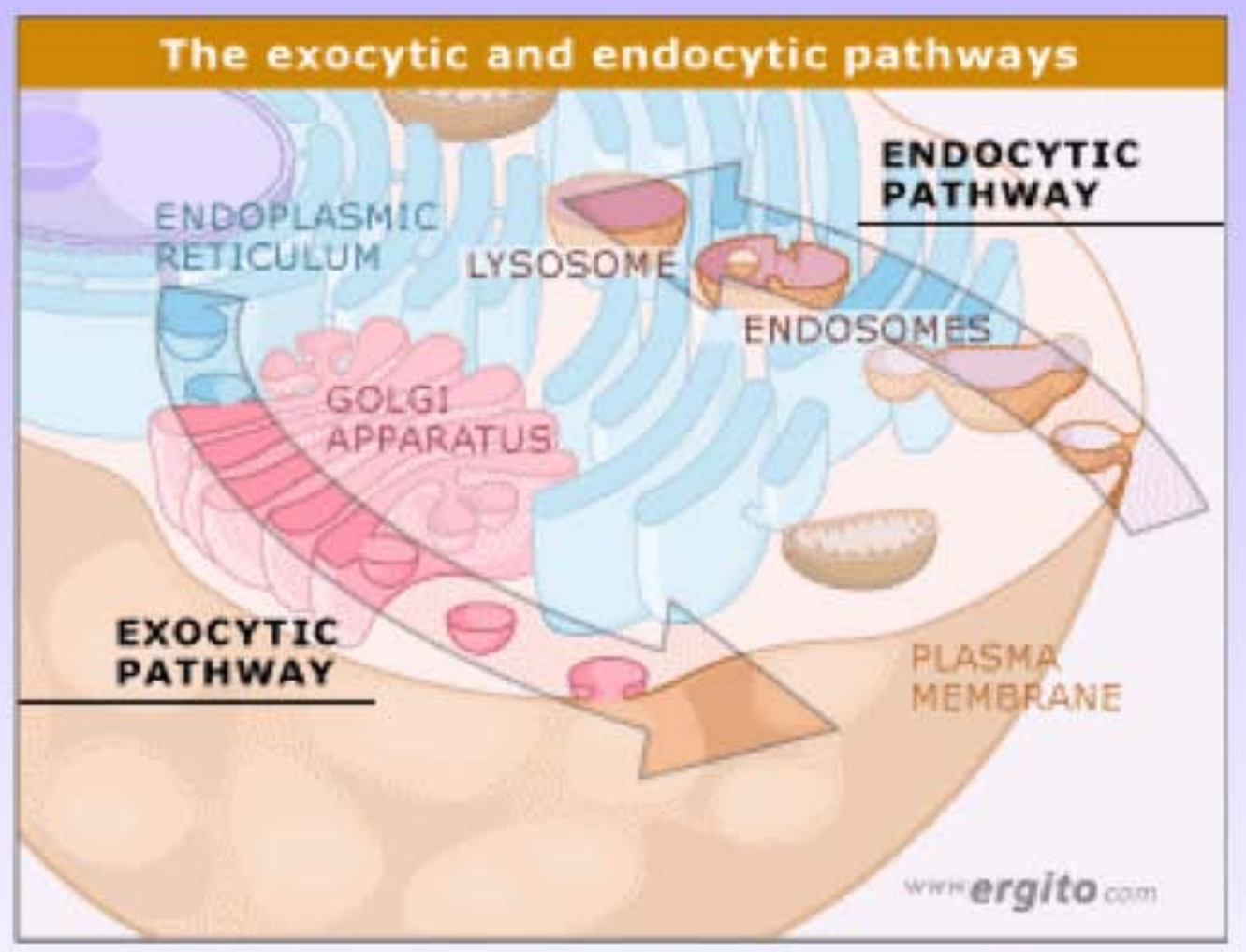
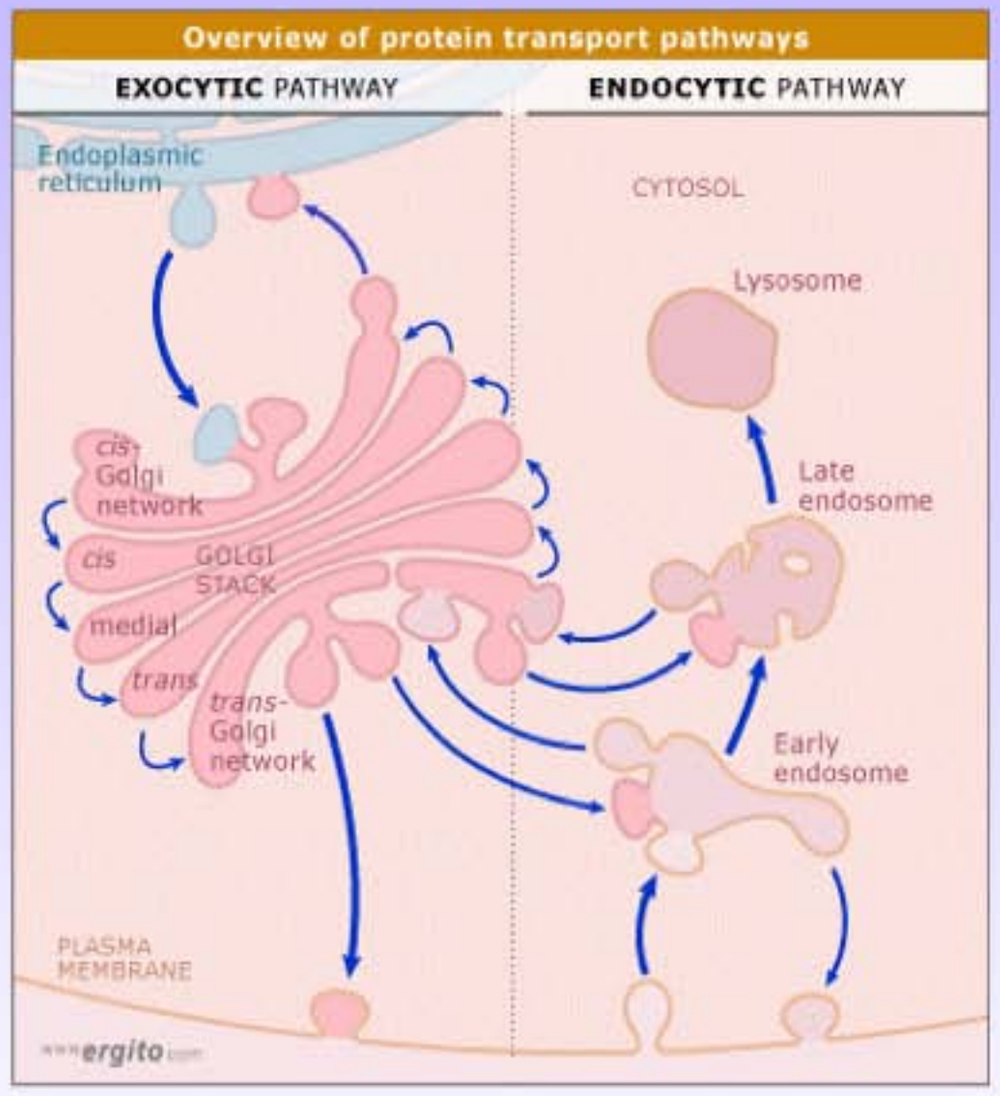
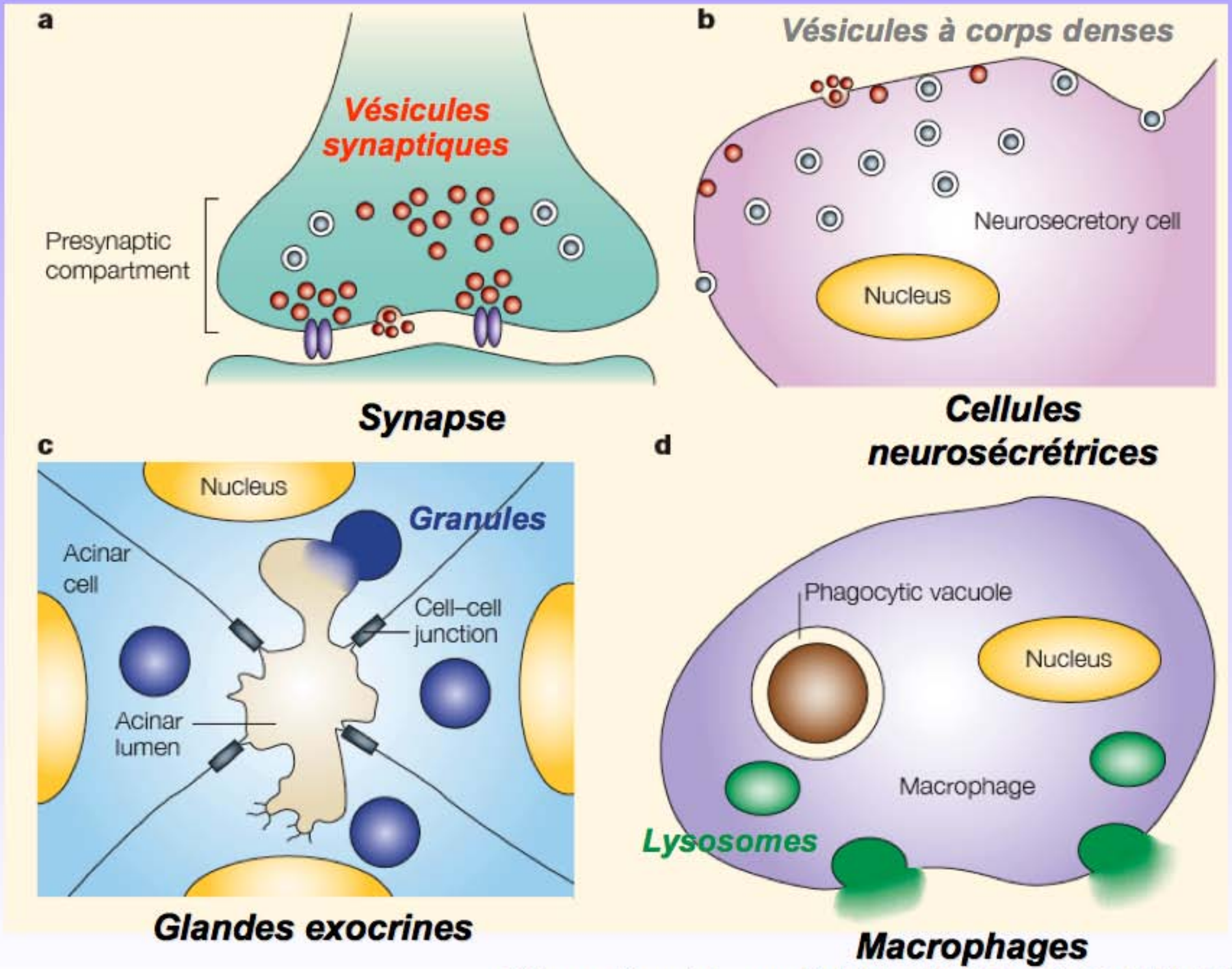
Exo-endocytose



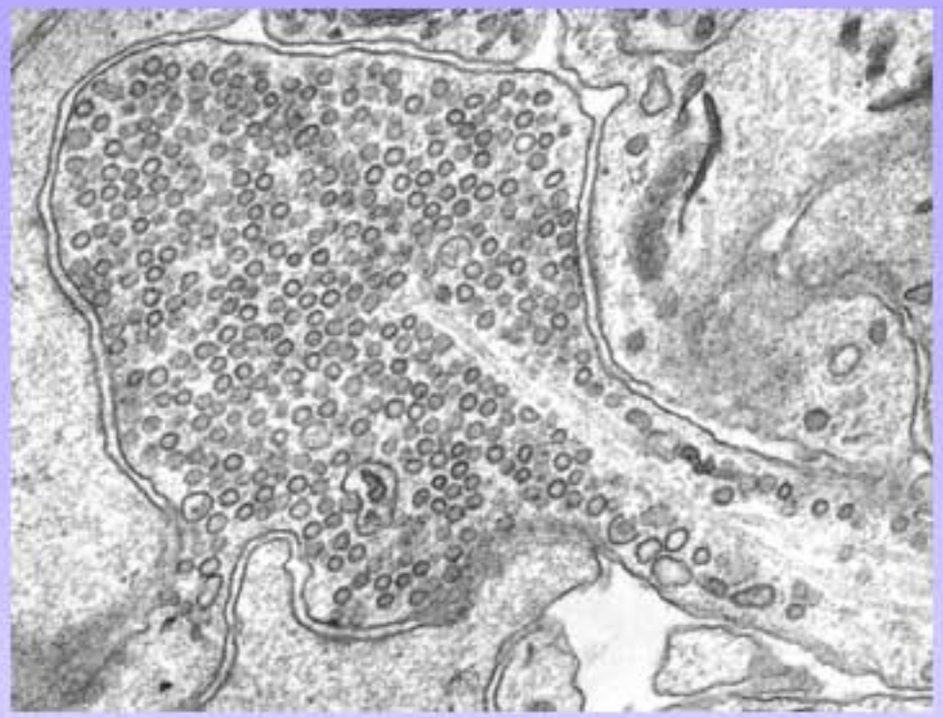


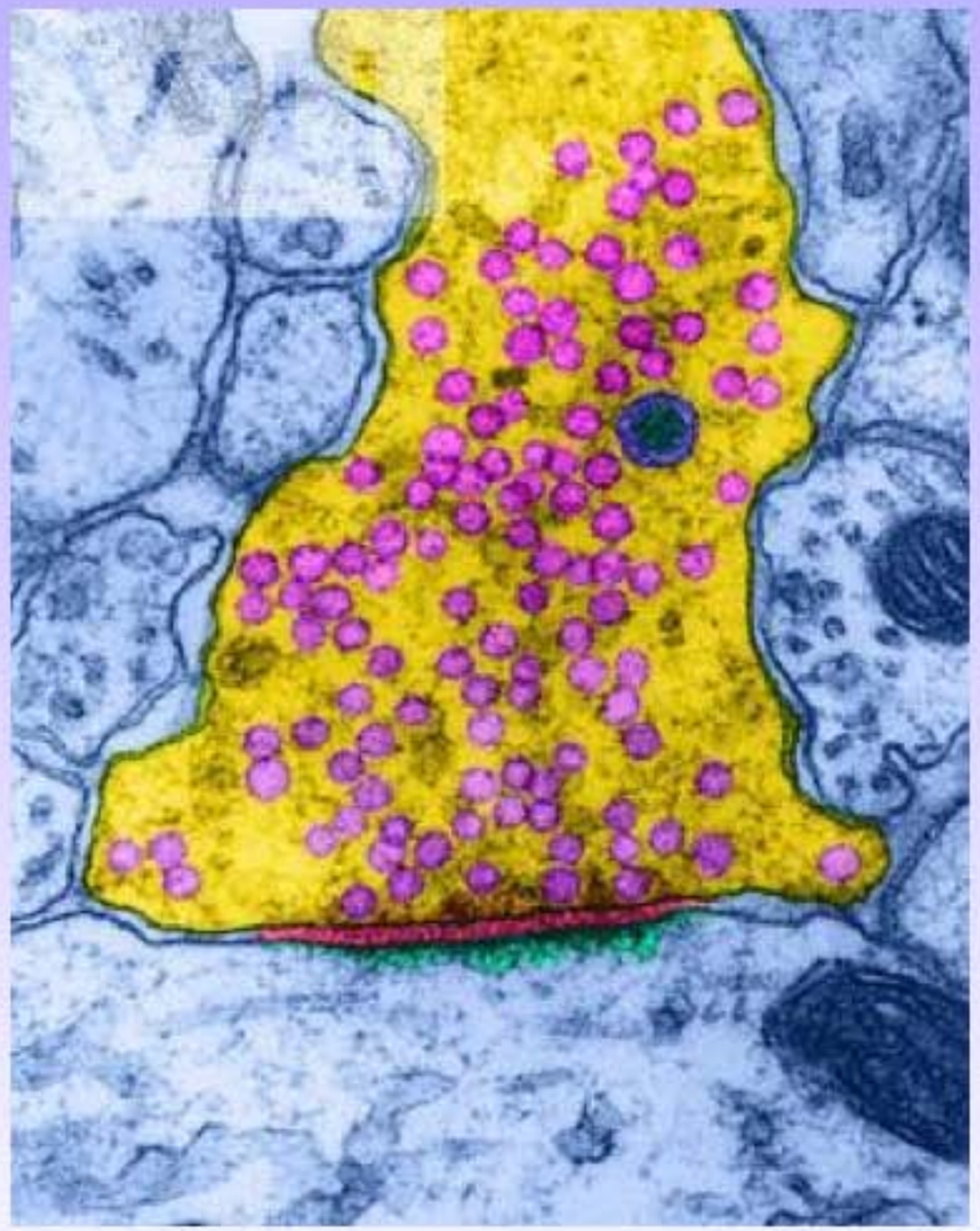
Exocytose régulée



Chieregatti and Jacopo Meldolesi Nat Rev Mol Cell Biol 2005

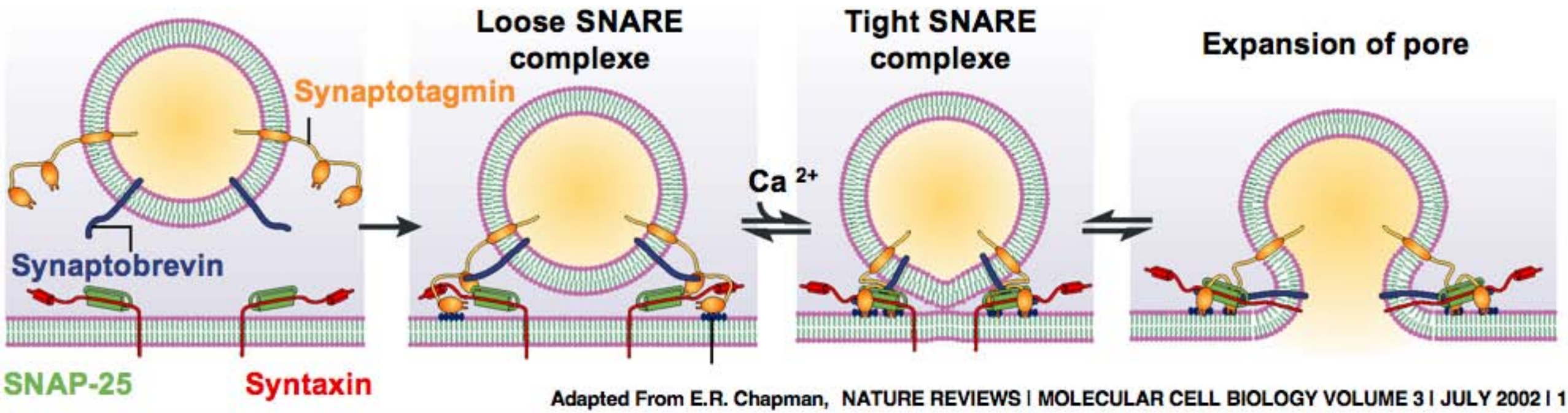
Les vésicules synaptiques



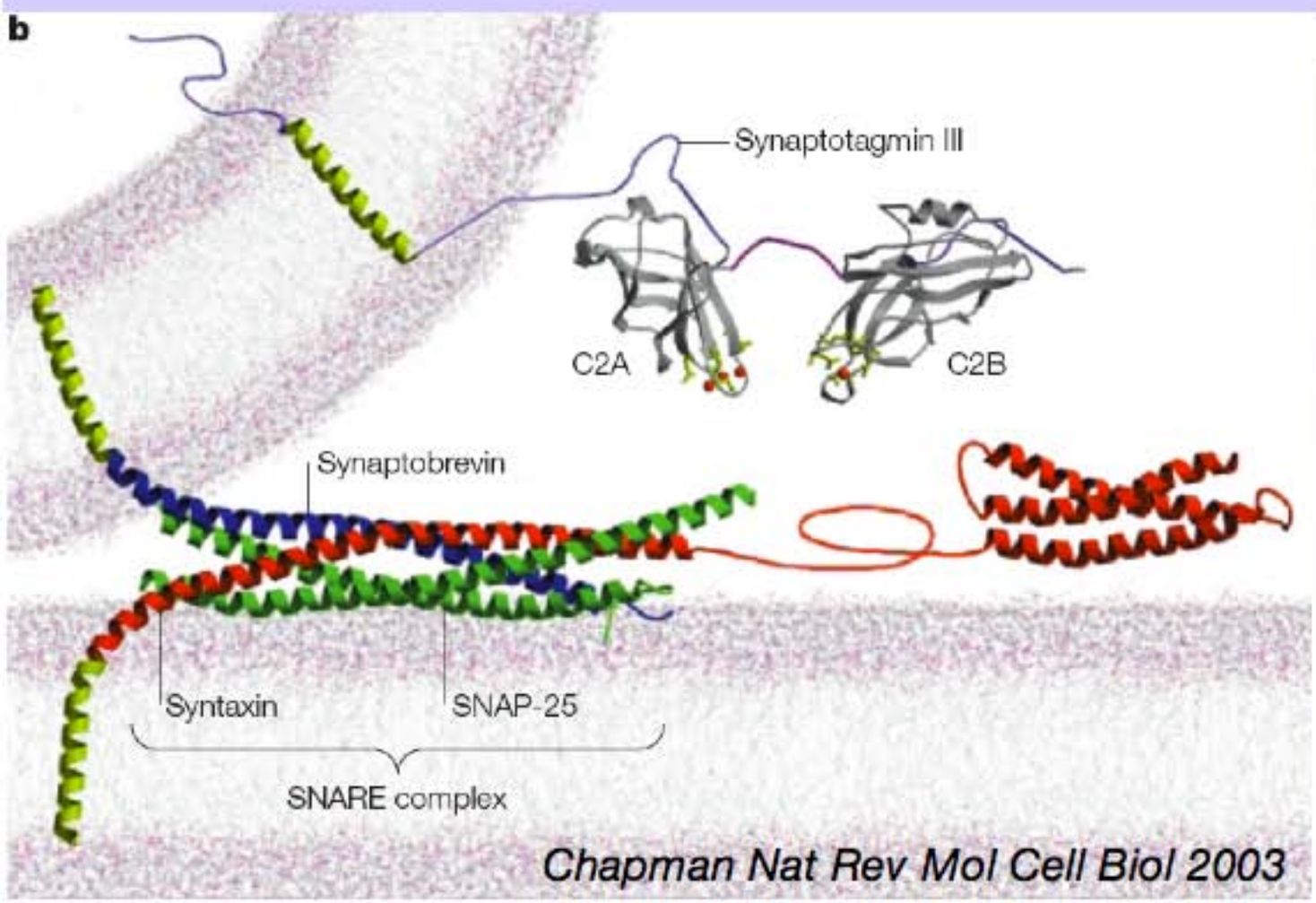


- 50 nm de diamètre
- 500 VS/terminaison
  - x10 000 contacts = 10^6 à 10^7 VS/neurone
  - x 10^{11} neurones = 10^{17} VS/SNC
- cholestérol:phospholipides = 1:2
- 12000 molécules de phospholipides / VS
- phospholipides:protéines = 1:1
- 20 à 40 protéines différentes / VS
- synaptophysine= 7% protéine VS = 0,3% protéines totales

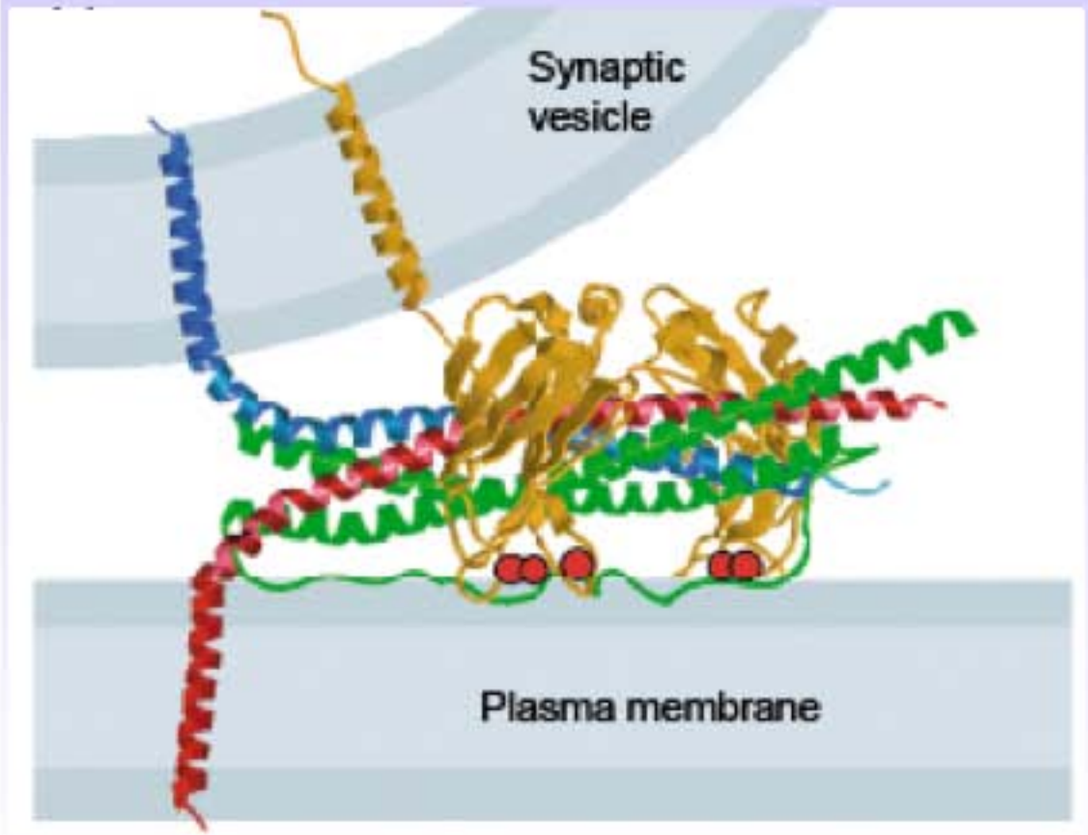
Les protéines SNARE et l'exocytose



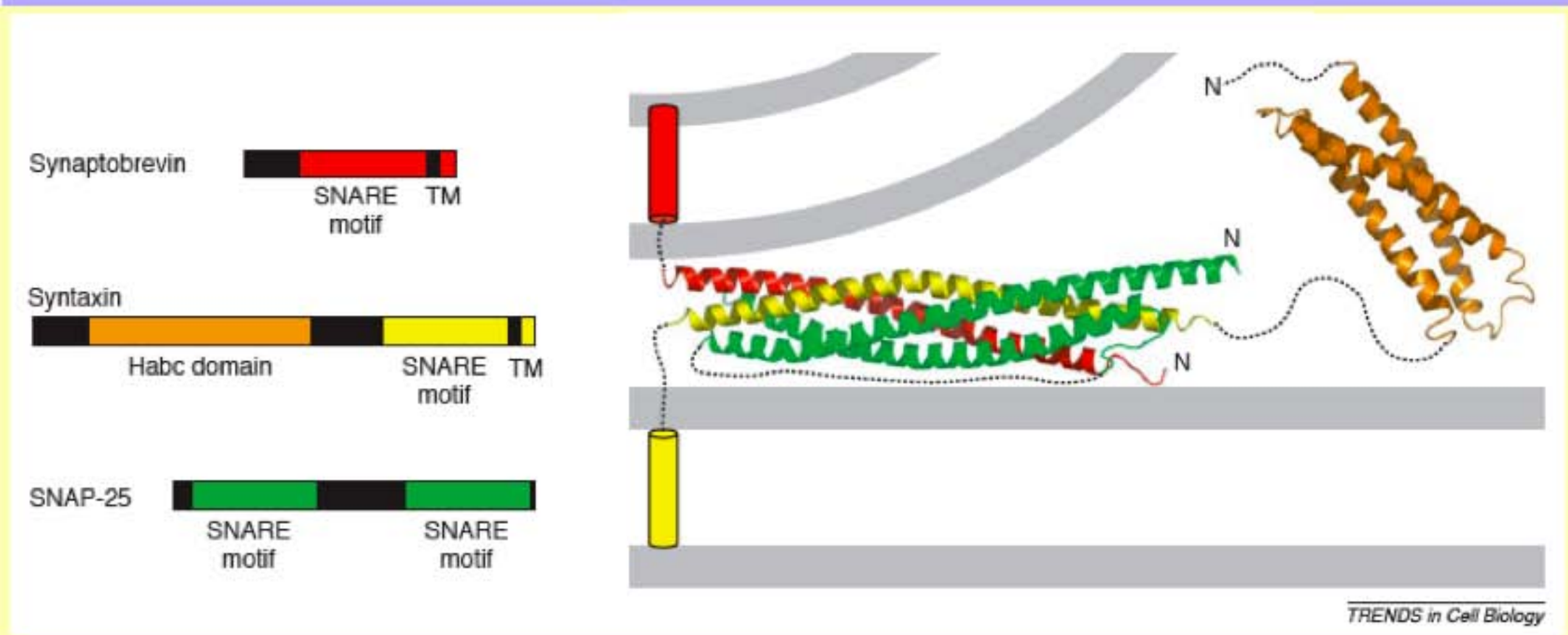
Adapted From E.R. Chapman, NATURE REVIEWS | MOLECULAR CELL BIOLOGY VOLUME 3 | JULY 2002 | 1



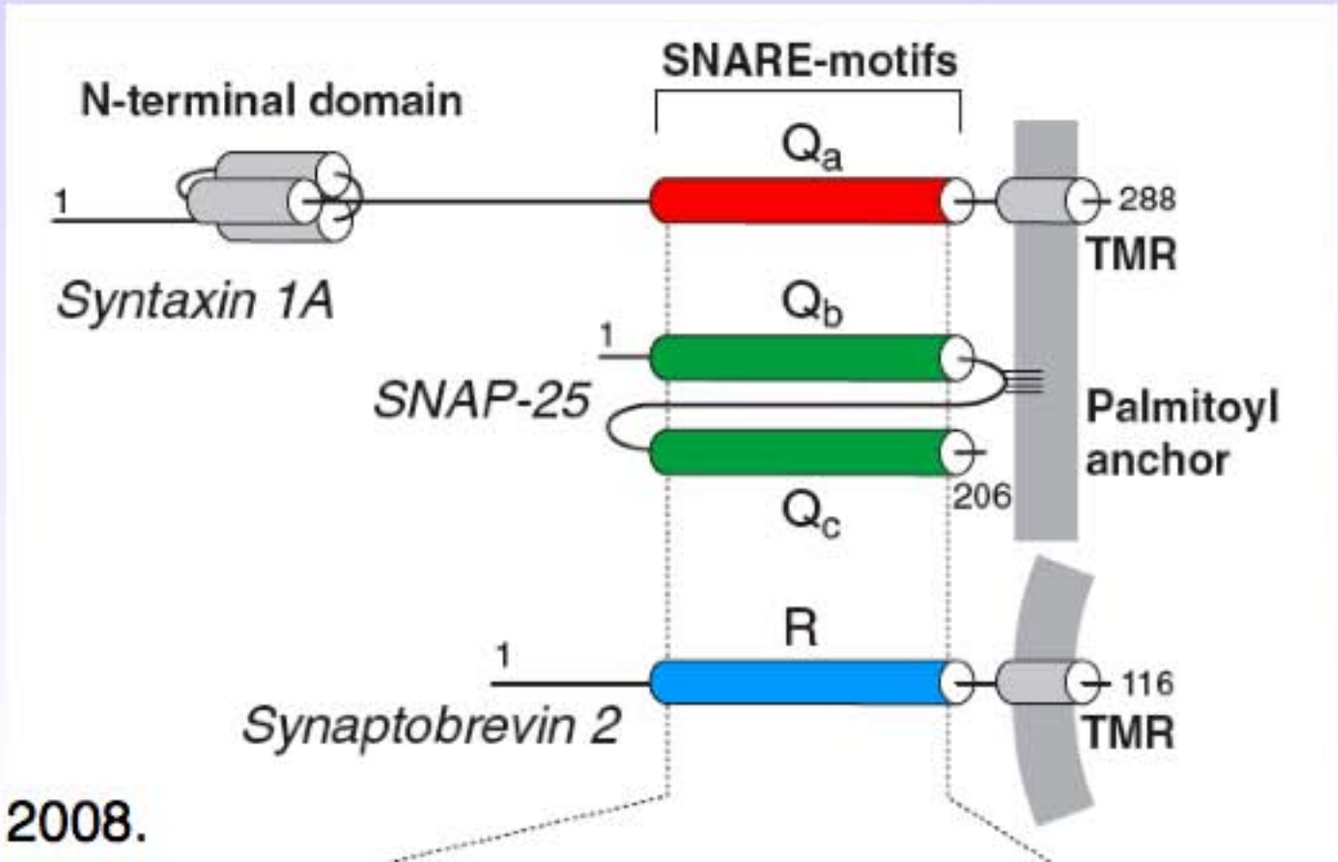
Chapman Nat Rev Mol Cell Biol 2003



Le complexe SNARE



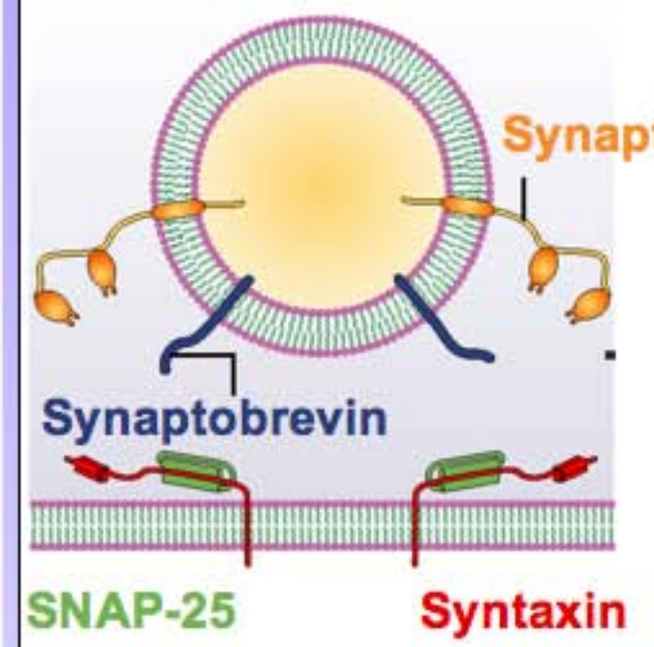
Rizo, Chen et d'Areç, Tins 2006.



Core Proteins of the Secretory

Lang and Jahn, Pharmacology of NT release, 2008.

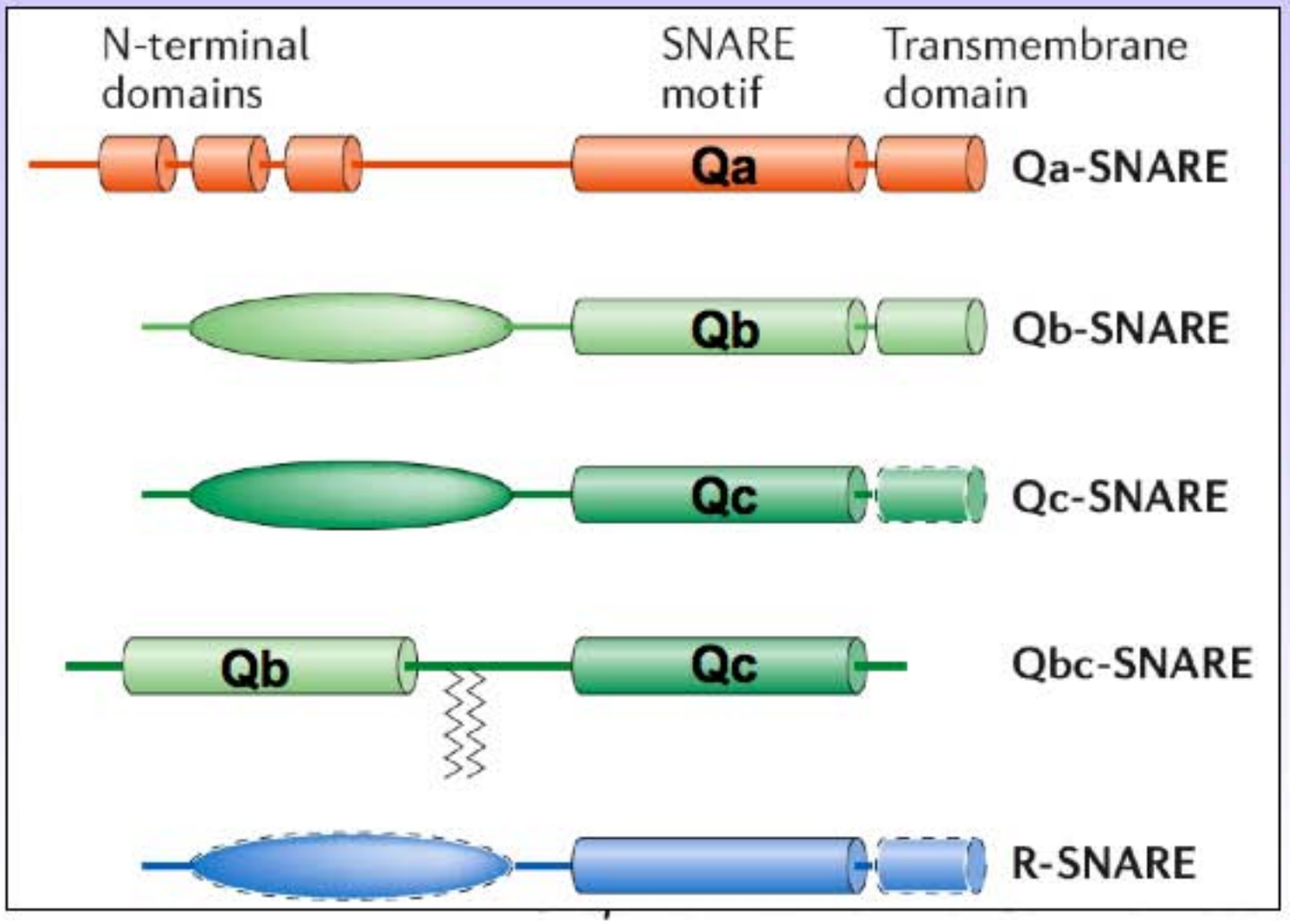
Les protéines SNARE et l'exocytose



- v-SNARE: sur la vesicule (vesicle)
- t-SNARE: sur la membrane cible (target)

- 1 complexe SNARE = 1 motif SNARE sur la vesicule (R)
  + 3 motifs SNAREs sur la membrane cible (Q)

- Les 3 motifs t-SNARE peuvent venir de :
  - 2 t-SNAREs :1 SNARE avec 1 motif (Qa), 1 SNARE avec 2 motifs (Qbc)
  - 3 t-SNAREs: 3 SNARES differents avec 1 motif chacun (Qa, Qb, Qc).



ex: Syntaxin 1 à 5, 11, 13, 16, 17, 18.

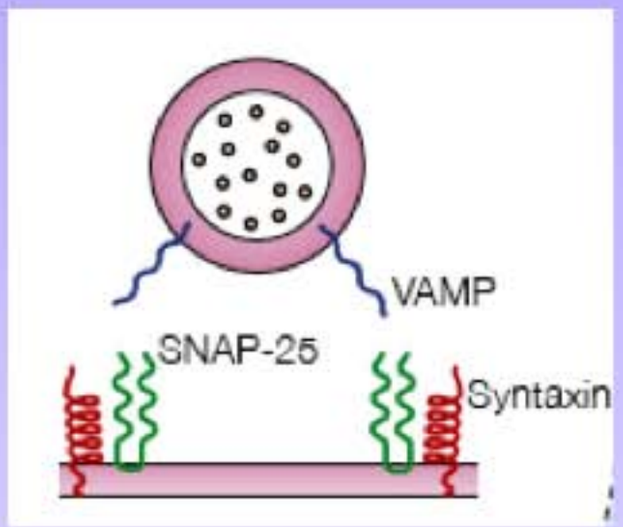
ex: Vti1a, Vti1b, GS27,GS28

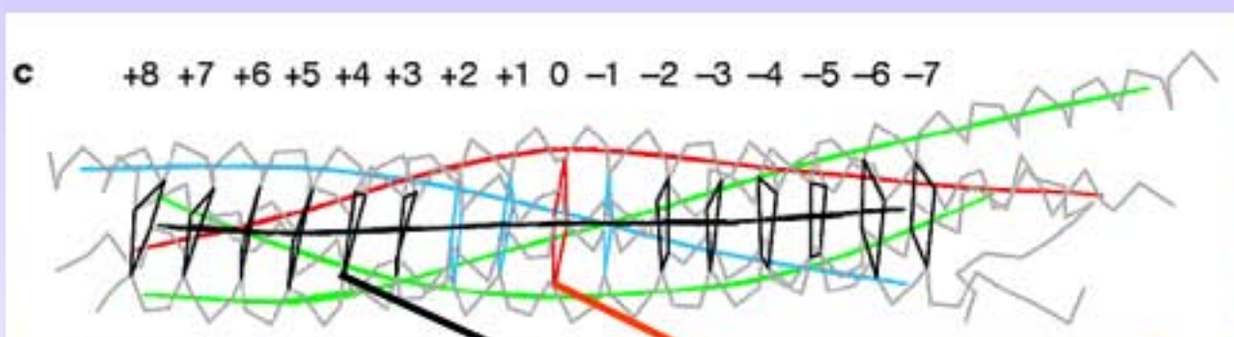
ex: Bet21, GS15, stx6, stx8, stx10

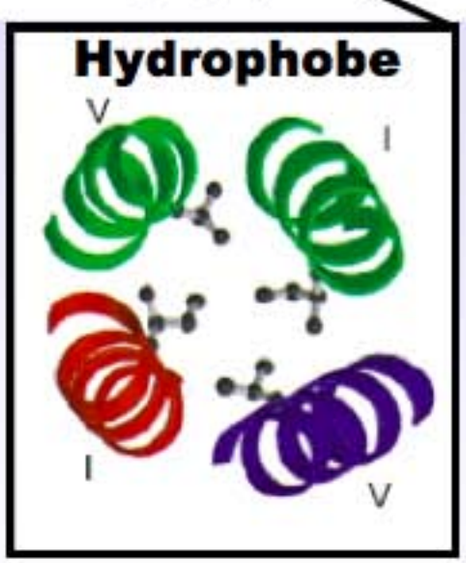
ex: SNAP-25, SNAP-23, SNAP-29

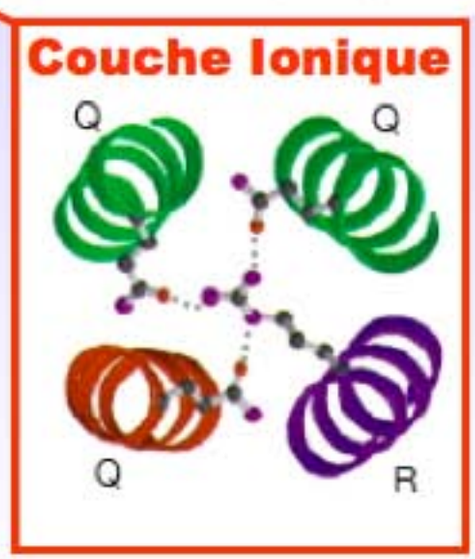
ex: Syb2, Tl-VAMP, Sec22, YKT6
VAMP1 à VAMP8

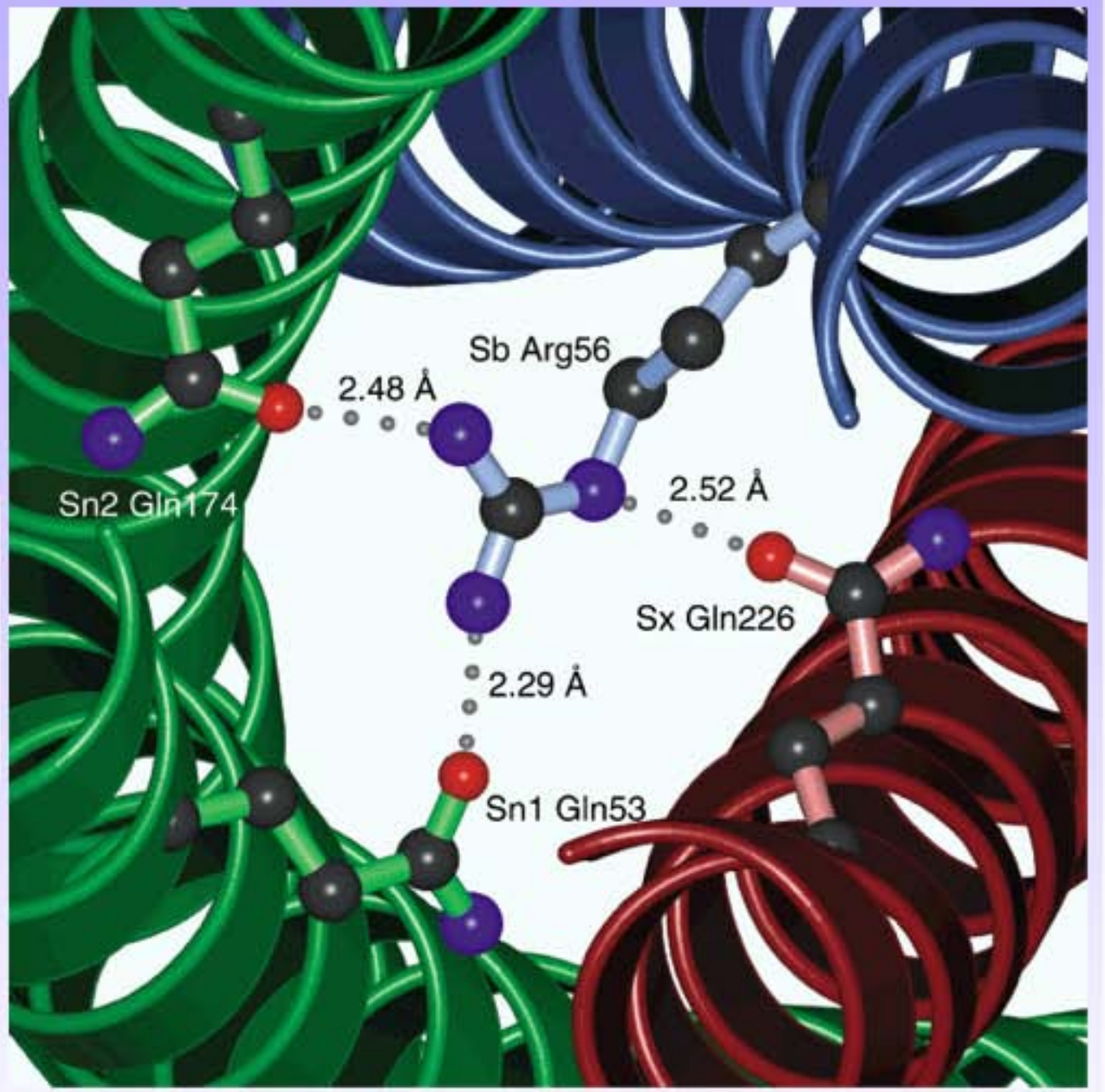
Le complexe SNARE : Q-SNARE & R-SNARE





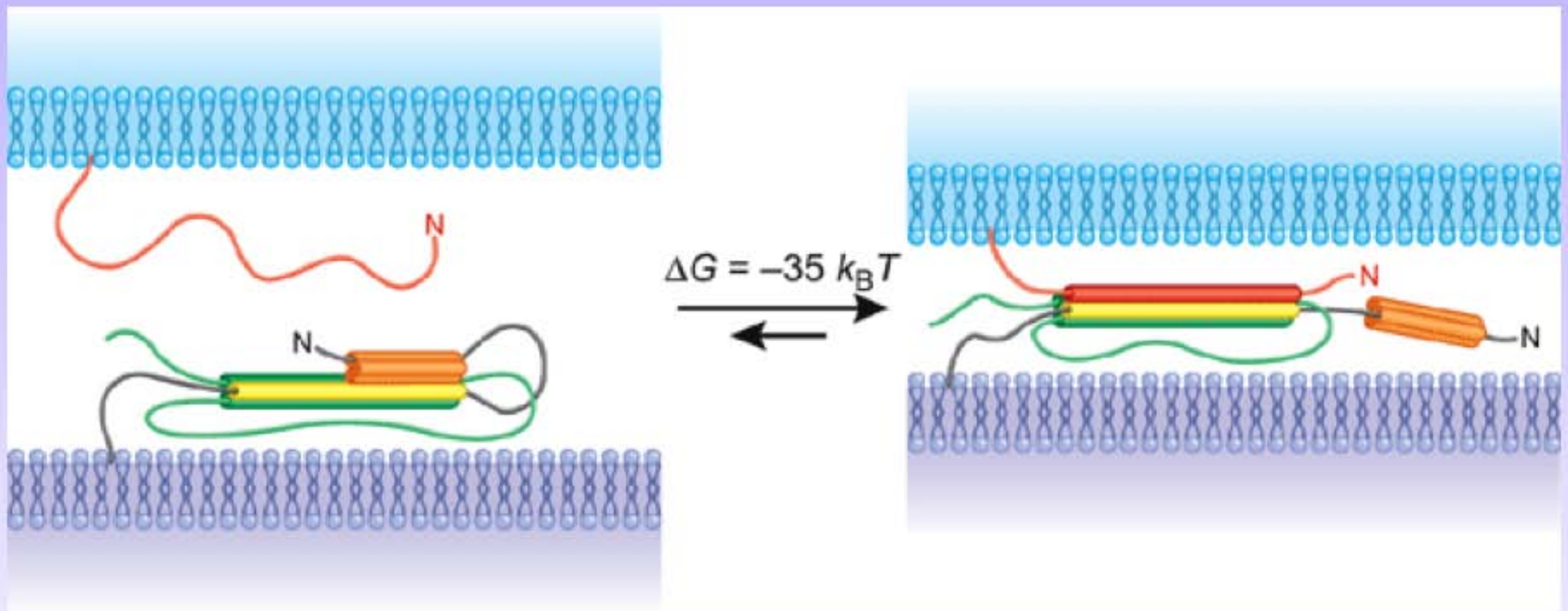






(Sutton et al., Nature 1998)

Chen & Scheller Nat Rev Neurosci 2001



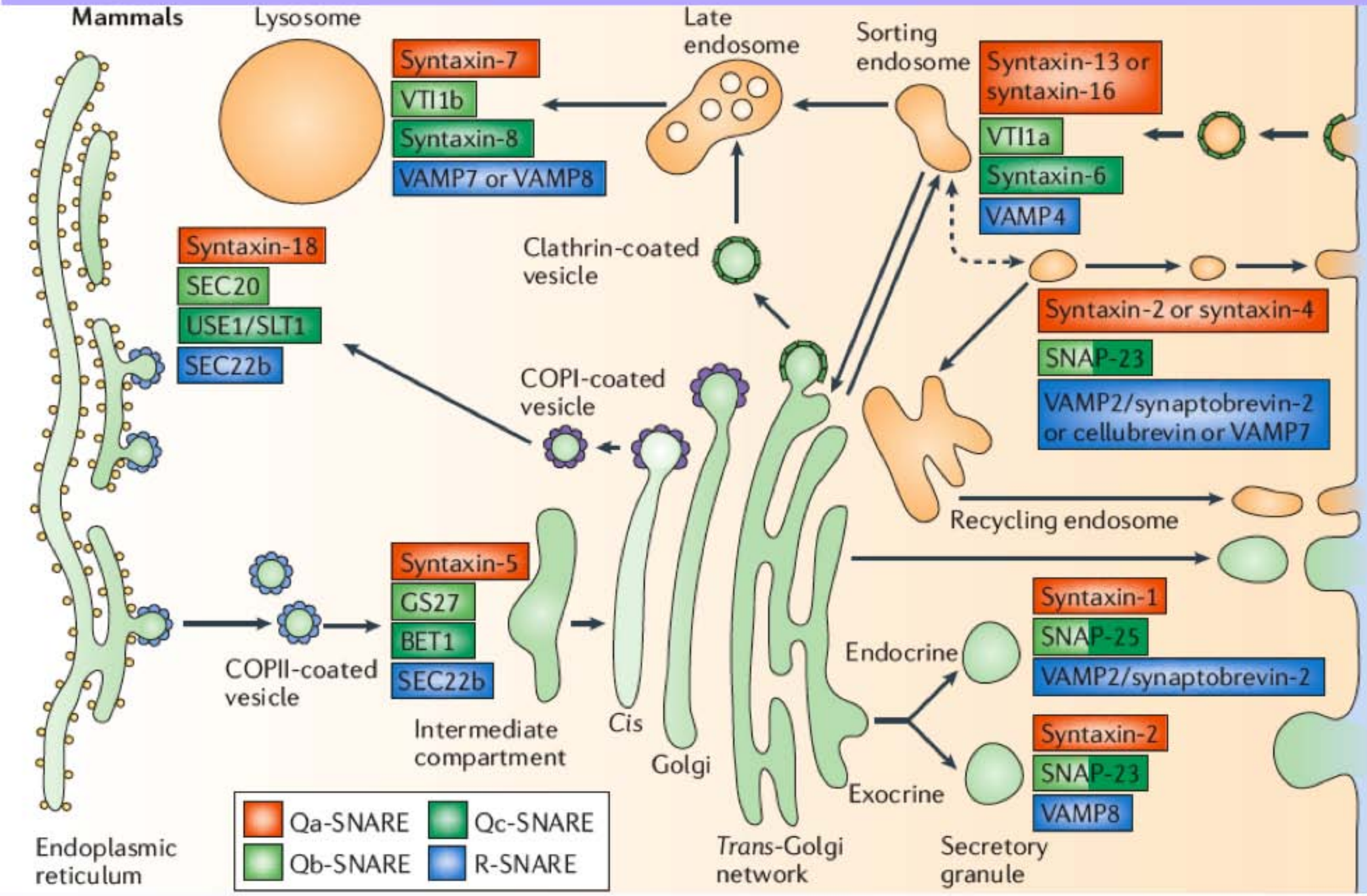
La haute stabilité du complexe SNARE est probablement cruciale pour leur rôle dans la fusion membranaire. L'énergie de stabilisation du complexe SNARE est de 35 kBT (cf. Li. et al. Nat. Struct. Mol. Biol.(2007): 14, 890–896) soit une des plus grande énergie de repliement mesurée.

Josep Rizo & Han Dai VOLUME 14 NUMBER 10 OCTOBER 2007 NATURE STRUCTURAL & MOLECULAR BIOLOGY

SNARE & compartiments

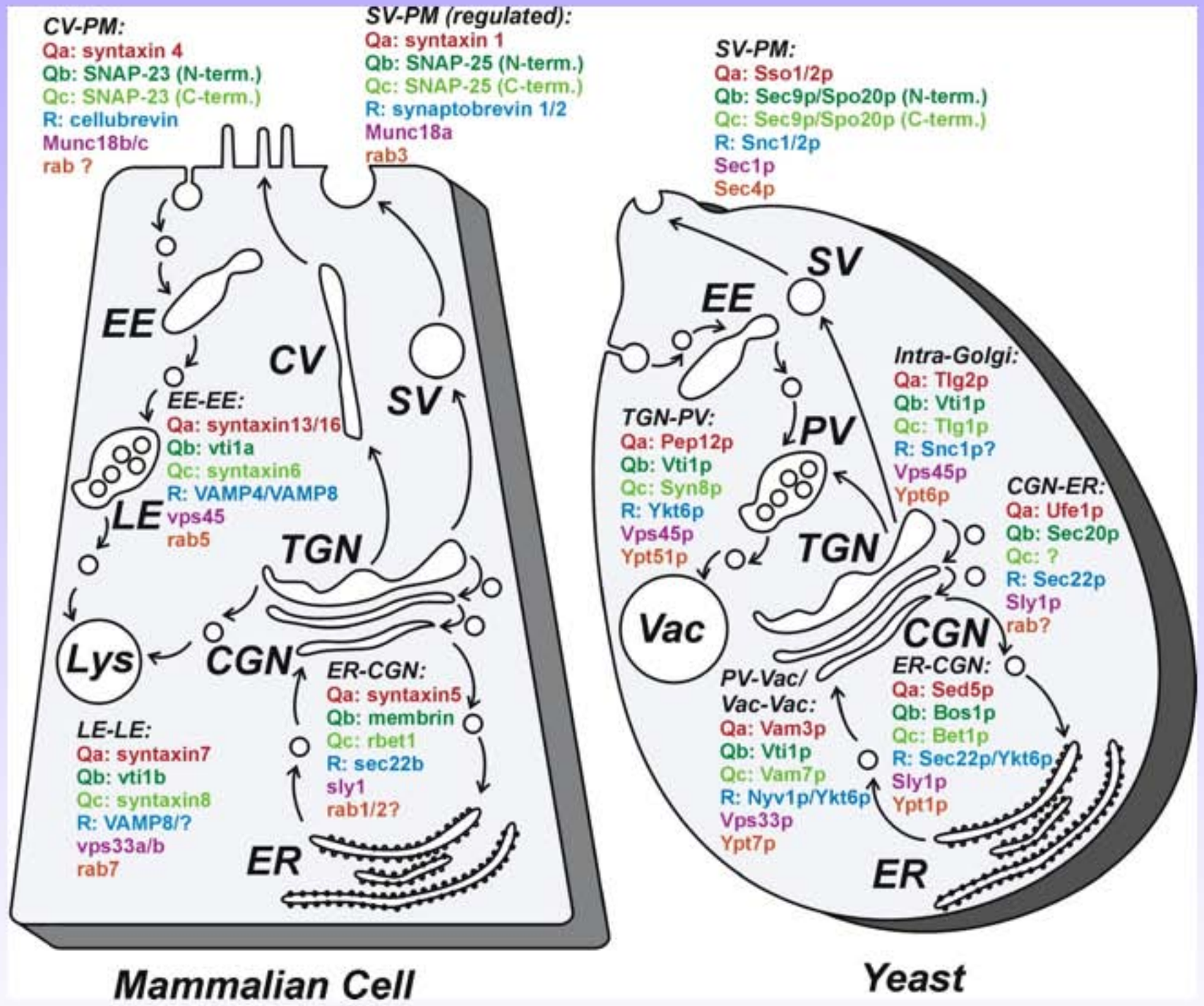
Chaîne	Levure	Nématode	Drosophile	Mammifères
SNAREs	21	23	20	35
Qa Syntaxines	7	9	7	12
Qb Nter SNAP25	5	7	5	9
Qc Cter SNAP25	6	4	5	8
R V-SNARE	5	6	5	9
Sec1	4	6	5	7
Rab	11	29	26	60

Les protéines SNARE et le trafic membranaire dans la cellule



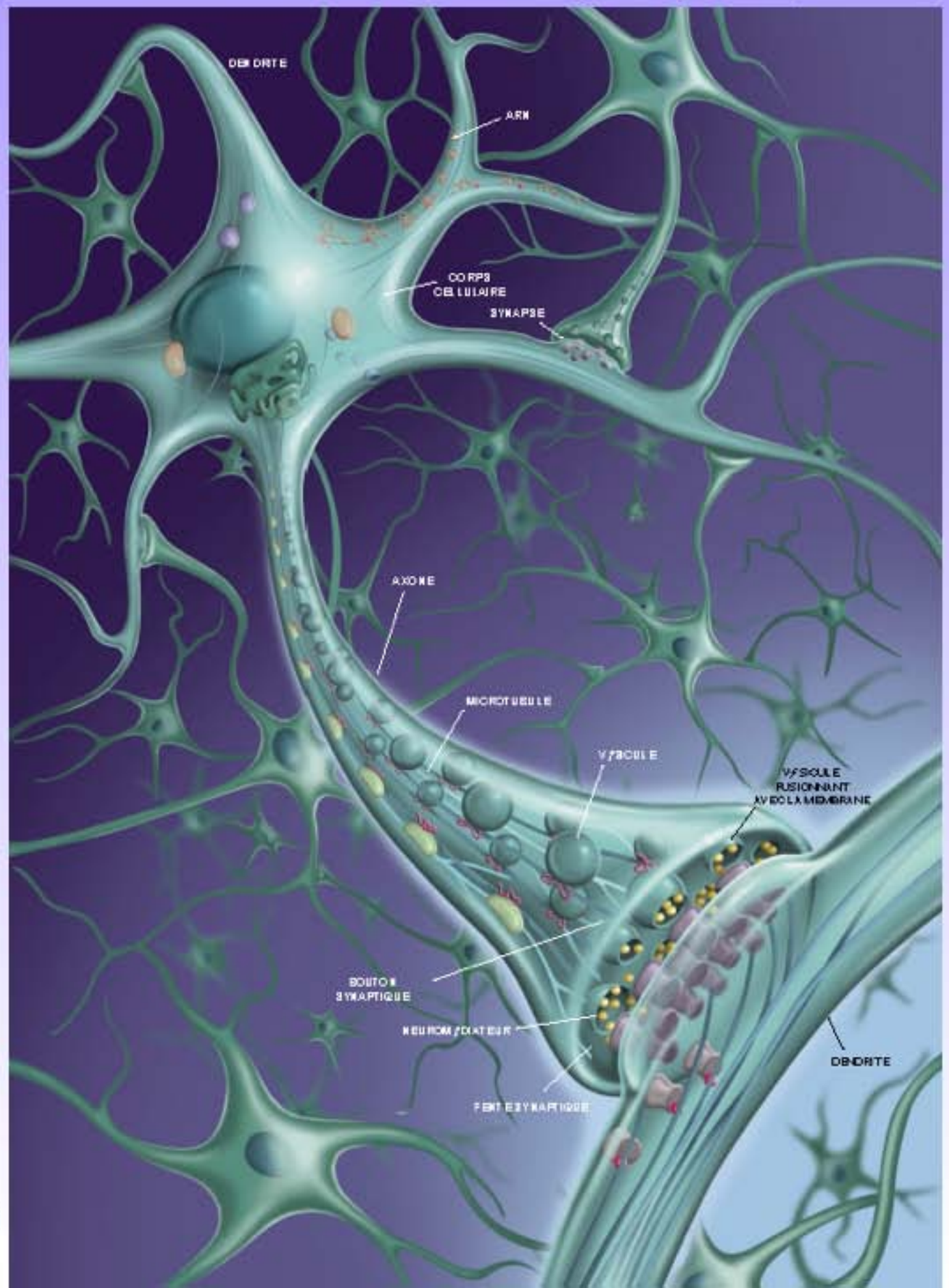
Jahn & Scheller Nat Rev Mol Cell Biol 2006

SNARE & compartiments



Machinerie d'exocytose: le modele neuronal : l'exocytose synaptique

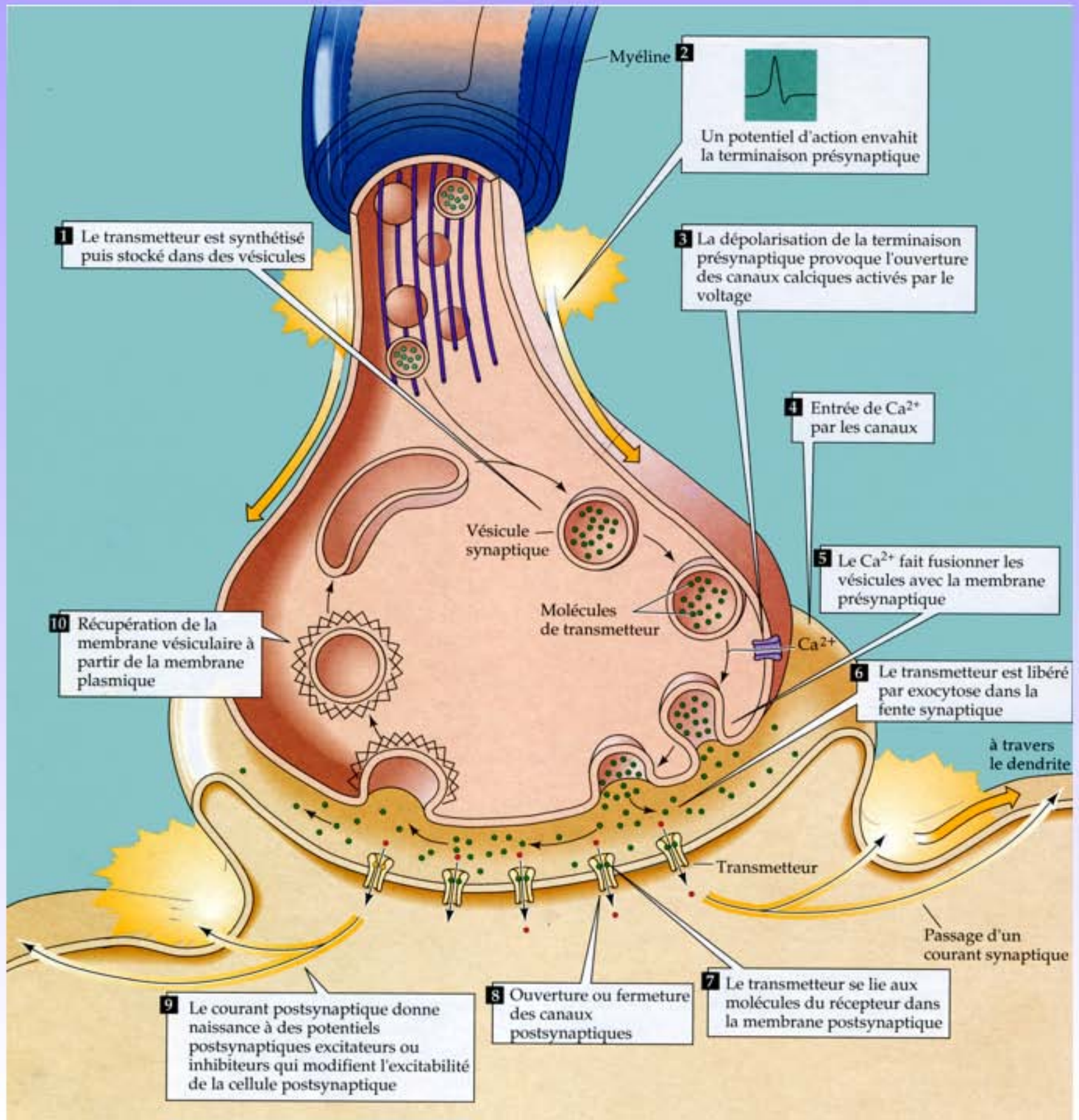
La fusion vésiculaire entre les vésicules synaptiques et la membrane présynaptique permet la libération des neurotransmetteur.



Thierry Galli & fabienne Paumet

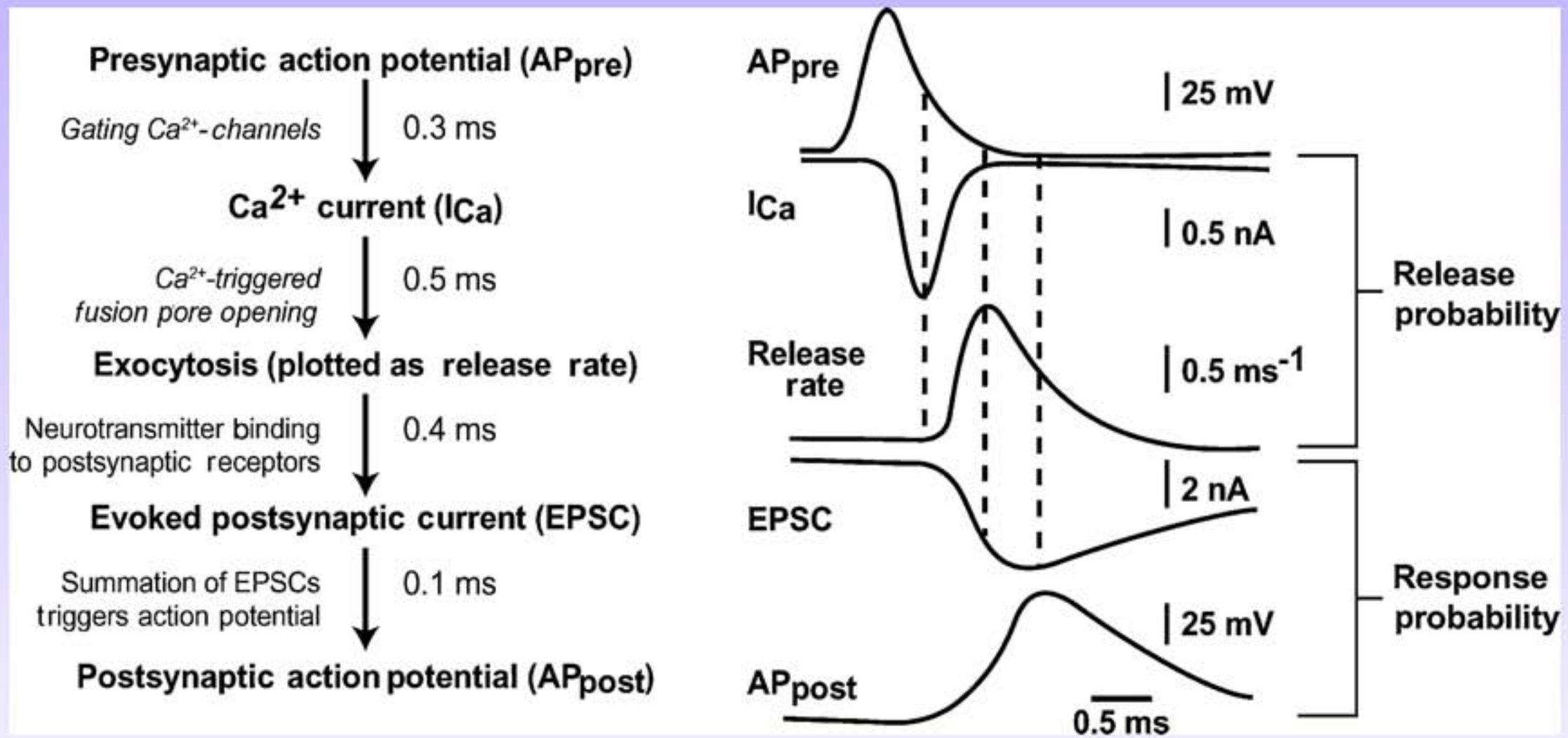
© POUR LA SCIENCE - N° 302 DÉCEMBRE 2002

L'exocytose synaptique



D'après Neurosciences, à la découverte du cerveau
M. F. Bear

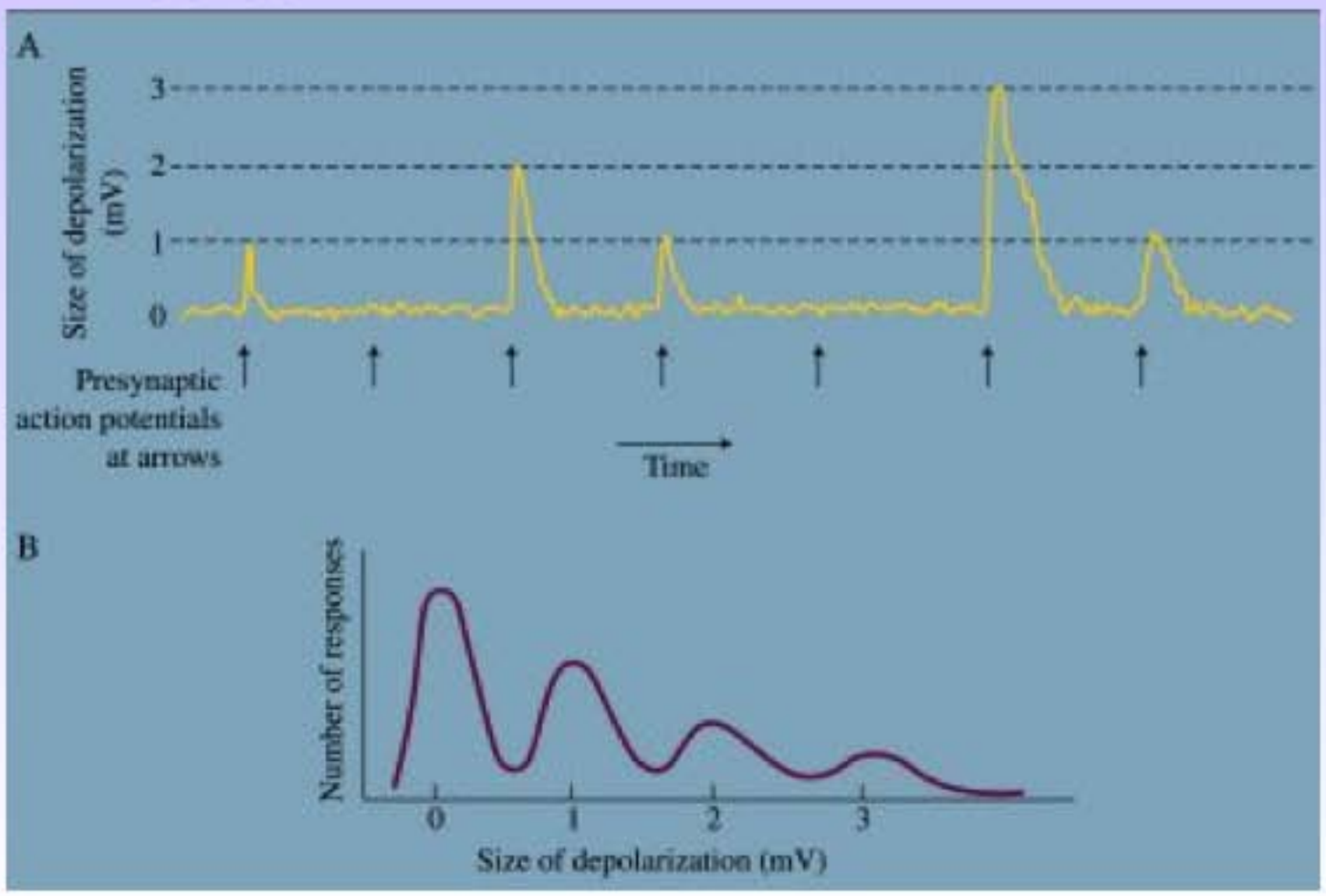
Chronologie: rapidité! Et rôle du calcium

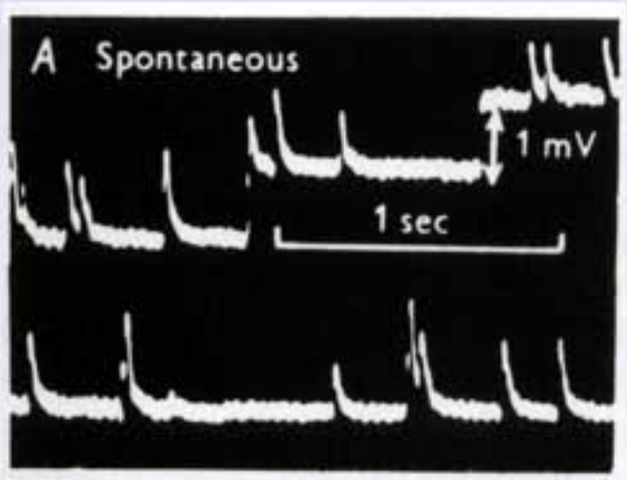


Annu. Rev. Neurosci. 2004.27:509-547.

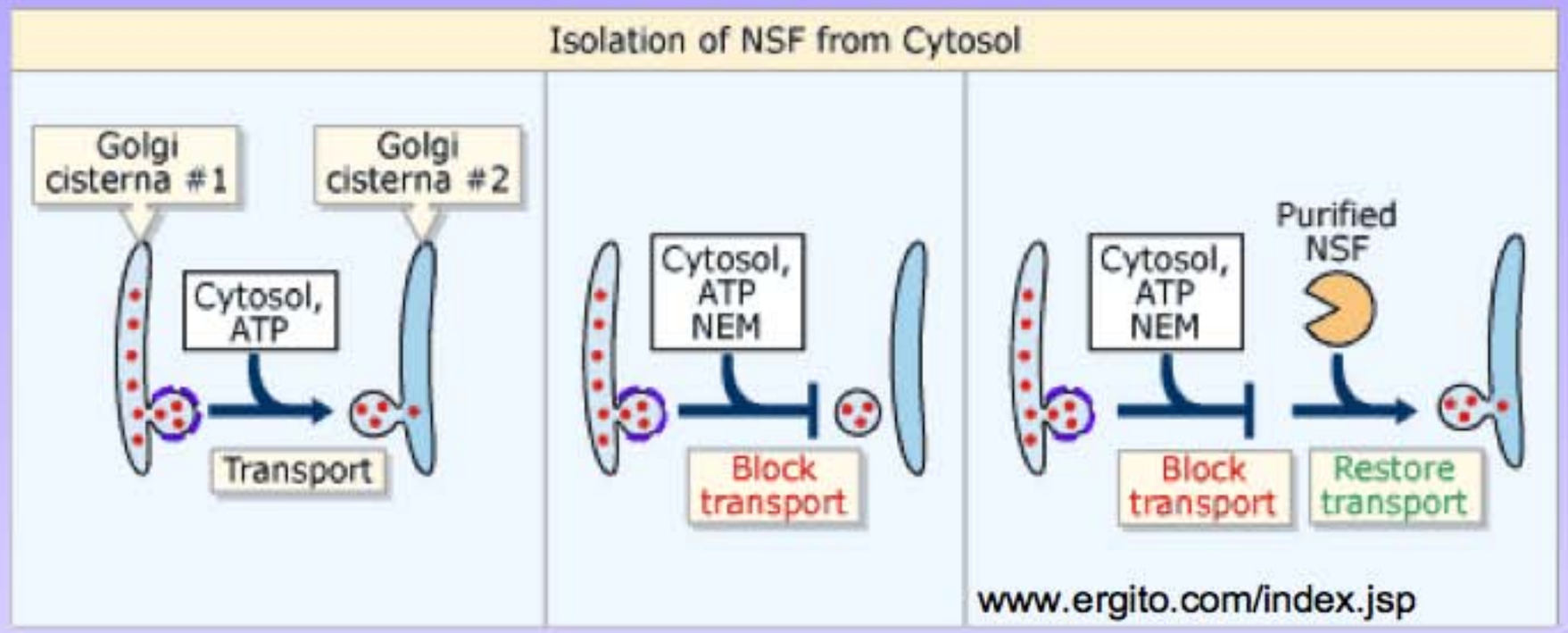
Libération de l'acétylcholine

- Théorie quantique: Prix Nobel pour Katz
  - Nt libéré par paquet de taille définie
  - 10,000 molécules d'ACh
- Libération en "tout ou rien"
  - Calcium extracellulaire réduit, seuls quelques quanta sont libérés





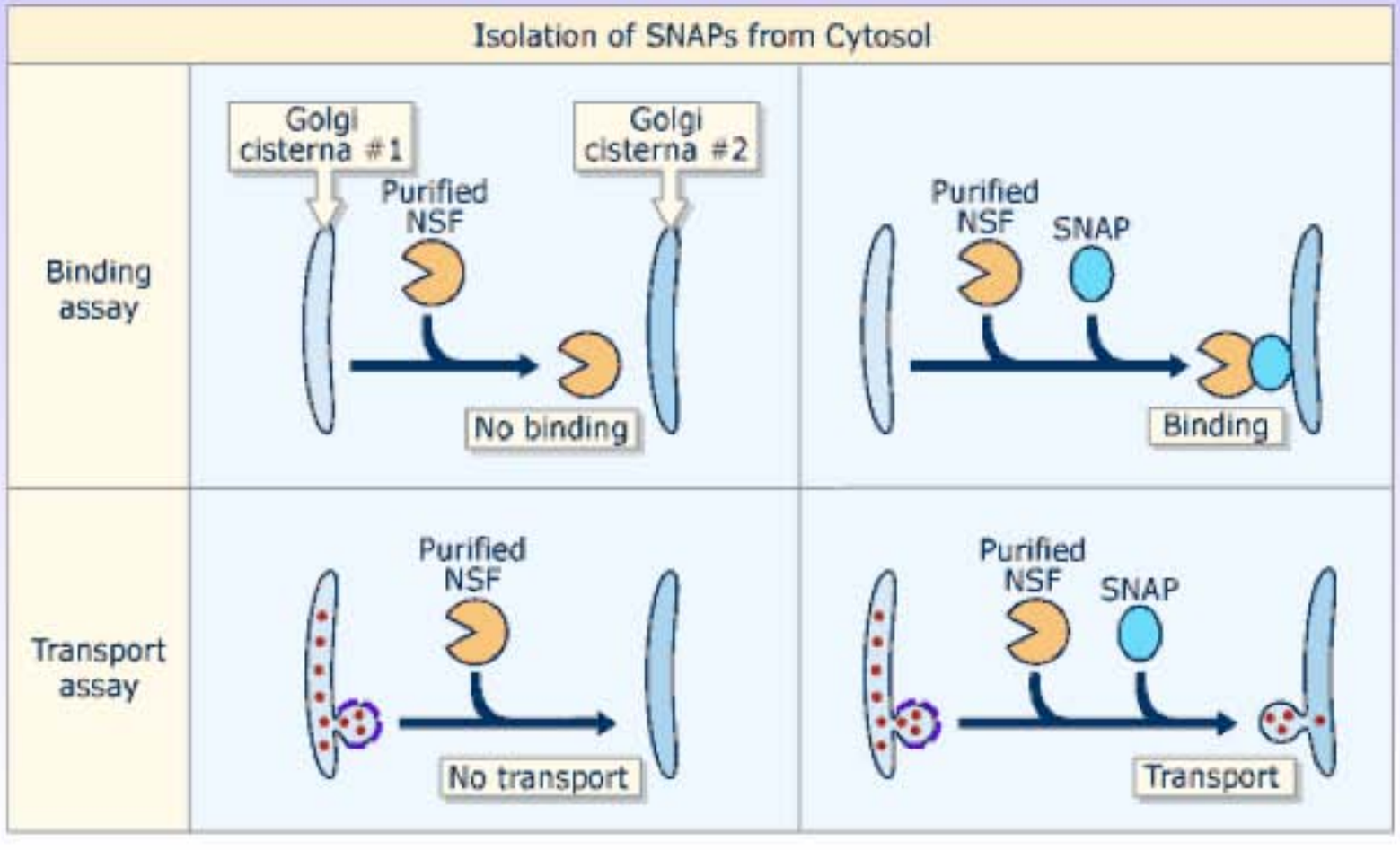
Découverte historique de NSF & SNAPs



Jim Rothman

NEM: N-Ethyl-Maleimide
NSF: NEM sensitive factor

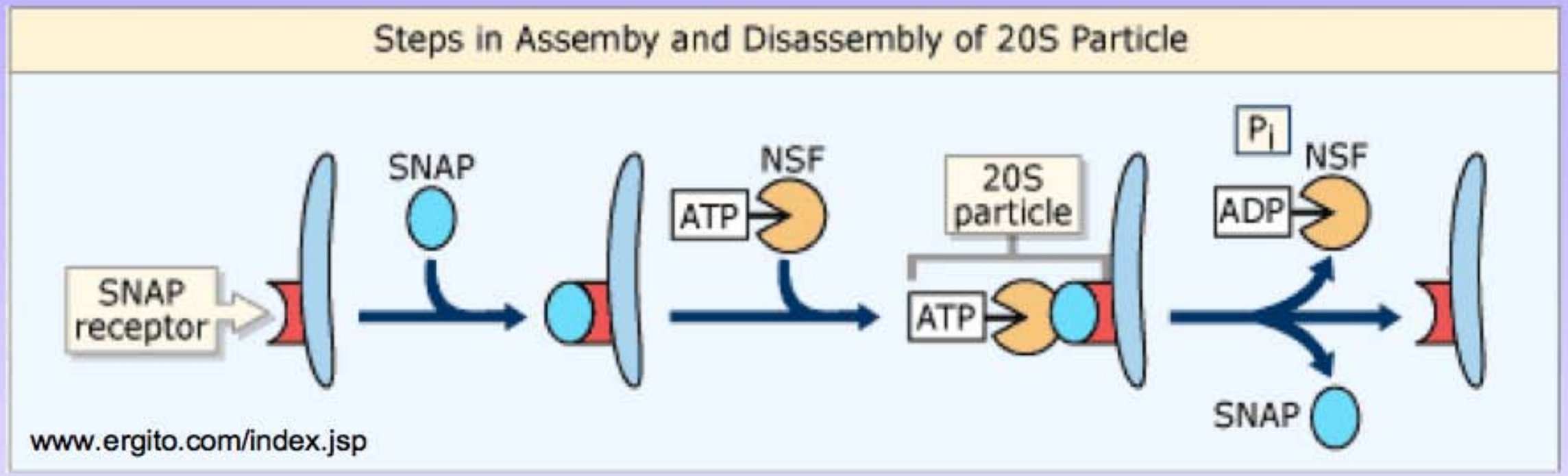
NSF est nécessaire à la fusion.
NSF est inhibée par le NEM.



SNAP:
Soluble NSF Attachment Factor

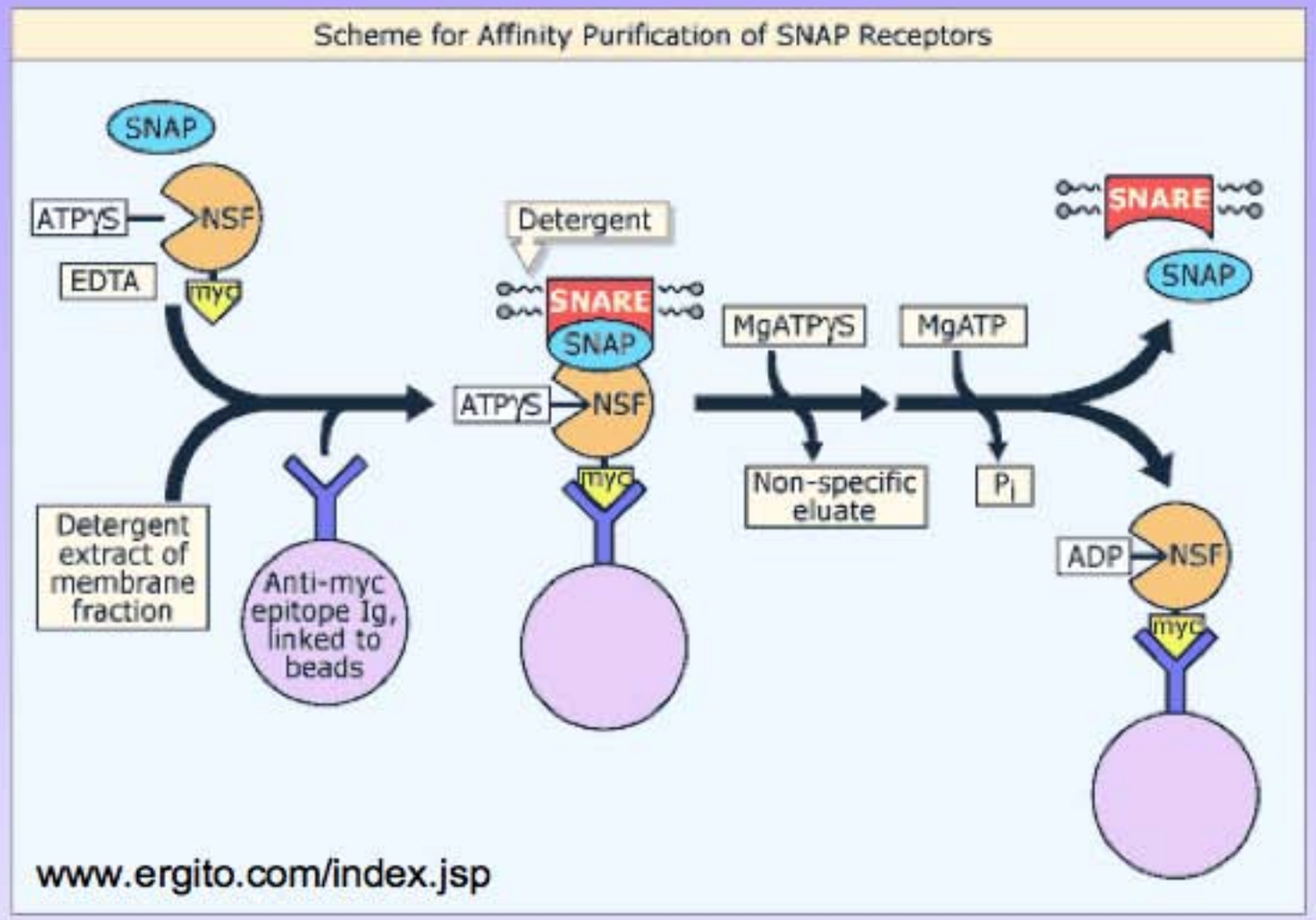
NSF est une protéine soluble qui ne peut se lier aux membranes que grâce aux SNAPs (3 isoformes α,β,γ).

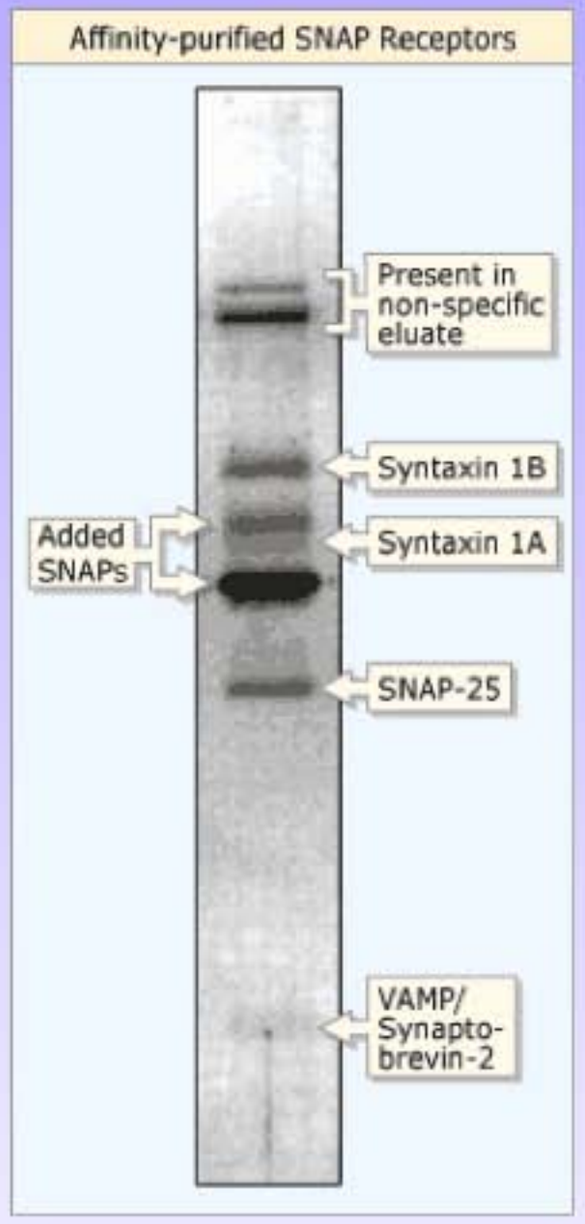
Découverte historique des récepteurs de SNAP: les SNARE

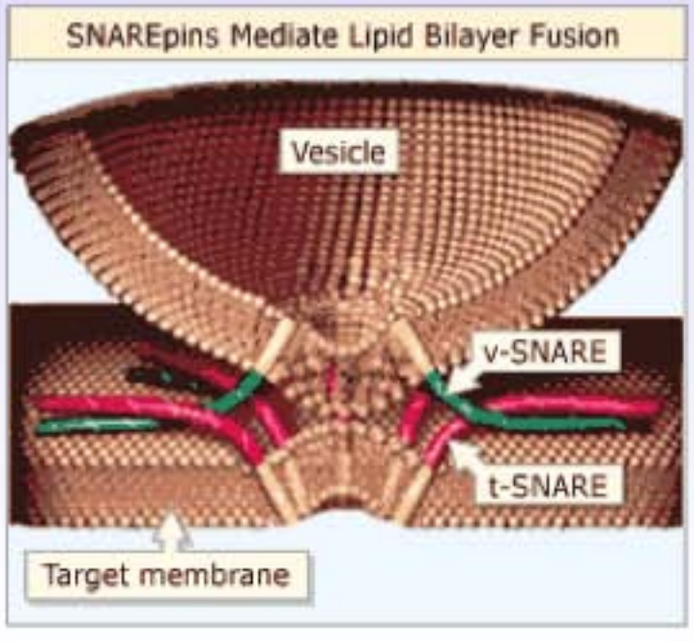


Comment isoler les recepteurs de SNAPs: les SNARE?

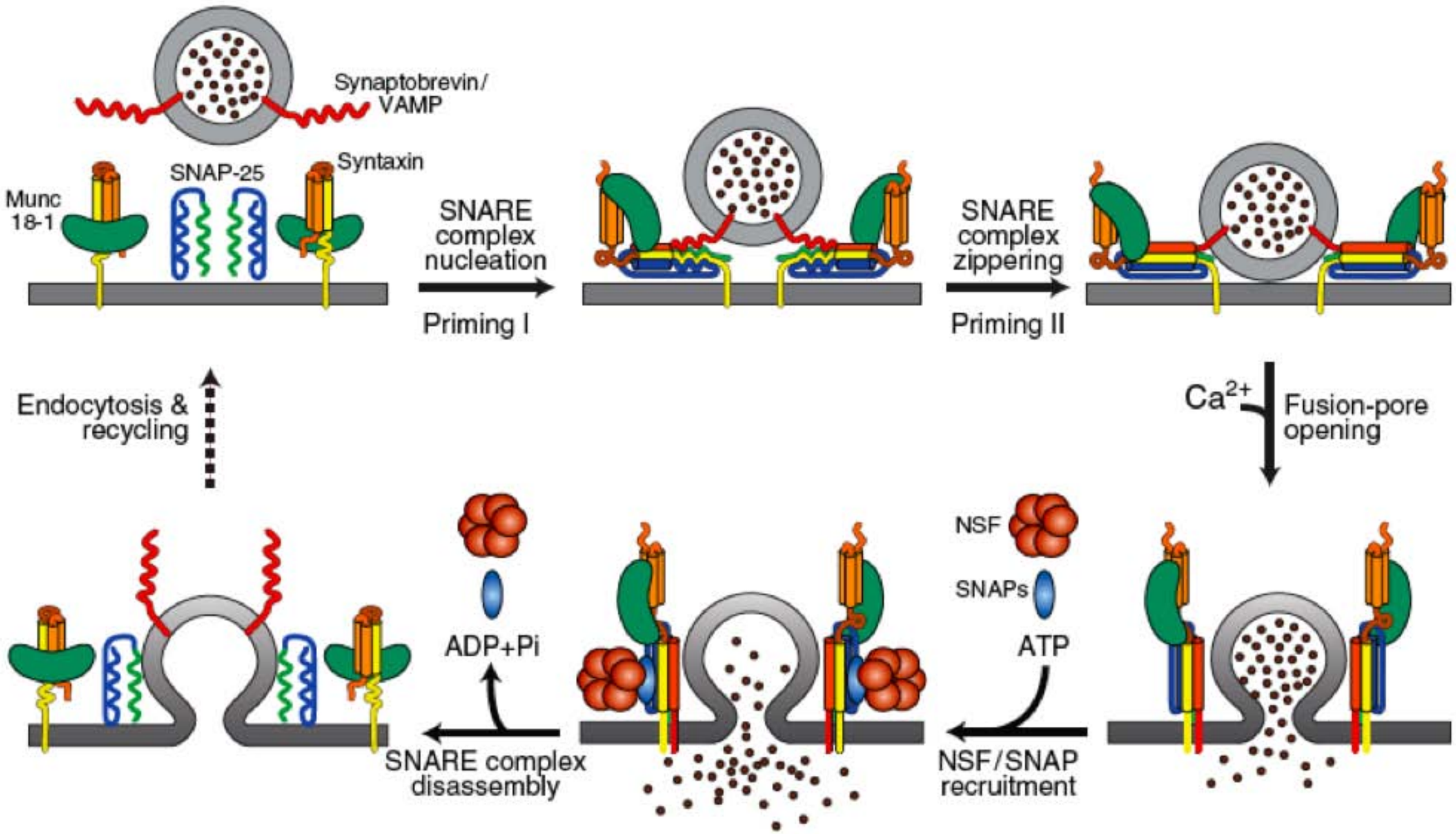
Isolement des SNAREs





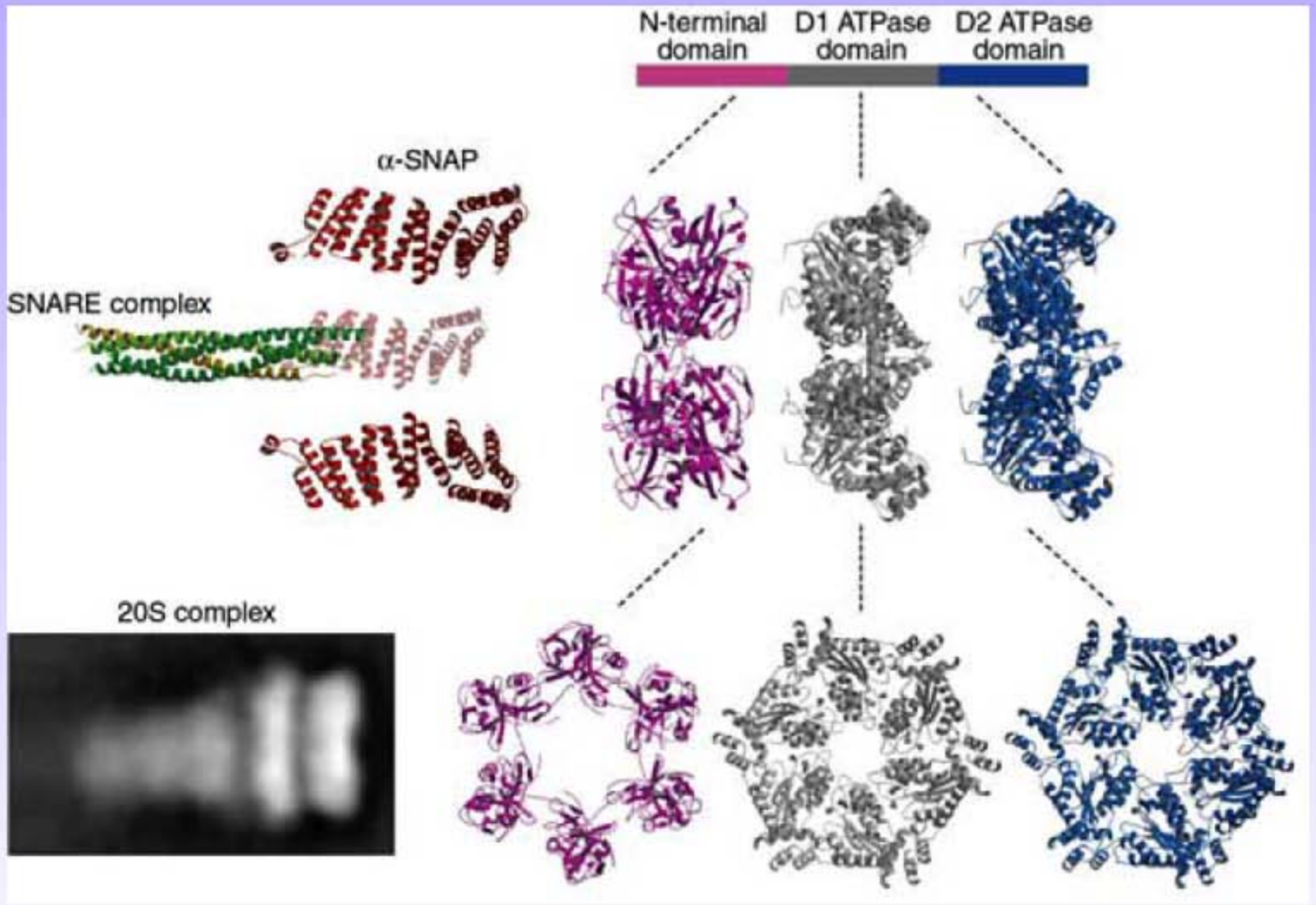


Dissociation des SNARE par NSF

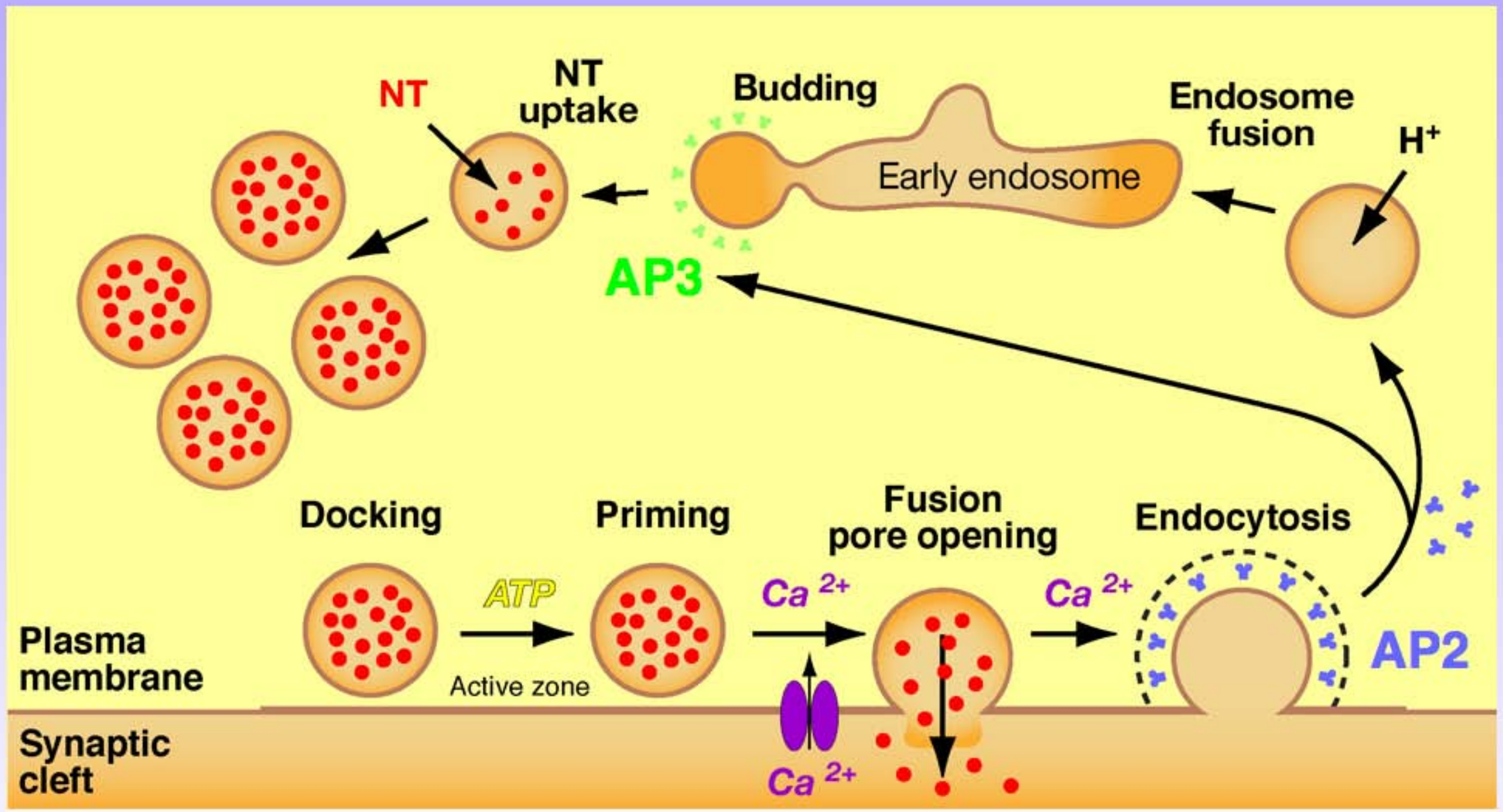


T.C. Südhof, K. Starke (eds.), *Pharmacology of Neurotransmitter Release. Handbook of Experimental Pharmacology 184.*

Structure de l'ATPase NSF

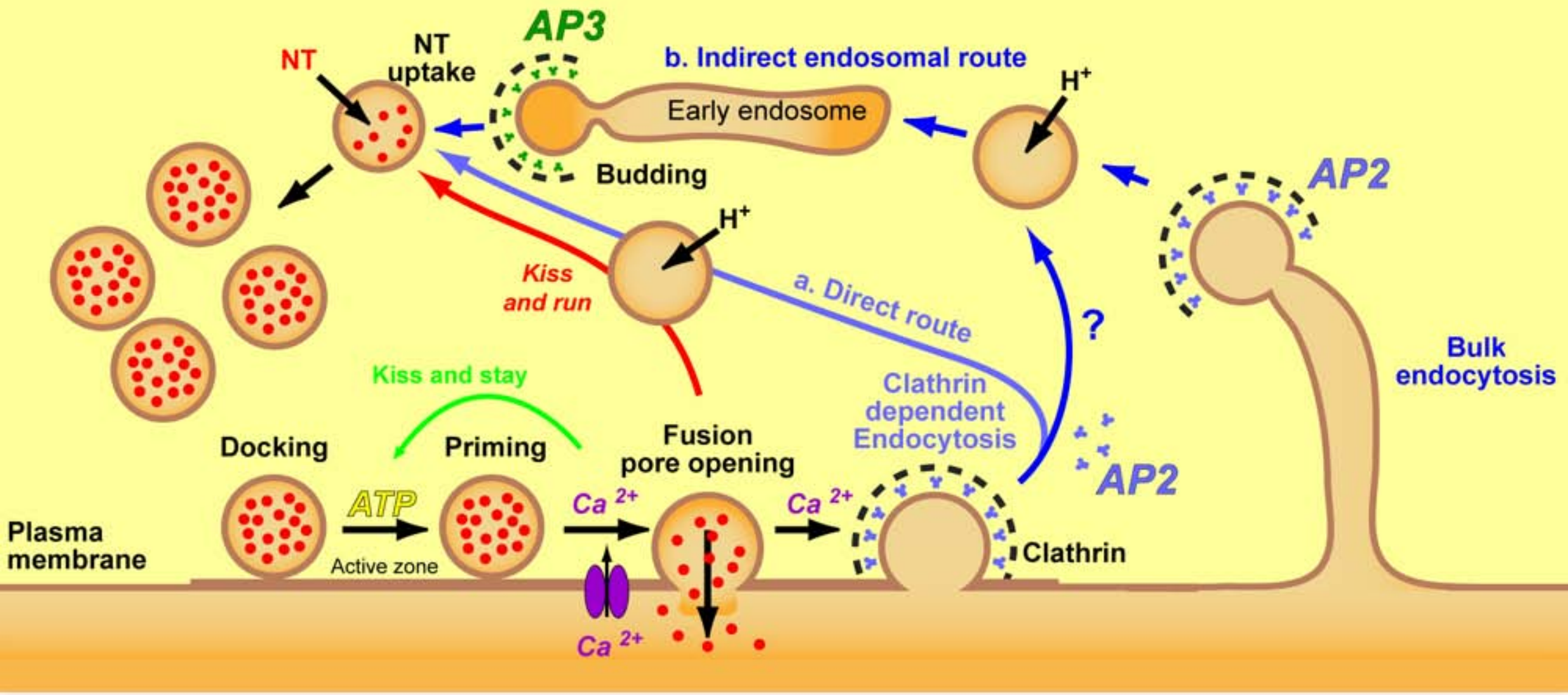


Recyclage des vésicules synaptiques



Danglot & Galli, Biology of the cell, 2003.

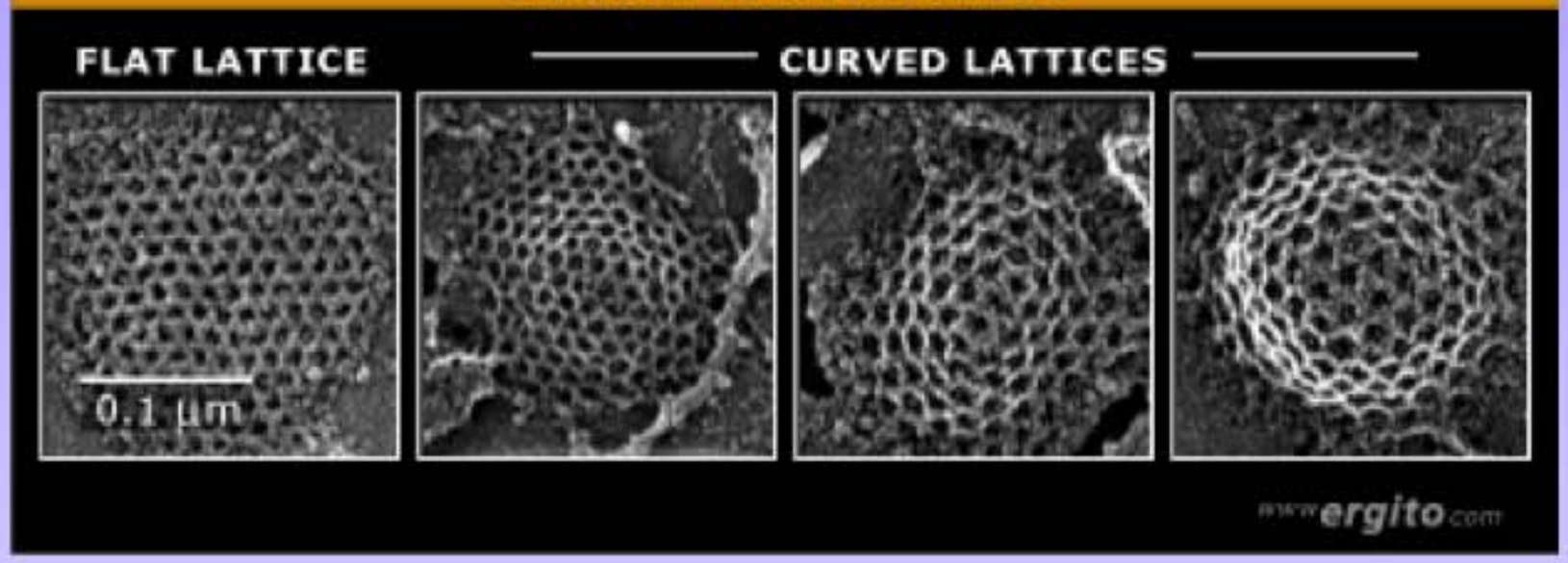
Recyclage des vésicules synaptiques



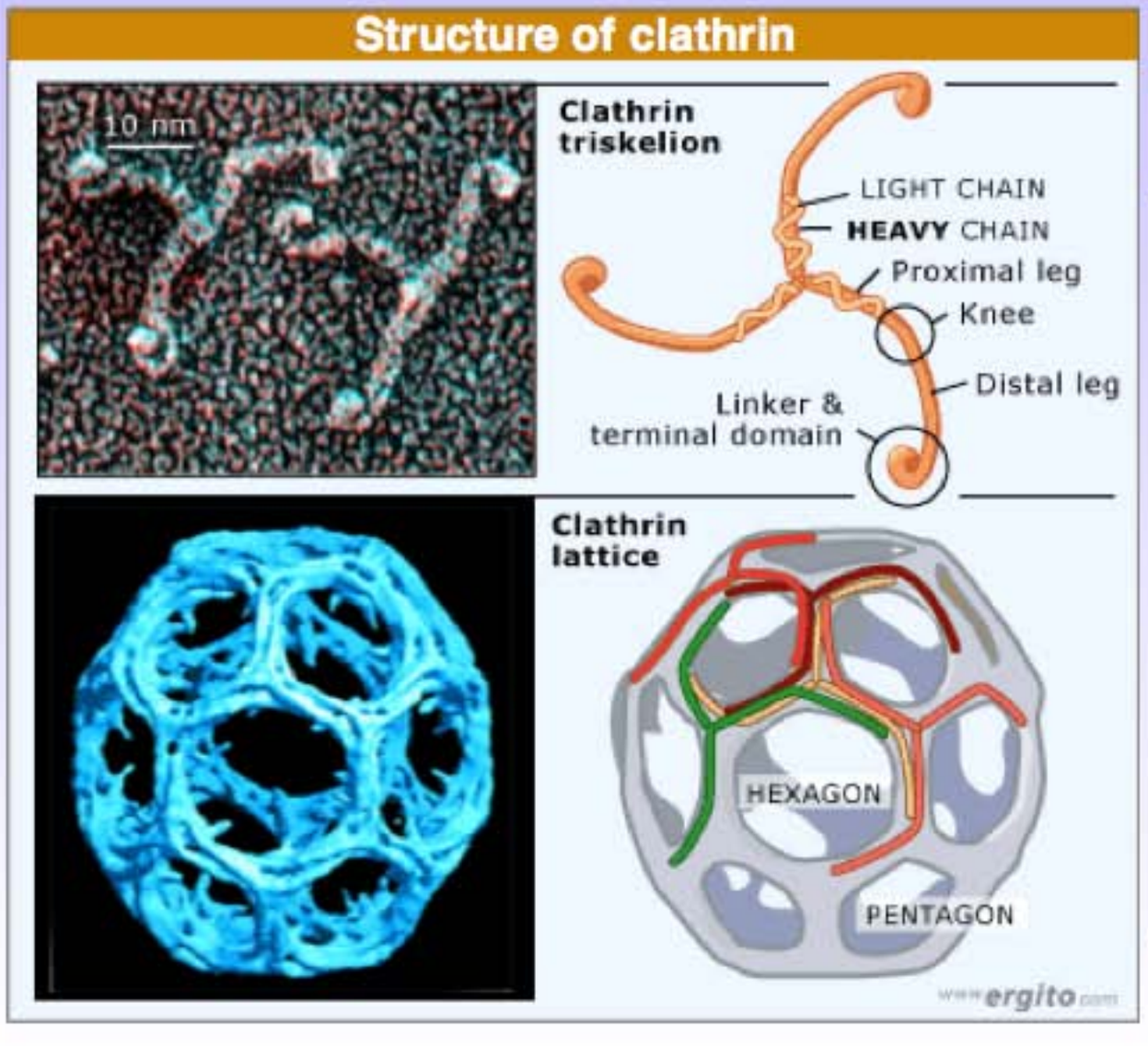
Danglot & Galli, Biology of the cell, 2003.

Clathrine

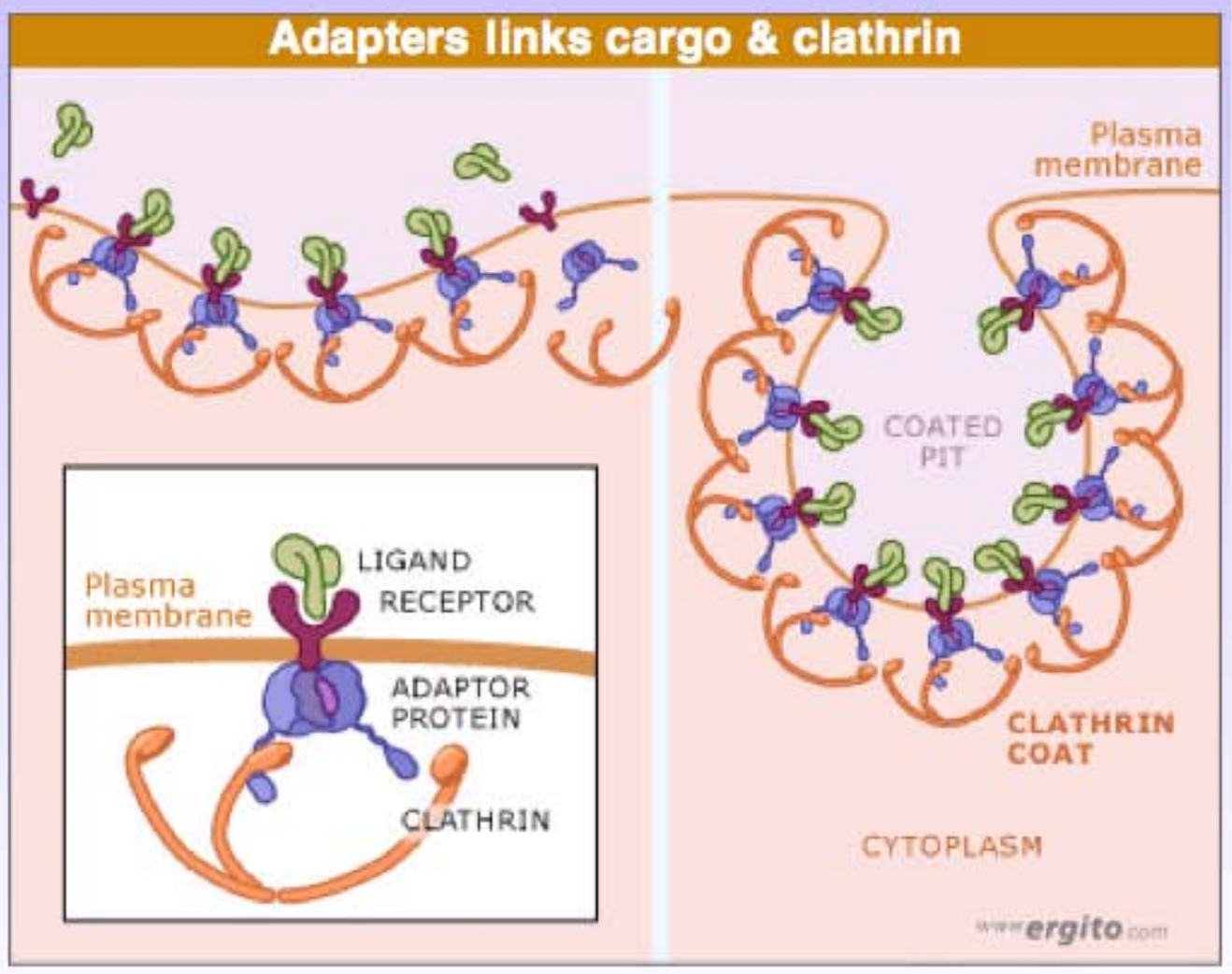
Clathrin forms lattices



Structure of clathrin

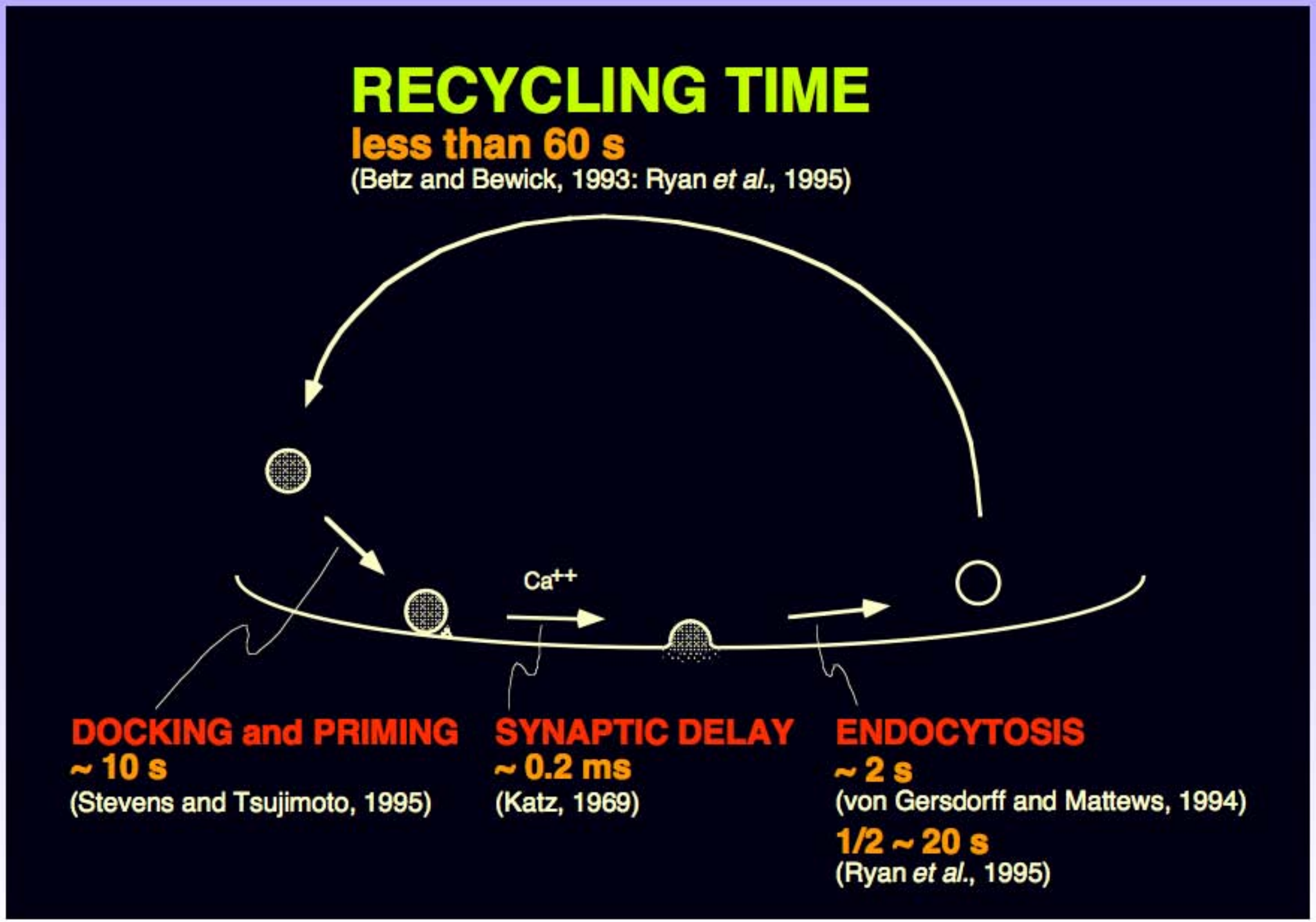


Adapters links cargo & clathrin



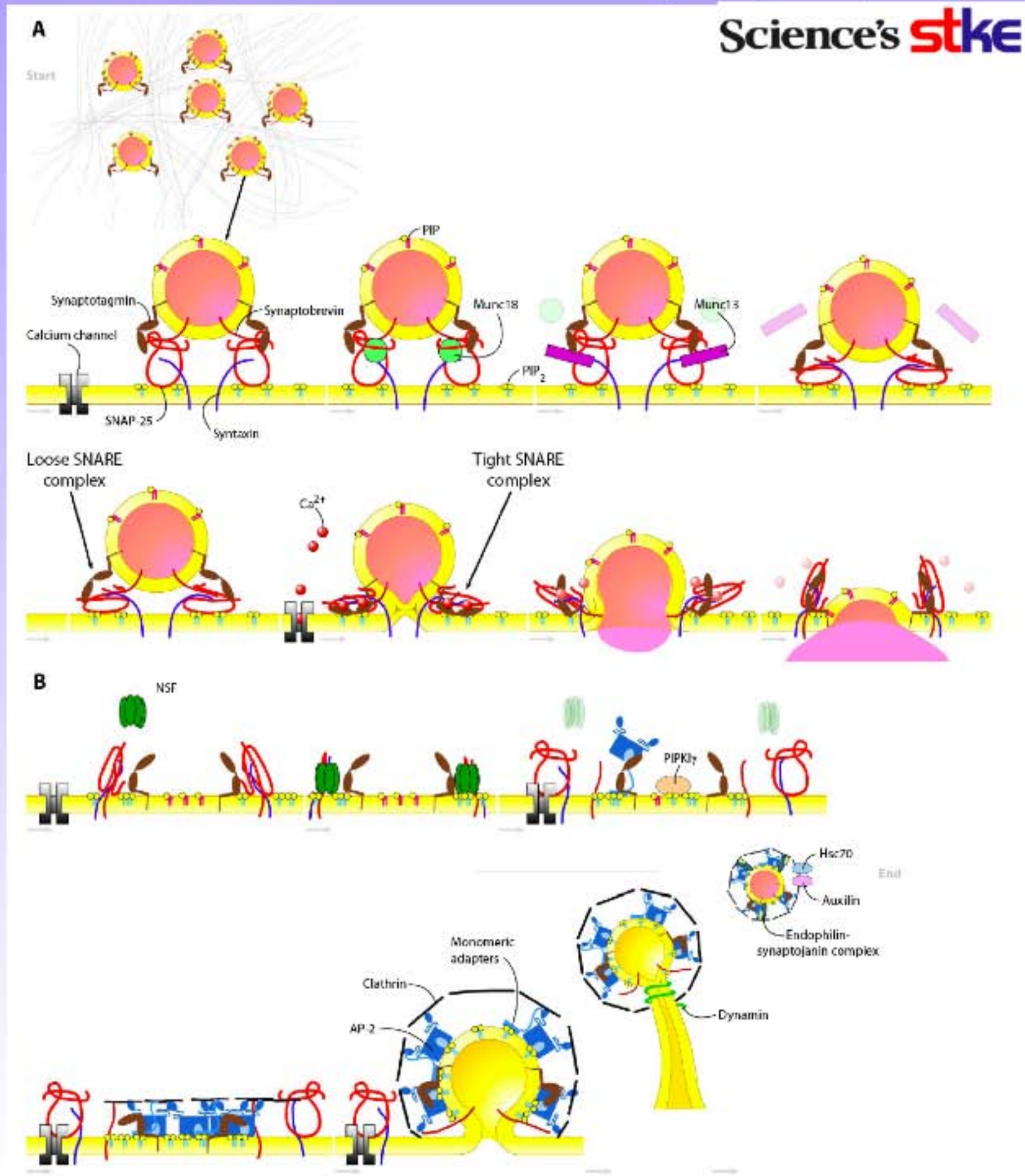
www.ergito.com/index.jsp

Recyclage des vésicules synaptiques



Recyclage des Vésicules synaptiques:

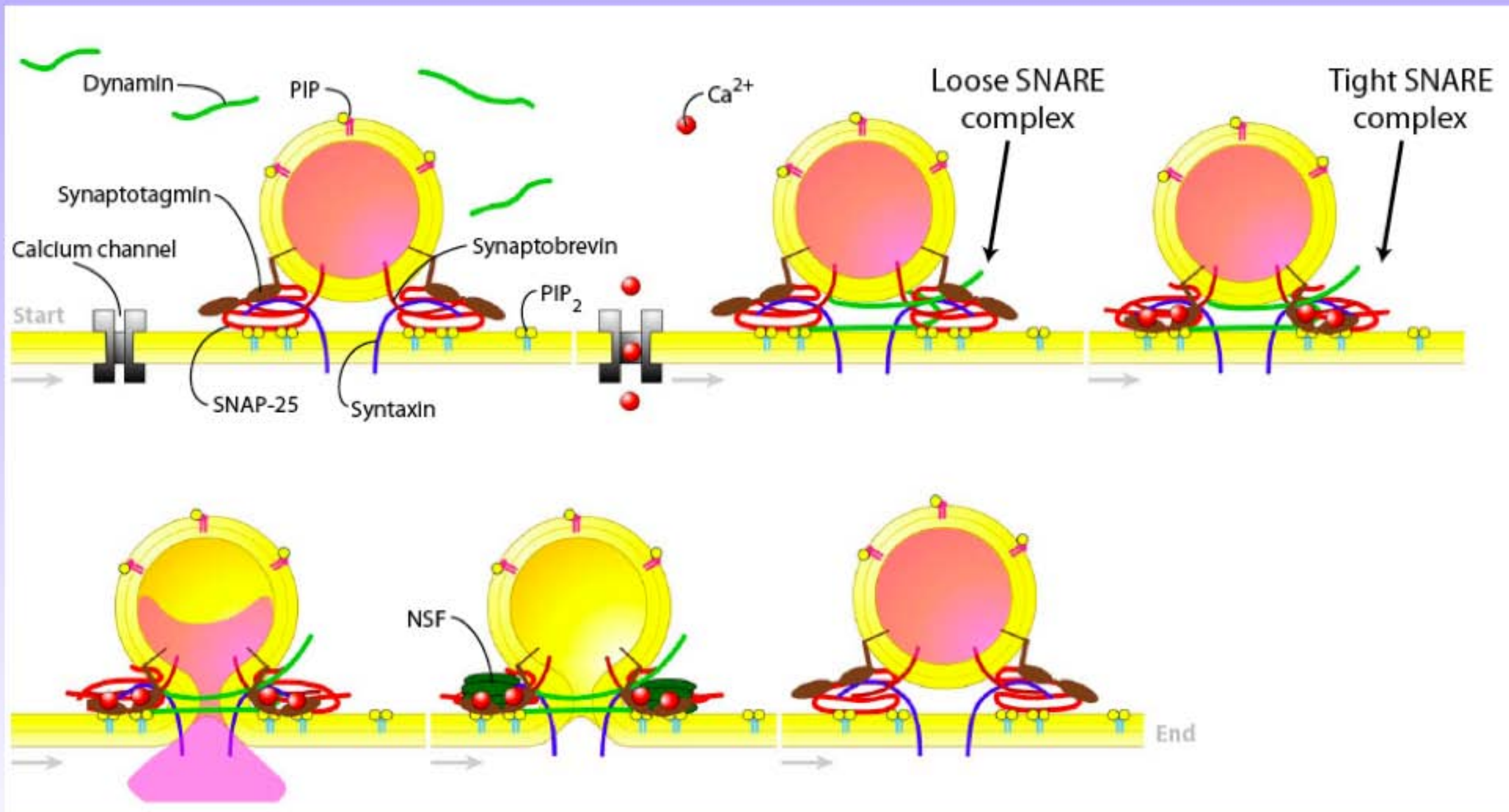
endocytose mediée par la clathrine (la voie lente)



Thierry Galli1 and Volker Haucke

www.stke.org/cgi/content/full/sigtrans;2004/264/re19

Kiss and Run ?

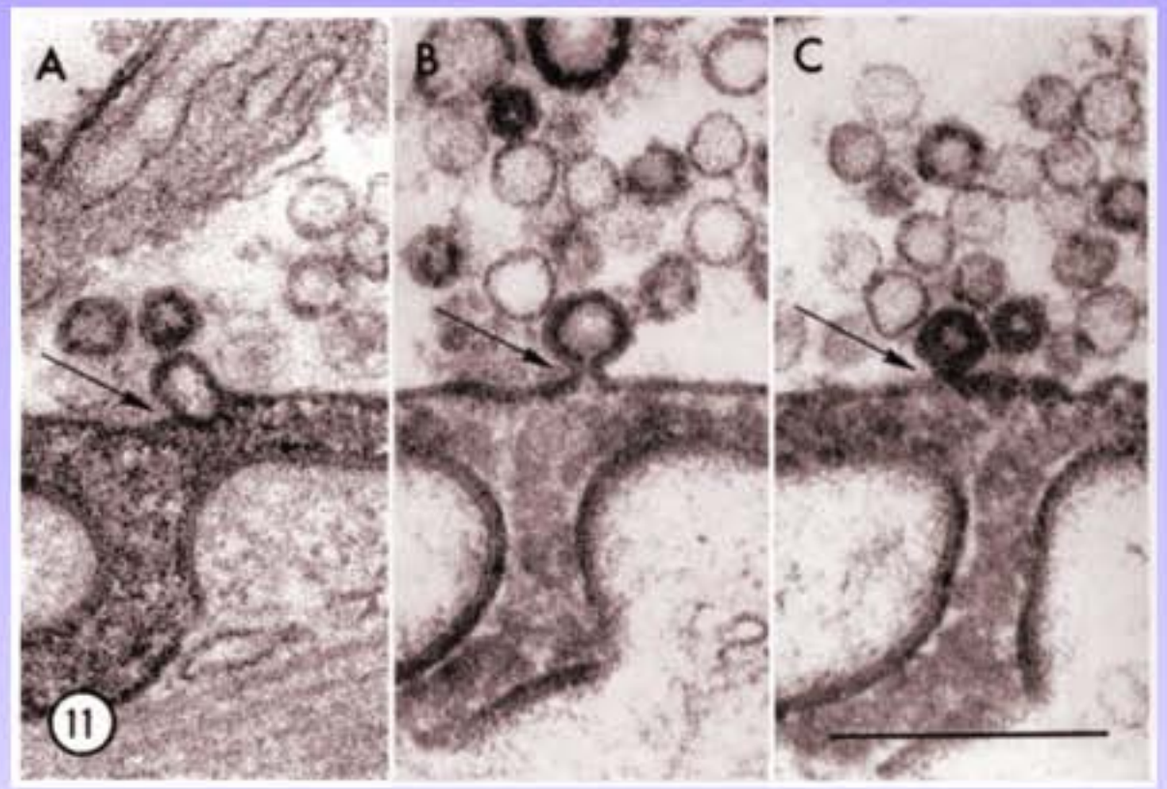


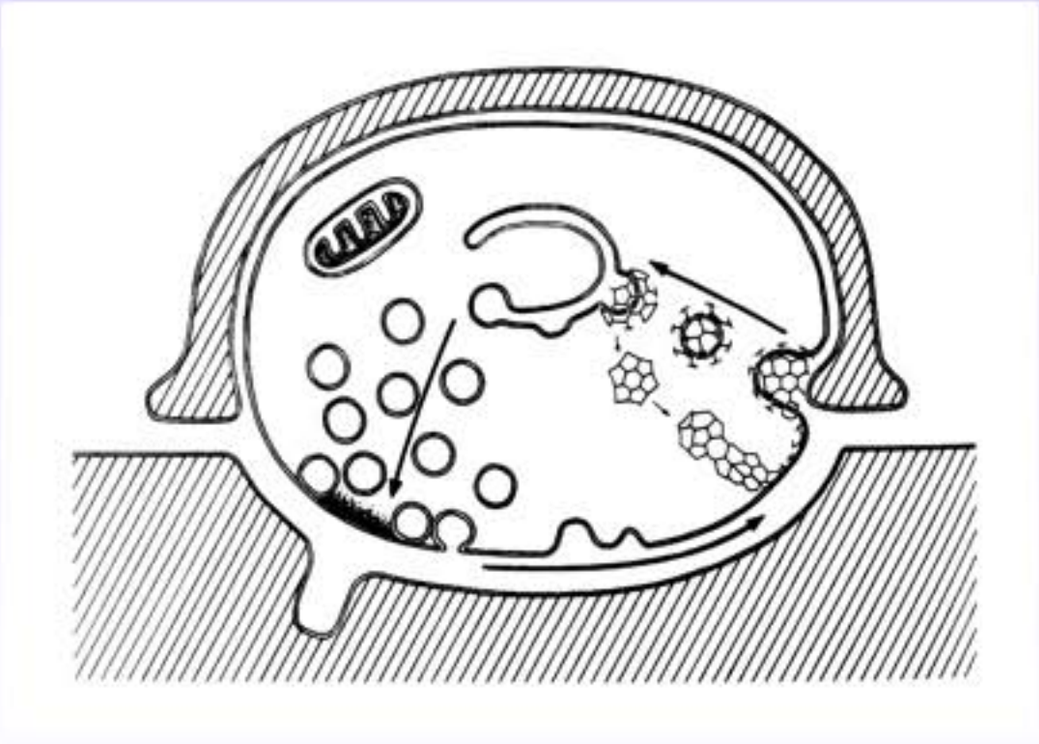
Thierry Galli1 and Volker Haucke

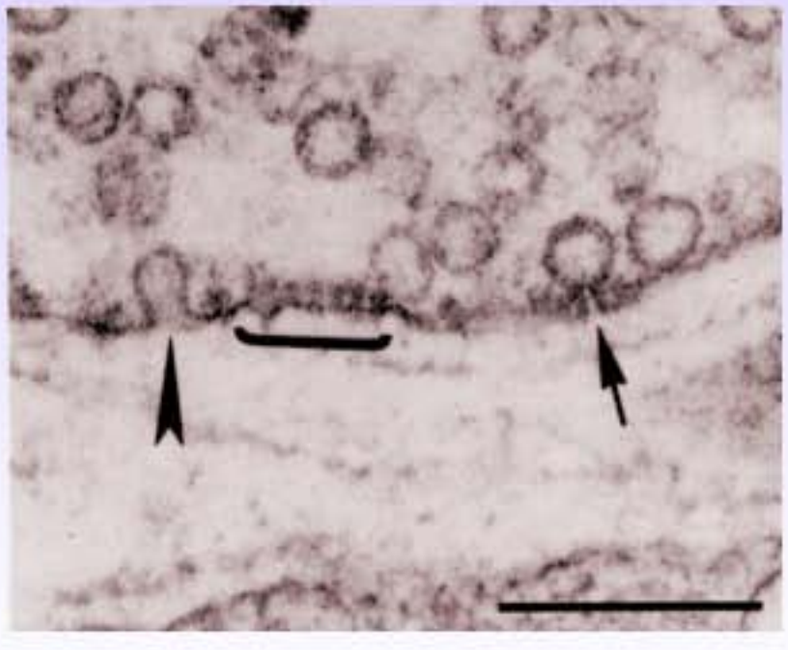
www.stke.org/cgi/content/full/sigtrans;2004/264/re19

Science's stke

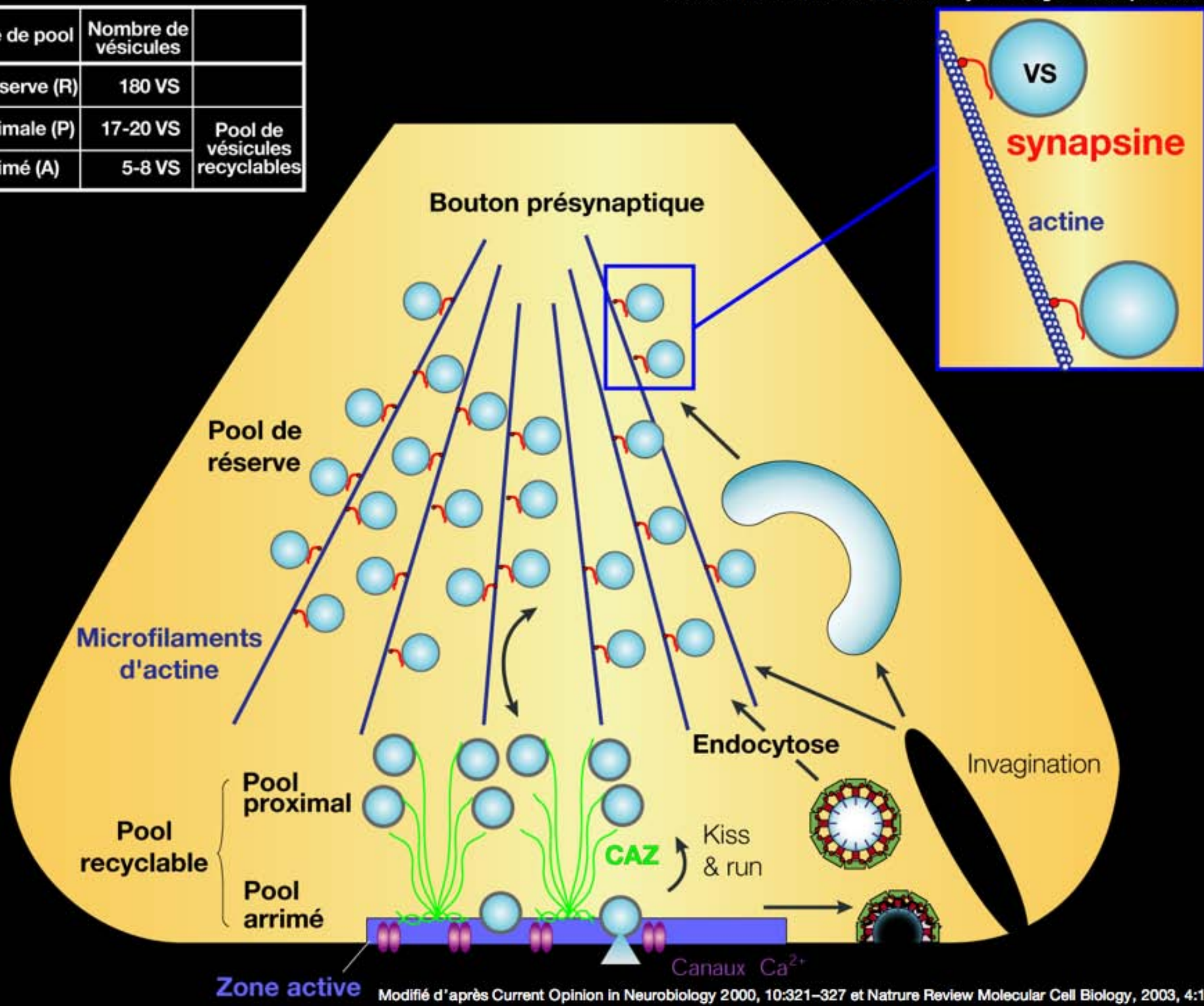
Et en microscopie électronique ?







Type de pool	Nombre de vésicules	
de réserve (R)	180 VS	
proximale (P)	17-20 VS	Pool de vésicules recyclables
arrimé (A)	5-8 VS	

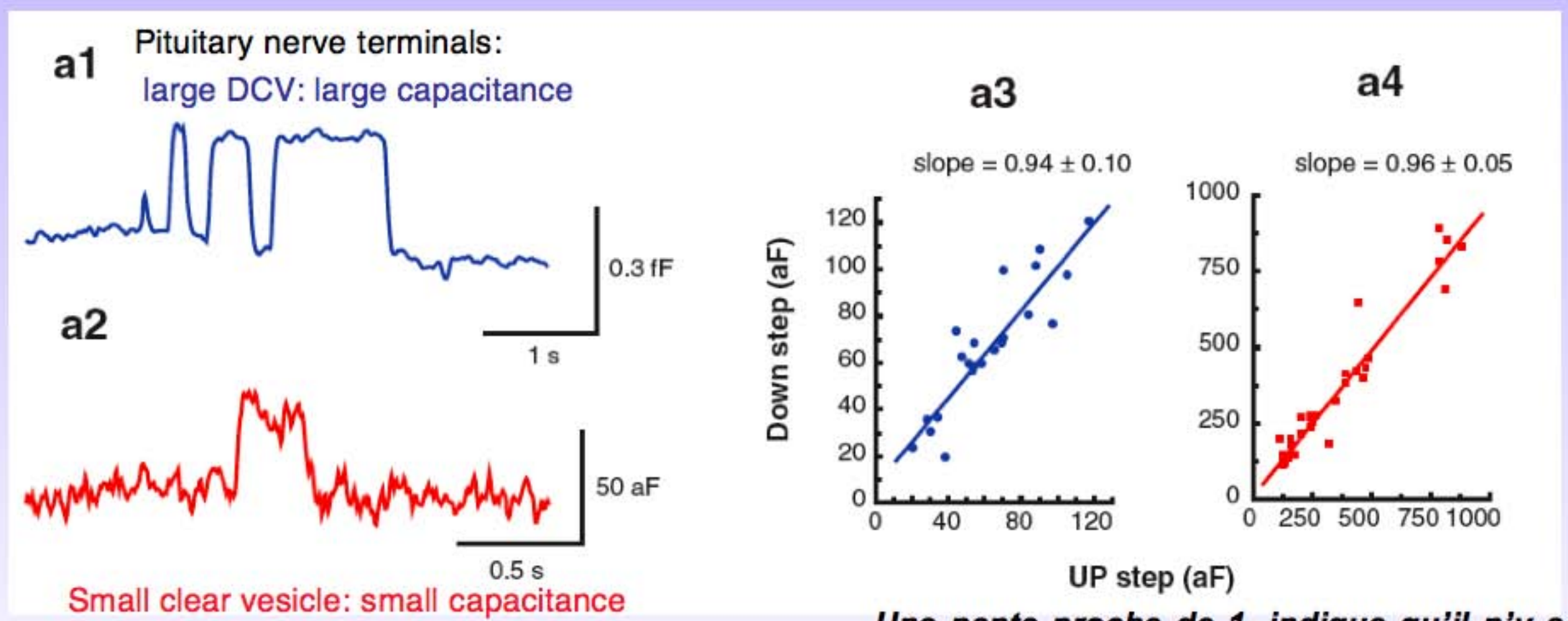


Modifié d'après Current Opinion in Neurobiology 2000, 10:321–327 et Natrure Review Molecular Cell Biology, 2003, 4:127-139.

Comment mesurer l'exocytose ?

1) Capacitance:

La mesure de la capacitance de la cellule est proportionnelle à la surface de la membrane.
L'enregistrement de la capacitance permet de mesurer l'addition de membrane provoquée lors d'un evènement de fusion membranaire.
Cellules chromaffines (medullosurrénales): la fusion d'une vésicules produit une augmentation de la capacitance de 1fF (Neher, PNAS 1982).
Mastocytes : ont des vesicules + larges: augmentation de 16fF



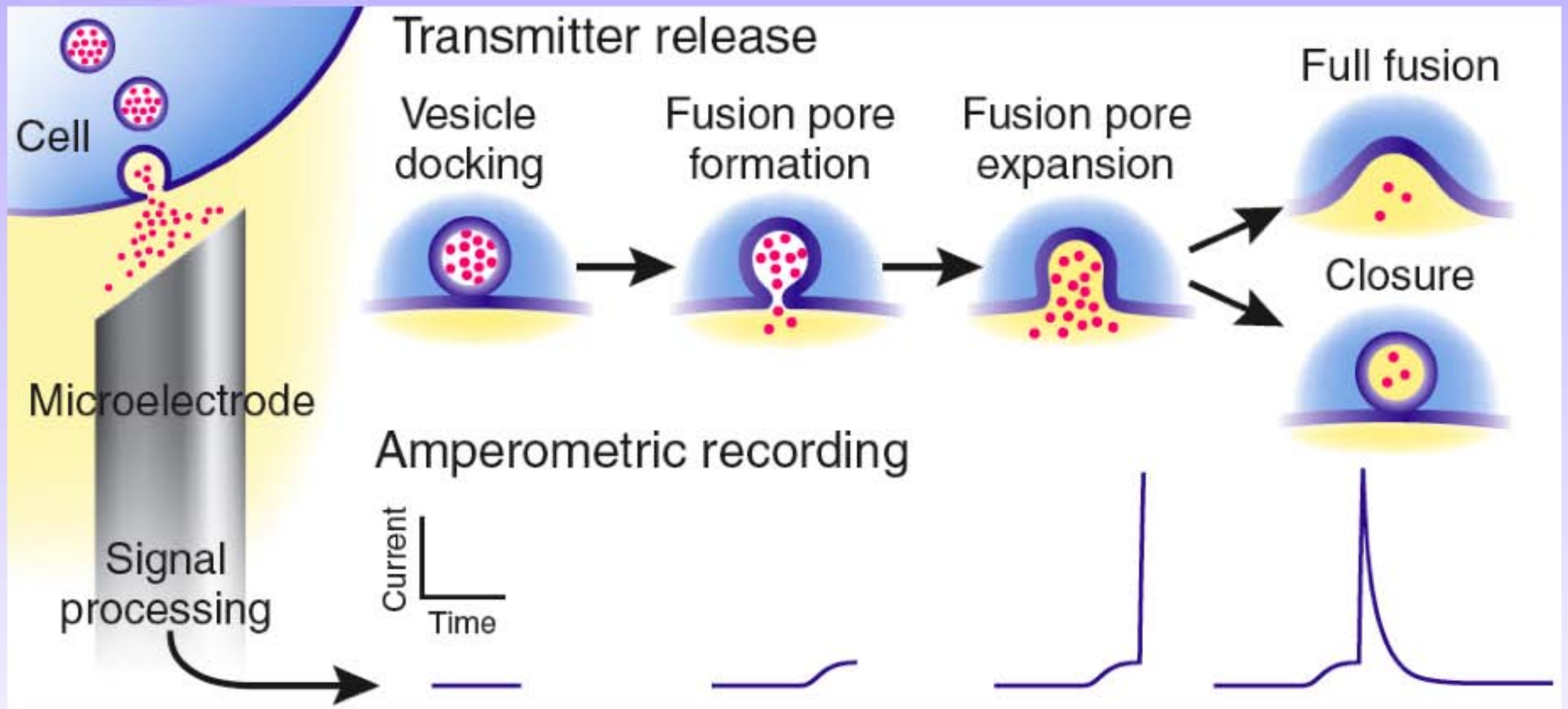
Une pente proche de 1, indique qu'il n'y a pas de transfert de membrane et indique plutot un evenement de type kiss-and-run.

Jackson & Chapman, Annual Rev. Biophys. Biomol. Struct. 2006

Comment mesurer l'exocytose ?

2) L'ampérométrie à fibre de carbone (5-10 microns de diamètre):

On stimule les cellules par une dépolarisation. La cellules sécrète alors des molécules. En presence d'un potentiel approprié, les molécules (catécholamines, indolamines) sécrétées s'oxydent et libèrent des électrons. La mesure du courant d'oxydation donne accès à la quantité de molecules sécrétées par événement unitaire d'exocytose.



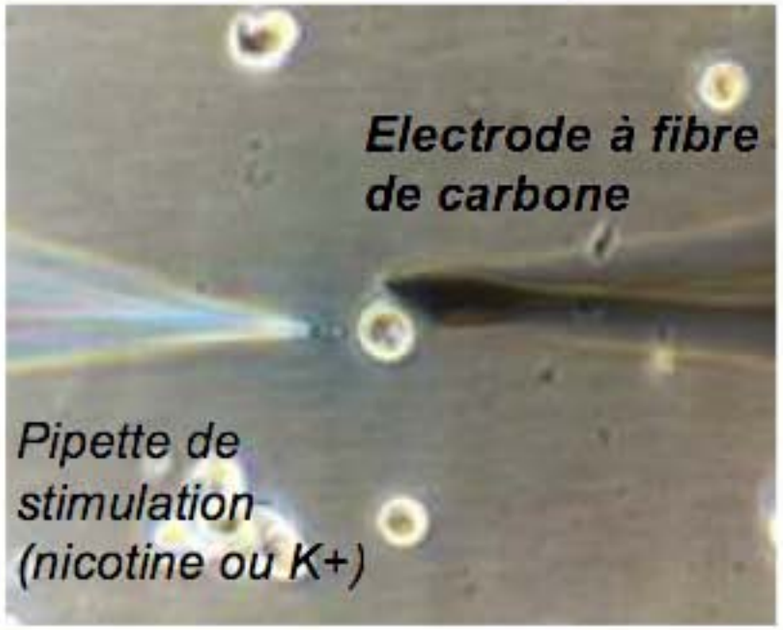
Cellules mesurées: *cellules chromaffines (noradrénaline, adrénaline), mastocytes (histamines, serotonines), et cellules ß du pancreas (insuline).*

Résolution temporelle: *<1ms*

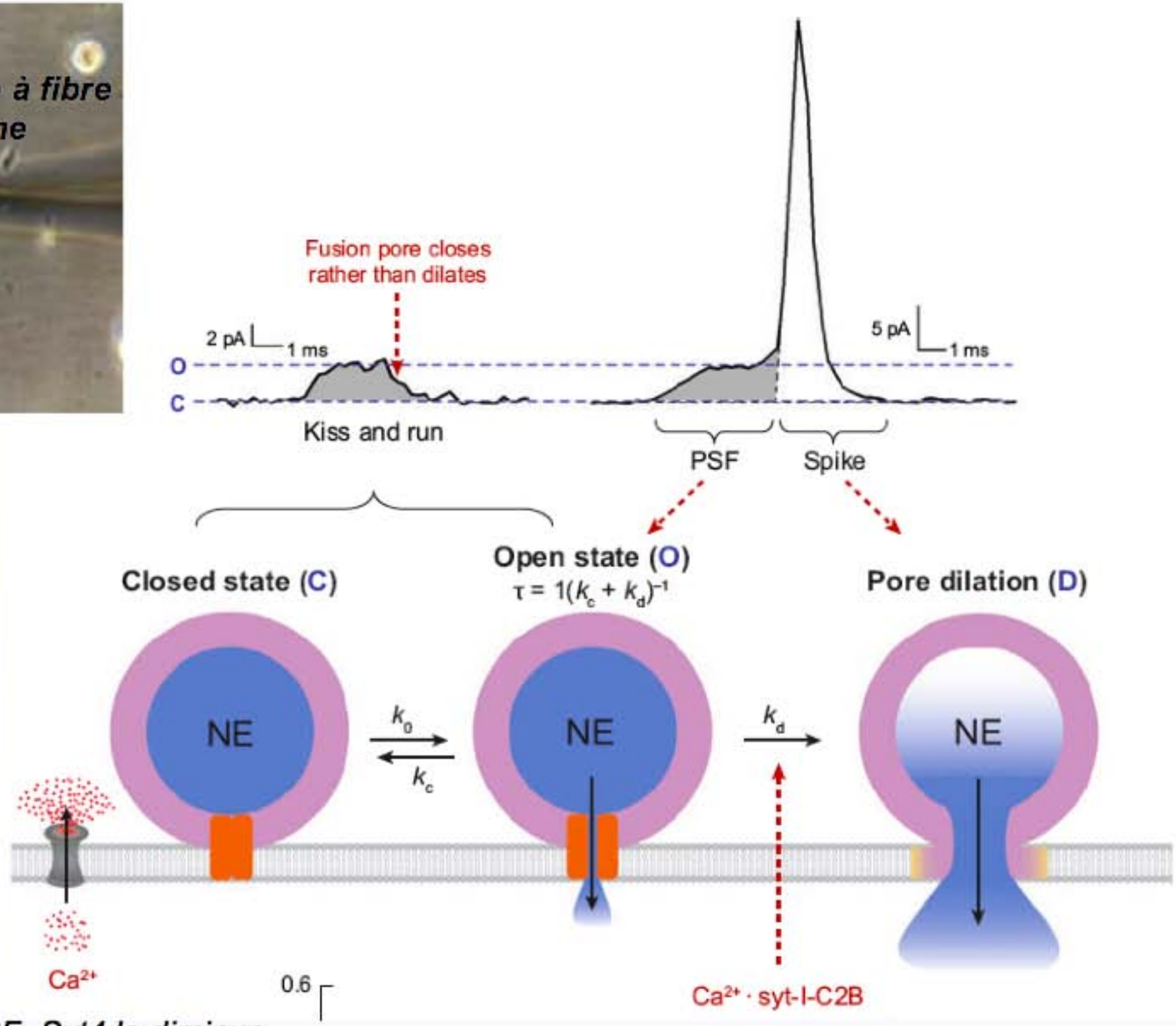
Sensibilité de détection: *quelques milliers de molecules (Chen et al., 1994)*

Comment mesurer l'exocytose ?

2) L'ampérométrie à fibre de carbone:



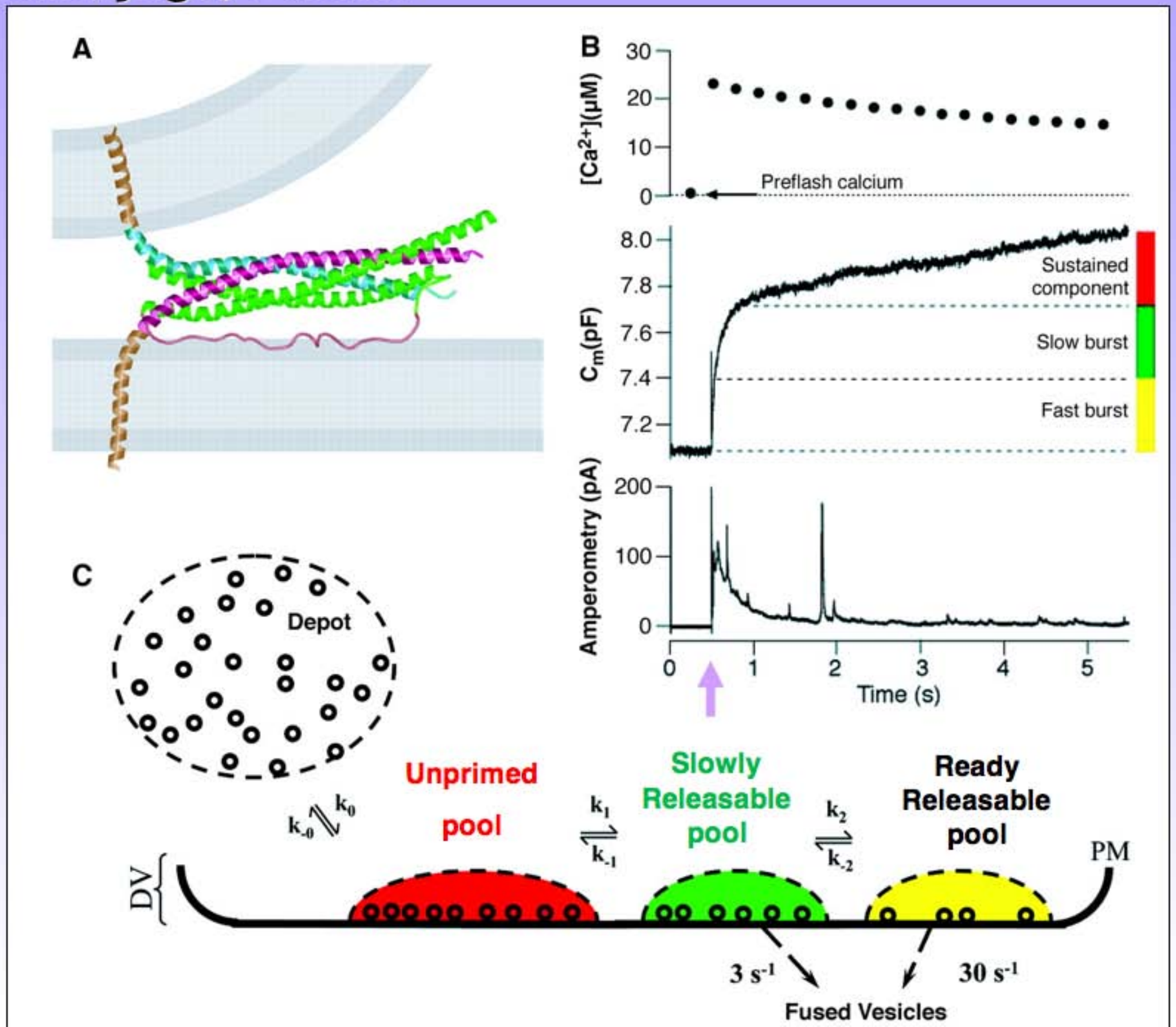
F. Darchen (UPR1929)



Ex: Syt1 prolonge le PSF, Syt4 le diminue.

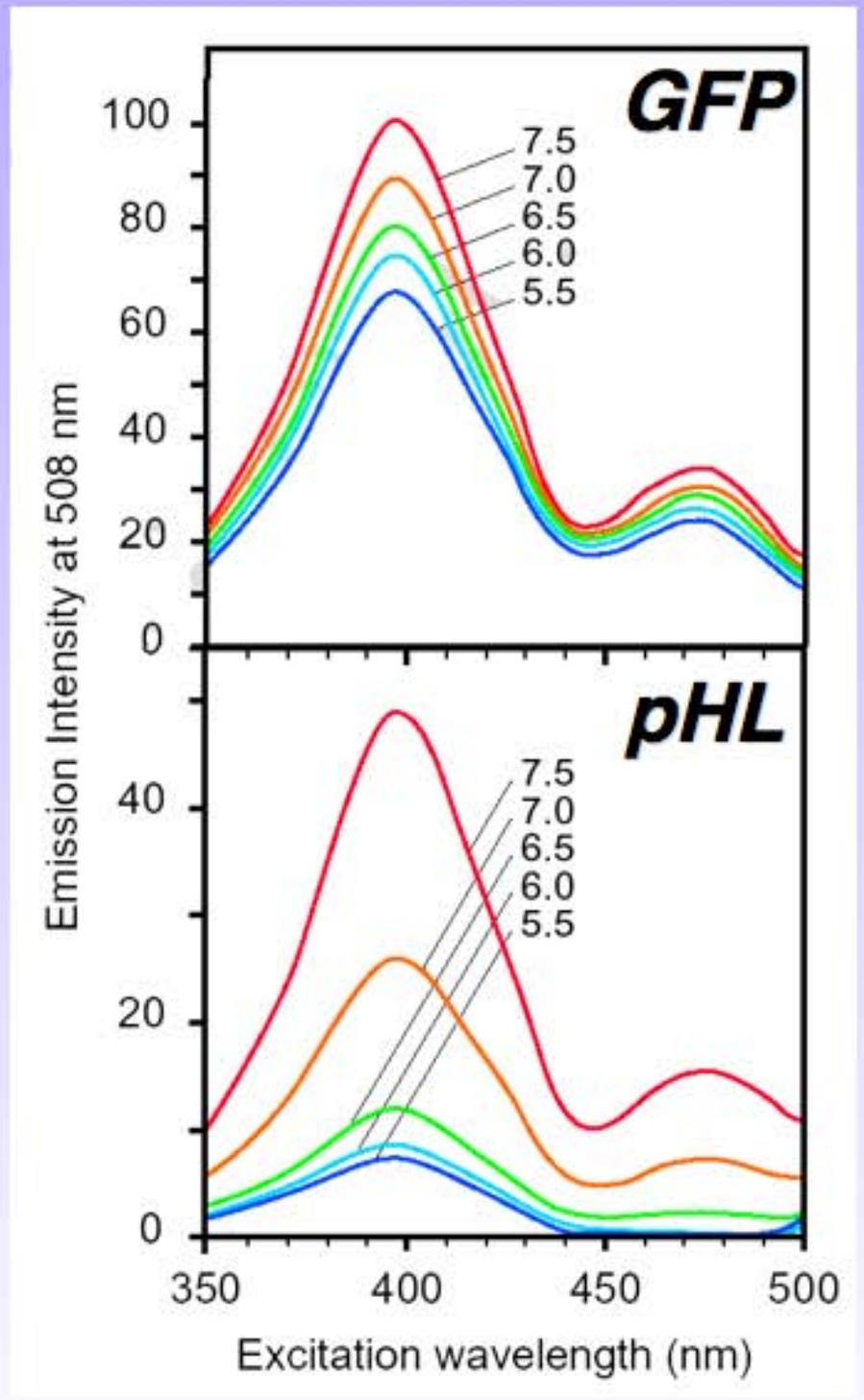
Chapman, Annu. Rev. Biochem. 2008.77:615-641

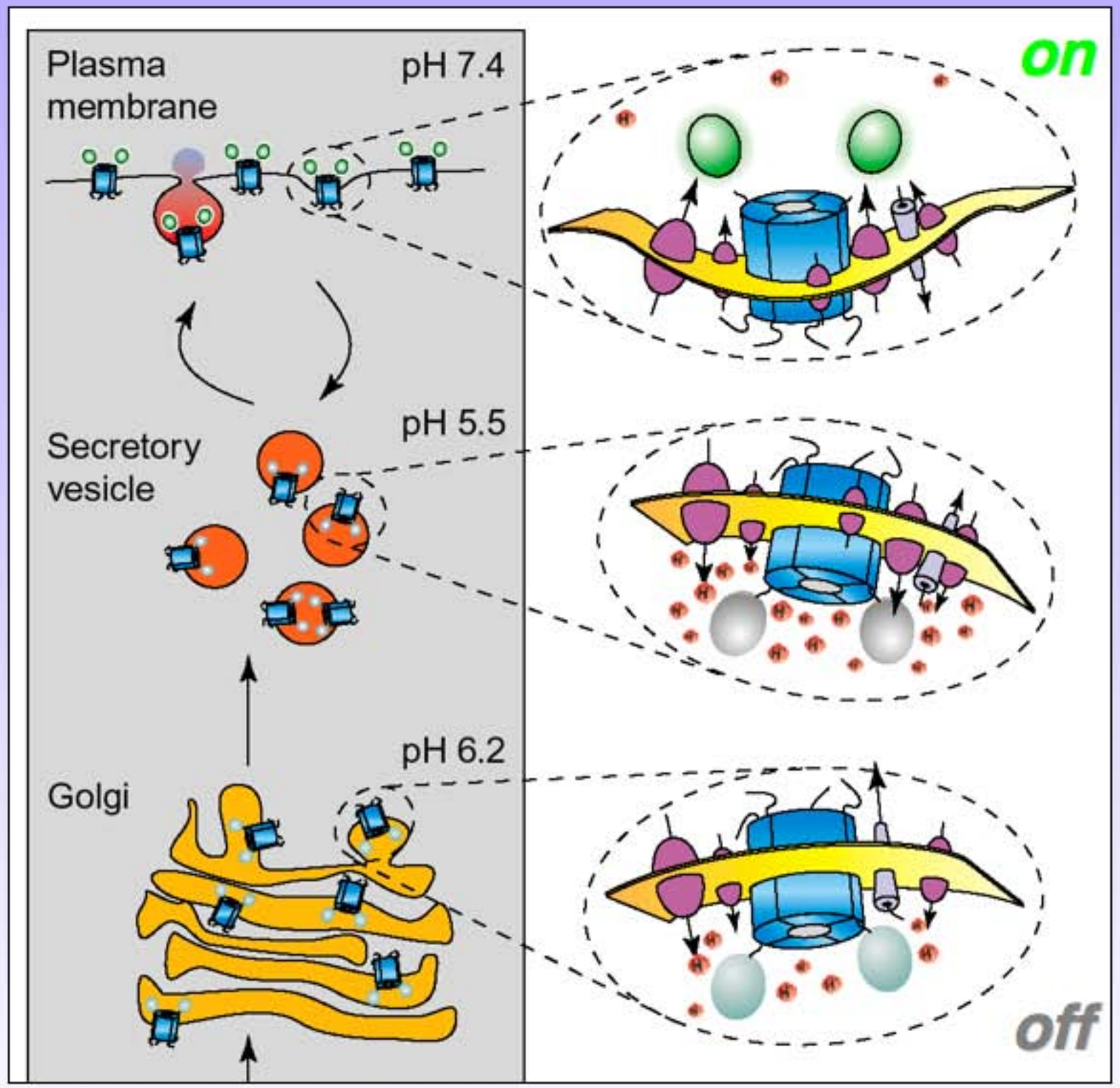
Réserve, Amorçage, Fusion



Comment mesurer l'exocytose ?

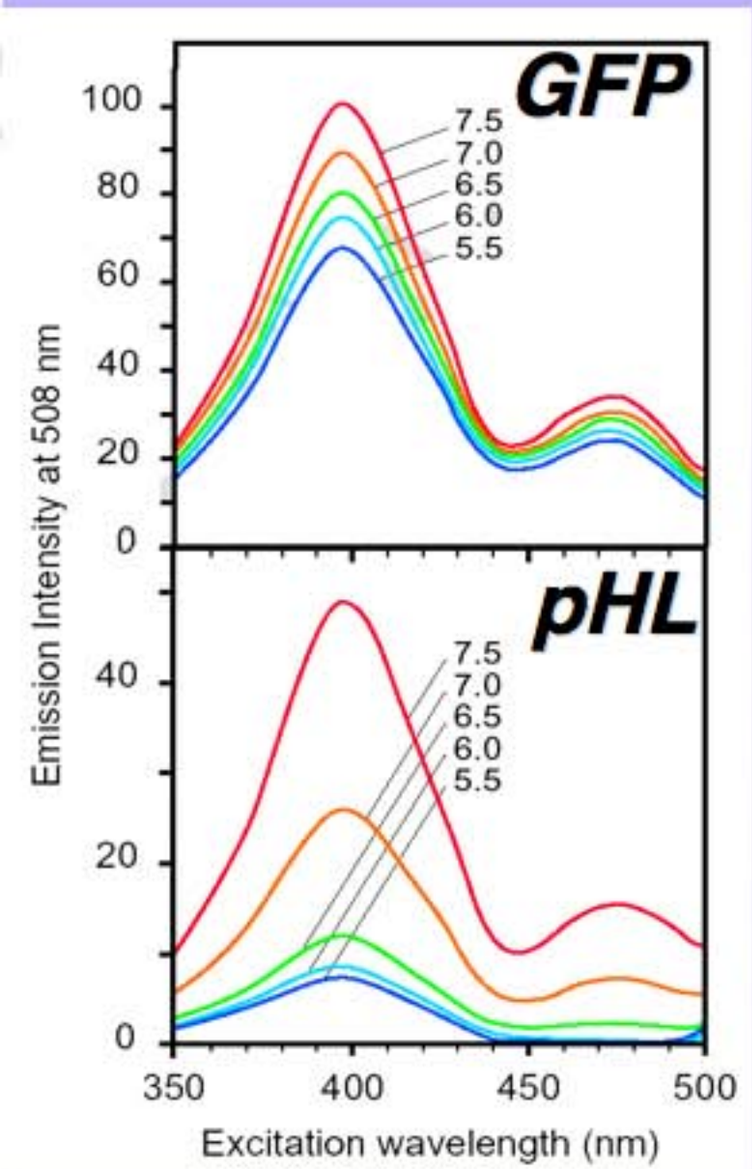
3) Mesure de fluorescence avec la GFP sensble au pH : la pHluorin

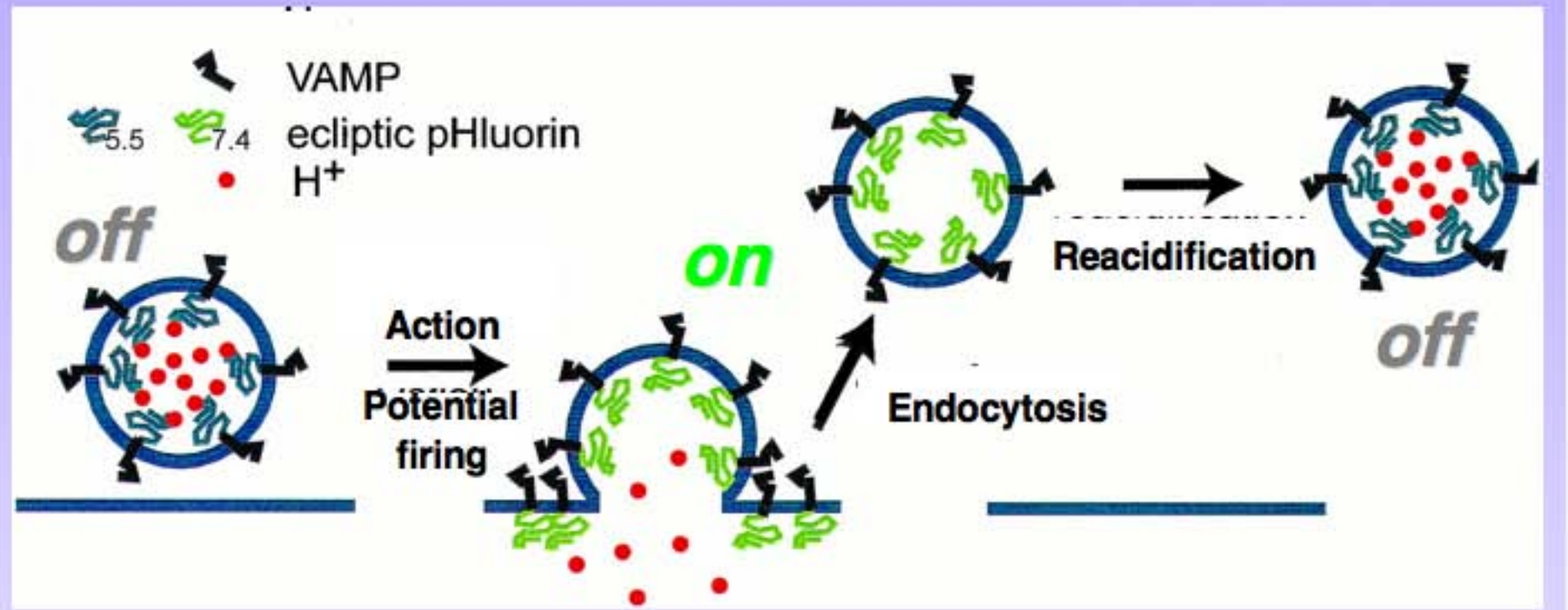


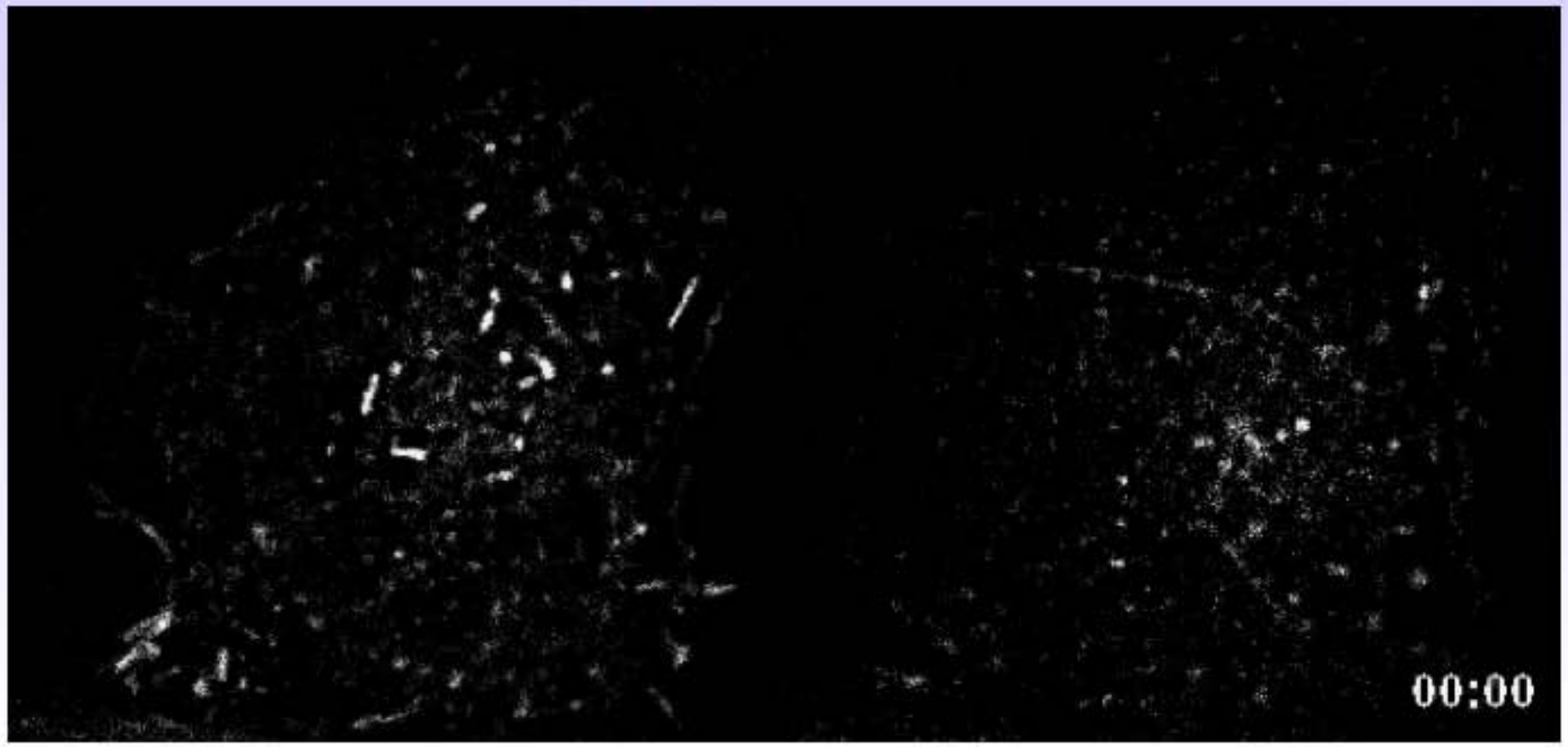


Comment mesurer l'exocytose ?

3) Mesure de fluorescence avec la GFP sensble au pH : la pHluorin

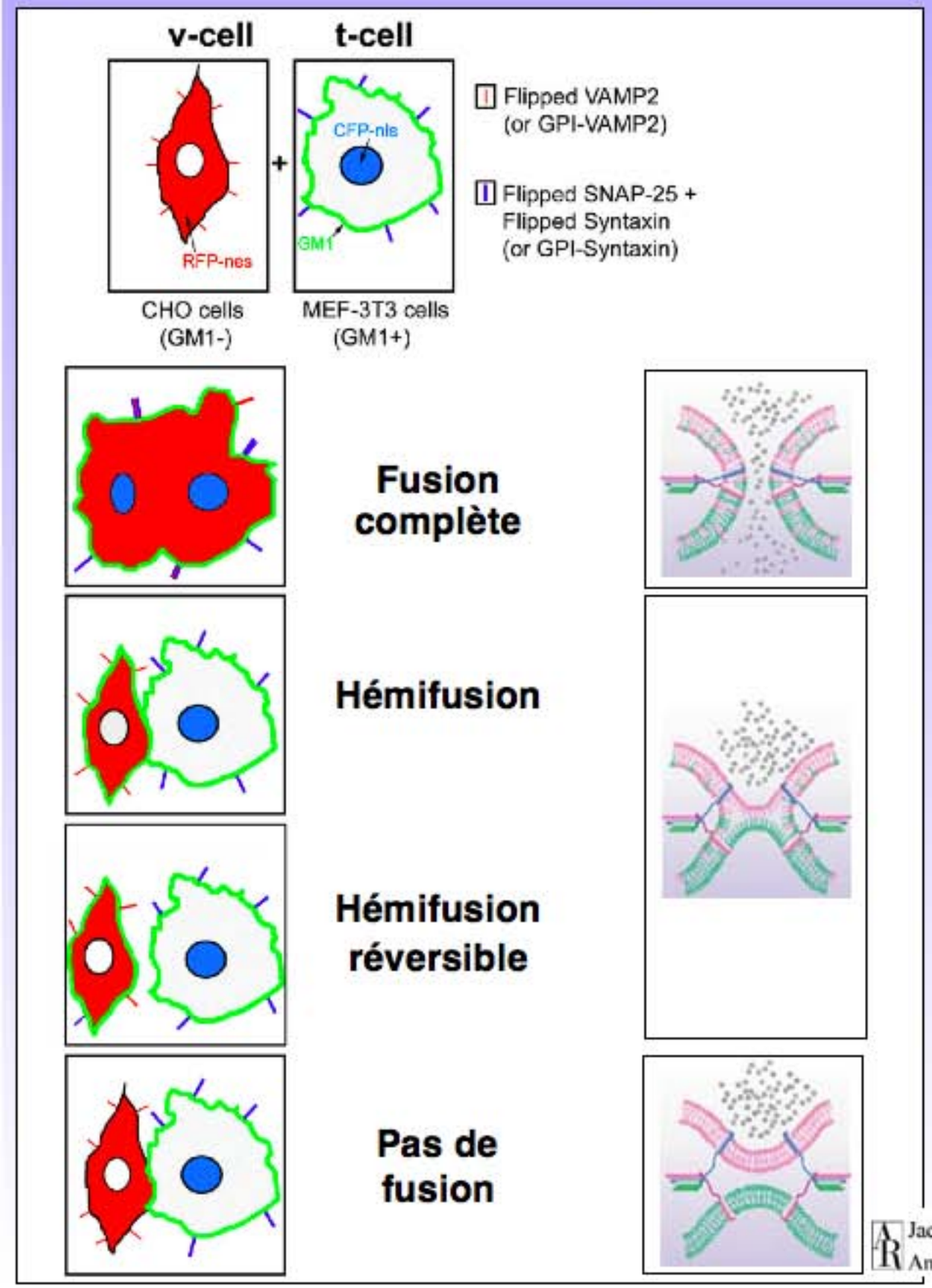


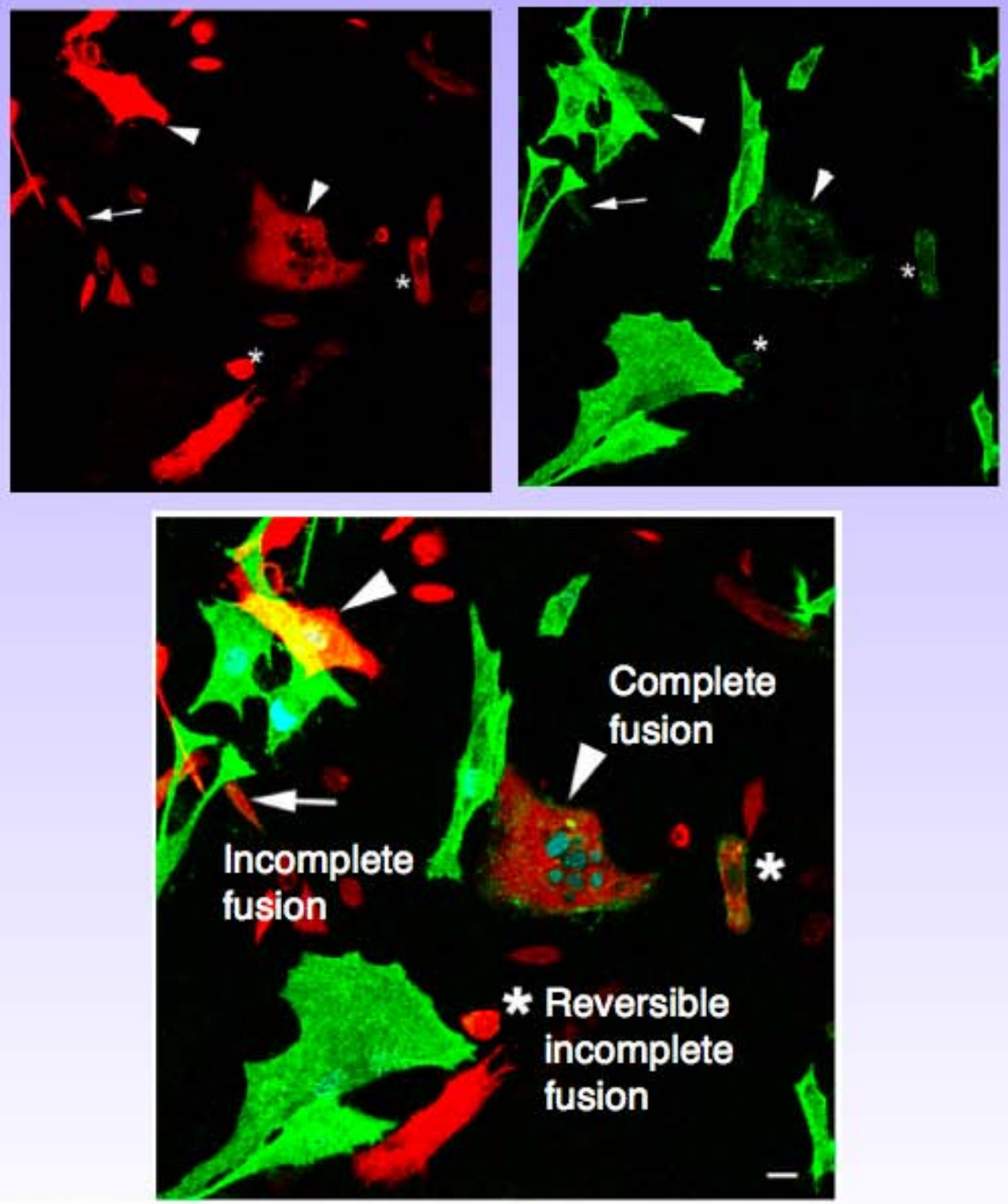




Comment mesurer l'exocytose ?

4) Evaluer la fusion par la technique des SNARE inversées (filpped SNARE fusion assay)





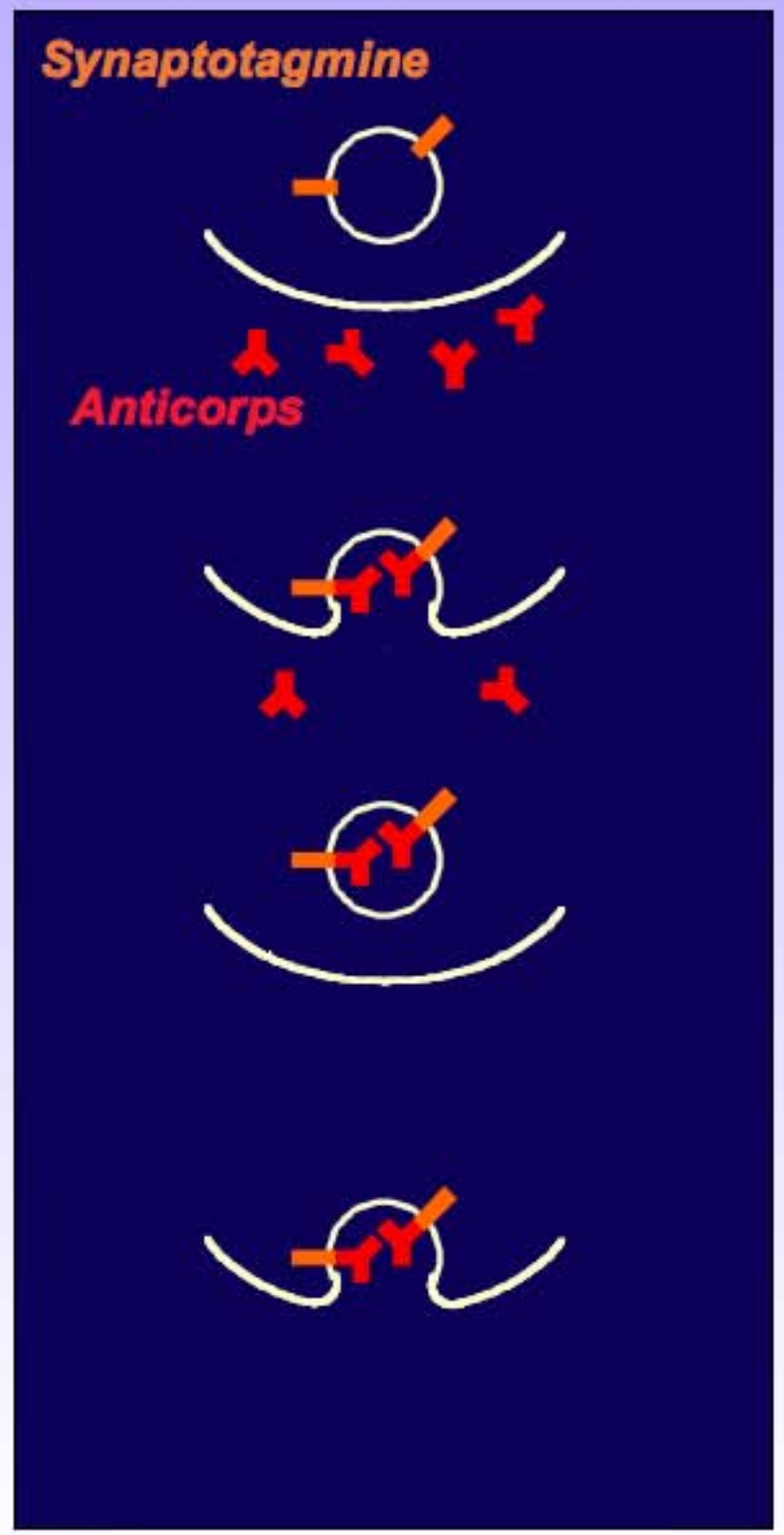
Jackson MB, Chapman ER. 2006.
Annu. Rev. Biophys. Biomol. Struct. 35:135–60

J Cell Biol. (2005), 170:249-260.

Comment mesurer le recyclage ?

1) L'utilisation d'anticorps anti-synaptotagmine

2) L'utilisation de sondes fluorescentes (FM Dyes)

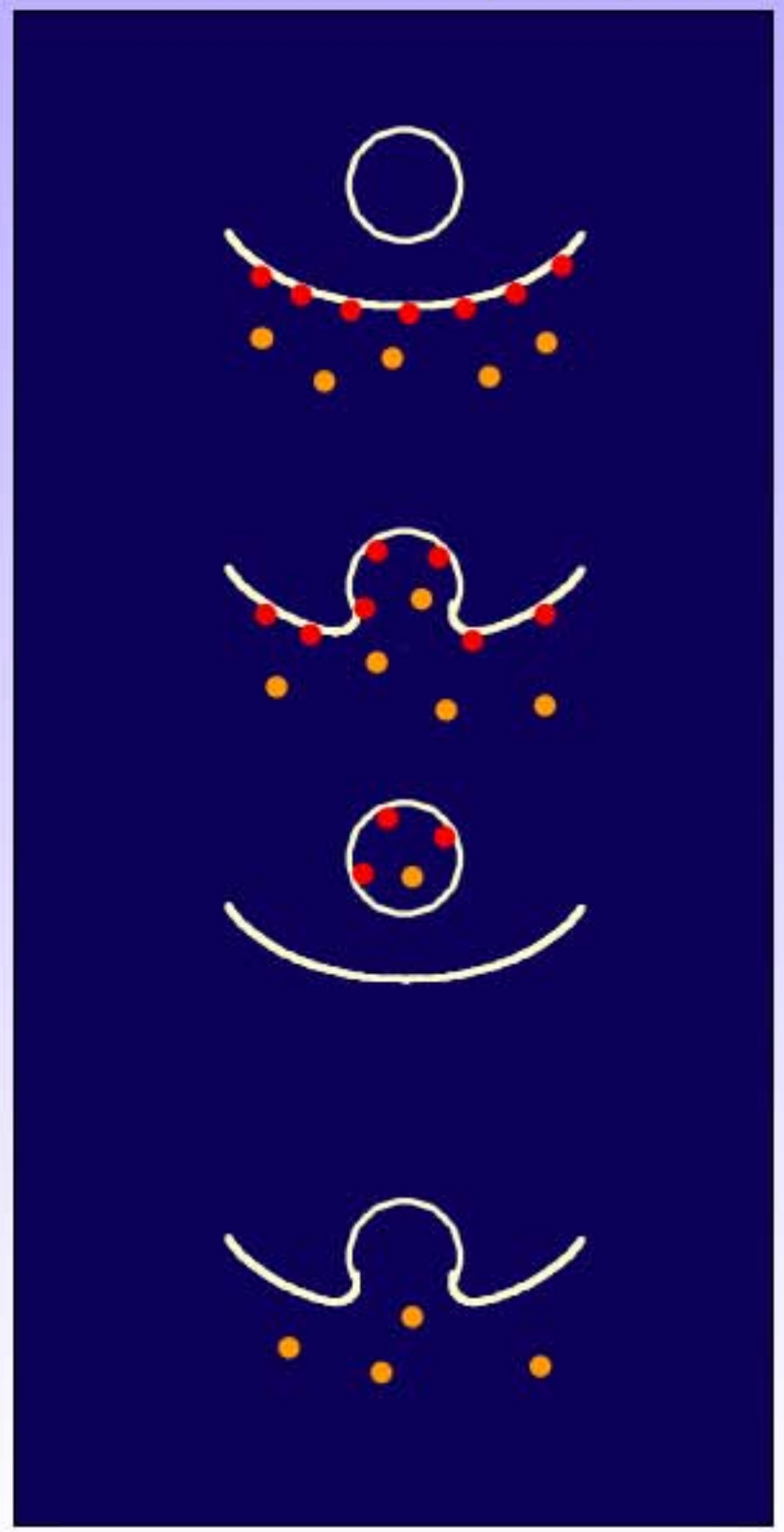


Incubation avec anticorps ou sonde

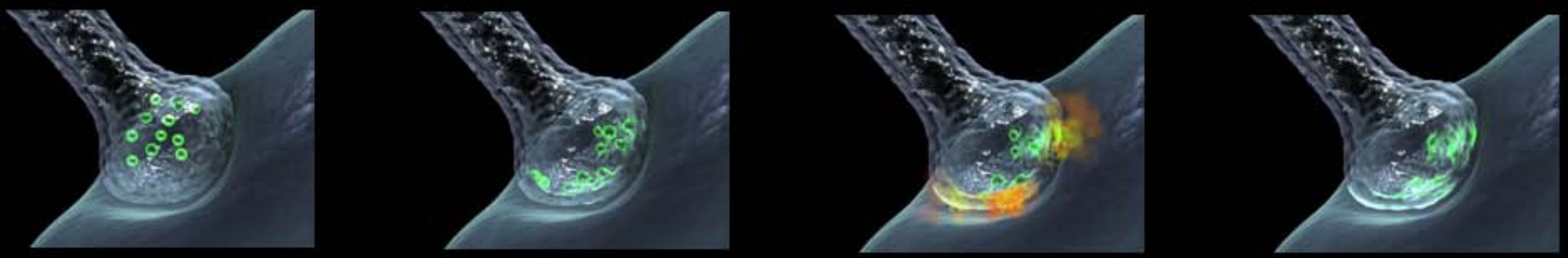
Endocytose

Vésicules chargées

Exocytose

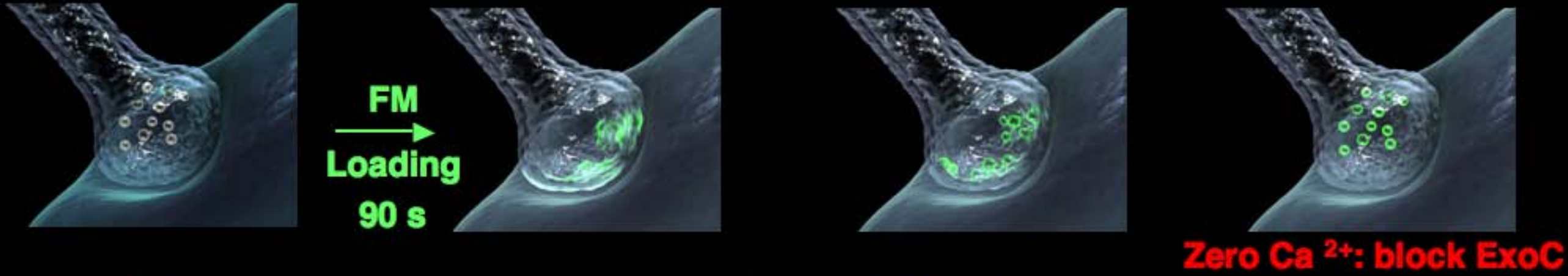


Neuronal transmission: exocytosis

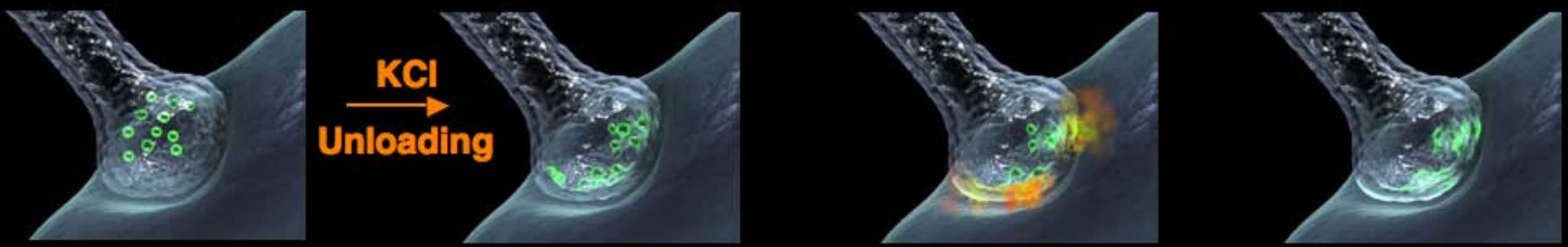


FM experiments

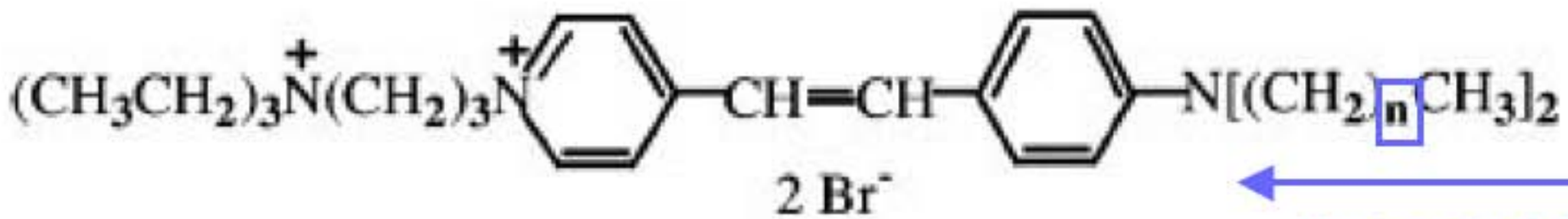
1. Loading of fluorescent dyes



2. Mesurement of the unloading of FM dyes



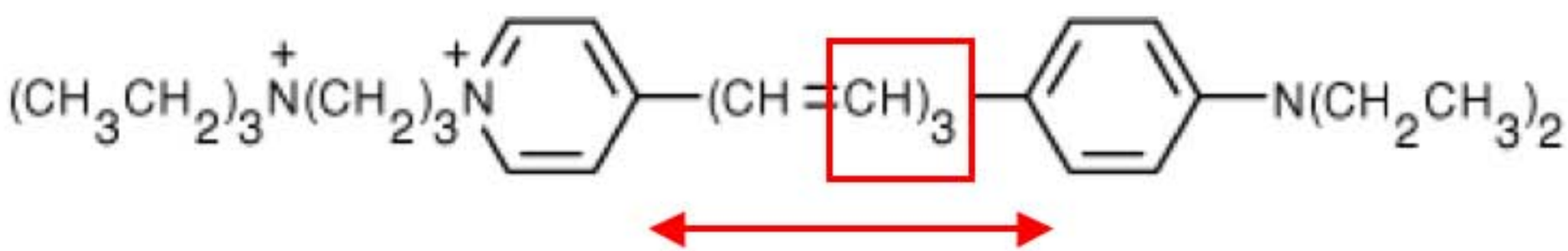
Basic properties of the FM dyes



Hydrophobic tail :
dissociation rate

n=1 FM 2-10
n=3 FM 1-43
n=4 FM 1-84

FIG. 1. **Chemical structures of FM 2–10, FM 1–43, and FM 1–84.**

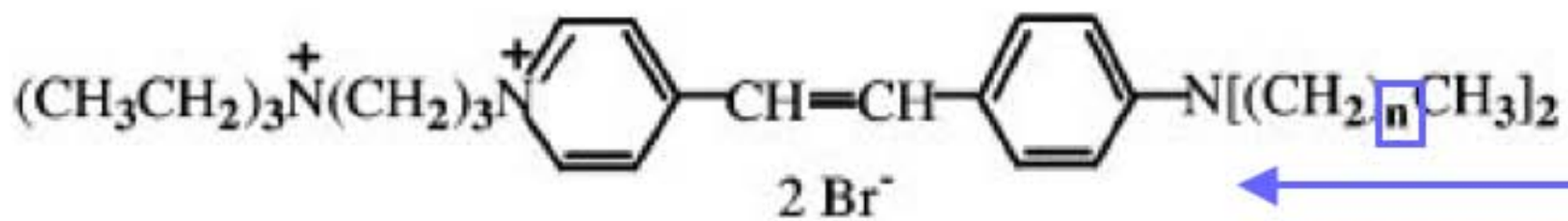


Carbon spacer :

Red-shiftes fluorescence

FM 4-64

Basic properties of the FM dyes



Hydrophobic tail : dissociation rate

n=1 FM 2-10
n=3 FM 1-43
n=4 FM 1-84

FIG. 1. **Chemical structures of FM 2–10, FM 1–43, and FM 1–84.**

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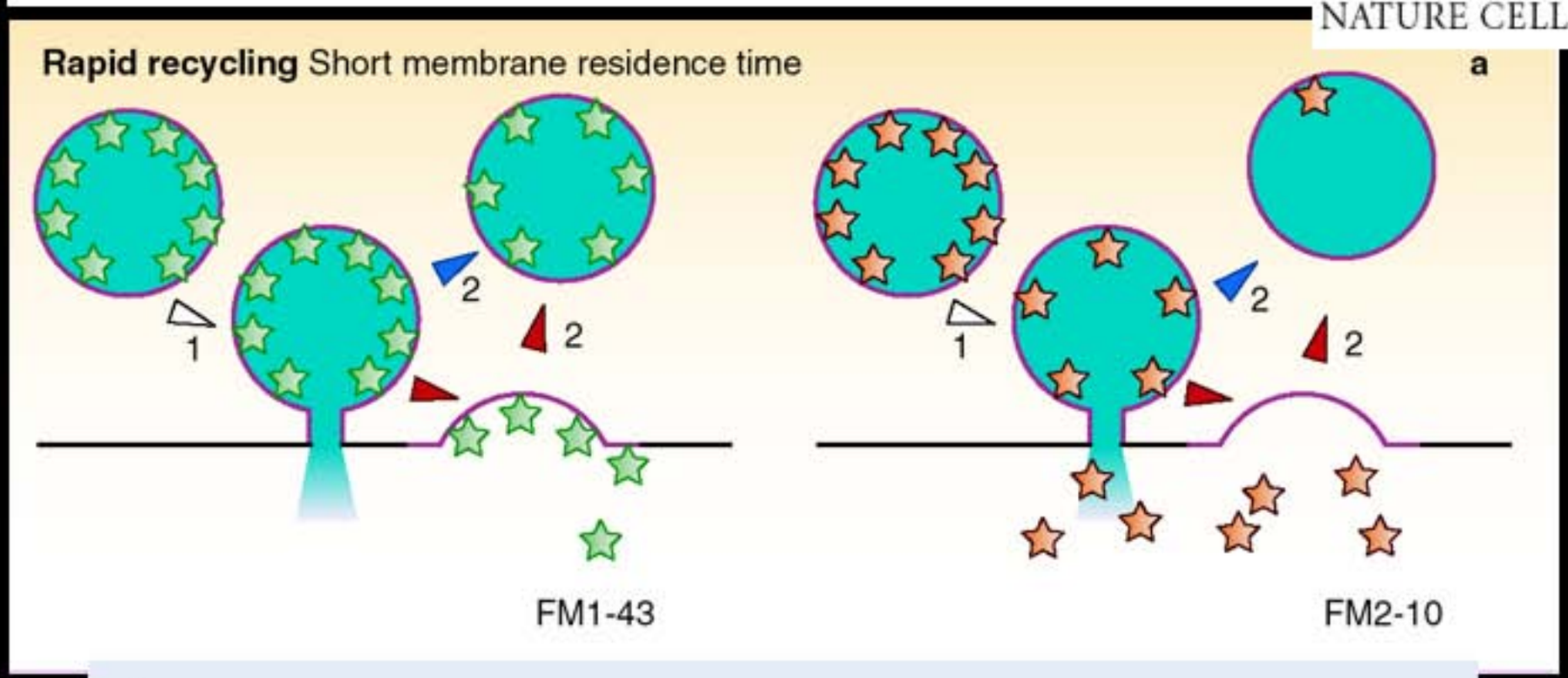
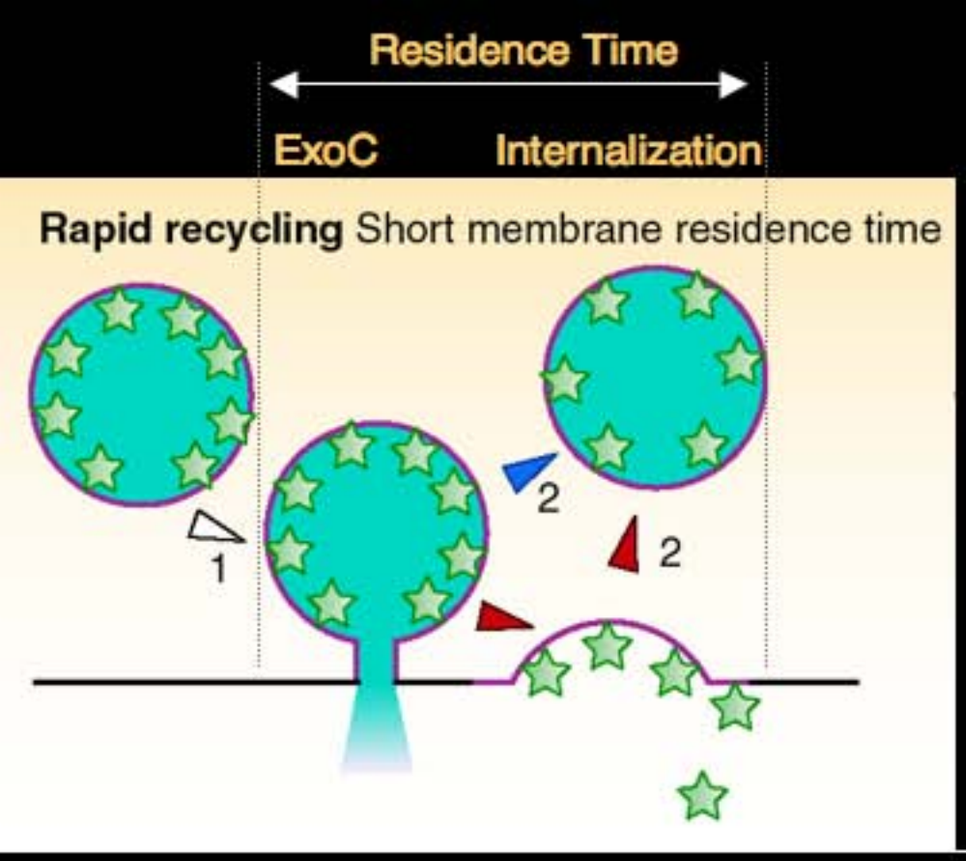


Dye with slow 'off time'
Dye with fast 'off time'
Vesicle membrane
Pre-synaptic membrane
Neurotransmitter

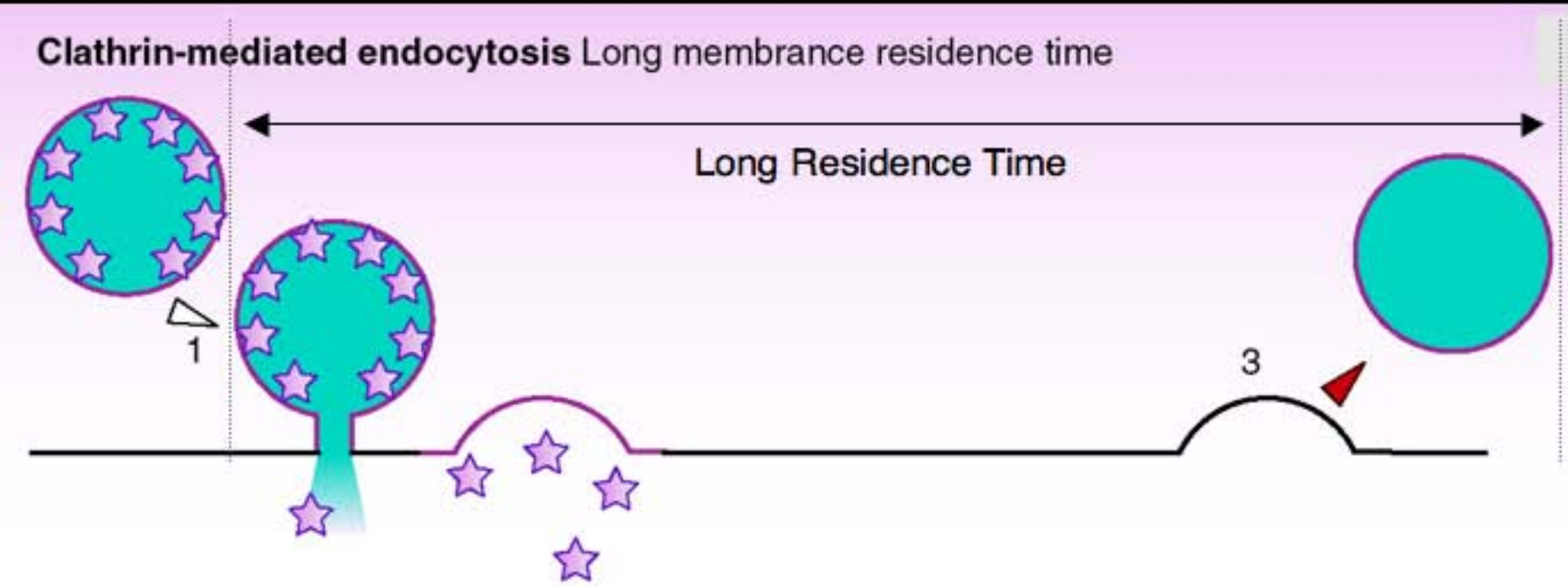
FM2-10 is faster than FM1-43

How to discriminate between Kiss & run and Endocytosis



Kiss and run :

Short Residence time (Res.T)



Clathrin mediated endocytosis:

Long Residence time

Dye with slow 'off time' — Vesicle membrane — Neurotransmitter

Dye with fast 'off time' — Pre-synaptic membrane

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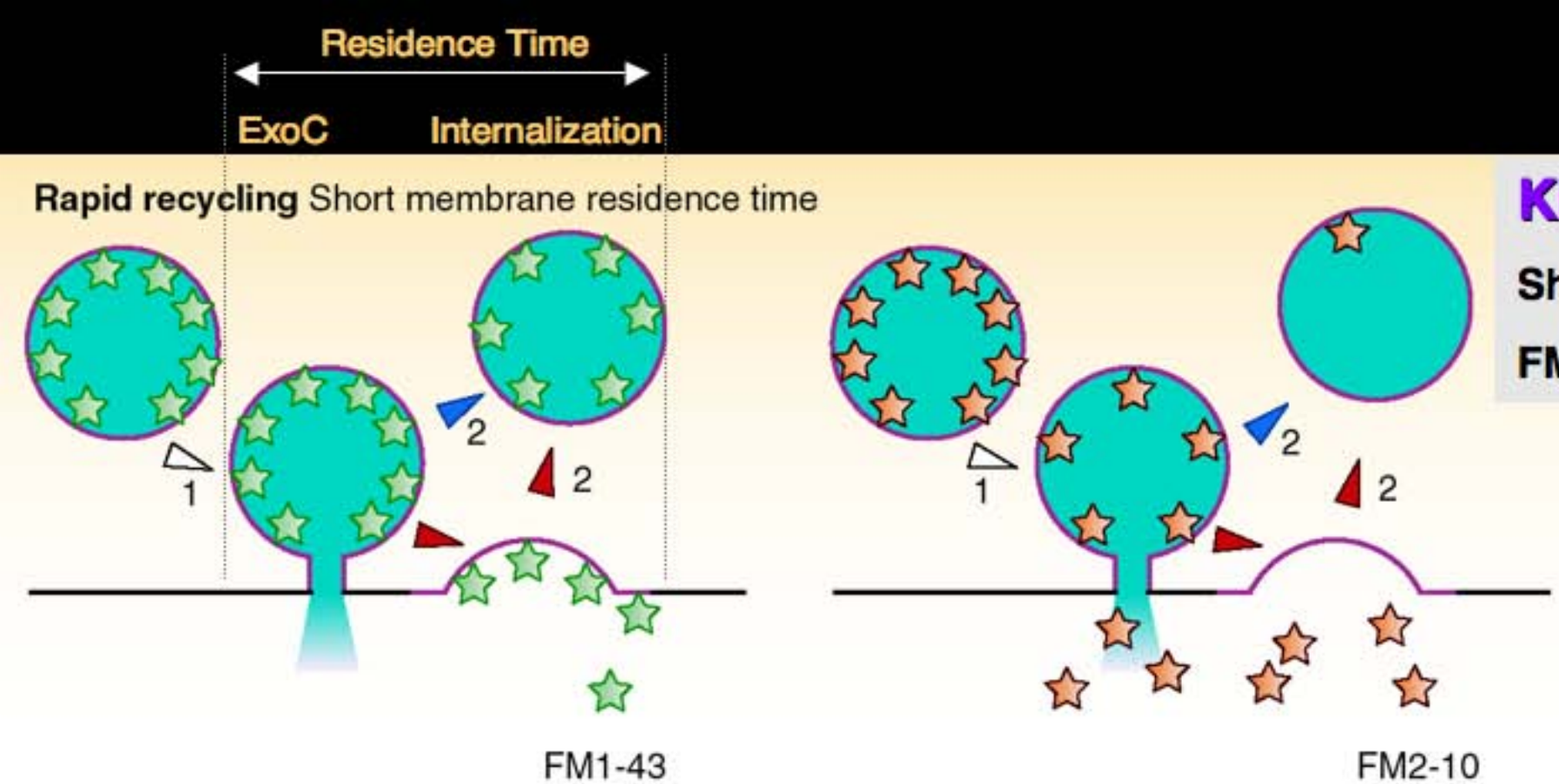


Kiss and run :

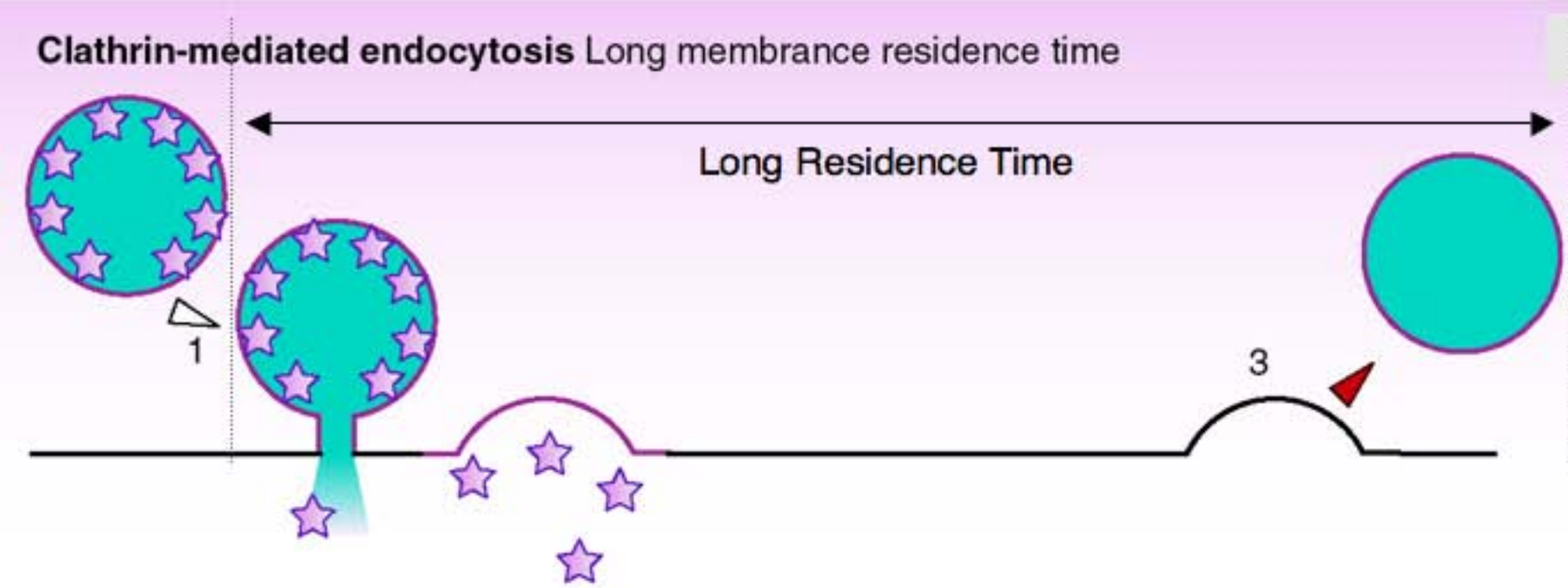
Short Residence time (Res.T)

FM2-10 < Res. T < FM 1-43

FM2-10 is faster than FM1-43 :

« Off time »

FM2-10 < FM 1-43



Clathrin mediated endocytosis:

Long Residence time

Residence time >> FM off time

Res. T >> FM 1-43 > FM2-10

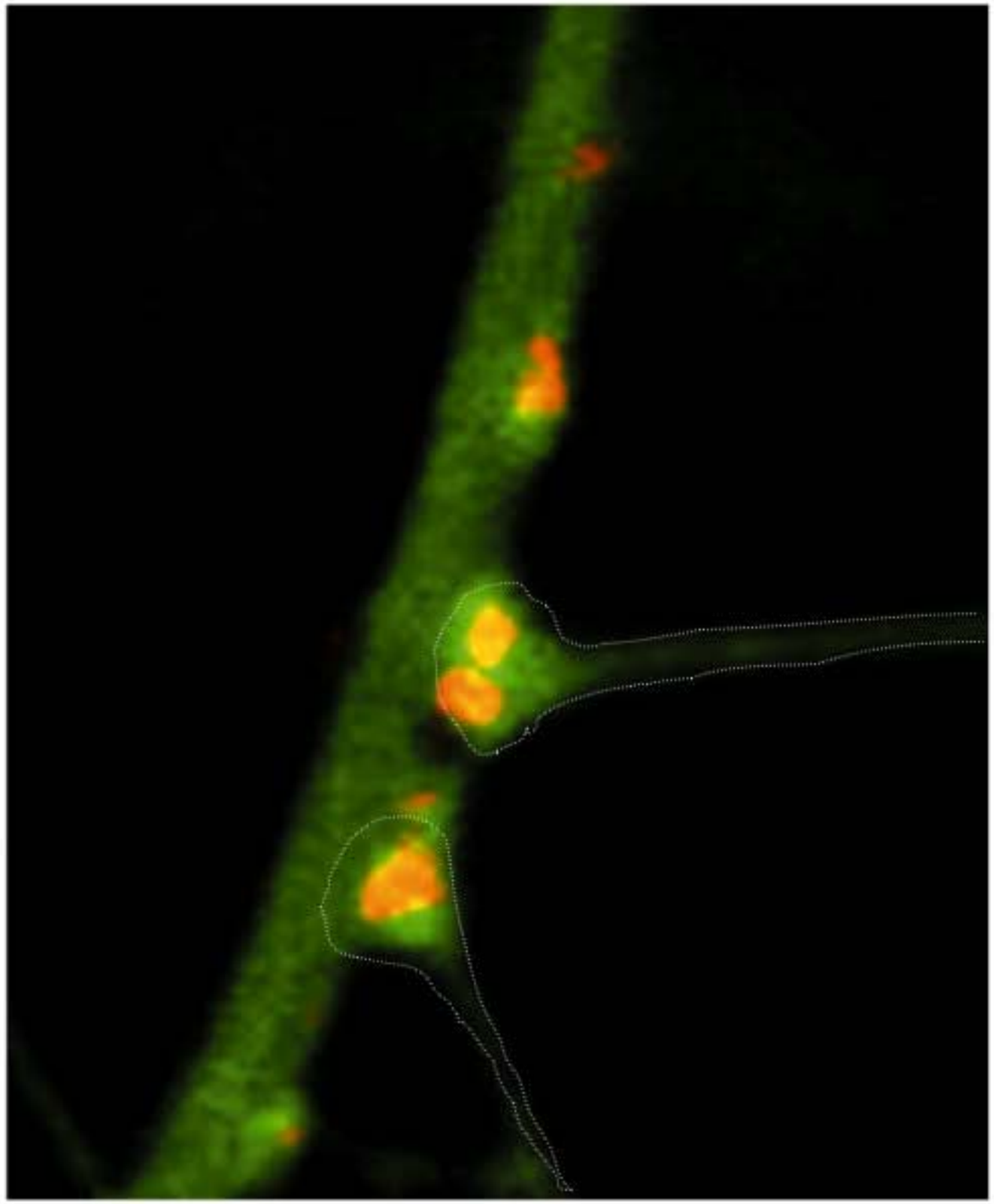
There is no difference between FM2-10 and FM1-43

Both can dissociate before internalization

Dye with slow 'off time' — Vesicle membrane — Neurotransmitter

Dye with fast 'off time' — Pre-synaptic membrane

NATURE CELL BIOLOGY | VOL 4 | NOVEMBER 2002 |



Current Opinion in Neurobiology

FM 4-64 labeling of synaptic vesicle clusters in hippocampal neurons. FM 4-64, which is a red-shifted variant of FM 1-43, was applied during AP firing to hippocampal neurons in cell culture. Two GFP-expressing cells that form an axo-dendritic contact containing two clusters of recycling vesicles labeled by FM 4-64 are shown.

Evidence for a Role of Dendritic Filopodia in Synaptogenesis and Spine Formation

Noam E. Ziv and Stephen J Smith Neuron, Vol. 17, 91–102, July, 1996.

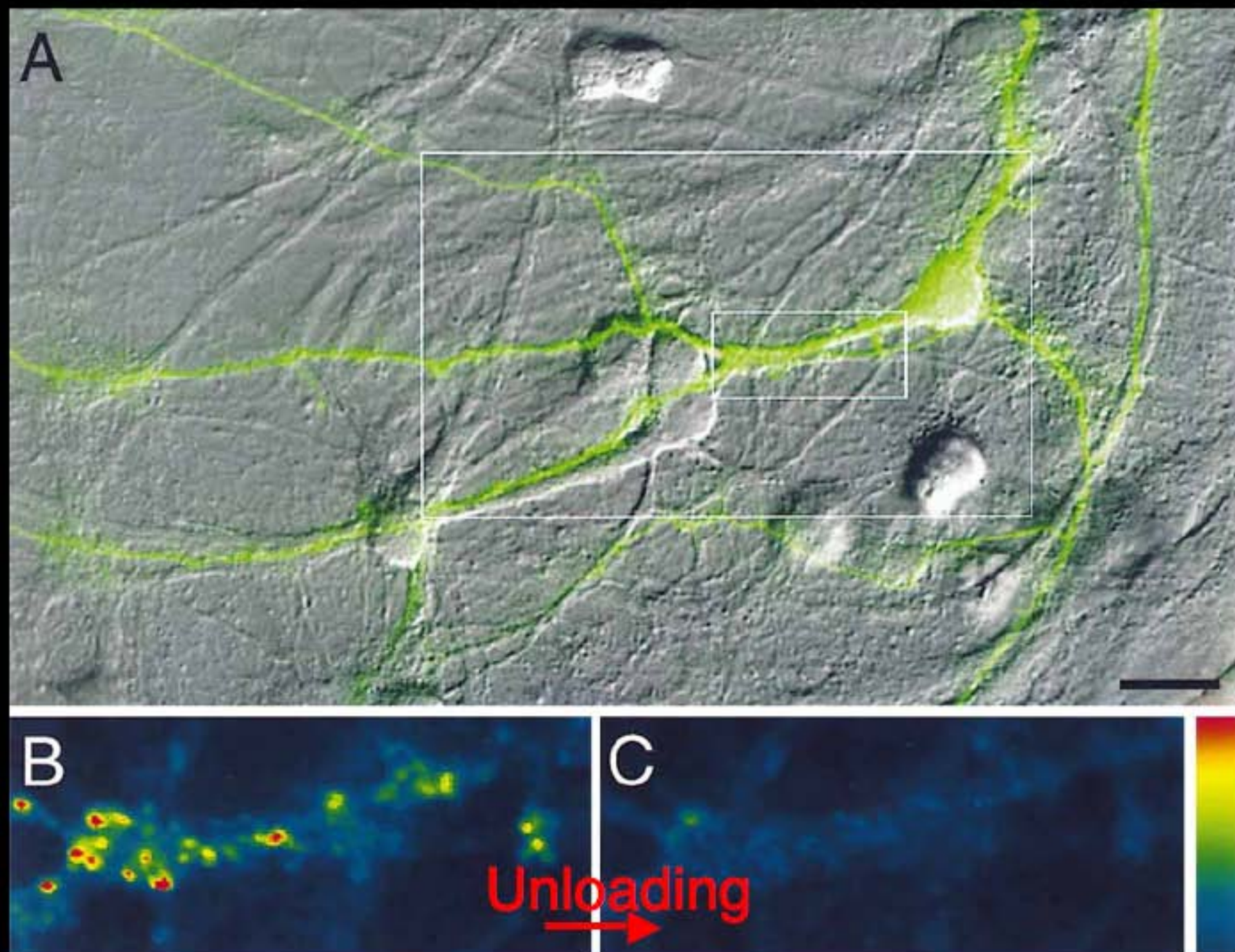


Figure 1. Imaging of Dendritic Structure and Presynaptic Boutons in Live Cultured Hippocampal Neurons

(A) A fluorescence image of a single pyramidal neuron labeled with FAST DiO, digitally overlaid on a DIC image of the same field. The neurons shown in this figure were grown for 13 DIV prior to the experiment.

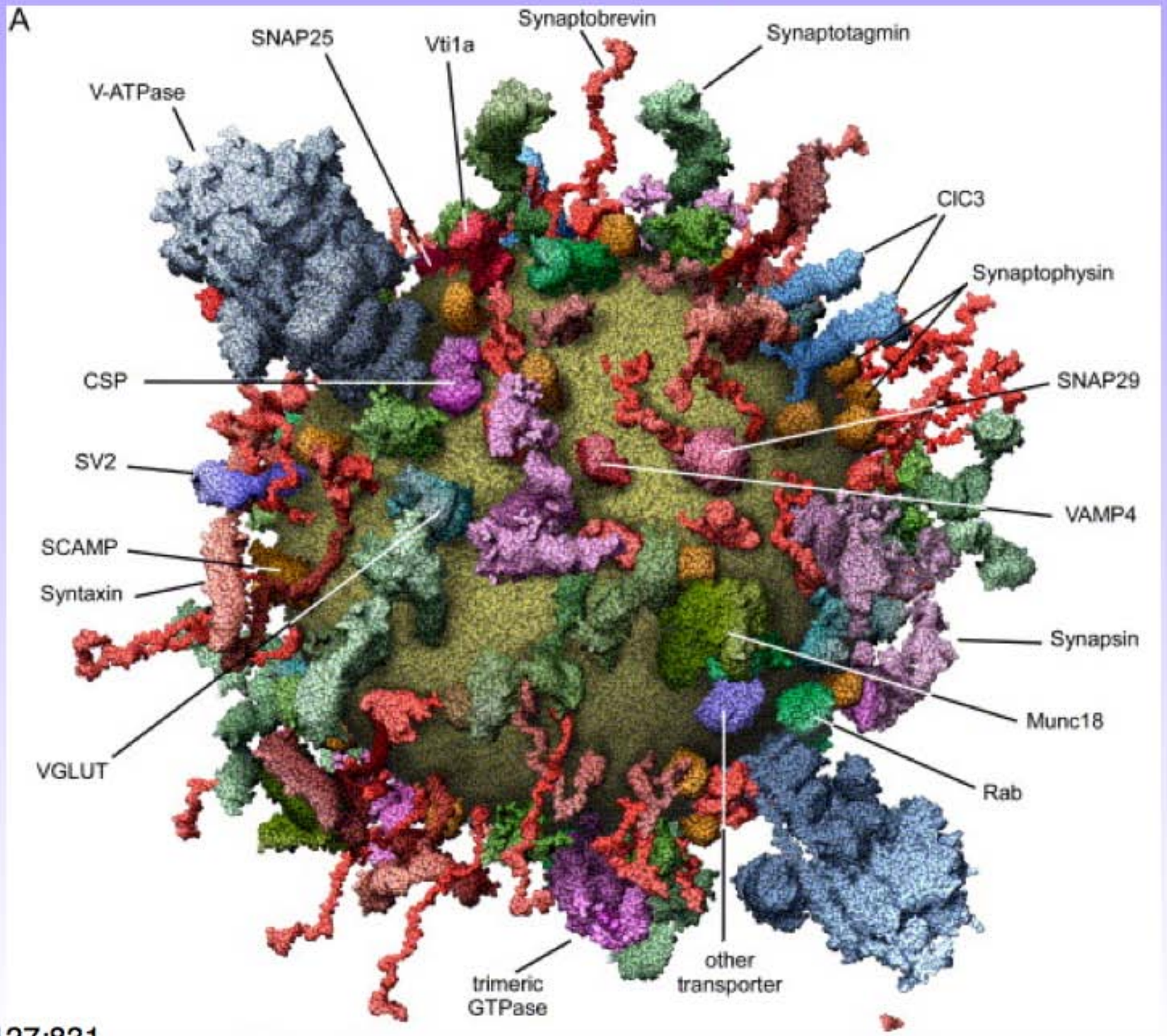
(B) A pseudocolor fluorescence image of presynaptic boutons loaded with FM 4–64. The area shown corresponds to the inner rectangle in (A). Fluorescence intensity is coded according to color bar on far right.

(C) The same field shown in (B) after the dye was unloaded by stimulating the neurons to fire action potentials for 60 s at 10 Hz.

(D) Digital superposition of the FM 4–64 difference image (red), created by subtracting the image in (C) from that in (B), onto the fluorescence image of the FAST DiO-labeled neuron (green). Area shown corresponds to outer rectangle in (A). Scale bars, 20 μm (A) and 10 μm (D).

Vésicules Synaptiques

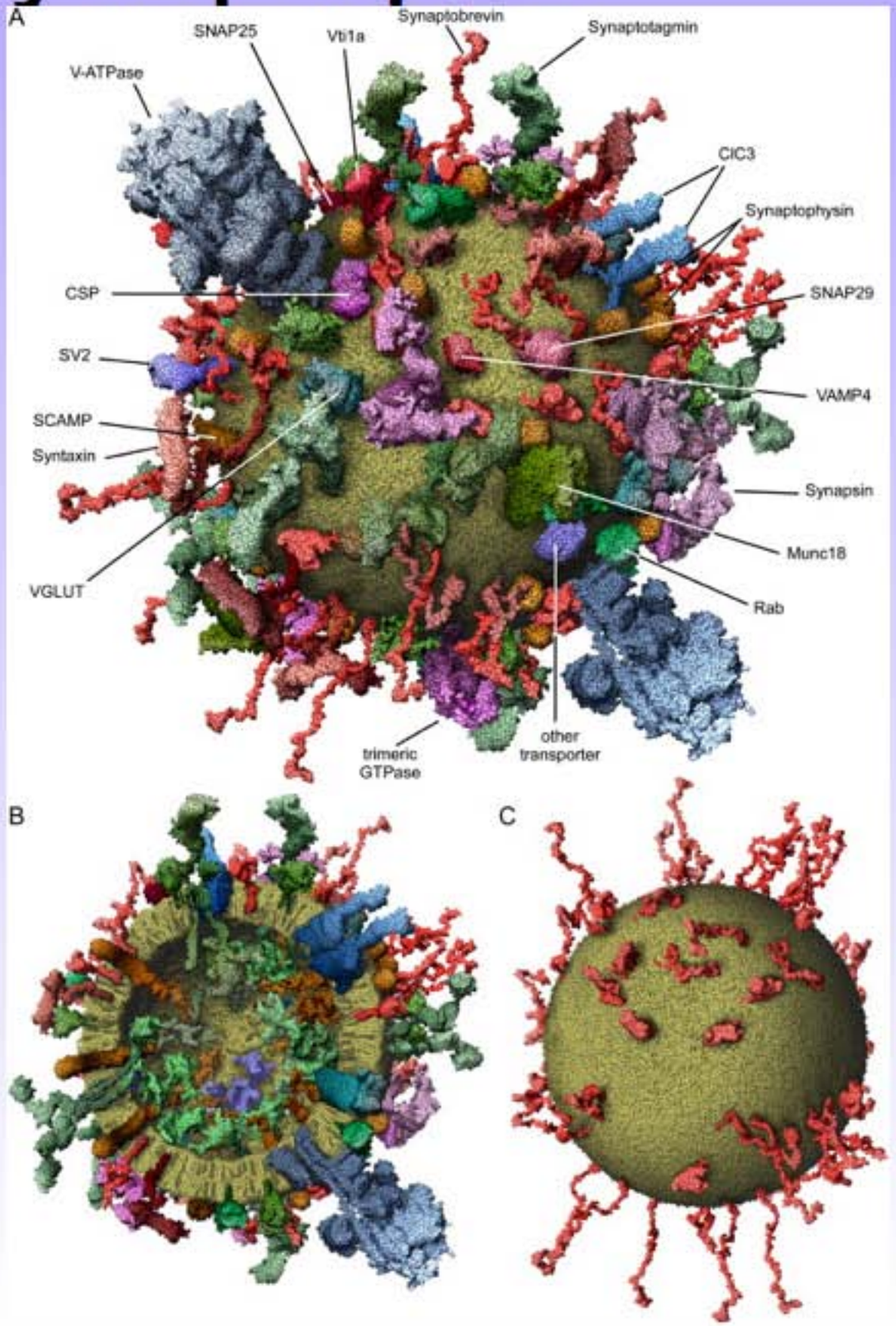
R. Jahn



Takamori et al. Cell (2006)127:831.

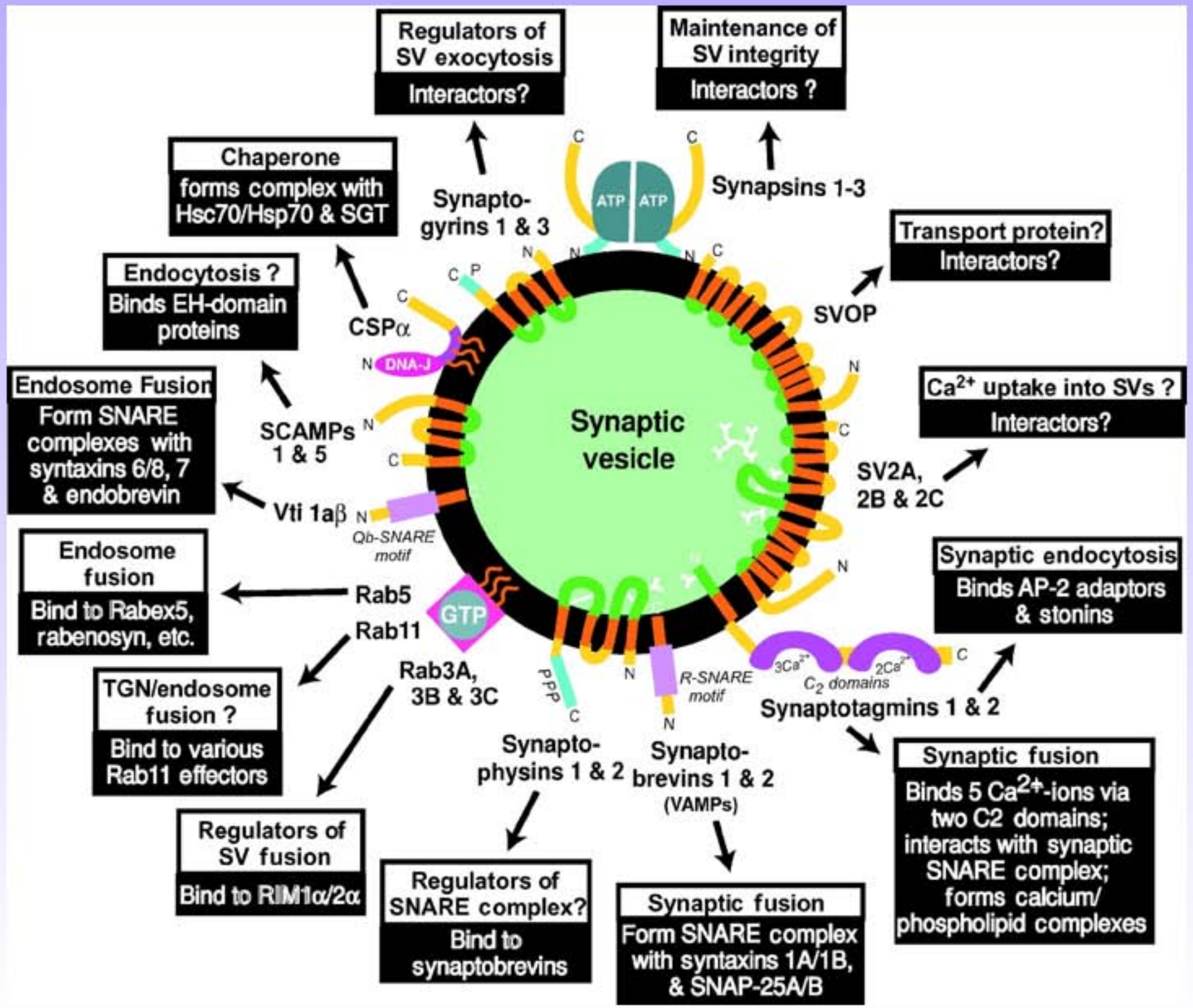
Vésicules Synaptiques

Protein	% of total SV proteins
Synaptophysin	10.20 ± 1.54[1,4]
Synaptobrevin 2	8.60 ± 1.55[1]
Syntaxin 1	2.00 ± 0.27[1,5]
SNAP25	0.40 ± 0.06[1,6]
Synapsins	6[2,3]
Rab3A	2.5[2]
Synaptotagmin 1	7[3]
Synaptogyrin 1	0.5[2]
SV2	1.4[2]
SCAMP	0.3[2]
CSP	0.6[2]
VGLUT1	5.36 ± 1.11[1,7]
VGLUT2	9.01 ± 2.31[1,7]
V-ATPase V1-B subunit	1.15 ± 0.21[1]

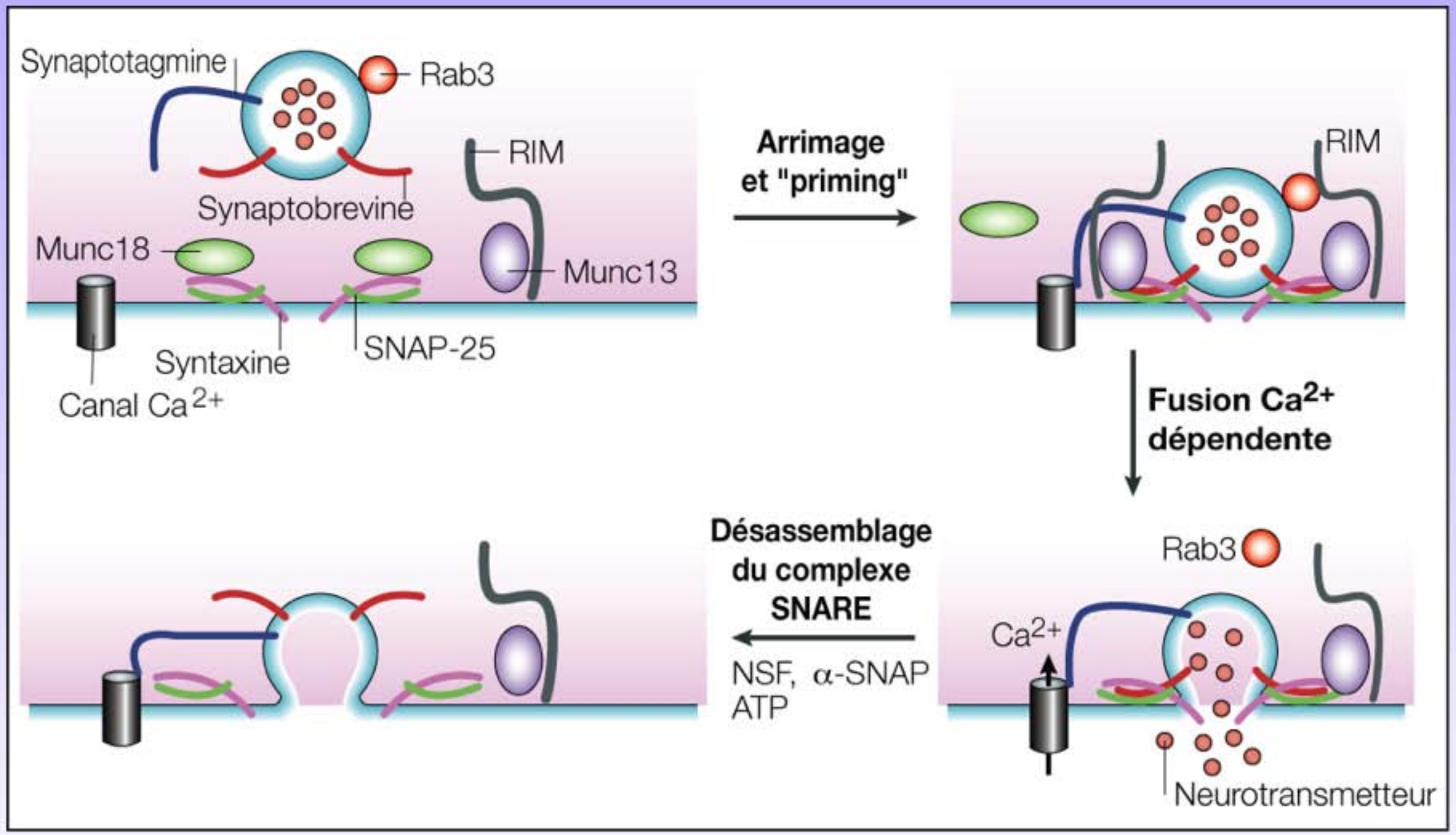


Takamori et al. Cell (2006)127:831.

Fonction des protéines des VS



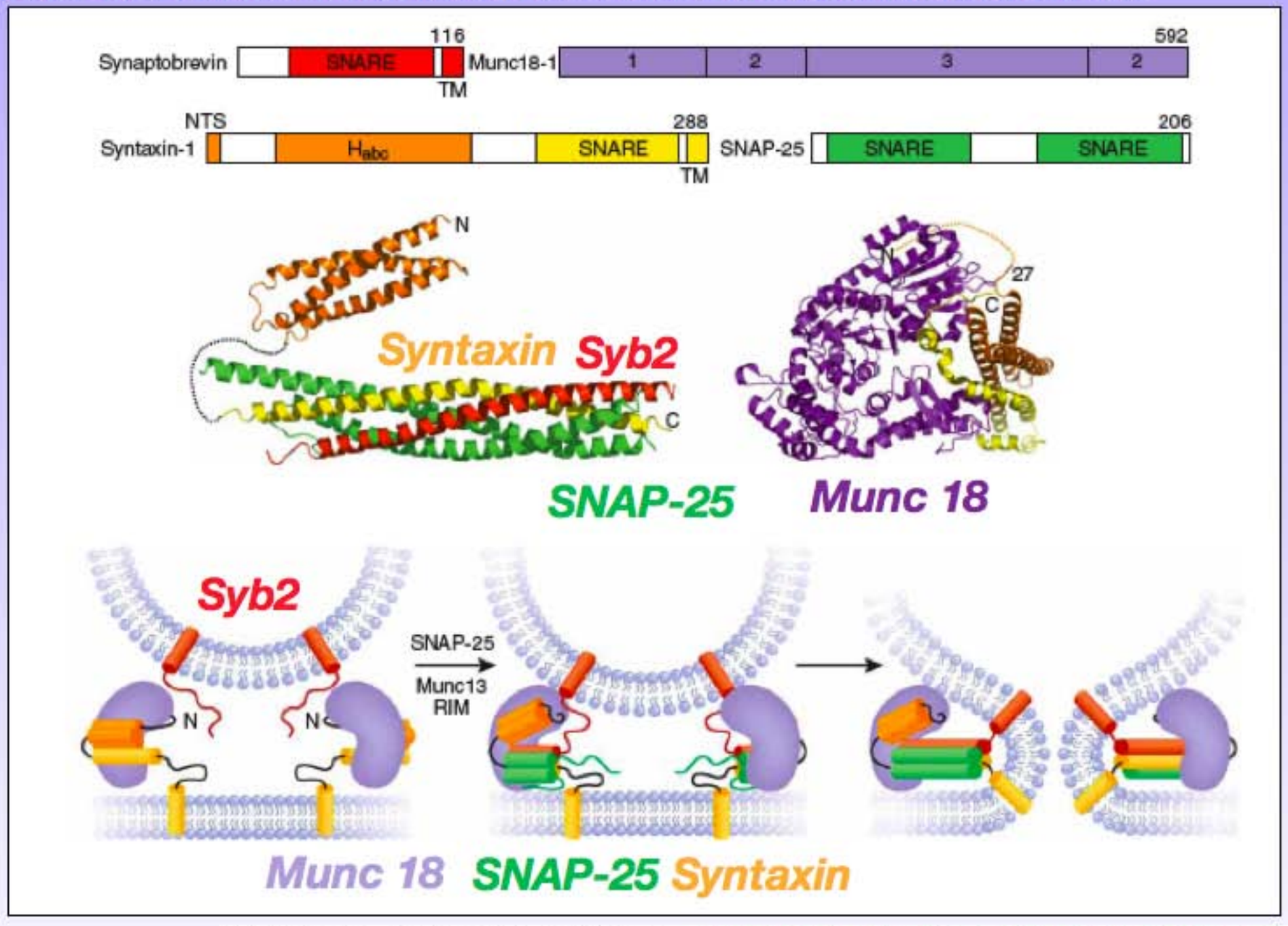
Régulation de l'exocytose par differentes protéines



Modifié d'après Gundelfinger at al. (Nat Rev Mol Cell Biol, Feb 2003, vol 4, p127).

Regulation par Munc18

SM proteins = Sec1 /Munc 18: découverte sur un sreen génétique (levure, c.elegans) pour des defauts dans le trafic mbR et la sécrétion. Ont un rôle essentiel dans la fusion.

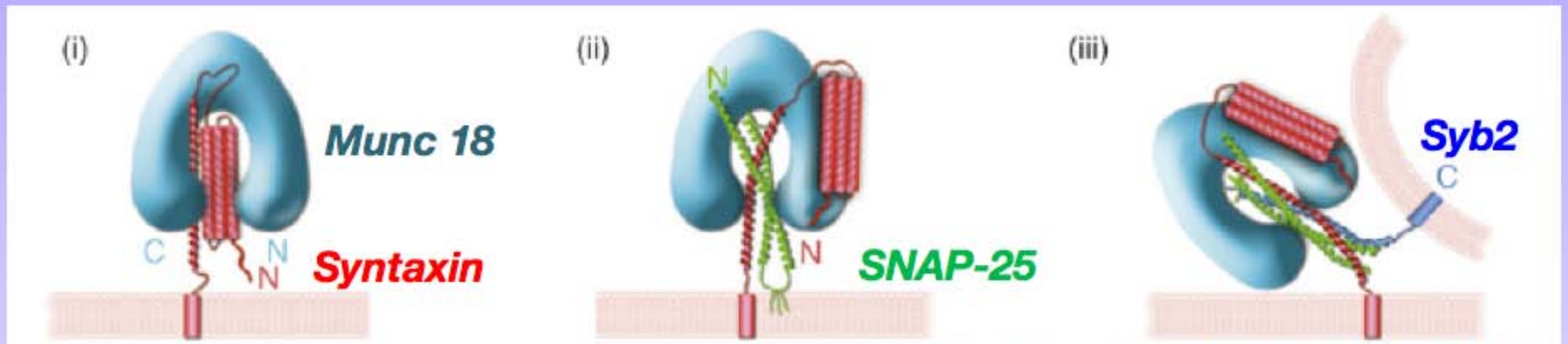


VOLUME 15 NUMBER 7 JULY 2008 NATURE STRUCTURAL & MOLECULAR BIOLOGY

Munc 18 lie la syntaxine 1 ansi que le complexe SNARE et promeut son assemblage en introduisant une vérification des couples de SNAREs (Peng & Gallwitz 2002).

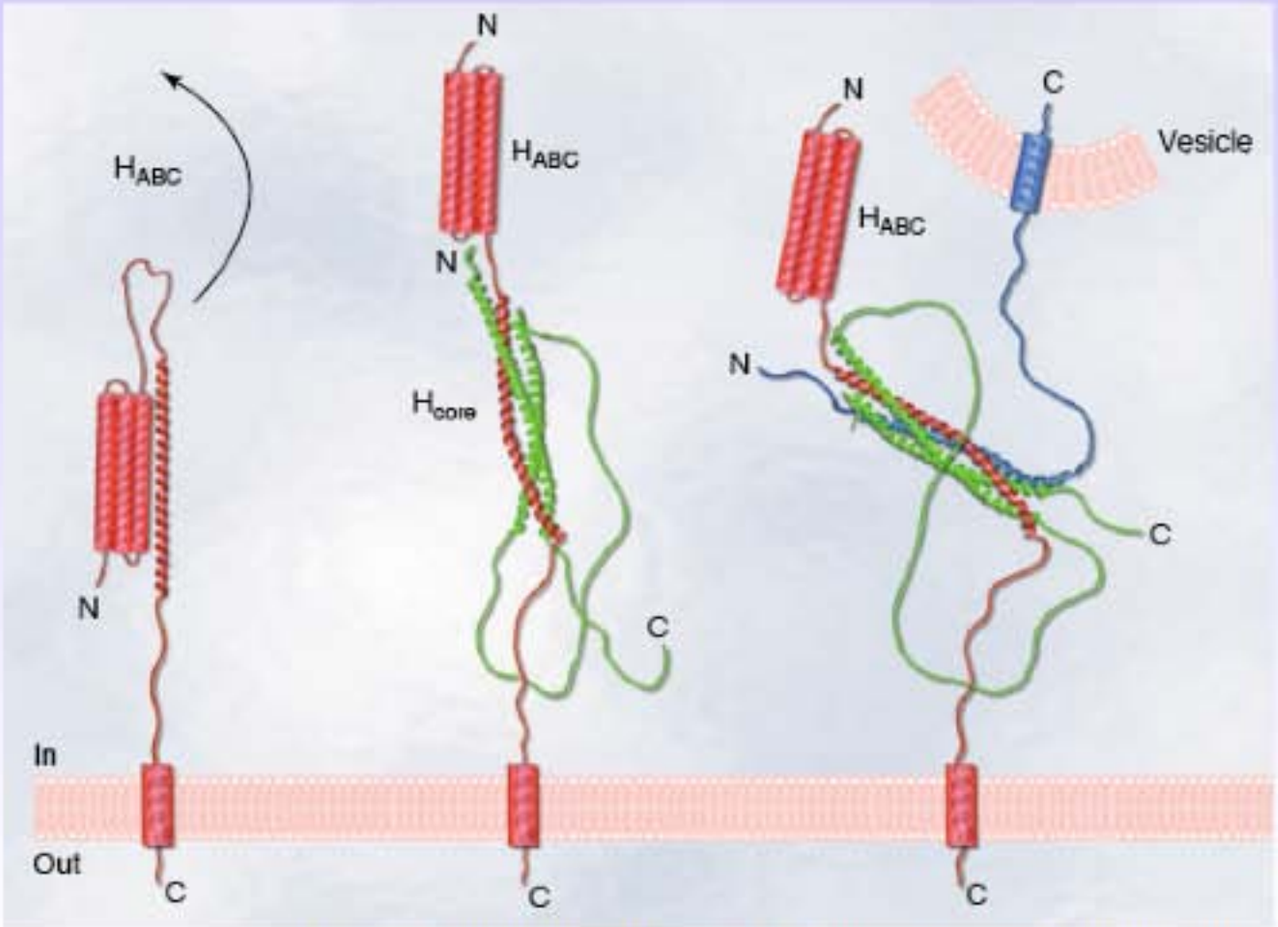
Regulation par Munc18

SM proteins = Sec1 /Munc 18: découverte sur un sreen génétique (levure, c.elegans) pour des defauts dans le trafic mbR et la sécrétion. Ont un rôle essentiel dans la fusion.



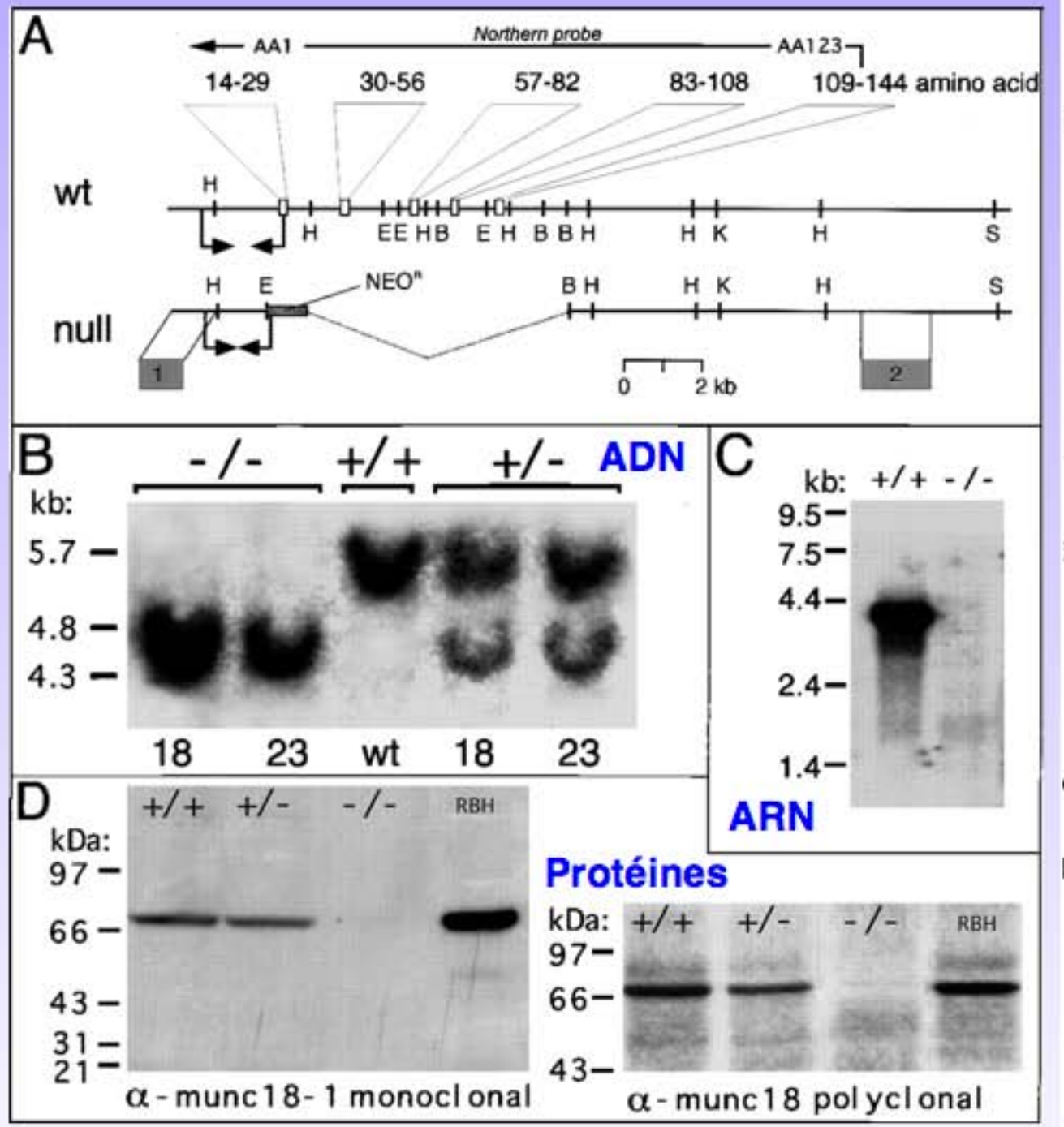
Toonen & Verhage, Trends in Neuroscience (2007) vol 30: 565.

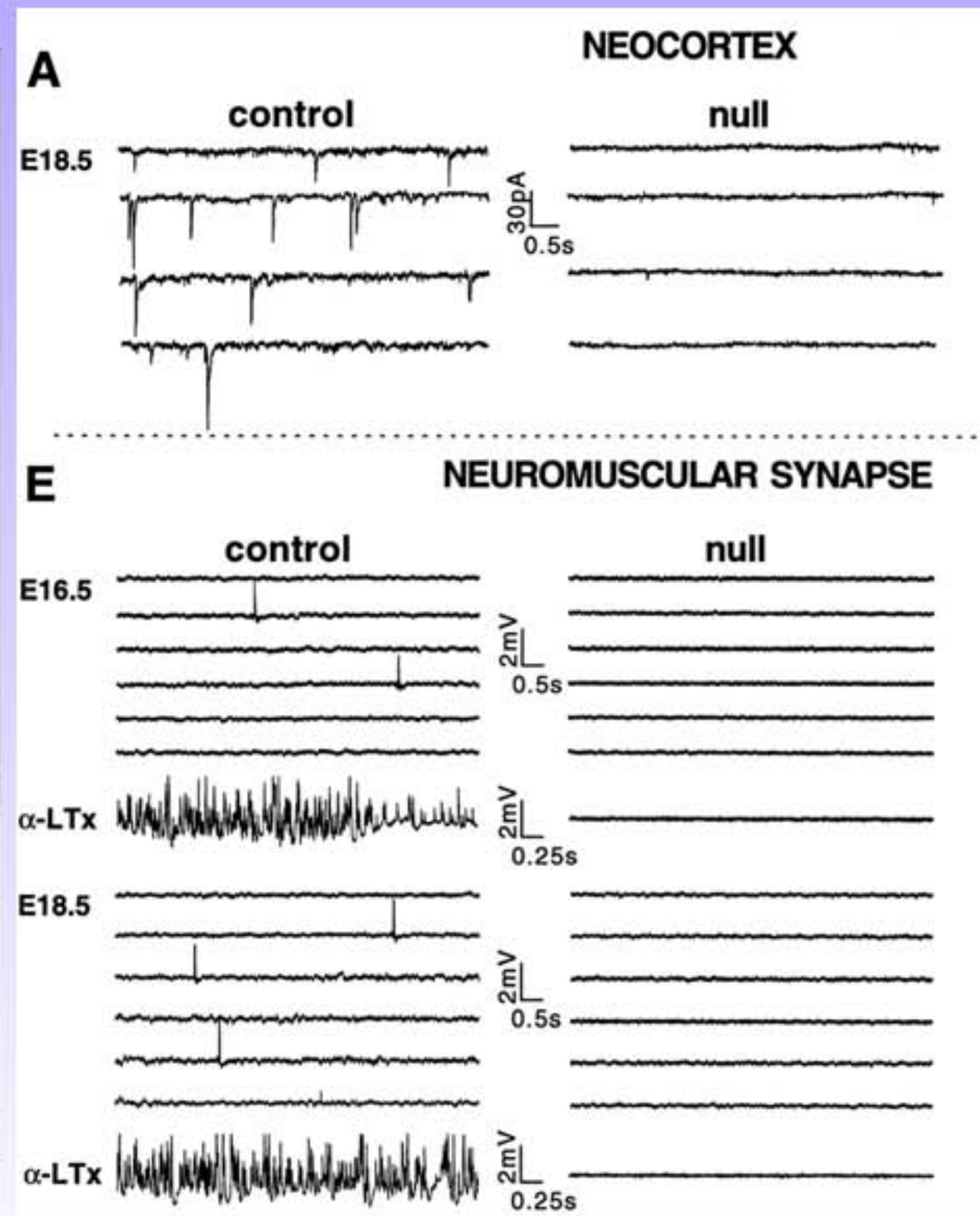
Ouverture de la syntaxine



Toonen & Verhage, Trends in Neuroscience (2003) vol 13: 177.

Munc18 KO

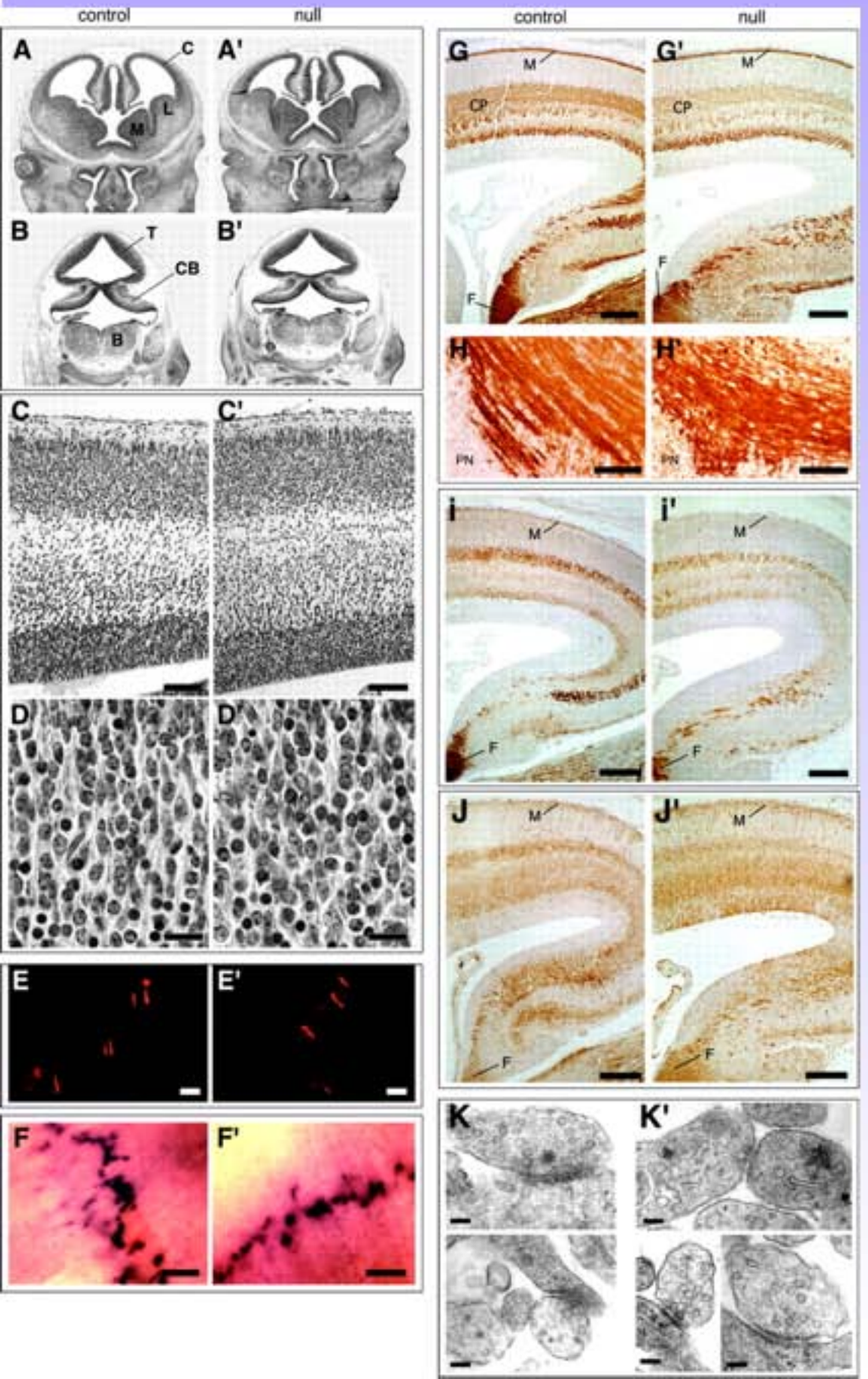




Les synapses sont totalement silencieuses: pas de libération de neurotransmetteur.

Science. 2000 Feb 4;287(5454):864-9

Munc18 KO

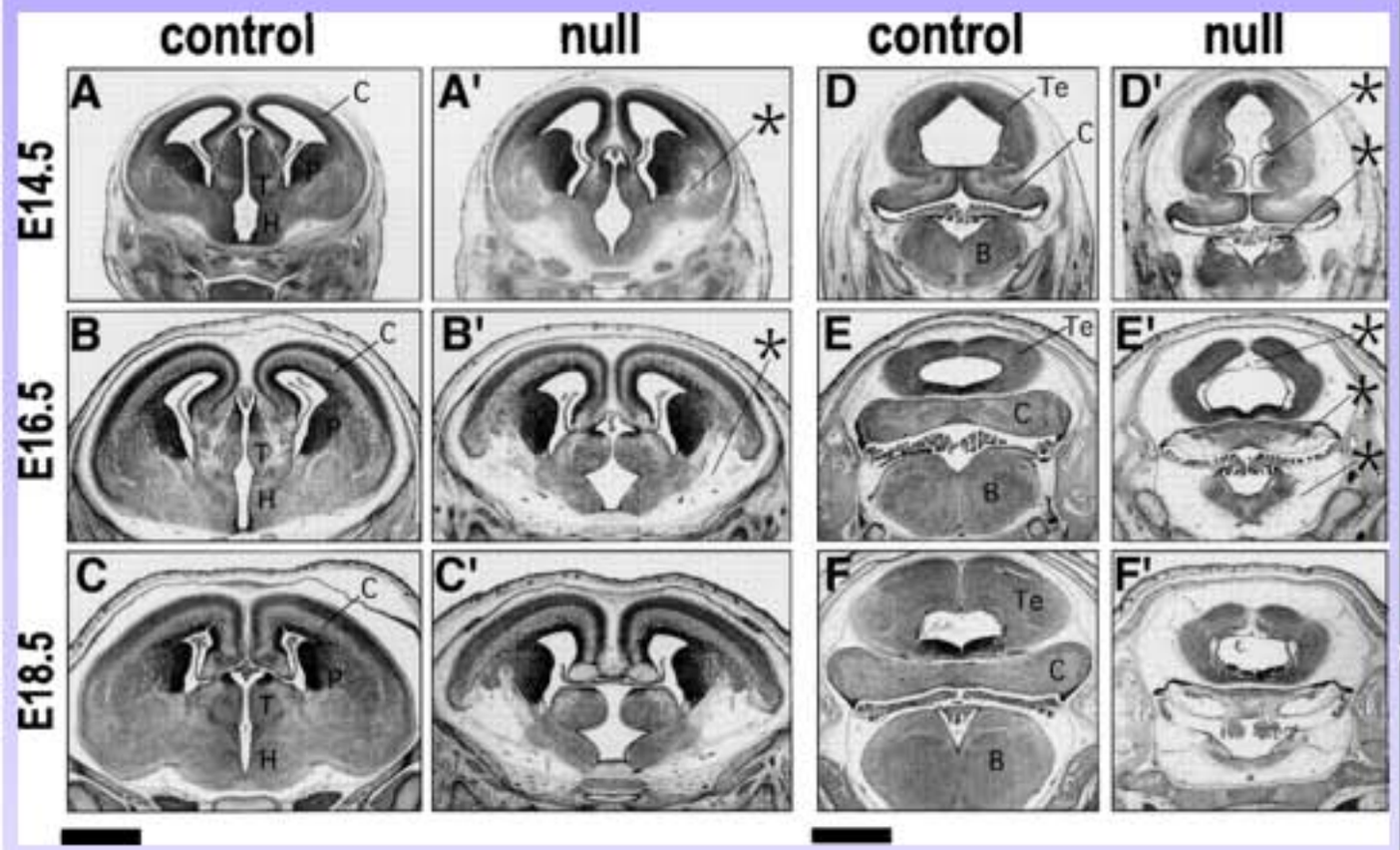


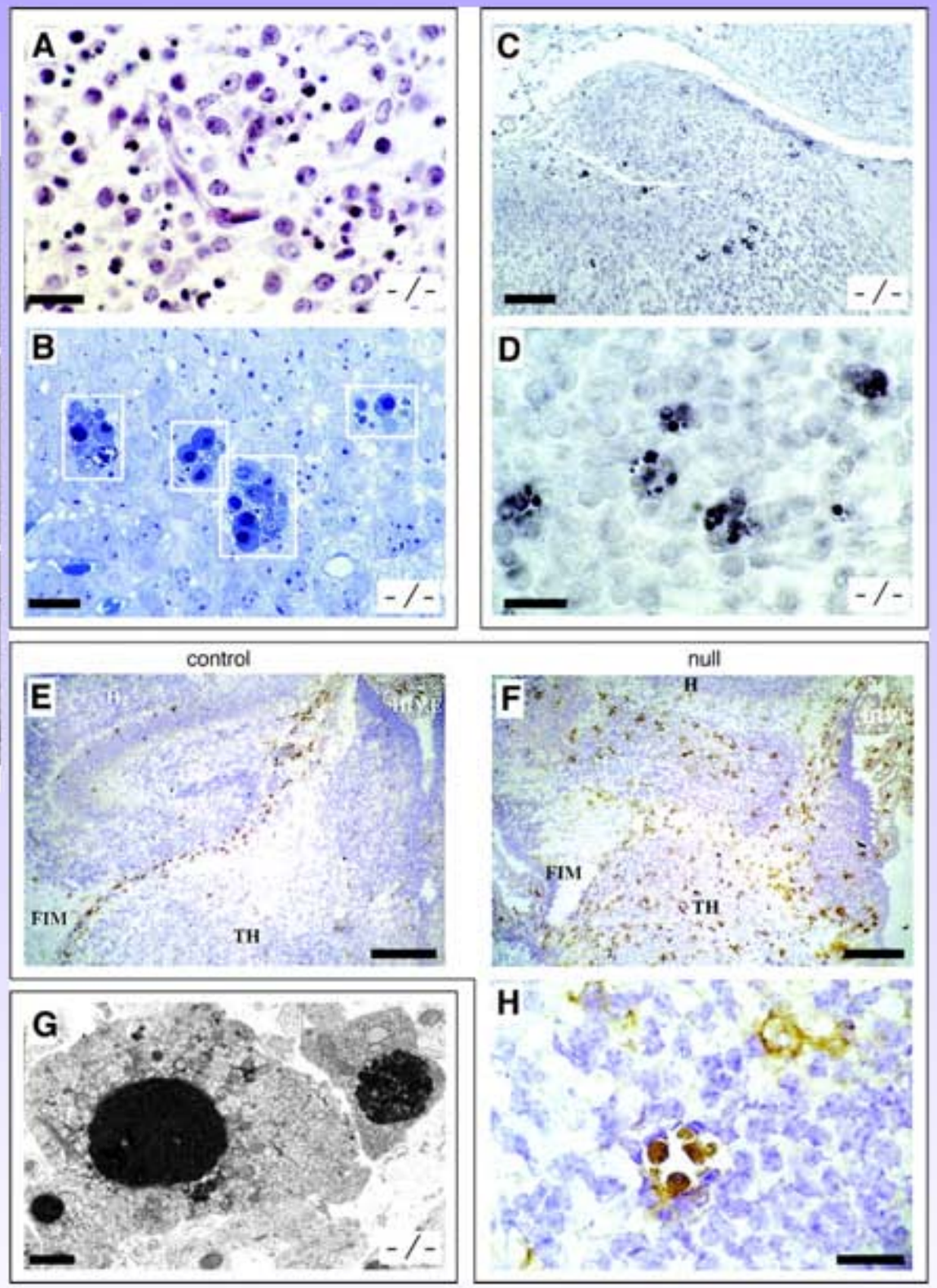
Matthijs Verhage

Le développement cérébral est normal même en absence de sécrétion de neurotransmetteur. On constate qu'on a bien: la formation de structures en couches, les tractus de fibres sont présents, les synapses sont morphologiquement définies.

Science. 2000 Feb 4;287(5454):864-9

Munc18 KO





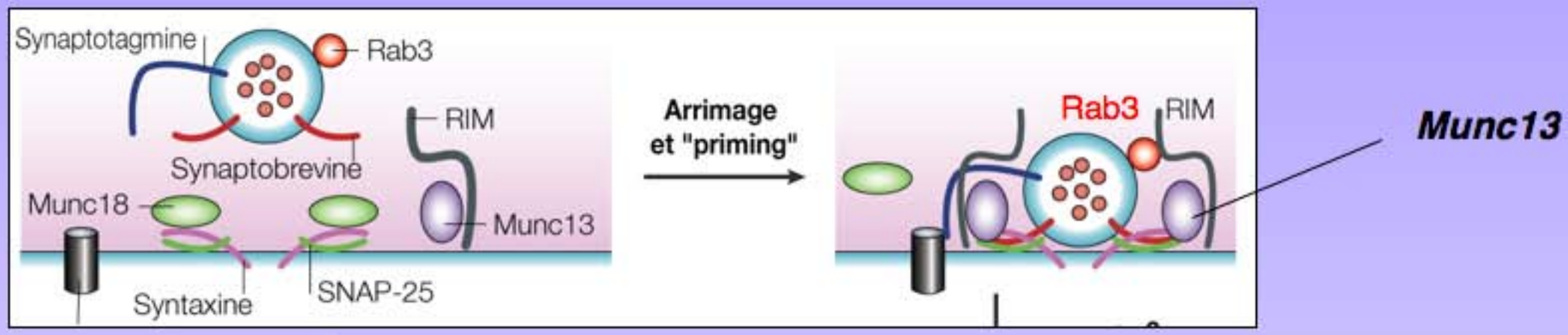
Apoptose massive après la synptogenese.

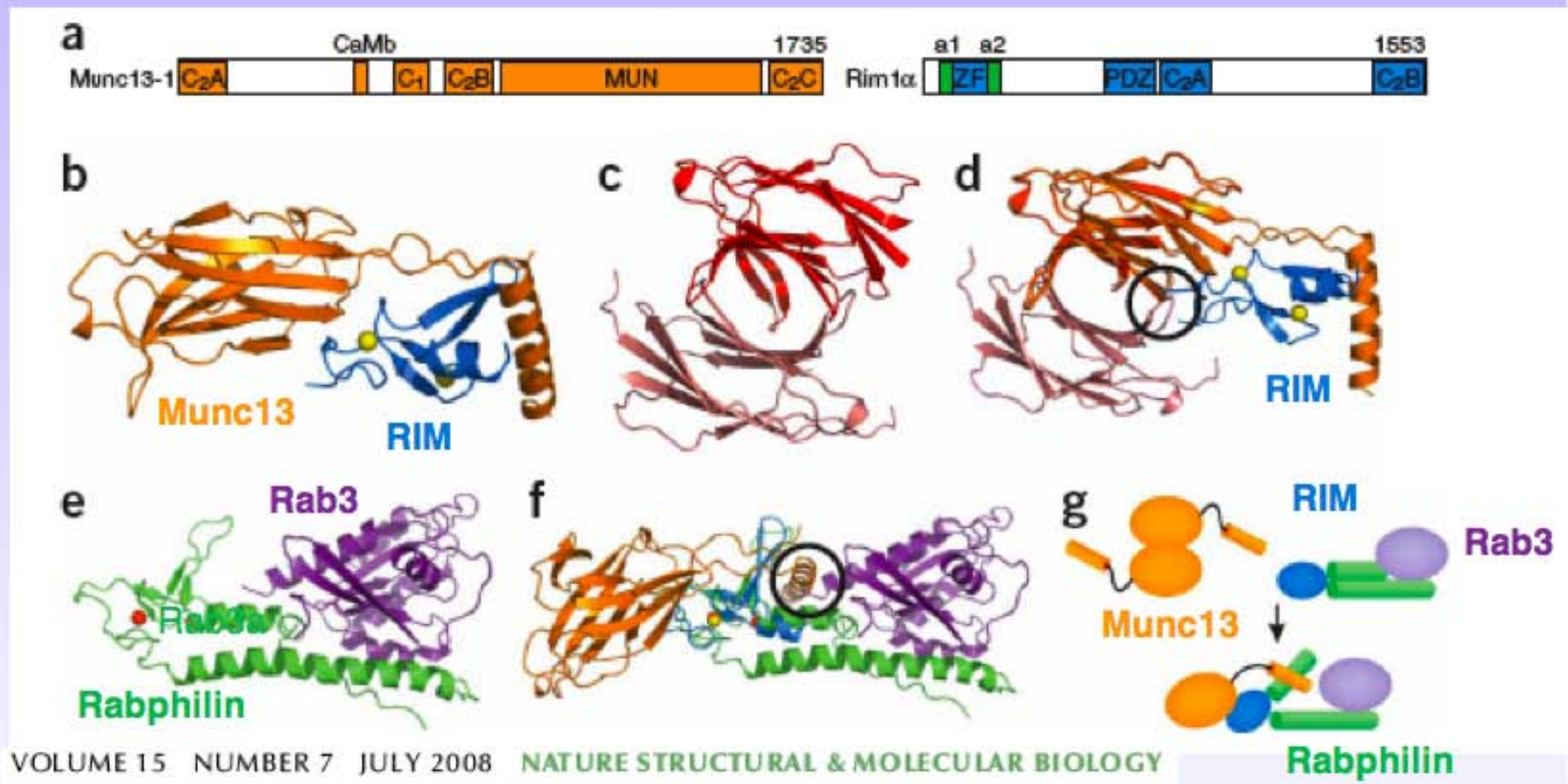
Par contre, après formation du système, les neurones subissent une apoptose massive suivi d'une dégénerescence massive (marquée d'une *).

Conclusion: La connectivité synaptique ne dépend pas de la sécrétion de NT, mais la maintenance du sytème nécéssite la sécrétion de neurotransmetteurs.

Science. 2000 Feb 4;287(5454):864-9

Régulation par Munc13





Munc 13 est essentiel pour le priming. Le double KO Munc 13 et Syntaxine est « sauvé » par la présence de syntaxine ouverte: d'où l'hypothère que munc13 permettrait l'ouverture de la syntaxine '(Brunger 2005). Formation d'un complexe tripartite avec Munc13, Rab3a et Rim.

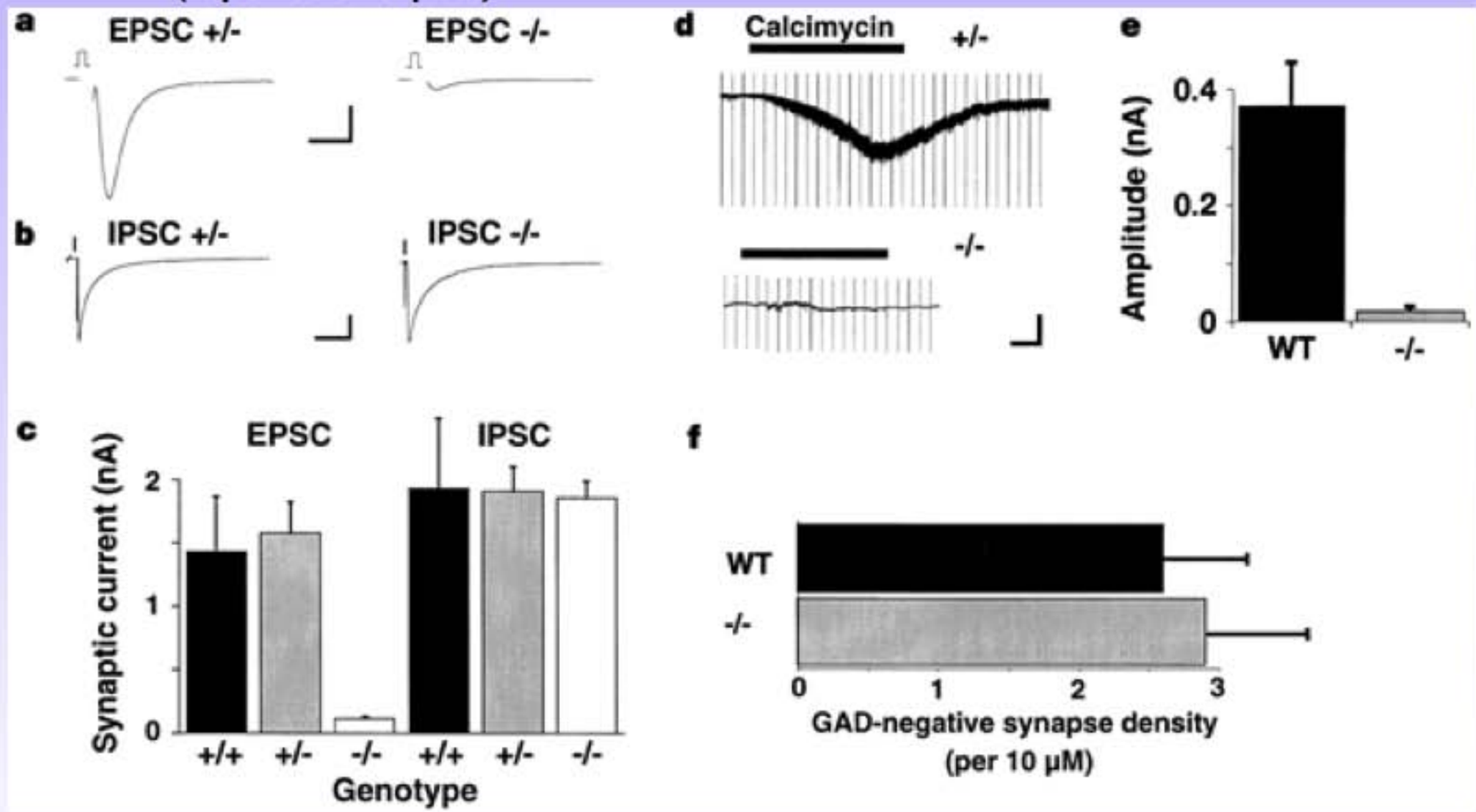
Munc13 KO

Nils Brose

Munc13-1 is essential for fusion competence of glutamatergic synaptic vesicles.
Augustin I, Rosenmund C, Südhof TC, Brose N. Nature. 1999: 400(6743):457-61.

Stimulation par potentiel d'action (réponse évoquée)

Stimulation par ionophore calcique

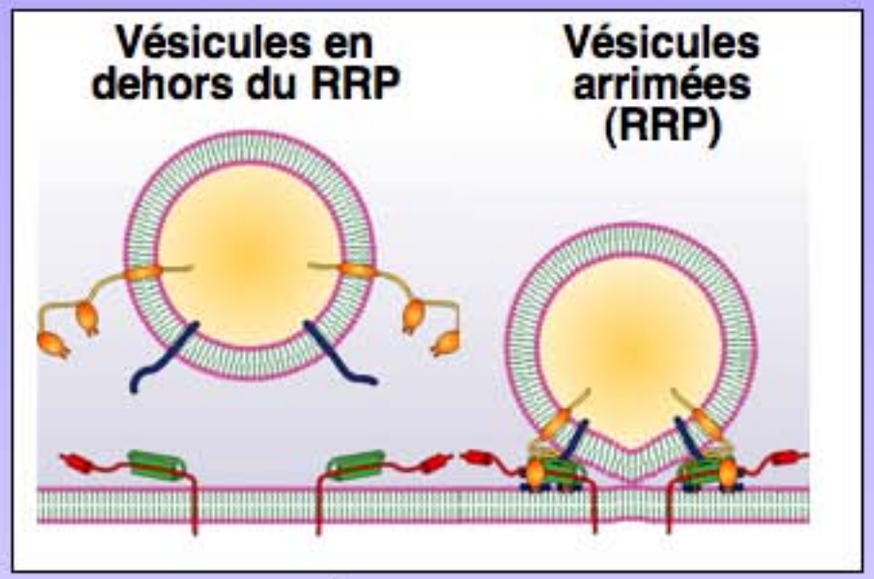


Cacimycin: Ionophore calcique qui déclenche la libération des NT.

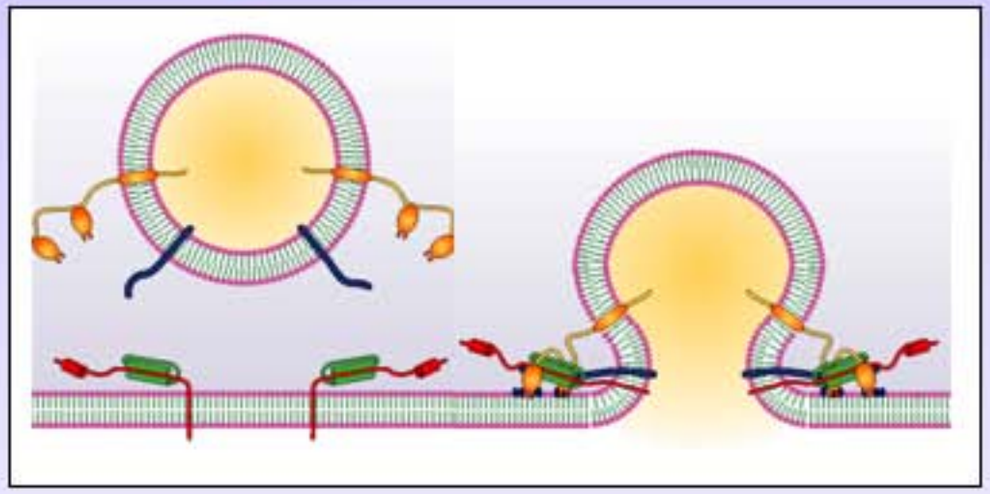
La libération des NT est bloquée dans les synapses glutamatergiques: on ne peut ni la déclencher par des potentiels d'action, ni par des ionosphères calciques. Les synapses inhibitrices ne sont pas atteintes.

Munc13 KO

Nature. 1999: 400(6743):457-61.

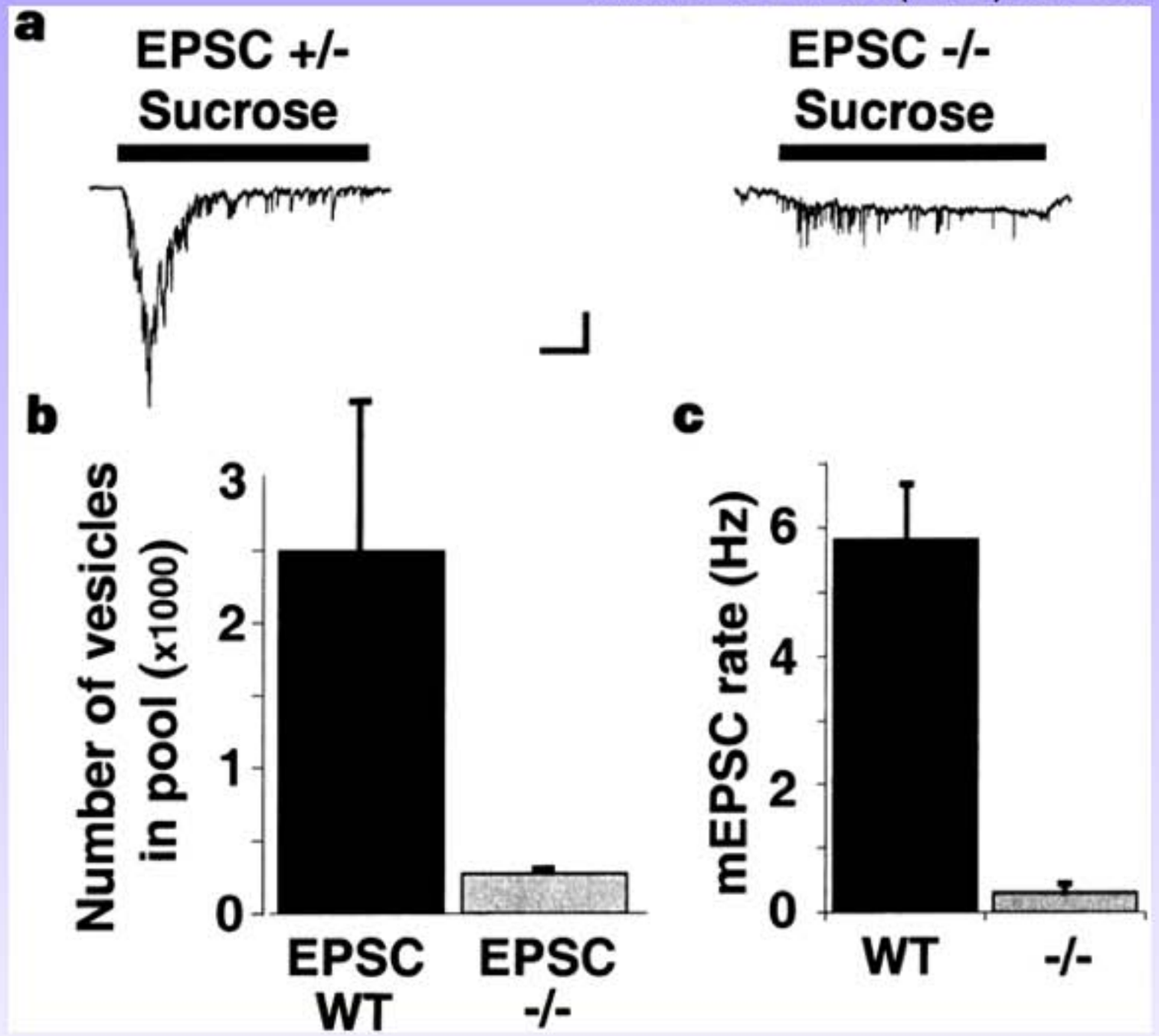


+ sucrose



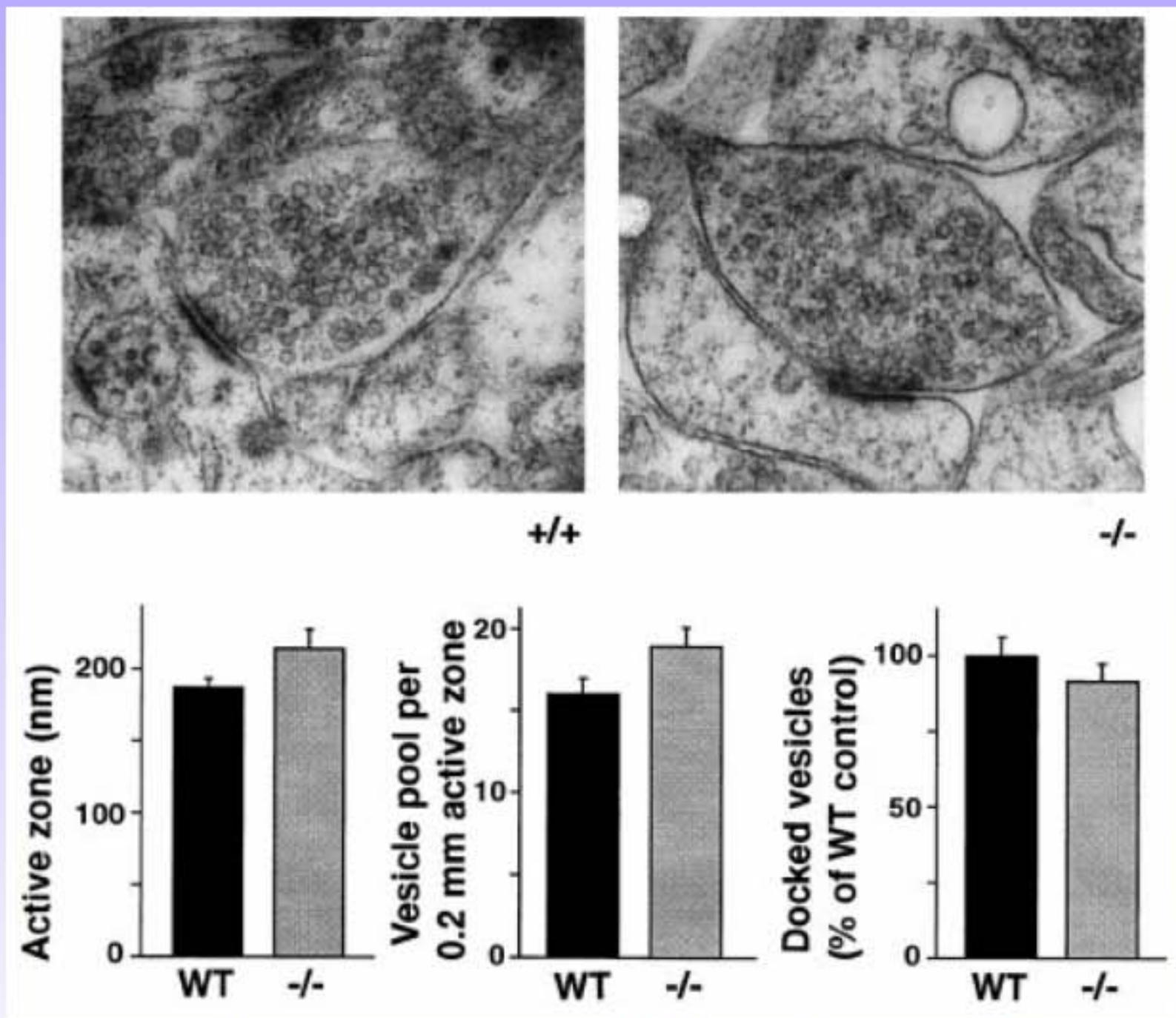
Seules les vésicules dejà arrimées (appartenant au RRP) fusionnent de manière Ca2+ indépendante. Permet d'evaluer le nombre de vésicules dans le RRP.

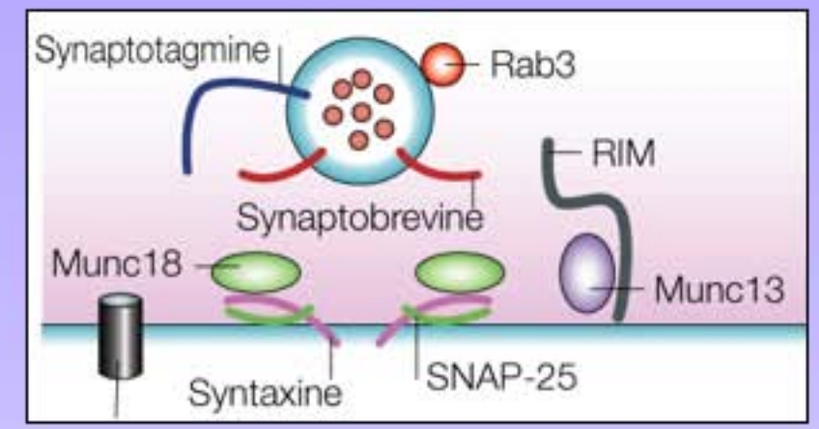
Cf. Rosenmund, C., and Stevens, C. F. (1996) Neuron 16, 1197–1207 & Lonart and Sudhof (2000) , JBC 275 : 27703-27707.



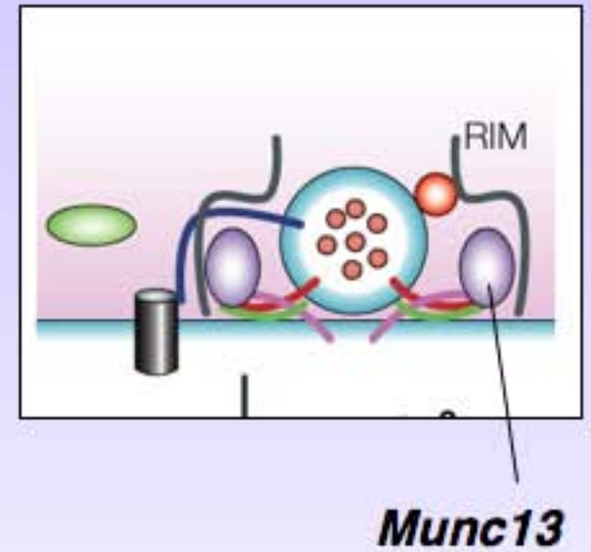
La libération ne peut pas être déclenchée par le sucrose: le RRP est donc très limité. En l'absence de munc13, le priming est donc altéré dans les synapses excitatrices.

Munc13 KO



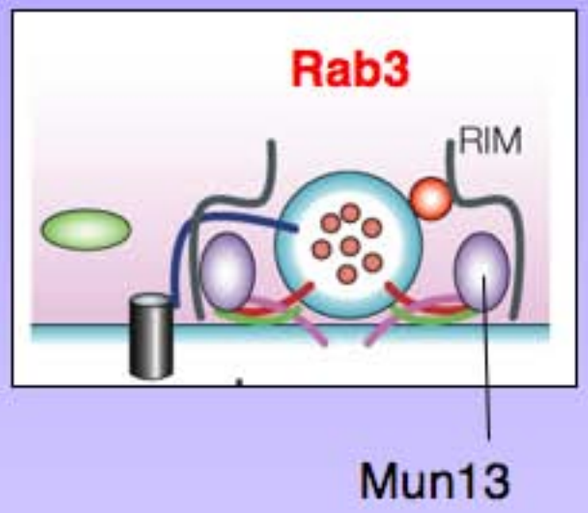


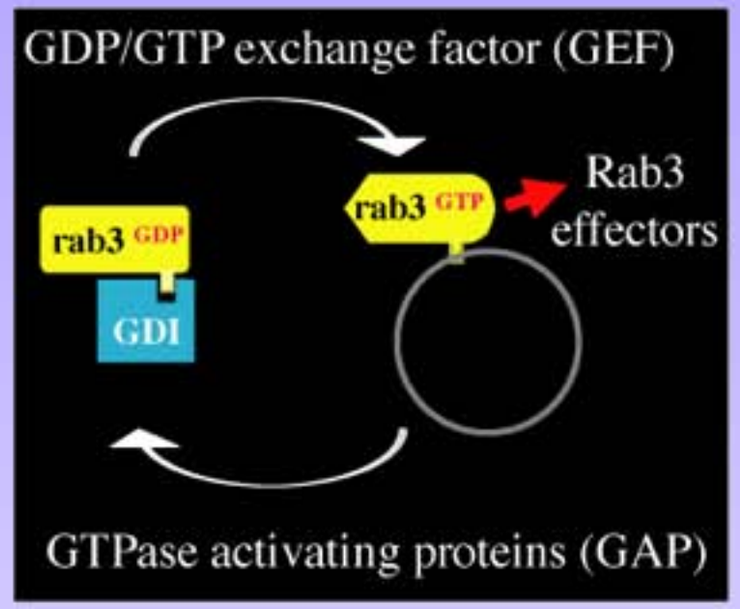
Docking & priming

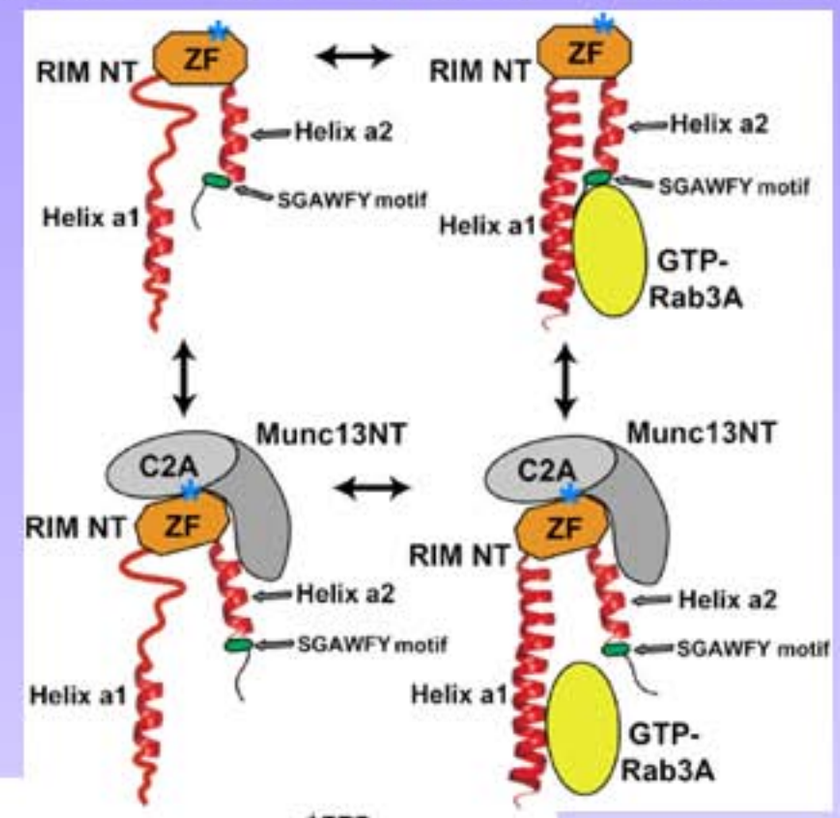


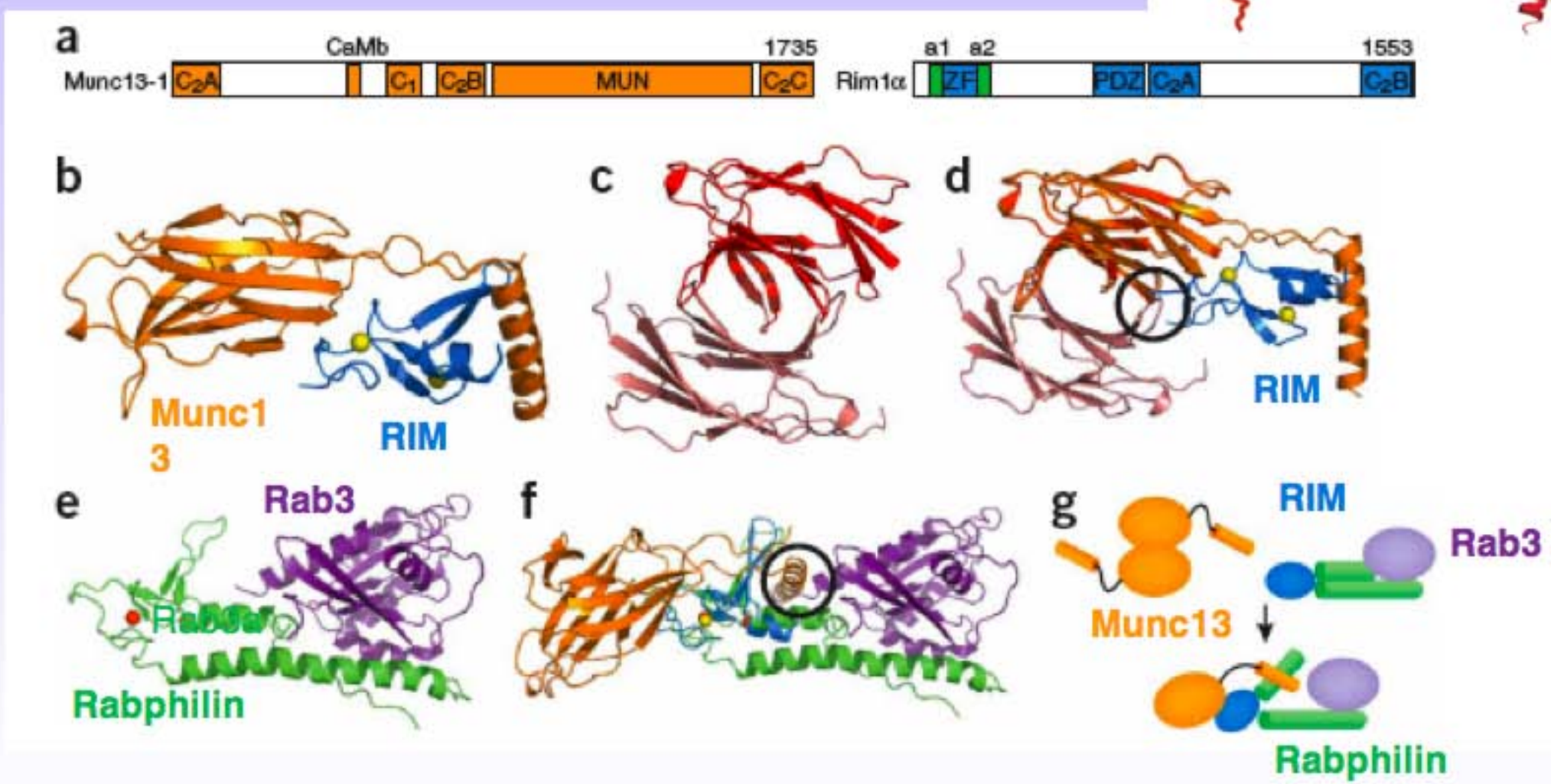
Les neurones d'hippocampe de souris KO Munc13-1 forment des synapses normales au niveau ultra structurales. En l'absence de munc13, la formation du RRP est compromise, le priming est donc altéré dans les synapses excitatrices. Les synapses inhibitrices ne sont pas atteintes.

Régulation par la GTPase Rab3





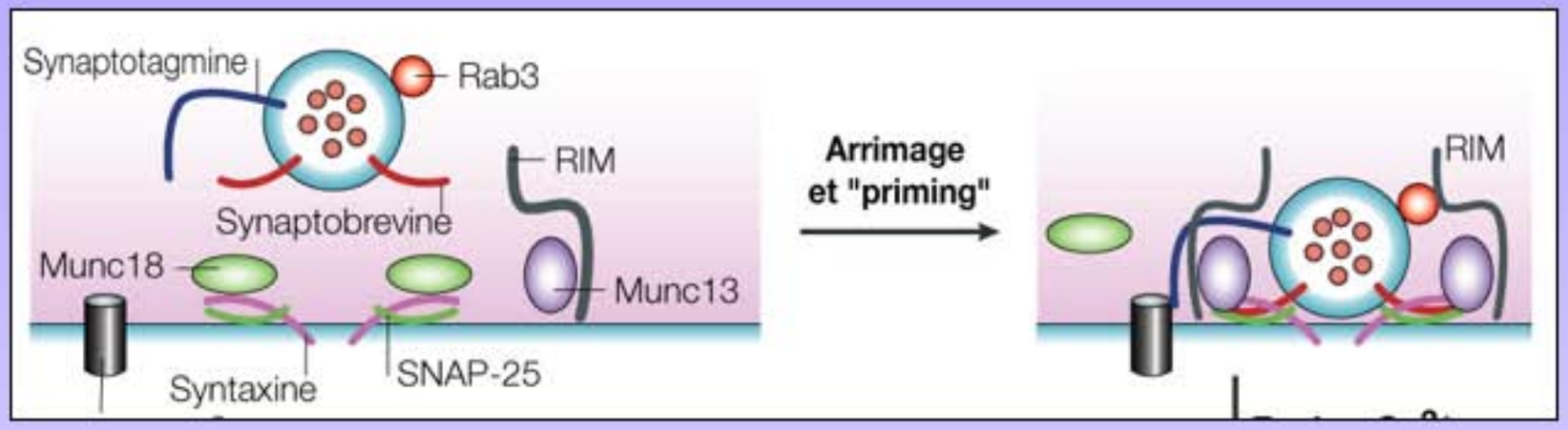




Rizo & Rosenmund, Nat Struct & Mol Biol (2008)

Formation d'un complexe tripartite avec Munc13, Rab3a et Rim.

Régulation de l'exocytose



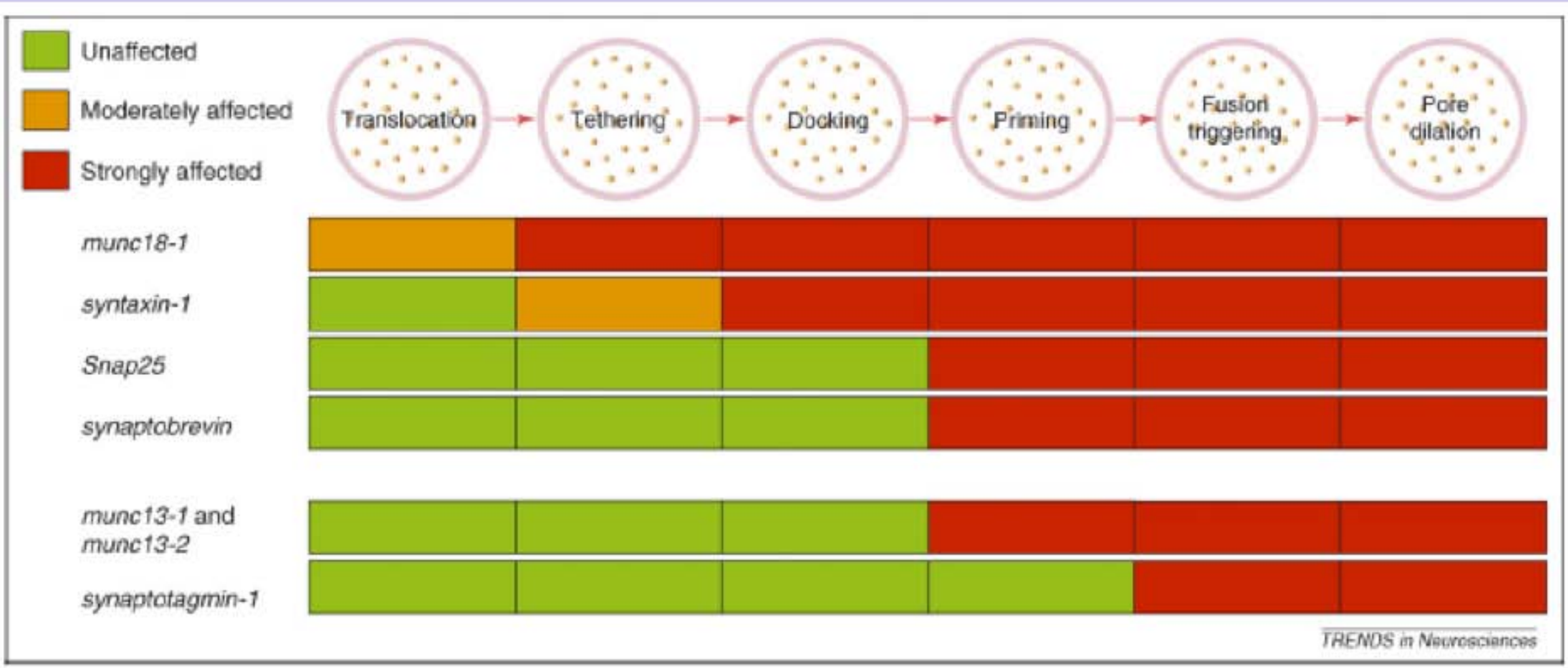


Figure 2. Overview of the steps in the secretory vesicle cycle that are affected by deletion of the respective genes. Deletion of *munc18-1* affects all steps in the cascade. Deletion of the SNARE genes (reviewed in [1]) results in priming defects with syntaxin-1 sharing a more upstream (docking) phenotype with Munc18-1 [26]. Deletion of *munc13-1* and *munc13-2* [68] and *synaptotagmin-1* [72] does not affect vesicle harboring at the membrane, but results in priming and fusion triggering defects, respectively.

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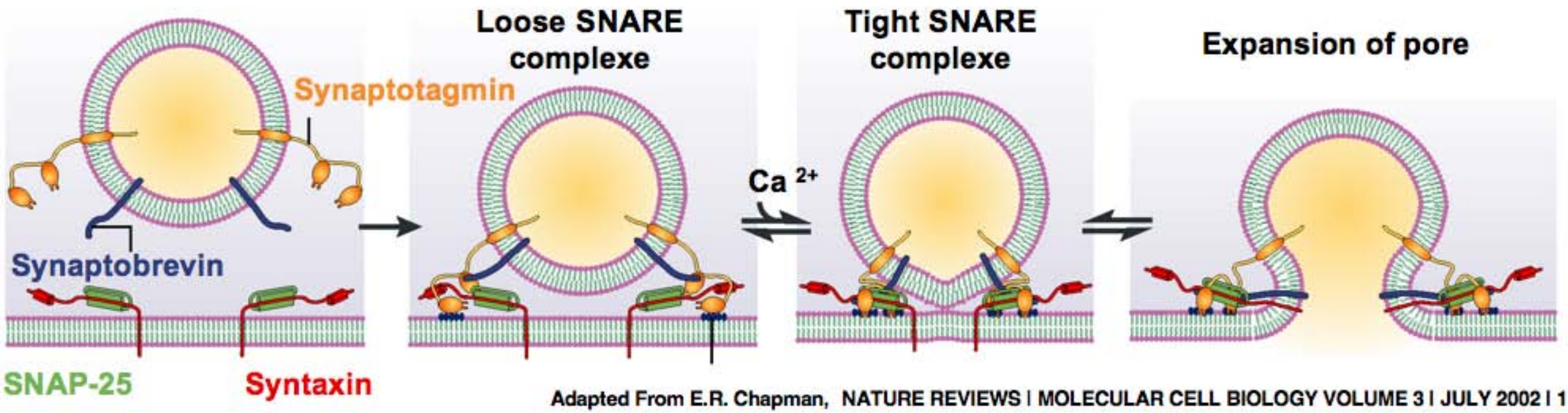
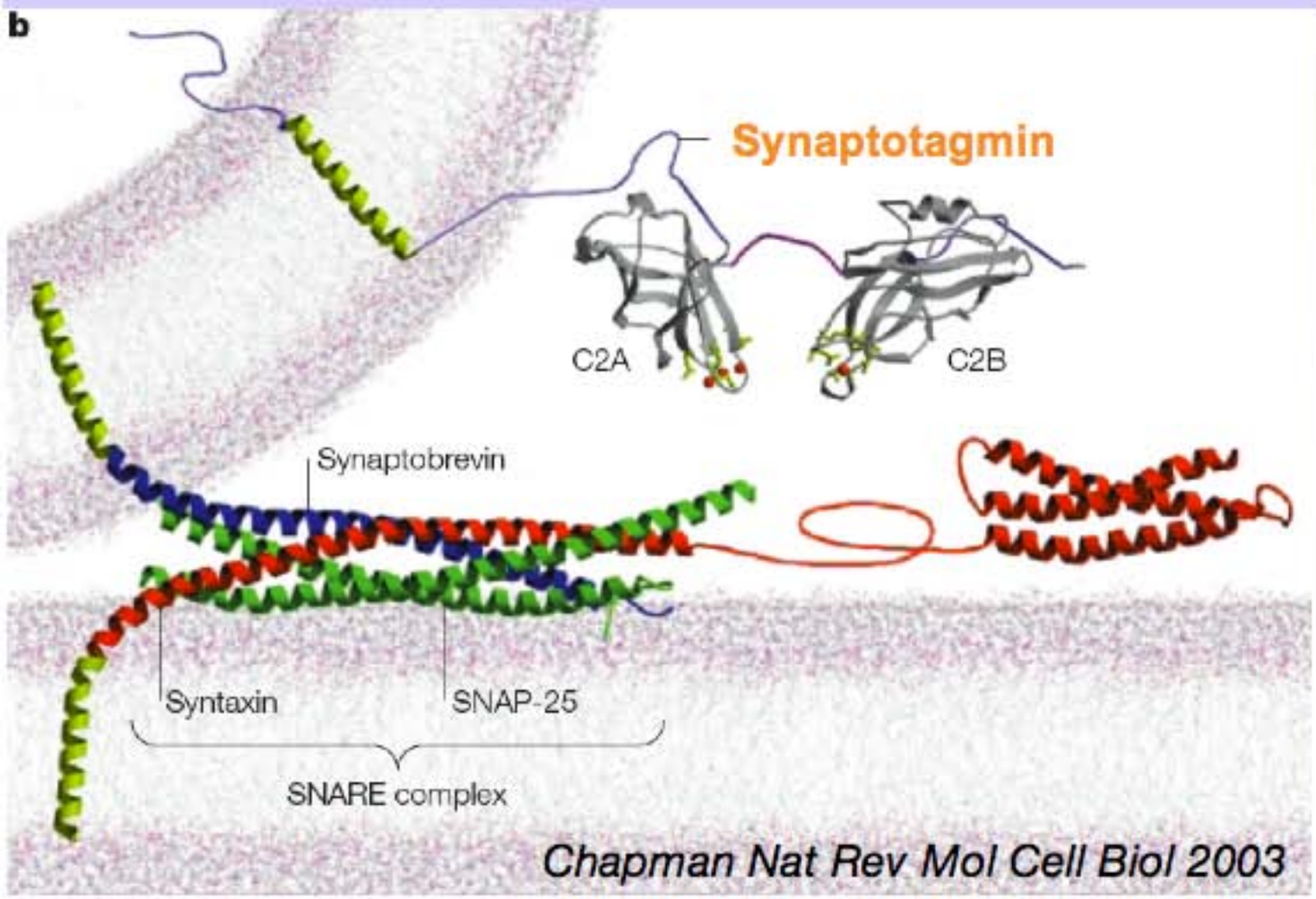
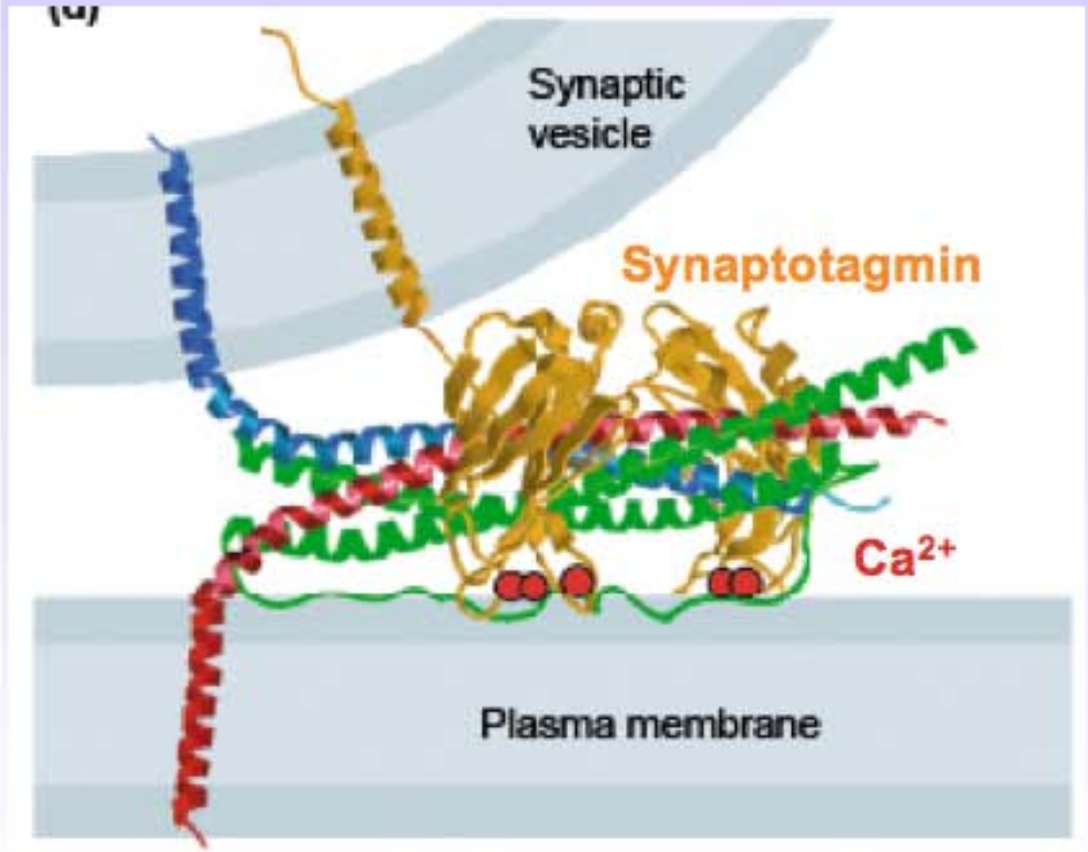
Régulation de l'exocytose par la synaptotagmine



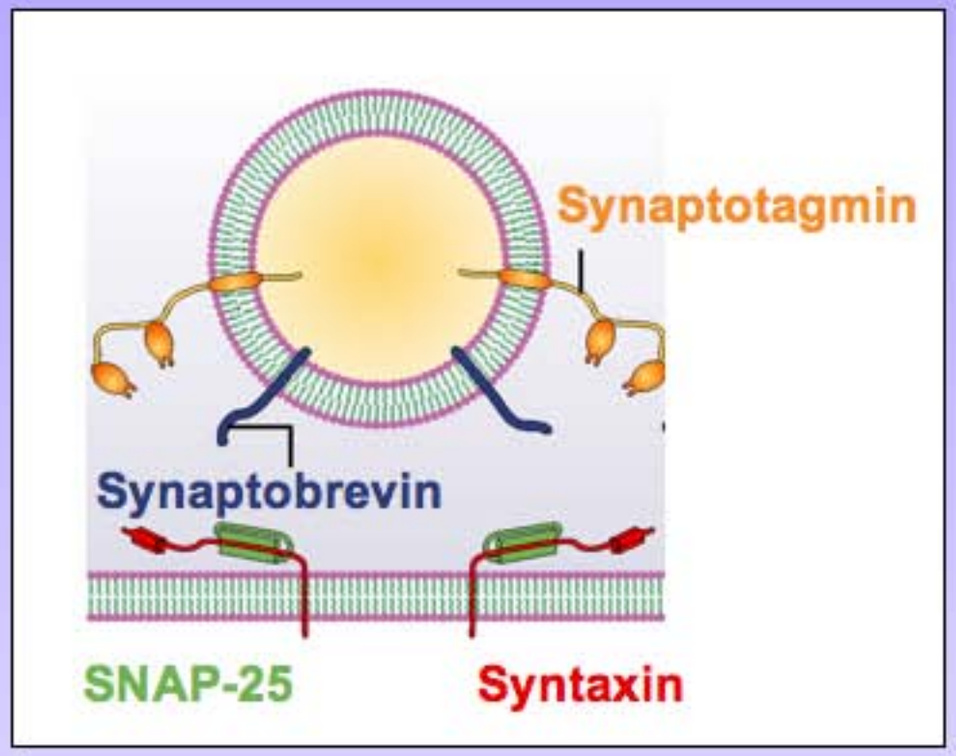
Adapted From E.R. Chapman, NATURE REVIEWS | MOLECULAR CELL BIOLOGY VOLUME 3 | JULY 2002 | 1

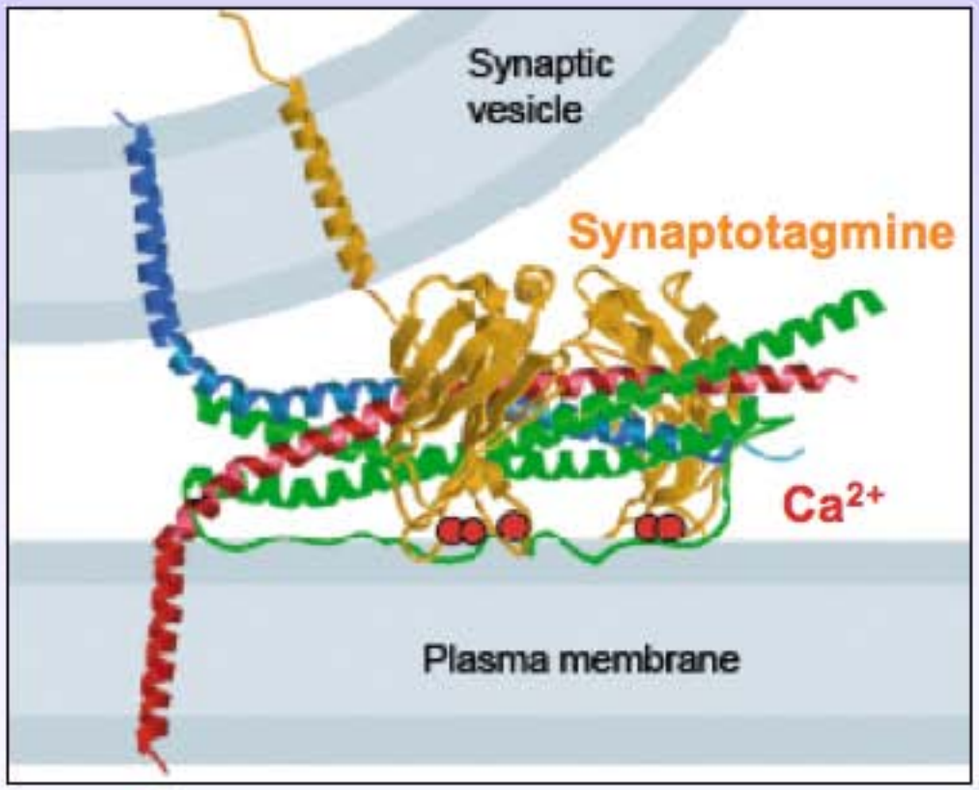


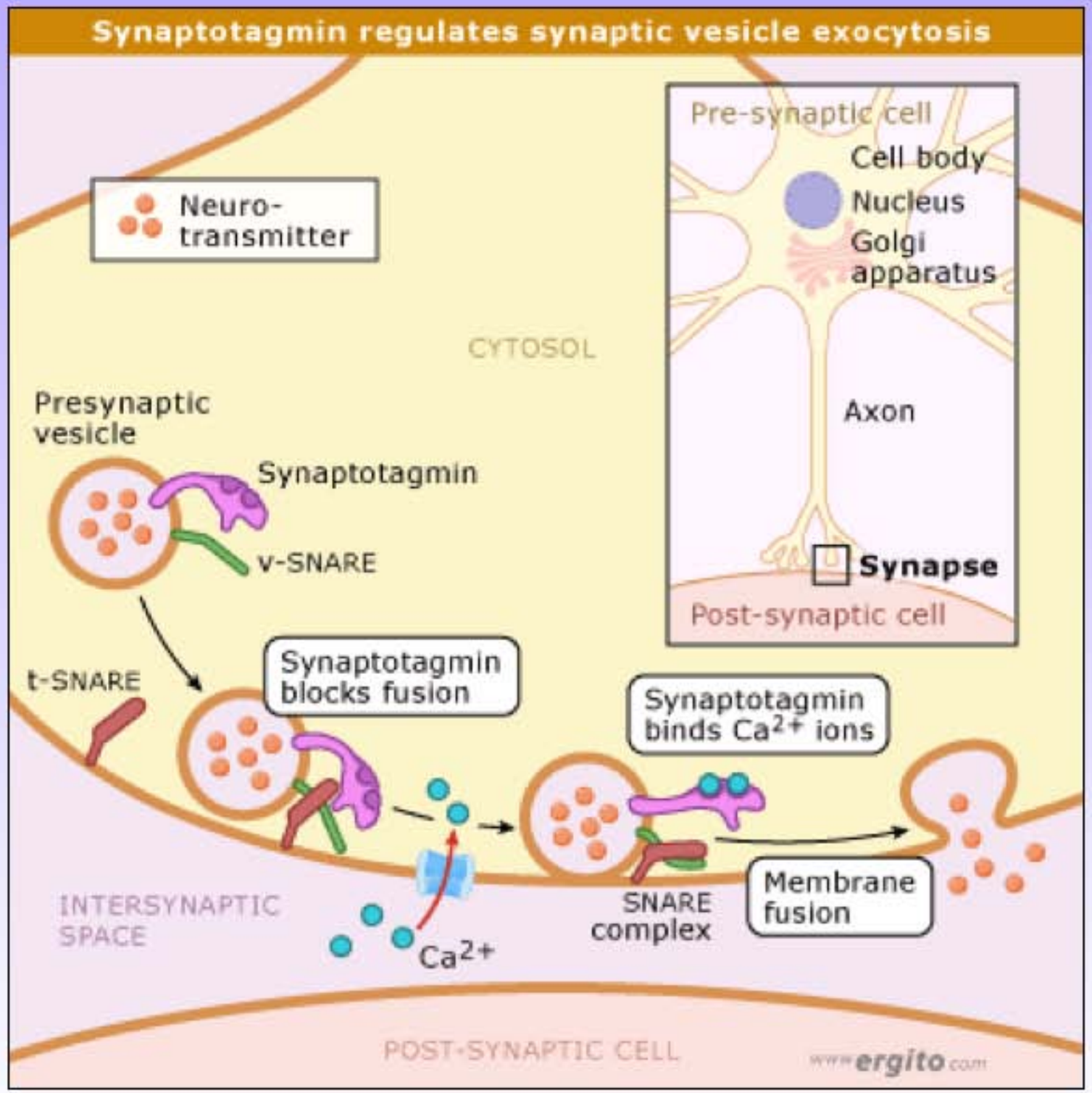
Chapman Nat Rev Mol Cell Biol 2003



Régulation de l'exocytose par la synaptotagmine

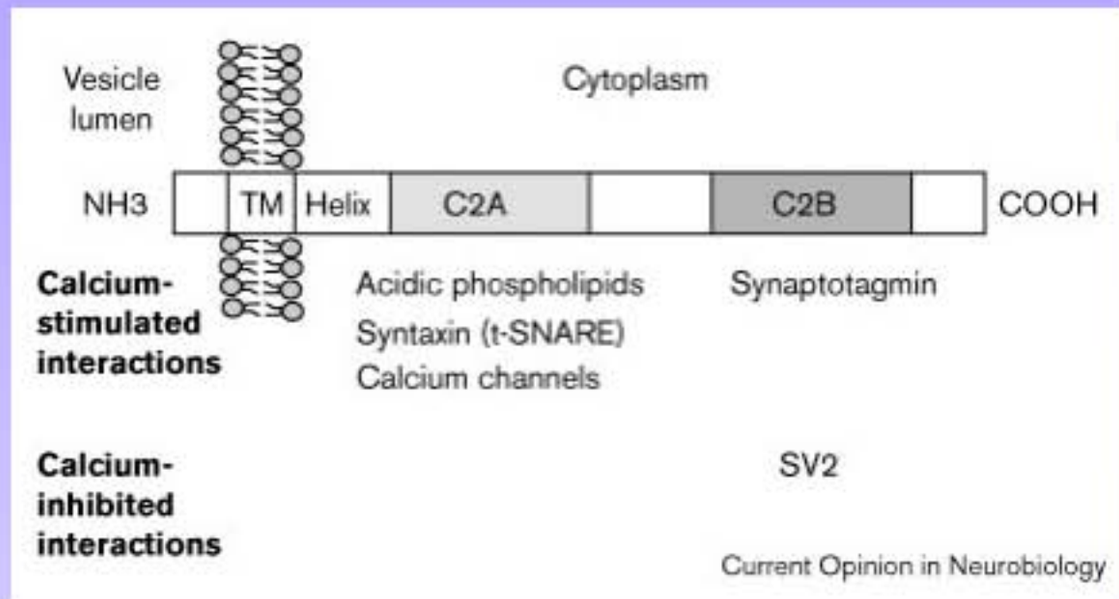


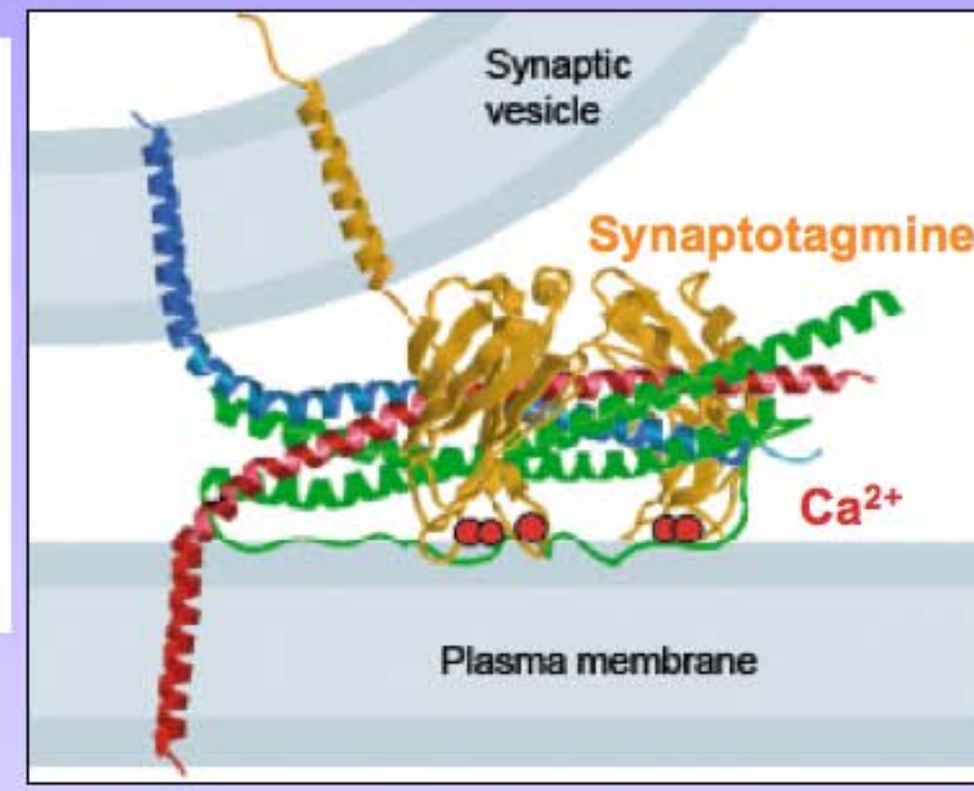


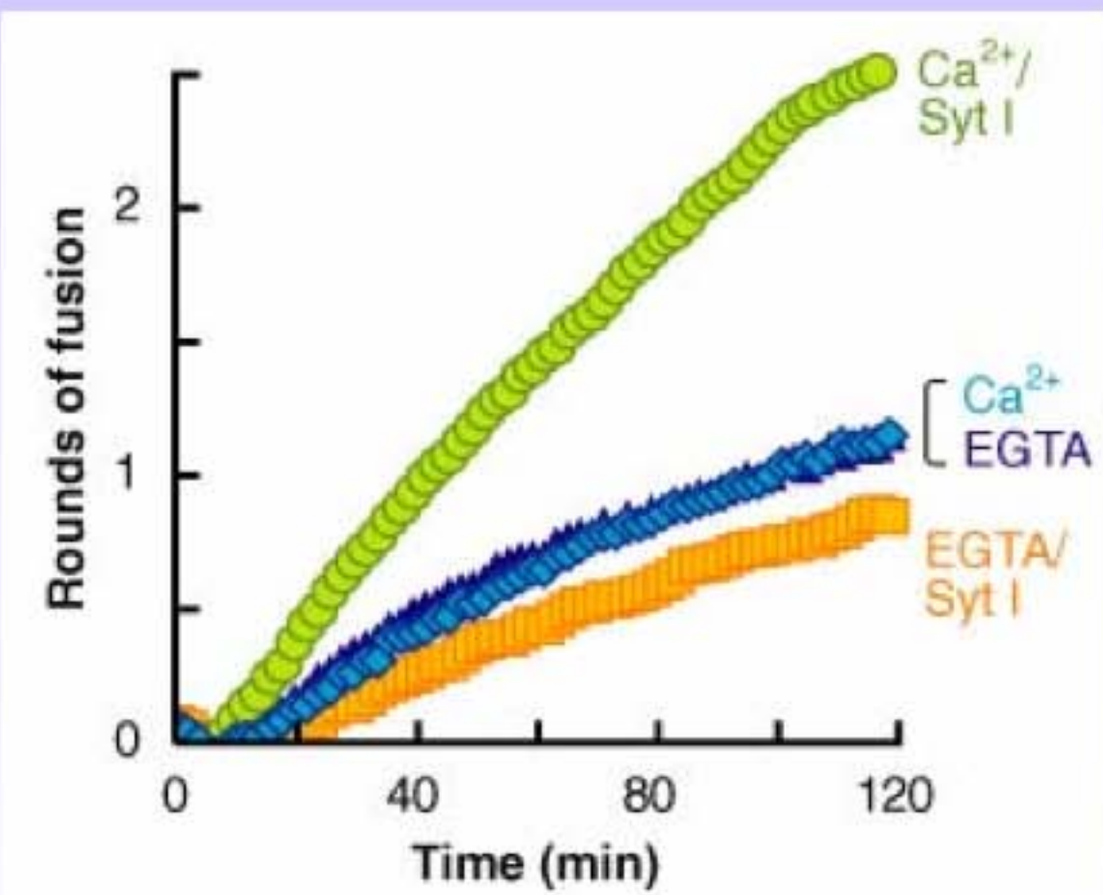


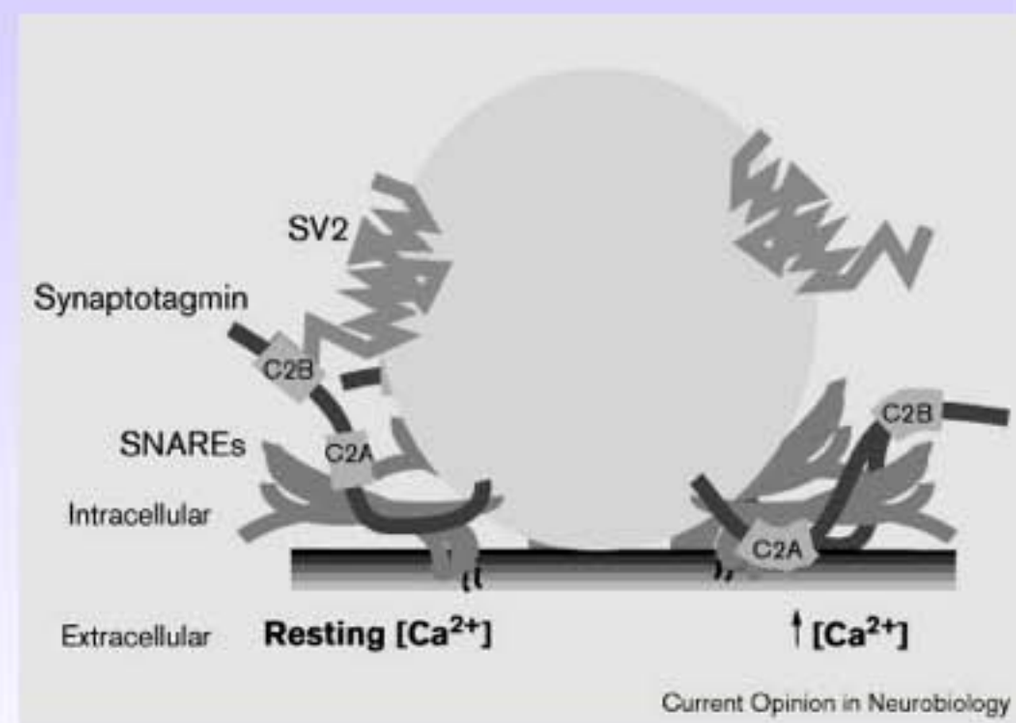
Régulation de l'exocytose par le calcium

Edwin Chapman









Jackson MB, Chapman ER. 2006.
Annu. Rev. Biophys. Biomol. Struct. 35:135–

Calcium et exocytose

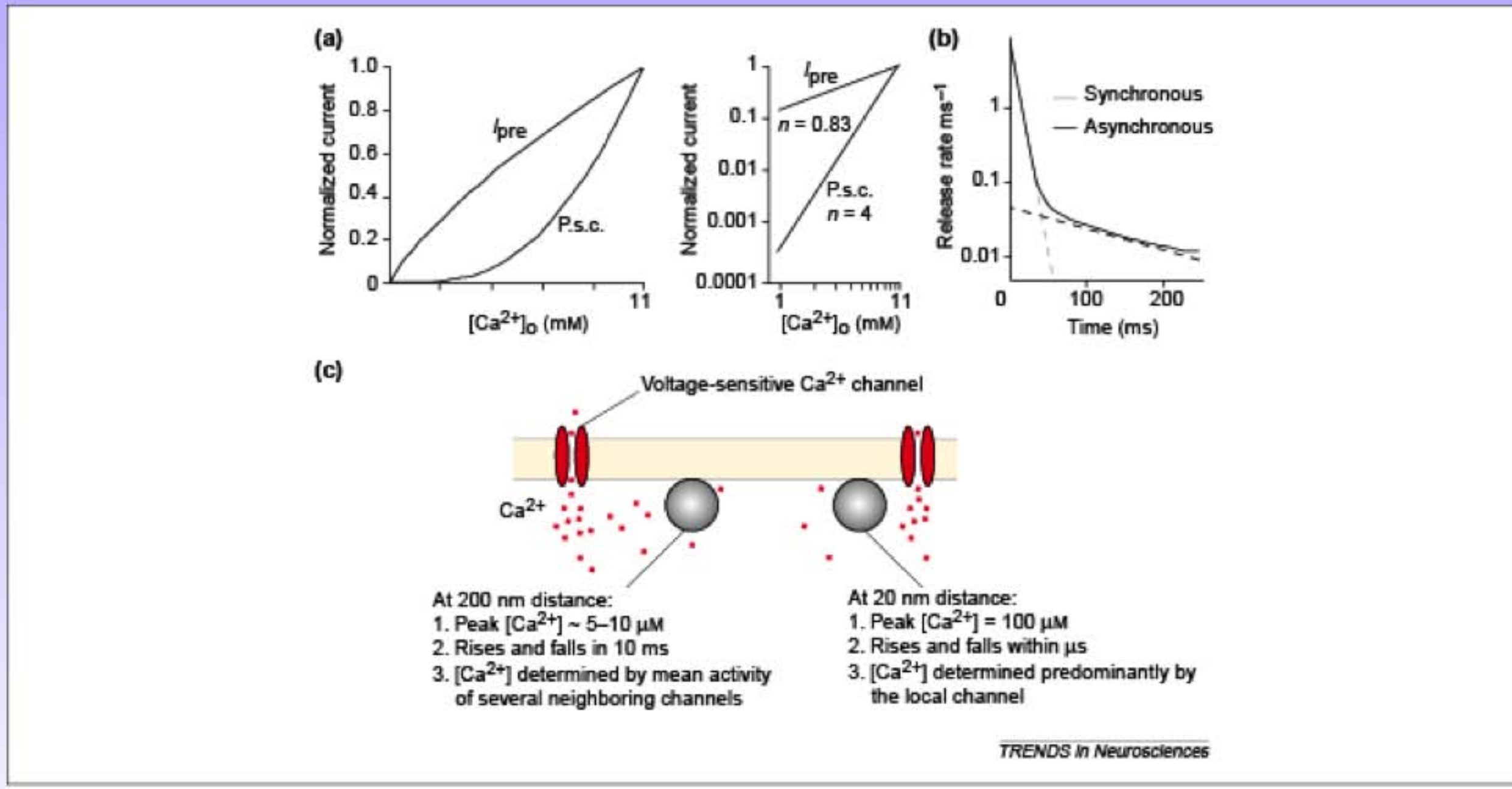
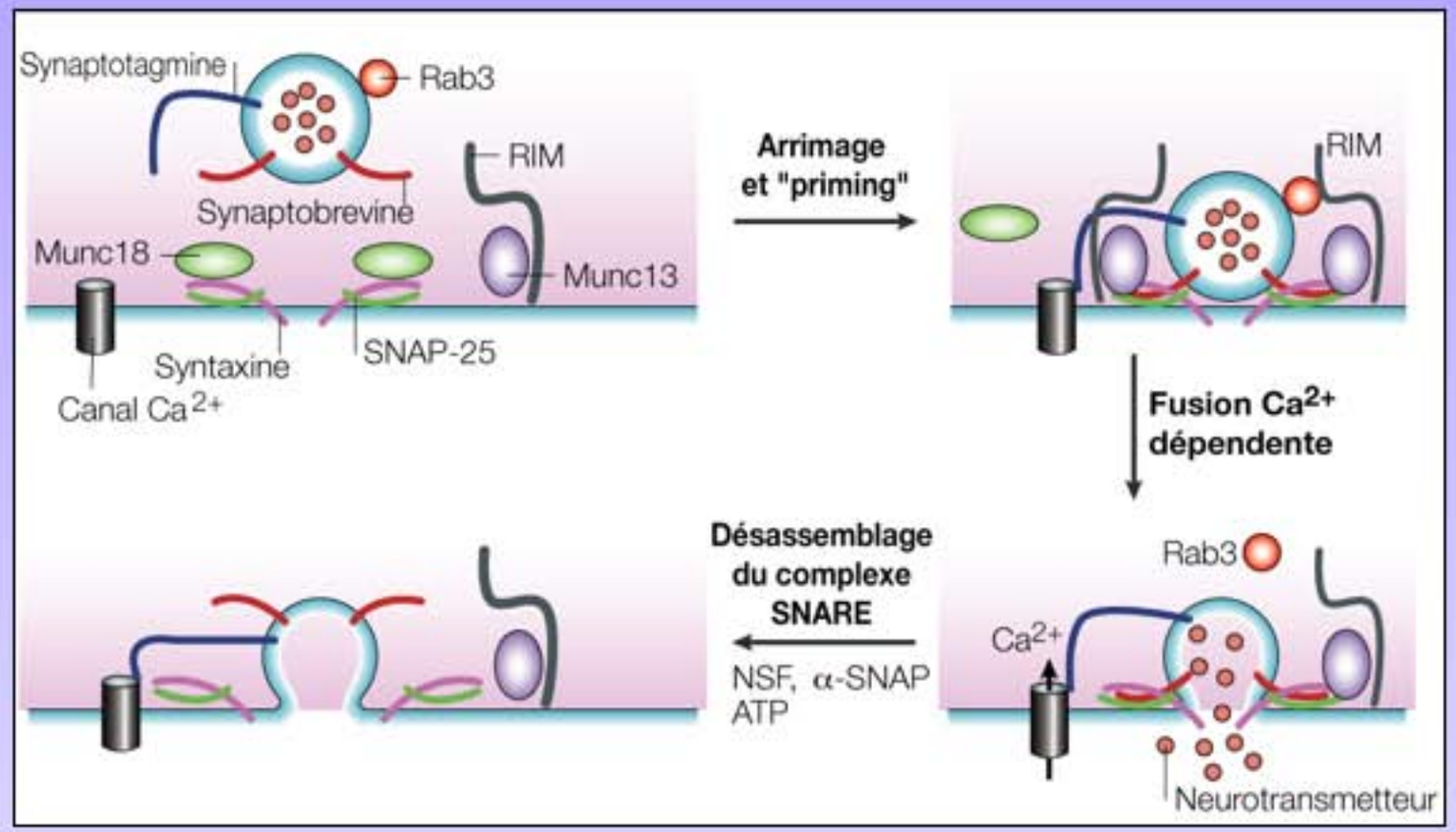
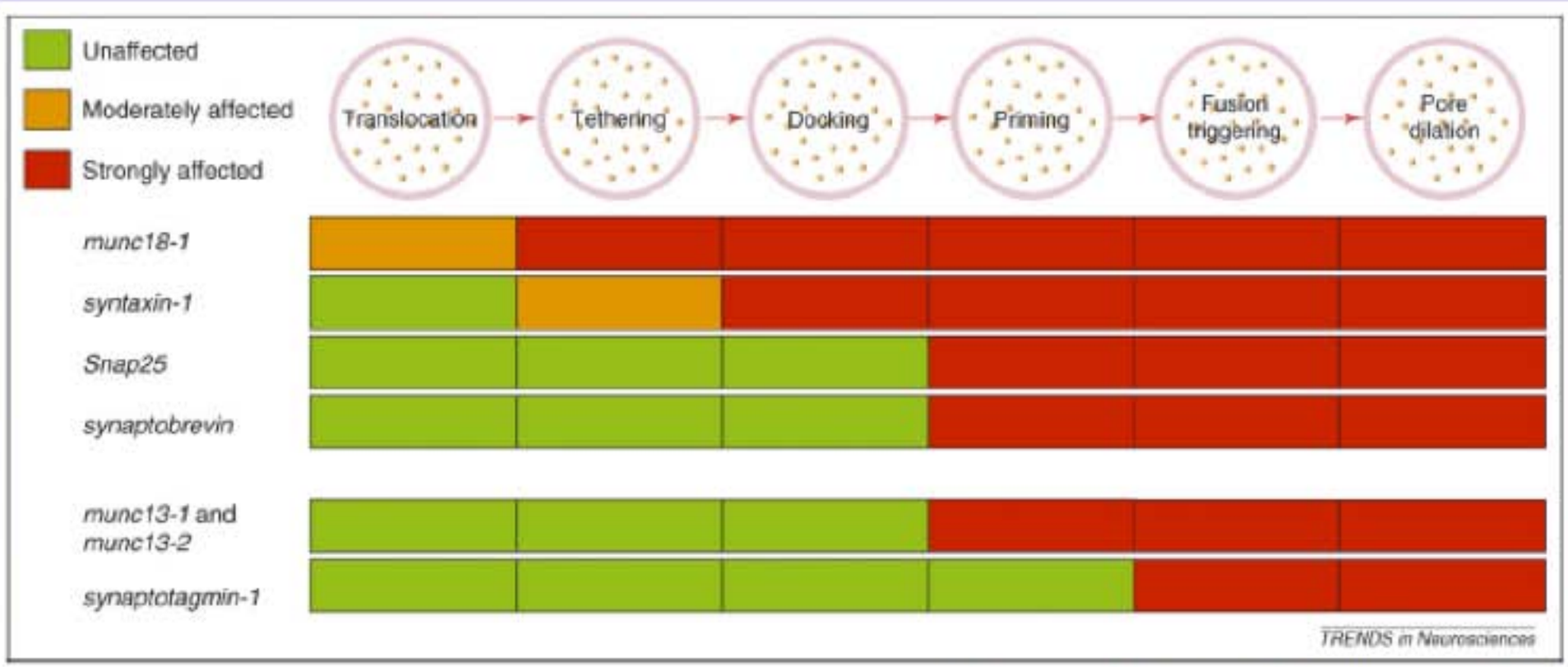


Fig. 1 . Ca^{2+} cooperativity and biphasic neurotransmitter release. (a) Relationships of presynaptic Ca^{2+} current (I_{pre}) and postsynaptic current (P.s.c.) with external Ca^{2+} concentration, $[Ca]_o$ [4]. Adapted, with permission, from Ref. [4]. The same data are represented schematically on linear (left) and log-log (right) coordinates. The exponential function (n) next to each log-log plot is a measure of the Ca^{2+}-dependent cooperativity of neurotransmitter release (see main text). Note that the differences in the slopes of I_{pre} and P.s.c. indicate that the cooperativity is mediated by binding sites downstream of the Ca^{2+} channel – that is, inside the terminal. (b) Under normal conditions, neurotransmitter release at a hippocampal synapse consists of a rapid, synchronous phase followed by a delayed, asynchronous phase. Using data from Ref. [6]. (c) Properties of Ca^{2+} domains around a Ca^{2+} channel. Small red circles represent Ca^{2+} and the gray spheres represent synaptic vesicles docked on the presynaptic membrane. Using data from Ref. [14].

Régulation de l'exocytose

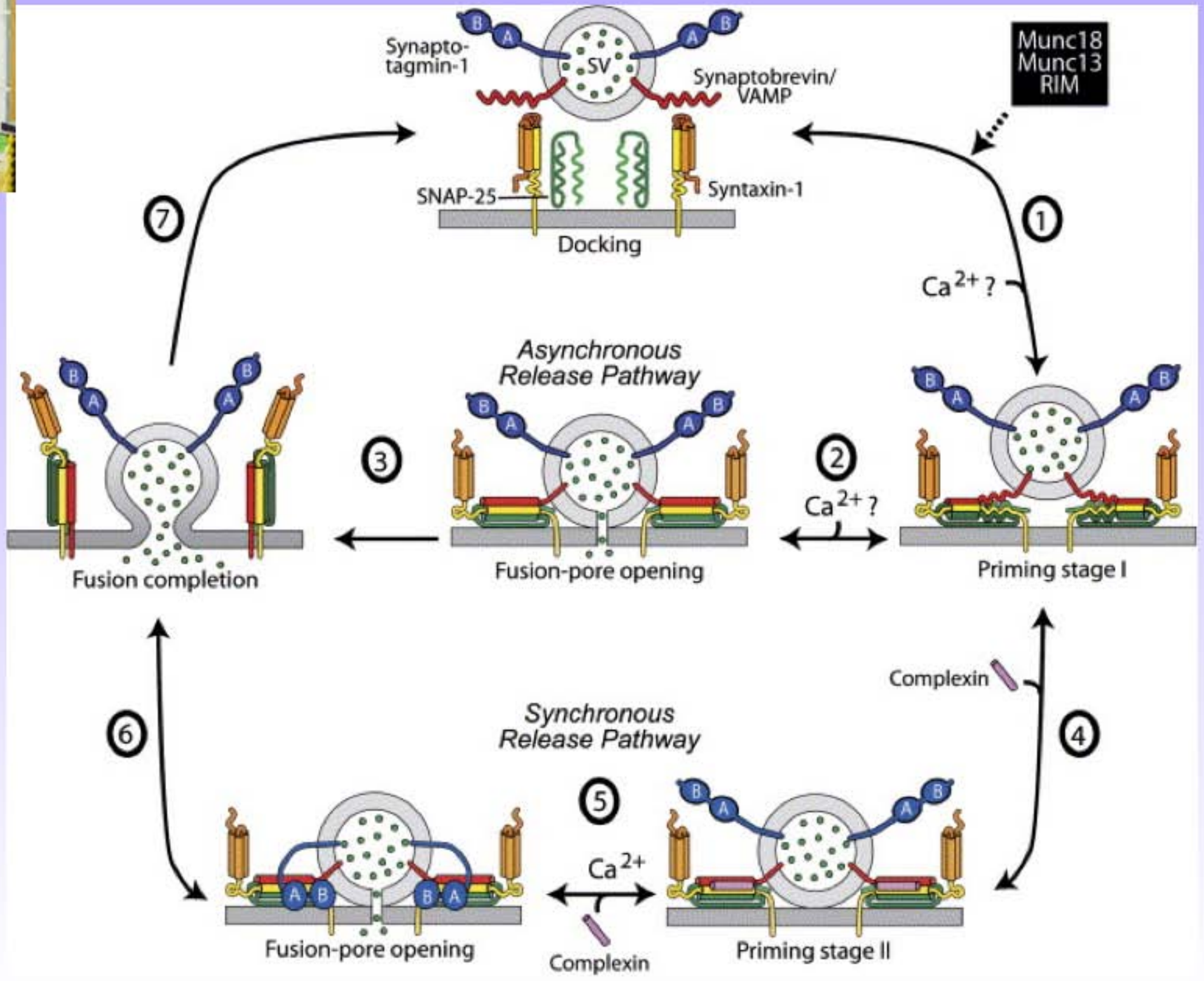




Toonen Verhage Trends in Neuroscience 2007

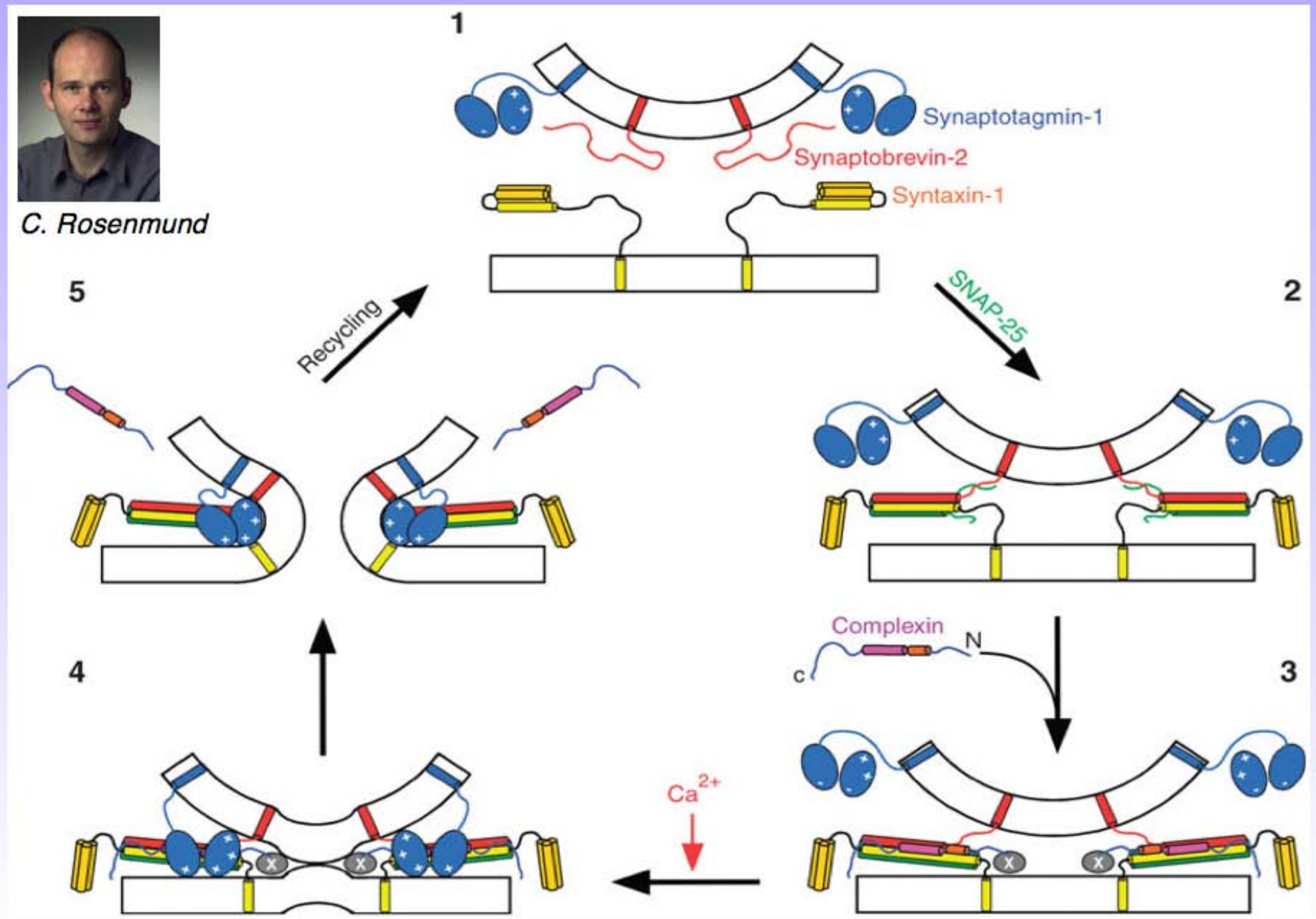
Régulation par la complexine

T. Sudhof

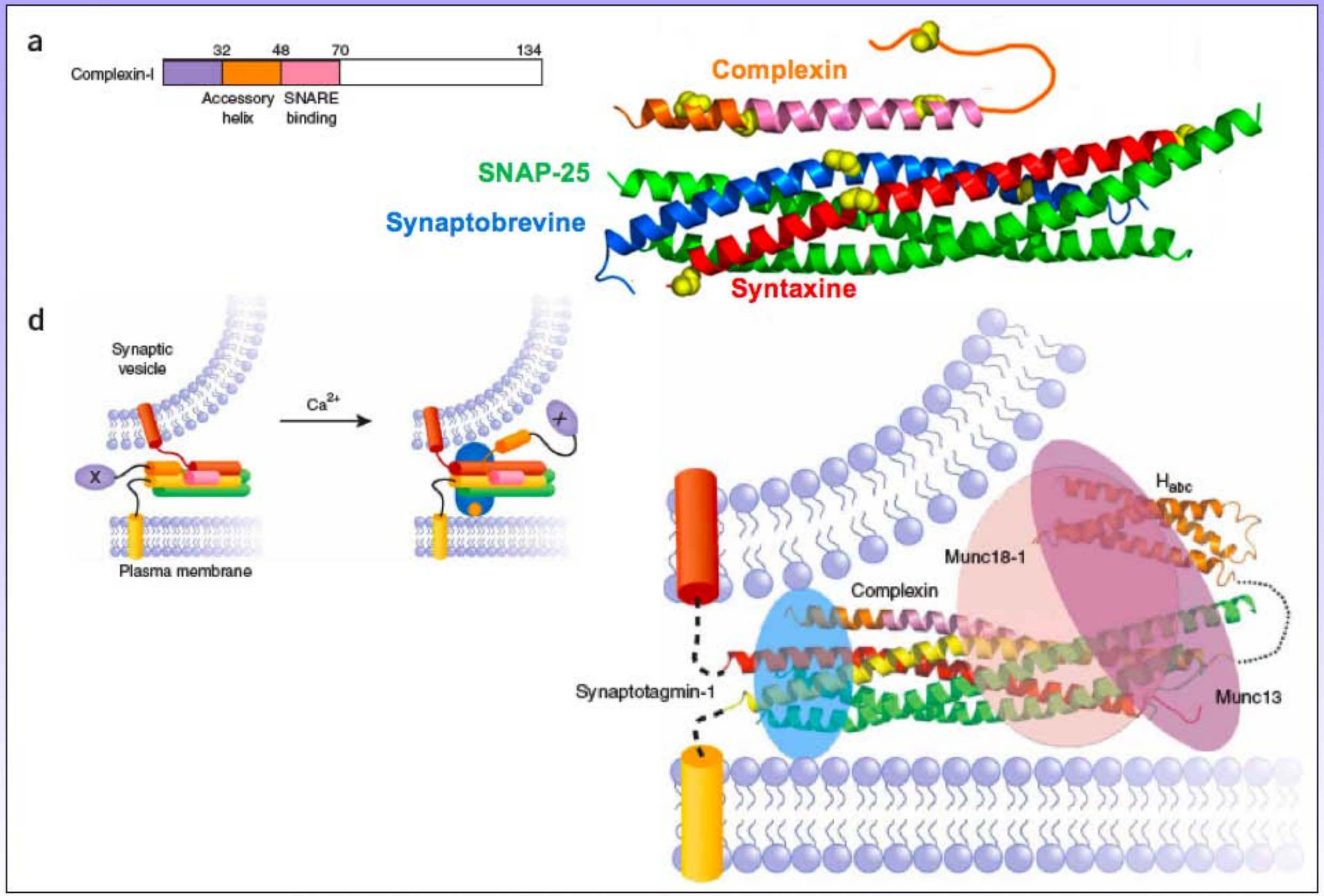


Régulation par la complexine

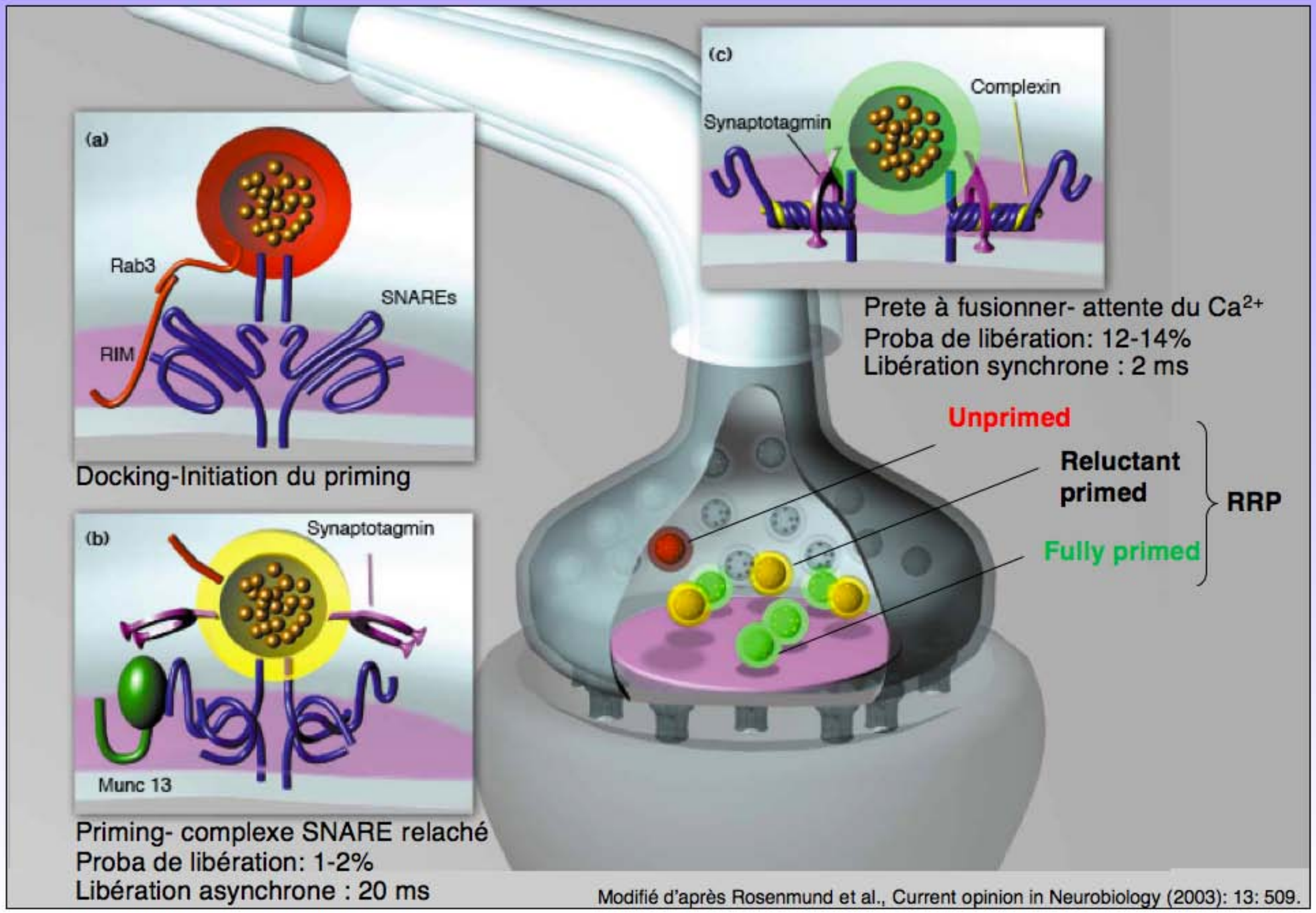
C. Rosenmund



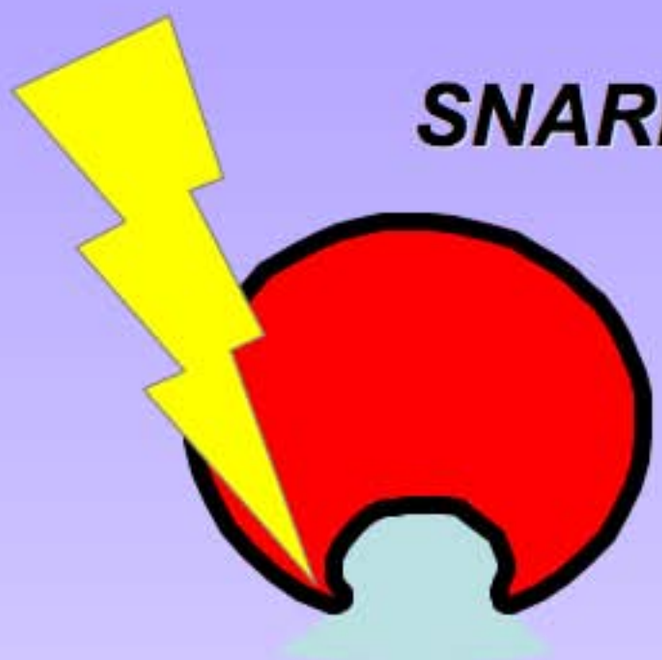
Régulation par la complexine

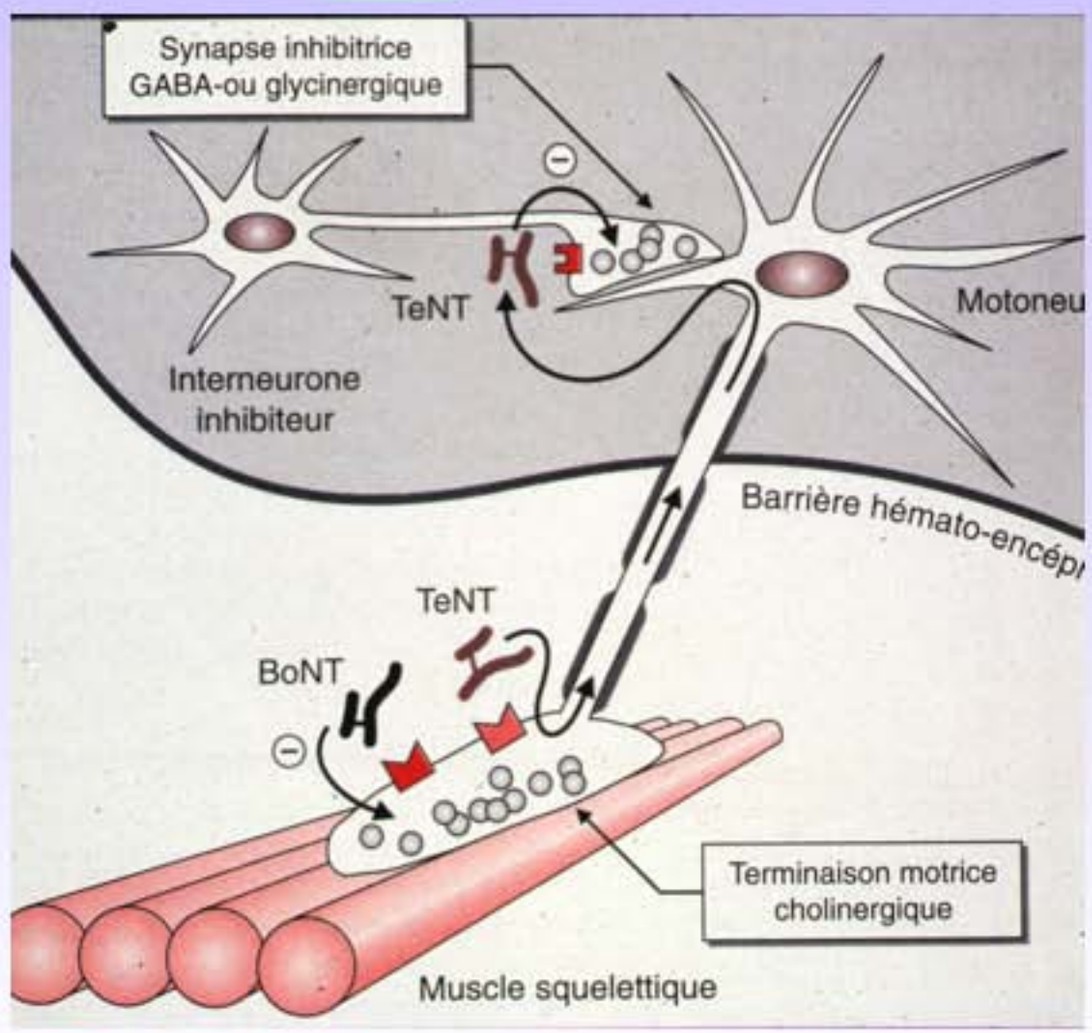


Régulation de l'exocytose

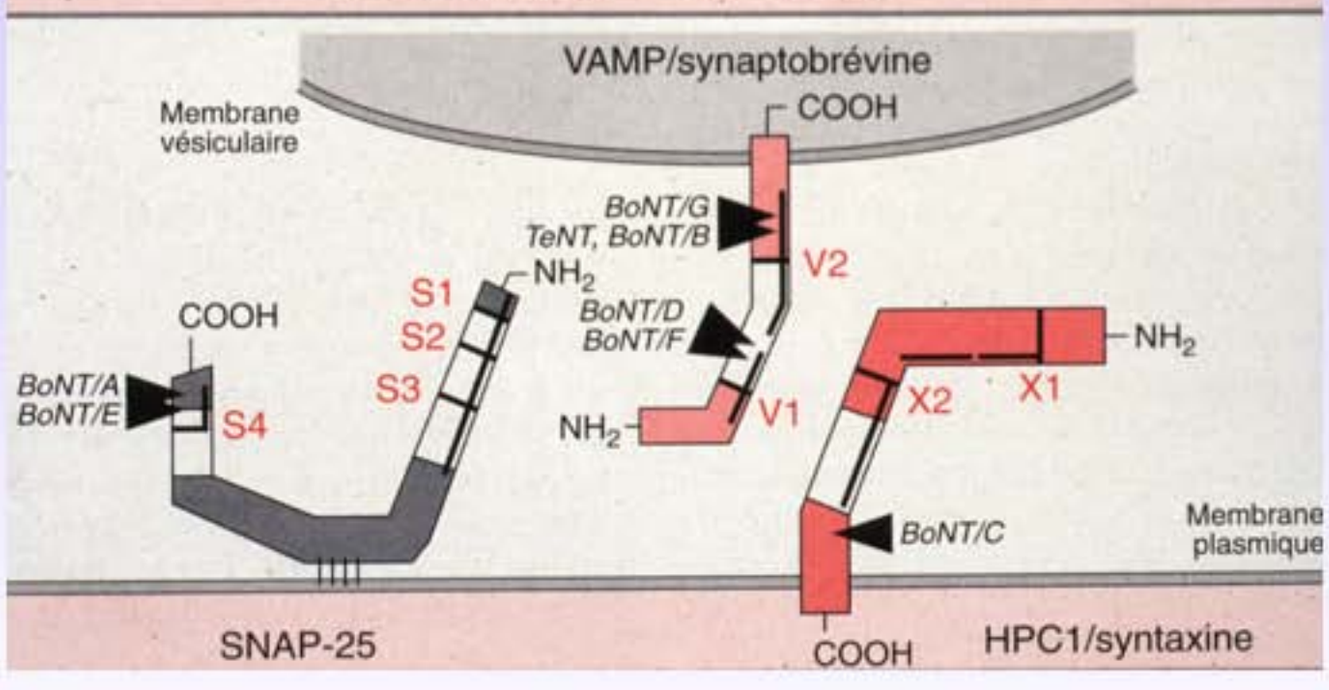


SNAREs: cibles des neurotoxines clostridiales

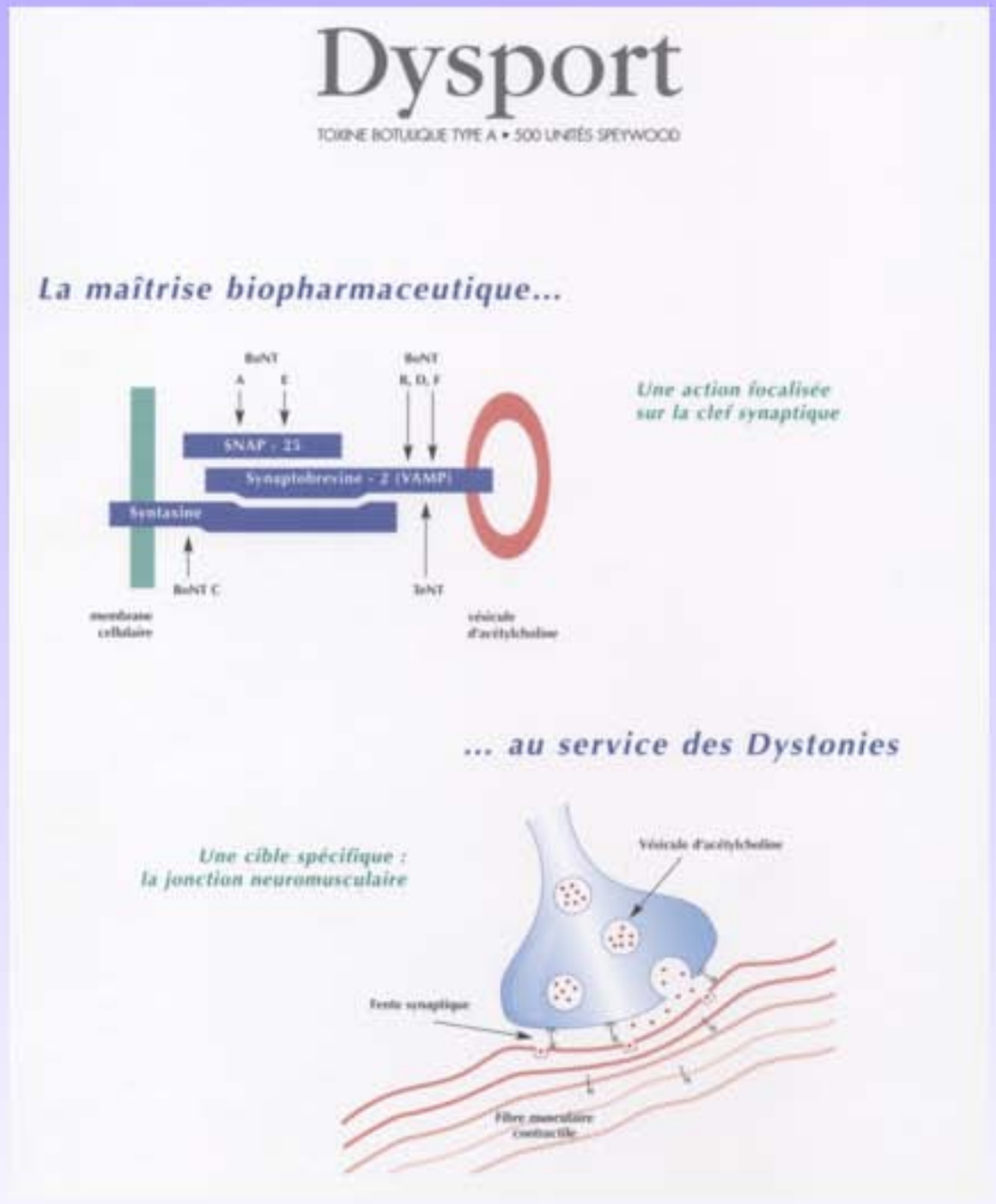




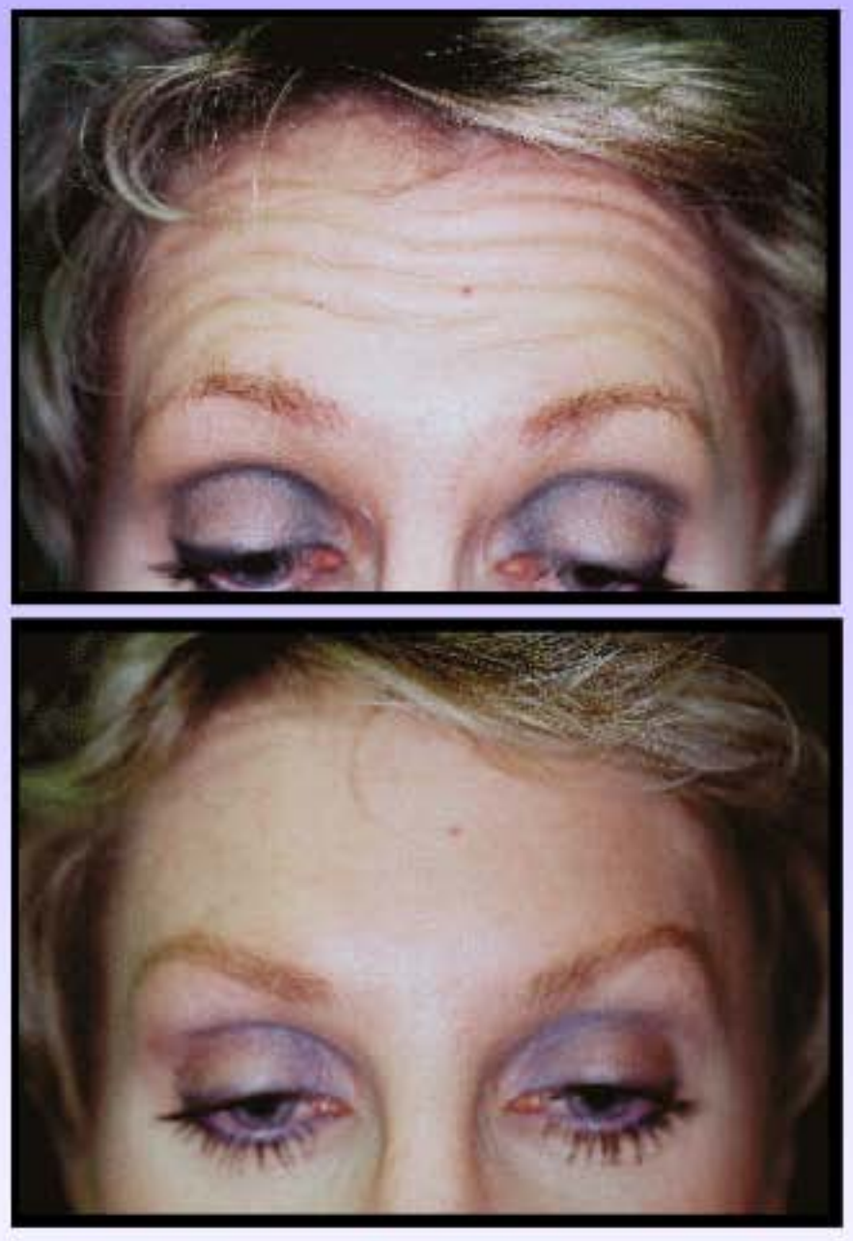
Toxine	Cible	Site de reconnaissance	Site de clivage
TeNT	VAMP	V2 : ELDDRADALQ	ASQFETS
BoNT/B	VAMP	V2 : ELDDRADALQ	ASQFETS
BoNT/D	VAMP	V1 : QVDEVVDIMR	DQKLSEL
BoNT/F	VAMP	V1 : QVDEVVDIMR	RDQKLSE
BoNT/G	VAMP	V2 : ELDDRADALQ	ESAAKLK
BoNT/A	SNAP-25	S4 : EMDENLEQVSG	ANQRATK
BoNT/E	SNAP-25	S4 : EMDENLEQVSG	KTRIDEA
BoNT/C	Syntaxine	X2 : ELEDMLESGN	TKKAVKY
	motif consensus	xh--xh-xhp	



Applications des Neurotoxines …

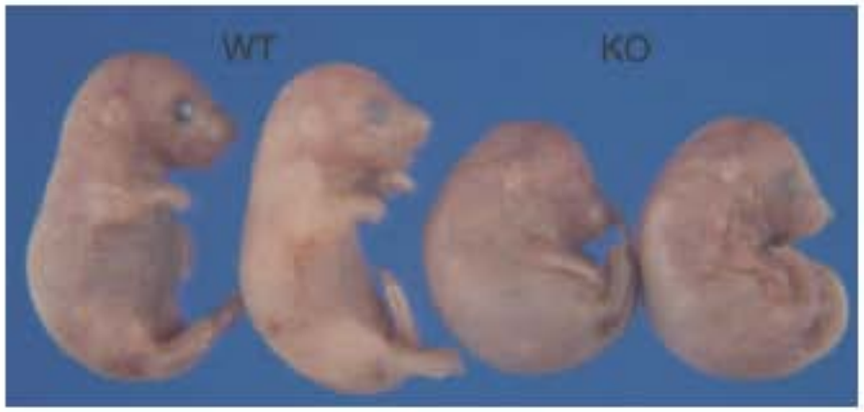


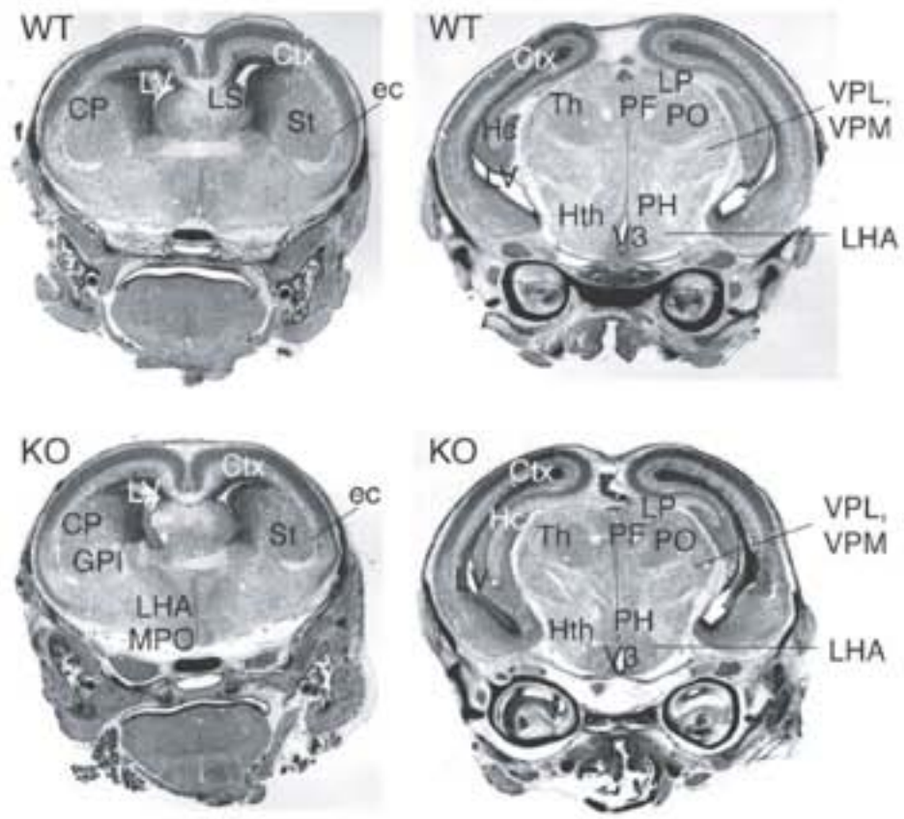
Traitement des dystonies (hypercontractions musculaires involontaires et douloureuses).

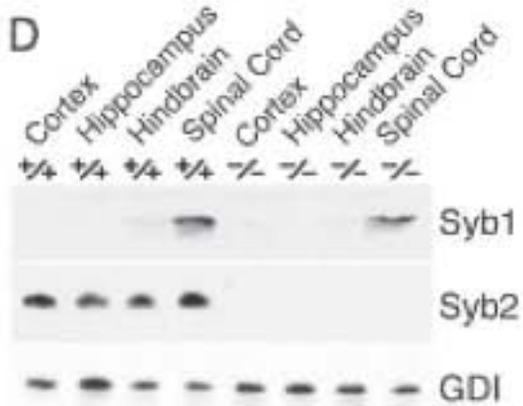


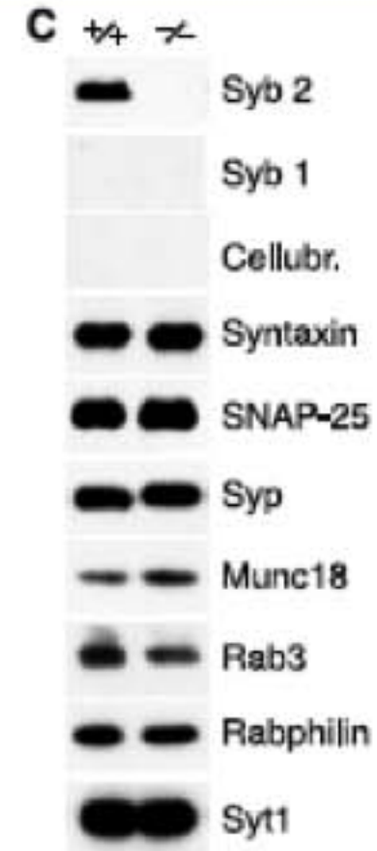
Estéthique: injection de « BOTOX »: Paralysie musculaire pendant 5 à 6 mois.

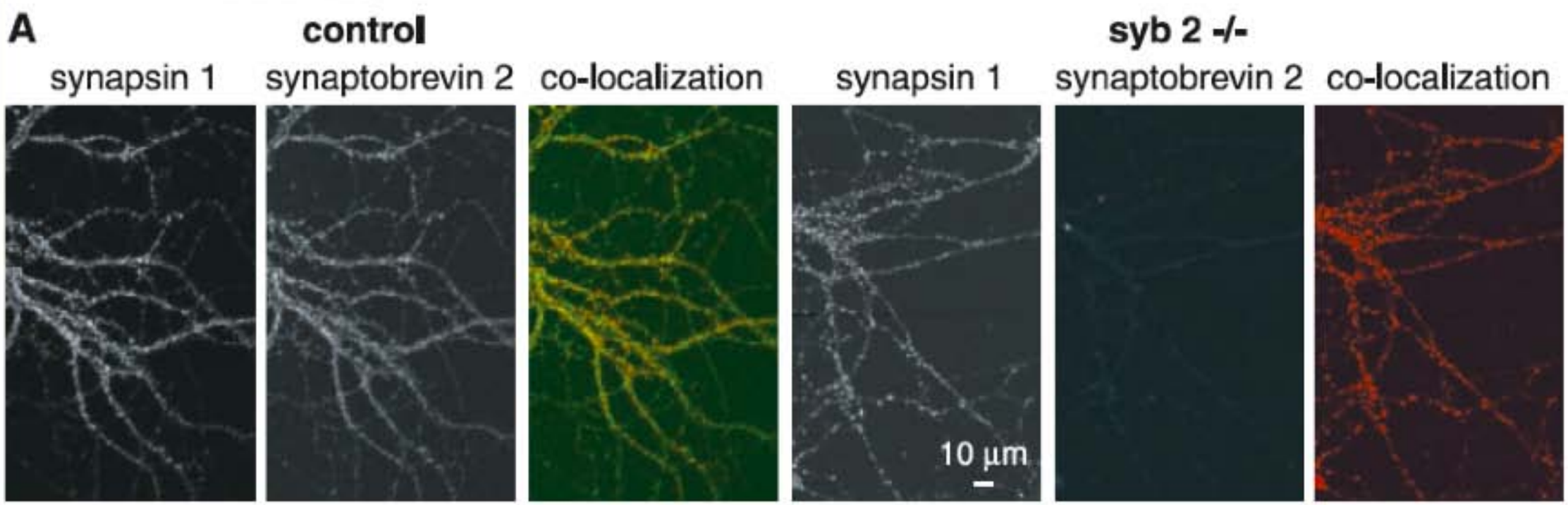
Synaptobrevin2 (Syb2) KO







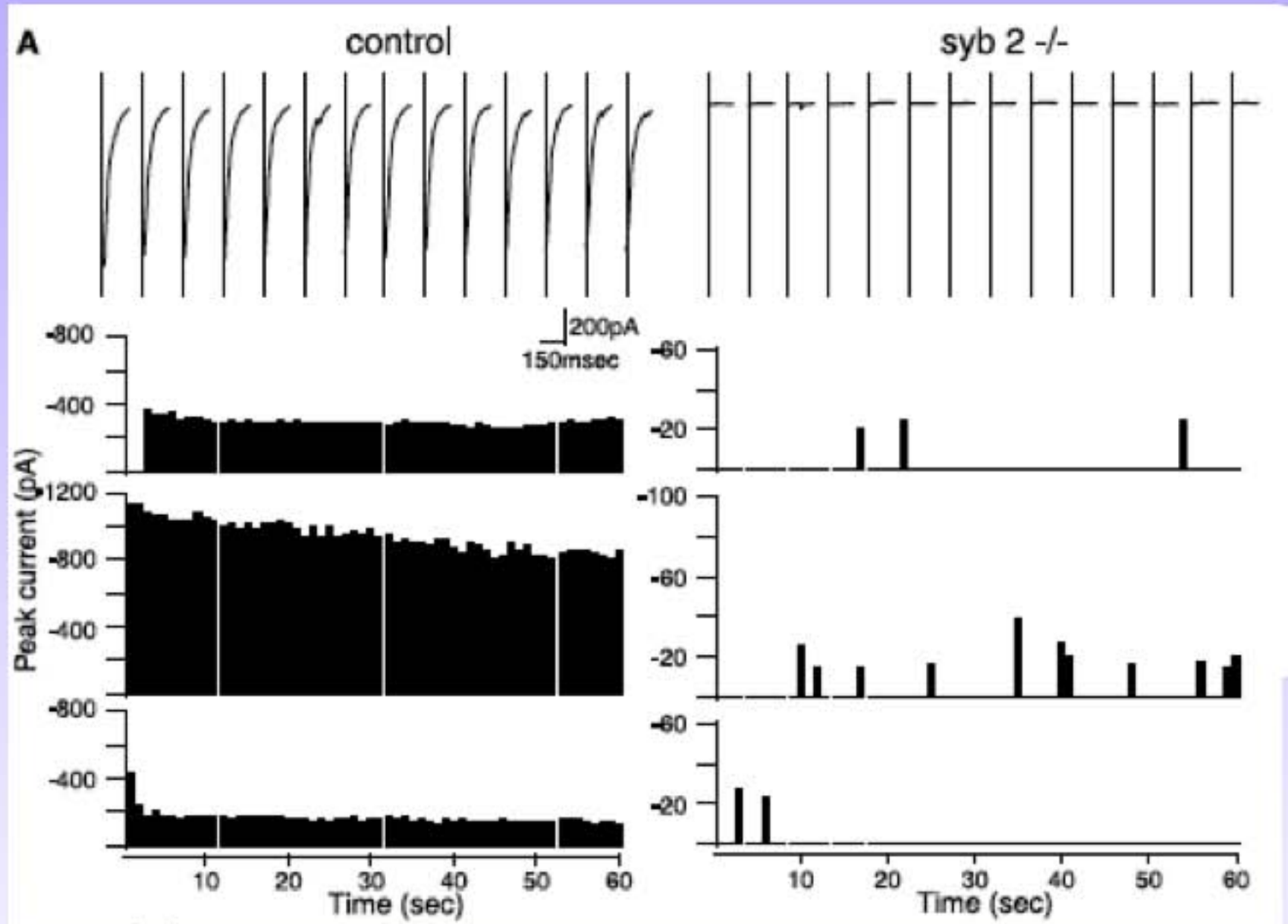


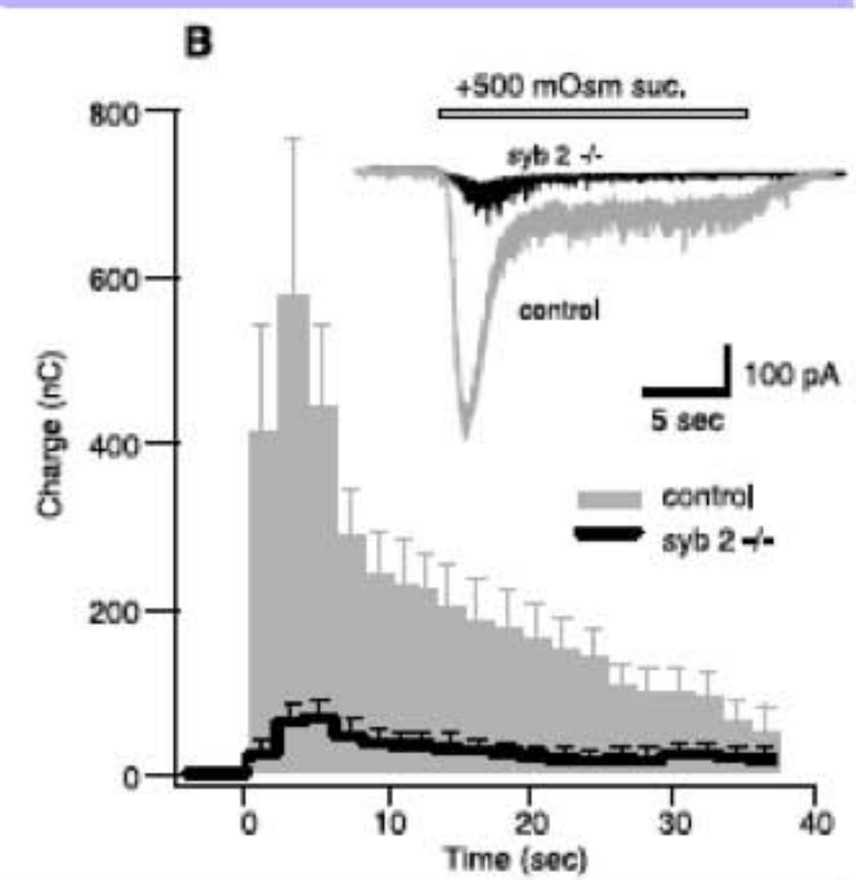


En l'absence de Syb2, les synapses sont toujours présentes, le cerveau se forme normalement mais les animaux meurent à la naissance.

Science 2 November 2001:Vol. 294. no. 5544, pp. 1117 - 112

Synaptobrevin2 (Syb2) KO

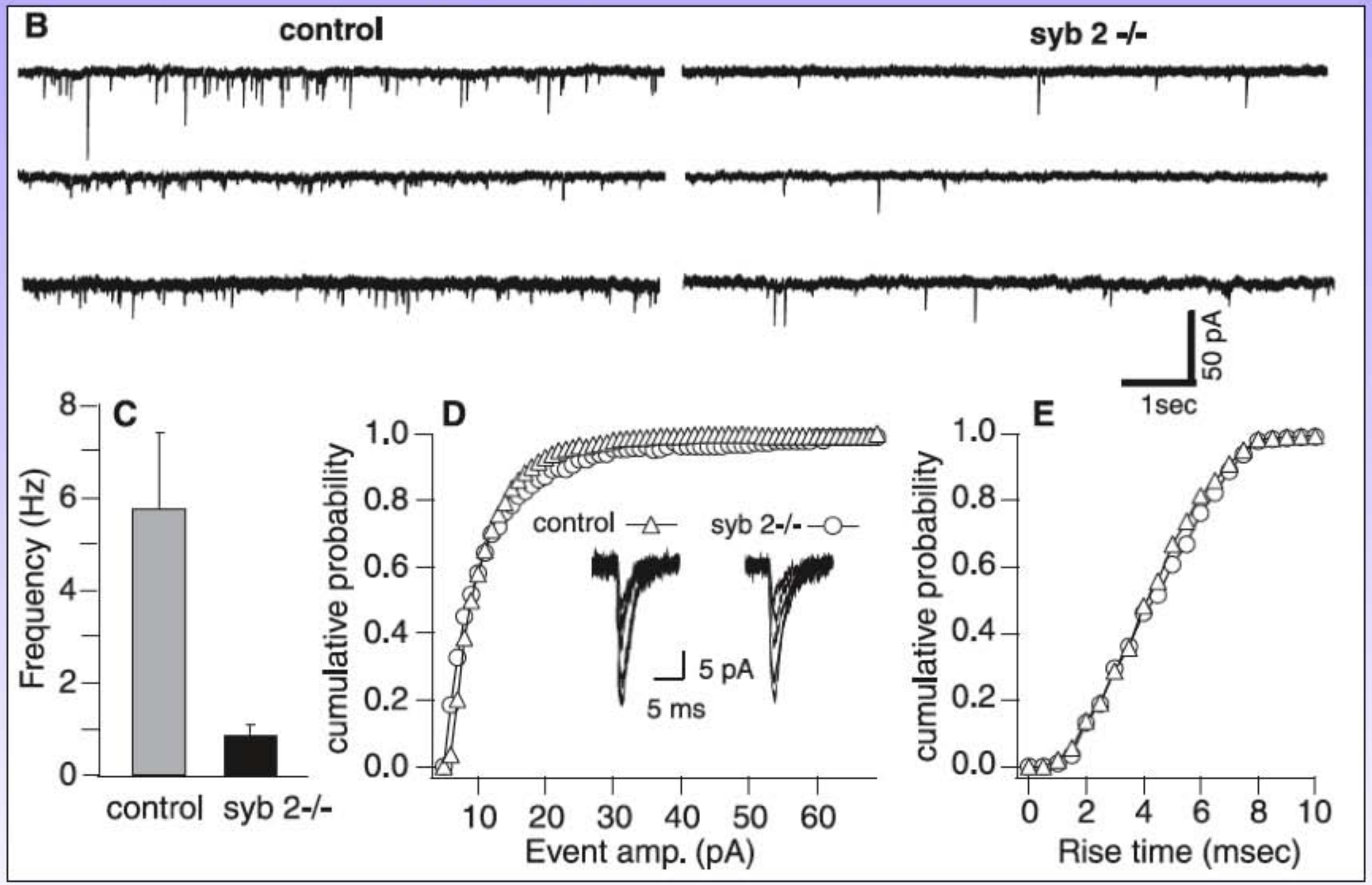




En l'absence de Syb2, la réponse évoquée est réduite d'un facteur 100.

Science 2 November 2001:Vol. 294. no. 5544, pp. 1117 - 1122

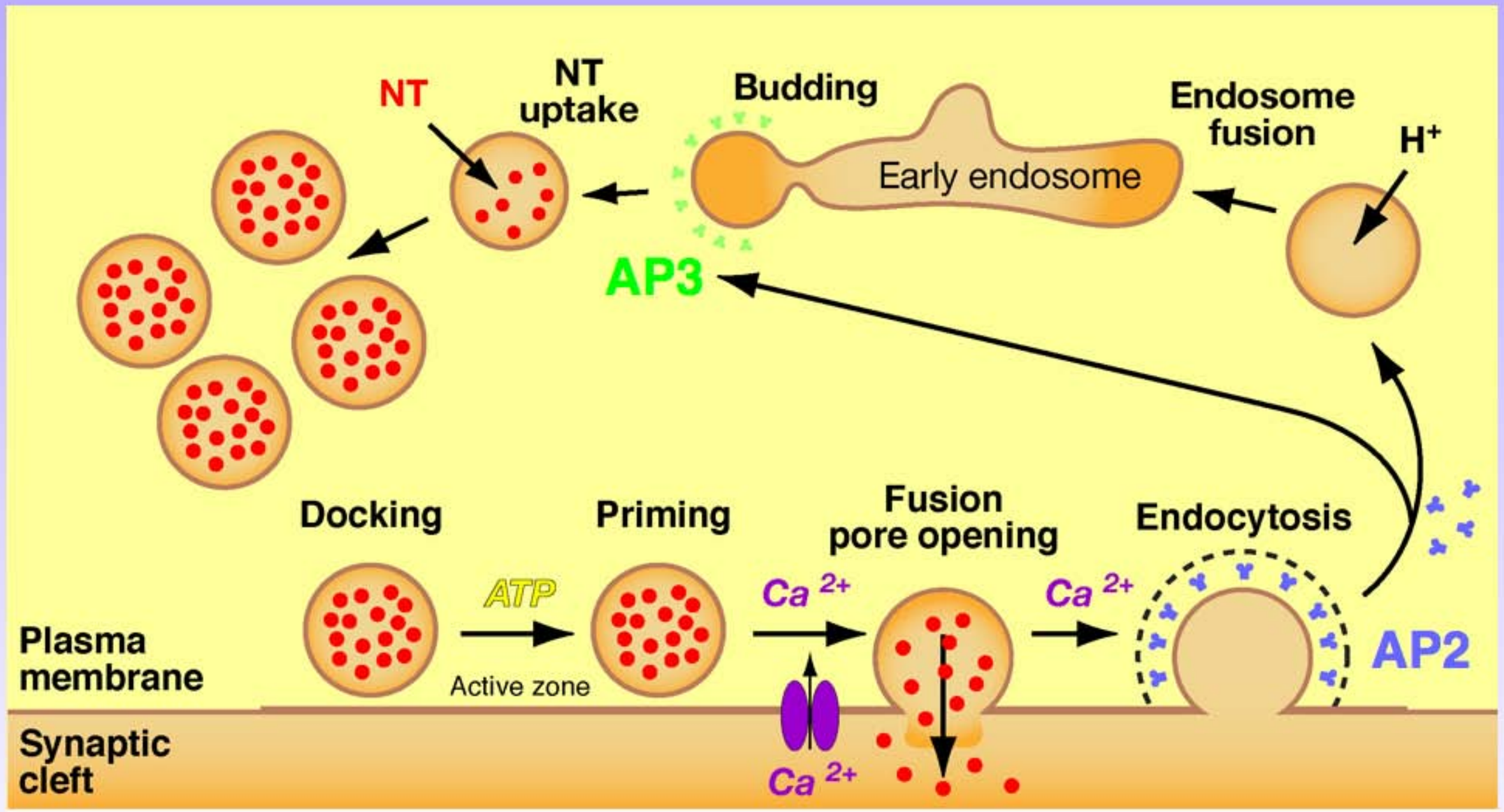
Synaptobrevin2 (Syb2) KO



En l'absence de Syb2, la réponse spontanée est réduite d'un facteur 10.

Science 2 November 2001:Vol. 294. no. 5544, pp. 1117 - 1122

SV recycling



AP3 est un complexe adaptateur heterotetramerique

Functions d' AP3:

Ciblage de certaines protéines vers les:

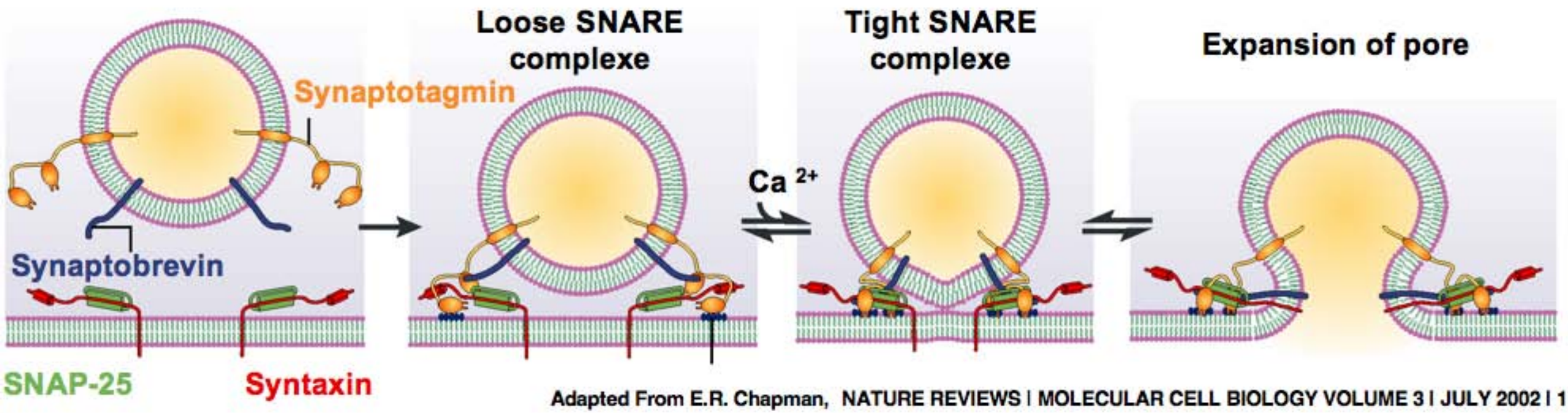
- **melanosomes,**
- **granules contenant les plaquettes,**
- **vésicules synaptiques**

Sont des mutanst nuls pour AP3 δ : suppression du complexe AP3

Les souris MOCHA (mh)

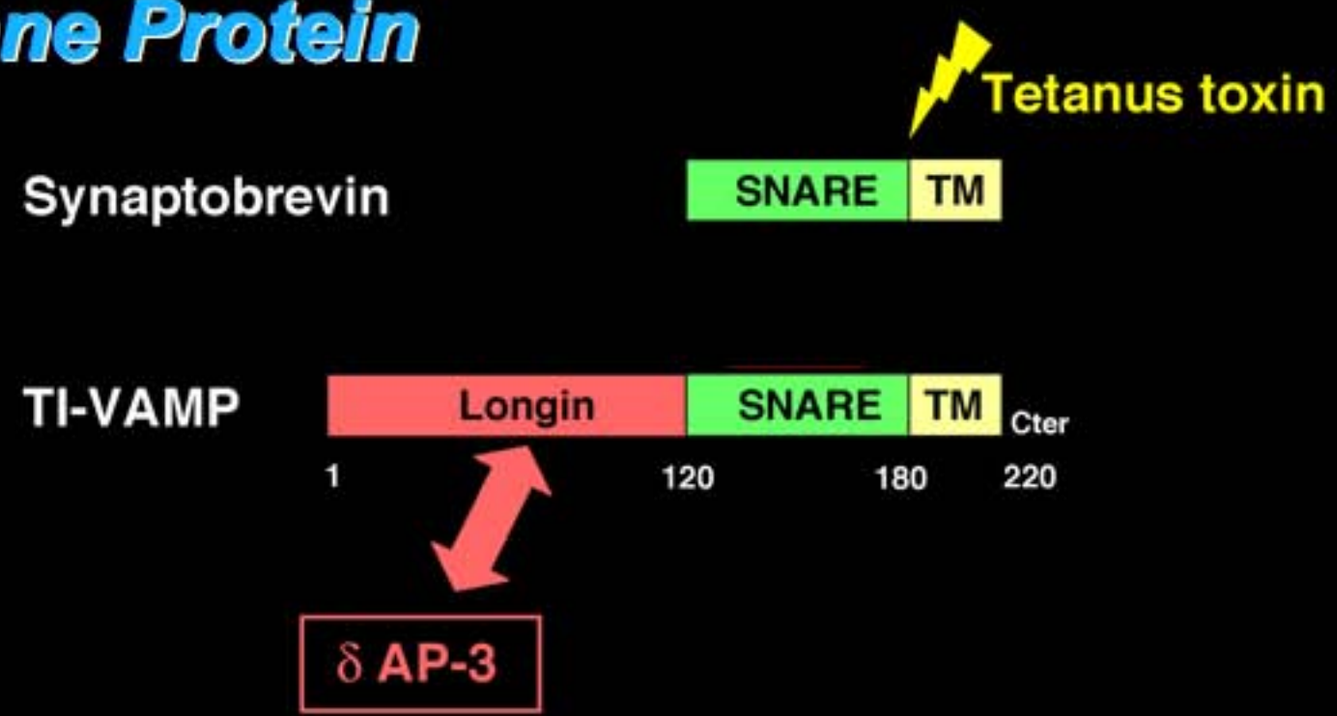
- **décoloration des yeux et des poils**
- **coagulation retardée (déficience du pool des granules (plaquettes).**
- **hyperactives**
- **rithme theta altéré dans l'electrocortigramme (hypersynchronisation).**
- **crises épileptiques**

SNARE proteins AND Exocytosis



Adapted From E.R. Chapman, NATURE REVIEWS | MOLECULAR CELL BIOLOGY VOLUME 3 | JULY 2002 | 1

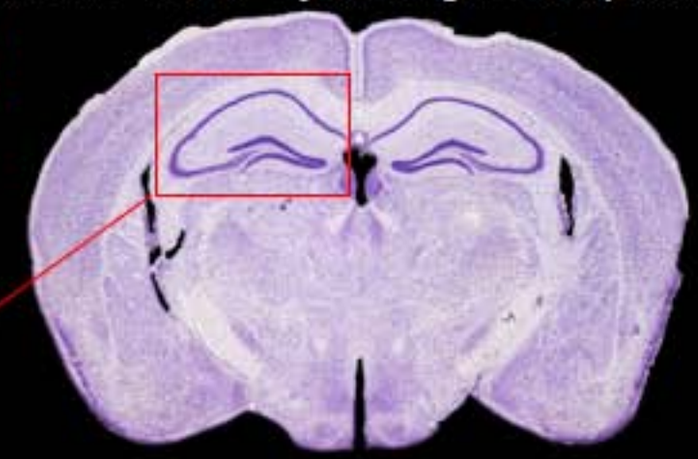
TI-VAMP : Tetanus Neurotoxin-Insenstitive Vesicle Associated Membrane Protein



- *gène lié au X*
- *v-SNARE de 25kDa*
- *ubiquitaire*
- *Ciblé via AP3*
- *Insensensible aux Neurotoxines*
- *Presente dans les terminaisons des fibres moussues.*

The mossy fiber-pyramidal cell synap

Transversal
slice



hippocampus

CA1

Pyramidal cell

CA3

Fimbria

Septum

Schaeffer collateral

s.luc

lrl

Mossy fiber

Dentate gyrus

Granule cell

Alveus

so

sr

slm

sm

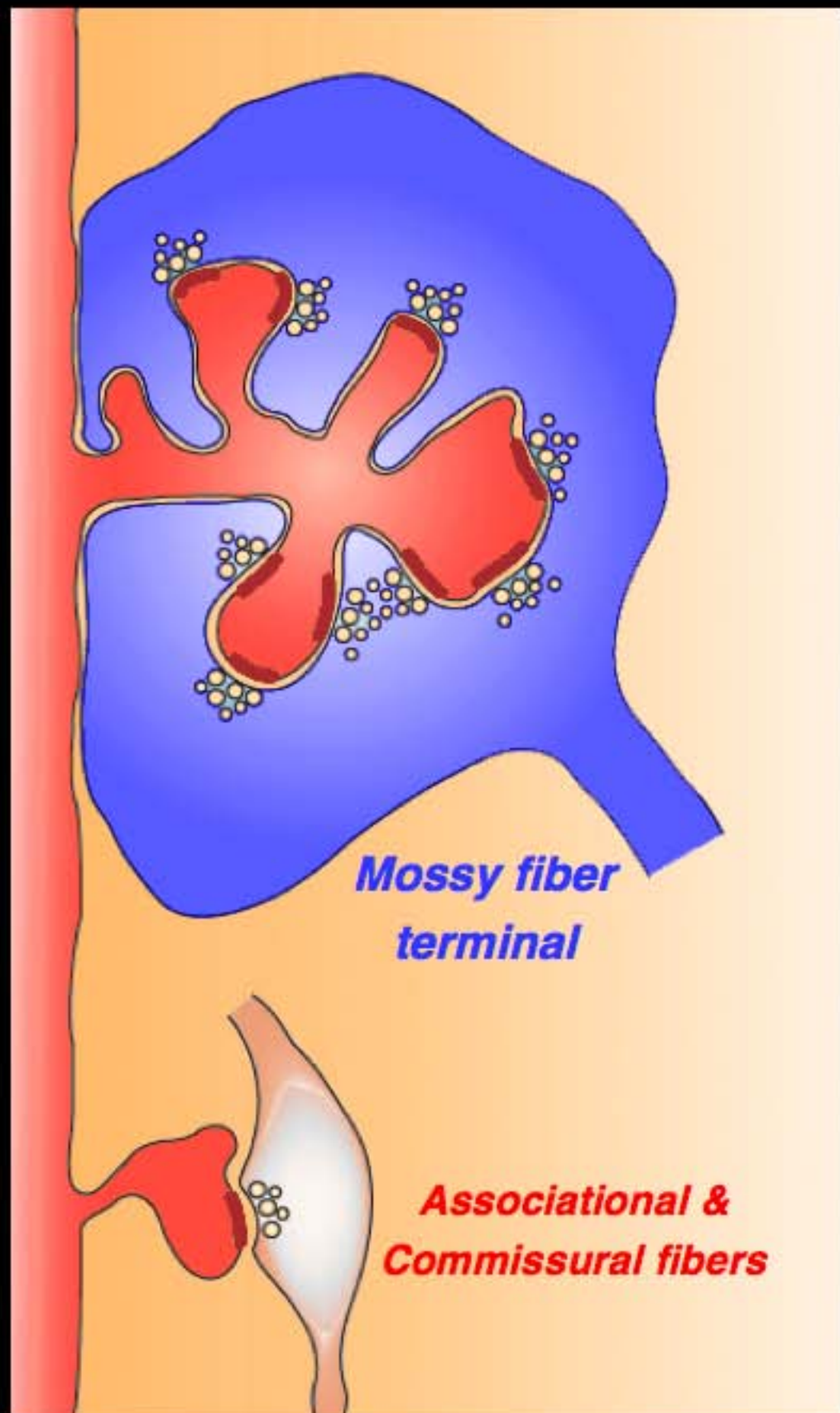
Perforant path (subiculum entorhinal cortex)

The mossy fiber-pyramidal cell synapse

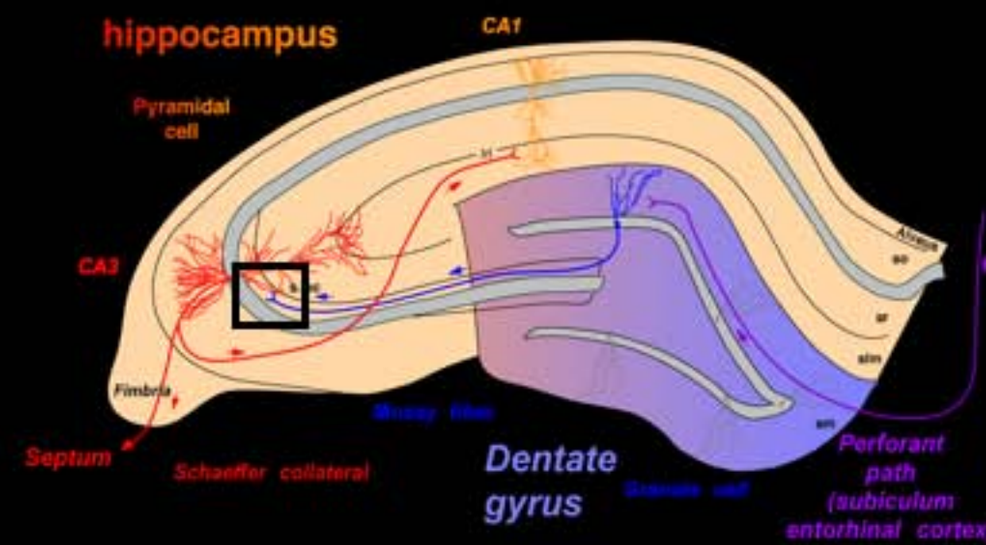
Thorny excrescence

PYRAMIDAL CELL

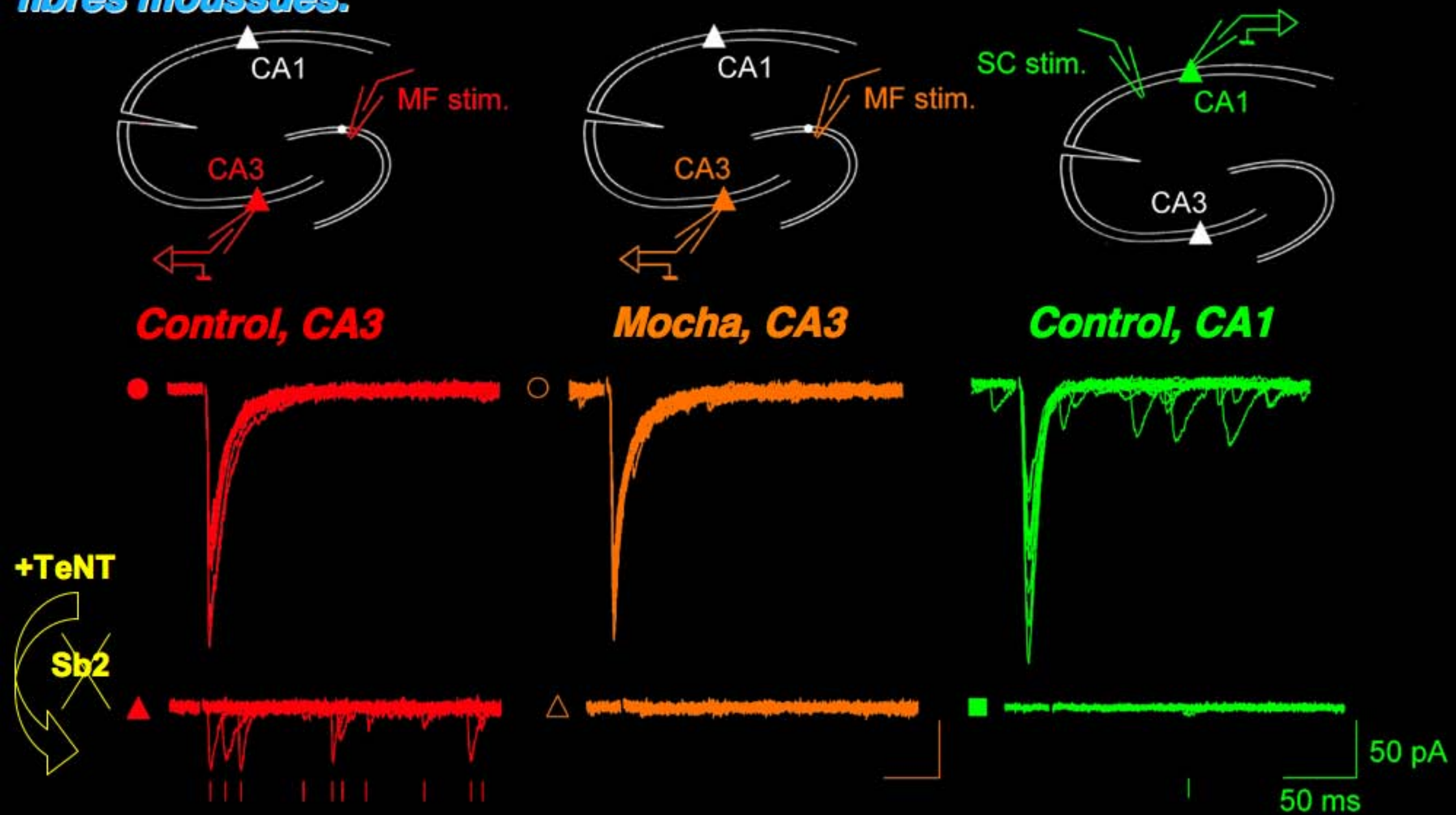
Classical spine



GRANULE CELL



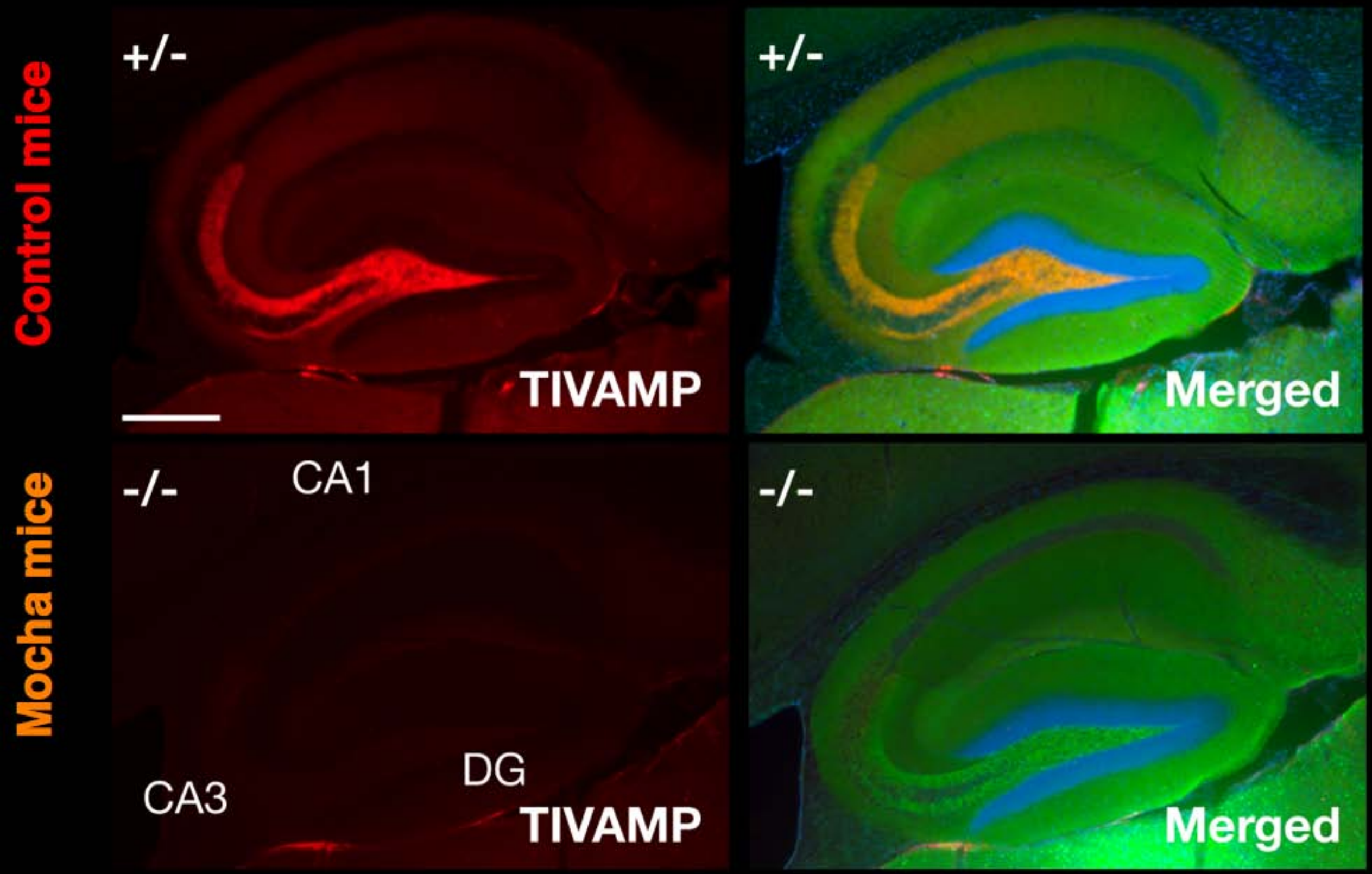
Libération Ca^{2+}-dépendente évoquée par la stimulation des fibres moussues.

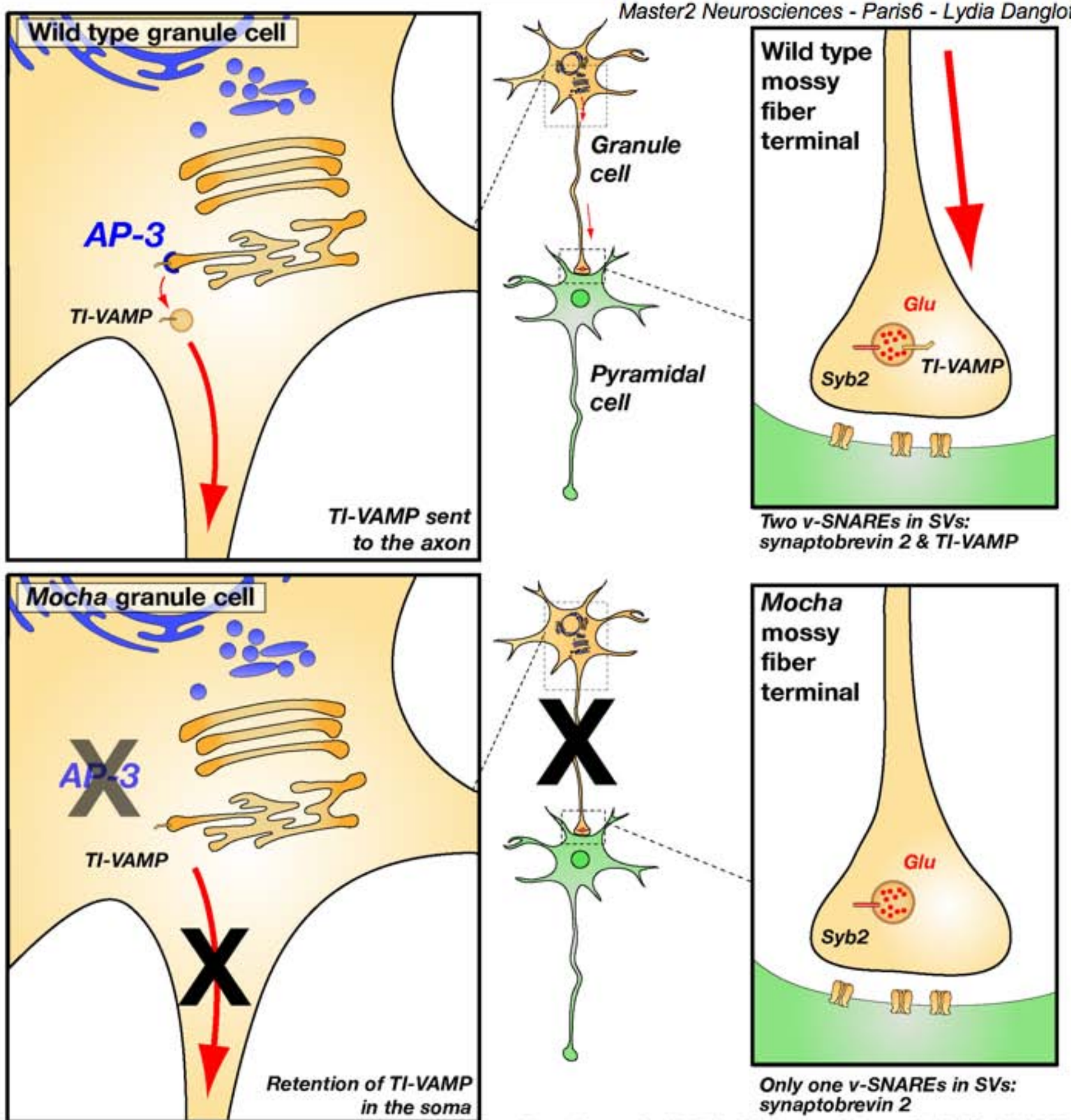


- La TeNT causes une réduction drammatique de la liberation des NT stimulée par PA.
- La libération est asynchrone, dépendante d'AP-3 et spécifique de CA3.

Danglot et al. PNAS (2006)

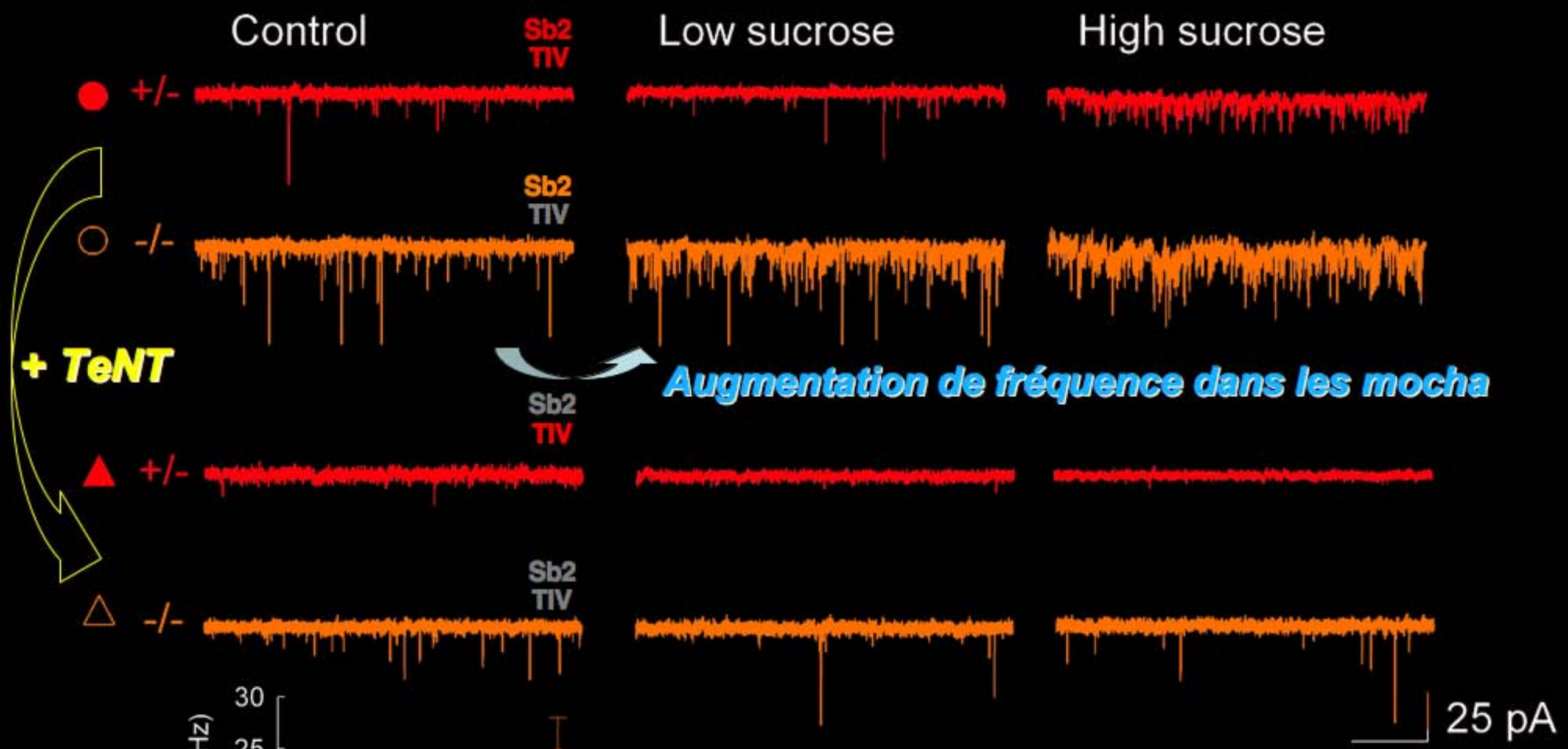
TI-VAMP est dans le Golgi des grains des mocha.



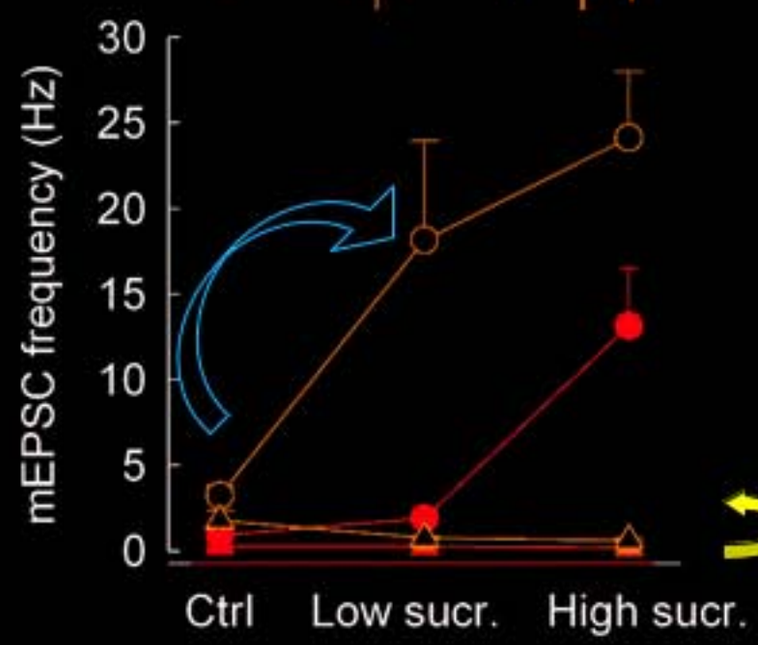


Danglot et al. (2007), Biology of the cell, 99(7):349-361

Augmentation du RRP dans les souris mocha



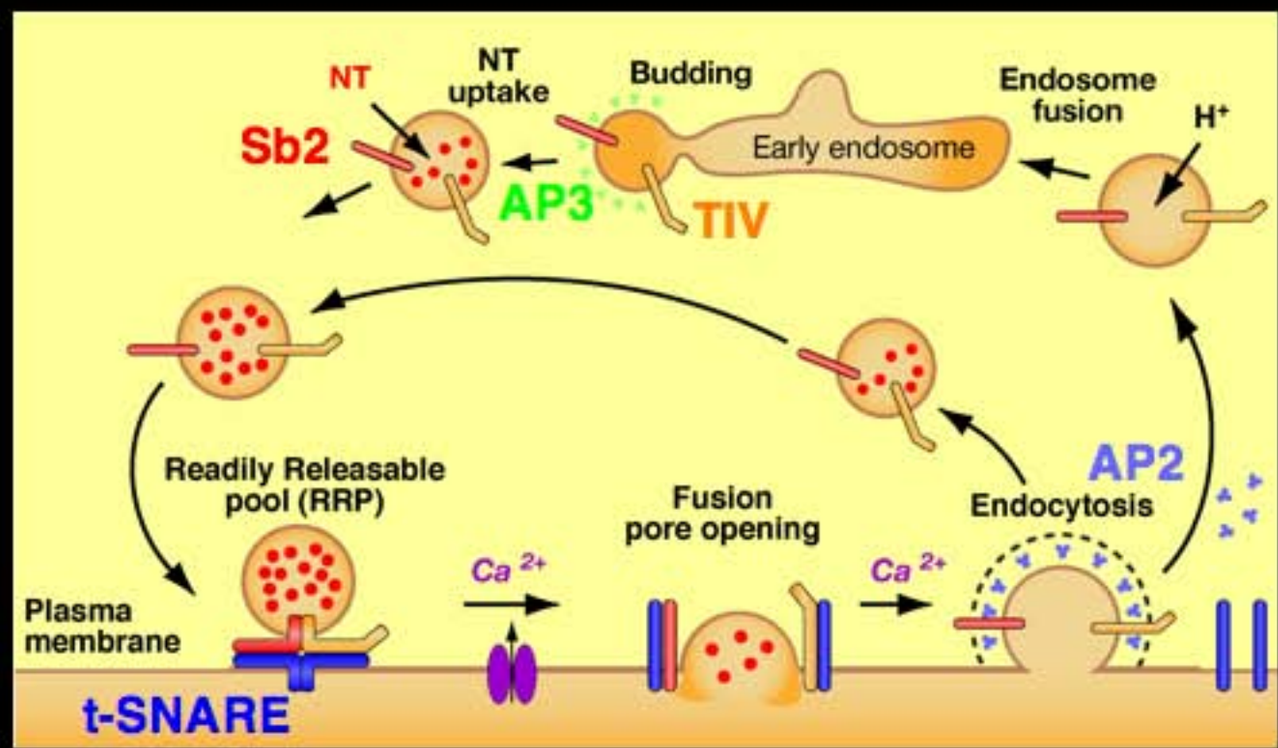
Augmentation de fréquence dans les mocha

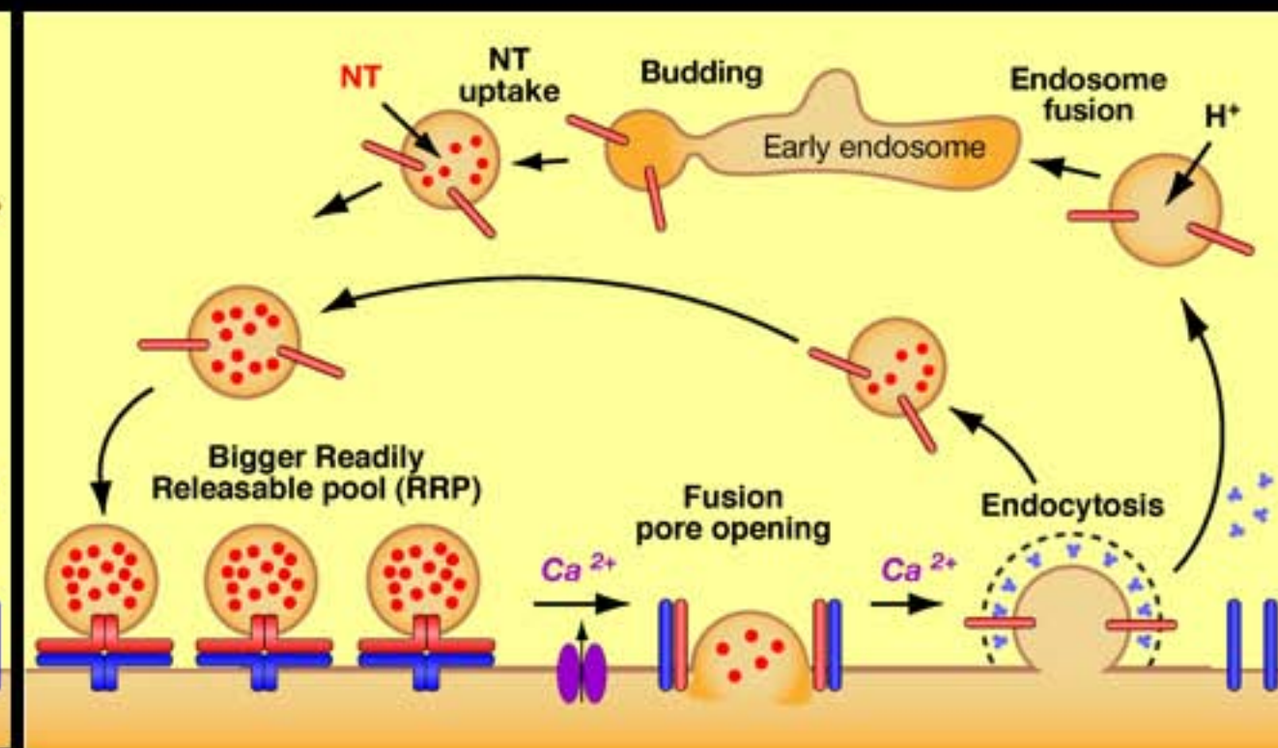


Fréquence augmentée dans les mocha : le RRP est plus grand chez les mocha

Après TeNT: pas ↗ de la freq des mEPSC
Le RRP ne peut plus etre recrute.

A la fois TI-VAMP & Sb2 medient la libération basale & evoquée aux terminaisons des fibres moussues





Souris control **Souris mocha**

En l'absence de TI-VAMP dans les terminaisons des fibres moussues (souris mocha) :

- le RRP devient plus important. La probabilité de libération basale augmente.
- La libération évoquée asynchrone, résistante à la TeNT, est perdue.

Lydia Danglot web page

Life Science & Imaging

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