Synaptic Transmission

Electrical Synapse

Chemical Synapse

Neurotransmitter Synthesis and Release

EPSP and IPSP

Quantal Analysis

EPSP Summation and IPSP Shunting

Modulation

Neuroglia

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National Taiwan University

Animated Tutorials: Neurobiology/Biopsychology

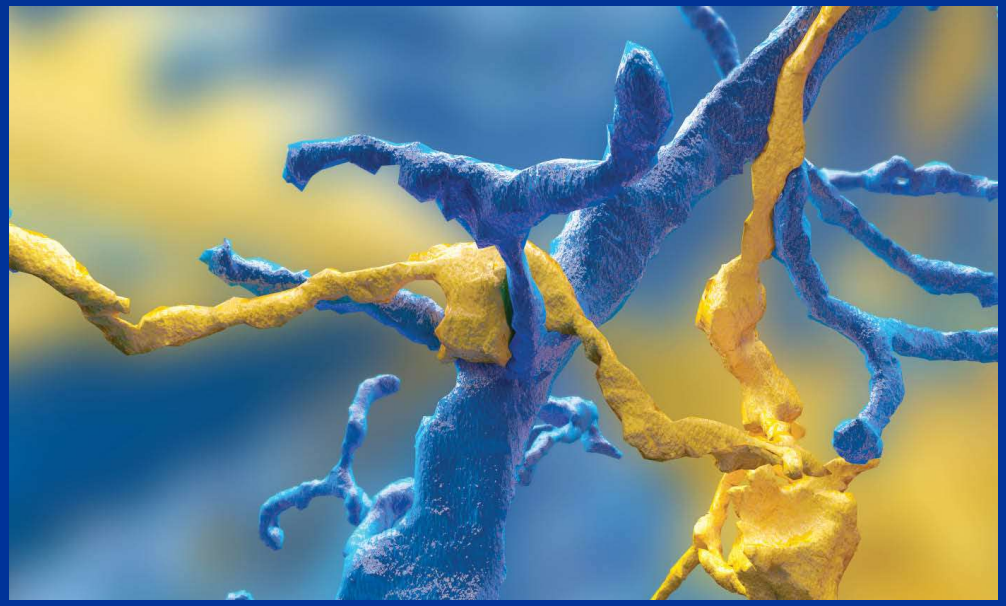
http://www.sumanasinc.com/webcontent/animations/neurobiology.html

Textbook: 1. Neuroscience Bear et al. 2. Neuroscience Purves et al

Remained rivals to the end

How to resolve this issue?

Neurites in Contact, Not Continuity



Reconstructed from a series of electron micrograph images

The Nobel Prize in Physiology or Medicine 1906

"in recognition of their work on the structure of the nervous system"

Camillo Golgi	Santiago Ramón y Cajal
1/2 of the prize	1/2 of the prize
Italy	Spain
Pavia University Pavia, Italy	Madrid University Madrid, Spain
b. 1843 d. 1926	b. 1852 d. 1934

http://nobelprize.org/nobel_prizes/medicine/laureates/1906/

The War of the Soup and the Spark

Electrical synapses and their functional interactions with chemical synapses Nature Reviews Neuroscience (2014) 15: 250–263 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4091911/

Box 1 | The debate over the nature of synaptic transmission

S. Ramón y Cajal and C. Sherrington, the fathers of modern neuroscience, established that networks of multiple elementary units, called 'neurons', communicate with each other through functional specializations called 'synapses'. Their seminal contributions were followed by a bitter debate over the nature of synaptic transmission: was it **mediated by chemical or electrical signals? This controversy was known as 'The War of the Soup and the Sparks'** (Ref. 170). Although several researchers, most notably T. R. Elliott[171] and later O. Loewi[172], demonstrated the existence of neurotransmitters with actions on postsynaptic cells, there was still controversy over whether transmitter release could occur in a fraction of a millisecond, the synaptic 'delay' indirectly measured by Sherrington[173]. B. Katz and colleagues[174]demonstrated that synaptic transmission at the frog neuromuscular junction was an electrically mediated, **calcium-dependent form of transmitter release**, which occurred within a fraction of a millisecond. Transmission by such a mechanism was also shown to occur in the CNS, leading to a general agreement that synaptic transmission was chemically mediated. However, in **1958**, D. Potter communicated at a 'Monday night fight' of the Marine Biological Laboratory in Woods Hole (USA) (so called because of the contentious nature of the scientific exchanges) the striking properties of synaptic transmission in **crayfish**, which challenged all the criteria established for chemical transmission. Postsynaptic signals reproduced the time course of presynaptic signals, and transmission was bidirectional and, surprisingly, voltage-dependent. The findings provided the earliest evidence in support of the existence of electrical synaptic transmission[175] and were soon followed by seminal studies in the teleost brain by M. V. L. Bennett and colleagues[176], J. D. Robertson and colleagues[177]and E. J. Furshpan[178], in which physiological and ultrastructural analyses were combined. Their search for the anatomical basis of electrical transmission greatly contributed to the identification of the cellular structures that we know today as gap junctions. The more recent demonstration of the ubiquitous presence of electrical synapses in the mammalian brain led to the indisputable conclusion that chemical transmission and electrical transmission **coexist** in all nervous systems.

Electrical Synapse

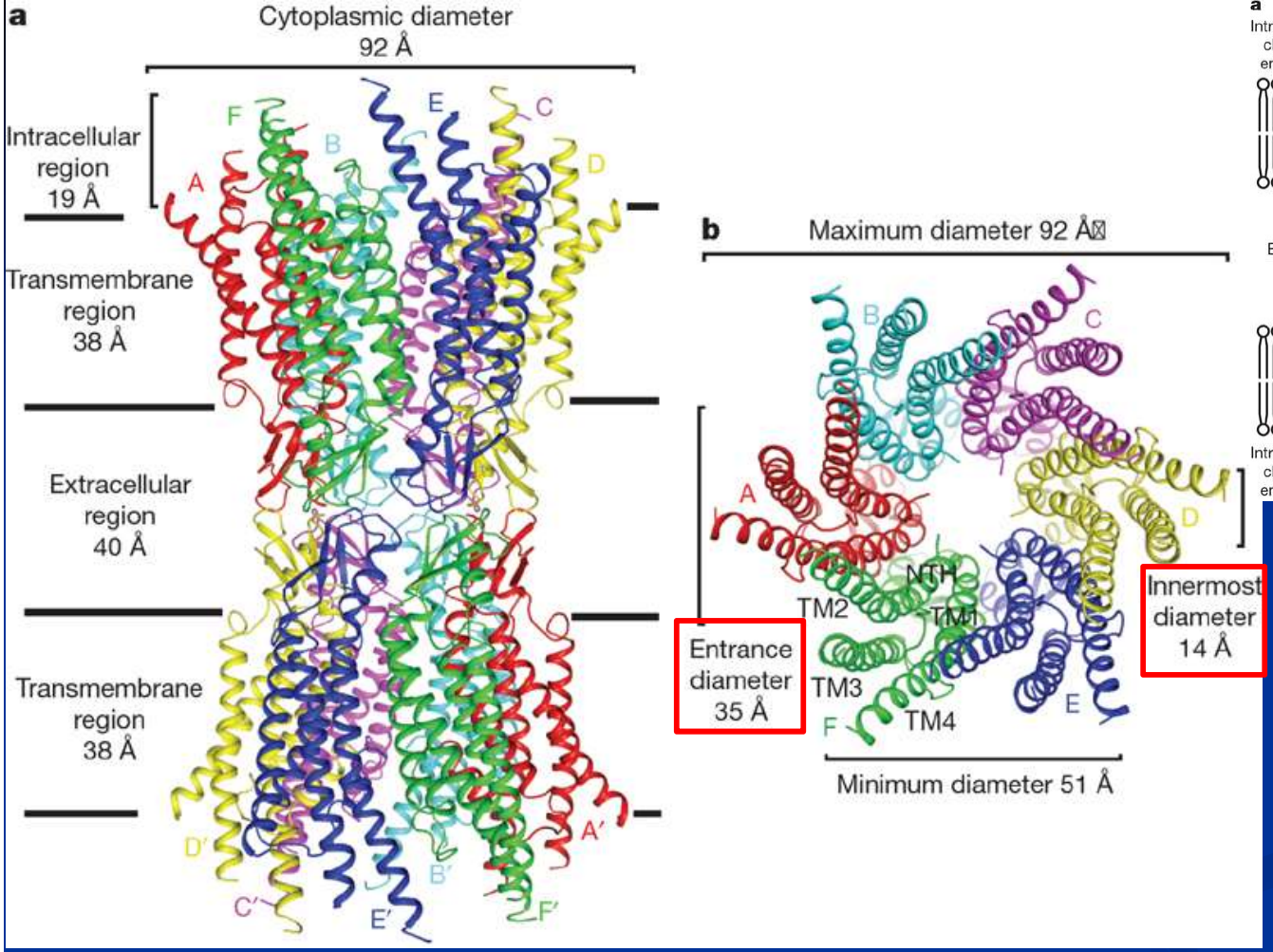
1897 Sherrington called the site, where transferring information from one neuron to the other occurs, synapse

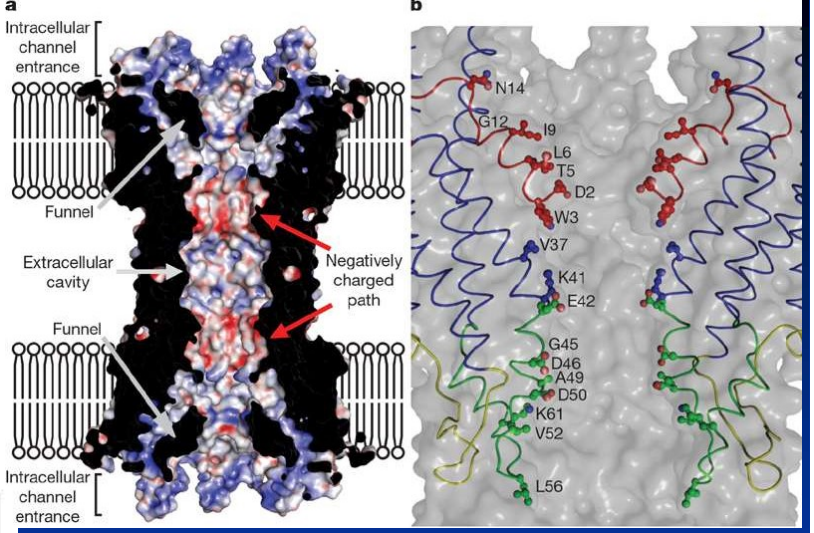
1958 Furshpan & Potter: the existence of electrical synapse in crayfish

1960s Electrical transmission in mammalian cardiac and smooth muscles

1970s Llinas & Korn: electrotonic synapses between mammalian neurons

Electrotonic: potential changes but not action potential



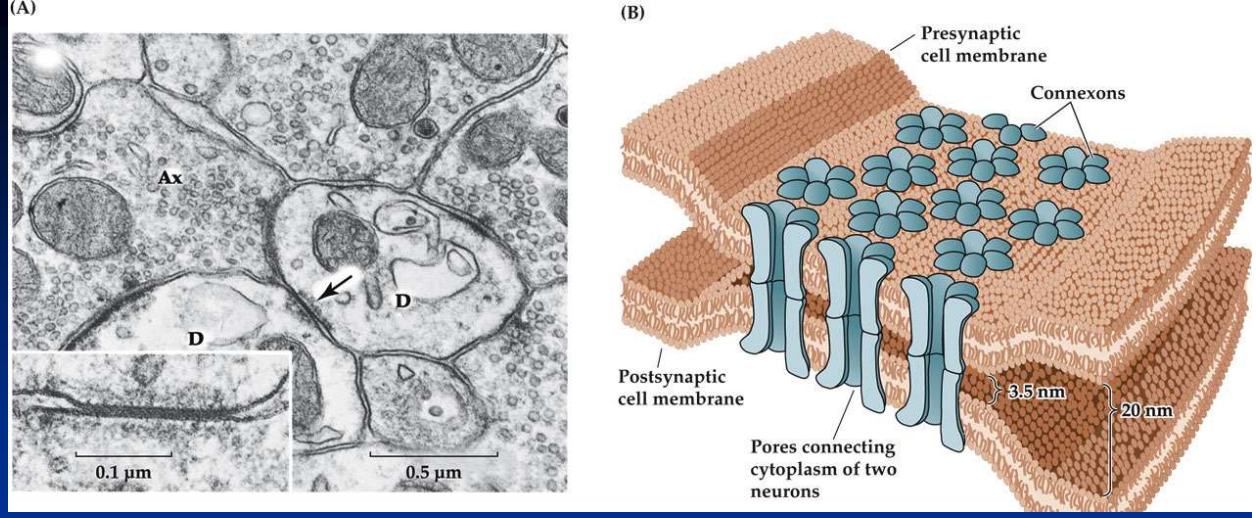


Structure of the connexin 26 gap junction channel at 3.5 Å resolution. *Nature* **458**, 597-602 (2 April 2009)

Connexin
Connexon
Hemi-gap
Gap junction

- Little delay, faster than chemical synapse
- Modulated by cytoplasmic environment: e.g. low pH or high Ca^{2+} usually closes the gap
- Can be bidirectional
- Synchronization for rhythmic electric activities

M1 is the major pore-lining helix; E1 and E2 loops form a tight, double-layered ring around the channel interior



The two rings interdigitate (交錯) in the center of the cleft with an overlap of ~6 nm.

Allow molecules up to 1 nm in diameter and 1 kD in mass.

Selectivity and conductance varies a lot depending on subunits

Cx43 >> Cx32 in ATP (100X) and glutamate (40X)

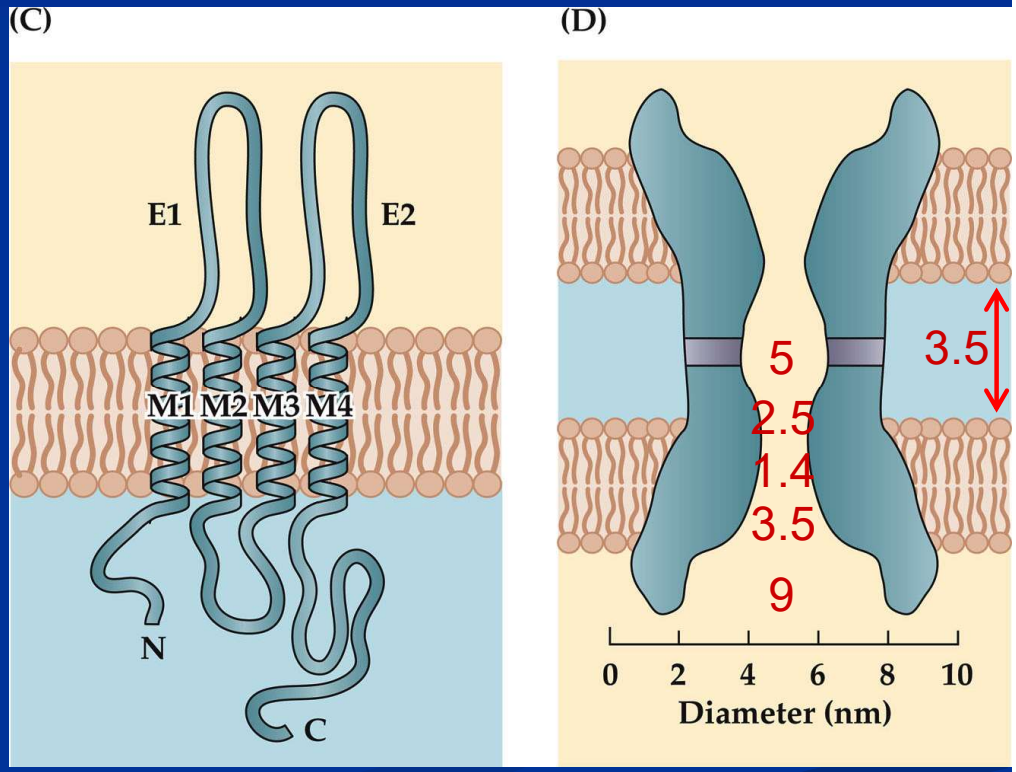
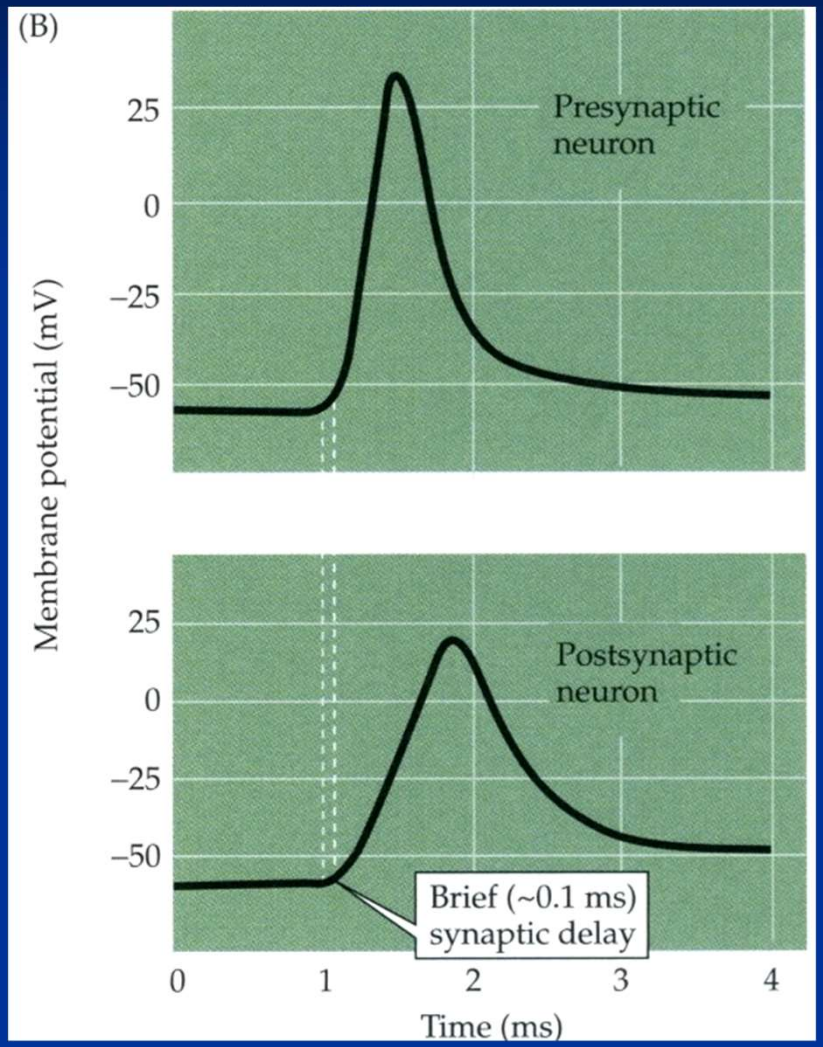


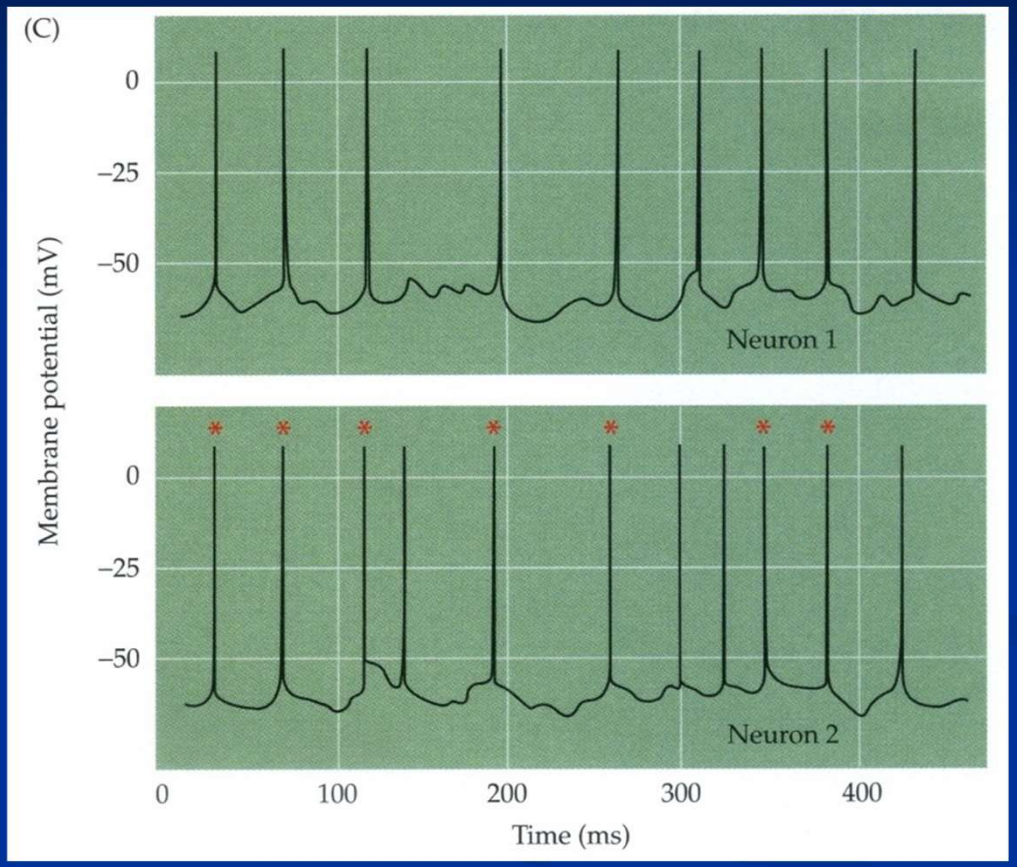
Figure 8.6 Gap Junctions between Neurons

High packing density, >300 connexon pairs in 0.2 μm diameter patch, 15 pS each x 300 = 4.5 nS (siemens, electric conductance)

Fast response, little delay in crayfish



Synchronization in hippocampal interneurons



Purves 5.2

0.2~0.5 ms for chemical synapse

Transmission at electrical synapse

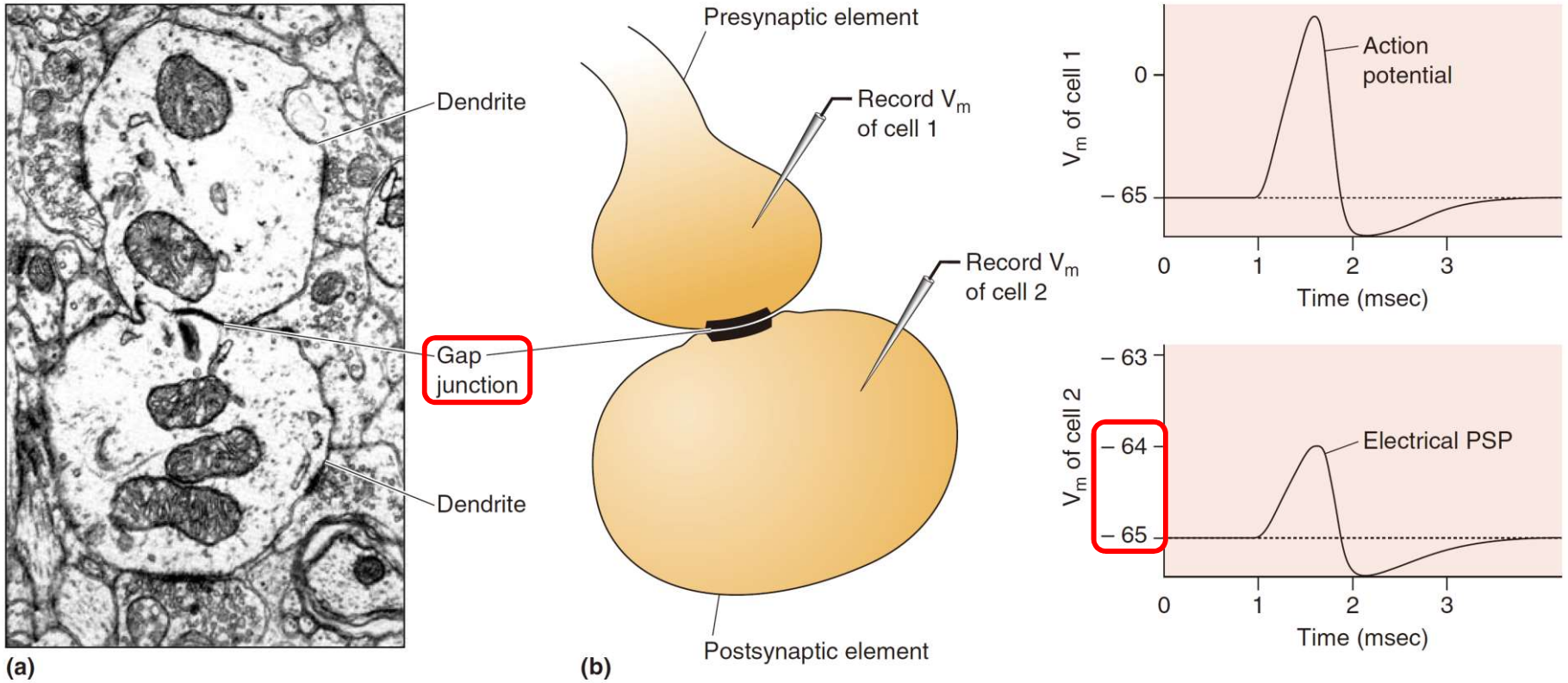


FIGURE 5.2
Electrical synapses. (a) A gap junction interconnecting the dendrites of two neurons constitutes an electrical synapse. (Source: Sloper and Powell, 1978.) **(b)** An action potential generated in one neuron causes a small amount of ionic current to flow through gap junction channels into a second neuron, inducing an electrical PSP.

5.2

Gap junction can control the amount of ionic current that flow through it. Resistor consumes the potential.

Electrical Synapse

Chemical Synapse

Neurotransmitter Synthesis and Release

EPSP and IPSP

Quantal Analysis

EPSP Summation and IPSP Shunting

Modulation

Neuroglia

Chemical Synapse

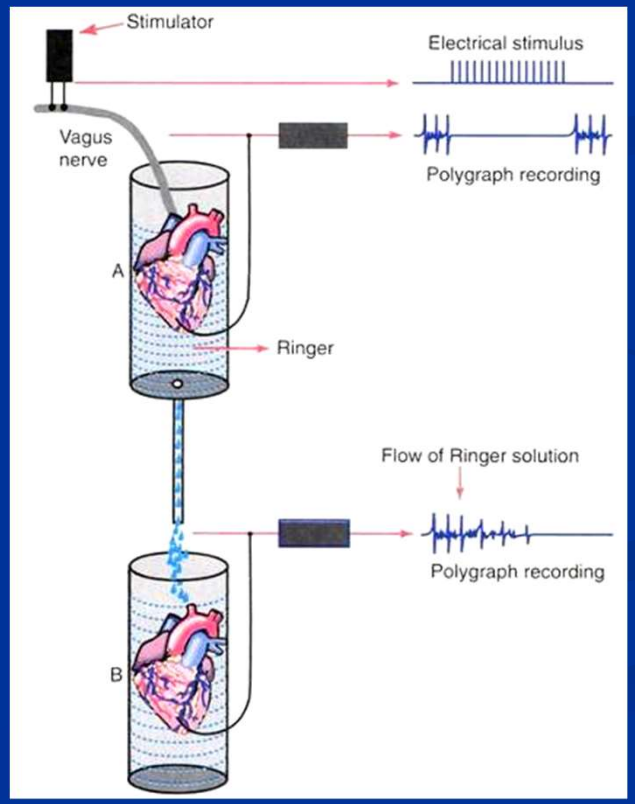
1921 Loewi: the concept of chemical synapse (shared 1936 Nobel Prize with Dale who isolated acetylcholine in 1914)

1951 Eccles: chemical transmitter (shared 1963 Nobel Prize with Hodgkin & Huxley)

1950s Katz: demonstrated chemically mediated fast transmission and the role of Ca^{2+} (1970 Nobel Prize awarded for work on neurotransmitters)

Vagusstoff
(Vagus stuff)

迷走神經



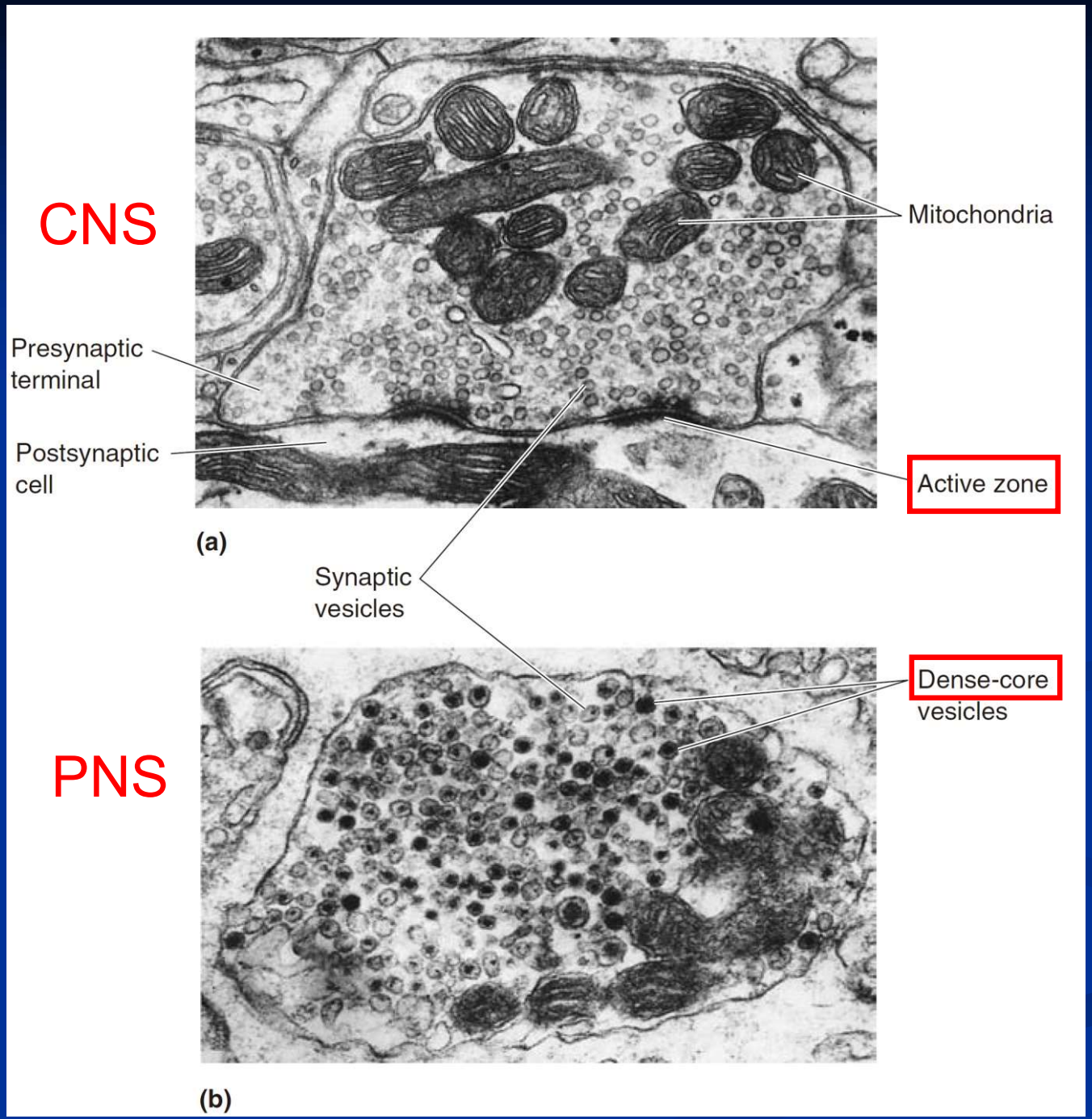
Vagus substance

↓

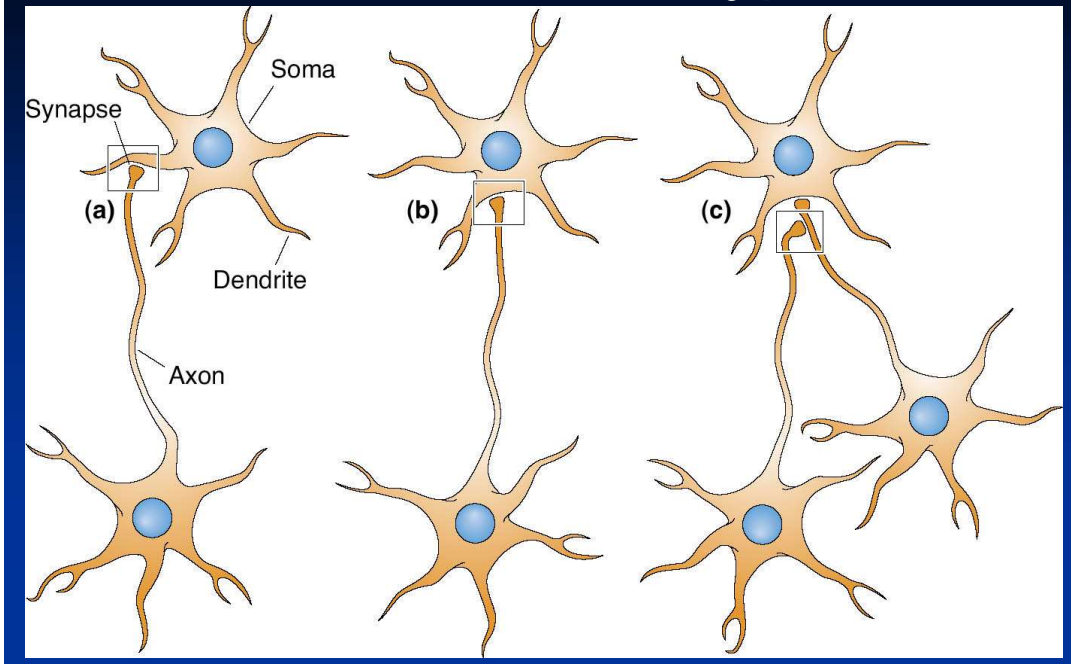
Acetylcholine

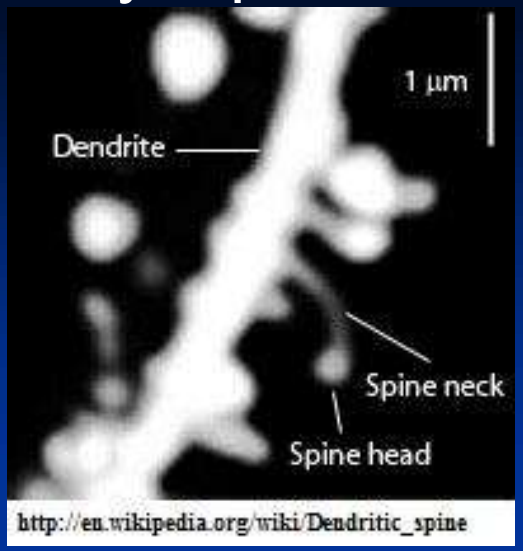
Loewi's dream?

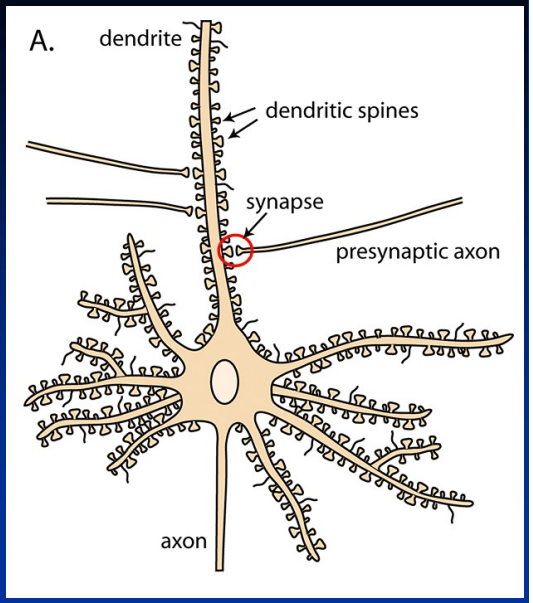
Synapse


CNS
Mitochondria
Presynaptic terminal
Postsynaptic cell
Active zone
(a)
Synaptic vesicles
PNS
Dense-core vesicles
(b)

Types of CNS Synapses







http://sciencespotlights.com/tag/dendrite/

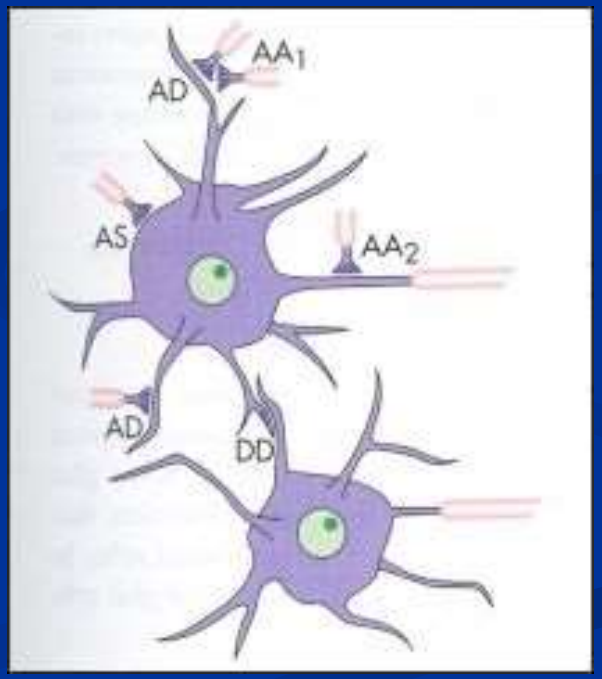
(a) Axodendritic: axon to dendrite

(b) Axosomatic: axon to cell body

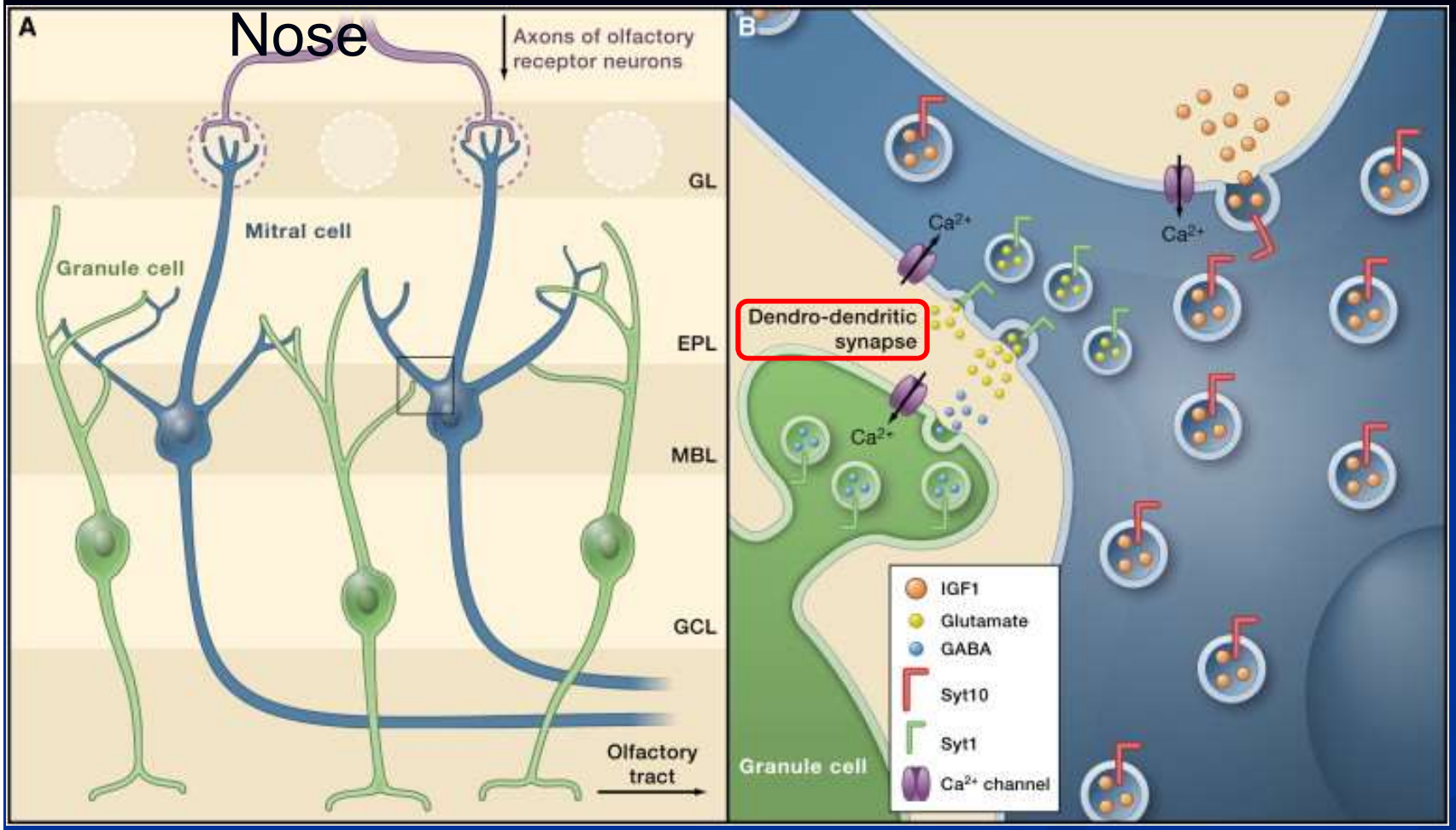
(c) Axoaxonic: axon to axon; inhibitory

Axospinous: axon to dendritic spine

Dendrodendritic: dendrite to dendrite



http://www.cram.com/flashcards/ch-1-introduction-to-the-nervous-system-2398761

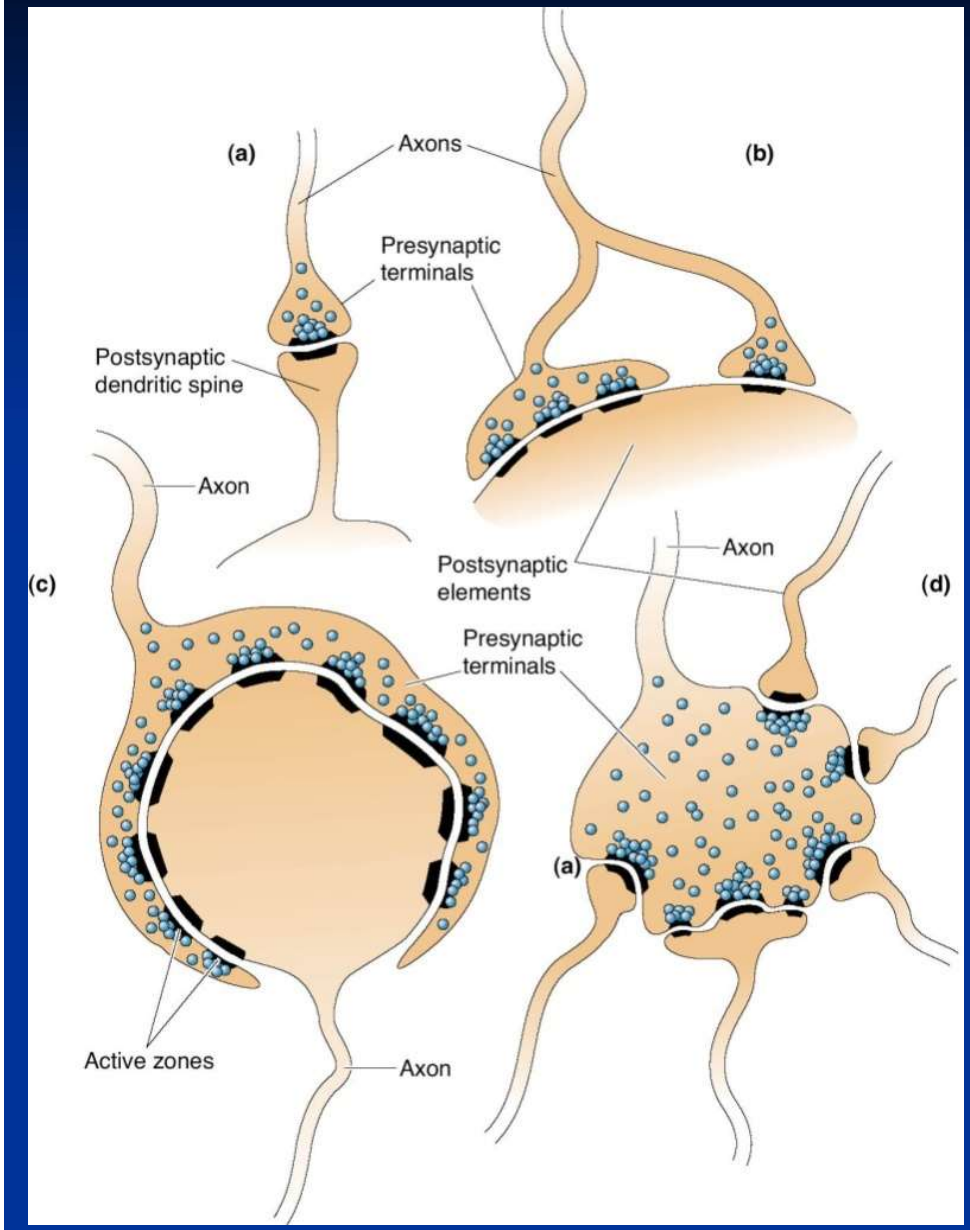


https://neuwritesd.org/2012/09/23/forming-functional-synapses/

The granule cell is the most common type of interneuron in the olfactory bulb. Granule cells are only able to produce inhibition very locally -- which they do by releasing GABA from specialized dendritic spines that contact long horizontal (secondary) dendrites of mitral cells. These inhibitory synapses are typically associated on the same spine with an excitatory synapse made between the mitral cell and interneuron, resulting in a reciprocal **dendrodendritic** synaptic connection.

http://neurosciences.case.edu/faculty/strowbridge/OlfactoryBulb/bulb1.htm

Various Sizes and Shapes of CNS Synapses



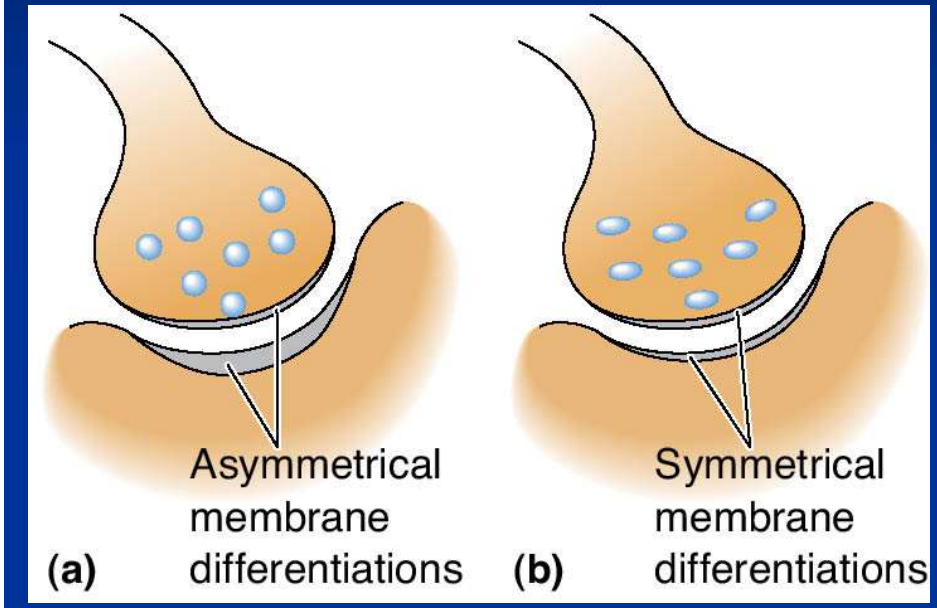
http://www.sciencedirect.com/science/article/pii/S0166223697011703

Central synapses exhibit a wide variety of structural features. (A) A small bouton containing a single synaptic specialization in contact with a dendritic spine. (B) An axon making multiple synaptic contacts with a soma or dendritic shaft of a postsynaptic neuron. Large boutons can contain many synaptic specializations. (C) An example of a calyx-type somatic terminal that might contain over a thousand individual synaptic specializations. (D) A glomerular terminal in contact with the dendrites of many different postsynaptic neurons.

Two Categories of CNS Synaptic Membrane Differentiations

(a) Gray's type I: asymmetrical, usually excitatory

(b) Gray's type II: symmetrical, usually inhibitory



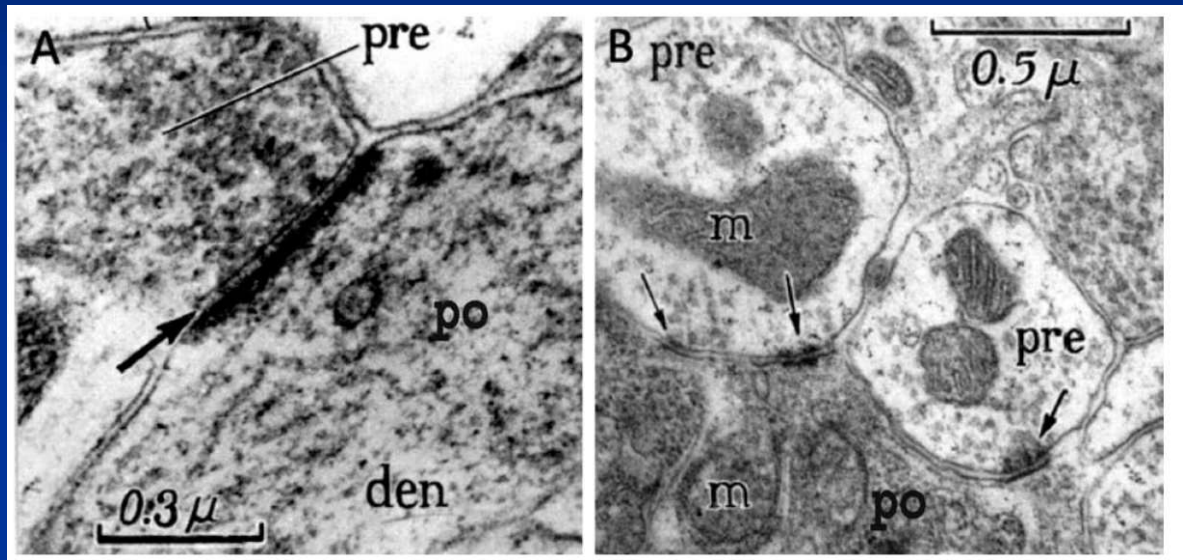
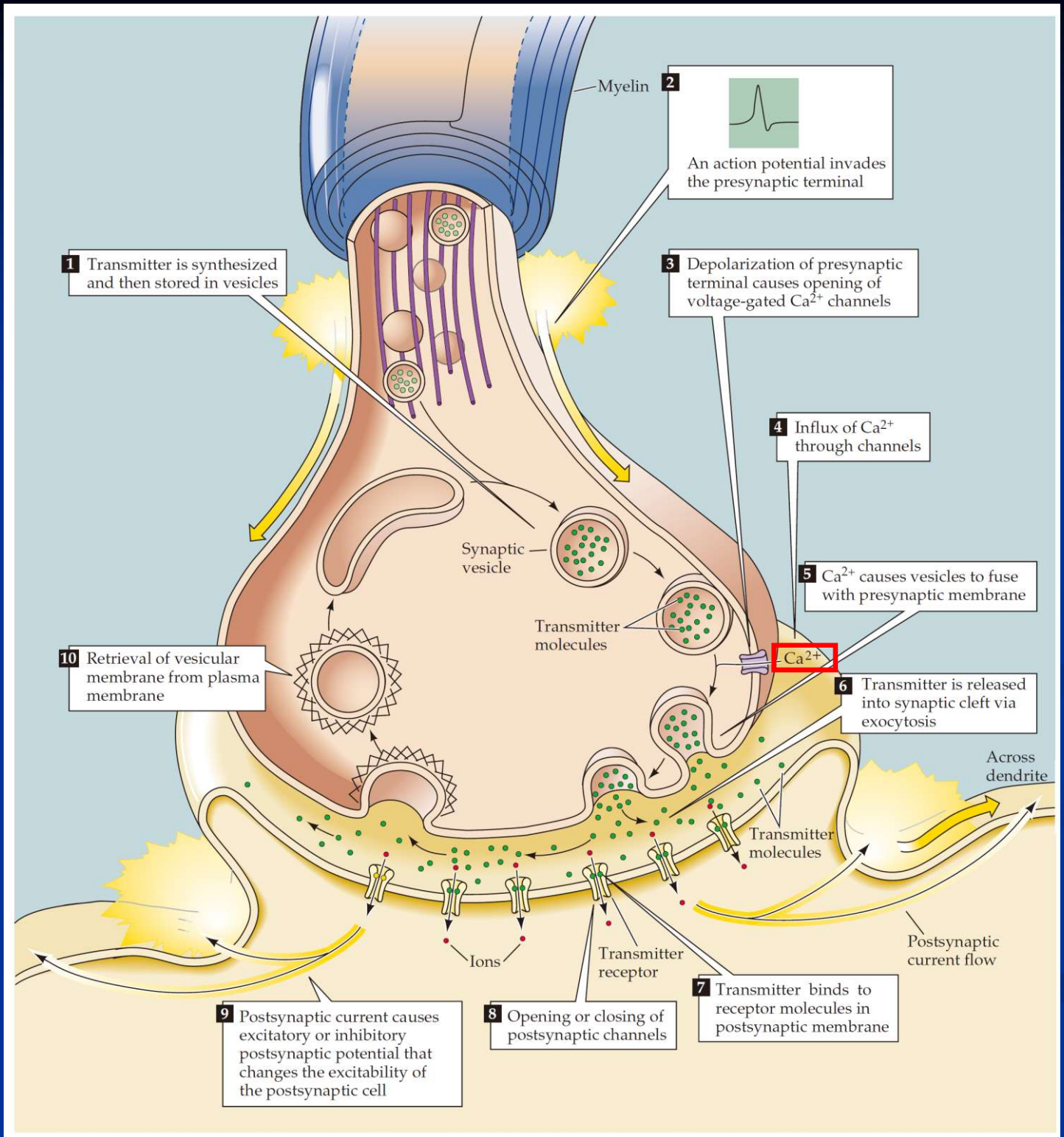


Fig. 2. Arrows indicate Gray Type I (asymmetric) (**A**) and Type II (symmetric) (**B**) synapses. In (A) the postsynaptic membrane is thicker than the presynaptic one. In (B) the presynaptic and postsynaptic membranes are of equal thickness. den, dendrite; m, mitochondrion; po, postsynaptic; pre, presynaptic. Modified from Gray (1959).

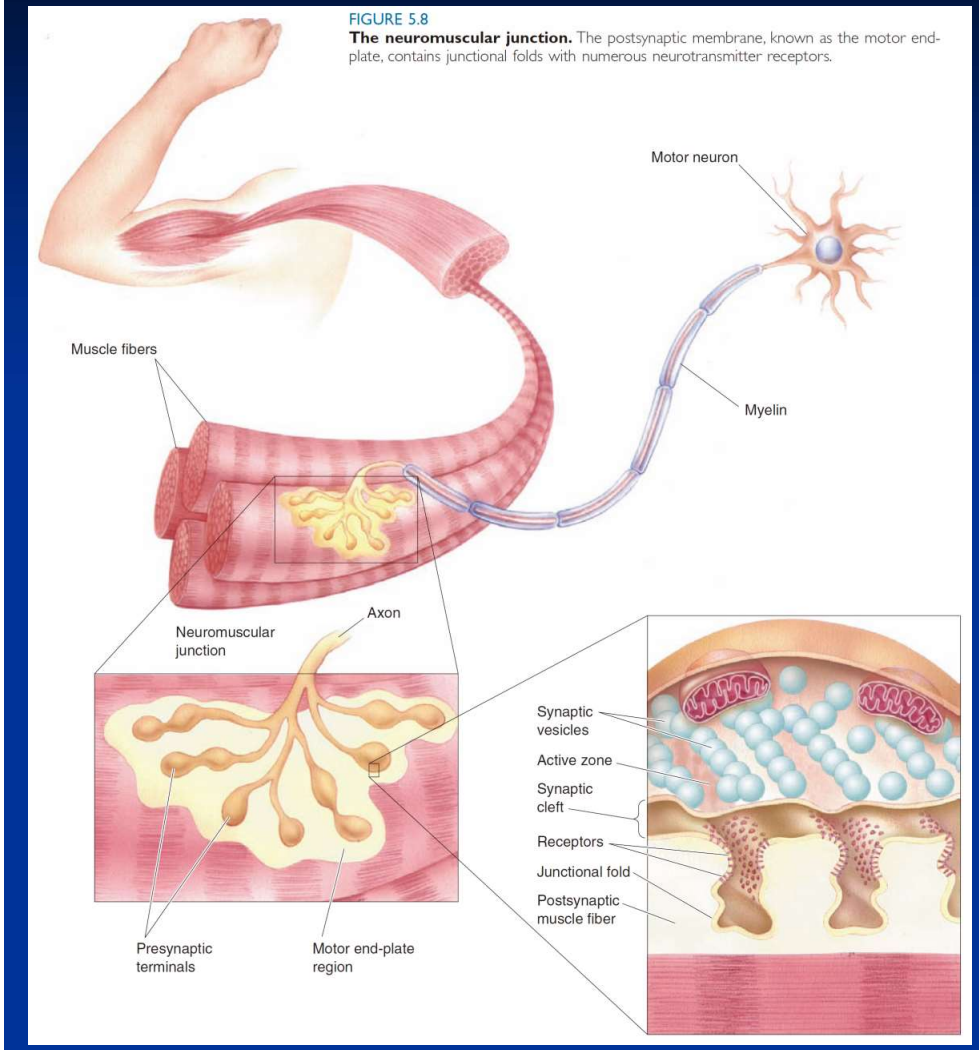
Synapse. 2011 Nov;65(11):1222-30.

Synapse

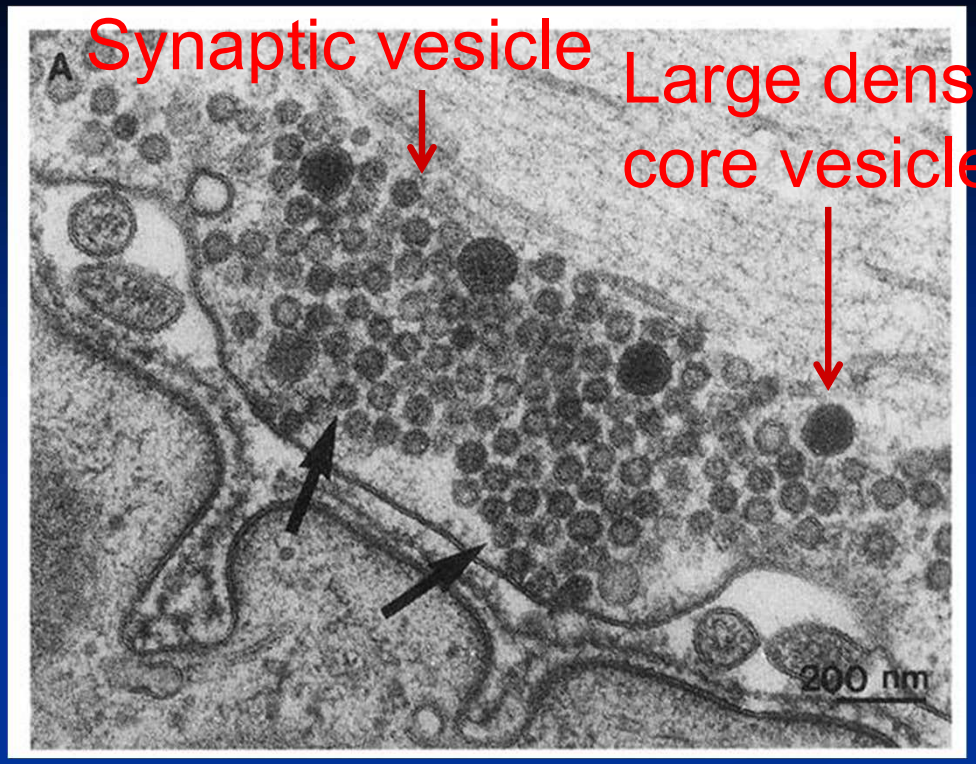


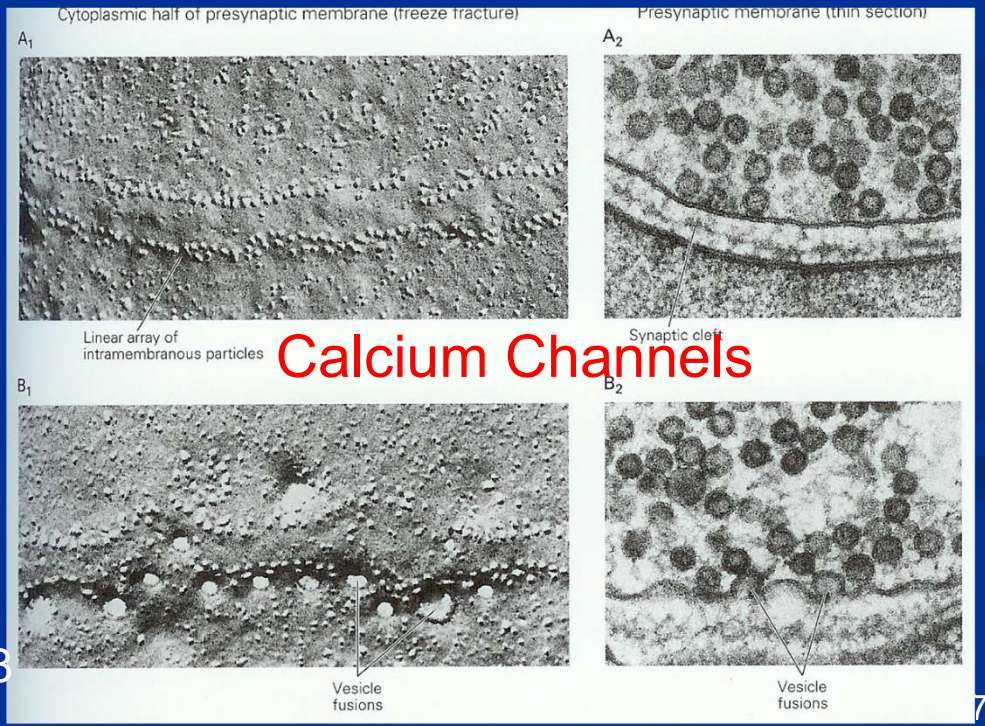
Purves 5.3

Neuromuscular Junction



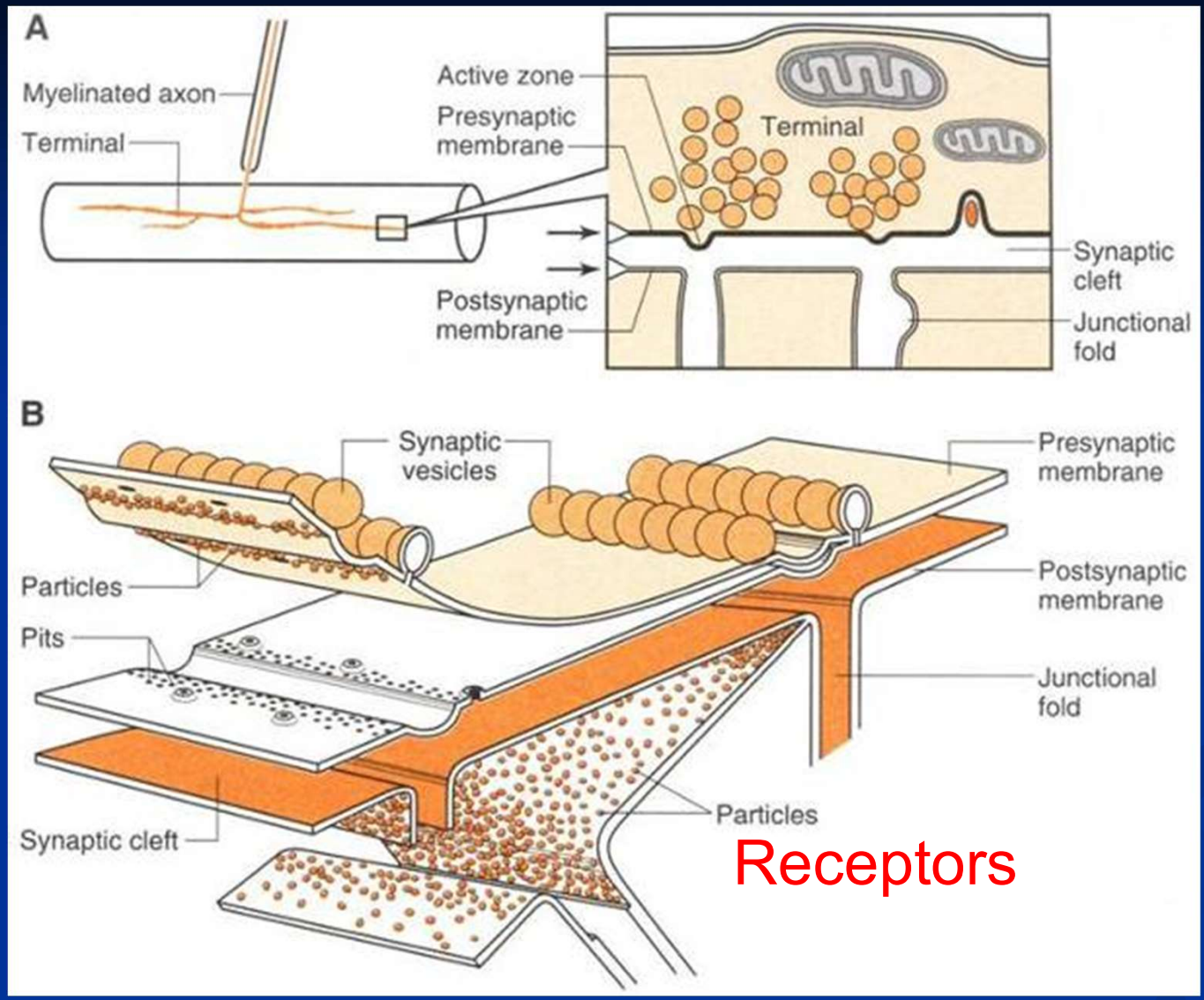
5.8



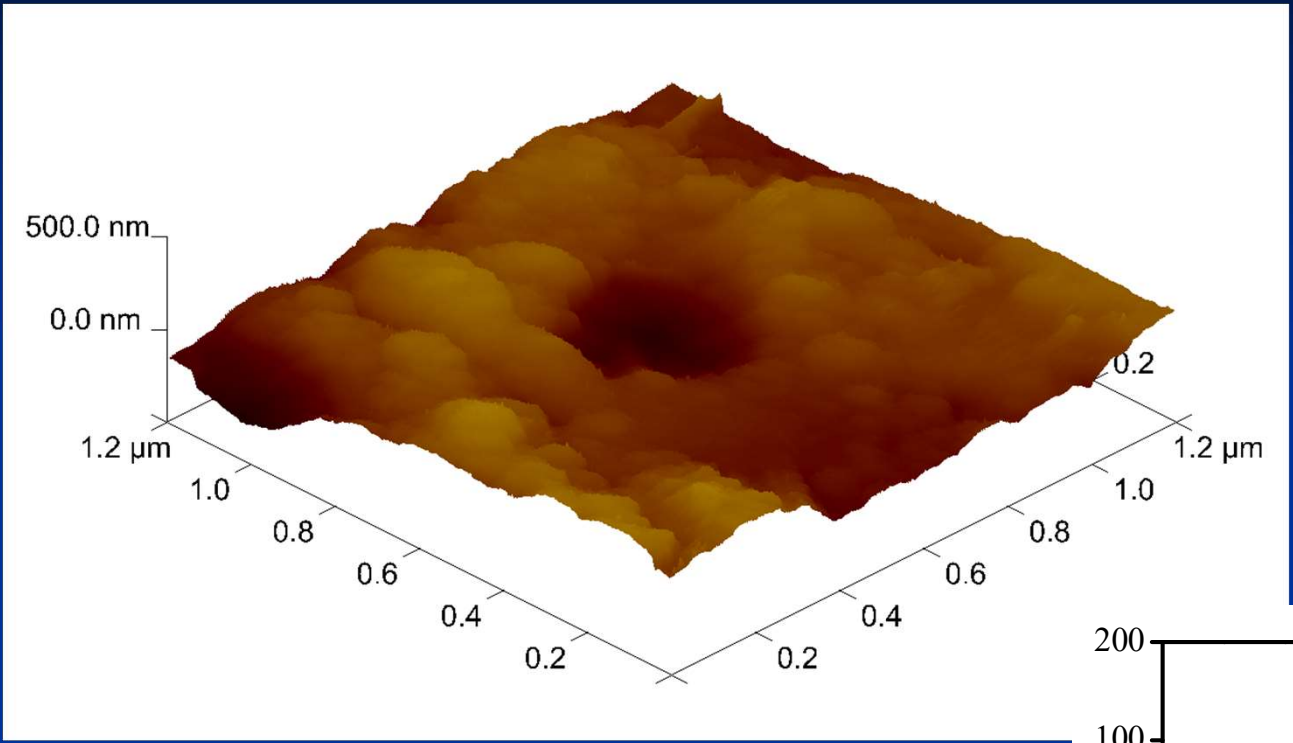


Kandel 14.8

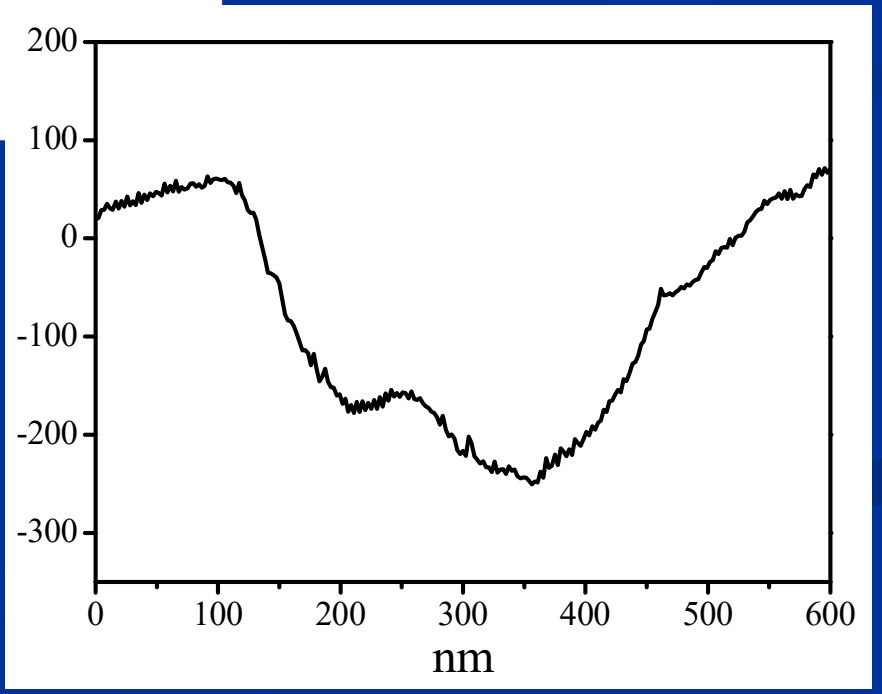
Ca^{2+} channels



Chromaffin cell surface scanned by atomic force microscopy



Pan's Lab



Chemical Synapse

Three Types of Neurotransmitters

Table 5.1 **The Major Neurotransmitters**

AMINO ACIDS	AMINES	PEPTIDES
Gamma-aminobutyric acid (GABA)	Acetylcholine (ACh)	Cholecystokinin (CCK)
Glutamate (Glu)	Dopamine (DA)	Dynorphin
Glycine (Gly)	Epinephrine	Enkephalins (Enk)
	Histamine	N-acetylaspartylglutamate (NAAG)
	Norepinephrine (NE)	Neuropeptide Y
	Serotonin (5-HT)	Somatostatin
		Substance P
		Thyrotropin-releasing hormone
		Vasoactive intestinal polypeptide (VIP)

- Synaptic delay (0.2~0.5 ms)
- Amplify signals
- Active zones
- One-way
- Same chemical neurotransmitter can have multiple effects depending on the receptor it binds to.
- Receptors of the synapse are of two types: ionotropic or metabotropic

Two Types of Receptors

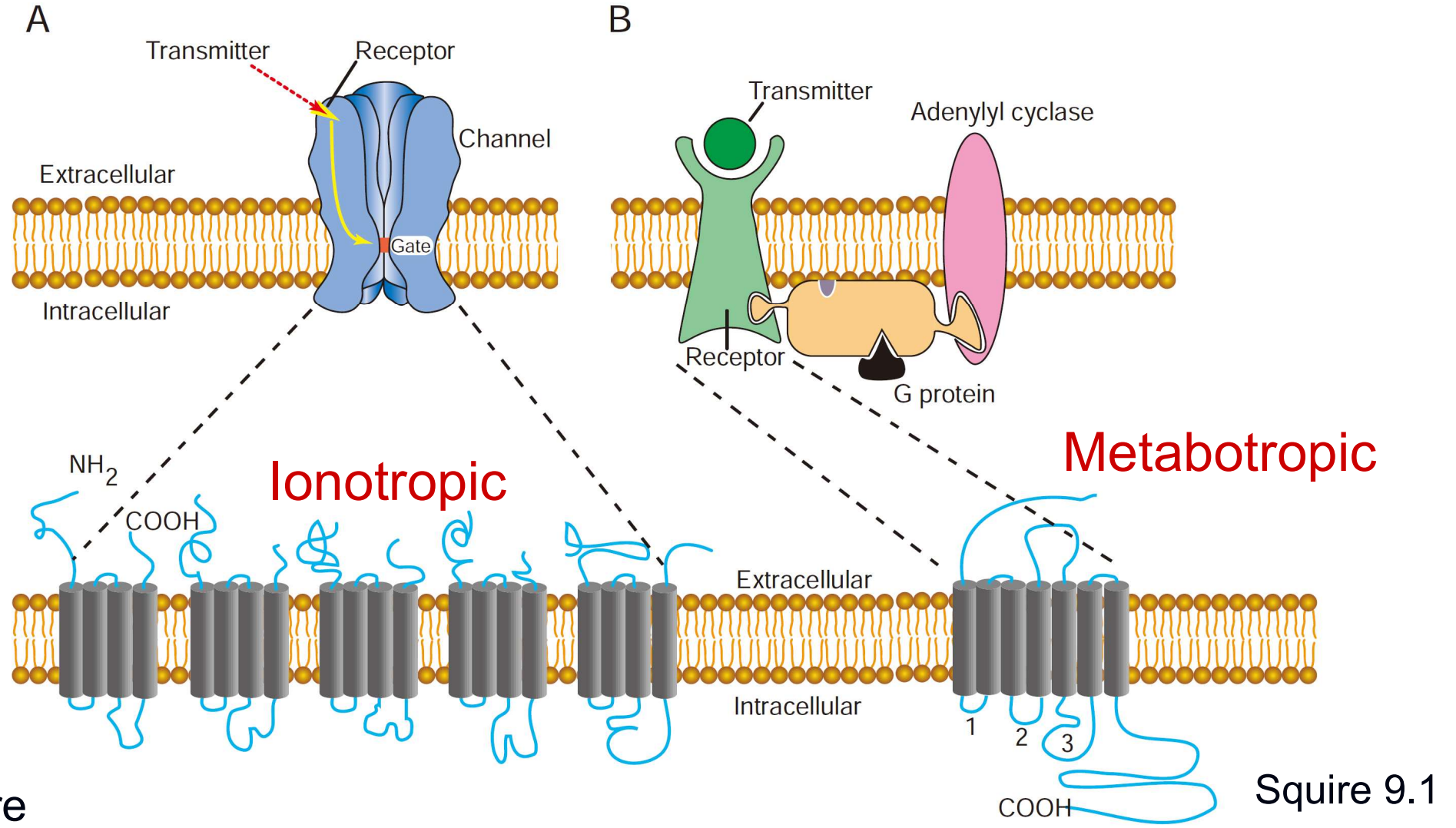


FIGURE 9.1 Structural comparison of ionotropic and metabotropic receptors. (A) *Ionotropic receptors* bind transmitter, and this binding translates directly into the opening of the ion channel through a series of conformational changes. Ionotropic receptors are composed of multiple subunits. The five subunits that together form the functional nAChR are shown. Note that each of the nAChR subunits wraps back and forth through the membrane four times and that the mature receptor is composed of five subunits. (B) *Metabotropic receptors* bind transmitter and, through a series of conformational changes, bind to G-proteins and activate them. G-proteins then activate enzymes such as adenylyl cyclase to produce cAMP. Through the activation of cAMP-dependent protein kinase, ion channels become phosphorylated, which affects their gating properties. Metabotropic receptors are single subunits. They contain seven transmembrane-spanning segments, with the cytoplasmic loops formed between the segments providing the points of interactions for coupling to G-proteins. Adapted from Kandel (1991).

Electrical Synapse

Chemical Synapse

Neurotransmitter Synthesis and Release

EPSP and IPSP

Quantal Analysis

EPSP Summation and IPSP Shunting

Modulation

Neuroglia

Different pathways for different neurotransmitters

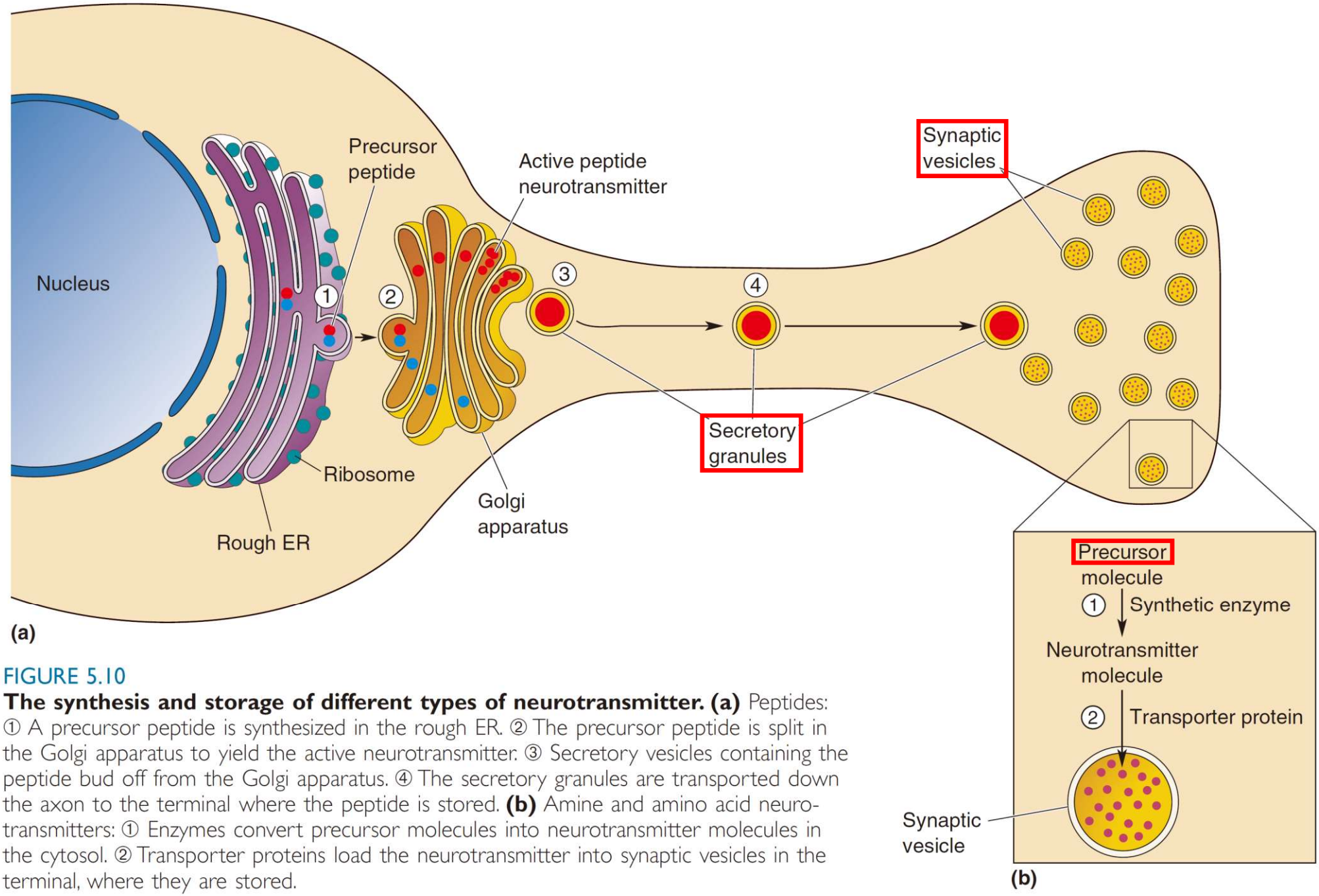
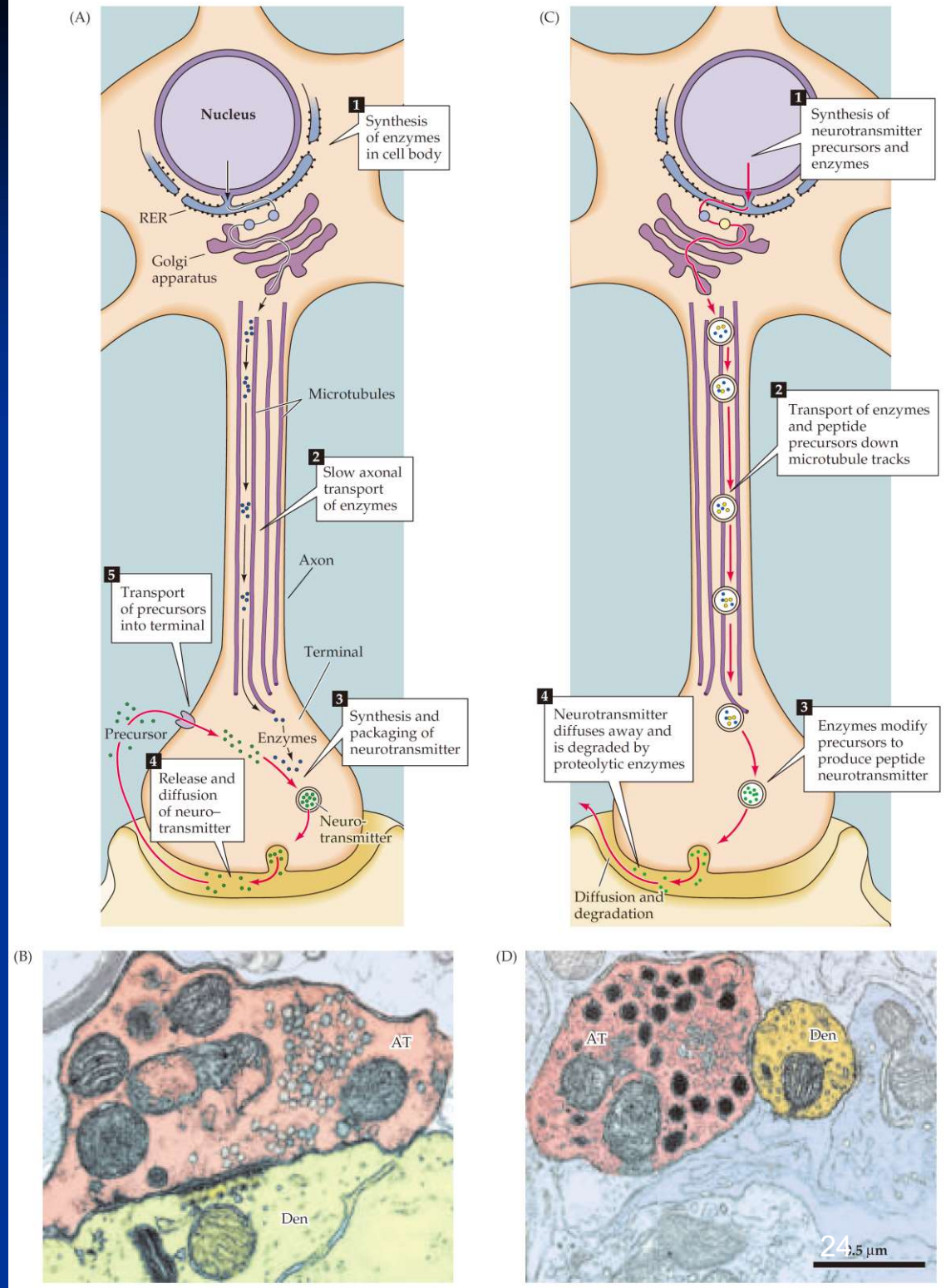


FIGURE 5.10

The synthesis and storage of different types of neurotransmitter. (a) Peptides: ① A precursor peptide is synthesized in the rough ER. ② The precursor peptide is split in the Golgi apparatus to yield the active neurotransmitter. ③ Secretory vesicles containing the peptide bud off from the Golgi apparatus. ④ The secretory granules are transported down the axon to the terminal where the peptide is stored. **(b)** Amine and amino acid neurotransmitters: ① Enzymes convert precursor molecules into neurotransmitter molecules in the cytosol. ② Transporter proteins load the neurotransmitter into synaptic vesicles in the terminal, where they are stored.

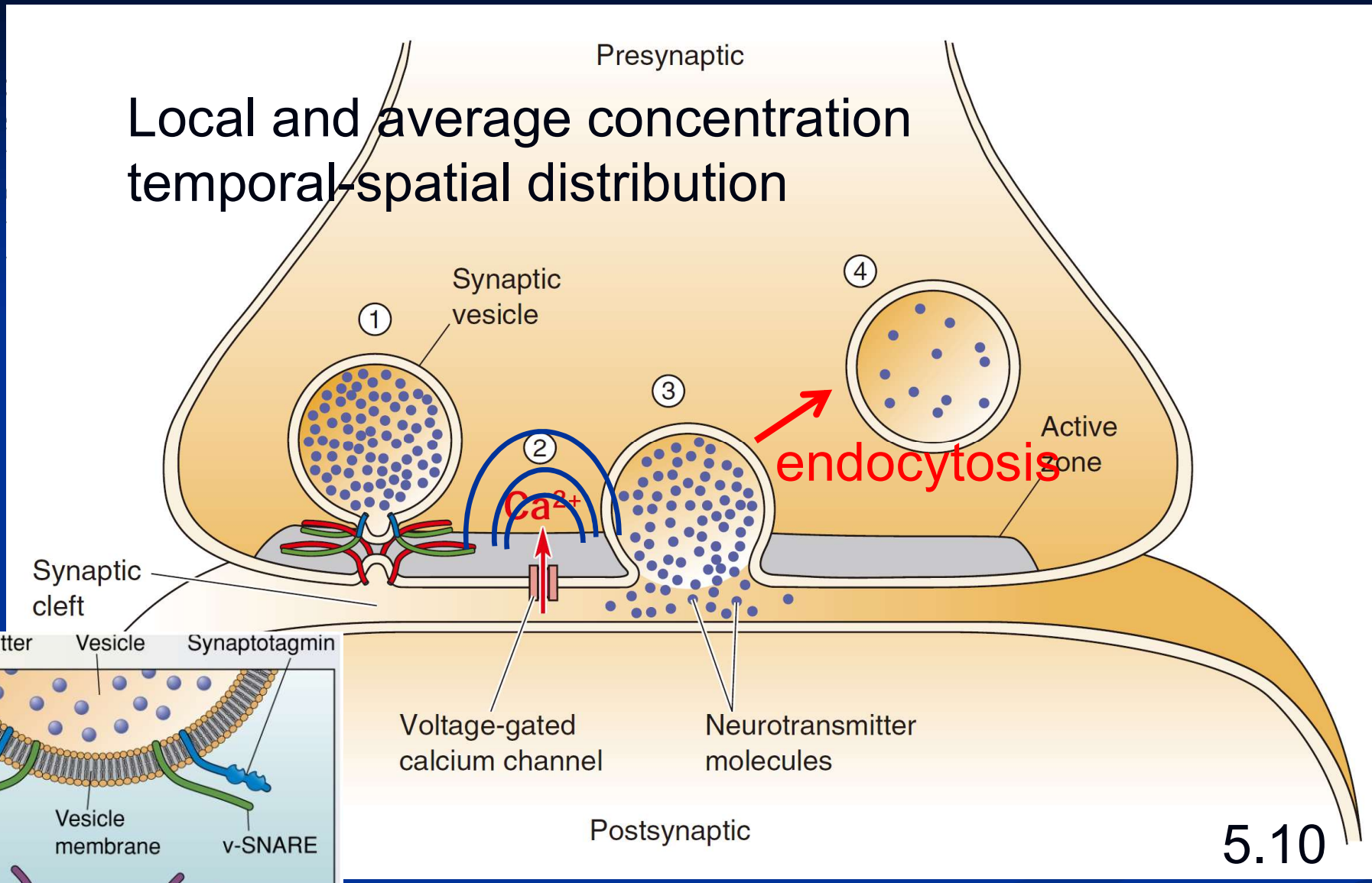
1. Small clear core vesicles: 40~60 nm in diameter, synthesized in the terminal, mostly small chemicals
2. Large dense core vesicles: 90~250 nm, peptides synthesized in the soma

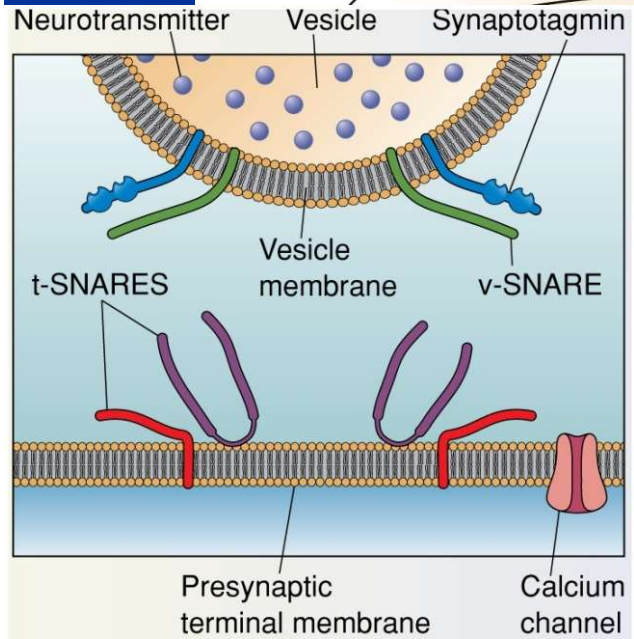
Purves 5.5



Ca^{2+} Microdomain

Local and average concentration
temporal-spatial distribution

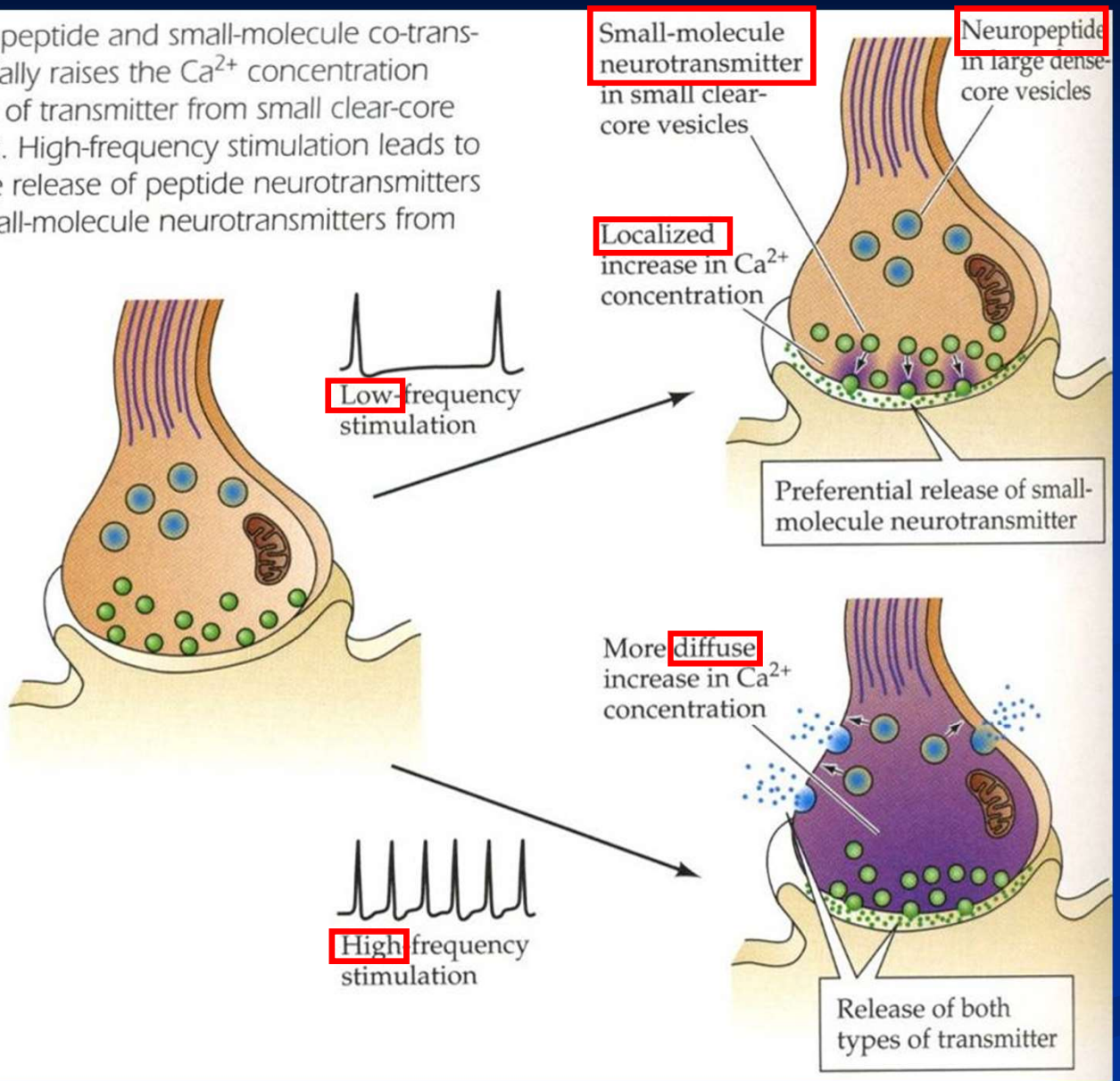




t- target
v- vesicle

Depends on the pattern of signaling

Figure 5.12 Differential release of neuropeptide and small-molecule co-transmitters. Low-frequency stimulation preferentially raises the Ca^{2+} concentration close to the membrane, favoring the release of transmitter from small clear-core vesicles docked at presynaptic specializations. High-frequency stimulation leads to a more general increase in Ca^{2+}, causing the release of peptide neurotransmitters from large dense-core vesicles, as well as small-molecule neurotransmitters from small clear-core vesicles.



Purves 5.12

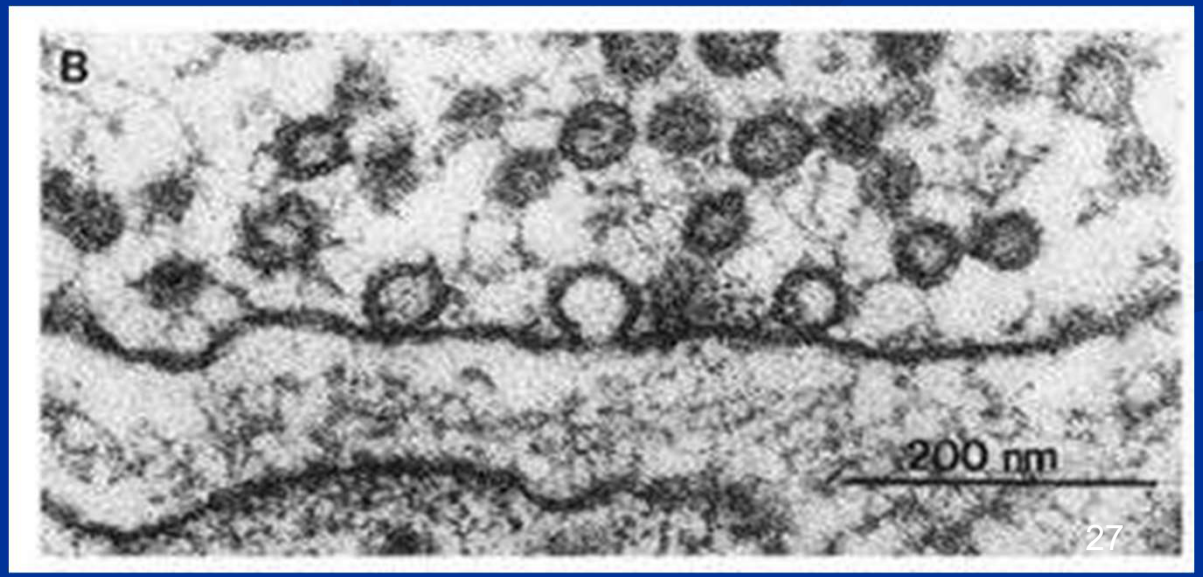
Active Zone

Presynaptic terminal membrane contains:

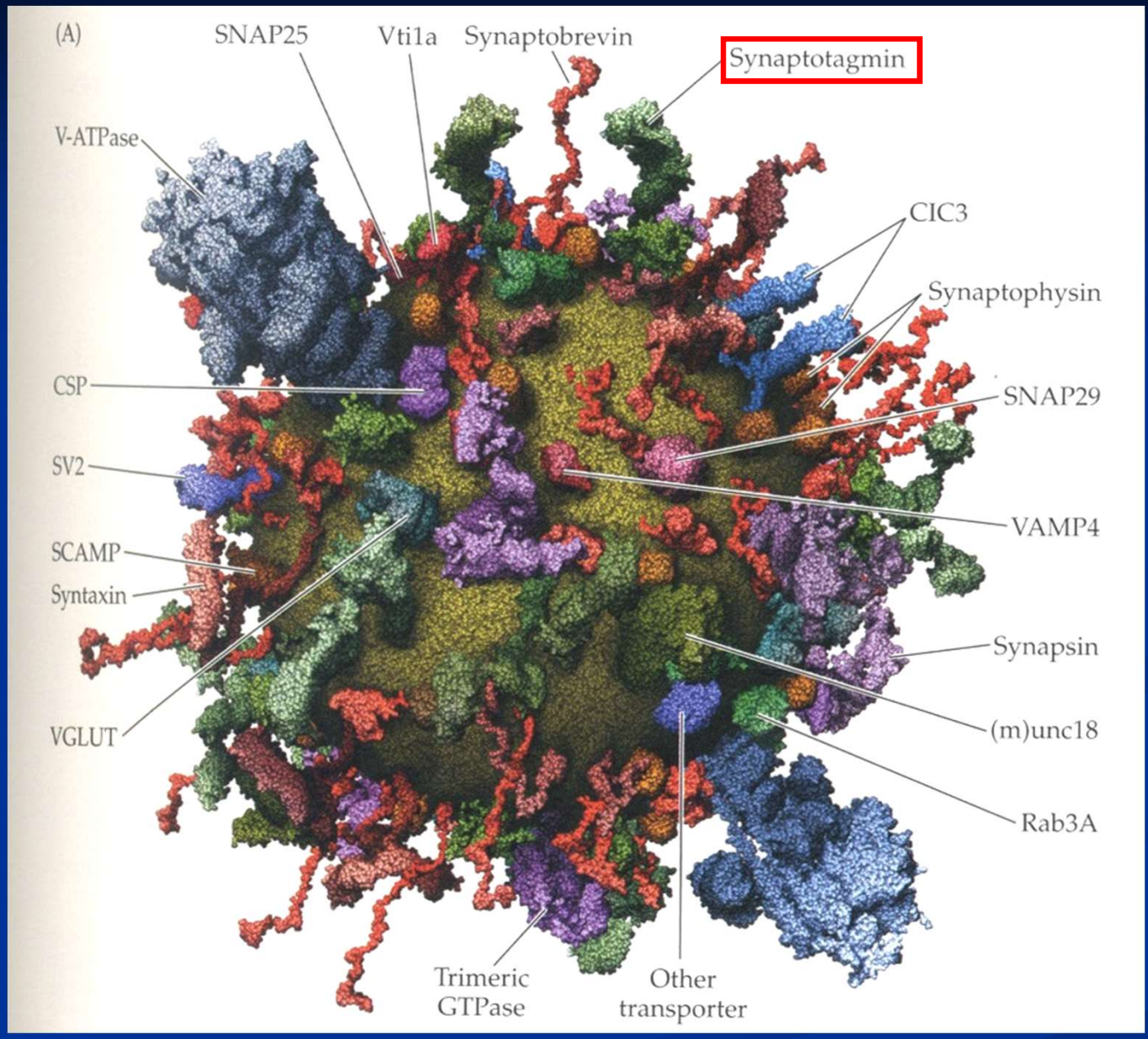
- specialized proteins for attachment of synaptic vesicles
- voltage sensitive Ca^{2+} channels
- sometimes other channels as well

For neuromuscular junction

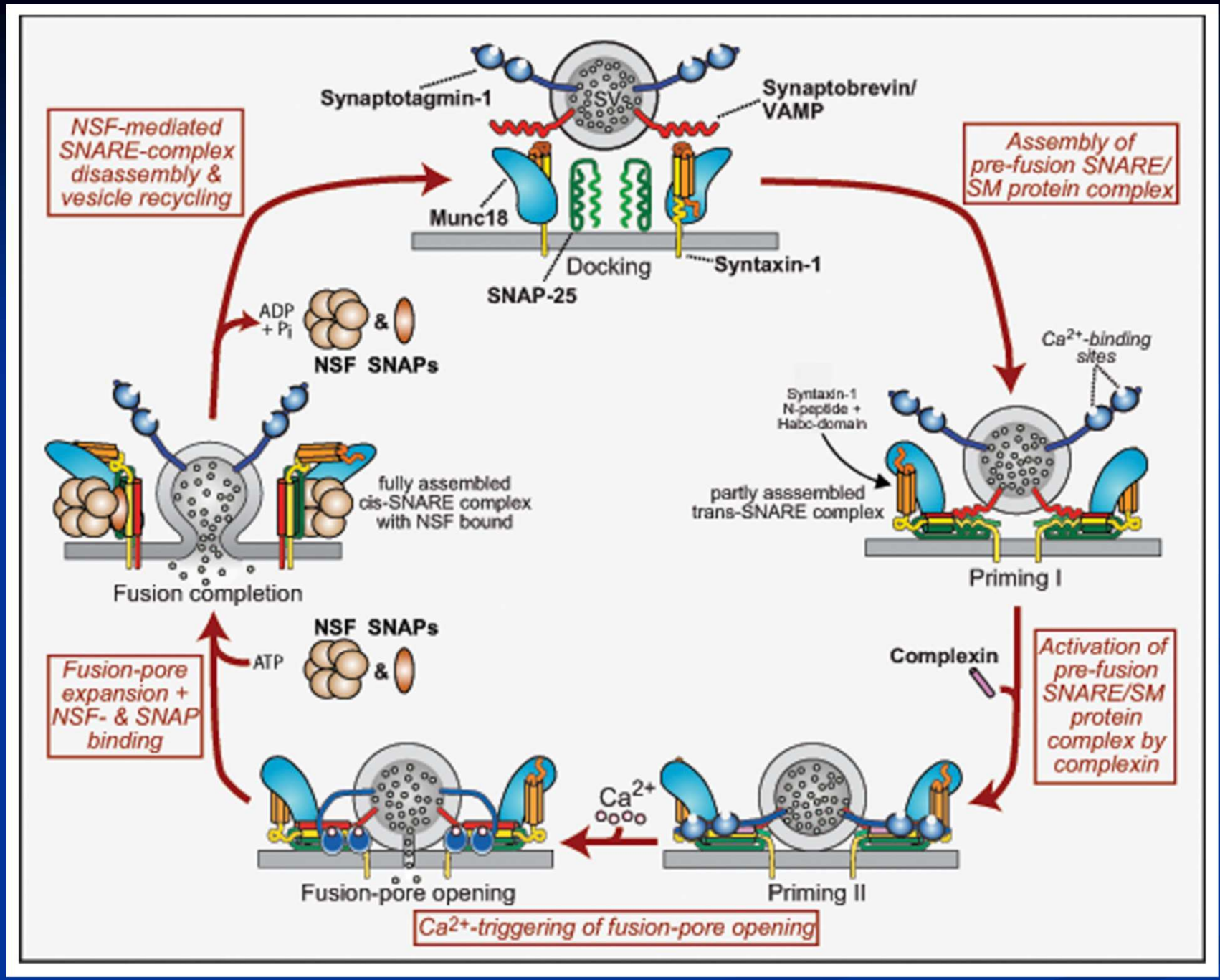
- synaptic vesicles in active zone aligned in double rows
- 20 to 30 nm from these are double rows of particles embedded in synaptic membrane, evidence these are Ca^{2+} channels.



Many proteins on the vesicles



Purves 5.13

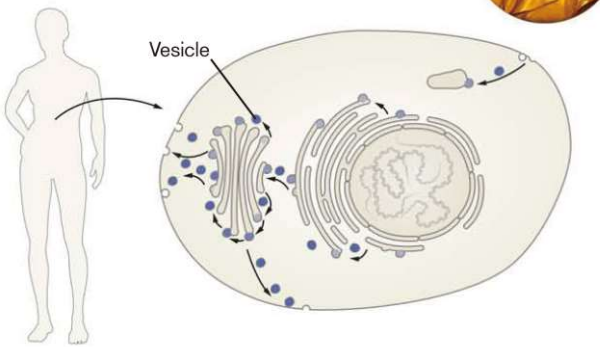


Neurotransmitter Release: The Last Millisecond in the Life of a Synaptic Vesicle (2013) Neuron 80(3), 675–690

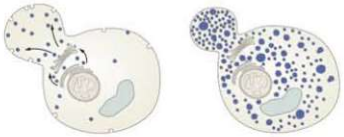
http://www.sciencedirect.com/science/article/pii/S0896627313009264

The Nobel Prize in Physiology or Medicine 2013

Proper functioning of the cells in the body depends on getting the right molecules to the right place at the right time. Some molecules, such as insulin, need to be exported out of the cell, whereas others are needed at specific sites inside the cell. Molecules produced in the cell were known to be packaged into vesicles (pictured in blue), but how these vesicles correctly deliver their cargo was a mystery.



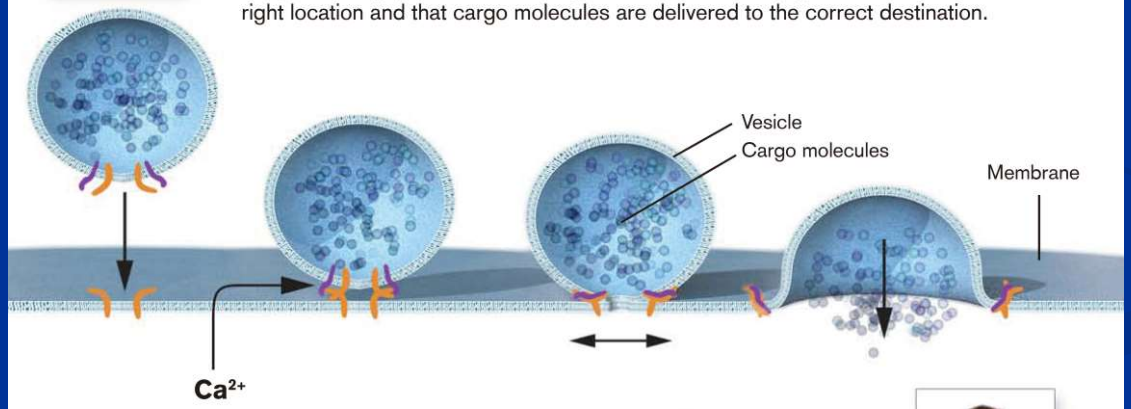
Randy W. Schekman



Randy W. Schekman discovered genes encoding proteins that are key regulators of vesicle traffic. Comparing normal (left) with genetically mutated yeast cells (right) in which vesicle traffic was disturbed, he identified genes that control transport to different compartments and to the cell surface.

James E. Rothman

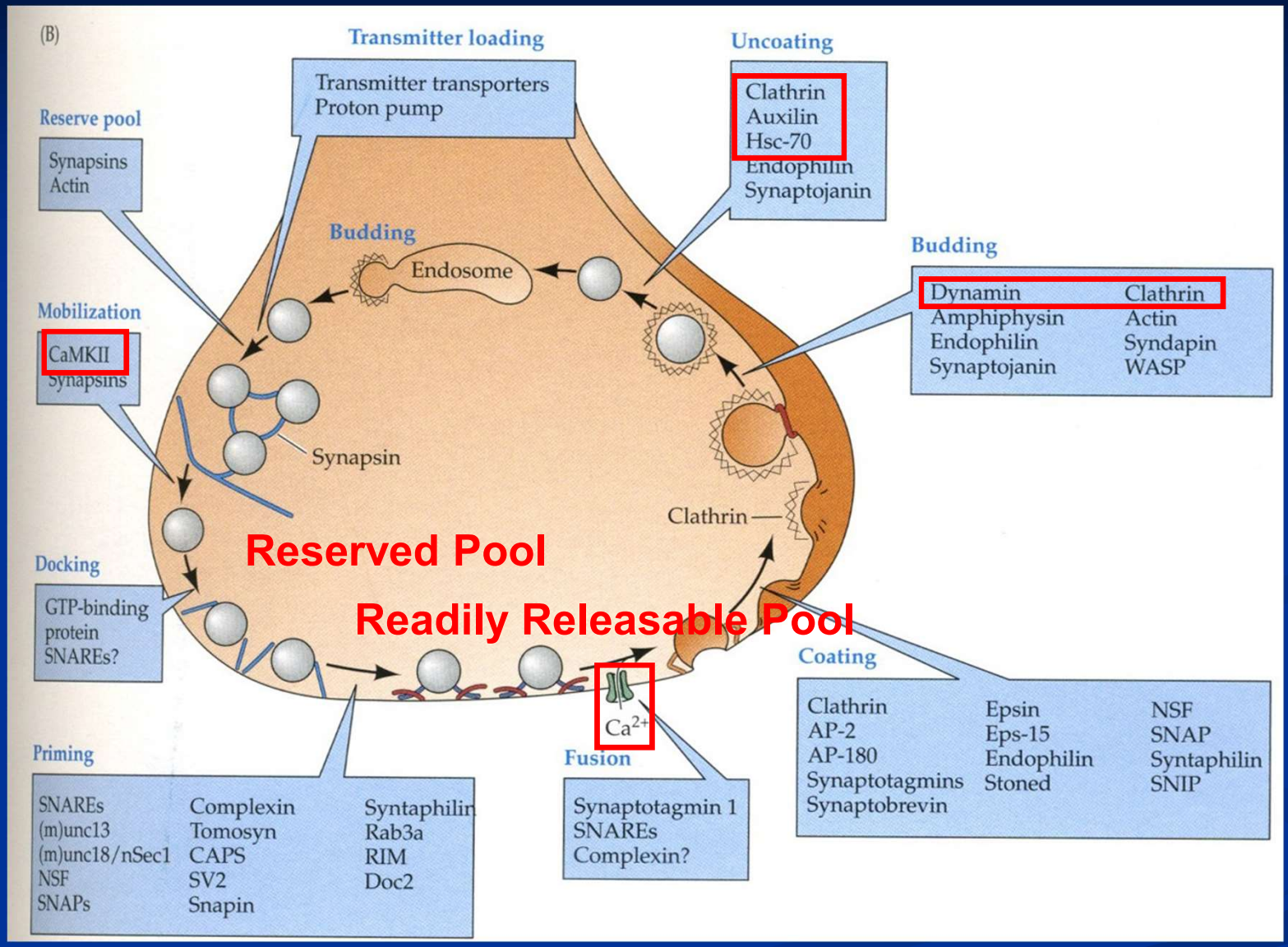
James E. Rothman discovered that a protein complex (pictured in orange) enables vesicles to fuse with their target membranes. Proteins on the vesicle bind to specific complementary proteins on the target membrane, ensuring that the vesicle fuses at the right location and that cargo molecules are delivered to the correct destination.



Thomas C. Südhof

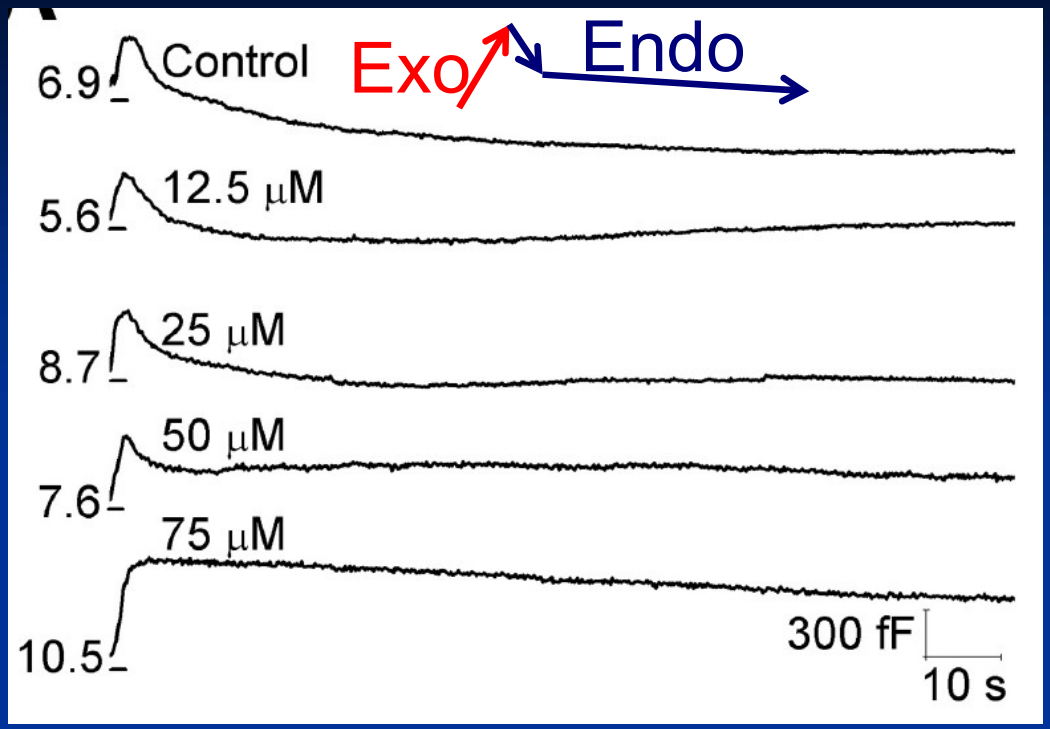
Thomas C. Südhof studied how signals are transmitted from one nerve cell to another in the brain, and how calcium controls this process. He identified molecular machinery (pictured in purple) that senses calcium ions (Ca^{2+}) and triggers vesicle fusion, thereby explaining how temporal precision is achieved and how signaling substances can be released from the vesicles on command.

Vesicle Recycling

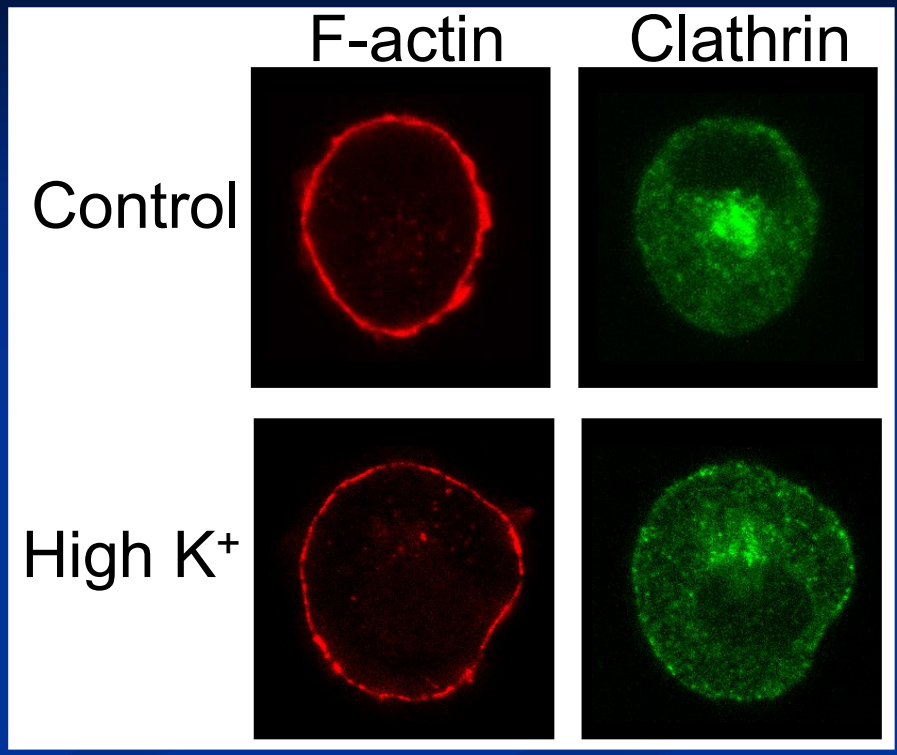


Purves 5.13

Inhibiting dynamin by dynasore



Chromaffin cell stimulated by high K^+ buffer



Pan's Lab

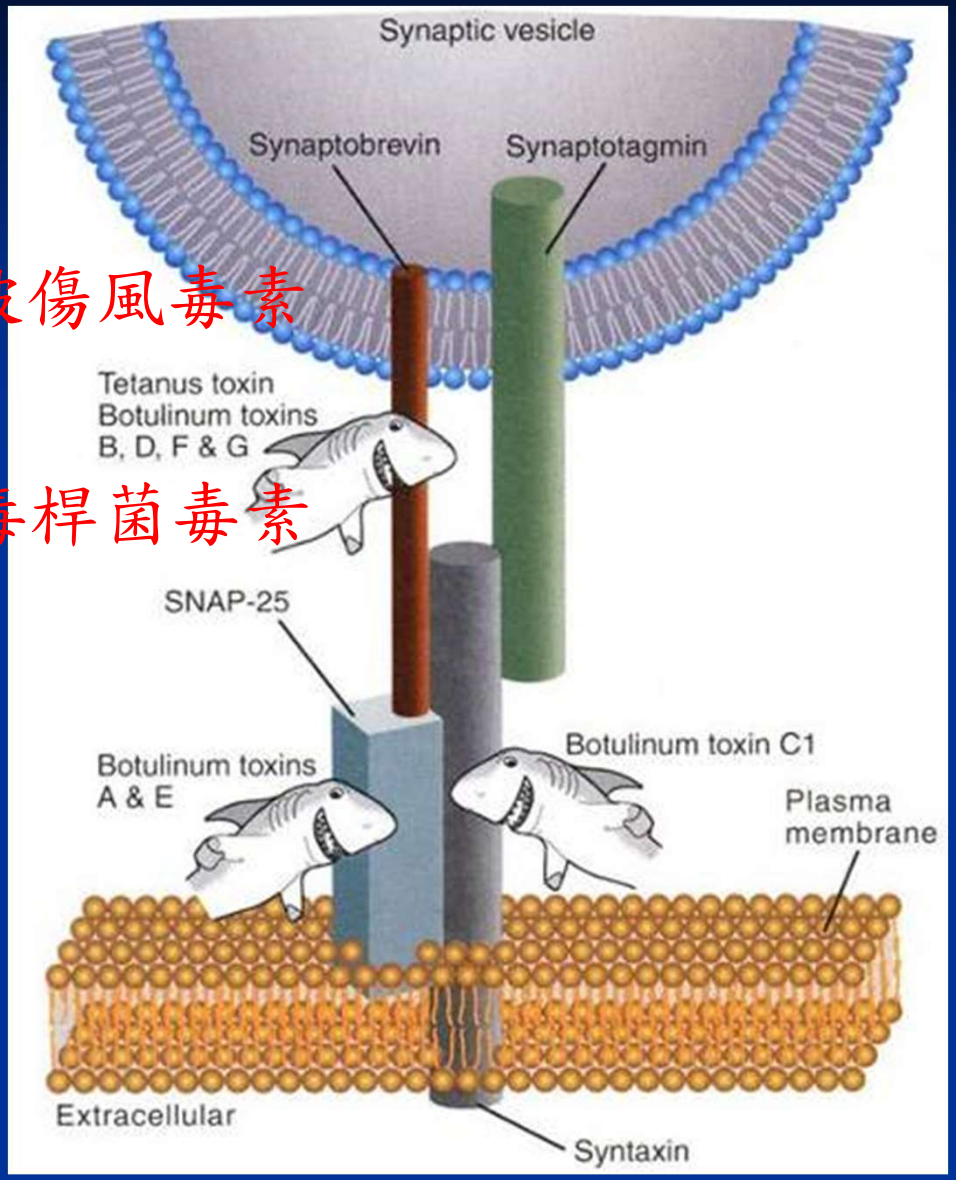
Whole-cell membrane capacitance traces recorded from bovine chromaffin cells, isolated from adrenal medulla.

Capacitance is proportional to membrane surface area and can be used to study exo-endocytosis.

Toxins blocking exocytosis

破傷風毒素

肉毒桿菌毒素



Botulinum Toxins: a biological weapon or magic bullet?

Document: CIA Plots to Kill Castro

http://en.wikipedia.org/wiki/Cuban_Project

botulinum toxin-contaminated cigars

http://en.wikipedia.org/wiki/Fidel_Castro

1926-2016

Electrical Synapse

Chemical Synapse

Neurotransmitter Synthesis and Release

EPSP and IPSP

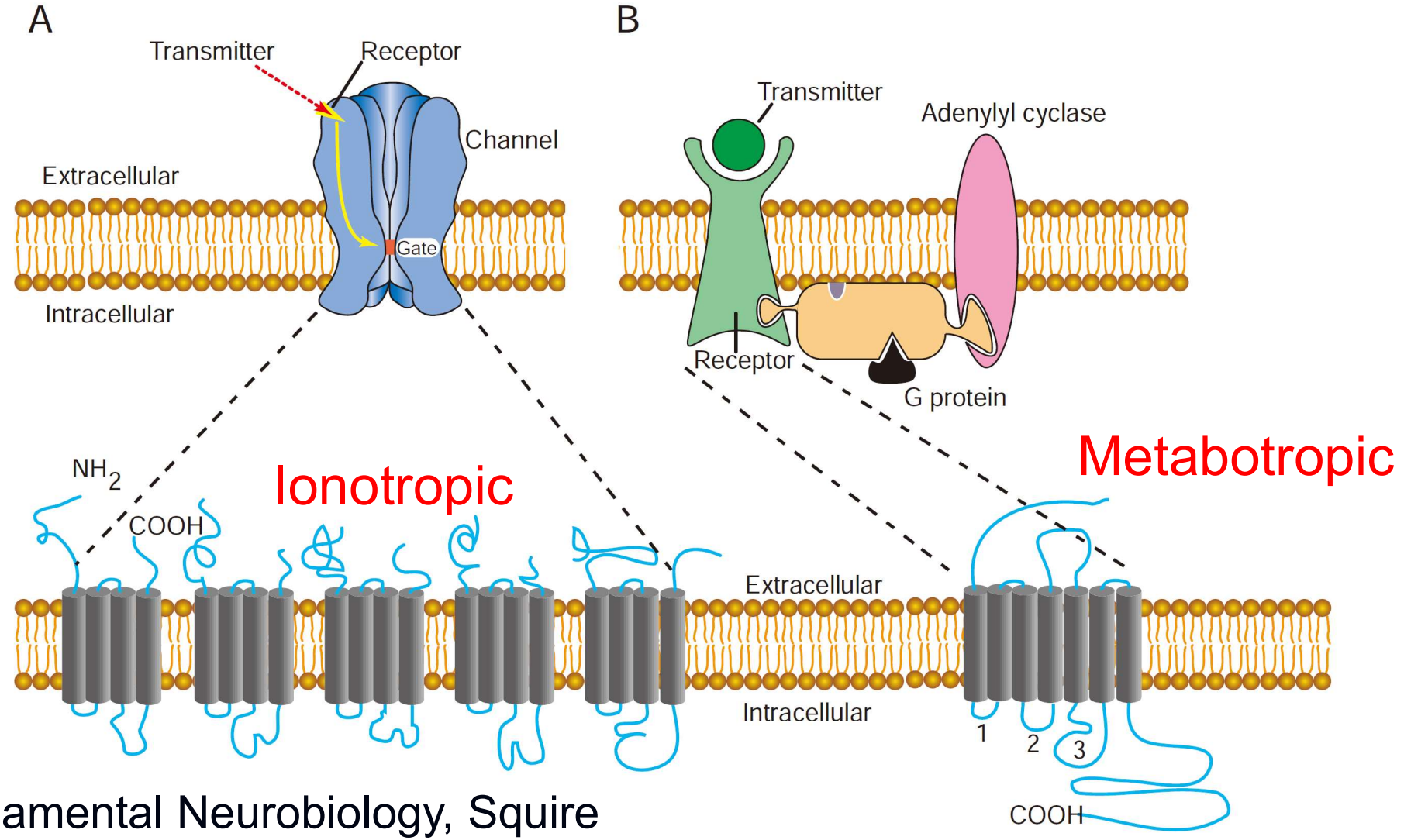
Quantal Analysis

EPSP Summation and IPSP Shunting

Modulation

Neuroglia

Two Types of Receptors



Fundamental Neurobiology, Squire

FIGURE 9.1 Structural comparison of ionotropic and metabotropic receptors. (A) *Ionotropic receptors* bind transmitter, and this binding translates directly into the opening of the ion channel through a series of conformational changes. Ionotropic receptors are composed of multiple subunits. The five subunits that together form the functional nAChR are shown. Note that each of the nAChR subunits wraps back and forth through the membrane four times and that the mature receptor is composed of five subunits. (B) *Metabotropic receptors* bind transmitter and, through a series of conformational changes, bind to G-proteins and activate them. G-proteins then activate enzymes such as adenylyl cyclase to produce cAMP. Through the activation of cAMP-dependent protein kinase, ion channels become phosphorylated, which affects their gating properties. Metabotropic receptors are single subunits. They contain seven transmembrane-spanning segments, with the cytoplasmic loops formed between the segments providing the points of interactions for coupling to G-proteins. Adapted from Kandel (1991).

The post-synaptic potential: determined by the permeability of ionotropic receptor

Voltage-independent

$I_{Na} = g_{Na} \times (V_m - E_{Na})$

$I_K = g_K \times (V_m - E_K)$

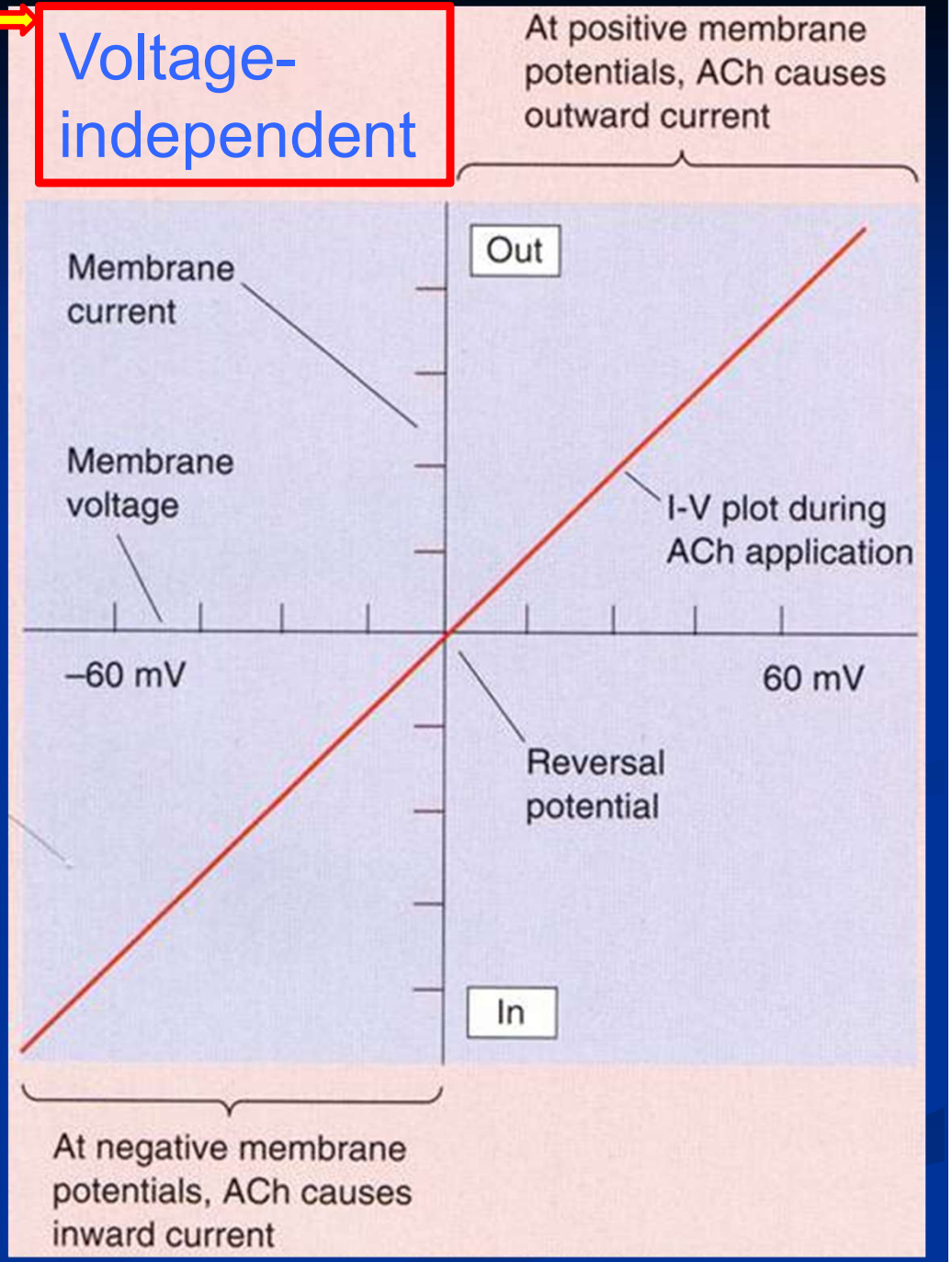
$I_{EPSP} = g_{EPSP} \times (V_m - E_{EPSP})$

$I_{Na} + I_K = 0$ at the reversal potential

$g_{Na} \times (E_{EPSP} - E_{Na}) + g_K \times (E_{EPSP} - E_K) = 0$

$$E_{EPSP} = \frac{\frac{g_{Na}}{g_K} \times E_{Na} + E_K}{\frac{g_{Na}}{g_K} + 1}$$

If E_K = -100 mV, E_{Na} = + 55 mV and E_{EPSP} = 0 mV, then g_{Na}/g_K = ??



Box 5.4

Ach: acetylcholine

Reversal Potential

- I = 0
- The current has opposite direction before and after this potential.
- Can be calculated by Goldman equation.
- Can reveal the selectivity property.

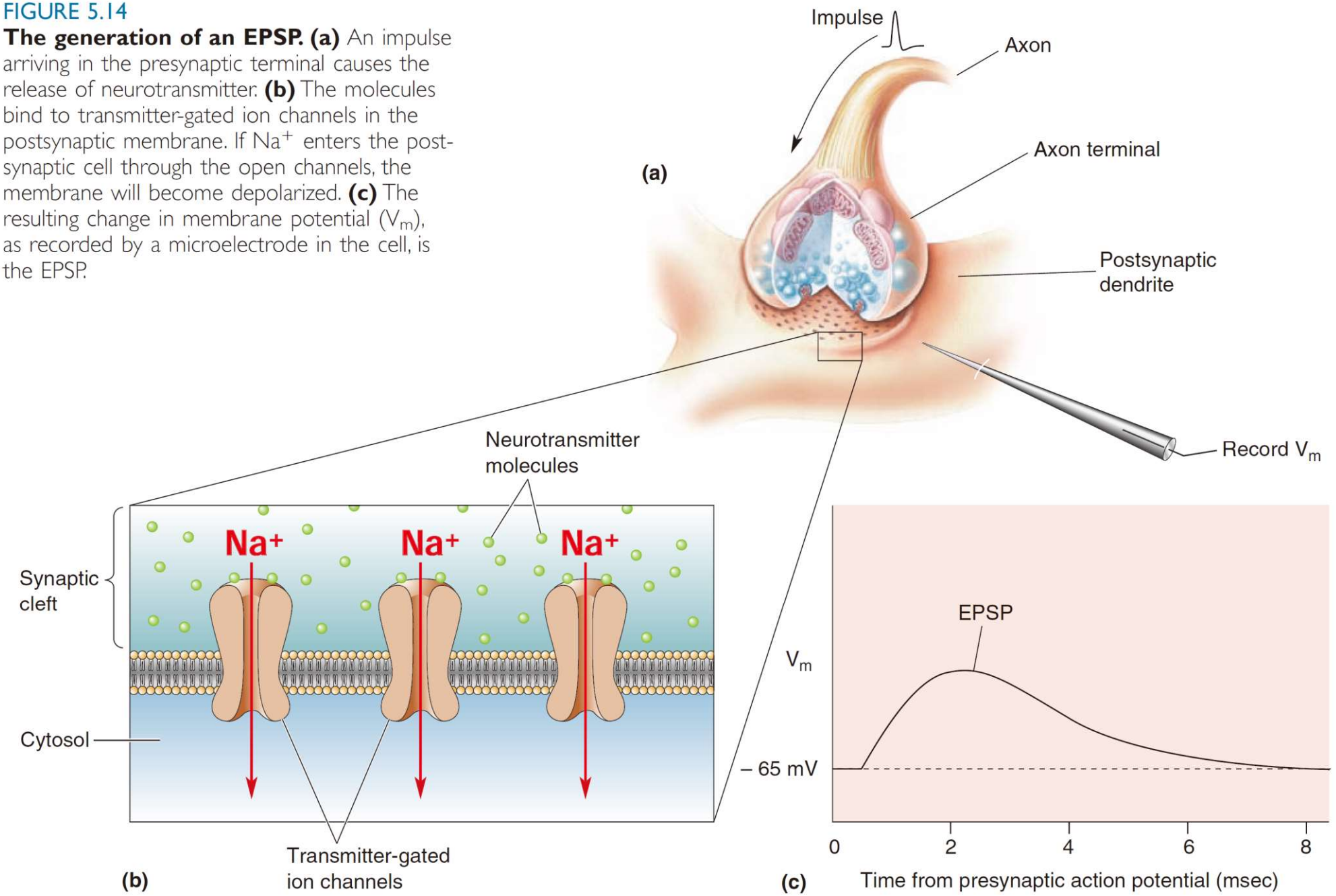
Differences between action and end-plate potentials

1. AchR alone generates the end-plate potential (at muscle) but action potential requires both Na^+ and K^+ channels.
2. Na^+ fluxes through Na^+ channel is regenerative but the number of AchR opened is determined by the amount of Ach available.

Cation Channel & Excitatory Postsynaptic Potential

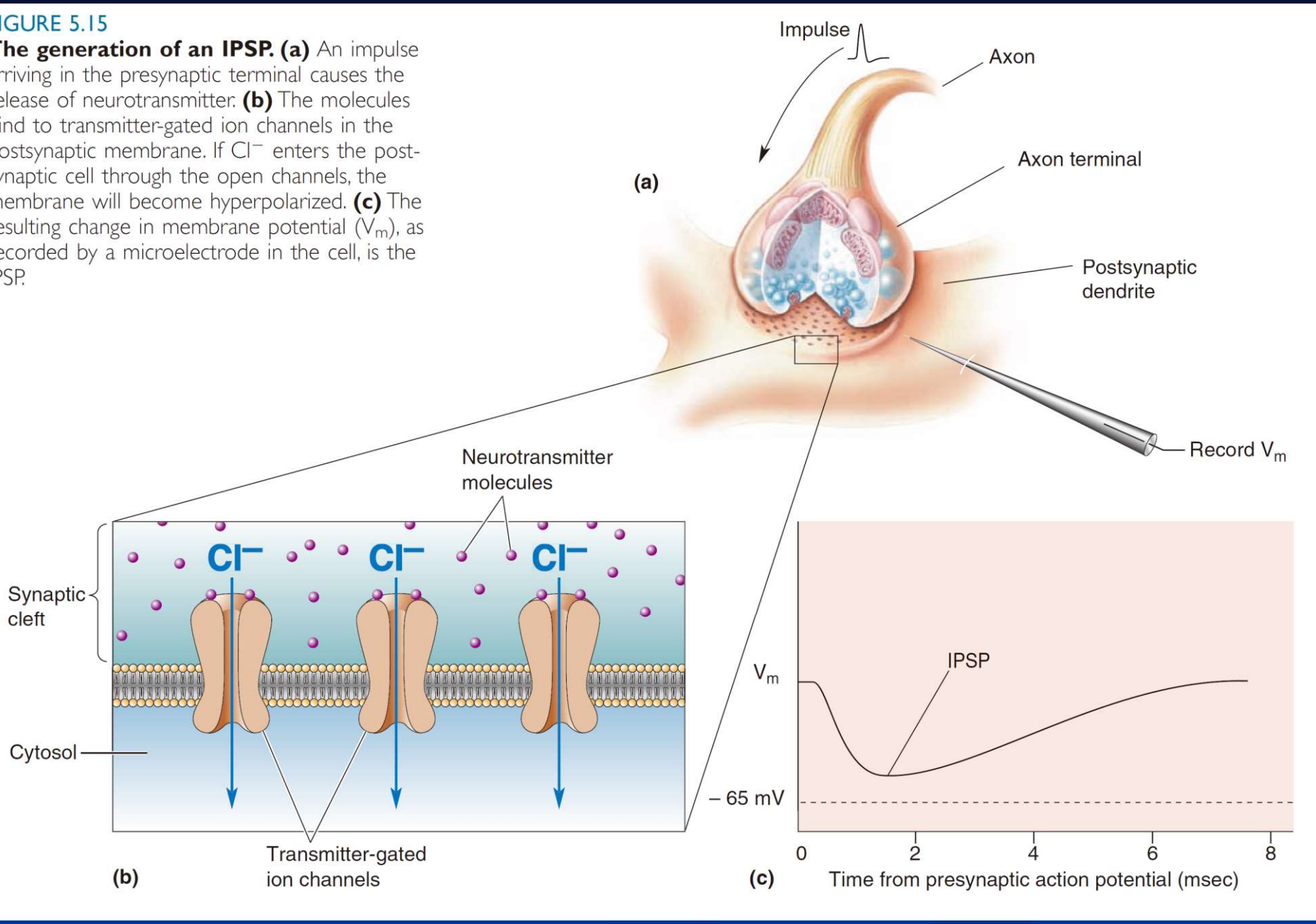
FIGURE 5.14

The generation of an EPSP. (a) An impulse arriving in the presynaptic terminal causes the release of neurotransmitter. **(b)** The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. If Na^+ enters the post-synaptic cell through the open channels, the membrane will become depolarized. **(c)** The resulting change in membrane potential (V_m), as recorded by a microelectrode in the cell, is the EPSP.



Anion Channel & Inhibitory Postsynaptic Potential

FIGURE 5.15
The generation of an IPSP. (a) An impulse arriving in the presynaptic terminal causes the release of neurotransmitter. **(b)** The molecules bind to transmitter-gated ion channels in the postsynaptic membrane. If Cl^- enters the post-synaptic cell through the open channels, the membrane will become hyperpolarized. **(c)** The resulting change in membrane potential (V_m), as recorded by a microelectrode in the cell, is the IPSP.



Must be hyperpolarized? (Olfactory neurons)

Electrical Synapse

Chemical Synapse

Neurotransmitter Synthesis and Release

EPSP and IPSP

Quantal Analysis

EPSP Summation and IPSP Shunting

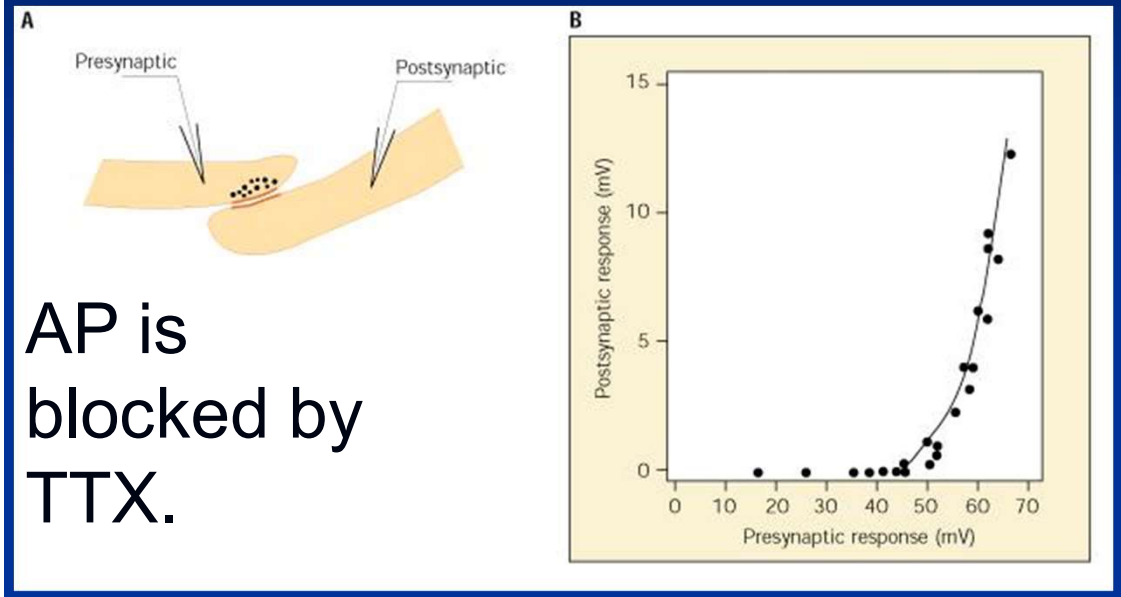
Modulation

Neuroglia

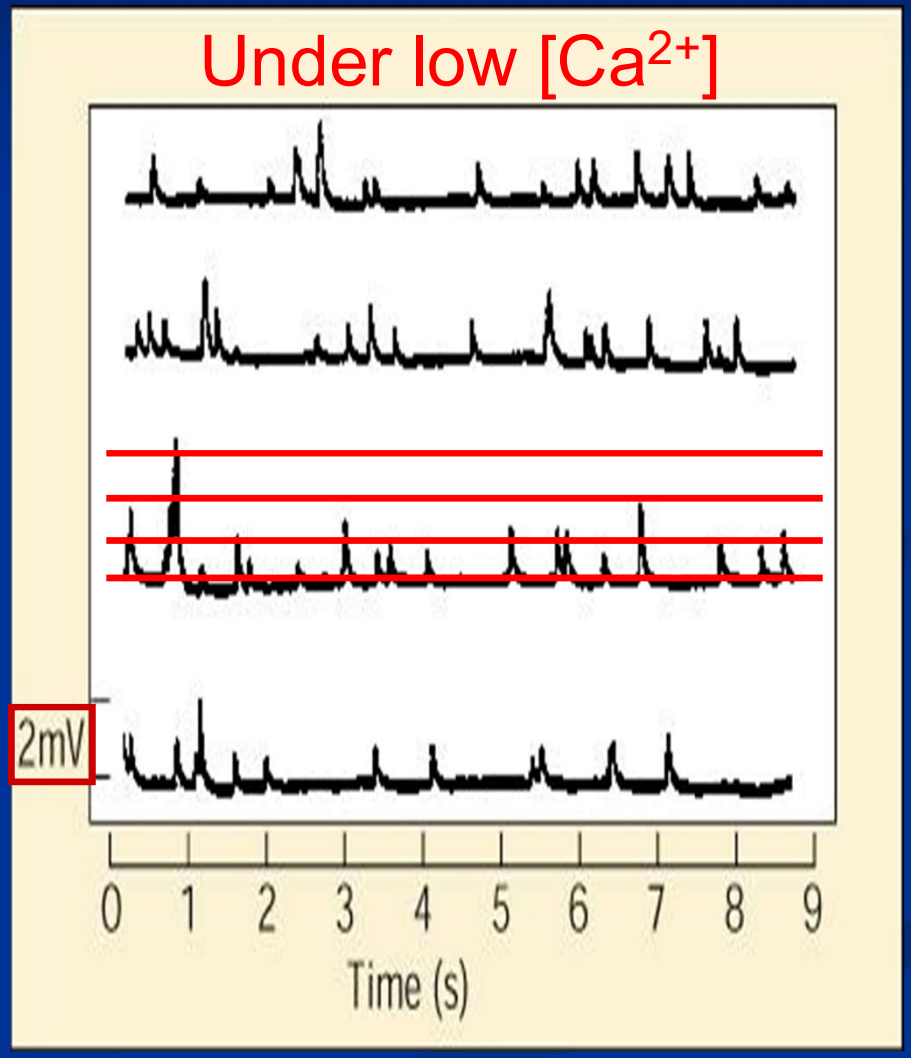
1960s Bernard Katz and Ricardo Miledi

Below 45 mV: no detectable EPSP.

Above 45 mV: depends on the presynaptic potential change



AP is blocked by TTX.



Quantal Analysis

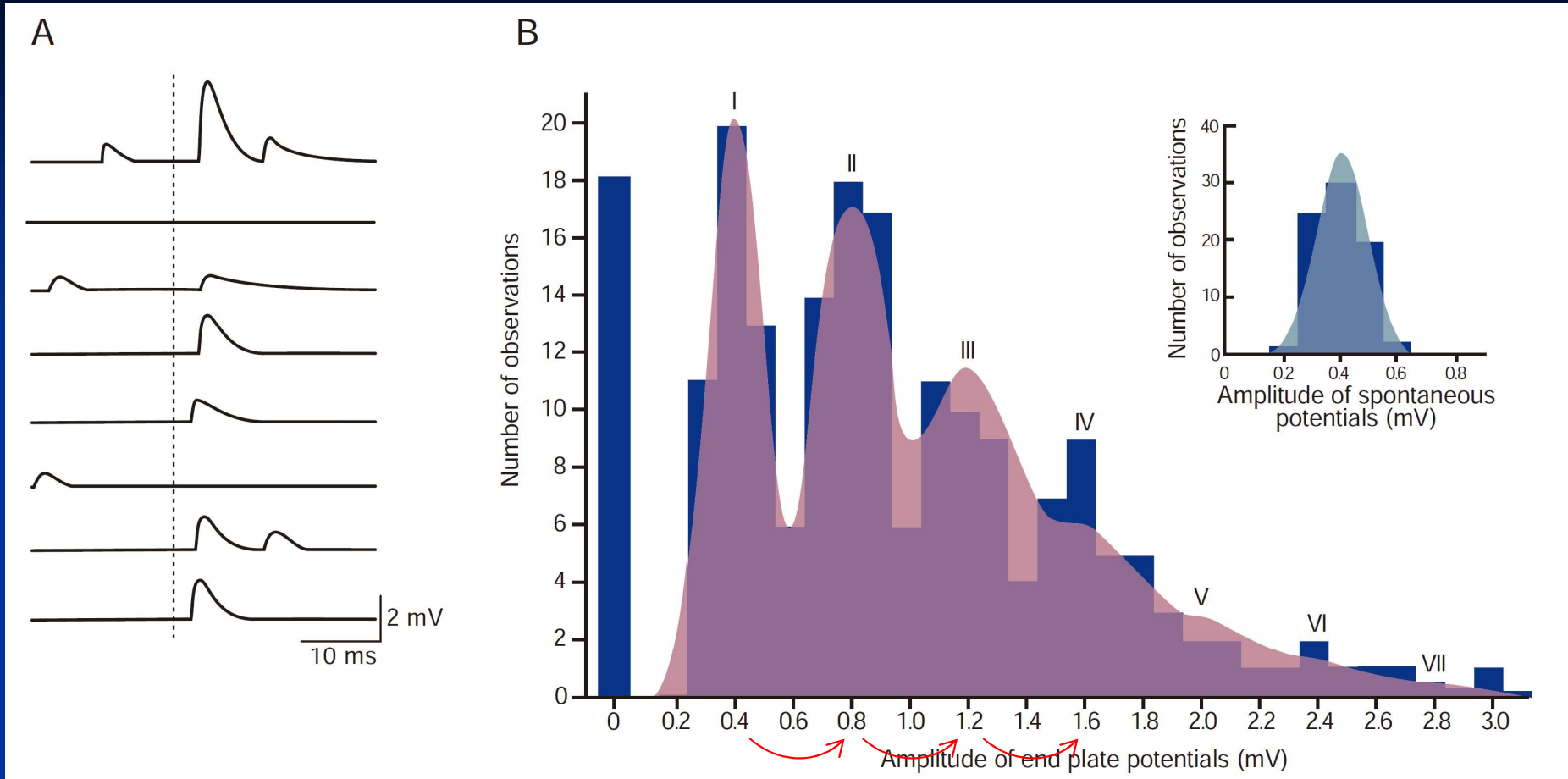
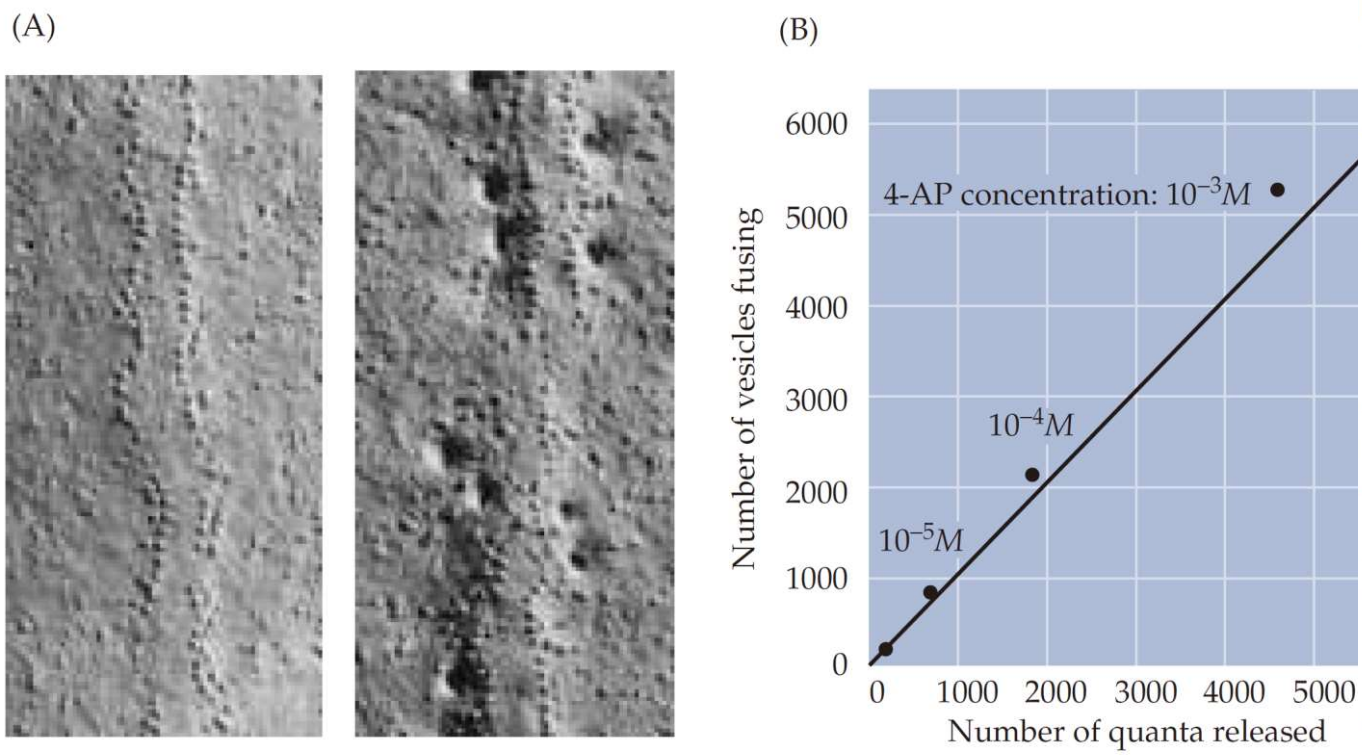
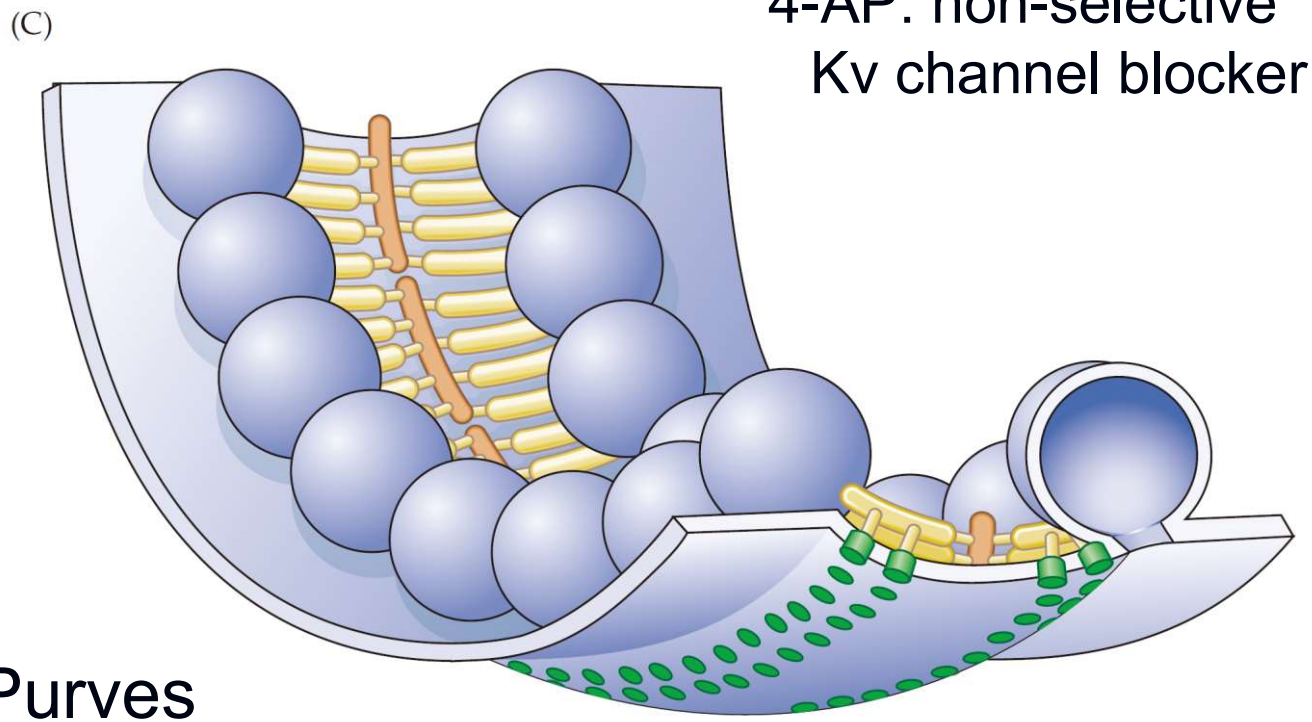


FIGURE 8.7 Quantal transmission at the neuromuscular junction. (A) Intracellular recordings from a rat muscle fiber in response to repeated presynaptic stimulation of the motor axon. Low extracellular [Ca^{2+}] and high [Mg^{2+}] restricted Ca^{2+} entry and so kept transmission to a very low level. The stimulus was given at the time marked by the dotted line. The size of the postsynaptic response fluctuated from trial to trial, with some trials giving failures of transmission. Spontaneous minis occurring in the background (e.g., those events that occur before the dotted line) had approximately the same amplitude as the smallest evoked responses, implying that they arose from the release of single quanta of acetylcholine. From Liley (1956). (B) Peak amplitudes of 200 evoked responses [end plate potentials (EPPs)] from a similar experiment, plotted as an amplitude histogram. Eighteen trials resulted in failures of transmission (indicated by the bar at 0 mV), and the rest gave EPPs whose amplitude tended to cluster at integral multiples of 0.4 mV. This coincides with the mean amplitude of the spontaneous minis, whose amplitude distribution is shown in the insert together with a Gaussian fit. Shading through the EPP histogram is a fit obtained by assuming a Poisson model of quantal release. Roman numerals indicate the number of quanta corresponding to each component in the distribution. From Boyd and Martin (1956).

Squire

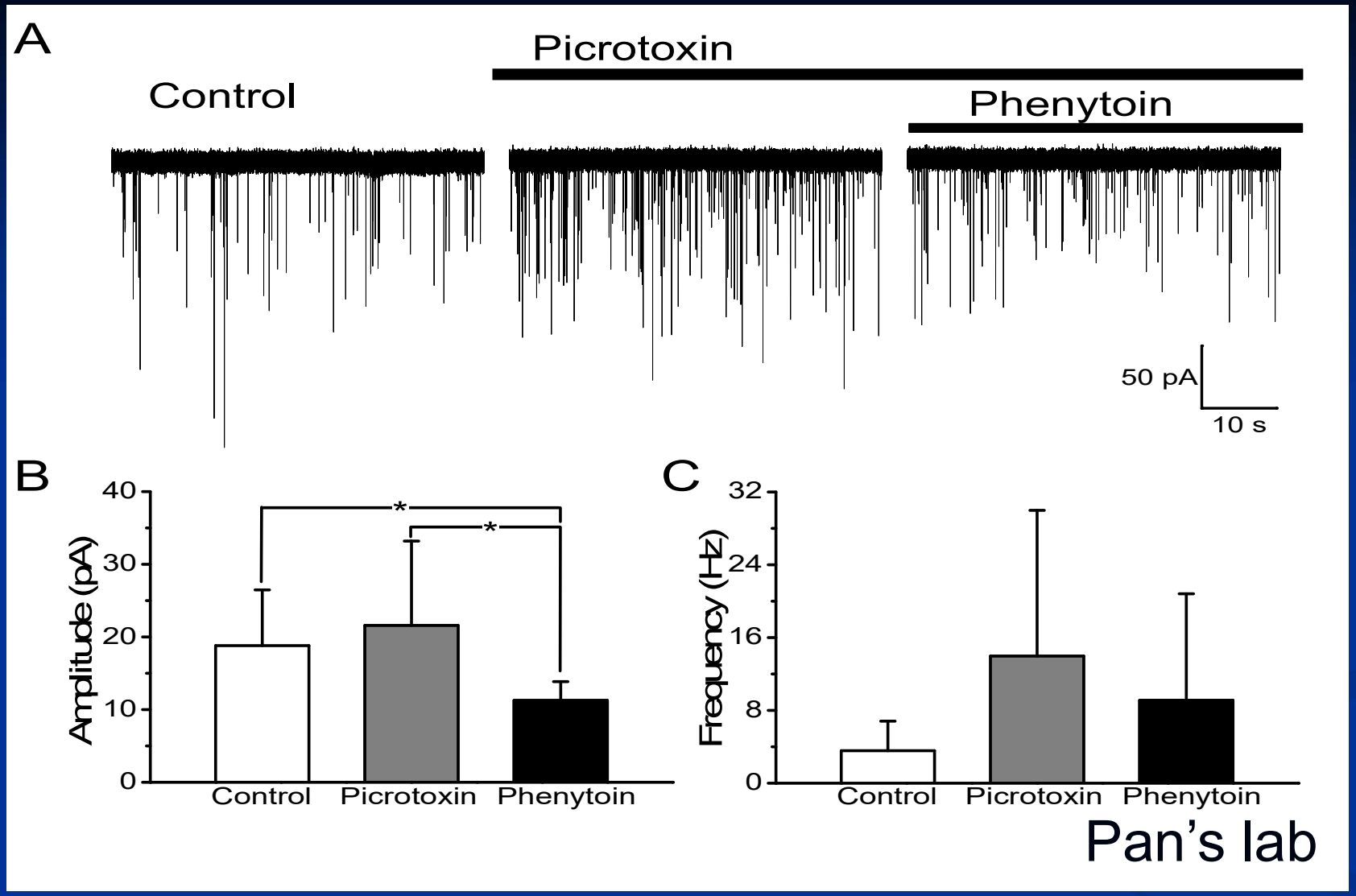


4-AP: non-selective Kv channel blocker



Purves

Figure 5.8 Relationship of synaptic vesicle exocytosis and quantal transmitter release. (A) A special electron microscopical technique called freeze-fracture microscopy was used to visualize the fusion of synaptic vesicles in presynaptic terminals of frog motor neurons. *Left:* Image of the plasma membrane of an unstimulated presynaptic terminal. *Right:* Image of the plasma membrane of a terminal stimulated by an action potential. Stimulation causes the appearance of dimple-like structures that represent the fusion of synaptic vesicles with the presynaptic membrane. The view is as if looking down on the release sites from outside the presynaptic terminal. (B) Comparison of the number of observed vesicle fusions to the number of quanta released by a presynaptic action potential. Transmitter release was varied by using a drug (4-AP) that affects the duration of the presynaptic action potential, thus changing the amount of calcium that enters during the action potential. The diagonal line is the 1:1 relationship expected if each vesicle that opened released a single quantum of transmitter. (C) Fine structure of vesicle fusion sites of frog presynaptic terminals. Synaptic vesicles are arranged in rows and are connected to each other and to the plasma membrane by a variety of proteinaceous structures (yellow). Green structures in the presynaptic membrane, corresponding to the rows of particles seen in (A), are thought to be Ca^{2+} channels. (A and B from Heuser et al., 1979; C after Harlow et al., 2001)



Picrotoxin: $GABA_A$ antagonist, inhibits the inhibitory synaptic activities

Phenytoin: a commonly prescribed epilepsy drug, suppress Na^+ currents

Vesicular Hypothesis: Vesicles are site of neurotransmitter storage and release into synaptic cleft.

Quantal Release: Vesicular hypothesis requires that neurotransmitter is released in discrete packets corresponding to contents of one vesicle, synaptic vesicles of a particular type in neuron are about same size.

Q: How many vesicles in an axon terminal?

Q: A quantum a vesicle?

Electrical Synapse

Chemical Synapse

Neurotransmitter Synthesis and Release

EPSP and IPSP

Quantal Analysis

EPSP Summation and IPSP Shunting

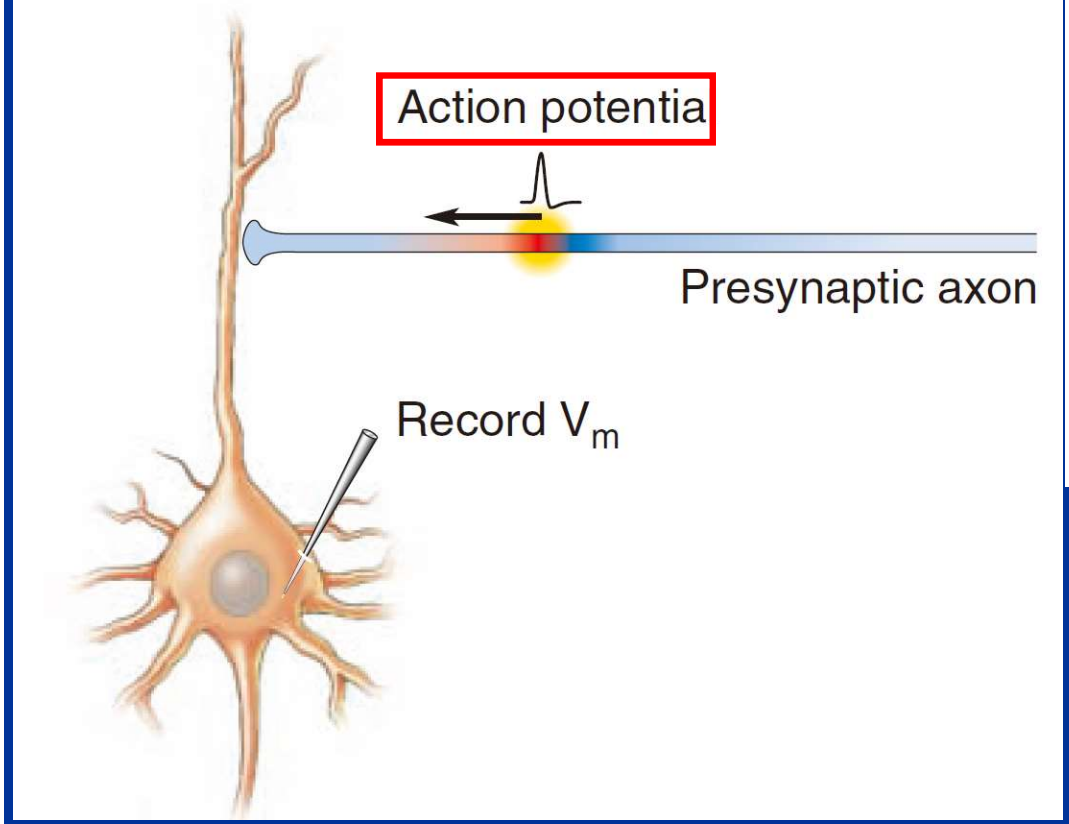
Modulation

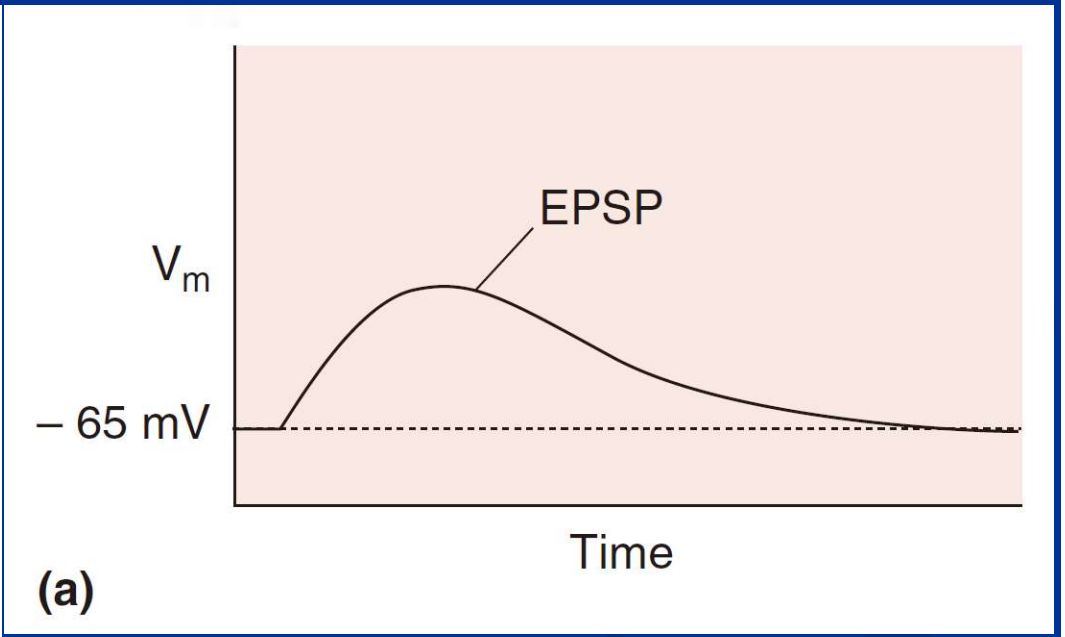
Neuroglia

Complexity of Synaptic Transmission

- Many input connections
- Both excitatory and inhibitory inputs
- Many kinds of neurotransmitters
- Synaptic efficacy

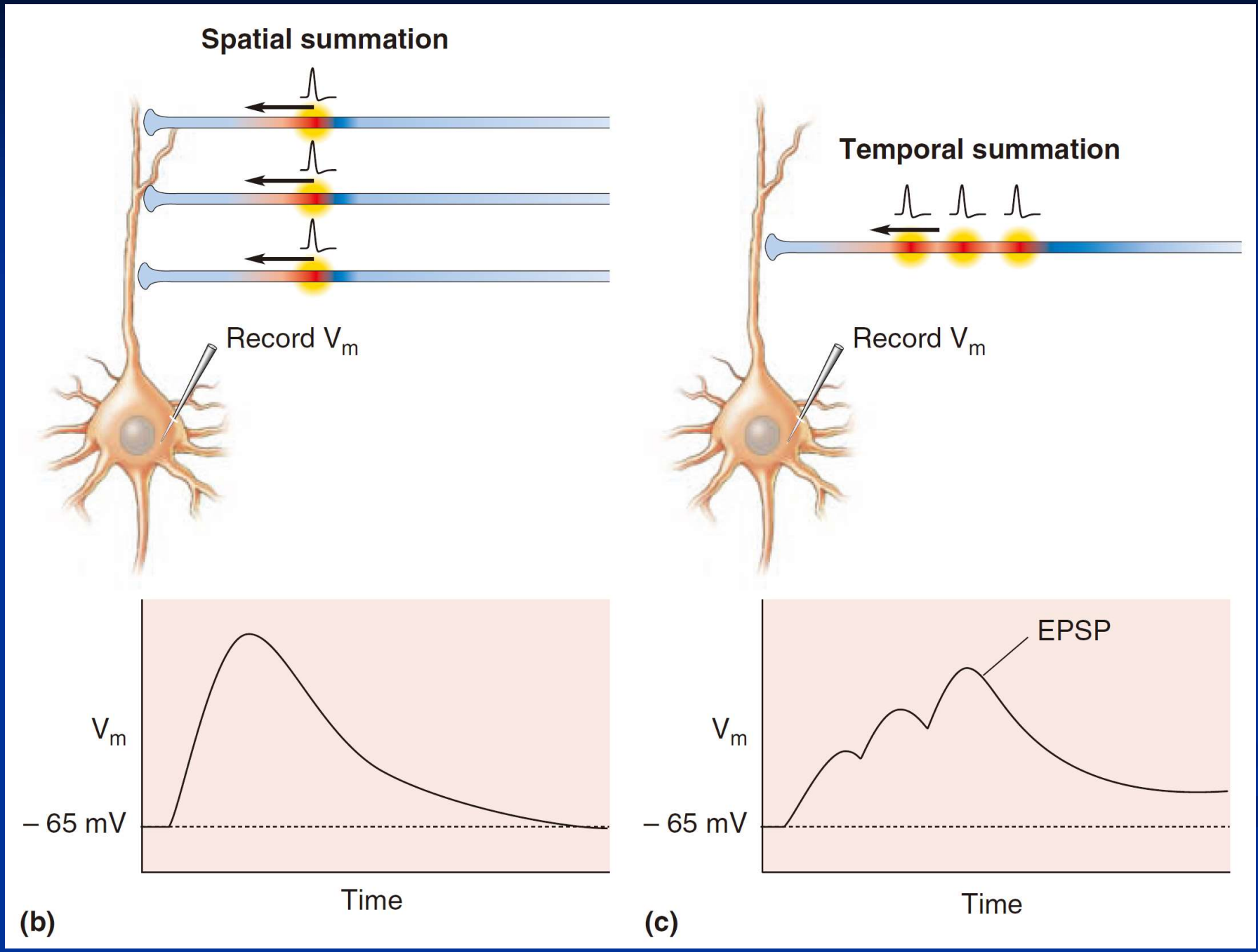
EPSP



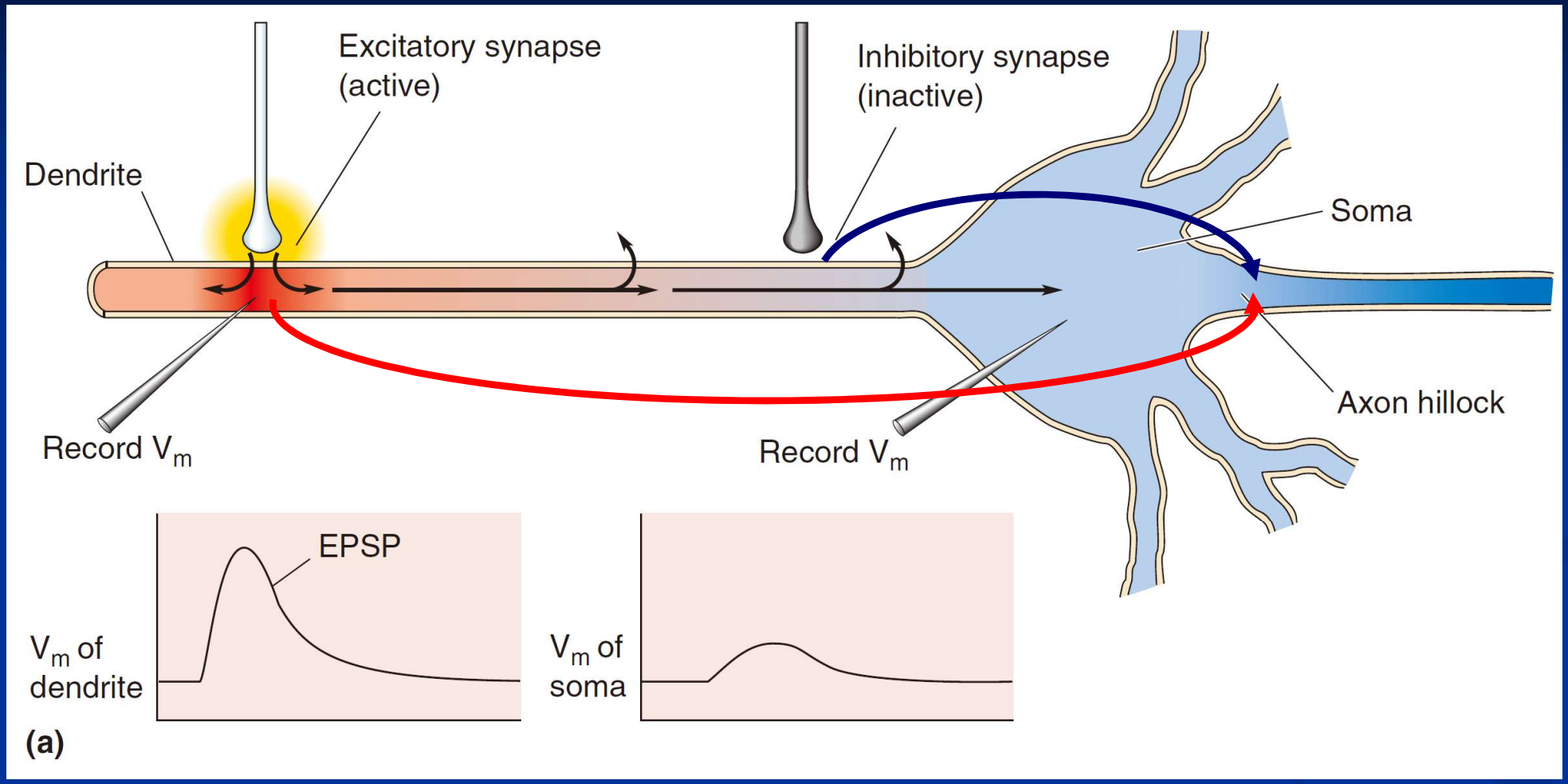


5.18

EPSP summation

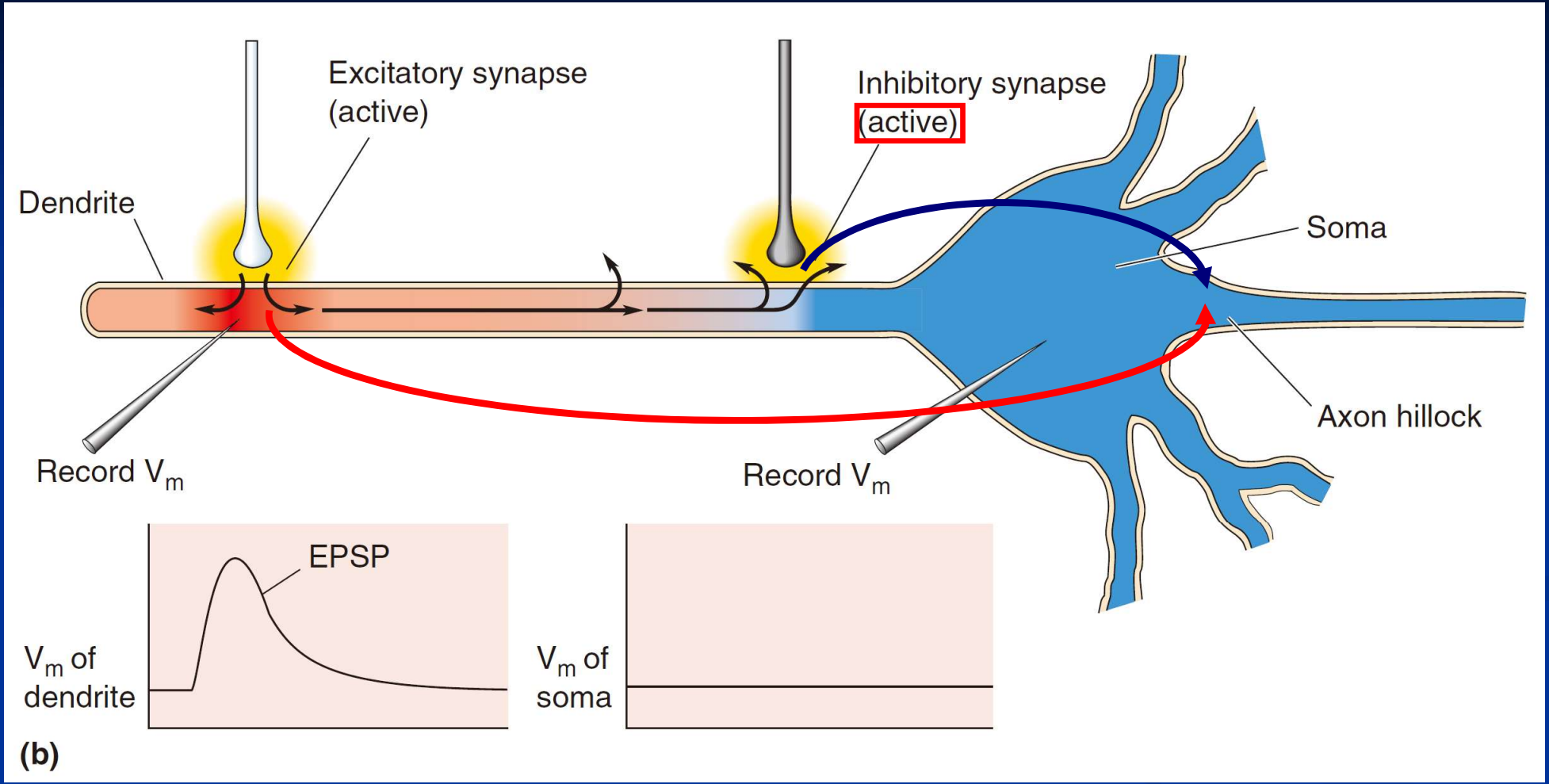


From AP to EPSP/IPSP



5.20

IPSP Shunting



5.20

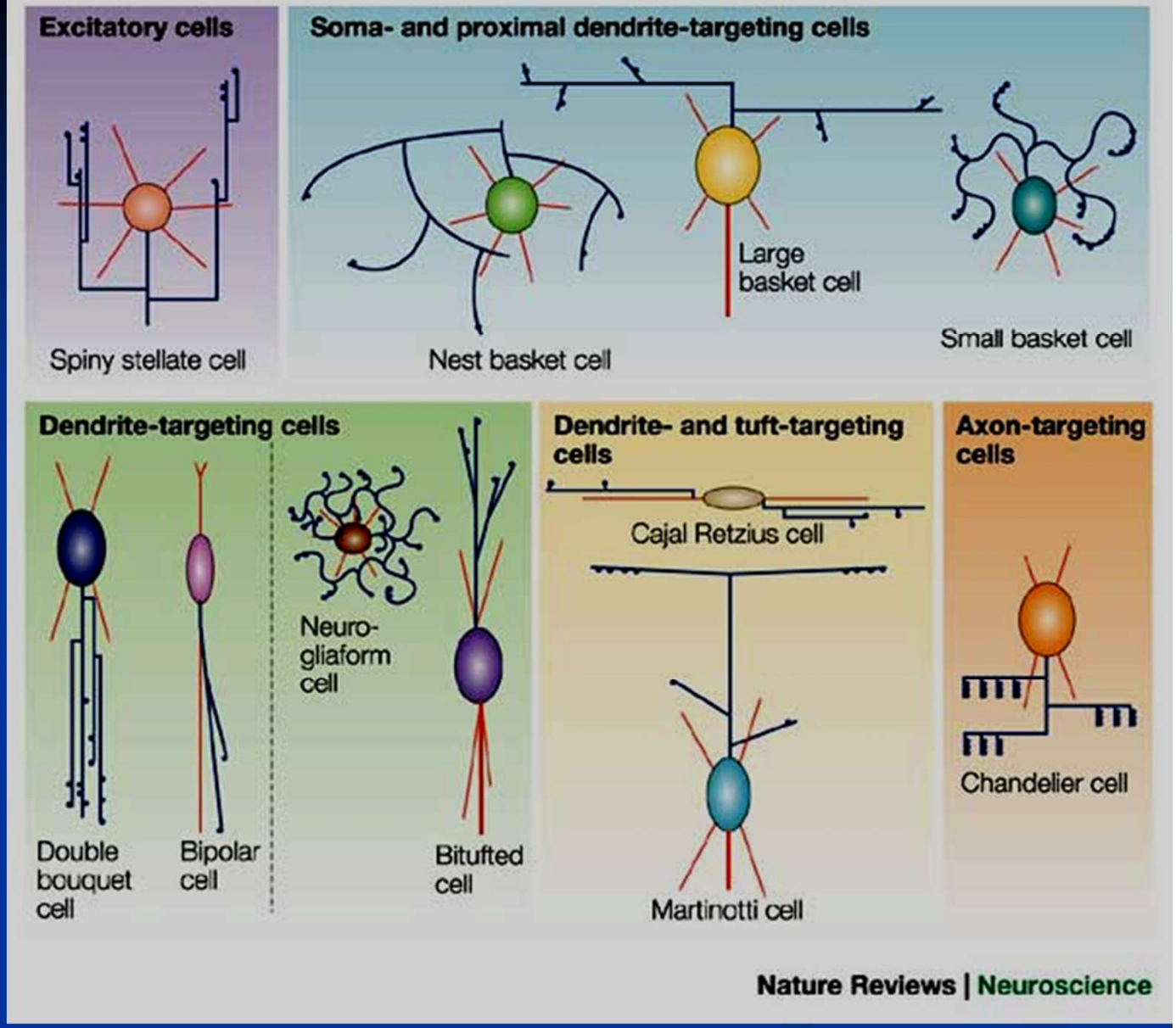
Inhibitory interneurons:

- γ-aminobutyric acid (GABA), GABAergic

Basket: axonal endings form a basket of terminals surrounding a pyramidal cell soma, III & V

Chandelier: synapse exclusively on the axon initial segment of pyramidal cells, III

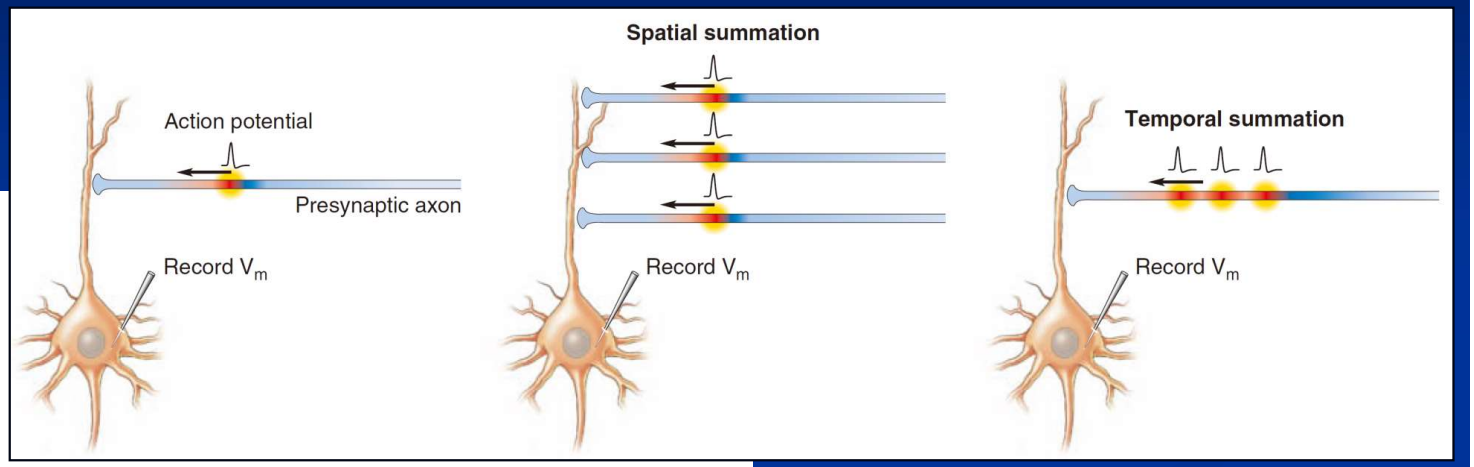
Double Bouquet cells: II, III, & V



Interneurons of the neocortical inhibitory system (2004) Nat. Rev. Neurosci. **5**, 795

Signal Integration

- Temporal summation: time constant τ
- Spatial summation: length constant λ



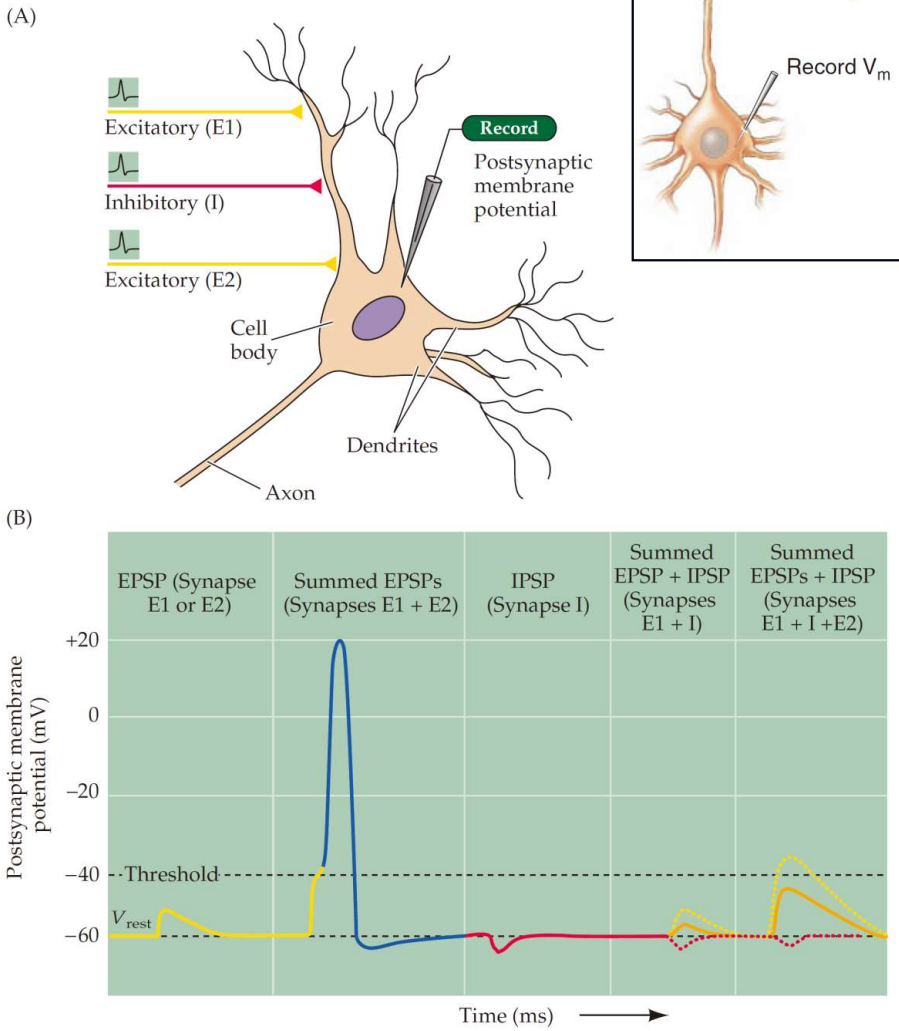
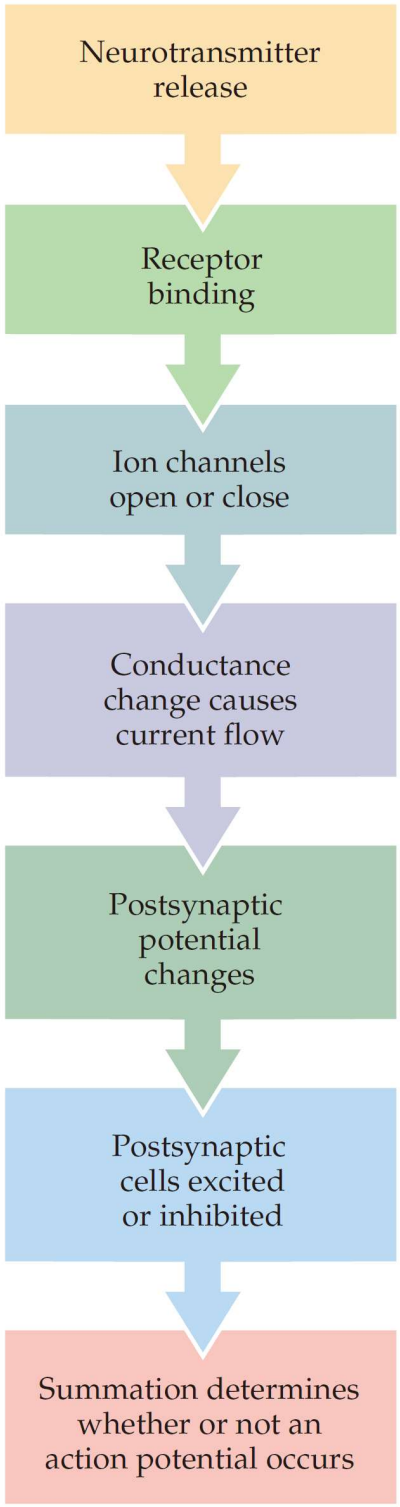


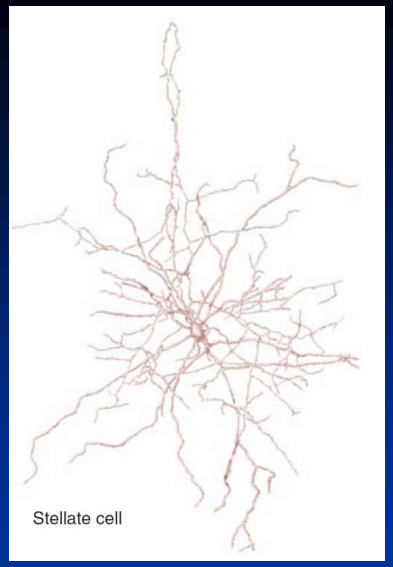
Figure 5.20 Summation of postsynaptic potentials. (A) A microelectrode records the postsynaptic potentials produced by the activity of two excitatory synapses (E1 and E2) and an inhibitory synapse (I). (B) Electrical responses to synaptic activation. Stimulating either excitatory synapse (E1 or E2) produces a subthreshold EPSP, whereas stimulating both synapses at the same time (E1 + E2) produces a suprathreshold EPSP that evokes a postsynaptic action potential (shown in blue). Activation of the inhibitory synapse alone (I) results in a hyperpolarizing IPSP. Summing this IPSP (dashed red line) with the EPSP (dashed yellow line) produced by one excitatory synapse (E1 + I) reduces the amplitude of the EPSP (orange line), while summing it with the suprathreshold EPSP produced by activating synapses E1 and E2 keeps the postsynaptic neuron below threshold, so that no action potential is evoked.

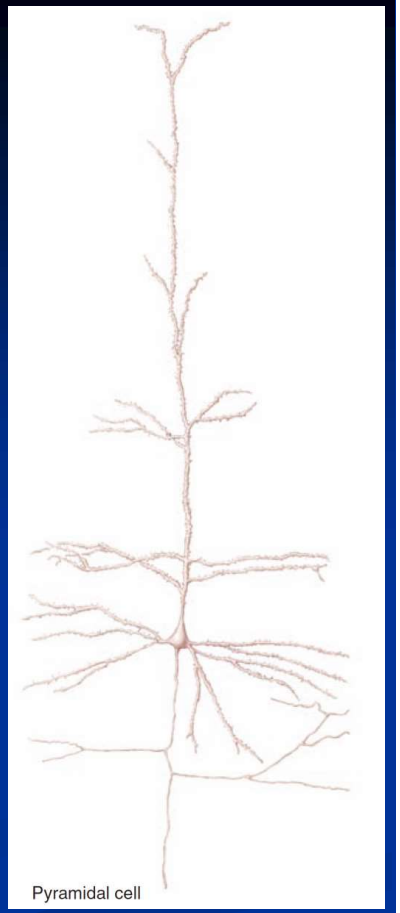
Purves



The length constant

1. Spatial summation
2. Propagation





EPSP & IPSP at dendrites → summation at axon hillock

Figure 5.21 Events from neurotransmitter release to postsynaptic excitation or inhibition. Neurotransmitter release at all presynaptic terminals on a cell results in receptor binding, which causes the opening or closing of specific ion channels. The resulting conductance change causes current to flow, which may change the membrane potential. The postsynaptic cell sums (or integrates) all of the EPSPs and IPSPs, resulting in moment-to-moment control of action potential generation.

Electrical Synapse

Chemical Synapse

Neurotransmitter Synthesis and Release

EPSP and IPSP

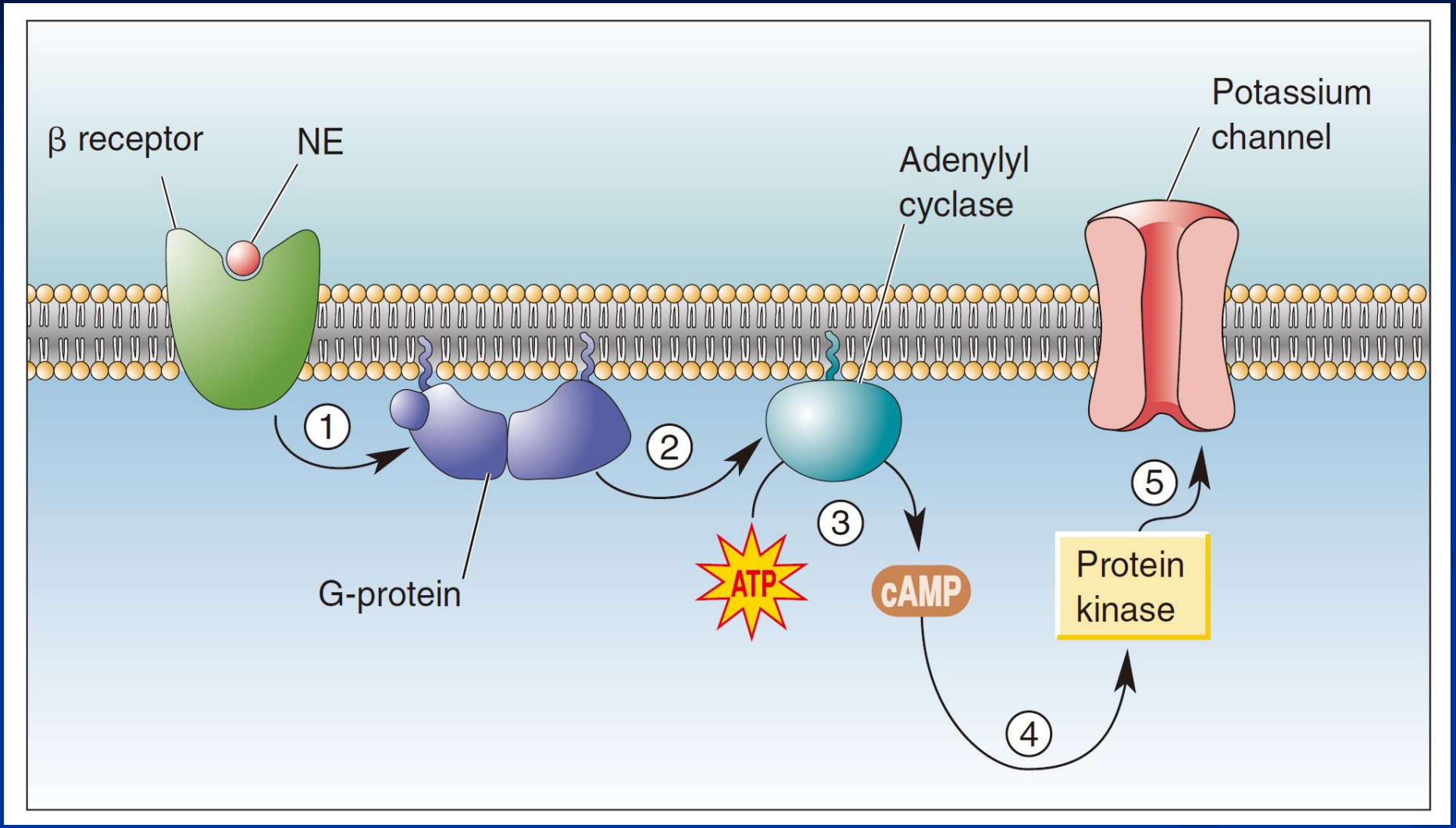
Quantal Analysis

EPSP Summation and IPSP Shunting

Modulation

Neuroglia

G-protein Coupled Receptor (GPCR)



5.21

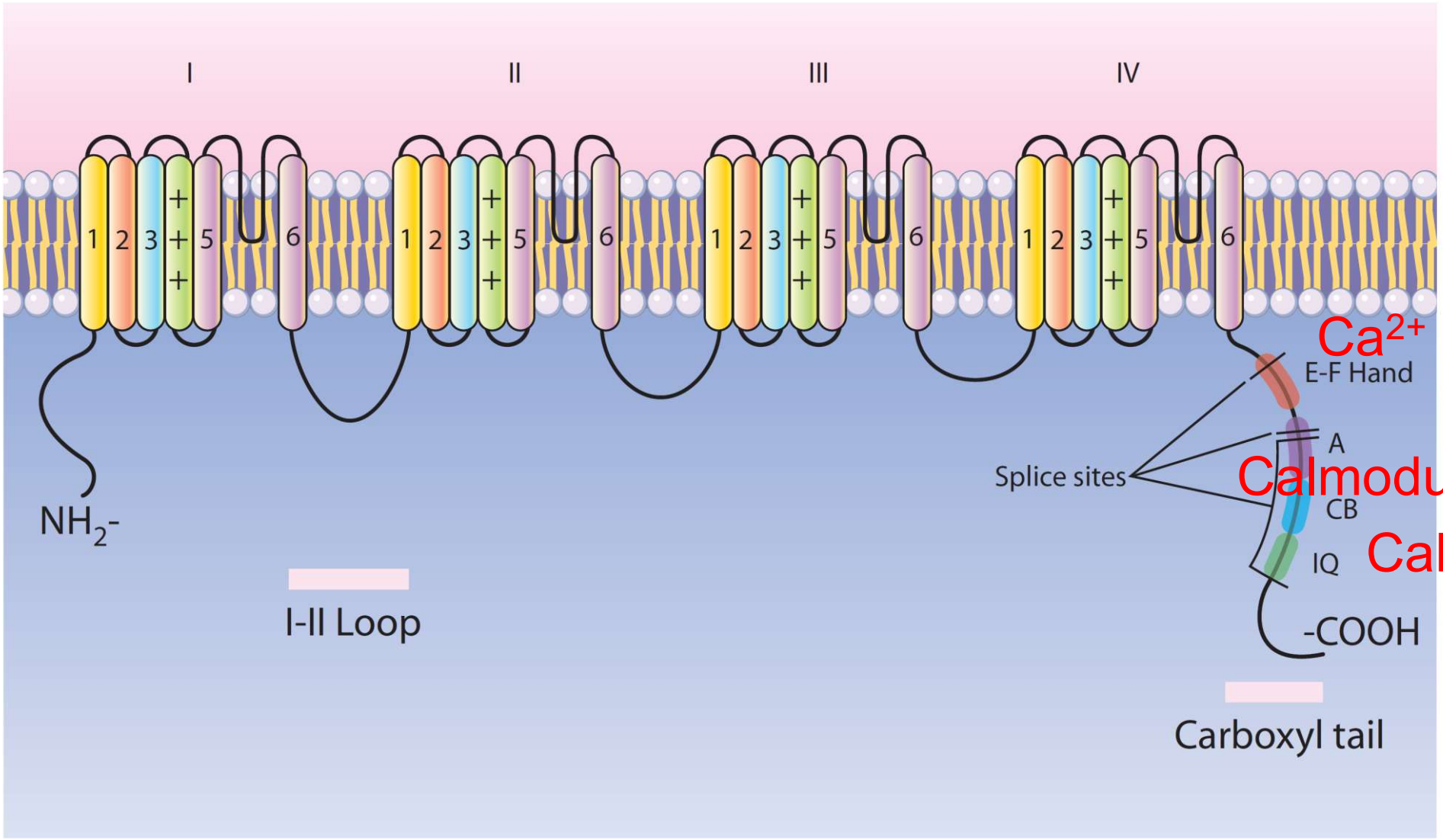
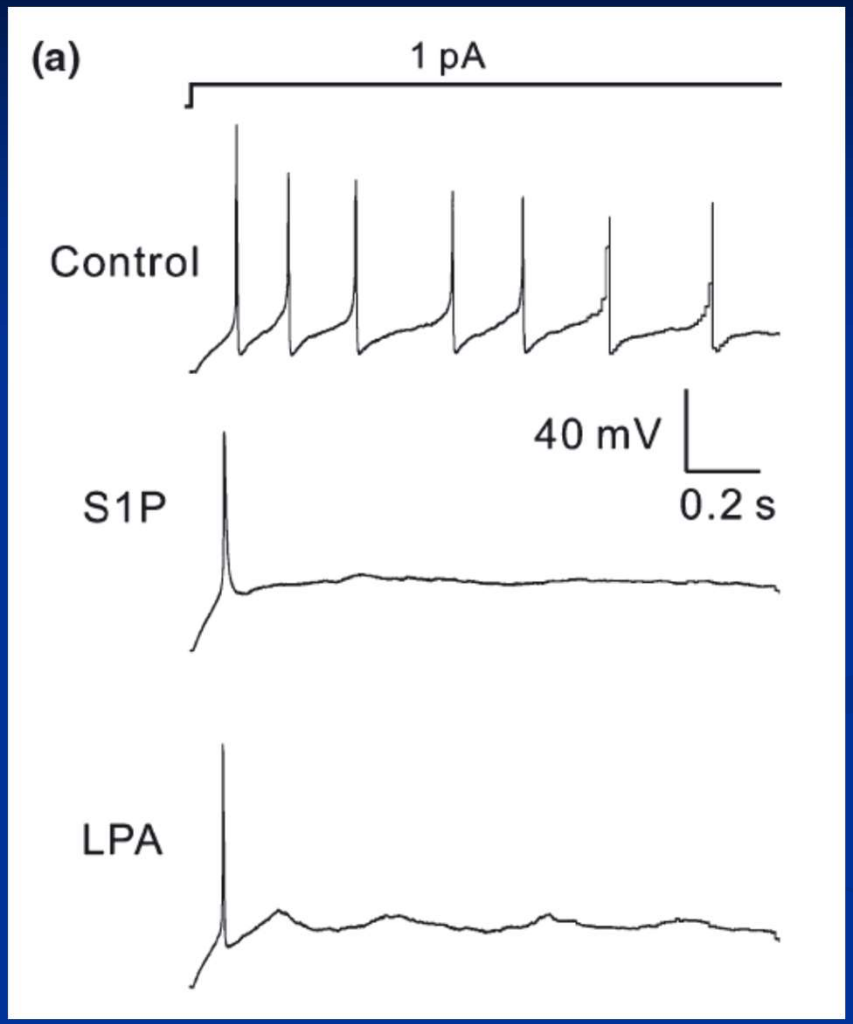


Fig. 1. The putative transmembrane arrangement of Cav1.2. This figure is based on the model of Snutch and Gilbert (*55*).

Regulation of Voltage-Gated Ca^{2+} Channels by Calmodulin
D. Brent Halling, Paula Aracena-Parks and Susan L. Hamilton, *Sci. STKE* 2005 (315), re15.

Repetitive action potential firing inhibited



Pan's Lab

Summary

- Synapse
- Active zone
- Quantal Release
- Signal Integration

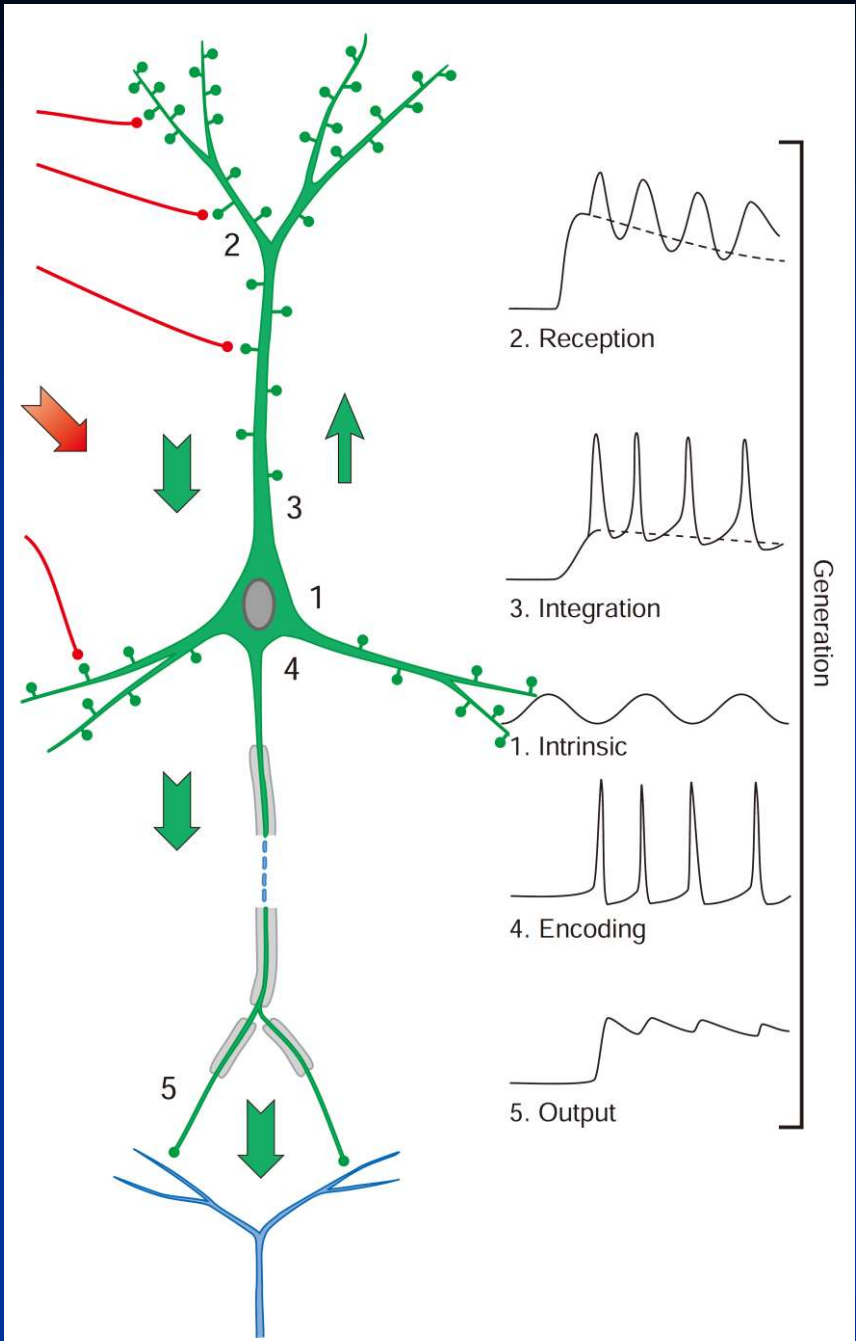


FIGURE 5.1 Nerve cells have four main regions and five main functions. Electrotonic potential spread is fundamental for coordinating the regions and their functions.

Squire 5.1

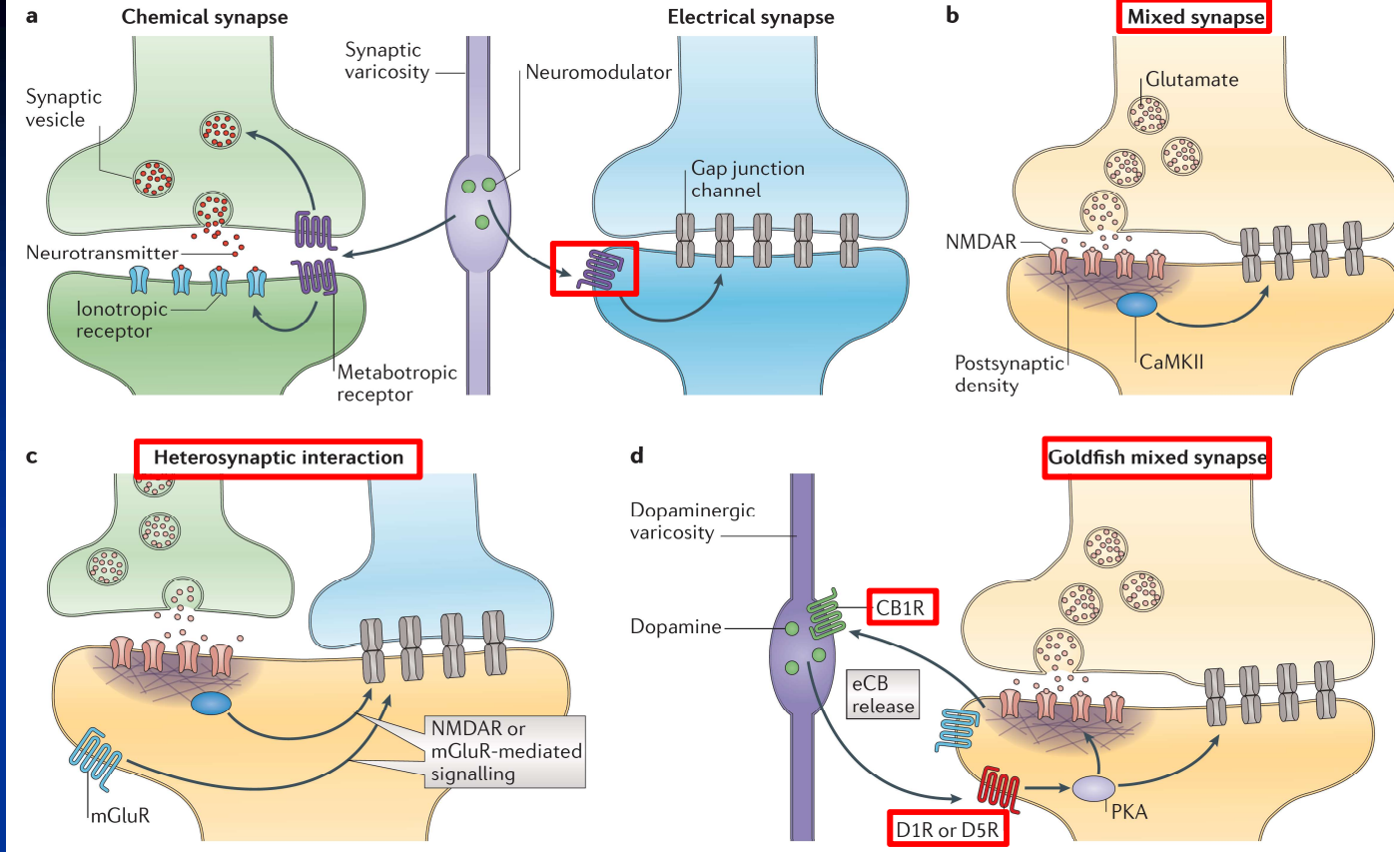


Figure 4 | **Types of interactions between electrical and chemical synapses in the adult nervous system.**

a | Neurotransmitter modulators released by nearby synaptic terminals (purple) regulate the synaptic strength of chemical and electrical synapses through activation of G protein-coupled metabotropic receptors. Regulation at chemical synapses could occur pre- or postsynaptically. **b** | Electrical and chemical synapses coexist at mixed synapses. Glutamatergic synapses regulate the strength of electrical synapses by a postsynaptic mechanism that includes the activation of NMDA receptors (NMDARs) and calcium/calmodulin-dependent protein kinase II (CaMKII). **c** | Regulation of electrical synapses by glutamatergic transmission could also be heterosynaptic. Nearby glutamatergic synapses can regulate electrical transmission through NMDAR or metabotropic glutamate receptor (mGluR) activation. **d** | Another mechanism of interaction at goldfish mixed synapses results when synaptic activity leads to mGluR activation, which in turn triggers endocannabinoid (eCB) release from the postsynaptic cell, and activates cannabinoid type 1 receptors (CB1Rs) on nearby dopaminergic fibres. CB1R activation leads to dopamine release that, by activating postsynaptic dopamine D1 receptors (D1Rs) and D5Rs and increasing protein kinase A (PKA) activity, is responsible for simultaneous enhancement of electrical and glutamatergic synaptic transmission.

Electrical synapses and their functional interactions with chemical synapses Nature Reviews Neuroscience (2014) 15: 250–263 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4091911/

Electrical Synapse

Chemical Synapse

Neurotransmitter Synthesis and Release

EPSP and IPSP

Quantal Analysis

EPSP Summation and IPSP Shunting

Modulation

Neuroglia

Neuron number: age & sex effect

TABLE 1. Major Structural Components of the Human Forebrain[1]

	Mean	CV	Sex-diff. (%)	Age-effect (%)
Neuron number, 10^9				
All	21.5	0.19	15.5	9.5
M	22.8	0.17		
F	19.3	0.17		
Neocortical neuronal density, $10^6/cm^3$				
All	44.0	0.13	NS	NS
M	44.1	0.13		
F	43.8	0.12		
Neocortical surface area, cm^2				
All	1,820	0.13	11.2	9.2
M	1,900	0.11		
F	1,680	0.14		
Neocortical volume, cm^3				
All	489	0.16	14.9	12.3
M	517	0.12		
F	440	0.15		
Neocortical thickness, mm				
All	2.69	0.10	4.1	NS
M	2.72	0.09		
F	2.61	0.12		

Neocortical neuron number in humans: Effect of sex and age
THE JOURNAL OF COMPARATIVE NEUROLOGY 384:312–320 (1997)

62 males (average age 52 years; range 19–87 years) and 32 females (average age 64 years; range 18–93 years)

100 Billion!

Total brain neurons 10^{11}

10%: $10^{10} \approx 400{,}000$/ day

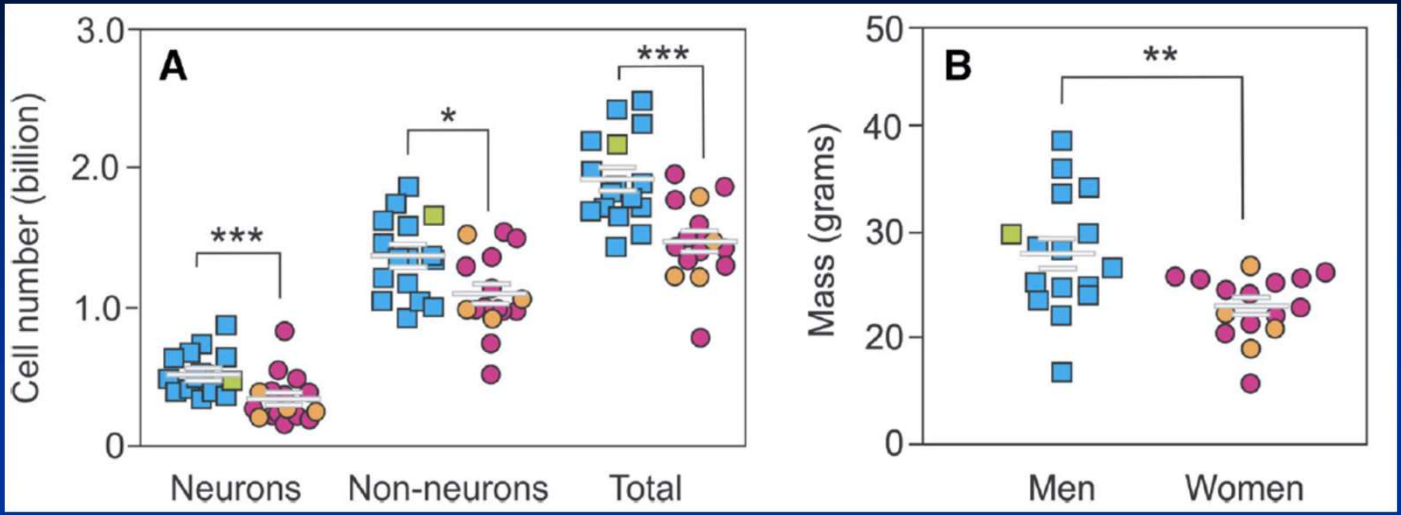
≈ 4.5 / sec

(20 to 90 years old)

Neuron loss = Function loss?

Neocortex: relatively recent invention of mammals; responsible for most complex mental activities

Do age and sex impact on the absolute cell numbers of human brain regions?
Brain Struct Funct. 2016 Sep;221(7):3547-59. doi: 10.1007/s00429-015-1118-4.



Number of cells and mass of the medial temporal lobes of men and women.

100 billion neurons, glia outnumber neurons by 10 fold – **TRUE?**

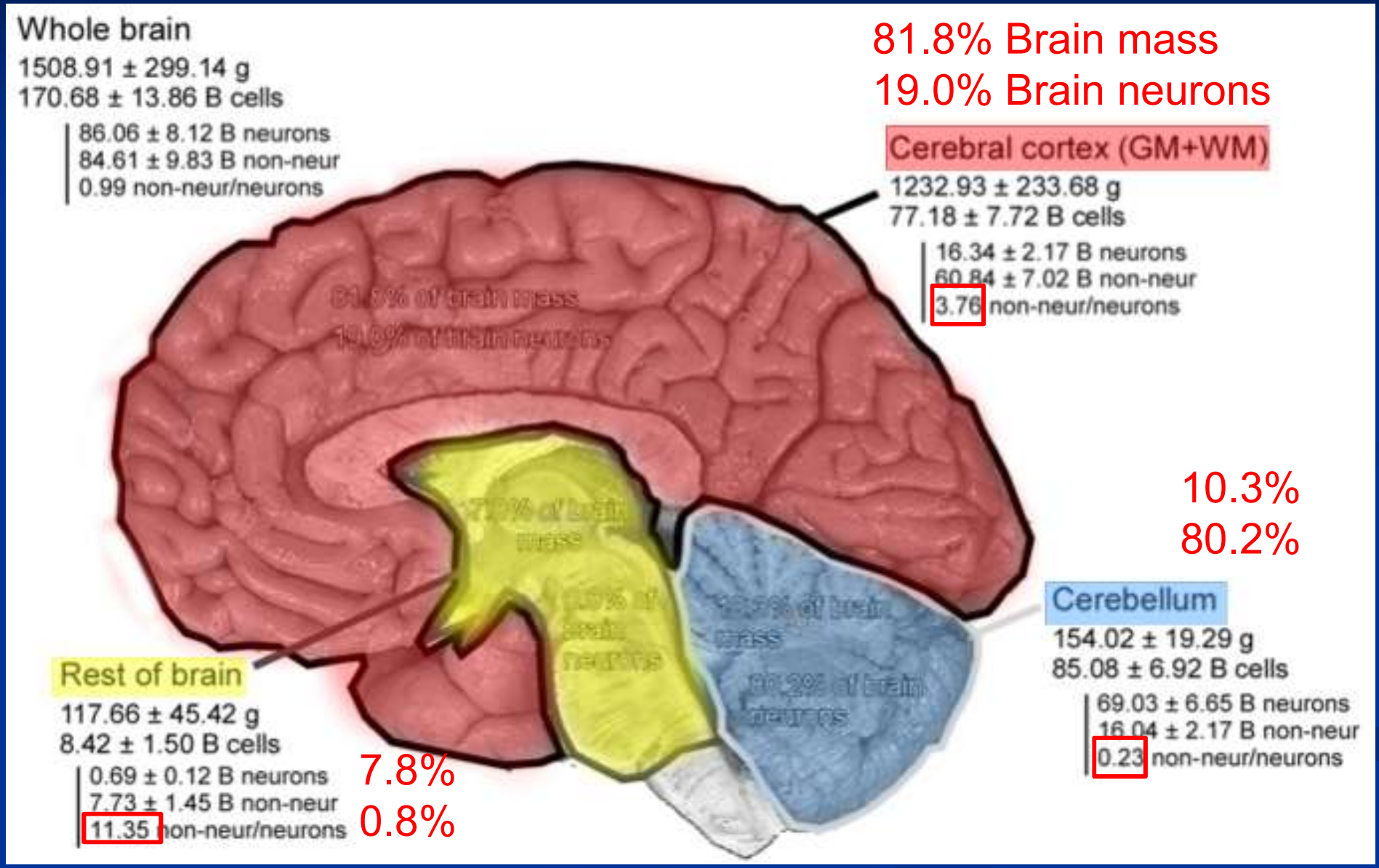
TABLE 4. Neocortical estimates of cell numbers, volume, and neuron/glia ratio In relation to gender

Gender	Neuron (mill.)	Glia (mill.)	Total (mill.)	Volume (mm3)	Neuron/glia ratio
F	1446	898	2344	–	1,61
F	1304	620	1924	8270	2,10
F	1202	628	1830	8458	1,91
F	1136	839	1975	8448	1,35
Average	1272	746	2018	8392	1,75
M	1373	748	2121	7548	1,84
M	1545	758	2303	8854	2,04
M	1302	958	2260	7862	1,36
M	1479	758	2237	10154	1,95
Average	1425	806	2230	8604	1,80

Neocortical and Hippocampal Neuron and Glial Cell Numbers in the Rhesus Monkey
THE ANATOMICAL RECORD 290:330–340 (2007)

Know Your Neurons: What Is the Ratio of Glia to Neurons in the Brain?

http://blogs.scientificamerican.com/brainwaves/2012/06/13/know-your-neurons-what-is-the-ratio-of-glia-to-neurons-in-the-brain/



Quantitative growth and development of human brain

Arch Dis Child. 1973 October; 48(10): 757–767.

Total brain DNA at different ages; (~6.7 pg per cell)

0.25 mmol at 10 weeks; 2 mmol at 2 years old

Rationales:

1. DNA amount is proportional to cell number
2. Neuron stop growing at birth but glia keep growing

Total neocortical cell number in the mysticete (鬚鯨) brain.

Anat Rec (Hoboken). 2007 Jan;290(1):83-95.

The total neocortical neuron number was 12.8 x 10^9, and the total neocortical glia number 98.2 x 10^9. (whale)(But cerebellum was not included)

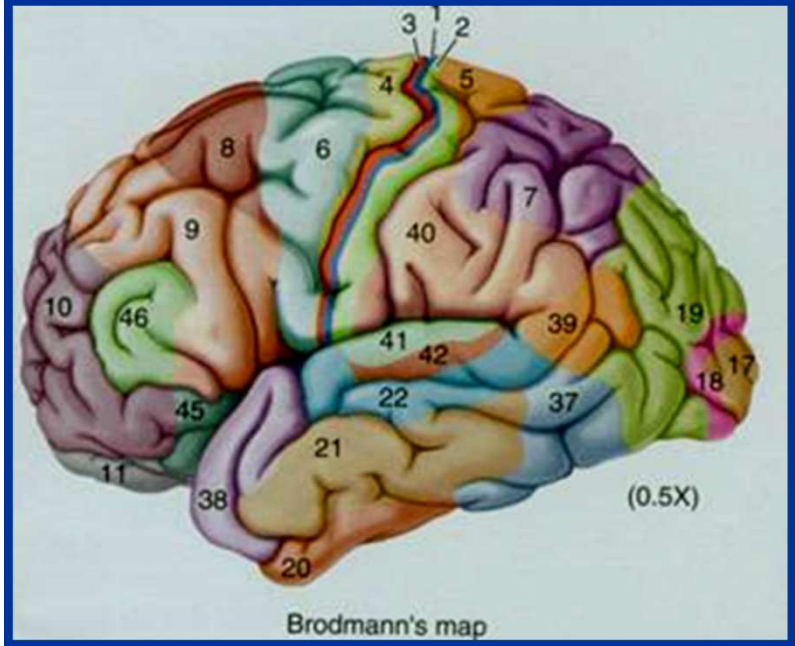
Einstein's brain: glia/neuron ratio

On the brain of a scientist: Albert Einstein.

Experimental Neurology 1985 Apr;88(1):198-204 Diamond et al. & Thomas Harvey

right and left prefrontal (9) and inferior parietal (39) cortex

Einstein had more glial cells per neuron than the average man, but in only the left inferior parietal area did he have statistically significantly more.



Brodmann's map

9: attention and working memory

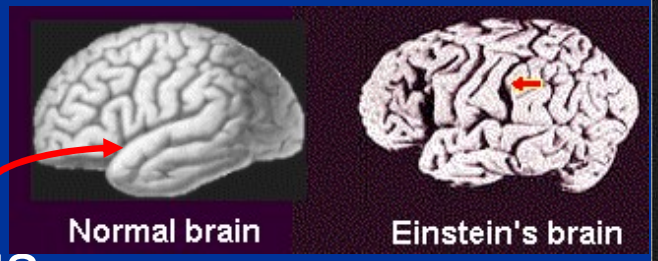
39: part of Wernicke's area

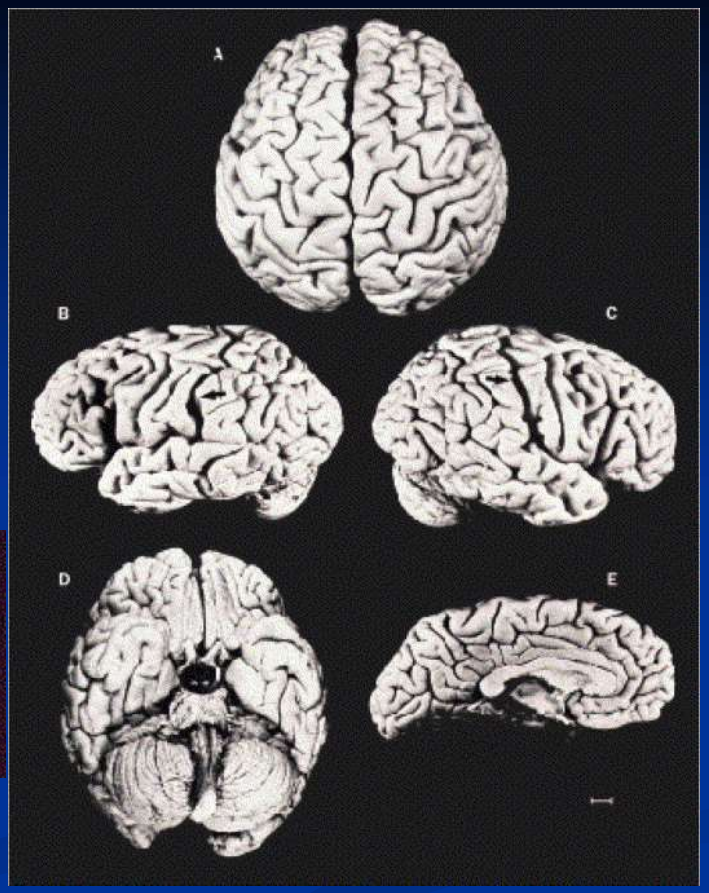
7.26

Thomas Harvey

1999 Sandra Witelson, *The Lancet* (vol. 353, pages 2149-2153)

1. Unusual pattern of grooves on left and right parietal lobes
2. Mathematical abilities and spatial reasoning
3. 15% wider
4. Shorter lateral sulcus





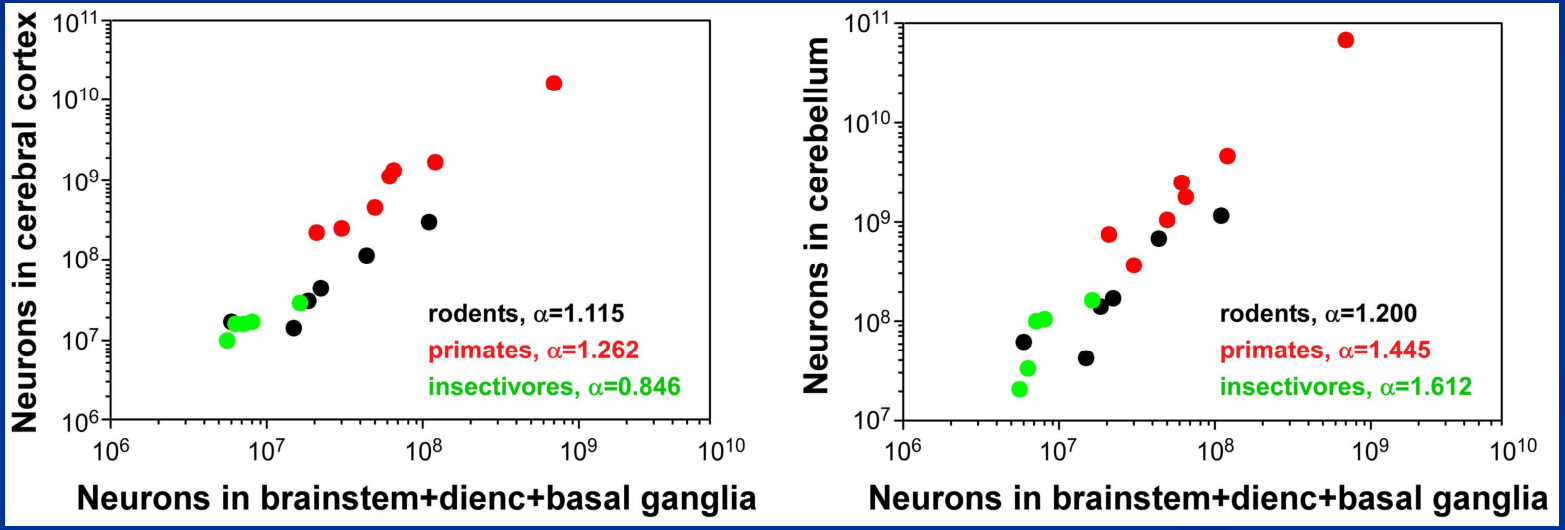
Please note that there is only one experimental object!

http://faculty.washington.edu/chudler/ein.html

星空特輯】愛因斯坦大腦傳奇誕生
http://case.ntu.edu.tw/blog/?p=1387
台灣大學科學教育發展中心

What makes us humans?

1. Brain size matters? Brain/Body ratio? White/Grey matter ratio?
2. An exception to the rule! Whatever the rule is.
3. Linearly scaled up of primate brain????



Numbers of neurons increase faster in the cerebral cortex and cerebellum than in the remaining brain areas

The human brain in numbers: a linearly scaled-up primate brain.
Front Hum Neurosci. 2009 Nov 9;3:31. doi: 10.3389/neuro.09.031.2009.

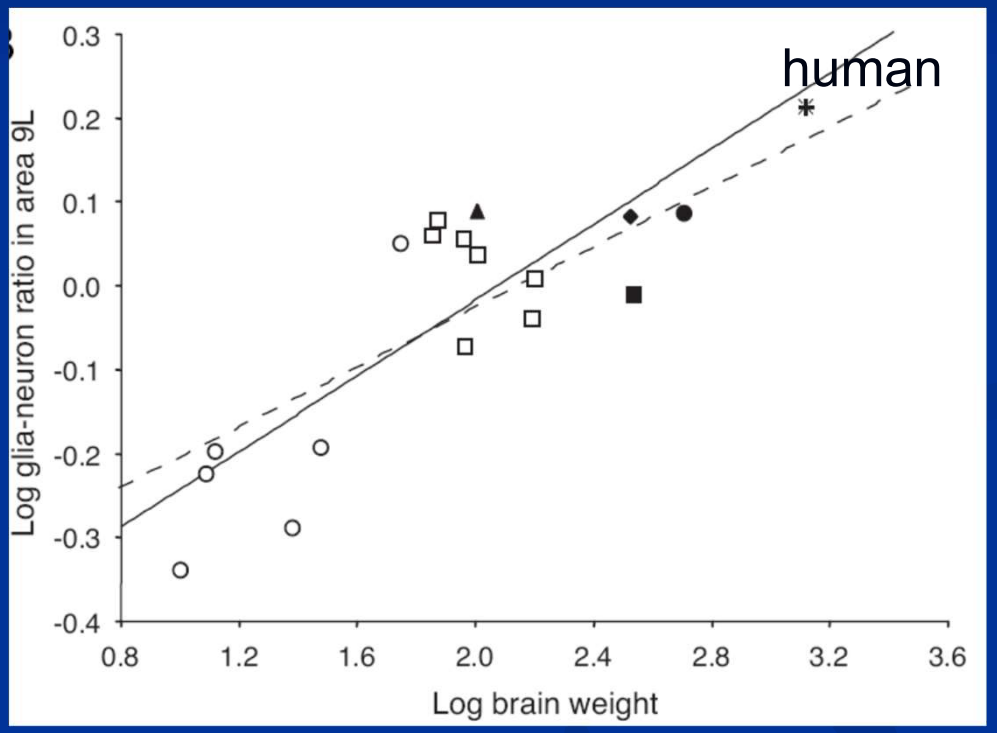
two advantages compared to other mammalian brains: compared to rodents, and probably to whales and elephants as well, it is built according to the very economical, space-saving scaling rules that apply to other primates; and, among economically built primate brains, it is the largest, hence containing the most neurons.

NEUROGLIA

1859 Rudolph Virchow, inactive “connective tissue” holding neurons together

Table 1. Brain weights and glia–neuron ratios for layer II/III of prefrontal area 9L (species mean)

Species	*n*	Brain weight, g	Glia–neuron ratio
Homo sapiens	6	1,373.3	1.65
Pan troglodytes	6	336.2	1.20
Gorilla gorilla	2	509.2	1.21
Pongo pygmaeus	2	342.7	0.98
Hylobates muelleri	1	101.8	1.22
Papio anubis	2	155.8	0.97
Mandrillus sphinx	1	159.2	1.02
Macaca maura	6	92.6	0.84
Erythrocebus patas	2	102.3	1.09
Cercopithecus kandti	1	71.6	1.15
Colobus angolensis	1	74.4	1.20
Trachypithecus francoisi	1	91.2	1.14
Alouatta caraya	1	55.8	1.12
Saimiri boliviensis	1	24.1	0.51
Aotus trivirgatus	1	13.2	0.63
Saguinus oedipus	1	10.0	0.46
Leontopithecus rosalia	2	12.2	0.60
Pithecia pithecia	1	30.0	0.64



PNAS (2006) 103 (37), 13606–13611

Human brain is not unique or anomalous; rather, the human brain is a product of changes in brain anatomy

Comment: http://www.pnas.org/content/103/37/13563.full

Similarities to neurons

1. Electrical potential difference across membrane as in neurons; sensitive to changes in this potential and to certain chemicals in the surrounding fluid
2. Some glia have neurite-like branches

Differences from neurons

1. Do not generate electrochemical impulses like those of neurons
2. Branches are symmetrical, and lack axon vs. dendrite asymmetry
3. Are generally smaller than neurons

Oligodendrocyte and Schwann cell

Astrocyte

Microglia

NG2

Why myelination?

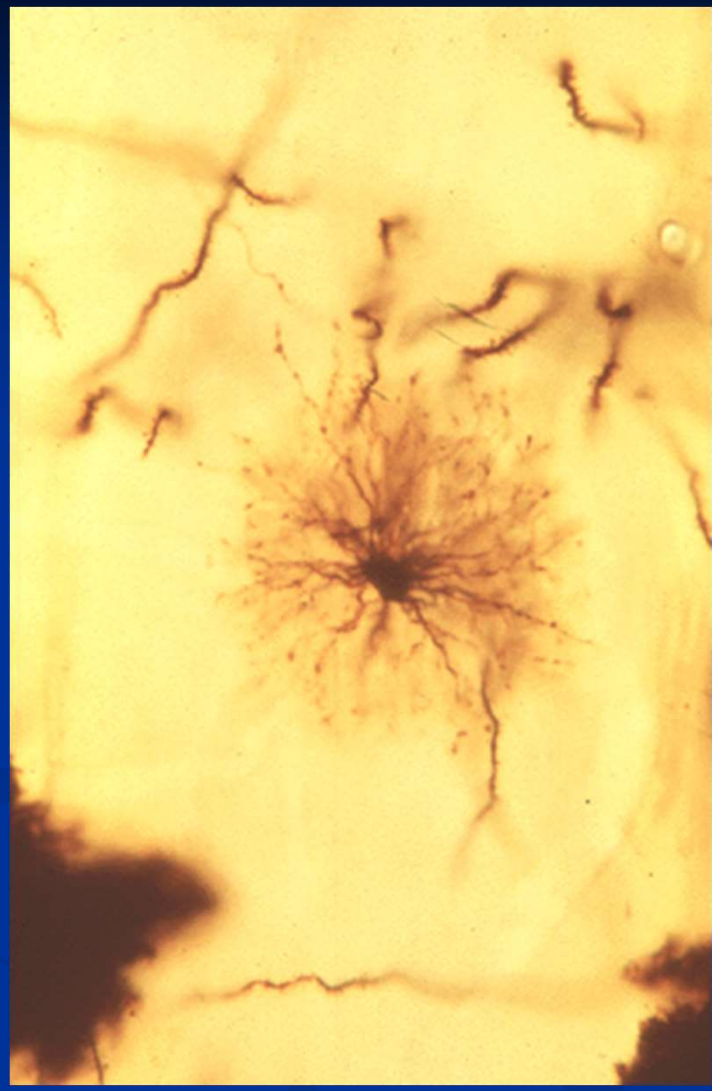
An insurmountable limit - a constraint imposed by axon size, evolution in vertebrate and invertebrate

- Conduction rate increases with axon diameter
- What if the nervous system has 10^{11} neurons as in human brain?
- To increase the conduction rate with fairly minute diameters.

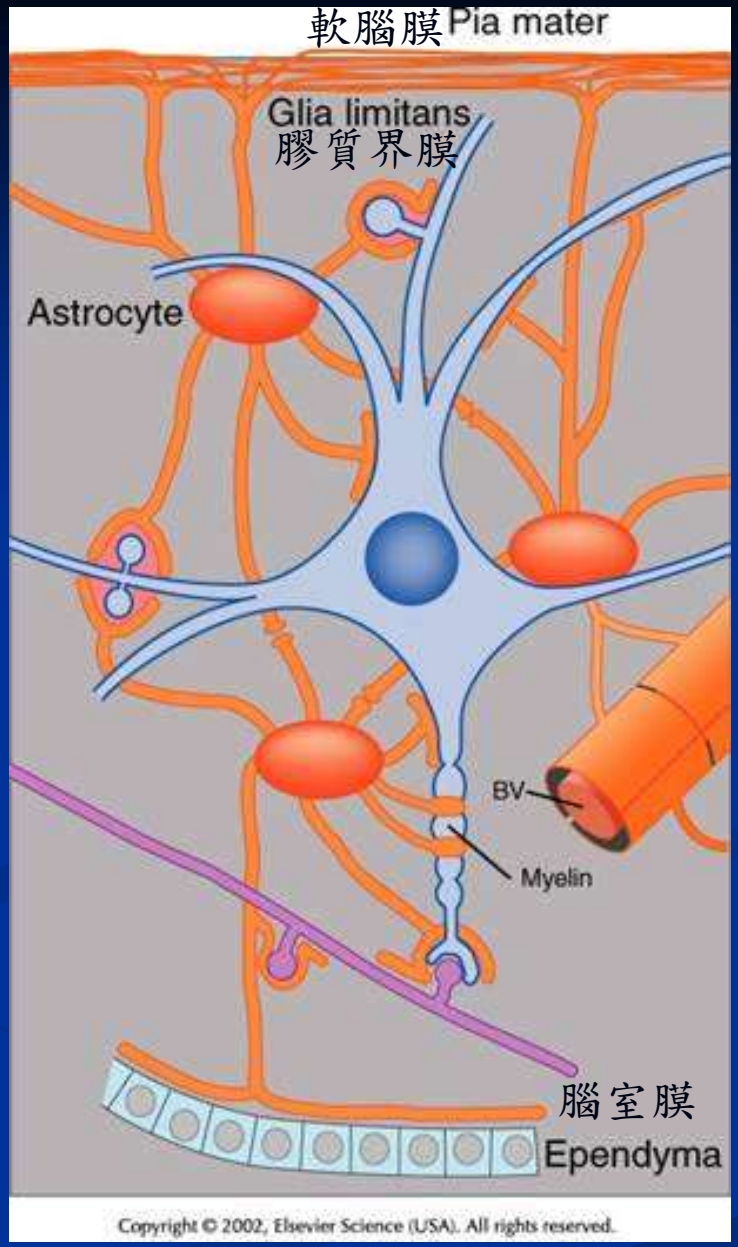
Astrocyte

constitutes 20 to 50% of the volume of most brain area

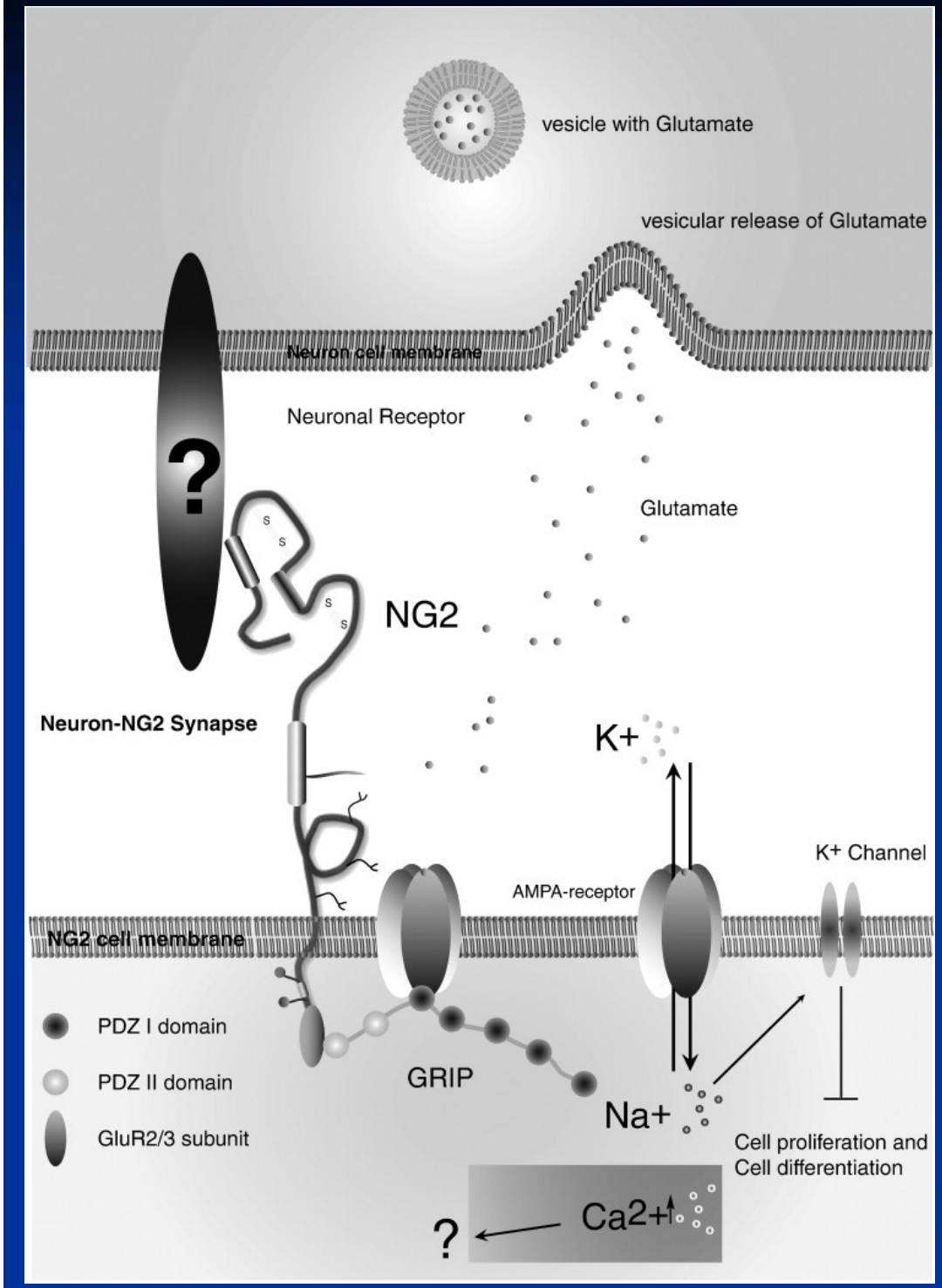
Star shape, glia end feet on capillaries, large bundle of intermediate filaments



1. Provide physical support for neurons
2. Regulate extracellular concentration of potassium ions
3. Role in neuronal communication: may influence the level of intracellular calcium ions in neurons; spatial buffering
4. May connect to each other by gap junctions, forming syncytium (calcium wave propagation)
5. Inducing tight junctions in endothelia cells to form blood brain barrier
6. Role of migration and guidance of neuron during early development
7. Produce growth factors and cytokines
8. Regulate neurotransmitter uptake and inactivation
9. Has ion channels and receptors
10. More to come



Squire 3.10



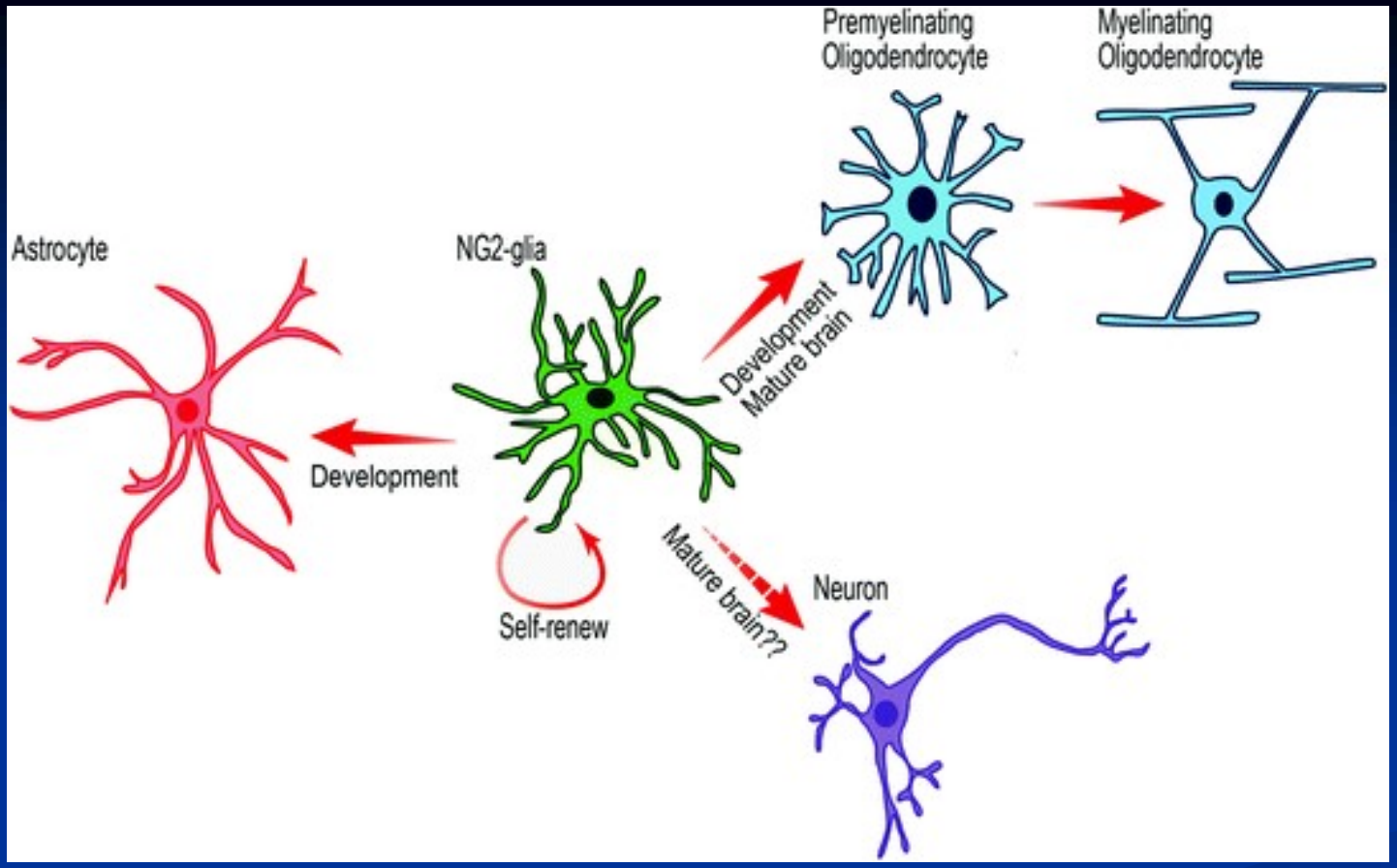
NG2: Neuron-glia 2, a proteglycan, 330 KDa, 2327 a.a.

5~10% glia cells stained with Ab against NG2

NG2 cells are interesting as niche components also because they receive synaptic input from neurons and might modulate glutamate signaling

(LEFT) The role of the NG2 protein at the neuron-glial synapse. The NG2 protein could play a role in clustering the glial AMPA receptors towards the site of neuronal glutamate release. Glutamate acting on NG2 cells may thus regulate proliferation and differentiation and also cause a rise in intracellular calcium

NG2 cells: Properties, progeny and origin. Brain Res Rev. 2010 May;63(1-2):72-82



Scheme representing the different cell fates of NG2-glia. Canonically, NG2-glia have the capability to proliferate and differentiate into oligodendrocytes in the immature and mature brain. However, NG2-glia can also differentiate into astrocytes in the ventrolateral forebrain during development. Additionally, some studies have suggested that, in the mature brain, NG2-glia could also differentiate into neurons, nevertheless, these claim is still under strong criticism.

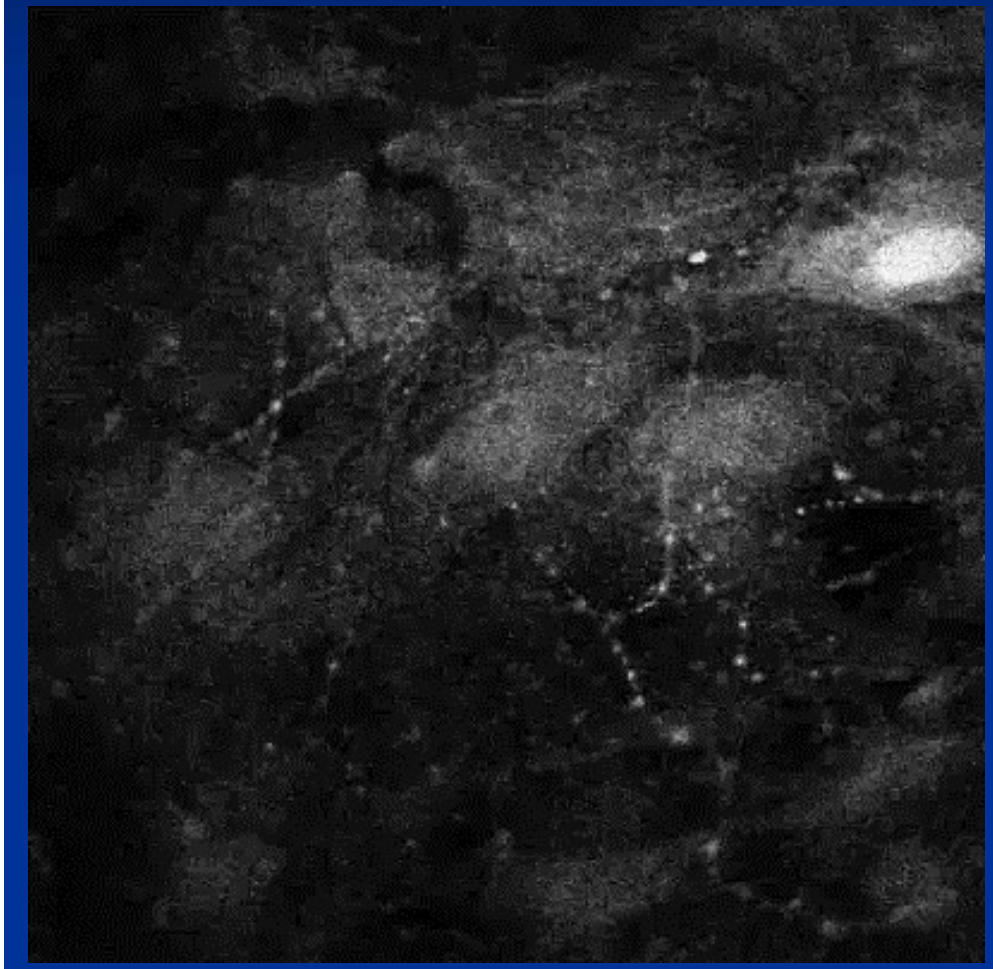
NG2-glia, More Than Progenitor Cells. Adv Exp Med Biol. 2016;949:27-45.

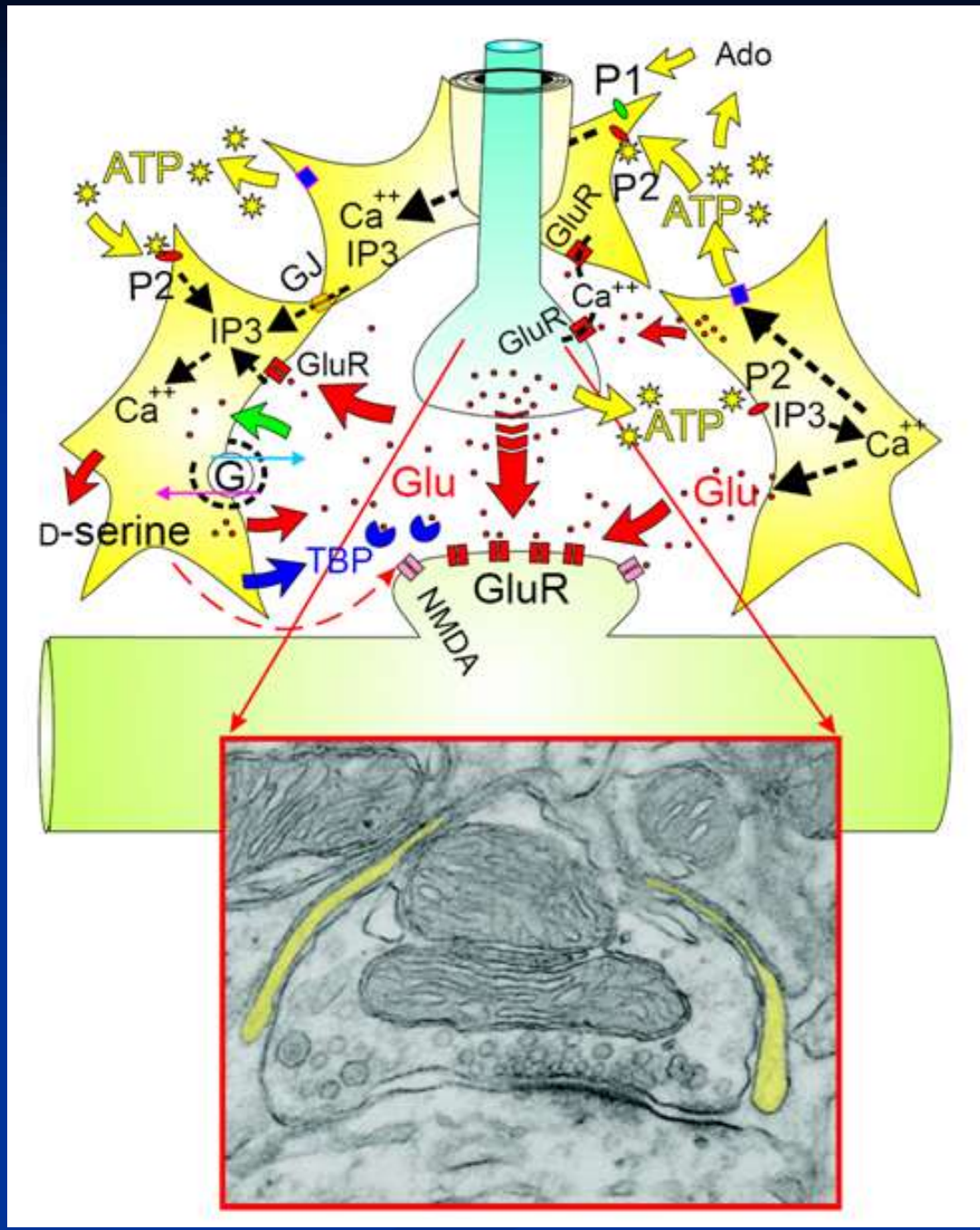
Is glia just for supportive?

Science (2002) 298(5593), 556-562

New Insights into Neuron-Glia Communication,

R. D. Fields & B. Stevens-Graham

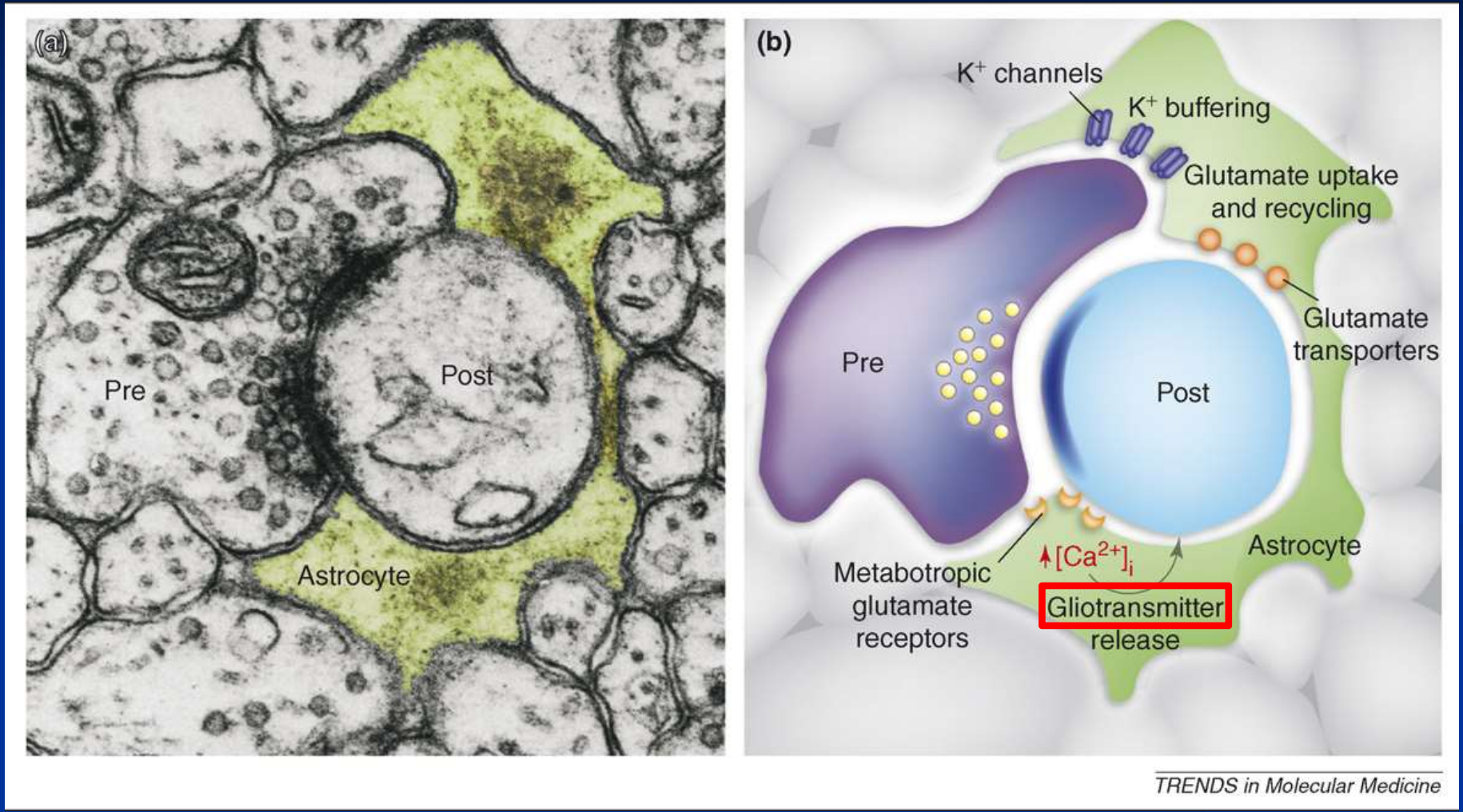




http://www.sciencemag.org/content/vol298/issue5593/images/data/556/DC1/1069939S1.mov

Science (2002) 298(5593), 556-562

Tripartite

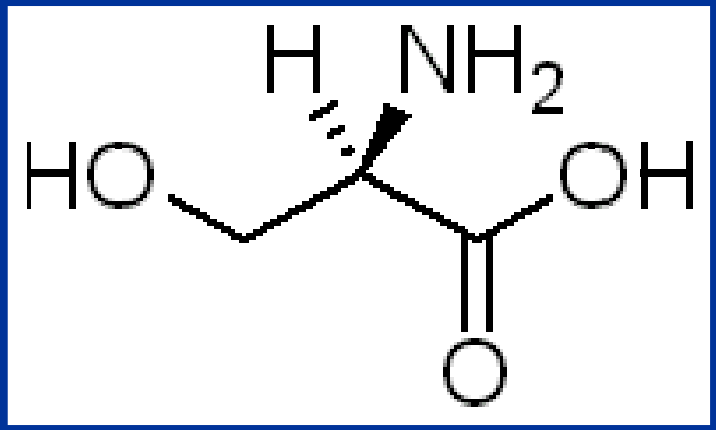


TRENDS in Molecular Medicine (2007) 13(2), 54-63

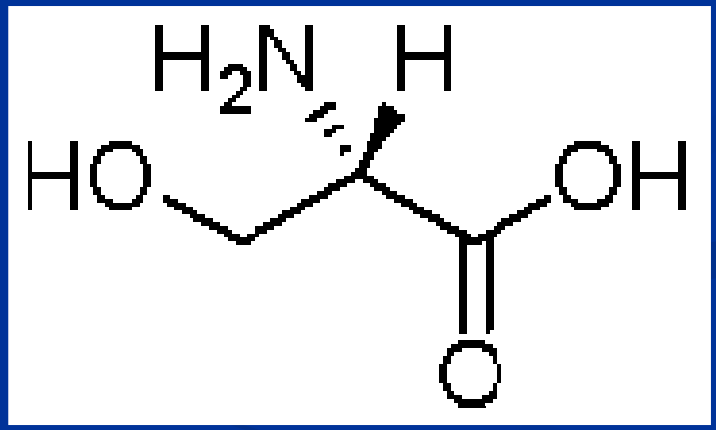
Gliotransmitter

glutamate, taurine, ATP, D-serine, TNF-α, and counting

D-serine

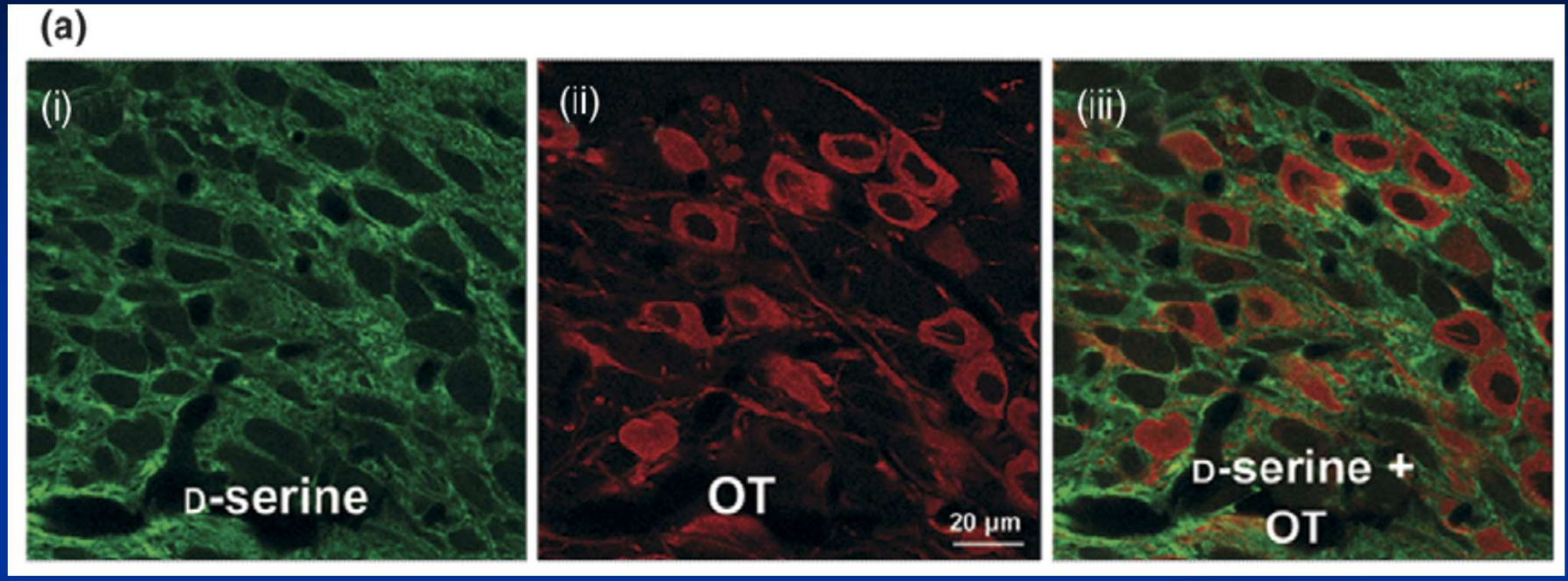


L-serine



general amino acids

Stored in glia

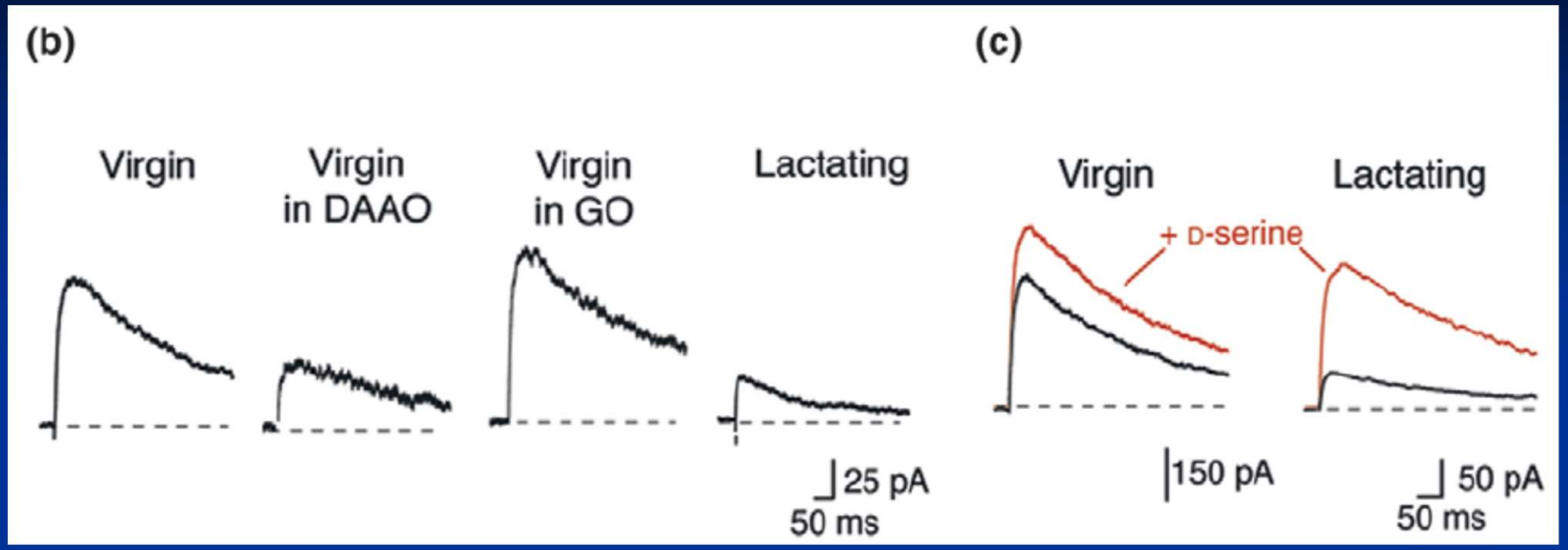


Supraoptic nucleus of rat hypothalamus: neurons synthesize oxytocin (OT) or vasopressin, projects to posterior pituitary gland

Immunostaining

Panatier et al. (2006) Cell 125, 775-784

Mimics function



DAAO: D-amino acid oxidase

GO: glycine oxidase

During lactation, glia coverage is reduced

Glia release D-serine to enhance neuron activity

D-serine is more potent than glycine in enhancing NMDA receptor

D-Serine enhance plasticity

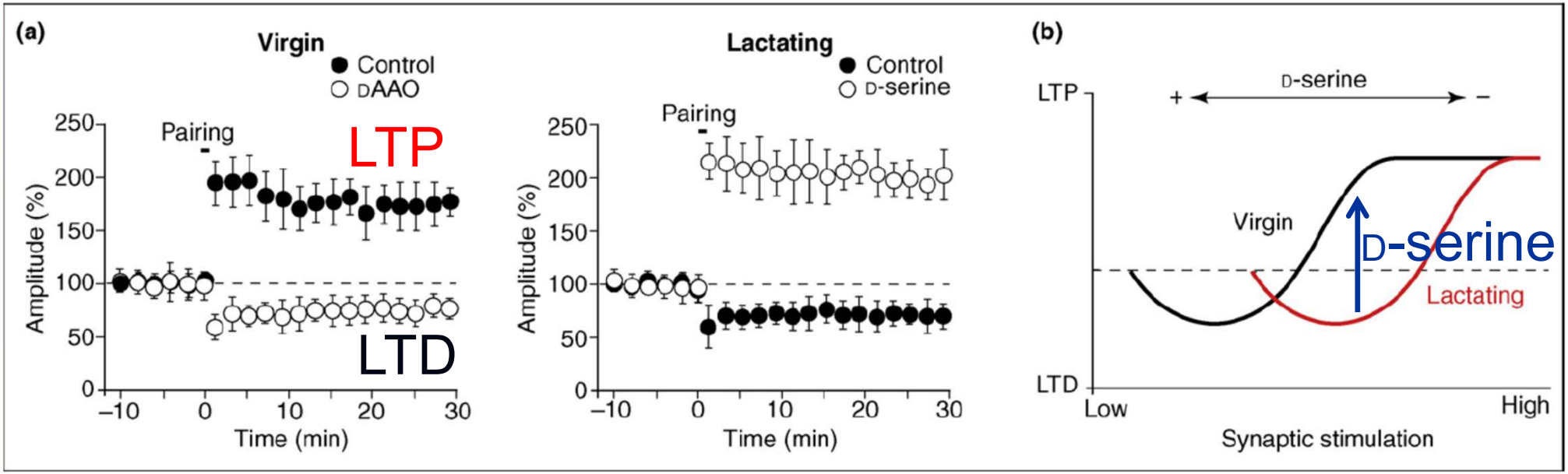


Figure 2. D -serine-mediated metaplasticity. **(a)** Pairing synaptic stimulation with membrane depolarization induces LTP in the supraoptic nucleus of virgin rats (left panel; control). By contrast, in lactating animals, where D-serine levels in the synaptic cleft are reduced, it causes LTD (right panel; control). LTP can be restored in lactating rats by supplying D-serine to the slices (right panel; D-serine), whereas LTP can be transformed into LTD in virgin animals when D-serine is degraded with DAAO (left panel; DAAO). The short bar represents the time during which the pairing protocol was applied. **(b)** At these synapses, the induction of plasticity depends on the rate of synaptic stimulation, according to the model described by Bienenstock, Cooper and Munro (black curve; virgin). Glial withdrawal in the supraoptic nucleus (red curve; lactating) causes a rightward shift of the activity dependence of synaptic plasticity. As a consequence, an LTP-inducing protocol in virgin animals causes LTD in lactating rats. Importantly, this relationship between plasticity and synaptic stimulation is governed by the availability of D-serine in the synaptic cleft, which is itself dependent on the glial environment (Adapted from [11]).

LTP: long-term potentiation

LTD: long-term depression

Summary

- Synapse
- Active zone
- Quantal Release
- Signal Integration
- Tripartite

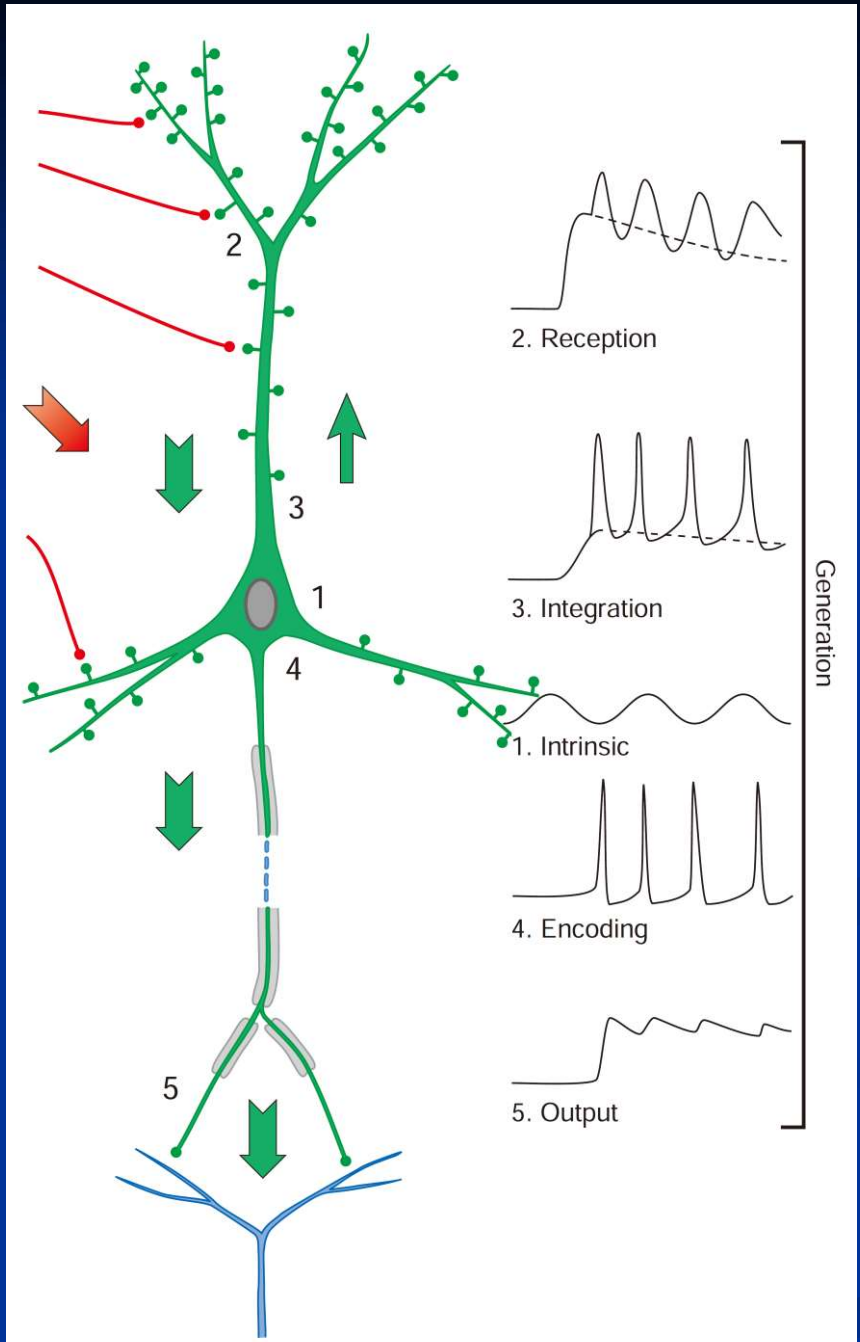


FIGURE 5.1 Nerve cells have four main regions and five main functions. Electrotonic potential spread is fundamental for coordinating the regions and their functions.

Squire 5.1

The BRAIN Initiative (Brain Research through Advancing Innovative Neurotechnologies, or Brain Activity Map Project, NIH, US)
https://braininitiative.nih.gov/

By accelerating the development and application of innovative technologies, researchers will be able to produce a revolutionary new dynamic picture of the brain that, for the first time, shows how individual cells and complex neural circuits interact in both time and space.

The Human Brain Project (HBP), European Union
https://www.humanbrainproject.eu/

aims to put in place a cutting-edge research infrastructure that will allow scientific and industrial researchers to advance our knowledge in the fields of neuroscience, computing, and brain-related medicine

In the next 10 years, these two “huge” projects will invest a lot of resources (over 1 billion) to study “neurons”. These projects will include not only the basic neuroscience but interdisciplinary researches.

日本**Brain/MINDS**, https://brainminds.jp/en/

(Brain Mapping by Integrated Neurotechnologies for Disease Studies)

With the goal of developing the common marmoset as a model animal for neuroscience, the project aims to build a multiscale marmoset brain map, develop new technologies for experimentalists, create transgenic lines for brain disease modeling, and integrate translational findings from the clinical biomarker landscape

大陸腦科學與類腦研究：納入十三五計劃 (2016-2020)及科技創新2030中。以腦認知原理為主體，以類腦計算與腦機智能、腦重大疾病診治為兩翼，搭建關鍵技術平臺，搶佔腦科學前沿研究制高點

韓國腦科學發展策略：2023年時完成超高解析度的腦部圖像以及10個以上的代表性腦研究成果；預計將在未來10年內挹注約3億美元推動腦科學研究。

http://iknow.stpi.narl.org.tw/post/Read.aspx?PostID=12508

科技部「腦科學專案研究計畫」，兩個發展主題：(1) 神經退化；(2) 慢性疼痛。每一主題均強調跨領域合作、針對需求發展創新技術、從基礎到應用的結合、人與動物模式並行研究。

NEW DIRECTIONS?

ARTIFICIAL INTELLIGENCE (AI)?

So, if you are interested in neuroscience, you may consider these topics as your future research directions.

Goals of neuroscience: how the nervous system functions at various levels

- Brain's activity reflected in behaviour
- Computer-assisted imaging techniques
- New treatments for nervous system disorders
- Noninvasive methods
- Experiments in live tissue

ETtoday

台灣快速高齡化2030將成超高齡社會 (2018/8/31)

大紀元 (新聞發布) - 17 小時前

報告指出，台灣未來仍維持高齡少子化趨勢，預估2030年老年人口將增 ... 減少及年齡偏高齡化影響，未來將持續下降，預估2030年將減少至268萬 ...

人口拉警報！台灣邁入高齡化社會長照勞動力教育都是問題

ETtoday - 7 小時前

不婚不生！2022年台灣人口轉負成長8年後進入超高齡社會

台灣好新聞 - 20 小時前

人口有危機政府還在打游擊

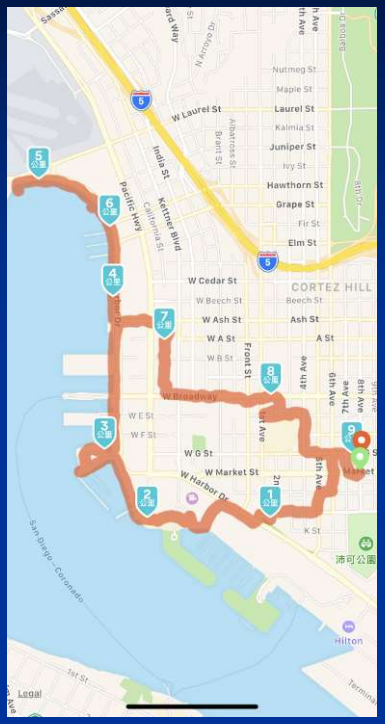
評論 - udn 聯合新聞網 - 10 小時前

國發會：2022年台灣人口負成長2027年人口紅

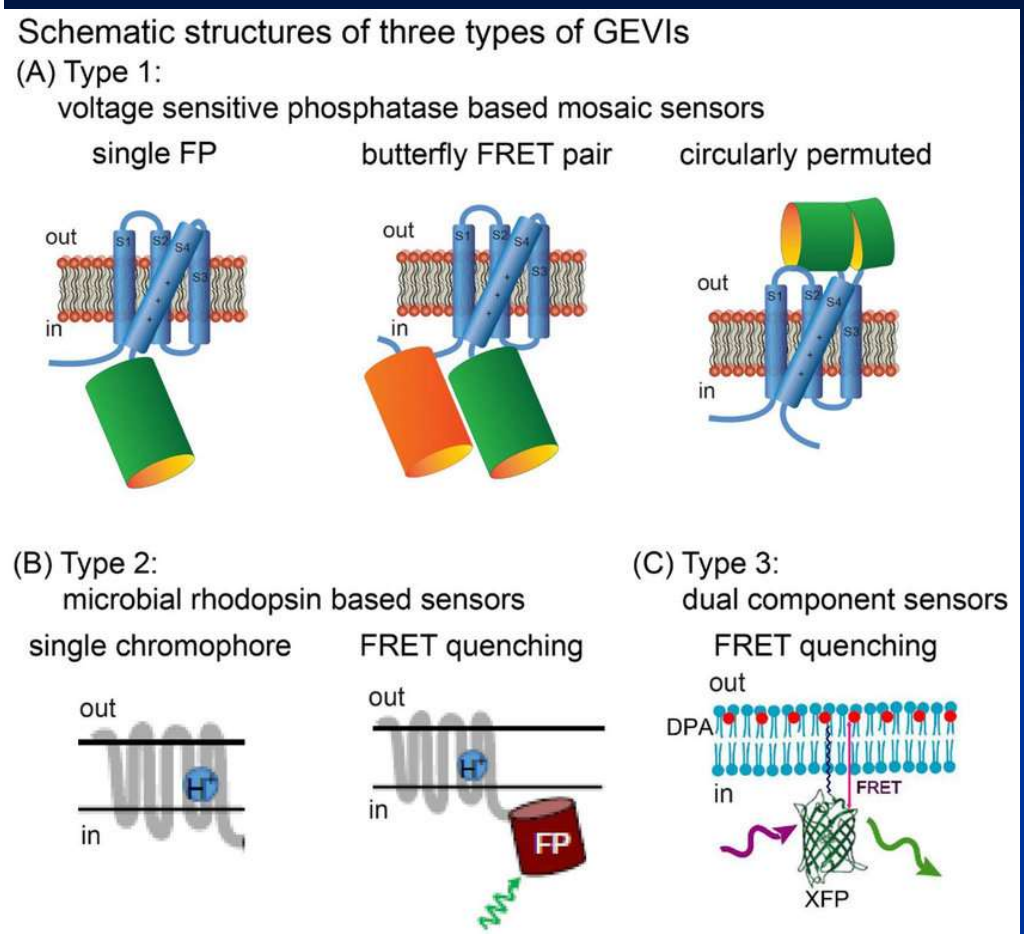
深入報導 - NOWnews - 18 小時前

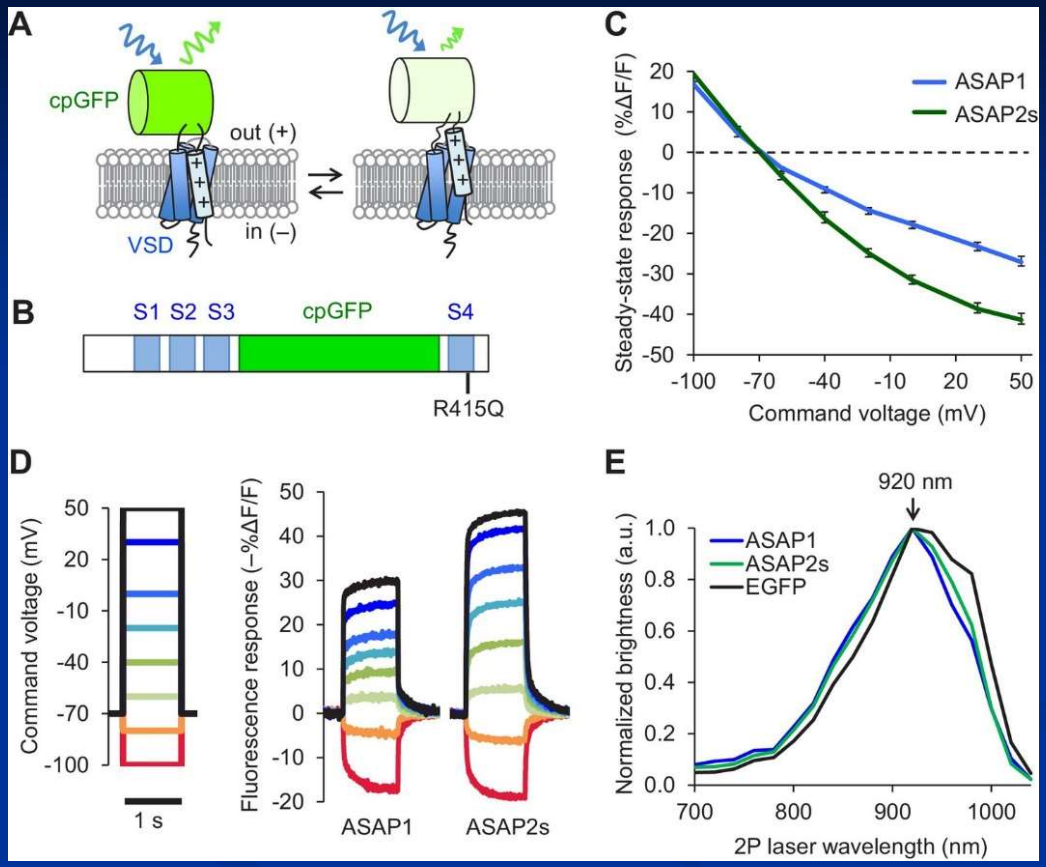
高齡化來臨國發會:2021年台人口負成長

Society For Neuroscience Meeting 2018/11/3-8, San Diego

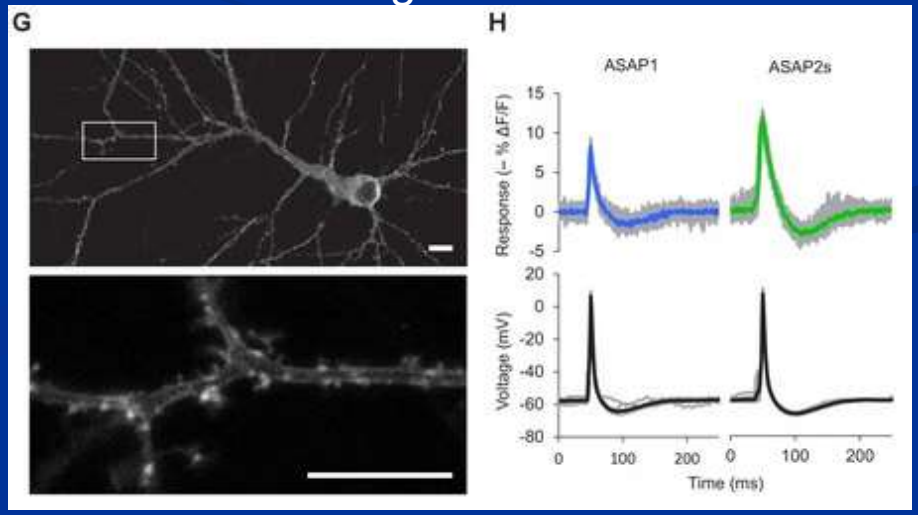


SPC18: The Need for Speed: Development and Use of Genetically Encoded Voltage Indicators Michael Lin, Neurobiology, Stanford University, Stanford, CA.

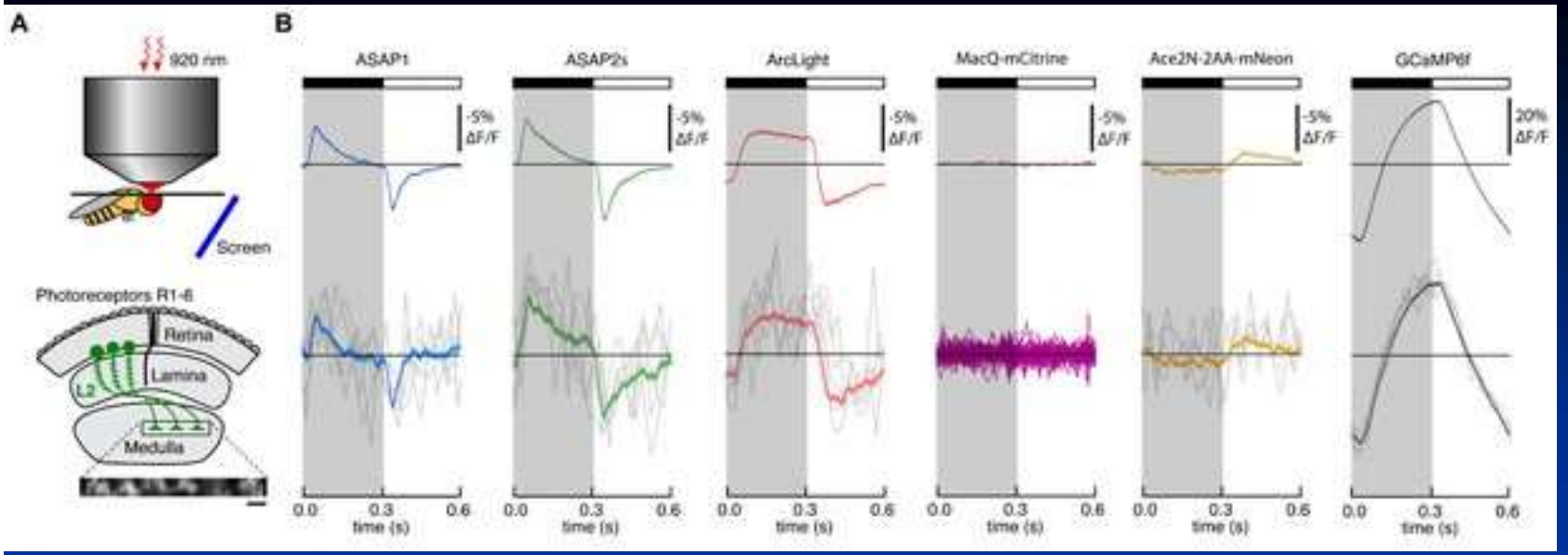


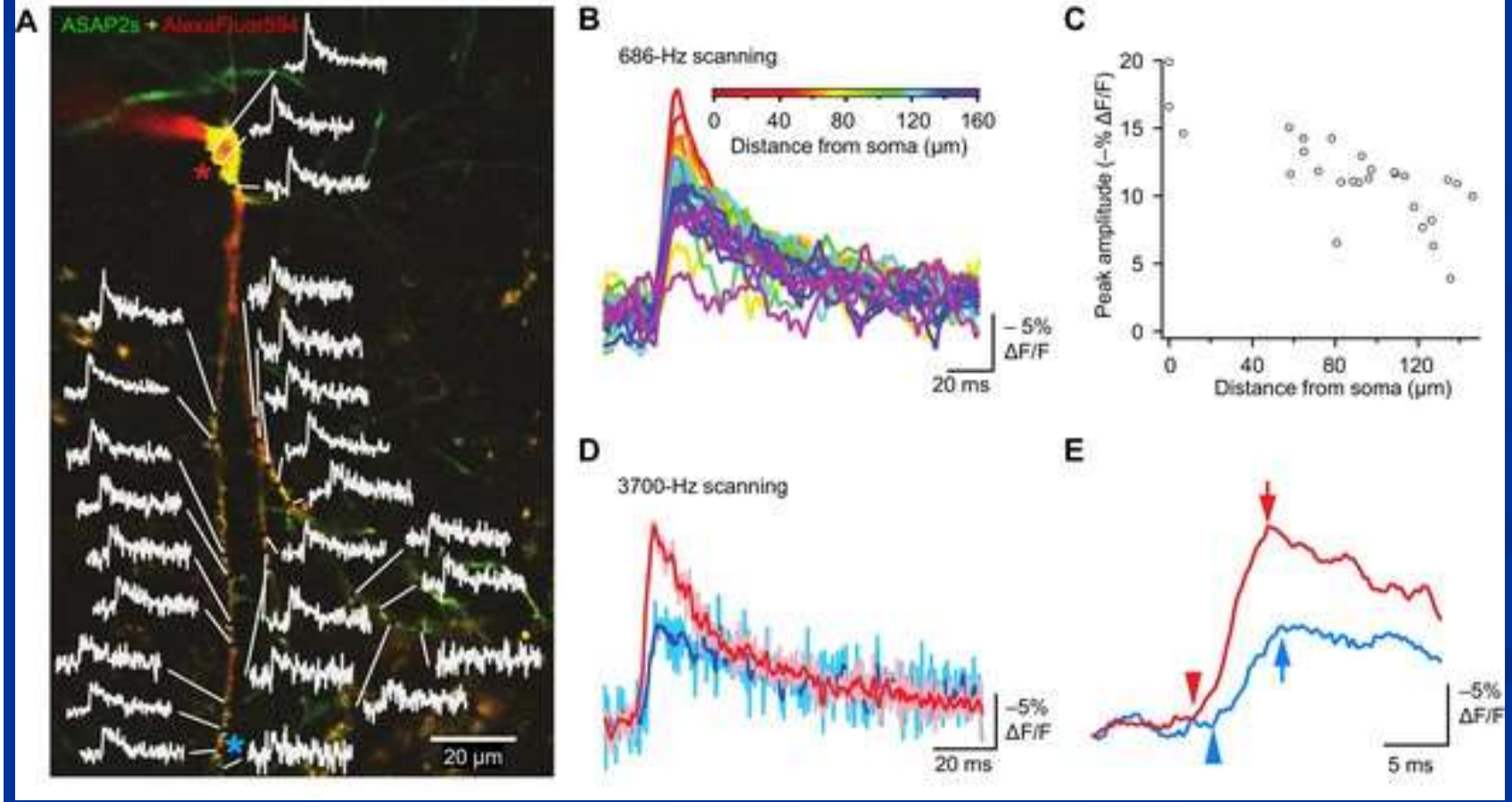


https://elifesciences.org/articles/25690



Trends in Neurosciences 39(5):277-89 · May 2016


A
920 nm
Screen
Photoreceptors R1-6
Retina
Lamina
L2
Medulla
B
ASAP1
ASAP2s
ArcLight
MacQ-mCitrine
Ace2N-2AA-mNeon
GCaMP6f
-5% ΔF/F
20% ΔF/F
0.0
0.3
0.6
time (s)

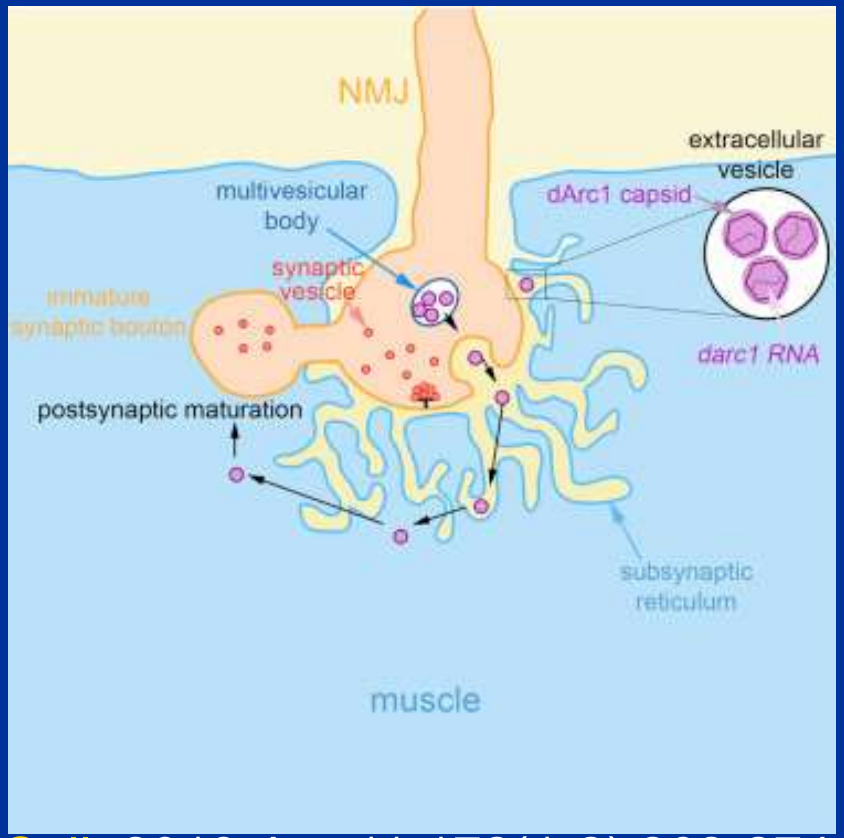

A
ASAP2s + AlexaFluor594
20 µm
B
686-Hz scanning
0
40
80
120
160
Distance from soma (µm)
– 5% ΔF/F
20 ms
C
Peak amplitude (–% ΔF/F)
20
15
10
5
0
0
40
80
120
Distance from soma (µm)
D
3700-Hz scanning
–5% ΔF/F
20 ms
E
–5% ΔF/F
5 ms

001 Dialogues between neuroscience and society: Music and the Brain – Pat Metheny, Musician & Composer, New York City, NY

Pat是爵士吉他音樂家，獲得20次Grammy award及3張金唱片。神經生物研究知道音樂經由耳道進入耳蝸，再到大腦皮質。而音樂家並不了解這些，但知道這是一個整體的感覺。且在不同時期，其音樂風格不同，這些則是creativity & innovation的展現。甚至利用42弦及他進行音樂創作。而對生物學家想知道的則是如何能控制這麼複雜 (雖然Pat覺得一點問題都沒有)，因此利用MRI imaging，研究音樂家彈奏音樂時，大腦的區域活動。

009 The dArc Matter of Synaptic Communication

V. BUDNIK, Dept. of Neurobio., Univ. of Massachusetts Med. Sch., Worcester, MA



Activity-Regulated Cytoskeleton-Associated protein (Arc/Arg3.1)

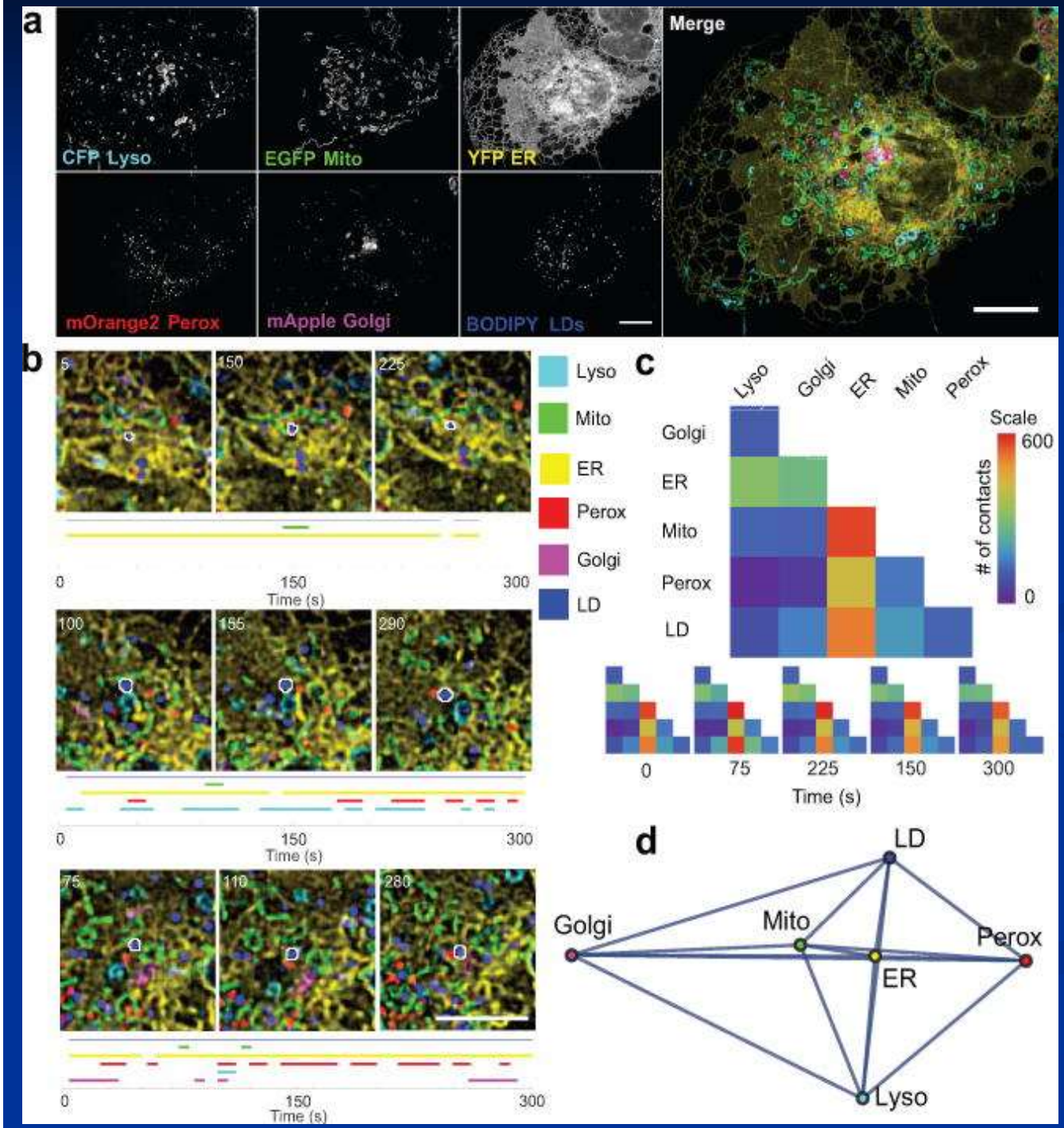
highly significant Arc/dArc1 role in trans-synaptic signaling; Arc/dArc1 proteins can form capsids capable of packaging RNAs. These capsids are loaded into EV-like vesicles that can be released from synaptic sites and taken up by synaptic partners.

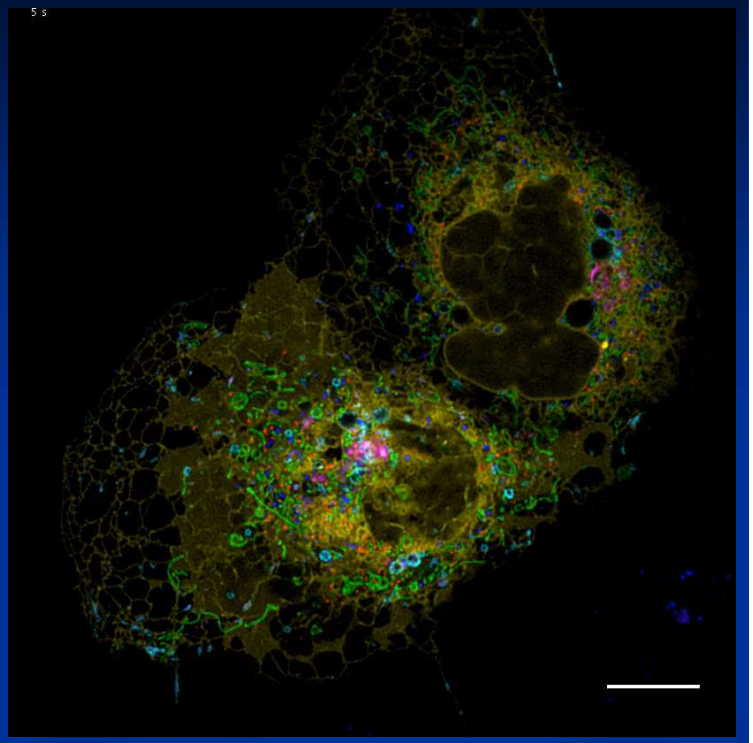
Cell. 2018 Jan 11;172(1-2):262-274.e11. doi: 10.1016/j.cell.2017.12.022.

Retrovirus-like Gag Protein Arc1 Binds RNA and Traffics across Synaptic Boutons.

256 Organelle Structure and Dynamics: What High-Resolution Imaging Is Uncovering

J. LIPPINCOTT-SCHWARTZ, Janelia Res. Campus, Ashburn, VA



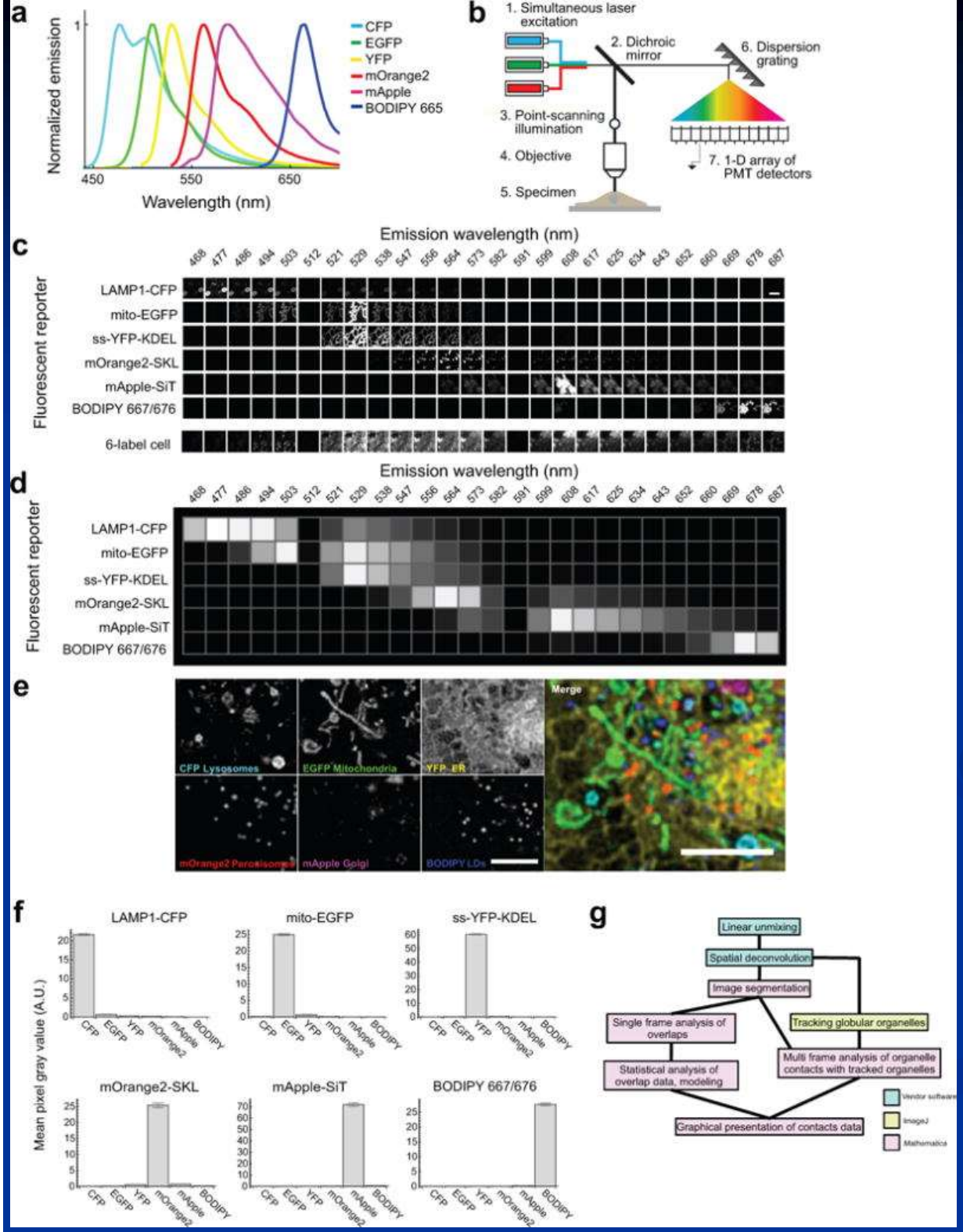


Applying systems-level spectral imaging and analysis to reveal the organelle interactome

Nature. 2017 Jun 1; 546(7656): 162–167.

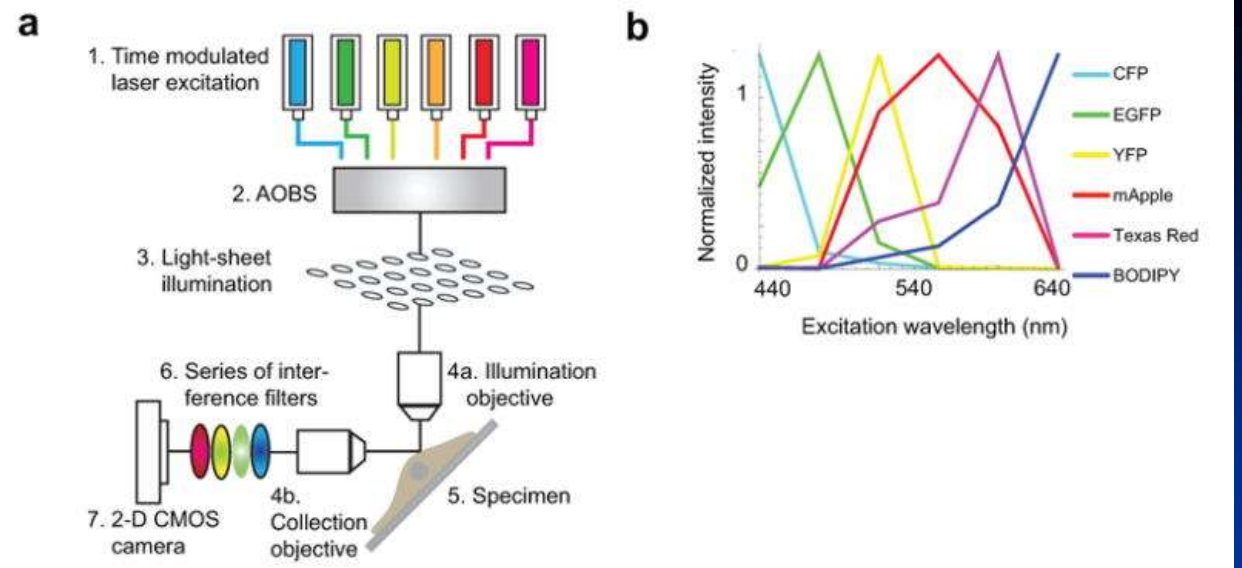
The organelle interactome: 2 organelles must be within 1 pixel, that is 160 nm in confocal imaging.

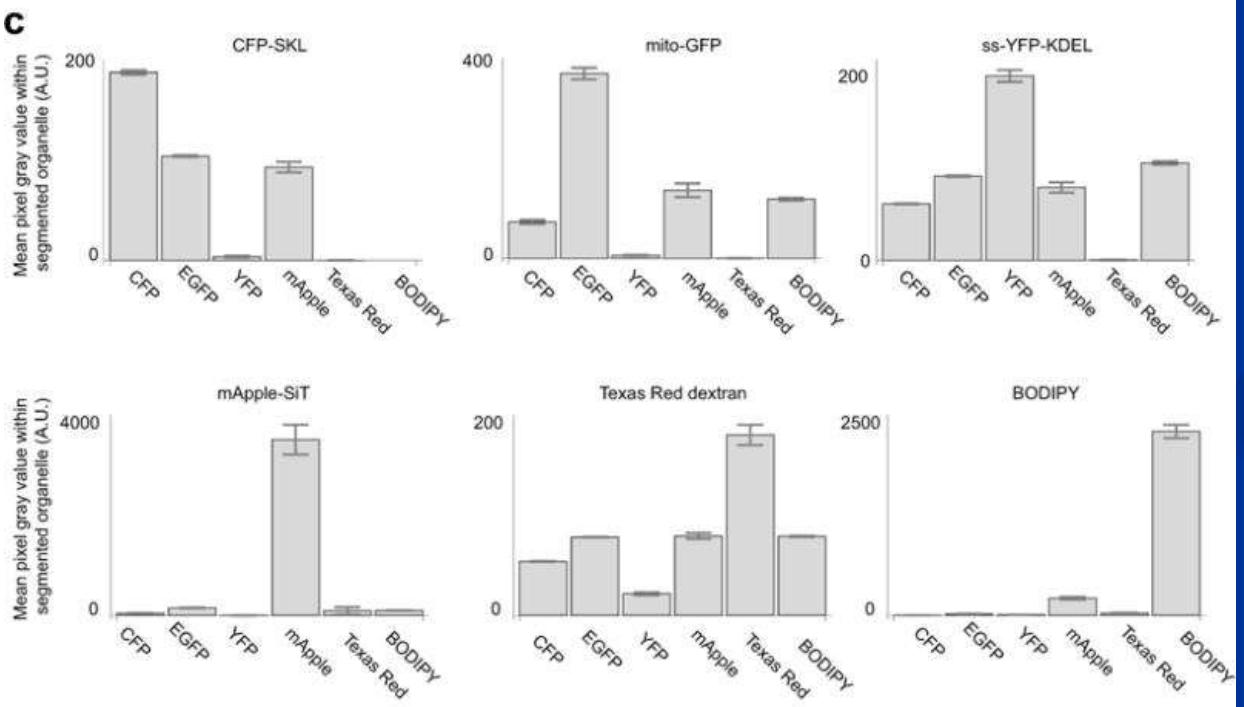
The interaction is cytoskeleton-dependent

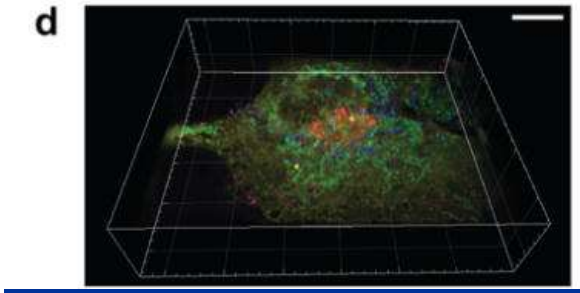


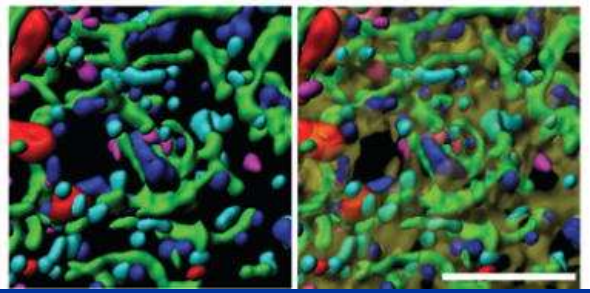
linear unmixing (LU), involves a matrix inverse operation to find the best fit of known fluorophore spectra to that of the recorded spectrum at every pixel in a digital image

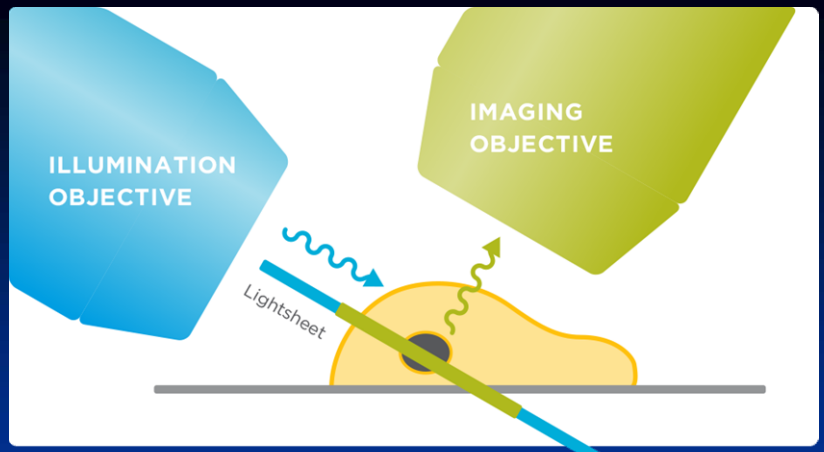
Point-scanning illumination. Emitted light was collected by a linear array of detector elements after being dispersed by a reflective dispersion grating.











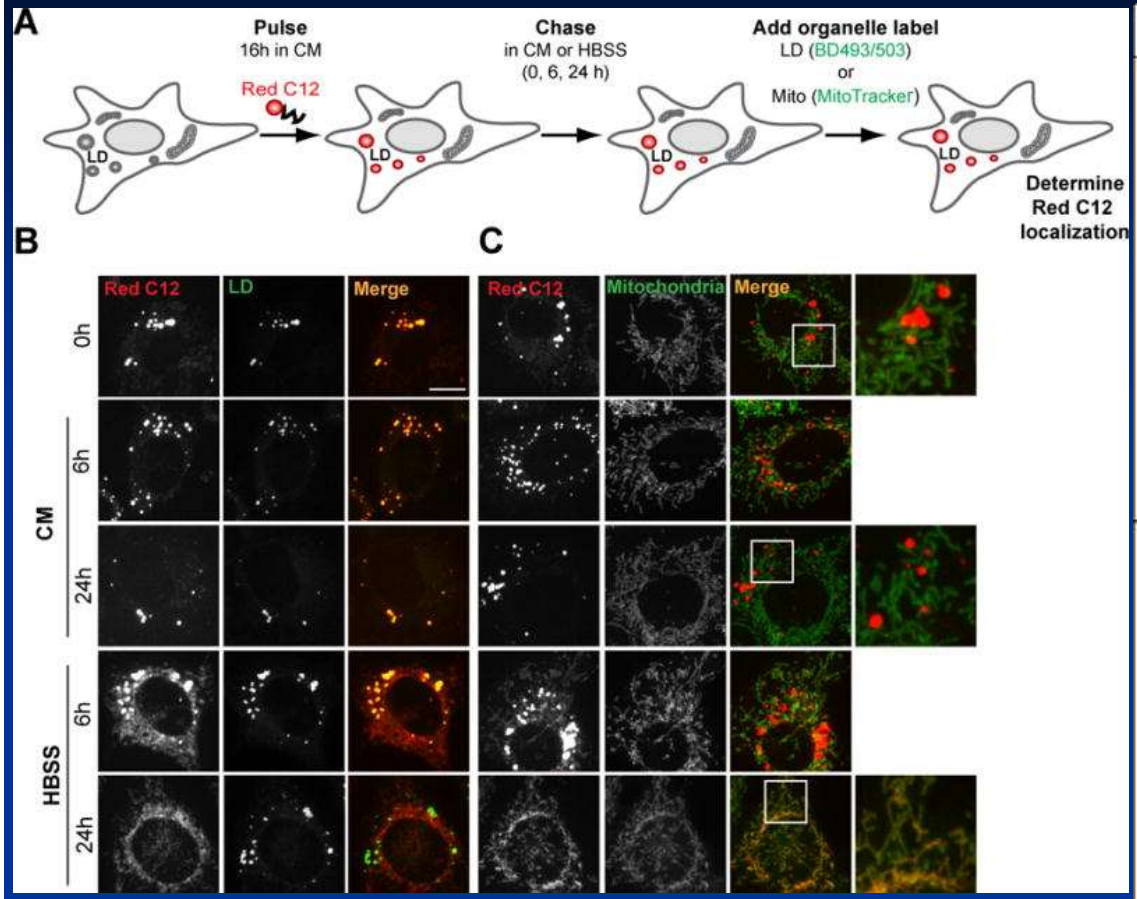
https://www.intelligent-imaging.com/lattice

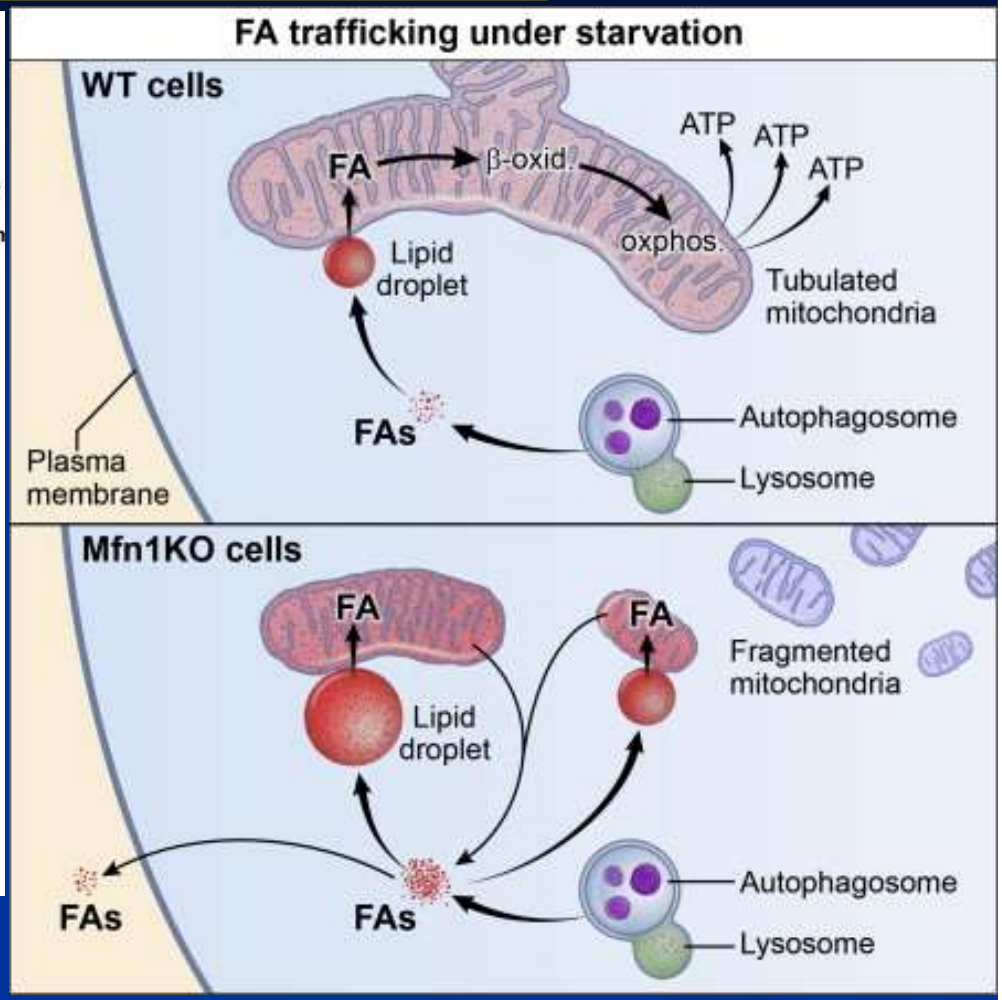
First developed by Nobel Laureate Dr. Eric Betzig, the 3i **Lattice Light Sheet** microscope; create an ultra-thin light sheet to image with unparalleled optical sectioning at extremely low photo- dosage and phototoxicity

Organelle measurement	Value
Lipid droplets	
Number per cell*	157 +/− 21
Mean volume*	0.41 +/− 0.05 μm^3
Total volume per cell*	65 +/− 10 μm^3
Maximum speed^	155.3+/−0.1 nm/s
Peroxisomes	
Number per cell*	186+/−19
Volume*	0.27 +/− 0.02 μm^3
Total volume per cell*	48 +/− 6 μm^3
Maximum speed^	148.9 +/− 0.1 nm/s
Lysosomes	
Number per cell*	89 +/− 10
Volume*	0.24 +/− 0.02 μm^3
Total volume per cell	20 +/− 2 μm^3
Maximum speed*	377.7+/− 0.1 nm/s
Golgi	
Total volume per cell*	42 +/− 3 μm^3
ER	
Total volume per cell*	1538 +/− 178 μm^3
Mitochondria	
Total volume per cell*	179 +/− 20 μm^3
ERMCSs	
Number per cell^	550 +/− 90
Total area^	60 +/− 10 μm^2
Whole Cell	
Total volume per cell*	6074 +/− 464 μm^2

Total is 37% of a cell

Fatty acid trafficking in starved cells: regulation by lipid droplet lipolysis, autophagy and mitochondrial fusion dynamics Dev Cell. 2015 Mar 23; 32(6): 678–692.





fluorescent FA pulse-chase assay: cells were pulsed with Red C12 overnight, washed, and incubated with CM for 1 h in order to allow the Red C12 to accumulate in LDs

Autophagy drives LD growth during starvation. Autophagy mobilizes phospholipids from cellular membranes during starvation

Mitochondrial fusion deficiencies result in increased FA storage

Overstimulated neurons form droplets because of too many pyruvate waiting to be converted to ATP. Compare Control, NMDA, NMDA+AP5. Such FA droplet cause fragmented mito., increased membrane peroxidation, and autophagy. The autophagy pathway will try to digest the FA droplets as a protection from FA toxicity.

Co-culture of neurons in one side and astrocyte in the other side gapped by coverslip distance. The FA droplet in neuron moves to astrocyte/microglia?

Collect the conditioned medium, in the high-speed (20,000 g?) fraction to identify ApoE/HDL/LDL particle. Red C12 labled from neuron to astrocyte mito.

In mouse brain, FA droplet accumulation in damaged region, preferentially in astrocytes and microglia.

So, 1. FA toxicity avoidance; 2. Transfer to glia; 3. Glia response to stimulation; 4. Astrocytes' protective role of over-excited neurons

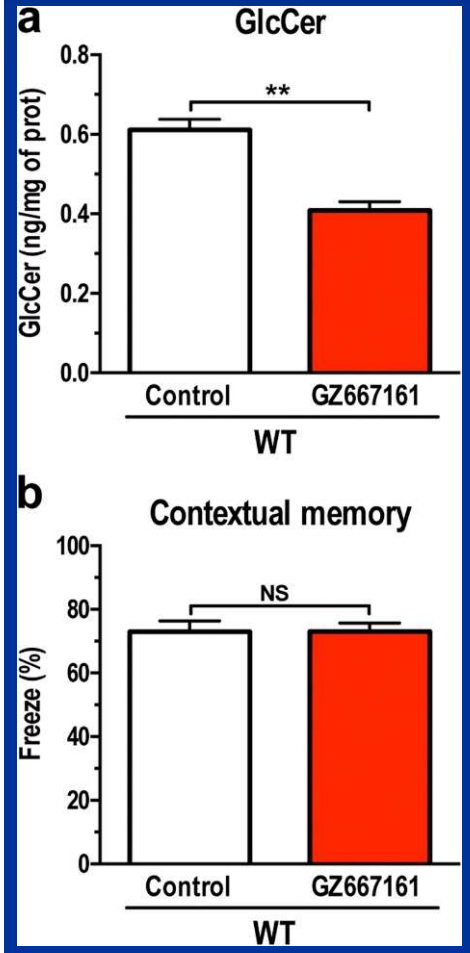
258.04 - GBA as a therapeutic target in Parkinson's disease

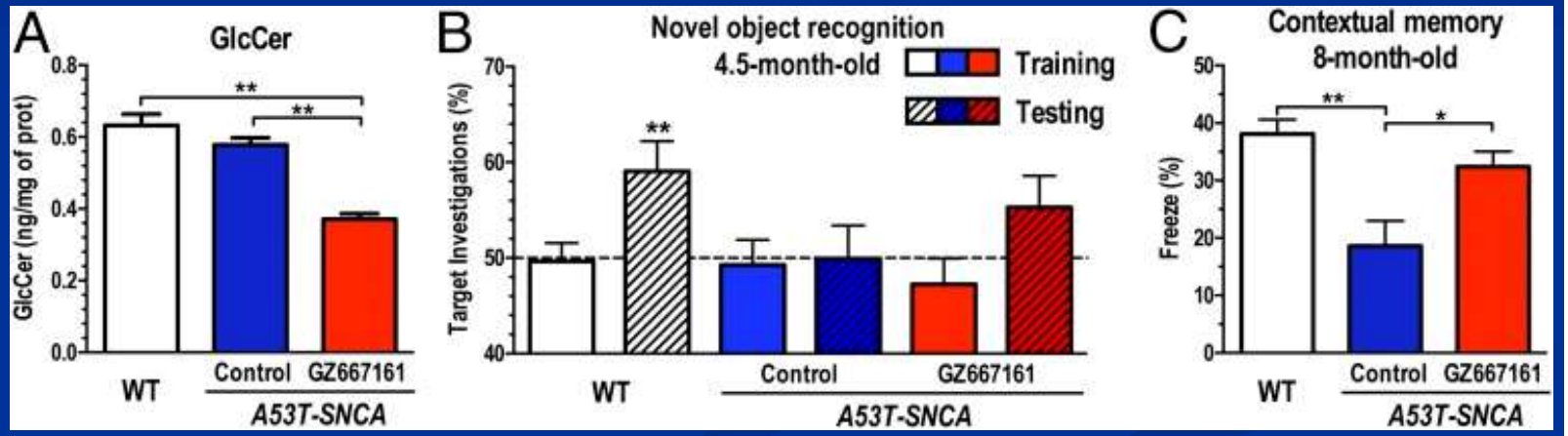
S. Sardi, Neuroscience, Sanofi, Framingham, MA.

Gaucher's disease: lysosomal storage disease, 7-10% of PD carry a GBA mutation.
GBA: glucocerebrosidase gene responsible for glucose+ceramide
The risk factor for PD is 5.43

Proc Natl Acad Sci U S A. 2017 Mar 7;114(10):2699-2704.

Glucosylceramide synthase inhibition alleviates aberrations in synucleinopathy models.





GCS inhibition reduces GlcCer and affects cognition in the A53T–SNCA mouse model of synucleinopathy. A53T–SNCA mice were fed GZ667161 from 6 wk of age to 8 mo.

The glucosylceramide synthase (GCS) inhibitor, GZ667161, reduces CNS glucosylceramide and does not affect memory in wild-type animals.

Ambroxol: a expectorant,祛痰劑
Pharmacological chaperones for GD and enhance endogenous GCase activity
Both PD (movement disorder) and dementia with Lewy bodies (DLB)(cognitive disorder) has a low GCase activity.

258.05 Critical path for Parkinson's disease: Increasing efficiency, safety, and speed in clinical trials

D. Stephenson; Critical Path for Parkinson's, Critical Path Institute, Tucson, AZ.

The right target/drug, the right patient at the right time/

Importance of low diagnostic Accuracy for early Parkinson's disease. Mov. Disorder (2018) 33(10): 1551-1554: Up to 15% patient take treatment at early stage may not have the disease

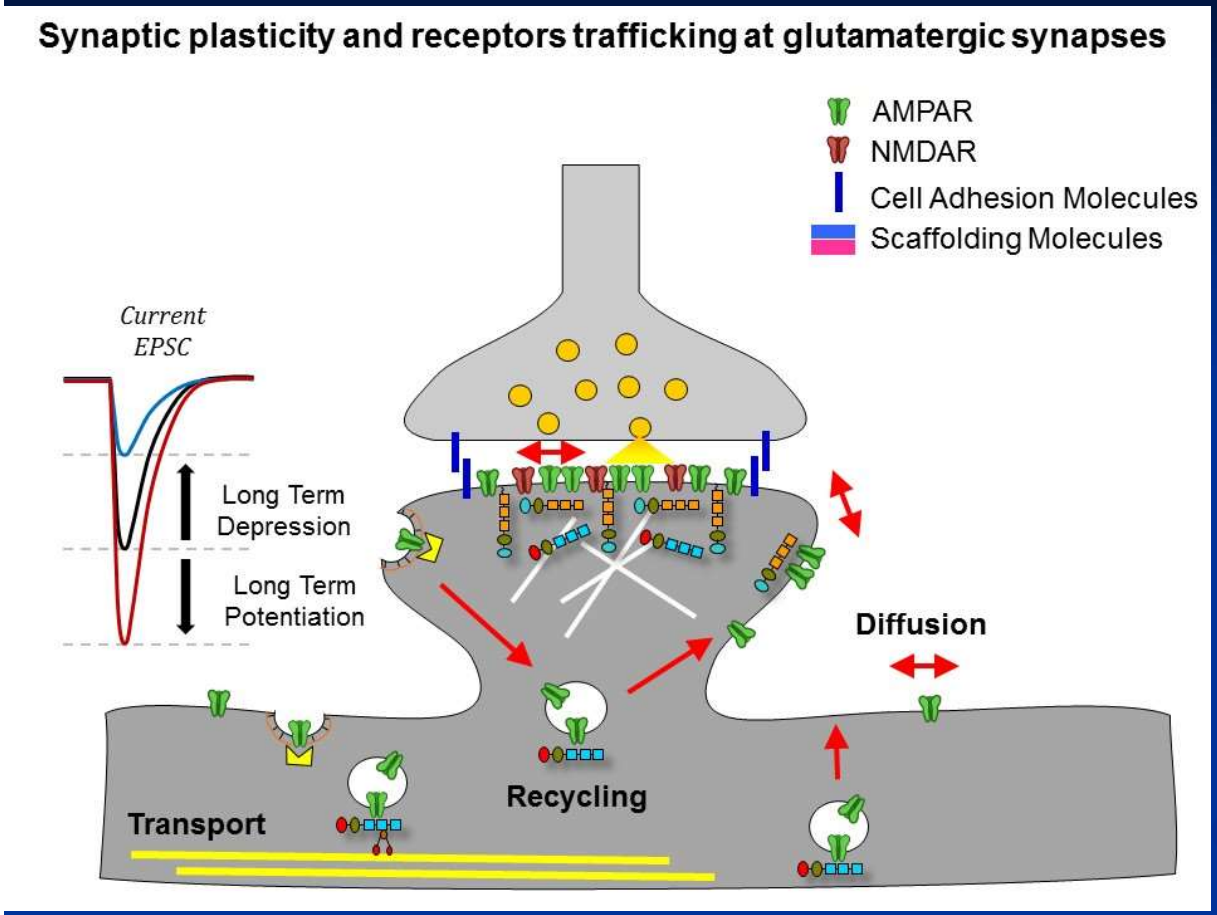
New drugs for Parkinson's disease: The regulatory and clinical development pathways in the United States. Mov Disorder (2018) 33(6): 920-927

TABLE 1. Selected promising therapies for PD that are in the pipeline[a]

Name	Sponsor	Mechanism/Indication	Stage	Regulatory Comments[b]
Short-term benefits or "Symptomatic"				
Opicapone	Bial	COMT inhibitor	III	Approved in Europe
Istradefylline	Kyowa-Kirin	A2A antagonist	III	Approved in Japan
Tozadenant	Acorda	A2A antagonist	III	505B1 pathway
CVT 301	Acorda	Inhaled L-dopa	III	505B2 pathway
APL130277	Sunovion	Sublingual apomorpine	III	Fast track
Amantadine ER	Adamas	NMDA antagonist for dysk	III	505B2 pathway
P2B001	Pharma2B	Low-dose prami/rasag combo	III	505B2 pathway
ND0612	Neuroderm	SC L-dopa/carbidopa	III	BE/505B2 pathway
Apo Infusion	USWM	Apomorphine infusion	III	505B2 pathway
Accordion pill	Intec	Long-acting L-dopa	III	505B2 pathway
PF-06649751	Pfizer	D1 agonist	IIB	505B1
LU-AE04621	Lundbeck	D1 agonist	IIB	505B1
SER-214	Serina	polymer-linked rotigotine	IIB	BE/505B2 pathway
AAV2-hAADC	Voyager	AAV2-gene delivery of AADC	II	Submitted through CBER
Light therapy	Photopharmics	Altered circadian rhythm	II	Device pathway
Dopafuse	Synagile	Continuous oral L-dopa delivery	II	Drug/device (505B2)
Disease modifying				
Isradipine	NIH	Ca+ + channel blocker	III	505B2
Inosine	NIH	Increase Urate as antioxidant	III	505B2
Nicotine Patch	Fox	Enhance nicotine levels	II	505B2
Affitope	Afferis	ImmunoRx target alpha syn	II	505B1 submitted through CDER
PRX002	Prothena	Monoclonal AB to alpha syn	IIa	505B1 submitted through CDER
BIIB054	Biogen	ImmunoRx target alpha syn	IIa	505B1 submitted through CDER
NPT 200-11	UCB	Antialpha syn aggregate	II	505B1
Nilotinib	Fox	CAbl kinase inhibitor	II	505B2 (approved in leukemia)
GZ/*SAR402671	Genzyme/Sanofie	GBA enhancer	II	505B1
Ambroxol	Weston Found	Enhances GCase activity	II	505B1
Exenatide	Cure PD Trust	Glucagon-like peptide 1	II	505B2
Deferiprone	APO Pharma	Iron chelator	II	505B2

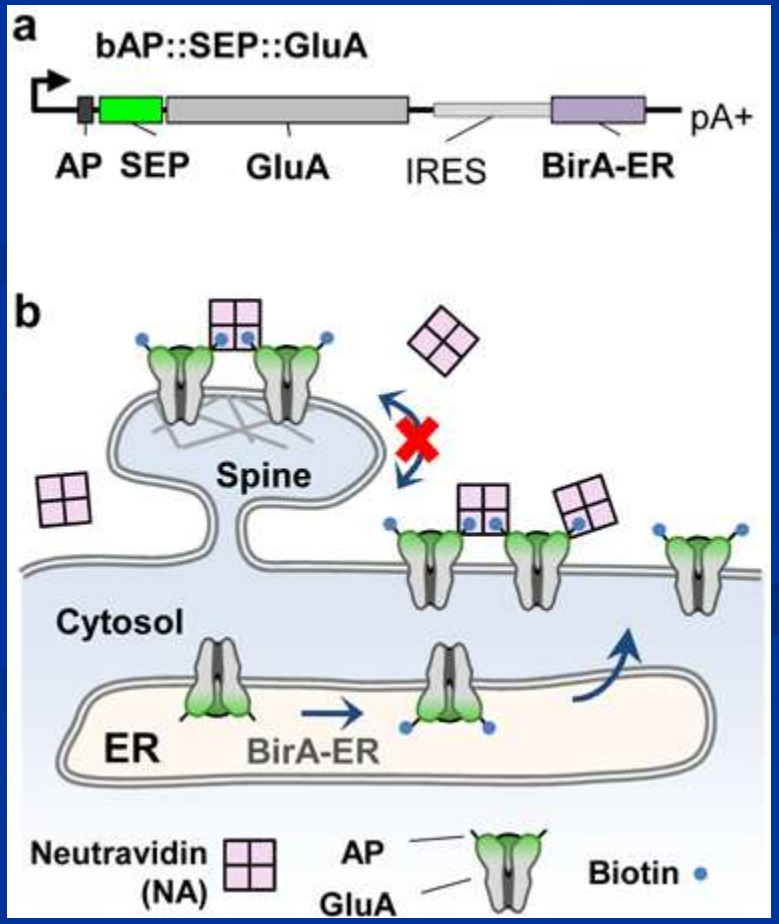
First-ever biomarker qualified for Parkinson's is a vital step toward improved clinical trials https://c-path.org/first-ever-biomarker-qualified-for-parkinsons-is-a-vital-step-toward-improved-clinical-trials/ an imaging test (biomarker) as a tool to enrich Parkinson's clinical trials; dopamine transport deficiency

352 From Nanoscale Dynamic Organization to Plasticity of Excitatory Synapses and Learning D. CHOQUET; CNRS, Univ. of Bordeaux, Bordeaux, France



The PSD complexity: silenced synapse can be unsilenced by AMPAR recruitment

1. AMPAR could be either exocytosis and endocytosis;
2. Extrasynaptic AMPAR are mobile;
3. AMPAR can exchange between synaptic and extra-synaptic sites.

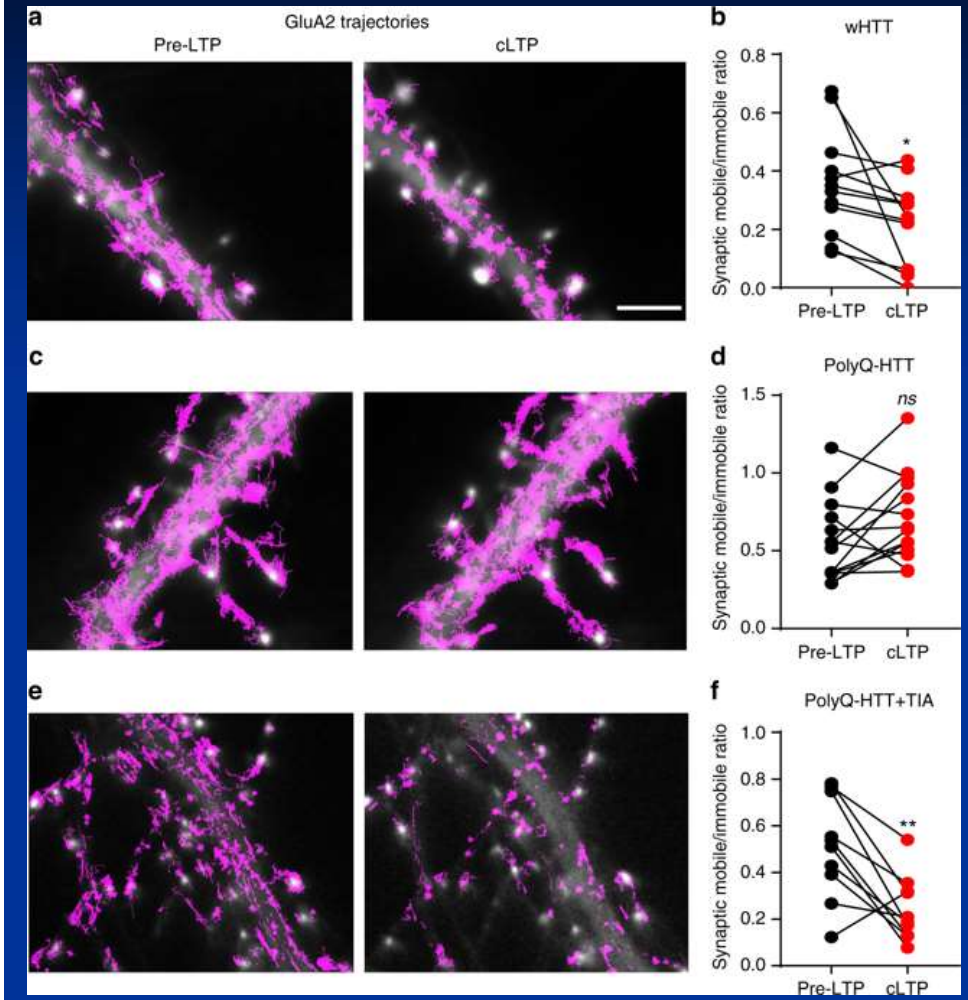


Nature. 2017 Sep 21;549(7672):384-388.
Hippocampal LTP and contextual learning require surface diffusion of AMPA receptors.

express recombinant biotin-tethered AMPAR subunits 1 and 221 (bAP::SEP::GluA1 and 2), which we could surface X-link by tetrameric biotin-binding proteins (BBPs, ~60 kDa, Fig. 1a-b).

Impair LTD, fear conditioning

Modulation of AMPA receptor surface diffusion restores hippocampal plasticity and memory in Huntington's disease models Nature Communications 9, 4272 (2018)



AMPAR fails to stabilize on the neuronal surface after LTP stimulation, an effect rescued by tianeptine (TIA) treatment in an HD cellular model.

defects in the brain-derived neurotrophic factor (BDNF)–tyrosine receptor kinase B (TrkB) signaling pathway contribute to the deregulated AMPAR trafficking by reducing the interaction between transmembrane AMPA receptor regulatory proteins (TARPs) and the PDZ-domain scaffold protein PSD95. The disturbed AMPAR surface diffusion is rescued by the antidepressant drug tianeptine via the BDNF signaling pathway.

175 From Axon Regeneration to Functional Recovery After CNS Injury

Z. HE; Boston Children's Hosp., BOSTON, MA

A. 神經死亡：需要再生

B. 必非全數死亡，但無法維持原有功能，造成癱瘓：增強其餘神經的功能

CNS神經為何無法再生？1. Extrinsic inhibitory factors (scar, …); 2. Low intrinsic growth ability.

神經可能跟Tumor有關，透過tumor suppressors抑制再生。研究策略：i. Identify these suppressors (Park et al. Science 2008): PTEN, 調控PI3K/mTOR途徑。ii. Neurotrophin可提高"young"神經細胞生長力，但對成熟細胞無效。尋找其他因子發現Osteopontin (OPN), 可與integrin結合，使neurons可對IGF有反應。發現OPN可促進IGF1 receptor dimerization.

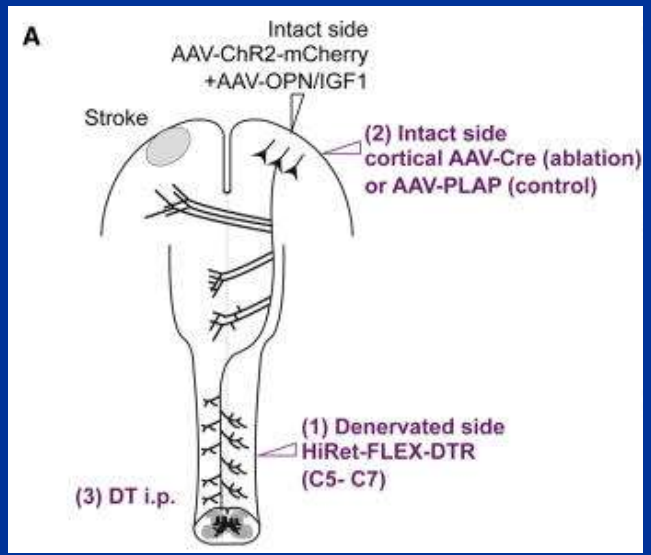
Belin et al (2015) Neuron Neuron. 2017 Aug 16;95(4):817-833 A Sensitized IGF1 Treatment Restores Corticospinal Axon-Dependent Functions.

再生3階段：

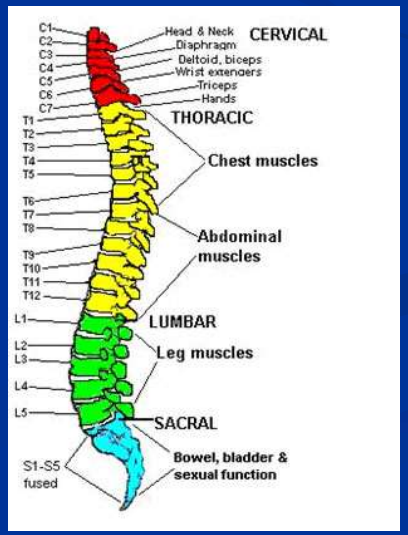
i. Injury signal: from the cell body at axotomy at the distal end.

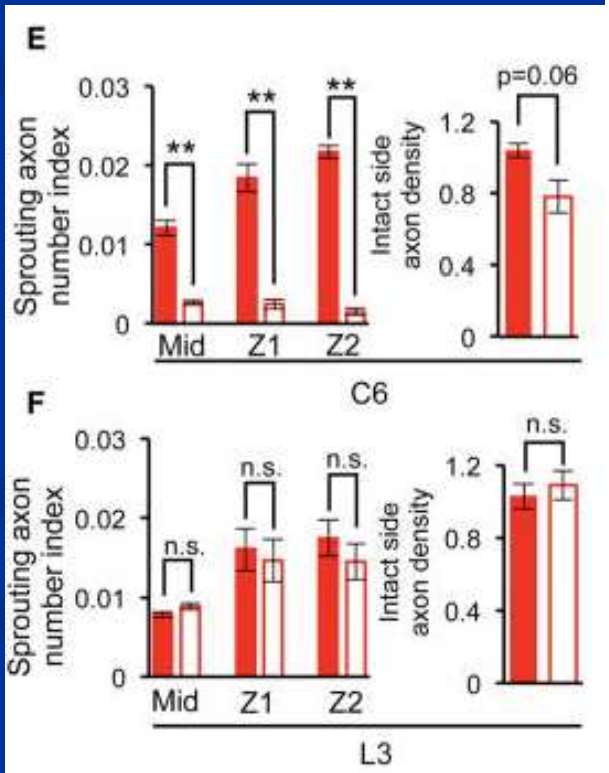
ii. Turn on axon growth program: from catabolic to anabolic

iii. 軸突延展：骨架重新排列組合及運輸



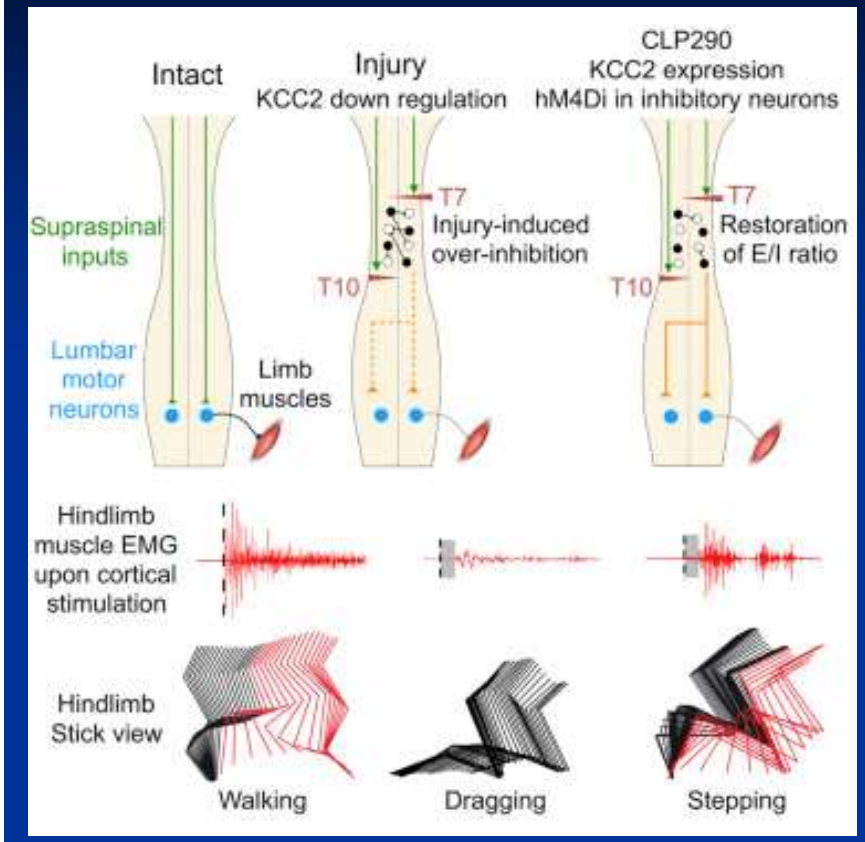
T10 hemisection model





Reactivation of Dormant Relay Pathways in Injured Spinal Cord by KCC2 Manipulations

Cell. 2018 Jul 26;174(3):521-535.e13

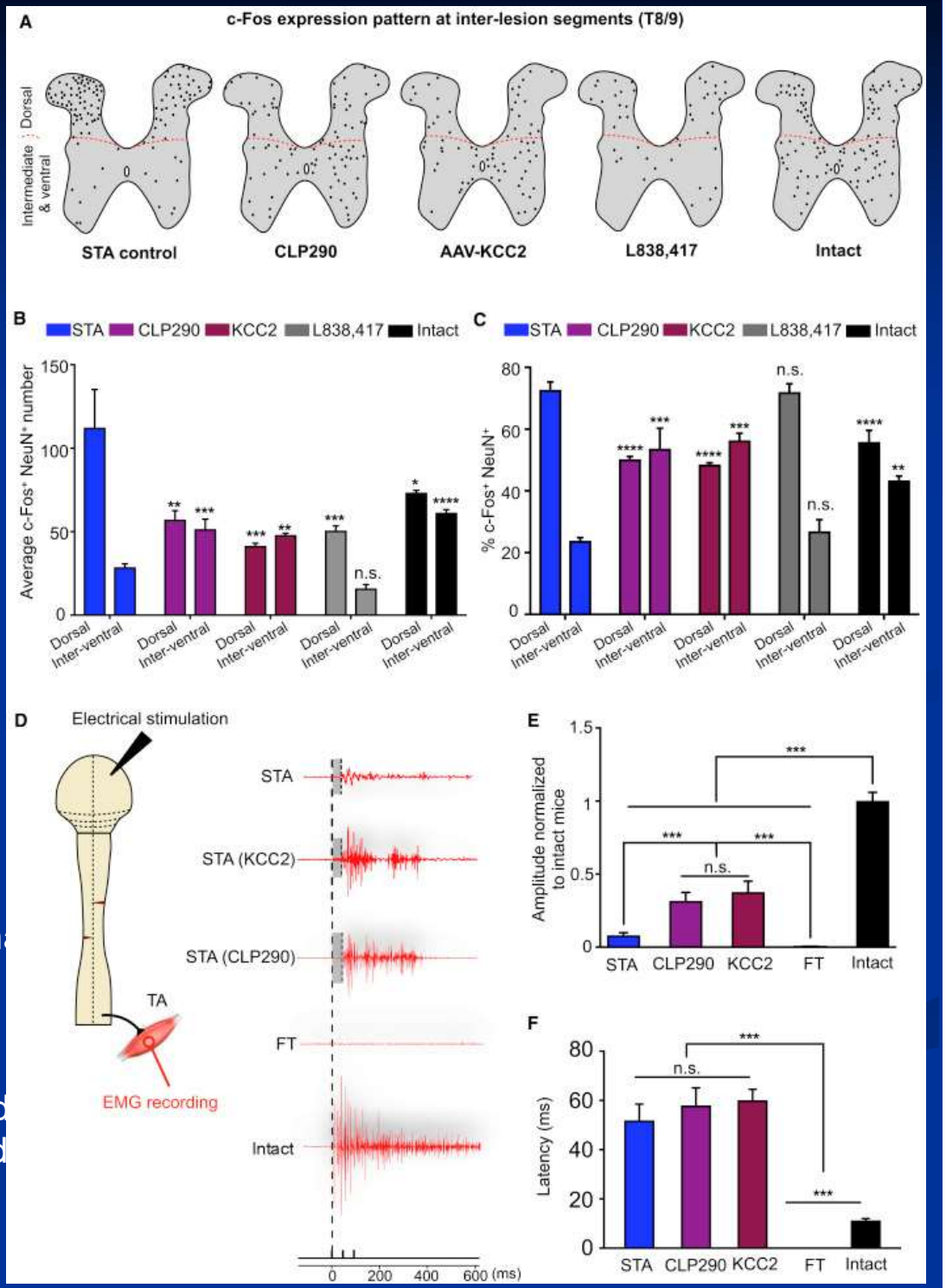


A KCC2 agonist (CLP290) restores stepping ability in paralyzed mice with spinal cord injuries

KCC2 expression in inhibitory neurons leads to functiona recovery

Restoration of inhibition in injured spinal cord leads to functional recovery

KCC2: K^+-Cl^- co-transporter; influences the efficacy and polarity of the chloride-permeable γ-aminobutyric acid (GABA) type A and glycine receptor (GlyR) mediated synaptic transmission.



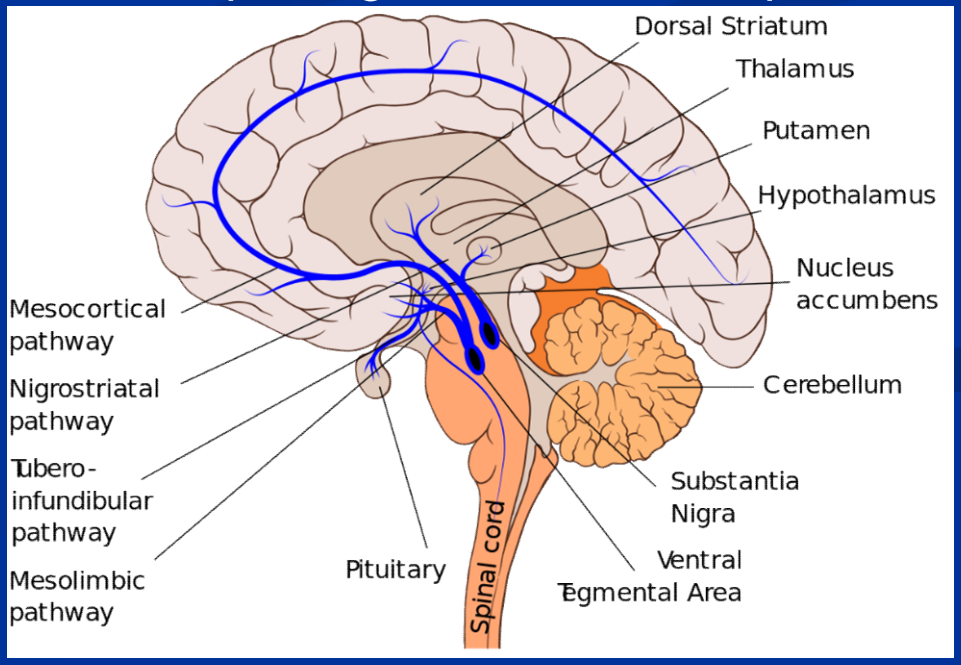
442 Neuronal Diversity Within the Ventral Tegmental Area and Co-Release of Neurotransmitters M. MORALES; Natl. Inst. on Drug Abuse, NIH, Baltimore, MD

Heterogeneous composition of dopamine neurons of the rat A10 region: molecular evidence for diverse signaling properties Brain Struct Funct. 2013 Sep;218(5):1159-76.

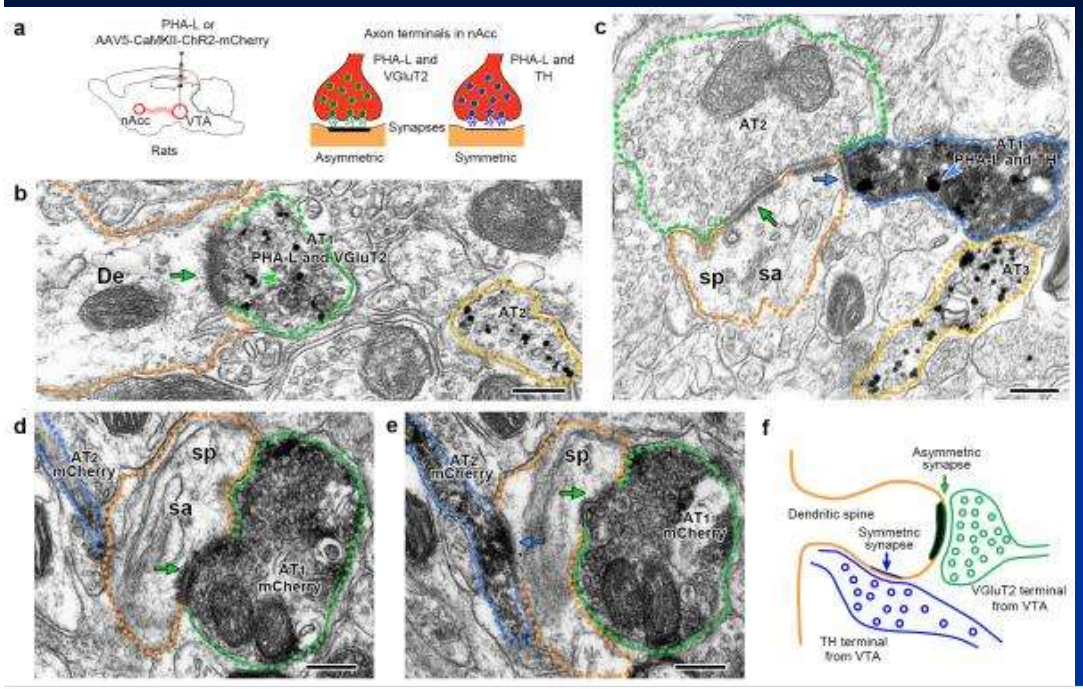
The A10 region contains different neurons: dopamine (expressing tyrosine hydroxylase; TH), GABA, glutamate-only (expressing the vesicular glutamate transporter 2; VGluT2), and TH-VGluT2 (coexpressing TH and VGluT2).

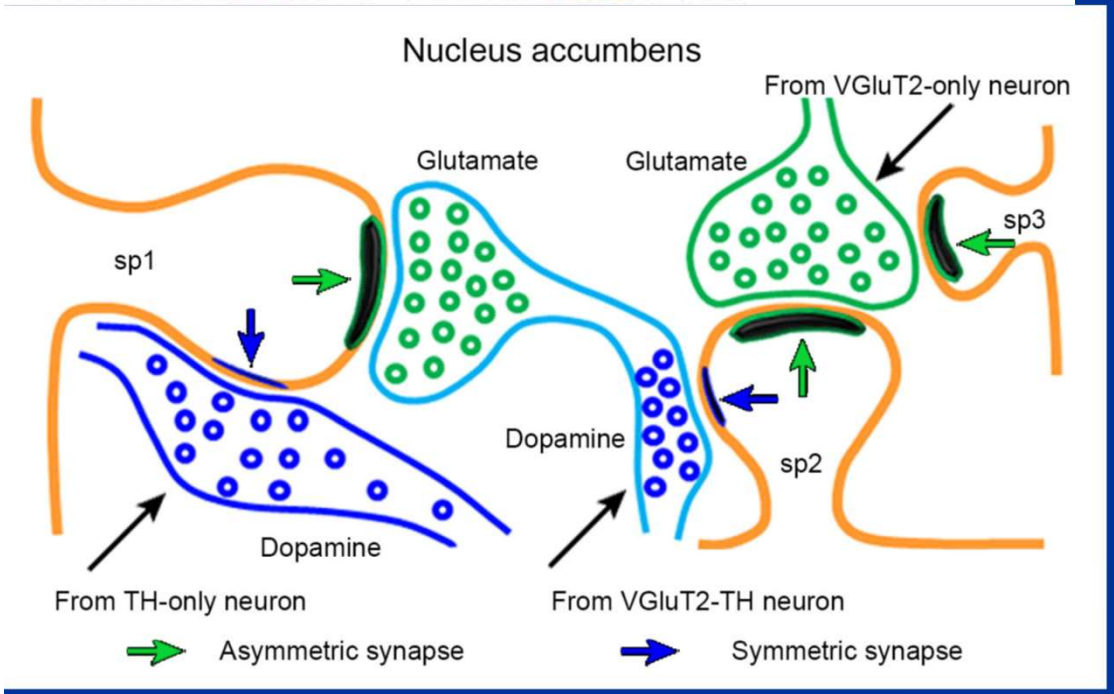
At mesoaccumbens, the dopamine inputs: 70% did not form synapse which means most dopamine is released by non-synaptic mechanism (volume transmission); for those form synapse with the dendrite as symmetric (inhibitory) right beside the glutamatergic input (asymmetry)

The mesoaccumbens projection: formed by ventral tegmental area dopamine neurons synapsing on nucleus accumbens GABA neurons, pathogenesis of schizophrenia and drug addiction.



Dopaminergic and glutamatergic microdomains in a subset of rodent mesoaccumbens axons. Nat Neurosci. 2015 Mar;18(3):386-92.

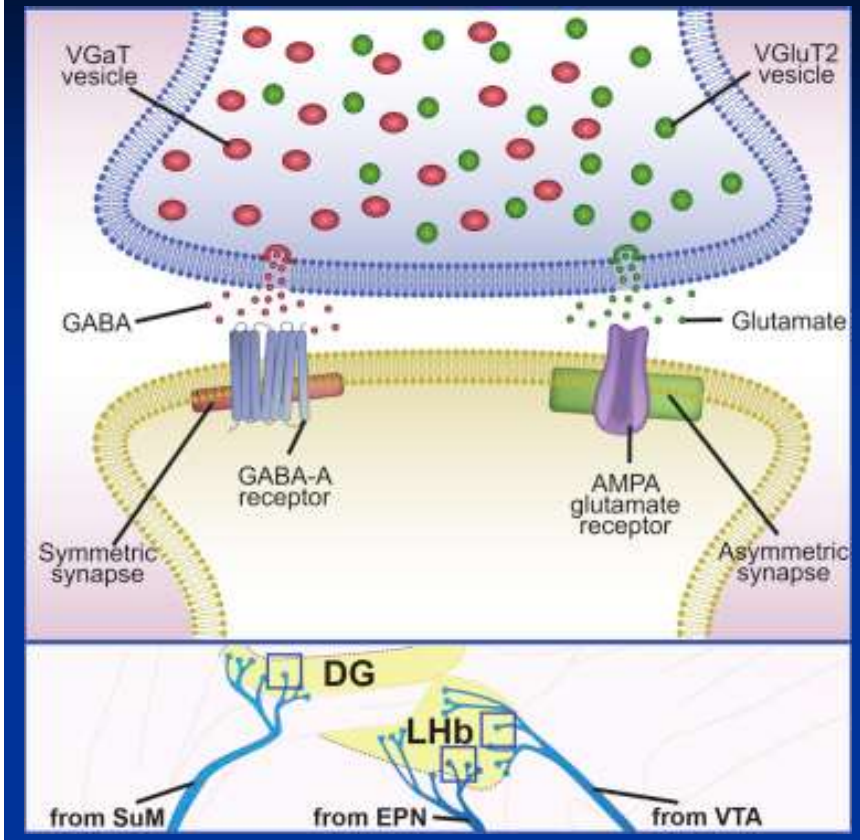




Mesoaccumbens neurons establish either VGluT2-asymmetric synapses or TH-symmetric synapses

Mesoaccumbens synapses established by 3 different classes of mesocorticolimbic neurons (TH-only, VGluT2-only and VGluT2-TH neurons), and subcellular segregation for dopaminergic and glutamatergic signaling. Axon terminals containing dopamine vesicles (blue circles) and establishing symmetric synapses on the side of dendritic spines (sp1) are originated from either TH-only or VGluT2-TH neurons. In contrast, axon terminals containing glutamate vesicles (green circles) derived from VGluT2-only or VGluT2-TH neurons make asymmetric synapses on the head of dendritic spines (or dendrites, no representation in this diagram).

Selective Brain Distribution and Distinctive Synaptic Architecture of Dual Glutamatergic-GABAergic Neurons. Cell Rep. 2018 Jun 19;23(12):3465-3479.



Single axon terminals established by VTA, EPN, or SUM neurons form a common synaptic architecture involving asymmetric (putative excitatory) and symmetric (putative inhibitory) synapses.

VGluT2 and VGaT are distributed on separate synaptic vesicles. We conclude that single axon terminals from VGluT2 and VGaT co-expressing neurons co-transmit glutamate and GABA from distinct synaptic vesicles at independent synapses.

At the asymmetric synapse, glutamate is released, which interacts with AMPA receptors within postsynaptic neurons. Therefore, each VGluT2+ VGaT+ axon terminal has the capability of co-releasing glutamate and GABA from independent vesicles and independent synapses within the same axon terminal. The postsynaptic reception of the co-released glutamate and GABA may be onto the same postsynaptic dendrite.