The chemical synapse

- Synapses are functional connections between neurons, or between neurons and other types of cells.
- A typical neuron gives rise to several thousand synapses, although there are some types that make far fewer.

Action potentials **cannot cross the synaptic cleft**
Nerve impulse is carried by **neurotransmitters**

Classification of synapses by:

- Cytoarchitecture
- Based on method of signal conduction (electrical/chemical)
- Based on conductance of postsynaptic membrane to selective ion species (excitatory/inhibitory)

Cytoarchitectural Classification of Synapses

– Axo-dendritic synapse

– Axo-somatic synapse

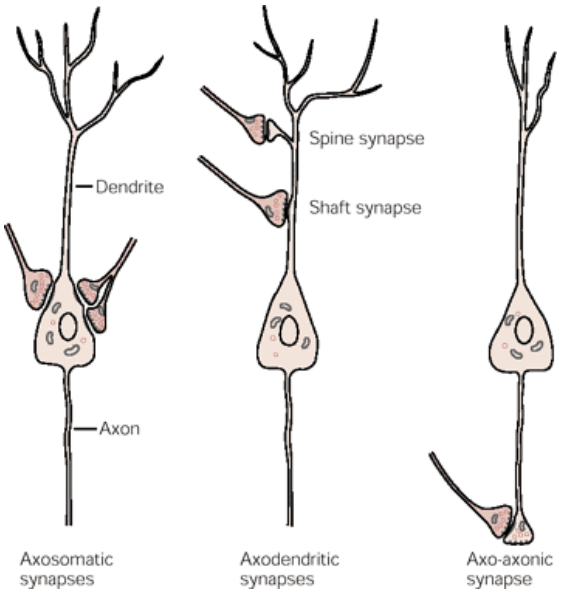
– Axo-axonic synapse

– Dendro-dendritic synapse

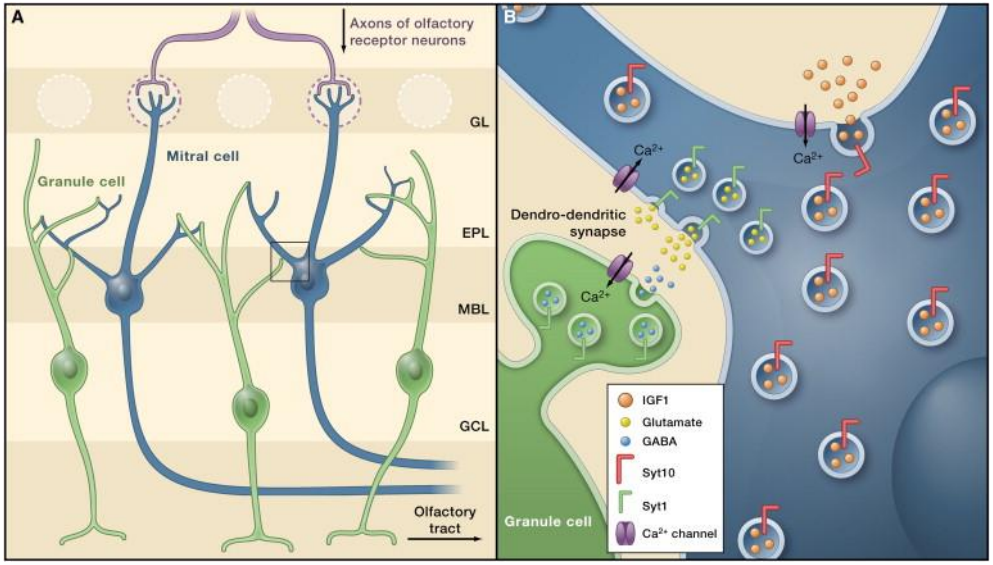
– Soma-somatic synapse

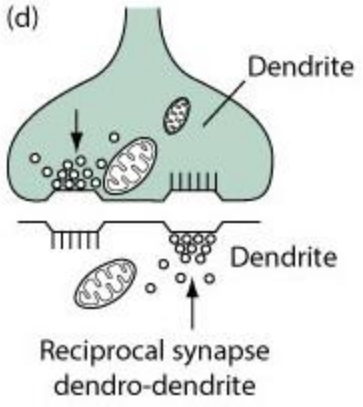
– Neuromuscular synapse (skel m.: NM junction)

– Neuroglandular synapse



Dendro-dendritic synapses are present only in few regions of the brain





Organization of the **olfactory bulb**. Axons of olfactory receptor neurons project onto glomeruli (GL) in the olfactory bulb. Within the external plexiform layer (EPL) of the bulb, dendrites from large excitatory neurons (mitral cells, MC) form **reciprocal dendrodendritic synapses** with small inhibitory neurons (granule cells [GC]). Mitral cells relay sensory signals to higher regions of the brain via the olfactory tract. GCL, granule cell layer; MBL, mitral cell body layer.

Asymmetric organization of (chemical) synaptic junctions

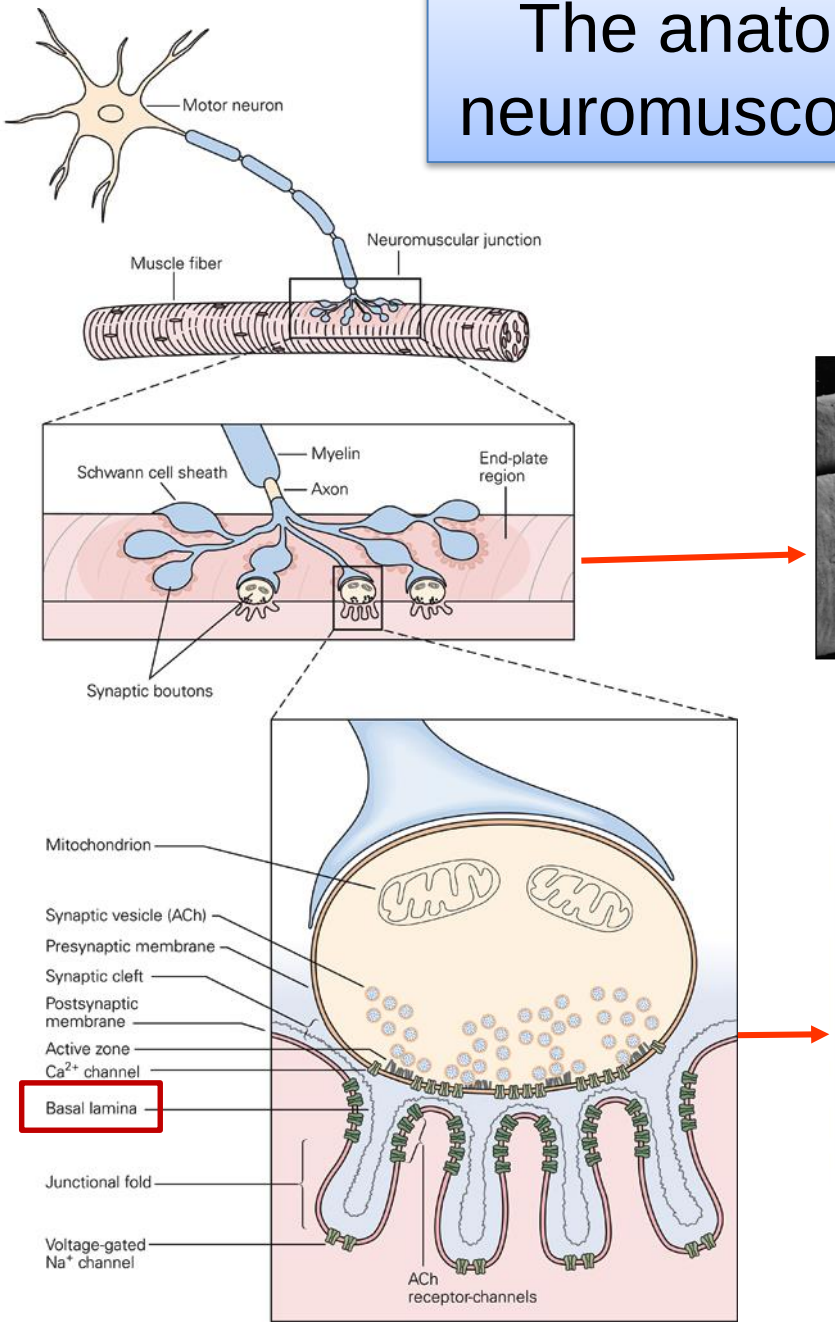
Synapses between neurons represent **a subtype of intercellular junctions** (adhesive junctions) highly specialized for cellular communication.

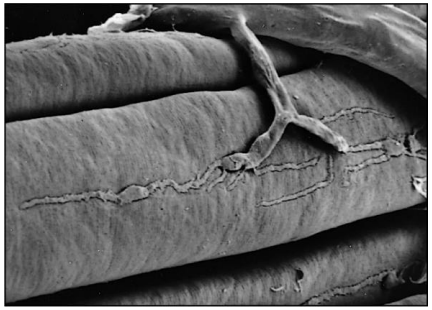
Differently from other junctions, synapses are **ASYMMETRICAL**:

• presynaptic specialization (usually axonal, contains the “active zone” for NT release)

•postsynaptic specialization (usually dendritic, contains the postsynaptic density translating the NT signal)

The anatomy of the neuromuscolar junction





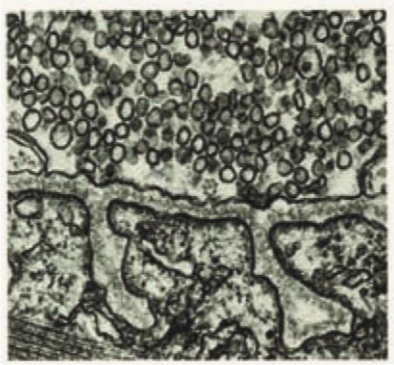


Figure 9–1 The neuromuscular junction is an ideal site for studying chemical synaptic signaling. At the muscle the motor axon ramifies into several fine branches approximately 2 µm thick. Each branch forms multiple swellings called *synaptic boutons*, which are covered by a thin layer of Schwann cells. The boutons lie over a specialized region of the muscle fiber membrane, the *end-plate*, and are separated from the muscle membrane by a 100-nm synaptic cleft. Each bouton contains mitochondria and synaptic vesicles clustered around *active zones*, where the neurotransmitter acetylcholine (**ACh**) is released. Immediately under each bouton in the end-plate are several junctional folds, the crests of which contain a high density of ACh receptors.

The muscle fiber and nerve terminal are covered by a layer of connective tissue, the basal lamina, consisting of collagen and glycoproteins. Unlike the cell membrane, the basal lamina is freely permeable to ions and small organic compounds, including the transmitter. Both the presynaptic terminal and the muscle fiber secrete proteins into the basal lamina, including the enzyme acetylcholinesterase, which inactivates the ACh released from the presynaptic terminal by breaking it down into acetate and choline. The basal lamina also organizes the synapse by aligning the presynaptic boutons with the postsynaptic junctional folds. (Adapted, with permission, from McMahan and Kuffler 1971.)

EM autoradiograph of the neuromuscular junction, showing localization of ACh receptors (black developed grains) at the top one-third of the postsynaptic junctional folds.

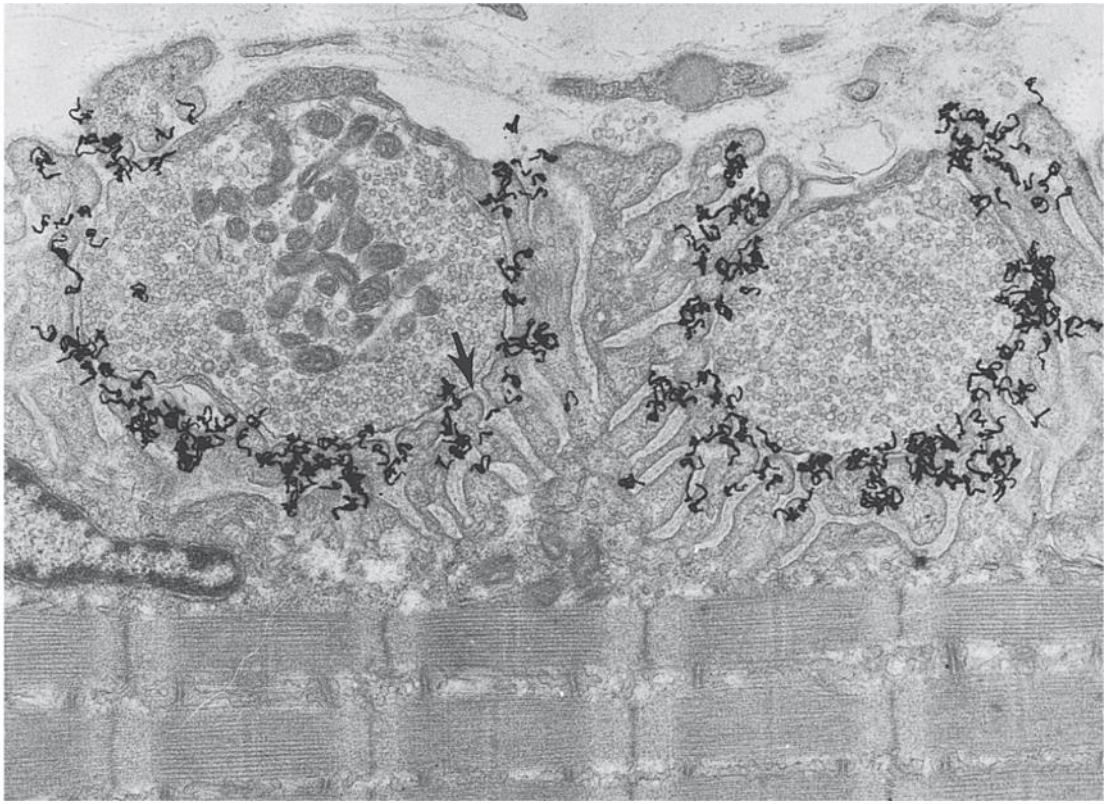


Figure 9–2 Acetylcholine receptors in the vertebrate neuromuscular junction are concentrated at the top one-third of the junctional folds. This receptor-rich region is characterized by an increased density of the postjunctional membrane (**arrow**). The autoradiograph shown here was made by first incubating the membrane with radiolabeled α-bungarotoxin, which binds to the ACh receptor (**black grains**). Radioactive decay results in the emittance of a particle that causes overlaid silver grains to become fixed along its trajectory (**black grains**). Magnification ×18,000. (Reproduced, with permission, from Salpeter 1987.)

Postsynaptic events leading to generation of action potential in the muscle fiber

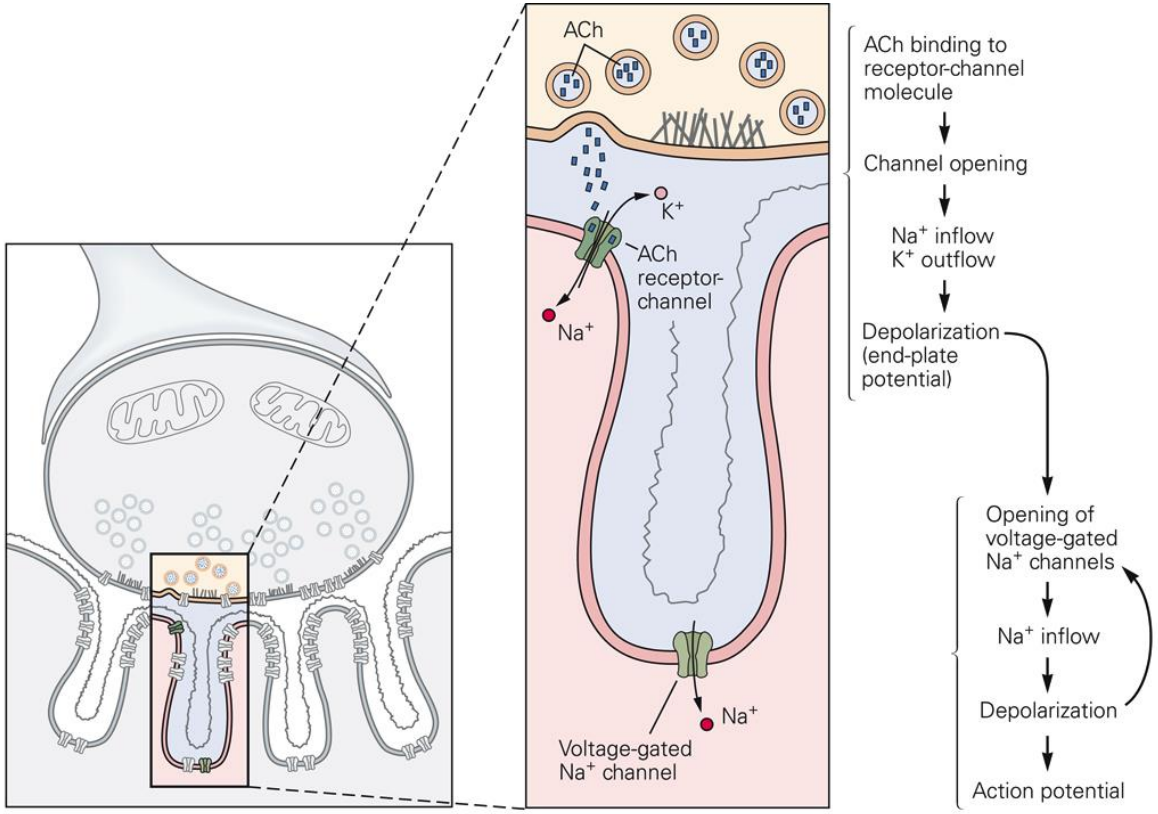


Figure 9–12 The depolarization resulting from the opening of ACh receptor-channels at the end-plate opens voltage-gated Na^+ channels. The depolarization of the muscle membrane during the end-plate potential opens neighboring voltage-gated Na^+ channels in the muscle membrane. The depolarization is normally large enough to open a sufficient number of Na^+ channels to exceed the threshold for an action potential. (Reproduced, with permission, from Alberts et al. 1989.)

Kandel, Principles of Neural Sciences, 2013

The CNS synapse

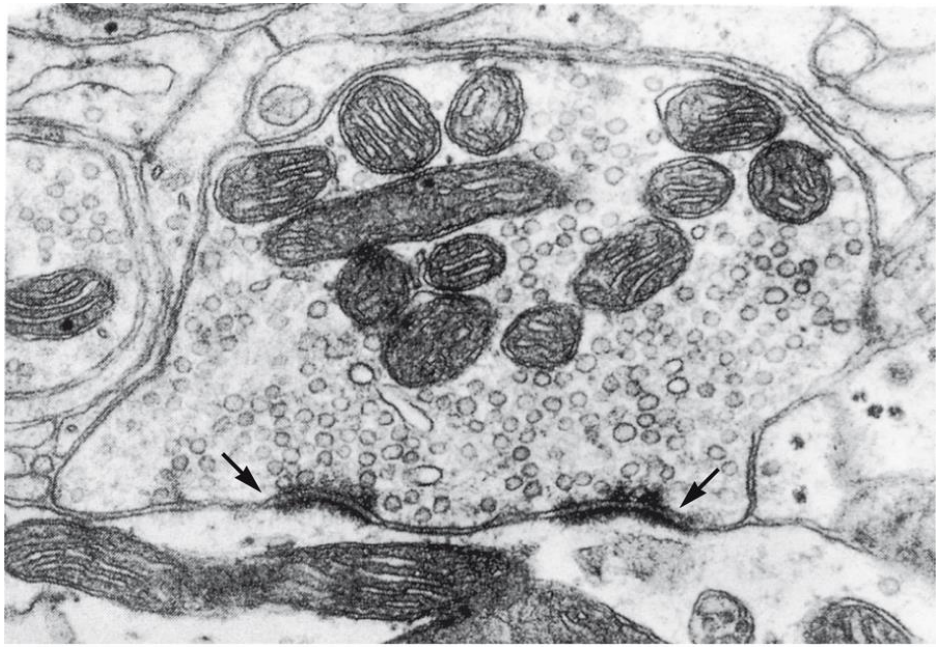
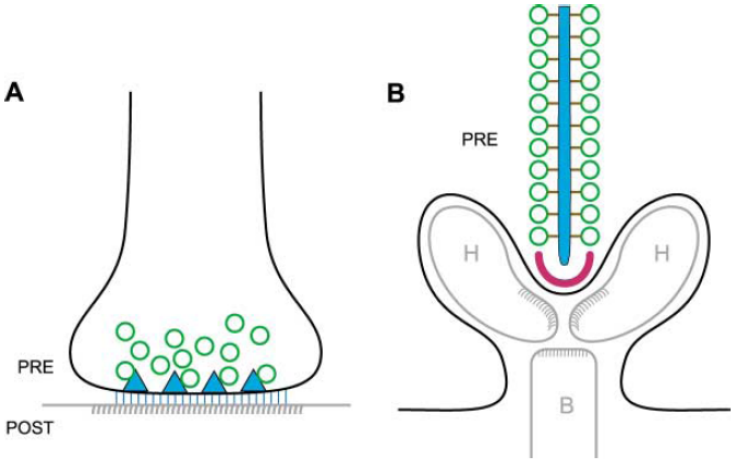


Figure 8–7 The fine structure of a presynaptic terminal. This electron micrograph shows a synapse in the cerebellum. The large dark structures are mitochondria. The many small round bodies are vesicles that contain neurotransmitter. The fuzzy dark thickenings along the presynaptic membrane (**arrows**) are the active zones, specialized areas that are thought to be docking and release sites for synaptic vesicles. The synaptic cleft is the space just outside the presynaptic terminal separating the pre- and postsynaptic cell membranes. (Reproduced, with permission, from J. E. Heuser and T. S. Reese.)

Kandel, Principles of Neural Sciences, 2013

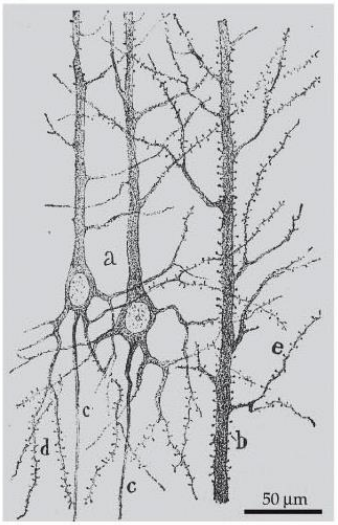


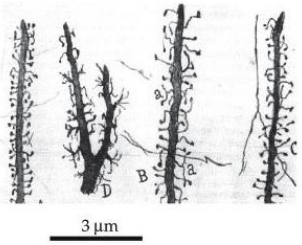
Presynaptic Structures at a Conventional and a Photoreceptor Ribbon Synapse

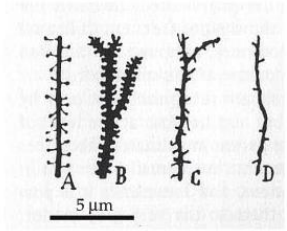
At conventional synapses (A) the right staining conditions can reveal a two-dimensional web of pyramidal particles apposed to the presynaptic membrane. These particles are thought to be linked by filaments and connected to the postsynaptic membrane by another set of filaments or pegs. Ribbon synapses (B) have a more complex structure. The presynaptic terminal of a rod or cone cell surrounds the dendrites of the postsynaptic cells, typically two horizontal cell processes and one bipolar cell process arranged in the characteristic pattern shown here. Aligned with this on the presynaptic side is a "ribbon," in fact, a plate seen here in cross-section, to which rows of vesicles are tethered by thin filaments. Between the bottom of the ribbon and the presynaptic membrane lies a structure sometimes called the arciform density.

Wilson, 2003
Neuron 37:728-30

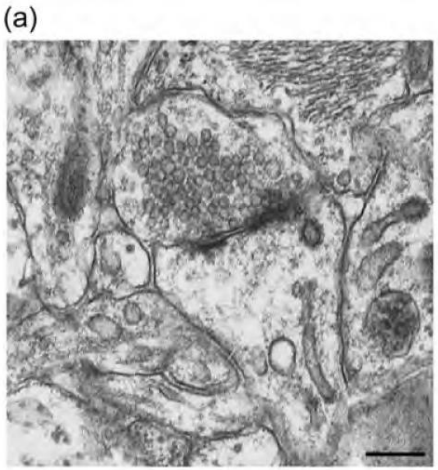
The structure of a CNS excitatory synapse

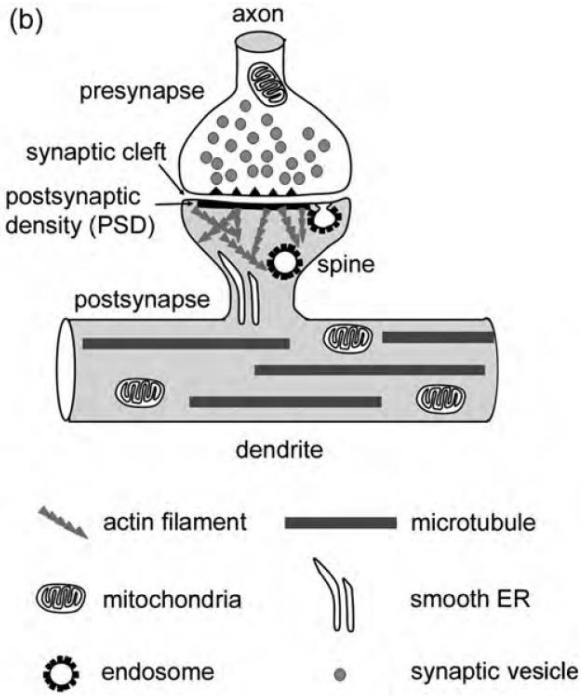






Cajal's classic drawings of dendritic spines

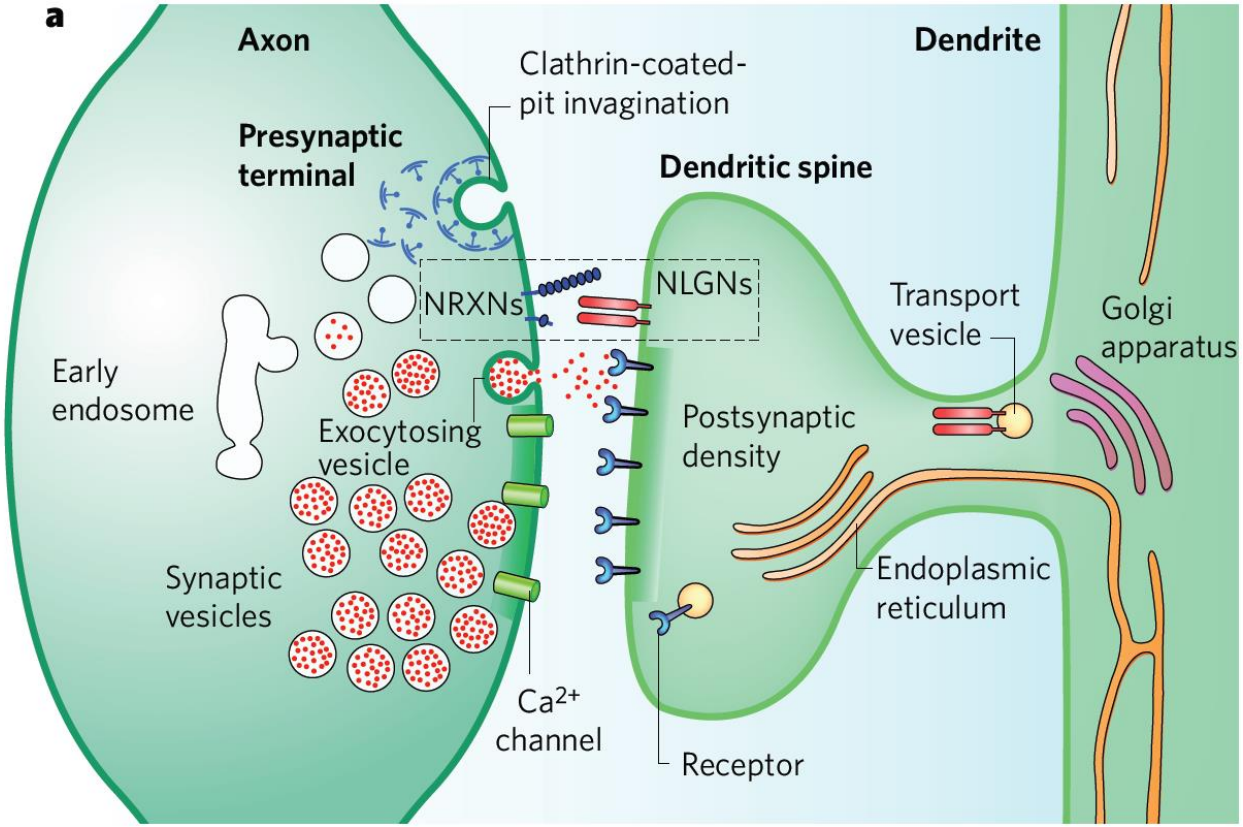




S. Okabe
Microscopy **62(1)**: 51–62 (2013)

Fig. 1. Ultrastructure of the excitatory synapse. (a) Transmission electron micrograph of an excitatory synapse in the mouse hippocampus. Scale bar, 200 nm. (b) Major cytoplasmic components of the presynaptic and postsynaptic cytoplasm of the excitatory synapses.

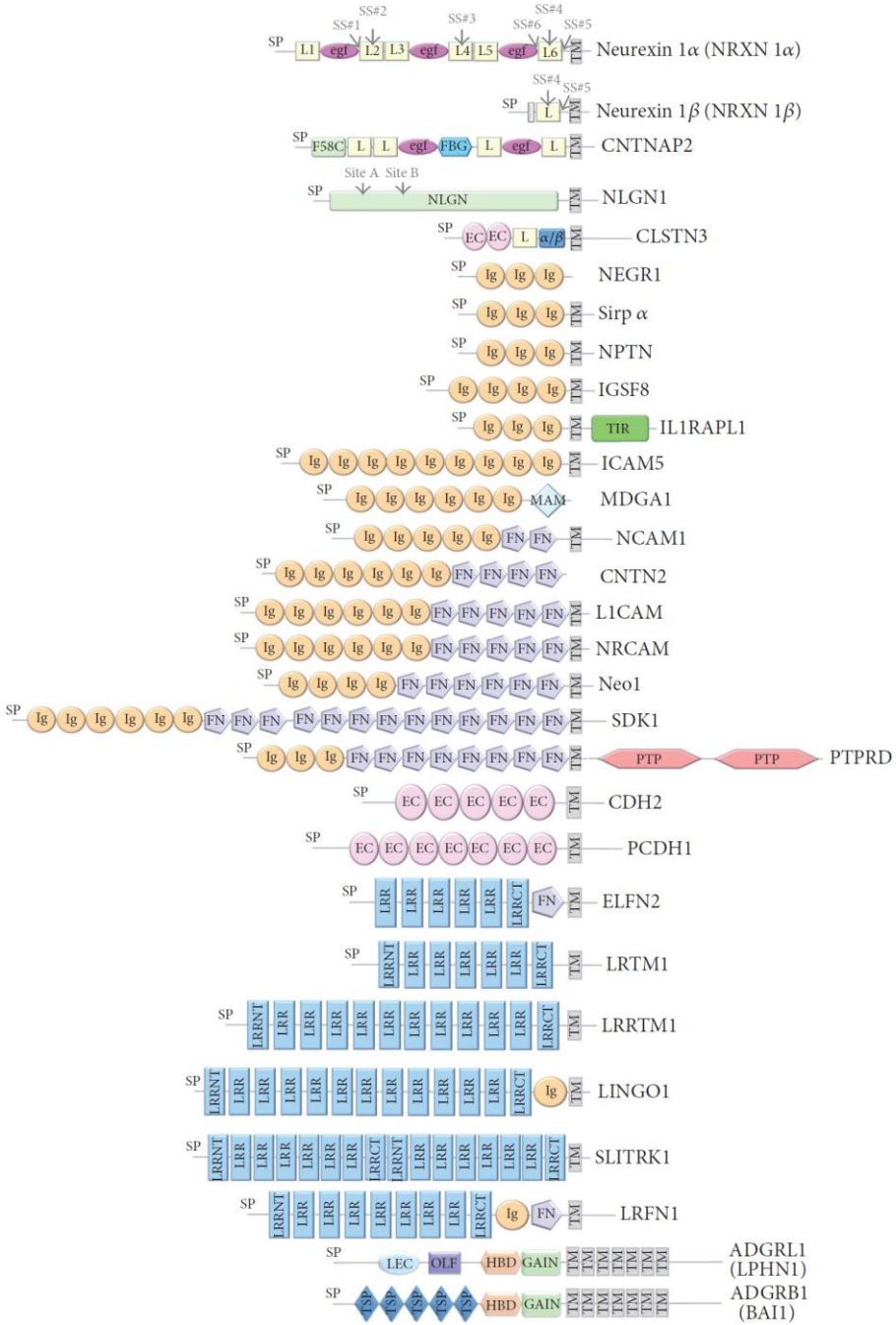
The asymmetric organization of a CNS excitatory synapse



Schematic diagram of a typical synapse formed by an axonal presynaptic terminal onto a postsynaptic spine, and of the role of the trans-synaptic cell-adhesion molecules neurexins and neuroligins in synapse alignment and specification. See Südhof, T.C. 2008. *Nature*455:903-911 for details.

CNS synapses do not display a basal membrane (as the neuromuscular junction) in the synaptic cleft. Pre- and post- synaptic terminal adhesion is assured by transmembrane **ADHESION MOLECULES**

Südof, 2008
Nature doi:10.1038/nature07456



Synaptic Adhesion Molecules (SAMs).

From top to bottom: **neurexin 1α and neurexin 1β (NRXN1α and NRXN1β; neurexins)**; CNTNAP2 (contactin associated protein-like); **NLGN1 (neuroligins)**; CLSTN3 (calsyntenins); NEGR1 (Iglons which include NEGR1, NTM, LSAMP, and OPCML); Sirp α (signal regulatory proteins); NPTN (neuroplastin); IGSF8 (immunoglobulin superfamily); IL1RAPL1 (interleukin 1 receptor accessory protein-like); ICAM5 (intercellular adhesion molecules); MDGA1 (MAM domain containing glycosylphosphatidylinositol anchor); **NCAM1 (neural cell adhesion molecules**); CNTN2 (contactins); **L1CAM (L1 cell adhesion molecules**); NRCAM (neuronal cell adhesion molecules); Neo1 (neogenin); SDK1 (sidekick cell adhesion molecules); PTPRD (protein tyrosine phosphatase receptor typesD, F, and S); **CDH2(cadherins)**; **PCDH1 (protocadherins**); ELFN2 (extracellular leucine rich repeat and fibronectin type III domain containing); LRTM1 (leucine rich repeats and transmembrane domains); LRRTM1 (leucine rich repeat transmembrane neuronal); LINGO1 (leucine rich repeat and Ig domain containing); SLITRK1 (SLIT and NTRK-like family member); LRFN1 (leucine rich repeat and fibronectin type III domain containing); ADGRL1 (adhesionG protein-coupled receptor type L; previously known as latrophilins); ADGRB1 (adhesionGprotein-coupled receptor type B, previously known as brain-specific angiogenesis inhibitor). Several large polymorphic families including the ephrin receptors, integrins, and plexins are not shown.The domain abbreviations used in the text are for laminin G or **laminin G/neurexin/sex hormone binding globulin or LNS domains** (**L**); **epidermal growth factor repeat (EGF)**; coagulation factor 5/8 type C (F58C); fibrinogen-like (FBG); extracellular cadherin (EC); alpha/beta (α/β); immunoglobulin (Ig); Toll/Il-1 receptor homology (TIR); meprin, A-5 protein, receptor protein tyrosine phosphatasemu (MAM); fibronectin type 3 (FN), protein tyrosine phosphatase (PTP); leucine rich repeat (LRR), N-terminal leucine rich repeat (LRRNT); C-terminal leucine rich repeat (LRRCT); galactose binding lectin domain (LEC); olfactomedin-like domain (OLF); hormone binding domain (HBD);GPCR-autoproteolysis inducing (GAIN); thrombospondin (TSP). Other abbreviations are signal peptide (SP) and transmembrane segment (TM). Alternative splice insert sites are indicted for the SAMs NRXN1α, NRXN1β, and NLGN1

Rudenko, 2017, Neural plasticity
https://doi.org/10.1155/2017/6526151

What are the major functions of SAMs at synapses?

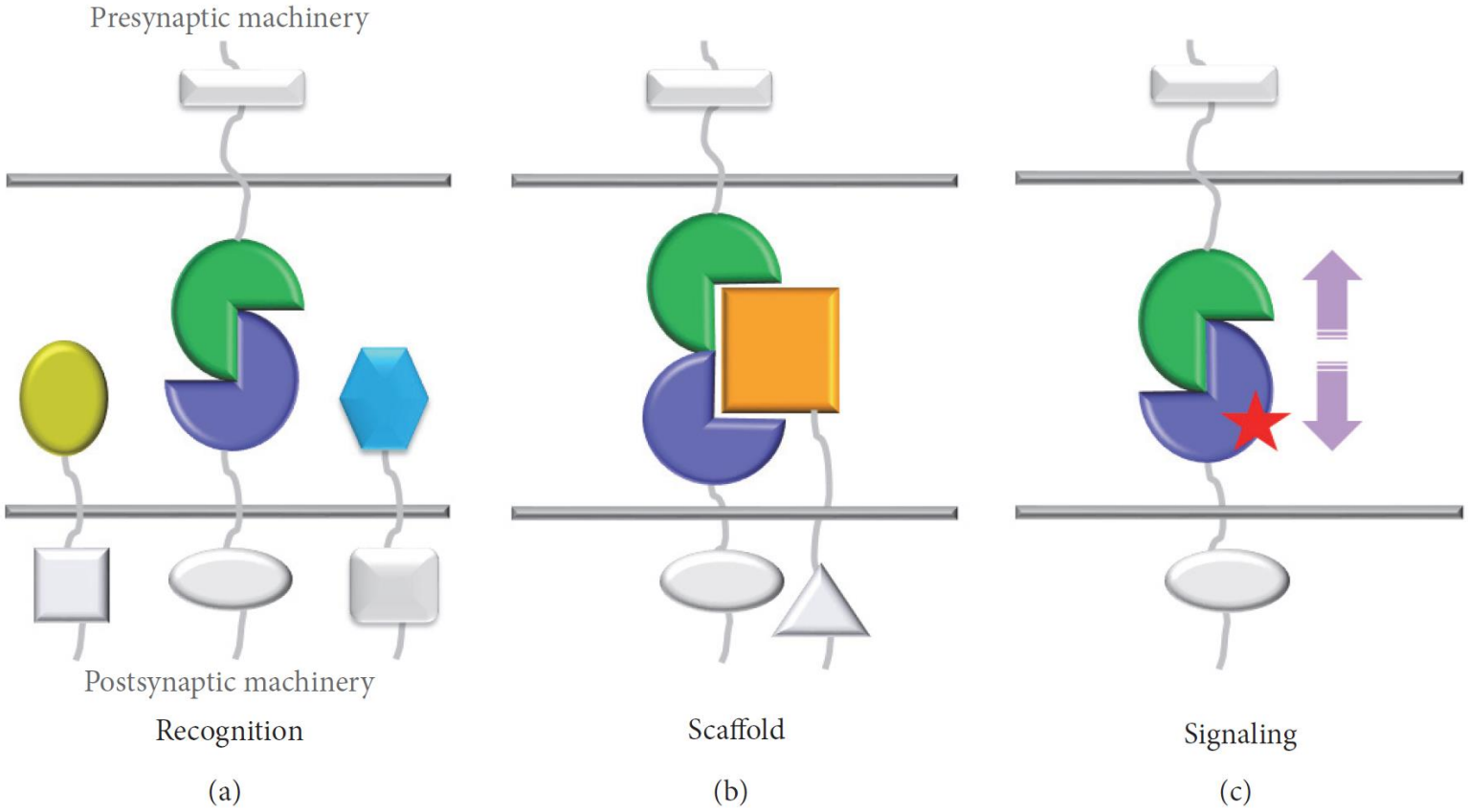


FIGURE 2: SAM function and mechanisms. SAMs can recruit and organize protein interaction networks in the synaptic cleft by (a) generating mechanisms to recognize specific SAM partners, but not others by binding through direct interactions; (b) binding other SAMs to generate a scaffold onto which a third protein can dock and this mechanism also supports the binding of SAMs through indirect interactions; (c) binding a partner and inducing a signaling event, for example, through (allo)steric mechanisms.

Rudenko, 2017, Neural plasticity
https://doi.org/10.1155/2017/6526151

SAMs interact with several molecular partners at the synapse

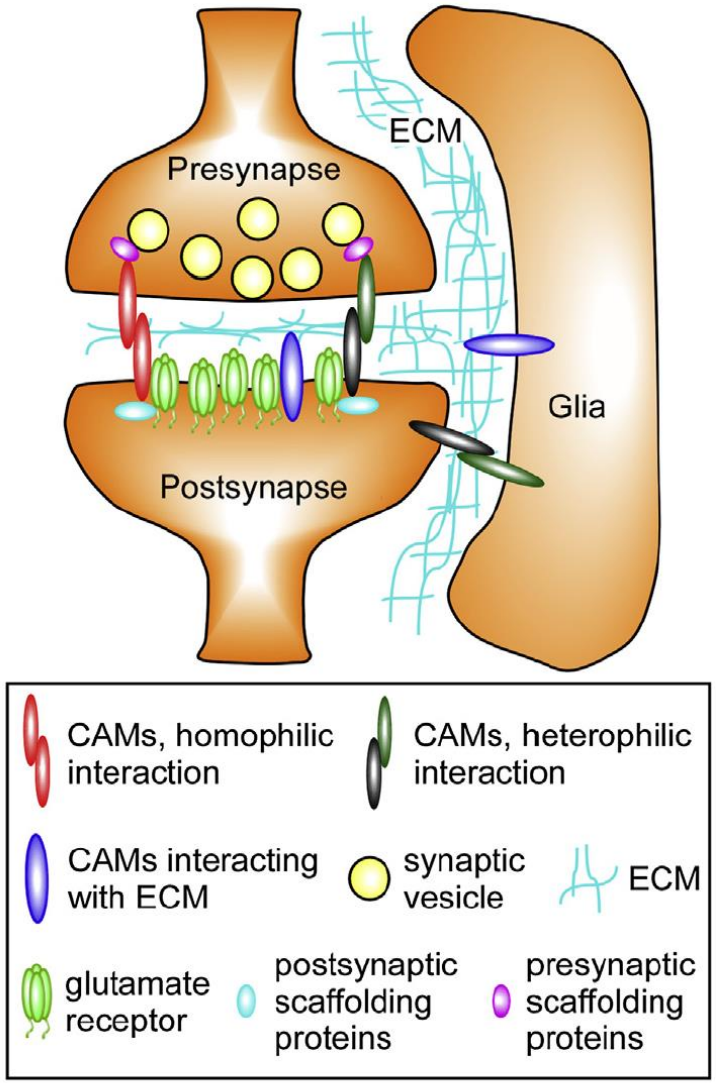


Fig. 1. Synaptic CAMs mediate interactions between different compartments of the synapse. Synaptic CAMs orchestrate structural and functional aspects of synaptic connections by recruiting scaffolding proteins and neurotransmitter receptors in response to the binding of specific counter-receptors and ligands. They mediate direct and indirect interactions between pre- and post-synaptic terminals, and between neurons and astrocytes. CAM interactions are either homophilic (red) or heterophilic (green/black) or with ECM proteins (blue).

Thalhammmer, 2014, Neuropharmacology
http://dx.doi.org/10.1016/j.neuropharm.2013.03.015

Synaptic adhesion molecules interact with different proteins in the pre- and post-synaptic terminal

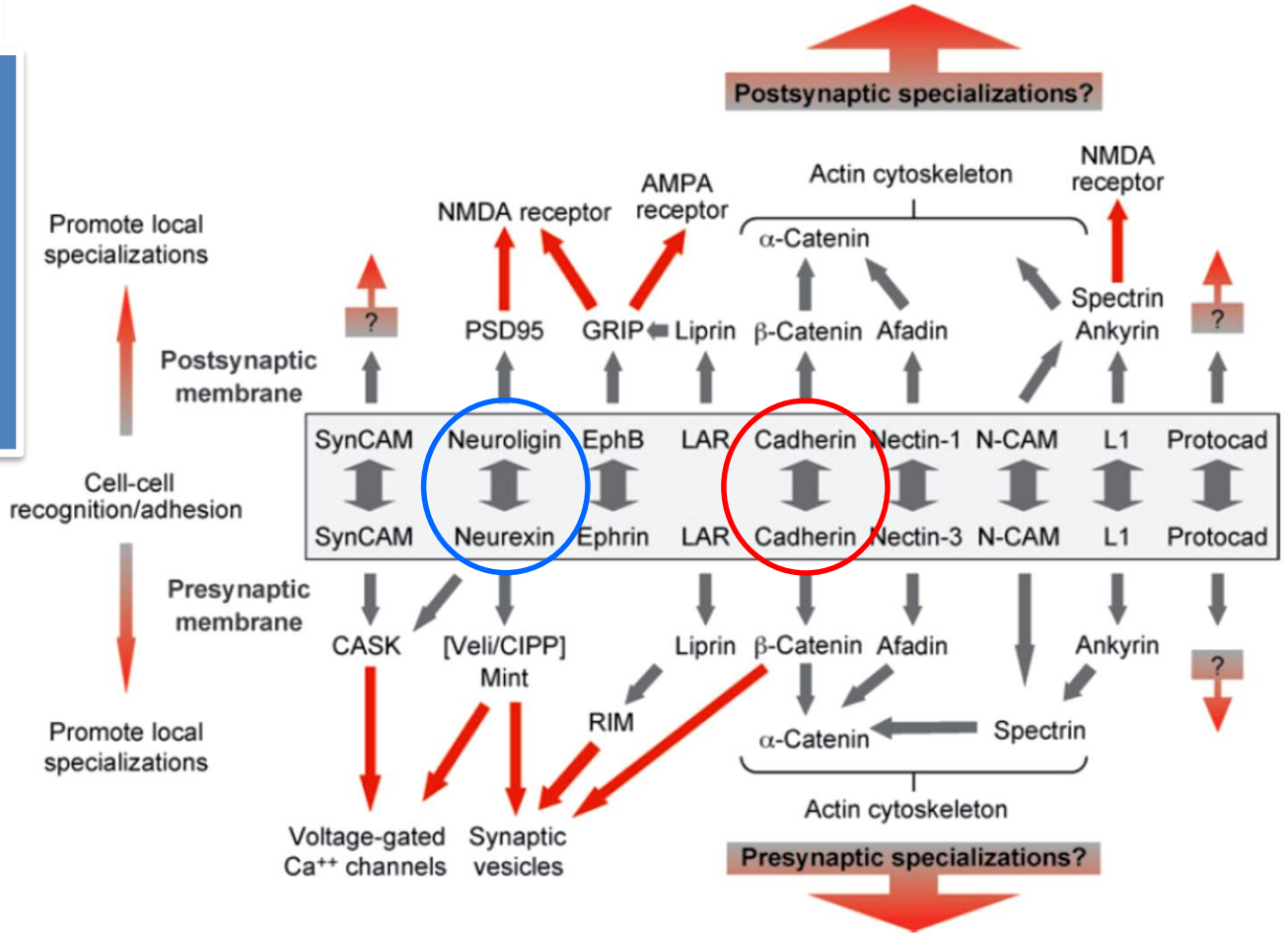


Figure 2

Schematic representations of the neuronal synapse (inset) and protein interactions at the pre- and postsynaptic membranes. Different cell adhesion proteins form homophilic or heterophilic adhesions (*boxed*) and interact with downstream protein networks that describe functional specification of the presynaptic (recruit Ca^{2+} channels, synaptic vesicles) and postsynaptic membranes (recruit neurotransmitter receptors). Abbreviations: AMPA, α-amino-5-hydroxy-3-methyl-4-isoxazole propionic acid; CASK, calcium/calmodulin-dependent serine protein kinase; CIPP, channel-interacting PDZ domain protein; GRIP, glutamate receptor-interacting protein; LAR, leukocyte common antigen-related protein; Mint, Munc-18-interacting protein; N-CAM, neural cell adhesion molecule; NMDA, N-methyl-D-aspartic acid; PSD95, postsynaptic density 95; RIM, Rab3-interacting molecule; Veli, vertebrate LIN-7.

Yamada & Nelson, 2007, Annu. Rev. Biochem.
doi:10.1146/annurev.biochem.75.103004.142811

Adhesion molecules in synaptogenesis

No single pair of synaptic adhesion molecules seems to be sufficient to organize all aspects of synapse development. They might have overlapping functions or act together at synaptic sites. One intriguing possibility is that the presence of particular sets of these molecules at synaptic sites might serve to specify certain classes or types of synapses.

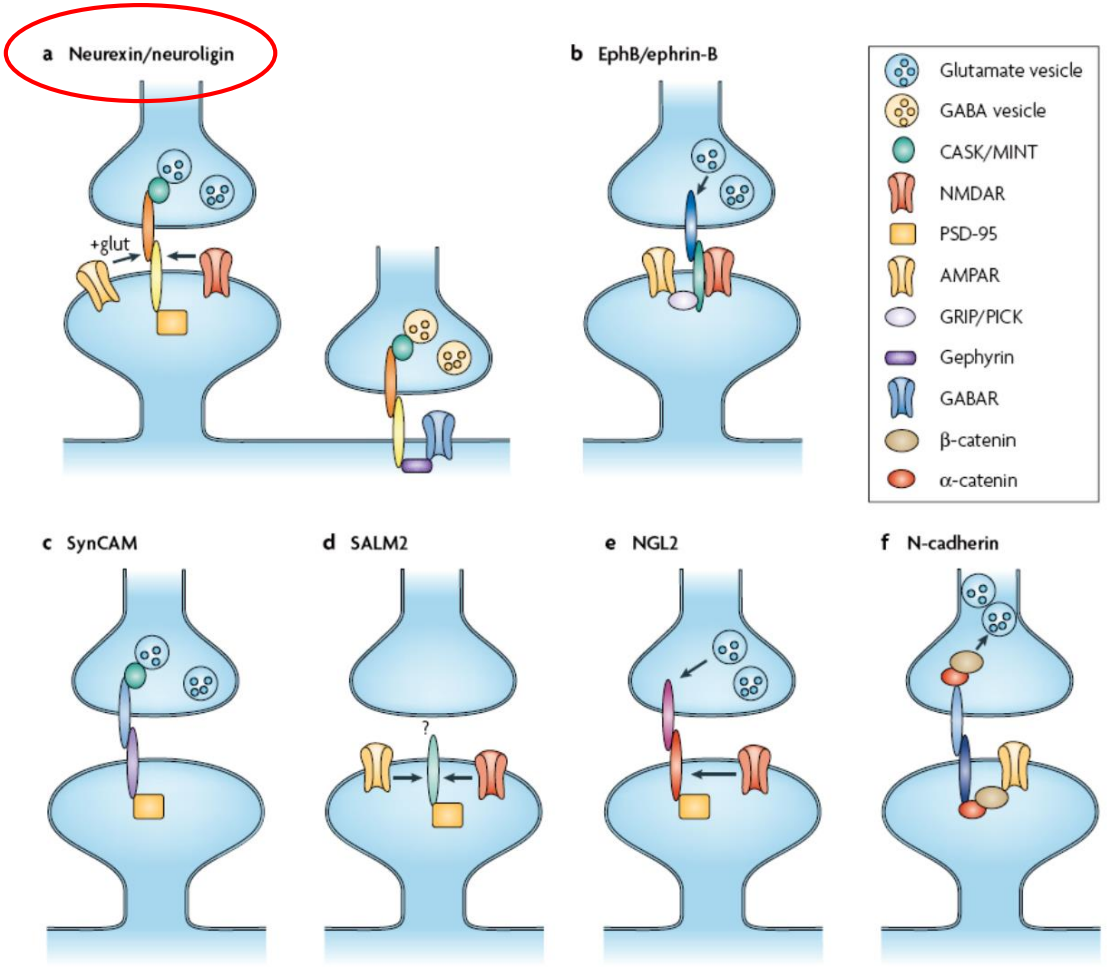
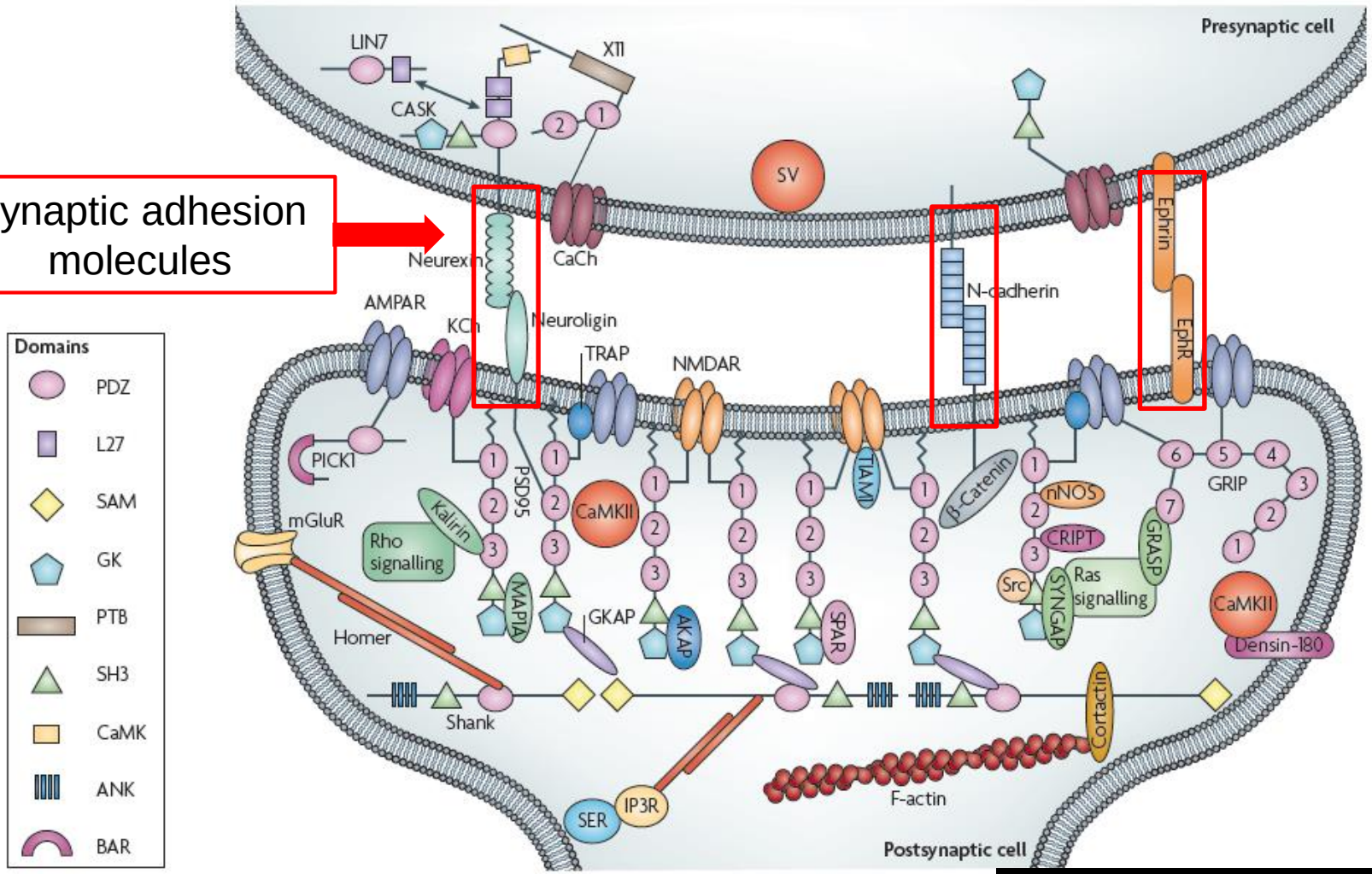


Figure 3 | **Trans-synaptic signalling during synaptogenesis: *in vitro* evidence.** A number of trans-synaptic adhesion molecules are able to control different aspects of synapse development in neuronal cultures and heterologous cell co-cultures. **a** | Neurexins and neuroligins can induce the formation of both excitatory and inhibitory synapses. **b** | EphBs can organize both pre- and postsynaptic glutamatergic terminals through mechanisms requiring defined EphB2 protein domains, and signal to induce dendritic spine formation. **c** | Synaptic cell adhesion molecule (SynCAM) triggers presynaptic maturation but does not yet have a defined role in postsynaptic differentiation. **d** | Synaptic adhesion-like molecule 2 (SALM2) can regulate the organization of the postsynaptic terminal but not the presynaptic terminal (its presynaptic ligand is unknown). AMPARs (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors), and to a lesser degree NMDARs (*N*-methyl-D-aspartate receptors), can be found at SALM2-induced synapses. **e** | Netrin G2 ligand (NGL2) can organize pre- and postsynaptic terminals of excitatory synapses. NMDARs are recruited to these sites, but not AMPARs. **f** | Finally, N-cadherin and catenins are required for the formation of normal presynaptic vesicle reserve pools and have a well-described role in the formation, development and stability of dendritic spines by signalling through Rho GTPases. Cadherins also associate with AMPARs through β-catenins. Arrows indicate that recruitment/clustering occurs, but the mechanism is unclear. '?' indicates that the presynaptic ligand is unknown. CASK, calcium/calmodulin-dependent serine protein kinase; GABAR, γ-aminobutyric acid receptor; GRIP, glutamate receptor interacting protein; MINT, (Munc 18 interacting protein; lin-10/X11); PICK, protein interacting with C kinase; PSD-95, postsynaptic density protein-95.

Dalva et al., 2007
NATURE REVIEWS NEUROSCIENCE
doi:10.1038/nrn2075

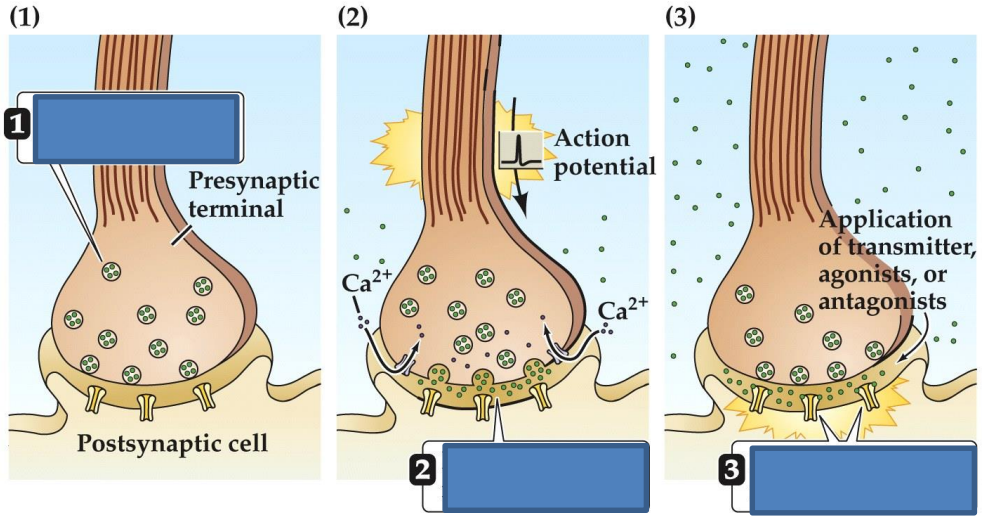
The molecular organization of excitatory synapses

Synaptic adhesion molecules

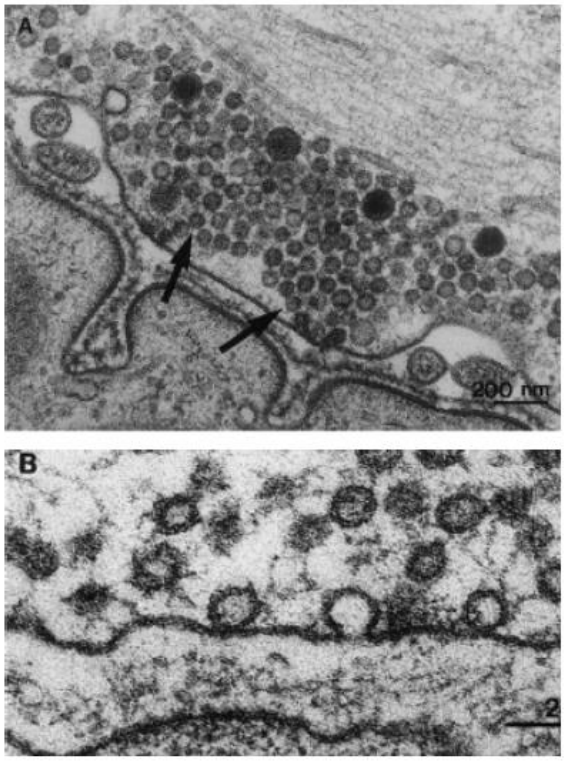


Feng & Zhang, 2009
NATURE REVIEWS NEUROSCIENCE
doi:10.1038/nrn2540

1) What are the criteria to demonstrate chemical transmission?



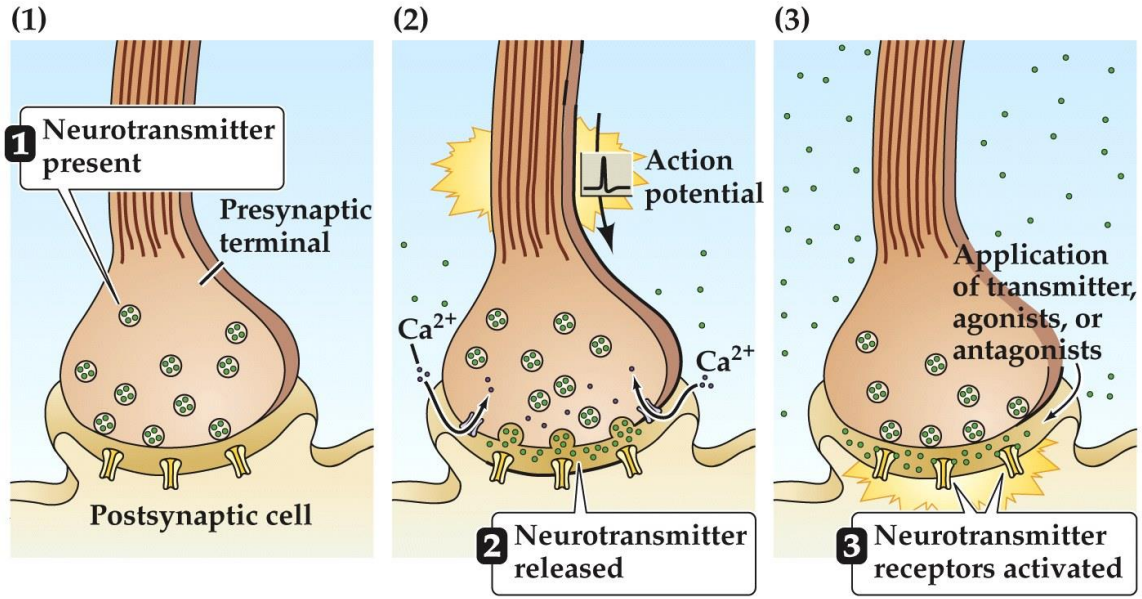
NEUROSCIENCE 5e, Box 5A



2) Why store transmitters in vesicles?

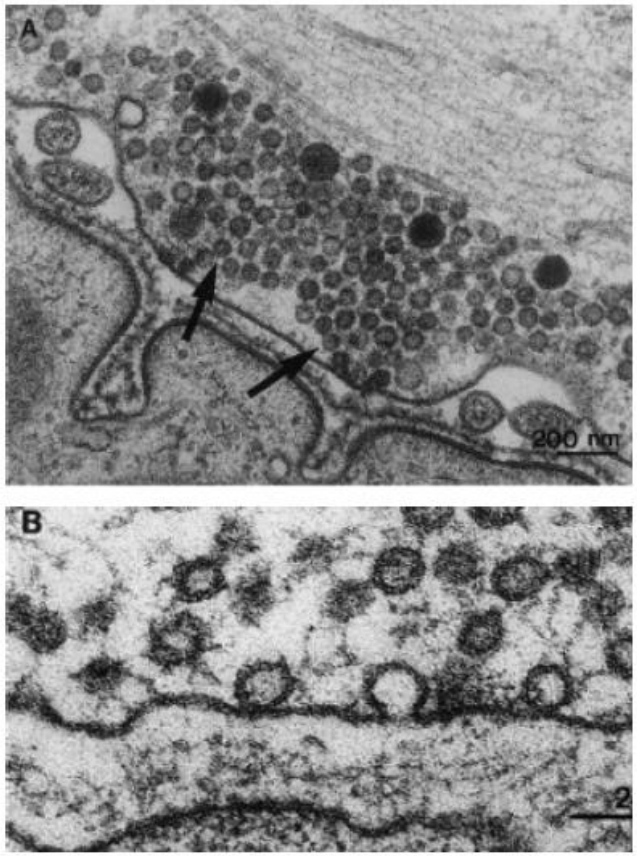
Criteria that demonstrate chemical transmission

1. Synthesis of the neurotransmitter in the ***presynaptic nerve terminals***
2. Storage of the neurotransmitter in ***secretory vesicles***.
3. ***Regulated release*** of neurotransmitter in the synaptic space between the pre- and post-synaptic neurons.
4. Presence of ***receptors on the postsynaptic*** **membrane**; receptor activation mimics the effect of nerve stimulation
5. A means for "***termination***" *of the action of the* released neurotransmitter.



NEUROSCIENCE 5e, Box 5A

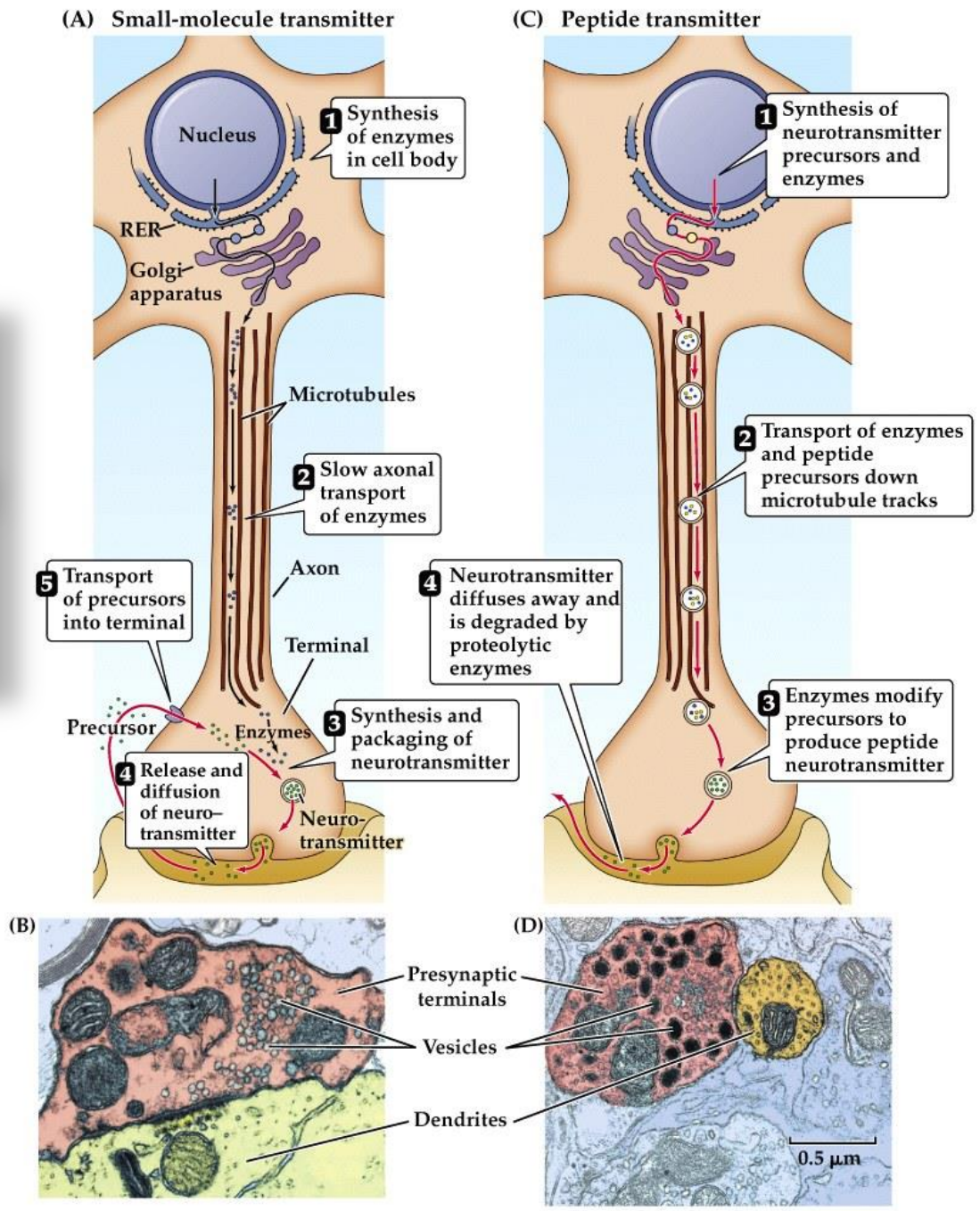
Why store transmitters in vesicles?



- Protection from degradation - by proteases and esterases
- Allows for regulation
- Provides a storage system
- Can be docked at active zone
- Differ for classical transmitters (small, clear-core) vs. neuropeptides (large, dense-core)

Comparison of:

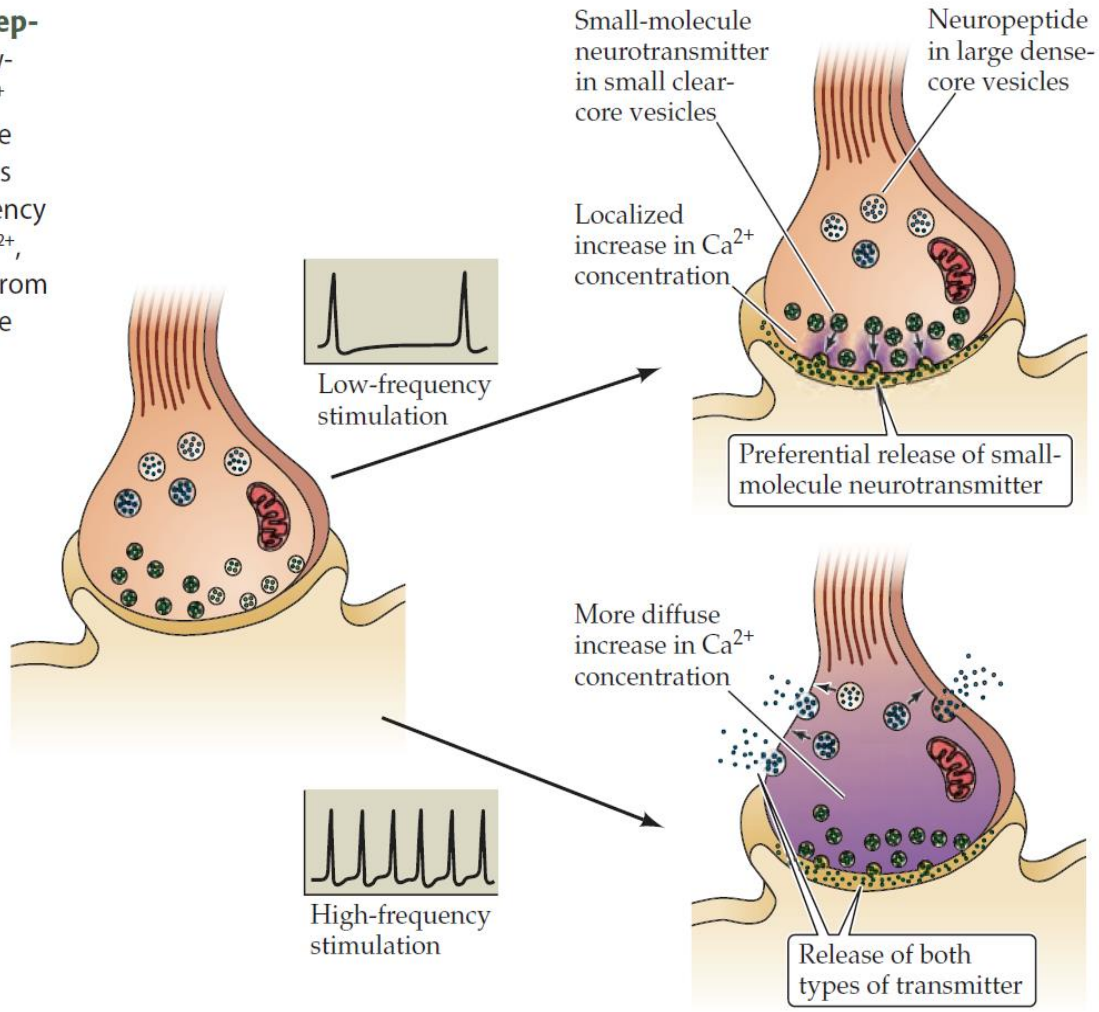
Synaptic vesicles for **small-molecule** (small/clear vesicles) and **peptide transmitters** (dense-core granules)



***NEUROSCIENCE 5e*, Figure 5.5**

Neuropeptides and small-molecule co-transmitters differ also in the release mechanism

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, Neuroscience, 2012