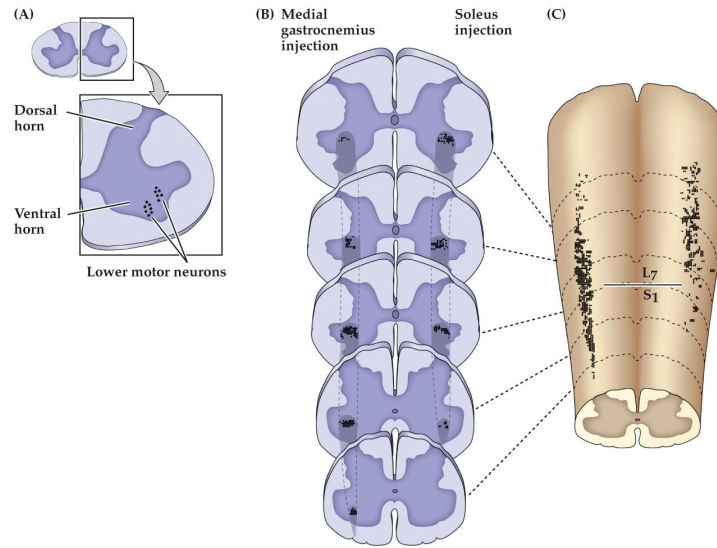


# Synaptogenesis PNS vs. CNS

## The Neuromuscular Junction

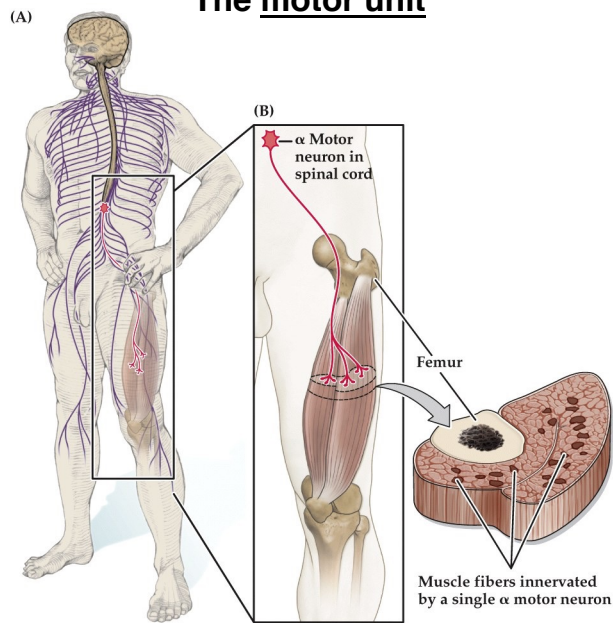


### The motor neuron pool



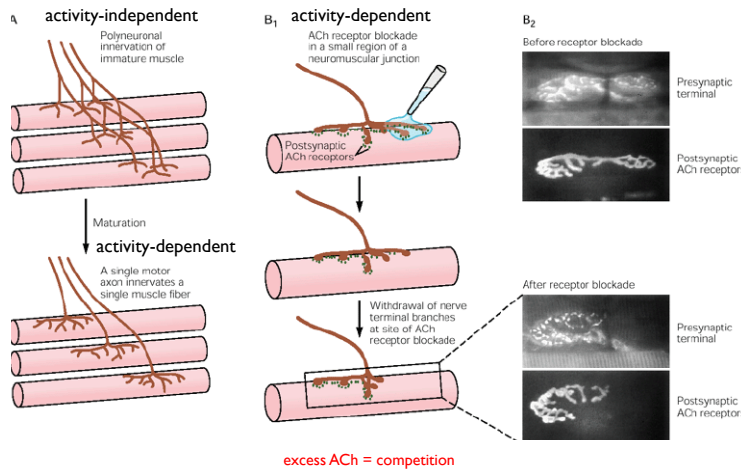
NEUROSCIENCE 5e, Figure 16.2  
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### The motor unit

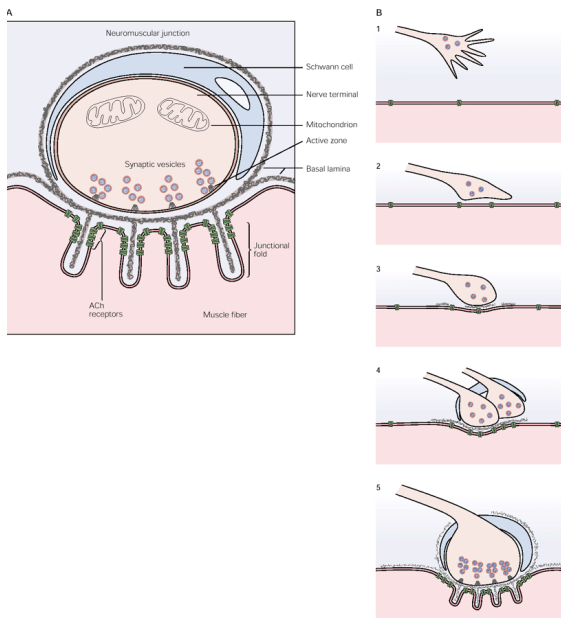


NEUROSCIENCE 5e, Figure 16.5  
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**In the beginning, the relationship between axons and muscle fibers in promiscuous and activity-independent**

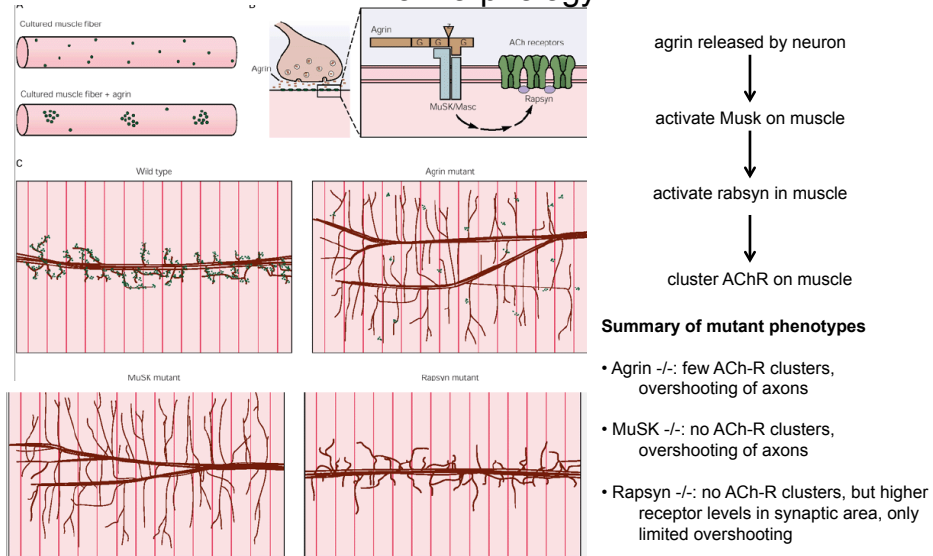


**Steps in NMJ formation**

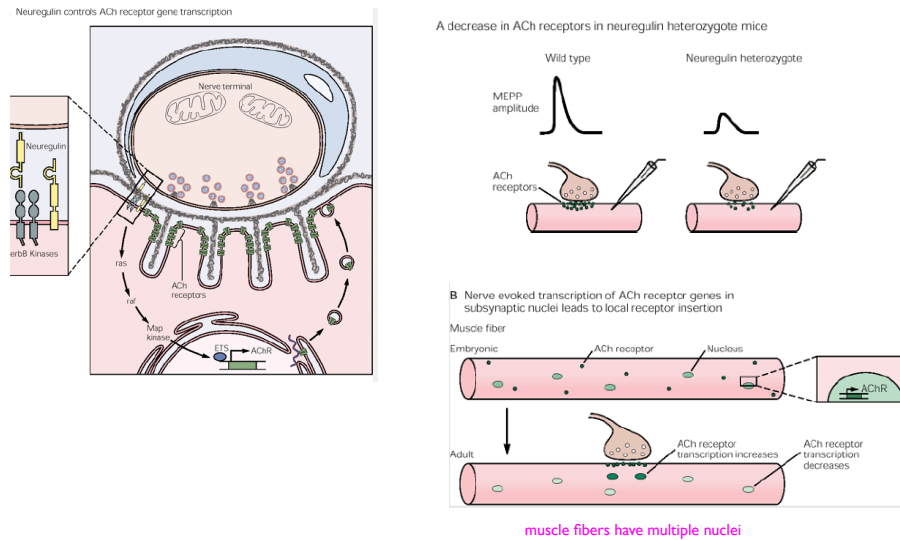


- **Activity-independent:**
  - Axon growth cone initiates contact with muscle fiber (signaling to muscle can precede contact)
- Clustering of AChRs begins (induced by agrin/MuSK, inhibited by ACh, nestin, Cdk5/p35)
- Cell-cell signaling leads to changes in extracellular matrix, cell-cell adhesion, clustering of molecules at the synapse, increased local transcription and down regulation of NMJ components in other areas of the muscle fiber
- Neuromuscular activity is **not** required to form a NMJ.
- **Activity based competition:**
  - eliminates all but one axon... "there can be only one"
  - requires ACh and axonal electrical activity

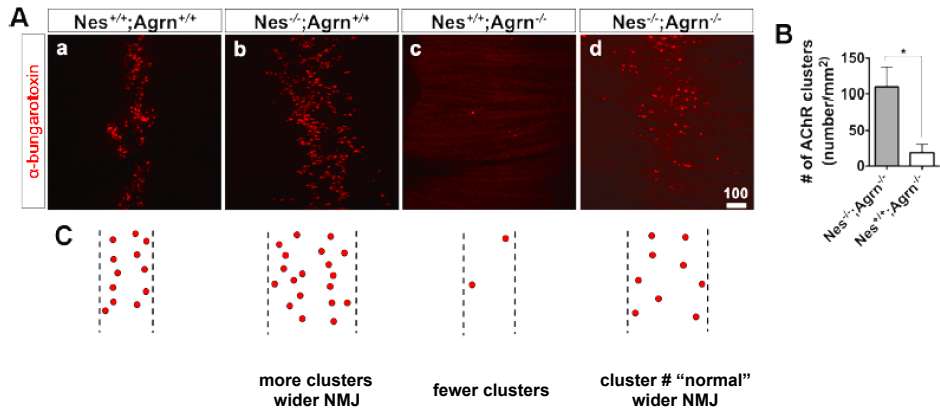
### Loss of agrin/Musk/Rapsyn signaling alters NMJ morphology



### Neuregulin/erbB positively regulate local AChR transcription

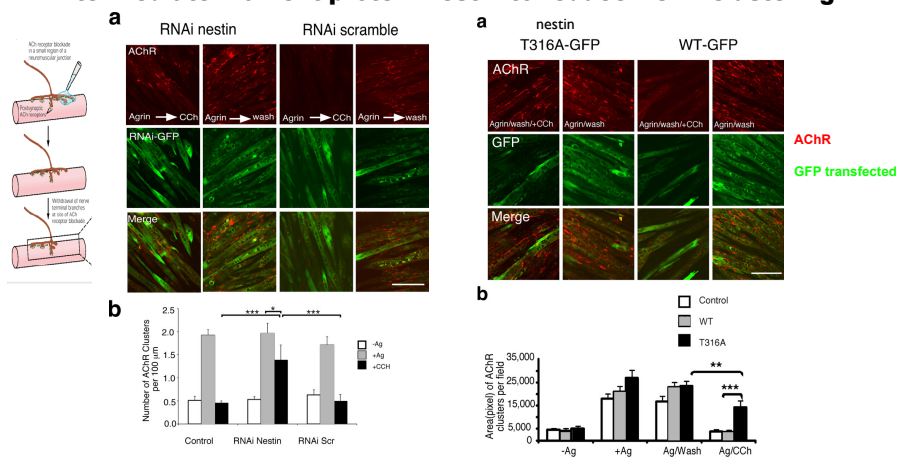


**The intermediate filament protein Nestin reduces AChR clustering by antagonizing agrin function**

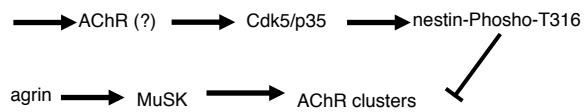


Mohensil et al (2011) The Journal of Neuroscience, August 10, 2011 • 31(32):11547–11552

**ACh competition acts via Cdk5/p35 phosphorylation of intermediate filament protein nestin to reduce AChR clustering**

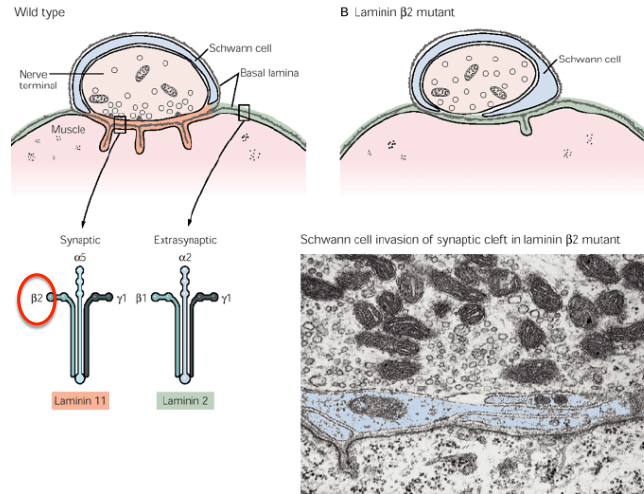


acetylcholine  
or carbachol (CCh)  
= competition, AChR  
removed from surface



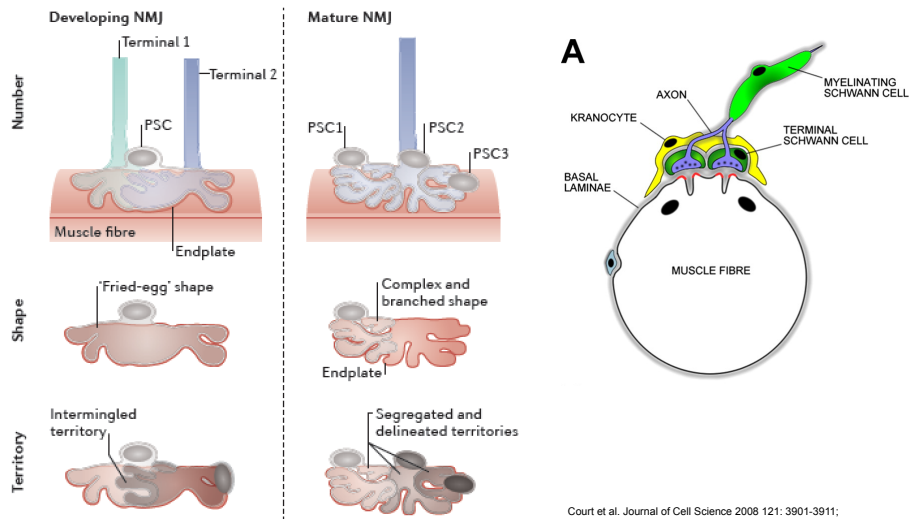
Yang et al. Nat Neurosci. 2011 Mar; 14(3): 324–330.

**Regional differences in the extracellular matrix laminas shape NMJ development**



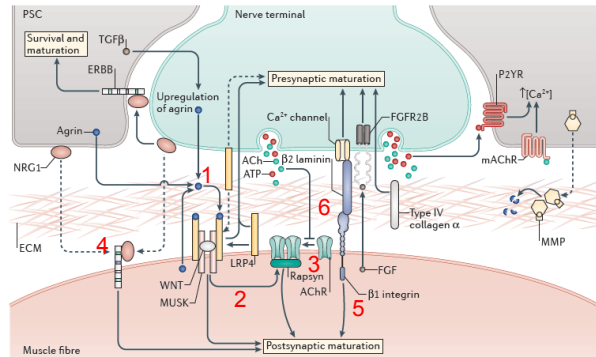
**Basal Lamina:**  
 - present at synaptic and non-synaptic regions, but specific molecular composition at synapse

**The NMJ endplate is covered by terminal non-myelinating Schwann cells**



# Synaptogenesis

## Molecules at the NMJ



Agrin signalling promotes NMJ formation:

1. TGFβ secretion by Schwann cells increases agrin release by the approaching pre-synaptic terminal
2. Agrin binds to and activates Musk, which phosphorylates Rapsyn
3. Phospho-rapsyn clusters the AChR

Neuregulin signalling promotes NMJ formation:

4. Nrg1 binding to ErbB (a receptor tyrosine kinase) acts via MAP Kinase to enhance local transcription of AChR

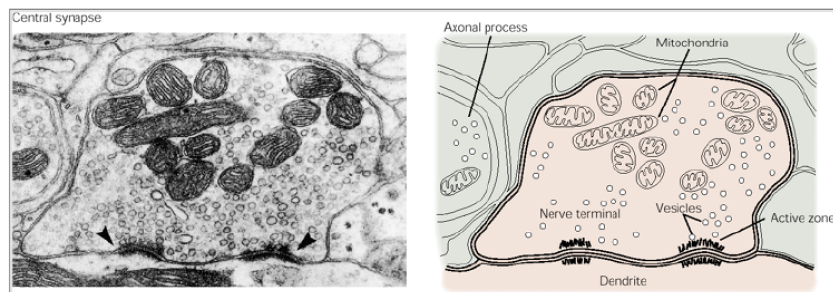
Local distribution of laminin

5. Differential activation of B1 integrin by β2 laminin (11) enhances NMJ formation and determines NMJ boundary

ACh signalling reduces NMJ formation:

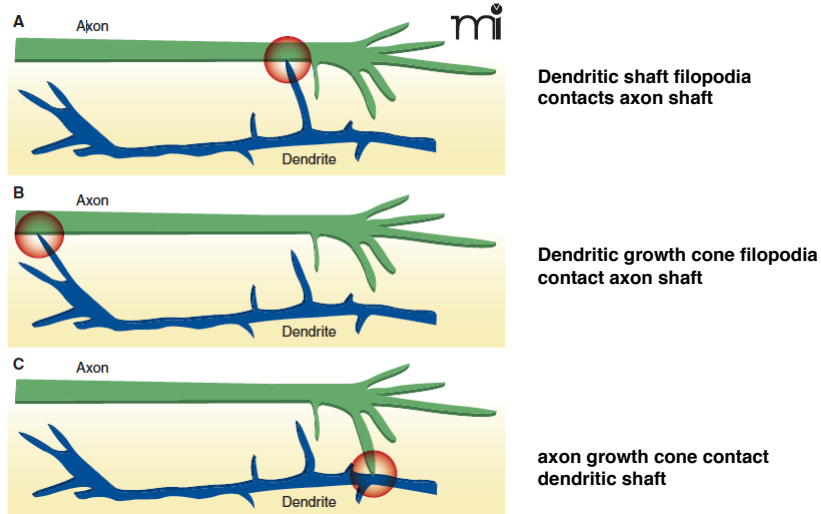
6. AChR release leads to cdk5-dependent activation of nestin and reduces AChR clustering

## The “typical” CNS synapse

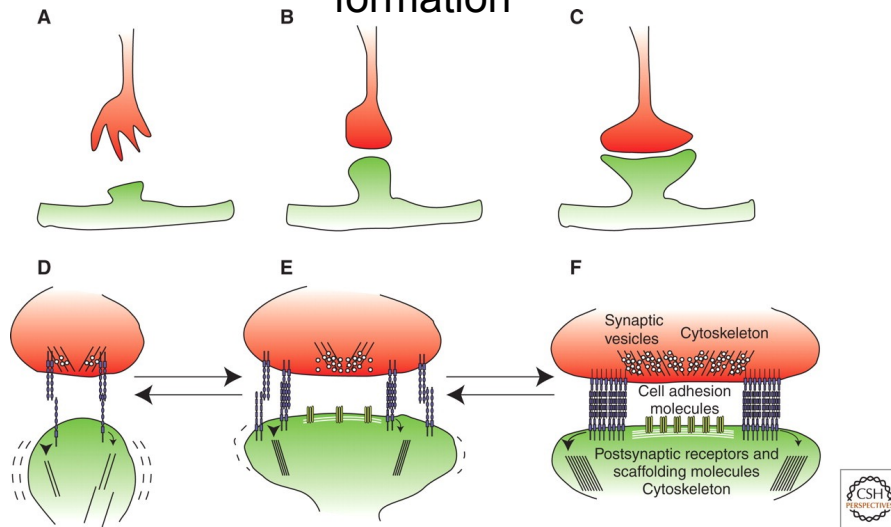


# Synaptogenesis

CNS synaptogenesis usually does NOT occur at the axonal growth cone



## Different stages of (glutamate) synapse formation



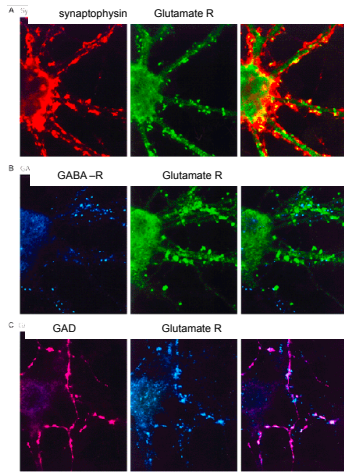
©2009 by Cold Spring Harbor Laboratory Press

Nikolaos Giagtzoglou et al. Cold Spring Harb Perspect Biol 2009;1:a003079



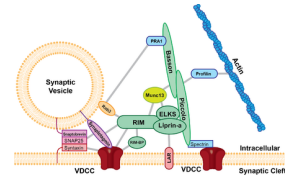
# Synaptogenesis

## CNS synapse "markers"



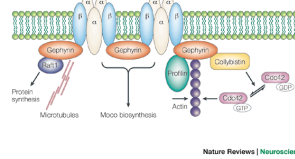
### Pre-synaptic General

Synapsin  
 synaptophysin  
 synaptotagmin  
 SV2  
 Bassoon  
 Piccolo



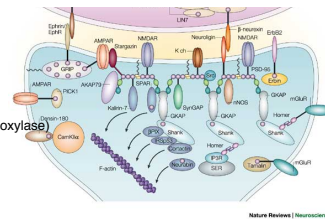
### Post-synaptic

Gephyrin (I)  
 PSD95 (E)

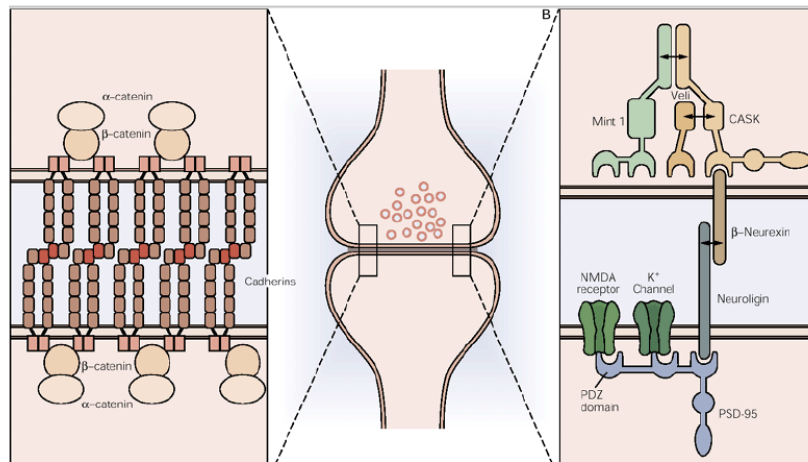


### cell-type specific (E/I)

vesicular transporters  
 VGLUT (E)  
 VIAAT (I)  
 NT synthetic enzyme (I)  
 GAD (glutamic acid decarboxylase)



## Peri-synaptic Adhesion molecules

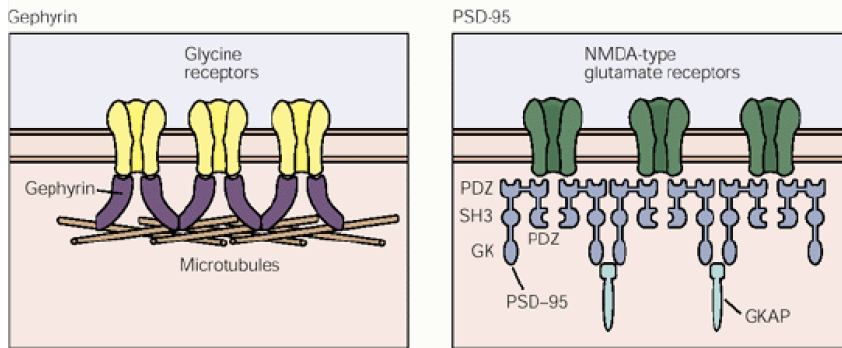


**Cadherins**  
**Beta-catenin**  
**alpha-catenin**

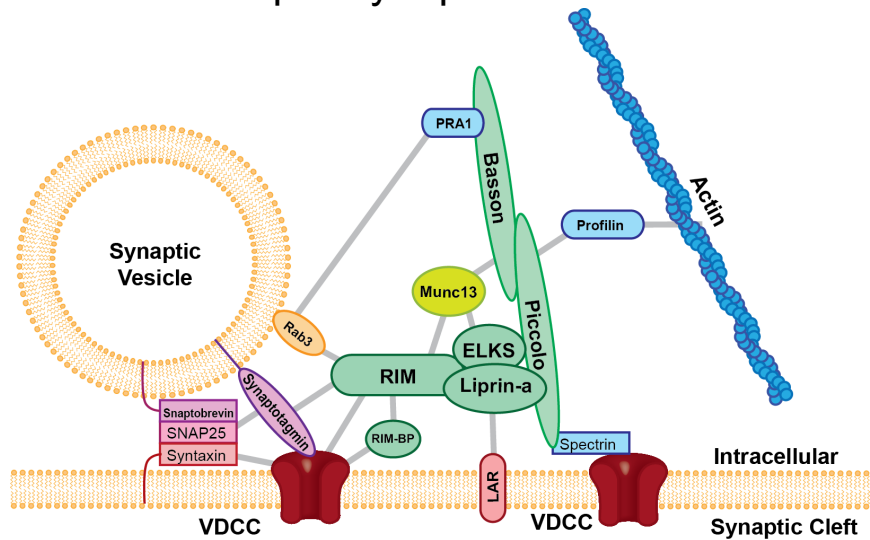
**pre: Beta-Neurexin -CASK**

**post: Neuroigin - PSD95**

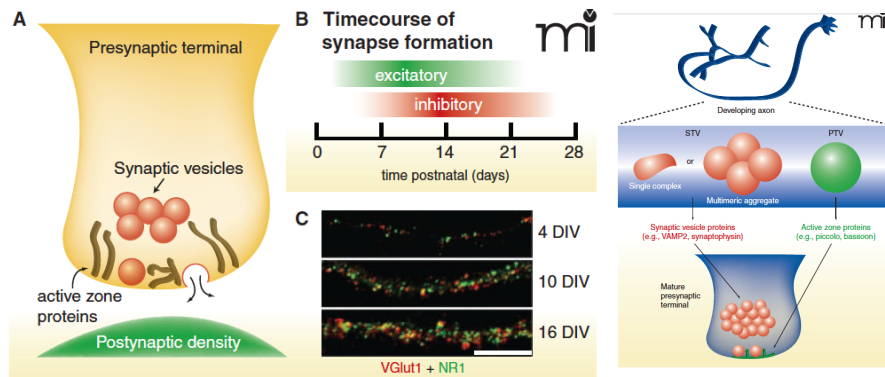
### Specific Inhibitory vs. Excitatory post-synaptic molecules



### General pre-synaptic molecules

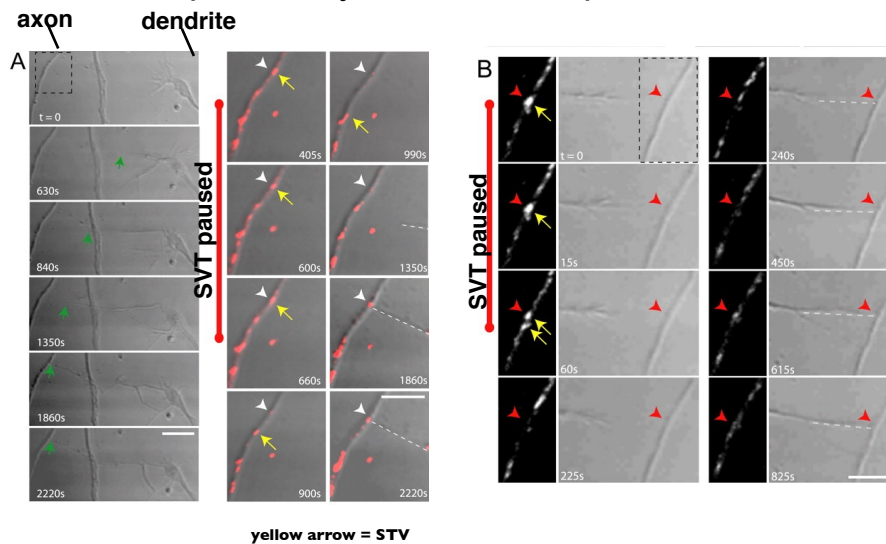


## Synaptic vesicle and active zone proteins are transported on different types of vesicles

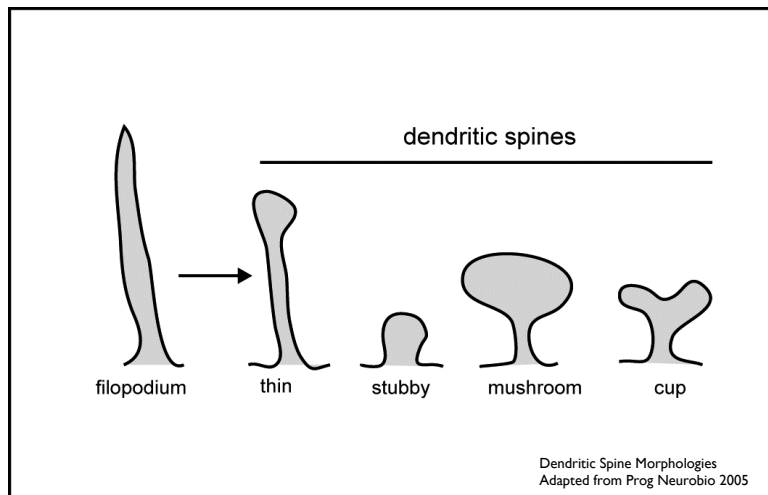
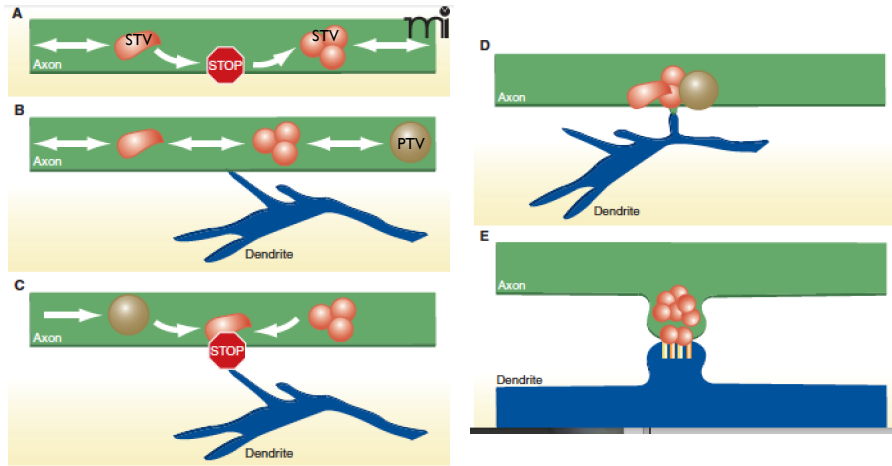


STV = synaptic protein transport vesicle  
PTV = active zone protein transport vesicle

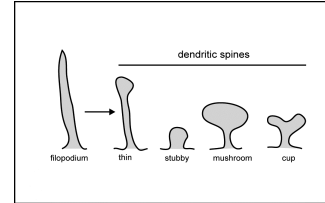
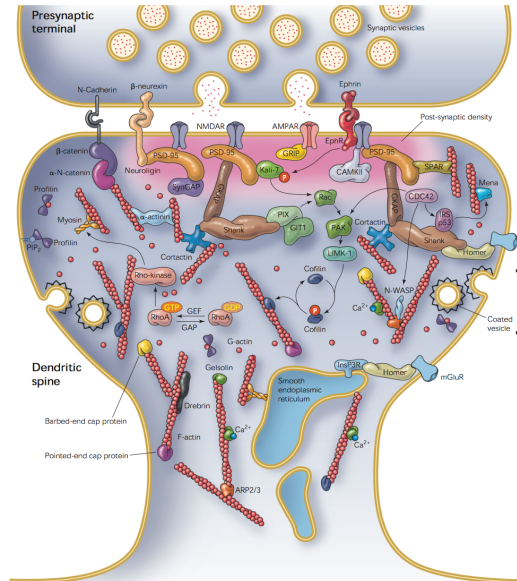
## Dendritic filopodial contacts are selectively stabilized at previously defined STV pause sites.



### A model of CNS synapse assembly



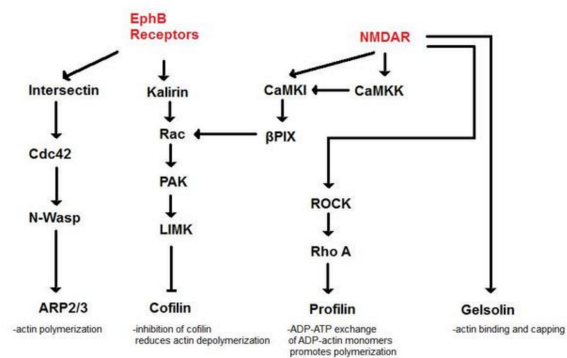
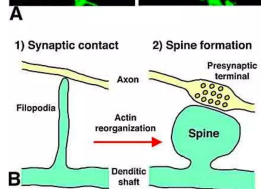
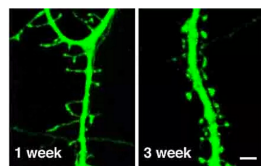
## Dendritic spines : new roles for “old friends”



- Spine formation requires cell-cell contact & NMDA-R activity
- Different subsets of proteins are involved in spine initiation, maturation and maintenance

Calebrese et al. PHYSIOLOGY • Volume 21 • February 2006

## Dendritic spine formation



- Requires NMDA-receptor activity AND axon-dendrite contact
- Enhanced by EphrinB/EphB activity
- Heterogeneity in mechanisms of CNS synaptogenesis likely reflects heterogeneity of CNS synapses
  - excitatory
  - inhibitory