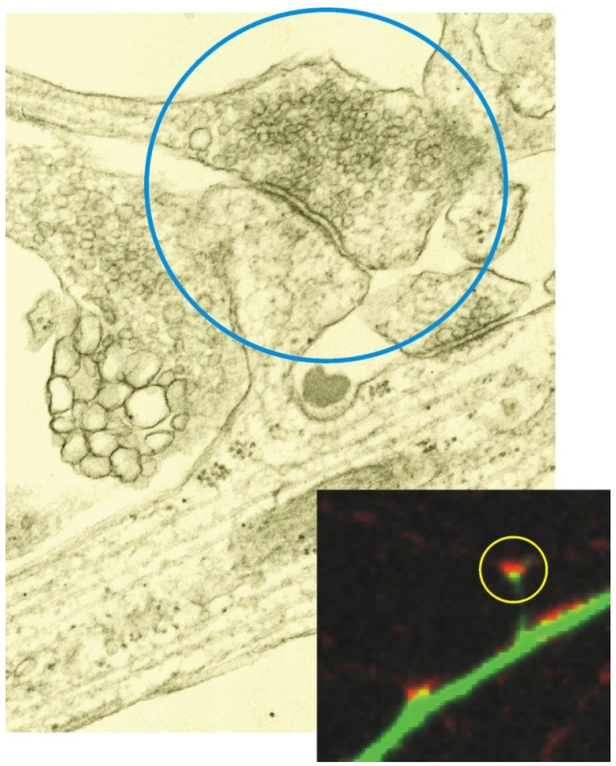
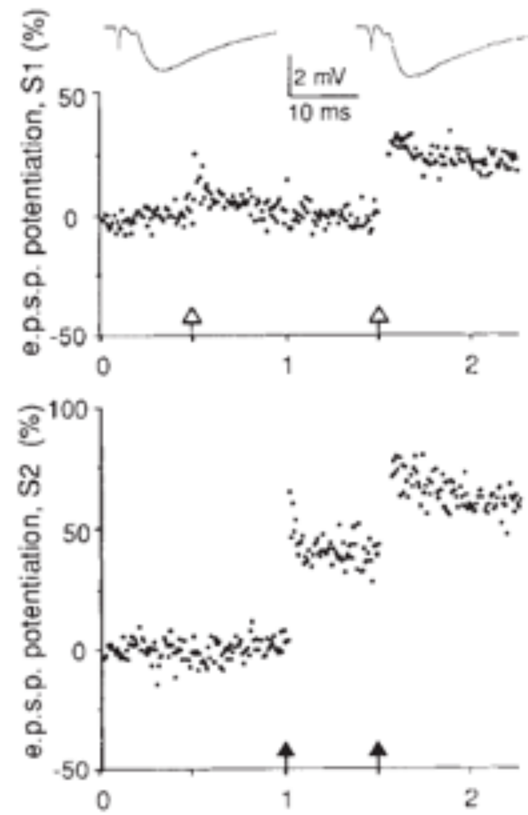
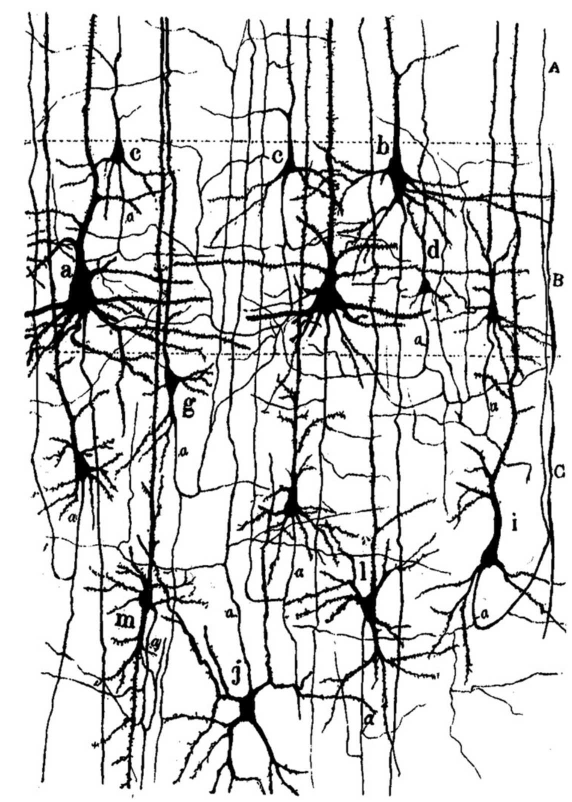
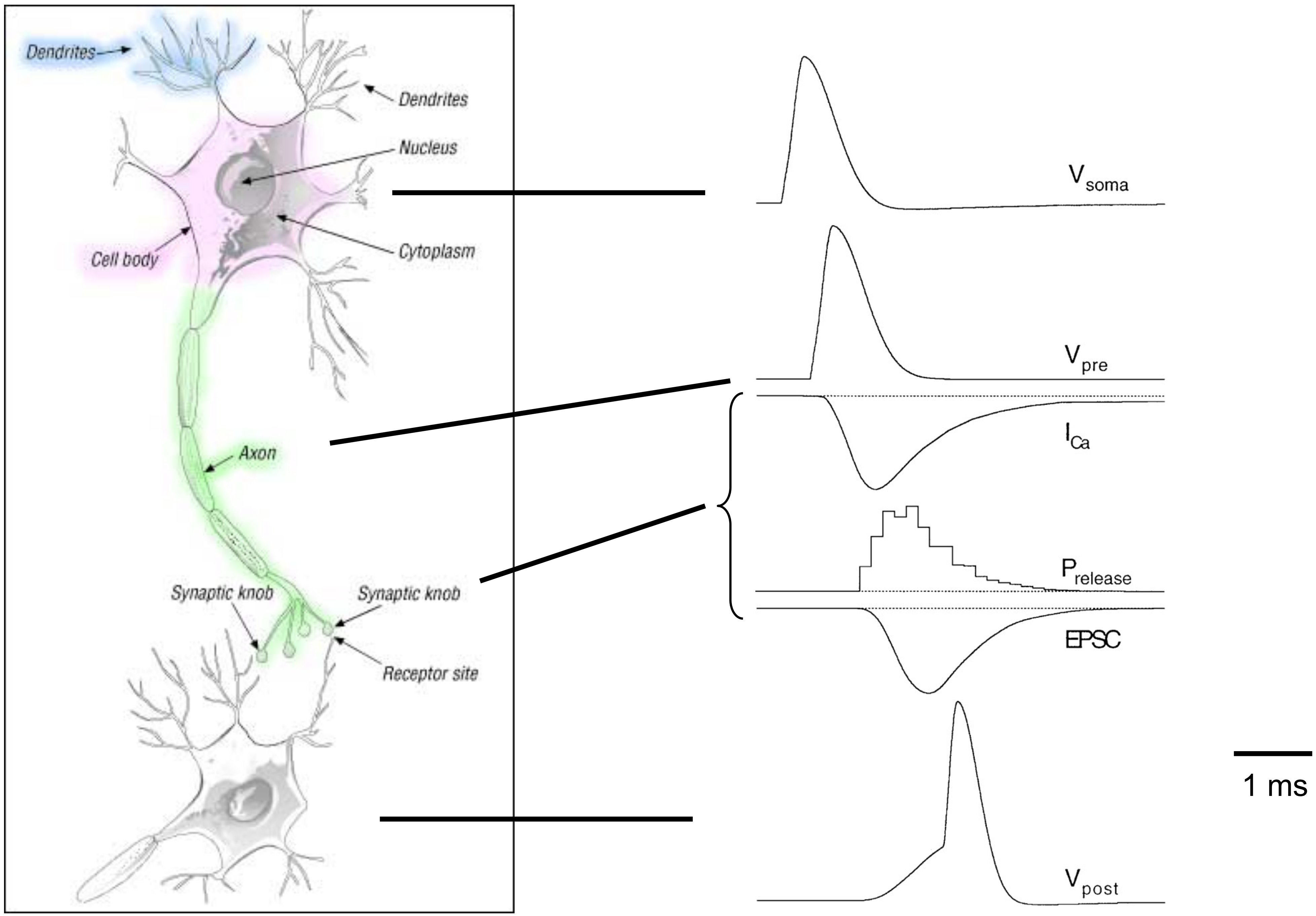
Module 1: Synapses, plasticity and circuits



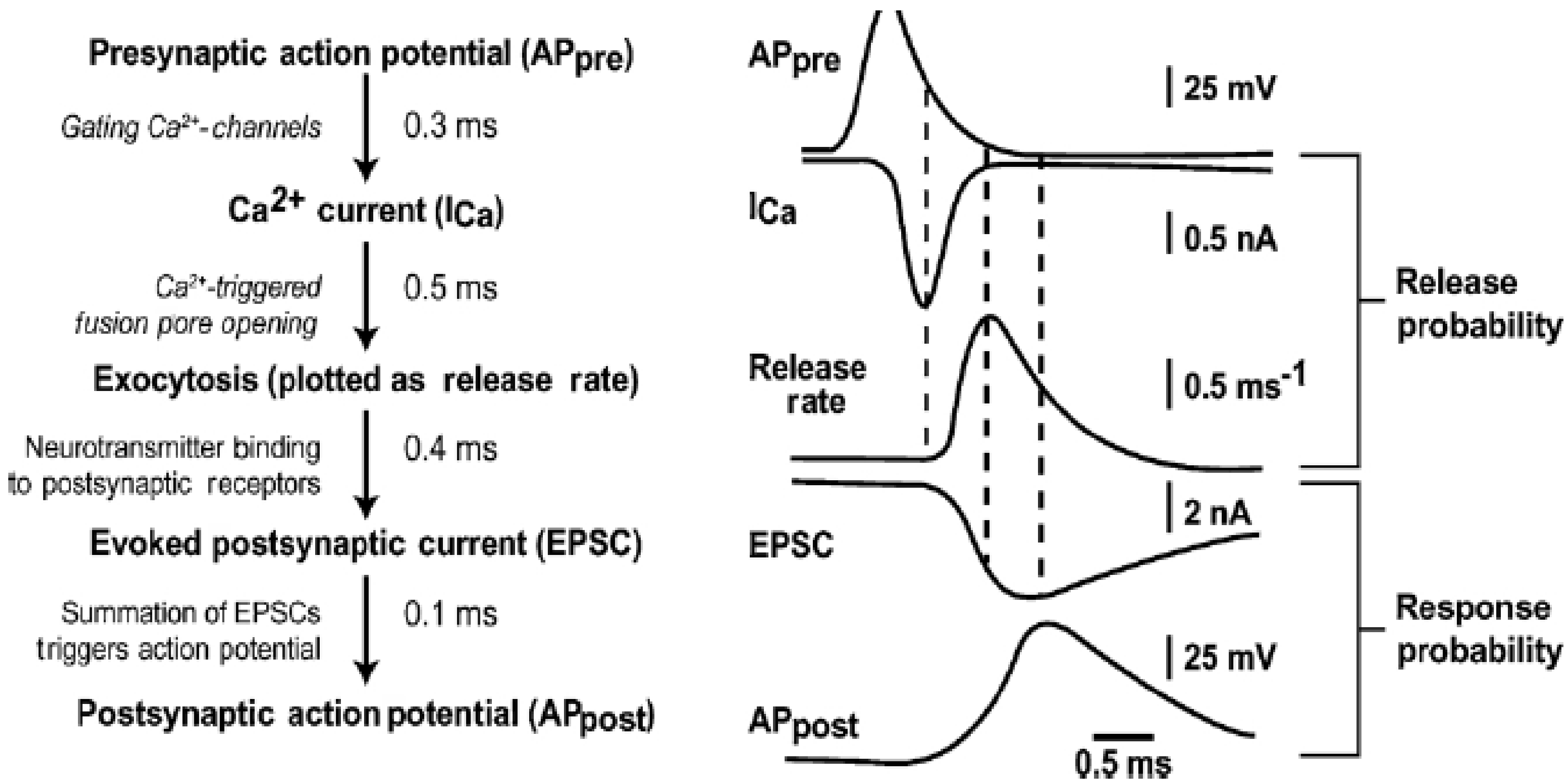




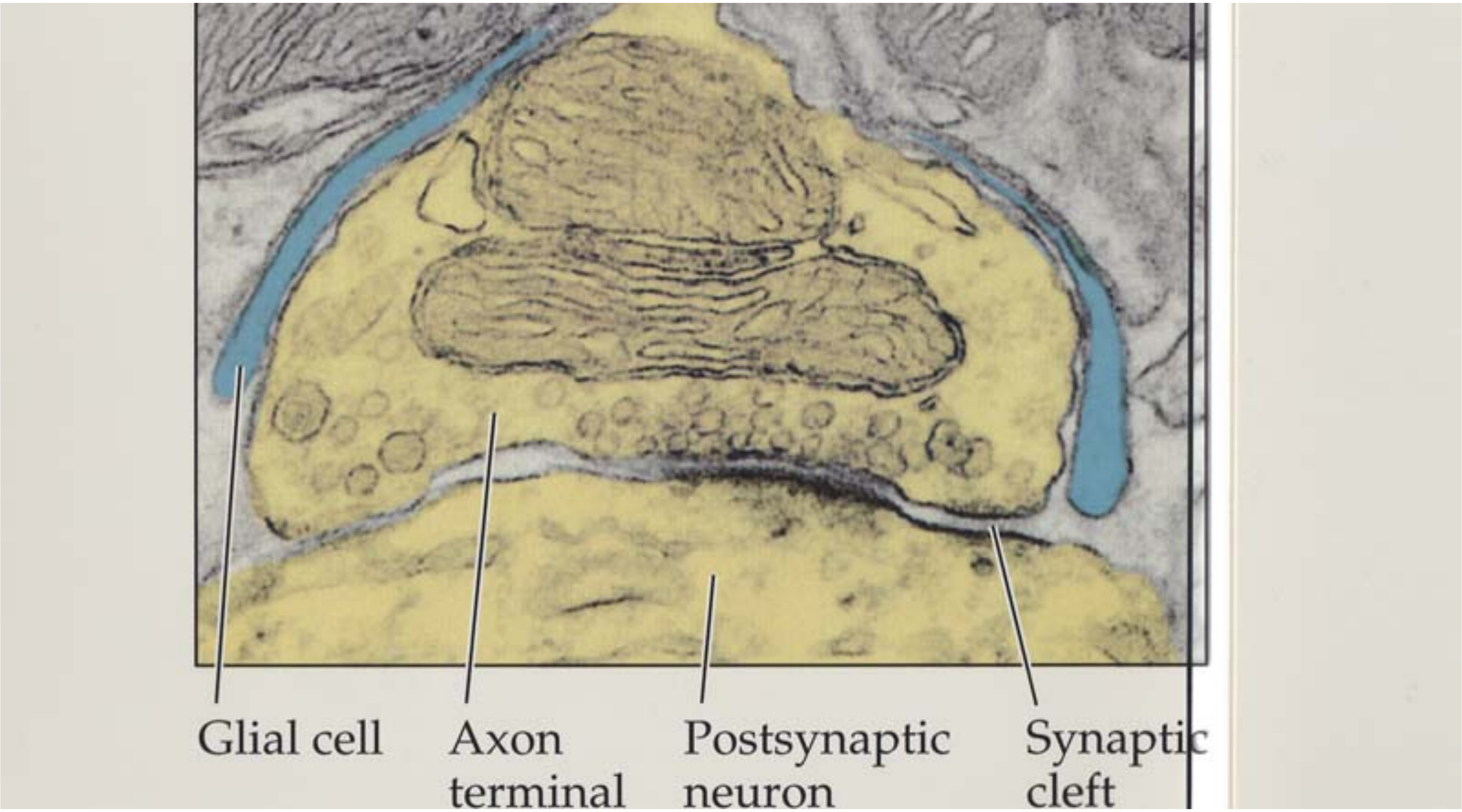
The synapse: transfer of information



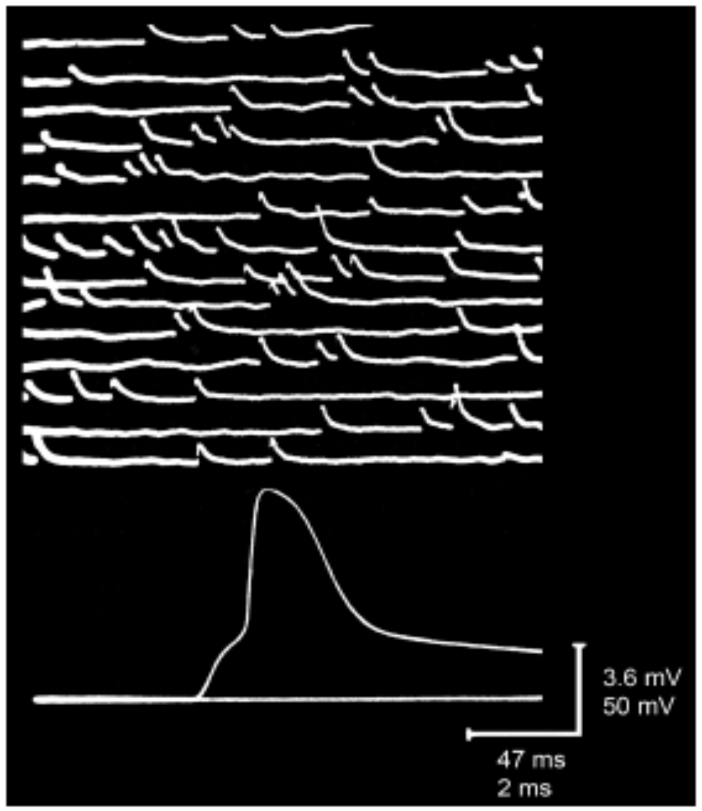
The synapse: transfer of information

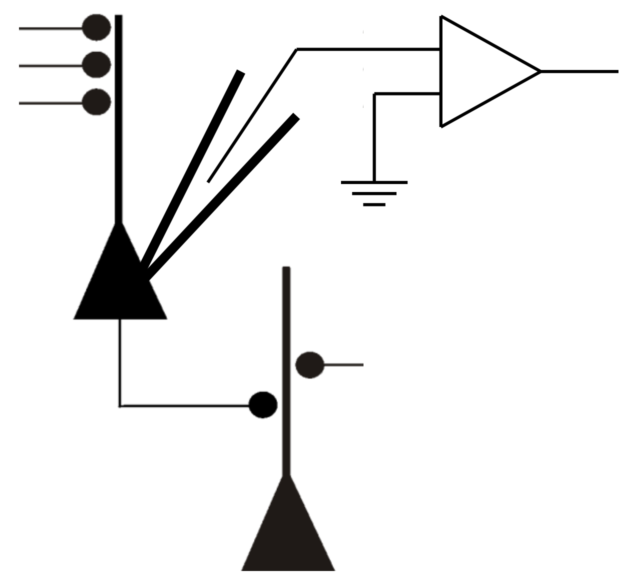


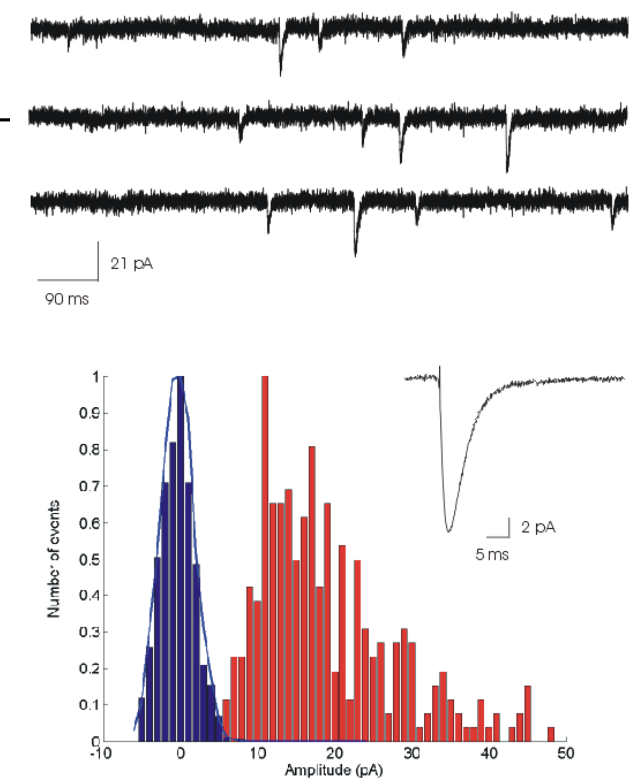
The synapse


Glial cell
Axon terminal
Postsynaptic neuron
Synaptic cleft

The miniature postsynaptic response (or 'mini')



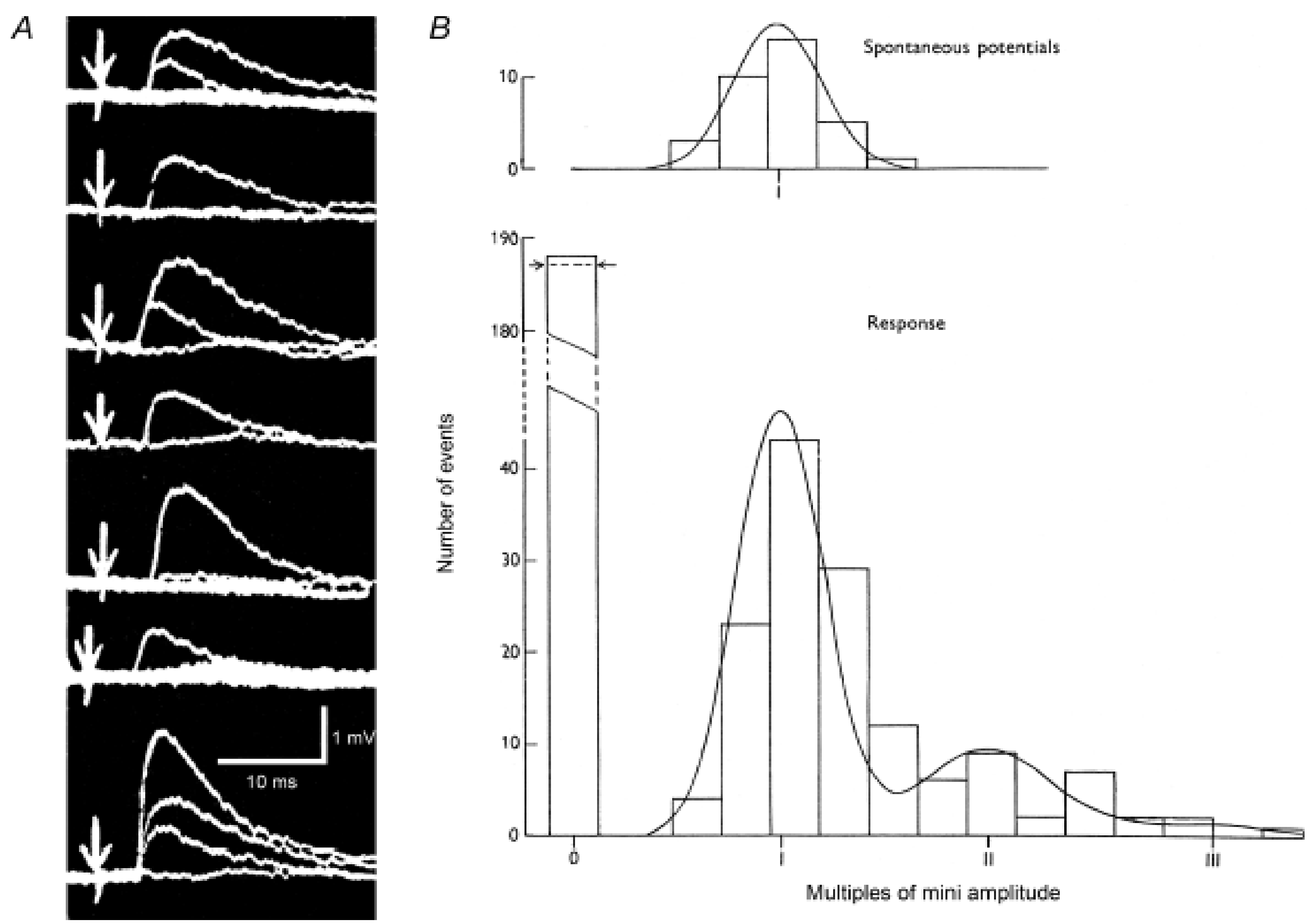




Fatt and Katz, 1952

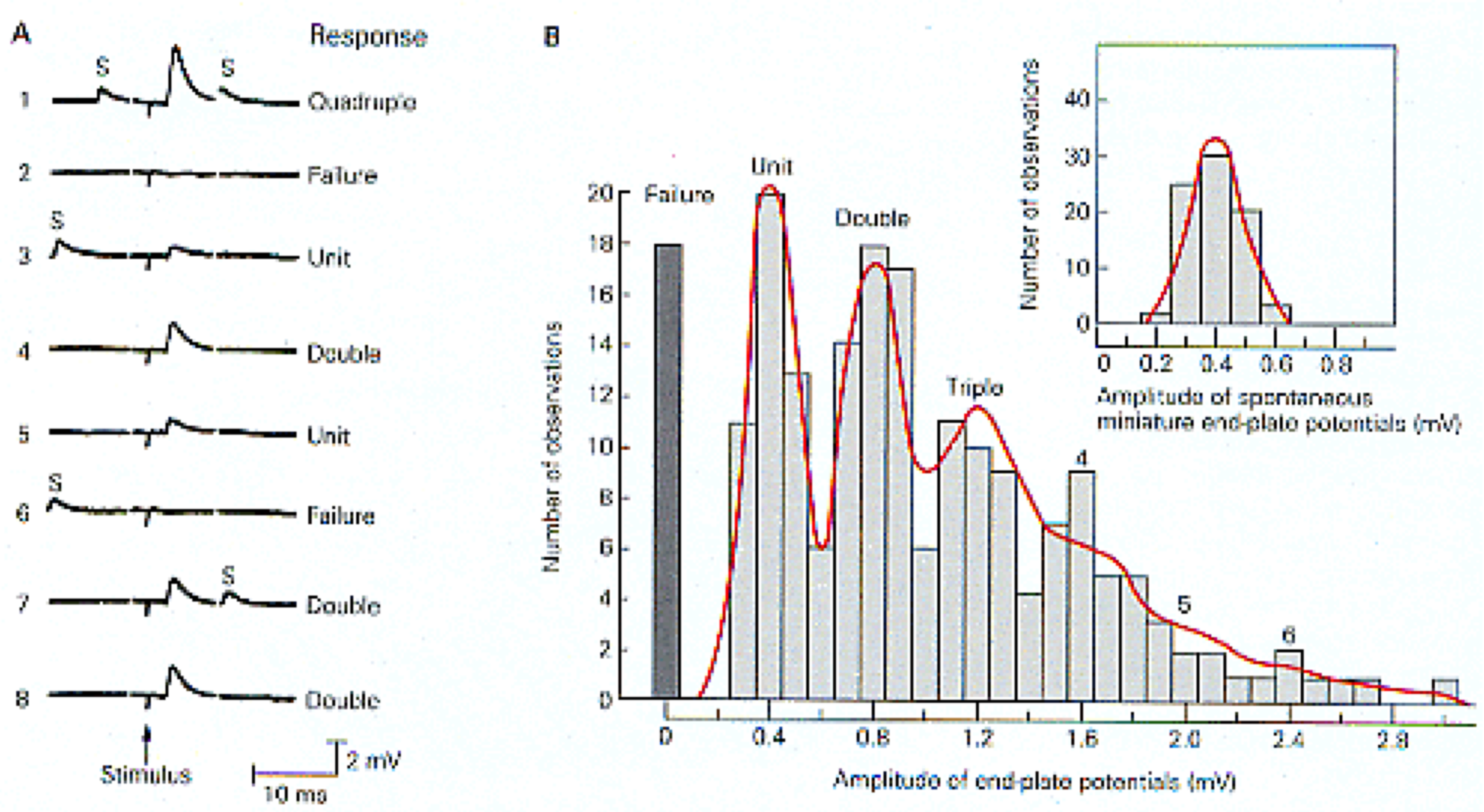
- Remain in the presence of TTX
- Prolonged by blockers of acetylcholine esterase
- Blocked by AChR antagonists

Quantal nature of neurotransmitter release



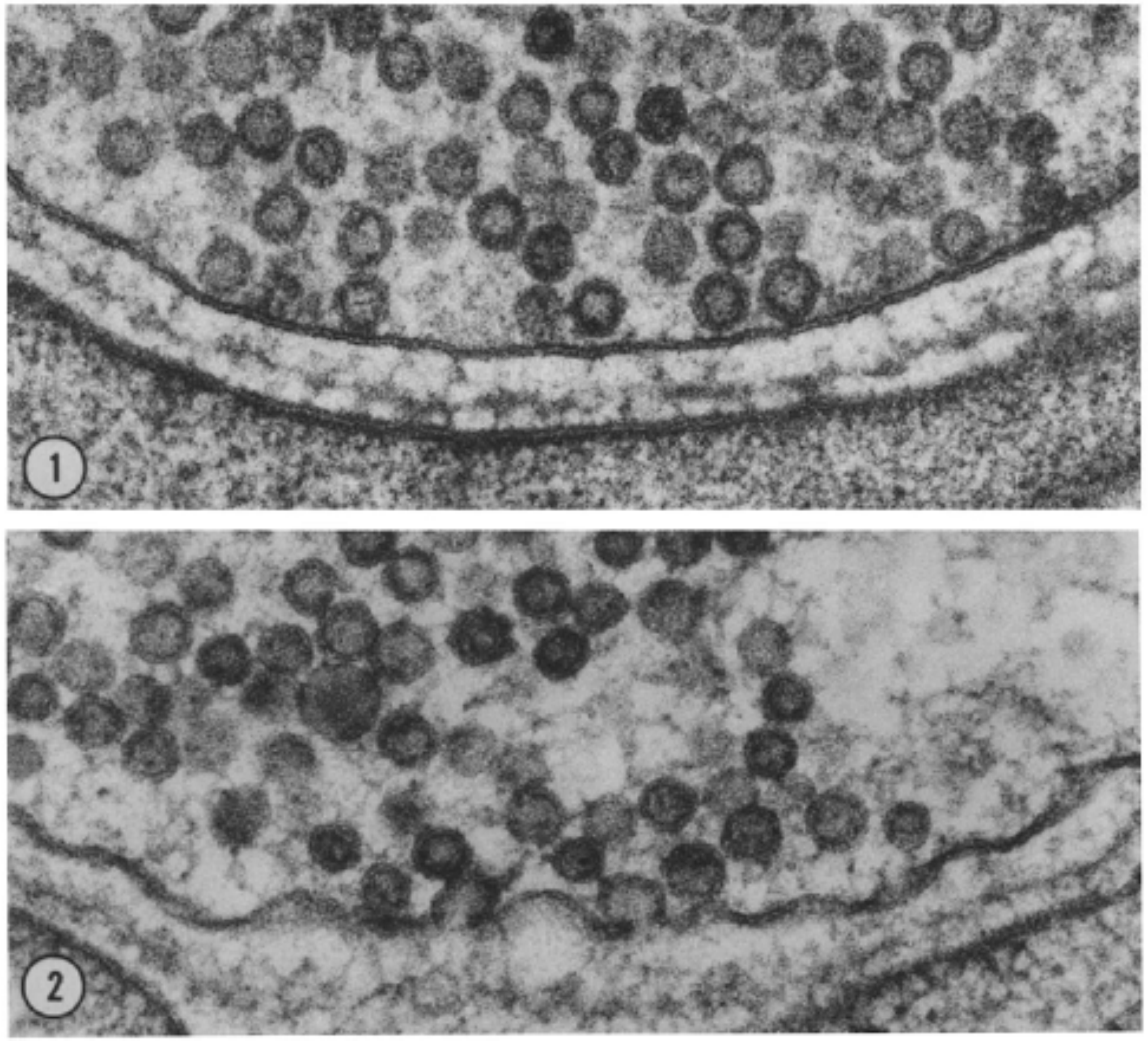
Del Castillo and Katz, 1954

Quantal nature of neurotransmitter release



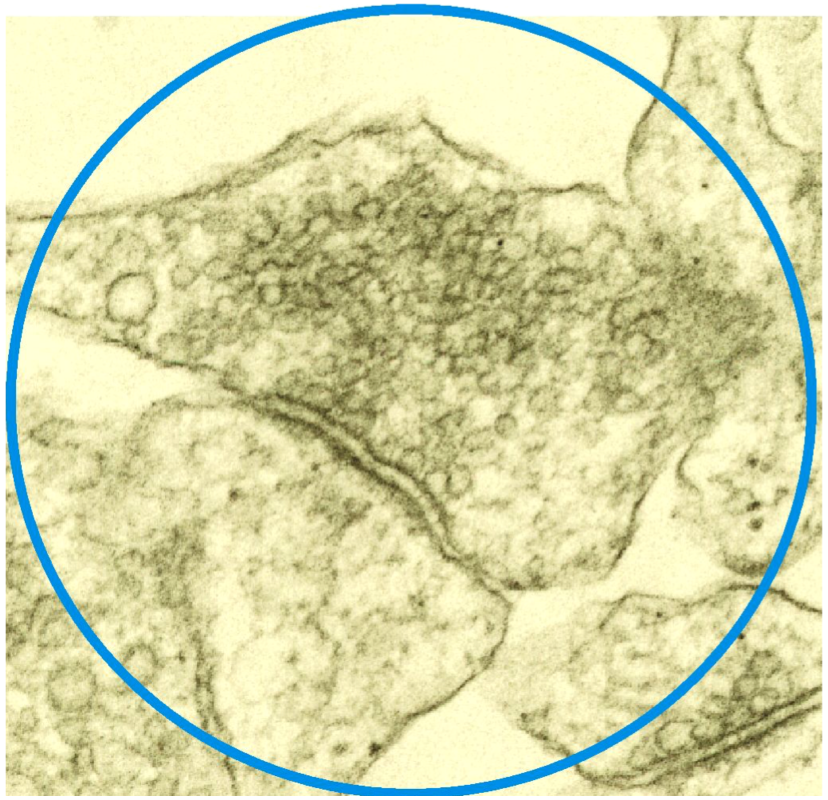
Quantal nature of neurotransmitter release

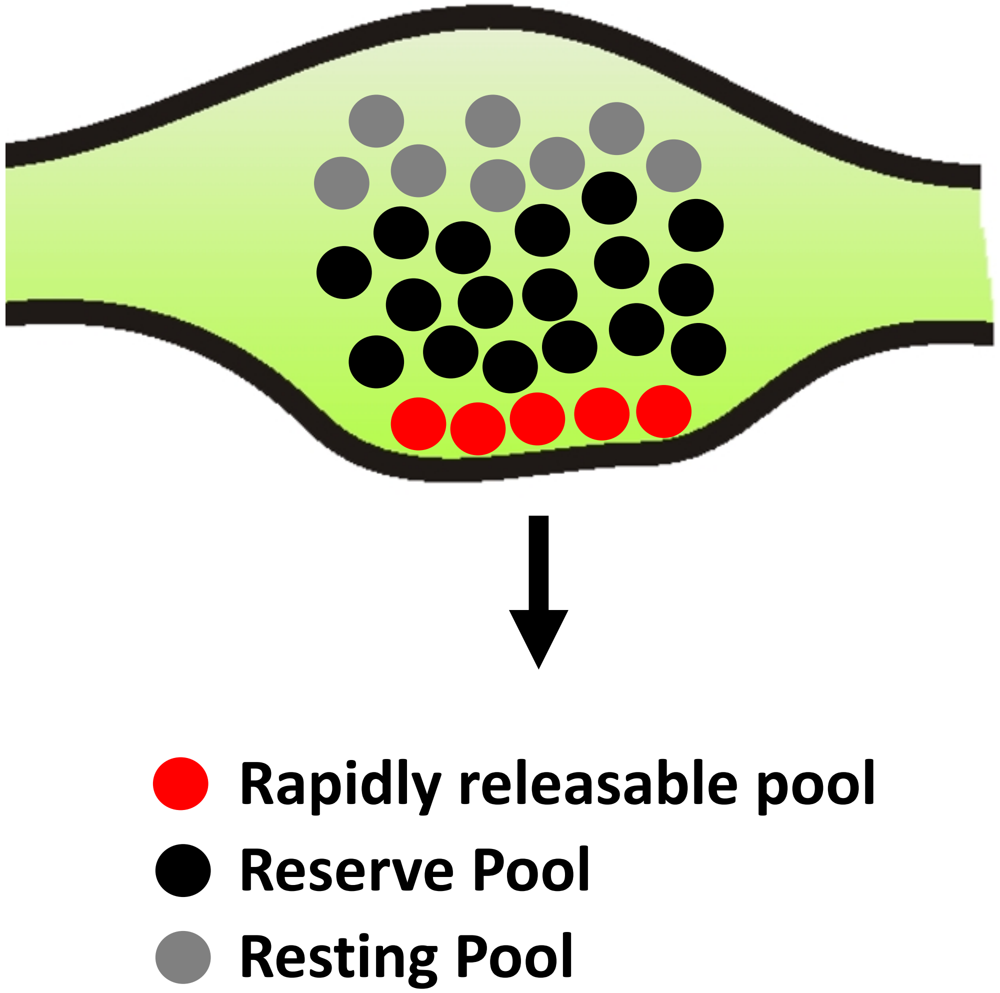
Freeze fracture: vesicles caught in the act



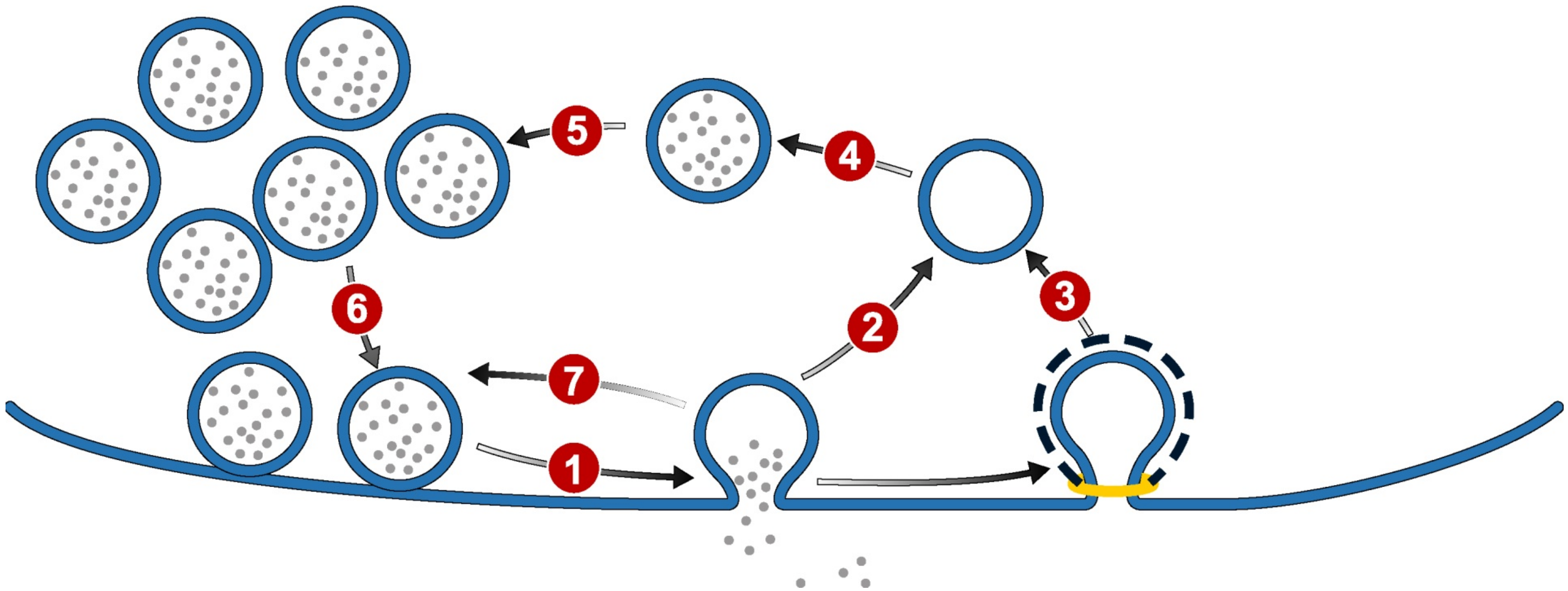
Heuser and Reese, 1981

Distinct vesicle pools

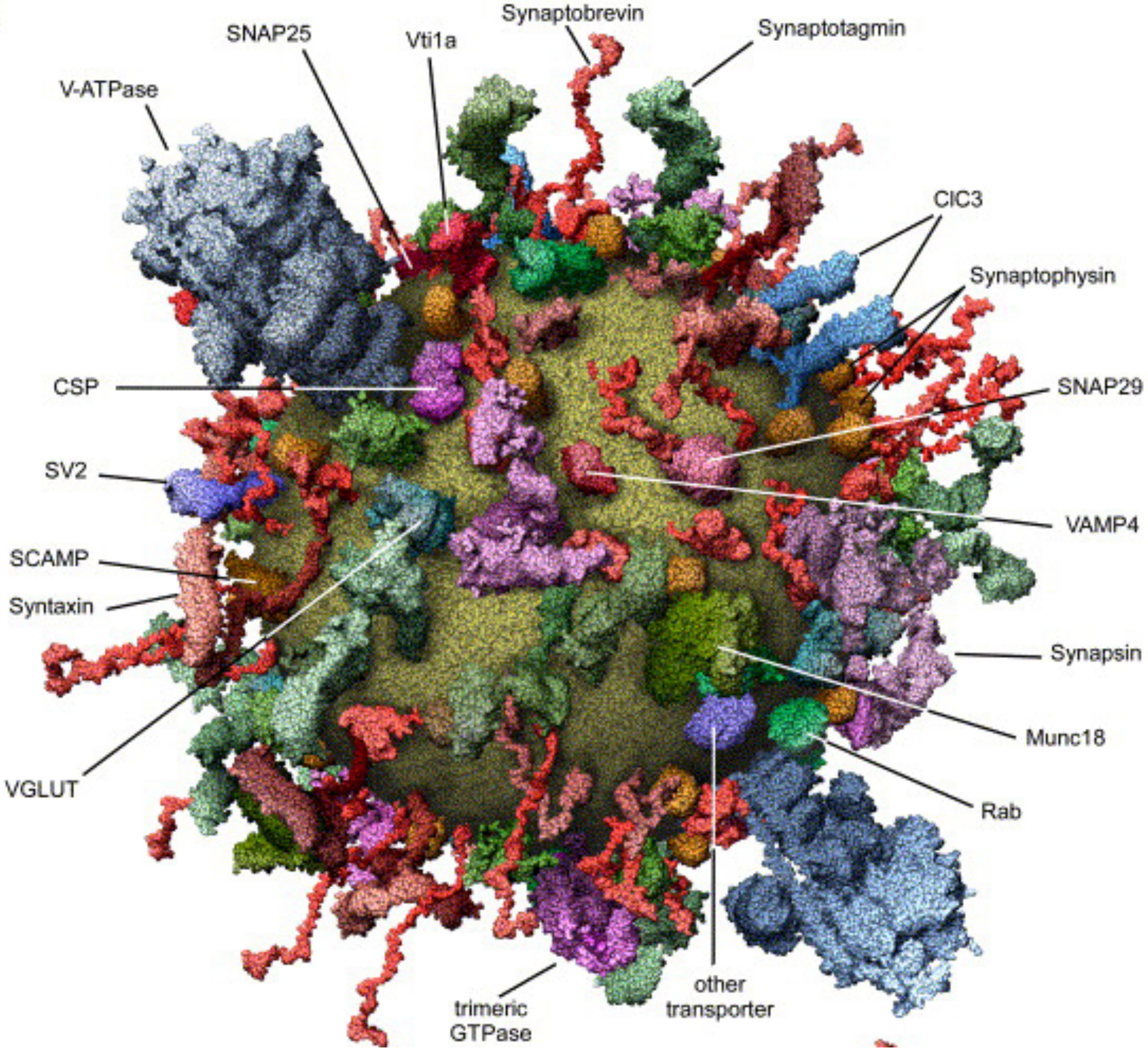




The presynaptic vesicle cycle

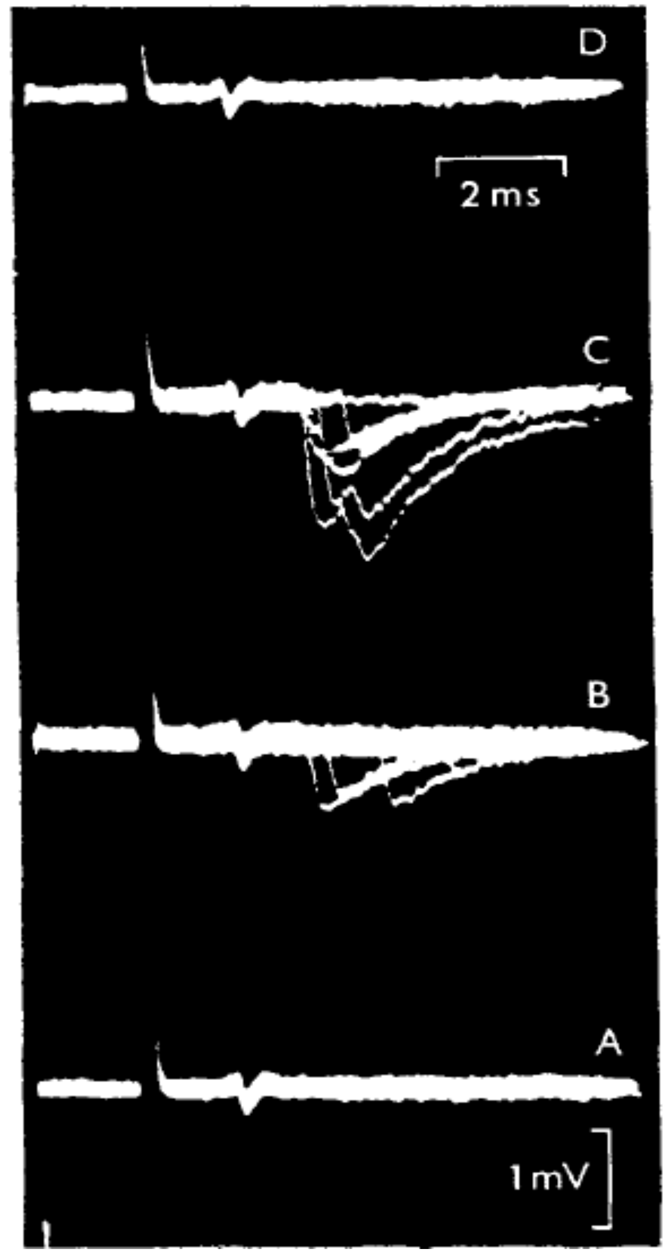


A



SNAP25
Vti1a
Synaptobrevin
Synaptotagmin
V-ATPase
ClC3
Synaptophysin
CSP
SNAP29
SV2
VAMP4
SCAMP
Syntaxin
Synapsin
Munc18
VGLUT
Rab
trimeric
GTPase
other
transporter

Calcium Dependence of Neurotransmitter release



4- No calcium

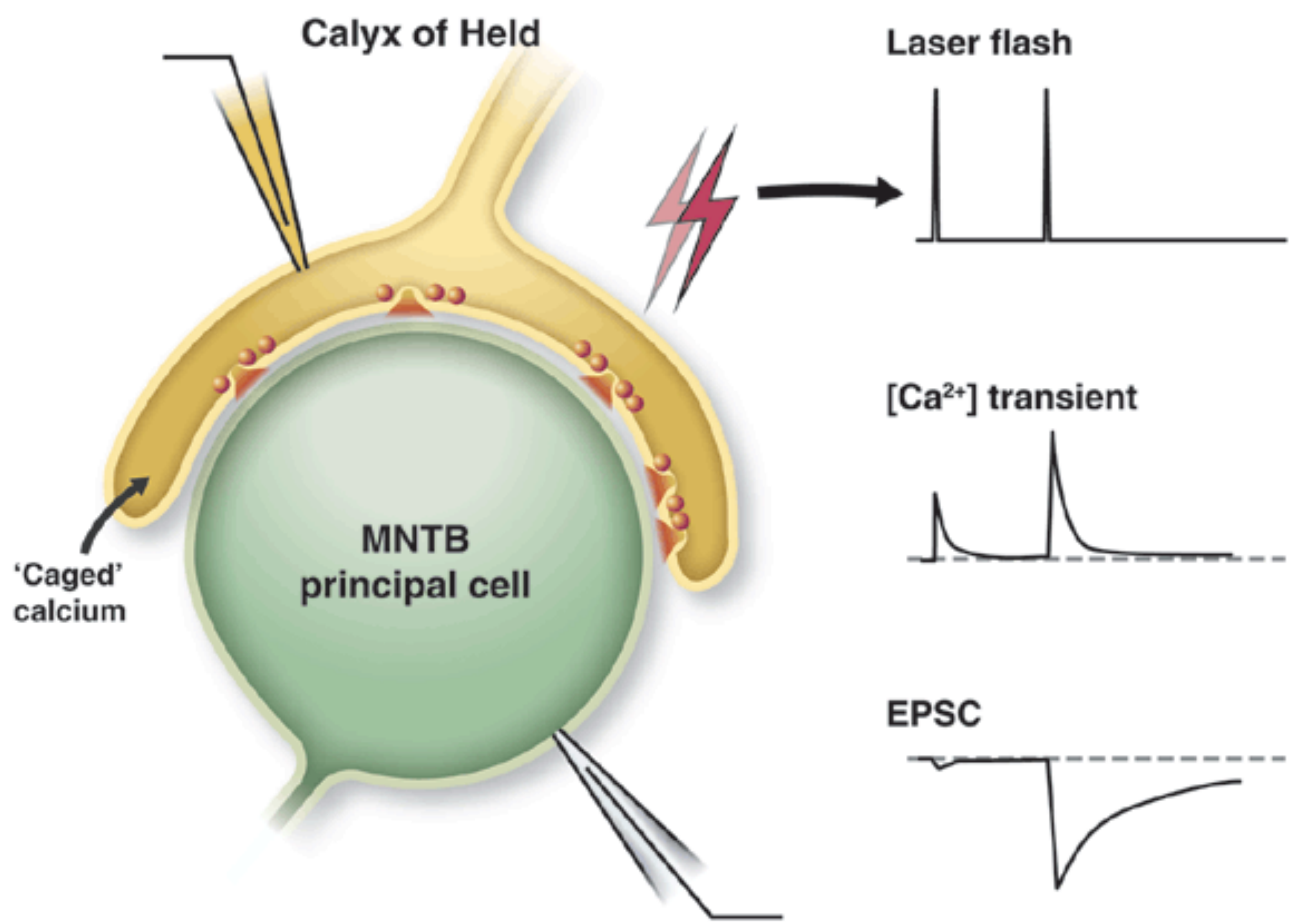
3- A little more calcium

2- A little calcium

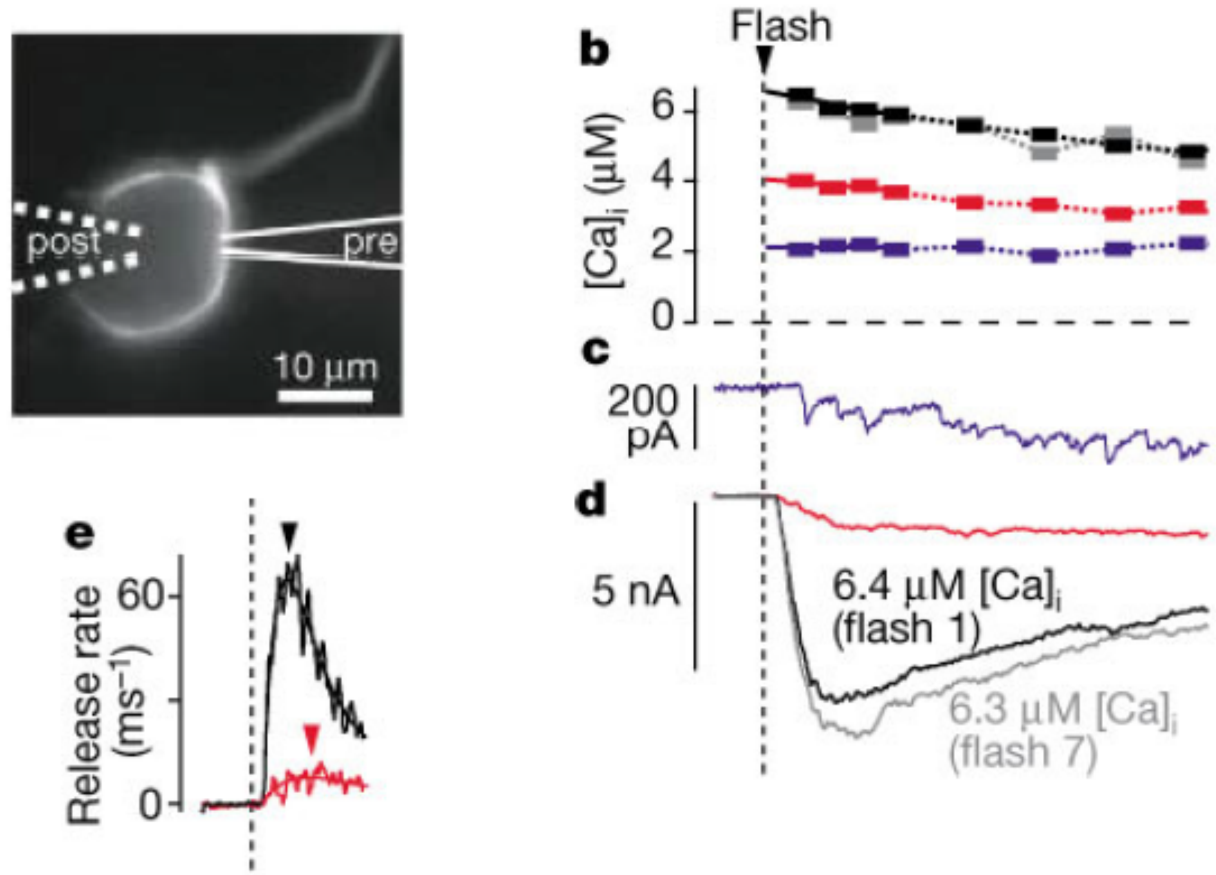
1- No calcium

Katz

Caged-calcium experiments

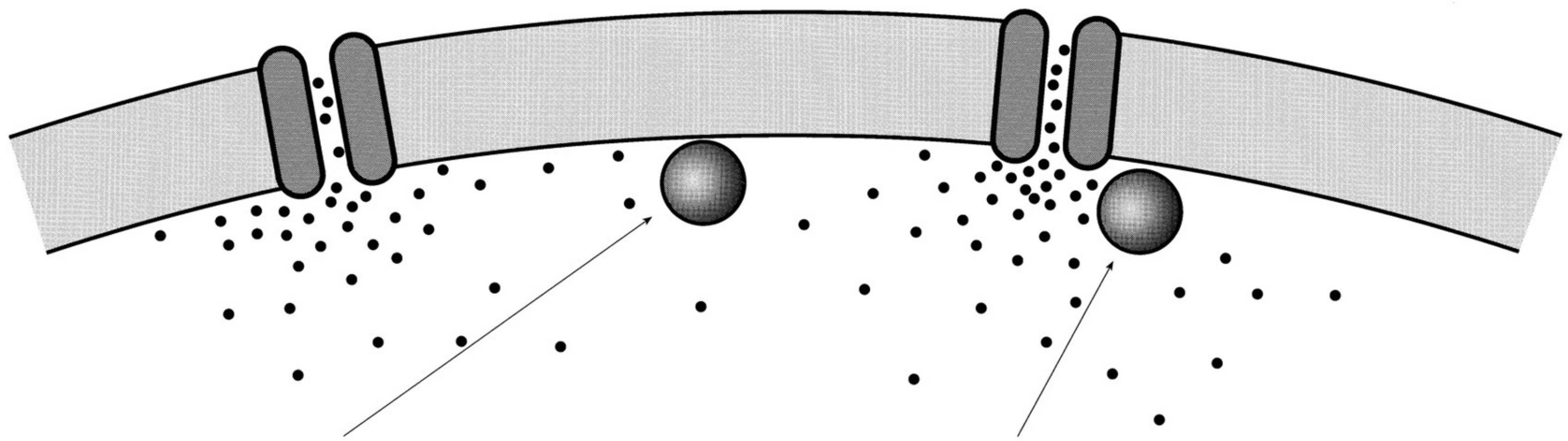


Dependence of Neurotransmitter release on $[Ca^{2+}]_{int}$



Schneggenberger and Neher, nature 2000

Calcium nanodomains



At 200 nm distance:

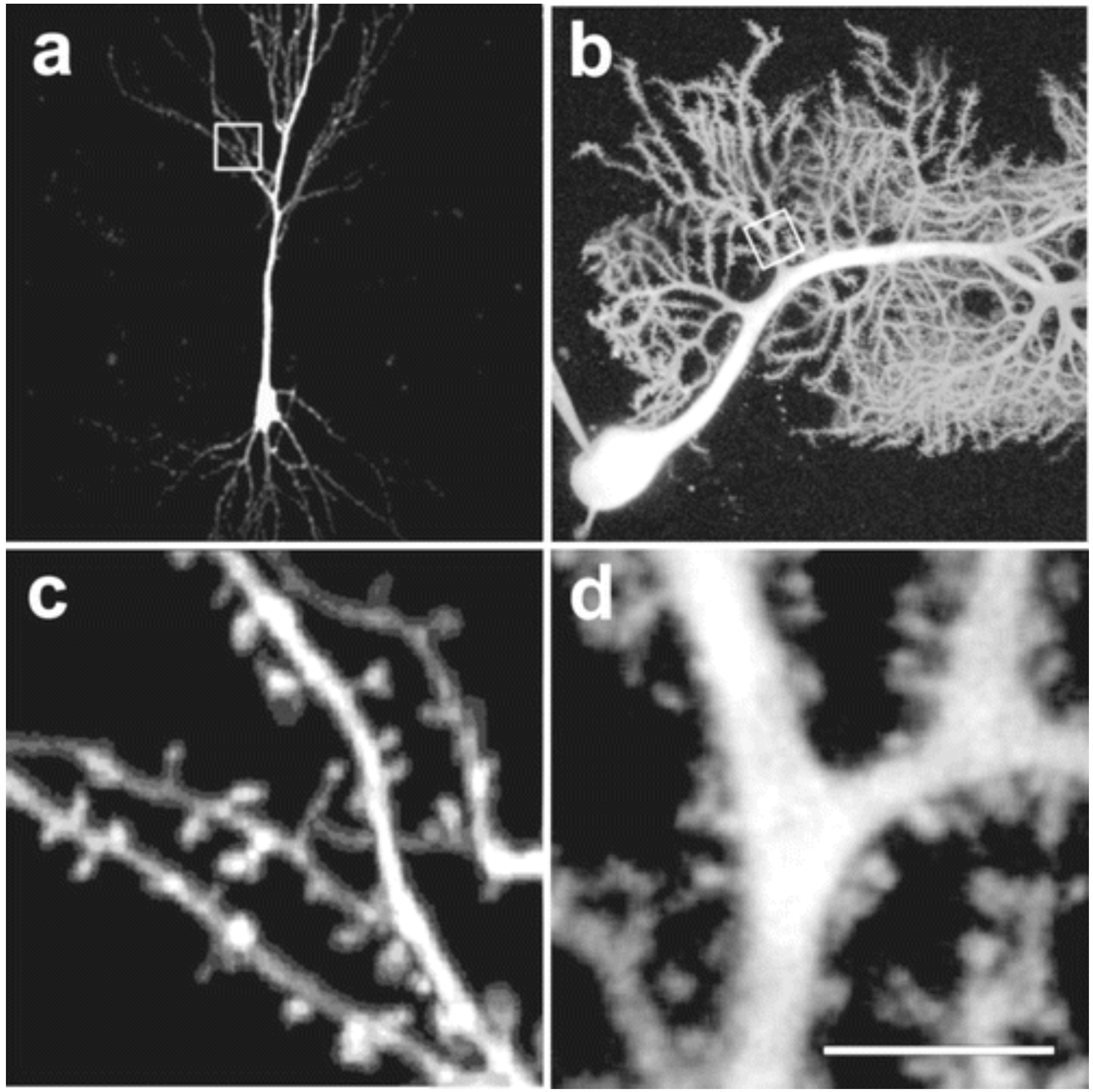
1.) $[Ca^{++}] \approx$ 5-10 μM
2.) Rises and falls in ≈ 10 msec
3.) Is at equilibrium with mobile buffers
4.) Strongly dependent on buffers; EGTA as effective as BAPTA
5.) $[Ca^{++}]$ determined by mean activity of several neighbouring channels

At 20 nm distance:

1.) $[Ca^{++}] \approx$ 100 μM
2.) Rises and falls within μsec
3.) Is not at equilibrium with mobile buffers
4.) Almost independent of Ca-buffers; EGTA totally ineffective
5.) $[Ca^{++}]$ predominantly determined by the <u>local</u> channel

Neher, CONB, 1998

Postsynaptic structures



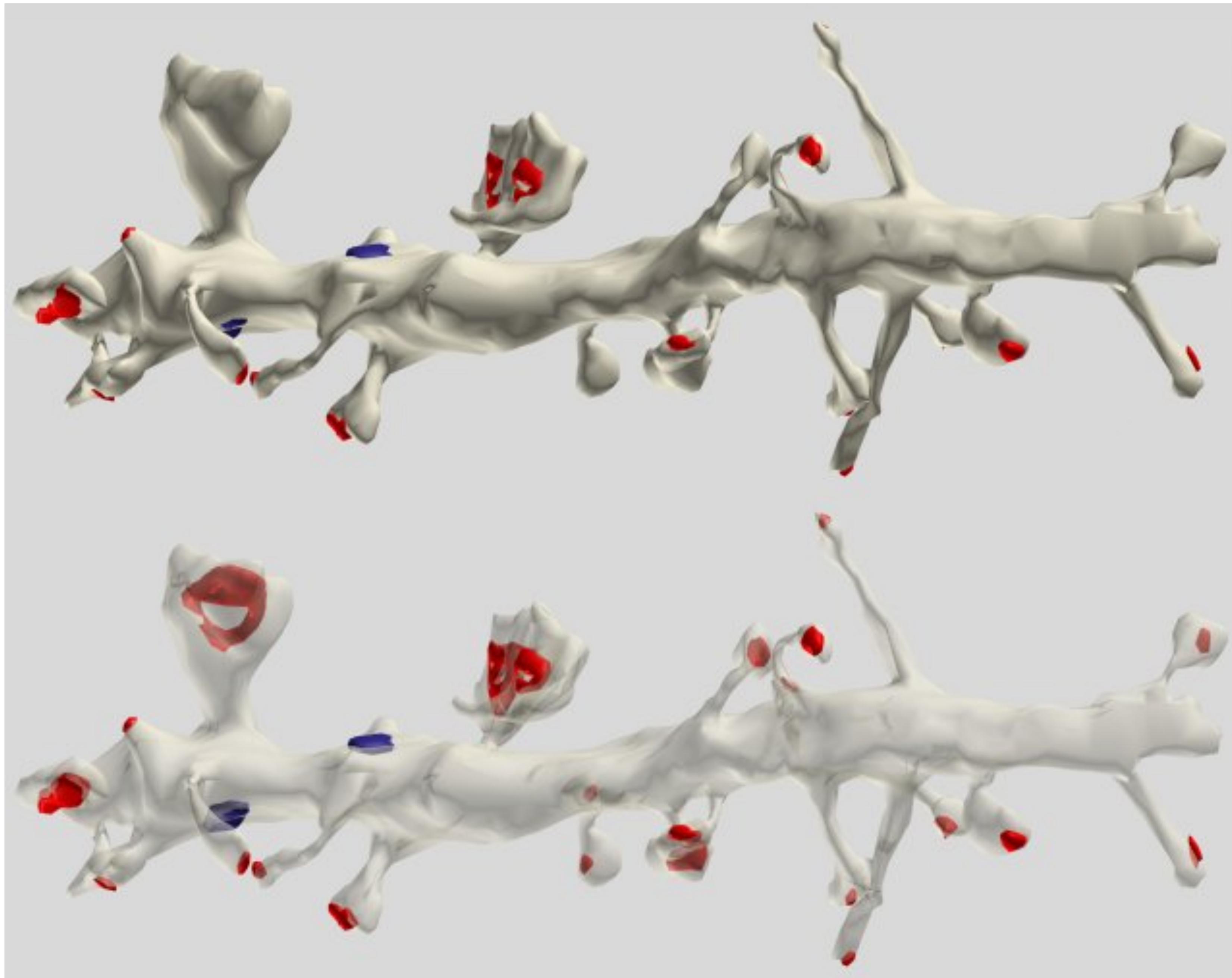
Why spines?

1- Increase surface area to optimize packing of many synapses

2- Serve as a separate electrical unit that modulates synaptic signals

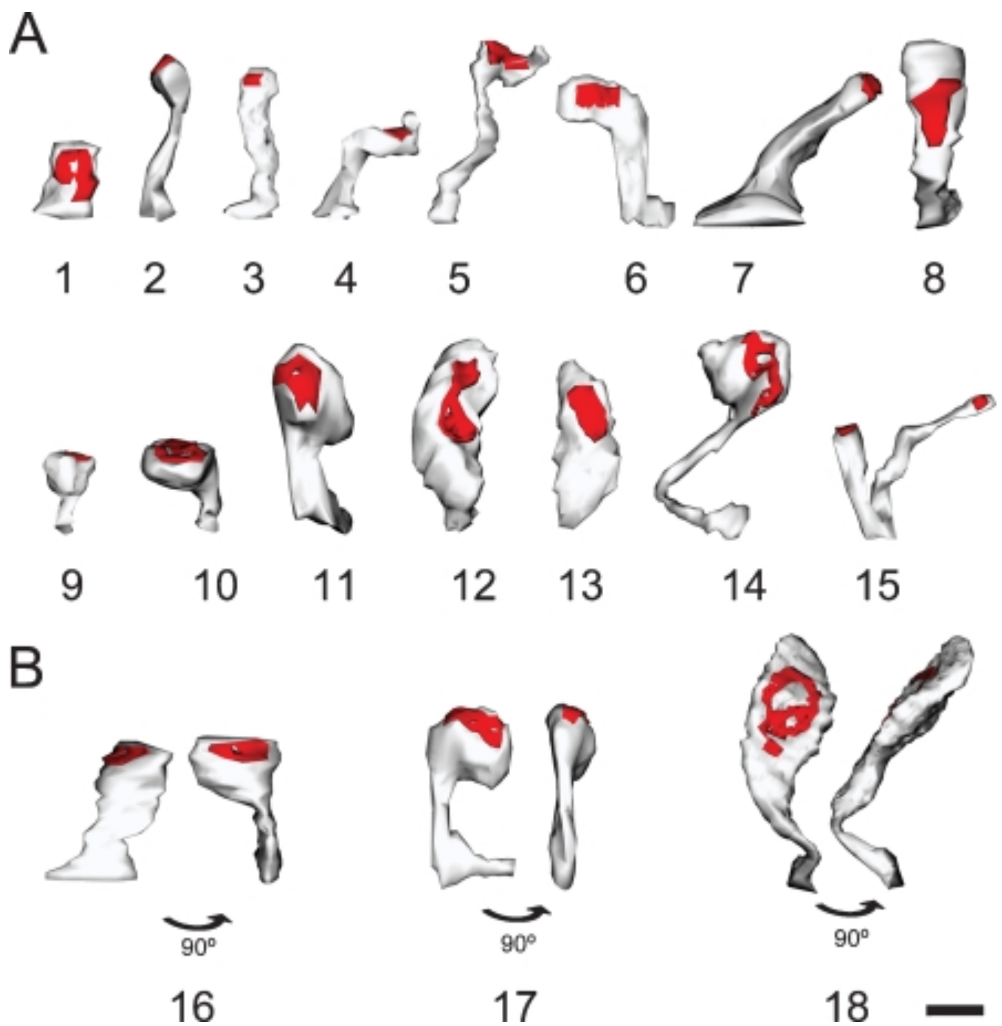
3- Provide a biochemical compartment that restricts mobility of molecules

Postsynaptic structure

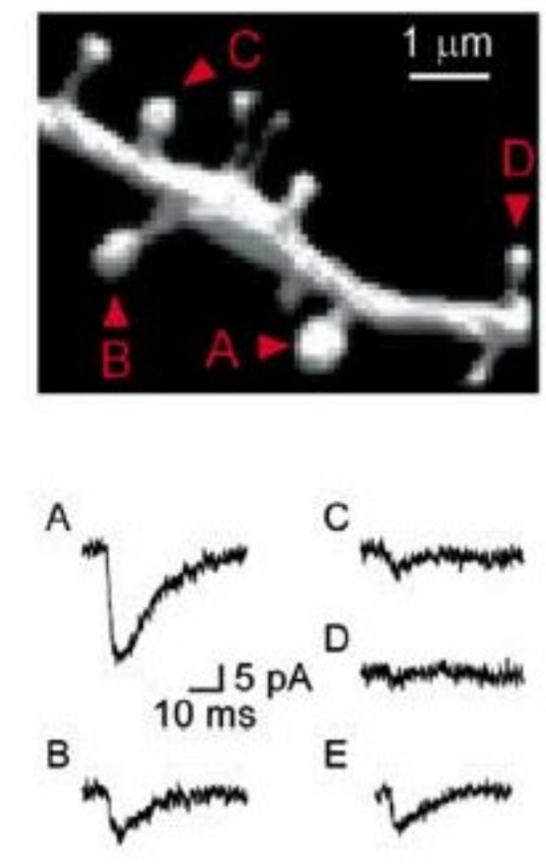


Spines: occur at around 1-10 per um of dendrite

Synapse diversity: postsynaptic spine

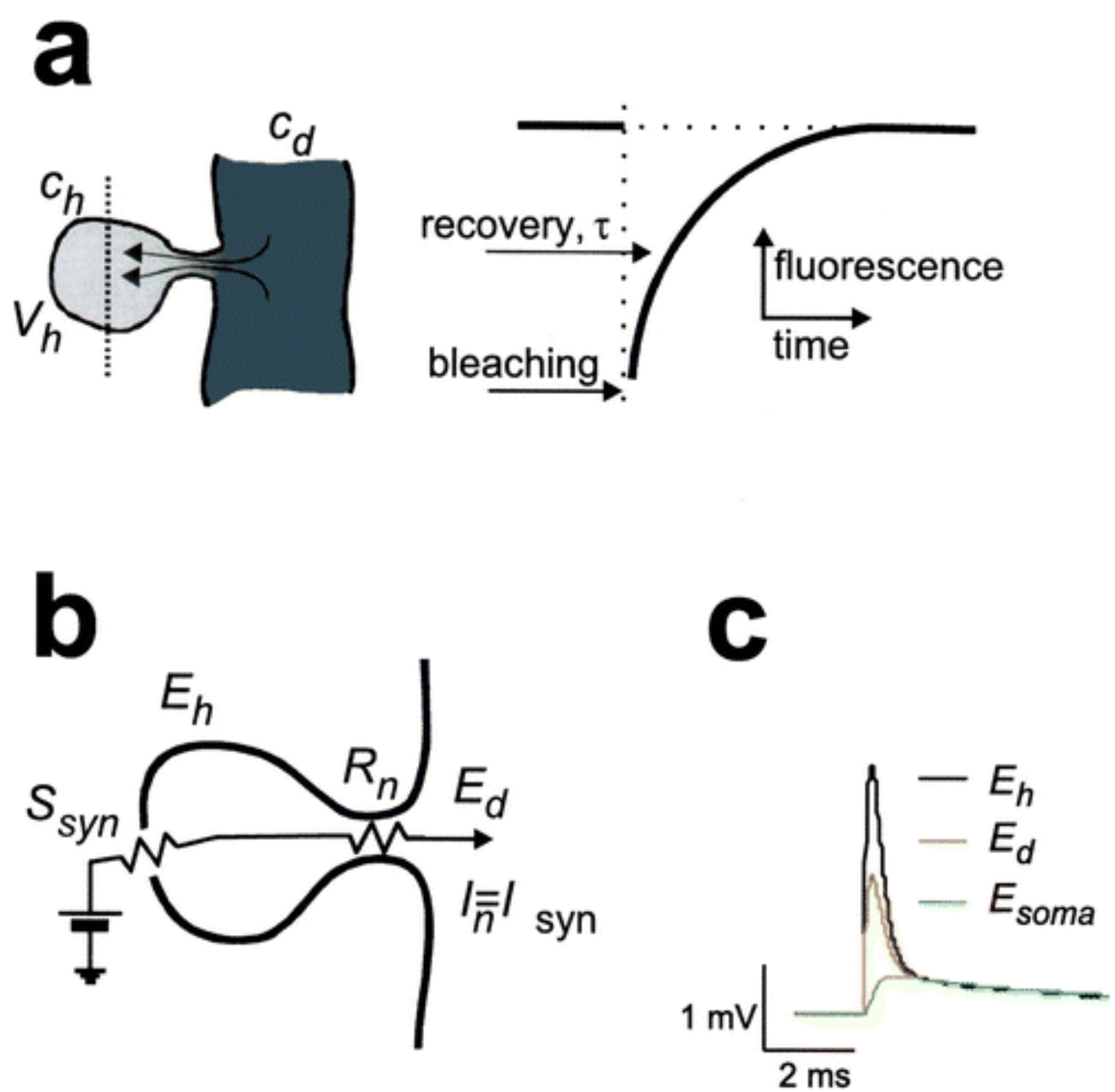


Arellano et al., 2007



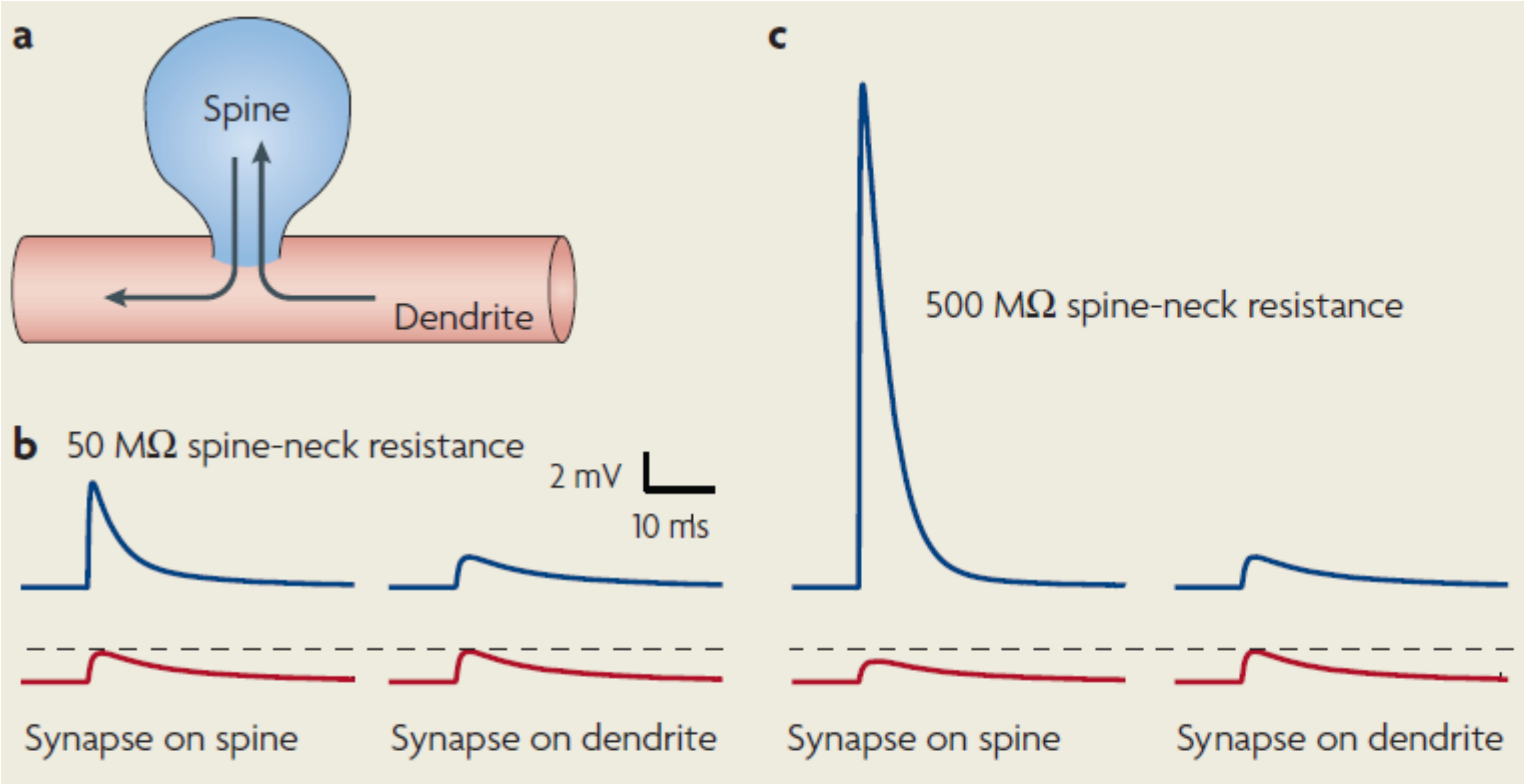
Matsuzaki et al., 2001

Postsynaptic structure: spines



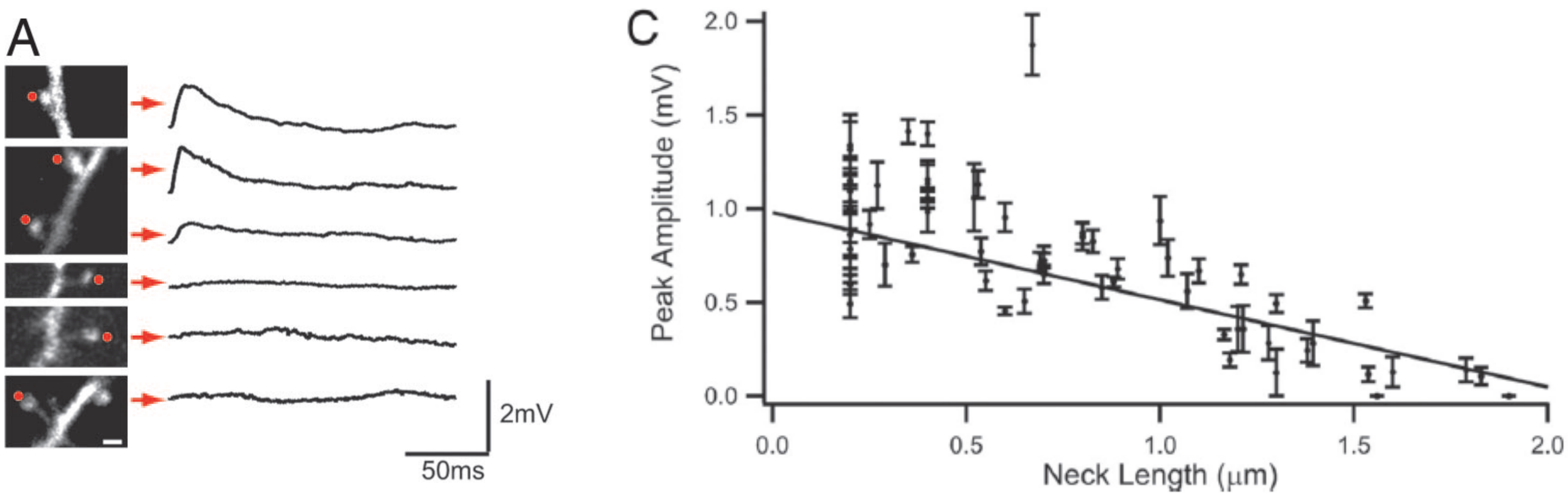
Nimchinsky et al., ARN, 2002

Postsynaptic spine shape



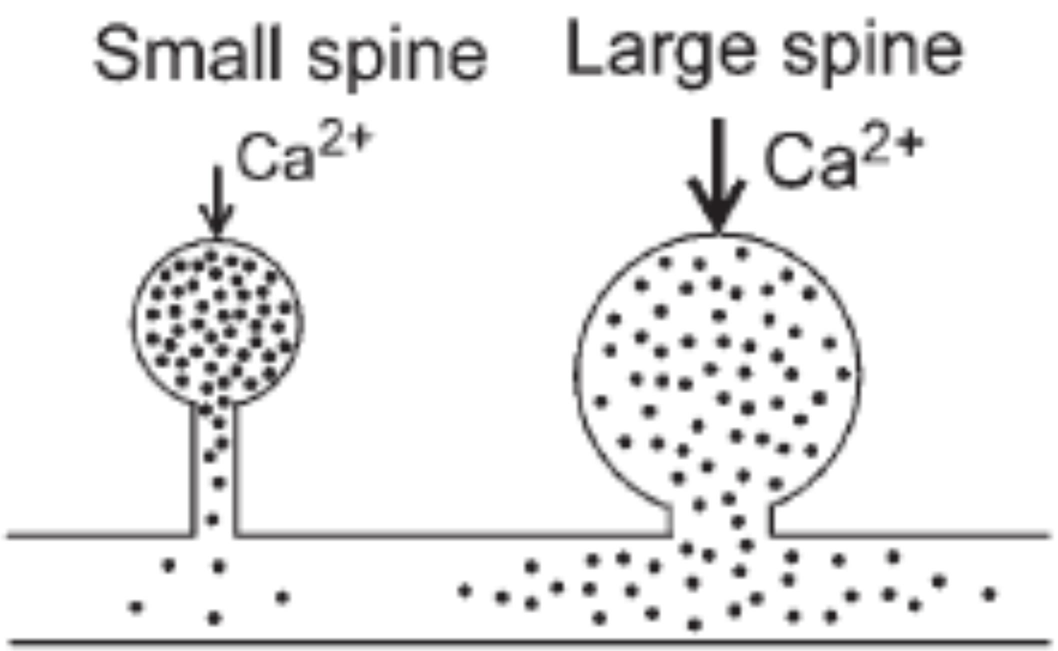
$R_{neck} = \rho L/A$, where L is length of neck and A is cross-sectional area and ρ is resistivity of cytoplasm

Spine neck can filter synaptic events



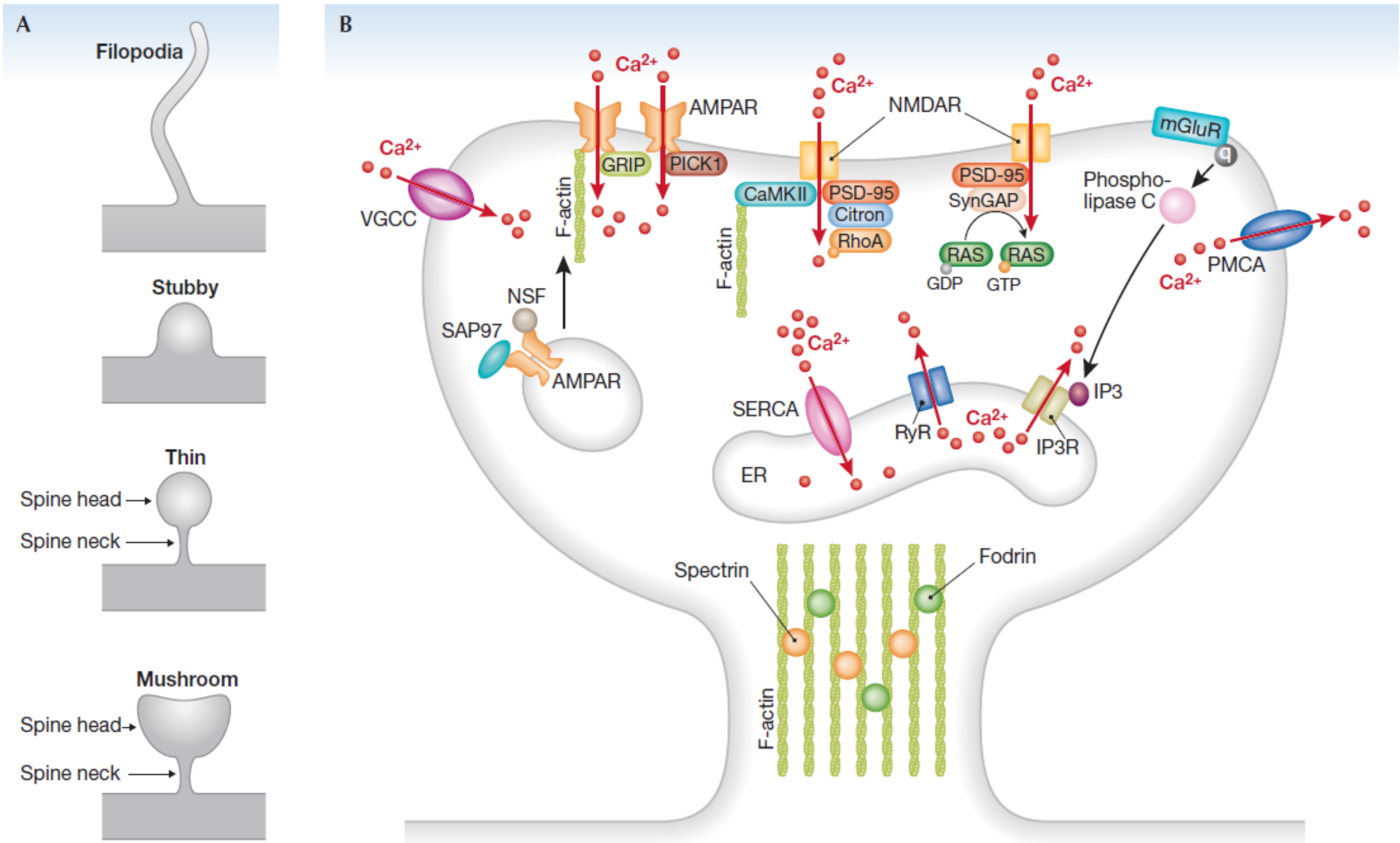
Araya et al., PNAS, 2006

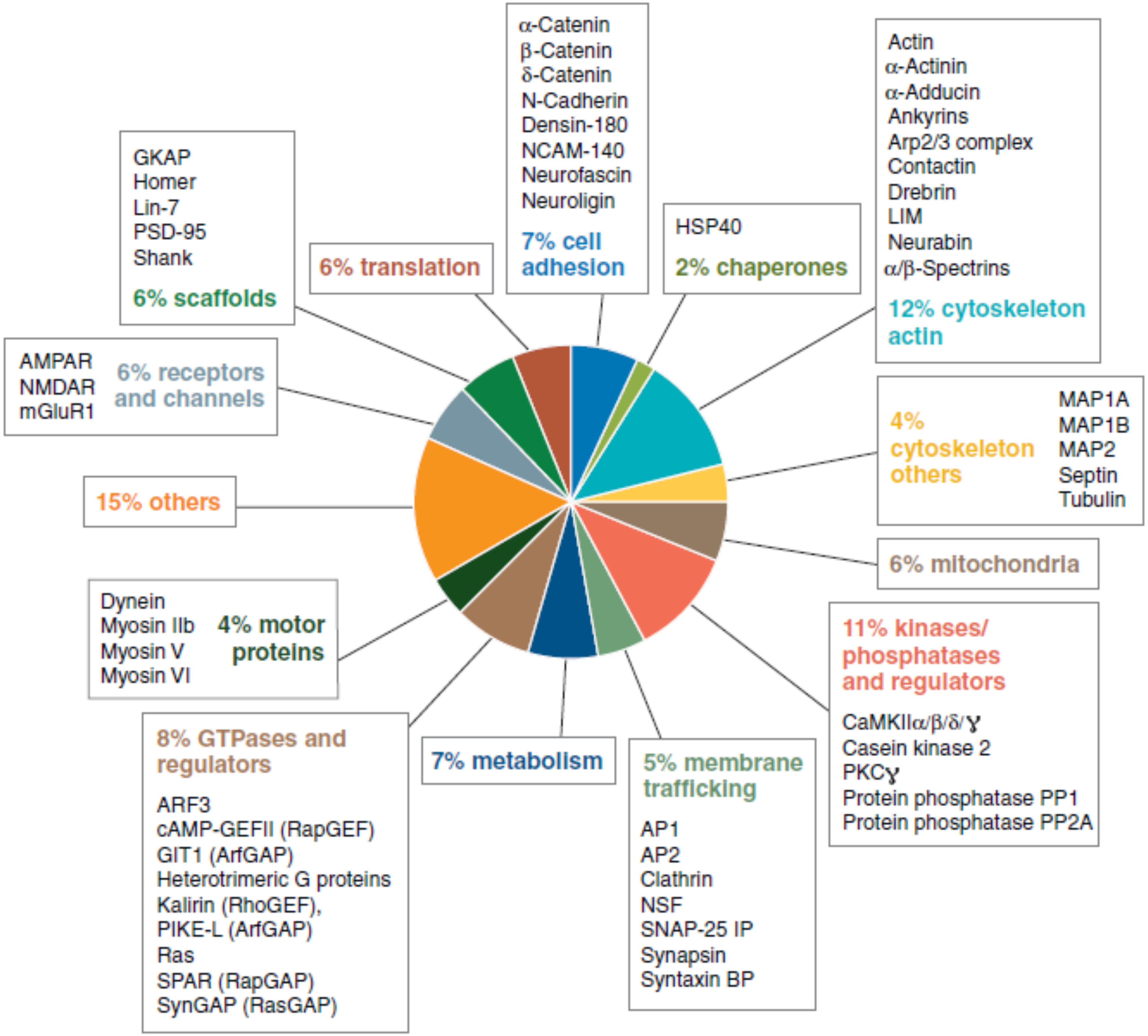
Postsynaptic spine shape: calcium diffusion



Noguchi et al., Neuron, 2005

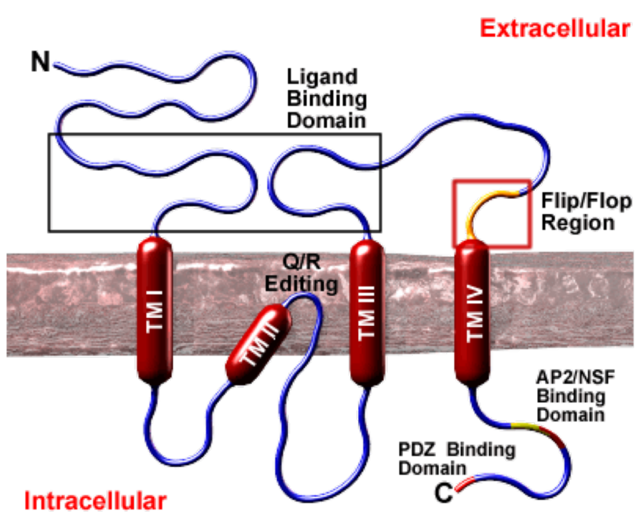
Molecular architecture of excitatory synapses



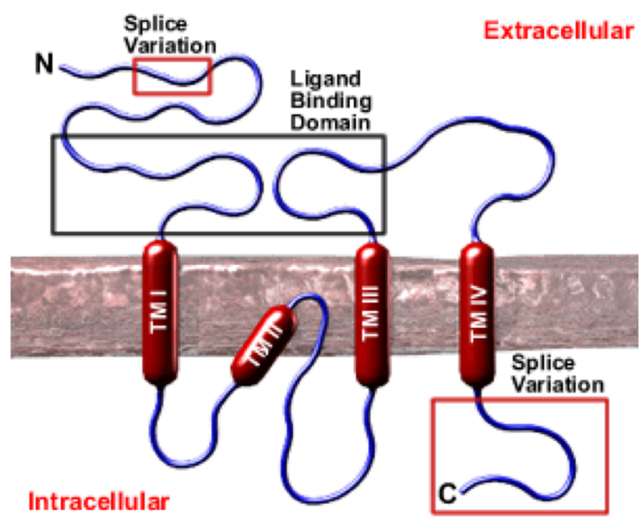

α-Catenin
β-Catenin
δ-Catenin
N-Cadherin
Densin-180
NCAM-140
Neurofascin
Neuroligin
7% cell adhesion
HSP40
2% chaperones
Actin
α-Actinin
α-Adducin
Ankyrins
Arp2/3 complex
Contactin
Drebrin
LIM
Neurabin
α/β-Spectrins
12% cytoskeleton actin
4% cytoskeleton others
MAP1A
MAP1B
MAP2
Septin
Tubulin
6% mitochondria
11% kinases/ phosphatases and regulators
CaMKIIα/β/δ/γ
Casein kinase 2
PKCγ
Protein phosphatase PP1
Protein phosphatase PP2A
5% membrane trafficking
AP1
AP2
Clathrin
NSF
SNAP-25 IP
Synapsin
Syntaxin BP
7% metabolism
8% GTPases and regulators
ARF3
cAMP-GEFII (RapGEF)
GIT1 (ArfGAP)
Heterotrimeric G proteins
Kalirin (RhoGEF),
PIKE-L (ArfGAP)
Ras
SPAR (RapGAP)
SynGAP (RasGAP)
Dynein
Myosin IIb
Myosin V
Myosin VI
4% motor proteins
15% others
AMPAR
NMDAR
mGluR1
6% receptors and channels
GKAP
Homer
Lin-7
PSD-95
Shank
6% scaffolds
6% translation

Glutamate-gated channels

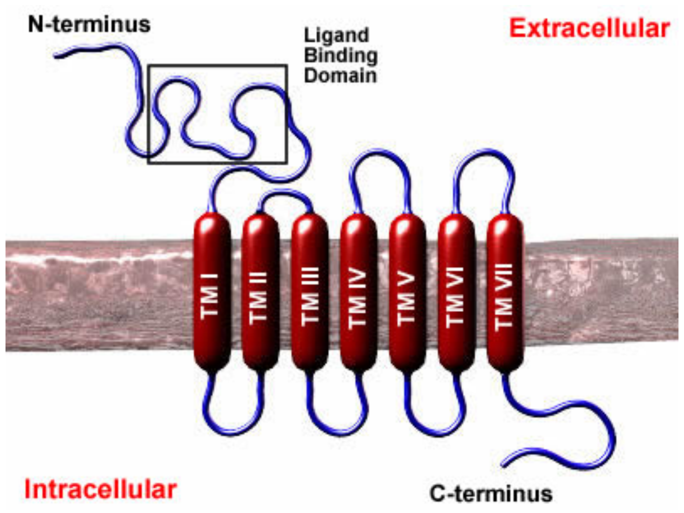
AMPAR



NMDAR



mGluRs



GluR1-4: Tetramers mostly of GluR2 and two others.

Flip/flop: alternative splice variants
Q/R editing: calcium permeability

Almost all GluR2 subunits are in the R form, which is Ca^{2+} impermeable.

GluN1-2: Tetramers of GluN1 (obligatory) and GluN2 A-D.

Calcium permeable.

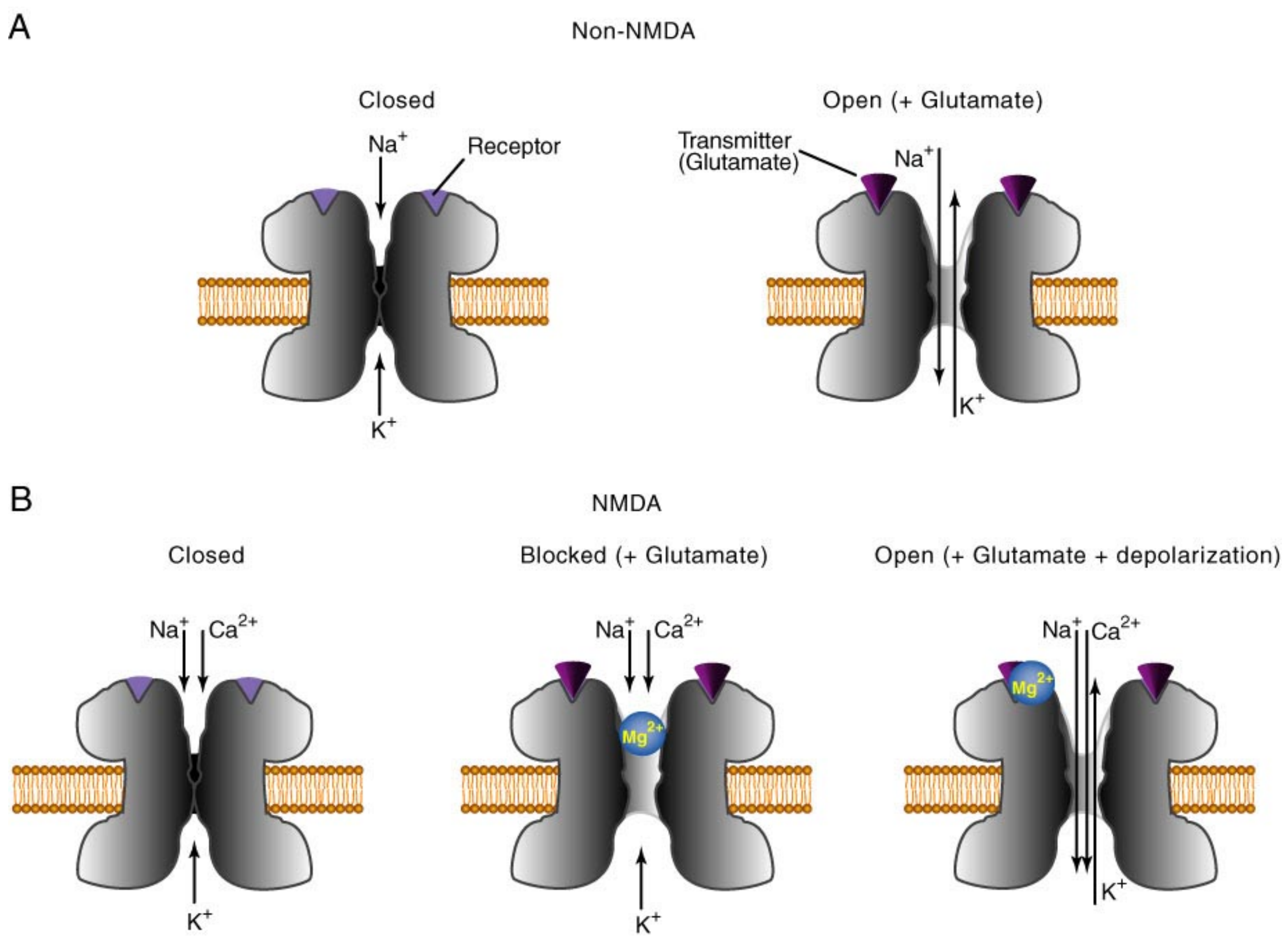
Co-agonist: glycine.

Blocked by Mg^{2+} at rest.

3 groups based on pharmacology Sequence and signalling.

Group 1: mGlu1 and 5.
Group 2: mGlu2 and 3.
Group 3: mGlu4, 6, 7 and 8.

AMPA and NMDA currents



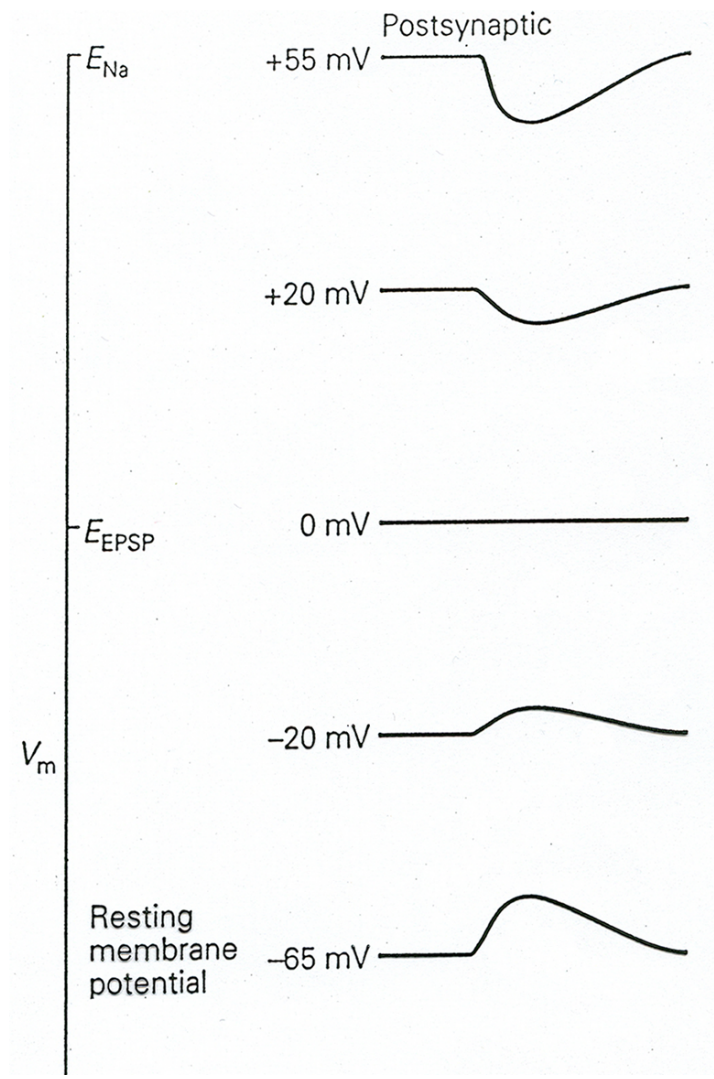
The EPSP: carried mainly by AMPA receptors

Inject even more current !

Inject more current

Inject current to depolarise to -20mV

Normal situation recording V_m



Na^+ no mvt
K^+ out

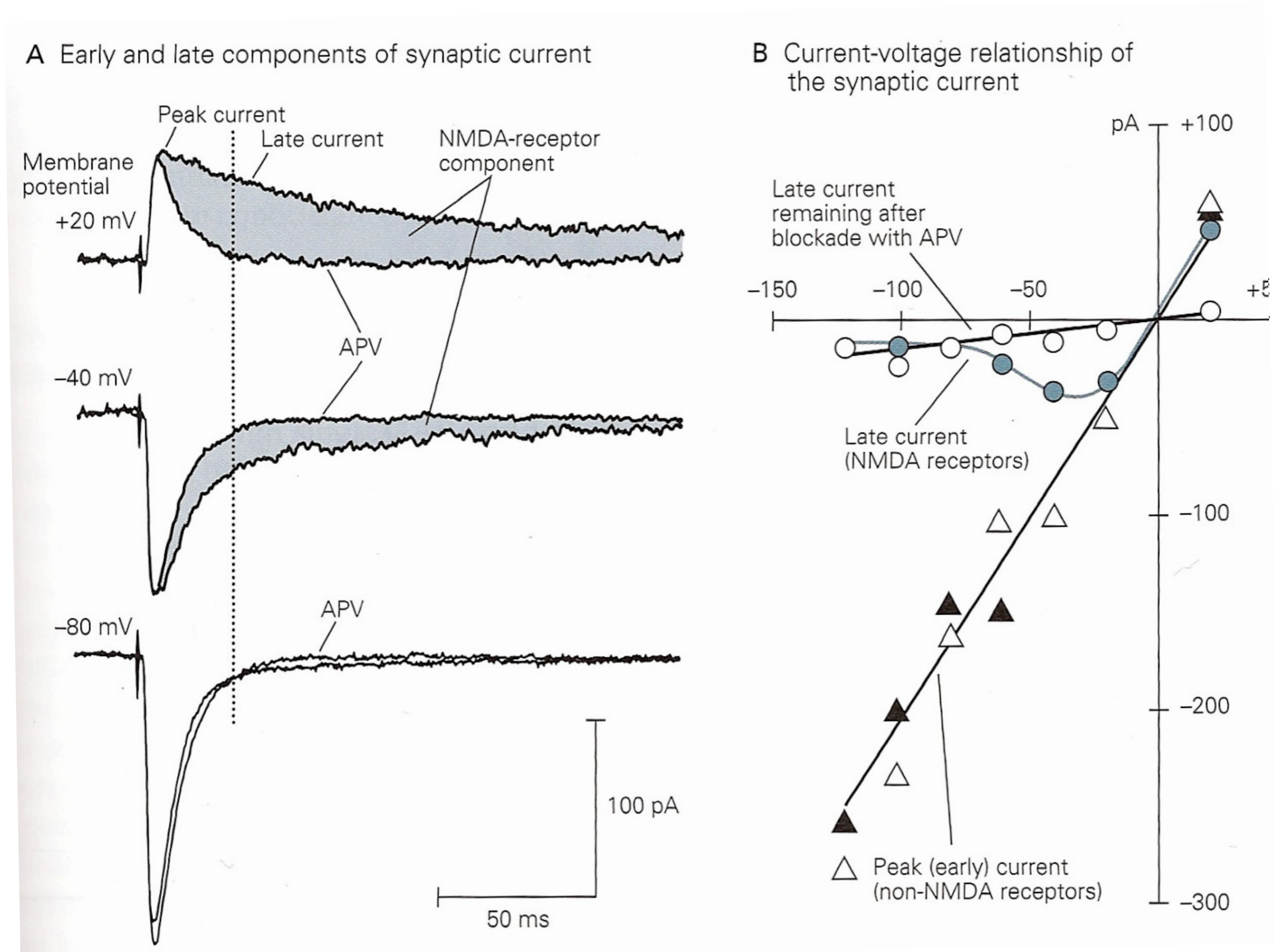
No ion movement

Less Na^+ in

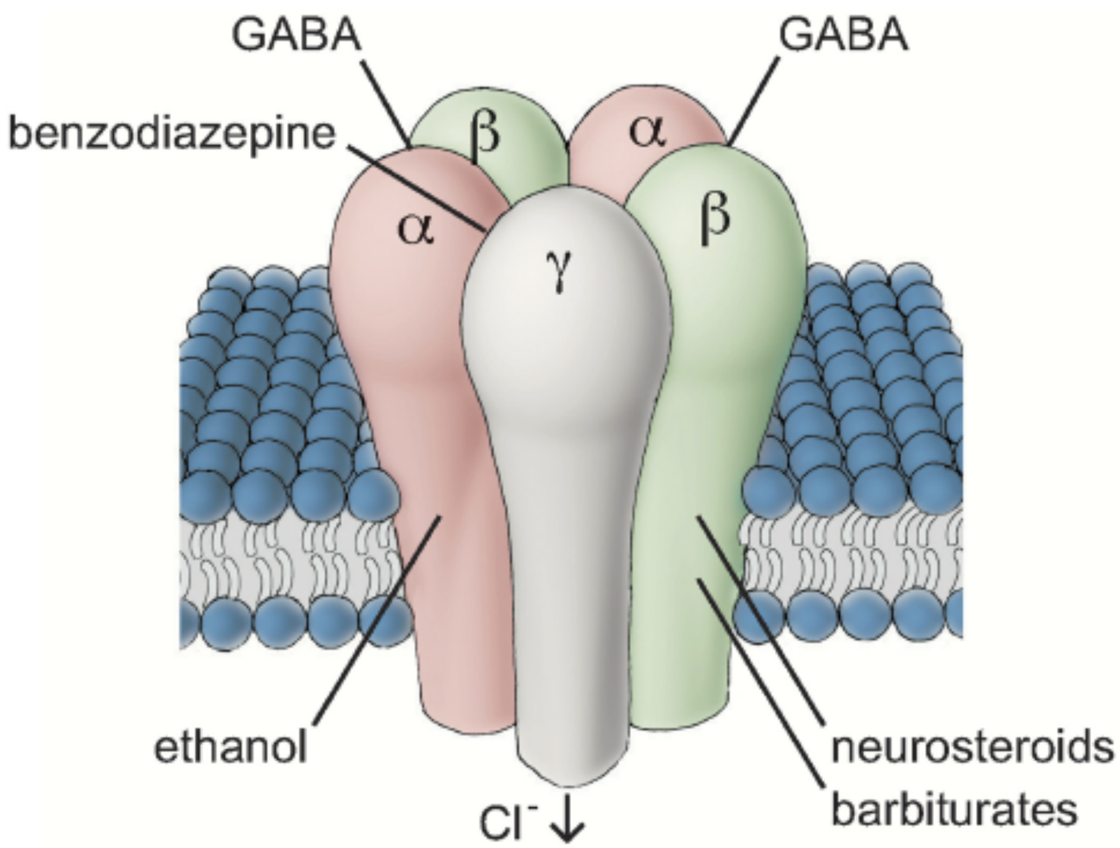
Na^+ in
K^+ out

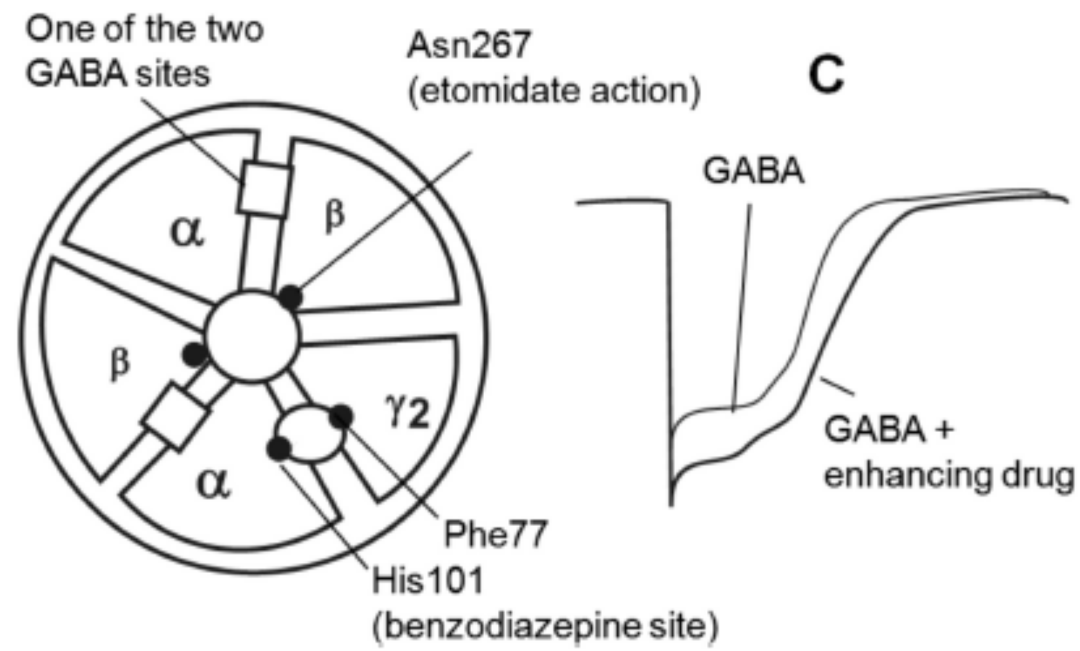
No ion movement at the EPSP's reversal potential

Glutamate postsynaptic currents

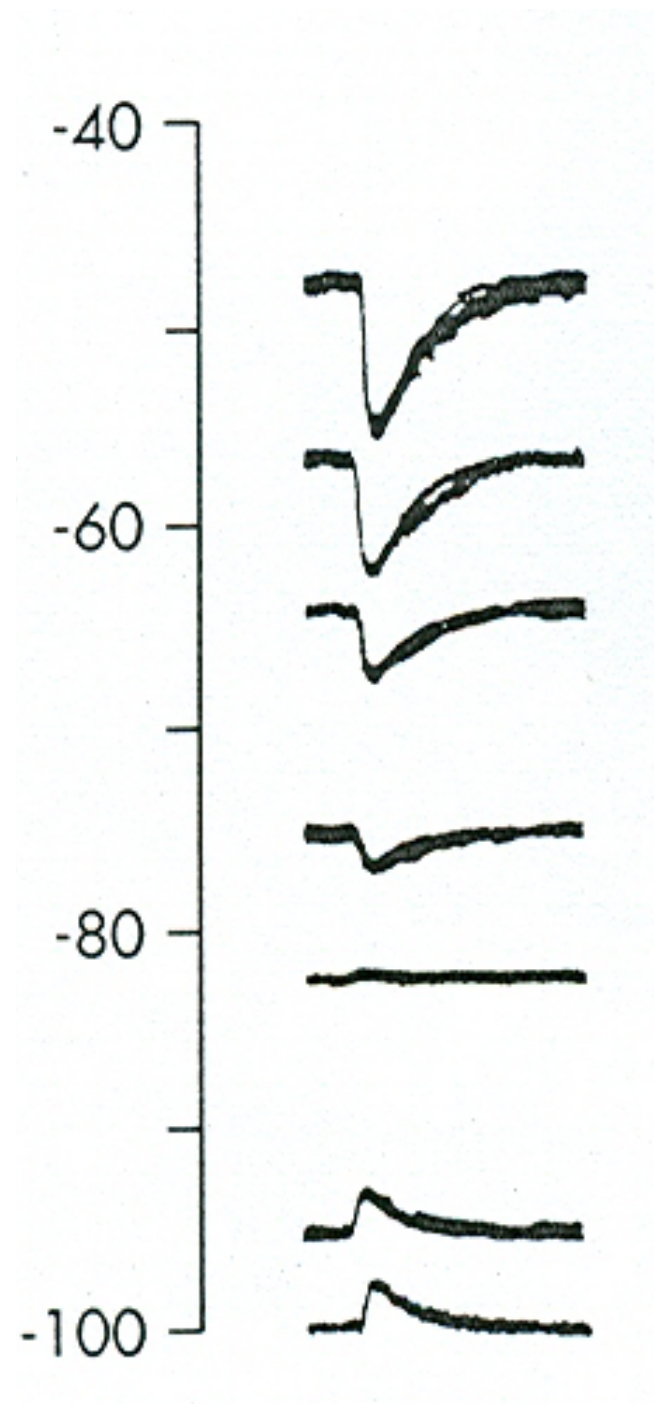


$GABA_A$ receptors





The IPSP



Normal situation recording V_m

Cl^- in

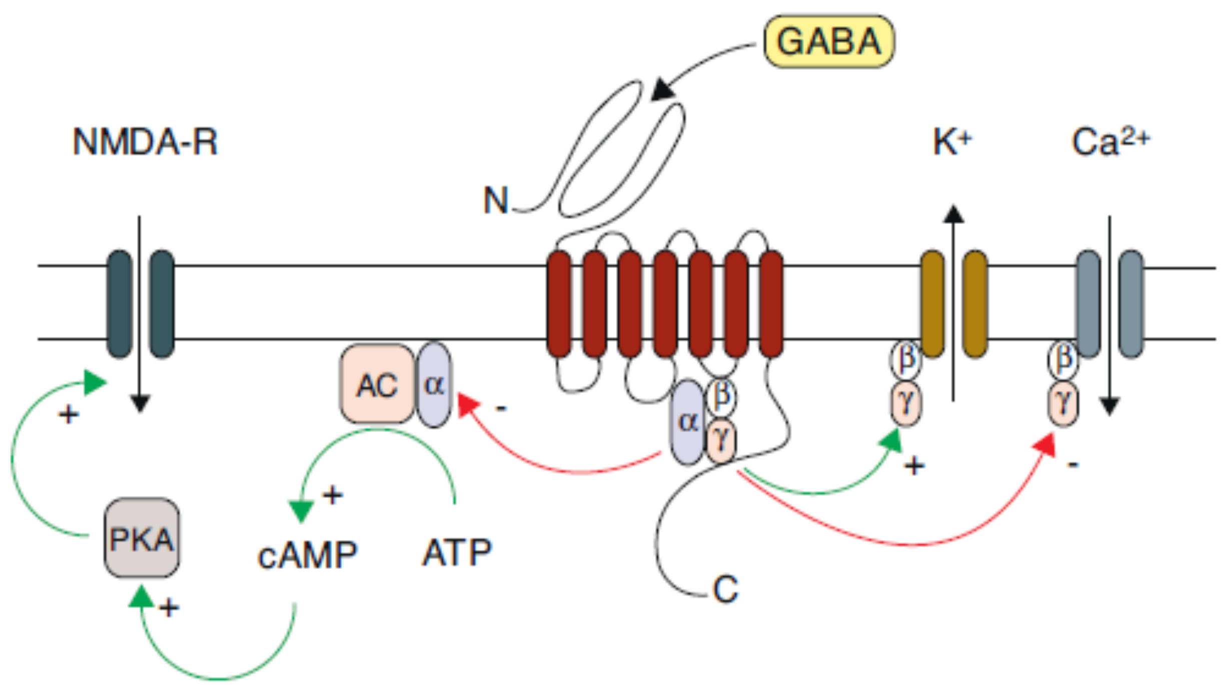
Inject hyperpolarising current

No ion movement

Inject more negative current

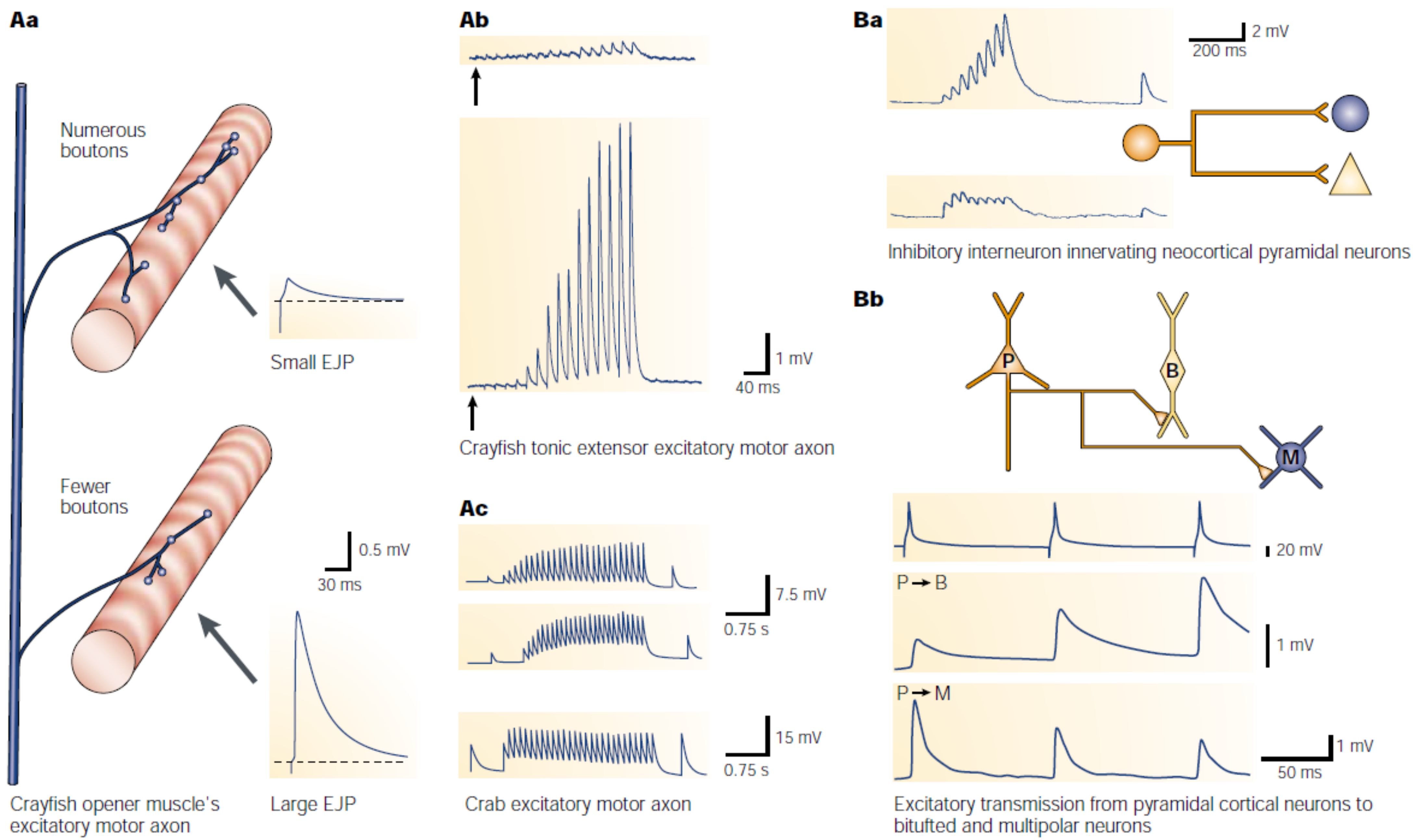
Cl^- Out

GABA$_B$ receptors



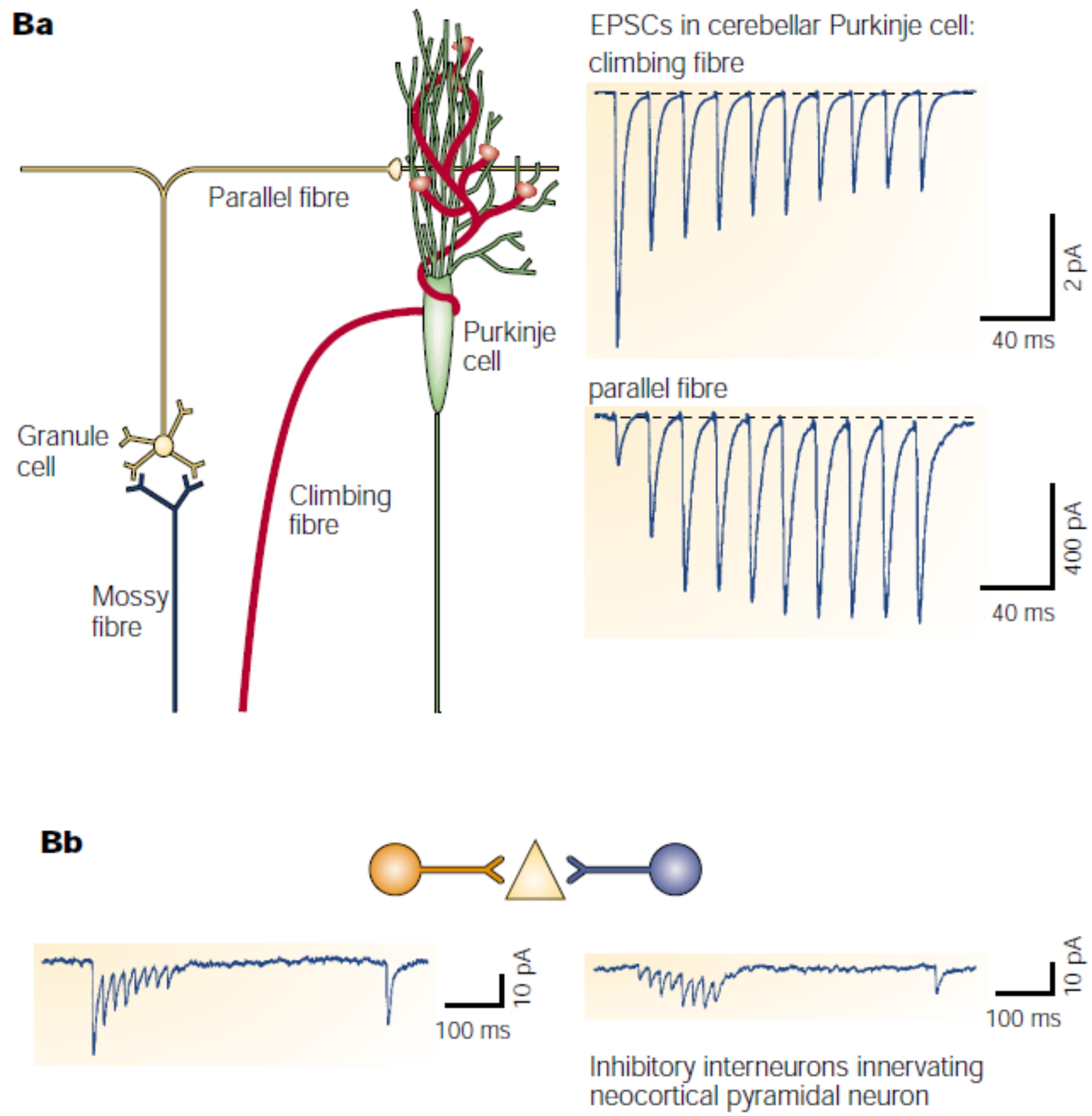
Plasticity of synapses and transmission: mechanisms

Short Term Plasticity: heterogeneous responses to spike trains



Same presynaptic neuron, different targets

Short Term Plasticity: heterogeneous responses to spike trains



Different presynaptic neurons, same target

Mechanisms: Possible Sites for Modulation

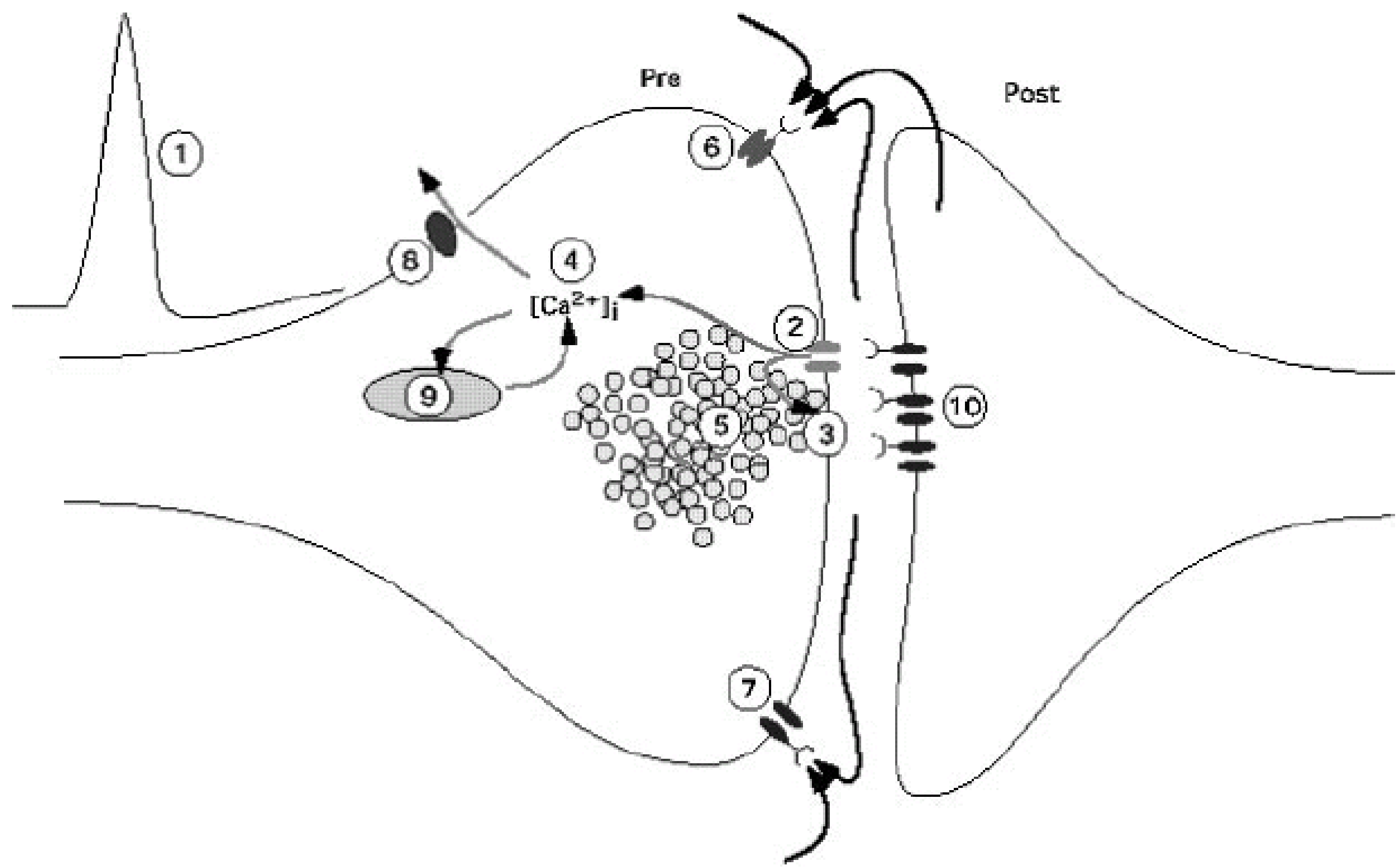
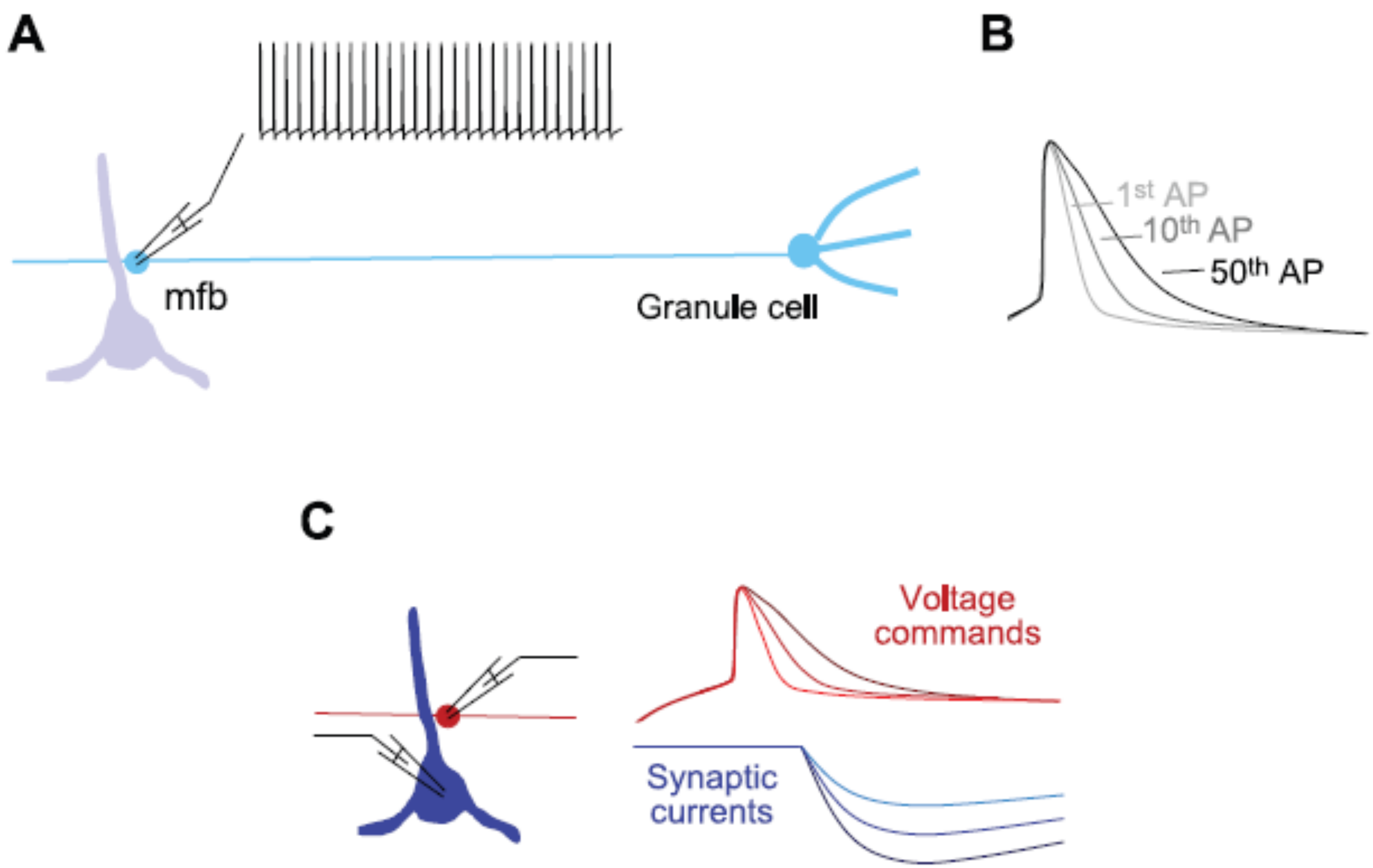


Figure 4 Sites of regulation of short-term synaptic plasticity. (1) AP waveform, (2) Ca^{2+} channel activation, (3) facilitation trigger and the readily releasable pool, (4) residual $[Ca^{2+}]_i$, (5) reserve pool, (6) metabotropic autoreceptors, (7) ionotropic autoreceptors, (8) Ca^{2+}-ATPase, regulating residual $[Ca^{2+}]_i$ in augmentation, (9) mitochondrial regulation of residual $[Ca^{2+}]_i$ in PTP, (10) postsynaptic receptor desensitization.

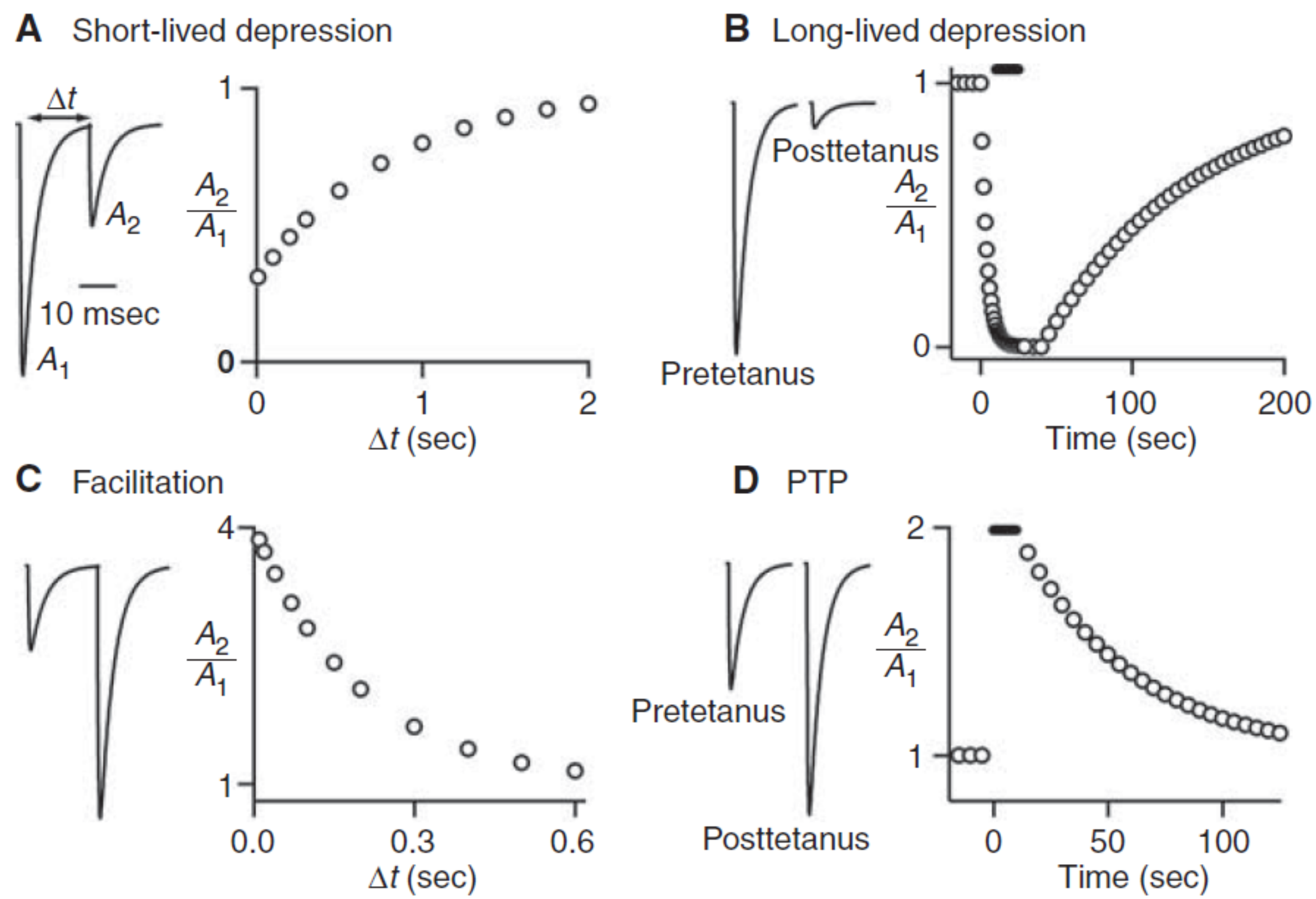
Annu. Rev. Physiol. 2002. 64:355–405

Width of an Action Potential

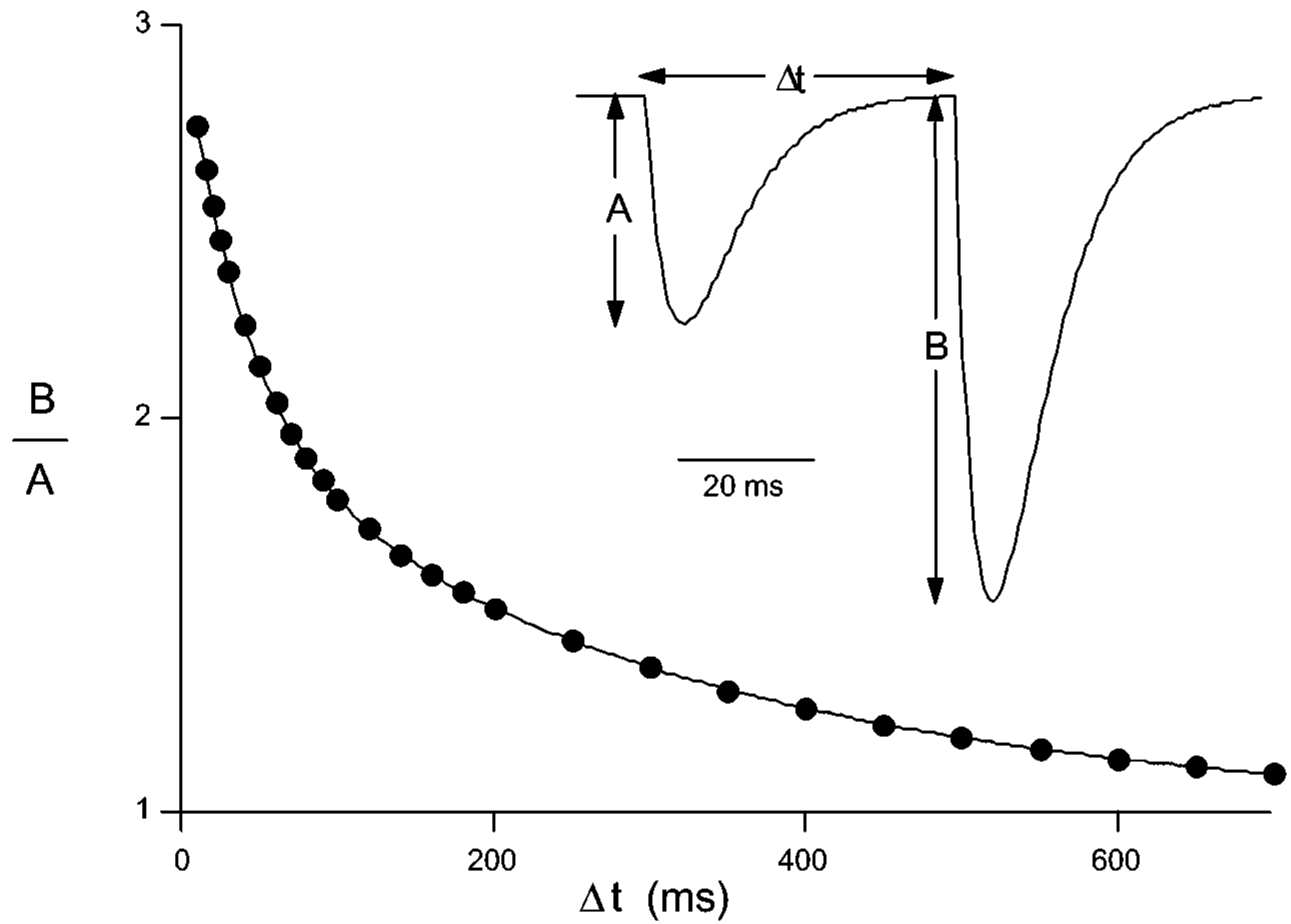


Geiger and Jonas, Neuron, 2000

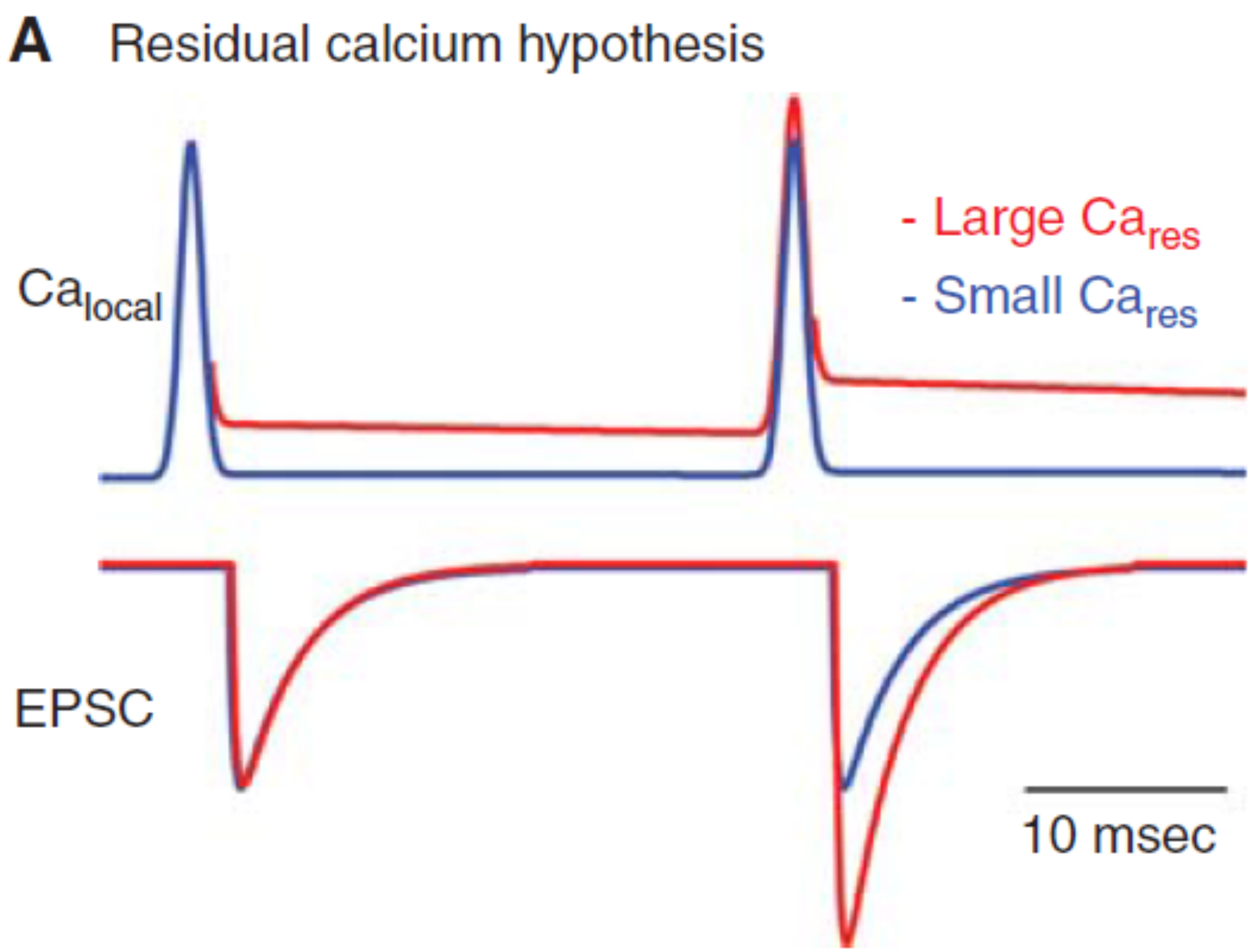
Types of short-term plasticity



Facilitation at Granule to Purkinje Synapse

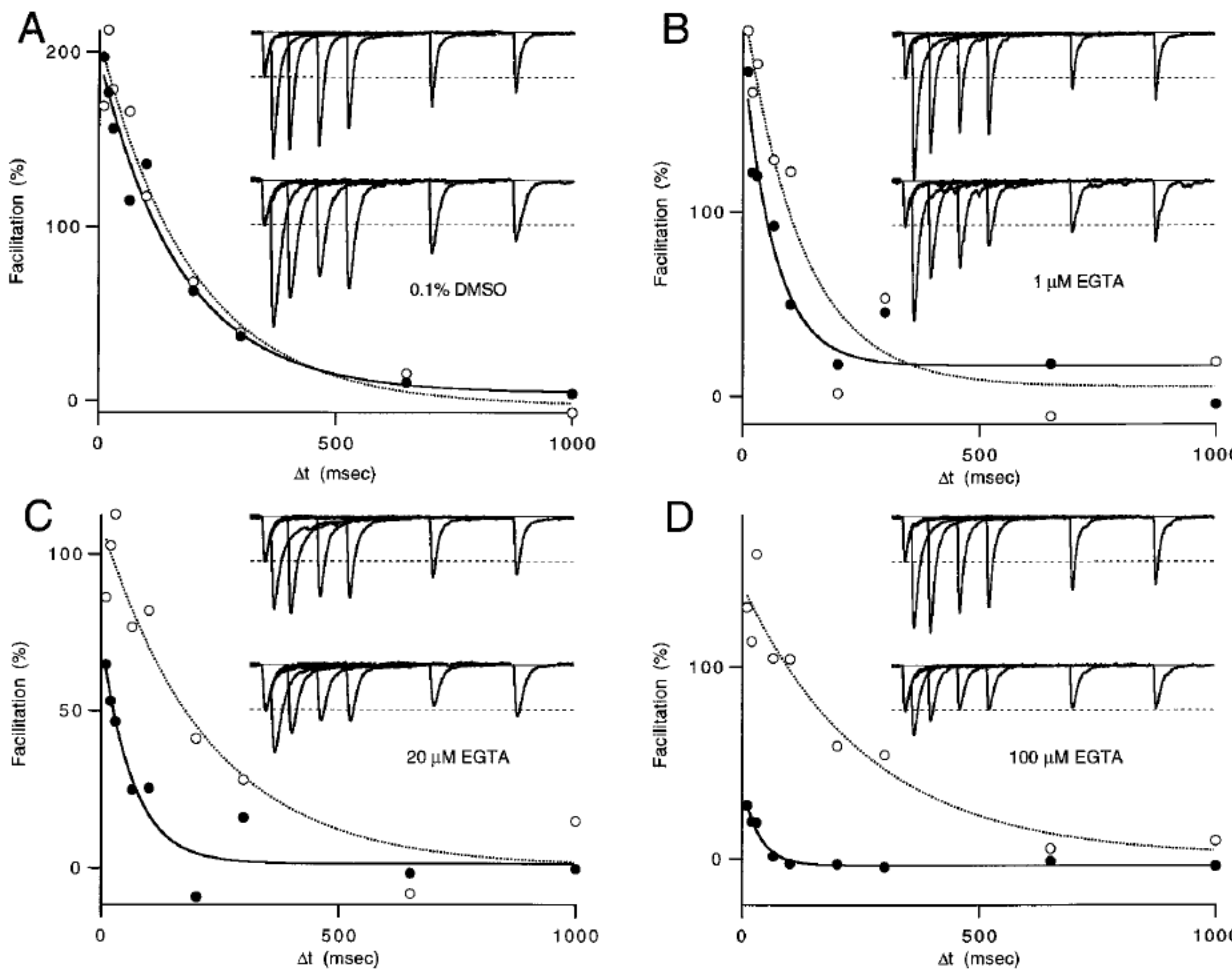


Facilitation and Residual Calcium



Could use slow buffer (eg: EGTA) to ‘mop up’ residual calcium

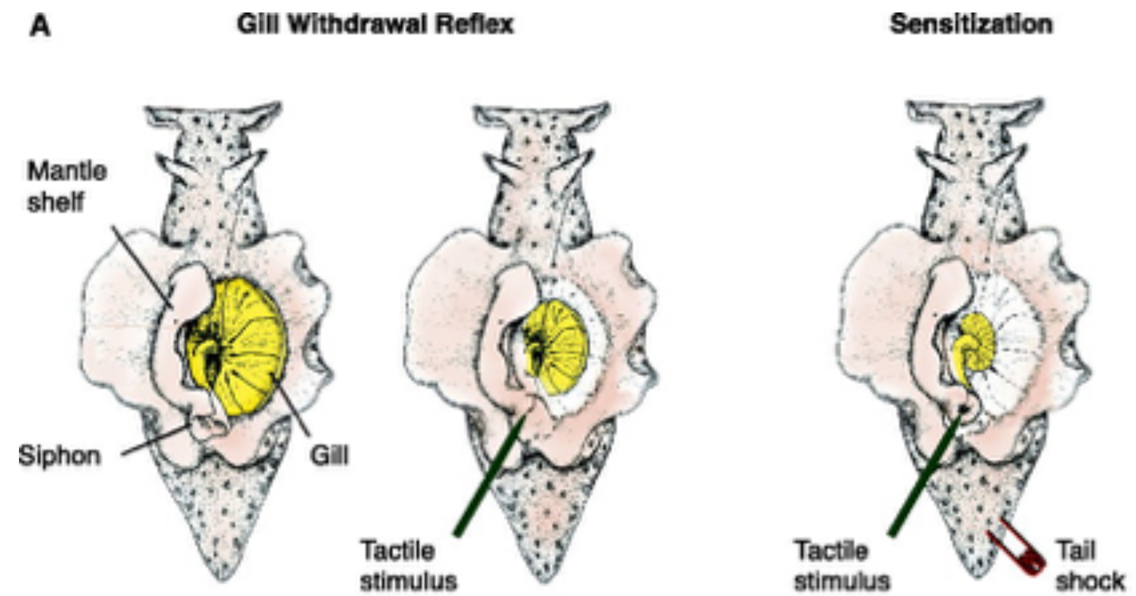
Facilitation and Residual Calcium

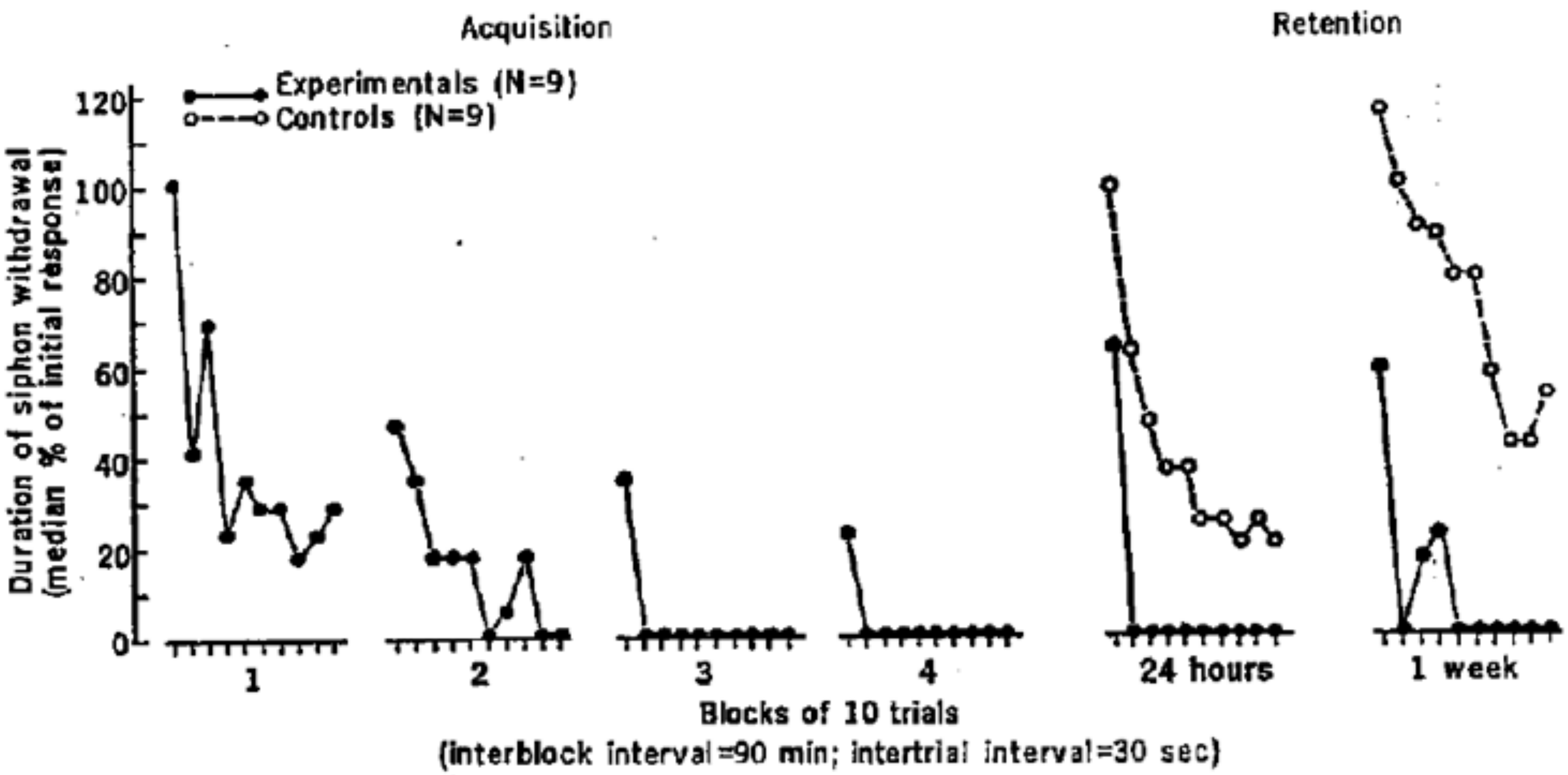


Process: high affinity, slow off rate

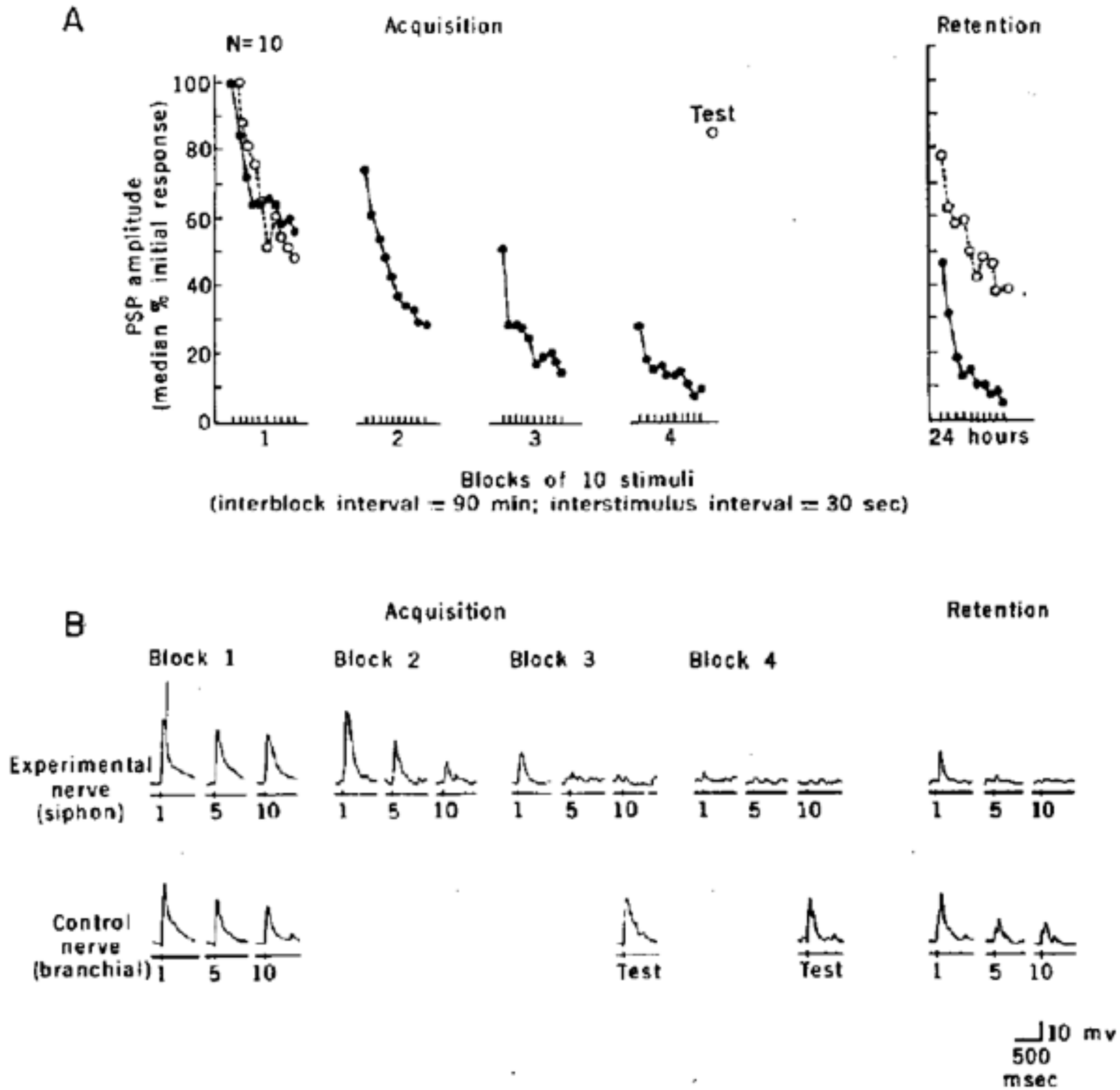
Alturi and Regehr, J. Neurosci., 1996

Plasticity of synapses and transmission: mechanisms and functional relevance

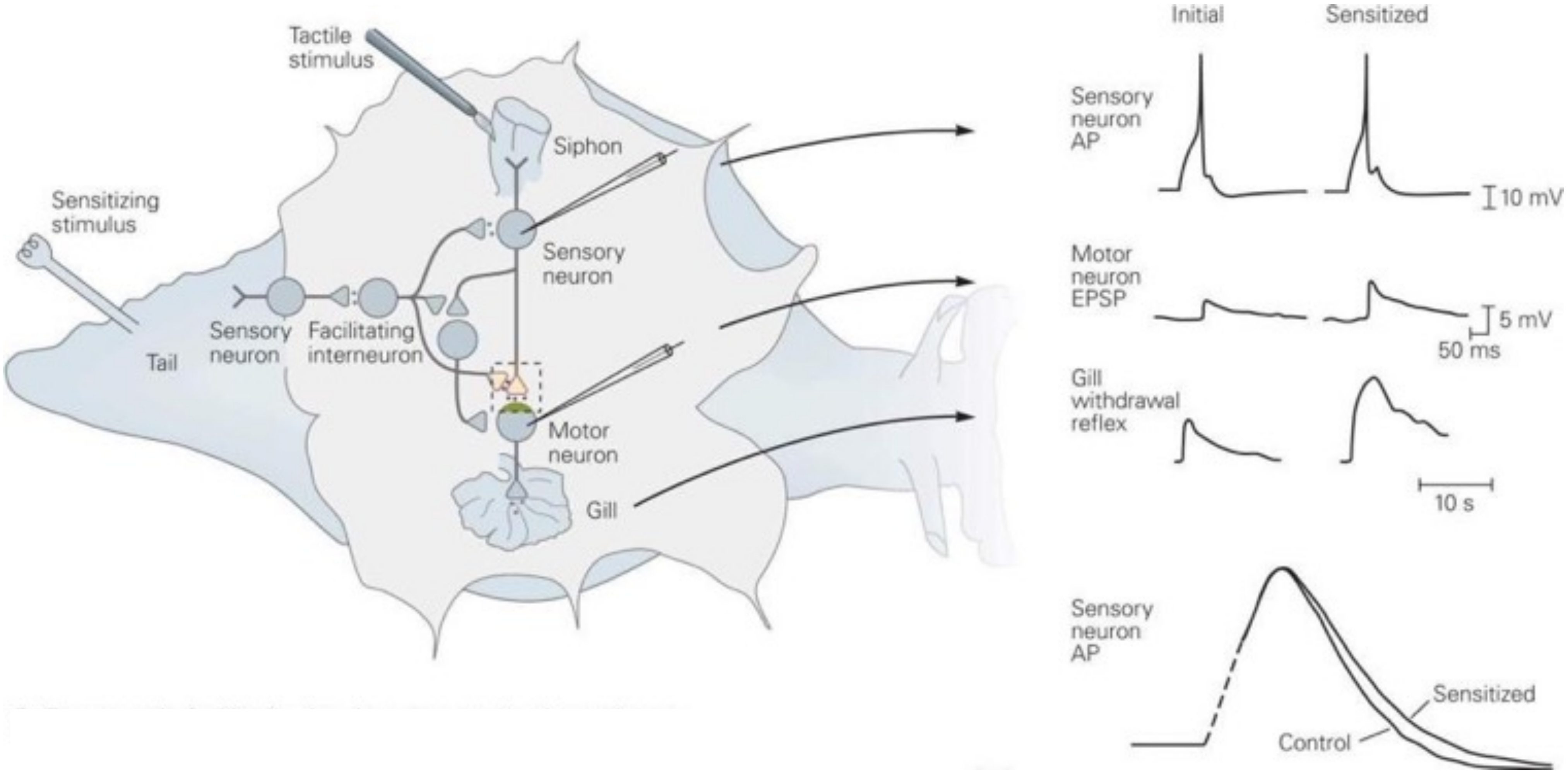




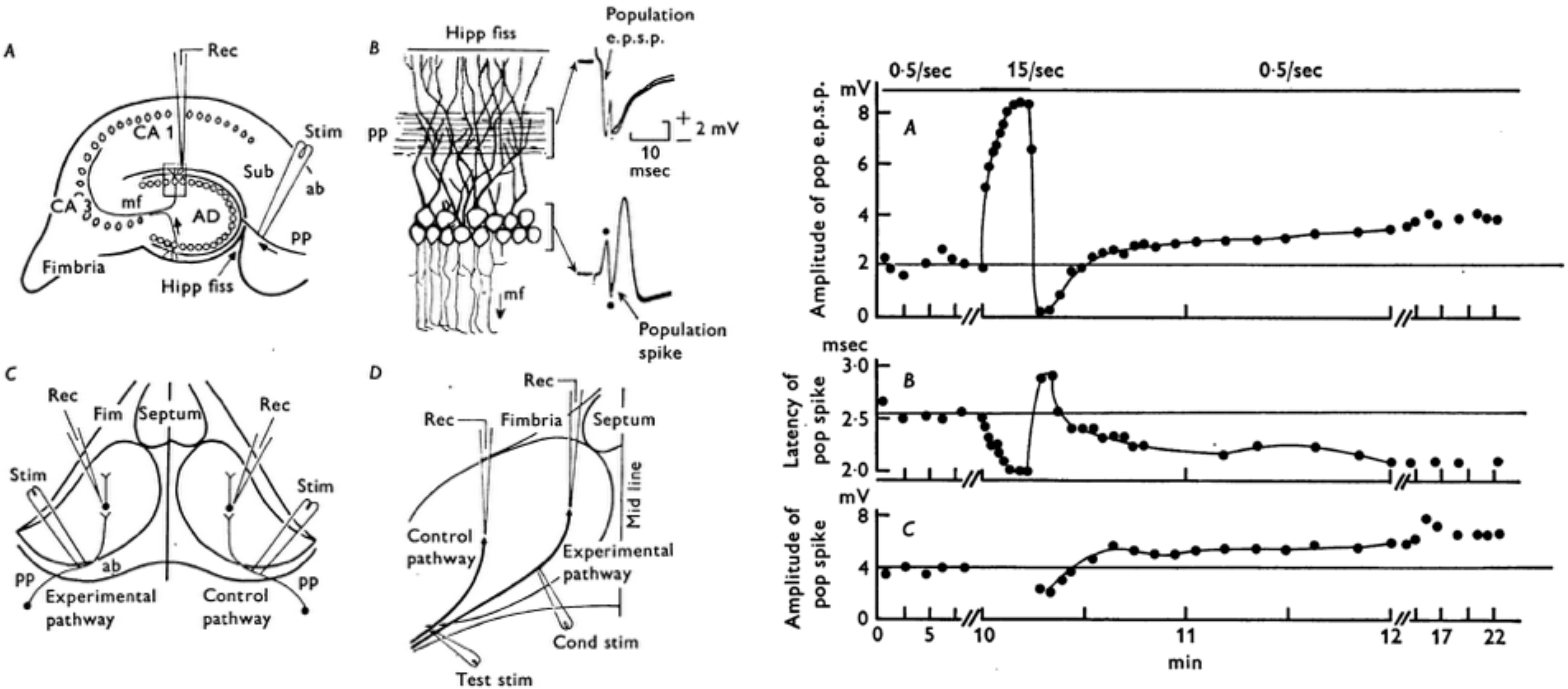
Carew and Kandel, 1973



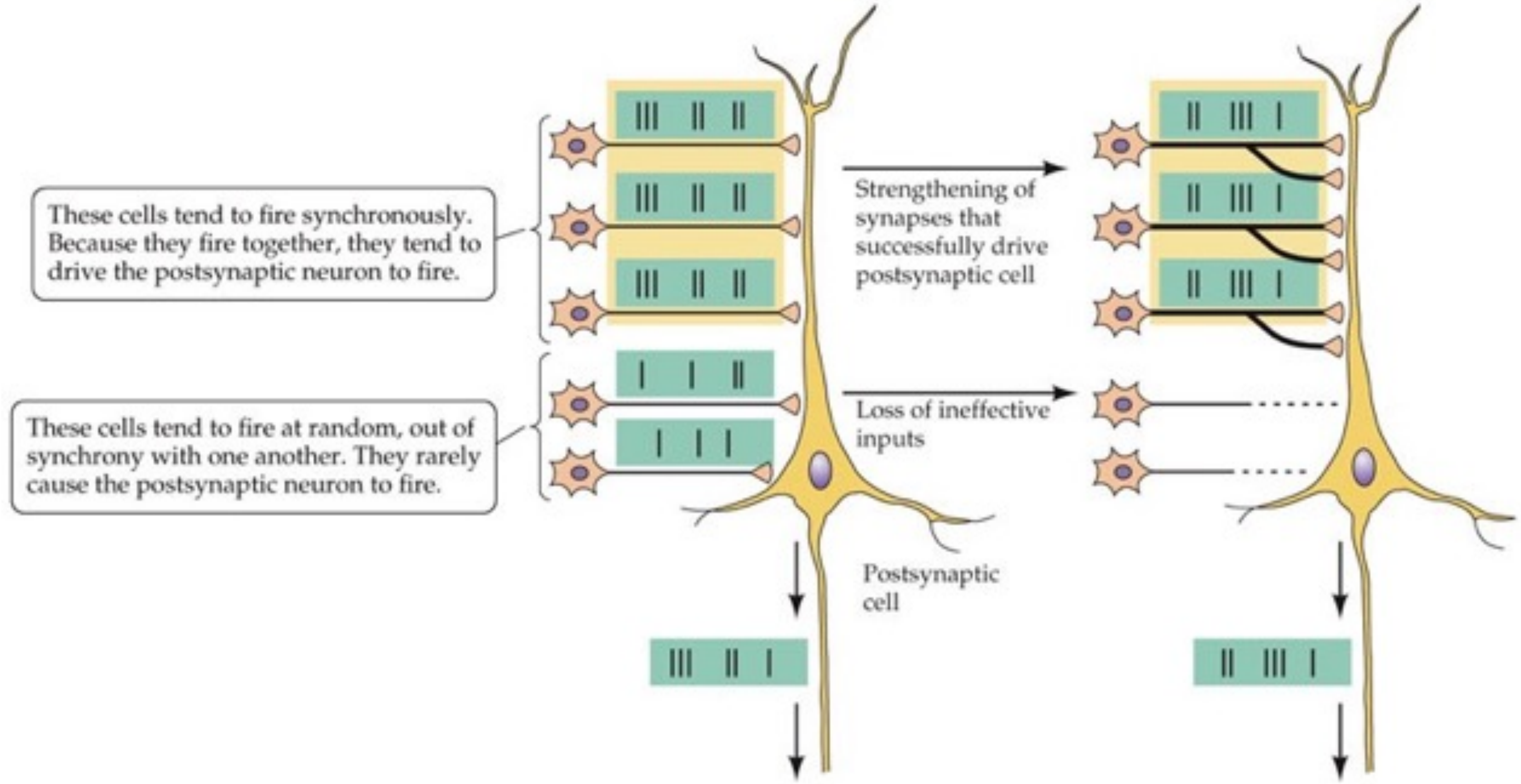
Carew and Kandel, 1973



Tactile stimulus
Siphon
Sensitizing stimulus
Sensory neuron
Tail
Sensory neuron
Facilitating interneuron
Motor neuron
Gill
Initial
Sensitized
Sensory neuron AP
10 mV
Motor neuron EPSP
5 mV
50 ms
Gill withdrawal reflex
10 s
Sensory neuron AP
Sensitized
Control



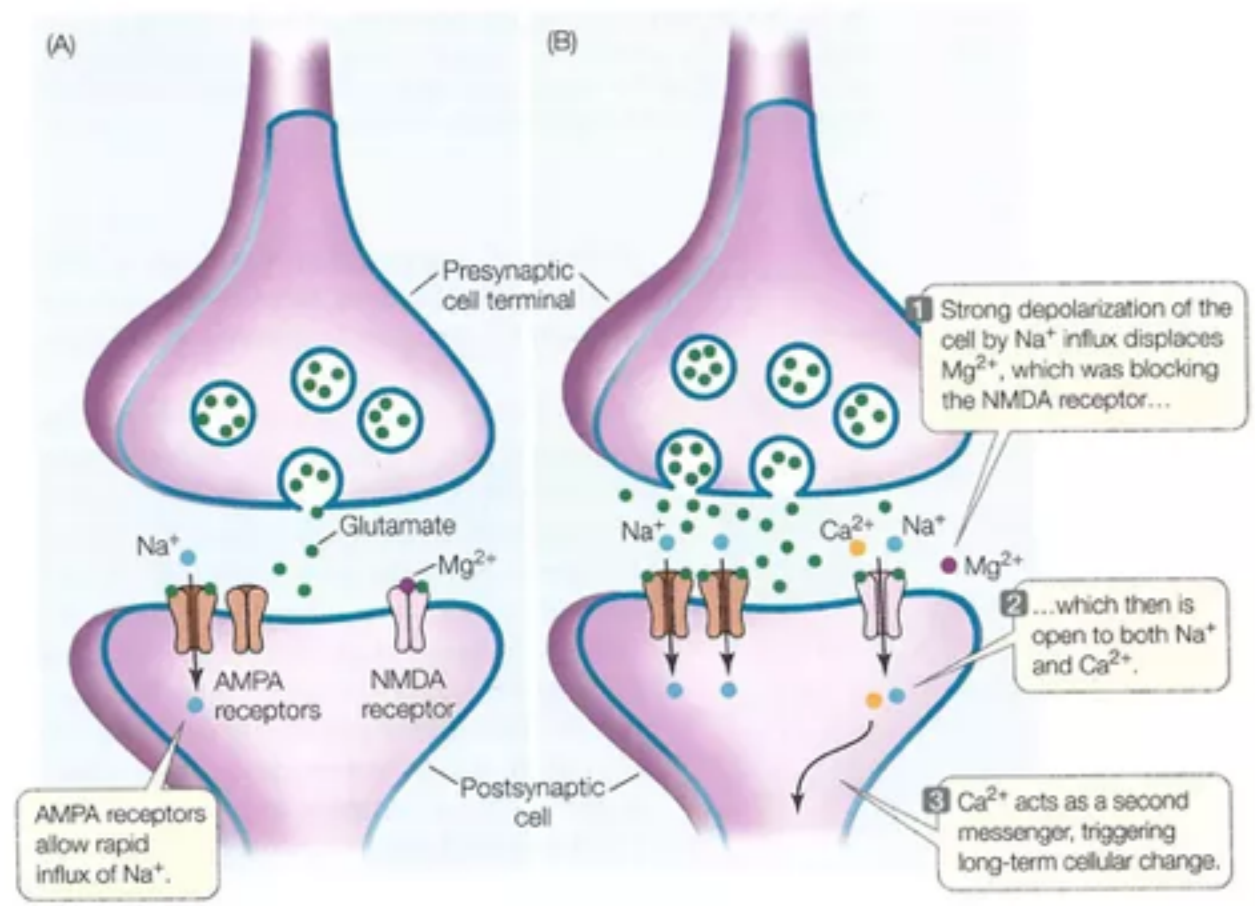
Bliss and Lomo, 1973



THE MIND'S MACHINE 2e, **Figure 13.23**

The Organisation of Behaviour (1949) When an axon of cell A is near enough to excite cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased.[3]

This is often paraphrased as "Neurons that fire together wire together." It is commonly referred to as Hebb's Law.



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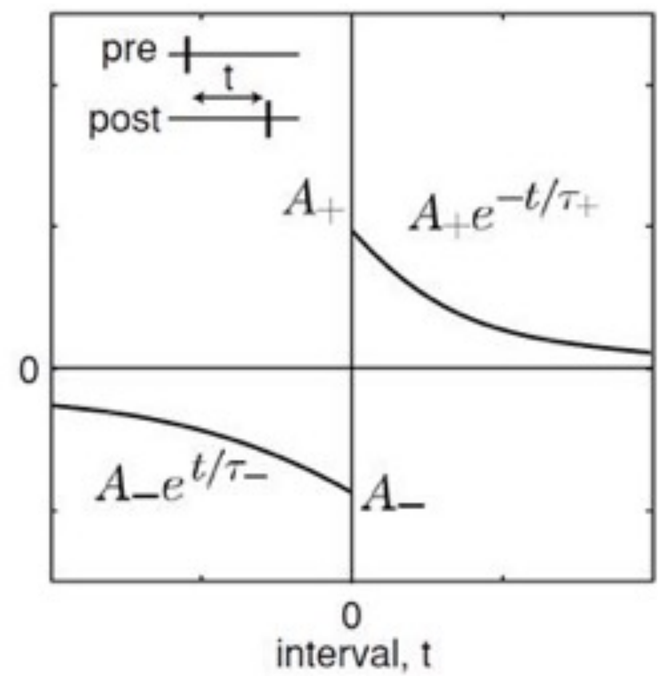
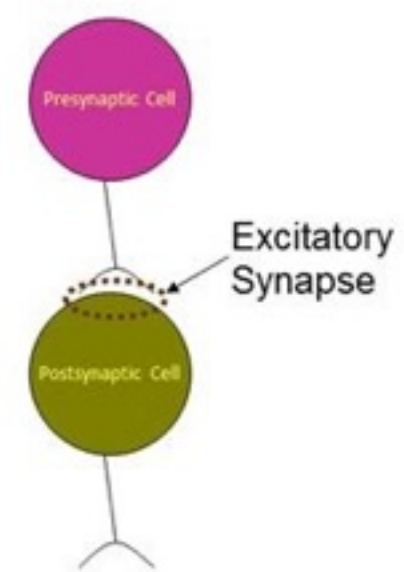
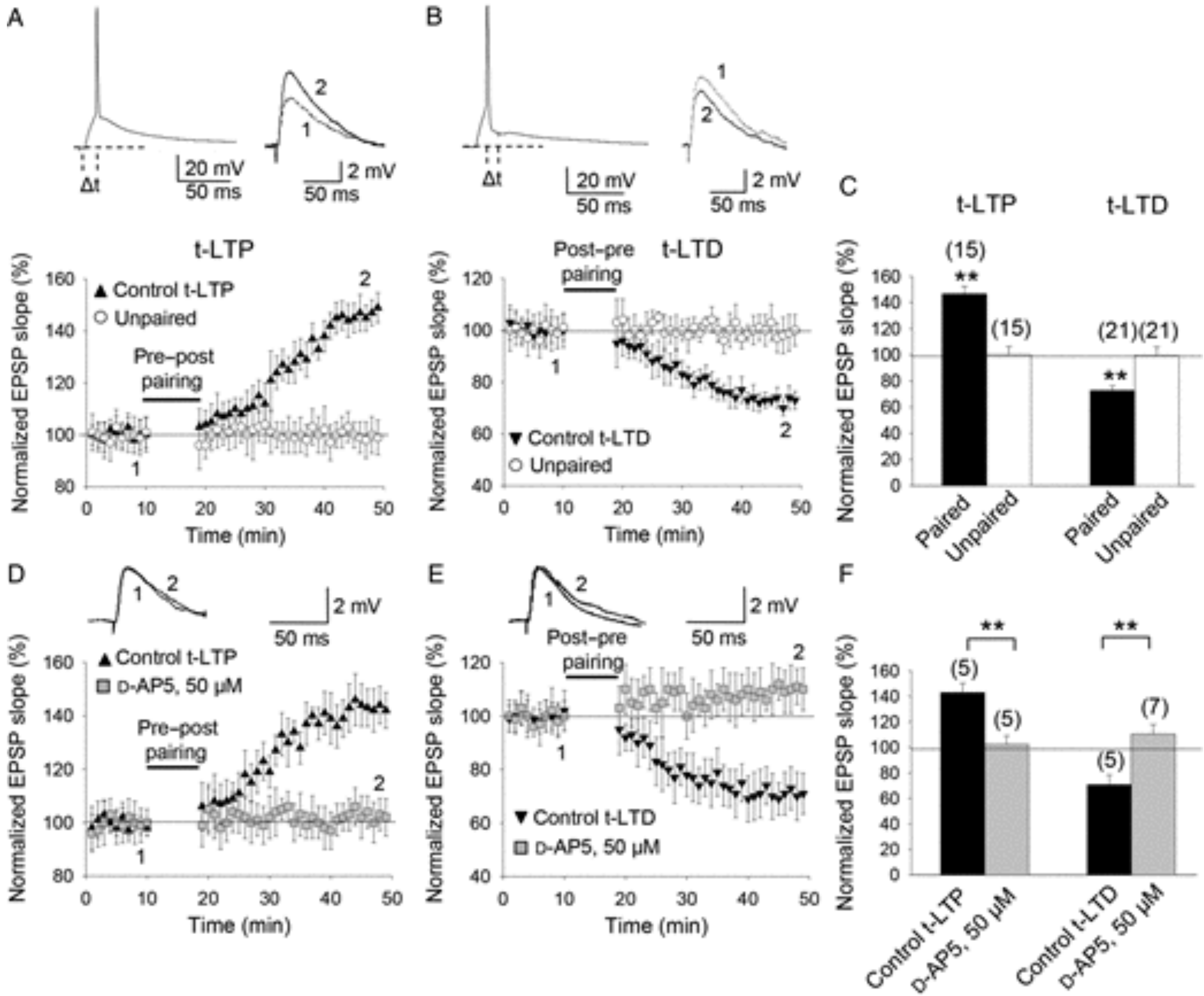
STDP rule (spike-timing-dependent plasticity)

- If the presynaptic spike arrives at the postsynaptic neuron before the postsynaptic neuron fires—for example, it causes the firing—the synapse is potentiated.






A
Δt
20 mV
50 ms
2 mV
50 ms
t-LTP
Control t-LTP
Unpaired
Pre–post pairing
Normalized EPSP slope (%)
Time (min)
B
Δt
20 mV
50 ms
2 mV
50 ms
Post–pre pairing
t-LTD
Control t-LTD
Unpaired
Normalized EPSP slope (%)
Time (min)
C
t-LTP
t-LTD
Normalized EPSP slope (%)
Paired
Unpaired
Paired
Unpaired
D
2 mV
50 ms
Control t-LTP
D-AP5, 50 μM
Pre–post pairing
Normalized EPSP slope (%)
Time (min)
E
2 mV
50 ms
Post–pre pairing
Control t-LTD
D-AP5, 50 μM
Normalized EPSP slope (%)
Time (min)
F
Normalized EPSP slope (%)
Control t-LTP
D-AP5, 50 μM
Control t-LTD
D-AP5, 50 μM

MicroNetwork Motifs