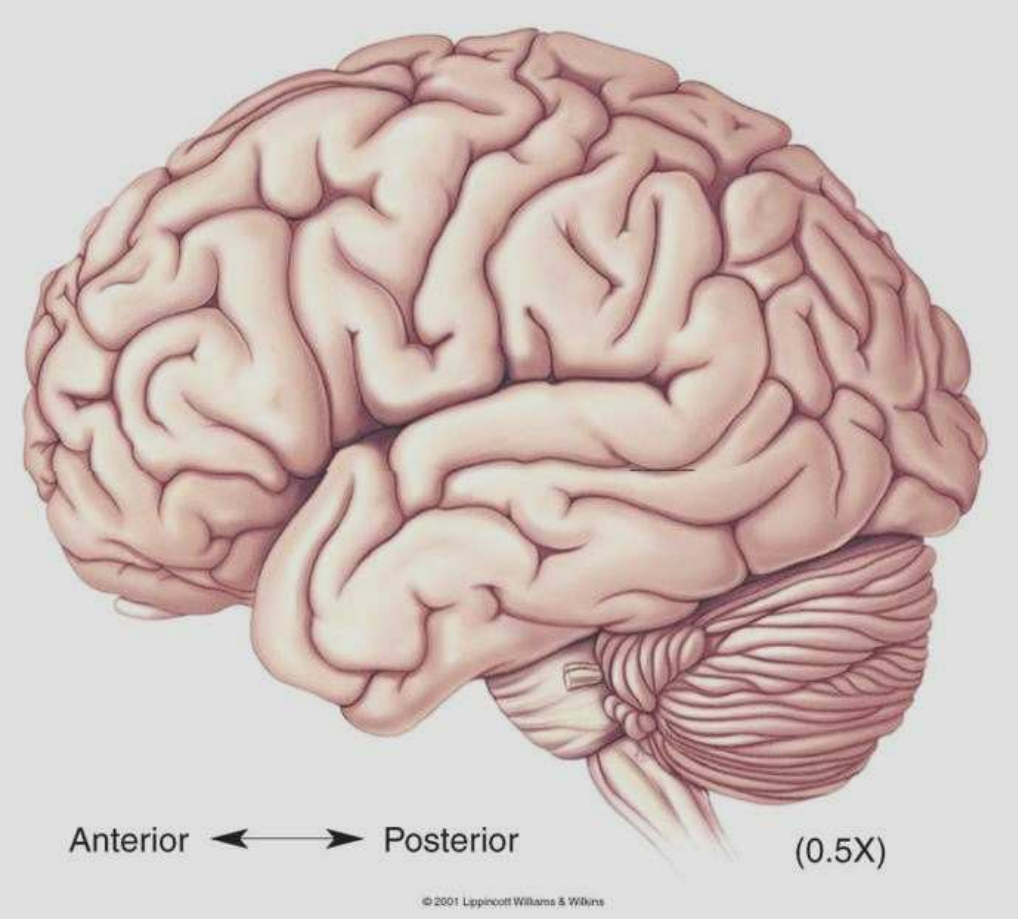
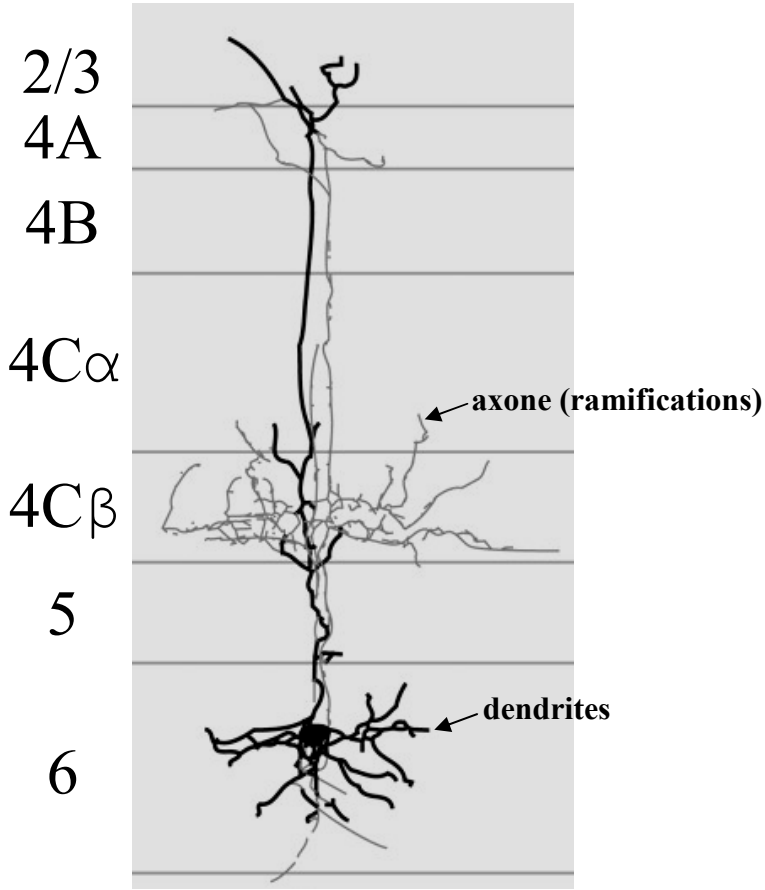
Cerveau Humain $>10^{10}$x

Vue latérale hémisphère gauche



Neurone(s)

Cellule pyramidale de la couche 6 du cortex visuel primaire



philippe.ascher@univ-paris5.fr

1. Signaux électriques

1.1. Gradient électrochimique
Courants ioniques. Potentiel de membrane
Voltage imposé

1.2. Potentiel d'action
Hodgkin et Huxley
Potentiels d'action dendritiques. Rétropropagation.
Activité répétitive

1.3. Potentiels synaptiques.
Récepteurs ionotropiques et métabotropiques
Récepteurs présynaptiques et post synaptiques

2. Signaux calciques

La mesure du Ca intracellulaire.
Flux calciques
Stocks calciques intracellulaires

3. Neuropharmacologie

4. Plasticité synaptique

LTP et LTD. Induction et expression
Métaplasticité
STDP
Mécanismes homéostatiques

Six notions

M2 BCPP Spécialité NEUROBIOLOGIE
2007-2008

UE1: Développement et Pathologies du Développement: 22 au 26 octobre

UE2/ UE5: Du neurone aux réseaux neuronaux/Imagerie cellulaire:
26 au 30 novembre

UE3: Neuropsychopharmacologie: 10 au 14 Décembre

Contact: Claire Legay, Responsable de la Spécialité
claire.legay@univ-paris5.fr 01 42 86 20 68

Cellular/Molecular

Spine Ca^{2+} Signaling in Spike-Timing-Dependent Plasticity

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Calcium is a second messenger, which can trigger the modification of synaptic efficacy. We investigated the question of whether a differential rise in postsynaptic Ca^{2+} ($[Ca^{2+}]_i$) alone is sufficient to account for the induction of long-term potentiation (LTP) and long-term depression (LTD) of EPSPs in the basal dendrites of layer 2/3 pyramidal neurons of the somatosensory cortex. Volume-averaged $[Ca^{2+}]_i$ transients were measured in spines of the basal dendritic arbor for spike-timing-dependent plasticity induction protocols. The rise in $[Ca^{2+}]_i$ was uncorrelated to the direction of the change in synaptic efficacy, because several pairing protocols evoked similar spine $[Ca^{2+}]_i$ transients but resulted in either LTP or LTD. The sequence dependence of near-coincident presynaptic and postsynaptic activity on the direction of changes in synaptic strength suggested that LTP and LTD were induced by two processes, which were controlled separately by postsynaptic $[Ca^{2+}]_i$ levels. Activation of voltage-dependent Ca^{2+} channels before metabotropic glutamate receptors (mGluRs) resulted in the phospholipase C-dependent (PLC-dependent) synthesis of endocannabinoids, which acted as a retrograde messenger to induce LTD. LTP required a large $[Ca^{2+}]_i$ transient evoked by NMDA receptor activation. Blocking mGluRs abolished the induction of LTD and uncovered the Ca^{2+}-dependent induction of LTP.

We conclude that the volume-averaged peak elevation of $[Ca^{2+}]_i$ in spines of layer 2/3 pyramids determines the magnitude of long-term changes in synaptic efficacy. The direction of the change is controlled, however, via a mGluR-coupled signaling cascade. mGluRs act in conjunction with PLC as sequence-sensitive coincidence detectors when postsynaptic precede presynaptic action potentials to induce LTD. Thus presumably two different Ca^{2+} sensors in spines control the induction of spike-timing-dependent synaptic plasticity.

Key words: LTP; LTD; synaptic plasticity; calcium; two-photon microscopy; spine; spike-timing-dependent plasticity; mGluR; NMDAR

Introduction

Long-term changes in synaptic efficacy are thought to be the cellular basis of information storage and memory formation (Bliss and Collingridge, 1993; Whitlock et al., 2006). Modifications in the efficacy of transmission at synaptic contacts can be induced by coincident presynaptic and postsynaptic activity (Magee and Johnston, 1997; Markram et al., 1997; Debanne et al., 1998). The precise timing and the order of presynaptic and postsynaptic action potentials (APs) determine the magnitude and the direction of the change in synaptic strength (Markram et al., 1997; Bi and Poo, 1998; Feldman, 2000; Sjostrom et al., 2001; Froemke and Dan, 2002). A postsynaptic AP that follows a presynaptic AP within a time window of tens of milliseconds results in long-term potentiation (LTP), whereas the reverse order results in depression (LTD). Therefore, spike-timing-dependent plasticity (STDP) is one possible cellular model for the induction of local synaptic modifications, which could account for experience-driven changes of the connectivity in neuronal networks (Song and Abbott, 2001; Senn, 2002).

For STDP pairing protocols as well as for other plasticity induction protocols, like presynaptic tetanic stimulation (Lynch et al., 1983) or repetitive low-frequency synaptic stimulation (Mulkey and Malenka, 1992), the elevation of postsynaptic $[Ca^{2+}]_i$ is essential. $[Ca^{2+}]_i$ probably acts as one second messenger on downstream metabolic cascades that are responsible for the eventual modification of synaptic efficacy (Lisman, 1989). A long-standing hypothesis suggests that the peak amplitude of postsynaptic $[Ca^{2+}]_i$ elevation determines the direction and the magnitude of such modifications (Bear et al., 1987; Artola and Singer, 1993; Hansel et al., 1997). Several studies have supported this hypothesis by measuring dendritic $[Ca^{2+}]_i$ (Cormier et al., 2001; Ismailov et al., 2004; Gall et al., 2005). Nevertheless, the problem of how a single variable, the increase in global $[Ca^{2+}]_i$, can control the differential induction of changes in synaptic efficacy has not been explained conclusively. According to this "Ca^{2+} control hypothesis" the level of $[Ca^{2+}]_i$ acts differentially on downstream protein cascades, activating either kinases or phosphatases, which, respectively, phosphorylate or dephosphorylate postsynaptic AMPA receptors (Lisman, 1989; Lee et al., 2000). Modified versions of this hypothesis include veto mechanisms for LTD at moderate Ca^{2+} levels (Rubin et al., 2005), differential microdomain Ca^{2+} signaling (Franks and Sejnowski, 2002), or the proposition of a second coincidence detector (Karmarkar and Buonomano, 2002) to account for the differential induction of LTD and LTP.

Here we characterize the Ca^{2+} signals in spines of basal dendrites of layer 2/3 (L2/3) pyramidal neurons in the somatosensory cortex during LTP- and LTD-inducing protocols. We found that postsynaptic elevation of $[Ca^{2+}]_i$ in spines is necessary, but by itself it is not sufficient, to account for both potentiation and

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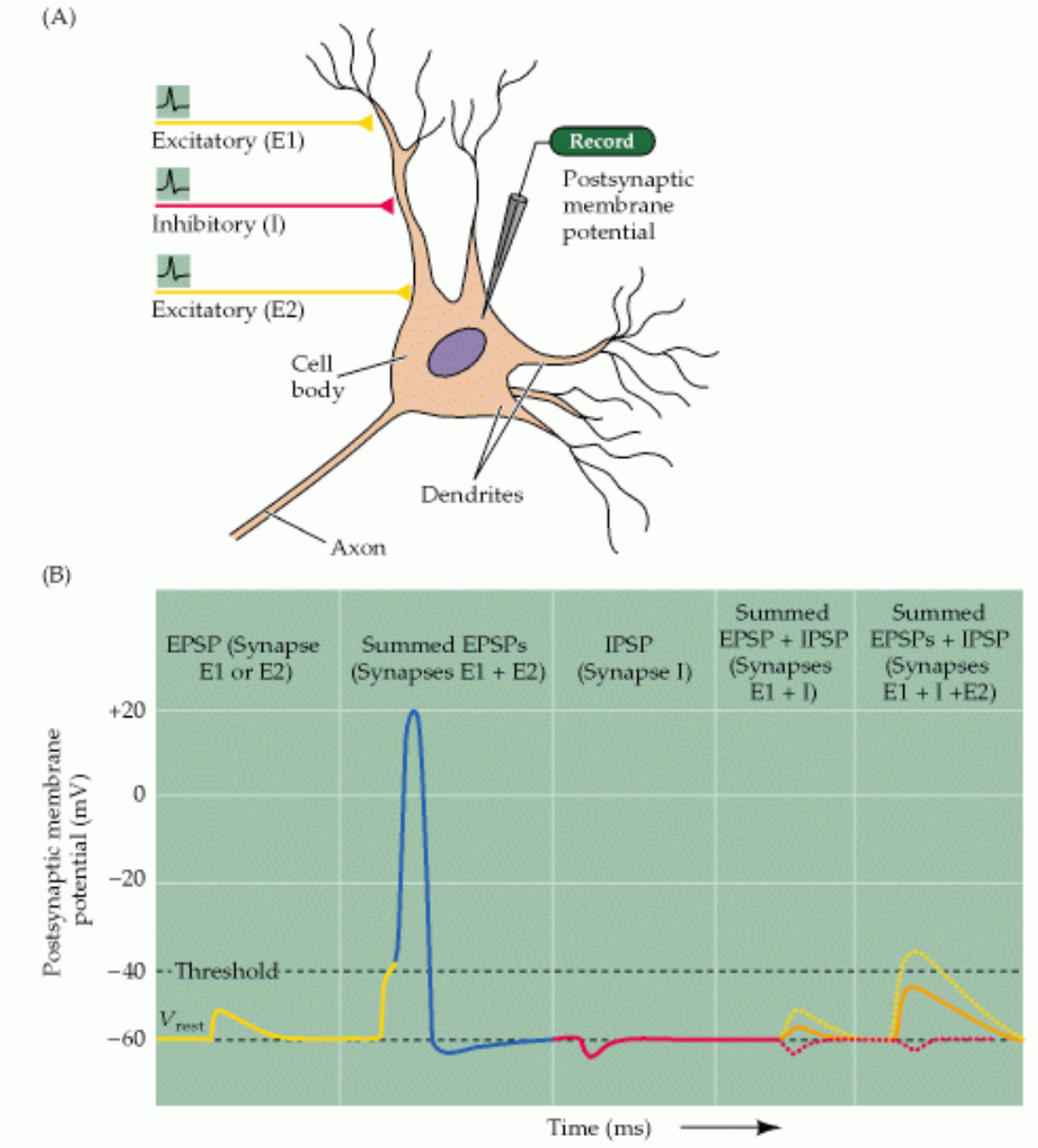
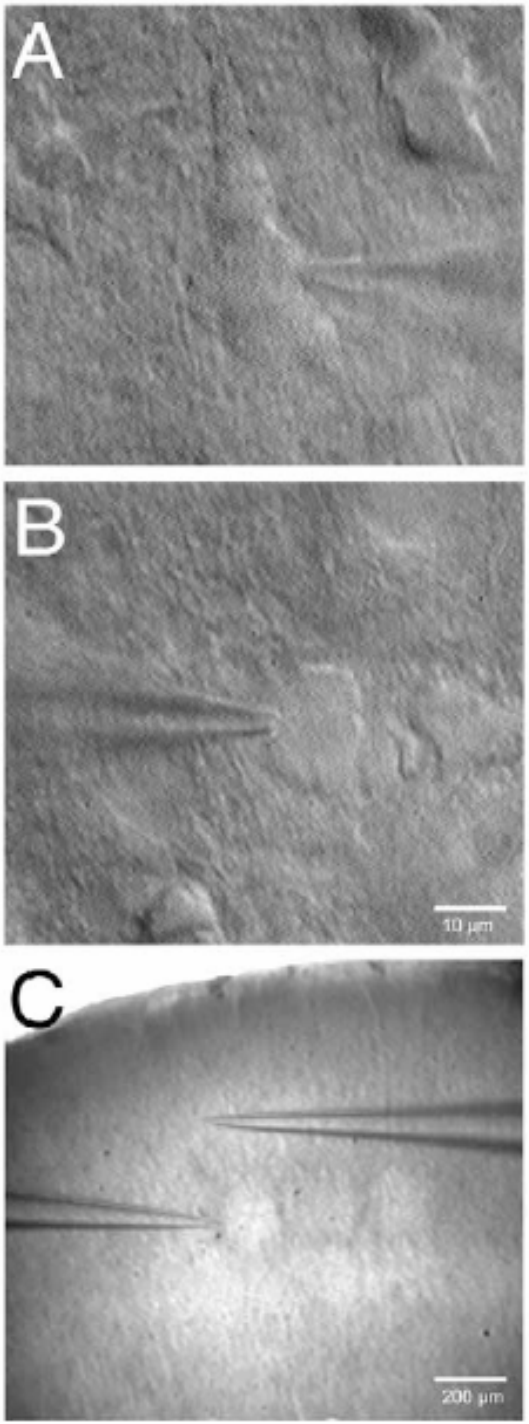
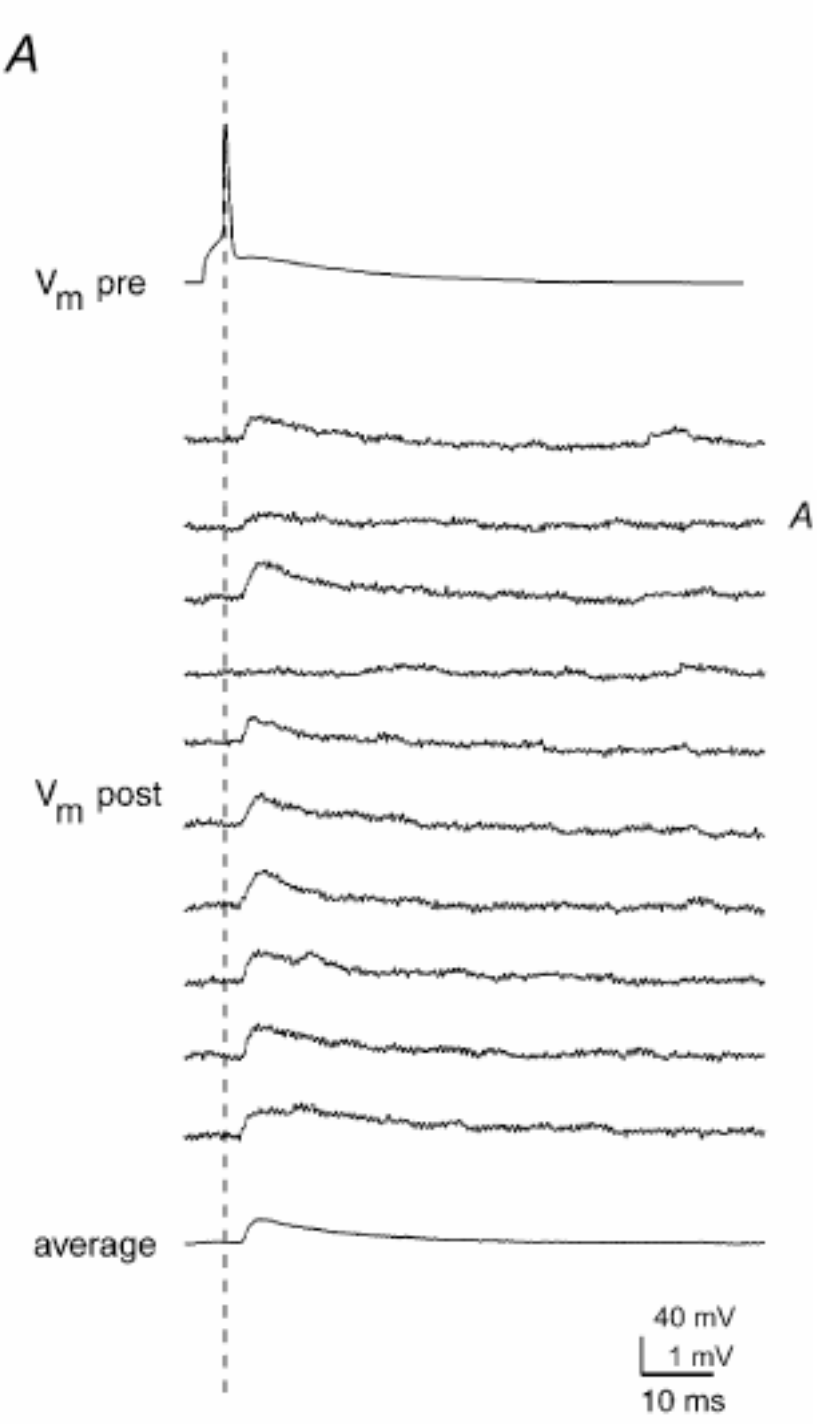
DOI:10.1523/JNEUROSCI.1749-06.2006

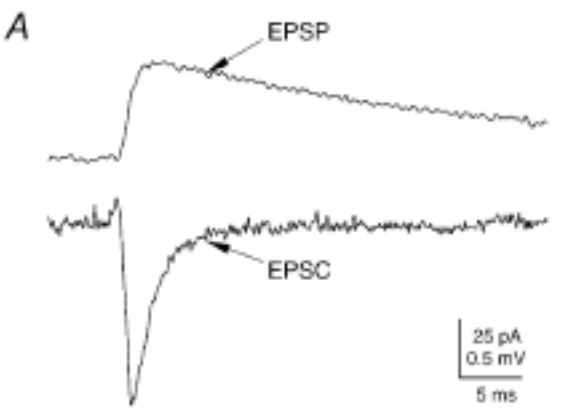
Nevian and Sakmann



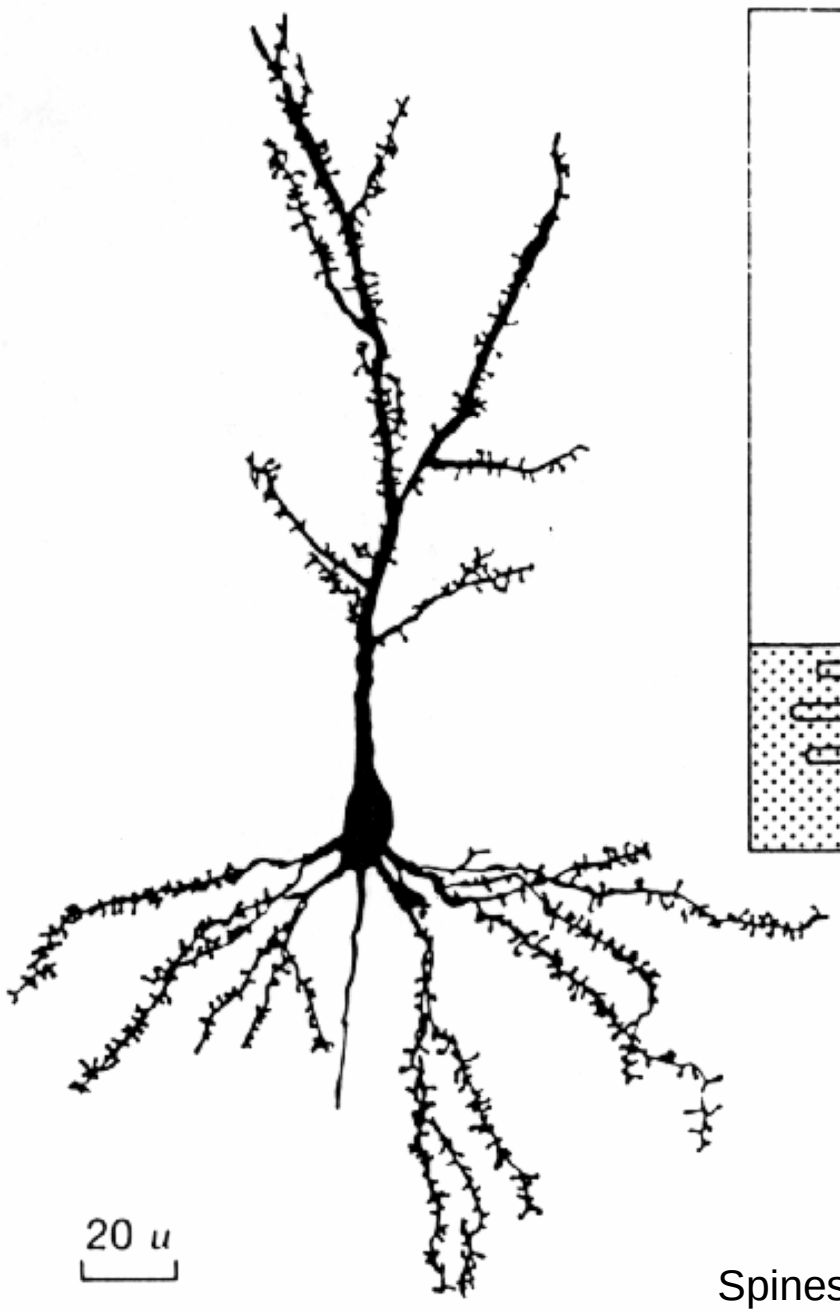
Purves et al., Neuroscience 2d edition

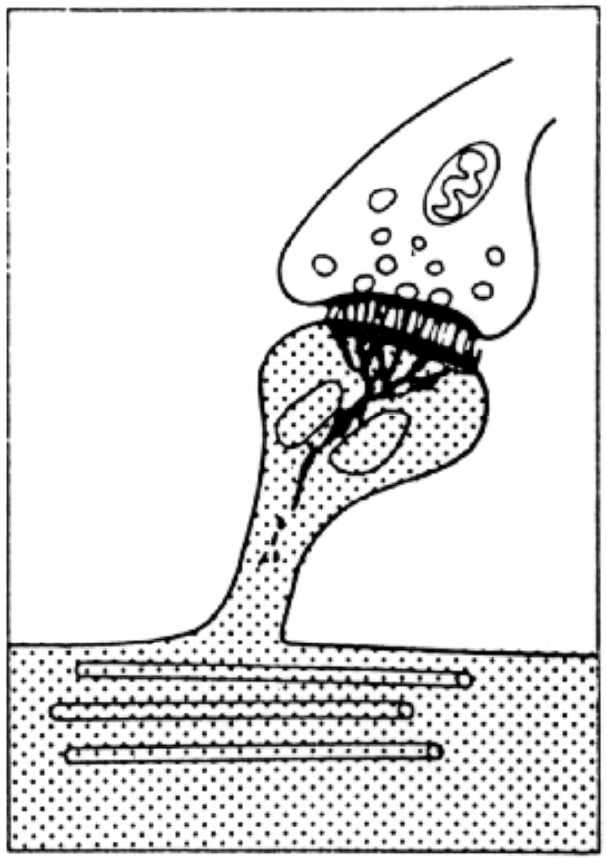




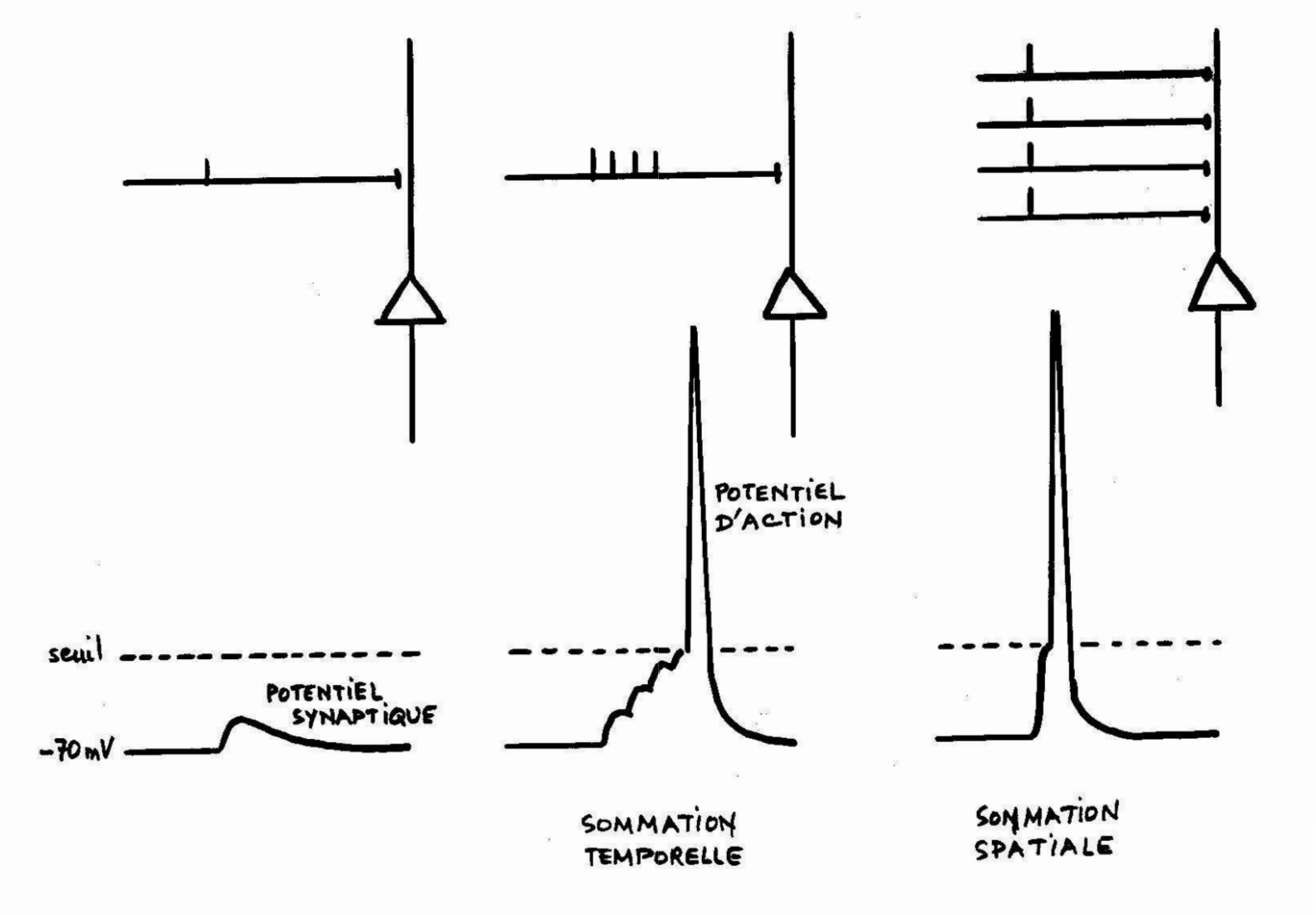


Feldmeyer et al . 2002

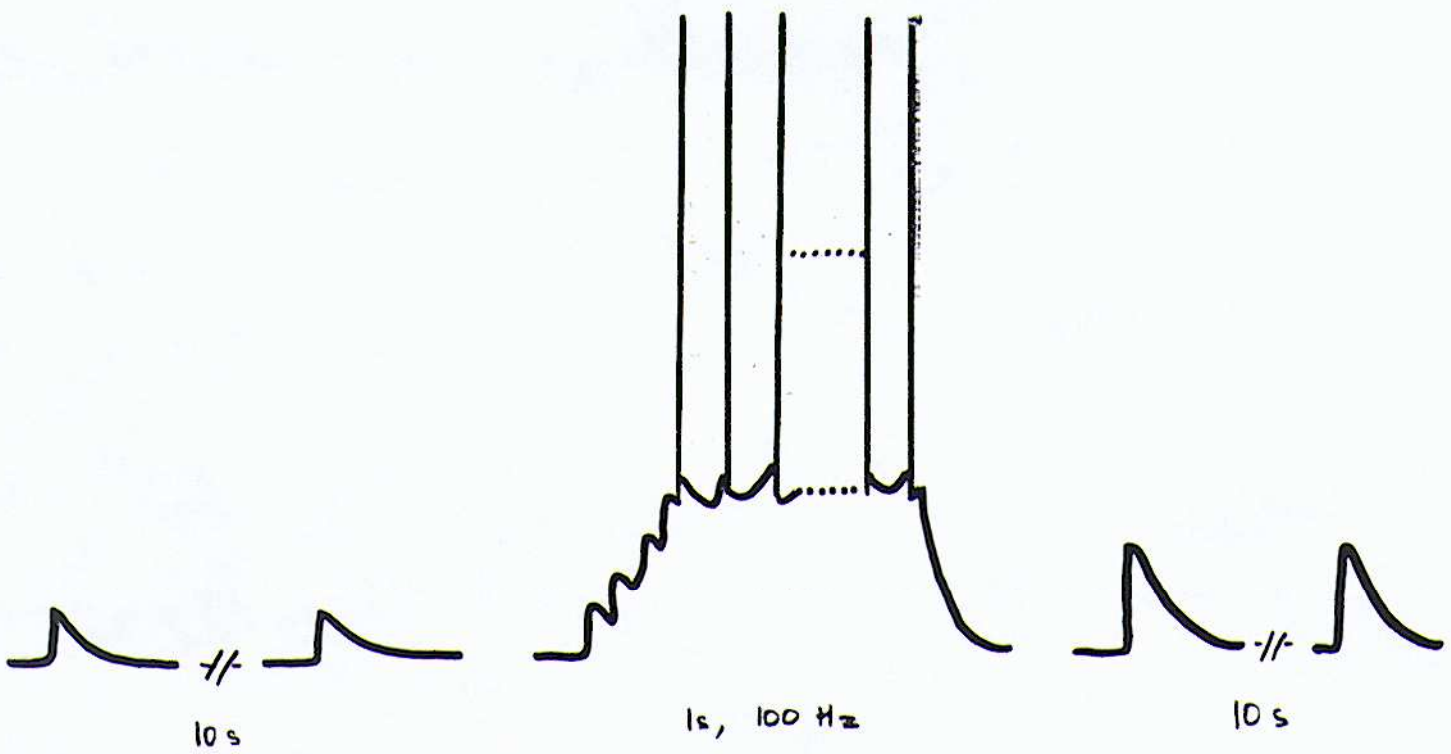




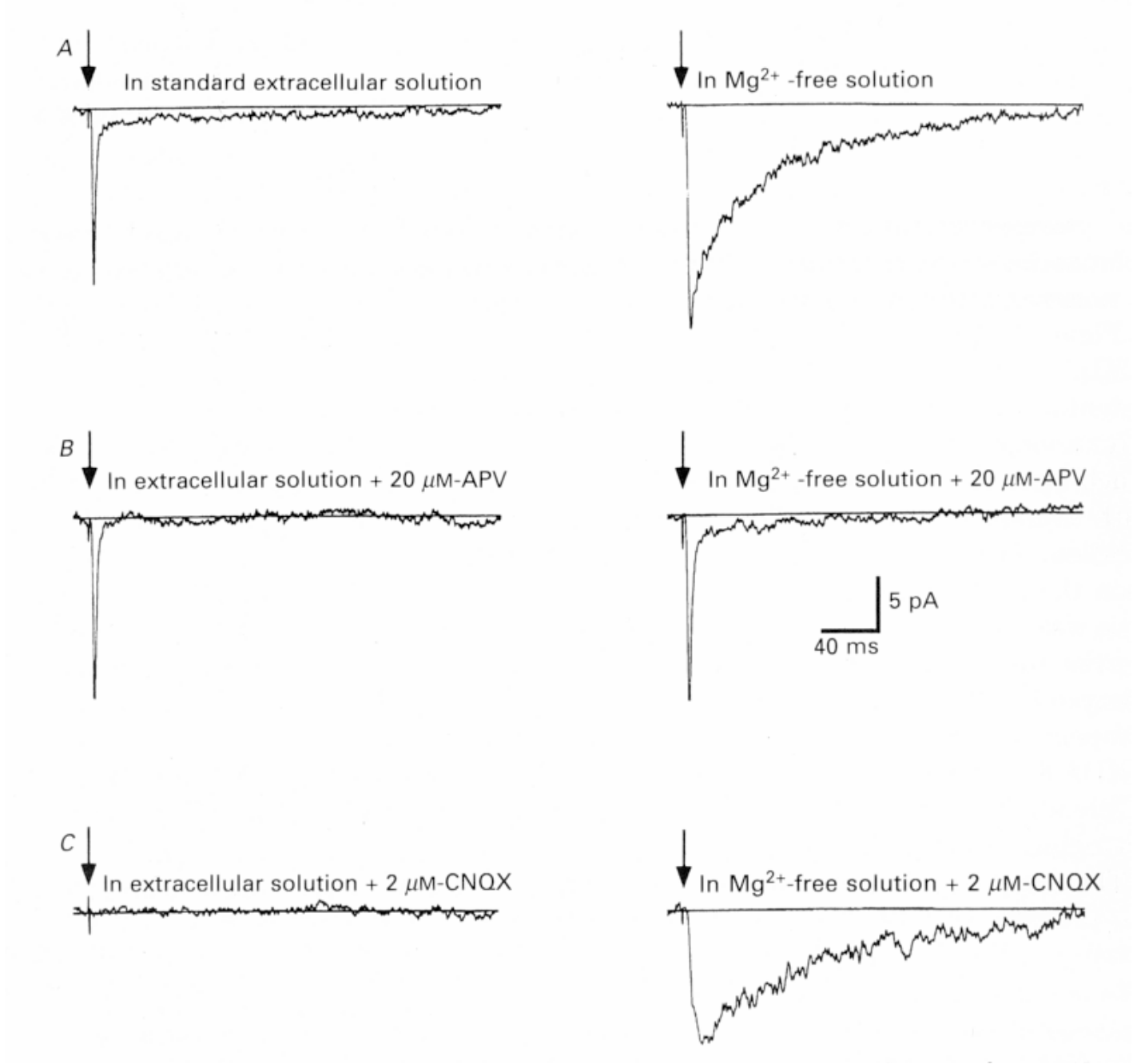
Spines


seuil
POTENTIEL SYNAPTIQUE
-70 mV
POTENTIEL D'ACTION
SOMMATION TEMPORELLE
SOMMATION SPATIALE

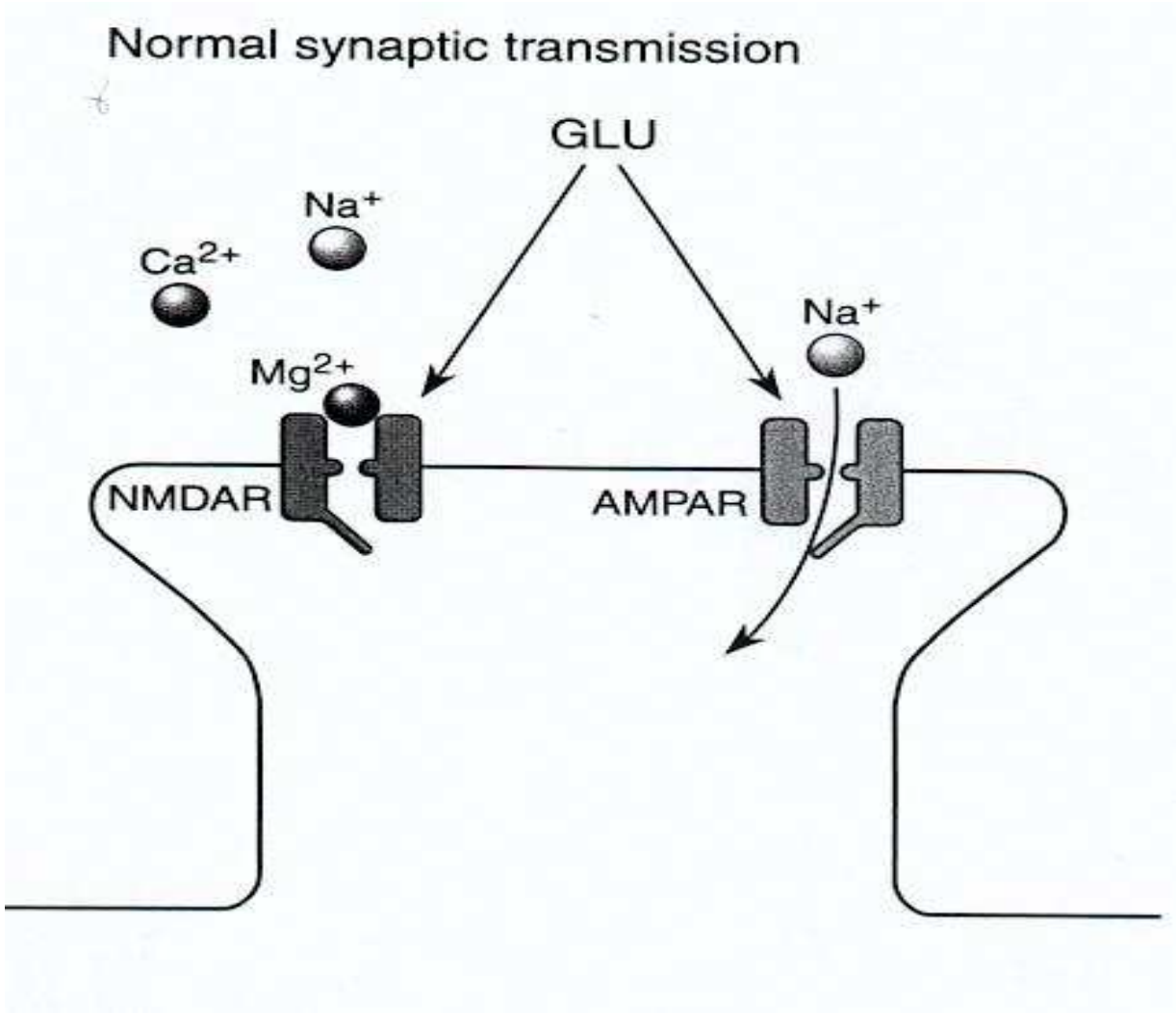
Sommation



LTP
Bliss et Lömo, 1973

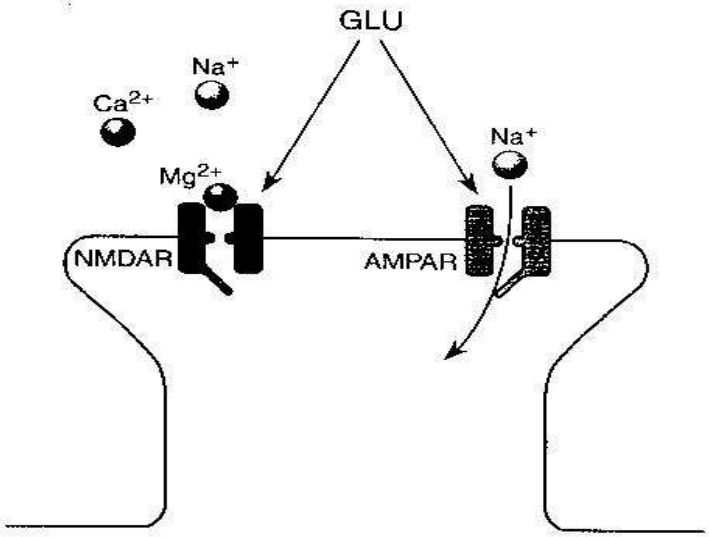


Stern et al. 1992

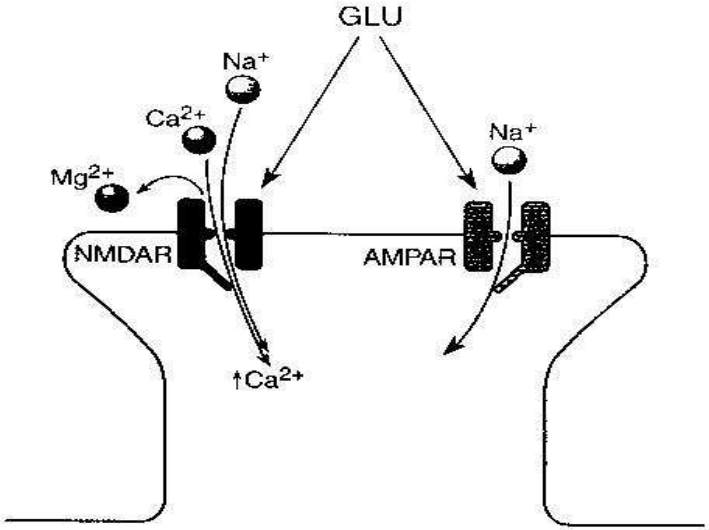


Malenka and Siegelbaum 2001

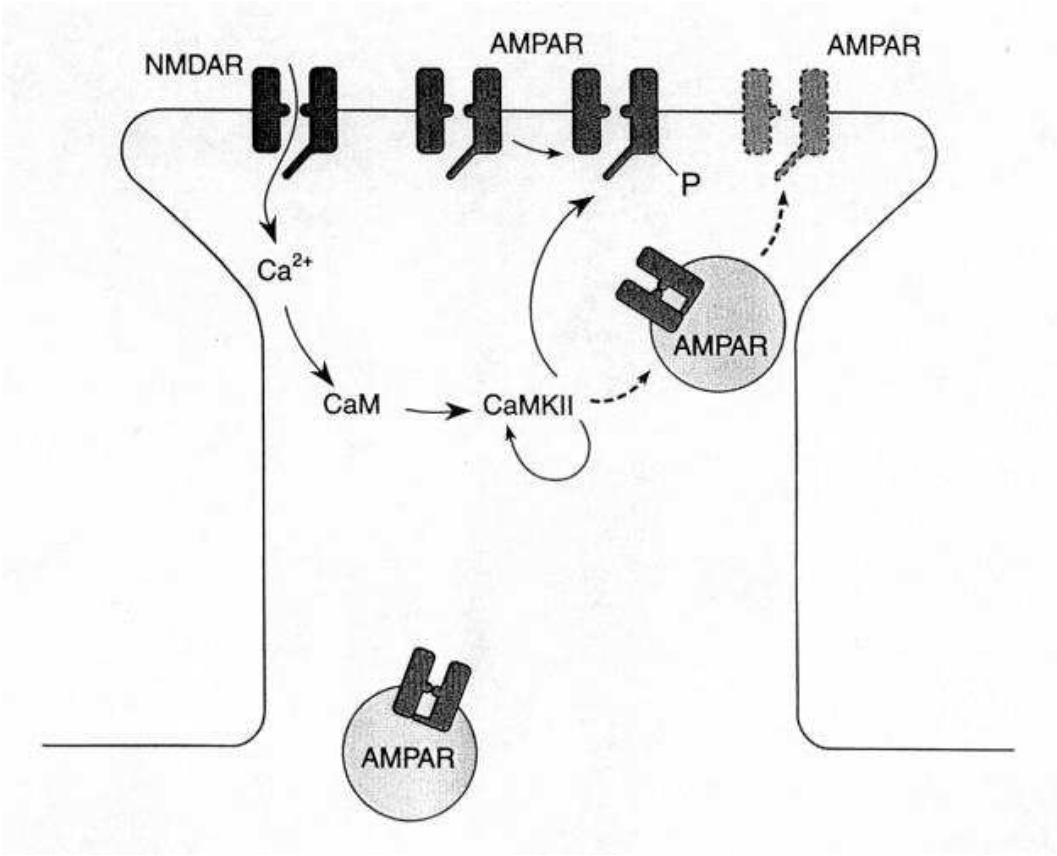
Normal synaptic transmission



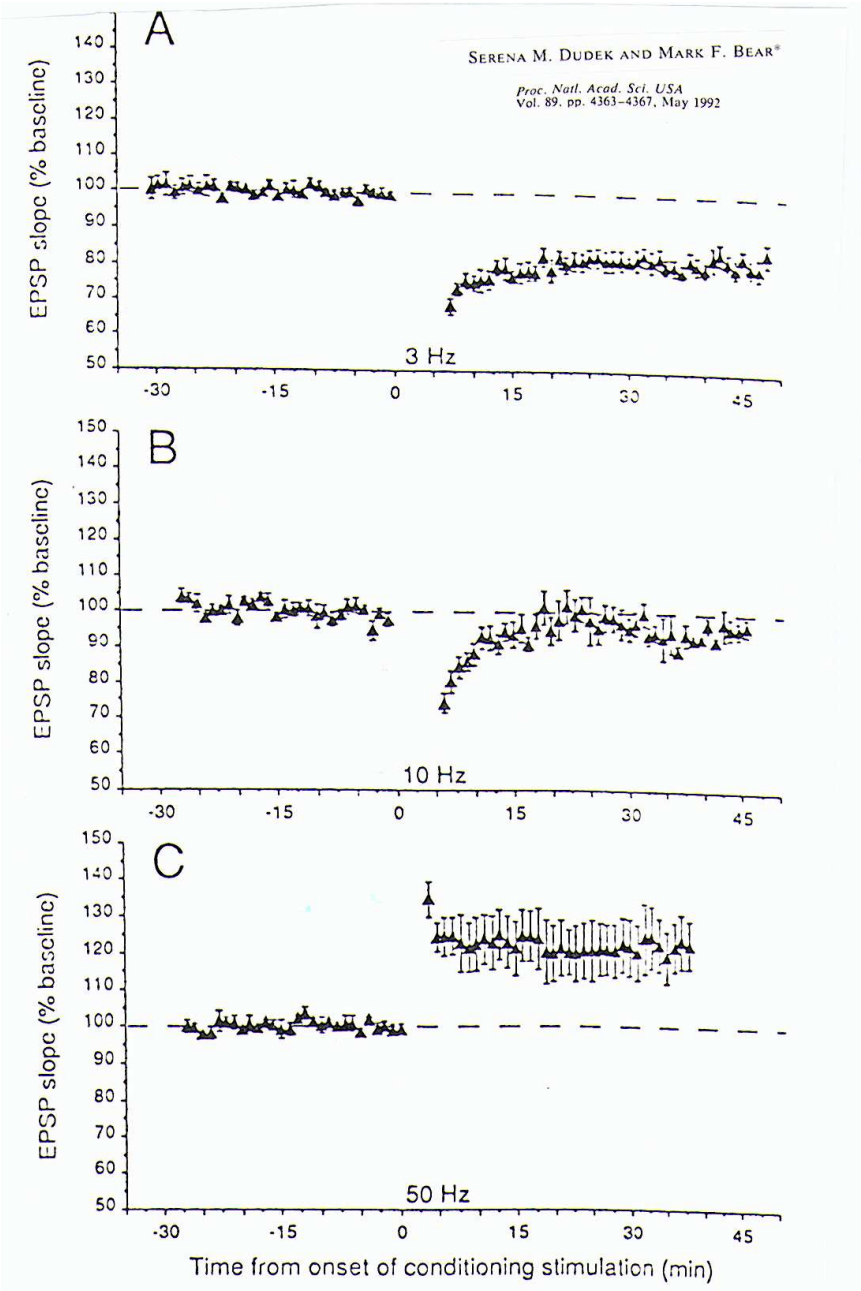
During depolarization



Malenka and Siegelbaum 2001



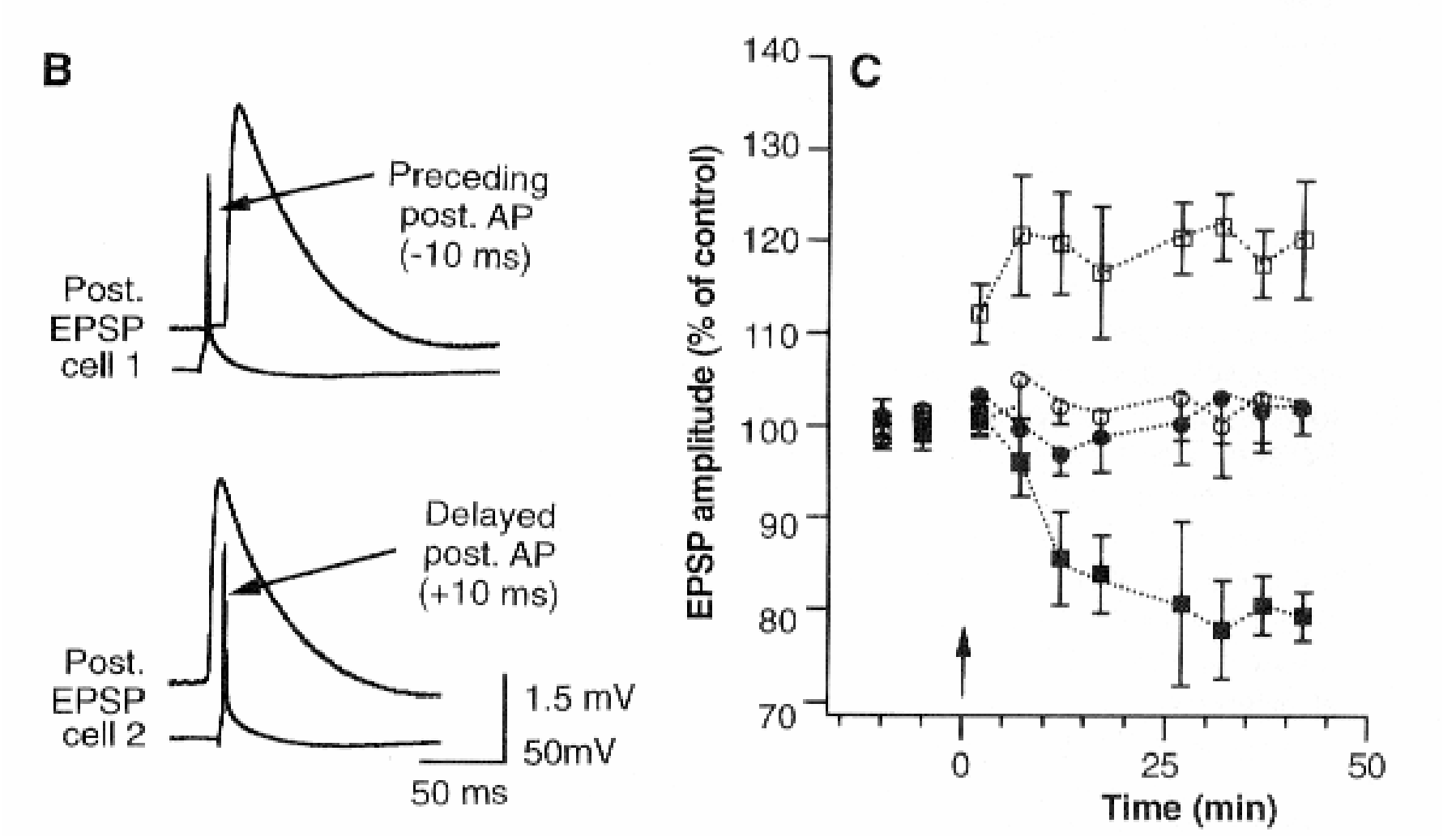
Malenka and Siegelbaum, 2001



SERENA M. DUDEK AND MARK F. BEAR*
Proc. Natl. Acad. Sci. USA
Vol. 89, pp. 4363–4367, May 1992

FIG. 2. Normalized averages of experiments in which 900 pulses were delivered at different frequencies. (*A*) 3 Hz, *n* = 5. (*B*) 10 Hz

Dudek and Bear, 1992



Markram et al., 1997

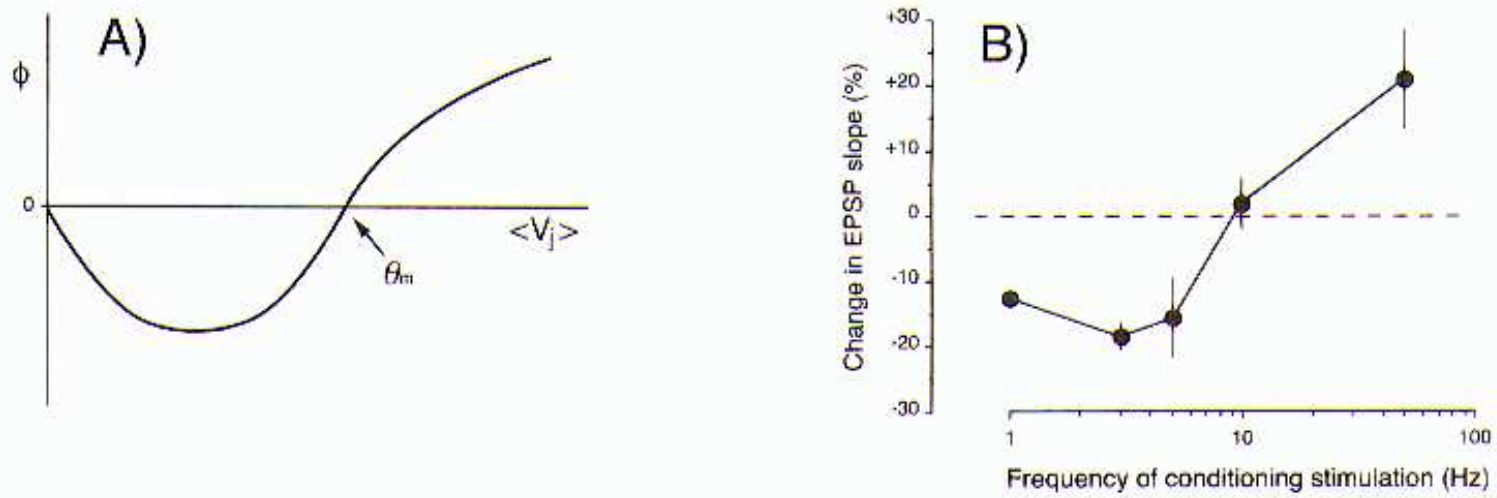
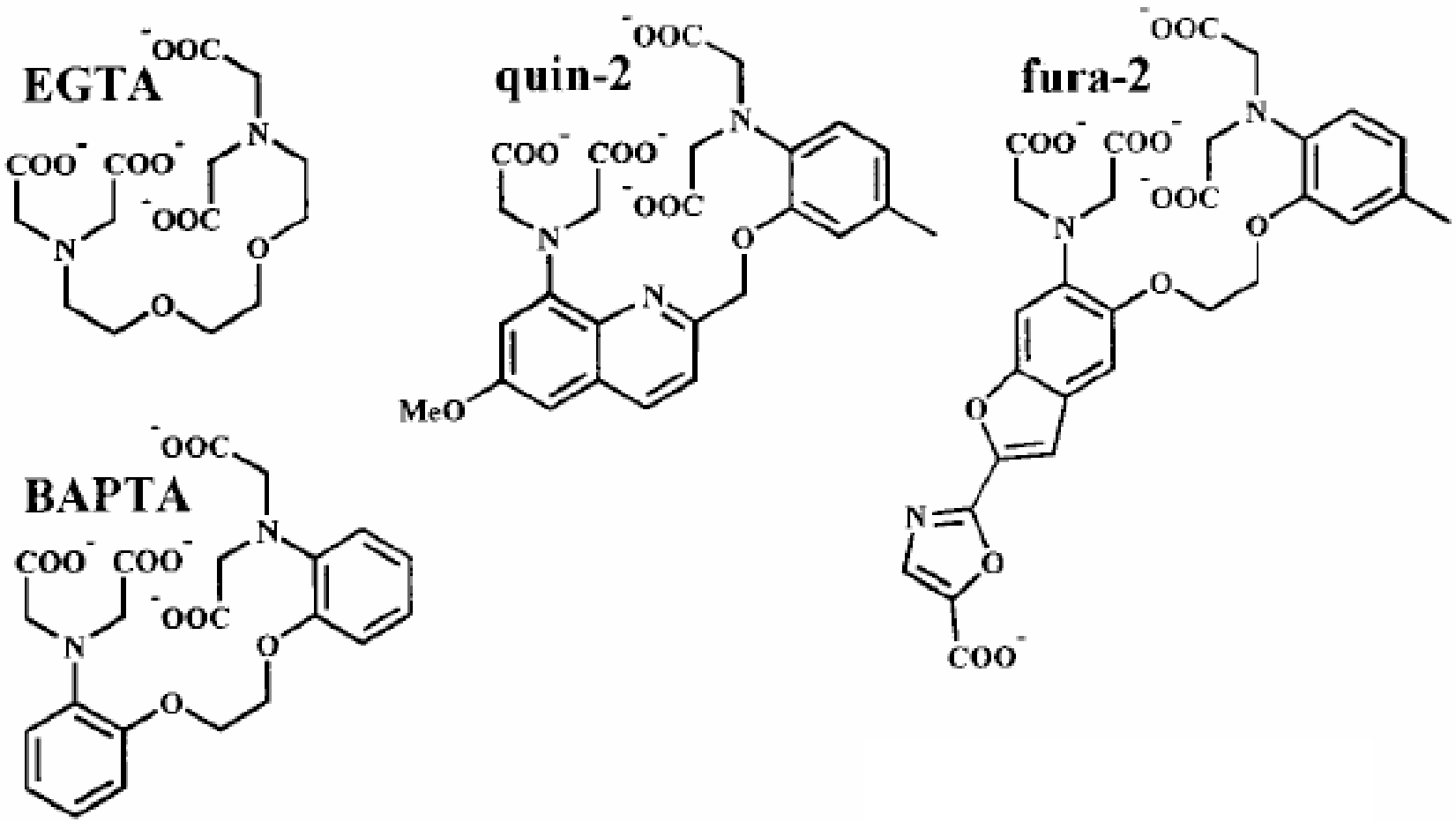


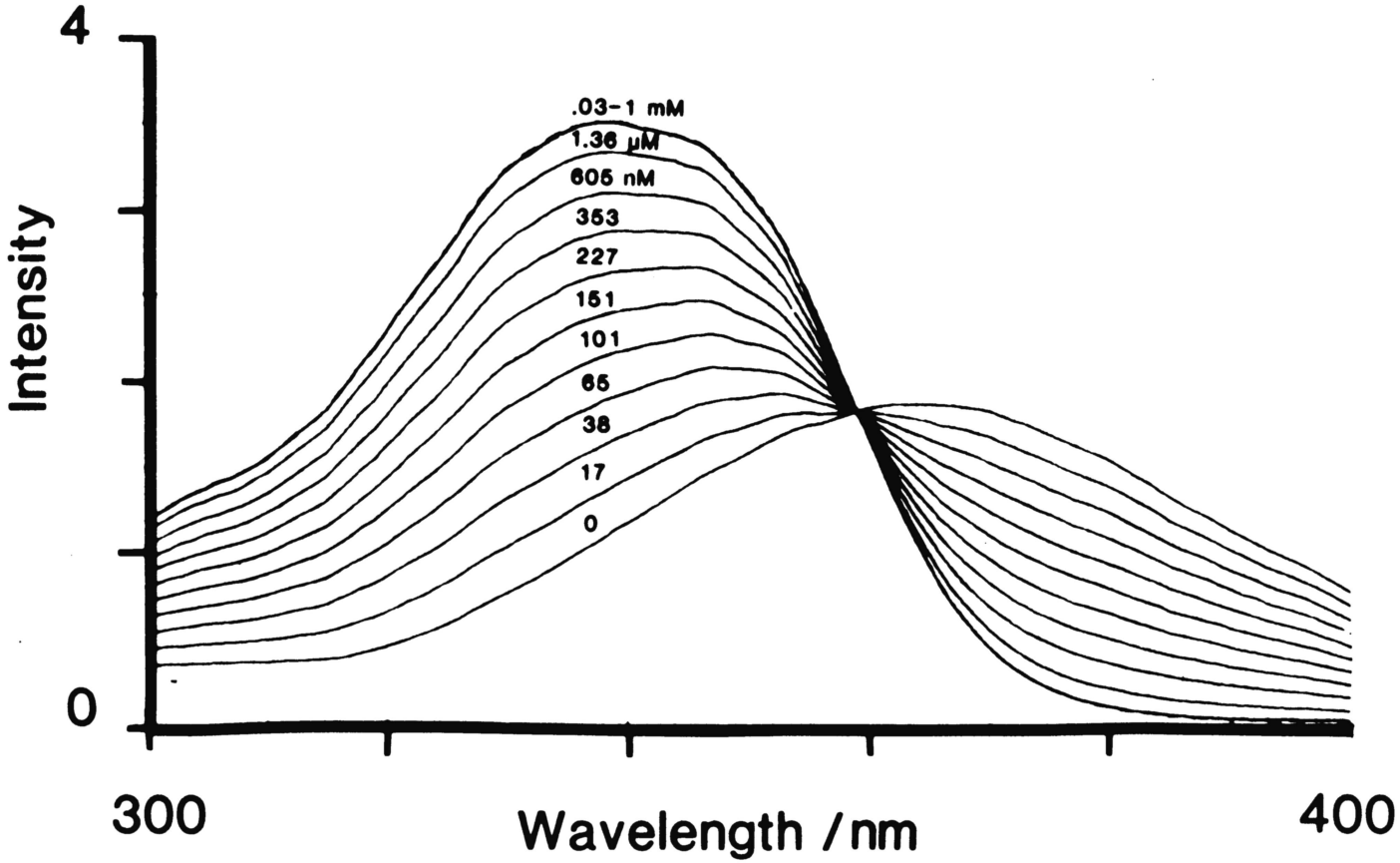
Fig. 13.7 "SLIDING THRESHOLD" THEORY OF SYNAPTIC LEARNING The Bienenstock, Cooper, and Munro (1982) learning rule, proposed within the context of developmental learning, is a Hebbian rule with a twist. The synaptic weight change is proportional to the product of the presynaptic activity and a function ϕ (Eq. 13.10). This function depends on the postsynaptic activity in the manner illustrated in **(A)**. A critical feature is the modifiable threshold θ_m: postsynaptic activity less than this threshold causes LTD, while higher activity leads to an increased synaptic weight (LTP). The sliding threshold changes as a supralinear function of the time-averaged postsynaptic activity. **(B)** Direct experimental evidence bolstering the arguments for the existence of ϕ with a similar shape as used in the BCM model (Dudek and Bear, 1992). Here, 900 spikes are generated in the Schaffer collaterals to the CA1 pyramidal cells in a hippocampal slice via electrical stimulation, varying at frequencies between 0.5 and 50 Hz. Presynaptic stimulation frequencies below 10 Hz always lead to a reduction in the slope of the EPSP (relative to baseline), that is, in LTD, which persists without any sign of recovery for at least one hour. Higher stimulation frequencies lead to LTP. These effects are dependent on NMDA receptor activation. Reprinted by permission from Dudek and Bear (1992).

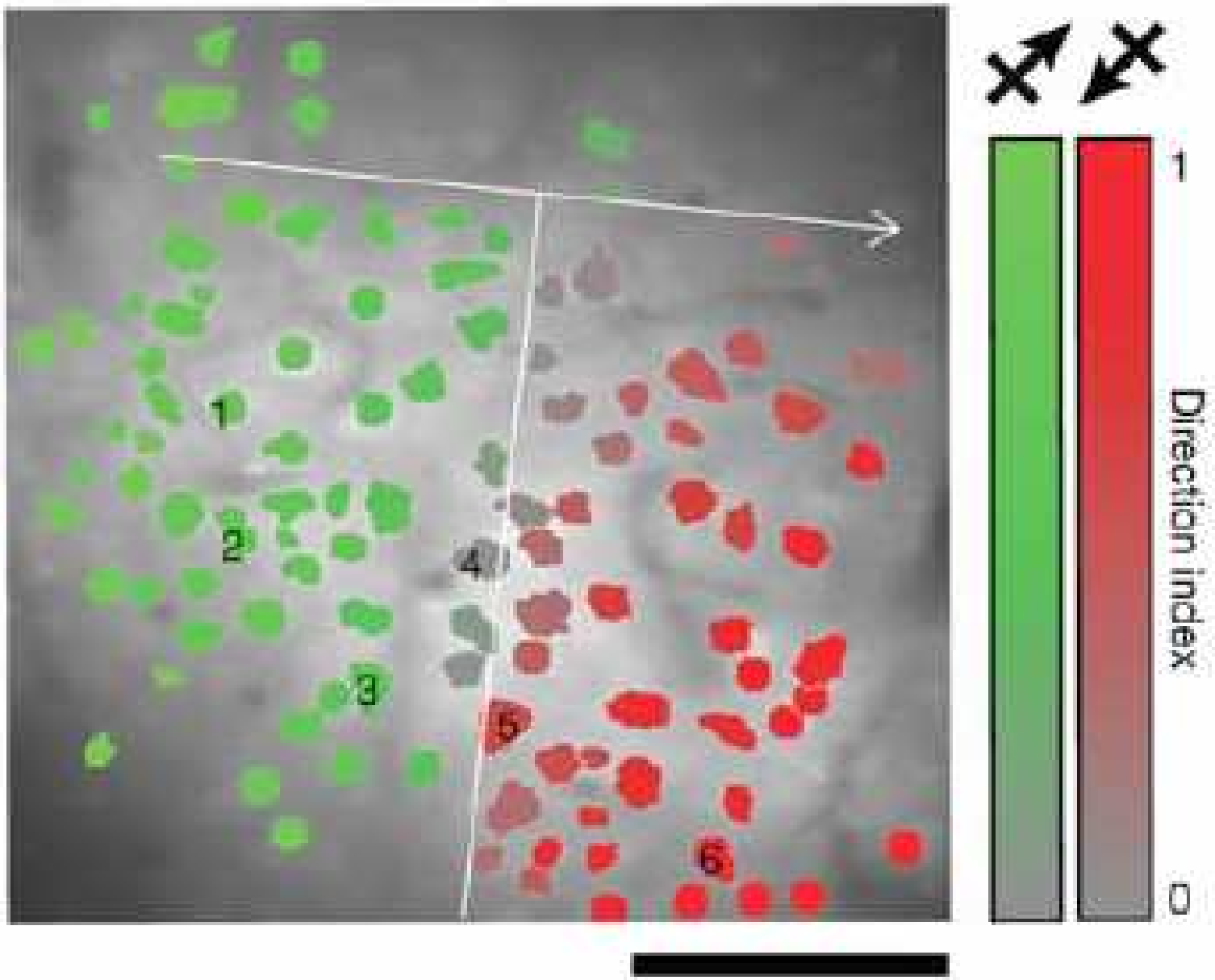
Koch, Biophysics of computation, 1999



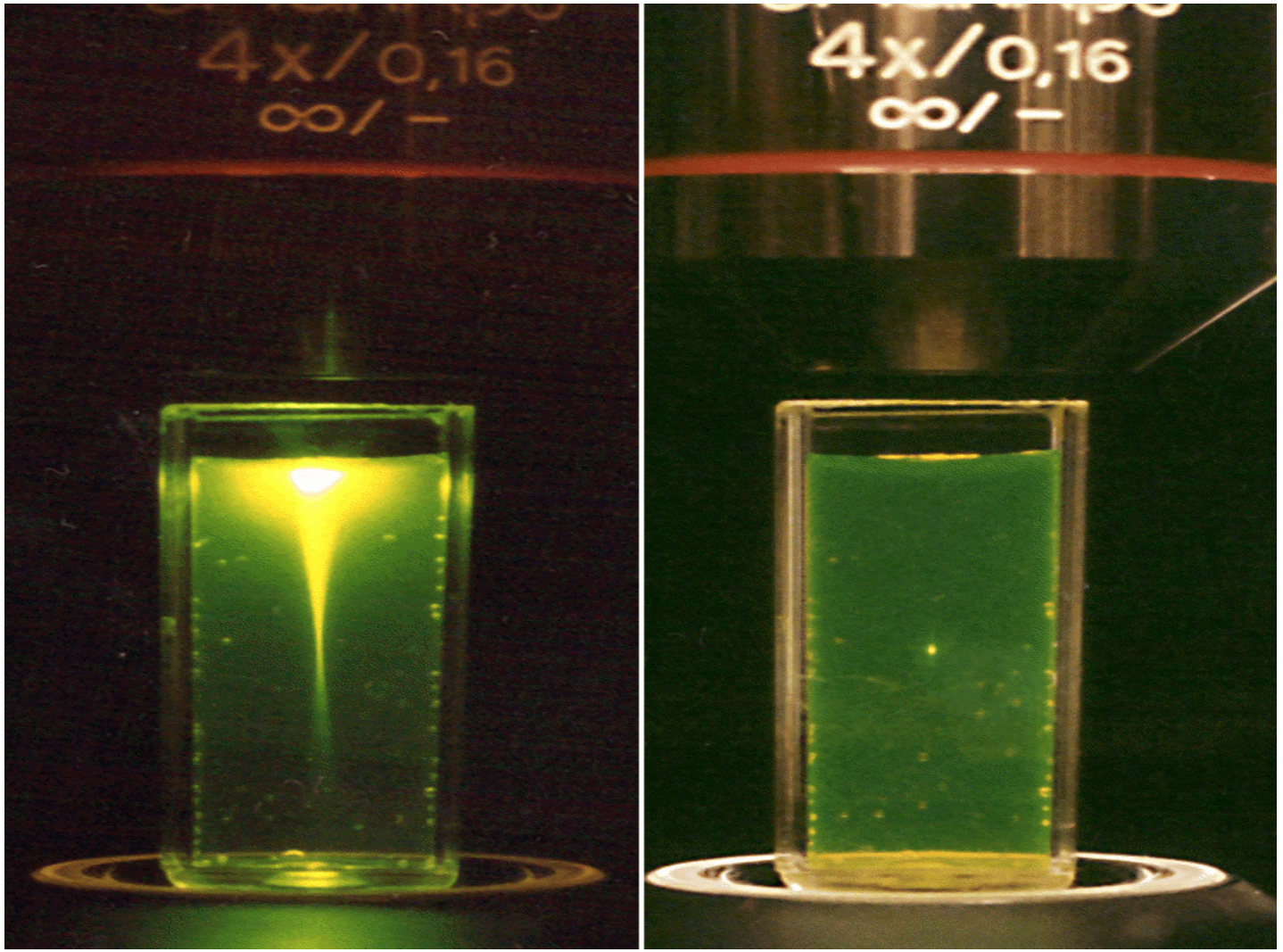
Ca indicators

Fura2 excitation spectrum

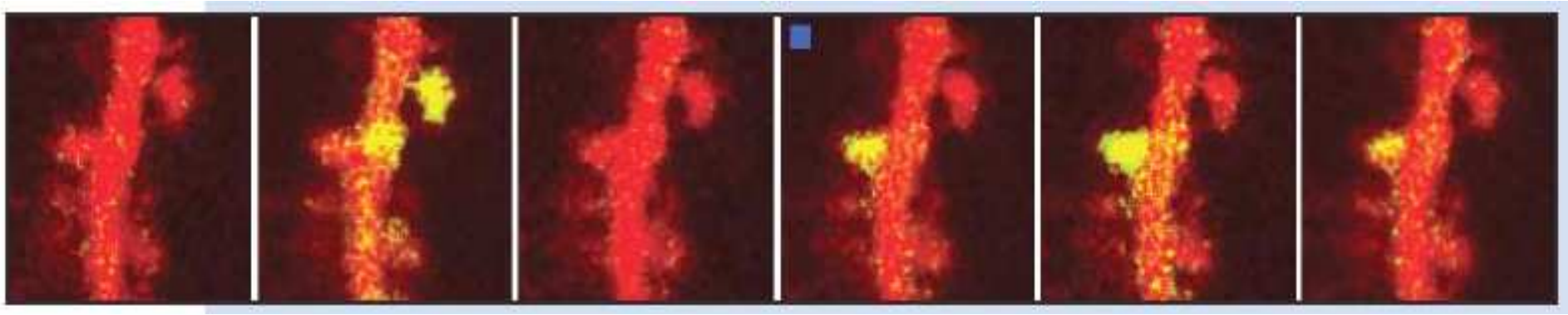




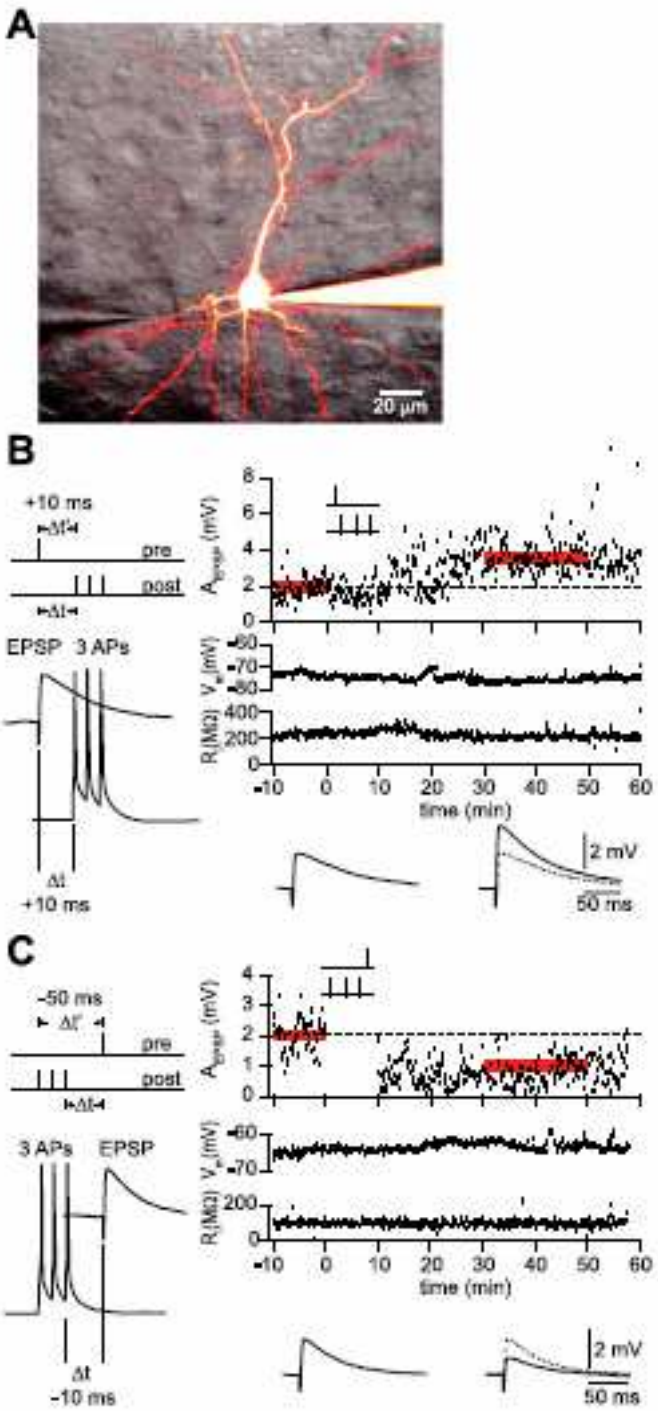
Ohki et al. 2005



2-photon: principle (Webb)

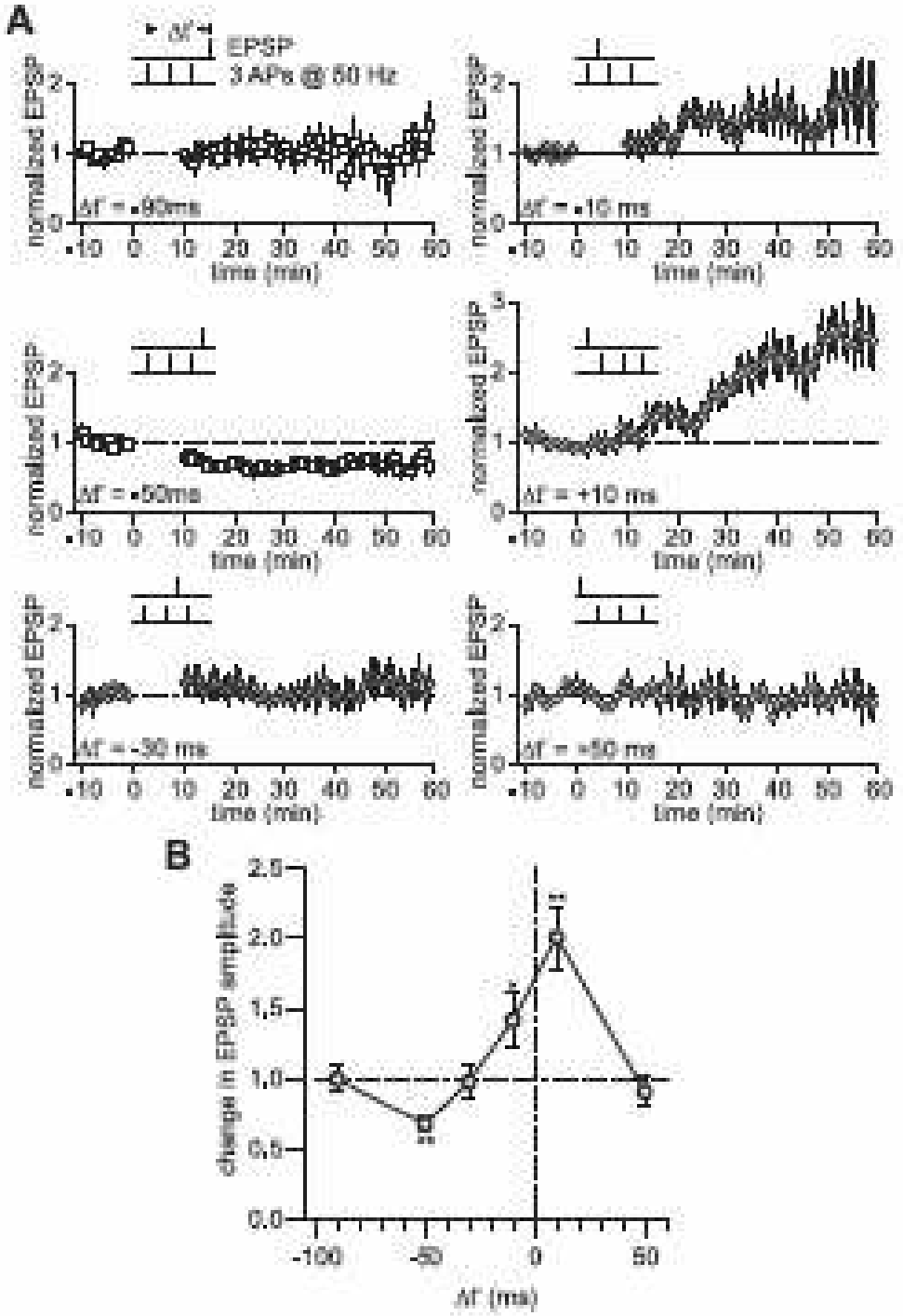


2-photon : spines
Svoboda

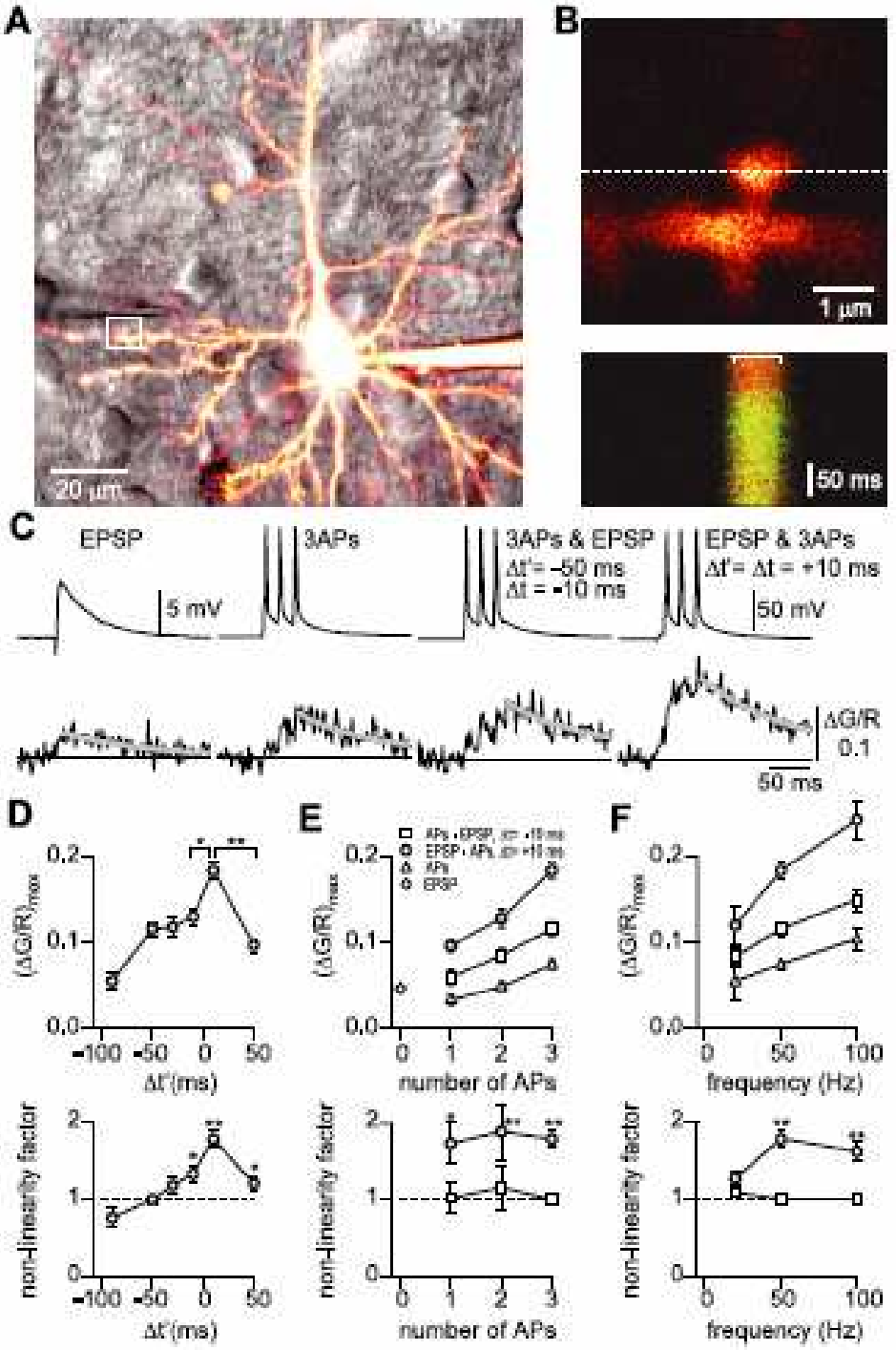


Nevian and Sakmann

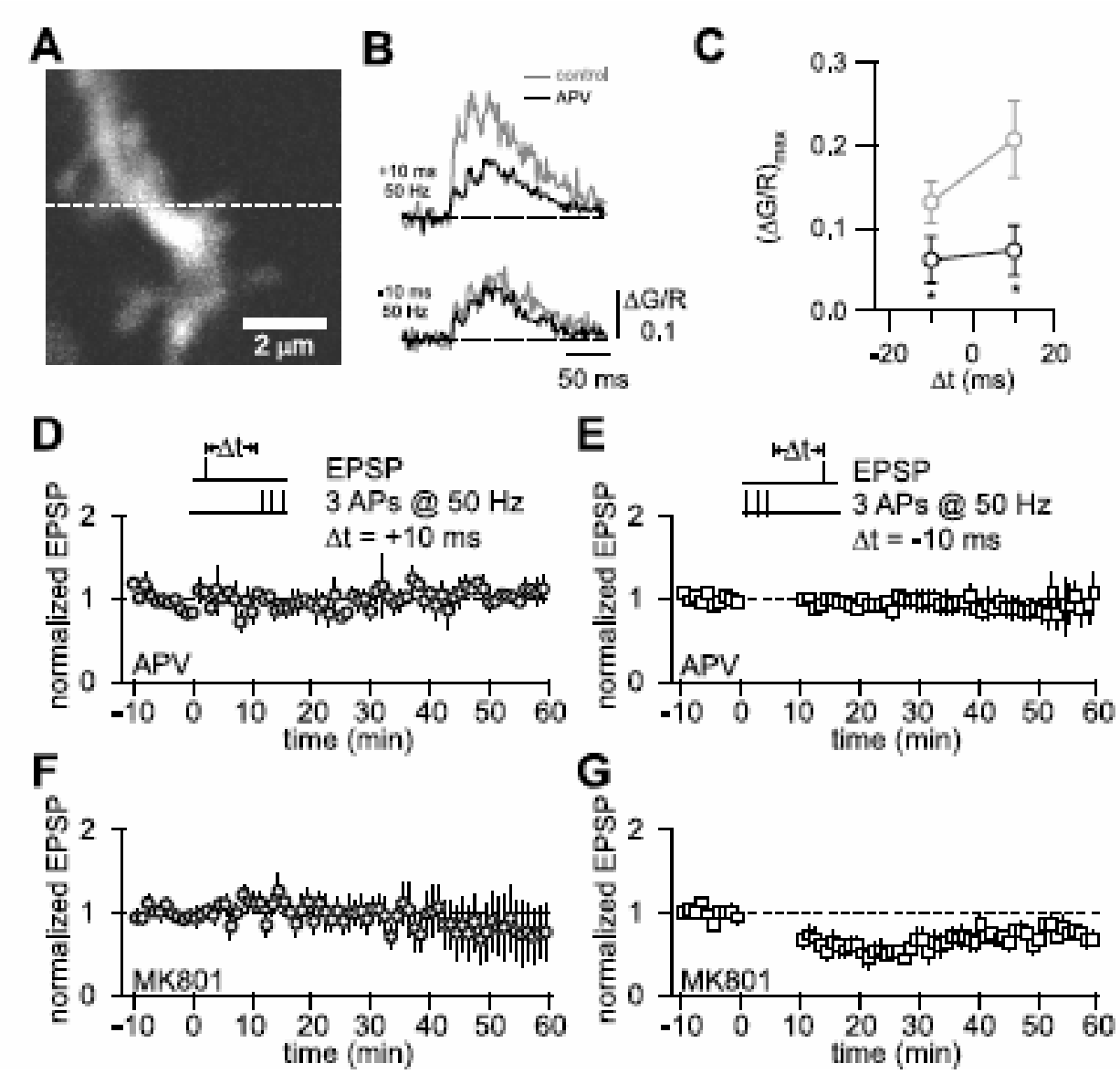
2006 Fig.1



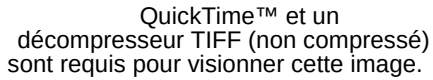
Nevian and Sakmann 2006
Fig. 2



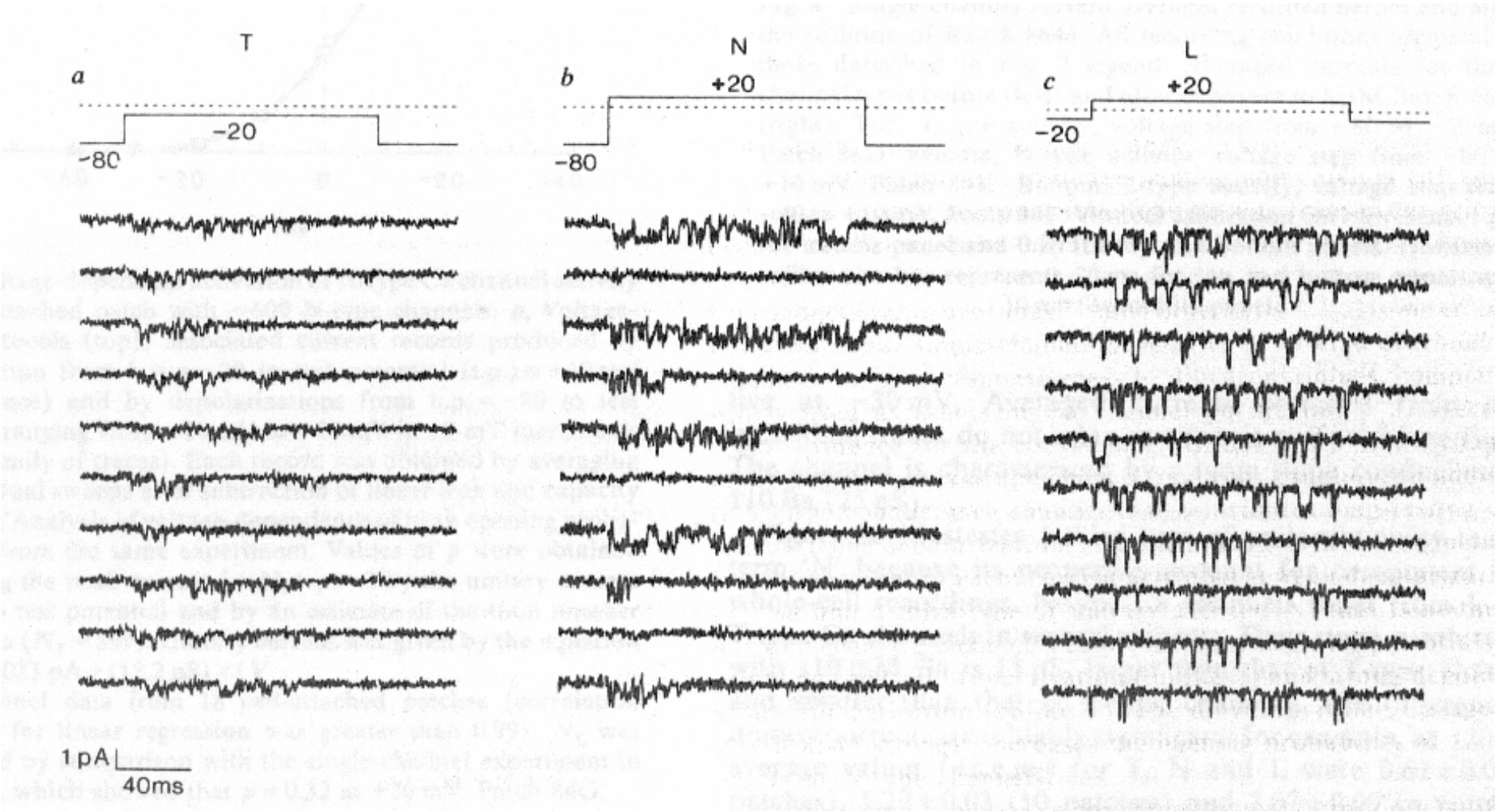
Nevian and Sakmann 2006 Fig.5



Nevian and Sakmann 2006 Fig.6
APV and MK-801

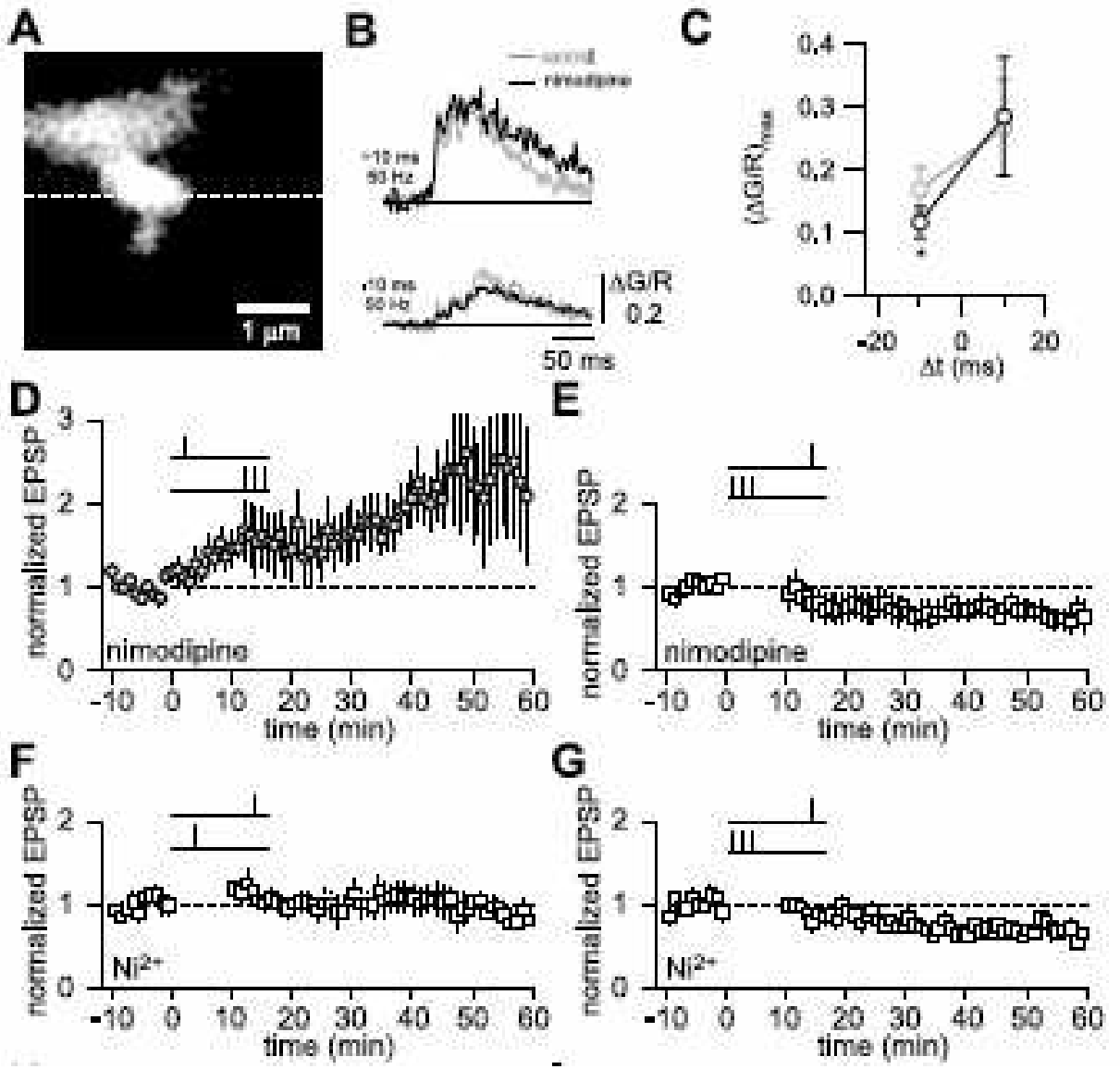


Presynaptic receptors: the sources of the agonists

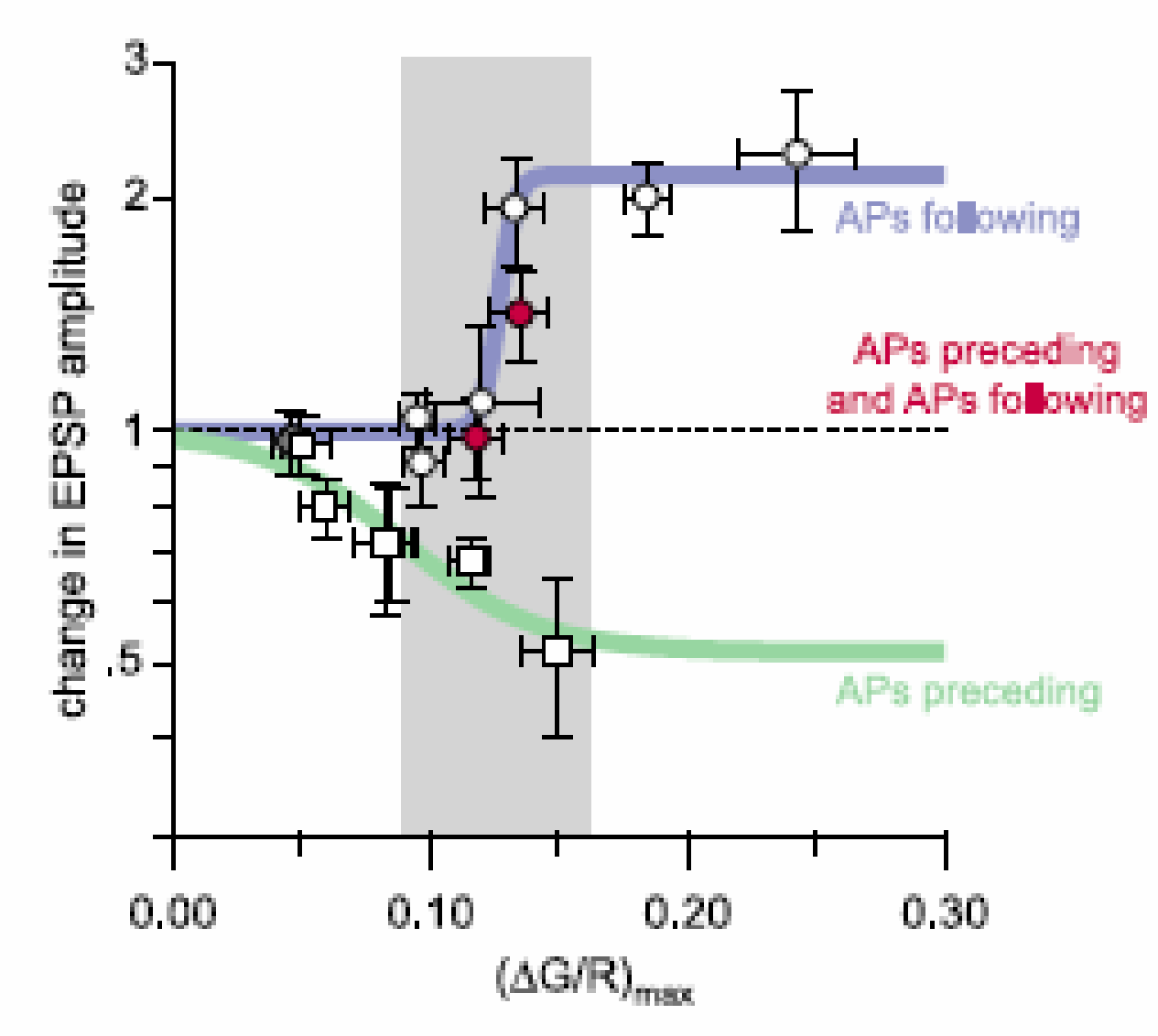


T, N and L channels

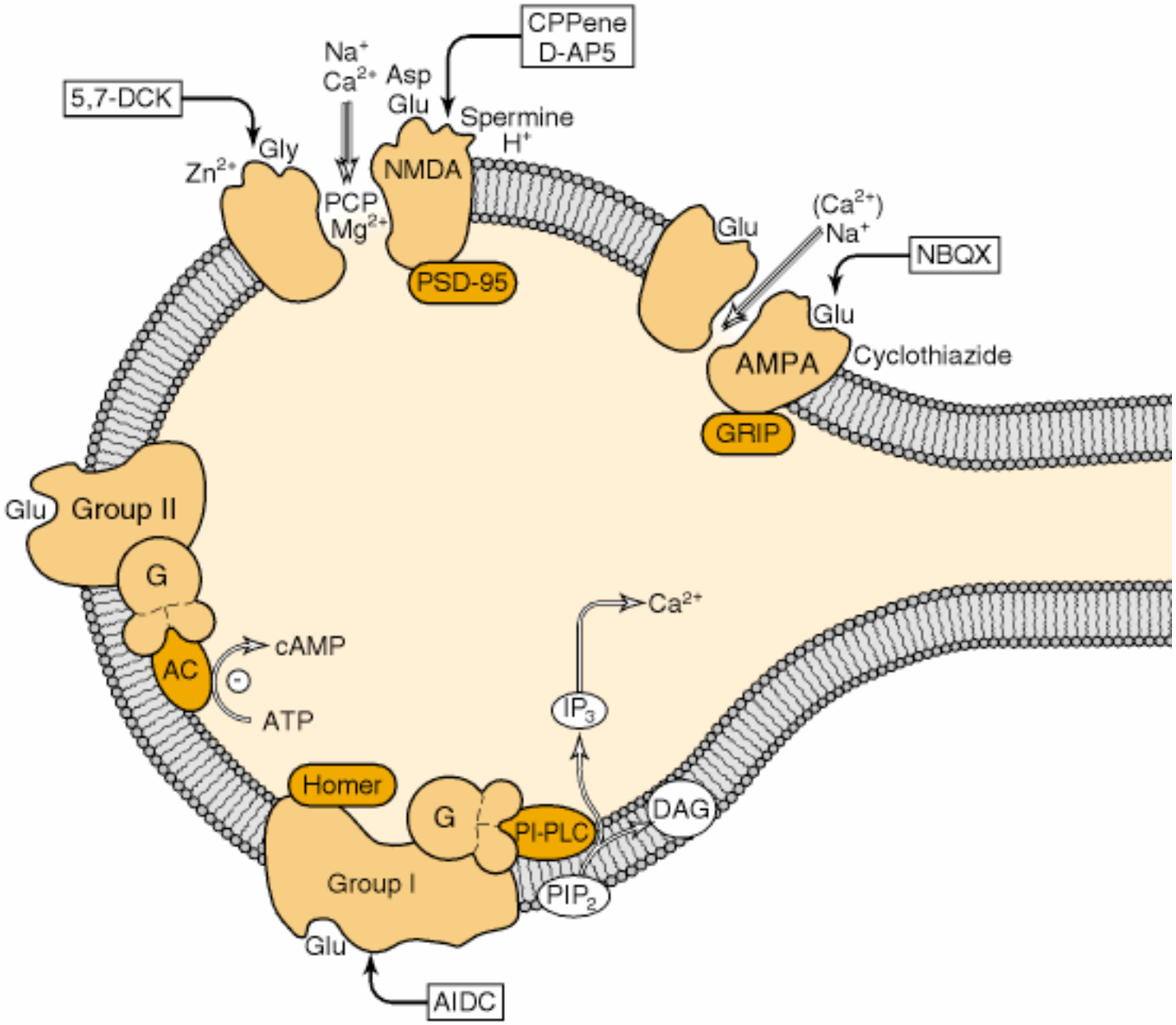
Nowicky, Fox and Tsien, 1985



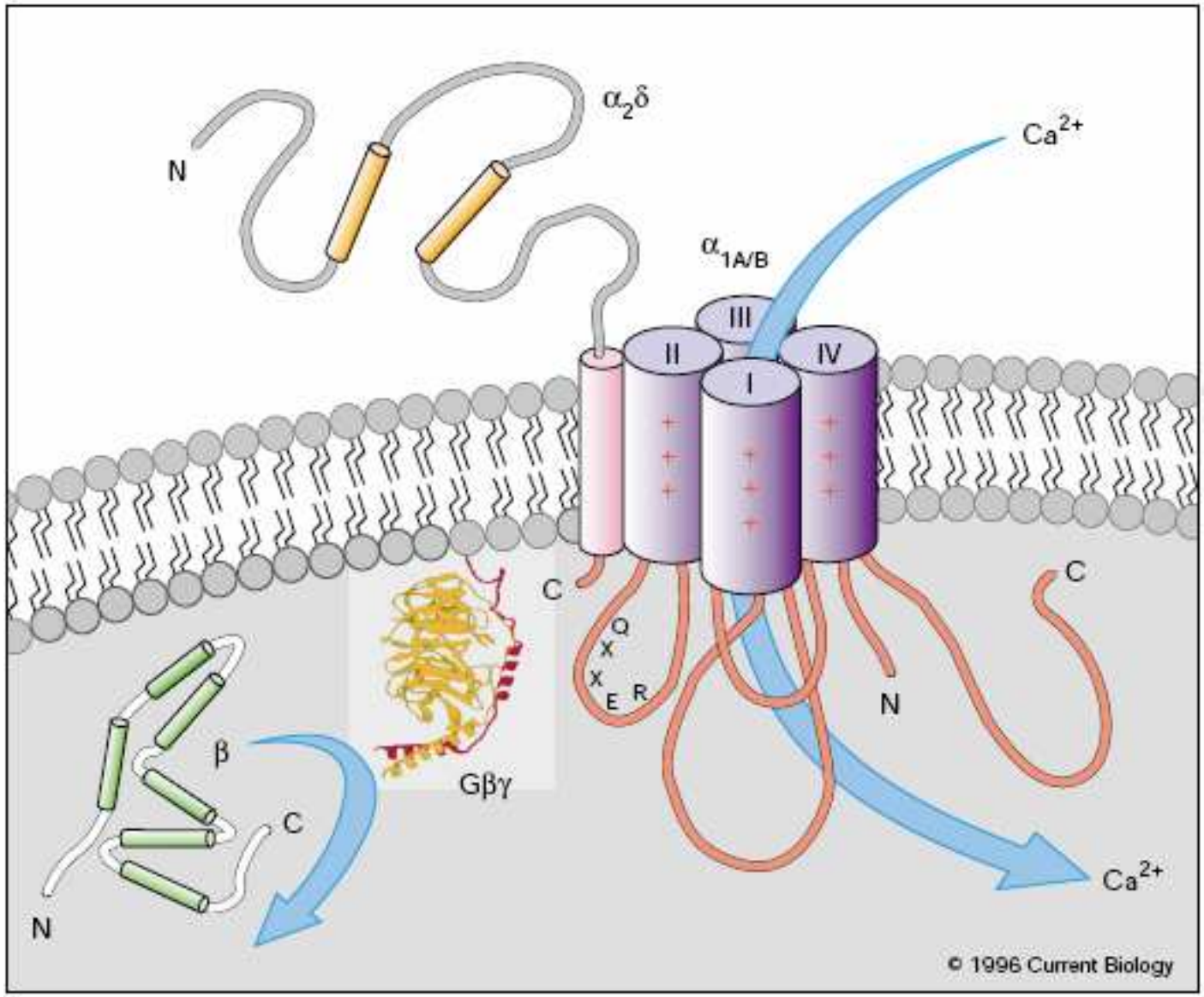
Nevian and
Sakmann 2006
Fig.7 Ni++



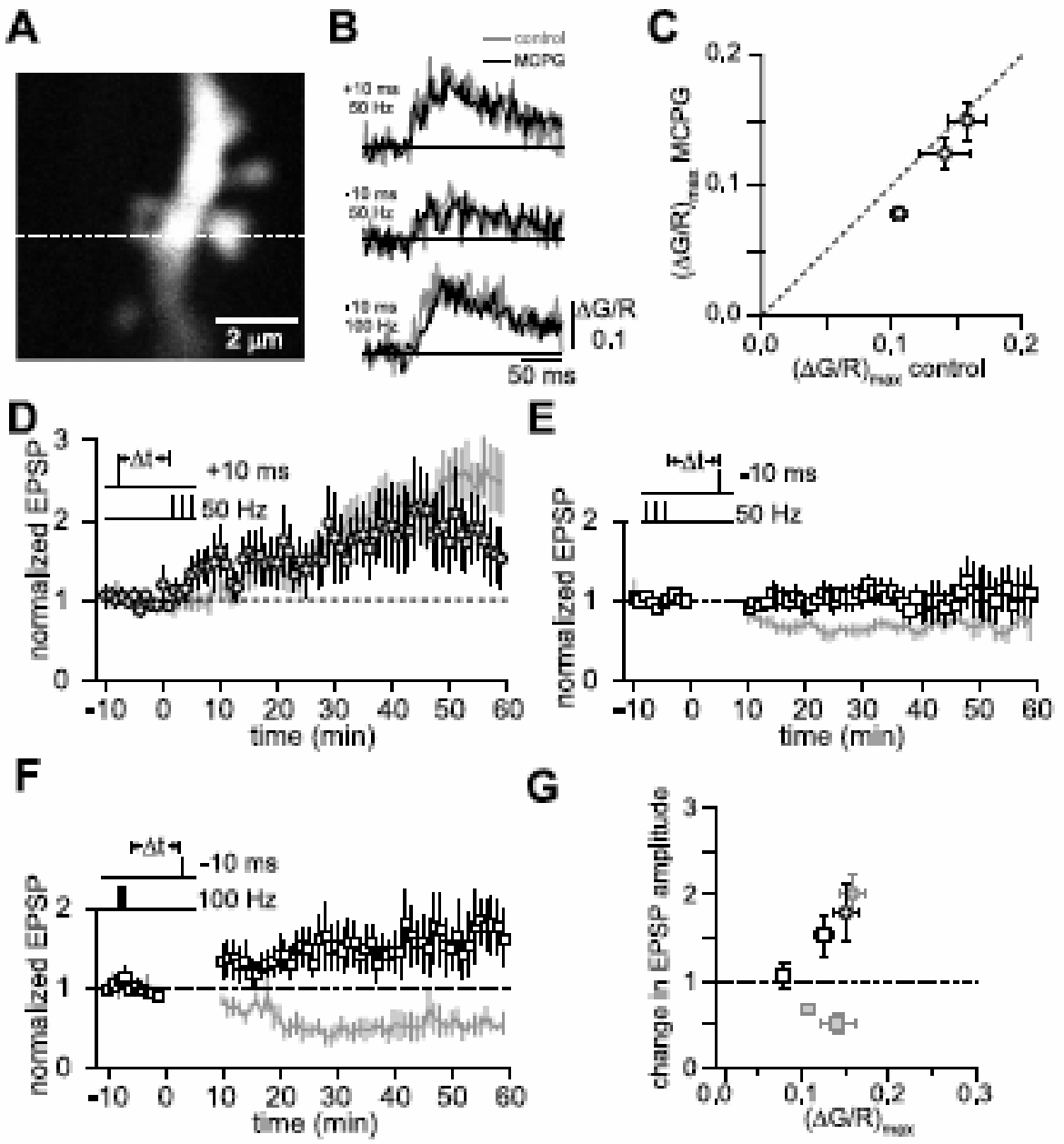
Nevian and Sakmann, 2006 Fig.8



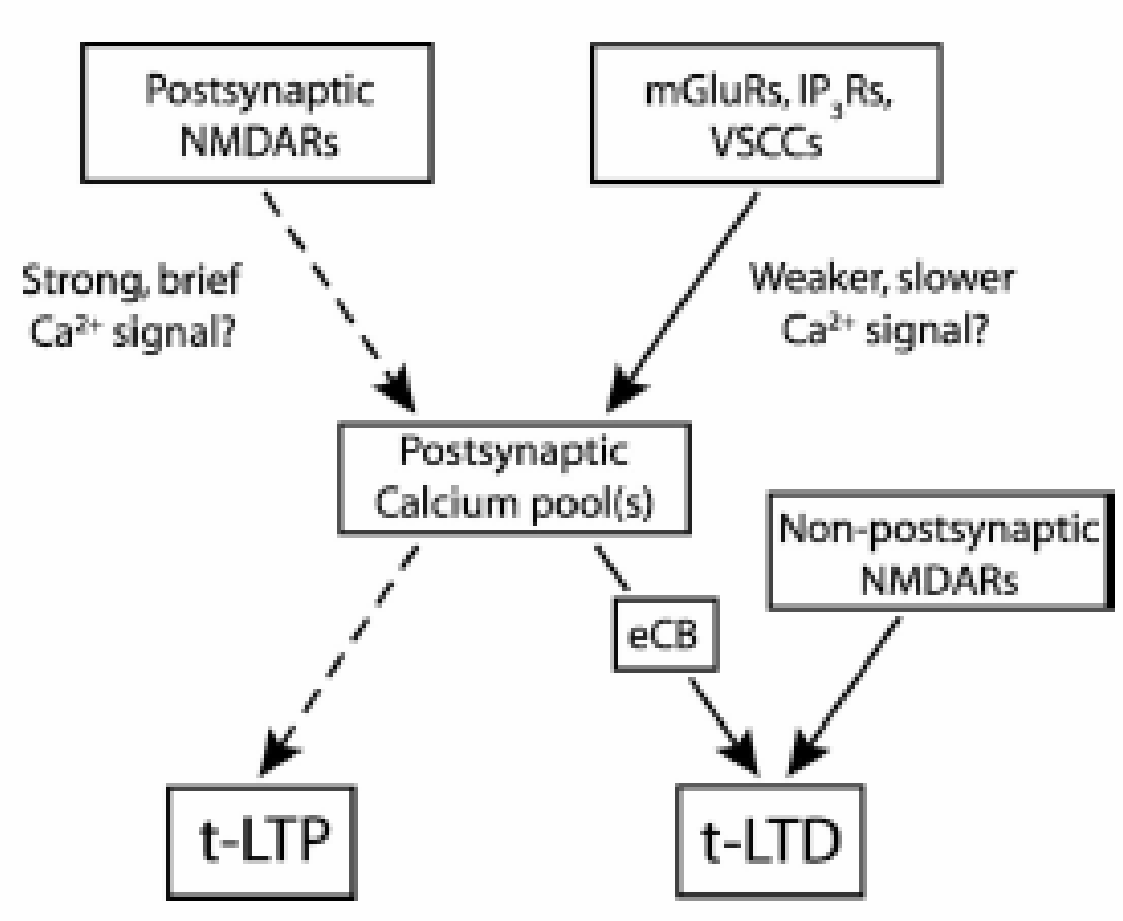
Siegel et al. Basic Neurochemistry Fig. 15-2



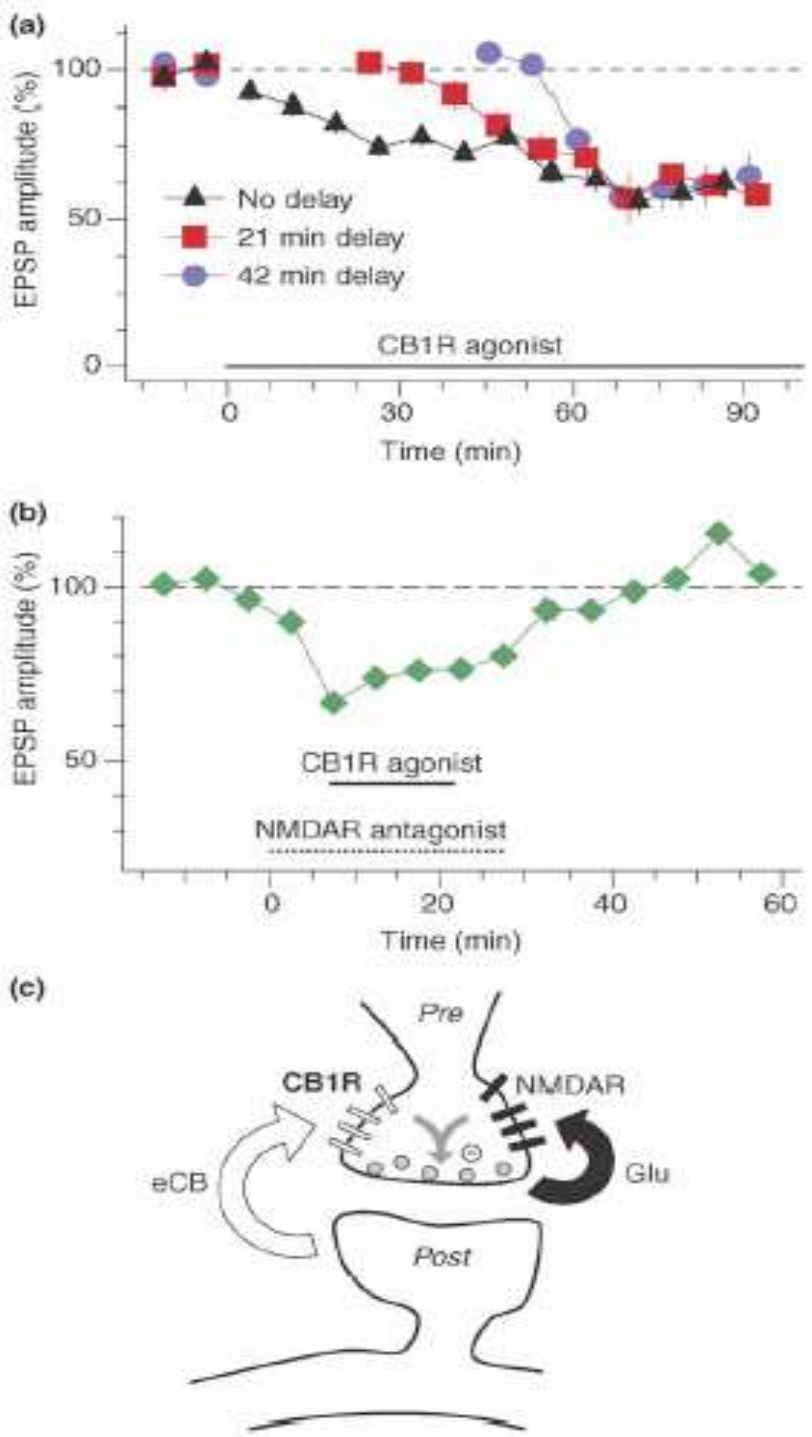
Clapham Current Biology 1996



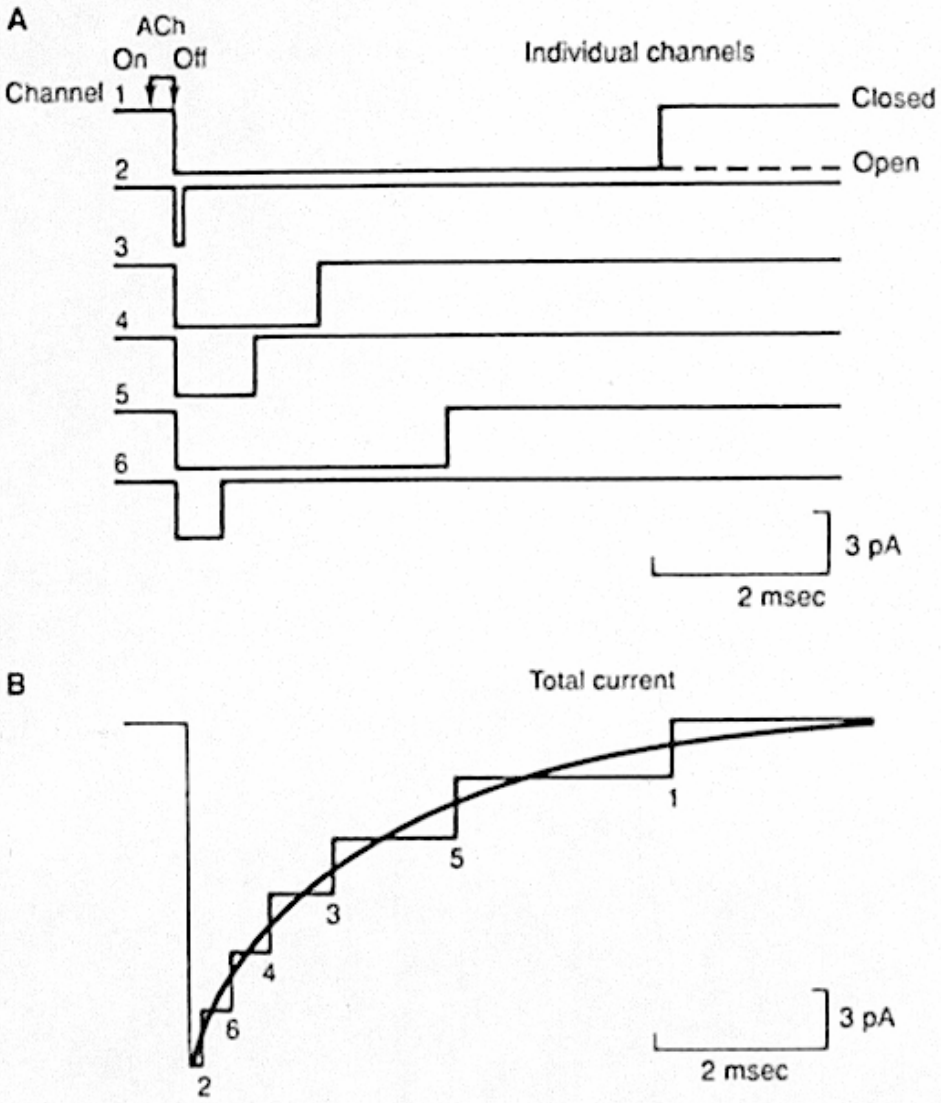
Nevian and Sakmann 2006 Fig.9
MCPG



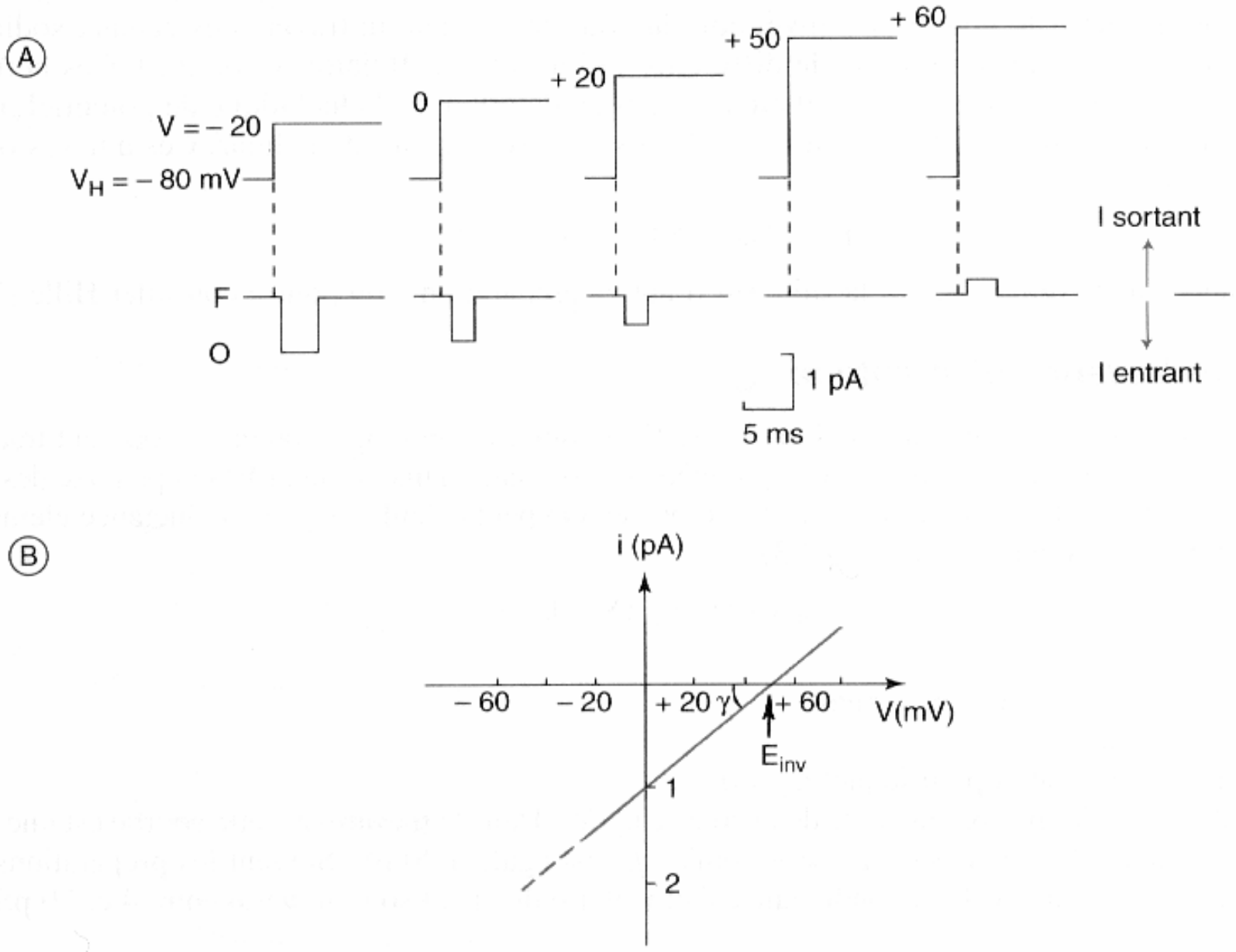
Bender et al. 2006
Two coincidence detectors for STDP



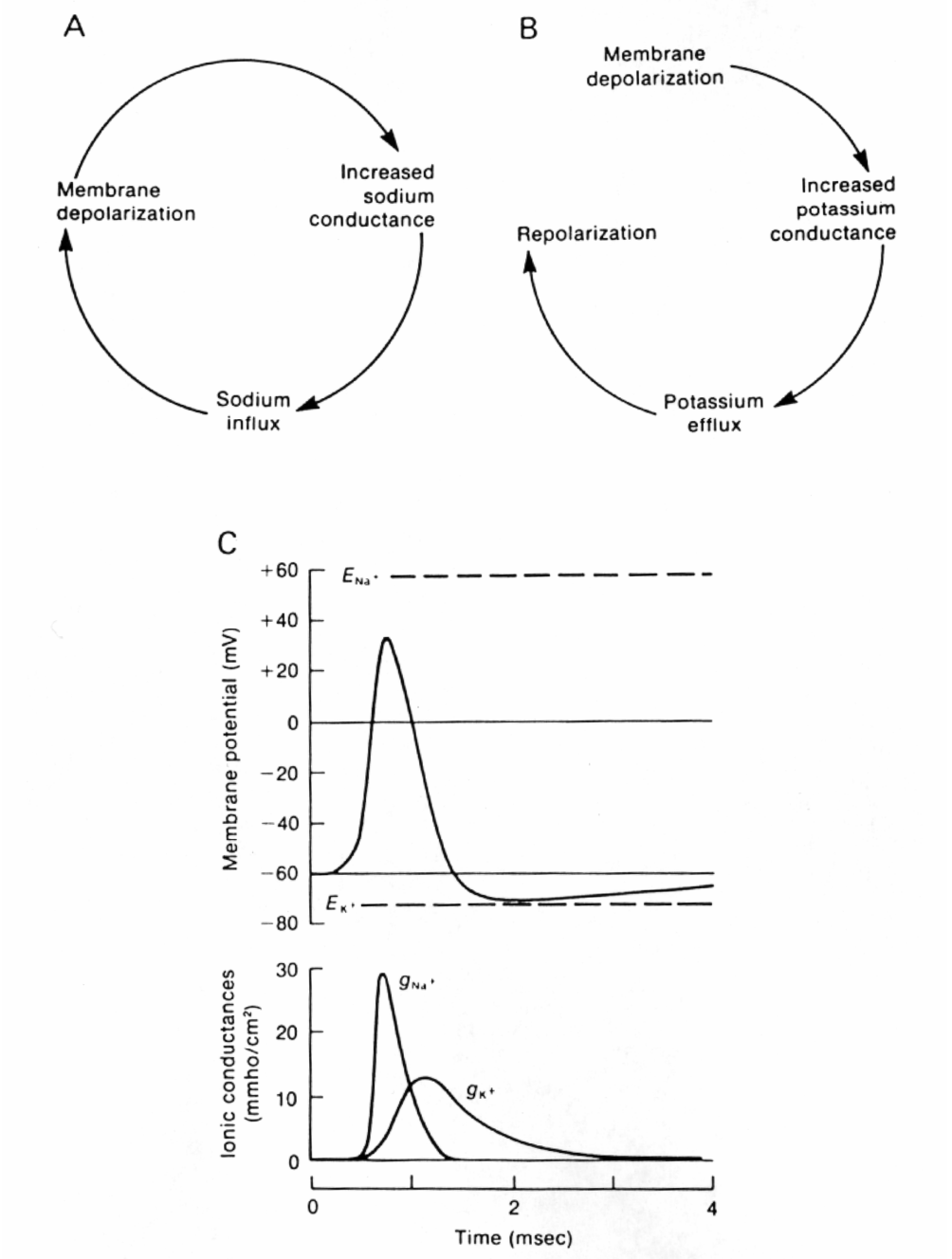
Sjöstrom et al.
2003

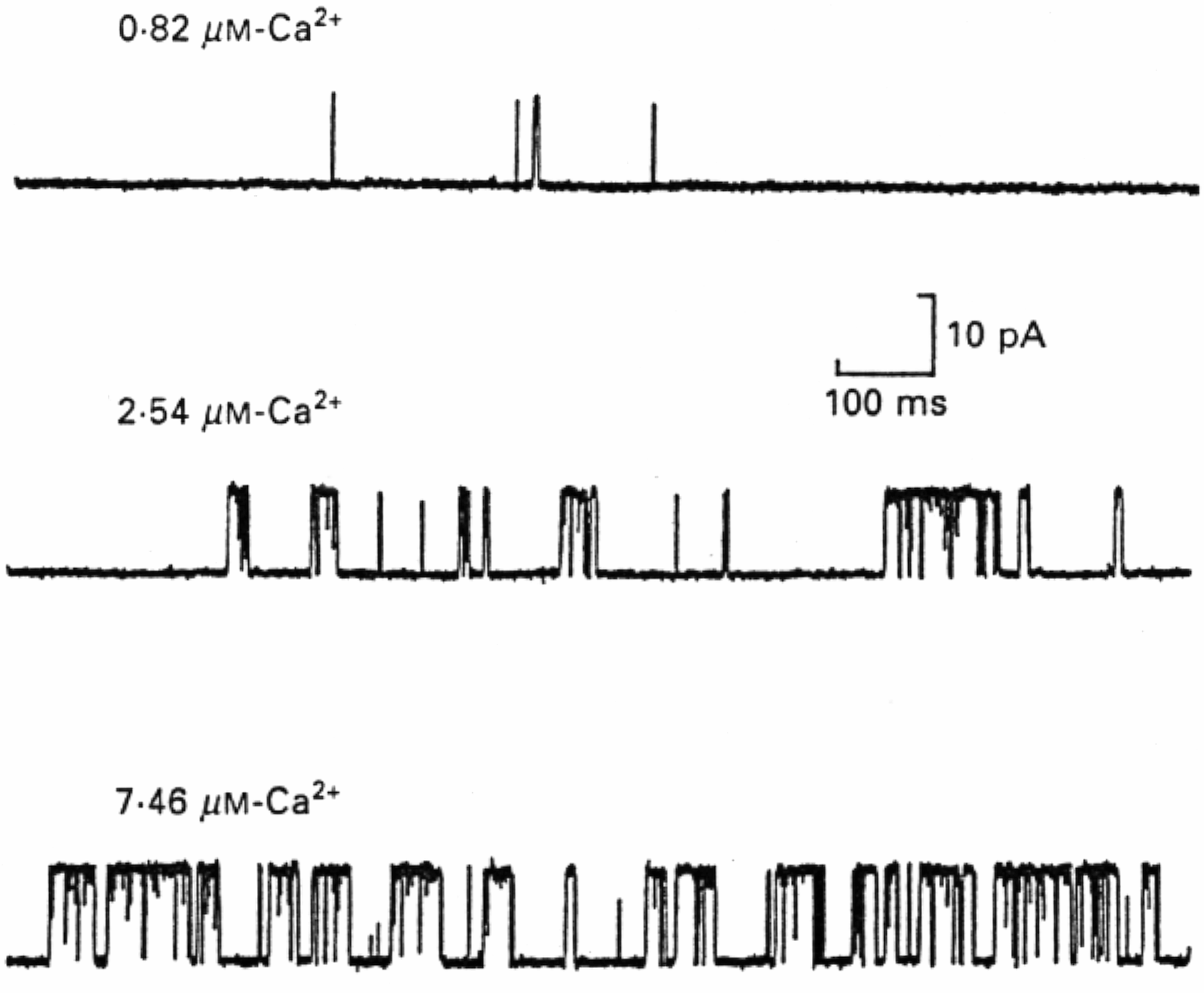


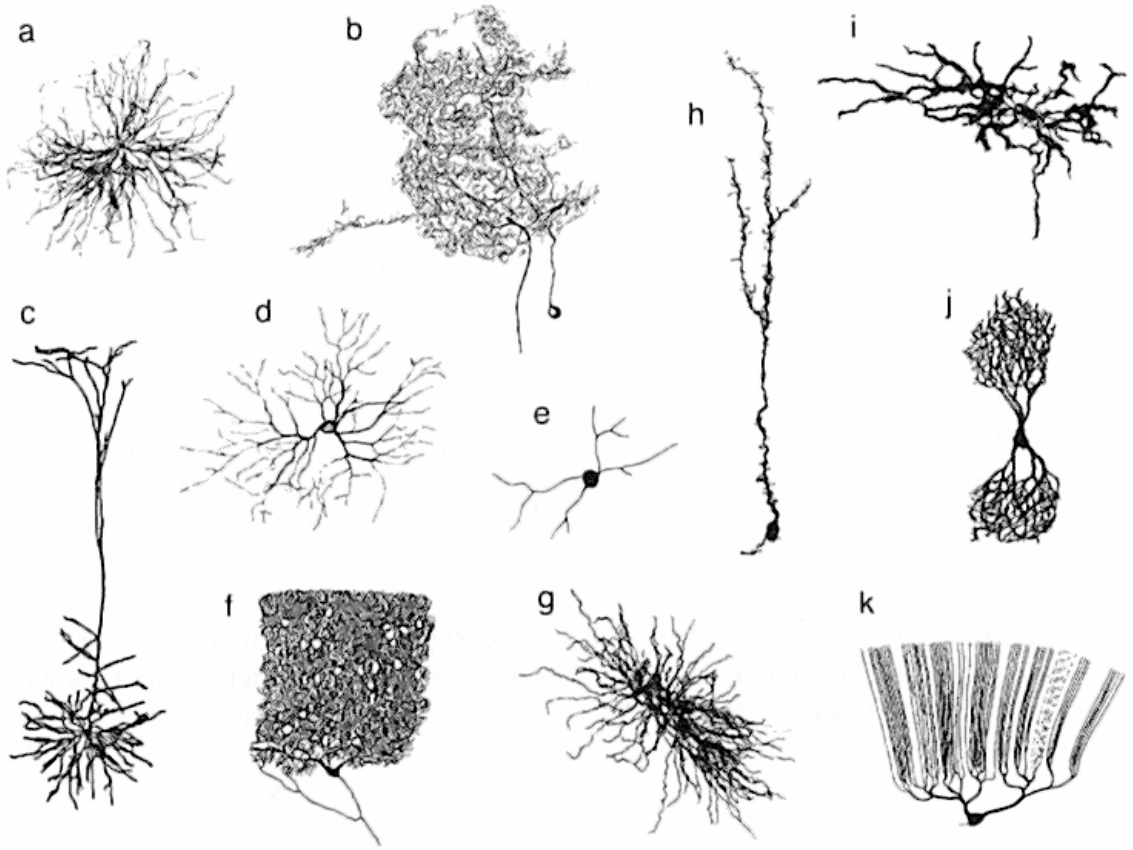
Colquhoun, T.I.P.S., 1981



Tritsch et al., 1998

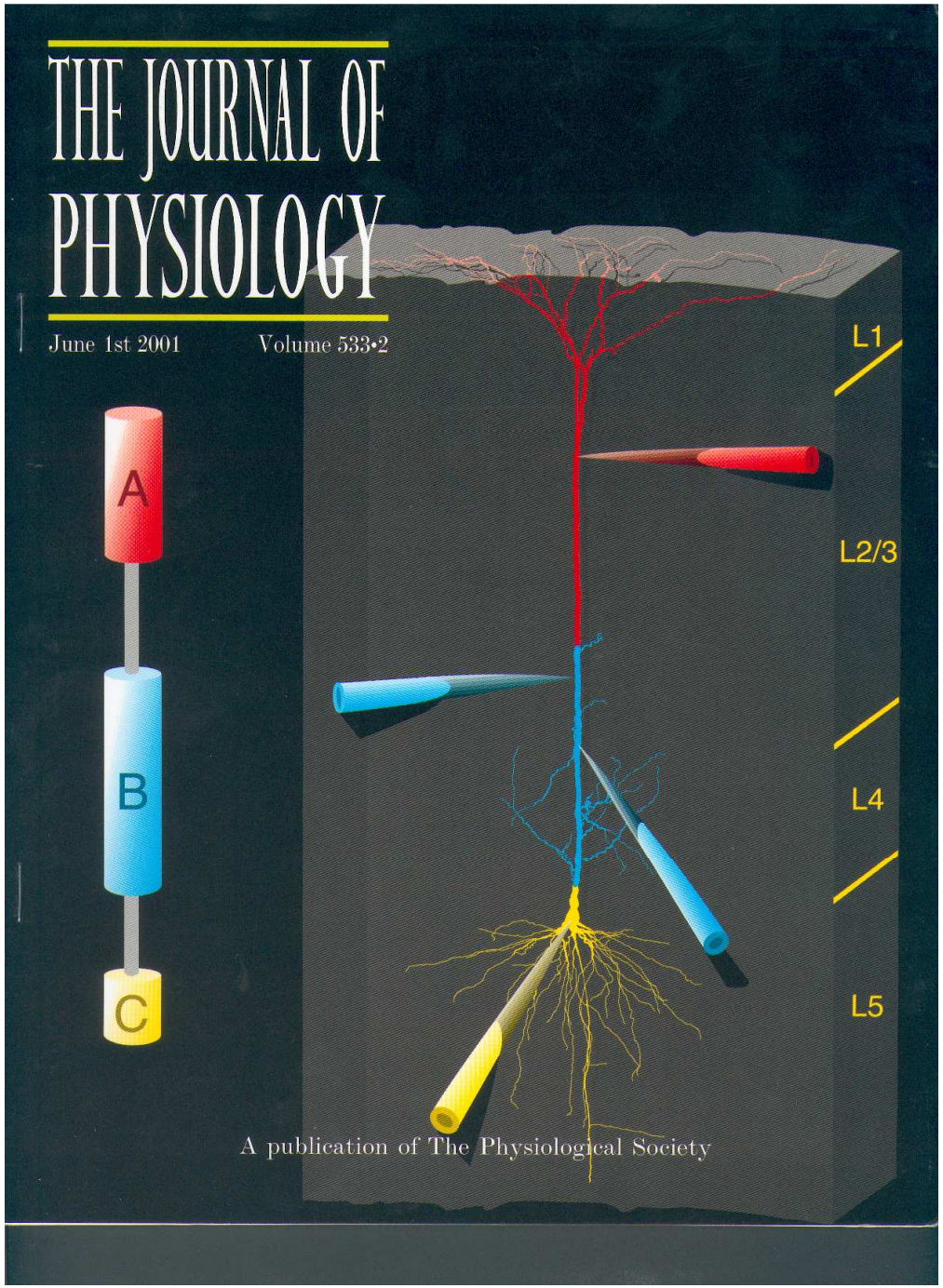

A
Membrane depolarization
Increased sodium conductance
Sodium influx
B
Membrane depolarization
Increased potassium conductance
Potassium efflux
Repolarization
C
Membrane potential (mV)
+60
+40
+20
0
−20
−40
−60
−80
E_{Na^+}
E_{K^+}
Ionic conductances (mmho/cm²)
30
20
10
0
g_{Na^+}
g_{K^+}
0
2
4
Time (msec)


0·82 μM-Ca2+
10 pA
100 ms
2·54 μM-Ca2+
7·46 μM-Ca2+

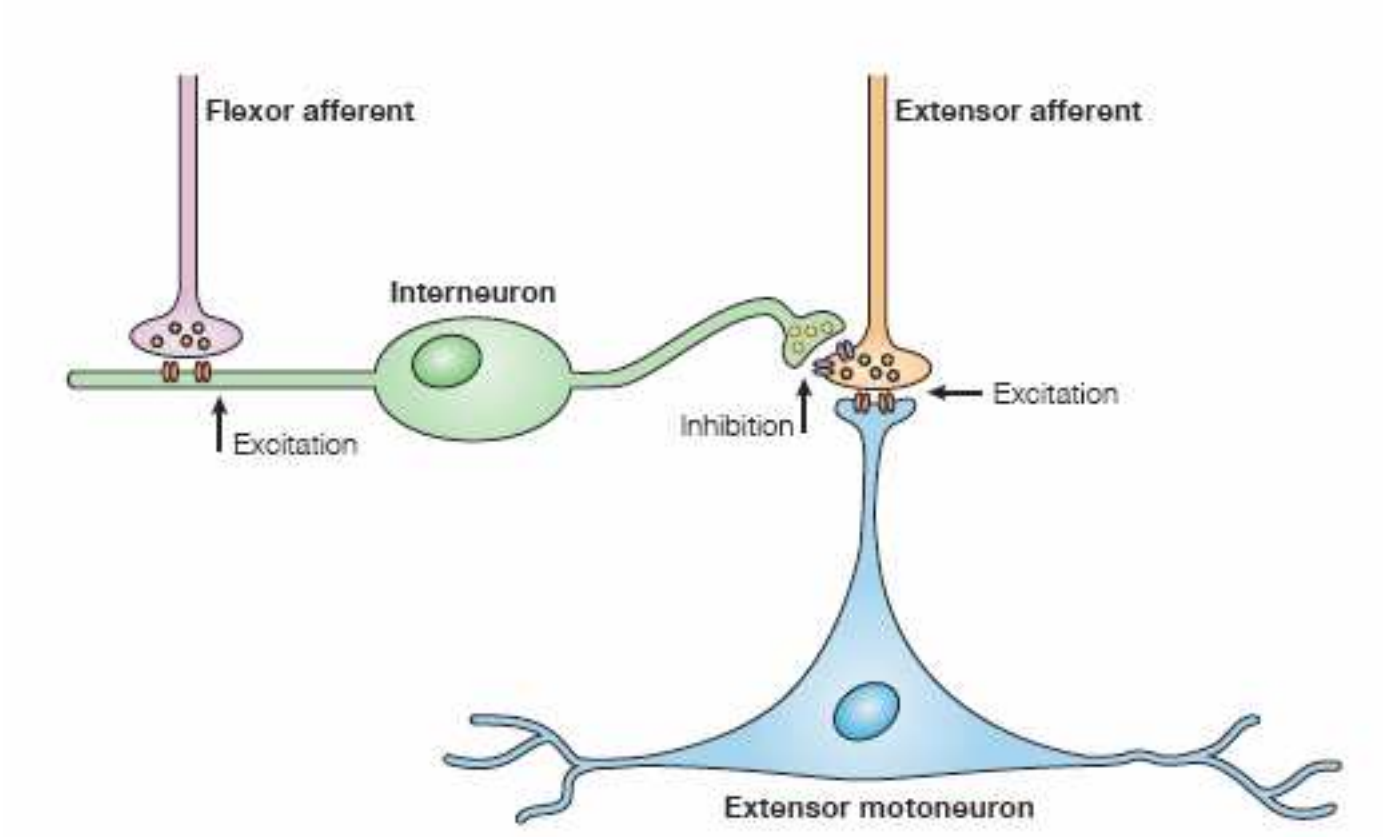


Dendritic trees come in different shapes and sizes. The size of the dendritic tree (largest dimension) is given in brackets. (a) Cat spinal motoneuron (2.6 mm). (b) Locust mesothoracic ganglion spiking interneuron (0.54 mm). (c) Rat neocortical layer 5 pyramidal neuron (1.03 mm). (d) Cat retinal ganglion neuron (0.39 mm). (e) Salamander retinal amacrine neuron (0.16 mm). (f) Human cerebellar Purkinje neuron. (g) Rat thalamic relay neuron (0.35 mm). (h) Mouse olfactory granule neuron (0.26 mm). (i) Rat striatal spiny projection neuron (0.37 mm). (j) Human nucleus of Burdach neuron. (k) Fish Purkinje neuron (0.42 mm). Modified from Mel, B. W. (1994). *Neural Computation*, **6**, 1031–1085.

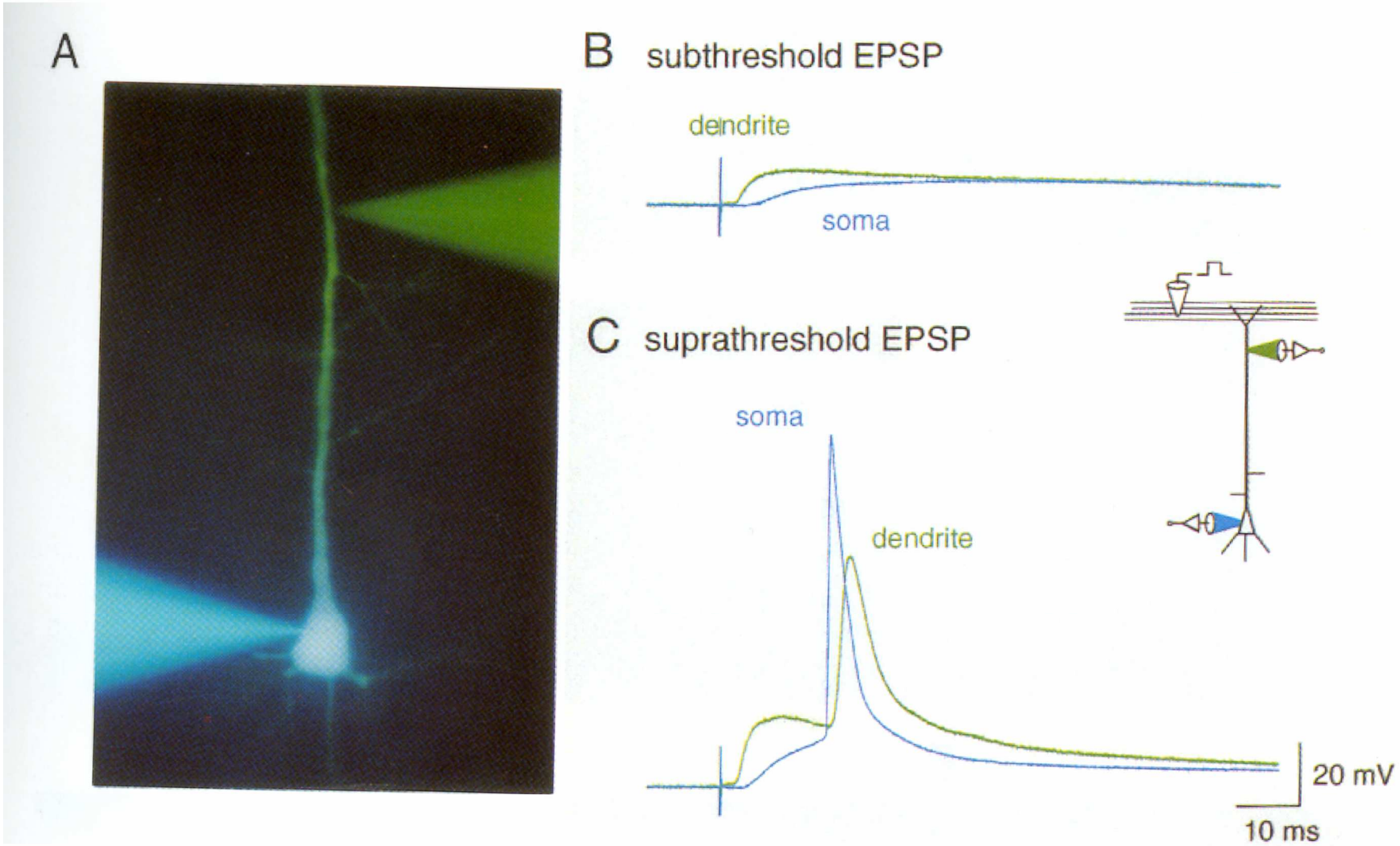
Stuart et al., Dendrites



Larkum, Zhu and Sakmann 2001



Presynaptic inhibition in the spinal cord (Engelman et al., NNR04)



Retropropagation

Camelions