From Science Magazine, 2005

Synaptic Plasticity — Lecture 2

Short-term synaptic plasticity

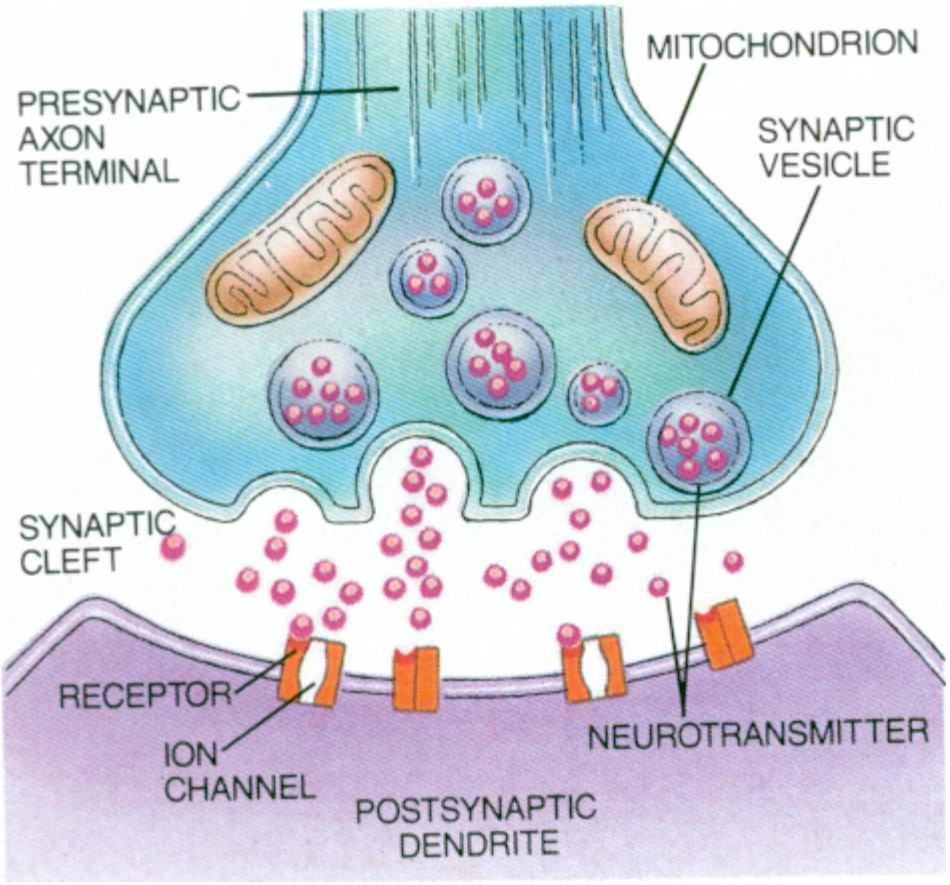
Neuronal Physiology and Plasticity

August 2018 Semester

How short is short?

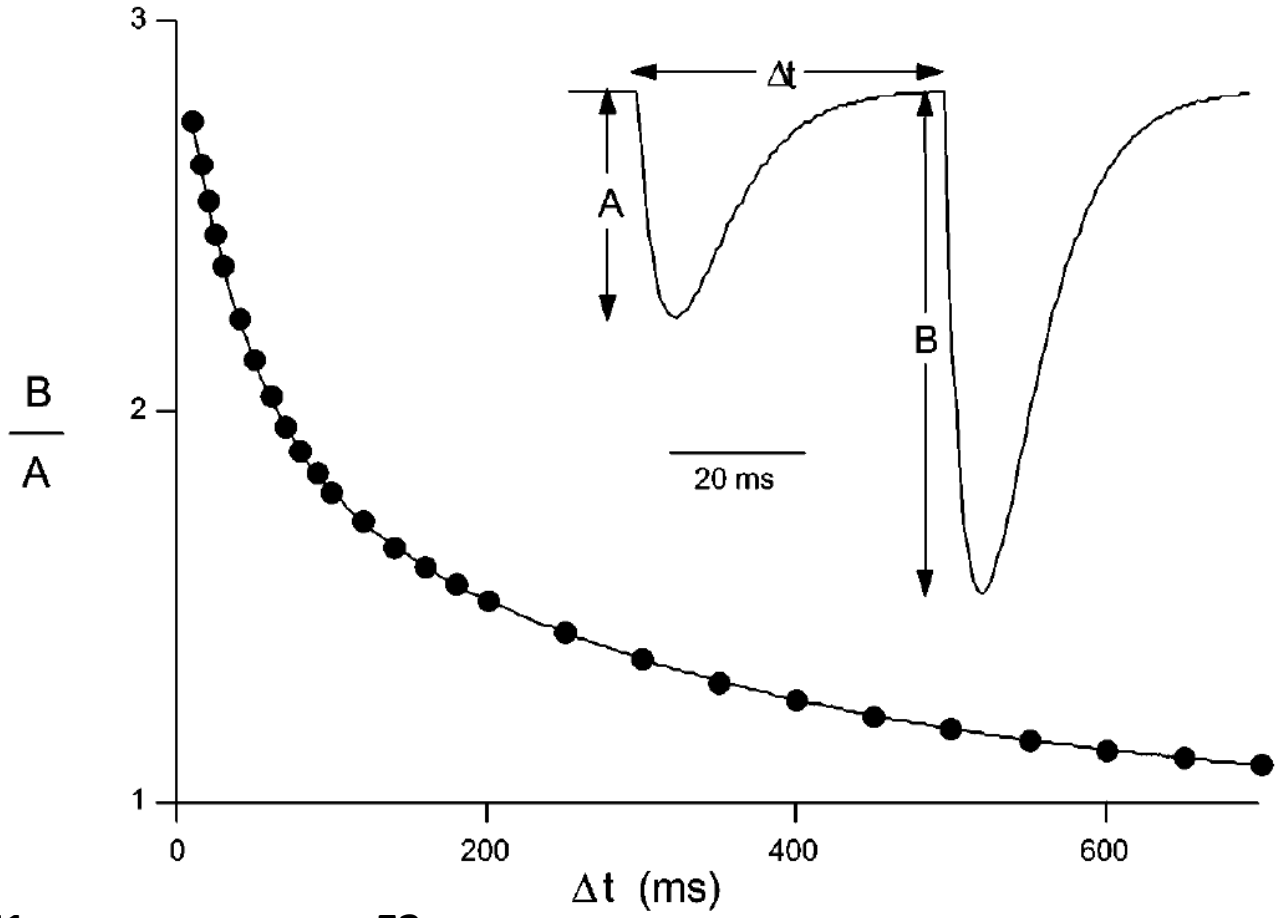
Use-dependent plasticity on the tens of milliseconds to several minutes time scale is usually referred to as short-term plasticity

Most such short-term plasticity mechanisms are presynaptic, rather than postsynaptic



Zucker and Regehr, Ann. Rev. Physiol., 2002

Paired pulse facilitation



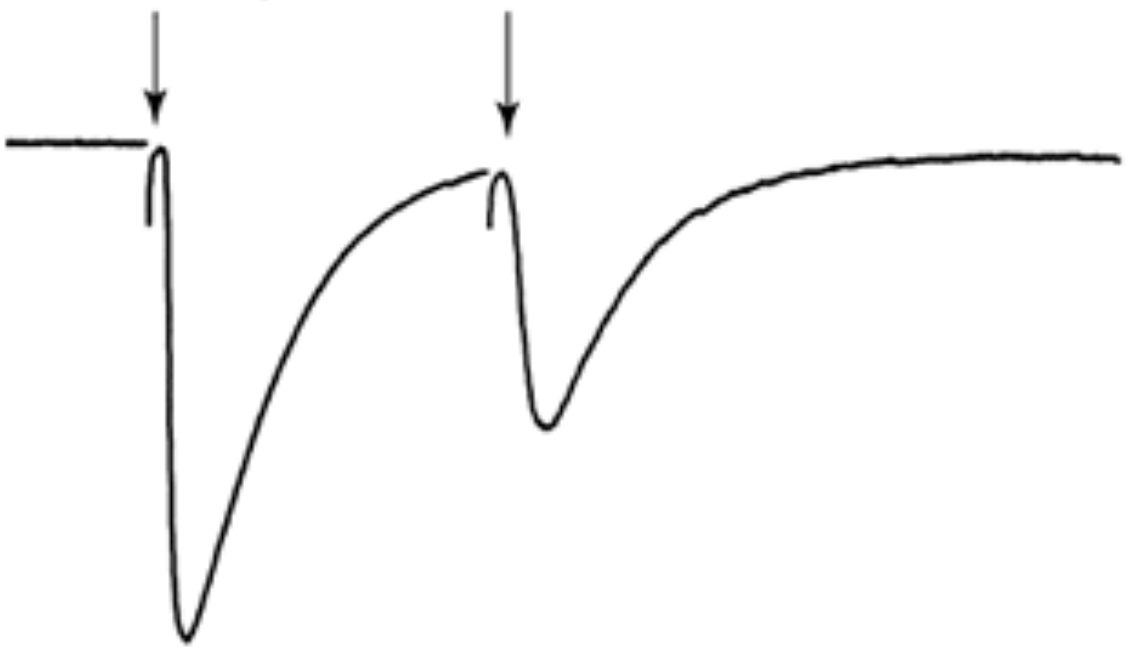
F1 F2

$C_0 + C_1\exp(-t/\tau_1) + C_2\exp(-t/\tau_2)$

Zucker and Regehr, Ann. Rev. Physio., 2002

Paired pulse depression

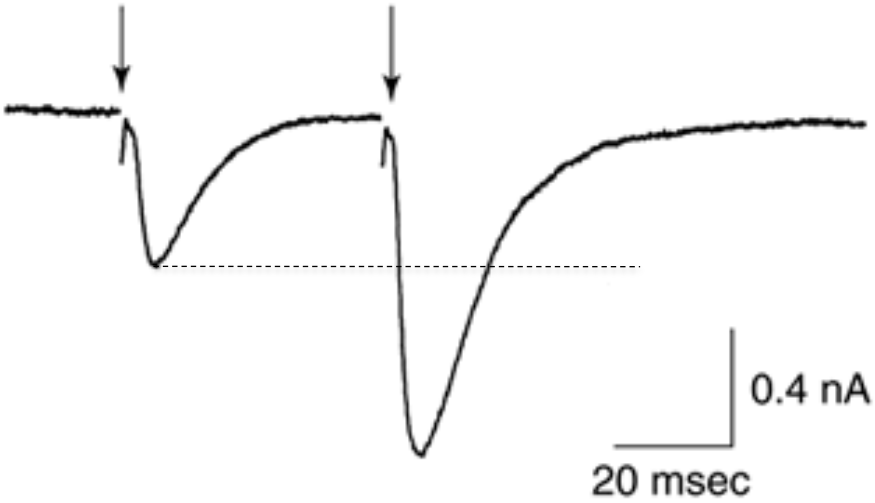
Some synapses show paired pulse depression



Swanson and Contractor, Curr. Protoc. Neurosci., 2004

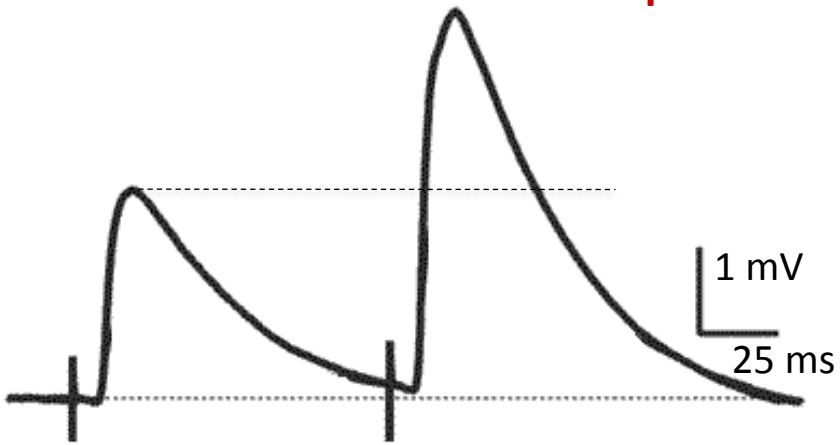
PPF in various modes of recording

Whole-cell voltage clamp



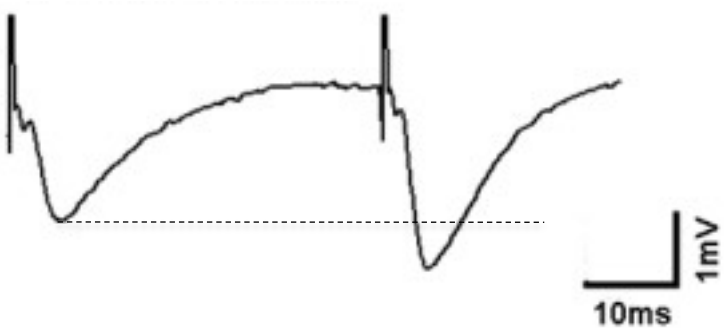
Swanson and Contractor, Curr. Protoc. Neurosci., 2004

Whole-cell current clamp



Ngo-Anh et al., Nature Neursoci., 2005

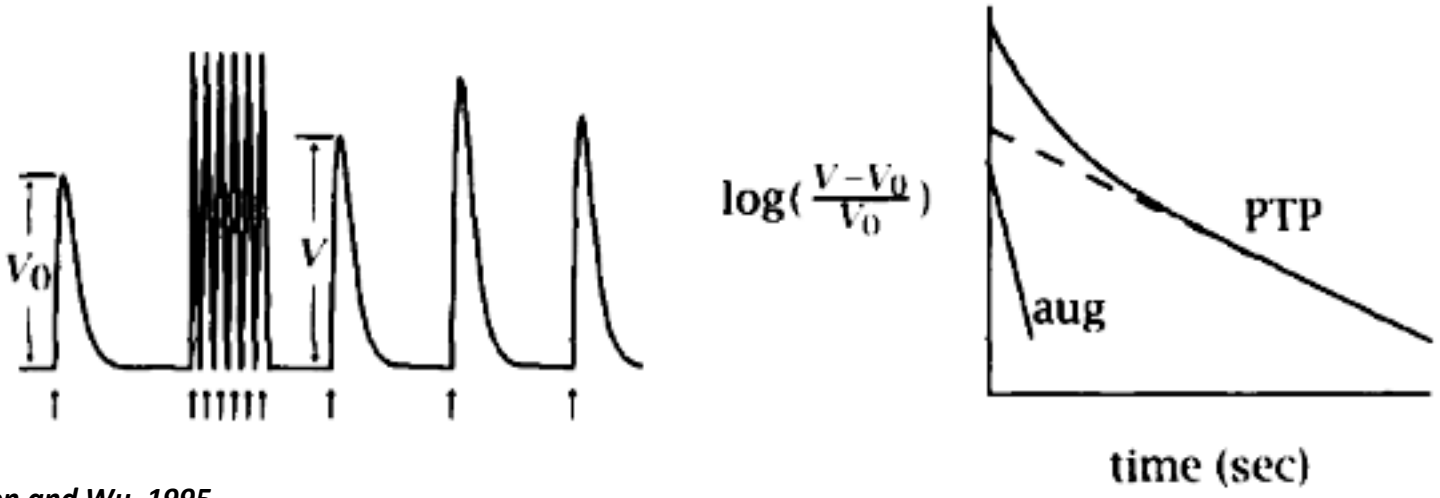
Field recordings



Yu et al. BMC Developmental Biology 2007

Field recordings are proportional to transmembrane currents

Augmentation & Post-tetanic potentiation



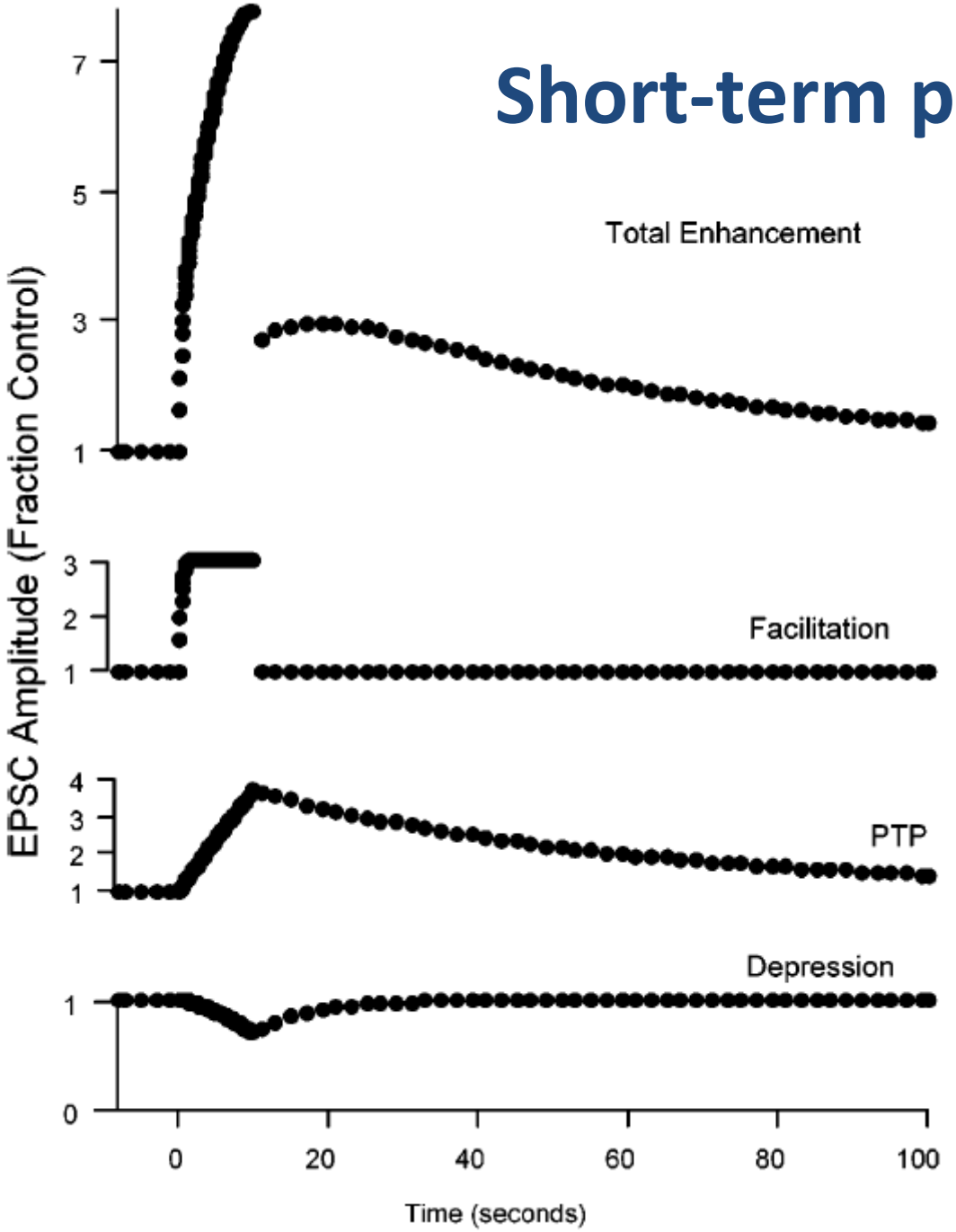
Johnston and Wu, 1995

Augmentation: Grows and decays with a time constant of ~5–10 s after a tetanic stimulus (high-frequency stimulation)

Post-tetanic potentiation (PTP): Lasts for 30 s to several minutes after tetanus

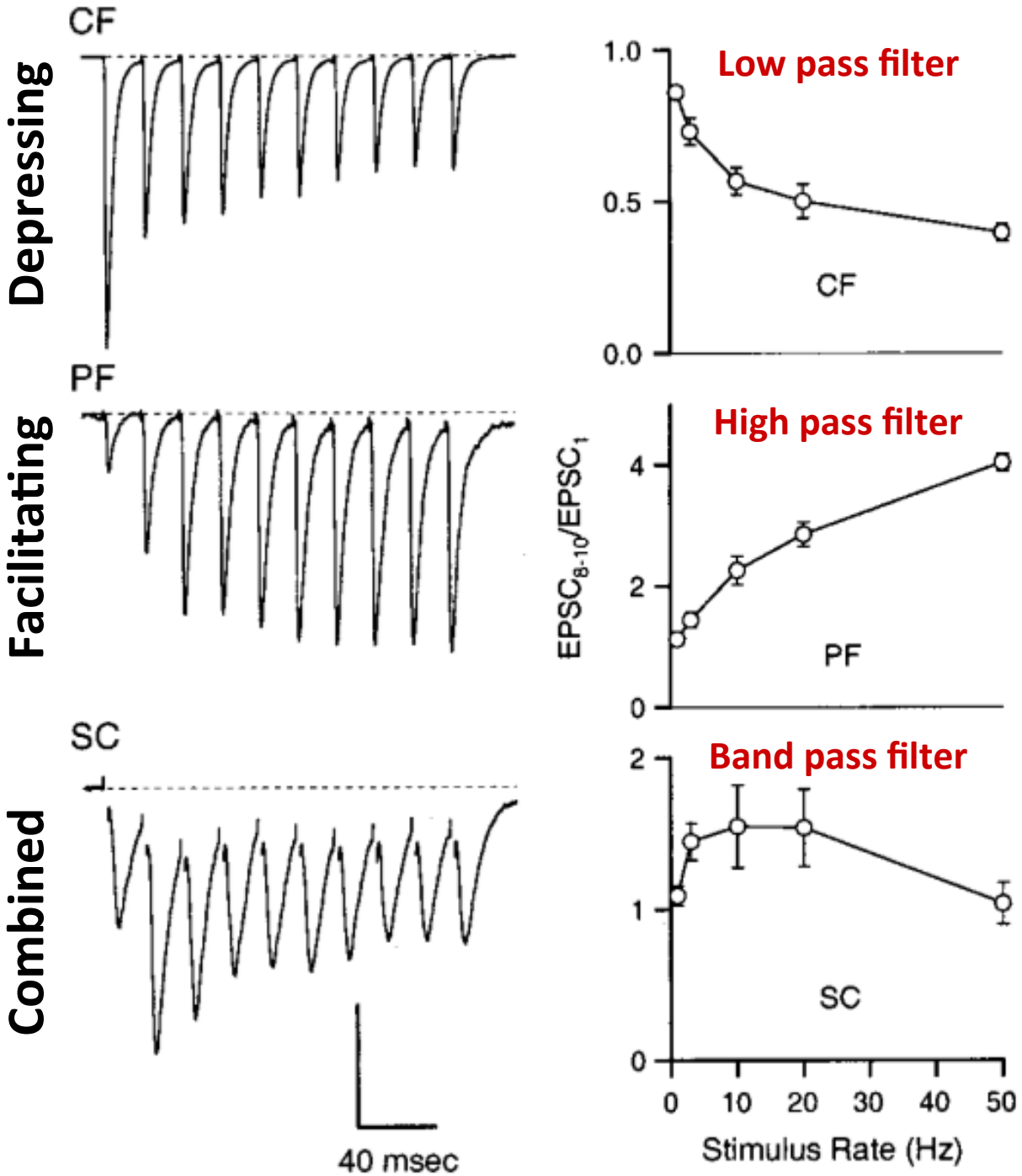
Plasticity properties are synapse-dependent. In some synapses these two merge into one, and is called as PTP

Short-term plasticity combine!



Probe stimulus — 0.5 Hz
Tetanus — 10 Hz for 10 s

Zucker and Regehr, Ann. Rev. Physiol., 2002



Short-term plasticity mediates synaptic filters!

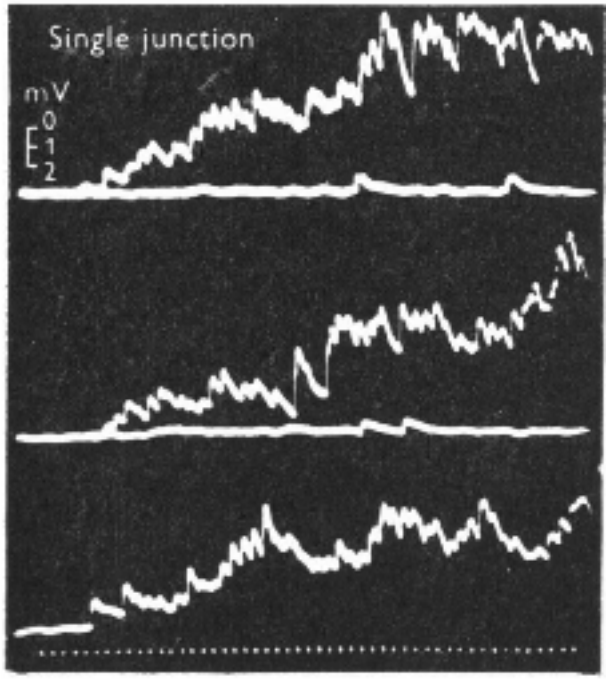
Dittman et al., JNS, 2000

Mechanisms behind short-term plasticity: A systematic analysis

Step 1: Is it presynaptic or postsynaptic?

Using quantal analysis short-term plasticity has been shown to be presynaptic in origin

Specifically, an increase in the number of transmitter quanta released by an AP without any change in quantal size or postsynaptic effectiveness



Del Castillo and Katz, J. Phys. 1954

Serial no. of nerve impulses during tetanus at 100 per sec	Total no. of nerve impulses	No. of end-plate responses	Proportion of failures (=exp(−m))
N_1	711	110	0·84
$N_6 - N_{15}$	1615	858	0·45
$N_{16} - N_{25}$	1140	799	0·31
$N_{36} - N_{45}$	1105	886	0·21

See Fisher et al., Trends in Neurosciences, 1997, for how this has been shown in various systems using quantal analysis.

It is presynaptic!

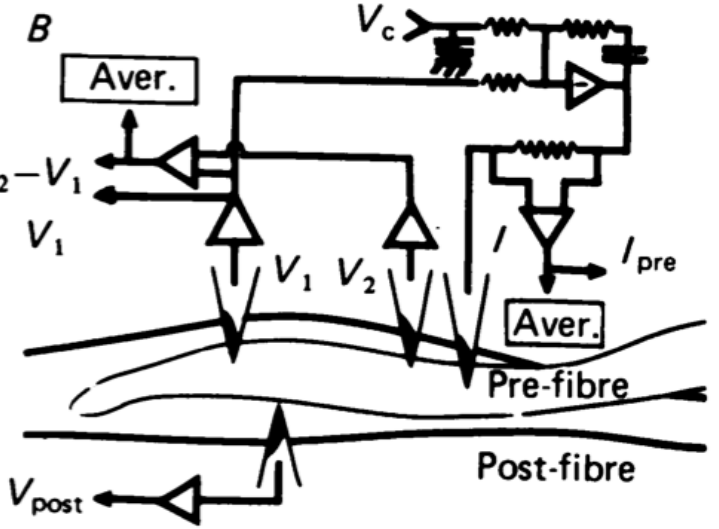
Step 2: What presynaptic component mediates short-term plasticity?

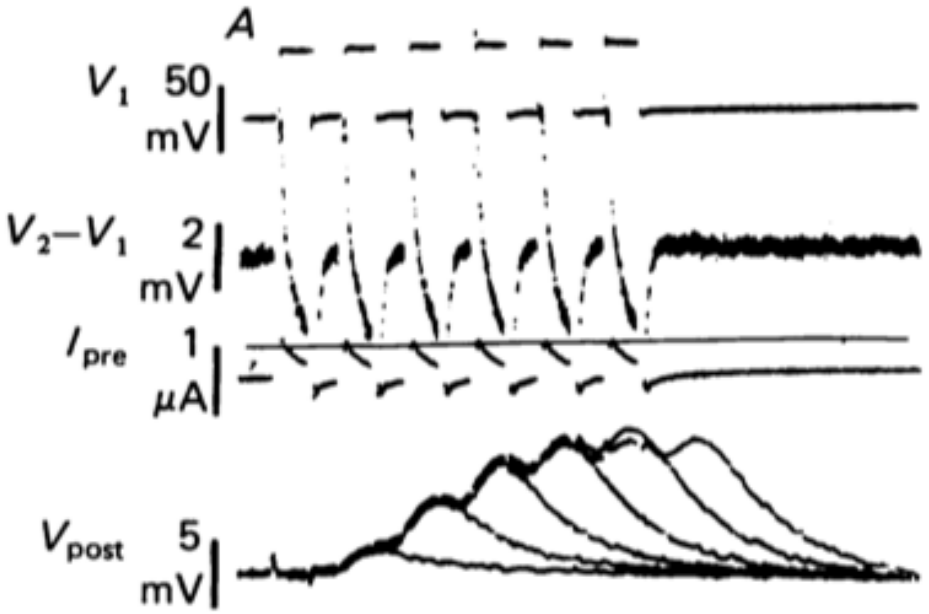
Could it be due to electrical events in presynaptic terminals?

— increased AP invasion into nerve terminals
— broadening APs,
— effects of afterpotentials

All these were eliminated in multiple preparations largely using extracellular recordings of action potentials at nerve terminals during facilitation

Facilitation can even be evoked by constant depolarizing pulses under voltage clamp that activates an invariant Ca^{2+} influx and constant presynaptic $[Ca^{2+}]_i$ change (4 electrodes recordings in squid giant synapse!)

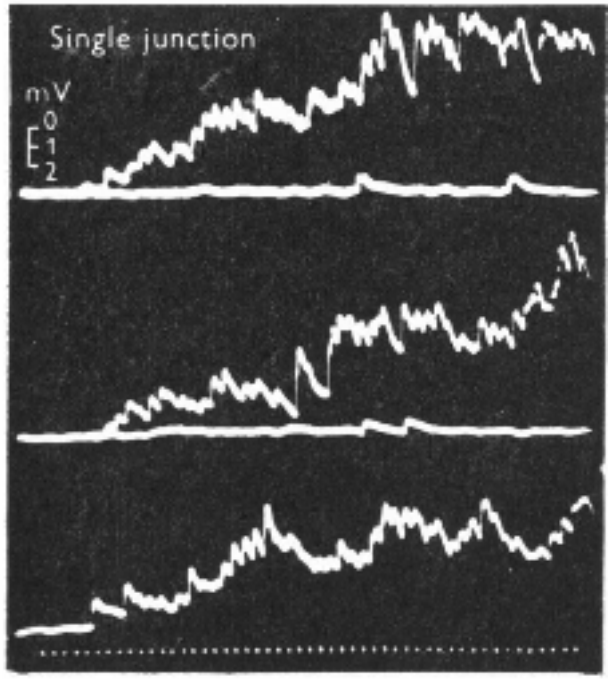




Charlton et al., J. Physiology, 1982

Putting Step 1 and Step 2 together…

So, it is presynaptic, but not mediated by action potential waveform!



Del Castillo and Katz, J. Phys. 1954

From Katz's analysis (Step 1):

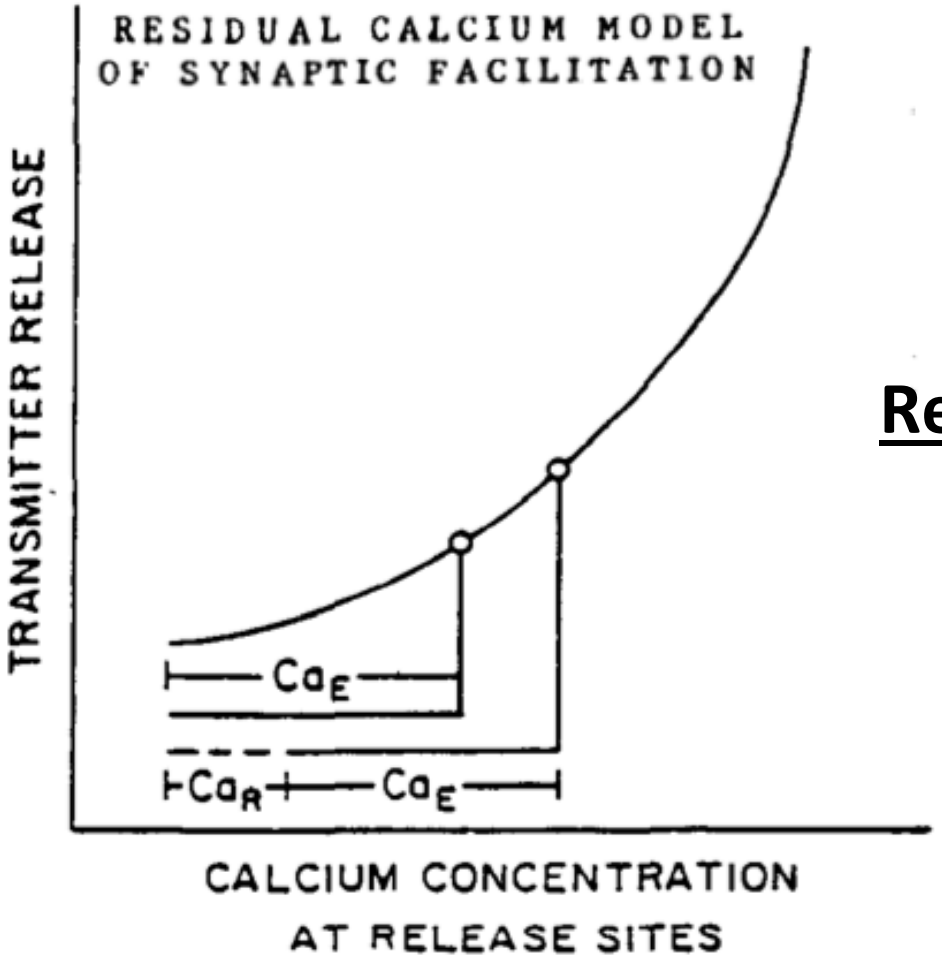
You don't really need release from a previous action potential to get "facilitation" with the next/ following ones.

➔ It should be due to some process between action potential invading the synapse and release.

Influx of calcium ions occurs between the invasion of action potential and the release

Step 3: Formulate a hypothesis for explaining the observations

Could facilitation be mediated by Ca^{2+} ions?



Residual calcium hypothesis

Zucker, Annual Rev. Neurosci., 1989

How to test this hypothesis experimentally?

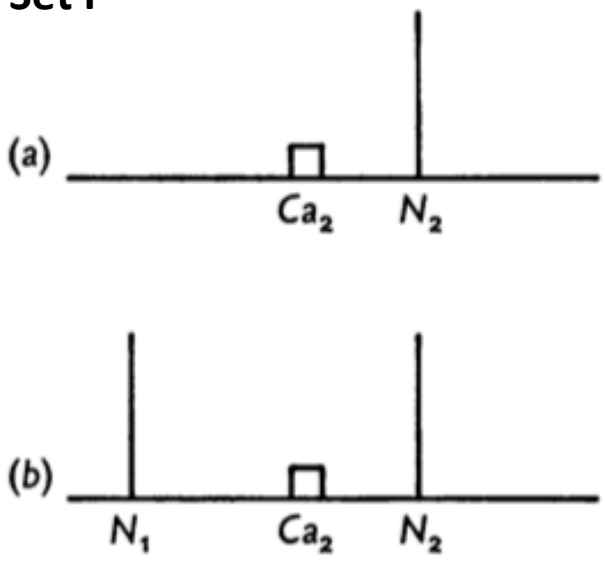
Always remember:

1. A good experimental design is one where even a negative result provides insights

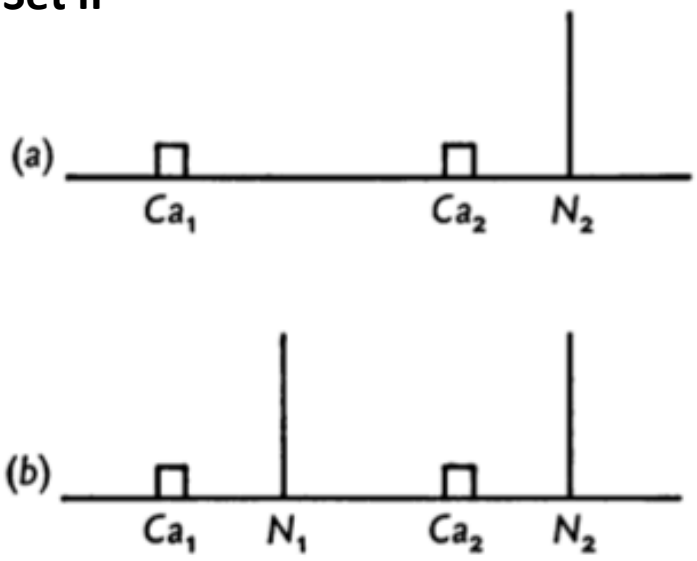
2. The amount of time spent logically designing a set of experiments towards testing a hypothesis is inversely proportional to probability that it will fail!!

Step 4: Test the residual calcium hypothesis

Set I



Set II



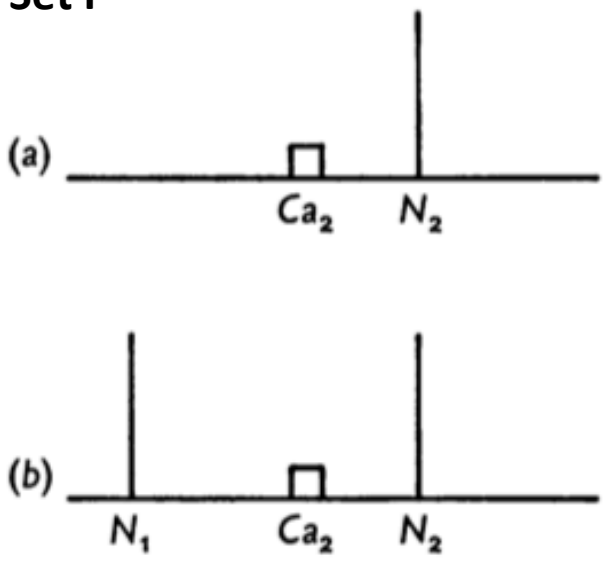
N_1–N_2=100 ms

<u>In the set II experiments there will be additional Ca due to Ca_1</u>

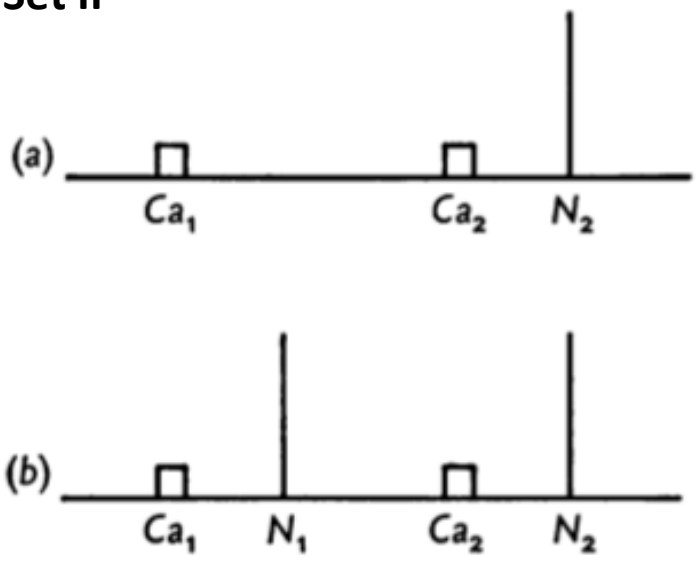
<u>Katz and Miledi, J. Phys., 1968</u>

Step 4: Test the residual calcium hypothesis

Set I



Set II

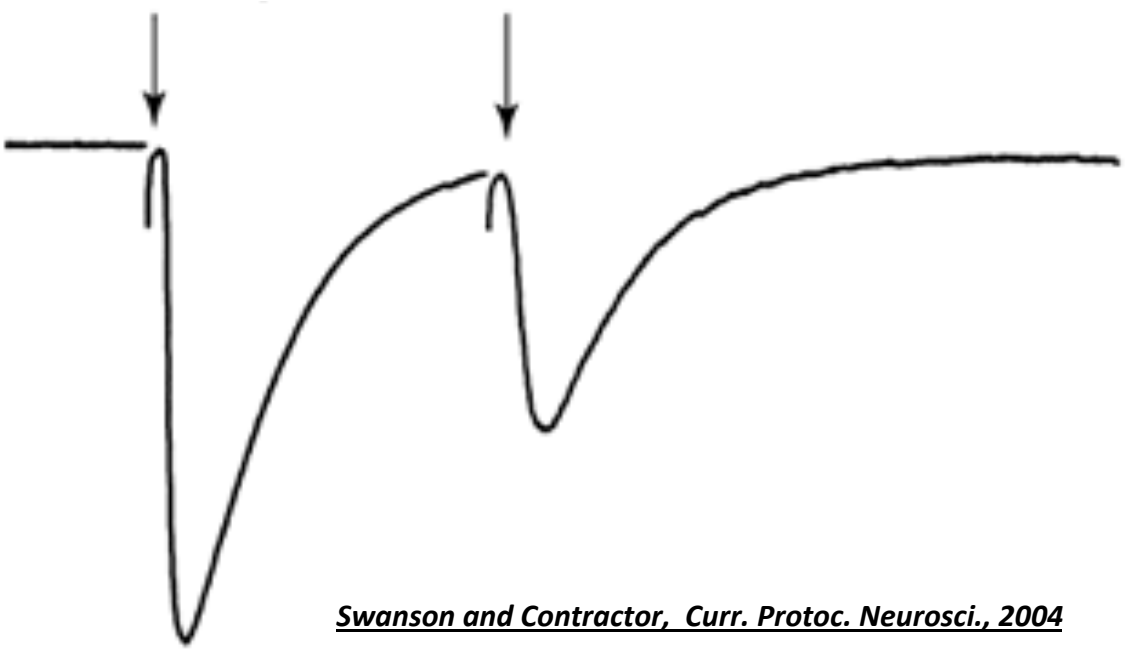


Katz and Miledi, J. Phys., 1968

	CaN_2	N_1CaN_2	$Ca_1Ca_2N_2$	$Ca_1N_1Ca_2N_2$
Responses/impulses...	1138/3299	1183/3318	706/2291	1180/2285
Proportion of failures (e^{-m})	0·654	0·642	0·691	0·483
Averaged 'm'	0·423	0·441	0·37	0·731
Facilitation f		1·045		1·98

Facilitation was greater when calcium was present during N_1 than when it was absent.

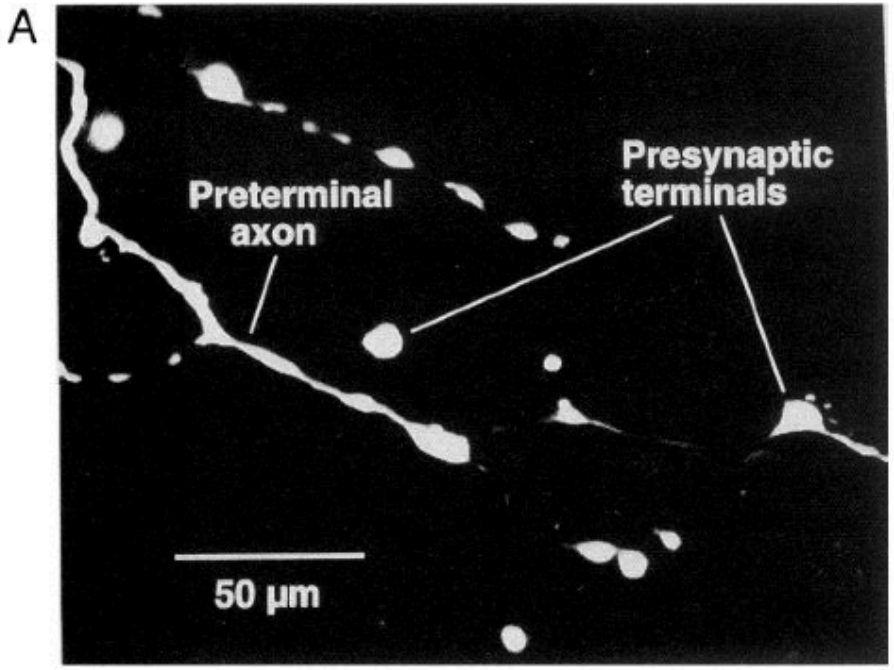
What about depression?

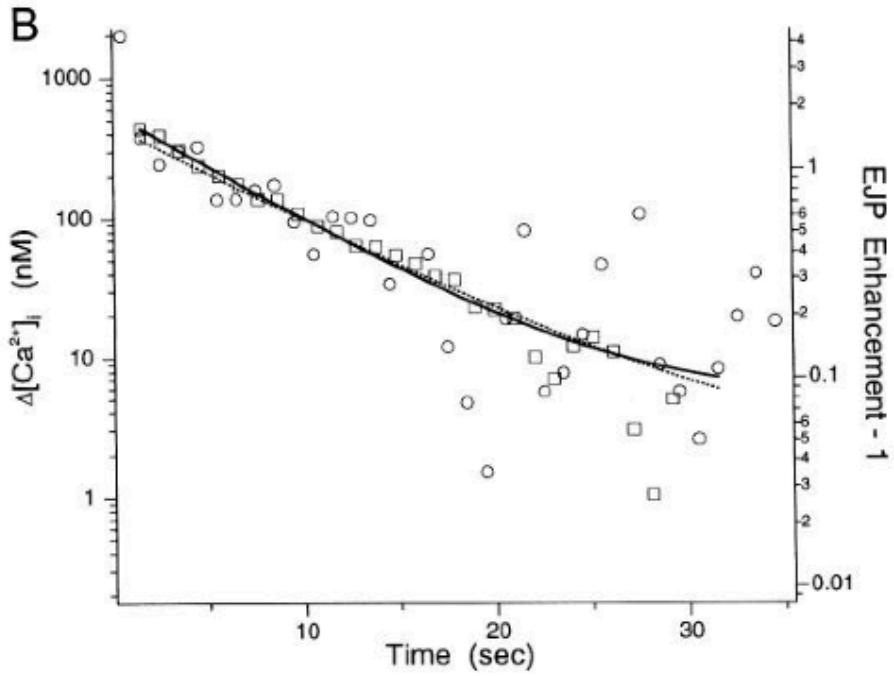


Swanson and Contractor, Curr. Protoc. Neurosci., 2004

Depression occurs in synapses where there is high initial probability of release. So, even if there is residual calcium there are lesser transmitters left in the readily releasable pool for it to release any higher!!!

Ever since, the residual calcium hypothesis has been tested in numerous systems in numerous ways, for facilitation, augmentation and PTP





I. Directly measuring presynaptic calcium and correlating it with postsynaptic facilitation

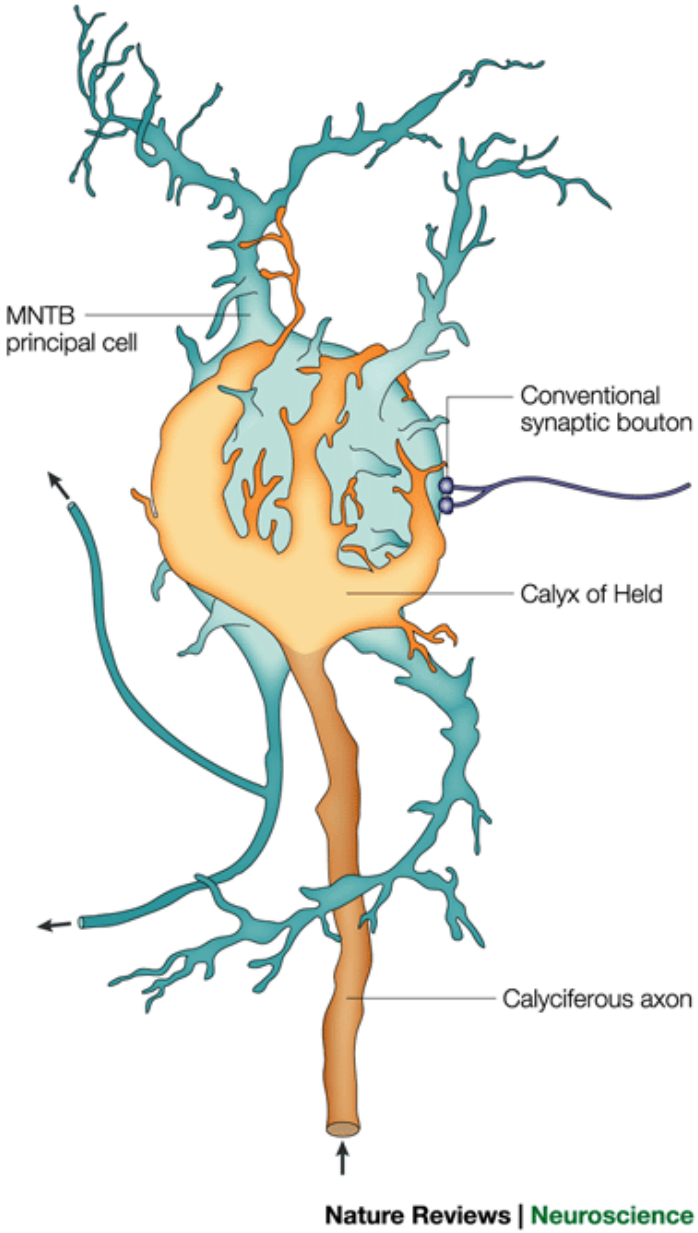
Augmentation

Presynaptic neuron filled with calcium dye to measure presynaptic calcium levels

Co-plotting the enhancement of postsynaptic (excitatory junction) potential shows correlation.

Delaney and Tank, J. Neurosci., 1994

A special preparation!



Calyx: cuplike cavity

Held: Using the Golgi method, Hans Held first reported the calyx terminal in the cat auditory brainstem in 1893

Advantages:

Fail-safe relay synapse

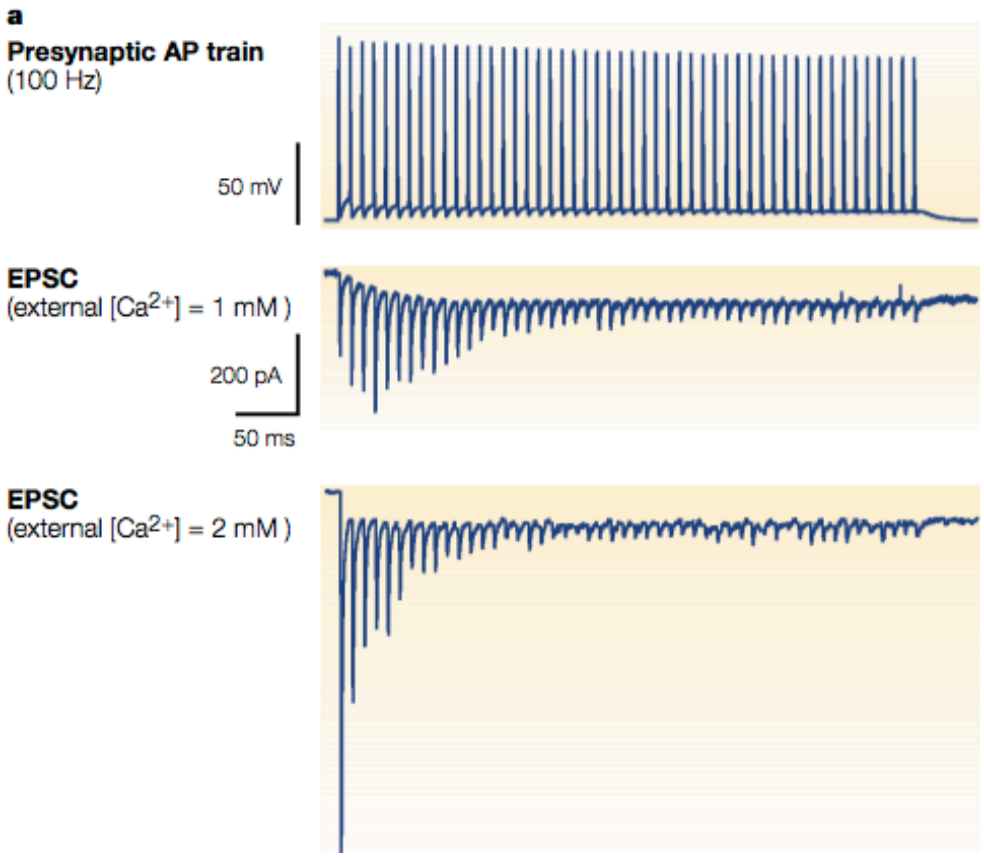
You can record both from the pre- and post-synaptic sides simultaneously and alter the cytoplasmic contents

No electrotonic distance problem! Synapse is on the soma!

It has a large dynamic range of functioning (can go up to several 100 Hz)

Gersdorff and Borst, NRN, 2002

Calyx of Held: Properties



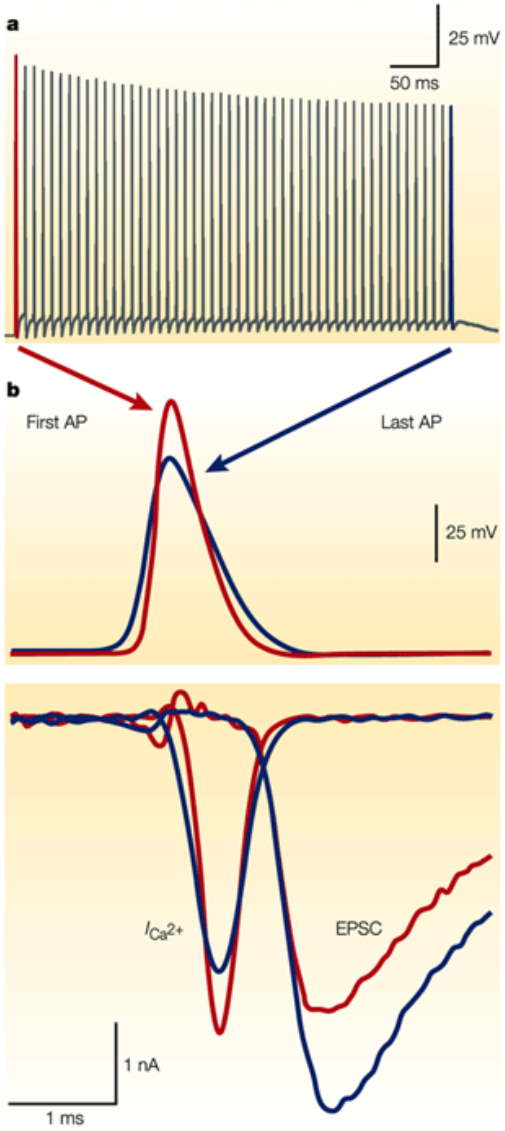
It is a depressing synapse, especially at high frequencies. Given reliability and consequent high probability of release, it usually has to be so !

Disadvantage: About 600 active zones in 9-day-old rats; so there is an inability to resolve quantal excitatory postsynaptic currents

It is a glutamatergic synapse.

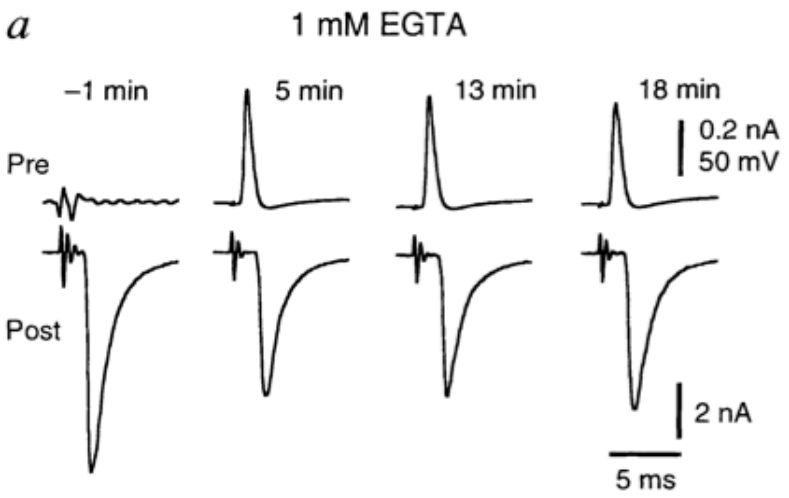
Gersdorff and Borst, NRN, 2002

Spike waveform & amount of [Ca^{2+}] influx matter for release

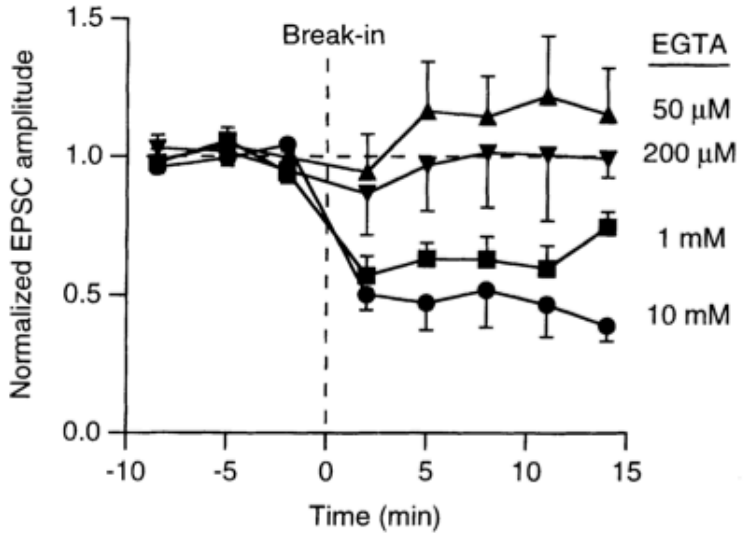


Gersdorff and Borst, NRN, 2002

Nature Reviews | Neuroscience



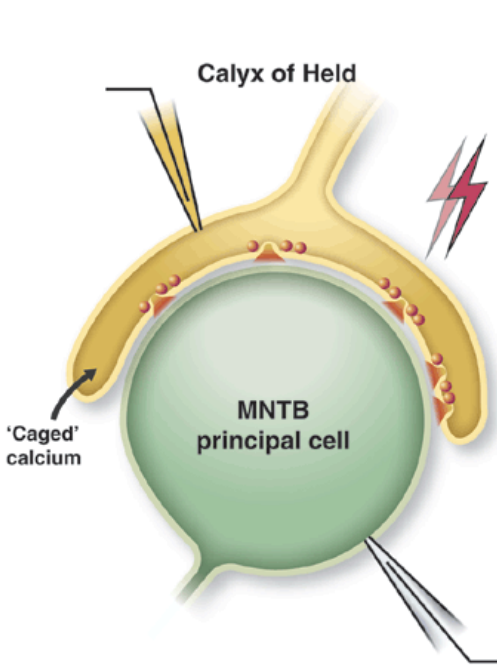
b Patching with EGTA at 0 min

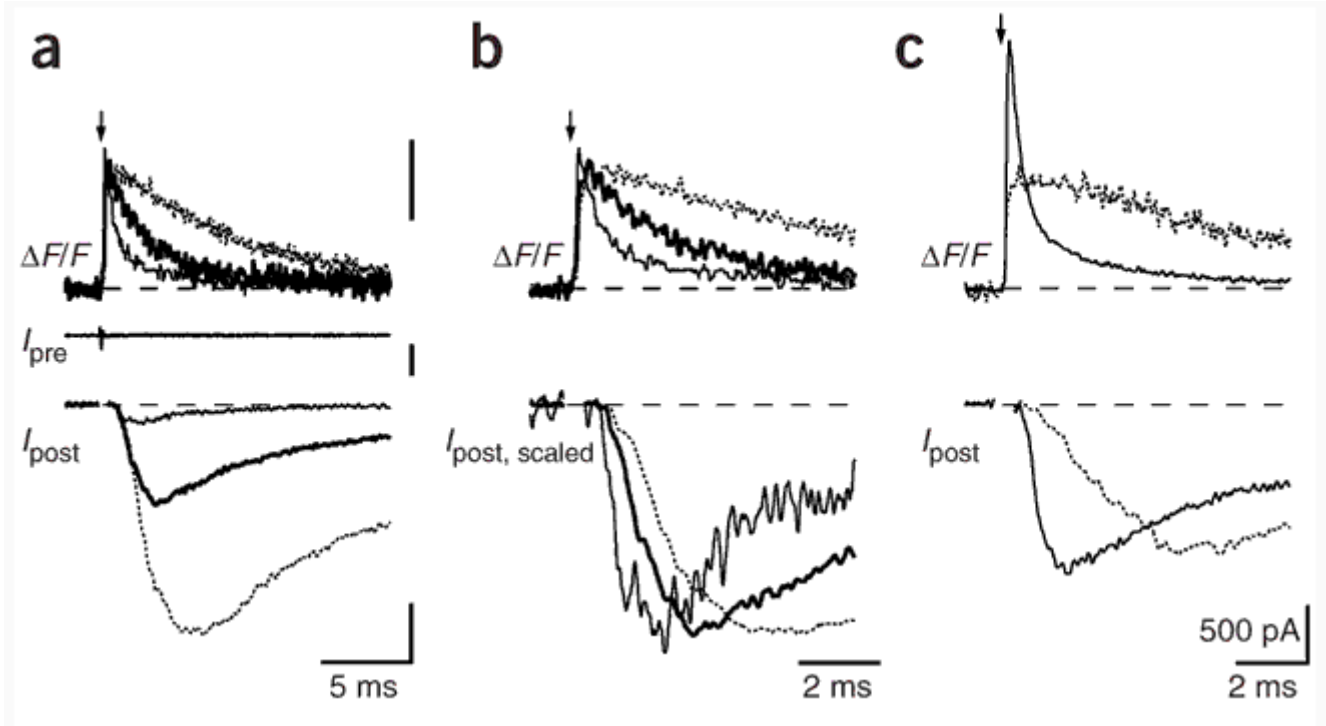


Borst and Sakmann, Nature., 1996.

Kinetics of presynaptic calcium regulates kinetics of postsynaptic current

Using caged calcium



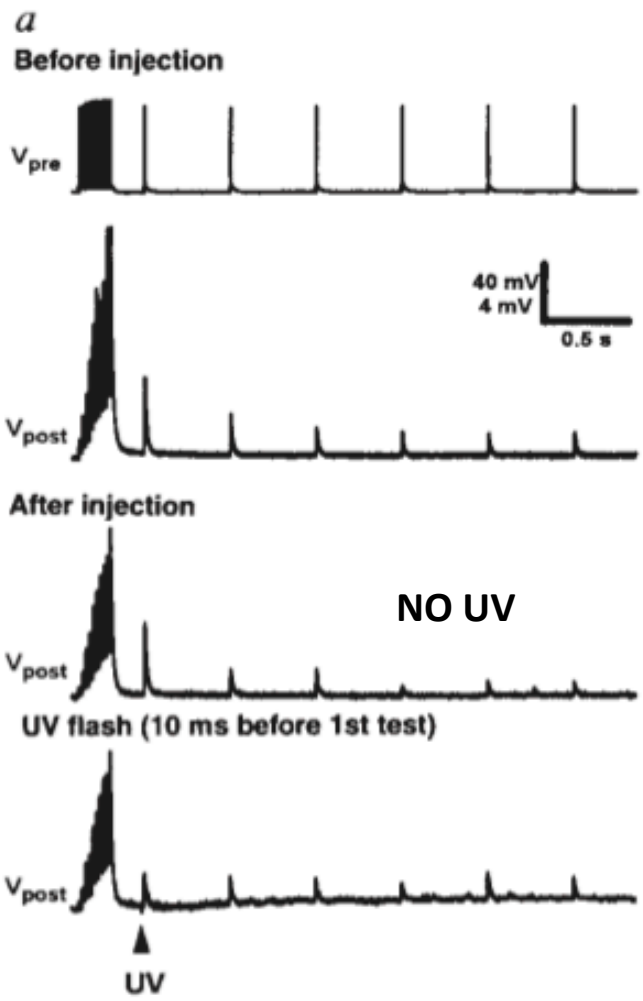


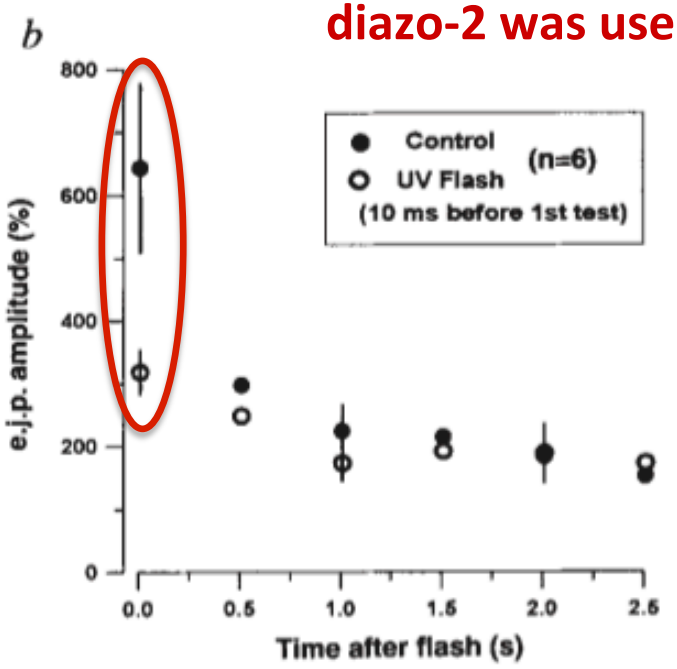
Heidelberger & Gersdorff, Nat. Neurosci., 2005

Bollmann and Sakmann, Nat. Neurosci., 2005

II. Chelating presynaptic calcium reduces short-term plasticity

Photolabile calcium chelator diazo-2 was used.



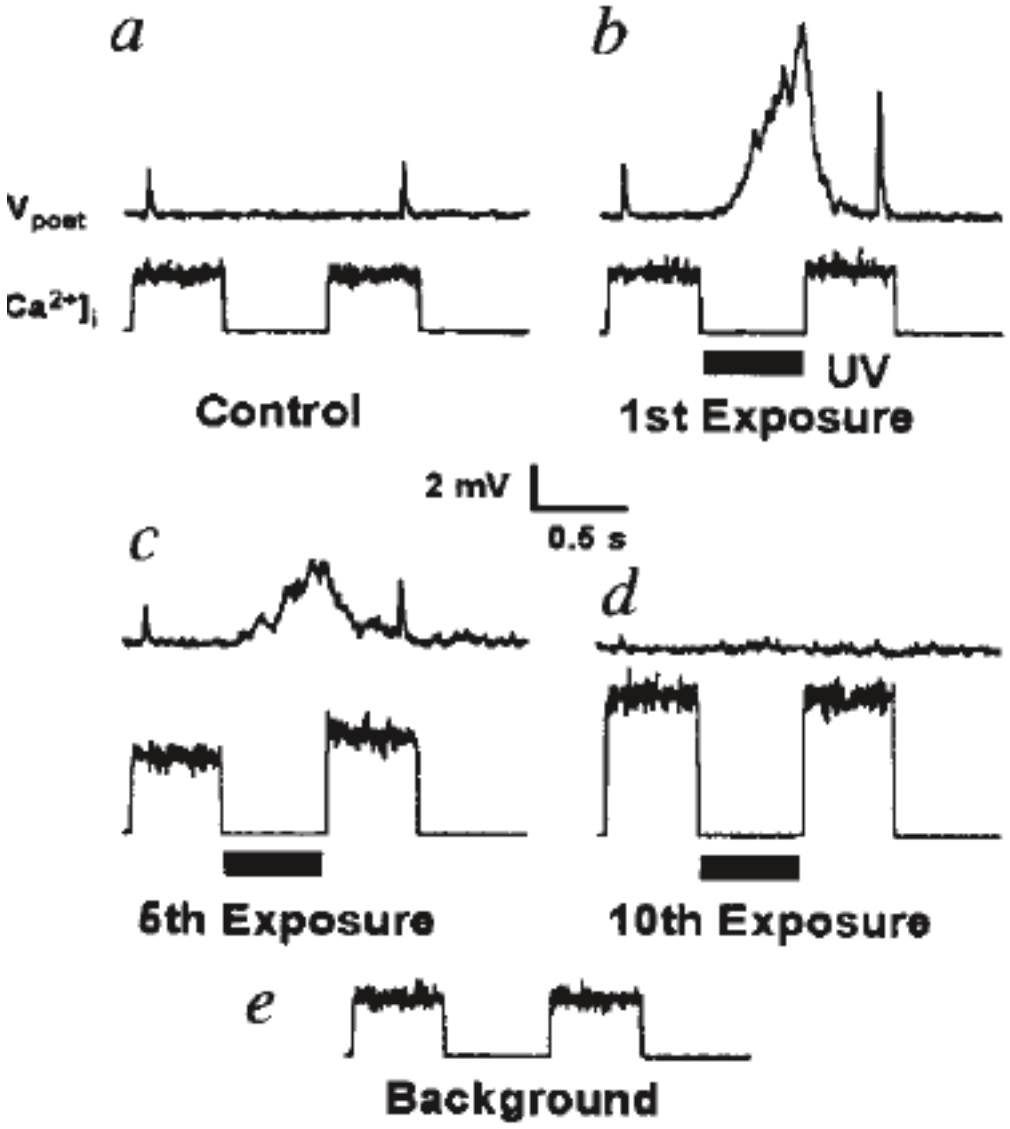


This has been repeated in umpteen systems with fast and slow calcium chelators BAPTA and EGTA arriving at similar conclusions!

Kamiya and Zucker, Nature, 1994.

Cray fish NMJ

III. Elevating presynaptic calcium enhances release



UV exposure causes release of Ca^{2+} from the caged calcium molecule.

During release there is heavy postsynaptic activity, and facilitation of the following pulse (b)

Towards the end all transmitters are exhausted (d)!

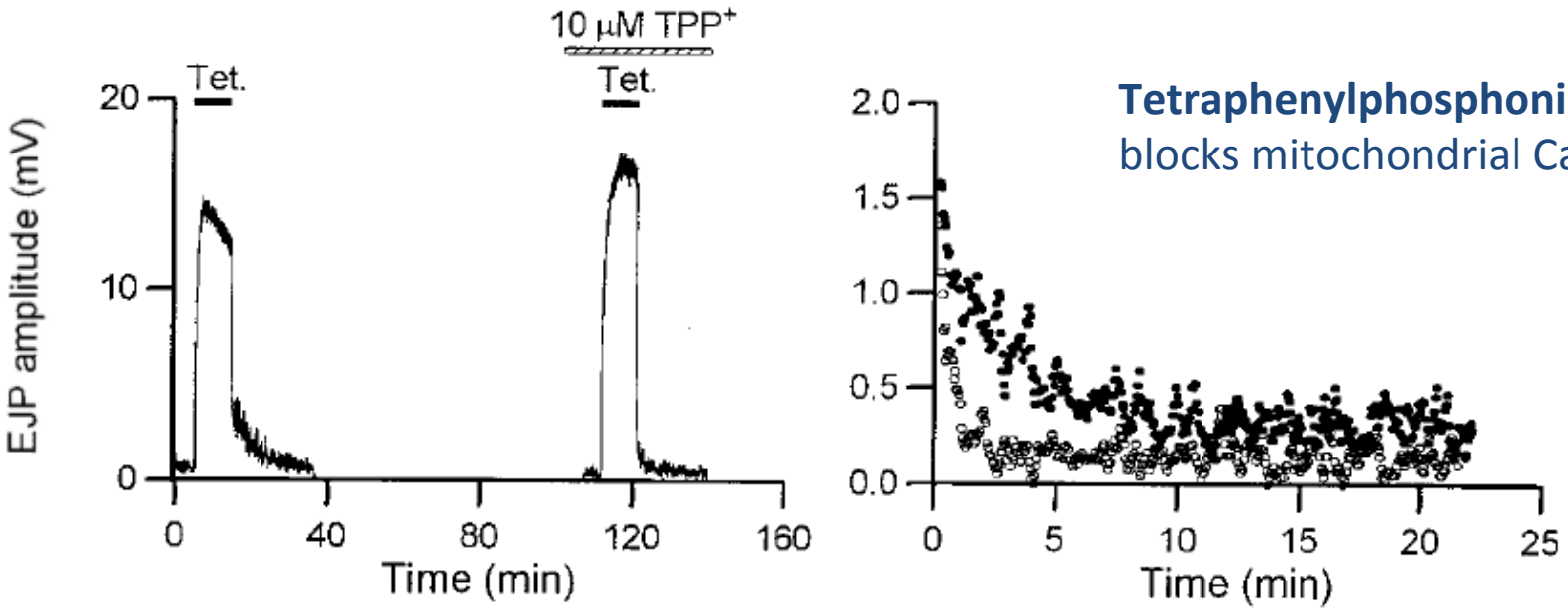
Kamiya and Zucker, Nature, 1994.

Mitochondria and ER calcium

In some synapses:

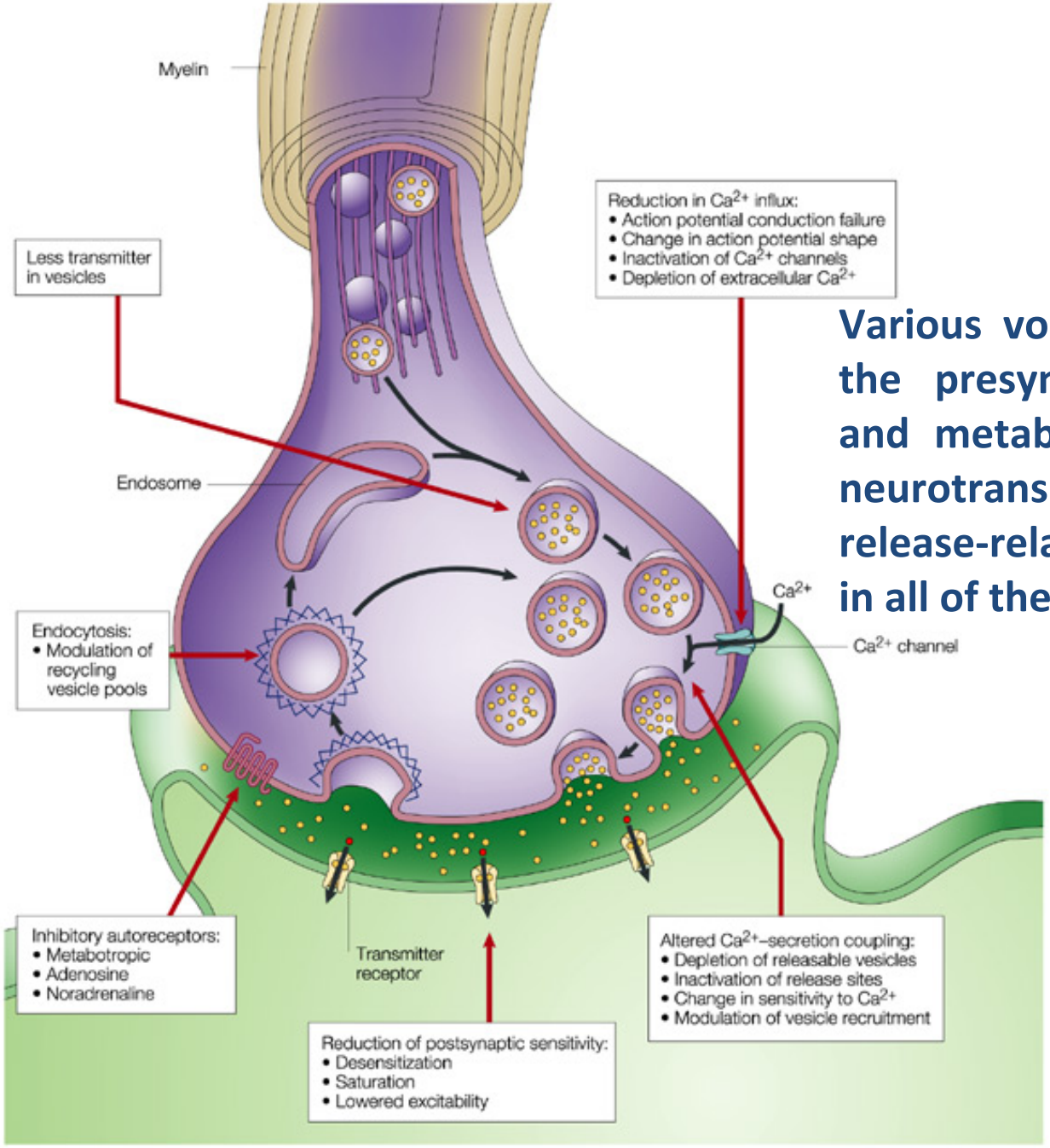
Augmentation and PTP are also regulated by calcium uptake by the mitochondria and the endoplasmic reticulum during the tetanus;

After tetanus there is leakage of calcium from these two structures, thus leading to a relatively longer elevation of residual calcium.



Tetraphenylphosphonium (TPP^+):
blocks mitochondrial Ca^{2+} efflux

Tang and Zucker, Neuron, 1997



Various voltage-gated ion channels in the presynaptic terminal, ionotropic and metabotropic receptors to other neurotransmitters, mitochondria, ER, release-related molecules and plasticity in all of these and more!!

Gersdorff and Borst, NRN, 2002

What did we learn today?

Short term plasticity: PPF/D (100s of ms), augmentation (5–10 s) and PTP (30 s – several minutes)

PPF/D, Augmentation and PTP are all presynaptic in nature and are an interplay between residual calcium and the amount of available vesicles for release (determined by previous releases and how fast they replenish)

PPF occurs in synapses with low initial release probability and PPD occurs in those with high initial release probability

Various parameters contribute to how STP expresses, and it is synapse dependent — **DO NOT GENERALIZE!**