Synaptic Transmission

Neuroscience 201A

Peter Sargent

1. Electrical vs. Chemical Synaptic Transmission
2. Characteristics of Ligand-Gated Ion Channels
3. Transmitter Release
4. Transmitter Release Statistics

"Non-traditional" methods of measuring transmitter release (voltage sensitive dyes, voltammetry, capacitance) – not covered

Integrative Mechanisms – Kevin Bender

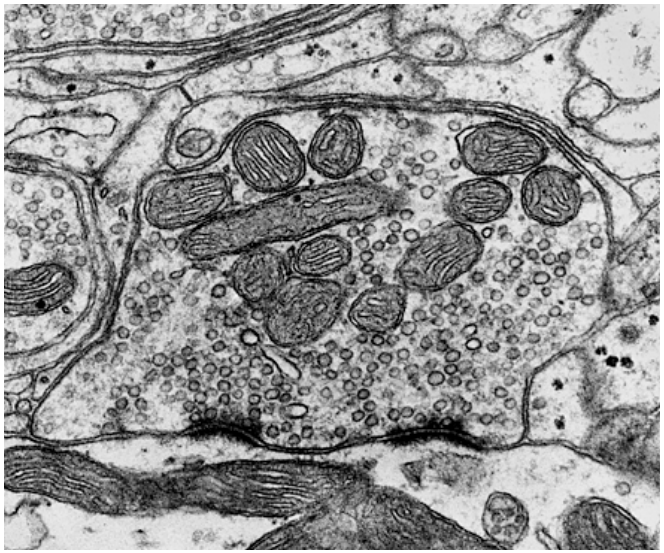
Synaptic Plasticity – Roger Nicoll

Neurotransmitter Release/Uptake – Rob Edwards

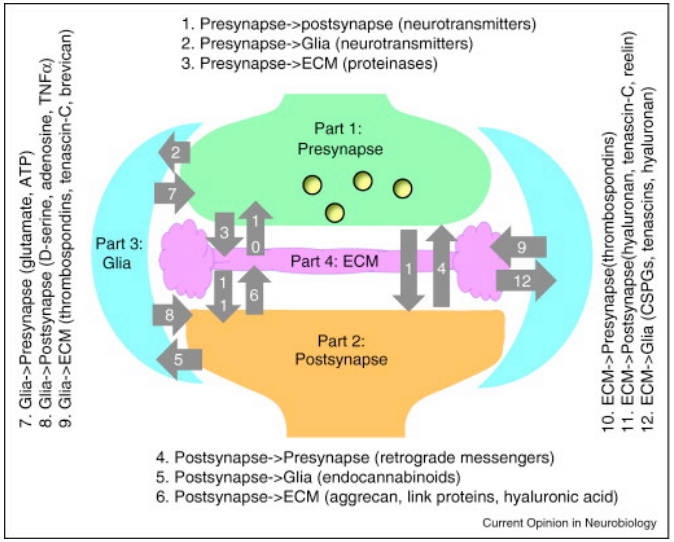
Synaptic Modulation (transmitters acting via metabotropic receptors) – Jennifer Whistler

What is a synapse?

- A synapse is a site of close apposition between a neuron and a target cell, where an electrical signal in a neuron leads to a change in the probability that its target cell will give an action potential.
  - if the probability increases, the synapse is excitatory
  - if the probability decreases, the synapse is inhibitory



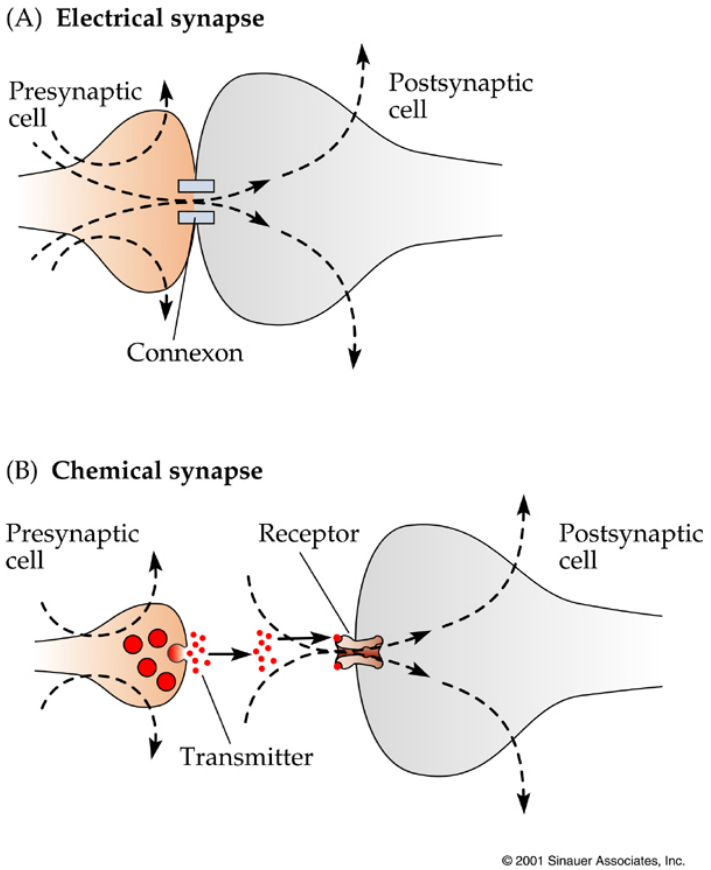
Here, we are looking at a section of a synaptic bouton with two **synaptic contacts**, or two synapses.

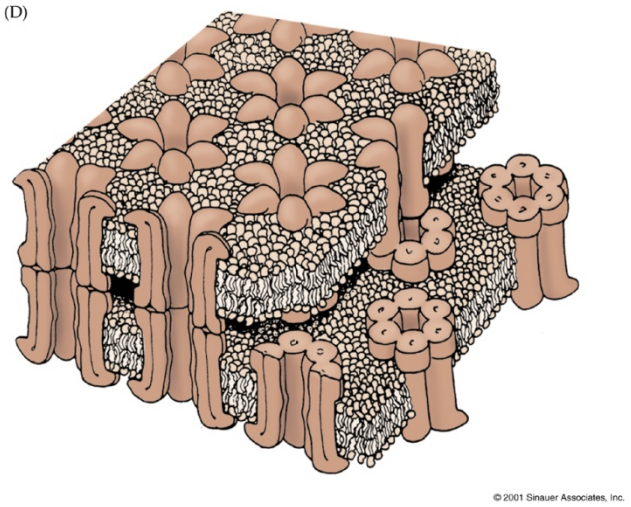


tripartite synapse (pre, post, glia)
tetrapartite synapse (pre, post, glia, ECM)
(ECM = extracellular matrix)

Dityatev A, Rusakov D (2011) Curr. Opin. Neurobiol. 21: 353-359.

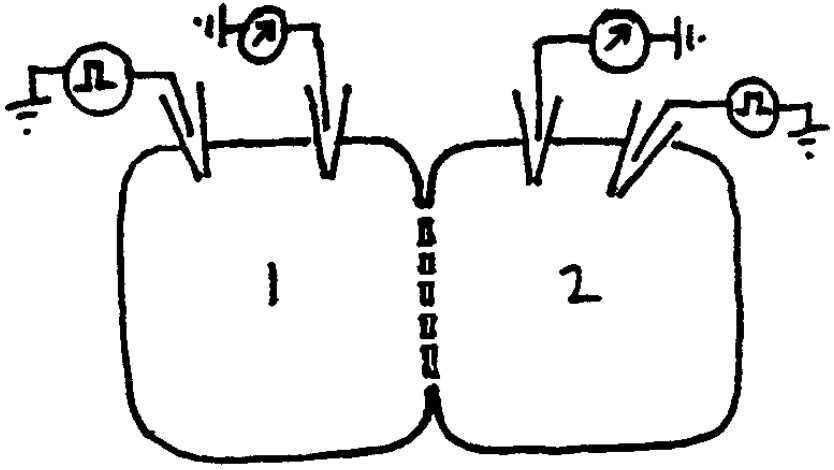
Electrical synapses

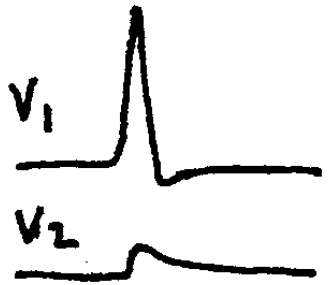


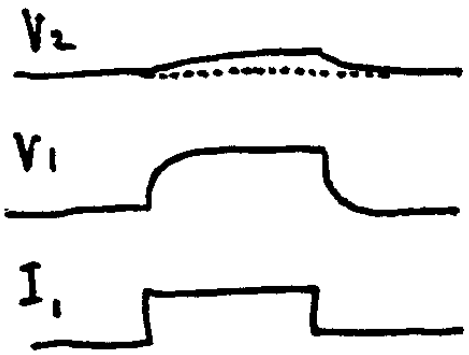


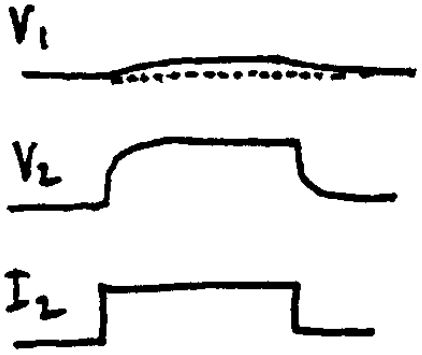
"gap junction" = collection of connexons

Electrical synapses permit direct current flow from one cell to the other





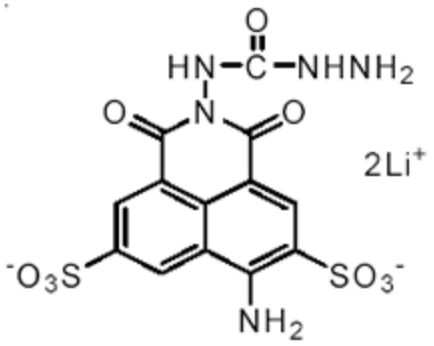


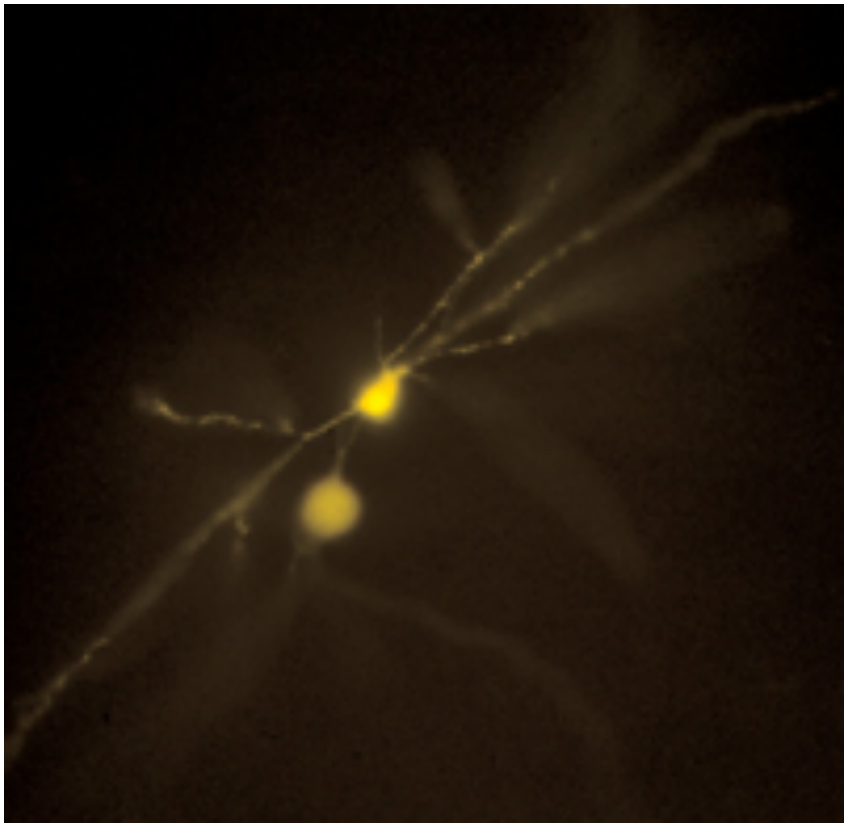


Small molecules can readily pass between cells connected by gap junctions (connexons)

- Molecules of up to ~ 2 kD can pass from a cell to its electrically coupled neighbors

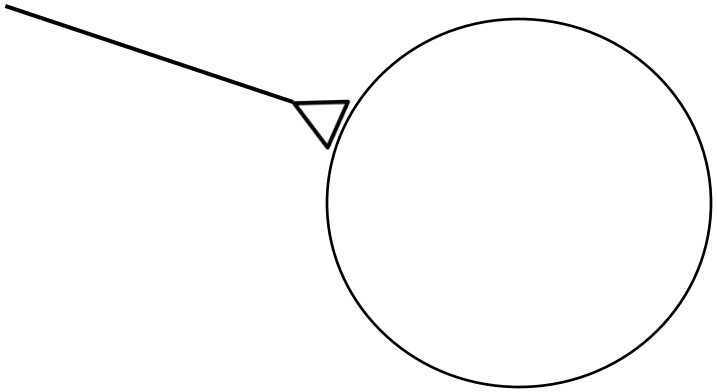
- Fluorescent molecules such as lucifer yellow will pass from cell to coupled cell – such cells are said to be "dye-coupled."





Patricio O'Donnell & Anthony A. Grace, Albany Medical College, Albany, NY and University of Pittsburgh, Pittsburgh, PA

Why have chemical synapses?



Advantages

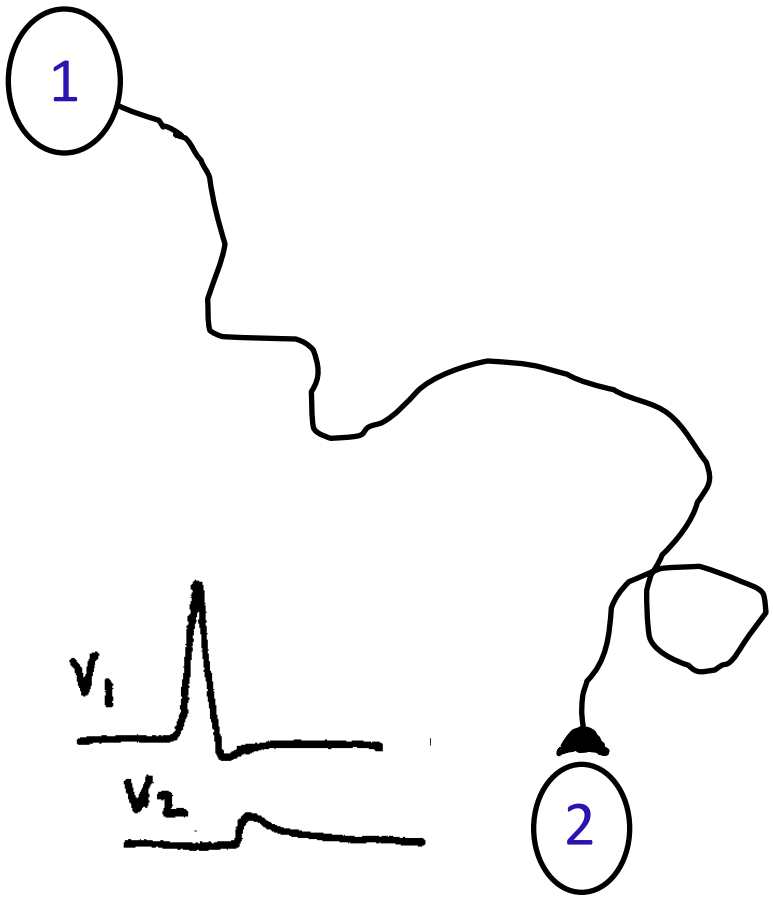
- Amplification
  - Unless the terminal and the target cell are comparable in size, electrical synapses are not likely to be effective (impedance mismatch)
- Polarity (+, -)
- Modifiability/Plasticity

Disadvantages

- Loss of reliability
- Speed (lose time due to synaptic delay) ??

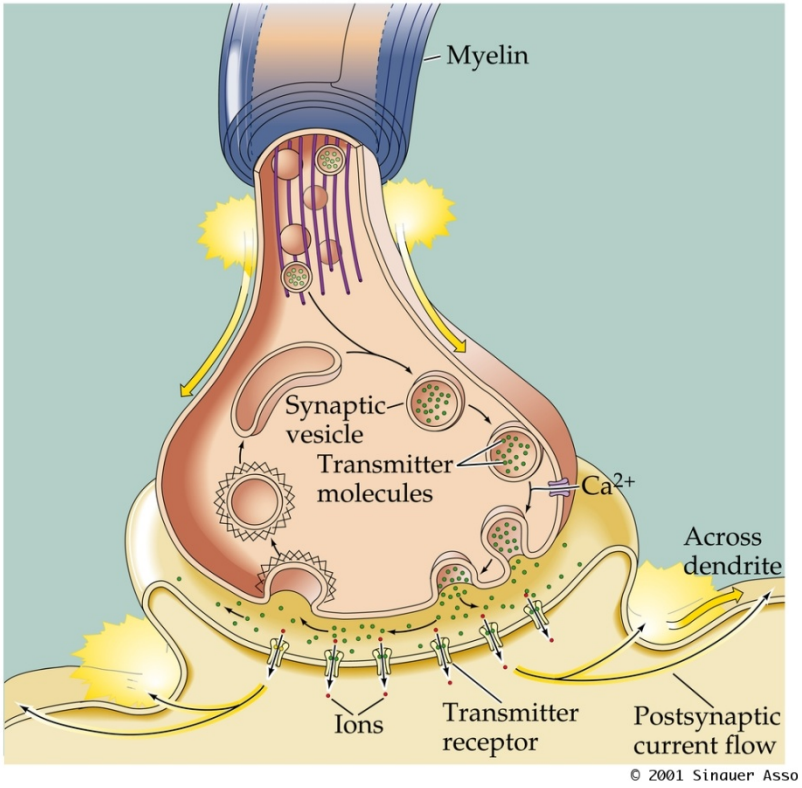
How do you distinguish an electrical from a chemical synapse?

- Anatomy
  - dye coupling?
- Physiology
  - synaptic delay?
  - quantal fluctuations?
  - reversal potential?



Sequence of events (chemical synapses)

1. An action potential arrives in the terminal, which
2. activates voltage-dependent calcium channels.
3. Calcium enters the terminal and promotes fusion of synaptic vesicles with the plasma membrane.
4. Transmitter is released into the synaptic cleft, and
5. binds to receptors on the postsynaptic membrane.
6. The channels associated with these receptors open, which allow ions to flow down their electrochemical gradient, exciting or inhibiting the cell.
7. Transmitter is removed from the cleft, and the synapse is "reset."



OUTLINE

(we are going backwards)

1. Electrical vs. Chemical Synaptic Transmission
2. Characteristics of Ligand-Gated Ion Channels
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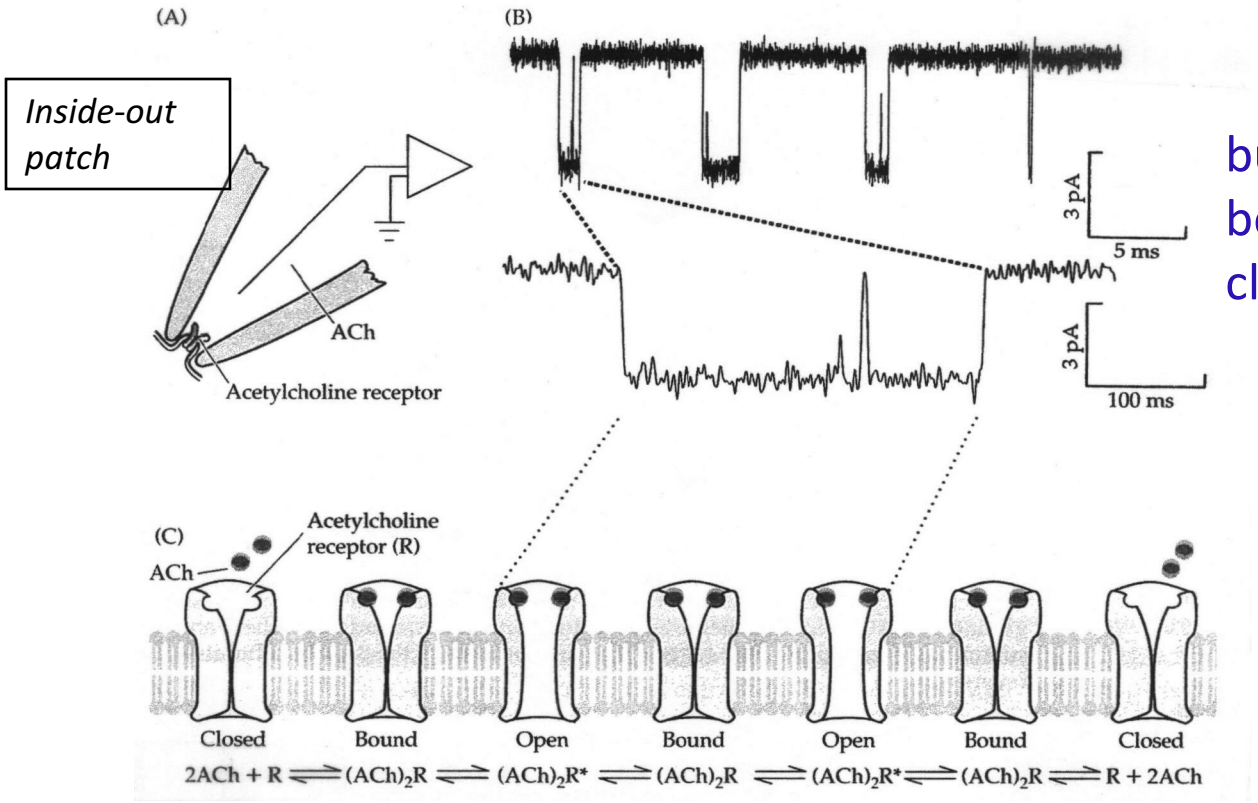
Simple state function for an ionotropic receptor

(skeletal muscle acetylcholine receptor – AChR)

$A + R \leftrightarrow AR + A \leftrightarrow A_2R \leftrightarrow A_2R^* \leftrightarrow A_2R$

closed closed closed open desensitized (closed)

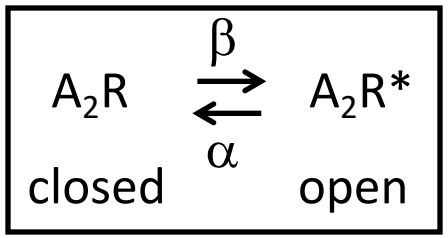


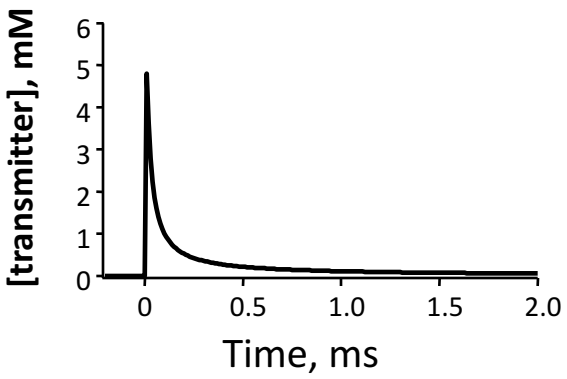
bursting: movement between open (A_2R^*) and closed (A_2R) states

What happens when transmitter is available for a brief period of time?

$$A + R \leftrightarrow AR + A \leftrightarrow A_2R \leftrightarrow A_2R^* \leftrightarrow A_2R$$

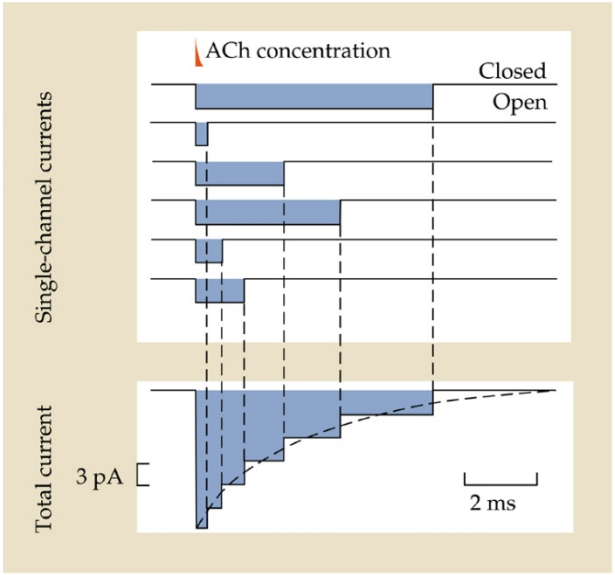
closed open desensitized (closed)





for the muscle AChR, α = 700 s^{-1} and β = 30,000 s^{-1}

In the absence of transmitter, the rate of closing will be governed by α. The time constant describing the fall in current will be $1/\alpha$, which is 1-2 ms, which outlasts the waveform of [ACh] when acetylcholinesterase is present. The decay time of the current thus reflects the behavior of the channels (not of the transmitter, which has been destroyed). At other synapses decay of current may be influenced by transmitter survival.



Principles of rapid/focal synaptic transmission *via* ionotropic receptors

- The affinity of transmitter for receptors is usually low (10-100 μM)
- Release leads to a high concentration of transmitter (1-10 mM) for a brief period of time in a small volume
- Receptor occupancy can be substantial, despite low affinity of receptors for transmitter (are receptors saturated?)
- Diffusion and uptake remove transmitter from the cleft quickly, so that transmitter typically has only "one chance" to bind to receptor
- The synapse is well designed for repeated use at high frequency (up to ≈1 kHz)

Ionic Basis of Excitation/Inhibition

- Excitation
  - Cation-selective channels

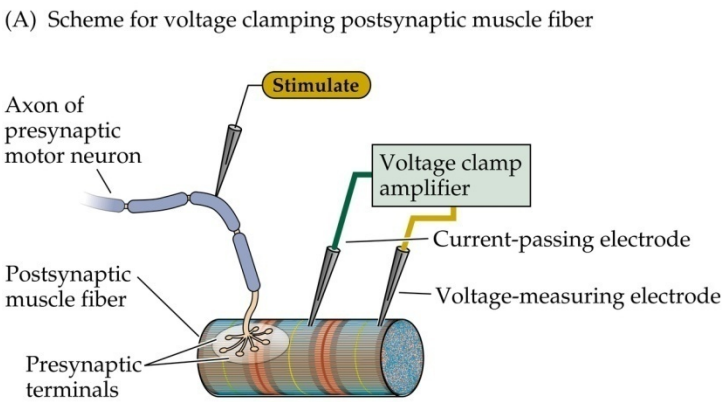
    (Na^+ is the major charge carrier)
    - ligand-gated: nicotinic, 5-HT_3, AMPA, NMDA, …
    - TRP channels (transient receptor potential)
- Inhibition
  - Anion-selective channels

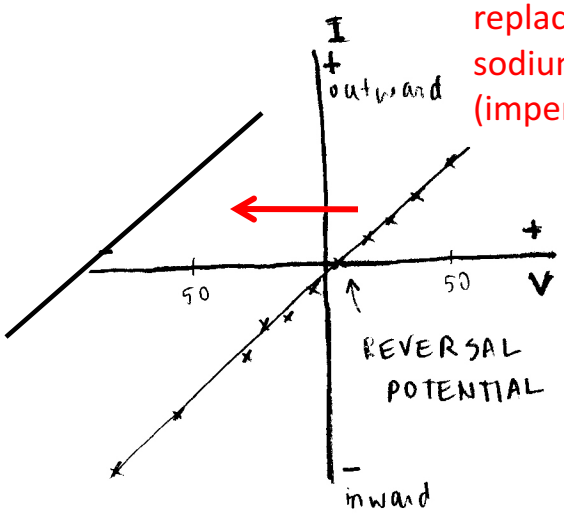
    (Cl^- is the major charge carrier, HCO_3^- is also involved)
    - ligand-gated: glycine, $GABA_A$, $GABA_C$
    - Q: Can activation of chloride-selective channels be excitatory?
  - K^+ selective channels

Measuring the relative permeabilities of ionotropic receptor channels

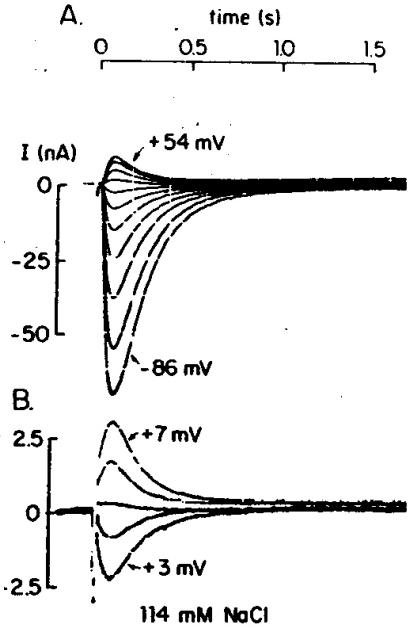
- Reversal potential: the potential at which the current is "reversed" in polarity, or nulled: the potential at which there is no net current produced by opening the channels
- What is the reversal potential of all of the leak channels of the cell, acting together?
- **Q:** How to measure the permeability of a channel (or a set of channels, acting together)?
- **A:** Measure effect of changing ionic composition upon reversal potential

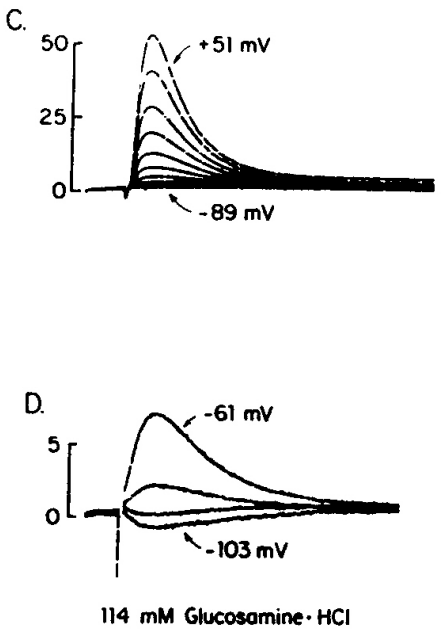
The nicotinic acetylcholine receptor channel is a cation channel





replace most of extracellular sodium with glucosamine (impermeant)





Adams DJ, Dwyer TM, Hille B (1980) The permeability of endplate channels to monovalent and divalent metal cations. J Gen Physiol 75:493-510.

The nicotinic acetylcholine receptor channel is a cation channel (cont.)

E1 and E2 represent reversal potentials for Na and for the ion X, respectively

$$E_1 = \frac{RT}{F} \ln \frac{K_o P_K + Na_o P_{Na} + Cl_i P_{Cl}}{K_i P_K + Na_i P_{Na} + Cl_o P_{Cl}}$$

exchange Na_o for X_o.

$$E_2 = \frac{RT}{F} \ln \frac{K_o P_K + X_o P_X + Cl_i P_{Cl}}{K_i P_K + Na_i P_{Na} + Cl_o P_{Cl}}$$

solve for $\Delta E = E_2 - E_1$

$$\Delta E = \frac{RT}{F} \ln \frac{P_X [X]_o}{P_{Na} [Na]_o}$$

$\frac{P_X}{P_{Na}}$ = permeability ratio for X (relative to Na)

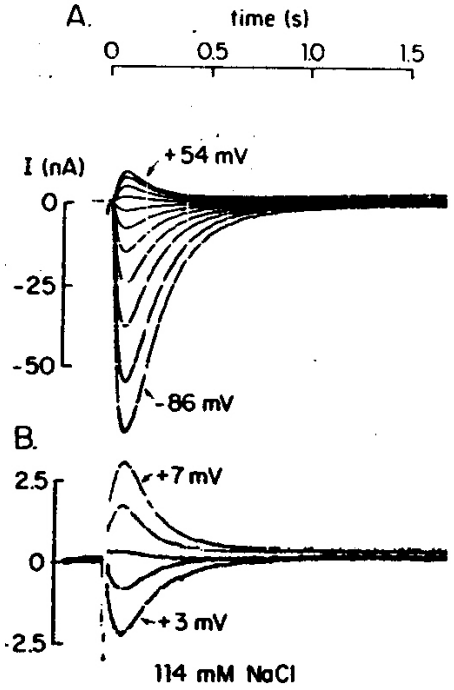
for nmj	P_S	
		Cs^+ 1.42
		Rb^+ 1.30
		K^+ 1.11
		Na^+ 1.00
		Li^+ 0.87
		NH_4^+ 1.79
		$HOCH_2CH_2\overset{+}{N}H_3$ 0.72

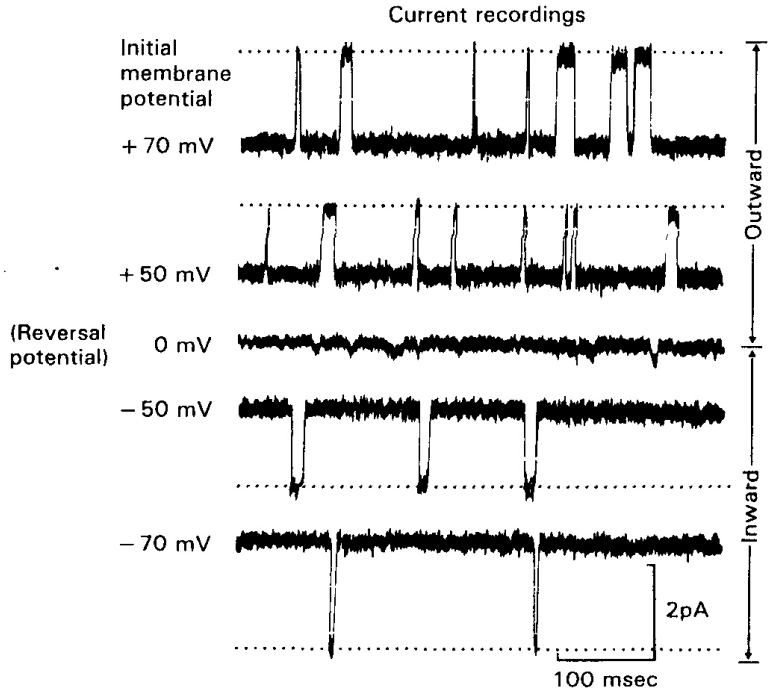
E in this equation can describe one channel or a family of channels (e.g., all leak channels).

Does ACh open one channel or two?

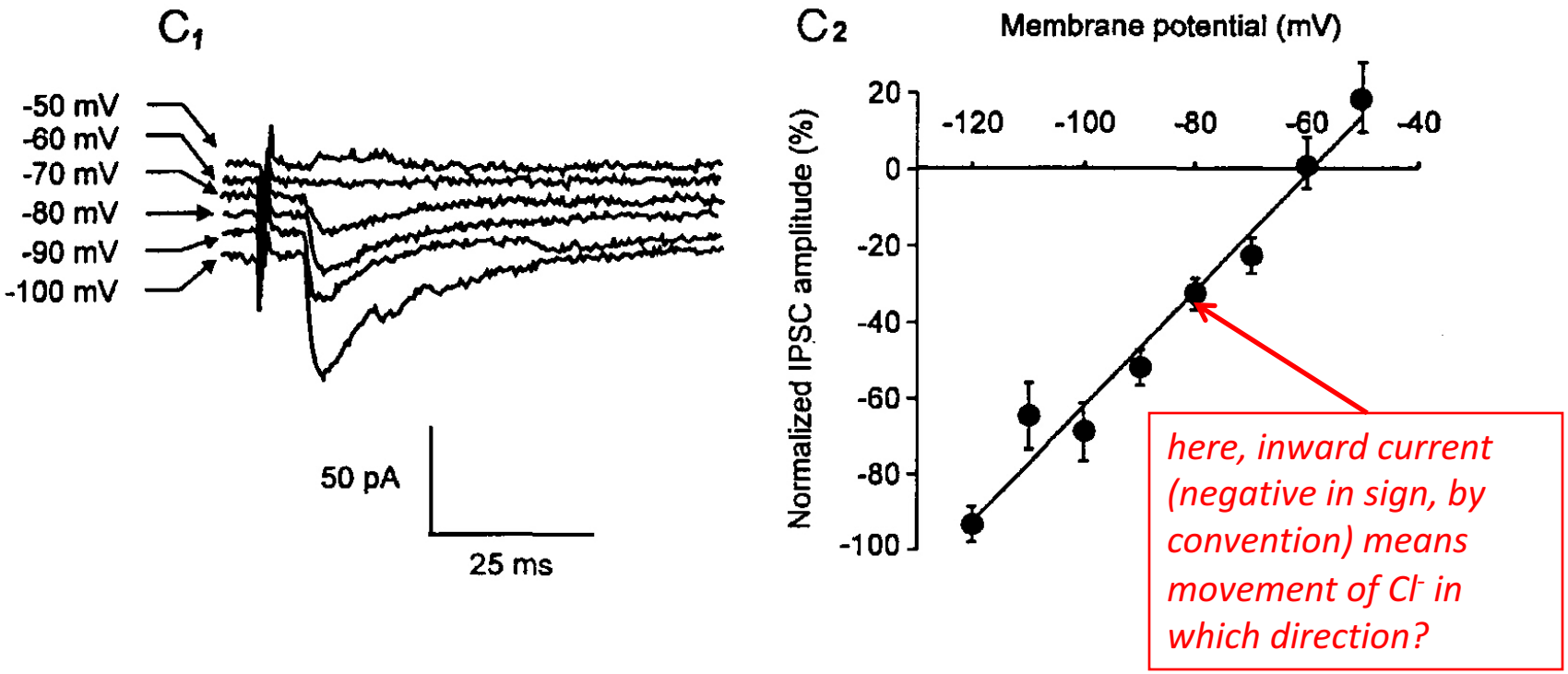
Fatt and Katz (1951) and Takeuchi and Takeuchi (1960) established that activation of AChRs drives the membrane potential to a value near 0 mV.

This could be explained if ACh opened one channel class permeable to both sodium and potassium, but a second possibility is that ACh opens two different channels, one for Na^+ and one for K^+.





The $GABA_A$ channel is an anion channel



Mouginot D, Kombian SB, Pittman QJ (1998) Activation of presynaptic $GABA_B$ receptors inhibits evoked IPSCs in rat magnocellular neurons in vitro. J Neurophysiol 79:1508-1517.

Under what conditions would movement of Cl^- be excitatory?

Inhibition occurs *via* two mechanisms

- Hyperpolarization
  - When the membrane is hyperpolarized, it is more distant from threshold and, generally, more current is required to reach threshold
- Shunting (short-circuiting)
  - Even if the membrane is not hyperpolarized much by the action of an inhibitory transmitter, the effect is still inhibitory, since Cl^- (or K^+) movement will oppose the consequences of inward current produced by the action of excitatory transmitters.
  - Shunting is the predominant form of inhibition in the nervous system!

OUTLINE

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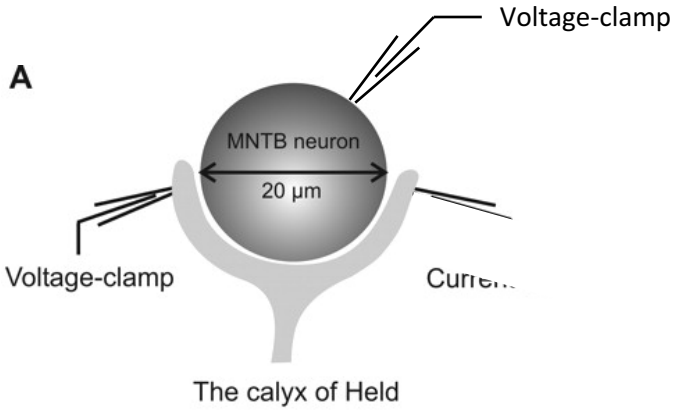
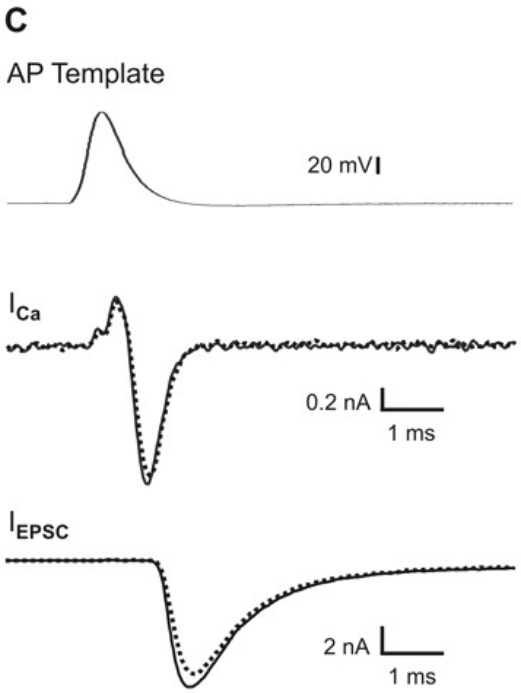
Calcium channels open in response to depolarization

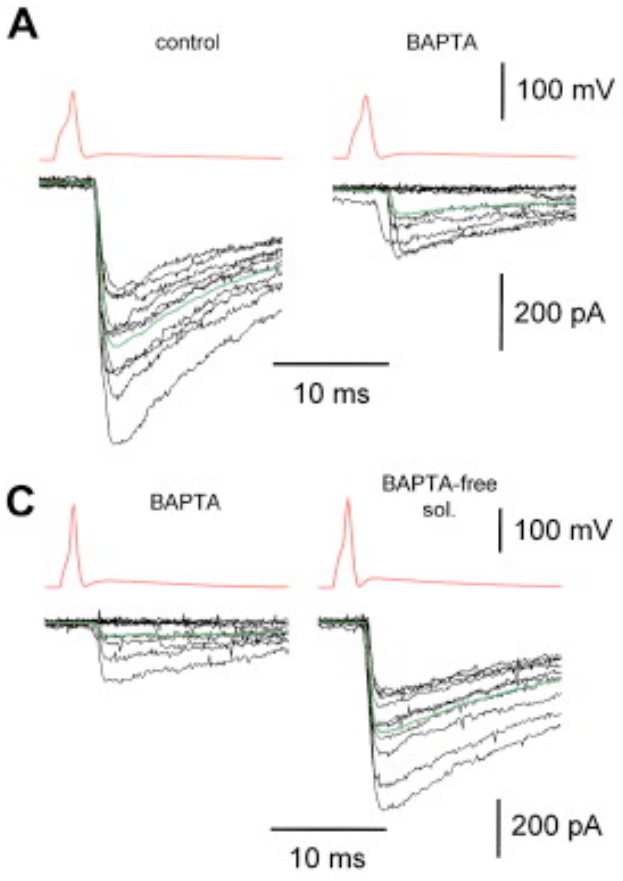


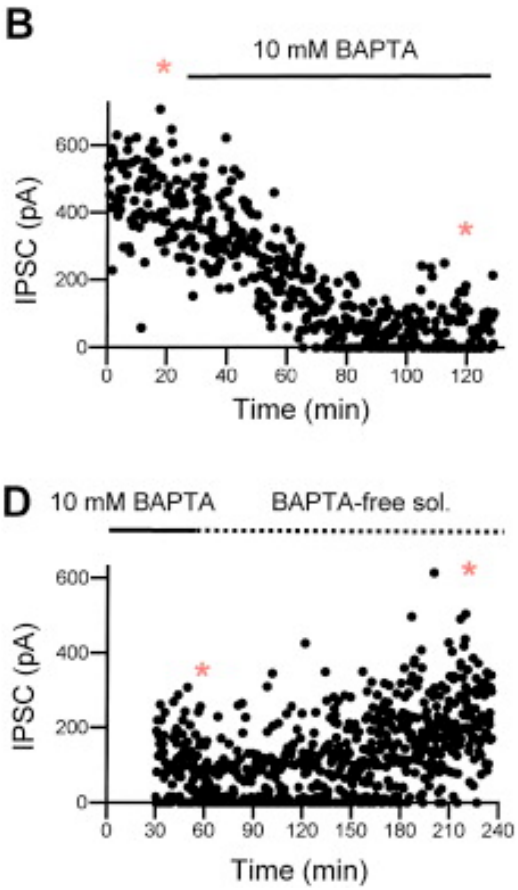


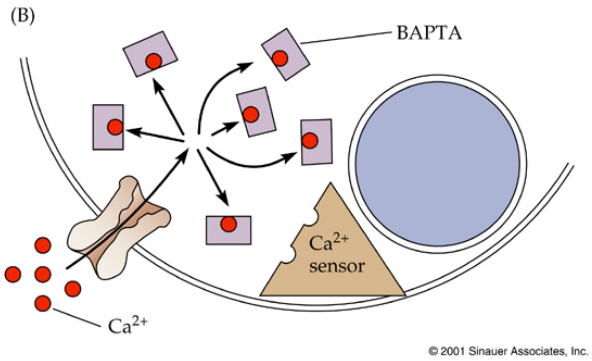
- Calyx of Held synapse
  Isolating calcium currents pharmacologically
- Sources of synaptic delay

Yang Y-M, Wang L-Y (2006) Amplitude and kinetics of action potential-evoked Ca^{2+} current and Its efficacy in triggering transmitter release at the developing calyx of Held synapse. J. Neurosci. 26: 5698-5708.

Calcium is necessary for release



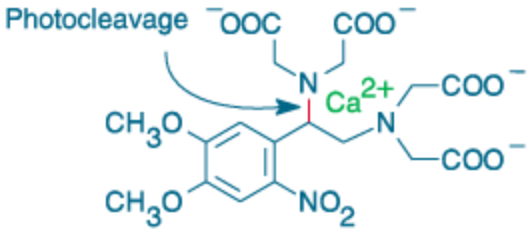




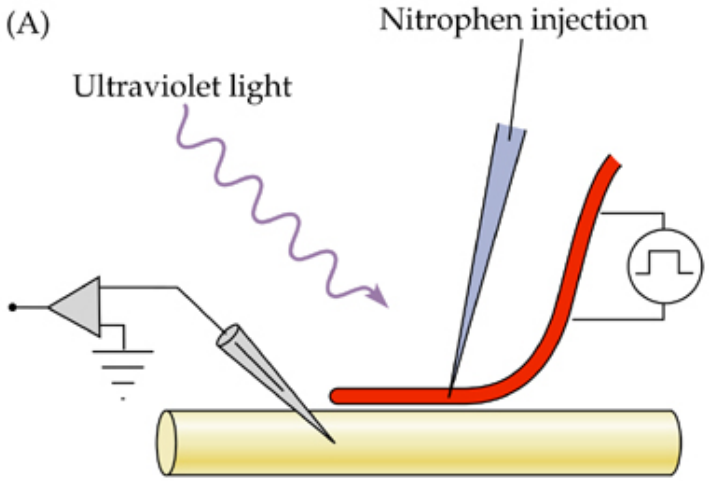
- Consequences of injecting BAPTA, a fast-acting Ca^{2+} buffer

Bucurenclu I, Kulik A, Schwaller B, Jonas P (2008) Nanodomain coupling between Ca2+ channels and Ca2+ sensors promotes fast and efficient transmitter release at a cortical GABAergic synapse. Neuron 57: 536-545.

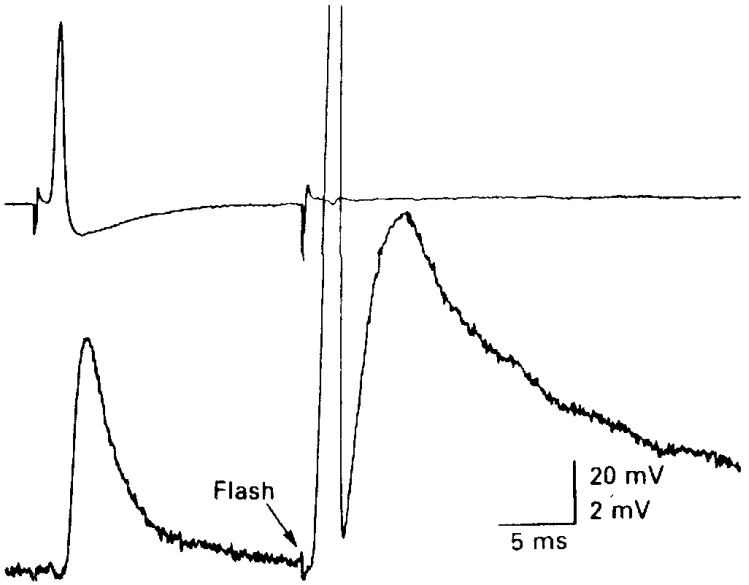
Calcium is sufficient for release



- Consequences of elevating $[Ca^{2+}]_i$ artificially.



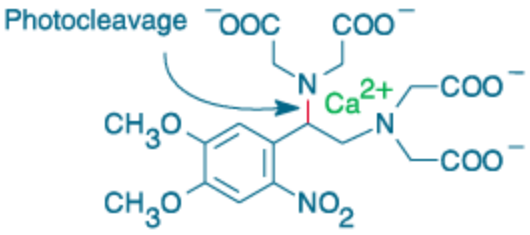
Squid giant synapse

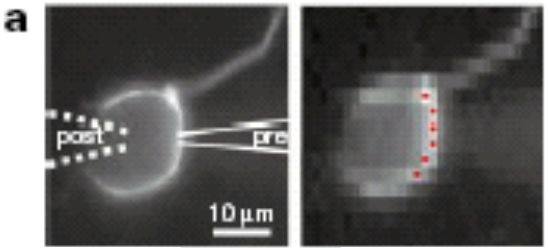


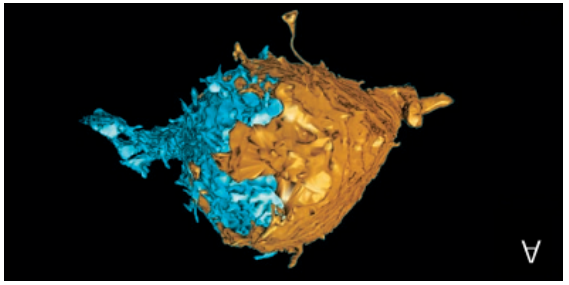
Delaney K, Zucker RS (1990) Calcium released by photolysis of DM-nitrophen stimulates transmitter release at squid giant synapse. J Physiol 426:473-498.

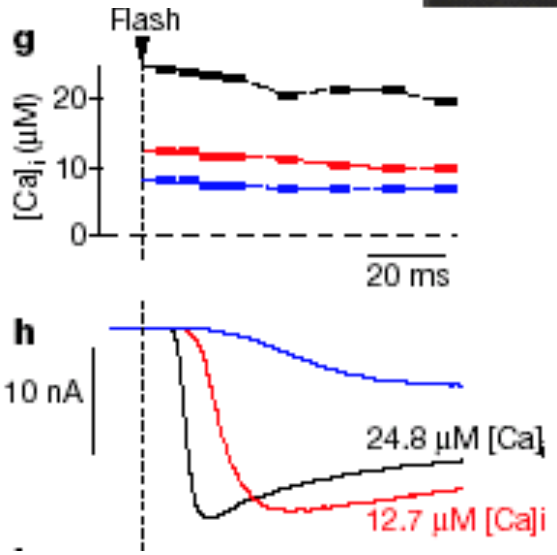
Release is dependent on the ≅4th power of $[Ca^{2+}]_i$

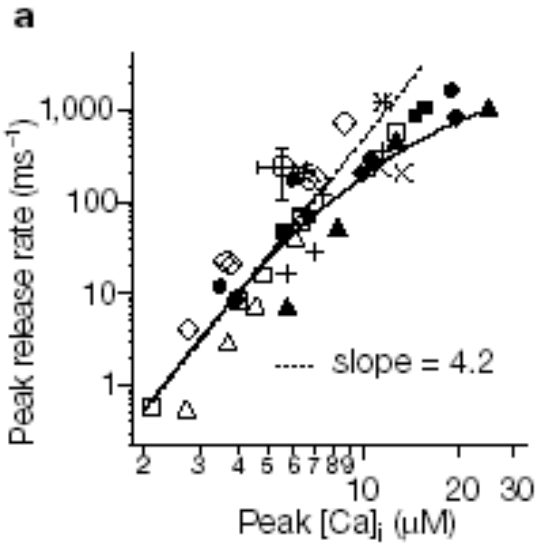
Calyx of Held (auditory brainstem)







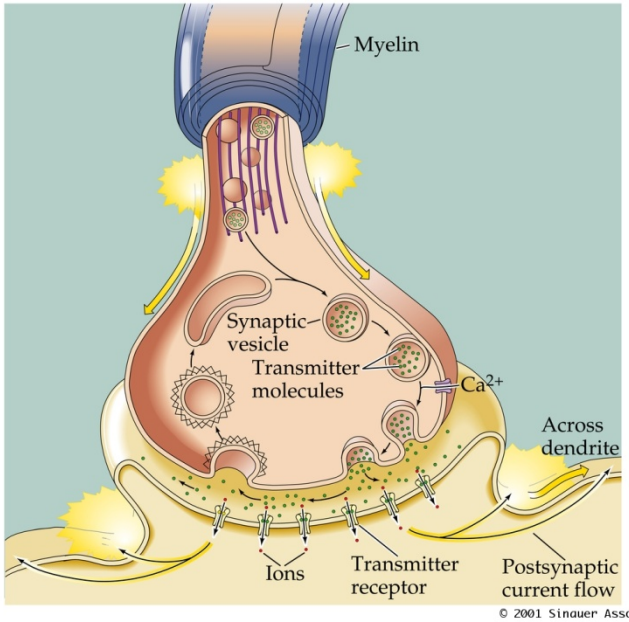




Schneggenburger R, Neher E (2000) Intracellular calcium dependence of transmitter release rates at a fast central synapse. Nature 406:889-893.

Fate of released transmitter

- Diffusion (D is ~0.5 μm^2/msec for transmitters)
  - Diffusion time is dependent on the square of distance ($t \approx x^2/D$)
- Binding to receptors
- Removal [Uptake, Hydrolysis (ACh)]
- What happens if you interfere with removal of transmitter?



Distance (μm)	Time (ms) (approx.)
0.1	0.01
1	1
10	100
100	10,000
1000	1,000,000
1 meter	32 years

Direct and indirect methods of measuring transmitter release

- Indirect
  - Postsynaptic Response
  - Presynaptic Response
    - Dye destaining (e.g., FM1-43)
    - Capacitance changes
- Direct
  - Voltammetry (amperometry)

OUTLINE

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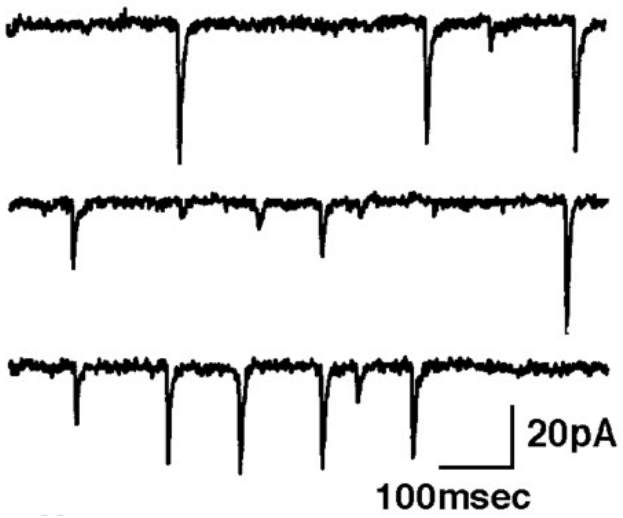
Spontaneous release (“minis”)

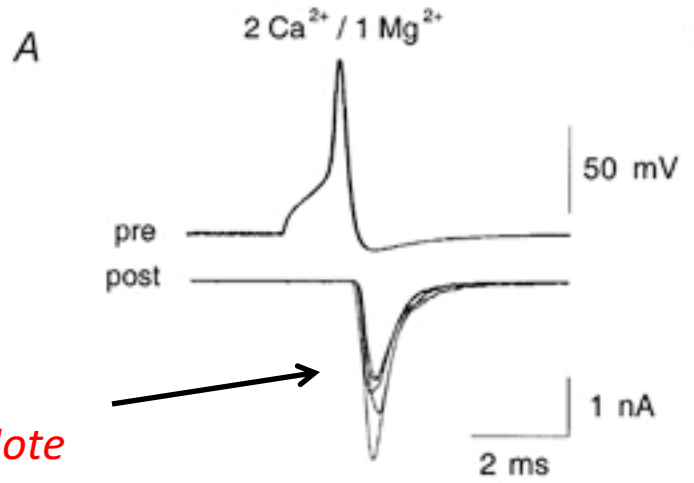
(following from the work of Bernard Katz in the 1950s)

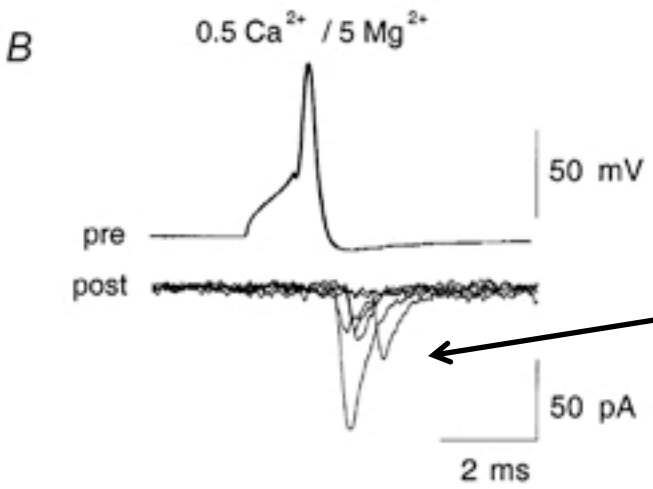


1. occur randomly
2. occur in the absence of electrical activity
3. caused by the release of multi-molecular packets of transmitter

Evoked release in low $[Ca^{2+}]_o$ shows "failures"

(following from the work of Bernard Katz in the 1950s)





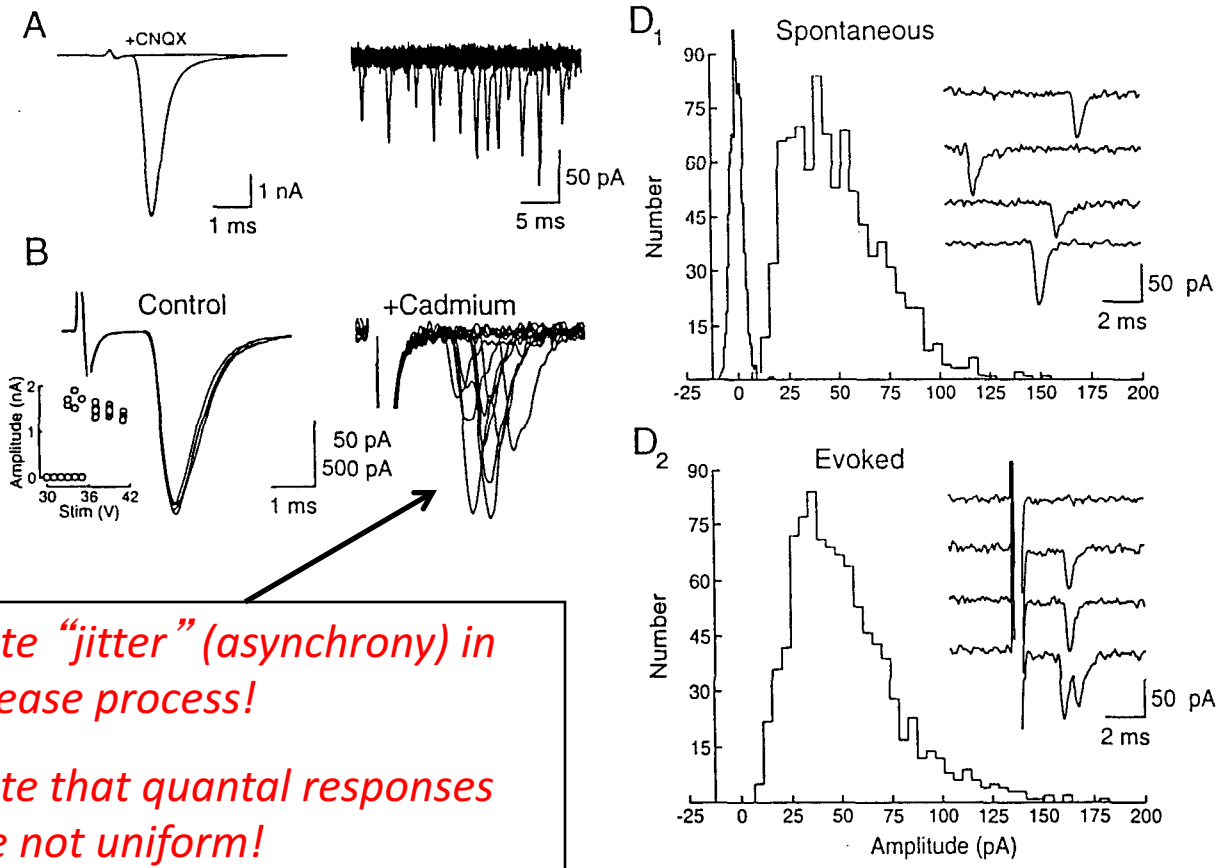
Sahara Y, Takahashi T (2001) J Physiol 536:189-197.

Note "jitter" (asynchrony) in release process!

Note fluctuation in response size.

- Reduction of $[Ca^{2+}]_o$ and or elevation of $[Mg^{2+}]_o$ reduces EPSC size and leads to "failures"

The smallest EPSCs are equal to the size of the spontaneously occurring events



Note "jitter" (asynchrony) in release process!

Note that quantal responses are not uniform!

Isaacson JS, Walmsley B (1995) Counting quanta: direct measurements of transmitter release at a central synapse. Neuron 15:875-884.

The "quantum hypothesis"

(del Castillo and Katz, 1954)

- Transmitter is released in multimolecular packets, or quanta. These packets are released spontaneously at low frequency. The arrival of an action potential in the nerve terminal greatly increases the frequency of release. (from 1 per sec to ~100 per msec in the case of the frog nerve-muscle junction)
- What is the signal directly responsible for increasing the frequency of release?

The Katz formalism

- "Suppose we have, at each nerve-muscle junction, a population of *N* units capable of responding to a nerve impulse. Suppose, further, that the average probability of responding is *P*, …, then the mean number of units responding to one impulse is $m = N * P$."

  (del Castillo and Katz, J. Physiol. 124: 560-573 (1954)

- What is the physical identity of the units?

- for each member of the population *N*, there may or may not a release event in response to the arrival of an action potential

- transmitter release is a probabilistic, or stochastic, event. It can be studied using statistics.

How to test the "quantum hypothesis?"
(does transmitter release really operate this way?)

- Try to predict the average number of quanta that are released, assuming that the hypothesis is correct, and compare this to a direct measurement of the "quantum content."
- The direct measurement of quantal content is the number of quanta. Usually, however, you cannot count quanta. Instead, you divide the average amplitude of the evoked response (epp) by the average amplitude of the mepp (assuming linear summation).
  - Is it OK to assume linear summation?

Use the binomial distribution to predict the quantal content

- The binomial theorem describes distributions of outcomes across a set of trials where there are only two possible outcomes (heads/tails, success/failure, release/no release) per trial per member of the population N.
- If p = probability of success per trial, then the probability P (caps!) of getting k successes in n trials is

$$P(k;n,p)=\binom{n}{k}p^{k}(1-p)^{(n-k)},$$ where $$\binom{n}{k}=\left(\frac{n!}{k!(n-k)!}\right)$$

- The average number of successes is m = N*p
- Problem! – what if you don't know N or p?

"n choose k"

Using the Poisson distribution to predict quantal content

(see "binomial" handout)

- Poisson is a special case of the binomial, where p<<1 and $n \to \infty$

$$P(k;n,p) = \frac{m^k}{k!} e^{-m}$$

You don't have to know p!!!

- Probability of getting 0 successes (a failure)

$$P(0;n,p) = \frac{m^0}{0!} e^{-m} = e^{-m}$$

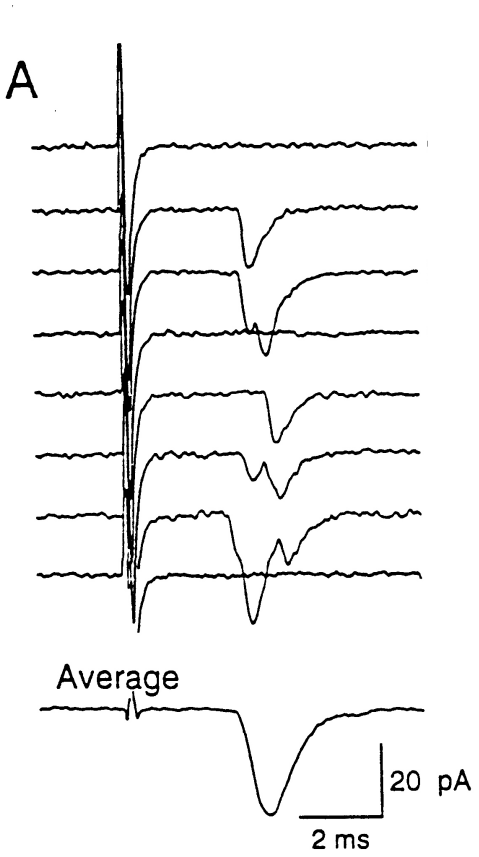
$$P(0;n,p) = \frac{T_0}{T}$$, *where T is the number of trials and T_0 is the number of trials resulting in a failure*

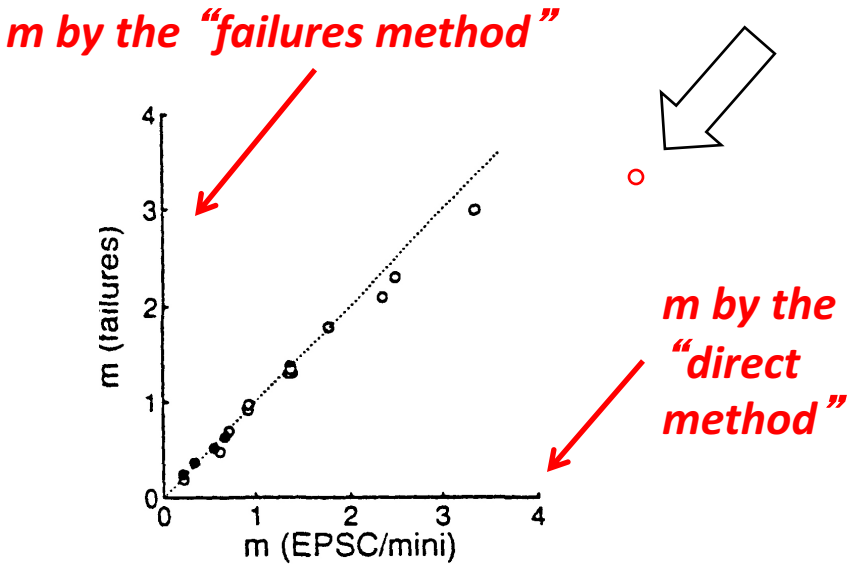
$$m = \ln\left(\frac{T}{T_0}\right)$$

the "failures method"

(later, the CV method ($m=1/CV^2$)

Synapses obey Poisson statistics at low probabilities of release





Isaacson JS, Walmsley B (1995) Counting quanta: direct measurements of transmitter release at a central synapse. Neuron 15:875-884.

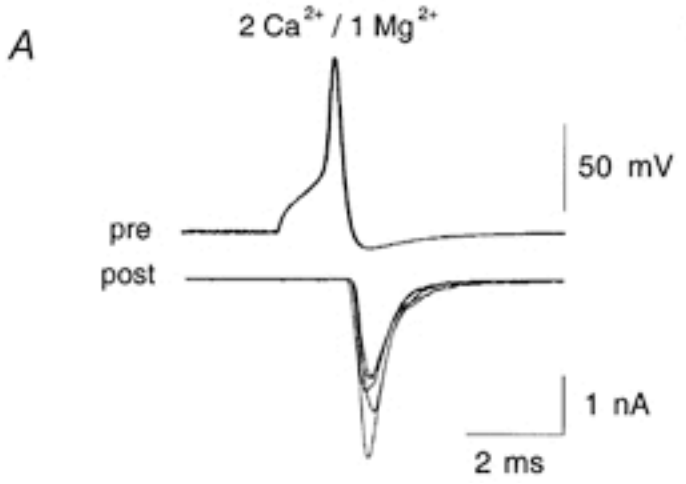
- Measure m (direct method) and compare to m calculated from the failures method

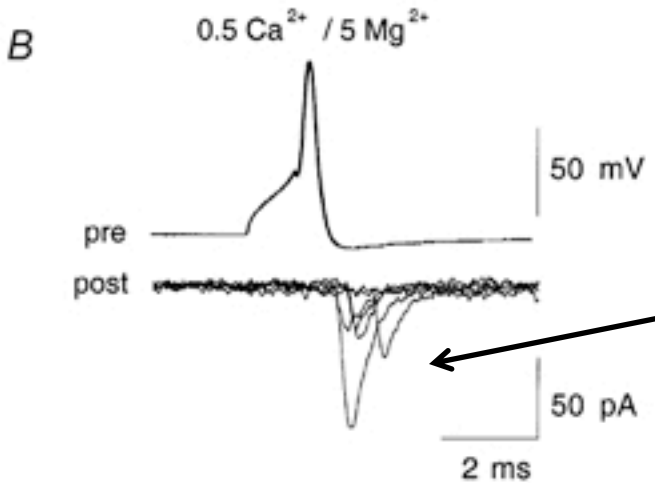
The quantum hypothesis is verified. So what?

- What is the significance of the fact that the poisson distribution successfully predicts m?
- Biology
  - that evoked responses are constructed from the same "units" that occur spontaneously (this is controversial – e.g., Kavalali's work)
  - that these "units" (releasable quanta) are released independently
- Methodology
  - you might be able to estimate whether a change in the size of an EPSC is caused by a change in quantal content

"Synchronous" vs. asynchronous release

Release is never truly synchronous,

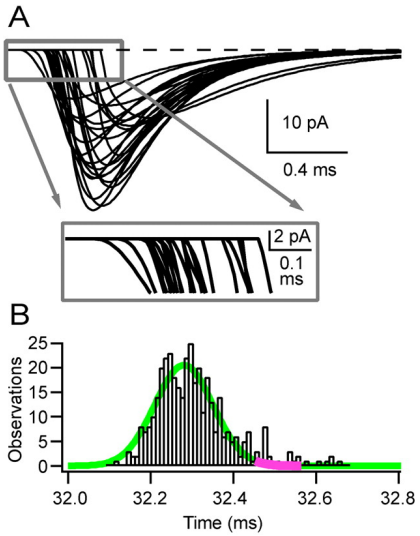




Sahara Y, Takahashi T (2001) J Physiol 536:189-197.

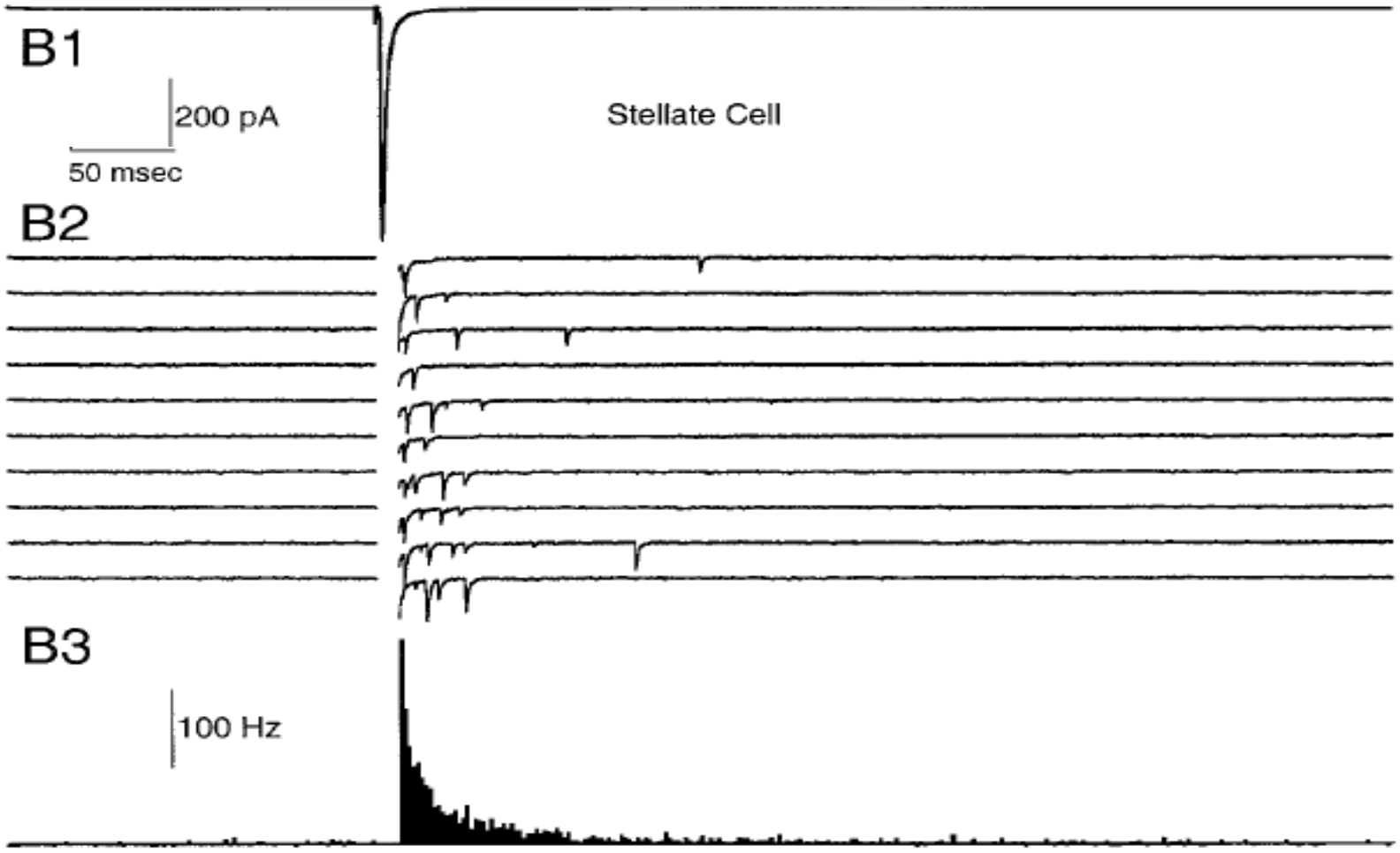
Note "jitter" (asynchrony) in release process!

but it can be close to synchronous (esp. at physiologic temperature).



Sargent PB, Saviane C, Nielsen TA, DiGregorio DA, Silver RA (2005) J. Neurosci. 25:8173-8187.

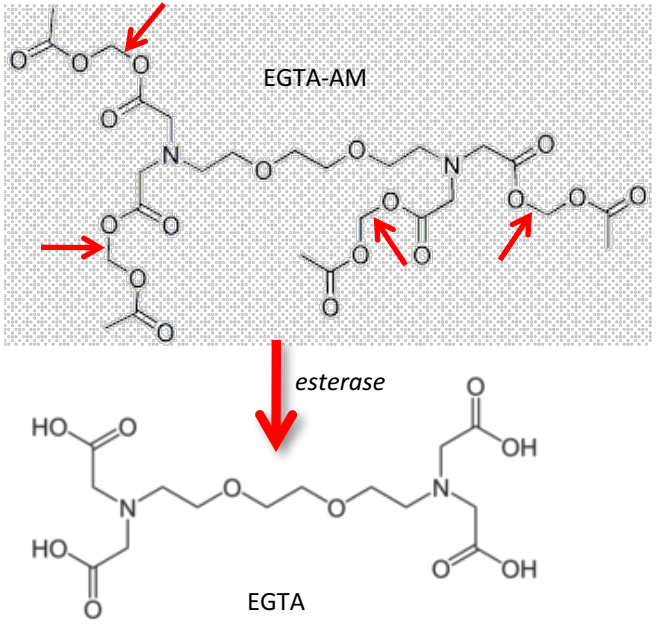
Asynchronous (Delayed) Release

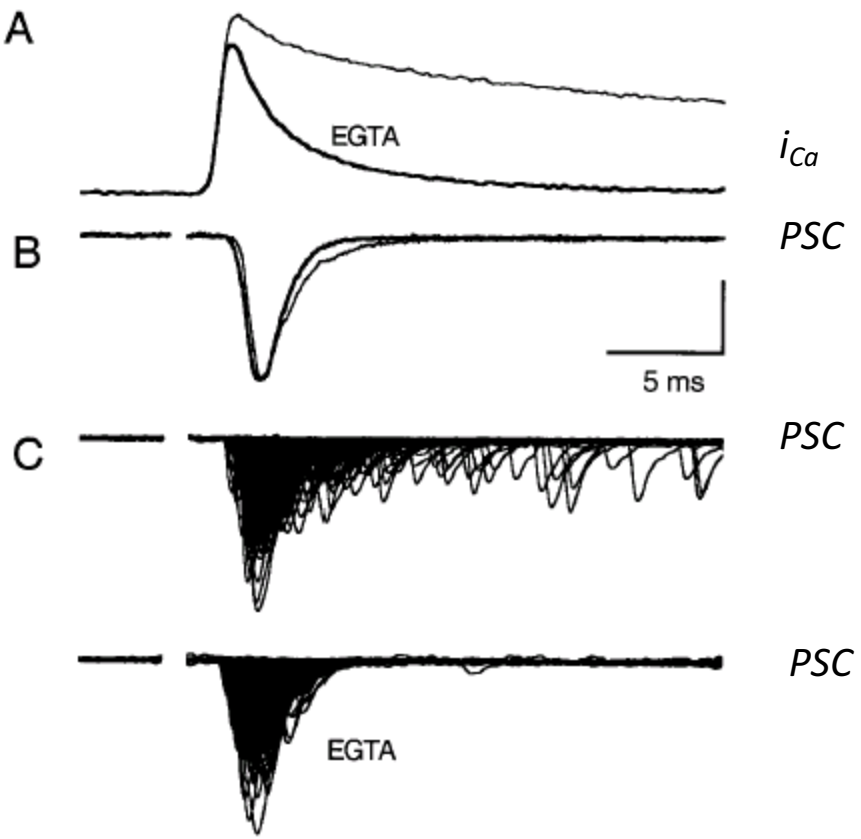


Atluri PP, Regehr WG (1998) Delayed release of neurotransmitter from cerebellar granule cells. J Neurosci 18:8214-8227.

Introducing a Ca^{2+} buffer into the terminal reduces delayed release

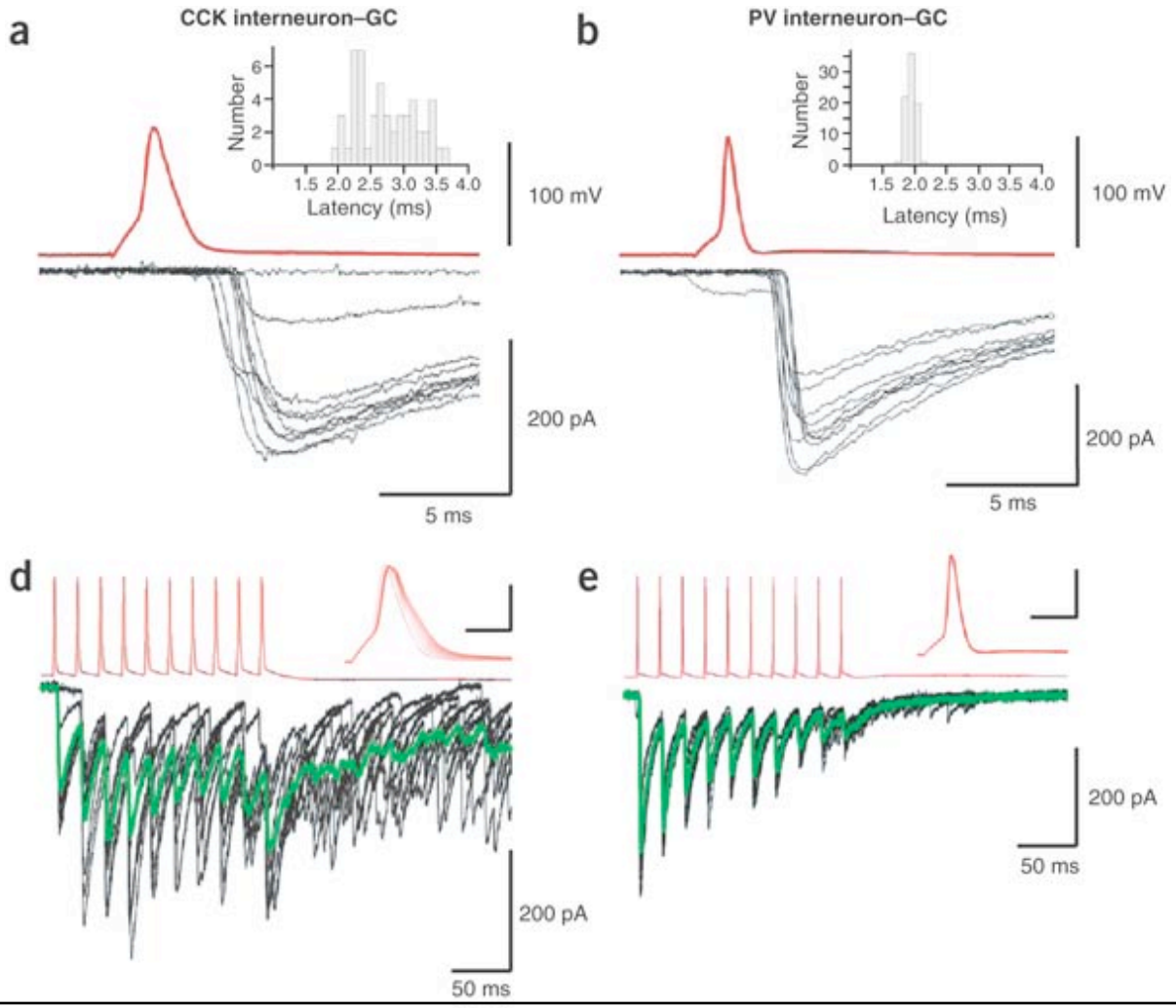
- parallel fiber – Purkinje cell synapse in cerebellum
- EGTA-AM into the bath





Chen C, Regeher WG (1999) Contributions of residual calcium to fast synaptic transmission. J Neurosci 19:6257-6266.

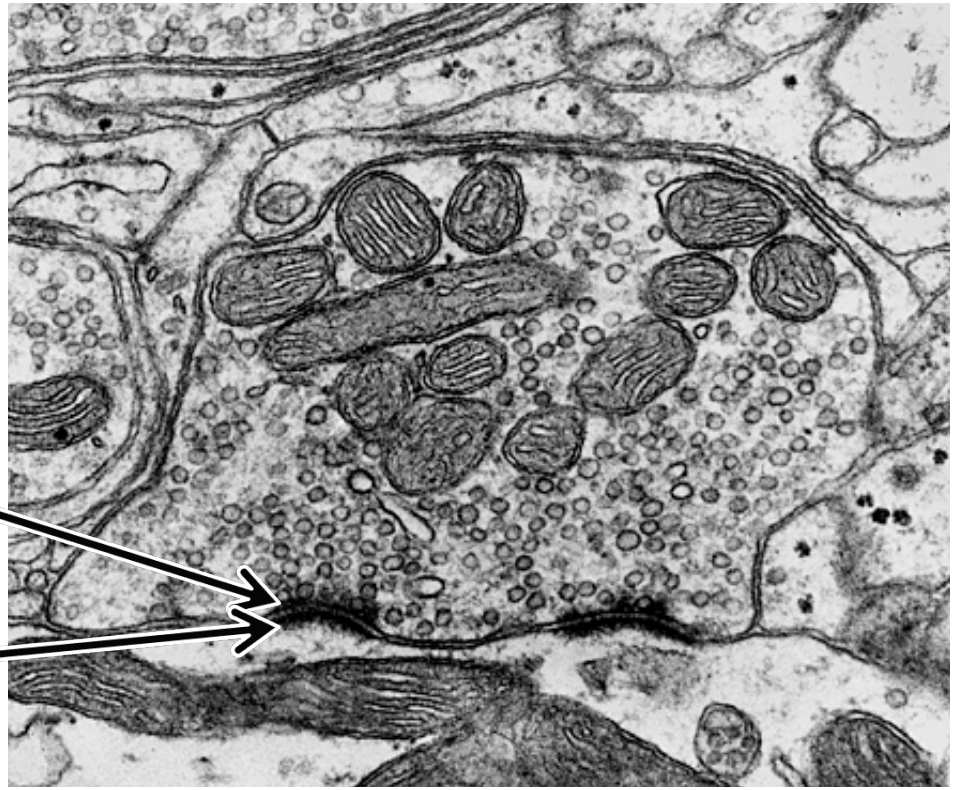
Synaptic connections show wide diversity in the importance of asynchronous release



Hefft S, Jonas P (2005) Asynchronous GABA release generates long-lasting inhibition at a hippocampal interneuron–principal neuron synapse. Nature Neurosci. 8:1319-1328.

Structure of the Nerve Terminal

- synaptic vesicles
- “docked” vesicles
- active zones (AZs)
- postsynaptic densities (PSDs)

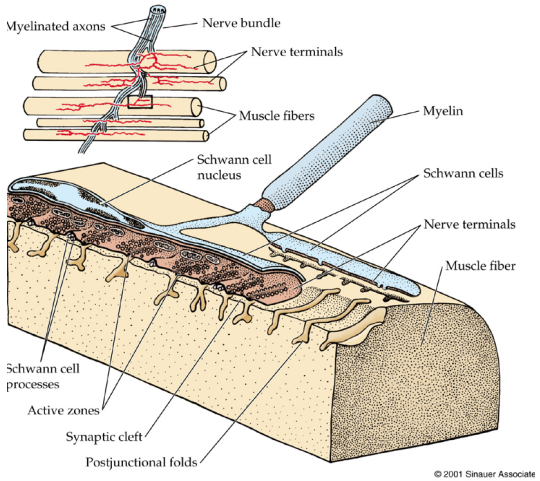


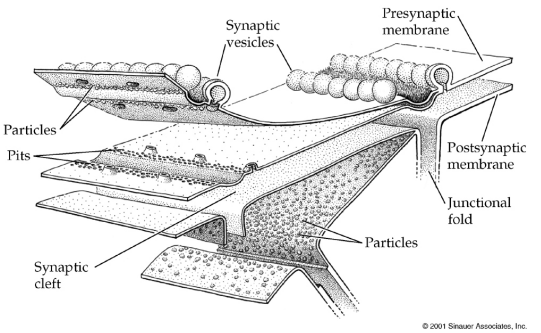
from Heuser lab web site

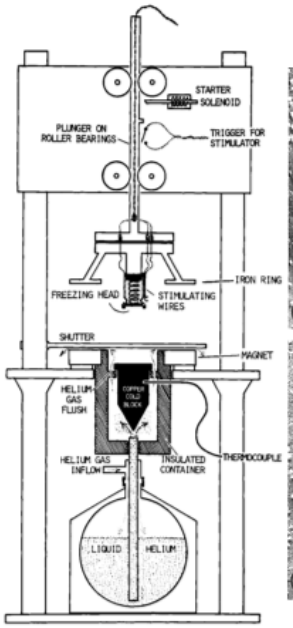
The vesicle hypothesis

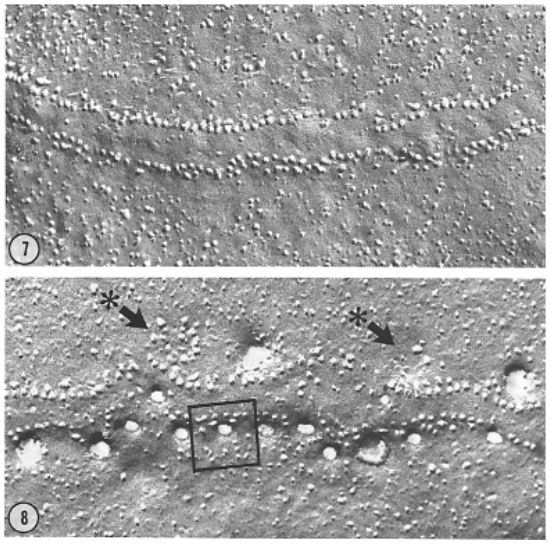
A quantum of transmitter is that amount stored in a synaptic vesicle. Release occurs *via* exocytosis.

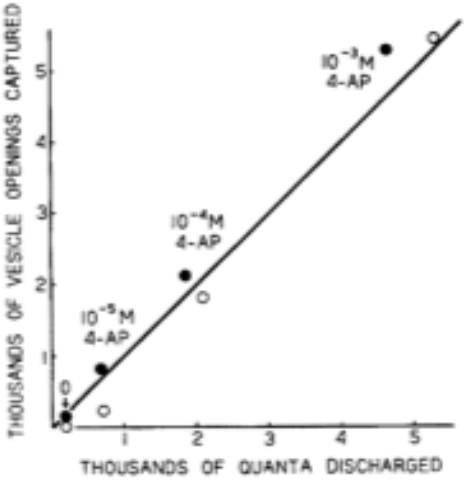
- Stimulation produces exocytotic events, here seen as pits on the C face of the plasma membrane in freeze fracture.









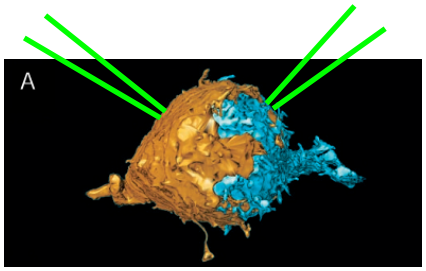


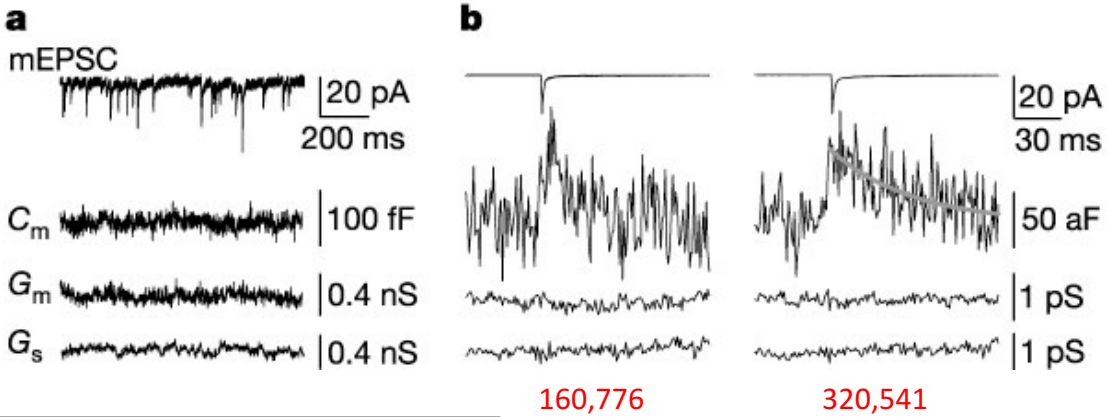
Heuser JE, Reese TS, Dennis MJ, Jan L, Jan YN, Evans L (1979) Synaptic vesicle exocytosis captured by quick freezing and correlated with quantal transmitter release. J. Cell Biol, 81: 275-300.

The vesicle hypothesis

A quantum of transmitter is that amount stored in a synaptic vesicle. Release occurs *via* exocytosis.

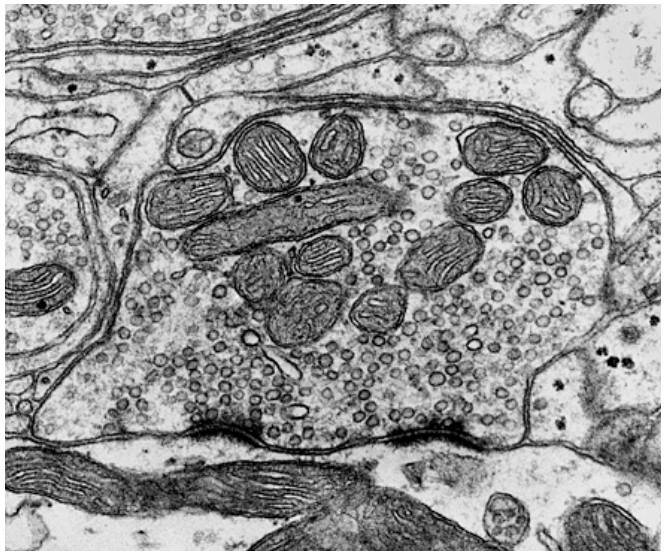
- Capacitance measurements show that release of a quantum of transmitter is accompanied by an increase in the surface area of the terminal by the surface area equivalent to a ~50 nm spherical vesicle.



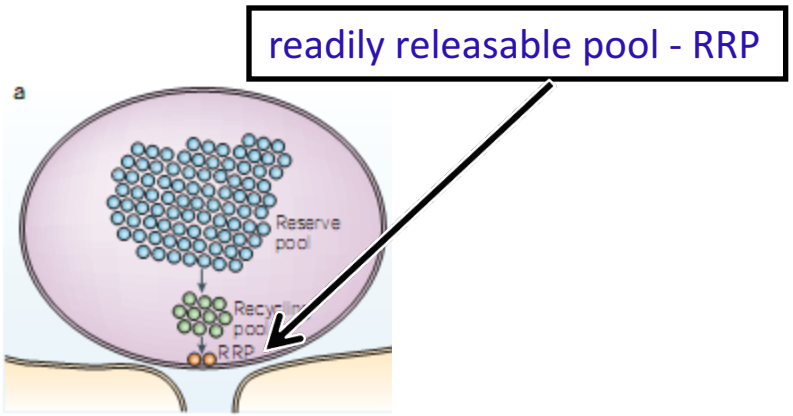


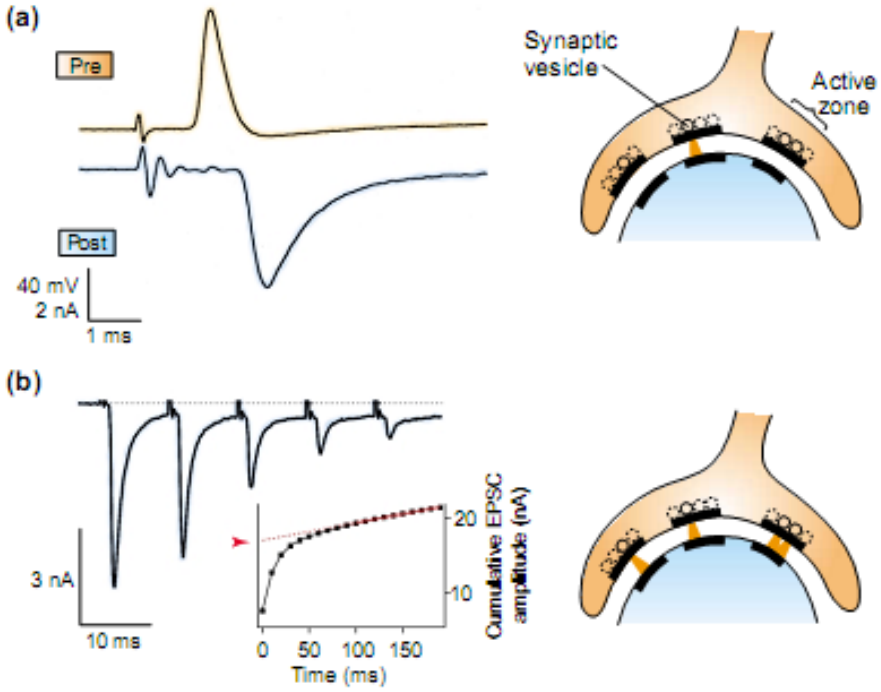
Sun J-Y, Wu X-S, Wu J-G (2002) Single and multiple vesicle fusion induce different rates of endocytosis at a central synapse. Nature 417:555-559.

Nerve terminals contain distinct pools of vesicles



- What is the physical correlate of N, the number of readily releasable vesicles?
- N << # vesicles
- N ≅ number of anatomically docked vesicles (very approximately!)





Rizzoli SO, Betz WJ (2005) Synaptic vesicle pools. Nat Rev Neurosci 6:57-69.

Schneggenburger R, Sakaba T, Neher E (2002) Trends Neurosci 25:206-212.

Remaining controversies (partial list!)

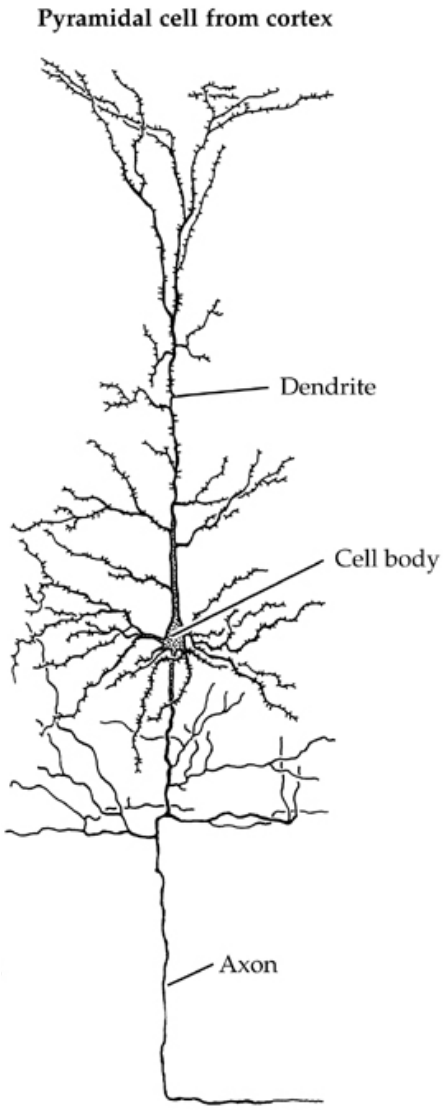
- Is exocytosis accompanied by "full collapse fusion" or the vesicle, or by a "kiss and run" mechanism?
  - Capacitance measurements suggest that "kiss and run" may not be prevalent. (What kind of data would support "kiss and run?")
  - "Kiss and run" and "full collapse fusion" may both occur naturally at different times, depending on the state of the terminal.
- Are spontaneously occurring events ("mEPSCs") identical to the building blocks of EPSCs?
- How is endocytosis linked to exocytosis?

Poisson and binomial distributions

- Is the poisson distribution relevant when synapses operate at physiological calcium?
- **NO!!!**
  - P is no longer small!
  - At many synapses, N is not large, and so the Poisson would not apply, strictly, even if $[Ca^{2+}]_o$ were reduced.
  - Note, however, that in practice, it does work, as long as p is small.
- For most CNS synapses at physiological $[Ca^{2+}]_o$, the binomial distribution, not the poisson one, should be used to analyze transmitter release.
- To predict the distribution of outcomes using the binomial, we need to know more than simply m, alas.

Additional challenges to studying the statistics of transmitter release in the CNS

1. In many cells, you cannot record synaptic responses faithfully from the cell body (space clamp errors).
2. Most central neurons are multiply innervated. You may be able to record evoked responses from one input, but you cannot easily study spontaneous release only from that input. (convergence)
3. Simple binomial models assume that P is uniform across the population N, but it's not. (non-uniformity of P)
4. Simple binomial models assume that Q is uniform, but it's not. (non-uniformity of Q)



Measuring quantal parameters without knowing about mEPSCs: variance-mean analysis

- Measure the mean and the variance of sets of responses to stimulation of a single input under different probabilities of release.
- You do not need to measure spontaneous events,
- From the binomial distribution, the variance and mean are related according to:

$$\sigma^2 = QI - I^2/N$$

where

I = the current,

Q = quantal size, meaning the response to one quantum, and

N = the number of releasable quanta

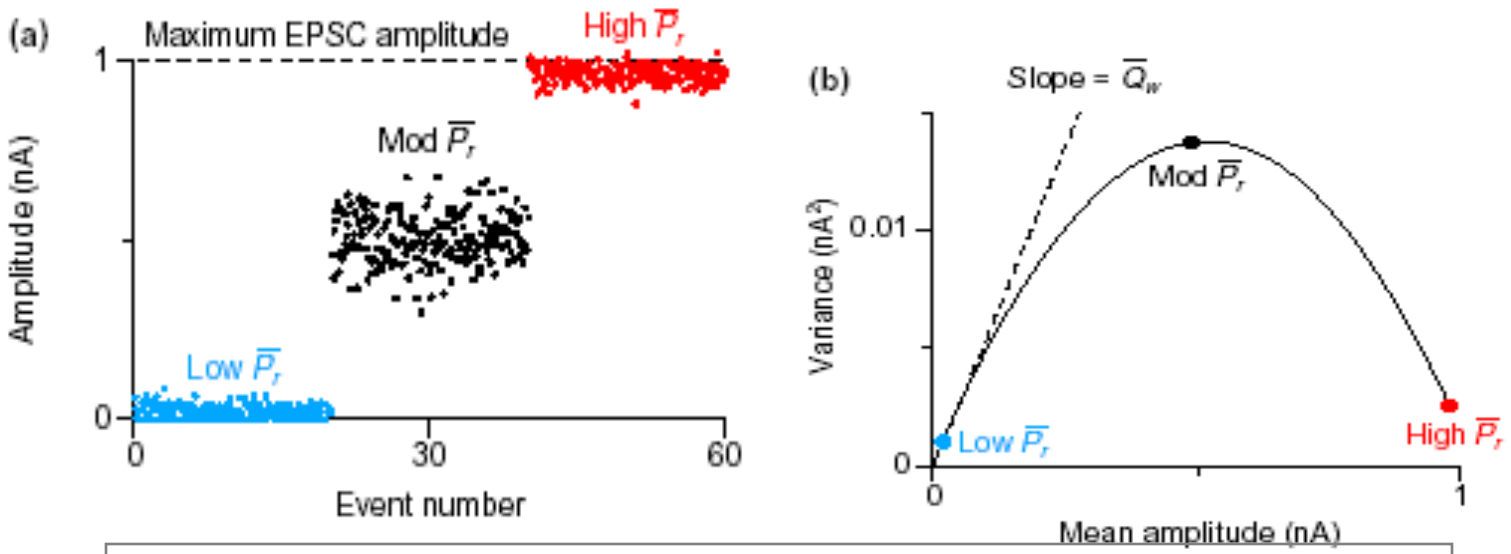
From the binomial

1. Mean = NP or NPQ
2. $\sigma^2 = NP(1-P)$ or $NPQ^2(1-P)$

Substitute for P

Estimating *N*, *P*, and *Q (cont.)*

$\sigma^2 = QI - I^2/N \longrightarrow y = Ax - Bx^2$



Clements JD, Silver RA (2000) Unveiling synaptic plasticity: a new graphical and analytical approach. Trends Neurosci 23:105-113.

Note: this is the simple binomial version of the expression, but this analysis can readily be morphed into one that accounts for non-uniformity in P and in Q (the multinomial).

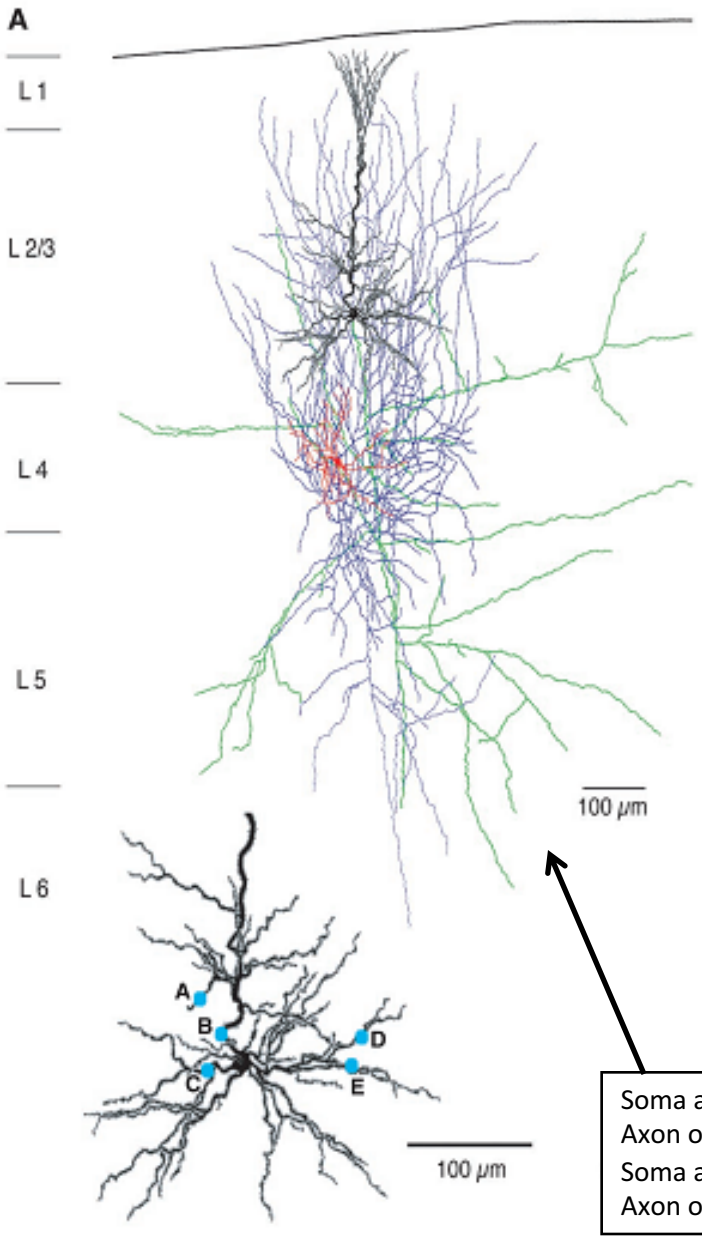
Is Q independent of P?

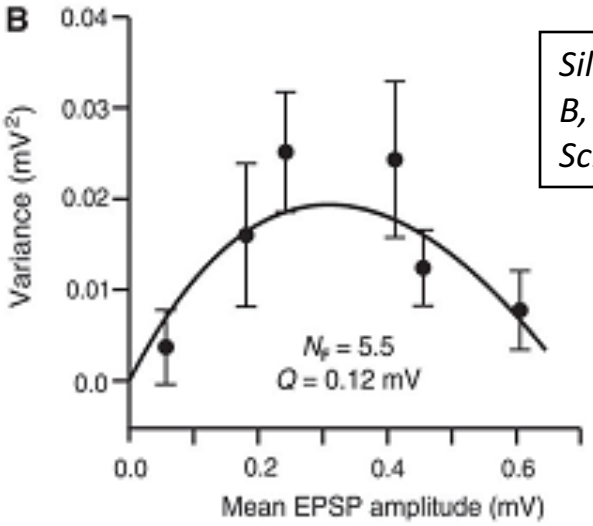
- Binomial-based analyses of transmitter release assume that the quantal response, Q, is independent of P
  - i.e., that the response to each quantum is the same, regardless of how many quanta are released
- Is this a good assumption? Are synapses "linear?" (i.e., does the postsynaptic cell provide a linear readout of the number of quanta released?)

Are synapses "linear?" (cont.)
(Is Q independent of P?)

- The suitability of the poisson statistics suggests that release occurs independently for members of the population N (presynaptic).
- But what about the consequences of release? Is the response to release of one quantum independent of the release of another? (postsynaptic)
  1. What is the spatial relationship between separate release sites that constitute a synaptic connection?
  2. Can more than one quantum of transmitter be released per active zone?
  - If release sites are well separated, and if no more than one quantum can be released per action potential per site, then the postsynaptic cell should be able to sum the responses to individual quanta linearly.

Univesicular Release



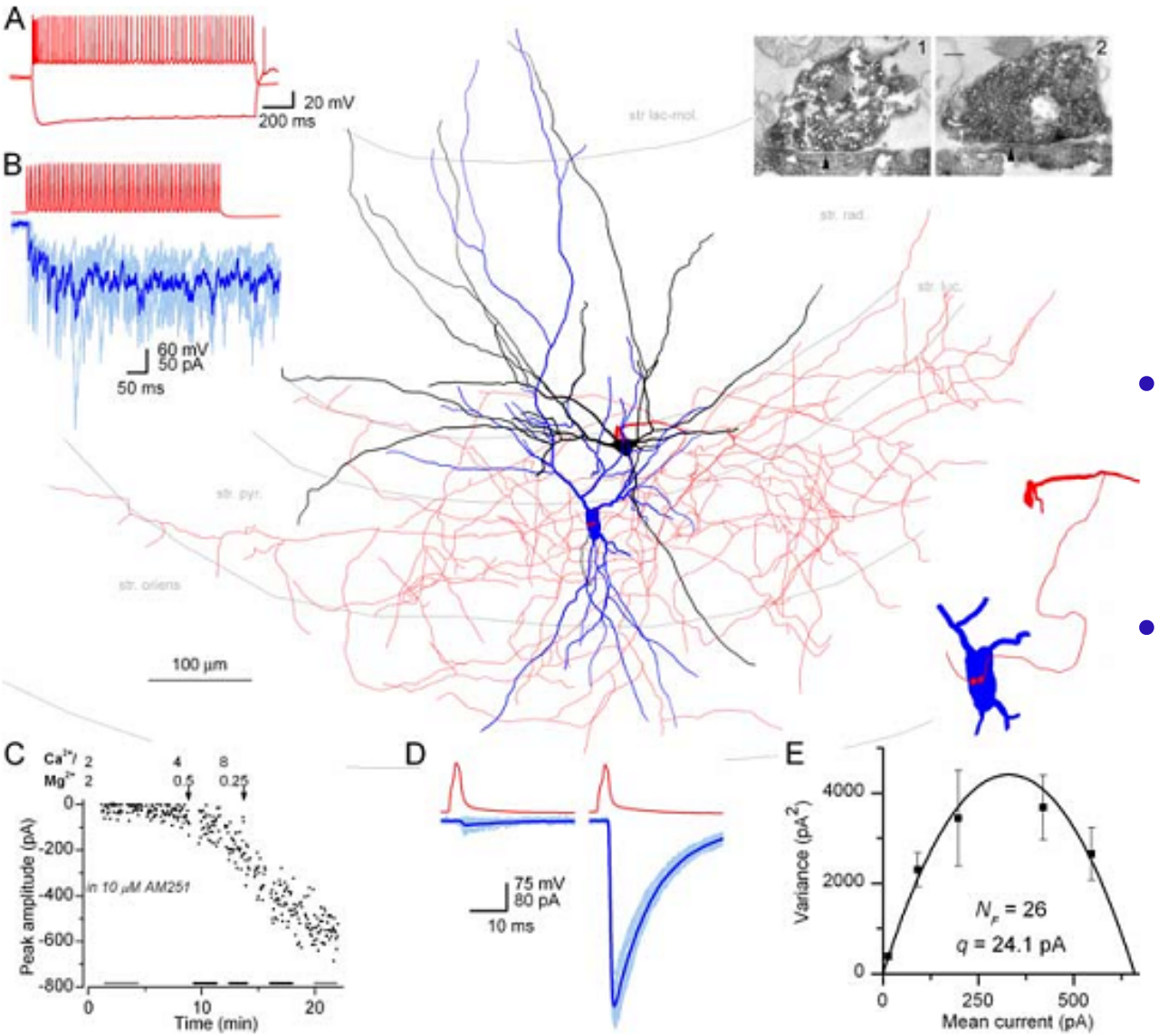


Silver RA, Lubke J, Sakmann B, Feldmeyer D (2003) Science 302: 1981-1984.

- Measure N (variance-mean analysis) and measure # boutons.
- N = # boutons.
- Release is univesicular, and since release sites are widely distributed, the response should scale linearly with the number of quanta released

Soma and dendrites of presynaptic cell are in red
Axon of presynaptic cell is in blue
Soma and dendrites of postsynaptic cell are in black
Axon of postsynaptic cell is in green,

Multivesicular Release



Biro AA, Holderith NB, Nusser Z (2006) J Neurosci. 26: 12487-12496.

- Measure N (variance-mean analysis) and measure # boutons.
- N > # boutons.

Further evidence for multivesicular release

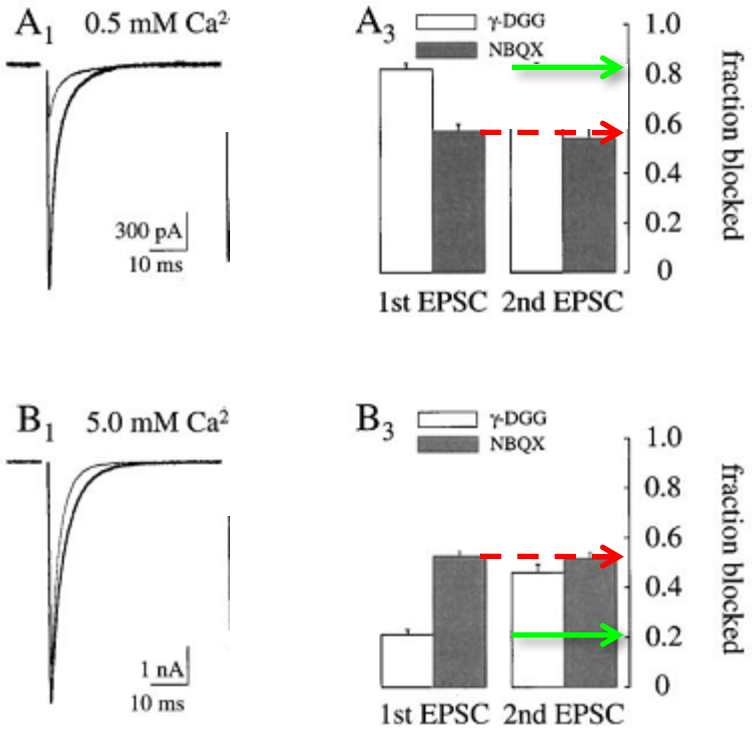
- As P increases, m will increase
- What happens to peak [glu]?
- Look at effects of slow-off and fast-off antagonists

Climbing fiber-Purkinje cell (CF-PC) synapse in cerebellum

NBQX is a high affinity competitive AMPAR antagonist. Its efficacy will not depend upon [glu].

γ-DGG is a low affinity, competitive AMPAR antagonist. Its efficacy will depend upon [glu].

Showing EPSC before and after γ-DGG



Wadiche JI, Jahr CE (2001) Multivesicular release at climbing fiber-Purkinje cell synapses. Neuron 32:301-313.

Further evidence for multivesicular release

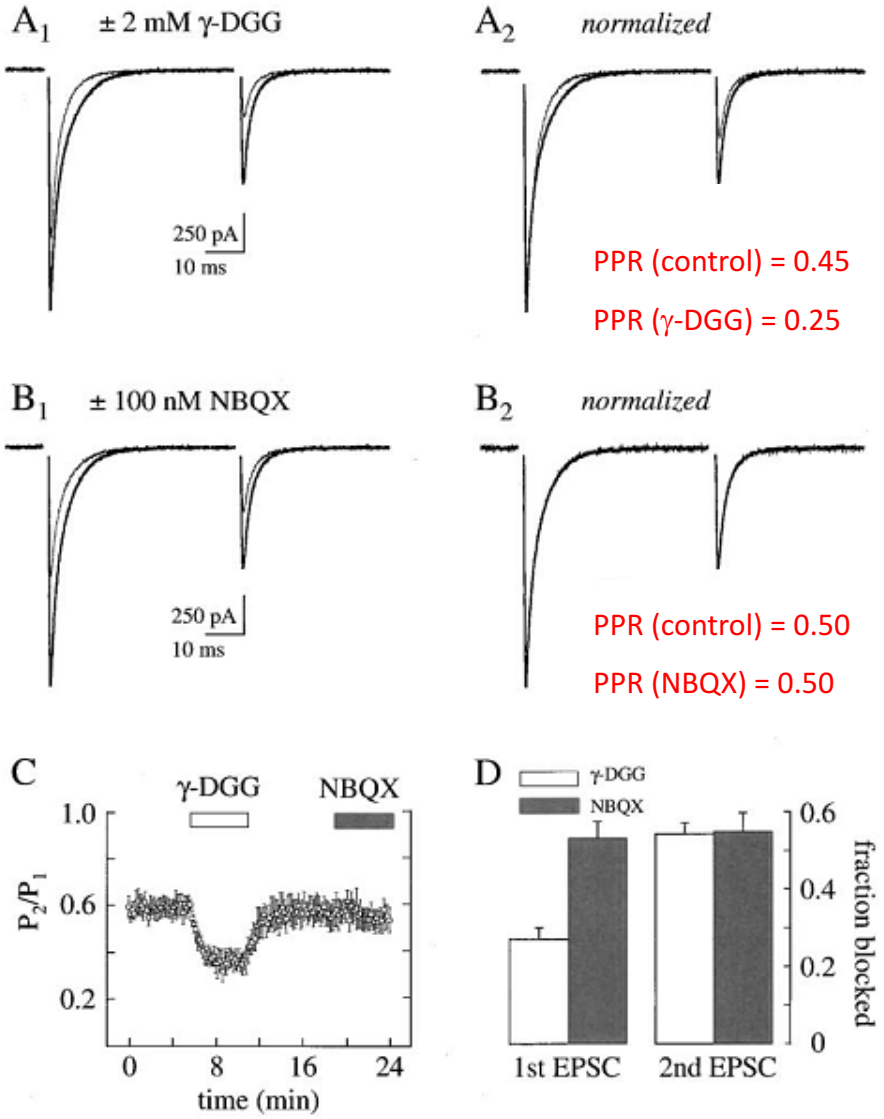
(cont.)

Paired pulse depression

PPR is different in control and in the presence of γ-DGG. It's not different in NBQX.

What's going on?

Depression is caused in part by depletion of vesicles. Fewer quanta are released in response to the second stimulus. The data suggest that peak [glu] is larger in response to the first pulse (γ-DGG is less effective). This again is evidence of multivesicular release.

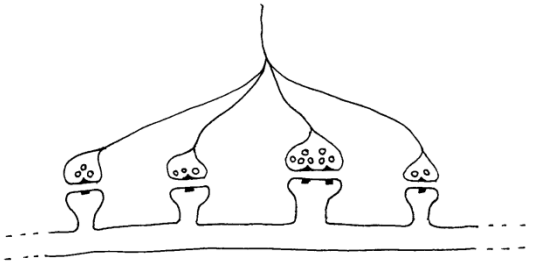


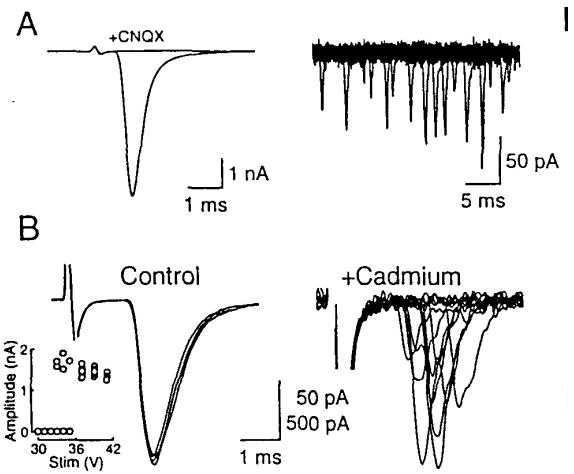
Climbing fiber-Purkinje cell synapse in cerebellum

Wadiche JI, Jahr CE (2001) Multivesicular release at climbing fiber-Purkinje cell synapses. Neuron 32:301-313.

Q (quantal size) is not uniform
CV is 0.2-0.6 (CV= S.D./mean)

- Intrasite/intersite variability





Isaacson and Walmsley (1995)

- Sources of variability
  - intrasite
    - amount of glutamate in vesicle?
    - is all of the glutamate in the vesicle released, and released rapidly? (are all exocytotic events similar?)
    - probabilistic nature of events (P_{open} for receptor's channel)
  - intersite
    - is the density/number of glutamate receptors (across sites) similar?
    - is the density/number of glutamate transporters (across sites) similar?
    - is the geometry of each synaptic contact similar?

OUTLINE

1. Electrical vs. Chemical Synaptic Transmission
2. Characteristics of Ligand-Gated Ion Channels
3. Transmitter Release
4. Transmitter Release Statistics
5. Synaptic Plasticity (if time)
   ICING!!!

Synaptic Strength

$$I = m*Q = N* P*Q$$

I = response, measured typically in current (e.g., peak of EPSC)

m = avg. number of quanta released (=N*P)

N = number of releasable quanta [readily releasable pool (RRP) of vesicles]

P = average probability of release, and

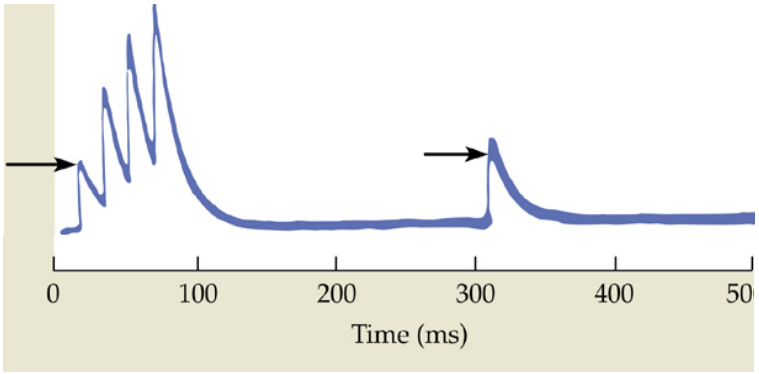
Q = quantal response: the size of the response of the postsynaptic cell to one quantum of transmitter

Note: this assumes that the system is linear!

Synaptic strength is dependent upon use (upon history)

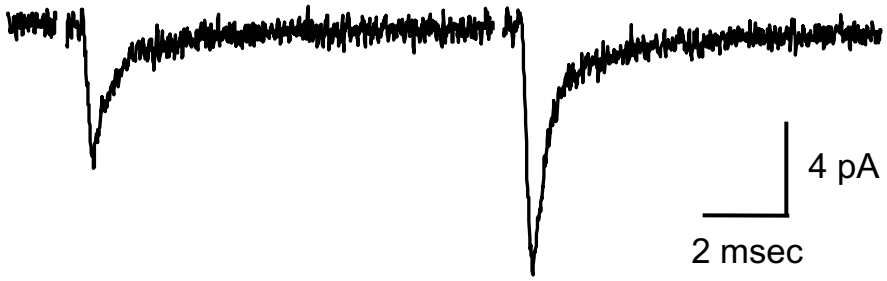
- Facilitation

neuromuscular junction (low Ca^{2+})



- Paired-pulse facilitation

mossy fiber – granule synapse in cerebellum

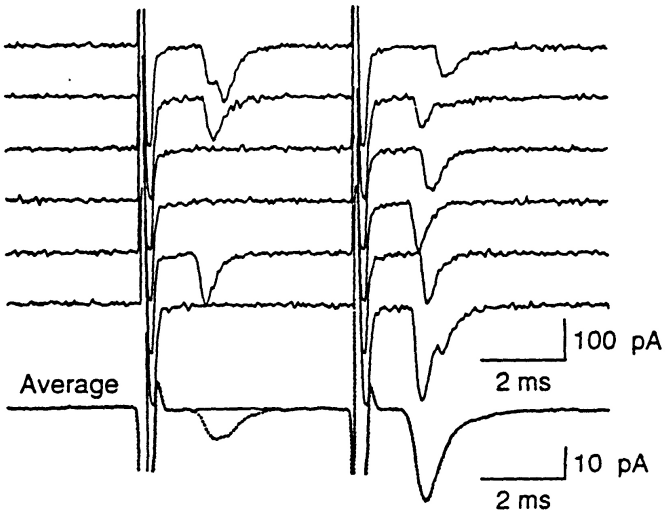


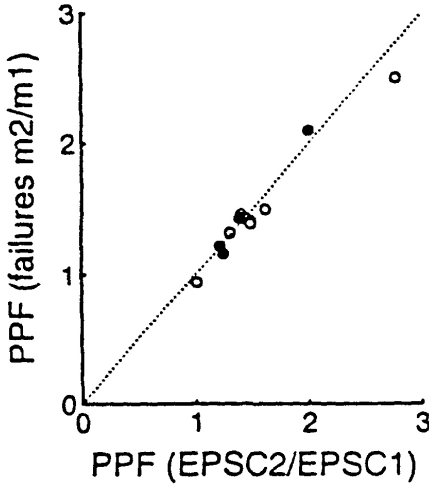
Is paired-pulse facilitation (PPF) presynaptic or postsynaptic?

- Synaptic strength: I = N*P*Q
  - N is generally associated with presynaptic factors
  - P is generally associated with presynaptic factors

    N * P = m (number of quanta)
  - Q is generally associated with postsynaptic factors
- How to resolve the question?
  - measure m, from the failures method

    $m = \ln (T/T_0)$





Isaacson JS, Walmsley B (1995) Counting quanta: direct measurements of transmitter release at a central synapse. Neuron 15:875-884.

What causes an increase in ***m*** for the second of two stimuli?

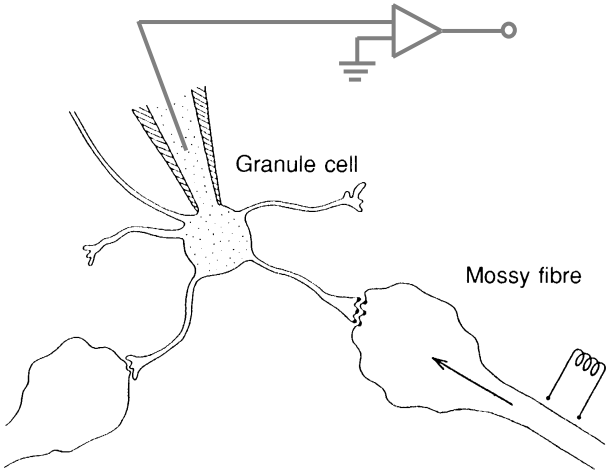
- Larger action potentials?
  - but aren't action potentials all or none?

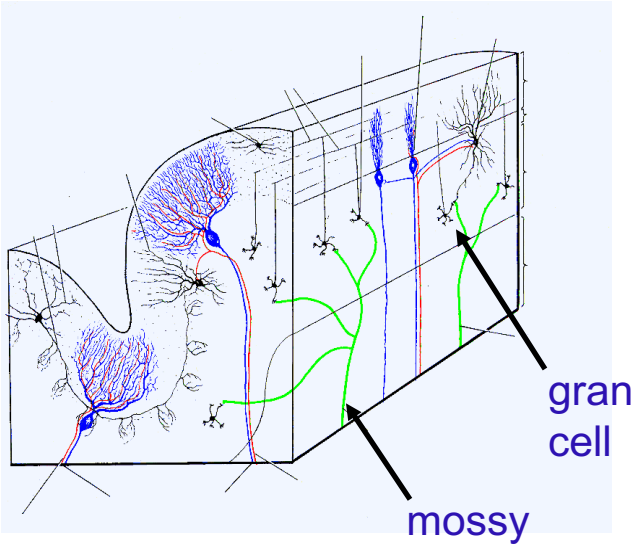
- More calcium entering during the action potential?
  - i_{Ca} can be larger for the second of two APs
  - however, facilitation can occur even i_{Ca} is unchanged.

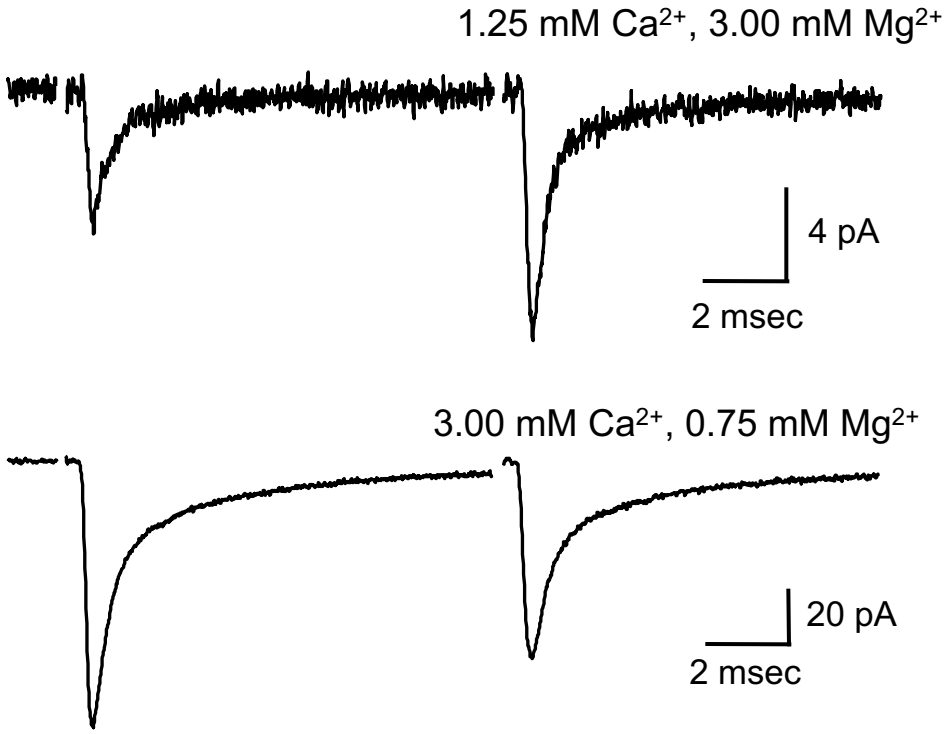
- Residual calcium hypothesis: Nerve terminals facilitate because some of the calcium that enters the terminal during the first action potential is still present when the second impulse arrives. This "residual calcium" is responsible for greater release after the second impulse.
  - This is unlikely to be the entire explanation, since the amount of "residual calcium" measurable is not sufficient to explain the degree of facilitation.

- Calcium buffer saturation hypothesis (related to the residual calcium hypothesis). Calcium buffers are partially saturated as a result of the calcium that enters the terminal in response to the first impulse, and less calcium is sequestered following the second impulse.

Interplay between facilitation and depression







Sargent PB, Nielsen T, DiGregorio DA, Silver RA (unpublished)

The probability of release is dependent upon two factors

- If there are anatomically definable sites from which transmitter is released, then P will depend both on whether the site is occupied with a vesicle and whether, if occupied, the vesicle fuses with the plasma membrane

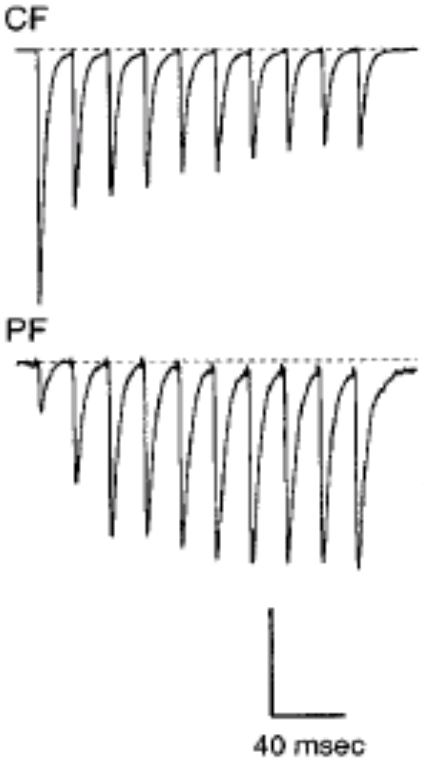
- $P = P_{occupied} * P_{fusion} = P_o * P_f$

- If the site is not occupied with a "release-ready" vesicle, then there will be no release event there.

Why does a synapse that facilitates at low $[Ca^{2+}]_o$ depress at high $[Ca^{2+}]_o$?

- Depression (some forms) is caused by the failure of the nerve terminal to replace vesicles released during the first response. This process takes time – generally tens of ms.
- Recall that $m = N * P = N * P_o * P_f$
  - "residual calcium" will increase P_f
  - depletion of vesicles will decrease P_o
  - if P_f increases more than P_o decreases, we will have facilitation. But when $[Ca^{2+}]_o$ is high, there will be much depletion in response to the first pulse, and P_o will decrease by more than P_f increases, resulting in depression.

Synapses vary in their response to trains of stimuli



Climbing fiber – Purkinje cell (cerebellum)

P high
depression during train

Parallel fiber – Purkinje cell (cerebellum)

P low
facilitation during train

Dittman JS, Kreitzer AC, Regehr WG (2000) Interplay between facilitation, depression, and residual calcium at three presynaptic terminals. J Neurosci 20:1374-1385.

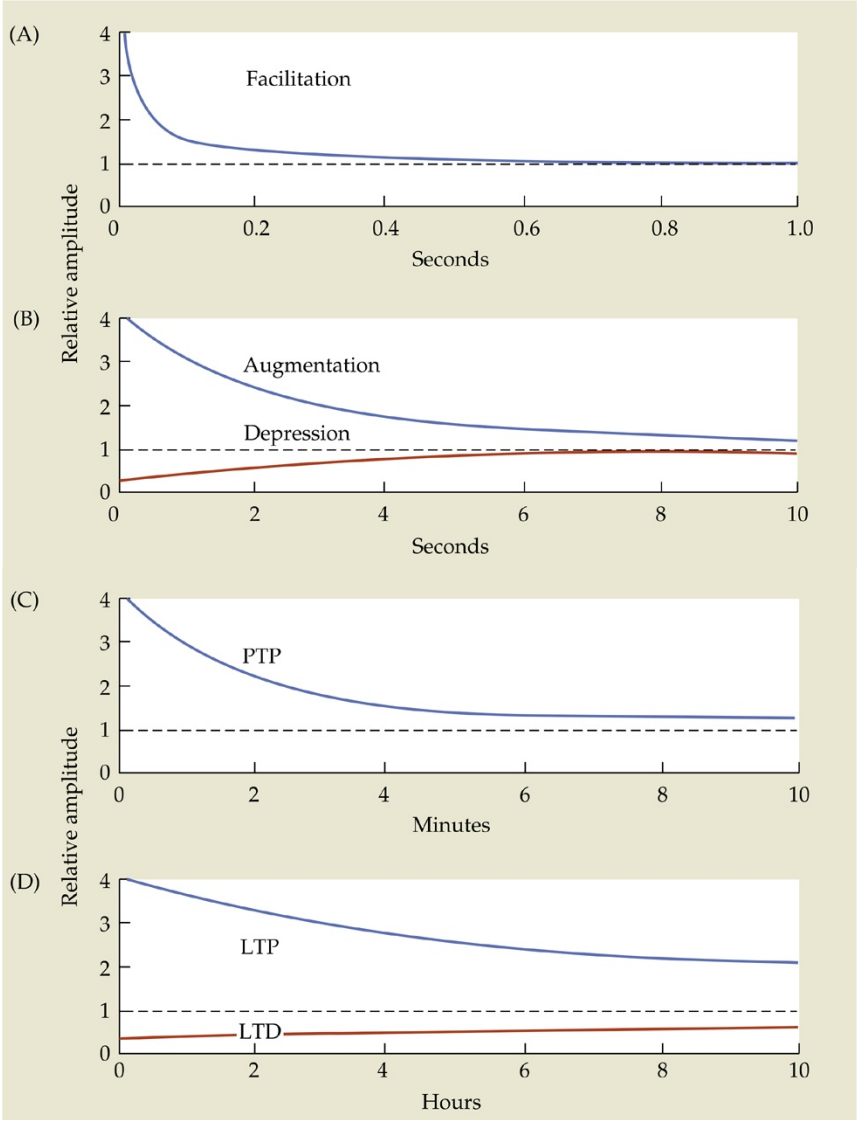
Longer-lasting forms of plasticity

Facilitation

Augmentation

PTP (post-tetanic potentiation)

LTP/LTD



fin!