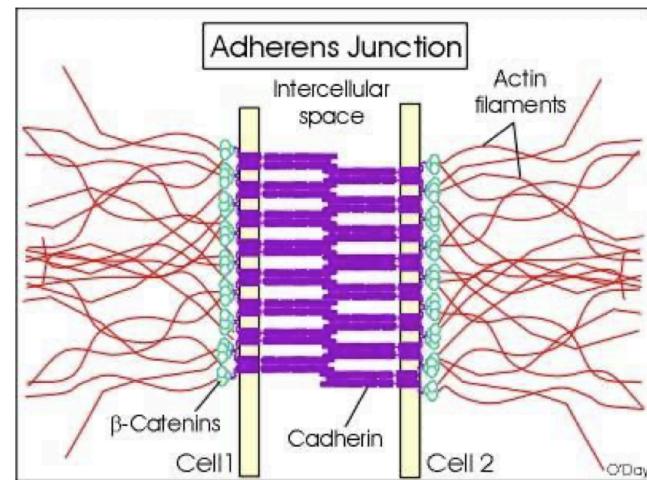


## Other Astrocyte Functions

- Astrocytes can communicate with neurons via  $\text{Ca}^{2+}$
- $[\text{Ca}^{2+}]$  rises in astrocytes are suggested to release gliotransmitters from vesicles or through ion channels
  - Glutamate, D-serine, ATP
- May alter neuronal excitability or modulate synaptic transmission
- $[\text{Ca}^{2+}]$  rises in astrocytes also generate vasoactive messengers, derivatives of arachidonic acid
  - Regulates blood vessel diameter
  - Capillary pericytes regulate blood flow
- Control energy supply to brain
- Regulate pH
- Secrete substances that control synapse formation
- Secrete D-serine → co-agonist with glutamate for NMDA receptors
- Release glutamate and ATP to modulate neuronal function
- Control blood flow

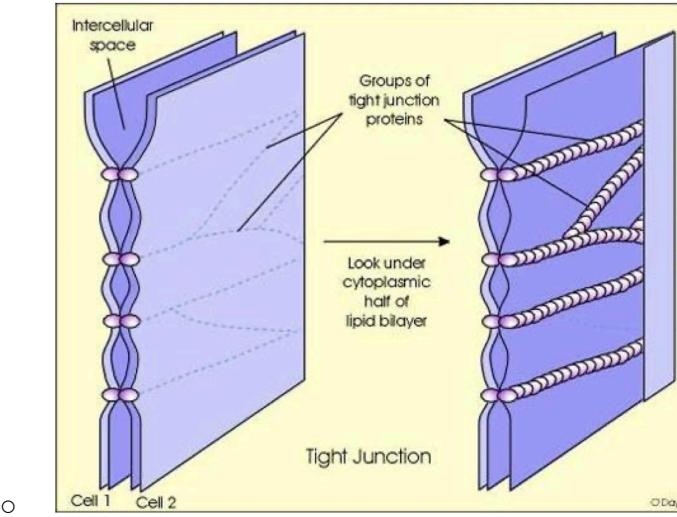
## Cell Junctions

- Adhering junctions
  - Join cells mechanically
  - Found in tissues subject to mechanical stress (e.g. heart, skin)
    - Heart needs to beat constantly, always under mechanical pressure experience strong forces, need to stay together



- Cadherin glue 2 cells together
- Open meshwork of cadherin, things can diffuse through extracellular space (e.g. glucose diffuses between 2 cells and get to places which may not be well supplied by arteries)
- Junctions designed to hold cells together

- Impermeable junctions (tight junctions)
  - In epithelia (e.g. gut)
  - Selectively reabsorb stuff
    - Allow transporters to absorb glucose from gut
    - Passive transporters export it to extracellular space/blood
  - Inhibit diffusion of transporters from 1 side of the cell to the other
    - Fluid mosaic model
  - Provide sealing of extracellular space in gut epithelium
    - Cannot leak back
    - Things cannot leak in



- Hemijunctions
  - Pannexin hemichannels may be opened by lower extracellular calcium or ischaemia
    - Releases intracellular constituents like ATP and glutamate

## Gap junctions

- Made of connexons
  - Hexagonal symmetry → 6 subunits for each connexon
  - Different variations depending on the arrangement of subunits
- Allow electrical impulse to travel through whole of junction
  - Discovered looking at neuromuscular junction (NMJ)
  - Hyperpolarisation of muscle → hyperpolarisation in nerve
    - Communication goes both ways
  - Remove calcium in extracellular space → no effect on flow of current through junction
    - Not chemical synapse
- Heart
  - Gap junctions between all cells of the heart
  - Mechanism
    - Impulse initiated in the SA node
    - Impulse spreads through atrium → contraction of atrium

- Current carried by potassium from 1 cell to another via gap junction
- Bundle of his → large diameter, lower resistance
  - Spread from atrium to ventricle
- AV node → not many gap junctions, causes delay between impulse spreading from atrium immediate to the ventricle, delay the contraction of ventricle, ventricle has time to fill completely
  - Clinicians look at delay
  - Some people don't have enough junctions in AV node → delay is too much or indicate that sodium is not enough
  - Bundle branches start spontaneously beating if no junctions in AV node, safety system to ensure heart beat
- Gut
  - Gap junctions couple cells of gut → peristalsis
- Cortex
  - Pyramidal cells have gap junctions → 1 pyramidal cell fires, and adjacent cell receives some depolarisation, synchronisation of neuronal firing
- Formation of gap junctions
  - Gap junctions between all cells of body except for a few
  - Gap junctional connexons float around in the membrane till they meet another connexon in an opposed membrane when they bind and open
    - Promiscuous: bind to connexons across cell and species barriers
    - Small % of connexons may be open when not bound to partner
    - Open state → diffusion can occur
      - Constantly open is not good because you lose solutes and the concentration gradient is disrupted
    - Closed → twisted conformation, nothing can pass through
- Experiment of forming of gap junctions
  - Baths with extracellular fluid
  - 2 cells put into bath
  - 1 cell has recording electrode + current passing electrode, the other only has recording
  - Pass constant current to make voltage of 2 cells different
  - 2 cells are pushed together
  - Voltage for cell only with recording electrode shows depolarisation in quanta (little steps)
    - Change in voltage towards positive direction = formation of gap junction
  - Inject calcium into cell
  - Quantum lowers as the gap junctions close and cells uncouple (no more depolarisations)
- Allows small sized substances to pass through
  - Metabolic cooperation
  - Experiment:
    - Thymidine kinase adds phosphate to thymidine

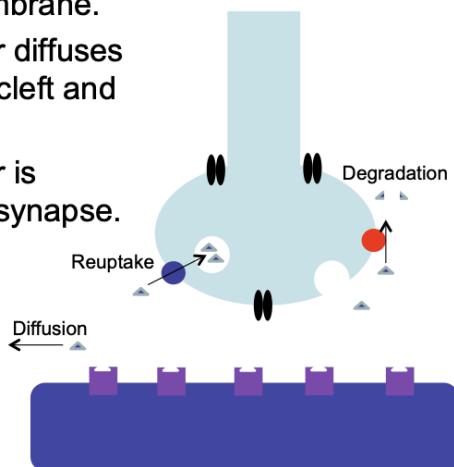
- Phosphate thymidine can enter nucleus
- Mutant cell lacks thymidine kinase (which adds phosphate to thymidine)
  - No silver grains in nucleus to show accumulation of radioactive labelled thymidine
- Normal cell
  - Silver grains showing accumulation of radioactive thymidine in nucleus
- Mutant cell coupled to normal cell
  - Mutant cell gains shows accumulation of thymidine in nucleus
  - Gap junction allows phosphorylated thymidine to pass from normal cell to mutant cell
- Calcium wave
  - IP<sub>3</sub> diffuse between cells → spreading wave of calcium release due to wave of IP<sub>3</sub> which diffuses between cells
  - Rise in calcium activate ATP release which acts on P2X/P2Y receptors to raise intracellular calcium further
  - Rise of calcium may fall with distance, giving a mechanism for differential gene expression according to location → could be relevant to specifying positional information in development
- Modulation of gap junction
  - Change pH
  - Plot magnitude of conductance against pH
    - **Very basic pH** → lots of conductance
    - Acidic pH closes gap junctions → low conductance
      - Acidic pH may indicate cell death, thus cells want to uncouple otherwise may cause electrical imbalance in other cells
  - High intracellular calcium closes gap junctions
    - Too much calcium indicates issue with cell, don't want this to be coupled to other normal cells
  - Regulated by voltage, hormones, protein kinase

## Synaptic Transmission

### Presynaptic Transmission

## Events leading to Synaptic Transmission

1. Action potential invades synaptic terminal.
2.  $\text{Ca}^{2+}$  channels open.
3. Vesicles fuse with presynaptic membrane.
4. Neurotransmitter diffuses across synaptic cleft and binds receptors.
5. Neurotransmitter is eliminated from synapse.



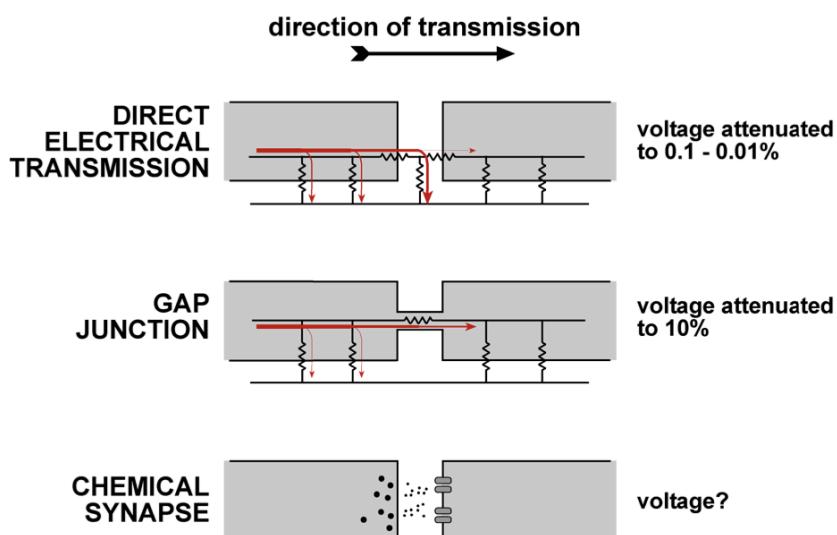
Golgi: Reticular theory (wrong):

- The NS was a large interconnected network comprised of the fused cytoplasm

Cajal: Neurone doctrine:

- Application of cell theory to nervous system (neurons were separate entities)

## Chemical vs. electrical transmission



Gap junctions:

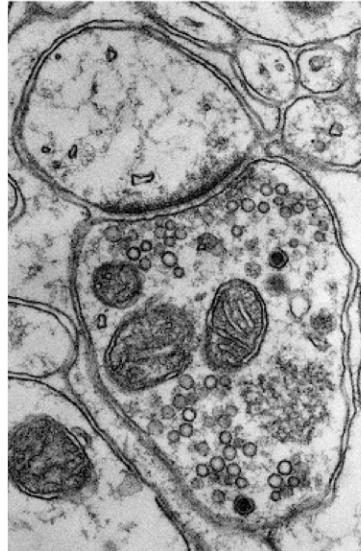
- Same sign signal
- Reciprocal
- Fast
- 2nd messengers diffuse
- Time course determined by presynaptic cell

Chemical synapse:

- Same sign or inverted
- Unidirectional
- Fast or slow
- The same signal (chemical) can be decoded differently by different targets
- Repertoire of interactions allows complex information processing

## CHEMICAL SYNAPSE - THE EVIDENCE

- LANGLEY – Curare blocked transmission in ciliary ganglion
- ELIOT – extract from adrenal glands mimicked the action of sympathetic nerves
- LOEWI – ‘vagusstoff’ (literally “vagus stuff”) liberated from one heart slowed the next one. Later identified as ACh
- DALE (& FELDBERG) – ACh was released at the neuromuscular junction and sympathetic ganglion
- ECCLES – last proponent of electrical transmission ‘converted’ to chemical synapses
- ROBERTSON – Electron microscopy first used to image ultrastructure of the synapse.



## $[Ca^{2+}]_o$ is required for synaptic transmission

4	Be
9.012	
12	Mg
24.31	
20	Ca
40.08	
38	Sr
87.62	
56	Ba
137.3	
88	Ra
(226)	

Inhibits synaptic transmission

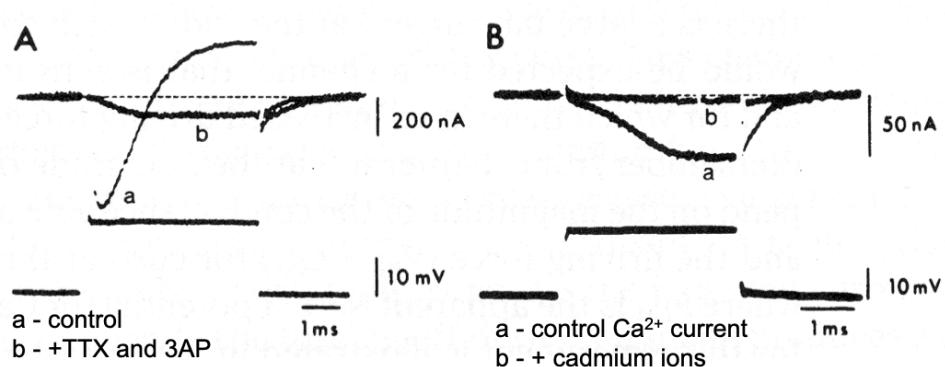
Locke and Ringer showed that extracellular calcium was required for nervous regulation of the heart.

Will partially support synaptic transmission

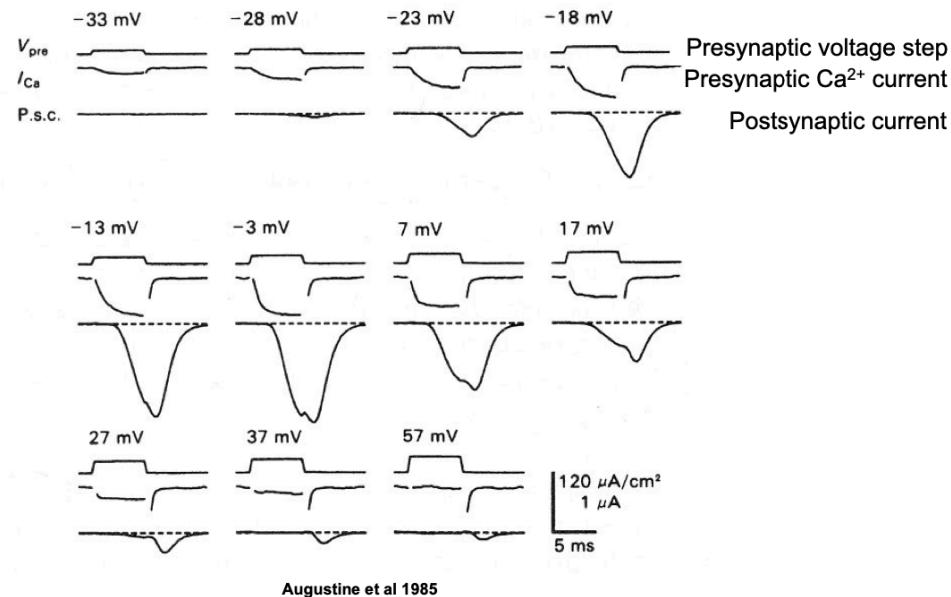
but, release is asynchronous

## SQUID GIANT SYNAPSE

Presynaptic calcium currents



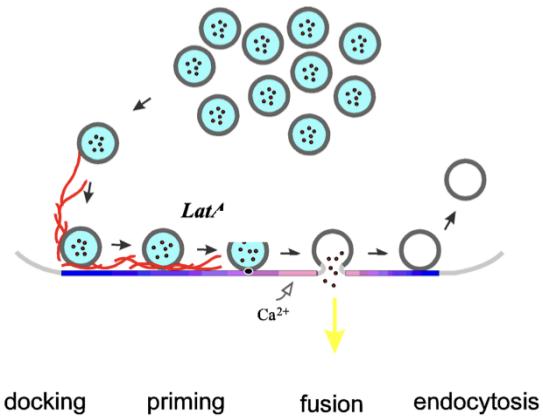
**RELATIONSHIP BETWEEN PRESYNAPTIC  
CALCIUM CURRENT AND TRANSMITTER RELEASE IN THE SQUID**



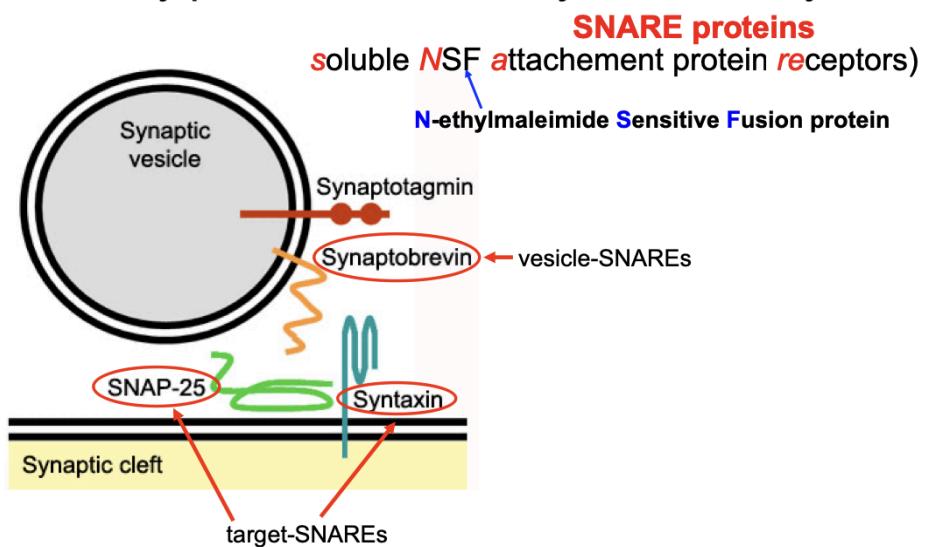
Augustine et al 1985

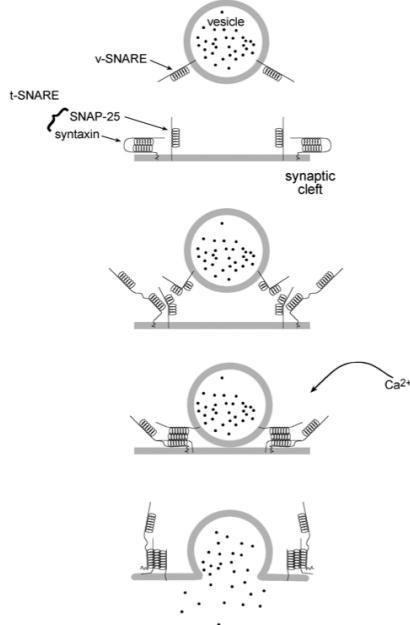
Bigger presynaptic Ca<sup>2+</sup> current = greater postsynaptic current → Ca<sup>2+</sup> important in signalling / eliciting a response in the postsynaptic current

## Neurotransmitter release mechanisms



### Key proteins of the exocytic machinery





NSF acts post-fusion to dissociate SNARE complexes for recycling of synaptic vesicles.

SNAREs form a tight complex consisting of a bundle of four  $\alpha$ -helices

⇒ one from v-SNARE

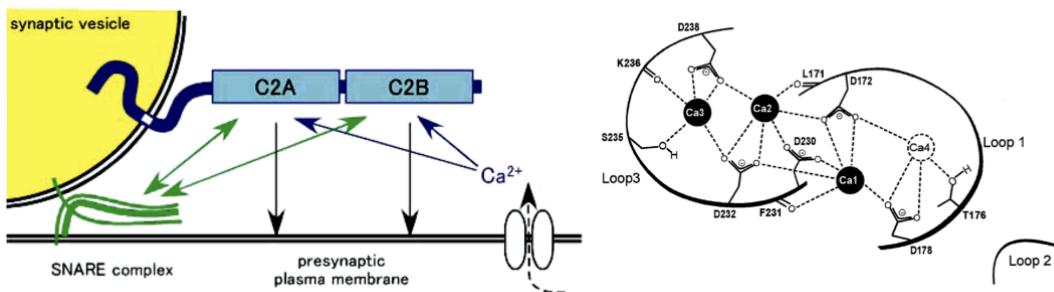
⇒ three from t-SNARE

→ energy gained from zippering to form the stable “*trans*” SNARE complex likely drives membrane fusion.

## Neurotransmitter release probability

- $\text{Ca}^{2+}$  central to release probability of NT
  - Rate of spontaneous vesicle fusion low in basal conditions
  - $\text{Ca}^{2+}$  influx increase rate of exocytosis (vesicle fusion)
  - Neurotransmitter are released within 100 microseconds of AP arrival
  - NT release displays non-linear dependence on extracellular calcium
- $\text{Ca}^{2+}$  channels provide  $\text{Ca}^{2+}$  microdomains for NT release
- $\text{Ca}^{2+}$  sensor must transduce the rise in intracellular calcium to trigger exocytosis machinery

## Synaptotagmin I is a major $\text{Ca}^{2+}$ sensor for exocytosis



Calcium regulates multiple steps in the vesicle fusion pathway but SYAPTOTAGMIN has attracted special interest. It could be the CALCIUM SENSOR for transmitter release.

- binds calcium cooperatively
- low affinity for calcium  $\mu\text{M}$
- it changes conformation on binding calcium
- genetic disruption leads to lack of synchronous vesicle release
- MAY NOT BE ONLY SENSOR

Synaptotagmin has high affinity for calcium → **Synaptotagmin may be the calcium sensor for NT release**

Synaptotagmin important because it binds to calcium and allows interaction with vesicle snare and target snares

## Neurotransmitter

Synaptic vesicles can fuse spontaneously without nerve stimulation → small postsynaptic response

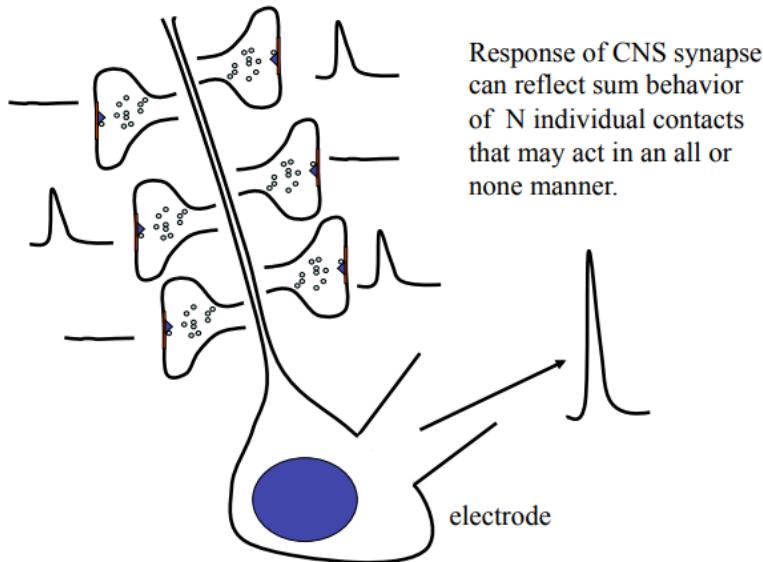
AP increases probability of vesicle fusion by promoting  $\text{Ca}^{2+}$  influx

Not all nerve stimulation will result in successful release of neurotransmitters

- Multiple release sites at nerve endings ensure depolarisation of target cell
- Giant synapses in the auditory system (e.g. calyx of Held)
- NMJ →  $10^3$  release sites

**Response of CNS synapse can show sum behaviour of # individual contacts that may act in an all or none manner**

Each release site can act independently from each other



- At synapses with only a single release site, changing the % of release does not affect the amplitude of the response
- At synapses with multiple release sites, changing % can change the response amplitude as summation could be different depending on how many synapses are activated

Depending on synapse, some release sites release the same NT (focus on this more simplicity sake) but others release different.

### Probability of # Synapse Release

At synapses with only a single release site, changing the probability of release site.

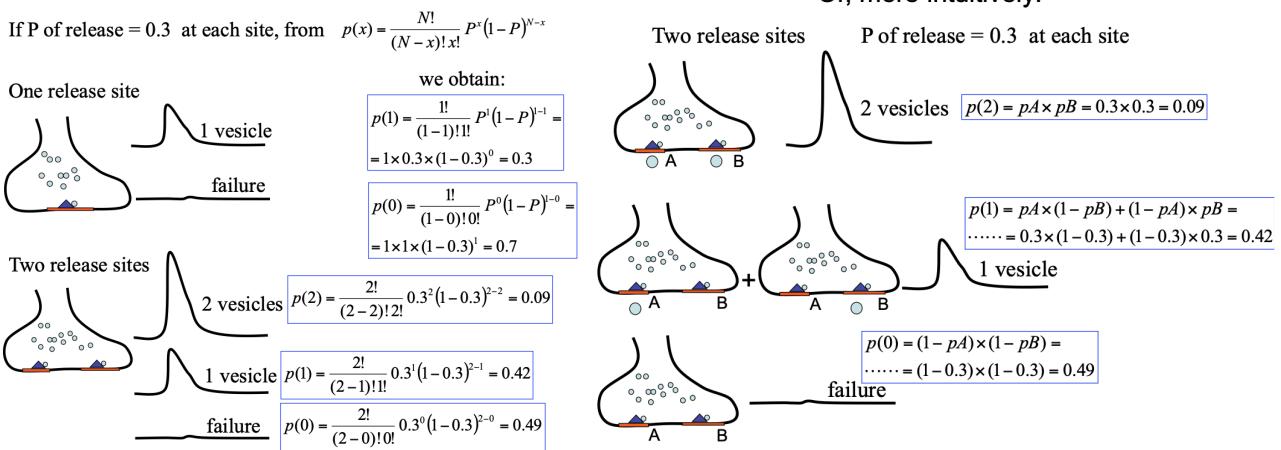
$$p(x) = \frac{N!}{(N-x)!x!} P^x (1-P)^{N-x}$$

N= number of release sites

P= probability of release at each site

p(x)= probability of observing x released vesicle out of N

$0! = 1$



## Quantal release = binomial model

Variance very high for intermediate probability of release

## Postsynaptic Current Size

Assuming a binomial distribution the mean amplitude of the synaptic response is

$$\bar{I} = NPQ \quad \text{Where } N \text{ is the number of release sites, } P \text{ is the probability of release and } Q \text{ is the quantal size and } \bar{I} \text{ is the mean current amplitude}$$

The variance for a binomial distribution is

$$\sigma_I^2 = NQ^2P(1-P) \quad \text{or} \quad \sigma_I^2 = Q(NPQ) - (NPQ)QP \quad \text{or} \quad \sigma_I^2 = Q(NPQ) - (NPQ)\frac{(NPQ)}{N}$$

$$\text{since} \quad \bar{I} = NPQ$$

the relationship between variance and mean current is

$$\sigma_I^2 = Q\bar{I} - \frac{\bar{I}^2}{N}$$

Measuring the mean current and its variance under different release probability conditions (i.e. changing the extracellular  $\text{Ca}^{2+}$  concentration) provides estimates of Q and N, while P can be derived from  $\bar{I} = NPQ$

Amplitude of current initiated: **I = NPQ**

To apply equation:

- Variability of quantal content (e.g. conc of NT in each vesicle) not taken into account

- Synapses with multiple release sites assumed to have % release and quantal size uniform across all sites
- Individual quantal events summate linearly

### **Variance of mean current will be affected by intrasite variation and intersite variation:**

- Intrasite
  - Variations in NT content in each vesicle
  - Stochastic properties of postsynaptic receptors
  - Multivesicular release (more than 1 vesicle release from same site)
- Intersite
  - Intrasite variation
  - Variations in average quantal size across sites
  - Number of sites from which a vesicle is successfully released (variance is low at very high or very low % of release)
  - Differences in probability of release at different sites

### **Probability of Release**

Docked synaptic vesicle → number of readily releasable vesicle available

Limited docked synaptic vesicles = depletion at high stimulus frequency

When multiple release sites are involved, facilitation = increase in release %

Short term plasticity = history dependent change in responsiveness:

- Residual  $\text{Ca}^{2+}$  facilitate transmission when not all quanta are released on the first stimulus
- If transmission is robust on the first stimulus most readily releasable vesicles will be gone and depression results

Transmitter is released and very rapidly reaches postsynaptic membrane

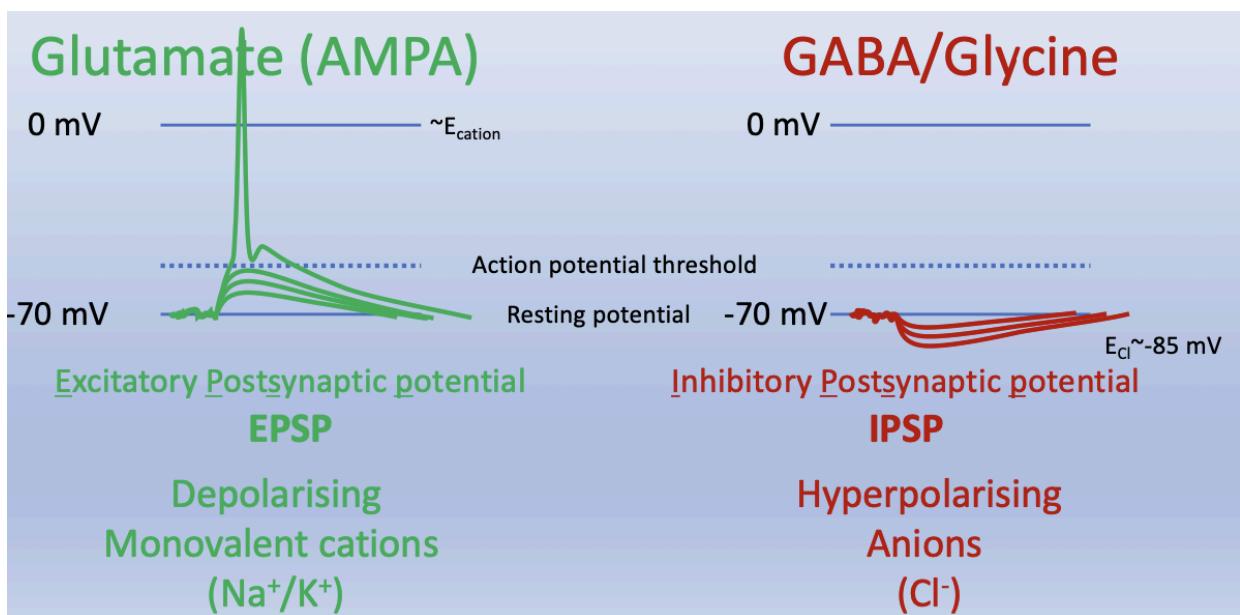
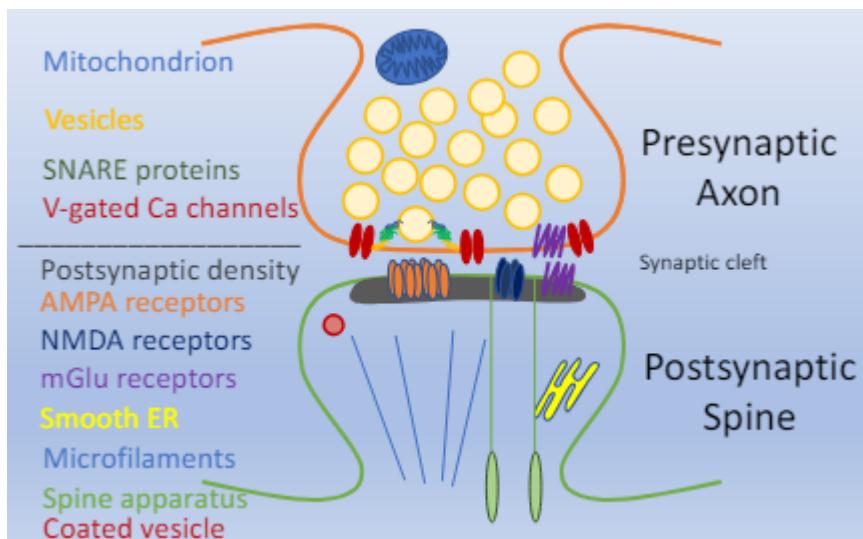
Concentration falls very rapidly because of diffusion away from release site

Diffusion applies to all neurotransmitters with similar diffusion coefficients, but it is not the only factor determining lifetime of transmitter in cleft

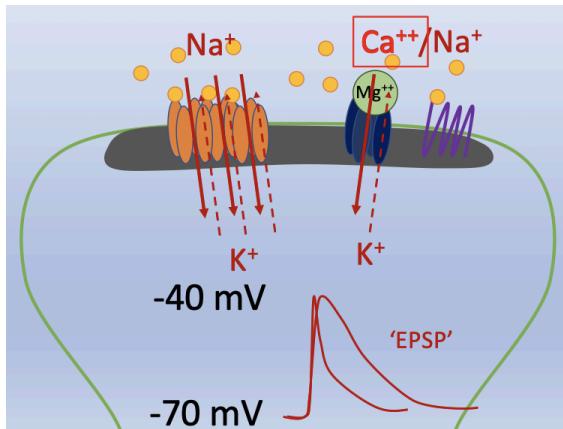
- ACh
  - Hydrolysed by extracellular enzymes
  - Block of AChE prolongs decay of synaptic potentials
- Glutamate
  - Taken up by family of sodium gradient powered transporters, either into neurones or glial cells
  - Glial cell route is thought to be quantitatively most important
  - Glutamate converted to glutamine in glial cells and sent back to glutamatergic neurones for reconversion to glutamate
- GABA

- Taken up by 3 transporters: GAT-1/2/3
  - GAT-1 = located mostly in axon terminals
  - GAT-3 = glial transporter
  - GAT-2 = less abundant and localised in neuronal and glial cells in some parts of the brain → typically distant from synaptic cleft
- Glycine
  - Taken up by GlyT1/2
    - GlyT1 = located in astrocyte
    - GlyT2 = located in presynaptic neuronal membrane

## Postsynaptic Transmission

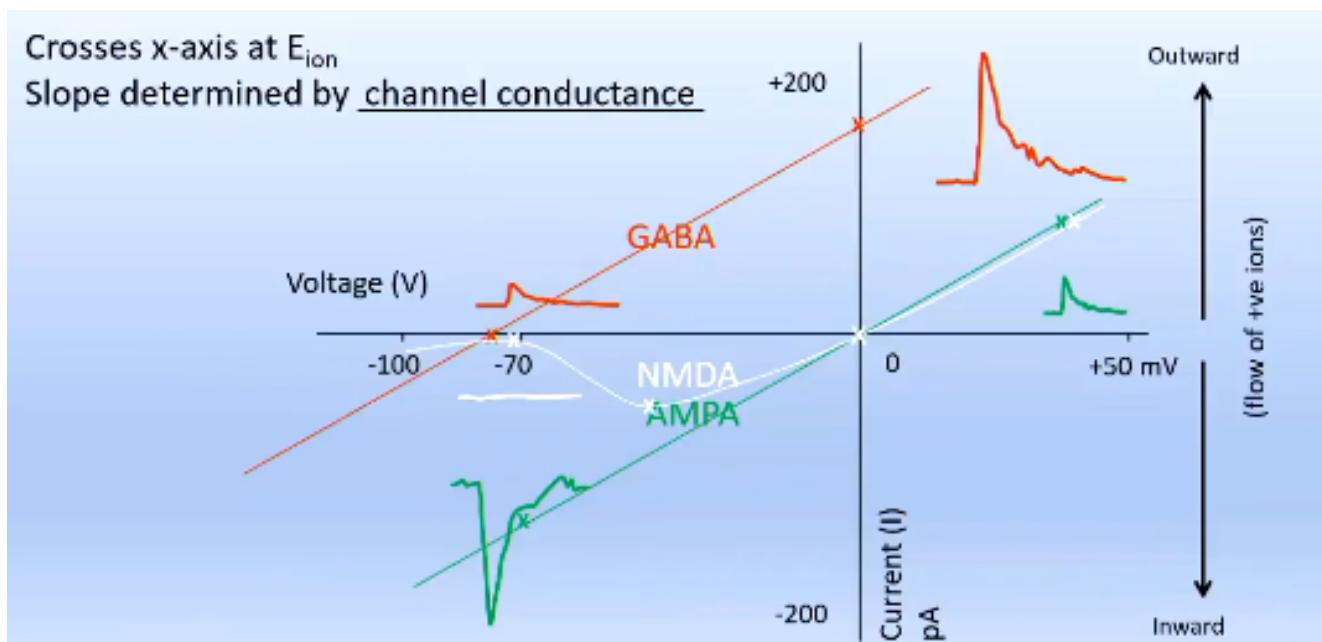


- AMPA receptors open to monovalent cations: sodium, which moves in, and potassium, which moves out (rarely calcium)
  - Depolarisation
  - Graded synaptic potentials (excitatory - EPSP)
  - Grading of EPSP → threshold reached = AP generation
- GABA open to anions: Cl<sup>-</sup> and sometimes bicarbonate
  - Hyperpolarisation
  - Graded synaptic potentials (inhibitory - IPSP)



1. Glutamate binds to AMPA and mGlu receptors
2. AMPA opens to allow inward flow of  $\text{Na}^+$  and outward flow of  $\text{K}^+$ 
  - a. Net flow of inward current → EPSC (downward = inward current)
  - b. EPSC cause EPSP
3. NMDA also open but immediately blocked by magnesium
4. Membrane potential reach  $\sim -40\text{mV}$
5. Magnesium propelled out of NMDA channels →  $\text{Na}^+ + \text{Ca}^{2+}$  move in
  - a. EPSP for NMDA receptors is longer in duration
    - i. Rise time is slow and decay time is slower
    - ii. Coincidence detector: detect presynaptic activity (release of glutamate, and hence binding of glutamate to NMDA) and postsynaptic activity (depolarisation of postsynaptic membrane)

## I-V Curve



### AMPA

- 0mV = reversal potential for AMPA
  - No net flow of current (no net movement of sodium and potassium)
- Outward current = positive membrane voltage
  - $K^+$  close to its rev potential
- Inward current = negative membrane voltage
  - $Na^+$  closer to its rev potential

### GABA

- -85mV = reversal potential for GABA
  - No net flow of current
- Outward current = positive membrane voltage
  - Inward flow of negative = outward current
- Inward current = negative membrane voltage
  - Outward flow of negative = inward current
  - Hyperpolarised voltages make GABA excitatory → outward flow of negative charges (inside membrane becomes more positive / depolarised)
  - **GABA isn't simply an inhibitory neurotransmitter, it depends on the voltage of the membrane to determine whether GABA binding causes inward or outward flow of chloride**

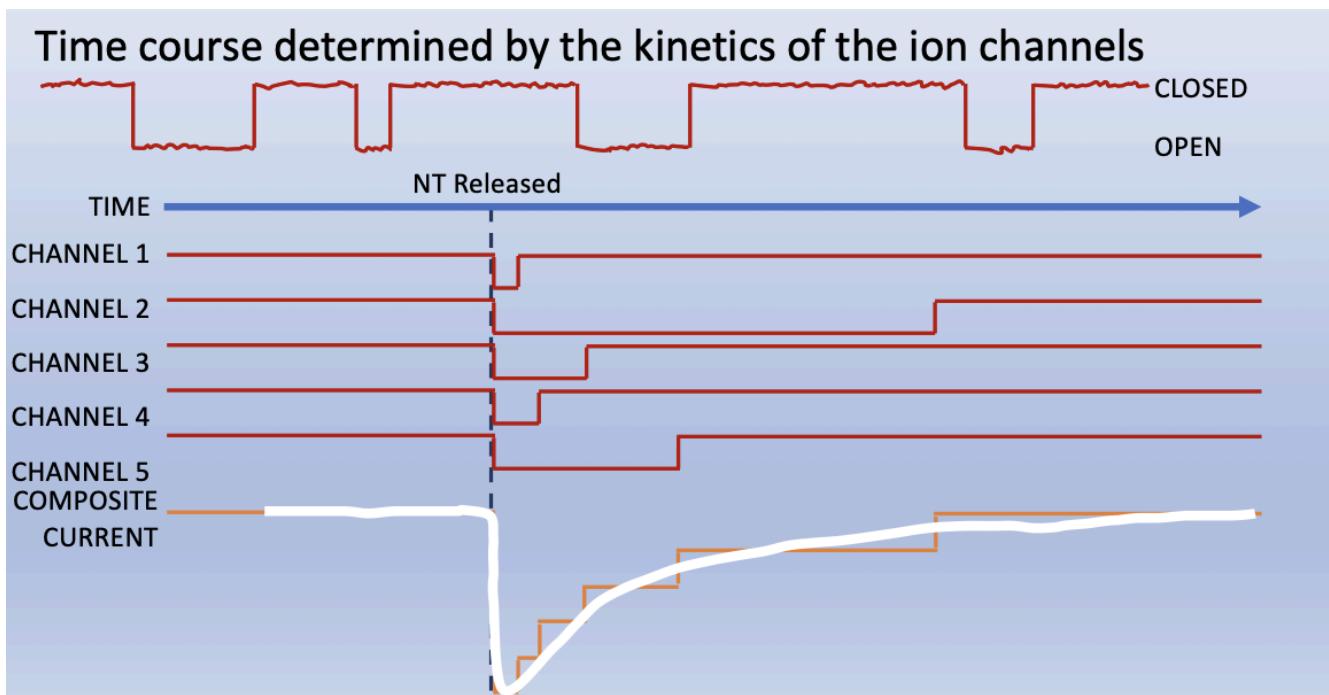
### NMDA

- 0mV = reversal potential for NMDA
  - Same as for AMPA as both allow for influx of sodium and potassium
- Unblocked similar to AMPA current
- No influx of ions at resting membrane potential (-70mV) which is because of  $Mg^{2+}$  block not allowing any flow of ions through the channel
- After -40mV the  $Mg^{2+}$  block is relieved
  - This allows the subsequent  $Na^+$  movement inwards
  - Starts to have inward current

- NMDA currents last longer than AMPA

Curves always cross x-axis at equilibrium potential (reversal potential)

Slope is determined by channel conductance (if individual channel allow for ions to pass through, the slope will be steeper)



### Fast initiation of current and slow decay

Individual AMPA channels can only have inward currents or none (usually open or close)

Multiple channels work together to produce synaptic current

- Closing of channel closes at different times but opens at the same time → hence the initial steep inward current (fast), and slow exponential decay of the current

### Synaptic Response

1 vesicle (quantum) of glutamate saturates the postsynaptic receptor

<b>Amplitude at single synapse (quantal amplitude):</b> <ul style="list-style-type: none"> <li>• Number of post synaptic channels per synapse</li> <li>• Conductance of postsynaptic channels</li> </ul>	<b>Overall amplitude:</b> <ul style="list-style-type: none"> <li>• Number of synapses (n)</li> <li>• % of release at each synapse (p)           <ul style="list-style-type: none"> <li>◦ AP does not always lead to release of NT</li> </ul> </li> <li>• Quantal amplitude (q)</li> </ul>
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<p>Amplitude at a single synapse = q</p> <p>(Different from NMJ, NMJ amplitude determined by pres-synaptic due to very large numbers of post-synaptic receptors)</p>	<p><math>q \times n \times p</math></p> <p>p and n are presynaptic factors q is postsynaptic factor</p> <p>Variation in response determined by number of synapses (n)</p> <p>1 synapse: No variation in successful responses 2 synapses: Variation</p> <ul style="list-style-type: none"> <li>• 2 successful response → summate</li> <li>• 1 successful, 1 unsuccessful</li> </ul> <p>N synapses: Huge variations</p> <p><b>Coefficient of variation (CV) =</b> Standard deviation of response / mean response, noise at synapse</p> <ul style="list-style-type: none"> <li>• <b>Number of synapses</b></li> </ul> <p>Central synapse excitatory neurotransmission has a low % of release → could have all failures (quite often)</p>
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## Synaptic Plasticity

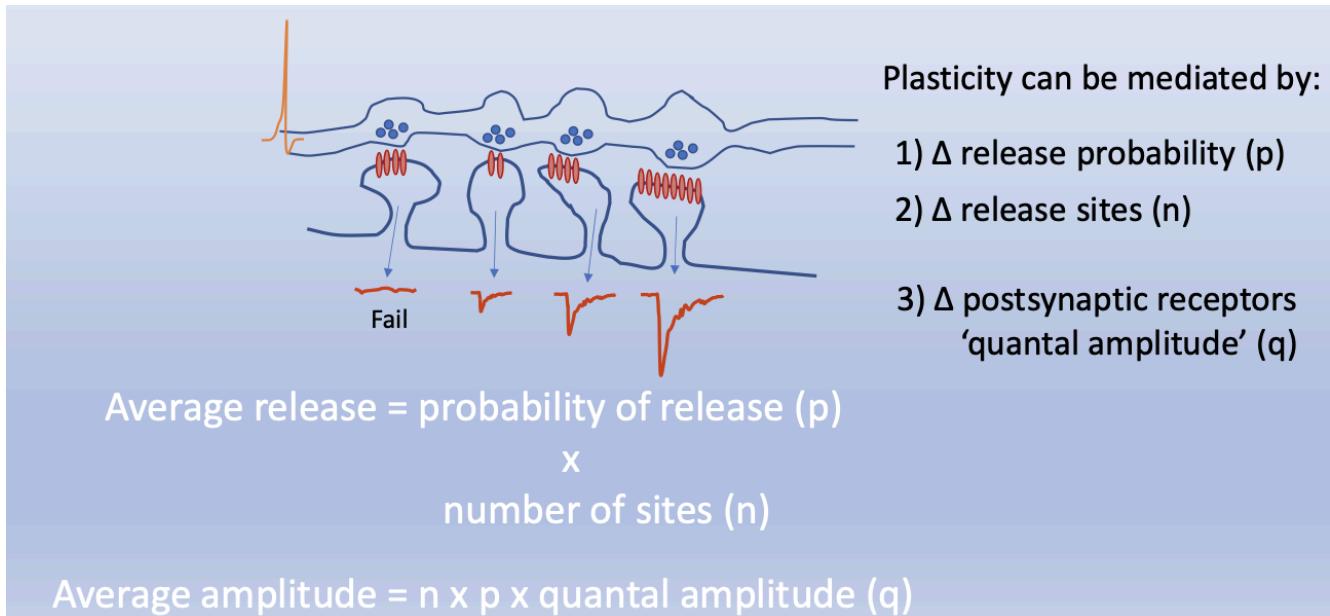
### Short Term Plasticity (STP)

Activity-dependent changes in synaptic efficacy (strength)  
Can increase and decrease

For a neuron:

Average release at the neuron = probability of release (p) x number sites (n)  
 Average amplitude of synaptic potential =  $n \times p \times q$  (quantal amplitude)

- Plasticity can be mediated by release of probability, release sites, number of sites

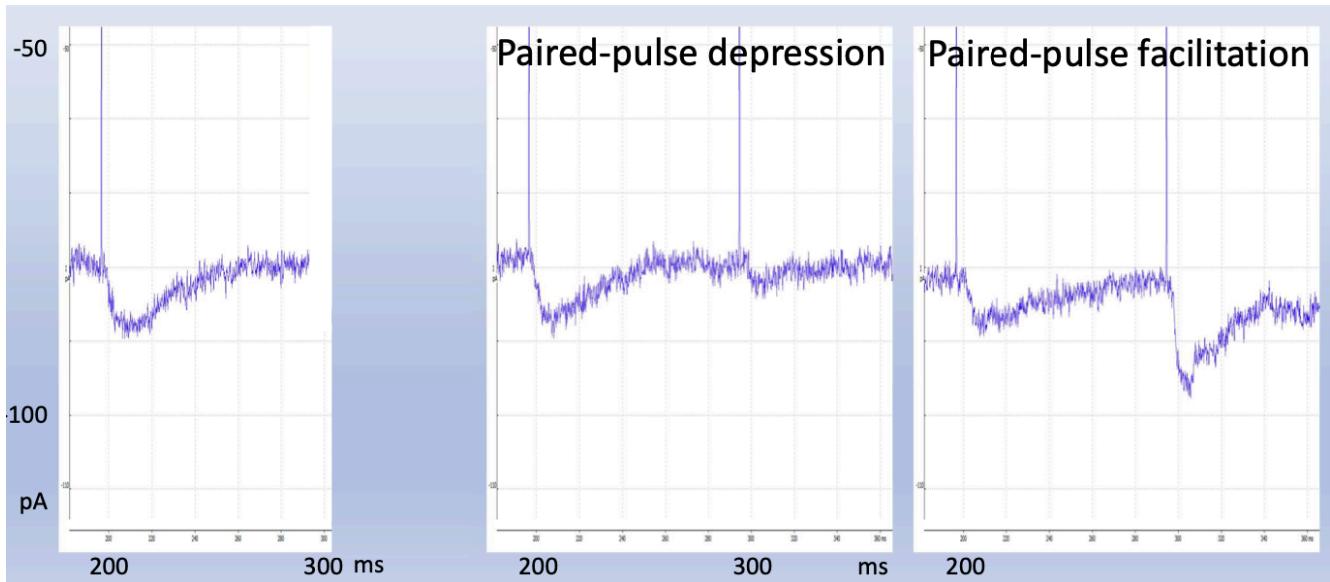


Very short-term plasticity: Paired pulse facilitation or depression (ms - sec)

Short-term plasticity: Post-tetanic potentiation or frequency dependent depression (minutes)

Long-term plasticity: Long term potentiation or depression (LTP/LTD) (hours - years)

## Paired-pulse Plasticity



Stimulate 2 times in quick succession (same synapse fired) → second response smaller than first (depression) or larger than first (facilitation)

Response different from summation, current returns fully to baseline before second response

Average amplitude of synaptic potential =  $n \times p \times q$   
⇒  $p$  changed

Facilitation caused by residual calcium from the presynaptic terminal → increase % release on second response

- First AP % release is low
  - Second AP % release will increase
1. Calcium influx and build up in presynaptic terminal
  2. Probability of release quite low for basal activity
  3. Not a lot NT release
    - a. Still has many readily release NT vesicles
  4. Small # synapses activated
  5. Second AP comes along
  6. Residual calcium + calcium influx
  7. % of NT release increase
  8. More NT release
  9. More synapses activated
  10. Larger current

Depression caused by depletion of readily release pool of NT vesicles → decrease % release on second response

- First AP % of release is high
- Second AP % of release will decrease

Typically only 1 vesicle is ready for release, the rest are in reserve pool

1. High probability of release
2. Calcium influx
3. High prob of release
4. Many release of NT
5. Many synapse activated
6. Second AP
7. Not many readily release vesicles left
  - a. Depletion of readily release pool
8. Less synapses activated than before
9. Smaller current

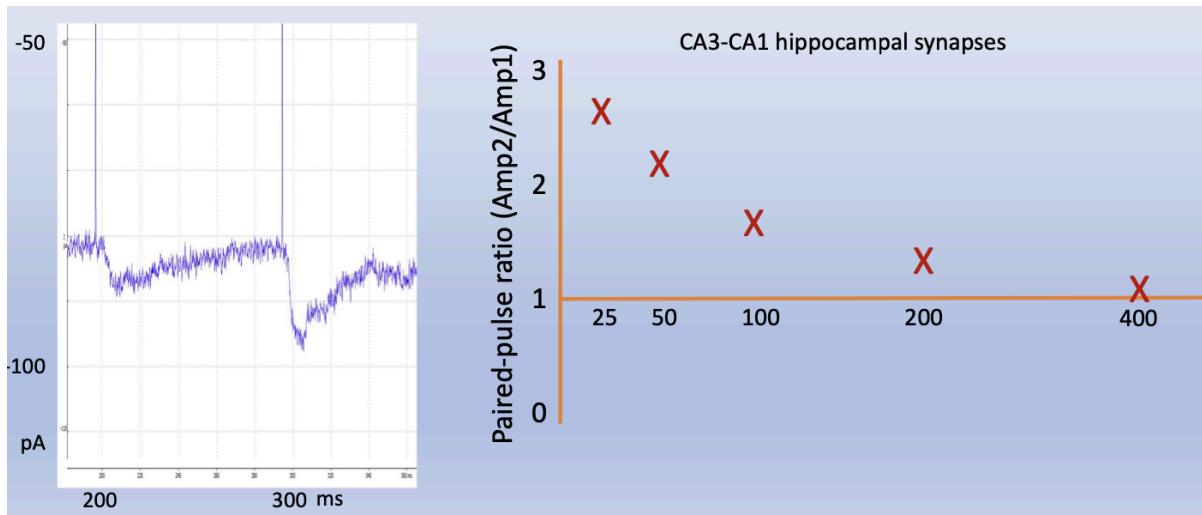
Alternative explanations for paired-pulse depression

1. Postsynaptic receptor desensitisation
2. Metabotropic receptors on presynaptic side
  - a. Homosynaptic
    - i. Glutamate released downregulate subsequent release
  - b. Heterosynaptic
    - i. For example: GABA released from interneurons downregulate release

## CA3-CA1 hippocampal synapse

### Time-dependent reaction

- As time drags on, decreased paired-pulse ratio due to residual  $\text{Ca}^{2+}$  cleared
  - Less likely to have facilitation
- Overall paired-pulse ratio is determined by balance between residual  $\text{Ca}^{2+}$  and depletion of readily-releasable pool of NT

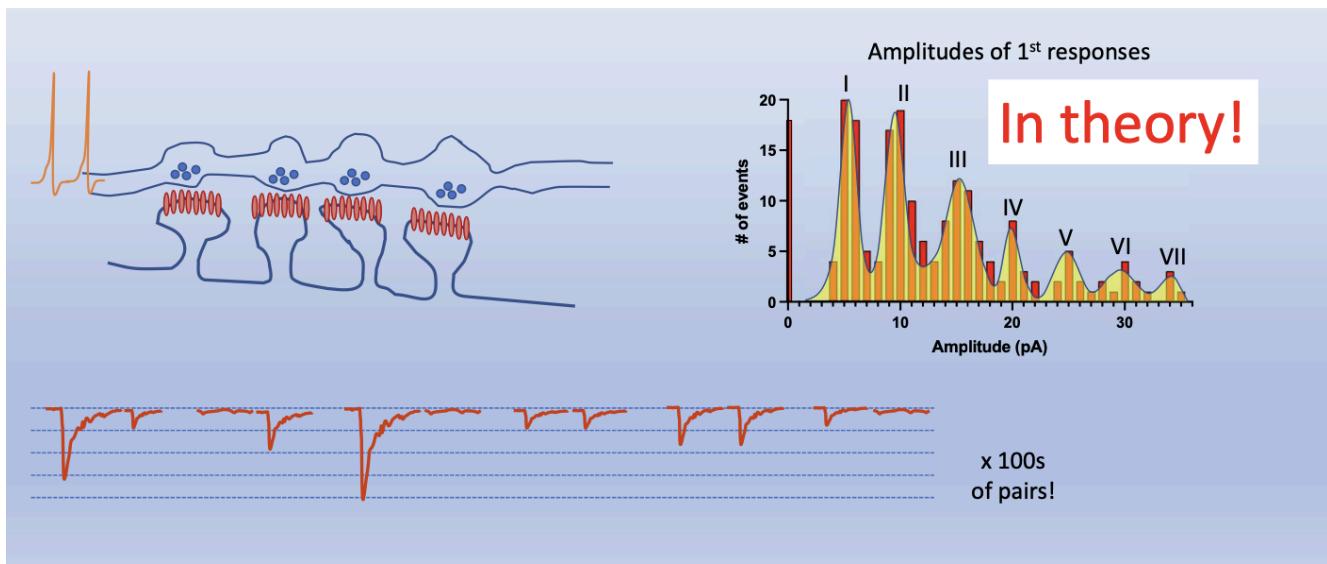


### Experimental evidence for paired-pulse facilitation:

1. Fluorescent calcium dyes in large terminals
  - a. Include calcium dye in preparation, intensity indicates concentrations of calcium
2. Calcium buffers
  - a. BAPTA → fast calcium buffer, inhibits both responses (fail to release NT)
    - i. Release of NT dependent on  $\text{Ca}^{2+}$
  - b. EGTA → slow calcium buffer, inhibits only second response (residual calcium)

## Quantal analysis

Measure sizes of single responses



Synapses have same number of channels

1. Paired-pulse stimulation applied to axon terminal
2. Measure responses of synapse for the 2 stimulations
3. Do it many times
4. Get amplitude frequency distribution
5. Plot how many times you see an event/response at each amplitude
  - a. And number of times u see failures

Position of peaks determined by: q

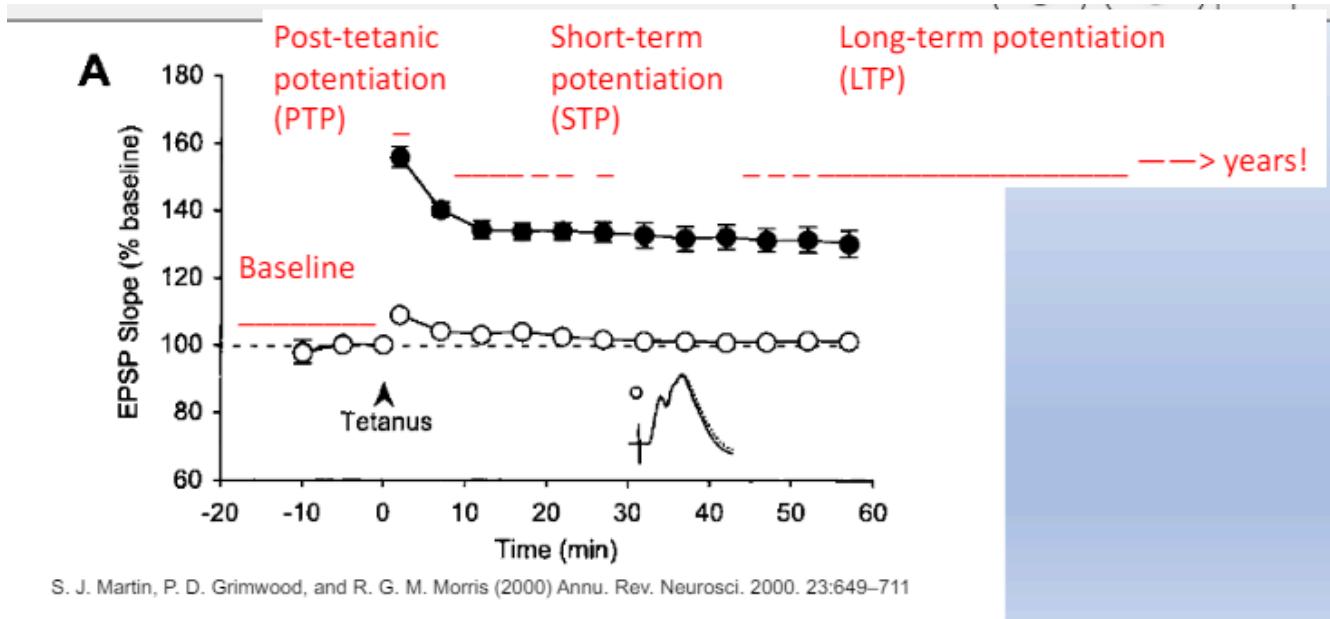
Relative height (number of peaks and failures) determined by: p and n

- n and p (presynaptic)
  - Decrease in p (% of release) heighten peaks at smaller amplitudes while shorten peaks at higher amplitudes because lower % release = less likely to generate current = lower amplitude of EPSP generated
    - Also increase peak at 0 amplitude because more failures of release, so less likely to have EPSP
  - Decrease in n (number of synapses) heightens peaks at smaller amplitudes because less AMPA receptors = less currents generated = lower amplitude of EPSP
    - Increase peak at 0 because less likely to have EPSP
- q (postsynaptic)
  - Decreased q (quantal amplitude) shifts every peak to the left because all responses will have smaller amplitude due to smaller amplitude for all synapses of the neuron

## Long Term Plasticity

- **Activity-dependent, long-lasting increase in synaptic efficacy (hours to years)**
- Attractive model for learning and memory

- Requires synchronous activity
- First experiment done on hippocampus → Hippocampus only have dendrites on 1 side and axon terminals on other side



- Only active pathway show potentiation
- Apply tetanus (high freq, 100Hz, burst of activity)
  - PTP
  - STP ~20 minutes
  - LTP
    - Activity remains higher than baseline

## LTP

Properties:

- Activity dependent
- Stable and long-lasting
- Input specificity: only active synapses undergo synaptic plasticity
  - Stimulating electrode in extracellular space
  - Axons surrounding electrode fire, LTP induced only in active pathways
- Cooperativity/associativity: overcoming induction threshold
  - Cooperativity
    - Weak synapses cooperate to overcome threshold for releasing  $Mg^{2+}$  block
  - Associativity
    - Weak synapses associate with strong synapse to overcome threshold for releasing  $Mg^{2+}$  block

**Input specificity, cooperativity/associativity all encoded by NMDA**

Basal transmission:

1. Bind to AMPA and NMDA
2. Sodium through AMPA receptor, none through NMDA
  - a. AMPA underlie basal activity

Induction of LTP/LTD on postsynaptic side:

1. During tetanus → repeated activation of AMPA receptors
2. Depolarisation
3.  $Mg^{2+}$  is released from NMDA channel
4.  $Na^+ + Ca^{2+}$  influx through NMDA channel
5.  $Ca^{2+}$  activate calcium calmodulin
6. Calmodulin activate CaMKII
7. CaMKII phosphorylates other CaMKII
  - a. Autophosphorylation → long lasting effects, carry on after stimulation
8. CaMKII phosphorylate AMPA receptors (LTP)
  - a. Improve conductance
  - b. More AMPA inserted into postsynaptic density from periphery
9. CaMKII phosphorylate GluR1 (LTP)
  - a. Increases its conductance
  - b. Alters GluR1 mobilisation, more inserted into postsynaptic density

CaMKII important for LTP, elimination of CaMKII = elimination of LTP

- CaMKII mutant mice have impaired LTP
- Affects long-term memory (water maze, learn visible platform, don't know where platform is anymore when you hide it)

## LTD

- Prolonged low-frequency stimulation induces depression (~5Hz)
- Can be induced by correctly timing the activation of presynaptic axons and postsynaptic neurons (aka STDP)
- Mechanism
  - LTD requires modest increase in  $Ca^{2+}$  (Malenka RC 1994)
    - Modest increase optimal for LTD
    - Large increase optimal for LTP (large depolarisation ⇒ more NMDAR activated  
⇒ good for LTP)
  - Activation of  $Ca^{2+}$  dependent protein phosphatase cascade which involves a protein named protein phosphatase 1 (PP1)
    - Loading CA1 pyramidal cells with PP1 enhances LTD (Morishita et al., 2001)
  - Dephosphorylation of postsynaptic PKA substrates
  - AMPA receptors are removed from membrane (endocytosis back into neuron)