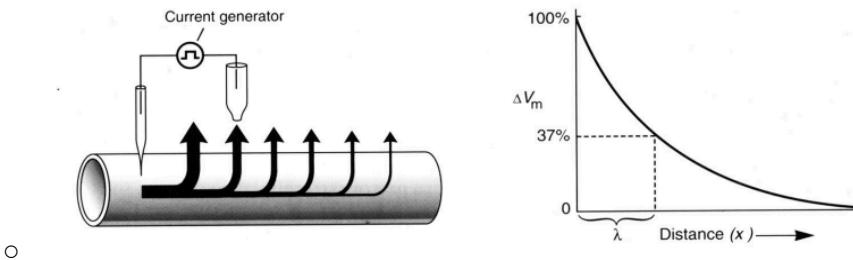


- - Axial resistance are the resistors connected in series on cytoplasm side
 - Resistance that applies to 1cm segment of an individual neuronal process with certain diameter (d)
 - $r_m \Rightarrow$ membrane resistance
 - $r_a \Rightarrow$ axial resistance

- Length and resistance
 - Longer cylindrical process length = more internal resistance (axial resistance)
 - Longer cylindrical process length = less membrane resistance because more channels are available for current to leak through the membrane



- - Inject current into axon
 - Current flows out across membrane
 - More current flows near site of injection than distant sites as axial resistance (r_a) increases with distance from site of injection
 - $V_m = I_m r_m \Rightarrow$ change in membrane potential produced by current becomes smaller moving away from injection site as current flowing out decreases
 - Decay with distance = exponential shape
- Membrane length constant

$$\lambda = \sqrt{r_m / r_a}$$

-
- Distance that a current will travel away from the site where it is injected/begins
 - Measure of efficiency of the electrotonic conduction in a given neuron
- Qualitatively corresponds to distance along neuronal process at which a constant applied voltage will decay to about 37% ($1/e$) of its original value
- Efficiency influences spatial summation and propagation
 - Spatial summation is the summation of 2 or more inputs from different locations occurring at the same time
- Cells with high $R_m = \lambda$ is large

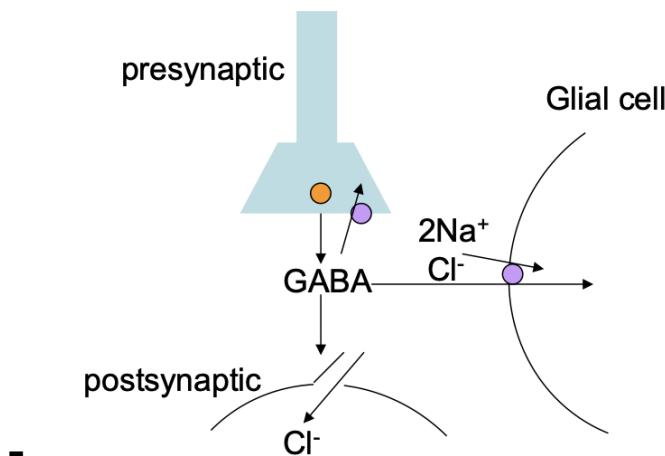
- Postsynaptic potential can spread farther because relatively few ions are lost across the membrane
- Cells with low $R_m = \lambda$ is small
 - Huge ionic leak, fewer ions travel and carry current farther down
- Cells with high $R_a = \lambda$ is small
 - Axons with small internal diameter, more resistance to internal flow
 - Current will not travel far
- Cells with small $R_a = \lambda$ is large
 - Axons with large diameter, does not impede flow of current
- Larger $\lambda \rightarrow$ potential can travel further down axon and still be effective in eliciting a postsynaptic response even if very far from synapse
 - No significant loss of amplitude
 - Hence if 1 postsynaptic potential has a larger λ , then when it summates with a distant postsynaptic potential, the amplitude will still be great than if the λ was small
- Specific axial resistance (R_a) \rightarrow internal longitudinal resistance of 1cm length of a cylindrical process 1cm^2 in cross-sectional area
 - Calculated from r_a (axial resistance)
 - Independent of geometry
 - Consider **resistance decrease as cross-sectional area increase**
- Specific membrane resistance (R_m) \rightarrow resistance of 1cm^2 of membrane
 - Calculated from r_m
 - Independent of geometry
 - Consider **membrane resistance goes down as lateral surface area (the surface area around the axon) goes up**
 - R_m depends primarily on resting permeability of the membrane to K^+ and Cl^-

Note: Neuronal action potentials do not summate!! EPSP and IPSP do
 \Rightarrow Postsynaptic potentials are graded and can sum, amplitude is proportional to the strength of the stimulus but it is usually small, and they have no refractory periods

Active Transport

- Active transport is the transport of substances across membranes, against their electrochemical gradient
- Energy equation
 - $RT \ln(\frac{C_2}{C_1})$
- Active transport requires energy
 - ~5.9kJ/mole to change concentration by ~10-fold
 - ~ 5.8 kJ/mole for moving against electrical gradient
- Power sources:
 - ATP hydrolysis
 - ATP splitting: $ATP \rightarrow ADP + Pi$

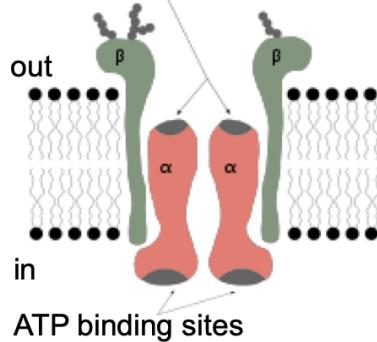
- 50 kJ/mole
- Ion gradients → transport an ion down its electrochemical gradient generates the energy for the transport of the one we want against its electrochemical gradient (e.g. Na^+ - glucose transporter)
 - Transport of 1 Na^+ gives 5.9 kJ from the concentration gradient
 - Transport of 1 Na^+ gives 5.8kJ from electrical gradient (into cell as it is attracted by negative charge inside)
 - Total = 11.7 kJ/mole
- Function
 - Establish transmembrane ion gradients and voltages
 - pH regulation
 - Many intracellular reactions are very pH-dependent, so pH regulation crucial
 - Solute accumulation
 - Termination of synaptic transmission
 - For glutamate and GABA synaptic action is terminated by transport into cells against their conc gradient



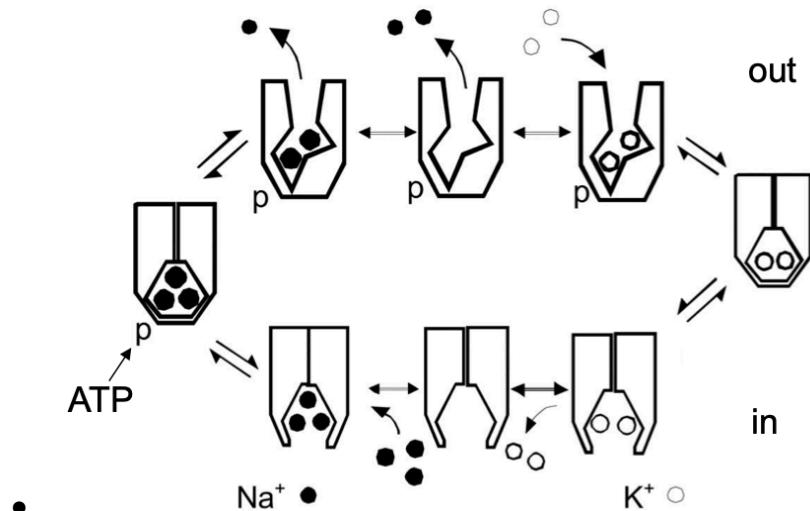
- Energy:
 - Energy obtained form 1 positive charge entering cell = 5.8 kJ/mole
 - 2Na^+ and 1Cl^- in = net 1 positive in
 - 2Na^+ going down conc gradient = 11.8kJ
 - 1Cl^- going down conc gradient = 5.9 kJ
 - Total energy gained = 23.5kJ/mole
 - Energy needed to move GABA = 5.9 kJ for 10-fold gradient
 - GABA is neutral, so no need to consider electrical gradient
 - Roughly 10^4 gradient
 - Similar for glutamate
 - Second messenger regulation
- Transporters:
 - Sodium-potassium ATPase
 - Structure:
 - P-type ATPase
 - 2 alpha subunits, 2 beta subunits
 - Alpha subunits bind to ATP insid
 - Ouabain (inhibitor) binds outside

- Beta subunits are not needed for the pumping of ions

Ouabain binding sites

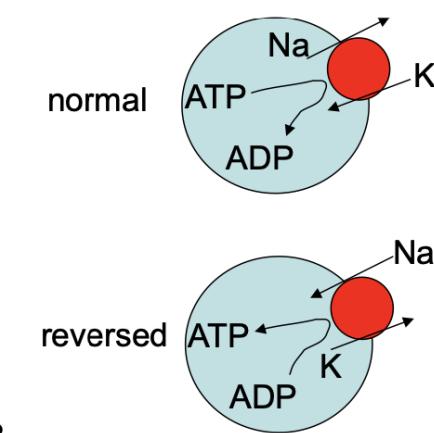


- Observations leading to conclusion that ATPase is the pump:
 - ATP not hydrolysed unless ions are transported
 - ATPase found wherever Na^+ and K^+ are pumped
 - ATPase and pump are both in membrane
 - Both inhibited by ouabain and stimulated by Na^+ and K^+
 - Mechanism:
 - 3 Na^+ binds inside
 - Sodium allows phosphorylation of the pump on an aspartate residue
 - Phosphate has 2 negative charges → transporter change conformation after binding
 - Faces the outside
 - Transporter binding site favors potassium
 - 2 K^+ binds outside
 - Potassium allows dephosphorylation
 - Conformation change → K^+ transported inside



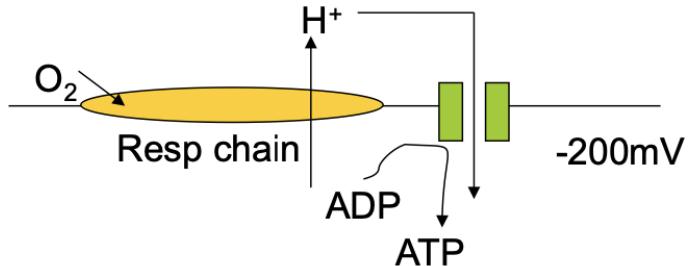
- Energy needed:
 - To move 2 K⁺ = ~ 0
 - Roughly at equilibrium potential at resting potential so moving in and moving out forces are balanced → no energy needed for any movement

- To move 3 Na⁺ = 3 x 11.7kJ = 35kJ
- Energy from ATP = 50kJ/mole
- Ca²⁺-ATPase
 - Types:
 - Plasma membrane calcium ATPase (PMCA)
 - Sarcoendoplasmic reticulum calcium ATPase (SERCA)
 - Number of ions transported by the two types may different
 - Mechanism
 - Aspartate phosphorylated during the carrier cycle
 - ATP only hydrolyzed when Ca²⁺ is pumped
 - Extrude 1 Ca²⁺ from cytoplasm to outside of the cell or into sarcoendoplasmic reticulum, and 2 H⁺ in / out
 - Conformational change moves the ion
 - ATP builds up calcium conc gradient across cell
 - High affinity for calcium but works slowly
 - Sodium-calcium exchanger has lower affinity but works faster
 - Km = 150nM
 - Sequence homologous to Na pump
 - P-type ATPase
 - Energy needed:
 - No energy needed for charge transfer → Ca²⁺ cancels 2H⁺
 - Energy to move 2H⁺ (2-fold conc change) in = 3.6 kJ
 - Energy to move Ca²⁺ (10-fold conc change) into SR or out of cell = 5.9 kJ
 - ATP = 50 kJ / mole
 - After moving 2 H⁺ = 46.4
 - 46.4 / 5.9 = 7.9
 - Ca²⁺ can change by 10^{7.9} fold
 - If 10mM Ca²⁺ in SR, an lower cytoplasm [Ca²⁺] to 10⁻²/10^{7.9}
- Reversal of ATPases
 - ATP hydrolysis is tightly coupled to ion movements
 - With the right ion gradients, Na⁺-K⁺ and Ca²⁺-ATPases can run backward getting energy from the ion gradients and using it to make ATP

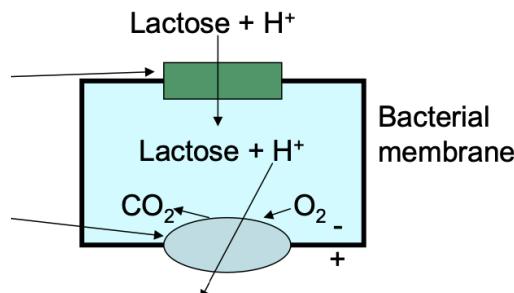


- Example:

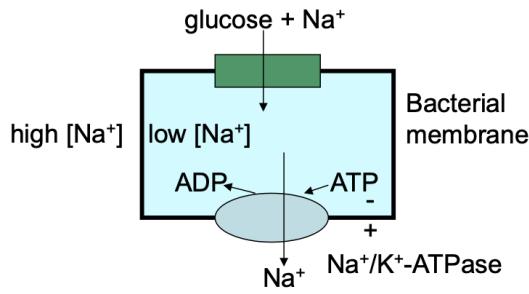
- H^+ - ATPase
 - Usually runs backwards, making ATP at the expense of proton gradient (generated by proton pumping fuelled by metabolism)



- H^+ co-transport came first
 - Energy from proton gradient and voltage gradient set up by respiratory chain
 - Mitochondria \rightarrow endosymbiosis
- F-type
 - Made of F0 membrane-spanning part and F1 catalytic subunits which bind ATP
- V-type ATPase
 - Found in vesicles, Golgi apparatus, bacteria, fungi
 - Pumps protons into vesicles and has many subunits
- Ion-coupled active transport
 - Powered by co-transport of ion, usually sodium or proton transport down gradients
 - Lac permease
 - Accumulate lactose, energy comes from H^+ gradient and voltage gradient set up by respiratory chain



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- Found in bacteria
- Glucose
 - Accumulate glucose in cell



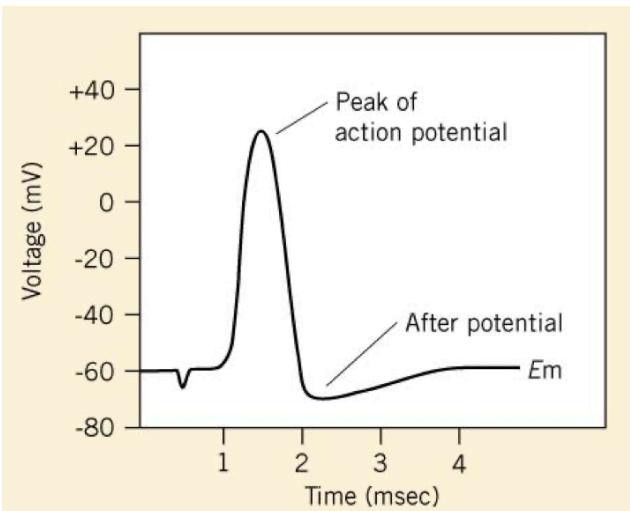
- Powered by Na⁺ gradient
- Na⁺/Ca²⁺ exchange
 - 3 sodium enter for 1 calcium leaving
 - Energy:
 - Energy gained from Na⁺ gradient = 17.7 kJ/mole
 - Energy gained from 1 net positive charge entering because inside cell is negative = 5.8 kJ/mole
 - Total energy gain = 23.5 kJ/mole
 - Energy needed to pump Ca²⁺ up conc gradient is 5.9 kJ mole per 10-fold gradient
 - 23.5/5.9 = 4
 - So 10⁴ gradient can be powered
 - Intracellular calcium can be lower to 2x10⁻⁷M

Action Potential

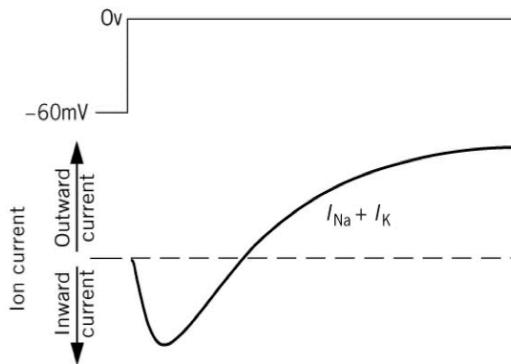
$$V = IR$$

$$R = 1/G$$

- Generation and propagation are different
- Action potential is a brief, transient reversal of the membrane potential that sweeps along the membrane of a neuron
 - Electrical signal

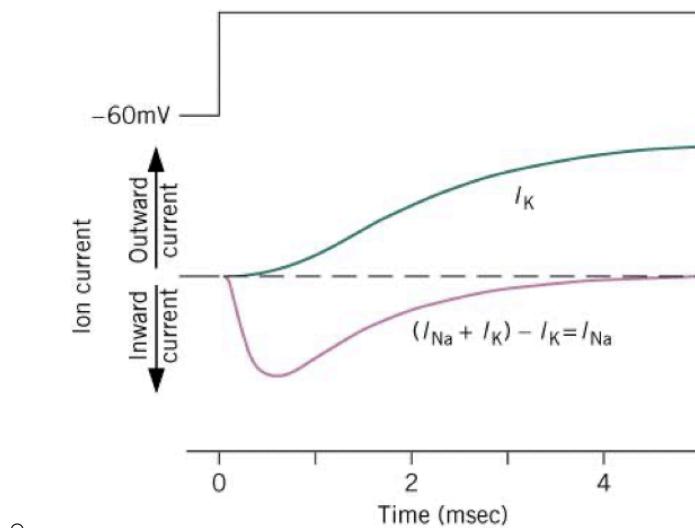


- Phases:
 - Depolarisation
 - Peak or overshoot
 - Positive signal
 - Between +20mV and +40mV
 - Below equilibrium potential for sodium (~50mV)
 - Repolarisation
 - Return of membrane potential towards negative / resting state
 - Afterhyperpolarisation
 - Undershoot
 - Short period, membrane potential more negative than at rest
- Characteristics:
 - Temporary
 - All or none
 - After reaching the threshold, AP will be fired or not occur at all
 - No change in amplitude no matter how much you exceed the threshold by
 - Threshold
 - Refractory period
 - Impossible/ more difficult to initiate another AP
- Ions responsible for AP:
 - Initiation of AP briefly switches its predominant permeability from K^+ to Na^+ → Different voltage-gated ion channels open during the different phases of the action potential
 - Conclusion from Hodgkin, Huxley, and Katz's experiment:
 - Method: Voltage-clamp technique
 - Decide at which voltage to fix membrane potential
 - Researcher in control of voltage → command voltage
 - Clamp (hold) the membrane at a particular potential
 - Used squid axon
 - Penetrate axon with electrodes
 - 1 to inject current
 - 1 to read current
 - If there are ion movements across the membrane that would change the potential, the voltage clamp amplifier detected any movement of potential away from command potential and set a current that will bring membrane potential back to clamped value (feedback)
 - By measuring current produced by device to keep membrane potential constant, we can measure the ion currents produced by the neurone under the different conditions
 - Sign inverted for injected current
 - We can separate different current components by:
 - Modifying concentration gradient of 1 of the critical ions
 - Substituting 1 of the critical ions with impermeant one
 - Selective pharmacological blockade of the different voltage-sensitive channels (TTX for sodium, TEA for potassium)
 - Demonstrated the existence of 2 types of voltage-gated currents



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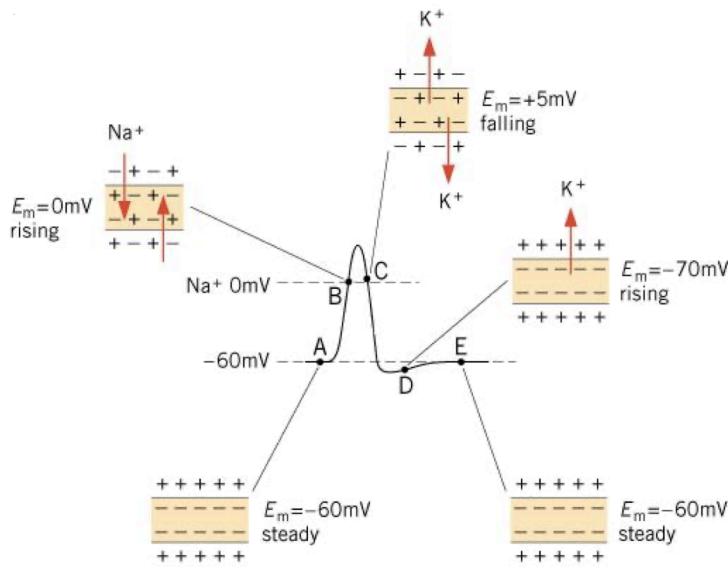
- Inward current followed by slower and sustained outward flow of current



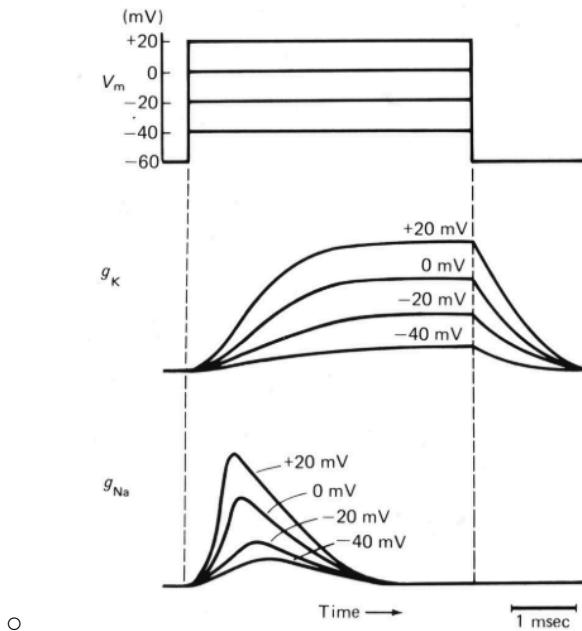
○

- Na^+ current is gone
- Only current observed is potassium
- Subtracting K^+ current from the current for both Na^+ and K^+ → got the specific current for both ions

- Changes in permeability occur due to different voltage-gated ion channels opening during different phases of AP

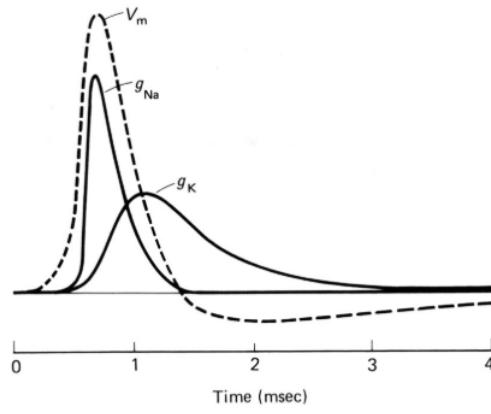


- - Inactivated sodium ion channels cannot conduct any more
 - Inactivation is not closing
 - Conductance to ions
 - $$g_K = \frac{I_K}{(V_m - E_K)}$$
 - $$g_{Na} = \frac{I_{Na}}{(V_m - E_{Na})}$$
 - I = Current
 - V_m = command potential
 - E = equilibrium potential from Nernst equation
 - Voltage step and conductance

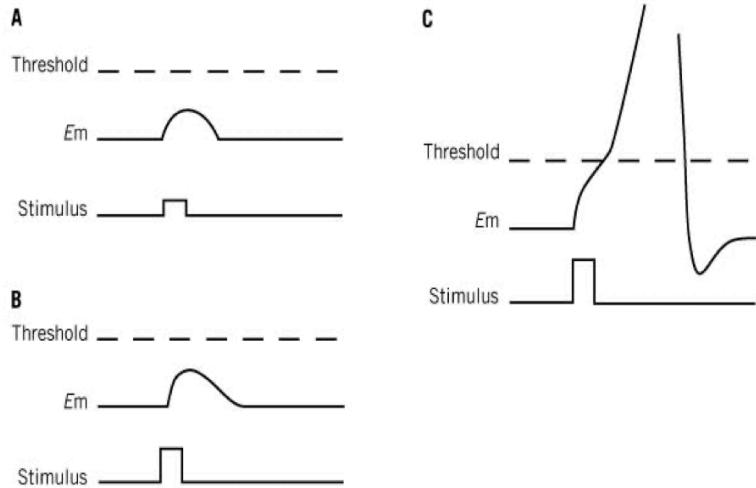


- Both K^+ and Na^+ open in response to depolarising voltage steps
- Greater depolarising step = greater extent of conductance and faster opening
- Different rates of onset and offset at all levels of depolarisation for K^+ and Na^+ channels

- Na^+ channels close more rapidly than K^+ channels
- Na^+ inactivate, so decrease in conductance during a maintained depolarising voltage step
 - Channel \rightleftharpoons Open \rightleftharpoons Inactive
 - Inactive state going back to channel state will need time and a negative V_m
- Currents for K^+ and Na^+ will reverse their directions when potential approaches one of the ion's equilibrium potential
- Shape of AP matches the conductance curves for K^+ and Na^+ at different phases which means that **different phases of the AP results form the opening and closing of voltage-gated K^+ and Na^+ channels**



- Features:
 - All or none
 - AP occurs and reaches full amplitude, or doesn't occur at all
 - Amplitude independent of the magnitude of stimulus that stimulated it
 - Small depolarisation = small inward current of Na^+ , but also increases outward currents of K^+ voltage channels and leak channels due to changing electrochemical driving forces
 - **Outward potassium current opposes depolarising sodium current when depolarisation not great enough**
 - Large enough depolarisation = great voltage sensitivity and rapid Na^+ voltage-gated channel activation process ensure that the membrane potential reaches threshold, where the Na^+ current exceeds the increase in outward K^+ channels



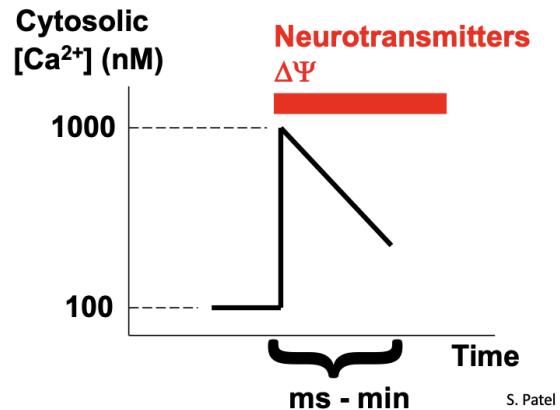
- Threshold is the specific value of V_m at which the net ionic current ($I_{Na} + I_K + I_{leak}$) just changes from outward to inwards, positive charge on the inside of membrane
- Refractory period
 - More difficult to excite a neurone to generate another AP
 - Caused by inactivation of Na^+ channels and elevated K^+ conductance immediately after an AP
 - Absolute refractory
 - Membrane is **repolarising and immediately afterward AP**
 - No new AP can be generated because threshold = infinite
 - Relative refractory
 - Threshold higher than normal (on its way back to normal level)
 - New AP can be generated if stimulus strong enough
 - More potassium outward current counterbalancing any sodium current coming in
 - Refractory period important for the direction that AP travels towards
 - Refractory period prevent AP from summatting
- Action potential propagation
 - AP can move along the length of an axon \Rightarrow long distance communication
 - Propagation = depolarisation \rightarrow excitation of regions of membrane adjacent to location of AP
 - Local spread followed by the active regenerative process
 - New action potential will not be generated backwards but will be generated forward if current is strong enough to reach threshold
 - **Membrane capacitance and axon diameter affect the velocity of AP propagation**
 - If axial resistance is large, it will oppose to passage of AP
 - Axons with small diameters will have high axial resistance \rightarrow hinder speed of propagation of action potential
 - R_a large = small axon, current flowing through is smaller, takes longer to change the charge on the membrane = slow
 - If membrane capacitance is large, more charge must be deposited on membrane to change the potential across the membrane
 - C_m large = current must flow for longer to produce a given depolarisation = slow

- Rate of passive spread varies inversely with $R_a C_m$
- Strategies for rapid AP propagation
 - Large axons = increase diameter of axon core
 - R_a decreases in proportion to square of axon radius
 - So R_a decrease a lot, decreases by the squared of its value
 - C_m increase in proportion to radius
 - Decreases $R_a C_m$
 - Myelin is a way to overcome the fact that humans and other mammals with complex nervous system cannot afford to have large axons (too much energy)
 - Decrease C_m as capacitance is inversely proportional to thickness of insulating material
 - Decreases $R_a C_m$
 - Saltatory conduction → insulation provided by myelin forces the depolarising current farther down the axon, thereby allowing AP to skip parts of the membrane
 - Nodes of Ranvier have greater density of sodium channels

Calcium Signalling

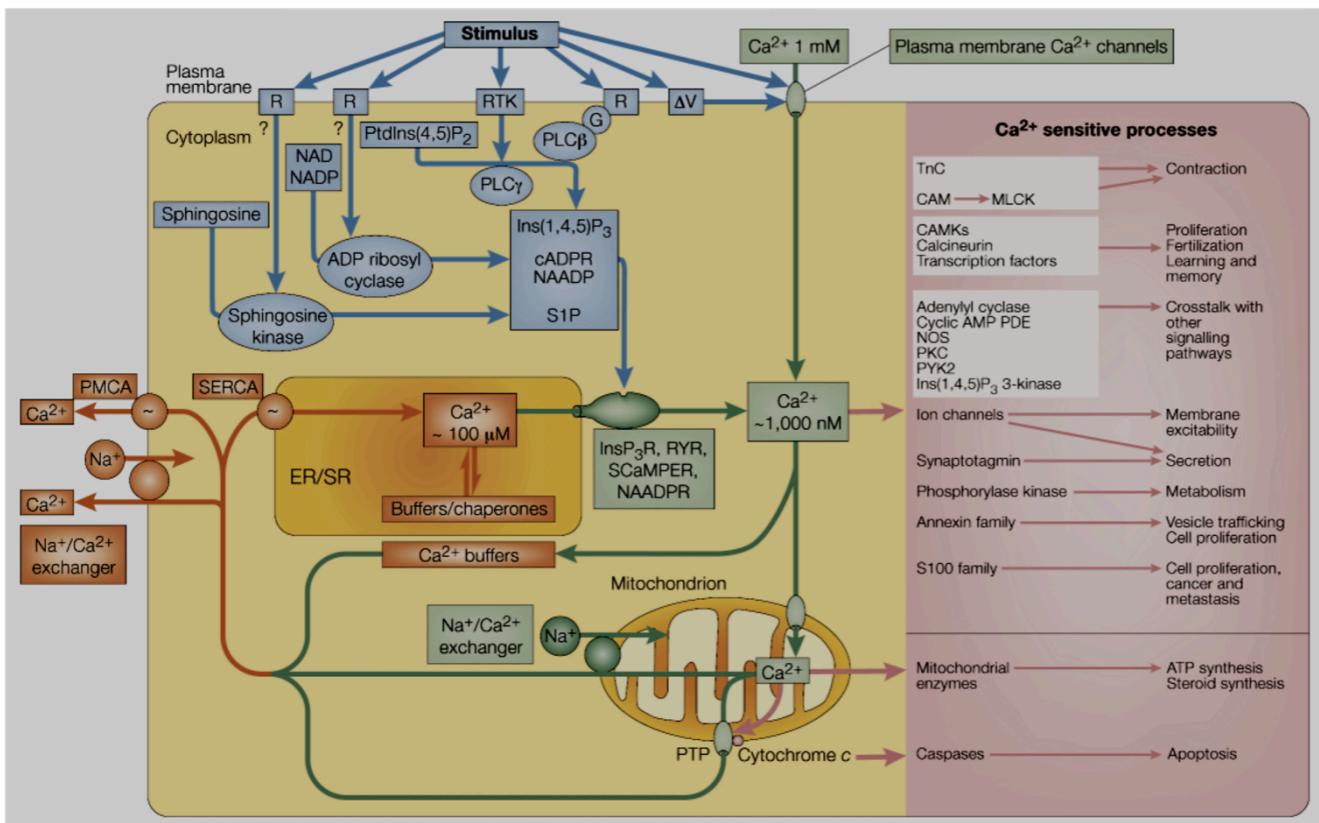
Calcium basics

- Calcium is a unique signalling molecules
 - Not synthesized from precursors
 - Cannot be broken down
- Calcium is versatile
 - Calcium controls a broad range of neuronal fuctions
 - NT release
 - Membrane excitability
 - Synaptic plasticity
 - Changes in gene expression
 - Growth and differentiation of neurons in development
 - Programmed neuronal death
- Important facts and number
 - Extracellular calcium concentration → 1-2mM
 - Intracellular calcium concentration → 50-100 nM
 - Diffusion constant for Ca^{2+} (D_{Ca}) depends on ion size and medium
 - D_{Ca} (water) = $\sim 600 \mu\text{m}^2/\text{s}$
 - D_{Ca} (cytoplasm) = $\sim 200 \mu\text{m}^2/\text{s}$
 - Calcium is estimated to migrate no further than 0.1-0.5 μm and lasts only $\sim 50 \mu\text{s}$ before encountering a binding protein

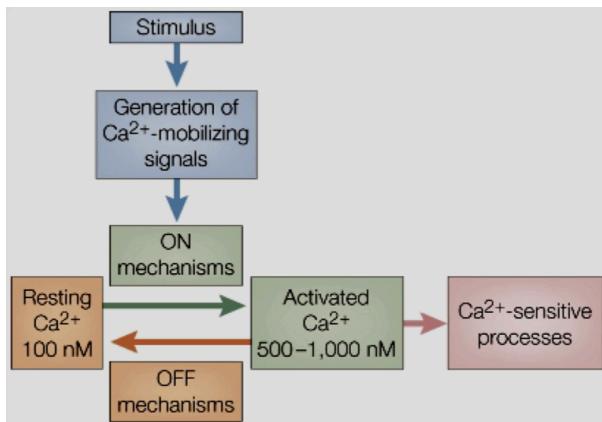


- Rapid increase in calcium which then quickly declines

- Ca²⁺ signals are highly regulated at 2 levels:
 - Spatially
 - Temporally
- Large concentration gradients are useful for signalling purposes
 - Calcium has tendency to move into cell cytoplasm from extracellular environment and from intracellular stores such as the ER (with high Ca²⁺ conc)
- We want the calcium to not last long in cells as it is toxic (e.g. can activate caspases which cause cell death)
 - A variety of homeostatic mechanisms are involved in maintaining calcium at low levels



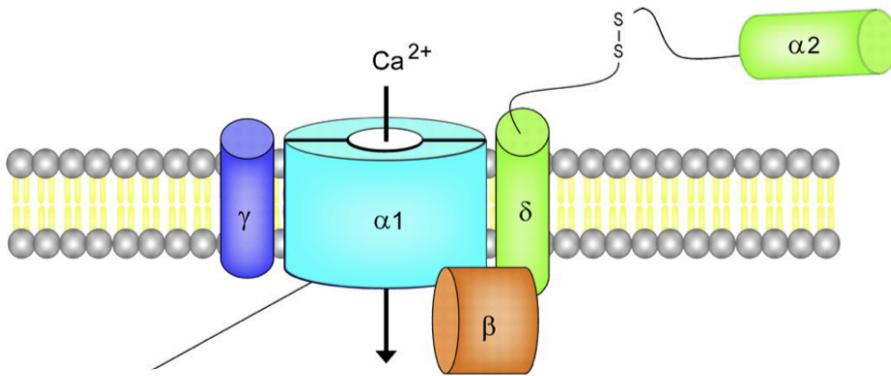
Due to these cascades (calcium sensitive processes), calcium is responsible for many processes



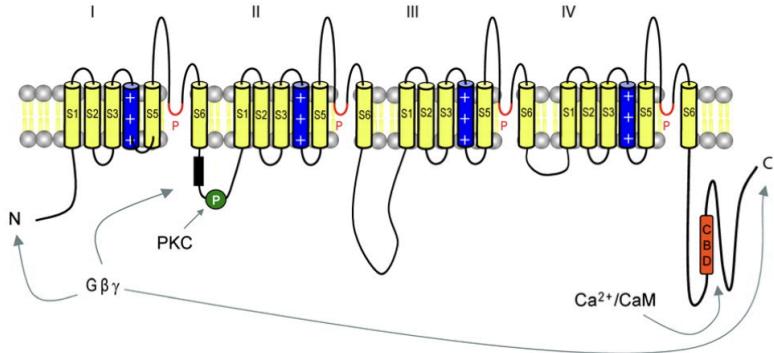
On Mechanism Extracellular

- **Voltage-gated Calcium Channels**

- In the plasma membrane
- Contains pore-forming alpha-1 subunit that determines their main biophysical and pharmacological properties

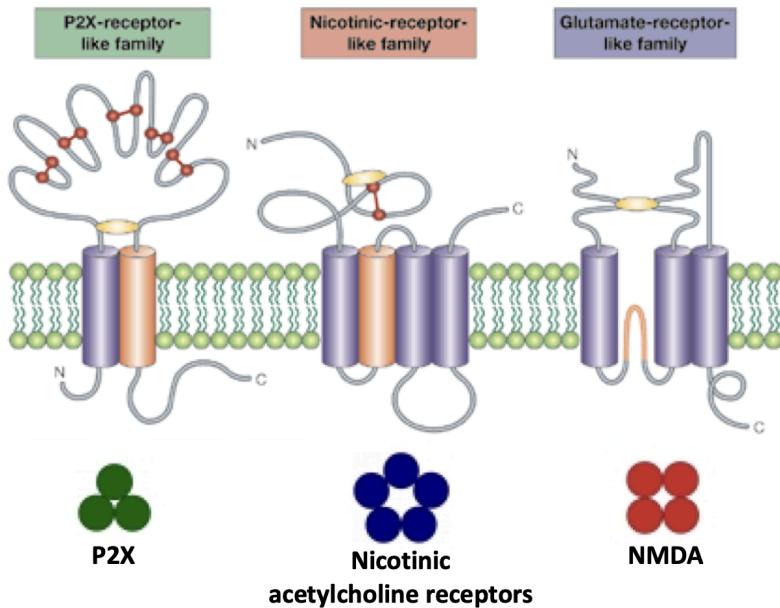


-
- The alpha-1 subunit consists of:
 - Intracellular amino and carboxyl termini
 - 4 domains all linked with a single very long polypeptide
 - Each domain contains 6 transmembrane spanning regions and a hairpin loop of amino acid that dips into membrane (but does not fully cross it)
 - S4 has highly positively charged amino acids → voltage sensing, highly selective only for Ca^{2+}
 - Hairpin loops line pore



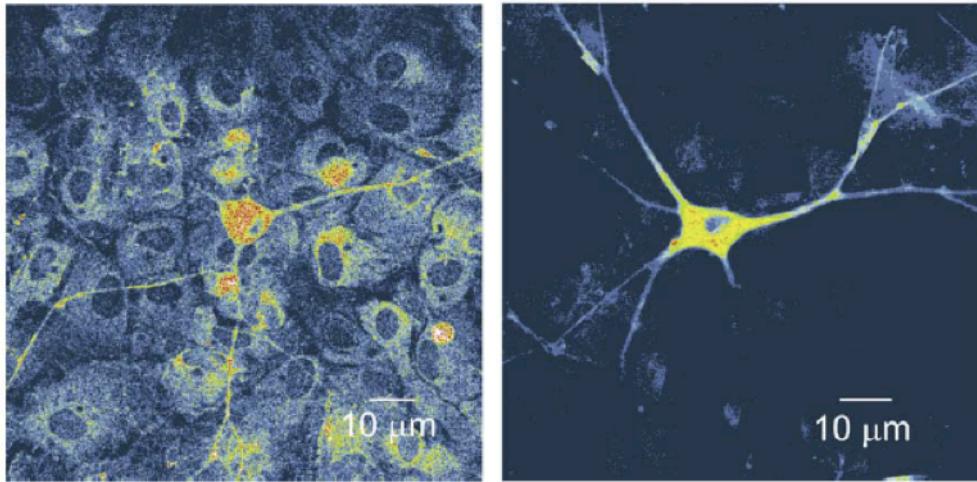
Benarroch EE, Neurology 2010;74:1310-1315

- - Additional subunits acting as chaperones and modulate alpha subunit function
 - Regulatory regions (e.g. N and C terminus) responsible for certain types of calcium channels with beta, gamma subunits → important for neuromodulation
- **Ligand-gated, calcium-permeable receptors**
 - Respond to different NT (e.g. ATP, ACh and glutamate)
 - Have different topologies and stoichiometries



- - Large extracellular loop for P2X → gated by ATP
 - Extracellular N and C terminus for nicotinic receptor
 - NMDA receptor = tetrameric, glutamate + glycine gated

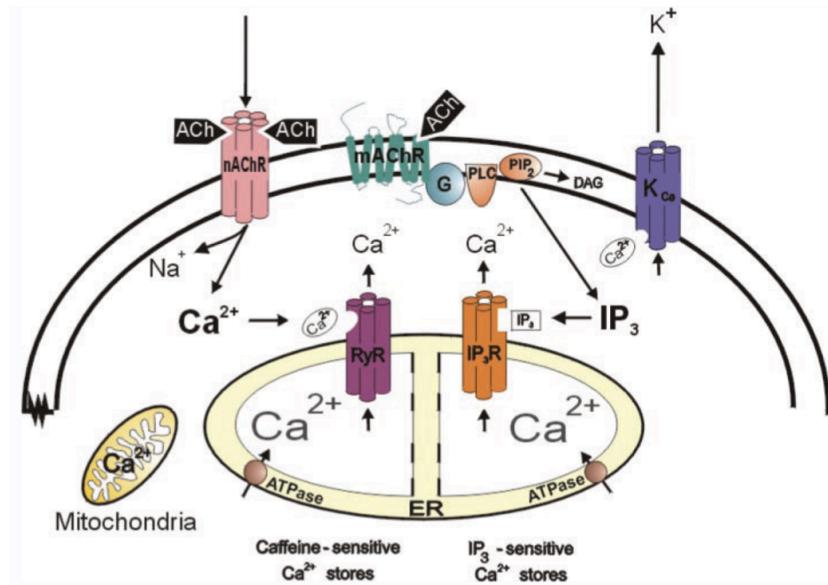
On Mechanism Intracellular



(Hippocampal neuronal cultures stained with fluorescent thapsigargin which binds to SERCA pumps and fluorescence tryanodine which binds to ryanodine receptors)

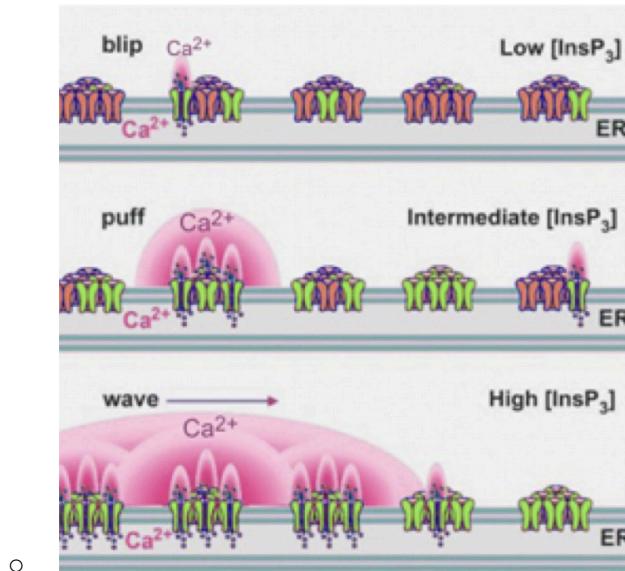
ER are calcium stores distributed throughout neuron (in cell body and dendrites) → Calcium signalling can happen independently in dendrites

The same neurotransmitter can activate multiple Ca^{2+} sources in neurons via distinct signalling pathways. This can lead to different final effects (depending on the location of the receptors and their effectors) can signal amplification, and synergistic effects



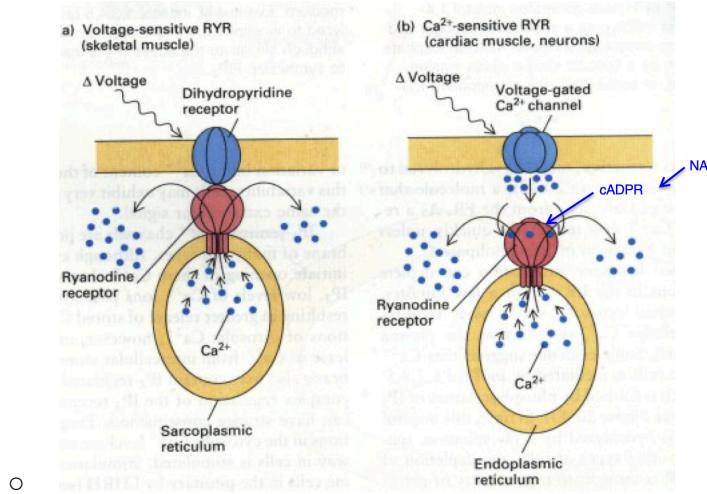
- IP_3 Receptors
 - IP_3 is synthesized from PIP_2
 - IP_3 receptors sit on surface of ER
 - Formed by 4 subunits

- For each subunit there are 3 paralogs, that can form homo- or heteromers → molecular variability
- Large N-terminal IP₃-binding domain on cytoplasmic side
- C terminus intraluminal (in the ER)
- Further ATP and calcium binding sites on their cytoplasmic side
- Inhibited by heparine
- Modulated by calcium in biphasic manner
 - Response to IP₃ is optimal when free calcium concentration in cytoplasm is ~300nM, but substantially inhibited at lower or higher calcium concentration
 - Reversible biphasic regulation by cytosolic Ca²⁺ is a characteristic shared by all 3 mammalian IP₃ receptors



- - IP₃ binding to receptor on smooth ER leads to release of Ca²⁺ into cytoplasm
 - Higher concentration of IP₃ will lead more sustained activation of receptors → to greater calcium elevation in cytoplasm

- Ryanodine Receptors
 - Leads to **calcium-induced calcium release (CICR)**



- - In muscles:

- As voltage-gated ion channel open, opening mechanism is mechanically coupled to activation of ryanodine receptors sitting in skeletal muscle sarcoplasmic reticulum
- Triggers opening of ryanodine receptors on SR → increase in calcium levels
- In neurons
 - Calcium flow through voltage-gated calcium channel
 - Primary cytoplasmic calcium concentration elevation
 - Calcium act as ligand and bind to ryanodine receptor, activating it
 - Secondary, more sustained calcium release
 - Large transmembrane proteins sitting in ER membrane
 - Formed by 4 subunits
 - 3 genes that can form homomers: RyR1, RyR2 and RyR3
 - Are activated by Ca^{2+} , cADPR, or by direct coupling to L-type VGCC in muscles
 - Have a large N-terminal domain on the cytoplasmic side
 - Are stimulated by caffeine
 - Ryanodine is a plant alkaloid and blocker
 - **CICR generates oscillations** in concentration of cytosolic free Ca^{2+} that underlie the waves that propagate via Ca^{2+} diffusion in many cell types
 - Can occur spontaneously or result of stimulation by external signal
 - Represent most widespread oscillatory phenomenon at cellular level
 - Seen in astrocytes
 - Waves can be localised to soma or dendrite, or move from cell to cell through gap junctions
 - Can underlie some pathological symptoms (e.g. migraines)

Off mechanism

Calcium buffer and NCX are the first mechanisms to decrease Ca^{2+} conc, the remaining is taken care of by PMCS

- **Re-uptake in ER by SERCA pump** → ER and Mitochondria are sinks and sources for Ca^{2+}
 - SERCA pump
 - Transports 2 Ca^{2+} per ATP
 - Energy consuming
 - 3 different genes
 - High density in ER membrane
 - Activated by high cytosolic Ca^{2+} concentration and inhibited by high ER Ca^{2+} concentration
 - Inhibited by phospholamban and inhibition is relieved by phosphorylation
- Re-uptake in mitochondria by uniporter or $\text{Na}^+/\text{Ca}^{2+}$ exchanger (NCX)
- **Expelling of calcium out of cells by plasma membrane PMCA pump and NCX**
 - PMCA
 - Transports 1 Ca^{2+} per ATP consumed with a rate of $\sim 30\text{Ca}^{2+}$ per second

- 4 different genes and multiple splice variants
- 10 transmembrane spanning regions
- Released from inhibition in response to elevation of intracellular calcium
 - Autoinhibitory domain with calmodulin binding site
 - Bound to calmodulin → inactive
 - Ca^{2+} bind to calmodulin
 - Activated by Ca^{2+} -bound calmodulin
- Regulated by phosphorylation of PKC and PKA
- NCX
 - **Powered by electrochemical gradient of Na^+**
 - Transports 3 Na^+ in against 1 Ca^{2+}
 - Operates without ATP
 - Antiporter membrane protein
 - 9 transmembrane spanning regions and a large cytosolic loop
 - Rate of ~2000-5000 Ca^{2+} per second
 - Low affinity for Ca^{2+}
 - Activated by high concentrations of cytosolic Ca^{2+}
- **Calcium buffers:**
 - Most calcium that enters cytoplasm is rapidly bound to various **cytosolic buffers**
 - **Parvalbumin** → has 4 binding sites for calcium, common amino acid motif favours calcium binding
 - High affinity for calcium, but slow off-rate (unbind very slowly)
 - Relatively high affinity for Mg^{2+} , intracellular high conc of Mg^{2+} , at rest most parvalbumin bound to Mg^{2+}
 - Will take time to unbind from magnesium and bind to calcium
 - This gives time for calcium to act
 - After Ca^{2+} unbinds it will be thrown out or back into cytoplasm
 - Calbindin-D28k
 - Cytosolic buffers are first loaded and then unloaded thus influencing the amplitude and duration of cytosolic Ca^{2+} signal
 - Buffer capacity varies considerably between cells

Experiment

Demonstrating involvement of Ca^{2+} in cellular response (does it act on a channel?):

1. Ionophores → mimic response of an ion
 - a. Ca^{2+} ionophores mimic Ca^{2+}
2. Ca^{2+} channel blockers/inhibitors should inhibit response
3. Ca^{2+} chelators (e.g. EGTA) should prevent or suppress the response
 - a. Bind to calcium

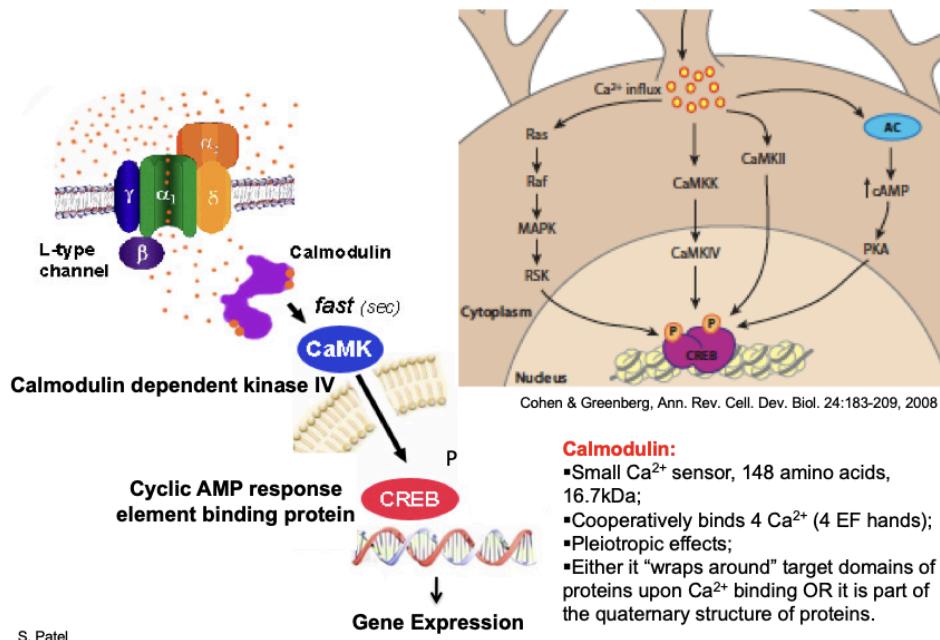
Response should correlate with a rise in intracellular free Ca^{2+} as revealed by Ca^{2+} sensitive dyes (e.g. FURA-2, Fluo-4)

Calcium effect on postsynaptic cell:

- Calcium mediates signal transduction from synapse to nucleus
 - Extracellular calcium enters postsynaptic cell via:
 - Synaptic and extrasynaptic ligand-gated channels
 - Voltage-gated channels
 - **NMDA receptor and L-type voltage-gated channel are major routes for calcium entry**
 - CICR can also amplify calcium signals via ryanodine receptors
- Calcium in various locations (channel mouth, cytoplasm, nucleus) can signal to transcription factors
 - Gene products influenced by calcium activity contribute to neuronal development and plasticity
 - Allows nucleus to communicate adaptive changes to synapse

Calmodulin

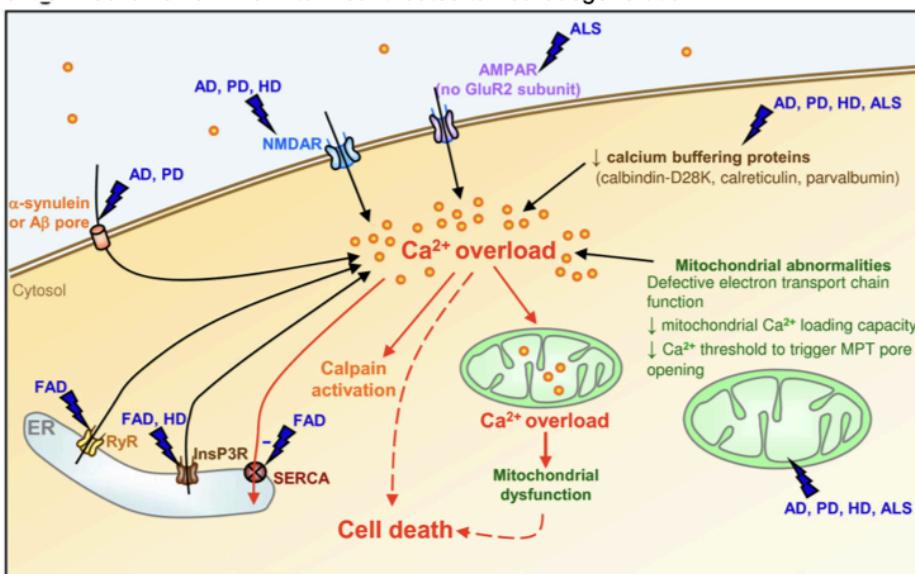
Calmodulin is the calcium sensor for gene expression



S. Patel

Dysfunctional aspects of Ca^{2+} signalling: Ca^{2+} overload in neurodegenerative diseases

AD/FAD, PD, HD, and ALS affect cytosolic calcium levels by deregulating different homeostatic control mechanisms. This in turn contributes to neurodegeneration.



AD: Alzheimer's disease; FAD: familial Alzheimer's disease;

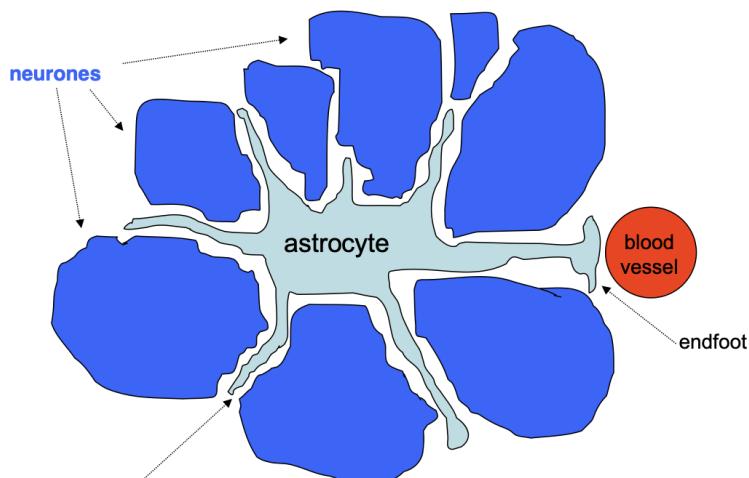
PD: Parkinson's disease; ALS: amyotrophic lateral sclerosis;

HD: Huntington's disease;

Marambaud et al. Molecular Neurodegeneration 2009. 4:20

Homeostasis and Glia

- Astrocyte function:
 - Buffering $[\text{K}^+]_o$ via Na/K pump and ion channels
 - Also spatial buffering
 - Taking up and recycling glutamate and other transmitter
 - Preventing extracellular glutamate reaching neurotoxic levels

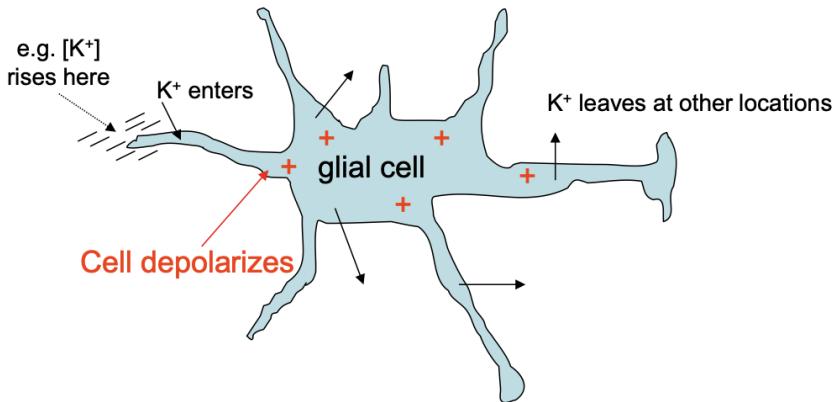


- Extracellular volume is small.
 - Need for a system to control the environment around neurons

- Control conc of ions and neurotransmitters
- Endfoot → contact with blood vessels

Removal of K^{\pm}

- Changes of $[K^+]$ in extracellular space
 - Cause: AP in neuron 1 → hyperpolarisation = K^+ efflux
 - Effect: Rise in extracellular potassium in extracellular space → Neuron 2 takes up the K^+ (diffusion into neuron 2 down a conc gradient)
 - Result: Depolarisation of neuron 2, possibly causing AP and hence leading to mixing of info being coded by 2 neurons → can get epileptic discharge
- Glial cells minimize extracellular potassium changes by:
 - Taking up K^+ through ion channels
 - Taking up K^+ through Na/K pump
- Nernst potential = no net flux

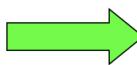


- - One end with the higher local extracellular potassium will depolarise due to influx of K^+
 - The other end does not have high extracellular potassium concentration
 - Potassium will diffuse out of the glial cell at the other end of the glial cell → **Spatial buffering**

The result is:

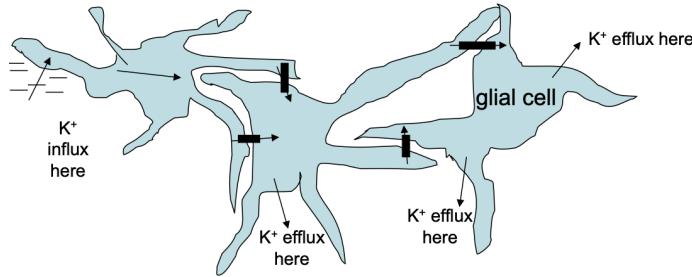
an inward K^+ current where $[K^+]_o$ is high

an outward K^+ current where $[K^+]_o$ is low

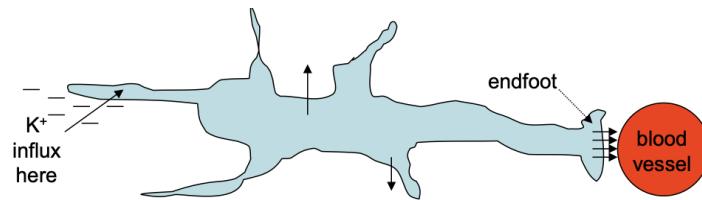


i.e. SPATIAL BUFFERING

- Spatial buffering is facilitated by:
 - Gap junctions between glial cells → allows K^+ to be buffered to a larger area



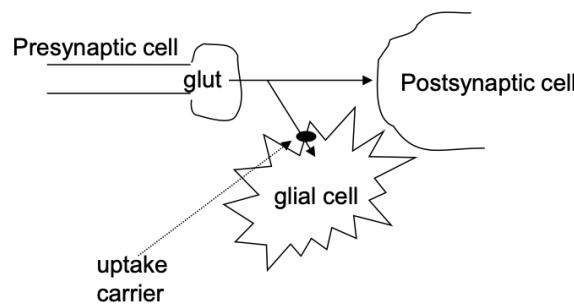
- Astrocyte endfoot → K⁺ leaves via endfoot to blood vessel, not deposited around other neurons



- Evidence:
 - Resulting depolarisation from injecting potassium is much larger when applied to the endfoot
 - Specialisation of endfoot membrane with potassium being deposited there
- Over 90% of cell's K⁺ conductance is in the endfoot → accumulated K⁺ is buffered to blood vessel
- High K⁺ conductance results from large number of K⁺ channels present

Removal of Neurotransmitter

- Neuromuscular junction → ACh
 - Inactivated by AChE
- Glutamatergic synapse → glutamate
 - No extracellular enzyme to inactivate it
 - **Glutamate is removed by uptake into glia**
 - Inside glia: glutamate is converted to glutamine (by **glutamine synthetase**) or enter the Krebs cycle



- Glutamate uptake is important:

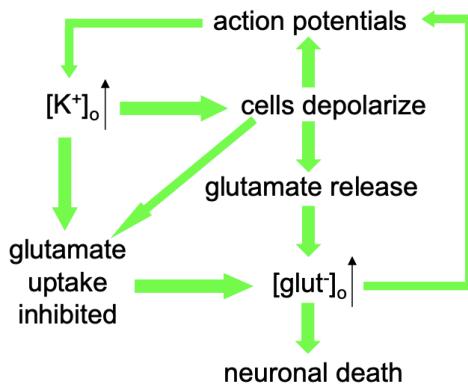
- Terminates synaptic transmission
 - Essential for sending brief signals through neurons
- Recycles synaptically released glutamate
- Prevents glutamate-induced neurotoxicity
 - Cause:
 - Glutamate activates NMDA receptors → Ca^{2+} influx ⇒ increase in Ca^{2+} levels
 - Ca^{2+} dependent enzymes will “eat” cell and trigger release of apoptosis-inducing cytochrome C from mitochondria
 - Ion fluxes resulting from glutamate acting on neurons and glia lead to water movements → cells swell and die (e.g. dendrites have very thin membranes, swell easily)
- Removal mechanism:
 - No ATP needed to accumulate glutamate against a conc gradient
 - Gets energy by **co-transporting Na^+ ions** down their electrochemical gradient into cell
 - 3 Na^+ transported in for every glut in
 - More Na^+ than glut are transported
 - Uptake generate inward current
 - Uptake inhibited by depolarisation because the the Na^+ gradient across the membrane is diminished, hence the glutamate transporter cannot rely on this gradient to transport glutamate in when there is depolarisation.

Failure of $[\text{K}^+]_o$ and $[\text{glut}]_o$ homeostasis

Occurs in anoxia and ischaemia



Positive feedback:



- - Cycle of potassium and glutamate imbalance