

Physiology of excitable cells



Excitable cells

- Cells that are able to produce and respond to electrical signals
 - Neurons
 - Muscles
 - Heart
 - Secretory cells (such as pituitary, insulin producing cells of pancreas, cells in adrenal medulla)



Why electricity?

- Fastest process in the cell
- Energy efficient
 - They use chemical gradients that already exist
- Dependable over long distances (gated channels act as transistors)



Why our neurons can use electrical signals?

- **The cell membrane is polarized** (it has different ions and charges on both sides) created by pumps
- If we have a difference (called membrane potential) we can discharge it
- The discharge is a signal (**information!**) called an action potential



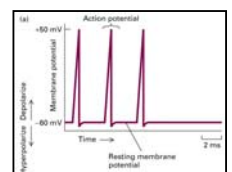
Cell as a capacitor

- Phospholipid bilayer is almost perfect isolator
- It can separate electrical charges between inside and outside (cell is a capacitor)
 - Capacitive properties of the membrane create a difference called membrane potential (inside has more negative charges than outside)
 - **The cell membrane is polarized** (it has different ions and charges on both sides)
 - Our excitable cells can be discharged because they have "holes" through which ions can escape (called gated ion channels)



Why our neurons can use electrical signals?

- These channels (voltage gated) work as transistors (they have a gate and if the gate opens it creates a signal that is always the same)
 - They allow for the spread of the action potentials without the loss of amplitude
- The discharge event is transient (otherwise it will not carry information)



What is necessary for the generation of action potential?

- Polarized membrane (separation of charges) = resting membrane potential
- Na^+ and K^+ voltage gated channels to discharge the polarization
- Stimulus to activate voltage-gated channels (or in short something that will initially change membrane potential)

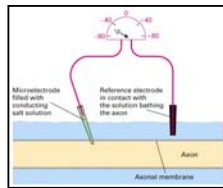


Resting potential



Cells maintain an electric potential across a cell membrane

- Difference of potential between inside and outside of the cell
- Resting membrane potential of most neurons is about -70 mV (inside negative in the respect to outside)



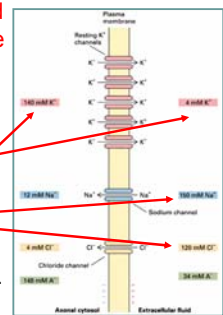
How is membrane potential generated?

- Arises from separation of charges across the membrane (an insulator)
- Unequal distribution of ions on both sides of the membrane created by
 - Electrogenic pump $3\text{Na}^+ / 2\text{K}^+$
 - Different membrane permeability for Na^+ and K^+ ions = membrane expresses different number of channels for Na^+ and K^+ ions



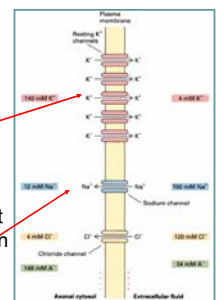
Ionic composition of intra- and extracellular fluids

- Ions are **unequally distributed at two sides of the membrane** (that's what the pump did)
- K^+ and negatively charged proteins are main ions inside the cell
- Na^+ and Cl^- are main ions outside
- This wouldn't generate electrical difference without...



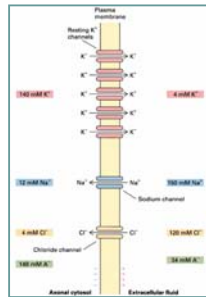
Generation of membrane potential

- Always open "leak" K^+ channels
- K^+ brought in by a pump tries to escape from the cell down the gradient through the always open "leak" K^+ channels
 - There are fewer or none always open Na^+ channels so Na^+ is not able to keep up (Na^+ is coming in down the gradient too but slower)



Generation of membrane potential

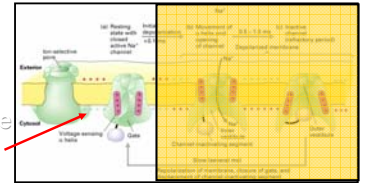
- Effectively more K^+ will go out than Na^+ come in (negative inside)
- In addition, organic anions (negatively charged proteins) are too big to follow and contribute to the difference



Channels contributing to membrane potential

- "Leak" or always open K^+ channel belong to TWIK family
- Kir K^+ channels are also open at resting potential

Voltage gated Na^+ and K^+ channels are closed (negative charges inside)



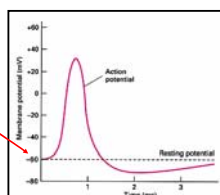
Action potential

Creation of action potential

- Now we have a difference and this difference can be cancelled by the inflow of positive charges (Na^+ , because there are so many of them outside and channels can only transport down the gradient)
- This inflow can happen through gated channels that are "normally" closed and open only when prompted by gating agent

Generation of action potential

- Action potential is created by opening of voltage gated Na^+ channels
- How does the membrane reach the potential necessary for activation of voltage gated channels?



Generation of action potential -the BIG picture

- Initial depolarization – voltage necessary to open voltage gated Na^+ channel has to come from some source
 - Generator potential in primary sensory neurons
 - Activation by neurotransmitter – synaptic transmission from presynaptic neuron

Generation of action potential in primary sensory afferents



Generation of action potential in primary sensory afferents



- Depolarization (discharge of capacitor is created by opening of gated channels)
 - Ligand gated (inflammatory mediators)
 - Mechanical stimulus
 - Heat
- Energy of the stimulus opens the gate in the channel

Generation of action potential in primary sensory afferents

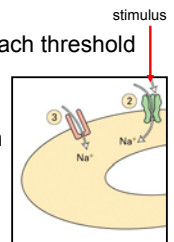
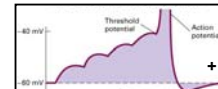


- Usually not very selective cation channels (inflow of $\text{Na}^+/\text{Ca}^{2+}$ which means inflow of $+++$ lowers the membrane potential enough to move the voltage sensor to open the voltage gated channels)
- Raise membrane potential just enough to initiate action potential

Sensory transmission



- A stimulus (heat, histamine, membrane stretch) opens non-selective cation channels
- Inflow of Na^+ and Ca^{2+}
- Some depolarization (enough to reach threshold of voltage gated channels)
- Opening of voltage-gated Na^+ channels and propagation of action potential



Creation of action potential



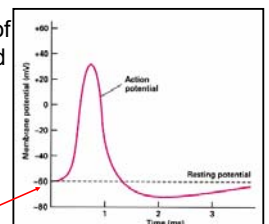
- Once the voltage of the membrane gets less negative = reaches threshold potential
- it will open voltage gated Na^+ channel and create

action potential

Action potential



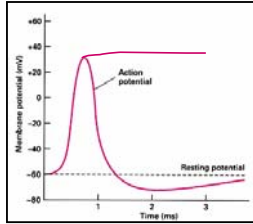
- Sequential opening, inactivation and closing of Na^+ and K^+ voltage gated channels
- Cause respectively **depolarization** and **repolarization** of the membrane



Before it works it has to reach threshold potential by different mechanisms

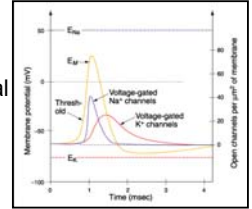
Why inactivation and closing?

- If Na^+ was coming in without inactivation the membrane will stay discharged (depolarized) and there will be no information, just a dead membrane
- Inactivation (ball and chain mechanism prevents never-ending depolarization)



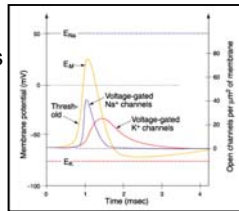
Changes in ion permeability during an action potential

- Action potential can be separated into flow of Na^+ and K^+ ions (both through respective voltage gated channels)
- Charges and ions have to be brought back to the initial state (repolarized) to be ready for the next message



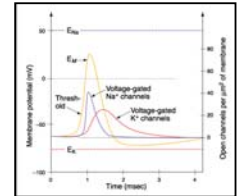
Changes in ion permeability during an action potential

- Opening of voltage-gated Na^+ channels –
 - Na^+ goes in and discharges = depolarizes the membrane
- After 0.5-1ms Na^+ channels inactivate – Na^+ no longer goes in
 - Channels are still open-membrane potential did not go down yet!!!



Changes in ion permeability during an action potential

- Opening of voltage gated K^+ channels
 - K^+ goes out and starts to reverse the situation (repolarize the cell)
 - Current is delayed in respect to the increase of Na^+ permeability
 - After 1-2 ms K^+ channels inactivate too

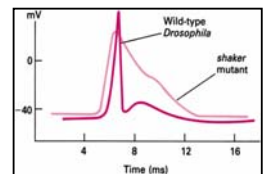


Changes in ion permeability during an action potential

- Once membrane potential is back to resting level both channels close (they are voltage gated and the “opener” no longer exist)
- Movements of ions and subsequent inactivation are very fast
 - Action potential lasts 1-2 ms
 - Movements of ions are local and do not affect the general membrane potential of the cell

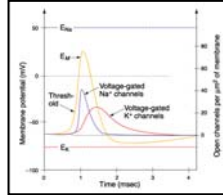
Shaker mutation of voltage-gated K^+ channel

- No repolarization due to mutation in voltage-gated K^+ channel protein
- Channel was named later after *Shaker* mutation



Electrical events in the excitable cells

- Resting potential – Na⁺/K⁺ pump and TWIK always open channels ⇒ distribution of charges
- Depolarization – voltage gated Na⁺ channels
- Repolarization – voltage gated K⁺ channels



Transmission of action potential over long distances (for example to the brain)

Transmission of action potential over long distances

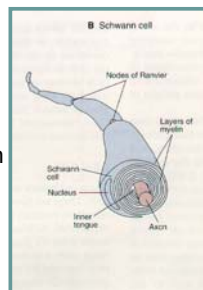
- Action potential is a self regenerating event
 - Every time the channels open the amplitude of action potential is identical because they always discharge existing condition (they do not produce anything, just "destroy" membrane potential of the cell)

Transmission of action potential over long distances

- Therefore they can move along the axon of a neuron and open and open and open, every time bringing the potential to 0 mV
 - They move without the change in amplitude
 - And can do it as long as there are voltage gated Na⁺ channels and polarized membrane on their way
 - Plus there is enough depolarization reaching next gate (to open voltage gated Na⁺ channel)

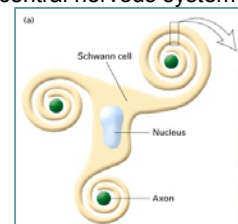
One special situation – myelinated nerve fibers

- Myelin provides additional isolation on the nerve
- Makes the initial stimulus last longer in order to be more successful in opening voltage gated channels and generation of action potential

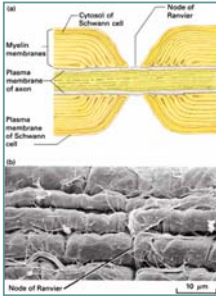


Myelin

- Produced by Schwann cells in peripheral nervous system
- Or oligodendrocytes in central nervous system
- Determines speed of transmission in nerves



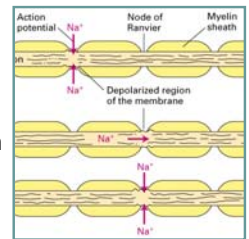
Node of Ranvier



- A gap that separates two Schwann cells
- Na^+ channels are localized only in the exposed spaces of Ranvier's nodes

Conduction of action potentials in myelinated axons

- Action potential is only produced in nodes of Ranvier
- Current spreads under myelin in amounts just enough to open next bunch of voltage gated Na^+ channels in the next node



Neurodegenerative diseases

- Loss of myelin (loss of isolation) produces more places to discharge membrane potential (action potentials) that take more time to reach a brain or do not reach it at all