Ion channels

Little appreciated fact of physiology

- Human beings (and other living organisms) are run by electricity, and "ion channels" are the core of our electrical system

Ion channels

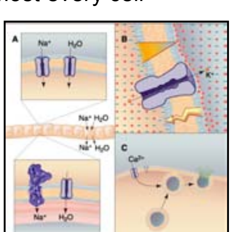
- Yet another type of membrane transport
- Pores in the membrane that open and close in a regulated manner and allow passage of ions
  - “Dispose” of the gradients
- Passive transporters
  - Ions flow from high to low concentration
  - No energy is used
  - If there is no gradient ions will not flow

Ion channels

- Small highly selective pores in the cell membrane
- Move ions or water
- Fast rate of transport 10^7 ions/s
- Transport is always down the gradient
  - Can not be coupled to the energy source

Ion channels are everywhere

- Channels are present in almost every cell
- Functions
  - Transport of ions and water
  - Regulation of electrical potential across the membrane
  - Signaling

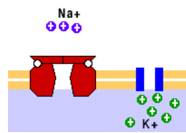


Ion channels function

- Responsible for processes such as
  - Heart beat
  - Muscle contraction
  - Hormone secretion
  - Vision and olfaction
  - Pain
  - Cognition
  - And pretty much everything else

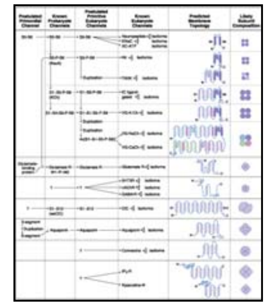
Channel proteins

- Integral membrane proteins
  - Multiple transmembrane domains (2-24)
- Multiunit complexes
- Form water filed pores
- Not always open = different gating mechanisms
- Many diverse families



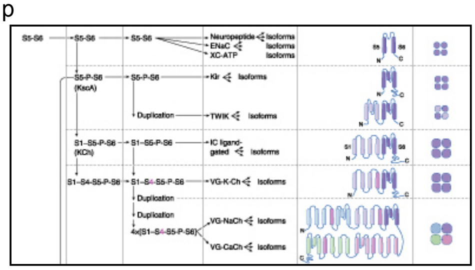
Genetics of ion channels

- Product of many genes
- Emerged from very few primordial genes through duplication and divergence
- Homology based on general structural features rather than ion selectivity



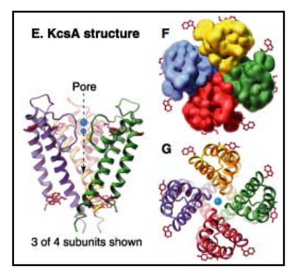
Genetics of ion channels

- Major cation channel families belong to S5/S6 group



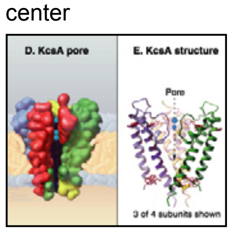
KcsA channel

- Bacterial K^+ channel
- Four subunits
- All contribute to ion pore



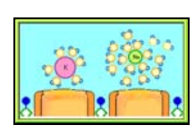
K^+ movement through the pore

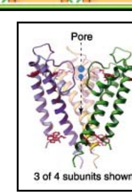
- Helix dipoles of the pore helices produce a cloud of negative charge which attracts the K^+ ions into the water filled cavity in the center
- Ions bind inside the pore



Selectivity filter

- Transmembrane helices are close together on the cytoplasmic side
- Form ion "sieve" – perfect fit
- In very selective channels dehydrated ion passes through the hole





Selectivity

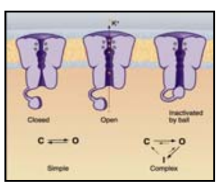
- Determined by an ion pore
  - Mutation in a pore region changes selectivity
  - Change from negative to positive charge within the pore will change a channel from cation to anion selective
- Selective (discriminate between very similar ions such as Na^+ and K^+)
- Non-selective (but still transport anions or cations, never both)

Regulation of channel activity

- Long term – expression (means simply number and type of channels on the cell)
  - Cells express different set of channel protein depending on the function
  - Expression can be regulated by growth factors, inflammatory mediators, hormones)
- Short term – gating (how long is channel open)

Gating mechanisms

- Two discrete states – **open** (conducting) or **closed** (nonconducting)
- Some channels have also **inactivated** state (open but nonconducting)
  - Part of the channel structure or external particle blocks otherwise open channel



What gates ion channels?

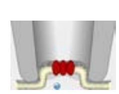
- Non gated - always open
- Gated
  - Voltage across the cell membrane
  - Ligand
  - Mechanical stimulus, heat (thermal fluctuations)

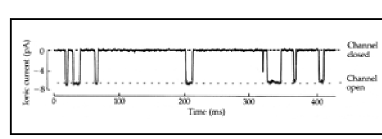
Gating mechanisms

- Conformational changes in channel protein are responsible for opening and closing of the pore
  - 3D conformational shape is determined by atomic, electric, and hydrophobic forces
- Energy to switch the channel protein from one conformational shape to another comes from the gating source

Single channel function

- Binary – conducting or nonconducting
- Transition is instantaneous
- Channels fluctuate between open and closed state on a millisecond timescale





Single channel function

- Function is encoded by the time a channel spends in an open state
  - this decides how much current flows through
- Transition between states is regulated by external stimuli
  - G proteins
  - Phosphorylation
  - Interaction with the receptors

Channels with four transmembrane segments

- TWIK
  - Four transmembrane segments and two P loops
  - Resting or "leak" K^+ channels
  - Always open
  - Help establish membrane potential

Channels with six transmembrane segments

- The remnant of S5/S6 family
- Voltage gated cation channels
  - Potassium
  - Sodium
  - Calcium
- Voltage gated chloride channels
- Channels gated by intracellular ligands (such as cGMP gated channels in rods and cones of a retina)

Voltage-gated cation channels

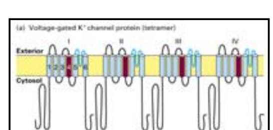
- Open in response to changes in membrane potential
- Subsequently open and inactivate
- Specific for a particular ion
- Common domain structure
- Regulated by external signals

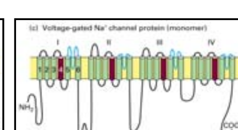
Voltage-gated cation channels - function

- Na^+ and K^+
  - Action potential
- Ca^{2+}
  - Secretion
  - Signaling
  - Muscle contraction
  - Gene expression

Voltage-gated cation channels - structure

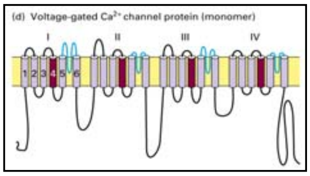
- Contain four subunits each containing six transmembrane segments
  - K^+ is a tetramer
  - Na^+ and Ca^{2+} 4 polypeptides are connected into one chain





Voltage-gated cation channels - structure

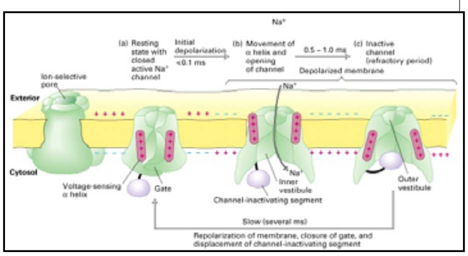
- S5 and S6 and P loop between them form selectivity filter
- S4 forms a voltage sensor



Voltage sensor

- Positively charged AA (lysine or arginine) every third residue in S4
- This part of the channel is attracted to the negative voltage
  - Resting potential - negative inside voltage sensor deep in the membrane
  - Action potential – reversal of charges voltage sensor moves up

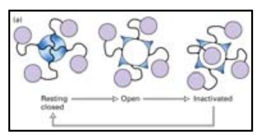
How does the Na^+ channel open and close?

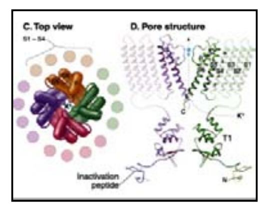


- In response to voltage change S4 rotates and moves toward exterior of the cell

Ball and chain mechanism of inactivation

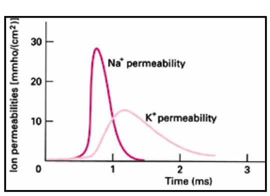
- Part of the channel protein forms inactivation peptide
- Channel must open first to be inactivated





Voltage - gated Na^+ channels

- One large polypeptide of four domains
- Responsible for depolarization phase of action potential
- Target for local anesthetics
  - Inactivation



Voltage - gated Ca^{2+} channels

- One large polypeptide of four domains
- Heavily regulated by cell surface receptors
  - Have the place for the direct interaction with G proteins and phosphorylation
- Responsible for ALL secretion
  - Presynaptic terminal and all secretory cells

Voltage-gated Ca^{2+} channels

- In neurons mostly responsible for the entry of calcium into the presynaptic ending following depolarization (and subsequent exocytosis of neurotransmitter)
- In heart excitation contraction coupling
- In all excitable secretory cells (adrenal medulla, pancreas) entry of calcium induces secretion

The rest of the bunch

- Ligand gated channels
  - Glutamate receptors
  - Nicotinic acetylcholine receptor
  - Vanilloid receptor family (TRPV)

Ligand gated ion channels

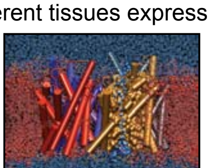
- Gated by ligands present outside of the cell
  - In fact they are receptors
- All of them are nonselective cation channels
- Mediate effects of neurotransmitters

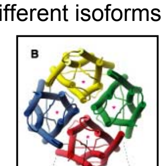
Glutamate receptors

- Two major groups
  - NMDA
  - AMPA (kainate)
- Both implicated in learning and memory

Aquaporins or water channels

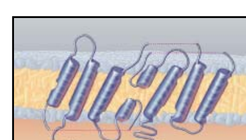
- Tetramers with four identical subunits
- Each with a water pore
- Predominantly expressed in cells that express high permeability to water (erythrocytes, kidney)
- Different tissues express different isoforms





Aquaporins or water channels

- Six membrane domains in each subunit
- Two halves of the polypeptide are identical and reversed
- Hormone vasopressin increases expression of aquaporins in collecting duct membranes



“Killer” channels

- Gramicidin A
- Bacteria produces small peptides that when inserted into the membrane of other cells form highly selective K^+ channels
- Escaping K^+ changes transmembrane potential and kills the cell

When ion channels fail to function normally…

- A number of diseases can occur
  - Epilepsy
  - Deafness
  - Blindness
  - Migraine headaches
  - Cardiac arrhythmias
  - Deregulation of cognitive dysfunction, as in Alzheimer's disease