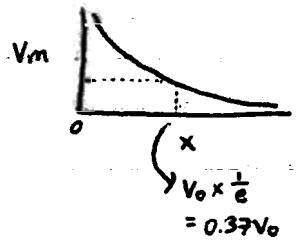
2/25/04

$\frac{dI}{dt} = kI$



$V_{(x)} = V_0 e^{-x/\lambda}$

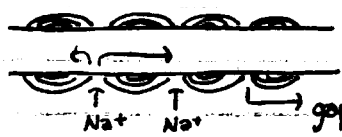
$\lambda = \sqrt{\frac{R_m}{R_i R_o}}$

↳ (not important for squid axons in water)

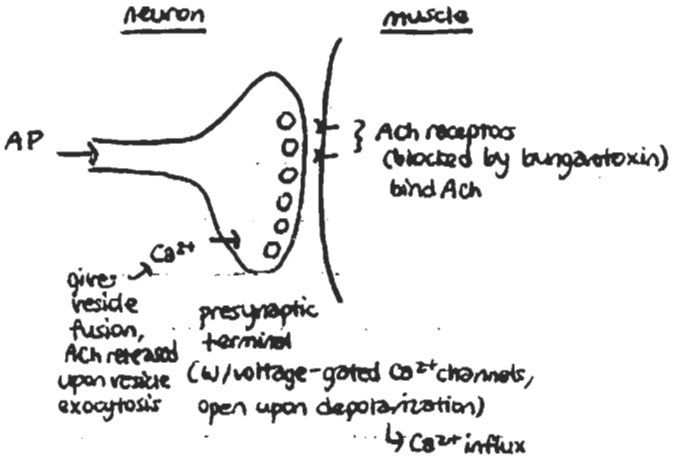
= scaling factor: distance it takes V_m (V_0) to drop to $\frac{1}{e}$ (37% V_0)

- all synapses not created equal; dendrites do not all get equal vote (influential ones sit right next to axon hillock)

- also important concepts in AP propagation (bigger λ = faster propagation)
  - velocity almost exactly proportional to length constant (capacitance swept under rug)
- fast responses, eg escape responses, require fast AP propagation
  - in squid, b/c $R_i = \rho_i \frac{l}{A}$, larger axonal diameter = greater λ: giant axons in escape reflex
    ↳ cross-sectional area — 20 m/s propagation velocity
  - in vertebrates, selective insulation to make R_m larger (increases R_o)
    - can't have sodium currents get through insulation; so, wrap insulator around most of axon but not all (leave gaps w/ g_K + g_{Na} channels), get <u>saltatory conduction</u>



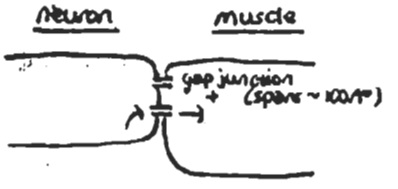
- insulation from Schwann cells (oligodendrocytes in CNS); spirals cell membrane around axon of neuron: <u>myelin</u> ↳ in PNS
- at node of Ranvier, Na^+ inward, undiminished (virtually) current to next node, increases g_{Na} there, etc all the way down axon
  - bidirectional Na^+ current, but refractory period from Na^+ channel inactivation causes only unidirectional propagation
    - DDT used to get rid of Na^+ inactivation (could fire lots of APs, seizure-like) but now bugs resistant b/c of mutation in Na^+ channel



chemical synapse

- prevalent in vertebrate brain

- squid giant axon synapses electrical, not chemical



pros:
- cheap
- fast
- reliable

cons:
- can't be changed (bad for behavior modification & learning)

- depolarization goes directly from presynaptic to postsynaptic cell (ionic current)

- embryonic systems very rich in electrically coupled cells (not well understood)

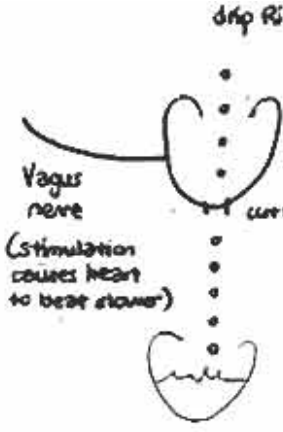
- synaptic cleft: ACh in collagen (like jello) but water & small molecules well conducted
  - some synapses have postjunctional folds, w/ enzymes that break down transmitter at bottom

- most research on synapses done by Bernard Katz

- synaptic vesicles line up by active zones

postsynaptic side:

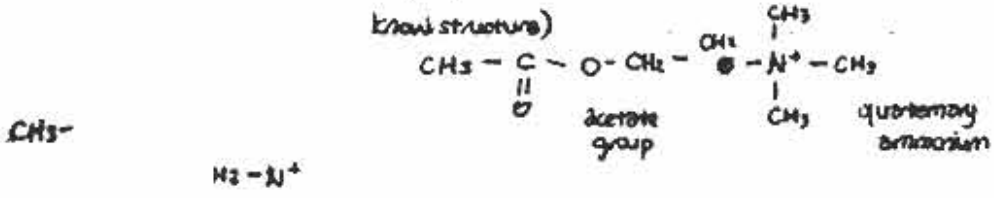
- first experiments done by Loewi, in frog hearts (can keep cooler than 37°C, need less oxygenation)
  - Ringer did experiments in frog heart (in Ringer solution)



second heart slows down in response to Vagus nerve stimulation of first

Vagusstoffe ("Vagus substance")

- Ringer purified w/ columns etc, found to be ACh (don't need to know structure)



choline - constituent of lipids

acetate - from acetyl-CoA

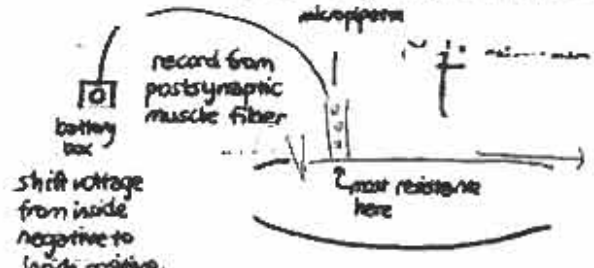
- Loewi got Nobel prize for finding first neurotransmitter

Bernard Katz - German Jew, escaped during WWII to London

- worked w/ H & H, built their voltage clamp

did most of early work on synapses (frog neuromuscular junctions: sartorius muscle) ← almost all transferable to mammalian muscles

- almost all principles of neurotransmission conserved between invertebrates + vertebrates, except for transmitters



shift voltage from inside negative to inside positive, spritz ACh at synapse iontophoretically

- if do this near neuromuscular junction surface, get EPSPs

↳ excitatory postsynaptic potentials

instead, iontophoresis (like electrophoresis but w/ ions)

↳ take ACh (positively charged b/c of quaternary ammonium)

autoimmune disease

↓

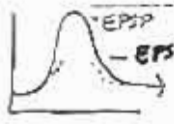
multiple sclerosis - focal breakdown of myelination in CNS/spinal cord, get uncoordination → dementia

- can use transmitter mimics (eg glutamylcholine)

want to find drugs that interfere w/ natural transmission, block ACh to measurable ratio (IC_{50}?)

IC_{50} = concentration (of an inhibitor) sufficient to block 50% of the response

(don't want to block all b/c unphysiologically large inhibitor concentrations + can't measure response) the lower your IC_{50}, the better the inhibitor binding



– EPSP w/ inhibitor (at molar concentration of IC 50)

↳ (similar to K_I)

- find range of inhibitors, find that for all inhibitors
  - eg succinylcholine (ACh antagonist at ACh receptor) ← muscle relaxant
    - 2 molecules of ACh bind receptor; antagonists bind to same site but keep closed
  - find concentration where blocks ACh to half transmission

competitive inhibitors of ACh: all bind AChR (nicotinic) w/ different binding constants)

- succinylcholine } (2 words) doctors use these
- flaxedil } (2 words) doctors use these

IC_{50} ↓

- β-D tubocu tubocurarine (curare) – respiratory paralyzer used by SA Indians; irreversible
- cobra toxin = irreversible antagonist
- α-bungarotoxin – smaller than cobra (krait) but higher affinity toxin

(in order of severity ↓) ↳ Taiwanese sea snake

= champion blocker, highest affinity binder to AChR

(used to purify it in cloning experiments)

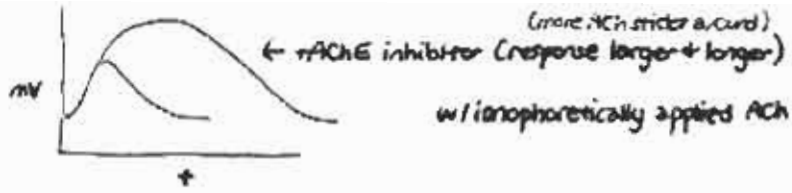
- want to turn neuromuscular junction response on rapidly, also off rapidly (for muscle control)
  - acetylcholinesterase at bottom of folds, breaks down ACh quickly to terminate response
    - can also interfere w/ this process w/ drugs: eserine, neostigmine } acetylcholinesterase inhibitors

(myasthenia gravis – really bad muscle weakness: Abs to own AChR) treat w/ compensate for less AChR by keeping ACh around longer

Raid – blocks acetylcholinesterase in insect CNS (organophosphorus) ← insect specific

(organophosphorus working on tumors)

nerve gases (Sarin, Tabun, Vx)



- Hussein had stacked atropine (muscarinic ACh receptor antagonist) (also messes w/ neuromuscular junction)

- can use drugs both to increase or decrease postsynaptic response