1

Cognitive Neuroscience

Psychology 202

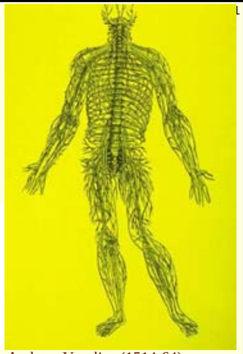
Neural Signaling

April 7, 2008

Main points:

Neurons operate *mechanically*.

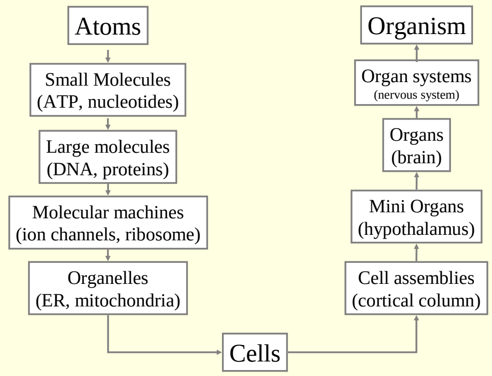
Compared with electronic devices, neurons are *exceedingly* slow.



Andreas Vesalius (1514-64)
De Humani Corporis Fabrica

Jeff Wine,
wine@stanford.edu

2



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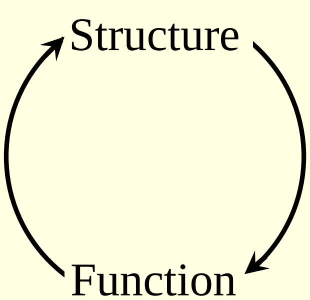


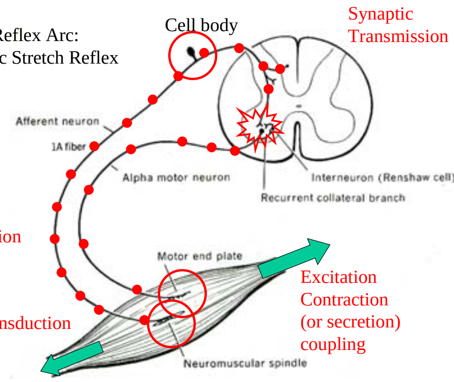
4

Neurons

1. Overview: a reflex arc
2. Impulse conduction is slow, myelin speeds somewhat.
3. The resting potential and nerve impulse.
4. Ion channels are central
5. Molecular Mechanism of channel inactivation.
6. Synaptic transmission.
7. Synaptic plasticity.

5

Modern view of Reflex Arc:
The Monosynaptic Stretch Reflex

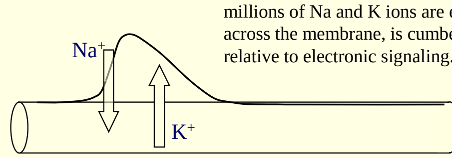


6

Ionic *vs.* electronic signaling.

- Protons and neutrons are ~ 1,800 times more massive than electrons.
- Thus a Na^+ is ~ 41,000 times more massive than an electron and a K^+ ion is ~70,000 times more massive than an electron.

Therefore a nerve impulse, in which millions of Na and K ions are exchanged across the membrane, is cumbersome relative to electronic signaling.



7

Ionic *vs.* electronic signaling.

- Protons and neutrons are ~ 1,800 times more massive than electrons.
- Thus a K^+ ion is ~70,000 times more massive than an electron.
- Neuronal signaling requires the flux of huge numbers of Na^+ and K^+.
- Thus, it is ponderous compared with signaling via electrons or photons.
- Conduction of an electrical signal along a copper wire is about 2.5 million times faster than impulse transmission in the fastest axons.
- It is ~10 million times faster than more typical axon conduction speeds.
- Or, one minute vs. 19 years.

8

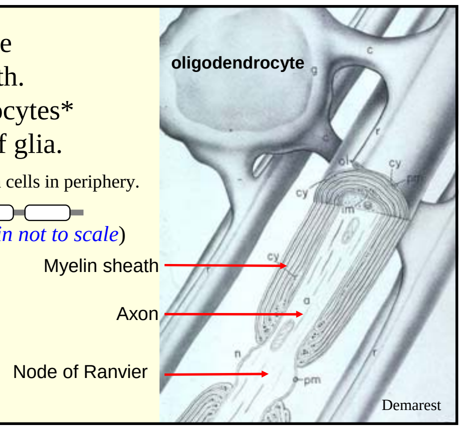
Modest increases in conduction speed have enormous consequences.

We can assess that by looking at the effects of the myelin sheath.

Glia form the myelin sheath. Oligodendrocytes* are a form of glia.

*Schwann cells in periphery.

(*most figs of myelin not to scale*)



Demarest

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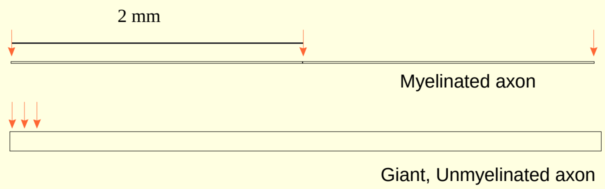
Here is the proper scale:

Axon is 20 µm in diameter, node is 2 µm in length, internode is 2,000 µm!



11

Myelin speeds transmission.

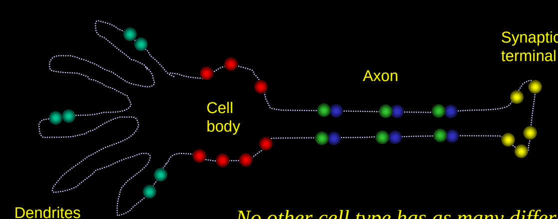
Computation is limited by signal transmission **speed**.

Myelin is perhaps the greatest innovation in neural structure.

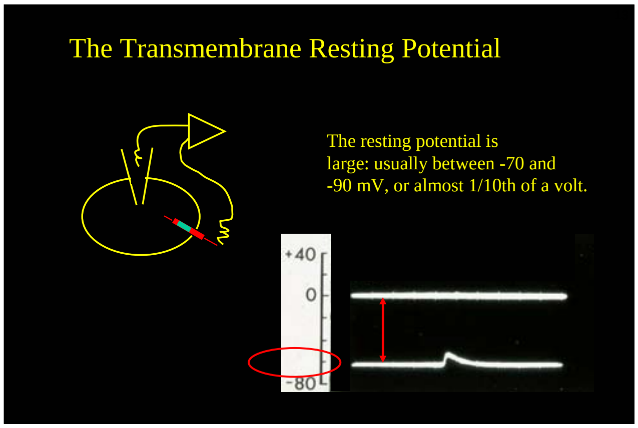
Myelin is probably the major reason for the superiority of **vertebrate *vs.* invertebrate** behavior.

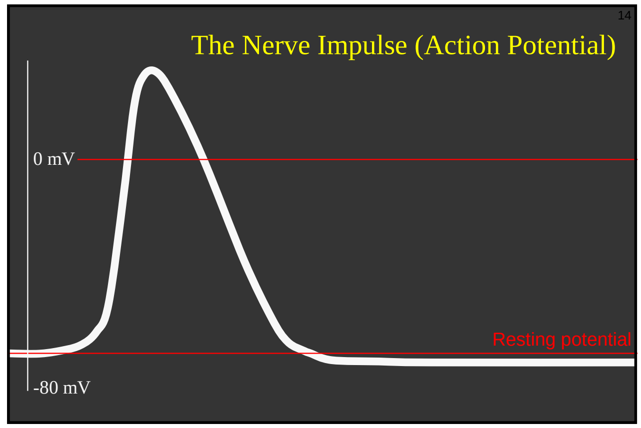
But, myelin increases speed maybe 100 fold, *vs.* the **millions-fold increases** in electrical (or fiber optic) transmission.

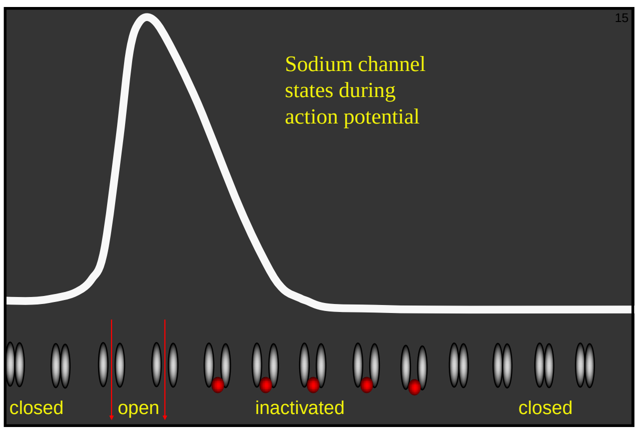
A neuron membrane is a complex *mosaic* of ion channels & transporters.

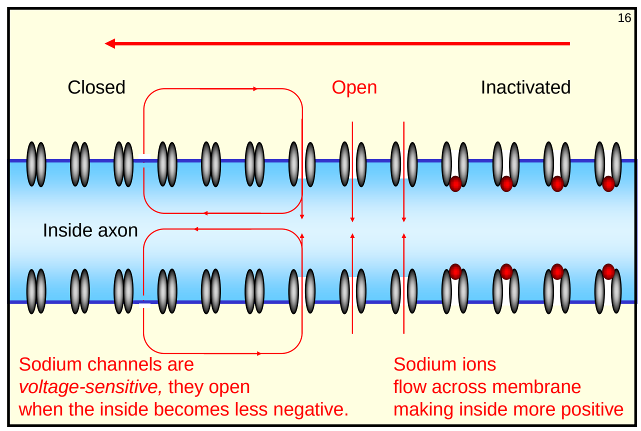


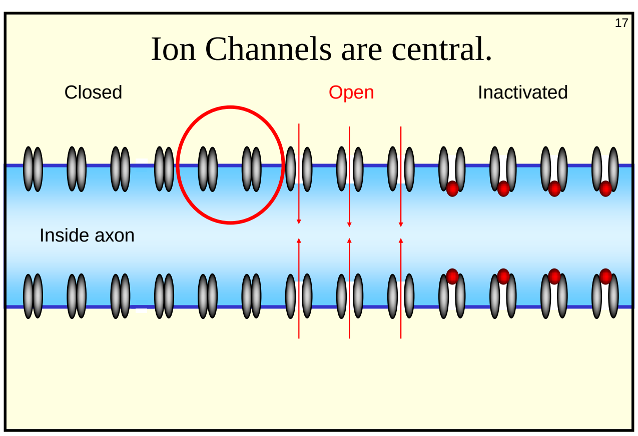
No other cell type has as many different transporters arrayed in such a complex fashion.

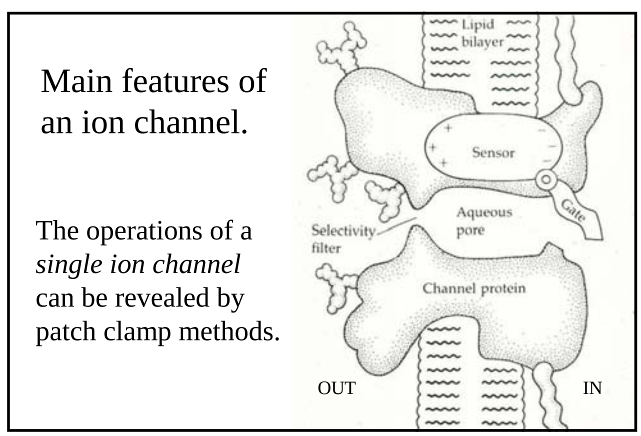

The Transmembrane Resting Potential
The resting potential is large: usually between -70 and -90 mV, or almost 1/10th of a volt.
+40
0
-80

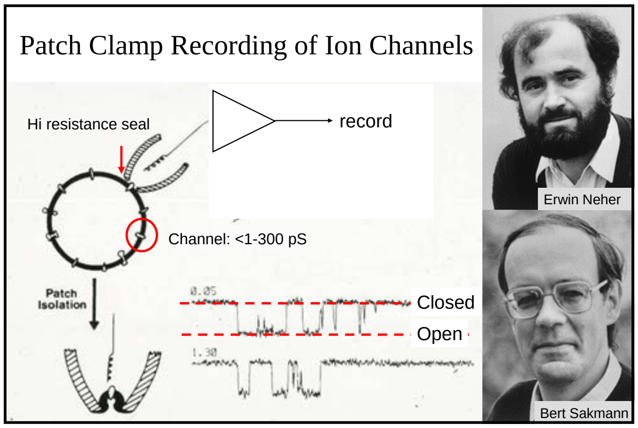

14
The Nerve Impulse (Action Potential)
0 mV
Resting potential
-80 mV

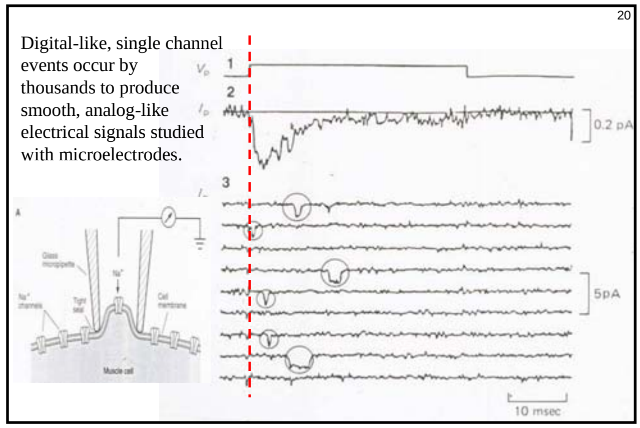

15
Sodium channel states during action potential
closed
open
inactivated
closed

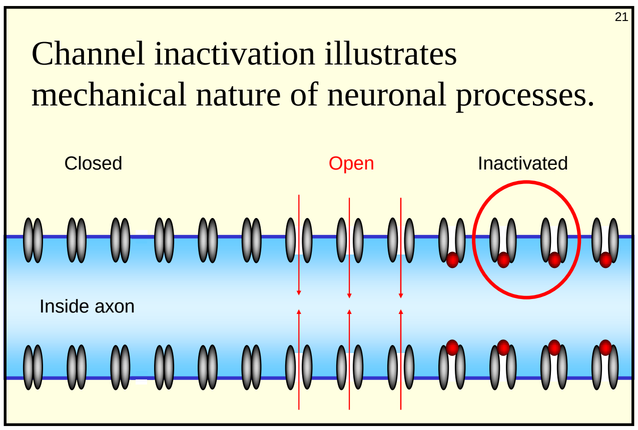

16
Closed
Open
Inactivated
Inside axon
Sodium channels are *voltage-sensitive*, they open when the inside becomes less negative.
Sodium ions flow across membrane making inside more positive


17
Ion Channels are central.
Closed
Open
Inactivated
Inside axon


Main features of an ion channel.
The operations of a *single ion channel* can be revealed by patch clamp methods.
Lipid bilayer
Sensor
Gate
Aqueous pore
Selectivity filter
Channel protein
OUT
IN



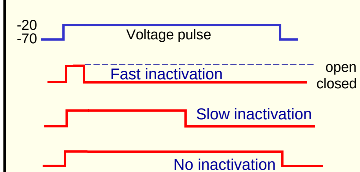




22

Mechanism of *inactivation* in a voltage-gated channel.

Channel is **activated** (opened) by depolarization.

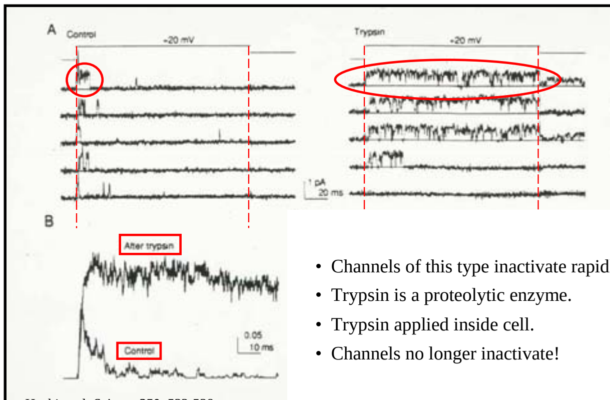


Channel **inactivates** (closes) even though voltage signal that opened it is still present.

Inactivation can be fast, slow, or absent.

Inactivation can be removed by treatment with a protease.

T. Hoshi, W. N. Zagotta, R. W. Aldrich, *Science* **250**, 533-538.



- Channels of this type inactivate rapidly.
- Trypsin is a proteolytic enzyme.
- Trypsin applied inside cell.
- Channels no longer inactivate!

Hoshi et al. *Science* **250**, 533-538.

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Conclusion:

Trypsin, which cleaves peptide bonds at Arginine and Lysine residues, essentially *washes away* channel inactivation!

How is this possible?

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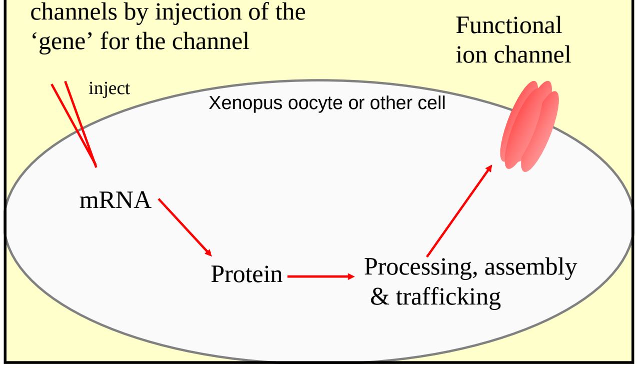
Expression of functional ion channels by injection of the ‘gene’ for the channel



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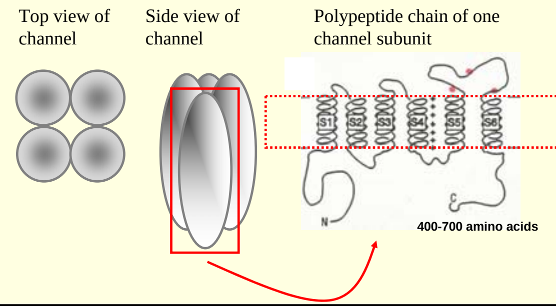
Structure of a ‘model’ channel: the fast-inactivating channel from *Drosophila*



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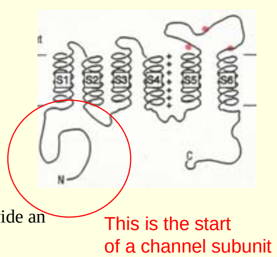
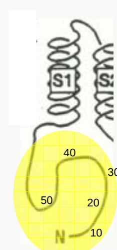
The ability to express ion channels has revolutionized the study of channel structure and function.

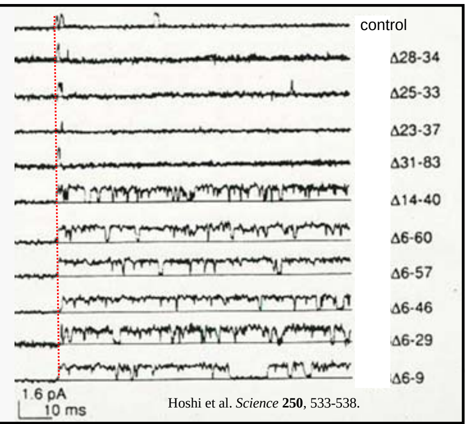
Site-directed mutagenesis can be used to change any amino acid in the molecule: to delete amino acids, or to add them.

In the following work, site-directed mutagenesis was combined with deep knowledge of channel kinetics to provide an extremely satisfying mechanistic explanation of channel inactivation.

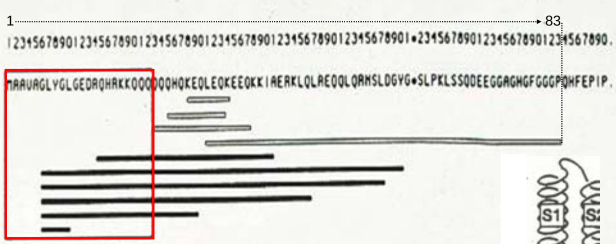


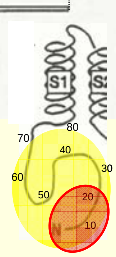
Deletion mutations in the N-terminal region of channels revealed a pattern.





Hoshi et al. *Science* **250**, 533-538.

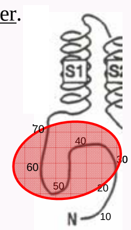


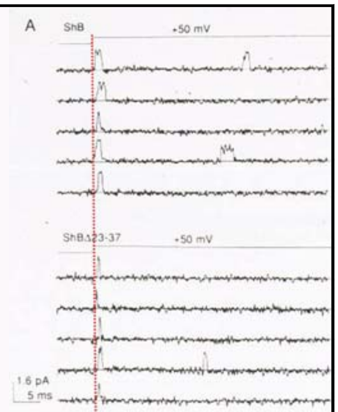


Mutations that deleted amino acids in the N-terminal region of 22 amino acids eliminated inactivation. Deletions outside of the region appeared to have no effect.

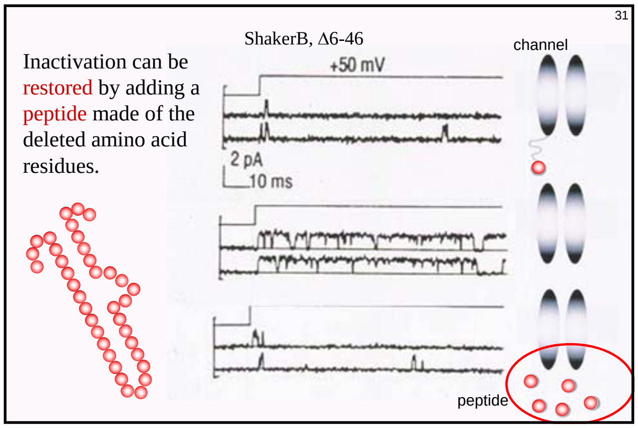
Hoshi et al. *Science* **250**, 533-538.

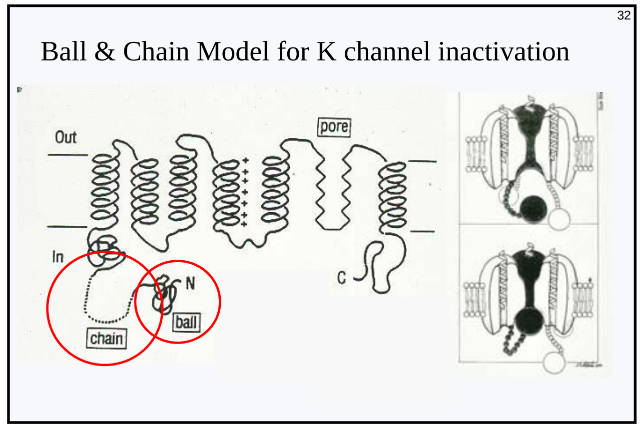
However, closer inspection of the deletions in the region from amino acid 23 to 70 showed that these channels inactivated faster.

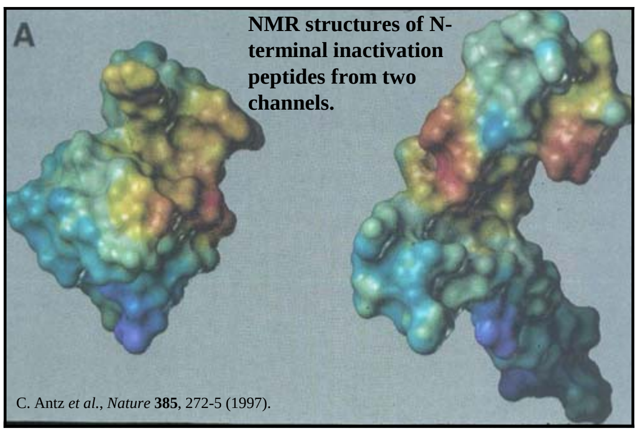


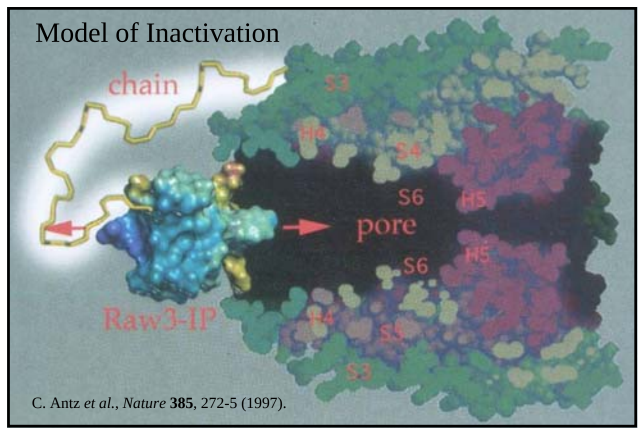


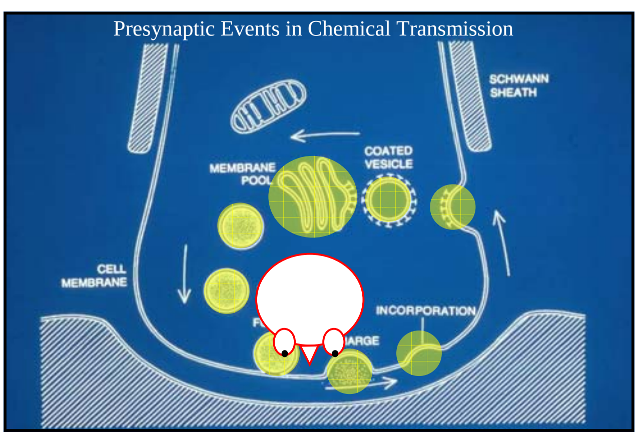
Hoshi et al. *Science* **250**, 533-538.

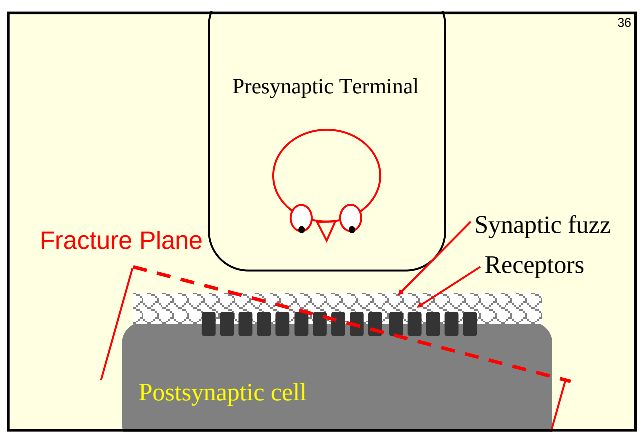

31
Inactivation can be restored by adding a peptide made of the deleted amino acid residues.
ShakerB, Δ6-46
+50 mV
2 pA
10 ms
channel
peptide

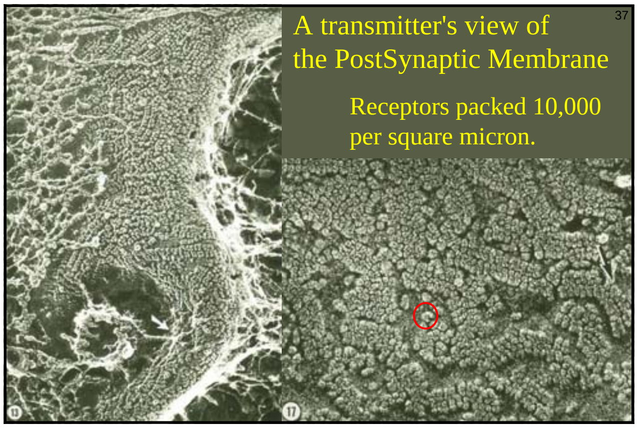

32
Ball & Chain Model for K channel inactivation
Out
In
pore
N
C
ball
chain


A
NMR structures of N-terminal inactivation peptides from two channels.
C. Antz et al., Nature 385, 272-5 (1997).


Model of Inactivation
chain
S3
H4
S4
S6
H5
pore
S6
H5
Raw3-IP
H4
S4
S3
C. Antz et al., Nature 385, 272-5 (1997).

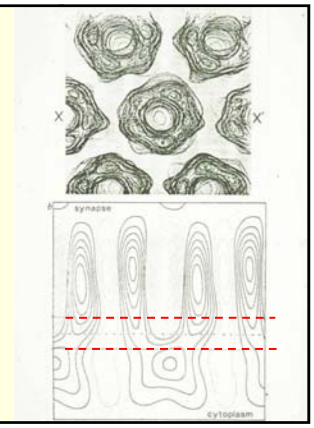

Presynaptic Events in Chemical Transmission
SCHWANN SHEATH
MEMBRANE POOL
COATED VESICLE
CELL MEMBRANE
INCORPORATION

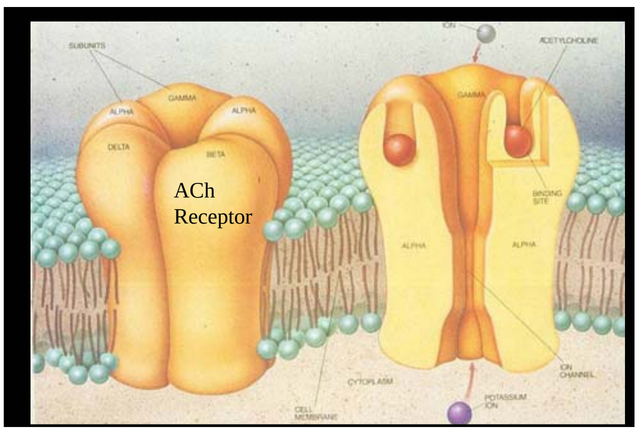

36
Presynaptic Terminal
Fracture Plane
Synaptic fuzz
Receptors
Postsynaptic cell



Images of the
Acetylcholine
Receptor (top view)

Side View: note how far above
the membrane the receptor sits.





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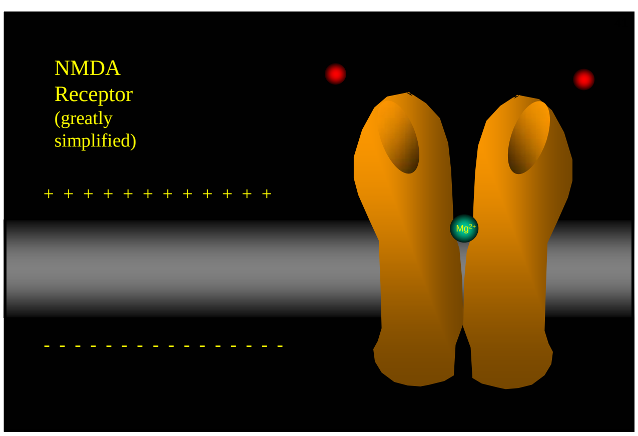
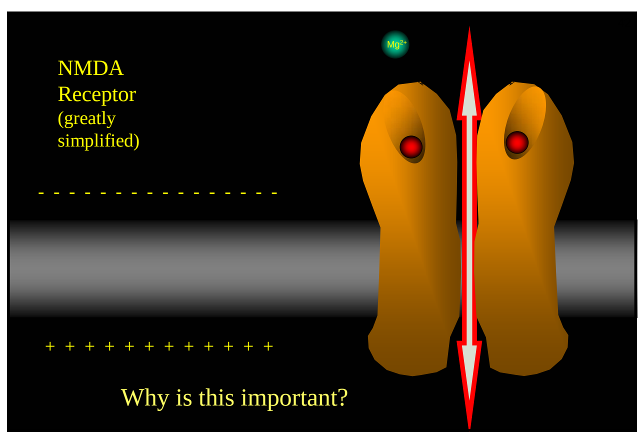
Four kinds of ion channels

- ***Voltage gated*** channels produce the nerve impulse.
- ***Ligand gated*** channels produce synaptic potentials.
- ***Mechanically gated*** channels
- A 4th kind of channel requires ***voltage*** *and* ***ligands***.





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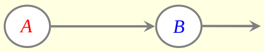
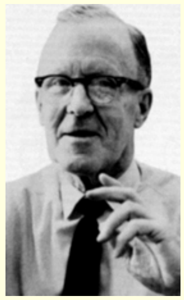
Hebb's Postulate

"When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."





Donald Hebb
1904-1985

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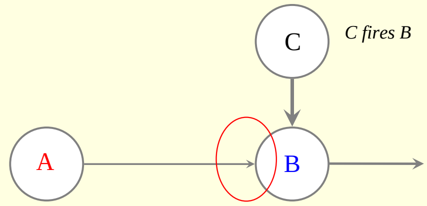

A has weak input to B.

If A + C fire in close proximity, then A is firing when B is firing, and connection to B gets stronger (according to Hebb).

The NMDA channel provides a basis for Hebb's postulate, because it allows synapses to behave differently if the postsynaptic cell is depolarized.

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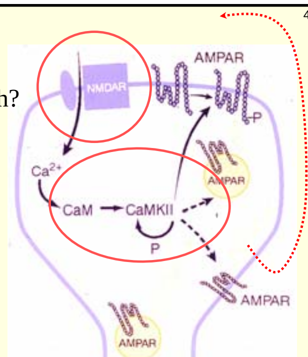
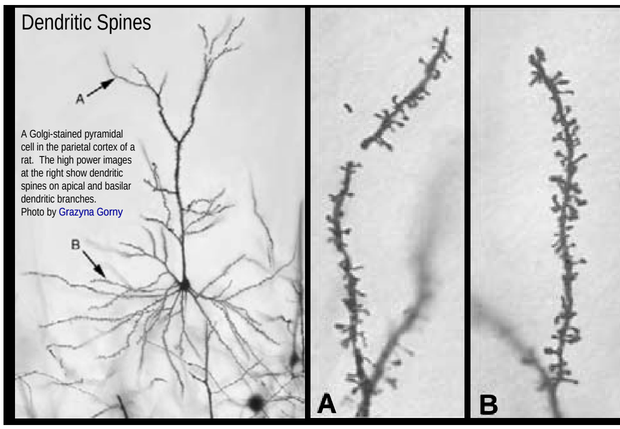
How can activity in NMDA receptor lead to long term increases in synaptic strength?

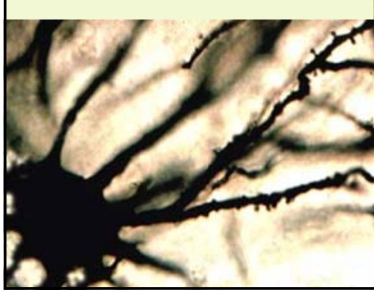
- The NMDA receptor conducts Ca^{2+} when stimulated by voltage + neurotransmitter.
- Increased cytosolic Ca^{2+} strengthens synaptic transmission via postsynaptic enzyme pathways.
- A diffusible signal also strengthens the presynaptic terminal.

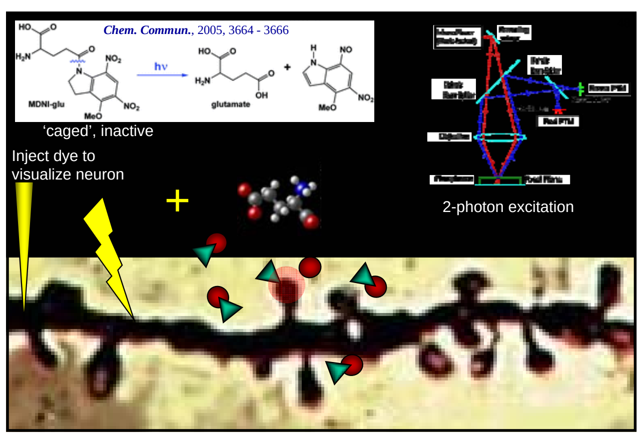


Dendritic Spine



Dendritic Spines preferentially receive synaptic input. Are these sites of plasticity?





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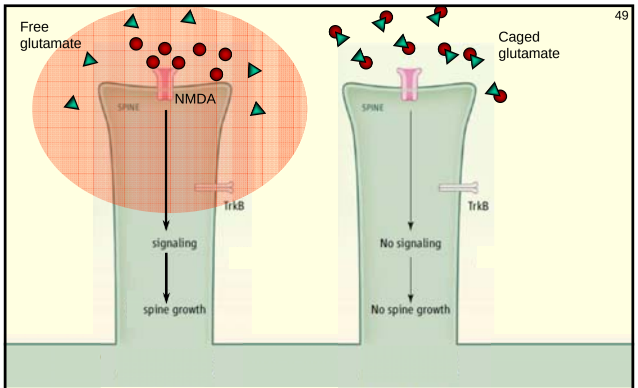

Based on Korte, *Science*, 319, 1627, 2008 and Tanaka, *Science*, 2008, **319,** 1683

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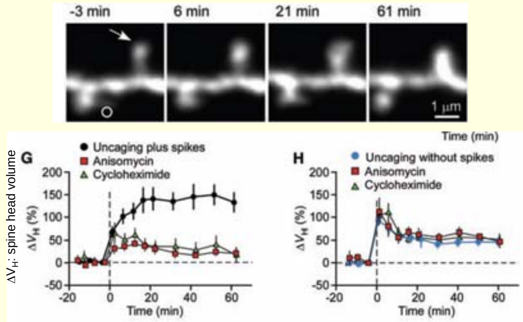
Protein Synthesis and Neurotrophin-Dependent Structural Plasticity of Single Dendritic Spines



Tanaka, *Science*, 2008, **319,** 1683

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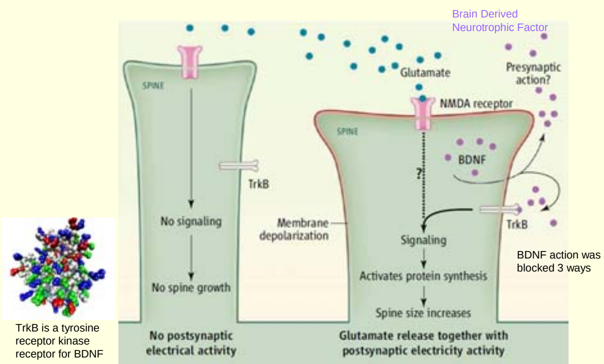

Korte, *Science*, 319, 1627, 2008 and Tanaka, *Science*, 2008, **319,** 1683

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Dendritic Spine Structure & Synpatic Plasticity

- Hippocampal pyramidal neurons of rat.
- Glutamate stimulation increase spine head volume transiently.
- Pairing with impulses→ longer term changes + shortening.
- BDNF is necessary and sufficient if paired with glutamate.
  - Blocking BDNF action 3 ways blocks effect
  - Adding BDNF + glutamate works.
- Protein synthesis is required.

Tanaka, *Science*, 2008, **319,** 1683

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EXPERIMENTAL NEUROLOGY **49**, 736–749 (1975)

Swelling of Dendritic Spines in the Fascia Dentata after Stimulation of the Perforant Fibers as a Mechanism Of Post-Tetanic Potentiation

A. Van Harreveld and E. Fifkova [1]

Division of Biology, California Institute of Technology, Pasadena, California 91125

Received July 3, 1975

“The marked swelling of dendritic spines observed in the fascia dentata after stimulation of the perforant fibers may constitute a postsynaptic mechanism for the post-tetanic potentiation demonstrated in this system.”

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In summary, neurons:

- Signal via *mechanical* means.
- Have ion channels as their central mechanism.
- Signal by mechanisms that are *very* slow.
- Use myelin for ~100x speed increase.
- Operate in analog and *digital* forms and form circuits.
- New methods are illuminating mechanisms of synaptic plasticity.