Cognitive Neuroscience
Psychology 202

Neural Signaling
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Main points:
Neurons operate mechanically.
Compared with electronic devices, neurons are exceedingly slow.

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Modern view of Reflex Arc:
The Monosynaptic Stretch Reflex

Structure
- Cell body
- Synaptic Transmission
- Impulse conduction
- Transduction

Function
- Excitation
- Contraction (or secretion)
- Coupling

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.

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.
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.

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)

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.
The Transmembrane Resting Potential

The resting potential is large: usually between -70 and -90 mV, or almost 1/10th of a volt.

The Nerve Impulse (Action Potential)

The nerve impulse (action potential) is a sudden change in the membrane potential that propagates down the axon.

Sodium Channel States During Action Potential

Sodium channels are voltage-sensitive, they open when the inside becomes less negative.

Inside axon

Ion Channels are Central

The operations of a single ion channel can be revealed by patch clamp methods.

Main Features of an Ion Channel

Sodium ions flow across the membrane, making the inside more positive.
Patch Clamp Recording of Ion Channels

Channel: <1-300 pS

Closed
Open

Erwin Neher
Bart Sakmann

Hi resistance seal

Digital-like, single channel events occur by thousands to produce smooth, analog-like electrical signals studied with microelectrodes.

Channel inactivation illustrates mechanical nature of neuronal processes.

Closed
Open
Inactivated

Inside axon

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.

Voltage pulse

Inactivation can be fast, slow, or absent.

Inactivation can be removed by treatment with a protease.


Conclusion:

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

How is this possible?
Expression of functional ion channels by injection of the ‘gene’ for the channel

- mRNA
- Protein
- Processing, assembly & trafficking

Functional ion channel

- Xenopus oocyte or other cell

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

- Top view of channel
- Side view of channel
- Polypeptide chain of one channel subunit

400-700 amino acids

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.
Inactivation can be restored by adding a peptide made of the deleted amino acid residues.

Ball & Chain Model for K channel inactivation

NMR structures of N-terminal inactivation peptides from two channels.

Model of Inactivation

Presynaptic Events in Chemical Transmission

Fracture Plane

Presynaptic Terminal

Synaptic fuzz

Receptors

Postsynaptic cell
A transmitter's view of the PostSynaptic Membrane
Receptors packed 10,000 per square micron.

Images of the Acetylcholine Receptor (top view)
Side View: note how far above the membrane the receptor sits.

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.

Why is this important?
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.”

Hebb’s Postulate

Donald Hebb
1904-1985

A B

C fires 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.

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

• The NMDA receptor conducts Ca²⁺ when stimulated by voltage + neurotransmitter.

• Increased cytosolic Ca²⁺ strengthens synaptic transmission via postsynaptic enzyme pathways.

• A diffusible signal also strengthens the presynaptic terminal.

Dendritic Spines

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

Dendritic Spines

Chen, C. et al., 2005, 3664 - 3666

‘caged’, inactive

Inject dye to visualize neuron

2-photon excitation

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


Dendritic Spine Structure & Synaptic 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.

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.