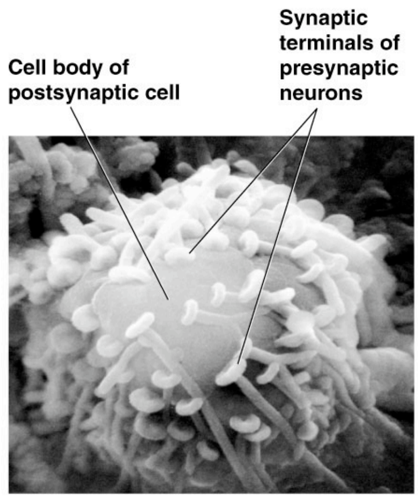
Cell Communication and Signalling I



1

Forms of Intercellular Signalling

Contact-dependent signalling:

- Signal molecule remains bound to cell surface.
- e.g. development, immune response.

Paracrine signalling:

- Secretion of signal molecule.
- Diffuse short distances with local effects.

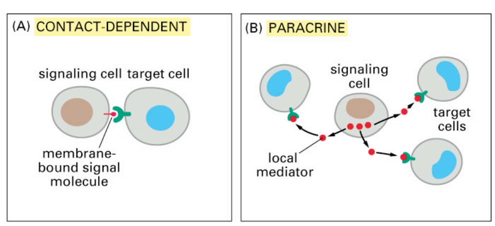


Figure 15–4 part 1 of 2. Molecular Biology of the Cell, 4th Edition.

2

Forms of Intercellular Signalling

Synaptic signalling:

- Signal molecules are delivered to target cells by cell extensions and across chemical synapses.
- e.g. neurons.

Endocrine signalling:

- Hormones secreted into blood.
- Slow signalling process.

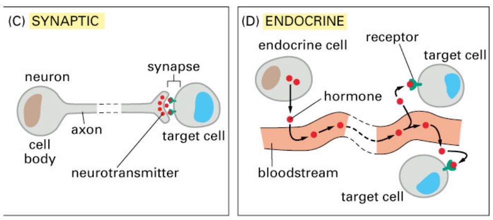


Figure 15–4 part 2 of 2. Molecular Biology of the Cell, 4th Edition.

3

Cell-Surface Receptors

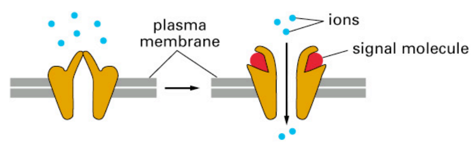
- 3 major classes of receptor proteins transform an *extracellular binding* event into an *intracellular signal*.
- This is called "*signal transduction*".

1. Ion-channel-linked receptors (i.e. *extracellular ligand gated ion channels*, or *ionotropic receptors*).
2. G-protein-coupled receptors (*metabotropic* receptors).
3. Enzyme-linked receptors (e.g. growth factor binding, autophosphorylation).

4

Ion-Channel-Linked (Ionotropic) Receptors

- Composed of several subunits with multiple transmembrane segments.
- Localized at specific sites in the plasma membrane (synapse).
- Reversibly bind chemical neurotransmitters (i.e. the "signal molecule") that induce a conformational change.
- Channel opens, and ions move down their electrochemical gradient.
- Thus, binding to receptor leads directly to a change in membrane permeability or conductance, and excitability.



From Fig. 15-15A Alberts et al.

5

Neurotransmitters

- Neurotransmitters are chemicals produced in the cytosol of a neuron, usually in the *presynaptic terminal*.
- Biosynthetic enzymes for these reactions are produced in the cell body and delivered throughout the cell by *slow axoplasmic flow*.
- Neurotransmitters are stored in *synaptic vesicles* for rapid release when necessary.
- Some neurotransmitters, called *neuropeptides*, are sorted through the ER and Golgi (as are other soluble proteins) and delivered to the cell periphery by fast *axonal transport*.

6

Signalling at a Chemical Synapse

- The *synapse*: specialized site of chemical communication between 2 electrically isolated cells.
- In the nervous system, a *presynaptic* cell associates with a *postsynaptic* cell.
- Neurotransmitters released from the presynaptic cell cross the synaptic cleft and bind to post-synaptic receptors.

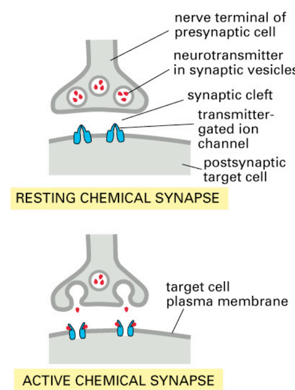


Figure 11–33. Molecular Biology of the Cell, 4th Edition.

7

Excitatory or Inhibitory Chemical Synapses

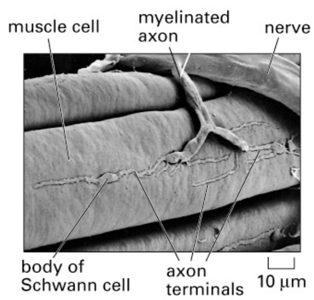
Excitatory
- Activation leads to net gain of positive charge.
- Increases excitability of the cell (i.e. its ability to depolarize).
- e.g. glutamate, acetylcholine.

Inhibitory
- Activation leads to net loss of positive charge.
- Decreases excitability.
- e.g. GABA (γ-aminobutyric acid), glycine.

8

The Neuromuscular Junction

- Synaptic interaction between motor neuron and skeletal muscle cell.
- Well-studied model of gating of ionotropic receptors by ACh.



Skeletal muscle cell of frog

Fig. 11-34 Alberts et al.

9

Acetylcholine (ACh) Receptor

- Contains 5 transmembrane subunits ($\alpha,\alpha,\beta,\gamma,\delta$), 2 of which are identical and form *ACh-binding sites*.
- Subunits arranged in a ring forming a water-filled pore.
- These channels have *little ion selectivity*, but negatively-charged amino acids near the pore promote passage of positively-charged ions (e.g. Na^+, K^+).
- Gated by hydrophobic side chains of 5 leucines.

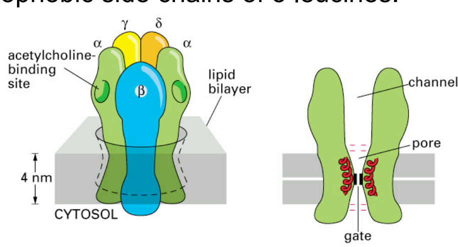


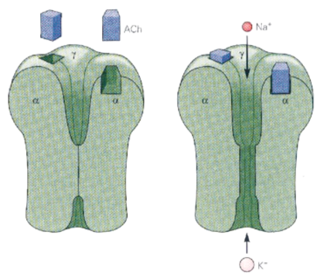
Figure 11–36. Molecular Biology of the Cell, 4th Edition.

10

Acetylcholine (ACh) Receptor

- 2 ACh molecules must bind to both α subunits for channel to open.
- Na^+ and K^+ flow in opposite directions, but the stronger inward driving force of Na^+ will produce a net gain of (+).

No ACh bound: Channel closed   *2 AChs bound: Channel open*

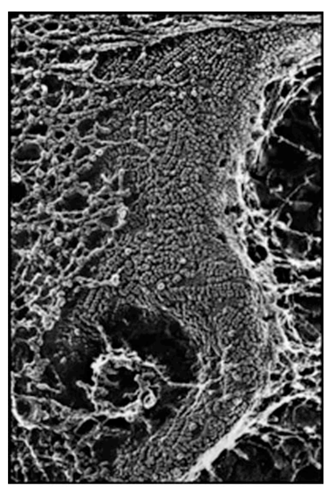


From Fig. 11-13 Kandel et al. 2000

11

SEM Image of AChR

- Postsynaptic membrane of cell from electric fish.
- Membrane is partially obscured by basal lamina.
- Basic structure of AChR can be seen.



Electrocyte from electric organ of *Torpedo*

Fig. 9.2 Squire et al. 2003

12

ACh Receptors in Muscle Contraction

1. A nerve impulse reaches the synaptic terminal of a presynaptic neuron causing influx of Ca^{2+} and release of ACh into the synaptic cleft.
2. ACh binds to postsynaptic receptor and induces local influx of Na^{+} and depolarization.
3. Voltage-gated Na^{+} channels open and further depolarize the cell.
4. Voltage-dependent effect on plasma membrane Ca^{2+} channel in T-tubule.
5. Opening of Ca^{2+} release channel in SR causes increase in cytosolic Ca^{2+} and muscle contraction.

13

ACh Receptors in Muscle Contraction

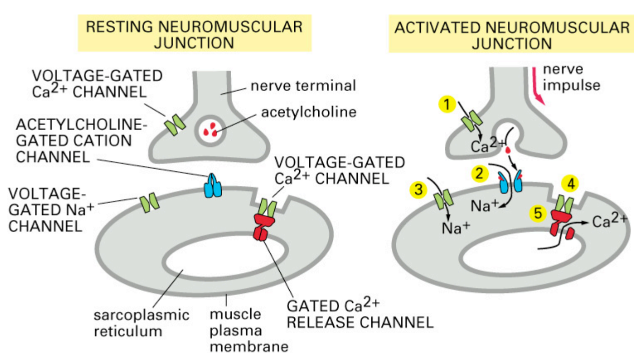


Figure 11–37. Molecular Biology of the Cell, 4th Edition.

Note: this occurs during contraction of skeletal muscle. The situation is different for cardiac muscle contraction.

14

Glutamate Receptors

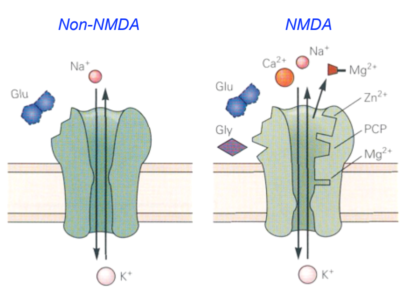
- Main excitatory neurotransmitter in the mammalian central nervous system.
- Therefore, many excitatory synapses utilize glutamate receptors at the postsynaptic membrane.
- Divided into 2 types, based on the type of synthetic agonist that activates them:
  - NMDA (*N*-methyl-D-aspartate)
  - non-NMDA (activated by AMPA and kainate).

- Basic structure and function similar to ACh receptors.
- However, *NMDA receptors* are also voltage-gated.

15

Glutamate Receptors

- Both receptor types depend on glutamate for activation.
- Both are permeable to Na^+ and K^+.
- However, NMDA receptors also *require glycine* for activation, are permeable to Ca^{2+}, and are *regulated* by many other factors.
- Importantly, NMDA receptors are *blocked by* Mg^{2+} inside the pore until the membrane is *depolarized* and Mg^{2+} is displaced.



From Fig. 12-5A Kandel et al. 2000

16

Role of Glutamate Receptors in Learning

- Glutamate receptors play a major role in learning and memory.
- Located in mammalian hippocampal neurons.
- Short "bursts" of activity from presynaptic neurons can have long-lasting effects on the glutamate sensitivity of postsynaptic receptors.
- This process is believed to underlie learning and is called "long-term potentiation" and can last hours, days or weeks.

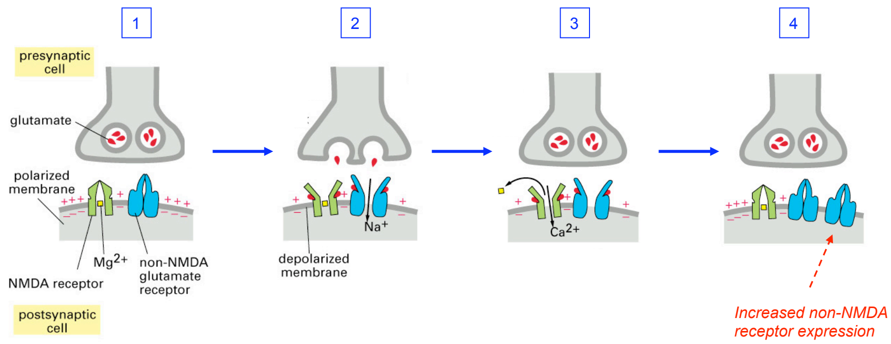
17

Long-Term Potentiation (LTP)

1. Both pre- and postsynaptic cells are at rest. Membranes are polarized.
2. Glutamate released by presynaptic cell into synaptic cleft binds to both NMDA and non-NMDA receptors. Na^{+} influx occurs via non-NMDA receptors and depolarizes postsynaptic membrane.
3. Depolarization displaces Mg^{2+} from pore of NMDA receptors and Ca^{2+} influx takes place.
4. Increased Ca^{2+} initiates intracellular pathway that leads to increased delivery of non-NMDA receptors to the plasma membrane.

18

Long-Term Potentiation (LTP)



A GRP, called cAMP response element binding protein (CREB), appears to be involved.

19