17.2 Excitation of Nerve Cells and Transmission of Excitation

Living things have the ability to sense external stimuli, react to it and move accordingly. Such mechanisms are also present in organisms such as bacteria (see **Column Figure 17-2**). Multicellular organisms have an even more sophisticated system with specialized cells dedicated to sensing information or movement. Such systems include sensory and nerve cells which sense information from the external environment (nerve cells are also called neurons: neurons not only transmit information but also play a role in sensing information), and nerve cells which transmit this information to the brain, and muscle cells comprising motor organs. When the sensory and nerve cells sense external information (stimulation), they become excited, and this excitation is transmitted to the brain and muscle cells via nerves, triggering a response (or movement), such as trying to avoid the stimuli by moving away from it.

17.2.1 Excitation of cells and changes in the membrane potential

The various ions in the cytoplasm are maintained at a certain concentration, since the cell membrane blocks unregulated ion penetration. For example, as shown in **Figure 17-5A**, the K+ concentration is maintained higher while Na+ is maintained lower inside animal cells, as compared to extracellular fluids (biological fluids such as blood and lymph fluid). By maintaining such concentration difference, cells can generate a potential difference (negative charge at the cytoplasm side) of tens of millivolts across the cell membrane. This potential, called **resting membrane potential**, is an **equilibrium potential** that results from the difference in concentration and selective permeability of ions across the cell membrane.

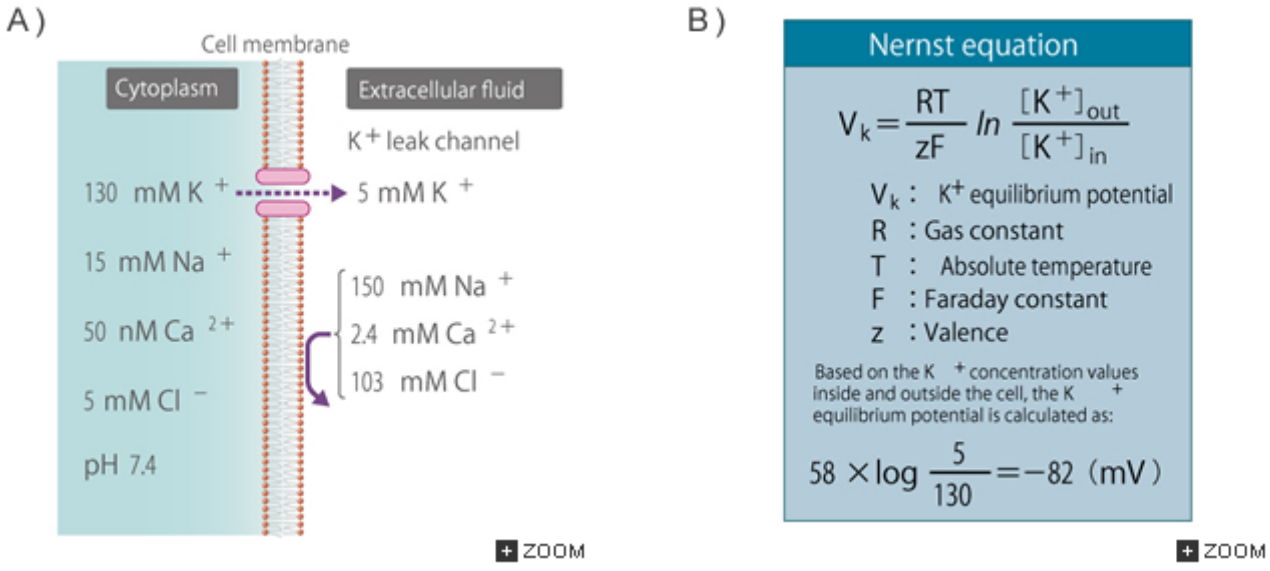


Fig 17-5 Generation of resting membrane potential and Nernst equation

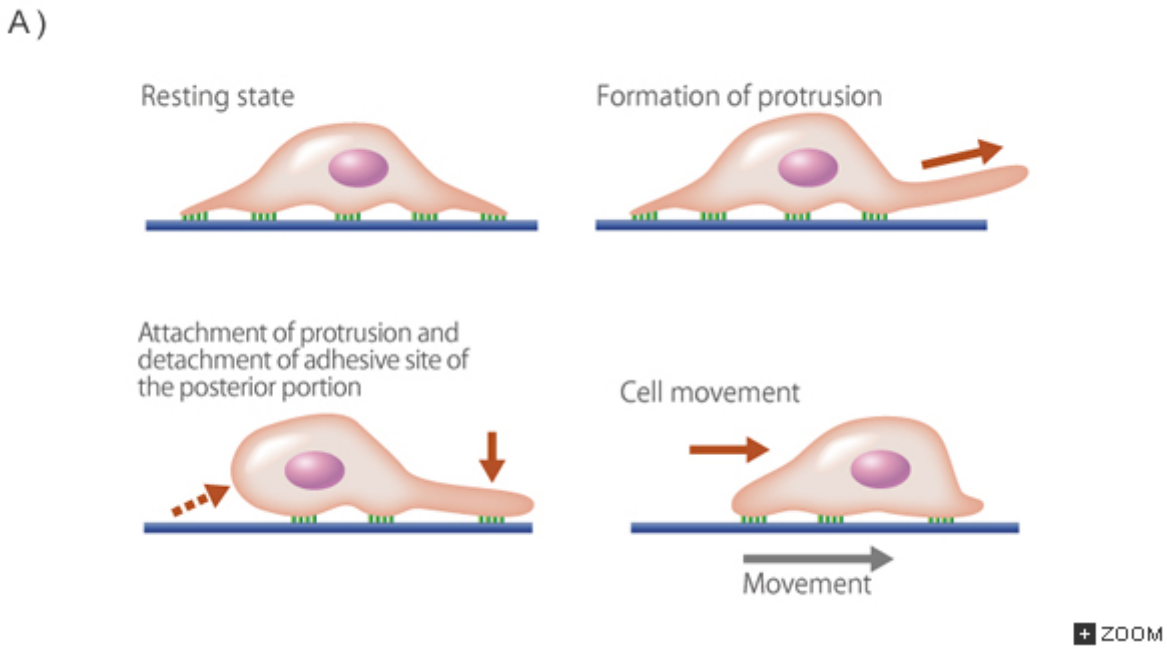
When the K^+ equilibrium potential resulting from the difference in concentration of ions across the cell membrane is calculated using the Nernst equation, an approximate value of the resting membrane potential of the cell membrane is obtained. The ion concentrations inside and outside the cell differ according to cell type. The figure shows an example.

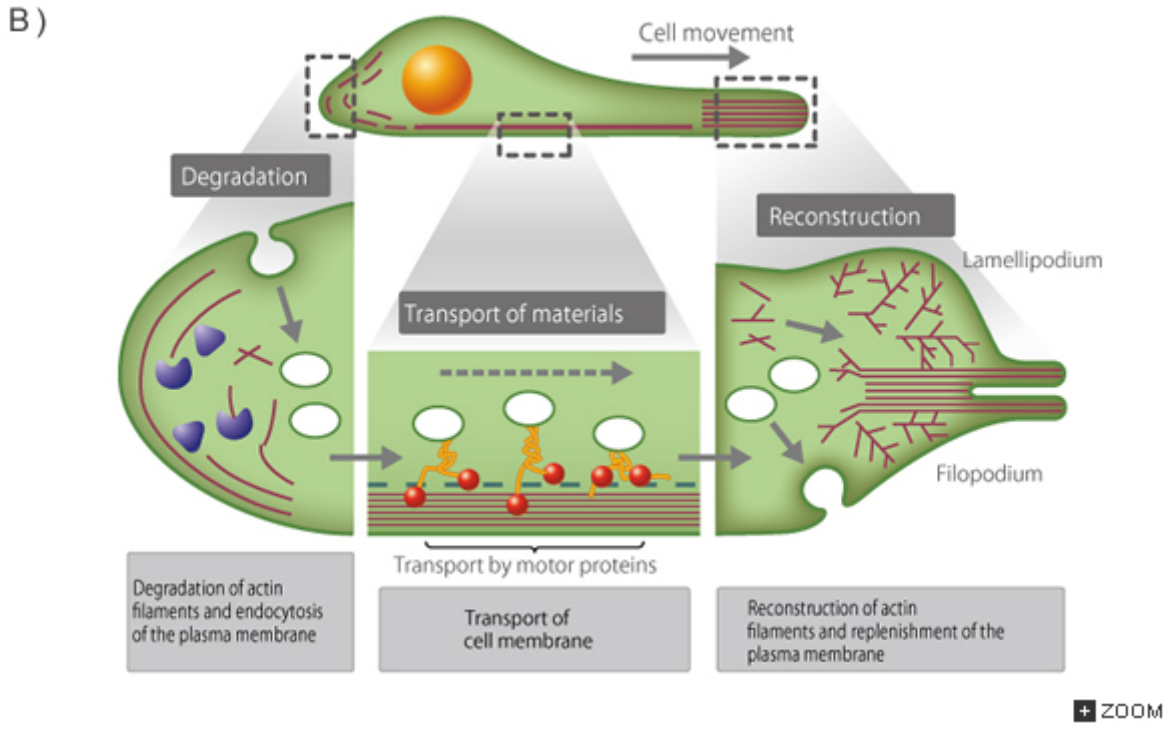
Column

Cell locomotion and cytoskeleton reconstruction

Cellular locomotion in a constant direction is carried out by the repetition of a series of actions such as formation of a cell protrusion in the advancing direction, attachment of the cell protrusion to the substratum, disassembly of the cell-substratum adhesion at the rear end of the cell, and contraction of cells in the advancing direction (**Column Figure 17-3A**). During this process, various activities are simultaneously taking place inside the cell, such as the

decomposition and reconstruction of various cytoskeletal fibers and transport of the cell membrane (**Column Figure 17-3B**). The cytoskeletal fibers are degraded at the rear end of the cell, and the degraded fibers are transported to the leading edge of the cell by motor proteins. At the leading edge, the degraded products are reused for the reconstruction of the cytoskeleton required for the formation of the cell protrusion. Besides the cytoskeleton, additional cell membrane is also required for the formation of a new cell protrusion at the leading edge. For this, the cell membrane is endocytosed as vesicles at the rear end of the cell and transported by motor proteins to the leading edge to be used as material for cell protrusion formation.





Column Figure 17-3 Cell movement
A) Modeling the mechanism of cell movement. B) Material transport and cell protrusion formation during cell movement. Materials of cytoskeletal fibers degraded at the posterior portion of the cell are transported by motor proteins moving along the cytoskeleton, to the anterior portion for reconstruction.

The major ion involved in the generation of resting membrane potential is K^+, which passes through the cell membrane and flows out. The cell membrane contains K^+ channels (called K^+ leak channels) which remain constantly open even in the

absence of stimulation and allow K^+ ions to leak outside the cell down the concentration gradient. In this way, the diffusion of positive ions passing through the membrane creates potential difference across the membrane (cytoplasm side is negative). At the same time, the potential difference also produces a driving force to pull the K^+ ions moving out of the cell back inside. The equilibrium potential forms when these two processes (pumping and leakage of ions) are in balance. This is known as the resting membrane potential. The K^+ equilibrium potential of the semipermeable cell membrane can be calculated using the Nernst equation. The calculated value is close to the measured resting membrane potential across the cell membrane (**Figure 17-5B**).

The excitation of sensory and nerve cells involves the opening/closing of certain ion channels in reaction to stimulation, resulting in a large, momentary change in the cell membrane potential. The fact that cell excitation is expressed as change in the membrane potential is common across all sensory and nerve cells, but the type of ion channel involved in the excitation differs according to the type of sensory cells. The following section discusses the excitation of nerve cells or neurons.

Excitation of neurons involves the opening/closing of Na^+ and K^+ channels that open and close depending on changes in the membrane potential (i.e. voltage-dependent channels) (see **Column Figure 17-4**). In neurons, when the membrane potential rises to a certain value (threshold value) due to stimulation, all the voltage-dependent Na^+ channels open simultaneously, causing the membrane potential to rapidly change to a positive value (**Figure 17-6**). This change in the membrane potential is called depolarization and is caused by the opening of the Na^+ channel, which allows Na^+ ions to flow inside the cell. When the membrane potential rises to the equilibrium potential of Na^+ ions, which is +40–+50 mV, the flow of Na^+ ions stops. At the same time, voltage-dependent K+ channels open, allowing K^+ ions to flow outside the cell. As a result, the risen membrane potential is rapidly decreased to its original state, and the Na^+ channels close. This transient, rapid change in membrane potential is called an action potential. The intracellular Na^+ and K^+ concentrations, which also significantly change during neuron excitation, are returned to their original states by a pump called Na^+/K^+-ATPase.

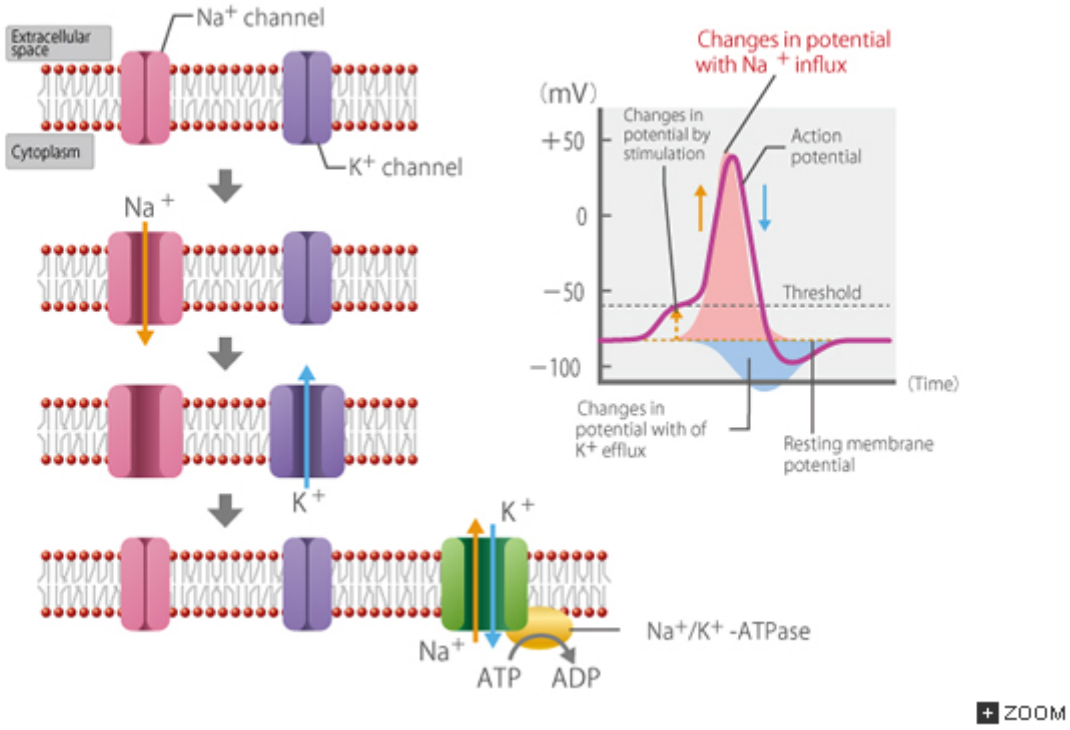


Figure 17-6 Generation mechanism of action potential

Excitation of neurons is caused by voltage-dependent Na^+ and K^+ channels. The intracellular concentration of ions changed by excitation is returned to the original resting state value by a pump called Na^+/K^+-ATPase. The bold red and black arrows in the figure indicate the changes in membrane potential caused by the influx of Na^+ and efflux of K^+ ions.

17.2.2 Dynein and kinesin

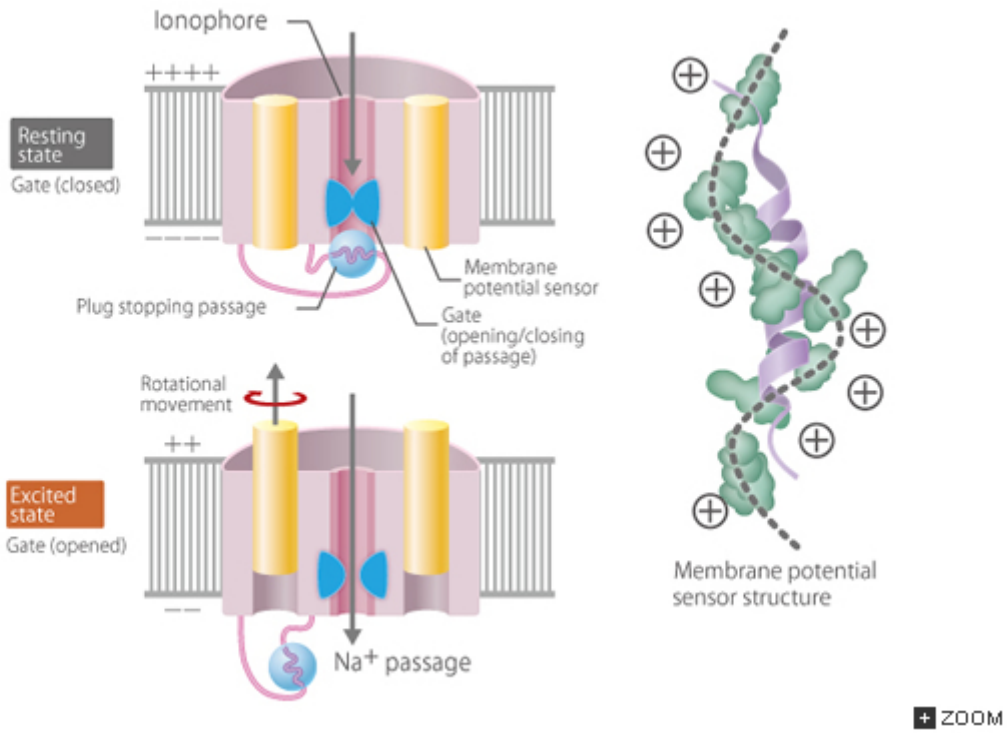
The stimulation sensed by sensory cells and neurons is transmitted to the brain and muscle cells via nerves in the form of the action potential (see Chapter 20). Even when the action potential is being conducted along the long nerve processes (dendrite and axon), voltage-dependent Na+ and K+ channels play important roles. When a Na+ channel senses a rise in the membrane potential due to the opening of an adjoining Na+ channel, they will start opening one after the other in a domino-like effect to conduct the change in the membrane potential (**Figure 17-7A**). Excitation is only conducted in one direction, because Na+ channels that have opened once will not respond to stimulation for some time— a state called the refractory period.

The neuronal axons are of two types: **unmyelinated fibers** and **myelinated fibers** in which Schwann cells and oligodendrocytes wrap around the axon at certain intervals. In unmyelinated fibers, excitation is conducted by the continuous generation of action potential along the axon. In myelinated fibers, Na^+ and K^+ channels are centered on an area called the node of Ranvier, which protrudes out between myelin sheaths, and therefore action potential is generated discontinuously at a certain distance (**Figure 17-7B, C**). Thus, the conduction speed of the action potential is overwhelmingly faster with myelinated fibers.

Column

Voltage-dependent Na^+ channels

Voltage-dependent ion channels are ion channels that open or close when the membrane potential reaches a certain value. It is thought that part of the ion channel structure changes in response to the change in the membrane potential, thus causing the channel to open/close.
The following model shows an example of how a voltage-dependent Na+ channel opens in response to changes in the membrane potential (**Column Figure 17-4**). In this example, a specific α-helix structure with membrane potential sensitivity rotates and moves when it senses certain change in the membrane potential, thereby opening the ion channel. This alpha-helical structure consists of basic amino acids such as positively charged arginine and lysine arranged in a spiral pattern. When it starts rotating and moving in response to the change in the membrane potential, the surrounding structure is affected, causing the gate of the ion channel to open.



Column Figure 17-4 Model of the opening/closing of voltage-dependent Na^+ channel

The opening/closing of voltage-dependent Na^+ channels is double-controlled by a gate and plug. The role of the membrane potential sensor is played by some alpha-helical structures, making up the ion channel. These structures include basic amino acids such as arginine and lysine arranged in a spiral pattern (side chain is indicated in red). They rotate and move when they sense changes in the membrane potential to control the opening/closing of the channel.

17.2.3 Dynein and kinesin

Excitation is transmitted from sensory cells to neurons, between neurons, and from neurons to muscle cells via the **synapse**. There are two types of synapses, **electrical** and chemical (**Figure 17-8A**). The electrical synapses are formed by coupling cells with gap junction, whereas **chemical** synapses transmit excitation between cells through chemical substances. Transmission speed is much faster through electrical synapses that are directly connected by cell junction rather than chemical synapses, which transmits excitation by secreting chemical substances. Electrical synapses and chemical synapses play a central role in invertebrates and vertebrates, respectively. However, electrical synapses also exist in the brain of vertebrate animals, playing a complementary role to chemical synapses.

With chemical synapses, **neurotransmitters** secreted from cells transmitting excitatory signals act on receptors present in the cell membrane receiving the transmission. Some receptors also serve as ion channels such as nicotine receptors. There are other receptor types such as the muscarinic receptor, in which signals from the receptors work on adjoining ion channels to control the opening and closing of the channels (see **Column Figure 17-5**). In either case, excitation is transmitted by opening the ion channel present in the partner cell membrane through the actions of neurotransmitters (**Figure 17-8B**).

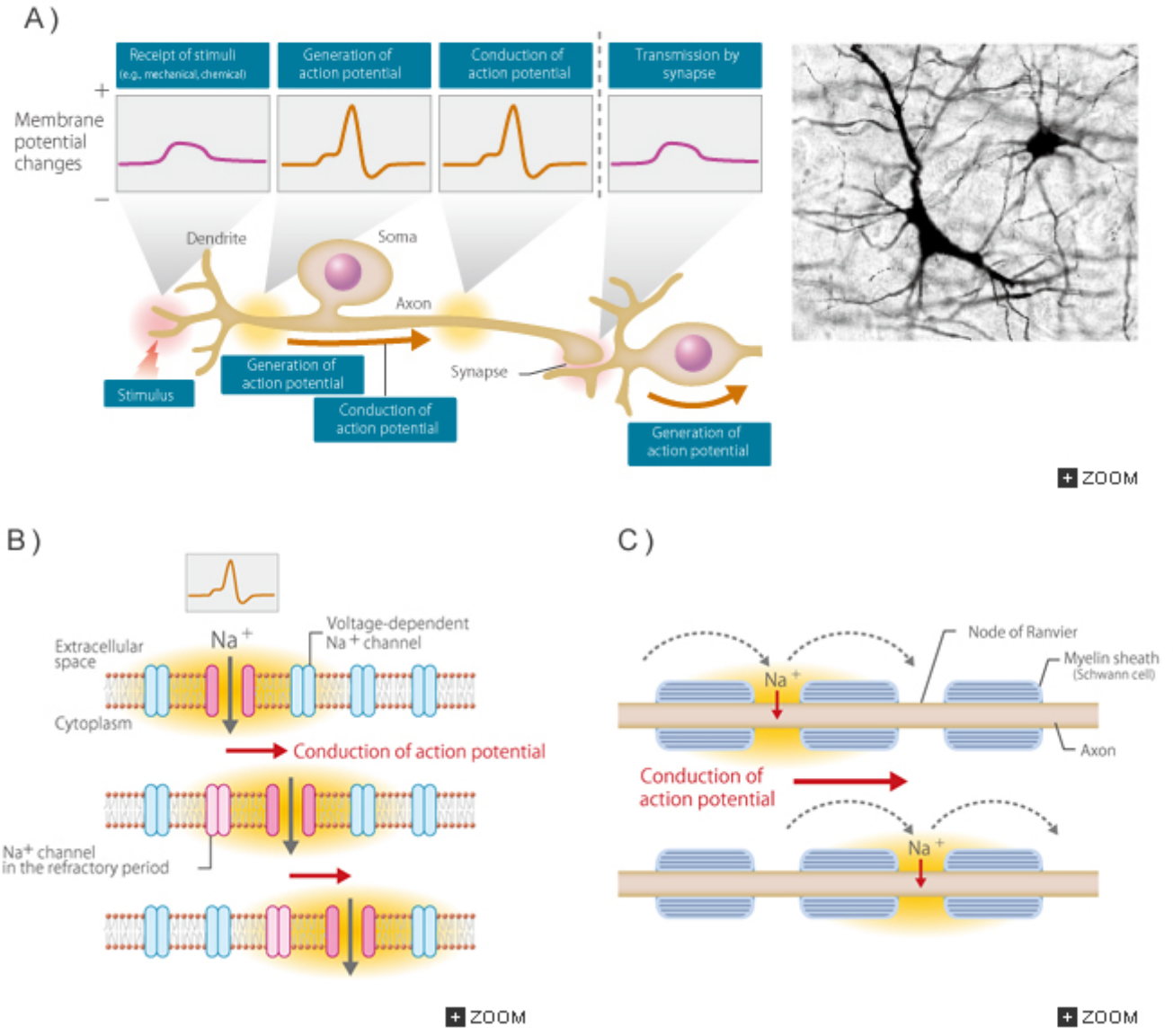


Figure 17-7 Conduction of action potential in neurons

A) Generation and conduction of action potential in neurons. The photo shows Golgi-stained brain neurons and dendrites. B) Conduction of action potential in unmyelinated fibers. Action potential is conducted through voltage-dependent Na+ and K+ channels. This figure illustrates how Na+ channels react to potential changes and open one after another in a chain reaction. Once opened, Na+ channels will not react to any changes in the membrane potential (refractory period) and therefore action potentials are conducted only in one direction. C) Conduction of action potential in myelinated fibers. Action potential is conducted in a discontinuous manner only using the filament parts not covered by the myelin sheath and therefore conduction speed is higher than in unmyelinated fibers.

Chemical synapses include two types, excitatory and inhibitory. The former functions to transmit excitation to other cells, while the latter functions to inhibit excitation by inhibiting the rise of membrane potential. At the excitatory synapse, secreted neurotransmitters such as **acetylcholine** and glutamic acid open the Na^+ channels in the cell membrane of the downstream cell. As a result, membrane potential increases and excites the cell. On the other hand, at inhibitory synapses, neurotransmitters such as gamma-aminobutyric acid (GABA) and glycine are secreted, which opens the Cl- and K+ channels of the cell membrane, thereby lowering the membrane potential and inhibiting cell excitation.

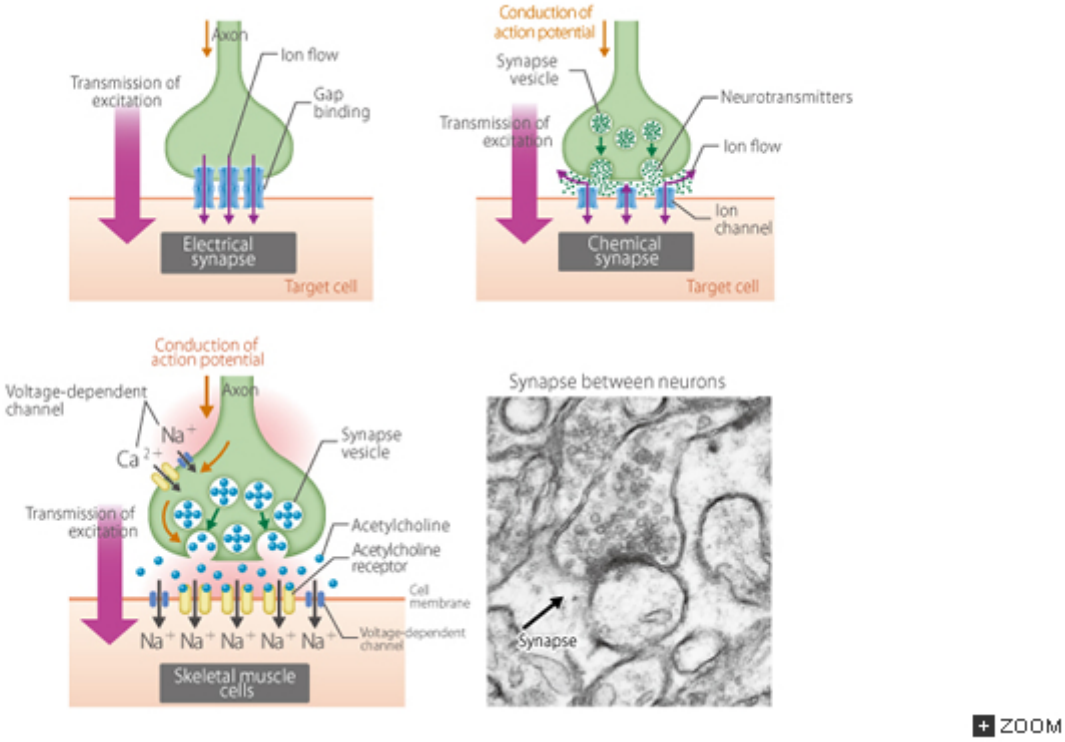


Fig. 17.8 Transmission of excitation by synapse

A) Two types of synapse: electrical synapse, which transmits excitation via gap binding, and chemical synapse, which transmits excitation between cells through chemical substances. B) Pattern drawing showing the transmission of excitation to skeletal muscle cells via synapse. Action potential conducted through the axon opens voltage-dependent Ca^{2+} channels of the synapse. An increased Ca^{2+} concentration in the synapse triggers the binding of the synapse vesicle and cell membrane, and thereby the secretion of acetylcholine. Acetylcholine binds to acetylcholine receptors in muscle cells, and opens their channels. As a result, Na+ ions flow into and excite the muscle cells. The microscopic photo shows a chemical synapse between brain neurons.