

# 23

## Nerve Cells

### *Review the Concepts*

1. Four types of glial cells interact with neurons. Oligodendrocytes and Schwann cells form the myelin sheath around neural axons in the central nervous system and peripheral nervous system, respectively. Interactions between glia and neurons control the placement and spacing of myelin sheaths, and the assembly of nerve transmission machinery at the nodes of Ranvier. Another type of glial cell, astrocytes, is important in producing synapses, forming contacts with synapses, and producing extracellular matrix proteins. Microglia produce survival factors and carry out immune functions.
2. The negative resting potential in animal cells is generated by the action of the  $\text{Na}^+/\text{K}^+$  ATPase. This pump uses the energy of ATP hydrolysis to move  $\text{Na}^+$  ions outside the cell and  $\text{K}^+$  ions into the cell. Three  $\text{Na}^+$  ions are pumped out for every two  $\text{K}^+$  ions pumped into the cell. Thus, operation of the  $\text{Na}^+/\text{K}^+$  pump generates a high- $\text{K}^+$  and low- $\text{Na}^+$  concentration inside the cell relative to the  $\text{K}^+$  and  $\text{Na}^+$  concentrations in the extracellular medium. This concentration gradient drives the movement of  $\text{K}^+$  ions across the plasma membrane to the outside the cell through nongated potassium channels, generating the resting membrane potential.
3. An action potential has three phases: depolarization, in which the local negative membrane potential goes to a positive membrane potential; repolarization, in which the membrane potential goes from positive to negative; and hyperpolarization, in which the resting negative membrane potential is exceeded. Depolarization corresponds to the opening of voltage-gated  $\text{Na}^+$  channels and a resulting influx of  $\text{Na}^+$ . Repolarization corresponds to the opening of

voltage-gated  $\text{K}^+$  channels. Hyperpolarization corresponds to a period of closure and inactivation of voltage-gated  $\text{Na}^+$  channels. The  $\text{Na}^+$  channels involved in the propagation of an action potential are referred to as voltage-gated channels because they open only in response to a threshold potential.

4. The voltage-sensing domains of voltage-gated potassium channel proteins are “arms” or “paddles” that protrude into the surrounding membrane from a central transmembrane pore formed by helices S5 and S6 from each of the four identical subunits in potassium ion channels. The voltage-sensing domains of the channel proteins involve helices S1–S4. S4 has a positively charged lysine or arginine every third or fourth residue. Changes in voltage cause the helices in the voltage domain to move across the membrane. Movement of voltage domain exerts a torque on a linker helix that connects S4 to S5. This causes the S5 helix to move in such a way that the central pore is either squeezed closed or opened.

The N-terminal part of each subunit of the *shaker* potassium channel protein forms a “ball” that extends into the cytosol and serves as the channel-inactivating segment. This domain tucks into a hydrophobic pocket as long as the channel remains open but moves to re-close the channel within milliseconds after the channel opens.

All voltage-gated channels are thought to have evolved from a monomeric ancestral channel protein that contained six transmembrane  $\alpha$  helices (S1–S6). Furthermore, all voltage-gated ion channels are thought to function in a similar manner. Thus even though some of the structural details are different, many of the biochemical insights revealed by protein crystal structures of

potassium channels apply to other ion channels as well.

5. Voltage-gated  $\text{Na}^+$  and  $\text{K}^+$  channels are clustered at the Nodes of Ranvier. When the membrane potential increases at one node, the  $\text{Na}^+$  channels at the next node “feel” the increased positive voltage. They open, causing sodium ions to flood into the cell at that point. The membrane potential increases and the  $\text{Na}^+$  channels at the next node “feel” the increased voltage. This continues until the action potential reaches the axon terminal.
6. Hyperpolarization that results from opening voltage-gated  $\text{K}^+$  channels delays opening of  $\text{Na}^+$  channels upstream. Sodium channels are also inactive for a few milliseconds after an action potential has passed. This refractory period prevents a nerve impulse from traveling backward.
7. Myelination is the development of a myelin sheath about a nerve axon. The myelin sheath is an outgrowth of neighboring glial (Schwann) cell plasma membrane about the axon that repeatedly wraps itself around the neural extension until all the cytosol between the layers of membrane is forced out. The remaining membrane is the compact myelin sheath. The myelin sheath serves as an insulator about the axon and hence speeds the rate of action potential propagation tenfold to a hundredfold.

The myelin sheath surrounding an axon is formed from many glial cells. Between each region of myelination is a gap, the node of Ranvier. The voltage-gated  $\text{Na}^+$  channels that generate the action potential are all located in the nodes. The action potential spreads passively through the axonal cytosol to the next node. This produces a situation in which the action potential in effect jumps from node to node. If the nodes are located too far apart, for example, a tenfold increase in spacing, then the passive spread of the action potential may become too slow to jump from node to node.

8. Both the accumulation of neurotransmitters in synaptic vesicles and the accumulation of sucrose

in the lumen of the plant vacuole are mediated by  $\text{H}^+$ -linked antiporters. In both cases, the proton moves down an electrochemical gradient to power the inward movement of the small organic molecule against a concentration gradient. Acetylcholine (as a released neurotransmitter) is degraded by acetylcholine esterase after its release into the synaptic cleft. Decreased acetylcholine esterase activity at the nerve-muscle synapse has the effect of prolonging signaling and hence prolonging muscle contraction.

9. Such rapid fusion of synaptic vesicles with plasma membrane in response to  $\text{Ca}^{2+}$  influx strongly indicates that the fusion machinery is assembled in a resting state and can rapidly undergo a conformational change. Synaptic vesicles loaded with neurotransmitter are localized near the pre-synaptic plasma membrane. Some synaptic vesicles are “docked” at the plasma membrane; others are in reserve in the active zone near the plasma membrane. In other words, the system is primed to respond rapidly. An increase in cytoplasmic  $\text{Ca}^{2+}$  signals exocytosis of the docked synaptic vesicles in a process that requires a membrane protein called synaptotagmin.
10. The dendrite is the neuron extension that receives signals at synapses and the axon is the neuron extension that transmits signals to other neurons or muscle cells. Typically, each neuron has multiple dendrites that radiate out from the cell body and only one axon that extends from the cell body. At the synapse, the dendrite may have either excitatory or inhibitory receptors. Activation of these receptors results in either a small depolarization or small hyperpolarization of the plasma membrane. These depolarizations move down the dendrite to the cell body and then to the axon hillock. When the sum of the various small depolarizations and hyperpolarizations at the axon hillock reaches a threshold potential, an action potential is triggered. The action potential then moves down the axon.
11. Dynamin is a GTP-binding protein that is required for pinching off of clathrin/AP coated vesicles during endocytosis. Fly mutants that lack dynamin can't recycle synaptic vesicles. These mutants can

- form clathrin-coated pits but can't pinch off vesicles.
12. Rhodopsin is a G protein-coupled receptor protein in rod and cone cell membranes. Rhodopsin contains a covalently bound light sensitive pigment, 11-*cis*-retinal. Upon absorption of a photon of light, 11-*cis*-retinal is converted to all-*trans*-retinal. This triggers a conformational change in rhodopsin. Activated rhodopsin interacts with an associated G protein called transducin and converts it to its active form, G $\alpha$ -transducin-GTP. G $\alpha$ -transducin-GTP activates a cGMP phosphodiesterase. cGMP phosphodiesterase hydrolyzes cGMP. This causes a decrease in the cGMP concentration. Less cGMP is bound to cGMP-gated cation channels in the rod or cone cell membranes, causing the channels to close. When these channels close, the photoreceptor cell membrane becomes hyperpolarized, eventually leading to transmission of the visual signal to the brain.
  13. Bipolar and retinal ganglion cells are involved in visual contrast detection. Both types of cells sense the relative light intensity in the center vs. surround, not the absolute amount of light in either place. A bipolar cell receives inputs from the center-surround, a group of photoreceptor cells covering the area of a circle. One type of bipolar cell, called "center-on," responds to light shining in the center of its receptive field by producing a set of action potentials, but action potentials are inhibited if light strikes photoreceptor cells surrounding the central part of the circle. The response is opposite in "center-off" bipolar cells.
  14. The receptors for salt and sour taste are ion channel membrane proteins. The receptors for sweetness, bitterness, and umami taste and odor receptors are seven-membrane domain proteins. With the salt taste receptors, the direct influx of Na<sup>+</sup> through the ion channel depolarizes the cell. Sour taste may work in a similar way except that depolarization is a result of H<sup>+</sup> flow through the receptor ion channel. The seven-membrane domain proteins are G-protein coupled receptors. They function through G proteins to release Ca<sup>2+</sup> into the cytoplasm, causing depolarization of the cell.
  15. Roger Sperry's experiments involved following the pattern of regeneration of a severed frog optic nerve to reveal the mechanism of how axons are guided on their pathways. Sperry surgically severed a frog optic nerve and then rotated the frog eye 180 so that ventral and dorsal were reversed (see Figure 23-41b). If the resonance hypothesis were correct, i.e. mechanical forces followed by a functional sorting-out process were governing regeneration, the visual system should have ended up functioning normally, since the proper connections would have been established and maintained (see Figure 23-41c, left). However, if the chemoaffinity hypothesis were correct, then vision should be inverted because despite the rotation the ventral axons would find their way to the lateral tectum and the dorsal ones to the medial tectum (see Figure 23-41c, right). In this case, the inverted eye would lead to the frog having inverted vision: it would see something above and would think it was below (see Figure 23-41d). The results were clear: after regeneration the frog would respond to a fly passing above by shooting its tongue *down*.

### Analyze the Data

- a. Taar6 and Taar7 are expressed in different neurons. If this expression pattern is observed with each TAAR member, then each olfactory neuron produces only a single member of the TAAR family, just as each olfactory neuron produces only one of the classical odorant receptors. In addition, the bottom panel of images in the text figure on page 1051 suggests that the cells that express TAAR are not the same cells that express classical odorant receptors. Thus, neurons in the nasal epithelium express a single type of olfactory receptor, be it an odorant receptor or a TAAR.
- b. The data suggest that different TAARs discriminate among various amines. Cells that do not express any TAAR do not secrete alkaline phosphatase, showing that the secretion is directly linked to the presence of these receptors. Some TAARs, such as mTAAR4 and mTAAR7f, appear to be very ligand specific. mTAAR4, for example, can distinguish between two amines that differ by the presence or absence of a single hydroxyl group.

Others, such as mTAAR5 which binds to more than one tertiary amine, show a broader spectrum of ligand binding. Alkaline phosphatase secretion (the SEAP assay) will occur only if alkaline phosphatase is expressed. Its expression depends on elevated cAMP levels. Such an elevation would occur if the TAARs, which are GPCRs, couple to a G protein that activates adenylyl cyclase.

- c. Cells expressing the mTAAR5 receptor appear to bind to a chemical present in the urine of two different species of adult male mice but not present in the urine of female mice nor in the urine of human males. This chemical may serve as a signal (pheromone) by which mice recognize the presence of sexually mature male mice. One would expect that one of the ligands that binds TAAR5, perhaps trimethylamine or methylpiperidine, would be present at appreciable concentrations in the urine of sexually mature male mice but not present in the urine of immature male mice nor in the urine of female mice nor in the urine of human males.