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CELLS OF THE NERVOUS SYSTEM

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 Na^+/K^+ ATPase. This pump uses the energy of ATP hydrolysis to move Na^+ ions outside the cell and K^+ ions into the cell. Three Na^+ ions are pumped out for every two K^+ ions pumped into the cell. Thus, operation of the Na^+/K^+ pump generates a high-K^+ and low-Na^+ concentration inside the cell relative to the K^+ and Na^+ concentrations in the extracellular medium. This concentration gradient drives the movement of K^+ ions across the plasma membrane to the outside of 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 Na^+ channels and a resulting influx of Na^+.

Repolarization corresponds to the opening of voltage-gated K^+ channels. Hyperpolarization corresponds to a period of closure and inactivation of voltage-gated Na^+ channels. The 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 α 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 Na^+ and K^+ channels are clustered at the nodes of Ranvier. When the membrane potential increases at one node, the Na^+ channels at the next node "feel" the increased positive voltage. They open, causing sodium ions to fl ood into the cell at that point. The membrane potential increases and the Na^+ channels at the next node "feel" the increased voltage. This continues until the action potential reaches the axon terminal.

6. As membrane potential approaches E_{Na}, Na^+ channels become inactivated, preventing additional influxofNa $^+$. K^+ channels open, facilitating an effluxof K^+ from the cell.

7. Once the threshold potential to start an action potential is reached, a full fi ring occurs. The signal information is therefore carried primarily not by the intensity of the action potentials, but by the timing and frequency of them.

8. Hyperpolarization that results from opening voltage-gated K^+ channels delays opening of 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.

9. During the refractory period, Na^+ channels are inactivated and are therefore unable to transport Na^+ ions across the membrane to depolarize the cell.

10. 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 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 around 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 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.

11. Under normal circumstances, leftover neurotransmitters released into the synaptic cleft are quickly removed from this location via reuptake or targeted degradation. Cocaine binds to and inhibits the re-uptake transporters for norepinephrine, serotonin, and dopamine. As a consequence, a higher than normal concentration of these neurotransmitters (especially dopamine) remains in the synaptic cleft, prolonging the stimulation of postsynaptic neurons. This extended stimulation leads to adaptation and the down-regulation of dopamine receptors and thus altered regulation of dopaminergic signaling, which is why habitual users tend to need to use more and more in order to achieve the same high.

12. Acetylcholine (as a released neurotransmitter) is degraded by ace-tylcholine esterase after its release into the synaptic cleft. Decreased acetylcholine esterase activity at the nerve-muscle synapse has the effect of prolonging signal-ing and hence prolonging muscle contraction.

13. The resting potential of the muscle plasma membrane (which is now permeable to Na^+ and K^+) is near E_K, so the opening of acetylcholine receptor channels in response to motor neuron stimulation causes little increase in the effluxofK^+ ions, but Na^+ ions rush into the cell (down their gradient) and depolarize the membrane. The shift in membrane potential triggers opening of voltage-gated Na^+ channels, leading to further depolarization and the generation and conduc-tion of an action potential in the muscle cell surface membrane stimulating the release of Ca^{2+} from sarcoplasmic reticulum stores.

14. Such rapid fusion of synaptic vesicles with plasma membrane in response to Ca^{2+} influxstronglyindicatesthatthefusionmachineryisassembledinaresting state and can rapidly undergo a conformational change. Synaptic vesicles loaded with neurotransmitter are localized near the presynaptic 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 Ca^{2+} signals exocytosis of the docked synaptic vessels in a process that requires a membrane protein called synaptotagmin.

15. 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.

16. At inhibitory synapses, the action potential in the pre-synaptic cell triggers the release of inhibitory neurotransmitters, which bind to the post-synaptic receptors activating K^+ and/or Cl^- channels. The opening of Cl^- channels results in an influx of Cl^- ions. The opening of K^+ channels results in an efflux of K^+ ions. In both cases, hyperpolarization of the post-synaptic cell occurs, making it more difficult for this cell to reach the required threshold to fire an action potential.

17. Dynamin is a GTP-binding protein that is required for pinching off of clathrin/AP-coated vesicles during endocytosis. Fly mutants that lack dynamin cannot recycle synaptic vesicles. These mutants can form clathrin-coated pits but cannot pinch off vesicles.

18.

Electrical	Chemical
Uni-directional impulse transmission	Bi-directional impulse transmission
Fast conduction velocity (0.5-5 ms)	Faster conduction velocity (fraction of a ms)
Direct electrical transmission between pre- and post-synaptic cells	Transmission between cells occurs via neurotransmitter release at the synaptic cleft, followed by the conversion of this chemical signal to an electrical signal in the post-synaptic cell
No need for the pre-synaptic cell to reach a certain threshold potential	Pre-synaptic cell must reach a threshold potential before transmission to the post-synaptic cell

19. 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^+ through the ion channel depolarizes the cell. Sour taste may work in a similar way except that depolarization is a result of H^+ flow through the receptor ion channel. The seven-membrane domain proteins are G–protein coupled receptors. They function through G proteins to release Ca^{2+} into the cytoplasm, causing depolarization of the cell.

20. Memories are stored as stimulus-induced changes in the strength of synaptic connections between neurons. As such, any mechanism that alters synaptic strength can serve as a synaptic mechanism underlying memory formation. These mechanisms can be divided into presynaptic, trans-synaptic and postsynaptic mechanisms. Presynaptic mechanisms include those that increase the amount of neurotransmitter that is released following neuronal stimulation, often as a consequence of activation of kinases. As one example, phosphorylation of synapsin, the protein that tethers synaptic vesicles to a reserve pool, increases the number of synaptic vesicles that release neurotransmitter following a given neuronal stimulus. As another example, phosphorylation of RIM, the protein that tethers calcium channels to the release machinery, increases the influxofcalcium and hence the release of neurotransmitters following a stimulus. Postsynaptic mechanisms can also involve the activation of kinases in the postsynaptic compartment. For example, once activated, the CamKIIα kinase can autophosphorylate itself and become constitutively active for up to 30 minutes following stimulation. As a result, the signaling induced by a neuronal stimulus can persist even after the stimulus ter-minates. Another well characterized postsynaptic mechanism involves stimulus- induced changes in AMPA glutamate receptor concentrations at the postsynaptic density, which changes the response to a given amount of neurotransmitter. Increased exocytosis or lateral diffusion of AMPA receptors into the postsynaptic density increases synaptic strength because a given amount of neurotransmitter binds to more receptors on the postsynaptic cell. In contrast, increased endocytosis or diffusion away from the postsynaptic density decreases synaptic strength because a given amount of neurotransmitter binds fewer receptors on the post-synaptic cell.