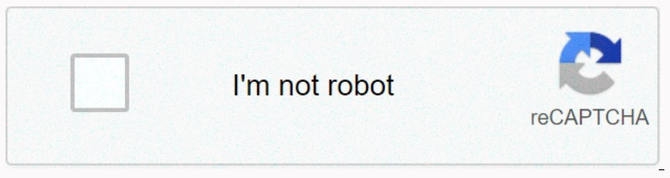

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Conduction of action potentials and synapses worksheet

We saw in chapter 15 that there is a voltage gradient, also called an electrical potential, over the plasma membrane of all cells. The potential over the plasma membrane of large cells can be measured with a microelectrode in the cell and a reference electrode placed in the extracellular fluid. The two are connected to a voltmeter that can measure small potential differences (Figure 21-7). In almost all cases, the inside of the cell membrane is negative relative to the outside; typical membrane possibilities are between −30 and −70 mV. The potential over the surface membrane of most animal cells generally does not vary with time. By contrast, neurons and muscle cells – the main types of electrically active cells – undergo controlled changes in their membrane potential (see Figure 21-2a). The characteristic electrical activity of neurons — their ability to transmit, transmit and receive electrical signals — is due to the opening and closing of specific ion channel proteins in the neuronplama membrane (Figure 21-8). Each open channel allows only a small number of ions to go from one side of the membrane to the other, but these ion movements cause significant changes in membrane potential. Here we explain the relationship between the opening and closing of ion channels and the resulting changes in the tension over the membrane that lead to the propagation of action possibilities. We investigate the structure and functioning of different types of ion channels that are crucial for the functioning of neurons later in the chapter. The concentration of K+ ions in typical metazoan cells is about 10 times higher than in the extracellular fluid, while the concentrations of Na+ and Cl−ions outside the cell are much higher than inside; these concentration gradients are maintained by Na+/K+ ATPases with the expenditure of cellular energy (see Figure 15-13). As noted in Chapter 15, the plasma membrane contains abundant open resting K+ channels that allow passage only from K+ to the table. The resting potential — within negative — is mainly determined by the movement of K+ ions: Movement of a K+ ion down over the membrane leaves an excessive negative charge on the cytosolic face and places a positive on the exoplasmatic face (Figure 21-9). Quantitatively, the usual resting potential of −60 mV is close to, but in size less than, the value of EK, the potassium equilibrium potential, calculated on the basis of the Nernst equation (see Equation 15-7) and the typical external and cytosollic K+ concentrations ([Ko] and [KI], respectively) in Figure 21-9. If the concentration of K+ around a resting cell is changed, the measured membrane potential assumes a new value, again close to the calculated value of EK; this is proof that the due mainly to movement of K+ through open K+ channels in the plasma membrane. The situation in cells is complicated because there are a number of open Na+ and Cl− channels in the plasma plasma of the rest cell. Cells naturally contain other ions, such as HPO42−, SO42−and Mg2+, but there are few channels that allow these ions. In addition, the membrane potential of electrically active cells such as neurons and muscle cells is primarily influenced by the opening and closing of channels for K+, Na+and Cl−; So these three ions are the only ones we should consider here. As we'll discuss later, Ca2+ channels are central to the release of neurotransmitters on synapses. To calculate the membrane potential as a function of the concentrations of different ions, it is useful to define a permeability constant P for each ion. P is a measure of the ease with which an ion can cross a unit area (1 cm2) of membrane, driven by a concentration difference of 1 M; it is proportional to the number of open ion channels and to the number of ions that each channel can run per second (the channel conduction). So PK, PNa, and PCl are measures of leaking a unit area of membrane to these ions. Permeability is generally not directly measured; the permeability of a membrane for a given ion is the product of the number of open ion channels and the conductivity of each channel; both parameters can be measured by the techniques that we describe later. Since the conductivity of the different ion channels is virtually the same, the differences in permeability of a membrane for Na+, K+and Cl largely reflect differences in the number of open channels specific to each ion. What is important is not the absolute size of the permeability for each ion, but the proportions of the permeability of Na+ and Cl- with those of K+. The electrical potential, E (in millivolt), over a cell surface trambraan is given by a more complex version of the Nernst equation in which the concentrations of the ions are weighed in relation to the relative greaterities of their permeability confections:where the subscripts o and i indicate the ion concentrations outside and within the cell. Because of their opposite charges (Z value in the Nernst equation), [Ko] and [Nao] are placed in the counter, but [Clo] is placed in the denominator; conversely, [Ki] and [Nai] are in the denominator, but [Cli] is in the counter. The membrane potential at any time and at any position in the neuron can be calculated with this equation if the relevant ion concentrations and permeability are known. Note that if PNa = PCl = 0, then the membrane is permeable only k+ ions and Equation 21-1 reduces to the Nernst equation for K+ (see Equation 15-7). Similarly, if PK = PCl = 0, then the membrane is permeable only for Na + ions and Equation 21-1 reduces to the Nernst equation for Na+ (see Equation 15-6). In rest neurons, the ion concentrations are usually those in Figure 21-9, and the permeability of the up to Na+ or Cl− ions is about a tenth that for K+ (i.e. PNa/PK = PCl/PK = 0.1). That is, there are about ten times more open K+ channels than open channels for Na + or Cl−. ion concentrations and these permeability ratios compared to 21-1, we can calculate the membrane potential as −52.9 mV, which is much closer to EK (−91.1 mV) than with ENa (+64.7 mV). Although ECl (−87.2 mV) is close to EK, there are so few open Cl channels that they contribute little to the resting potential. The resting potential is not equal to EK because the membrane also contains a number of open Na+ channels; inflow of Na+ ions down the concentration gradient adds positive charges to the inside of the cell membrane, making the membrane potentially more positive (or less negative). It is clear from comparison 21-1 that changes in the permeability of the membrane in different ions will change the membrane potential. Figure 21-10 illustrates several quantitative changes. Here we summarize the direction of predicted changes due to the opening and closing of several channels:1.Opening of Na + channels (increasing PNa) causes depolarization of the membrane; the membrane potential becomes less negative, and if the increase in PNa is large enough, the potential inside can become positive, approaching ENa. Intuitively, Na+ions tend to flow in from the extracellular medium, their concentration gradient, causing excess negative ions to pass onto the outer surface of the membrane and putting more positive ions on the cytosollic surface. Conversely, closing Na+ channels, decreasing PNa, membrane hypodermization, causes a more negative potential.2.Opening of K+ channels (increasing PK) causes hyperpolarization of the membrane; the membrane potential becomes more negative, which makes EK approaching. Intuitively, this happens because more K+ ions flow out of the cytosol, their concentration gradient, putting excess negative ions on the cytosolic surface of the membrane and putting more positive ones on the outer surface. Conversely, closing K+ channels, decreasing PK, depolarization of the membrane and a less negative potential.3.Opening of non-specific cation channels that allow Na+ and K+ also causes membrane depolarization. Such channels allow K+ ions to flow out of the cytosol and Na+ ions; the net effect is to drive the membrane potential to zero.4.Opening of Cl− channels (rising PCl) causes hyperpolarization of the membrane, and potential ECl approaches. Intuitively, Cl-ions tend to flow in from the extracellular medium, their concentration gradient, causing excess positive ions to pass onto the outer surface of the membrane and placing more negative ions on the cytosollic surface. In muscle cells, resting Cl− channels, not resting K+ channels, the main determinants of the inside are negative resting potential. Vice versa the closure of CL channels, decreasing PCl depolarisation and less negative potential. At the resting potential, tension-gated ion channels are closed; no ions move through them. However, when an area of the plasma membrane is slightly depolarized, the open for a short period, causing the influx of Na+ ions which causes the sudden and transient depolarization associated with an action potential. After opening (and closing) voltage-gated Na+ channels during an action potential, the temporary opening of voltage-gated K+ channels ensures that the membrane potential returns to the resting state and becomes even more negative (hyperpolarized) for a short time (see Figure 21-2a). The ability of axons to perform action over long distances without reduction therefore depends on controlled opening and closure of voltage-gated Na+ and K+ channels (see Figure 21-8b). Binding of neurotransmitters to ligand-gated ion channels in postynaptic cells leads to changes in postynaptic membrane potential during impulse transfer in synapses (see figure 21-8c). To understand how voltage-gated Na+ and K+ channels can potentially perform an action in an axon in one direction, we first need to investigate how a plasma membrane with only resting K+ channels would perform an electrical depolarization. In its electrical properties, a nerve cell with only resting K+ channels resembles a long underwater telephone cable. It consists of an electric insulator, the poorly conductive cell membrane, separating two media - the cell cytosol and the extracellular liquid - which have a high conductivity for ions. Suppose that a single micro-electrode is inserted into the axon and that the electrode is connected to a source of electrical current (e.g. a battery) in such a way that the electrical potential at that point is suddenly depolarized and maintained at this new voltage. On this site, the inside of the membrane will have a relatively surplus of positive loads, mainly K+ ions. These ions will tend to move away from the original depolarization site, depolarizing adjacent parts of the membrane. This is called the passive spread of depolarization. Unlike an action potential, passive dispersion takes place equally in both directions. Also, the extent of depolarization decreases with the distance to the site of the first depolarization, because some of the excess cations leak back over the membrane through resting channels (Figure 21-11). Only a small proportion of the excess katie's are carried along the axon for long distances along the axon. The extent of this passive spread of depolarization is a function of two properties of the nerve cells: the permeability of the membrane to ions and the conductivity of the cytosol. The passive spread of depolarization is greater for neurons with a large diameter than for neurons with a small diameter, because the conductivity of the cytosol of a nerve cell depends on the cross-sectional area. The larger the area, the larger the ions will be there (per unit length of neuron) to perform current. So k+ ions are able to move, on average, further along a large axon than a small one before they leak back over the membrane. As a result, large diameter neurons neurons depolarization faster and beyond thin. Nevertheless, membrane depolarization can spread passively for only a short distance, from 0.1 to about 5 mm. Depolarisations in dendrites and the cell body generally spread in this way, although some dendrites carry out an action potential. Neurons with very short axoons also perform axal depolarisations through passive spread. However, passive dispersion does not allow the propagation of long-distance electrical signals. As we discuss below, some axons are surrounded by a myelin sheath, which impedes the leakage of excess katiems associated with membrane depolarization. So small micred neurons and large unmyelinated ones have similar length constants for passive spread of membrane depolarisations. The action potential is a cycle of membrane depolarization, hyperpolarization and return to rest value (Figure 21-12a). The cycle lasts 1 – 2 ms, and can occur hundreds of times per second. These cyclical changes in membrane potential are due to a temporary increase in the permeability of an area of the membrane, first to Na+ ions, then to K+ ions (Figure 21-12b). More specifically, these electrical changes are due to voltage-gated Na+ and K+ channels that open and close in response to changes in the membrane potential. The role of these channels in the generation and conduction of action potentials was clarified in classic studies done on the giant axon of the squid, in which multiple microelectrodes can be inserted without harming the integrity of the plasma membrane. However, the same basic mechanism is used by all neurons. The sudden but momentary depolarization of an area of the plasma membrane during an action potential is caused by a sudden massive but transient influx of Na+ ions through open voltage-gated Na+ channels in that region. At the rest membrane potential, these tension gap channels are closed. The depolarization of the membrane changes the conformation of the channel proteins, opens the Na+-specific channels and allows After+ inflow through it. During the conduction of an action potential, the passive spread of depolarization to the adjacent distal area of membrane somewhat depolarizes the new region, causing the opening of a few tension gated Na+ channels and an increase in Na+ inflow. A combination of two forces working in the same direction drives Na+ ions into the cell: the concentration gradient of Na+ ions and the residual membrane potential — inner negative — that attracts after+ ions in the cell. As more Na+ ions spout into the cell, the inside of the cell membrane becomes more positive and the membrane becomes further depolarized. This

depolarization causes more voltage-gated Na+ channels to be opened, creating a inflow of Na+ ions is set in motion completed within a fraction of a millisecond. For a fraction of a millisecond, at the height of the action potential, the permeability of this area from the membrane to Na+ Na+ much larger than that for K+ or Cl−, and the membrane potential approaches ENa, the equilibrium potential for a membrane that can only be penetrated for Na+ ions (see Figure 21-12). When the membrane potential almost reaches ENa, further net inner movement of Na+ ions ceases, because the concentration gradient of Na+ ions (outside>inside) is balanced by the membrane potential ENa (in positive). The potential for action is at its peak. The measured peak value of the action potential for the squid giant axon is 35 mV, which is close to the calculated value of ENa (55 mV) based on Na+ concentrations of 440 mM outside and 50 mM inside. The relationship between the extent of the action potential and the concentration of Na+ ions inside and outside the cell is experimentally confirmed. For example, if the concentration of Na + ions in the solution baths the squid axon is reduced to a third of normal, the extent of depolarization is reduced by 40 mV, almost as predicted. Like all channel proteins, voltage-gated Na+ channels contain a watery pore through which the ions flow. Entering the channel from the outside, one first meets a wide vestibule, then selects a narrow pore that allows the type ion to pass. The pore leads to a large inner vestibule and, at the cytosollic end, a segment of the protein - the gate - that closes the pore in the resting state. As depicted in Figure 21-13, at halftime state tension gated After + channels are closed, but can be opened if the membrane is depolarized. The greater the depolarization, the more likely a channel will open. Opening is triggered by movement of voltage estimation α helices in response to the membrane depolarization, causing a small conformation change in the port that opens the channel and makes ions flow. Once opened, the channels remain open about 1ms, during which time about 6000 Na+ ions pass through. Further influx Na+ is prevented by movement of the channel-inactivating segment in the channel opening. As long as the membrane remains depolarized, the channel is inactivated and cannot be reopened. As we discuss later, this refractory period of the Na+ channel is important in determining the one-way ionality of the action potential. A few milliseconds after the inside-negative resting potential is restored, the channels return to the closed rest state, once again primed before being opened by depolarization. During the time that the voltage-gated Na+ channels close and fewer Na+ ions are entering the cell, voltage gated K+ channel proteins open. This causes the observed increase in potassium ion permeability and an increased efflux of K+ of the cytosol that repolarizes the plasma membrane to its resting potential. Actually, the membrane becomes hyperpolarized for a short moment, potentially approaching EK, which is more negative than the resting potential (see Figure 21-12). The opening of the voltage-gated K+ channels is caused by membrane depolarization of the potential for action. Unlike the voltage-gated Na+ channels, most types of voltage gated K+ channels remain open as long as the membrane is depolarized, and closes only when the membrane potentially has returned to an inside-negative value. Because the voltage-gated K+ channels open a fraction of a millisecond or so after the initial depolarization, they are called delayed K+ channels. Eventually all voltage-gated K+ and Na+ channels close. The only open channels are the non-voltage-gated K+ channels that generate the inside-negative potential feature of the resting state; as a result, the membrane potential returns to its resting value. At the height of an action potential, passive dispersion of the membrane depolarization is sufficient to depolarize a downstream segment of membrane. This causes a few Na+ channels in this region to open, increasing the extent of depolarization in this region, causing an explos-ive opening of more Na+ channels. In this way, the spread of the action potential without reduction is ensured. Because voltage-gated Na+ channels remain inactive for several milliseconds after opening, those Na+ channels cannot immediately reopen behind the action potential, although the potential in this segment is depolarized due to passive spread (Figure 21-14). The inability of Na + channels to reopen during the refractory period causes action potentials to be propagated one way from the cell body to the axon endpoint, and limits the number of action possibilities per second that a neuron can perform. Reopening of Na+ channels behind the action potential is also prevented by the membrane hyperpolarization that results from the opening of voltage-gated K+ channels. The changes in membrane potential characteristic of a potential for action are caused by rearrangements in the balances of ions on either side of the membrane, not by changes in the concentrations of ions in the solutions on both sides. The voltage changes are generated by the movements of Na+ and K+ ions over the plasma membrane via voltage gap channels, but the actual number of ions moving is very small compared to the total number in the neuronal cytosol. In fact, measurements of the amount of radioactive sodium entering and leaving some squid axons and other axons during a single action potentially show that, Depending on the size of the neuron, only about one K+ ion per 3000 - 300,000 in the cytosol (0.0003 - 0.03 percent) is exchanged for extraceller Naular+ to generate the reversals of membrane polarity. As previously discussed, the rest membrane potential in nerve cells is primarily due to the course of K+ ions generated and maintained by the Na+/K+ ATPase. This ATPase does not play role in impulse conduction. If dinitrophenol or another inhibitor of ATP production is added to cells, the membrane potentially gradually falls to zero as all ions equilibrate over the membrane. In large nerve cells such as in the squid this balance is extremely slow, which takes hours, but with smaller mammalian nerves this balance occurs in just 5 minutes. In both cases, the membrane potential is essentially independent of the delivery of ATP during the short time span required for nerve cells to generate and perform action capabilities. Nerve cells can normally fire thousands of times in the absence of an energy supply, as the ion movements during each discharge include only a minute fraction of the K+ and Na+ ions of the cell. In humans, the cell body of a motor neuron that innervates a leg muscle in the spinal cord and axon is about one meter long (see figure 21-5). Because the axon is covered with a myelin shede (Figure 21-15), which increases the speed of impulse conduction, it only takes about 0.01 seconds for an action potential to travel the length of the axon and stimulate muscle contraction. Several deined neurons perform action capabilities at speeds of 10 to 100 meters per second (m/s). Without myelin, the speed would be ≈1 m/s, and coordination of movements such as running would be impossible. Myelin is a stack of specialized plasma membrane plates produced by a glial cell that wraps around the axon. In the peripheral nervous system, these glial cells are called Schwann cells; in the central nervous system, they are called oligodendrocytes. Often, several axons are surrounded by a single glial cell (Figure 21-16a). In both vertebrate and some invertebrates, axons along their length are guided by glial cells, but specialization of these glial cells to form myelin occurs mainly in vertebrates. Vertebrate glial cells that will later form myelin have on their surface a myelin-associated glycoprotein and other proteins that bind to adjacent axons and cause the formation of myelin. A myelin membrane, like all membranes, contains phospholipid bilayers, but unlike many other membranes, it contains only a few types of protein. The predominant myelin protein in the peripheral nervous system is Po, which causes adjacent plasma membranes to stack firmly on top of each other (Figure 21-16b). Myelin in the central nervous contains a cytosolic and a membrane protein, called myelin basic protein and proteolipides, respectively, which function together in the same way as Po.De myelin sheath around an axon formed from many glial cells. Each region of myelin formed by an individual glial cell is separated from the next region by an unmyelinated area called the node of Ranvier (or simply, node); only at nodes is the axonal membrane in direct contact with the extracellular fluid (Figure 21-17). Because the myelin shear prevents the transfer of ions between the axonal cytosol and the extracellular fluids, all electrical activity in limited to the nodes of Ranvier, where ions can flow over the axonal membrane. Glial cells secrete protein hormones that somehow activate the clustering of Na+ channels on the nodes. As a result, the node node a high density of voltage-gated Na+ channels (≈10,000 per square micrometer of axonal plasma membrane), while areas of axonal membrane between the nodes have few or no Na+ channels. Na+/K+ ATPase, which maintains the ionic gradients in the axon, has also been located to the nodes. The fibrous cytoskeletal protein ankyrin binds to these proteins and holds them in the nodal membrane. Myelinated nerves have lengthconst constants of several millimeters for passive spread of depolarization, because ions can move across the axonal membrane only at the myelin-free nodes (see Figure 21-11). Thus, the excess cytosollic positive ions generated at a node during the membrane depolarization associated with an action potentially spread passively through the axonal cytosol to the next node with very little loss or weakening, causing a depolarization at a node to quickly spread to the next node. This makes it possible to jump the action, in fact, from node to node (Figure 21-18). For this reason, the conductivity rate of myyelinated nerves is about the same as that of much larger unmyelinated nerves. For example, a 12-µm-diameter myelinated vertebrate axon and a 600-µm-diameter unmyelinated squid axon both guided impulses at 12 m/s; the onmyelinated squid giant axon takes up several thousand times the space of this myelin vertebrate axon and uses several thousand-fold more energy. Not surprisingly, myelinated nerves are used for signaling in circuits where speed is important. Evolution of the myelin sheath also allowed many more fast-conducting axons to occupy a smaller space, and clearly was essential for the evolution of the vertebrate brain. One of the most important serious neurological diseases in human adults is multiple sclerosis (MS), usually characterized by spasms and weakness in one or more limbs, bladder dysfunction, local sensory losses and visual impairments. This condition - the prototype demyelinating disease - is caused by patchy loss of myelin in areas of the brain and spinal cord. In MS patients, the conductivity of action by the demyelinated neurons is slowed down and the Na+ channels spread outward from the nodes. The cause of the disease is not known, but seems to involve either the body's production of auto-antibodies (antibodies that bind to normal body proteins) that react with myelin base protein or the secretion of proteases that destroy myelin proteins. SUMMARY There is an electrical potential across the plasma membrane of all eukaryotic cells because the ion compositions of the cytosol and extracellular fluid differ, as well as the permeability of the plasma membrane to the main cellular ions: Na+, K+, and Ca2+. In most nerve and muscle cells, the resting membrane potential is about 60 mV, negative on the inside; the potential is mainly due to the relatively large number of open K+ channels in the membrane (see Figure 21-9). Without voltage-gated cation channels, membrane depolarisations would passively only briefly (0,1 to about 5 mm) before the membrane potential returns to its original value. An action potentially stems from the sequential opening and closure of tension-gated cation channels. First, opening Na+ channels allows influx of Na+ ions for about 1 ms, causing a sudden major depolarization of a segment of the membrane. The channel then closes and cannot be opened for several milliseconds (refractory), preventing further Na+ flow (see Figure 21-13). Opening K+ channels when the action potential reaches its peak allows the rollout of K+ ions, which initially hyperpolarizes the membrane. When these channels close, the membrane returns to its resting potential. The depolarization associated with an action potentially generated at one point along an axon spreads passively to the adjacent segment, where it leads to opening of voltage-gated Na+ channels and thus another action potential. Reproduction of the action potential occurs only in one direction due to the short inactive period of the Na+ channels and the short hyperpolarization due to K+ efflux (see Figure 21-14). Thick neurons conduct impulses faster than thin ones. Myelination increases the rate of impulse conduction to one hundredfold. In deinated neurons, voltage-gated Na+ channels are concentrated on nodes of Ranvier. Depolarization on one node quickly spreads to the next node with little damping, so the action potential jumps from node to node (see Figure 21-18). 21-18).