C2.2 Neural signalling

Interaction and interdependence—Cells

Standard level and higher level: 3 hours

Additional higher level: 3 hours

Guiding questions

• How are electrical signals generated and moved within neurons?

• How can neurons interact with other cells?

SL and HL

C2.2.1–Neurons as cells within the nervous system that carry electrical impulses
Students should understand that cytoplasm and a nucleus form the cell body of a neuron, with elongated nerve fibres of varying length projecting from it. An axon is a long single fibre. Dendrites are multiple shorter fibres. Electrical impulses are conducted along these fibres.

Nervous tissue makes up the nervous system and is composed of neurons and glial cells. **Neurons** are considered to be the functional cells of the nervous system as they are responsible for electrical signalling and communication of information within the body. **Glial cells** ('glia' meaning 'glue' in Greek) are supporting cells that help neurons carry out their functions.

The main part of a neuron is the **soma** ('soma' meaning 'body'), also known as the **cell body**, which contains the nucleus and major organelles within the cytoplasm.

What makes neuron cells special are **fibers**, which are protrusions or appendages of the plasma membrane that extend from the soma. These fibers can be dendrites or axons.

Dendrites are highly branched and short extensions of the plasma membrane (fibers) that receive signals from other neurons. They tend to taper towards the end and are covered with **spines** (tiny bumps) to increase surface area for receiving input from other neurons.

Axons are long singular fibres that emerge from the cell body and propagate the action potential (neural signal) from the soma unidirectionally towards the **axon terminal**, in which several small branches extend towards the neighboring neuron (or target cell) to transmit the signal via **synapses** (small junctions between neurons that allow for the transmission of signals). The initial segment of the axon is called the **axon hillock** in which the cytoplasm changes to a solution of limited organelles and components called the **axoplasm**.

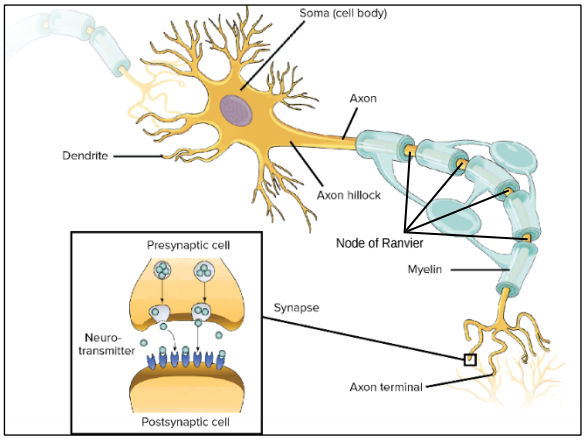

Figure 1: anatomy of a neuron cell (Khan Academy).

C2.2.2–Generation of the resting potential by pumping to establish and maintain concentration gradients of sodium and potassium ions

Students should understand how energy from ATP drives the pumping of sodium and potassium ions in opposite directions across the plasma membrane of neurons. They should understand the concept of a membrane polarization and a membrane potential and also reasons that the resting potential is negative.

Electricity is the phenomena associated with stationary or moving charged particles (positive and/or negative). Thus, the movement of charged ions across the plasma membrane of neurons is what creates the electrical signals within the nervous system.

The electrical state of a cell depends on its **membrane potential**, which is a measure of the distribution of positive and negative ions across the cell membrane and is measured in millivolts (mV). The standard method of representing membrane potential is to denote the intracellular membrane charge based on the extracellular side being zero, relatively speaking.

When a neuron is at rest (not transmitting a signal), its **resting membrane potential** is around -70mV, meaning that the cytosol is more negatively charged than the extracellular fluid. Generally, potassium ions are concentrated intracellularly whereas sodium ions are concentrated in the extracellular matrix. This distribution of ions within and around the cell is critical for neural function. The cell takes advantage of this ion distribution to maintain a negative charge relative to the outside through the following mechanisms:

- The **sodium-potassium pump** moves 3 sodium ions out and 2 potassium ions in by active transport (since both are cations, the *net total* is a loss of 1 cation from the cytoplasm per pump, making it more negative)
- **Leakage channels** that open randomly to allow Na^+ and K^+ ions to travel down their concentration gradients. However, K^+ leakage channels are around 50 times more 'leaky' than Na^+ channels which ensures that the cell loses more cations than it gains (thus will be more negative than the outside)
- The existence of more organic anions inside the cell than outside, contributing to a negative charge

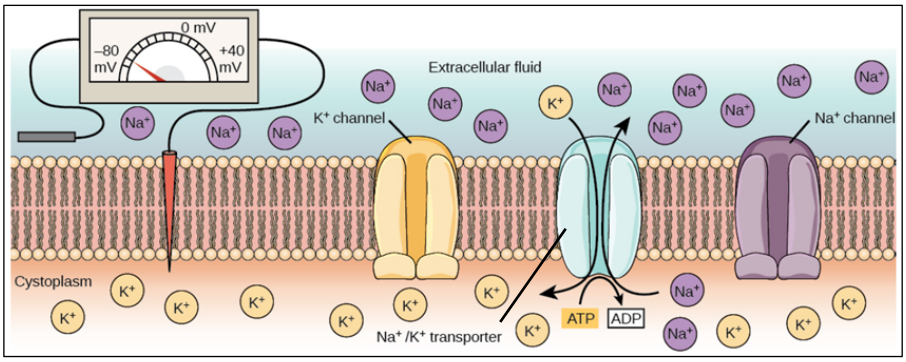

Figure 2: measuring resting membrane potential using a voltmeter (Gordon Betts).

The sodium-potassium pump functions as follows:

1. To begin, the pump is open to the inside of the cell. In this form, the pump really likes to bind (has a high affinity for) sodium ions, and will bind to three of them
2. When the sodium ions bind, ATP hydrolysis is triggered and the pump is phosphorylated, releasing ADP as a by-product
3. Phosphorylation makes the pump change shape, re-orienting itself so it opens towards the extracellular space. In this conformation, the pump loses its affinity to sodium ions, releasing them outside of the cell
4. In its outward-facing form, the pump switches allegiances and now really likes to bind to (has a high affinity for) potassium ions. It will bind two of them, causing the pump to be dephosphorylated and returning it to its original in-ward conformation
5. Affinity for potassium ions becomes low so they are released into the cytoplasm and the cycles repeats

C2.2.3–Nerve impulses as action potentials that are propagated along nerve fibres

Students should appreciate that a nerve impulse is electrical because it involves movement of positively charged ions.

Action potentials (nerve impulses) are simply very rapid changes in the membrane potential of a cell caused by ions moving in and out of the cell. They occur in 3 main stages:

1. **Initiation**: triggering an action potential requires receiving signals from other cells through neurotransmitters. This signal is received by the target neuron's dendrites, and can either be **excitatory** or **inhibitory**. The combined action of all neurotransmitters on the target neuron determines whether an action potential will take place or not.
2. **Depolarization**: If an action potential is triggered, **voltage-gated** sodium ion channels open to allow for the flow of Na^+ ions into the cell, causing the membrane to become **depolarized** (a decrease in the voltage difference between the inside and outside of the cell) – reaching a final membrane potential of around +40mV. Potassium ion channels are still closed at this point.
3. **Repolarization**: this stage restores the membrane potential back to its resting state of -70mV immediately after complete depolarization (at the action potential peak) by closing sodium ion channels and opening potassium ion channels. For a short moment in time the neural membrane is **hyperpolarized** at around -80mV, at which point the potassium ion channels close and the membrane potential is slowly brought back to -70mV by the sodium-potassium pump.

Until resting potential is reached, the cell enters a **refractory period** in which another action potential cannot be produced until resting potential is restored. This also prevents the action potential from travelling backwards, maintaining its unidirectionality as it is propagated along nerve fibers.

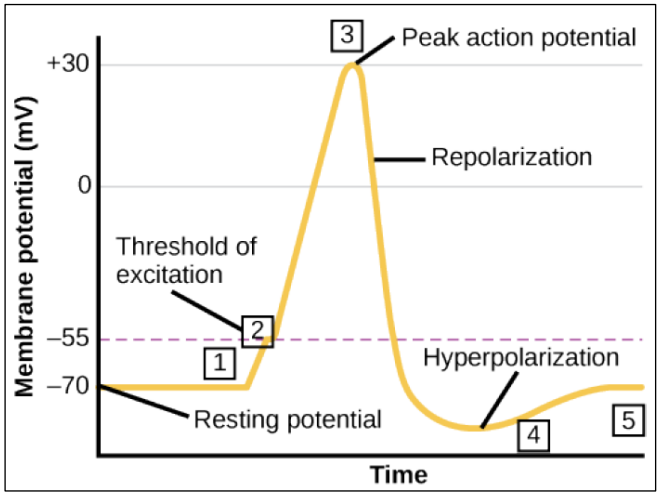

Figure 3: membrane potential of a neuron during an action potential (Ann Clarks).

C2.2.4–Variation in the speed of nerve impulses

Compare the speed of transmission in giant axons of squid and smaller non-myelinated nerve fibres. Also compare the speed in myelinated and non-myelinated fibres.
Application of skills: Students should be able to describe negative and positive correlations and apply correlation coefficients as a mathematical tool to determine the strength of these correlations. Students should also be able to apply the coefficient of determination (R^2) to evaluate the degree to which variation in the independent variable explains the variation in the dependent variable. For example, conduction speed of nerve impulses is negatively correlated with animal size, but positively correlated with axon diameter.

Some types of glial cells – **oligodendrocytes** in the CNS and **Schwann cells** in the PNS – produce a lipid-rich substance that surrounds the axon called the **myelin sheath**. This sheath acts as a barrier (electrical insulator) between the axon membrane and the extracellular matrix, preventing ions from entering or exiting, essentially blocking depolarization. This reduces the surface area of the axon membrane that needs to depolarize, resulting in a faster transmission of neural signals along nerve fibers. Hence, myelinated axons only depolarize at **Nodes of Ranvier**, which are small sections of the axon that are not covered with myelin.

This is useful for many organisms. For example, squids have giant axons with a diameter of 500 μm and a conduction rate of 25 m/s to allow them to escape from danger through their jet-propulsion response.

Factors affecting the velocity of action potentials include:

- **Myelination**: for example, myelinated axons can conduct neural signals at velocities up to 150m/s whereas unmyelinated axon velocities of conduction range from around 0.5 to 10m/s.
- **Axon diameter**: the larger the diameter of the axon the faster the transmission of the signal as the ions have more space to travel in and thus face less resistance.
- **Ion channel density**: higher density of sodium ion channels at Nodes of Ranvier allow for faster depolarization and thus transmittance of signals across the axon.

Determining whether a certain independent variable will affect action potential velocity can be done statistically through the **Coefficient of Determination**, **R^2**. This method evaluates the degree to which variation in the independent variable explains the variation in the dependent variable. This relationship between the two variables is represented by a number between 0 and 1 as found in the table below. For example, while the independent variable of axon diameter is positively correlated with conduction speed, the size of an animal is negatively correlated with it.

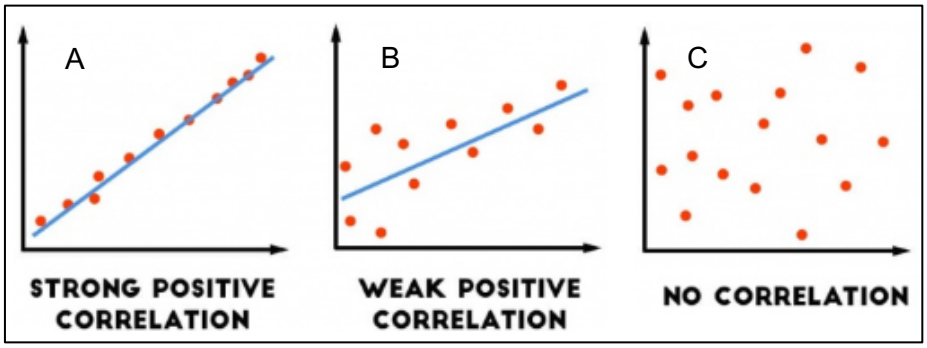

Figure 4: (A) R^2 = 0.90, (B) R^2 = 0.35, (C) R^2 = 0.00 (Shiebler).

Value of Coefficient of Determination (R^2)	Relationship between the two variables
0.85 – 1.00	Very Strong
0.60 – 0.84	Strong
0.40 – 0.59	Moderate
0.20 – 0.39	Weak
0.00 – 0.19	Very Weak

C2.2.5–Synapses as junctions between neurons and between neurons and effector cells

Limit to chemical synapses, not electrical, and these can simply be referred to as synapses. Students should understand that a signal can only pass in one direction across a typical synapse.

Synapses are junctions between neurons (sensory, interneural, motor) and between neurons and effector cells (muscles, glands). The synapse is usually only 20nm wide to allow for fast and unidirectional signal transmission. Chemical synaptic transmission involves the release of a neurotransmitter from the presynaptic membrane, transmitting it through the synaptic cleft (gap), receiving the neurotransmitter on the postsynaptic membrane, and depolarization of the postsynaptic neuron/effector cell.

C2.2.6–Release of neurotransmitters from a presynaptic membrane

Include uptake of calcium in response to depolarization of a presynaptic membrane and its action as a signalling chemical inside a neuron.

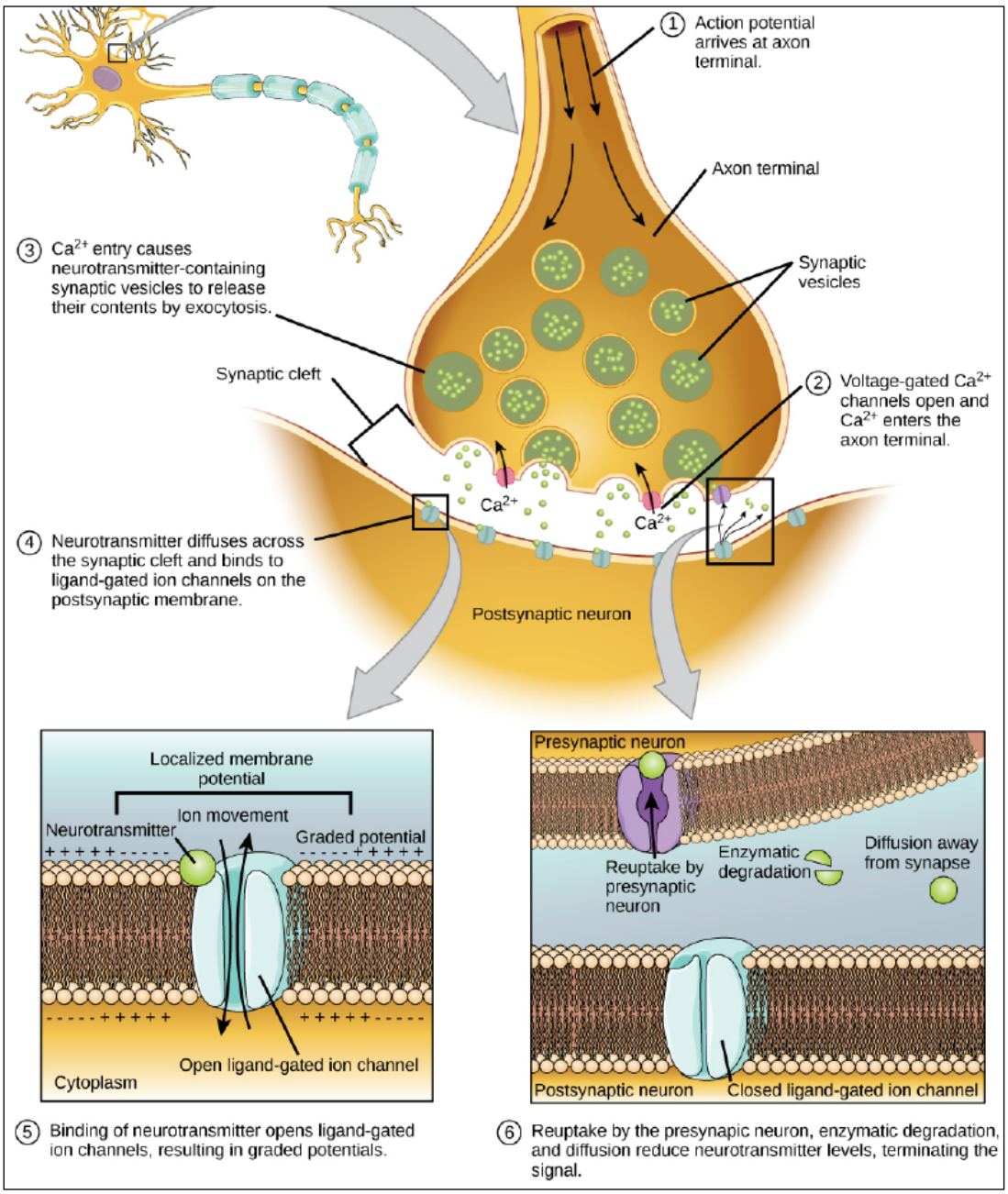

Figure 5: synaptic transmission visual process (Ann Clark).

Synaptic transmission occurs through the following steps:

1. The action potential reaches the axon terminal, causing the presynaptic membrane to depolarize
2. Depolarization causes voltage-gated calcium channels to open, allowing Ca^{2+} to diffuse in
3. Ca^{2+} ions act as second messengers by initiating a signalling cascade that causes **synaptic vesicles** containing neurotransmitters to release these neurotransmitters into the synaptic cleft via exocytosis

C2.2.7–Generation of an excitatory postsynaptic potential

Include diffusion of neurotransmitters across the synaptic cleft and binding to transmembrane receptors. Use acetylcholine as an example. Students should appreciate that this neurotransmitter exists in many types of synapse including neuromuscular junctions.

4. The neurotransmitter diffuses down its concentration gradient across the synaptic cleft (the extracellular space between the presynaptic and postsynaptic membranes) and binds to *ligand-gated* sodium ion channels on the postsynaptic membrane
5. Depolarization of the local postsynaptic membrane occurs if the neurotransmitter is an excitatory molecule, and if the threshold potential is reached an action potential is triggered and propagated away from the synapse and across the postsynaptic neuron's axon
6. To reset the postsynaptic neuron so it can be ready to receive another signal, the neurotransmitter must be removed from the synaptic cleft. This can be achieved in three ways (**DRD**):
    - **D**egradation through enzymes in the synaptic cleft
    - **R**ecycling (reuptake) by the presynaptic neuron
    - **D**iffusion of neurotransmitter away from synaptic cleft

For example, **acetylcholine** is an excitatory neurotransmitter used between neurons and muscle cells (neuromuscular junctions) to stimulate muscle contraction. Once they bind to their receptors on the postsynaptic membrane and cause depolarization, they are degraded by the enzyme **acetylcholinesterase** and the monomers are recycled by the presynaptic neuron.

Additional higher level

C2.2.8–Depolarization and repolarization during action potentials
Include the action of voltage-gated sodium and potassium channels and the need for a threshold potential to be reached for sodium channels to open.

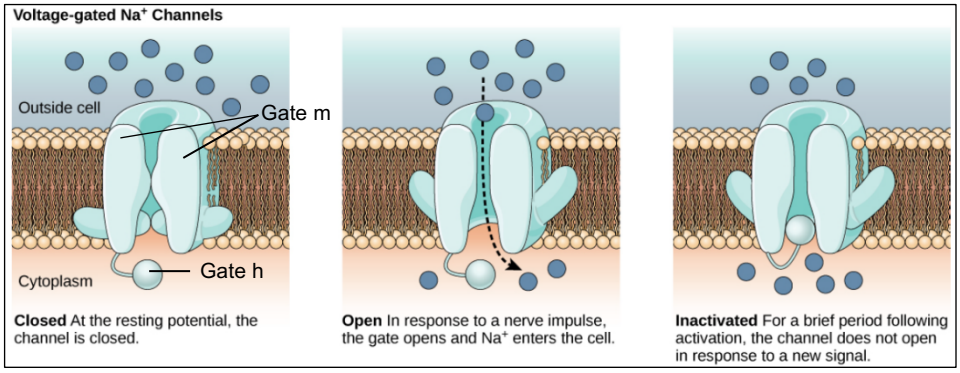

Figure 6: structure and function of voltage-gated sodium ion channels (Ann Clark).

The **threshold potential** is a certain critical membrane potential value (around -50mV) that needs to be reached in order for voltage-gated sodium ion channels to depolarize/open. Thus, a neuron *only* fires if the signal from the neurotransmitter is strong enough to reach the threshold potential.

Ligand-gated sodium ion channels respond to neurotransmitters whereas voltage-gated sodium ion channels respond to changes in the membrane potential. Thus, ligand-gated ones are found within the postsynaptic membrane and voltage-gated ones are found across the axon.

Voltage-gated sodium ion channels are made up of two subunits:

1. **Alpha (α) subunit**, which is the porous channel that is selectively permeable to Na^+ ions only
2. **Beta (β) subunit**, which is responsible for gating the alpha subunit and consists of two gates:
   - **Gate m** (the activation gate), which is normally closed and opens during depolarization
   - **Gate h** (the 'ball' or deactivation gate) which is normally open and closes (swings shut) at the action potential peak

Voltage-gated sodium ion channels exist in three primary states:

1. **Deactivated (Closed)** – the cell is at resting potential; gate *m* is closed and gate *h* is swinging open.
2. **Activated (Open)** – stimulated by a nerve impulse, both gates of the β subunit are open to allow Na^+ ions to flow through the α subunit
3. **Inactivated** – at the action potential peak, gate *h* swings shut while gate *m* remains open until the refractory period ends

Voltage-gated potassium ion channels also have a similar structure to sodium ion channels. Even though both sodium and potassium ions are small and positively charged, their channels are able to distinguish them from each other by accounting for the difference in ionic radius. This selectivity is accomplished through the primary, secondary, and tertiary structures of the voltage-gated channels that allows them to only attract their respective ions through their pores.

C2.2.9–Propagation of an action potential along a nerve fibre/axon as a result of local currents

Students should understand how diffusion of sodium ions both inside and outside an axon can cause the threshold potential to be reached.

When sodium ions diffuse through their channels during depolarization, that specific section of the membrane which has its sodium ion channels open becomes positively charged at around +40mV due to the large numbers of sodium ions that entered it. This establishes an electrochemical gradient between nearby areas of the membrane that are at resting potential, since the depolarized membrane is more positive *and* contains more sodium ions. Thus, sodium ions begin to diffuse into the nearby areas of the membrane, causing the threshold potential to be reached and depolarization to occur at the neighboring membrane area. Out of these two nearby areas, only one will depolarize, since the other side is at its refractory period.

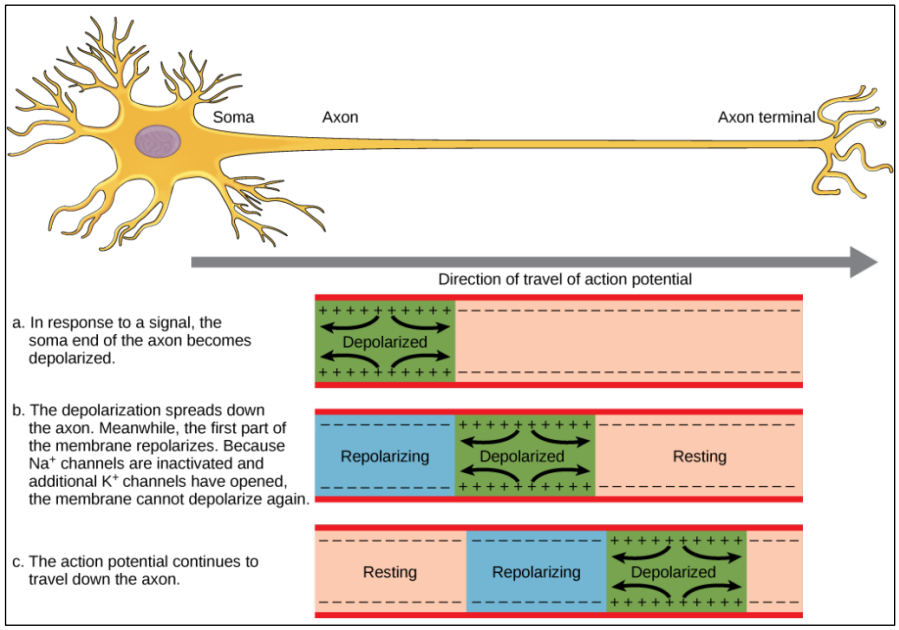

Figure 7: propagation of action potential an axon through local currents (Lumen Learning).

C2.2.10–Oscilloscope traces showing resting potentials and action potentials

Application of skills: Students should interpret the oscilloscope trace in relation to cellular events. The number of impulses per second can be measured.

Oscilloscopes measure membrane potential across time; the horizontal lines represent the resting potential whereas the spikes depict the action potential.

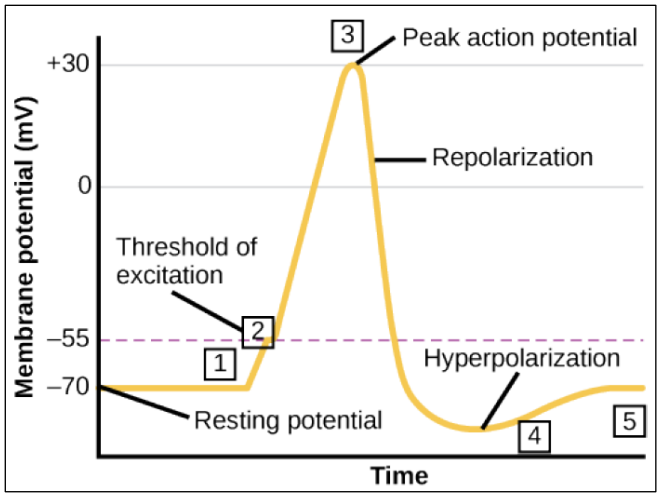

Figure 8: oscilloscope trace of an action potential (Ann Clarks).

C2.2.11−Saltatory conduction in myelinated fibres to achieve faster impulses

Students should understand that ion pumps and channels are clustered at nodes of Ranvier and that an action potential is propagated from node to node.

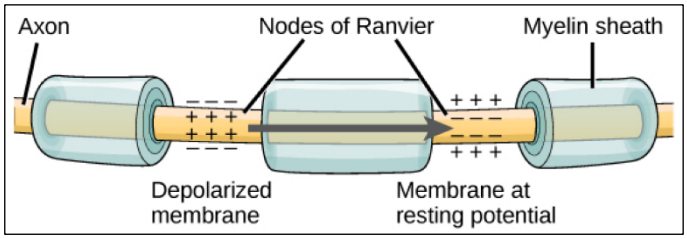

Figure 9: saltatory conduction in myelinated fibers (Ann Clark).

Nodes of Ranvier are gaps in myelin coverage along an axon and about one micrometer long. They provide insulation for the axon and increase the speed of action potential conduction by decreasing the membrane surface area needed to depolarize and propagate the neural signal. This allows the action potential to 'jump' or 'skip' the membrane area wrapped in myelin and cause depolarization only at nodes of Ranvier, which is called **saltatory conduction**. This type of conduction also saves energy for the neuron since the ion channels only need to be present at nodes of Ranvier and not along the whole axon.

C2.2.12−Effects of exogenous chemicals on synaptic transmission

Use neonicotinoids as an example of a pesticide that blocks synaptic transmission, and cocaine as an example of a drug that blocks reuptake of the neurotransmitter.

Exogenous chemicals are substances within an organism's body that have entered from an external source. Some of these chemicals can affect synaptic transmission by either promoting it or inhibiting it.

Nicotinoids are insecticides that bind to acetylcholine receptors in the CNS's **cholinergic synapses** (synapses that use acetylcholine as a neurotransmitter), preventing synaptic transmission. This leads to paralysis and eventual death. Nicotinoids are not very toxic to mammals and humans but very lethal to insects as they have more cholinergic synapses in their CNS, making them effective pesticides. However, their effects on non-insect species and the environment has sparked concern.

Cocaine is a stimulant psychoactive drug that prevents dopamine reuptake into the presynaptic neuron, causing it to accumulate in the synaptic cleft and leading to continuous excitation of the postsynaptic neuron. This gives false feelings of euphoria and pleasure.

C2.2.13—Inhibitory neurotransmitters and generation of inhibitory postsynaptic potentials

Students should know that the postsynaptic membrane becomes hyperpolarized.

Neurotransmitters that inhibit depolarization bind to the postsynaptic membrane and cause the opening of **chloride ion channels**. This leads to the influx of Cl^- ions into the cytoplasm, causing the membrane potential to become even more negative (**hyperpolarization**). As a result, this increases the amount of sodium ions needed to make the membrane potential positive enough for the threshold potential to be reached, making the neuron less likely to fire.

C2.2.14–Summation of the effects of excitatory and inhibitory neurotransmitters in a postsynaptic neuron

Multiple presynaptic neurons interact with all-or-nothing consequences in terms of postsynaptic depolarization.

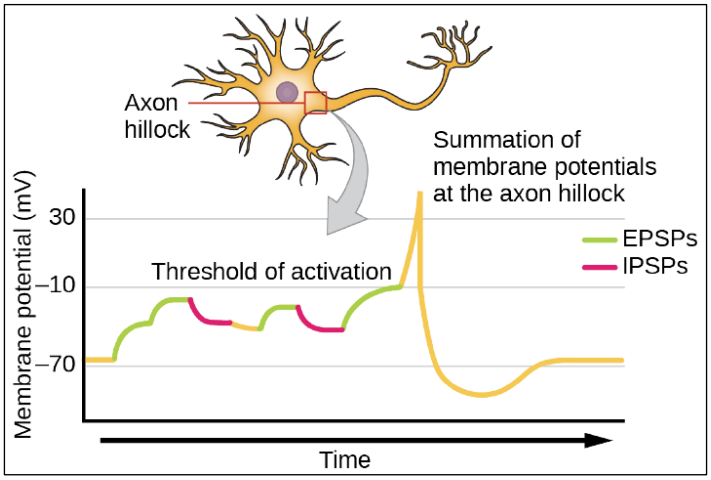

Figure 10: summation of membrane potentials at the axon hillock (Ann Clark).

Neurons receive input signals from multiple other neurons, which can be either **excitatory postsynaptic potentials (EPSPs)** or **inhibitory postsynaptic potentials (IPSPs)**. EPSPs cause depolarization whereas IPSPs cause hyperpolarization, and they both cancel out each other's effects (for example, if an EPSP caused the membrane potential to increase by 10mV and an IPSP caused it to decrease by 10mV, net change in membrane potential is 0).

These inputs are added together at the axon hillock in a process called **summation**. If the EPSPs are strong enough to overcome IPSPs and reach threshold potential at the axon hillock, an action potential is propagated along the axon. If the IPSPs are stronger, hyperpolarization occurs and no action potential is triggered. Hence, multiple presynaptic neurons interact with all-or-nothing consequences in terms of postsynaptic depolarization.

C2.2.15–Perception of pain by neurons with free nerve endings in the skin

Students should know that these nerve endings have channels for positively charged ions, which open in response to a stimulus such as high temperature, acid, or certain chemicals such as capsaicin in chilli peppers. Entry of positively charged ions causes the threshold potential to be reached and nerve impulses then pass through the neurons to the brain, where pain is perceived.

Perception of sensations like pain, taste, and smell occur through receptors in skin nerve endings. These receptors detect the specific sensation (for example, pain receptors detect the chemical within hot spices) and open in response to the stimulus, allowing positively charged ions to flow into the neuron. This causes the threshold potential to be reached and nerve impulses then pass through the neurons to the brain, where pain is perceived.

C2.2.16—Consciousness as a property that emerges from the interaction of individual neurons in the brain

Emergent properties such as consciousness are another example of the consequences of interaction.

Consciousness is a property of the human body that emerges from the interaction of all individual neurons in the brain. Like other emergent properties, it only occurs due to interaction and interdependence of billions of cells in the body.

Linking questions

• In what ways are biological systems regulated?

• How is the structure of specialized cells related to function?

Review questions

SL and HL

- State the type of cell(s) found in nervous tissue. [1]
- Outline how membrane potential is measured. [2]
- Lidocaine is an anesthetic drug that reduces the influx of sodium ions by targeting voltage-gated sodium ion channels. Outline the consequences of this drug on pain signals in patients. [2]
- Even though pain was the first sensation to evolve, it is one of the slowest to be transmitted throughout the human body compared to the sense of touch. Outline the potential evolutionary advantages of having such differences in signal transmission. [2]
- Procainamide is a potassium channel blocker used to treat abnormal electrical activity in the heart by impeding the movement of potassium ions through voltage-gated channels. Outline the part of the action potential that would be affected by this drug. [2]
- Outline how the resting membrane potential is maintained. [2]
- Multiple sclerosis (MS) is an autoimmune disease in which the antibodies produced by the immune system's lymphocytes mark the myelin sheath in the CNS as a foreign body, causing its destruction. Outline the consequences of MS, suggesting symptoms. [3]
- Describe the structure of a neuron. [3]
- Explain how the sodium-potassium pump maintains electrochemical gradients in neurons. [4]
- Explain the roles of membrane proteins before, during, and after neural firing. [6]
- Explain how electrical signals are generated and moved within neurons. [7]
- Explain how neurons communicate with other cells in the human body. [8]

Additional Higher Level

- State two examples of an emergent property in humans. [1]
- State how consciousness occurs in the human body. [1]
- Distinguish between the roles of voltage-gated and ligand-gated sodium ion channels. [2]
- Outline the perception of pain in free nerve endings within the skin. [3]
- Explain the role of saltatory conduction in nerve cells. [3]
- Explain how action potentials are propagated along a neuron. [3]
- Hormonal regulation in the endocrine system often involves balancing stimulating and inhibiting signals to maintain homeostasis. Similarly, EPSPs and IPSPs in neurons also help balance the signals within the nervous system. Explain the evolutionary advantages of such dual regulatory systems in living organisms. [3]
- Explain the effect of one excitatory and one inhibitory exogenous chemical on synaptic transmission in living organisms. [4]
- Explain how inhibitory neurotransmitters prevent a neuron from depolarizing. [4]
- Epilepsy is a condition where nerve cells in the brain fire too much, causing seizures. Explain the importance of a balance between EPSPs and IPSPs in managing this disease, and suggest how Phenytoin, a drug that reduces the frequency of action potentials, may help. [4]
- Explain how the structure of neurons is related to their function. [5]
- Describe how multiple transmembrane proteins regulate membrane potentials in neurons. [8]

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