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Physiology of excitable tissue

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The four basic types of tissue found in the body are connective tissue, epithelial tissue, muscle tissue, and nervous tissue. Nerves and muscles are capable of generating and propagating action potentials (APs). They are therefore called excitable tissues. Excitation of these tissues may be electrical, chemical, or mechanical. The human body relies on the proper functioning of excitable tissues to facilitate vital physiological processes, including muscle contraction, nerve conduction, and cardiac activity.[1,2]

Nerve tissue comprises neurons, which are responsible for transmitting electrical signals, while muscle tissue generates mechanical force in response to electrical stimulation. These tissues share common characteristics related to their excitability, AP generation, and conduction properties.[1,2] The ability of excitable tissue to generate and propagate APs depends upon the electrical properties of the cell membrane at rest.[3]

The resting membrane potential (RMP)

An electrical potential difference exists across all cell membranes. The RMP of a cell is defined as the electrical potential difference across the cell membrane when that cell is in a non-excited state.[1,2]

The cytosol along the inner surface of the membrane has a negative charge compared to the outside. Excitable tissues have a more negative RMP when compared to non-excitable tissues. The negative RMP is an absolute requirement for a functioning nervous system and is generated by the distribution of certain important ions across the cell membrane. The RMP in the neuron is -70 millivolts (mV) and -90 mV in skeletal and cardiac muscle fibres.[1–3]

The RMP of a cell depends on the ionic distribution across the membrane, the membrane permeability, and other factors like the presence of ion channels and the sodium-potassium (Na^+/K^+) pump.[1]

Movement of ions

Most electrically charged ions on either side of a phospholipid bilayer membrane can only pass across the membrane through protein/ion channels as the membrane is only semipermeable to ions. Although ion channels allow the movement of ions across the cell membrane, the mere opening of these channels does not result in the movement of ions across the membrane. Instead, an external force, more often a chemical or electrical gradient, is required to drive this movement.[1–3]

The chemical movement of ions (diffusion): Diffusion entails ions shifting from high to low concentration areas, usually through the ion-permeable channels.[1,3]

The electrical movement of ions: Ions, being electrically charged, move continuously across the phospholipid bilayer in response to an applied electrical field, until an electrochemical equilibrium is reached.[1,3]

At equilibrium, the chemical driving force is balanced by the electrical driving force of an ion.[1] The Gibbs-Donnan theory describes the unequal distribution of permeant charged ions on either side of a semipermeable membrane, which occurs in the presence of impermeant charged ions. In this state, the electrical and chemical energies on both sides of the membrane are balanced despite the difference in ion concentrations on either side of the membrane.[1]

If the relative concentration of an ion across a cell membrane is known, the Nernst equation can be used to calculate the equilibrium potential (Nernst potential) of that ion along this membrane (Figure 1a). The Nernst potential denotes the precise potential difference across the membrane that prevents the overall movement of an ion in either direction through the membrane. This concept is valuable for understanding how ions contribute to the electrical behaviour of excitable cells.[1–4] When using this equation, the calculated Nernst potential is the potential inside the membrane, and the sign of the potential is positive if the ion under consideration is a negative ion, and negative if it is a positive ion.[1,3]

Understanding the Nernst equation and equilibrium potentials explains how changes in ion concentrations or shifts in ion channel permeability impact the electrical excitability and functioning of excitable tissues. Given that, at a state of rest and

a) The **Nernst equation** for any univalent ion at a normal body temperature of 37°C:

$$\text{EMF(millivolts)} = \pm 61 \log \frac{C1}{C2}$$

Where:
EMF is the electromotive force (voltage) for the ion of interest.
C1 is concentration of the ion inside.
C2 is the concentration of the ion outside.

b) The **Goldman constant field equation** (Goldman- Hodgkin-Katz equation):

$$\text{EMF (millivolts)} = -61 \times \log \frac{C_{Na_i^+} P_{Na^+} + C_{K_i^+} P_{K^+} + C_{Cl_o^-} P_{Cl^-}}{C_{Na_o^+} P_{Na^+} + C_{K_o^+} P_{K^+} + C_{Cl_i^-} P_{Cl^-}}$$

Where:
P is permeability to each ion
C is concentration of each ion

Figure 1: Nernst and Goldman constant field equations

normal body temperature, the cell membrane is predominantly permeable to potassium ions, it is understandable that the calculated Nernst potential of -80 mV for potassium aligns closely with the RMP observed in many excitable cells.[1,3]

As the membrane is permeable to several different ions, the actual RMP that develops depends on the polarity of each ion, the membrane permeability of each ion, and the ionic concentration on either side of the membrane. This can be calculated using the Goldman constant field equation (Figure 1b).[1,3]

Ion channels and pumps

An ion channel is a protein-based "channel" consisting of four to six protein molecules that traverse the cell membrane, allowing the transit of one or more ions. The configuration of these subunits varies across different channels.[1–4]

The sodium-potassium pump (Na^+/K^+ pump)

All cell membranes contain a potent electrogenic pump reliant on energy – the Na^+/K^+ pump. This pump operates continuously, pumping $3Na^+$ ions out of the cell while pumping in $2K^+$ ions. Consequently, a surplus of positive ions outside the cell leads to a negative intracellular charge. Additionally, this pump gives rise to substantial concentration differences of Na^+ and K^+ across the resting membrane.[1,2]

The potassium-sodium "leak" channel (K^+/Na^+ "leak" channels)

These channels are around 100 times more permeable to K^+ compared to Na^+, resulting in a much greater leakage of K^+ ions than Na^+ ions during rest. Thus, the diffusion of K^+ makes a significantly more substantial contribution to the RMP when compared to the diffusion of Na^+.[1,2]

Voltage-gated sodium channels (Na^+ channels)

The voltage-gated Na^+ channel has two gates: the activation gate, positioned near the outside of the channel; and the inactivation gate, situated closer to the inside of the channel. When the cell is at rest, the activation gate remains closed, preventing the influx of Na^+ ions. As the membrane potential becomes less negative (between -70 and -50 mV), the activation gate undergoes a conformational change, allowing it to open. This change in voltage also results in a conformational change of the inactivation gate leading to its closure, albeit at a slower pace. This means the inactivation gate takes a fraction of a second longer to close compared to the time it takes for the activation gate to open, allowing Na^+ to leak in. The inactivation gate remains closed until the membrane potential reverts to or closely approaches the original RMP.[1,2]

The operational behaviour of Na^+ channels is influenced by the concentration of extracellular calcium (Ca^{2+}). A reduction in extracellular Ca^{2+} levels enhances the ease of activation of Na^+ channels, causing them to open with a lesser alteration in the membrane potential. As a result, nerve fibres become notably more excitable in patients with hypocalcaemia.[2]

Voltage-gated potassium channels (K^+ channels)

The voltage-gated K^+ channel has one gate that remains closed during the resting state. When the membrane potential becomes less negative, this gate undergoes a slow conformational change, occurring as the Na^+ channels close, resulting in the gate opening and allowing K^+ ions to diffuse outwards.[1,2]

The calcium pump (Ca^{2+} pump)

Almost all cell membranes have a Ca^{2+} pump, like the Na^+ pump, that pumps Ca^{2+} out of the cell.[1,2]

Voltage-gated calcium channels (Ca^{2+} channels)

These are found predominantly in cardiac and smooth muscle. They are partially permeable to Na^+ and permeable to Ca^{2+}. They are called slow channels as they take 10 to 20 times longer than the Na^+ channels to open. When they open, both Na^+ and Ca^{2+} flow inside.[1,2]

The AP

Signals are transmitted by APs, which are simply rapid, brief reversals of the RMP so the inside of the cell becomes positive compared to the outside and then ends with an almost equally rapid change back to the negative potential.[3] APs occur to produce physiological effects, such as the transmission of

impulses along nerve fibres, the release of neurotransmitters, muscle contractions, and activation or inhibition of glandular secretions.[1–4]

Stages of the AP (Figure 2)

Resting stage: The membrane is "polarised" during this stage with a negative membrane potential. The voltage-gated Na^+ channel has its activation gate closed and its inactivation gate opened. The voltage-gated K^+ channel is closed.[1–4]

Depolarisation stage: During this stage, any event causing the membrane potential to become less negative results in a conformational change in the activation gate of the voltage-gated Na^+ channel, causing it to open, increasing the membrane's Na^+ permeability by as much as 500–5 000-fold. With the movement of Na^+ ions inside, the membrane potential rises rapidly in the positive direction. In large nerve fibres, the membrane potential overshoots beyond the zero level and becomes slightly positive. In smaller fibres, the membrane potential merely approaches the zero level and does not overshoot to the positive state.[1–4]

Plateau (only in some APs) (Figure 3): This occurs when the excitable membrane does not repolarise immediately after depolarisation but instead the potential remains on a plateau near the peak of the spike for a few milliseconds before repolarisation. This occurs in heart muscle because of two factors: firstly, the presence of slow voltage-activated Ca^{2+} channels; and secondly, the K^+ channels are slower to open, thus delaying the return of the membrane potential to the resting state. The slow Ca^{2+} channels start opening later than the Na^+ channels and allow the movement of Ca^{2+} and a little Na^+ into the cell. They also remain open for longer, thus resulting in the plateau of the AP.[1,2]

Repolarisation stage: In most APs during this stage (a fraction of a second after the activation gate of the Na^+ channel opens) the inactivation gate of the Na^+ channels begins to close and the voltage-gated K^+ channels open. This allows rapid diffusion of K^+ to the outside, which re-establishes the normal negative RMP (repolarisation of the membrane).[1–4]

"Positive" afterpotential/hyperpolarisation: After repolarisation, the membrane potential becomes more negative than the original RMP for a few milliseconds. This occurs because the voltage-gated K^+ channels remain open for a few milliseconds after repolarisation, allowing K^+ to flow out and make the inside more negative.[1,3]

Propagation of the AP: An AP elicited at a point on an excitable membrane will usually excite the adjacent portions, which will result in the propagation of the AP. This propagation will occur in both directions away from the stimulus until the entire membrane has been depolarised. The depolarisation process that travels along the length of the nerve or muscle fibre is called a nerve or muscle impulse. In the neuron, a nerve impulse carries information along the neuron to the central nervous system (sensory fibre) or they conduct signals from the central nervous system to the periphery (motor fibre). In the muscle cell, the

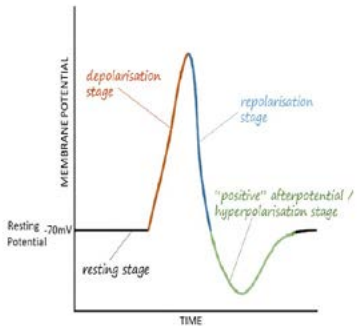

Figure 2: Stages of an AP

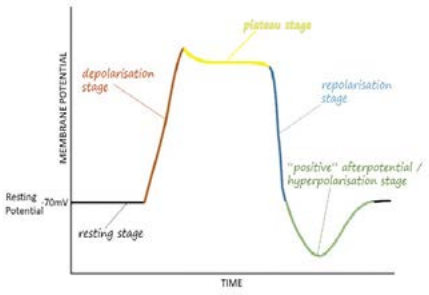

Figure 3: AP with plateau phase

muscle impulse spreads all over the muscle to initiate muscle contraction required for all motor activities. The duration of APs in skeletal muscle and neurons is about five milliseconds.[1,2]

Recharging: Finally, the Na^+ and K^+ ion concentration differences across the membrane need to be re-established. This is achieved by the energy-requiring Na^+/ K^+ pump, pumping Na^+ out of and K^+ into the cell. The activity of the Na^+/ K^+ ATPase pump increases approximately in proportion to the third power of the increase of the Na^+ concentration inside the cell.[4]

Important terminology (Figure 4)

The threshold for initiation of an AP: The membrane potential at which the occurrence of the AP is inevitable. This occurs when enough voltage-gated Na^+ channels are opened, resulting in the relative ionic permeability of the membrane favouring Na^+ over K^+.[1–3]

Acute subthreshold potential: If a stimulus does not result in the threshold current being reached, then an AP will not be generated.[1–3]

Accommodation of the membrane: If the stimulating current rises too slowly, then an AP will not be generated because the neuron will adapt. This occurs because the inactivation Na^+ gates start to close during depolarisation and remain closed.[3]

All-or-nothing principle: Once the threshold value for excitation is reached, a full AP is produced. Any further increases in stimulation intensity will not result in any change in the AP.[1–3]

Absolute refractory period: The period during which a second AP cannot be elicited, even with a strong stimulus. Voltage-

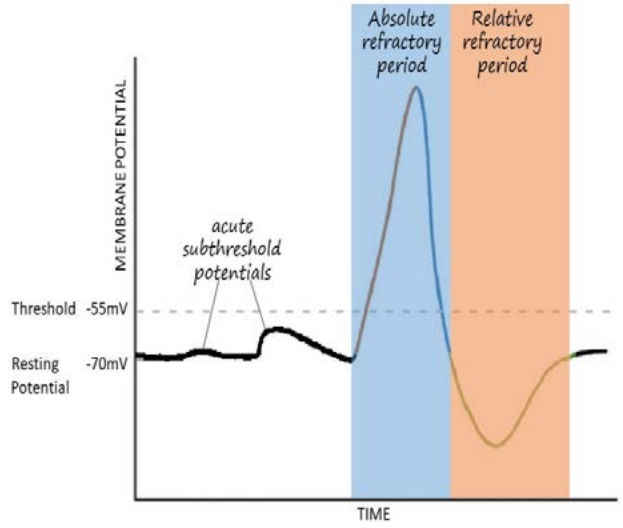

Figure 4: Acute subthreshold potentials, absolute and relative refractory periods

gated Na^+ channels are inactivated by a strongly depolarised membrane. Therefore, they cannot be activated until the membrane potential has become sufficiently negative.[1–3]

Relative refractory period: New APs can be triggered if the stimulus is greater than normal. In this period the membrane is hyperpolarised due to the continued activation of voltage-gated K^+ channels, but voltage-gated Na^+ channels are reactivated.[1–3]

Generation of multiple APs: Multiple APs will be produced if a stimulating current is applied to a neuron. The frequency of firing will increase in proportion to the magnitude of the stimulus current until a maximum firing frequency is reached (usually around 100 Hz).[3]

Orthodromic conduction: In humans and other mammals, conduction is normally in one direction only, from a receptor or synapse to their termination. Conduction in the other direction (antidromic conduction) will be prevented by the first synapse encountered.[3]

Saltatory conduction (Figure 5)

The speed at which an AP propagates in nerves depends on the axon diameter and whether it is myelinated or not. The larger the axon diameter, the faster the conduction of the impulse.[3]

Myelin is a fatty substance that forms a protective sheath around the axons of neurons. Schwann cells are a type of glial cell found in the peripheral nervous system (PNS). Schwann cells play a crucial role in the formation and maintenance of myelin sheaths around axons in the PNS. Oligodendrocytes form myelin around neurons in the central nervous system. Nodes of Ranvier are small gaps or interruptions in the myelin sheath along the length of an axon.[5]

Myelin is an extremely effective insulator that prevents APs from being transmitted regularly along the neuronal cell membrane. The AP "jumps" from one node of Ranvier to the next. This is called saltatory conduction. In this situation, the current sink

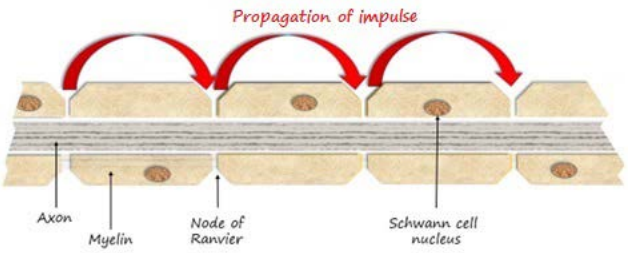

Figure 5: Saltatory conduction

at one node of Ranvier acts to depolarise the cell membrane at the next node. Saltatory conduction velocities may be up to 50 times faster than unmyelinated nerve conduction velocities and conserve energy because only the nodes depolarise.[1–5]

Synaptic transmission

A synapse, also known as a neuronal junction, is where electrical nerve impulses are transmitted between two neurons or between a neuron and a muscle cell or gland. When a neuron connects with a muscle cell, it forms a neuromuscular junction.[1,2]

Two primary categories of synapses

Electrical synapses: These occur when two cells are interconnected through gap junctions. These junctions facilitate the flow of current between cells via nonselective pores.[2]

Chemical synapses: In this type of synapse, a chemical transmitter is released by one cell and it influences the activity of another cell. Chemical synapses exhibit the following functional characteristics:

- neurotransmitter chemicals are stored in vesicles within the presynaptic terminals;
- the synaptic cleft refers to the small gap that separates two adjacent neurons; and
- the postsynaptic neuron is the recipient of the chemical signal.

When APs occur in the presynaptic cell, they trigger the release of chemical neurotransmitters. This neurotransmitter traverses the narrow synaptic cleft and binds to specific receptors on the postsynaptic cell. Excitatory neurotransmitters, like glutamate, elicit an excitatory postsynaptic potential, while inhibitory neurotransmitters like gamma-aminobutyric acid (GABA) generate an inhibitory postsynaptic potential.[1,2]

The neuromuscular junction

Skeletal muscle fibres are voluntary muscles innervated by motor neurons. When a motor neuron reaches a muscle, its axon transforms where the myelin sheath stops and the axon branches out into multiple extensions. Each of these branches forms a distinct connection with an individual muscle fibre. This point of connection between the motor neuron and the muscle fibre is referred to as the neuromuscular junction.[2]

Upon the arrival of an AP at the axon terminal of a motor neuron, acetylcholine (ACh) is released. ACh binds to the plasma

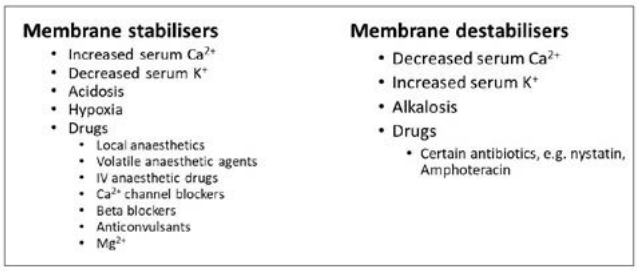

Figure 6: Membrane stabilisers and destabilisers[1,2,4]

membrane of the muscle, resulting in the opening of Na^+ channels. This event triggers an AP in the muscle membrane, which then propagates throughout the entire muscle fibre via transverse tubules (t-tubules). This propagation sets in motion the process of muscle contraction, known as excitation-contraction coupling.[1,2]

Effects of anaesthetic agents on excitable tissue

Anaesthetic agents exert their effects on excitable tissue by modulating ion channels and altering neurotransmitter function. For example, inhalational anaesthetics enhance the inhibitory function of GABA receptors, resulting in neuronal hyperpolarisation and decreased excitability. Intravenous anaesthetics, such as propofol and barbiturates, potentiate inhibitory neurotransmission through GABA receptors too. Local anaesthetics block voltage-gated Na^+ channels, preventing the generation and conduction of APs in sensory neurons.[6]

Membrane stabilisers and destabilisers (Figure 6)

Membrane stabilisers and destabilisers affect the RMP and AP of cells. Membrane stabilisers increase the threshold for depolarisation and decrease the rate of rise of the AP. Conversely, membrane destabilisers decrease the threshold for depolarisation and increase the rate of rise of the AP.[1,2,4]

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