Action potential: generation and propagation

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Abstract

In the normal resting state, the plasma membrane of nerve and muscle cells generates a transmembrane electrical potential difference – the intracellular surface of the membrane being approximately 70 –80 mV negative to the extracellular surface. This is a result of markedly different concentrations of ions inside and outside the cell, together with different membrane permeabilities to different ions that permits K^+ to flow down their concentration gradient from inside to outside the cell. Nerve and muscle cells are 'excitable' because they can react to external stimuli by generating an extremely rapid change in transmembrane electrical potential difference known as the action potential. This comprises an initial explosive increase in membrane Na^+ permeability that allows these ions to flood down their concentration gradient into the cell, thereby depolarizing the membrane such that the potential difference is transiently reversed to a positive value. However, in nerve and skeletal muscle this lasts for only a millisecond, at which time the membrane potential is just as rapidly restored to its resting negative value (repolarization). These events are controlled by the brief opening and closing of voltage-activated sodium and potassium channels in the membrane. The key features of the action potential are that it is: (i) an all-or-none event, rather than a graded response; (ii) it is self-propagating, such that the wave of depolarization travels rapidly along the plasma membrane; and (iii) it is transient, such that membrane excitability is quickly restored. These features of the action potential allow rapid transfer of information along nerve axons in the nervous system.

Keywords Action potential; depolarization; membrane potential; potassium ions; repolarization; sodium ions; voltage-activated ion channels

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Learning objectives

After reading this article, you should be able to:

- describe the resting membrane potential of excitable tissues in terms of membrane permeability and the status of the sodium and potassium channels traversing the membrane
- account for the action potential in terms of changing membrane permeability and status of these channels
- illustrate the process by which an action potential is transmitted along an unmyelinated fibre and to be able to compare it with saltatory conduction. Also, to be able to explain the advantage of myelinated compared to unmyelinated fibres

It is normal for most cells to possess an electrical potential (voltage) gradient across the plasma membrane, such that the interior is electrically negative to the exterior. In 'excitable' (nerve and muscle) cells this potential difference, together with the operation of specialized membrane ion channels, is used to generate action potentials (i.e. transient membrane depolarizations that propagate along the length of the cell in order to transmit information [in neurones] or trigger muscle cell contraction).

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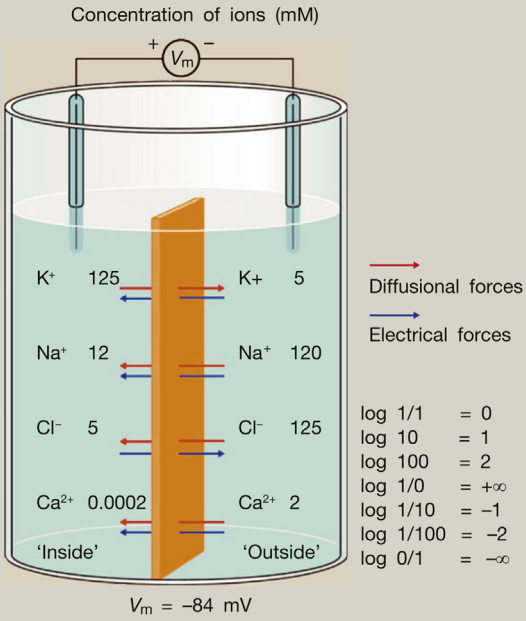
The resting membrane potential

An electrical potential difference exists across the plasma membrane of all living cells by virtue of differences in the concentration of charged ions in the cytosol and in the interstitial fluid and differences in membrane permeability to these ions. The two ions mainly involved in establishing a resting potential (and generation of action potentials) are K^+ and Na^+. Imbalances in the concentrations of these ions either side of the plasma membrane are created by the operation of an ionic 'pump' located in the membrane. This is the Na^+, K^+-ATPase protein, which uses energy from adenosine triphosphate (ATP) molecules to actively pump Na^+ out of the cell (simultaneously K^+ are pumped in at a 3:2 ratio, i.e. for every 3 Na^+ pumped out, 2 K^+ are pumped in). Therefore, the intracellular K^+ concentration is approximately 20-fold higher than the extracellular concentration, whereas the concentration (or 'chemical') gradient for Na^+ runs in the opposite direction (approximately a tenfold excess outside the cell compared with the interior). The resting membrane potential difference of approximately –70 mV (the cell interior is negative relative to the exterior) arises largely because of the fact that the cell membrane is relatively permeable to K^+ (owing to the presence of 'leak' potassium channels in the membrane), but not to Na^+ since the channels that would allow movement of Na^+ are normally closed in the resting state. Therefore, K^+ are able to flow down their concentration gradient (from inside to outside the cell) and generate a membrane potential. Negatively charged ions cannot move through the membrane, which creates a slightly excess negative charge inside the cell and a slightly excess positive charge outside. Because K^+ are allowed to move across the membrane, the resting membrane potential is similar to the 'ionic equilibrium potential' for K^+ (Figure 1). At rest, relatively few Na^+ move across the membrane because the channels that allow this ion to cross are predominantly closed. However, the electrochemical gradient (combined chemical and electrical gradients) would favour the movement of Na^+ from the outside to the inside of the cell. The sodium ions 'want' to move from a region of high concentration (outside the cell) to low concentration (inside the cell) – and they are also driven to move down a gradient of electrical potential (towards the negatively charged interior of the cell). The basis of the action potential is the abrupt opening of sodium channels in the membrane, allowing Na^+ to 'flood' down these gradients into the cell and to depolarize the membrane.

Distribution of ions across the plasma membrane



A representation of the excitable cell membrane which acts as a barrier that is selectively permeable to the main ions contributing to excitable cell function. The approximate normal concentrations of these ions are shown inside and outside the cell. V_m, the resting membrane potential, is due largely to the movement of K^+ down their concentration gradient (through leak channels), creating a potential difference across the membrane. At a certain membrane potential (the equilibrium potential), the movement of K^+ ceases because at that point the electrical potential tending to attract ions back into the cell exactly balances the tendency of the ions to move down their concentration gradient. For any ion, its equilibrium potential can be calculated from the Nernst equation:

$$E = 2.303 \frac{RT}{zf} \log \frac{[ion]_o}{[ion]_i}$$

where R = the gas constant
T = absolute temperature
z = charge valency of the ion (i.e. 1 for Na^+, 2 for Ca^{2+} etc.)
F = Faraday's constant
log = log to the base 10
$[ion]_o$ = ion concentration outside the cell
$[ion]_i$ = ion concentration inside the cell

At normal body temperature, the constants can be summarized in a single number to give:

$$E = 61.54 \log \frac{[ion]_o}{[ion]_i} \text{ (for a monovalent ion) or}$$

$$30.77 \log \frac{[ion]_o}{[ion]_i} \text{ (for a divalent ion)}$$

Substituting the values in the figure for K^+ concentrations gives an equilibrium potential for potassium ions of –86 mV, which is a close approximation of the resting membrane potential. The values do not coincide precisely because the membrane is not completely impermeable to other ions such as Na^+, so the actual resting potential is the overall result of several types of ion moving down their concentration gradients. The Goldman equation (a refinement of the Nernst equation) takes into account the relative membrane permeabilities of different ions as well as their concentrations to give an accurate calculation of the resultant membrane potential.

Figure 1

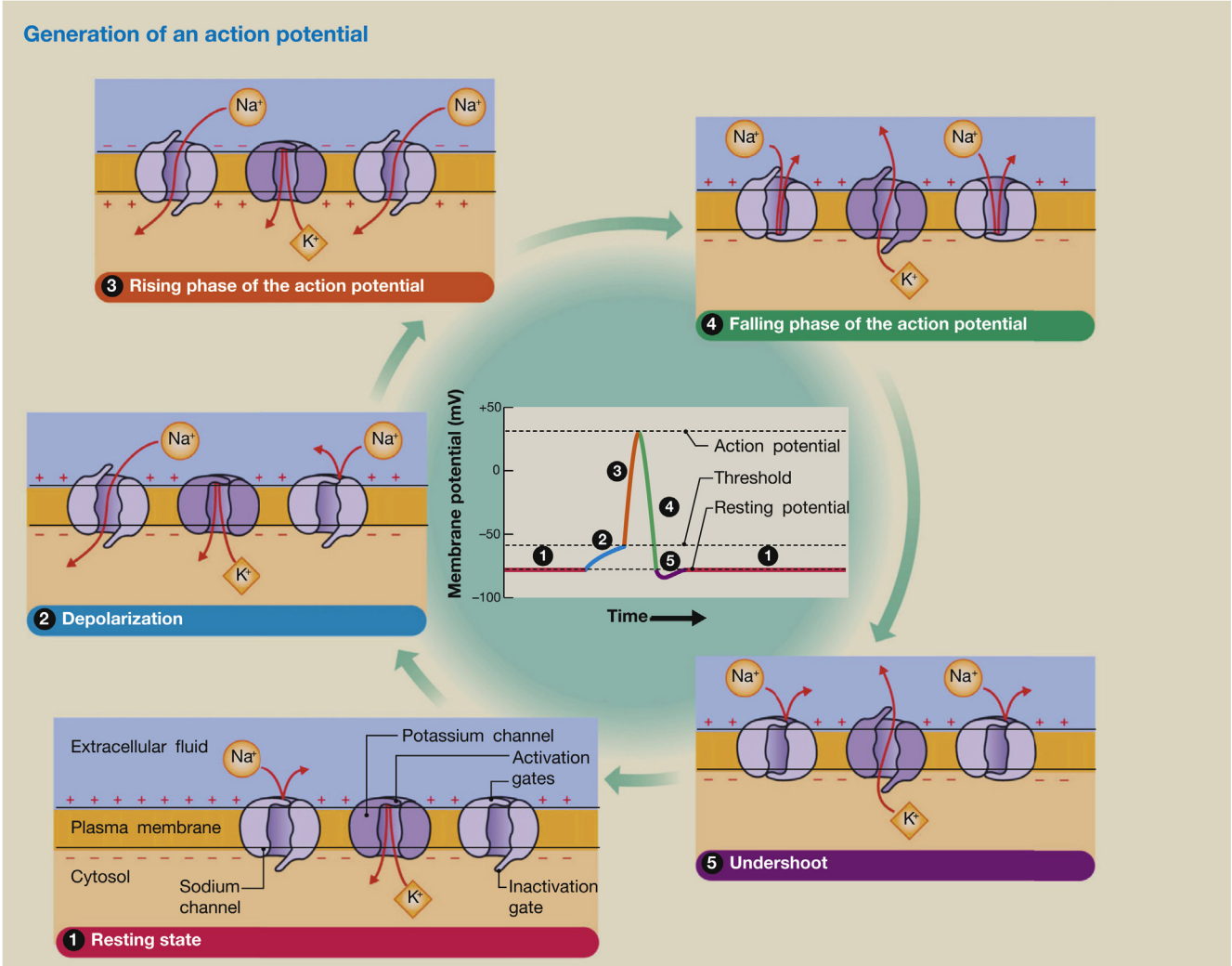
Membrane depolarization and the action potential

In addition to the membrane potassium channels mentioned above, there are also many other types of ion channel embedded in the phospholipid matrix of the plasma membrane. One of these channels, the voltage-gated sodium channel, is selectively permeable to sodium ions but is normally closed. If the membrane is depolarized by approximately 20 mV (say from −70 mV to −50 mV) to attain a 'threshold' potential, an action potential is triggered by the abrupt opening of these channels, allowing Na^+ to rush inside the cell and depolarize the membrane (i.e. the influx of positively charged sodium ions 'cancels out' the excess negative charge inside the cell, and even reverses the potential difference such that the interior becomes slightly positively charged — the membrane potential 'overshoots' neutrality). Another way of considering this is that, once the Na^+ are free to pass through the membrane, their movement takes the membrane potential towards the equilibrium potential for Na^+ (which is approximately +60 mV). However, this is a very transient situation because no sooner have the sodium channels opened than they close again (after a period of only about 1 ms). An efflux of K^+ then rapidly and effectively restores the resting membrane potential difference (i.e. the membrane is rapidly repolarized). The efflux of K^+ is mediated not only by the leak channels (described above), but also by the opening of voltage-gated potassium channels that open as the sodium channels are closing. Therefore, potassium ions can move down an electrochemical gradient from high concentration (inside the cell) to low concentration (outside the cell) and from the now positively charged interior to the negatively charged exterior. Because the voltage-gated potassium channels open after a short delay, the resultant flow of potassium ions is referred to as the 'delayed rectifier current'. Over the short timescale of this process, the operation of the Na^+, K^+-ATPase ionic pump plays an insignificant role in membrane repolarization (the overall number of ions that move across the membrane during the action potential is very small relative to the total concentrations in the cytosol and interstitial fluid, and they tend to remain close to either surface of the plasma membrane such that the bulk of cytoplasm and interstitial fluid is electrically neutral).

The extracellular concentration of K^+ must be critically controlled because of the relatively high permeability of the plasma membrane to these ions. An excessive rise in extracellular K^+ concentration would result in the ions flowing into the cell, causing uncontrolled membrane depolarization. Conversely, an excessive decrease in extracellular K^+ concentration would result in an efflux of K^+, causing membrane hyperpolarization (and, therefore, lack of response to normal depolarizing stimuli).

Propagation of the action potential

The process described above is restricted to a small region of the membrane where sodium channels are opened temporarily to depolarize the membrane transiently. However, a key feature of the action potential is that it is self-propagating (i.e. depolarization of a small region of the membrane triggers the opening of adjacent sodium channels — and so on — such that a wave of depolarization travels along the length of the cell; Figure 2). Furthermore, the wave of depolarization cannot 'double back' upon itself because once an action potential is triggered in one region of the membrane, the voltage-gated sodium channels become temporarily unresponsive to further stimuli (inactivated) and that region of membrane is said to be 'refractory' to further depolarization until



The voltage changes occurring across the membrane as recorded from an intracellular microelectrode following amplification and display on an oscilloscope are shown in the centre. The initial resting potential (1) is approximately –75 mV, at which time both the voltage-gated sodium and potassium channels are closed (centre diagram 1); the open 'leak' potassium channels are not shown. Note that there are two separate mechanisms controlling the gating of the sodium channel: an 'activation' gate, which opens in response to a depolarizing stimulus, and an inactivation gate, which 'swings' closed approximately 1 ms after the activation gate opens. When a suitable stimulus depolarizes the membrane (2), some sodium channels open, followed by many other channels when the depolarization attains threshold for triggering the action potential (3). At this stage, Na^+ flood down their concentration gradient into the cell (3) and the membrane potential rapidly moves towards the equilibrium potential for Na^+ (about +60 mV). However, although the membrane potential does become positive, it does not attain the Na^+ equilibrium potential because the sodium channels quickly close. Approximately 1 ms after opening, the voltage-gated sodium channels close because of the 'inactivation' gate 'slamming' shut. At this time, the voltage-gated potassium channels open (4), allowing K^+ to 'flood' out of the cell to rapidly repolarize the membrane. With the inactivation gates shut, the sodium channels are inactivated and unresponsive to any depolarizing stimulus; this represents the absolute refractory period when the membrane cannot respond to any stimulus. When the membrane potential again reaches the normal resting value (owing to the sustained opening of the voltage-activated potassium channels), the inactivation gates of the sodium channels 'swing' open (deinactivation of the channels) and the membrane is again responsive to depolarizing stimuli. The voltage-gated potassium channels actually remain open long enough for the membrane potential to 'undershoot' the resting value transiently (i.e. the membrane is temporarily hyperpolarized) (5). At this time (the relative refractory period), the sodium channels are again responsive (deinactivated) but a larger depolarizing stimulus is required to trigger an action potential.

Figure 2

the sodium channels are returned to their normal resting state (deinactivated). Restoration of the normal membrane resting potential deinactivates the sodium channels, and the membrane again becomes responsive to depolarizing stimuli. The period of unresponsiveness caused by inactivation of the sodium channels is called the absolute refractory period. However, another period of comparative unresponsiveness (relative to the normal resting state of the membrane) is caused by the voltage-gated potassium channels remaining open and allowing the potassium efflux to take the membrane potential past the normal resting potential difference; the membrane potential difference temporarily becomes slightly more negative than the normal resting potential until the potassium channels close and the normal membrane potential is restored. This temporary period of membrane

hyperpolarization is called 'undershoot' and represents a phase of decreased responsiveness (relative refractory period) (i.e. a bigger depolarizing stimulus than normal is required to trigger an action potential because the cell interior is temporarily more negative than the normal resting potential; Figure 2).

Action potential initiation

An important feature of the action potential is that it is an 'all-or-none' event. For a given excitable cell, all action potentials are essentially identical with regard to the magnitude of the membrane depolarization (i.e. an action potential is not a graded response that varies with the magnitude of the depolarizing stimulus). In contrast, the initial membrane depolarization that takes the membrane potential towards the threshold for action potential initiation is a localized, graded response. At the neuromuscular junction, for example (see pages 177–182 of this issue), an action potential is triggered in the post-synaptic muscle cell by a localized membrane depolarization caused by release of transmitter (acetylcholine) from the motor neurone, which activates post-synaptic nicotinic acetylcholine receptors. The nicotinic receptors are ligand-gated cation channels that open in response to acetylcholine, allowing sodium ions to enter the post-synaptic cell and to partially depolarize it. The magnitude of this depolarization is proportional to the amount of neurotransmitter released (and therefore to the number and frequency of opening of the ligand-gated channels). At the neuromuscular junction, this localized post-synaptic graded depolarization is called the end-plate potential (EPP); at synapses between neurones, it is called the excitatory post-synaptic potential (or EPSP; see pages 177–182 of this issue). If the EPP or EPSP reaches the critical threshold potential, an action potential is triggered. In specialized sensory neurones, other types of stimuli can shift the membrane potential to threshold; for example, the modified dendritic terminals of some sensory neurones (skin 'touch' receptors, vascular baroreceptors, etc.) respond to mechanical stimuli such as stretching of the plasma membrane. An important consequence of the 'all-or-none' nature of the action potential is that information cannot be transferred in the form of variations in action potential magnitude (amplitude modulated) – it is encoded by variations in the frequency of action potential production, and in the patterns of repetitive neuronal firing (e.g. as 'bursts' rather than steady repetitive firing).

Speed of action potential propagation

The rate of action potential propagation is a particularly critical feature in neurones. Information must be transferred quickly along neuronal axons in order to process information rapidly (in the brain) or to control voluntary muscle contraction (e.g. some axons of sciatic nerve motor neurones must transfer instructions for contraction of the leg muscles over a distance of more than a metre). Speed of action potential propagation along neuronal axons is increased greatly by myelination (i.e. insulation of the axon by myelin-containing glial cells which wrap themselves around the axon to form an insulating sheath). The myelin sheath is discontinuous such that it comprises short segments interrupted by nodes of Ranvier, where the voltage-gated sodium channels are clustered. Depolarization at a node results in the rapid spread of positive charge (caused by the influx of Na^+) inside the axon membrane to trigger depolarization at the adjacent node and so on (i.e. the action potential 'jumps' from one node to the next – saltatory conduction; Figure 3). This greatly increases the rate of action potential propagation (relative to an unmyelinated axon) because the spread of charge from one node to the next is considerably quicker than would be the successive opening of sodium channels along the length of the myelinated segment. Myelination also has another important consequence in the brain by virtue of the fact that, in order to achieve high propagation rates along an unmyelinated axon, its diameter must be comparatively large (about 1 mm). It would be impossible to accommodate a human brain composed of unmyelinated neurones inside the human head because they would have to possess large-diameter axons to achieve the required conduction velocities. Large-diameter myelinated axons in the human body can conduct action potentials at speeds of over 100 m/second,

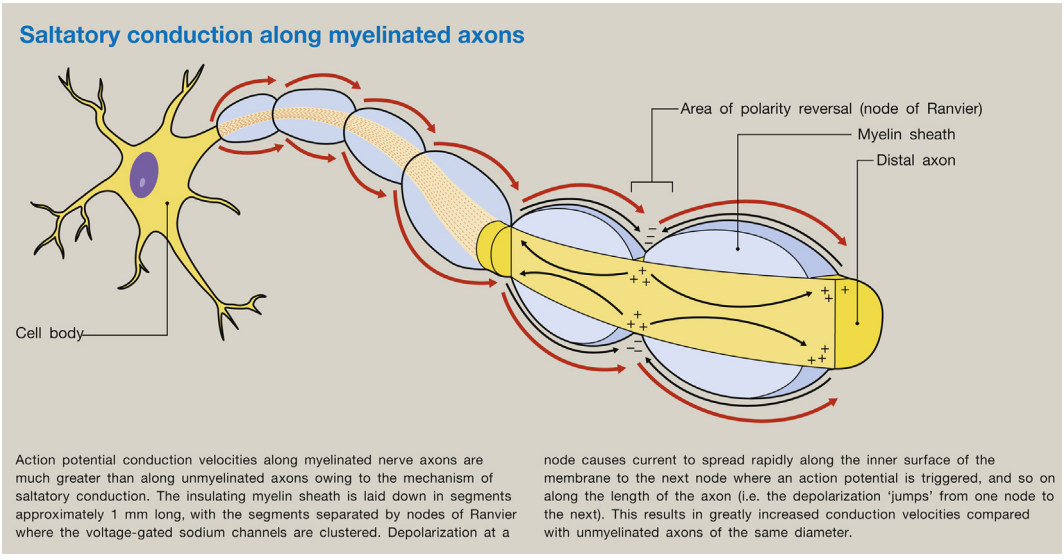


Figure 3

whereas small-diameter unmyelinated fibres may operate at conduction speeds of only 0.5—2.0 m/second.

Effects of drugs and toxins

The electrical activity of excitable cells can be influenced by a variety of drugs and naturally occurring toxins that have selective effects on ion channel function or on the physico chemical properties of the plasma membrane itself. Drug-induced disruption of neuronal generation of action potentials is obviously a potentially highly toxic action — a property that is utilized by many organisms for defence purposes. Tetrodotoxin is a highly potent and selective voltage-gated sodium channel blocker that is produced by the Japanese puffer fish. Saxitoxin is another potent sodium channel blocker that is produced by marine protozoa. Conversely, some naturally occurring toxins prolong the opening of voltage-gated sodium channels, for example batrachotoxin (contained in the skin of an Ecuadorian tree frog), veratridine and aconitine (plant toxins contained in lilies and buttercups, respectively). Several therapeutically useful synthetic drugs also target sodium channels, for example local anaesthetics, some antiepileptics and cardiac antiarrhythmics. Some venomous animals produce toxins that target the voltage-gated potassium channels; for example, dendrotoxins (contained in mamba snake venom) block these channels, thereby prolonging the depolarization phase of the action potential. Drugs such as tetraethylammonium (TEA) or 4-aminopyridine (4-AP) also block these channels selectively and are used as research tools — active programmes of drug discovery research are currently attempting to develop therapeutically useful novel drugs which target these potassium channels. ◆

FURTHER READING

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