Action potential: generation and propagation

Allan Fletcher

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 millivolts (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: (1) an all-or-none event, rather than a graded response; (2) it is self-propagating, such that the wave of depolarization travels rapidly along the plasma membrane; and (3) 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).

The resting membrane potential

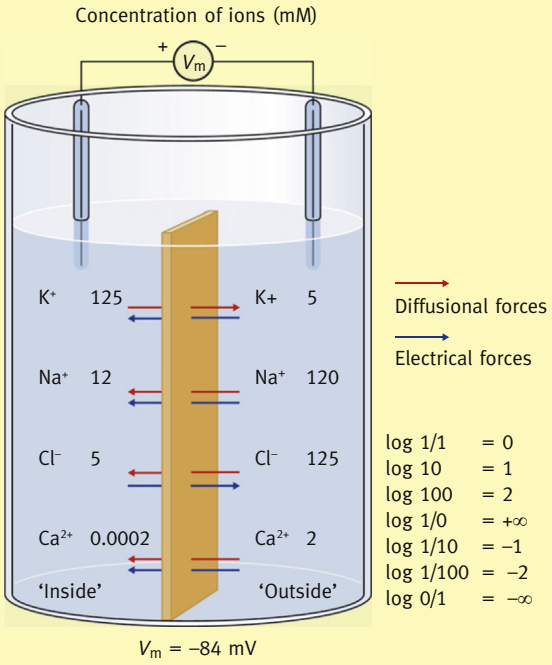
An electrical potential difference exists across the plasma membrane of all living cells by virtue of differences in the concentration of charged ions in the cytosol and in the interstitial fluid and differences in membrane permeability to these ions. The two ions mainly involved in establishing a resting 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 10-fold excess outside the cell compared with the interior). The resting membrane potential difference of approximately −70 millivolts (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.

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

Allan Fletcher *BSc is currently an e-tutor for the Department of Biomedical Sciences, University of Ulster, UK. Conflicts of interest: none.*

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

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 sodium channels are returned to their normal resting state (deinactivated). Restoration of the normal