Action Potentials: Generation and Propagation

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Introductory article

Article Contents

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All cells maintain a voltage across their plasma membranes. Only excitable cells, however, can generate action potentials, the rapid, transient changes in membrane potential that spread along the surface of these unique cells. Action potential generation and propagation occurs through, and is regulated by, the function of voltage-gated ion channels – proteins with ion-selective pores that span the cell membrane. Ion channels undergo changes in their structural conformation in response to changes in the electrical field across the membrane. These structural changes cause the opening of pores – channels – through which ions can flow down their electrochemical gradient. The charge carried by ions creates an electrical current and rapidly alters the membrane potential with time- and voltage-dependent properties. This rapid, transient membrane potential change is called the action potential. Action potentials transmit information within neurons, trigger contractions within muscle cells, and lead to exocytosis in secretory cells.

Introduction

All cells maintain a voltage across their plasma membranes. Only excitable cells, however, can generate action potentials, the rapid, transient changes in membrane potential that spread along the surface of these unique cells. Action potentials transmit information within neurons, trigger contractions within muscle cells and lead to exocytosis in secretory cells. **See also**: Cell Structure; Membrane Potential

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Equilibrium and Selective Permeability

The recognition that cells have a membrane potential is crucial to understand how an action potential is generated and propagated. Voltage is a measure of electrical energy that has the potential to do work, much like water accumulated behind a dam. The membrane potential (V_m) is the voltage measured when the inside of a cell is compared to the outside. This voltage is caused by a separation of charged particles – ions – which arises from a combination of ionic concentration differences and selective permeability of the membrane.

Ions are distributed such that there is a higher concentration of potassium (K^+) on the inside of cells than outside, and a higher concentration of sodium (Na^+) outside cells than on the inside. These differences in ionic concentrations create, for each ion, an electrical and chemical imbalance. This imbalance disappears for each ion at its equilibrium potential (abbreviated E_{ion}), a voltage at which the chemical force (concentration gradient) acting on the ion is equal and opposite to the electrical force (charge gradient) acting on the ion. Ions can flow in either direction across the membrane at voltages other than the equilibrium potential, but it is far more likely that an ion will cross from high concentration to the low concentration (i.e. the chemical gradient) or from the side where there is a greater number of similarly charged ions to the side where there are fewer similarly charged ions (i.e. the electrical gradient). The relationship between the chemical driving force and the equilibrium potential is given by the Nernst equation:

$$E_{ion} = RT/zF \log_e [ion]_{outside}/[ion]_{inside}$$

where R is the gas constant, T the temperature, z the valence of the ion, F the Faraday's constant, $[ion]_{outside}$ the concentration of the ion outside the cell and $[ion]_{inside}$ the concentration of the ion within the cell. Since the only variables in the Nernst equation are the concentrations of the ion inside and outside the cell, the equilibrium potential only varies if the concentrations change, which does not happen physiologically to a significant extent. The equilibrium potential for an ion is, therefore, constant. **See also**: Nernst, Walther Hermann

These concepts are illustrated in **Figure 1**, where it can be seen that the inside of the cell has a high concentration of potassium ions (K^+) and a low concentration of sodium ions (Na^+). By contrast, the extracellular milieu has a high concentration of Na^+ and a low concentration of K^+. Because of these concentration differences, and because a cell at rest is selectively permeable to K^+, the resting membrane potential (abbreviated V_{rest}) is close to the equilibrium potential for K^+ (E_K). As potassium ions move down their concentration gradient (from the inside where K^+ concentration is high to the outside where K^+ concentration is low) the resting membrane potential tends towards E_K, which is about −60 millivolts (mV), based on the physiological concentration of K^+, inside and outside the cell. If the selective permeability changes to another ion, then the membrane potential shifts towards the equilibrium potential for that other ion. Such a change in selective permeability is the basis for the action potential. **See also**: Cell Membranes: Intracellular pH and Electrochemical Potential

Normal ionic concentrations (in mmol L^{-1})

	Intracellular	Extracellular
K^+	100	10
Na^+	10	100

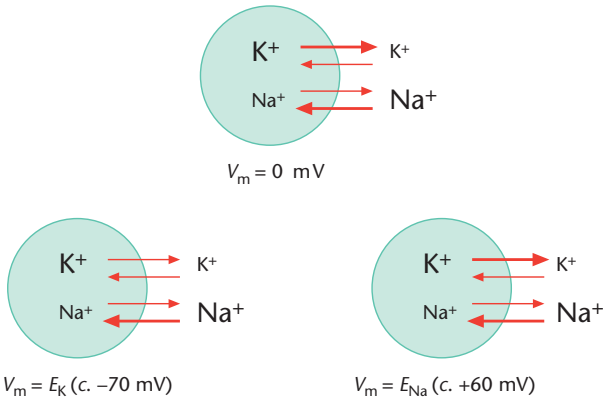

Figure 1 Electrochemical gradients arise from unequal distributions of ions across cell membranes. Ionic concentrations shown here are approximations of physiological conditions. Weight of arrow shows relative electrochemical driving force.

Ion Channels: Activation, Deactivation and Inactivation

How is it that ions cross the membrane in response to a driving force if phospholipid membranes are generally impermeable to ions? The answer lies in the protein component of membranes. Recalling the fluid mosaic model of membranes, many proteins are located in the membrane. Some of these proteins fully traverse the lipid bilayer and have both extracellular and cytoplasmic domains. One class of these proteins can form pores for ions to flow into and out of cells and are thus called ion channels. Some ion channels will only form a pore at certain membrane voltages and are thus called voltage-gated ion channels. When an ion channel is open, the ion that can pass through the channel (i.e. the 'permeant' ion) will flow across or 'permeate' the membrane. Certain voltage-gated channels are selectively permeable to K^+ and are called potassium channels (Gutman *et al.*, 2005) whereas sodium channels are selectively permeable to Na^+ (Catterall *et al.*, 2005). **See also**: Sodium Channels; Voltage-gated Potassium Channels

Unlike the equilibrium potential for an ion, selective permeability varies with voltage; in other words, some channels are 'sensitive' to voltage. Most ion channels – particularly those involved in the action potential – are closed at the resting membrane potential. (An exception to this is the K^+ channels that contribute to the resting membrane potential.) Depolarisation of the membrane, meaning the membrane becomes more positive than −60 mV, results in the opening of an ion channel, and is called 'activation' (Bezanilla, 2008). Channel activation involves a change in the proteins' shape that results in a pore through which ions can flow. Thus, when a channel changes its conformational state from closed to open, it activates. Similarly, a channel deactivates when its conformational state changes from open to closed, usually in response to a rapid return to a more negative voltage. These state transitions are represented in **Figure 2**. A third conformational change results as a consequence of more prolonged activation; a portion of the channel can block the open pore (Kellenberger *et al.*, 1996). This self-blocking process is called 'inactivation', and results in a cessation of ionic flow through the channel. Channels recover from inactivation after the voltage returns to the resting membrane potential, or hyperpolarises. It is important for the reader to understand that, in different types of ion channels, these conformational changes happen at different voltages and will do so with different rates. For instance, sodium channels open with increasing probability over a range of membrane potentials from about −60 mV to about −10 mV. At voltages more positive than 0 mV, the probability of sodium channel opening does not increase any further. Voltage-gated potassium channels also open with increasing probability at voltages starting at about −60 mV, but they open far more slowly than do sodium channels. This delay between the opening of Na^+ channels

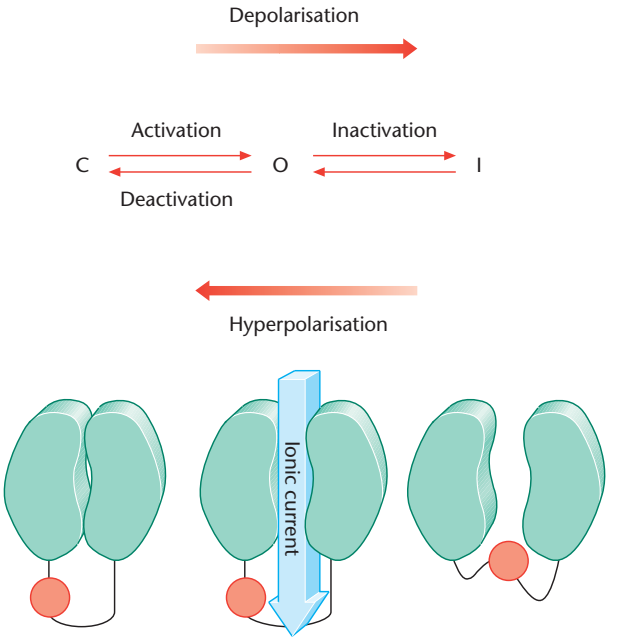

Figure 2 Voltage-dependent gating of a Na^+ channel. Voltage-gated channels change their conformational state from closed to open to inactivated in response to depolarisation. When open, ions can flow through the channels.

and the opening of K^+ channels is critical for the shape and duration of the action potential. We will next see how the features of these voltage-gated sodium and potassium channels contribute to action potential generation. **See also**: Action Potential: Ionic Mechanisms; Transition States: Substrate-induced Conformational Transitions

Action Potential Initiation and Na^+ Channel Activation

Depolarising the membrane potential past a critical 'threshold' voltage results in an action potential. As we previously discussed, voltage-gated Na^+ channels open with increasing probability during depolarisation. Threshold is reached when the amount of Na^+ entering the cell is (1) greater than the resting efflux of K^+, and (2) when the change in membrane potential with Na^+ influx activates neighbouring Na^+ channels. Condition (1) is necessary because K^+ efflux due to the concentration gradient and resting selective permeability to K^+ tends to maintain the resting membrane potential near E_K at about -60 mV. Condition (2) is also necessary because the initial depolarising stimulus (often an excitatory synaptic potential) is usually an insufficiently large depolarisation to open many sodium channels. Sodium ions, however, are positively charged and can thus influence the electrical field 'sensed' by neighbouring Na^+ channels. When enough Na^+ enters the cell, these ions depolarise the membrane potential sufficiently to activate additional Na^+ channels. In turn, these channels open, letting even more Na^+ into the cell, leading to the activation of even more channels. In other words, the action potential is a regenerative, positive-feedback cycle – one of the few found in nature. Hence, an increase in selective permeability to Na^+ results in a sodium influx and a shift in the membrane potential towards the equilibrium potential for Na^+ (E_{Na}), which is about $+60$ mV, based on the physiological concentration of Na^+ inside and outside the cell.

The initial influx of Na^+ into the cell is known as the 'rising phase' of an action potential. A recording of membrane voltage, as shown by the top line in **Figure 3**, demonstrates the reason for this name; when positively charged Na^+ enters the cell, the membrane depolarises as the voltage becomes less negative and even overshoots the 0 mV level. The second line in **Figure 3** shows Na^+ conductance – a term meaning the ability of an electrical circuit to carry current. When all ion channels in a membrane are closed, there is high membrane resistance and little or no conductance. As channels open, conductance increases and ionic current flows through the open channels. As more channels open, conductance continues to increase until all available Na^+ channels are open. To review, the increase in selective permeability (conductance increase) to Na^+ causes the membrane potential to depolarise towards E_{Na}, thereby producing the rising phase of the action potential. All of these events occur within a duration of less than 1 ms – the time it takes Na^+ channels to activate. **See also**: Repetitive Action Potential Firing

Action Potential Termination: Na^+ Channel Inactivation and K^+ Channel Activation

After channels are open for about a millisecond, they inactivate by the pore-blocking mechanism previously discussed, leading to a decrease in sodium conductance. Sodium channel inactivation is the first step in action potential termination; the decrease in selective permeability to Na^+ causes the membrane potential to shift away from E_{Na} and towards the normal resting membrane potential (which is due to a selective permeability to K^+). This part of the action potential is called the 'falling phase'. Although Na^+ channel inactivation could, by itself, terminate the action potential, K^+ channel activation provides a fail-safe mechanism to terminate the action potential. When we recall that E_K is near the resting membrane potential, then it is easy to see that a conductance increase to K^+ will tend to drive the membrane potential towards more negative voltages, thus contributing to the falling phase of the action potential. The key to this contribution is that K^+ channels activate slowly as compared to Na^+ channels (Adrian *et al.*, 1970). Try to

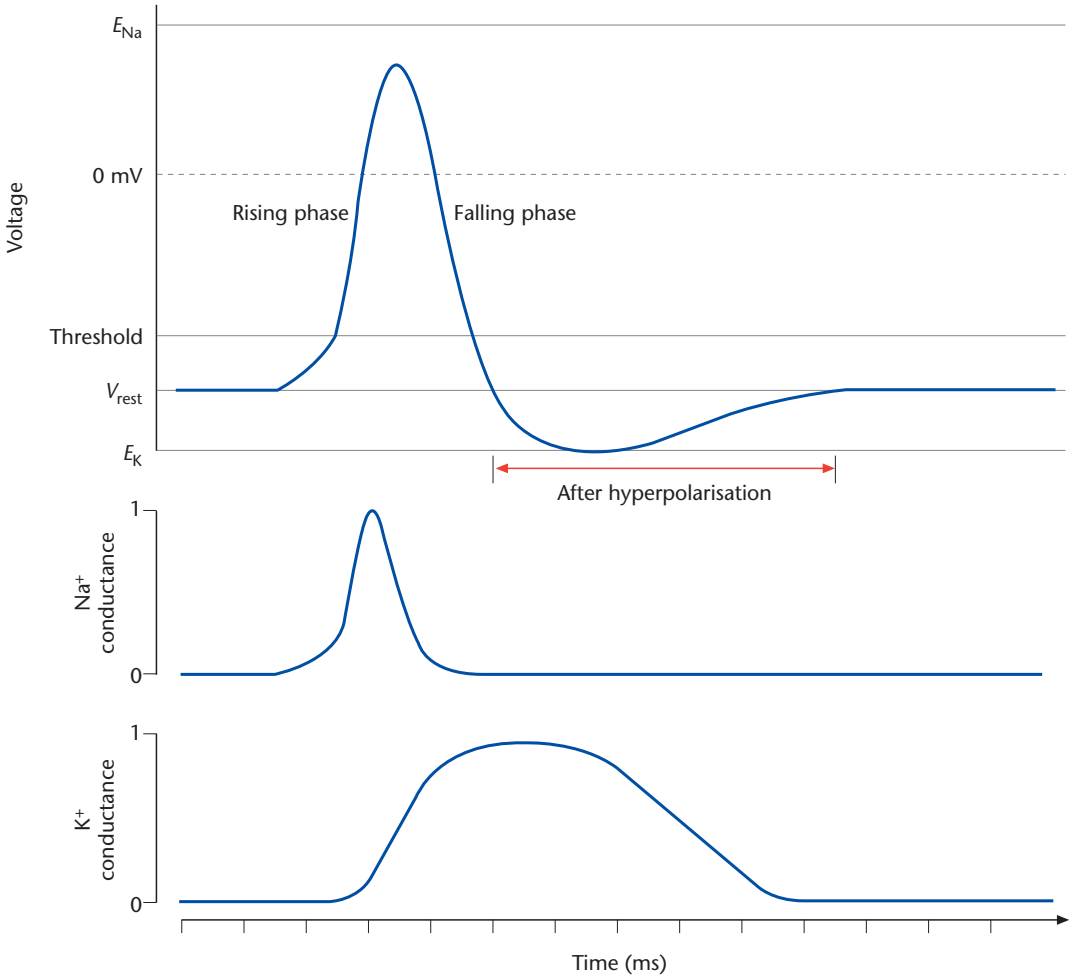

Figure 3 Ionic basis of the action potential. Top trace shows the voltage recording during an action potential, with relative positions along the voltage axis of V_{rest}, threshold potential, E_K, E_{Na}, and, as a reference point, 0 mV. Middle trace shows Na^+ conductance during the action potential. Bottom trace shows K^+ conductance during the action potential. Note the overlap between K^+ conductance increase and the after-hyperpolarisation.

imagine what might happen if the two classes of channels activated with similar rates; E_K is about -60 mV and E_{Na} is about $+60$ mV, so simultaneous activation of both channel types would drive the membrane potential to about 0 mV. Since the action potential overshoots 0 mV, we must conclude that K^+ channels activate with a delay compared to Na^+ channel activation.

The contribution of K^+ channels to action potential termination is also evident by the presence of a period of hyperpolarisation, during which the membrane potential is briefly more negative than the resting membrane potential. This arises under conditions where E_K is more negative than V_{rest} so an increase in K^+ conductance hyperpolarises the membrane potential. The after-hyperpolarisation also arises because K^+ channel inactivation is slower than Na^+ channel inactivation. As K^+ channels finally inactivate, the after-hyperpolarisation declines to the resting membrane potential.

Action Potential Properties: All-or-Nothing and Refractoriness

Action potentials differ in a number of ways from other transient, passive changes in voltage. First, once the membrane potential has reached threshold, a full-amplitude action potential is inevitable. If, however, the membrane potential does not reach threshold, no action potential will occur. This all-or-nothing property can be attributed to the voltage-dependent behaviour of Na^+ channel activation leading to a positive-feedback cycle and membrane depolarisation. As we saw earlier, activation depends on membrane depolarisation. If the depolarisation is sufficiently great (i.e. surpassing threshold), then there will be enough Na^+ influx to depolarise the membrane around neighbouring channels and they, too, will become activated. This positive-feedback, regenerative

cycle leads to an action potential. If, however, the depolarisation does not reach the threshold, then not enough Na^+ will have entered the cell and neighbouring channels will not become activated. The maximum amplitude of an action potential – the peak voltage that is attained – is a function of E_{Na} (towards which the membrane potential tends during an increase in selective permeability to Na^+) and the number of open sodium channels relative to the number of inactivated channels. Since E_{Na} is constant, the amplitude of an action potential will only fluctuate with a change in the proportion of open to inactivated channels. In a rapidly firing cell, the amplitude can decrease because there is not enough time between action potentials for sodium channels to recover from inactivation. The time required for recovery from inactivation has other important consequences, as we will see in the next section.

Absolute refractory period

A second property that distinguishes action potentials from other changes in membrane potential is that, once an action potential has been initiated, there is a period of time during which the membrane is inexcitable or 'refractory'. The period of inexcitability can be subdivided into two periods, each of which has a different molecular basis. The absolute refractory period begins once the membrane potential has reached threshold and lasts approximately until the beginning of the after-hyperpolarisation. During this period, it is physiologically or experimentally impossible to elicit another action potential. The basis for the absolute refractory period centres on Na^+ channels. Soon after they activate, Na^+ channels inactivate and only membrane hyperpolarisation and time will allow the channels to recover from their inactivated state. While Na^+ channels are inactivated, they are unavailable for activation, as depolarisation will only maintain their inactivation. If the membrane cannot sustain a conductance increase to Na^+, then the membrane potential will not tend towards E_{Na} as it does during an action potential. Under these conditions, another action potential cannot be generated. The absolute refractory period sets the maximum rate of action potentials for a cell.

Relative Refractory Period

When K^+ channels become activated and contribute to the falling phase of the action potential, the membrane hyperpolarises sufficiently for Na^+ channels to recover from inactivation, after which the channels are once again available for activation. This marks the end of the absolute refractory period and the beginning of the second phase of inexcitability – the relative refractory period. During this period, a larger depolarisation is required to elicit an action potential. The basis for the relative refractory period centres on K^+ channels. First, increased potassium conductance drives the membrane potential away from threshold, so a greater depolarisation is necessary to drive the membrane potential to threshold. Second, any open channels lower the total membrane resistance, thus making the membrane less responsive than it would be at rest to a stimulus of any amplitude. The relative refractory period subsides as K^+ channels inactivate and, ultimately, close. Normal membrane excitability resumes once the membrane potential returns to its resting level (Poulter and Padjen, 1995).

Action Potential Propagation

Another unique characteristic of action potentials is their ability to conduct or propagate along a membrane. Although passive responses (such as synaptic potentials or subthreshold voltage fluctuations in an axon) decay as a function of distance along the membrane, action potentials do not decay. Instead, action potentials spread from their point of origin along the cell membrane; an action potential, artificially elicited in the middle of a length of axon, will spread in two directions away from the point of origin. The mechanism for propagation is the same that underlies the spread of passive voltage fluctuations, and relies upon the fundamental 'cable properties' of the cell, including (a) membrane resistance (R_M), (b) extracellular resistance (R_O) and (c) intracellular resistance (R_I). These electrical elements can be combined to form an equivalent circuit of a cell membrane, as shown in **Figure 4**. The relative magnitudes of these elements determine the 'cable properties' of a cell and, in particular, the 'length constant', or the distance over which a voltage deflection will electrotonically spread along the membrane. (Included in the equivalent circuit is another element, membrane capacitance (C_M) that, along with membrane resistance, controls the time constant – the rate at which membrane voltage changes in response to an applied stimulus. Although this only becomes important in a more detailed discussion of membrane properties, an equivalent circuit describing the membrane would be incomplete without membrane capacitance.) **See also**: Myelin and Action Potential Propagation

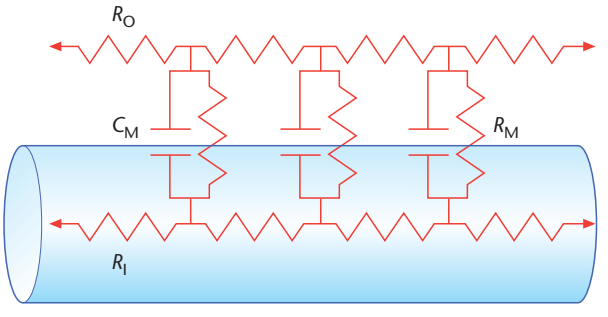

Figure 4 Equivalent circuit of an axon showing the essential features for the basis of cable properties. R_M, membrane resistance; R_O, extracellular resistance; R_I, intracellular resistance; C_M, membrane capacitance.

Local currents

What is the cause of this electrotonic spread of voltage along the membrane? When ions cross the cell membrane, they comprise an electrical current, as does any movement of charged particles. For an electrical circuit to be complete, however, an equivalent amount of charge must move back out of the cell at another point along the membrane. Just as current travels electrotonically within a wire by movement of an electrical field, so does current travel electrotonically within an axon. This so-called 'local current' will seek the path of least resistance, whether that is within the axoplasm or across the membrane, as illustrated in **Figure 5**. The field must eventually cross the membrane, however, to complete the electrical circuit. When this happens, that portion of the membrane will be depolarised. An action potential will be evoked if the depolarisation is of sufficient magnitude to reach the threshold potential. Hence, action potentials propagate by means of membrane depolarisation due to the spread of local currents inside and, ultimately, across the membrane.

Why does an action potential not propagate back on itself once it has passed over a section of membrane? Recall that the membrane becomes refractory during an action potential. Refractory membrane will be unresponsive to local currents such that, even though local currents flow across the membrane, either the Na^+ channels in the refractory membrane are inactivated or the K^+ channels are activated, so another action potential cannot be generated.

The distance over which local currents spread is a function of the length constant, denoted as λ and equivalent to the distance over which a voltage deflection will decay to $1/e$ of its original magnitude, where 1 is the natural logarithm of e. In turn, the length constant determines the rate at which action potentials will propagate along the membrane. As noted above, the length constant is a function of membrane resistance and capacitance, and both intracellular (cytoplasmic) and extracellular resistances, as follows:

$$\lambda = (R_M / R_I + R_O)^{1/2}$$

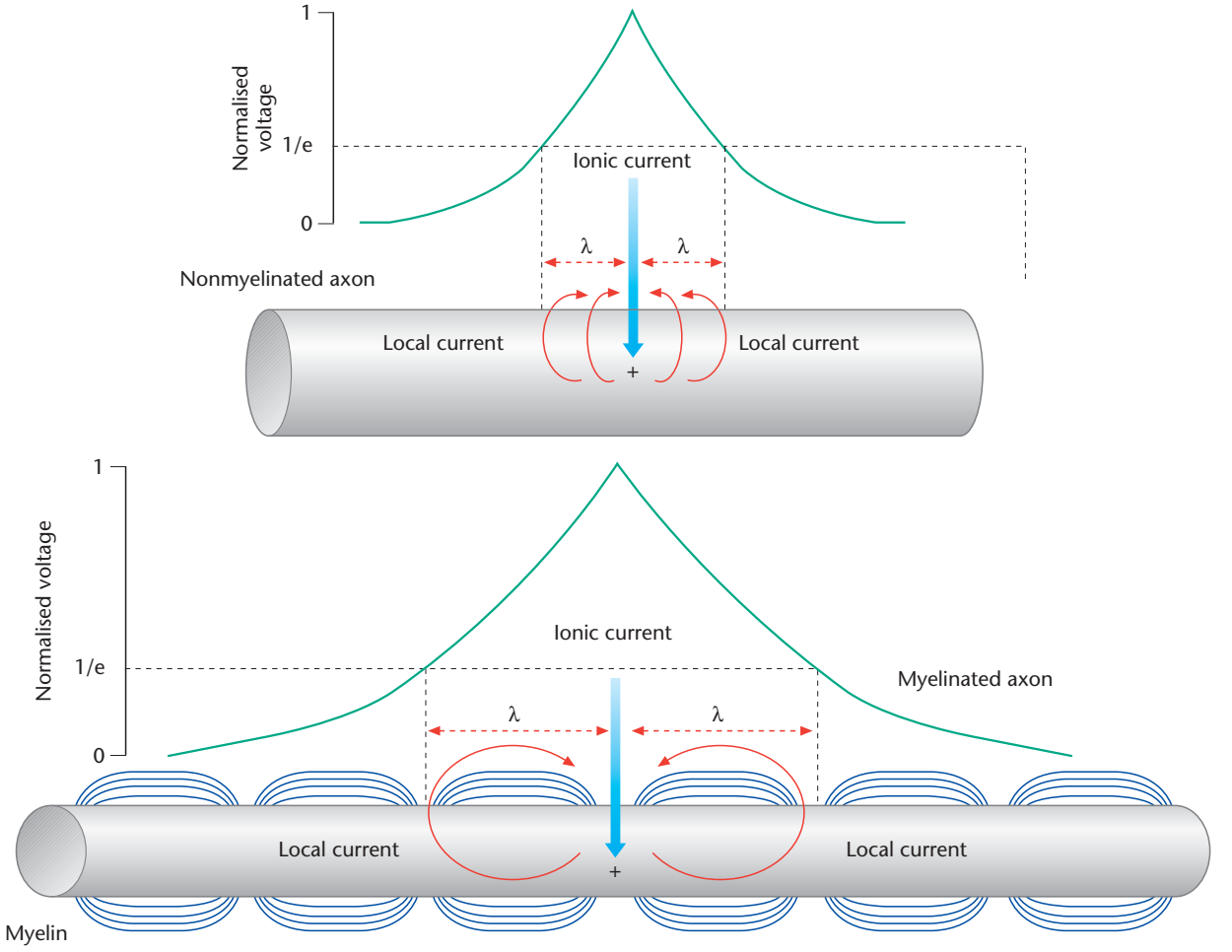

Figure 5 Electrotonic decay of voltage along a nonmyelinated (top) and a myelinated (bottom) axon. Note that the voltage deflection caused by the same influx of Na^+ is larger in a myelinated axon because of higher effective membrane resistance. Also note that the length constant (λ) is greater in the myelinated axon so the local currents travel farther within the axon.

where R_M is the membrane resistance, R_I is the intracellular resistance and R_O is the extracellular resistance. Hence, if R_M is large, or if either R_I or R_O is small, then the length constant will increase. The local current will spread a greater distance along the membrane before finding a path across the membrane, more distant portions of the membrane will be depolarised, and the action potential will thus spread more rapidly along the membrane. Since the local current results from movement of an electrical field that, as within a wire, travels at approximately the speed of light, the only delay in action potential propagation, once the voltage of neighbouring sections of membrane have been depolarised to threshold, is the time taken for Na^+ channel activation.

Firecracker fuses and leaping sparks: mechanisms of accelerating propagation

The rate of continuous action potential propagation along an axon varies over a range from about $0.5\,m\,s^{-1}$ to $120\,m\,s^{-1}$. Certain neural circuits, such as those underlying escape reflexes and sensory input, require fast rates of communication. Animals solve the need for rapid propagation in two different ways, both of which increase the length constant. Invertebrates, with their relatively few neurons (compared to vertebrates), generally increase the diameter of axons to propagate action potentials more rapidly. This increases the length constant by lowering R_I. Referring back to the equation for λ, it can be seen that lowering R_I will increase the length constant. With an increased λ, each action potential depolarises a larger section of membrane because local currents spread over greater distances. Thus, the rate of propagation increases with an increase in axon diameter. The action potential rapidly travels along the axon, like a spark along a firecracker fuse, continuously depolarising adjacent sections of membrane.

Most vertebrates have more complex behaviours and, accordingly, more neurons than most invertebrates. Vertebrates cannot, therefore, allow axons to increase in diameter to achieve high propagation rates. Instead, vertebrates (and a few invertebrates) have evolved a special way of attaining high conduction velocity. Schwann cells are a specialised class of glial cells that wrap many layers of membrane around the axons of neurons, as shown in **Figure 5**. This phenomenon is called 'myelination'. The high lipid content of the glial membrane increases the effective membrane resistance of the myelinated axon and decreases its effective capacitance. Referring again to the equation for the length constant, it can be seen that any increase in R_M will increase λ. Local currents tend to spread farther along the axon's interior because they cannot find a low resistance pathway across the membrane. Gaps between Schwann cells, called nodes of Ranvier, provide this low resistance pathway, and this is where action potentials occur in myelinated axons. Thus, an action potential in a myelinated cell sets up local currents that spread to and depolarise neighbouring nodes of Ranvier. The action potential effectively jumps from one node to the next – a process called 'saltatory conduction', even though the local current is spreading along the entire length of the axon (Frankenhauser, 1952). Interestingly, Na^+ channels in myelinated axons are most highly concentrated in nodal membrane and are relatively sparse in internodal regions. This explains why demyelination diseases, such as amyotrophic lateral sclerosis (Lou Gehrig disease), are devastating; the affected axons are no longer able to propagate action potentials along their lengths. **See also**: Amyotrophic Lateral Sclerosis; Multiple Sclerosis; Myelin and Action Potential Propagation; Schwann Cells

Summary

Action potentials are transient changes in the membrane potentials of excitable cells that carry important cellular information. The membrane potential of these cells fluctuates when first Na^+ and then K^+ channels activate and then inactivate in a voltage- and time-dependent manner. Sodium channel activation causes an increase in selective permeability to Na^+, allows an influx of Na^+ down its electrochemical gradient, and causes the membrane potential to tend towards E_{Na}. When the membrane potential reaches a threshold voltage, neighbouring Na^+ channels are activated in a positive-feedback cycle. This cycle is broken when the Na^+ channels inactivate, the selective permeability for Na^+ decreases and the membrane potential falls away from E_{Na}. Sodium channel inactivation is responsible for the initial part of the falling phase. Membrane depolarisation also activates K^+ channels after a delay longer than that for Na^+ channel activation. Potassium efflux through the open K^+ channels contributes to the repolarising, or falling phase of the action potential by causing the membrane potential to shift towards E_K. The slower activation and inactivation rates of K^+ channels allow the initial Na^+ influx to produce its full effect on the membrane potential before the action of K^+ channel opening. In addition, the slower K^+ channel rates produce an after-hyperpolarisation, a period during which the membrane potential is more negative than the resting membrane potential. Sodium channel inactivation causes a period during which the cell is inexcitable – the absolute refractory period. Potassium channel activation causes the relative refractory period – a period during which a greater-than-usual stimulus is necessary to evoke another action potential. When both Na^+ and K^+ channels have recovered to their closed states, the cell is again normally excitable. Unlike passive voltage fluctuations, action potentials propagate along the cell membrane. Ion flux through activated channels sets up local currents, carried by electrical fields, that depolarise adjacent sections of membrane, activate Na^+ channels, and elicit an action potential in this new section of membrane. The distance over which local current spreads is dependent on the membrane resistance and the internal cytoplasmic resistance. Neurons have greater rates of propagation when their

diameter is greater, lowering internal resistance, or when they are myelinated, effectively increasing membrane resistance.

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