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The action potential

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It is over 60 years since Hodgkin and Huxley[1] made the first direct recording of the electrical changes across the neuronal membrane that mediate the action potential. Using an electrode placed inside a squid giant axon they were able to measure a transmembrane potential of around −60 mV inside relative to outside, under resting conditions (this is called the resting membrane potential). The action potential is a transient (<1 millisecond) reversal in the polarity of this transmembrane potential which then moves from its point of initiation, down the axon, to the axon terminals. In a subsequent series of elegant experiments Hodgkin and Huxley, along with Bernard Katz, discovered that the action potential results from transient changes in the permeability of the axon membrane to sodium (Na^+) and potassium (K^+) ions. Importantly, Na^+ and K^+ cross the membrane through independent pathways that open in response to a change in membrane potential.

As testimony to their pioneering work, the fundamental mechanisms described by Hodgkin, Huxley and Katz remain applicable to all excitable cells today. Indeed, the predictions they made about the molecular mechanisms that might underlie the changes in membrane permeability showed remarkable foresight. The molecular basis of the action potential lies in the presence of proteins called ion channels that form the permeation pathways across the neuronal membrane. Although the first electrophysiological recordings from individual ion channels were not made until the mid 1970s,[2] Hodgkin and Huxley predicted many of the properties now known to be key components of their function: ion selectivity, the electrical basis of voltage-sensitivity and, importantly, a mechanism for quickly closing down the permeability pathways to ensure that the action potential only moves along the axon in one direction.

ION DISTRIBUTION AND THE RESTING MEMBRANE POTENTIAL

The resting membrane potential is essential for the normal functioning of the neuron and is maintained through an unequal distribution of ions across the neuronal membrane. Figure 1A:i illustrates the distribution of ions across the membrane of a typical neuron. The different ion concentrations are established and maintained by ATP-dependent pumps, most significantly one that exchanges internal Na^+ for external K^+, thereby concentrating Na^+ outside, and K^+ inside, the neuron. Consider what happens if membrane permeability to Na^+ ions suddenly increases. What forces act on the Na^+ ions? The high external concentration of Na^+ means there is a concentration gradient. Na^+ diffuses down

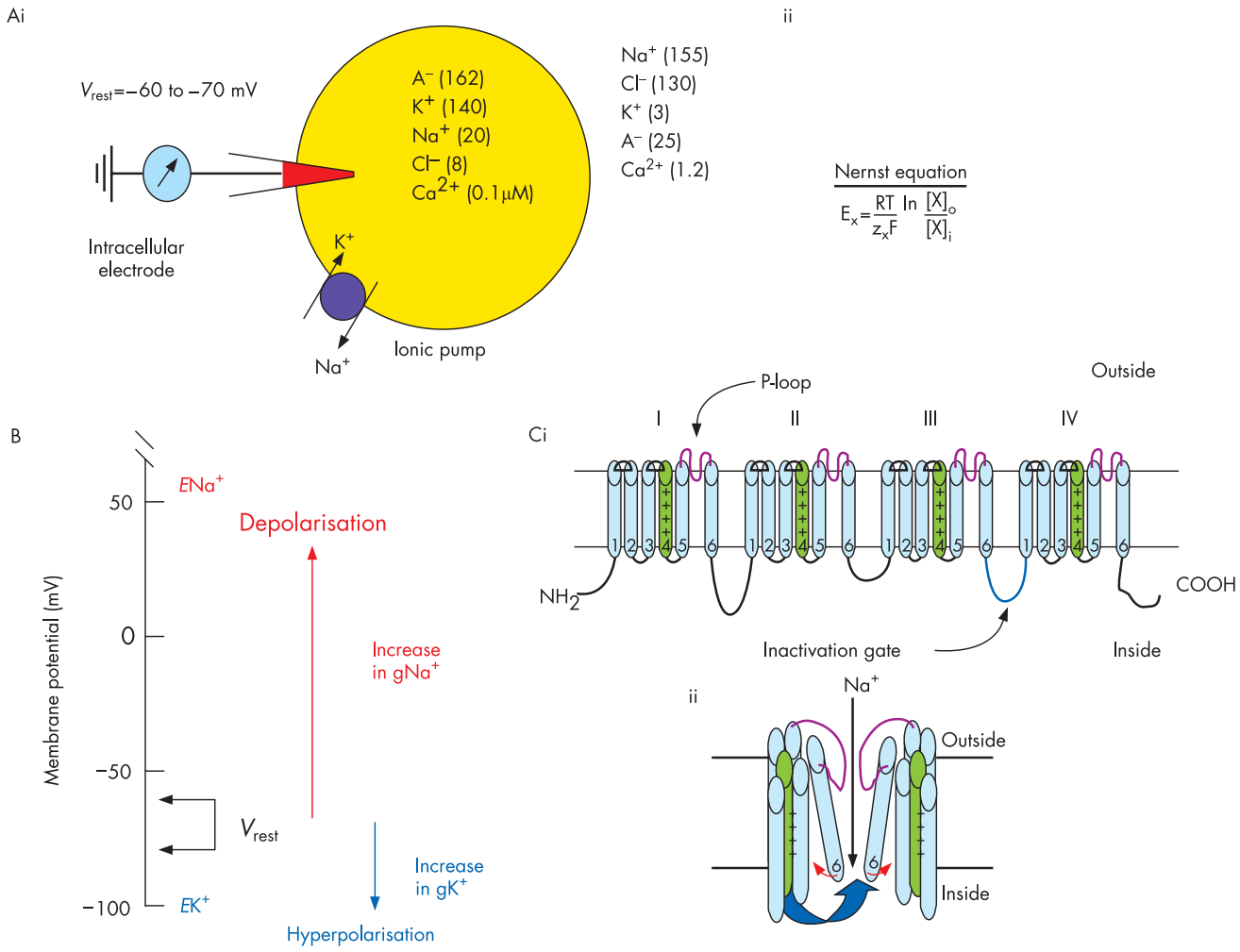

Figure 1

(Ai) Diagrammatic representation of the unequal distribution of ions across a typical neuronal membrane. All concentrations are in millimolar (mM) except where indicated otherwise. Internal and external Na^+ and K^+ concentrations are maintained by the ATP-dependent Na^+/K^+ pump. A^- represents the large internal anionic charge carried by non-membrane permeable proteins. Cytoplasmic Ca^{2+} is usually maintained at nanomolar (10^{-9}M) concentrations by sequestration into membrane localised stores. The resting membrane potential (V_{rest} = −60 to −70 mV) is measured inside the neuron relative to outside. (A:ii) The Nernst equation used to determine the equilibrium potential (E) for the ion, *x*, where R is the gas constant, T is the temperature in °K, F is the Faraday constant and z_x is the valency of ion, *x*. $[X]_o$ and $[X]_i$ are the external and internal concentrations of ion *x*, respectively. (B) Illustration of the membrane potential changes resulting from either an increase in conductance to Na^+ (gNa^+) or K^+ (gK^+). The change in membrane potential is determined by the difference between the resting membrane potential (*V*rest) and the equilibrium potential for that ion (E_{Na}+ or E_K+). (Ci), a two dimensional, diagrammatic, representation of the molecular structure of the pore forming α subunit of the voltage-sensitive Na^+ channel. It is a single protein that has four domains (I, II, III, IV). Each domain has six transmembrane (TM) spanning regions (1–6). The region between the TM5 and TM6 in each domain dips into the membrane but does not cross fully before coming back out on the extracellular side. These are called the P-loops (coloured magenta). Voltage-sensitivity is conferred predominantly by TM4 (green) in each domain. Each TM4 contains several positively charged amino-acid residues (++++). A change in voltage across the membrane promotes a movement of TM4 that induces a conformational change, opening the channel pore. The linker region between domains III and IV (blue) forms the inactivation gate. (Cii) A proposed 3D view through the voltage-sensitive Na^+ channel. Each of the domains forms the outside of a cylindrical structure with a central pore, lined by TM6 of each domain. The P-loops (magenta) form a selectivity filter at the extracellular entrance to the channel that determines which ions pass through the channel. Movement of the voltage sensors (TM4) is thought to induce movements of the intracellular ends of TM6 in the direction indicated by the red arrows thereby opening the activation gate. The blue arrow indicates the movement of the inactivation gate resulting in blockage of the open pore from the intracellular side.

this concentration gradient into the neuron carrying with it a net positive electrical charge. The movement of positive charge makes the inside of the neuron more positive (known as depolarisation) leading to a reduction and eventual reversal of the transmembrane potential. This change in membrane potential also has an effect on the movement of Na^+ ions. As the electrical gradient across the membrane is diminished it starts to oppose the movement of the positively charged ions into the cell. Thus, two opposing forces act on the Na^+ ion—a concentration gradient and an electrical

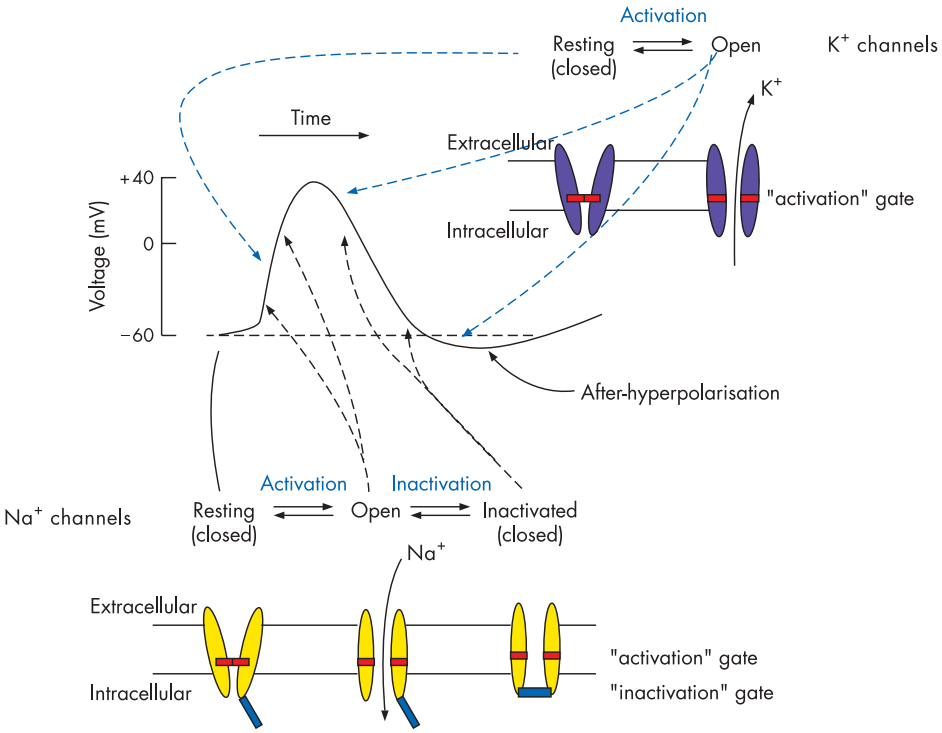

Figure 2
A diagrammatic representation of the action potential and associated models depicting the sequence of activation and inactivation of the voltage-sensitive Na^+ and K^+ channels. Arrows indicate the state of the respective ion channels during different phases of the action potential. The broken line on the action potential trace indicates the resting membrane potential and is used to highlight the rebound after-hyperpolarisation.

gradient. These two forces will eventually reach equilibrium at a new, stable, membrane potential. This is called the *equilibrium potential* for Na^+, defined as the membrane potential at which there is no net flow of Na^+ across the membrane. The equilibrium potential can be determined from the Nernst equation (fig 1Aii). Thus, for our typical ionic concentrations, equilibrium potentials for Na^+ and K^+ would be +55 mV and −103 mV at 37 ℃, respectively.

What determines the resting membrane potential? At rest the neuronal membrane is permeable to several ions, thus, the resting potential is not equivalent to the equilibrium potential of any one ion but lies between the equilibrium potentials for the individual ions. If K^+ permeability dominates, the resting potential will be close to the K^+ equilibrium potential. If permeability to K^+ and Na^+ is equal, the resting potential will lie between the equilibrium potentials for these ions. This means, that when additional ion channels open, the direction of ion movement and, therefore, the change in membrane potential, will be determined by the difference between the resting membrane potential and the equilibrium potential for that ion or ions (fig 1B).

IONIC PERMEABILITY CHANGES UNDERLYING THE ACTION POTENTIAL

The action potential can be divided into three main phases. The initial phase is a rapid change in membrane potential from around −60 to +40 mV (depolarisation). The second phase is a return towards the resting membrane potential (repolarisation), and the third phase is a slowly recovering overshoot of the resting potential, termed the after-hyperpolarisation (fig 2). The initial depolarising phase is mediated by an increase in membrane permeability to Na^+. If Na^+ is removed from the extracellular solution, action potentials cannot be generated and the membrane current that underlies the depolarisation from −60 to +40 mV is abolished. This has been confirmed using tetrodotoxin (TTX), a neurotoxin found in the ovaries and liver of the puffer fish, which, by potently blocking Na^+ channels, abolishes action potentials in neurons.

In Hodgkin and Huxley's original experiments they initiated an action potential by applying a very short electrical current to the outside of the nerve. This promotes a local, depolarising disturbance in the resting membrane potential that induces the opening of a small number of Na^+ channels generating

what is termed a "local depolarising response" of the membrane. But what normally triggers an action potential? In sensory neurons stimulation of specialised sensory nerve endings may lead to a local depolarising response. In the central nervous system, synaptic events received over the dendritic tree of a neuron are integrated into a signal that may be sufficient to promote the generation of action potentials in the axon of the neuron.

Na^+ channels open because they possess a sensor mechanism that detects depolarisation in transmembrane voltage. Triggering this sensor promotes their opening, or activation, through a conformational change in a part of the ion channel close to the inner face of the membrane, commonly termed the activation "gate" (fig 1Cii). This is why Na^+ channels are said to be voltage-sensitive ("voltage-gated" or "voltage-activated" are synonymous terms). A few Na^+ channels open in response to the local depolarisation and the influx of Na^+ through these channels then adds to the depolarisation. If the membrane potential depolarises to a "threshold" value around −45 mV, then there will be a rapid recruitment of all the voltage-sensitive Na^+ channels leading to the fast depolarising phase of the action potential. This recruitment of Na^+ channels is "regenerative" in the sense that Na^+ going through one channel adds to the depolarisation which triggers more Na^+ channels to open. As such, the action potential is termed an "all or nothing" response; once threshold is reached the full action potential is always generated. The molecular mechanisms which have been proposed to underlie voltage-sensitivity and the subsequent opening of the activation gate are illustrated in figure 1Ci and ii.

The depolarising phase of the action potential overshoots zero mV so reversing the transmembrane potential; however, the depolarisation stops before it reaches the predicted equilibrium potential for Na^+. This is for two reasons:

- The first is an inherent property of voltage-gated Na^+ channels, known as inactivation. After being open for only a very short time (~1 millisecond), the Na^+ channel switches to a conformation that no longer allows Na^+ to pass through even though the membrane potential is still depolarised and the activation gate is still open (fig 2). This conformation of the channel is the result of another part of the channel protein structure that occludes the pore and so prevents further movement of Na^+. The pore blocking structure is termed the inactivation gate. At a molecular level the inactivation gate is a part of the channel that is found on the intracellular side of the membrane that flips up and occludes the inner entrance to the pore (fig 1Ci and ii).

- The second reason for the termination of the depolarisation is the opening of another set of voltage-sensitive channels in the membrane. These channels are selectively permeable to K^+ ions. As we have seen already, the intracellular K^+ concentration is high resulting in an equilibrium potential more negative than the resting membrane potential. Thus, when the membrane potential is depolarised during the action potential, K^+ flows out of the neuron bringing the membrane potential back towards more negative potentials. Two properties tailor these voltage-sensitive K^+ channels to this role; compared to Na^+ channels, they require a greater depolarisation of the membrane potential before they open, and they activate more slowly (over several milliseconds) than Na^+ channels. These properties allow the depolarising phase of the action potential to be initiated before the K^+ channels open (fig 2).

Thus, an increase in K^+ permeability initially puts a brake on the depolarising phase of the action potential and then, as all the K^+ channels activate and the Na^+ channels start to inactivate, the membrane potential is driven back towards the resting state. This K^+ conductance is termed the "Delayed Rectifier" K^+ conductance because it activates after, and it repolarises or "rectifies" the change in membrane potential caused by the opening of Na^+ channels. In addition, the channel does not inactivate, thus K^+ permeability is terminated by closing the activation gate, or deactivation, as the membrane potential hyperpolarises. This process is, however, slow (like the opening of K^+ channels) which means these channels remain open for a period after the action potential and this can result in an overshoot of the resting membrane potential, generating what is termed an after-hyperpolarisation. We will return to this shortly.

HOW DOES THE ACTION POTENTIAL PROPAGATE DOWN THE AXON?

The depolarisation of the membrane by the action potential generates local currents that depolarise adjacent parts of the axon membrane. If these local currents depolarise the adjacent membrane to threshold, the action potential will be propagated to this part of the membrane and so on down the axon. The speed at which the action potential propagates down the axon, or conduction velocity, is largely the result of how far the local currents extend down the axon before an action potential is produced. The further the local currents travel down the axon, while being of sufficient amplitude to still allow the membrane to reach threshold, the faster the propagation of the action potential. This distance depends on the electrical properties of the axon, in particular the electrical resistance of the membrane and the internal contents of the axon. Large diameter axons have low internal resistance while the greater the number of open channels in the membrane, the lower the membrane resistance. High internal resistance and low membrane resistance will result in slow propagation of the action potential.

A commonly used analogy for the spread of these local currents is a leaky garden hose. Water pushing down the hose follows the path of least resistance; thus, if the diameter is narrow and there are many holes, water leaks out limiting the distance it can travel down the core of the hose. There are two solutions to getting water further down the hose. Either, increase the diameter of the hose thereby making the core a lower resistance pathway, or patch up the holes in the hose with tape thereby preventing leakage. The squid adopts the first solution with axon diameters of ~1 mm. The second alternative is preferred by the mammalian central nervous system where the number of neurons is greater and space at a premium. Specialised glial cells called oligodendrocytes wrap themselves around the axon to form a high resistance insulating membrane called the myelin sheath (in the peripheral nervous system myelination is provided by another type of glial cell, the Schwann cell). Thus, the local currents are unable to leak across the membrane because of the insulating myelin, resulting in their greater penetration down the core of the axon. But even with the insulating myelin there is a limit to how far a local current can propagate in the absence of high densities of Na^+ channels, thus, at intervals down the axon, gaps in this myelin sheath called "nodes of Ranvier" are found. The density of voltage-gated channels in the axonal membrane is high at these nodes to allow the action potential to propagate by jumping from node to node by what is called "saltatory conduction" (from the Latin meaning "to jump").

WHY DOES THE ACTION POTENTIAL ONLY PROPAGATE IN ONE DIRECTION ALONG THE AXON?

Action potentials usually propagate from the cell body, down the axon, to the axon terminals. This polarity is largely due to the action potential being triggered by synaptic input received across the dendritic tree of the neuron. Action potentials do not normally propagate back into the dendrites because, in general, they do not have a sufficiently high density of voltage-sensitive Na^+ channels. However, once the action potential reaches the axon terminals what prevents it turning round and coming back up the axon? Remember, that after the initial depolarising phase of the action potential, voltage-gated Na^+ channels are in an inactivated state. This inactivation means that once an action potential has occurred, that part of the membrane enters a period during which another action potential cannot be initiated. Thus, the action potential propagates towards the axon terminals because only the membrane "ahead" of it has Na^+ channels ready to open. The axon "behind" the action potential, where it has just come from, has inactivated Na^+ channels so cannot generate another action potential until these channels recover from the inactivated state, a process which is both time- and voltage-dependent, occurring faster at hyperpolarised potentials. The membrane "behind" the action potential is said to be "refractory". Indeed, because the Na^+ channels are unable to conduct Na^+ in this state, an action potential cannot be generated no matter how big the local membrane depolarisation. The time during which no action potential can be generated is termed the "absolute refractory period".

In addition, for a short time, the axon membrane "behind" the action potential, has high permeability to K^+ because K^+ channels close relatively slowly. Open K^+ channels mediate the after-hyperpolarisation (fig 2) and also confer low membrane resistance, conditions which oppose the chance of reaching threshold. This also contributes to the reluctance of the membrane "behind" the action potential to initiate another action potential. The transient after-hyperpolarisation, however, speeds up the recovery of Na^+ channels from inactivation. Therefore, once enough Na^+ channels have recovered from inactivation, an action potential can be initiated but a greater stimulus is required because the K^+ permeability is still high. This period is termed the "relative refractory period".

By the time Na^+ channels have recovered from inactivation and K^+ channels have closed, the action potential will have moved a distance away from this part of the axon membrane such that the local currents that spread back (and the depolarisation they cause) will not be big enough to reach threshold. This ensures that in response to a single stimulus an action potential only propagates in one direction—down, not up, the axon. Another action potential can only be generated by further stimulation after an interval determined by Na^+ channel inactivation and relatively slow K^+ channel closure. Therefore, these properties also tightly govern the maximum frequency at which an axon can generate action potentials.

It is worth noting, however, that if the stimulus that triggers the action potential occurs at the axon terminals then an action potential will propagate *towards* the cell body. We might do this experimentally in which case we would call it an "antidromic" action potential. Also, sensory nerves with specialised axon terminals that act as sensory receptors in the skin propagate action potentials towards, rather than away from, the cell body, but again only in one direction. Thus, the properties of the channels that mediate the action potential do not confer a direction of propagation on the axon per se but do ensure that an action potential only propagates *away* from the stimulus source.

WHAT HAPPENS WHEN THINGS GO WRONG?

Action potentials are fundamental for neuronal communication, their frequency and pattern being the code for information transfer throughout the nervous system. There are 10 distinct types of mammalian Na^+ channel and more than 90 K^+ channel types, each with subtly different properties. Different neuronal types have different channel combinations, therefore, the frequencies at which they conduct action potentials vary greatly. In the peripheral nervous system sensory neurons conduct action potentials at frequencies between 1 and 20/second. In the central nervous system, there are many examples of neuronal types coding action potentials at these frequencies but there are others that can generate must faster bursts of action potentials. For example, the Purkinje cells of the cerebellum can generate action potentials up to 200/second while some neurons in the hippocampus, thalamus and cortex can produce action potential bursts of up to 300/second. It is not surprising then that disrupting the mechanisms that underlie this signalling system can have disastrous consequences. In several forms of epilepsy the characteristic hyperexcitability of neurons that mediates seizure activity can be attributed to mutations that alter the normal function of voltage-sensitive Na^+ or K^+ channels (see Ashcroft for review).[3] In a similar way, changes in sensory neuron excitability associated with some chronic pain states may be attributable to changes in voltage-sensitive ion channel function. Finally, the symptoms associated with multiple sclerosis are linked to impaired action potential propagation caused by a disruption of axon myelination.

Thus, the mechanisms first described over 60 years ago remain vital to our continued progress in the understanding of a range of nervous system disorders.

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