Ion channels, action potentials and disease

Catherine McCrohan

Neuroscientist Catherine McCrohan explains how some disorders are caused by ion channels malfunctioning

Diseases of the nervous system can be extremely debilitating. They can affect our ability to sense the world around us, to move properly, and even to think and learn. Some diseases are due to changes in ion channels. Such changes can disrupt the transmission of impulses in the brain, leading to diseases including epilepsy and deafness.

Key words

- Voltage-gated ion channel
- Neurone
- Brain
- Action potential
- Brain disease

A huge amount of information is transmitted through our nervous systems. The information takes the form of nerve impulses called action potentials. These impulses result from changes in the voltage across the cell surface membrane of nerve cells (neurones), which are in turn caused by the movement of ions through the membrane. Ion channels are essential for the production of action potentials. They consist of proteins in the cell surface membrane which form pores that allow ions to pass through (see Box 1). When ion channels go wrong, brain function can be severely affected. Understanding how ion channels work to generate action potentials is essential for understanding and treating these disorders.

Ions and membrane voltage

All biological fluids are based on a salt solution containing positively and negatively charged ions, such as calcium (Ca^{2+}), sodium (Na^+), potassium (K^+) and chloride (Cl^-) ions. Maintaining the correct concentrations of these ions inside and outside the cell is critical for life. Nerve and muscle cells use ions to generate electrical signals because ions carry an electrical charge. All living cells have a potential difference across the cell surface membrane between the inside and outside of the cell. It is negative inside, and may vary from less than 50 to more than 100 millivolts (a millivolt is a thousandth of a volt). This resting membrane potential provides the potential energy for the action potential.

The phospholipid membrane surrounding the cell prevents the movement of charged ions, at least in part because it is **hydrophobic**. To cross the cell surface membrane, ions must flow through ion channels consisting of proteins that span the membrane (see Box 1). Ion channels open and close in response to a stimulus, allowing the passage of different types of ion. One class of ion channel, the voltage-gated ion channels, open in response to a change in voltage across the membrane (see Figure 1). This happens because the shape (conformation) of the protein changes when it is exposed to a change in voltage. When this happens to the proteins forming an ion channel it leads to

Box 1 Ion channels

Proteins that span the cell surface membrane can form ion channels (see Figure 1.1). These channels consist of four to six protein molecules — subunits — arranged around a central pore. The pore is hydrophilic, so it allows charged ions to pass through. It may be open or closed at any given time. Most are selective for a particular ion or ions (e.g. Na^+ or K^+ or Ca^{2+} ions). All these properties depend on which proteins form the subunits. Once a channel is open, the ions for which it is selective can flow through. The opening and closing of ion channels is termed gating.

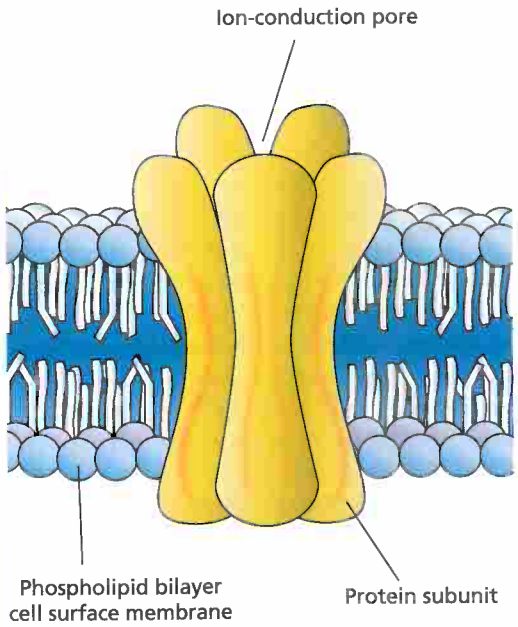


Figure 1.1 Diagram of membrane-spanning ion channel consisting of five protein subunits surrounding a central pore

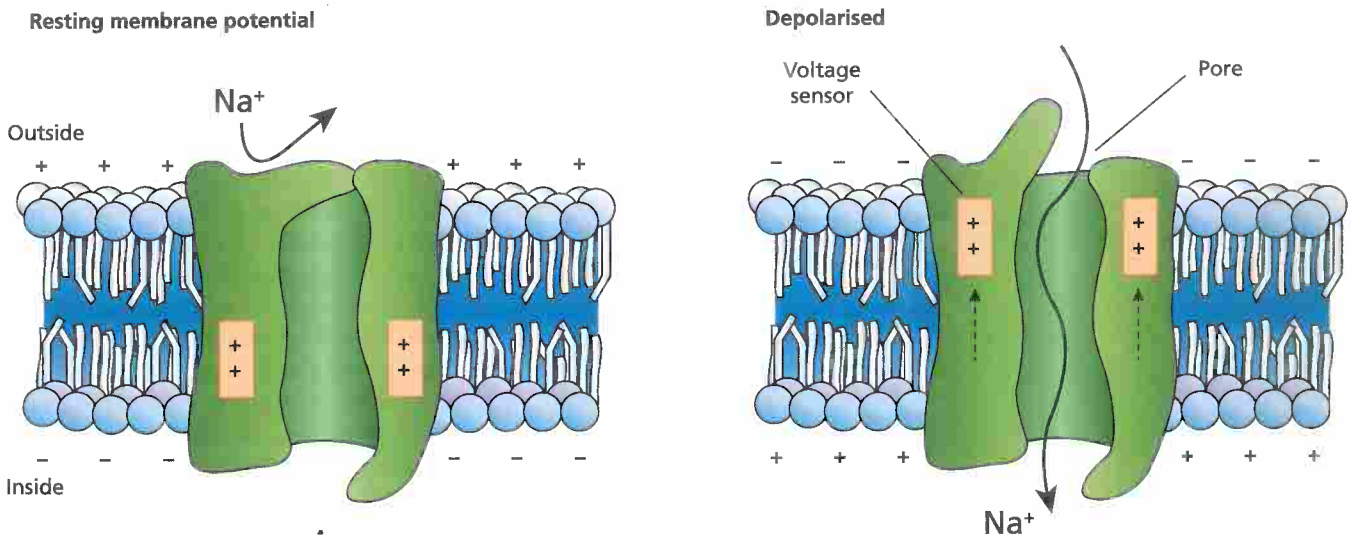


Figure 1 Simple model of how a voltage-gated ion channel might work. The voltage sensor triggers a change in the conformation of the protein subunits to open the pore

the opening of the pore through the membrane. The pore is **hydrophilic** and its internal charge, shape and size determine which ions can pass through. Ions always flow through ion channels down an electrochemical gradient which depends on the charge and ion concentrations on both sides of the membrane (see Box 2).

Ion channels and action potentials

There are hundreds of different types of ion channel. The first voltage-gated ion channels to be studied in detail were those responsible for the generation of electrical impulses — action potentials — in neurones. In most neurones, the action potential is due to the opening and closing of two main types of voltage-gated ion channel — Na^+ and K^+ channels. The sequence of events is summarised in Figure 2.

An action potential is triggered by a small reduction in the voltage across the membrane, which makes the inside of the cell less negative. This change in voltage is called depolarisation and may be due to an incoming signal from a **synapse** impinging on the nerve cell, a sensory stimulus (e.g. a chemical or movement), or an action potential occurring in an adjacent region of the same neurone. The change in voltage is the stimulus required to open the ion channels. Na^+ channels open first, leading to rapid movement of Na^+ ions

Terms explained

Anions Negatively charged ions.

Hydrophilic Attracting or attracted by water.

Hydrophobic Repelling or repelled by water or other charged substances.

Synapse Junction between two nerve cells across which signals are transmitted.

Box 2 Electrochemical gradients

The concentration of different ions on either side of the cell surface membrane is maintained by energy-requiring ion pumps. The consequence of these concentration differences is that there is usually more negative charge inside the cell than outside — mainly due to large, negatively charged **anions** that are unable to leave the cell. In other words, the membrane has a voltage across it — the membrane potential. When ion channels for a specific ion open, that ion flows passively through, with the direction of flow determined by both the chemical gradient (concentration difference — green arrows in Figure 2.1) and electrical gradient (charge difference — black arrows in Figure 2.1). These two gradients in combination are known as the electrochemical gradient. When the cell is at rest, both chemical and electrical gradients for Na^+ ions are directed from outside to inside — positively charged Na^+ ions flow from high concentration to low concentration and from positive to negative (see Figure 2.1). For K^+ ions, the two gradients oppose each other. However, when K^+ channels open at the peak of the action potential, when the cell is positive inside, K^+ ions flow out down both chemical and electrical gradients.

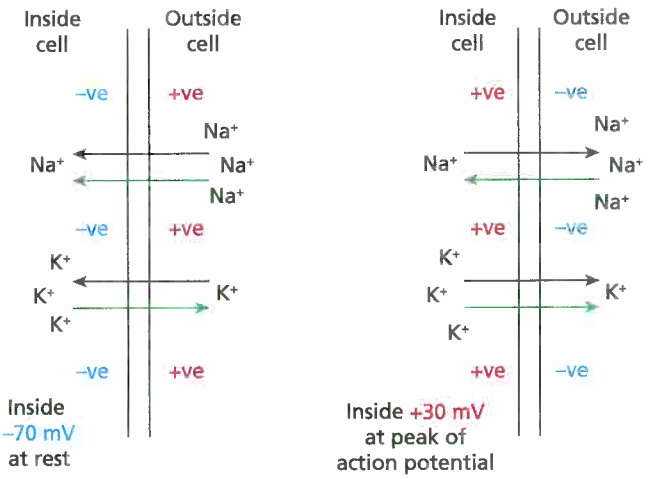


Figure 2.1 The electrochemical gradient for an ion is made up of a combination of the chemical gradient (green) and the electrical gradient (black). Na^+ ions are more concentrated outside than inside the cell. The reverse is true for K^+ ions. Ions flow passively across the membrane down their electrochemical gradient, but only when ion channels are open

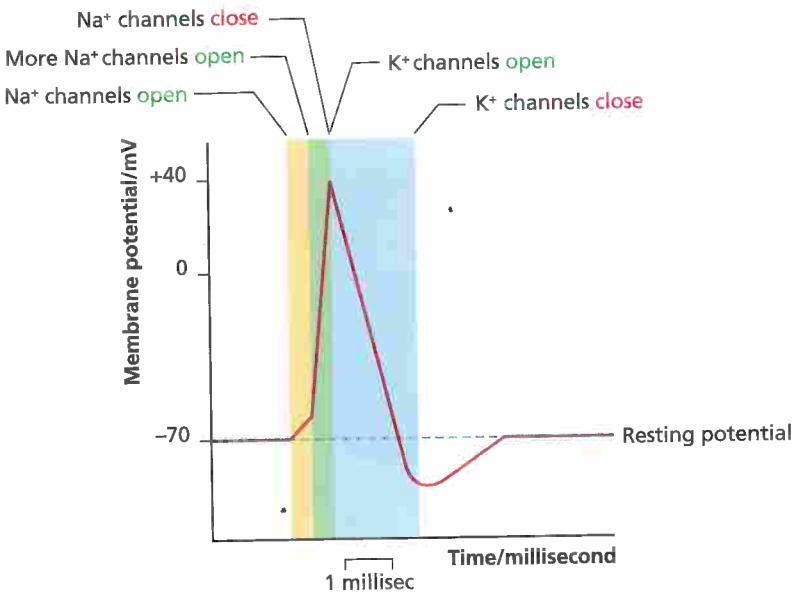
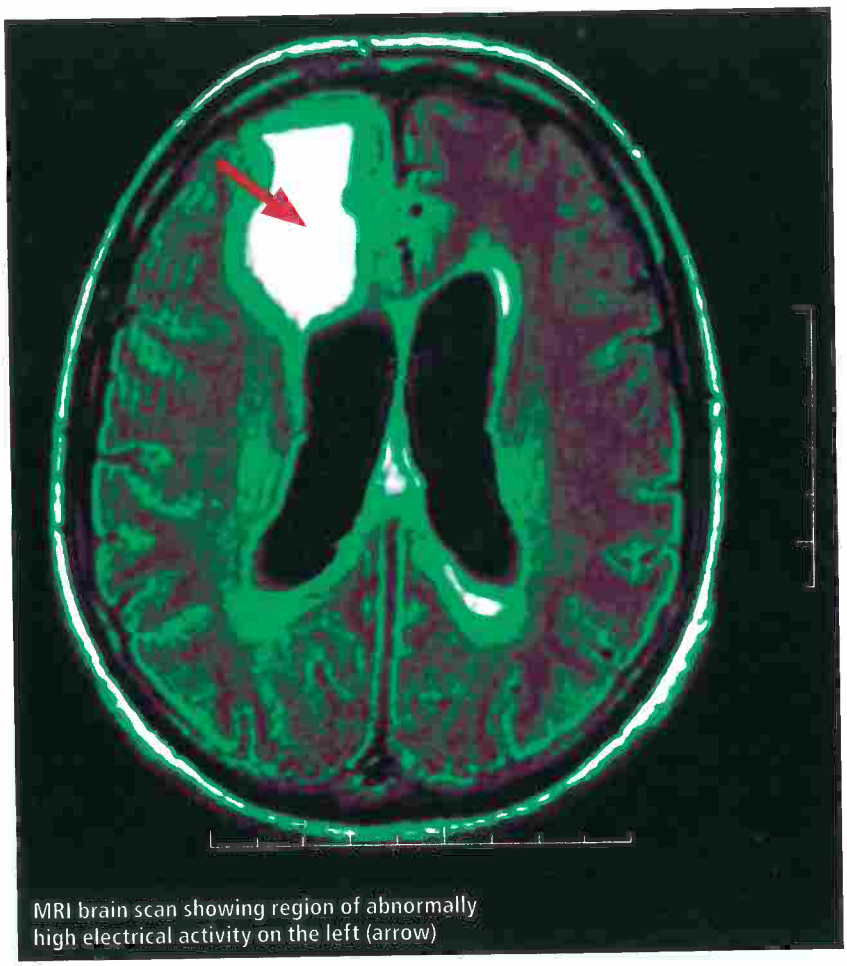


Figure 2 Sequence of events during an action potential

into the cell from a high to a low concentration and from positive to negative charge (see Box 2). This movement leads to further depolarisation as the positively charged ions enter the cell. Increased depolarisation opens yet more Na^+ channels, leading to more depolarisation.



MRI brain scan showing region of abnormally high electrical activity on the left (arrow)

The opening of voltage-gated Na^+ channels underlies the very rapid rising phase of the action potential during which the membrane potential reverses from about –70 mV (negative inside) to about +40 mV (positive inside) within about a millisecond (thousandth of a second) — see Figure 2. The membrane voltage becomes positive rather than just discharging because Na^+ ions are more concentrated outside than inside the cell. They therefore continue to diffuse into the cell even when the cell begins to become positive inside. At this point the Na^+ channels start to close. This is a property of the Na^+ channels that is not affected by voltage. It happens because the open conformation of the channel is unstable.

The channels close automatically after a very brief opening period — a process called inactivation. At the same time voltage-gated K^+ channels open. Their opening is also triggered by initial depolarisation but is delayed because they are slow to open. This means that they don't come into play until the Na^+ channels have started to close. When K^+ channels open, K^+ ions leave the cell (see Box 2). They take positive charge with them, returning the cell to its resting, negative state. The action potential is over in just 1 or 2 milliseconds (see Figure 2).

Channelopathies: when ion channels go wrong

In some individuals a genetic defect or mutation produces a small but important change in the amino acid composition of a channel protein. This changes its shape and function so that the ion channels don't work properly. Such changes can result in minor or more debilitating diseases that tell us much about how ion channels work, but also present a challenge to patients and doctors.

There are several ways in which voltage-gated ion channels may malfunction. A defect in the way the protein responds to a change in voltage may make it open too readily, or make it more difficult to open. Once open, a channel may remain open for too long before closing, or it may close prematurely. All of these possibilities can lead to potentially catastrophic changes in the ability of the neurone to generate action potentials.

Inherited epilepsies

Epilepsy is a fairly common neurological disorder. It takes many different forms and is caused by episodes of abnormally high electrical activity in a region of the brain. Around 40% of cases of epilepsy have at least some genetic basis and some are due to a single gene mutation. Several different mutations give rise to epilepsy or make an individual more susceptible to the disease. These include channelopathies.

One example involves mutation of one of the genes that encodes voltage-gated K^+ channels. When

these channels malfunction, neurone excitability is increased. This is because the movement of K^+ ions out of the neurone is normally responsible for returning the membrane potential to its resting level of –70 mV (see Box 2). In some cases, mutations cause the Na^+ channels to open in response to depolarisation of the membrane, but then they do not close effectively so the membrane stays depolarised — generating excessive and abnormal action potentials. Another mutation is thought to affect the voltage sensor on the Na^+ channel so that it becomes hypersensitive to a change in voltage and the channels open too readily. Understanding how these and other mutations affect electrical activity of neurones will aid the development of improved anticonvulsant drugs.

Hereditary hearing loss

Some forms of deafness are inherited. When the cause is a mutation in a single dominant gene, whole families can be affected. One such mutation affects the voltage-gated K^+ channels in sensory hair cells of the inner ear. These cells convert sound waves into electrical impulses for transmission to the brain. When the K^+ channels aren't working, the cells start to degenerate, leading to deafness. Scientists are looking at ways of preventing this. Possibilities might include drug treatment to keep the K^+ channels open, or gene therapy to restore normal channel function.

Too much or too little pain

Patients with a condition called erythromelalgia experience excruciating, burning pain in their hands and/or feet. This condition has a number of causes, but one is a mutation in a gene coding for a protein in a Na^+ channel. These particular channels are found in neurones that carry impulses from pain receptors in the limbs to the central nervous system. The change in protein conformation of the channels makes them open too easily and they stay open for longer than normal. This means that more action potentials are generated in response to weak stimuli such as heat or pressure, causing pain.

Interestingly, a different mutation in the same gene was identified in a street performer in Pakistan, together with members of his family. The mutation meant that the Na^+ channels were much less responsive than normal. The performer has no sense of pain and entertains the public by walking over hot coals and sticking knives into himself.

Different mutations in the same gene can lead to excruciating pain or no sense of pain

Channelopathies have been implicated in many other disorders, including some affecting the heart, kidneys and skeletal muscle. The more we understand how normal ion channels function, the better we can develop new therapies for these often life-changing diseases.

Catherine McCrohan is professor of comparative neurobiology at The University of Manchester and one of the editors of Biological Sciences Review. She teaches about the nervous system and researches how sensory information is coded in the fruit fly.

Further reading

www.epilepsysociety.org.uk

From *New Scientist*, more on the use of gene therapy to treat deafness:
http://tinyurl.com/o4cmx7c

History of Nobel prizewinning research to understand signal transmission in the nervous system:
http://tinyurl.com/q5cjxul

Key points

- Voltage-gated ion channels in the nerve cell membrane underlie the generation of action potentials.
- These channels open in response to a change in voltage across the membrane.
- During an action potential, first Na^+ and then K^+ channels open, allowing movement of ions, producing an electrical signal.
- Channelopathies are diseases in which specific ion channels do not function properly. Examples are types of epilepsy and deafness.