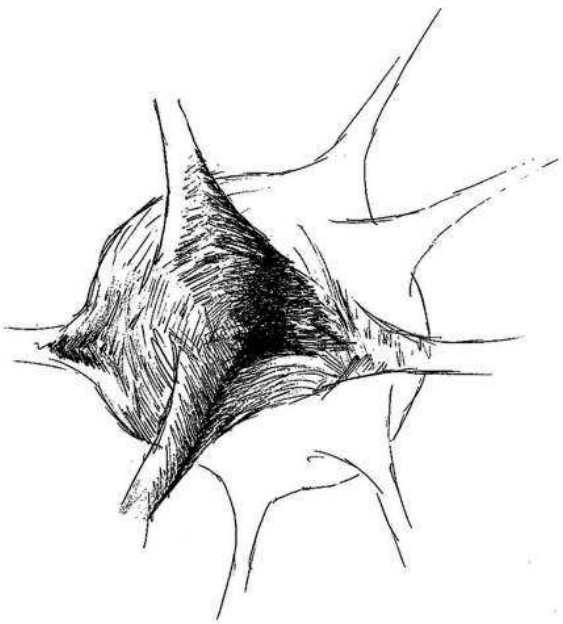
1 Neurons and Neural Communication



Brain Cells and Basic Structure

From the tallest tree to the simplest bacteria, the basic unit of any living organism is the cell. All structures within our bodies are composed of cells, which include heart cells, liver cells, skin cells, hair cells and brain cells. Brain cells can be divided into two main types: neurons, which allow us to feel, taste, see, move, feel emotions, remember and communicate; and glial cells, which help to support and protect neurons. Within the human brain there are billions of neurons and trillions of connections among them. When you look up at the night sky and consider that our Milky Way galaxy is thought to contain 200 billion stars, you can begin to appreciate the sheer number of cells located within your brain, a structure that is slightly larger than a closed fist.

Neurons come in all shapes and sizes, but there is a basic structure that is common to all (Figure 1.1). The cell body or *soma* contains the nucleus and other structures critical to keeping the cell alive and functioning. The *axon* is a long fibre that emanates from the cell body and is involved in sending information from the cell body to the end of the neuron. This information is passed as a small electrical pulse called an *action potential*, which will be discussed in more detail later. The axon is covered by a myelin sheath, which both insulates the axon so the information is kept within the one neuron and ensures that the action potential is passed quickly from one end of the neuron to the other. Some axons are small, but others are very long; for example, one axon runs from the base of your spine to your big toe. The axon can branch many times, but each branch ends with a small bulb called the *synaptic terminal* or *synaptic bouton*. It is at this junction, the synapse, that one neuron communicates to the next one. However, information must pass from one neuron to the next across a small gap called the synaptic cleft (see Figure 1.1); for this to occur, the electrical signal is converted into a chemical signal that readily crosses the gap and triggers a signal in the dendrites of the second neuron. *Dendrites* are branchlike fibres that serve as receivers of signals from multiple neurons. The message continues in the second neuron and keeps going until it is terminated. Therefore, the main function of the neuron is to process signals and pass the signals along.

Glial cells make up the majority of cells in the brain. In fact there are about 10

glial cells to every neuron. There are four main types of glial cells: oligodendrocytes, Schwann cells, microglia, and astrocytes.

Oligodendrocytes are cells whose extensions, composed of a fatty substance called myelin, wrap around the axons of neurons. It is these cells that allow for the fast transmission of an action potential down a neuron. Oligodendrocytes are found mainly in the central nervous system (CNS; brain and spinal cord).

Schwann cells perform a similar function by wrapping around neurons, but they do so in the peripheral nervous system (PNS, nerves extending from the spinal cord to other parts of the body – heart, lungs, toes, fingers, etc.) as opposed to the CNS. Schwann cells can also help with the regeneration of neurons, a task that oligodendrocytes are unable to do. This explains why regeneration is easier following damage to peripheral nerves, compared to neurons in the brain. Another major difference between these two classes of glial cells is that each Schwann cell wraps around a segment of the neuron, whereas the extensions of an oligodendrocyte can wrap around multiple neurons (Figure 1.2).

Microglial cells, or *microglia,* are smaller than the other cells types and are involved in the inflammation response. They protect the brain from invading microorganisms. In addition, if neurons become damaged and die, the job of the microglial cells is to break down these cells even further, and then clean them up by engulfing the remaining debris by a process termed *phagocytosis.*

Astrocytes, as their name suggests, are cells that are star-shaped. These cells, similar to microglia,

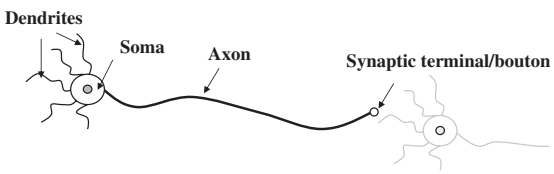


Figure 1.1 Diagram of a neuron and its various components.

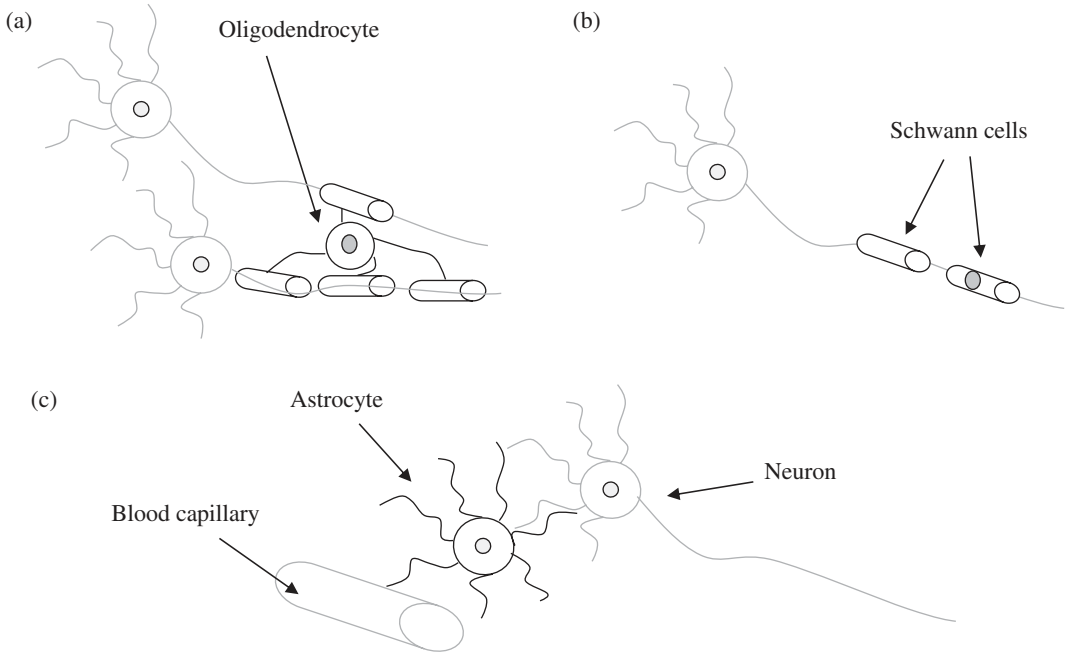


Figure 1.2 Diagram of different glial cells including (a) oligodentrocytes, (b) Schwann cells and (c) astrocytes.

function by cleaning up the debris of dying neurons. In addition, astrocytes are thought to provide a mechanism by which neurons receive nutrients and get rid of any waste material by acting as a mediator between neurons and blood capillaries. Astrocytes receive glucose from the blood, which is converted into lactate which, in turn, is taken up by neurons and is used as a source of energy. Recent research indicates that astrocytes not only perform a supporting role for neurons, but maybe involved in signal communication as well.

Communication within Neurons

The Cell Membrane

One of the critical structures of any cell is its membrane. The membrane helps to give the cell its shape and helps keep all the internal organelles within the cell, and it also functions to regulate what goes in and out of the cell, a very important function. We can imagine cells to be like balloons, which come in different shapes and sizes. Likewise, some brain cells are spherical and some are pyramidal. It is the membrane that gives a cell its shape. If we blow into a balloon, it will expand and eventually burst; if air is removed it will shrivel. Further, the air that you have blown into the balloon is different to the air outside. When you tie an inflated balloon, nothing can come in or out. Likewise, the fluid within a cell, the intracellular fluid, is of different composition than the extracellular fluid, and must be regulated.

The cell membrane is composed of what is termed a *phospholipid bilayer* (Figure 1.3), and it is this layer that prevents fluids and other substances from entering and leaving the cell. Because the double layer is composed of lipid, a fat-like substance, water and other fluids are unable to pass through. But cells need to receive nutrients and get rid of waste material, so how can the materials get through this membrane?

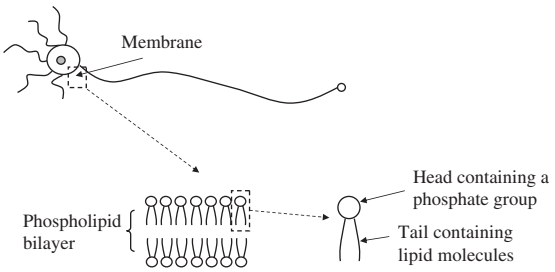


Figure 1.3 The membrane of a neuron is composed of a phospholipid bilayer, which regulates the movement of substances in and out of the cell.

Embedded within the cell membrane are large proteins, and it is through these proteins that materials can pass in and out of the cell. Proteins have the fantastic ability to change shape, and it is this property that makes them so useful and versatile. There are different types of proteins embedded within the membrane. Some proteins form a channel through the membrane, but are of a particular size and shape that only allow very specific ions (charged atoms) through (Figure 1.4a). For example, there are protein channels that only allow sodium ions (Na^+) through, and there are other channels that only allow potassium ions (K^+) through. Other protein channels, called *ligand-gated channels*, only allow ions through the channel when a molecule is attached. When a particular molecule attaches to the protein channel, the channel changes shape, forming a hole through the centre and allowing ions to flow into the cell (Figure 1.4b). A third type of channel operates as a pump, changing dimensions so that the channel pumps some ions into the cell and pumps others out of the cell (Figure 1.4c). We will meet these channel types and others as we progress through the chapter.

Resting Membrane Potential

Imagine if we were to take a very fine electrode (a small wire about the size of a single strand of hair), place it into a neuron and record its voltage or electrical charge. We would notice that the inside of the cell is more negative

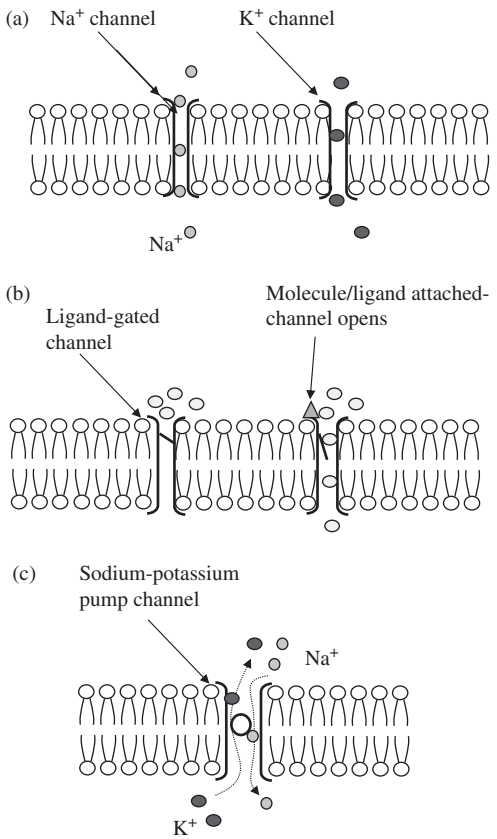


Figure 1.4 Representation of different channels that are embedded in the cell membrane. (a) Some channels have a particular shape, which regulates the flow in and out of the cell. (b) Some act like a gate and only open in the presence of a particular molecule; (c) others act as a pump, transporting ions in and out.

than the outside. The voltage difference between the inside and outside of the cell is about –65 or –70 mV (millivolts). The inside of the cell has a charge of approximately –70 mV. This is known as the *resting membrane potential*. Why is the inside of the cell more negative compared to the outside? Recall we suggested that the air blown into a balloon is different than the air outside. The neuron is similar. The composition of the intracellular fluid in a neuron is different compared to the fluid outside the cell. This difference in composition is due mainly to distribution of various ions inside and outside of the cell.

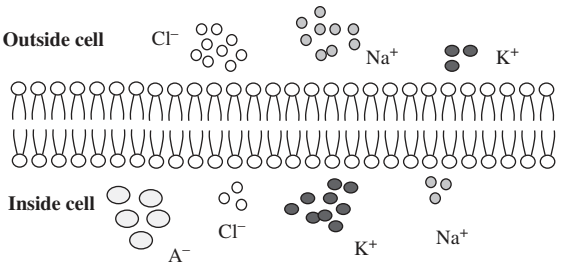


Figure 1.5 Distribution of various ions inside and outside of the cell.

Figure 1.5 shows the four main ions and their distribution on either side of the cell membrane. One of the main reasons that the inside of the cell is more negative compared to the outside is the presence of large negatively charged proteins (represented by A^-), these are unable to pass through the membrane. Although potassium (K^+), sodium (Na^+) and chloride (Cl^-) ions are found on both sides of the membrane, the distribution is not even. Extracellular fluid consists mostly of a saline-like solution, and therefore has a large presence of Na^+ and Cl^- ions, whereas there is a larger concentration of K^+ ions on the inside of the cell.

If the membrane just contained the phospholipid bilayer without any channels, as is illustrated in Figure 1.5, there would be no difficulty in maintaining the balance of composition between inside and outside of the cell. However, there are channels within the membrane that allow ions to flow in and out. How is it that the voltage inside of the cell remains fairly constant, at –70 mV without fluctuating? There are two major forces that help maintain this situation. The first is termed the *diffusion gradient* and the second is called *electrostatic pressure*. Diffusion refers to the fact that molecules will spread or diffuse from an area of high concentration to an area of low concentration. For example, if we were to put some salt into water, it would initially be concentrated in a small area, but with time it would spread evenly throughout the container, thereby spreading from an area of high concentration to areas of low concentration. The second factor, electrostatic pressure, means

that particles of different charges are attracted to each other. Positively charged ions (cations; for example Na^+ and K^+) are attracted to areas that more negatively charged. Negatively charged ions (anions; for example, Cl^-) are attracted to areas that are positively charged.

When we look at Figure 1.6 we can see the forces that are working on each of the ions. As mentioned, the inside of the cell is more negative compared to the outside due to the large proteins that cannot escape; this is represented by the minus signs inside the cell in Figure 1.6. The K^+ ions are concentrated on the inside of the cell. Forces of diffusion want them to flow out of the cell, but they are attracted by the negativity on the inside of the cell. The net result is that they do not really move. Likewise, Cl^- ions want to flow into the cell (diffusion) but are repelled by the negativity on the inside. So these ions do not really move either. Finally, the Na^+ ions want to flow into the cell, both due to diffusion and by attraction to the negativity, but they remain outside, mainly because the Na^+ channels *remain closed*. There is, however, some leakage into the cell, but it is the job of the sodium-potassium channel pump to pump the Na^+ ions back out (and for balance, to bring K^+ ions back in). There are 3 sodium ions (Na^+) pumped out for every 2 potassium ions (K^+) pumped in.

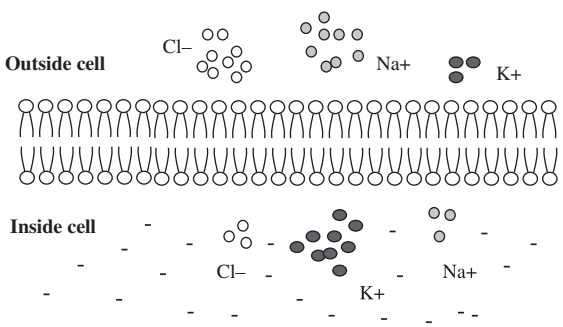


Figure 1.6 The inside of the cell is more negative compared to the outside due the presence of large negative ions.

Action Potential

Generation of the action potential

Information is sent down axons of neurons via small electrical pulses called *action potentials*, represented in Figure 1.7a by the stars. Imagine we were again to insert a small electrode into the axon and record what we would see. Figure 1.7a

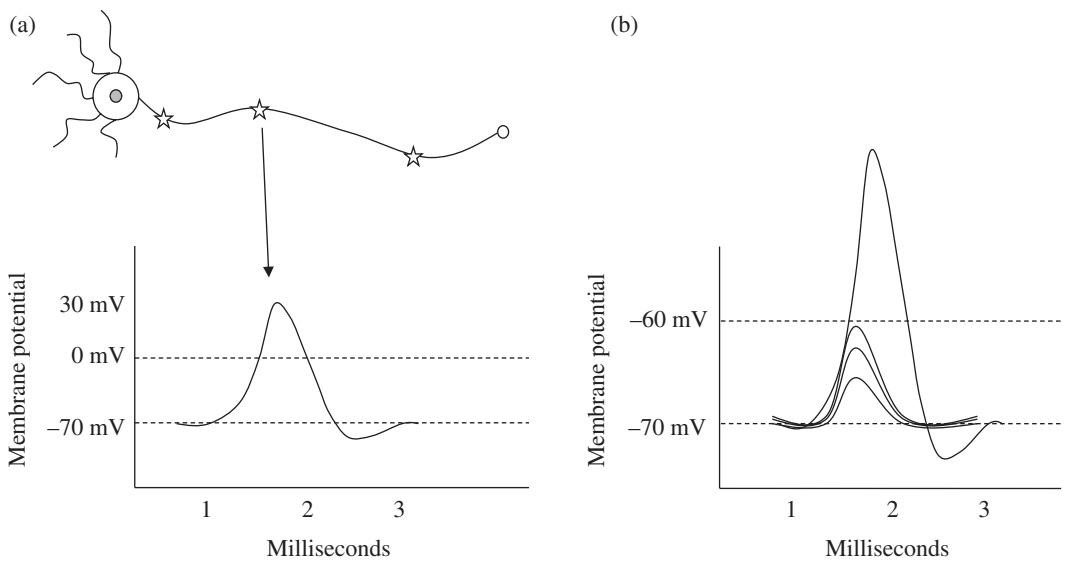


Figure 1.7 (a) The change in the resting membrane potential as an action potential is generated. (b) An action potential is not generated until a certain threshold is reached.

gives an idea of what an action potential looks like, its shape and dynamics. Essentially, what we see is a rapid change in the resting membrane potential. The inside of the cell briefly becomes more positive (termed *depolarisation*), moving from approximately –70 mV to +30 mV before returning to its normal negative baseline state (termed *hyperpolarisation*) of –70 mV. This is all completed in less than 3 milliseconds – an extremely rapid event. The generation of an action potential is, however, an "all or nothing" event. A threshold must be reached before the action potential is fired. The threshold is approximately –60 mV, that is, the inside of the cell must change from approximately –70 mV to –60 mV. If it does not, an action potential will not be generated (Figure 1.7b).

The change in the resting membrane potential during the expression of an action potential must be reflected by the change in the flow of ions in and out of the cell. The next section will provide a step-by-step account of what happens at the cellular level and how this is represented by the various phases of the action potential (Figure 1.8).

1. Once the threshold is reached, Na^+ channels open and sodium ions flow into the cell. They are attracted inwards due to negativity on the inside (electrostatic pressure) and because they are moving from an area of high concentration to a region of low concentration (diffusion gradient). As these positive ions rush in, the inside of the cell becomes more positive, and this is reflected by the upward depolarisation phase of the action potential (Figure 1.9).
2. Next, the K^+ channels start to open slowly and potassium begins to flow out of the cell. The K^+ ions want to move from an area of high

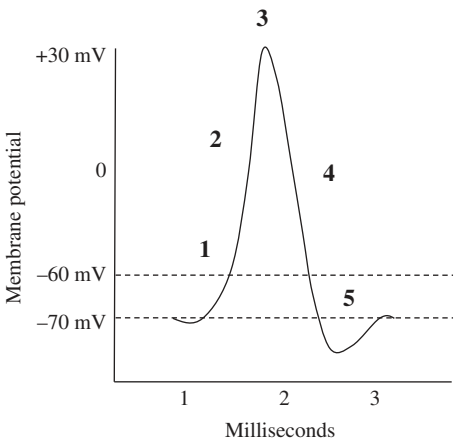


Figure 1.8 The various phases of the action potential. The cellular and the corresponding electrical changes are described for each phase (1–5) are described in the text.

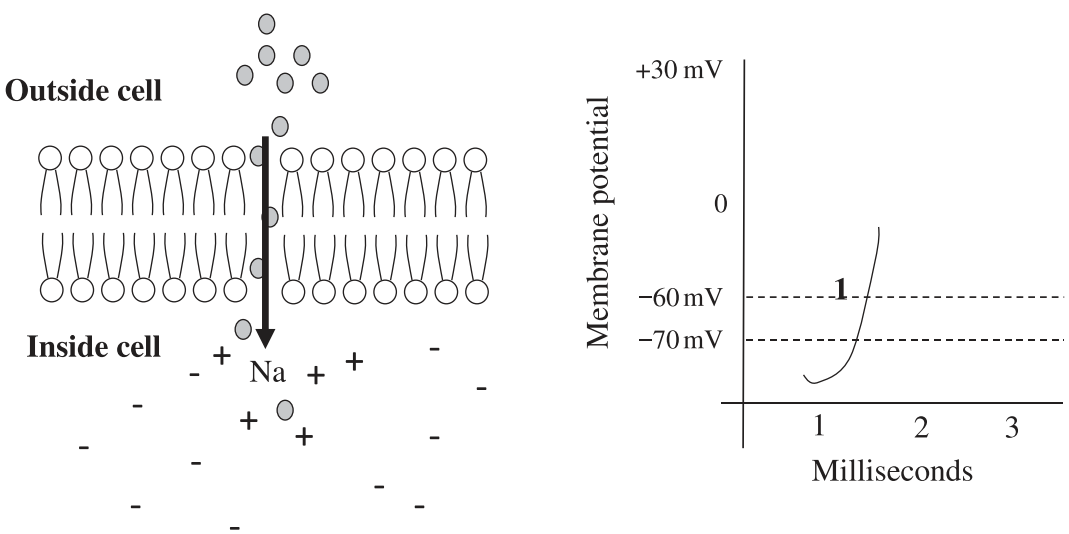


Figure 1.9 Phase 1. Na^+ ions flow in, in the upward depolarisation phase of the action potential.

concentration to one of low concentration, and because the inside of the cell is now starting to get more positive (due to the entry of sodium ions), the positive potassium ions are being repelled outwards (Figure 1.10).

3. As the action potential reaches its peak, the sodium channels close and no more Na^+ ions can come into the cell; this is often termed the *refractory period*.
4. At this stage, the inside of the cell has reached its maximum peak positivity, thereby forcing more and more positive potassium ions out of the cell (Figure 1.11, first panel). All the potassium channels are now open. As K^+ ions flow out of the cell, the inside starts to lose its positivity, and thereby begins to regain its negativity (Figure 1.11, middle panel).
5. As the inside of the cell regains its negativity, the potassium channels close. No more ions can come in or out of the cell. But often too many positive ions have left, so the membrane potential dips below the resting membrane potential of –70 mV (Figure 1.11, right panel). The sodium-potassium pump helps to restore the balance.

Conduction of the Action Potential Down the Axon

Information must go from one end of the axon to the other. All action potentials are very similar in nature; they travel in one direction from the site of generation at the soma to the synaptic bouton. All action potentials remain at the same

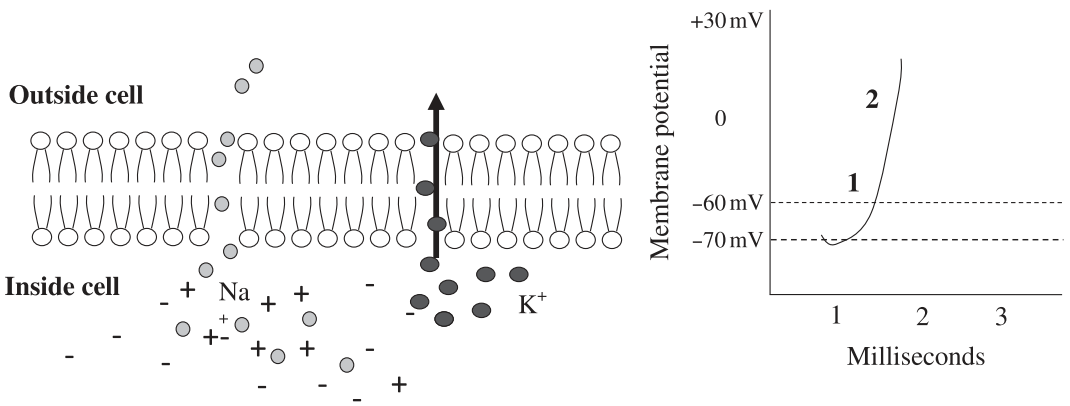


Figure 1.10 Phase 2. K^+ ions move out.

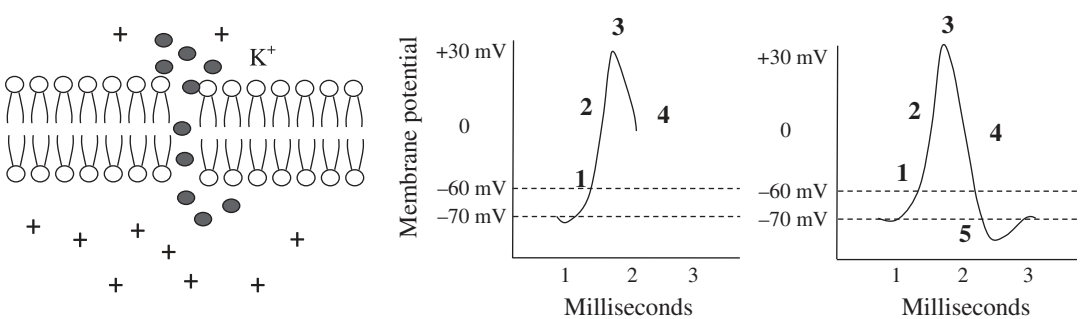


Figure 1.11 Phase 4 and 5. As K^+ ions flow out of the cell (left), the inside starts to lose it positivity (middle). However, too many positive ions have left, so the membrane potential dips below the resting membrane potential of –70 mV (right).

magnitude. Despite the long distances some action potentials have to travel, they do not diminish in size. The rate of firing does, however, change. A strong stimulus, for example, may evoke many action potentials in rapid succession, whereas a weaker stimulus may only evoke one or two.

So far we have described changes that occur in the resting membrane at a particular point along the axon. But how does the action potential 'move' along the axon? Imagine that we wanted to blow a hole in a wall. Using some gunpowder we could create a trail from the wall to a more distant, safer place. We then light the powder at one end, watch the flame move along the trail and see the wall blow up. For all intents and purposes it seems like the flame moves along the path, but in fact it does not. Each single grain of gunpowder lights up and dies out. However, the heat generated from that grain sparks the grain beside it, so the second grain lights up and dies out, and this continues on until it reaches the end. Because the action of heating up the next grain is so quick, it looks as if it is the flame is moving along the trail. If we imagine that an action potential is like a flame moving along an axon, the mechanism is very similar. As the positive ions rush into the cell, an action potential occurs at that particular point. However, these positive ions do not just remain at the point of entry – they spread along the inside of the axon. Therefore, the next segment along the axon becomes more positive, allowing the threshold to be reached and the next action potential to be triggered. As the positive ions flow towards each subsequent segment, action potentials are continually produced until the end of the axon is reached (Figure 1.12).

Continuing with the example of the gunpowder trail, we can see that if the grains are further away from each other, the heat generated from one grain may not be strong enough to spark the next one, and so the flame dies out. The axons of some neurons are wrapped with a myelin sheath from the oligodendrocytes. Along this myelin sheath there are tiny gaps called *nodes of Ranvier*. It is the myelin sheath that allows for the fast transmission

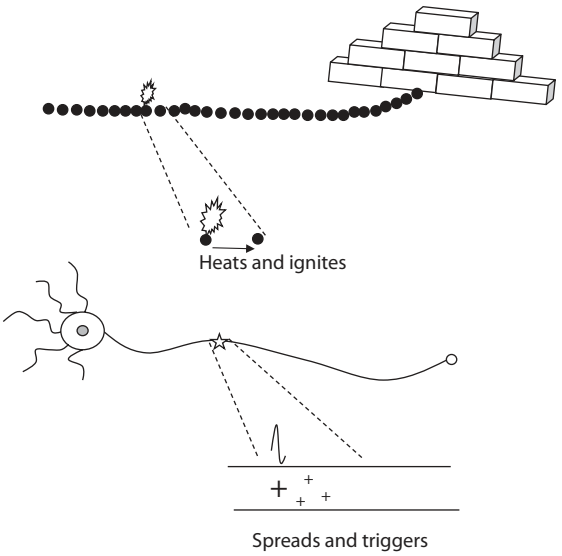


Figure 1.12 Like a flame that seems to be moving along gunpowder (top), the action potential is conducted along the axon (bottom).

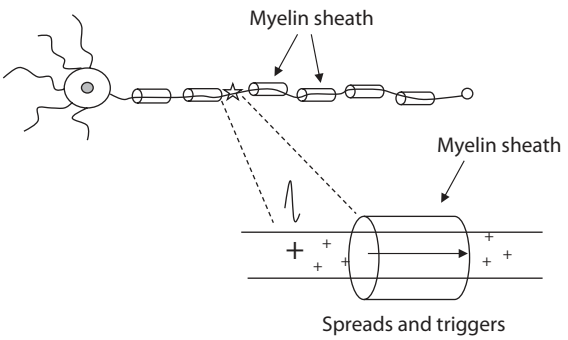


Figure 1.13 The myelin sheath helps speed up the conduction of action potentials along the axon.

of the action potential down the axon. Rather than activating each segment along the axon, the sheath allows the positivity to jump, jumping to the next gap or node of Ranvier, located between the sheaths. The action potential gets retriggered at each gap by the passive spread of positivity through the sheath (Figure 1.13). Conduction of action potentials through myelinated axons offers two advantages over conduction through nonmyelinated neurons. First, the action potential reaches the end of the axon much quicker (up to 15 times faster).

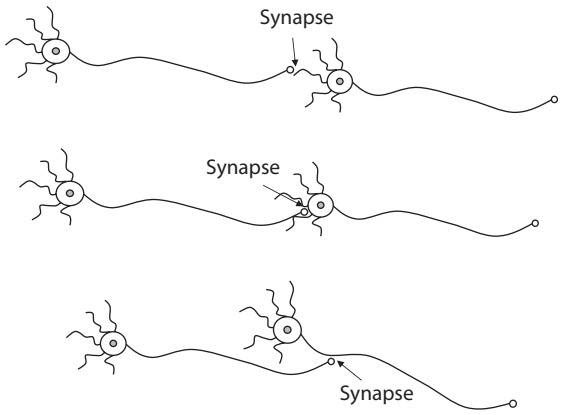


Figure 1.14 Examples of different types of synapses: axondentric (top), axosomatic (middle) and axoaxonic (bottom).

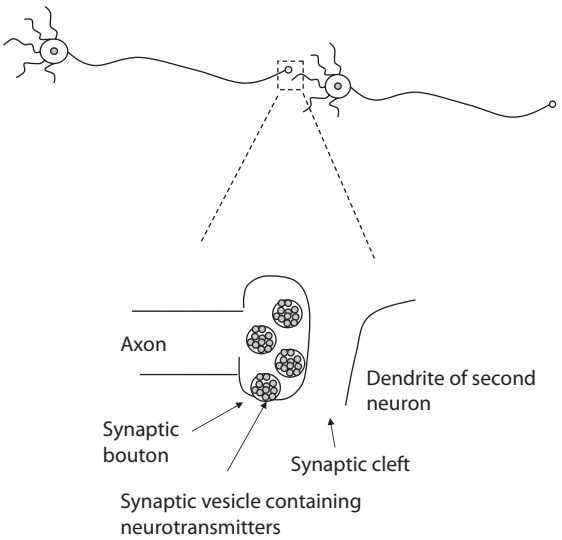


Figure 1.15 Close-up of a synapse, depicting its various components.

Second, the neuron saves energy: fewer action potentials means less use of the sodium–potassium pump to maintain the resting membrane balance at each segment. Note that in patients with multiple sclerosis, an inflammatory disease resulting in damage to the myelin sheath, neural conduction is much slower. This leaves patients with a variety of symptoms including loss of sensitivity, difficulty with movement, balance issues and visual problems.

Synaptic Transmission

As the action potential makes it way towards the end of the axon, it reaches the synaptic terminal/bouton. Information must pass from one neuron to the next, and it does so at junctions formed with a second neuron; these junctions are termed *synapses*. Synapses can occur in three places on the second neuron – on the dendrites, soma or axons, and so the synapses are referred to as axondentric, axosomatic and axoaxonic synapses, respectively (Figure 1.14). Information, however, cannot pass directly from one neuron to the other, as there is a small gap between neurons; this gap is called the *synaptic cleft*. This information must be transmitted by other means: by converting the electrical signal of the first neuron to a chemical signal that can pass across the gap before it is converted back into an electrical signal in the second neuron.

If we were zoom in on the synapse using a powerful microscope, we would see that the synaptic bouton contains a number of small oval or round organelles called *synaptic vesicles*. Each of these vesicles contains neurotransmitters (Figure 1.15). The majority of neurotransmitters fall into three categories. The first category includes amino-acid molecules, which have an amine (NH_2) and carboxyl (COOH) groups in their molecular structure. Examples of neurotransmitters that fall into this family include glutamate, the main excitatory neurotransmitter in the brain; and GABA (gamma-aminobutyric acid), the brain's main inhibitory neurotransmitter. The second category includes amine molecules. Examples of these neurotransmitters are dopamine, adrenaline, noradrenaline, serotonin and acetylcholine. The third category contains the peptides, which include neuropeptide Y and substance P.

When an action potential reaches the synaptic bouton, neurotransmitters are released from the synaptic vesicles into the synaptic cleft. The released neurotransmitters then cross the cleft, attach onto specialised receptors on the second

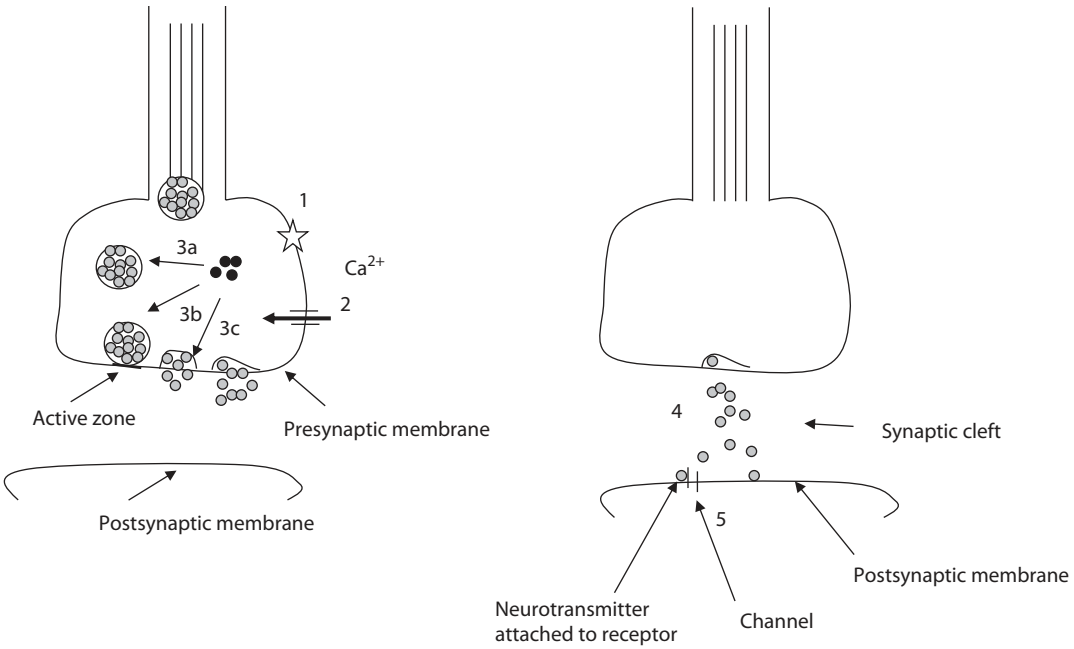


Figure 1.16 Step-by-step description of synaptic transmission (see text for details).

neuron and trigger a response. Thus, information is passed from one neuron to another. There are a number of steps that allow this to occur (see Figure 1.16): The action potential reaches the synaptic bouton (1), which opens voltage-dependent calcium channels (2). Calcium ions (Ca^{2+}), like sodium ions, are in high concentration outside the cell. So when the action potential arrives, the voltage on the inside of the cell becomes more positive, causing the channel to open. Calcium then flows into the cell via diffusion. The influx of calcium into the synaptic bouton has the effect of causing synaptic vesicles to move towards the presynaptic membrane's active zone (3a), to dock to the presynaptic membrane (3b) and to fuse with the membrane, releasing the neurotransmitter into the synaptic cleft (3c). The neurotransmitter crosses the synaptic cleft (4) and attaches onto receptors located in the postsynaptic membrane (5).

What happens when the neurotransmitter attaches onto the receptors depends upon the neurotransmitter involved. Neurotransmitters attach onto receptors that are part of the channel structure. Once the neurotransmitter is attached, the channel modifies its shape and allows either positive or negative ions to flow into the postsynaptic membrane (Figure 1.17). For example, glutamate, the main excitatory neurotransmitter in the brain, attaches onto specific receptor sites on the channel, which then open and allow positive sodium ions (Na^+) into the cell. As a result, the inside of the cell becomes more positive. This positive change in the resting membrane potential in the dendrites of the second neuron is termed an *excitatory postsynaptic potential* (EPSP). GABA, on the other hand is the brain's main inhibitory neurotransmitter; it attaches to receptors and the channel opens, but this channel only allows negative chloride ions in (Cl^-). The resting membrane potential of cell in this case becomes more negative; this transient negative change is termed an *inhibitory postsynaptic potential* (IPSP). These types of channels are termed *ligand-gated ionotropic channels*: 'ligand' because they need a neurotransmitter to activate

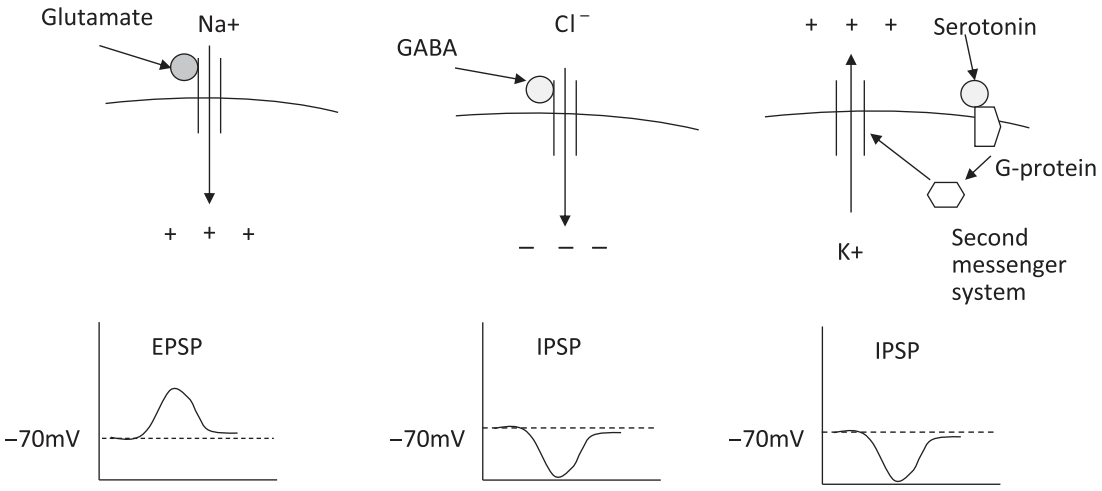


Figure 1.17 Changes in the internal electrical dynamics of the postsynaptic membrane depend on the neurotransmitter involved; e.g. glutamate (left), GABA (middle) and serotonin (right).

them and 'ionotropic' because they allow ions to flow through them. This is the most direct way of converting the chemical signal of the first neuron to an electrical signal in the second.

An indirect method of converting a chemical signal to an electrical one is when the neurotransmitter attaches onto specialised non-iontrophic receptors; these are termed *metabotropic receptors*. In this case there is no modification of the channel to allow ions to flow in; rather, the receptor activates a specialised phospholipid membrane-bound protein termed a *G protein*, which in turn activates a whole cascade of molecular events. The net result of these events is that some of the molecules can activate other channels, away from the original site, which then allow ions to flow in or out of the cell. Although the net results of activation of a metabotropic receptor and an ionotropic receptor may be the same, that is, the inside of the cell becomes transiently more negative or positive, the indirect method is a much slower process (Figure 1.17, right).

At this stage, the neurotransmitters have done their job and are no longer of any use, as such. They are then deactivated through a number of different mechanisms. Some neurotransmitters simply diffuse away. Some are deactivated and broken down by special enzymes located in the synaptic cleft. For example, the neurotransmitter acetylcholine (ACh) is deactivated by the enzyme acetylcholinesterase (AChE). Other neurotransmitters are taken back up into the presynaptic terminal and are recycled. Still other neurotransmitters may be removed via glial cells.

So far we have described the synaptic transmission between two neurons. However, the receiving neuron does not just get messages from a single neuron; it receives information from multiple neurons, which synapse on its dendrites, axon and cell body (Figure 1.18a). The receiving neuron must gather all this information and 'decide' whether to generate an action potential, thereby continuing the process, or not. Therefore, the final step in the process involves integrating all the excitatory and inhibitory inputs that it has received. The more excitatory inputs a neuron receives (i.e. if more EPSPs are produced), the greater the chance that the neuron will generate an action potential. Excitation from the dendrites spreads into the soma and reaches the axon hillock, which is where the soma and axon meet. If the excitation threshold in the axon hillock

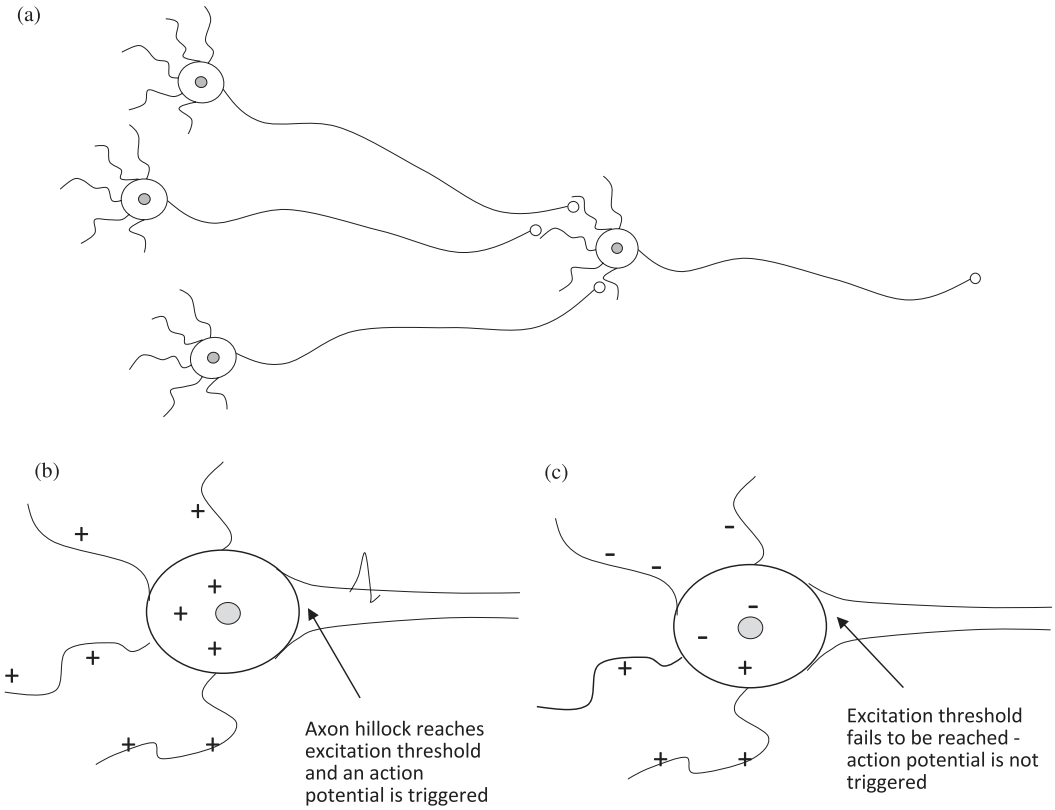


Figure 1.18 Integration of excitatory and inhibitory signals from multiple input neurons (a) determines whether an action potential is generated (b) or not (c).

is reached, an action potential is generated and the information continues to be passed along the axon of the neuron (Figure 1.18b). However, if the dendrites receive inhibitory inputs (i.e. if more IPSPs than EPSPs are produced), this serves to dampen the spread of excitation, the threshold for the generation of an action potential is therefore not reached and so the process stops (Figure 1.18c). It is important to note that neural inhibition does not necessarily produce a behavioural inhibition. Imagine a group of neurons in the brain that are in charge of inhibiting a behaviour, e.g. stopping an arm from moving. If this group of neurons is itself inhibited, the net result is a movement of the arm.

Summary

The composition of the cell is key to understanding how it functions. Due to the cell membrane and the proteins embedded within this membrane, there is an imbalance between the concentration of ions on the inside of the cell compared to concentration on the outside. The inside of the neuron is more negative (–70 mV) compared to the outside. This is known as the *resting membrane potential*.

An *action potential* is the means by which information is passed along the length of a neuron. The action potential is a change in the electrical charge at a particular point along the axon. The change occurs as a result of positive ions flowing into the cell, making the inside of the cell temporarily more positive. Then ions flow back out of the cell, returning it to a normal resting state. The change at one point along the axon triggers a change at the next point and so forth, allowing the action potential to propagate along the axon.

As the action potential reaches the end of the neuron, it triggers the release of chemical molecules called *neurotransmitters*. These neurotransmitters cross the gap between neurons (synaptic cleft) in a process called *synaptic transmission*. The neurotransmitters then attach onto receptors on a second neuron, which changes the electrical dynamic in the dendrites. This change may then trigger the initiation of a second action potential in the second neuron. Information is therefore passed from one neuron to another.