Section I

Anatomy and Physiology of the Nervous System

1
Cells of the CNS and How They Communicate

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INTRODUCTION

The neurone (or nerve cell) is the most important component of the nervous system. Its main function is to rapidly process and transmit information. The human nervous system contains about 300–500 billion neurones (approximately 80,000/mm^2), integrated into an intricate functional network by millions of connections with other neurones. Neurones communicate primarily via chemical synapses**.** The action potential is the fundamental process underlying synaptic transmission. It occurs as a result of waves of voltage that are generated by the electrically excitable membrane of the neurone.

This chapter will explore the histology of the nervous tissue and the physiology of neurotransmission.

COMPONENTS OF THE NEURONE AND THEIR FUNCTIONS

Neurones contain components and organelles that are crucial to normal cellular function and these generally resemble those of non-neuronal cells. Neurones of various types have different morphologies and functional features, depending on their location in the central nervous system (CNS). The prototypical neurone (Figure 1.1) consists of a stellate cell body (soma), a single axon that emerges from the soma, a number of thin processes called dendrites (the axon and dendrites are collectively known as neurites) and points of functional contact at the axon terminal with other cells, glands or organs, called synapses. The integrative functions of these unique structures are what differentiate neurones from non-neuronal cells and underlie the generation and transmission of information, which is so unique and fundamental to nervous system activity.

Like other cells in the body, the neurone is enclosed by a bi-layered lipoprotein-rich cell membrane, called the neuronal membrane. This membrane is approximately 5–7.5 nm thick and separates the cytoplasmic contents from the extracellular environment.

As in non-neuronal cells, the soma, (or cell body, also known as the perikaryon), is roughly spherical in shape and measures around 20 µm in diameter. The soma of smaller neurones may measure as little as 5 µm, whereas in the case of large motor neurones, they can be as much as 135 µm in diameter. The soma is the site of routine cellular housekeeping functions, including the synthesis of all the neuronal proteins that are necessary for the upkeep of the axon and axon terminals (Longstaff, 2000). In common with non-neuronal cells, the soma also includes important cellular organelles, such as the nucleus, Golgi apparatus, endoplasmic reticulum (ER), ribosomes, lysosomes and mitochondria.

The nucleus

The nucleus is approximately 5–10 µm in diameter and is surrounded by a granular, double-layered membrane, known as the nuclear envelope, which is perforated by small pores measuring around 0.1 µm wide. These small pores act as passageways between the nucleoplasm (interior of the nucleus) and the surrounding cytoplasm. By comparison with non-neuronal cells, the nuclei of neurones tend to be larger, which is thought to be related to the high levels of protein synthesis within the neurone. The nucleus contains the genetic material, deoxyribonucleic acid (DNA), which is responsible for directing the metabolic activities of the cell. Messenger ribonucleic acid

Neuroscience Nursing: Evidence-Based Practice, 1st Edition.
Edited by Sue Woodward and Ann-Marie Mestecky

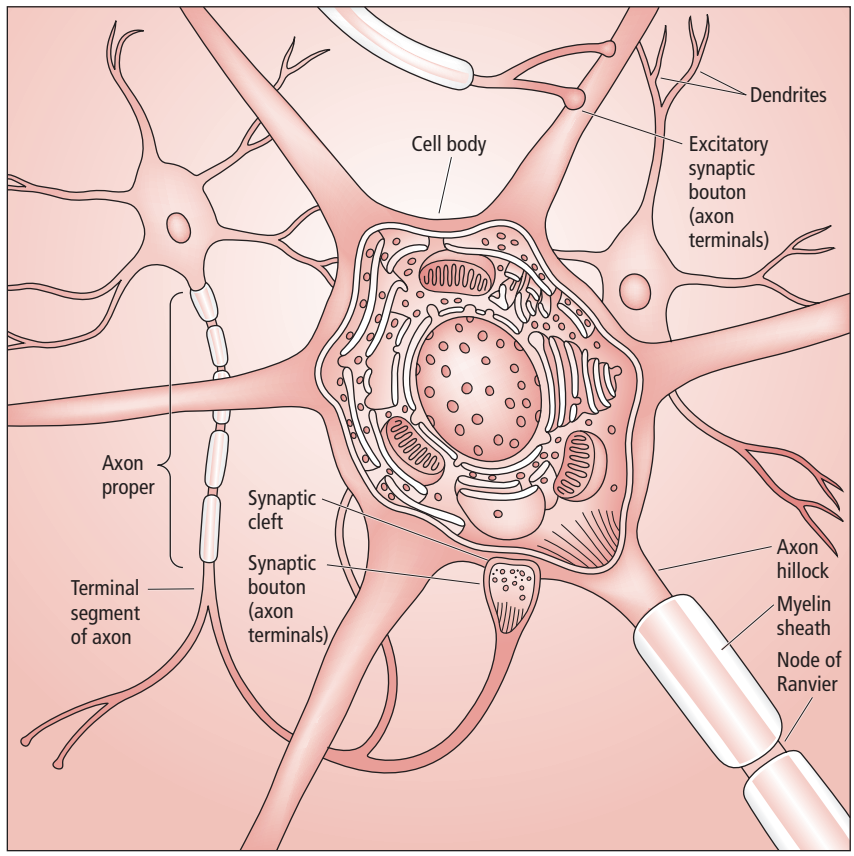

Figure 1.1 Diagram of a multipolar neurone. Note that the processes of other neurones make synaptic contacts with it. Synapses may be formed, as illustrated, with the soma or with the dendrites, although other types of synapses also occur. Reproduced from Maria A Patestas and Leslie P Gartner, *A Textbook of Neuroanatomy*, Wiley-Blackwell, with permission.

(mRNA) is also found within the nucleus. It is responsible for copying the specific genetic instructions from the DNA (transcription) for protein synthesis and carrying it to the site of protein production in the cytoplasm.

The rough endoplasmic reticulum (RER)

The RER is adjacent to the nucleus and is composed of rows of plate-like membranous sacs, which are covered in granular ribosomes. The RER synthesises the majority of protein needed to meet the functional demands of the neurone. It does this under the direction of mRNA. The ribosomes build proteins from amino acids delivered by transfer RNA from the genetic instructions held within messenger RNA. Rough ER is especially abundant in neurones, more so than in glia or other non-neuronal cells. It is densely packed within the soma and the shafts of dendrites, giving rise to distinct structures called *Nissl bodies.*

The smooth endoplasmic reticulum (SER)

The SER is made up of an extensive network of stacked membranous structures that are continuous with the nuclear membrane and RER. It is thought to be the main site of protein-folding. Smooth ER is heterogeneous in function and, depending on its location in the soma, it has important functions in several metabolic processes including protein synthesis, carbohydrate metabolism and regulation of calcium, hormones and lipids. It also serves as a temporary storage area for vesicles that transport proteins to various destinations throughout the neurone.

The Golgi apparatus

The Golgi apparatus is a highly specialised form of smooth endoplasmic reticulum that lies furthest away from the nucleus. In most neurones, the Golgi apparatus completely

surrounds the nucleus and extends into the dendrites; however it does not extend into axons. It is composed of aggregated, smooth-surfaced cisternae that are perforated by circular openings to allow the two-way passage of proteins and other molecules. It is surrounded by a mixed group of smaller organelles, which includes mitochondria, lysosomes, multivesicular bodies and vacuoles. The primary function of the Golgi apparatus is to process and package large molecules, primarily proteins and lipids, that are destined for different parts of the neurone such as the axon or dendrites.

Lysosomes

Lysosomes are the principal organelles responsible for the degradation of cellular waste-products. They are membrane-bound vesicles that contain various enzymes (acid hydrolases) that catalyse the breakdown of large unwanted molecules (bacteria, toxins, etc.) within the neurone. Lysosomes are more numerous and conspicuous in injured or diseased neurones. For this reason, they are often used as biomarkers for ageing and neurodegeneration. *Multivesicular bodies* are derived from primary lysosomes and are made up of several tiny spherical vesicles that also contain acid hydrolases. They are small oval shaped, single membrane-bound sacs, approximately 0.5 µm in diameter and have also been noted in various forms of neurodegeneration.

Mitochondria

Mitochondria are the 'power houses' of cells. They are responsible for oxidative phosphorylation and cellular respiration – crucial for the function of all aerobic cells, including neurones. Measuring between 1 µm and 10 µm in length, these organelles are concentrated in the soma and the synaptic terminals, where they produce adenosine triphosphate (ATP), the cell's energy source (Hollenbeck and Saxton, 2005). In addition to energy production, mitochondria also perform a number of other essential functions within the neurone, which include buffering cytosolic calcium levels (Gunter *et al.*, 2004) and sequestering proteins involved in apoptosis (see Chapter 32) (Gulbins *et al.*, 2003). The complex folding of the cristae within mitochondria provides a large surface area to harbour a number of enzymes. These enzymes, which diffuse through the mitochondrial matrix, catalyse the critical metabolic steps involved in cellular respiration. Because of the high energy demands of cellular function and protein synthesis, the number of mitochondria correlates with the neurone's level of metabolic activity.

The cytoskeleton

The cytoskeleton provides a dynamically regulated 'scaffolding' that gives neurones their characteristic shape and facilitates the transport of newly synthesised proteins and organelles from one part of the neurone to another (Brown, 2001). The main components of the cytoskeleton include microfilaments, microtubules and neurofilaments.

Microfilaments

Microfilaments are particularly abundant in axons and dendrites (neurites), but they are also distributed throughout the neuronal cytoplasm. They are also abundant in the expanded tips of growing neurites, known as growth cones (Dent *et al.*, 2003; Kiernan, 2004). They are made from a polymer called actin, a contractile protein that is most commonly associated with muscle contraction. They are composed of two intertwined chains of actin, arranged to create double helix filaments, measuring around 4–6 nm in diameter and a few hundred nanometres in length. The main role of microfilaments is the movement of cytoskeletal and membrane proteins.

Microtubules

Microtubules measure 20–24 nm in diameter and can be several hundred nanometres in length. They are made of strands of globular protein, tubulin, arranged in a helix around a hollow core, to give the microtubule its characteristic thick-walled, tube-like appearance. Microtubules play an important role in maintaining neuronal structure and they also act as tracks for the two-way transport (see: Axonal transport) of cellular organelles.

Neurofilaments (NFs)

Neurofilaments are a type of intermediate filament (IF), seen almost exclusively in neuronal cells. Measuring about 10 nm in diameter, neurofilaments can be several micrometres long and they frequently occur in bundles (Raine, 1999). Like their IF counterparts in non-neuronal cells, they are assembled in a complex series of steps that give rise to solid, rod-like filaments. These filaments are made up of polypeptides that are coiled in a tight, spring-like configuration. They are sparsely distributed in dendrites but they are abundant in large axons, where they facilitate axonal movement and growth.

Axonal transport

Protein synthesis does not usually occur within the axon, therefore any protein requirements for the repair and upkeep of the neurone must be met by the soma. In the soma, various components (including organelles, lipids

and proteins) are assembled and packaged into membranous vesicles and transported to their final cellular destination by a process known as *axonal transport* (axoplasmic transport). Axonal transport involves movement from the soma, towards the synapse, called *anterograde transport* and movement away from the axon, towards the soma, called *retrograde transport*.

Axonal transport can be further divided into fast and slow subtypes. *Fast anterograde transport* occurs at a rate of 100–400 mm/day and involves the movement of free elements including synaptic vesicles, neurotransmitters, mitochondria, and lipid and protein molecules (including receptor proteins) for insertion/repair of the plasma membrane. *Slow anterograde transport* on the other hand, occurs at a rate of 0.3–1 mm/day and involves the movement of soluble proteins (involved in neurotransmitter release at the synapse) and cytoskeletal elements (Snell, 2006). Both types of anterograde transport are mediated by a group of motor proteins called kinesins (Brown, 2001). Retrograde transport involves the movement of damaged membranes and organelles towards the soma, where they are eventually degraded by lysosomes (found only in the soma). It is mediated by a different kind of motor protein known as dynein.

The axon

The organelles and cellular components already discussed are not unique to neurones and may be found (with a few exceptions) in almost any cell in the body. However, the main feature that distinguishes neurones from other cells is the axon, the projection that emerges from the soma, and its associated elaborate process of dendrites. Under the microscope, it is hard to distinguish the axon from dendrites of some neurones, but in others it is easily identified on the basis of length. Whilst some neurones have no axons at all (e.g. the amacrine cell, found in the retina), most neurones have a single axon. The axons of some neurones branch to form axon collaterals, along which the impulse splits and travels to signal several cells simultaneously.

Neurones can be broadly classified according to length of their axonal processes. *Golgi type I* neurones contain long-projecting axonal processes, whilst *Golgi type II* neurones have shorter axonal processes. Another way of classifying neurones is according to their location within the central nervous system, or on the basis of their morphological appearance. Examples of specific types of neurones include Basket, Betz, Medium spiny, Purkinje, Renshaw and Pyramidal cells. Neurones may also be classified according to the number of branches that originate from the soma (Figure 1.2):

- Unipolar or pseudounipolar neurones are characterised by a single neurite that emerges and branches or divides a short distance from the soma. Most sensory neurones of the peripheral nervous system are unipolar.

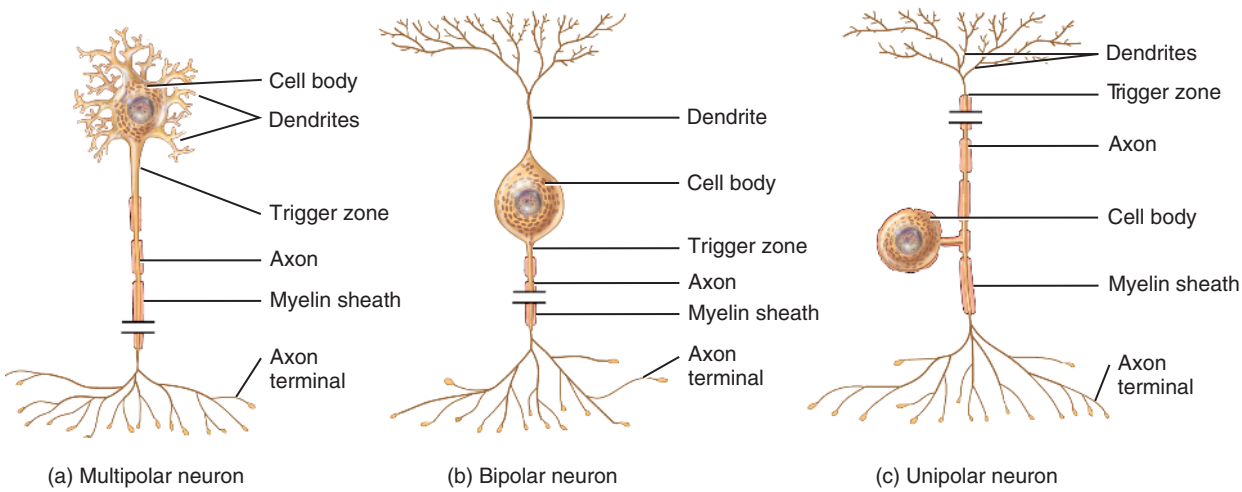

Figure 1.2 Structural classification of neurones. Breaks indicate that axons are longer than shown. (a) Multipolar neurone. (b) Bipolar neurone. (c) Unipolar neurone. Reproduced from *Principles of Anatomy and Physiology 12e* by Gerard Tortora and Bryan Derrickson. Copyright (2009, John Wiley & Sons). Reprinted with permission of John Wiley & Sons Inc.

- Bipolar neurones are characterised by a single axon and a single dendrite that emerge from opposite ends of an elongated soma. These types of neurones are found in the sensory ganglia of the cochlear and vestibular system and also in the retina.
- Multipolar neurones are characterised by a number of dendrites that arise and branch close to the soma. They make up the majority of neurones in the CNS.

The primary function of the axon is to transmit electrochemical signals to other neurones (sometimes over a considerable distance). Transmission occurs at rates that are appropriate to the type and function of the individual neurone. Because of this, the axonal length of a given neurone may vary from as little as a few micrometres, to over 1 metre in humans. For example, the sciatic nerve, which runs from the base of the spine to the foot, may extend a metre or even longer. Typical diameters can range from 0.2 to 20 µm for large myelinated axons.

The axon has four regions: the axon hillock (or trigger zone), the initial segment, the axon proper and the axon terminals. The *axon hillock* originates at the soma; adjacent to the axon hillock is the *initial segment*. The plasma membranes of these two regions contain large numbers of specialised, voltage sensitive ion channels and most action potentials originate in this area (see below: Action potentials). Beyond the initial segment, the *axon proper* maintains a relatively uniform, cylindrical shape, with little or no tapering. The consistent diameter of the axon (axon calibre) is maintained by components of the cytoskeleton and this feature also helps to maintain a uniform rate of conduction along the axon. In addition to the axon calibre, the rate of conduction along the axon is influenced by the presence of the myelin sheath, which begins near the axon hillock and ends short of the *axon terminals*.

Myelination

Myelin is a specialised protein, formed of closely apposed glial cells that wrap themselves several times around the axon (Kiernan, 2004). In the central nervous system, the glial cells making up the myelin sheath are called oligodendrocytes, whereas in the peripheral nervous system, they are known as Schwann cells (see: Neuroglia). Several axons may be surrounded simultaneously by a single glial cell.

The myelin sheath insulates the axon and prevents the passive movement of ions between the axoplasm and the extracellular compartment. Myelinated axons also contain gaps at evenly-spaced intervals along the axon, known as nodes of Ranvier (Figures 1.1 and 1.3). These nodes are

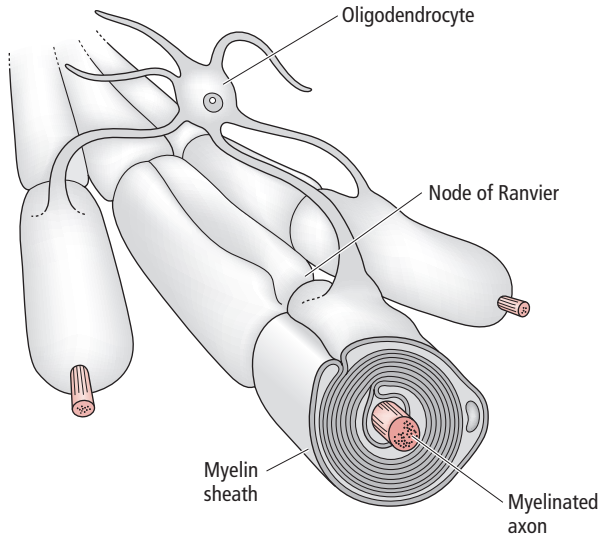

Figure 1.3 A single oligodendrocyte is capable of myelinating a single internode of numerous axons. Reproduced from Maria A Patestas and Leslie P Gartner, *A Textbook of Neuroanatomy*, Wiley-Blackwell, with permission.

the only points where the axonal membrane is in direct contact with the extracellular compartment and where ions can readily flow across the axonal membrane. Therefore, any electrical activity in the axon is confined to this part. In myelinated axons, the nodes of Ranvier contain clusters of voltage-gated sodium (Na^+) channels, whereas in unmyelinated axons, these voltage-gated Na^+ channels are distributed uniformly along the *whole* of the axon. This feature enables the axon to conduct action potentials over long distances, with high fidelity and a constant speed, and underlies the ability of the neurone to conduct impulses by a process known as saltatory conduction. Saltatory conduction (from the Latin *saltare*, to 'jump'), enables action potentials to literally jump from one node to the next, rather than travelling along the membrane (Ritchie, 1984). Saltation allows significantly faster conduction (between 10 and 100 metres per second) in myelinated axons, compared with the slower conduction rates seen in their unmyelinated counterparts.

The increased speed afforded by saltatory conduction therefore allows the organism to process information more quickly and to react faster, which confers a distinct advantage for survival. In addition to this, the high concentrations of ion channels at the nodal intervals conserve energy, as they reduce the requirements for sodium–potassium pumps

throughout the axonal membrane. Multiple sclerosis (MS) is a demyelinating disease, characterised by patchy loss of myelin in the brain and spinal cord. As a result of the demyelinating process, plaques develop in the white matter, which result in a reduced concentration of sodium ion channels at the nodes of Ranvier and a slowing of action potentials (see Chapter 28).

The terminal portion of the axon is known as the axon terminal, where the axon arborises (or branches) and enlarges. This region goes by a variety of other names, including the terminal bouton, the synaptic knob or the axon foot. The axon terminal contains synaptic vesicles which contain neurotransmitters (see: Neurotransmitters).

Dendrites

Dendrites are the afferent components of neurones, i.e. they receive incoming information. The dendrites (together with the soma) provide the major site for synaptic contact made by the axon endings of other neurones. Dendrites are generally arranged around the soma of the neurone in a stellate (or star-shaped), configuration. In some neurones, dendrites arise from a single trunk, from which they branch out, giving rise to the notion of a dendritic tree (Raine, 1999). Under the microscope, it can be difficult to distinguish the terminal segments of axons from small dendrites, or small unmyelinated axons. However, unlike the diameters of axons, the main distinguishing feature of dendrites is that they taper, so that successive branches become narrower as they move further away from the soma. In addition, unlike axons, small branches of dendrites tend to lack any neurofilaments, although they may contain fragments of Nissl substance; however, large branches of dendrites proximal to the axon may contain small bundles of neurofilaments. The synaptic points of contact on dendrites occur either along the main stems or at small eminences known as dendritic spines – the axon terminals of other neurones adjoin these structures.

NEUROGLIA

Neuroglia (Figure 1.4), usually referred to simply as glia (from the Greek word meaning 'glue') or glial cells, are morphologically and functionally distinct from neurones. Neuroglia comprise almost half the total volume of the brain and spinal cord. They are smaller than neurones and more numerous – outnumbering them almost 10-fold (Snell, 2006). Although they have complex processes extending from their cell bodies, they lack any axons or dendritic processes.

Previously it was assumed that glia do not participate directly in any signalling or synaptic interactions with other neurones. However, recent studies have indicated that their supportive functions help to define synaptic contacts and that they are crucial facilitators of action potentials. Other roles attributed to neuroglia include: maintaining the ionic environment in the brain, modulating the rate of signal propagation, and having a synaptic action by controlling the uptake of neurotransmitters. They also provide a scaffold for some aspects of neural development, and play an important role in recovery from neuronal injury (or, in some instances, prevention). They also have an important nutritive role and release factors which modulate pre-synaptic function.

There are four main types of glial cells in the mature CNS: astrocytes, oligodendrocytes, microglial cells and ependymal cells – the description, location and function of these are summarised in Table 1.1.

COMMUNICATION BY NEURONES

The resting membrane potential

The neuronal membrane is about 8 nm thick and is made up of a hydrophobic lipid bi-layer, which acts as a selective barrier to the diffusion of ions between the cytoplasm (intracellular) and extracellular compartments. The unequal distribution of ions (positively or negatively charged atoms) either side of the cell membrane results in a difference of electrical charge (potential difference) between the inside and the outside of the cell membrane. The overall effect of this gives rise to the resting membrane potential. It is called the resting membrane potential because it occurs when the neurone is in an unstimulated state, i.e. not conducting an impulse. In this state, the neurone is said to be polarised, because there is a relative excess of positive electrical charge outside the cell membrane and a relative excess of negative charge inside. To maintain a steady resting membrane potential, the separation of charges across the membrane must be constant, so that any efflux of charge is balanced against any charge influx (Gilman and Winans Newman, 2003). By convention therefore, the charge outside the neuronal membrane is arbitrarily defined as zero, whilst the inside of the neurone (relative to the outside) is negatively charged (−70 mV).

The extracellular fluid contains a dilute solution of sodium (Na^+) and chloride (Cl^-) ions. By contrast, the axoplasm contains high concentrations of potassium (K^+) ions and organic anions (large negatively charged organic acids, sulphates, amino acids and proteins) (Holmes, 1993). Two passive forces (diffusional and electrostatic) act simultaneously upon these ions to maintain the resting potential. Diffusional (chemical) forces drive Na^+ ions

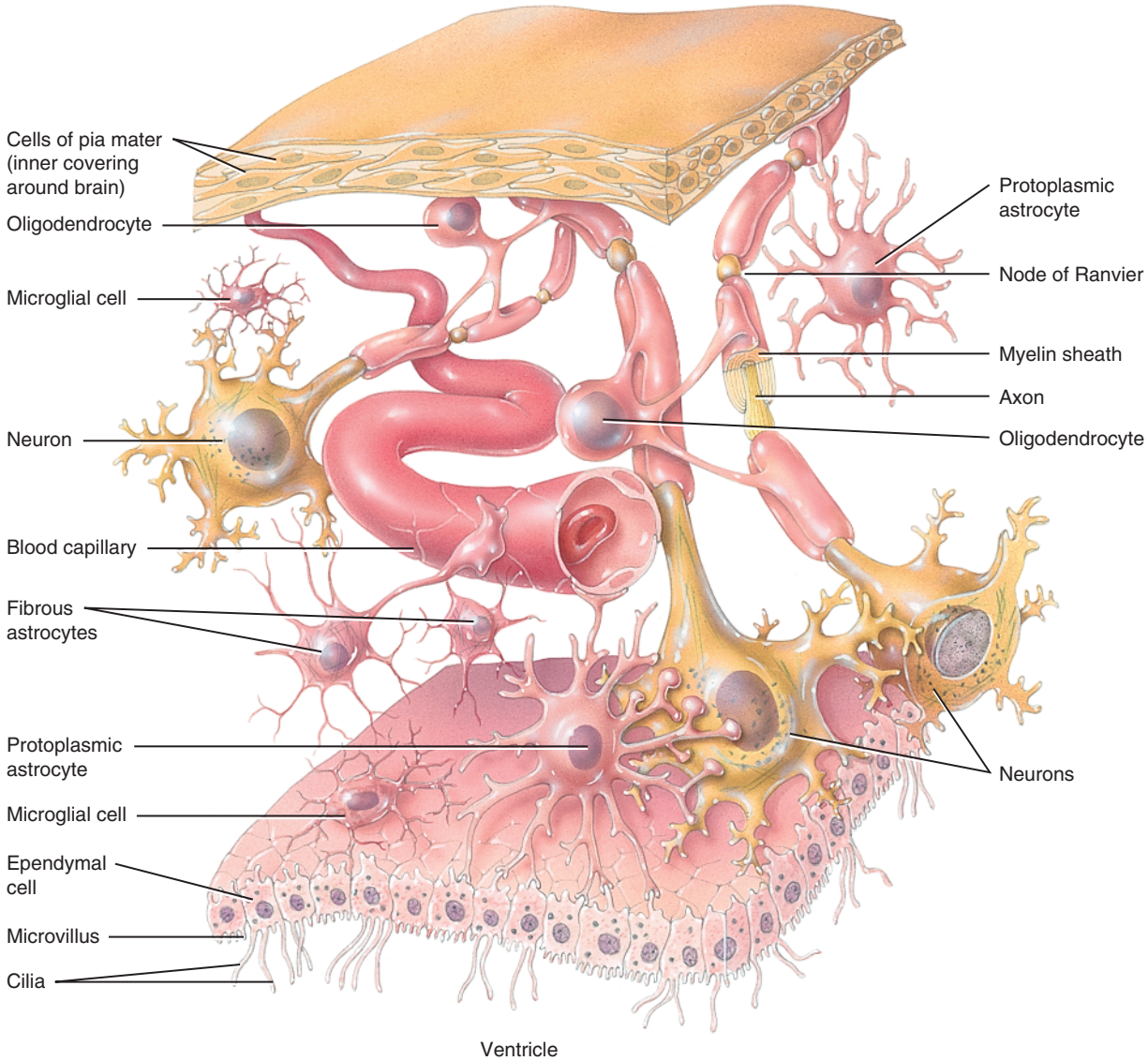

Figure 1.4 Neuroglia of the central nervous system (CNS). Reproduced from *Principles of Anatomy and Physiology 12e* by Gerard Tortora and Bryan Derrickson. Copyright (2009, John Wiley & Sons). Reprinted with permission of John Wiley & Sons Inc.

inwards and K^+ ions outwards, from areas of high concentration to areas of low concentration, i.e. down their respective chemical concentration gradients. Secondly, electrostatic forces (charge) move ions across the membrane, in a direction that depends on their electrical charge, so that the positively charged Na^+ and K^+ ions are attracted towards the negatively-charged cell interior (Waxman, 2000).

In addition to these diffusional and electrostatic forces, the resting potential is also influenced by the action of ion-specific membrane-spanning channels. These ion channels selectively allow the passage of certain ions, whilst excluding others. Two types of ion channels exist, which can be in an open or closed state: voltage gated and non-gated ion channels. Non-gated channels, which are primarily important in maintaining the resting potential are

Table 1.1 Description, location and function of specific neuroglia.

Neuroglial cell	Structural features	Location	Function
Astrocytes			
Fibrous astrocytes	Small cell bodies and long slender processes – contain cytoplasmic filaments and sparsely branched processes that extend between nerve fibres	White matter	• Maintain integrity of blood–brain barrier (BBB) • Structural support for mature neurones and migrating immature neurones during embryonic development • Cover synaptic contacts and act as insulators – preventing axon terminals from influencing neighbouring, unrelated neurones • Role in synaptic transmission – contributing to the reuptake of γ-aminobutyric acid (GABA) and glutamate from synaptic terminal & limiting influences of these neurotransmitters • Role in maintaining a favourable ionic environment (ionic homeostasis) & maintenance of K^+ ion concentration in the extracellular spaces
Protoplasmic astrocytes	Multiple, short branching processes – end as expansions on capillaries (perivascular feet)	Grey matter	• Produce substances that have a trophic influence on surrounding neurones • Nutritive role & glycogen storage in the cytoplasm • Role in phagocytosis – taking up degenerating/damaged synaptic axon terminals • Proliferate and occupy spaces previously left by disease /dead neurones – *replacement gliosis*
Oligodendrocytes	Small cell bodies with a few delicate processes. Do not contain any cytoplasmic filaments	Myelinated neurones of the CNS and PNS	• Myelination of neurones and formation of the myelin sheath in the CNS and PNS
Microglial cells	Smallest of the neuroglia, with long spiny processes – derived from haematopoietic stem cells	Found scattered throughout the CNS	• Release of growth factors during development • In collaboration with tissue macrophages, prominent role in phagocytosis and removal of cellular debris in response to normal cell turnover or brain injury

Table 1.1 *Continued*

Neuroglial cell	Structural features	Location	Function
Ependymal cells			
Ependymocytes	Cuboidal and columnar shape, with microvilli, cilia and gap junctions	Found lining the ventricles and the central canal of the spinal cord	• Cilia assist in circulation of CSF within brain cavities and central canal of the spinal cord • Role in absorption of CSF
Tanycytes	Long processes, with end feet on blood capillaries	Found lining floor of third ventricle and overlying the medial eminence of the hypothalamus	• Transport of blood-derived hormones and substances from the CSF into capillaries that supply medial eminence of the hypothalamus (hypophyseal-portal system)
Choroidal epithelial cells	Sides and bases tightly folded – held together by tight junctions to prevent leakage of CSF into underlying structures	Cover the surfaces of the choroid plexuses	• Production and secretion of CSF

CNS – central nervous system; PNS – peripheral nervous system; BBB – blood–brain barrier; CSF – cerebrospinal fluid.

always open and are not influenced significantly by extrinsic factors, these gates allow for the passive diffusion of K^+ and Na^+ ions. Gated channels, however, open and close in response to specific electrical, mechanical, or chemical signals and their conformational states (i.e. whether they are open or not) depend on the voltage across them (Longstaff, 2000). When the neurone is polarised (i.e. is at resting membrane potential) these gates are closed.

At resting membrane potential, the neuronal membrane is relatively permeable to K^+ ions, which passively diffuse out of the cell, through non-gated potassium channels. This causes a net increase in the negative charge on the inside of the cell membrane. In addition to the outward leakage of potassium, negatively charged anions (which cannot diffuse across the membrane because of their large size) add further to the overall negative intracellular charge. The majority of sodium channels are closed at resting membrane potential, so diffusion of Na^+ along its own ionic gradient is prevented. In addition, the *sodium–potassium pump* actively transports Na^+ ions out of the cell, while taking in K^+. The pump moves three sodium ions out of the cell for every two potassium ions that it brings in. The sodium–potassium pump therefore moves Na^+ and K^+ *against* their net electrochemical gradients, which requires the use of energy (from the hydrolysis of ATP).

As long as the force of the K^+ ions diffusing outwards exceeds the oppositely oriented electrical charge, a net efflux of K^+ continues from inside the cell. But as more K^+ ions travel out (along the K^+ concentration gradient), the electrical force (negative charge) attracting K^+ ions into the cell, gradually increases (Wright, 2004; Barnett and Larkman, 2007). If a state was reached whereby the chemical and electrical forces balanced, (equilibrium potential of potassium) there would be no K^+ ion movement. This equilibrium potential for potassium occurs at –90 mV. However an equilibrium potential for potassium is never quite reached due to the small continual leakage of sodium from the cell.

Changes in the resting membrane potential

Changes in the resting membrane potential will occur when a stimulus causes gated ion channels to open thereby changing the membrane's permeability to an ion. Depending on the type and strength of the stimulus, the

change in the resting membrane potential will produce either a graded potential or an action potential. If the stimulus alters a local area of the membrane only and does not conduct far beyond the point of stimulation it is referred to as a graded potential (see below: Neurotransmitters). If the stimulus is of sufficient strength to cause a change in the entire membrane potential the response is referred to as an action potential.

An increase in the negativity of the resting membrane potential, e.g. −70 mV to −80 mV is referred to as hyperpolarisation. Conversely, any reduction in the negativity of the membrane potential, e.g. −70 mV to −65 mV, is referred to as depolarisation.

The action potential

An action potential (Figure 1.5) is initiated when a stimulus causes the voltage gated sodium channels to open. Sodium ions rapidly diffuse through the neuronal membrane down their electrochemical gradient attracted by the negative charge inside the neurone. The most common site of initiation of the action potential is the axon hillock (also called the trigger zone), where the highest concentration of voltage-gated ion channels is found (previously described).

The rush of Na^+ into the neurone briefly reverses the polarity of the membrane from a negative charge of −70 mV (resting membrane potential) typically to a positive charge of +30 mV (depolarisation). The influx of Na^+ and subsequent depolarisation of one section of the axonal membrane, i.e. the trigger zone, is the stimulus to open additional voltage gated sodium channels in the adjacent membrane, thus the depolarisation spreads forward along the axonal membrane. The voltage gated sodium channels are open only briefly, they become inactivated when the charge reaches +30 mV, stopping any further influx of Na^+ into the neurone. This brief alteration in charge lasts approximately 5 milliseconds.

Whilst the voltage gated sodium channels are closing, voltage-gated potassium channels open resulting in a huge efflux of K^+ ions (downward stroke) which continues until the cell has repolarised to its resting potential (from +30 mV to −70 mV). During repolarisation the voltage gated sodium channels remain inactivated.

Following repolarisation, the neurone is briefly unyielding to any further action potentials, a phase known as the recovery/relative refractory period. The absolute refractory period is the time during which a second action potential absolutely cannot be initiated (see Figure 1.5). The sodium–

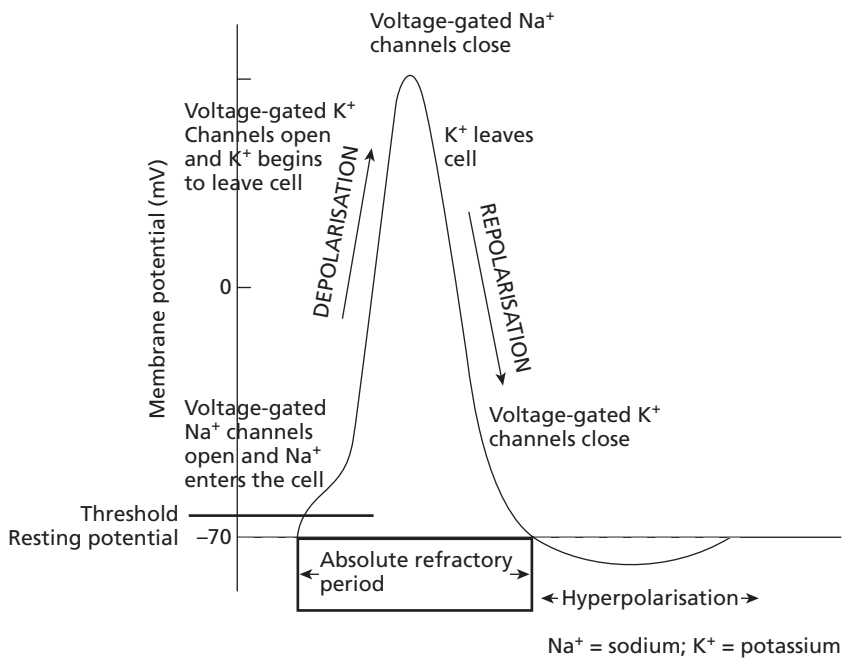

Figure 1.5 Action potential in a neurone.

potassium pump actively transports K^+ and Na^+ ions across the membrane, (against their respective chemical concentration gradients), to re-establish the resting potential.

Threshold stimulus and the all-or-none phenomenon

The stimulus must depolarise the membrane potential to a threshold value, which is typically to −55 mV for an action potential to occur. If the membrane does not reach the threshold value an action potential will not occur. If the threshold is reached the action potential will propagate forward at maximal strength regardless of the strength of the initial stimulus. Therefore the action potential will occur maximally or not at all. This is the 'all-or-none phenomenon'.

NEUROTRANSMISSION

Synapses

Once the action potential reaches the axon terminal it needs to transfer to another cell. The *synapse* (Figure 1.6) is the location of signal transmission from one neurone to another or, in most cases, many other neurones. The synapse is typically between the axon terminal of a neurone (pre-synaptic) and the surface of a dendrite or cell body of another neurone (post-synaptic). The number of synaptic inputs to a typical neurone in the human nervous system ranges from 1 to about 100,000, with an average in the thousands.

Two types of synapse exist: electrical and chemical. In *electrical synapses*, ion channels (connections) arrange themselves around a central hollow core to form gap junctions. These gap junctions allow electrical coupling and the passage of water, small molecules (<1.2 nm diameter) and various ions between adjacent cells. Electrical synapses are predominantly associated with electrical activity in cardiac and smooth muscle. They are also found between astrocytes and are crucially involved in the coupling of horizontal cells found in the retina. Electrical signalling is bi-directional in electrical synapses.

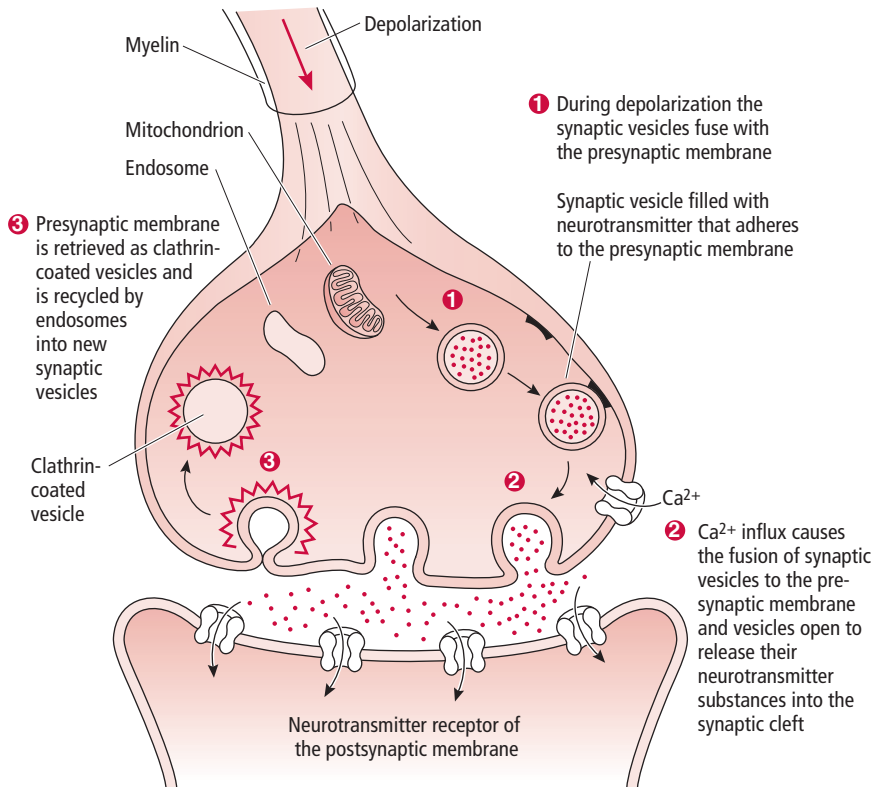

Figure 1.6 An example of an ionotropic effect occurring at a synapse indicating the events that occur before, during, and after the release of neurotransmitter substances. Reproduced from Maria A Patestas and Leslie P Gartner, *A Textbook of Neuroanatomy*, Wiley-Blackwell, with permission.

In humans, the majority of synapses are *chemical synapses* and therefore rely on the release of neurotransmitters and their binding with receptor proteins on the post-synaptic membrane of the target neurone. Typically, the pre-synaptic terminal is immediately adjacent to a post-synaptic region but there is no physical continuity between these regions. Instead, the components communicate by chemical neurotransmitters that cross the extracellular space known as the *synaptic cleft* to bind to receptors in the post-synaptic region.

Neurotransmitters

Neurotransmitters are the molecules responsible for chemical signalling in the nervous system. Neurotransmitters are synthesised in the soma and are transported to the terminal parts of the axon (near the synaptic region), where they are packaged into vesicles and stored in areas known as active zones, ready for release at the synapse. When an action potential reaches the axon terminal voltage gated calcium channels open, the influx of calcium ions cause the vesicles to fuse with the pre-synaptic membrane and vesicular contents are released in discreet packets or quanta, into the synaptic cleft, by a process of *exocytosis*. Each quantum represents the release of the contents of a single vesicle (around 4000 molecules of neurotransmitter) (Longstaff, 2000). Following exocytosis, the vesicular membrane proteins are recycled by a process known as *endocytosis* .

The first neurotransmitter to be described was *acetylcholine* (*ACh*), by Loewi in 1926, following his extensive work on frog cardiac muscle. Subsequently, a wide range of other neurotransmitters have been described, each of which may be chemically differentiated on the basis their molecular structure, patterns of distribution, localisation to specific brain areas and their association with specific functions (Michael-Titus *et al.*, 2007).

The effects of the main neurotransmitters and their mode of action are summarised in Table 1.2.

In addition to the principal neurotransmitters, other chemicals can also *modulate* the impact of neurotransmitter on the post-synaptic neurone. They do this by enhancing, prolonging, inhibiting or limiting the effect of a particular neurotransmitter on the post-synaptic neurone, so that the response of metabotropic receptors (see below) may last several minutes or longer. These substances are called *neuromodulators*, because they modulate the response of the neurone to other inputs. It is widely accepted that some molecules can act simultaneously as a neurotransmitter or a neuromodulator (termed *co-transmission*) and classification largely depends on whether its action occurs over a long range or is localised to the synapse.

Neurotransmitters exert their effects on post-synaptic receptors of target neurones. The action of a given neurotransmitter on a target neurone or indeed peripherally on a particular effector organ (see Chapter 5) largely depends on the types of receptors present on that target. Most types of neurotransmitters have a number of specific receptor subtypes that they can activate. These receptors can be classified according to their overall structure and function. The effects of neurotransmitters depend on the summation of responses at the post-synaptic membrane.

Two broad superfamilies of receptor have been described, which include ionotropic and metabotropic receptors. The *ionotropic*, or *ligand-gated ion channel* receptors, are made up of ion-selective channels that are integral to the receptor. Binding of neurotransmitter directly results in the selective opening or closure of the channel and directly increasing or decreasing its permeability to particular ions, as described above.

Ionotropic or ligand-gated ion channel receptors

The binding of a neurotransmitter to an ionotropic receptor will cause a change in the post-synaptic membrane potential by either bringing about the opening or closing of ion channels. When the neurotransmitter causes the opening of positive ion channels (e.g. Na^+ channels) in the post-synaptic membrane the net effect is to reduce the negativity of the membrane potential (e.g. from −70 mV to −68 mV). This is known as an *excitatory post-synaptic potential* (EPSP). This is below the level required to lift the potential to threshold level for an action potential to occur. When the neurotransmitter causes the opening of potassium channels, thereby allowing positive ions to leave the neurone, or opens chloride (Cl^-) channels the effect is to reduce the resting potential i.e. make it more negative this is known as *inhibitory post-synaptic potential* (IPSP). The IPSP reduces the post-synaptic neurone's ability to generate an action potential. These small shifts are called graded potentials. Whether an action potential is generated or not depends on the summation of the graded potentials. Several EPSPs are needed to convert resting potential to an action potential. Summation may be temporal (the cumulative effect of repeated impulses from a single synapse) or spatial (the net effect of simultaneous impulses from different synapses along the membrane).

The second superfamily of receptors are known as the *metabotropic receptors*. Binding of neurotransmitters to these receptors has longer lasting effects on the post-synaptic cell. When a neurotransmitter binds to these

Table 1.2 Key central nervous system neurotransmitters.

Group	Neurotransmitter	Source	Action
Biogenic amines (classical)			
	Acetylcholine	• Found in many brain areas and large pyramidal cells • Some cells of basal ganglia • Motor neurones that innervate skeletal muscle • Pre-ganglionic neurones – autonomic nervous system • Postganglionic neurones of sympathetic and parasympathetic nervous system	• Usually excitatory • Inhibitory effect on parasympathetic organs (e.g. reduced heart rate, as a result of vagus nerve stimulation)
Catecholamines	**Dopamine**	• Neurones in substantia nigra and projections to basal ganglia that are involved in coordinated skeletal muscle activity	• Usually inhibitory
	Noradrenaline	• Neurones with cell bodies in brain stem and hypothalamus and postganglionic neurones of sympathetic nervous system	• Usually excitatory, occasionally inhibitory
	Adrenaline	• Synthesised and stored in chromaffin tissue in adrenal medulla	• Excitatory
	Serotonin (5-hydroxytryptamine; 5-HT)	• Median raphe nuclei of brain stem and projections to other areas, including hypothalamus and dorsal horns of spinal cord	• Inhibitory – modulates neurone voltage potentials to inhibit glutamate activity and neurotransmitter firing. Key role in control of mood and sleep
Amino acids (classical)	**Glutamate**	• Presynaptic terminals of sensory nerves and some cortical areas	• Excitatory – acts on ionotropic (kainite, AMPA and NMDA) receptors and metabotropic receptors
	Aspartate	• Brain stem and spinal cord	• Excitatory
	γ-aminobutyric acid (GABA)	• Nerve terminals of the spinal cord, cerebellum, basal ganglia and some cortical regions. Found in 30–40% of all synapses	• Inhibitory – the main inhibitory NT in the mammalian CNS. Regulates activity of glutamate and prevents overstimulation

Continued

Table 1.2 *Continued*

Group	Neurotransmitter	Source	Action
	Glycine	• Brain stem and spinal cord	• Inhibitory neuromodulator – regulates excitatory neurotransmission in much the same way as GABA
Opioids (peptides)	**Endorphins**	• Pituitary gland and other brain areas	• Excitatory to systems that inhibit pain and binds to opiate receptors in the brain and pituitary gland
	Encephalins	• Nerve terminals in the spinal cord, brain stem, thalamus and hypothalamus	• Excitatory to systems that inhibit pain and binds to opiate receptors
	Dynorphins	• Hypothalamus, hippocampus and spinal cord	• Inhibitory – opiate-like activity. Role in oxytocin secretion and control of appetite
Tachykinins (peptides)	**Substance P**	• Basal ganglia, hypothalamus and pain fibre terminals in dorsal horn of spinal cord	• Excitatory

receptors, small intracellular proteins called *G-proteins* are activated. G-proteins exert their effects on the post-synaptic membrane by binding ion channels directly, or by indirectly activating *second messenger*s. Second messengers are molecules that are produced or released inside the cell; the most common being cyclic-adenosine monophosphate (cAMP). Second messengers can activate other enzymes in the cytosol that can regulate ion-channel function or alter the metabolic activities of the cell, hence the name metabotropic.

Inactivation and removal of neurotransmitters

Typically, neurotransmitter binding takes less than 5 µs, but not all neurotransmitter that has been released binds to the post-synaptic membrane of the target neurone. The distance between the pre- and post-synaptic membrane is as little as 12 nm across, but due to reuptake of neurotransmitter, passive diffusion away from the synaptic cleft and inactivation by various enzymes, the amount of transmitter available for binding is reduced. For example, enzymatic degradation of ACh (by *acetylcholinesterases*) takes place in the synaptic cleft at the neuromuscular junction or other cholinergic synapses. These enzymes cleave ACh into its inactive components, acetate and choline, which are recycled and used to synthesise further ACh by combination with acetyl-coenzyme-A.

Other neurotransmitters are inactivated in a similar way, or they may be inactivated by direct removal from the synaptic cleft. Direct removal from the synaptic cleft is carried out by reuptake transporters, which actively transport unused neurotransmitter to surrounding neurones or glia. The importance of the mechanisms of reuptake is highlighted by the impact of certain drugs on brain function. Illicit drugs, such as ecstasy (3, 4-methylenedioxy-N-methamphetamine; MDMA), for example, block the reuptake of serotonin (5-hydroxytryptamine; 5HT). This results in an excess of serotonin in the synaptic cleft, which contributes to its euphoric effects (McCann *et al.*, 2005). Similarly, other illicit drugs such as cocaine inhibit the reuptake of dopamine, which is responsible for its euphoric and addictive effects (Mash *et al.*, 2002). Of course, neurotransmitter reuptake blockade can also have more useful, therapeutic applications, for example in the treatment of depression with selective serotonin reuptake inhibitors (SSRIs), which block the reuptake of serotonin. The therapeutic use of drugs that inhibit reuptake of neurotransmitters will be discussed in the relevant chapters on specific diseases.

SUMMARY

The nervous system is vital for maintaining the homeostasis of the body. It continuously receives information which it must process and rapidly respond to. These vital functions are made possible by the generation of action potentials and chemical synapses. Neurotransmitters released at a synapse can have either excitatory or inhibitory effects whereas neuromodulators prolong, inhibit, or limit the effect of a particular neurotransmitter on the post-synaptic neurone.

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