Nerve cell function and synaptic mechanisms

Allan Fletcher

Abstract

Nerve cells (neurones) are 'excitable' cells that can transduce a variety of stimuli into electrical signals, continuously sending information about the external and internal environment (in the form of sequences of action potentials) to the central nervous system (CNS). Interneurones in the CNS integrate this information and send signals along output (efferent) neurones to various parts of the body for the appropriate actions to be taken in response to environmental changes. Networks of neurones have been arbitrarily classified into various nervous systems that gather and transmit sensory information and control skeletal muscle function and autonomic function, etc. The junctions between neurones (synapses) are either electrical or chemical. The former permit the direct transfer of electrical current between cells, whereas the latter utilize chemical signalling molecules (neurotransmitters) to transfer information between cells. Neurotransmitters are mainly amino acids, amines or peptides (although other molecules such as purines and nitric oxide are utilized by some cells), and can be excitatory or inhibitory. Individual neurones within the CNS may receive synaptic inputs from thousands of other neurones. Therefore, each neurone 'integrates' this vast complexity of inputs and responds accordingly (either by remaining silent or firing action potentials to other neurones). Adaptations in the function and structure of chemical synapses in particular (synaptic plasticity) are thought to underlie the mechanisms mediating cognitive functions (learning and memory).

Keywords Neurone; synapse; synaptic integration; synaptic plasticity

Royal College of Anaesthetists CPD Matrix: 1A01

Learning objectives

After reading this article, you should be able to:

- distinguish between the functions of an afferent neurone, efferent neurone and interneurone, and be able to draw and label a 'typical neurone'
- compare and contrast the origin, ionic basis and role of an end-plate potential, an excitatory post-synaptic potential and an inhibitory post-synaptic potential
- illustrate how the neurone fulfils its role of acting as an integrator of the many inputs it receives, and the role of the axon hillock in this process

Nerve cells (neurones), together with muscle cells, are 'excitable' in the sense that their plasma membranes can respond to external stimuli by generating changes in electrical potential difference across the membrane – this leads to the initiation of a self-propagating 'wave' of depolarization (the action potential; see pages 243–247 of this issue). This excitable property allows sensory (afferent) neurones to respond rapidly to changes in the internal or external environment, and to send information about these changes to the central nervous system (CNS). The human CNS contains at least 10^{11} neurones, whose functions are to integrate this vast quantity of sensory information and to issue commands via efferent neurones in order to react appropriately to environmental changes. Taking appropriate action also usually requires the recall of previous experience (i.e. CNS neurones have the ability to store information and modify behaviour accordingly – learning and memory). Junctions between neurones (and between neurones and target cells such as muscle tissue) are critically important for transferring information between cells – these junctions are termed 'synapses', and are usually chemical in nature (signalling molecules are released from one cell to initiate responses in the second cell). Changes in synaptic function are thought to underlie the cognitive functions of learning and memory. The basic nature of neuronal function and the ways in which information is passed between neurones (synaptic function) will be reviewed in this article.

Neuronal networks

The billions of neurones within the human body are organized into complex neuronal networks that have been arbitrarily divided into different 'nervous systems' according to their main physiological roles. The broadest subdivision distinguishes the 'central nervous system' (brain and spinal cord) from the 'peripheral nervous system'. The terminology 'afferent' and 'efferent' refers, respectively, to neurones sending information into the CNS or transmitting commands out from the CNS. The peripheral nervous system comprises the autonomic nervous system (sympathetic and parasympathetic), the somatic nervous system (motor neurones controlling skeletal muscle) and systems of afferent neurones that transmit sensory information into the CNS. Functionally, the neurones constituting these nervous systems can be broadly classified as follows.

- Sensory (afferent) neurones that transduce sensory stimuli into electrical potential changes. The nature of the stimuli ranges from those of the five senses to internal stimuli such as changes in blood pressure (baroreceptors respond to changes in stretch of vascular walls) and interstitial fluid osmolarity (detected by osmoreceptors in the hypothalamus). Proprioceptors in skeletal muscle, tendons and skeletal joints continuously monitor muscle stretch and contraction and the orientation of joints.
- Interneurones in the CNS integrate information from afferent neurones, allowing information processing, storage and retrieval.
- Efferent neurones that transmit commands arising from the activity of interneurones, in order to execute appropriate reactions to external and internal stimuli.

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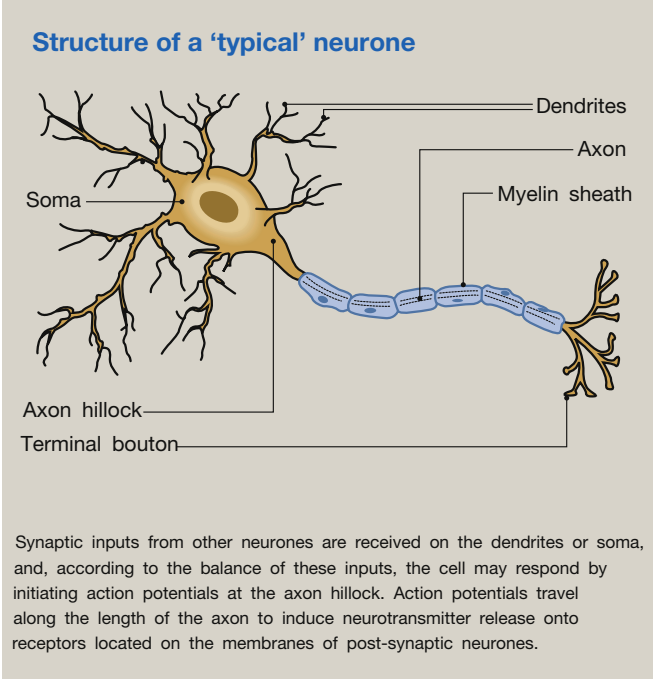
Neuronal morphology

As a reflection of the many different specialist functions of neurones throughout the body's nervous systems, the shape and size of these specialized cells varies enormously. However, most neurones have many common morphological features that we can consider in a 'typical' neurone, for example a spinal motor neurone (Figure 1). Neurones have a 'polar' structure such that one end of the cell is specialized to receive incoming information from other neurones, and the other end makes synaptic contacts in order to transmit information to other (post-synaptic) cells. The roughly spherical central part of a 'typical' neurone, which contains the cell nucleus, is the soma, and is about 20 μm in diameter. Dendrites are processes extending out from the soma that receive synaptic input from pre-synaptic neurones. According to the activity of these pre-synaptic neurones, an action potential (or a train of action potentials) may be triggered in a 'typical' neurone. These action potentials travel along the axon – a long process (emerging from the soma) that divides into terminal branches, each of which forms a synapse with a post-synaptic cell (another neurone or, in the case of a motor neurone, a skeletal muscle cell). The initial portion of the axon where it emerges from the soma is called the axon hillock – this is an important region of the plasma membrane because it is where the action potential is usually initiated, depending on the balance of the inputs of many pre-synaptic neurones (see below). The axons of most neurones are myelinated (i.e. they are wrapped in an insulating sheath, consisting mainly of myelin [a lipoprotein], which is formed by glial cells [Schwann cells or oligodendrocytes in the peripheral or central nervous systems, respectively]). The myelin sheath is discontinuous such that it is separated into segments, approximately 1 mm long, by nodes of Ranvier. Myelination allows action potentials to travel much more rapidly along the length of the axon by saltatory conduction (see pages 243–247 of this issue). The speed of action potential propagation is a crucial aspect of nervous system function – the basic survival of an organism depends on its ability to respond rapidly to environmental changes. This, in turn, is determined by the rates of information transfer between neurones. In general, the larger the diameter of an unmyelinated axon, the faster it can conduct action potentials. Myelination permits smaller-diameter axons to conduct action potentials more rapidly. Large-diameter myelinated axons in the human body can conduct action potentials at speeds of over 100 m/second, whereas small-diameter unmyelinated fibres (e.g. C fibres, which transmit some types of pain signals) may operate at conduction speeds of only 0.5–2 m/second.



Synaptic inputs from other neurones are received on the dendrites or soma, and, according to the balance of these inputs, the cell may respond by initiating action potentials at the axon hillock. Action potentials travel along the length of the axon to induce neurotransmitter release onto receptors located on the membranes of post-synaptic neurones.

Figure 1

The synapse

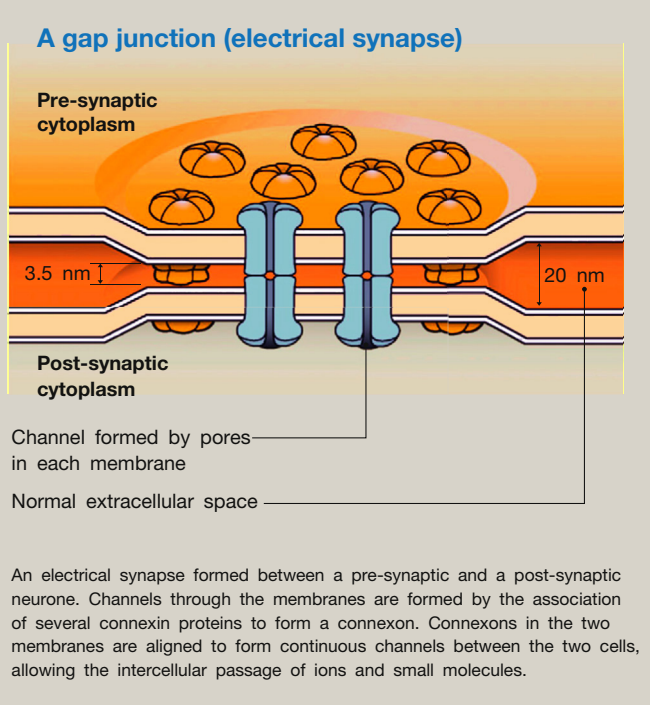
The connections, or junctions, between neurones are termed synapses. Although there are many neurones in the body, the true complexity of the body's central nervous system is reflected particularly in the astonishing total number of interconnections, or synapses, between neurones. The human brain comprises approximately 10^{11} neurones, each of which may receive thousands of synaptic contacts from other neurones, such that the cerebral cortex alone probably contains at least 10^{14} synapses. Modifications in synaptic function (so-called 'synaptic plasticity') are believed to underlie the brain's most complex and advanced functions (learning, memory and 'thinking'). Most synapses are 'chemical' in the sense that intercellular communication is achieved by the release of signalling molecules; however, the contact between some cells is sufficiently intimate to allow the formation of electrical synapses where the direct intercellular passage of ionic current occurs.

Electrical synapses

Electrical synapses are found in the CNS and occur at specialized intercellular contact regions called gap junctions where the membranes of the two cells involved are separated by only approximately 3 nm. Integral membrane proteins called connexins combine to form channels (connexons, each comprising six connexins) in each cell membrane. The connexons of the two cells are aligned to form gap junction channels that span the gap between the cells and allow the direct passage of ions from one cell to the other (Figure 2). The two cells are said to be electrically coupled – an action potential arriving from one cell acts extremely rapidly to induce a potential change (post-synaptic potential; PSP) in the second cell. The potential change caused by current flowing through an electrical synapse is small, so several synapses on the same cell must be active simultaneously in order to trigger an action potential (an example of synaptic integration). One of the main functions of electrical synapses is thought to be the synchronization of the activity of groups of neurones (or glial, cardiac muscle, epithelial or liver cells which can also form gap junctions).

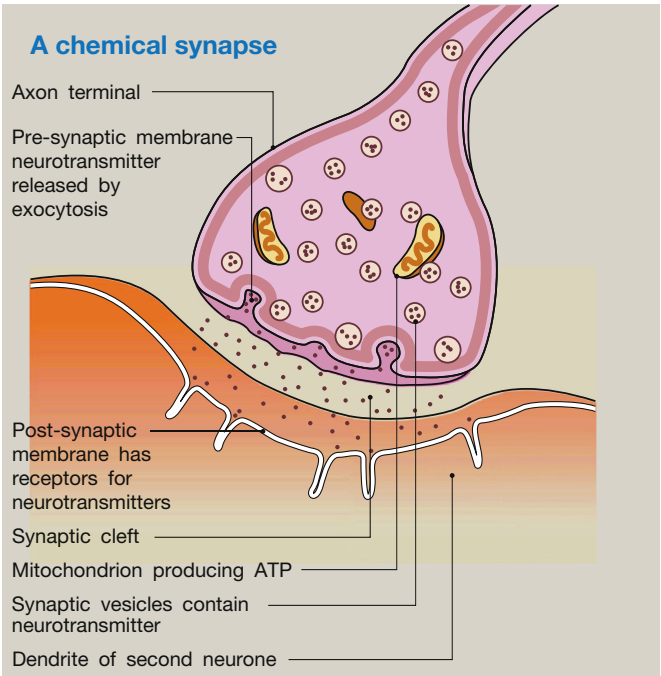
Chemical synapses

At a chemical synapse the terminal of an axon branch is expanded into a terminal bouton where the chemical signalling molecules (neurotransmitter) are synthesized and packaged in spherical membrane vesicles awaiting release. Between the pre-synaptic membrane of the terminal bouton and the post-



An electrical synapse formed between a pre-synaptic and a post-synaptic neurone. Channels through the membranes are formed by the association of several connexin proteins to form a connexon. Connexons in the two membranes are aligned to form continuous channels between the two cells, allowing the intercellular passage of ions and small molecules.

Figure 2



At chemical synapses the terminal of the pre-synaptic axon is expanded into a bouton, which contains the machinery for synthesis, vesicular compartmentation and release of neurotransmitter. Depolarization, caused by the arrival of action potentials, triggers calcium influx, which initiates the process of release. Neurotransmitter molecules bind to receptors on the post-synaptic membrane to initiate a response in the post-synaptic neurone. ATP, adenosine triphosphate.

Figure 3

synaptic membrane of the target cell is a gap (of approximately 30 nm) across which the released neurotransmitter molecules must diffuse in order to bind to receptors located on the post-synaptic membrane. Dense accumulations of proteins (membrane differentiations) are associated with the cell membranes either side of the synaptic gap; pre-synaptically, these are the sites of neurotransmitter release (active zones), and post-synaptically they are the location of receptors (collectively called the post-synaptic density). Binding of an excitatory neurotransmitter to its receptors partially depolarizes the post-synaptic membrane. If this depolarization attains a critical magnitude, an action potential may be triggered in the post-synaptic cell. However, some neurotransmitters are inhibitory (i.e. they render the post-synaptic membrane less excitable). In the CNS, the thousands of synaptic inputs that a neurone may receive will comprise those utilizing either excitatory or inhibitory neurotransmitters. Therefore, whether or not the post-synaptic neurone fires action potentials will depend on the balance of excitatory and inhibitory inputs at any one time (this is the basis of integrating information within the CNS and issuing appropriate efferent commands).

Pre-synaptic events

The pre-synaptic axon terminal is a rather busy place. Many mitochondria are present in order to supply energy (in adenosine triphosphate [ATP] molecules) required for synthesis, temporary vesicular storage and release of neurotransmitter (Figure 3). Speed is of the essence because, if the information encoded in the frequency of trains of pre-synaptic action potentials is to be transmitted accurately, neurotransmitter must be released rapidly in pulses at sub-millisecond rates. For the same reason, released neurotransmitter must be removed quickly from the synapse. To achieve this, most transmitters have a specific re-uptake mechanism in the form of protein carrier molecules embedded in the pre-synaptic membrane. Neurotransmitter clearance can also be mediated by carriers in the post-synaptic membrane and in surrounding glial cells. In the case of acetylcholine, a hydrolytic enzyme (acetylcholinesterase, located on the post-synaptic membrane) rapidly cleaves the transmitter molecule into choline and acetate. Choline is then taken back into the pre-synaptic terminal by a specific carrier for more acetylcholine synthesis. Neurotransmitters are amino acids (glutamate [excitatory]; γ-aminobutyric acid [GABA] and glycine [both inhibitory]), amines (e.g. acetylcholine, norepinephrine, serotonin [5-HT]) or peptides (e.g. enkephalins, somatostatin, substance P). Peptides are temporarily stored in secretory granules (rather than vesicles) prior to release. Neurotransmitter release from vesicles is a complex process which is triggered by calcium influx into the pre-synaptic terminal via voltage-gated calcium channels (i.e. membrane depolarization caused by the arrival of action potentials opens the channels). Calcium ions then act via a membrane protein called synaptotagmin to initiate the interaction of SNARE proteins that are embedded in the vesicular and pre-synaptic membranes. The SNARE proteins mediate fusion of the vesicle and pre-synaptic membranes at an active zone such that the transmitter is released by the process of exocytosis. The vesicular membrane then invaginates and 'buds off' intracellularly (endocytosis) to be recycled for subsequent transmitter release. Peptide transmitter release is also triggered

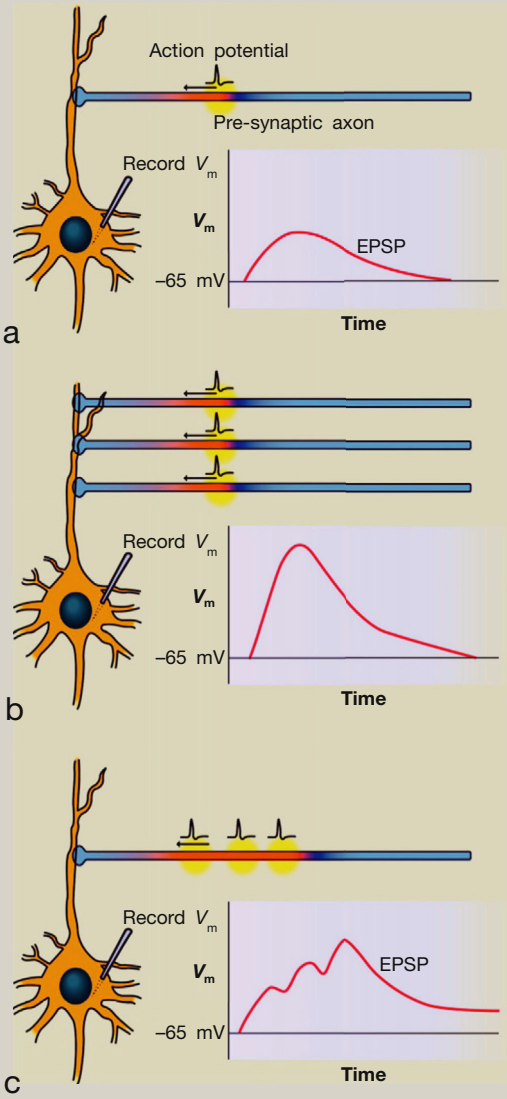
by calcium entry, but differs from vesicle exocytosis in that it is slower and occurs away from the active zones. Initially, it was thought that an individual pre-synaptic terminal could release only one type of transmitter (Dale's principle), but it is now known that many terminals co-release modulatory signalling molecules (e.g. peptides, purines or even nitric oxide) along with the main transmitter. In addition to the post-synaptic receptors for the neurotransmitter (which mediate intercellular signalling), there are also pre-synaptic receptors in the pre-synaptic membrane. These receptors mediate feedback mechanisms whereby the released neurotransmitter can modulate its own rate of synthesis and release.

Post-synaptic events

Released neurotransmitter molecules bind to and activate protein receptors embedded in the post-synaptic membrane. If the neurotransmitter is excitatory (e.g. glutamate), this results in a partial depolarization of the post-synaptic membrane (the excitatory post-synaptic potential; EPSP). The EPSP, like the end-plate potential (EPP) at the neuromuscular junction, is fundamentally different from an action potential – it is a graded response (the magnitude depends on the number of receptors activated) and it is localized (its magnitude declines rapidly at increasing distance from the receptors). In contrast, the action potential is an 'all-or-none' event and is self-propagating (it travels like a wave along the membrane). The corresponding localized change in membrane potential induced by inhibitory neurotransmitters (e.g. GABA) is called the inhibitory post-synaptic potential (IPSP) and is a hyperpolarization. At the neuromuscular junction, the EPSP (end-plate potential) is always of sufficient magnitude to initiate action potentials in the muscle cell membrane. However, at CNS synapses each individual EPSP is insufficient to trigger action potentials in the post-synaptic neurone. Many synapses on one cell must be active simultaneously in order to induce EPSPs of sufficient magnitude to initiate an action potential (see below). Post-synaptic receptors are generally either ionotropic or metabotropic (i.e. they are either ligand-gated ion channels or G protein-coupled receptors [GPCRs]). The former operate quickly by briefly opening an ion channel, allowing influx of particular ions, whereas the latter operate over a longer time-scale and are linked to enzymatic mechanisms which generate intracellular signalling molecules (second messengers, e.g. cyclic adenosine monophosphate [AMP]).

Synaptic integration

The complexity of the CNS is reflected in the fact that many individual CNS neurones receive synaptic contacts from thousands of other neurones. The probability of the post-synaptic neurone firing action potentials is determined by the process of synaptic integration (i.e. the balance of excitatory–inhibitory inputs, and the patterns of excitatory inputs are integrated by the post-synaptic neurone into an overall response or non-response). If we initially just consider the excitatory inputs, it must be emphasized that the EPSP generated by a single active synapse is not sufficient to trigger post-synaptic action potentials in most cases (the neuromuscular junction is an exception). Several EPSPs must summate in order to initiate an action potential at the axon hillock – this summation may be spatial or temporal (i.e. the simultaneous activation of several separate inputs, or high-frequency activation of a single input; Figure 4). However, most of the pre-synaptic inputs are located on the dendrites, which are some distance from the axon hillock. There is a danger, therefore, that the EPSP may decay with distance and never be able to depolarize the axon hillock membrane sufficiently. This problem is solved in many neurones by the presence



(**a**) A single pre-synaptic input generates an excitatory post-synaptic potential (EPSP) that is insufficient to trigger a response from the post-synaptic cell. (**b**) However, simultaneous activation of three pre-synaptic inputs results in the spatial summation of individual EPSPs to form a greater EPSP that can trigger post-synaptic action potentials. (**c**) High-frequency stimulation of a single pre-synaptic input causes temporal summation, i.e. before the previous EPSP can decay a second EPSP is induced, resulting in an additive effect to produce an EPSP of greater magnitude.
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Figure 4

of voltage-gated channels in the dendritic membranes that act to boost the EPSP such that it does not decay completely before reaching the soma and axon hillock.

Now, if we re-introduce the inhibitory pre-synaptic inputs, we can complete the picture of synaptic integration. A common type of inhibitory synapse mediates a process called shunting inhibition. These inhibitory synapses are located nearer to the soma than excitatory synapses and they operate by opening ligand-gated ion channels which allow chloride ions to flow into the cell. GABA is the most common type of inhibitory neurotransmitter that operates by this mechanism. If an EPSP is generated by an excitatory synapse on a distal region of a dendrite, it must pass by the inhibitory synapse before reaching the soma. If the inhibitory synapse is activated, the chloride channels will open and allow Cl^- to flow into the cell and 'cancel out' the depolarization of the EPSP. Therefore, even if the EPSP is of sufficient magnitude to generate an action potential, it can be 'snuffed out' by the simultaneous activation of inhibitory synapses.

Synaptic plasticity

Chemical synapses are dynamic, plastic structures in the sense that they can change their function (and structure) in response to changes in functional demands placed upon them. Such synaptic changes can be temporary or permanent, and are believed to underlie the cognitive processes of learning and memory. A simple type of synaptic plasticity is caused by changes in post-synaptic receptor sensitivity or number in response to sustained high or low synaptic levels of neurotransmitter. Synaptic hyperactivity would cause increased receptor stimulation, leading to reduced post-synaptic responsiveness due to a reduction in receptor numbers (downregulation) and/or sensitivity. The converse would occur in response to prolonged synaptic hypoactivity (receptor upregulation). These changes also occur in response to chronic administration of drugs that are receptor agonists or antagonists, respectively. Withdrawal syndromes precipitated by abrupt cessation of chronic drug administration are caused largely by these changes in receptor populations. Permanent changes in synaptic function permit the brain to store information and to modify behaviour (learning and memory). Two main types of synaptic plasticity, long-term depression (LTD) and long-term potentiation (LTP), whereby synaptic function is inhibited or enhanced, respectively, are thought to mediate these cognitive functions. ◆

FURTHER READING

Bear MF, Connors BW, Paradiso MA. Neuroscience: exploring the brain. 4th edn. New York: Wolters Kluwer, 2015.

