

The human nervous system is one of the most intricate of all bodily organs and new insights into its structure and function over recent decades have gone only part of the way towards unravelling the mysteries of this complex computer. The system is easiest to understand when broken down into manageable parts. Both the central and peripheral nervous systems are composed of nerve cells or neurons, which are organised in networks and serve various functions.

The processes underpinning these functions are complex, and can go wrong in lots of different ways. Much of the functioning, and malfunctioning, of the brain remains closed to us, and research continues apace. However, we are now gaining insights across a range of neurological diseases of the fundamental mechanisms that cause those diseases, and these are reviewed here. Of course, as information marches on some of what follows may prove to be at best an approximation of biological truth; but it is a better, more complete approximation than has been possible at any time in the past.

### Neurons and synapses

Neurons are shaped like a tree, with a cell body (the central part of the tree), an axon (the trunk) which conveys information from the cell body to the next nerve or muscle cell in the network, and dendrites (the roots) which receive inputs from other cells (Fig. A). The connection between two nerve cells is called a synapse, and information is transmitted between cells across synapses by chemicals called neurotransmitters. Neurons in the central nervous system are very small, but in the peripheral nervous system can transmit information across long distances; a lumbar anterior horn motor neuron axon (travelling from the lumbar region of the spinal cord to the feet) can be as long as 1 m, but only 10  $\mu\text{m}$  wide. This

is the equivalent of a drinking straw (5 mm wide) that is 500 m long! A sensory nerve from the big toe ending in the post-central sensory strip of the brain could be equivalent to a drinking straw of 1 km in length.

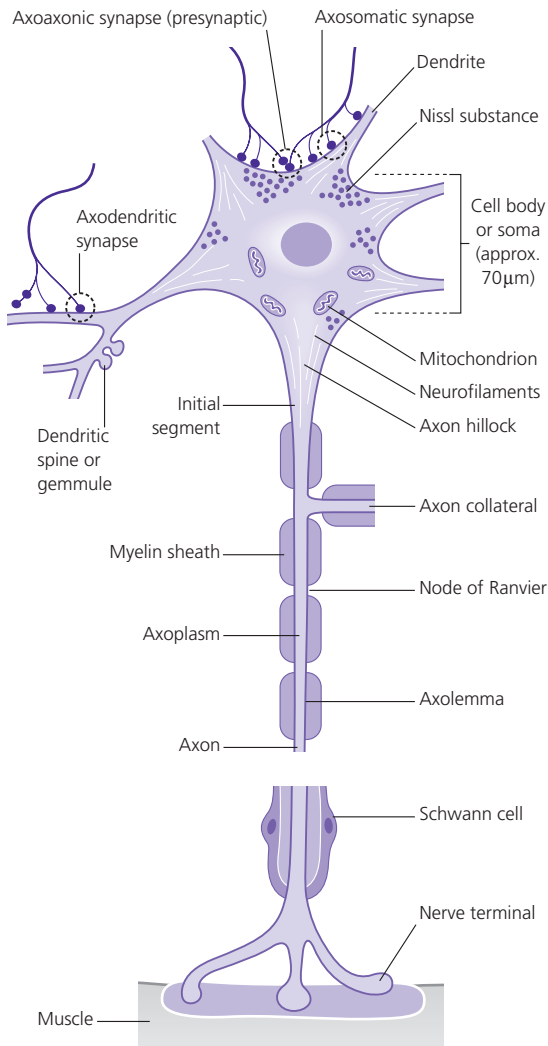
Like cardiac myocytes, neurons are excitable cells, meaning that they rely on electrical impulses to transmit information. The electric charge of a neuron is created and maintained by a delicate balance between positively and negatively charged ions, which enter and leave the cell through channels (such as sodium and potassium channels), the opening of which is usually regulated by pumps (such as sodium–potassium ATPase) in the cell membrane. When a neuron fires, rapid changes in ions within the cell (and their associated electric charges) cause depolarisation and repolarisation of the cell.

### The action potential

The various inputs to any given neuron lead to changes in the transmembrane potential in the region of the axon hillock. When the depolarisation raises the potential from the resting value (around  $-90\text{ mV}$ ) to around  $-40\text{ mV}$ , specialised voltage gated sodium channels open, allowing the influx of sodium ions down their concentration gradient, with depolarisation and reversal of transmembrane potential to around  $+40\text{ mV}$ . This leads to changes in the transmembrane potential further down the neuron, and when sodium channels there sense that this has reached  $-40\text{ mV}$  they too open, and so the depolarisation is propagated down the neuron into the axon itself. In time the sodium channels close, and the resting balance of ions across the membrane is restored by sodium–potassium ATPase, a pump that consumes around two-thirds of neuronal energy expenditure.

Neuronal axons are covered in an insulating substance called myelin, which is a component of Schwann cells (in the peripheral nervous system) and oligodendrocytes (in the central nervous system). The effect of the myelin sheath is to provide insulation and allow faster conduction along the axon, as well as providing metabolic

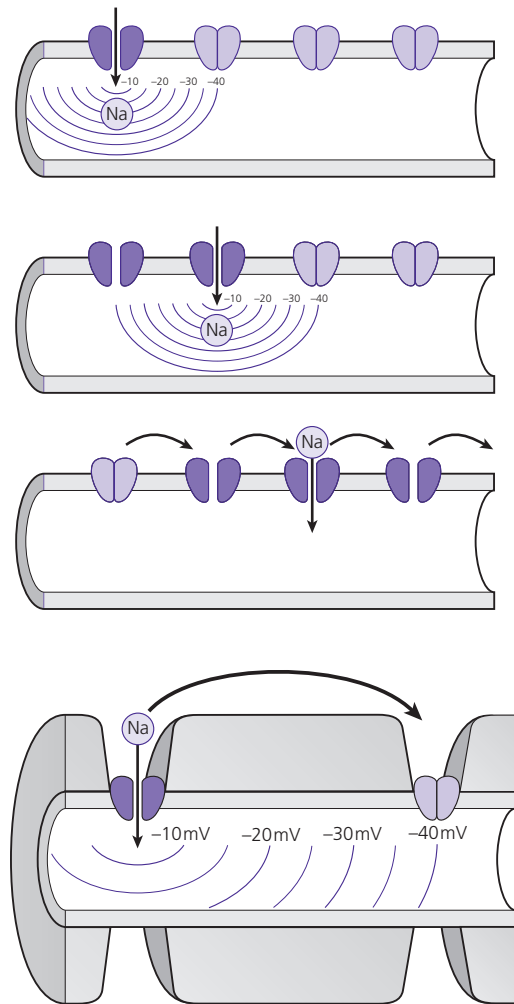
## 2 Part 1: Basics



**Figure A** The structure of a neuron.

support for the cell. Along the course of the axon there are tiny gaps between myelinating cells called nodes of Ranvier (which are up to 2 mm apart). The action potential jumps between these nodes by a process called saltatory conduction, which speeds up the process of conduction (Fig. B).

Disorders affecting the myelin sheath are usually immune-mediated and include multiple sclerosis and Guillain-Barré syndrome. When the myelin sheath is damaged, conduction velocity along the axon is reduced and the cell may die, producing neuronal atrophy. Multiple sclerosis (MS) is a disorder of cell-mediated immunity caused by recurrent attacks on oligodendrocytes, and results in sustained impairment because of incomplete remyelination and secondary axonal



**Figure B** Saltatory conduction.

damage. Neuromyelitis optica (NMO) is a related condition with recurrent episodes of optic neuritis and spinal cord inflammation. NMO is a disorder of humoral immunity caused by antibodies to the astrocyte water channel aquaporin, and the prognosis is worse than that of MS.

Guillain-Barré syndrome is a disorder of humoral immunity resulting from a (usually monophasic) attack on Schwann cells causing demyelination. Antibodies raised in response to infection such as *Campylobacter* cross react with gangliosides expressed on the surface of Schwann cells and invoke an inflammatory response. The principal effect on nerve conduction is reduced conduction velocity rather than the reduced compound action potential seen in axonal neuropathies. This reflects the

fact that while the axons are usually stripped of their myelin sheath, the underlying axons seldom die off, so that conduction is slower but the number of cells contributing to the compound action potential remains relatively constant.

### Synaptic transmission

Neurons generally use chemical signalling to communicate with each other and with muscles at specialised structures called synapses (or, in the case of muscles, the neuromuscular junction). When a neuron depolarises, the wave of depolarisation spreads along the axon and reaches the presynaptic terminal at the end of the axon. The resultant change in membrane potential is sensed by voltage gated calcium channels which then open, leading to the influx of calcium. The resulting increase in intracellular calcium triggers the binding and fusion of presynaptic vesicles, which contain the neurotransmitters to the presynaptic membrane, leading to the release of transmitter to the synaptic cleft. The neurotransmitters diffuse across the synaptic cleft to reach the postsynaptic membrane on the next neuron in the network (Fig. C).

There follows a rapid increase in transmitter concentration at the postsynaptic membrane. Some of this transmitter binds to receptors on the postsynaptic membrane, some undergoes re-uptake by the presynaptic nerve terminal and some is metabolised by enzymes (such as acetylcholinesterase or catechol-*O*-methyl transferase).

### Postsynaptic receptor binding

When it reaches the postsynaptic membrane, the neurotransmitter binds to receptors which are usually proteins. There are two main types of receptor: ion channel-

associated receptors and G-protein-coupled receptors. The latter are associated with G-proteins that result in the activation or inhibition of GTPases. The former are associated with ion channels (ligand gated) so that binding of the neurotransmitter to the receptor causes opening of the channel allowing influx or efflux of ions along their concentration gradient. Opening of a single ion channel could never cause sufficient ion flows to raise the intracellular potential enough to result in neuronal depolarisation, but if the summation of inputs from different ion channels at different postsynaptic membranes is sufficient, depolarisation will occur, with opening of voltage gated channels and thereby initiation of an action potential.

These same receptors are the site of action of many of the drugs used in the treatment both of neurological diseases and of other conditions. For instance, many of the clinical manifestations of Parkinson's disease are caused by degeneration of neuronal pathways between the substantia nigra and the striatum (so-called nigrostriatal pathways). The neurons that are involved in abnormal degeneration in Parkinson's disease have their cell bodies in the substantia nigra ('nigra', or black, at histological examination because of the presence of the machinery needed to make dopamine) and terminate in the striatum, where the dopamine is released.

The clinical manifestations of Parkinson's disease can be alleviated, in many patients, by drugs that are given systemically and which bind to, and activate, striatal dopamine receptors. These are called dopamine agonists. Similarly, some of the more florid manifestations of schizophrenia can be ameliorated by drugs that block dopamine signalling at specific receptor subtypes, and these are called dopamine antagonists.

### Drug-receptor interactions

Information about the interaction of drugs (and endogenous chemical ligands) with receptors on neurons can be used to work out how often the drug should be given and what the appropriate dose should be. The rate at which a drug binds to (or associates with) a receptor can be described by an association constant  $k(a)$ , and the rate at which drug-receptor complexes break up can be described by a dissociation constant,  $k(d)$ . The rates of association and dissociation depend on these constants and on the amount of ligand (L), receptor (R), and ligand-receptor (LR) complexes:

$$\text{Rate of association} = k(a) \cdot [L] \cdot [R]$$

$$\text{Rate of dissociation} = k(d) \cdot [LR]$$

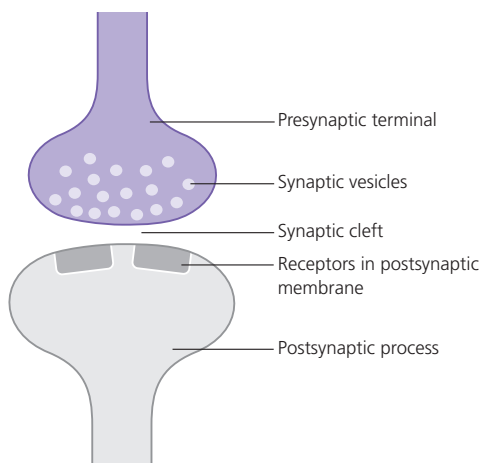


Figure C A synapse.

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Soon after neurotransmitter release or drug delivery, an equilibrium is reached where the rates of association and dissociation are equal, and so:

$$[L] \cdot [R] / [LR] = k(d) / k(a) = K$$

The effect of a drug is manifest when it is bound to the receptor, and the amount of bound drug is:

$$[LR] = [L] \cdot [R] / K$$

Because the total amount of receptor is fixed (at least in the short term), the maximum effect of any drug is also fixed:

$$R_{\text{tot}} = [R] + [LR]$$

Therefore,

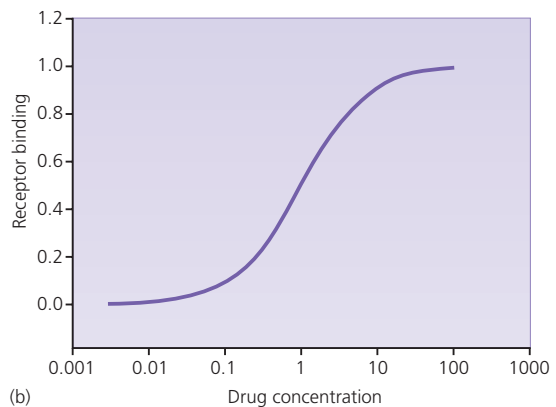
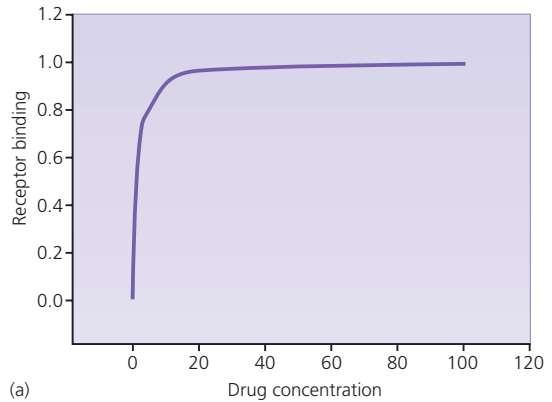
$$[LR] = ([L] \cdot ([R_{\text{tot}}] - [LR])) / K$$

Rearranging,

$$[LR] = [R_{\text{tot}}] / (1 + (K/[L]))$$

In other words, because the number of receptors for a drug or neurotransmitter does not change at a given point in time, only a certain amount of chemical can bind to the postsynaptic cell. Once the receptors are full, no more chemical can produce an effect. Therefore sequential increases in drug concentration at the active site do not result in the same increase in receptor occupancy. In fact, over the active range of drug concentrations, there is a logarithmic relationship between drug concentration and receptor occupancy (Fig. D). At higher doses, very little can be gained from increasing drug dose. This is important when escalating agonist drug doses, for instance dopamine agonists in Parkinson's disease.

However, the relationship between drug concentration and drug metabolism (and the rate at which the drug is cleared) should also be considered. For many drugs, the rate of metabolism is proportional to drug concentration (first order kinetics), so that the more drug is available, the more enzymes there are working to clear it. However, some drugs cause the induction of the enzymes responsible for their metabolism (second order kinetics, e.g. phenobarbitone and the cytochrome p450 system), and this can result in lower concentrations both of the drug and also of other drugs, or hormones, which share that pathway. Finally, for some drugs, the metabolic pathway can become saturated (zero order kinetics), such that small subsequent increases in dose lead to substantial increases in drug concentration (e.g. phenytoin) because there are not sufficient enzymes available to clear the increased dose of drug.



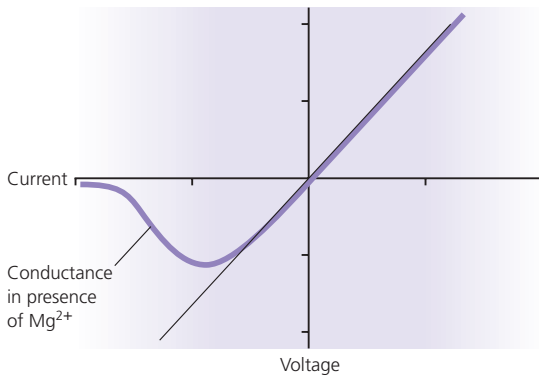
**Figure D** (a) Dose–response and (b) log dose–response curves.

### Excitatory transmission

Neurotransmitters may be excitatory (causing the next cells in the network to become excited and fire) or inhibitory (suppressing the next cells in the network and reducing their chances of firing). The predominant excitatory neurotransmitter in the mammalian nervous system is the amino acid glutamate. Glutamate binds to a number of different receptors, some of which are linked to ion channels and others of which are coupled to G-proteins. One particular receptor deserves a special mention: the *N*-methyl-D-aspartate (NMDA) receptor has characteristics that allow it to fulfil special functions in information processing, but these very characteristics also make it a key player in disease states.

### NMDA receptors: inward rectification

The NMDA receptor is a ligand gated ion channel. Under normal conditions, in a cell at rest, conductance through the NMDA receptor is low even when the channel is



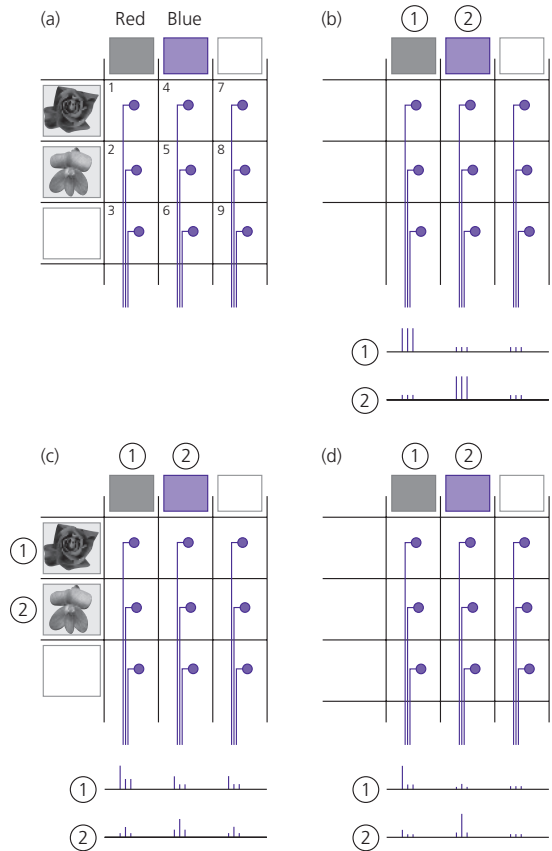
**Figure E** Inward rectification at the NMDA receptor.

open. This is because magnesium ions in the extracellular fluid are drawn in to the mouth of the receptor along the electrochemical gradient but are too large to pass through, so they block it. However, if the neuron becomes depolarised that electrochemical gradient is less strong, the cell is less attractive to magnesium ions, and the blockade of traffic through the ion channel is reduced, allowing other cations (predominantly calcium and sodium) to flow down their concentration gradient and enter the cell. This process is called inward rectification and can be shown in a plot of current flowing against membrane potential (Fig. E).

### Long-term potentiation and memory

This property of NMDA receptors is important in the formation of memory. If a cell with several NMDA receptors is depolarised, leading to calcium and sodium influx, these ions cause the cell to remain depolarised (and therefore less attractive to magnesium ions), meaning that other ions can continue to flow into the cell for a longer period. Therefore the response of the cell to subsequent stimuli is potentiated. This phenomenon persists for some hours, and is called long-term potentiation. It provides a mechanism whereby different streams of information can be integrated, and the convergence of different signalling pathways can be recorded.

For example, imagine a set of neurons situated at the convergence of two pathways, one conveying the colour of objects and the other conveying the identification of plants (Fig. F). If different neurons receive different inputs from each of these pathways an array can be constructed. After exposure to lots of different plants, neurons receiving information on the colour 'blue' and on violets will be potentiated in response to inputs of



**Figure F** Illustration of how long term potentiation can be a substrate for memory. (a) An array of 9 neurons responds to red or blue or other colour (vertical); and to roses or violets or other flowers (horizontal). (b) Exposure to red causes activation of neurons 1–3, and exposure to violet causes activation of neurons 4–6. (c) Exposure to red and roses causes preferential activation of neuron 1, and some activation of neurons 2,3,4 and 7; Exposure to blue and violets causes preferential activation of neuron 5 and some activation of neurons 2,4,6 and 8. (d) Subsequent exposure to red causes preferential activation of neuron 1 and some activation of neurons 2 and 3; while subsequent exposure to blue causes preferential activation of neuron 5 and some activation of neurons 4 and 6. When challenged with red, neuron 1 'remembers' the rose, and when challenged with blue neuron 5 'remembers' the violet.

either 'blue' or violets, and the same will hold for those receiving information on 'red' or roses. In contrast, those capable of receiving inputs about 'blue' and roses, or 'red' and violets, will not have their inputs potentiated. So when faced with a stimulus 'rose', it is much more likely to be associated in the mind with 'red' than with 'violet'.

## Excitotoxicity

As mentioned above, the NMDA receptor can also be important in disease states. The capacity for long-term potentiation and progressive increases in excitability brings with it a susceptibility to overwhelming stimulation. Where neurons are exposed to multiple, repetitive inputs over a short period (as happens during seizure activity), or where the extracellular concentration of excitatory agonists is too high for too long (as happens with failure of glial glutamate uptake) or where neurons are unable to maintain their membrane potential, then NMDA receptor channels remain open for prolonged periods, resulting in substantial rises in intracellular calcium. This in turn invokes a number of processes including activation of neuronal nitric oxide synthase, free radical production and subsequent damage to DNA, membranes and mitochondria.

If there is a failure in the delivery of oxygen or glucose to the brain (as occurs in stroke, syncope, cardiac arrest or hypoglycaemia), then neurons become unable to synthesise adenosine triphosphate (ATP), the high energy phosphate that acts as the energy source for important enzymes including sodium–potassium ATPase, and this means that action potentials can no longer occur. At intermediate levels of blood flow (e.g. syncope), or where the insult is of short duration (e.g. a transient ischaemic attack), this may have few other consequences, and neuronal viability is not impaired.

However, in the longer run the neuron must retain sufficient resources to exclude sodium (using sodium–potassium ATPase), to normalise the membrane potential, to close voltage activated channels (including the induction of voltage-dependent blocks of the NMDA receptor) and to sequester intracellular calcium. Glial cells must have sufficient energy resources to take up extracellular glutamate, or levels will rise, causing activation of the NMDA receptor. When these processes fail (e.g. in an ischaemic stroke or prolonged cardiac arrest) then neurons undergo anoxic depolarisation and swell and eventually the cell membrane will burst.

Even if the neuron is able to normalise these processes, it may be that damage incurred at the time of the insult has been such that the integrity of the cell is compromised (perhaps, for instance, through free radical-induced DNA mutations) to the extent that apoptosis occurs.

## Inhibitory transmission

As well as excitatory neurotransmitters (that cause neighbouring cells to become excitable and fire), there are inhibitory neurotransmitters that suppress firing in asso-

ciated cells. The major inhibitory neurotransmitter is gamma-amino-butyric acid (GABA), largely used by inhibitory interneurons. In contrast to glutamate, a major role of GABA signalling is the opening of a chloride channel, leading to influx (down a concentration gradient but against an electrostatic gradient) of chloride ions, leading in turn to hyperpolarisation of the postsynaptic membrane.

## Mutations and epilepsy

Abnormalities of neurotransmitter systems are thought to be important in the pathogenesis of epilepsy and seizures. Under normal conditions, cells are prevented from firing by the inhibitory neurotransmitters, but during a seizure this inhibitory control is lost or excitatory input is overwhelming, and overactivity of the neural network results. Most brains, even in individuals without epilepsy or structural brain disease, are capable of manifesting seizure activity given a large enough insult. The Levant nut (*Cocculus indicus*) is also known as the fishberry, because when it is thrown into water the fish are stunned, float to the surface and can be easily captured; this is due to the presence of picrotoxin, a non-competitive GABA-A antagonist, which is a powerful stimulus to seizure activity. Drugs in more common use can also provoke seizures, either during acute intoxication (e.g. opiates, amphetamines) or, through the induction of tolerance, on withdrawal (e.g. alcohol).

In most patients with epilepsy the cause is not known. Some may have a history of brain injury, or of birth injury, or learning disability, or their seizures may be the consequence of a developing brain tumour. Under these circumstances, it is thought that a disruption of neuronal circuitry, and in particular of inhibitory pathways, is at fault.

Occasionally, the susceptibility to seizures can be attributed to mutations in genes encoding important regulators of neuronal excitability. For instance, mutations in the voltage gated calcium channel CaV3.2 have been found in families with idiopathic generalised epilepsy; mutations in the voltage gated sodium channel NaV1.1 have been found in families with generalised epilepsy febrile seizures plus (GEFS+); and mutations in the ligand gated nicotinic acetylcholine receptor (which has a role in modulating synaptic glutamate release) have been in found families with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE).

## The neuromuscular junction

For a neural signal to result in movement of a muscle, information must be transmitted between the end of the

motor neuron and the associated muscle across a specialised structure called the neuromuscular junction. When the electrical message reaches the end of the motor nerve, depolarisation of the presynaptic membrane leads to release of acetylcholine to the synaptic cleft, and this diffuses across the synaptic cleft (around  $0.2\ \mu\text{m}$ ) to bind to nicotinic acetylcholine receptors on the muscle membrane. These are ligand gated ion channels that allow the influx of sodium and egress of potassium. The resulting increased intracellular potential is sensed by voltage-dependent calcium channels sited on the sarcoplasmic reticulum, resulting in a large increase in intracellular calcium concentrations, which in turn leads to actin–myosin crosslinking, shortening of muscle fibrils and muscle contraction.

### Disorders of neuromuscular transmission

In myasthenia gravis, autoantibodies directed against the nicotinic acetylcholine receptor provide competitive inhibition, such that the degree of postsynaptic depolarisation in response to a given concentration of acetylcholine is diminished. This leads to a compensatory increase in presynaptic acetylcholine release, which may be temporarily sufficient to restore normal contractility; but in time and with repeated stimulation, presynaptic stores of acetylcholine become depleted, leading to a fatiguable weakness and a prominence of symptoms towards the end of the day. Similarly, the Lambert–Eaton myasthenic syndrome is caused by antibodies against the presynaptic voltage gated calcium channel and so inhibits presynaptic calcium entry.

### Manipulation of neuromuscular transmission

Synaptic concentrations of acetylcholine can be increased by inhibitors of the enzyme responsible for its breakdown, acetylcholinesterase, and these drugs form the basis for the treatment of the myasthenic syndromes. However, the nicotinic acetylcholine receptor has an unusual property in that sustained concentrations of acetylcholine lead to sustained channel opening and a depolarising neuromuscular blockade. As well as being the basis of the cholinergic crisis that can result from over-treatment with cholinesterase inhibitors, this phenomenon is also responsible for the action of many neuromuscular blockers used in anaesthesia, and also for the lethal effects of some chemical weapons such as SARIN.

The clinical (botulism) and therapeutic (cosmetic or antispasticity) effects of botulinum toxin are due to interference with the process through which presynaptic vesicles dock to the presynaptic membrane.

### Mutations and migraine

Genetic factors can also be important in other neurological diseases. For example, familial hemiplegic migraine involves a motor aura (that is to say, unilateral loss of power rather than simply sensory change), and is caused by mutations in the pore-forming subunit of the CaV2.1 channel, the voltage gated sodium channel NaV1.1, or the  $\alpha 2$  subunit of sodium–potassium ATPase. In transgenic animals, the calcium channel mutation causing familial hemiplegic migraine is associated with enhanced cortical spreading depression, thought to be the pathophysiological basis of migraine aura. Given the high heritability of migraine it is likely that mutations or polymorphisms in the genes encoding similar proteins are responsible for other more common forms of migraine.

### Cerebral blood supply

Blood reaches the brain via two carotid arteries and two vertebral arteries. The carotid arteries divide in the neck to form Internal and external branches. The internal carotid artery enters the skull through the carotid canal to supply the brain itself. The rest of the head, including the meninges, is supplied by the external carotid artery. The middle meningeal artery enters the brain through the foramen lacerum, and is commonly damaged following head injury, resulting in the accumulation of blood between the inner surface of the skull and the dura, an extradural haematoma. No arteries cross the subdural space, but small bridging veins are present, and trauma to these causes blood to accumulate between the dura and the brain surface, known as a subdural haematoma.

The vertebral arteries join in the midline in front of the brainstem to form the basilar artery, and this divides about 5 cm later, in front of the midbrain, to form two posterior cerebral arteries. Through two posterior communicating arteries these link with the distal carotid arteries on each side, which each in turn divide to form the middle and anterior cerebral arteries. The anterior cerebral arteries are linked by the anterior communicating artery, and the anastomotic ring thus formed – the circle of Willis – ensures that occlusion of one of the major vessels in the neck does not lead to ischaemia in one-quarter of the brain (Fig. G).

However, beyond the circle of Willis arteries supply regionally defined areas with little in the way of anastomoses between these. Occlusions of the posterior, middle or anterior cerebral arteries are therefore highly likely to lead to irreversible brain injury unless reperfusion occurs.

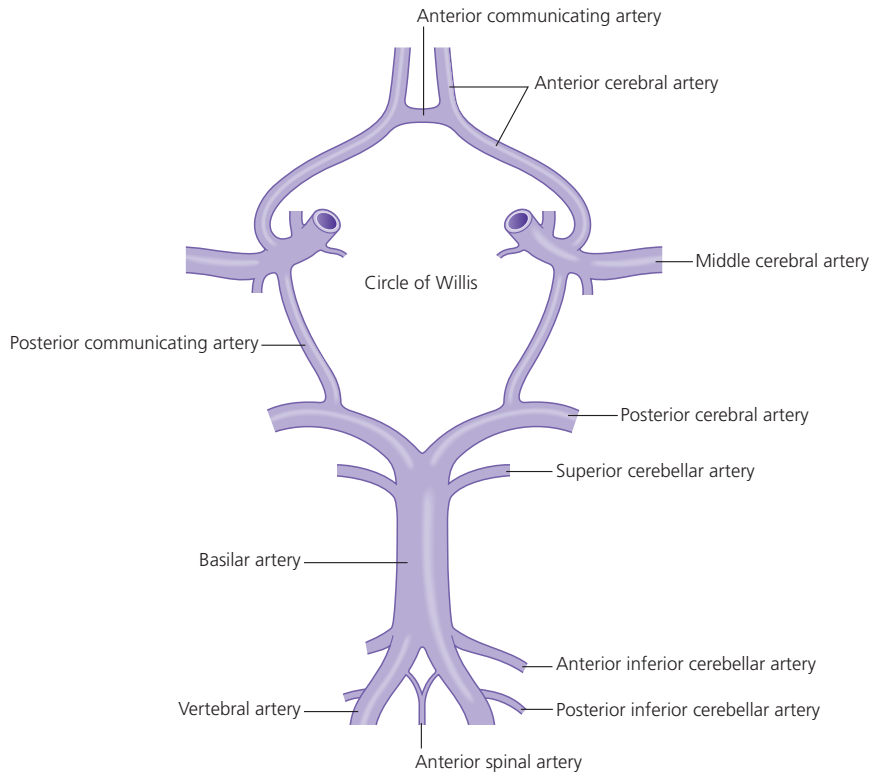
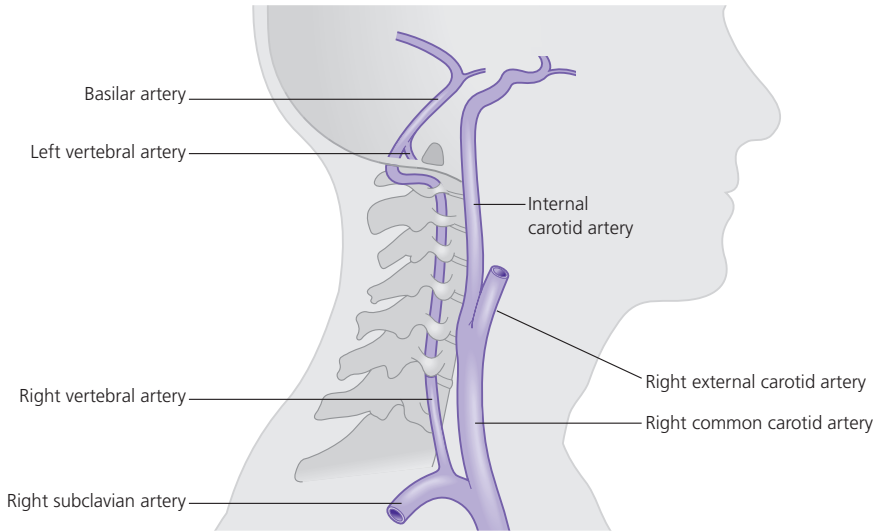


Figure G Blood supply to the brain.



## Neurodegeneration

In some conditions, particular populations of neurons seem to be particularly susceptible to accelerated aging. This is probably a consequence of disruptions to processes which are unique to that population of neurons. For instance, in Parkinson's disease (PD) there is a progressive loss of tyrosine hydroxylase containing dopamine-synthesising neurons in the substantia nigra. In PD, neurons contain cytoplasmic Lewy bodies, thought to represent the accumulation of aggregates of proteins which have not been broken down in the usual way.

Around 60–80% of dopaminergic neurons are lost before the motor signs of PD become evident. The basal ganglia motor circuit consists of direct and indirect pathways and provides additional modulation to the cortical control of movement. Striatal neurons projecting to the globus pallidus and expressing D1 receptors constitute the direct pathway and those expressing D2 receptors are part of the indirect pathway. In PD, decreased striatal dopamine is held to increase inhibitory output from the globus pallidus externa/substantia nigra pars reticulata, which suppresses movement and thereby causes the clinical features of PD.

Similarly, degeneration of different neuronal populations results in the development of Huntington's disease, motor neuron disease, Alzheimer's disease, spinocerebellar ataxias and many others.

## Autoimmune neurological diseases

Particular neurological dysfunctions may occur due to the presence of antibodies that bind to specific parts of the nervous system. These appear to develop because of some similarity between their intended target – an antigen on an infectious agent such as *Campylobacter* or expressed on the surface of a tumour cell – and the part of the nervous system in question. Some tumours (for instance small cell lung cancer) seem to be particularly good at provoking such responses, including a paraneoplastic cerebellar degeneration due to anti-Purkinje cell antibodies and a limbic encephalitis due to anti-voltage gated potassium channel antibodies.

## CSF dynamics and idiopathic intracranial hypertension

Cerebrospinal fluid (CSF) is synthesised in the choroid plexes of the lateral ventricles and flows through the ventricular system and then to the subarachnoid space through the foramina of Luschka and Magendie of the fourth ventricle. Bathing the brain and spinal cord, CSF is reabsorbed to the blood through specialised arachnoid granulations in the walls of cerebral veins and venous sinuses.

Obstruction to the flow of CSF within the ventricular system usually occurs at the cerebral aqueduct (between the third and fourth ventricles) and results in dilation of the lateral and third ventricles and a non-communicating hydrocephalus. Where the obstruction affects the absorption of CSF (arachnoid granulations can become obstructed by blood following subarachnoid haemorrhage or by bacteria and inflammatory cells following meningitis), then all ventricles become dilated and this is a communicating hydrocephalus. Where CSF volume is depleted, for instance following dural puncture (post-lumbar puncture headache), spontaneous dural leak (idiopathic or spontaneous intracranial hypotension) or dehydration (as may occur after a night out), then the headache which follows is usually very positional, is better when lying flat and becomes much worse within 10 minutes of sitting or standing. Finally, in some circumstances, there appears to be an imbalance between the rates of production and absorbance of CSF. This results in raised CSF pressure, which in turn can cause pressure on the optic nerves, reduced visual fields and, if untreated, blindness. The reasons for this imbalance are not clear but may be hormonally mediated, being much more common in the overweight, in women and in those taking vitamin A preparations.

Because the spinal subdural space is in continuity with the ventricular system, CSF pressure can be measured directly at lumbar puncture. However, this should not be done where there is a non-communicating hydrocephalus, or where the presence of an intracranial mass lesion means that decompressing the lumbar CSF would rapidly establish a pressure gradient which might lead to the intracerebral contents (particularly the brainstem) being forced through the foramen magnum.