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Introduction to Neuropsychopharmacology

All things are ready, if our minds be so.

*Henry V*, IV, iii (William Shakespeare)


*In omnibus negotiis prius quam aggreari, adhibenda est praeparation diligens.*

(In all matters, before beginning, a diligent preparation should be made.)

(Marcus Tillius Cicero)

1.1 Overview

Neuropsychopharmacology is a relatively new subject area in the neurosciences and may be viewed as the amalgamation of the principles of neuropharmacology and psychopharmacology. Neuropharmacology mainly deals with the effects of drugs on neurones, synapses and brain circuits and their interaction with neurotransmitters and other neurochemicals at their receptors and ion channels, both at a molecular and systems level. Psychopharmacology is the study of drugs that have the ability to alter mental states, such as emotional behaviours and cognition. Neuropsychopharmacology is, therefore, a field of study that describes the effects of drugs from the molecular to the behavioural level and requires integration and synthesis of knowledge from various disciplines, including neuroanatomy, physiology, pharmacology, molecular biology, genetics, psychology, psychiatry, sociology, biochemistry and chemistry. The principles of neuropsychopharmacology are important in (i) discovering more about the workings of the brain and the impact on behaviour, (ii) learning about the cellular, receptor and neurochemical changes that accompany brain dysfunctional states and (iii) the development of drugs to treat central nervous system (CNS) disorders and psychiatric conditions.

The authors of most textbooks on neuropharmacology and psychopharmacology presuppose that the reader has almost no knowledge of basic pharmacology, neurotransmitters and neurotransmission, receptor mechanisms, cell signalling, neuroanatomy, the fundamental principals of molecular biology and...
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genetics. Therefore, they spend the first few chapters of their books explaining the essential principals of these subject areas. Here, on the other hand, I will assume that the reader of this book has a working knowledge of these subjects. However, a lot of the basic information is covered in the different chapters of this book. In this chapter, some of the useful terms and concepts referred to in subsequent chapters are explained and brief overviews are given of (i) the anatomy and functions of the brain, (ii) important neurotransmitters in the CNS, (iii) some of the CNS depressant and stimulant drugs that are used in the treatment of the disorders that are discussed in subsequent chapters, and (iv) the experimental and clinical techniques that are used to obtain information on brain function.

1.2 A Brief Overview of the Anatomy and Function of the Brain

Reviewed briefly in this section are some of the important structures in the brain and their main functions. More detailed information on the anatomy and function of brain areas pertinent to specific CNS disorders are covered in the relevant chapters.

1.2.1 The Brainstem

The brainstem is made up of three structures, the medulla oblongata, the pons and the midbrain (Figure 1.1).

- The Medulla Oblongata (commonly referred to as the medulla) is a division of the brain known as the myelencephalon. It forms the most posterior or lowest part of the brain and is often considered an extension of the spinal cord within the skull. It is a small structure of about one inch (2.5 cm) in length and lies below the pons. It is composed largely of projection tracts carrying information between the body (via the spinal cord) and the rest of the brain. The medulla also has a network of cells that occupy the core of the brainstem, extending through the pons and midbrain, known as the reticular formation (reticulum means ‘little net’). The ascending projections from the reticular formation project to the thalamus and cortex and play an important role in arousal and, for this reason, they are also known as the ascending reticular activating system (ARAS) (Chapter 8). Various nuclei in the medulla’s reticular formation have diverse functional roles. There are cardiac, vasomotor and respiratory centres that regulate cardiovascular, circulatory and respiratory reflexes, respectively, as well as other nuclei that regulate reflexes, including vomiting, swallowing, coughing and sneezing.

- The Pons (which means bridge) is a structure, with a characteristic bulge, that lies above the medulla and is considered a ‘bridge’ between the medulla and the midbrain (which is located above it). Ascending and descending fibre tracts pass through the pons, which is also part of the reticular formation. It is a division of the brain known as the metencephalon. It is connected to another division of the metencephalon, the cerebellum (Section 1.2.2), by bundles of transverse fibre tracts. The pons contains centres for reflexes that are mediated by the fifth (trigeminal), sixth (abducens), seventh (facial) and eighth (vestibulocochlear) cranial nerves. The pons also has the pneumotaxic centres that, together with the medulla, control respiration.

- The midbrain is a division of the brain known as the mesencephalon and lies above the pons. Ascending and descending fibre tracts pass through the midbrain and it is also part of the reticular formation. The roof or tectum of the midbrain consists of two pairs of folds called colliculi (meaning ‘little hills’); these form the upper part of the midbrain that lies immediately above the cerebellum. The two inferior colliculi have auditory centres and are involved in auditory function. The superior colliculi, which lie in front of the inferior colliculi, have visual centres and are involved in the regulation of pupillary reflexes and eye movements that are mediated by the third and fourth cranial nerves, respectively. Under, or ventral to the tectum, is another subdivision of the midbrain, the tegmentum,
which contains part of the brainstem reticular formation. In addition, it contains a number of other key nuclei: the periaqueductal grey, which is involved in the regulation of pain and species-specific startle reflexes (Chapter 8); the substantia nigra and the red nucleus, which are involved in the regulation of motor movements (Chapter 2); and nuclei that are involved in the regulation of motivation and reinforcement (Chapters 10 and 11).

1.2.2 The Metencephalon

The cerebellum (meaning 'little brain') is a division of the metencephalon (Figure 1.1). It is a highly convoluted structure that has two hemispheres and is located behind the brainstem, to which it is connected. The cerebellum is the second largest part of the brain after the cerebral cortex and occupies about one-tenth of the brain’s volume. It is densely packed with neurones and has more than half the total number of neurones in the brain. It can be divided anatomically into three parts, known as the inferior, middle and superior cerebellar peduncles, which carry nerve fibre tracts between the medulla, pons and midbrain, respectively, and the cerebellum. The cerebellar cortex (outer layer) consists of grey matter (cell bodies) and the central core consists of white matter (myelinated nerve fibres). The cerebellar white matter has nerve fibre tracts that run to and from the thalamus and cortex.

The main function of the cerebellum is the coordination of movement; this operates below the level of consciousness. The cerebellum receives incoming sensory information from the ears (equilibrium receptors), skeletal muscles (proprioceptors), the brainstem and the cerebral cortex. It integrates this information and sends it to the motor cortex and skeletal muscle to coordinate posture, balance and movement. The cerebellum also acts, in conjunction with the cortex, to plan motor movements. In addition, the cerebellum has a role in ‘storage’ and ‘execution’ of motor memories, such as riding a bicycle or playing the piano, which once learnt can be carried out reflexively without conscious thought. More recently, there has been evidence to suggest that the cerebellum may also have a role in the regulation of cognitive functions, such as nonmotor learning and attention.

Figure 1.1 The human brain.
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Damage to the cerebellum, due to haemorrhage, tumours or injury, may result in ataxia (which is loss of muscle coordination), tremor, vertigo (dizziness), slurred speech and an inability to walk. Drugs, such as alcohol, benzodiazepines and barbiturates (Sections 1.6.1 and 1.6.2; Chapters 9 and 11), may depress neural activity in the cerebellum and produce symptoms such as ataxia and slurred speech.

1.2.3 Diencephalon

The diencephalon (which means ‘between brain’) is the division of the brain that is located between the cerebral cortex and the midbrain. The main structures of the diencephalon are the thalamus and hypothalamus (Figure 1.1). There are other smaller structures, such as the pineal gland (Chapter 9), in the diencephalon.

- The thalamus is a structure consisting of two large lobes that are situated on each side of the third ventricle (Section 1.2.6) and joined together by the massa intermedia that extends through the ventricle. Fibre tracts carrying sensory and other information from the spinal cord, the brainstem, cerebellum and parts of the cortex synapse in the thalamus. This information is processed in the thalamus and then sent to various areas of the cortex. The thalamus is, therefore, a major relay station in the brain. The thalamus consists of many pairs of nuclei. Some of these are specific sensory relay nuclei that receive information from sensory receptors, such as those for touch, temperature, pressure, pain, vision and sound, process them and then transmit them to appropriate sensory areas in the cortex. Thus, the lateral and medial geniculate nuclei of the thalamus are important for processing visual and auditory inputs, whereas the ventral posterior nuclei play a role in processing somatosensory information. In fact, within the thalamus, impulses from sensory receptors can produce conscious recognition of the crude sensations of pain, temperature and touch. There are also association nuclei in the thalamus, where signals of different sensory modalities are integrated and sent to association areas in the cortex for further processing. In addition, the thalamus plays an important role in mechanisms involved in alertness and attention (Chapter 9), emotions (Chapters 6, 7, 8, 10 and 11) and complex motor and reflex movements (Chapter 2).

- The hypothalamus is located below the anterior portion of the thalamus and above the midbrain and the pituitary gland (Figure 1.1). The hypothalamus, which is about the size of a peanut in the human brain, consists of several nuclei that regulate diverse bodily functions:
  - It regulates autonomic functions in both the sympathetic and parasympathetic divisions of the autonomic nervous system.
  - It plays a major role in the control of endocrine functions. Axons from the hypothalamus secrete releasing-hormones that act on the pituitary gland to regulate the secretion of various hormones into the bloodstream, including growth hormone and other hormones that, in turn, act on the adrenal gland, the sex glands and thyroid gland to elicit the release of the adrenal hormones, sex hormones and thyroid hormones, respectively. For example, corticotrophin hormone (CRH), released from axons in the hypothalamus, acts on secretory cells in the anterior pituitary gland to secrete a hormone called adrenocorticotrophin hormone (ACTH) into the blood stream. ACTH then acts on cells in the adrenal cortex, situated above the kidneys, to cause the release the hormone cortisol (Chapter 6; Figure 6.5).
  - The hypothalamus plays an essential role in the regulation of eating and drinking. Neurones in the ventromedial nucleus and lateral nucleus of the hypothalamus are involved in the regulation of food intake and energy homeostasis, while neurones in supraventricular and paraventricular nuclei of the hypothalamus are involved in the control of water intake and water balance.
  - The hypothalamus also plays an important role in the sleep–wake cycle by modulating arousal mechanisms (Chapter 9).
The hypothalamus has an important functional role in regulating body temperature, which has to be maintained within very narrow limits to prevent damage to cells and cellular processes. By regulating autonomic output and somatic centres in the brain, the hypothalamus can cause vasoconstriction and shivering if body temperature falls below a certain limit, and vasodilation and sweating if body temperature increases beyond a certain limit.

Thus, the hypothalamus plays a crucial role in almost all bodily function by virtue of its endocrine, autonomic and other functional roles, and is a target for drugs to treat obesity, anorexia, sleep disorders (Chapter 9), fever and hormonal disorders (Chapter 6).

1.2.4 The Telencephalon

The telencephalon is the division of the brain that is involved with higher brain functions, including learning and memory, voluntary actions, interpretation of sensory information and making judgements. The cerebrum, the largest part of the brain, consists of two cerebral hemispheres, the right and left hemispheres. The two hemispheres are connected together by bundles of nerve fibres known as the corpus callosum. The cerebral hemispheres are covered by a thin layer of grey matter (consisting of neuronal cell bodies) approximately 2–4 mm thick, known as the cerebral cortex. The interior of the cerebrum consists mainly of white matter fibre tracts made up of the myelinated axons of the neurones that descend from and ascend to the cerebral cortex. However, buried deep within the white matter of the cerebrum are nuclei of grey matter that form structures collectively known as the basal ganglia and the limbic system.

- The basal ganglia (BG) consists of three main nuclei, the caudate nucleus, the putamen and the globus pallidus (Figure B2.1). The BG is part of the extrapyramidal system and plays an essential role in voluntary motor responses and in the fine-tuning of motor movements. Degeneration of a pathway from the substantia nigra in the midbrain (Section 1.2.1) to the BG results in Parkinson’s disease, which is characterized by tremor, rigidity and slowness of movement. This topic is discussed in more detail in Chapter 2. The BG also plays an important role in conjunction with the premotor and supplementary premotor areas of the cerebral cortex (Figure 5.1A) in the planning of motor activity. Abnormalities in the circuits from the cortex to the BG may result in the hyperactivity that is characteristic of attention deficit hyperactivity disorder (ADHD) (Chapter 5).

- The limbic system plays an important role in the control of emotional (Chapters 6 and 8) and motivated (Chapter 11) behaviours. It comprises a circuit of structures that circles the thalamus and includes the cingulate cortex, the hippocampus, the amygdala, the fornix and septum (Figure 5.1B). The amygdala is an almond-shaped structure located in the anterior temporal lobe in front of the hippocampus; it is involved in the physiology of fear, apprehension, anxiety and aggression (Chapter 6). The hippocampus (which means ‘seahorse’ because it resembled this creature to early neuroanatomists) is involved with learning and memory (Chapter 3). The fornix is an important white fibre tract connecting different parts of the limbic system and circles from the hippocampus around the thalamus to the septum (located at the tip of the anterior cingulate cortex and connected to the fornix with the corpus callosum) and the mammillary bodies (located on the inferior (bottom) surface of the hypothalamus near the pituitary gland and is involved in relaying information between the fornix and thalamus). The cingulate cortex is part of the cerebral cortex and, in association with the prefrontal cortex, plays a major role in the regulation of selective attention and other forms of behaviour (Chapter 5).

- The cerebral cortex (commonly referred to as the cortex) is the outermost covering of the brain and is the largest part of the brain in humans. The cortex has six layers. Layer I, nearest the surface of the brain, has relatively few cell bodies and consists mainly of axons and dendrites. Layer II and layer IV
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consist mainly of stellate cells (which are cortical interneurones with star-shaped cell bodies and short axons). Stellate cells are also found in layers I, III, V and VI. Pyramidal cells (which are large cortical neurones with a pyramid-shaped cell body, long axons and apical dendrites) are found mainly in layer V but also in layers II, III and VI. The stellate cells receive information from subcortical and cortical areas; for example, the stellate cells in layer IV receive sensory information from the thalamus. On the other hand, the pyramidal cells mainly relay information from the cerebral cortex to subcortical regions, but also relay information between cortical regions largely via their apical dendrites. In fact, each stellate and pyramidal cell connect to many thousands of other cells in the cortex, thus allowing a huge amount of information to be processed. As skull size is limited, the cerebral cortex in humans is deeply convoluted (consisting of ‘furrows’ and ‘ridges’ or, in layman’s terms, ‘valleys and hills’), so that a greater area of tissue may be contained within the skull without a significant increase in cortical volume.

Not all animals have convoluted cortices. Rats and mice have smooth cerebral cortices, while dogs, cats and monkeys have convoluted ones. It appears that the degree of convolution may depend on body size, at least in mammalian species, and not necessarily on intellectual capacity. The furrows are referred to as fissures, if they are large, and sulci (or sulcus – singular), if they are small. The ridges are referred to as gyri (or gyrus – singular). The fissures and gyri on the surface of the cerebral cortex are used by neuroanatomists to describe different regions of the structure.

The cerebral cortex consists of four lobes (Figure 1.1 and Figure 5.1A in Chapter 5): the frontal lobe (also referred to as the frontal cortex), the parietal lobe (also referred to as the parietal cortex), the occipital lobe (also referred to as the occipital cortex) and the temporal lobe (also referred to as the temporal cortex). The anterior portion of the frontal lobe (known as the prefrontal cortex) has areas that are responsible for planning, judgements, the capacities to multitask, analyse and evaluate complex problems, stay focused on a particular task despite external distractions, suppress urges governed by emotions, inhibit inappropriate behaviours and delay gratification for needs, such as sex, money, influence or food, by balancing future goals in relation to short-term and long-term rewards (Chapter 5). The posterior portion of the frontal lobe has the areas involved in the planning (premotor cortex and supplementary motor cortex) and execution of motor activity (motor cortex). The control of motor activity is discussed in Chapter 2. The parietal lobe has areas where somatosensory information (such as touch, pressure, pain, heat and cold) is consciously experienced. The occipital lobe has areas that are concerned with vision. The temporal lobe is involved in auditory and olfactory functions.

Each of the senses – visual, auditory, olfactory, somatosensory, gustatory – are processed in selective regions of the cortex. The way the cerebral cortex processes and interprets sensory information involves three important stages. (i) There are primary cortical areas where sensory information is received. For example, separate sets of neurones in the primary visual cortex (which is located in the occipital lobe) will fire in response to different shapes of lines (straight line, curved lines, horizontal lines, vertical lines and so forth). So, if a person is looking at a face, different sets of neurones in the primary visual cortex will respond to the different shapes of lines that make up the face. (ii) Adjacent to the primary cortical areas are association areas that are responsible for connecting the various bits of information together to make sense of them. For example, the visual associative cortex will put together the various bits of information (different shapes of lines) and interpret them as a face. (iii) There are integrative areas in the cerebral cortex that integrate the information from the association areas with other information, so that it becomes meaningful. For example, the visual integrative area will provide information that the face is female, is someone that the person recognizes and links a name to the face. Impairments in the visual integrative area may result in a person, for example, being able to be able to recognize a face but not being able to put a name to the face.

There are areas in the cerebral cortex that are dedicated to speech and language. In the second half of the nineteenth century, Pierre Broca discovered an area (referred to as Broca’s area) located in the left frontal cortex that is a premotor area for speech. Its output is to the face and tongue regions of the motor cortex. In the late nineteenth century, Karl Wernicke described a sensory area in the temporal lobe
in the left hemisphere (referred to as Wernicke’s area) that was responsible for understanding language. Wernicke’s area is connected to Broca’s area by bundles of fibres. People with damage to Broca’s area can understand speech but are unable to form coherent speech (Broca’s aphasias). On the other hand, people with damage to Wernicke’s area have trouble comprehending speech but can produce fluent speech that is a meaningless jumble of words that lacks any meaning (Wernicke’s aphasia).

The cerebral cortex is also the brain division where learning occurs and memory is stored. As mentioned above, the hippocampus, in association with the cortex, is also involved in the physiological control of learning and memory. The role of the hippocampus and cortex in learning and memory is discussed in Chapter 3.

It is important to note that the right hemisphere controls functions on the left side of the body and the left hemisphere controls functions on the right side of the body. For example, the movement in the right hand is under the control of the left motor cortex and vice versa, and the visual pathway from the right eye crosses over to the left visual cortex and vice versa. In addition, brain functions are also divided between the two hemispheres. Thus, as mentioned above, the speech and language areas are located in the left hemisphere. Damage to one hemisphere may produce a condition known as unilateral neglect, where the patient displays unusual behaviour, such as only shaving on one side of the face or eating from one side of the plate and ignoring food on the other side.

1.2.5 The Cerebral Ventricles and Cerebrospinal Fluid

Within the brain there are four fluid-filled spaces called ventricles. The ventricles contain cerebrospinal fluid (CSF) that is similar to blood plasma but without the plasma proteins. One ventricle is located under the right hemisphere and another under the left hemisphere of the cerebrum. They are known as the lateral ventricles. The CSF from both lateral ventricles drains into the third ventricle via the interventricular foramen (also known as the foramen of Monro). The CSF seeps into the fourth ventricle via the cerebral aqueduct (also known as the aqueduct of Sylvius). Some of the CSF drains from the fourth ventricle into the cisterna magna (which is a space behind the medulla that is continuous with the subarachnoid space that surrounds the brain and cord). The CSF circulates in the subarachnoid space and then is absorbed into venous blood.

CSF circulates in the subarachnoid space around the brain and spinal cord and fills the spaces within the brain and the central canal of the spinal cord. CSF is formed by the separation of the plasma-like fluid from blood by a network of blood capillaries known as the choroid plexuses. CSF is made in the lateral ventricles and the roof of the third ventricles. The main functions of CSF are to (i) keep the surface of the brain and spinal cord moist, (ii) provide a protective cushion against injury to the brain, (iii) afford a medium for providing oxygen and nutrients to brain tissue, and (iv) provide a means of ridding the brain of waste products.

1.3 Important Neurotransmitters

Some of the important neurotransmitters that are involved in brain function and dysfunction are shown in Table 1.1. Their functional roles are discussed in the different chapters of the book. The synthesis, release, action and termination of action for many of these neurotransmitters are also discussed. In this chapter, the actions of the two principal amino acid neurotransmitters in the CNS are discussed, namely γ-aminobutyric acid (GABA) and glutamate.

1.3.1 GABA and GABA Receptors

GABA (γ-aminobutyric acid) is an amino acid and is the main inhibitory neurotransmitter in the brain. It plays a key role in reducing neuronal excitability throughout the CNS. It is found in about 60% of brain
### Table 1.1 Some important neurotransmitters in the CNS.

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptors</th>
<th>Receptor Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine (ACh)</td>
<td>Two main ACh receptors: Muscarinic (m) and nicotine (n) ACh receptors.</td>
<td>Both ionotropic and metabotropic.</td>
</tr>
<tr>
<td></td>
<td>(There are various subtypes of the mACh and nACh receptors.) The mACh</td>
<td>[Ionotropic receptors open ion channels when activated;</td>
</tr>
<tr>
<td></td>
<td>receptor is a metabotropic receptor and the nACh receptor is a</td>
<td>metabotropic receptors are linked to G-proteins and 2nd</td>
</tr>
<tr>
<td></td>
<td>ligand-gated ionotropic receptor.</td>
<td>messengers.]</td>
</tr>
<tr>
<td>Noradrenaline (NA)</td>
<td>Alpha adrenoceptors and beta adrenoceptors. NA receptors (various</td>
<td>Metabotropic.</td>
</tr>
<tr>
<td></td>
<td>subtypes).</td>
<td></td>
</tr>
<tr>
<td>5-Hydroxytryptamine</td>
<td>Seven 5-HT receptors [5-HT₃–5-HT₇ receptors] with each of the 5-HT</td>
<td>Metabotropic, with the exception of 5-HT₁ receptors, which</td>
</tr>
<tr>
<td>(5-HT)</td>
<td>receptors having a number of subtypes, e.g. 5HT₁A, 5-HT₁B,</td>
<td>are ionotropic receptors.</td>
</tr>
<tr>
<td></td>
<td>5-HT₁D, and 5-HT₁E.</td>
<td></td>
</tr>
<tr>
<td>Dopamine (DA)</td>
<td>Five DA receptors [D₁–D₅ receptors].</td>
<td>Metabotropic.</td>
</tr>
<tr>
<td></td>
<td>The DA D₁ and D₅ receptors belong to the family of D₁-like receptors;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>the D₃, D₄ and D₅ receptors belong to the family of D₂-like receptors.</td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>Four histamine receptors [H₁–H₄ receptors].</td>
<td>Metabotropic.</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Three adenosine receptors [A₁, A₂ and A₃ receptors]. Some have multiple</td>
<td>Metabotropic.</td>
</tr>
<tr>
<td></td>
<td>subtypes.</td>
<td></td>
</tr>
<tr>
<td>Neuropeptides</td>
<td>Various neuropeptides act as neurotransmitters and neuromodulators with</td>
<td>Metabotropic.</td>
</tr>
<tr>
<td></td>
<td>the CNS, e.g. orexin, dynorphin, galanin, cholecystokinin and angiotensin.</td>
<td></td>
</tr>
<tr>
<td>Glutamate (Glu)</td>
<td>There are two classes of glutamate receptor: the ionotropic receptors</td>
<td>Both ionotropic and metabotropic.</td>
</tr>
<tr>
<td></td>
<td>and the metabotropic receptors. The glutamate ionotropic receptors are</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(i) NMDA receptor, (ii) AMPA receptor and (iii) Kainate receptor.</td>
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</tr>
<tr>
<td></td>
<td>There are eight subtypes of the metabotropic receptors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[mGlu1–mGlu8].</td>
<td></td>
</tr>
<tr>
<td>Gamma-aminobutyric</td>
<td>Two main types of GABA receptors: GABAₐ receptors (ionotropic) and</td>
<td>Both ionotropic and metabotropic.</td>
</tr>
<tr>
<td>acid (GABA)</td>
<td>GABA₉ receptors (metabotropic). There is also a third type, GABA₉</td>
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</tr>
<tr>
<td></td>
<td>receptors (ionotropic). However, some investigators classify it as a</td>
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<td></td>
<td>subtype of the GABAₐ receptor.</td>
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</table>
The GABA<sub>A</sub> receptor complex comprises five subunits arranged around a central chloride ion channel. The GABA<sub>A</sub> receptor binding site is located between the α and β subunits. Benzodiazepines do not bind to the same receptor site on the GABA<sub>A</sub> receptor complex as GABA but bind to distinct benzodiazepine binding sites situated at the interface between the α and γ subunits.

Figure 1.2 The GABA<sub>A</sub> receptor complex comprises five subunits arranged around a central chloride ion channel. The GABA<sub>A</sub> receptor binding site is located between the α and β subunits. Benzodiazepines do not bind to the same receptor site on the GABA<sub>A</sub> receptor complex as GABA but bind to distinct benzodiazepine binding sites situated at the interface between the α and γ subunits.
and the effects of GABA or baclofen on GABA<sub>B</sub> receptors may be blocked with the GABA<sub>B</sub> receptors antagonists saclofen or CGP35348.

1.3.2 Glutamate and Glutamate Receptors

Glutamate is an amino acid that is widely distributed in the CNS. Until fairly recently, it was assumed that the presence of vast amounts of glutamate in the brain was due to the fact that it plays an important role in central metabolic functions and is also an amino acid that is a component of many brain proteins. However, about four decades ago, it was demonstrated that glutamate also acts as a central neurotransmitter, and it is now recognized to be the major mediator of excitatory neurotransmission in the mammalian CNS. Glutamate receptors are found in over 90% of neurons in the brain and glutamate acts on its various receptor subtypes to control most aspects of normal brain function, including synaptic plasticity, cognition, memory, learning, brain development, motor function, nociception and various other sensory functions. While glutamate is an important neurotransmitter in regulating many physiological functions, excess release of glutamate is toxic to both neurons and glia, causing neuronal atrophy and cellular death. Glutamatergic dysfunction may result in a number of neurologic and psychiatric conditions, including schizophrenia (Chapter 10), Parkinson’s disease (Chapter 2), Alzheimer’s disease (Chapter 3), affective disorders (Chapter 6 and 7), cerebral ischaemia, multiple sclerosis, pain, stroke, epilepsy (Chapter 4) and addictive behaviours (Chapter 11).

Like GABA, glutamate also acts on two main groups of receptors: ionotropic and metabotropic receptors (Table 1.1). The ligand-gated ionotropic glutamate receptors are associated with an ion channel pore that opens when glutamate binds to the receptor. There are three ionotropic glutamate receptor subtypes, known as the NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and kainate receptors. They have been named according to chemical substances that were shown to be potent and selective agonists for these receptor subtypes. On the one hand, the metabotropic glutamate receptors (mGluRs) are linked to G-proteins and may indirectly activate ion channels on the neuronal membrane through a signalling cascade. There are eight mGluRs, divided into three groups: Group 1 (mGluR<sub>1</sub> and mGluR<sub>5</sub>) increases calcium ions levels in the cytoplasm and increases potassium ions efflux from cells; Group 2 (mGluR<sub>2</sub> and mGluR<sub>3</sub>) inhibit adenylate cyclase and inhibit cAMP production; Group 3 (mGluR<sub>4</sub>, mGluR<sub>6</sub>, mGluR<sub>7</sub> and mGluR<sub>8</sub>) activate calcium ion channels to allow more calcium ions to enter the cell.

The ligand-gated ionotropic glutamate receptors are normally postsynaptic receptors that work together to modulate the excitatory effects of glutamate. The AMPA and kainate receptors act to open sodium ion channels on the cell membrane to mediate rapid excitatory neurotransmission. On the other hand, the effects of glutamate on neurotransmission mediated by NMDA receptor are slower. This is because the receptor is both ligand gated and voltage gated. Figure 1.3 shows an illustration of the NMDA receptor in the resting state. There is a glutamate binding site, a glycine allosteric site and an ion channel. For glutamate to activate the opening of the channel to allow the entry of calcium and sodium ions, the following must occur. Firstly, glutamate must bind to the glutamate receptor binding site. However, glutamate cannot open the ion channel in the absence of glycine or D-serine. It has been found that there is an absolute necessity for glycine or D-serine to bind to the glycine allosteric site to activate the opening of the ion channel. However, when the channel opens, magnesium ions rapidly enter and block the channel (Figure 1.4), thus inhibiting further influx of calcium and sodium ions. It has been found that magnesium ions are expelled from the channel when the membrane potential is above ~30 mV. Therefore, depolarization has to occur to allow the membrane potential to increase so that the magnesium ions can be expelled. The actions of glutamate on its other receptors causes depolarization of the membrane, so the NMDA channel can open and allow the influx of calcium ions. Thus, three events have to happen to activate the NMDA receptor: (i) glutamate must act on its binding site; (ii) glycine or D-serine must act on the glycine allosteric site; and (iii) glutamate, acting thought its other receptors, must depolarize the membrane to expel magnesium ions from the channel. Drugs that block
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Figure 1.3 The glutamate NMDA receptor in the resting state.

Figure 1.4 The glutamate NMDA receptor when it is activated by glutamate. The ion channel opens when (i) glutamate acts on its receptor site and (ii) glycine binds to its allosteric site. Note that magnesium ions (Mg\(^{2+}\)) block the channel at membrane potentials below –30 mV. Glutamate, acting through its other receptor subtypes, must depolarize the membrane to expel magnesium ions from the channel. There is also a phencyclidine binding site within the ion channel on which drugs, such as phencyclidine and ketamine, can act to block the ion channel.

The NMDA receptor ion channels and inhibit NMDA receptor function are phencyclidine (Chapter 10), ketamine (Chapters 6, 7 and 10) and memantine (Chapter 3).

1.4 Central Nervous System Stimulant and Depressant Drugs

It is well known that when you are tired and at a low level of arousal (Chapter 9) your performance in a physical or mental task will be poor. When you are awake and alert, then your performance in such tasks will be almost optimal. However, if you are very stressed about something, then you become overaroused and you will find it difficult to perform adequately in both mental and physical tasks. In 1908, two American psychologists, Robert Yerkes and John Dodson, demonstrated that performance in a given task is related to level of arousal by an inverted U-shape curve (Figure 1.5). This relationship between performance and arousal is known as the Yerkes–Dodson law. They demonstrated that performance increases with arousal until it reaches some optimal level. Thereafter, as arousal increases further, performance...
begins to decreases (Figure 1.5). It has been found that different tasks need different levels of arousal for optimal performance.

Stimulant drugs, such as amphetamine (Section 1.5.1.1), increase level of arousal in a dose-dependent manner, whereas depressant drugs, such as the benzodiazepines (Section 1.6.1), reduce level of arousal in a dose-dependent manner. However, the effects of stimulant or depressant drugs on performance in a given task will depend on the baseline level of arousal of the subject when the drug was administered and on the dose of the drug (Figure 1.5). Thus, for example, imagine a subject (we shall refer to him as Graham) who is very tired and is, therefore, at a very low level of arousal (arousal level: A in Figure 1.5). If Graham is given some simple mathematical problem to solve, his performance in this task (performance level: 1) will not be very good as he is tired and, therefore, finds it difficult to focus his attention on the problem. He is then given a low dose of a stimulant drug. The effects of the drug will increase his level of arousal to B in Figure 1.5 and his performance in the task will improve considerably (performance level: 2). If, on the other hand, Graham is given a higher dose of the stimulant drug when he was feeling tired, his level of arousal will increase to C in Figure 1.5 and his performance in the task will become optimal (performance level: 3).

Now imagine that Graham is at the level of arousal (arousal level: C) for optimal performance (performance level: 3). If he is given a small dose of the stimulant drug, his level of arousal will increase to D in Figure 1.5 and his performance in the task will decrease (performance level: 2). If he were given a higher dose of the stimulant drug, then his arousal level will increase to E in Figure 1.5 (in other words, he will become overaroused) and his performance (performance level: 1) will be no better than when he was tired. Thus, a stimulant drug can both increase or decrease performance in a given task depending on the baseline level of arousal of the subject and the dose of drug administered.

As depressant drugs decrease arousal, if Graham is given a low dose of a depressant drug when he is performing optimally on the task (arousal level: C; performance level: 3), his level of arousal will decrease to point B in Figure 1.5 and his performance on the task will also be reduced (performance level: 2). However, if Graham is very stressed or anxious or excited (Chapters 6 and 8), his baseline level of arousal will be high (arousal level: E). In this case, a low or high dose of a depressant drug will decrease his level of arousal to D and C, respectively, and his performance on the task will improve. Thus, a depressant drug can also increase or decrease performance in a given task depending on the baseline level of arousal of the subject and the dose of drug administered.
It is noteworthy that both stimulant and depressant drugs might improve or diminish performance on a given task depending on the baseline level of arousal of the subject. Most students know that when they are studying for an examination or trying to finish a piece of work and are feeling fairly exhausted, they might drink a cup of coffee (Section 1.5.1.3) to keep them awake. However, the danger is that if they drink too much strong coffee they may become slightly overaroused and then find it difficult to concentrate on their work. Conversely, if a person is feeling slightly stressed or anxious and finding it difficult to concentrate on the task at hand, then he or she may go and do something else (for example, play a game on the computer) to relax, so that their level of stress (arousal) is reduced. Some people may indulge in more pharmacological methods, by drinking an alcoholic beverage (Chapter 11) to ‘steady their nerves’ or ‘calm them down’. At a clinical level, individuals who are very anxious or stressed may be prescribed depressant drugs, such as the benzodiazepines (Section 1.6.1), by their doctor for a short period to reduce their levels of arousal, so that they can cope more easily with daily life.

1.5 Central Nervous System (CNS) Stimulant Drugs

CNS stimulant drugs fall into two main categories: (i) psychomotor stimulants, such as amphetamine, cocaine and caffeine, which cause increased alertness and changes in mood; and (ii) analeptic stimulants, such as bicuculline, picrotoxin and strychnine, which may increase alertness but tend to produce convulsions at higher doses.

Discussed briefly here are the main pharmacological properties, clinical uses and mechanism of action of three psychomotor stimulants – amphetamine, cocaine and caffeine – and three analeptic drugs – bicuculline, picrotoxin and strychnine – as they illustrate the fundamental principles of CNS stimulants. Some of these drugs are referred to in future chapters.

1.5.1 Psychomotor Stimulants

1.5.1.1 Amphetamine

Amphetamine is a potent CNS psychoactive stimulant that was first synthesized in 1887 and exists in two isomeric forms, dextroamphetamine or dexamphetamine (D-amphetamine) and laevoamphetamine (L-amphetamine). The racemic mixture, that is (DL)-amphetamine, is sometimes referred to as ‘benzedrine’. The D-isomer is normally regarded as the active isomer of the drug, but the L-isomer retains some of the pharmacological activity of the drug. The term ‘amphetamine’ is used here to refer to D-amphetamine or (DL)-amphetamine. More potent analogues of amphetamine, such as methamphetamine, have a similar pharmacological profile to D-amphetamine. Amphetamine and methamphetamine (known colloquially as ‘speed and ice’, respectively) have high abuse potential (Chapter 11); this has limited the therapeutic uses of these drugs.

The main action of amphetamine is to act at the presynaptic terminal of noradrenergic and dopaminergic neurons to potentiate the levels of these monoamines in the synaptic cleft. The mechanisms involved are complex, as illustrated for dopamine (DA) in Figure 1.6. Amphetamine increases the levels of norepinephrine (NA) in the synaptic cleft in a similar manner (NA can be substituted for DA in Figure 1.6).

The basic mechanisms, with reference to Figure 1.6, are:

- Amphetamine competes with DA and NA for reuptake via dopamine transporters (DAT) or norepinephrine transporters (NAT) into the cytoplasm of the presynaptic terminal (1). This process is referred to as Uptake 1 and is a major physiological mechanism to terminate the action of these monoamines after they are released (Chapters 2 and 6). This results in more DA or NA in the synaptic cleft.
Once in the cytoplasm of the presynaptic nerve terminal, amphetamine can enter the monoamine vesicles by ‘hitching a ride’ on the vesicular monoamine transporters (VMAT) (2) and displacing DA and NA from their vesicular storage sites into the cytoplasm within the presynaptic nerve terminals (3).

Normally, free DA and NA in the cytoplasm is metabolized by monoamine oxidase (MAO). Amphetamine is a weak inhibitor of MAO (4), thus preventing the catabolic effects of MAO and causing a rise in cytoplasmic levels of DA and NA.

Amphetamine then facilitates the release of cytoplasmic presynaptic monoamines by reversing DA and NA transporters (5). The monoamine transporters normally operate in one direction by transporting released DA and NA from the synaptic cleft into the cytoplasm where they can be repackaged in vesicles. However, amphetamine can modify the mode of operation of the transporters, so that they can also transport free monoamines from the cytoplasm of the presynaptic nerve terminal into the synaptic cleft.

Amphetamine can also facilitate the opening of channels on the presynaptic nerve terminal membrane, so DA or NA can diffuse from the cytoplasm of the nerve terminal into the synaptic cleft (6).

The increased concentrations of DA or NA in the synaptic cleft will result in the monoamines having greater and more sustained effects on their respective postsynaptic receptors. In addition, high doses of amphetamine display agonist activity at receptors for DA and 5-hydroxytryptamine (5-HT) and antagonist activity at alpha-adrenoceptors. Note that the D-isomer of amphetamine has high affinity for both DA and NA transporters. By contrast, the L-isomer has low affinity for DA transporters but a slightly higher affinity for NA transporters. So, (DL)-amphetamine will enhance synaptic concentrations of NA in the CNS to a greater extent than synaptic concentrations of DA.

Amphetamine is used clinically in the treatment of narcolepsy (Chapter 9), attention deficit hyperactivity disorder (ADHD) (Chapter 5) and to overcome excessive sedation caused by overdose of certain CNS depressants, such as the barbiturates. Amphetamine has been used successfully in the treatment of obesity and in nasal decongestion medication (because of its action as a vasoconstrictor). However, it is not recommended for such clinical use these days because of its abuse potential.
Amphetamine is metabolized in the liver by the hepatic P450 enzymes into a variety of metabolic products, including 4-hydroxyamphetamine, 4-hydroxynorephedrine, norephedrine, benzoic acid and 4-hydroxyphenylacetone. 4-hydroxyamphetamine, 4-hydroxynorephedrine and norephedrine are active sympathomimetic metabolites. The half-life of D-amphetamine is between 9 and 11 hours and that of L-amphetamine between 11 and 14 hours. About 30–40% of the drug is excreted unchanged by the renal route at normal pH. The metabolites are also excreted in the urine.

As discussed above, the effects of amphetamine will depend to a large extent on the dose of drug administered and the prevailing level of arousal of the individual at the time of administration. It has been found, in laboratory settings, that doses of amphetamine in the therapeutic range (that is 5–40 mg) will increase alertness, motor activity, mood, self-confidence and libido, and decrease appetite for food. These doses will also decrease sleep time, especially the time spent in rapid eye movement (REM) sleep (Chapters 2 and 9). The performance of simple tasks, such as basic arithmetic, may be improved, as well may physical activity in sports. These effects are probably more apparent in individuals who are fatigued or tired because of a lack of sleep (remember the inverted U-shaped curve relating level of arousal to performance). Low doses of amphetamine also produce euphoria (elevation of mood), which may be responsible for its drug abuse potential (Chapter 11).

Acute ingestion of high doses of amphetamine can produce a psychotic-like state, which can be accompanied by hallucinations and is very much like paranoid schizophrenia (Chapter 10). In the early 1970s, it was found that a number of individuals who had been diagnosed as suffering from paranoid schizophrenia had, in fact, taken an overdose of amphetamine. It was later realized that they were not suffering from schizophrenia when they recovered from their amphetamine overdose. These observations were crucial in identifying increased central levels of dopamine as a possible cause of schizophrenia (Chapter 10). It should be noted that, at therapeutic doses, the occurrence of amphetamine-induced psychosis is very rare.

Acute ingestion of high doses of amphetamine may, additionally, cause some of the following central and peripheral effects: nausea, vomiting, agitation, anxiety, insomnia, confusion, delirium, hypertension and cardiac arrhythmias. In some cases death may result as a consequence of cerebral haemorrhage or cardiovascular and respiratory collapse. Chronic use (or abuse) of amphetamine can lead to both physical and psychological dependence (Chapter 11) and cessation of use will produce ‘withdrawal symptoms’ in patients, characterized by dysphoria, fatigue, anxiety, depression, hyperphagia and hypersomnia with rebound REM sleep (Chapter 9).

Studies carried out in man and in animals have indicated that the increased alertness and ability to pay attention to tasks produced by amphetamine is due to increased synaptic concentrations of NA and DA in the cortex, particularly the prefrontal cortex (Chapter 5). The euphoric produced by ingestion of amphetamine is believed to be due to increased DA in the limbic system, particularly an area known as the nucleus accumbens (Chapter 11). Interestingly, high doses of amphetamine that result in excessive release of DA in the nucleus accumbens area of the brain have been shown to cause the psychotic effects of the drug (Chapter 10). Thus, while moderate levels of DA in the nucleus accumbens enhance mood, high levels of the neurotransmitter will induce a psychotic state.

### 1.5.1.2 Cocaine

Cocaine is an alkaloid present in the leaves of the coca plant, *Erythroxylon coca*, which was originally cultivated in South America. The pure alkaloid was isolated and purified by chemists in the late 1850s. Cocaine was found to be a potent local anaesthetic and was widely used for this purpose. Its use started to wane in the first half of the twentieth century with the development and introduction of synthetic local anaesthetics, such as procaine. Cocaine also has CNS stimulant properties that are similar to those of amphetamine (Section 1.5.1.1). In fact, the leaves of *E. coca* have been chewed by the South American Indians for many centuries to reduce fatigue and increase stamina, and for its ability to induce euphoria and sense of well-being. Cocaine has become a highly abused substance because of its marked hedonic effects (Chapter 11). The illicit use of cocaine has escalated in the past twenty years with the introduction of freebase cocaine (‘crack’).
Cocaine, extracted from the leaves of *E. coca*, is converted into water-soluble cocaine hydrochloride. This form of cocaine is well absorbed from mucous membranes and can also be injected intravenously. A common method that recreational drug users employ is to ‘snort’ lines of cocaine because it is absorbed from mucous membranes in the nostrils. However, cocaine, like amphetamine, is a potent vasoconstrictor; it is estimated that only about 30% of the snorted drug is absorbed through the nasal mucosa into the bloodstream, reaching peak plasma levels about 30–60 minutes later. This is because the vasoconstrictor action of the drug limits its own absorption. Cocaine hydrochloride is destroyed by heat and, therefore, it cannot be smoked. However, freebase cocaine (‘crack’) is converted into a stable vapour of cocaine when it is heated and can be inhaled into the lungs when smoked. Incidentally, the name ‘crack’ for freebase cocaine came from the crackling sound that cocaine crystals make when they burn. The onset of the effects of cocaine taken by inhalation is rapid (within seconds) and this form of delivery to the brain increases the chances of addiction to the drug (Chapter 11). The plasma half-life of cocaine is approximately one hour.

Cocaine is mainly metabolized in the liver by the P450 hepatic enzymes but is also metabolized to a small extent by enzymes in the plasma. The main metabolite is benzoylecgonine. There are other minor metabolites, such as ecgonine methyl ester (EME) and norcocaine. The metabolites are mainly excreted in the renal route. Interestingly, benzoylecgonine is detected in the urine up to two days after ingestion of cocaine in occasional users and many companies do spot checks on their employees on Monday mornings to see if they have been taking cocaine over the weekend. In chronic users of cocaine, benzoylecgonine may even be detected in the urine 10–14 days later, suggesting that the metabolite is accumulated in body tissue and is slowly excreted.

The actions of cocaine are very similar to the effects of amphetamine. It has been observed that, under laboratory conditions, addicts cannot initially distinguish between the effects of cocaine or dextroamphetamine administered intravenously at a dose of 10 mg. However, the effects of intravenous administration of cocaine only last for about 10–20 minutes, compared to the much longer effects (hours) of amphetamine, so, eventually, the subjects are able to deduce what drug they were given.

The effects of low acute doses of cocaine in man will initially produce a feeling of euphoria and well-being. The person may become more talkative and also displays other signs of increased arousal, such as restlessness, excitement and insomnia (Chapter 9). Fatigue is diminished, which can lead to an increase in stamina and the capacity for muscular work. Thus, for example, the South American Indians who mine copper in the mountains of Bolivia continuously chew coca leaves to enable them to carry out the hard physical work involved. As the dose of cocaine increases there may be a sudden switch from a feeling of euphoria to dysphoria. The subject may display signs of anxiety and agitation. Further increases in dose may cause vomiting, from stimulation of the emetic centre in the medulla. There is also a loss of coordination and the occurrence of tremors. Additionally, cocaine has direct and indirect effects on the sympathetic division of the autonomic nervous system to cause sweating, tachycardia and hypertension. Acute intoxication of high doses (>150 mg) results in the occurrence of a toxic psychosis, fever, convulsions and general depression of the CNS. Death may result from cardiovascular or respiratory collapse or from convulsions. People who have consumed high doses of cocaine acutely may be treated pharmacologically with the antipsychotic drug chlorpromazine (Chapter 10), which will be useful in treating the psychotic effects, as well as the hypertension and fever. The convulsions are usually treated with benzodiazepines, such as diazepam (Section 1.6.1; Chapter 4).

Addicts who consume large doses of cocaine, usually by intravenous injection or smoking ‘crack’, on a repeated basis (chronic use) will become dependent on the drug and display withdrawal symptoms if deprived (Chapter 11). Many suffer from a psychosis, which may be clinically similar to paranoid schizophrenia (see also the effects of amphetamine described previously). The patients sometimes display delusions of parasitosis (a feeling of something crawling under the skin) and may constantly scratch the skin on various areas of the body. Pregnant women who are cocaine addicts put their babies at risk of suffering from withdrawal symptoms when they are born. Cocaine crosses the placenta from the mother’s circulation and may affect the foetus. In fact, many hundreds of babies are born each year that have...
become dependent on cocaine because of their mothers’ addiction. Studies have indicated that this might stunt the normal development of the brain of the infants and may result in psychiatric disorders in later life (Chapter 6).

There are very few clinical uses for cocaine today because of its abuse potential. It is used as a local anaesthetic for certain types of eye (for example, lacrimal duct), oral and nasal surgery. As it also is a vasoconstrictor, it is occasionally used to stop nose bleeds and bleeding from mouth ulcers. A concoction called the ‘Brompton mixture’, which contains heroin, cocaine, chlorpromazine and alcohol, was given to terminal ill patients, especially those suffering from cancer, to treat pain (heroin), prevent nausea (chlorpromazine) and to induce a state of wakefulness and euphoria (cocaine). It was widely used in the last century until the mid-1980s but its use in the twenty-first century is ‘almost’ obsolete.

Cocaine mediates its pharmacological effects by increasing the levels of NA and DA in the CNS and the periphery. It accomplishes this by inhibiting the presynaptic transporters for DA (DAT) and NA (NAT), thus preventing the reuptake of the monoamines into the cytoplasm of the presynaptic terminal. This results in greater concentrations of DA and NA in monoaminergic synapses and an enhancement of their effects on their postsynaptic receptors. The process is illustrated for DA in Figure 1.7 (as cocaine increases the levels of NA in the synaptic cleft in a similar manner, NA can be substituted for DA in Figure 1.7). Cocaine acts in similar areas of the CNS as to exert it pharmacological effects as described above for amphetamine.

### 1.5.1.3 Caffeine

Caffeine is a methylxanthine. The three most important alkaloids derived from xanthines are caffeine, theophylline and theobromine. Caffeine is the most commonly consumed psychoactive drug worldwide. It is consumed by most people on an almost daily basis in the form of beverages and certain foods, including coffee, tea, cocoa, fizzy (carbonated) drinks and chocolate. A cup of percolated coffee contains about 100 mg of caffeine, while a cup of tea has between 20 and 80 mg, and a bar of chocolate has between 10 and 30 mg (if it is made from cacao). Caffeine is found in various plants and their fruits, such as the coffee berry, the guarana berry, the yaupon holly and the tea bush, where it acts as a natural pesticide.

![Figure 1.7](image_url)  
*Figure 1.7  Mechanism of action of cocaine at a dopaminergic nerve terminal. Cocaine increases DA concentrations in the synaptic cleft by blocking the dopamine transporters and inhibiting the uptake 1 process. (Abbreviations: DA, dopamine; DAT, dopamine transporter; MAO, monoamine oxidase.)*
Caffeine is normally ingested by the oral route and is slowly absorbed from the gut. Its effects are observed within 30 minutes after consumption, but it may take approximately two hours before peak plasma concentrations are reached. The half-life of caffeine is between 4.5 and 6 hours. It is metabolized in the liver by the hepatic P450 enzymes into the active metabolites paraxanthine (84%), theobromine (12%) and theophylline (4%), which are excreted in the urine.

Caffeine is a psychoactive stimulant that reduces drowsiness and fatigue. Low doses improve attention and concentration, especially if the person is tired. There may also be a reduction in reaction time after ingestion of caffeine, depending on the baseline level of arousal of the person (the Yerkes–Dobson law, Section 1.4). Caffeine will also increase the capacity for muscular work. However, in contrast to other psychoactive stimulants, such as amphetamine and cocaine, caffeine and the other methylxanthines do not produce euphoria, stereotyped behaviours or psychotic like symptoms in large doses. Other pharmacological effects of caffeine include the following:

- It causes vasoconstriction, which is useful in the treatment of migraines.
- It stimulates cardiac muscle and thereby increases the force and rate of contraction of the heart.
- It acts on the kidney to cause diuresis.
- It relaxes smooth muscle, especially the bronchial muscles of the lungs. In fact, the methylxanthine, theophylline, which is also a metabolite of caffeine, is used clinically for the treatment of asthma.

Tolerance and dependence develops in individuals who are regular caffeine consumers; for example, those who drink a few cups of coffee a day will develop a mild dependency on the drug. Withdrawal symptoms include headaches, irritability, fatigue, difficulty with concentration and a craving for caffeine. Consumption of caffeine will relieve these symptoms. Withdrawal symptoms peak about 24–48 hours after cessation of caffeine intake and will last for a few days. Caffeine does cross placenta but there is no evidence to suggest that it constitute a significant toxic hazard to the foetus.

Caffeine produces a number of pharmacological effects on the CNS. The mechanisms involved are complex. For a long time it was believed that the sole mechanism by which caffeine mediated its effects was by virtue of by its ability to inhibit the enzyme phosphodiesterase, which is responsible for the breakdown of the intracellular second messenger cAMP (cyclic adenosine monophosphate) to the inactive 5’AMP. As the effects of a number of G-protein linked neurotransmitters, such as the effects of noradrenaline on \( \beta \)-adrenoceptors, are mediated intracellularly by cAMP, it was believed that the pharmacological effects of caffeine were due to its ability to inhibit the breakdown of cAMP. So, for example, noradrenaline will act on bronchial smooth muscle to produce relation of the muscle and bronchodilation by acting at \( \beta_2 \)-adrenoceptors. At an intracellular level, stimulation of \( \beta_2 \)-adrenoceptors will activate G-proteins, which will, in turn, activate the production of cAMP. cAMP causes a cascade of intracellular processes that results in the relaxation of the bronchial smooth muscle. It is suggested that by inhibiting the phosphodiesterase enzyme, caffeine increases the duration that cAMP remains in an active state, and thus potentiates the effects of NA on bronchial smooth muscle. It has, therefore, been proposed that caffeine enhances the effects of NA, DA and other neurotransmitters in the CNS by inhibiting the breakdown of the phosphodiesterase enzyme and the metabolism of cAMP into the inactive 5’AMP.

However, more recently, scientists have questioned the validity of this mechanism because it has been found that the minimum concentration of caffeine needed to inhibit the phosphodiesterase enzyme \textit{in vitro} is a several fold higher than the peaks levels of caffeine that are detected in blood plasma \textit{in vivo} after consumption of beverages such as percolated coffee. Thus, many investigators have rejected this mechanism as clinically plausible. However, it should be noted that \textit{in vitro} and \textit{in vivo} effective concentrations of drugs do not always match. For example, certain effects of digitalis \textit{in vitro} need about a 100 times greater concentration of the drug than are needed \textit{in vivo}. Therefore, it may be premature to reject or disregard the effects of caffeine on the phosphodiesterase enzyme and intracellular concentrations of cAMP.
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The methylxanthines, such as caffeine, have also been found to be nonspecific antagonists at adenosine receptors. Adenosine, which is a main constituent part of ATP (adenosine triphosphate) and cAMP, is an endogenous purine nucleoside that also acts as a neuromodulator. Adenosine acts on four receptor subtypes, the $\text{A}_1$, $\text{A}_{2A}$, $\text{A}_{2B}$ and $\text{A}_3$ receptors, which are all G-protein linked receptors. Adenosine is an inhibitory neuromodulator and generally decreases the release of a number of neurotransmitters, such as NA and DA, in the CNS. It therefore has depressant effects on the CNS and will produce sedation and sleep (Chapter 9) as levels of the neuromodulator increase. Caffeine is an antagonist at adenosine $\text{A}_1$, $\text{A}_2$ and $\text{A}_3$ receptors. Therefore, antagonising the effects of adenosine at its receptor sites will increase the release of neurotransmitters, such as NA, DA and acetylcholine (ACh), which, in turn, will elicit the stimulant and other pharmacological actions of caffeine.

Syntheses of experimental data suggest that caffeine mediate its pharmacological actions by acting as a non-specific antagonist at adenosine receptors. However, it is likely that it may also synergistically enhance these effects by inhibiting the phosphodiesterase enzyme to increase the intracellular actions of cAMP.

There are a few clinical uses for caffeine. It is used for counteracting the respiratory depression induced by barbiturates, alcohol or opioid drugs. In combination with ergot derivatives, such as ergotamine, caffeine has been used in the treatment of migraine; it is believed that the vasoconstrictor effects of caffeine on the cerebral blood vessels improve the therapeutic response. Caffeine is sometimes used as a mild stimulant to help overcome fatigue (Chapter 9).

1.5.2 Analeptic Drugs

Analeptic drugs are CNS stimulants that are proconvulsant at low doses and convulsant at higher doses. Unlike the psychoactive stimulant drugs, they have very little effect on mental function.

1.5.2.1 Strychnine

Strychnine is an alkaloid found in the seeds of the tree *Strychnos nux-vomica* that grows in India. It has no clinical uses. However, strychnine has been used as a pesticide, mainly for exterminating rats, and can get into the food chain and cause toxic effects in animals and man. In addition, strychnine has been used to adulterate heroin used by drug addicts. The lethal dose of strychnine taken orally is 100 mg in adults and around 15 mg in children but much lower doses can be fatal if injected intravenously.

Strychnine is an antagonist of the inhibitory central neurotransmitter glycine. It is a potent convulsant and mediates its effects by blocking the postsynaptic action of glycine released from the terminals of Renshaw cells on motor neurones in the spinal cord (Figure 1.8). As the main action is on the spinal cord, the convulsions induced by strychnine are different from other convulsant drugs that act on the brain (Section 1.5.2.2). Let us now briefly examine what happens to someone who has been poisoned with strychnine. In the early period following consumption of the drug, there is an increase in reflex excitability and any sensory stimulus may produce violent extensor spasms of body musculature. Eventually, all the voluntary muscles of the body will go into a state of full contraction. This hyperextension of the body musculature results in a characteristic posture known clinically as opisthotonus, in which the back is arched and only the crown of the head and the heels of the feet are touching the ground. As the muscles are hyperextended, the subject will not be able to move his arms, legs and the rest of his body. Also, as the action of strychnine is mainly confined to the spinal cord, the subject remains conscious and fully aware of sensory stimuli but will not be able to respond in any form. Death will eventually results from asphyxia due to impaired respiration. A person that is poisoned with strychnine needs to be artificially ventilated and benzodiazepines, such as diazepam, are used to treat the hyperextension of the body musculature.
Motor Pathway from Brain

Ventral Horn of the Spinal Cord

Renshaw Cell

Glycine Receptors
(Blocked by Strychnine)

Glycine

ACh

Motor Neurone

Recurrent Collateral

ACh

Skeletal Muscle

Figure 1.8  Processed motor information from the motor cortex is transmitted by axons that synapse on motor neurones in the ventral horn of the spinal cord, from where it is sent via motor axons to skeletal muscle to elicit muscle contraction. However, these motor signals need to be processed further at the level of the ventral horn of the spinal cord before they are transmitted to skeletal muscle because they can cause the release of too much ACh at the neuromuscular junction and result in overstimulation of the muscles. Motor information, in direct proportion to incoming motor signals from the brain, is transmitted down the recurrent collateral, resulting in the release of ACh. The ACh stimulates nicotinic ACh (nACh) receptors on the Renshaw cell body of an interneurone that synapses back on the motor neurone and releases glycine. Glycine is an inhibitory neurotransmitter and inhibits the activity of the motor neurone, thus reducing the amount of motor information that is transmitted to skeletal muscle. This ‘self-damping’ system in the ventral horn therefore modulates the motor signals transmitted to skeletal muscle to fine tune muscle contraction and motor movements. Strychnine is an antagonist at glycine receptors in the ventral horn and, therefore, suppresses the self-damping system, which results in the motor problems caused by strychnine poisoning.

1.5.2.2 Picrotoxin and Bicuculline

**Picrotoxin** is a naturally occurring substance that is found in the berries of the plant *Anamirta Cocculus*. The active principle in picrotoxin is picrotoxinin. It is a potent convulsant agent and acts by blocking the chloride ion channels on the GABA<sub>A</sub> receptor (Section 1.3.1; Figure 1.2) in a noncompetitive manner. At low doses, it is proconvulsant, which means that it decreases seizure threshold. Thus, for example, if an experiment animal that has been injected with a low dose of picrotoxin is suddenly startled by a loud noise, it will start convulsing. Higher doses of the drug cause convulsions. Picrotoxin has no clinical uses but can be used in creating animal models of epilepsy (Chapter 4) to test novel drugs for anticonvulsant activity and by experimental scientists investigating the actions of GABA on GABA<sub>A</sub> receptors.

**Bicuculline** is a plant alkaloid that is also a potent convulsant agent. It is a competitive antagonist at GABA binding sites on GABA<sub>A</sub> receptors (Figure 1.2). It therefore acts to inhibit the inhibitory actions of the GABA in the CNS. It is proconvulsant at low doses and convulsant at higher doses. Like picrotoxin,
1.6 Depressant Drugs

1.6.1 Benzodiazepines

In the late 1950s, Leo Sternbach and his colleagues at Hoffman La Roche found that a 4,5-benzo-hept-1,2,6-oxidiazine, which was a benzodiazepine labelled RO5-0690, had properties indicative of sedative and tranquilizing agents in animal experiments. Subsequent clinical testing reaffirmed these properties and, in 1960, RO5-0690, generically named chlordiazepoxide, was marked as a ‘tranquilizing’ agent under the trade name Librium®. The success of chlordiazepoxide as a drug to treat anxiety was immediate. About three years later, Hoffman La Roche introduced diazepam (Valium®) as a more potent benzodiazepine tranquilizer. Since then, a large number of benzodiazepines have been synthesized and marketed for clinical use for the treatment of various disorders. Most of them are dealt with in subsequent chapters and will not be discussed in any detail here. The main clinical uses of the benzodiazepines are for the short-term treatment of anxiety disorders (Chapter 8), for the short-term treatment of sleep disorders, such as insomnia (Chapter 9), as muscle relaxants (Chapter 9), for the treatment of certain forms of epilepsy, particularly a form epilepsy known as status epilepticus (Chapter 4), for the treatment of acute mania (Chapter 7) and as a premedication for general anaesthesia. Benzodiazepines are particularly effective as a premedication for general anaesthesia as they calm the patient before surgery (because of their antianxiety or anxiolytic effects), ensure the patient have a good night’s sleep prior to surgery (because of their sleep-inducing or hypnotic effects) and produce anterograde amnesia during surgery (so that the patient does not remember too much of the events surrounding the surgical procedure and the recovery process). Benzodiazepines, such as midazolam, are used for minor surgical procedures, such as endoscopy. Chronic use of benzodiazepines results in the development of tolerance and dependence (Chapters 8, 9 and 10); for this reason it is recommended that the benzodiazepines should not be used for more than two weeks.

The mechanism of action of the benzodiazepines is illustrated in Figure 1.9. When GABA binds to its receptors, it opens chloride ion channels to allow entry of chloride ions to hyperpolarize the membrane, thus making it more difficult to generate an action potential (Section 1.3.1). When a benzodiazepine binds to the benzodiazepine binding site in the absence of GABA, the GABA<sub>A</sub> receptor remains in the resting state. Thus, the benzodiazepines have no intrinsic activity of their own. However, when both GABA and a benzodiazepine bind to their respective sites, there is a conformational change in the GABA<sub>A</sub> receptor. It goes into a high affinity state typified by an increase in the frequency of opening of chloride ion channels and an increase in the influx of chloride ions. This is called allosteric modulation. The increase in chloride ion conductance increases the hyperpolarization of the membrane to a greater extent than with GABA alone. Therefore, the benzodiazepines act to enhance the inhibitory effects of GABA on GABA<sub>A</sub> receptor by allosteric modulation. They are sometimes referred to as positive modulators of the GABA<sub>A</sub> receptor.

At a cellular and molecular level, it has been shown that the GABA<sub>A</sub> receptor binding site is located between α and β subunits (Section 1.3.1; Figure 1.2). Benzodiazepines do not bind to the same receptor site on the GABA<sub>A</sub> receptor complex as GABA or muscimol but bind to distinct benzodiazepine binding sites situated at the interface between the α and γ subunits. There are at least six subtypes of the α...
Figure 1.9 The effects of GABA and the benzodiazepines on the GABA_A receptor complex. (A) The GABA_A receptor in the resting state. (B) When GABA binds to its receptor site it opens chloride ion channels to allow entry of chloride ions to hyperpolarize the membrane, thus making it more difficult to generate an action potential. (C) When a benzodiazepine binds to the benzodiazepine binding site in the absence of GABA, the GABA_A receptor remains in the resting state. Thus, the benzodiazepines have no intrinsic activity of their own. (D) When both GABA and a benzodiazepine bind to their respective sites, there is a conformational change in the GABA_A receptor complex. It goes into a high affinity state typified by an increase in the opening of chloride ion channels and an increase in the entry of chloride ions (Cl^-). Thus, benzodiazepines enhance the inhibitory effects of GABA on GABA_A receptors.

subunit. The GABA_A receptors that have α_1, α_2, α_3, or α_5 subunits are sensitive to the benzodiazepines. The benzodiazepines appear to be insensitive to GABA_A receptors that have the α_4 subunit. It has recently been found that benzodiazepines that (i) act on GABA_A receptors that possess α_2 and/or α_3 subunits produce anxiolytic and calming effects, (ii) act on GABA_A receptors that have α_1 and α_5 subunits causes sedation, hypnosis (at higher doses) and ataxia, and (iii) act at GABA_A receptors that possess α_1, α_2, α_3, or α_5 subunits have anticonvulsant activity. Interestingly, drug companies are focusing their efforts on making benzodiazepines that act selectively at GABA_A receptors containing the α_2 subunit to make anticonvulsant benzodiazepines without the sedative effects of current drugs.

When scientists designed drugs that did not have a benzodiazepine chemical structure but still bound to the benzodiazepine site on the GABA_A receptor, they found that they had strange effects. One such group of compounds was the β-carbolines. When these drugs were administered to animals they produced the opposite effects to the benzodiazepines. They had anxiogenic effects (increased anxiety), they caused insomnia (decreased sleep time), they increased motor activity and were convulsant at high doses, and they increased muscle tension. Further investigation revealed that when both GABA and a β-carboline bind to their respective sites on the GABA_A receptor complex, a conformational change is induced. The GABA_A receptor goes into a very low affinity state that is typified by a reduction in the opening of chloride ion channels. Thus, the inhibitory effects of GABA on neuronal activity in the brain will be significantly reduced. These agents are known as benzodiazepine inverse agonists, as they produce the
opposite effects to the benzodiazepines; they are sometimes referred to as negative modulators of the GABA<sub>A</sub> receptor.

Flumazenil is a clinically available drug that is a competitive antagonist at the benzodiazepine binding site. It has been found to have no intrinsic activity of its own and does not modulate the effects of GABA on the GABA<sub>A</sub> receptor. However, it blocks the effects of the benzodiazepines and the inverse agonists in a dose-dependent manner. Flumazenil is used clinically to treat patients who have taken an overdose of benzodiazepines.

### 1.6.2 Other Depressant Drugs

Barbiturates (Chapter 4) and alcohol (Chapter 11) are depressant drugs that also act on allosteric sites on the GABA<sub>A</sub> receptor complex to enhance the effects of GABA. These barbiturate and alcohol binding sites are different from each other, and have no activity at the benzodiazepine binding site.

### 1.7 Genetics

Advances in molecular biology have made it possible to identify chromosomes, region of chromosomes, genes and variants in genes that are associated with CNS disorders. Genes are made up of deoxyribonucleic acid (DNA), which exists in the nucleus as a double helix. DNA consists of four nucleotide bases in which the nucleotides are paired: adenine with thymine, and guanine with cytosine. The genetic code in DNA is written in triplets containing three of the nucleotides. During protein synthesis, one strand of DNA is used as a template for the synthesis of messenger ribonucleic acid (mRNA). mRNA is then translated into specific proteins in the ribosomes that are found in the cytoplasm of the cell by transfer RNA (tRNA) and chaperone molecules. Mutations or variants of the genes will result in abnormal synthesis of proteins that may have important roles in cellular function and result in psychiatric and neurological conditions, such as Parkinson’s disease (Chapter 2), depression (Chapter 6) and schizophrenia (Chapter 10). There are approximately 10 000–15 000 genes that effect the development, growth and regulation of the brain and the rest of the central nervous system. However, it has been estimated that about half of these genes are dependant on environmental factors to be activated.

Many neurological and psychiatric conditions appear to depend on an interaction between inherited genes that may predispose a person to a particular CNS condition, such as depression, but the condition will only be expressed when the person is exposed to certain environment conditions, such as stress (see, for example, Chapter 6). This process is known as epigenetic modification. Epigenetic mechanisms can regulate the expression of genes; they can switch genes on and off. Chromatin, which is a substance that consists of histone protein, is wrapped around the strands of DNA that constitute the chromosomes. Epigenetic regulation of whether a gene is switched on or off is dependent on chemical modification of the chromatin. For example, methylation (addition of a methyl group) of the histones can silence a gene by binding tightly to the DNA and preventing translation to mRNA. On the other hand, demethylation can switch on a gene. Other chemical modifications of the chromatin, such as acetylation, can also switch off gene expression, while deacetylation can switch on gene expression. The mechanisms by which environmental factors, such as stress, diet and drug abuse, mediate these epigenetic changes is under intense investigation. However, it should be noted that some epigenetic modifications that occur, especially in childhood, could persist throughout life and some may even be passed on to offspring.

There are a number of methods that scientists have used to determine the genetic changes that may be responsible for CNS disorders. Linkage studies are used to identify common chromosomal regions associated with neurological or psychiatric disorders by examining the pattern of inheritance of specific regions of chromosomes in healthy controls subjects and patients with the disorder. Genome-wide association studies involve whole genome scans across all chromosomes of a group of patients with a
specific mental disorder and a group of control subjects to identify common gene variants (commonly single nucleotide polymorphisms or SNPs) to see if any variation is associated with a psychiatric trait.

1.8 Electroencephalography and Imaging Techniques

There are a number of noninvasive techniques that allow researchers and clinicians to image the brain and investigate brain function. The include electroencephalography, X-rays, computerized tomography (CT) scans, magnetic resonance imaging (MRI) and functional MRI.

1.8.1 Electroencephalography

Neurones in the brain communicate with each other by electrical (action potentials) and chemical (release of neurotransmitters) signals. It is possible to record brainwaves generated by these electrical signals by placing electrodes on the scalp. These brainwaves are referred to as the electroencephalogram or EEG. The waveforms of the EEG reflect changes in the level of neuronal activity in the brain. Thus, when a person is awake and alert there is more activity in the brain than when the person is drowsy or sleeping and these changes can be detected in the EEG. β-Waves are high frequency, low amplitude waves that are recorded in the EEG when a subject is awake and alert. β-Waves have a frequency between 13.1 and 35 Hz. The frequency increases as level of arousal increases. α-Waves are recorded in the EEG when the subject is relaxed (usually with the eyes closed) and have a frequency between 8 and 13 Hz. δ-Waves are low frequency, high amplitude waves. They are recorded in the EEG when the subject is drowsy or asleep and have a frequency between 0.1 and 4 Hz. EEG recordings of the various waveforms are shown in Figure 9.1 (Chapter 9). The EEG recordings are useful in the diagnosis of epilepsy (Chapter 4), dementia (Chapter 3), sleep disorders (Chapter 9), brain tumours and certain forms of encephalitis. The EEG is also used as a noninvasive ‘window into the brain’ to assess the effects of psychoactive drugs on brain function.

1.8.2 X-Rays

X-rays consist of electromagnetic short-wave radiation and was first described by Wilhelm Rontgen almost 120 years ago. X-ray images show the contrast between tissues of different densities. Material that absorbs X-rays, such as the bone of the skull, appears white on the image, while brain tissues absorbs less X-rays and appear in varying shades of grey depending on the density of the tissue. Air-filled structures, such as the nasal cavity, appear black, as no radiation is absorbed. X-rays are useful in detecting regions in the brain where there is dense tissue (such as brain tumours), some epileptic foci (Chapter 4) and structural damage to the brain. For contrast X-rays, patients are injected with contrast media (usually iodine based) that absorb X-rays into arteries or veins, so that they could be imaged. Contrast X-ray can be used to image blood vessels in the brain; for example cerebral angiography may be used to diagnose a brain tumour, bleeding in the brain or an aneurysm.

1.8.3 Computed Tomography

Computed tomography (CT), also referred to as computed axial tomography (CAT), is an imaging technique that is based on taking multiple X-rays around an object and using a computer program to construct a three-dimensional cross-sectional image of that area. A CT scanner has an X-ray source and an X-ray detector on the other side. To perform a CT scan on the brain, the subject is put into the scanner and the brain is X-rayed. The X-ray source and detector are rotated slowly around the head and X-rays are taken each time. Following a complete rotation, the X-ray source and detector move a set distance downwards
and the next rotation starts. The two-dimensional X-ray images can be built up into a three-dimensional image of the brain using complex computer calculations. The three-dimensional images of the brain may be used for diagnosing brain tumours, bleeds in the brain, epileptic foci (Chapter 4) and brain injury.

1.8.4 **Positron Emission Tomography**

Positron emission tomography (PET) may be regarded as a variation of CT imaging and uses similar technology. A radioactive substance is injected intravenously and will be detected as a bright image on the X-ray image. The amount of radioactivity taken up by different areas of the brain is dependent on tissue type and the level of activity. Thus, PET imaging allow clinicians to determine the differential functional characteristics of particular areas in the brain.

1.8.5 **Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) is a technique that produces detailed cross-sectional images of the brain using a powerful magnetic field, which is between 10 000 and 30 000 times the magnetic field of the earth, and radio waves. To perform an MRI scan on the brain, the subject is put head-first into the scanner, which consists of a large doughnut-shaped magnet. MRI exploits the observation that the tissue in the body contains a certain amount of water. When a subject is placed in a strong magnetic field, the hydrogen atoms within the tissue line up towards the 'magnetic north'. The hydrogen atoms are then excited by delivery of a short burst of radio waves that makes them "vibrate". During this process they absorb electromagnetic radiation. Once the radio waves cease, they line up again under the influence of the powerful magnetic field and the hydrogen atoms emit electromagnetic radiation and produce a signal known as the nuclear magnetic resonance signal. A computer is used to detect the different signals that result from the changes in the behaviour of the hydrogen atoms and construct cross-sectional black-and-white images of the brain. These images can be converted into three-dimensional colour pictures of the scanned area that can help identify problems in the brain. MRI may be used to detect brain tumours, epileptic foci and brain injury. MRI images can also help in the diagnosis of dementias and other neurodegenerative conditions of the brain.

1.8.6 **Functional MRI**

Functional MRI (fMRI) uses similar technology to MRI but instead of using hydrogen atoms it uses the change in effects of the magnetic field on the absorption and emission of electromagnetic radiation between oxygen-rich and oxygen-poor blood as its basic measure. The fMRI technique relies on the observation that neuronal activity is related to cerebral blood flow. In other words, when an area of the brain is active, blood flow to that region also increases, and when an area of the brain is not active, blood flow to that region decreases. fMRI can detect changes in brain activity while a subject performs a task in the scanner. This has been particularly useful in determining brain functional changes in CNS disorders, such as ADHD (Chapter 5) depression (Chapter 6), anxiety disorders (Chapter 8) and schizophrenia (Chapter 10).

1.9 **Diagnostic Criteria for Mental Disorders**

There are two publications that are used by clinicians for the coding, classification and diagnosis of mental disorders. As there is a marked paucity of biochemical and other tests that may be carried out to identify many psychiatric conditions, these publications provide important guideline criteria for their diagnosis. The first is *The Diagnostic and Statistical Manual of Mental Disorders (DSM)* produced by
the American Psychiatric Association (APA). The DSM describes about 400 mental disorders. It is now in the 5th edition (DSM-5), published in May 2013. The second is The International Classification of Disease (ICD) published by the World Health Organization. The ICD is classification of general medical conditions and the 10th edition (ICD-10) published in 2010 is currently available. The ICD-10 consists of 21 chapters, with Chapter 4 containing the diagnostic classification for psychiatric disorders. The two classification systems are generally similar. The ICD is a diagnostic classification system that is normally used in Europe, while the DSM classification is used in the USA. In the United Kingdom, both systems are used for the diagnosis of psychiatric disorders. In this book, criteria for psychiatric disorders based on the DSM are mainly referred to rather than the ICD because the DSM is more widely used for this purpose. However, the ICD criteria are also referred to if there are marked discrepancies between the two. The criteria used as the basis for diagnosis of psychiatric condition have undergone minor and, sometimes, major changes in successive editions of these manuals as more evidence-based knowledge of these disorders is revealed by advances in research.

1.10 Animals Models for CNS Disorders

The basic neuroanatomy of the brains of humans is remarkably similar to those of most other mammalian species, including monkey, pig, rat and mouse. Animals are, therefore, used for investigating the central mechanisms that underpin neurological and psychiatric disorders, clarifying the effects of drugs on the CNS and assessing the suitability of novel pharmacological agents for the treatment of CNS disorders.

It is possible to genetically manipulated rodents, particularly mice, so that, firstly, particular genes can be deleted from the genome, thus enabling investigators to determine the biological functions of these genes in these ‘knock-out’ animals, and, secondly, normal or mutant genes (including human genes) can be inserted into the genome to allow scientists to establish the effects of overexpression of particular genes or the effects of mutant genes on the occurrence of CNS disorders and their progression. Furthermore, it is possible to lesion or stimulate specific CNS areas, recorded the activity of single or multiple neurones, sample neurotransmitter release under different conditions or measure the effects of a variety of experimental manipulations on the behaviour of experimental animals. Such studies have provided a wealth of knowledge on the physiological processes that are involved in the normal and pathological functioning of the brain.

Animals, such as rats and mice, do not develop many of the psychiatric conditions, such as depression and schizophrenia, that humans suffer from. Scientists have, therefore, used behavioural, ablation, pharmacological and genetic techniques to develop animal models of human neurological and psychiatric disorders, so that they can conduct preclinical trials to assess the effects of novel drugs for use in CNS disorders. Investigators also use these animal models to learn more about CNS conditions, although many scientists consider this approach controversial. Animal models vary in the degree to which they replicate CNS disorders. There are three main criteria that an ideal animal model should fulfil:

(1) Predictive validity (in which performance in the animal test predicts performance in the neurological or psychiatric condition being modelled).
(2) Face validity (which is an estimation of the degree of descriptive resemblance between the behavioural dysfunction in the animal model and dysfunction in the human disorder).
(3) Construct validity (which is an estimation of the degree of similarity between the mechanisms underpinning behaviour in the animal model and the mechanisms underpinning the behaviour in the psychiatric or neurological condition).

Most animals models will meet will meet either criterion 1 or 2, or both criteria. Criterion 3 is much more difficult to meet. Construct validity is hypothesis driven, in that it reflects our current understanding.
of a condition. It requires that the animal model should be similar, in terms of symptoms, pathophysiology and underlying mechanisms, to that of the actual human disorder. The ability of scientists to use advanced genetic techniques that have become available in recent years as well as a variety of other nongenetic techniques has at last given them the tools to achieve all three criteria in their quest to develop animal models with greater validity.

The advances in our understanding of the aetiology and pathophysiology of psychiatric and neurological disorders, and the mechanism of actions of the drugs that are used to treat them, have largely come from experiments in animals, using the techniques and models briefly discussed here. Details of animal experiments are described, sometimes in detail and sometime in passing, in the subsequent chapters of this book.

1.11 Summary

In this chapter, some of the basic concepts that the reader may find useful when reading the subsequent chapters of the book have been introduced. However, a lot of basic information is also covered in the different chapters, to supplement the information presented here. Briefly reviewed in this chapter are the anatomy and functions of the brain, important neurotransmitters in the central nervous system (CNS), the relationship between arousal and performance, CNS stimulant and depressant drugs, and the experimental and clinical techniques that are used to obtain information on brain function. It is likely that the majority of readers will have a fairly good knowledge of most of these subject areas already and these brief reviews will act as a memory prompt. However, readers who have not been schooled in these disciplines and who want to learn more about basic neuroanatomy, pharmacology and molecular biology should consult standard textbooks for further information.