Understanding Drugs and Behaviour

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For Felicity, Rebecca and Laura
For Mary, Ciarán and Gareth
For Holly Mae
For Lola
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Andy Parrott has published over 300 journal articles and conference papers, covering a wide range of psychoactive drugs. The first publications from his PhD at the University of Leeds were concerned with antipsychotic medications. Then, as a postdoctoral researcher with the Human Psychopharmacology Research Unit at Leeds University, he investigated the effects of second-generation antidepressants and benzodiazepines on cognitive performance and car-driving skills. Moving to the Institute of Naval Medicine in Hampshire, he was tasked with determining the practical utility of anti-seasickness medications, such as transdermal scopolamine, in land and sea trials. Further trials investigated the cognitive side effects of nerve agent prophylactics. At the University of East London he established the Recreational Drugs Research Group, which investigated a number of disparate topics: caffeine in shift workers, anabolic steroids in weightlifters, amphetamine and LSD in party goers and nootropics as potential “smart drugs”. At Humboldt State University in California, he assessed the everyday functioning of excessive cannabis users. However, his two main research areas are nicotine and MDMA/Ecstasy. In an extensive research programme he has shown how nicotine dependency is psychologically damaging and causes increased psychological distress. The Recreational Drugs Research Group which he founded at the University of East London is, however, most well known for its work with recreational MDMA/Ecstasy users. Their cognitive research papers have been awarded the British Association for Psychopharmacology Organon prize on two occasions. Professor Parrott’s work is featured regularly in the media. He sits on the editorial boards of leading psychopharmacology journals, and he has organised a number of international symposia. Recently, he moved to the University of Wales at Swansea. Here, he is continuing with a number of collaborative studies, including a large UK/US prospective study investigating the effects of recreational drug use during pregnancy.

Alun Morinan graduated in Biochemistry from the University of Wales at Aberystwyth and went on to complete an MSc in Pharmacology at the University of London and a PhD in Neuropharmacology at the National University of Ireland in Galway. After postdoctoral research in Pharmacology at Galway and Biochemistry at the Institute of Psychiatry, he was appointed Lecturer
in Pharmacology at North East Surrey College of Technology before moving to his current post of Principal Lecturer at the University of East London. His publications have been mainly in the fields of experimental psychopharmacology and neurochemistry covering topics such as alcohol dependence, anxiety, schizophrenia and enzymology.

Mark Moss studied applied chemistry and spent 10 years in industry before returning to university to study Psychology. He completed his PhD in 1999 and was involved in the establishment of the Human Cognitive Neuroscience Unit at Northumbria University. His research portfolio has focused primarily on aspects of cognitive functioning in healthy young volunteers, with journal articles and conference presentations relating to both enhancement through natural interventions and drug-induced impairments. Mark is currently programme leader for the Division of Psychology at Northumbria University.

Andrew Scholey is a Reader in Psychology at the Division of Psychology, Northumbria University, Newcastle-upon-Tyne. He has published hundreds of journal articles and conference papers, covering the cognitive effects of many recreational and medicinal drugs. His PhD and postdoctoral fellowship at the Brain and Behaviour Research Group, Open University, examined the neurochemical substrates of memory formation. He moved to Northumbria University in 1993, where his research has concentrated on the acute and chronic impairing and enhancing effects of various drugs including benzodiazepines, alcohol, caffeine, glucose, oxygen (with Mark Moss) and herbal extracts. In 1999 Andrew established the Human Cognitive Neuroscience Unit, of which he is the director. The work of this unit concentrates on the potential for non-mainstream treatments to enhance cognitive performance. These have ranged from metabolic interventions (notably glucose and oxygen) to low doses of alcohol and even to drinking water (in thirsty individuals) and to chewing gum. Andrew is also the co-director of the Medicinal Plant Research Centre. His present focus of research aims to disentangle the neurocognitive effects of herbal extracts, to attempt to identify relationships between their behavioural effects and their neurochemical properties and to identify safe treatments that may be effective in the treatment of conditions where cognition becomes fragile, including dementia. He is currently involved in trials examining the effects of herbal extracts in Alzheimer’s disease. Andrew is also committed to the public dissemination of science which has led to numerous appearances in the print, radio and television media.
Preface

Drugs are a crucial part of modern society. Many are used for recreational purposes, with alcohol, nicotine and caffeine all being legal. However, others are illegal, and they include cannabis, Ecstasy, cocaine and heroin. In the past 50 years a number of medicinal compounds have been developed for schizophrenia, depression and other clinical disorders. They have dramatically improved the well-being of many people diagnosed with these disorders. But what exactly are the effects of these different types of drug? How precisely do they alter behaviour? How is it that such small chemicals can have such dramatic effects on mood and cognition, sensation and awareness, health and well-being? Why are only some drugs highly addictive? Our core aim is to provide detailed answers for all these questions.

We hope this book will not only be of interest to students of psychology, behavioural sciences, health sciences and nursing but also to undergraduates of physiology and pharmacology who wish to find out more about the behavioural aspects of drug use. Our aim throughout is to present the material in a reader-friendly fashion. We have taught undergraduates in many different disciplines and have therefore become skilled at explaining this material to students without any formal scientific background. We will describe how psychoactive drugs can alter brain chemistry and, hence, modify behaviour. We offer an accessible route through basic aspects of brain organisation and functioning. Normally, these areas are difficult for many undergraduate students. However, by approaching them through the mechanisms of drug action, we hope to stimulate an active interest in this area.

We have planned every chapter to be self-contained. Each commences with a general overview, before the core material is presented in depth; this is followed by a list of questions that should prove useful for both students and their lecturers. Finally, there are several key articles, followed by a list of further references. Many of the chapters in this book have been tested out on our students. Not only did they report that the chapters were all excellent (in feedback sessions that were obviously not blind!) they also informed us that they particularly liked this reference format. They found it useful when writing essays, preparing projects and, most importantly, when “cramming” for exams.
In terms of its overall structure, we have focused on the main types of drug used in society. Thus, alcohol and nicotine have chapters largely dedicated to them. Similarly, there is a whole chapter on cannabis, while another is shared by LSD and Ecstasy/MDMA. We also cover opiates, such as heroin, and CNS stimulants, such as amphetamine and cocaine. Turning to drugs for clinical disorders, one chapter is dedicated to antipsychotic medications for schizophrenia, while another covers antidepressant drugs. We also look at more novel areas, such as drugs for Alzheimer’s disease, as well as nootropics and herbal preparations to improve cognitive functioning. In every chapter we have focused not only on drug effects but also on how these interact with environmental factors. We have also noted how drugs often need to be combined with psychological therapy to achieve the optimal clinical outcome.

One of the benefits of working as a team of four co-authors is that between us we have a great deal of knowledge about all aspects of drugs and behaviour. Thus, every chapter is informed by a high level of research expertise. Indeed, in several fields the authors are leading international research authorities. We believe that drugs are not only very important for society but also very fascinating in their own right. Certainly, they have intrigued us for many years, and we hope to pass on some of this interest and fascination to our readers.

Andy Parrott  
Alun Morinan  
Mark Moss  
Andy Scholey

Universities of Swansea, East London and Northumbria
PART I

Drugs and Their Actions

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Chapter 1

Psychoactive drugs: introduction and overview

Overview

Psychoactive drug use is not just a phenomenon of the 20th century; many different types of drug have been used throughout recorded history. In this chapter we will outline the main classes of psychoactive drug. We are able to do this in a single chapter because, despite there being thousands of different drugs, they can be classified in a few main groups (Table 1.1). The crucial role of neurotransmitters will also be described because psychoactive drugs alter mood and behaviour by modifying nerve activity in various ways. Thus, a basic understanding of neurotransmitter actions is vital in order to understand how drugs can affect behaviour. Tolerance and addiction may also develop, when regular drug use causes long-term changes in neurotransmission activity. Next, we will emphasise that all drugs have a range of positive and negative behavioural effects. Positive or desirable effects, such as feelings of pleasure, are the reasons people take drugs. But drugs also cause negative effects, which is why drug taking can cause so many psychosocial problems.

Psychoactive drugs over the ages

Since before the dawn of civilisation, humans have used drugs¹ to alter their mood and behaviour. Opium poppy (Papaver somniferum) seeds have been found by archaeologists in Neolithic burial sites. Some of the earliest writing on clay tablets from Mesopotamia described laws to control the alcohol consumption in local taverns. Many societies have discovered that different species of plant and fungi can induce powerful hallucinations. Native Americans have used the peyote cactus (Lophophora williamsii) (containing mescaline) to foster spiritual insights during their religious ceremonies. Vikings used the Amanita muscaria mushroom for its hallucinogenic and excitatory effects, before raiding and pillaging

¹ Boldface terms are defined in the Glossary.
in their longboats. In ancient Greece, Homer’s epic poem *Odysseus* describes how the hero and his crew were drugged by the sorceress Circe, a skilled “polypharmakos”, or drug user, who laced their wine with drugs that stunned their memories and ensnared their minds. The wary Odysseus managed to avert this only because he had taken the precaution of taking an antidote beforehand (Caldwell, 1970; Palfai and Jankiewicz, 1996).

Many drugs are taken for their curative or medicinal effects. In South American silver mines, for many centuries the miners have chewed coca leaves (containing cocaine), to aid their physical and mental vigilance working high in the oxygen-poor Andes (Chapter 4). Tea, which contains caffeine, was recommended as a general tonic by sages in Ancient China (Chapter 4). In the Indian subcontinent the Indian snake root *Rauwolfia serpentina* was used as a treatment for people suffering manic excitement, or hallucinations and delusions. Its effectiveness at reducing the symptoms of schizophrenia has been scientifically confirmed in the 20th century. *Rauwolfia* contains reserpine, a powerful psychoactive drug that depletes dopamine stores; this is how it leads to calmer and more manageable behaviour. In some ways, reserpine displays properties similar to more modern antipsychotic drugs. However, its broad spectrum of effects in deleting the stores of several neurotransmitters means that it can also cause feelings of severe depression. Thus, reserpine is not used clinically, since modern antipsychotic drugs do not have this unwanted side effect (Chapters 3 and 11).

Psychoactive drug use remained popular throughout the 20th century. Several drugs are legal, and their use has grown during the past 100 years. The advent of machines to produce cigarettes at the beginning of the 20th century led to a marked increase in tobacco consumption. By the end of the second world war, helped by the free distribution of cigarettes to the armed forces, around 70% of the male population in the UK were regular nicotine users. In global terms the world consumption of

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tobacco is still increasing, despite reductions in a few Western countries where its adverse health effects have been emphasised. Yet, even where marked reductions have occurred, particularly in the USA, Britain and Australia, this decrease in consumption has not been maintained. Recent years have shown a resurgence of cigarette smoking among the young, particularly adolescent females (Chapter 5). Alcohol use also shows no sign of reduction, and at the same time the age of first drinking continues to fall. In the USA many high schools offer formal programmes to help their teenage pupils to quit smoking, or reduce excessive alcohol consumption (Chapters 9 and 10). Another legal drug – caffeine – is consumed by over 90% of the adult population in their daily tea and coffee. Caffeine is also present in the fizzy soft drinks and chocolate bars consumed by children each day (Chapter 4). Many other psychoactive drugs are deemed illegal, yet even the threat of long prison terms does not halt their popularity. Around 50 million Americans have smoked cannabis (marijuana), although only 49,999,999 admit to inhaling since former President Bill Clinton admitted to having tried marijuana but without inhaling! (Chapters 7 and 15). The use of amphetamine, cocaine and heroin has increased in recent decades, while new recreational drugs have also been specifically “designed” for their mood-altering effects (Shulgin, 1986). Ecstasy (MDMA, or methylenedioxymethamphetamine) first became popular in the mid-1980s and since then its use has steadily increased, with young people trying it at an increasingly early age (Chapter 6).

One of the most dramatic changes for modern society was the advent of effective psychoactive medicines in the 1950s. The first antipsychotic drug chlorpromazine was developed in 1950, and since then the management and treatment of schizophrenia has been transformed, with most patients now seen as outpatients and the majority of “mental hospitals” being closed (Chapters 11 and 15). The advent of antidepressant drugs in 1957 led to a similar change in the treatment of people suffering from depression (Chapter 12). Thus, we now have a range of drug treatments for two of the most severe psychiatric disorders. It should be emphasised that the advent of these drugs has not been entirely beneficial. Numerous schizophrenics now suffer greatly, because society has failed to provide the support mechanisms. Antipsychotic drugs are only partially effective on their own. To maximise their effectiveness, they need to be complemented by behavioural therapy, or social skills training. This is expensive, and in most Westernised countries this support structure is generally lacking. Another contentious area is the treatment of “hyperactive” young children with CNS (central nervous system) stimulant drugs. The clinical diagnosis of Attention Deficit Hyperactivity Disorder (ADHD) is a very recent phenomenon, but since the early 1980s an increasing number of young children have been given this diagnosis. Is it defensible to label continuous fidgeting or poor concentration on school work as clinical symptoms in 5 and 6-year-olds and then administering them with powerful psychoactive drugs, especially when it is the parents and teachers who are “suffering” the most? This issue will be critically examined in Chapter 4. Pharmaceutical companies are now attempting to develop nootropic drugs for Alzheimer’s disease and other disorders associated with ageing (Chapter 13). If effective drugs for the elderly are successfully developed, the impact on society could become even more marked than was the development of antipsychotic and antidepressant drugs in the 1950s. Finally, there have been numerous attempts to produce cognitive enhancers that modulate cell metabolism and brain activity in various ways (Chapter 14).
How many types of psychoactive drug are there?

There are hundreds of different drugs that can affect mood and behaviour, although they can be categorised into a few basic drug types. Table 1.1 outlines the main categories of psychoactive drug. This classification system also reflects their psychopharmacological effects. Thus, CNS-stimulant drugs, such as amphetamine and cocaine, generate feelings of alertness and lead to faster behavioural responses; indeed, this is why they are banned in sport (Chapter 4). CNS-depressant drugs generate feelings of sleepiness and impair skilled psychomotor performance; this is why piloting a plane or driving a car are so dangerous under the influence of alcohol, with numerous road deaths being caused each year (Chapter 9). Opiate drugs, like heroin and morphine, are again similar in their effects, leading to feelings of euphoria and reduced pain, in relation to both physical and mental pain (Chapter 8). Many other drugs are not categorised so readily. Thus, cannabis is unlike many other drugs (Chapter 7), while LSD (lysergic acid diethylamide) also has many unique properties (Chapter 6).

The reason some drugs have similar behavioural effects is that they have similar pharmacological effects. Take amphetamine and cocaine as an example. Their origins are quite dissimilar: cocaine is extracted from the leaves of the coca plant (*Erythroxylon coca*), whereas amphetamine is artificially manufactured in the laboratory; amphetamine is an amine, whereas cocaine is an alkaloid. However, they each stimulate the release of the neurotransmitter dopamine and inhibit its inactivation; this explains why their psychoactive effects are so similar, in terms of boosting mood and alertness. In fact, most CNS-stimulant drugs boost dopamine and/or noradrenaline, which is why they have broadly similar behavioural effects (Chapters 3 and 4). Let us now consider another drug group – the opiates. Different drugs in the opiate class all tend to have similar types of effect on other types of neurotransmitters, such as the neuropeptides, which is why they have similar behavioural effects (Chapter 8). In an equivalent fashion, CNS-depressant drugs all seem to affect the GABA (γ-aminobutyric acid) receptor – again helping to explain why they all tend to have similar effects on behaviour (Chapter 9).

Drug effects on neurotransmission

Normal behaviour is dependent on a complex system of chemical messages passed between neurons in the brain. Each nerve cell or neuron communicates with the next neuron by means of chemicals called neurotransmitters (e.g., dopamine, noradrenaline, serotonin, acetylcholine, histamine, GABA). Psychoactive drugs exert their effects by increasing or decreasing the activity of these neurotransmitters, this is why a basic understanding of the CNS and neuronal activity is essential for a psychoactive drugs textbook (Chapter 2). Only then will it become clear how drugs can modify neurotransmission and thus alter behaviour (Chapter 3). Hence, a thorough understanding of these two introductory chapters is necessary before attempting to read the other sections. This knowledge also helps to explain related phenomena like drug addiction (Chapter 10). The very first time a drug is taken it has a different effect on neurotrans-
mission than when it is taken a hundred times later. The first ever cigarette will lead to nausea and sickness, because nicotine stimulates the neurons in the vomiting centres of the brainstem. However, the 100th cigarette no longer induces feelings of nausea, because neuronal tolerance has developed. In a similar way a small amount of alcohol will induce feelings of light-headedness and tipsiness in a novice drinker, whereas a heavy regular drinker would have no perceptible response. Tolerance explains why heavy drinkers need to binge-drink in order to feel drunk (Chapters 9 and 10). Neurons tend to adapt and change following regular drug use and neuronal tolerance reflects these adaptive changes in neurotransmitter systems. Neuronal tolerance also helps explain why it can be so easy to become addicted to certain drugs, although many non-pharmacological factors are also important; these will all be described in Chapter 10, where they will illustrate how and why heroin addiction, nicotine dependency and alcoholism have become such enormous problems for society.

**Positive and negative drug effects**

Psychoactive drugs modify behaviour by altering neurotransmission. However, each neurotransmitter system generally underlies various diverse aspects of behaviour; this means that any one drug will generally have a wide range of behavioural effects. Some of these may be pleasant, but others may be unpleasant. Recreational drugs are taken for their pleasant effects. Alcohol can release social inhibitions and help foster feelings of closeness with other people. The caffeine in tea and coffee can help regular users maintain feelings of alertness. Similarly, psychoactive medicines are taken for specific purposes. Antidepressant drugs can help relieve feelings of profound sadness. Antipsychotic drugs can reduce delusions and hallucinations and can enable those suffering from schizophrenia to lead more normal and contented lives. Every psychoactive drug has some positive uses – which is why they are taken (Chapters 4–15).

Yet, these same drugs also produce a range of negative effects. Alcohol can lead to increased aggression and antisocial behaviour, while its disinhibitory effects cause many individuals to commit crimes that they would not have undertaken if they had remained sober. Most antidepressant and antipsychotic drugs generate unpleasant side effects, such as drowsiness and dry mouth. Therefore, the main focus of many pharmaceutical company research programmes is to develop new drugs that are more specific in their effects, so that they relieve the target symptom while causing the fewest side effects (Chapters 11 and 12). Other problems include tolerance and dependence (see above and Chapter 10). Cigarette smokers soon develop nicotine dependency and gain no real benefits from their tobacco; they just need nicotine to function normally (Chapter 5). Opiate users similarly develop drug dependency. One reason for these negative effects is drug tolerance. The basic mechanism behind the development of tolerance and dependence are described in Chapters 3 and 10. Therefore, most drugs have a balance of positive and negative effects. Thus, cocaine can make people feel alert, dynamic and sexy … all pleasant or desirable effects. Yet, it can also make them anxious, aggressive and suspicious and reduce their inhibitions. This combination of behavioural changes can be dangerous: initially, they may want to socialise with their friends but soon argue, leading in extreme cases to their committing murder on the spur of the moment (some examples are given in Chapter 4). There is marked individual
variation in the development of drug-related problems; this is best understood in relation to the diathesis stress model, where any behavioural outcome is seen as the result of an interaction between internal factors (e.g., genetic and biochemical predispositions) and environmental events (abuse, poverty, stress, psychoactive drugs). This model is debated more fully in Chapters 6 and 10.

However, every chapter will describe both positive and negative drug effects. One core aim will be to assess their cost–benefit ratios (Chapter 15). Most psychotherapeutic drugs have an advantageous ratio, with the benefits outweighing the unwanted side effects (Chapters 11 and 12). Estimating the cost–benefit ratio for recreational drugs can however be more difficult, since their positive and negative effects are influenced by numerous factors including dosage, frequency of use and duration of use. There is often little correspondence between the legal status of each drug and the amount of harm it causes. Thus, two of the most widely used drugs in society, nicotine and alcohol, have numerous deleterious consequences. In the UK tobacco smoking causes around 350–400 deaths each day, but regular cigarette smokers get no genuine psychological benefits from nicotine dependency (Chapter 5). The regular use of illicit recreational drugs, such as cannabis, opiates and CNS stimulants, are also linked with numerous problems (Chapters 4–10). The notion of cost–benefit ratios will be debated more fully in the final chapter.

Questions

1. Is drug taking just a phenomenon of the 20th century?
2. Explain how you might categorise psychoactive drugs into just a few groups.
3. Provide examples of psychoactive drug use from earlier periods.
4. Why is knowledge about neurotransmission necessary in order to understand psychoactive drug effects?
5. Do all psychoactive drugs have a mixture of good and bad behavioural effects?

If you have just started this book your answers to these questions may be rather brief. Try answering the same questions after you have read the whole book, and compare your answers!

Key references and reading

Palfai T and Jankewicz H (1996). Drugs and Human Behavior. Wm. C. Brown, Madison, WI.
Chapter 2

The brain, neurons and neurotransmission

Overview

The structure and functions of the central nervous system (CNS) and peripheral nervous system (PNS) will be briefly outlined. The most important type of cell in the nervous system is the electrically excitable neuron, with most being found in the cerebral cortex. There are three main types of neuron: sensory afferents which are stimulated by environmental events (light, sound, touch), interneurons which process this information in the CNS and motor efferents which activate muscles or glands – and thus cause behaviour. The conduction of information throughout the nervous system occurs via a combination of electrical and chemical events. Communication within each individual neuron is by means of electrical changes in the cellular membrane. This action potential will be described in detail. Communication between neurons occurs at the synapse and is chemical or molecular in nature. The molecules involved in synaptic transmission are called neurotransmitters, and the ways in which neurons communicate by means of these neurotransmitters will also be covered in some detail. Psychoactive drugs exert their behavioural effects by either reducing or increasing this neurotransmitter activity. Hence, a basic knowledge of neurotransmitters and their actions is essential in order to understand how drugs affect neurotransmission and behaviour.

Structure of the nervous system

Anatomically, the human nervous system may be divided into the central nervous system (CNS) and the peripheral nervous system (PNS). The major subdivision of the central nervous system is into the brain and spinal cord. The peripheral nervous system is divided into the motor or efferent system (efferent = “away from”), and the sensory or afferent (afferent = “toward”) nervous systems (Figure 2.1).
The nerve cells or neurons of the sensory afferent nervous system convey information about our internal and external environments. There are five types of sensory receptors which provide all sensory information. Chemoreceptors respond to chemical stimuli, with the best example being the taste buds on the tongue. Mechanoreceptors respond to pressure, with many being in the skin, while others are situated on the hair cells of the inner ear, being stimulated indirectly by sound. Nociceptors respond to pain and are located throughout the body, in the skin, intestines and other inner organs. Photoreceptors are sited in the retina of the eye, where blue, green and red cones are selectively stimulated by coloured wavelengths, while the rods respond to all visible light waves and, thus, convey black-and-white information. Thermoreceptors are sited in the skin and are sensitive to changes in temperature. Most sensory receptors are unimodal, being only activated by one type of stimulus. They behave as transducers, converting one form of energy (light, sound) into an electrical signal that can be conducted along the axon of the neuron.

Each sensory afferent neuron connects with an interneuron or accessory neuron. These interneurons are located entirely within the CNS, with the majority occurring in the cerebral cortex. They form numerous interconnections and are the means by which all cognitive information, thoughts and feelings, are processed. It should be emphasised that the main role of this processing of information is inhibitory. The sensory receptors provide the CNS with a massive amount of data. The interneurons process and filter this into a limited amount of useful and important information. Conscious information processing forms just one part of this activity. A great deal of brain activity is concerned with routine processes, which continue without conscious awareness.

At the end of this processing sequence, some of the interneurons connect with motor efferent neurons. These motor efferents leave the CNS and stimulate the peripheral effectors. Most of the effectors are muscles of various types: smooth,
cardiac and striated or skeletal muscle. The other effectors comprise all the exocrine glands and some of the endocrine glands.

“Motor” implies movement, and here it means muscular contraction/relaxation. Other effectors stimulate the secretion of a mixture of chemicals from a gland: for instance, saliva from the exocrine salivary glands or catecholamine hormones from the adrenal medulla – which is an endocrine gland. The latter contributes to the so-called “adrenaline rush” and the feeling of “butterflies” in one’s stomach. Skeletal muscle contraction is controlled by voluntary (somatic) motor efferents, whereas the cardiac muscles, smooth muscles and glands are regulated by autonomic motor efferents (Figure 2.1). The autonomic nervous system (ANS) can be subdivided according to anatomical (CNS origin and axonal length), biochemical (neurotransmitter type) and physiological (functional) criteria into the parasympathetic and sympathetic branches. Many tissues are innervated by both branches, and this dual innervation means that they can experience opposing physiological effects. For example, stimulation of the parasympathetic vagus nerve decreases the electrical activity of the sinoatrial node (pacemaker), thus slowing the heart rate and resulting in “bradycardia”. In contrast, stimulation of the sympathetic cardiac accelerator nerve leads to faster heart rate or “tachycardia”. As a general guide to the different physiological effects of the ANS, remember these five words: rest and digestion for the parasympathetic system and fright, fight and flight for the sympathetic system. The parasympathetic nervous system stimulates anabolism, the building up of the body’s energy stores, and predominates during periods of rest. In contrast, the sympathetic nervous system stimulates catabolism, the breaking down of stored chemicals to release energy for physical activity and work, or dealing with threat and danger.

An interneuron together with a sensory afferent and motor efferent form a polysynaptic reflex (Figure 2.2); this comprises the initial stage of information input (sensory afferent), the processing/computing an appropriate response (interneurons) and the execution of a behavioural response (motor efferent). The simplest reflexes in the nervous system are monosynaptic reflexes, such as the familiar tendon (knee) jerk, these do not involve an interneuron. The sensory afferent activated by the mechano-receptor (the tap of the patellar hammer) forms a synapse with the motor efferent in the spinal cord, which then causes the skeletal muscle to contract and the crossed leg to jerk forward. With a synaptic delay of 1 millisecond (ms), the time between input and output increases with the number of synapses introduced into the circuit. As an
example, the knee jerk reflex typically takes around 30 ms (0.03 s) from the onset of the stimulus (tendon tap) to the behavioural response (contraction of the quadriceps muscle). Contrast this with the time it takes to process even the simplest piece of information. In a simple reaction time task you would be required to press a button as quickly as possible when a single, anticipated stimulus appeared on a screen. It usually takes humans upwards of 200 ms (0.2 s) between stimulus and response in this task. During a choice reaction task, when you would be required to respond as quickly as possible while making a decision about a stimulus or stimuli (e.g., whether it was the word “YES” or the word “NO” on the screen), your reaction time would typically increase to above 450 ms. Hence, reaction times increase as a function of the amount of information processing. They have proved very useful in human psychopharmacology, being very sensitive to drug effects. CNS-stimulant drugs reduce reaction time, whereas CNS-depressant drugs retard it; this has made reaction time a very useful index for the degree of stimulant or sedative drug action (Hindmarch et al., 1988).

The brain

In terms of understanding how medicinal and recreational psychoactive drugs affect behaviour, knowledge of the basic anatomy of the brain and spinal cord is required. To say the brain is the most complex organ in the human body is an obvious understatement. Some years ago Professor Steven Rose described it as two fistfuls of pink-grey tissue, wrinkled like a walnut and something of the consistency of porridge, [that] can store more information than all the computers and the libraries of the world can hold. Despite recent developments in information technology and artificial intelligence, the brain stills remains the greatest challenge for science (Rose, 1976, p. 21). For a more recent popular account of the brain, Greenfield (1998) is worth reading, while Barker et al. (1999) and Bloom et al. (2001) provide more detailed but useful overviews. For those who would like an even more in-depth coverage of neuroscience there are a number of full-colour textbooks (some with an accompanying CD-ROM) to recommend, including Carlson (1999), Kolb and Whishaw (2001), Matthews (2001), Nicholls et al. (2001) and Purves et al. (2001).

The 1.4-kg human brain is enclosed within the skull of the skeleton and protected by a triple layer of connective tissue called the meninges. Meningitis, or inflammation of the meninges caused by a virus or bacterium, is medically quite serious and can occasionally prove fatal. The outermost of the three layers, closest to the inside of the skull, is the dura mater, the innermost the pia mater, while the arachnoid membrane lies in-between them. Damage to the blood vessels in the pia mater (e.g., by cerebral trauma) allows blood to leak into the subarachnoid space between this layer and the arachnoid membrane, causing a subarachnoid haemorrhage. The brain is cushioned within the skull by a liquid, the cerebrospinal fluid, which circulates through four internal chambers. There are two lateral ventricles and a 3rd cerebral ventricle in the forebrain; these are linked via the cerebral aqueduct to the hindbrain’s 4th ventricle. This whole system acts as a general “shock absorber” for the brain and
reduces its effective weight by almost 95%. Obstruction of the flow of cerebrospinal fluid, arising either congenitally or from a tumour, results in the medical condition hydrocephalus.

Textbooks on neuroscience often describe the location and function of hundreds of individual brain regions (see references above). However, for current purposes these will be kept to a minimum (Figure 2.1). Anatomically, the brain can be subdivided into the forebrain containing the telencephalon and diencephalon, the midbrain or mesencephalon and the hindbrain (metencephalon and myelencephalon). The telencephalon includes the left and right cerebral hemispheres encompassed by the cerebral cortex (neocortex). Cortex is a translation of the word “bark” and is so-called because its surface, made up of numerous sulci (grooves or invaginations) and gyri (raised areas), is on the outer surface of the brain like the bark of a tree. Each hemisphere is divided into four lobes, named from the front (rostral) to back (caudal) of the brain: frontal, temporal, parietal and occipital.

The left and right hemispheres perform different functions (Greenfield, 1998), but somewhat surprisingly they have not been a focus for much psychopharmacological research; perhaps this will change in the future. The corpus callosum is a dense neuronal network that bridges the hemispheres and enables the overall integration of information. Damage to the corpus callosum results in a “split brain” where the left and right hemispheres operate independently. Within the cerebral cortex are discrete regions that integrate and interpret inputs from our environment. The primary somatosensory cortex together with its association area processes information from mechanoreceptors, nociceptors and thermoreceptors. The auditory, gustatory, olfactory and visual cortices and their respective association areas are involved in hearing, taste, olfaction and vision, respectively. The primary motor and premotor cortices, together with several extra-cortical structures, are involved in the central control of voluntary movement. The cerebral cortex together with the limbic system are important in emotional responses, learning and memory. Finally, there are a number of “higher cortical functions” that in terms of their level of complexity and sophistication delineate human beings from other primates; these are language and cognitive processes (cognition), including intelligence, reasoning, decision making, complex problem solving and consciousness.

Deep within the telencephalon are the subcortical limbic system and basal ganglia; these are a collection of networked structures involved in the regulation of a number of behaviours: moods and emotions, learning and memory (limbic system) and voluntary movement (basal ganglia). The major limbic structures are the hippocampus (memory) and amygdala (mood). The basal ganglia include the caudate nucleus and putamen (making up the corpus striatum, or neostriatum), globus pallidus and in the mesencephalon the substantia nigra. The limbic system and the basal ganglia connect “upstream” with the cerebral cortex and “downstream” with the hypothalamus (limbic system), thalamus (basal ganglia) and ANS – to produce a fully integrated response. The hypothalamus controls the release of hormones from the pituitary gland and indirectly influences the output from the adrenal cortex. This Hypothalamic–Pituitary–Adrenal (HPA) axis means that the limbic system interfaces with the endocrine system. Its functioning is important for health and well-being, but many types of drug can adversely influence its actions; this may help explain why so many forms of drug taking result in adverse health consequences.
The cerebellum is located in the metencephalon of the hindbrain, and like the basal ganglia it has an important role in the control of voluntary movement. The cerebellum is responsible for the execution of fine-controlled movements and the maintenance of posture and balance. The medulla oblongata of the myelencephalon provides the anatomical connection between the two parts of the CNS and contains a number of regions controlling autonomic and voluntary nervous system function; these are often referred to as brainstem reflexes (the brainstem comprising the medulla together with the pons) and include the vasomotor centre (blood pressure), cardiac centre, respiratory centre, vomiting centre and cough centre. Complete cessation of these reflexes is referred to as brainstem death and can occur with an overdose of CNS depressants (Chapter 9). Running through the core of the brainstem up into the thalamus is a dense neuronal network called the Ascending Reticular Activating System (ARAS). ARAS maintains arousal, and as sedative–hypnotic drugs reduce basic ARAS activity they induce sleepiness. In contrast, antipsychotic drugs, such as chlorpromazine, attenuate the sensory and cortical input into the ARAS; this leaves the person awake but less arousable, either by events in the environment or by their own thoughts and feelings; this is possibly the mechanism by which hallucinations and delusions are reduced (Chapter 11). The thalamus is the brain’s higher “relay station” where messages from sensory receptors via afferents to the spinal cord are processed for onward transmission to the cerebral cortex.

The neuron

Neurons were first described by Purkinje in 1839 (whose name is attached to a particular type found in the cerebellum), but much of our understanding of their structure comes through the pioneering work of Ramon y Cajal (cited in Raine, 1976). There are some 100 trillion (100,000,000,000,000) neurons in our nervous system, the vast majority of them located in the cerebral cortex. Each neuron can synapse and thus communicate with between 1,000 to 10,000 other neurons: a single gramme of brain tissue may contain up to 400 billion synapses. The neuron comprises a cell body (or soma), which contains various subcellular organelles, including nucleus, mitochondria, ribosomes and endoplasmic reticulum. Radiating outward is a profusion of dendrites and a longer and thicker axon emerging from the soma at the axon hillock (Figure 2.3). Visually, the neuron might be conceptually compared with a rolled-up hedgehog, with the dendrites being the spines. However, in a field of these “hedgehogs”, none of them would be visually similar; this is because the sizes and shapes of neurons are extremely variable. Indeed, they are the most polymorphic cells in the body, following no standard shape or size. Neurons may be unipolar (one axon), bipolar (one axon and one dendrite) or multipolar (one axon and many dendrites), and their axons may be of similar length to their dendrites, up to 100 mm in length.

The total human complement of neurons is laid down around birth, and if they die they cannot be replaced – unlike most cells in our body. However, this central dogma of neuroscience has been challenged by the recent finding that neurogenesis can occur in the adult rat hippocampus, and these new cells seem to be required for at least one type of memory (Shors et al., 2001). Whether this will also be the case in
humans is currently unknown. What is known is that from a relatively young age, neurons are lost at an apparently alarmingly high rate of 20,000 per day. Fortunately, given the total of 100 trillion, this number is somewhat insignificant. However cerebral trauma (head injury), neurodevelopmental insult in utero (some forms of schizophrenia?), senile dementia and some neurotoxic drugs (possibly MDMA, or methylenedioxymethamphetamine), may aggravate age-related neuronal loss and result in faster cognitive decline. If neurons do not increase in number, how then do we learn and remember things? Neurons modify the strength of existing synapses and form new synapses with their neighbours, and this underlies new learning and memory. Neuronal networks are not “rigid”, fixed in time and space, but rather demonstrate a degree of plasticity which even in comparatively simple nervous systems is exquisitely complex.

**Action potential**

Neurons are described as electrically excitable cells, having the ability to generate and propagate an electrical signal (current); this is referred to as the action potential, or nerve impulse. Like other cells, the internal compartment of neurons is separated from the outside by a plasma membrane. The unique information-processing capacity of neurons is partly due to the presence of a large electrochemical gradient across the plasma membrane of the neuron arising from the unequal separation of ions (charged molecules) on either side of the membrane. Sodium (Na\(^+\)) and chloride (Cl\(^-\)) ions are found at concentrations 10 times higher in the extracellular fluid outside the cell than inside it in the cytoplasm, while potassium (K\(^+\)) ion concentration is 20 times higher in the cytoplasm. However the concentration of calcium ions (Ca\(^{2+}\)) is up to 10,000 times higher in the extracellular fluid than in the cytoplasm. The overall difference in ion distribution across the membrane is termed “the electrochemical gradient” (when referring to the difference in charge between the inside and outside of the cell) or concentration gradient (when referring to the difference in ion concentration). The
difference in electrical charge for the cell at rest is approximately 70 mV (millivolts). The inside of the cell is negatively charged compared with the outside, and this is conventionally denoted as $-70 \text{mV}$, a value referred to as the resting membrane potential (Figure 2.4).

This electrochemical gradient arises from two core properties of the plasma membrane: first, its relative impermeability to all but K\textsuperscript{+} ions and, second, the presence of a highly active sodium/potassium pump, which drives any Na\textsuperscript{+} ions that have leaked into the cytoplasm back outside the cell, in exchange for those K\textsuperscript{+} ions that have left. Each sodium/potassium pump is extremely active, transporting hundreds of ions across the membrane per second. Since there are about a million such pumps on even a small neuron, the movement of these ions against the concentration gradient requires a great deal of energy; this is provided by adenosine triphosphate (ATP) (often described as the universal “energy currency” of nature). The hydrolysis (breakdown) of one ATP molecule releases around 31 kilojoules or 7 kilocalories of energy. Around 80% of the neuron’s energy production is used to fuel this Na\textsuperscript{+}/K\textsuperscript{+} pump, and since most ATP is synthesised via the aerobic breakdown of D-glucose the importance of an adequate supply of this carbohydrate and oxygen is evident. In Chapter 14 the roles of these chemicals are described more fully, since some cognitive enhancers may be influencing these basic metabolic processes. The crucial importance of energy is illustrated by the fact that, while the human brain comprises 2% of body weight, it consumes 20% of the body’s glucose and receives 20% of its cardiac output. This rate remains constant, day and night, sleeping or studying.

When a neuron is stimulated electrically, either artificially via electrodes or chemically via neurotransmitters or drugs, there is a rapid and transient reversal of the resting membrane potential; this is caused by the opening of normally closed voltage-operated sodium channels in the plasma membrane. The Na\textsuperscript{+} ions passively flow down their concentration gradient into the cytoplasm and slowly change the resting membrane potential from $-70 \text{mV}$ to the threshold potential of $-55 \text{mV}$. On reaching this threshold there is a rapid depolarisation to about $+30 \text{mV}$, which

![Figure 2.4. The action potential.](image-url)