49 Psychoactive drugs

OVERVIEW

In its broadest sense, the term 'psychoactive drug' would cover all drugs that act on the brain to produce changes in perception, mood, consciousness and behaviour, and would thus include anaesthetic, anxiolytic, antipsychotic and antidepressant drugs, which are described elsewhere in this book. Here we describe psychoactive drugs that are not covered in detail elsewhere. Some of these drugs have proven therapeutic usefulness in the treatment of behavioural disorders such as attention deficit/hyperactive disorder and narcolepsy. Others may prove to have clinical potential as cognition enhancers.

Many psychoactive drugs described in this chapter are used to alter mood and perception, or to satisfy addiction, and are drugs of abuse. This aspect is also discussed in Chapters 50 and 59.

Further information on psychoactive drugs is contained in Miller (2015).

INTRODUCTION

Attempting to classify psychoactive drugs according to their pharmacological mechanisms of action and their behavioural effects is a challenging task. Several of the drugs exert more than one important pharmacological action, drugs with apparently similar pharmacological activity can induce different subjective experiences (e.g. amphetamine and MDMA) and for a single drug the behavioural response may change with dose (e.g. ethanol induces excitement at low doses but is depressant at higher doses). Here, for convenience, we have grouped psychoactive drugs as

- Psychomotor stimulants
- Psychedelics
- Ketamine and related drugs
- Depressants
- Synthetic cannabinoids

The 21st century has seen an explosion in the availability of novel psychoactive substances (NPS). By and large, these have been developed to circumvent legal restrictions on more established drugs (e.g. amphetamines, cocaine, MDMA and cannabinoids) and were for a time referred to as 'legal highs'. This has led to changes in the law in the United Kingdom to make any NPS illegal. NPS are appearing so rapidly – over 600 were recorded between 2008 and 2015 – that any catalogue of them would likely be out of date by the time it had been compiled. In this chapter we concentrate on psychoactive drugs for which good evidence of their behavioural effects and mechanisms of action are available.

PSYCHOMOTOR STIMULANTS

Table 49.1 lists the major psychomotor stimulants, their mechanisms of action and clinical uses.

AMPHETAMINES[1]

DL-amphetamine (*speed* or *billy whizz*), its active dextroisomer **dextroamphetamine** (*dexies*), and **methamphetamine** (*crystal meth* or *ice*) have very similar chemical and pharmacological properties (Fig. 49.1).

Pharmacological effects

The amphetamines act by releasing monoamines, primarily dopamine and noradrenaline, from nerve terminals in the brain. They do this in a number of ways. They are substrates for the neuronal plasma membrane monoamine uptake transporters DAT and NET but not SERT (see Chs 15, 16 and 40), and thus act as competitive inhibitors, reducing the reuptake of dopamine and noradrenaline. In addition, they enter nerve terminals via the uptake processes or by diffusion and interact with the vesicular monoamine pump VMAT-2 to inhibit the uptake into synaptic vesicles of cytoplasmic dopamine and noradrenaline. The amphetamines are taken up into the storage vesicles by VMAT-2 and displace the endogenous monoamines from the vesicles into the cytoplasm. At high concentrations, amphetamines can inhibit monoamine oxidase, which otherwise would break down cytoplasmic monoamines, and monoamine oxidase inhibitors (see Ch. 48) potentiate the effects of amphetamine. The cytoplasmic monoamines can then be transported out of the nerve endings via the plasma membrane DAT and NET transporters working in reverse, a process that is thought to be facilitated by amphetamine binding to these transporters. All of the above will combine to increase the concentration of extracellular dopamine and noradrenaline in the vicinity of the synapse (see Chs 15 and 40).

In animals, prolonged administration results in degeneration of monoamine-containing nerve terminals and eventually cell death. This effect is observed with toxic doses and is probably due to the accumulation of reactive metabolites of the parent compounds within the nerve terminals. In human brain-imaging studies a reduction in the levels of

[1]As discussed in the Preface to this book, in Chapters 49 and 50, where mainly illicit drug use is being described, we use common drug names and spellings (e.g. amphetamine and heroin) rather than their recommended international non-proprietary names (amfetamine and 3,6-diacetyl morphine).

Table 49.1 Major central nervous system psychomotor stimulants

Drugs	Mode(s) of action	Clinical significance	Notes
Amphetamine and related compounds (e.g. dexamphetamine, methamphetamine)	Release of DA and NA Inhibition of DA and NA uptake	Dexamphetamine used to treat ADHD in children; otherwise very limited clinical use Some use to treat narcolepsy	Risk of dependence, sympathomimetic side effects and pulmonary hypertension Mainly important as drugs of abuse **Fenethylline** is a prodrug that is broken down to release both amphetamine and theophylline. It is a popular drug of abuse in Arab countries
Methylphenidate	Inhibition of DA and NA uptake	Used to treat ADHD in children.	Structurally related to amphetamines (see Fig. 49 1) **Ethylphenidate** has simi ar actions
Modafinil	Inhibition of DA reuptake	May have use to reduce fatigue and enhance cognition	—
Cocaine	Inhibition of DA, 5-HT and NA uptake Local anaesthetic	Risk of fetal damage Occasionally used for nasopharyngeal and ophthalmic anaesthesia (see Ch. 44)	Major drug of abuse
MDMA (ecstasy)	Releases 5-HT and inhibits uptake	May have potential in the treatment of post-traumatic stress disorder	Other related drugs are **3,4-methylenedioxyamphetamine** (MDA), **4-bromo-2,5-dimethoxyphenethylamine** (2CB) and **4-methylthioamphetamine** (4-MTA)
Paramethoxyamphetamine (PMA)	Releases 5-HT and blocks uptake	—	Often added to, or sold as, MDMA, **paramethoxymethamphetamine** (PMMA) is similar but less potent
Methylone	Inhibits NA, DA and 5-HT uptake	—	Cathinone derivative containing the dioxy ring of MDMA **Ethylone** and **butylone** are similar
Benzofuran derivatives	Releases 5-HT and NA and inhibit uptake	—	Have both MDMA and amphetamine-like properties Examples include **1-(benzofuran-5-yl)-propan-2-amine** (5APB) and **1-(benzofuran-6-yl)-propan-2-amine** (6APB)
Mephedrone	Inhibition of DA and 5-HT uptake	—	Drug of abuse Derived from cathinone **Methedrone** and **mexedrone** are similar
Benzylpiperazine (BZP)	Inhibition of DA, NA and 5-HT uptake α_2-adrenoceptor agonist, 5-HT_{2A} agonist	—	Drug of abuse
Methylxanthines (e g. caffeine, theophylline)	Inhibition of phosphodiesterase Antagonism of adenosine A_2 receptors	Theophylline used for action on cardiac and bronchial muscle (see Chs 22 and 29)	Caffeine is a constituent of beverages and tonics. It is also available in tablet form
Nicotine	Stimulates and desensitises nicotinic receptors (see Chs 14 and 40)	—	—
Arecoline	Muscarinic agonist	—	Mild stimulant contained in betel nut. Use is widespread in India, Thailand, Indonesia and other Asian countries

ADHD, attention deficit/hyperactivity disorder; *DA,* dopamine; *5-HT,* 5-hydroxytryptamine; *NA,* noradrenaline.

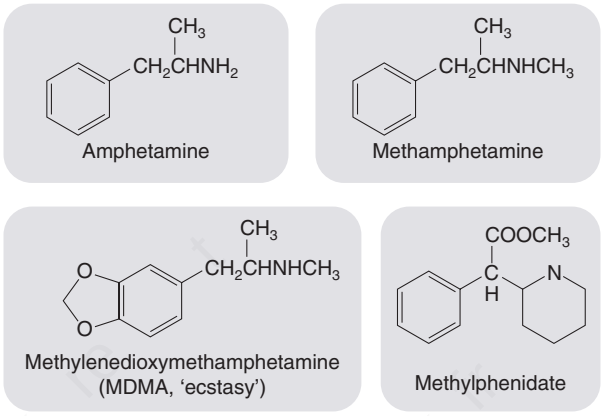

Fig. 49.1 Structures of amphetamine, MDMA and related drugs.

DAT and D_2 receptors has been observed in the brains of amphetamine users. It is unclear, however, whether this is due to long-term exposure to the drug inducing nerve damage or is an underlying pathology that was responsible for drug-seeking in the first instance.

The main central effects of amphetamine-like drugs are:

- locomotor stimulation
- euphoria and excitement
- insomnia
- increased stamina
- anorexia
- long-term psychological effects: psychotic symptoms, anxiety, depression and cognitive impairment

In addition, amphetamines have peripheral sympathomimetic actions (Ch. 15), producing a rise in blood pressure and inhibition of gastrointestinal motility.

In humans, amphetamines cause euphoria; with intravenous injection this can be so intense as to be described as 'orgasmic'. Rats quickly learn to press a lever in order to obtain a dose of amphetamine – an indication that the drug is rewarding. Humans become confident, hyperactive and talkative, and sex drive is said to be enhanced. Fatigue, both physical and mental, is reduced. Amphetamines (and similar drugs such as **dexfenfluramine** and **sibutramine**) cause marked anorexia, but with continued administration this effect wears off and food intake returns to normal. They are no longer used clinically for weight reduction (Ch. 33). They are ineffective in producing maintained weight loss, and their central nervous system (CNS) and cardiovascular effects are harmful.

Adverse effects of amphetamines include feelings of anxiety, irritability and restlessness. High doses may induce panic and paranoia.

The locomotor and rewarding effects of amphetamine are due mainly to release of dopamine rather than noradrenaline, since destruction of the dopamine-containing nucleus accumbens (see Ch. 40) or administration of D_2-receptor antagonists (see Ch. 47) inhibit these responses, which are absent in mice genetically engineered to lack DAT.

Chronic use, tolerance and dependence

If amphetamines are taken repeatedly over a few days, a state of 'amphetamine psychosis' can develop, resembling an acute schizophrenic attack (see Ch. 47), with hallucinations, paranoia and aggressive behaviour. At the same time, repetitive stereotyped behaviour may develop. The close similarity of this condition to schizophrenia, and the effectiveness of antipsychotic drugs in controlling it, is consistent with the dopamine theory of schizophrenia (see Ch. 47).

Tolerance develops rapidly to euphoric and anorexic effects of amphetamines, but more slowly to the other effects. Presumably tolerance is due to depletion of dopamine in nerve terminals.

Psychological dependence on amphetamines, a consequence of the insistent memory of euphoria, is very strong (see Ch. 50). When drug taking is stopped there is usually a period of deep sleep, and on awakening the subject feels lethargic, depressed, anxious, irritable (sometimes even suicidal) and hungry. These after effects may be the result of depletion of the normal stores of dopamine and noradrenaline. It is estimated that about 10%–15% of users progress to full dependence, the usual pattern being that the dose is increased as tolerance develops, and then uncontrolled 'binges' occur in which the user takes the drug repeatedly over a period of a day or more, remaining continuously intoxicated. Large doses may be consumed in such binges, with a high risk of acute toxicity, and the demand for the drug displaces all other considerations.

Experimental animals, given unlimited access to amphetamine, take it in such large amounts that they die from the cardiovascular effects within a few days Given limited amounts, they too develop a binge pattern of dependence.

Pharmacokinetic aspects

Amphetamines are readily absorbed from the gastrointestinal tract, but to increase the intensity of the hit the drugs can be snorted or injected. In crystal form, the free base of methamphetamine can be ignited and smoked in a manner similar to crack cocaine (see p 627). Amphetamines freely penetrate the blood–brain barrier. They do this more readily than other indirectly acting sympathomimetic amines such as **ephedrine** or **tyram ne** (Ch. 15), which probably explains why they produce more marked central effects than those drugs. Amphetamines are mainly excreted unchanged in the urine, and the rate of excretion is increased when the urine is made more acidic (see Fig. 10.6).

METHYLPHENIDATE

Methylphenidate (*Ritalin*) inhibits the NET and DAT transporters on the neuronal plasma membrane. Unlike the amphetamines, methylphenidate is not a substrate for these transporters and thus does not enter the nerve terminals to facilitate noradrenaline (NA) and dopamine (DA) release (Heal et al., 2009). It nevertheless produces a profound and sustained elevation of extracellular NA and DA.

Methylphenidate is orally active, being absorbed from the intestine, but it undergoes presystemic metabolism such that only ~20% enters the systemic circulation. Absorption is slow following oral administration – T_{max} ~2 hours which may limit the intensity of any euphoric response to the drug It is metabolised by carboxylesterase and has a half-life of ~2–4 h. It is used therapeutically to treat attention deficit/hyperactivity disorder (ADHD; see p 626) and may also have cognition-enhancing effects (see p. 633).

Amphetamines

- The main effects are:
  - increased motor activity
  - euphoria and excitement
  - insomnia
  - anorexia
  - with prolonged administration, stereotyped and psychotic behaviour
- Effects are due mainly to release of catecholamines especially dopamine and noradrenaline.
- Stimulant effect lasts for a few hours and is followed by depression and anxiety.
- Tolerance to the stimulant effects develops rapidly, although peripheral sympathomimetic effects may persist.
- Amphetamines induce strong psychological dependence.
- Amphetamine psychosis, which closely resembles schizophrenia, can develop after prolonged use.
- Amphetamines may be useful in treating narcolepsy, and also (paradoxically) to control hyperkinetic children. They are no longer prescribed as appetite suppressants.
- Their main importance is in drug abuse.

MODAFINIL

Modafinil is the primary metabolite of **adrafinil**, a drug that was introduced as a treatment for narcolepsy in the 1980s. Since 1994, modafinil has been available as a drug in its own right. It inhibits dopamine reuptake by binding to DAT but with low potency. In the human brain, modafinil blocks DAT and increases extracellular dopamine levels in the caudate, putamen and nucleus accumbens. It also produces a number of other effects including α_1-drenoceptor activation, enhanced release of 5-hydroxytryptamine (5-HT), glutamate and histamine, and inhibition of GABA release, as well as enhanced electrotonic coupling between neurons. The contribution of each action to the behavioural effects of modafinil remains to be clarified. Modafinil enhances some aspects of cognitive performance (see p. 633), and has gained popularity as a 'lifestyle drug' (see Ch. 59) for this reason.

Modafinil is well absorbed from the gut, metabolised in the liver and has a half-life of 10–14 h. While reported to 'brighten mood' there is little evidence that modafinil produces significant levels of euphoria when administered by mouth, but tablets can be crushed and snorted to obtain a quicker onset of effect. Modafinil is too insoluble for intravenous injection to be practical.

CLINICAL USE OF STIMULANTS

Attention deficit/hyperactivity disorder (ADHD)

The main use of amphetamines and me hylphenidate is in the treatment of ADHD, a common and increasingly diagnosed condition, estimated as occurring in up to 9% of children whose overactivity and limited attention span disrupt their education and social development. The efficacy of drug treatment (e.g. with methylphenidate) has been confirmed in controlled trials, but there is concern as to possible long-term adverse effects since treatment is sometimes continued into adolescence and beyond. Drug treatment should be part of a programme that includes psychological intervention if available, and is started after the diagnosis has been confirmed by an expert. Disorders of noradrenaline and dopamine pathways in the frontal cortex and basal ganglia are thought to underlie ADHD symptomatology, but there is still controversy over the relative importance of each monoamine and the specific brain regions involved in the actions of drugs used to alleviate the symptoms of ADHD.

Slow-release formulations of amphetamine and methylphenidate have been developed to deliver more stable concentrations of drug, lower than that required to produce euphoria. D-amphetamine conjugated to lysine (**lisdexamphetamine**) is an inactive prodrug that, following oral administration, is cleaved enzymatically to release D-amphetamine, resulting in a slower onset of action and potentially a reduced abuse potential.

▼ Other drug treatments for ADHD include the noradrenaline reuptake inhibitor **atomoxetine** (Ch. 48), and α_2-adrenoceptor agonists such as **clonidine** and **guanfacine**. The monoamine uptake inhibitor modafinil is not approved for paediatric use but may be effective in adult ADHD, as is **bupropion**. **Melatonin** (Ch. 40) improves sleep patterns in ADHD sufferers The pharmacology of drugs used to treat ADHD is reviewed by Heal et al. (2009).

Narcolepsy

This is a rare, disabling sleep disturbance in which the patient suddenly and unpredictably falls asleep at frequent intervals during the day, while suffering nocturnal insomnia. Amphetamine is helpful but not completely effective. Modafinil is also effective in reducing attacks. Narcolepsy is often accompanied by *cataplexy* (abrupt onset of paralysis of variable extent often triggered by emotion, sometimes with 'frozen' posture). Treatment is usually with **fluoxetine**, a selective 5-HT reuptake inhibitor or **venlafaxine,** a 5-HT and norepinephrine reuptake inhibitor (see Ch. 48). **Sodium oxybate**, the sodium salt of γ-hydroxybutyrate (also known as GHB and frequently abused, see Ch. 39), is a CNS depressant that paradoxically is used to prevent cataplexy.

Clinical uses of CNS stimulants

- Central nervous system (CNS) stimulants have few legitimate therapeutic indications. Where appropriate they are usually initiated by experts.
- Attention deficit/hyperactivity disorder (ADHD): **methylphenidate**, **atomoxetine** (see Ch. 48). **Dexamphetamine** is an alternative in children who do not respond.
- Narcolepsy: **modafinil** for the excessive sleepiness; **oxybate** to reduce cataplexy (which can be associated with narcolepsy).
- Apnoea of prematurity: *xanthine alkaloids* (under expert supervision in hospital) are effective; **caffeine** is preferred to **theophylline**.

COCAINE

Cocaine is found in the leaves of the South American shrub coca. These leaves are used for their stimulant properties by natives of South America, particularly those in mountainous

areas, who use it to reduce fatigue during work at high altitude.

Considerable mystical significance was attached to the powers of cocaine to boost the flagging human spirit, and Freud tested it extensively on his patients and his family, publishing an influential monograph in 1884 advocating its use as a psychostimulant.[2] Freud's ophthalmologist colleague, Köller, obtained supplies of the drug and discovered its local anaesthetic action (Ch. 44), but the psychostimulant effects of cocaine have not proved to be clinically useful. On the other hand, they led to it becoming a widespread drug of abuse in Western countries. The mechanisms and treatment of cocaine abuse are discussed in Chapter 50.

Pharmacological effects

Cocaine binds to and inhibits the transporters NET, DAT and SERT (see Chs 15, 16 and 40), thereby producing a marked psychomotor stimulant effect, and enhancing the peripheral effects of sympathetic nerve activity.

In humans, cocaine produces euphoria, garrulousness, increased motor activity and a magnification of pleasure. Users feel alert, energetic and physically strong and believe they have enhanced mental capabilities. Its effects resemble those of amphetamines, although it has less tendency to produce stereotyped behaviour, delusions, hallucinations and paranoia Evidence from transgenic knock-out mice indicates that the euphoric effects of cocaine involve inhibition of both dopamine and 5-HT reuptake The peripheral sympathomimetic actions lead to tachycardia, vasoconstriction and an increase in blood pressure. Body temperature may increase, owing to the increased motor activity coupled with reduced heat loss. With excessive dosage, tremors and convulsions, followed by respiratory and vasomotor depression, may occur.

Experimental animals rapidly learn to press a lever to self-administer cocaine and will consume toxic amounts of the drug if access is not limited. In transgenic mice lacking the D_2 receptor, the enhanced locomotor effects of cocaine are reduced, but surprisingly self-administration of cocaine is increased, in contrast to what is found with other self-administered drugs such as ethanol and morphine

Chronic use, dependence and tolerance

Cocaine undoubtedly causes strong psychological dependence (see Ch. 50), but there is some debate about whether or not its continued use induces tolerance and physical dependence. Users may increase their intake of the drug but this may reflect a desire for an increased effect rather than the development of tolerance. In experimental animals, sensitisation (the opposite of tolerance) can be observed but the relevance of this to the situation in humans is unclear. Cocaine does not produce a clear-cut withdrawal syndrome but depression, dysphoria and fatigue may be experienced following the initial stimulant effect. Cocaine induces psychological dependence where users crave the drug's euphoric and stimulatory effects. The cellular mechanisms underlying craving, and pharmacological approaches to reduce craving, are discussed in Chapter 50. The pattern of dependence, evolving from occasional use through escalating dosage to compulsive binges is similar to that seen with amphetamines.

Pharmacokinetic aspects

Cocaine is readily absorbed by many routes. For many years illicit supplies have consisted of the hydrochloride salt, which could be taken by nasal inhalation or intravenously. The latter route produces an intense and immediate euphoria, whereas nasal inhalation produces a less dramatic sensation and also tends to cause atrophy and necrosis of the nasal mucosa and septum.

Cocaine use increased dramatically when the f ee-base form ('crack') became available as a street drug When an aqueous solution of cocaine hydrochloride is heated with sodium bicarbonate, free-base cocaine, water, CO_2 and NaCl are produced. The free-base cocaine is insoluble in water, precipitates out and can then be rolled into 'rocks' of crack. Free-base cocaine vaporises at around 90°C, much lower than the melting point of cocaine hydrochloride (190°C), which burns rather than vaporises. Thus crack can be smoked, with the uncharged free base being rapidly absorbed across the large surface area of the alveolae, giving rise to a greater CNS effect than that obtained by snorting cocaine. Indeed, the effect is nearly as rapid as that of intravenous administration. The social, economic and even political consequences of this small change in formulation have been far-reaching.

The duration of its stimulant effect, about 30 min, is much shorter than that of amphetamine. It is rapidly metabolised in the liver. Heroin users may inject cocaine and heroin together intravenously (known as *speedballing*) to obtain the rapid effect of cocaine before the prolonged effect of heroin kicks in.

A cocaine metabolite is deposited in hair, and analysis of its content along the hair shaft allows the pattern of cocaine consumption to be monitored, a technique that has revealed a much higher incidence of cocaine use than was voluntarily reported. Cocaine exposure in utero can be estimated from analysis of the hair of neonates.

Cocaine is still occasionally used topically as a local anaesthetic, mainly in ophthalmology and minor nose and throat surgery, where its local vasoconstrictor action is an advantage, but has no other clinical uses.

Adverse effects

Toxic effects occur commonly in cocaine abusers. The main acute dangers are serious cardiovascular events (cardiac dysrhythmias, aortic dissection, and myocardial or cerebral infarction or haemorrhage). Progressive myocardial damage can lead to heart failure, even in the absence of a history of acute cardiac effects.

Cocaine can severely impair brain development in utero. The brain size is significantly reduced in babies exposed to cocaine in pregnancy, and neurological and limb malformations are increased. The incidence of ischaemic and haemorrhagic brain lesions, and of sudden infant death, is also higher in cocaine-exposed babies. Interpretation of the data is difficult because many cocaine abusers also take other illicit drugs that may affect fetal development, but the probability is that cocaine is highly detrimental.

[2]In the 1860s a Corsican pharmacist, Mariani devised cocaine-containing beverages, Vin Mariani and Thé Mariani, which were sold very successfully as tonics. Imitators soon moved in, and Thé Mariani became the forerunner of Coca-Cola. In 1903, cocaine was removed from Coca-Cola because of its growing association with addiction and criminality.

Dependence, the main psychological adverse effect of amphetamines and cocaine, has potentially severe effects on quality of life (Ch. 50).

Cocaine

- **Cocaine** acts by inhibiting catecholamine uptake (especially dopamine) by nerve terminals.
- Behavioural effects of cocaine are very similar to those of amphetamines, although psychotomimetic effects are rarer. Duration of action is shorter.
- **Cocaine** used in pregnancy impairs fetal development and may produce fetal malformations
- **Cocaine** produces strong psychological dependence.

MDMA

MDMA (3,4-methylenedioxymethamphetamine, 'ecstasy' or 'molly') and related drugs are widely used as 'party drugs' because of the feelings of empathy and euphoria, and the loss of inhibitions, heightened sensations and energy surge, that they produce. They are sometimes referred to as 'empathogens' or 'enactogens'. They also have mild hallucinogenic effects. Common examples are listed in Table 49.1 In conjunction with psychotherapy MDMA is in phase III clinical trials for the treatment of post-traumatic stress disorder.

Pharmacological effects

Although an amphetamine derivative (see Fig. 49.1), MDMA affects monoamine function in a different manner from the amphetamines. It inhibits monoamine transporters, principally the 5-HT transporter, and also releases 5-HT, the net effect being a large increase in free 5-HT in certain brain regions, followed by depletion. Similar but smaller changes occur in relation to dopamine and noradrenaline release. Simplistically, the effects on 5-HT function determine the psychotomimetic effects, while dopamine and noradrenaline changes account for the initial euphoria and later rebound dysphoria. MDMA does not induce psychological or physical dependence but its use carries serious risks. Unintentional consumption of high doses may occur if pills have a higher than expected MDMA content or when MDMA is taken in powdered form. Also, illicit MDMA tablets or powders may be contaminated with or entirely substituted with ***para*-methoxyamphetamine** (PMA) a more dangerous psychoactive agent.

Common adverse effects of MDMA ingestion are:

- Acute hyperthermia (Fig. 49.2), resulting in damage to skeletal muscle and consequent renal failure. It is still unclear how hyperthermia is produced in humans. It may be mediated centrally through release of 5-HT, dopamine and noradrenaline acting on various receptors for these monoamines (Docherty & Green, 2010). It could also reflect an action of MDMA on mitochondrial function. It is exacerbated by energetic dancing and high ambient temperature and certain individuals may be particularly susceptible to this danger.
- Excess water intake and water retention. Users may consume large amounts of water as a result of increased physical activity and feeling hot. In addition, MDMA causes inappropriate secretion of antidiuretic hormone (see Ch. 34). This can lead to overhydration and hyponatraemia ('water intoxication'). Symptoms include dizziness and disorientation, leading to collapse into coma.
- Heart failure in individuals with an undiagnosed heart condition.

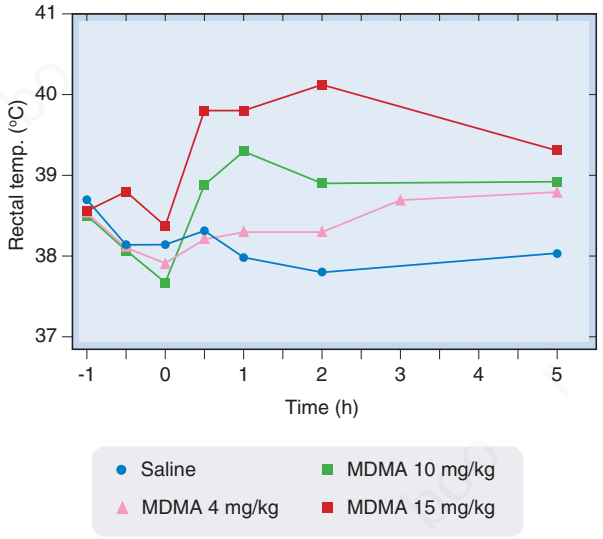

Fig. 49.2 A single injection of MDMA causes a dose-related increase in body temperature in rats. Drug administered at time zero. (Reproduced with permission from Green et al., 2004. Eur. J. Pharmacol. 500, 3–13.)

The after effects of MDMA persist for a few days and comprise depression, anxiety, irritability and increased aggression – the 'mid-week blues'. There is also evidence of long-term deleterious effects on memory and cognitive function in heavy MDMA users. In animal studies, MDMA can cause degeneration of 5-HT and dopamine neurons, but whether this occurs in humans is uncertain (see Green et al., 2012).

MDMA (ecstasy)

- **MDMA** is an amphetamine analogue that has powerful psychostimulant as well as mild psychotomimetic effects.
- **MDMA** inhibits monoamine transporters, principally the 5-hydroxytryptamine (5-HT) transporter, and releases 5-HT.
- **MDMA** can cause an acute hyperthermic reaction as well as overhydration and hyponatraemia, sometimes fatal.
- **MDMA** does not cause physical dependence.

CATHINONES

Cathinone and **cathine** are the active ingredients in the khat shrub. Chewing the leaves is popular in parts of Africa, such as Ethiopia and Somalia, and its use is spreading through immigrant populations in Western countries.

Synthetic cathinone derivatives have become popular street drugs as they produce feelings of elevated mood and improved mental function. **Mephedrone** elevates extracellular levels of both dopamine and 5-HT, possibly by inhibiting reuptake and enhancing release.

METHYLXANTHINES

Various beverages, particularly tea, coffee and cocoa, contain methylxanthines, to which they owe their mild central stimulant effects. The main compounds responsible are **caffeine** and **theophylline**. The nuts of the cola plant also contain caffeine, which is present in cola-flavoured soft drinks. However, the most important sources, by far, are coffee and tea, which account for more than 90% of caffeine consumption. Further information on the pharmacology and toxicology of caffeine is presented by Fredholm et al. (1999).

Pharmacological effects

Methylxanthines have the following major pharmacological actions:

- CNS stimulation
- mild diuresis, not clinically significant
- stimulation of cardiac muscle (see Ch. 22)
- relaxation of smooth muscle, especially bronchial muscle (see Ch. 29)

The latter two effects resemble those of β-adrenoceptor stimulation (see Chs 15, 22 and 29). This is thought to be because methylxanthines (especially **theophylline**) inhibit phosphodiesterase, which is responsible for the intracellular metabolism of cAMP (Ch. 3). They thus increase intracellular cAMP and produce effects that mimic those of mediators that stimulate adenylyl cyclase. Methylxanthines also antagonise many of the effects of adenosine, acting on both A_1 and A_2 receptors (see Ch. 17). Transgenic mice lacking functional A_2 receptors are abnormally active and aggressive, and fail to show increased motor activity in response to caffeine, suggesting that antagonism at A_2 receptors accounts for part, at least, of its CNS stimulant action. Caffeine also sensitises ryanodine receptors (see Ch. 4) but this effect occurs at higher concentrations (>10 mmol/L) than those achieved by recreational intake of caffeine. The concentration of caffeine reached in plasma and brain after two or three cups of strong coffee – about 100 μmol/L – is sufficient to produce appreciable adenosine receptor block and a small degree of phosphodiesterase inhibition. Adenosine receptor block probably causes the diuretic effect by reducing proximal tubular reabsorption of sodium.

Caffeine and theophylline have very similar stimulant effects on the CNS. Human subjects experience a reduction of fatigue, with improved concentration and a clearer flow of thought. This is confirmed by objective studies, which have shown that caffeine reduces reaction time and produces an increase in the speed at which simple calculations can be performed (although without much improvement in accuracy). Performance at motor tasks, such as typing and simulated driving, is also improved, particularly in fatigued subjects. Mental tasks, such as syllable learning, association tests and so on, are also facilitated by moderate doses (up to about 200 mg of caffeine, or about two cups of coffee) but impaired by larger doses Insomnia is common. By comparison with amphetamines, methylxanthines produce less locomotor stimulation and do not induce euphoria, stereotyped behaviour patterns or a psychotic state, but their effects on fatigue and mental function are similar.

Tolerance and habituation develop to a small extent, but much less than with amphetamines; withdrawal effects are modest but can be troublesome.[3] Caffeine is not self-administered by animals, and it cannot be classified as a dependence-producing drug.

Clinical use and unwanted effects

There are few clinical uses for caffeine. It is included with aspirin in some preparations for treating headaches and other aches and pains, and with ergotamine in some antimigraine preparations, the objective being to produce a mildly agreeable sense of alertness. Methylxanthines are effective respiratory stimulants in the treatment of apnoea of prematurity (a developmental disorder caused by immaturity of central respiratory control), for which indication caffeine is preferred to theophylline because of its long half-life and safety. Theophylline (formulated as **aminophylline**) is used mainly as a bronchodilator in treating severe asthmatic attacks (see Ch. 29). In vitro tests show that it has mutagenic activity, and large doses are teratogenic in animals. However, epidemiological studies have shown no evidence of carcinogenic or teratogenic effects of tea or coffee drinking in humans.

Methylxanthines

- **Caffeine** and **theophylline** produce psychomotor stimulant effects.
- Average **caffeine** consumption from beverages is about 200 mg/day.
- Main psychological effects are reduced fatigue and improved mental performance, without euphoria. Even large doses do not cause stereotyped behaviour or psychotomimetic effects.
- Methylxanthines act mainly by antagonism at A_2 purine receptors, and partly by inhibiting phosphodiesterase.
- Peripheral actions are exerted mainly on heart, smooth muscle and kidney.
- **Theophylline** is used clinically as a bronchodilator; **caffeine** is used as a respiratory stimulant for apnoea of prematurity and as an additive in many beverages and over-the-counter analgesics.

NICOTINE

Nicotine[4] is the psychoactive ingredient in tobacco.

Tobacco growing, chewing and smoking was indigenous throughout the American subcontinent and Australia at the time that European explorers first visited these places. Smoking spread through Europe during the 16th century,

[3]Caffeine withdrawal symptoms are a well-recognised cause of adverse events (headache, irritability) in residential phase I clinical trial units where caffeine-containing beverages are routinely prohibited

[4]From the plant *Nicotiana*, named after Jean Nicot, French ambassador to Portugal who presented seeds to the French king in 1560, having been persuaded by natives of South America of the medical value of smoking tobacco leaves. Smoking was believed to protect against illness, particularly the plague.

coming to England mainly as a result of its enthusiastic espousal by Walter Raleigh at the court of Elizabeth I. James I strongly disapproved of both Raleigh and tobacco, and in the early 17th century initiated the first antismoking campaign, with the support of the Royal College of Physicians. Parliament responded by imposing a substantial duty on tobacco, thereby giving the state an economic interest in the continuation of smoking at the same time that its official expert advisers were issuing emphatic warnings about its dangers.

Until the latter half of the 19th century, tobacco was smoked in pipes, and primarily by men. Cigarette manufacture began at the end of the 19th century. Filter cigarettes (which give a lower delivery of carcinogenic tars and nicotine than standard cigarettes) and 'low-tar' cigarettes (which are also low in nicotine) became available in the 1950s and were thought to be less harmful.[5] More recently, the use of electronic cigarettes (e-cigarettes) to deliver nicotine, without the carcinogenic tars of cigarette smoke, has become popular. Laws banning smoking in public places and the increased use of e-cigarettes has led to a reduction in cigarette consumption in the United Kingdom.

PHARMACOLOGICAL EFFECTS OF NICOTINE

EFFECTS ON THE CNS

At the neuronal level, nicotine acts on nicotinic acetylcholine receptors (nAChRs) (see Ch. 40), which are widely expressed in the brain, particularly in the cortex and hippocampus, and are believed to play a role in cognitive function, as well as in the ventral tegmental area (VTA), from which dopaminergic neurons project to the nucleus accumbens (the reward pathway, Fig. 40.3). nAChRs are ligand-gated cation channels located both pre- and postsynaptically, causing, respectively, enhanced transmitter release and neuronal excitation (see Wonnacott et al., 2005). Nicotine increases the firing rate and phasic activity of VTA dopaminergic neurons (see Fig. 49.3). Of the various subtypes of nAChR (see Table 40.2), the α4β2, α6β2 and α7 subtypes have received most attention, but other subtypes may also be involved in the rewarding effects of nicotine. As well as activating the receptors, nicotine also causes desensitisation, so the effects of a dose of nicotine are diminished in animals after sustained exposure to the drug. Chronic nicotine administration leads to a substantial increase in the number of nAChRs (an effect opposite to that produced by sustained administration of most receptor agonists), which may represent an adaptive response to prolonged receptor desensitisation. It is likely that the overall effect of nicotine reflects a balance between activation of nAChRs, causing neuronal excitation, and desensitisation, causing synaptic block.

The higher level functioning of the brain, as reflected in the subjective sense of alertness or by the electroencephalography (EEG) pattern, can be affected in either direction by nicotine, according to dose and circumstances. Nicotine wakes people up when they are drowsy and calms them down when they are tense, and EEG recordings broadly bear this out. It also seems that small doses of nicotine tend to cause arousal, whereas large doses do the reverse. Tests of motor and sensory performance (e g. reaction time measurements or vigilance tests) in humans generally show improvement with nicotine, and nicotine enhances learning

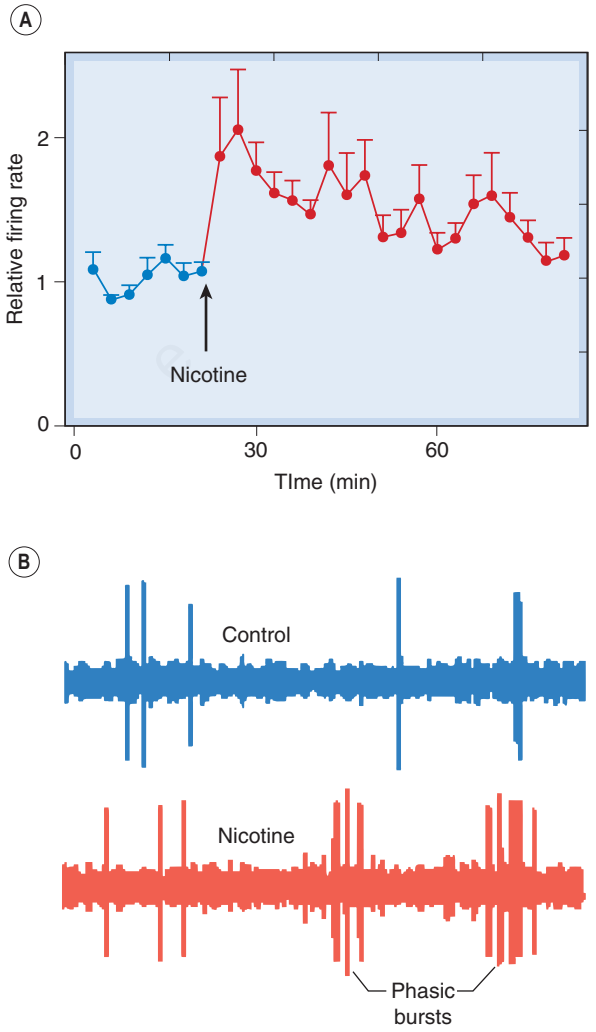

Fig. 49.3 Nicotine alters action potential firing characteristics of VTA dopaminergic neurons in freely moving rats. (A) Neuronal firing rate increases after nicotine injection i.p. (B) Action potential firing is phasic after nicotine injection. (Adapted from De Biasi et al., 2011.)

in rats. Nicotine and other nicotinic agonists such as **epibatidine** (Ch. 43) have significant analgesic activity in animal models, but, taken in the form of tobacco smoke or administered by other delivery systems such as patch or nasal spray, has only a weak analgesic effect in man.

Peripheral effects

The peripheral effects of small doses of nicotine result from stimulation of autonomic ganglia (see Ch. 14) and of peripheral sensory receptors, mainly in the heart and lungs. Stimulation of these receptors produces tachycardia, increased cardiac output and arterial pressure, sweating, and a reduction of gastrointestinal motility. When people take nicotine for the first time, they usually experience nausea and sometimes vomit, probably because of stimulation of sensory receptors in the stomach All these effects decline with repeated dosage, although the central effects remain. Secretion of adrenaline and noradrenaline from the adrenal medulla contributes to the cardiovascular effects,

[5]Smokers, however, adapt by smoking more low-tar cigarettes and inhaling more deeply to maintain their nicotine consumption.

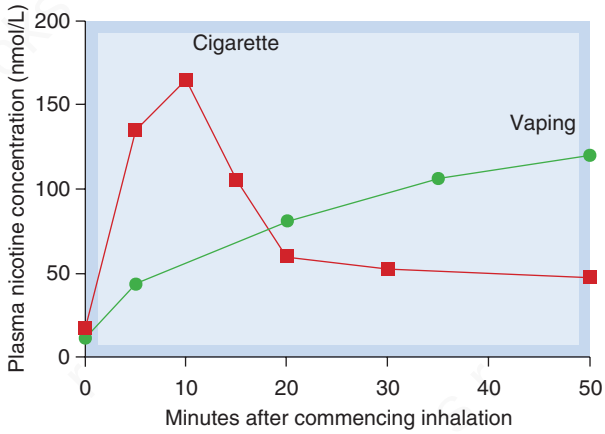

Fig. 49.4 Nicotine concentration in plasma during smoking or vaping. The subjects were habitual users who inhaled from a traditional cigarette or an e-cigarette according to their usual habit. (Data from Bowman, W.C., Rand, M., 1980. Chapter 4. In: Textbook of Pharmacology. Blackwell, Oxford and Farsalinos et al., 2015. Sci. Rep. 5, 11269.)

and release of antidiuretic hormone from the posterior pituitary causes a decrease in urine flow.[6] The plasma concentration of free fatty acids is increased, probably owing to sympathetic stimulation and adrenaline secretion.
Smokers weigh, on average, about 4 kg less than non-smokers, mainly because of reduced food intake; giving up smoking usually causes weight gain associated with increased food intake.

PHARMACOKINETIC ASPECTS

Nicotine is rapidly absorbed from the lungs but less readily from the mouth and nasopharynx.[7] Therefore inhalation is required to give appreciable absorption of nicotine, each puff delivering a distinct bolus of drug to the CNS. The amount of nicotine absorbed varies greatly with the habits of the user and the way in which nicotine is self-administered.

An average cigarette, smoked over 10 min, causes the plasma nicotine concentration to rise to 15–30 ng/mL (100–200 nmol/L), falling to about half within 10 min and then more slowly over the next 1–2 h (Fig. 49.4). The rapid decline results mainly from redistribution between the blood and other tissues; the slower decline is due to hepatic metabolism, mainly by oxidation to an inactive ketone metabolite, *cotinine*. This has a long plasma half-life, and measurement of urinary cotinine provides a useful indication of nicotine consumption.

E-cigarettes work by heating a liquid (usually propylene glycol and glycerin) to generate a vapour containing nicotine which is then inhaled (a process commonly referred to as vaping). Vaping avoids inhalation of the toxic chemicals present in tobacco smoke. Early e-cigarette devices were found to deliver only minimal amounts of nicotine to the user. However, the technology has advanced rapidly and new-generation devices have been developed that deliver more nicotine more rapidly, but as yet, not quite as fast as a traditional cigarette (see Fig. 49.4).
Other routes of nicotine administration that provide a more sustained delivery are used by smokers trying to quit. A transdermal nicotine patch applied for 24 h causes the plasma concentration of nicotine to rise to 75–150 nmol/L over 6 h and to remain fairly constant for about 20 h. Administration by nasal spray or chewing gum results in a time course intermediate between that of smoking and the nicotine patch.

TOLERANCE AND DEPENDENCE

As with other dependence-producing drugs, three separate processes – psychological dependence, physical dependence and tolerance – contribute to the overall state of dependence, in which taking the drug becomes compulsive. For reviews on nicotine and addiction see De Biasi et al (2011) and Leslie et al. (2013).

The effects of nicotine associated with peripheral ganglionic stimulation show rapid tolerance, perhaps as a result of desensitisation of nAChRs. With large doses of nicotine, this desensitisation produces a block of ganglionic transmission (see Ch. 14). Tolerance to the central effects of nicotine (e.g. in the arousal response) is much less than in the periphery. The increase in the number of nAChRs in the brain produced by chronic nicotine administration in animals also occurs in heavy smokers. Because the cellular effects of nicotine are diminished, it is possible that the additional binding sites represent desensitised rather than functional receptors.

The addictiveness of nicotine is due to the effects of the drug combined with the ritual of taking it (see Le Foll & Goldberg, 2005). Rats choose to drink dilute nicotine solution in preference to water if given a choice and in a situation in which lever pressing causes an injection of nicotine to be delivered – admittedly at high doses – they quickly learn to self-administer it. Similarly, monkeys who have been trained to smoke, by providing a reward in response to smoking behaviour, will continue to do so spontaneously (i.e. unrewarded) if the smoking medium contains nicotine, but not if nicotine-free tobacco is offered instead. Humans, however, are unlikely to become addicted to nicotine delivered from patches, suggesting that other factors are also involved, such as the controlled pulsatile delivery associated with smoking and vaping.

Like other addictive drugs, nicotine causes excitation of the mesolimbic reward pathway and increased dopamine release in the nucleus accumbens. Transgenic mice lacking the β2 subunit of the nAChR lose the rewarding effect of nicotine and its dopamine-releasing effect, confirming the importance of the β2-containing nAChR subtypes and mesolimbic dopamine release in the response to nicotine. In contrast to normal mice, the mutant mice could not be induced to self-administer nicotine, even though they did so with cocaine.

In contrast to euphoria, induction of physical dependence involves nicotinic receptors containing α5 and β4 subunits in the medial habenula–interpeduncular nucleus pathway. A physical withdrawal syndrome occurs in humans on cessation of smoking. Its main features are increased irritability, impaired performance of psychomotor tasks, aggressiveness and sleep disturbance. The withdrawal syndrome is much less severe than that produced by opioids, and can be alleviated by replacement nicotine. It lasts for 2–3

[6]This may explain why, in years gone by, men smoked cigars while chatting over drinks after dinner.
[7]Nicotine absorbed from cigar smoke is via the buccal mucosa but cigars deliver a much higher dose per puff than cigarettes, so a substantial amount gets in despite a low fraction absorbed.

weeks, although the craving for cigarettes persists for much longer than this; relapses during attempts to quit occur most commonly at a time when the physical withdrawal syndrome has long since subsided.

Pharmacology of nicotine

- At the cellular level, **nicotine** acts on nicotinic acetylcholine receptors (nAChRs) to enhance neurotransmitter release and increase neuronal excitation. Its central effects are blocked by receptor antagonists such as **mecamylamine**.
- At the behavioural level, nicotine produces a mixture of inhibitory and excitatory effects.
- **Nicotine** shows reinforcing properties, associated with increased activity in the mesolimbic dopaminergic pathway, and self-administration can be elicited in animal studies.
- Electroencephalography changes show an arousal response, and subjects report increased alertness accompanied by a reduction of anxiety and tension.
- Learning, particularly under stress, is facilitated by **nicotine**.
- Peripheral effects of **nicotine** are due mainly to ganglionic stimulation: tachycardia, increased blood pressure and reduced gastrointestinal motili y. Tolerance develops rapidly to these effects.
- **Nicotine** is metabolised to cotinine, mainly in the liver, within 1–2 h.
- **Nicotine** gives rise to tolerance physical dependence and psychological dependence (craving). Attempts at long-term cessation succeed in only about 20% of cases.
- **Nicotine** replacement therapy (e-cigarettes, chewing gum or skin patch preparations) improves the chances of giving up smoking when combined with active counselling.

HARMFUL EFFECTS OF TOBACCO SMOKING

The life expectancy of smokers is shorter than that of non-smokers. Smoking causes almost 90% of deaths from lung cancer, about 80% of deaths from bronchitis and emphysema, and 17% of deaths from heart disease. The increased use of e-cigarettes should reduce the number of such deaths. About one-third of all cancer deaths can be attributed to smoking. Smoking is, by a large margin, the biggest preventable cause of death, responsible for about 1 in 10 adult deaths worldwide. Despite the introduction of e-cigarettes, deaths from smoking worldwide are continuing to rise. In 2015, it was estimated that smoking was responsible for some 6.4 million deaths (and approximately 800,000 additional deaths of non-smokers from involuntary secondary inhalation).

The main health risks are as follows:

- *Cancer, particularly of the lung and upper respiratory tract but also of the oesophagus, pancreas and bladder.* Smoking 20 cigarettes per day is estimated to increase the risk of lung cancer about 10-fold Tar, rather than nicotine, is responsible for the cancer risk. Genetic variants of nicotinic-receptor subunits have been associated with lung cancer although the mechanisms behind this association are unclear (see Hung et al., 2008).
- *Coronary heart disease and other forms of peripheral vascular disease.* The mortality among men aged 55–64 from coronary thrombosis is about 60% greater in men who smoke 20 cigarettes per day than in non-smokers. Although the increase in risk is less than it is for lung cancer, the actual number of excess deaths associated with smoking is larger, because coronary heart disease is so common. Other kinds of vascular disease (e.g. stroke, intermittent claudication and diabetic gangrene) are also strongly smoking related. E-cigarettes and nicotine preparations, used to help smokers give up cigarettes, are not thought to carry a serious risk Carbon monoxide (see later) could be a factor. However, there is no clear increase in ischaemic heart disease in pipe and cigar smokers, even though similar blood nicotine and carboxyhaemoglobin concentrations are reached, suggesting that other factors may be responsible for the risk associated with cigarettes.
  Chronic obstructive pulmonary disease (COPD; see Ch. 29) is a major global health problem. Cigarette smoking is the main cause. Stopping smoking slows the progression of the disease. Bronchitis, inflammation of the mucous membranes of the bronchi, is much more common in smokers than in non-smokers. These effects are probably due to tar and other irritants rather than nicotine.
- *Harmful effects in pregnancy.* Smoking, particularly during the latter half of pregnancy, significantly reduces birth weight (by about 8% in women who smoke 25 or more cigarettes per day during pregnancy) and increases perinatal mortality (by an estimated 28% in babies born to mothers who smoke in the last half of pregnancy). There is evidence that children born to smoking mothers remain behind, in both physical and mental development, for at least 7 years. By 11 years of age, the difference is no longer significant. These effects of smoking, although measurable, are much smaller than the effects of other factors, such as social class and birth order. Various other complications of pregnancy are also more common in women who smoke, including spontaneous abortion (increased 30%–70% by smoking) premature delivery (increased about 40%) and placenta praevia (where the placenta obstructs normal vaginal delivery, increased 25%–90%). Nicotine is excreted in breast milk in sufficient amounts to cause tachycardia in the infant.

The agents probably responsible for the harmful effects are as follows:

- Tar and irritants, such as nitrogen dioxide and formaldehyde. Cigarette smoke tar contains many known carcinogenic hydrocarbons, as well as tumour promoters, which together account for the high cancer risk. It is likely that the various irritant substances are also responsible for the increase in bronchitis and emphysema.
- Nicotine probably accounts for retarded fetal development because of its vasoconstrictor properties.
- Carbon monoxide. Cigarette smoke contains about 3% carbon monoxide. Carbon monoxide has a high

affinity for haemoglobin, and the average carboxyhaemoglobin content in the blood of cigarette smokers is about 2.5% (compared with 0.4% for non-smoking urban dwellers). In very heavy smokers, up to 15% of haemoglobin may be carboxylated, a level that affects fetal development in rats. Fetal haemoglobin has a higher affinity for carbon monoxide than adult haemoglobin, and the proportion of carboxyhaemoglobin is higher in fetal than in maternal blood.
- Increased oxidative stress may contribute to atherogenesis (Ch. 24) and COPD (Ch. 29).

OTHER EFFECTS OF TOBACCO SMOKING

Parkinson's disease is approximately twice as common in non-smokers as in smokers. It is possible that this reflects a protective effect of nicotine. Ulcerative colitis appears to be a disease of non-smokers. Former smokers are at high risk for developing ulcerative colitis, while current smokers have the least risk. This tendency indicates that smoking cigarettes may prevent the onset of ulcerative colitis. In contrast, smoking tends to worsen the effects of Crohn's disease (another type of inflammatory bowel disease). Earlier reports that Alzheimer's disease is less common in smokers have not been confirmed; indeed there is evidence that smoking may increase the occurrence of Alzheimer's disease in some genetic groups.

Effects of tobacco smoking

- Smoking accounts for more than 10% of deaths worldwide, mainly due to:
  - cancer, especially lung cancer, of which about 90% of cases are smoking related; carcinogenic tars are responsible;
  - chronic bronchitis; tars are mainly responsible.
- Smoking in pregnancy reduces birth weight and retards childhood development. It also increases abortion rate and perinatal mortality. **Nicotine** and possibly carbon monoxide are responsible.
- Use of e-cigarettes (vaping) avoids the inhalation of tar and carbon monoxide that occurs with smoking.
- The incidence of Parkinson's disease is lower in smokers than in non-smokers.

COGNITION-ENHANCING DRUGS

'Cognition' embraces many aspects of mental function, including memory, reasoning and problem-solving skills, situational judgements, decision-making and executive function. A variety of different test batteries have been designed to measure these functions in humans (e.g. Cambridge Neuropsychological Test Automated Battery, CANTAB) and test the effects of drugs. Many clinical disorders, such as Alzheimer's disease (Ch. 41), schizophrenia (Ch. 47), depression (Ch. 48) and drug addiction (Ch. 50) impair these functions, and the hope is to develop cognition-enhancing drugs to restore them. Progress has been limited, though much hyped, as much with the questionable aim of 'improving mental function in healthy humans, as in alleviating deficits in the sick.

Drugs currently available have been shown to:

- alter memory processing (i.e. enhance memory);
- reduce fatigue (stimulants), thus permitting the user to function for longer (i.e. perform complex tasks, study for examinations, overcome jet lag);
- increase motivation, energy, confidence and concentration.

They are also referred to as 'smart drugs' or 'nootropics'

Drugs reported to enhance cognitive performance are caffeine, amphetamines, methylphenidate, modafinil, arecoline, **donepezil**, **vortioxetine** and **piracetam** but the clinical efficacy of these drugs is limited, and development of more effective cognition enhancers could have significant benefits for many patient groups.

Cognition-enhancing drugs are also used by healthy individuals a ming to enhance their performance e.g. in revising for and taking examinations (d'Angelo et al., 2017) or in demanding professional roles. The use of drugs by healthy individuals to enhance academic performance does raise ethical issues in relation to fairness, academic pressure and fears of coercion by 'pushy' parents. There are also safety issues. Although many of the drugs taken are available as medicines (i.e. have gone through standard drug safety testing) there is still a lack of information on their acute and long-term effects in children and adolescents whose brains are still in development. In healthy individuals, cognitive performance can be enhanced by improved sleep and mood as well as reduced anxiety. It would seem more appropriate to achieve this by lifestyle changes and behavioural therapy rather than resorting to the use of drugs.[8]

EFFECTIVENESS

While the effectiveness of cognition enhancers on healthy individuals is often trumpeted by individuals who use them and in the media, their actual effectiveness as assessed in scientific studies is somewhat inconclusive and ambiguous. Also, drugs may affect different forms of memory differently (d'Angelo et al., 2017). It is important to distinguish between drugs that only improve a subject's abilities when they are fatigued and those that might improve cognitive ability in non-fatigued individuals.

Many studies have shown that amphetamines improve mental performance in fatigued subjects. Mental performance is improved for simple tedious tasks much more than for difficult tasks. Amphetamines are thought to increase ability to focus and maintain self-control In addition to reducing fatigue, methylphenidate has a positive effect on long-term memory consolidation. Amphetamines and modafinil have been used to improve the performance of soldiers, military pilots and others who need to remain alert under extremely fatiguing conditions. Modafinil appears to enhance cognition in non-fatigued individuals (Battleday & Brem, 2015) while also improving wakefulness, memory and executive functions in sleep-deprived individuals. Evidence for efficacy in patients with chronic cognitive impairment is controversial.

[8]A new phenomenon is 'microdosing' with very small quantities of psychedelic drugs such as LSD, psilocybin or mescaline (see p. 634) every few days with the aim of improving concentration, creativity and problem solving. At such low doses users do not experience psychedelic effects. Properly controlled scientific studies are required to determine whether this form of drug taking really is effective.

NON-STIMULANT DRUGS

The novel antidepressant, vortioxetine (see Ch. 48), improves cognitive dysfunction in patients suffering from major depression.

Piracetam, which is a positive allosteric modulator at AMPA receptors (see Ch 39), enhances memory in non-fatigued adults, and there is limited clinical evidence of reading improvement in dyslexic children. **Phenylpiracetam** is said to be more potent and may also have nicotinic antagonist properties. As with many CNS disorders, the possible importance of glutamate and its receptors is widely speculated on, but new, effective drugs acting on the glutamatergic system are still awaited (see for example, Collingridge et al., 2013; Harms et al., 2013).

PSYCHEDELIC DRUGS

Psychedelic drugs (also sometimes referred to as *hallucinogenic* or *psychotomimetic* drugs) affect thought, perception and mood, without causing marked psychomotor stimulation or depression (see Nichols, 2004). Thoughts and perceptions tend to become distorted and dream-like, rather than being merely sharpened or dulled, and the change in mood is likewise more complex than a simple shift in the direction of euphoria or depression. Importantly, psychedelic drugs do not cause dependence. Common psychedelic drugs are listed in Table 49.2.

LSD PSILOCYBIN AND MESCALINE

Lysergic acid diethylamide (LSD) is an exceptionally potent psychotomimetic drug capable of producing strong effects in humans in doses less than 1 μg/kg. It is a chemical derivative of lysergic acid, which occurs in the cereal fungus ergot (see Ch. 16).

▼ LSD was first synthesised by Hoffman in 1943 Hoffman deliberately swallowed about 250 μg of LSD (the threshold dose is now known to be around 20 μg) and wrote 30 years later of the experience: 'the faces of those around me appeared as grotesque coloured masks … marked motoric unrest, alternating with paralysis … heavy feeling in the head, limbs and entire body, as if they were filled with lead … clear recognition of my condition, in which state I sometimes observed, in the manner of an independent observer, that I shouted half insanely.' These effects lasted for a few hours, after which Hoffman fell asleep, 'and awoke next morning feeling perfectly well.' Apart from these dramatic psychological effects, LSD has few physiological effects in humans at doses that cause hallucinations.

Mescaline, which is derived from the Mexican peyote cactus and has been known as a hallucinogenic agent for many centuries was made famous by Aldous Huxley in *The Doors of Perception*.

Psilocybin is obtained from fungi ('magic mushrooms'). It is rapidly dephosphorylated to psilocin, the active moiety. Its effects are similar to those experienced with LSD. The potential of psilocybin as a treatment for depression and some forms of anxiety is debated in Carhart-Harris and Gregory (2017).

Pharmacological effects

The main effects of these drugs are on mental function, most notably an alteration of perception in such a way that sights and sounds appear distorted and fantastic. Hallucinations – visual, auditory, tactile or olfactory – also occur, and sensory modalities may become confused, so that sounds are perceived as visions. Thought processes tend to become illogical and disconnected, but subjects retain insight into the fact that their disturbance is drug-induced, and generally find the experience exhilarating. Occasionally, especially if the user is already anxious, LSD produces a syndrome that is extremely disturbing (the 'bad trip'), in which the hallucinatory experience takes on a menacing quality and may be accompanied by paranoid delusions. 'Flashbacks' of the hallucinatory experience have been reported weeks or months later.

LSD acts on various 5-HT-receptor subtypes (see Chs 16 and 40); its psychotomimetic effects are thought to be mediated mainly by its 5-HT_{2A}-receptor agonist actions (see Nichols 2004). It inhibits the firing of 5-HT-containing neurons in the raphe nuclei (see Ch. 40), apparently by acting as an agonist on the inhibitory somatodendritic 5-HT_{1A} receptors on these cells. The significance of this response to its psychotomimetic effects is unclear. Psilocybin is dephosphorylated to psilocin, which is a weak agonist at several 5-HT receptors including the 5-HT_{2A} receptor. The mechanism of action of mescaline is less well defined. There are contradictory reports about its activity at 5-HT_{2A} receptors. It has also been reported to act as an inhibitor of monoamine transport.

Dependence and adverse effects

LSD, psilocybin and mescaline are seldom self-administered by experimental animals. Indeed, in contrast to most of the drugs that are widely abused by humans, they have aversive rather than reinforcing properties in behavioural tests Tolerance to their effects develops quite quickly, but there is no physical withdrawal syndrome in animals or humans.

Table 49.2 Major psychedelic drugs

Drugs	Mode(s) of action	Notes
LSD	Interacts with 5-HT and DA receptors Psychedelic effects are thought to be mainly through 5-HT_{2A} receptor activation	No current clinical use
Mescaline	Agonist at 5-HT_{2A} and other 5-HT receptors Chemically related to amphetamine	No current clinical use Found in Peyote cactus plant
Psilocybin	Rapidly metabolised to psilocin, a partial agonist at 5-HT_{2A} receptors Chemically related to 5-HT	No current clinical use May have potential for the treatment of depression and some forms of anxiety
Salvinorin A	κ Opioid receptor agonist (see Ch. 43)	No clinical use Found in *Salvia divinorum* (plant)

5-HT, 5-hydroxytryptamine; *DA*, dopamine; *LSD*, lysergic acid diethylamide.

The main effects of these psychedelic drugs are subjective, so it is not surprising that animal tests that reliably predict psychedelic activity in humans have not been devised.[9].

OTHER PSYCHEDELIC DRUGS

Salvinorin A is a hallucinogenic agent contained in the American sage plant *Salvia divinorum*, a member of the mint family. It was originally used by the Mazatecs in Mexico; in recent years its use has spread and it has become known as *herbal ecstasy*. It is a κ opioid receptor agonist (see Ch. 43).[10] It also produces dissociative effects (see later) and at high doses, delirium.

Other hallucinogens include **α–MT** (methyltryptamine) and **DMT** (dimethyltryptamine), which are naturally occurring and **DPT** (dipropyltryptamine) and **DOM** (2,5-dimethoxy-4-methylamphetamine).

Muscarinic receptor antagonists (see Chs 14 and 40), **hyoscine**, **hyoscyamine** and **atropine** are contained in various plants, including henbane and mandrake. Consumption can cause hallucinations, drowsiness and disorientation.

Ibogaine is contained in the root bark of iboga shrubs in Africa, South America and Australia. At high doses, it is hallucinogenic. Users have reported experiencing a reduced desire to take other drugs such as cocaine and heroin, leading to ibogaine being investigated as a potential treatment for drug craving (see Ch. 50).

Psychedelic drugs

- The main types are lysergic acid diethylamide (LSD), psilocybin and mescaline.
- They act as 5-hydroxytryptamine (5-HT)$_{2A}$ receptor agonists.
- They cause sensory distortion and hallucinatory experiences.
- **LSD** is exceptionally potent, producing a long-lasting sense of dissociation and disordered thought. Hallucinatory episodes can recur after a long interval.
- In animal behavioural tests, they exhibit aversive rather than rewarding properties.
- **Salvinorin A** is a κ opioid receptor agonist that causes hallucinatory and dissociative effects.

KETAMINE AND RELATED DRUGS

Ketamine ('Special K'), a dissociative anaesthetic (Ch. 42), is also used for its psychoactive properties (see Morgan & Curran, 2012). Its fore-runner **phencyclidine** (PCP, 'angel dust'), was a popular hallucinogen in the 1970s but its use has declined. These drugs produce a feeling of euphoria. At higher doses they cause hallucinations and feelings of detachment, disorientation and numbness. PCP was reported to cause psychotic episodes and is used in experimental animals to produce a model of schizophrenia (see Ch. 47 and Morris et al., 2005).

Pharmacological effects

The r main pharmacological effect is non-competitive block of the NMDA-receptor channel (see Ch. 39). **Methoxetamine**, a chemical derivative of ketamine, is an NMDA antagonist as well as an inhibitor of 5-HT reuptake, which may contribute to its CNS effects.

Adverse effects

Tolerance develops with repeated use of ketamine, resulting in higher doses being taken to achieve the same effect Repeated use is associated with serious and persistent toxic effects, including abdominal pain, ulcerative cystitis (with associated severe bladder pain), liver damage and cognitive impairment (Morgan & Curran, 2012). Combination of ketamine with depressant drugs such as **alcohol**, **barbiturates** and **heroin** can result in dangerous overdose.

Nitrous oxide is a weak general anaesthetic that acts as an antagonist at NMDA receptors (see Ch. 42). At low doses it produces feelings of euphoria – it is often referred to as 'laughing gas' – relaxation and dissociation.

DEPRESSANTS

Many CNS depressant drugs (Table 49.3) that are used for their psychoactive effects also have important therapeutic uses that are described in detail elsewhere in this book. Here we will concentrate on ethanol, which has little or

Table 49.3 Depressant drugs

Drugs	Described in detail in Chapter	Notes
Benzodiazepines (diazepam, temazepam, diclazepam)	45	Etizolam and pyrazolam are derived from benzodiazepines and act similarly
Zopiclone and other Z drugs	45	Short acting but similar effects to benzodiazepines
Gabapentin and pregabalin	46	Often taken in high doses to induce a feeling of drunkenness and stupor May enhance likelihood of overdose in opioid users
γ-Hydroxybutyric acid (GHB)	39	γ-Butyrolactone (GBL) and 1,4-butanediol (BD) are broken down to GHB in the body
Ethanol	This chapter	
Propofol	42	Sub-anaesthetic doses induce a general feeling of well-being, euphoria, and sexual disinhibition

[9]One of the more bizarre attempts involves spiders, whose normal elegantly symmetrical webs become jumbled and erratic if the animals are treated with LSD. Search the web (worldwide rather than arachnid) for 'spiders LSD' to see images.

[10]In phase I clinical trials of synthetic κ-opioid receptor agonists as potential analgesic agents, the drugs were reported to induce a feeling of dysphoria. Perhaps the 'normal' volunteers in those trials were disturbed by the hallucinations they probably experienced. Interesting then that a naturally occurring κ agonist has now become a drug of abuse.

no therapeutic value but is widely used in many countries for its psychoactive properties.

ETHANOL

It may at first seem strange to categorise ethanol as a depressant drug[11] given that its consumption in alcoholic beverages can make people excited, garrulous and violent. However, as with general anaesthetics (see Ch. 42), at low concentrations ethanol depresses inhibitions resulting in apparent behavioural stimulation whereas at higher concentrations all brain functions are depressed.

Judged on a molar basis, the consumption of ethanol far exceeds that of any other drug. The ethanol content of various drinks ranges from about 2.5% (weak beer) to about 55% (strong spirits), and the size of the normal measure is such that a single drink usually contains about 8–12 g (0.17–0.26 mol) of ethanol. Its low pha macological potency is reflected in the range of plasma concentrations needed to produce pharmacological effects: minimal effects occur at about 10 mmol/L (46 mg/100 mL), and 10 times this concentration may be lethal. The average per capita consumption of ethanol in the United Kingdom doubled between 1970 and 2007, but has fallen slightly since then. There has been an increase in non-drinkers, mainly amongst young people. Amongst those who do drink, the main changes have been a growing consumption of wine in preference to beer among adults, greater consumption in the home and an increasing tendency for binge drinking, especially among young people.

For practical purposes, ethanol intake is often expressed in terms of units. One unit is equal to 8 g (10 mL) of ethanol, and is the amount contained in half a pint of normal strength beer, one measure of spirits or one small glass of wine. The current UK government's guidelines state that for both men and women it is safest not to drink regularly more than 14 units per week, and that if as much as 14 units per week are drunk, it is best to spread this evenly over 3 days or more. It is estimated that in the United Kingdom, about 31% of men and 16% of women exceed these levels. Governments in most developed countries are attempting to curb alcohol consumption.

An excellent detailed review of all aspects of alcohol and alcoholism is provided by Spanagel (2009)

PHARMACOLOGICAL EFFECTS OF ETHANOL

Effects on CNS neurons

The main effects of ethanol are on the CNS, where its depressant actions resemble those of volatile anaesthetics (Ch. 42). At a neuronal level, the effect of ethanol is depressant, although it increases neuronal activity – presumably by disinhibition – in some parts of the CNS, notably in the mesolimbic dopaminergic pathway that is involved in reward. The main acute cellular effects of ethanol that occur at concentrations (5–100 mmol/L) relevant to alcohol consumption by humans are:

- enhancement of both GABA- and glycine-mediated inhibition
- inhibition of Ca^{2+} entry through voltage-gated calcium channels
- activation of certain types of K^+ channel
- inhibition of ionotropic glutamate receptor function
- inhibition of adenosine transport

For review, see Harris et al. (2008).

Ethanol enhances the action of GABA on $GABA_A$ receptors in a similar way to benzodiazepines (see Ch. 45). Its effect is, however, smaller and less consistent than that of benzodiazepines, and no clear effect on inhibitory synaptic transmission in the CNS has been demonstrated for ethanol. This may be because the effect of ethanol is seen only on some subtypes of $GABA_A$ receptor (see Ch. 39) e.g. the extrasynaptic $\alpha6\beta3\delta$ $GABA_A$ receptor subtype has been reported to be sensitive to ethanol. Ethanol may also act presynaptically to enhance GABA release.

Ethanol enhances glycine receptor function, due both to a direct interaction with the $\alpha1$ subunit of the glycine receptor and to indirect effects mediated through protein kinase C (PKC) activation. Ethanol can also enhance glycine release from nerve terminals.

Ethanol reduces transmitter release in response to nerve terminal depolarisation by inhibiting the opening of voltage-gated calcium channels in neurons. It also reduces neuronal excitability by activating G protein-activated inwardly rectifying K^+ (GIRK) channels as well as potentiating calcium-activated potassium (BK) channel activity.

The excitatory effects of glutamate are inhibited by ethanol at concentrations that produce CNS depressant effects in vivo. NMDA receptor activation is inhibited at lower ethanol concentrations than are required to affect AMPA receptors (see Ch. 39). Other effects produced by ethanol include an enhancement of the excitatory effects produced by activation of nAChRs and $5\text{-}HT_3$ receptors. The relative importance of these various effects in the overall effects of ethanol on CNS function is not clear.

The depressant effects of ethanol on neuronal function resemble those of adenosine acting on A_1 receptors (see Ch. 17). Ethanol in cell culture systems increases extracellular adenosine by inhibiting adenosine uptake, and there is some evidence that inhibition of the adenosine transporter may account for some of its CNS effects.

Endogenous opioids also play a role in the CNS effects of ethanol, because both human and animal studies show that the opioid receptor antagonist **naltrexone** reduces the reward associated with ethanol.

Behavioural effects

The effects of acute ethanol intoxication in humans are well known and include slurred speech, motor incoordination, increased self-confidence and euphoria. The effect on mood varies among individuals, most becoming louder and more outgoing, but some becoming morose and withdrawn. At higher levels of intoxication, the mood tends to become highly labile, with euphoria and melancholy, aggression and submission, often occurring successively. The association between alcohol consumption and violence is well documented.

Intellectual and motor performance and sensory discrimination are impaired by ethanol, but subjects are generally unable to judge this for themselves.[12] Much effort has gone

[11] In some countries ethanol is classed as a food, not a drug! This reflects the lobbying power of the alcohol industry. Ethanol meets the criteria for 'What is a drug?' given in Chapter 1.

[12] Bus drivers were asked to drive through a gap that they selected as the minimum for their bus to pass through; ethanol caused them not only to hit the barriers more often at any given gap setting, but also to set the gap to a narrower dimension, often narrower than the bus.

into measuring the effect of ethanol on driving performance in real life, as opposed to artificial tests under experimental conditions. In a US study of city drivers, it was found that the probability of being involved in an accident was unaffected at blood ethanol concentrations up to 50 mg/100 mL (10.9 mmol/L); by 80 mg/100 mL (17.4 mmol/L) the probability was increased about four-fold, and by 150 mg/100 mL (32.6 mmol/L) about 25-fold. In Scotland, driving with a blood ethanol concentration greater than 50 mg/100 mL is illegal whereas in the rest of the United Kingdom the legal limit is 80 mg/100 mL.

The relationship between plasma ethanol concentration and effect is highly variable. A given concentration produces a larger effect when the concentration is rising than when it is steady or falling. A substantial degree of cellular tolerance develops in habitual drinkers, with the result that a higher plasma ethanol concentration is needed to produce a given effect. In one study, 'gross intoxication' (assessed by a battery of tests that measured speech, gait and so on) occurred in 30% of subjects between 50 and 100 mg/100 mL and in 90% of subjects with more than 150 mg/100 mL. Coma generally occurs at about 400 mg/100 mL, and death from respiratory failure is likely at levels exceeding 500 mg/100 mL.

Ethanol significantly enhances – sometimes to a dangerous extent – the CNS depressant effects of many other drugs, including benzodiazepines, antidepressants, antipsychotic drugs and opioids.

Neurotoxicity

In addition to the acute effects of ethanol on the nervous system, chronic administration also causes irreversible neurological damage (see Harper & Matsumoto, 2005). This may be due to ethanol itself, or to metabolites such as acetaldehyde or fatty acid esters or to dietary deficiencies (e.g. of thiamine) that are common in alcoholics. Binge drinking is thought to produce greater damage; probably due to the high brain concentrations of ethanol achieved and to repeated phases of withdrawal between binges. Heavy drinkers often exhibit convulsions and may develop irreversible dementia and motor impairment associated with thinning of the cerebral cortex (apparent as ventricular enlargement) detectable by brain-imaging techniques. Degeneration of the cerebellar vermis, the mammillary bodies and other specific brain regions can also occur, as well as peripheral neuropathy.

Effects on other systems

The main acute cardiovascular effect of ethanol is to produce cutaneous vasodilatation, central in origin, which causes a warm feeling but actually increases heat loss.[13] It has been proposed that mild consumption of ethanol reduces the incidence of coronary heart disease, by increasing circulating levels of high-density lipoproteins (HDL) thus reducing the incidence of atherosclerosis (see Ch. 24). The much hyped notion that a glass of red wine each day (red wine contains the antioxidant, resveratrol) reduces coronary artery disease has come in for criticism in recent years. Moderate ethanol consumption may protect against ischaemic heart disease, especially in older people, perhaps partly by inhibiting platelet aggregation. This effect occurs at ethanol concentrations in the range achieved by moderate drinking (10–20 mmol/L) and probably results from inhibition of arachidonic acid formation from phospholipid. However, chronic or intermittent drinking of excessive amounts of ethanol causes raised blood pressure, which is one of the most important risk factors for having a heart attack or a stroke.

Diuresis is a familiar effect of ethanol. It is caused by inhibition of antidiuretic hormone secretion, and tolerance develops rapidly, so that the diuresis is not sustained. There is a similar inhibition of oxytocin secretion, which can delay parturition.

Ethanol increases salivary and gastric secretion, perhaps a reason in some cultures for the popularity of a glass of sherry before dinner. However, heavy consumption of spirits causes damage directly to the gastric mucosa, causing chronic gastritis. Both this and the increased acid secretion are factors in the high incidence of gastric bleeding in alcoholics. CNS depression predisposes to aspiration pneumonia and lung abscess formation. Acute pancreatitis may become chronic with pseudocyst formation (collections of fluid in the peritoneal sac), fat malabsorption and ultimately loss of B-cell function, and insulin-dependent diabetes mellitus.

Ethanol produces a variety of endocrine effects. In particular, it increases the output of adrenal steroid hormones by stimulating the anterior pituitary gland to secrete adrenocorticotrophic hormone. However, the increase in plasma hydrocortisone usually seen in alcoholics (producing a 'pseudo-Cushing's syndrome' [Ch. 34]) is due partly to inhibition by ethanol of hydrocortisone metabolism in the liver

Acute toxic effects on muscle are exacerbated by seizures and prolonged immobility; severe myositis ('rhabdomyolysis') with myoglobinuria can cause acute renal failure. Chronic toxicity affects particularly cardiac muscle, giving rise to alcoholic cardiomyopathy and chronic heart failure.

Chronic ethanol consumption may also result in immunosuppression, leading to increased incidence of infections such as pneumonia (immunisation with pneumococcal vaccine is important in chronic alcoholics); and increased cancer risk, particularly of the mouth, larynx and oesophagus.

Male alcoholics are often impotent and show signs of feminisation. This is associated with impaired testicular steroid synthesis, but induction of hepatic microsomal enzymes by ethanol, and hence an increased rate of testosterone inactivation, also contributes.

Effects of ethanol on the liver

Together with brain damage, liver damage is the most common serious long-term consequence of excessive ethanol consumption (see Lieber, 1995). Ethanol increases fat accumulation in the liver even after a single dose. Increased fat accumulation (fatty liver) progresses to hepatitis (i.e. inflammation of the liver) and eventually to irreversible hepatic necrosis and fibrosis. Cirrhosis is an end stage, with extensive fibrosis and foci of regenerating hepatocytes that are not correctly 'plumbed in' to the blood and biliary systems Diversion of portal blood flow around the cirrhotic liver often causes portal hypertension and the development of oesophageal varices, which can bleed suddenly and catastrophically.

[13]The image of a large St Bernard dog carrying a small keg of brandy around its neck to revive avalanche victims is an apocryphal one created by the English painter Edwin Landseer, who in 1820 produced a painting called 'Alpine Mastiffs Reanimating a Distressed Traveller'. With their keen sense of smell, such dogs were useful in searching for people buried in the snow, but taking a tot of brandy would only have enhanced the victim's heat loss.

With chronic ethanol consumption, many other factors contribute to the liver damage. One is malnutrition, for alcoholic individuals may satisfy much of their calorie requirement from ethanol itself Three hundred grams of ethanol (equivalent to one bottle of whisky) provides about 2000 kcal but, unlike a normal diet, it provides no vitamins, amino acids or fatty acids. Thiamine deficiency is an important factor in causing chronic neurological damage. Folate deficiency (Ch. 26) is also common in alcoholics, often associated with macrocytosis of red blood cells.

The overall incidence of chronic liver disease is a function of cumulative ethanol consumption over many years. An increase in the plasma concentration of the liver enzyme γ-glutamyl transpeptidase (a marker of cytochrome P450 induction, Ch. 10) often raises the suspicion of ethanol-related liver damage, although not specific to ethanol.

The effect of ethanol on fetal development

Drinking alcohol, especially in the first 3 months of pregnancy, increases the risk of miscarriage, premature birth and low birth weight. The adverse effect of heavier ethanol consumption during pregnancy on fetal development was demonstrated in the early 1970s, when the term *fetal alcohol syndrome* (FAS) was coined.

The features of full FAS include:

- abnormal facial development, with wide-set eyes, short palpebral fissures and small cheekbones;
- reduced cranial circumference;
- retarded growth;
- mental retardation and behavioural abnormalities, often taking the form of hyperactivity and difficulty with social integration;
- other anatomical abnormalities, which may be major or minor (e.g. congenital cardiac abnormalities, malformation of the eyes and ears).

A lesser degree of impairment, termed *alcohol-related neurodevelopmental disorder* (ARND), results in behavioural problems, and cognitive and motor deficits, often associated with reduced brain size. Full FAS occurs in about 3 per 1000 live births and affects about 30% of children born to alcoholic mothers. It is rare with mothers who drink less than about 5 units/day, and most common in binge drinkers who sporadically consume much larger amounts, resulting in high peak levels of ethanol. ARND is about three times as common. Although there is no clearly defined safe threshold, there is no evidence that amounts less than about 2 units/day are harmful. There is no critical period during pregnancy when ethanol consumption is likely to lead to FAS, although one study suggests that FAS incidence correlates most strongly with ethanol consumption very early in pregnancy, even before pregnancy is recognised, implying that not only pregnant women, but also women who are likely to become pregnant, should be advised not to drink heavily. Experiments on rats and mice suggest that the effect on facial development may be produced very early in pregnancy (up to 4 weeks in humans), while the effect on brain development is produced rather later (up to 10 weeks).

PHARMACOKINETIC ASPECTS

Metabolism of ethanol

Ethanol is rapidly absorbed an appreciable amount being absorbed from the stomach. A substantial fraction is cleared by first-pass hepatic metabolism. Hepatic metabolism of ethanol shows saturation kinetics (see Chs 10 and 11) at quite low ethanol concentrations, so the fraction of ethanol removed decreases as the concentration reaching the liver increases. Thus, if ethanol absorption is rapid and portal vein concentration is high, most of the ethanol escapes into the systemic circulation, whereas with slow absorption more is removed by first-pass metabolism. This is one reason why drinking ethanol on an empty stomach produces a much greater pharmacological effect. Ethanol is quickly distributed throughout the body water, the rate of its redistribut on depending mainly on the blood flow to individual tissues, as with volatile anaesthetics (see Ch. 42).

Ethanol is about 90% metabolised, 5%–10% being excreted unchanged in expired air and in urine. This fraction is not pharmacokinetically significant but provides the basis for estimating blood ethanol concentration from measurements on breath or urine. The ratio of ethanol concentrations in blood and alveolar air, measured at the end of deep expiration, is relatively constant, 80 mg/100 mL of ethanol in blood producing 35 µg/100 mL in expired air; this being the basis of the breathalyser test. The concentration in urine is more variable and provides a less accurate measure of blood concentration.

Ethanol metabolism occurs almost entirely in the liver, and mainly by a pathway involving successive oxidations, first to acetaldehyde and then to acetic acid (Fig. 49.5). Since ethanol is often consumed in large quantities (compared with most drugs), 1–2 mol daily being by no means unusual it constitutes a substantial load on the hepatic oxidative systems. The oxidation of 2 mol of ethanol consumes about 1.5 kg of the co-factor nicotinamide adenine dinucleotide (NAD^+). Availability of NAD^+ limits the rate of ethanol oxidation to about 8 g/h in a normal adult,

Effects of ethanol

- **Ethanol** acts as a general central nervous system depressant, similar to volatile anaesthetic agents, producing the familiar effects of acute intoxication.
- Several cellular mechanisms are postulated: enhancement of GABA and glycine action, inhibition of calcium channel opening, activation of potassium channels and inhibition at NMDA receptors.
- Effective plasma concentrations:
  - threshold effects: about 20 mg/100 mL (5 mmol/L)
  - severe intoxication: about 150 mg/100 mL
  - death from respiratory failure: about 500 mg/100 mL
- Main peripheral effects are self-limiting diuresis (reduced antidiuretic hormone secretion), and cutaneous vasodilatation.
- Neurological degeneration occurs with heavy and binge drinking, causing dementia and periphera neuropathies.
- Long-term ethanol consumption causes liver disease, progressing to cirrhosis and liver failure.
- Excessive consumption in pregnancy causes impaired fetal development, associated with small size, abnormal facial development and other physical abnormalities, and mental retardation.
- Psychological dependence, physical dependence and tolerance all occur with **ethanol**.

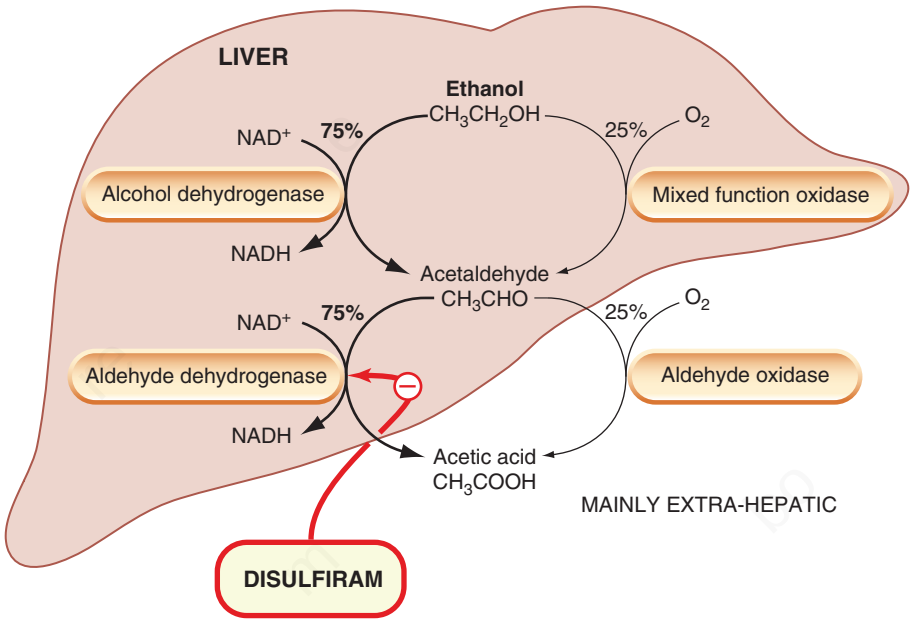

Fig. 49.5 Metabolism of ethanol. *NAD*, nicotinamide adenine dinucleotide.

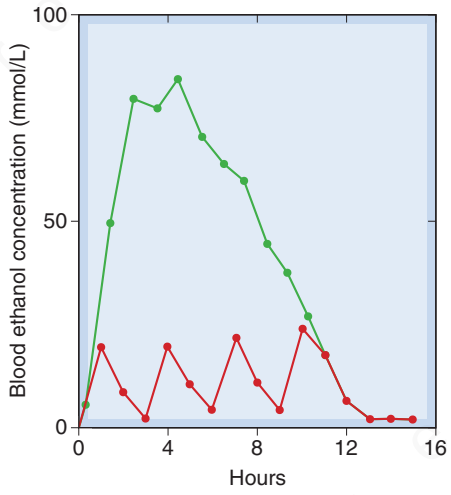

Fig. 49.6 Zero-order kinetics of ethanol elimination in rats. Rats were given ethanol orally (104 mmol/kg) either as a single dose or as four divided doses. The single dose results in a much higher and more sustained blood ethanol concentration than the same quantity given as divided doses. Note that, after the single dose, ethanol concentration declines linearly, the rate of decline being similar after a small or large dose, because of the saturation phenomenon. (From Kalant, H. et al., 1975. Biochem. Pharmacol. 24, 431.)

independently of ethanol concentration (Fig. 49.6), causing the process to show saturating kinetics (Ch. 11). It also leads to competition between the ethanol and other metabolic substrates for the available NAD^+ supplies, which may be a factor in ethanol-induced liver damage (see Ch. 58). The intermediate metabolite, acetaldehyde, is a reactive and toxic compound, and this may also contribute to the hepatotoxicity. A small degree of esterification of ethanol with various fatty acids also occurs in the tissues, and these esters may also contribute to long-term toxicity.

Alcohol dehydrogenase is a soluble cytoplasmic enzyme, confined mainly to liver cells, which oxidises ethanol at the same time as reducing NAD^+ to NADH (see F g. 49.5). Ethanol metabolism causes the ratio of NAD^+ to NADH to fall, and this has other metabolic consequences (e.g. increased lactate and slowing down of the Krebs cycle). The limitation on ethanol metabolism imposed by the limited rate of NAD^+ regeneration has led to attempts to find a 'sobering up' agent that works by regenerating NAD^+ from NADH. One such agent is fructose, which is reduced by an NADH-requiring enzyme. In large doses, it causes a measurable increase in the rate of ethanol metabolism, but not enough to have a useful effect on the rate of return to sobriety.

Normally, only a small amount of ethanol is metabolised by the microsomal mixed function oxidase system (see Ch. 10), but induction of this system occurs in alcoholics Ethanol can affect the metabolism of other drugs that are metabolised by the mixed function oxidase system (e.g. **phenobarbital**, **warfarin** and **steroids**), with an initial inhibitory effect produced by competition, followed by enhancement due to enzyme induction.

Nearly all the acetaldehyde produced is converted to acetate in the liver by *aldehyde dehydrogenase* (see Fig. 49.5). Normally, only a little acetaldehyde escapes from the liver, giving a blood acetaldehyde concentration of 20–50 µmol/L after an intoxicating dose of ethanol in humans. The circulating acetaldehyde usually has little or no effect, but the concentration may become much larger under certain circumstances and produce toxic effects This occurs if aldehyde dehydrogenase is inhibited by drugs such as **disulfiram**. In the presence of disulfiram, which produces no marked effect when given alone ethanol consumption is followed by a severe reaction comprising flushing, tachycardia, hyperventilation and considerable panic and distress, which is due to excessive acetaldehyde accumulation in the bloodstream. This reaction is extremely

unpleasant but not usually harmful, at least in otherwise relatively healthy drinkers, and disulfiram can be used as aversion therapy to discourage people from taking ethanol. Some other drugs (e.g. **metronidazole**; see Ch. 52) produce similar reactions to ethanol. Interestingly, a Chinese herbal medicine used traditionally to cure alcoholics contains **daidzin**, a specific inhibitor of aldehyde dehydrogenase.[14]

Genetic factors

In 50% of Asian people, an inactive genetic variant of one of the aldehyde dehydrogenase isoforms (ALDH-2) is expressed; these individuals experience a disulfiram-like reaction after alcohol, and the incidence of alcoholism in this group is extremely low (see Tyndale, 2003).

Metabolism and toxicity of methanol and ethylene glycol

▼ Methanol is metabolised in the same way as ethanol but produces formaldehyde instead of acetaldehyde from the first oxidation step. Formaldehyde is more reactive than acetaldehyde and reacts rapidly with proteins, causing the inactivation of enzymes involved in the tricarboxylic acid cycle. It is converted to another toxic metabolite, formic acid. This, unlike acetic acid, cannot be utilised in the tricarboxylic acid cycle and is liable to cause tissue damage. Conversion of alcohols to aldehydes occurs not only in the liver but also in the retina, catalysed by the dehydrogenase responsible for retinol–retinal conversion. Formation of formaldehyde in the retina accounts for one of the main toxic effects of methanol, namely blindness, which can occur after ingestion of as little as 10 g. Formic acid production and derangement of the tricarboxylic acid cycle also produce severe acidosis.

Methanol is used as an industrial solvent and also to adulterate industrial ethanol in order to make it unfit to drink. Methanol poisoning is quite common, and used to be treated by administration of large doses of ethanol, which acts to retard methanol metabolism by competition for alcohol dehydrogenase. **Fomepizole** inhibits alcohol dehydrogenase and is now preferred, if available. Such treatment may be in conjunction with haemodialysis to remove unchanged methanol, which has a small volume of distribution.

Poisoning with ethylene glycol, used in automobile antifreeze and brake fluid, is a medical emergency. It is rapidly absorbed from the gut and metabolised to glycolate and then more slowly to oxalate. Glycolate interferes with metabolic processes and produces metabolic acidosis. It affects the brain, heart and kidneys. Trea ment is with fomepizole or, with caution, ethanol,[15] and haemodialysis.

TOLERANCE AND DEPENDENCE

Tolerance to the effects of ethanol can be demonstrated in both humans and experimental animals, to the extent of a two- to three-fold reduction in potency occurring over 1–3 weeks of continuing ethanol administration. A small component of this is due to the more rapid elimination of ethanol. The major component is cellular tolerance, which accounts for a roughly two-fold decrease in potency and which can be observed in vitro (e.g. by measuring the inhibitory effect of ethanol on transmitter release from synaptosomes) as well as in vivo. The mechanism of this tolerance is not known for certain. Ethanol tolerance is associated with tolerance to many anaesthetic agents, and alcoholics are often difficult to anaesthetise.

Chronic ethanol administration produces various changes in CNS neurons, which tend to oppose the acute cellular effects that it produces. There is a small reduction in the density of $GABA_A$ receptors, and a proliferation of voltage-gated calcium channels and NMDA receptors.

A well-defined physical abstinence syndrome develops in response to ethanol withdrawal. As with most other dependence-producing drugs, this is probably important as a short-term factor in sustaining the drug habit, but other (mainly psychological) factors are more important in the longer term (see Ch. 50). The physical abstinence syndrome usually subsides in a few days, but the craving for ethanol and the tendency to relapse last for very much longer. Treatment of alcohol dependence is described in Chapter 50.

The physical abstinence syndrome in humans, in severe form, develops after about 8 h. In the first stage, the main symptoms are tremor, nausea, sweating, fever and sometimes hallucinations. These last for about 24 h. This phase may be followed by seizures ('rum fits'). Over the next few days, the condition of 'delirium tremens' develops, in which the patient becomes confused, agitated and often aggressive, and may suffer much more severe hallucinations. Treatment of this medical emergency is by sedation with large doses of a benzodiazepine such as **chlordiazepoxide** (Ch. 45) together with large doses of thiamine.

Metabolism of ethanol

- **Ethanol** is metabolised mainly by the liver first by alcohol dehydrogenase to acetaldehyde, then by aldehyde dehydrogenase to acetate About 25% of the acetaldehyde is metabolised extrahepatically.
- Small amounts of **ethanol** are excreted in urine and expired air.
- Hepatic metabolism shows saturation kinetics, mainly because of limited availability of nicotinamide adenine dinucleotide (NAD^+). Maximal rate of **ethanol** metabolism is about 10 mL/h. Thus plasma concentration falls linearly rather than exponentially.
- Acetaldehyde may produce toxic effects. Inhibition of aldehyde dehydrogenase by **disulfiram** accentuates nausea, etc., caused by acetaldehyde, and can be used in aversion therapy.
- **Methanol** is similarly metabolised to formic acid, which is toxic, especially to the retina
- Asian people show a high rate of genetic polymorphism of alcohol and aldehyde dehydrogenase, associated with alcoholism and alcohol intolerance, respectively.

SYNTHETIC CANNABINOIDS

The endogenous cannabinoid system and cannabinoids contained in the *Cannabis sativa* plant (phytocannabinoids) are described in detail in Chapter 20. Here we will focus on synthetic cannabinoids, which have names such as *Spice,*

[14] In hamsters (which spontaneously consume alcohol in amounts that would defeat even the hardest two-legged drinker, while remaining, as far as one can tell in a hamster, completely sober), daidzin markedly inhibits alcohol consumption.

[15] When presented with a late evening emergency poisoning of a dog with ethylene glycol, a veterinarian colleague of one of the authors ran to the local supermarket and purchased a bottle of vodka – the dog survived!

K2 or *Black Mamba*. The chemical structures of synthetic cannabinoids are diverse, with over 10 chemical families having been described (see Davidson et al., 2017). Some originated from legitimate attempts by pharmaceutical companies to develop new analgesic compounds but more recently others have been developed purely for non-medicinal purposes. Synthetic cannabinoids are commonly sprayed on herbal material and smoked but are also available in crystal and powder form. They are agonists at the CB_1 cannabinoid receptor, the target through which **Δ^9-tetrahydrocannabinol** (THC), the major psychoactive ingredient in cannabis, has its effects. Synthetic cannabinoids are said to exert a 'more forceful' activation of the CB_1 receptor, in that users often become 'zombie-like' or cataleptic. This may explain their popularity amongst the homeless and prisoners in jail, allowing them a period of escape from their daily lives.

Unlike cannabis itself, synthetic cannabinoids are quite harmful and can induce hallucinations, psychotic episodes, seizures and death. The precise reasons for these toxic effects are not known. They may have 'off-target' effects unrelated to their actions on CB_1 receptors. Furthermore, when smoked, the parent compounds are subject to pyrolysis giving rise to unexpected derivatives, which may be responsible for some of the damaging effects. Quality control is not a priority for the producers of these agents and so there may be toxic contaminants in occasional batches of chemicals.

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