46 Antipsychotic drugs

OVERVIEW

In this chapter we focus on schizophrenia and the drugs used to treat it. We start by describing the illness and what is known of its pathogenesis, including the various neurochemical hypotheses and their relation to the actions of the main types of antipsychotic drugs that are in use or in development. Further information can be found in Gross & Geyer (2012).

INTRODUCTION

Psychotic illnesses include various disorders, but the term antipsychotic drugs – previously known as *neuroleptic drugs*, *antischizophrenic drugs* or *major tranquillisers* – conventionally refers to those used to treat schizophrenia, one of the most common and debilitating forms of mental illness. These same drugs are also used to treat mania (Ch. 47) and other acute behavioural disturbances (see clinical box, p. 568). Pharmacologically, most are dopamine receptor antagonists, although many of them also act on other targets, particularly 5-hydroxytryptamine (5-HT) receptors, which may contribute to their clinical efficacy. Existing drugs have many drawbacks in terms of their efficacy and side effects. Gradual improvements have been achieved with newer drugs, but radical new approaches will require a better understanding of the causes and underlying pathology of the disease, which are still poorly understood.[1]

THE NATURE OF SCHIZOPHRENIA

Schizophrenia[2] (see Stahl, 2008) affects about 1% of the population. It is one of the most important forms of psychiatric illness, because it affects young people, is often chronic and is usually highly disabling.[3] There is a strong hereditary factor in its aetiology, and evidence suggestive of a fundamental biological disorder. The main clinical features of the disease are as follows.

Positive symptoms
- Delusions (often paranoid in nature).
- Hallucinations (often in the form of voices, which may be exhortatory in their message).
- Thought disorder (comprising wild trains of thought, delusions of grandeur, garbled sentences and irrational conclusions).
- Abnormal, disorganised behaviour (such as stereotyped movements, disorientation and occasionally aggressive behaviours).
- Catatonia (can be apparent as immobility or purposeless motor activity).

Negative symptoms
- Withdrawal from social contacts.
- Flattening of emotional responses.
- Anhedonia (an inability to experience pleasure).
- Reluctance to perform everyday tasks.

Cognition
- Deficits in cognitive function (e.g. attention, memory).

In addition, anxiety, guilt, depression and self punishment are often present, leading to suicide attempts in up to 50% of cases, about 10% of which are successful. The clinical phenotype varies greatly, particularly with respect to the balance between positive and negative symptoms, and this may have a bearing on the efficacy of antipsychotic drugs in individual cases. Schizophrenia can present dramatically, usually in young people, with predominantly positive features such as hallucinations, delusions and uncontrollable behaviour, or more insidiously in older patients with negative features such as flat mood and social withdrawal. The latter may be more debilitated than those with a florid presentation, and the prognosis is generally worse. There is debate about whether cognitive impairment can develop even before the onset of other symptoms. Schizophrenia can follow a relapsing and remitting course, or be chronic and progressive, particularly in cases with a later onset. Chronic schizophrenia used to account for most of the patients in long-stay psychiatric hospitals; following the closure of many of these in the UK, it now accounts for many of society's outcasts.

A characteristic feature of schizophrenia is a defect in 'selective attention'. Whereas a normal individual quickly accommodates to stimuli of a familiar or inconsequential nature, and responds only to stimuli that are unexpected or significant, the ability of schizophrenic patients to discriminate between significant and insignificant stimuli seems to be impaired. Thus, the ticking of a clock may command as much attention as the words of a companion; a chance thought, which a normal person would dismiss as inconsequential, may become an irresistible imperative.

[1] In this respect, the study of schizophrenia lags some years behind that of Alzheimer's disease (Ch. 40), where understanding of the pathogenesis has progressed rapidly to the point where promising drug targets have been identified. On the other hand, pragmatists can argue that drugs against Alzheimer's disease are so far only marginally effective, whereas current antipsychotic drugs deliver great benefits even though we do not quite know how they work.

[2] Schizophrenia is a condition where the patient exhibits symptoms of psychosis (e.g. delusions, hallucinations and disorganized behaviour). Psychotic episodes may also occur as a result of taking certain recreational drugs (see Ch. 48); as an adverse effect of drug treatment, for example steroid-induced psychoses; or in disorders such as mania, depression (see Ch. 47) and Alzheimer's disease (see Ch. 40).

[3] A compelling account of what it is to suffer from schizophrenia is contained in Kean (2009) Schizophrenia Bulletin 35, 1034-1036. The author is now a pharmacology graduate.

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AETIOLOGY AND PATHOGENESIS OF SCHIZOPHRENIA

GENETIC AND ENVIRONMENTAL FACTORS

The causes of schizophrenia remain unclear but involve a combination of genetic and environmental factors. Thus a person may have a genetic makeup that predisposes them to schizophrenia, but exposure to environmental factors may be required for schizophrenia to develop.

The disease shows a strong, but incomplete, hereditary tendency. In first-degree relatives, the risk is about 10%, but even in monozygotic (identical) twins, one of whom has schizophrenia, the probability of the other being affected is only about 50%, pointing towards the importance of environmental factors. Genetic linkage studies have identified more than 100 potential susceptibility genes (see Aberg et al., 2013; Ripke et al. 2014), but it is clear that no single gene is responsible. There are significant associations between polymorphisms in individual genes and the likelihood of an individual developing schizophrenia but there appears to be no single gene that has an overriding influence. Some of the genes implicated in schizophrenia are also associated with bipolar disorder (see Ch. 47).

▼ The most robust associations are with genes that control neuronal development, synaptic connectivity and glutamatergic neurotransmission. These include *neuregulin*, *dysbindin*, *DISC-1*, *TCF4* and *NOTCH4*. Transgenic mice that underexpress neuregulin-1, a protein involved in synaptic development and plasticity and which controls NMDA receptor expression, show a phenotype resembling human schizophrenia in certain respects. Malfunction of NMDA receptors is further implicated by genetic association with the genes for D-amino acid oxidase (DAAO), the enzyme responsible for metabolising D-serine, an allosteric modulator of NMDA receptors (see Ch. 38), and for DAAO activator (G72). Dysbindin is located in postsynaptic density domains and may be involved in tethering receptors including NMDA receptors. DISC-1 – which stands for **d**isrupted **i**n **sc**hizophrenia**-1 –** is a protein that associates with cytoskeletal proteins and is involved with cell migration, neurite outgrowth and receptor trafficking. Population genetic studies have suggested that *NOTCH4*, a developmentally expressed gene, and TCF-4, a gene also associated with mental retardation, are strongly associated with susceptibility for schizophrenia (Lennertz et al., 2011; Ikeda et al., 2013) but their precise roles in its aetiology remain to be elucidated. Among other suggested susceptibility genes, some (such as the genes for monoamine oxidase A [MAO-A], tyrosine hydroxylase and the D_2 dopamine receptor) are involved in monoamine transmission in the CNS. However, the weight of current evidence seems to suggest that schizophrenia may result from abnormal glutamatergic transmission, involving a decrease in NMDA receptor function (see p. 561).

Some environmental influences early in development have been identified as possible predisposing factors, particularly maternal virus infections. This and other evidence suggests that schizophrenia is associated with a neurodevelopmental disorder affecting mainly the cerebral cortex and occurring in the first few months of prenatal development. This view is supported by brain-imaging studies showing cortical atrophy apparent in the early course of the disease which may increase with time and correlate with the progression of the disorder (van Haren et al., 2007). Studies of postmortem schizophrenic brains show evidence of misplaced cortical neurons with abnormal morphology. Other environmental factors such as cannabis consumption in adolescence and early adulthood (see Chs 19 and 48) may also reveal schizophrenia.

THE NEUROANATOMICAL AND NEUROCHEMICAL BASIS OF SCHIZOPHRENIA

Different symptoms of schizophrenia appear to result from malfunctions in different neuronal circuits. Changes in the mesolimbic pathway (the neuronal projection from the ventral tegmental area (VTA) to the nucleus accumbens, amygdala and hippocampus) being associated with positive symptoms, whereas negative symptoms are associated with changes in the mesocortical pathway (the projection from the VTA to areas of the prefrontal cortex).

The main neurotransmitters thought to be involved in the pathogenesis of schizophrenia are dopamine and glutamate.

Dopamine

The original dopamine theory of schizophrenia was proposed by Carlson – awarded a Nobel Prize in 2000 – on the basis of indirect pharmacological evidence in humans and experimental animals. **Amphetamine** releases dopamine in the brain and can produce in humans a behavioural syndrome reminiscent of an acute schizophrenic episode. Also, hallucinations are a side effect of levodopa and dopamine agonists used for Parkinson's disease (see Ch. 40). In animals, dopamine release causes a specific pattern of stereotyped behaviour that resembles the repetitive behaviours sometimes seen in schizophrenic patients. Potent D_2-receptor agonists, such as **bromocriptine**, produce similar effects in animals, and these drugs, like amphetamine, exacerbate the symptoms of schizophrenic patients. Furthermore, dopamine antagonists and drugs that block neuronal dopamine storage (e.g. **reserpine**) are effective in controlling the positive symptoms of schizophrenia, and in preventing amphetamine-induced behavioural changes.

▼ It is now believed that positive symptoms result from *overactivity* in the mesolimbic dopaminergic pathway activating D_2 receptors (for a more detailed description of the dopamine pathways in the brain, see Ch. 39) whereas negative symptoms may result from a *decreased activity* in the mesocortical dopaminergic pathway where D_1 receptors predominate. Other dopaminergic pathways in the brain (i.e. nigrostriatal and tuberoinfundibular; see Ch. 39) appear to function normally in schizophrenia.

There is a strong correlation between antipsychotic potency in reducing positive symptoms and activity in blocking D_2 receptors (Fig. 46.1) and receptor-imaging studies have shown that clinical efficacy of antipsychotic drugs is consistently achieved when D_2-receptor occupancy reaches about 80%.[4] Furthermore, brain imaging studies have revealed an increased dopamine synthesis and release in the striatum of schizophrenic patients (Laruelle et al., 1999).[5] Similar changes have also been reported in non-schizophrenic close relatives indicating that such changes may indicate predisposition to schizophrenia rather than the exhibition of symptoms. Injection of amphetamine caused dopamine release that was greater by a factor of two or more in schizophrenic subjects compared with control subjects. The effect was greatest in schizophrenic individuals during acute attacks, and absent during spontaneous remissions – clear evidence linking dopamine release to the symptomatology.

Thus, therapeutically it might be desirable to *inhibit* dopaminergic transmission in the limbic system yet *enhance* dopaminergic transmission in the prefrontal cortex (how this might be achieved is discussed further below, p. 561).

[4]There are, however, exceptions to this simple rule. Up to one-third of schizophrenic patients fail to respond even when D_2-receptor blockade exceeds 90%, and clozapine (see Table 46.1) can be effective at much lower levels of block.

[5]An increase in dopamine receptor density in schizophrenia has been reported in some studies, but not consistently, and the interpretation is complicated by the fact that chronic antipsychotic drug treatment is known to increase dopamine receptor expression.

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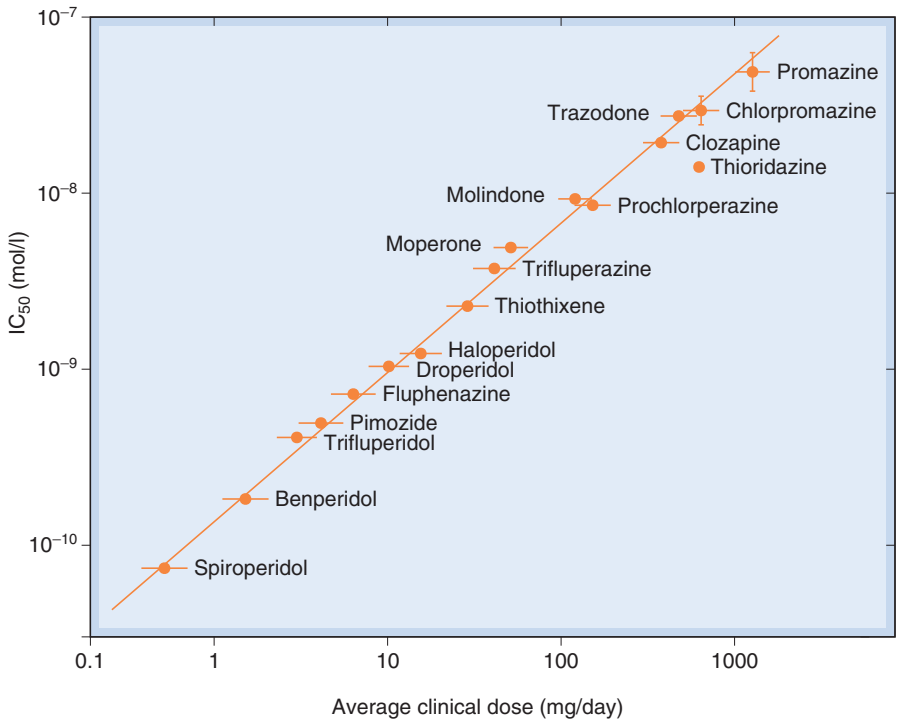

Fig. 46.1 Correlation between the clinical potency and affinity for dopamine D_2 receptors among antipsychotic drugs. Clinical potency is expressed as the daily dose used in treating schizophrenia, and binding activity is expressed as the concentration needed to produce 50% inhibition of haloperidol binding. *(From Seeman P et al. 1976 Nature 361, 717.)*

Glutamate

In humans, NMDA receptor antagonists such as **phencyclidine**, **ketamine** and **dizocilpine** (Ch. 38) can produce positive, negative and cognitive deficit symptoms – in contrast to amphetamine, which produces only positive symptoms. In the brains from schizophrenic patients expression of the glutamate uptake transporter VGLUT1 is reduced, which may indicate a disruption of glutamatergic nerve terminals. It has therefore been postulated that schizophrenia may result from disruption of glutamatergic neurotransmission, evident as a reduction in the function of NMDA receptors (the NMDA hypofunction hypothesis; see Coyle et al., 2012). Consistent with this hypothesis, transgenic mice in which NMDA receptor expression is reduced (not abolished, because this is fatal) show stereotypic behaviours and reduced social interaction that are features of human schizophrenia and that respond to antipsychotic drugs.

▼ Glutamatergic neurons and GABAergic neurons play complex roles in controlling the level of activity in neuronal pathways involved in schizophrenia. NMDA receptor hypofunction is thought to *reduce* the level of activity in mesocortical dopaminergic neurons. This would result in a decrease in dopamine release in the prefrontal cortex and could thus give rise to negative symptoms of schizophrenia. NMDA receptor hypofunction in the cortex may affect GABAergic interneurons and alter cortical processing, giving rise to cognitive impairment. In addition, NMDA-receptor hypofunction on GABAergic neurons would reduce inhibition of the excitatory cortical input to the VTA and thus *enhance* activity in the mesolimbic dopaminergic pathway. Thus NMDA-receptor hypofunction could give rise to enhanced dopamine release in limbic areas such as the nucleus accumbens, resulting in the production of positive symptoms.

Given the evidence that schizophrenic symptoms may be due to a reduction in NMDA-receptor function, efforts have been made to develop new drugs to enhance NMDA-receptor function but not to a level where it becomes neurotoxic (see Ch. 40), e.g. by activating the facilitatory glycine site on the NMDA receptor (see Ch. 38) with an agonist or by raising extracellular glycine levels by inhibiting the GlyT1 transporter.[6]

Other glutamate pathways thought to be involved in schizophrenia are the corticostriatal, thalamocortical, corticothalamic and corticobrainstem pathways. The thalamus normally functions as a sensory filter to limit unnecessary sensory input to the cortex. Disruption of the normal inputs to the thalamus, for example from a reduction in glutamatergic or GABAergic transmission, disables this 'sensory gate' function, allowing uninhibited input to reach the cortex. The role of the thalamus in schizophrenia is reviewed by Sim et al. (2006).

Neurodegeneration

Factors such as structural abnormalities in the brains of schizophrenics and progression of the disease – absence of symptoms in early childhood, the likelihood of positive symptoms becoming apparent before negative symptoms, progressive worsening, reduced responsiveness to drugs with time and the development of dementia – are all suggestive of ongoing neurodegeneration in the disease. The causes of such neurodegeneration are unclear at present but may involve glutamate-induced excitotoxicity (see Ch. 40).

The hope is that a fuller understanding of the altered function of glutamate transmission in schizophrenia will lead to the development of new, improved antipsychotic drugs.

Animal models

There is a need for the development of animal models of schizophrenia that simulate the positive, negative and cognitive deficit components of this disorder. Schizophrenia presents as a heterogeneous disorder with sufferers

[6]Sadly the GlyT1 transporter inhibitor **bitopertin** failed in clinical trials as an antipsychotic, although it may still have potential as a treatment for obsessive–compulsive disorder.

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exhibiting different combinations of symptoms that may result from different neuronal abnormalities. Traditional models by and large reflect behaviours resulting from heightened dopaminergic transmission in the brain. Thus they were likely to show positive results with drugs that have dopamine receptor antagonist activity. Models based on inhibition of NMDA function by phencyclidine (PCP) and related drugs have become popular in recent years. In humans, PCP causes a schizophrenia-like syndrome (see Ch. 48). Also, various genetic models are being examined. These have focused on proteins such as DISC-1 that are implicated in schizophrenia and on receptors and transporters for neurotransmitters such as glutamate and dopamine. However, as described above, the genetic basis of schizophrenia is multifactorial and environmental factors are also important. Thus mutation of a single gene may provide only limited information. Models of cognitive deficits and negative symptoms are lacking. The development of such models is a major challenge that requires a better understanding of the pathophysiological processes that underlie different symptoms. For further details on the development of new animal models of schizophrenia see Pratt et al. (2012).

The nature of schizophrenia

- Psychotic illness characterised by delusions, hallucinations and thought disorder (positive symptoms), together with social withdrawal and flattening of emotional responses (negative symptoms), and cognitive impairment.
- Acute episodes (mainly positive symptoms) frequently recur and may develop into chronic schizophrenia, with predominantly negative symptoms.
- Incidence is about 1% of the population, with a significant hereditary component. Genetic linkage studies suggest involvement of multiple genes, but no single 'schizophrenia gene'.
- Pharmacological evidence is generally consistent with dopamine dysregulation and glutamate underactivity hypotheses, supported by biochemical findings, clinical efficacy and imaging studies.

ANTIPSYCHOTIC DRUGS

CLASSIFICATION OF ANTIPSYCHOTIC DRUGS

More than 40 different antipsychotic drugs are available for clinical use. These have been divided into two groups – those drugs that were originally developed (e.g. **chlorpromazine**, **haloperidol** and many similar compounds), often referred to as *first-generation*, *typical* or *conventional antipsychotic drugs*, and more recently developed agents (e.g. **clozapine**, **risperidone**), which are termed *second-generation* or *atypical antipsychotic drugs*. Table 46.1 summarises the main drugs that are in clinical use.

▼ The term 'atypical' has been widely used but not clearly defined. In effect, it refers to the diminished tendency of later compounds to cause unwanted motor side effects, but it is also used to describe compounds with a different pharmacological profile from first-generation compounds. In practice, however, it often serves – not very usefully – to distinguish the large group of similar first-generation dopamine antagonists from the more diverse group of later compounds described below.

The therapeutic activity of the prototype drug, **chlorpromazine**, in schizophrenic patients was discovered through the acute observations of a French surgeon, Laborit, in 1947. He tested various substances, including **promethazine**, for their ability to alleviate signs of stress in patients undergoing surgery, and concluded that promethazine had a calming effect that was different from mere sedation. Elaboration of the phenothiazine structure led to chlorpromazine, the antipsychotic effect of which was demonstrated in man, at Laborit's instigation, by Delay and Deniker in 1953. This drug was unique in controlling the symptoms of psychotic patients. The clinical efficacy of phenothiazines was discovered long before their mechanism was guessed at (let alone understood).

Pharmacological investigation showed that phenothiazines, the first-generation antipsychotic agents, block many different mediators, including histamine, catecholamines, acetylcholine and 5-HT, and this multiplicity of actions led to the trade name Largactil for chlorpromazine. It is now clear (see Fig. 46.1) that antagonism of dopamine is the main determinant of antipsychotic action.

Classification of antipsychotic drugs

- Main categories are:
  - first-generation ('typical', 'classical' or 'conventional') antipsychotics (e.g. **chlorpromazine**, **haloperidol**, **fluphenazine**, **flupentixol**, **clopentixol**)
  - second-generation ('atypical') antipsychotics (e.g. **clozapine**, **risperidone**, **sertindole**, **quetiapine**, **amisulpride**, **aripiprazole**, **zotepine**, **ziprasidone**).
- Distinction between first- and second-generation drugs is not clearly defined but rests on:
  - receptor profile
  - incidence of extrapyramidal side effects (less in second-generation group)
  - efficacy (specifically of **clozapine**) in 'treatment-resistant' group of patients
  - efficacy against negative symptoms.

CLINICAL EFFICACY

The clinical efficacy of antipsychotic drugs in enabling schizophrenic patients to lead more normal lives has been demonstrated in many controlled trials. The inpatient population (mainly chronic schizophrenics) of mental hospitals declined sharply in the 1950s and 1960s. The introduction of antipsychotic drugs was a significant enabling factor, as well as the changing public and professional attitudes towards hospitalisation of the mentally ill.

Antipsychotic drugs have severe drawbacks that include:

- Not all schizophrenic patients respond to drug therapy. It is recommended to try **clozapine** in patients who are resistant to other antipsychotic drugs. The 30% of patients who do not respond are classed as 'treatment resistant' and present a major therapeutic problem. The reason for the difference between responsive and unresponsive patients is unknown at present, although there is some evidence (not conclusive) that polymorphisms within the family of dopamine and 5-HT receptors may be involved.
- While they control the positive symptoms (thought disorder, hallucinations, delusions, etc.) effectively, most are ineffective in relieving the negative

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Table 46.1 Characteristics of some major antipsychotic drugs

	Receptor affinity						Main side effects				
Drug	*D_1*	*D_2*	*α_1*	*H_1*	*mACh*	*5-HT_{2A}*	*EPS*	*Sed*	*Hypo*	*Other*	**Notes**
Chlorpromazine	++	++	+++	+++	++	+++	++	+++	++	Increased prolactin (gynaecomastia)	Phenothiazine class
										Hypothermia	Fluphenazine, trifluperazine are similar but: • do not cause jaundice • cause less hypotension • cause more EPS
										Anticholinergic effects	
										Hypersensitivity reactions	
										Obstructive jaundice	
											Fluphenazine available as depot preparation
											Pericyazine, pipotiazine cause less EPS probably due to their greater muscarinic antagonist actions
Haloperidol	++	+++	++	+	–	++	+++	–	+	As chlorpromazine but does not cause jaundice	Butyrophenone class
										Fewer anticholinergic side effects	Widely used antipsychotic drug
											Strong EPS tendency
											Available as depot preparation
Flupentixol	+++	+++		+++	–	+	++	+	+	Increased prolactin (gynaecomastia)	Thioxanthine class
										Restlessness	Clopentixol is similar
											Available as depot preparation
Sulpiride	–	++	–	–	–	–	+	+	–	Increased prolactin (gynaecomastia)	Benzamide class
											Selective D_2/D_3 antagonist
											Less EPS than haloperidol (reason for this unclear, but could result from action at D_3 or very weak partial agonism at D_2)
											Increases alertness in apathetic patients
											Poorly absorbed
											Amisulpride and pimozide (long-acting) are similar
Clozapine	+	+	+++	++++	++	+++	–	++	++	Risk of agranulocytosis (~1%): regular blood counts required	Dibenzodiazepine class
										Seizures	No EPS (first second-generation antipsychotic)

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Table 46.1 Continued

Drug	Receptor affinity						Main side effects				Notes
	D_1	D_2	α_1	H_1	mACh	5-HT_{2A}	EPS	Sed	Hypo	Other	
Clozapine, cont'd										Salivation	Shows efficacy in 'treatment-resistant' patients and reduces incidence of suicide
										Anticholinergic side effects	Effective against negative and positive symptoms
										Weight gain	Olanzapine is somewhat less sedative, without risk of agranulocytosis, but questionable efficacy in treatment-resistant patients
Risperidone	+	+++	+++	++	–	++++ (IA?)	+	++	++	Weight gain	Significant risk of EPS
										EPS at high doses	?Effective against negative symptoms
										Hypotension	Potent on D_4 receptors
											Available as depot preparation
											Paliperidone is a metabolite of risperidone
Quetiapine	+	+	+++	+++	+	+	–	++	++	Tachycardia	Low incidence of EPS
										Drowsiness	No increase in prolactin secretion
										Dry mouth	5-HT_{1A} partial agonist
										Constipation	Short-acting (plasma half-life ~6 h)
										Weight gain	
Aripiprazole	+	++++ (PA)	++	++	–	+++	–	+	–	–	Long-acting (plasma half-life ~3 days)
											Unusual D_2 partial agonist profile may account for paucity of side effects
											Also a 5HT_{1A} partial agonist
											No effect on prolactin secretion
											No weight gain
											Available as a depot preparation
Ziprasidone	++	+++	+++	++	–	++++	+	–	+	Tiredness	Low incidence of EPS
										Nausea	No weight gain
											?Effective against negative symptoms
											Short-acting (plasma half-life ~8 h) but a depot preparation is available

+, pKi 5–7; ++, pKi 7–8; +++, pKi 8–9; +++, pKi >9.

5-HT_{1A}, 5-HT_{2A}, 5-hydroxytryptamine types 1A and 2A receptors; α_1, α_1 adrenoceptor; D_1, D_2, D_3, D_4, dopamine types 1, 2, 3 and 4 receptor, respectively; ECG, electrocardiograph; EPS, extrapyramidal side effects; H_1, histamine type 1 receptor; Hypo, hypotension; mACh, muscarinic acetylcholine receptor; IA, inverse agonist; PA, partial agonist; Sed, sedation.

Table based on data contained in Guide to Pharmacology (www.guidetopharmacology.org/) and NIMH Psychoactive Drug Screening Program database (http://pdsp.med.unc.edu/). Where available, data obtained on human receptors are given.

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symptoms (emotional flattening, social isolation) and cognitive impairment.
- They induce a range of side effects that include extrapyramidal motor, endocrine and sedative effects (see Table 46.1) that can be severe and limit patient compliance.
- They may shorten survival through cardiac (pro-arrhythmic) effects (see Ch. 21).

Second-generation antipsychotic drugs were believed to overcome these shortcomings to some degree. However, a meta-analysis (Leucht et al., 2009) concluded that only some of the second-generation antipsychotic drugs examined, showed better overall efficacy. There is a definite need for the development of new treatments.

Abrupt cessation of antipsychotic drug administration may lead to a rapid onset psychotic episode distinct from the underlying illness.

PHARMACOLOGICAL PROPERTIES

DOPAMINE RECEPTORS

The classification of dopamine receptors in the central nervous system is discussed in Chapter 39 (see Table 39.1). There are five subtypes, which fall into two functional classes: the D_1 type, comprising D_1 and D_5, and the D_2 type, comprising D_2, D_3 and D_4. Antipsychotic drugs owe their therapeutic effects mainly to blockade of D_2 receptors.[7] As stated above, antipsychotic effects require about 80% block of D_2 receptors. The first-generation compounds show some preference for D_2 over D_1 receptors, whereas some of the later agents (e.g. **sulpiride**, **amisulpride**, **remoxipride**) are highly selective for D_2 receptors. D_2 antagonists that dissociate rapidly from the receptor (e.g. **quetiapine**) and D_2 partial agonists (e.g. **aripiprazole**) have been introduced in an attempt to reduce extrapyramidal motor side effects (see p. 566).

It is the antagonism of D_2 receptors in the mesolimbic pathway that is believed to relieve the positive symptoms of schizophrenia. Unfortunately, systemically administered antipsychotic drugs do not discriminate between D_2 receptors in distinct brain regions and D_2 receptors in other brain pathways will also be blocked. Thus, antipsychotic drugs produce unwanted motor effects (block of D_2 receptors in the nigrostriatal pathway), enhance prolactin secretion (block of D_2 receptors in the tuberoinfundibular pathway), reduce pleasure (block of D_2 receptors in the reward component of the mesolimbic pathway) and perhaps even worsen the negative symptoms of schizophrenia (block of D_2 receptors in the prefrontal cortex, although these are only expressed at a low density – D_1 receptors being in greater abundance). While all antipsychotic drugs block D_2 receptors and should therefore in theory induce all of these unwanted effects, some have additional pharmacological activity (e.g. mACh receptor antagonism and 5-HT_{2A} receptor antagonism) that, to varying degrees, ameliorate unwanted effects. 5-HT_{2A} antagonism may also help to alleviate the negative and cognitive impairments of schizophrenia.

Antipsychotic drugs have classically been thought to have a delayed onset to their therapeutic actions, even though their dopamine receptor-blocking action is immediate. This view has, however, been called into question (Kapur et al., 2005; Leucht et al., 2005). In animal studies, chronic antipsychotic drug administration does produce compensatory changes in the brain, for example a reduction in the activity of dopaminergic neurons and proliferation of dopamine receptors, detectable as an increase in haloperidol binding, with a pharmacological supersensitivity to dopamine reminiscent of the phenomenon of denervation supersensitivity (Ch. 12). The mechanism(s) of these delayed effects are poorly understood. They are likely to contribute to the development of unwanted *tardive dyskinesias*. The sedating effect of antipsychotic drugs is immediate, allowing them to be used in acute behavioural emergencies.

Mechanism of action of antipsychotic drugs

- Most antipsychotic drugs are antagonists or partial agonists at D_2 dopamine receptors, but they also block a variety of other receptors.
- Antipsychotic potency generally runs parallel to activity on D_2 receptors, but activities at other receptors (e.g. 5-HT_{2A} and muscarinic) may reduce extrapyramidal side effects.
- Activity at muscarinic, H_1 and α receptors may determine unwanted side effect profile.
- Imaging studies suggest that therapeutic effect requires about 80% occupancy of D_2 receptors.

5-HYDROXYTRYPTAMINE RECEPTORS

The idea that 5-HT dysfunction could be involved in schizophrenia has drifted in and out of favour many times (see Busatto & Kerwin, 1997). It was originally based on the fact that LSD, a partial agonist at 5-HT_{2A} receptors (see Chs 15 and 48), produces hallucinations. Nowadays, conventional wisdom is that 5-HT is not directly involved in the pathogenesis of schizophrenia. Nevertheless, pharmacological manipulation of 5-HT receptor activity, combined with D_2 receptor antagonism, has resulted in new drugs with improved therapeutic profiles.[8] There is a plethora of 5-HT receptors (see Chs 15 and 39), with disparate functions in the body. It is the 5-HT_{2A} receptor and, to a lesser extent, the 5-HT_{1A} receptor that are important in the treatment of schizophrenia.

5-HT_{2A} receptors are G_i/G_o-coupled receptors and their activation produces neuronal inhibition (through decreased neuronal excitability at the soma and decreased transmitter release at the nerve terminals; see Ch. 39). In this way, in the nigrostriatal pathway, 5-HT_{2A} receptors control the release of dopamine. Drugs with 5-HT_{2A} antagonist properties (e.g. **olanzapine** and risperidone)

[7]The D_4 receptor attracted attention on account of the high degree of genetic polymorphism that it shows in human subjects, and because some of the newer antipsychotic drugs (e.g. clozapine) have a high affinity for this receptor subtype. However, a specific D_4-receptor antagonist proved ineffective in clinical trials.

[8]Early antipsychotic drugs (e.g. chlorpromazine) had actions at various receptors but also had unwanted side effects that resulted from activity at other receptors. Towards the end of the 20th century, drug development, not just of antipsychotic drugs, was focused largely on developing agents with a single action with the intention of reducing unwanted side effects. This philosophy drove the search for selective D_4-receptor antagonists, which proved ineffective. What is now apparent is that drugs with selected multiple actions (e.g. a combination of D_2 antagonism and 5-HT_{2A} antagonism) may have a better therapeutic profile.

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enhance dopamine release in the striatum by reducing the inhibitory effect of 5-HT. This will reduce extrapyramidal side effects (see below). In contrast, in the mesolimbic pathway, the combined effects of D_2 and 5-HT_{2A} antagonism are thought to counteract the increased dopamine function that gives rise to positive symptoms of schizophrenia. Further, enhancing both dopamine and glutamate release in the mesocortical circuit, 5-HT_{2A} receptor antagonism may improve the negative symptoms of schizophrenia (Stahl, 2008).

5-HT_{1A} receptors are somatodendritic autoreceptors that inhibit 5-HT release (see Ch. 39). Antipsychotic drugs that are agonists or partial agonists at 5-HT_{1A} receptors (e.g. **quetiapine**; see Table 46.1) may work by decreasing 5-HT release thus enhancing dopamine release in the striatum and prefrontal cortex.

The concept of 5-HT receptors as targets for novel antipsychotic drug development is discussed at the end of this chapter.

MUSCARINIC ACETYLCHOLINE RECEPTORS

Some phenothiazine antipsychotic drugs (e.g. **pericyazine**) have been reported to produce fewer extrapyramidal side effects than others, and this was thought to correlate with their muscarinic antagonist actions. Also, some second-generation drugs possess muscarinic antagonist properties (e.g. olanzapine). In the striatum, dopaminergic nerve terminals are thought to innervate cholinergic interneurons that express inhibitory D_2 receptors (Pisani et al., 2007). It is suggested that there is normally a balance between D_2 receptor activation and muscarinic receptor activation. Blocking D_2 receptors in the striatum with an antipsychotic agent will result in enhanced acetylcholine release on to muscarinic receptors, thus producing extrapyramidal side effects, which are counteracted if the D_2 antagonist also has muscarinic antagonist activity. Maintaining the dopamine/acetylcholine balance was also the rationale for the use of the muscarinic antagonist **benztropine** to reduce extrapyramidal effects of antipsychotic drugs (see Ch. 40). Muscarinic antagonist activity does, however, induce side effects such as constipation, dry mouth and blurred vision.

UNWANTED EFFECTS

EXTRAPYRAMIDAL MOTOR DISTURBANCES

Antipsychotic drugs produce two main kinds of motor disturbance in humans: *acute dystonias* and *tardive dyskinesias*, collectively termed *extrapyramidal side effects*. These all result directly or indirectly from D_2 receptor blockade in the nigrostriatal pathway. Extrapyramidal side effects constitute one of the main disadvantages of first-generation antipsychotic drugs. Second-generation drugs were thought to have less tendency to produce extrapyramidal side effects. However, a long-term study of olanzapine, risperidone, quetiapine and **ziprasidone** concluded that they too can induce extrapyramidal side effects (see Lieberman & Stroup, 2011). Even aripiprazole, which is a D_2 partial agonist, has been reported to produce this unwanted effect.

Acute dystonias are involuntary movements (restlessness, muscle spasms, protruding tongue, fixed upward gaze, neck muscle spasm), often accompanied by symptoms of Parkinson's disease (Ch. 40). They occur commonly in the first few weeks, often declining with time, and are reversible on stopping drug treatment. The timing is consistent with block of the dopaminergic nigrostriatal pathway. Concomitant block of muscarinic receptors and 5-HT_{2A} receptors mitigates the motor effects of dopamine receptor antagonists (see above).

Tardive dyskinesia (see Klawans et al., 1988) develops after months or years (hence 'tardive') in 20–40% of patients treated with first-generation antipsychotic drugs, and is one of the main problems of antipsychotic therapy. Its seriousness lies in the fact that it is a disabling and often irreversible condition, which often gets worse when antipsychotic therapy is stopped and is resistant to treatment. The syndrome consists of involuntary movements, often of the face and tongue, but also of the trunk and limbs, which can be severely disabling. It resembles that seen after prolonged treatment of Parkinson's disease with **levodopa** (see Ch. 40). The incidence depends greatly on drug, dose and age (being commonest in patients over 50).

▼ There are several theories about the mechanism of tardive dyskinesia (see Casey, 1995). One is that it is associated with a gradual increase in the number of D_2 receptors in the striatum, which is less marked during treatment with second-generation than with first-generation antipsychotic drugs. Another possibility is that chronic block of inhibitory dopamine receptors enhances catecholamine and/or glutamate release in the striatum, leading to excitotoxic neurodegeneration (Ch. 40).

Drugs that rapidly dissociate from D_2 receptors (e.g. clozapine, olanzapine, **sertindole**) induce less severe extrapyramidal side effects. A possible explanation for this (see Kapur & Seeman, 2001) is that with a rapidly dissociating compound, a brief surge of dopamine can effectively overcome the block by competition (see Ch. 2), whereas with a slowly dissociating compound, the level of block takes a long time to respond to the presence of endogenous dopamine, and is in practice non-competitive. Adverse motor effects may be avoided if fractional receptor occupation falls during physiological surges of dopamine. An extension of this idea is that perhaps a little D_2 receptor activation may be beneficial. This could be produced, for example, by drugs that are D_2 partial agonists (e.g. aripiprazole) in contrast to simple antagonists. It is thought that partial agonists reduce D_2 hyperactivation in the mesolimbic pathway, thus alleviating positive symptoms of schizophrenia, but provide enough D_2 receptor stimulation in the mesocortical pathway to prevent negative symptoms, and in the nigrostriatal pathway to lower the incidence of extrapyramidal side effects. Newer D_2 partial agonists were being developed, although questions about their efficacy and safety have arisen.

ENDOCRINE EFFECTS

Dopamine, released in the median eminence by neurons of the tuberohypophyseal pathway (see Chs 33 and 39), acts physiologically via D_2 receptors to inhibit prolactin secretion. Blocking D_2 receptors by antipsychotic drugs can therefore increase the plasma prolactin concentration (Fig. 46.2), resulting in breast swelling, pain and lactation (known as 'galactorrhea'), which can occur in men as well as in women. As can be seen from Figure 46.2, the effect is maintained during chronic antipsychotic administration, without any habituation. Other less pronounced endocrine changes have also been reported, including a decrease of growth hormone secretion, but these, unlike the prolactin response, are believed to be relatively unimportant clinically. Because of its D_2 receptor partial agonist action aripiprazole, unlike other antipsychotic drugs, reduces prolactin secretion.

OTHER UNWANTED EFFECTS

Most antipsychotic drugs block a variety of receptors, particularly acetylcholine (muscarinic), histamine (H_1), noradrenaline (α) and 5-HT receptors (Table 46.1). This gives rise to a wide range of side effects.

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Antipsychotic-induced motor disturbances

- Major problem of antipsychotic drug treatment.
- Two main types of disturbance occur:
  - acute, reversible dystonias and Parkinson-like symptoms (indeed, antipsychotic drugs generally worsen Parkinson's disease and block the actions of drugs used to treat the disorder)
  - slowly developing tardive dyskinesia, often irreversible.
- Acute symptoms comprise involuntary movements, tremor and rigidity, and are probably the direct consequence of block of nigrostriatal dopamine receptors.
- Tardive dyskinesia comprises mainly involuntary movements of the face and limbs, appearing after months or years of antipsychotic treatment. It may be associated with proliferation of dopamine receptors in the corpus striatum. Treatment is generally unsuccessful.
- Incidence of acute dystonias and tardive dyskinesia is less with newer, second-generation antipsychotics, and particularly low with **clozapine**, **aripiprazole** and **zotepine**.

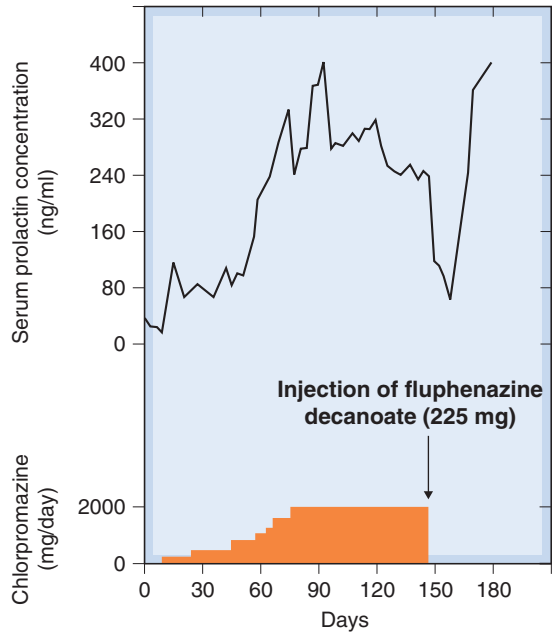

Fig. 46.2 Effects of antipsychotic drugs on prolactin secretion in a schizophrenic patient. When daily dosage with chlorpromazine was replaced with a depot injection of fluphenazine, the plasma prolactin initally dropped, because of the delay in absorption, and then returned to a high level. *(From Meltzer HY et al. 1978 In: Lipton et al. (eds) Psychopharmacology: A Generation in Progress. Raven Press, New York.)*

They can produce sexual dysfunction – decreased libido and decreased arousal as well as erection and ejaculation difficulties in men – through block of dopamine, muscarinic and α_1 receptors.

Drowsiness and sedation, which tend to decrease with continued use, occur with many antipsychotic drugs. Antihistamine (H_1) activity is a property of some phenothiazine antipsychotics (e.g. chlorpromazine and **methotrimeprazine**) and contributes to their sedative and antiemetic properties (Chs 39 and 44), but not to their antipsychotic action.

While block of muscarinic receptors produces a variety of peripheral effects, including blurring of vision and increased intraocular pressure, dry mouth and eyes, constipation and urinary retention (see Ch. 13), it may, however, also be beneficial in relation to extrapyramidal side effects (see p. 566).

Blocking α adrenoceptors causes *orthostatic hypotension* (see Ch. 14) but does not seem to be important for their antipsychotic action.

Weight gain is a common and troublesome side effect. Increased risk of diabetes and cardiovascular disease occurs with several second-generation antipsychotic drugs. These effects are probably related to their antagonist actions at H_1, 5-HT and muscarinic receptors.

Antipsychotic drugs can prolong the QT interval in the heart (see Ch. 21) giving rise to arrhythmia and risk of sudden death (Jolly et al., 2009).

Various idiosyncratic and hypersensitivity reactions can occur, the most important being the following:

- *Jaundice*, which occurs with older phenothiazines such as chlorpromazine. The jaundice is usually mild, associated with elevated serum alkaline phosphatase activity (an 'obstructive' pattern), and disappears quickly when the drug is stopped or substituted by a chemically unrelated antipsychotic.
- *Leukopenia* and *agranulocytosis* are rare but potentially fatal, and occur in the first few weeks of treatment. The incidence of leukopenia (usually reversible) is less than 1 in 10 000 for most antipsychotic drugs, but much higher (1–2%) with clozapine, whose use therefore requires regular monitoring of blood cell counts. Provided the drug is stopped at the first sign of leukopenia or anaemia, the effect is reversible. Olanzapine appears to be free of this disadvantage.
- *Urticarial skin reactions* are common but usually mild. Excessive sensitivity to ultraviolet light may also occur.
- *Antipsychotic malignant syndrome* is a rare but serious complication similar to the malignant hyperthermia syndrome seen with certain anaesthetics (see Ch. 41). Muscle rigidity is accompanied by a rapid rise in body temperature and mental confusion. It is usually reversible, but death from renal or cardiovascular failure occurs in 10–20% of cases.

PHARMACOKINETIC ASPECTS

Chlorpromazine, in common with other phenothiazines, is erratically absorbed after oral administration. Figure 46.3 shows the wide range of variation of the peak plasma concentration as a function of dosage in 14 patients. Among four patients treated at the high dosage level of 6–8 mg/kg, the variation in peak plasma concentration was nearly 90-fold; two showed marked side effects, one was well controlled and one showed no clinical response.

The relationship between the plasma concentration and the clinical effect of antipsychotic drugs is highly variable, and the dosage has to be adjusted on a trial-and-error basis. This is made even more difficult by the fact that at

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Unwanted effects of antipsychotic drugs

- Important side effects common to many drugs are:
  - motor disturbances (see *Antipsychotic-induced motor disturbances* box)
  - endocrine disturbances (increased prolactin release)
  - these are secondary to dopamine receptor block.
- Sedation, hypotension and weight gain are common.
- Obstructive jaundice sometimes occurs with phenothiazines.
- Other side effects (dry mouth, blurred vision, hypotension, etc.) are due to block of other receptors, particularly muscarinic receptors and α adrenoceptors.
- Some antipsychotic drugs cause agranulocytosis as a rare and serious idiosyncratic reaction. With **clozapine**, leukopenia is common and requires routine monitoring.
- Antipsychotic malignant syndrome is a rare but potentially dangerous idiosyncratic reaction.

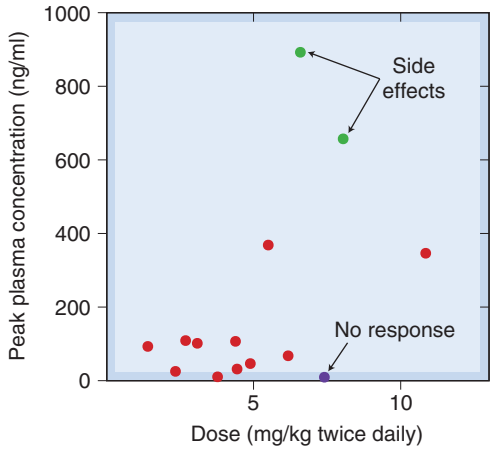

Fig. 46.3 Individual variation in the relation between dose and plasma concentration of chlorpromazine in a group of schizophrenic patients. *(Data from Curry SH et al. 1970 Arch Gen Psychiatry 22, 289.)*

least 40% of schizophrenic patients fail to take drugs as prescribed. It is remarkably fortunate that the acute toxicity of antipsychotic drugs is slight, given the unpredictability of the clinical response.

The plasma half-life of most antipsychotic drugs is 15–30 h, clearance depending entirely on hepatic transformation by a combination of oxidative and conjugative reactions.

Most antipsychotic drugs can be given orally or in urgent situations by intramuscular injection. Slow-release (depot) preparations of many are available, in which the active drug is esterified with heptanoic or decanoic acid and dissolved in oil. Given as an intramuscular injection, the drug acts for 2–4 weeks, but initially may produce acute side effects. These preparations are widely used to minimise compliance problems.

FUTURE DEVELOPMENTS

The cognition enhancer **modafinil** (see Ch. 48) may be useful in treating the cognitive deficit in schizophrenia.

Clinical uses of antipsychotic drugs

- *Behavioural emergencies* (e.g. violent patients with a range of psychopathologies including *mania*, *toxic delirium*, *schizophrenia* and others):
  - antipsychotic drugs (e.g. **chlorpromazine**, **haloperidol**, **olanzapine**, **risperidone**) can rapidly control hyperactive psychotic states
  - note that the intramuscular dose is lower than the oral dose of the same drug because of presystemic metabolism.
- *Schizophrenia*:
  - many chronic schizophrenic patients are treated with first-generation antipsychotic drugs. Depot injections (e.g. **flupentixol decanoate**) may be useful for maintenance treatment when compliance with oral treatment is a problem
  - **flupentixol** has antidepressant properties distinct from its antipsychotic action
  - newer antipsychotic drugs (e.g. **amisulpride**, **olanzapine**, **risperidone**) are used if extrapyramidal symptoms are troublesome or if symptom control is inadequate
  - **clozapine** can cause *agranulocytosis* but is distinctively effective against 'negative' features of schizophrenia. It is reserved for patients whose condition remains inadequately controlled despite previous use of two or more antipsychotic drugs, of which at least one is a second-generation drug. Blood count is monitored weekly for the first 18 weeks, and less frequently thereafter.
- *Other clinical uses*: to some extent, the term 'antipsychotic drug' is misleading as some of these drugs are used to treat disorders other than schizophrenia. These include:
  - bipolar disorder, mania and depression (see Ch. 47)
  - short-term treatment of psychomotor agitation and severe anxiety (**chlorpromazine** and **haloperidol**)
  - agitation and restlessness in the elderly (**risperidone**), although this is highly questionable
  - restlessness and pain in palliative care (**levomepromazine**)
  - nausea and vomiting (e.g. **chlorpromazine** and **haloperidol**) reflecting antagonism at dopamine, muscarinic, histamine and possibly 5-HT receptors
  - motor tics and intractable hiccup (**chlorpromazine** and **haloperidol**)
  - antisocial sexual behavior (**benperidol**)
  - the treatment of involuntary movements caused by Huntington's disease (mainly haloperidol; see Ch. 40).

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Preclinical and clinical studies have provided encouraging evidence that orthosteric and allosteric agonists of $mGluR_2$ and $mGluR_3$ metabotropic glutamate receptors (see Ch. 38) are effective in the treatment of the positive symptoms of schizophrenia. Paradoxically, activating presynaptic $mGluR_2$ and $mGluR_3$ autoreceptors reduces glutamate release but this may result in a compensatory upregulation of NMDA receptors which might be beneficial. $mGluR_2$ receptors form heteromers with $5\text{-}HT_{2A}$ receptors (see Ch. 3) with altered intracellular signalling properties and targeting the dimer may offer hope for future drug development. Agonists at postsynaptic $mGluR_5$ receptors may improve positive and negative symptoms as well as cognitive function. $mGluR_5$ receptors are closely associated with NMDA receptors and activation of $mGluR_5$ may enhance NMDA receptor function by increasing NMDA receptor phosphorylation.

A number of current antipsychotic drugs have among their myriad of actions $5\text{-}HT_6$ and $5\text{-}HT_7$ receptor antagonist properties; more specific antagonists at these receptors are being investigated; their ability to produce cognitive improvement is controversial.

Also in various stages of development are inhibitors of phosphodiesterase (PDE10), α_7 nicotinic receptor agonists, histamine H_3 antagonists and $5\text{-}HT_6$ antagonists. Selective agonist action at M_1 muscarinic receptors (either orthosteric or allosteric) has significant potential for cognition enhancement in both schizophrenia and Alzheimer's disease but to date drug development has been hampered by a lack of selectivity across muscarinic receptor subtypes (e.g. **xanomeline** is an M_1 and M_4 agonist and M_5 antagonist) that gives rise to significant unwanted effects.

Further information about novel targets can be found in Ellenbroek (2012) and Geyer & Gross (2012).

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47 Antidepressant drugs

OVERVIEW

Depression is an extremely common psychiatric condition, about which a variety of neurochemical theories exist, and for which a corresponding variety of different types of drug are used in treatment. It is a field in which therapeutic empiricism has led the way, with mechanistic understanding tending to lag behind, part of the problem being that it has been difficult to develop animal models that replicate the characteristics that define the human condition. In this chapter, we discuss the current understanding of the nature of the disorder, and describe the major drugs that are used to treat it.

THE NATURE OF DEPRESSION

Depression is the most common of the *affective disorders* (defined as disorders of mood); it may range from a very mild condition, bordering on normality, to severe (psychotic) depression accompanied by hallucinations and delusions. Worldwide, depression is a major cause of disability and premature death. In addition to the significant suicide risk, depressed individuals are more likely to die from other causes, such as heart disease or cancer. Depression is a heterogeneous disorder, with patients presenting with one or more core symptoms, and depression is often associated with other psychiatric conditions, including anxiety, eating disorders and drug addiction.

The symptoms of depression include emotional and biological components. Emotional symptoms include:

- low mood, excessive rumination of negative thought, misery, apathy and pessimism
- low self-esteem: feelings of guilt, inadequacy and ugliness
- indecisiveness, loss of motivation
- anhedonia, loss of reward.

Biological symptoms include:

- retardation of thought and action
- loss of libido
- sleep disturbance and loss of appetite.

There are two distinct types of depressive syndrome, namely *unipolar depression*, in which the mood changes are always in the same direction, and *bipolar disorder*, in which depression alternates with mania. Mania is in most respects exactly the opposite, with excessive exuberance, enthusiasm and self-confidence, accompanied by impulsive actions, these signs often being combined with irritability, impatience and aggression, and sometimes with grandiose delusions of the Napoleonic kind. As with depression, the mood and actions are inappropriate to the circumstances.

Unipolar depression is commonly (about 75% of cases) non-familial, clearly associated with stressful life events, and usually accompanied by symptoms of anxiety and agitation; this type is sometimes termed *reactive depression*. Other cases (about 25%, sometimes termed *endogenous depression*) show a familial pattern, unrelated to obvious external stresses, and with a somewhat different symptomatology. This distinction is made clinically, but there is little evidence that antidepressant drugs show significant selectivity between these conditions.

Bipolar disorder, which usually appears in early adult life, is less common and results in oscillating depression and mania over a period of a few weeks. It can be difficult to differentiate between mild bipolar disorder and unipolar depression. Also, bipolar manic episodes can be confused with episodes of schizophrenic psychosis (see Ch. 46). There is a strong hereditary tendency, but no specific susceptibility genes have been identified either by genetic linkage studies of affected families, or by comparison of affected and non-affected individuals.

Depression cannot be attributed to altered neuronal activity within a single brain region; rather, the circuitry linking different parts of the brain may be affected. Brain imaging studies have indicated that the prefrontal cortex, amygdala and hippocampus may all be involved in different components of these disorders.

THEORIES OF DEPRESSION

THE MONOAMINE THEORY

The monoamine theory of depression, first proposed by Schildkraut in 1965, states that depression is caused by a functional deficit of the monoamine transmitters, noradrenaline and 5-hydroxytryptamine (5-HT) at certain sites in the brain, while mania results from a functional excess.

The monoamine hypothesis grew originally out of associations between the clinical effects of various drugs that cause or alleviate symptoms of depression and their known neurochemical effects on monoaminergic transmission in the brain. This pharmacological evidence, which is summarised in Table 47.1, gives general support to the monoamine hypothesis, although there are several anomalies. Attempts to obtain more direct evidence, by studying monoamine metabolism in depressed patients or by measuring changes in the number of monoamine receptors in postmortem brain tissue, have tended to give inconsistent and equivocal results, and the interpretation of these studies is often problematic, because the changes described are not specific to depression. Similarly, investigation by functional tests of the activity of known monoaminergic pathways (e.g. those controlling pituitary hormone release) in depressed patients have also given equivocal results.

The pharmacological evidence does not enable a clear distinction to be drawn between the noradrenaline and 5-HT theories of depression. Clinically, it seems that inhibitors of noradrenaline reuptake and of 5-HT reuptake are

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Table 47.1 Pharmacological evidence supporting the monoamine hypothesis of depression

Drug(s)	Principal action	Effect in depressed patients
Tricyclic antidepressants	Block noradrenaline and 5-HT reuptake	Mood ↑
Monoamine oxidase (MAO) inhibitors	Increase stores of noradrenaline and 5-HT	Mood ↑
Reserpine	Inhibits noradrenaline and 5-HT storage	Mood ↓
α-Methyltyrosine	Inhibits noradrenaline synthesis	Mood ↓ (calming of manic patients)
Methyldopa	Inhibits noradrenaline synthesis	Mood ↓
Electroconvulsive therapy	? Increases central nervous system responses to noradrenaline and 5-HT	Mood ↑
Tryptophan (5-hydroxytryptophan)	Increases 5-HT synthesis	Mood ? ↑ in some studies
Tryptophan depletion	Decreases brain 5-HT synthesis	Induces relapse in SSRI-treated patients

5-HT, 5-hydroxytryptamine; SSRI, selective serotonin reuptake inhibitor.

equally effective as antidepressants, although individual patients may respond better to one or the other.

Other evidence in support of the monoamine theory is that agents known to block noradrenaline or 5-HT synthesis consistently lower mood and reverse the therapeutic effects of antidepressant drugs that act selectively on these two transmitter systems (see Table 47.1).

Any theory of depression has to take account of the fact that the direct neurochemical effects of antidepressant drugs appear very rapidly (minutes to hours), whereas their antidepressant effects take weeks to develop. A similar situation exists in relation to antipsychotic drugs (Ch. 46) and some anxiolytic drugs (Ch. 44), suggesting that secondary, adaptive changes in the brain, rather than the primary drug effect, are responsible for the clinical improvement. Rather than thinking of the monoamine deficiency as causing direct changes in the activity of putative 'happy' or 'sad' neurons in the brain, we should think of the monoamines as regulators of longer-term trophic effects, whose time course is paralleled by mood changes.

Recent studies in healthy volunteers and depressed patients as well as in rodents suggest that antidepressant drugs may exert acute effects on the way information is processed (cognitive processing), leading to a positive effect on emotional behaviour. Whilst subjects may not be consciously aware of these acute effects, the drugs, by altering cognitive processes, will influence new learning and behaviour. Thus, over time and with chronic drug administration, these effects develop until the patient becomes subjectively aware of the improvement in their mood.

With improved neuroimaging methods for studying neurotransmitter function in the living human brain, as described in Chapter 36, our understanding of the causes of depression and how drugs can alleviate depression should improve.

NEUROENDOCRINE MECHANISMS

Various attempts have been made to test for a functional deficit of monoamine pathways in depression. Hypothalamic neurons controlling pituitary function receive noradrenergic and 5-HT inputs, which control the discharge of these cells. Hypothalamic cells release corticotrophin-releasing hormone (CRH), which stimulates pituitary cells to secrete adrenocorticotrophic hormone (ACTH), leading in turn to cortisol secretion (Ch. 33). The plasma cortisol concentration is usually high in depressed patients. Other hormones in plasma are also affected, for example growth hormone concentration is reduced and prolactin is increased. While these changes are consistent with deficiencies in monoamine transmission, they are not specific to depressive syndromes.

Corticotrophin-releasing hormone (CRH) is widely distributed in the brain and has behavioural effects that are distinct from its endocrine functions. Injected into the brain of experimental animals, CRH mimics some aspects of depression in humans, such as diminished activity, loss of appetite and increased signs of anxiety. Furthermore, CRH concentrations in the brain and cerebrospinal fluid of depressed patients are increased. Therefore CRH hyperfunction, as well as monoamine hypofunction, may be associated with depression. Raised CRH levels are associated with stress and, in many cases, depression is preceded by periods of chronic stress.

TROPHIC EFFECTS AND NEUROPLASTICITY

It has been suggested that lowered levels of brain-derived neurotrophic factor (BDNF) or malfunction of its receptor, TrkB, plays a significant role in the pathology of this condition (see Baudry et al., 2011). Depressive behaviour is often associated with a reduction in BDNF expression and treatment with antidepressants elevates BDNF levels. Glycogen synthase kinase 3 (GSK3β) has been implicated in the pathogenesis of depression following its identification as a target of the mood stabiliser **lithium** (see p. 587).

Changes in glutamatergic neurotransmission may also be involved in depression. Sufferers from depression have been shown to have elevated cortical levels of glutamate. Antidepressant treatment may reduce glutamate release and depress NMDA receptor function. The effects of antidepressants on activity-induced long-term potentiation (LTP; see Ch. 38) at hippocampal glutamatergic synapses is complex – both depression and facilitation have been observed and may occur quickly after antidepressant administration, thus calling into question the relevance to the therapeutic response.

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Another view (see Racagni & Popoli, 2008) is that major depression is associated with neuronal loss in the hippocampus and prefrontal cortex, and that antidepressant therapies of different kinds act by inhibiting or actually reversing this loss by stimulating neurogenesis.[1] This surprising idea is supported by various lines of evidence:

- Brain imaging and postmortem studies show ventricular enlargement as well as shrinkage of the hippocampus and prefrontal cortex of depressed patients, with loss of neurons and glia. Functional imaging reveals reduced neuronal activity in these regions.
- In animals, the same effect is produced by chronic stress of various kinds, or by administration of glucocorticoids, mimicking the increased cortisol secretion in human depression. Excessive glucocorticoid secretion in humans (Cushing's syndrome; see Ch. 33) often causes depression.
- In experimental animals, antidepressant drugs, or other treatments such as electroconvulsions (see later section on Brain Stimulation Therapies), promote neurogenesis in these regions, and (as in humans) restore functional activity. Preventing hippocampal neurogenesis prevents the behavioural effects of antidepressants in rats.
- 5-HT and noradrenaline, whose actions are enhanced by many antidepressants, promote neurogenesis, probably through activation of 5-HT_{1A} receptors and α_2 adrenoceptors, respectively. This effect may be mediated by BDNF.

Monoamine theory of depression

- The monoamine theory, first proposed in 1965, suggests that depression results from functionally deficient monoaminergic (noradrenaline and/or 5-hydroxytryptamine) transmission in the central nervous system.
- The theory is based on the ability of known antidepressant drugs (tricyclic antidepressants and monoamine oxidase inhibitors) to facilitate monoaminergic transmission, and of drugs such as **reserpine** to cause depression.
- Biochemical studies on depressed patients do not clearly support the monoamine hypothesis in its simple form.
- Although the monoamine hypothesis in its simple form is insufficient as an explanation of depression, pharmacological manipulation of monoamine transmission remains the most successful therapeutic approach.
- Recent evidence suggests that depression may be associated with neurodegeneration and reduced neurogenesis in the hippocampus.
- Current approaches focus on other mediators (e.g. corticotrophin-releasing hormone), signal transduction pathways, growth factors, etc., but theories remain imprecise.

[1]Neurogenesis (see Ch. 40) – the formation of new neurons from stem cell precursors – occurs to a significant degree in the adult hippocampus, and possibly elsewhere in the brain, contradicting the old dogma that it occurs only during brain development.

- Exercise has been shown to promote neurogenesis in animals and to be effective in some patients with mild to moderate depression.

Figure 47.1 summarises the possible mechanisms involved. It should be stressed that these hypotheses are far from proven, but the diagram emphasises the way in which the field has moved on since the formulation of the monoamine hypothesis, suggesting a range of possible targets for the next generation of antidepressant drugs.[2]

ANTIDEPRESSANT DRUGS

TYPES OF ANTIDEPRESSANT DRUG

Antidepressant drugs fall into the following categories.

Inhibitors of monoamine uptake

- Selective serotonin (5-HT) reuptake inhibitors (SSRIs) (e.g. **fluoxetine**, **fluvoxamine**, **paroxetine**, **sertraline**, **citalopram**, **escitalopram**, **vilazodone**).
- Classic tricyclic antidepressants (TCAs) (e.g. **imipramine**, **desipramine**, **amitriptyline**, **nortriptyline**, **clomipramine**). These vary in their activity and selectivity with respect to inhibition of noradrenaline and 5-HT reuptake.
- Newer, mixed 5-HT and noradrenaline reuptake inhibitors (e.g. **venlafaxine** [somewhat selective for 5-HT, although less so than SSRIs], **desvenlafaxine**, **duloxetine**).
- Noradrenaline reuptake inhibitors (e.g. **bupropion**, **reboxetine**, **atomoxetine**).
- The herbal preparation St John's wort, whose main active ingredient is hyperforin: it has similar clinical efficacy to most of the prescribed antidepressants. It is a weak monoamine uptake inhibitor but also has other actions.[3]

Monoamine receptor antagonists

- Drugs such as **mirtazapine**, **trazodone**, **mianserin** are non-selective and inhibit a range of amine receptors including α_2 adrenoceptors and 5-HT_2 receptors. They may also have weak effects on monoamine uptake.

Monoamine oxidase inhibitors (MAOIs)

- Irreversible, non-competitive inhibitors (e.g. **phenelzine**, **tranylcypromine**), which are non-selective with respect to the MAO-A and -B subtypes.
- Reversible, MAO-A-selective inhibitors (e.g. **moclobemide**).

[2]Cynics may feel that these mechanisms, in which glutamate, neurotrophic factors, monoamines and steroids all interact to control neuronal death, survival and plasticity, are being invoked just as enthusiastically to account for almost every neurological and psychiatric disorder that you can think of, from stroke and Parkinson's disease to schizophrenia. 'Are we missing something,' they may feel, 'or are all these diseases basically the same? If so, why are their effects so different? Is this just a scientific bandwagon, or does this mechanistic convergence point to some fundamental principles of neural organisation?' We do not have the answers, of course, but it is a field worth watching.

[3]Although relatively free of acute side effects, hyperforin activates cytochrome P450, resulting in loss of efficacy (Ch. 9), with serious consequences, of several important drugs, including ciclosporin, oral contraceptives, some anti-HIV and anticancer drugs, and oral anticoagulants – underlining the principle that herbal remedies are not inherently safe, and must be used with the same degree of informed caution as any other drug.

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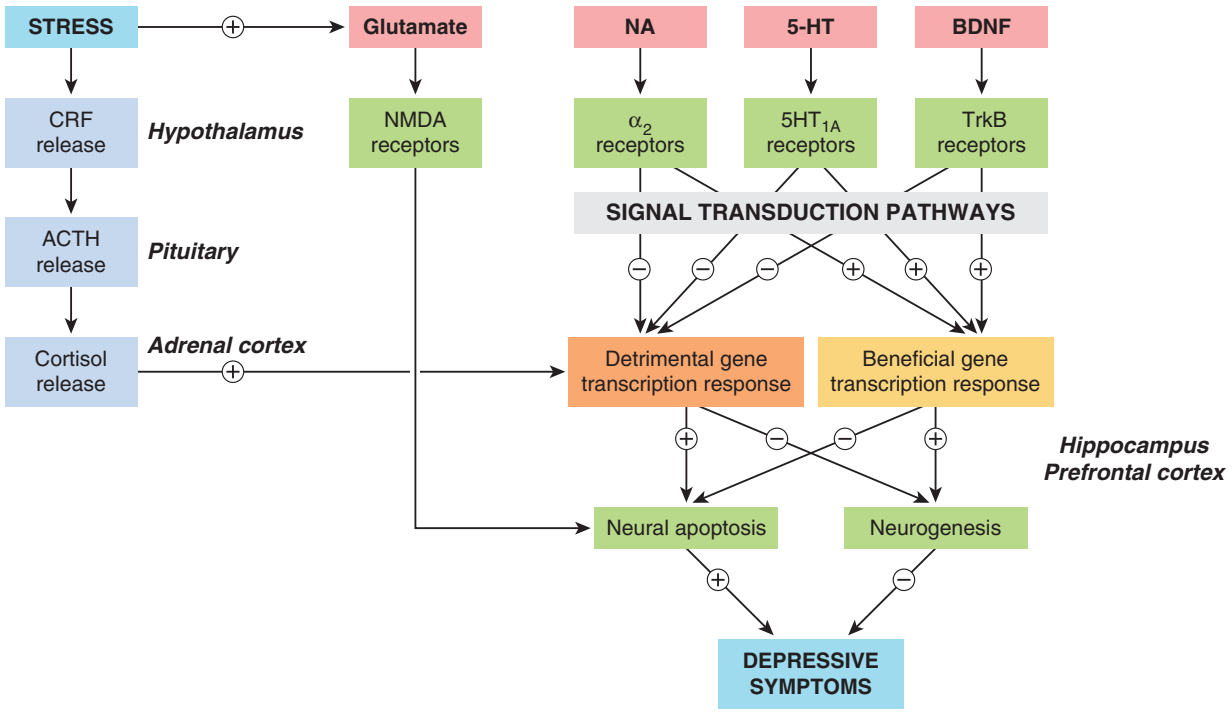

Fig. 47.1 Simplified diagram showing mechanisms believed to be involved in the pathophysiology of depression. The main prodepressive pathways involve the hypothalamic–pituitary–adrenal axis, which is activated by stress and in turn enhances the excitotoxic action of glutamate, mediated by NMDA receptors (see Ch. 38), and switches on the expression of genes that promote neural apoptosis in the hippocampus and prefrontal cortex. The antidepressive pathways involve the monoamines noradrenaline (NA) and 5-hydroxytryptamine (5-HT), which act on G protein-coupled receptors, and the brain-derived neurotrophic factor (BDNF), which acts on a kinase-linked receptor (TrkB), switching on genes that protect neurons against apoptosis and also promote neurogenesis. For further detail, see Charney & Manji (2004). ACTH, adrenocorticotrophic hormone; CRF, corticotrophin-releasing factor.

Types of antidepressant drugs

- Main types are:
  - monoamine uptake inhibitors (tricyclic antidepressants, selective serotonin reuptake inhibitors, newer inhibitors of noradrenaline and 5-HT reuptake)
  - monoamine receptor antagonists
  - monoamine oxidase (MAO) inhibitors.
- Monoamine uptake inhibitors act by inhibiting uptake of noradrenaline and/or 5-HT by monoaminergic nerve terminals.
- α_2-Adrenoceptor antagonists can indirectly elevate 5-HT release.
- MAO inhibitors inhibit one or both forms of brain MAO, thus increasing the cytosolic stores of noradrenaline and 5-HT in nerve terminals. Inhibition of type A MAO correlates with antidepressant activity. Most are non-selective; **moclobemide** is specific for MAO-A.
- All types of antidepressant drug appear to take at least 2 weeks to produce any perceived beneficial effects, even though their pharmacological effects are produced immediately, indicating that secondary adaptive changes are important.
- Recent evidence suggests that antidepressants may act by increasing neurogenesis in the hippocampus and other brain areas.

Melatonin receptor agonist

- **Agomelatine** is an agonist at MT_1 and MT_2 melatonin receptors, and a weak 5-HT_{2C} antagonist.

Table 47.2 summarises the main features of these types of drug. Mention should also be made of electroconvulsive therapy (ECT), electromagnetic therapy, deep brain stimulation and vagus stimulation, which are effective and usually act more rapidly than antidepressant drugs (see p. 585).

TESTING OF ANTIDEPRESSANT DRUGS

ANIMAL MODELS

Progress in unravelling the neurochemical mechanisms is, as in so many areas of psychopharmacology, limited by the lack of good animal models of the clinical condition. There is no known animal condition corresponding to the inherited form of depression in humans, but various procedures have been described that produce in animals

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Table 47.2 Types of antidepressant drugs and their characteristics

Type and examples	Action(s)	Unwanted effects	Risk of overdose	Pharmacokinetics	Notes
Monoamine uptake inhibitors					
(1) SSRIs	All highly selective for 5-HT	Nausea, diarrhoea, agitation, insomnia, anorgasmia Inhibit metabolism of other drugs, so risk of interactions	Low risk in overdose but must not be used in combination with MAO inhibitors	–	–
Fluoxetine	As above	As above	As above	Long $t_{1/2}$ (24–96 h)	–
Fluvoxamine	As above	As above	As above	$t_{1/2}$ 18–24 h	Less nausea than with other SSRIs
Paroxetine	As above	As above	As above	$t_{1/2}$18–24 h	Withdrawal reaction
Citalopram	As above	As above	As above	$t_{1/2}$ 24–36 h	–
Escitalopram	As above	As above	As above	$t_{1/2}$ 24–36 h	Active *S* isomer of citalopram Fewer side effects
Vilazodone	As above. Also has 5-HT_{1A} receptor partial agonist activity	As above	As above	$t_{1/2}$ 25 h	–
Sertraline	As above	As above	As above	$t_{1/2}$ 24–36 h	–
(2) Classical TCA group[a]	Inhibition of NA and 5-HT reuptake	Sedation Anticholinergic effects (dry mouth, constipation, blurred vision, urinary retention, etc.) Postural hypotension Seizures Impotence Interaction with CNS depressants (especially alcohol, MAO inhibitors)	Ventricular dysrhythmias High risk in combination with CNS depressants	–	'First-generation' antidepressants, still very widely used, although newer compounds generally have fewer side effects and lower risk with overdose
Imipramine	Non-selective Converted to desipramine	As above	As above	$t_{1/2}$ 4–18 h	–
Desipramine	NA selective	As above	As above	$t_{1/2}$ 12–24 h	–
Amitriptyline	Non-selective	As above	As above	$t_{1/2}$ 12–24 h; converted to nortriptyline	Widely used, also for neuropathic pain (Ch. 42)
Nortriptyline	NA selective (slight)	As above	As above	Long $t_{1/2}$ (24–96 h)	Long duration, less sedative
Clomipramine	Non-selective	As above	As above	$t_{1/2}$ 18–24 h	Also used for anxiety disorders

[a]Other TCAs include dosulepin, doxepin, lofepramine, trimipramine.

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Table 47.2 Continued

Type and examples	Action(s)	Unwanted effects	Risk of overdose	Pharmacokinetics	Notes
(3) Other 5-HT/NA uptake inhibitors					
Venlafaxine	Weak non-selective NA/5-HT uptake inhibitor Also non-selective receptor-blocking effects	As SSRIs Withdrawal effects common and troublesome if doses are missed	Safe in overdose	Short $t_{1/2}$ (~5 h) Converted to desvenlafaxine which inhibits NA uptake	Claimed to act more rapidly than other antidepressants, and to work better in 'treatment-resistant' patients Usually classed as non-selective NA/5-HT uptake blocker, although *in vitro* data show selectivity for 5-HT
Duloxetine	Potent non-selective NA/5-HT uptake inhibitor No action on monoamine receptors	Fewer side effects than venlafaxine Sedation, dizziness, nausea Sexual dysfunction	See SSRIs above	$t_{1/2}$ ~14 h	Also used to treat urinary incontinence (see Ch. 29) and for anxiety disorders
St John's wort (active principle: hyperforin)	Weak non-selective NA/5-HT uptake inhibitor Also non-selective receptor-blocking effects	Few side effects reported Risk of drug interactions due to enhanced drug metabolism (e.g. loss of efficacy of ciclosporin, antidiabetic drugs, etc.)		$t_{1/2}$ ~12 h	Freely available as crude herbal preparation Similar efficacy to other antidepressants, with fewer acute side effects but risk of serious drug interactions
NA-selective inhibitors					
Bupropion	Selective inhibitor of NA over 5-HT uptake but also inhibits dopamine uptake Converted to active metabolites (e.g. radafaxine)	Headache, dry mouth, agitation, insomnia	Seizures at high doses	$t_{1/2}$ ~12 h Plasma half-life ~20 h	Used in depression associated with anxiety Slow-release formulation used to treat nicotine dependence (Ch. 49)
Maprotiline	Selective NA uptake inhibitor	As TCAs; no significant advantages	As TCAs	Long $t_{1/2}$ ~40 h	No significant advantages over TCAs
Reboxetine	Selective NA uptake inhibitor	Dizziness Insomnia Anticholinergic effects	Safe in overdose (low risk of cardiac dysrhythmia)	$t_{1/2}$ ~12 h	Less effective than TCAs The related drug atomoxetine now used mainly to treat ADHD (Ch. 48)

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Table 47.2 Continued

Type and examples	Action(s)	Unwanted effects	Risk of overdose	Pharmacokinetics	Notes
(4) Monoamine receptor antagonists					
Mirtazapine	Blocks α_2, 5-HT_{2C} and 5-HT_3 receptors	Dry mouth Sedation Weight gain	No serious drug interactions	$t_{1/2}$ 20–40 h	Claimed to have faster onset of action than other antidepressants
Trazodone	Blocks 5-HT_{2A} and 5-HT_{2C} receptors as well as H_1 receptors Weak 5-HT uptake inhibitor (enhances NA/5-HT release)	Sedation Hypotension Cardiac dysrhythmias	Safe in overdose	$t_{1/2}$ 6–12 h	Nefazodone is similar
Mianserin	Blocks α_1, α_2, 5-HT_{2A} and H_1 receptors	Milder antimuscarinic and cardiovascular effects than TCAs Agranulocytosis, aplastic anaemia	–	$t_{1/2}$ 10–35 h	Blood count advised in early stages of use
MAO inhibitors	Inhibit MAO-A and/or MAO-B Earlier compounds have long duration of action due to covalent binding to enzyme				
Phenelzine	Non-selective	'Cheese reaction' to tyramine-containing foods (see text) Anticholinergic side effects Hypotension Insomnia Weight gain Liver damage (rare)	Many interactions (TCAs, opioids, sympathomimetic drugs) – risk of severe hypertension due to 'cheese reaction'	$t_{1/2}$ 1–2 h Long duration of action due to irreversible binding	–
Tranylcypromine	Non-selective	As phenelzine	As phenelzine	$t_{1/2}$ 1–2 h Long duration of action due to irreversible binding	–
Isocarboxazid	Non-selective	As phenelzine	As phenelzine	Long $t_{1/2}$ ~36 h	–
Moclobemide	MAO-A selective Short acting	Nausea, insomnia, agitation	Interactions less severe than with other MAO inhibitors; no 'cheese reactions' reported	$t_{1/2}$ 1–2 h	Safer alternative to earlier MAO inhibitors
Melatonin agonist					
Agomelatine	MT_1 and MT_2 receptor agonist. Weak 5-HT_{2C} antagonist	Headache, dizziness, drowsiness, fatigue, sleep disturbance, anxiety, nausea, GI disturbances, sweating	Limited data available at present	$t_{1/2}$ 1–2 h	Should not be combined with ethanol Usually taken once daily before bed

5-HT, 5-hydroxytryptamine; ADHD, attention deficit/hyperactivity disorder; CNS, central nervous system; MAO, monoamine oxidase; NA, noradrenaline; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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behavioural states (withdrawal from social interaction, loss of appetite, reduced motor activity, etc.) typical of human depression (see Neumann et al., 2011; O'Leary & Cryan, 2013). The use of genetically modified mice (e.g. 5-HT transporter knockdown) to mimic various aspects of the disorder may provide useful models. However, the similarity of these animal models to human depression is questionable.

TESTS ON HUMANS

Clinically, the effect of antidepressant drugs is usually measured by a subjective rating scale such as the 17-item Hamilton Rating Scale. Clinical depression takes many forms, and the symptoms vary between patients and over time. Quantitation is therefore difficult, and the many clinical trials of antidepressants have generally shown rather weak effects, after allowance for quite large placebo responses. There is also a high degree of individual variation, with 30–40% of patients failing to show any improvement, possibly due to genetic factors (see later section on Clinical Effectiveness).

MECHANISM OF ACTION OF ANTIDEPRESSANT DRUGS

CHRONIC ADAPTIVE CHANGES

Given the discrepancy between the fast onset of the neurochemical effects of antidepressant drugs and the slow onset of their antidepressant effects, efforts have been made to determine whether the therapeutic benefits arise from slow adaptive changes induced by chronic exposure to these drugs (Racagni & Popoli, 2008).

This approach led to the discovery that certain monoamine receptors, in particular β_1 and α_2 adrenoceptors, are consistently downregulated following chronic antidepressant treatment and, in some cases, by electroconvulsive therapy too. This can be demonstrated in experimental animals as a reduction in the number of binding sites, as well as by a reduction in the functional response to agonists (e.g. stimulation of cAMP formation by β-adrenoceptor agonists). Receptor downregulation probably also occurs in humans, because endocrine responses to **clonidine**, an α_2-adrenoceptor agonist, are reduced by long-term antidepressant treatment. However, the relevance of these findings to the antidepressant response is unclear. Loss of β adrenoceptors as a factor in alleviating depression does not fit comfortably with theory, because β-adrenoceptor antagonists are not antidepressant.

On acute administration, one would expect inhibition of 5-HT uptake (e.g. by SSRIs) to increase the level of 5-HT at the synapse by inhibiting reuptake into the nerve terminals. However, the increase in synaptic 5-HT levels has been observed to be less than expected. This is because increased activation of 5-HT_{1A} receptors on the soma and dendrites of 5-HT-containing raphe neurons (Fig. 47.2A) inhibits these neurons and thus reduces 5-HT release, thus cancelling out to some extent the effect of inhibiting reuptake into the terminals. On prolonged drug treatment, the elevated level of 5-HT in the somatodendritic region desensitises the 5-HT_{1A} receptors, reducing their inhibitory effect on 5-HT release from the nerve terminals. The need to desensitise somatodendritic 5-HT_{1A} receptors could thus explain in part the slow onset of antidepressant action of 5-HT uptake inhibitors.

NORADRENERGIC CONTROL OF 5-HT RELEASE

Block of presynaptic α_2 autoreceptors on noradrenergic nerve terminals throughout the central nervous system (CNS) will reduce the negative feedback from released noradrenaline and thus enhance further noradrenaline release (see Chs 14 and 37). In addition, α_2-adrenoceptor antagonists can indirectly enhance 5-HT release.

The effect of α_2-adrenoceptor antagonists on synaptic noradrenaline and 5-HT levels would be rapid in onset and so these changes must somehow induce other, slower adaptive responses that give rise to the slowly developing antidepressant effects.

GENE EXPRESSION AND NEUROGENESIS

More recently, interest has centred on intracellular signalling pathways, changes in gene expression and neurogenesis. Much attention has been focused on how antidepressants may activate the transcription factor, CREB, a cAMP response element-binding protein. The role of other transcription factors, such as those of the Fos family and NF-κB, have been less extensively studied. As described above, several antidepressant drugs appear to promote neurogenesis in the hippocampus, a mechanism that could account for the slow development of the therapeutic effect. The role of raised synaptic noradrenaline and 5-HT levels in inducing changes in gene expression and neurogenesis, and the mechanisms involved, await further elucidation.

MONOAMINE UPTAKE INHIBITORS

SELECTIVE 5-HYDROXYTRYPTAMINE UPTAKE INHIBITORS (SSRIs)

These are the most commonly prescribed group of antidepressants. Examples include **fluoxetine**, **fluvoxamine**, **paroxetine**, **citalopram**, **escitalopram** and **sertraline** (see Table 47.2). As well as showing selectivity with respect to 5-HT over noradrenaline uptake (Fig. 47.3), they are less likely than TCAs to cause anticholinergic side effects and are less dangerous in overdose. In contrast to MAOIs, they do not cause 'cheese reactions'. They are also used to treat anxiety disorders (see Ch. 44) and premature ejaculation. **Vortioxetine,** recently approved in the US, is a novel SSRI that also has partial agonist activity at 5-HT_{1A} and 5-HT_{1B} receptors and is an antagonist at 5-HT_{3A} and 5-HT_{7} receptors.

Individual patients may respond more favourably to one SSRI than another. This may reflect other pharmacological properties of each individual drug as none is devoid of other actions. Fluoxetine has 5-HT_{2C} antagonist activity, a property it shares with other non-SSRI antidepressants such as **mirtazapine**. Sertraline is a weak inhibitor of dopamine uptake. Escitalopram is the *S* isomer of racemic citalopram. It lacks the antihistamine and CYP2D6 inhibitory properties of the *R* isomer.

Pharmacokinetic aspects

The SSRIs are well absorbed when given orally, and most have plasma half-lives of 18–24 h (fluoxetine is longer acting: 24–96 h). Paroxetine and fluoxetine are not used in combination with TCAs, whose hepatic metabolism they inhibit through an interaction with CYP2D6, for fear of increasing TCA toxicity.

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Unwanted effects

Common side effects include nausea, anorexia, insomnia, loss of libido and failure of orgasm.[4] Some of these unwanted effects result from the enhanced stimulation of postsynaptic 5-HT receptors as a result of the drugs increasing the levels of extracellular 5-HT. This can be either stimulation of the wrong type of 5-HT receptor (e.g. 5-HT_2, 5-HT_3 and 5-HT_4 receptors) or stimulation of the same receptor that gives therapeutic benefit (e.g. postsynaptic 5-HT_{1A} receptors) but in the wrong brain region (i.e. enhanced stimulation of 5-HT receptors can result in both therapeutic and adverse responses).

In combination with MAOIs, SSRIs can cause a 'serotonin syndrome' characterised by tremor, hyperthermia and cardiovascular collapse, from which deaths have occurred.

There have been reports of increased aggression, and occasionally violence, in patients treated with fluoxetine, but these have not been confirmed by controlled studies. The use of SSRIs is not recommended for treating depression in children under 18, in whom efficacy is doubtful

[4]Thus, conversely, SSRIs can be used to treat premature ejaculation. Dapoxetine has a short half-life and is taken 1–3 hours before sex.

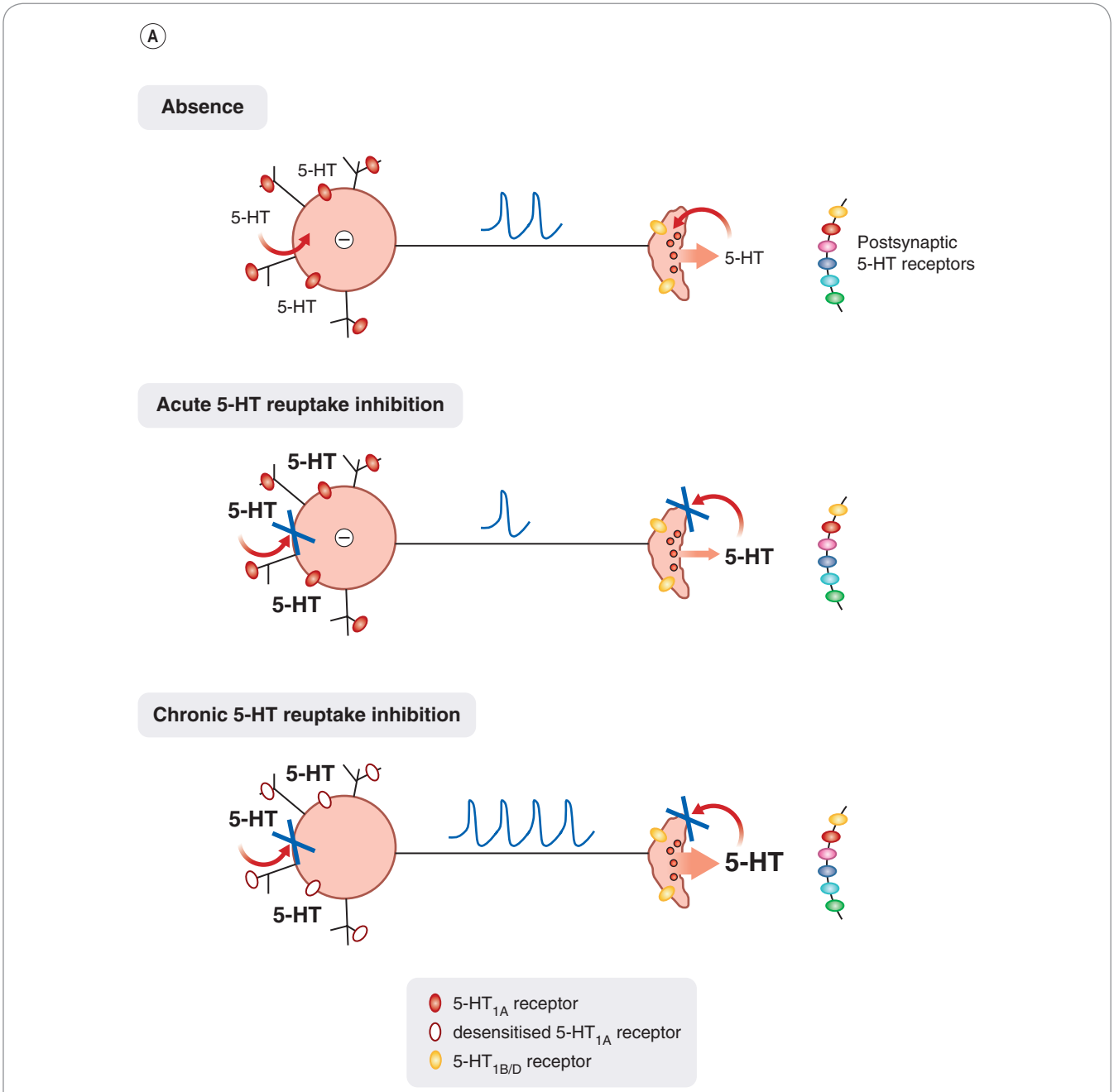

Fig. 47.2 Control of 5-hydroxytryptamine (5-HT) release. [**A**] 5-HT release is controlled by the inhibitory action of 5-HT on somatodendritic 5-HT_{1A} receptors. Acute inhibition of 5-HT reuptake results in increased extracellular levels of 5-HT but this increases somatodendritic 5-HT_{1A} receptor-mediated inhibition, hence synaptic 5-HT levels do not rise as much as expected. 5-HT_{1A} receptors eventually desensitise, resulting in reduced inhibition and thus greater 5-HT release.

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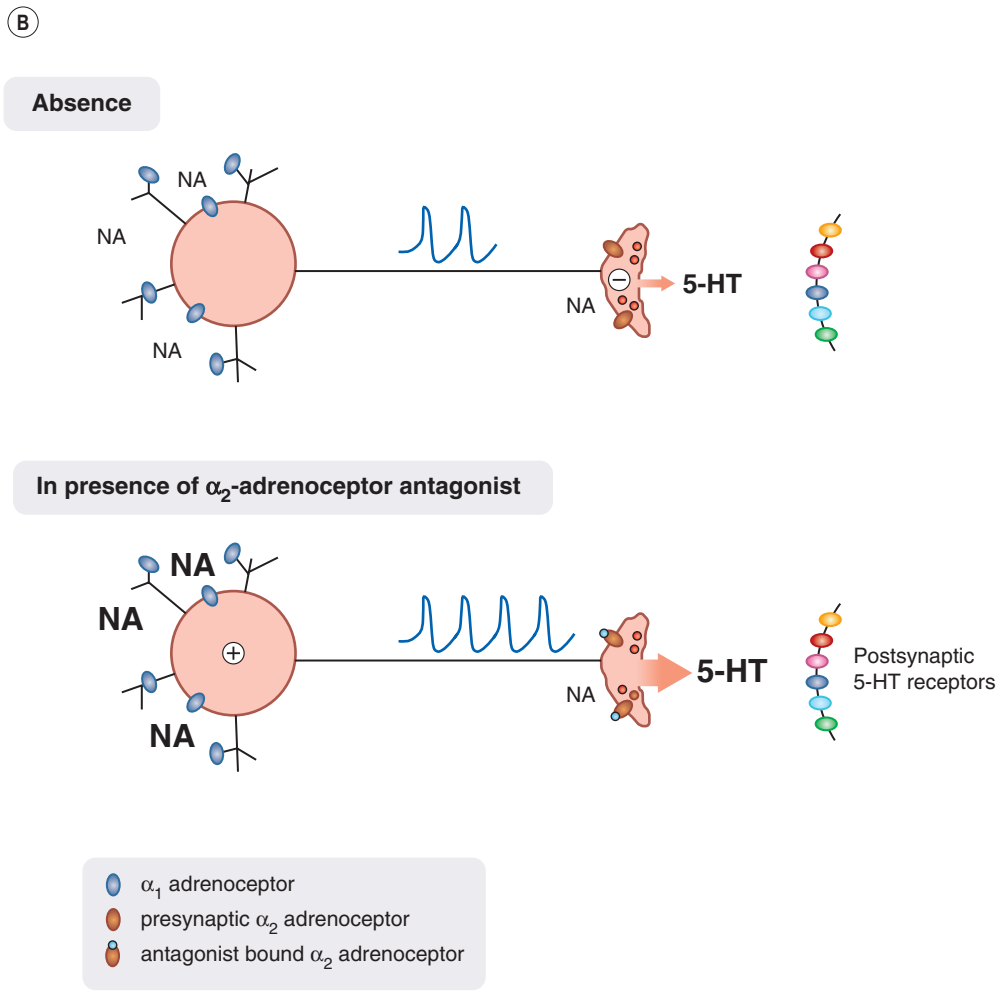

Fig. 47.2, Continued [**B**] 5-Hydroxytryptamine (5-HT) release is controlled by both an excitatory action of noradrenaline (NA) on somatodendritic α_1 adrenoceptors and an inhibitory action on α_2 adrenoceptors on serotonergic nerve terminals. Block of α_2 adrenoceptors located on noradrenergic neurons (not shown) enhances noradrenaline release resulting in further excitation of serotonergic neurons, while block of α_2 adrenoceptors on serotonergic neurons removes presynaptic inhibition and thus 5-HT release is enhanced.

and adverse effects, including excitement, insomnia and aggression in the first few weeks of treatment, may occur. The possibility of increased suicidal ideation is a concern in this age group (see p. 586).

Despite the apparent advantages of 5-HT uptake inhibitors over TCAs in terms of side effects, the combined results of many trials show little overall difference in terms of patient acceptability (Song et al., 1993; Cipriani et al., 2009).

They are relatively safe in overdose, compared with TCAs (see p. 580-581) but can prolong the cardiac QT interval, giving rise to ventricular arrhythmias (see Ch. 21) and risk of sudden death (Jolly et al., 2009).

5-HT uptake inhibitors are used in a variety of other psychiatric disorders, as well as in depression, including anxiety disorders and obsessive–compulsive disorder (see Ch. 44).

TRICYCLIC ANTIDEPRESSANT DRUGS

Tricyclic antidepressants (TCAs; **imipramine**, **desipramine**, **amitriptyline**, **nortriptyline**, **clomipramine**) are still widely used. They are, however, far from ideal in practice, and it was the need for drugs that act more quickly and reliably,

Selective serotonin reuptake inhibitors (SSRIs)

- Examples include **fluoxetine**, **fluvoxamine**, **paroxetine**, **sertraline**, **citalopram**, **escitalopram**.
- Antidepressant actions are similar in efficacy and time course to TCAs.
- Acute toxicity (especially cardiotoxicity) is less than that of MAOIs or TCAs, so overdose risk is reduced.
- Side effects include nausea, insomnia and sexual dysfunction. SSRIs are less sedating and have fewer antimuscarinic side effects than the older TCAs.
- No food reactions, but dangerous 'serotonin reaction' (hyperthermia, muscle rigidity, cardiovascular collapse) can occur if given with MAOIs.
- There is concern about the use of SSRIs in children and adolescents, due to reports of an increase in suicidal thoughts on starting treatment.
- Also used for some other psychiatric indications, e.g. anxiety.

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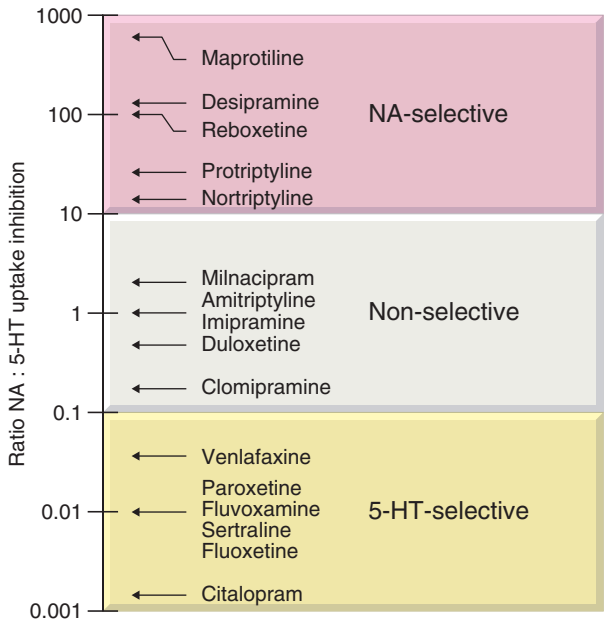

Fig. 47.3 Selectivity of inhibition of noradrenaline (NA) and 5-hydroxytryptamine (5-HT) uptake by various antidepressants.

produce fewer side effects and are less hazardous in overdose that led to the introduction of newer 5-HT reuptake inhibitors and other antidepressants.

TCAs are closely related in structure to the phenothiazines (Ch. 46) and were initially synthesised (in 1949) as potential antipsychotic drugs. Several are tertiary amines and are quite rapidly demethylated *in vivo* (Fig. 47.4) to the corresponding secondary amines (e.g. imipramine to desipramine, amitriptyline to nortriptyline), which are themselves active and may be administered as drugs in their own right. Other tricyclic derivatives with slightly modified bridge structures include **doxepin**. The pharmacological differences between these drugs are not very great and relate mainly to their side effects, which are discussed below.

Some TCAs are also used to treat neuropathic pain (see Ch. 42).

Mechanism of action

As discussed above, the main immediate effect of TCAs is to block the uptake of amines by nerve terminals, by competition for the binding site of the amine transporter (Ch. 14). Most TCAs inhibit noradrenaline and 5-HT uptake (Fig. 47.3) but have much less effect on dopamine uptake. It has been suggested that improvement of emotional symptoms reflects mainly an enhancement of 5-HT-mediated transmission, whereas relief of biological symptoms results from facilitation of noradrenergic transmission. Interpretation is made difficult by the fact that the major metabolites of TCAs have considerable pharmacological activity (in some cases greater than that of the parent drug) and often differ from the parent drug in respect of their noradrenaline/5-HT selectivity (Table 47.3).

In addition to their effects on amine uptake, most TCAs affect other receptors, including muscarinic acetylcholine receptors, histamine receptors and 5-HT receptors. The antimuscarinic effects of TCAs do not contribute to their antidepressant effects but are responsible for various side effects (see below).

Table 47.3 Inhibition of neuronal noradrenaline and 5-hydroxytryptamine (5-HT) uptake by tricyclic antidepressants and their metabolites

Drug/metabolite	NA uptake	5-HT uptake
Imipramine	+++	++
Desmethylimipramine (DMI) (also known as desipramine)	++++	+
Hydroxy-DMI	+++	–
Clomipramine (CMI)	++	+++
Desmethyl-CMI	+++	+
Amitriptyline (AMI)	++	++
Nortriptyline (desmethyl-AMI)	+++	++
Hydroxynortriptyline	++	++

Unwanted effects

In non-depressed human subjects, TCAs cause sedation, confusion and motor incoordination. These effects occur also in depressed patients in the first few days of treatment, but tend to wear off in 1–2 weeks as the antidepressant effect develops.

Tricyclic antidepressants produce a number of troublesome side effects, mainly due to interference with autonomic control.

Anti-muscarinic effects include dry mouth, blurred vision, constipation and urinary retention. These effects are strong with amitriptyline and much weaker with desipramine. Postural hypotension occurs with TCAs. This may seem anomalous for drugs that enhance noradrenergic transmission, and possibly results from an effect on adrenergic transmission in the medullary vasomotor centre. The other common side effect is sedation, and the long duration of action means that daytime performance is often affected by drowsiness and difficulty in concentrating.

TCAs, particularly in overdose, may cause ventricular dysrhythmias associated with prolongation of the QT interval (see Ch. 21). Usual therapeutic doses of TCAs increase, slightly but significantly, the risk of sudden cardiac death.

Interactions with other drugs

TCAs are particularly likely to cause adverse effects when given in conjunction with other drugs (see Ch. 57). They rely on hepatic metabolism by microsomal cytochrome P450 (CYP) enzymes for elimination, and this may be inhibited by competing drugs (e.g. antipsychotic drugs and some steroids).

TCAs potentiate the effects of alcohol and anaesthetic agents, for reasons that are not well understood, and deaths have occurred as a result of this, when severe respiratory depression has followed a bout of drinking. TCAs also interfere with the action of various antihypertensive drugs (see Ch. 22), with potentially dangerous consequences, so their use in hypertensive patients requires close monitoring.

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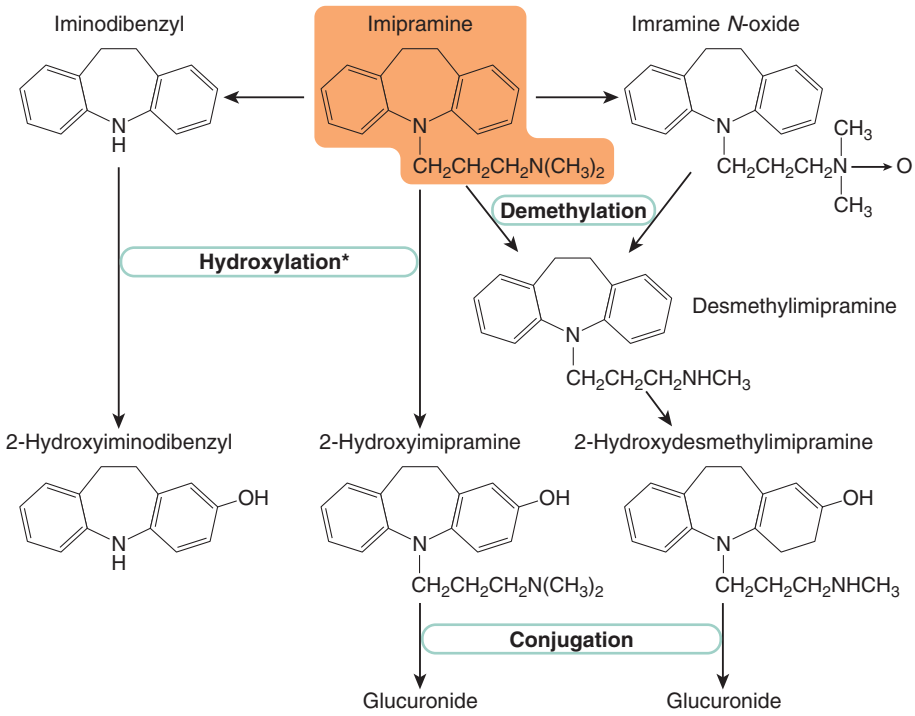

Fig. 47.4 Metabolism of imipramine, which is typical of that of other tricyclic antidepressants. The hydroxylating enzyme CYP2D6 is subject to genetic polymorphism, which may account for individual variation in response to tricyclic antidepressants (see Ch. 11).

Acute toxicity

TCAs are dangerous in overdose, and were at one time commonly used for suicide attempts, which was an important factor prompting the introduction of safer antidepressants. The main effects are on the central nervous system and the heart. The initial effect of TCA overdosage is to cause excitement and delirium, which may be accompanied by convulsions. This is followed by coma and respiratory depression lasting for some days. Atropine-like effects are pronounced, including dry mouth and skin, mydriasis and inhibition of gut and bladder. Anticholinesterase drugs have been used to counter atropine-like effects but are no longer recommended. Cardiac dysrhythmias are common, and sudden death (rare) may occur from ventricular fibrillation.

Pharmacokinetic aspects

TCAs are all rapidly absorbed when given orally and bind strongly to plasma albumin, most being 90–95% bound at therapeutic plasma concentrations. They also bind to extravascular tissues, which accounts for their generally very large distribution volumes (usually 10–50 l/kg; see Ch. 8) and low rates of elimination. Extravascular sequestration, together with strong binding to plasma albumin, means that haemodialysis is ineffective as a means of increasing drug elimination.

TCAs are metabolised in the liver by two main routes, *N*-demethylation and ring hydroxylation (Fig. 47.4). Both the desmethyl and the hydroxylated metabolites commonly retain biological activity (see Table 47.3). During prolonged treatment with TCAs, the plasma concentration of these metabolites is usually comparable to that of the parent drug, although there is wide variation between individuals. Inactivation of the drugs occurs by glucuronide conjugation of the hydroxylated metabolites, the glucuronides being excreted in the urine.

The overall half-times for elimination of TCAs are generally long, ranging from 10 to 20 h for imipramine and desipramine to about 80 h for **protriptyline**. They are even longer in elderly patients. Therefore, gradual accumulation is possible, leading to slowly developing side effects. The relationship between plasma concentrations and the therapeutic effect is not simple. Indeed, a study on nortriptyline (Fig. 47.5) showed that too high a plasma concentration actually reduces the antidepressant effect, and there is a narrow 'therapeutic window'.

SEROTONIN AND NORADRENALINE UPTAKE INHIBITORS (SNRIs)

These drugs are relatively non-selective for 5-HT and NA uptake. They include **venlafaxine**, **desvenlafaxine** and **duloxetine** (see Table 47.2). These have become extensively used antidepressant drugs due to manufacturers' claims of greater therapeutic efficacy and low side effect profiles, the evidence for which is rather weak.

As the dose of venlafaxine is increased, its efficacy also increases, which has been interpreted as demonstrating that its weak action to inhibit noradrenaline reuptake may add to its 5-HT uptake inhibition that occurs at lower doses, the combination providing additional therapeutic benefit. They are all active orally; venlafaxine is available in a slow-release formulation that reduces the incidence of nausea. Venlafaxine, desvenlafaxine and duloxetine are effective in some anxiety disorders (see Ch. 44). Desvenlafaxine may be useful in treating some perimenopausal

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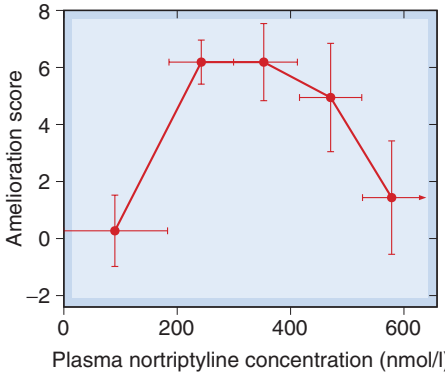

Fig. 47.5 'Therapeutic window' for nortriptyline. The antidepressant effect, determined from subjective rating scales, is optimal at plasma concentrations between 200 nmol/l and 400 nmol/l, and declines at higher levels.

Tricyclic antidepressants

- Tricyclic antidepressants are chemically related to phenothiazines, and some have similar non-selective receptor-blocking actions.
- Important examples are **imipramine**, **amitriptyline** and **clomipramine**.
- Most are long acting, and they are often converted to active metabolites.
- Important side effects: sedation (H_1 block); postural hypotension (α-adrenoceptor block); dry mouth, blurred vision, constipation (muscarinic block); occasionally mania and convulsions. Risk of ventricular dysrhythmias.
- Dangerous in acute overdose: confusion and mania, cardiac dysrhythmias.
- Liable to interact with other drugs (e.g. alcohol, anaesthetics, hypotensive drugs and non-steroidal anti-inflammatory drugs; should not be given with monoamine oxidase inhibitors).
- Also used to treat neuropathic pain.

symptoms such as hot flushes and insomnia. Duloxetine is also used in the treatment of neuropathic pain and fibromyalgia (see Ch. 42) and urinary incontinence.

Venlafaxine and duloxetine are metabolised by CYP2D6. Venlafaxine is converted to desvenlafaxine, which shows greater inhibition of noradrenaline reuptake. Unwanted effects of these drugs – largely due to enhanced activation of adrenoceptors – include headache, insomnia, sexual dysfunction, dry mouth, dizziness, sweating and decreased appetite. The most common symptoms in overdose are CNS depression, serotonin toxicity, seizure and cardiac conduction abnormalities. Duloxetine has been reported to cause hepatotoxicity and is contraindicated for patients with hepatic impairment.

OTHER NORADRENALINE UPTAKE INHIBITORS

Bupropion inhibits both noradrenaline and dopamine (but not 5-HT) uptake but, unlike cocaine and amphetamine (see Ch. 48), does not induce euphoria and has so far not been observed to have abuse potential. It is

Other monoamine uptake inhibitors

- **Venlafaxine** is a 5-HT uptake inhibitor, but less selective for 5-HT versus noradrenaline than SSRIs. It is metabolised to **desvenlafaxine**, which is also antidepressant.
- **Duloxetine** inhibits NA and 5-HT uptake.
- **Bupropion** is a noradrenaline and dopamine uptake inhibitor.
- Generally similar to tricyclic antidepressants but lack major receptor-blocking actions, so fewer side effects.
- Less risk of cardiac effects, so safer in overdose than tricyclic antidepressants.
- Can be used to treat other disorders:
  - **venlafaxine**, **desvenlafaxine** and **duloxetine** – anxiety disorders
  - **duloxetine** and **milnacipran** – neuropathic pain and fibromyalgia
  - **duloxetine** – urinary incontinence
  - **bupropion** – nicotine dependence.

metabolised to active metabolites. It is also used to treat nicotine dependence (see Ch. 49). At high doses it may induce seizures. **Reboxetine** and **atomoxetine** are highly selective inhibitors of noradrenaline uptake but their efficacy in depression is less than that of TCAs. Atomoxetine is approved for the treatment of attention deficit/hyperactivity disorder (see Ch. 48).

MONOAMINE RECEPTOR ANTAGONISTS

Mirtazapine blocks not only α_2 adrenoreceptors but also other receptors, including 5-HT_{2C} receptors, which may contribute to its antidepressant actions. Block of α_2 adrenoceptors will not only increase noradrenaline release but will also enhance 5-HT release (see Fig 47.2B); however, by simultaneously blocking 5-HT_{2A} and 5-HT_3 receptors it will reduce unwanted effects mediated through these receptors (e.g. sexual dysfunction and nausea) but leave intact stimulation of postsynaptic 5-HT_{1A} receptors. It also blocks histamine H_1 receptors, which may cause sedation. **Trazodone** combines 5-HT_{2A} and 5-HT_{2C} receptor antagonism with 5-HT reuptake inhibition.

Mianserin, another α_2-adrenoceptor antagonist that also blocks H_1, 5-HT_{2A} and α_1 adrenoreceptors, can cause bone marrow depression, requiring regular blood counts, so its use has declined in recent years.

MONOAMINE OXIDASE INHIBITORS

Monoamine oxidase inhibitors (MAOIs) were among the first drugs to be introduced clinically as antidepressants but were largely superseded by other types of antidepressants, whose clinical efficacies were considered better and whose side effects are generally less than those of MAOIs. The main examples are **phenelzine**, **tranylcypromine** and **iproniazid**. These drugs cause irreversible inhibition of the enzyme and do not distinguish between the two main isozymes (see below). The discovery of reversible inhibitors that show isozyme selectivity has rekindled interest in this class of drug. Although several studies have shown a reduction in platelet MAO activity in certain groups of depressed

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Table 47.4 Substrates and inhibitors for type A and type B monoamine oxidase

	Type A	Type B
Preferred substrates	Noradrenaline 5-Hydroxytryptamine	Phenylethylamine Benzylamine
Non-specific substrates	Dopamine Tyramine	Dopamine Tyramine
Specific inhibitors	Clorgyline Moclobemide	Selegiline
Non-specific inhibitors	Pargyline Tranylcypromine Isocarboxazid	Pargyline Tranylcypromine Isocarboxazid

Other antidepressant drugs

- **Mirtazapine** blocks α_2 adrenoceptors and 5-HT_{2C} receptors, enhancing noradrenaline and 5-HT release.
- **Mirtazapine** may act more rapidly than other antidepressants, and causes less nausea and sexual dysfunction than SSRIs.
- **Trazodone** blocks 5-HT_{2A} and 5-HT_{2C} receptors and blocks 5-HT reuptake.
- **Mianserin** is an antagonist at multiple 5-HT receptors (including 5-HT_{2A}) as well as at α_1 and α_2 receptors. It is also an inverse agonist at H_1 receptors. Use is declining because of risk of bone marrow depression. Regular blood counts are advisable.
- Cardiovascular side effects of these drugs are fewer than those of tricyclic antidepressants.
- **Agomelatine** is an agonist at MT_1 and MT_2 melatonin receptors.

patients, there is no clear evidence that abnormal MAO activity is involved in the pathogenesis of depression.

Monoamine oxidase (see Ch. 14) is found in nearly all tissues, and exists in two similar molecular forms coded by separate genes (see Table 47.4). MAO-A has a substrate preference for 5-HT and is the main target for the antidepressant MAOIs. MAO-B has a substrate preference for phenylethylamine and dopamine. Type B is selectively inhibited by **selegiline**, which is used in the treatment of Parkinson's disease (see Ch. 40). Disruption of the MAO-A gene in mice causes increased brain accumulation of 5-HT and, to a lesser extent, noradrenaline, along with aggressive behaviour. A family has been reported with an inherited mutation leading to loss of MAO-A activity, whose members showed mental retardation and violent behaviour patterns. Most antidepressant MAOIs act on both forms of MAO, but clinical studies with subtype-specific inhibitors have shown clearly that antidepressant activity, as well as the main side effects of MAOIs, is associated with MAO-A inhibition. MAO is located intracellularly, mostly associated with mitochondria, and has two main functions:

1. Within nerve terminals, MAO regulates the free intraneuronal concentration of noradrenaline or 5-HT. It is not involved in the inactivation of released transmitter.
2. MAO in the gut wall is important in the inactivation of endogenous and ingested amines such as tyramine that would otherwise produce unwanted effects.

Chemical aspects

Monoamine oxidase inhibitors are substrate analogues with a phenylethylamine-like structure, and most contain a reactive group (e.g. hydrazine, propargylamine, cyclopropylamine) that enables the inhibitor to bind covalently to the enzyme, resulting in a non-competitive and long-lasting inhibition. Recovery of MAO activity after inhibition takes several weeks with most drugs, but is quicker after **tranylcypromine**, which forms a less stable bond with the enzyme. **Moclobemide** acts as a reversible competitive inhibitor.

Monoamine oxidase inhibitors are not specific in their actions, and inhibit a variety of other enzymes as well as MAO, including many enzymes involved in the metabolism of other drugs. This is responsible for some of the many clinically important drug interactions associated with MAOIs.

Pharmacological effects

Monoamine oxidase inhibitors cause a rapid and sustained increase in the 5-HT, noradrenaline and dopamine content of the brain, 5-HT being affected most and dopamine least. Similar changes occur in peripheral tissues such as heart, liver and intestine, and increases in the plasma concentrations of these amines are also detectable. Although these increases in tissue amine content are largely due to accumulation within neurons, transmitter release in response to nerve activity is not increased. In contrast to the effect of TCAs, MAOIs do not increase the response of peripheral organs, such as the heart and blood vessels, to sympathetic nerve stimulation. The main effect of MAOIs is to increase the cytoplasmic concentration of monoamines in nerve terminals, without greatly affecting the vesicular stores that are releasable by nerve stimulation. The increased cytoplasmic pool results in an increased rate of spontaneous leakage of monoamines, and also an increased release by indirectly acting sympathomimetic amines such as amphetamine and tyramine (see Ch. 14 and Fig. 14.8). Tyramine thus causes a much greater rise in blood pressure in MAOI-treated animals than in controls. This mechanism is important in relation to the 'cheese reaction' produced by MAOIs in humans (see below).

In normal human subjects, MAOIs cause an immediate increase in motor activity, and euphoria and excitement develop over the course of a few days. This is in contrast to TCAs, which cause only sedation and confusion when given to non-depressed subjects. The effects of MAOIs on amine metabolism develop rapidly, and the effect of a single dose lasts for several days. There is a clear discrepancy, as with SSRIs and TCAs, between the rapid biochemical response and the delayed antidepressant effect.

Unwanted effects and toxicity

Many of the unwanted effects of MAOIs result directly from MAO inhibition, but some are produced by other mechanisms.

Hypotension is a common side effect; indeed, **pargyline** was at one time used as an antihypertensive drug. One possible explanation for this effect – the opposite of what might have been expected – is that amines such as dopamine or octopamine accumulate within peripheral

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sympathetic nerve terminals and displace noradrenaline from the storage vesicles, thus reducing noradrenaline release associated with sympathetic activity.

Excessive central stimulation may cause tremors, excitement, insomnia and, in overdose, convulsions.

Increased appetite, leading to weight gain, can be so extreme as to require the drug to be discontinued.

Atropine-like side effects (dry mouth, blurred vision, urinary retention, etc.) are common with MAOIs, although they are less of a problem than with TCAs.

MAOIs of the hydrazine type (e.g. phenelzine and iproniazid) produce, very rarely (less than 1 in 10000), severe hepatotoxicity, which seems to be due to the hydrazine moiety of the molecule. Their use in patients with liver disease is therefore unwise.

Interaction with other drugs and foods

Interaction with other drugs and foods is the most serious problem with MAOIs and is the main factor that caused their clinical use to decline. The special advantage claimed for the new reversible MAOIs, such as moclobemide, is that these interactions are reduced.

The 'cheese reaction' is a direct consequence of MAO inhibition and occurs when normally innocuous amines (mainly tyramine) produced during fermentation are ingested. Tyramine is normally metabolised by MAO in the gut wall and liver, and little dietary tyramine reaches the systemic circulation. MAO inhibition allows tyramine to be absorbed, and also enhances its sympathomimetic effect, as discussed above. The result is acute hypertension, giving rise to a severe throbbing headache and occasionally even to intracranial haemorrhage. Although many foods contain some tyramine, it appears that at least 10 mg of tyramine needs to be ingested to produce such a response, and the main danger is from ripe cheeses and from concentrated yeast products such as Marmite. Administration of indirectly acting sympathomimetic amines (e.g. **ephedrine** – a nasal decongestant – or amphetamine – a drug of abuse) also causes severe hypertension in patients receiving MAOIs; directly acting agents such as noradrenaline (used, for example, in conjunction with local anaesthetics; see Ch. 43) are not hazardous. Moclobemide, a specific MAO-A inhibitor, does not cause the 'cheese reaction', probably because tyramine can still be metabolised by MAO-B.

Hypertensive episodes have been reported in patients given TCAs and MAOIs simultaneously. The probable explanation is that inhibition of noradrenaline reuptake further enhances the cardiovascular response to dietary tyramine, thus accentuating the 'cheese reaction'. This combination of drugs can also produce excitement and hyperactivity.

Monoamine oxidase inhibitors can interact with **pethidine** (see Ch. 42) to cause severe hyperpyrexia, with restlessness, coma and hypotension. The mechanism is uncertain, but it is likely that an abnormal pethidine metabolite is produced because of inhibition of demethylation.

MELATONIN AGONIST

Agomelatine is an agonist at MT_1 and MT_2 receptors (see Ch. 39), and has a short biological half-life. It is used to treat severe depression, usually taken once daily before bed. It may work by correcting disturbances in circadian rhythms often associated with depression. There are reports of hepatotoxicity in a few patients, and it should not be used in patients with liver disease.

Monoamine oxidase inhibitors (MAOIs)

- Main examples are **phenelzine**, **tranylcypromine**, **isocarboxazid** (irreversible, long-acting, non-selective between MAO-A and B) and **moclobemide** (reversible, short-acting, MAO-A selective).
- Long-acting MAOIs:
  - main side effects: postural hypotension (sympathetic block); atropine-like effects (as with TCAs); weight gain; CNS stimulation, causing restlessness, insomnia; hepatotoxicity and neurotoxicity (rare)
  - acute overdose causes CNS stimulation, sometimes convulsions
  - 'cheese reaction', i.e. severe hypertensive response to tyramine-containing foods (e.g. cheese, beer, wine, well-hung game, yeast or soy extracts); such reactions can occur up to 2 weeks after treatment is discontinued.
- Interaction with other amines (e.g. **ephedrine** in over-the-counter decongestants, **clomipramine** and other TCAs) and some other drugs (e.g. **pethidine**) are also potentially lethal.
- **Moclobemide** is used for major depression and social phobia. 'Cheese reaction' and other drug interactions are less severe and shorter lasting than with irreversible MAOIs.
- MAOIs are used much less than other antidepressants because of their adverse effects and serious interactions. They are indicated for major depression in patients who have not responded to other drugs.

MISCELLANEOUS AGENTS

Methylfolate, given as a dietary supplement, may be effective in depressed individuals who have lowered folate levels.

Oestrogen, which is known to elevate mood in perimenopausal women, may also be of value for the treatment of postnatal depression. Its effectiveness in treating other forms of depression is unclear. In addition to its well-documented hormonal actions in the body (see Ch. 35), it also has actions on monoaminergic, GABAergic and glutamatergic systems in the brain (see Chs 38 and 39).

FUTURE ANTIDEPRESSANT DRUGS

After a fallow period, there are now several promising new drugs in development (see Lodge & Li, 2008; Mathew et al., 2008).[5] These can be classified broadly into the following:

- Broad spectrum monoamine uptake inhibitors, i.e. affecting 5-HT, NA and DA uptake. One such drug, **tedatioxetine**, is in clinical trials.

[5]Hopes for an antidepressant drug targeting nicotinic receptors have been dashed by the failure of an α4β2 subtype antagonist in Phase III clinical trials.

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- Drugs inhibiting 5-HT, NA and DA uptake as well as having one or more of the following properties: β_3-adrenoreceptor agonism, D_2 dopamine-receptor agonism or antagonism, 5-HT_{1A}-receptor agonism or partial agonism and 5-HT_{2A}-receptor antagonism.
- Interest in drugs acting at the NMDA receptor has been stimulated by the observation that a single, intravenous, subanaesthetic dose of **ketamine** (see Ch. 41) rapidly alleviates depression, an effect that lasts for days.
- Antagonists at the κ opioid receptor are in clinical trials as antidepressants (see Ch. 42). κ opioid receptor agonists have long been known to induce dysphoria, anhedonia and hallucinations.
- Drugs acting at novel receptor targets – such as GRII cortisol receptor antagonists, melanocyte inhibiting factor (MIF-1) analogues, $GABA_B$ receptor antagonists.

Other avenues of research are into the development of compounds that act on the signal transduction pathways responsible for neurogenesis, neural plasticity and apoptosis (see Baudry et al., 2011).

Clinical uses of drugs in depression

- Mild depression is often best treated initially with non-drug measures, with antidepressant drugs being used in addition if the response is poor.
- The use of antidepressant drugs is advisable in the treatment of moderate to severe depression.
- The clinical efficacy of antidepressant drugs is limited, and varies between individuals. Clinical trials have produced inconsistent results, because of placebo responses and spontaneous fluctuations in the level of depression.
- Different classes of antidepressant drugs have similar efficacy but different side effects.
- Choice of drug is based on individual aspects including concomitant disease (TCAs in particular have several indications) and treatment (MAOIs and TCAs cause important interactions), suicide risk and previous response to treatment. Other things being equal, an SSRI is preferred as these are usually better tolerated and are less dangerous in overdose.
- Antidepressant drugs take several weeks before taking effect, so decisions on dose increment or switching to another class should not be made precipitately. Use of MAOIs is by specialists.
- An effective regimen should be continued for at least 2 years.
- In urgent situations, specialist consideration should be given to possible use of electroconvulsive therapy.
- Anxiolytic (e.g. benzodiazepine, Ch. 44), or antipsychotic drugs (Ch. 46) are useful adjuncts in some patients.

BRAIN STIMULATION THERAPIES

A number of brain stimulation techniques are now being used or developed to treat depression. Bright light stimulation has been proposed as a treatment for seasonal affective disorder. The most established brain stimulation techniques are electroconvulsive therapy (ECT) and repetitive transcranial magnetic stimulation (TMS). Brain stimulation treatments are often used as the therapeutic approach of last resort for patients who have not responded to antidepressant drugs.

ECT involves stimulation through electrodes placed on either side of the head, with the patient lightly anaesthetised, paralysed with a short-acting neuromuscular-blocking drug (e.g. **suxamethonium**; Ch. 13) so as to avoid physical injury, and artificially ventilated. Controlled trials have shown ECT to be at least as effective as antidepressant drugs, with response rates ranging between 60% and 80%; it appears to be an effective treatment for severe suicidal depression and has the advantage of producing a fast-onset response. The main disadvantage of ECT is that it often causes confusion and memory loss lasting for days or weeks. TMS gives electrical stimulation without anaesthesia or convulsion and does not produce cognitive impairment, but comparative studies suggest that its antidepressant efficacy is less than that of conventional ECT.

The effect of ECT on experimental animals has been carefully analysed to see if it provides clues as to the mode of action of antidepressant drugs, but the clues it gives are enigmatic. 5-HT synthesis and uptake are unaltered, and noradrenaline uptake is somewhat increased (in contrast to the effect of TCAs). Decreased β adrenoceptor responsiveness, both biochemical and behavioural, occurs with both ECT and long-term administration of antidepressant drugs, but changes in 5-HT-mediated responses tend to go in opposite directions.

There have been reports that deep brain stimulation, which has also been used in the treatment of Parkinson's disease (see Ch. 40), in which stimulation is delivered in a specific brain region through surgically implanted electrodes, is effective in patients not responding to other treatments (see Mayberg et al., 2005). The effectiveness of another technique, vagal stimulation, in producing long-term benefit in depression is still unclear (see Grimm & Bajbouj, 2010).

CLINICAL EFFECTIVENESS OF ANTIDEPRESSANT TREATMENTS

The overall clinical efficacy of antidepressants is generally accepted for severe depression, though there is concern that the published clinical trials evidence may be misleading, because many negative trials have gone unreported. Trials data suggest that 30–40% of depressed patients fail to show improvement, and those that do show only limited improvement. Clear evidence of benefit in mild to moderate depression is lacking. Interpretation of trials data is complicated by a high placebo response, and spontaneous recovery independent of any treatment. Current trials data do not suggest that drugs currently in use differ in terms of efficacy. Nevertheless, clinical experience suggests that individual patients may, for unknown reasons, respond better to one drug than another. Overall, it is now believed that antidepressant drugs are less effective than was originally thought, though they remain among the most commonly prescribed. Current treatment guidelines recommend evidence-based psychological procedures as first-line treatments in most cases, before antidepressant drugs.

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Pharmacogenetic factors

▼ The individual variation in response to antidepressants may be partly due to genetic factors, as well as to heterogeneity of the clinical condition. Two genetic factors have received particular attention, namely:

- polymorphism of the cytochrome P450 gene, especially *CYP2D6* (see Kirchheiner et al., 2004), which is responsible for hydroxylation of TCAs
- polymorphism of monoamine transporter genes (see Glatt & Reus, 2003).

Up to 10% of Caucasians possess a dysfunctional *CYP2D6* gene, and consequently may be susceptible to side effects of TCAs and various other drugs (see Ch. 11) that are metabolised by this route. The opposite effect, caused by duplication of the gene, is common in Eastern European and East African populations, and may account for a lack of clinical efficacy in some individuals. There is some evidence to suggest that responsiveness to SSRIs is related to polymorphism of one of the serotonin transporter genes (see Gerretsen & Pollock, 2008).

Although genotyping may prove to be a useful approach in the future to individualising antidepressant therapy, its practical realisation is still some way off.

Suicide and antidepressants

▼ There have been reports that antidepressants increased the risk of 'suicidality' in depressed patients, especially in children and adolescents (see Licinio & Wong, 2005). The term *suicidality* encompasses suicidal thoughts and planning as well as unsuccessful attempts; actual suicide, although one of the major causes of death in young people, is much rarer than suicidality. Clinical trials to determine the relationship between antidepressants and suicidality are difficult, because of the clear association between depression and suicide, and have given variable results, with some studies suggesting that suicidality may be increased during the first few weeks of antidepressant treatment, although not thereafter, and some showing a small increase in the risk of actual suicide (see Cipriani et al., 2005). Although antidepressants, including SSRIs, may carry a small risk of inducing suicidal thoughts and suicide attempts in young people, the risk is less in older age groups. There is no evidence to suggest that SSRIs carry any greater risk than other antidepressants. Furthermore, the risk has to be balanced against the beneficial effects of these drugs, not only on depression but also on anxiety, panic and obsessive–compulsive disorders (see Ch. 44).

OTHER CLINICAL USES OF ANTIDEPRESSANT DRUGS

To some extent, the term 'antidepressant drug' is misleading, as many of these drugs are now used to treat disorders other than depression. These include:

- neuropathic pain (e.g. **amytriptyline**, **nortryptyline**, duloxetine; Ch. 42)
- anxiety disorders (e.g. SSRIs, venlafaxine, duloxetine; Ch. 44)
- fibromyalgia (e.g. duloxetine, venlafaxine, SSRIs, TCAs; Ch. 42)
- bipolar disorder (e.g. fluoxetine in conjunction with **olanzapine**; see below)
- smoking cessation (e.g. buproprion; Ch. 49)
- attention deficit/hyperactivity disorder (e.g. atomoxetine; Ch. 48).

DRUG TREATMENT OF BIPOLAR DISORDER

A range of drugs are now used to control the mood swings characteristic of manic-depressive (bipolar) illness. The major drugs are:

- **lithium**
- several antiepileptic drugs, e.g. **carbamazepine**, **valproate**, **lamotrogine**
- some antipsychotic drugs, e.g. **olanzapine**, **risperidone**, **quetiapine**, **aripiprazole**.

When used to treat bipolar disorder, lithium and antiepileptic agents are often referred to as *mood-stabilising* drugs.

Other agents that may have some beneficial effects in the treatment of bipolar disorder are benzodiazepines (to calm, induce sleep and reduce anxiety), **memantine**, **amantadine** and **ketamine**. The use of antidepressant drugs in bipolar disorder is somewhat controversial. It is recommended that they are given in combination with an antimanic agent because, in some patients, they may induce or enhance mania.

Used prophylactically in bipolar disorder, drugs prevent the swings of mood and thus can reduce both the depressive and the manic phases of the illness. They are given over long periods, and their beneficial effects take 3–4 weeks to develop. Given in an acute attack, they are effective only in reducing mania, but not the depressive phase (although lithium is sometimes used as an adjunct to antidepressants in severe cases of unipolar depression).

LITHIUM

The psychotropic effect of lithium was discovered in 1949 by Cade, who had predicted that urate salts should prevent the induction by uraemia of a hyperexcitability state in guinea pigs. He found lithium urate to produce an effect, quickly discovered that it was due to lithium rather than urate, and went on to show that lithium produced a rapid improvement in a group of manic patients.

Antiepileptic and atypical antipsychotic drugs (see below) are equally effective in treating acute mania; they act more quickly and are considerably safer, so the clinical use of lithium is mainly confined to prophylactic control of manic-depressive illness. The use of lithium is declining.[6] It is relatively difficult to use, as plasma concentration monitoring is required, and there is the potential for problems in patients with renal impairment and for drug interactions, for example with diuretics (see Ch. 57). Lithium may have beneficial effects in neurodegenerative diseases such as Alzheimer's disease (see Ch. 40).

Pharmacological effects and mechanism of action

Lithium is clinically effective at a plasma concentration of 0.5–1 mmol/l, and above 1.5 mmol/l it produces a variety of toxic effects, so the therapeutic window is narrow. In normal subjects, 1 mmol/l lithium in plasma has no appreciable psychotropic effects. It does, however, produce many detectable biochemical changes, and it is still unclear how these may be related to its therapeutic effect.

Lithium is a monovalent cation that can mimic the role of Na^+ in excitable tissues, being able to permeate the voltage-gated Na^+ channels that are responsible for action potential generation (see Ch. 4). It is, however, not pumped out by the Na^+-K^+-ATPase, and therefore tends to accumulate inside excitable cells, leading to a partial loss of intracellular K^+, and depolarisation of the cell.

[6]The decline in lithium use may have been influenced by the imbalance in the marketing of this simple inorganic ion versus more profitable pharmacological agents.

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The biochemical effects of lithium are complex, and it inhibits many enzymes that participate in signal transduction pathways. Those that are thought to be relevant to its therapeutic actions are as follows:

- Inhibition of inositol monophosphatase, which blocks the phosphatidyl inositol (PI) pathway (see Ch. 3) at the point where inositol phosphate is hydrolysed to free inositol, resulting in depletion of PI. This prevents agonist-stimulated inositol trisphosphate formation through various PI-linked receptors, and therefore blocks many receptor-mediated effects.
- Inhibition of glycogen synthase kinase 3 (GSK3) isoforms, possibly by competing with magnesium for its association with these kinases. GSK3 isoforms phosphorylate a number of key enzymes involved in pathways leading to apoptosis and amyloid formation (see Phiel & Klein, 2001). Lithium can also affect GSK3 isoforms indirectly by interfering with their regulation by Akt, a closely related serine/threonine kinase regulated through PI-mediated signalling and by arrestins (see Ch. 3; Beaulieu et al., 2009).

Lithium also inhibits hormone-induced cAMP production and blocks other cellular responses (e.g. the response of renal tubular cells to antidiuretic hormone, and of the thyroid to thyroid-stimulating hormone; see Chs 29 and 34, respectively). This is not, however, a pronounced effect in the brain.

The cellular selectivity of lithium appears to depend on its selective uptake, reflecting the activity of sodium channels in different cells. This could explain its relatively selective action in the brain and kidney, even though many other tissues use the same second messengers. Notwithstanding such insights, our ignorance of the nature of the disturbance underlying the mood swings in bipolar disorder leaves us groping for links between the biochemical and prophylactic effects of lithium.

Pharmacokinetic aspects and toxicity

Lithium is given by mouth as the carbonate salt and is excreted by the kidney. About half of an oral dose is excreted within about 12 h – the remainder, which presumably represents lithium taken up by cells, is excreted over the next 1–2 weeks. This very slow phase means that, with regular dosage, lithium accumulates slowly over 2 weeks or more before a steady state is reached. The narrow therapeutic window means that monitoring of the plasma concentration is essential. Na^+ depletion reduces the rate of excretion by increasing the reabsorption of lithium by the proximal tubule, and thus increases the likelihood of toxicity. Diuretics that act distal to the proximal tubule (Ch. 29) also have this effect, and renal disease also predisposes to lithium toxicity.

The main toxic effects that may occur during treatment are as follows:

- nausea, vomiting and diarrhoea
- tremor
- renal effects: polyuria (with resulting thirst) resulting from inhibition of the action of antidiuretic hormone. At the same time, there is some Na^+ retention associated with increased aldosterone secretion. With prolonged treatment, serious renal tubular damage may occur, making it essential to monitor renal function regularly in lithium-treated patients
- thyroid enlargement, sometimes associated with hypothyroidism
- weight gain
- hair loss.

Acute lithium toxicity results in various neurological effects, progressing from confusion and motor impairment to coma, convulsions and death if the plasma concentration reaches 3–5 mmol/l.

ANTIEPILEPTIC DRUGS

Carbamazepine, **valproate** and **lamotrogine** (see Ch. 45) have fewer side effects than lithium and have proved efficacious in the treatment of bipolar disorder.

It is assumed that the mechanisms of action of anticonvulsant drugs in reducing bipolar disorder are related to their anticonvulsant activity. While each drug has multiple actions (see Table 45.1), the antiepileptic drugs effective in bipolar disorder share the property of sodium channel blockade, although there are subtle differences in their effectiveness against the different phases of bipolar disorder. Valproate and carbamazepine are effective in treating acute attacks of mania and in the long-term treatment of the disorder, although carbamazepine may not be as effective in treating the depression phase. Valproate is sometimes given along with other drugs such as lithium. Lamotrogine is effective in preventing the recurrence of both mania and depression.

ATYPICAL ANTIPSYCHOTIC DRUGS

Atypical antipsychotic drugs (e.g. **olanzapine**, **risperidone**, **quetiapine**, **aripiprazole**) are second-generation drugs developed for the treatment of schizophrenia (see Ch. 46). These agents have D_2-dopamine and 5-HT_{2A}-receptor antagonist properties as well as actions on other receptors and amine transporters that may contribute to their effectiveness in bipolar depression. All appear to be effective against mania while some may also be effective against bipolar depression. In bipolar depression, atypical antipsychotics are often used in combination with lithium or valproate. Olanzapine is given in combination with the antidepressant fluoxetine.

Treatment of bipolar disorder

- **Lithium**, an inorganic ion, taken orally as lithium carbonate.
- Mechanism of action is not understood. The main biochemical possibilities are:
  - interference with inositol trisphosphate formation
  - inhibition of kinases.
- Antiepileptic drugs (e.g. **carbamazepine**, **valproate**, **lamotrogine**):
  - better side effect and safety profile.
- Atypical antipsychotic drugs (e.g. **olanzapine**, **risperidone**, **quetiapine**, **aripiprazole**).

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Clinical uses of mood-stabilising drugs

- **Lithium** (as the carbonate) is the classical drug. It is used:
  - in prophylaxis and treatment of *mania*, and in the prophylaxis of *bipolar* or *unipolar disorder* (manic depression or recurrent depression).
- Points to note include the following:
  - there is a narrow therapeutic window and long duration of action
  - acute toxic effects include cerebellar effects, nephrogenic *diabetes insipidus* (see Ch. 29) and *renal failure*
  - dose must be adjusted according to the plasma concentration
  - elimination is via the kidney and is reduced by proximal tubular reabsorption. Diuretics increase the activity of the reabsorptive mechanism and hence can precipitate lithium toxicity
  - *thyroid disorders* and mild *cognitive impairment* occur during chronic use.
- **Carbamazepine valproate** and **lamotrogine** (sodium-channel blockers with antiepileptic actions; Ch. 45) are used for:
  - the prophylaxis and treatment of manic episodes in patients with *bipolar disorder*
  - the treatment of *bipolar disorder* (**valproate**, **lamotrogine**).
- **Olanzapine**, **risperidone**, **quetiapine**, **aripiprazole** (atypical antipsychotic drugs) are used to treat *mania*.

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CNS stimulants and psychotomimetic drugs

48

OVERVIEW

In this chapter we describe drugs that have a predominantly stimulant effect on the central nervous system (CNS); these fall into two broad categories:

1. psychomotor stimulants
2. psychotomimetic (hallucinogenic) drugs.

Drugs in the first category (see Table 48.1) have a marked effect on mental function and behaviour, producing excitement and euphoria, reduced sensation of fatigue, and an increase in motor activity. Some enhance cognitive function.

Drugs in the second category (see Table 48.2) mainly affect thought patterns and perception, distorting cognition in a complex way.

Several of these drugs have no clinical uses but are used for recreational purposes and are recognised as drugs of abuse. This aspect is also discussed in Chapters 49 and 58.

For more detailed information see Iversen et al. (2009).

PSYCHOMOTOR STIMULANTS

AMPHETAMINES

DL-amphetamine (*speed* or *billy whizz*), its active dextroisomer **dextroamphetamine** (*dexies*), and **methamphetamine** (*crystal meth* or *ice*) have very similar chemical and pharmacological properties (see Fig. 48.1). **Methylphenidate** (*Ritalin*) and **MDMA** (3,4-methylenedioxymethamphetamine, *ecstasy*) are chemically related but considered separately below as they differ in the neurochemical and behavioural effects they produce.

Pharmacological effects

The amphetamines act by releasing monoamines, primarily dopamine and noradrenaline, from nerve terminals in the brain (see Green et al., 2003). 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 14, 15 and 39), 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. 47) 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 14 and 39).

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 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. 14), 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 cause marked anorexia, but with continued administration this effect wears off and food intake returns to normal.

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. 39) or administration of D_2-receptor antagonists (see Ch. 46) 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. 46), 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

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Table 48.1 Central nervous system stimulants

Drugs	Mode(s) of action	Clinical significance
Amphetamine and related compounds (e.g. dexamphetamine, methamphetamine)	Release of catecholamines Inhibition of catecholamine uptake	Dexamphetamine used to treat attention deficit/hyperactivity disorder in children; otherwise very limited clinical use Some use to treat narcolepsy and as appetite suppressants Risk of dependence, sympathomimetic side effects and pulmonary hypertension Mainly important as drugs of abuse para-Methoxymethamphetamine acts similarly
Methylphenidate	Inhibition of catecholamine uptake	Used to treat attention deficit/hyperactivity disorder in children
Modafinil	Still unclear, possibly acts by inhibiting dopamine reuptake	May have use to reduce fatigue and enhance cognition
Cocaine	Inhibition of catecholamine uptake Local anaesthetic	Important as drug of abuse Risk of fetal damage Occasionally used for nasopharyngeal and ophthalmic anaesthesia (see Ch. 43)
Mephedrone	Inhibition of dopamine and 5-HT uptake	It is considered a drug of abuse in many countries
Methylxanthines (e.g. caffeine, theophylline)	Inhibition of phosphodiesterase Antagonism of adenosine A_2 receptors	Clinical uses unrelated to stimulant activity Theophylline used for action on cardiac and bronchial muscle (see Chs 21, 28) Caffeine is a constituents of beverages and tonics. It is also available in tablet form

5-HT, 5-hydroxytryptamine.

Table 48.2 Psychotomimetic drugs

Drugs	Mode(s) of action	Clinical significance
LSD	Agonist at 5-HT_{2A} receptors (see Chs 15 and 39)	No clinical use Important as drug of abuse
MDMA (ecstasy)	Releases 5-HT and blocks reuptake	No current clinical use. May have potential in the treatment of post traumatic stress disorder Important as drug of abuse
Mescaline	Not known Chemically similar to amphetamine	–
Psilocybin	Chemically related to 5-HT; acts on 5-HT_{2A} receptors	–
Ketamine	Phencyclidine (PCP) and methoxetamine are chemically similar Blocks NMDA receptor-operated ion channels (see Ch. 38)	Dissociative anaesthetic, antidepressant action Important as drug of abuse PCP used as a model for schizophrenia
Δ^9-tetrahydrocannabinol	Activates CB_1 and CB_2 receptors (see Ch. 19)	Has analgesic and antiemetic properties (see Ch. 19) Active ingredient in cannabis
Salvinorin A	κ Opioid receptor agonist	No clinical use Drug of abuse

5-HT, 5-hydroxytryptamine; LSD, lysergic acid diethylamide; MDMA, methylenedioxymethamphetamine.

consistent with the dopamine theory of schizophrenia (see Ch. 46). When the drug is stopped after a few days, there is usually a period of deep sleep and on awakening the subject feels lethargic, depressed, anxious (sometimes even suicidal) and hungry. These after-effects may be the result of depletion of the normal stores of dopamine and noradrenaline, but the evidence is not clear-cut.

Tolerance develops rapidly to euphoric and anorexic effects of amphetamines, but more slowly to the other effects.

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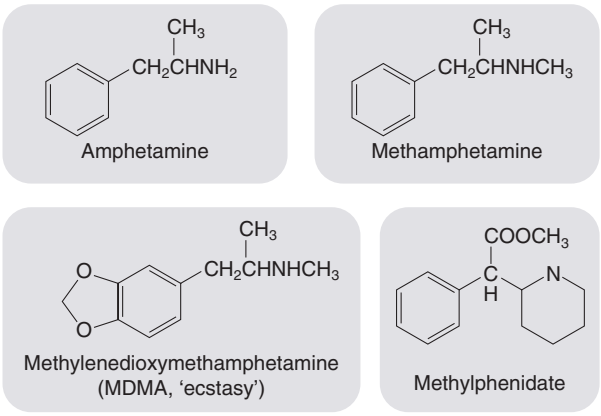

Fig. 48.1 Structures of amphetamine-like drugs.

Dependence on amphetamines appears to be a consequence of the insistent memory of euphoria. There is no clear-cut physical withdrawal syndrome such as occurs with opioids. 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. 593). Amphetamines freely penetrate the blood–brain barrier. They do this more readily than other indirectly acting sympathomimetic amines such as **ephedrine** or **tyramine** (Ch. 14), 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 Ch. 9). The plasma half-life of amphetamines varies from 5 to 30 hours, depending on urine flow and urinary pH (see Fig. 9.6).

METHYLPHENIDATE

Like the amphetamines, **methylphenidate** inhibits the NET and DAT transporters on the neuronal plasma membrane (and, with much lower potency, inhibits the 5-HT transporter, SERT). 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 produces a profound and sustained elevation of extracellular NA and DA.

Methylphenidate is orally active, being absorbed from the intestine and colon, but it undergoes presystemic metabolism such that only ~20% enters the systemic circulation. Absorption is slow following oral administration – peak level after ~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 (see clinical box below).

Clinical uses of CNS stimulants

- CNS stimulants have few legitimate therapeutic indications. Where appropriate they are usually initiated by experts.
- Attention deficit/hyperactivity disorder (ADHD): **methylphenidate**, **atomoxetine** (see Ch. 47). **Dexamphetamine** is an alternative in children who do not respond.
- Narcolepsy: **modafenil** 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**.

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 a human brain imaging study modafinil was shown to block DAT and increase extracellular dopamine levels in the caudate, putamen and nucleus accumbens (Volkow et al., 2009). It also produces a number of other effects including α_1-drenoceptor activation, enhanced release of 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 is claimed to enhance cognitive performance (see p. 594), and is gaining popularity as a 'lifestyle drug' (see Ch. 58) 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 methylphenidate 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 may need to be continued into adolescence and beyond. Drug treatment should be part of a programme that includes psychological intervention if available, and is started after

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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 to alleviate the symptoms of ADHD.

Slow-release formulations of amphetamine and methylphenidate have been developed to deliver more stable levels 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. 47), 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. **Melatonin** (Ch. 39) 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. It is often accompanied by *cataplexy* (abrupt onset of paralysis of variable extent often triggered by emotion, sometimes with 'frozen' posture). Amphetamine is helpful but not completely effective. Modafinil is also effective in reducing the need for sleep. **Sodium oxybate**, the sodium salt of γ-hydroxybutyrate (also known as GHB and frequently abused, see Ch. 38), is a CNS depressant that paradoxically is licensed for the prevention of cataplexy.

Appetite suppression

Amphetamines and similar drugs such as dexphenfluramine reduce appetite, but are no longer used for this purpose. They are ineffective in producing maintained weight loss, and have harmful CNS and cardiovascular side effects, in particular pulmonary hypertension, which can be so severe as to necessitate heart–lung transplantation.

COCAINE

Cocaine (see Streatfeild, 2002) 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.[1] Freud's ophthalmologist colleague Köller obtained supplies of the drug and discovered its local anaesthetic action (Ch. 43), 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 49.

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.

Pharmacological effects

Cocaine binds to and inhibits the transporters NET, DAT and SERT (see Chs 14, 15 and 39), 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 knockout mice indicate that the euphoric effects of cocaine involve inhibition of both dopamine and 5-HT reuptake. With excessive dosage, tremors and convulsions, followed by respiratory and vasomotor depression, may occur. 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.

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 (see De Mei et al., 2009).

Chronic use, dependence and tolerance

Cocaine undoubtedly causes strong psychological dependence (see Ch. 49), but there is some debate about

[1] 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 (see Courtwright, 2001, for a lively account).

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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. Like amphetamine, cocaine produces no 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 49. 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 given 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 free-base form ('crack') became available as a street drug. When an aqueous solution of cocaine hydrochloride is heated with sodium bicarbonate, then 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.

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* (see Volpe, 1992). 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.

Dependence, the main psychological adverse effect of amphetamines and cocaine, has potentially severe effects on quality of life (Ch. 49).

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.

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. A cup of instant coffee or strong tea contains 50–70 mg of caffeine, while filter coffee contains about twice as much. Among adults in tea- and coffee-drinking countries, the average daily caffeine consumption is about 200 mg. 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
- diuresis (see Ch. 29)
- stimulation of cardiac muscle (see Ch. 21)
- relaxation of smooth muscle, especially bronchial muscle (see Ch. 28).

The latter two effects resemble those of β-adrenoceptor stimulation (see Chs 14, 21 and 28). 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. 16). 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

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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. The diuretic effect probably results from vasodilatation of the afferent glomerular arteriole, causing an increased glomerular filtration rate.

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, and withdrawal effects are modest. 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 apnea 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. 28). *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.

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.

Some cathinone derivatives have recently appeared as recreational drugs that 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. Drugs with similar action include **methedrone** and **methylone**. The latter is reported anecdotally to be more MDMA-like in the effects it produces.

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, thus producing effects similar to those of β-adrenoceptor agonists.
- 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 apnea of prematurity and as an additive in many beverages and over-the-counter analgesics.

OTHER STIMULANTS

Benzylpiperazine (BZP), another banned recreational drug, produces stimulation and euphoria similar to amphetamine. It has a 'rich' pharmacology, inhibiting 5-HT reuptake as well as dopamine and noradrenaline reuptake but with lower potency. It is also an antagonist at α_2 adrenoceptors and a 5-HT_{2A} agonist.

Arecoline, a cholinergic agonist, is a mild stimulant contained in the betel nut, which improves learning and memory. Its use is widespread in India, Thailand, Indonesia and other Asian cultures.

COGNITION-ENHANCING DRUGS

'Cognition enhancers' are drugs that:

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

In this regard 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 even in non-fatigued individuals.

Cognition enhancers have therapeutic potential in the treatment of psychiatric conditions associated with cognitive impairment, such as Alzheimer's disease (Ch 40), schizophrenia (Ch. 46), depression (Ch. 47) and drug addiction (Ch. 49), or (controversially) to make normal people more 'intelligent'.

The main drugs used to enhance cognitive performance, often in the absence of medical advice, are caffeine, amphetamines, methylphenidate, modafinil, arecoline and **piracetam**. While their effectiveness is often trumpeted by individuals who use them, and in the media, their actual effectiveness as assessed in scientific studies is inconclusive and ambiguous (Repantis et al., 2010; Smith and Farah, 2011).

Many studies have shown that amphetamines improve mental performance in fatigued subjects. Mental

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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. Modafinil improves attention in rested individuals, while improving wakefulness, memory and executive functions in sleep-deprived individuals.

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. They have also been in vogue as a means of helping students to concentrate before and during examinations, but the improvement caused by reduction of fatigue are said sometimes to be offset by the mistakes of overconfidence and a decreased ability to deal with large amounts of information.[2]

Piracetam, which is a positive allosteric modulator at AMPA receptors, enhances memory in non-fatigued adults, and there is limited clinical evidence of reading improvement in dyslexic children.

A number of other drugs have been proposed to possess cognition-enhancing activity but firm evidence of their efficacy is still awaited. A wide range of novel targets are being investigated. As with many CNS disorders, the importance of glutamate and its receptors is widely speculated but new, effective drugs acting on the glutamatergic system are still awaited (see, for example, Collingridge et al., 2013; Harms et al., 2013).

PSYCHOTOMIMETIC DRUGS

Psychotomimetic drugs (also referred to as *psychedelic* or *hallucinogenic* 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, psychotomimetic drugs do not cause dependence, even though their psychological effects overlap those of highly addictive major psychostimulants such as cocaine and amphetamines.

Psychotomimetic drugs include the following:

- Drugs that act on 5-hydroxytryptamine (5-HT) receptors and transporters. These include **lysergic acid diethylamide** (**LSD**), **psilocybin** and **mescaline**, which are agonists at 5-HT_2 receptors (see Chs 15 and 39), and **MDMA** (ecstasy), which acts by inhibiting 5-HT uptake. MDMA also acts on several other receptors and transporters, and has powerful psychostimulant effects typical of amphetamines, as well as psychotomimetic effects.
- **Ketamine** and **phencyclidine**, antagonists at NMDA-type glutamate receptors.
- **Δ^9-Tetrahydrocannabinol** (THC, Ch.19), the active ingredient in cannabis, produces a mixture of psychotomimetic and depressant effects similar to, but less pronounced than, those of LSD.
- **Salvinorin A,** a κ-opioid-receptor agonist (Ch. 42).

LSD, PSILOCYBIN AND MESCALINE

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. 15).

▼ 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.

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

Psilocybin is obtained from fungi ('magic mushrooms'). Its effects are similar to those experienced with LSD.

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 15 and 39); 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. 39), apparently by acting as an agonist on the inhibitory autoreceptors of these cells. The significance of this response to its psychotomimetic effects is unclear. Psilocybin is dephosphorylated to psilocin, which is an 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.

The main effects of psychotomimetic drugs are subjective, so it is not surprising that animal tests that reliably predict psychotomimetic activity in humans have not been devised.[3]

[2]Pay heed to the awful warning of the medical student who, it is said, having taken copious amounts of dextroamphetamine, left the examination hall in confident mood, having spent 3 hours writing his name over and over again – a good example of amphetamine-induced stereotyped behaviour.

[3]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 (World Wide rather than arachnid) for 'spiders LSD' to see images.

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Dependence and adverse effects

Psychotomimetic agents 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.

MDMA (ECSTASY)

MDMA (3,4-methylenedioxymethamphetamine) is widely used as a 'party drug' because of the euphoria, loss of inhibitions and energy surge that it induces. It is a stimulant drug that also has mild hallucinogenic effects. Users describe feelings of empathy and emotional closeness to others and the terms 'empathogen' and 'enactogen' have been coined to describe MDMA and related drugs. There is ongoing debate about whether MDMA, in conjunction with psychotherapy, may be useful in treating post-traumatic stress disorder.

Pharmacological effects

Although an amphetamine derivative (Fig. 48.1), 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 changes occur in relation to dopamine and noradrenaline. 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. Although not addictive, MDMA carries serious risks, both acute and long term.

Sudden illness and death can occur even after small doses of MDMA. This can be due to several factors:

- Acute hyperthermia (see Fig. 48.2), 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. 33). 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.

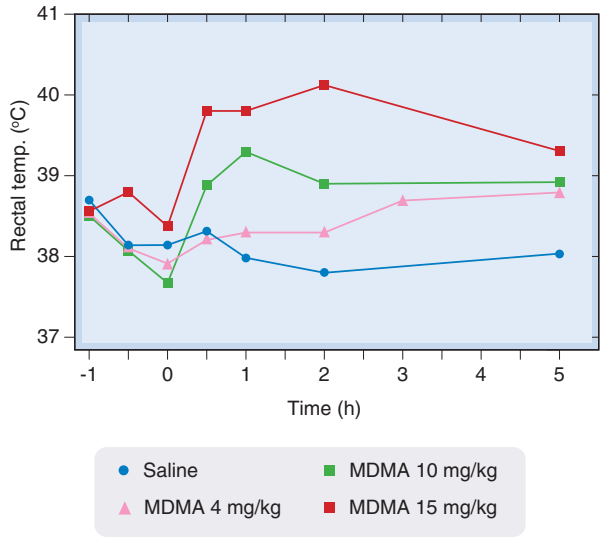

Fig. 48.2 A single injection of MDMA causes a dose-related increase in body temperature in rats. Drug administered at time zero. *(Reproduced with permission from Green et al., 2004.)*

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).

Illicit 'ecstasy' tablets and powder are sometimes contaminated or entirely substituted with ***para*-methoxyamphetamine**, which produces similar behavioural effects but which may be more dangerous to the user. Other related drugs are **4-bromo-2,5-dimethoxyphenethylamine** (2CB) and **4-methylthioamphetamine** (4-MTA).

KETAMINE AND PHENCYCLIDINE

Ketamine ('*Special K*') is a dissociative anaesthetic (Ch. 41) now also used as a recreational drug (see Morgan & Curran, 2012). An analogue, **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 a feeling 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. 46 and Morris et al., 2005).

Pharmacological effects

Their main pharmacological effect is block of the NMDA-receptor channel (see Ch. 38). This was at one time mistakenly described as 'acting at σ opioid receptors'. **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.

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OTHER PSYCHOTOMIMETIC 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. 42).[4] At high doses, delirium may be produced.

DMT (dimethyltryptamine), **DPT** (dipropyltryptamine) and **DOM** (2,5-dimethoxy-4-methylamphetamine) are synthetic hallucinogenic drugs that produce effects similar to LSD.

Muscarinic receptor antagonists (see Chs 13 and 39), **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. 49).

[4]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 recreational drug.

Psychotomimetic drugs

- The main types are:
  - **lysergic acid diethylamide** (**LSD**), **psilocybin** and **mescaline**
  - **methylenedioxymethamphetamine** (**MDMA**, 'ecstasy')
  - **ketamine** and **phencyclidine**.
- Their main effect is to cause sensory distortion and hallucinatory experiences.
- **LSD** is exceptionally potent, producing a long-lasting sense of dissociation and disordered thought, sometimes with frightening hallucinations and delusions, which can lead to violence. Hallucinatory episodes can recur after a long interval.
- **LSD** and **phencyclidine** precipitate schizophrenic attacks in susceptible patients, and **LSD** may cause long-lasting psychopathological changes.
- **LSD** appears to act as an agonist at 5-HT_{2A} receptors.
- **MDMA** is an amphetamine analogue that has powerful psychostimulant as well as mild psychotomimetic effects.
- **MDMA** can cause an acute hyperthermic reaction as well as over-hydration and hyponatraemia, sometimes fatal.
- Psychotomimetic drugs do not cause physical dependence and tend to be aversive, rather than reinforcing, in animal models.
- **Ketamine** and **phencyclidine** act by blocking the glutamate-activated NMDA receptor channel.

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49 Drug addiction, dependence and abuse

OVERVIEW

In this chapter we consider drugs that are consumed because people choose to, and not because they are advised to by their doctor. Drugs in sport are discussed in Ch. 58. Largely, the drugs described in this chapter are taken because they are pleasurable (hedonic). A list of the more frequently used drugs is given in Table 49.1. It includes drugs that are also used for medicinal purposes (e.g. general anaesthetics, benzodiazepines, opioids and some psychostimulants), non-therapeutic drugs that are legal in many countries (e.g. nicotine and ethanol) and many other drugs that are widely used although their manufacture, sale and consumption have been declared illegal in most Western countries.

The reasons why the use of a particular drug is viewed as a problem to society – and hence may be considered 'drug abuse' – are complex and largely outside the scope of this book. The drug and its pharmacological activity are only the starting point. For many, but not all, drugs of abuse, continued use leads to dependence. Here, we briefly review the relevant classes of drug and the biological processes underlying drug dependence. We also describe in detail the pharmacology of two important drugs that are consumed in large amounts, namely **nicotine** and **ethanol**. Other drugs that are abused are described elsewhere in this book (see Table 49.1). 'Lifestyle' and 'sport' drugs are discussed in Chapter 58.

For further information on various aspects of drug abuse, see Koob & Le Moal (2006).

DRUG USE AND ABUSE

A number of terms are used, sometimes interchangeably and sometimes incorrectly, to describe drug use and the consequences of administration of drugs. Terms that are best avoided are listed in Table 49.2. Other, more useful, terms are defined in the text below.

A vast and ever-increasing array of drugs is used to alter mood and perception. These range from drugs that are also used as medicines, through non-medicinal synthetic drugs to herbal preparations (Table 49.1). The popularity of each varies between different societies across the world, and within societies popularity differs among different groups of individuals.[1] Frequently, users will take more than one drug concomitantly or sequentially. Polydrug use is a very under-researched area in regard to why it is done, how different drugs may interact and the potential harm that may arise from such practices. For example, ethanol alters cocaine metabolism, resulting in the production of *cocaethylene*, which is more potent than cocaine and has greater cardiovascular toxicity. Sequential use is often intended to reduce adverse effects when coming down off the first drug (e.g. use of benzodiazepines when coming down from stimulants).

At first sight, the drugs listed in Table 49.1 form an extremely heterogeneous pharmacological group; we can find little in common at the molecular and cellular level between say, **morphine**, **cocaine** and **LSD** (lysergic acid diethylamide). What links them is that people find their effects pleasurable (hedonic) and tend to want to repeat the experience. The drug experience may take the form of intense euphoria, mood elevation, hallucinations, stimulation, sedation or calming depending upon the specific drug taken. In this regard drug use can be described as *thrill seeking*. Many drug users, however, have existing mental health problems and for them drug taking is a means of escaping reality and this can be described as *self-medicating*.

Abuse of prescription drugs, largely opioid analgesics such as **oxycodone** and **fentanyl** (see Ch. 42) as well as benzodiazepines (Ch. 44), has dramatically increased in recent years, especially in the USA. Thus a person may initially be prescribed an opioid drug to treat mild to moderate pain but continue to take the drug when the pain has receded, thus experiencing the pleasurable effects of the drug leading to addiction. In the USA, deaths from overdose of prescription drugs have tripled since 1990 – of over 38 000 deaths due to drug overdoses in 2010, 60% were due to prescription drugs. These overdose deaths include both prescription drug users and illicit **heroin** users who have obtained diverted supplies of these medicines. Illicit drugs such as heroin and cocaine are no longer the number one cause of drug overdose deaths.

Drug use involves effects on the brain that can be both acute and chronic (Fig. 49.1). The immediate, acute effect on mood is the reason the drug is taken. For some drugs (e.g. **amphetamines**, Ch. 48), this may be followed by a rebound negative or depressed phase. Persistent use of a drug may lead to compulsive drug use (addiction/dependence – a complex state that involves both psychological and physiological dependence) and to the development of tolerance. Psychological dependence can give rise to intense craving even when the user has been drug-free for months or years.

DRUG ADMINISTRATION

For drugs that induce strong feelings of euphoria, there are two components to the experience: an initial rapid effect (the *rush* or *buzz*) and a more prolonged pleasurable effect (the *high*). The intensity of the initial effect is determined by how fast the drug enters the brain and activates its effector mechanism. For many casual drug users, ease of administration defines how the drug is taken (e.g. smoking, swallowing or snorting a drug is relatively easy). However, for other drug users chasing a more intense experience, the route of administration and the

[1] A survey in one UK city showed that among Friday-night clubbers the choice of drug was associated with the type of music the clubs played (Measham & Moore, 2009).

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Table 49.1 The main drugs of abuse

Type	Examples	Dependence liability	See Chapter
Opioids	Morphine	Very strong	42
	Diamorphine (heroin)	Very strong	42
	Methadone	Very strong	42
	Oxycodone	Very strong	42
	Hydrocodone	Very strong	42
General central nervous system depressants	Ethanol	Strong	This chapter
	Barbiturates	Strong	44
	General anaesthetics (e.g. N_2O, propofol)	Moderate	41
	Ketamine	Moderate	41, 48
	Organic solvents (e.g. glue sniffing)	Strong	–
Anxiolytic and hypnotic drugs	Benzodiazepines	Moderate	44
	GHB	Probably moderate	38
Psychomotor stimulants	Amphetamines	Strong	48
	Cocaine	Very strong	48
	MDMA (ecstasy)	Weak or absent	48
	Cathinones	Weak or absent	48
	Nicotine	Very strong	This chapter
Psychotomimetic agents	Lysergic acid diethylamide (LSD)	Weak or absent	48
	Mescaline	Weak or absent	48
	Cannabis and synthetic derivatives	Weak	19, 47

Table 49.2 Glossary of frequently used and 'abused' terms

Addict	Person for whom the desire to experience a drug's effects overrides any consideration for the serious physical, social or psychological problems that the drug may cause to the individual or others. Often used in non-scientific circles to convey criminal intent and so has fallen out of favour with those involved in treating people with drug problems
Drug misuse	Non-medicinal drug use (although some would not consider taking drugs to alter mood/induce hallucinations as 'misuse' or 'abuse')
Junkie	Pejorative term for someone who is dependent upon a drug
Narcotics	Originally used as a term to describe opioids as they induce sleep (narcosis). Subsequently this term has been used by non-scientists to describe a wide range of drugs of abuse (including cocaine which is a stimulant!)
Recreational drug use	Originally used to describe all drug abuse, it is now sometimes used to describe drug use in the bar/club/dance scene
Substance use	Some governments do not consider ethanol to be a drug, hence 'substance use' (or 'substance abuse') is used to include ethanol

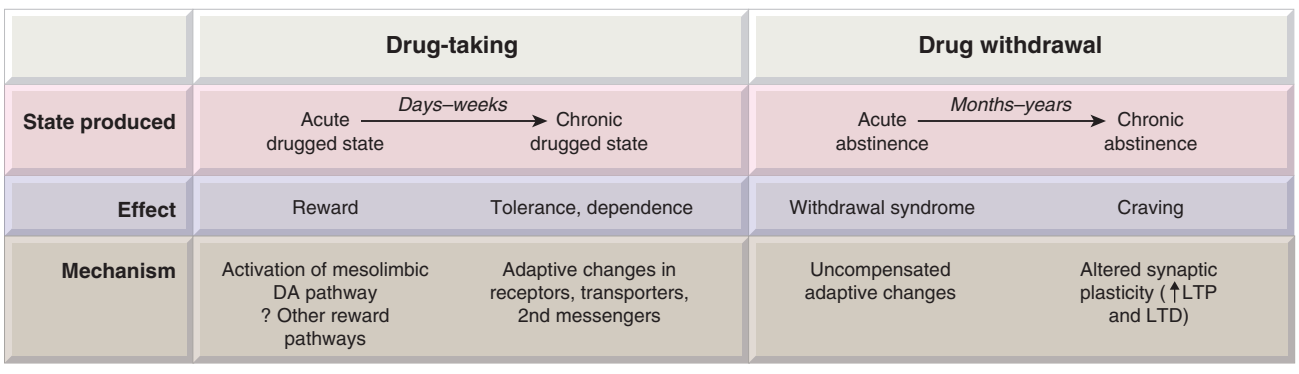

Fig. 49.1 Cellular and physiological mechanisms involved in drug dependence showing the relationship between the immediate and delayed effects of drug taking and drug withdrawal. DA, dopamine; LTD, long-term depression; LTD, long-term potentiation.

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choice of individual drug become important. Intravenous injection or smoking results in faster absorption of a drug than when it is taken orally. Heroin (official name diamorphine), cocaine, amphetamines, tobacco and **cannabis** are all taken by one or other of these routes. Heroin is more popular as a drug of abuse than morphine. This is because it enters the brain more rapidly than morphine. However, heroin itself does not interact with opioid receptors but is rapidly deacetylated to 6-acetylmorphine and morphine, μ-opioid-receptor agonists (see Ch. 42).

DRUG HARM

All drugs of abuse are harmful to a varying extent. Adverse effects can be the result of drug overdose (e.g. respiratory depression produced by opioids), of effects on tissues other than the brain (e.g. necrosis of the nasal septum resulting from chronic cocaine use), of the route of administration (e.g. HIV and other infections in drug users who share needles), of effects unrelated to the specific actions of the drug (e.g. carcinogenicity of tobacco smoke, severe bladder pain in regular ketamine users) or of use for illegal purposes (e.g. **flunitrazepam** or **γ-hydroxybutyrate** (**GHB**) as date-rape drugs). Many major harms relate to the ability of some drugs to induce dependence (e.g. psychostimulants, opioids, ethanol and tobacco) or to reveal a susceptibility to psychotic illness in some individuals (e.g. amphetamines and cannabis).

An attempt to produce a rational scale of harm, based on assessment by an expert panel of physical risk, dependence liability and social cost, was reported by Nutt et al. (2010), who have argued that such ratings should influence how governments police and punish people for supplying and using particular drugs. As expected, ethanol, heroin and cocaine were judged to be the most harmful, with cannabis, LSD and ecstasy (**MDMA**, see Ch. 48) much less so – an order that is not reflected in the classification of these drugs under UK law.[2]

DRUG DEPENDENCE

Drug dependence describes the human condition in which drug taking becomes compulsive, taking precedence over other needs, often with serious adverse consequences. Dependence becomes a problem when:

- the want becomes so insistent that it dominates the lifestyle of the individual and damages his or her quality of life
- the habit itself causes actual harm to the individual or the community.

Examples of the latter are the mental incapacity and liver damage caused by ethanol, the many diseases associated with smoking tobacco, the high risk of infection when injecting intravenously (especially HIV), the serious risk of overdose with most opioids and the criminal behaviour resorted to when drug users need to finance their habit.

Dependence involves both psychological and physical components. Family studies show clearly that susceptibility to dependence is an inherited characteristic. Around 50% of the risk of becoming dependent is genetic, with the remainder being developmental (adolescents are more at risk than adults) and environmental, e.g. stress, social pressures and drug availability. Variants of many different genes may each make a small contribution to the overall susceptibility of an individual to addiction – a familiar scenario that provides few pointers for therapeutic intervention. Polymorphisms in ethanol-metabolising genes (see later section on ethanol) are the best example of genes that directly affect the tendency to abuse a drug.

DRUG-INDUCED REWARD

The common feature of the various types of psychoactive drugs that are addictive is that all produce a *rewarding* experience (e.g. an elevation of mood or a feeling of euphoria or calmness).

In animal studies, where the state of mood cannot be inferred directly, reward is manifest as *positive reinforcement*, i.e. an increase in the probability of occurrence of any behaviour that is associated with the drug experience. In *conditioned place preference* studies, animals receive a drug or placebo and are then placed in different environments. Subsequently, when tested in a drug-free state, they will spend more time in the environment associated with a previous rewarding drug experience. Another way of determining if a drug is rewarding is to test whether or not animals will self-administer the drug by pressing a lever to obtain it. All dependence-producing drugs are self-administered by experimental animals. Hallucinogenic drugs are not, however, normally self-administered by experimental animals, which may indicate that, unlike humans, they find the experience non-rewarding.

Humans have a choice as to whether or not they wish to experiment with and continue taking drugs – there may therefore be an element of risk-taking when experimenting with drugs. In behavioural tests, some rats are observed to be much more impulsive than others (Dalley et al., 2007). These impulsive rats show a higher rate of cocaine self-administration and have a lower level of expression of D_2 and D_3 dopamine receptors in the nucleus accumbens (see below for the importance of this brain region in drug use). Impulsive rats are not, however, more prone to self-administering opioids.

Reward pathways

▼ Virtually all dependence-producing drugs so far tested, including opioids, nicotine, amphetamines, ethanol and cocaine, activate the *reward pathway* – the mesolimbic dopaminergic pathway (see Ch. 39), that runs, via the medial forebrain bundle, from the ventral tegmental area (VTA) of the midbrain to the nucleus accumbens and limbic region. Even though for some of these drugs their primary sites of action may be elsewhere in the brain, they all increase the extracellular level of dopamine in the nucleus accumbens, as shown by microdialysis in animals and *in vivo* brain imaging techniques in humans. Opioids enhance the firing of VTA dopaminergic neurons by reducing the level of GABAergic inhibition (disinhibition) within the VTA, whereas amphetamine and cocaine act on dopaminergic nerve terminals in the nucleus accumbens to release dopamine or prevent its reuptake (see Ch. 14). Given that dopamine release in the nucleus accumbens is also enhanced by naturally rewarding stimuli, such as food, water, sex and nurturing, it would appear that drugs are simply activating, or overactivating, the body's own pleasure system. In experienced drug users the anticipation of the effect may become sufficient to elicit the release of dopamine. Paradoxically, brain imaging studies have revealed that in chronic users the increase in dopamine may be less than expected when compared to what is seen in naïve subjects even although the subjective high is

[2]In determining society's attitude towards drugs, the media play an influential role. In the UK, deaths following consumption of ecstasy (around 60 per year) are often widely reported in the press and on television, but deaths due to heroin overdose (much more prevalent, at around 700 per year) are largely ignored unless the victim is famous.

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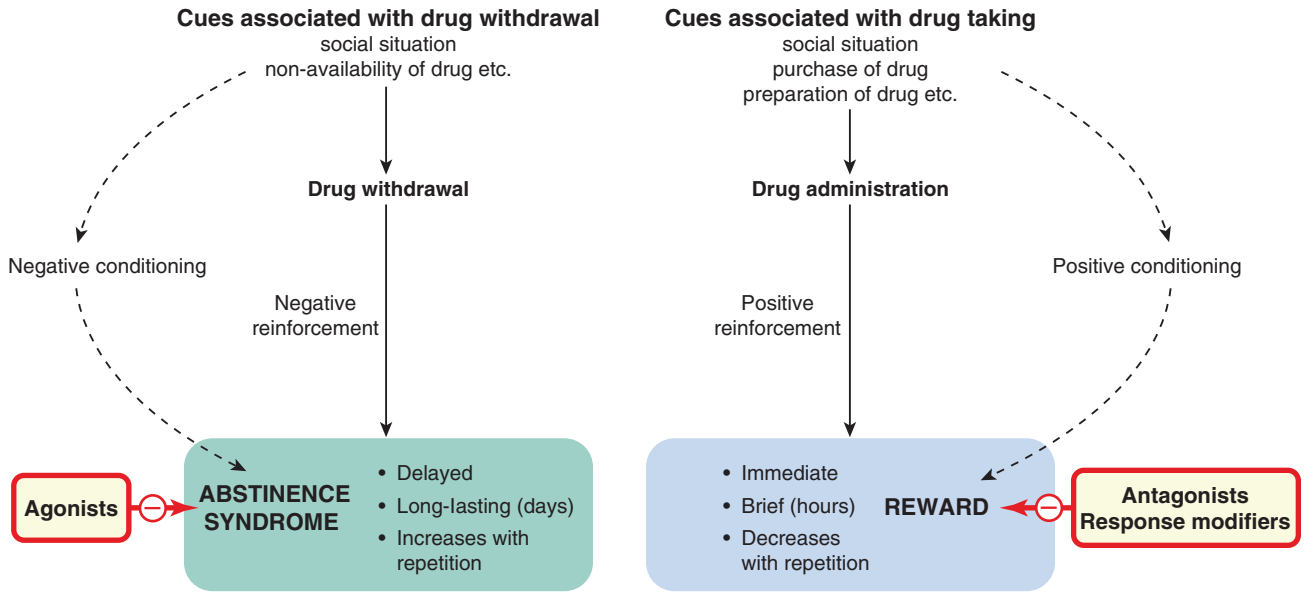

Fig. 49.2 A simplified scheme of some of the psychological factors involved in drug dependence.

still intense. This may reflect some degree of sensitisation but the mechanism is not well understood.

Chemical or surgical interruption of the VTA–accumbens dopaminergic pathway impairs drug-seeking behaviours in many experimental situations. Deletion of D_2 receptors in a transgenic mouse strain eliminated the rewarding properties of morphine administration without eliminating other opioid effects, and it did not prevent the occurrence of physical withdrawal symptoms in morphine-dependent animals (Maldonado et al., 1997), suggesting that the dopaminergic pathway is responsible for the positive reward but not for the negative withdrawal effects. However, D_2-receptor antagonists (antipsychotic drugs; see Ch. 46) have not been successful in treating addiction, and more recent evidence suggests that D_1 and possibly D_3 receptors play important roles. The development of D_3-receptor antagonists or partial agonists as treatments for drug abuse is awaited (see Newman et al., 2012).

PSYCHOLOGICAL DEPENDENCE

Having experienced the rewarding effects of a drug, an individual may desire to repeat the experience. The memory of previous drug-induced experiences can be very intense and long-lasting, giving rise to *craving*; it may drive an individual to take the drug again – referred to as *relapse* – even after a prolonged period of abstinence (see Weiss, 2005).

Craving may be triggered by stress or by cues such as experiencing the environment that a person associates with previously taking the drug or the sight of drug administration paraphernalia (e.g. a crack pipe or syringe). Coupled with the direct rewarding effect of the drug, cessation of drug use may be associated with an aversive psychological effect from which the subject will attempt to escape by self-administering the drug.

The psychological factors in drug dependence are discussed in detail by Koob & Le Moal (2006) and summarised in Figure 49.2.

PHYSICAL DEPENDENCE

This condition is characterised by a *withdrawal* or *abstinence syndrome* whereby on cessation of drug administration or on administering an antagonist, adverse physiological effects are experienced. On cessation of drug administration the withdrawal effects can persist for a period of days or weeks, the precise withdrawal responses being characteristic of the type of drug taken. Withdrawal responses can be observed in animals after chronic drug administration. The intensity of the withdrawal syndrome also varies between drugs of the same type but different pharmacokinetic characteristics. Pharmacological intervention can be used to reduce the intensity of the withdrawal (see Table 49.3). Several types of therapeutic drug, including antidepressant and antipsychotic agents, also produce withdrawal symptoms on cessation of administration but it is important to distinguish this type of commonly observed 'rebound' phenomenon from the physical dependence associated with drugs of abuse.

Physical dependence is less important in sustaining drug-seeking behaviour than psychological dependence. A degree of physical dependence is common when patients receive opioid analgesics in hospital for several days, but this rarely leads to addiction. On the other hand, heroin users who are nursed through and recover fully from the physical abstinence syndrome are still extremely likely to revert to drug taking later. Therefore although physical dependence may influence the drive to retake a drug, it is not the major factor in long-term drug dependence and relapse following a prolonged period of abstinence.

TOLERANCE

Tolerance (see Ch. 2) describes the decrease in pharmacological effect on repeated administration of a drug – it develops over time, as does the state of dependence. It does not occur with all drugs of abuse.

MECHANISMS OF DEPENDENCE AND TOLERANCE

▼ Drug users report that visual cues – such as the sight of a crack pipe or of a syringe – can evoke intense memories of the drug experience and induce strong craving for the drug, which may

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Table 49.3 Pharmacological approaches to treating drug dependence

Mechanism	Example(s)
To alleviate withdrawal symptoms	Methadone (orally active) used short term to blunt opioid withdrawal Ibogaine (a naturally occurring psychoactive agent) used by some to reduce opioid withdrawal α_2-Adrenoceptor agonists (e.g. clonidine, lofexidine) to diminish opioid, alcohol and nicotine withdrawal symptoms β-Adrenoceptor antagonists (e.g. propranolol) to diminish excessive peripheral sympathetic activity Benzodiazepines, clomethiazole, topiramate and γ-hydroxybutyric acid (GHB) to blunt alcohol withdrawal
Long-term substitution	Methadone, buprenorphine or legal heroin to maintain opioid-dependent patients Nicotine patches or chewing gum Varenicline (α4β2 nicotinic receptor partial agonist)
Blocking response	Naltrexone to block opioid effects in drug-withdrawn patients Naltrexone and nalmefene to reduce ethanol use Mecamylamine to block nicotine effects Immunisation against cocaine and nicotine to produce circulating antibody (still being developed)
Aversive therapies	Disulfiram to induce unpleasant response to ethanol
Reducing continued drug use (may act by reducing craving)	Bupropion (antidepressant with some nicotinic receptor antagonist activity) to reduce tobacco use Clonidine (α_2-adrenoceptor agonist) to reduce craving for nicotine[a] Acamprosate (NMDA-receptor antagonist) to treat alcoholism[a] Topiramate and lamotrogine (antiepileptic agents) to treat alcoholism and cocaine use[a] γ-Hydroxybutyric acid (GHB) reported to reduce craving for alcohol and cocaine[a] Baclofen reported to reduce opioid, alcohol and stimulant use[a] Modafinil to reduce cocaine use[a] Ibogaine reported to reduce craving for stimulants and opioids[a]

[a]How effective these agents are at reducing the continued use of other drugs of abuse over and above the ones listed remains to be determined.

Notes: Antidepressant, mood stabilising, anxiolytic and antipsychotic medications are useful when treating patients who, in addition to their drug use, also suffer from other mental disorders. The cannabinoid CB_1-receptor antagonist rimonabant, in addition to its antiobesity effects, also reduces nicotine, ethanol, stimulant and opioid consumption. However, it also induces depression and its use has been discontinued.

See Web links in the reference list for further information on treatments of drug dependence.

Drug dependence

- Dependence occurs when, as a result of repeated administration of the drug, the desire to experience the effects of a drug again becomes compulsive.
- Dependence occurs with a wide range of psychotropic drugs, acting by many different mechanisms.
- Dependence can be subdivided into psychological dependence and physical dependence.
- Psychological dependence (craving) is the major factor leading to relapse among treated addicts.
- The common feature of psychological dependence-inducing drugs is that they have a positive reinforcing action ('reward') associated with activation of the mesolimbic dopaminergic pathway.
- Physical dependence is characterised by an abstinence syndrome, which varies in type and intensity for different classes of drug.
- On repeated administration, tolerance may occur to the effects of the drug.
- Although genetic factors contribute to drug-seeking behaviour, no specific genes have yet been identified.

precipitate relapse. This suggests that associative learning may be a major factor in psychological dependence (Robbins et al., 2008). It has been suggested that drugs alter memory formation to enhance the recollection of previous drug experience. In this regard, it is of interest that several drugs produce changes in synaptic plasticity, a cellular correlate of memory formation (see Ch. 38). While cocaine, morphine, nicotine and ethanol enhance long-term potentiation (LTP) in the VTA by increasing the expression of AMPA receptors on the plasma membrane, cocaine also increases long-term depression (LTD) in the nucleus accumbens (Hyman et al., 2006).

Contrary to earlier thinking, physical dependence and tolerance are now though to involve different mechanisms (see Bailey & Connor, 2005).

The mechanisms responsible for the withdrawal syndrome have been most fully characterised for opioid dependence but similar mechanisms may apply to cocaine and ethanol withdrawal. At the cellular level, opioids inhibit cAMP formation, and withdrawal results in a rebound increase as a result of 'superactivation' of adenylyl cyclase, as well as upregulation of the amount of this enzyme. This results in activation of protein kinase A (PKA), in an increase in adenosine as a consequence of the conversion of cAMP to adenosine, and in activation of a transcription factor – cAMP response element binding protein (CREB). The rise in PKA activity increases the excitability of nerve terminals by phosphorylating neurotransmitter transporters to increase their ionic conductance (see Bagley et al., 2005) as well as increasing neurotransmitter release by a direct action on the secretory process (Williams et al., 2001). Withdrawal results in enhanced GABA release in various parts of the brain, probably through the mechanisms described above (see Bagley et al., 2011).

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The release of other neurotransmitters is also likely to be enhanced. On the other hand, the enhanced extracellular levels of adenosine, acting on presynaptic A_1 receptors (see Ch. 16), inhibits glutamate release at excitatory synapses, and thus counteracts the neuronal hyperexcitability that occurs during drug withdrawal, suggesting the possibility – not yet clinically proven – that adenosine agonists might prove useful in treating drug dependence. CREB, which is upregulated in the nucleus accumbens by prolonged administration of opioids or cocaine, plays a key role in regulating various components of cAMP signalling pathways, and transgenic animals lacking CREB show reduced withdrawal symptoms (see Chao & Nestler, 2004).

For drugs such as opioids that are agonists at specific receptors (see Ch. 42), cellular tolerance results in part from desensitisation of the receptors. On prolonged activation by an agonist, the μ opioid receptor (MOPr) is phosphorylated by various intracellular kinases (Williams et al., 2013) – which either directly desensitises the receptor or causes the binding to the receptor of other proteins, such as arrestins, that uncouple the receptor from its G protein (see Ch. 3). In the intact animal, inhibition or knockout of these kinases reduces the level of tolerance.

Clinical use of drugs in substance dependence

Tobacco dependence

- Short-term **nicotine** is an adjunct to behavioural therapy in smokers committed to giving up; **varenicline** is also used as an adjunct but has been linked to suicidal ideation.
- **Bupropion** is also effective but lowers seizure threshold, so is contraindicated in people with risk factors for seizures (and also if there is a history of eating disorder).

Alcohol dependence

- Long-acting benzodiazepines (e.g. **chlordiazepoxide**) can be used to reduce withdrawal symptoms and the risk of seizures; they should be tapered over 1–2 weeks and then discontinued because of their abuse potential.
- **Disulfiram** is used as an adjunct to behavioural therapy in suitably motivated alcoholics after detoxification; it is contraindicated for patients in whom hypotension would be dangerous (e.g. those with coronary or cerebral vascular disease).
- **Acamprosate** can help to maintain abstinence; it is started as soon as abstinence has been achieved and maintained if relapse occurs, and it is continued for 1 year.

Opioid dependence

- Opioid agonists or partial agonists (e.g., respectively, **methadone** or **buprenorphine**) administered orally or sublingually may be substituted for injectable narcotics, many of whose harmful effects are attributable to the route of administration.
- **Naltrexone**, a long-acting opioid antagonist, is used as an adjunct to help prevent relapse in detoxified addicts (opioid free for at least 1 week).
- **Lofexidine**, an α_2 agonist (cf. **clonidine**; Ch. 14), is used short term (usually up to 10 days) to ameliorate symptoms of opioid withdrawal, and is then tapered over a further 2–4 days.

PHARMACOLOGICAL APPROACHES TO TREATING DRUG ADDICTION

From the discussion above, it will be clear that drug abuse involves many psychosocial and some genetic factors, as well as neuropharmacological mechanisms, so drug treatment is only one component of the therapeutic approaches that are used. The main pharmacological approaches (see Heidbreder & Hagan, 2005) are summarised in Table 49.3. For information on other approaches to the treatment of drug addiction, readers are advised to consult the National Institute on Drug Abuse (NIDA) website at www.nida.nih.gov/.

NICOTINE AND 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, 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, and now cigarettes account for 98% of tobacco consumption. Filter cigarettes (which give a somewhat lower delivery of tar and nicotine than standard cigarettes) and 'low-tar' cigarettes (which are also low in nicotine) constitute an increasing proportion of the total.[3] Cigarette consumption across the globe continues to rise (Fig. 49.3), although it is decreasing in some countries such as the UK[4] and Australia. There are about 1.1 billion smokers in the world (18% of the population), and the number in developing countries is increasing rapidly. Six trillion (6×10^{12}) cigarettes are sold each year, more than 900 cigarettes for every man, woman and child on the planet. In 2010, 12 million cigarettes per minute were smoked around the world.

PHARMACOLOGICAL EFFECTS OF SMOKING

Nicotine[5] is the main pharmacologically active substance in tobacco smoke. The acute effects of smoking can be mimicked by injection of nicotine and are blocked by

[3]Smokers, however, adapt by smoking more low-tar cigarettes and inhaling more deeply so as to maintain their nicotine consumption.
[4]In the UK consumption has dropped by over 50% from its peak in the 1970s, the main factors being increased price, adverse publicity, restrictions on advertising, the compulsory publication of health warnings and a ban on smoking in public places. Still, however, around 9.4 million adults (just over 20% of the adult population) in the UK smoke, with little difference between men and women. About 10% of children aged 10–15 are regular smokers.
[5]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.

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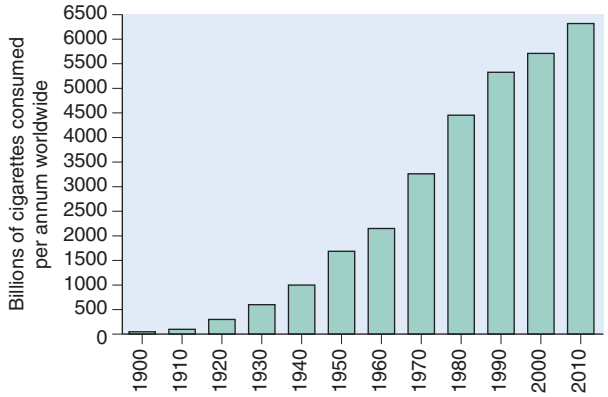

Fig. 49.3 Cigarette consumption per annum. *(Data from www.tobaccoatlas.org.)*

Tobacco smoking

- Cigarette consumption across the world continues to rise, although in the UK it is now declining after reaching a peak in the mid-1970s.
- The worldwide prevalence of smoking is now about 18% of the adult population, each smoker using on average 5000 cigarettes per year.
- **Nicotine** is the main pharmacologically active agent in tobacco, apart from carcinogenic tars and carbon monoxide.
- The amount of **nicotine** absorbed from an average cigarette is about 1–1.5 mg, which causes the plasma **nicotine** concentration to reach 130–200 nmol/l. These values depend greatly on the type of cigarette and on the extent of inhalation of the smoke.

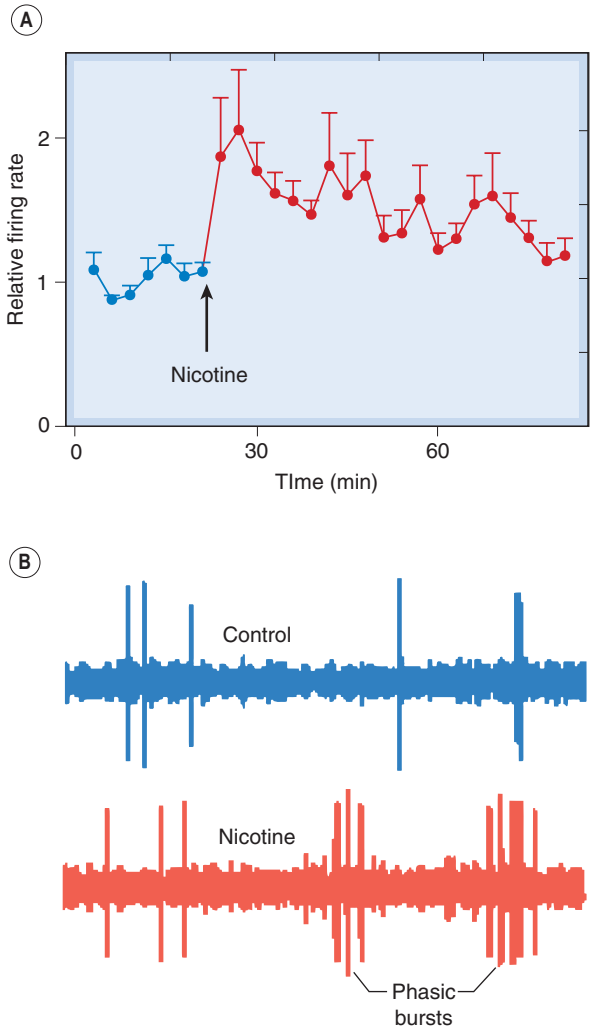

Fig. 49.4 Nicotine alters action potential firing characteristics of VTA dopaminergic neurons in freely moving rats. [**A**] Neuronal firing rate increases after nicotine injection i.p. [**B**] Action potential firing is phasic after nicotine injection. *(Adapted from De Biasi et al. 2011.)*

mecamylamine, an antagonist at neuronal nicotinic acetylcholine receptors (nAChRs; see Ch. 13). For reviews on nicotine and addiction see (De Biasi et al., 2011; Leslie et al., 2013).

Effects on the central nervous system

At the neuronal level, nicotine acts on nAChRs (see Ch. 39), 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 VTA, from which dopaminergic neurons project to the nucleus accumbens (the reward pathway, see Fig 39.3). 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 (Fig. 49.4). Of the various subtypes of nAChR (see Table 39.2), 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.

At the spinal level, nicotine inhibits spinal reflexes, causing skeletal muscle relaxation that can be measured by electromyography. This may be due to stimulation of the inhibitory Renshaw cells in the ventral horn of the spinal cord. 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. Smokers report that smoking wakes them 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

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vigilance tests) in humans generally show improvement after smoking, and nicotine enhances learning in rats. Nicotine and other nicotinic agonists such as **epibatidine** (Ch. 42) have significant analgesic activity.

Peripheral effects

The peripheral effects of small doses of nicotine result from stimulation of autonomic ganglia (see Ch. 13) and of peripheral sensory receptors, mainly in the heart and lungs. Stimulation of these receptors produces tachycardia, increased cardiac output and increased arterial pressure, reduction of gastrointestinal motility and sweating. When people smoke 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, 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

An average cigarette contains about 0.8 g of tobacco and 9–17 mg of nicotine, of which about 10% is normally absorbed by the smoker. This fraction varies greatly with the habits of the smoker and the type of cigarette.

Nicotine in cigarette smoke is rapidly absorbed from the lungs but poorly from the mouth and nasopharynx. Therefore, inhalation is required to give appreciable absorption of nicotine, each puff delivering a distinct bolus of drug to the CNS. Pipe or cigar smoke is less acidic than cigarette smoke, and the nicotine tends to be absorbed from the mouth and nasopharynx rather than the lungs. Absorption is considerably slower than from inhaled cigarette smoke, resulting in a later and longer-lasting peak in the plasma nicotine concentration (Fig. 49.5). 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. 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 cotinine concentration provides a useful measure of smoking behaviour. A 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.

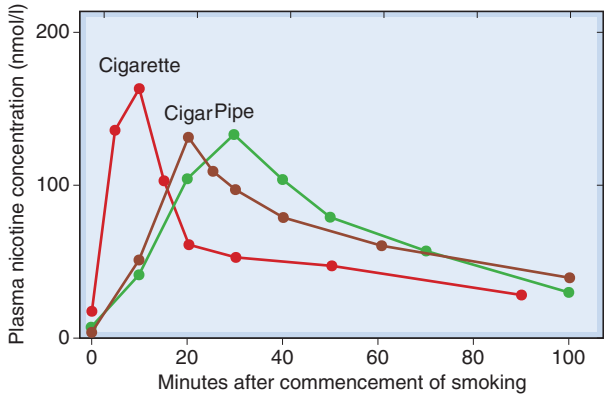

Fig 49.5 Nicotine concentration in plasma during smoking. The subjects were habitual smokers who smoked a cigarette, cigar or pipe according to their usual habit. *(From Bowman WC, Rand M 1980 Chapter 4. In: Textbook of Pharmacology. Blackwell, Oxford.)*

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. 13). 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 (see p. 604) 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 smoking is due to the effects of nicotine combined with the ritual of smoking (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.

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

[6]This may explain why, in years gone by, men smoked cigars while chatting over drinks after dinner.

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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 weeks, although the craving for cigarettes persists for much longer than this; relapses during attempts to give up cigarette smoking 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 motility. Tolerance develops rapidly to these effects.
- **Nicotine** is metabolised, mainly in the liver, within 1–2 h.
- The inactive metabolite, cotinine, has a long elimination half-life. Urinary cotinine excretion can be used as a measure of smoking habits.
- **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 (chewing gum or skin patch preparations) improves the chances of giving up smoking when combined with active counselling.

HARMFUL EFFECTS OF 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. 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. Deaths from smoking are continuing to rise. In 2011, smoking was responsible for about 6 million deaths worldwide (and approximately 600 000 non-smokers died in 2011 from involuntary secondary inhalation); by 2030, deaths are expected to increase to 10 million, mainly due to the growth of smoking in Asia, Africa and Latin America.

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. Pipe and cigar smoking carry much less risk than cigarette smoking, although the risk is still appreciable. 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. A causal link between nicotine and cardiovascular risk has not been demonstrated. Indeed nicotine preparations, used to help smokers give up cigarettes, are not thought to carry a serious risk. Carbon monoxide (see p. 607) 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. 28) 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 (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:

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- Tar and irritants, such as nitrogen dioxide and formaldehyde. Cigarette smoke tar contains many known carcinogenic hydrocarbons, as well as tumour promoters, which 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 be responsible for atherogenesis (Ch. 23) and chronic obstructive pulmonary disease (Ch. 28).

OTHER EFFECTS OF 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. 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 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.
- The incidence of Parkinson's disease is lower in smokers than in non-smokers.

PHARMACOLOGICAL APPROACHES TO TREATING NICOTINE DEPENDENCE

Most smokers would like to quit, but few succeed.[7] The most successful smoking cure clinics, using a combination of psychological and pharmacological treatments, achieve a success rate of about 25%, measured as the percentage of patients still abstinent after 1 year. The main pharmacological treatments are **nicotine replacement therapy**, **varenicline** and **bupropion** (originally used to treat depression; see Ch. 47, Table 47.2).

Nicotine replacement therapy is used mainly to assist smokers to quit by reducing craving and physical withdrawal symptoms. Because nicotine is relatively short-acting and not well absorbed from the gastrointestinal tract, it is given in the form of chewing gum, lozenges and oral or nasal sprays that can be used several times a day or as a transdermal patch that is replaced daily.[8]

These preparations cause various side effects, particularly nausea and gastrointestinal cramps, cough, insomnia and muscle pains. There is a risk that nicotine may cause coronary spasm in patients with heart disease. Transdermal patches may cause local irritation and itching. Combined with professional counselling and supportive therapy, nicotine replacement therapy roughly doubles the chances of successfully breaking the smoking habit. Nicotine on its own, without counselling and support, is no more effective than placebo. In Sweden, the use of 'smokeless tobacco' is encouraged and the smoking-related death rate is much lower than elsewhere in Europe or North America.

nAChR subtypes containing the α4β2 subunits are thought to mediate the rewarding properties of tobacco smoking, which may allow selective agonists to be developed as nicotine substitutes with fewer side effects. Varenicline is a partial agonist at the α4β2 nAChR subtype and has differing levels of efficacy at other subtypes. Being a partial agonist it may provide a level of substitution while at the same time blocking the rewarding effect of smoking. It is effective in preventing relapse but there was concern that it may induce suicidal thoughts, suicide attempts, aggression and homicide. However, a large retrospective study (Gunnell et al., 2009) found no evidence of increased suicide or suicidal thoughts with varenicline, compared with other antismoking treatments.

Bupropion (see Ch. 47) is a nicotinic antagonist. It may also act by increasing dopamine activity in the nucleus accumbens as it is a weak blocker of dopamine and noradrenaline uptake, but it is not clear that this accounts for its efficacy in treating nicotine dependence. It is usually given as a slow-release formulation. It appears to be as effective as nicotine replacement therapy, even in non-depressed patients, and has fewer side effects. However, bupropion lowers the seizure threshold so should not be prescribed if there are other risk factors for seizures (including other drugs that lower seizure threshold). It is also contraindicated if there is a history of eating disorders or of bipolar mood disorder, and is used only with caution in patients with liver or renal disease. Because of these problems, nicotine remains the pharmacological treatment of choice in most cases.

Although an early method of making the body produce antibodies that bind and inactivate nicotine was shown to be no better than placebo in clinical trials, it is still hoped that the use of genetically modified viruses to induce higher levels of circulating antibodies will prove to be more effective.

[7]Sigmund Freud tried unsuccessfully to give up cigars for 45 years before dying of cancer of the mouth at the age of 83.

[8]Electronic cigarettes – basically inhalers that deliver nicotine – are designed to mimic cigarettes in their use and appearance. The dose of nicotine delivered/inhaled is variable and their effectiveness remains to be determined.

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ETHANOL

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 pharmacological potency is reflected in the range of plasma concentrations needed to produce pharmacological effects: minimal effects occur at about 10 mmol/l (46 mg/100ml), and 10 times this concentration may be lethal. The average per capita consumption of ethanol in the UK doubled between 1970 and 2007, falling slightly since then. 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. Based on the health risks described below, the recommendation is a maximum of 21–28 units/week for men and 14–21 units/week for women. It is estimated that in the UK, about 33% of men and 13% of women exceed these levels. The annual spend on drinks is £15 billion, providing a tax revenue of about £9 billion. The health cost is estimated at £3 billion, and the social cost as £8 billion for crime and disruptive behaviour plus £2 billion in absenteeism from work. 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 central nervous system neurons

The main effects of ethanol are on the CNS (see review Spanagel, 2009), where its depressant actions resemble those of volatile anaesthetics (Ch. 41). At a cellular 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. 44). 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. 38). Exactly which $GABA_A$ receptor subtypes are sensitive to ethanol is still unclear but those containing δ subunits appear to be important. Ethanol may also act presynaptically to enhance GABA release. The benzodiazepine inverse agonist **flumazenil** (see Ch. 44) reverses the central depressant actions of ethanol by a non-competitive interaction on the $GABA_A$ receptor. The use of flumazenil to reverse ethanol intoxication and treat dependence has not found favour for several reasons. Because flumazenil is an inverse agonist (see Ch. 2) at benzodiazepine receptors, it carries a risk of causing seizures, and it could cause an increase in ethanol consumption and thus increase long-term toxic manifestations.

Ethanol produces a consistent enhancement of glycine receptor function. This effect is likely to be due both to a direct interaction of ethanol with the α1 subunit of the glycine receptor and to indirect effects of ethanol mediated through 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. 38). 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. 16). 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 (Melendez & Kalivas, 2004).

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 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. For example, 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.

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Much effort has gone into measuring the effect of ethanol on driving performance in real life, as opposed to artificial tests under experimental conditions. In an American 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 the UK, driving with a blood ethanol concentration greater than 80 mg/100 ml is illegal.

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.[9] Paradoxically, there is a positive correlation between ethanol consumption and hypertension, possibly because ethanol withdrawal causes increased sympathetic activity. The beneficial effect of moderate drinking on cardiovascular function is discussed below.

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. 33]) 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). 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 oesophageal varices to develop, which can bleed suddenly and catastrophically. Increased fat accumulation in the liver occurs, in rats or in humans, after a single large dose of ethanol. The mechanism is complex, the main factors being:

- increased release of fatty acids from adipose tissue, which is the result of increased stress, causing sympathetic discharge
- impaired fatty acid oxidation, because of the metabolic load imposed by the ethanol itself.

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

[9]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.

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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.

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 [CYP] induction, Ch. 9) often raises the suspicion of alcohol-related liver damage, although not specific to ethanol.

Effects on lipid metabolism, platelet function and atherosclerosis

Moderate drinking reduces mortality associated with coronary heart disease, the maximum effect – about 30% reduction of mortality overall – being achieved at a level of 2–3 units/day (see Groenbaek et al., 1994). The effect is much more pronounced (>50% reduction) in men with high plasma concentrations of low-density-lipoprotein cholesterol (see Ch. 23).[10] Most evidence suggests that ethanol, rather than any specific beverage, such as red wine, is the essential factor.

Two mechanisms have been proposed. The first involves the effect of ethanol on the plasma lipoproteins that are the carrier molecules for cholesterol and other lipids in the bloodstream (see Ch. 23). Epidemiological studies, as well as studies on volunteers, have shown that ethanol, in daily doses too small to produce obvious CNS effects, can over the course of a few weeks increase plasma high-density-lipoprotein concentration, thus exerting a protective effect against atheroma formation.

Ethanol may also protect against ischaemic heart disease by inhibiting platelet aggregation. This effect occurs at ethanol concentrations in the range achieved by normal drinking in humans (10–20 mmol/l) and probably results from inhibition of arachidonic acid formation from phospholipid. In humans, the magnitude of the effect depends critically on dietary fat intake, and it is not yet clear how important it is clinically.

The effect of ethanol on fetal development

The adverse effect of 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, must 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).

Effects of ethanol

- **Ethanol** consumption is generally expressed in units of 10 ml (8 g) of pure **ethanol**. Per capita consumption in the UK is more than 10 l/year.
- **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-type glutamate 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), cutaneous vasodilatation and delayed labour (reduced oxytocin secretion).
- Neurological degeneration occurs with heavy and binge drinking, causing dementia and peripheral neuropathies.
- Long-term ethanol consumption causes liver disease, progressing to cirrhosis and liver failure.
- Moderate **ethanol** consumption has a protective effect against ischaemic heart disease.
- 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**.
- Drugs used to treat alcohol dependence include **disulfiram** (aldehyde dehydrogenase inhibitor), **naltrexone** (opiate antagonist) and **acamprosate** (NMDA receptor antagonist). **Topiramate** and **bupropion** are also used.

[10]This beneficial effect of moderate drinking outweighs the risk of adverse effects (e.g. accidents, cancers, liver damage) only in men over 45 and women over 55.

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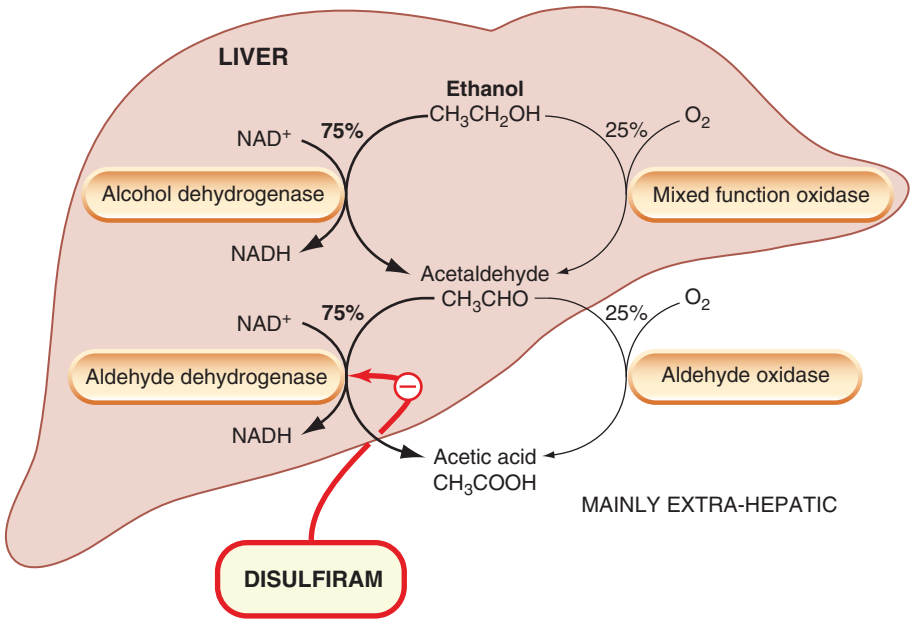

Fig. 49.6 Metabolism of ethanol. NAD, nicotinamide adenine dinucleotide.

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 9 and 10) 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 redistribution depending mainly on the blood flow to individual tissues, as with volatile anaesthetics (see Ch. 41).

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. 49.6). 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, independently of ethanol concentration (Fig. 49.7), causing the process to show saturating kinetics (Ch. 10). 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. 57). 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.

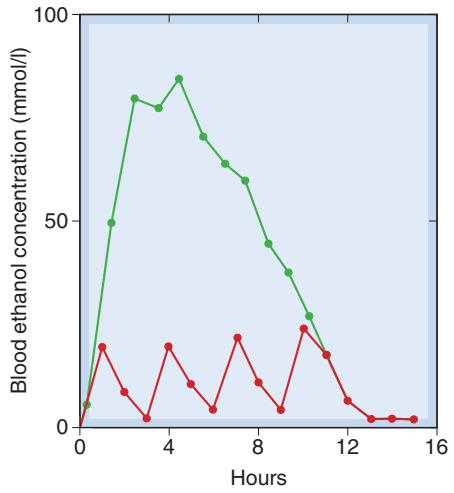

Fig. 49.7 Zero-order kinetics of ethanol elimination in rats. Rats were given ethanol orally (104 mmol/kg) either as a single dose or as four divided doses. The single dose results in a much higher and more sustained blood ethanol concentration than the same quantity given as divided doses. Note that, 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.)*

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Alcohol dehydrogenase is a soluble cytoplasmic enzyme, confined mainly to liver cells, which oxidises ethanol at the same time as reducing NAD^+ to NADH (Fig. 49.6). 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. 9), 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. **phenobarbitone**, **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* (Fig. 49.6). 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 harmful, and disulfiram can be used as aversion therapy to discourage people from taking ethanol. Some other drugs (e.g. **metronidazole**; see Ch. 51) produce similar reactions to ethanol. Interestingly, a Chinese herbal medicine used traditionally to cure alcoholics contains **daidzin**, a specific inhibitor of aldehyde dehydrogenase.[11]

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. Treatment is with fomepizole or, with caution, ethanol,[12] and haemodialysis.

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.

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

[11] 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.

[12] 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!

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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 p. 601). 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.

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. 44) together with large doses of thiamine.

PHARMACOLOGICAL APPROACHES TO TREATING ALCOHOL DEPENDENCE

Alcohol dependence ('alcoholism') is common (4–5% of the population) and, as with smoking, difficult to treat effectively. The main pharmacological approaches (see Garbutt, 2009; Table 49.3) are the following:

- To alleviate the acute abstinence syndrome during 'drying out', **benzodiazepines** (see Ch. 44) and **clomethiazole** are effective; **clonidine** and **propranolol** are also useful. Clonidine (α_2-adrenoceptor agonist) is believed to act by inhibiting the exaggerated transmitter release that occurs during withdrawal, while propranolol (β-adrenoceptor antagonist) blocks some of the effects of excessive sympathetic activity.
- To render alcohol consumption unpleasant, **disulfiram**.
- The non-selective opioid antagonists **naltrexone** and **nalmefene** are effective in reducing alcohol consumption, indicating the possible involvement of endorphins (see Ch. 42) in the rewarding properties of alcohol.
- To reduce craving, **acamprosate** is used. This taurine analogue is a weak antagonist at NMDA receptors, and may work by interfering in some way with synaptic plasticity. Several clinical trials have shown it to improve the success rate in achieving alcohol abstinence, with few unwanted effects.
- To alleviate both withdrawal and craving, the antiepileptic agent **topiramate**, which has multiple effects on the brain (see Ch. 45), shows promise as does **γ-hydroxybutyric acid** (GHB), a short-chain fatty acid structurally similar to the inhibitory neurotransmitter γ-aminobutyric acid (see Ch. 38).

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Useful Web resources

<www.ash.org.uk/> (*ASH, an antismoking organisation*)

<www.drugscope.org.uk/> (*DrugScope, an independent organisation providing advice on various aspects of drug abuse*)

<www.nida.nih.gov/> (*National Institute on Drug Abuse [NIDA], US government organisation providing information to scientists and the general public on various aspects of drug abuse*)

<www.drugabuse.gov/PODAT/PODATIndex.html> (*Provides access to the NIDA publication Principles of Drug Addiction Treatment: A Research Based Guide, second edn*)

<www.ias.org.uk> (*The Institute of Alcohol Studies [UK] provides a Knowledge Centre offering an excellent range of factsheets relating to all aspects of alcohol consumption and its consequences*)

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50 Basic principles of antimicrobial chemotherapy

OVERVIEW

Chemotherapy is the term originally used to describe the use of drugs that are 'selectively toxic' to invading microorganisms while having minimal effects on the host. It also refers to the use of drugs to treat tumours, and in the public mind at least, 'chemotherapy' is usually associated with cytotoxic anticancer drugs that cause unwanted effects such as loss of hair, nausea and vomiting. In this chapter, we focus on antimicrobial chemotherapy. Anticancer drugs are covered in Ch. 56.

All living organisms are vulnerable to infection. Humans, being no exception, are susceptible to diseases caused by viruses, bacteria, protozoa, fungi and helminths (collectively referred to as pathogens). The use of chemotherapeutic agents dates back to the work of Ehrlich and others and to the development of selectively toxic arsenical drugs such as salvarsan for the treatment of syphilis.[1] The successful development of such agents during the past 80 years, particularly the 'antibiotic revolution', which began in the 1940s with the advent of penicillin, constitutes one of the most important therapeutic advances in the history of medicine.

The feasibility of the selective toxicity strategy depends on the ability to exploit such biochemical differences as may exist between the infecting organism and the host. While the bulk of the chapters in this section of the book describe the drugs used to combat such infections, in this introductory chapter we consider the nature of these biochemical differences and outline the molecular targets of drug action.

BACKGROUND

The term *chemotherapy* was coined by Ehrlich himself at the beginning of the 20th century to describe the use of synthetic chemicals to destroy infective pathogens. In recent years the definition of the term has been broadened to include *antibiotics* – substances produced by some microorganisms (or by pharmaceutical chemists) that kill or inhibit the growth of other microorganisms.

Unhappily, our success in developing drugs to attack these invaders has been paralleled by their own success in counteracting the effects of the drugs, resulting in the emergence of drug resistance. And at present, the invaders – particularly some bacteria – seem close to getting the upper hand. This is a very important problem, and we will devote some space to the mechanisms of resistance and the means by which it is spread.

[1]Mercury-containing compounds were also once used for treating syphilis. 'One night with Venus, a lifetime with Mercury' was a saying prior to the advent of the antibiotic era.

THE MOLECULAR BASIS OF CHEMOTHERAPY

Chemotherapeutic agents, then, are chemicals intended to be toxic to the pathogenic organism but innocuous to the host. It is important to remember that many microorganisms share our body spaces (e.g. the gut[2]) without causing disease (these are called *commensals*), although they may become pathogenic under adverse circumstances (i.e. if the host is immunocompromised or if barrier breakdown results in them setting up shop elsewhere in our bodies).

All living organisms can be classified as either *prokaryotes*, cells without nuclei (e.g. bacteria), or *eukaryotes*, cells with nuclei (e.g. protozoa, fungi, helminths). In a separate category are the viruses, which need to utilise the metabolic machinery of the host cell to replicate, and they thus present a particular kind of problem for chemotherapeutic attack. There remain those mysterious proteinaceous agents, *prions* (see Ch. 40), which cause disease but resist all attempts at classification and treatment.

Virtually all creatures, host and parasite alike, have the same basic DNA blueprint (an exception being the RNA viruses), so some biochemical processes are common to most, if not all, organisms. Finding agents that affect pathogens but not other human cells necessitates finding either qualitative or quantitative biochemical differences between them.

Bacteria cause most infectious diseases, and Figure 50.1 shows, in simplified diagrammatic form, the main components of a 'generalised' bacterial cell and their functions. Surrounding the cell is the *cell wall*, which characteristically contains *peptidoglycan* in all forms of bacteria except *Mycoplasma*. Peptidoglycan is unique to prokaryotic cells and has no counterpart in eukaryotes. Within the cell wall is the *plasma membrane*, which, like that of eukaryotic cells, consists of a phospholipid bilayer and proteins. It functions as a selectively permeable membrane with specific transport mechanisms for various nutrients. However, in bacteria the plasma membrane does not contain any *sterols* (e.g. cholesterol), and this may alter the penetration of some chemicals.

The cell wall supports the underlying plasma membrane, which is subject to an internal osmotic pressure of about 5 atmospheres in *Gram-negative* organisms, and about 20 atmospheres in *Gram-positive* organisms. The plasma membrane and cell wall together comprise the *bacterial envelope*.

As in eukaryotic cells, the plasma membrane contains the *cytoplasm* but bacterial cells have no nucleus; instead, the genetic material, in the form of a single *chromosome* containing all the genetic information, lies in the cytoplasm with no surrounding nuclear membrane. In further contrast to eukaryotic cells, there are no *mitochondria*

[2]Humans harbour about 2 kg of bacteria in the gut, comprising a large 'forgotten organ' in the body with important metabolic functions.

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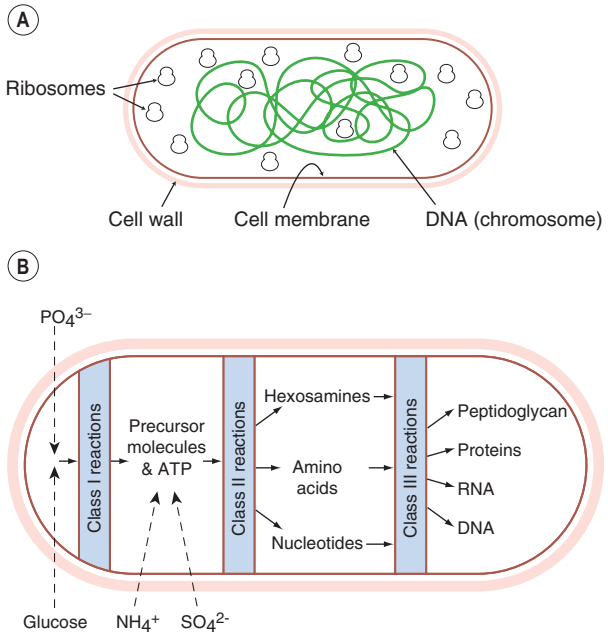

Fig. 50.1 Diagram of the structure and metabolism of a 'typical' bacterial cell. [**A**] Schematic representation of a bacterial cell. [**B**] Flow diagram showing the synthesis of the main types of macromolecule of a bacterial cell. Class I reactions result in the synthesis of the precursor molecules necessary for class II reactions, which result in the synthesis of the constituent molecules; these are then assembled into macromolecules by class III reactions. *(Modified from Mandelstam J, McQuillen K, Dawes I (eds) 1982 Biochemistry of Bacterial growth. Blackwell Scientific, Oxford.)*

– cellular energy is generated by enzyme systems located in the plasma membrane.

Some bacteria have additional components relevant to chemotherapy, including an *outer membrane* on the outside of the cell wall. This determines whether they take up *Gram's stain* ('Gram-positive') or not ('Gram-negative'; for more details, see Ch. 51). In Gram-negative bacteria, this membrane prevents penetration of some antibacterial agents.

Biochemical reactions that are potential targets for antibacterial drugs are shown in Figure 50.1. There are three groups:

- *Class I*: the utilisation of glucose, or some alternative carbon source, for the generation of energy (ATP) and synthesis of simple carbon compounds used as precursors in the next class of reactions.
- *Class II*: the utilisation of these precursors in an energy-dependent synthesis of all the amino acids, nucleotides, phospholipids, amino sugars, carbohydrates and growth factors required by the cell for survival and growth.
- *Class III*: assembly of small molecules into macromolecules – proteins, RNA, DNA, polysaccharides and peptidoglycan.

Other potential drug targets are *formed structures*, for example the cell membrane, the *microtubules* in fungi or muscle tissue in helminths. In considering these targets, emphasis will be placed on bacteria, but reference will also be made to protozoa, helminths, fungi and viruses.

The classification that follows is not rigid; a drug may affect more than one class of reactions or more than one subgroup of reactions within a class.

The molecular basis of antibacterial chemotherapy

- Chemotherapeutic drugs should be toxic to invading organisms and innocuous to the host. Such selective toxicity depends on the discovery of biochemical differences between the pathogen and the host that can be appropriately exploited.
- Three general classes of biochemical reaction are potential targets for chemotherapy of bacteria:
  - *class I*: reactions that utilise glucose and other carbon sources to produce ATP and simple carbon compounds
  - *class II*: pathways utilising energy and class I compounds to make small molecules (e.g. amino acids and nucleotides)
  - *class III*: pathways that convert small molecules into macromolecules such as proteins, nucleic acids and peptidoglycan.

BIOCHEMICAL REACTIONS AS POTENTIAL TARGETS

CLASS I REACTIONS

Class I reactions are not promising targets for two reasons. First, bacterial and human cells use similar mechanisms to obtain energy from glucose (the *Embden–Meyerhof pathway* and the *tricarboxylic acid cycle*). Second, even if glucose oxidation is blocked, many other compounds (amino acids, lactate, etc.) can be utilised by bacteria as an alternative energy source.

CLASS II REACTIONS

Class II reactions are better targets because some pathways exist in pathogens, but not human, cells. There are several examples.

Folate

The folate biosynthesitic pathway is found in bacteria but not in humans. Folate is required for DNA synthesis in both bacteria and in humans (see Chs 25 and 51). As it cannot be synthesised by humans it must be obtained from the diet and concentrated in cells by specific uptake mechanisms. By contrast, most species of bacteria, as well as the asexual forms of malarial protozoa, lack these essential transport mechanisms. Therefore they cannot make use of preformed folate but must synthesise this *de novo*. **Sulfonamides** contain the sulfanilamide moiety – a structural analogue of *p*-aminobenzoic acid (PABA), which is essential in bacterial synthesis of folate (see Ch. 51, Fig. 51.1). Sulfonamides compete with PABA, and thus inhibit bacterial growth without impairing mammalian cell function.

The utilisation of folate, in the form of *tetrahydrofolate*, as a co-factor in thymidylate synthesis is a good example of a pathway where human and bacterial enzymes exhibit a differential sensitivity to chemicals (Table 50.1; see Volpato & Pelletier, 2009). Although the pathway is

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Table 50.1 Specificity of inhibitors of dihydrofolate reductase

	IC_{50} (μmol/l) for dihydrofolate reductase		
Inhibitor	*Human*	*Protozoal*	*Bacterial*
Trimethoprim	260	0.07	0.005
Pyrimethamine	0.7	0.0005	2.5
Methotrexate	0.001	~0.1[a]	Inactive

[a]Tested on *Plasmodium berghei*, a rodent malaria.

virtually identical in microorganisms and humans, one of the key enzymes, *dihydrofolate reductase*, which reduces dihydrofolate to tetrahydrofolate (Ch. 51, Fig. 51.2), is many times more sensitive to the inhibitor **trimethoprim** in bacteria than in humans. In some malarial protozoa, this enzyme is somewhat less sensitive than the bacterial enzyme to trimethoprim but more sensitive to **pyrimethamine** and **proguanil**, which are used as antimalarial agents (Ch. 54). The relative IC_{50} values (the concentration causing 50% inhibition) for bacterial, malarial, protozoal and mammalian enzymes are given in Table 50.1. The human enzyme, by comparison, is very sensitive to the effect of the folate analogue **methotrexate**, which is used to treat inflammatory arthritis (Ch. 26), severe psoriasis (Ch. 27) and cancer (Ch. 56).

▼ The use of sequential blockade with a combination of two drugs that affect the same pathway at different points, for example sulfonamides and the folate antagonists, may be more successful than the use of either alone. Thus, pyrimethamine and a sulfonamide (**sulfadoxine**) are used to treat *falciparum* malaria. **Co-trimoxazole** is an antibacterial formulation that contains both a sulfonamide and trimethoprim. Once widely used, this combination has become less popular for treating bacterial infections because trimethoprim alone is similarly effective and does not cause sulfonamide-specific adverse effects; its use is now mainly restricted to treatment of *Pneumocystis jirovecii*, for which high doses are required (Ch. 54).

CLASS III REACTIONS

As pathogen cells cannot take up their own unique macromolecules, class III reactions are particularly good targets for selective toxicity, and there are distinct differences between mammalian cells and parasitic cells in this respect.

The synthesis of peptidoglycan

The cell wall of bacteria contains peptidoglycan, a substance that does not occur in eukaryotes. It is the equivalent of a non-stretchable string bag enclosing the whole bacterium. In Gram-negative bacteria, this bag consists of a single thickness, but in Gram-positive bacteria there may be as many as 40 layers of peptidoglycan. Each layer consists of multiple backbones of amino sugars – alternating *N*-acetylglucosamine and *N*-acetylmuramic acid residues (Fig. 50.2) – the latter having short peptide side-chains that are cross-linked to form a polymeric lattice, which may constitute up to 10–15% of the dry weight of the cell and is strong enough to resist the high internal osmotic pressure. The cross-links differ in different species. In staphylococci, they consist of five glycine residues.

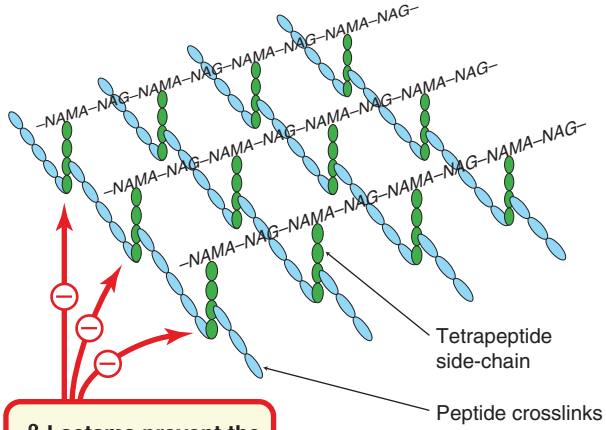

Fig. 50.2 Schematic diagram of a single layer of peptidoglycan from a bacterial cell (e.g. *Staphylococcus aureus*), showing the site of action of the β-lactam antibiotics. In *S. aureus* the peptide crosslinks consist of five glycine residues. Gram-positive bacteria have several layers of peptidoglycan. NAG, *N*-acetylglucosamine; NAMA, *N*-acetylmuramic acid (more detail in Fig. 50.3).

▼ To build up this very large insoluble peptidoglycan layer on the outside of the cell membrane, the bacterial cell has the problem of how to transport the hydrophilic cytoplasmic 'building blocks' through the hydrophobic cell membrane structure. This is accomplished by linking them to a very large lipid carrier, containing 55 carbon atoms, which 'tows' them across the membrane. The process of peptidoglycan synthesis is outlined in Figure 50.3. First, *N*-acetylmuramic acid, attached to uridine diphosphate (UDP) and a pentapeptide, is transferred to the C_{55} lipid carrier in the membrane, with the release of uridine monophosphate. This is followed by a reaction with UDP–*N*-acetylglucosamine, resulting in the formation of a disaccharide pentapeptide complex attached to the carrier. This complex is the basic building block of the peptidoglycan. In *Staphylococcus aureus*, the five glycine residues are attached to the peptide chain at this stage. The building block is now transported out of the cell and added to the growing end of the peptidoglycan, the 'acceptor', with the release of the C_{55} lipid, which still has two phosphates attached. The lipid carrier then loses one phosphate group and thus becomes available for another cycle. Crosslinking between the peptide side-chains of the sugar residues in the peptidoglycan layer then occurs, the hydrolytic removal of the terminal alanine supplying the requisite energy.

This synthesis of peptidoglycan is a vulnerable step and can be blocked at several points by antibiotics (Fig. 50.3 and see Ch. 51). **Cycloserine**, which is a structural analogue of D-alanine, prevents the addition of the two terminal alanine residues to the initial tripeptide side-chain on *N*-acetylmuramic acid by competitive inhibition. **Vancomycin** inhibits the release of the building block unit from the carrier, thus preventing its addition to the growing end of the peptidoglycan. **Bacitracin** interferes with the regeneration of the lipid carrier by blocking its dephosphorylation. **Penicillins**, **cephalosporins** and other β-lactams inhibit the final transpeptidation by forming covalent bonds with *penicillin-binding proteins* that have transpeptidase and carboxypeptidase activities, thus preventing formation of the crosslinks.

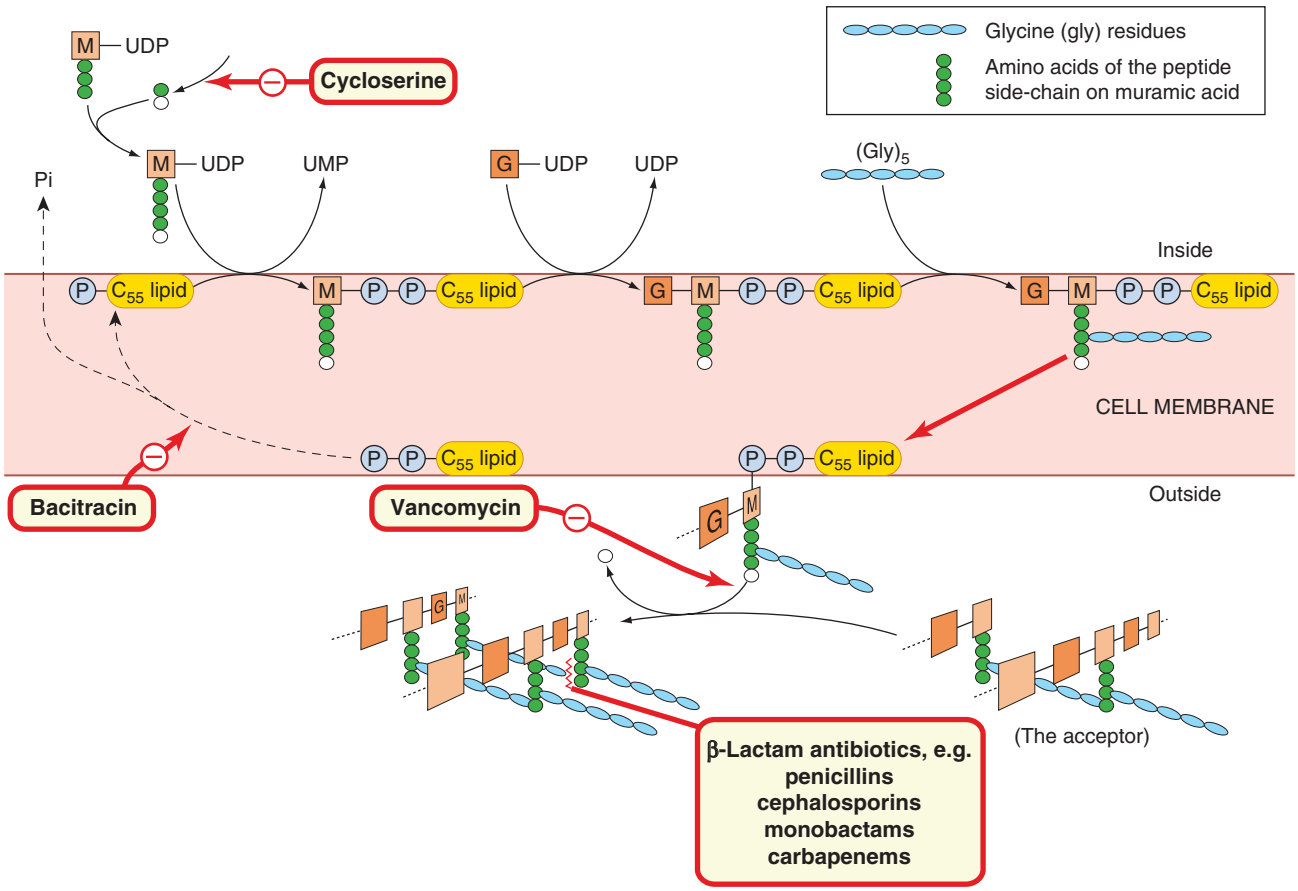

Fig. 50.3 Schematic diagram of the biosynthesis of peptidoglycan in a bacterial cell (e.g. *Staphylococcus aureus*), with the sites of action of various antibiotics. The hydrophilic disaccharide–pentapeptide is transferred across the lipid cell membrane attached to a large lipid (C_{55} lipid) by a pyrophosphate bridge (–P–P–). On the outside, it is enzymically attached to the 'acceptor' (the growing peptidoglycan layer). The final reaction is a transpeptidation, in which the loose end of the (Gly) 5 chain is attached to a peptide side-chain of an M in the acceptor and during which the terminal amino acid (alanine) is lost. The lipid is regenerated by loss of a phosphate group (Pi) before functioning again as a carrier. G, *N*-acetylglucosamine; M, *N*-acetylmuramic acid; UDP, uridine diphosphate; UMP, uridine monophosphate.

Protein synthesis

Protein synthesis takes place on the ribosomes. Eukaryotic and prokaryotic ribosomes are different, and this provides the basis for the selective antimicrobial action of some antibiotics. The bacterial ribosome consists of a 50S subunit and a 30S subunit (Fig. 50.4), whereas in the mammalian ribosome the subunits are 60S and 40S. The other elements involved in peptide synthesis are messenger RNA (mRNA), which forms the template for protein synthesis, and transfer RNA (tRNA), which specifically transfers the individual amino acids to the ribosome. The ribosome has three binding sites for tRNA, termed the A, P and E sites.

A simplified version of protein synthesis in bacteria is shown in Figure 50.4. To initiate translation, mRNA, transcribed from the DNA template, is attached to the 30S subunit of the ribosome. The 50S subunit then binds to the 30S subunit to form a 70S subunit,[3] which moves along the mRNA such that successive codons of the messenger pass along the ribosome from the A position to the P position. Antibiotics may affect protein synthesis at any one of these stages (Fig. 50.4 and see Ch. 51).

Nucleic acid synthesis

Gene expression and cell division also require nucleic acid synthesis, interference with which is an important mechanism of action of many chemotherapeutic drugs. It is possible to interfere with nucleic acid synthesis in five different ways:

- by inhibiting the synthesis of the nucleotides
- by altering the base-pairing properties of the DNA template
- by inhibiting either DNA or RNA polymerase
- by inhibiting DNA gyrase, which uncoils supercoiled DNA to allow transcription
- by a direct effect on DNA itself. Some anticancer drugs, but no antimicrobial drugs work in this way.

Inhibition of the synthesis of the nucleotides

This can be accomplished by an effect on the metabolic pathways that generate nucleotide precursors. Examples of agents that have such an effect have been described under class II reactions.

[3]You query whether 30S + 50S = 70S? Yes it does, because we are talking about *Svedberg units*, which measure sedimentation *rate*, not *mass*.

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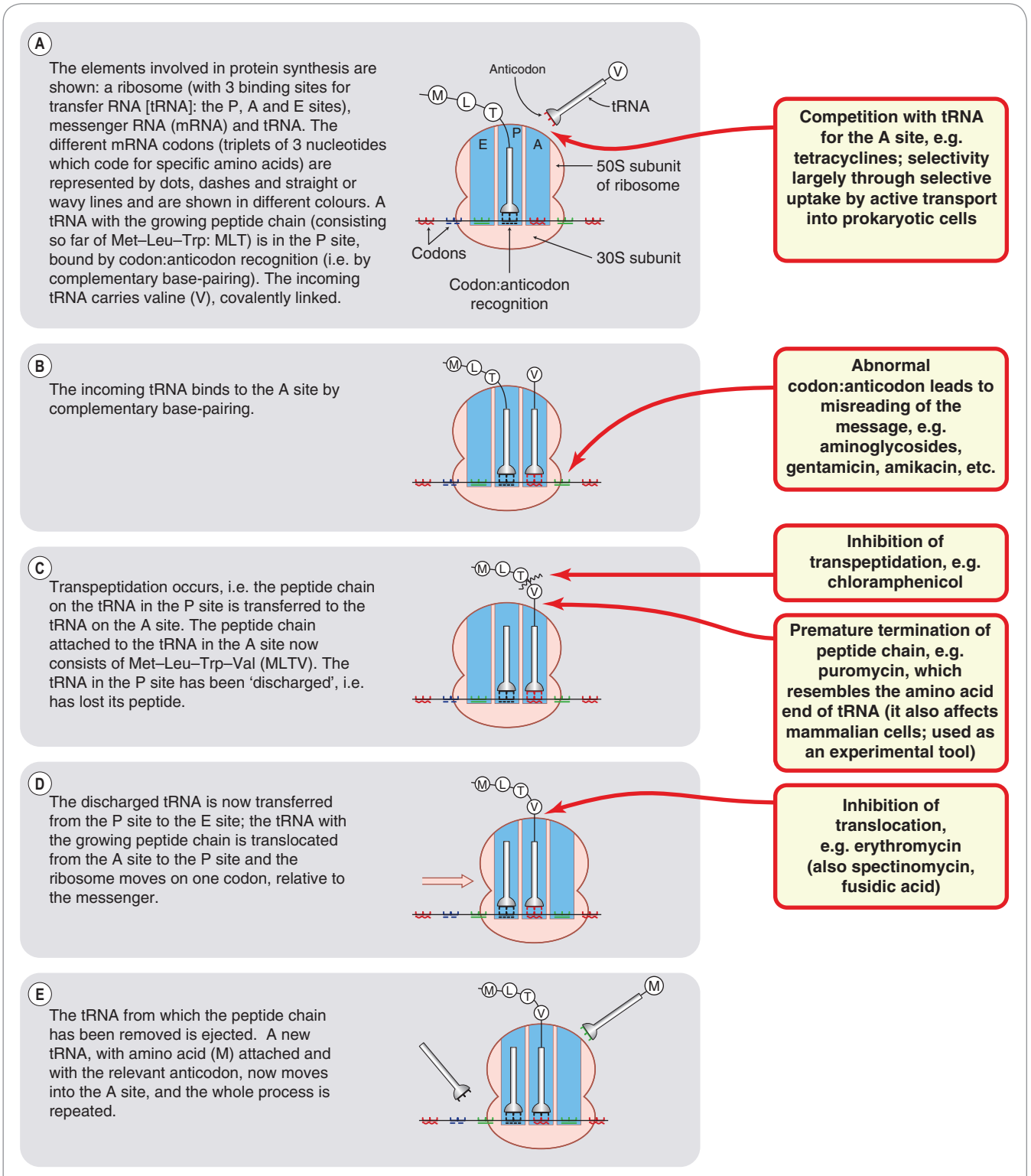

Fig. 50.4 Schematic diagram of bacterial protein synthesis, indicating the points at which antibiotics inhibit the process.

Alteration of the base-pairing properties of the template

Agents that intercalate in the DNA have this effect. Examples include acridines (**proflavine** and **acriflavine**), which are used topically as antiseptics. The acridines double the distance between adjacent base pairs and cause a *frameshift mutation*, whereas some purine and pyrimidine analogues cause base *mispairing*.

Inhibition of either DNA or RNA polymerase

Specific inhibitors of bacterial RNA polymerase that act by binding to this enzyme in prokaryotic but not in eukaryotic cells include **rifamycin** and **rifampicin**, which are particularly useful for treating tuberculosis (see Ch. 51). **Aciclovir** (an analogue of guanine) is phosphorylated in cells infected with herpes virus, the initial

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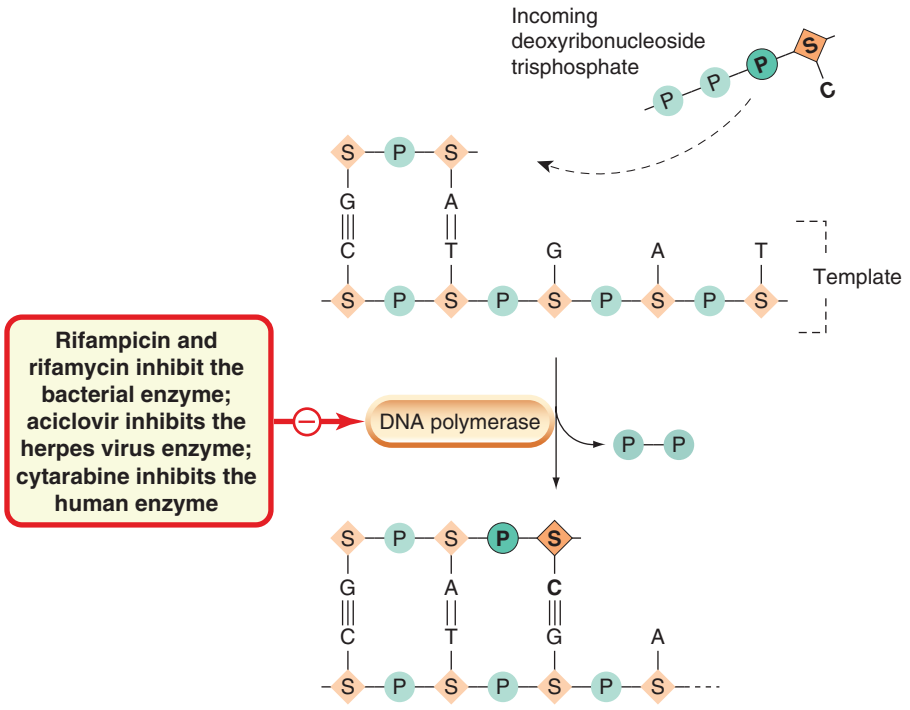

Fig. 50.5 Schematic diagram of DNA replication, showing some antibiotics that inhibit it by acting on DNA polymerase. Nucleotides are added, one at a time, by base pairing to an exposed template strand, and are then covalently joined together in a reaction catalysed by DNA polymerase. The units that pair with the complementary residues in the template consist of a base linked to a sugar and three phosphate groups. Condensation occurs with the elimination of two phosphates. The elements added to the template are shown in darker colours and bold type. A, adenine; C, cytosine; G, guanine; P, phosphate; S, sugar; T, thymine.

phosphorylation being by a virus-specific kinase to give the aciclovir trisphosphate, which has an inhibitory action on the DNA polymerase of the herpes virus (Ch. 52; Fig. 50.5).

RNA retroviruses have a *reverse transcriptase* (*viral RNA-dependent DNA polymerase*) that copies the viral RNA into DNA that integrates into the host cell genome as a provirus. Various agents (**zidovudine**, **didanosine**) are phosphorylated by cellular enzymes to the trisphosphate forms, which compete with the host cell precursors essential for the formation by the viral reverse transcriptase of proviral DNA.

Inhibition of DNA gyrase

Figure 50.6 is a simplified scheme showing the action of DNA gyrase. The *fluoroquinolones* (**cinoxacin**, **ciprofloxacin**, **nalidixic acid** and **norfloxacin**) act by inhibiting DNA gyrase, and these chemotherapeutic agents are particularly useful for treating infections with Gram-negative organisms (Ch. 51). They are selective for the bacterial enzyme.

THE FORMED STRUCTURES OF THE CELL AS POTENTIAL TARGETS

THE MEMBRANE

The plasma membrane of bacterial cells is similar to that in mammalian cells in that it consists of a phospholipid bilayer in which proteins are embedded, but it can be more easily disrupted in certain bacteria and fungi.

Polymixins are cationic peptide antibiotics, containing both hydrophilic and lipophilic groups, which have a selective effect on bacterial cell membranes. They act as detergents, disrupting the phospholipid components of the membrane structure, thus killing the cell.

Unlike mammalian and bacterial cells, fungal cell membranes comprise large amounts of *ergosterol*. This facilitates the attachment of *polyene antibiotics* (e.g. **nystatin** and **amphotericin**; Ch. 53), which act as ionophores and cause leakage of cations from the cytoplasm.

Azoles such as **itraconazole** kill fungal cells by inhibiting ergosterol synthesis, thereby disrupting the function of membrane-associated enzymes. The azoles also affect Gram-positive bacteria, their selectivity being associated with the presence of high levels of free fatty acids in the membrane of susceptible organisms (Ch. 53).

Biochemical reactions as potential targets for chemotherapy

- Class I reactions are poor targets.
- Class II reactions are better targets:
  - *folate synthesis* in bacteria is inhibited by sulfonamides
  - *folate utilisation* is inhibited by folate antagonists, for example **trimethoprim** (bacteria), **pyrimethamine** (malarial parasite).
- Class III reactions are important targets:
  - *peptidoglycan synthesis* in bacteria can be selectively inhibited by β-lactam antibiotics (e.g. **penicillin**)
  - *bacterial protein synthesis* can be selectively inhibited by antibiotics that prevent binding of tRNA (e.g. tetracyclines), promote misreading of mRNA (e.g. aminoglycosides), inhibit transpeptidation (e.g. **chloramphenicol**) or inhibit translocation of tRNA (e.g. **erythromycin**)
  - *nucleic acid synthesis* can be inhibited by altering base pairing of DNA template (e.g. the antiviral **vidarabine**), by inhibiting DNA polymerase (e.g. the antivirals **aciclovir** and **foscarnet**) or by inhibiting DNA gyrase (e.g. the antibacterial **ciprofloxacin**).

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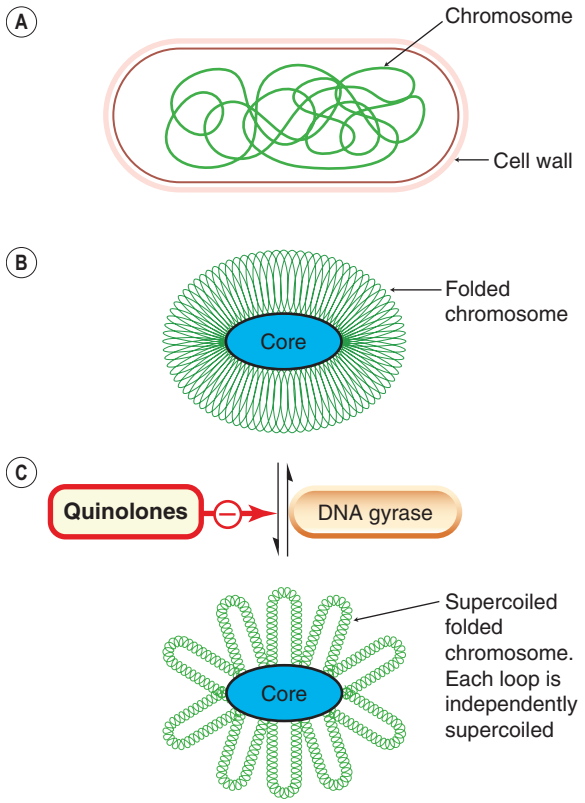

Fig. 50.6 Schematic diagram of the action of DNA gyrase: the site of action for quinolone antibacterials. [**A**] Conventional diagram used to depict a bacterial cell and chromosome (e.g. *Escherichia coli*). Note that the *E. coli* chromosome is 1300 mm long and is contained in a cell envelope of 2 μm × 1 μm; this is approximately equivalent to a 50 m length of cotton folded into a matchbox. [**B**] Chromosome folded around RNA core, and then [**C**], supercoiled by DNA gyrase (topoisomerase II). Quinolone antibacterials interfere with the action of this enzyme. *(Modified from Smith JT 1985 In: Greenwood D, O'Grady F (eds) Scientific Basis of Antimicrobial Therapy. Cambridge University Press, Cambridge, p. 69.)*

INTRACELLULAR ORGANELLES

Microtubules and/or microfilaments

The benzimidazoles (e.g. **albendazole**) exert their anthelmintic action by binding selectively to parasite tubulin and preventing microtubule formation (Ch. 55).

Food vacuoles

The erythrocytic form of the malaria plasmodium feeds on host haemoglobin, which is digested by proteases in the parasite food vacuole, the final product, haem, being detoxified by polymerisation. **Chloroquine** exerts its antimalarial action by inhibiting plasmodial haem polymerase (Ch. 54).

MUSCLE FIBRES

Some anthelmintic drugs have a selective action on helminth muscle cells (Ch. 55). **Piperazine** acts as an agonist on parasite-specific chloride channels gated by GABA in nematode muscle, hyperpolarising the muscle fibre membrane and paralysing the worm; **avermectins** increase Cl^- permeability in helminth muscle – possibly by a similar mechanism. **Pyrantel** (now seldom used) and **levamisole** are agonists at nematode acetylcholine nicotinic receptors on muscle, causing contraction followed by paralysis (Ch. 55).

Formed structures of the cell that are targets for chemotherapy

- The plasma membrane is affected by:
  - **amphotericin**, which acts as an ionophore in fungal cells
  - azoles, which inhibit fungal membrane ergosterol synthesis.
- Microtubule function is disrupted by:
  - benzimidazoles (anthelmintics).
- Muscle fibres are affected by:
  - avermectins (anthelmintics), which increase Cl^- permeability
  - **pyrantel** (anthelmintic), which stimulates nematode nicotinic receptors, eventually causing muscle paralysis.

RESISTANCE TO ANTIBACTERIAL DRUGS

Since the 1940s, the development of effective and safe drugs to deal with bacterial and other infections has revolutionised medical treatment, and the morbidity and mortality associated with these diseases has been dramatically reduced. Unfortunately, the development of effective antibacterial drugs has been accompanied by the emergence of drug-resistant organisms.

However, the bacterial 'resistome' (as the pool of genes that determines resistance is called) actually predates the advent of pharmaceutical antibiotics. It originally evolved to counteract naturally occurring bactericidal compounds encountered in their natural habitats and has changed to meet the challenges posed by modern antibiotic drugs used in the clinic (Cox & Wright, 2013). The short generation time of many bacterial species affords ample opportunity for such evolutionary adaptations. The phenomenon of resistance imposes serious constraints on the options available for the medical treatment of many bacterial infections. Resistance to chemotherapeutic agents can also develop in protozoa, in multicellular parasites (and also in populations of malignant cells, discussed in Ch. 56). Here, however, we will confine our discussion mainly to the mechanisms of resistance in bacteria.

Antibiotic resistance may be *innate* or *acquired*. There are three basic mechanisms by which resistance is spread:

1. by transfer of resistant bacteria between people
2. by transfer of resistance genes between bacteria (usually on plasmids)
3. by transfer of resistance genes between genetic elements within bacteria, on transposons.

Understanding the mechanisms involved in antibiotic resistance is crucial for the sensible clinical use of existing medicines ('antibiotic stewardship') and in the design of new antibacterial drugs. One byproduct of the studies of resistance in bacteria was the development of plasmid-based techniques for DNA cloning, leading to the use of bacteria to produce recombinant proteins for therapeutic use (see Ch. 59).

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GENETIC DETERMINANTS OF ANTIBIOTIC RESISTANCE

CHROMOSOMAL DETERMINANTS: MUTATIONS

▼ The spontaneous mutation rate in bacterial populations for any particular gene is very low, and the probability is that approximately only 1 cell in 10 million will, on division, give rise to a daughter cell containing a mutation in that gene. However, as there are likely to be very many more cells than this over the course of an infection, the probability of a mutation causing a change from drug sensitivity to drug resistance can be quite high. Fortunately, the presence of a few mutants is not generally sufficient to produce resistance: despite the selective advantage that the resistant mutants possess, the drastic reduction of the population by the antibiotic usually enables the host's natural defences (see Ch. 6) to prevail at least in acute, if not chronic, infections. However, the outcome may not be quite so happy if the primary infection is caused by a drug-resistant strain.

GENE AMPLIFICATION

▼ *Gene duplication* and *amplification* are important mechanisms for resistance in some organisms (Sandegren & Andersson, 2009). According to this idea, treatment with antibiotics can induce an increased number of copies for pre-existing resistance genes such as antibiotic-destroying enzymes and efflux pumps.

EXTRACHROMOSOMAL DETERMINANTS: PLASMIDS

▼ In addition to the chromosome itself, many species of bacteria contain extrachromosomal genetic elements called *plasmids* that exist free in the cytoplasm. These are also genetic elements that can replicate independently. Structurally, they are closed loops of DNA that may comprise a single gene or as many as 500 or even more. Only a few plasmid copies may exist in the cell but often multiple copies are present, and there may also be more than one type of plasmid in each bacterial cell. Plasmids that carry genes for resistance to antibiotics (*r genes*) are referred to as *R plasmids*. Much of the drug resistance encountered in clinical medicine is plasmid-determined. It is not known how these genes arose.

The whole process can occur with frightening speed. *Staphylococcus aureus*, for example, is a past master of the art of antibiotic resistance. Having become completely resistant to penicillin through plasmid-mediated mechanisms, this organism, within only 1–2 years, was able to acquire resistance to its replacement, **meticillin** (de Lencastre et al., 2007).

THE TRANSFER OF RESISTANCE GENES BETWEEN GENETIC ELEMENTS WITHIN THE BACTERIUM

Transposons

▼ Some stretches of DNA are readily transferred (transposed) from one plasmid to another and also from plasmid to chromosome or vice versa. This is because integration of these segments of DNA, which are called *transposons*, into the acceptor DNA can occur independently of the normal mechanism of homologous genetic recombination. Unlike plasmids, transposons are not able to replicate independently, although some may replicate during the process of integration (Fig. 50.7), resulting in a copy in both the donor and the acceptor DNA molecules. Transposons may carry one or more resistance genes and can 'hitch-hike' on a plasmid to a new species of bacterium. Even if the plasmid is unable to replicate in the new host, the transposon may integrate into the new host's chromosome or into its indigenous plasmids. This probably accounts for the widespread distribution of certain of the resistance genes on different R plasmids and among unrelated bacteria.

Gene cassettes and integrons

▼ Plasmids and transposons do not complete the tally of mechanisms that natural selection has provided to confound the hopes of the microbiologist/chemotherapist. Resistance – in fact, *multidrug resistance* – can also be spread by another mobile element, the *gene cassette*, which consists of a resistance gene attached to a small recognition site. Several cassettes may be packaged together in a *multicassette array*, which can, in turn, be integrated into a larger mobile DNA unit termed an *integron*. The integron (which may be located on a transposon) contains a gene for an enzyme, *integrase* (*recombinase*), which inserts the cassette(s) at unique sites on the integron. This system – transposon/integron/multiresistance cassette array – allows particularly rapid and efficient transfer of multidrug resistance between genetic elements both within and between bacteria.

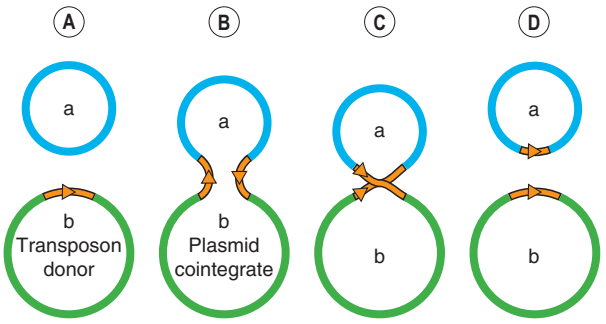

Fig. 50.7 An example of the transfer and replication of a transposon (which may carry genes coding for resistance to antibiotics). [**A**] Two plasmids, a and b, with plasmid b containing a transposon (shown in brown). [**B**] An enzyme encoded by the transposon cuts DNA of both donor plasmid and target plasmid a to form a cointegrate. During this process, the transposon replicates. [**C**] An enzyme encoded by the transposon resolves the cointegrate. [**D**] Both plasmids now contain the transposon DNA.

THE TRANSFER OF RESISTANCE GENES BETWEEN BACTERIA

▼ The transfer of resistance genes between bacteria of the same and indeed of different species is of fundamental importance in the spread of antibiotic resistance. The most important mechanism in this context is *conjugation*. Another gene transfer mechanism, *transduction* is less important in spreading resistance genes.

Conjugation

▼ Conjugation involves cell-to-cell contact during which chromosomal or extrachromosomal DNA is transferred from one bacterium to another, and is the main mechanism for the spread of resistance. The ability to conjugate is encoded in *conjugative plasmids*; these are plasmids that contain transfer genes that, in coliform bacteria, code for the production by the host bacterium of proteinaceous surface tubules, termed *sex pili*, which connect the two cells. The conjugative plasmid then passes across from one bacterial cell to another (generally of the same species). Many Gram-negative and some Gram-positive bacteria can conjugate. Some *promiscuous plasmids* can cross the species barrier, accepting one host as readily as another. Many R plasmids are conjugative. Non-conjugative plasmids, if they co-exist in a 'donor' cell with conjugative plasmids, can hitch-hike from one bacterium to the other with the conjugative plasmids. The transfer of resistance by conjugation is significant in populations of bacteria that are normally found at high densities, as in the gut.

Transduction

▼ *Transduction* is a process by which plasmid DNA is enclosed in a bacterial virus (or *phage*) and transferred to another bacterium of the same species. It is a relatively ineffective means of transfer of genetic material but is clinically important in the transmission of resistance genes between strains of staphylococci and of streptococci.

Transformation

▼ A few species of bacteria can, under natural conditions, undergo *transformation* by taking up DNA from the environment and incorporating it into the genome by normal homologous recombination. However, this mechanism is probably not of importance clinically.

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Resistance to antibiotics

- Drug resistance in bacterial populations can be spread from person to person by bacteria, from bacterium to bacterium by plasmids and from plasmid to plasmid (or chromosome) by transposons.
- Multicassette arrays of drug resistance genes can be transferred between bacteria, leading to spread of multidrug resistant strains.
- Plasmids are extrachromosomal genetic elements that can replicate independently and can carry genes coding for resistance to antibiotics (r genes).
- The main method of transfer of r genes from one bacterium to another is by conjugative plasmids. The bacterium forms a connecting tube with other bacteria through which the plasmids pass.
- A less common method of transfer is by transduction, i.e. the transmission by a bacterial virus (phage) of a plasmid bearing an r gene into another bacterium.
- Transposons are stretches of DNA that can be transposed from one plasmid to another, from a plasmid to a chromosome or vice versa. A plasmid containing an r gene-bearing transposon may code for enzymes that cause the plasmid to be integrated with another. Following their separation, this transposon replicates so that both plasmids then contain the r gene.

BIOCHEMICAL MECHANISMS OF RESISTANCE TO ANTIBIOTICS

THE PRODUCTION OF AN ENZYME THAT INACTIVATES THE DRUG

Inactivation of β-lactam antibiotics

The most important example of resistance caused by inactivation is that of the *β-lactam antibiotics*. The enzymes concerned are *β-lactamases*, which cleave the β-lactam ring of penicillins and **cephalosporins** (see Ch. 51). Cross-resistance between the two classes of antibiotic is not complete, because some β-lactamases have a preference for penicillins and some for cephalosporins.

▼ Staphylococci are the principal bacterial species producing β-lactamase, and the genes coding for the enzymes are on plasmids that can be transferred by transduction. In staphylococci, the enzyme is inducible (i.e. it is not expressed in the absence of the drug) and minute, sub-inhibitory, concentrations of antibiotics de-repress the gene and result in a 50- to 80-fold increase in expression. The enzyme passes through the bacterial envelope and inactivates antibiotic molecules in the surrounding medium. The grave clinical problem posed by resistant staphylococci secreting β-lactamase was tackled by developing semisynthetic penicillins (such as meticillin) and new β-lactam antibiotics (the **monobactams** and **carbapenems**), and cephalosporins (such as **cephamandole**), that are less susceptible to inactivation. The growing problem of meticillin-resistant *Staphylococcus aureus* (MRSA) infection is discussed below.

Gram-negative organisms can also produce β-lactamases, and this is a significant factor in their resistance to the semisynthetic broad-spectrum β-lactam antibiotics. In these organisms, the enzymes may be coded by either chromosomal or plasmid genes. In the former case, the enzymes may be inducible, but in the latter they are produced constitutively. When this occurs, the enzyme does not inactivate the drug in the surrounding medium but instead remains attached to the cell wall, preventing access of the drug to membrane-associated target sites. Many of these β-lactamases are encoded by transposons, some of which may also carry resistance determinants to several other antibiotics.

Inactivation of chloramphenicol

Chloramphenicol is inactivated by *chloramphenicol acetyltransferase*, an enzyme produced by resistant strains of both Gram-positive and Gram-negative organisms, the resistance gene being plasmid borne. In Gram-negative bacteria, the enzyme is produced constitutively, resulting in levels of resistance five-fold higher than in Gram-positive bacteria, in which the enzyme is inducible.

Inactivation of aminoglycosides

Aminoglycosides are inactivated by phosphorylation, adenylation or acetylation, and the requisite enzymes are found in both Gram-negative and Gram-positive organisms. The resistance genes are carried on plasmids, and several are found on transposons.

Many other examples of this kind are given by Wright (2005) and Giedraitiene et al (2011).

ALTERATION OF DRUG-SENSITIVE OR DRUG-BINDING SITE

The aminoglycoside-binding site on the 30S subunit of the ribosome may be altered by chromosomal mutation. A plasmid-mediated alteration of the binding site protein on the 50S subunit also underlies resistance to **erythromycin**, and decreased binding of fluoroquinolones because of a point mutation in DNA gyrase A has also been described. An altered DNA-dependent RNA polymerase determined by a chromosomal mutation is reported to be the basis for **rifampicin** resistance.

In addition to acquiring resistance to β-lactams susceptible to β-lactamase, some strains of *S. aureus* have even become resistant to some antibiotics that are not significantly inactivated by β-lactamase (e.g. meticillin), because they express an additional β-lactam-binding protein coded for by a mutated chromosomal gene. See Lambert (2005) for other examples of this type of action.

DECREASED DRUG ACCUMULATION IN THE BACTERIUM

An important example of decreased drug accumulation is the plasmid-mediated resistance to **tetracyclines** encountered in both Gram-positive and Gram-negative bacteria. In this case, resistance genes in the plasmid code for inducible proteins in the bacterial membrane, which promote energy-dependent efflux of the tetracyclines, and hence resistance. This type of resistance is common and has greatly reduced the therapeutic value of the tetracyclines in human and veterinary medicine. Resistance of *S. aureus* to erythromycin and the other macrolides, and to fluoroquinolones, is also brought about by energy-dependent efflux. Inhibitors of such pumps may be useful adjuncts to antibiotics (Van Bambeke et al., 2006).

There is also recent evidence of plasmid-determined inhibition of *porin* synthesis, which could affect those hydrophilic antibiotics that enter the bacterium through these water-filled channels in the outer membrane. Altered permeability as a result of chromosomal mutations involving the polysaccharide components of the outer membrane of Gram-negative organisms may confer enhanced resistance to **ampicillin**. Mutations affecting

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envelope components have been reported to affect the accumulation of aminoglycosides, β-lactams, chloramphenicol, peptide antibiotics and tetracycline.

ALTERATION OF ENZYME PATHWAYS

Resistance to trimethoprim is the result of plasmid-directed synthesis of a *dihydrofolate reductase* with low or zero affinity for trimethoprim. It is transferred by transduction and may be spread by transposons.

Sulfonamide resistance in many bacteria is plasmid-mediated and results from the production of a form of *dihydropteroate synthetase* with a low affinity for sulfonamides but no change in affinity for PABA. Bacteria causing serious infections have been found to carry plasmids with resistance genes to both sulfonamides and trimethoprim.

Biochemical mechanisms of resistance to antibiotics

The principal mechanisms are as follow:

- *Production of enzymes that inactivate the drug*: for example, β-lactamases, which inactivate **penicillin**; acetyltransferases, which inactivate **chloramphenicol**; kinases and other enzymes, which inactivate aminoglycosides.
- *Alteration of the drug-binding sites*: this occurs with aminoglycosides, **erythromycin**, **penicillin**.
- *Reduction of drug uptake by the bacterium*: for example, tetracyclines.
- *Alteration of enzyme pathways*: for example, dihydrofolate reductase becomes insensitive to **trimethoprim**.

CURRENT STATUS OF ANTIBIOTIC RESISTANCE IN BACTERIA

The most disturbing development of resistance has been in staphylococci, one of the commonest causes of hospital bloodstream infections, many strains of which are now resistant to almost all currently available antibiotics (de Lencastre et al., 2007). In addition to resistance to some β-lactams through production of β-lactamase and the production of an additional β-lactam-binding protein that also renders them resistant to meticillin, *S. aureus* may also manifest resistance to other antibiotics as follows:

- to **streptomycin** (because of chromosomally determined alterations of target site)
- to aminoglycosides in general (because of altered target site and plasmid-determined inactivating enzymes)
- to chloramphenicol and the macrolides (because of plasmid-determined enzymes)
- to trimethoprim (because of transposon-encoded drug-resistant dihydrofolate reductase)
- to sulfonamides (because of chromosomally determined increased production of PABA)
- to rifampicin (because of chromosomally and plasmid determined increases in efflux of the drug)
- to **fusidic acid** (because of chromosomally determined decreased affinity of the target site or a plasmid-encoded decreased permeability to the drug)
- to quinolones, for example **ciprofloxacin** and norfloxacin (because of chromosomally determined reduced uptake).

Infections with MRSA are a major problem, particularly in hospitals, where they can spread rapidly among elderly and/or seriously ill patients, and patients with burns or wounds. Until recently, the glycopeptide **vancomycin** was the antibiotic of last resort against MRSA but, ominously, strains of MRSA showing decreased susceptibility to this drug were isolated from hospitalised patients in the USA and Japan in 1997 and, more recently, in the community. MRSA infections are rising globally.

The fact that vancomycin resistance seems to have developed spontaneously could have major clinical implications – and not only for hospital-acquired MRSA infections. It had been thought that antibiotic-resistant bacteria were dangerous only to seriously ill, hospitalised patients, in that the genetic burden of multiple resistance genes would lead to reduced virulence. Distressingly, however, there is now evidence that the spectrum and frequency of disease produced by meticillin-susceptible and meticillin-resistant staphylococci are similar.

▼ In the past few years, *enterococci* have been rapidly developing resistance to many chemotherapeutic agents and have emerged as the second most common hospital-acquired pathogen. Non-pathogenic enterococci are ubiquitous in the intestine, have intrinsic resistance to many antibacterial drugs and can readily become resistant to other agents by taking up plasmids and transposons carrying the relevant resistance genes. Such resistance is easily transferred to invading pathogenic enterococci.

Enterococci, already multiresistant, have recently developed resistance to vancomycin (see Arias & Murray, 2012). This is apparently achieved by substitution of D-Ala-D-Ala with D-Ala-D-lactate in the peptide chain attached to *N*-acetylglucosamine-*N*-acetylmuramic acid (G-M) during the first steps of peptidoglycan synthesis (see Fig. 50.3; Ch. 51). A particular concern is the possibility of transfer of vancomycin resistance from enterococci to staphylococci, because they can co-exist in the same patient.

Many other pathogens are developing or have developed resistance to commonly used drugs. This list includes *Pseudomonas aeruginosa*, *Streptococcus pyogenes*, *S. pneumoniae*, *Neisseria meningitidis*, *N. gonorrhoeae*, *Haemophilius influenzae* and *H. ducreyi*, as well as *Mycobacterium*, *Campylobacter* and *Bacteroides* species. Some strains of *Mycobacterium tuberculosis* are now able to evade every antibiotic in the clinician's armamentarium, and tuberculosis, once easily treatable, is now once again a major killer. Fortunately, some glycopeptide and other antibiotics (e.g. **teicoplanin**, **daptomycin** and **linezolide**, see Ch. 51) that are used to treat resistant Gram-positive strains have largely maintained their potency. Even so, there is a danger of resistance arising if they are wrongly utilised.

Prescribers and consumers must also bear a responsibility for the burgeoning problem of resistance. Indiscriminate use of antibiotics in human and veterinary medicine, and their use in animal foodstuffs, has undoubtedly encouraged the growth of resistant strains. Some governmental and regulatory bodies (e.g. the European Union) have devised political and social measures to curb such excesses, and these have been at least partly successful.

The issue around declining antibiotic efficacy is, however, not solely to do with bacterial countermeasures. Historically, antibiotics were one of the mainstays of the pharmaceutical industry, and by 1970 it was thought that infectious diseases had been effectively vanquished.[4]

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Most of the drugs developed since are the result of incremental changes in the structures of a relatively small number of well-known molecular structures, such as the β-lactams, to which resistance has developed rapidly. Many pharmaceutical companies scaled down their efforts in the area, despite the continuing need for compounds acting by novel mechanisms to keep pace with the adaptive potential of pathogens. Drug-resistant infections are now seen as a serious global threat by the World Health Organization, needful of major incentives for research in what has become a somewhat neglected area.

[4]In 1967 the US Surgeon General announced (in effect) that infectious diseases had been vanquished, and that the researchers should turn their attention to chronic diseases instead.

Multidrug resistance

Many pathogenic bacteria have developed resistance to the commonly used antibiotics. Examples include the following:

- Some strains of staphylococci and enterococci that are resistant to virtually all current antibiotics, the resistance being transferred by transposons and/or plasmids; such organisms can cause serious and virtually untreatable nosocomial infections.
- Some strains of *Mycobacterium tuberculosis* that have become resistant to most antituberculosis agents.

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