Neurotransmitters, Drugs and Brain Function.
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17 Schizophrenia

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SYMPTOMS AND GENERAL ASPECTS

Schizophrenia may be defined as the progressive disintegration of an individual's personality and of the relationship between that person and the world in general. The main symptoms are:

(1) *Auditory hallucinations*. Voices repeating the person's thoughts and commenting on their actions.
(2) *Thought disorders*. The patient believes that other people can read and control their thoughts.
(3) *Physical catatonia*. An ability to maintain exaggerated and often bizarre postures for long periods.
(4) *Emotional problems*. Withdrawal, diminished emotions and response, reduced speech.

The first three characteristics are considered to be the 'positive' symptoms of the disorder. The fourth are described as 'negative' symptoms although they can be divided into true negative symptoms, i.e. diminished emotions and speech and reactive ones, i.e. social apathy and withdrawal brought on by the positive symptoms. Schizophrenics do not have a split personality. Normally their reaction to the positive symptoms is to withdraw quietly but occasionally they will react violently to the voices they hear and shout at them.

There are a number of drugs that reduce the positive symptoms and in so doing can make the patient less withdrawn. Consequently they appear to produce some beneficial effect on the negative symptoms. The good responders with positive symptoms have been categorised as type I schizophrenics and those with true negative symptoms and poor response to drugs as type II (Crow 1985). Approximately 1% of the population may develop schizophrenia during life and generally it appears in late adolescence or early adulthood (18–30 years). A general assessment of treatment is that some 25% recover fully and an almost equal number not at all, with many of them requiring long-term hospitalisation. The remaining half have fluctuating episodes often requiring chronic therapy.

AETIOLOGY

Schizophrenia is not a neurodegenerative disease but there is some general neuropathology. There is also evidence for a genetic influence. In monozygotic twins with

identical genes, if one twin develops schizophrenia there is a 50% chance that the other will, even it seems if they live apart but as the offspring of both have an equal chance of showing symptoms the tendency can lie dormant. Certainly the siblings of a schizophrenic show an increased risk of developing the disorder.

Although there is no specific lesion nearly all schizophrenic brains show some pathology such as reduced neuron number and brain size or some minor lesions, particularly in amygdala hippocampus and prefrontal cortex, where PET studies also show reduced blood flow. Surprisingly such changes are often more pronounced on the left side. There is also evidence of increased ventricular size, especially in those with true negative symptoms. Glyosis is not apparent, lesions are not ongoing and many could have arisen at birth.

THERAPY — OUTLINE

In 1952 reserpine, an alkaloid extract from the Indian snakewort plant, *Rauwolfia serpentina*, which had been used in that country to treat 'madness', was first tried in schizophrenia. The beneficial impact on patients and the hospital wards was dramatic, as was that a year later of chlorpromazine, a phenothiazine derivative and haloperidol, a butyrophenone. These latter two drugs and closely related derivatives remained the mainstay of therapy for almost 40 years.

Chlorpromazine had been shown to produce a tranquil state in animals and since it had a similar effect in humans it became known as a major tranquiliser but the term is rarely used today. Sometimes the drugs used to treat schizophrenia are called antipsychotics but more commonly neuroleptics. Leptic means to activate (take hold of) and in animals these compounds produce a state of maintained motor tone known as catalepsy. This is an extrapyramidal effect and in schizophrenics the neuroleptics can cause a number of extrapyramidal side-effects (EPSs) including Parkinsonism. The new term 'neuroleptic' is unsatisfactory as a description of clinically useful drugs. It really describes a condition (catalepsy) seen in animals and is more indicative of a compound's ability to produce EPSs than to treat schizophrenia. 'Antipsychotic' is more descriptive but could imply a more general efficacy in psychoses than is the case. It would seem more appropriate to call a drug that is used to treat schizophrenia an 'antischizophrenic' just as we use the terms 'antidepressant' or 'antiepileptic' irrespective of how the drug works. Despite such personal reservations, the term 'neuroleptic' will be used in this text.

The ability of neuroleptics to produce EPSs immediately suggests that they reduce or antagonise dopamine (DA) function and this is supported by a number of other observations (Table 17.1).

Table 17.1

CNS effect	Known change in DA function	Neuroleptic effect	Presumed change in DA function
Parkinsonism	Reduced	Induction of Parkinsonism	Reduced
Elevated plasma prolactin	Reduced	Elevated proloctin	Reduced
Vomiting	Increased	Anti-emetic	Reduced
Hallucinations	Increased	Decrease hallucinations in schizophrenics	Reduced?

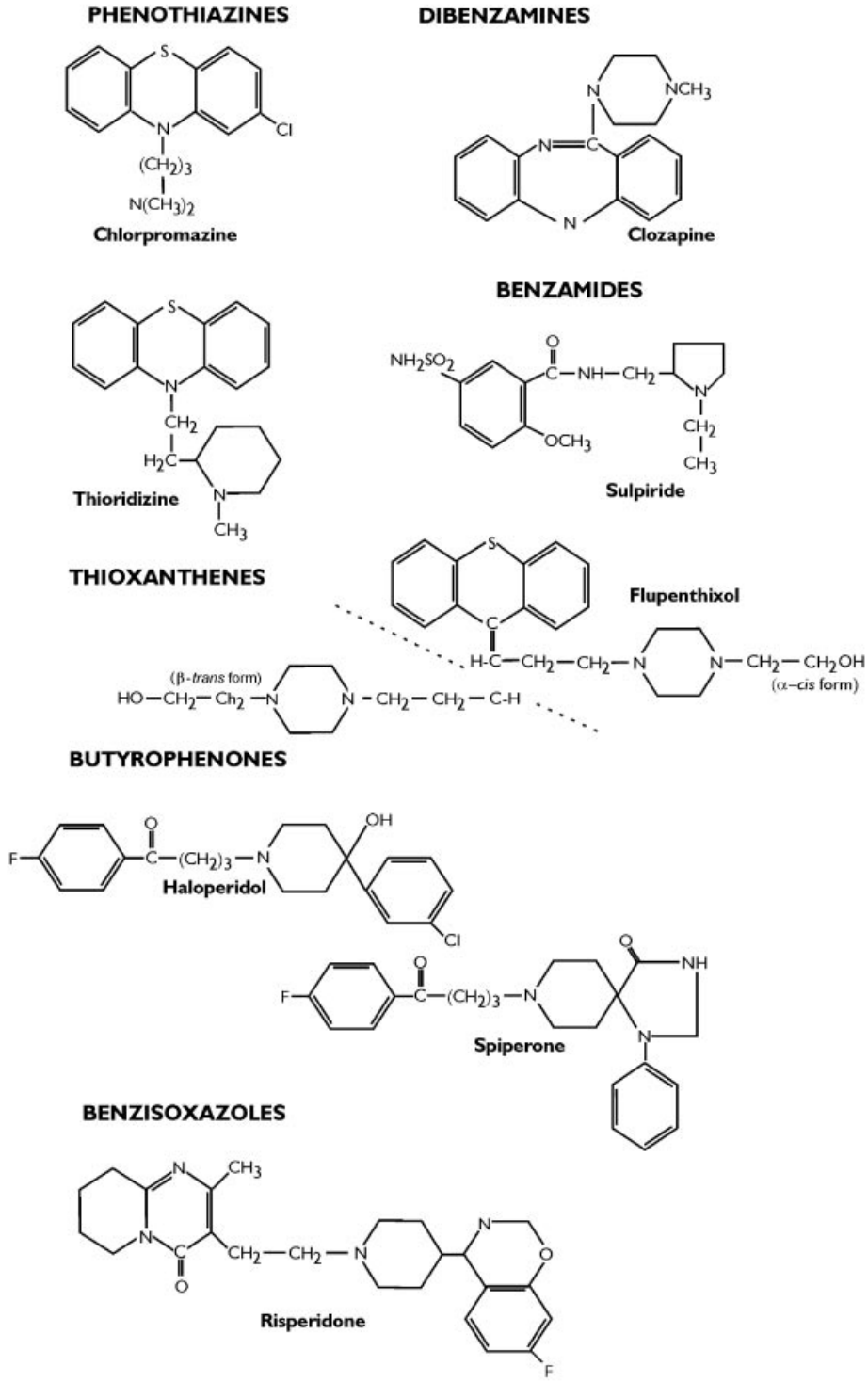

Figure 17.1 The structures of some neuroleptic drugs

In addition, amphetamine causes hallucinations in humans similar to those in schizophrenia and in rats it induces stereotyped behaviour (rearing, grooming and sniffing). This is dependent on the release of DA and blocked by the neuroleptics, which are DA antagonists.

There is now a whole range of neuroleptics (Fig. 17.1) but their ability to block the D_1-receptor-mediated stimulation of adenylate cyclase does not correlate with clinical potency. By contrast, their potency in displacing DA or more commonly an appropriately (^{3}H) labelled ligand, such as haloperidol, from D_2 binding sites on striatal membranes shows a surprisingly good correlation with clinical efficacy (Fig. 17.2). Most effective neuroleptics are indeed dopamine D_2-receptor antagonists. The importance of DA antagonism generally is underlined by the finding that while the thioxanthene flupenthixol exists in two forms α (*cis*) and β (*trans*) only the former is effective in schizophrenia and it is a hundred times more potent as a DA antagonist than the β form.

This raises two obvious questions:

(1) If effective neuroleptics are DA antagonists, is there any evidence for increased DA function in schizophrenia?
(2) How can blocking DA-mediated activity overcome the symptoms of schizophrenia and which DA pathways are involved?

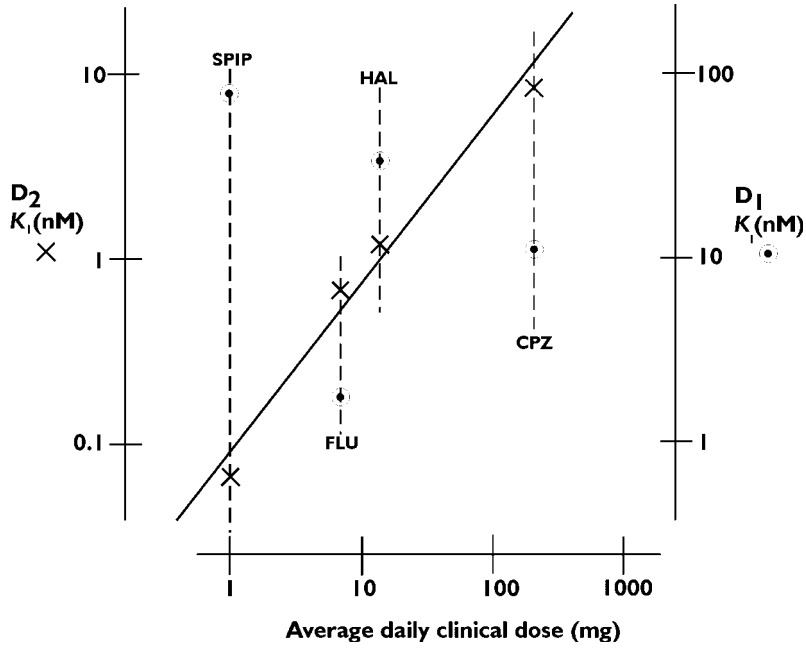

Figure 17.2 Comparison between the clinical dose of some neuroleptic drugs in the therapy of schizophrenia and their affinity for D_1 receptors, measured indirectly by inhibition (ki) of dopamine stimulated adenylate cyclase ((•) right-hand ordinate) or D_2 receptors indicated as displacement of haloperidol binding ((×) left-hand ordinate). Data are given for only four selected compounds but many more neuroleptics fall on the regression line between clinical dosing and D_2 antagonism (see Seeman 1980, 1992). The clinical doses used are based on those generally prescribed while K_1 (nM) values are averaged from a number of published figures. SPIP — spiperone, FLU — fluphenazine, HAL — haloperidol, CPZ — chlorpromazine

IS DA FUNCTION INCREASED IN SCHIZOPHRENICS?

There is no evidence of a general overactivity in DA function in schizophrenic patients. Plasma prolactin is not reduced, so the DA inhibitory control of its release is normal; there is no recorded increase in DA turnover as CSF and plasma levels of its major metabolite HVA are normal; and dyskinesias, which would reflect increased DA activity, are rare. PM studies have shown no consistent increases in DA brain levels, although some reports show an increase in the left amygdala, or in the activity of enzymes involved in its synthesis (tyrosine hydroxylase) or metabolism (MAO). For a review of the neurochemistry see Reynolds (1995).

Many post-mortem measurements have been made of the number of D_2 receptors in the striatum of schizophrenics, even though the striatum is unlikely to be the seat of schizophrenic symptoms. These invariably showed an increase above normal but this was not always significant if studied in patients who had not been on neuroleptic therapy. Neuroleptics alone would, by virtue of being DA antagonists, produce the equivalent of denervation supersensitivity and automatically increase DA receptor number. PET studies on newly diagnosed untreated patients were disappointingly inconclusive, possibly due to the lack of specificity of the ligands used. Generally it is felt that there might be a slight increase in striatal D_2 receptors in schizophrenia which is independent of neuroleptic treatment. If this was so and DA release remained normal, then increased DA function would follow. It should be borne in mind, however, that an increase in receptor number is normally the response to a defect in NT release (transmission).

Possibly increased DA function is not the actual cause of schizophrenia and its symptoms are just mediated by normally functioning DA systems that appear overactive because of the loss of some counteracting function or other NT(s). To date there is no evidence to fully implicate any other NT but there is growing interest in 5-HT and glutamate (see below).

BLOCKADE OF DA PATHWAYS IN SCHIZOPHRENIA

There are three main ascending DA pathways in the brain (Fig. 7.2).

(1) The nigrostriatal from substantia nigra (SN), the A9 nucleus
(2) The mesolimbic from the ventral tegmentum (VTA, A10) to the nucleus accumbens, olfactory tubercule, amygdala and pyriform cortex
(3) The mesocortical also from the VTA (A10) but to the prefrontal cortex (PFC)

Sometimes (2) and (3) are grouped together and called the mesocorticolimbic pathway. It is not clear which pathway is responsible for which schizophrenic symptom.

The VTA (A10) neurons innervating the cortex certainly show features that distinguish them from those in A9. They have a faster basal discharge rate (10 Hz, cf. 3 Hz in A9), a higher turnover of DA, fewer autoreceptors and are less easily inhibited by DA agonists (Bannon and Roth 1983; Farde *et al*. 1989).

There is no doubt that the nigrostriatal pathway is concerned with motor function and blocking DA transmission in it with most neuroleptics would certainly produce signs of Parkinsonism (see Chapter 15). The nucleus accumbens (and some other subcortical regions) are generally assumed to be concerned with psychotic effects although its core is also regarded as part of the basal ganglia. In rats it is involved in motor

function since the locomotor activity caused by low doses of amphetamine is abolished by 6-OHDA lesions of the nucleus, and DA antagonist injections into it. By contrast stereotypy induced by high doses of amphetamine is dependent on the striatum.

The prefrontal cortex (PFC) and in particular the dorsal lateral part (DLPFC) appear to be particularly important in schizophrenia (Kerwin 1992). Lesions there are known to produce functional defects in humans reminiscent of many of the negative symptoms of schizophrenia, such as attention and cognitive defects and withdrawal. Despite this, no specific pathology is seen in the DLPFC in schizophrenics although there is some atrophy and neuronal loss which are normally old and could be congenital. That being so, it is necessary to explain why the symptoms become apparent only in adolescence.

Weinberger (1987) points out that myelination is not complete in DLPFC until around the age of 20 and that lesions of that area in young monkeys do not seem to affect their behaviour immediately but do impede their ability to perform delayed response tasks in later life. Early adulthood is also apparently a time of maximal DA activity in the brain as evidenced by its concentration, turnover and receptor number. Thus it is possible (Weinberger 1987) that the full effect of DLPFC lesions will only manifest itself as behavioural defects when the DA system is fully functional. Lesions within the DLPFC would obviously make it difficult for DA to function properly in that region and this could initiate negative symptoms. How this would account for the positive mesolimbic symptoms is less clear but no area of the brain works in isolation and the prefrontal cortex (PFC) has intricate relationships with the basal ganglia projecting to, and receiving inputs from, them. In fact, 6-OHDA-induced lesions in the PFC in rats, which destroy DA cortical afferents (Pycock, Kerwin and Carter 1980), somehow result in increased subcortical DA function, as evidenced by increased HVA levels, receptor number and motor response to apomorphine and amphetamine. Whether this results from reduced DA inhibition in PFC is uncertain but stimulation of, or local injections of glutamate into, the ventromedial prefrontal and ventral anterior cingulate cortices have been found to increase A10 neuron firing and DA release in the nucleus accumbens.

Although there is no evidence that the DA afferents to DLPFC are damaged in schizophrenics, if the cortical pathology does reduce the ability of DA to function there, this would be equivalent to deafferentation and, as in the experimental studies, lead to increased subcortical mesolimbic activity and positive symptoms (Fig. 17.3). Unfortunately there is no good evidence that the nucleus accumbens is more active in schizophrenics or is even the origin of positive symptoms (but see 'Animal models'). Nevertheless it is a useful working hypothesis.

A DA antagonist could certainly counter the increased mesolimbic activity and the positive symptoms. On the other hand, they would not be expected to reduce negative symptoms if these arise through an already inadequate DA influence. This fits with clinical experience because most of the neuroleptics are ineffective in treating negative symptoms. In fact if the negative symptoms do result from loss of the actual cortical neurons, rather than input to them, they will be difficult to reverse and much will depend on the precise role of DA in the DLPFC (see later).

ANIMAL MODELS

There are few experimental models. Even if appropriate lesions could be produced it will always be difficult to tell if an animal is experiencing hallucinations. Neuroleptics

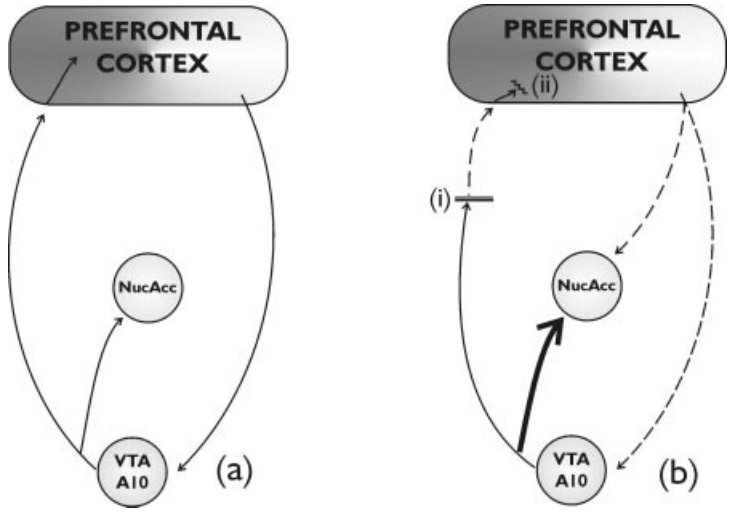

Figure 17.3 Effect of lesions in the prefrontal cortex on the activity of the dopamine mesolimbic pathway. DA neurons from the ventral tegmentum (A10 nucleus) not only innervate the prefrontal cortex (PFC) and limbic areas and in particular the nucleus accumbens (NucAcc) but are influenced by descending projections to them from the prefrontal cortex. Under normal circumstances the system appears to be balanced (a). Experimental lesions of the DA pathway to prefrontal cortex in rats (i) disturbs the balance and appears to increase the activity of VTA neurons and DA input to the limbic system (Pycock, Kerwin and Carter 1980), possibly through a change in cortico-limbic or cortico-VTA activity (b). While there is no evidence for such a lesion in the schizophrenic brain the general pathology found in the PFC could reduce the influence of DA there (ii) and so be equivalent to deafferentation. This could then result in a change in cortical influence on the limbic system and VTA resulting in increased activity in the DA mesolimbic pathway. Such increased mesolimbic activity is thought to mediate the positive symptoms of schizophrenia (see Weinberger 1987)

block DA-induced stereotypy or locomotor activity but this merely reflects their DA antagonism and restricts the discovery of new neuroleptics to those which antagonise DA. They are little better than *in vitro* binding studies.

More recently animal models based on the startle response have been developed which do in fact reflect some of the behavioural changes seen in schizophrenia (Geyer *et al*. 1990). It is believed that schizophrenics cannot adequately process (filter) incoming sensory information, become inundated with it and show cognitive impairment. The startle reflex is a motor response to sensory input (sensorimotor reflex) which is common to both animals and humans. The whole body reaction of rats to a sound or tactile (air-puff) stimulus can be monitored in a special chamber (stabilimeter) while in humans eyelid movements or electromyograms from the facial muscles can be monitored. In both species, if a smaller subthreshold stimulus (the pre-pulse) is presented some time (100–1000 ms) before the actual startle inducing stimulus (pulse) is given, then the response to the standard pulse is inhibited. Such pre-pulse inhibition (PPI) is attenuated in schizophrenics and in rats in which DA activity has been supplemented by giving apomorphine or amphetamine; although in neither case is the response to the actual pulse altered. This DA-increased inhibition of PPI in rats is counteracted by neuroleptics as is the attenuation of PPI in schizophrenics.

Based just on these results, PPI could simply be just another index of DA function but phencyclidine, an NMDA rather than DA receptor antagonist, which exacerbates

schizophrenic symptoms and induces such symptoms when abused, also inhibits PPI (Bashki, Swerdlow and Geyer 1994). In contrast with DA augmentation, which initiates only positive symptoms in humans, phencyclidine also produces negative symptoms and its inhibition of PPI in rats is not affected by DA antagonists. Thus PPI may be one model that is not solely dependent on DA, although phencyclidine does enhance DA release in the mesolimbic system.

The injection of 6-OHDA into the rat nucleus accumbens produces the expected proliferation of DA receptors and resulting supersensitivity so that doses of apomorphine lower than normal produce a significant attenuation of PPI. This is not seen after the production of supersensitivity by toxin lesions of the substantia nigra and prefrontal cortex. The effects of amphetamine were also mainly modified by accumbens lesions. Thus as DA agonists primarily augment the positive symptoms such findings link these with the accumbens.

OTHER NEUROTRANSMITTERS IN SCHIZOPHRENIA

Neurotransmitters other than dopamine have been implicated in the aetiology of schizophrenia. But, as with DA, most of the evidence for their possible involvement has come from finding that their activity is modified by neuroleptic drugs (see later section on atypical neuroloptics), rather than from any evidence of their malfunction in schizophrenic patients. Nevertheless 5-HT and glutamate justify some consideration although interest again stems from drug observations, namely that LSD which is a 5-HT_{2A} receptor agonist and phencyclidine a glutamate NMDA antagonist can both cause hallucinations and schizophrenic-like symptoms.

Consistent changes in 5-HT levels or receptor number have not been reported in schizophrenic brain but a possible genetic link between 5-HT and schizophrenia comes from the finding of allelic variations in genes encoding 5-HT receptors and in particular polymorphism of the 5-HT_{2A} receptor gene in schizophrenics. There is also an indicator from animal studies which shows that habituation to the startle response is slowed by the hallucinogenic drug LSD and that this slowing is blocked by 5-HT_2 antagonists. Interestingly, schizophrenic patients, apart from showing attenuation of pre-pulse inhibition, also show a much slower habituation in response to a repeated startle stimulus which might reflect an inability to show selective attention through not being able to dismiss a repeated stimulus. DA does not appear to modify such habituation.

While there are some reports of increased NMDA and non-NMDA receptor number in various cortical regions of schizophrenics including the prefrontal cortex, there are also indications of impaired glutamate innervation, such as reduction in its neuronal uptake sites (Ishimaru, Kurumaji and Toru 1994). Also it has been found that levels of the mRNA for the NRI subunit of the NMDA receptor in the hippocampus and its D-aspartate binding sites in the temporal cortex are both reduced more on the left than right side in schizophrenic brain. This is another indication of greater malfunction on the left side of the brain and the possibility that some schizophrenic symptoms arise from an imbalance between cross-cortical activity.

NEUROLEPTICS (ANTISCHIZOPHRENIC DRUGS)

There is no shortage of these. The established ones belong to four main chemical groups (Fig. 17.1), the phenothiazines, thioxanthenes, butyrophenones and dibenzazepines.

They are all DA antagonists acting predominantly at D_2 receptors. As a result, they reduce the positive symptoms of schizophrenia but as their potency in this respect increases in line with their affinity for D_2 receptors, so does their tendency to produce extrapyramidal side-effects. They block DA inhibition of prolactin release and the resulting raised plasma levels can lead to amenorrhoea (reduced gonadal function) and galactorrhoea (lactation) in both sexes. They have little beneficial effect on negative symptoms. Neuroleptics showing this pattern of activity are called *typical neuroleptics*. Outside of schizophrenia many of them are used as anti-emetics (not motion sickness) counteracting the effects of DA on the chemoreceptor trigger zone of the vomiting centre. Some compounds, e.g. thioridizine and clozapine produce few extrapyramidal side-effects and are therefore known as *atypical* neuroleptics*. Even when effective the anti-schizophrenic action of all neuroleptics takes 2–3 weeks to develop and only clozapine has any appreciable effect on the negative symptoms.

Before trying to determine how the neuroleptics may reduce some of the symptoms of schizophrenia through modifying NT function it is necessary to consider:

(1) What are the effects of DA antagonism on the function of DA neurons themselves?
(2) Why do neuroleptics take 2–3 weeks to work?
(3) What forms of extrapyramidal side-effects occur and how they might arise?

NEUOLEPTICS AND THE FUNCTION OF DA NEURONS

The consequences of DA antagonism on DA neuron activity are shown diagrammatically in Fig. 17.4. Acutely neuroleptics increase the firing of DA neurons and the release of DA. This is because DA antagonists:

(1) Block the inhibitory feedback effect of released DA on terminal autoreceptors.
(2) Block the action of DA on similar inhibitory receptors on the DA neuron cell body itself.
(3) Block postsynaptic DA receptors on neurons inhibited by released DA which can initiate positive feedback to the DA neurons.

The receptor mediating all three effects appears to be the D_2 (or D_3) receptor.

Thus initially neuroleptics may increase DA turnover and possibly even its action depending on the degree of postsynaptic block. This may also change as the block induces compensating increases in receptor number. Clearly it is a rather fluid and somewhat uncertain situation.

LATENCY OF NEUROLEPTIC EFFECT

There is no reason why DA receptor block should not occur as soon as the antagonist reaches the brain. Antagonism of DA agonist-induced behavioural or electrophysiological

*Reference has been made already to the shortcomings of the term 'neuroleptic'. We now have a situation in which the drugs that are most useful in schizophrenia are regarded as atypical. While the term was introduced to cover those neuroleptics that do not cause EPSs, it has become synonymous with clozapine which has additional advantages over other neuroleptics (e.g. reduces negative symptoms, see text). Thus it is not always clear what is meant or covered by atypical. Hopefully this distinction between the neuroleptics will become unnecessary as better compounds are developed and the older ones become obsolete.

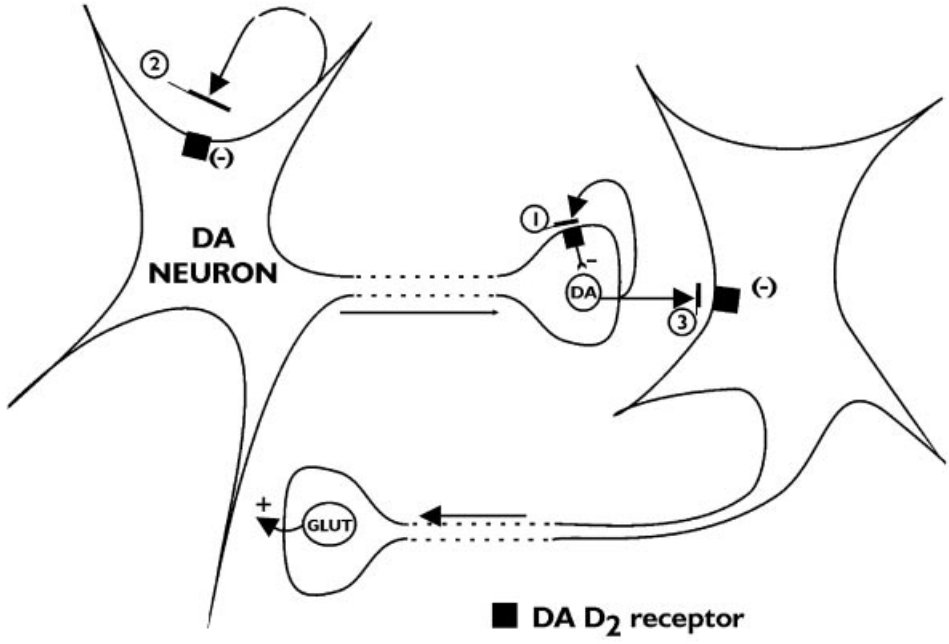

Figure 17.4 The effect of neuroleptics on the activity of DA neurons. Although neuroleptics (DA antagonists) are used primarily to inhibit the postsynaptic effects of released DA they also increase the activity of the DA neuron itself since they (1) inhibit the effect of synaptic DA on nerve terminal autoreceptors and so increase DA release; (2) block inhibitory DA autoreceptors on the soma of the DA neuron so that they cannot be stimulated by endogenous DA, possibly released from the neuron's own dendrites; and (3) facilitate feedback excitation to the DA neuron from those neurons normally inhibited by distally released DA. All the DA receptors involved are D_2 (or possibly D_3). — Blocked by D_2 antagonists (neuroleptics)

effects is immediate and the elevated plasma prolactin level plateaus in humans within a few days. So why is the antipsychotic effect so slow?

One possibility is that even with a potentially effective drug, the necessary readjustments in the neuronal circuitry to reverse or compensate for the disorder-induced malfunction just requires time. Another hinges on the degree of polarisation of A10 and A9 neurons.

These neurons are usually not very active but DA antagonists increase their excitability through the mechanisms outlined above so that their firing rates rise, the pattern of discharge changes from single- to multiple-spike burst discharges and the proportion of neurons firing increases. These changes are also aided by the fact that the excitatory inputs to A9 and A10 neurons normally promote a dendritic release of DA which through inhibitory soma D_2 autoreceptors will automatically counteract the excitation (Fig. 17.5). Clearly when these autoreceptors are blocked by acute neuroleptic administration in rats they cannot be activated by released DA, and the neurons fire much more frequently.

It was found, however, that if neuroleptic administration was continued for two weeks then neuronal firing stopped. Also while the neurons could not be made to fire by the excitatory NT glutamate, the inhibitory NT GABA activated them by reducing the

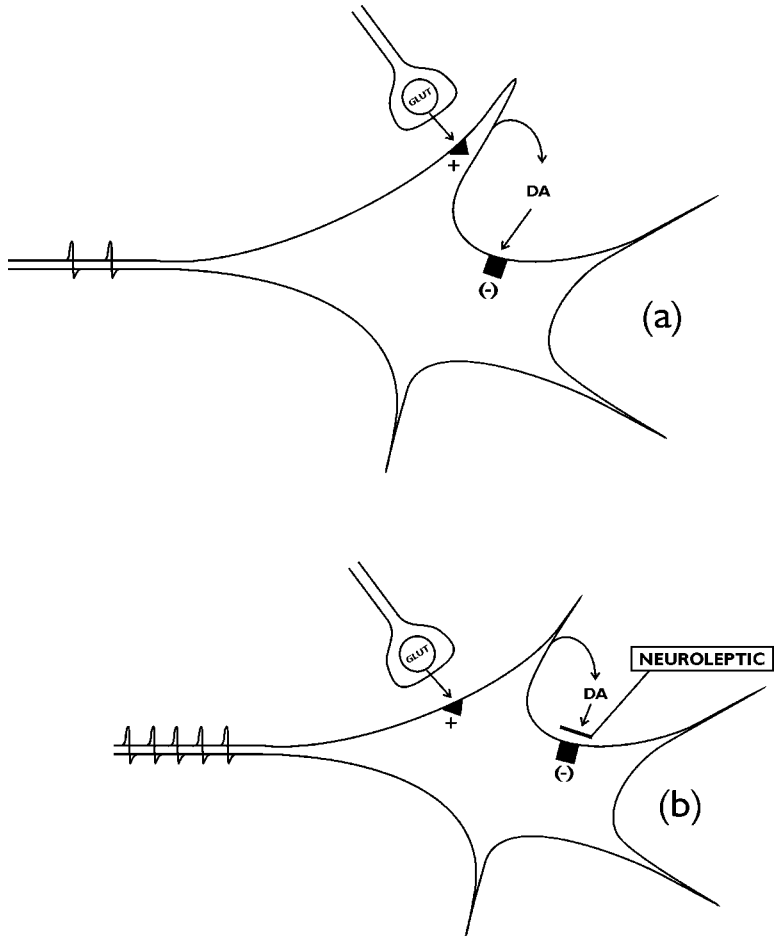

Figure 17.5 Possible scheme for the initiation of depolarisation block of DA neurons. In (a) the excitatory effect of glutamate released on to the DA neuron from the afferent input is counteracted by the inhibitory effect of DA, presumed to be released from dendrites, acting on D_2 autoreceptors. In the absence of such inhibition due to the presence of a typical neuroleptic (b) the neuron will fire more frequently and eventually become depolarised. Atypical neuroleptics, like clozapine, will be less likely to produce the depolarisation of A9 neurons because they are generally weaker D_2 antagonists and so will reduce the DA inhibition much less allowing it to counteract the excitatory input. Additionally some of them have antimuscarinic activity and will block the excitatory effect of ACh released from intrinsic neurons (see Fig. 17.7)

depolarisation (Grace *et al.* 1997). Thus it appears that due to their continuous intense activity the neurons eventually become permanently depolarised (confirmed by intracellular recording) and inactive (Fig. 17.6). This would obviously reduce output from the DA nuclei A9, A10 and have just the same effect as antagonising the postsynaptic action of DA released from their axons' terminals in the striatum, nucleus accumbens and cortex, etc.

Two features require some comment. The induction of depolarisation block in DA neurons needs afferent input to the nuclei, since prior lesion of the striatum and nucleus

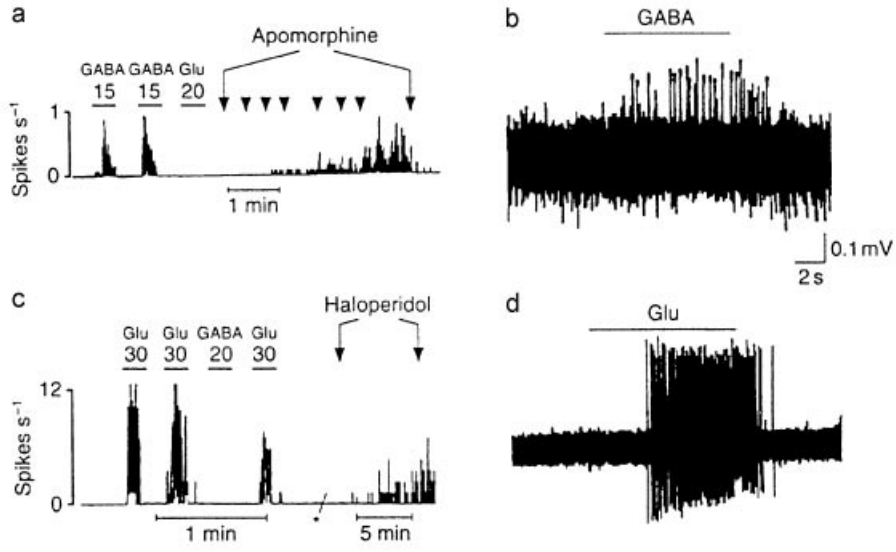

Figure 17.6 Response of DA neurons in the substantia nigra of normal rats and those having received chronic neuroleptic (haloperidol) treatment. (a) The firing rate histogram (spikes s^{-1} monitored at 10 s intervals) recorded extracellularly from a presumed DA neuron after three weeks dosing with haloperidol ($0.5\,mg\,kg^{-1}\,day^{-1}$). Iontophoretic application of GABA the inhibitory NT, at the currents indicated (nA) actually induced firing which is shown as an oscilloscope sweep in (b). The excitatory NT glutamate failed to stimulate the neuron but apomorphine, which normally has an inhibitory effect through D_2 receptors, increased firing when given intraventricularly in increasing amounts from 2–5 to $160\,\mu g\,kg^{-1}$. These effects are consistent with the neurons being overstimulated and depolarised as a result of chronic neuroleptic dosing and so requiring to be hyperpolarised (inhibited) in order to become active. In a neuron from an untreated rat (c), GABA produces the expected inhibition and glutamate the rapid excitation, shown as an oscilloscope sweep in (d). The DA antagonist haloperidol ($0.1\,mg\,kg^{-1}$) systemically also induced firing by blocking DA inhibition. (Reproduced from Grace *et al.* 1997 with permission from Elsevier Science)

accumbens prevent its development in A9 and A10 respectively and an established block can be reversed by such lesions. This again emphasises the importance of feedback loops in DA neuron function and schizophrenia as discussed above.

Second, although typical neuroleptics produce depolarisation block of both A9 and A10 neurons, the atypical neuroleptics only induce it in A10 neurons (Chiodi and Bunney 1983). So after an atypical neuroleptic the A9 neurons of the nigrostriatal tract remain functional, which would explain why EPSs are not seen. Another difference is seen with the expression of an immediate-early gene, *c-fos*, and although its functional significance is not clear, typical neuroleptics induce its protein production in both the striatum and nucleus accumbens while the atypicals only achieve it in the accumbens.

The slow time-course of depolarisation block not only offers an explanation for the latency of action of neuroleptic drugs but its occurrence may explain how they actually reduce DA function. Whether it explains their antischizophrenic effect is less certain since it is not possible to determine if such depolarisation occurs in patients on neuroleptic drugs. Certainly if this is how neuroleptics work it cannot be claimed that they have returned brain function to normal.

THE EXTRAPYRAMIDAL SIDE-EFFECTS (EPSs) OF NEUROLEPTIC DRUGS

These take three basic forms

(1) Acute dyskinesias
(2) Parkinsonian-like symptoms, e.g. akinesia
(3) Tardive dyskinesias

Dyskinesias are thought to be due to increased DA function, which would not be an obvious effect of a DA antagonist but the early acute ones could reflect the increase in DA neuron firing and release produced by such drugs, in the manner described above, overcoming the postsynaptic DA receptor block achieved in the striatum.

It is not surprising that a DA antagonist (especially those acting primarily on D_2 receptors) should produce the symptoms of Parkinsonism, a disorder caused by inadequate DA function (see Chapter 15), nor that its intensity or rate of onset over some weeks or months should increase with D_2 antagonistic potency. Tolerance to this adverse effect can develop without affecting antipsychotic activity but the speed with which Parkinsonism resolves after stopping therapy may be from 3 to 12 months and can persist indefinitely in some cases.

The late (tardive) dyskinesias, which mainly involve facial muscles, can take months or years to develop. They occur in 20–40% of patients, may not cease after stopping the drug and in fact can get worse, or even start then. Since they can be reduced temporarily by increasing neuroleptic dose it would appear that they do really result from DA overactivity and that the antagonism is not adequate. Certainly many experimental studies show that long-term neuroleptic dosing causes a compensatory increase in DA receptor number which would predispose to dyskinesias. Against this view are the findings that the increase in receptor number may precede dyskinesias by many weeks, receptor number but not dyskinesias routinely decline after drug withdrawal and while all patients should develop increased receptor number only some show dyskinesias. The dyskinesias are also more common in schizophrenics with clear negative symptoms and most brain damage and, since they have been seen in some untreated schizophrenics, could be a latent feature brought out by neuroleptics. Of course if the A9 neurons have been depolarised by the neuroleptics (see above) it is difficult to see how they can become so active unless the depolarisation also wears off.

ATYPICAL NEUROLEPTICS

Typical neuroleptics reduce the positive symptoms of schizophrenia at the expense of producing EPSs but the so-called atypical neuroleptics have less tendency to cause EPSs. With most of them, e.g. thioridizine, that is the extent of their atypicality but a few others, such as clozapine (and to a lesser extent risperidone and olanzapine) also reduce negative symptoms. Clozapine can even be effective in patients refractory to other neuroleptics. It is clearly a special drug, so special in fact that although it was once withdrawn because it causes agranulocytosis in some patients (2%), it has been reintroduced, alongside careful blood monitoring, for refractory cases. It will be given special consideration below.

MODE OF ACTION

There is certainly evidence that whereas typical neuroleptics are equally active in mesolimbic/cortical areas as well as the striatum, the atypical drugs are much less effective in the latter. This has been shown by (1) increased DA turnover through DOPAC and HVA production *in vitro*, (2) augmented DA and DOPAC release by microdialysis *in vivo* and (3) increased *c-fos*-like expression.

How the atypical neuroleptics achieve this differential effect is less clear but they could achieve some control of schizophrenia without producing EPSs by:

(1) Acting primarily on a particular subset of DA receptors
(2) Antagonising (or augmenting) some other NT(s) instead of, or in addition to, DA
(3) Having a particular but appropriate profile of DA and other NT (antagonistic) effects

These possibilities will be considered in turn.

Significance of different DA receptors

So far we have generally just alluded to the neuroleptics as DA receptor antagonists. The reader will know that there are five such receptors (Chapter 7). Clearly, if the DA released at the terminals of one dopaminergic tract acted on a subset of DA receptors that were different from those found postsynaptically at other tracts then some specificity of antagonist action might be achieved. Unfortunately there is no evidence that different pathways innervate different DA receptor populations and as with the use of agonists in PD, the D_2 receptor is dominant. Specific D_1 antagonists have no antischizophrenic effect and antischizophrenic efficacy increases with neuroleptic affinity (potency) at D_2 receptors — as unfortunately does the tendency to produce EPSs. Thus there is no great advantage in producing more potent D_2 antagonists, other than that less drug needs to be incorporated into long-term release depot preparations.

PET studies show that at effective therapeutic plasma concentrations most neuroleptics occupy some 80% of brain D_2 receptors (in the striatum at least) and this is therefore considered to be a requirement for efficacy (Pilowsky, Costa and Eli 1992; Farde 1996). If that is so then clozapine, which occupies only 20–40% of the D_2 receptors at a therapeutic concentration, must have some other action which accounts for its therapeutic effectiveness.

Its activity at D_1 receptors has been put forward as a possibility and although it has a relatively higher affinity for D_1 than D_2 receptors, compared with typical neuroleptics, it is still a weak antagonist at both and in the absence of evidence for D_1 (or D_5) receptor involvement in schizophrenia the significance of any D_1 antagonism is unclear.

K_1 (nM) values for clozapine at D_2 and D_1 receptors are 56 and 141 compared with 0.5 and 27 for haloperidol giving D_1/D_2 ratios of 2.5 and 54 for the two drugs. A relatively strong block of D_1 compared with D_2 receptors may not be the answer for schizophrenia but it could reduce the tendency to produce dyskinesias, if this depends on D_1 receptor activation (see Fig. 17.2).

Among the D_2 family of receptors (D_2, D_3 and D_4) the D_2 receptor itself seems to be the most important. At a therapeutic concentration, most neuroleptics, except clozapine (and risperidone), should, according to *in vitro* binding studies, be occupying 50–70% of brain D_2 receptors. The picture is similar for D_3 receptors but only clozapine (and

risperidone and olanzapine) occupy more than 50% of D_4 receptors at a therapeutic dose.

This relative selectivity of clozapine for D_4 receptors with their restricted location, even if it is in small numbers, to the prefrontal cortex has stimulated much interest in their involvement in schizophrenia and the control of negative symptoms. There has been one report (Seeman, Guan and Van Tol 1993), refuted by others, of a sixfold increase in D_4 receptors in schizophrenic brain. Unfortunately the measurements were made in striatum rather than cortex and depended on the difference in the binding of a D_2, D_3, D_4 antagonist nemonopride compared with that of a D_2 and D_3 antagonist raclopride. D_4 occupancy was thus inferred rather than established by a specific D_4 antagonist. When such a selective D_4 antagonist, L-745,870, became available and was tested in 38 schizophrenics it proved ineffective at what were considered to be doses sufficient to occupy 50% of the D_4 receptors (Bristow *et al.* 1997). It has not been used apparently to assess D_4 receptor number in schizophrenic brain.

There are few specific drugs for D_3 receptors but D_3 knock-out mice show no behavioural defects. Thus the significance of any DA receptor other than the D_2 still remains to be established (see Seeman and Van Tol 1994; Sokoloff and Schwartz 1995; Strange 1994).

Involvement of other NTs

Acetylcholine

Neuroleptic-induced Parkinsonism (but not tardive dyskinesias) can be reduced by antimuscarinic drugs. It is generally assumed that neuroleptic antagonism of DA-mediated inhibition in the striatum leaves the excitatory muscarinic action of ACh unchecked (Fig. 15.9) so that blocking it will restore normality. The atypical neuroleptics thioridizine and clozapine both have potent inherent antimuscarinic activity with PA_2 values (7–8) similar to that for atropine and more than a hundredfold that of a typical neuroleptic-like haloperidol. Thus each compound has the ability to nullify its own antidopamine effect in the striatum and stop Parkinsonian symptoms developing (Fig. 17.7) without affecting DA antagonism, and possible antischizophrenic effects elsewhere. There is no evidence that antimuscarinic activity has any effect on schizophrenia and thioridizine has no more effect on negative symptoms than typical neuroleptics. Of course, since clozapine is also a weaker D_2 antagonist than thioridizine this automatically reduces its ability to produce EPSs anyway.

5-HT

Some neuroleptics, including clozapine, are potent 5-HT-receptor antagonists and the possible role of 5-HT in the action of neuroleptics and the development of schizophrenia has recently generated much interest (Busatto and Kerwin 1997). This has centred primarily on 5-HT_{2A} receptors found in the limbic cortex, which are linked to neuronal excitation and believed to mediate the hallucinogenic effects of drugs such as lysergic acid diethylamide (LSD).

Generally most atypical neuroleptics have higher affinity for 5-HT_2 than D_2 receptors while typical ones retain a preference for the D_2 receptor. There is, however, no infallible separation since chlorpromazine (typical neuroleptic) is more active at 5-HT_{2A}

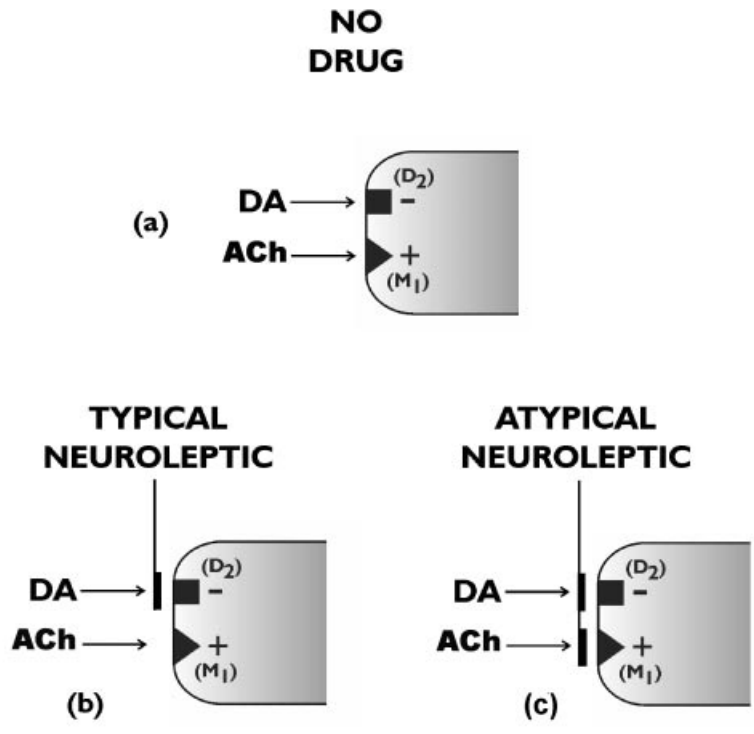

Figure 17.7 Possible mechanism by which atypical neuroleptics with antimuscarinic activity produce few EPSs. Normally the inhibitory effects of DA released from nigrostriatal afferents on to striatal neuron D_2 receptors is believed to balance the excitatory effect of ACh from intrinsic neurons acting on muscarinic (M2) receptors (a). Typical neuroleptics block the inhibitory effect of DA which leaves unopposed the excitatory effect of ACh (b) leading to the augmented activity of the striatal neurons and EPSs (see Fig. 15.2). An atypical neuroleptic with intrinsic antimuscarinic activity reduces this possibility by counteracting the excitatory effects of released ACh as well as the inhibitory effects of DA (c). Thus the control of striatal neurons remains balanced

than D_2 receptors and remoxidpride (atypical) more active at D_2 than 5-HT_{2A}. Also differences in the values for the dissociation constants between experimental studies (see later) make comparisons between D_2 and 5-HT_{2A} potency somewhat difficult.

No neuroleptic has purely 5-HT_{2A} antagonist activity and a pure 5-HT_{2A} antagonist drug may not have neuroleptic activity. Risperidone, an atypical neuroleptic with some benefit against negative symptoms, is the most potent of all neuroleptics at 5-HT_{2A} receptors (K_1: 0.2 nM). Some *in vitro* measurements show it to have up to 25 times more affinity for 5-HT_{2A} than D_2 receptors and PET studies indicate that at therapeutic doses it displaces a 5-HT_2 ligand in preference to a D_2 one. Clozapine is also claimed to occupy over 80% of 5-HT_2 and less than half this number of D_2 receptors at clinical doses. Neuroleptics with 5-HT_2 antagonist activity not only produce fewer EPSs but 5-HT_2 antagonists reduce neuroleptic-induced EPSs.

Fibres from 5-HT neurons in the raphé nucleus innervate and yet, despite the observed 5-HT_{2A} receptor link with neuronal excitation, appear to inhibit DA neurons in the SN (A9). Thus antagonism of 5-HT released onto them would increase their firing and so reduce the likelihood of EPSs, although how 5-HT_{2A} antagonists can

overcome the established motor side-effects of another neuroleptic is less clear if that compound has already caused a depolarising block of the neurons.

The mechanism by which 5-HT_2 antagonism could ameliorate schizophrenic symptoms and what effect 5-HT has on mesolimbic and mesocortical pathways through A10 neurons is even less certain. It is more likely that 5-HT's action occurs postsynaptically in the limbic system or PFC. The probability that neuroleptics benefit from a particular balance of DA and 5-HT_{2A} antagonism is developed later.

The 5-HT_3 receptor is found appropriately in mesocortical areas and while behavioural studies with their antagonists in rodents showed potential antipsychotic activity, they have proved ineffective in patients. 5-HT_{1A} agonists may be more useful. They have been found to increase the extracellular concentration of DA in the frontal cortex of rats but diminish apomorphine-induced stereotypy (striatal effect). So they could be of some benefit, especially against negative symptoms, without causing EPSPs (see Chapter 9).

Noradrenaline

Many of the neuroleptics are α-adrenoceptor antagonists. Some, like chlorpromazine, block α_1 postsynaptic receptors while clozapine (and risperidone) are as potent at α_2 as D_2 receptors. There is no evidence that either of these actions could influence striatal or mesolimbic function but NA is considered important for function of the prefrontal cortex and any increase in its release, achieved by blocking α_2-mediated autoinhibition, might contribute to a reduction in negative symptoms and provide a further plus for clozapine (see Nutt *et al.* 1997). Centrally, however, most α_2-receptors are found post-synaptically and their function, and the effect of blocking them, is uncertain.

Glutamate

Although there is no evidence that any of the neuroleptics have any significant effect on glutamate receptors, it will be of no surprise to learn that clozapine, but not pure D_2 or 5-HT_2 antagonists nor any typical neuroleptic, can overcome phencyclidine disruption of PPI in animals. Interestingly, the efficacy of clozapine (but not risperidone or olanzopine) is increased by the antiepileptic drug lamotrigine that has inhibition of glutamate release as one of its actions (see Chapter 16). Also glycine (and serine) have been shown to improve the negative symptoms by what is assumed (but not proven) to be a potentiation of NMDA receptor activity, but they can make positive symptoms worse.

Profile of NT antagonism in neuroleptic action

In deciphering the role of the different NTs, or more precisely their antagonists, in the antischizophrenic action of neuroleptic drugs it must be remembered that published binding data and calculated dissociation constants vary considerably, which, of course, affects correlation coefficients made with clinical activity. Factors to bear in mind are:

(1) *In vitro* binding studies use different cell lines or membrane preparations and generally only yield the apparent dissociation constants for a number of antagonists obtained by comparative displacement of one labelled ligand. Unfortunately few

such ligands are specific for the receptor being analysed, i.e. they bind to other receptors to differing extents as do the displacing compounds. Reported values for clozapine's binding affinity vary from 84–388 nM depending on the D_2 ligand being displaced. Real dissociation constants can be obtained from direct measurements of the binding of the neuroleptic alone in labelled form but because neuroleptics also bind to more than one receptor, the preparation must express only the receptor being studied.

(2) PET studies have almost always centred on measurements of binding and DA receptor number in the striatum rather than other DA-innervated areas of more significance in schizophrenia. Also in PM measurements of receptor number it is invariably the striatum which is used, because of its high density of DA receptors.

(3) Functional activity (clinical effect, catalepsy in animals, etc.) is invariably correlated with plasma concentrations whereas the brain levels of many neuroleptics, which are very lipophilic compounds, could be much higher. Some clinicians also believe that many newer compounds achieve atypical status compared with older ones because they are used at minimal dosage while older ones are prescribed at established levels which may be unnecessarily high.

Despite these problems it remains necessary to attempt some explanation in terms of differential NT antagonism, of why clozapine is so effective (see Reynolds 1997) in that it causes fewer EPSs, reduces negative symptoms and is effective in some patients refractory to other drugs. Considering these benefits in turn:

(1) *Reduced EPSs*. This may be achieved with clozapine because it is a:

   (a) Relatively weak D_2 antagonist. The one thing that is reasonably certain about the neuroleptics is that irrespective of the role of D_2 antagonism in controlling schizophrenia the more potent the D_2 antagonist, the more likely are EPSs. Just as Parkinsonian symptoms only occur in PD patients when 50–80% of the DA innervation to the striatum is lost (Chapter 15) so neuroleptic-induced Parkinsonism only follows blockage of some 80% of D_2 receptors. Clozapine only achieves about half of this at therapeutic doses and its weak binding may allow DA to override its antagonism at appropriate times in the striatum. Thus clozapine has little potential for inducing EPSs and what it has could be reduced by its other activities.
   (b) Potent antimuscarinic. ACh excitation counteracts DA inhibition in the striatum.
   (c) Strong 5-HT_2 antagonist. Compounds with this property appear to reduce EPSs.
   (d) Relatively strong D_1 antagonist. This may not stop PD symptoms but could reduce dyskinesias (Fig. 15.8).

   As a result of these features clozapine is likely to have little effect on A9 (SN) neurons and does not cause their depolarisation in chronic dosing.

(2) *Negative symptoms*. These may be reduced because either clozapine antagonises appropriate receptors in the prefrontal cortex or it does not act as an antagonist there. This apparently stupid statement is prompted by the lack of knowledge of what is required to reduce negative symptoms. D_4 and D_1 receptors are found in the prefrontal cortex and only clozapine among current neuroleptics is more active at both of these than the D_2 receptor. Thus on this basis it is well placed to block DA's

influence but if negative symptoms follow an impairment of DA input (see above) further blockage is undesirable. In fact clozapine would have to augment DA function and based on the knowledge that D_1 receptor activation appears to be required for optimal cognitive performance it has been suggested that neuroleptics should optimise activation of D_1 receptors in addition to blocking D_2 receptors (Lidow, Williams and Goldman-Rakic 1998). Little is known of the effect of DA or its agonists on cortical neurons, although most studies show it to be inhibitory. Even less is known about clozapine's action on neuronal firing but in one study on the prefrontal cortex of anaesthetised rats it was found to mimic the action of the DA agonist apomorphine, an effect blocked by haloperidol (Dalley and Webster 1993). A number of microdialysis studies have also shown that it is the only neuroleptic to increase DA efflux in the prefrontal cortex although most of them have that effect in the striatum. So perhaps clozapine can in some way increase DA transmission in PFC, even if that is achieved through initially antagonising an effect of DA or another NT. Recently risperidone has also been shown to increase both 5-HT and DA release in the rat prefrontal cortex (Knoble and Weinberger 1997) but possibly through α_2 and 5-HT receptor antagonism. In view of the strong antimuscarinic activity of clozapine it is interesting that cholinergic overactivity has been reported to induce behaviour in animals that was thought to reflect negative symptoms.

(3) *Refractory cases respond to clozapine*. If D_2 antagonism is considered necessary, or at least desirable, for counteracting positive symptoms it is surprising that a relatively weak D_2 antagonist like clozapine should not only be so effective but also prove successful in patients who have not responded to other neuroleptics more potent at D_2 receptors.

Certainly clozapine can avoid EPSs by only blocking a fraction of D_2 receptors but that seems insufficient on its own to make clozapine so effective in schizophrenia. That is probably achieved by a unique combination of other blocking actions, at D_1, D_4, 5-HT_2, α_2 and possibly other receptors (see Fig. 17.8). It may simply be that clozapine is so effective because it is so 'dirty', a view held for many years about the first neuroleptic chlorpromazine. Indeed it is unlikely that the varied symptoms of such a complicated disorder could be rectified by manipulating just one NT.

Unfortunately although much is known about the pathways and receptors involved in extrapyramidal activity and the mechanism of the EPSs that follow neuroleptic therapy and even the possible origin of negative symptoms in the prefrontal cortex, the precise site of origin and NT involvement in the overriding positive symptoms is less clear. Until that is corrected, permutations of NT antagonisms are likely to multiply with the neuroleptics.

PERSPECTIVE

What is obvious from all the experimental evidence is that it is easier to unravel the cause of the undesirable than it is to explain the desirable effects of neuroleptic drugs. EPSs occur because such drugs all have some D_2 antagonist activity and so reduce DA transmission in the striatum. The degree to which they achieve this and whether they are typical or atypical depends on their affinity for D_2 striatal receptors, since EPSs

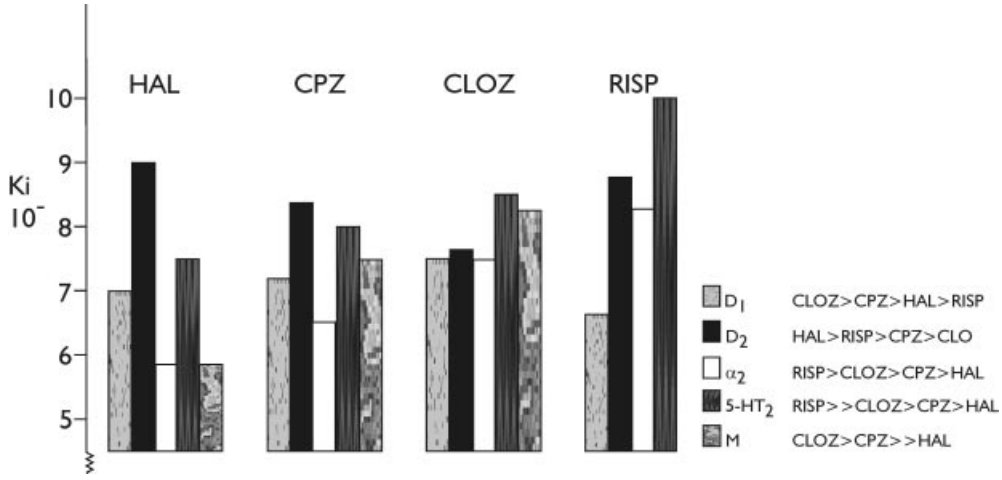

Figure 17.8 Comparison of the antagonist potencies of some neuroleptics on different NT receptors. Data are shown for haloperidol (HAL), chlorpromazine (CPZ), clozapine (CLOZ) and risperidone (RISP) acting on dopamine D_1 and D_2, 5-HT_2 (S_2), alpha (α_2) adrenoceptors and cholinergic muscarinic receptors (M). The height of each column shows an average of the dissociation constants obtained from a number of publications (see Seeman 1990). The values, which can vary some fiftyfold, are expressed as the negative logarithms (i.e. $9 = 10^{-9}$ M,lnM) so that the higher the column, the more potent the compound. The order of potency of the four compounds at each receptor is shown alongside

diminish with low D_2 affinity and their ability to block ACh muscarinic or 5-HT_2 or other receptors. Trying to translate from *in vitro* binding studies to an explanation of antipsychotic effectiveness is also made more difficult by the fact that they do not readily distinguish between agonist and antagonist activity. More functional studies of neuroleptic activity in different brain areas is required.

Measuring the expression of the early-immediate gene *c-fos* supports the striatal role of neuroleptics in the induction of EPSs because although all neuroleptics induce such expression in both the nucleus accumbens and striatum, the atypical neuroleptics do so more in the accumbens while clozapine, but not risperidone, also achieve it in the prefrontal cortex (Robertson, Matsumura and Fibiger 1994). How this arises is uncertain but since risperidone is a more potent 5-HT_2 antagonist than clozapine, it cannot be through that mechanism.

Establishing the possible site of action of a drug *in vivo* first and then trying to unravel what it actually does at the cellular or molecular level is an alternative approach to the analysis of drug action. In this respect much was, and is, hoped of PET (SPECT) studies in humans and non-human primates. Of course, these tell us primarily where drugs are not located and therefore certainly do not act. Locating their labelled form in particular brain regions does, however, indicate where they may act, although a high concentration in one area does not automatically make that the drug's primary site of action. Nevertheless, this approach does help to clarify the origin of EPSs since although both typical and atypical drugs appear to bind to limbic and cortical areas to a similar extent it is only the typical ones that show high striatal levels.

On this evidence one can confidently equate EPS with neuroleptic DA receptor (D_2) antagonism in the striatum and possibly a reduction in the positive symptoms of schizophrenia through similar action in the limbic system (nucleus accumbens).

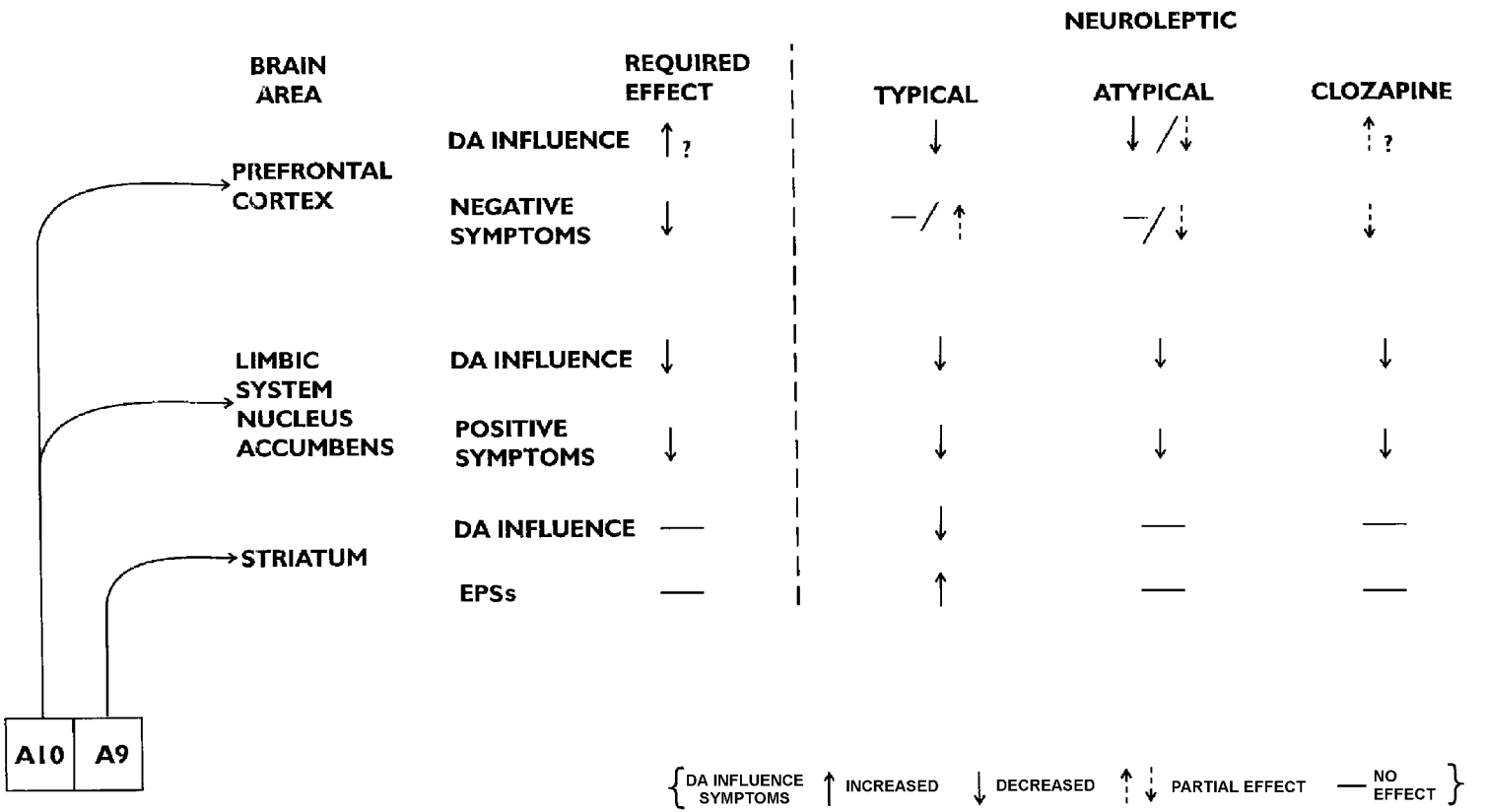

Figure 17.9 Schematic representation of the proposed activity profile of an ideal neuroleptic. The figure shows DA pathways to the prefrontal cortex, mesolimbic nucleus accumbens and striatum; the effects required for an ideal drug on the DA influence and symptoms there and to what extent they are met by most typical and atypical neuroleptics and by clozapine. Note that while all atypical neuroleptics induce few extrapyramidal side-effects (EPSs) few of them, apart from clozapine, have much beneficial effect in overcoming negative symptoms of schizophrenia

Whether the amelioration of negative symptoms results from an action in the cortex and, in particular, the prefrontal cortex requires further study. The fact that clozapine, the atypical drug that is currently most effective in this respect, has actions there which are not shown by other compounds is encouraging even though the precise mechanism by which it works remains to be elucidated.

It appears that an ideal neuroleptic may need to reduce DA activity in the mesolimbic system (nucleus accumbens) to counter the positive symptoms of schizophrenia, increase it in the prefrontal cortex to overcome negative symptoms and have little or possibly no effect on it in the striatum so EPSs do not arise (Fig. 17.9). No wonder we still await the ideal drug.

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