Receptor pharmacology of neuroleptics

Richard M Pearson

The term 'neuroleptic' originated from animal experiments — these drugs caused profound sedation and abnormal posturing as if the animal had been 'seized' (Greek 'lepsis', meaning seizure). All early neuroleptic drugs had antipsychotic actions and vice versa. Now there are drugs which are potent antipsychotics without the classic neuroleptic actions known as atypical neuroleptics.

The clinical aspects of atypical neuroleptics were recently reviewed in this journal (Pandarakalam, 2000). The terms neuroleptic and antipsychotic are now used interchangeably and refer to desirable effects of these drugs in improving bizarre behaviour, delusions and hallucinations. The typical neuroleptic drugs such as chlorpromazine act selectively on dopamine receptors in the brain. However, the more recently introduced drugs also act at 5-HT (5-hydroxytryptamine or serotonin) receptors. Most of the side-effects of neuroleptic drugs arise from their actions on the cholinergic, adrenergic and histaminergic receptors. In order to understand the relevance of receptor pharmacology to the effects and classification of neuroleptic drugs, it is important to appreciate details of the classification of receptors (Cooper et al, 1996; Hoyer and Humphrey, 1997; Alexander and Peters, 2000).

DOPAMINE RECEPTORS

The dopamine theory of schizophrenia postulates that overactivity of dopamine transmission in the central nervous system, especially at D_2 dopamine receptors, occurs in schizophrenia and may account for the positive symptoms. The neuroleptics are all antagonists at dopamine receptors, which suggests that schizophrenia is associated with increased activity in dopaminergic pathways. Neuroleptics also have effects on other receptors including muscarinic cholinergic and α-receptors which cause autonomic and central side-effects and on histaminergic receptors which cause sedation.

The dopaminergic system arises from clusters of cells in the midbrain and hypothalamus. There are two main groups of dopaminergic cells in the midbrain:

1. Those arising in the substantia nigra whose neurons ascend to the striatum (nigrostriatal pathway). These are primarily involved in the modulation of motor activity
2. Those arising from the ventral tegmental area which project to various limbic and cortical areas (mesolimbic pathway) and which are involved in cognition, motivation, emotion and reward-linked behaviour (mesocortical pathway).

In addition, there are discrete groups of dopaminergic cells with their cell bodies in the hypothalamus that project to the pituitary gland and are involved in the neuroendocrine regulation of prolactin secretion.

Originally, it was suggested that the effects of dopamine could be explained by the existence of only two distinct receptor subtypes, D_1 and D_2. However, more recent advances in sequence data from cloning, signal transduction mechanisms and pharmacological specificity have lead to the identification of further subtypes and it is now considered that the dopamine system consists of two receptor families: D_1 and D_2.

D_1 family

This category contains the original D_1-receptor and the recently cloned D_5-receptor. These receptors are coded for by similar genetic sequences and both activate adenyl cyclase and increase the synthesis of cyclic adenosine monophosphate (cAMP) as a second messenger (*Table 1*).

D_2 family

This category is pharmacologically more important in the CNS and includes the original D_2-receptor and the more recently identified D_3- and D_4-receptor subtypes. The neuroleptic

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drugs probably owe their therapeutic effects mainly to blockade of D_2-receptors. The main groups of neuroleptic drugs, phenothiazines, thioxanthines and butyrophenones, show some preference for binding at D_2- rather than at D_1-receptors. The D_2 family is grouped together because they have a high degree of genetic homology and a similar pharmacological profile. The D_2-receptors are mainly expressed in the caudate and putamen while the D_3- and D_4-receptors are mainly distributed in the limbic areas of the brain.

Neuroleptic drugs, with affinities for limbic rather than striatal sites, have different clinical properties (Arnt and Skarsfeldt, 1998). The classification is made more complex by the discovery of high- and low-affinity forms of both the D_1-and D_2-receptors and it has been suggested that the high affinity forms may be more important in signal transduction and implicated in psychotic symptoms. There is polymorphism of the D_4-receptor in humans with a varying number of 16 amino acid repeat sequences.

Dopamine receptors are located both presynaptically and postsynaptically. The D_1-receptors are primarily postsynaptic while the D_2- and D_3-receptors are found both presynaptically and postsynaptically. However, recent studies suggest that virtually all striatal neurones contain dopamine receptors from both D_1- and D_2-receptor families (Aizman et al, 2000).

ACTIONS OF NEUROLEPTICS ON DOPAMINE RECEPTORS

The one feature that all neuroleptic drugs share is their ability to bind selectively at dopamine receptors and antagonize the actions of dopamine. The antipsychotic action seems to be more closely linked to antagonism at D_2- rather than at D_1-receptors. Support for these hypotheses comes from three main lines of evidence:

1. Neuroleptic drugs are prescribed at doses that achieve concentrations that have been shown in vitro to block 70% of the D_2-receptors but to have little effect on D_1-receptors
2. Drugs that act on and block D_2-receptors only are effective antipsychotics, but drugs that act exclusively on D_1-receptors are not effective antipsychotic agents
3. For D_2-receptors, there is a good correlation between the affinity of a drug and the dose at which it is used as an antipsychotic agent (Seeman et al, 1976). No such correlation exists for D_1-receptors. Also, PET (positron emission tomography) imaging studies have shown a positive correlation between the percentage of D_2-receptors blocked and the antipsychotic response in psychiatric patients (Nordstrom et al, 1998).

An ideal neuroleptic drug would block the mesolimbic and mesocortical tracts exclusively. However, the current drugs in use, especially the classical neuroleptics such as fluphenazine and trifluoperazine, also block the nigrostriatal pathway resulting in parkinsonian side-effects. Similarly dopaminergic blockade of the hypothalamic–hypophyseal pathways results in the release of follicle-stimulating hormone (FSH) and prolactin, causing amenorrhoea and galactorrhoea in women and gynaecomastia and occasionally galactorrhoea in men.

Clozapine has a relatively high affinity as an antagonist at the D_4-receptor as compared with affinity for the D_1- and D_2-receptors (Wilson et al, 1998). There is also some evidence that clozapine acts as an agonist at D_1-receptors (Ahlenius, 1999). At doses used in clinical practice, clozapine is an effective antipsychotic drug without causing parkinsonian side-effects and hyperprolactinaemia.

TABLE 1.
Comparison of dopamine receptor subtypes

		Receptor subtype				
		D_1	D_2	D_3	D_4	D_5
D_1 family		+				+
D_2 family			+	+	+	
Distribution	Cortex	++	++			
	Limbic system	+++	+++	+	+	
	Basal ganglia	++	+++	+	+	+
	Hypothalamus	++				+
	Pituitary gland		+++			
Chromosome		5	11	3	11	4
Adenyl cyclase		Stimulates	Inhibits	Inhibits	Inhibits	Stimulates
Antagonist		SCH-23390	Sulpiride	UH 232	Clozapine	SCH-23390

ACTIONS OF NEUROLEPTICS ON 5-HT (SEROTONIN) RECEPTORS

Clozapine has a higher affinity for the 5-HT_{2A}-receptor than for the D_2-receptor (Meltzer, 1999). The possible involvement of 5-HT receptors in schizophrenia derives from the observation that lysergic acid diethylamide (LSD) produces schizophrenia-like symptoms and has a high affinity for 5-HT_2-receptors. Currently there are seven main receptor types (5-$HT_{1–7}$) recognized on the basis of sequence data from cloning, signal transduction mechanisms and pharmacological specificity. Type 5-HT_1 and 5-HT_2 receptors are each further divided into 3 or 4 subtypes denoted A-D.

Some of the newer atypical neuroleptic drugs (e.g. clozapine, risperidone, olanzapine) are more potent antagonists at 5-HT receptors than at dopamine receptors.

Combining 5-HT_2 and D_2-receptor blockade improves the antipsychotic effect and reduces the Parkinsonian side-effects of neuroleptic drugs (Remington and Kapur, 1999). The 5-HT system inhibits the dopamine system in the nigrostriatal pathway. When patients take neuroleptic drugs, their nigrostriatal pathway is inhibited from two sources, namely inhibition from endogenous 5-HT and inhibition from the administered D_2-receptor-blocking neuroleptic drug. The use of an atypical neuroleptic with the addition of 5-HT_2-receptor-blocking properties releases the nigrostriatal pathway from the endogenous 5-HT inhibition and this results in relief of parkinsonian symptoms. These drugs such as risperidone are a very important advance since they are effective in controlling the negative as well as the positive symptoms of schizophrenia, are effective in the 'treatment-resistant' group of patients and are less likely to cause extrapyramidal effects than the older neuroleptics.

ACETYLCHOLINE RECEPTORS

There is some evidence that cholinergic modulation affects both positive and negative symptoms and polysomnographic studies suggest increased muscarinic cholinergic activity in schizophrenia (Tandon, 1999). Some neuroleptic drugs such as chlorpromazine, thioridazine and clozapine, and, to a lesser extent, perphenazine and loxapine block peripheral muscarinic-type cholinergic receptors. The adverse effects caused by this property include dry mouth, constipation, hesitancy of micturition and blurred vision. Blockade of central muscarinic receptors may account for memory deficits.

In the brain, there is normally a balance between the cholinergic and dopaminergic inputs into the neurones of the striatum (caudate and putamen). When this is shifted by blockade of the dopaminergic receptors by a neuroleptic, the cholinergic effects become relatively excessive resulting in parkinsonian signs and dystonias.

ADRENERGIC RECEPTORS

Neuroleptic drugs have direct antagonist effects on α-adrenoceptors. These adrenergic effects are most evident with chlorpromazine, thioridazine, perphenazine, loxapine and atypical agents such as clozapine and risperidone. The side-effects often encountered are tachycardia, vasodilatation, dizziness and orthostatic hypotension.

HISTAMINE RECEPTORS

Neuroleptic drugs such as fluphenazine, chlorpromazine, clozapine and quetiapine act on histamine H_1 receptors in the brain to produce unwanted side-effects, e.g. sedation and weight gain. HM

Conflict of interest: none.

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KEY POINTS

- Atypical antipsychotics were developed because of problems with typical agents including lack of efficacy in some patients, lack of improvement of negative symptoms and adverse effects, especially extrapyramidal symptoms (EPS) and tardive dyskinesia.
- Atypical neuroleptic drugs differ pharmacologically from typical antipsychotics in their 'limbic-specific' D_2-receptor family binding and the high ratio of 5-HT_2-receptor binding to D_2-receptor family binding.
- Blockade of D_2-receptors in the limbic system is a desirable effect since it relieves the positive symptoms of schizophrenia.
- Blockade of 5-HT_{2A} receptors is thought to increase dopamine in those sites where it is deficient, including the cortical and striatal areas, and 5-HT acts as a modulator of dopamine. This may explain the lesser incidence of EPS and tardive dyskinesia with atypical neuroleptics.
- Neuroleptics also block other receptors including muscarinic cholinergic and α-receptors which cause autonomic and central side-effects. Neuroleptic blockade of histaminergic receptors causes sedation.