REVIEW ARTICLE

CNS Drugs 2006; 20 (5): 389-409
1172-7047/06/0005-0389/$39.95/0

Mechanism of Action of Atypical Antipsychotic Drugs and the Neurobiology of Schizophrenia

Jiri Horacek,[1,2,3] *Vera Bubenikova-Valesova*,[1] *Milan Kopecek*,[1,2] *Tomas Palenicek*,[1,2,3] *Colleen Dockery*,[1,2] *Pavel Mohr*[1,2] and *Cyril Höschl*[1,2,3]

1 Prague Psychiatric Centre, Prague, Czech Republic
2 Centre of Neuropsychiatric Studies, Prague, Czech Republic
3 3rd Medical Faculty of Charles University, Prague, Czech Republic

Contents

Abstract

Atypical antipsychotics have greatly enhanced the treatment of schizophrenia. The mechanisms underlying the effectiveness and adverse effects of these drugs are, to date, not sufficiently explained. This article summarises the hypothetical mechanisms of action of atypical antipsychotics with respect to the neurobiology of schizophrenia.

When considering treatment models for schizophrenia, the role of dopamine receptor blockade and modulation remains dominant. The optimal occupancy of dopamine D_2 receptors seems to be crucial to balancing efficacy and adverse effects – transient D_2 receptor antagonism (such as that attained with, for example, quetiapine and clozapine) is sufficient to obtain an antipsychotic effect, while permanent D_2 receptor antagonism (as is caused by conventional antipsychotics) increases the risk of adverse effects such as extrapyramidal symptoms. Partial D_2 receptor agonism (induced by aripiprazole) offers the possibility of maintaining optimal blockade and function of D_2 receptors. Balancing presynaptic and postsynaptic D_2 receptor antagonism (e.g. induced by amisulpride) is another mechanism that can, through increased release of endogenous dopamine in the striatum, protect against excessive blockade of D_2 receptors.

Serotonergic modulation is associated with a beneficial increase in striatal dopamine release. Effects on the negative and cognitive symptoms of schizophrenia relate to dopamine release in the prefrontal cortex; this can be modulated by combined D_2 and serotonin 5-HT_{2A} receptor antagonism (e.g. by olanzapine and risperidone), partial D_2 receptor antagonism or the preferential blockade of inhibitory dopamine autoreceptors.

In the context of the neurodevelopmental disconnection hypothesis of schizophrenia, atypical antipsychotics (in contrast to conventional antipsychotics) induce neuronal plasticity and synaptic remodelling, not only in the striatum but also in other brain areas such as the prefrontal cortex and hippocampus. This mechanism may normalise glutamatergic dysfunction and structural abnormalities and affect the core pathophysiological substrates for schizophrenia.

The development of antipsychotics represents one of the most important successes of applied neuroscience. In most patients, antipsychotic drugs bring a significant improvement in psychotic symptoms and better health and quality of life. However, while antipsychotic drugs provide a basic therapeutic tool for the treatment of schizophrenia and other psychotic conditions, their effectiveness is associated with a series of unresolved questions. It is not clear, for example, which neurobiological mechanism (beyond dopamine D_2 receptor antagonism) is the final therapeutic target responsible for the beneficial effect on distorted information processing in schizophrenia and for subsequent elimination or reduction of psychotic symptoms. Also, the principal question of whether the effectiveness of antipsychotic drugs represents a causal intervention into the pathophysiological chain of events leading to psychotic information processing or whether their effect only compensates for this deficit at a symptomatologic level, remains unanswered.

Newer (atypical) antipsychotic drugs offer not only a better therapeutic tool but, because of their stratified effect on the finer dimensions of psychotic symptoms, they also provide deeper insight into the pathophysiology of schizophrenia itself. While the majority of models explaining the effects of antipsychotic drugs indicate that these drugs modulate various monoaminergic systems, novel theories of schizophrenic pathophysiology are predominantly focused on different levels of cortical and corticosubcortical disconnection. This article surveys contemporary concepts and hypotheses of the effects of antipsychotic drugs and the neurobiological basis of schizophrenia with respect to the integration of these aspects.

1. Classification of Atypical Antipsychotics

The original classification of antipsychotics according to their chemical structure (phenothiazines, thioxanthenes, butyrophenones, perathiepines and diphenylpiperidines) and prevailing sedative or antipsychotic (incisiveness) potential is still relevant for the conventional (typical) antipsychotic agents. The classification of atypical antipsychotics is linked essentially to their pharmacodynamic properties, which reflect their affinities for specific receptors. Atypical antipsychotics with a high selectivity for serotonin 5-HT_{2A} receptors and dopamine D_2 receptors (and also α_1-adrenoceptors) are called serotonin-dopamine antagonists (SDA). Drugs showing an affinity for 5-HT_{2A}, D_2 and receptors of other systems (cholinergic, histaminergic, 5-HT_{1A}, 5-HT_{2C} and others) are designated as multi-acting receptor-targeted antipsychotics (MARTA).[1] Drugs that preferentially block D_2 and D_3 subtypes of the D_2-like receptors are classified as combined D_2/D_3 receptor antagonists. A final class of atypical antipsychotics are the partial dopamine receptor agonists. Table I provides a summary of the typical representatives of each class.

2. Clinical Effect of Atypical Antipsychotics

Conventional antipsychotics are characterised by undesirable effects, such as extrapyramidal symptoms (EPS), hyperprolactinaemia and neuroleptic malignant syndrome, which are specific to the group as a whole and associated typically with high doses. From the clinical point of view, atypical antipsychotic drugs can be differentiated from conventional antipsychotics by their effectiveness, influence on behaviour and increased safety.[4]

The clinical efficacy of atypical antipsychotics has been tested in numerous double-blind, randomised, controlled trials in which the newer agents have been compared with both placebo and conventional antipsychotics in schizophrenia and other psychotic disorders. Study results have invariably confirmed the comparable effects of atypical and conventional antipsychotics in the control of positive symptoms and the superiority of atypicals on negative and affective symptoms, cognitive dysfunction and aggression.[5] Furthermore, during the course of illness, atypical antipsychotics are associated with the following benefits:[2,4]

- higher rate of responders;
- efficiency in patients with refractory disease;
- lower risk of suicides;
- better functional capacity;
- improved quality of life;
- favourable pharmacoeconomic profile.

They also have a more favourable adverse effect profile, being associated with a lower risk of EPS and tardive dyskinesias, hyperprolactinaemia, morphological changes in the CNS and noncompliance, as well as better overall tolerability.[5] However, atypical antipsychotics, as a class, are associated with their own unique adverse effects; their metabolic adverse effects, for example, are currently of great interest to clinicians.[6]

Nevertheless, based on study findings and growing empirical evidence, atypical antipsychotics are becoming the first-line treatment of schizophrenia. Thus far, there has been a general consensus that atypical antipsychotics are effective and reliable in the treatment of schizophrenia, and similar in their efficacy,[7,8] although clozapine appears to be more effective than other atypicals.[9]

Interestingly, two recent meta-analyses of published clinical trials have suggested that atypicals are no better than conventional antipsychotics, which stimulated great controversy. First, Geddes et al.[10] concluded that when the dosage of conventional antipsychotics used in the published studies, which appeared to be higher than that recommended (haloperidol ≤12 mg/day or equivalent), is controlled for, the difference between the two groups of drugs in terms of efficacy and overall tolerability disappears. Second, in a systematic review and meta-analysis of studies that used low-potency conventional antipsychotics, Leucht et al.[11] found that atypicals were moderately more efficacious and, with the exception of clozapine, equally as prone as low-potency conventional drugs to induce EPS. However, the conclusions of Geddes et al.[10] and

Table I. Pharmacodynamic characteristics and classification of selected antipsychotics and clinical criteria characterising atypical antipsychotics

Antipsychotic	Classification	Criteria for atypical antipsychotic[2]	Receptor affinity (K_i)[a]									
			D_2	D_2 dissociation (k_{off})[b]	5-HT_{2A}	5-HT_{2A}/D_2	5-HT_{1A}	5-HT_{2C}	α_2	α_1	H_1	M_3
Amisulpride	D_2/D_3 antagonist	0EPS (?), 0PRL	1.3	0.02	2000	1538	<10 000	<10 000	1600	7100	<10 000	<10 000
Aripiprazole	Partial dopamine receptor agonist[c]	0EPS, 0PRL	2.3	0.037	4.6	2	5.6	181	74	25	23	4677
Clozapine	MARTA	0EPS, 0PRL	187	1.386	130	0.07	140	6.1	142	1.6	0.23	20
Fluphenazine	Conventional	NA	0.6	0.01	80	133	2829	658	304	9	67	<10 000
Haloperidol	Conventional	NA	2.4	0.017	50	20	2832	4475	1130	12	4160	<10 000
Chlorpromazine	Conventional	NA	6.7	0.02	12	1.8	3115	6.1	184	0.3	0.18	67
Iloperidone	SDA	0EPS	37	0.59	5. 6	0.19	93	146	162	0.31	12.3	<10 000
Loxapine	Conventional	NA	22	0.444	4	0.18	2900	17	2400	28	2.8	390
Melperone	Conventional[d]	0EPS, 0PRL	143	2.27	102	0.71	2200	1342	150	180	580	<10 000
Olanzapine	MARTA	mEPS, mPRL	31	0.039	3.5	0.11	2720	14	314	109	0.65	51
Quetiapine	MARTA	0EPS, 0PRL	700	3.013	96	0.13	320	1184	3630	22	2.2	1942
Remoxipride	D_2/D_3 antagonist	0EPS	51	1.23	<10 000	<500	<10 000	5500	<10 000	<10 000	<10 000	<10 000
Risperidone	SDA	mEPS	1.65	0.026	0.55	0.33	420	33	151	4.5	27	<10 000
Sertindole	SDA	0EPS, 0PRL	7	0.11	0.35	0.05	280	0.7	640	3.9	130	<5000
Sulpiride	D_2/D_3 antagonist		0.21–78	0.003	<10 000	<500	<10 000	<10 000	4300	<10 000	<10 000	<10 000
Thioridazine	Conventional	NA	8.3	0.14	60	7.2	NA	46	453	5	16	15
Ziprasidone	SDA	0EPS	4.6	0.073	1.4	0.30	112	4.1	160	18	130	<10 000

a Affinity constants (K_i) for individual receptors involved in antipsychotic action are reviewed by Roth et al.[2] and National Institute of Mental Health databases (http://pdsp.cwru.edu/pdsp.asp).

b Reflects the rate of unbinding from D_2 receptors.[3]

c Also has 5-HT_{2A} receptor antagonist properties.

d Melperone is classified as a conventional antipsychotic but its low affinity for D_2 receptors gives it a clinical profile similar to that of atypical agents.

0EPS = none or low induction of EPS; **0PRL** = no prolactin elevation; **EPS** = extrapyramidal syndrome; **MARTA** = multi-acting receptor-targeted antipsychotics; **mEPS** = moderate induction of EPS; **mPRL** = moderate prolactin elevation; **NA** = not applicable; **SDA** = serotonin-dopamine antagonists.

Leucht et al.[11] have been rebuffed by other authors. For example, Davis et al.,[12] in their meta-analysis of 124 trials, found that the effect of the dosage of the comparator is an artifact; analysing haloperidol-equivalent dosages of conventional antipsychotics did not affect the results. The authors also found that some atypicals (clozapine, amisulpride, olanzapine and risperidone) were significantly more efficacious than conventional drugs; some atypicals also produced a better functional recovery and were more cost effective. Olanzapine and risperidone were slightly superior to conventional antipsychotics with respect to positive symptoms and moderately superior with respect to negative and cognitive symptoms, mood and impulse control/excitement.

Based on information from current meta-analyses, it seems that the atypical antipsychotics are a heterogeneous group in terms of effectiveness and adverse effects, and that in addition to their superior antipsychotic effects, some of the drugs cause an EPS rate similar to that of a placebo.[12,13]

3. Mechanisms of Action of the Atypical Antipsychotics

The hypothetical mechanisms of action of atypical antipsychotics are hereinafter classified into dopaminergic, serotonergic and combined modulation effects. Since the atypical antipsychotics share several pharmacodynamic mechanisms which are often intermingled, the classification is largely motivated by the quest to develop a comprehensive overview. Subsequently, within the context of the neurodevelopment theory of schizophrenia, the neuroplastic effect of antipsychotics is also important.

3.1 Dopaminergic Modulation

Dopamine is a neuromodulator acting in the brain by means of two basic groups of receptors. The D_1 and D_5 receptors have similar structures and intracellular signalling mechanisms (increased levels of cyclic adenosine monophosphate [cAMP]) and are termed 'D_1-like receptors'. The D_2, D_3 and D_4 receptors reduce cAMP levels and are termed 'D_2-like receptors'.[14-16]

3.1.1 Dopamine D_2 Receptor Blockade

D_2 receptor blockade in the brain is a general pharmacodynamic property of all antipsychotics, and without it a drug will not show any antipsychotic properties.[17] With conventional antipsychotics, the level of D_2 receptor blockade is directly related to the antipsychotic effect, but with atypical agents the situation is more complicated. Currently, the concept of a 'therapeutic window' of the percentage of D_2 receptors blocked is being evaluated by a series of neuroimaging studies in relation to treatment efficacy and development of EPS. It has been repeatedly confirmed that D_2 receptor occupancies >80% are, in most cases, associated with EPS.[18-23] A lower striatal D_2 receptor occupancy mediated by lower affinity for D_2 receptors (table I) or by increased extracellular dopamine release (see sections 3.2 and 3.3) would explain the clinical characteristics of atypical antipsychotics.

3.1.2 D_1 Receptor Blockade

D_1 receptor blockade was once considered a key mechanism for atypical antipsychotics, particularly in light of the very high D_1 receptor antagonistic activity of clozapine. The affinity of clozapine for D_1 receptors is even higher than that for D_2 receptors.[4] D_1 receptors are the principal dopamine receptors in the prefrontal cortex, and an effect on these receptors is usually linked to therapeutic effects on the negative[24] and cognitive symptoms of schizophrenia.[25] From a development/hierarchy point of view, the D_1 receptors of the prefrontal cortex may influence the lower levels of the nervous system[26] associated with positive symptoms (related to the temporal or limbic regions), and may explain the efficacy of clozapine in patients with treatment-resistant symptoms.[27] D_1 receptors interact with D_2 receptors at the cellular level and, thus, D_1 receptor antagonism may directly influence schizophrenia at the level of D_2 receptor modulation.[28,29] However, the fact that atypical antipsychotic drugs other than clozapine lack affinity for D_1 receptors[2] and that pure D_1 receptor antagonists have not shown any pronounced antipsychotic potential does not support the role of D_1 receptors in antipsychotic drug efficacy.[30,31] The role of D_1

receptors therefore appears to be important for the delicate coordination of other receptor modulations (see sections 3.3 and 4).[32,33]

3.1.3 D_4 Receptor Blockade

D_4 receptor blockade was also considered as a possible mechanism by which clozapine is effective in treating schizophrenia. Clozapine shows a higher affinity for the D_4 compared with the D_2 subtype of the D_2-like receptors. On the other hand, conventional antipsychotics show approximately equal affinity for D_4 and D_2 receptors. Furthermore, in laboratory animals, the rate of induction of catalepsy (a model of EPS) decreases in relation to the increasing D_4 receptor affinity of the drug.[34] The increase of dopamine output into the basal ganglia and prefrontal cortex induced by D_4 receptor antagonists may explain the lower risk of EPS and the therapeutic influence on cognitive symptoms with these agents.[35] In connection with D_4 receptor antagonism, it is also interesting that in schizophrenia, the D_4 receptors are over-expressed.[36,37] However, drugs selectively influencing only D_4 receptors have not shown themselves to be therapeutically effective.[38]

In summary, D_4 receptor antagonism should be considered only as supplementary to D_2 receptor blockade for a therapeutic effect.

3.1.4 Blockade of D_2/D_3 Receptors

The properties of the substituted benzamides (sulpiride, remoxipride and especially amisulpride) can be understood only if the D_2 and D_3 subtypes of the D_2-like receptors are distinguished. These drugs have a higher affinity for D_3 than D_2 receptors.[39] D_3 receptors are localised in the limbic cortex, and preferential blockage of these receptors offers regionally selective antidopaminergic activity, resulting in an accentuated effect on positive symptoms.[40,41] The 'atypical' features of amisulpride and other substituted benzamides may also result from the pro-dopaminergic effect mediated by blocking of presynaptic D_2 autoreceptors. Blockade of these presynaptic inhibitory D_2 receptors leads to increased dopamine output into the striatum (reduction of EPS), maintaining a high rate of D_3/D_2 receptor blockade in the thalamus and temporal cortex. The increased level of dopamine in the prefrontal cortex is responsible for the effects on negative and cognitive symptoms.[42,43]

3.1.5 Rapid Dissociation from D_2 Receptors

Rapid dissociation from D_2 receptors ('fast OFF') is one explanation for the improved EPS profile of atypical antipsychotics, and one that is also consistent with the theory of a lower affinity for D_2 receptors for these drugs. The baseline occupation of D_2 receptors by endogenous dopamine is within the range of 25–40%,[44] and antipsychotics compete with endogenous dopamine for binding to D_2 receptors. The drugs with faster dissociation (k_{off}) from D_2 receptors can more effectively reach the equilibrium between association (k_{on}) and k_{off} in the dynamic process of binding to the receptor against a background of ongoing endogenous dopamine binding and release. At an equilibrium state, a drug with a faster dissociation, such as clozapine, can go on and off the receptor 100 times more frequently than haloperidol. By this mechanism, clozapine (and other antipsychotics with rapid dissociation; see table I) can more effectively interfere with or attenuate the phasic release of endogenous dopamine than drugs with slow k_{off}, even at an equal level of receptor occupancy.[45] Rapid dissociation from D_2 receptors is, according to proponents of this idea, necessary for a more robust antipsychotic effect, but insufficient for induction of EPS and hyperprolactinaemia.[3,4,45] The mechanism of rapid dissociation is especially useful for explaining the properties of quetiapine and clozapine (table I), but the properties of other atypical antipsychotic drugs with low EPS risk but lacking rapid k_{off} (e.g. ziprasidone, aripiprazole, amisulpride and sertindole) are not explained by such reasoning.

The development of the rapid dissociation concept may be considered a supplement to the D_2 receptor occupancy therapeutic window theory, one which adds a temporal aspect to explaining how the drug exerts its effect on the receptor.

3.1.6 Partial Agonism of D_2 Receptors

Partial agonism of D_2 receptors is one of the newest models for explaining the properties of atypical antipsychotics.[46] Partial agonism means that

when binding to the receptor, the drug blocks the effects of the extracellular physiologically active substance (e.g. dopamine), while at the same having an agonistic effect on this receptor. The partial agonism model has been successfully applied within the framework of the development of aripiprazole. Aripiprazole is a drug showing, in clinical practice, the characteristics of an atypical antipsychotic with a low risk of EPS.[46] However, when administered in therapeutic doses, aripiprazole occupies about 95% of the striatal D_2 receptors, which does not correspond to a low incidence of EPS.[47,48] In the case of aripiprazole, the concept of rapid dissociation cannot be applied because this drug shows one of the highest D_2 receptor affinities and its k_{off} for D_2 receptors is even lower than that of many conventional antipsychotic drugs (table I).

Although the partial agonism of D_2 receptors exhibited by aripiprazole is the drug's most frequently mentioned attribute, in order to explain the incongruity between the low potency of EPS with aripiprazole and its high degree of D_2 receptor blockade, its effects on other monoaminergic receptors should not be overlooked. Aripiprazole is a partial agonist of a series of receptors that are involved in antipsychotic effects, namely 5-HT_{1A}, 5-HT_{2C}, D_2, D_3, D_4 and, to a much lesser extent, 5-HT_{2A} receptors.[48-51] In fact, at D_3, D_4, 5-HT_{1A} and 5-HT_{2C} receptors, aripiprazole shows 40–80% the activity of a full agonist. At D_2 receptors, the agonistic activity of aripiprazole reaches about 30% (maximum 40%) of the effects of dopamine as an endogenous ligand; on 5-HT_{2A} receptors, however, it shows a weak 5% agonistic activity. At therapeutic dosages (15–30 mg/day), aripiprazole thus occupies 95% of striatal D_2 receptors and if we subtract about 30% of the intrinsic agonistic activity there is approximately a 65% blockade of D_2 receptor activity, a level analogous to the optimum therapeutic window for most antipsychotics.[52] Partial D_2 receptor agonism by aripiprazole at the level of the tubero-infundibular dopaminergic projection is responsible for its prolactin-neutral or prolactin-reducing effect.[53]

Furthermore, the dopaminergic effect of aripiprazole, and therefore the ratio between its agonistic/antagonistic effects, is dependent on the type and function of the respective neuronal populations.[54] This effect also mediates its functional (and anatomical) selectivity on various dopaminergic pathways. In addition, antagonism of 5-HT_{2A} receptors (with only a slight intrinsic agonistic activity) allows aripiprazole to manifest 5-HT_{2A}/D_2 receptor antagonistic properties as well.

An interesting possibility is suggested by the long-term influence of partial agonists on D_2 receptor availability. Agonists of D_2 receptors cause downregulation (internalisation) of receptors.[55] There is still the unanswered question of whether a 30–40% agonistic effect, as seen with aipiprazole, is sufficient for internalisation of D_2 receptors (yielding a long-term positive therapeutic effect).

3.2 Serotonergic Modulation

From the historical point of view, interest in serotonergic modulation for the treatment of schizophrenia arose from the finding that 5-HT_{2A} receptor agonists (e.g. lysergic acid diethylamide [LSD]) are strong psychedelic drugs that can elicit psychotic symptoms.[2,56]

3.2.1 Serotonin 5-HT_{2A} Receptor Blockade

Experience with LSD suggests that 5-HT_{2A} receptor blockade might be a promising method of treating schizophrenia. However, a heuristic problem remains: the phenomenology of the psychotic symptoms caused by 5-HT_2 receptor agonists differs substantially from the symptoms of schizophrenic psychoses.[57,58]

On the other hand, the anatomical localisation of 5-HT_{2A} receptors supports their possible role in antipsychotic effects. 5-HT_{2A} receptors are localised on hippocampal and cortical pyramidal cells, as well as on GABA neurons. The highest density of 5-HT_{2A} receptors is in the fifth neocortex layer where the inputs of various cortical and subcortical brain areas are integrated (and 'computed').[59,60] This fact makes 5-HT_{2A} receptor blockade an extraordinarily interesting area, given the aetiopathogenesis of schizophrenia.

Because agonism at 5-HT_{2A} receptors induces depolarisation of pyramidal cells, it has been speculated that 5-HT_{2A} receptor blockade is responsible for normalisation of pyramidal cell activity, which leads to the therapeutic effect of atypical antipsychotics.[61] The psychomimetic effect of glutamate NMDA receptor antagonists may be blocked by selective antagonists of 5-HT_{2A} receptors,[61] but the antipsychotic potential of pure 5-HT_{2A} receptor antagonists has not been convincingly proven.[62,63]

5-HT_{2A} receptors are also localised on dopaminergic neurons in the substantia nigra and ventral tegmentum, as well as on their terminals.[64] 5-HT_{2A} receptor antagonism may modulate the activity of dopamine neurons differentially in nigrostriatal, mesolimbic and mesocortical projections.[65] The fundamental interaction of 5-HT_{2A} and D_2 receptor antagonism is discussed in section 3.3.1.

The activity of the striato-pallidal GABA neurons is also regulated by 5-HT_{2A} receptors.[66] D_2 receptors regulate, in a tonic inhibitory manner, the indirect three neuronal GABAergic inhibitory projection to the thalamus and cortex. The administration of D_2 receptor antagonists leads to dis-inhibition of this projection with facilitation of inhibitory effects on locomotion and subsequent EPS.[67] Therefore, the antagonism of 5-HT_{2A} receptors located at pallidal GABA cells would counteract the inhibition of movement. This mechanism may explain the reduced risk of EPS seen with atypical antipsychotics. The role of 5-HT_{2A} receptor antagonism in the pharmacological profile of atypical antipsychotics may also be supported by the fact that, conversely, SSRIs may induce EPS.[68]

3.2.2 5-HT_{2C} Receptor Blockade

5-HT_{2C} receptor blockade has received relatively little attention in studies of antipsychotics. Binding affinity for the 5-HT_{2C} receptor does not distinguish conventional from atypical antipsychotics (table I). Some atypicals (clozapine and risperidone), but also some conventional antipsychotics (chlorpromazine, mesoridazine, loxapine and fluphenazine) have high affinities for 5-HT_{2C} receptors. 5-HT_{2C} receptors have been found in cortical areas and in the hippocampus, striatum, septal nuclei, thalamic nuclei, midbrain nuclei and brain stem. These receptors have somato-dentritic localisation and, in cortical areas, appear to be mostly expressed on pyramidal (glutamatergic) cells. It has also been suggested that 5-HT_{2C} receptors control monoaminergic and cholinergic neurons. In the substantia nigra, 5-HT_{2C} receptors are co-localised with GABA, indicating that 5-HT_{2C} receptors yield indirect control of dopaminergic transmission.[69] Consequently, the blockade of 5-HT_{2C} receptors on GABA cells in the substantia nigra would potentiate the D_2 receptor-mediated tonic inhibitory control of the three neuronal striato-pallido-talamo-cortical projection,[67] with protective effect against EPS. In this regard, administration of a 5-HT_{2C} receptor antagonist may increase dopamine levels in the nucleus accumbens and prefrontal cortex.[70]

Because of the increase in limbic dopamine levels induced by 5-HT_{2C} receptor antagonism, this effect on these receptors is not sufficient for an antipsychotic effect. Moreover, systematic administration of an antagonist of 5-HT_{2C} receptors (SB-242084) activates mesolimbic dopamine neuronal function in an animal model of schizophrenia-like behaviour (induced by a noncompetitive NMDA receptor antagonist) and is associated with worsening of hyperlocomotion and a deficit in information processing.[71]

3.2.3 Agonism of 5-HT_{1A} Receptors

Agonism of 5-HT_{1A} receptors is considered a possible mechanism associated with the activity of some atypical antipsychotic drugs.[65] The only antipsychotics that manifest 5-HT_{1A} receptor agonism are aripiprazole, clozapine, quetiapine, ziprasidone and risperidone. 5-HT_{1A} receptor blockade (with WAY100635) prevents the increase in dopamine in the prefrontal cortex induced by these drugs, even with olanzapine[72] which does not express 5-HT_{1A} receptor affinity. Therefore, it seems that these receptors play an important role in the action of atypical antipsychotics, irrespective of whether they are directly agonised by the drug (see section 3.3.3).

Generally, it may be concluded that a simple effect at serotonergic receptors is probably not suffi-

cient for an antipsychotic effect in schizophrenia. More promising seems to be the assumption that serotonergic activity takes part in the antipsychotic effect in combination with D_2 receptor blockade, and possibly with other systems as well.

3.3 Combined Modulations

3.3.1 Blockade of 5-HT$_{2A}$ and D$_2$ Receptors

Blockade of 5-HT$_{2A}$ and D_2 receptors was, in 1989, first labelled a pharmacodynamic mechanism that differentiated conventional from atypical antipsychotics.[73,74] Meltzer et al.[73,74] defined atypical antipsychotic drugs as drugs showing a higher affinity for 5-HT$_{2A}$ receptors than for D_2 receptors and a lower affinity for D_2 receptors than was seen with conventional antipsychotics. These two criteria enabled these investigators and other authors[2] to classify the antipsychotics in two groups and confirmed, in most cases, their ability to predict the clinical properties of antipsychotic drugs with respect to the affinity constants for 5-HT$_{2A}$ and D_2 receptors.

For the nigrostriatal dopaminergic pathway, a model was suggested in which blockade of 5-HT$_{2A}$ receptors leads to increased output of dopaminergic neurons into the striatum. Such increased extracellular activity of dopamine in the striatum 'displaces' the antipsychotic drug from its binding to D_2 receptors and thus decreases the risk of EPS development.[75]

5-HT$_{2A}$/D_2 receptor antagonism on the mesolimbic dopaminergic pathway into the nucleus accumbens is linked with the greater efficacy of atypical antipsychotics against the positive symptoms of schizophrenia. In these projections, 5-HT$_{2A}$ receptor agonists cause increased dopaminergic output,[76] while antagonists reduce dopaminergic output.[77] Moreover, administration of 5-HT$_{2A}$ receptor antagonists results in a decrease in haloperidol-induced release of dopamine into the mesolimbic system.[78] Therefore, 5-HT$_{2A}$ receptor antagonism should augment the antipsychotic (antidopaminergic) potential of the drug by decrease of dopamine release, even in the case of an existing lower affinity for D_2 receptors.

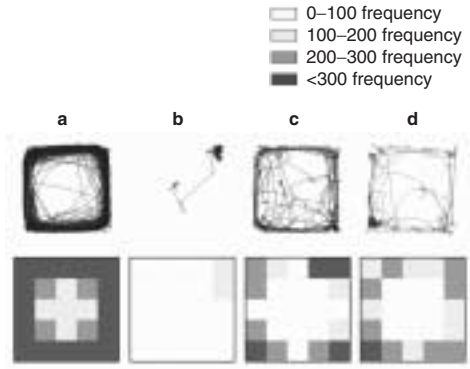

Fig. 1. The effect of tryptophan depletion in combination with the dopamine D_2 receptor antagonist haloperidol (0.1 mg/kg) on locomotion in an acute animal model of schizophrenia induced by the administration of the noncompetitive NMDA antagonist dizocilpine (MK-801) [0.3 mg/kg]. Tryptophan depletion produced a significant 37.2% decrease in serotonin in the brain and, combined with haloperidol in dizocilpine-treated rats, was used as a probe for the role of antiserotonergic activity in the mechanism of atypical antipsychotics. Upper images show samples of trajectories registered within the open field arena (68 × 68 × 30cm) during a 90-minute testing period. The images below show sums of trajectory lengths of all animals within the individual group (n = 9) calculated for each quadrant of the arena. The animals treated with dizocilpine (**a**) show the typical hyperlocomotion in comparison with the trajectory of control animals (**d**). Haloperidol treatment (**b**) inhibits the locomotion in comparison with both dizocilpine (**a**) and controls (**d**; $p \leq 0.05$ for all analyses), and because of the low dose (0.1 mg/kg) of haloperidol administered, it is more representative of a model of incomplete remission or negative symptoms than catalepsy. The trajectories were normalised both in length and spatial distribution in comparison with controls when brain serotonin was decreased by tryptophan depletion in dizocilpine- and haloperidol-treated rats (**c** vs **d**, p = not significant) [reproduced from Bubeníková et al.,[79] with permission from Elsevier].

5-HT$_{2A}$ receptor antagonism modulates the activity of dopaminergic neurons differentially in the mesocortical projections. 5-HT$_{2A}$ receptor antagonists increase dopamine release into the prefrontal cortex and this effect is potentiated by concomitant haloperidol administration in doses producing <80% of D_2 receptor occupancy.[84,85] This effect would be expected to be linked with effects on cognitive and negative symptoms.

The experiments shown in figures 1 and 2 demonstrate the interaction between serotonin and D_2 receptor antagonism in antipsychotic action. The decrease of extracellular serotonin (induced by tryptophan depletion) restores the hypolocomotion induced by haloperidol in an animal model of schizo-

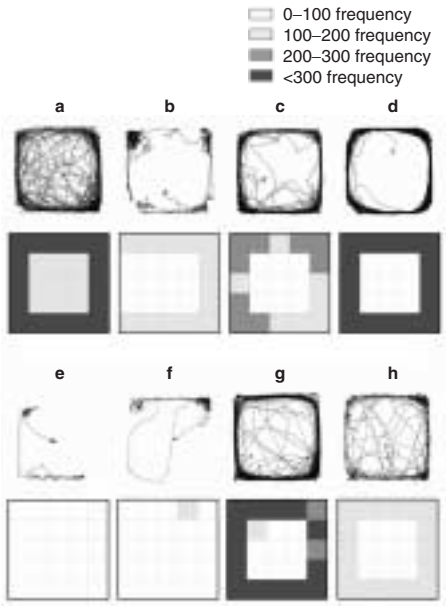

Fig. 2. The effect of specific agonists and antagonists of serotonin receptors in combination with dopamine D_2 receptor antagonism (haloperidol, 0.1 mg/kg) on locomotion in an acute animal model of schizophrenia. The experimental setting is the same as in figure 1. The upper images show samples of the trajectories and the images below show sums of trajectory lengths of all the animals within the individual group (n = 10), calculated in each quadrant of the arena. The animals treated with dizocilpine (MK-801) 0.3 mg/kg [a model of psychosis] (**a**) show the typical hyperlocomotion in comparison with the control animals (**h**) [$p \leq 0.01$]. Administration of haloperidol 0.1 mg/kg to the dizocilpine-treated animals (**b**) blocks the hyperlocomotion, but the total trajectory length and the spatial characteristics of the animal's movement differ from those of controls (**h**).[80] The 5-HT_{1A} receptor agonist 8-hydroxy-dipropylaminotetralin [8-OH DPAT] (**c**, 0.1 mg/kg; **d**, 1.0 mg/kg) counteracts the haloperidol-induced hypolocomotion and prolongs the trajectory of the animals within the arena ($p \leq 0.01$). Moreover, it affects the spatial characteristics of the animals' movement; animals treated with high doses of 8-OH-DPAT (**d**, 1.0 mg/kg) prefer the peripheral zones of the arena ($p < 0.01$).[81] The 5-HT_2 receptor antagonist ritanserin (**e**, 2.5 mg/kg; **f**, 5.0 mg/kg), in contrast to 8-OH-DPAT, facilitates the inhibitory effect of haloperidol, leading to a decrease in total locomotion ($p < 0.05$),[82] a finding indicative of a synergistic effect of 5-HT_{2A} and D_2 receptor antagonism. The selective 5-HT_{2C} receptor antagonist SB-242084 1.0 mg/kg (**g**) significantly prolongs the trajectory of the animals treated with dizocilpine and haloperidol ($p < 0.05$), indicating that it counteracts the effect of haloperidol.[83]

phrenia (figure 1) and supports the role of serotonin in the amelioration of negative and cognitive symptoms. However, selective 5-HT_{2A} receptor antagonism facilitates the inhibitory effect of D_2 receptor antagonism and a synergistic effect was observed (figures 2e and f). The interaction between both systems in mesolimbic projections would explain this effect. These findings indicate the role of other serotonergic receptors such as 5-HT_{1A} and 5-HT_{2C} in the action of atypical antipsychotics (see sections 3.3.2 and 3.3.3).

From the point of view of understanding the mechanism of atypical antipsychotics, it is important that, for their long-term administration, adaptive changes in the serotonergic system occur in the same direction as in the case of an acute blockade. Long-term administration leads to a reduced downregulation (internalisation) of 5-HT_{2A} receptors.[86,87]

The concept of 5-HT_{2A}/D_2 receptor antagonism has led to the development of several new, efficient drugs and some progress in understanding the functioning of antipsychotics. However, the 5-HT_{2A}/D_2 model does not explain the effects of all atypical antipsychotics, such as aripiprazole and amisulpride, for which pharmacodynamic criteria (5-HT_{2A}/D_2) are not consistent with clinical criteria (see sections 3.1.4 and 3.1.6). These exceptions shift our attention from the pharmacodynamic level to a physiological approach (such as measuring the extracellular concentrations of monoamines), which brings us closer to the pathophysiological substrate of schizophrenic disorder.

3.3.2 Blockade of 5-HT_{2C} and D_2 Receptors

Blockade of 5-HT_{2C} and D_2 receptors represents a third possible serotonergic effect of antipsychotics.[65] Because 5-HT_{2C} receptors regulate the tonic inhibition of dopaminergic output using serotonin from the ventral tegmentum, antagonism of these receptors may cause an effect analogous to 5-HT_{2A} receptor blockade.[88,89] There is some evidence that a combination of 5-HT_{2A} and 5-HT_{2C} receptor blockade is more efficient than 5-HT_{2A} receptor blockade at increasing dopamine release in the nucleus accumbens and in the prefrontal cortex.[65,90] The effect in the prefrontal cortex would be expected to result in an effect on cognitive and affective symptoms. Moreover, antagonism of 5-HT_{2C} receptors produces a significant reversal of haloperidol-induced catalepsy (figure 2h),[83] and 5-

HT_{2C} receptor antagonism in combination with dopamine receptor blockade should therefore increase the safety of the drugs.[91]

5-HT_{2C} receptors also play a role in food intake and are involved in weight gain, which is an adverse effect of some atypical antipsychotics. Recent reports indicate that −759C/T polymorphism of the 5-HT_{2C} receptor gene is associated with weight gain in schizophrenic patients treated with olanzapine and clozapine.[92,93]

3.3.3 Agonism of 5-HT_{1A} and Blockade of D_2 Receptors

Agonism of 5-HT_{1A} and blockade of D_2 receptors represents another possible combination which, from a theoretical point of view, complies with the 5-HT_{2A}/D_2 hypothesis. To a certain extent, 5-HT_{2A} and 5-HT_{1A} receptors show functionally opposite effects.[65] Thus, like 5-HT_{2A} receptor antagonists, 5-HT_{1A} receptor agonists increase dopamine output in the neocortex and striatum.[72] However, the 5-HT_{1A} receptor agonist buspirone also increases extracellular dopamine levels, even in the limbic area (nucleus accumbens).[94] Therefore, it is likely the role of 5-HT_{1A} receptor agonism is more important for influencing negative and cognitive symptoms than positive symptoms. Also, the ratio between the influence of postsynaptic and presynaptic 5-HT_{1A} receptors may play an important role; bimodal dependence based on this ratio cannot be excluded.[81]

Experimental data from our laboratory prove that a decrease in serotonergic activity (tryptophan depletion) is essential for normalisation of locomotor activity in combination with D_2 receptor antagonism in an animal model of schizophrenia induced by short-term administration of the NMDA receptor antagonist dizolcipine (MK-801) [figure 1].[79] Administration of a specific 5-HT_{2A} receptor antagonist or 5-HT_{1A} receptor agonist in combination with haloperidol did not show such a beneficial effect (figure 2). Interestingly, 5-HT_{1A} receptor agonism (figures 2c and d) or 5-HT_{2C} receptor antagonism (figure 2g) prolonged the hypolocomotion induced by haloperidol, but strongly affected the spatial characteristics of the behaviour (preferences for peripheral regions of the open field), hypothetically because of facilitation of limbic dopamine release. 5-HT_2 receptor antagonism, contrary to the 5-HT_{2A}/D_2 receptor antagonism concept, facilitated the inhibitory effect of haloperidol in this experimental setting (figures 2e and f).[80-83] The more sophisticated (in terms of the combination of different receptor targets) the interaction between serotonin and dopamine, the more important it seems to be in influencing the optimal orchestration of an antipsychotic effect.

3.3.4 D_2 Antagonism and Interaction with Muscarinic Receptors

Some atypical antipsychotics, such as olanzapine and clozapine, have a marked affinity for cholinergic muscarinic receptors (M_1 and M_4). These receptors are predominately expressed in the frontal and limbic areas of the brain and have extensive interactions with dopaminergic neurons.[96,97] On the other hand, risperidone, haloperidol, ziprasidone and quetiapine do not have high affinities for muscarinic receptors, and direct interaction with muscarinic receptors is not important in their pharmacology.[97] The main effect of antimuscarinics is to antagonise antipsychotic-induced EPS, and the affinity of antipsychotics for muscarinic receptors has been shown to be inversely correlated with their propensity for causing EPS.[98] In contrast to the effect induced by antagonism of muscarinic receptors, atypical antipsychotics also increase extracellular levels of acetylcholine in the prefrontal cortex, striatum and nucleus accumbens. Conventional antipsychotics such as haloperidol and thioridazine, on the other hand, do not increase acetylcholine levels in the prefrontal cortex, but they do increase acetylcholine levels in the nucleus accumbens and striatum.[99] The effect of antipsychotics on acetylcholine levels could be due to an interaction between the dopaminergic and acetylcholinergic systems. There are some findings that agonists of muscarinic receptors have antipsychotic features and act as dopamine receptor antagonists.[97] Taken together, the antimuscarinic activity of clozapine and olanzapine could be hypothetically responsible for the effect on positive and cognitive symptoms.

There are no data indicating that antipsychotics bind at nicotinic receptors. However, the effect of agonists of the α_7 subunit of the nicotinic receptor in improving perceptual disturbances and cognitive deficit in schizophrenia was recently described.[100]

3.3.5 Blockade of α-Adrenergic and D_2 Receptors

Atypical antipsychotics are, with some exceptions (e.g. benzamides), relatively strong antagonists of α_1-adrenoceptors. In atypical antipsychotic function, the role of α_1-adrenoceptor antagonism is supported by findings which demonstrate that prazosin (an α_1-adrenoceptor antagonist) administered simultaneously with haloperidol reduces the risk of EPS and leads to higher haloperidol binding to limbic D_2 receptors.[101,102] This phenomenon may be explained by the fact that blockade of α_1-adrenoceptors leads to inhibition of serotonin neurons in the raphe nuclei and thus may induce an effect similar to that of 5-HT_2 receptor blockade by 5-HT_2/D_2 receptor antagonists.[103]

In addition, α_2-adrenoceptor antagonism by some atypical antipsychotics may play a role in 'atypical' properties. Research in animals confirms that yohimbine, MK-912 and other antagonists of α_2-adrenoceptors reduce the cataleptic effect of haloperidol.[104]

4. The Neurobiology of Schizophrenia and the Effects of Atypical Antipsychotics

In the last decade, a new theory of schizophrenia has been proposed. According to this theory, schizophrenia develops as a result of a disconnection of the distributed networks of pyramidal neurons, which represent the principal substrate for information processing.[105]

There is much evidence to indicate dysfunction in the connectivity of glutamatergic neurons in schizophrenia. For example, reductions in the density of prefrontal cortex pyramidal cell dendrites, the number of glutamatergic synaptosomes and the expression of messenger RNA (mRNA) for the synaptic density marker synaptophysin are found at postmortem in patients who had schizophrenia.[106-110] The reduced brain volume in schizophrenia, with the simultaneous increased density in pyramidal neurons, supports the fact that the morphological substrate of the disorder consists of a reduced number of neuronal fibres and synapses, rather than a reduced number of neurons. The absence of gliosis in the brains of patients with schizophrenia contradicts the theory of a degenerative/inflammatory process and also supports the neurodevelopmental aetiology of the morphological findings in schizophrenia.[111,112] In addition, the abnormalities are even present prior to onset of the disease.[26]

The theory of glutamatergic dysfunction in schizophrenia is also supported by the fact that phencyclidine and other antagonists of glutamatergic NMDA receptors may, from the phenomenological point of view, model the schizophrenic symptoms in healthy persons better than serotonergic psychotomimetic drugs (e.g. LSD; see section 3.2), and may aggravate or exacerbate psychosis in patients with schizophrenia.[57]

Novel and very promising findings in schizophrenia implicate the pathology of myelin. Morphologic and neurocytochemical evidence, myelin-related gene abnormalities and abnormalities in the oligodendroglia demonstrated in the brains of patients with schizophrenia support changes in white matter as an alternative mechanism for disconnection.[113,114]

The target structures for all antipsychotics are primarily the monoaminergic receptors associated with G-proteins. Using the above-mentioned mechanisms of direct/indirect modulation, antipsychotic drugs change the behaviour (excitability) of pyramidal cells. Such an effect might be considered compensatory. From a theoretical perspective of information processing, they may, by means of shifting the signal/noise ratio, partially normalise the activity of the pyramidal cells altered by neuro-development.[115-117] Such a mechanism would be topographically selective; blockade of D_2 receptors in the medio-temporal cortex and striatum is associated with remission of positive symptoms. Moreover, typical and atypical antipsychotics affect the glutamatergic system directly as partial agonists at the NMDA receptor-associated glycine recognition

site[118] and indirectly by the blockade of glycine and glutamate transporters at the synaptic level.[119] By this mechanism, deficient glutamatergic signalling would be potentiated.

This explanation is supported by the finding that the glutamate co-agonist glycine and its derivatives (D-serine, D-cycloserine), as well as inhibitors of glycine reuptake, potentiate the clinical effect of conventional antipsychotics.[119]

Dopaminergic activity in the prefrontal cortex is mediated more by D_1 receptors than D_2 receptors.[14,33,120] The negative symptoms of schizophrenia and reduced performance in cognitive functions associated with the disorder may hypothetically be influenced by antipsychotics that increase dopaminergic activity in the prefrontal cortex. This assumption has been confirmed in animal studies that evaluated the effect of atypical antipsychotics on dopamine levels in the frontal cortex.[121] This hypothesis is not fully consistent with the expected positive therapeutic role of D_1 receptor blockade, which is particularly notable for clozapine (see section 3.1.2). This situation confirms the complexity of the problem and may be explained by the different functions of the tonic and phasic effect of dopamine in the neocortex.[116]

4.1 Neuroplastic Effect of Antipsychotics

Neuroplasticity refers to the ability of the nervous system to adapt to environmental changes, and includes both synaptic plasticity (remodelling of the synapses and development of new neuronal connections) and neurogenesis (development of new neurons). Antipsychotic drugs appear to induce restructuring of neuronal networks by inducing neuroplastic changes. This effect contributes to a more substantial description of the interaction between antipsychotics and the neurodevelopmentally altered function and structure of the brain in patients with schizophrenia. In addition, it can explain the delayed onset of the antipsychotic effect, suggesting a remodelling of neuronal structures and circuits is required for this effect rather than exclusively receptor blockade or changes in neurotransmitter levels.

In the case of haloperidol, induction of synaptic plasticity has been particularly well documented in the striatum,[122-124] where the highest concentration of D_2 receptors exists. This is indirectly supported by volumetric studies that have found extension of the basal ganglia after haloperidol treatment.[125-127] The increase in basal ganglia volume is reversible after therapy is discontinued or after switching to clozapine, which has significantly lower D_2 receptor affinity.[125,128]

The neuroplastic changes are based on the cAMP increase after the D_2 receptors are blocked. cAMP activates protein kinase A (PKA), which phosphorylates (reinforces) NMDA and other receptors. PKA also activates transcription factors, which regulate the expression of genes of neuronal growth factors.[127,129] A regionally stratified increase in neurotrophin nerve growth factor (NGF) was reported after administration of antipsychotics.[122] The increase in NGF is mediated by D_2 receptor blockade; it is also increased by conventional antipsychotics.[123,124]

It has been shown that haloperidol treatment in rats upregulates binding of NMDA receptors in the parietal and frontal cortices,[130,131] and an increase in this binding level probably results from an increase in the maximal density of NMDA receptors.[118] There is evidence that antipsychotics change the expression of NMDA and non-NMDA receptors in different brain structures.[119] However, findings related to the effect of antipsychotics on the mRNA level of glutamate receptor subunits are inconsistent and depend on the antipsychotics used and the duration of treatment.[132]

The expression of the neuronal growth factor brain-derived neurotrophic factor (BDNF) is also influenced by antipsychotics. However, the effects of the respective antipsychotics on this neurotrophin differ significantly from each other. After chronic administration of haloperidol and risperidone, reduced production of mRNA for BDNF was found in the hippocampus and the frontal and orbital cortical regions in rats.[133,134] On the other hand, after chronic administration of olanzapine, increased expression of BDNF in CA1 and CA3 of the hippocampus

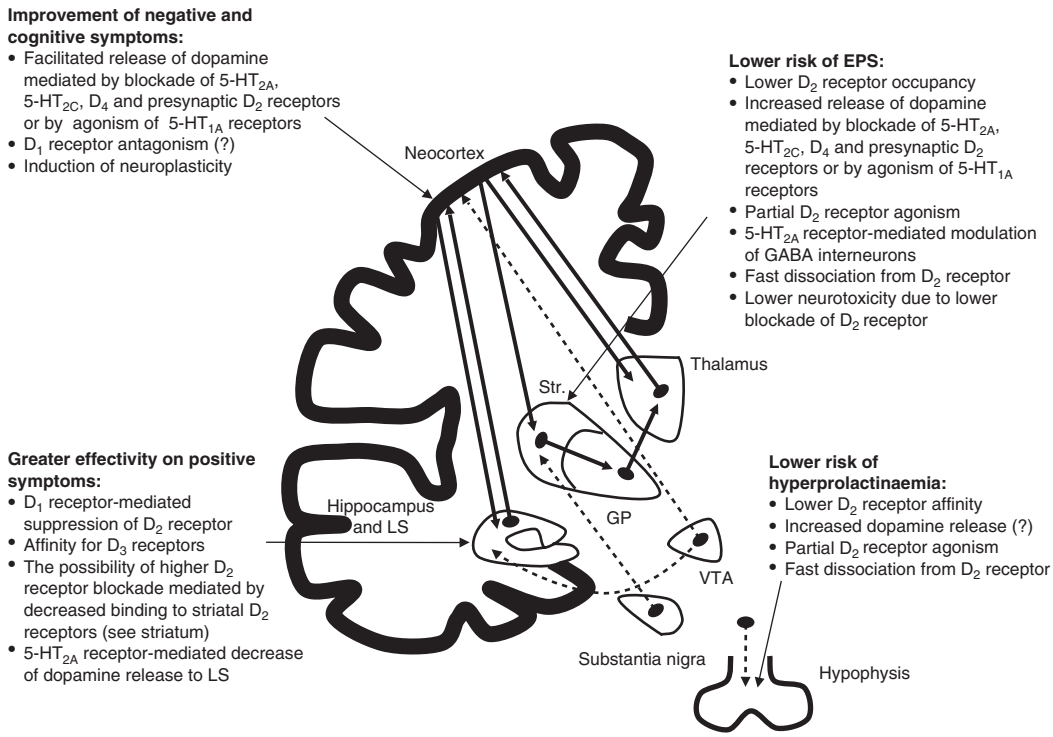

Fig. 3. Schematic illustration of the hypothetical mechanisms of action of atypical antipsychotics. Solid arrows show the main neuronal circuits involved in the pathophysiology of schizophrenia. The reciprocal pathways connect the neocortex with the hippocampus, mediotemporal structures and limbic system (LS). The second circuit represents connections between the cortex, striatum (Str.), globus pallidus (GP), thalamus and back to the cortex. Dashed lines symbolise dopaminergic projections from the ventral tegmental area (VTA) to the neocortex and limbic areas. The nigrostriatal projection connects the substantia nigra with striatal GABAergic interneurons. The tuberoinfundibular projection from the hypothalamus to the adenohypophysis regulates prolactin release (modified from Konradi and Heckers[95]). **EPS** = extrapyramidal syndrome.

area and in the dentate gyrus was found.[135] In addition, olanzapine is able to normalise a haloperidol-induced decrease in the levels of BDNF.[136]

The neurotrophic or protective effect of atypical antipsychotics was also recently proven in humans by promising results from a magnetic resonance imaging study. Patients with first-episode psychosis were treated by haloperidol or olanzapine and followed-up for up to 2 years. A significantly lower whole brain grey matter volume reduction was found after olanzapine treatment compared with after haloperidol treatment. A lower reduction in grey matter volume was detected in the frontal, temporal and parietal cortical regions after 24 weeks, although after 104 weeks this effect was apparent only in the parietal cortex.[137,138]

From the point of view of the glutamatergic theory of schizophrenia, there is a very interesting observation that dizocilpine, a noncompetitive antagonist of NMDA receptors, reduces BDNF expression.[139] In an animal model, coadministration of dizocilpine with haloperidol amplifies this reduction; olanzapine, on the other hand, normalises the dizocilpine-induced decrease in expression of BDNF.[140] When considering the effects of atypical antipsychotics, it is noteworthy that 5-HT_{2A} receptor antagonism itself leads to a higher production of BDNF,[134,141,142] and that, conversely, D_2 receptor antagonism reduces BDNF.[143] This explains the BDNF-stimulating effect of olanzapine. Risperidone is also a strong 5-HT_{2A} receptor antagonist, but because of its very high affinity for D_2 receptors,

its D_2 receptor-mediated suppression of BDNF may prevail. Therefore, the effect of risperidone is similar to that of haloperidol and thus BDNF is reduced. This speculation is supported by the finding that for very low doses of risperidone, when the 5-HT_{2A} receptor blockade prevails over the unsaturated D_2 receptor blockade, risperidone loses its BDNF-reducing effect or does not change the BDNF level.[144]

Quetiapine has also been shown to have an effect on BDNF. Quetiapine blocks the stress-induced reduction of BDNF[145] and induces the expression of BDNF and another trophic factor (fibroblast growth factor-2) when coadministered with dizocilpine,[146] and is probably similar in this respect to olanzapine.

Both phosphorylation of NMDA receptors and induction of growth factors (NGF and BDNF) play a role in the development of new synapses or their remodelling;[95] in this way, antipsychotic drugs may therapeutically influence the deficit of neurodevelopment linked with the reduction of synaptic connections.[145] This mechanism, however, can lead to neurotoxic damage in the case of haloperidol,[138,147] caused by extensive facilitation of NMDA receptors and excessive influx of calcium into neurons.[95] The macroscopic results consist of a reduction in the size of the basal ganglia and development of tardive dyskinesia.[148,149]

Therefore, according to current knowledge, some atypical antipsychotics (unlike haloperidol) increase not only NGF but also BDNF. It is probable that induction of neuroplastic changes by atypical antipsychotics occurs not only in the striatum but also in other areas involved with the neurobiology of schizophrenia.[95] This assumption may be supported by the fact that, at present, early gene expression in the prefrontal cortex and other brain areas is primarily induced by atypical antipsychotics with a simultaneous lower rate of gene expression changes in the striatum compared with the conventional antipsychotics.[150-153] This may explain the superior therapeutic effect of atypicals on the more subtle dimensions of psychopathology (negative, cognitive or possibly emotional symptoms). Influencing synaptic plasticity shifts therapy with antipsychotics more towards a causal therapeutic influence on the assumed causes of schizophrenic psychosis.

The current 'hot topic' concerning the neuroplastic effects of antipsychotics is whether antipsychotics may, like antidepressant drugs,[154] induce neurogenesis (development of new neurons). It has been demonstrated that in the gerbil hippocampus, short-term haloperidol treatment can induce mitotic activity.[155] But for the evaluation of the clinical relevance of neurogenesis, chronic treatment is more pertinent. It has been shown that 3–4 weeks of treatment with clozapine,[156] quetiapine[157] and olanzapine,[158] but not with haloperidol, induces an increase in the number of cells positive for bromodeoxyuridine (a marker of DNA synthesis) in the rat dentate gyrus and (olanzapine only) in the prefrontal cortex.[159] However, the further study[160] did not detect any change in the total number of newly dividing cells in the dentate gyrus after subchronic haloperidol or clozapine treatment, and even in the studies with positive results, the newly generated neurons did not survive for many weeks following bromodeoxyuridine administration.[156,159]

The idea that atypical antipsychotics could induce neurogenesis is attractive with respect to the cognitive and emotional clinical effects of these drugs,[161] but the results are inconclusive and the survival and physiological influence of newly dividing cells in antipsychotic-treated adult individuals remains unresolved.

5. Conclusion

A summary of the hypothetical mechanisms of action of atypical antipsychotics with respect to their interactions and anatomical specificity is shown in figure 3 and table II.

The arguments supporting the key role of dopaminergic receptor blockade as the mechanism of action of antipsychotics still unequivocally prevail. However, the optimum orchestration of dopaminergic modulation during antipsychotic therapy depends on adequate D_2 receptor blockade, the intensity and duration of the effect, and also on the regional distribution of the dopaminergic effect. Serotonergic modulation through 5-HT_{2A}, 5-HT_{1A}

Table II. Hypothetical mechanisms involved in the action of atypical antipsychotics

Dopaminergic modulation
Blockade of D_2 receptors: shared by all antipsychotics, optimal blockade is within 65–75% of D_2 receptors, leads to effectiveness with preserved safety (EPS and hyperprolactinaemia)
Blockade of D_1 receptors: D_1 are localised in PFC, leads to therapeutic effect on negative and cognitive symptoms. D_1 receptors modulate activity of D_2 receptors (potentiation of efficiency). D_1 antagonism alone does not exert an antipsychotic effect
Blockade of D_4 receptors: decreases catalepsy and induces dopamine release in the basal ganglia and PFC. D_4 antagonism alone does not exert an antipsychotic effect
Blockade of D_2/D_3 receptors: preferential antagonism of inhibitory D_2 autoreceptors; increased striatal (lower risk of EPS) and neocortical dopamine release (cognitive and negative symptoms). Blockade of D_3 receptors in temporal cortex, leads to stereoselectivity and efficacy on positive symptoms without induction of EPS
Rapid dissociation from D_2 receptors ('fast OFF'): shorter duration of the drug binding to the D_2 receptor is sufficient for an antipsychotic action but insufficient to induce EPS and hyperprolactinaemia (quetiapine and clozapine)
Partial D_2 agonism: with aripiprazole, 30–40% of intrinsic D_2 receptor agonism in connection with high D_2 blockade exerts an antipsychotic effect with a low risk of EPS and hyperprolactinaemia
Serotonergic modulation
Blockade of 5-HT_{2A} receptors: 5-HT_{2A} receptors integrate cortical and subcortical inputs. Antagonism of 5-HT_{2A} receptors blocks the effect of NMDA antagonists and induces striatal and neocortical dopamine release
5-HT_{1A} receptor agonism: induces dopamine release into the striatum and neocortex (analogous to 5-HT_{2A} receptor blockade) and also into limbic structures
Blockade of 5-HT_{2C} receptors: induces neocortical dopamine release
Modulation of 5-HT_{2A}, 5-HT_{1A} and 5-HT_{2C} receptors alone does not have an antipsychotic effect
Combined modulations
Blockade of 5-HT_{2A} and D_2 receptors: higher affinity for 5-HT_{2A} receptors than for D_2 receptors, leads to lower risk for EPS (SDA and MARTA antipsychotics). 5-HT_{2A}/D_2 receptor antagonism increases dopamine release to the PFC and striatum (improvement in negative and cognitive symptoms and lower EPS). Also valid for partial dopamine receptor agonism with 5-HT_{2A} antagonism (aripiprazole)
5-HT_{1A} receptor agonism and blockade of D_2 receptors: increases dopamine release to the PFC, striatum and limbic structures
Blockade of 5-HT_{2C} receptors and blockade of D_2 receptors: analogous to 5-HT_{2A} receptor blockade or its facilitation
Blockade of α-adrenoceptors and D_2 receptors: α_1-adrenoceptor antagonism decreases activity of serotonin projections, and in combination with D_2 receptor blockade would mimic/simulate 5-HT_{2A}/D_2 receptor antagonism. Similarly with α_2-adrenoceptor antagonism
Blockade of D_2 receptors and interaction with muscarinic receptors: lower risk of EPS and probable pro-cognitive effect (acetylcholine stimulation) [?]
Induction of neuroplasticity
Phosphorylation of receptors, potentiation of glutamate/glycine and induction of neuronal growth factors (NGF and BDNF): reinforcement of NMDA receptor activity and development of new synapses or their remodelling

BDNF = brain-derived neurotrophic factor; **EPS** = extrapyramidal syndrome; **MARTA** = multi-acting receptor targeted antipsychotics; **NGF** = nerve growth factor; **PFC** = prefrontal cortex; **SDA** = serotonin-dopamine antagonists.

and 5-HT_{2C} receptors may accommodate the aim of higher dopamine output in the striatum and prefrontal cortex (figure 3). These mechanisms are consistent with the proposed anatomically selective effect of atypical antipsychotics.[162,163] The concept of regional selectivity assumes that blockade of D_2-like receptors in the limbic areas (temporal cortex, thalamus) reduces positive symptoms with a minimal blockade of striatal D_2 receptors, thereby minimising the incidence of EPS. This theory is supported by neuroimaging studies, which found a lower occupancy of striatal D_2-like receptors in patients treated with atypical antipsychotics in comparison to patients treated with haloperidol but with the same occupancy of D_2-like receptors in the temporal cortex.[164,165] This theory has been impeached by other authors, who suggest that it is the result of a methodological error caused by a non-equipotent dosage comparison between conventional and atypical antipsychotics.[166,167] The effect on negative and cognitive symptoms is induced by dopamine output into the prefrontal cortex. In this area, dopamine may optimise information processing or possibly compensate for information process-

ing deficits caused by neurodevelopmental damage to pyramidal glutamatergic neuronal networks.

The open question is whether the effects of antipsychotics on various monoaminergic receptors (such as D_2, 5-HT_{2A}, 5-HT_{1A}, 5-HT_{2C}, α_1, etc.) are therapeutically complementary or additive. This matter may be resolved by more trials with ligands specific for subtypes of receptors. Clarification is also necessary in terms of distinguishing between acute, subchronic and chronic effects of drugs and subsequent changes in receptor expression in relation to the onset of the clinical effect. This topic deserves particular scrutiny in the field of partial agonists.

The monoaminergic modulations caused by antipsychotics induce neuroplastic changes in the brain through receptor phosphorylation and NGF/BDNF stimulation. Atypical antipsychotic drugs (unlike the conventional antipsychotics) induce remodelling of synapses and neuronal circuits not only in the striatum but also in other areas of the brain, particularly in the prefrontal cortex. Thus, the effect of atypical antipsychotics may hypothetically shift from a neurochemical compensatory effect to a causal influence on the pathophysiological basis of schizophrenia. However, the clinical relevance of the antipsychotic-induced neuroplastic effect must be confirmed. Imaging methods in long-term treatment are very promising in this field. If neuroplastic changes are really essential for beneficial treatment outcomes, alternative methods for inducing them could be tested as monotherapies or in combination with antipsychotics. The unresolved question remains why the compensatory and, especially, causal (neuroplastic) effect of antipsychotics is reversible and hence why, after discontinuation of treatment, the risk of relapse significantly increases.

Acknowledgements

Preparation of this review and our work reviewed in the article was supported by grant NF/7578 – 3 from MZ CR and the research project 1M0517 MSMT CR. The authors have no conflicts of interest that are directly relevant to the content of this review.

References

1. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 1996; 14: 87-96
2. Roth BL, Sheffler D, Potkin SG. Atypical antipsychotic drug actions: unitary or multiple mechanisms for "atypicality"? Clin Neurosci Res 2003; 3: 108-17
3. Kapur S, Seeman P. Antipsychotic agents differ in how fast they come off the dopamine D2 receptors: implications for atypical antipsychotic action. J Psychiatry Neurosci 2000; 25: 161-6
4. Remington G. Understanding antipsychotic "atypicality": a clinical and pharmacological moving target. J Psychiatry Neurosci 2003; 28: 275-84
5. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. Schizophr Res 1999; 35: 51-68
6. Melkersson K, Dahl ML. Adverse metabolic effects associated with atypical antipsychotics: literature review and clinical implications. Drugs 2004 (7); 64: 701-723
7. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2004; 161: 1-56
8. Tandon R, Jibson MD. Efficacy of newer generation antipsychotics in the treatment of schizophrenia. Psychoneuroendocrinology 2003; 28 Suppl. 1: 9-26
9. Tuunainen A, Wahlbeck K, Gilbody SM. Newer atypical antipsychotic medication versus clozapine for schizophrenia. Cochrane Database Syst Rev 2000; (2): CD000966
10. Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000; 321: 1371-6
11. Leucht S, Wahlbeck K, Hamann J, et al. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet 2003; 361: 1581-9
12. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003; 60: 553-64
13. Kinon BJ, Ahl J, Stauffer VL, et al. Dose response and atypical antipsychotics in schizophrenia. CNS Drugs 2004; 18: 597-616
14. Knable MB, Weinberger DR. Dopamine, the prefrontal cortex and schizophrenia. J Psychopharmacol 1997; 11: 123-31
15. Tzschentke TM. Pharmacology and behavioral pharmacology of the mesocortical dopamine system. Prog Neurobiol 2001; 63: 241-320
16. Vile JM, Strange PG. Atypical antipsychotics: serotonergic mechanisms but don't forget dopamine. J Psychopharmacol 1997; 11: 24-5
17. Seeman P. Atypical antipsychotics: mechanism of action. Can J Psychiatry 2002; 47: 27-38
18. Farde L, Wiesel FA, Jansson P, et al. An open label trial of raclopride in acute schizophrenia: confirmation of D2-dopamine receptor occupancy by PET. Psychopharmacology (Berl) 1988; 94: 1-7
19. Farde L, Nordstrom AL, Halldin C, et al. PET studies of dopamine receptors in relation to antipsychotic drug treatment. Clin Neuropharmacol 1992; 15 Suppl. 1 Pt A: 468-9A
20. Goyer PF, Berridge MS, Morris ED, et al. PET measurement of neuroreceptor occupancy by typical and atypical neuroleptics. J Nucl Med 1996; 37: 1122-7

21. Kapur S, Zipursky RB, Remington G. Clinical and theoretical implications of 5-HT2 and D2 receptor occupancy of clozapine, risperidone, and olanzapine in schizophrenia. Am J Psychiatry 1999; 156: 286-93
22. Kapur S. Neuroimaging and drug development: an algorithm for decision making. J Clin Pharmacol 2001 Jul; Suppl.: 64-71S
23. Sedvall G, Pauli S, Karlsson P, et al. PET imaging of neuroreceptors in schizophrenia. Eur Neuropsychopharmacol 1995; 5 Suppl.: 25-30
24. Lynch MR. Schizophrenia and the D1 receptor: focus on negative symptoms. Prog Neuropsychopharmacol Biol Psychiatry 1992; 16: 797-832
25. Sawaguchi T, Goldman-Rakic PS. D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 1991; 251: 947-50
26. Weinberger DR. The biological basis of schizophrenia: new directions. J Clin Psychiatry 1997; 58 Suppl. 10: 22-7
27. Kane JM, McGlashan TH. Treatment of schizophrenia. Lancet 1995; 346: 820-5
28. Seeman P. Antypsychotic drugs, dopamine receptors, and schizophrenia. Clin Neurosci Res 2001; 1: 53-60
29. Waddington JL. Therapeutic potential of selective D-1 dopamine receptor agonists and antagonists in psychiatry and neurology. Gen Pharmacol 1988; 19: 55-60
30. Den Boer JA, van Megen HJ, Fleischhacker WW, et al. Differential effects of the D1-DA receptor antagonist SCH39166 on positive and negative symptoms of schizophrenia. Psychopharmacology (Berl) 1995; 121: 317-22
31. Labelle A, de Beaurepaire R, Boulay LJ, et al. A pilot study of the safety and tolerance of SCH 39166 in patients with schizophrenia. J Psychiatry Neurosci 1998; 23: 93-4
32. Castner SA, Williams GV, Goldman-Rakic PS. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. Science 2000; 287: 2020-2
33. Goldman-Rakic P. The relevance of the dopamine-D1 receptor in the cognitive symptoms of schizophrenia. Neuropsychopharmacology 1999; 21: S170-80
34. Wong AH, Van Tol HH. The dopamine D4 receptors and mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27: 1091-9
35. Broderick PA, Piercey MF. Clozapine, haloperidol, and the D4 antagonist PNU-101387G: in vivo effects on mesocortical, mesolimbic, and nigrostriatal dopamine and serotonin release. J Neural Transm 1998; 105: 749-67
36. Seeman P. Dopamine receptor sequences. Therapeutic levels of neuroleptics occupy D2 receptors, clozapine occupies D4. Neuropsychopharmacology 1992; 7: 261-84
37. Van Tol HH, Bunzow JR, Guan HC, et al. Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. Nature 1991; 350: 610-4
38. Kramer MS, Last B, Getson A, et al. The effects of a selective D4 dopamine receptor antagonist (L-745,870) in acutely psychotic inpatients with schizophrenia. D4 Dopamine Antagonist Group. Arch Gen Psychiatry 1997; 54: 567-72
39. Scatton B, Claustre Y, Cudennec A, et al. Amisulpride: from animal pharmacology to therapeutic action. Int Clin Psychopharmacol 1997; 12 Suppl. 2: S29-36
40. Bressan RA, Erlandsson K, Jones HM, et al. Is regionally selective D2/D3 dopamine occupancy sufficient for atypical antipsychotic effect? An in vivo quantitative [123I]epidepride SPET study of amisulpride-treated patients. Am J Psychiatry 2003; 160: 1413-20
41. Leucht S, Pitschel-Walz G, Engel RR, et al. Amisulpride, an unusual "atypical" antipsychotic: a meta-analysis of randomized controlled trials. Am J Psychiatry 2002; 159: 180-90
42. McKeage K, Plosker GL. Amisulpride: a review of its use in the management of schizophrenia. CNS Drugs 2004; 18: 933-56
43. Moller HJ. Amisulpride: limbic specificity and the mechanism of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27: 1101-11
44. Laruelle M, D'Souza CD, Baldwin RM, et al. Imaging D2 receptor occupancy by endogenous dopamine in humans. Neuropsychopharmacology 1997; 17: 162-74
45. Kapur S, Seeman P. Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics? A new hypothesis. Am J Psychiatry 2001; 158: 360-9
46. Ozdemir V, Fourie J, Ozdener F. Aripiprazole (Otsuka Pharmaceutical Co.). Curr Opin Investig Drugs 2002; 3: 113-20
47. Dean B, Scarr E. Antipsychotic drugs: evolving mechanisms of action with improved therapeutic benefits. Curr Drug Targets CNS Neurol Disord 2004; 3: 217-25
48. Burris KD, Molski TF, Xu C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D2 receptors. J Pharmacol Exp Ther 2002; 302: 381-9
49. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. CNS Drugs 2004; 18: 251-67
50. Jordan S, Koprivica V, Chen R, et al. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. Eur J Pharmacol 2002; 441: 137-40
51. Jordan S, Koprivica V, Dunn R, et al. In vivo effects of aripiprazole on cortical and striatal dopaminergic and serotonergic function. Eur J Pharmacol 2004; 483: 45-53
52. Grunder G, Carlsson A, Wong DF. Mechanism of new antipsychotic medications: occupancy is not just antagonism. Arch Gen Psychiatry 2003; 60: 974-7
53. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 2003; 60: 681-90
54. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003; 28: 1400-11
55. Barbier P, Colelli A, Maggio R, et al. Pergolide binds tightly to dopamine D2 short receptors and induces receptor sequestration. J Neural Transm 1997; 104: 867-74
56. Peroutka SJ. Molecular biology of serotonin (5-HT) receptors. Synapse 1994; 18: 241-60
57. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans: psychotomimetic, perceptual, cognitive, and neuroendocrine responses. Arch Gen Psychiatry 1994; 51: 199-214
58. Vollenweider FX. Advances and pathophysiological models of hallucinogenic drug actions in humans: a preamble to schizophrenia research. Pharmacopsychiatry 1998; 31 Suppl. 2: 92-103
59. Willins DL, Deutch AY, Roth BL. Serotonin 5-HT2A receptors are expressed on pyramidal cells and interneurons in the rat cortex. Synapse 1997; 27: 79-82
60. Jakab RL, Goldman-Rakic PS. 5-Hydroxytryptamine2A serotonin receptors in the primate cerebral cortex: possible site of action of hallucinogenic and antipsychotic drugs in pyramidal cell apical dendrites. Proc Natl Acad Sci U S A 1998; 95: 735-40

61. Martin P, Waters N, Schmidt CJ, et al. Rodent data and general hypothesis: antipsychotic action exerted through 5-Ht2A receptor antagonism is dependent on increased serotonergic tone. J Neural Transm 1998; 105: 365-96
62. Abi-Saab W, Seibyl JP, D'Souza DC, et al. Ritanserin antagonism of m-chlorophenylpiperazine effects in neuroleptic-free schizophrenics patients: support for serotonin-2 receptor modulation of schizophrenia symptoms. Psychopharmacology (Berl) 2002; 162: 55-62
63. Wiesel FA, Nordstrom AL, Farde L, et al. An open clinical and biochemical study of ritanserin in acute patients with schizophrenia. Psychopharmacology (Berl) 1994; 114: 31-8
64. Doherty MD, Pickel VM. Ultrastructural localization of the serotonin 2A receptor in dopaminergic neurons in the ventral tegmental area. Brain Res 2000; 864: 176-85
65. Meltzer HY, Li Z, Kaneda Y, et al. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27: 1159-72
66. Bubser M, Backstrom JR, Sanders-Bush E, et al. Distribution of serotonin 5-HT(2A) receptors in afferents of the rat striatum. Synapse 2001; 39: 297-304
67. Umbricht D, Kane JM. Understanding the relationship between extrapyrimidal side effects and tardive dyskinesia. In: Kane JM, Moller HJ, Awouters E, editors. Serotonergic mechanisms in antipsychotic treatment. New York: Marcel Dekker, 1996: 221-51
68. Gill HS, DeVane CL, Risch SC. Extrapyramidal symptoms associated with cyclic antidepressant treatment: a review of the literature and consolidating hypotheses. J Clin Psychopharmacol 1997; 17: 377-89
69. Leysen JE. 5-HT2 receptors. Curr Drug Targets CNS Neurol Disord 2004; 3: 11-26
70. Di Matteo V, De Blasi A, Giulio C, et al. Role of 5-HT(2C) receptors in the control of central dopamine function [abstract]. Trends Pharmacol Sci 2001; 22: 229-32
71. Hutson PH, Barton CL, Jay M, et al. Activation of mesolimbic dopamine function by phencyclidine is enhanced by 5-HT(2C/2B) receptor antagonists: neurochemical and behavioural studies. Neuropharmacology 2000; 39: 2318-28
72. Ichikawa J, Ishii H, Bonaccorso S, et al. 5-HT(2A) and D(2) receptor blockade increases cortical DA release via 5-HT(1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem 2001; 76: 1521-31
73. Meltzer HY, Matsubara S, Lee JC. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. J Pharmacol Exp Ther 1989; 251: 238-46
74. Meltzer HY, Matsubara S, Lee JC. The ratios of serotonin2 and dopamine2 affinities differentiate atypical and typical antipsychotic drugs. Psychopharmacol Bull 1989; 25: 390-2
75. Kapur S, Remington G. Serotonin-dopamine interaction and its relevance to schizophrenia. Am J Psychiatry 1996; 153: 466-76
76. Yan QS. Activation of 5-HT2A/2C receptors within the nucleus accumbens increases local dopaminergic transmission. Brain Res Bull 2000; 51: 75-81
77. Pehek EA, McFarlane HG, Maguschak K, et al. M100,907, a selective 5-HT(2A) antagonist, attenuates dopamine release in the rat medial prefrontal cortex. Brain Res 2001; 888: 51-9
78. Liegeois JF, Ichikawa J, Meltzer HY. 5-HT(2A) receptor antagonism potentiates haloperidol-induced dopamine release in rat medial prefrontal cortex and inhibits that in the nucleus accumbens in a dose-dependent manner. Brain Res 2002; 947: 157-65
79. Bubeníková V, Horáček J, Kožený J, et al. The effect of tryptophan depletion on the action of haloperidol in MK-801-treated rats. Eur J Pharmacol 2004; 502: 109-16
80. Páleníček T, Horáček J, Bubeníková V. Effects of haloperidol on locomotion in animal model of schizophrenia induced by MK-801. Psychiatrie 2003; 7: 50-4
81. Páleníček T, Horáček J, Bubeníková V, et al. Effects of 5-HT1a receptor agonist 8-OH-DPAT and D2 receptor antagonist haloperidol on locomotion: animal model of schizophrenia [abstract]. Schizophr Res 2004; 67 (1 Suppl.): 122
82. Palenicek T, Bubenikova V, Horacek J, et al. Atypicka antipsychotika: 5-HT2A antagonismus nebo 5HT1a agonismus [abstract]. In: Raboch J, Doubek P, Zrzavecka I, editors. Psychiatrie v medicine a medicina v psychiatrii. Praha: Galen, 2002: 165.
83. Palenicek T, Bubenikova V, Horacek J, et al. The effect of 5-HT_{1C} antagonism (SB242084) in the animal model of schizophrenia (MK-801). Prague: Centre of Neuropsychiatric Studies, 2005. (Data on file)
84. Seeman P, Van Tol HH. Dopamine receptor pharmacology. Trends Pharmacol Sci 1994; 15: 264-70
85. Ichikawa J, Meltzer HY. The effect of chronic clozapine and haloperidol on basal dopamine release and metabolism in rat striatum and nucleus accumbens studied by in vivo microdialysis. Eur J Pharmacol 1990; 176: 371-4
86. Gray JA, Roth BL. Paradoxical trafficking and regulation of 5-HT(2A) receptors by agonists and antagonists. Brain Res Bull 2001; 56: 441-51
87. Gray JA, Sheffler DJ, Bhatnagar A, et al. Cell-type specific effects of endocytosis inhibitors on 5-hydroxytryptamine(2A) receptor desensitization and resensitization reveal an arrestin-, GRK2-, and GRK5-independent mode of regulation in human embryonic kidney 293 cells. Mol Pharmacol 2001; 60: 1020-30
88. Gobert A, Rivet JM, Lejeune F, et al. Serotonin(2C) receptors tonically suppress the activity of mesocortical dopaminergic and adrenergic, but not serotonergic, pathways: a combined dialysis and electrophysiological analysis in the rat. Synapse 2000; 36: 205-21
89. Millan MJ, Dekeyne A, Gobert A. Serotonin (5-HT)2C receptors tonically inhibit dopamine (DA) and noradrenaline (NA), but not 5-HT, release in the frontal cortex in vivo. Neuropharmacology 1998; 37: 953-5
90. Bonaccorso S, Meltzer HY, Li Z, et al. SR46349-B, a 5-HT(2A/2C) receptor antagonist, potentiates haloperidol-induced dopamine release in rat medial prefrontal cortex and nucleus accumbens. Neuropsychopharmacology 2002; 27: 430-41
91. Reavill C, Kettle A, Holland V, et al. Attenuation of haloperidol-induced catalepsy by a 5-HT2C receptor antagonist. Br J Pharmacol 1999; 126: 572-4
92. Ellingrod VL, Perry PJ, Ringold JC, et al. Weight gain associated with the -759C/T polymorphism of the 5HT2C receptor and olanzapine. Am J Med Genet B Neuropsychiatr Genet 2005; 134: 76-8
93. Miller DD, Ellingrod VL, Holman TL, et al. Clozapine-induced weight gain associated with the 5HT2C receptor -759C/T polymorphism. Am J Med Genet B Neuropsychiatr Genet 2005; 133: 97-100
94. Sakaue M, Somboonthum P, Nishihara B, et al. Postsynaptic 5-hydroxytryptamine(1A) receptor activation increases in vivo dopamine release in rat prefrontal cortex. Br J Pharmacol 2000; 129: 1028-34

95. Konradi C, Heckers S. Antipsychotic drugs and neuroplasticity: insights into the treatment and neurobiology of schizophrenia. Biol Psychiatry 2001; 50: 729-42
96. Levey AI. Immunological localization of m1-m5 muscarinic acetylcholine receptors in peripheral tissues and brain. Life Sci 1993; 52: 441-8
97. Bymaster FP, Felder CC, Tzavara E, et al. Muscarinic mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27: 1125-43
98. Snyder S, Greenberg D, Yamamura HI. Antischizophrenic drugs and brain cholinergic receptors: affinity for muscarinic sites predicts extrapyramidal effects. Arch Gen Psychiatry 1974; 31: 58-61
99. Parada MA, Hernandez L, Puig DP, et al. Selective action of acute systemic clozapine on acetylcholine release in the rat prefrontal cortex by reference to the nucleus accumbens and striatum. J Pharmacol Exp Ther 1997; 281: 582-8
100. Martin LF, Kem WR, Freedman R. Alpha-7 nicotinic receptor agonists: potential new candidates for the treatment of schizophrenia. Psychopharmacology (Berl) 2004; 174: 54-64
101. Chiodo LA, Bunney BS. Possible mechanisms by which repeated clozapine administration differentially affects the activity of two subpopulations of midbrain dopamine neurons. J Neurosci 1985; 5: 2539-44
102. Lane RF, Blaha CD, Rivet JM. Selective inhibition of mesolimbic dopamine release following chronic administration of clozapine: involvement of alpha 1-noradrenergic receptors demonstrated by in vivo voltammetry. Brain Res 1988; 460: 398-401
103. Lejeune F, Audinot V, Gobert A, et al. Clozapine inhibits serotoninergic transmission by an action at alpha 1-adrenoceptors not at 5-HT1A receptors. Eur J Pharmacol 1994; 260: 79-83
104. Kalkman HO. The role of alpha2-adrenoceptor antagonism in the anti-cataleptic properties of the atypical neuroleptic agent, clozapine, in the rat. Br J Pharmacol 1998 Aug; 124 (7): 1550-6
105. Horacek J. Schizophrenia as the deficit of information processing [in Czech]. Psychiatrie 2001; 5 (2 Suppl.): 43-4
106. Glantz LA, Lewis DA. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Arch Gen Psychiatry 2000; 57: 65-73
107. Bartzokis G. Schizophrenia: breakdown in the well-regulated lifelong process of brain development and maturation. Neuropsychopharmacology 2002; 27: 672-83
108. DeLisi LE, Hoff AL, Schwartz JE, et al. Brain morphology in first-episode schizophrenic-like psychotic patients: a quantitative magnetic resonance imaging study. Biol Psychiatry 1991; 29: 159-175
109. Weinberger DR, Egan MF, Bertolino A, et al. Prefrontal neurons and the genetics of schizophrenia. Biol Psychiatry 2001; 50: 825-44
110. Marenco S, Weinberger DR. The neurodevelopmental hypothesis of schizophrenia: following a trail of evidence from cradle to grave. Dev Psychopathol 2000; 12: 501-527
111. Selemon LD, Rajkowska G, Goldman-Rakic PS. Abnormally high neuronal density in the schizophrenic cortex: a morphometric analysis of prefrontal area 9 and occipital area 17. Arch Gen Psychiatry 1995; 52: 805-18
112. Selemon LD, Mrzljak J, Kleinman JE, et al. Regional specificity in the neuropathologic substrates of schizophrenia: a morphometric analysis of Broca's area 44 and area 9. Arch Gen Psychiatry 2003; 60: 69-77
113. Davis KL, Stewart DG, Friedman JI, et al. White matter changes in schizophrenia: evidence for myelin-related dysfunction. Arch Gen Psychiatry 2003; 60: 443-56
114. Tkachev D, Mimmack ML, Ryan MM, et al. Oligodendrocyte dysfunction in schizophrenia and bipolar disorder. Lancet 2003; 362: 798-805
115. Cohen JD, Servan-Schreiber D. Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychol Rev 1992; 99: 45-77
116. Cohen JD, Braver TS, Brown JW. Computational perspectives on dopamine function in prefrontal cortex. Curr Opin Neurobiol 2002; 12: 223-9
117. Spitzer M. A neurocomputational approach to delusions. Compr Psychiatry 1995; 36: 83-105
118. Heresco-Levy U. Glutamatergic neurotransmission modulation and the mechanisms of antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27: 1113-23
119. Millan MJ. N-Methyl-D-aspartate receptors as a target for improved antipsychotic agents: novel insights and clinical perspectives. Psychopharmacology (Berl) 2005; 179: 30-53
120. Goldman-Rakic PS, Muly EC, Williams GV. D(1) receptors in prefrontal cells and circuits. Brain Res Brain Res Rev 2000; 31: 295-301
121. Kuroki T, Meltzer HY, Ichikawa J. Effects of antipsychotic drugs on extracellular dopamine levels in rat medial prefrontal cortex and nucleus accumbens. J Pharmacol Exp Ther 1999; 288: 774-81
122. Angelucci F, Aloe L, Gruber SH, et al. Chronic antipsychotic treatment selectively alters nerve growth factor and neuropeptide Y immunoreactivity and the distribution of choline acetyl transferase in rat brain regions. Int J Neuropsychopharmacol 2000; 3: 13-25
123. Ozaki T. Comparative effects of dopamine D(1) and D(2) receptor antagonists on nerve growth factor protein induction. Eur J Pharmacol 2000; 402: 39-44
124. Ozaki T, Mui K, Yamagami S. Comparison of the effects of dopamine D1 and D2 receptor antagonists on nerve growth factor mRNA expression. Eur J Pharmacol 1999; 369: 133-43
125. Chakos MH, Lieberman JA, Alvir J, et al. Caudate nuclei volumes in schizophrenic patients treated with typical antipsychotics or clozapine. Lancet 1995; 345: 456-7
126. Chakos MH, Lieberman JA, Bilder RM, et al. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. Am J Psychiatry 1994; 151: 1430-6
127. Angelucci F, Mathe AA, Aloe L. Neurotrophic factors and CNS disorders: findings in rodent models of depression and schizophrenia. Prog Brain Res 2004; 146: 151-65
128. Bilder RM, Wu H, Chakos MH, et al. Cerebral morphometry and clozapine treatment in schizophrenia. J Clin Psychiatry 1994; 55 Suppl. B: 53-6
129. Konradi C, Heckers S. Molecular aspects of glutamate dysregulation: implications for schizophrenia and its treatment. Pharmacol Ther 2003; 97: 153-79
130. Gandolfi O, Dall'Olio R. Modulatory role of dopamine on excitatory amino acid receptors. Prog Neuropsychopharmacol Biol Psychiatry 1996; 20: 659-71
131. Ossowska K, Pietraszek M, Wardas J, et al. Chronic haloperidol and clozapine administration increases the number of cortical NMDA receptors in rats. Naunyn Schmiedebergs Arch Pharmacol 1999; 359: 280-7
132. Pietraszek M. Significance of dysfunctional glutamatergic transmission for the development of psychotic symptoms. Pol J Pharmacol 2003; 55: 133-54

133. Angelucci F, Mathe AA, Aloe L. Brain-derived neurotrophic factor and tyrosine kinase receptor TrkB in rat brain are significantly altered after haloperidol and risperidone administration. J Neurosci Res 2000; 60: 783-94
134. Chlan-Fourney J, Ashe P, Nylen K, et al. Differential regulation of hippocampal BDNF mRNA by typical and atypical antipsychotic administration. Brain Res 2002; 954: 11-20
135. Bai O, Chlan-Fourney J, Bowen R, et al. Expression of brain-derived neurotrophic factor mRNA in rat hippocampus after treatment with antipsychotic drugs. J Neurosci Res 2003; 71: 127-31
136. Parikh V, Khan MM, Mahadik SP. Olanzapine counteracts reduction of brain-derived neurotrophic factor and TrkB receptors in rat hippocampus produced by haloperidol. Neurosci Lett 2004; 356: 135-9
137. Kahn R, Lieberman J, Charles C, et al. Antipsychotic treatment effects on progression of brain pathomorphology in first episode schizophrenia [abstract]. 16th Annual European College of Neuropsychopharmacology; 2002 Sep 20-24; Prague
138. Lieberman JA, Tollefson GD, Charles C, et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. Arch Gen Psychiatry 2005; 62: 361-70
139. Castren E, da Penha BM, Lindholm D, et al. Differential effects of MK-801 on brain-derived neurotrophic factor mRNA levels in different regions of the rat brain. Exp Neurol 1993; 122: 244-52
140. Fumagalli F, Molteni R, Roceri M, et al. Effect of antipsychotic drugs on brain-derived neurotrophic factor expression under reduced N-methyl-D-aspartate receptor activity. J Neurosci Res 2003; 72: 622-8
141. Vaidya VA, Terwilliger RM, Duman RS. Role of 5-HT2A receptors in the stress-induced down-regulation of brain-derived neurotrophic factor expression in rat hippocampus. Neurosci Lett 1999; 262: 1-4
142. Vaidya VA, Marek GJ, Aghajanian GK, et al. 5-HT2A receptor-mediated regulation of brain-derived neurotrophic factor mRNA in the hippocampus and the neocortex. J Neurosci 1997; 17: 2785-95
143. Meredith GE, Switzer RC, Napier TC. Short-term, D2 receptor blockade induces synaptic degeneration, reduces levels of tyrosine hydroxylase and brain-derived neurotrophic factor, and enhances D2-mediated firing in the ventral pallidum. Brain Res 2004; 995: 14-22
144. Chlan-Fourney J, Ashe P, Nylen K, et al. Differential regulation of hippocampal BDNF mRNA by typical and atypical antipsychotic administration. Brain Res 2002; 954: 11-20
145. Hoffman RE, McGlashan TH. Parallel distributed processing and the emergence of schizophrenic symptoms. Schizophr Bull 1993; 19: 119-40
146. Fumagalli F, Molteni R, Bedogni F, et al. Quetiapine regulates FGF-2 and BDNF expression in the hippocampus of animals treated with MK-801. Neuroreport 2004; 15: 2109-12
147. Harrison PJ. The neuropathological effects of antipsychotic drugs. Schizophr Res 1999; 40: 87-99
148. Dalgalarrondo P, Gattaz WF. Basal ganglia abnormalities in tardive dyskinesia: possible relationship with duration of neuroleptic treatment. Eur Arch Psychiatry Clin Neurosci 1994; 244: 272-7
149. Mion CC, Andreasen NC, Arndt S, et al. MRI abnormalities in tardive dyskinesia. Psychiatry Res 1991; 40: 157-66
150. Robertson GS, Fibiger HC. Effects of olanzapine on regional C-Fos expression in rat forebrain. Neuropsychopharmacology 1996; 14: 105-10
151. Robertson GS, Matsumura H, Fibiger HC. Induction patterns of Fos-like immunoreactivity in the forebrain as predictors of atypical antipsychotic activity. J Pharmacol Exp Ther 1994; 271: 1058-66
152. Robertson GS, Fibiger HC. Neuroleptics increase c-fos expression in the forebrain: contrasting effects of haloperidol and clozapine. Neuroscience 1992; 46: 315-28
153. Leveque JC, Macias W, Rajadhyaksha A, et al. Intracellular modulation of NMDA receptor function by antipsychotic drugs. J Neurosci 2000; 20: 4011-20
154. Duman RS, Malberg J, Thome J. Neural plasticity to stress and antidepressant treatment. Biol Psychiatry 1999; 46: 1181-91
155. Dawirs RR, Hildebrandt K, Teuchert-Noodt G. Adult treatment with haloperidol increases dentate granule cell proliferation in the gerbil hippocampus. J Neural Transm 1998; 105: 317-27
156. Halim ND, Weickert CS, McClintock BW, et al. Effects of chronic haloperidol and clozapine treatment on neurogenesis in the adult rat hippocampus. Neuropsychopharmacology 2004; 29: 1063-9
157. Luo C, Xu H, Li XM. Quetiapine reverses the suppression of hippocampal neurogenesis caused by repeated restraint stress. Brain Res 2005; 1063: 32-9
158. Kodama M, Fujioka T, Duman RS. Chronic olanzapine or fluoxetine administration increases cell proliferation in hippocampus and prefrontal cortex of adult rat. Biol Psychiatry 2004; 56: 570-80
159. Wang HD, Dunnavant FD, Jarman T, et al. Effects of antipsychotic drugs on neurogenesis in the forebrain of the adult rat. Neuropsychopharmacology 2004; 29: 1230-8
160. Schmitt A, Weber S, Jatzko A, et al. Hippocampal volume and cell proliferation after acute and chronic clozapine or haloperidol treatment. J Neural Transm 2004; 111: 91-100
161. Wakade CG, Mahadik SP, Waller JL, et al. Atypical neuroleptics stimulate neurogenesis in adult rat brain. J Neurosci Res 2002; 69: 72-9
162. Xiberas X, Martinot JL, Mallet L, et al. Extrastriatal and striatal D(2) dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. Br J Psychiatry 2001; 179: 503-8
163. Horacek J. Novel antipsychotics and extrapyramidal side effects: theory and reality. Pharmacopsychiatry 2000; 33 Suppl. 1: 34-42
164. Xiberas X, Martinot JL, Mallet L, et al. Extrastriatal and striatal D(2) dopamine receptor blockade with haloperidol or new antipsychotic drugs in patients with schizophrenia. Br J Psychiatry 2001; 179: 503-8
165. Pilowsky LS, O'Connell P, Davies N, et al. In vivo effects on striatal dopamine D2 receptor binding by the novel atypical antipsychotic drug sertindole: a 123I IBZM single photon emission tomography (SPET) study. Psychopharmacology (Berl) 1997; 130: 152-8
166. Nyberg S, Farde L. Non-equipotent doses partly explain differences among antipsychotics: implications of PET studies. Psychopharmacology (Berl) 2000; 148: 22-3
167. Kopecek M, Hoschl C, Hajek T. Regional selectivity of novel antipsychotics. Br J Psychiatry 2002; 181: 254-5

Correspondence and offprints: Dr *Jiri Horacek*, Prague Psychiatric Centre, Ùstavni 91, Prague 8, 181 00, Czech Republic.
E-mail: horacek@PCP.LF3.CUNI.CZ