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SPECIAL ISSUE

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Antipsychotic and antidepressive effects of second generation antipsychotics

Two different pharmacological mechanisms?

Abstract Second generation antipsychotics display antidepressive effects in schizophrenic patients that are more pronounced than those of traditional neuroleptics and that go beyond antidepressive effects secondary to the reduction of positive symptoms. The antidepressive potential of second generation antipsychotics is presumably related to their pharmacological mechanisms, which differ from those of traditional neuroleptics. Among others, 5-HT_{2A} antagonism is of special relevance for most of the new antipsychotics in this respect. But also special interactions with the dopaminergic system, as is the case with amisulpride and aripiprazole, or noradrenalin- and/or serotonin-reuptake-inhibition, as with ziprasidone and zotepine, should be considered. It can be summarised that the antipsychotic and antidepressive effects of second generation antipsychotics are mostly based on different pharmacological mechanisms. This might be especially true for direct antidepressive effects, i. e. antidepressive effects that are not mediated by the reduction of positive symptoms.

Key words second generation antipsychotics · antidepressive efficacy · schizophrenia · depression

Introduction

Depressive symptoms during schizophrenic psychoses represent an important part of the overall spectrum of psychopathological symptoms, not only in the schizoaffective types but also in the core groups of schizophrenic psychoses diagnosed according to ICD-10 or DSM-IV (Bottlender et al. 2000; Häfner et al. 1999; Wassink et al. 1999).

For a long time traditional neuroleptics were mostly discussed with respect to possible depressiogenic side effects, although there were reports that traditional neuroleptics may also have certain antidepressive effects. Studies performed in recent years have shown that second generation antipsychotics have antidepressive effects which are significantly stronger than those of the traditional antipsychotics (Möller 2005). In addition, it was demonstrated that this antidepressive effect can only partially be explained as being secondary to the improvement of positive symptoms, and is apparently predominantly due to a direct (primary) effect on depressive symptoms. It is of special relevance in this context that the antidepressive effect of atypical neuroleptics was recently demonstrated in depression. Especially the positive results from some studies in bipolar depression are impressive.

According to the data available so far (Möller 2000a), the second generation antipsychotics appear to represent a new option for the treatment of depressive symptoms in schizophrenia. This seems to be of special importance given the fact that the efficacy of treatment with antidepressants is limited and furthermore, particularly when SSRIs are used, there is a risk of pharmacokinetic interactions (Siris and Bench 2003; Whitehead et al. 2002).

The expectations concerning an antidepressive effect of novel neuroleptics are based on theoretical deliberations. These are derived from the pharmacological mechanisms of the novel neuroleptics, which differ from those of the classical neuroleptics. Especially antipsychotics with a multireceptor profile have stimulated the formulation of such hypotheses. However, antidepressive efficacy also appears to be theoretically explainable for amisulpride, a selective D_2/D_3 antagonist with balanced pre- and postsynaptic effects, and for aripiprazole with its predominant partial agonism at dopaminergic receptors.

Given the great relevance of this issue, this paper will

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review the current pharmacological knowledge, focussing among others on the question whether the antipsychotic and antidepressive effects are based on different biological mechanisms.

Classical neuroleptics: D_2 receptor antagonism as the pharmacological basis for the effects on positive symptoms, and its relationship to depressive symptoms

It has been known for a long time that the postsynaptic blockade of the dopaminergic D_2 receptor is the pharmacological basis for the antipsychotic effect of neuroleptics, especially their effect on positive symptoms. Data, especially those available for the traditional neuroleptics, show that there is a close relationship between D_2 blockade and the effects on positive symptoms (Farde et al. 1992; Seeman et al. 1977). There is not a single neuroleptic which does not block postsynaptic dopaminergic D_2 receptors. The blocking effect on postsynaptic D_2 receptors in the limbic system is seen as the biological correlate of the antipsychotic efficacy, while the D_2 blockade in the nigrostriatal system is related to extrapyramidal-motor side effects (EPS).

There are several clinical observations that traditional neuroleptics, especially strong D_2-receptor blockers such as haloperidol, can induce depressive symptoms (Awad 1993; Browne et al. 1998). Such observations were published in the early stages of the classical neuroleptics under different concepts such as 'pharmacogenic depression', 'akinetic depression', 'neuroleptic-induced dysphoria' and 'postpsychotic depression' (Helmchen and Hippius 1967; McGlashan and Carpenter 1976; Rifkin et al. 1975; Van Putten and May 1978). Especially the concept of 'akinetic depression' focuses on an association of parkinsonian effects and depression (Rifkin et al. 1975). All together, a depressiogenic effect of traditional neuroleptics, especially by the strong and more-or-less selective D_2-blockers such as haloperidol, which block all dopaminergic pathways in the brain in an indifferent manner, seems plausible on a theoretical level because neuroleptic medications block dopamine receptors, and dopamine receptors are known to be involved in brain pathways which mediate 'reward' (Harrow et al. 1994; Wise 1982). This was demonstrated convincingly in animal research, where for example raclopride and haloperidol, which have higher affinities for D_2 receptors, reduced the rewarding effect, while D_3 and D_4 antagonists had no influence on it (Nakajima and Patterson 1997). The reasoning is that if a neuroleptic interfered with the experience of reward or pleasure, the resultant experience of relative anhedonia could become a phenocopy of a depressed state (Siris and Bench 2003).

Indeed, clinical evidence for the depression-inducing effect of traditional neuroleptics could be demonstrated. However, it was not possible to attribute all depressions present after easing off of the acute psychosis to the neuroleptic treatment alone (Möller et al. 1985; Möller and von Zerssen 1982, 1986). Overall the picture of depressive symptoms during schizophrenia, the possible causal factors and differential diagnosis is very complex. Nevertheless, the possibility that depression may be caused by traditional neuroleptics, at least in a subgroup of patients, should still be seen as a clinically relevant problem (Awad 1993; Browne et al. 1998; Siris and Bench 2003). This assumption is supported by the studies mentioned above as well as some other studies from the early phases of neuroleptic treatment (e. g. De Alarcon and Carney 1969; Floru et al. 1975; Galdi et al. 1981; Galdi 1983; Johnson 1981). Two studies from the 1990s also deliver further indications in this direction: A large prospective study found that patients who were maintained on neuroleptic medication manifested more depression than those who were randomised to receive neuroleptic medication only on an 'early intervention' or 'crisis intervention' basis, and patients in that study were found to have lower depression ratings after being taken off neuroleptic medication (Bandelow et al. 1992). Another well-designed study specifically comparing anhedonia in schizophrenic patients on versus off neuroleptics found significantly more anhedonia as well as more depression in those patients who were being treated with neuroleptics (Harrow et al. 1994). At least one study did find a positive relationship between haloperidol plasma levels and depressive symptoms in the context of a positive association between extrapyramidal and depressive symptoms (Krakowski et al. 1997), and another study found a trend level association between the degree of depression and neuroleptic dose (Perenyi et al. 1998).

Without denying a depressiogenic effect of the traditional neuroleptics seen in a subgroup of schizophrenic patients, in general, traditional neuroleptics have a certain antidepressive effect at least in acute schizophrenic patients, apparently resolving depressive symptoms that accompany positive symptoms (Knights and Hirsch 1981; Möller et al. 1985; Möller and von Zerssen 1982, 1986). Unfortunately this antidepressive effect was not very well evaluated, especially not in a placebo-controlled manner, until the time that traditional neuroleptics such as haloperidol were used as the standard comparator in clinical trials on novel neuroleptics. Thus most of the earlier evidence was obtained from naturalistic studies. The placebo-controlled comparator studies performed in the past decade could confirm this antidepressive effect, however, they also demonstrated that second generation antipsychotics are superior in this respect (Möller 2000a, 2000b, 2005).

There are several pharmacological hypotheses to explain the atypicality (atypicality in the strict sense, i. e. low or no EPS) of the second generation antipsychotics as well as the broader clinical efficacy spectrum including negative symptoms, cognitive disturbances and depressive symptoms (atypicality in the broader sense). The hypothesised mechanisms of atypicality in the stricter or broader sense are more or less related to each other. Although certain mechanisms are apparently

more closely related to antidepressive effects, some more general mechanisms of atypicality might also be relevant for such effects, or at least for the lack of depressiogenic effects. Therefore the pharmacological mechanisms for atypicality in the broader sense also have to be discussed.

In the following, the mechanisms of both atypicality and antidepressive effects that are related only to the dopaminergic system will first be discussed. Thereafter other mechanisms outside the dopaminergic system, especially those related to the serotonergic system, will be covered.

Mechanisms of atypicality/antidepressive activity related to the dopaminergic system

It is known that binding to postsynaptic D_2 receptors obviously correlates directly with the antipsychotic efficacy in treating schizophrenic positive symptoms (Creese et al. 1976; Peroutka and Snyder 1980; Seeman et al. 1976). Today, one distinguishes between a total of five dopamine receptor subtypes. The D_1 and D_5 receptors are combined as the D_1 receptor family, the D_2, D_3 and D_4 receptors as the D_2 receptor family. It was attempted to explain the atypical profile of the newer neuroleptics using characteristics regarding binding to various dopamine receptor subtypes. Amongst other things, a balanced relationship between the blockade of D_1 and D_2 receptors was associated with a better antipsychotic effect, or with a better extrapyramidal-motor tolerability, based on the finding that clozapine blocks D_1 and D_2 receptors to approximately the same degree (Nordström et al. 1993). However, it must be considered that, in contrast to classical neuroleptics such as haloperidol or perphenazine, which hardly block D_1 receptors, there are also traditional neuroleptics, such as flupentixole, for example, which bind equally strongly to D_1 and D_2 receptors. If this hypothesis is assumed, one would expect that blockade of the D_1 receptors would contribute to the effect. However, selective D_1 receptor antagonists (SCH 23390) and selective antagonists of the D_1 and D_5 receptors (SCH 39166) did not show any antipsychotic efficacy in humans, and a certain tendency to extrapyramidal-motor disturbances in animal trials and in humans (Casey 1995; Karlsson et al. 1995; Tice et al. 1994).

Clozapine is a relatively weak D_2 receptor blocker. It preferentially binds to D_4 receptors at therapeutic concentrations. The hypothesis was therefore expressed that this specific dopamine receptor binding profile may possibly be associated with the atypical action profile of this substance. However, some traditional neuroleptics also have a high affinity for D_4 receptors, for example fluphenazine and thioridazine (Roth et al. 1995). Furthermore, not all atypical neuroleptics have a high affinity for D_4 receptors. The question to what extent blocking of the D_4 receptors is important for antipsychotic efficacy can only be clarified using selective D_4 receptor ligands. No antipsychotic efficacy could be demonstrated for fananserin, a selective D_4 and 5-HT_2 blocker (Truffinet et al. 1999). The development of a selective D_4 receptor blocker by the company Merck Sharp & Dohme was discontinued because the substance showed insufficient antipsychotic efficacy. A selective D_4 receptor blocker from the company Pharmacia is still undergoing pre-clinical investigation (Möller 2000a). Based on animal studies the blockade of dopamine D_4 receptors appears not to influence the rewarding effect (Nakajima and Patterson 1997).

Clozapine also has a higher affinity than other neuroleptics for D_3 receptors, although it is lower than its affinity for D_2 receptors. The possible relevance of this characteristic will become apparent when further results from a selective D_3 receptor antagonist, UH232, are available (Lahti et al. 1998; Sotnikova et al. 2001; Taubes 1994). Taken together, the implications of the blockade of D_3 receptors are still unclear (Schwartz et al. 2000). On the basis of animal studies it was suggested that dopamine D_1 and D_2 but not D_3 or D_4 receptors are critically involved in producing the rewarding effect of brain stimulation (Nakajima and Patterson 1997; Nakajima and McKenzie 1986; Shippenberg et al. 1993; Guyon et al. 1993).

A D_2/D_3-only hypothesis had been advanced for atypical antipsychotic drug actions, based in particular on the atypical features of several drugs with predominant actions on D_2- and D_3-dopamine receptors, including the benzamides amisulpride, remoxipride and sulpride (see Curran and Perry 2001). These benzamides are quite remarkable since all drugs of this class are relatively selective for D_2- and D_3-dopamine receptors and are virtually devoid of actions at tested 5-HT receptors, including 5-HT_{2A}. Amisulpride has been best evaluated in this respect. There is good evidence that amisulpride is an atypical neuroleptic (Leucht et al. 2002) and that it has antidepressive effects, especially at lower doses (Möller 2005; Muller et al. 2002; Pani and Gessa 2002; Peuskens et al. 2002). However, it is unclear whether the atypicality of amisulpride is related to the combination of a postsynaptic D_2 and a postsynaptic D_3 blockade (Möller 2003a). This uncertainty is based on the limited knowledge about the impact of D_3 receptors in general. It seems more likely that other mechanisms are prominently relevant for the atypicality of amisulpride (see below).

Aripiprazole is distinct from all other known antipsychotic drugs by virtue of its partial agonism at a number of receptors, including D_2-, D_3- and D_4-dopamine and 5-HT_{1A}-, 5-HT_{2A}, and 5-HT_{2C}-serotonin receptors (Burris et al. 2002; Jordan et al. 2002; Oshiro et al. 1998). In terms of partial agonist actions, aripiprazole is a partial agonist with high efficacy (40–80 % efficacy of full agonist) at D_3-, D_4-dopamine and 5-HT_{1A}- and 5-HT_{2C}-serotonin receptors (< 5 % of full agonist). Aripiprazole has demonstrated efficacy in schizophrenia with a favourable safety profile (e. g. low EPS, good tolerability) (Ozdemir et al. 2002) and represents the

first partial agonist with efficacy for the treatment of schizophrenia. Aripiprazole was also able to demonstrate some antidepressive efficacy (Kasper et al. 2003; Octavio et al. 2004). Although aripiprazole was initially thought to be merely a D_2-dopamine receptor partial agonist, recent studies (Shapiro et al. 2003) suggest a more complex pharmacological profile, including functional antagonism at 5-HT_{2A} receptors. Some authors therefore suspect aripiprazole's net effect as being similar to that of the D_2/5-HT_{2A} atypicals, in the sense of a partial blockade of D_2 and full blockade of 5-HT_{2A} (Roth et al. 2003).

Limbic selectivity of the antidopaminergic effects of second generation antipsychotics

It has been suggested that the atypical character of certain neuroleptics arises from a preferential effect on the limbic system, which is thought to be involved in emotional and cognitive processes, compared to the effect on the extrapyramidal system, which is closely related to the control of motor behaviour (Bischoff 1992; Meltzer 1993; Möller 2003a; Scatton and Zivkovic 1985). Beside other pharmacological mechanisms of atypicality, limbic selectivity was hypothesised and could be demonstrated for the selective D_2/D_3 receptor antagonist amisulpride. Other atypical neuroleptics with a multireceptor profile, such as clozapine, for example, could also demonstrate a certain limbic selectivity. In the following section data related to this mechanism of limbic selectivity will be presented, whereby amisulpride will be predominantly discussed, as an example.

Amphetamine-induced hyperactivity is probably one of the most important behavioural tests used to investigate antipsychotic effects. Amisulpride, like all other antipsychotics, acts as an antagonist of amphetamine-induced motor hyperactivity in rats, whereby doses of 3 mg/kg are more effective. In contrast to many other antipsychotics, even at significantly higher doses amisulpride does not block the stereotype movements caused by amphetamine. Clozapine also shows this selective effect, whereas several other drugs do not (Sanger et al. 1999).

The explanation for the selective blockade of amphetamine-induced hyperactivity could be that this amphetamine effect involves dopaminergic neurones, which project from the ventral tegmentum to the nucleus accumbens in the limbic system (the mesolimbic path), while stereotype movements may involve neurones that project from the substantia nigra to the striatum (the nigrostriatal path). It is assumed that the mesolimbic path is of special relevance for the antipsychotic effect of neuroleptics, while the nigrostriatal neurones mediate the EPS.

Biochemical and electrophysiological studies are also consistent with the hypothesis that amisulpride selectively blocks dopamine receptors in limbic brain regions. Thus, after injection of amisulpride in rats the increased synthesis and metabolisation of dopamine (which reflects a dopamine receptor blockade) was stronger in the limbic system than in the striatum. This effect is probably associated with the observation that an administered dose of amisulpride occupies more dopamine receptors in the limbic system than in the striatum (Schoemaker et al. 1997). Similar results were found for clozapine, while such limbic selectivity was not observed with typical neuroleptics such as haloperidol (Bischoff 1992; Scatton et al. 1977).

The firing rate of dopaminergic neurones in the ventral tegmentum (mesolimbic path) and in the substantia nigra was measured in electrophysiological experiments in rats. Acute injections of amisulpride increased activity in both areas, whereby this substance had stronger effects, and a larger maximal effect, in the limbic neurones. Chronic treatment with amisulpride also generated limbic-selective activity; this effect could not be observed with haloperidol under the same investigational conditions (Di Giovanni et al. 1998).

By using [^{3}H]raclopride, a high-affinity radioligand for dopamine D_2 and D_3 receptors, it was shown that amisulpride as well as its analog sulpiride, but not haloperidol or remoxipride, displayed a preferential affinity for limbic dopamine D_2/D_3 receptors. Similar findings were obtained with the non-benzamide dopamine antagonist [^{3}H]spiperone as the radioligand (Bischoff 1992; Schoemaker et al. 1997). It seems that the regional differences in displacing potencies of amisulpride are not related to a selective inhibition of binding of a particular dopamine receptor subtype, because in vitro, amisulpride displays a similar affinity for D_2 and D_3 dopamine receptors. Moreover, the low density and restricted distribution of the mRNA coding for the D_3 subtype (Sokoloff et al. 1990) suggests that the presence of dopamine D_3 receptors cannot account for the in vivo pharmacological differences between limbic and striatal [^{3}H]raclopride binding sites.

These and other neurochemical data show that after systemic administration, amisulpride preferentially interacts with limbic dopamine D_2/D_3 receptors. Regional differences in pharmacological effects may be related to the regional brain distribution of systematically administered amisulpride, as has been shown with remoxipride (Köhler et al. 1992). Alternatively a regional selectivity may arise from the differential involvement of dopamine D_2 and D_3 receptor subtypes in the striatal and limbic systems (for a review see Möller 2003a; Schoemaker et al. 1997).

It is unclear whether this limbic selectivity is only related to atypicality in the sense of a reduced risk for EPS or whether it might also have an impact on the antidepressive properties of amisulpride and other neuroleptics. Whatever the case, it might at least be of relevance in the avoidance of both negative and depressive symptoms that are secondary to extrapyramidal symptoms.

Presynaptic dopamine autoreceptor selectivity as a potential basis for atypicality/antidepressive effects

It is assumed that antipsychotics display their therapeutic effects via blockade of the dopamine receptors on postsynaptic neurones in the limbic system. However, the D_2 and D_3 subtypes of the dopamine receptors are also found on presynaptic neurones, where they act as autoreceptors and modulate cell activity. Substances that block postsynaptic dopaminergic receptors would also block these presynaptic receptors, resulting in an increased neuronal release of the transmitter. Functional consequences would not be expected due to the blockade of the postsynaptic receptors. This seems to apply to most antipsychotics, especially the traditional ones, but amisulpride at low doses seems to preferentially occupy presynaptic receptors, which leads to increased dopaminergic transmission (Sanger et al. 1999).

Blockade of presynaptic receptors can be directly investigated in that neurones are electrically stimulated and the rate of dopamine release subsequently measured by means of the extracellular dopamine level (Suaud-Chagny et al. 1991). By using this procedure it was determined that amisulpride at doses of 1, 3 and 10 mg/kg increased dopamine release (Schoemaker et al. 1997). These doses are significantly lower than the doses at which a significant number of postsynaptic dopamine receptors are occupied and corresponding biochemical effects generated (Schoemaker et al. 1997).

It could be expected that the selective antagonistic effect on dopamine autoreceptors would lead to increased dopaminergic neurotransmission and thus functional activity in certain brain regions. This was investigated in rats via measurement of glucose consumption in various brain regions after administration of a low dose of amisulpride (Cudennec et al. 1997). At a dose of 5 mg/kg, which occupies only about 10 % of the total population of brain D_2 and D_3 receptors and selectively blocks presynaptic receptors (see above), amisulpride increased the functional neuronal activity in several cortical and limbic regions. This pattern of activity differs significantly from the pattern seen after administration of a low dose of haloperidol.

These and other available data suggest that in vivo amisulpride affects presynaptic parameters of dopaminergic neurotransmission at doses lower than those that block postsynaptic dopamine receptors. These data are in full agreement with the observation that amisulpride preferentially blocks behavioural effects thought to be associated with the stimulation of presynaptic dopamine receptors (Perrault et al. 1997; Schoemaker et al. 1997).

The increased activity of dopaminergic neurones after administration of low doses of amisulpride does not result in a generalised intensification of behaviour as is the case with direct and indirect dopamine agonists. However, it has been reported that low doses of amisulpride cause behavioural patterns that are described as prohedonic. Guyon et al. (1993) applied a procedure in which rats were taught to associate a certain part of the text box with food, so that they developed a conditioned position preference. This preference was intensified when very low doses of amisulpride were administered before the conditioning sessions in which the animals could obtain food. However, in contrast to psychomotor stimulating drugs, amisulpride did not intensify the conditioned preference if it was administered without food being present. It can therefore be hypothesised that the intensification of dopamine transmission, which is caused by selective blocking of presynaptic receptors, is sufficient to produce small prohedonic or anti-anhedonic effects without direct reward effects (for a review see Möller 2003a; Sanger et al. 1999).

It is always difficult to interpret the clinical relevance of such animal data. Nevertheless, these results might not only be related to negative symptoms but also to depressive symptoms, and could bridge the gap between animal and clinical studies, where antidepressive efficacy of amisulpride in the context of schizophrenic episodes was found (Muller et al. 2002; Peuskens et al. 2002). There is also widespread clinical experience that amisulpride, and also sulpiride (Jenner and Marsden 1982), in low dosages induce antidepressive effects beyond the spectrum of schizophrenia.

Fast dissociation hypothesis of atypicality

Clinically effective dosages of antipsychotic drugs occupy between 60 to 80 % of brain dopamine D_2 receptors in patients, as measured by positron emission tomography (PET) or single photon emission tomography (SPECT) in the human striatum (Dresel et al. 1999; Martinot et al. 1996; Meisenzahl et al. 2000; Schmitt et al. 2002; Tauscher et al. 2002). Clozapine and quetiapine, however, have consistently been apparent exceptions. For example, in patients taking therapeutically effective antipsychotic dosages of clozapine or quetiapine, these drugs only occupy up to 40 or 50 % of striatal dopamine D_2 receptors, as measured in PET or SPECT studies. This could mean that only part of their antipsychotic efficacy is explained by D_2 receptor blockade, while other parts are explained by interaction with the 5-HT system or other transmitter systems. However, Seeman (2002) has proposed that the low D_2 receptor occupancy of clozapine and quetiapine may result from the fact that these antipsychotics rapidly dissociate from the dopamine D_2 receptor. This may also be the case for remoxipride and amisulpride. For example, human cloned dopamine D_2 receptors release [^{3}H]clozapine, [^{3}H]quetiapine, [^{3}H]remoxipride and [^{3}H]amisulpride at least one hundred times faster than they release [^{3}H]haloperidol or chlorpromazine; olanzapine and sertindole show intermediate release rates (Kapur and Seeman 2000; Seeman and Tallerico 1999). It is important to emphasise that the rapid release of quetiapine and clozapine is a molecular event which occurs quickly, regardless of the clinical dosage used. In other words, even though high dosages

of the neuroleptics may be used, these drugs continue to go on and off the D_2 receptor rapidly, allowing extensive and frequent access of endogenous dopamine to the receptor. The fast dissociation or "fast-off" theory of antipsychotic action is based on the assumption that the atypicals have low affinity for the dopamine D_2 receptor and are loosely bound to and rapidly released from these receptors (Kapur and Seeman 2001; Möller 2003a).

It is unclear whether, beside its relevance for atypicality, this mechanism is also related to antidepressive effects. Given the impact of dopaminergic pathways on the reward system (Harrow et al. 1994; Wise 1982), it seems reasonable to assume that the intermittent blockade of postsynaptic D_2 receptors guarantees at least to a certain degree the functionality of the reward system. This could mean that at least antihedonic effects, and consequently also negative symptoms and depressive symptoms secondary to extrapyramidal symptoms, might be avoided by this mechanism.

Mechanisms of atypicality/antidepressive activity related to serotonin receptors

Serotonin 5-HT_{2A} receptor blockade as the background for atypicality/antidepressive activity

Many second generation antipsychotics, like the prototypes clozapine and risperidone, bind with high affinity to 5-HT_{2A} receptors (Meltzer et al. 1989). This is also the case for some typical neuroleptics, e. g. chlorpromazine. However, what distinguishes the subgroup of novel/atypical antipsychotics with 5-HT_{2A} antagonism from the typical antipsychotics that are also potent 5-HT_{2A} antagonists, is that all the atypical agents, but none of the typical antipsychotics, have significantly greater affinity for the 5-HT_{2A} receptor than they do for the D_2 receptor (Meltzer et al. 1989; Sakaue et al. 2000). Risperidone, quetiapine, olanzapine and ziprasidone, among others, were chosen for development because they fit this model, and many compounds have now been identified that are consistent with this model (for review, see Meltzer 1999). Indeed, all compounds that fit this model have proved to have atypical antipsychotic properties, whether in animal models, e. g., dose-related differential blockade of dopaminergic models of psychosis versus catalepsy, or in clinical trials, where they produce minimal or no EPS at doses that are antipsychotic (Meltzer et al. 2003). All these second generation antipsychotics have also demonstrated effects on negative symptoms (Leucht et al. 1999; Möller 2003b) as well as on depressive symptoms in schizophrenia (Kasper et al. 2003; Keck et al. 1998; Marder et al. 1997; Möller 2005; Muller et al. 2002).

5-HT_{2A} receptor antagonism may confer atypicality on antipsychotics with relatively weaker D_2 receptor antagonism (or partial D_2 receptor agonism) because of the ability of 5-HT_{2A} receptors to modulate the activity of dopaminergic neurones differentially in different regions of the brain.

Considerable information as to how 5-HT_{2A} receptor antagonists modulate dopaminergic activity differentially in the nigrostriatal, mesolimbic and mesocortical systems has been obtained from microdialysis as well as electrophysiological studies (for a review see Meltzer et al. 2003). Administration to rodents of selective D_2 receptor antagonists, such as haloperidol or sulpiride, produces a large increase in extracellular dopamine concentrations in the neostriatum and in the nucleus accumbens, whereas the increase in extracellular dopamine in the prefrontal cortex produced by these agents when given alone is modest (Kuroki et al. 1999; Liegeois et al. 2002; Moghaddam and Bunney 1990; Pehek and Yamamoto 1994; Pycock et al. 1980). In contrast, the predominant effect of second generation antipsychotics (Salmi and Ahlenius 1996) is to increase dopamine levels in the mouse prefrontal cortex (mPFC) with smaller increases in the other two regions (Kuroki et al. 1999; Moghaddam and Bunney 1990; Pehek and Yamamoto 1994).

Among others, this provides clear support for the importance of potent 5-HT_{2A} receptor antagonism coupled with weak D_2 receptor blockade and suggests that it may be possible to generate a clozapine-like profile, at least for the effect on cortical dopamine release, with doses of haloperidol which have slight impact on nigrostriatal function, by augmentation with a 5-HT_{2A} receptor antagonist. The 5-HT_{2A} antagonist M100907 suppressed the haloperidol-induced release of dopamine in the nucleus accumbens at both low and high doses of haloperidol (Carlsson and Lindquist 1963; Lee et al. 1994; Liegeois et al. 2002). These observations suggest that concomitant blockade of 5-HT_{2A} and D_2 receptors may stimulate the mesocortical dopamine pathway relative to the nigrostriatal and mesolimbic pathways. This idea has been confirmed with a series of mixed 5-HT_{2A}/D_2 receptor antagonists, including the atypical antipsychotics risperidone, olanzapine, ziprasidone, zotepine and quetiapine, which all cause a marked rise in extracellular dopamine concentrations in mesocortical projection areas (Kuroki et al. 1999; Rollema et al. 2000; Volonte et al. 1997; Westerink et al. 2001). Low-dose haloperidol, by itself, does not reproduce the cortical effects of clozapine on dopamine release (Marcus et al. 2002). This mesocortical dopaminergic activity might be important for the broad clinical efficacy spectrum of these drugs, especially with respect to impact on negative symptoms, cognition and depression. The enhanced activation of the mesocortical dopaminergic system, compared to the nigrostriatal system, may also explain why the novel antipsychotics show antipsychotic effects at doses that do not produce EPS.

The notion that serotonergic neurotransmission is involved in the control of affective symptoms has been popular for a long time, and this is the neurochemical target of many of the most widely used antidepressant drugs (Bosker et al. 2004; Nutt 2002). In particular, certain 5-HT_{2A} receptor antagonists are used in the treatment of major depressive disorders, namely, trazodone

and nefazodone (DeVane 1998), whereas ritanserin has been shown to be useful in the treatment of dysthymia (Lapierre 1994). It has also been suggested that augmentation treatment with risperidone (Ostroff and Nelson 1999) or olanzapine/quetiapine (Calabrese et al. 2004; Shelton et al. 2001) can improve outcome in patients with treatment-resistant depression treated with selective 5-HT reuptake inhibitors (SSRIs), although patient numbers in these trials were small. Nonetheless, these studies have generated much interest in the notion that such atypical antipsychotics may have a more universal clinically useful effect on affective symptoms (Thase 2002). In the context of improving depressive symptoms in schizophrenic patients treated with antipsychotic drugs, it has long been recognised that clozapine has a more beneficial effect on mood than do typical antipsychotic medications (Anonymous 1998; Ranjan and Meltzer 1996). In several of the recent clinical trials of mixed 5-HT_{2A}/D_2 receptor antagonists in schizophrenia, improvement on clinical rating scales for depression has been demonstrated (see above and Möller 2005). This effect may be related, in part, to 5-HT_{2A} receptor antagonism and its effects on neurotransmitter release, e. g. dopamine, norepinephrine and 5-HT (Meltzer et al. 2003). Of special interest in this context is that two compounds of this group, olanzapine and quetiapine, have shown remarkable antidepressive efficacy in well-designed placebo-controlled studies in the acute treatment of bipolar depression (Calabrese et al. 2004; Tohen et al. 2003). Thus the antidepressive efficacy of these two drugs was not only demonstrated in the context of depressive symptoms in schizophrenia but in addition also in (bipolar) depression, allowing much more confidence to be placed in their antidepressive properties.

Serotonin 5-HT_{1A} receptor agonism

The 5-HT_{1A} receptor subtype can be considered as functionally antagonistic to the 5-HT_{2A} receptor, both at the presynaptic and postsynaptic level. Activation of inhibitory 5-HT_{1A} autoreceptors on the cell bodies in the raphe nucleus attenuates firing of these neurones (Blier and de Montigny 1987; Sprouse et al. 1999; Sprouse and Aghajanian 1986). Activation of 5-HT_{2A} receptors, in contrast, generally leads to activation of serotonergic neurones by multiple mechanisms, including a direct or indirect mechanism to inhibit GABAergic inhibitory interneurones, and a direct effect to excite glutamatergic and other neurones (Celada et al. 2001; Matsuyama et al. 1997; for a review see Meltzer et al. 2003).

The opposition between the two 5-HT receptor subtypes suggests that agonists at 5-HT_{1A} receptors may modulate dopaminergic neurotransmission in the brain in a similar fashion to 5-HT_{2A} receptor antagonists. 5-HT_{1A} receptor agonists can stimulate the release of dopamine in the prefrontal cortex as well as potentiate the effect of D_2 receptor blockers on dopamine release (Ichikawa and Meltzer 1999). This potentiation is antagonised by the selective 5-HT_{1A} receptor antagonist WAY100635. Local administration of WAY100635 into the rat prefrontal cortex blocked the effect of subcutaneous MKC-242, a potent selective 5-HT_{1A} agonist, to increase cortical dopamine release in the cortex (Sakaue et al. 2000). These authors also found that fluoxetine and buspirone increased dopamine release in the prefrontal cortex. Buspirone, a 5-HT_{1A} partial agonist, but not fluoxetine, increased dopamine release in the nucleus accumbens as well. MKC-242 also increased dopamine release in the hippocampus. These results suggest that 5-HT_{1A} receptor activation is critically involved in the regulation of dopamine release in these two brain regions, which are involved in key cognitive function (Meltzer et al. 2003) and possibly also in mood regulation.

Taken together, the results of several pharmacological studies suggest that atypical antipsychotics exert their effects on dopaminergic neurotransmission, at least in part, via activation of 5-HT_{1A} receptors (Millan 2000), presumably due to concomitant potent 5-HT_{2A} and relatively weak D_2 receptor antagonism (Ichikawa et al. 2001). The 5-HT_{1A} agonistic activity, e. g. of ziprasidone, might be relevant not only for improving cognitive function but also depressive mood. In this context, it should be mentioned that besides 5-HT_{2A} antagonism, the antidepressant nefazodone has 5-HT_{1A} agonistic properties and that the 5-HT_{1A} agonist gepirone demonstrated antidepressive properties (Jenkins et al. 1990; McGrath et al. 1994; Rausch et al. 1990; Wilcox et al. 1996).

Noradrenalin/serotonin reuptake inhibition and indirect influences on monoaminergic transmitters via receptor blockade

There are other pharmacological mechanisms that might be relevant for atypicality and/or antidepressive activity. Most of them are still somewhat speculative. Others are of obvious relevance due to everything that is known about the most relevant mechanisms of antidepressants. Noradrenalin as well as serotonin reuptake inhibition have been proven as the best way to develop an antidepressant. Dopamine reuptake inhibition apparently also results in antidepressive effects. Apart from this mechanism, other mechanisms which are able to increase directly or indirectly serotonin, noradrenalin or dopamine concentrations in the synaptic cleft, like MAO inhibition, presynaptic α_2-adrenoreceptor blockade or postsynaptic 5-HT_{2A} blockade, may also be the pharmacological background for antidepressive efficacy (Bosker et al. 2004; Möller and Volz 1996; Nutt et al. 1997). Mechanisms related to the increase of dopamine via preferential presynaptic D_2 receptor blockade or via postsynaptic 5-HT_{2A} receptor blockade (Rayevsky et al. 1995) were already mentioned in the above sections. Based on microdialysis studies in rats it can be con-

cluded that there is a close coupling between the release of dopamine and noradrenalin in the medial prefrontal cortex (Westerink et al. 1998; Li et al. 1998).

The effects of different antipsychotic medications on the release of dopamine, noradrenalin and serotonin in the brain have been studied by several groups using microdialysis in living rats. Consistent with its effect on dopamine neuronal firing, in the study by Hertel et al. (1996) clozapine was found to increase selectively dopamine release in the prefrontal cortex but not in the striatum. Olanzapine and risperidone also increased dopamine release in the prefrontal cortex, whereas haloperidol did not. Moreover, typical neuroleptics increased dopamine release in the striatum, but had no effect in the prefrontal cortex (Hertel et al. 1996). In studies by Zhang et al. (2000) and Li et al. (1998) clozapine and olanzapine were found also to increase noradrenalin release in the prefrontal cortex. In contrast, risperidone alone had a more modest effect on noradrenalin and dopamine release in the prefrontal cortex.

Based on their microdialysis animal studies, Westerink et al. (2001) concluded that typical and atypical antipsychotics increase extracellular dopamine in the medial prefrontal cortex to different degrees via a synergistic interaction by blocking $5HT_2$ as well as dopamine D_2 receptors. The increase in extracellular noradrenaline in the medial prefrontal cortex that was observed after administration of atypical antipsychotics is explained by the authors as a consequence of the inhibition of 5-HT_2 receptors and not dopamine D_2 receptors.

In a microdialysis study in rats, Ichikawa et al. (1998) found that risperidone and clozapine significantly increase extracellular 5-HT levels in the medial prefrontal cortex and nucleus accumbens, respectively. Olanzapine, haloperidol and the selective 5-HT_{2A} receptor antagonist M100907 have no significant effect on extracellular 5-HT levels in either region. Thus, the ability to increase extracellular 5-HT levels in the medial prefrontal cortex and the nucleus accumbens by these atypical antipsychotics is not directly related to their affinity for 5-HT_{2A} receptors because olanzapine and M100907 had no significant effect on extracellular 5-HT levels (Ichikawa et al. 1998). Other groups also reported an increase of 5-HT levels (Antoniou et al. 2000; Hertel et al. 1996) in acute and chronic studies of 5-HT turnover in the hippocampus.

A variety of mechanisms other than those involving 5-HT_{2A} receptors, e. g. blockade of α_2-adrenoceptors (olanzapine and clozapine), may contribute to the ability to increase extracellular 5-HT levels in the brain (Meltzer et al. 2003).

Of interest is that two of the second generation antipsychotics – zotepine and ziprasidone – have relatively strong effects on noradrenalin (zotepine) or both serotonin and noradrenalin (ziprasidone) reuptake (Caley and Cooper 2002; Schmidt et al. 2001; Stahl and Shayegan 2003; Tatsumi et al. 1999). The reuptake inhibition is in the range of tricyclic antidepressants like imipramine (Müller et al. 1995; Prakash and Lamb 1998; Schmidt et al. 2001). In this context it is noteworthy that also the traditional neuroleptic chlorpromazine has moderate blocking properties on both the serotonin and the noradrenaline transporter, and that chlorprotixene has blocking effects only on the noradrenalin transporter (Tatsumi et al. 1999). The degree to which these pharmacological effects of multireceptor drugs such as zotepine and ziprasidone penetrate is unclear. Theoretically, these effects may not be able to develop their full strength due to inhibition, for example by antagonistic effects due to receptor blockade. This requires further exploration in animal models and clinical studies.

Clinical studies have not delivered any indications that zotepine or ziprasidone are superior to other second generation antidepressants in terms of antidepressive efficacy in the context of schizophrenia. However, it must be admitted that these questions were not investigated carefully enough.

Unfortunately in general there are only a few studies on the efficacy of neuroleptics in animal models of depression (Gorka and Janus 1985; Vaccheri et al. 1984) and especially no published study in this respect on ziprasidone or zotepine. Levomepromazine, thioridazine and cis-chlorprothixene, when chronically administered, were found not to display 'antidepressive activity' on the behaviour of rats (reduction of the motility) in the forced swimming test (Gorka and Janus 1985). In another study using the forced swimming test, among others, neither haloperidol nor the (–)-enantiomer of sulpiride demonstrated 'antidepressive activity', while the (+)-enantiomer of sulperide did (Vaccheri et al. 1984).

Recently, the effect on neurotransmitter release of combining a selective serotonin reuptake-inhibitor (SSRI) with different antipsychotic agents was examined (Zhang et al. 2000). In this study, rats were administered various antipsychotics alone, fluoxetine alone, or the combination. Haloperidol had no additive effect on transmitter release when combined with fluoxetine. Risperidone plus fluoxetine had a synergistic effect only on dopamine release, but did not affect noradrenalin levels. In contrast, clozapine plus fluoxetine demonstrated synergistic effects only on noradrenaline release. Olanzapine plus fluoxetine increased the release of both noradrenalin and dopamine much more than each drug alone. Furthermore, the combination of olanzapine and sertraline did not elicit the same amount of noradrenalin release as olanzapine plus fluoxetine (Zhang et al. 2000). The hypothesis that various antipsychotics and SSRIs do not have interchangeable effects is at least credible and provides a rationale for particular treatment combinations with greater and lesser effects on prefrontal cortex monoamine release (Thase 2002).

Conclusions

The antidepressive potential of second generation antipsychotics is presumably related to their different pharmacological mechanisms. Among others, 5-HT_{2A} antagonism is of special relevance for most of the new antipsychotics in this respect. But also special interactions with the dopaminergic system, as is the case with amisulpride and aripiprazole, or noradrenalin- and/or serotonin-reuptake-inhibition, as with ziprasidone and zotepine, should be considered. Apart from the antidepressive effect, these pharmacological mechanisms have also been made responsible for the therapeutic effects on negative symptoms and cognitive disorders in the context of schizophrenic psychoses.

The classical neuroleptics' D_2 blockade, which is predominantly responsible for the therapeutic effects on positive symptoms and which is not only the dominant mechanism of traditional neuroleptics but which also plays a central role in the antipsychotic effects of second generation antipsychotics, may be relevant for indirect reduction of depressive symptoms secondary to the reduction of positive symptoms. On the other side, complete D_2 blockade and a simultaneous lack of antagonistic modulation via other transmitter systems, which is the characteristic feature of traditional neuroleptics like haloperidol, appears to be associated with a risk of inducing depressive symptoms.

Thus it can be summarised that the antipsychotic and antidepressive effects of second generation antipsychotics are mostly based on different pharmacological mechanisms. This is especially true for direct antidepressive effects, i. e. antidepressive effects that are not mediated by the reduction of positive symptoms.

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