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Review

Can antipsychotic drugs be classified by their effects on a particular group of dopamine neurons in the brain?

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Abstract

During the four decades that research has been carried out on antipsychotic drugs, a variety of methods have been used to study the effects of these compounds on dopamine neurotransmission. An important issue in this research was to find an explanation for the difference between ''typical'' and ''atypical'' antipsychotic drugs. The hypothesis that the beneficial properties and the motor side effects of antipsychotic drugs result from their effects on different groups of dopamine neurons has received considerable attention. Numerous researchers have tried to discover regiospecific actions of antipsychotic drugs in mesolimbic and in mesocortical dopamine neurons. An overview of these research attempts is presented here. Electrophysiological studies showed a selective action of atypical antipsychotic drugs on A10 dopamine neurons. It was found that chronic treatment with these compounds induced a preferential depolarisation block of the A10 neurons that project to the mesolimbic areas. The model represents certain clinical features of antipsychotic drug use and offers a possible explanation for the lack of extrapyramidal side effects of atypical antipsychotic drugs. Dopamine neurons projecting from A10 to the frontal cortex are also considered as a possible site of action of atypical antipsychotic drugs. Microdialysis studies have shown that certain atypical antipsychotic drugs selectively enhance the release of dopamine in the prefrontal cortex when compared with typical antipsychotic drugs. The finding that repeated treatment with antipsychotic drugs increased dopamine D_2 receptor binding in the frontal cortex confirms the significance of this brain area. These properties might indeed explain certain beneficial effects of atypical antipsychotic drugs such as improvement of cognitive dysfunction. However the effects of typical and atypical antipsychotic drugs in the frontal cortex could not be fully differentiated, which illustrates the difficulty of localising clinical effects of antipsychotic drugs in terms of regional dopamine neurons. Recently new insights into the mechanism of action of typical and atypical antipsychotic drugs have been published. Clinical positron emission tomography (PET) studies have indicated that a moderate dopamine D_2 receptor occupancy, probably combined with a high dissociation rate, might provide the optimal clinical conditions for an antipsychotic drug, without inducing extrapyramidal side effects. Moreover the efficacy of benzamides as atypical antipsychotic drugs suggests that low to moderate dopamine D_2 blockade is probably the most important—if not the only—criterion that determines ''atypicality''. Interestingly these new insights are based on PET studies of the human basal ganglia and not on the comparison of different brain areas. Apparently, according to this concept an ideal antipsychotic drug need not to act on a particular type of dopamine neurons, as it is the moderate dopamine D_2 receptor occupancy that determines the desirable clinical effects. It is concluded that both beneficial actions and side effects, of antipsychotic drugs might be dose dependently localised in A9 as well as A10 dopamine neurons.

Keywords: Dopamine; Mesolimbic; Antipsychotic drug; Clozapine; Prefrontal cortex

1. Introduction

1.1. Antipsychotic drugs and dopamine

Widespread clinical application of chlorpromazine and related compounds as antipsychotic drugs, initially referred to as ''neuroleptics'', started about four decades ago. From the time of these compound's discovery, several behavioural and biochemical techniques have been used to unravel the underlying biological mechanisms responsible for their clinical effects. In the early 1960s, the pharmacological effects of the antipsychotic drugs were elucidated when Swedish workers discovered that these compounds increased the utilization and metabolism of dopamine in the brain of experimental animals (Carlsson and Lindqvist, 1963; Andén et al., 1964; Nyback et al., 1968).

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The first report that described an interaction between antipsychotic drugs and dopamine metabolism was published by Carlsson and Lindqvist (1963), who observed that chlorpromazine and haloperidol increased the levels of the dopamine metabolite, 3-methoxytyramine, in the mouse brain. Soon afterwards, Andén et al. (1964) reported that these compounds also increased the levels of the acidic dopamine metabolites homovanillic acid and 3,4-dihydroxyphenylacetic acid in the brains of rabbits. In the years to follow various authors clearly confirmed these observations (Laverty and Sharman, 1965; Roos, 1965; Da Prada and Pletscher, 1966; O'Keeffe et al., 1970). Similar results were obtained when the effects of antipsychotic drugs on dopamine "utilization" or "turnover" were studied. Using [^{14}C]-radio-labelled precursors, it was shown that the conversion of [^{14}C]-tyrosine to dopamine and the rate of disappearance of labelled amines were accelerated by antipsychotic drugs (Nyback et al., 1968). When the synthesis of dopamine was blocked with the tyrosine-hydroxylase inhibitor, α-methyl-para-tyrosine, an increased rate of disappearance of dopamine was observed when the animals were pretreated with antipsychotic drugs (Andén et al., 1971; Andén, 1972).

Soon after the discovery that antipsychotic drugs increased dopamine metabolism in the brain of experimental animals, hypotheses about their mechanism of action were proposed. It was shown that the antipsychotic drugs inhibit the abnormal behaviour seen in experimental animals following administration of amphetamine and apomorphine, both of which mimic the action of dopamine. Moreover, in patients, the antipsychotic drugs induced motor effects resembling parkinsonism and catalepsy in experimental animals. Taken together these date led several workers to consider antipsychotic drugs as dopamine receptor antagonists (Carlsson and Lindqvist, 1963; Van Rossum, 1966; Hornykiewicz, 1966; Andén et al., 1971). The enhancement of dopamine metabolism and synthesis by antipsychotic drugs was explained by a "negative feedback" response of the dopamine neurons as a result of dopamine receptor blockade (Carlsson and Lindqvist, 1963).

Several interpretations were given for the mechanisms involved in the "negative feedback" response of dopamine neurons. Some authors explained this effect by a response of postsynaptically located neuronal feedback loops (Groves et al., 1975; Walters and Roth, 1976; Chiodo and Bunney, 1983), whereas others proposed an "autoreceptor"-type of mechanism, localized on dopaminergic nerve terminals and cell bodies (Kehr et al., 1972; Di Chiara et al., 1977; Westerink and De Vries, 1989). Although both mechanisms have been further explored in more detail, their respective roles in the "negative feedback" hypothesis have never been fully elucidated.

The hypothesis that antipsychotic drugs block dopamine receptors was fully confirmed several years later, when specific dopamine receptor binding techniques became available (Burt et al., 1975; Creese et al., 1976; Seeman et al., 1976). The assumption that all clinically effective antipsychotic drugs are dopamine receptor antagonists had a great impact on the research to follow.

The efficacy of antipsychotic drugs in treating psychotic patients was also one of the cornerstones of the "dopamine hypothesis" of schizophrenia (Van Rossum, 1966), in which "an overactivity of dopamine neurons" is assumed.

1.2. Atypical antipsychotic drugs

Antipsychotic drugs improve positive symptoms in schizophrenia, but they also induce a number of side effects of which extrapyramidal symptoms such as parkinsonism and akathesia are the most severe and frequent. In animal experiments, these side effects are expressed as "catalepsy" or "inhibition of apomorphine-induced stereotypy". In the early 1970s, it was noticed that certain antipsychotic drugs induced fewer motor side effects in patients and experimental animals. In this regard the compound, clozapine, was of great significance, as it was shown to possess antipsychotic activity without inducing extrapyramidal disorders in humans or catalepsy in rats (Gross and Langner, 1966; Angst et al., 1971). Based on these findings Hippius and Angst defined clozapine as an "atypical" antipsychotic drug (see for review, Hippius, 1989). In addition, the non-cataleptogenic bezamide analogue, sulpiride (Tagliamonte et al., 1975), and the weak cataleptogenic antipsychotics, thioridazine and perlapine, were also reported to induce relatively few extrapyramidal side effects in patients. In subsequent years, clozapine, sulpiride, thioridazine and perlapine were defined as "atypical antipsychotics" and differentiated from the parkinsonism—inducing "typical" antipsychotics, of which haloperidol and chlorpromazine were the representatives. An atypical antipsychotic drug was initially defined as a drug that does not induce extrapyramidal side effects. Later other beneficial properties such as improvement of negative symptoms and of cognitive dysfunction and efficacy in neuroleptic-resistant schizophrenia were included. In the present review "atypical" refers to the absence of extrapyramidal side effects.

1.3. Scope of review

During the four decades that research has been carried out on antipsychotic drugs, a variety of methods have been used to study the effects of antipsychotic drugs on dopamine neurotransmission. Initial experiments used post-mortem tissue analysis, or studied the in vitro release of dopamine from brain slices and synaptosomes. In 1973, a series of electrophysiological studies on the interaction of antipsychotic drugs with dopamine neurons was initiated, and in 1975 specific radiolabelled ligands for dopamine receptors became available which prompted an overwhelming number of receptor-binding studies. In the meantime, in vivo release studies methods, based on push–pull perfusion, voltammetry or microdialysis were developed and applied for further

elucidation of the mechanisms of action of antipsychotic drugs in the brain of awake animals. More recently, non-invasive methods, using the PET and single-photon emission computerized tomography (SPECT) were used to estimate the dopamine receptor occupancy of various antipsychotic drugs in human volunteers, schizophrenic patients and non-human primates.

Many of these reports involved comparisons of the properties of typical and atypical antipsychotic drugs. Taken together these studies represent hundreds of papers. An overview of these research efforts is presented here. The hypothesis that the beneficial properties and the motor side effects of antipsychotic drugs result from their effects on different groups of dopamine neurons will be discussed in some detail.

2. Antipsychotic drugs and dopamine metabolism

2.1. Neurochemical studies on striatal dopamine

When the effects of clozapine and other atypical antipsychotic drugs were observed in the clinic, various authors looked for neurochemical explanations in experimental animals. Initial experiments were based on post-mortem analysis of whole brain or striatal tissue. Bartholini et al. (1972) determined the effect of clozapine on dopamine metabolism and they speculated that clozapine might cause a blockade of striatal dopamine receptors that is of a "surmountable type". Burki et al. (1974, 1975) and Rollema et al. (1976) determined dose–response curves for the effects of clozapine and several typical antipsychotic drugs on the activation of tyrosine hydroxylase or on homovanillic acid levels in rat striatum. The dose–response curves for all compounds were found to be parallel, with perlapine, thioridazine and clozapine showing activity in the higher dose range. These findings were consistent with the relatively high clinical doses of atypical antipsychotic drugs that are required to achieve an antipsychotic effect in patients. The rightward shift in the dose–response curves of the antipsychotic drugs therefore could not explain the atypical effects of the antipsychotic drugs. However, Burki et al. (1975) emphasised that clozapine was the only compound that—other than its stimulatory effect on homovanillic acid and the dopamine synthesis rate common to other antipsychotic drugs—increased the levels of dopamine itself in the rat striatum. This finding contrasted with other observations that potent neuroleptics caused a slight reduction in dopamine tissue levels. Burki et al. speculated that clozapine stimulated the synthesis of striatal dopamine more pronouncedly than its disappearance, and that the compound did not necessarily block dopamine receptors to the same degree as typical neuroleptics were assumed to. In this regard the observation of Hyttel (1974) that all antipsychotic drugs except clozapine increase the disappearance rate of [^{14}C]-dopamine in a dose-dependent manner is also of interest.

In 1975, Tagliamonte et al. (1975) demonstrated that sulpiride increased dopamine metabolite levels in the striatum of rats, with a potency consistent with the high doses used in the clinic. The relatively low potency of sulpiride was later attributed to its poor ability to penetrate into the brain (Nishibe et al., 1982). In contrast with the findings for clozapine (Burki et al., 1974, 1975), sulpiride did not produce an increase in dopamine levels. Sulpiride was the first member of a class of distinct chemical compounds called the benzamides. Benzamides block dopamine D_2/D_3 receptors and virtually do not interact with other known binding sites in the brain. Interestingly, in addition to sulpiride, certain benzamides including remoxipride and amisulpride were classified, in both preclinical and clinical studies, as atypical antipsychotic drugs (Perrault et al., 1997; Peuskens et al., 1999).

2.2. Striatal versus mesolimbic dopamine neurons

Blockade of dopamine receptors in the basal ganglia provided a straightforward explanation for the extrapyramidal disorders that antipsychotic drugs cause in patients and experimental animals. However, it soon became debatable whether this blockade was also required for the antipsychotic action (Bartholini et al., 1972). The finding of several dopamine pathways in the brain added to the debate (Ungerstedt, 1971). The discovery that dopamine was also present in "mesolimbic" brain structures provided a possible explanation for the beneficial action of atypical antipsychotic drugs. Andén et al. (1972) (Andén, 1972; Andén and Stock, 1973) were the first to investigate the effects of clozapine on regional dopamine metabolism. The limited sensitivity of analytical chemical methods at the time demanded larger brain samples so that rabbits were used as experimental animals. Andén found that clozapine was somewhat more potent to stimulate dopamine metabolism in the mesolimbic areas than in the striatum. Although he speculated that the anticholinergic properties of clozapine could explain this selective action, his observations laid the groundwork for the hypothesis that the extrapyramidal side effects and antipsychotic actions of neuroleptics might be due to blockade of dopamine neurotransmission in the corpus striatum and mesolimbic-mesocortical system, respectively (Crow et al., 1976).

Speculation about possible selective actions of clozapine in the brain led many researchers to study the effect of typical and atypical antipsychotic drugs on different dopamine neuronal systems. Histochemical studies (Ungerstedt, 1971; Thierry et al., 1973; Hokfelt et al., 1974) had shown that the striatum is mainly innervated by dopamine neurons, cell bodies of which are localized in the A9 nucleus (the substantia nigra), whereas the mesolimbic or mesocortical areas are innervated by dopamine neurons that originate in the A10 nucleus (the ventral tegmental area). As "mesolimbic or mesocortical areas", the nucleus accumbens (often

called the "ventral striatum") the olfactory tubercle and the prefrontal cortex received much attention.

The potentially selective effects of typical and atypical antipsychotic drugs on the different dopamine neuronal systems led to many studies using various in vitro, ex vivo and in vivo approaches (e.g. post-mortem tissue analysis, electrophysiology, binding studies and microdialysis) to investigate this matter in more detail. The results will be discussed below.

2.3. Summary

(1) Initial neurochemical studies on antipsychotic drugs, e.g. the dose-effect studies, did not provide a full explanation for the different clinical properties of typical and atypical drugs.
(2) Burki speculated that clozapine did not necessarily block dopamine receptors to the same degree as did typical antipsychotic drugs. This weak potency of clozapine may lead to a "surmountable" effect on dopamine receptors and stronger stimulation of dopamine metabolism than that of dopamine release.

3. Effects of antipsychotic drugs on regional dopamine metabolism in post-mortem tissue

3.1. Acute studies

Since the mid-1970s, a large number of studies have described the effect of typical and atypical antipsychotic drugs on regional dopamine metabolism. Several authors found that clozapine and sulpiride have a preferential action on dopamine metabolism in the mesolimbic brain areas (Bowers and Rozitis, 1974; Bartholini, 1976; Crow et al., 1977; Scatton et al., 1977) or frontal cortex (Laduron et al., 1977; Bowers, 1984). However, others found no such differentiation or reported only slightly preferential effects of the atypical antipsychotic drugs for mesolimbic tissue (Stawarz et al., 1975; Wiesel and Sedvall, 1975; Westerink and Korf, 1975; Wilk et al., 1975; Bowers and Rozitis, 1976; Waldmeier and Maitre, 1976a; Westerink and Korf, 1976a,b; Wilk and Glick, 1976; Stanley and Wilk, 1980; Burki, 1986; Magnusson et al., 1986; Chang et al., 1988; Fujiwara, 1992).

We (Westerink et al., 1977) tested a large series of antipsychotic drugs and non-antipsychotic drugs. The ratio of dopamine metabolites in the striatum versus that in the mesolimbic areas indeed differentiated atypical antipsychotic drugs (clozapine, sulpiride and thioridazine) from the typical antipsychotic drugs. However, a similar specific effect was observed for the heterogeneous group of non-antipsychotic drugs. The latter group of drugs was administered at relatively high doses. Studies on atypical antipsychotic drugs often use high doses. The finding that, at higher doses, various drugs inhibit the efflux of acidic dopamine metabolites from the brain, and that this inhibition is more pronounced in mesolimbic areas than in striatal tissue (Moleman et al., 1978; Westerink and Kikkert, 1986), might contribute to or even explain the selective mesolimbic action of atypical antipsychotic drugs.

In spite of the vast amount of experimental data generated, the question as to whether typical and atypical antipsychotic drugs are differentiated by a selective action on limbic brain areas was still not answered conclusively.

3.2. Chronic studies and tolerance

The clinical antipsychotic effects of antipsychotic drugs are usually only observed after a delay of days to weeks but persist over time. In contrast, the extrapyramidal side effects of antipsychotic drugs appear soon after treatment and tend to diminish with time. Therefore, it seemed reasonable to investigate whether tolerance to changes in dopamine metabolism occurs earlier in the striatum than in the mesolimbic-cortical areas.

It is well established that repeated administration of typical antipsychotic drugs does indeed induce tolerance to enhanced dopamine metabolism in striatal tissue (which means that the initial biochemical effects disappear during chronic treatment) (Burki et al., 1974; Sayers et al., 1975; Waldmeier and Maitre, 1976b; Bowers and Rozitis, 1976; Lerner et al., 1977; Scatton, 1977; Stanley and Wilk, 1980). However, the results for clozapine were not unequivocal in that some authors found tolerance after clozapine (Bowers and Rozitis, 1976; Waldmeier and Maitre, 1976b), but others did not (Burki et al., 1974; Von Stralendorff et al., 1976).

It was of course of great interest to find whether differences in the development of tolerance could be detected between striatal and mesolimbic tissue. Bowers and Rozitis (1976), Waldmeier and Maitre (1976b), Scatton (1977) and Stanley and Wilk (1980) did not observe differences between striatum and mesolimbic areas. However Von Stralendorff et al. (1976) found tolerance to increased homovanillic acid levels in both striatum and mesolimbic tissue after repeated treatment with haloperidol, whereas both areas displayed no tolerance after clozapine. Scatton (1977) observed tolerance both in striatum and mesolimbic areas for the increase in dopamine metabolites after chronic administration of either haloperidol or sulpiride. The threshold doses for inducing tolerance were lower for the striatum than for the mesolimbic areas. Moreover, tolerance developed earlier in the striatum than in the mesolimbic areas. Scatton (1977) emphasized that the induction of tolerance depends on the dose and time of dosing and suggested that all brain regions will ultimately develop tolerance. Stanley and Wilk (1980) also commented on the variability of the outcome of chronic studies on tolerance. These latter authors emphasized that tolerance—in the striatum as well as mesolimbic tissue—is only seen after high doses of haloperidol, and in their opinion the development of tolerance is dependent on the potency and dose of the particular antipsychotic drug studied. They further speculated that the

short duration of action of clozapine might have prevented the induction of tolerance.

3.3. The prefrontal cortex

After it was discovered that dopaminergic terminals are also present in the frontal cortex (Thierry et al., 1973; Hokfelt et al., 1974), considerable attention was directed to studies of the functional properties of these neurons, which were subsequently implicated in the therapeutic action of antipsychotic drugs.

Some authors (Laduron et al., 1977; Matsumoto et al., 1983) suggested that the prefrontal cortex is preferentially sensitive to haloperidol at very low doses, and that this unique property supports the notion that this region is the site of action of antipsychotic drugs. However, Chang et al. (1988) and Kolenik et al. (1989) could not confirm these observations.

Burki (1986) continued his series of investigations on clozapine and studied the effect of clozapine on homovanillic acid levels in the striatum and frontal cortex. He concluded that the low incidence of extrapyramidal side effects of clozapine and related compounds is probably due to their weak and relatively short-lasting effect on dopamine neurons, rather than to a selective action on mesolimbic dopamine neurons.

As in the studies on the development of tolerance in striatal versus mesolimbic areas, the development of tolerance to repeated treatment with antipsychotic drugs in the frontal cortex was investigated in detail. Laduron et al. (1977) found little tolerance to enhanced homovanillic acid levels after haloperidol, although the rats in this study were treated for only 4 days. A mentioned above, Scatton (1977) concluded that repeated treatment with haloperidol and sulpiride induced tolerance to the increase in homovanillic acid in striatum and mesolimbic areas. He observed similar effects in the frontal cortex. Bacopoulos (1981) also reported tolerance to the increase in homovanillic acid levels after fluphenazine in the prefrontal cortex. Mefford et al. (1988) administered haloperidol, chlorpromazine, thioridazine and clozapine for 21 days to rats. Tolerance developed in the prefrontal cortex to chlorpromazine and thioridazine (expressed as homovanillic acid/dopamine ratio), but not for clozapine.

3.4. Summary

Although many of the results from post-mortem tissue analysis are ambiguous, some general conclusions may be drawn:

(1) Mesolimbic areas generally have a lower threshold for display of an increase in dopamine metabolism for atypical antipsychotic drugs. This effect was also observed for a heterogeneous group of non-neuroleptic drugs.

(2) Repeated treatment with antipsychotic drugs induces tolerance to the enhancing effects on dopamine metabolism. The threshold for inducing tolerance is lower in the striatum than in mesolimbic areas. Various authors have emphasized that the development of tolerance in various brain regions depends on the dose, timing of the dose and duration of action. Finally, all regions develop tolerance to increased dopamine metabolism, although the cortical areas have the most persistent tolerance.

4. Electrophysiological studies

Midbrain dopamine neurons were identified by single unit extracellular recording techniques for the first time in 1973 (Bunney et al., 1973). Soon thereafter evidence started to accumulate that antipsychotic drugs increase the firing rate of dopamine neurons. This finding was in excellent agreement with the antipsychotic drug-induced enhancement of dopamine metabolism and turnover, which had been established a decade earlier. The electrophysiological experiments also confirmed the existence of dopamine autoreceptors. These autoreceptors were identified on the somatodendritic sites of both A9 and A10 neurons (Aghajanian and Bunney, 1973), and had the pharmacological characteristics of the dopamine D_2 subtype (White and Wang, 1984a,b).

4.1. Acute effects of antipsychotic drugs

Various authors have compared the effect of antipsychotic drugs on A9 and A10 cell firing activity. It was found that acute treatment with typical antipsychotic drugs increased the firing rate of A9 as well as of A10 neurons. However, the results obtained with atypical antipsychotic drugs were somewhat controversial. Several authors reported that atypical antipsychotic drugs affected exclusively A10 neurons (Hand et al., 1987; Grenhoff et al., 1990; Goldstein et al., 1993; Fu et al., 2000), but others found that these compounds increased the firing rate of both A10 and A9 neurons (Chiodo and Bunney, 1983; Okuyama et al., 1997; Di Giovanni et al., 1998). In addition, Skarsfeldt (1992) reported that the atypical antipsychotic drug, sertindole, neither affected A9 nor A10 cells. In agreement with the results of post-mortem tissue studies A10 neurons showed a tendency to lower threshold values towards atypical antipsychotic drugs when compared to typical antipsychotic drugs. A9 neurons did not show this tendency.

4.2. Repeated treatment

Whereas the acute administration of antipsychotic drugs *increased* the number of spontaneously active dopamine neurons, chronic treatment had the opposite effect and markedly *decreased* the number of cells encountered (Bun-

ney and Grace, 1978; Chiodo and Bunney, 1983; White and Wang, 1983a,b; Todorova and Dimpfel, 1994; Skarsfeldt, 1988, 1994). This reduction in the number of spontaneously firing dopamine neurons was shown to result from the induction of a state of tonic depolarisation. Typical antipsychotic drugs converted both A9 and A10 neurons to a state of depolarization block, but repeated treatment with atypical antipsychotic drug (thioridazine, clozapine, sertindole and amisulpride) affected only the A10 neurons while the A9 neurons remained unaffected (Chiodo and Bunney, 1983; White and Wang, 1983a,b; Todorova and Dimpfel, 1994; Skarsfeldt, 1988, 1992, 1994). Again, some studies reported divergent results: Chiodo and Bunney (1983) found that repeated sulpiride blocked A9 as well as A10 neurons, while Skarsfeldt (1988) observed only small differences between the effect of thioridazine on A9 and that on A10 neurons.

The observation that chronic treatment with antipsychotic drugs converted A10 dopamine neurons to a state of tonic depolarization inspired various authors to implicate this feature in the clinical effects of these compounds. It was speculated that a delayed block of A10 cells parallels the time lag in clinical improvement seen after antipsychotic drugs (White and Wang, 1983a,b; Chiodo and Bunney, 1983; Skarsfeldt, 1994; Grace et al., 1997). The results of repeated-treatment studies supported the hypothesis that the antipsychotic effects and extrapyramidal side effects of antipsychotic drugs are mediated via receptors localized in the mesolimbic area and in the striatum, respectively.

Further evidence for the mechanism of depolarization block was provided by Bunney and Grace (1978) and Grace et al. (1997). The "silent" dopamine neurons were believed to be in an apparent state of tonic depolarization inactivation, since they could be discharged by the microiontophoretic application of the inhibitory neurotransmitter, γ-aminobutyric acid, but not by the excitatory amino acid, glutamate. Lesion studies suggested that depolarization inactivation of the dopamine neurons is secondary to postsynaptic receptor blockade in the forebrain (Chiodo and Bunney, 1983).

4.3. Mesocortical A10 dopamine neurons

The mesocortical A10 neurons have received special attention in several studies. Chiodo and Bunney (1983) described a subpopulation of A10 neurons displaying less sensitivity for autoreceptors; this group was identified as mesocortical cells. In addition, it was found that these neurons do not undergo inactivation during repeated treatment with antipsychotic drugs. By using both electrophysiological and neurochemical methods, Chiodo et al. (1984) provided evidence that A10 dopamine cells innervating the frontal and cingulate cortex lack autoreceptors. However others—using different techniques—could not confirm a lack of autoreceptors on these dopamine neurons (Talmaciu et al., 1986; Gessa et al., 2000).

4.4. Interaction with other receptors as explanation for the mesolimbic selectivity

The different response of A9 and A10 dopamine neurons to antipsychotic drugs suggests that the two dopamine cell groups are regulated by different mechanisms (e.g. Hand et al., 1987; Clark and Chiodo, 1988; Grenhoff et al., 1988). As most atypical antipsychotic drugs bind with high affinity to multiple receptor types and subtypes, blockade or activation of a non-dopamine receptor subtype might provide an explanation for their differential effects on A9 and A10 neurons.

The antimuscarinic property of clozapine has been considered as a possible explanation for its atypical properties. As antimuscarinic compounds are often co-administered with antipsychotic drugs to treat extrapyramidal disorders, this property might contribute to the unique clinical features of clozapine. Chiodo and Bunney (1985) reported that pretreatment with an anticholinergic compound turned the typical profile of haloperidol into the atypical profile of clozapine. Chiodo and Bunney (1985) observed similar effects when animals were pretreated with a α_1-adrenoceptor antagonist. Skarsfeldt (1988) emphasised that the α_1-adrenoceptor is of crucial importance for a selective action on A10 neurons, as he reported that the atypical antipsychotic drug, tefludazine, which in addition to blocking the D_2/5-HT_2 receptor, is a potent α_1-adrenoceptor antagonist.

Several authors have emphasized that most atypical antipsychotic drugs bind with greater affinity to 5-HT_{2A} than to D_2 receptors. The role of the antagonism of 5-HT_{2A} receptors in the mode of action of atypical antipsychotic drugs has received much attention (Saller et al., 1990: Meltzer, 1991; Kahn and Davidson, 1993; Leysen et al., 1993, 1994; Stockmeier et al., 1993). Various authors provided evidence that blockade of the 5-HT_{2A} receptor might contribute to the clinical effects of atypical antipsychotic drugs. Results of a number of electrophysiological studies are in agreement with this hypothesis. A good example of differentiation between A9 and A10 cells was described by Skarsfeldt and Perregaard (1990) for the 5-HT_{2A} receptor antagonist sertindole that displays a preference for A10 neurons of more than 2 orders of magnitude. The effects of the selective 5-HT_{2A} receptor antagonists (ICI169,369 and MDL100907) on A9 and A10 cell firing resemble that of clozapine (Goldstein et al., 1989; Sorensen et al., 1993). Andersson et al. (1995) found that the 5-HT_2 receptor antagonist ritanserin activated midbrain dopamine neurons with a higher sensitivity for A10 neurons. Okuyama et al. (1997) noticed few differences between the acute effect of clozapine on A9 and A10 neurons, but found a tenfold difference in potency for a D_4/5-HT_{2A} receptor antagonist towards A10 neurons. They also found that the 5-HT_2 receptor antagonist, NRA0045, reversed the metamphetamine induced decrease in firing rate of A9 and A10 neurons. In these experiments NRA0045 was 10 times more potent on A10 than on A9 neurons.

4.5. The use of anaesthesia

Most, if not all, of the electrophysiological experiments mentioned here were carried out in anaesthetised rats. The use of anaesthesia during recording of dopamine cells has frequently been criticized, since it introduces a variable of considerable concern (Kelland et al., 1990). General anesthetics depress the ability of dopamine antagonists to increase dopamine cell firing rate and enhance the potency of agonists to inhibit the dopamine cell firing rate. Mereu et al. (1983) found that sulpiride increases firing of A9 neurons in halothane-anaesthetized rats, but not in awake rats. These researchers also provided evidence that depolarization block does not occur in conscious rats (Mereu et al., 1994). However Grace et al. (1997) have explained the results of Mereu et al. by using high doses of tubocurarine (for more discussion on this issue, see Grace et al., 1997).

4.6. Interpretation

A consistent observation in the electrophysiological research is that A10 dopamine neurons are more sensitive to acute as well as to chronic treatment with atypical antipsychotic drugs than A9 neurons. However, the crucial issue is whether or not the typical antipsychotic drugs are also more potent to activate A10 than A9 cells. Should this be the case, the potency—and not the "atypicality"—of the antipsychotic drug determines the specificity. A precise comparison of reliable dose–response curves of typical antipsychotic drugs would be required to answer this question. Unfortunately, the literature is not always clear on this point. In some studies haloperidol indeed showed a tendency to be more active on the A10 than on the A9 neurons in the lower dose range (White and Wang, 1983a,b; Hand et al., 1987; Skarsfeldt, 1988).

Interestingly, dopamine agonists display little specificity towards A9 and A10 neurons (Clark and Chiodo, 1988; Cox and Waszczak, 1990). This suggests that the dopamine D_2 receptor itself has no different properties in A9 and A10 neurons. An additional receptor interaction might therefore explain the selective action of an atypical antipsychotic drug on A10 neurons. Evidence was indeed provided that blockade of the muscarinic, α_1 or 5-HT_2 receptor "drives" the selectivity of dopamine cells for atypical antipsychotic drugs towards A10 neurons. The hypothesis that additional 5-HT_{2A} receptor blockade turns a typical antipsychotic drug into an atypical one was one of the cornerstones of the "5-HT_{2A}/D_2 hypothesis" (Meltzer, 1989) that prompted the development and introduction of a series of new antipsychotic drugs (e.g. risperidone, amperozide, zotepine, quetiapide, olanzapine and ziprasidone).

If the latter hypothesis is correct, one important question remains to be answered: why do atypical benzamides, which are relatively pure D_2 receptor antagonists, and have no effect on 5-HT_{2A} receptors, display mesolimbic selectivity? Dose–response curves for amisulpride suggest that the compound is about threefold more active on A10 than on A9 neurons (Di Giovanni et al., 1998). However, Andersson et al. (1994, 1995) found a much greater separation between effects on A10 and A9 neurons—of the order of two decades—in the case of raclopride. A "benzamide binding site" that is more expressed on A10 neurons, especially at presynaptic sites (Schoemaker et al., 1997; Perrault et al., 1997), might be responsible for a selective action of these compounds.

4.7. Summary and conclusions

1. In accordance with the findings, the post-mortem tissue studies A10 neurons showed a tendency to lower threshold values towards atypical antipsychotic drugs than did typical antipsychotic drugs.
2. Chronic treatment with typical antipsychotic drug induced a depolarisation block in A9 as well as A10 neurons. Chronic treatment with atypical antipsychotic drugs induced a depolarization block only in A10 neurons.
3. Dopamine receptor agonists do not differentiate between A10 and A9 neurons.
4. Additional muscarinic, 5-HT_2 receptor or α_1-adrenoceptor blockade drives the selectivity of antipsychotic drugs towards A10 neurons.
5. The selective action of benzamides towards A10 neurons is still unexplained.

5. Binding studies

With the availability of specific radiolabelled ligands dopamine receptor binding was introduced in the mid-1970s (Burt et al., 1975). Soon afterwards it was discovered that antipsychotic drugs all behaved like dopamine receptor antagonists and a good correlation was found between the clinical potency of antipsychotic drugs and their ability to inhibit [^{3}H]haloperidol binding (Creese et al., 1976; Seeman et al., 1976).

A large number of studies, predominantly carried out with striatal tissue, compared the effects of typical and atypical antipsychotic drugs on dopamine receptor binding. The results are summarized in Tables 1 and 2.

5.1. Acute experiments

In acute experiments (using [^{3}H]spiperone as the radioligand), it was found that the typical antipsychotic drug, haloperidol, did not discriminate between displacement of the ligand in mesolimbic and in striatal tissue (Kohler et al., 1979; Ogren et al., 1984). Binding studies on atypical antipsychotic drugs (sulpiride, clozapine, remoxipride) showed variable results. Some authors reported no differences between displacement of the D_2 receptor ligands in the various brain regions (Seeman and Ulpian, 1983; Chiv-

Table 1
Acute treatment with atypical APD's on dopamine receptor binding

Reference	Compound	Effect
Kohler et al. (1979)	sulpiride	mesolimbic preference; but not in nucleus accumbens
Seeman and Ulpian (1983)	clozapine, thioridazine	even distribution in the brain
Ogren et al. (1984)	remoxipride	mesolimbic preference
Schotte et al. (1993, 1996)	clozapine, sulpiride, risperidone	even distribution in the brain
Schoemaker et al. (1997)	amisulpride, sulpiride, remoxipride	mesolimbic preference; except remoxipride

ers et al., 1989), whereas others found preferential binding to mesolimbic areas (Kohler et al., 1979; Ogren et al., 1984). For example, Schoemaker et al. (1997) found that sulpiride and amisulpride (but not remoxipride) displaced the in vivo binding of [^{3}H]raclopride about two- to threefold more potently in the limbic system than in the striatum, while no differences were observed for inhibition of the binding by haloperidol.

Schotte et al. (1996) followed a slightly different approach. They administered antipsychotic drugs to rats and performed ex vivo autoradiography. Several typical and atypical antipsychotic drugs were tested but no regional selectivity for D_2 receptor occupancy in mesolimbic versus striatal areas was detected for any of the compounds tested. The results are summarized in Table 1.

5.2. Chronic experiments: striatal versus mesolimbic areas

Many studies investigated the effect of chronic antipsychotic drug administration (range: 4 weeks to 20 months) on dopamine receptor binding in rat brain. The results of these studies are summarized in Table 2. A consistent observation was that typical antipsychotic drugs such as haloperidol and fluphenazine elicited an increase (range 20–25%) in striatal dopamine receptor binding. This enhanced binding represents an increase in the number of receptor sites and may explain the behavioral supersensitivity to dopamine receptor stimulants that chronic antipsychotic drugs induce in animals. Various authors speculated that the tardive dyskinesia seen in patients chronically treated with typical antipsychotic drugs is also related to an increase in the number of dopamine receptors.

The atypical antipsychotic drugs behaved differently in this respect. None of the nine studies with chronic clozapine treatment found a change in D_2 receptor binding. Results of studies on the effects of chronic sulpiride treatment were more varied, in that three authors reported an increase in striatal receptor binding, whereas three others found no effect. However, Memo et al. (1981) found the opposite result for chronic sulpiride and haloperidol treatment: after sulpiride they observed an increase in D_2 receptor binding, whereas haloperidol had no effect.

Extensive studies were carried out by Rupniak et al. (1985b) and Jenner et al. (1985), who treated rats for up to 20 months with haloperidol, clozapine or sulpiride. Haloperidol, but not sulpiride and clozapine, increased dopamine

Table 2
Effect of chronic treatment (4 weeks to 1 year) with typical and atypical APDs on dopamine receptor binding

Reference	Effect of typical APDs	Effect of atypical APDs
Burt et al. (1977)	haloperidol, fluphenazine: 20–25% increase in striatum	not determined
Bannet et al. (1980)	haloperidol 28% increase in striatum	sulpiride: no effect in striatum
Memo et al. (1981)	haloperidol: no effect in striatum	sulpiride: increase in striatum
Jenner et al. (1982)	haloperidol: increase in striatum	sulpiride: increase in striatum
Seeger et al. (1982)	haloperidol: increase in striatum and mesolimbic tissue	clozapine: no effect in striatum and mesolimbic tissue
Severson et al., 1984	haloperidol: 29% increase in striatum	clozapine: no effect in striatum; tioridazine: 25% increase in striatum
Rupniak et al. (1984)	haloperidol: B_{max} increased in striatum (12 months)	sulpiride: no effect in striatum (12 months)
Rupniak et al. (1985a)	haloperidol: B_{max} increased in stratum (4 weeks)	sulpiride, clozapine: no effect in striatum (4 weeks)
Rupniak et al. (1985b)	haloperidol: B_{max} increased in striatum (20 months)	clozapine: no effect in striatum (12 months)
Jenner et al. (1985)	haloperidol: B_{max} increased in striatum (12 months)	clozapine: no effect in striatum; sulpiride: no effect but increased [3H]NPA-binding in striatum
Prosser et al. (1989)	haloperidol: increase in striatum not in mesolimbic tissue	sulpiride: increase in striatum not in mesolimbic tissue
See et al. (1990)	haloperidol: increase in striatum	clozapine no effect in striatum
Svartengren and Celander (1994)	not determined	amperozide: no effect in stratum or mesolimbic tissue
Kusumi et al. (1995)	haloperidol: increase in striatum	clozapine: no effect in striatum
Wan et al. (1996)	haloperidol: increase in striatum	clozapin: no effect in striatum
Florijn et al. (1997)	haloperidol: increase in striatum dependent on type D2-ligand	clozapine: no effect in striatum
Tarazi et al. (1997)	fluphenazine: increase in D2/D4 binding in striatum, mesolimbic and prefrontal cortex	clozapine: increase in D2/D4 binding in prefrontal cortex

D_2 receptor binding in the striatum. However, no changes in the [^{3}H]-spiperone binding to mesolimbic tissue were found for any of three antipsychotic drugs. The authors concluded that dopamine receptor blockade is not maintained in the mesolimbic area following chronic treatment with haloperidol, sulpiride or clozapine. They suggested that under these conditions, the antipsychotic drugs investigated do not act selectively on mesolimbic dopamine receptors.

However, Florijn et al. (1997) and Tarazi et al. (1997) investigated the effect of repeated treatment with haloperidol, raclopride and clozapine on a large number of dopamine ligands in different brain areas. They reported a remarkable diversity in the apparent degree of dopamine receptor up-and down regulation, depending on the dopamine receptor ligand used and the anatomical localisation of the affected binding sites. Haloperidol, but not clozapine, up-regulated D_2 receptor binding in the striatum and accumbens and it was speculated that this region possibly plays a role in the induction of tardive dyskinesia and other neurological side effects. Few effects were seen for D_1 and D_3 binding sites, but a D_4 type dopamine receptor was uncovered in the caudate-putamen that was up-regulated by chronic haloperidol, raclopride or clozapine treatment.

5.3. Chronic experiments: frontal cortex

Several authors studied D_2 receptor binding in the frontal cortex after chronic treatment with antipsychotic drugs. Meller et al. (1982) found no change in [^{3}H]spiroperidol binding in the frontal cortex after chronic sulpiride or haloperidol. However Kazawa et al. (1990), detecting sulpiride-displaceable sites, noticed a 25% increase in D2 dopamine receptor density in the striatum as well as in the frontal cortex after haloperidol. Using autoradiography, Janowsky et al. (1992) showed that chronic treatment with haloperidol or clozapine increased D_2 receptor binding in the prefrontal cortex, whereas only haloperidol was active in the striatum. Similar results were reported by Florijn et al. (1997) who found an increase in D_2 sulpiride binding in the prefrontal cortex after repeated treatment with haloperidol, sulpiride and clozapine. The latter authors speculated that the frontal cortex is particularly involved in the clinical effects of both typical and atypical antipsychotic drugs.

Apparently dopamine receptor density in the frontal cortex is more sensitive to up-regulation during chronic treatment with antipsychotic drugs than that in mesolimbic or striatal tissue. Typical and atypical antipsychotic drugs behaved similarly.

5.4. Dopamine D_1 binding

Clozapine, unlike haloperidol, altered D_1 function as indicated by increased [^{3}H]-pitflutixol binding in the striatum (Rupniak et al., 1985a). Consisted with these findings, Jenner et al. (1985) found that sulpiride and clozapine, but not haloperidol, enhanced D_1 function as assessed by [^{3}H]-pitflutixol binding and dopamine-stimulated adenylate cyclase. Clozapine protected D_1 as well as D_2 sites in an *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) inactivation test (Saller et al., 1989). See et al. (1990) found that D_1 dopamine receptor binding in the nucleus accumbens was increased after clozapine. Both haloperidol and clozapine increased D_1 receptor density in the olfactory tubercle (Wan et al., 1996). Huang et al. (1997) using autoradiography, found increased D_1 binding in striatal and mesolimbic structures after chronic clozapine treatment, whereas haloperidol was without effect. At variance with these observations was the finding by Florijn et al. (1997) that chronic treatment with clozapine or haloperidol did not affect D_1 receptor binding. Most studies agree that D_1 binding is increased after chronic clozapine but not after chronic haloperidol.

5.5. PET and SPECT studies

Various authors determined the effects of antipsychotic drugs on dopamine receptors in the brain of humans and other primates by means of PET or SPECT methods. All authors agree that—at clinical doses—typical antipsychotic drugs occupy a high proportion (70–90%) of D_2 dopamine receptors in the human brain. The atypical antipsychotic drugs olanzapine and risperidone displayed lower occupancy values (60–75%), whereas clozapine and quetiapine occupied only 20–60% of the dopamine D_2 receptors (Farde et al., 1988, 1994; Farde and Nordstrom, 1992; Kapur et al., 1995; Nyberg et al., 1997; Gefvert et al., 1998; Mukherjee et al., 2001). SPECT studies have confirmed these findings (Pilowsky et al., 1996; Kufferle et al., 1997; Kasper et al., 1998; Dresel et al., 1998; Tauscher et al., 1999).

Data on regional effects of antipsychotic drugs are scarce. In most of the PET studies, D_2 binding was not quantified in areas other than the basal ganglia. Two recent studies (Mukherjee et al., 2001; Talvik et al., 2001) determined the extra-striatal dopamine receptor occupancies of antipsychotic drugs; however no regional differences were observed between occupancy rates of typical and atypical antipsychotic drugs. Interestingly, Xiberas et al. (2001) found that low plasma concentrations of amisulpride were associated with marked extra-striatal and low striatal binding, whereas higher plasma concentrations were associated with marked binding in striatal as well as in extra-striatal regions.

An important finding was that the threshold for clinical response and that for extrapyramidal side effects could be separated. Clinical responses were obtained at D2 dopamine receptor occupancy rates between 65% and 75%, whereas extrapyramidal side effects were seen at occupancies $>75\%$ (Farde et al., 1992; Nordstrom et al., 1993; Scherer et al., 1994; Knable et al., 1997; Kapur et al., 2000).

As in animal studies, clozapine was found to cause an increase in D_1 dopamine receptor occupancy of 33–59% which is considerably higher than the small changes (0–36%) seen after typical antipsychotic drugs (Wiesel et al.,

1990; Farde and Nordstrom, 1992; Farde et al., 1994; Nordstrom et al., 1995).

Most of the atypical antipsychotic drugs (such as clozapine, risperidone, olanzapine and quetiapine and ziprasidone) cause high occupancy rates (75–90%) for the 5-HT_2 receptors (Nyberg et al., 1993; Farde et al., 1995; Nordstrom et al., 1995; Kapur et al., 1998; Nyberg et al., 1999; Kapur and Remington, 2001; Gefvert et al., 2001). However, this effect is not common to all atypical antipsychotic drug, since after amisulpiride no occupation of 5-HT_2 receptors was seen (Farde et al., 1994; Trichard et al., 1998). Various authors have investigated a possible correlation between occupancy rates of D_2 and 5-HT_2 receptors and extrapyramidal side effects. Nyberg et al. (1999) concluded that the degree of 5-HT_2 receptor blockade (high for risperidone and low for haloperidol) did not correlate with extrapyramidal side effects. Similarly Kapur et al. (1997, 2000) concluded that concomitant 5-HT_{2A} blockade does not protect against extrapyramidal side effects.

5.6. Summary

(1) In acute studies, typical antipsychotic drugs did not discriminate between displacement of the ligand in mesolimbic and in striatal tissue. Some authors reported preferential binding of atypical antipsychotic drugs to mesolimbic areas, but others found no preference.
(2) Chronic experiments showed that haloperidol, but not clozapine, up-regulated D_2 receptor binding in the striatum. Few effects were seen in mesolimbic tissue.
(3) The dopamine receptor density in the frontal cortex is particularly sensitive to up-regulation during chronic treatment with both typical and atypical antipsychotic drugs.
(4) Results of most studies agree that D_1 receptor binding in striatal and mesolimbic tissue is increased after chronic clozapine treatment, but not after chronic haloperidol.
(5) PET studies showed that the D_2 occupancy threshold for clinical response (>60%) and that for extrapyramidal side effects (>75%) could be separated. No such relation was found between the degree of 5-HT_{2A} receptor blockade.

6. Microdialysis

The introduction of microdialysis as an in vivo sampling method has prompted extensive research on the effect of antipsychotic drugs on the release of dopamine in different brain regions of conscious animals.

6.1. Acute studies

Most microdialysis studies evaluated the acute effect of antipsychotic drugs on dopamine release. All authors agree that the typical antipsychotic drug, haloperidol, stimulates the release of dopamine in the striatum and nucleus accumbens, but not—or only transiently—in the prefrontal cortex (Moghaddam and Bunney, 1990; Pehek et al., 1993; Volonte et al., 1997; Kuroki et al., 1999; Rollema et al., 2000; Westerink et al., 2001). The 5-HT_2 blocking atypical antipsychotic drugs such as clozapine, olanzapine, amperozide, risperidone, zotepine and ziprasidone are effective in the striatum as well as in the prefrontal cortex. Most atypical antipsychotic drugs are approximately equipotent in the two brain structures, however clozapine was clearly more potent in the prefrontal cortex than in the striatum. Seroquel was the only atypical antipsychotic drug that did not stimulate dopamine release in any of the brain areas studied, including the prefrontal cortex (Volonte et al., 1997).

The benzamides show an activity profile different from that of the other atypical antipsychotic drugs. Both sulpiride and raclopride strongly stimulate dopamine release in the striatum, but have no effect on dopamine release in the prefrontal cortex (Moghaddam and Bunney, 1990; Nomikos et al., 1994; Westerink et al., 2001). Kuroki et al. (1999) reported that sulpiride increased dopamine release in the prefrontal cortex, but only at a high dose (25 mg/kg).

The typical pattern of dopamine release induced in the prefrontal cortex by the 5-HT_2 blocking antipsychotic drugs is probably not unique for the prefrontal cortex and might also be present in other cortical or limbic structures. In a voltammetric study, Marcus et al. (1996) investigated the effects of several antipsychotic drugs on the release of dopamine in the shell of the nucleus accumbens. It appeared that the antipsychotic drug-induced changes in dopamine release were comparable to those measured by micodialysis in the prefrontal cortex. Carboni et al. (2000) studied the effect of a series of typical and atypical antipsychotic drugs, including benzamides, on dopamine release in the nucleus stria terminalis. They found changes very similar to those described for antipsychotic drug-induced effects in the prefrontal cortex: marked stimulation of dopamine release by the 5-HT_2 receptor blocking antipsychotic drugs and no effect for haloperidol and raclopride.

6.2. Other receptors involved in controlling dopamine release in the prefrontal cortex

The mechanism by which clozapine and other atypical antipsychotic drugs increase dopamine in the frontal cortex—and probably also in several other cortical or limbic areas—is unlikely to be solely attributable to blockade of dopamine D_2 receptors. Various authors have investigated the role of additional receptor interactions in the stimulation of dopamine release in the prefrontal cortex. It was found that a combination of D_2 and 5-HT_2 receptor blockade was needed to enhance dopamine release in the prefrontal cortex (Millan et al., 1998; Kuroki et al., 1999; Rollema et al., 2000; Westerink et al., 2001). Similar effects had been reported earlier by Andersson et al. (1995) for a voltammetric study. It is emphasized that this is a synergistic effect since admin-

istration of a pure 5-HT_{2A} receptor antagonist or a pure dopamine D_2 receptor antagonist alone is not effective to stimulate the release of dopamine in the prefrontal cortex. The important role of 5-HT_{2A} receptor blockade in this regard was illustrated by the observation that co-administration of the 5-$HT_{2A/2C}$ receptor agonist (±)-2,5-dimethoxy-4-iodoamphetamine (DOI) but not of the 5-HT_{2C} receptor agonist, Ro 60-0175, suppressed the effects of clozapine on dopamine release in the prefrontal cortex (Ichikawa et al., 2001; Westerink et al., 2001).

Other than D_2 and 5-HT_{2A}, receptor interactions have been proposed to contribute to effects of atypical antipsychotic drugs on the release of dopamine in the prefrontal cortex. In this respect, α_2-adrenoceptors (Hertel et al., 1999) and histamine H_1 receptors (Dringenberg et al., 1998) have been suggested to play a role. Evidence was provided by Rollema et al. (1997, 2000) that 5-HT_{1A} receptor agonism contributes to the increase in dopamine release produced by clozapine and—more markedly—by ziprasidone, which are moderate and potent 5-HT_{1A} receptor agonists, respectively. Ichikawa et al. (2001) provided evidence that 5-HT_{2A} receptor stimulation increases cortical dopamine release via 5-HT_{1A} receptor stimulation.

Gessa et al. (2000) have shown that the changes in cortical dopamine release after antipsychotic drugs do not match with firing rate of identified mesocortical dopamine cells. This finding suggests that local presynaptic interactions might contribute to the release observed in the prefrontal cortex, a possibility supported by reports that infusion—via retrograde dialysis—with clozapine, but not with haloperidol, increased dopamine release (Pehek and Yamamoto, 1994; Gessa et al., 2000).

6.3. Chronic studies

The effect of repeated administration of haloperidol on basal levels of dopamine was evaluated in numerous studies. The results are ambiguous. It was reported that basal striatal dopamine release after chronic haloperidol was increased (See et al., 1995), decreased (Ichikawa and Meltzer, 1990, 1992), or unchanged (Yamamoto and Cooperman, 1994). Ichikawa and Meltzer (1991) showed that repeated treatment with clozapine had no effect on basal dopamine release in the striatum, whereas Yamamoto and Cooperman (1994) found an increase in basal dopamine release in the prefrontal cortex. In a subsequent study, Ichikawa and Meltzer (1992) reported that chronic treatment with amperozide and clozapine increased basal levels of dopamine in the striatum; and that only amperozide, but not clozapine, decreased dopamine release in the nucleus accumbens.

Repeated treatment with haloperidol induced tolerance to the haloperidol-induced increase in dopamine release in the striatum, but not in the nucleus accumbens (Ichikawa and Meltzer, 1991). Repeated treatment with clozapine induced tolerance to the increase in dopamine release in the nucleus accumbens (Ichikawa and Meltzer, 1991). However, Imperato et al. (1994) found no tolerance after haloperidol and sulpiride in the striatum.

The marginal effect of repeated haloperidol or clozapine treatment on basal dopamine releases values is not consistent with the depolarisation block of dopamine neurons that was observed in electrophysiological studies. Grace et al. (1997) have discussed this issue and provided evidence that damage following implantation of the microdialysis probe might have counteracted the depolarisation block.

6.4. Summary

(1) Most of the microdialysis studies focussed on dopamine release in the frontal cortex. It was found that atypical antipsychotic drugs—except the benzamides—stimulate the release of dopamine in the frontal cortex with the same order of magnitude as in the striatum. However the increase of dopamine release in the frontal cortex was not related to the clinical effects of the atypical antipsychotic drugs, as the benzamides were not effective in this brain area.
(2) It is not the dopamine D_2 receptor affinity, but a combination of 5-HT_{2A}, 5-HT_{1A} and D_2 affinity that determines the potency of antipsychotic drugs to enhance the release of dopamine in the frontal cortex. Local mechanisms at dopamine nerve endings (probably mediated by 5-HT_2 or 5-HT_{1A} receptors) are responsible for the clozapine-induced increase in dopamine release in the prefrontal cortex.

7. Conclusions

When we combine the results from the various methodological approaches, what conclusions can be drawn about the differential effects of antipsychotic drugs on dopamine neurons?

Post mortem tissue studies on acute administration of antipsychotic drugs provided some indication for a selective action of atypical antipsychotic drugs on dopamine metabolism in mesolimbic-cortical areas. However interference with the efflux of dopamine metabolites, being more pronounced in mesolimbic tissue might contribute to, or explain, the selective action of atypical antipsychotic drugs.

Results from repeated antipsychotic drug treatment showed that tolerance developed to the stimulation of dopamine metabolism. This tolerance was seen earlier in the striatum than in mesolimbic-cortical areas. The latter finding implies an interesting parallel with the clinical properties of the antipsychotic drugs, as tolerance to extrapyramidal effects is more pronounced than that to antipsychotic effects. This finding is also consistent the view that dopamine in the striatum and mesolimbic-cortical projections represents the extrapyramidal and antipsychotic effects, respectively. However, various authors have emphasised that the development of tolerance to antipsychotic drugs depends

on dose, time of dosing and duration of action. Finally, all regions develop tolerance, although the cortical areas are most persistent in this respect.

The results from *electrophysiological studies* are more conclusive for a regiospecific action of atypical antipsychotic drugs. The consistent observation that chronic treatment with clozapine and sulpiride induces a depolarisation block in mesolimbic dopamine neurons only suggests a selective action on A10 neurons. The depolarisation block of mesolimbic dopamine neurons seems to parallel most of the clinical properties of antipsychotic drugs. However, the mesocortical A10 neurons, considered by many authors to be crucial for antipsychotic activity, do not display depolarisation block after repeated treatment. Moreover, it is of great concern that virtually all electrophysiological studies have been carried out in anaesthetised rats.

Another significant result from the electrophysiological studies is the finding that additional blockade of the 5-HT_{2A}, the α_1-adrenoceptors and/or the muscarinic receptor drives the selectivity of dopamine cells for atypical antipsychotic drugs towards A10 neurons. These results suggest that A10 and A9 neurons are differently regulated by afferent projections. Electrophysiogical and microdialysis studies have indeed provided evidence that A10 neurons—at the somatodendritic level—are more sensitive than A9 neurons to certain receptor-specific compounds (e.g. drugs acting on cholinergic and γ-aminobutyric acid receptors; Westerink et al., 1998).

The *receptor binding studies*—measuring replacement by [^{3}H-spiperone] or more selective D_2 dopamine ligands—in general did not support a selective action of atypical antipsychotic drugs on A10 neurons. Although some authors provided evidence for selective actions, others could not confirm these conclusions. Results of chronic binding studies also provided little support for regio-selective effects. Repeated treatment with haloperidol, but not with clozapine, increased dopamine D_2 receptor binding in the striatum, while results for sulpiride were equivocal. Atypical as well as typical antipsychotic drugs had virtually no effect on mesolimbic tissues. Interestingly, increased dopamine D_2 receptor binding was observed after repeated treatment with antipsychotic drugs in the frontal cortex. However, no differentiation between typical and atypical antipsychotic drugs was observed in this brain area, as clozapine, sulpiride as well as haloperidol, all increased dopamine D_2 receptor binding.

The *PET binding studies* in humans produced results in good agreement with those of the animal studies. The occupancy numbers of dopamine D_2 receptors found for the various antipsychotic drugs are very important. These studies indicated that antipsychotic effects are evident at a D_2 receptor occupancy >60%, whereas extrapyramidal side effects occur at D_2 receptor occupancy >80%, irrespective of whether a typical or atypical antipsychotic drug is administered. Evidence was provided that administration of atypical antipsychotic drugs results in lower occupancies (< 75%) than do typical antipsychotic drug (70–90%). According to this view, even with a typical compound such as haloperidol, an antipsychotic effect without extrapyramidal side effects can be obtained just by optimising D_2 receptor occupancy. The issue of regional aspects of the occupancy of antipsychotic drugs has not yet been addressed in PET studies, because dopamine D_2 receptor binding was generally not detectable in areas other than the basal ganglia.

Most of the *microdialysis studies* that investigated the regional effects of antipsychotic drugs have focussed on the release of dopamine in the prefrontal cortex. It was found that atypical antipsychotic drugs that are 5-HT_{2A} receptor antagonists are equally effective to stimulate the release of dopamine in the frontal cortex and striatum, except clozapine, which is more effective in the frontal cortex. Haloperidol, but also the benzamides, were ineffective in the frontal cortex. Evidence was provided that the effect of antipsychotic drugs on dopamine release in the prefrontal cortex is largely determined by 5-HT_2 blocking properties; although other receptor interactions, such as 5-HT_{1A} agonism and α_2 adrenoceptor antagonism may play an additional role.

7.1. A regiospecific action for atypical antipsychotic drugs?

The present survey has provided evidence for two types of regiospecific actions that relate to mesolimbic and to mesocortical dopamine neurons. Based on electrophysiological studies, it was found that chronic treatment with atypical antipsychotic drugs induces a preferential depolarisation block of A10 dopamine neurons that project to the mesolimbic areas. The model represents certain clinical features of antipsychotic drug use and yields a possible explanation for the lack of extrapyramidal side effects of atypical antipsychotic drugs. However the mesocortical A10 cortical neurons are not active in this model and improvement of cognitive dysfunction and negative symptoms are difficult to account for in this model.

The frontal cortex has been much studied. Microdialysis studies have shown that atypical antipsychotic drugs that block 5-HT_2 receptors selectively enhance the release of dopamine in the prefrontal cortex when compared with typical antipsychotic drugs. These properties might explain certain beneficial effects of atypical antipsychotic drugs, such as improvement of cognitive dysfunction. The finding that repeated treatment with antipsychotic drugs increased dopamine D_2 receptor binding in the frontal cortex is also of interest in this regard. However, the fact that neither the microdialysis nor binding studies could show a clear differentiation between typical and atypical antipsychotic drugs, illustrates the difficulty of localising clinical effects of antipsychotic drugs in terms of regional dopamine neurons.

Recently new insights have been published that might change our view of the mechanism of action of typical and atypical antipsychotic drugs. PET studies repeatedly showed that additional 5-HT_2 receptor blockade does not

protect against extrapyramidal side effects. This is a significant finding, as most of the modern antipsychotic drugs were designed on the basis of a favourable "5-HT_2-D_2 receptor ratio". Another important consideration is the increasingly popular notion that certain benzamides (remoxipride and amisulpride) are full members of the atypical antipsychotic drug class. Interestingly these compounds do not have 5-HT_{2A} receptor blocking properties. Benzamides are weak, but relatively pure dopamine $D_{2/3}$ antagonists, the D_2 receptor blocking properties of which were shown to be pharmacologically most relevant (Vanhauwe et al., 2000).

The efficacy of the benzamides as typical antipsychotic drugs suggests that low to moderate dopamine D_2 receptor blockade is probably the most important—if not the only—criterion that determines atypicality (Westerink et al., 2001). Kapur and Seeman (2001) reached similar conclusions when they discussed the dopamine D_2 occupancy rates in clinical PET studies. A moderate dopamine D_2 receptor occupancy, probably in combination with a high dissociation rate, might fulfil optimal clinical conditions for an antipsychotic drug, without inducing extrapyramidal side effects. Whether this concept is also valid for other "atypical" effects of antipsychotic drugs, such as the improvement of negative symptoms and cognitive dysfunction and efficacy in neuroleptic-resistant schizophrenia, needs further investigation.

The concept of Kapur and Seeman has a close resemblance to explanations that were given about 30 years ago, at the start of the long search for what constitutes an atypical antipsychotic drug, when it was hypothesised that the atypical actions of clozapine resulted from its "surmountable blockade of dopamine receptors" (Bartholini et al., 1972; Burki et al., 1974, 1975).

Interestingly these new insights are based on PET-studies of the human basal ganglia and not on the comparison of different brain areas. Apparently, for this concept, it is not necessary that an ideal antipsychotic drug should act on a particular type of dopamine neuron, as it is the moderate dopamine D_2 receptor occupancy that determines the desired clinical effects. Both beneficial and side effects of antipsychotic drugs might be, dose dependently, localised in A9 as well as A10 dopamine neurons.

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