Chapter 8
Summary and general discussion

Antipsychotic drugs are not only effective for psychosis, but also for Tourette's syndrome. Their use is limited by their extrapyramidal side-effects (EPS). An atypical antipsychotic can be defined as a compound that has a significant antipsychotic action on positive symptoms but with no or few EPS (Meltzer 2000). This definition is often expanded to include efficacy in treatment-resistant schizophrenia, amelioration of negative- and cognitive symptoms, and the lack of sustained prolactin elevation.

The main objectives of the present thesis, divided in a preclinical and a clinical part, were to study the atypical antipsychotic risperidone with respect to 1) its mechanism of atypical action, and 2) its potentials in Tourette's syndrome.

The major findings of the present thesis are as follows:

PART I (chapter 2-4) investigated some aspects of the mechanism of the "atypical" action of the atypical antipsychotic risperidone in the basal ganglia, using in vivo extracellular single cell recordings. In our electrophysiological studies of the firing pattern of midbrain dopamine neurons in vivo, risperidone displayed a so-called mesolimbic-selective profile, corresponding to an atypical action profile. Secondly, in similar studies of GABA-ergic neurons in the substantia nigra reticulata (SNr), we found that the neuronal activity of the SNr readily discriminates between the classical neuroleptic haloperidol and the atypical antipsychotics risperidone and clozapine. Thus we propose that these experimental models possess significant predictive validity in the identification of drugs with an atypical antipsychotic profile.

PART II (chapters 5-7) aimed at determining risperidone's therapeutic potential in Tourette's syndrome, a disorder thought to be strongly related to a dopamine dysfunction within the basal ganglia. The conclusion to be drawn from the three clinical studies described here is that atypical antipsychotics, such as risperidone, may possess significant therapeutic efficacy in the treatment of Tourette's syndrome.
**Chapter 8**

Risperidone differentially affects midbrain dopamine neurons

Chapter 2 describes the acute effects of risperidone and haloperidol on firing pattern of mesocorticolimbic dopamine neurons in the ventral tegmental area (VTA) and the nigrostriatal dopamine neurons originating in the substantia nigra compacta (SNC), dopamine pathways generally associated with the antipsychotic action and EPS liability of antipsychotic drugs, respectively.

Using extracellular single cell recordings in vivo, we found that risperidone increased the firing rate and the burst firing of VTA dopamine neurons in a dose dependent manner. Yet, risperidone failed to significantly affect the firing pattern of SNC-dopamine neurons. In contrast, haloperidol increased the firing rate of both VTA and SNC neurons, whereas burst firing increased only at the highest dose tested, and did so in both populations. These results demonstrate that risperidone, but not haloperidol, preferentially activates mesocorticolimbic dopamine neurons originating in the VTA, with a relative sparing of the striatal projecting SN dopamine neurons. This lower propensity to activate the nigrostriatal dopamine system is compatible with comparative less impairment of dopamine function in motor control circuitry, implicating a low propensity for EPS, i.e. an atypical mode of action.

The activation of burst firing in VTA dopamine neurons induced by risperidone may indicate an improvement of the antipsychotic efficacy of this drug in comparison to classical antipsychotics. Thus, an increase in burst firing of limbocortical projecting neurons, i.e. a more phasic than tonic activity, implies an enhanced signal-to-noise ratio of dopamine signaling in these neurons. This may consequently lead to a more adequate responsiveness to novel stimuli, which may be of importance during behavioral adaptation to new environments and during learning (Schultz et al., 1993, Schultz et al., 1997; Svensson, 2000). Burst activation of cortical VTA dopamine neurons has previously been proposed to represent a novel mechanism by which potent 5-HT₂ antagonist antagonists ameliorate prefrontal cortical dopamine function, a dopamine projection frequently associated with negative and cognitive symptomatology in schizophrenia (see Svensson et al., 1995; Weinberger, 1987).

The present study supports previous evidence, which indicates that 5-HT₂ antagonist antagonism, when added to relatively moderate dopamine D₂-antagonism, preferentially activates mesocorticolimbic dopamine projections as well as burst firing in VTA neurons (Anderson et al., 1995; Svensson et al., 1995). The mechanism of action for risperidone presumably involves interference with a number of neurotransmitter systems. These neurotransmitters, apart from dopamine receptor antagonism, e.g. 5-HT and NA, may act upon remote systems, such as cortical structures with neuronal input to the midbrain dopamine neurons. In addition, serotonergic and noradrenergic inputs to the VTA have both been
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demonstrated to modulate the firing pattern of VTA dopamine neurons (Ugedo et al., 1989; Grenhoff and Svensson, 1988). Renewed studies on risperidone with pretreatment with a 5-HT agonist and a NA-agonist appear warranted to determine the relative contributions of e.g. 5-HT2A, α1-, or α2- receptor antagonism in the specific responses elicited by risperidone in the SNc and VTA.

There are some caveats to this study. The study is limited to only acute administration of drugs, while long-term treatment with antipsychotics has also been reported to alter the firing pattern of midbrain dopamine neurons. In this respect, it should also be noticed that acute administration of high doses of risperidone in this model did not further alter the response profile, although it is known that risperidone in corresponding doses in psychiatric patients often can lead to development of EPS (see introduction). Comparisons with chronic treatment with these antipsychotics appear warranted in order to more faithfully model the clinical situation, in which both antipsychotic action and most of the motor side effects are observed only after several weeks of treatment. Nevertheless, this apparently lower face validity of this type of study does not necessarily alter the empirically established predictive validity of this type of experiment (Grace et al., 1997).

In the present study depolarization-block was not subject of study. According to the studies of Grace et al. (cf. Grace et al., 1997) the depolarization block theory of antipsychotic action proposes that inactivation of midbrain dopamine neurons is a crucial and delayed event in the induction of the therapeutic effect of neuroleptics. However, this phenomenon apparently cannot be reproduced in the awake, paralyzed preparation and may well be an artifact induced by use of chloral hydrate anesthesia (Mereu et al., 1995; Melis et al., 1998). In the present study, some cells did show an acute depolarization block during the dose response trial, resulting in a silencing of the dopamine neuron, which returned to a firing mode after apomorphine administration (data not shown). These results were excluded from further analysis. Regardless of the putative influence of chloral hydrate anesthesia on the responsiveness of the firing patterns of midbrain dopamine neurons to antipsychotic drugs, this experimental paradigm remains a robust and reliable means of differentiating antipsychotic drugs with classical from atypical profiles, and has thus empirically been shown to possess a high predictive validity (Grace et al., 1997). Novel techniques e.g. electrophysiology in awake animals hold promise by entirely circumventing the shortcomings of use of anesthesia in the near future. Nevertheless the theory of depolarization block appears incompatible with adequate physiological functioning of the individual since widespread depolarization block of dopamine neurons in vivo would not allow sufficient dopamine response dynamics for the individual to respond in a timely manner to various stimuli and situations.
As for Tourette's syndrome, these findings can be interpreted as follows. The mesolimbic dopamine system projects onto the ventro-medial striatum, a region intimately coupled to limbocortical circuitry. In rodents strong mesolimbic dopamine output is correlated with rewarding and addictive stimuli, with behavioral activation, i.e., an increased locomotor activity and with stereotypy (Fibiger et al., 1992; Westerink et al., 1997; Gessa et al., 1998). All these effects can readily be blocked by both classical and atypical antipsychotics. It has been hypothesized that the ventral-medial striatum is involved in the clinical characteristics of Tourette's syndrome (see Brito, 1997). Tentatively, risperidone's preferential effect on the mesolimbic system may implicate an improved efficacy for Tourette's symptoms. Concomitantly, the relative sparing of the nigrostriatal DA system is compatible with a low incidence of EPS. Following this theory of mesolimbic selectivity other atypical antipsychotics might also be expected to be beneficial in Tourette's syndrome. Indeed, recent findings with olanzapine and ziprasidone, both atypical antipsychotics with a high 5HT₂/D₂ affinity ratio were shown to be effective agents in Tourette's syndrome (see below). However, clozapine was not found to be effective in a small study in hyperkinetic disorders (Caine et al., 1979). Conceivably, this may be due to the fact that clozapine has a very low affinity for the D₂ receptor. The significant therapeutic responses of tics to substituted benzamides, tiapride, sulpiride and remoxipride, lent further support for a role of the mesolimbic selectivity (Eggers et al., 1988; Robertson et al., 1991; Buitelaar et al., 1995). These atypical antipsychotics also have been proposed to possess high affinity for the ventromedial striatum. Yet, the benzamides are not "multireceptor" antagonists like clozapine but relatively selective dopamine D₂/D₃ antagonists. This suggests a different mechanism underlying their atypical action, tentatively based on e.g. their much higher affinity for the D₃-receptors, which are found in high concentrations in the target areas of the mesolimbic dopamine system (see Sokoloff et al., 1992; Den Boer and Korf, 2000).

The increased burst firing of the VTA dopamine neurons, as seen with risperidone may indicate an improved capacity of dopamine cells to respond adequately to salient stimuli (Svensson et al., 1995). In this respect, the brain's disturbed gating function as proposed by Carlsson (1988) to underlie schizophrenia, may also serve as a putative model to understand the neurobiology of Tourette's syndrome. Such a gating function may very well be not restricted to a "thalamic filter", but can also be located in several other parts of the brain, e.g. the prefrontal cortex or the nucleus accumbens (Carlsson et al., 2000, Grace, 2000). Tourette's syndrome is characterized by a heightened sensitivity to internal somatosensory as well as external environmental cues (See Anderson et al., 1999), suggesting that the brain is in a state of "hypersalience". Clearly the dopamine system has a strong modulating influence on this salience system.
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Dynamic variations of dopamine cells, as seen with increased burst firing, may be an important mechanism for the brain to adapt to new situations (Shultz et al., 1993). Tentatively, in Tourette’s syndrome an improvement of the dynamic response range of dopamine activity in response to environmental stimuli may help to alleviate situationally inappropriate or irrelevant behavioral output, e.g., tics (cf. Carlsson et al., 2000; Grace, 2000; Svensson, 2000).

Research to elucidate the mechanisms of action of atypical antipsychotics in tic suppression is sparse and therefore any hypothesis is still rather speculative. Obviously, there may very well be several pathophysiological differences between schizophrenia and Tourette’s syndrome that may explain differences in therapeutic efficacy in these two conditions. Nevertheless, improving dopaminergic functions in the mesolimbocortical system may be hypothesized as means for atypical antipsychotics to exert both antipsychotic and tic-suppressive action. On balance these findings suggest that there may theoretically be several pharmacological means to achieve an “atypical” antipsychotics profile not only in schizophrenia, but in tic-disorders as well.

Effect of risperidone, clozapine and haloperidol on neuronal activity of the SNr

The model described above reliably detects differential effects of antipsychotics on the mesolimbic-mesocortical vs. the nigrostriatal dopaminergic system at the cell body level. However, these two dopaminergic systems are part of the basal ganglia, in which their role is clearly modulatory in character (review: DeLong, 1990). Projections of these two dopaminergic systems are not confined to limbic vs. striatal postsynaptic structures (Nauta and Domesick, 1984; Gerfen et al., 1985). Therefore, insight in the consequences of specific changes in dopaminergic activity for postsynaptic structures should contribute to understanding how therapeutic and side effects of neuroleptics are mediated.

The output neurons of the basal ganglia may provide good alternative structures to investigate. The SNr, together with the GPi, is considered to represent a major part of these output nuclei. The SNr neurons receive cortically originating afferents via the dorsolateral striatum and they exert an inhibitory action on thalamo-cortical target areas. Thus, the SNr is located in a postsynaptic target area of the striatum and may therefore play a pivotal role in the routing of information from the cortex through the basal ganglia onto the thalamus and related cortical areas.

We therefore hypothesized, in chapter 3, that the SNr may prove useful as an experimental basis for understanding some aspects of the antipsychotic action-mechanisms. Using extracellular recordings, we compared risperidone, clozapine and haloperidol with respect to their effects on the neuronal activity of GABA-ergic neurons in the SNr. This study demonstrates that risperidone and
clozapine inhibits SNr neurons, whereas haloperidol had little effect or slightly enhanced the neuronal activity. Thus, our data suggested a correlation between the activity level of the SNr and the atypical character of antipsychotics.

The role of 5HT₂/D₂ antagonism in the atypical action on SNr activity
Several authors have postulated that concurrent 5-HT₂ and D₂-antagonism is essential for the atypical character of a number of these new antipsychotics; more specifically, a high 5-HT₂/D₂ occupancy ratio (Meltzer, 1989, Deutch et al., 1997). We therefore evaluated the role of serotonin (5-HT) in this differential effect of typical and atypical antipsychotics on the SNr activity. Indeed, pretreatment with the non-specific 5-HT agonist quipazine partially blocked the characteristic inhibitory effect of risperidone, thus suggesting a serotonergic involvement in the modulation of the SNr neuronal activity.

In chapter 4 the contribution of the 5-HT₂ receptors antagonism was further investigated. Our hypothesis was that a combination of LY 53857, a potent and selective 5-HT₂, receptor antagonist and raclopride, a selective D₂-receptor antagonist would induce a similar effect on SNr activity as observed with the atypical antipsychotics. It was found that such a combined 5-HT₂/D₂ receptor blockade could mimic the action profile of risperidone and clozapine on the SNr neurons. Interestingly, the dosages of the D₂ antagonist pretreatment turned out to be essential for the atypical-like effect. Thus, modification of the neuronal response by the 5HT₂ receptors antagonist was accomplished by pretreatment with low but not high doses of the D₂-receptor antagonist raclopride. This observation corresponds with a number of pre-clinical data (see introduction). It also is in accordance with the clinical notion that the atypical profile of most atypical antipsychotics is lost when the D₂-receptor blockade exceeds a certain threshold, i.e. > 75-80% D₂ receptor occupancy (Farde et al., 1992; Kapur et al., 1996, Kapur et al. 1999).

The neuronal activity of the SNr as experimental model to predict an atypical action profile
Using the same experimental setup, Timmerman and co-workers found that the acute administration of the atypical antipsychotic olanzapine also inhibits the SNr activity (Timmerman et al., 1999). This finding supports the SNr-neuronal activity model as a screening test for atypical antipsychotics.

For a paradigm to have predictive validity, it should first be determined whether the observed effect predicts a therapeutic action or unwanted side effects, or both. In general, similarities between new drugs and haloperidol may select for drugs with an antipsychotic action, but also with the propensity to induce EPS. Differences between a new drug and haloperidol may hint to an atypical profile. Moreover, similarities with clozapine may give clues to an aty-
pical mechanism, e.g., low propensity for EPS, alleviation of negative symptoms or improvement of cognitive functioning. However, it should be kept in mind that efficacy on these latter symptom clusters are most reliably studied in specific behavioral models. Nevertheless, since administration of haloperidol showed an effect opposite to clozapine and risperidone, the response of the SNr neurons may apparently not be related to an antipsychotic effect, as the three compounds do not essentially differ in this respect. Therefore, the clinical correlates of the SNr neuronal activity could theoretically point to certain specific atypical aspects of these compounds (see also Middleton and Strick, 2000).

A general criterion for a screening model states that drugs of different chemical structures should be active in this model (see Ellenbroek, 1993; Ellenbroek and Cools, 2000). Using the SNr neuronal activity as a screening model for atypicality, two dibenzazepines (olanzapine and clozapine) and one benzisoxazol-derivative (risperidone) tested “positive”, whereas one butyrophenone (haloperidol) tested “negative”. The 5-HT receptor agonist quipazine was able to antagonize the effect of risperidone. This compound has not been used as a clinical probe. Notably, combined 5-HT2/D2 antagonism also tested “positive”, i.e. had an inhibitory effect on SNr neuronal firing. The D2-receptor antagonist raclopride tested “negative”, i.e. its response was similar to haloperidol. Raclopride has undergone clinical trials, but it was not marketed since it did not possess an atypical antipsychotic profile. The 5-HT2A/2C receptor antagonist LY53878 tested “negative” in the low dose range, but gave an inhibitory “atypical-like” response in the high dose range. Whether this inhibitory effect of LY 53857 would relate to an atypical action profile for 5-HT2-receptor antagonists is an interesting issue that awaits clinical confirmation. The novel and highly selective 5-HT2A receptor antagonist M 100,907 is undergoing advanced clinical testing and the tentative efficacy of this compound may shed further light on this issue.

In the present experiments, the SNr activity was evaluated in an acute dose-response curve model. The characteristic inhibitory effects were achieved already at low doses. If the inhibition of SNr activity does indeed relate to the modulation of motor side effects, it appears predicted that the “atypical-like” response of risperidone may change into a “typical-like” response for the higher dose-range, since the atypical profile of risperidone does not hold for high doses in schizophrenic patients. However, the acute experiments with risperidone did not show a dose-dependent correlation between the doses of risperidone and the atypical-like response. In fact, the inhibitory effects of risperidone on the SNr seemed to plateau already in the lower dose range and to stay unchanged afterward. In contrast, in the pretreatment experiments, there was a differential effect between low and high doses of D2 blockade. Thus, for the combination of the 5HT2 - and the D2-antagonists, an atypical-like response
was found only with low, but not high doses of D₂ receptor antagonist.

Another important aspect of animal models for antipsychotic treatment concerns the delayed onset of the antipsychotic effect in clinical practice. The issue of chronic treatment was not addressed in the current work. In the publication by Timmerman et al. (1999) the effect of chronic treatment was studied for olanzapine and clozapine. It was found that after chronic treatment with 1 mg/kg per day for three weeks, challenge with olanzapine resulted in an inhibition of the SNr activity, similar to the one seen with acute treatment of olanzapine and clozapine. In addition, the long-term treatment experiments in the study by Timmerman and co-workers evaluated the effect of two different dosage regimens of the atypical antipsychotic olanzapine (Timmerman et al., 1999). In that study, a low dosage regimen of olanzapine yielded a similar response for both acute and chronic treatment (see above). However, following chronic treatment with a relatively high dose of olanzapine (5mg/kg/day), the challenge with cumulative doses of olanzapine did not significantly affect the neuronal activity of the SNr, comparable with long-term administration of haloperidol. Thus, the atypical profile within this model was lost in a high dose regimen of olanzapine. Treatment with comparable high doses of olanzapine has yielded catalepsy in rats in one study, whereas in other electrophysiological studies mesolimbic selectivity was preserved at even higher doses (Skarsfeldt, 1995; Stockton and Rasmussen, 1996). Interestingly, clozapine yielded an atypical-like reaction after chronic high dose treatment (Timmerman et al, 1999). We did not test chronic treatment with risperidone in these studies. Further experiments may reveal if chronic treatment with high dosages of risperidone would give similar results as olanzapine.

Finally, a general point of discussion concerns the effect of general anesthesia on the firing pattern in the SNr preparations. In awake animals slow oscillations are seen that presumably are dependent on the ongoing activity in afferent structures, whereas there is a remarkable lack of significant oscillatory activity under chloral hydrate anesthesia (cf. Ruskin et al., 1999). Moreover, in freely moving rats, movement-related elevations of firing in SNr-neurons were seen as the major response, although inhibitions were also observed (Gulley et al., 1999).

Taken together, the present studies and the report by Timmerman et al., (1999), support predictive validity of this experimental paradigm within the SNr as a novel technique to assess the putative atypical antipsychotic effects of experimental drugs, since

1) classical neuroleptics differentiate from atypical antipsychotics;
2) combined 5HT₂ and low D₂-antagonism mimics an atypical-like profile;
3) results in acute vs. chronic studies are readily comparable;
4) chronic treatment results suggest a dose-dependent relation between the compounds and their effects.
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To further validate the paradigm of SNr neuronal activity for atypicality studies in awake animals appear warranted. Moreover, studies are needed with e.g. additional classical (pimozide) and atypical antipsychotics (ziprasidone, zotepine), atypical drugs using other mechanisms (substituted benzamides), drugs with EPS but without antipsychotic action, non-dopaminergic putative antipsychotics and with noradrenergic, histaminergic, cholinergic and serotonergic agents. Finally, studies in experimental models for schizophrenia, such as the phencyclidine model, may lend promise in the improvement of our insight into the role of the SNr in the mechanism of action of antipsychotic drugs.

Functional implications SNr atypical antipsychotics and Tourette’s syndrome.

Is it then possible to correlate the results of our SNr-recordings to the mechanisms of action of the atypical antipsychotics and to the current concepts of basal ganglia functioning?

Firstly, risperidone shows similarities with clozapine and olanzapine and contrasts haloperidol. This suggests that the effects seen in the SNr correspond to the atypical properties of clozapine and not to the dopamine-related antipsychotic action or motor-related side effects. Consequently, the observed effects may relate to the characteristic properties of atypical antipsychotics.

We found that the atypical antipsychotics induced a decrease of SNr-neuronal activity. The above outlined neuroanatomical schematic model of cortico-subcortical circuitry predicts that not dopamine receptor blockade, but dopamine receptor stimulation induces a decrease in the firing rate of the SNR-neurons (Albin et al., 1989; Delong 1990). In other words, the atypical antipsychotics produced effects that are compatible with dopamine agonistic activity, within the cortico-subcortical circuitry model. A cautious interpretation of these findings would thus be that the dopaminergic-like activity of the atypical antipsychotics, found in the SNr, reflects ways to counteract EPS. It may also indicate a means to alleviate symptoms of motivational disturbance, anhedonia, and cognitive impairment, conditions generally associated with the hypodopaminergic state of hypofrontality in schizophrenia (Weinberger, 1987).

In our SNr-studies dopamine D2 receptor blockade by haloperidol and raclopride did not change or, in a certain dose range, slightly increased SNR activity. This latter response is in accordance with the cortico-subcortical circuitry model that predicts that dopamine receptor blockade corresponds with an increased inhibitory action of the basal ganglia output neurons. Previous experimental studies with dopamine agonists have yielded variable effects, with both increased and decreased activity (Waszczak et al., 1984; Walters et al., 1987). Moreover, the clinical implications of an inhibitory effect on the SNR-neurons are still far from elucidated. For example, Beijani et al. (1999) published
a case report on electrical stimulation of the SNr in a patient with Parkinson Disease. The deep brain stimulation, most probably resulting in a functional inhibition of GABAergic neurons, induced clinical features of an acute depression, but did not affect her motor symptoms. In another case report, cerebral vascular insult affecting the SNr caused hallucinations and desorientation (McKee et al., 1990). Therefore, one must be cautious to interpret the present data too rigidly in view of a simplified model of the basal ganglia functioning (for a critical review on basal ganglia functioning see Chesselet and Delfs, 1996; also Parent and Cicchetti, 1998).

In conclusion, at present it is impossible to be conclusive regarding a potential association between the SNR activity and the mechanisms underlying atypical antipsychotic efficacy, although the present findings present an attractive heuristic hypothesis.

To draw up an analogy between the effects of risperidone on the SNR-activity and risperidone’s clinical effect in Tourette’s syndrome may be equally complex. Increased activity of the SNR is widely proposed to represent part of the mechanism underlying hypokinetic disorders such as Parkinson’s disease (see above). Conversely, hyperkinetic disorders such as Huntington’s Chorea or possibly even Tourette’s syndrome are linked to a hyperactivity of thalamocortical circuitry, and hence with a decreased activity of the SNR. In this paradigm, the inhibition of SNR activity induced by risperidone would predict a clinical worsening of tic-symptoms, which is obviously not the case (cf. below). Interestingly, worsening of tics was found after a low dose of clozapine in a small group of hyperkinetic patients, but no effects were seen in the higher dosages of clozapine (Caine et al., 1979). However, the reports on clozapine are of limited number.

There is an apparent paradox between hyperkinetic disorders, the inhibition of the SNR activity by atypical antipsychotics and the beneficial effects of risperidone in Tourette’s syndrome. Furthermore, these data are at variance with neurosurgical treatments of Tourette’s syndrome, which presumably exert their action via severing thalamo-cortical and cortico-thalamic projections (see Vandewalle et al., 1999). An explanation for this discrepancy may be found in the temporal aspect of the medical treatment, i.e. there is a delayed onset of risperidone’s effect on tics of one to two weeks. However, the pathological changes in Tourette’s syndrome are still unknown and the effects of chronic risperidone treatment on the SNR neuronal activity have not been studied yet.
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The therapeutic potential of risperidone in the treatment of Tourette's syndrome

The second part of this thesis aims at identifying the role of risperidone in the treatment of Tourette's syndrome. Rationale for these studies is the notion that dopamine antagonists are the mainstay of pharmacotherapy for tic disorders but that their use is restricted by their unwanted side effects. Therefore, studying the potentials of risperidone may provide new therapy options.

The first step was to assess risperidone's efficacy - if any - on tics. Next was then to determine whether its side effect profile is advantageous to that of the classical compounds. In chapter 5 risperidone is shown to be effective for reducing tic symptoms in a small open-label 4-week study in eleven patients. The drug was well tolerated with sedation as the most frequently occurring adverse reaction. Similar positive results were reported shortly after our study by Lombroso et al., (1995) and by Bruun and Budman (1996), who both published an open study in children and adolescents with tic-disorders. Robertson and coworkers did find a substantial number (24%) of non-responders, next to a 58% of responders in their group of 24 patients in a case-finding study (1996). Notably, these authors also reported a worsening of tics in 3% of their patient cohort. The positive findings in these preliminary studies warranted a double-blind comparative trial for risperidone.

In chapter 6 risperidone is compared with pimozide in a multicentre, double-blind parallel group study with a 12-week duration. Pimozide was chosen for comparison since it has been the first choice drug for tic-suppression, superior to haloperidol both in efficacy and tolerability. There was significant improvement of the tics in respect to the Tourette Symptom Severity Scale (TSSS) for both groups. Forty-one of the 50 patients completed the study. At the completion to the study, 54% patients in the risperidone group and 38% patients in the pimozide group had only very mild or no symptoms on the global severity rating of the TSSS. Statistical analysis demonstrated that both treatment strategies were equally effective in terms of tic-suppression. The severity of EPS was low in both groups, with a lower incidence of people reporting akathisia for risperidone.

We further studied whether risperidone would be better than pimozide in reducing severity of obsessive-compulsive symptoms. Although OCB improved in both treatment groups, symptom reduction, as measured on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), achieved statistical significance only in the risperidone group. It can be concluded that risperidone is as efficacious as pimozide in tic suppression and that risperidone is well tolerated in patients with Tourette's syndrome. Because of this more favorable efficacy- and tolerability profile, risperidone is proposed as a first-line drug in the treatment of Tourette's syndrome.
However, results from clinical trials in Tourette's syndrome do not easily translate into guidelines for daily practice since they are often hampered by short durations, selective entry-criteria, exclusion of co-morbidity, restriction of other psychotropic drugs and/or placebo-responses. From this perspective, longer treatment studies are indicated to determine the role of risperidone in TS treatment. Chapter 7 describes the treatment of Tourette patients with risperidone and/or sulpiride in a retrospective survey over a three-year period. The main objective of this study was to describe the acceptability and dosing requirements of these two atypical antipsychotics over the long term. Sulpiride was included because of its widespread use as a first line drug in a number of European and South African countries.

The results of this naturalistic study show that long-term treatment with risperidone and sulpiride leads to discontinuation in approximately half of the patients within 12 months. Adverse events (such as sedation, depression and weight gain) and planned drug-withdrawals were the main reasons for discontinuation. EPS were reported in a substantial number of patients in both groups. However, patients who continued risperidone or sulpiride did not differ from patients free of medication, with respect to EPS and subjective feelings of well being. Moreover, this 3-year survey of 36 patients did not reveal a single case of tardive dyskinesia. The naturalistic setting yielded a wide variety of co-medications and co-morbidity, emphasizing the occurrence of possible drug-drug interactions. Limitations of this study include its retrospective nature and the use of both drugs in a small number of patients. Furthermore the study was biased towards patients, who successfully completed planned drug-withdrawals. Thus, for a selected portion of Tourette's syndrome patients, both risperidone and sulpiride were acceptable drugs for tic suppression, in a mean dosage of 2.67 mg/day and 493 mg/day respectively. It can be concluded that, when medication is needed in Tourette's syndrome, atypical antipsychotics, such as risperidone or sulpiride, should be tried first, before considering for example a classical neuroleptic.

**Mechanism of action of risperidone in Tourette's syndrome**

The present findings raise the question how atypical antipsychotics can produce tic-suppression. The doses of risperidone used in this study (0.5-6 mg/day) are expected to yield both a high 5-HT_{2A}-receptor occupancy and a moderate up to high D_{2}-receptor occupancy. Hence it is feasible that the dopamine D_{2}-receptor blockade accounts for the observed efficacy of risperidone in tic-suppression. Of note, motor side effects were not completely absent in this study, pointing to a certain degree of dopamine blockade in the nigrostriatal system. On the other hand, the fewer EPS-like adverse events, *i.e.* less akathisia, in the...
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Risperidone group lends support to the mesolimbic selectivity for risperidone. In this respect, the high affinity for 5-HT2 receptors relative to D2-receptors may have been contributory to risperidone’s favorable EPS profile. Moreover, one should realize that the 5 HT2A antagonistic properties of an antipsychotic do not necessarily implicate an overall anti-serotonergic effect. In fact, in experimental studies risperidone has been shown to indirectly enhance serotonergic activity (Hertel et al., 1996). Therefore, in addition to the 5-HT2 receptor blockade, an increased output of 5-HT in the cortex acting upon other postsynaptic 5-HT-receptors may have been supportive for the drug’s effects on the obsessive-compulsive symptoms in this study. This notion is strengthened by other studies that have suggested a beneficial role for 5HT2/D2 antagonists such as risperidone and olanzapine (Stein et al., 1997; Koran et al., 2000; McDougle et al., 2000) in the treatment of concurrent OCD and tic disorders. Finally, the alpha-1 and alpha-2 adrenoceptor blockade by risperidone may also have contributed to its efficacy in Tourette’s syndrome, considering e.g. clonidine’s efficacy in Tourette’s syndrome.

From a clinical and a research point of view, dosage requirements are of importance. The mechanism of tic-suppression of antipsychotics in Tourette’s syndrome is probably related to their blockade of striatal dopamine receptors. It is generally accepted that extensive blockade (i.e. > 80%) of striatal dopamine-D2 receptors by neuroleptics causes EPS and hyperprolactinaemia. In PET-studies with schizophrenic patients risperidone at 3 mg/day corresponds with 70-80% D2 receptor occupancy, which is sufficient to induce an antipsychotic effect but insufficient to induce EPS (cf. Farde et al., 1992; Kapur et al., 1999). Similar PET-studies in Tourette’s syndrome may evaluate the D2 receptor occupancy needed for effective tic suppression. This may learn that doses that are prescribed nowadays in clinical practice may be relatively high. In addition, such studies may answer the question whether Tourette patients have a lower threshold for EPS and/or other side effects in comparison to schizophrenic patients.

Finally, a comparatively larger therapeutic index for the new atypical drugs, i.e. a clear separation between the efficacious tic suppressive dose and the EPS inducing dose, would suggest that the atypical mode of action of these new drugs is also applicable to the mechanism of tic suppression. This would be circumstantial evidence for the predominance of the mesolimbic system in the pathology of Tourette’s syndrome (see introduction) or it would support the hypothesis that atypical antipsychotics call upon additional non-dopaminergic receptors for their beneficial effects in Tourette’s syndrome.
Treating tics with atypical antipsychotics.

Neuroleptic-treatment for Tourette’s syndrome carries several risks and limitations and the new atypical antipsychotics may offer the clinician new therapeutic tools. To date, risperidone’s efficacy on tics is well established; other drugs are in the phase of clinical testing.

Several preliminary studies suggested efficacy for olanzapine in tic-suppression (Benji Semerci, 2000, Karam-Hage and Ghaizuddin, 2000). Recently olanzapine was found effective in tic suppression in an open study with 14 patients with Tourette’s syndrome, with sedation and weight gain as the major side effects (Stamenkovic et al., 2000). Another atypical antipsychotic, ziprasidone was effective and well tolerated in a group of 28 children and adolescents with Tourette’s syndrome in a double-blind placebo controlled study (Sallee et al., 2000). Transient somnolence was the most commonly reported side effect; akathisia was observed in one patient, no other EPS were detected. Lack of weight gain and only transient prolactin elevation were encouraging findings. Ziprasidone has 5HT2A/D2 antagonistic properties with additional 5HT1A receptor agonistic properties and it is a reuptake inhibitor for serotonin en noradrenaline. This pharmacological profile may be advantageous in the complex symptomatology of Tourette’s syndrome. Another intriguing probe to be tested will be quetiapine, which has a very low dopamine D2 affinity closely resembling clozapine. Clearly, further controlled and naturalistic studies of atypical antipsychotics are indicated.

If the atypical agents will appear to be equally effective in the treatment of tic-disorders, side effect profiles will become increasingly important. With respect to EPS, both acute and tardive, low doses of risperidone have an advantageous profile over classical neuroleptics. However, of the atypical antipsychotics risperidone has the highest affinity for dopamine receptors. And in Tourette’s syndrome risperidone is clearly not completely devoid of motor side effects. Moreover, of all the new atypical antipsychotics, risperidone is most potent in terms of prolactin elevation. In this respect it has no clear advantage over sulpiride. Thus, in case of prolactin related sexual or endocrine side effects with either risperidone or sulpiride, a trial with e.g. olanzapine may offer an alternative treatment option. Albeit that sedation is reported in all the Tourette studies, risperidone is probably one of the least sedative of the new drugs. Weight gain, a serious problem with both classical and new antipsychotics including risperidone, causes large somatic and psychological burden. In a recent meta-analysis in schizophrenic patients risperidone induced relatively little weight gain (Allison et al., 1999). Whether this sustains also in Tourette’s syndrome needs further study. The threshold for epileptic seizures is lowered by most classical and atypical antipsychotics, for risperidone the risk of seizures is relatively low (Kasper et al., 1999). In addition, based on its lack of anti-
cholinergic activity risperidone may also be preferable with respect to cognitive functioning. This may be especially significant, since patients with Tourette’s syndrome are extremely aware of both their surrounding stimuli and their own internal cognitive processes.

To summarize, in Part II the therapeutic potential of risperidone in the treatment of Tourette’s syndrome was assessed. First, the efficacy of risperidone as a tic-suppressive agent was shown in an open dose-finding trial. Next, risperidone was demonstrated as efficacious as pimozide in a double-blind study. Risperidone was well tolerated and induced few EPS, with reportedly less akathisia than pimozide. In addition, it was suggested that risperidone has beneficial effects on obsessive-compulsive symptoms. Finally, in a retrospective survey on risperidone we found that, after one year of treatment, a large number of patients had discontinued risperidone, due to general side effects or planned drug-withdrawal. After one year, circa one-third of the patients was still using risperidone safe and effectively in a dose less than 3 mg/day. The clinical implication that is supported by this thesis is that risperidone may be a first-line drug in the treatment of Tourette’s syndrome.