CNS Drug Reviews
Vol. 7, No. 3, pp. 265–282
© 2001 Neva Press, Branford, Connecticut

# Pharmacology of the Atypical Antipsychotic Remoxipride, a Dopamine $D_2$ Receptor Antagonist

Roser Nadal, Ph.D.

*Department of Psychobiology and Methodology of Health Sciences, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, Spain*

**Key Words:** Atypical antipsychotics—Dopamine—Remoxipride—Schizophrenia.

## ABSTRACT

Remoxipride is a substituted benzamide that acts as a weak but very selective antagonist of dopamine $D_2$ receptors. It was introduced by Astra (Roxiam®) at the end of the eighties and was prescribed as an atypical antipsychotic. This article reviews its putative selective effects on mesolimbic versus nigrostriatal dopaminergic systems. In animals, remoxipride has minimal cataleptic effects at doses that block dopamine agonist-induced hyperactivity. These findings are predictive of antipsychotic activity with a low likelihood of extrapyramidal symptoms. Remoxipride also appears to be effective in more recent animal models of schizophrenia, such as latent inhibition or prepulse inhibition. In clinical studies, remoxipride shows a relatively low incidence of extrapyramidal side effects and its effects on prolactin release are short-lasting and generally mild. The clinical efficacy of remoxipride is similar to that of haloperidol or chlorpromazine. Although its clinical use was severely restricted in 1993, due to reports of aplastic anemia in some patients receiving remoxipride, this drug has been found to exhibit relatively high selectivity for dopamine $D_2$ receptors making remoxipride an interesting tool for neurochemical and behavioral studies.

## INTRODUCTION

Schizophrenia and other psychotic disorders have huge economic and social costs. Medical scientists began, however, only recently to understand the biological basis of these diseases. Chlorpromazine was synthesized in 1950 and first used in the treatment of

Address correspondence and reprint requests to: Roser Nadal, Ph.D. Area de Psicobiologia, Facultat de Psicologia, Universitat Autònoma de Barcelona, Bellaterra, Barcelona, E-08193 Spain.
Phone: +34 (93) 581-2881; Fax:+34 (93) 581-2001; E-mail: Roser.Nadal@uab.es

mania a year later in France. In 1954 the drug was used to treat psychosis in the United States under the brand name Thorazine®. Since then, the effective use of antipsychotic drugs has resulted in a dramatic decrease in the population of hospitalized schizophrenics throughout the world. One class of drugs, that has been effective in the treatment of psychotic disorders, is the dopamine receptor antagonists.

Remoxipride is a very selective antagonist of dopamine $D_2$ receptors that has been used as an antipsychotic drug. Even though the pathogenesis of schizophrenia remains unknown, much attention has been focused on brain dopaminergic systems (14). Some of the evidence for the involvement of dopaminergic systems in the pathogenesis of schizophrenia has been reviewed previously (132). It is summarized here as follows: 1) dopaminergic agents can induce a schizophrenic-like state that can be reversed by dopaminergic $D_2$ antagonists, 2) the clinical efficacy of antipsychotic agents correlates well with the affinity to the $D_2$ receptor, 3) a still controversial finding, that $D_2$ receptor binding sites are increased in the brain of schizophrenic patients (unrelated to chronic treatment with neuroleptics).

Remoxipride was selected as a potential antipsychotic drug by Astra in 1978. It gained approval for clinical use in 15 countries as Roxiam®. In the UK it was introduced in 1989. In general, clinical studies (for a review see refs. 91,124) showed that remoxipride had clinical efficacy similar to that of haloperidol (2,4,21,58,60,67,77,93,97) or chlorpromazine (15,16,48,76,96), although it produced less extrapyramidal side effects (EPS) than standard treatments. Remoxipride was found to be superior to placebo in maintaining remission over a 6-month period. However, there were no consistent data to confirm that the drug could be more useful in the treatment of negative symptoms than haloperidol (7,57). The efficacy of remoxipride in the elderly has also been assessed (96). Some studies reported that remoxipride was well tolerated over a 6-month to 1-year period (40,121). However, in November 1993 two deaths due to aplastic anemia, supposedly related to the use of remoxipride, have been reported. This report severely restricted the clinical use of remoxipride (91). In some countries remoxipride is still available but with several restrictions. Its relatively specific neurochemical profile may, however, provide a framework for the study of pathogenesis and treatment of schizophrenia. An extensive review of its pharmacology and clinical use has been published in 1990 (123).

Remoxipride belongs to the atypical/novel antipsychotic or neuroleptic group of drugs, as opposed to the typical/classical antipsychotics. This broad group of novel antipsychotics includes drugs such as clozapine, olanzapine, raclopride, risperidone and ritanserin (6,56,69,74,99,105,118). What makes an antipsychotic drug atypical? Several criteria have been considered (51): 1) they produce less EPS; 2) they have increased therapeutic efficacy; and 3) they are less likely to increase prolactin levels. However, several antipsychotic drugs have been classified as "atypical" on the basis of animal studies before clinical results were complete. The following criteria have been used in these studies to suggest the atypical nature of an antipsychotic (51): 1) dose-response separation between the cataleptic and the behavioral effects; 2) selectivity of drug for certain brain structures; and 3) specific pharmacological actions on certain neurotransmitter receptors. Atypical antipsychotics fulfill these criteria differently. As stated by other investigators (6,44,105), there is no single neurochemical basis to account for the atypical nature of a new antipsychotic drug. Drugs that bind to different subtypes of receptors are often included in the same group of new neuroleptics. For instance, drug discrimination studies have shown

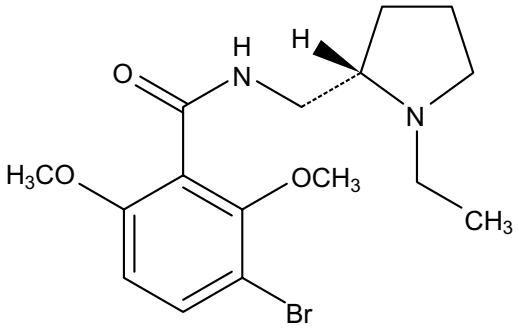


**Fig. 1.** Chemical structure of remoxipride.

that remoxipride, at any dose, does not substitute for clozapine in a reliable manner (13,98).

Neuroleptics, such as haloperidol or chlorpomazine, often cause EPS such as dystonia, akathisia and Parkinsonian symptoms (rigidity, tremor, and akinesia). Other novel antipsychotics are considered "atypical" because they do not produce (or produce less) unwanted motor effects. It has been suggested (105) that tardive dyskinesia should not be used to distinguish between typical and atypical antipsychotics (49), because this side effect develops only after several years of therapy and its incidence with atypical antipsychotics is unknown. In another context, the term "atypical" may also include the fact that some of the new antipsychotics, which are useful in the treatment of the negative symptoms of schizophrenia, are also effective in at least some patients that are resistant to classical antypsychotics (43), and produce less hyperprolactinemic side effects (49).

## CHEMISTRY

Remoxipride is a substituted benzamide [(S)-3-bromo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2,6-dimethoxybenzamide] with a molecular weight of 371.27 (Fig. 1) and a p$K_a$ of 8.9 (117). Sulpiride and raclopride are other members of the same chemical class.

## PHARMACOKINETICS

### Rodent Pharmacokinetics

There are important differences in the metabolism of remoxipride across species (130). In rodents, the bioavailability (due to first pass metabolism) and protein binding are lower, while the volume of distribution is higher than in humans (130). In rats, there are several active metabolites that must be taken into account when studying the behavioral effects of the drug. The main metabolic reactions in the rat are hydroxylation and oxidation in the aromatic moiety of remoxipride, a pathway that is not as important in humans (130).

There are several metabolites of remoxipride found mainly in rat (FLA 797, FLA 908, NCQ 436, and NCQ 469[1]) that have more affinity for dopamine $D_2$ and $D_3$ receptors than remoxipride itself (78). Regarding the relevance of those metabolites in *in vivo* studies the data are more conflicting. Ögren and colleagues (88,89) found that the behavioral effects of remoxipride (cataleptic effect and the ability to block hypothermia induced by dopamine $D_2$ receptor stimulation) were more pronounced when the drug was administered to rats by i.v. or s.c. and not by i.p. route. More recent work (1) documented a more extensive behavioral evaluation of some remoxipride metabolites (FLA 797, FLA 908, NCQ 344, NCQ 436, and NCQ 469) in comparison to remoxipride and reported that the effects of remoxipride depended on exposure to hepatic metabolism in rats. Remoxipride was more effective by i.p. administration than by the s.c. route, whereas by intracerebroventricular (i.c.v.) administration the drug had almost no effect. It was concluded that in rats metabolites of remoxipride could be responsible for *in vivo* effects of this drug (1).

## Human Pharmacokinetics

Human pharmacokinetics of remoxipride has been extensively described previously (123). It has been found (122) that, in healthy subjects, remoxipride is rapidly absorbed after oral administration. The absorption takes place mainly in the small intestine, but can also occur in the large intestine. The absolute bioavailability of remoxipride is above 90%, without first-pass effect. After i.v. administration to healthy subjects, remoxipride is rapidly distributed following a one-compartment model; it is extensively (80%) bound to plasma proteins (122). The elimination of remoxipride is by metabolism (about 75%) and by excretion of unchanged drug in the urine (81,122). Remoxipride metabolites in humans (FLA 838, FLA 850, NCL 118, or NCM 001[2]) do not seem to be active (78). Remoxipride has low clearance and its half-life is 4 to 7 h. The pharmacokinetics of remoxipride in schizophrenics is not different from that in healthy subjects (16). Renal clearance is affected by urinary pH (129). A decrease in urinary pH increases both the percentage of the drug excreted unchanged in the urine and the elimination rate. Plasma half-life of remoxipride is prolonged and elimination slowed in patients with renal or liver disorders, as well as in elderly patients (80,122). The disposition of remoxipride is similar in Chinese schizophrenic patients (66) and also in elderly psychiatric patients with or without tardive dyskinesia (128). Finally, with regard to drug interactions, the kinetics of remoxipride after oral administration to healthy subjects does not seem to be affected by diazepam, ethanol, anticholinergics or anticoagulants (132).

[1] FLA 797, (S)-3-Bromo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-6-methoxysalicylamide;
FLA 908, (S)-5-Bromo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-6-methoxysalicylamide;
NCQ 344, (S)-3-Bromo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-hydroxy-6-methoxysalicylamide;
NCQ 436, (S)-3-Bromo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5,6-dihydroxy-2-methoxybenzamide;
NCQ 469, (S)-3-Bromo-N-[(1-ethyl-2-pyrrolidinyl)methyl]-5-hydroxy-2,6-dimethoxybenzamide.

[2] FLA 838, (–)-(S)-3-Bromo-N-[(2-pyrrolidinyl)methyl]-2,6-hydroxy-2,6-dimethoxybenzamide;
FLA 850, (–)-(S)-5-[(3-Bromo-2,6-dimethoxybenzamido)methyl]-1-ethyl-2-pyrrolidinone;
NCL 118, (–)-(S)-5-[(3-Bromo-2,6-dimethoxybenzamido)methyl]-2-pyrrolidinone;
NCM 001, 5-[(3-Bromo-2,6-dimethoxybenzamido)methyl]-1-ethyl-5-hydroxy-2-pyrrolidinone.

# PHARMACODYNAMICS

## Effects on Neurotransmitter Receptors

The effects of remoxipride on dopaminergic receptors are reviewed in this section. For better understanding of its pharmacodynamics subtypes of dopamine receptors and the anatomy of the dopaminergic pathways are briefly reviewed first. There are four main dopaminergic pathways in the CNS: the nigrostriatal, mesolimbic, mesocortical and tuberoinfundibular. The nigrostriatal pathway arises from the substantia nigra, pars compacta (A9) to the neostriatum (caudate + putamen) and is largely involved in motor control. The mesolimbic pathway projects from the ventral tegmental area (A10) and the retrorubral field (A8) to the nucleus accumbens, olfactory tubercle, amygdala and septum. The mesocortical system also arises from A10 and A8 but projects primarily to the prefrontal, entorhinal, piriform and anterior cingulate cortices. The mesolimbic and the mesocortical systems are often included as parts of the same system; they appear to be involved in emotional and cognitive functions (61,127). The mesocorticolimbic dopaminergic system, together with its anatomical relationship to the hippocampal formation, may provide an anatomical substrate for schizophrenic disorders (14,18,35). It has also been suggested that a dopaminergic deficit in the prefrontal cortex may be related to the negative symptoms of schizophrenia, while hyperfunctioning of the mesolimbic system may be involved in the positive symptoms of the disease (19). The dopaminergic blockade produced by antipsychotics at the nigrostriatal level will produce EPS, while blockade at the tuberinfundibular level will lead to hyperprolactinemia.

Five types of dopamine receptors have been described: $D_1$–$D_5$ (119). Since $D_1$ and $D_5$ receptors have structural and pharmacological similarities, and $D_3$ and $D_4$ are similar to the $D_2$ receptors, the most frequently used dopamine classification system includes the $D_1$-like and $D_2$-like subfamilies (for a detailed description of dopamine receptors see refs. 109,113). $D_1$- and $D_2$-like receptors are positively and negatively coupled, respectively, to adenylate cyclase. $D_1$ and $D_2$ receptors are more abundant in the CNS than $D_3$, $D_4$, or $D_5$ receptors. $D_3$, $D_4$, and $D_5$ receptors are expressed more in the limbic regions of the brain than in the dorsal striatum. $D_2$ receptors are selectively blocked by remoxipride, they are expressed primarily in the neostriatum, the core and the septal pole of the nucleus accumbens, the substantia nigra and the ventral tegmental area. They are present only at very low levels in cortical areas.

## *In Vitro* Dopaminergic Binding

Remoxipride is a weak but relatively selective dopamine $D_2$ receptor antagonist. Even though it is also a potent σ antagonist (see below), it has little or no affinity for other receptors, such as α-adrenoceptors, serotonergic, histaminic, muscarinic or the other dopamine receptors (12,87,104; and see for a review ref. 6). Remoxipride and other substituted benzamides represent a culmination of a highly selective approach to the development of new antipsychotic drugs that are selective for $D_2$ receptors. Since the blockade of $D_2$ receptors appears to be related not only to the therapeutic actions of antipsychotics, but also to the development of EPS, it has been proposed that novel antipsychotic drugs act differentially in limbic vs. striatal tissues. As stated previously (26), the blockade of limbic dopamine receptors is believed to be critical in the blockade of the positive symptoms of

schizophrenia, whereas dopamine antagonism in the striatum appears to be related to the development of EPS.

Although *in vitro* affinity of remoxipride for $D_2$ receptors differs with the radioligand in competition studies, its affinity is lower than that of haloperidol and other typical neuroleptics (for a review see ref. 54). It has been suggested (78) that the affinity values obtained using [$^3$H]raclopride as the radioligand are more reliable than those using high-affinity radioligands, such as [$^3$H]spiperone. The affinity of remoxipride for $D_2$ receptors in rat striatum ($K_i$) ranges between 113 ± 38 (78) and 275 ± 180 nM (12) using [$^3$H]raclopride as the radioligand. With [$^3$H]spiperone as a radioligand, the affinity ($IC_{50}$) for $D_2$ in rat striatum is approximately 1570 nM (87). Seeman et al. have calculated the radioligand-independent dissociation constants of several atypical antipsychotics, including remoxipride (106). For the atypical antipsychotics these values are approximately 30 (remoxipride) to 90 nM, while the constants of most typical neuroleptics range from 0.3 to 5 nM.

The differential $D_2$ affinity of remoxipride and other atypical antipsychotics for striatal vs. limbic tissues has been a controversial issue. One would expect the affinity of remoxipride to be lower for striatal than for limbic $D_2$ receptors. However, no significant difference was found in the affinity of remoxipride for $D_2$ receptors in rat striatum, nucleus accumbens and tuberculum olfactorium. With [$^{125}$I]2′-iodospiperone as a radioligand, the affinity ranged between 1445 to 1949 nM in all areas studied (62). Also with [$^3$H]raclopride as a radioligand the affinity of several "typical" and "atypical" neuroleptics, including remoxipride, was the same in human nucleus accumbens and putamen (108). In human caudate nucleus, the affinity ($K_i$) of remoxipride, with [$^3$H]raclopride as the radioligand, was approximately 78.8 nM, ranging from 69.6 to 90.9 nM (38).

In respect to the differential affinity of remoxipride for $D_{2A}$ (long) vs. $D_{2B}$ (short) cloned human receptors, the findings are also controversial. Using [$^{125}$I]2′-iodospiperone as the radioligand ($D_{2A}$, $IC_{50}$ = 2884 nM; $D_{2B}$, $IC_{50}$ = 2570 nM)some authors found no difference in the affinity of remoxipride for these subtypes of $D_2$ receptors. Other authors (75), however, used [$^3$H]raclopride as radioligand and found that the affinity of remoxipride was substantially lower for $D_{2A}$ than for $D_{2B}$ receptors ($D_{2A}$, $K_i$ = 125 ± 15 nM; $D_{2B}$, $K_i$ = 54.3 ± 5 nM). It is now generally accepted that the short form of the $D_2$ receptor is more sensitive to benzamide antipsychotics (107).

## *In Vivo* Dopaminergic Binding: Neuroimaging Studies

It is a point of great scientific interest to demonstrate which receptors are occupied at clinically effective doses of antipsychotic drugs. *In vivo* occupancy of dopamine $D_2$ receptors by remoxipride has been demonstrated in humans using positron emission (30,31) and single photon emission tomographies (PET and SPET, respectively) (11,52). The specific *in vivo* occupancies of $D_2$ extrastriatal sites by remoxipride would have been more relevant to the therapeutic antipsychotic action of the drug. To the author's knowledge, this has not been yet studied.

PET studies (30,31), with [$^{11}$C]raclopride as the radioligand, showed that the occupancy of central $D_2$ receptors after remoxipride was identical (71 to 73%) in a healthy male subject after 3 days of treatment (100 mg, t.i.d.) and in schizophrenic patients after 9 days or 4 weeks of treatment (200 mg, t.i.d.). This level of occupancy is within previously reported (31) range of values for patients on typical antipsychotics (65–85%). In the study,

using [$^{11}$C]remoxipride as the radioligand, it was found that the radioactivity was evenly distributed to all regions of the brain with no apparent specificity for the regions with a high density of $D_2$ receptors.

In EPS free schizophrenic and schizo-affective patients, remoxipride (150–450 mg/day for 2 weeks), produces high levels of striatal $D_2$ blockade (as measured by [$^{123}$I]IBZM SPET). The specific binding (measured by the ratio between basal ganglia: frontal cortex) was comparable to that observed in patients on classical antipsychotics. Despite the high degree of $D_2$ blockade, EPS were scarcely seen. For this reason, Busatto et al. (11) have argued against a direct relationship between striatal $D_2$ occupancy and the presence of EPS. Similar results were obtained by other authors (52) who found a comparable $D_2$ blockade with the high-potency typical antipsychotics and remoxipride (300–600 mg/day).

## Functional Dopaminergic Studies

As stated previously, $D_2$ receptors control adenylate cyclase activity. The low affinity of remoxipride for the $D_2$ receptor predicts a low potency in functional assays of dopaminergic activity. Remoxipride antagonizes dopamine $D_2$-mediated inhibition of cAMP formation in rat striatal tissue. Its potency is, however, substantially lower than that of haloperidol, sulpiride or raclopride (125).

Another method used to characterize second messenger activity is to study receptor G protein interactions by measuring agonist-dependent exchange of GDP for GTP at G-proteins. In rat striatal membranes remoxipride inhibits $D_2$-receptor mediated stimulation of binding of a radiolabeled nonhydrolyzable analogue of GTP. In this respect its potency is also lower than that of haloperidol, clorpromazine, raclopride, or sulpiride (101).

## Dopaminergic Upregulation and Downregulation after Chronic Treatment

Chronic treatment with neuroleptics produces a compensatory increase in the number of $D_2$ receptors (upregulation). Repeated oral administration of remoxipride to rats (4.2 mg/kg daily) produces the expected $D_2$ upregulation in the striatum (39). However, as reviewed previously (51), the striatal upregulation produced by several antipsychotics does not seem to have functional implications and is, therefore, not useful in the differentiation between typical and atypical antipsychotics.

More recently, attention has been focused on the upregulation of the receptors in the cerebral cortex that has been suggested to be a key factor in the therapeutic actions of the antipsychotic drugs and not in the development of EPS (64). It has been reported (65) that in rhesus monkeys remoxipride (p.o., b.i.d., for 6 months at a dose range recommended for human schizophrenic patients, 3.7 mg/kg) upregulated $D_{2A}$ and $D_{2B}$ mRNA isoforms of the $D_2$ receptor in the prefrontal and the temporal cortex. This effect was observed also with other typical or atypical antipsychotic drugs. Upregulation of the receptors in the neostriatum was produced by remoxipride, but was not consistently observed with some of the other antipsychotics. The dopaminergic upregulation produced by chronic treatment with remoxipride does not include $D_4$ receptors. It has been found (65) that remoxipride has no effect on $D_4$ mRNA levels in cortical or striatal tissues.

The upregulation of $D_2$ receptors in the cerebral cortex produced by several neuroleptics appears to be associated with the downregulation of cortical $D_1$ receptors (63,64). Autoradiographic studies (64) showed that remoxipride, as well as clozapine and haloperidol, downregulated $D_1$ receptors in the prefrontal and temporal association cortex. In agreement with this finding, it has been found (63) that remoxipride, at the same dosage regimen, downregulated $D_1$ and $D_5$ mRNAs in the prefrontal cortex but not in the neostriatum.

## Effects on Prolactin Release

Since remoxipride is a dopamine antagonist, it may have an inhibitory effect at the $D_2$ receptor in the anterior pituitary, leading to an increase in prolactin release. This effect leads to some of the undesirable actions of neuroleptics, such as amenorrhea, other menstrual alterations, galactorrhea, gynecomastia, or impotence. Remoxipride increases prolactin release, but its effect is short-lasting and generally mild; after chronic treatment a tolerance to this effect may develop. This pattern of effects is observed in healthy subjects (82) and in elderly patients with or without tardive dyskinesia (128).

## Dopamine Metabolism

Since neuroleptics block dopamine receptors, they may produce a compensatory increase in the dopamine turnover due to the activation of tyrosine hydroxylase. Several *ex vivo* studies have addressed the effects of remoxipride on dopamine metabolism by examining possible differential actions of the drug on limbic vs. striatal tissues. High pressure liquid chromatography (HPLC) is one of the methods classically used to measure dopamine turnover. HPLC measures the increase in the concentration of dopamine metabolites: dihydroxyphenylacetic acid (DOPA) and homovanillic acid (HVA), without changing the concentration of dopamine (124). The effects of remoxipride on dopamine turnover have been tested (70,90) in the rat striatum and nucleus accumbens. Remoxipride was administered at two dose levels: 1) at a dose lower than that needed to prevent apomorphine-induced hyperactivity (putative antipsychotic dose); and 2) at a higher dose, that is expected to block the stereotypy produced by apomorphine and is likely to cause EPS. Remoxipride increased the turnover of dopamine at the same doses at which it blocked apomorphine-induced stereotypies. The effective doses of remoxipride were higher than those needed to antagonize apomorphine-induced hyperactivity. The same effect of remoxipride was observed in the striatum as in the nucleus accumbens. In contrast to remoxipride, haloperidol produces a higher increase in dopamine turnover in striatal than in limbic tissues (87). It is important to realize that following repeated administration of remoxipride tolerance can develop to the increase in dopamine turnover either in striatum or in olfactory tubercle + nucleus accumbens. The tolerance after remoxipride is, however, less pronounced than that with haloperidol (71).

Other investigators studied dopamine turnover after remoxipride using dopamine fluorescence in the brain of rats treated with α-methyl-*p*-tyrosine, which inhibits tyrosine hydroxylase (33, 87). In these studies remoxipride, at doses that blocked apomorphine-induced hyperactivity, increased dopamine turnover in the olfactory tubercle without affecting turnover in the striatum or in the nucleus accumbens. At doses that antagonized apomorphine-induced stereotypies, remoxipride produced a greater increase in dopamine

turnover in olfactory tubercle than in striatum or nucleus accumbens. There was, therefore, no evidence for any difference between the effects of remoxipride in the striatum and in the nucleus accumbens. It is conceivable, however, that the effects of remoxipride may depend on the area of nucleus accumbens or striatum studied. For example, it has been found (33) that remoxipride, at doses sufficient to block either apomorphine-induced hyperactivity or stereotypies, increased dopamine turnover only in the medial part of caudate nucleus.

More recent microdialysis data confirm that, as expected for a dopamine antagonist, remoxipride increases dopamine as well as dopamine metabolite levels in the rat striatum. This effect was observed after acute administration of remoxipride at 16.7 mg/kg s.c. (34), 3 mg/kg s.c. (36), or 2.4 mg/kg i.p. (37). No tolerance to this effect developed after repeated administration of the drug (34). To this author's knowledge, the effects of remoxipride on dopamine levels in the nucleus accumbens have not been reported.

## Binding to σ-Receptors

Several antipsychotics ("typical" and "atypical") bind to σ-receptors in the brain, although the significance of this has not been totally established (20). It has been suggested, however, that binding to σ-receptors may be related to the development of neuroleptic-induced dystonia (44). It has been found (59) that remoxipride binds to σ-receptors (using (+)[$^3$H]3-PPP as a radioligand) in the rat brain with 15 times higher affinity than to $D_2$ receptors ($IC_{50}$ = 60 nM). However, by subchronic administration remoxipride (10 mg/kg/day s.c. by osmotic minipumps, for 14 days) did not affect either the density of or the affinity to σ-receptors in the rat brain (determined using [$^3$H](+)-3-PPP as the radioligand) (29). In this last study, repeated treatment with haloperidol decreased the density of σ-receptors. Haloperidol was used at a dose level equivalent to that of remoxipride needed to block $D_2$ receptors in striatum.

## Expression of c-fos

The blockade of $D_2$ receptors by remoxipride affects second messenger systems that may produce an induction of the immediate early gene, c-fos and its protein product *Fos*. It appears that several clinically effective antipsychotic drugs increase *Fos* expression in the nucleus accumbens of rats (25,102). In this way, acute remoxipride administration does induce *Fos* expression in the nucleus accumbens (25,102). The medial striatum, a brain area related to cognitive functions that shares connections with the nucleus accumbens, is another structure very sensitive to the increase in *Fos* expression produced by remoxipride and other antipsychotics (for a more detailed discussion see ref. 102). After acute administration of remoxipride *Fos* expression also seems to be elevated in the lateral septum, a component of the limbic system (102). In contrast, remoxipride and other atypical antipsychotics do not increase *Fos* expression in the dorsolateral striatum, an effect that has been proposed to be related to the production of EPS (102).

The effects of remoxipride on *Fos* expression in the prefrontal cortex are contradictory. The prefrontal cortex has been related to the negative and/or cognitive symptoms of schizophrenia (10,53). Although some data show that remoxipride, at 3.0 but not at 1.5 mg/kg, s.c., may increase *Fos* expression in this area (102), other authors have not obtained any effect in the prefrontal cortex (27) or in the paraventricular nucleus of the

thalamus (24) after 2.5 mg/kg s.c. of remoxipride. The paraventricular nucleus of the thalamus is a region that sends projections to the prefrontal cortex of the rat, and clozapine, at doses of comparable clinical equivalence, induces *Fos* expression in both areas (24,27).

## Chronic Effects on Dopaminergic Neurons

It has been suggested that the antipsychotic potential of a drug is related to a reduction in the number of active dopamine neurons in the ventral tegmental area seen after chronic treatment with an antipsychotic drug. The reduction in the activity of the dopamine neurons in the substantia nigra pars compacta may, however, account for the development of EPS (6,127). Rats treated with remoxipride (0.02–5 mg/kg s.c., twice daily for 21 days) presented a dose-dependent reduction (with a U-shaped curve) in the number of spontaneously active neurons in ventral tegmental area, but not in substantia nigra pars compacta (110).

## Neurochemical Substrates for the Atypical Nature of Remoxipride

There is no simple neurochemical effect that can account for the atypical nature of remoxipride. Some authors proposed that the effect of remoxipride, and other "atypical" antipsychotics, may be different in striatal vs. limbic tissues (26). As observed in rats by autoradiography (55), remoxipride, at the doses that block apomorphine-induced hyperactivity, occupies 30% of the $D_2$ receptors in caudate and 50% of the $D_2$ receptors in olfactory tubercle. However, in another study, the affinity of remoxipride for $D_2$ receptors has been similar in striatum and olfactory tubercle (114). It appears that the above described data on the effects of remoxipride on dopamine turnover or the affinity of remoxipride for $D_2$ receptors in different tissues are not sufficiently conclusive as to affirm that remoxipride exerts different actions in limbic vs. striatal areas as some authors suggested (26). Also, as reviewed previously (51), mesolimbic region is more responsive than striatum to all kind of drugs (dopaminergic or non-dopaminergic). In contrast to inconclusive data in binding and dopamine turnover studies, the elegant *Fos* expression data lend support to the assumption that remoxipride affects primarily mesolimbic rather than nigrostriatal tissues. Neuroimaging studies in humans may provide more data on the selectivity of neurochemical profile of remoxipride and related drugs.

Another possibility is that remoxipride may act in some unknown subpopulation of $D_2$ receptors present only in some areas of the nucleus accumbens or the striatum, as suggested previously (43). Biochemical data indicate that nucleus accumbens (94) as well as striatum (41,92) are complex structures with different neurochemical compartments. It has been found (33) that remoxipride increases dopamine turnover in the medial part of the nucleus caudatus, and not in other parts of the nucleus. In addition, it has been found (102) that remoxipride induces c-fos expression only in the medial and not in the dorsolateral striatum.

Another explanation, proposed for the atypical nature of remoxipride and other novel neuroleptics is related to a differential sensitivity of different part of the brain to the endogenous dopamine (105,106,131). Dopamine levels in the striatum are higher than in nucleus accumbens, prefrontal cortex or hypothalamus. The "loosely bound" (low affinity) neuroleptics, such as remoxipride, could be easily displaced by dopamine in the brain

areas with a high dopamine output. They could be more effective in limbic or hypothalamic areas with a low dopamine output, providing an explanation for less EPS with remoxipride and similar antipsychotics.

## BEHAVIORAL PHARMACOLOGY

### Antipsychotic Profile

Remoxipride has been shown to be active in a variety of tests predictive of antipsychotic activity. One of the commonly used tests involves blockade of hyperlocomotion, induced by dopaminergic agents, such as amphetamine or apomorphine. Remoxipride blocks amphetamine- and apomorphine-induced locomotion at non-cataleptic, non-sedative doses (1,5,42,85,87,90,111). The high degree of separation of the $ED_{50}$ for blockade of apomorphine (0.3–0.38 mg/kg, i.p.)- or amphetamine (1.2 mg/kg i.p.)-induced hyperactivity and the $ED_{50}$ (8.3–15.8 mg/kg, i.p.) for induction of catalepsy in rats has been one of the most striking features of remoxipride that has been used in prediction of a low liability for EPS (85,87). Moreover, remoxipride is more potent at blocking apomorphine-induced hyperlocomotion than apomorphine-induced stereotypies (stereotypies $ED_{50}$ = 2.3 to 2.7 mg/kg i.p.) (85,87). This finding has been used as evidence for the preferential blockade of mesolimbic dopamine neurotransmission by remoxipride (87). With typical antipsychotics, such as haloperidol or chlorpromazine, the ranges of doses for these effects largely overlap (85). However, in one recent study remoxipride inhibited at the same dose, hypermotility and stereotypies, induced by a dopamine agonist (95).

Several antipsychotics were found to block hyperlocomotion, induced by the non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist, phencyclidine (PCP). NMDA receptors have been related to the pathogenesis of schizophrenia (28,45). At non-cataleptic doses remoxipride has been shown to block PCP-induced hyperlocomotion (42,86). This finding may also be relevant to the mechanism of the antipsychotic action of remoxipride.

Another popular test used to assess antipsychotic properties of drugs is the ability to block the acquisition and retention of the two-way active avoidance response in rats (17). Remoxipride, haloperidol and clozapine impair this task (84). Remoxipride effects in this paradigm were detected at doses much lower (0.42–0.83 mg/kg i.p.) than those producing cataleptic effects or those that block apomorphine-induced stereotypies. These doses are only slightly higher than doses that block apomorphine-induced hyperactivity.

The latent inhibition paradigm is a recently developed animal model of schizophrenia that focuses on the attentional deficits presented in schizophrenia (79). In this test, the repeated non-reinforced preexposure to a stimulus inhibits the formation of subsequent associations to that stimulus. Antipsychotics facilitate the formation of latent inhibition and block amphetamine-induced disruption of this phenomenon (79). Like haloperidol (120), remoxipride (1 or 5 mg/kg i.p.) facilitated latent inhibition.

Prepulse inhibition of the startle reflex is another animal model of schizophrenia that consists of measuring the decrease in the amplitude of the startle reflex when the startling stimulus is preceded by a weaker stimulus (115). Several antipsychotics block the disruption of prepulse inhibition induced by an increase in dopamine transmission (115). Al-

though remoxipride alone did not potentiate prepulse inhibition (22,23,47), it blocked PCP-induced disruption of this phenomenon in rats at doses ranging from 5 to 25 mg/kg, s.c. (46), higher than needed to block dopamine agonist-induced hyperactivity.

### Instrumental Behavior

The effects of remoxipride upon instrumental responding have also been studied. Like a whole variety of $D_1$ and $D_2$ antagonists, remoxipride ($ED_{50}$ = 1 mg/kg i.m.) decreases responding of squirrel monkeys under a fixed-interval schedule of stimulus-shock termination (8). This effect of remoxipride appears to be related to the binding of the drug to $D_2$ or $D_1$ receptors. There is a positive correlation between the affinity for the receptor and the potency for decreasing instrumental responding. Remoxipride ($ED_{50}$ = 1.2 mg/kg i.p.) also decreased instrumental responding in rats trained to lever press for food (103). Not all atypical antipsychotics produced that effect under the same experimental conditions.

Some animal data have shown that remoxipride may attenuate self-administration of addicting drugs. It has been observed (3) that remoxipride did not induce self-administration behavior, whereas at 10 mg/kg i.p. it decreased amphetamine self-administration in rats in an operant situation. At the same dose, remoxipride decreased ethanol self-administration in the sucrose-feeding procedure in rats (32). However, in other studies, remoxipride at 2.5–10 mg/kg increased i.v. self-administration of cocaine in rats (9). These paradoxical effects are not surprising because dopaminergic antagonists produce opposite effects on drug self-administration as a function of several factors (for a discussion see ref. 83). In any case, the doses of remoxipride needed to decrease drug self-administration seem to be higher than those needed to block dopamine agonist-induced hyperactivity. Moreover, remoxipride effects on drug self-administration have to be evaluated by taking into account its detrimental effects on instrumental responding in general (see above).

## CONCLUSIONS

Remoxipride, a weak, but highly selective dopamine $D_2$ antagonist, provides an interesting neurochemical and behavioral tool to study the pathogenesis of schizophrenia. Like several atypical antipsychotics with different mechanisms of action, remoxipride, by chronic administration, upregulates $D_2$ receptors in the prefrontal cortex. This effect is associated with the downregulation of $D_1$ and $D_5$ receptors in the prefrontal cortex, an effect that seems to be related to the antipsychotic efficacy (63–65). Another interesting neurochemical effect of remoxipride, shared by other atypical antipsychotics, is the increase in *Fos* expression in the nucleus accumbens and the lack of effect in the dorsolateral striatum. The later effect has been correlated with the development of EPS (25,102). In addition to the *Fos* expression data, other studies support the assumption of a relative specificity of remoxipride for mesolimbic vs. nigrostriatal regions. Another interesting observation that may account for the atypical nature of remoxipride is its low affinity for $D_2$ receptors. This property makes this drug easily displaceable by dopamine in the brain areas with a high dopamine output, such as striatum, and more effective in other limbic and hypothalamic structures which have a low dopamine output (105,106,131).

Remoxipride has been found effective in several animal models that are predictive of antipsychotic efficacy. The following finding in experimental models support its efficacy:

1) blockade, at non-sedative and non-cataleptic doses, of hyperlocomotion produced by dopaminergic drugs or by non-competitive NMDA antagonists; 2) blockade of acquisition and retention of two-way active avoidance response; 3) blockade of latent inhibition, and 4) of prepulse inhibition.

More studies with remoxipride are needed in animal models of schizophrenia, which are focused on the understanding of genetics and developmental biology of brain development (68,116). The role of remoxipride in the treatment of drug addiction should also be studied further. Other potential indications for remoxipride, such as its analgesic properties, should be further explored (72,73). Although clinical use of remoxipride is currently severly restricted, this drug remains a valuable reference substance for blockade of $D_2$ receptors in a variety of behavioral studies (100,112,126).

**Acknowledgement.** The author is thankful to Dr. Forrest Files for helpful criticism.

## REFERENCES

1. Ahlenius S, Ericson E, Hillegaart V, Nilsson LB, Salmi P, Wijkström A. *In vivo* effects of remoxipride and aromatic ring metabolites in the rat. *J Pharmacol Exp Ther* 1997;283:1356–1366.
2. Ahlfors UG, Rimon R, Appelberg B, et al. Remoxipride and haloperidol in schizophrenia: A double-bind multicentre study. *Acta Psychiatr Scand* 1990;82(Suppl 358):99–103.
3. Amit Z, Smith BR. Remoxipride, a specific $D_2$ dopamine antagonist: An examination of its self-administration liability and its effects on D-amphetamine self-administration. *Pharmacol Biochem Behav* 1991;41: 259–261.
4. Andersen J, Korner A, Ostegaard P, et al. A double blind comparative multicentre study of remoxipride and haloperidol in schizophrenia. *Acta Psychiatr Scand* 1990;82(Suppl 358):104–107.
5. Arnt J. Differential effects of classical and newer antipsychotics on the hypermotility induced by two dose levels of D-amphetamine. *Eur J Pharmacol* 1995;283:55–62.
6. Arnt J, Skarsfeldt T. Do novel antipsychotics have similar pharmacological characteristics? A review of the evidence. *Neuropsychopharmacology* 1998;18:63–101.
7. Awad, AG, Lapierre YD, Angus C, Rylander A. Quality of life and response of negative symptoms in schizophrenia to haloperidol and the atypical antipsychotic remoxipride. The Canadian remoxipride group. *J Psychiatry Neurosci* 1997;22:244–248.
8. Bergman J, Madras BK, Spealman RD. Behavioral effects of $D_1$ and $D_2$ dopamine receptor antagonists in squirrel monkeys. *J Pharmacol Exp Ther* 1991;258:910–917.
9. Bourland JA, French ED. Effects of remoxipride, an atypical antipsychotic, on cocaine self-administration in the rat using fixed- and progressive-ratio schedules of reinforcement. *Drug Alcohol Dependence* 1995;40:111–114.
10. Bunney WE, Bunney BG. Evidence for a compromised dorsolateral prefrontal cortical parallel circuit in schizophrenia. *Brain Res Rev* 2000;31:138–146.
11. Busatto GF, Pilowsky LS, Costa DC, Ell PJ, Verhoeff NPLG, Kerwin RW. Dopamine $D_2$ receptor blockade *in vivo* with the novel antipsychotics risperidone and remoxipride — an $^{123}$I-IBZM single photon emission tomography (SPET) study. *Psychopharmacology* 1995;117:55–61.
12. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. *Neuropsychopharmacology* 1996;14:87–96.
13. Carey GJ, Bergman J. Discriminative-stimulus effects of clozapine in squirrel monkeys: Comparison with conventional and novel antipsychotic drugs. *Psychopharmacology* 1997;132:261–269.
14. Carlsson A, Waters N, Waters S, Carlsson ML. Network interactions in schizophrenia — therapeutic implications. *Brain Res Rev* 2000;31:342–349.
15. Chouinard G. A placebo-controlled clinical trial of remoxipride and chlorpromazine in newly admitted schizophrenic patients with acute exacerbation. *Acta Psychiatr Scand* 1990;82(Suppl 358):111–119.

16. Chouinard G, Turnier L. An early phase II clinical trial of remoxipride in schizophrenia with measurement of plasma neuroleptic activity. *Psychopharmacol Bull* 1986;22:267–271.
17. Cook L, Davidson AB. Behavioral pharmacology: animal models involving aversive control of behavior. In: Lipton A, Damasio A, Killam K, eds. *Psychopharmacology, a generation of progress.* New York: Raven Press, 1978;563–567.
18. Csernansky JG, Bardgett ME. Limbic cortical neuronal damage and the pathophysiology of schizophrenia. *Schizophr Bull* 1998;24:231–248.
19. Davis KL, Kahn RS, Ko G, Davidson M. Dopamine in shizophrenia: A review and reconceptualization. *Am J Psychiatry* 1991;148:1474–1486.
20. Debonnel G, de Montigny C. Modulation of NMDA and dopaminergic neurotransmissions by sigma ligands: Possible implications for the treatment of psychiatric disorders. *Life Sci* 1996;58:721–34.
21. Deo R, Soni S, Rastogi SC, et al. Remoxipride and haloperidol in the acute phase of schizophrenia: A double-blind comparison. *Acta Psychiatr Scand* 1990;82(Suppl 358):120–124.
22. Depoortere R, Perrault G, Sanger DJ. Some, but not all, antipsychotic-drugs potentiate a low level of prepulse inhibition shown by rats of the Wistar strain. *Behav Pharmacol* 1997;8:364–372.
23. Depoortere R, Perrault G, Sanger DJ. Potentiation of prepulse inhibition of the startle reflex in rats: Pharmacological evaluation of the procedure as a model for detecting antipsychotic activity. *Psychopharmacology* 1997;132:366–374.
24. Deutch AY, Duman RS. The effects of antipsychotic drugs on fos protein expression in the prefrontal cortex: Cellular localization and pharmacological characterization. *Neuroscience* 1996;70:377–389.
25. Deutch AY, Lee MC, Iadorola MJ. Regionally specific effects of atypical antipsychotic drugs on striatal fos expression: The nucleus accumbens shell as a locus of antipsychotic action. *Mol Cell Neurosci* 1992;3: 332–341.
26. Deutch AY, Moghaddam B, Innis RB, et al. Mechanisms of action of atypical antipsychotic drugs: Implications for novel therapeutic strategies for schizophrenia. *Schizophr Res* 1991;4:121–156.
27. Deutch AY, Öngür D, Duman RS. Antipsychotic drugs induce fos protein in the thalamic paraventricular nucleus: A novel locus of antipsychotic drug action. *Neuroscience* 1995;66:337–346.
28. Duncan GE, Sheitman BB, Lieberman JA. An integrated view of pathophysiological models of schizophrenia. *Brain Res Rev* 1999;29:250–264.
29. Ericson H, Ross SB. Subchronic treatment of rats with remoxipride fails to modify X binding sites in the brain. *Eur J Pharmacol* 1992;226:157–161.
30. Farde L, Nordström A-L, Wiesel F-A, Pauli S, Halldin C, Sedvall G. Positron emission tomographic analysis of central $D_1$ and $D_2$ dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine. *Arch Gen Psychiatry* 1992;49:538–544.
31. Farde L, von Bahr C. Distribution of remoxipride to the human brain and central $D_2$-dopamine receptor binding examined *in vivo* by PET. *Acta Psychiatr Scand* 1990;82(Suppl 358):67–71.
32. Files FJ, Denning CE, Samson HH. Effects of the atypical antipsychotic remoxipride on alcohol self-administration. *Pharmacol Biochem Behav* 1998;59:281–285.
33. Fuxe K, Ögren SO. The unique effect of remoxipride on dopamine utilization in the basal ganglia. *Acta Physiol Scand* 1991;141:577–578.
34. Georgieva J, Mohringe B, Magnusson O. Neurochemical effects of prolonged treatment with remoxipride as assessed by intracerebral microdialysis in freely moving rats. *Prog Neuropsychopharmacol Biol Psychiatry* 1994;18:1187–1201.
35. Gray JA. A model of the limbic system and basal ganglia: applications to anxiety and schizophrenia. In: Gazzaniga MS, ed. *The cognitive neurosciences.* Cambridge: The MIT Press, 1995;1165–1176.
36. Gudelsky GA, Nash JF. Neuroendocrinological and neurochemical effects of sigma ligands. *Neuropharmacology* 1992;31:157–162.
37. Guinetdinov RR, Bogdanov MB, Kudrin VS, Rayevsky KS. Remoxipride and raclopride differ from metoclopramide by their effects on striatal dopamine release and biosynthesis in rats. *Neuropharmacology* 1994;33:215–219.
38. Hall H, Farde L, Sedvall G. Human dopamine receptor subtypes — *in vitro* binding analysis using $^3$H-SCH 23390 and $^3$H-raclopride. *J Neural Transm* 1988;73:7–21.
39. Hall H, Sallemark M. Effects of chronic neuroleptic treatment on agonist affinity sates of the dopamine-$D_2$ receptor in the rat brain. *Pharmacol Toxicol* 1987;60:359–363.
40. Holm AC, Edsman I, Lundberg T, Odlind B. Tolerability of remoxipride in the long term treatment of schizophrenia. An overview. *Drug Safety* 1993;8:445–456.
41. Holt DJ, Hersh LB, Saper CB. Cholinergic innervation in the human striatum: A three-compartment model. *Neuroscience* 1996;74:67–87.

42. Jackson DM, Johansson C, Lindgren L-M, Bengtsson A. Dopamine receptor antagonists block amphetamine and phencyclidine-induced motor stimulation in rats. *Pharmacol Biochem Behav* 1994;48:465–471.
43. Jackson DM, Ryan C, Evenden J, Mohell N. Preclinical findings with new antipsychotic agents: what makes them atypical? *Acta Psychiatr Scand* 1994;89(Suppl 380):41–48.
44. Jeanjean AP, Laterre EC, Maloteaux JM. Neuroleptic binding to sigma receptors: Possible involvement in neuroleptic-induced acute dystonia. *Biol Psychiatry* 1997;41:1010–1019.
45. Jentsch JD, Roth RH. The neuropsychopharmacology of phencyclidine: From NMDA receptor hypofunction to the dopamine hypothesis of schizoprenia. *Neuropsychopharmacology* 1999;20:201–225.
46. Johansson C, Jackson DM, Svensson L. The atypical antipsychotic, remoxipride, blocks phencyclidine-induced disruption of prepulse inhibition in the rat. *Psychopharmacology* 1994;116:437–442.
47. Johansson C, Jackson DM, Zhang J, Svensson L Prepulse inhibition of acoustic startle, a measure of sensorimotor gating: Effects of antipsychotics and other agents in rats. *Pharmacol Biochem Behav* 1995;52: 649–654.
48. Keks N, McGrath J, Lambert T, et al. The Australian multicentre double-bind comparative study of remoxipride and thioridazine in schizophrenia. *Acta Psychiatr Scand* 1994;90:358–365.
49. Kerwin RW. The new atypical antipsychotics. A lack of extrapyramidal side-effects and new routes in schizophrenia research. *Br J Psychiatry* 1994;164:141–148.
50. King DJ, Blomqvist M, Cooper SJ, Doherty MM, Mitchell MJ, Montgomery RC. A placebo controlled trial of remoxipride in the prevention of relapse in chronic schizophrenia. *Psychopharmacology* 1992;107: 175–179.
51. Kinon BJ, Lieberman JA. Mechanisms of action of atypical antipsychotic drugs: A critical analysis. *Psychopharmacology* 1996;124:2–34.
52. Klemm E, Grünwald, F, Kasper S, et al. [$^{123}$I]IBZM SPECT for imaging of striatal $D_2$ dopamine receptors in 56 schizophrenic patients taking various neuroleptics. *Am J Psychiatry* 1996;153:183–190.
53. Knable MB, Weinberger DR. Dopamine, the prefrontal cortex and schizophrenia. *J Psychopharmacol* 1997; 11:123–131.
54. Köhler C, Hall H, Magnusson O, Lewander T, Gustafsson K. Biochemical pharmacology of the atypical neuroleptic remoxipride. *Acta Psychiatr Scand* 1990;82(Suppl 358):27–36.
55. Köhler C, Radesäter AC, Karlsson-Boethius G, Bryske B, Widman M. Regional distribution and *in vivo* binding of the atypical antipsychotic drug remoxipride. A biochemical and autoradiographic analysis in the rat brain. *J Neural Transm* 1992;87:49–62.
56. Lahti AC, Lahti RA, Tamminga CA. New neuroleptics and experimental antipsychotics: Future roles. In: Breier A, ed. *The new pharmacotherapy of schizophrenia*. Washington: American Psychiatric Press, 1996;57–87.
57. Lapierre YD, Angus C, Awad AG, et al. The treatment of negative symptoms: A clinical and methodological study. *Int Clin Psychopharmacol* 1999;14:101–112.
58. Lapierre YD, Nair NP, Chouinard G, et al. A controlled dose-ranging study of remoxipride and haloperidol in schizophrenia- a Canadian multicentre study. *Acta Psychiatr Scand* 1990;82(Suppl 358):72–77.
59. Largent BL, Wikström H, Snowman AM, Snyder SH. Novel antipsychotic drugs share high affinity for X receptors. *Eur J Pharmacol* 1988;155:345–347.
60. Laux G, Klieser E, Schroder HG, et al. A double-bind multicentre study comparing remoxipride, two and three times daily, with haloperidol in schizophrenia. *Acta Psychiatr Scand* 1990;82(Suppl 358):125–129.
61. Le Moal M. Mesocorticolimbic dopaminergic neurons. Functional and regulatory roles. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology. The fourth generation of progress.* New York: Raven Press, 1995; 283–294.
62. Leysen JE, Gommeren W, Mertens J, et al. Comparison of *in vitro* binding properties of a series of dopamine antagonists and agonists for cloned human dopamine $D_2$S and $D_2$L receptors and for $D_2$ receptors in rat striatal and mesolimbic tissues, using [$^{125}$I]2′-iodospiperone. *Psychopharmacology* 1993;110:27–36.
63. Lidow MS, Elsworth JD, Goldman-Rakic PS. Down-regulation of the $D_1$ and $D_5$ dopamine receptors in the primate prefrontal cortex by chronic treatment with antipsychotic drugs. *J Pharmacol Exp Ther* 1997;281: 597–603.
64. Lidow MS, Goldman-Rakic PS. A common action of clozapine, haloperidol, and remoxipride on $D_1$- and $D_2$-dopaminergic receptors in the primate cerebral cortex. *Proc Natl Acad Sci USA* 1994;91:4353–4356.
65. Lidow MS, Goldman-Rakic PS. Differential regulation of $D_2$ and $D_4$ dopamine receptor mRNAs in the primate cerebral cortex vs. neostriatum: Effects of chronic treatment with typical and atypical antipsychotic drugs. *J Pharmacol Exp Ther* 1997;283:939–946.
66. Lin SK, Chang WH, Chien CP, Lam YWF, Jann MW. Disposition of remoxipride in Chinese schizophrenic patients. *Int J Clin Pharmacol Ther* 1996;34:17–20.

67. Lindstrom LH, Wieselgren IM, Struwe G., et al. A double-bind comparative multicentre study of remoxipride and haloperidol in schizophrenia. *Acta Psychiatr Scand* 1990;82(Suppl 358):130–135.
68. Lipska BK, Weinberger DR. To model a psychiatric disorder in animals: Schizophrenia as a reality test. *Neuropsychopharmacology* 2000;23:223–239.
69. Logan J, Finley P. Risperidone: Refining tools to treat schizophrenia. *CNS Drug Rev* 1999;5:249–264.
70. Magnusson O, Fowler CJ, Köhler C, Ögren S-O. Dopamine $D_2$ receptors and dopamine metabolism. Relationship between biochemical and behavioural effects of substituted benzamide drugs. *Neuropharmacology* 1986;25:187–197.
71. Magnusson O, Mohringe B, Thorell G, Lake-Bakaar DM. Effects of the dopamine $D_2$ selective receptor antagonist remoxipride on dopamine turnover in the rat brain after acute and repeated administration. *Pharmacol Toxicol* 1987;60:368–373.
72. Main DCJ, Waterman AE, Kilpatrick IC. Behavioural analysis of changes in nociceptive thresholds produced by remoxipride in sheep and rats. *Eur J Pharmacol* 1995;287:221–231.
73. Main DCJ, Waterman AE, Kilpatrick IC. Investigation into the antinociceptive potential of remoxipride administered intrathecally in sheep. *Naunyn-Schmiedeberg's Arch Pharmacol* 1997;355:524–530.
74. Malhotra AK, Pinsky DA, Breier A. Future antipsychotic agents: Clinical implications. In: Breier A, ed. *The new pharmacotherapy of schizophrenia*. Washington: American Psychiatric Press, 1996;41–56.
75. Malmberg A, Jackson DM, Eriksson A, Mohell N. Unique binding characteristics of antipsychotic agents interacting with human dopamine $D_{2A}$, $D_{2B}$, and $D_3$ receptors. *Mol Pharmacol* 1993;43:749–754.
76. McCreadie RG, Todd N, Livingston M, et al. A double-bind comparative study of remoxipride and thioridazine in the acute phase of schizophrenia. *Acta Psychiatr Scand* 1988;78:49–56.
77. Mendlewicz J, de Bleeker E, Cosyns P, et al. A double-bind comparative study of remoxipride and haloperidol in schizophrenic and schizophreniform disorders. *Acta Psychiatr Scand* 1990;82(Suppl 358):138–141.
78. Mohell N, Sällemark M, Rosqvist S, Malmberg A, Högberg T, Jackson DM. Binding characteristics of remoxipride and its metabolites to dopamine $D_2$ and $D_3$ receptors. *Eur J Pharmacol* 1993;238:121–125.
79. Moser PC, Hitchcock JM, Lister S, Moran PM. The pharmacology of latent inhibition as an animal model of schizophrenia. *Brain Res Rev* 2000;33:275–307.
80. Movin-Osswald G, Boelaert J, Hammarlund-Udenaes M, Nilsson LB. The pharmacokinetics of remoxipride and metabolites in patients with various degrees of renal function. *Br J Clin Pharmacol* 1993;35:615–622.
81. Movin-Osswald G, Hammarlund-Udenaes M. Remoxipride: Pharmacokinetics and effect on plasma prolactin. *Br J Clin Pharmacol* 1991;32:355–360.
82. Movin-Osswald G, Hammarlund-Udenaes M, von Bahr C, Eneroth P, Walton-Bowen K. Influence of the dosing interval on prolactin release after remoxipride. *Br J Clin Pharmacol* 1995;39:503–510.
83. Nadal R, Prat G, Pallarés M, Hernández-Torres M, Ferré N. Effects of bromocriptine on self-administration of sweetened ethanol solutions in rats. *Psychopharmacology* 1996;128:45–53.
84. Ögren SO, Archer T. Effects of typical and atypical antipsychotic drugs on two-way active avoidance: Relationship to DA receptor blocking profile. *Psychopharmacology* 1994;114:383–391.
85. Ögren SO, Florvall L, Hall H, Magnusson O, Ängeby-Möller K. Neuropharmacological and behavioural properties of remoxipride in the rat. *Acta Psychiatr Scand* 1990;82(Suppl 358):21–26.
86. Ögren SO, Goldstein M. Phencyclidine- and dizocilpine-induced hyperlocomotion are differentially mediated. *Neuropsychopharmacology* 1994;11:167–177.
87. Ögren SO, Hall H, Köhler C, et al. Remoxipride, a new potential antipsychotic compound with selective antidopaminergic actions in the rat brain. *Eur J Pharmacol* 1984; 102:459–474.
88. Ögren SO, Lundstrom J, Nilsson LB. Concentrations of remoxipride and its phenolic metabolites in rat brain and plasma. Relationship to extrapyramidal side effects and atypical antipsychotic profile. *J Neural Transm* 1993;94:199–216.
89. Ögren SO, Lundstrom J, Nilsson LB. Widman M. Dopamine $D_2$ blocking activity and plasma concentrations of remoxipride and its main metabolites in the rat. *J Neural Transm* 1993;93:187–203.
90. Ögren SO, Rosén L, Fuxe K. The dopamine $D_2$ antagonist remoxipride acts *in vivo* on a subpopulation of $D_2$ dopamine receptors. *Neuroscience* 1994;61:269–283.
91. Owens DG. Adverse effects of antipsychotic agents. Do newer agents offer advantages? *Drugs* 1996;51: 895–930.
92. Parent A, Côté P-Y, Lavoie B. Chemical anatomy of primate basal ganglia. *Progr Neurobiol* 1995;46: 131–197.
93. Patris M, Agussol P, Alby JM, et al. A double-bind multicentre comparison of remoxipride, at two dose levels, and haloperidol. *Acta Psychiatr Scand* 1990;82(Suppl 358):78–82.
94. Pennartz CMA, Groenewegen HJ, Lopes Da Silva FH. The nucleus accumbens as a complex of functionally distinct neuronal ensembles: An integration of behavioural, electrophysiological and anatomical data. *Progr Neurobiol* 1994;42:719–761.

95. Perrault GH, Depoortere R, Morel E, Sanger DJ, Scatton B. Psychopharmacological profile of amisulpride: An antipsychotic drug with presynaptic $D_2/D_3$ dopamine receptor antagonist activity and limbic selectivity. *J Pharmacol Exp Ther* 1997;280:73–82.
96. Phanjoo AL, Link C. Remoxipride vs. thioridazine in ederly psychotic patients. *Acta Psychiatr Scand* 1990;82(Suppl 358):181–185.
97. Pflug B, Bartels M, Bauer H, et al. A double-bind multicentre study comparing remoxipride, controlled release formulation, with haloperidol in schizophrenia. *Acta Psychiatr Scand* 1990;82(Suppl 358):142–146.
98. Porter JH, Varvel SA, Vann RE, Philibin SD, Wise LE. Clozapine discrimination with a low training dose distinguishes atypical from typical antipsychotic drugs in rats. *Psychopharmacology* 2000;149:189–193.
99. Remington GJ. Dopaminergic and serotonergic mechanisms in the action of standard and atypical neuroleptics. In: Shriqui CL, Nasrallah HA, eds. *Contemporary issues in the treatment of schizoprenia.* Washington: American Psychiatric Press, 1995;295–328.
100. Riegel AC, French ED. Acute toluene induced biphasic changes in rat spontaneous locomotor activity which are blocked by remoxipride. *Pharmacol Biochem Behav* 1999;62:399–402.
101. Rinken A, Finnman U-B, Fuxe K. Pharmacological characterization of dopamine-stimulated [$^{35}$S]-guanosine 5′-(-thiotriphosphate) ([$^{35}$S]GTP S) binding in rat striatal membranes. *Biochem Pharmacol* 1999;57: 155–162.
102. Robertson GS, Matsumura H, Fibiger HC. Induction patterns of fos-like immunoreactivity in the forebrain as predictors of atypical antipsychotic activity. *J Pharmacol Exp Ther* 1994;271:1058–1066.
103. Sanger DJ, Perrault G. Effects of typical and atypical antipsychotic drugs on response decrement patterns in rats. *J Pharmacol Exp Ther* 1995:272:708–713.
104. Schilcker E, Marr I. The moderate affinity of clozapine at $H_3$ receptors is not shared by its two major metabolites and by structurally related and unrelated atypical neuroleptics. *Naunyn-Schmiedeberg's Arch Pharmacol* 1996;353:290–294.
105. Seeman P. Atypical neuroleptics: Role of multiple receptors, endogenous dopamine, and receptor linkage. *Acta Psychiatr Scand* 1990;82(Suppl 358):14–20.
106. Seeman P, Corbett R, Van Tol HHM. Atypical neuroleptics have low affinity for dopamine $D_2$ receptors or are selective for $D_4$ receptors. *Neuropsychopharmacoly* 1997;16:93–110.
107. Seeman P, Nam D, Ulpian C, Liu ISC, Tallerico T. New dopamine receptor, $D_{2longer}$, with unique TG splice site, in human brain. *Mol Brain Res* 2000;76:132–141.
108. Seeman P, Ulpian C. Neuroleptics have identical potencies in human brain limbic and putamen regions. *Eur J Pharmacol* 1983;94:145–148.
109. Seeman P, Van Tol HHM. Dopamine receptor pharmacology. *Trends Pharmacol Sci* 1994;15:264–270.
110. Skarsfeldt T. Comparison of the effect of substituted benzamides on midbrain dopamine neurons after treatment of rats for 21 days. *Eur J Pharmacol* 1993;240:269–275.
111. Skuza G, Rogoz Z, Wieczorek A. Neuropsychopharmacological profile of remoxipride in comparison with clozapine. *Pol J Pharmacol* 1997;49:5–15.
112. Smith HP, Nichols DE, Mailman RB, Lawler CP. Locomotor inhibition, yawning and vacuous chewing induced by novel dopamine $D_2$ post-synaptic receptor agonist. *Eur J Pharmacol* 1997;323:27–36.
113. Sokoloff P, Schwartz J-C. Novel dopamine receptors half a decade later. *Trends Pharmacol Sci* 1995;16: 270–275.
114. Stockmeier CA, DiCarlo JJ, Zhang Y, Thompson P, Meltzer HY. Characterization of typical and atypical antipsychotic drugs based on *in vivo* occupancy of serotonin$_2$ and dopamine$_2$ receptors *J Pharmacol Exp Ther* 1993;266:1374–1384.
115. Swerdlow NR, Gever MA. Using an animal model of deficient sensoriomotor gating to study the pathophysiology and new treatments of schizophrenia. *Schizophr Bull* 1998;24:285–301.
116. Tallman JF. Development of novel antipsychotic drugs. *Brain Res Rev* 2000;31:385–390.
117. *The Merck Index*. Whitehouse station, NJ: Merck Research Laboratories, 1996.
118. Tollefson GD, Taylor CC. Olanzapine: Preclinical and clinical profiles of a novel antipsychotic agent. *CNS Drug Rev* 2000;6:303–363.
119. Trends in pharmacological sciences. Receptor ion channel nomenclature. Suppl 1999. Elsevier Sciences.
120. Trimble KM, Bell R, King DJ. Enhancement of latent inhibition in the rat by the atypical antipsychotic agent remoxipride. *Pharmacol Biochem Behav* 1997;56:809–816.
121. Vartiainen H, Leinonen E, Putkonen A, Lang S, Hagert U, Tolvanen U. A long-term study of remoxipride in chronic schizophrenic patients. *Acta Psychiatr Scand* 1993;87:114–117.
122. von Bahr C, Movin G, Yisak W-A, Jostell K-G, Widman M. Clinical pharmacokinetics of remoxipride. *Acta Psychiatr Scand* 1990;82(Suppl 358):41–44.
123. Wadworth AN, Heel RC. Remoxipride. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in schizophrenia. *Drugs* 1990;40:863–879.

124. Westerink BHC. The effects of drugs on dopamine biosynthesis and metabolism in the brain. In: Horn AS, Korf J, Westerink BHC, eds. *The neurobiology of dopamine*. London: Academic Press, 1979; 255–291.
125. Westlind-Danielsson A, Gustafsson K, Andersson I. Remoxipride shows low propensity to block functional striatal dopamine $D_2$ receptors *in vitro*. *Eur J Pharmacol* 1994;288:89–95.
126. Wettstein JG, Host M, Hitchcock JM. Selectivity of action of typical and atypical anti-psychotic drugs as antagonists of the behavioral effects of 1-[2,5-dimethoxy-4-iodophenyl]-2-aminopropane (DOI). *Prog Neuropsychopharmacol Biol Psychiatry* 1999;23:533–544.
127. White FJ. Synaptic regulation of mesocorticolimbic dopamine neurons. *Annu Rev Neurosci* 1996;19: 405–436.
128. Widerlöv E, Andersson U, von Bahr C, Nilsson M-I. Pharmacokinetics and effects of prolactin of remoxipride in patients with tardive dyskinesia. *Psychopharmacology* 1991;103:46–49.
129. Widerlöv E, Termander B, Nilsson M-I. Effect of urinary pH on the plasma and urinary kinetics of remoxipride in man. *Eur J Clin Pharmacol* 1989;37:359–363.
130. Widman M, Nilsson LB, Bryske B, Lundström J. Disposition of remoxipride in different species: Species differences in metabolism. *Arzneim Forsch Drug Res* 1993;43:287–297.
131. Wilson JM, Sanyal S, van Tol HHM. Dopamine $D_2$ and $D_4$ receptor ligands: Relation to antipsychotic action. *Eur J Pharmacol* 1998;351:273–286.
132. Yisak W, von Bahr C, Farde L, Grind M, Mattila M, Ogenstad S. Drug interaction studies with remoxipride. *Acta Psychiatr Scand* 1990;82(Suppl 358):58–62.