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REVIEW

Atypical Neuroleptics Have Low Affinity for Dopamine D_2 Receptors or Are Selective for D_4 Receptors

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This review examines the possible receptor basis of the atypical action of those atypical antipsychotic drugs that elicit low levels of Parkinsonism. Such an examination requires consistent and accurate dissociation constants for the antipsychotic drugs at the relevant dopamine and serotonin receptors. It has long been known, however, that the dissociation constant of a given antipsychotic drug at the dopamine D_2 receptor varies between laboratories. Although such variation depends on several factors, it has recently been recognized that the radioligand used to measure the competition between the antipsychotic drug and the radioligand is an important variable. The present review summarizes information on this radioligand dependence. In general, a radioligand of low solubility in the membrane (i.e., low tissue:buffer partition) results in a low value for the antipsychotic dissociation constant when the drug competes with the radioligand. Hence, by first obtaining the antipsychotic dissociation constants using different radioligands of different solubility in the membrane, one can then extrapolate the data to low or "zero" ligand solubility. The extrapolated value represents the radioligand-independent dissociation constant of the antipsychotic. These values are here given for dopamine D_2 and D_4 receptors, as well as for serotonin 5-HT_{2A} receptors. These values, moreover, agree with the dissociation constant directly obtained with the radioactive antipsychotic itself.

For example, clozapine revealed a radioligand-independent value of 1.6 nM at the dopamine D_4 receptor, agreeing with the value directly measured with [^{3}H]-clozapine at D_4. However, because clozapine competes with endogenous dopamine, the in vivo concentration of clozapine (to occupy dopamine D_4 receptors) can be derived to be about 13 nM, agreeing with the value of 12 to 20 nM in the plasma water or spinal fluid observed in treated patients. The atypical neuroleptics remoxipride, clozapine, perlapine, seroquel, and melperone had low affinity for the dopamine D_2 receptor (radioligand-independent dissociation constants of 30 to 90 nM). Such low affinity makes these latter five drugs readily displaceable by high levels of endogenous dopamine in the caudate or putamen. Most typical neuroleptics have radioligand-independent values of 0.3 to 5 nM at dopamine D_2 receptors, making them more resistant to displacement by endogenous dopamine. Finally, a relation was found between the neuroleptic doses for rat catalepsy and the D_2:D_4 ratio of the radioligand-independent K values for these two receptors. Thus, the atypical neuroleptics appear to fall into two groups, those that have a low affinity for dopamine D_2 receptors and those that are selective for dopamine D_4 receptors. ***[Neuropsychopharmacology 16:93–110, 1997]***

KEY WORDS: *Dopamine D_4 receptors; Neuroleptics; Serotonin$_2$ receptors; Parkinsonism; Clozapine; Catalepsy*

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Received January 30, 1996; revised May 19, 1996; accepted May 27, 1996.

NEUROPSYCHOPHARMACOLOGY 1997–VOL. 16, NO. 2

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/97/$17.00
PII S0893-133X(96)00187-9

RECEPTOR HYPOTHESES FOR ATYPICAL NEUROLEPTIC ACTION

The blockade of dopamine D_2 receptors alleviates psychosis but also produces Parkinsonism (Seeman et al. 1974, 1975; Creese et al. 1976; Seeman 1992a, 1995a). Antipsychotic drugs (neuroleptics) that elicit few or none of the extrapyramidal signs of Parkinsonism are referred to as *atypical antipsychotic drugs* (Meltzer and Nash 1991). What is the receptor basis for this atypical action of these particular neuroleptics? There are several current views:

1. Some atypical neuroleptics may have a low affinity for dopamine D_2 receptors and may thus be readily displaced by high endogenous concentrations of dopamine in the caudate or putamen.
2. Atypical neuroleptics may block both dopamine D_2 receptors and muscarinic receptors.
3. Atypical neuroleptics may have a balanced block of dopamine D_2 receptors and serotonin$_{2A}$ (5-HT_{2A}) receptors (Meltzer 1989, 1995; Leysen et al. 1994; Huttunen 1995).
4. Atypical neuroleptics may selectively block dopamine D_4 receptors.

We examined these various hypotheses after first considering the values for the neuroleptic dissociation constants at the dopamine D_2, D_4, and 5-HT_{2A} receptors.

THE NEUROLEPTIC DISSOCIATION CONSTANT VARIES WITH THE TISSUE: BUFFER PARTITION OF THE RADIOLIGAND

To derive the therapeutic receptor-blocking concentrations of neuroleptics and to assess the different hypotheses for atypical neuroleptic action, it is essential to use neuroleptic dissociation constants that have been measured with the minimum experimental artifacts.

For example, it has been found that the dissociation constant of a neuroleptic (e.g. [^{3}H]-spiperone) can range from 30 pM up to 1,600 pM as the final concentration of tissue is increased (Seeman et al. 1984). Currently, however, the final concentrations of tissue in most laboratories is kept very low to minimize tissue dependence.

Although many other factors may also determine the dissociation constant of an antipsychotic drug at various receptors, the literature on this topic is not extensive. The pH, for example, determines not only the surface activities (Seeman and Bialy 1963) and the membrane: buffer partition coefficients of neuroleptics (Seeman 1966a, 1966b; Seeman and Weinstein 1966; Seeman and Kwant 1969), but also the dissociation constant of the neuroleptic at the dopamine D_2 receptor (e.g., sulpiride; Presland and Strange 1991). The surface charge of the membrane also determines the membrane:buffer partition coefficient of neuroleptics (Kwant and Seeman 1969), as does the membrane lipid composition (Kwant and Seeman 1971). Many of these physicochemical factors, including temperature, that affect the partition of the neuroleptic in the membrane have been previously reviewed (Seeman 1972). As for the role of physicochemical factors on the dissociation constant of agonists and antagonists, the sodium and magnesium ion concentrations determine the proportion of the dopamine D_2 receptors that are in the high-affinity state (Grigoriadis and Seeman 1985; Watanabe et al. 1985). Sodium also is essential for the high-affinity binding of benzamide neuroleptics to dopamine receptors (Jarvie et al. 1987).

Nevertheless, despite standard laboratory experimental conditions internationally (e.g., pH of 7.4 and physiological concentrations of Na^+, Mg^{++}, and other ions), it has long been known that the dissociation constant of a particular neuroleptic may vary considerably between laboratories, particularly when different radioligands are used. For example, the dissociation constant for clozapine at the dopamine D_2 receptor is approximately 150 nM (range 70–400 nM), when using [^{3}H]-spiperone as a radioligand (Seeman 1992a). However, when [^{3}H]-raclopride is used as the radioligand, the dissociation constant for clozapine at D_2 is between 35 and 60 nM (Malmberg et al. 1993).

Recently, therefore, this dependence of the neuroleptic dissociation constant on the radioligand was studied in more detail (Seeman and Van Tol 1995; Seeman 1995b). It was found that the neuroleptic dissociation constant depended on the tissue:buffer partition coefficient of the radioligand. A similar finding has recently been made by Durcan et al. (1995).

For example, clozapine at the D_2 receptor revealed a dissociation constant of 390 nM with [^{3}H]-nemonapride, 186 nM with [^{3}H]-spiperone, and 83 nM with [^{3}H]-raclopride. Haloperidol also had a dissociation constant of 9.6 nM at dopamine D_2 receptors using [^{3}H]-nemonapride, 2.7 nM using [^{3}H]-spiperone, and 0.67 nM using [^{3}H]-raclopride. These neuroleptic dissociation constants were related to the tissue:buffer partition coefficients of the radioligands, as shown in Figures 1 and 2.

THE RADIOLIGAND-INDEPENDENT DISSOCIATION CONSTANT

It is possible to eliminate the dependence of the neuroleptic dislocation constant on the radioligand and thereby obtain the dissociation constant of the neuroleptic in the absence of any competing radioligand. This may be done by extrapolating the relation shown (Figure 2) down to either unity or zero partition, yielding an intercept. This intercept represents the dissociation constant

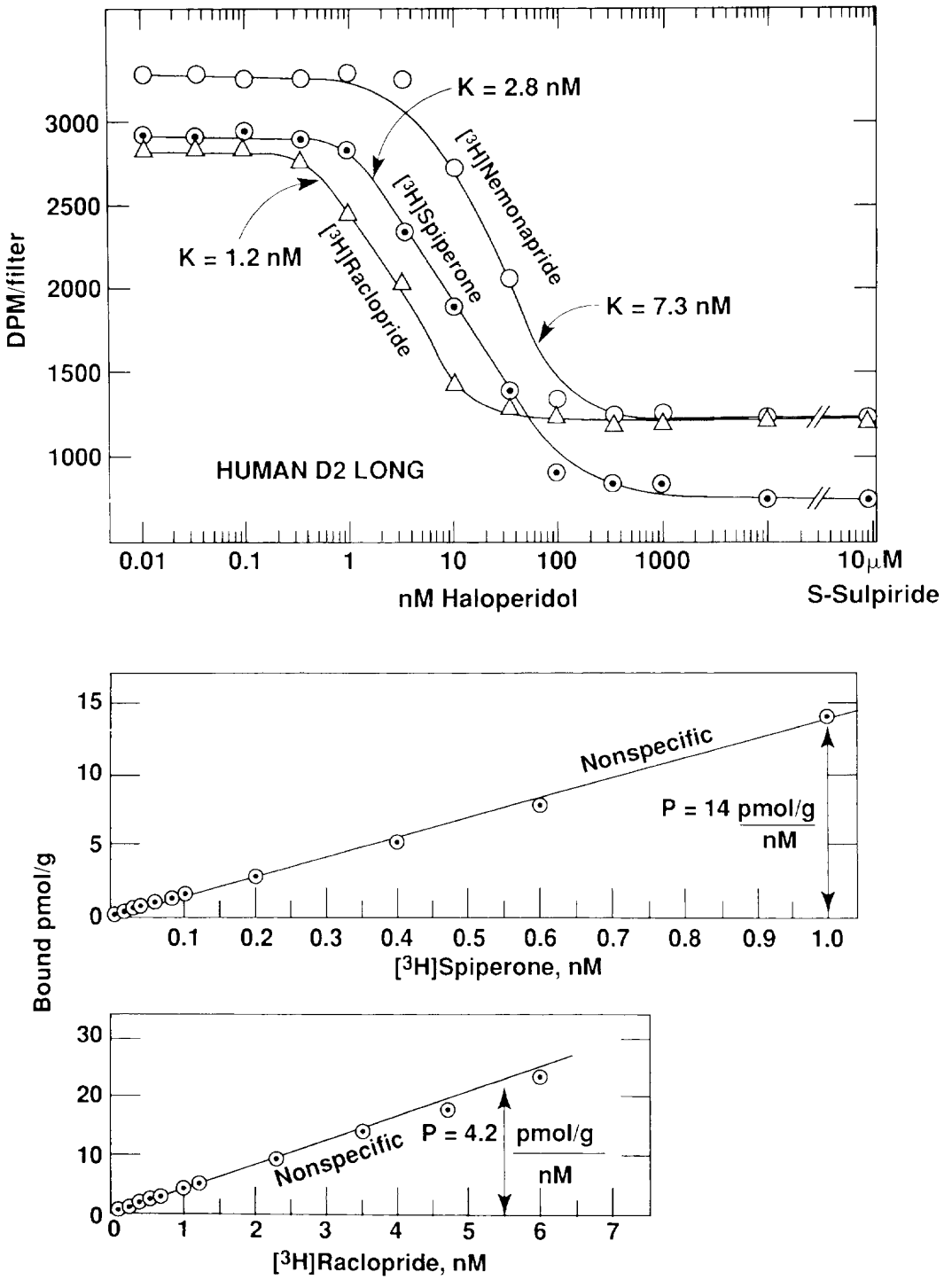


Figure 1. *Top*, a representative experiment showing that the haloperidol dissociation constant (or inhibition constant) was high (7.3 nM) when competing versus [^{3}H]-nemonapride, but lower when competing versus [^{3}H]-spiperone (2.8 nM) and even lower when using [^{3}H]-raclopride (1.2 nM). These *K* values were derived by the Cheng–Prusoff (1973) equation, using the appropriate K_d value for each [^{3}H]-ligand (adapted from Seeman and Van Tol 1995). (The Hill coefficient for the competition of haloperidol with each radioligand was not significantly different from unity). *Bottom*, the tissue:buffer partition for each radioligand was defined as the nonspecific binding that occurs at 1 nM ligand. The tissue was postmortem human brain caudate nucleus. Nonspecific binding was defined as that obtained in the presence of 1 μM (+)butaclamol. (Adapted from Seeman and Van Tol 1995.)

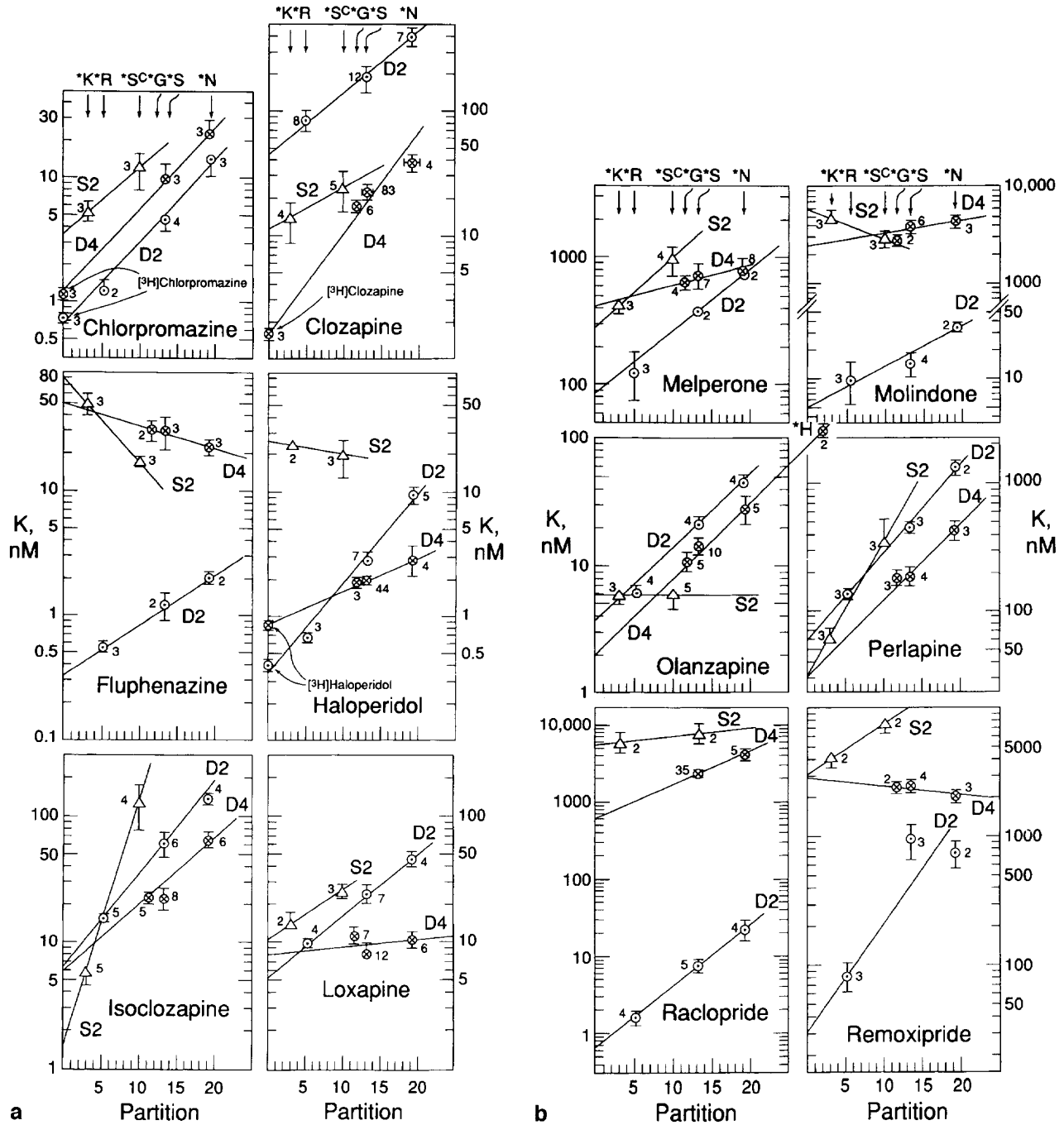
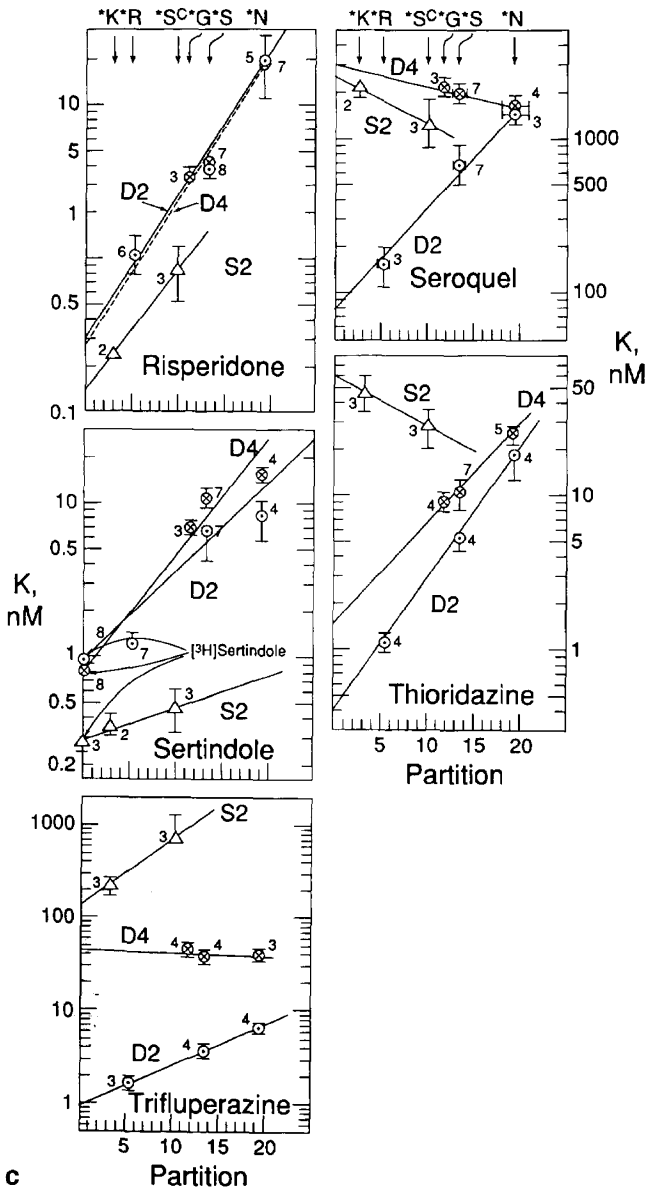


Figure 2. Using data of the sort shown in Figure 1, the dissociation constant (*K* value) for a neuroleptic at a given receptor depends on the tissue:buffer partition of the [^{3}H]-ligand. Extrapolating down to the intercept yields the radioligand-independent dissociation constant. This value represents the dissociation constant for the neuroleptic in the absence of any competing [^{3}H]-ligand and is therefore referred to as the radioligand-independent dissociation constant. The [^{3}H]-ligands for the serotonin 5-HT_{2A} receptor (rat cerebral cortex) were: [^{3}H]-ketanserin (*K) and [^{3}H]-spiperone (*S^c). The [^{3}H]-ligands for the human cloned D_2 receptor were [^{3}H]-nemonapride (*N) (formerly emonapride or YM-09151-2), [^{3}H]-spiperone (*S) or [^{3}H]-raclopride (*R). The data using either D_{2short} (Bunzow et al. 1988; Owolabi et al. 1994) or D_{2long} (O'Dowd et al. 1990; in COS-7 cells) yielded identical *K* values for each neuroleptic. The [^{3}H]-ligands for the human cloned D_4 receptor (Van Tol et al. 1991) were [^{3}H]-nemonapride, [^{3}H]-spiperone, or [^{3}H]-Sandoz GLC756 (*G) (Markstein et al., 1996). The data using either D4.2 or D4.7 (Van Tol et al. 1992) yielded identical dissociation constants for each neuroleptic. The number of independent measurements is given beside each point. The tissue:buffer partition coefficients for the [^{3}H]-ligands were for the postmortem human caudate nucleus (see Figure 1), except that for *K and *S^c, which were based on the rat cerebral cortex. Using partition coefficients based on the [^{3}H]-ligands partitioning between tissue culture cells and buffer yielded essentially similar results for the radioligand-independent dissociation constants (Seeman and Van Tol 1995). Note that the dissociation constants K_d using [^{3}H]-



chlorpromazine, [^{3}H]-clozaprine, and [^{3}H]-haloperidol were identical to the radioligand-independent dissociation constants for chlorpromazine, clozapine, and haloperidol, respectively. The K_d values of these [^{3}H]-neuroleptics are shown at a low partition (zero) because the [^{3}H]-ligand does not compete with any other compound for binding to the receptor.

of the neuroleptic in the absence of any competing radioligand. Thus, a low partition or a partition of "zero" indicates that the neuroleptic would be competing against a water-soluble radioligand with low or negligible partition and that would be readily displaced by the neuroleptic.

Several examples of this approach are shown in Figures 2A–2C. Thus, the extrapolated dissociation constant (or radioligand-independent dissociation constant) for clozapine at dopamine D_4 receptors is 1.6 nM, in agreement with the value of 1.5 nM as directly measured with [^{3}H]-clozapine at the dopamine D_4 receptor (see Figure 2A). This value, moreover, agrees with that found by Kusumi et al. (1995a, 1995b) for a dopamine D_4-like binding site labeled by [^{3}H]-clozapine in the rat frontal cortex.

It is important to note this identity between the radioligand-independent dissociation constant (Figure 2) and the dissociation constant (K_d) as determined directly using the [^{3}H]-neuroleptic. This identity holds for [^{3}H]-chlorpromazine, [^{3}H]-clozapine, and [^{3}H]-haloperidol, as shown in Figure 2A, as well as for [^{3}H]-sertindole (Figure 2c). The K_d values of these [^{3}H]-neuroleptics are shown at a low partition (zero) because the [^{3}H]-ligand does not compete with any other compound for binding to the receptor.

The extrapolated radioligand-independent dissociation constant is not a new parameter in any way. It merely is the dissociation constant of the competing nonradioactive compound that would be obtained if very high volumes of incubation were used (Seeman and Van Tol 1995; Seeman 1995b). For example, when the volume of incubation was increased from the customary 1.5 ml to a larger volume of 8 ml, the radioligand-dependence of the competing nonradioactive drug was considerably reduced but not eliminated (Seeman and Van Tol 1995; Seeman 1995b). The dependence of the dissociation constant on the partition coefficient of the radioligand does not arise from depletion of the radioligand, because no depletion occurs (Seeman and Van Tol 1995; Seeman 1995b). In fact, when very high volumes of 10 ml are used, the radioligand dependence may disappear, and the dissociation constant of the radioactive drug appears to agree with the dissociation constant of the competing nonradioactive drug (Malmberg et al. 1996). The radioligand dependence is not a result of inadequate time of equilibration, as identical results were obtained when the standard incubation period of 2 hours was extended to either 4 or 6 hours (Seeman and Van Tol 1995; Seeman 1995b).

A summary of the radioligand-independent dissociation constants for 17 neuroleptics at the dopamine D_2 receptor (cloned), the dopamine D_4 receptor (cloned), and the serotonin 5-HT_{2A} (rat cortex) receptor is given in Table 1.

DRUG SELECTIVITY IS LIGAND-DEPENDENT

An examination of the data in Figure 2 indicates that the receptor selectivity of a drug depends on the radioligands used. For example, the data in Figure 2B for olanzapine show that olanzapine has a radioligand-independent dissociation constant of 2 ± 0.4 nM at the

Table 1. Radioligand-Independent Dissociation Constants

	D_2	D_4	5-HT_{2A}	D_2:5-HT_{2A} Ratio	D_2:D_4 Ratio
Chlorpromazine	0.66 ± 0.05(12)	1.15 ± 0.04(9)	3.5 ± 0.06(9)	0.19	0.58
Clozapine	44 ± 8(27)	1.6 ± 0.4(96)	11 ± 3.5(9)	4.00	28.00
Fluphenazine	0.32 ± 0.03(7)	50 ± 10(11)	80 ± 19(6)	0.004	0.0064
Haloperidol	0.35 ± 0.05(18)	0.84 ± 0.05(54)	25 ± 8(5)	0.014	0.42
Isoclozapine	6 ± 0.06(15)	5.8 ± 0.08(19)	1.5 ± 0.05(9)	4.20	1.03
Loxapine	5.2 ± 0.03(15)	7.8 ± 1.5(25)	10.2 ± 1.2(5)	0.51	0.67
Melperone	88 ± 30(7)	410 ± 70(19)	280 ± 90(7)	0.31	0.22
Molindone	6 ± 3(9)	2,400 ± 800(11)	5,800 ± 1,300(6)	0.001	0.0025
Olanzapine	3.7 ± 0.6(12)	2 ± 0.4(22)	5.8 ± 0.7(14)	0.64	1.85
Perlapine	60 ± 10(8)	30 ± 10(10)	30 ± 12(6)	2.00	2.00
Raclopride	0.64 ± 0.12(13)	620 ± 100(40)	5,400 ± 1,700(4)	0.00012	0.001
Remoxipride	30 ± 25(8)	2,800 ± 400(9)	3,100 ± 400(4)	0.01	0.011
Risperidone	0.3 ± 0.1 (19)	0.25 ± 0.1(17)	0.14 ± 0.1(5)	2.14	1.2
Seroquel	78 ± 28(13)	3,000 ± 300(14)	2,500 ± 600(5)	0.03	0.026
Sertindole	0.95 ± 0.4(22)	0.85 ± 0.2(18)	0.3 ± 0.06(8)	3.1	1.12
Thioridazine	0.4 ± 0.12(12)	1.5 ± 0.5(16)	60 ± 15(6)	0.007	0.27
Trifluperazine	0.96 ± 0.2(11)	44 ± 6(11)	135 ± 50(6)	0.007	0.022

In nM ± SE (*n* experiments in duplicate).

dopamine D_4 receptor. This value is statistically significantly lower than that of 3.7 ± 0.6 nM for the dopamine D_2 receptor and lower than that of 5.8 ± 0.7 nM for the 5-HT_{2A} receptor. However, if only the data for olanzapine using [^{3}H]-spiperone were considered, then olanzapine would be viewed as preferring the 5-HT_{2A} receptor (see Figure 2B). Selectivity is here defined as a statistically significant preference of the neuroleptics for one receptor over another, as examined by their radioligand-independent dissociation constants (Table 1). The receptor selectivities of haloperidol and isoclozapine (Figure 2A) also depend on the ligand considered.

NEUROLEPTICS WITH HIGH AND LOW AFFINITY FOR THE DOPAMINE D_2 RECEPTOR

The data in Table 1 indicate that the neuroleptic values for the radioligand-independent dissociation constants fall into two groups, those that have high values at dopamine D_2 receptors (between 30 and 90 nM) and those that have low values (between 0.3 and 5 nM).

CLOZAPINE THERAPEUTIC CONCENTRATION, AS DERIVED FROM THE RADIOLIGAND-INDEPENDENT DISSOCIATION CONSTANT AT THE DOPAMINE D_4 RECEPTOR

One important example of the usefulness of the value for the radioligand-independent dissociation constant is that it may be used to derive the therapeutic concentration of a neuroleptic. For example, although the data in Figure 2 show that clozapine has a radioligand-independent dissociation constant of 1.6 nM at the dopamine D_4 receptor, clozapine in vivo must compete with endogenous dopamine in the synapse, estimated to be of the order of 10 nM (Kawagoe et al. 1992). Hence, the in vivo concentration of clozapine for 50% occupation of dopamine D_4 receptors may be derived from the commonly used Cheng–Prusoff equation (Cheng and Prusoff 1973; Munson and Rodbard 1988). Thus, the in vivo concentration of clozapine for 50% occupation of dopamine D_4 receptors would be approximately equal to $K \times [1 + D/6.2\ \text{nM}])$, or 4.2 nM, where K is the radioligand-independent dissociation constant of 1.6 nM for clozapine (Figure 2), D is the synaptic concentration of the order of 10 nM, and where 6.2 nM is the dissociation constant of dopamine at the high-affinity state of the dopamine D_4 receptor (Table 2 in Asghari et al. 1994).

We previously used the value of 50 nM for the synaptic concentration of dopamine (Seeman and Van Tol 1995). This value of 50 nM, however, was from Ross (1991), who estimated it by an indirect method of in vivo competition of tritiated dopamine agonists and comparing the results with in vitro competition by dopamine. The value of 10 nM, however, was obtained more directly by Kawagoe et al. (1992) and is used, therefore, in this present review. This value for 10 nM, moreover, refers to the dopamine concentration that is time-averaged for a frequency of 5 Hz over a distance of 2 microns. In addition, although we previously used the value of 16 nM for the high-affinity state of dopamine at the dopamine D_4 receptor (Seeman and Van Tol 1995), the more recent value of 6.2 nM is based on 18 experi-

ments for the different variants of D_4 (Table 2 in Asghari et al. 1994).

This approximate synaptic concentration of 4.2 nM clozapine, however, only applies for the blockade of 50% of the dopamine D_4 receptors. Hence, the synaptic concentration of clozapine required to block 75% of the dopamine D_4 receptors will be three times higher, or about 13 nM. [Actually, the clinical requirement to block 75% of the dopamine receptors to achieve antipsychotic action applies to the occupation of dopamine D2 receptors (Farde et al. 1992). The percent occupancy of dopamine D_4 receptors required for the clinical control of psychotic symptoms is not yet known.]

This predicted in vivo concentration of 13 nM clozapine for 75% occupation of dopamine D_4 receptors compares to an observed value in the plasma water or spinal fluid of treated patients of between 12 and 20 nM (Olesen et al. 1995; see References and analysis in Seeman 1992a), using 1.85% as the proportion of free (unbound) clozapine in the plasma (Table 1 in Seeman 1992a).

These considerations (as well as those below in Parkinson's disease) do not prove but only suggest that clozapine might be clinically operative at the dopamine D_4 receptor, despite the fact that clozapine is known to bind to many receptors. At the very least, these calculations indicate that dopamine D_4 receptors are at least 75% occupied by clozapine under therapeutic conditions.

THERAPEUTIC CONCENTRATIONS OF OTHER NEUROLEPTICS

Using the same considerations for haloperidol, it can be shown that the haloperidol therapeutic concentration required for 75% blockade of dopamine D_2 receptors in vivo will be approximately 2 to 3 nM, using the radioligand-independent dissociation constant of 0.35 nM (Table 1; Figure 2). This predicted value of 2 to 3 nM haloperidol agrees with the observed value in the spinal fluid (or plasma water) of between 1 and 3 nM (Table 1 in Seeman 1992a). Approximately 75% to 80% of the brain dopamine D_2 receptors are occupied (Wolkin et al. 1989; Nyberg et al. 1995) by 1 nM haloperidol in the plasma water, using 8.5% as the average proportion of free (i.e., unbound) haloperidol in the plasma (Seeman 1992a).

Furthermore, using this same type of calculation for the antipsychotics listed in Table 1, it may be shown that the molarity for 75% blockade of dopamine D_2 receptors (and allowing for competition with endogenous dopamine) results in a final concentration of antipsychotic drug that matches that found in patients (i.e., the concentration in the plasma water or in the spinal fluid). For example, using this calculation, remoxipride yields a molarity of 235 nM; the value observed in patients is 200 nM (Seeman 1992a). Molindone yields a value of 47 nM; the value observed in patients is 50 nM (Seeman 1992a). Chlorpromazine yields a value of 5.2 nM; that found in patients is 6 nM (Seeman 1992a). Raclopride yields a value of 5 nM; that found in patients is 3 nM (Seeman 1992a). Thioridazine yields a value of 3.1 nM; that found in patients is 3 nM (Seeman 1992a). In effect, therefore, these radioligand-independent dissociation constants at the dopamine D_2 receptor, when corrected for competition with endogenous dopamine and with allowance made for 75% occupation of dopamine D_2 receptors, closely match the free neuroleptic concentrations in the patient's plasma water, as previously shown using other radioligands (Seeman 1992a; Seeman et al. 1976).

DERIVING THE CLOZAPINE THERAPEUTIC CONCENTRATION IN L-DOPA PSYCHOSIS IN PARKINSON'S DISEASE

Parkinson's disease provides a second important example of the usefulness of radioligand-independent dissociation constants. In excellent agreement with the findings of Meltzer et al. (1995), who measured plasma clozapine in Parkinson's patients who had become psychotic on L-DOPA, the clozapine concentration (in the plasma water or spinal fluid) for 75% blockade of dopamine D_4 receptors can be derived to be approximately 1.7 nM (using the previous equation, where D is known to be less than 5% of normal). This value is in agreement with the value of approximately 1.2 nM found by Meltzer et al. (1995), after allowance is made for clozapine binding to plasma proteins (see above).

CLOZAPINE OCCUPATION OF DOPAMINE RECEPTORS, AS SEEN BY POSITRON TOMOGRAPHY

A third important example of the principle shown in Figure 2 is the resolution of different positron tomography findings in the proportion of dopamine D_2 receptors occupied by clozapine in humans. The data in Figure 2, using [^{3}H]-raclopride and [^{3}H]-spiperone, may explain why clozapine occupies 48% of the dopamine D_2 receptors in patients when measured with [^{11}C]-raclopride (Farde et al. 1992, 1994; Nordström et al. 1994), but between 0% and 22% when measured with [^{18}F]-methylspiperone (Karbe et al. 1991) or [^{18}F]-fluoroethylspiperone (Louwerens et al. 1993). By graphing the percentage of D_2 receptors occupied by clozapine versus the tissue:buffer partition of the radioligand, it is possible to extrapolate to "zero" partition, as is done

with the in vitro data (Figure 2). Thus, the percentage of D_2 receptors occupied by clozapine is extrapolated to approximately 85%, if using a radioligand of "zero" partition (e.g., radiodopamine). Under clinical conditions, therefore, in the absence of any radioligand, clozapine occupies high levels of D_2 receptors in neuroleptic-treated patients (Seeman and Kapur, submitted). The antipsychotic action of clozapine may stem, therefore, from its occupation of high levels of D_2, D_4, or 5-HT_{2A} receptors.

RECEPTOR BASES FOR ATYPICAL NEUROLEPTIC ACTION

The different receptor hypotheses for the clinically atypical action of the atypical neuroleptics may now be examined using the values for the radioligand-independent dissociation constants.

Neuroleptics Displaceable by Endogenous Dopamine

The first group are those atypical neuroleptics that have low affinity for dopamine D_2 receptors and thus may be readily displaced by high endogenous concentrations of dopamine in the caudate or putamen, as depicted in Figure 3. This group includes remoxipride, clozapine, perlapine, seroquel, and melperone, all of which have very high values (30–90 nM; Table 1) for their radioligand-independent dissociation constants. This is in contrast to most typical neuroleptics that have radioligand-independent dissociation constants of 0.3 to 5 nM (Table 1). Molindone is borderline with a radioligand-independent dissociation constant of 6 nM (Table 1). Of the 12 atypical neuroleptics listed by Roth et al. (1995), nine have dissociation constants (using [^{3}H]-spiperone) that are between 45 and 1,584 nM, suggesting that these compounds would be readily displaced at the dopamine D_2 receptor by high local concentrations of endogenous dopamine in the striatum. Of the 11 typical neuroleptics tested by Roth et al. (1995), 10 have dissociation constants (using [^{3}H]-spiperone) that are between 0.06 and 8 nM, suggesting that these compounds would be less readily displaced at the dopamine D_2 receptor by high local concentrations of endogenous dopamine in the striatum.

It should first be noted that the therapeutic concentrations (in spinal fluid or plasma water) of remoxipride and molindone are identical to the concentrations that block 75% of the dopamine D_2 receptors (Seeman 1992a, 1995b, 1995c), as noted. Thus, remoxipride and molindone are not exceptions to the general rule that therapeutic levels of neuroleptics occupy dopamine D_2 receptors (with the exception of clozapine, which prefers dopamine D_4 receptors; Seeman 1992a, 1995b).

However, the high radioligand-independent dissociation constants of 30 to 90 nM for these atypical drugs indicates that they are loosely attached to the dopamine D_2 receptors and may, therefore, be readily displaced by endogenous dopamine. The principle of displacement of a neuroleptic by endogenous dopamine has been shown for [^{3}H]-raclopride (Seeman et al. 1989a; Young et al. 1991), [^{11}C]-raclopride (Dewey et al. 1992, 1993a, 1993b; Innis et al. 1992; Wong et al. 1995), [^{3}H]-spiperone and [^{3}H]-methylspiperone (De Jesus et al. 1986; Seeman et al. 1989a; Young et al. 1991), [^{18}F]-N-methylspiperone (Logan et al. 1991; Dewey et al. 1991), and [^{123}I]-iodobenzamide (Innis et al. 1992; Laruelle et al. 1995a, 1995b).

Neuroleptics with high dissociation constants have low tissue:buffer partition values and are more extensively displaced by endogenous dopamine than neuroleptics with low dissociation constants that have high tissue:buffer partition values (Seeman et al. 1989a). The five atypical neuroleptics remoxipride, clozapine, perlapine, seroquel, and melperone would be expected to be readily displaced by endogenous dopamine, although no experimental work has been reported for these particular five neuroleptics.

It is reasonable to expect, moreover, variations in the synaptic dopamine concentration in different brain regions, based on the different concentrations of homovanillic acid (HVA) found in these various regions. For example, the basal concentration of HVA in the rat striatum is four times higher than that in the limbic region (Anden and Stock 1973) and 20 times higher than that in the prefrontal cortex (Bowers 1984).

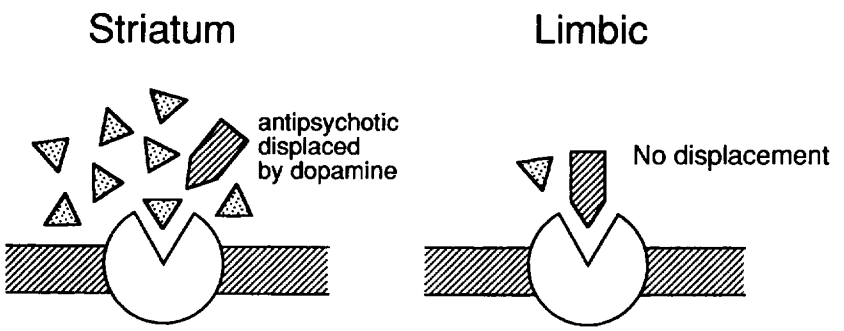


Figure 3. Dopamine displaces antipsychotic drugs that bind with low affinity to dopamine D_2 receptors in the striatum (where the dopamine concentration is high), but not in the limbic regions of the brain where the dopamine content is low.

Hence, neuroleptics with high dissociation constants would occupy more dopamine receptors in brain regions that have a low dopamine output (limbic regions, hypothalamus, and prefrontal cortex), but would occupy fewer dopamine receptors in regions that have high dopamine output (caudate/putamen) as a result of the neuroleptic competition with endogenous dopamine (Figure 3). Hence, the fraction of dopamine receptors that are blocked in the caudate/putamen would be less than the fraction blocked in the nonstriatal regions, with corresponding fewer extrapyramidal signs than found in the typical neuroleptics that have low radioligand-independent dissociation constants. These considerations may explain why seroquel (450 mg) occupies only 27% to 44% of the D_2 receptors in patients (using [^{11}C]-raclopride, Gefvert et al. 1995) and why clozapine occupies only 48% of the dopamine D_2 receptors in patients (using [^{11}C]-raclopride, Farde et al. 1992, 1994; Nordström 1994), than the typical neuroleptics that occupy 70% to 80% of the dopamine D_2 receptors (Farde et al. 1992, 1994; Nordström 1994).

Combined Block of Dopamine D_2 Receptors and Muscarinic Receptors

A second small group of two atypical neuroleptics, clozapine and thioridazine, strongly block both dopamine D_2 and muscarinic receptors. Clozapine, for example, is of the order of 20- to 50-fold more potent in blocking muscarinic acetylcholine receptors than blocking dopamine D_2 receptors (see references in Seeman 1990), making clozapine an extremely potent anticholinergic drug. Clozapine blocks muscarinic receptors between 1.5 (Snyder et al. 1974) and 36 nM (Clineschmidt et al. 1979). Because anticholinergic drugs have an anti-Parkinson action, it might appear that the low values of 1.5 to 36 nM may readily account for the atypical action of clozapine. However, this simple explanation is probably not correct, because isoclozapine is equally anticholinergic (K of 11 nM; Rupard et al. 1989), yet elicits catalepsy in animals at low doses, in contrast to clozapine. Moreover, it has been argued that the combination of antagonists for dopamine (i.e., neuroleptic) and acetylcholine (i.e., benztropine) is not as effective in minimizing Parkinsonism as clozapine itself (Sayers et al. 1975; Kane et al. 1988).

Thioridazine also blocks muscarinic receptors at about the identical concentrations that it blocks dopamine D_2 receptors (see references in Seeman 1990). Thus, the relatively low level of Parkinsonism caused by thioridazine may stem from its anticholinergic action.

Balanced Block of Dopamine D_2 Receptors and 5-HT_{2A} Receptors

A third mechanism that may account for the clinically atypical action of atypical neuroleptics is that these drugs may have a balanced block of D_2 and 5-HT_{2A} receptors (Meltzer 1989, 1995; Leysen et al. 1994; Huttunen 1995).

The blockade of serotonin receptors increases the release of dopamine, as measured indirectly by the fall in [^{11}C]-raclopride binding to D_2 receptors (Smith et al. 1994; Dewey et al. 1995; Pehek 1995; see additional references on dopamine-serotonin interactions in Meltzer and Nash 1991). In turn, therefore, the increased release of endogenous dopamine displaces some of the neuroleptic from the dopamine D_2 receptors, thereby alleviating to some extent the Parkinsonism caused by the dopamine D_2 receptor blockade.

This mechanism (of enhancing dopamine release) may explain the modest alleviation of neuroleptic-induced catalepsy (in rats) by ritanserin, a serotonin antagonist (Bligh-Glover et al. 1995). This alleviation only occurs, however, if the catalepsy is submaximum (Bligh-Glover et al. 1995), but not if the catalepsy is maximum, as produced by a relatively high dose of haloperidol (Wadenberg 1992; Jaskiw et al. 1994).

Ritanserin has been reported to alleviate neuroleptic-induced Parkinsonism and akathisia in patients (Bersani et al. 1990; Miller et al. 1992). However, ritanserin does not alleviate haloperidol-induced dystonia in monkeys, unlike clozapine, which is very effective in reversing this extrapyramidal syndrome (Casey 1991, 1993, 1995a, 1995b).

Clozapine, the most atypical neuroleptic, also is potent at many other receptors, including 5-HT_{2C} (Leysen 1990; Kuoppamäki et al. 1993), 5-HT_5, and 5-HT_6 receptors (Roth et al. 1994), and alpha$_1$-adrenoceptors (Lejeune et al. 1994), but not potent at 5-HT_3 receptors (Hoyer et al. 1989). It is possible, therefore, that such other receptor sites contribute to the atypical action of clozapine.

Overall, however, there is mixed evidence supporting the concept of a balanced block of D_2 and 5-HT_{2A} receptors to account for the low level or absence of Parkinsonism by clozapine and other atypical neuroleptics (Seeman 1992b).

To investigate this important D_2/5-HT_{2A} block hypothesis further, the above radioligand-independent dissociation constants (Table 1) may be used for these two receptors. These values at the 5-HT_{2A} receptor are approximately the same as those reported by others for the neuroleptic dissociation constants at this receptor, using [^{3}H]-ketanserin (Leysen et al. 1982; Wander et al. 1987).

In principle, the ratio of the neuroleptic radioligand-independent dissociation constants for these two receptors should be related to the dose that elicits either Parkinsonism in patients or catalepsy in rats. Such doses vary considerably, depending on how the Parkinsonism or the catalepsy are measured. To test the D_2:5-HT_{2A} hypothesis, therefore the catalepsy doses as obtained in a single laboratory would be more meaningful. Figure 4

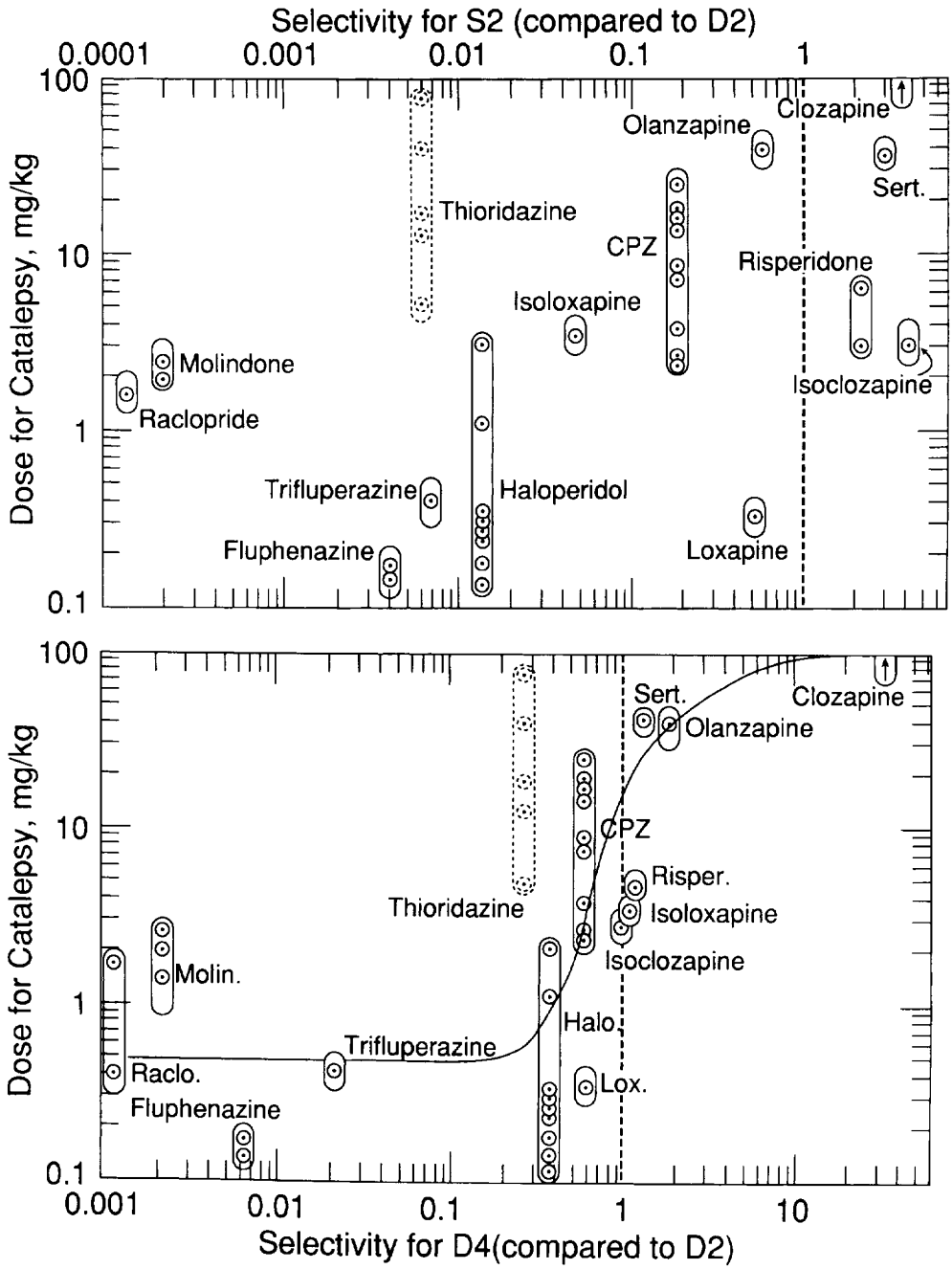


Figure 4. *Top,* published doses for neuroleptic-induced catalepsy (in rats) graphed versus the ratio of the neuroleptic radioligand-independent dissociation constants (from Table 1) for the dopamine D_2 and 5-HT_{2A} receptors. Thus, the horizontal axis indicates the neuroleptic selectivity for 5-HT_{2A} relative to that for the dopamine D_2 receptor. Data for the four neuroleptics having low affinity for the dopamine D_2 receptors (remoxipride, perlapine, seroquel, and melperone) that have high radioligand-independent dissociation constants were omitted because these neuroleptics are atypical by virtue of being displaced by endogenous dopamine. Although clozapine and isoclozapine have identical D_2:5-HT_{2A} ratios, the catalepsy dose for clozapine is in excess of 100 mg/kg (*arrow*) The references for the catalepsy doses are: chlorpromazine (CPZ) (Janssen et al. 1965; Stille et al. 1965b; Dlabac et al. 1975; Hunziker et al. 1981; Dubinsky et al. 1982; Gustafsson and Christensson 1990; Hirose et al. 1990; Usuda et al. 1981; Moore et al. 1992); clozapine (Bürki et al. 1977; Moore et al. 1992); fluphenazine (Janssen et al. 1965); haloperidol (Halo.) (Stille et al. 1965b; Bürki et al. 1977; Usuda et al. 1981; Dubinsky et al. 1982; Gustafsson and Christensson 1990; Hirose et al. 1990; Högberg et al. 1990; Megens et al. 1992; Moore et al. 1992); isoclozapine (Stille et al. 1965a; Schmutz 1973); isoloxapine (Schmutz and Eichenberger 1992); loxapine (Lox.) (Stille et al. 1965b; Bürki et al. 1977); molindone (Molin.) (Moore et al. 1992; R. Corbett, unpublished); olanzapine (Moore et al. 1992); raclopride (Raclo.) (R. Corbett, unpublished); risperidone (Risper.) (Megens et al. 1992; Moore et al. 1992); sertindole (Sert.) (Arnt et al. 1994); thioridazine (Thior.) (Janssen et al. 1965; Bürki et al. 1977; Hirose et al. 1990); trifluperazine (Janssen et al. 1965). Thioridazine is drawn differently (dotted lines) because it is a very potent anticholinergic drug; its anticataleptic action, therefore, may be attributed to

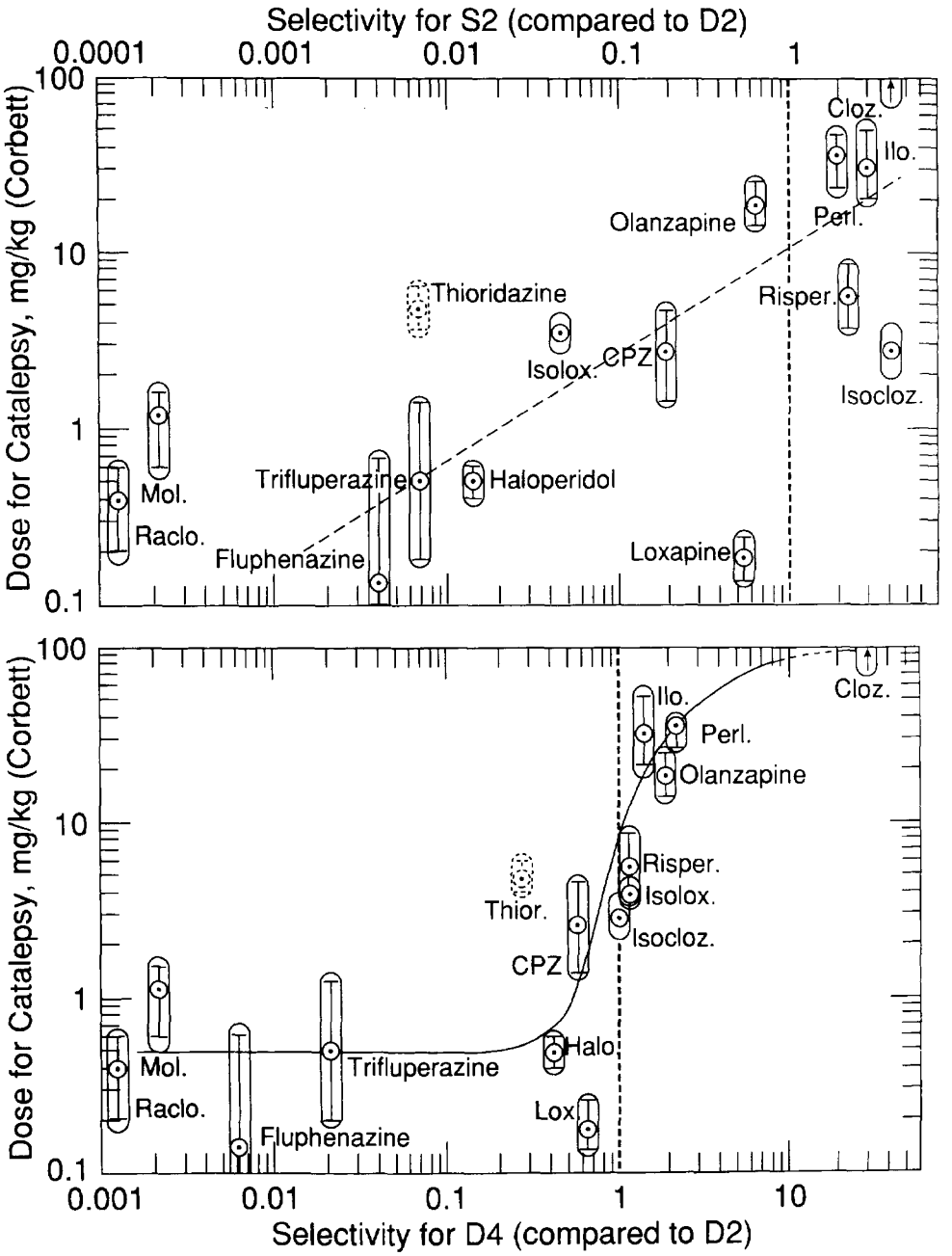


Figure 5. *Top*, neuroleptic doses for eliciting catalepsy in 50% of the rat graphed versus the ratio of the neuroleptic radioligand-independent dissociation constants for the dopamine D_2 receptor and the serotonin 5-HT_{2A} receptors, as in Figure 4, except that the doses are all from one laboratory (Corbett et al. 1995). As in Figure 4, data for the four neuroleptics who have low affinity for the dopamine D_2 receptors (remoxipride, perlapine, seroquel, and melperone), which have high radioligand-independent dissociation constants, were omitted, based on the concept that these neuroleptics are atypical by virtue of being displaced by endogneous dopamine. Vertical bars indicate SE. See legend to Figure 4 (*top*) for additional details and references. *Bottom*, same as in Figure 5 (*top*) except that the catalepsy doses (Corbett et al. 1995) are graphed versus the ratio of the neuroleptic radioligand-independent dissociation constants for the dopamine D_2 and D_4 receptors (from Table 1). Thus, the horizontal axis indicates the neuroleptic selectivity for the dopamine D_4 receptor relative to that for the dopamine D_2 receptor.

its anticholinergic efficacy. *Bottom*, same as for the top part of the figure except that the published catalepsy doses are graphed versus the ratio of the neuroleptic radioligand-independent dissociation constants for the dopamine D_2 and D_4 receptors (from Table 1). Thus, the horizontal axis indicates the neuroleptic selectivity for the dopamine D_4 receptor relative to that for the dopamine D_2 receptor.

(top) attempts to relate the radioligand-independent dissociation constants for the D_2:5-HT_{2A} ratio with the rat catalepsy doses for various neuroleptics using the published catalepsy doses from many laboratories wherein different criteria were used to measure catalepsy.

Figure 5 (top) shows the same type of data, but using catalepsy doses from a single laboratory (Corbett et al. 1995), where the same criteria were used to measure catalepsy for all the neuroleptics tested.

In examining Figures 4 (top) and 5 (top), it is important to note that clozapine and isoclozapine have almost identical selectivity for the 5-HT_{2A} receptor (compared to the dopamine D_2 receptor). Nevertheless, isoclozapine elicits catalepsy at about 3 mg/kg, whereas clozapine does not produce catalepsy at 100 mg/kg.

Although there is no clear relation between rat catalepsy and the D_2:5-HT_{2A} ratios of the radioligand-independent dissociation constants (Figures 4 and 5), other studies have found a difference between typical and atypical neuroleptics in their relative occupancy of dopamine D_2 and 5-HT_{2A} receptors (Meltzer et al. 1989a, 1989b; Matsubara et al. 1993; Stockmeier et al. 1993).

Selective Block of Dopamine D_4 Receptors

A fourth possible mechanism for atypical neuroleptic action may be the selective blockade of dopamine D_4 receptors. There is a relation between the neuroleptic doses for rat catalepsy and the D_2:D_4 ratio of the radioligand-independent dissociation constants. This is shown in Figures 4 (bottom) and 5 (bottom).

An important feature of the data in Figure 4 is that clozapine and isoclozapine are considerably different in their values for the D_2:D_4 ratio of radioligand-independent dissociation constants, in good relation to their different cataleptic potencies. This stands in contrast to their identical values for the D_2:5-HT_{2A} ratios of radioligand-independent dissociation constants, as noted.

Roth et al. (1995) also have found that perlapine, olanzapine, and clozapine are selective for the dopamine D_4 receptor, compared to the dopamine D_2 receptor.

Although sertindole is only now beginning to be tested in large numbers of patients, it has been reported that it does not elicit Parkinsonism (Daniel et al. 1995; Wallin et al. 1995). The low level or absence of extrapyramidal signs with sertindole might be related to its ability to block dopamine D_2 and dopamine D_4 receptors equally well, as illustrated in Figure 2C and shown in Table 1).

The clinical role of dopamine D_4 receptors may be clarified when the new D_4-selective drugs (Kulagowski et al. 1996; TenBrink et al. 1996) are developed and tested on psychotic patients. The blockade of dopamine D_4 receptors by these D_4-selective drugs may or may not be associated with clinical antipsychotic action. However, if such dopamine D_4-selective drugs do not turn out to be antipsychotic, they may possibly mitigate against the extrapyramidal side effects of dopamine D_2 antagonists by activating locomotion. Nafadotride, for example, a dopamine D_3 receptor antagonist, activates locomotion in rats (Sautel et al. 1995).

Furthermore, to test whether or not the occupation of dopamine D_4 receptors is related to catalepsy, it will be helpful to have tritiated congeners of the new D_4-selective compounds (Tallman 1994; Kulagowski et al. 1996; TenBrink et al. 1996) so that they may serve as radioligands for the dopamine D_4 receptors.

However, because D_4-selective radioligands have not hitherto been generally available, dopamine D_4 receptors have been measured indirectly. One method, for example, has been to use [^{3}H]-nemonapride (formerly YM-9151-2 or emonapride) to detect D_2, D_3, and D_4 receptors and to use [^{3}H]-raclopride or [^{125}I]epidepride to label D_2 and D_3 sites. Hence, the difference in densities between the sites labeled by [^{3}H]-nemonapride and those labeled by [^{3}H]-raclopride (or [^{125}I]-epidepride) has been ascribed to D_4-like receptors or binding sites (Seeman et al. 1993, 1995; Murray et al. 1995; Sumiyoshi et al. 1995; Schoots et al. 1995; Tarazi et al. 1995; Lahti et al. 1995, 1996a, 1996b). This procedure resulted in the detection of elevated D_4-like sites in postmortem schizophrenia tissues (Seeman et al. 1993, 1995; Murray et al. 1995; Sumiyoshi et al. 1995). Although Reynolds and Mason (1995) did not detect elevated D_4-like sites in schizophrenia tissues, they assumed that the specific activity of [^{125}I]-epidepride fell with time; however, as outlined elsewhere (Seeman et al. 1995), the specific activity of [^{125}I]-epidepride remains constant because the molecule self-destructs upon decay. Further discussion of the D_4-like binding sites in schizophrenia is given by Kerwin and Collier (1996).

However, recent preliminary findings, with D_4-selective [^{3}H]-ligands indicated little (Lahti et al. 1996b) or no detectable amounts of true D_4 dopamine receptors in either human control or schizophrenia striata (Seeman et al. 1995). This means that the existence of the elevated D_4-like sites in schizophrenia (Seeman et al. 1993, 1995; Murray et al. 1995; Sumiyoshi et al. 1995), although not representing genuine D_4 receptors, may actually represent altered features of D_2 or D_2-like receptors. It is known, for example, that the density of [^{3}H]benzamide sites exceeds the density of [^{3}H]-spiperone sites in both native tissues and in cloned dopamine D_2 receptors (Niznik et al. 1985; Seeman et al. 1992), giving rise to the idea that dopamine D_2 receptors may exist as either monomers or dimers (Seeman et al. 1992). Recent work on postmortem human tissues indicates that this is the case (G. Ng, S. George, P. Seeman, B. O'Dowd, in preparation). Moreover, in schizophrenia, the proportion of D_2 monomers and dimers may change so as to yield an apparent elevation of D_4-like sites. An example of this

latter phenomenon is seen for cholinergic muscarinic receptors (Wreggett and Wells 1995). A change in the association of G proteins with the muscarinic receptor alters the relative densities of two muscarinic radioligands. This change is associated with an apparent increase in the difference between the two radioligand densities and reflects a change in the oligomeric state of the muscarinic receptors (Wreggett and Wells 1995). A similar situation may occur in the dopamine D_2 receptors in schizophrenia, because it is known that G regulation in the schizophrenia postmortem tissues is abnormal (Seeman et al. 1989b, 1993).

If the dopamine D_4 receptors do alleviate the cataleptic effects of neuroleptics, as suggested by the data in Figure 5, it will be important to determine the neuron pathways or interactions between the dopamine D_2 and D_4 receptors. The low levels or absence of dopamine D_4 receptors in the striatum are matched by the low levels of D_4 mRNA in the human caudate nucleus and the substantia nigra (Van Tol et al. 1991; Matsumoto et al. 1995). Hence, the existence of D_4-containing cell bodies in the striatum is ruled out. It is possible, therefore, that D_4-containing neurons may extend from the cerebral cortex down to D_2-containing neurones in the striatum (Seeman 1992a). Much research remains to be done on the cell–cell or intracellular nature of the D_2-D_4 interaction.

Clozapine Stimulation of 5-HT_{1A} Receptors

An effective alleviation of neuroleptic-induced catalepsy is produced by 8-OH-DPAT (8-hydroxy-2-dipropylaminotetralin), a 5-HT_{1A} agonist (Invernizzi et al. 1988; Broekkamp et al. 1988; Hicks 1990; Wadenberg and Ahlenius 1991; Wadenberg 1992; Casey 1992; Neal-Beliveau 1993). In fact, it has recently been found that clozapine does act as a partial agonist at the human cloned 5-HT_{1A} receptor (Newman-Tancredi et al. 1996). This may well be the basis for the anticataleptic or anti-Parkinsonian action of clozapine. However, much research remains to be done to confirm that this particular mechanism is shared by other neuroleptics that elicit little Parkinsonism.

In summary, the atypical neuroleptics appear to have either a low affinity for dopamine D_2 receptors, or they appear to be moderately selective for dopamine D_4 receptors.

ACKNOWLEDGMENTS

We thank Dr. H.-C. Guan for technical assistance and Diane Nam for helping with the references. We thank Dr. M. Sasa and the *Japanese Journal of Phamacology* for permission to adapt and include Figures 5 and 6 (here as Figures 3 and 5) from Seeman et al. (1996). We thank Janssen Pharmaceitica, Inc., for donating risperidone and haloperidol; Sandoz Pharmaceuticals for clozapine, isocloxapine (HF 2046), perlapine, and thioridazine; Rhône-Poulenc Rorer Pharmaceuticals, Inc., for chlorpromazine; Bristol Myers Squibb Co. for fluphenazine; Lederle Laboratories Division of American Cyanamid Co. for loxapine; Lilly Research Laboratories for olanzapine; ICI Pharmaceuticals Group for seroquel; AB Ferrosan for melperone; Endo Laboratories, Inc., of E.I. du Pont de Nemours & Co., Inc., for molindone; Astra Arcus AB for raclopride and remoxipride; SmithKline Beecham Pharmaceuticals for trifluperazine; H. Lundbeck A/S for sertindole; and Allelix Biopharmaceuticals, Inc., Mississauga, Ontario for GH4C1 cells. This work was supported by the Ontario Mental Health Foundation, the Medical Research Council of Canada, Eli Lilly Canada Inc., Eva and Leon Adomavicius, the Medland family, NARSAD (National Alliance for Research on Schizophrenia and Depression), the Stanley Foundation and the National Alliance for the Mentally Ill, and the National Institute on Drug Abuse (RO 1 DA07223-05).

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