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Dopamine Receptors and the Dopamine Hypothesis of Schizophrenia

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ABSTRACT The discovery of neuroleptic drugs in 1952 provided a new strategy for seeking a biological basis of schizophrenia. This entailed a search for a primary site of neuroleptic action. The Parkinsonian effects caused by neuroleptics suggested that dopamine transmission may be disrupted by these drugs. In 1963 it was proposed that neuroleptics blocked "monoamine receptors" or impeded the release of monoamine metabolites. The neuroleptic concentration in plasma water or cerebrospinal fluid was of the order of 2 nM for haloperidol in clinical therapy. A systematic research was made between 1963 and 1974 for a primary site of neuroleptic action which would be sensitive to 2 nM haloperidol and stereoselective for (+)-butaclamol. Direct evidence that neuroleptics selectively blocked dopamine receptors occurred in 1974 with the finding that nanomolar concentrations of these drugs stereoselectively inhibited the binding of [^{3}H]-dopamine or [^{3}H]-haloperidol. These binding sites, now termed D_2 dopamine receptors (which inhibit adenylate cyclase), are blocked by neuroleptics in direct relation to the antipsychotic potencies of the neuroleptics. No such correlation exists for D_1 receptors (which stimulate adenylate cyclase).

Based on the fact that dopamine-mimetic drugs elicited hallucinations, and that neuroleptics caused rigidity, Van Rossum in 1966 had suggested a hypothesis that dopamine pathways may be overactive in schizophrenia. The D_2-selective blockade by all neuroleptics (except the monoamine-depleting reserpine) provided strong support for the dopamine hypothesis. Further support now comes from postmortem data and in vivo positron tomographic data, both of which indicate that the density of D_2 receptors are elevated in the schizophrenic brain. The postmortem data indicate a bimodal pattern with half the schizophrenics having striatal D_2 densities of 14 pmol/g (control is 13 pmol/g) and the other half having 26 pmol/g. Current positron tomographic data indicate D_2 densities of 14 pmol/g in control subjects, but values of 34 pmol/g in drug-naive schizophrenics. Future tests of the dopamine hypothesis of schizophrenia may entail an examination of the amino acid composition and genes for D_2 receptors in schizophrenic tissue, an examination of the ability of the D_2 receptor to become phosphorylated and to desensitize into the low-affinity state, and an examination of the interaction of D_2 receptors with D_1 receptors or other neurotransmitters.

INTRODUCTION: THE NEUROLEPTIC SITES-OF-ACTION RESEARCH STRATEGY

For many years it has been difficult or impossible to obtain objective and reproducible evidence for any of the many biological theories of schizophrenia (Table I). The situation changed in 1952 with the discovery of the neuroleptic drugs which alleviate psychotic symptoms (Delay et al., 1952; Hamon et al., 1952). As previously noted (Seeman, 1966; Matthysse, 1973), these neuroleptic drugs provided a new type of research strategy in seeking a possible biological basis for schizophrenia. The strategy entailed a systematic search for the primary site of neuroleptic action (Seeman et al., 1974a, 1975a; Seeman, 1977) followed by a search for possible abnormal properties of these sites in schizophrenia (Seeman and Lee, 1977; Lee and Seeman, 1977). The detailed findings within these two aspects of this research strategy have led to the so-called dopamine hypothesis of schizophrenia. Many reviews have been written on dopamine receptors and/or the dopamine hypothesis of schizophrenia (Baldessarini, 1977; Carlsson, 1978a,b; Creese and Leff, 1982; Creese et al., 1983; Crow, 1979; Crow et al., 1976, 1979; Iversen et al., 1983; Matthysse, 1973, 1974; Matthysse and Lipinski, 1975; Meltzer, 1980; Melzer and Stahl, 1976; Rotrosen et al., 1976; Seeman, 1980, 1986; Seeman and Grigoriadis, 1987; Synder, 1976; Stevens, 1973).

THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

The dopamine hypothesis of schizophrenia proposes that certain dopaminergic pathways are overactive in schizophrenia (Matthysse, 1973; Meltzer and Stahl, 1976;

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TABLE I: Sample References for some biological findings or theories in schizophrenia

Acetylcholine	McGeer and McGeer (1977)
	Davis et al. (1978)
	Watanabe et al. (1983)
Asymmetry (in dopamine)	Reynolds (1986)
Cholecystokinin	Moroji et al. (1982)
	Hommer et al. (1984)
	Tamminga et al. (1986)
Environmental factors	DeLisi et al. (1986)
GABA	Perry et al. (1979)
Genetics	Pollin (1972)
	Matthysse and Kidd (1976)
	Kendler et al. (1982)
	Kety (1983)
Immune	Heath (1966)
	Boehme et al. (1973)
	Watanabe et al. (1982)
	Durell and Archer (1976)
Methylation	Smythies (1976)
	Baldessarini et al. (1979)
Neurotransmitters and noradrenaline	Kety (1959, 1965)
	Friedhoff (1973)
	Matthysse and Sugarman (1978)
	Sternberg et al. (1982)
	Hornykiewicz (1982)
	Van Kammen and Antelman (1984)
Opiates	Terenius et al. (1976)
	Lindström et al. (1978)
	Lehmann et al. (1979)
	Davis et al. (1979)
	Watson et al. (1982)
	Pickar et al. (1982)
	Van Ree and DeWied (1982)
Peptides	Post et al. (1982)
	Roberts et al. (1983)
Ventricular enlargement	Andreasen et al. (1982a,b, 1986)
	Weinberger et al. (1983)
	Luchins et al. (1984)
	Reveley (1985)
	Brown et al. (1986)
Virus	Crow (1984)
	Torrey and Peterson (1976)

1952:	Antipsychotic effect of chlorpromazine.	Delay et al.
1963:	Neuroleptics raise NA & DA metabolities.	Carlsson et al.
1964:	Neuroleptics elevate DOPAC and HVA.	Anden et al.
1966:	Neuroleptics selective on DA receptors?	Van Rossum
1970:	Hallucinations worse on L-DOPA.	Yaryura-Tobias
1971:	2 nM Haloperidol in plasma water.	Zingales
1974:	2.5 nM Haloperidol blocks ^{3}H-DA receptors.	Seeman et al.
1974:	Synthesis of (+)-butaclamol.	Humber
1975:	Binding of ^{3}H-haloperidol to DA receptors.	Seeman et al.
1975:	Neuroleptic dose related to D_2 block.	Seeman et al.
1977:	Elevated D_2 Receptors in schizophrenia.	Seeman & Lee
1984:	Two modes of D_2 densities in SZ.	Seeman et al.
1984:	SZ lymphocytes: High ^{3}H-spiperone binding.	Bondy et al.
1986:	SZ brain in vivo: High D_2 (no drugs).	Wong et al.

Fig. 1. Some major findings in the dopamine hypothesis of schizophrenia (SZ).

Meltzer, 1980; Seeman, 1980; Van Rossum, 1967). The earliest and clearest outline of the dopamine hypothesis of schizophrenia is from Van Rossum (1967): "... The hypothesis that neuroleptic drugs may act by blocking dopamine receptors in the brain has been substantiated by preliminary experiments with a few selective and potent neuroleptic drugs. There is an urgent need for a simple isolated tissue that selectively responds to dopamine so that less specific neuroleptic drugs can also be studied and and the hypothesis further tested ..."

"... When the hypothesis of dopamine blockade by neuroleptic agents can be further substantiated it may have fargoing consequences for the pathophysiology of schizophrenia. Overstimulation of dopamine receptors could then be part of the aetiology. Obviously such an overstimulation might be caused by overproduction of dopamine, production of substances with dopamine actions (methoxy derivatives), abnormal susceptibility of the receptors, etc. In agreement with this hypothesis is the clinical observation that patients with Parkinson disease do not develop schizophrenia and that schizophrenics who become affected with the disease of van Economo improve with respect to their psychosis. The fact that monoamine oxydase inhibitors and psychomotor-stimulant drugs as amphetamine aggravate schizophrenia is also in agreement with the dopamine hypothesis..."

The hypothesis evolved from the following five major lines of evidence, all related to the supposition that neuroleptics (particularly haloperidol, chlorpromazine, and (+)-butaclamol) selectively block dopamine receptors, an hypothesis which has since received direct experimental support (Seeman et al., 1974a, 1975a,b):

Clinical side effects of neuroleptics

Psychotomimetic effects of dopamine-mimetic drugs

Neuroleptic acceleration of catecholamine turnover

Antipsychotic potency correlation to D_2 blockade by nanomolar concentrations of neuroleptics

Elevated densities of D_2 dopamine receptors in schizophrenia.

A summary of some major steps in the evolution of the dopamine hypothesis of schizophrenia is presented in Figure 1.

CLINICAL SIDE EFFECTS AND ANTILOCOMOTOR EFFECTS OF NEUROLEPTICS

Neuroleptic-induced Parkinsonism

Very soon after the introduction of neuroleptics it became apparent that approximately 75% of neuroleptic-medicated schizophrenics exhibited Parkinson-like signs of tremor, rigidity, and akinesia. In fact, virtually all such medicated patients revealed some degree of akinesia, readily demonstrable by their handwritten cramped signature.

Since it was later found that the basis for Parkinson's disease was a deficiency in brain dopamine (Hornykiewicz, 1973), the neuroleptic-induced Parkinsonian signs suggested that neuroleptics somehow interfered with brain dopamine transmission. It is rare, furthermore, for schizophrenia and Parkinson's disease to occur in the same patient, although dopamine-mimetic drugs, in alleviating the Parkinson's, can elicit temporary psychosis (Hale and Bellizzi, 1980).

Since Parkinson-like signs commonly occurred with almost all neuroleptics, the screening and preclinical testing for neuroleptic potencies was conveniently measured by their abilities to elicit catalepsy and antistereotyped behavior in rats (Janssen and Allewijn, 1969).

Neuroleptic-induced hyperprolactinemia and galactorrhea

It had also been observed that neuroleptics elicited breast-swelling (gynecomastia in men), galactorrhea, and amennorhea in approximately 10% of patients. These effects stem from a hyperprolactinemia induced by the neuroleptic. Since it had been established that dopamine was an important prolactin-inhibiting factor, the elevation of plasma prolactin by neuroleptics further suggested that neuroleptics interfered with the target action of dopamine, as later found by Brown et al. (1976).

Neuroleptic blockade of dopamine-mimetic drugs

The anti-emetic effect of neuroleptics had been a further clue to their possible antidopaminergic action, since the vomiting center is particularly sensitive to dopamine congeners such as apomorphine (see refs. in Seeman, 1980).

Psychotomimetic effects of dopamine-mimetic drugs

A variety of dopamine-mimetic compounds have been tested for their ability to modify the intensity of schizophrenic symptoms.

L-DOPA

High doses of L-DOPA intensify the positive symptoms of schizophrenia (particularly hallucinations and delusions; Angrist et al., 1973, 1974, 1975, 1978; Gerlach and Lühdorf, 1975; Lal and de la Vega, 1975; Yaryura-Tobias et al., 1970a) and also elicit hallucinations in L-DOPA-overmedicated patients who have Parkinson's disease (Gerlach, 1976; Goodwin, 1972; Yaryura-Tobias et al., 1970b). Low doses of L-DOPA, on the other hand—no higher than 0.5 g per day—can alleviate psychotic symptoms in about 50% of schizophrenic patients (Alpert et al., 1978; Corsini et al., 1981; Del Zompo et al., 1981; but see Ferrier et al., 1984a,b; Levy et al., 1984; and Hollister et al., 1981, Inanaga et al., 1971, 1972, 1975; Smith et al., 1977; reviewed by Meltzer, 1980). It is possible that the exacerbating effect of high doses of L-DOPA may be attributed to stimulation of postsynaptic dopamine receptors, while the alleviating action may be associated with dopamine acting at its autoreceptors (see below).

Amphetamine

Amphetamine, which acts among other mechanisms (Cantrill et al., 1983; Niddam et al., 1985) by releasing dopamine, aggravates the positive symptoms of schizophrenia (Angrist et al., 1974; Snyder, 1973; but see Kornetsky, 1976). A similar situation occurs with methylphenidate (Janowsky et al., 1973; Janowsky and Davis, 1976).

Disulfiram

This drug, used to prevent alcoholism, appears to be dopamine-mimetic and cause short-term psychotic features. Disulfiram inhibits dopamine beta-hydroxylase, the enzyme which converts dopamine to noradrenaline. Thus, disulfiram can result in the accumulation of dopamine, possible accounting for disulfiram's ability to precipitate a psychosis (Bennett et al., 1951).

LSD

The psychotomimetic actions of LSD (d-lysergic acid diethylamide) are well known (Jacobs and Trulson, 1979). LSD, however, affects at least three separate neurotransmitter systems: serotonin, noradrenaline, and dopamine (Peroutka and Snyder, 1979; Whitaker and Seeman, 1978). Although it now appears likely that the psychotic action of LSD (Bowers, 1977) can be attributed to its dopaminergic action, its multiple nonselective action on several neurotransmitter systems did not by itself provide any definite clue that dopamine may be involved in psychosis.

Altogether, the psychotomimetic effects of amphetamine, methylphenidate, L-DOPA, disulfiram, and LSD, each acting through different dopaminergic mechanisms, indirectly suggested that there may be dopaminergic abnormalities underlying the positive symptoms in schizophrenia. However, since none of these drugs is selective for the dopamine transmitter system (e.g., they all modify noradrenaline transmission), these in vivo psychotomimetic data were at best only suggestive that dopamine contributed to psychotic features.

NEUROLEPTIC ACCELERATION OF CATECHOLAMINE TURNOVER

In searching for the mechanism of neurolepsis by reserpine, chlorpromazine, and haloperidol, Carlsson and Lindqvist (1963) found that these drugs elevated the methoxylated metabolites of noradrenaline and dopamine (normetanephrine and 3-methoxytyramine, respectively). These authors suggested " ... that chlorpromazine and haloperidol block monoaminergic receptors in brain ...," an effect which might result in neural reflex activation of neurones for both noradrenaline and dopamine. It was not at that time possible to conclude that these neuroleptics were selective for a particular catecholamine receptor (i.e., alpha-adrenoceptors, beta-adrenoceptors, or dopamine receptors). Furthermore, Carlsson's students, Andén et al. (1964), concluded that "it seems as if chlorpromazine and haloperidol reduce the elimination rate of these acids (i.e., dopamine metabolites DOPAC and HVA)[1] and possibly also increase their synthesis."

Throughout the 1960s, therefore, it was difficult to establish which of the several catecholamine receptors was most selectively affected by neuroleptics. For example, some studies indicated that neuroleptics accelerated the turnover of noradrenaline more than that of dopamine (Corrodi et al., 1967), while others pointed to a selective acceleration of dopamine turnover (Andén et al., 1970; Nybäck et al., 1967).

The hypothesis that neuroleptics might be selective for dopamine receptors remained as a promising theory (Van Rossum, 1966, 1967) until 1974, at which time direct evidence in vitro confirmed the speculation (Seeman et al., 1974a).

In an attempt to relate the clinical antipsychotic potencies of various neuroleptics with their abilities to elevate homovanillic acid (HVA), Matthysse (1974; see

[1]HVA, homovanillic acid; DOPAC, dihydroxyphenylacetic acid.

Matthysse and Sugarman, 1978) found that the correlation was good in general but that thioridazine, clozapine, and sulpiride were disproportionately weak in elevating HVA (Andén and Stock, 1973; Rollema et al., 1976). These apparently weaker metabolic actions of thioridazine and clopazine presumably arise from their strong inhibitory action at cholinergic muscarinic receptors (Laduron and Leysen, 1978; Richelson and Nelson, 1984).

The neuroleptic-induced elevation of HVA, however, is generally transient, since HVA concentrations generally return to normal or below normal during the course of several weeks of continuous neuroleptic administration (Post and Goodwin, 1975; Bowers Jr. and Rozitis, 1976; Scatton, 1977, 1981a; Laduron et al., 1977; Bacopoulos et al., 1979).

Clinically, a fall in the HVA concentration in the cerebrospinal fluid or plasma of neuroleptic-medicated schizophrenic patients is generally associated with an improvement in the patient's psychiatric condition (Bowers, 1974; Kendler et al., 1981; Pickar et al., 1986; Post et al., 1975; Van Kammen et al., 1983).

These observations suggest, therefore, that prolonged blockade of dopamine receptors by neuroleptics; while elevating D_2 dopamine receptors by about 30% (reviewed by Seeman, 1980), results in a compensatory reduction in dopamine turnover. Although the mechanism for this reduction is unknown, one possibility is that D_2 receptors may shift into a nonfunctional low-affinity state (see below); another possibility is that prolonged neuroleptic administration may slightly depolarize dopamine-sensitive neurones (Bunney, 1984; Skirboll and Bunney, 1979; White and Wang, 1983).

D_1 AND D_2 RECEPTORS: ANTIPSYCHOTIC POTENCY CORRELATES WITH D_2 BLOCKADE BY NANOMOLAR CONCENTRATIONS OF NEUROLEPTICS

In searching for a specific target site for neuroleptic action, an essential criterion was that the site should be sensitive to neuroleptic concentrations which existed in the plasma *water* or in the cerebrospinal fluid of schizophrenic patients who are in a maintained steady state of remission. This criterion has been previously discussed (Seeman, 1977).

The therapeutic concentration (in the water compartment) was soon found to be approximately 2 nM for haloperidol (Zingales, 1971; Forsman et al., 1974) and approximately 10 to 30 nM for chlorpromazine (reviewed by Seeman, 1977).

This objective of finding a site vulnerable to 2 nM haloperidol and 20 nM chlorpromazine was particularly elusive for at least 10 years (Seeman and Bialy, 1963; Seeman and Weinstein, 1966; Seeman, 1966, 1972, 1977). In fact, all of the target sites studied between 1963 and 1973 required concentrations of haloperidol generally exceeding 100 nM (see Table II). More recently, haloperidol-sensitive sites have been found (e.g., the sigma opiate receptor; Table II), but none of these sites fulfill the criteria of having nanomolar sensitivity to several neuroleptics or having appropriate stereoselectivity for (+)-butaclamol (Table II).

A second important criterion in identifying a neuroleptic-specific site of action was that of stereoselectivity. Because the neuroleptics are surface-active (Seeman and Bialy, 1963; Seeman, 1972), fat-soluble, and, hence, membrane-soluble (Seeman, 1972, 1980), any neuroleptic action on, or binding to, biological membranes was not by itself a sufficient criterion for identifying that site as being "specific" for neuroleptics. It required the stereoselective effect of (+)-butaclamol (Humber and Bruderlein, 1974; Voith, 1974; Voith and Herr, 1975), in order to help define that site as truly specific for neuroleptics. For example, in the 100–1,000 nM concentration zone the neuroleptics are nonspecifically membrane-anesthetic (Seeman et al., 1974b), while in the nM concentration region they are stereoselective (Seeman et al., 1975a,b).

The first direct evidence that nanomolar concentrations of neuroleptics selectively blocked dopamine receptors was obtained in 1974 (Seeman et al., 1974a) wherein it was reported that 2.5 nM haloperidol inhibited the binding of [^{3}H]-dopamine to synaptosomes. Identical results were soon found with [^{3}H]-haloperidol (Seeman et

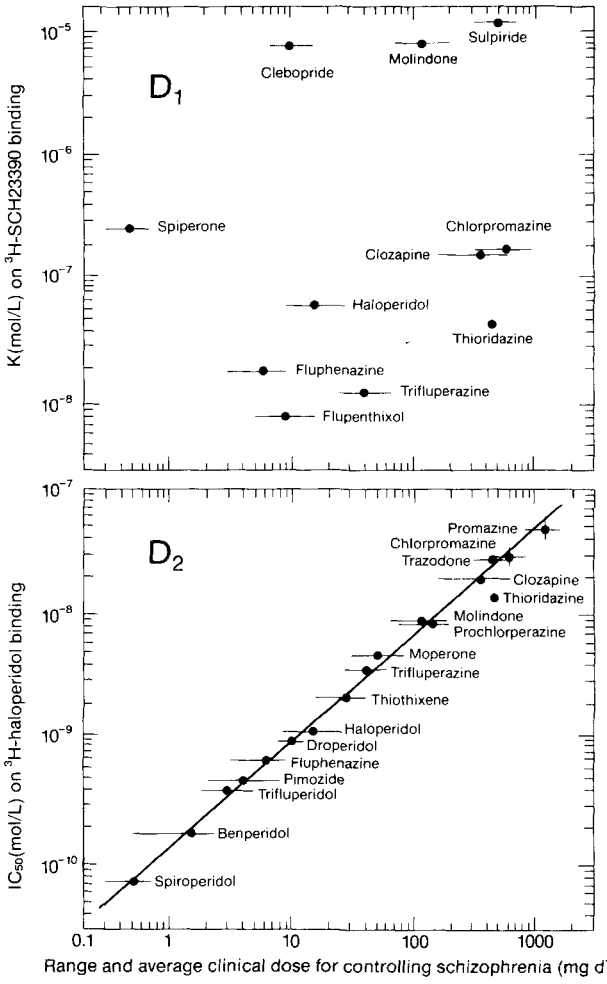

Fig. 2. The clinical antipsychotic doses of various neuroleptics correlate with their potencies at the D_2 receptor (bottom), but not with their potencies at the D_1 receptor (top). The neuroleptic dissociation constant at the D_1 receptor was obtained by the procedure of Seeman et al. (1985a), with calf caudate nucleus tissue. The neuroleptic potencies at D_2 are the concentrations which inhibited 50% of the specific binding of [^{3}H]-haloperidol binding (data from Seeman et al., 1976). The clinical dose of clebopride is generally 1/50th to 1/100th that of sulpiride (Roberts, 1982). (See also Seeman et al., 1986b).

TABLE II. Sensitivity of different sites to haloperidol, chlorpromazine and (+)-butaclamol

Site	Concentration for 50% block (nM)		Stereo-selective for (+)– butaclamol	Reference
	By haloperidol	By chlorpromazine		
	K or IC_{50}*		(Enna et al., 1976)	
[^{3}H]-spiperone on D_2	1.2	3	Yes	Seeman et al. (1985b)
[^{3}H]haloperidol on D_2	2	20	Yes	Seeman et al. (1975a,b) Creese et al. (1975)
[^{3}H]dopamine on D_2	2.5		Yes	Seeman et al. (1974a)
[^{3}H]haloperidol on sigma	2		No	Largent et al. (1984)
[^{3}H](+)3-PPP on sigma	2.4		No	Largent et al. (1984)
[^{3}H](+)allylnormetazocine	3.9*	1,400*	No	Martin et al. (1984)
[^{3}H](+)SKF 10047 on sigma	4	180	No	Tam and Cook (1984)
[^{3}H]prazosin	~9	~4	Yes?	Richelson and Nelson (1984) U-Prichard et al. (1977)
[^{3}H]ketanserin	48	20		Leysen et al. (1982)
[^{3}H]SCH 23390	60	190	Yes	This lab (see Fig. 2)
Stimulated release (DA)	95	700	Yes	Seeman and Lee (1975)
Nerve impulses	100	400		Seeman et al. (1974b)
DA-cyclase	220	66		Clement-Cormier et al.
Dopamine uptake	300	11,000		Seeman and Lee (1974)
[^{3}H]indalpine	>10,000			Bénavidès et al. (1985)
[^{3}H]pyrilamine	1,300	15		Coupet and Szuch-Myers
[^{3}H]serotonin	1,500	1,500	Yes	Seeman et al. (1980)
[^{3}H]doxepin	1,700	3	No?	Kanba and Richelson (1984)
[^{3}H]nitrendipine	2,000 *	50,000*		Gould et al. (1984)
[^{3}H]cocaine	3,000	10,000		Shoemaker et al. (1985)
[^{3}H]mepyramine	3,300	36		Tran et al. (1978)
[^{3}H]LSD	>3,500	850	Yes	Whitaker and Seeman (1978)
Serotonin uptake	3,800			Hiekkila et al. (1976)
[^{3}H]rauwolscine	~4,700	~850	Yes?	Richelson and Nelson Perry et al. (1983)
[^{3}H]dihydromorphine			No	Enna et al. (1976)
[^{3}H]morphine	5,000*	25,000*		Boublik and Funder (1985)
[^{3}H]methylphenidate	6,000*	3,200*		Schweri et al. (1985)
[^{3}H]naloxone	7,900*	71,000*	No	Boublik and Funder (1985)
Noradrenaline uptake		180		Heikkila et al.
[^{3}H]desipramine	>10,000	320*		Rehavi et al. (1982)
[^{3}H]GBR-12935	>10,000			Janowsky et al. (1986)
[^{125}I]iodocholecystokinin	>10,000			Chang et al. (1982)
[^{3}H]QNB binding	~20,000*	~300*	No	Richelson and Nelson (1984) Laduron and Leysen (1978)
[^{3}H][D-Ala^2, D-Leu^5]enkeph.	22,000*	60,000*		Boublik and Funder (1985)
[^{3}H]ethylketocyclazocine	35,000*	89,000*		Boublik and Funder (1985)
Calmodulin	50,000	35,000	No	Nelson et al. (1983)
[^{3}H]diazepam	100,000	87,000		Mackerer et al. (1978) Braestrup and Squires (1978)
[^{3}H]dihydroalprenolol			No	Enna et al. (1976)
[^{3}H]GABA			No	Enna et al. (1976)

al., 1975a,b), the binding of which was 50% inhibited by 1.5 nM haloperidol, 20 nM chlorpromazine, and 3 nM (+)-butaclamol. These particular finding sites, labelled by either [^{3}H]-dopamine or by [^{3}H]-haloperidol and inhibited by 1 to 20 nM neuroleptic, were subsequently termed D_2 dopamine receptors, as follows.

The concept of two types of dopamine receptors, one mediating excitation (now known as D_1) and the other mediating inhibition (now known as D_2), was clearly outlined by Cools and Van Rossum (1976) and Van Rossum (1978). In 1978 Spano and his colleagues (Garau et al., 1978; Spano et al., 1978) also suggested " . . . that dopamine receptors are two different populations of which only one is directly coupled to the activation of adenylate cyclase." This suggestion led Kebabian and Calne (1979; see Kebabian et al., 1984) to use D_1 as a term for dopamine receptors which stimulated adenylate cyclase (Kebabian et al., 1972) and D_2 for those dopamine receptors that did not stimulate adenylate cyclase. It has now been established that the D_2 dopamine receptor inhibits adenylate cyclase in the anterior pituitary gland (Borgundvaag and George, 1985; De Camilli et al., 1979; Enjalbert and Bockaert, 1982; Pawlikowski et al., 1981) in the intermediate pituitary lobe (Meunier and Labrie, 1982; Munemura et al., 1980), and in the brain striatum (Onali et al., 1985a,b). In isolated tissues, D_1 elicits electrical excitation, while D_2 causes inhibition (Israel et al., 1985; Stoof et al., 1985).

The clinical doses of neuroleptics for antipsychotic action correlated very well with their ability to block the D_2 receptors, whether labeled by [^{3}H]-dopamine (on synaptosomes) or by [^{3}H]-haloperidol (Seeman et al., 1975b). This correlation, later further corroborated (Creese et al., 1976; Seeman et al., 1976;) has become a pivotal point about which the dopamine hypothesis of schizophrenia revolves (See Fig. 2).

Although neuroleptics can also block other receptors (Table II), neuroleptics have the highest affinity for D_2 dopamine receptors, with dissociation constants ranging from 45 pM for spiperone (spiroperidol) to 1.2 nM for haloperiodol (Seeman et al., 1985b).

In addition to the relation in Figure 2, the neuroleptic

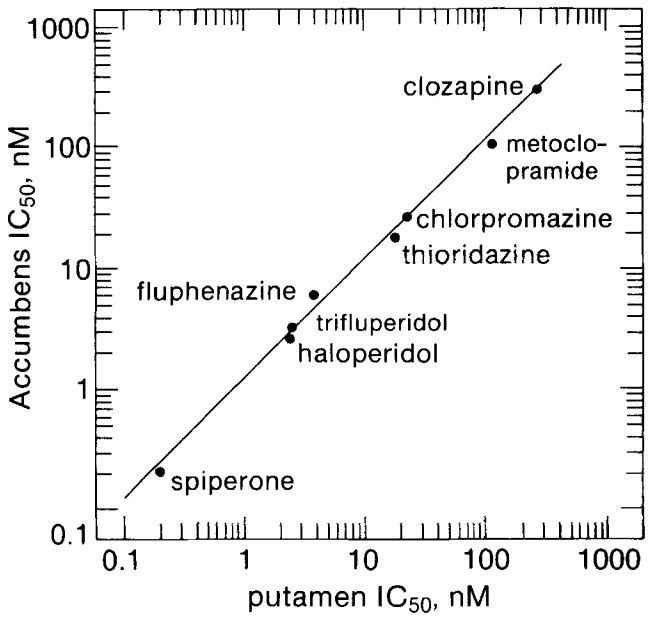

Fig. 3. The sensitivity of the D_2 receptor in the human nucleus accumbens to various neuroleptics is identical with that for the D_2 receptor in the human putamen, since the neuroleptic concentrations which 50% inhibited the binding of [^{3}H]-spiperone were identical in the two tissue regions (modified from Seeman and Ulpian, 1983).

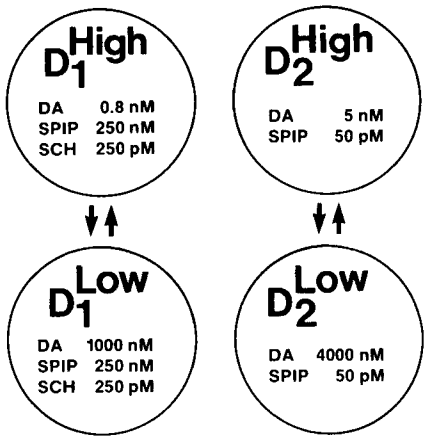

Fig. 4. Dissociation constants (K values) for dopamine (DA) and the dopamine receptor antagonists spiperone (SPIP) and SCH-23390 (or SCH) at D_1 and D_2 dopamine receptors. The dissociation constants of dopamine, spiperone, and SCH 23390 for the high- and low-affinity states of D_1 were obtained from competition experiments with [^{3}H]-SCH-23390 on calf caudate nucleus homogenate (Seeman et al., 1985a; see also Niznik et al., 1986a). The K for SCH-23390 on D_1 is 90 pM in canine striatum (Niznik et al., 1986a,b), 250 pM in calf striatum (Seeman et al., 1985a), and 500 pM in human striatum (unpublished). The dissociation constants for dopamine and spiperone at D_2 are for rat striatum and pig anterior pituitary (Seeman and Grigoriadis, 1985; George et al., 1985b; Seeman et al., 1985b).

potencies for elevating plasma prolactin also generally correlate with the neuroleptic dissociation constants for blocking the D_2 receptor in the anterior pituitary gland (see refs. in Meltzer, 1980; Meltzer and Stahl, 1976).

It is important to note that D_2 receptors in the human limbic system (nucleus accumbens) have identical neuroleptic sensitivities as those D_2 receptors in the striatum (Fig. 3). In other words, there are *no* limbic-specific neuroleptics (Reynolds et al., 1982; Richelson and Nelson, 1984; Seeman and Ulpian, 1983), as had been previously reported (Borsion et al., 1981, 1983).

D_1 and D_2 densities; technical problems

Both D_1 and D_2 receptors have now been examined in postmortem human schizophrenic brain tissues. Before discussing these data, it is important to note that each receptor can exist in two states wherein the high-affinity state has approximately a thousand times higher affinity for dopamine that that of the low-affinity state (Fig. 4). Figure 5 illustrates how these dissociation constants for the high-affinity and low-affinity states are obtained experimentally.

We had formerly used the term "D_3" to indicate D_1^{High} (List et al., 1980; List and Seeman, 1982; Titeler et al., 1979), and had used "D_4" to indicate D_2^{High} (Seeman, 1980; but see Sokoloff et al., 1984). The D_3 and D_4 terms are no longer necessary, since it has now proven possible to convert *all* the high-affinity states of each receptor into its low-affinity state in pituitary tissue (George et al., 1985b,c; Sibley et al., 1982; Watanabe et al., 1985a,b; Wreggett and De Lean, 1984) as well as in brain tissue (Bacopoulos, 1983, 1984; Hamblin and Creese, 1982; Hamblin et al., 1984; Wreggett and Seeman, 1984; Grigoriadis and Seeman 1984, 1985, 1986; Seeman et al., 1985a; Leff and Creese, 1984; Leff et al., 1985; Hess et al., 1986; Urwyler and Markstein, 1986). This conversion is facilitated by temperature, guanine nucleotides, and sodium ions (Watanabe et al., 1985a,b). There are still two laboratories which report that some of these neuroleptic binding sites are *insensitive* to guanidine nucleotides (De Keyser et al., 1985; Sokoloff et al., 1984). Such insensitivity to guanine nucleotides, however, may simply be a result of the particular conditions for that particular tissue (Grigoriadis and Seeman, 1985; Lazereno, 1983; Wreggett and Seeman, 1984).

Parenthetically, it may be noted that the vascular DA_1 receptor appears to be identical to the D_1 receptor (unpublished data), while the vascular DA_2 receptor appears to be identical to the D_2 receptor (see refs. in Seeman, 1982; Seeman and Grigoriadis, 1987).

Because D_1 and D_2 each have two affinity states, a number of technical and theoretical problems arise in measuring the densities of these two receptors in postmortem human brain tissues.

First, since dopamine is about 1,000 times more avid for the high-affinity state of the receptor (D_1 or D_2), the use of between 1 and 10 nM [^{3}H]-dopamine, therefore, will primarily label the high-affinity states of D_1 and D_2, but will *not* label the entire population of either D_1 or D_2 (Seeman and Grigoriadis, 1985).

Second, since the affinity of D_1 for dopamine is about ten times higher than that of D_2, this means that 1 nM [^{3}H]-dopamine will usually and preferentially label D_1^{High}, while 10 nM [^{3}H]-dopamine will label both D_1^{High} and D_2^{High}. These two principles, which also generally hold for other dopamine [^{3}H]-agonists, are illustrated in Figure 6. It may be noted, however, that different tissue preparations may have different proportions of D_1 and D_2 receptors, such that [^{3}H]-dopamine would have different patterns of binding. For example, the synaptosome preparation studied previously (Seeman et al., 1974a) bound [^{3}H]-dopamine, a portion of which was displaceable by 2.5 nM haloperidol, indicating that under those conditions an appreciable amount of [^{3}H]-dopamine bound to D_2 receptors.

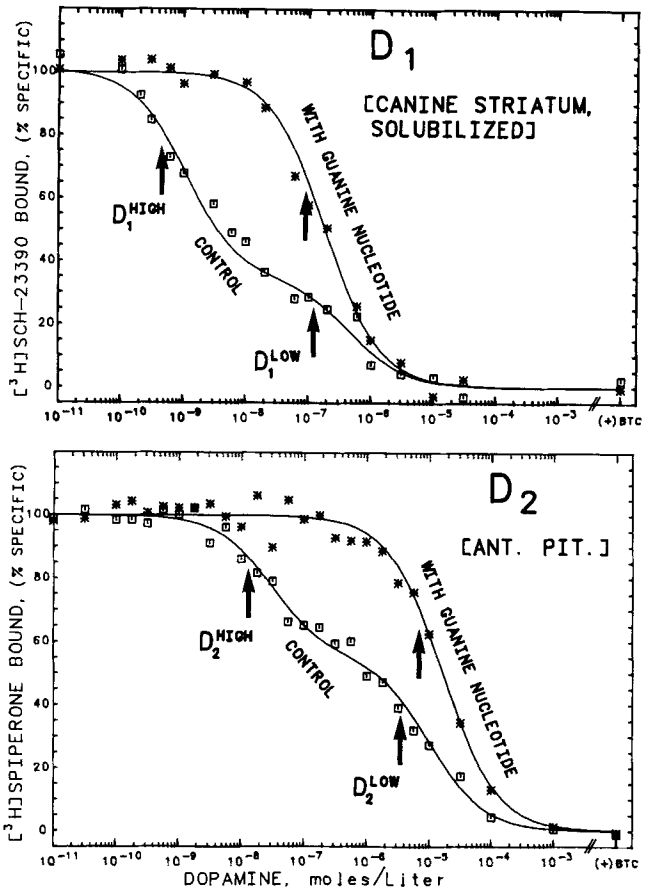

Fig. 5. Complete conversion of the high-affinity state of D_1 (top) or D_2 (bottom) into their low-affinity states, using 100 μM guanilylimidodiphosphate (Gpp[NH]p). The D_1 receptors were solubilized by digitonin, labelled with 8 nM [^{3}H]-SCH-23390, and separated by Sephadex G-50 chromatography (adapted from Niznik et al., 1986a,b). The data for D_2 are adapted from George et al. (1985c). The arrows indicate the dissociation constants of dopamine at the high- and low-affinity states, as determined by computer-assisted analysis (LIGAND; see Grigoriadis and Seeman, 1984, 1985, 1986). It is important to note that the guanine nucleotide consistently elevated the *absolute* amount of bound [^{3}H]-SCH-23390 or of bound [^{3}H]-spiperone in the absence of any exogenous dopamine (e.g., see Niznik et al., 1985a). This effect presumably results from the nucleotide uncoupling the receptor from the G protein. The receptor converts to the low-affinity state and loses some of the endogenous dopamine which had been attached to the high-affinity state of the receptor; thus, the removal of dopamine provides more binding sites for the [^{3}H]-antagonist (Lazareno, 1983; George et al., 1985b).

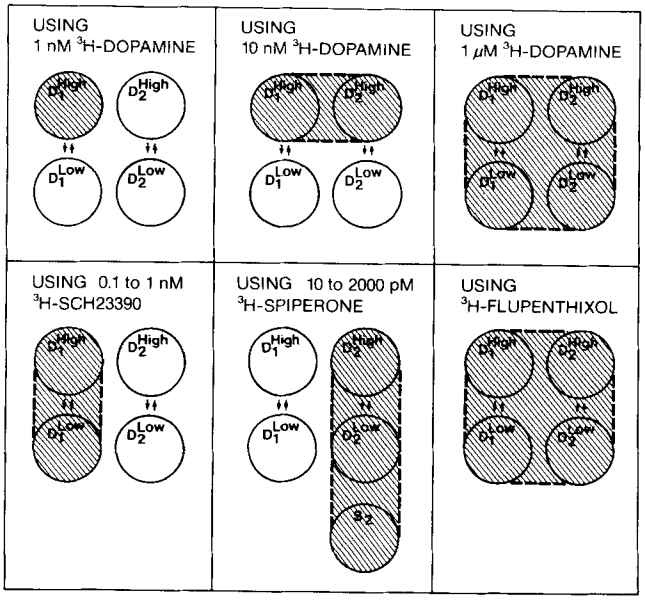

Fig. 6. Different concentrations of [^{3}H]-dopamine will label different components on D_1 and D_2 in accordance with the dissociation constants in Figure 4. The [^{3}H]-antagonists, while not discriminating between the high- and low-affinity states, are not completely selective; [^{3}H]-flupentixol labels both D_1 and D_2 receptors.

In general, therefore, the densities of D_1 and D_2 are best measured by using the radioactive antagonist (see Fig. 6). We have found that the densities of these [^{3}H]-antagonist sites are constant in postmortem human brain tissues stored at −70°C for many years (in the case of D_2). The effect of storage on the D_1 density has not yet been examined.

A third problem is that of washing the tissue, in order to remove endogenous dopamine (which may occlude the high-affinity sites; Lazareno, 1983) or neuroleptics, etc. However, we no longer wash human postmortem tissues, since we have established that this consistently lowers the absolute density of receptors (in terms of pmols/g of original tissue) by 20% or more (Seeman et al., 1984b), while removing little of the highly fat-soluble neuroleptic, While it is possible to remove endogenous dopamine by preincubation (Mackay et al., 1982), we have found that a 10-min preincubation period consistently lowers the absolute density of D_2 by 10% to 20%.

A fourth problem, particularly severe with human tissue, is the method of tissue homogenization. This is illustrated in Figure 7, where it can be seen that a typical homogenization by a Polytron (20 sec at setting 6) resulted in a fall in D_2 density of 9% for rat striatum and 28% for human striatum (cf. Csernansky et al., 1985). Although these final incubates were centrifuged at 11,000g for 6 min, even more receptors were lost when the incubates were filtered. Hence, we now merely use glass homogenizers with Teflon pistons in order to have larger pieces of disrupted tissue, readily centrifuged or filtered.

A fifth problem is that the final concentration of tissue should be less than 1 mg original tissue per final ml of incubate. At higher concentrations of tissue, the *free* concentration of the fat-soluble [^{3}H]-ligand is depleted by the nonreceptor mass of the tissue, artifactually elevating the apparent density (Seeman et al., 1984b).

Sixth, specific binding of [^{3}H]-spiperone to D_2 receptors is best defined by 10 μM S-sulpiride (List and Seeman, 1981) since most other neuroleptic baselines will permit the detection of serotonin S_2 receptors. Since it now becoming possible to measure the *absolute* density of brain dopamine receptors (in pmols per ml or g of striatum; Farde et al., 1985, 1986; Gjedde et al., 1986; Wong et al., 1986), it is important that the above factors be recognized such as to yield the true absolute density of receptors in vitro.

DOPAMINE RECEPTORS IN THE POSTMORTEM SCHIZOPHRENIC BRAIN AND IN SCHIZOPHRENIC LYMPHOCYTES

The content of dopamine in schizophrenic striatum is

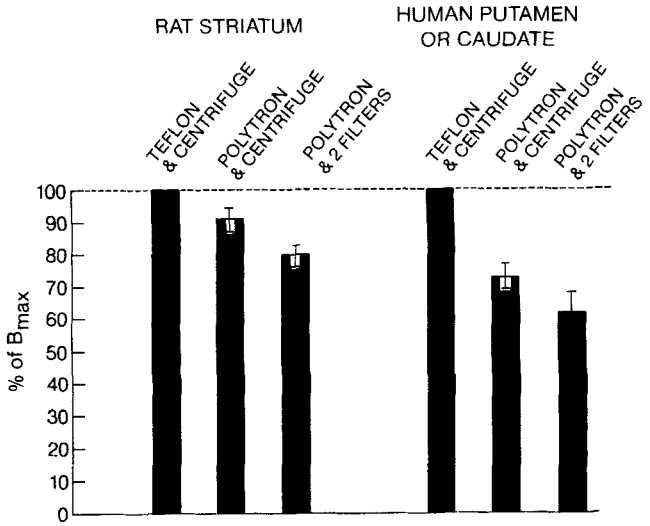

Fig. 7. Artifactual reduction of D_2 density by Polytron homogenization and by filtration. The value for 100% indicates the D_2 density obtained using a Teflon-glass homogenizer (10 up-and-down strokes) with a final centrifugation at 11,000g for 6 min. Polytron homogenization (setting 6, 20 sec), followed by centrifugation, caused a loss of 9% of the receptors in rat striatum and 28% in human striatum. Filtration through two glass fiber filters (GF/A-like; Skatron) resulted in a further 10% loss. [Ten independent experiments, with each density obtained by saturation analysis by using 10 to 2,000 pM [^{3}H]-spiperone (Seeman et al., 1984b). Specific binding was defined by 10 μM S-sulpiride (List and Seeman, 1981)].

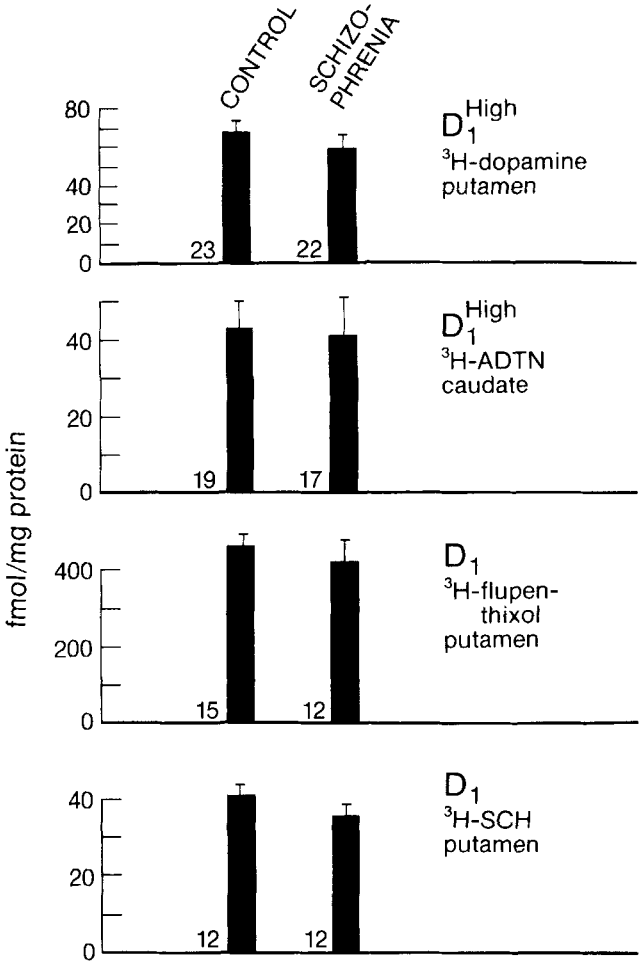

Fig. 8. Normal densities for D_1 and D_1^{High} in postmortem striata from schizophrenia patients. The D_1^{High} data were obtained with 0.25 to 2.5 nM [^{3}H]-dopamine (Seeman and Lee, 1982) or a range of [^{3}H]-ADTN (6,7-dihydroxy-2-aminotetralin) concentrations (Cross et al., 1983). D_1 was measured by either 7.5 nM [^{3}H]-flupentixol in the presence of 100 nM domperidone (Crow et al., 1982) or by using 0.4 nM [^{3}H]-SCH-23390 (Pimoule et al., 1985). The number at the foot of each column indicates the number of patients studied; the error bar indicates the S.E.M.

normal (Bird et al., 1977) but elevated in the nucleus accumbens (Bird et al., 1977, 1979). Such findings, however, are not consistent (Crow et al., 1979).

The density of D_1 receptors, as well as the density of the D_1^{High} subpopulation, is normal in postmortem human striatal tissues from schizophrenic pateints (Fig. 8). The magnitude of the D_1-associated adenylate cyclase stimulated by dopamine, however, has been reported to be elevated in postmortem tissues from schizophrenics (Memo et al., 1983), but this observation has not been found by others (Carenzi et al., 1975).

The density of D_2 receptors, on the other hand, has been found to be consistently elevated in the postmortem schizophrenic striatum and nucleus accumbens, starting with the observation in 1977 on 22 brains (Lee et al., 1978; Lee and Seeman, 1977; Seeman and Lee, 1977). This finding has been repeatedly confirmed (Cross et al., 1981, 1983, 1985; Crow, 1982a,b; Crow et al., 1978, 1981a,b, 1982; Kleinman et al., 1982; Mackay et al., 1978, 1980, 1982; Owen et al., 1978; Reisine et al.,1980; but see also Toru et al., 1982), a summary of which is in Figure 9 (see also Seeman, 1981).

A critical question has been whether the elevated density of dopamine receptors is associated with the schizophrenia or whether it is simply a result of the neuroleptic medication taken by the patients in the months and years before their death. This question naturally arises because many studies have shown that long-term neuroleptic administration can result in elevated D_2 densities in animal striata (MacKenzie and Zigmond, 1984, 1985; Meller et al., 1985; Seeman, 1980), and a doubling of the D_2 density can be achieved under certain conditions (Grigoriadis et al., 1984).

In order to pursue this question, an extensive series of 59 schizophrenic brains was examined (Seeman et al., 1984a), each tissue studied by means of a full range of [^{3}H]-spiperone concentrations to obtain the value for the D_2 density (B_{max}). The results revealed a bimodal distribution for the D_2 densities in schizophrenic striatum. That is, approximately half the schizophrenic brains showed D_2 densities about 25% higher than those of the control, while the other half of the schizophrenic brains exhibited D_2 densities about 2.3 -fold higher than those of the control. It should be noted that virtually all of the schizophrenics had been medicated, so that it does appear that the neuroleptic medication could have caused the bimodal pattern. Moreover, since the average dissociation constant of [^{3}H]-spiperone was the same for both groups (approximately 140 pM), it is reasonable to consider that the average neuroleptic dose or residual neuroleptic (remaining in the brain tissue) was not significantly different between the two groups.

This series of 52 schizophrenic brains (Seeman et al., 1984a) was extended to 91 brains by 1986 (Seeman, unpublished). The bimodal pattern in the schizophrenic

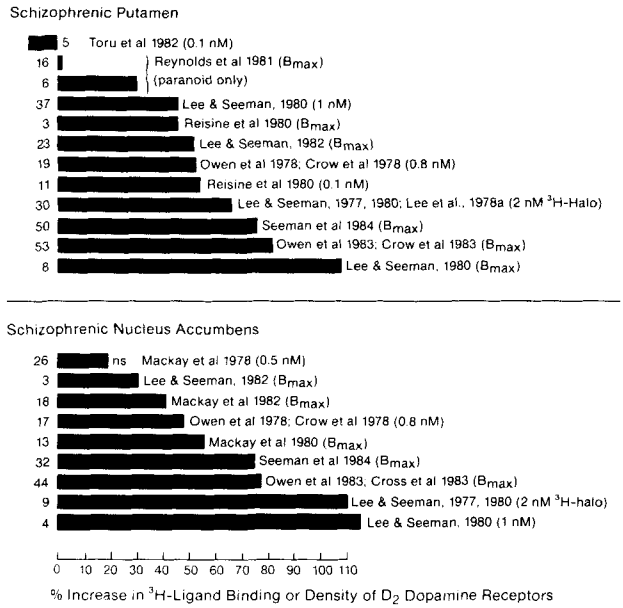

Fig. 9. Dopamine D_2 receptor densities (or amount of binding at a single concentration of [^{3}H]-neuroleptic) in postmortem brain tissues from patients who had schizophrenia. The values are in % of the neurological control values of 100% for nonschizophrenic control brain tissues. The number on the left side of each column indicates the number of different brain tissues measured. The majority of these patients had received neuroleptic medication. Unless otherwise specified, the number in parentheses indicates the final single concentration of [^{3}H]-spiperone used. B_{max} indicates that the density was measured by saturation analysis of the D_2 receptors, with a range of [^{3}H]-spiperone concentrations. [^{3}H]-FPT indicates [^{3}H]-flupentixol; [^{3}H]-Halo indicates [^{3}H]-haloperidol.

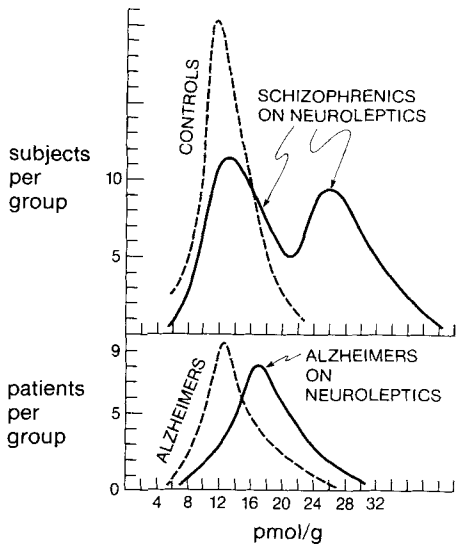

Fig. 10. Current data in this lab (unpublished) for D_2 dopamine receptor densities in postmortem striata from 91 schizophrenics reveals a bimodal distribution of densities, as had previously been found (Seeman et al., 1984a). Virtually all the patients had been on neuroleptics. The effect of long-term neuroleptics in 36 Alzheimer striata was to elevate the D_2 density by 27%. The D_2 density in the striatum was an average of the values in the caudate nucleus and the putamen. Units are pmol receptor per gram of original tissue.

striata continues to persist (see Fig. 10) with the striatal D_2 densities exhibiting one mode at 14 pmol/g and another mode at 26 pmol/g, each having an SE of 2 pmol/g. (The D_2 density in the striatum is an average of the values in the putamen and the caudate nucleus; the two values are generally within 10% of each other). The D_2 densities of 204 control striata, however, continue to reveal only a single normally distributed population of values, having a mean of 12.9 pmol/g.

This bimodal distribution of D_2 receptor densities is only seen in schizophrenia, and not in postmortem striata from Alzheimer patients or Huntington patients who had reliably received neuroleptics during their illness. For example, the D_2 densities in striata from 36 neuroleptic-medicated Alzheimer patients had a normally distributed set of values, the average being 16.5 pmol/g; this compared to a value of 13 pmol/g for Alzheimer tissues wherein the patients had definitely not received neuroleptics (Fig. 10). In other words, the long-term neuroleptic administration had elevated the average D_2 density in the Alzheimer striata by approximately 27%, but the pattern was not bimodal. An identical situation was found in Huntington's disease wherein the long-term neuroleptic therapy had resulted in an elevation of 26% in the striatal D_2 density, but the pattern of D_2 distribution was normal and not bimodal (Bzowej and Seeman, 1986).

Crow et al. (1981b), furthermore, examined a series of 15 schizophrenics who had never received neuroleptics, and found a direct relation between the severity of psychotic symptoms before death and the postmortem density of D_2 receptors in the striata from the same patient.

Thus, the bimodal pattern for the D_2 data in schizophrenia cannot solely be attributed to neuroleptic administration, but may well be associated with some aspect of the psychosis itself.

The two apparent subgroups of schizophrenic brain D_2 dopamine receptor densities are consistent with, but not necessarily synonymous with, the two-syndrome concept of schizophrenia suggested by Crow (1980, 1982a,b, 1984). The higher density mode at 26 pmol/g might represent Crow's type I syndrome of hallucinations and delusions. The subgroup at 14 pmol/g might possibly be related to those schizophrenic patients exhibiting ventricular enlargement, corresponding to Crow's suggested type II schizophrenia with negative symptoms of withdrawal and poverty of speech.

The finding of elevated binding of [^{3}H]-spiperone in lymphocytes in schizophrenia, but not in other psychiatric illnesses, is of considerable interest and practical importance (Bondy et al., 1984a,b 1985, 1986; Le Fur et al., 1983). Although dopaminergic in mice (Uzan et al., 1981), the nature of these binding sites for [^{3}H]-spiperone in human lymphocytes has not been established as dopaminergic (Fleminger et al., 1982; Madras et al., 1983; Maloteaux et al., 1982; Rotstein et al., 1983; Wazer and Rotrosen, 1984).

DOPAMINE RECEPTORS *IN VIVO* MEASURED BY POSITRON TOMOGRAPHY

Brain D_2 dopamine receptors have been successfully labelled in vivo by positron tomography in both humans (Wong et al., 1984) and animals (see refs. in Arnett et al., 1985). Using two or more injections of a short-lived radioactive neuroleptic, we can measure the absolute

density of D_2 receptors in volunteers and patients in vivo (Gjedde et al., 1986; Farde et al., 1986; Wong et al., 1986a,b).

Using [^{11}C]-raclopride, Sedvall and Farde and their colleagues (see DeLisi et al., 1986; Farde et al., 1986) have found that the D_2 densities in the striata of eight never-medicated schizophrenic patients ranged from 14 to 21 pmol/cm^3, compared to control values of 13 to 18 pmol/cm^3 [mean of 14.4 $\pm$ 1.9 pmol/cm^3].

Using a single dose of [^{11}C]-N-methylspiperone, Wong et al. (1985) found that the amount of this isotope that bound to dopamine D_2 receptors in the striata of 12 chronic schizophrenics was the same as that found in control subjects. These data were obtained from an image taken at 43 min, at which time less than 50% of the [^{11}C]-N-methylspiperone binding had equilibrated (Wong et al., 1984). [^{11}C]-raclopride, on the other hand, achieves steady-state binding to the striatum by 15 min (Farde et al., 1985, 1986). More recently, Wong et al. (1986a,b) and Gjedde have used two injections of [^{11}C]-N-methylspiperone to derive an absolute value for the D_2 density in pmol/gram. They found that the D_2 density was 14 $\pm$ 3 pmol/g in six control young men and was 34 to 41 pmol/g in drug-naive schizophrenics of the same age. Drug-treated schizophrenics revealed a caudate D_2 density of 43 $\pm$ 6 pmol/g; thus, the rise from 34 to 43 pmol/g was the typical 27% increase caused by long-term neuroleptics.

Using gamma-scintigraphy and [^{77}Br]-bromospiperone, Crawley et al. (1986) found that the amount of [^{77}Br]-bromospiperone bound in vivo to the striata of 12 schizophrenics (free of medication for at least 6 months) was statistically significantly elevated by 11%. This latter value may have been much higher if it were possible to occupy a higher proportion of the D_2 receptors (see Seeman and Guttman, 1986).

Clearly, therefore, further in vivo data on unmedicated schizophrenic patients are essential to determine the D_2 parameters in this disease.

FUTURE EXPERIMENTATION ON THE DOPAMINE HYPOTHESIS OF SCHIZOPHRENIA

In summary, there are only two main observations suggesting a hyperactive dopamine system in schizophrenia: first, nanomolar concentrations of all neuroleptics block D_2 receptors; and second, the D_2 densities in the striata of many schizophrenic patients reveal abnormally elevated values.

At best, the D_2 receptor is only a starting point for unravelling the biochemical neuropathology in schizophrenia. There are several experimental directions that may reasonably be pursued. These are discussed below.

Possible abnormal molecular properties of the D_2 receptor

The D_2 receptor needs to be examined for possible molecular abnormalities in the various forms of schizophrenia. It is now feasible, for example, to obtain the molecular weight of D_2 in tissues, by using one of the following radioactive photoaffinity labels selective for D_2, but with only [^{3}H]-azidomethylspiperone being commercially available:

[^{3}H-]-azidofluphenazine .....Lew et al., (1985)
[^{125}I]-iodoazidoclebopride.....Neumeyer et al. (1985)
[^{3}H]-azidosulpride.....Redouane et al. (1985)
[^{125}I]-iodoazido-N-(p-aminophenyl)spiperone .....
Amlaiky and Caron (1985), Amlaiky et al. (1984)
[^{3}H]-azidomethylspiperone .....Niznik et al. (1986c),
Seeman and Niznik (1986)

Possible abnormalities in the D_2 molecular weight would suggest abnormal functional properties (phosphorylation, desensitization; Sibley et al., 1985) or abnormal composition and structure. Not all D_2 receptors are alike. For example, while most species exhibit a molecular weight for D_2 of 94,000 (Amlaiky and Caron, 1986), the D_2 MW in canine striatum is consistently lower at 92,000 (Amlaiky and Caron, 1986; Niznik et al., 1986).

It will soon be possible to examine the composition and genetic makeup of pure D_2 receptors, since these are being solubilized (Madras et al., 1980; Madras and Seeman, 1985; Niznik et al., 1985a,b, 1986a,b) and purified by means of the following neuroleptic-linked affinity gels:

Dehydroxyaminohaloperidol-sepharose .....Chan and Madras (1983)
Haloperidol hemisuccinate-sepharose .....
Antonian et al. (1986)
Haloperidol-sepharose..... Ramwani and Mishra (1986)
(Carboxymethylene)oximinospiperone-sepharose .....
Senogles et al. (1986)
Clebopride(allyloxy)-sepharose..... Niznik et al. (1986)

Possible abnormal functional states of the D_2 receptor

Of the two affinity states in which D_2 can exist (see Fig. 4), it is the high-affinity state which is functional in the anterior pituitary gland (George et al., 1985a; McDonald et al., 1984). This conclusion is based on the observation that the absolute molarities of various dopamine agonists which inhibit the release of prolactin in vitro are identical with the dissociation constants of these agonists at D_2^{High}.

An identical situation occurs for D_2 autoreceptors on the nerve terminals of nigrostriatal dopamine neurones, wherein D_2^{High} is also the functional state controlling the release of dopamine. That is, the concentrations of various dopamine agonists which inhibit the stimulated release of [^{3}H]-dopamine are identical with the dissociation constants of these agonists for D_2^{High}. This is illustrated in Figure 11.

It is not yet clear whether the postsynaptic D_2 receptor operates in the high-affinity state or in the low-affinity state (Fig. 12). The important paper of Fujita et al. (1985) clearly demonstrated that an intrastriatal injection of pertussis toxin reduced the stereotyped behaviour induced by apomorphine. Since pertussis toxin selectively uncouples G_i from D_2^{High}, converting it into D_2^{Low}, the data of Fujita et al. strongly suggest that D_2^{High} is the functional state of the postysynaptic D_2 receptor.

On the other hand, there is some indirect evidence which suggests that D_2^{Low} may be the functional state of the postsynaptic D_2 receptor. For example, the concentrations of dopamine agonists which act on postsynaptic D_2 receptors to inhibit the release of [^{3}H]-acetylcholine from striatal slices are similar to the dissociation constants of these same agonists for D_2^{Low}. This is generally true for the data of Scatton (1981b, 1982), Starke et

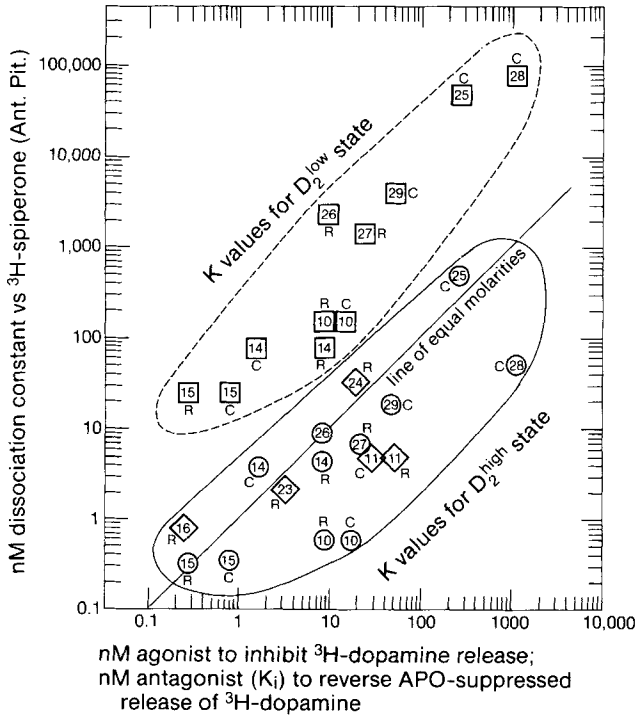

Fig. 11. Presynaptic D_2 dopamine receptors function in the high-affinity state, D_2^{High}, since the agonist dissociation constants (K values) at this site had the same absolute values as those which inhibited the release of [^{3}H]dopamine from striatal slices. C—cat caudate nucleus slices: 1 Hz × 2 min (Lehmann and Langer, 1982a,b, 1983; Lehmann et al., 1983). R—rabbit caudate nucleus slices: 3 Hz × 2 min (Starke et al., 1983), wherein the IC_{50} values were divided by 4, since the IC_{50} was fourfold higher at 3 Hz (Lehmann and Langer, 1982; see also James and Cubeddu, 1983). Circles, K at D_2^{High}; squares, K at D_2^{Low}; diamonds, $K^{High} = K^{Low}$. Numbers: 10, (−)apomorphine; 11, bromocriptine; 14, pergolide; 15, (±)-N-propylnorapomorphine; 16, haloperidol; 23, chlopromazine; 24, S-sulpiride; 25, (+)apomorphine; 26, BHT 920; 27, dipropyldopamine; 28, (−)-N-chlorethylnorapomorphine; 29, (±)-LY 141865 (racemate of LY 171455) (Seeman et al. 1986a).

al. (1983), Markstein (1981, 1983), Stoof and Kebabian (1982), and Closse et al. (1985; as reviewed by Seeman et al., 1986; see also Baud et al., 1985; Cubeddu et al., 1983; Cubeddu, 1984; James and Cubeddu, 1983; Seiler and Marstein, 1984; Stoof et al., 1979, 1982).

Although it is possible for a low-affinity state of a receptor to be electrically functional, as in the case of the nicotinic receptor (Giraudat and Changeux, 1980), a reasonable conclusion is the D_2^{High} is consistently the functional state, while D_2^{Low} may possibly represent a desensitized state, similar to the situation for the beta-adrenoceptor (Sibley and Lefkowitz, 1985; Toews et al., 1983).

These considerations are relevant to the dopamine hypothesis of schizophrenia in two ways. First, it is possible that more D_2 receptors in schizophrenia may be in the high-affinity state; and second, D_2 receptors may not normally desensitize into the low-affinity state (Arbilla et al., 1985; Bergstrom et al., 1982). Either of these possibilities would result in a hyperdopaminergic state, despite a normal density of D_2 receptors. The ideal compound for measuring D_2^{High} in vivo by positron tomography would be radioactive (−)-LY-171555, since this compound has 1,800-fold greater affinity for D_2^{High} (unpublished; see also Seeman et al., 1986b). Although [^{11}C]-

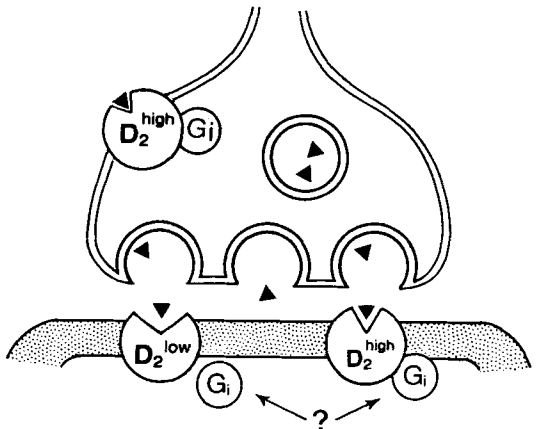

Fig. 12. Scheme indicating that the D_2 autoreceptor operates in the high-affinity state. It is not yet clear whether the postsynaptic D_2 receptor functions in the high-affinity state (with G_i attached) or in the low-affinity state (with G_i uncoupled from the receptor).

apomorphine or [^{11}C]-N-propylnorapomorphine can now be prepared, these ligands have virtually an identical affinity for D_1^{High} and D_2^{High} (Seeman et al., 1986b). Behavioural work also indicates that the ergots are more selective for D_2 than apomorpine (Herrera-Marschitz and Ungerstedt, 1984, 1985).

Possible abnormal interactions of D_2 with D_1 and other receptors

It has been found that D_1 and D_2 can have opposing actions in brain slices (Stoof and Kebabian, 1981, 1982), in homogenates (Saller and Salama, 1986; Dumbrille-Ross et al., 1985), and on certain behaviours (Rosengarten et al., 1983). A clear example of this opposing action is the production of oral dyskinesia and chewing motion in normal rats upon injection of a D_1 agonist, SK&F 38393 (which by itself has little effect), when given together with a moderate dose of S-sulpiride, a D_2-selective blocker (Rosengarten et al., 1983; Friedhoff, 1985). These data of Rosengarten et al. were recently confirmed by Vasse et al. (1985), who observed that moderate doses of S-sulpiride or (± amisulpride) potentiated the effect of apomorphine in eliciting licking and gnawing in mice. Haloperidol does not have this potentiating effect (Vasse et al., 1985), possibly because it has a low D_2/D_1 selectivity ratio of 37 (see Fig. 2) compared to the high selectivity ratio of 1,800 for S-sulpiride (unpublished; see Fig. 2). High doses of S-sulpiride (Vasse et al., 1985) or doses of S-sulpiride directly injected into the striatum (Arnt, 1985a) inhibit apomorphine-induced licking and biting.

D_1 contributes to several components of stereotyped behaviour elicited by dopamine-related congeners: grooming (Molloy and Waddington, 1984): locomotion and exploration (Fletcher and Starr, 1985); and licking, paw treading, and self-mutilative behaviour (Breese et al., 1985; Goldstein et al., 1986).

Although D_1 and D_2 have opposing influences for oral dyskinesia, the D_2 receptor has a *permissive* effect in allowing D_1 stimulation to be expressed. This principle has important clinical ramifications. For example, Barone et al. (1986) have shown that SK&F 38393 does not elicit rotation unless the D_2 agonist LY 171555 is also given. This synergism is even more pronounced in dopamine-depleted animals, wherein combined stimula-

tion with D_1 and D_2 agonists yield far more intense behaviours than driving either receptor alone (Arnt, 1985b,c, 1986; Arnt and Hyttel, 1984; Barone et al., 1985; Braun et al., 1986; Close et al., 1985; Gershanik et al., 1983; Jackson and Jenkins, 1985; Nomoto et al., 1985).

Arnt (1985b,c, 1986) has shown, furthermore, that D_1 and D_2 are normally coupled, but become uncoupled in the dopamine-depleted animal, findings also observed by Breese and Mueller (1985). The D_1 and D_2 receptors appear to be functionally linked in brain slices as well [Plantjé et al., 1984a,b]. An attempt at summarizing these observations is given in the scheme in Figure 13.

From a clinical point of view, it is reasonable to expect that D_1 blockade by SCH 23390 might be antipsychotic. This supposition is based on the fact that D_1 and D_2 are linked, and that selective blockade of D_1 by SCH 23390 produces catalepsy similar to that caused by clinically active neuroleptics (Morelli and Di Chiara, 1985; Meller et al., 1985b; Boyce et al., 1985; Onali et al., 1985a; Arnt, 1985c; Breese and Mueller, 1985).

Clinical experience indicates, however, that there is no relation between the D_1-blocking potency of a neuroleptic and its clinical antipsychotic potency, as illustrated in the top of Figure 2. Nevertheless, since D_1 and D_2 receptors are normally linked and can have opposing actions, it will be important to measure both D_1 and D_2 parameters at the same time in the same schizophrenic brain.

Long-term blockade of D_1 receptors with SCH 23390 increased the density of D_1 receptors without affecting the D_2 density (Creese and Chen, 1985; Porceddu et al., 1985). Such animals, however, were supersensitive to the locomotor and stereotypy actions of the D_2-specific agonist (−)LY171555 (Creese et al., 1985). This supersensitivity may arise because of the coupling that normally exists between D_1 and D_2. Long-term haloperidol also increased the density of D_1 receptors whereas S-sulpiride or clebopride had no effect on D_1 density (Fleminger et al., 1983; Porceddu et al., 1986).

Thus the lack of sulpiride-induced elevation of D_1 density suggests that long-term sulpiride may have a low risk for the development of the possibly D_1-associated oral-lingual components of tardive dyskinesia. Such speculation has not yet been examined clinically for sulpiride (Casey et al., 1979; Gerlach and Casey, 1984; Häggström, 1980, 1984; Rao et al., 1981; Tarsy and Baldessarini 1977). On the other hand, long-term sulpiride causes rats to become behaviorally supersensitive to apomorphine (Jenner et al., 1982; Rapniak et al., 1984, 1985).

Although the focus of this review has been on dopamine, it is well known that many neurotransmitters can alter the release of dopamine or the properties of the D_2 receptor. These include cholecystokinin (Dumbrille-Ross and Seeman, 1985; but see Widerlöv et al., 1982), noradrenaline (Antelman and Caggiula, 1977), GABA (Christenson, 1981; Giorgulieff et al., 1978; see Table II), opiates (Schoffelmeer et al., 1985, see Table II), adenosine (Green et al., 1982),and acetylcholine (Ehlert et al., 1981; Olianas et al., 1983; see Table II).

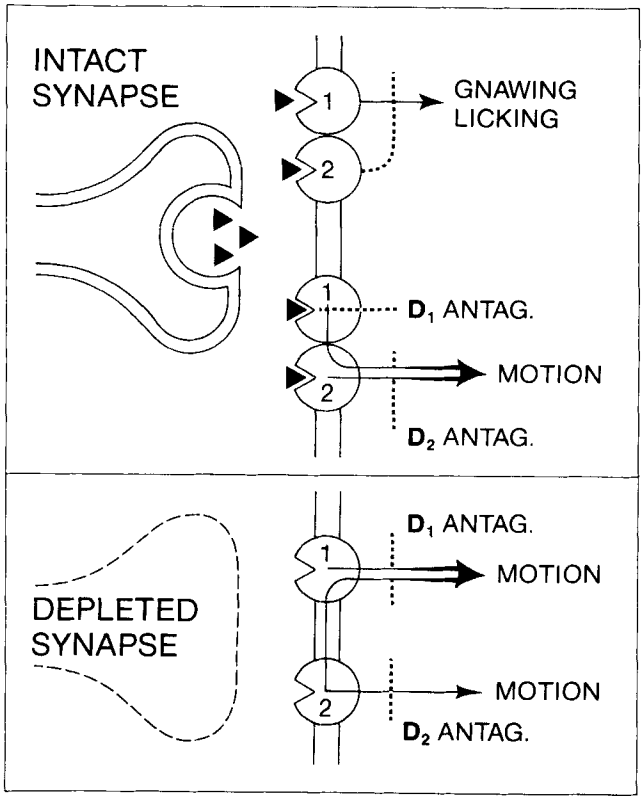

Fig. 13. In the intact synapse (top) the D_1 and D_2 receptors are linked and synergistic for locomotion or rotation but oppose each other for gnawing and licking. Here, a D_2 agonist permits rotation to be elicited by a D_1 agonist (Barone et al., 1986). Since D_1 is synergistic to D_2, D_1 antagonists cause catalepsy which appears similar to D_2-blocked catalepsy.

In the dopamine-depleted synapse (bottom) the D_1 and D_2 receptors are weakly coupled. Here, a D_1 agonist permits the rotation to be elicited by a D_2 agonist (such as an ergot; Gershanik, 1983; Jackson and Jenkins, 1985). Furthermore, since D_1 and D_2 can independently lead to motion, selective D_1 antagonists do not affect D_2 agonist action; likewise, D_2 antagonists do not affect D_1 agonist action.

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