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Brain Dopamine Receptors

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"Alfred H., 36 years old, had been admitted April 22, 1952, with severe psychomotor agitation, vague ideas of persecution, and auditory hallucinations. He had a similar episode of 8 months duration at age 18.... On the third day of chlorpromazine his speech was more coherent, he was oriented, he could sleep; he was transformed, he responded to questions, he read. He was discharged two months later." [Delay, Deniker, and Harl (282), describing their early use of chlorpromazine (RP4560) against schizophrenia.]

I. Introduction

SINCE neuroleptic drugs are effective in preventing the delusions and hallucinations of paranoid schizophrenia, it has long been suggested (985, 726, 991) that these drugs may provide a research strategy for determining the abnormal site or sites in the brain in schizophrenia (646, 649, 652).

Of the many sites of neuroleptic action, dopamine receptors are the most susceptible to blockade by practically all the neuroleptics. Although there had been indirect evidence for this conclusion before 1974, since then the most direct evidence has come from studies (1023) measuring the specific binding of ^{3}H-haloperidol and other ^{3}H-neuroleptics to dopamine-rich brain regions. The purpose of this review is to summarize and analyze this direct evidence. (For previous reviews on other aspects of dopamine receptors, see refs. 491, 1065, 1070, 548, 1068, 611, 550, 1258, 735, 824.)

A. Terminology for Dopamine Receptors

"α-Dopaminergic" and "β-dopaminergic" were two early terms used to designate different types of dopamine receptors (568). These terms are not in current use, however, since they were readily confused with the α-adrenoceptor and the β-adrenoceptor (570).

Although the concept of multiple receptors for dopamine had been discussed by Cools and Van Rossum in 1976 (210), it has been difficult to obtain a simple and generally acceptable biochemical classification. Spano initially suggested a D-1 and D-2 nomenclature (see 570 for further refs.), which was summarized by Kebabian and Calne (570) as follows: The D-1 receptor is that

dopamine receptor which is linked to dopamine-sensitive adenylate cyclase, and the D-2 receptor is that dopamine receptor which is not linked to dopamine-sensitive adenylate cyclase. These definitions, however, are not completely convenient since, first, there is disagreement as to whether dopamine-sensitive adenylate cyclase exists in some tissues [e.g. pituitary (1278, 966, 735, 568, 7); intermediate pituitary cells, however, contain dopamine-inhibited adenylate cyclase (754a)]; second, there is no practical biochemical way to separate the amount of linked and nonlinked receptors; and, third, it will be shown in this review that there is no relation between the biological potencies (for producing behavioural effects) of dopaminergic agonists or antagonists and their potencies on the enzyme. (See fig. 1a for terminology.)

A slight modification of the terminology results in a simple, practical, and convenient set of designations for these dopamine-sensitive sites. For the purposes of this review, therefore, the term D_1 simply refers to the site for dopamine-sensitive adenylate cyclase, without any implications as to whether this enzyme is linked to any other dopamine receptors or associated with any behavioural response. As detailed later, this D_1 site is characterized by being stimulated by micromolar concentrations of dopamine and antagonized by micromolar concentrations of most neuroleptics. The term D_2 herein refers to a dopaminergic site or receptor (labeled by any ^{3}H-ligand) that is sensitive to micromolar concentrations of dopamine but nanomolar concentrations of neuroleptics. The term D_3 herein refers to a dopaminergic site (labeled by any ^{3}H-ligand) that is sensitive to nanomolar concentrations of dopamine (1 to 10 nM) but micromolar concentrations of neuroleptics. The term D_4 here refers to a dopaminergic site that is sensitive to nanomolar concentrations of both dopamine and neuroleptics. Clear evidence for the existence of such a site has been obtained in Labrie's laboratory [Meunier et al. (754a)] for dopamine-inhibited adenylate cyclase in intermediate pituitary cells. This review will summarize the evidence indicating that the D_1, D_2, and D_3 sites are distinctly separate entities, and that only the D_2 site fulfills all the criteria for a receptor associated with or mediating the majority of dopaminergic behaviours and responses. Thus, the word "receptor" is used in this text only in connection with D_2, since this is the only site that has properties related to dopaminergic behaviours and responses. The word "site" in this text merely signifies that a binding site or an enzymatic site exists with a *pattern* of drug sensitivities as summarized in figure 1a. It is conceivable that a site may have different states, such that one state may reveal a "D_4-like pattern," while another state may reveal a "D_2-like pattern."

B. Electrophysiological Action of Dopamine

Although there is considerable literature on dopamine electrophysiology, it is not the purpose of this review to examine this area [see York (1272) for a review of this topic]. Direct application of dopamine onto neurones or spontaneously firing cells may block action potentials

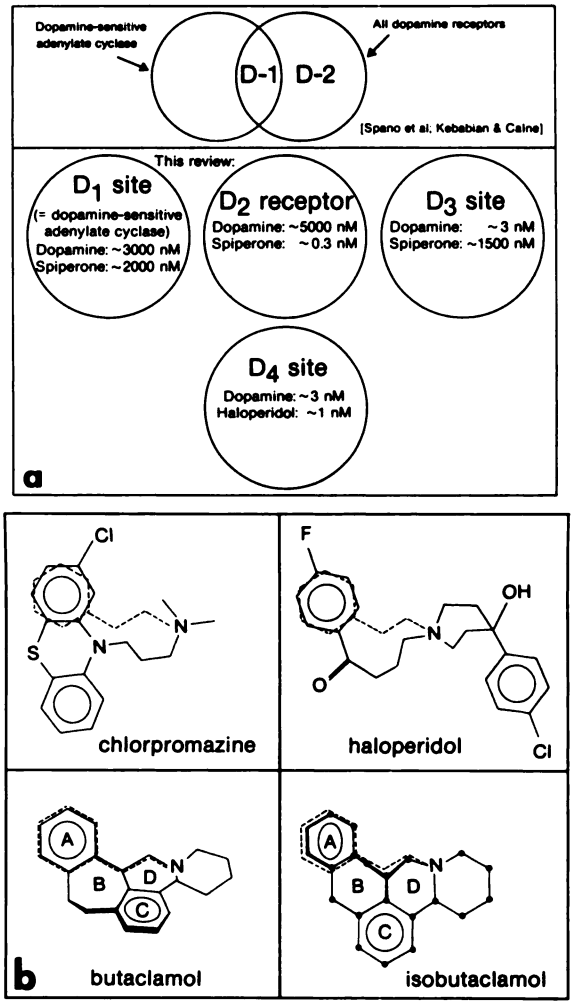

FIG. 1a. Terminology for dopamine-sensitive sites and receptors. Spano et al. (1072–1078) and Kebabian and Calne (570) separated all dopamine receptors into two classes. The D-1 receptors were those that were linked to dopamine-sensitive adenylate cyclase, while the D-2 receptors were those that were not linked to this enzyme. It appears necessary to modify this terminology, because there is no biochemically practical method for determining the proportion of linked and nonlinked dopamine receptors, and because there is no relation between the behavioural potencies of dopamine agonists or antagonists and their potencies on this enzyme. For the purposes of this review, therefore, the D_1 site is simply defined as the dopamine-sensitive adenylate cyclase itself, which is characterized by being stimulated by micromolar concentrations of dopamine (~3000 nM) and antagonized by micromolar concentrations of neuroleptics (e.g. ~2000 nM spiperone). The D_2 site is defined herein as the dopaminergic site or receptor (labeled by any ^{3}H-ligand) that is sensitive to micromolar concentrations of dopamine (~5000 nM) but nanomolar concentrations of neuroleptics (e.g. 0.3 nM spiperone). The D_3 site is herein defined as that dopaminergic site (labeled by any ^{3}H-ligand) that is sensitive to nanomolar concentrations of dopamine (~2 to 4 nM) but is antagonized by very high concentrations of neuroleptics (e.g. ~1500 nM spiperone). The D_4 site may be defined as that which is sensitive to nanomolar concentrations of both dopamine and neuroleptics, as found for dopamine-inhibited adenylate cyclase in intermediate pituitary cells (754a). This review summarizes evidence that warrants terming the D_2 site as a "receptor," since the behavioural potencies of various dopamine agonists and antagonists correlate primarily with their potencies on this site.

FIG. 1b. Structural fit between dopamine (dashed line) and neuroleptics, using Dreiding models. Dopamine can overlap haloperidol in two ways: 1) as shown above; or 2) the ring of dopamine can overlap the benzyl ring to which chlorine is attached (1161). In the case of isobutaclamol, the ring of dopamine and the A ring of isobutaclamol are at slight angles to one another, as shown above.

(471, 383a, 305a) or cause excitation or both (95, 740, 1272, 1050–1052, 1079, 1266). Upon stimulating nigral neurones, the caudate neurones respond with increased firing within a few milliseconds [see work of Buchwald and others in York (1272)]. This early excitation, however, does not appear to be dopaminergic in nature since the impulses occur too soon after the onset of stimulation. Over the next hundreds of milliseconds the caudate neurones become electrically inhibited. The basis of this inhibition may be that dopamine elicits a prolonged inhibitory postsynaptic potential (IPSP) or that it simply elicits a depolarization blockade (383a). There is at present no information on the relation between the electrical effects of dopamine and the receptor sites for dopamine, as measured by methods using ^{3}H-ligands.

II. Indirect Evidence for Neuroleptic Action on Dopamine Receptors

Before the advent of direct binding methods for labeling dopamine receptors with ^{3}H-haloperidol (1023, 1011, 995), ^{3}H-dopamine (1022, 990), or other ^{3}H-ligands, there was considerable circumstantial evidence that neuroleptic drugs blocked dopamine receptors in the nervous system. This indirect evidence included the following.

A. Dopamine Turnover

The early findings of accelerated catecholamine turnover by neuroleptics (161; see 13 and 15 for refs.) implied that neuroleptics might block receptors for both noradrenaline and dopamine. Although some work (211) indicated that the turnover of noradrenaline was more affected than that of dopamine, other studies (see 835 and 839 for refs.) soon pointed to a selective acceleration of dopamine turnover by the neuroleptics (see 272, 930, 1232, 926b, 215, 772, 726, 727, 836, 980, 1090, 38 for additional refs.). This accelerated turnover of dopamine, reflected by the elevation of homovanillic acid (HVA), was considered to be a neural reflex activation of dopamine neurones in their attempt to overcome dopamine receptor blockade by the neuroleptics. Although there is in general a good correlation between the clinical doses (for antipsychotic action) and the doses that elevate HVA (930, 726–729), there are three neuroleptics (thioridazine, clozapine, and sulpiride) that are disproportionately weak in elevating HVA (1232, 15, 930) [presumably because of the anticholinergic receptor action of these drugs (627, 760, 111a, 956a); see also 56, 1084, 791, and 798].

B. Neuroleptic Blockade of Dopamine-Mimetic Drug Action

Additional indirect support for the hypothesis of neuroleptic blockade of dopamine receptors came from the observations that neuroleptics inhibited the actions of dopamine-mimetic drugs. Apomorphine, for example, directly stimulates dopamine receptors (325, 14), while amphetamine acts indirectly by releasing endogenous dopamine (325, 777). Since neuroleptics antagonize the behavioural effects of apomorphine (823, 824), amphetamine (904, 905, 777, 349, 1200), and methylphenidate (180), Van Rossum suggested (1199, 1200) that neuroleptics were selective in blocking dopamine receptors, rather than blocking all types of catecholamine receptors.

More recently, Vetulani et al. (1205, 748, 1053a) noted that neuroleptics considerably reduced the entry of apomorphine into the brain, appreciably accounting for antagonism of apomorphine action by haloperidol. Westerink and Horn (1233) have confirmed this and have suggested that the vasodilatory action of apomorphine may facilitate its own net permeation into brain, an effect that may be antagonized by neuroleptics.

C. Neuroleptic-induced Catalepsy and Parkinsonism

Neuroleptic drugs block a variety of behaviours elicited by dopamine-related congeners, particularly rotation and locomotion (1175, 271, 411, 1143, 826, 555, 836a, 891, 261, 1090), stereotypy (799, 218, 219), and emesis (823, 824, 548, 827, 550). Thus, the neuroleptics cause catalepsy in animals (217, 329, 332) and parkinsonian-like signs in patients. Since it had been established that Parkinson's disease was associated with a deficiency in brain dopamine (497–502, 881, 921), while neuroleptics only accelerated the turnover of dopamine without much effect on the content of brain dopamine, the existence of neuroleptic-induced catalepsy or parkinsonism provided evidence that neuroleptics blocked dopamine receptors. This evidence, however, was only circumstantial, since these dopamine-dependent behaviours are also affected by other neurotransmitters such as gamma-aminobutyric acid (452, 1263), noradrenaline, and serotonin (889, 929, 1217a).

D. Neuroleptic Blockade of the Neurophysiological Action of Dopamine

More direct evidence that neuroleptics block the neurophysiological action of dopamine has come from iontophoretic experiments in vivo (740, 1272). The net effect of dopamine generally is to produce a prolonged IPSP. There are, however, difficulties in the interpretation of the iontophoretic findings, since there are early transient excitant actions possibly associated with the electrode, the drug concentrations are impossible to determine, and it is known that there is an interdependence of the nigrostriatal dopaminergic systems on the two sides of the brain (829). Nonetheless, the major finding that neuroleptics can selectively block certain neurophysiological actions of dopamine has been confirmed by in vitro experiments wherein the absolute drug concentrations were controlled (471, 383a).

E. Neuroleptic-induced Hyperprolactinemia and Galactorrhea

Further evidence that neuroleptics block dopamine receptors has come from endocrine studies. It is known that various dopamine congeners reduce the release of prolactin from pituitary cells. This effect is blocked by

neuroleptics (see 449, 981, 636, 327 for further refs.), resulting in hyperprolactinemia and galactorrhea in some instances.

F. Conformational Fit between Dopamine and Neuroleptics

Indirect support for the concept that neuroleptics may act on dopamine receptors has come from conformational considerations. With conformations of dopamine and its congeners derived by x-ray analysis (495, 496, 400–401a, 71, 1132, 138a), molecular orbital methods (445), or with Dreiding models (496, 867), it can be seen that there is a reasonably good structural fit between dopamine and the neuroleptic drugs (495, 496, 548, 550, 611, 513, 771, 163, 491, 1161). This fit extends to new neuroleptics such as butaclamol (511, 1206, 108, 688, 884, 484, 185, 1208, 512, 609) and isobutaclamol (514, 867), as illustrated in figure 1.

G. Neuroleptics and the Dopamine Hypothesis of Schizophrenia

Finally, further circumstantial evidence that neuroleptic drugs interfere with dopamine transmission comes from the observation that high doses of L-DOPA (dihydroxyphenylalanine) or amphetamine exacerbate the symptoms of schizophrenia and elicit hallucinations in patients with Parkinson's disease (1269, 21, 430, 1064, 22, 1066, 318); such symptoms, particularly delusions and hallucinations, are readily and selectively suppressed by neuroleptics. These observations, together with those cited in the previous six subsections, have provided the basis for the dopamine hypothesis of schizophrenia (726, 727, 729, 1094, 1066, 263, 43, 1197, 156, 157, 503), which may be succinctly stated as follows: "*certain (but unknown) dopaminergic pathways are overactive in schizophrenia.*" Additional minor support for this hypothesis stems from the observation that drugs that inhibit dopamine synthesis potentiate the antipsychotic actions of neuroleptic drugs (162, 179).

Although there is much evidence compatible with the dopamine "overactivity" hypothesis of schizophrenia (see section XXI on D_2 receptors and schizophrenia), additional observations need to be explained. For example, although high doses of L-DOPA are psychotomimetic, low doses of L-DOPA or other dopamine congeners (apomorphine) have sedating as well as distinctly antipsychotic actions (23); presumably these effects are mediated through dopamine autoreceptors (see section XVII).

It is difficult to separate the clinical antidopaminergic actions of neuroleptics from dopaminergic abnormalities in schizophrenia. Some studies report an elevation in the dopamine and/or HVA content of striatum in schizophrenia (337, 259), while other studies have not found any significant alteration in the striatal dopamine content (81, 82, 40). In the case of nucleus accumbens in schizophrenia, once again some studies report an elevation in dopamine and/or HVA content (337, 265, 81, 82), while others have not found this (259). Such different findings may arise from the different medication histories of the patients (738). Bacopoulos et al. (40) have found, for example, that the HVA content in the cortex of schizophrenic brain was significantly elevated only in that group of patients who had been treated with neuroleptics.

A similar difficulty arises in studying the HVA content in cerebrospinal fluid in schizophrenia. As mentioned in section II A, neuroleptics invariably increase the turnover of dopamine, as revealed by an increase in the amount of HVA released. With prolonged administration of neuroleptics, however, the HVA levels return to normal or below normal in both schizophrenic patients (877, 878) and animals (957, 959, 960). The low levels of HVA in cerebrospinal fluid found by Bowers (97) (in schizophrenic patients who had been off neuroleptics for 2 weeks) may be similar to this long-term accommodation effect. Alternatively, the finding may indicate that the "unmedicated" patient is supersensitive to his own dopamine so that the neural feedback results in less dopamine than normal being released.

If such a dopaminergic supersensitivity does exist in schizophrenia, it would probably be primarily restricted to certain dopamine-containing regions, possibly the limbic areas and the striatum (754, 1268, 588, 1094, 1095, 503, 43, 738, 1095, 84, 82, 96). Since the serum prolactin concentrations are normal in unmedicated schizophrenic patients (744), this indicates that either the dopamine-containing tuberoinfundibular neurones are not overactive or that the prolactin-containing cells in the pituitary gland in schizophrenia are normal in their sensitivity to dopamine. The administration of apomorphine to acutely ill schizophrenic patients, however, elicits significantly higher responses in plasma levels of growth hormone (850, 943); this is not seen in chronic schizophrenia or in schizophrenic patients who are adequately medicated (850, 943).

Direct measurement of dopamine receptors in postmortem schizophrenic brain has now revealed abnormally high numbers of dopamine receptors (D_2 receptors) in the limbic and striatal regions, as reported by Lee and Seeman in 1977 (646); this subject is reviewed in section XII C. No difference has been found in dopamine-sensitive adenylate cyclase (D_1 sites) in caudate nucleus (148) between control subjects and schizophrenic patients.

III. Criteria for Specific and Nonspecific Neuroleptic Sites of Action

The many different sites of action of neuroleptics may be classified as either specific or nonspecific according to the criteria based on *stereoselectivity* and drug *concentration*.

The criterion of *stereoselectivity* refers to the fact that nonspecific actions on the membrane depend primarily on the fat solubility of the drug, and there is very little difference between enantiomers in producing such effects. The *nanomolar concentration* criterion for specific

neuroleptic action refers to the fact that the therapeutic concentrations of the neuroleptics in plasma water are between 0.1 and 50 nM. Hence, of the many neuroleptic sites proposed, only those affected by nanomolar concentrations (up to 100 nM) would have any likelihood of being truly specific.

A. Stereoselective Criterion of Neuroleptic Action

Since neuroleptic drugs are highly fat-soluble (987) and surface-active (993, 985, 550), they are very soluble in biological membranes (1013) (table 1).

It is not surprising, therefore, that neuroleptics can interfere with many membrane-associated events (987, 1014), because the neuroleptic concentration within the membrane phase can attain extremely high values, particularly in vitro. For example, when the aqueous phase contains 10^{-6} M haloperidol, the haloperidol concentration in the membrane phase immediately attains the value of 200×10^{-6} moles per liter of membrane, where 200 is the value for the membrane/buffer partition coefficient (synaptosome membranes; 1013) for haloperidol. Such enormous concentrations within the membrane phase (e.g. 0.2 mmolal) elicit a variety of nonspecific membrane-disturbing actions (989). These include expansion of the membrane and its proteins (997–999, 941, 1019, 1010, 992), fluidization of the membrane (998, 1001), alterations of transmembrane fluxes (987, 996, 1012), and inhibition of membrane excitability (anesthetic action) (987, 1085, 1013, 857).

These nonspecific membrane actions depend chiefly on the membrane solubility of the drug, and there is very little difference between the potencies of enantiomers. For example, opiate enantiomers (dextrorphan and levorphanol) are equally active in their local anesthetic action when applied in the 1 to 100 μM concentration range (994, 1085). In the nanomolar concetration range, however, the *levo-* form of the opiate is generally 100 to 1000 times more potent than the *dextro-* form on opiate receptors (675, 677, 1068).

Thus, because the neuroleptics are highly membrane-soluble, any neuroleptic action on, or binding to, biological membranes would not be sufficient by itself to identify that action or binding as being associated with a "specific" neuroleptic site. It would require the stereoselective effect of (+)-butaclamol (fig. 1b; 108, 511, 513, 1206, 1208, 995; see 814a for clinical potency) to identify that site as specific for neuroleptics. The neuroleptics are nonspecifically membrane-anesthetic in the concentration range between 100 and 1000 nM (1085, 857, 1013) but are stereoselective and specifically active on neuroleptic receptors in the 0.1 to 50 nM concentration range, as discovered by Seeman, Wong, and Tedesco in 1975 (1023, 1011). Since the (+)- and (−)-butaclamol enantiomers have identical partition coefficients, any difference in their biological potencies may be attributed to a specific and stereoselective action.

TABLE 1
Partition coefficients of neuroleptics

	Octanol/ Water* (991)	Membrane/ Buffer (1013)
Chlorpromazine sulfoxide	1,900	
Promethazine	22,400	19
Promazine	35,500	30
Imipramine	41,700	295
Chlorpromazine	191,000	1,700
Haloperidol	555,000	200
Fluphenazine	912,000	
Prochlorperazine	1,350,000	
Trifluperidol	1,700,000	
Pimozide	2,000,000 (620)	
Penfluridol	40,000,000 (620)	

* Coefficient for the nonionized form of the drug.

B. Nanomolar Concentration Criterion for Specific Neuroleptic Action

Since the therapeutic concentrations of neuroleptics in plasma water are between 0.1 and 50 nM (991), it is reasonable to search for neuroleptic-specific sites that are affected by neuroleptics in this low concentration range. Aqueous concentrations exceeding 100 nM are generally toxic.

IV. Nonreceptor Sites of Neuroleptic Action

The foregoing indirect evidence indicating a selective action of neuroleptic drugs on dopamine transmission encouraged the search for neuroleptic-specific sites of action, particularly in the dopamine-sensitive regions of the brain. These regions include: (a) striatum (caudate nucleus and putamen) (1127, 1128); (b) nucleus accumbens; (c) olfactory tubercle (402); (d) median eminence and pituitary regions (87); (e) substantia nigra (497–499; 952); (f) frontal cortex (687, 85, 717a); (g) retina (711).

Experiments before 1973 were not particularly successful, however, in localizing neuroleptics to dopamine-rich or dopamine-sensitive tissues, although they did establish the properties of nonspecific and hydrophobic binding of neuroleptics (1000, 995, 997, 952, 1013, 615–617, 549, 704). Assays for neuroleptics were then not very sensitive, and radioisotopes of neuroleptics were of very low specific activity (below 0.1 Ci/mmole), such that it was difficult or impossible to measure the binding to tissue of radio-neuroleptics at concentrations below 100 nM in vitro (1013).

In order to locate neuroleptic-specific sites of action that fulfilled the above-mentioned stereoselective and nanomolar criteria, therefore, it has been necessary to study the neuroleptic sensitivities of a wide variety of neurone cell events. As summarized in table 2, the sites that have proved to be the most sensitive to neuroleptics are those for the specific binding of ^{3}H-haloperidol (1023) and closely related ^{3}H-ligands. Before discussing these ^{3}H-neuroleptic receptor sites, it is worth reviewing the nonreceptor sites of neuroleptic action.

A. Nerve Impulses

Neuroleptics can block the conduction of nerve impulses (987, 1013, 996, 1009, 1085, 857; see further refs. in 991). This local anesthetic-like effect of the neuroleptics generally occurs in the concentration region between 100 and 1000 nM (table 2; 1013, 857, 996, 941). These concentrations, therefore, are from 10 to 50 times higher than those detected in the serum water of patients who are adequately medicated with neuroleptics (Table 2; 991). Since small diameter axones are considerably more sensitive to anesthetic blockade (by neuroleptics) than are large ones (1085, 1086), it is possible that very small preterminal fibers (0.1 μm diameter) may become blocked by high serum levels of neuroleptics.

B. Neuroleptic Block of Presynaptic Autoreceptors and of Presynaptic Coupling

The presynaptic actions of drugs (317) can be studied in vitro with either isolated tissues (341), or tissue slices (339, 342, 1002, 1100), or synaptosomes (280, 281, 900).

As reviewed in a later section, there are presynaptic receptors for dopamine that generally respond to apomorphine with an inhibition of dopamine release (340, 1235, 860, 759, 908); such inhibitory action is not always obtained (26, 901), and it is difficult if not impossible to demonstrate a clear dependence on the apomorphine concentration (340, 759).

These presynaptic dopamine autoreceptors can be blocked by neuroleptics, resulting in an increase in the stimulated-release of ^{3}H-dopamine (340, 860, 1235, 759, 908). In other studies, however, neuroleptics did not enhance but consistently inhibited the stimulated-release of ^{3}H-dopamine from striatal slices (1002, 26, 901, 902; table 2). A resolution of these disparate findings was provided by Miller and Friedhoff (759), who observed that haloperidol concentrations below 100 nM enhanced the stimulated-release of ^{3}H-dopamine, while those above 100 nM inhibited the release of ^{3}H-dopamine from striatal slices.

The inhibition of stimulated-release of ^{3}H-dopamine by the neuroleptics is probably based on the inhibition of the entry of Ca^{++} into excitable cells by neuroleptics (996, 615, 617; see Quastel et al. in ref. 991). Thus, the neuroleptics can inhibit the coupling between the presynaptic impulse and the secretion of the neurotransmitter, the release of which requires the entry of Ca^{++} into the nerve terminal (1002). Whether one detects neuroleptic-induced enhancement of inhibition of stimulated-release of ^{3}H-dopamine from slices, therefore, presumably depends on the experimental conditions that control the "tightness" of impulse-secretion coupling.

TABLE 2

Sensitivities of various sites to neuroleptics (IC_{50} values in nM)

	Haloperidol	Chlorpromazine
Conc. in patient's serum water	1.5–2.8*	9–96*
Inhibition of ^{3}H-haloperidol binding	2 (1023)	20 (1023)
Enhancement of stimulated release (dopamine)	~10 (759)	~1,000 (26)
	~100 (908)	~1,000 (908)
Block of nerve impulses	100 (1013)	400 (1013)
	600 (857)	
Block of stimulated release of ^{3}H-dopamine	95 (1002)	100 (860)
	100 (860)	700 (1002)
	400 (759)	900 (542)
	1,900 (542)	10,000 (26)
	10,000 (26)	
Enhancement of spontaneous release (dopamine)	100 (1001)	2,600 (542)
	4,000 (542)	3,500 (1001)
Block of dopamine uptake	300 (1001)	1,000 (860)
	1,300 (860)	2,800 (908)
	2,300 (908)	10,000 (1001)
	4,400 (459)	10,000 (542)
		10,600 (459)
Block of noradrenaline uptake		180*
		500*
Block of serotonin uptake		3,800*
		5,100*
Disinhibition of tyrosine hydroxylase	16 (542)	500 (542)
	20*	1,000*
	110*	
	500*	
Inhibition of dopamine-sensitive cyclase (see fig. 2)	600 (620)	500–1,500 (493)
	700 (562)	(571)
	700 (762)	(537)
	1,000 (571)	(191)
	2,000 (191)	(564)

* See Seeman (991) for refs.

The neuroleptic inhibition of stimulated release of ^{3}H-dopamine is stereoselective (1002), and the inhibitory concentrations correlate very well with the clinical potencies (1002). However, despite fulfilling this stereoselectivity criterion for neuroleptic action, the neuroleptic concentrations for this inhibitory effect range from 50 to 1000 nM, which are about 10 times higher than those found in serum water in patients (991; table 2).

C. Enhanced Spontaneous Release and Membrane Fluidization by Neuroleptics

At aqueous concentrations of neuroleptics above 500 to 1000 nM, the neuroleptic concentration within the membrane phase is extremely high (1013, 987, 709). These concentrations, therefore, tend to fluidize all types of membranes, including vesicle membranes (987). This process promotes fusion between membranes, thus leading to an enhanced spontaneous release of neurotransmitters (1001, 26, 268). Because of the very high concentrations required, this transmitter-releasing action may be of importance only in toxic aspects of neuroleptic action, such as in tardive dyskinesia (1014).

D. Neuroleptic Block of Transmitter Uptake

The uptake sites for dopamine, noradrenaline, and serotonin are all relatively insensitive to neuroleptics (table 2; 273). There is also little stereoselective difference between the potencies of alpha- and beta-flupenthixol (542).

E. Disinhibition of Tyrosine Hydroxylase by Neuroleptics

Tyrosine hydroxylase is inhibited by apomorphine, and this inhibition is in turn reversed by many neuroleptics but not by clozapine or thioridazine (see 991 for refs.). This enzyme is unlikely to be an important site of specific neuroleptic action, since there is poor stereoselectivity by butaclamol (542), the neuroleptic concentrations required are high, and they do not correlate with clinical potency (991).

F. Inhibition of Dopamine-Sensitive Adenylate Cyclase by Neuroleptics

Dopamine-sensitive adenylate cyclase is frequently referred to as the D_1 site (570), simply because it was the first dopamine-sensitive and membrane-associated site to be studied in vitro (571). The pattern of D_1 stimulation by a variety of dopaminergic agonists is given in table 3, while various values for D_1 inhibition by neuroleptics are shown in figure 2. One of the main features of this enzyme is that it requires from 500 to 5000 nM dopamine in order to be stimulated by 50% (EC_{50} values, table 3).

As shown in figure 2, there is a rough correlation between the neuroleptic IC_{50} values (concentrations for 50% inhibition) and the clinical antipsychotic doses of the phenothiazines and butaclamol. There is no such correlation for the butyrophenones. Iversen et al. (542) did find a correlation for the butyrophenone IC_{50} values and the butyrophenone potencies in animals. This correlation (within the butyrophenones), however, can almost entirely be explained by the partition coefficients of the butyrophenone drugs (table 1).

Although dopamine-sensitive adenylate cyclase fulfills the criteria for being a neuroleptic-specific receptor (870, 884), the neuroleptic IC_{50} values (between 100 and 10,000 nM) do not correlate with clinical potency. The neuroleptic K_i values can be derived from IC_{50} values. These K_i values are in the nanomolar range, and they indicate the neuroleptic concentrations that would be needed to inhibit the enzyme at infinitely low levels of dopamine. There is reason to think, however, that the dopamine concentration in the synaptic cleft during the discharge of dopaminergic vesicles is between 1,000 nM and 10,000 nM (1157). These high dopamine concentrations are in accordance with the observed EC_{50} values (table 3). In vivo, therefore, this enzyme would require high concentrations (100 to 10,000 nM) of neuroleptics for inhibition; such high concentrations, however, do not occur clinically. This situation differs considerably from the case of the D_2 receptor, however, which is sensitive to 0.3 nM spiperone and 5000 nM dopamine (fig. 1a). Under physiological conditions in the synaptic cleft, therefore, the low concentration of 0.3 nM spiperone would effectively compete against the much higher concentration of 5000 nM dopamine. Finally, a further problem with the D_1 site as a receptor common to all neuroleptics is that certain antipsychotic drugs, such as sulpiride, metoclopramide, etc., do not inhibit this enzyme (958, 945, 946, 553a).

V. Receptor Sites for Neuroleptic Action

In 1974, two developments occurred that permitted the establishment of a radioreceptor assay for neuroleptic-specific sites (1023). It was first necessary to prepare ^{3}H-haloperidol with as high specific activity as possible, in order to detect neuroleptic-specific receptors in the clinical nanomolar concentration range. Our first preparation of ^{3}H-haloperidol (in 1972 and 1973) was only 0.1 Ci/mmole (995). Our repeated requests in 1973 and 1974, with the encouragement of Dr. P.A.J. Janssen and Dr. J. Heykants, persuaded I.R.E. Belgique (National Institut Voor Radio-Elementen, Fleurus, Belgium; Mr. M. Winand) to prepare ^{3}H-haloperidol at 10.5 Ci/mmole by June 1974 (1023, 995).

The second critical development in 1974 was the synthesis of (+)- and (−)-butaclamol by Humber and Bruderlein (511). Ayerst Research Laboratories soon made these enantiomers available to us, and by April 1975 the first report (1023) on the specific binding of ^{3}H-haloperidol was submitted to the Society for Neuroscience for its annual May deadline. That report (1023) listed the following important IC_{50} values: 2 nM for haloperidol, 3 nM for (+)-butaclamol, over 1000 nM for (−)-butaclamol, 20 nM for chlorpromazine, and 10,000 nM for dopamine.

The excellent stereoselectivity of the (+)-butaclamol

TABLE 3

Dopamine congeners on D_1 sites (dopamine-sensitive adenylate cyclase)

	EC_{50}* (nM)	IC_{50} (nM)
Phenethylamine-related		
Dopamine	500 (714)	
	2,000 (539, 530, 763)	
	3,000 (1038)	
	3,100 (140)	
	3,500 (122)	
	4,000 (571)	
	4,000 (966)	
	4,300 (1040)	
Epinine [N-methyl-dopamine]	1,500 (539)	
	3,400 (1038)	
2-Methyl-dopamine	2,700 (1038)	
N,N-dimethyl-dopamine	5,000 (1038)	
	20,000 (539)	
N,N,N-trimethyl-dopamine	30,000 (539)	
N,N-diethyl-dopamine	40,000 (1038)	
(−)-Noradrenaline	40,000 (539)	
2-Phenyl-dopamine	50,000 (1038)	
α-Methyl-dopamine	100,000 (539)	
	300,000 (1038)	
N-ethyl-dopamine	120,000 (1038)	
N-propyl-dopamine	120,000 (1038)	
6-Methyl-dopamine	300,000 (1038)	
Aminotetralins (AT)		
(+)-6,7-Dihydroxy-2-AT	800 (1259)	
(−)-6,7-Dihydroxy-2-AT	87,000 (1259)	
(±)-6,7-Dihydroxy-2-aminotetralin (ADTN; TL-304)	2,630 (140, 603)	
	3,500 (1262)	
	4,000 (1040, 763)	
(±)-6,7-Dihydroxy-N,N-dipropyl-2-AT (TL-232)	1,000 (1040)	
	6,300 (140)	
(±)-5,6-Dihydroxy-N,N-dipropyl-2-AT	3,300 (140)	
(±)-6,7-Dihydroxy-N-methyl-2-AT (TL-218)	3,000 (1040)	
	5,500 (140)	
(±)-5,6-Dihydroxy-N,N-diethyl-2-AT	4,360 (140)	
(±)-5,6-Dihydroxy-N,N-dimethyl-2-AT (M-7)	30,000 (1040)	
	60,000 (1262)	
(±)-6,7-Dihydroxy-N-propyl-2-AT (TL-196)	30,000 (1040)	
	30,000 (140)	
(±)-6,7-Dihydroxy-N,N-dimethyl-2-AT (TL-99)	40,000 (1040)	
(±)-5,6-Dihydroxy-2-AT	52,000 (140, 603)	
	200,000 (1262)	
(±)-7,8-Dihydroxy-2-AT (JOD-173)	200,000 (1262)	
Aporphines		
Isoboldine	1,000 (1038)	
(−)-Apomorphine	1,500 (571)	>10,000 (761)
	2,000 (539, 761)	
(±)-N-propyl-norapomorphine	4,000 (761)	>10,000 (761)
Nuciferine		4,000 (1038)
Bulbocapnine		5,000 (1038)
		~10,000 (761)
Nuciferoline		7,000 (1038)
S(+)-apomorphine		10,000 (1038)
(±)-Isoapomorphine		>10,000 (761)
Nornuciferine		20,000 (1038)
Roemerine		40,000 (1038)
Ergot alkaloids; miscellaneous		
(±)-3-Methoxy-protoberberine	500 (755)	
Ergocristine	~3,000 (966)	12,000 (966)
d-Lysergic acid diethylamide	~5,000 (966)	4,000 (966)
S-584 metabolite of piribedil	6,000 (539, 765)	
Dihydroergotamine		500 (1076)
Ergotamine	≫100,000 (966)	700 (1076)
		33,000 (966)
Bromocriptine	≫625,000 (718)	750 (1076, 1166)

TABLE 3—*Continued*

	EC_{50}* (nM)	IC_{50} (nM)
Dihydroergocryptine		3,000 (1076)
Dihydroergocristine		3,000 (1076)
Lergotrile	≫100,000 (966)	4,200 (966)
Dihydroergocornine		4,500 (1076)
3,4-Dihydroxynomifensine		8,000 (1259)
Ergonovine		19,000 (966)
Isoquinolines	(see 1041)	

* EC_{50} was the congener concentration required to produce 50% of the maximum stimulation of adenylate cyclase elicited by 100 μM dopamine (rat striatum or limbic tissue), or, in some instances (where partial agonism and antagonism occurred simultaneously), the EC_{50} was the concentration required for 50% of the maximum stimulation by that congener.

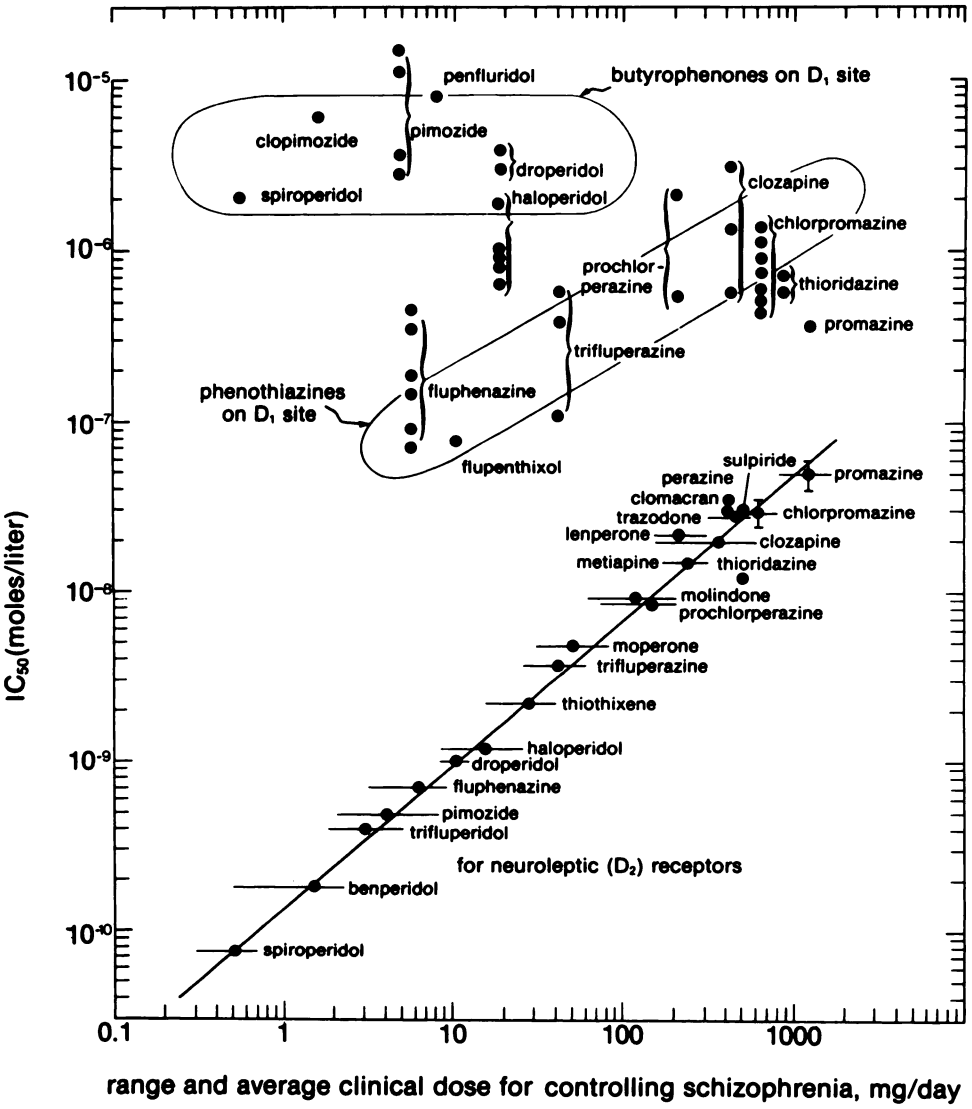

FIG. 2. The average clinical doses of neuroleptics for controlling subacute schizophrenia correlate with the IC_{50} values on D_2 dopamine receptors [i.e. concentrations of neuroleptics that inhibit by 50% the specific binding of ^{3}H-haloperidol to homogenates of calf brain caudate nucleus (1023, 1011, 995, 1005, 1006, 991)]. The clinical doses do not correlate with the neuroleptic IC_{50} values on the D_1 site (i.e. dopamine-sensitive adenylate cyclase); each neuroleptic has several values listed, and the original source of each value may be located in Seeman (991). The ranges and average clinical doses of the neuroleptics may be located through Seeman and coworkers (1002, 1005). The IC_{50} values for the D_2 receptor are similar to those found in the plasma water of patients taking neuroleptics. The conversion of the neuroleptic IC_{50} values (on the D_1 site) to K_i values lowers the values by a factor of 10 or so, but these concentrations are still much higher than those detected in the plasma water of medicated patients.

neuroleptic thus permitted one to distinguish between specific and nonspecific binding of ^{3}H-haloperidol. That is, specific (or stereospecific) binding of ^{3}H-haloperidol was defined as the amount that was inhibited by 100 nM (+)-butaclamol (995). Any binding of ^{3}H-haloperidol that remained in the presence of 100 nM (+)-butaclamol was

considered to be nonspecific (hydrophobic) binding (995). In 1975, therefore, this laboratory mailed samples of the butaclamol enantiomers to other laboratories in order to foster this approach (e.g. see Burt et al., 118).

It is important to note that these data for the binding of ^{3}H-haloperidol (1023) were completely different from those which we found in 1974 (990, 1022) for the specific binding of ^{3}H-dopamine, and were also different from those reported by Burt et al. (120, 121) in 1975 for the specific binding of ^{3}H-dopamine. Dopamine, for example, inhibited the specific binding of ^{3}H-haloperidol at 10,000 nM (1023), as just mentioned. In the case of ^{3}H-dopamine binding, however, we found that dopamine inhibited its own binding by 50% at about 1 nM (1022, 990, 995), while Burt et al. (120, 121) also reported that dopamine was self-inhibited at about 7 nM.

Thus, this enormous difference between the dopamine IC_{50} values of 10,000 nM (against ^{3}H-haloperidol binding; 1023) and of 1 to 7 nM (against ^{3}H-dopamine binding) strongly suggested that these two ^{3}H-ligands were labeling different receptors (1149, 1153). The receptor primarily labeled by ^{3}H-haloperidol is now often termed the D_2 receptor (570), while the *site* labeled by ^{3}H-dopamine has been termed the D_3 site (690a, 691a, 1148). For a time it had been argued that perhaps these two ^{3}H-ligands actually bound to the same receptor, such that ^{3}H-dopamine attached to the agonist state while ^{3}H-haloperidol labeled the antagonist state (233). It is now clear, however, that these ^{3}H-ligands label separate binding sites, as reviewed in section VI (also see discussions in 373, 30, 644, 1083, 1133).

The clinical significance of specific ^{3}H-haloperidol binding (1023, 995) was apparent from the outset, for two reasons. The first reason was that the binding site for ^{3}H-haloperidol had a value for haloperidol IC_{50} of 2 nM, which was in good agreement with the value found in the serum water of patients receiving the drug (table 2). Earlier work (1131), with ^{14}C-fluphenazine to detect neuroleptic-specific sites, was not successful since the neuroleptic IC_{50} values were between 4,600 and 380,000 nM, values too high to be clinically meaningful. The second reason was that the IC_{50} values for the various neuroleptics correlated with the clinical potencies of these drugs (995, 236, 742; fig. 2).

VI. Types of ^{3}H-Ligands for Dopamine Receptors

There are now a variety of dopaminergic ^{3}H-ligands available for labeling various types of dopaminergic binding sites, as listed in table 4. The most suitable ^{3}H-ligand for the D_1 site is ^{3}H-*cis*-flupenthixol (520–522b), where there is an excellent correlation between the IC_{50} values for neuroleptics on dopamine-sensitive adenylate cyclase and the IC_{50} values on the binding of ^{3}H-*cis*-flupenthixol (520).

D_2 receptors can be labeled not only by ^{3}H-haloperidol (1023, 1011, 995, 1203, 118, 233, 238, 240) but also by many other ^{3}H-neuroleptics, including ^{3}H-spiperone (626, 856, 465, 243, 256), ^{3}H-pimozide (977, 59), ^{14}C-tiapride (779), ^{3}H-halopemide (705), ^{3}H-domperidone (723, 628, 59a), ^{3}H-(±)-sulpiride (1139, 554a, 554b), and ^{3}H-thioproperazine (88b). Although all neuroleptics inhibit the D_2 receptor (fig. 2), some ^{3}H-neuroleptics have a somewhat higher affinity for other sites as well. For example, ^{3}H-clozapine has a high affinity for muscarinic binding sites (467), while, as already mentioned, ^{3}H-*cis*-flupenthixol has a higher preference for the D_1 site.

D_2 and D_4 sites can be labeled by fat-soluble ^{3}H-agonists, including ^{3}H-N-propylnorapomorphine (1153, 241), ^{3}H-apomorphine (406, 1007, 1016, 1024, 668, 669, 242, 250a), ^{3}H-RU-24213 (or N-propyl, N-phenethyl-*m*-tyramine; 618, 295a), and the ^{3}H-ergot agonists, such as ^{3}H-bromocriptine (196a), ^{3}H-pergolide (1254), ^{3}H-dihydroergocryptine (1158, 198), ^{3}H-lisuride (371a), and ^{3}H-lysergic acid diethylamide (LSD) (1240, 302, 303, 1099).

Since often there are multiple binding sites in the brain for each of these ^{3}H-ligands, it is sometimes necessary to add other receptor-blocking drugs to the incubation mixture in order to prevent the ^{3}H-ligand from binding to those receptors that are not under study (1159, 1158, 1153, 1151, 1239, 1240). For example, in order to label D_2 receptors by ^{3}H-LSD, ^{3}H-bromocriptine, or by ^{3}H-dihydroergocryptine, it is necessary to add excess concentrations of phentolamine and/or serotonin to preclude the binding of these ^{3}H-ligands to adrenoceptors and serotonin sites (1158, 302, 1240, 1246, 196a). Such procedures result in similar IC_{50} values, as demonstrated in table 5 for three very different types of ^{3}H-ligands.

The example in table 5, therefore, showing a similar pattern of IC_{50} values for the binding of three ^{3}H-ligands (^{3}H-antagonist, ^{3}H-agonist-antagonist, and ^{3}H-agonist, respectively), illustrates that it is *not* necessary to refer to a binding site as an "agonist site" or as an "antagonist site." The general pattern or profile of drug IC_{50} values will generally be similar for any particular binding site whether one employs an agonist or antagonist type of ^{3}H-ligand.

Finally, there are ^{3}H-ligands that label D_3 sites. These binding sites have a high affinity for dopamine, with dissociation constants of between 1 and 9 nM (1022, 690, 690a, 691a, 1148). The sites can be labeled not only by ^{3}H-dopamine, but also by ^{3}H-(±)-6,7-dihydroxy-2-aminotetralin (ADTN) (1024), ^{3}H-N-propyl-norapomorphine (1153), ^{3}H-LSD (1240), or by ^{3}H-apomorphine (1007, 1148, 691b).

VII. ^{3}H-Ligands for in Vivo Analysis of Dopamine Receptors

In order to measure dopamine receptors and neuroleptic receptors in vivo, it is necessary to have ^{3}H-ligands with a very high affinity for these receptors. The most convenient ^{3}H-ligand for this purpose is ^{3}H-spiperone (623, 625, 626, 485, 803, 608, 804, 592), although ^{3}H-pimozide (59, 977), ^{3}H-reserpine (802), and ^{14}C-tiapride (779) have also been used. ^{3}H-Domperidone is highly

TABLE 4

^{3}H-ligands for dopamine receptors and other sites

	K_D (nM)	Dopamine IC_{50} (nM)	Tissue	Early Refs.
For D_1 sites				
^{3}H-flupenthixol	3.8	3,400	Rat striatum	(521, 522b)
For D_2 receptors				
^{3}H-apomorphine	2	300*	Rat striatum	(242, 406, 669)
^{3}H-dihydroergocryptine	0.5	650	Calf caudate	(165, 1158)
^{3}H-(±)-N-propylnorapomorphine		700	Calf caudate	(1153)
^{3}H-(±)-sulpiride	27	1,200	Rat striatum	(1139)
^{3}H-haloperidol	2.7	~2,000	Striata	(1011, 1023, 995)
^{3}H-pergolide	2.8	~2,000	Rat striatum	(1254)
^{3}H-lisuride	0.5	7,000	Rat striatum	(371a)
^{3}H-bromocriptine	0.43	8,500	Calf caudate	(196a)
^{3}H-spiperone	0.06–0.2	~10,000*	Striata	(350, 626, 856)
^{3}H-domperidone	0.7	12,000	Striatum	(59a, 723, 628)
^{3}H-lysergic acid diethylamide	0.5	20,000	Snail ganglia	(302)
^{3}H-RU-24213†	25	~100,000	Bovine striatum	(618, 295a)
^{3}H-pimozide	?	?	Mouse striatum	(977)
^{3}H-halopemide	?	?	Rat brain	(705)
^{3}H-thioproperazine	0.3	?	Rat striatum	(88b)
^{3}H-clopimozide	?	?	Rat brain	(628)
For D_3 Sites				
^{3}H-dopamine	2.3	2–5*	Striata	(1022, 690a)
^{3}H-(±)-6,7-dihydroxy-2-aminotetralin	1	3	Calf caudat	(1024)
^{3}H-N-propylnorapomorphine		3.5	Calf caudate	(1153)
^{3}H-lysergic acid diethylamide		3.5	Calf caudate	(1240)
^{3}H-apomorphine	2.1	~7	Striata	(1007, 1148)
For other sites				
^{35}S-chlorpromazine				(534)
^{11}C-chlorpromazine				(206a)
^{14}C-fluphenazine	4,900	3×10^7	Rat striatum	(1131)
^{3}H-clozapine	1.3	≫10,000	Rat brain	(467)
^{3}H-dihydroergotamine				(197, 198)
^{14}C-tiapride			Rat brain	(779)

* See other tables for range of values.

†^{3}H-N-propyl-N-phenethyl-*m*-tyramine.

TABLE 5

IC_{50} values (nM) on ^{3}H-agonist and ^{3}H-antagonist binding to D_2 receptors (calf caudate)

^{3}H-Ligand	^{3}H-Spiperone	^{3}H-Dihydro-ergocryptine	^{3}H-Bromo-criptine
Conc.	0.15 nM	0.7 nM	0.2 nM
Ref.	(196a)	(1158)	(196a)
Phentolamine conc.	0 nM	500 nM	1000 nM
Binding defined by	1 μM spip.*	1 μM (+)-B	1 μM (+)-B
Spiperone	0.7	0.7	0.8
Pimozide	4.4	2.4	1.9
Haloperidol	18	16	12
Clozapine	300	200	220
Apomorphine	1350	250	970
Dopamine	5400 (243)	4500	8500

* Abbreviations used are: spip., spiperone; +B, (+)-butaclamol.

selective for dopamine receptors (723), but it does not permeate the blood-brain barrier (628, 977).

An indirect method for measuring dopamine receptors in vivo is to use the ex vivo approach. This involves administering a nonradioactive drug to the animal, killing the animal some time later, and measuring the amount of ^{3}H-ligand that can then be bound to the tissue after its removal from the animal (112, 628).

A third approach, which may be of enormous clinical use, is that of positron emission tomography. This requires such positron-emitting ligands as ^{11}C-chlorpromazine (206a) or ^{18}F-haloperidol (1133a).

VIII. Binding Properties of ^{3}H-Ligands to D_2 Receptors

As discussed more extensively elsewhere (1011, 995), successful identification of brain dopamine receptors by a ^{3}H-ligand requires the fulfillment of the following criteria:

A. Saturability

The ^{3}H-ligand should bind to the tissue or homogenate in a saturable fashion, thus permitting the calculation of a dissociation constant, K_D. These values for various dopaminergic ^{3}H-ligands are listed in tables 6 and 7.

B. Stereoselectivity

Since many ^{3}H-ligands are highly fat-soluble and membrane-soluble (table 1), it is essential to distinguish between specific and nonspecific (usually hydrophobic) binding of the ^{3}H-ligand. In developing the radioreceptor assay for ^{3}H-haloperidol, the enantiomers of (+)- and (−)-butaclamol were exceedingly helpful in this regard,

since enantiomers have identical solubilities in hydrophobic media, including biological membranes (942, 994, 987). As summarized in table 8, (+)-butaclamol is generally 100 to 10,000 times more potent than (−)-butaclamol in inhibiting the binding of various dopaminergic ^{3}H-ligands, particularly the ^{3}H-neuroleptics. Hence, as originally developed (995), it has become useful to define the specific binding of a ^{3}H-neuroleptic as that which can be

TABLE 6

*Receptor density (B_{max}) and K_D for dopaminergic ^{3}H-ligands (striatum)**

Striatum*	^{3}H-Ligand	B_{max} (fmol/mg pro.)		K_D (nM)	Defined by nM Drug	Ref.
Rat μs.	^{3}H-spip.	(1,700)		0.14	2,000 SSB	(671)
Rat	^{3}H-spip.	600		0.15	100 B	(504)
Rat	^{3}H-spip.	510		0.15	300,000 DA	(506)
Rat	^{3}H-spip.	456		0.03	100 B	(856)
Rat	^{3}H-spip.	335		0.36	100 B	(841)
Rat	^{3}H-spip.	290		1.1	10,000 Halo.	(103)
Rat	^{3}H-spip.	266†	313	0.36	1,000 B	(250a)
Rat	^{3}H-spip.	194†		0.5	10,000 DA	(311)
Rat	^{3}H-spip.	169		0.34	100 B	(856)
Rat	^{3}H-spip.	~160†		0.44	1,000 B	(975)
Rat	^{3}H-spip.	135		0.24	10,000 Halo.	(103)
Rat μs.	^{3}H-halo.	(1,100)		1.6	2,000 SSB	(671)
Rat	^{3}H-halo.	530		3	100,000 DA	(88a)
Rat	^{3}H-halo.	510		2.3	300,000 DA	(506)
Rat	^{3}H-halo.	~290†	302	2.3	100 B	(667)
Rat	^{3}H-halo.	102		2.1	2,000 B	(769)
Rat	^{3}H-halo.	~78			1,000 B	(112)
Calf	^{3}H-spip.	320		0.1	100 Spip.	(465)
Calf	^{3}H-spip.	~165†	208	0.3	1,000 B	(243)
Calf	^{3}H-spip.	140†		0.38	1,000 B	(250a)
Calf	^{3}H-halo.	140		2.7	100 SSB	(1007)
Calf	^{3}H-halo.	~120†	120	3.3	100 B	(118)
Calf	^{3}H-halo.	~100†		3.2	100 B	(1136)
Human (c)	^{3}H-spip.	270		0.25	100 B	(350)
Human (c)	^{3}H-spip.	109†	196	0.38	1,000 B	(250a)
Human (c)	^{3}H-spip.	167			100 B	(842)
Human (p)	^{3}H-spip.	239			100 B	(350)
Monkey	^{3}H-spip.	120		1.1	1,000 S	(1137)
Mouse	^{3}H-domp.	443		0.95	?	(977)
Mouse	^{3}H-domp.	386		0.96	500 Domp.	(723)
Mouse	^{3}H-pimo.	~270†			?	(977)
Rat syn.	^{3}H-DA	>40		0.6	100 DA	(1022)
Rat	^{3}H-DA	440		10	1,000 DA	(88a)
Rat	^{3}H-DA	226	250	28	30,000 apo.	(254)
Rat	^{3}H-DA	84		2.3	1,000 DA	(1148)
Rat	^{3}H-apo.	~440†		9.2	10,000 DA	(667)
Rat	^{3}H-apo.	73	182	2.1	1,000 DA	(1148)
Rat	^{3}H-apo.	32		1.3	1,000 B	(808)
Rat	^{3}H-ADTN	100		6	1,000 B	(249)
		230		35	1,000 B	(249)
Calf	^{3}H-DA	~205†		17	1,000 DA	(118)
Calf	^{3}H-DA	~140†	130	15	1,000 DA	(1136)
Calf	^{3}H-DA	45		1.3	1,000 B	(1007)
Calf	^{3}H-apo.	148		2.6	500 DA	(1148)
Calf	^{3}H-apo.	~134†		4.4	1,000 DA	(1136)
Calf	^{3}H-apo.	124		3.5	1,000 SSB	(1007)
Calf	^{3}H-ADTN	100		1	500 ADTN	(1024)
Calf	^{3}H-ADTN	180		9	1,000 DA	(258)
Calf	^{3}H-DHEC	138		0.55	1,000 B*(ph.)	(1158)
Bovine	^{3}H-NPA	110		1.5	1,000 B	(241)
Human (p)	^{3}H-ADTN	42			1,000 DA	(258)
Human (p) SZ	^{3}H-ADTN	49			1,000 DA	(258)
Dog	^{3}H-DA	16,000			1 mM DA	(954)

* Abbreviations used are: Rat, rat striatum; calf, calf caudate; human (c), human caudate; human (p), human putamen; dog, dog caudate; mouse, mouse striatum; monkey, monkey caudate; bovine, bovine caudate; SZ, tissue from schizophrenic patient; spip., spiperone; halo., haloperidol; domp., domperidone; pimo., pimozide; APO., apomorphine; DA, dopamine; ADTN, 6,7(OH)$_2$-2-aminotetralin; NPA, N-propylnorapomorphine; DHEC, dihydroergocryptine; B, (+)-butaclamol; SSB, stereospecific binding; using (+)- and (−)-butaclamol; ph, phentolamine; μs, microsomes; syn., synaptosomes; c, caudate; p, putamen.

† Assuming 15% of tissue is protein.

TABLE 7

*Receptor density (B_{max}) and K_D for dopaminergic ^{3}H-ligands (nonstriatal tissues)**

Tissue	^{3}H-Ligand	B_{max} (fmol/mg pro.)	K_D (nM)	Defined by nM Drug	Ref.
Anterior pituitary					
Sheep	^{3}H-spip.	343	0.9	1,000 SSB	(255)
Steer	^{3}H-spip.	210	0.38	1,000 SSB	(255)
Bovine	^{3}H-spip.	66	0.49	1,000 B	(746)
Steer	^{3}H-spip.	~47*	0.2	1,000 B	(243)
Sheep	^{3}H-DHEC	373	5.2	5,000 Apo.	(254)
Bovine	^{3}H-DHEC	320	2.2	10,000 B	(164)
Rat	^{3}H-DA	408	50	50,000 Apo.	(254)
Sheep	^{3}H-DA	267	80	80,000 Apo.	(254)
Bovine	^{3}H-DA	336	0.4	10,000 DA	(131)
		2340	47	10,000 DA	(131)
Median eminence					
Sheep	^{3}H-spip.	107	2.9	1,000 SSB	(255)
Steer	^{3}H-spip.	55	1.2	1,000 SSB	(255)
Sheep	^{3}H-DHEC	229	3.9	5,000 Apo.	(254)
Olfactory tubercle					
Calf	^{3}H-halo.	~28*	1.6	100 B	(1136)
Calf	^{3}H-DA	~100	25.9	1,000 DA	(1136)
Calf	^{3}H-Apo.	~87*	10.8	1,000 DA	(1136)
Rat	^{3}H-spip.	~180	0.25	10,000 Sulp.	ud
Rat	^{3}H-Apo.	~70	2.5	10,000 DA	ud
Rat	^{3}H-DA	~40	1.4	10,000 Apo.	ud
Cerebral cortex					
Rat	^{3}H-halo.	200	2.3	300,000 DA	(506)
Rat (F)	^{3}H-spip.	47	0.02	100 B	(856)
		279	0.35	100 B	(856)
Rat (L)	^{3}H-spip.	260	0.25	100 B	(504)
Rat (L)	^{3}H-halo.	240	3	100,000 DA	(88a)
Rat (L)	^{3}H-DA	180	10	1,000 DA	(88a)
Calf (F)	^{3}H-spip.	75	0.57	500 S	(1020)
Calf (F)	^{3}H-spip.	54	0.33	10,000 LSD	(1020)
Human (O)	^{3}H-spip.	92		100 B	(350)
Human (F)	^{3}H-spip.	80		100 B	(350)
Monkey	^{3}H-spip.	~60*	1	1,000 S	(1137)
Cerebellum					
Human	^{3}H-spip.	15		100 B	(350)
Rat	^{3}H-halo.	60	2.3	300,000 DA	(506)
Globus pallidus					
Human	^{3}H-spip.	101		100 B	(350)
Hypothalamus					
Human	^{3}H-spip.	56–76		100 B	(350)
Hippocampus					
Human	^{3}H-spip.	18		100 B	(350)
Substantia nigra					
Rat	^{3}H-spip.	18	0.4	300,000 DA	(892)
Human	^{3}H-spip.	14		100 B	(350)
Thalamus					
Human	^{3}H-spip.	18		100 B	(350)

* Assuming 15% of tissue was protein. F, frontal cortex; O, occipital cortex; L, limbic cortex; sulp., sulpiride; LSD, *d*-lysergic acid diethylamide; ud, D. Helmeste and P. Seeman (unpublished data). Other abbreviations as in table 6.

inhibited by an excess concentration of (+)-butaclamol, but which is not inhibited by a matching concentration of (−)-butaclamol (fig. 3).

For defining specific binding of ^{3}H-neuroleptics, dexclamol (1021) will do just as well as (+)-butaclamol. Other neuroleptic enantiomers are also available (196, 903, 1021), including (±)-sulpiride, where the (−)-form is over 100 times more potent than the (+)-form (1074, 554, 788a, 876, 482, 553a). The optical enantiomers are better than *cis-trans* isomers (260, 262), since the latter type of isomers may not always have identical fat solubilities.

This criterion of stereoselectivity assists only in separating the nonspecific (hydrophobic) binding of the ^{3}H-ligand. This criterion alone does not assist in identifying whether the specific binding sites are dopaminergic, adrenergic, etc. While it is true that (+)-butaclamol has the highest stereoselectivity for dopaminergic sites (table 8), it also has very high stereoselectivity for serotoninergic sites (table 8; 321).

C. Regional Localization

In principle it would seem reasonable to expect a correlation between the density of dopaminergic receptor sites and the dopamine content for a number of different

TABLE 8

*Butaclamol stereoselectivity on ^{3}H-ligand binding to tissues**

Tissue	Ligand	IC_{50} (nM)		Stereo-selectivity†	Ref.
		(+)-Butacl.	(−)-Butacl.		
Dopamine receptors					
Anterior pituitary					
Bovine	^{3}H-DHEC	6	100,000	17,000	(164)
Sheep	^{3}H-spip.	4.1	43,000	11,000	(255)
Bovine	^{3}H-spip.	2.1	20,000	9,500	(243)
Sheep	^{3}H-DHEC	5.4	6,500	1,200	(254)
Striatum					
Bovine	^{3}H-spip.	2.1	30,000	14,000	(243)
Calf	^{3}H-spip.	5	40,000	8,000	(1020)
Rat	^{3}H-spip.	14	100,000	7,200	(677)
Rat	^{3}H-spip.	0.6	5,000	>5,000	(856)
Human (c)	^{3}H-spip.	0.9	1,800	2,000	(896)
Rat	^{3}H-spip.	15	10,000	670	(671)
Rat	^{3}H-spip.	4	2,500	500	(506)
Monkey (c)	^{3}H-spip.	31	>10,000	>300	(1137)
Rat	^{3}H-spip.	6.6	900	136	(896)
Rat	^{3}H-FPT	6.8	61,000	9,000	(520)
Rat	^{3}H-halo.	1.5	11,000	7,300	(520)
Calf	^{3}H-halo.	1	1,300	1,300	(118)
Calf	^{3}H-halo.	1.3	1,300	1,000	(233)
Rat syn.	^{3}H-halo.	3	>1,000	>300	(1023)
Rat syn.	^{3}H-halo.	1	300	300	(995)
Mouse	^{3}H-domp.	45	150,000	3,300	(723)
Rat	^{3}H-ADTN	4	16,000	4,000	(1193)
Rat	^{3}H-ADTN	6	10,000	>1,700	(249)
Rat syn.	^{3}H-DA	70	30,000	500	(995)
Bovine	^{3}H-DA	320	>6,100	>200	(667)
Calf	^{3}H-DA	125	17,000	140	(121)
Calf	^{3}H-DA	100	16,000	160	(118)
Calf	^{3}H-DA	130	>10,000	>80	(233)
Calf	^{3}H-apo.	80	20,000	250	(1007)
Calf	^{3}H-apo.	200	>40,000	200	(1136)
Calf	^{3}H-DHEC; ph	5	≫1,000	≫200	(1158)
Helix gangl.	^{3}H-LSD	4.6	54,000	12,000	(303)
Rat brain	^{3}H-spip.	1.6	8,000	5,000	(350)
Serotonin receptors					
Cortex					
Rat (F)	^{3}H-spip.	0.6	>5,000	5,000	(856)
Human (F)	^{3}H-spip.	28	130,000	4,700	(896)
Rat (F)	^{3}H-spip.	46	3,500	760	(710)
Monkey (F)	^{3}H-spip.	29	>10,000	>300	(1137)
Rat (F)	^{3}H-spip.	180	10,000	56	(671)
Rat	^{3}H-LSD	50	7,000	140	(321)
Rat	^{3}H-5HT	1,000	8,000	8	(321)
Striatum					
Calf	^{3}H-LSD	80	≫1,000	≫125	(1239)
Calf	^{3}H-5HT	120	1,000	10	(1237)
Beta-adrenoceptors					
Calf striatum	^{3}H-DHA	1,000	1,000	1	(991)
Cholinergic receptors					
Rat forebrain	^{3}H-QNB	100,000	40,000	<1	(321)
Opiate receptors					
Rat forebrain	^{3}H-NAL	18,000	20,000	1	(321)
Nonstereoselective neuroleptic sites					
Neuroblastoma	^{3}H-spip.	>10,000	30,000	<3	(465)

* Abbreviations used are: FPT, *cis*-flupenthixol; 5HT, serotonin; NAL, naloxone; DHA, dihydroalprenolol; QNB, quinuclidinyl benzilate; gangl., ganglion.

† Stereoselectivity ratio, [(−)-butaclamol IC_{50}]/[(+)-butaclamol IC_{50}].

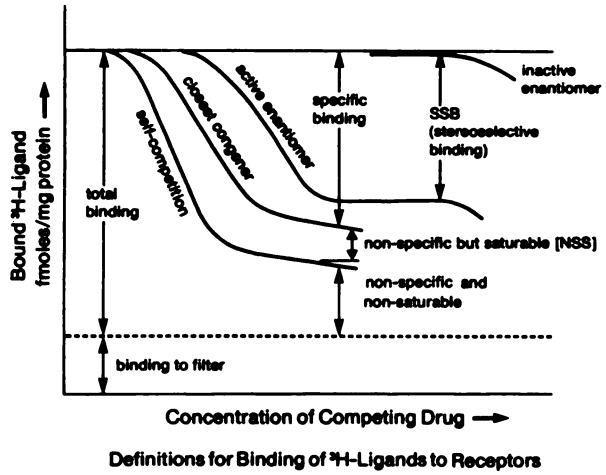

FIG. 3. Definitions for components of binding of ^{3}H-ligands to tissue. A small amount of the ^{3}H-ligand generally binds to the glass fiber filter (commonly Whatman GF/B filters). Although the total binding to the tissue is composed of specific and nonspecific binding, there are two types of nonspecific binding. The amount of ^{3}H-ligand bound in the presence of an excess concentration of the *same* nonradioactive compound is defined as the nonspecific and nonsaturable component ("self-competition" in this figure), and this type of binding has been reviewed (987, 617, 615). There are also nonspecific but saturable sites (NSS sites), defined as that amount of ^{3}H-ligand bound in the presence of an excess concentration of the *closest congener* (670). It is best, therefore, to define specific binding as that amount of bound ^{3}H-ligand that can be inhibited by an excess concentration of the *closest congener*, thus precluding all of the nonspecific sites. Stereoselective binding (SSB) is defined as that amount of bound ^{3}H-ligand that can be inhibited by the presence of an active enantiomer but not by an inactive enantiomer. Specific binding and stereoselective binding are usually identical. They are sometimes not identical when one uses an antagonist ^{3}H-ligand with an agonist compound to define specific binding.

brain regions (tables 6 and 7). There are instances, however, where a high density of receptors (e.g. alpha$_2$-adrenoceptors, using ^{3}H-clonidine) is not related to the low level of noradrenaline (e.g. in striatum).

D. Drug Profile

In order for the binding of a ^{3}H-ligand to be termed "dopaminergic," it is essential that dopamine be the most effective endogenous compound to displace that ^{3}H-ligand. In other words, dopamine should be more potent than noradrenaline (or adrenaline), which should in turn be more potent than serotonin and other neurotransmitters. The data for these IC_{50} values are given in tables 9 and 10, all indicating a dopaminergic profile for those ^{3}H-ligands listed. It has been claimed by Lahti et al. (632) that there is endogenous material of molecular weight less than 500, other than dopamine, that inhibits the binding of ^{3}H-spiperone. Although such inhibitory components have been reported by Leysen et al. (673, 678), they are of very high molecular weight (over 200,000) and they are not specific for any receptor.

In the cerebral cortex and hippocampus, however, serotonin is more effective than dopamine in inhibiting the binding of ^{3}H-spiperone (676, 674, 672, 248, 1020), as summarized in table 11. It had also been noted that there was a tryptaminergic component in the binding of ^{3}H-haloperidol (1236).

It is clear, therefore, that ^{3}H-neuroleptics can label both dopamine receptors (D_2 receptors) and serotonin receptors (S_2 receptors; 862, 1020). It thus becomes essential to separate these components when reporting data on ^{3}H-neuroleptic binding.

E. Correlates of ^{3}H-Neuroleptic Binding Properties

In order for a binding site to be termed a "receptor," it would be desirable to show some sort of biological correlation or function unique for that binding site. As already illustrated in figure 2, the IC_{50} values for neuroleptics (on ^{3}H-haloperidol binding) correlate with the clinical antipsychotic doses (995, 1067, 235, 238, 245, 246, 648). High concentrations of beta-adrenoceptor-blocking drugs (102) and antidepressants (1049) also inhibit the ^{3}H-neuroleptic/dopamine receptor (D_2 receptor); thus, very high doses of these drugs may be neuroleptic-like [see refs. in Bremner et al. (102)].

Although it is convenient to use calf caudate tissue as a source of D_2 receptors, this tissue is not as sensitive to sulpiride as human or rat striatum (648, 691b, 686a). Despite these species differences, the ^{3}H-neuroleptic radioreceptor assay is convenient for screening potentially useful neuroleptics (610, 1112, 662). Further correlates of the D_2 receptor are given in section XIV.

F. Appropriate Absolute Concentrations for IC_{50} Values

In addition to meaningful correlations, it is desirable that the absolute concentrations of the IC_{50} values for agonists and antagonists be appropriate. In the case of the D_2 receptor labeled by ^{3}H-haloperidol, for example, all the neuroleptic IC_{50} values have absolute levels that correspond to those detected in the serum water of medicated patients (table 2).

Since the IC_{50} values become higher as one raises the concentration of ^{3}H-ligand used (174, 169, 465), some reports list the K_i values instead of the IC_{50} values (see legend to table 9). Although accurate K_i values would ultimately be desirable, it is very difficult at present to derive reliable K_i values. There are several reasons for this difficulty. First, since neuroleptics are very surface-active (see section III A), they adsorb to the tissue and the surfaces used in the receptor assay, such that the free concentration of neuroleptic or ^{3}H-ligand is much lower than that added to the test tube (465). Appropriate corrections for this can result in a lowering of the K_D by a factor of 3 in the case of ^{3}H-spiperone (465). A second reason is that a ^{3}H-ligand, such as ^{3}H-spiperone, may bind to more than one site (e.g. D_2 as well as S_2 sites; see section IX E on multiple binding sites), such that rather complicated corrections need to be applied in order to get the K_i for a single receptor.

TABLE 9

Inhibition of ^{3}H-neuroleptic binding (to brain striatum) by neuroleptics

	^{3}H-Spiperone (IC_{50} (nM))			^{3}H-Haloperidol IC_{50} (nM)	
	Rat	Calf	Human	Rat	Calf
p-F-spiperone	1.8 (671)			0.4 (671)	0.05 (1005)
Spiperone	0.5 (975)	0.5 (465)	0.3 (648)	0.17 (520)	0.07 (1005)
	0.8 (s)*	0.8 (243)		0.3 (995)	0.44 (118)
	1.3 (676)	3 (919)		0.4 (676)	
		3.5 (644)		0.6 (429)	
Benperidol	4.5 (671)	0.1 (s)	1 (648)	0.9 (671)	0.2 (1005)
					0.6 (118)
Fluphenazine	2 (250a)	2.3 (s)	3 (250a)	3.4 (520)	0.7 (1005)
	8 (350)	5 (250a)	4 (648)	16 (671)	1.5 (118)
	14 (s)				
	39 (671)				
Droperidol	8 (671)	1 (s)		2 (671)	0.8 (1005)
				3 (520)	1.8 (118)
Clofluperol				0.4 (520)	0.9 (118)
Fluspirilene		54 (919)		3.1 (520)	1.1 (118)
		95 (644)			
Haloperidol	4.8 (856)	10 (243)	5 (648)	1 (376)	1.2 (1005)
	5 (250a)	10 (250a)	5 (250a)	1.2 (667)	2.5 (118)
	5.6 (896)	15 (919)		1.4 (852)	
	7.5 (s)	19 (s)		2 (1023)	
	10 (350)			3 (995)	
	11 (504)			3 (520)	
	20 (676)			3.2 (676)	
	34 (231)			3.3 (269)	
				4 (102)	
				4 (88a)	
Domperidone	4.5 (s)	6 (s)		1.4 (628)	
cis-Flupenthixol	3 (896)			1.5 (520)	1.7 (118)
	14 (s)			20 (671)	0.4 (1005)
	59 (671)				
trans-Flupenthixol				120 (520)	300 (1005)
cis-thiothixene	28 (671)	17 (s)	3 (648)	0.7 (520)	2.2 (1005)
				6.3 (671)	2.6 (118)
				14 (102)	
trans-Thiothiexene				250 (102)	250 (118)
Bromoperidol	19 (671)			1.7 (520)	2.5 (118)
				16 (671)	
Clopimozide	93 (671)			7.9 (671)	
(+)-butaclamol	2 (350)	2.2 (243)		1.3 (429)	1 (118)
	3.3 (s)	3.5 (s)		3.9 (667)	3 (1023)
	20 (671)			6.5 (102)	
				10 (671)	
				18 (269)	
(−)-Butaclamol	10,000 (350)	30,000 (243)		6,000 (102)	1,200 (118)
	450,000 (s)	40,000 (s)		21,000 (269)	2,000 (995)
Trifluoperazine	28 (671)	58 (s)		3.4 (520)	3.5 (1005)
				10 (671)	3.7 (118)
Triflupromazine					3.7 (118)
S(+)-octoclothepin		4.5 (1021)			
(±)-Octoclothepin	10 (671)			3.2 (671)	
R(−)-octoclothepin		40 (1021)			
Trifluperidol	14 (671)	4.7 (s)	1 (648)	1.6 (671)	1.7 (118)
					4 (1005)
Teflutixol					4.5 (118)
					3.3 (118)
Moperone	36 (671)		10 (648)	10 (671)	4.5 (1005)
Pimozide	10 (350)	24 (s)	5 (648)	1 (102)	1.4 (118)
	10 (504)			1.3 (520)	5 (1005)
	16 (671)			3.2 (671)	
cis-Clopenthixol					5.4 (118)
trans-Clopenthixol					154 (118)
Fluanisone					6.8 (118)
Chlorprothixene (*cis*)					7.7 (118)
Prochlorperazine		55 (s)	20 (648)		9 (1005)

TABLE 9—*Continued*

	^{3}H-Spiperone (IC_{50} (nM))						^{3}H-Haloperidol IC_{50} (nM)			
	Rat		Calf		Human		Rat		Calf	
Thioridazine	40	(250a)	50	(250a)	30	(250a)	19	(520)	13	(1005)
	220	(671)			40	(648)	40	(671)	26	(118)
Molindone	200	(250a)	1,000	(250a)	150	(648)	290	(520)	9	(118)
					200	(250a)			120	(118)
Halopemide	130	(671)					10	(671)		
Metiapine	10	(671)			70	(648)	10	(671)	2.5	(118)
(Methiothepin)									15	(1005)
Penfluridol	63	(671)					25	(671)	9.8	(118)
							28	(520)		
Azaperone									18	(118)
Loxapine	101	(231)					17	(520)		
7-OH-loxapine	22	(231)								
Clozapine	249	(504)	400	(250a)	150	(648)	210	(520)	20	(1005)
	300	(250a)	700	(s)	300	(250a)	400	(671)	210	(118)
	474	(231)								
	1,300	(671)								
Lenperone					22	(648)			20	(1005)
Chlorpromazine (CPZ)	10	(250a)	20	(250a)	10	(250a)	7	(240)	18	(118)
	27	(s)	23	(243)	30	(648)	12	(852)	29	(1005)
	46	(504)	41	(s)			12	(520)		
	140	(676)	74	(919)			20	(1023)		
	171	(231)	78	(644)			120	(995)		
							130	(676)		
3,7-$(OH)_2$-CPZ							2.8	(240)		
3,8-$(OH)_2$-CPZ							270	(240)		
des-Methyl-CPZ							20	(240)		
Clebopride	31	(553)					8.7	(522b)		
							20	(553)		
Sultopride	230	(553)					130	(522b)		
							180	(553)		
(−)-Sulpiride	122	(s)					100	(1074)		
	360	(553a)								
(±)-Sulpiride	250	(s)	2,000	(919)	400	(648)	79	(671)	30	(1006)
	600	(250a)	6,000	(250a)	600	(250a)	160	(520)		
	870	(671)	4,000	(s)			360	(360)		
	1,000	(553)								
	3,800	(504)								
(+)-Sulpiride	3,000	(s)					30,000	(1074)		
	11,000	(553a)								
Promazine	100	(671)	260	(s)	200	(648)	170	(520)	45	(1005)
	300	(250a)	300	(250a)	300	(250a)	250	(671)	128	(118)
Metoclopramide	660	(553)	900	(919)	1,000	(250a)	60	(102)		
	1,000	(250a)	3,000	(250a)			110	(671)		
	1,600	(671)					420	(553)		
	1,900	(504)					830	(520)		
Melperone									50	(1005)
Pipamperone	130	(671)					320	(671)	54	(118)
							360	(520)		
Promethazine							830	(520)	420	(118)
									2,000	(1005)
Phenylethylamine-related										
Epinine			730	(s)					930	(118)
N-P-3-(3-OH-ϕ†)-piperidine (3PPP)			4,200	(s)						
Dopamine	1,200	(269)	5,400	(243)	10,000	(250a)	340	(521)	720	(852)
	2,200	(1193)	10,000	(250a)	60,000	(896)	1,000	(88a)	900	(1005)
	2,200	(242)	15,800	(919)	60,000	(710)	1,000	(102)	1,200	(118)
	2,500	(856)	20,000	(1159)			1,000	(676)	7,000	(1159)
	3,000	(250a)	37,000	(s)			2,900	(140)		
	5,800	(896)	47,000	(644)			10,000	(1023)		
	6,300	(671)					30,000	(372)		
	10,000	(506)								
	19,000	(s)								
	20,000	(350)								
	30,000	(372)								

TABLE 9—*Continued*

	^{3}H-Spiperone (IC_{50} (nM))					^{3}H-Haloperidol IC_{50} (nM)			
	Rat		Calf		Human	Rat		Calf	
2-F-dopamine			35,000	(357)					
5-F-dopamine			50,000	(357)					
6-F-dopamine			63,000	(357)					
Phentolamine			6,000	(s)		10,000	(102)	3,500	(118)
Phenoxybenzamine								245	(118)
3-OH-N-DP-tyramine (VI-182)			9,000	(s)					
DP-dopamine	2,500	(671)	10,500	(s)		500	(671)		
(−)-Adrenaline	16,000	(248)	44,000	(243)				4,500	(118)
(+)-Adrenaline								65,000	(118)
(−)-Isoproterenol			>100,000	(243)		200,000	(521)		
Propranolol			>100,000	(243)		100,000	(102)	4,900	(118)
Tolamolol						9,000	(102)		
Alprenolol						15,000	(102)		
(−)-Noradrenaline	21,000	(248)	50,000	(1159)		6,400	(521)	9,000	(852)
	66,000	(140)	66,000	(243)		11,800	(671)	9,800	(118)
	178,000	(671)				200,000	(1023)	15,000	(1159)
	200,000	(s)							
(+)-Noradrenaline			60,000	(s)				37,000	(118)
N-cyclo-P-dopamine			40,000	(s)					
AS-7003			125,000	(s)					
m-Tyramine			190,000	(s)					
p-Tyramine			380,000	(s)					
Serotonin-related and miscellaneous									
Cyproheptadine	257	(504)				79	(676)	114	(118)
	200	(676)							
Imipramine								315	(118)
Benztropine								400	(118)
Piribedil	47	(896)	3,000	(s)		870	(671)		
	2,500	(671)							
Mianserin	2,000	(676)	4,000	(s)		1,600	(676)	1,100	(118)
Cianserine	3,700	(896)				4,000	(676)		
	10,000	(676)							
Pizotifen	500	(676)				250	(676)		
Dimethyltryptamine	8,900	(894)	5,600	(s)					
Diethyltryptamine	10,000	(894)	13,000	(s)					
Harmaline			20,000	(s)					
5-CH_3O-tryptamine	35,000	(248)							
Mescaline			30,000	(s)					
Quipazine	120,000	(896)	40,000	(s)					
Serotonin	41,000	(248)	65,000	(243)		32,000	(676)	60,000	(234)
	44,000	(1193)				70,000	(1023)		
	55,000	(856)				27,000	(521)		
	80,000	(676)				100,000	(995)		
	80,000	(896)							
Bufotenin	35,000	(248)	400,000	(s)		20,000	(671)		
	40,000	(671)							
Tryptamine	82,000	(896)				425,000	(671)		
	89,000	(671)							
Aporphine-related									
Number 6 (1039)			90	(s)					
(−)-N-P-norapomorphine			160	(s)					
(±)-N-P-norapomorphine	110	(s)	120	(s)					
(±)-Number 2 (1039)			200	(s)					
(−)-2,10-11$(OH)_3$-N-P-norapomorphine			240	(s)					
S-number 3 (1039)			330	(s)					
R-Nuciferine (1039)			350	(s)					
R-(−)-apomorphine	40	(250a)	225	(243)		23	(376)	40	(1005)
	80	(242)	400	(250a)		50	(676)	90	(118)
	500	(676)	650	(s)		50	(521)		
	500	(350)	1,100	(644)		56	(852)		
	500	(372)	1,180	(919)		58	(667)		
	800	(269)	m:300	(1137)		500	(372)		
	943	(s)	h:200	(250a)		1,000	(1023)		
	1,000	(506)							

TABLE 9—*Continued*

	^{3}H-Spiperone (IC_{50} (nM))			^{3}H-Haloperidol IC_{50} (nM)	
	Rat	Calf	Human	Rat	Calf
S(+)-apomorphine‡		2,500 (s)			
R-Nornuciferine (1039)		1,000 (s)			
(−)-2,10,11(OH)$_3$-aporphine		1,360 (s)			
(±)-11-OH-N-P-norapomorphine		1,500 (s)			
Bulbocapnine					1,600 (118)
S(+)-aporphine		1,700 (s)			
R(−)-aporphine		8,000 (s)			
R-Roemerine (1039)		3,000 (s)			
(±)-Nuciferoline (1039)		3,000 (s)			
Morphothebaine		4,000 (s)			
R-pukateine (1039)		4,000 (s)			
(±)-10-OH-N-P-norapomorphine		5,400 (s)			
R-apocodeine (1039)		8,000 (s)			
R-number 1 (1039;635)		10,000 (s)			
R-number 4 (1039)		10,000 (s)			
S-glaucine (1039)		10,000 (s)			
S-isoboldine (1039)		10,000 (s)			
TL-301		10,000 (s)			
Iso-apomorphine‡		20,000 (s)			
TL-302		30,000 (s)			
R-laurepukine (1039)		100,000 (s)			
Aminophenanthrene (145a)		100,000 (s)			
Opiates					
Levallorphan	3,000 (269)				
Dextrallorphan	22,000 (269)				
Methadone				4,700 (118)	
Pentazocine	9,000 (269)			6,100 (118)	
Levorphanol	10,000 (269)				
Dextrorphan	140,000 (269)				
Enkephalins (leu;met)	>100,000 (269)				
β-Endorphin	>100,000 (269)				
Morphine	>100,000 (269)				
Naloxone	>100,000 (269)				
Peptides					
TRH	54 (269)				
ACTH 1-39	300 (269)				
Somatostatin	30,000 (269)				
Substance P	80,000 (269)				
LHRH	>100,000 (269)				
Quinolines; indanes					
TL-140		150 (s)			
TL-121		500 (s)			
GJH-166		700 (s)			
TL-98		2,000 (s)			
TL-137		2,400 (s)			
DR-4-7 (DP-aminoindane)		6,400 (s)			
TL-301		100,000 (s)			
TL-302		300,000 (s)			
TL-303		100,000 (s)			
TL-304		70,000 (s)			
TL-305		20,000 (s)			
TL-306		6,000 (s)			
TL-307		6,000 (s)			
TL-308		2,500 (s)			
TL-309		>300,000 (s)			
TL-310		>300,000 (s)			
TL-311		5,000 (s)			
TL-312		4,000 (s)			
Ergot alkaloids		7 (1154)		450 (522b)	1 (118)
Ergocornine	24 (s)	8 (1154)			
Dihydroergocryptine		68 (644)			

TABLE 9—*Continued*

	^{3}H-Spiperone (IC_{50} (nM))					^{3}H-Haloperidol IC_{50} (nM)			
	Rat		Calf		Human	Rat		Calf	
Ergocristine			11	(s)				3	(118)
β-Ergoptine			20	(1154)					
Brom-LSD			21	(s)				7	(118)
Bromocriptine	1.6	(509)	5	(243)		3.5	(429)	4	(118)
	2.7	(975)	35	(s)		8.1	(522b)	50	(s)
	36	(896)	104	(919)		10	(376)		
	38	(s)	240	(644)		22	(667)		
						200	(88a)		
Dihydroergotamine			30	(s)					
β-Ergocryptine			30	(s)					
α-Ergocryptine			50	(1154)		3	(118)		
Ergotamine	40	(671)	65	(1154)		3.3	(522b)		
						4	(671)		
Lisuride	1.8	(509)				5	(372)		
	4.8	(196a)							
	5	(372)							
d-LSD	56	(676)				50	(676)	35	(118)
	315	(s)							
l-LSD								35,000	(118)
Metergoline	19	(509)	60	(s)					
Pergolide	145	(196a)							
Lergotrile	221	(509)	150	(s)		40	(88a)		
						130	(667)		
						560	(249)		
8-Iso-bromocriptine			600	(1154)					
Ergonovine			800	(s)					
Methysergide	77	(896)				500	(676)	79	(118)
	320	(676)	960	(s)					
Ergometrine						4.9	(522b)	280	(118)
d-Lysergic acid amide								680	(118)
2-Aminotetralins									
(−)-5-OH-N,N-DP			190	(s)					
(±)-5-OH-N,N-DP (JGC-174)			290	(s)					
(±)-5,6(OH)$_2$-N,N-DP (TL-102)	125	(676)	490	(s)		16	(676)		
						20	(140)		
(+)-6,7(OH)$_2$[=(+)-ADTN]			1,200	(s)					
(±)-7-OH-N,N-DP			1,450	(s)					
(±)-6,7(OH)$_2$-N,N-DP (TL-232)	316	(671)	1,900	(s)		63	(671)		
						76	(140)		
(±)-5,6(OH)$_2$-N,N-DE (JM-18)			2,100	(s)		101	(140)		
(+)-5-OH-N,N-DP			2,100	(s)					
(±)-6,7(OH)$_2$-N,N-DM (TL-99)			4,400	(s)		92	(140)		
(±)-5,6(OH)$_2$-N-E						121	(140)		
(±)-6,7(OH)$_2$[(±)-ADTN]	100	(250a)	1,000	(250a)		160	(671)	210	(118)
	230	(896)	2,400	(919)		263	(140)		
	1000	(671)	3,700	(s)		390	(522b)		
	1500	(s)	8,000	(644)					
	h:375	(896)							
	h:400	(250a)							
(±)-5,6(OH)$_2$-N,N-DM (M-7)			3,600	(s)		278	(140)		
(±)-6,7(OH)$_2$-N-M (TL-218)			5,000	(s)		129	(140)		
(±)-5,6(OH)$_2$-N-M (M-8)			4,300	(s)		362	(140)		
(±)-6,7(OH)$_2$-N-P (TL-196)						441	(140)		
N,N-dipropyl (TL-68)			6,100	(s)		2,400	(140)		
(±)-5,6(OH)$_2$-N-P	125	(671)	8,800	(s)		15	(671)		
						17	(140)		
(±)-6-OH-N,N-DP			6,000	(s)					
(±)-5-OH-6M-N-DP (DK-118)			7,000	(s)					
(±)-5,6(OH)$_2$ (JOD-173)	11,200	(671)	9,000	(s)		1,400	(671)		
						1,900	(140)		

TABLE 9—*Continued*

	^{3}H-Spiperone (IC_{50} (nM))			^{3}H-Haloperidol IC_{50} (nM)	
	Rat	Calf	Human	Rat	Calf
N-methyl-N-P (DR-4-9)		13,000 (s)			
(−)-6,7(OH)$_2$[(−)-ADTN]		20,000 (s)			
(±)-5-OH-6M-N-DE (DK-121)		20,000 (s)			
				4,830 (140)	
(±)-5,6(OH)$_2$-N-B				8,650 (140)	
N,N-dimethyl				9,130 (140)	
(±)-5,6(OH)$_2$-N-iP (JOD-176)		80,000 (s)			

* S, most recent value from this laboratory, where the IC_{50} was the drug concentration that inhibited the specific binding of ^{3}H-apomorphine (1 to 3 nM), ^{3}H-dopamine (0.5 to 3 nM), ^{3}H-haloperidol (2 nM), or ^{3}H-spiperone (0.02 to 0.3 nM) by 50% to calf caudate nucleus homogenate. The K_i values for ^{3}H-neuroleptic binding were consistently lower by about 30% compared to the IC_{50} values. The K_i values may be obtained by the equation: $K_i = IC_{50}/(1 + C^*/K_D)$, where C^* is the concentration of ^{3}H-spiperone (generally 0.15 nM) and K_D the dissociation constant of ^{3}H-spiperone (0.3 nM). Specific binding of ^{3}H-spiperone was defined as that inhibited by 100 nM spiperone (465). The specific binding of ^{3}H-apomorphine was defined in this laboratory as that inhibited by 200 nM apomorphine, while that for dopamine was defined as that inhibited by either 500 nM apomorphine or 1μM dopamine.

† Abbreviations used are: ϕ, phenyl; i, iso; D, di; P, propyl; M, methyl; E, ethyl; B, butyl; h, human; m, monkey; ADTN, (±)-6,7-dihydroxy-2-aminotetralin; LSD, lysergic acid diethylamide.

‡ (S(+)-apomorphine has −OH in positions 10 and 11, identical to that for R(−)-apomorphine. S(+)-apomorphine is sometimes referred to as "iso-apomorphine" (1039). More commonly, however, iso-apomorphine is used, as in this review, to indicate (±)-9,10-dihydroxyaporphine (817, 139, 761).

In order for the binding site to be considered as a receptor, there should also be a similarity between the absolute concentrations of an agonist in the brain and in the test tube (i.e. the IC_{50} value). In the case of apomorphine, for example, it can be seen in table 9 that the apomorphine IC_{50} on ^{3}H-haloperidol binding to rat striatum is of the order of 50 nM (see also ref. 671). Since the 50% effective dose of apomorphine for eliciting stereotyped behaviour in rats is of the order of 2 mg/kg (i.p. or s.c.), since the brain apomorphine concentrations (566, 1202, 922) at such a dose are of the order of 4 nmol/g (569, 1233, 122, 1109), and since the nonspecific partitioning of ^{3}H-apomorphine is known (1007), it can be derived that the aqueous concentration of apomorphine in the brain striatum is of the order of 30 to 60 nM under the conditions just specified. Hence, there is reasonable correspondence between the apomorphine IC_{50} value (on D_2 receptors) and the brain apomorphine concentration. It is also interesting to note in the work of Baudry et al. (59) that 50% of the in vivo binding of ^{3}H-pimozide was inhibited by approximately 2 to 5 mg/kg of apomorphine.

As summarized in table 9, it is important to note that the IC_{50} values for dopamine on the D_2 receptor are all in the micromolar concentration range. This concurs with the high dopamine concentrations required in physiological experiments (383a, 373).

IX. Types of Sites Labeled by ^{3}H-Neuroleptics

Amalgamation of some of the important factors mentioned in earlier sections makes it clear that there are a number of different sites or components that can be labeled by ^{3}H-neuroleptics.

A. Nonspecific and Nonsaturable Sites

As illustrated in figure 3, the nonspecific and nonsaturable component of ^{3}H-neuroleptic binding is that amount which cannot be inhibited by an excess of the *same* nonradioactive neuroleptic, usually 100 to 1000 nM. The physicochemical factors that control this nonspecific binding have already been reviewed (987). The thermodynamic constants of these nonspecific binding sites for chlorpromazine have been described by Kwant and Seeman (617, 615). Rigorously, these nonspecific sites can be saturated at extremely high (membrane-lytic) concentrations of chlorpromazine, the results thus revealing a K_D of 6000 nM with a density (B_{max}) of 150 nmoles/mg of membrane protein (617; see also 687).

B. Nonspecific but Saturable Sites (NSS Sites)

As shown in figure 3, there is usually a difference between the amount of nonspecific binding defined by an excess of the *same* nonradioactive compound and that defined by an excess of the closest congener. Ideally, these two nonspecific components should be identical, but they rarely are. These NSS sites have been extensively studied by Leysen and Gommeren (670), and there are numerous examples of this for ^{3}H-spiperone (e.g. 505), ^{3}H-domperidone (e.g. 59a), etc.

C. Specific Binding and Stereoselective Binding Sites

It is in general desirable, therefore, to define specific binding as that amount of ^{3}H-ligand that can be inhibited by an excess concentration of the *closest* congener. This procedure should preclude the component of NSS sites. For example, in the case of ^{3}H-haloperidol, a suitable congener would be (+)-butaclamol or sulpiride or some other neuroleptic, but not haloperidol itself (995). In the case of ^{3}H-spiperone, the suitable close congeners would be (+)-butaclamol or haloperidol. An example of this is given in figure 5. It can be seen that at the excess concentration of 100 to 1000 nM, spiperone self-inhibited about 100% while (+)-butaclamol and haloperidol only inhibited about 90% of the ^{3}H-spiperone binding.

TABLE 10

Inhibition of ^{3}H-agonist binding (to brain striatum)

Drug	Source*	^{3}H-Apomorphine IC_{50} (nM)		^{3}H-Dopamine IC_{50} (nM)	
		Rat	Calf	Rat	Calf
Phenylethylamine-related compounds					
Dopamine		6 (667)	1.1 (1148)	1 (1022)	2 (644)
		7 (1148)	1.1 (919)	5 (1148)	4 (1159)
		13 (1016)	2 (644)	20 (376)	8 (690)
		40 (668)	2.6 (1016)	20 (429)	9 (128)
		250 (242)	3.5 (1007)	38 (600)	9 (1007)
		300 (250a)	6 (667)	380 (121)	16 (667)
		h:20 (250a)	10 (1136)		22 (118)
			11 (242)		
			30 (250a)		
2-F-dopamine	KK		2.5 (s)		1 (s)
N-M-dopamine (epinine)	HS		2.5 (s)	180 (12)	1.6 (s)
					29 (118)
5-F-dopamine	KK		2.8 (s)		2.8 (s)
2-Phenyl-dopamine	HS		4.3 (s)		1.9 (s)
6-F-dopamine	KK		8.2 (s)		0.9 (s)
N-DM-dopamine	JC		11 (s)		5.6 (s)
2-M-N-DM-dopamine	HS		14 (s)		4.5 (s)
N-E-dopamine	HS		25 (s)		17 (s)
(−)-Noradrenaline		200 (668)	15 (1007)	250 (s)	12 (s)
		350 (1148)	38 (s)		46 (1007)
		1,000 (242)			250 (118)
(+)-Noradrenaline		150 (668)	145 (s)		70 (s)
					1,020 (118)
(−)-Adrenaline		1,500 (242)	20 (1007)		68 (1007)
					350 (118)
(+)-Adrenaline					1,500 (118)
N-DE-dopamine	HS		55 (s)		32 (s)
N-P-3-(3-OH-ϕ)-piperidine	AC		60 (s)		
N-DP-dopamine	JC		74 (s)		15 (s)
6-M-dopamine	HS		105 (s)		
m-Tyramine	BC		112 (s)		37 (s)
6-M-N-DM-dopamine	HS		139 (s)		98 (s)
L-DOPA			150 (s)		
5M-N-DM-dopamine	HS		200 (s)		
N-P-dopamine	HS		215 (s)		92 (s)
D,L-α-M-2M-dopamine	HS		232 (s)		110 (s)
D,L-α-M-2M-N-DM-dopamine	HS		341 (s)		
R,S-α-M-2-phenyl-N-DM-dopamine	HS		358 (s)		210 (s)
2-Phenyl-N-DM-dopamine	HS		360 (s)		140 (s)
N-cyclo-P-dopamine	MJ		400 (s)		
3-OH-N-DP-tyramine (VI-182)	JC		400 (s)		
p-OH-phenylethylamine			500 (s)		
2-[3,4(OH)$_2\phi$]-cyclo-Pamine	AS		600 (324)		
N-DB-dopamine [HF-26]	JC		625 (s)		280 (s)
D,L-α-M-6M-N-DM-dopamine	HS		710 (s)		
R-(−)-α-M-dopamine	HS		750 (s)		
3-OH-4-Methoxy-dopamine	BC		1,100 (s)		
N-M$_3$-dopamine	HS		1,200 (s)		750 (s)
S-(+)-α-M-dopamine	HS		1,300 (s)		
3-OCH$_3$-4-OH-ϕethylamine	BC		1,350 (s)		
N-iP-dopamine	HS		2,500 (s)		1,500 (s)
3-[3,4(OH)$_2$-ϕ]-Pamine	BC		2,500 (s)		
R,S-α-M-2-ϕ-dopamine	HS		3,300 (s)		
β-Phenylethylamine			3,730 (s)		
D,L-α-M-6-dopamine	HS		4,000 (s)		
Phentolamine					31,000 (118)
Phenoxybenzamine					110,000 (118)
Propranolol					>100,000 (118)
Aporphine-related drugs					
R-(−)-apomorphine		1.9 (1148)	1.3 (1007)	3.5 (1148)	1 (690)
		3 (667)	1.8 (1148)	10 (376)	2 (1007)
		3 (668)	2.4 (919)	10 (429)	3 (128)
		7 (250a)	3.4 (644)	45 (1005)	4 (644)

TABLE 10—*Continued*

Drug	Source*	^{3}H-Apomorphine IC_{50} (nM)		^{3}H-Dopamine IC_{50} (nM)	
		Rat	Calf	Rat	Calf
R-(−)apomorphine (contd.)		13 (242)	3.5 (1016)	180 (121)	4 (1136)
		18 (1016)	4.5 (242)		8 (667)
		h: 8 (250a)	7 (250a)		11 (118)
(−)-N-P-norapomorphine	JN		4 (s)		3 (s)
(±)-N-P-norapomorphine	JN	3.4 (1148)	12 (s)	6 (1148)	22 (s)
(−)-2-OH-apomorphine	JN		15 (s)		8 (s)
(±)-11-OH-N-P-noraporphine	JN		43 (s)		
R-nornuciferine (1039)	HS		140 (s)		
S(−)-H_4-papaveroline			217 (s)		
R-pukateine (1039)	HS		260 (s)		
(±)-Number 2 (1039)	HS		280 (s)		
S-(+)-bulbocapnine	HL		350 (s)		1,000 (118)
S-(+)-apomorphine	HL		400 (s)		
S-glaucine (1039)	HS		400 (s)		
R-nuciferine (1039)	H		500 (s)		
(±)-10(OH)-N-P-aporphine	JN		515 (s)		
(+)-Nuciferoline (1039)	HS		660 (s)		
(±)-Iso-apomorphine	GW		675 (s)		630 (s)
N-M-apomorphine	JC		710 (s)		1,450 (s)
R-(+)-H_4-papaveroline			917 (s)		
R-apocodeine (1039)	HS		1,000 (s)		
6aS-(+)-10(OH)-aporphine	Br		1,250 (s)		
6aR-(−)-aporphine	Br		1,300 (s)		
6aS-(+)-aporphine	Br		1,500 (s)		
S-(+)-1,10$(OH)_2$-aporphine	HL		1,600 (s)		
R-Number 1 (1039, 635)	HS		1,700 (s)		
R-Number 4 (1039)	HS		1,800 (s)		
S-Number 3 (1039)	HS		3,000 (s)		
R-roemerine (1039)	HS		3,000 (s)		
8-OH-aporphine	JN		4,000 (s)		
8-OH-N-P-norapomorphine	JN		5,000 (s)		2,000 (s)
R-laurepukine (1039)	HS		8,000 (s)		
S-isoboldine (1039)	HS		10,000 (s)		
Quinolines; indanes					
TL-121	JC		4.2 (s)		
GJH-166	JC		4.3 (s)		5.9 (s)
TL-140	JC		4.5 (s)		
TL-137	JC		23 (s)		
TL-307	JC		47 (s)		
TL-305	JC		110 (s)		
TL-306	JC		160 (s)		
TL-308	JC		90 (s)		
S-(−)-salsolinol	HS		300 (s)		
TL-224	JC		300 (s)		
DP-aminoindane [DR-4-7]	JC		500 (s)		
GJH-171	JC		600 (s)		
R-(+)-salsolinol	HS		2,250 (s)		
TL-310	JC		2,000 (s)		
TL-309	JC		3,800 (s)		
3,4$(OH)_2$-N-DM-aminoindane	JC		2,400 (s)		
GJH-176	JC		3,000 (s)		
GJH-173	JC		5,500 (s)		
GJH-175	JC		8,000 (s)		
Serotonin-related; miscellaneous drugs					
Cyproheptadine					1,500 (118)
Mianserin [GB-94]	Or		900 (s)		3,100 (118)
Dimethyltryptamine			1,000 (1236)		24,000 (117)
5-OCH_3-N-DM-tryptamine			3,000 (1236)		
Bufotenin			5,000 (1236)		21,000 (117)
Serotonin			6,000 (1236)		18,000 (234)
					100,000 (1007)
Diethyltryptamine			6,000 (1236)		
Mescaline			14,000 (1236)		135,000 (117)
Piribedil product S-584			15,000 (s)		7,500 (s)
Tryptamine					17,000 (117)

TABLE 10—*Continued*

Drug	Source*	^{3}H-Apomorphine IC_{50} (nM)		^{3}H-Dopamine IC_{50} (nM)	
		Rat	Calf	Rat	Calf
psilocin					22,000 (117)
2,5-DM-4M-amphetamine			300,000 (1236)		
Ergot alkaloids					
Lisuride		1.5 (668)			
d-LSD		10 (1148)	6 (1236)	13 (1148)	38 (118)
			20 (1148)		40 (690)
					70 (128)
l-LSD					70,000 (118)
Lergotrile		16 (667)	10 (s)	60 (429)	30 (128)
				400 (88a)	31 (667)
Ergotamine					15 (1154)
					38 (118)
α-Ergocryptine					45 (1154)
					86 (118)
Ergocornine					45 (118)
					50 (1154)
					70 (128)
β-Ergoptine					60 (1154)
β-Ergosine					60 (1154)
Bromo-LSD					67 (118)
Ergocristine					65 (118)
					70 (1154)
Ergometrine					83 (117)
Dihydroergocryptine		45 (1148)	55 (1148)	100 (1148)	80 (1154)
			317 (644)		254 (644)
Bromocriptine		20 (667)	115 (1136)	100 (376)	132 (117)
		35 (668)	120 (919)	100 (429)	300 (1154)
		230 (1148)	120 (1148)	400 (1148)	370 (667)
			1121 (644)	3300 (88a)	1,347 (644)
8-Isolergotrile					200 (128)
Methysergide			70 (1236)		360 (118)
8-Isobromocriptine					6,000 (1154)
2-Aminotetralins					
(±)-6,7(OH)$_2$ [(±)-ADTN]	JC	1.5 (1148)	0.9 (1148)	1.5 (1148)	2 (s)
	JM	30 (250a)	2.7 (919)		4 (644)
	GW	h:30 (250a)	3.3 (1016)		10 (1016)
			3 (644)		10 (690)
			9 (250a)		14 (118)
(+)-6,7(OH)$_2$ [(+)-ADTN]	JM		1.7 (s)		18 (732)
(±)-6,7(OH)$_2$-N-M [TL-218]	JC		2.4 (s)		2 (s)
(±)-6,7(OH)$_2$-N-DM [TL-99]	JC		4.8 (s)		0.6 (s)
(±)-5,6(OH)$_2$-N-DE	JM		5.5 (s)		4.8 (s)
(±)-5,6(OH)$_2$-N-DM [M-7]	JC		10 (s)		1 (s)
(±)-5,6(OH)$_2$-N-DP [TL-102]	JM		11 (s)		7.5 (s)
(±)-5,6(OH)$_2$-N-M [M-8]	JC		11.5 (s)		14 (s)
(±)-6,7(OH)$_2$-N-DP [TL-232]	JC		17 (s)		10 (s)
(−)-6,7(OH)$_2$ [(−)-ADTN]	JM		18 (s)		290 (732)
(−)-5(OH)-N-DP	JM		18 (s)		4 (s)
(±)-5(OH)-N-DP [JGC-174]	JM		21 (s)		25 (s)
(±)-6,7(OH)$_2$-N-P [TL-196]	JC		43 (s)		25 (s)
(±)-5,6(OH)$_2$ [JOD-17]	JC		81 (s)		48 (s)
(±)-5,6(OH)$_2$-N-P	JM		175 (s)		103 (s)
(+)-5(OH)-N-DP	JM		360 (s)		200 (s)
(±)-N-DP [JGC-154; TL-68]	JM		500 (s)		650 (s)
(±)-7(OH)-N-DP	JM		520 (s)		88 (s)
(±)-2-aminotetralin	JC		725 (s)		230 (s)
(±)-6(OH)-N-DP	JM		950 (s)		290 (s)
(±)-5-OH-6-CH$_3$-N-DP [DK-118]	JC		1,000 (s)		
N-M-N-P [DR-4-9]	JC		1,000 (s)		
(±)-5,6(OH)$_2$-N-iP	JC		1,400 (s)		
(±)-5-OH-6M-N-DE [DK-121]	JC		2,200 (s)		
5,8(OCH$_3$)$_2$-N-M [DR-31]	JC		2,300 (s)		
(±)-5,6(OH)$_2$-N-c-hexyl	JM		3,040 (s)		
(±)-5,6(OCH$_3$)$_2$-N-iP	JC		>1,000 (s)		

TABLE 10—*Continued*

Drug	Source*	^{3}H-Apomorphine IC_{50} (nM)		^{3}H-Dopamine IC_{50} (nM)	
		Rat	Calf	Rat	Calf
Neuroleptics					
Piflutixol					84 (118)
(+)-Butaclamol		3 (668)	70 (242)	160 (1148)	100 (118)
		5 (242)	150 (1148)	290 (121)	270 (121)
		30 (667)			320 (667)
		100 (1148)			
(−)-Butaclamol		15,000 (668)	20,000 (s)		>6,100 (667)
					>13,000 (110)
α-Flupenthixol		2 (668)		210 (121)	225 (118)
β-Flupenthixol					10,000 (118)
Methiothepin					260 (118)
Fluphenazine		7 (668)	70 (250a)	100 (121)	290 (118)
		9 (250a)		500 (1148)	
		160 (1148)			
		h:300 (250a)			
Haloperidol		5 (668)	300 250a)	35 (1005)	300 (1007)
		30 (242)	500 (1007)	200 (376)	900 (121)
		30 (250a)	650 (1148)	200 (1148)	900 (690)
		200 (1148)	940 (1136)	200 (429)	1,200 (118)
		335 (667)	980 (242)	4,800 (121)	1,500 (1159)
		h:500 (250a)	6,600 (919)		
cis-Chlorprothixene					310 (118)
Clofluperol					450 (118)
cis-Clopenthixol					600 (118)
trans-Clopenthixol					16,000 (118)
Triflupromazine					660 (118)
cis-Thiothixene			3,000 (s)		680 (118)
trans-Thiothixene			20,000 (s)		19,000 (118)
Bromperidol		2 (668)			750 (118)
Trifluperidol			2,500 (s)		930 (118)
Trifluoperazine					930 (118)
Fluanisone					1,000 (118)
Droperidol		1.5 (668)	6,000 (s)		1,100 (118)
Chlorpromazine		10 (668)	1,100 (1148)	250 (121)	1,100 (118)
		65 (242)	1,250 (1136)	420 (1005)	1,500 (690)
		850 (1148)	1,300 (242)	500 (1148)	2,000 (1007)
			1,500 (1007)		25,000 (1159)
			14,400 (644)		27,000 (644)
			14,000 (919)		
Moperone					1,500 (118)
Spiperone		0.4 (242)	2,200 (s)	1,200 (1148)	1,700 (118)
		60 (242)	13,400 (644)		4,000 (1007)
		0.6 (668)	17,000 (919)		11,300 (644)
		1,000 (1148)			
Penfluridol					2,000 (118)
Azaperone					2,100 (118)
Thioridazine		1.5 (668)			2,300 (118)
Teflutixol					2,400 (118)
Clozapine		100 (668)	25,000 (s)		2,500 (118)
Metoclopramide			35,000 (919)		
(±)Sulpiride		200 (668)	67,000 (919)		
(−)-Sulpiride			~20,000 (s)		
(+)-Sulpiride			~20,000 (s)		
Benperidol			7,000 (s)		5,100 (118)
Pipamperone		40 (668)			6,100 (118)
Pimozide		2 (668)	~10^9 (s)		6,600 (118)
Fluspirilene			670,000 (919)		1,700 (118)
			>10^5 644)		>10^5 (644)
Promazine				1,650 (121)	8,900 (118)
Promethazine				20,000 (121)	15,000 (118)
Molindone				24,000 (118)	
Domperidone		5 (668)	10,000 (s)		
		7,000 (s)			

* JC, Dr. J. G. Cannon, University of Iowa, BC, Dr. B. Costall; JM, Dr. J. McDermed, Burroughs-Wellcome; HL, Hoffmann-La Roche; Br, Brossi, N.I.H., Bethesda; AC, Dr. Arvid Carlsson, Göteborg; HS, Dr. H. Sheppard, Hoffmann-La Roche; JN, Dr. J. Neumeyer, Northeastern University; KK, Dr. Kenneth Kirk; GW, Dr. G. Woodruff, University of Southhampton; Se, Servier Labs., France; AS, Arnar Stone Labs., Illinois; MJ, Mead Johnson; Or, Organon, Netherlands. For definitions of other abbreviations and symbols in table, see footnote, table 9.

TABLE 11

Neuroleptic/serotonin receptors (S_2 sites) in cerebral cortex

	IC_{50} Values on ^{3}H-Spiperone (nM)									
	Frontal Cortex								Hippocampus	
	Rat		Human		Calf (c); monkey (m)				Rat	
Cyproheptadine	20	(676)								
Methiothepin					c:	10	(1020)			
Metergoline					c:	13	(1020)			
d-LSD*	25	(676)			c:	120	(1020)			
Pizotifen	20	(676)								
Methysergide	8	(896)			c:	240	(1020)			
	36	(676)								
Mianserin	40	(676)			c:	40	(1020)			
Cinanserine	50	(894)	1,000	(710)						
	54	(896)								
	125	(676)								
Psilocin					c:	980	(1020)			
Bromocriptine	160	(896)								
Bufotenin	1,600	(676)			c:	1,900	(1020)		700	(248)
	2,300	(248)								
Quipazine	2,600	(896)								
$(CH_3)_2$-tryptamine	4,500	(894)			c:	2,000	(1020)			
Serotonin	3,200	(676)	10,000	(710)	c:	4,500	(1020)		1,600	(248)
	4,400	(242)								
	5,400	(856)								
	12,000	(896)								
	25,000	(894)								
Tryptamine	17,000	(676)								
	29,000	(894)								
	31,000	(896)								
Apomorphine	3,900	(248)			m:	1,100	(1137)		2,600	(248)
	10,000	(676)								
Piribedil	29,000	(896)								
Dopamine	240,000	(1193)	1.5 mM	(710)	c:	250,000	(1020)		210,000	(248)
	250,000	(676)	1.5 mM	(896)						
	290,000	(856)								
	415,000	(896)								
Adrenaline	800,000	(248)							160,000	(248)
ADTN	930,000	(896)	>100,000	(896)						
Noradrenaline	>1,000,000	(248)							120,000	(248)
NEUROLEPTICS										
Spiperone	0.15	(506)			c:	2.6	(1020)			
					m:	8.6	(1137)			
Pipamperone	9	(674)								
α-Flupenthixol	9	(896)								
(+)-Butaclamol	46	(896)	28	(896)						
(−)-Butaclamol	3,500	(896)	130,000	(896)						
Chlorpromazine	62	(676)			c:	23	(1020)			
Haloperidol	94	(856)			c:	12	(1020)			
	148	(676)			m:	180	(1137)			
	190	(896)								
Pimozide	3.5	(856)								
	100	(676)								
Domperidone	400	(628)								
Sulpiride	90,000	(674)								

* Abbreviations as in footnote, table 10.

Stereoselective binding of a ^{3}H-ligand may be defined as that amount bound in the presence of an inactive enantiomer minus that in the presence of an active enantiomer, as shown in figure 3. Specific binding and stereoselective binding are usually identical. They are not always identical, however, when one uses an agonist enantiomer for an antagonist ^{3}H-ligand, or vice versa. This is why it is best to employ the *closest congener* in order to separate specific from nonspecific binding.

D. D_1 Sites (Dopamine-Sensitive Adenylate Cyclase)

At present the only ^{3}H-neuroleptic that appears to be selective for the D_1 site is ^{3}H-*cis*-flupenthixol (520–522b), as already mentioned.

E. Dopaminergic, Serotonergic, and Adrenergic Receptors Labeled by ^{3}H-Neuroleptics

^{3}H-spiperone binds primarily to dopamine receptors in the striatum, as summarized in table 9, but primarily to serotonin sites in the cerebral cortex, as summarized in table 11. In the case of the human prefrontal cortex, moreover, ^{3}H-spiperone preferentially labels α_1-adrenergic sites (18b). Hence, in measuring the specific binding of ^{3}H-spiperone to any particular brain region, it has now become essential to resolve these two important components of ^{3}H-spiperone binding. Spiperone also has an 18 nM affinity for the α_1 site (863).

In order to facilitate this resolution into dopaminergic and serotonergic sites, Quik et al. (894–896) have suggested that 10^{-5} M ADTN be used as the base line to define the dopaminergic component of ^{3}H-spiperone binding, while excess cinanserin be used to define the serotonergic component. In this laboratory (S. List and P. Seeman, unpublished data), however, we have found that 10^{-5} M ADTN is not particularly selective, since it inhibits the binding of ^{3}H-spiperone in both the striatum (dopaminergic binding) and the frontal cortex (serotonergic binding).

Withy et al. (1253a) have also attempted to measure the binding of ^{3}H-spiperone to dopamine receptors and serotonin receptors (bovine caudate) by choosing different base lines for defining specific binding. They proposed that 100 μM dopamine would inhibit the dopamine component of ^{3}H-spiperone, while 300 nM mianserin would inhibit the serotonin component of binding. This procedure is not sufficient; there is nothing to prevent the ^{3}H-spiperone from labeling either site during the course of the experiment. It is necessary to have a receptor-blocking drug present to preclude ^{3}H-spiperone from binding to the unwanted site.

Figure 4 shows the procedure that we have used in this laboratory (S. List and P. Seeman, in preparation) to separate the dopaminergic (D_2) and serotonergic (S_2) components of ^{3}H-spiperone binding. The total amount

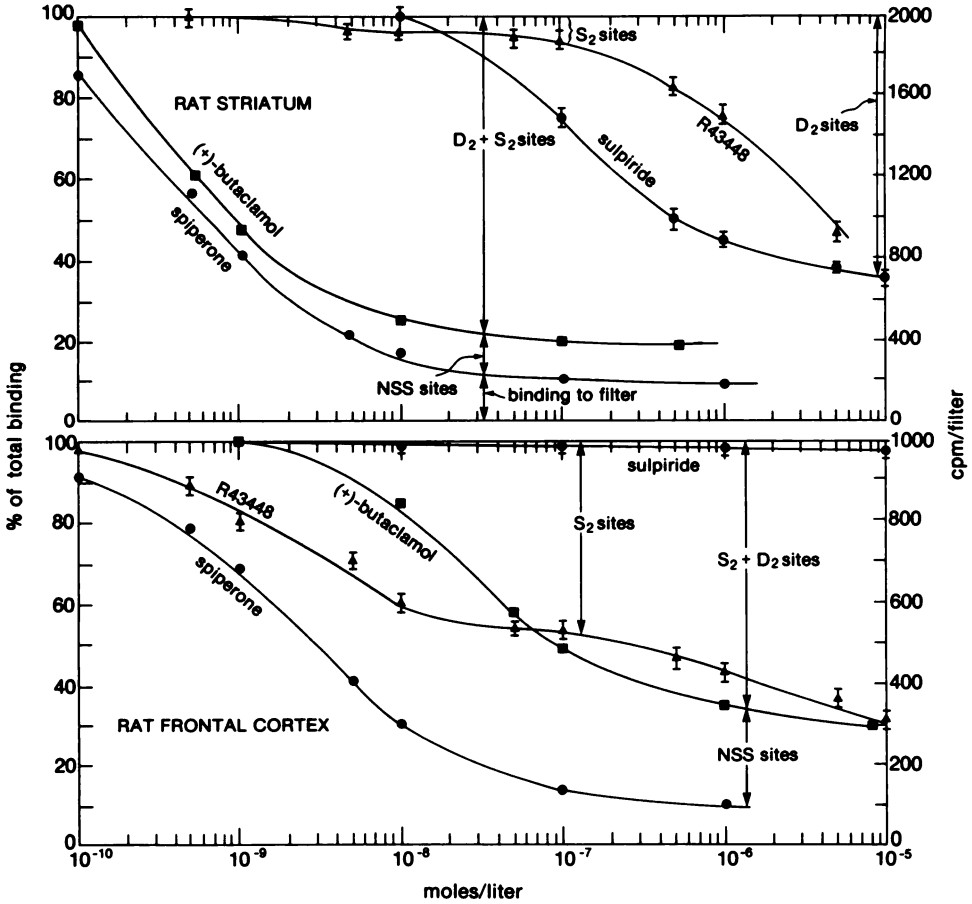

FIG. 4. Resolution of the dopaminergic (D_2) and serotonergic (S_2) components of ^{3}H-spiperone binding to rat brain tissue (S. List and P. Seeman, unpublished data). The total amount of specific binding of ^{3}H-spiperone is that which was inhibited by an excess of a close congener, in this case (+)-butaclamol. Note that the amount inhibited by spiperone itself was more than that inhibited by (+)-butaclamol, the difference being the NSS sites (see fig. 3). The selective labeling of D_2 receptors by ^{3}H-spiperone is done in the presence of 100 nM R43448, a serotonin receptor blocker (672); thus, the specific binding of ^{3}H-spiperone to D_2 receptors is that which occurs in the presence of excess R43448, but which can be inhibited by 10^{-5} M sulpiride. The selective labeling of S_2 sites is defined as that amount of bound ^{3}H-spiperone occurring in the presence of 10^{-5} M sulpiride, but which can be inhibited by 100 nM R43448. It can be seen that the striatum has predominantly D_2 sites, while the frontal cortex has mostly S_2 sites.

of specific binding of ^{3}H-spiperone is defined as that inhibited by an excess of (+)-butaclamol. This specific binding is composed of D_2 and S_2 components that can be separated as follows. The labeling of D_2 receptors by ^{3}H-spiperone is carried out in the co-incubated presence of an excess amount of R43448, a highly specific serotonin-receptor blocker (672). Figure 5 shows that at a concentration of 10^{-7} M, this drug only inhibits binding of ^{3}H-spiperone to cortex but has no effect on the striatal tissue. Figure 5 also shows that 10^{-5} M sulpiride selectively inhibits the binding of ^{3}H-spiperone to striatal tissue without much effect on the binding of this ^{3}H-ligand to cortex.

Thus, the specific binding of ^{3}H-spiperone to D_2 receptors is defined as that binding of ^{3}H-spiperone that occurs in the presence of excess R43448 and that is inhibited by an excess concentration of sulpiride. Along this line of thinking, therefore, the specific binding of ^{3}H-spiperone to S_2 receptors is defined as that binding of ^{3}H-spiperone that occurs in the presence of excess sulpiride and that can be inhibited by an excess concentration of R43448.

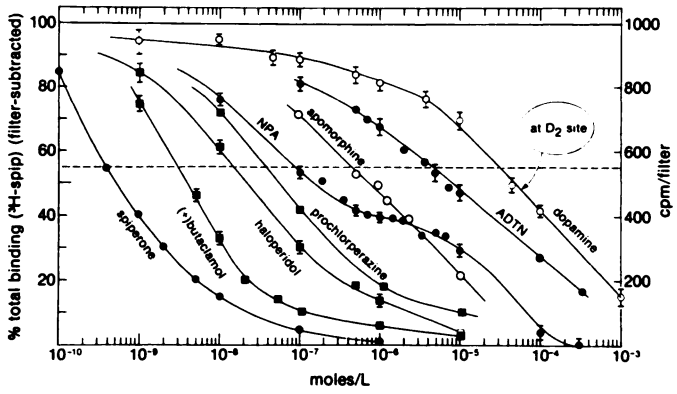

FIG. 5. Typical results for drug inhibition of ^{3}H-spiperone binding to calf brain striatum homogenate (this laboratory). The total binding of 0.15 nM ^{3}H-spiperone was generally about 1000 cpm/filter, of which approximately 50 cpm were attached to the glass fiber filter itself. Specific binding of ^{3}H-spiperone was defined as that which was inhibited by an excess of neuroleptic, generally 100 nM spiperone (465) or 1 μM (+)-butaclamol (1021). Thus, the IC_{50} for each drug was the concentration that inhibited the specific binding of ^{3}H-spiperone by 50%. In the above data approximately 96% of total binding was specific; thus, the IC_{50} values were those concentrations that inhibited the total binding by 48%. NPA, (±)-N-propyl-norapomorphine; ADTN, (±)-6,7(OH)$_2$-2-aminotetralin; vertical bars, S.E. for three to six experiments at room temperature (20°C).

Table 12 gives an example of the kind of data resulting from Scatchard analyses, using this approach for resolving the densities of D_2 and S_2 receptors. These results indicate that the K_D of ^{3}H-spiperone for the D_2 receptors is generally 0.07 ± 0.02 nM in a variety of brain regions, while that for S_2 is of the order of 1 nM.

The observation that ^{3}H-neuroleptics bind to multiple sites (1159) has been known for some time (103, 856, 18a, 65, 1137, 570, 1107, 508, 202c), and a variety of graphical methods (286, 508, 285) have been used to resolve the components. However, the experimental procedure used to generate the data in table 12 unambiguously identifies the sites as dopaminergic or serotonergic.

The serotonergic S_2 sites (labeled by ^{3}H-spiperone) are different from S_1 sites (labeled by ^{3}H-serotonin; 353), as judged by a number of criteria (1020, 862). It also appears that the sites labeled by ^{3}H-LSD (343, 67, 69, 354, 1238) are derived from the sum of the densities of S_1 and S_2 sites (1020, 862). The functions (457, 3, 346, 320, 347, 8) of the different sites for different serotonergic drugs (335) need investigation.

X. Binding Properties of the Dopaminergic Agonist ^{3}H-Ligands

Although the specific binding of ^{3}H-dopamine to rat synaptosomes had been detected (1022, 990) well before that of ^{3}H-haloperidol (1023), there have been many more interpretational difficulties with data from experiments using ^{3}H-dopamine, ^{3}H-apomorphine (1007), or ^{3}H-ADTN (1024). The reasons for this may have something to do with the different conditions used by different workers. The difficulty, however, primarily arises in connection with rat striatal tissue.

There appears to be general agreement that there is a high-affinity site for ^{3}H-dopamine and/or ^{3}H-apomorphine in the calf striatum, wherein the IC_{50} for dopamine is between 1 and 10 nM (figs. 6, 6a, 6b; table 10; 1148, 919, 644, 690, 1007, 667). This site has been termed the D_3 site (690–691b, 1148). The D_3 site is not an artifact of freezing (S. Watanabe and P. Seeman, unpublished data), and there are a number of features that indicate that the D_3 sites are distinctly different from the D_2 receptors (see section XI). Figure 6 shows the agreement between two different laboratories for IC_{50} values on ^{3}H-dopamine binding to D_3 sites in the calf.

Figure 6a shows examples of competition-type experi-

TABLE 12

Resolution of ^{3}H-Spiperone binding to D_2 and S_2 receptors [List and Seeman (691c)]

Rat Brain Region	D_2 Sites B_{max} (K_D) (fmoles/mg protein)	S_2 Sites B_{max} (K_D) (fmoles/mg protein)	NSS* Sites B_{max} (K_D) (fmoles/mg protein)	Total Sites (fmoles/mg protein)
Striatum	434 (0.06 nM)	134 (0.57 nM)	1470 (7 nM)	2038
Olfactory tubercle	107 (0.08 nM)	174 (0.75 nM)	3246 (10 nM)	3527
Hypothalamus	36 (0.15 nM)	128 (1.4 nM)	530 (7 nM)	694
Substantia Nigra	31 (0.11 nM)	Not found	966 (9 nM)	997
Frontal cortex	Not found	666 (1.2 nM)	991 (3 nM)	1657

* NSS, nonspecific saturable sites.

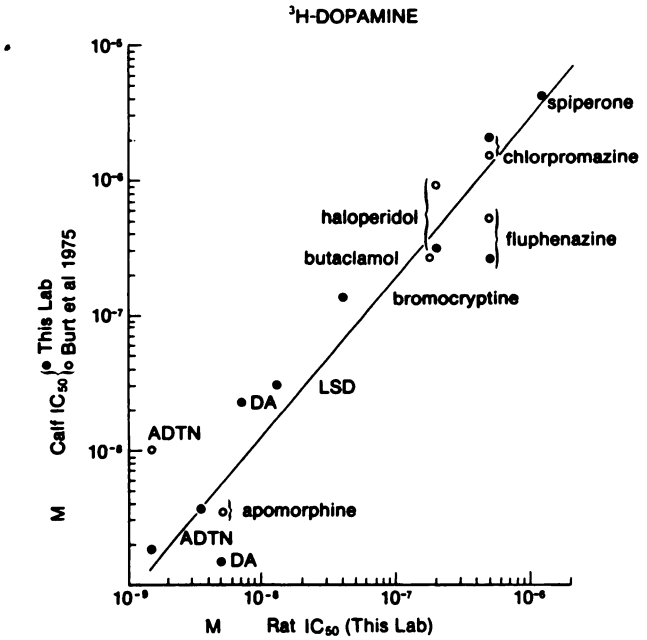

FIG. 6. The D_3 site is defined as that site bound by a ^{3}H-ligand that can be inhibited by 1 to 10 nM dopamine and by 200 to 2000 nM neuroleptics. This high-affinity site for dopamine has been detected in this laboratory for the human, calf, and rat brain striatum (690–691b, 1148), and also by Burt et al. (118) for the calf striatum.

ments that define the D_3 and D_4 sites. As already mentioned, the D_3 site is basically characterized by the fact that dopamine (or ADTN or apomorphine) has an IC_{50} value (or K_i value) of between 1 and 10 nM, whereas the neuroleptics have IC_{50} values between 200 and 2000 nM. As shown in figure 6a, this pattern for the D_3 site is most clearly detected by means of ^{3}H-dopamine; in this figure, the dopamine IC_{50} value is 6 nM (versus ^{3}H-dopamine), while that for spiperone is 1500 nM. Other workers have also reported binding sites with such high affinity for ^{3}H-dopamine in the rat striatum (667, 600, 128).

The inhibition of binding of ^{3}H-ADTN or of ^{3}H-apomorphine is more complicated, however, since there is reason to think that these ^{3}H-ligands bind to the D_4 and D_2 sites as well as to the D_3 site. Thus, as shown in figure 6a, low concentrations of neuroleptics (0.1 to 50 nM) significantly inhibit the binding of these two ^{3}H-ligands presumably for the D_4 receptor, whereas higher concentrations of neuroleptics (200 to 2000 nM) inhibit the binding of ^{3}H-ADTN and ^{3}H-apomorphine at the D_3 site (S. List and P. Seeman, to be published; 690–691a; 1148).

The observation that ^{3}H-apomorphine labels two sites has also been made by Sokoloff et al. (1070a). The IC_{50} values of their "class II" sites are virtually identical to the IC_{50} values for the D_3 site (see table 3).

The pattern of binding for ^{3}H-(±)-N-propylnorapomorphine (1153) further emphasizes that these aporphine ^{3}H-ligands bind to multiple sites. This is shown in figure 6b, which illustrates the selective labeling of either the D_4 site or the D_3 site by ^{3}H-N-propylnorapomorphine (or ^{3}H-NPA). Dopamine clearly inhibits the binding of ^{3}H-NPA in two phases, one phase being between 1 and 10 nM dopamine, and the other phase being between 10 and 10,000 nM dopamine. Hence, in the presence of 25 nM dopamine (to occlude the sites with high affinity for dopamine) the IC_{50} values yielded a D_4 pattern. However,

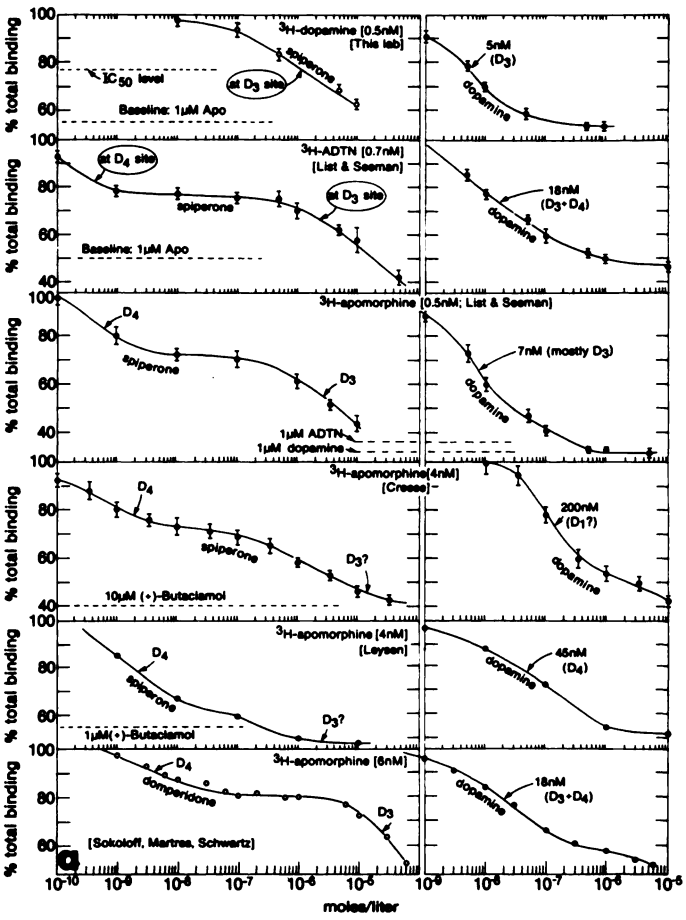

FIG. 6a. Examples and possible interpretations of competition-type experiments that describe the D_3 and D_4 dopaminergic sites in homogenates of rat striatum (see Fig. 1a). The D_3 site is defined by the fact that dopamine has an IC_{50} value (or K_i value) between 1 and 10 nM, while the neuroleptics have IC_{50} values between 200 and 2000 nM (see Fig. 1a). This pattern for D_3 is most clearly seen using ^{3}H-dopamine (top chart) (690–691b; 1148). The D_4 site is defined by the fact that dopamine has an IC_{50} value (or K_i value) between 1 and 10 nM, but with the neuroleptics also having low IC_{50} values of between 0.1 and 10 nM (see Fig. 1a). Both the D_3 and D_4 sites, however, are labeled by both ^{3}H-(±)-ADTN and ^{3}H-apomorphine. Thus, low concentrations of spiperone or domperidone (0.2 to 1 nM), for example, inhibit the binding of these ^{3}H-ligands, while higher concentrations of neuroleptics (200 to 2000 nM) further inhibit the binding of these ^{3}H-ligands at the D_3 site. For these two ^{3}H-ligands the overall IC_{50} for the neuroleptic will reflect its combined action at the D_3 and D_4 sites. Using 4 nM ^{3}H-apomorphine, Leysen (669) and Creese et al. (242) have obtained somewhat different results, but which we interpret as being consistent with the existence of separate sites for D_3 and D_4. The data of Creese et al. (242) indicate that, under their conditions, high concentrations of dopamine were required to inhibit the binding of ^{3}H-apomorphine. The dopamine IC_{50} value was 250 nM, while that for spiperone was about 0.24 nM; both of these values typify the D_4 receptor. It appears that the D_3 site is not labeled when using the conditions of Creese et al. Specific binding of each ^{3}H-ligand was defined as that inhibited by either 1 μM apomorphine (Apo), 1 μM dopamine (DA), or 1 or 10 μM (+)butaclamol (But.), as indicated in the figure. In almost all cases the points are averages (± S.E.M.) from three to five independent experiments.

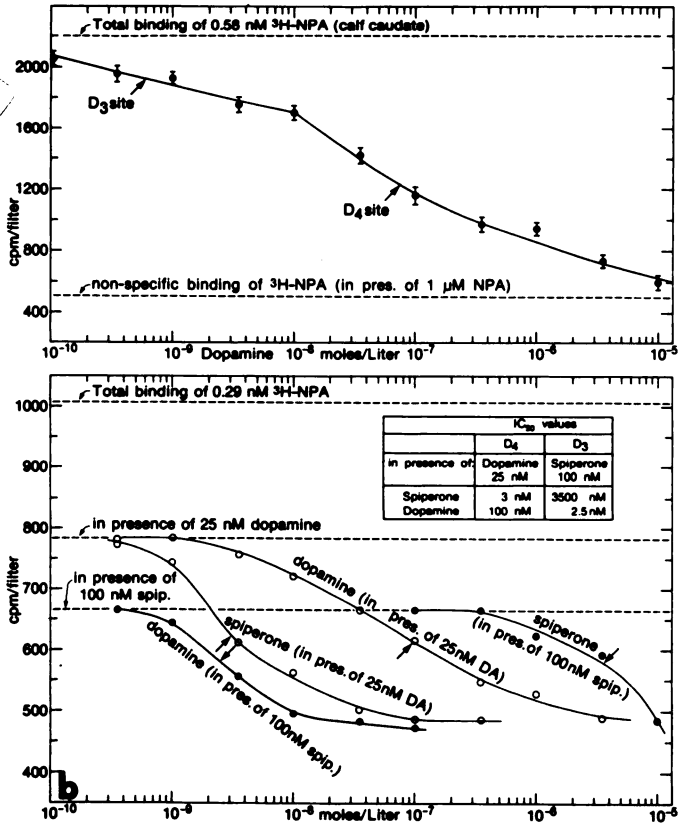

FIG. 6b. Selective labeling of either D_4 sites or D_3 sites by means of ^{3}H-NPA [i.e. ^{3}H-N-propylnorapomorphine; further details in Titeler and Seeman (1153)]. The top part illustrates that dopamine inhibited the binding of ^{3}H-NPA (to calf caudate nucleus homogenate) in two clearly defined phases. Approximately 20% of the total binding was inhibited by dopamine concentrations in the range of 1 to 10 nM (sites with high affinity for dopamine), while an additional 50% or so was separately inhibited by dopamine concentrations ranging from 10 to 10,000 nM (sites with low affinity for dopamine). Thus, the presence of 25 nM dopamine served to occlude the high-affinity dopamine sites, and, therefore, precluded the ^{3}H-NPA from binding to these sites. This is shown in the lower half of the figure, where 25 nM dopamine inhibited the binding of 0.29 nM ^{3}H-NPA by about 20%. Hence, in the presence of 25 nM dopamine, the IC_{50} value for spiperone was 3 nM and that for dopamine was about 100 nM, these two IC_{50} values qualitatively resembling a rank order for the D_4 site. In the same way, therefore, it was found that the IC_{50} values for dopamine (2.5 nM) and spiperone (3500 nM) were identical to those for the D_3 site when the binding of ^{3}H-NPA was measured in the presence of 100 nM spiperone.

in the presence of 100 nM spiperone (to occlude the D_4 site), the IC_{50} values yielded a D_3 pattern.

Thus, since the ^{3}H-aporphines label D_2, D_3, and D_4 sites, the pattern of IC_{50} values will depend on the experimental conditions, including the final concentration of ^{3}H-aporphine in the test tube. Other minor differences in experimental methods (see table 14 and also refs. 1 and 187), include the use of plastic test tubes and whether the membrane aliquot is added first or last into the test tube (688, 690a).

Figure 6a also shows the results of Creese et al. (242) for the binding of ^{3}H-apomorphine. Here, low nanomolar concentrations of dopamine did *not* inhibit the binding of ^{3}H-apomorphine. The dopamine IC_{50} value was 250 nM, while that for spiperone was approximately 0.4 nM. Both of these values typify the D_2 receptor. Thus, it appears that under the conditions used by Creese et al., the D_3 site is not being labeled. The major difference between the conditions used by Creese and by others is that Creese's buffer has a much higher ascorbate concentration and does not have any ethylenediaminetetraacetate (EDTA) (table 14). Since it is known that ascorbate without EDTA is highly destructive to dopamine receptors (1193a, 664a), it is possible that the D_3 sites had degraded under the conditions used by Creese.

In addition to the high-affinity (1 to 10 nM) and low-affinity (40 to 300 nM) sites for ^{3}H-apomorphine (table

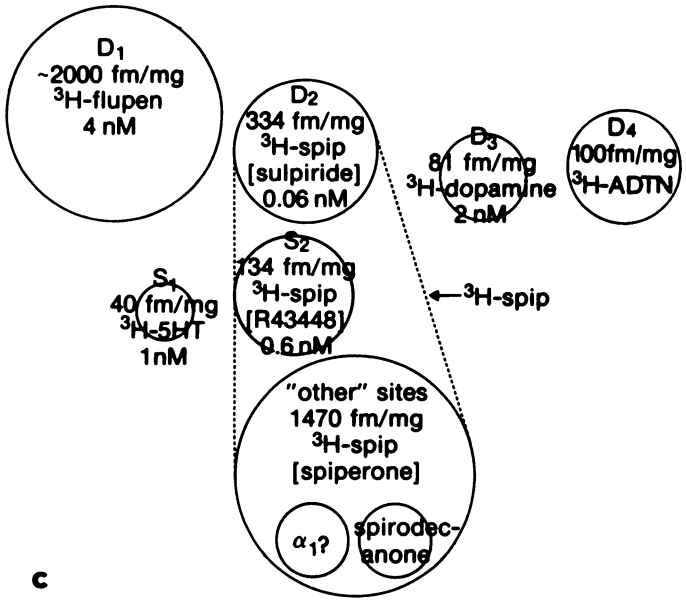

FIG. 6c. Relative densities of sites or receptors for dopamine and serotonin in the rat brain striatum. The area of each circle only qualitatively indicates the density (B_{max}) of binding sites (in fmoles/mg of protein) for each ^{3}H-ligand. The K_D (in nM units) is given immediately below each ^{3}H-ligand. The D_1 sites (i.e. dopamine-sensitive adenylate cyclase) were defined as those labeled by ^{3}H-*cis*-flupenthixol (here abbreviated as ^{3}H-flupen.) and blocked by 1 μM (+)-butaclamol [Hyttel (520) obtained a B_{max} of 410 fm/mg, while S. List in this laboratory (unpublished data) obtained B_{max} values of 2000 to 3000 fm/mg]. The D_2 dopamine receptor sites were defined as those labeled by ^{3}H-spiperone in the presence of 100 nM R43448 (to occlude serotoninergic sites) and which were blocked by 10 μM sulpiride [List and Seeman (691c)]. The D_3 dopaminergic sites were defined as those labeled by ^{3}H-dopamine and blocked by 1 μM apomorphine (690a; 1148). The D_4 dopaminergic sites were defined as those labeled by ^{3}H-(±)-ADTN (displaceable by 30 nM spiperone). This D_4 density was the same as that labeled by ^{3}H-(±)-ADTN (displaceable by 1 μM apomorphine), but which remained after subtracting the density for the D_3 sites (S. List and P. Seeman, to be published). The S_1 serotonergic sites were defined as those labeled by ^{3}H-serotonin and blocked by the closest congener (10^{-4} M tryptamine). S_2 serotonergic sites were defined as those labeled by ^{3}H-spiperone *in the presence of 10 μM sulpiride* (to occlude dopamine sites) and blocked by 100 nM R43448 [List and Seeman (691c)]. "Other" sites for ^{3}H-spiperone were defined as that amount of ^{3}H-spiperone binding inhibited by 1 μM spiperone and which remained after the subtracting the number of D_2 and S_2 sites (691c). These "other" sites include NSS sites (i.e., nonspecific, saturable sites) that may also be termed as "spirodecanone" sites (see text); these "other" sites may also include adrenoceptors of the alpha$_1$ type (18b). See also table 12 for further relative components of some of these binding sites for other brain regions.

13), there are other reports of sites labeled by ^{3}H-ADTN (925, 272a, 1259) and by ^{3}H-dopamine (954, 74, 954a) that are sensitive to dopamine in the low-affinity region (i.e. micromolar). It is possible that the D_1 or D_2 sites were being labeled in these studies.

Since there is no effect of either cocaine or desipramine on the specific binding of ^{3}H-dopamine or ^{3}H-apomorphine, it is unlikely that these ^{3}H-ligands label sites that mediate the uptake of dopamine into nerve terminals. These uptake sites would also be expected to be sensitive to dopamine in the concentration range between 100 and 5000 nM (536, 232, 1032, 115, 837, 470, 464, 477, 486, 840, 515, 846, 493, 1173, 1129, 935–937, 868, 869, 458, 469, 459, 385, 60, 899, 273, 899, 924, 492).

XI. Distinction between D_2 Receptors and D_3 Sites

Different physiological effects of dopaminergic drugs may arise from different types of dopamine receptors (1257, 208–210, 1174, 830, 680, 1201). There is good reason to think that the D_2 receptor is a distinctly separate entity from the D_3 site, as supported by the following evidence.

A. D_2 and D_3 Differ in Affinity for Agonists and Antagonists

The D_2 receptor has a low affinity for dopamine (about 1000 nM) and a high affinity for neuroleptics (0.1 to 50 nM). The D_3 site has just the opposite characteristics, a high affinity for dopamine (1 to 10 nM) and a low affinity for neuroleptics (300 to 3000 nM). These patterns are summarized in tables 9 and 10 (see also 1149, 373, 919, 674, 1159); such data are incompatible with a two-state receptor that oscillates between an agonist and antagonist form. Since the neuroleptic drugs are very surface-active (see section III A), they accumulate within the membrane phase. Thus, as pointed out by Leysen (669a), the neuroleptic concentration near the membrane-associated dopamine receptor may be considerably different than that in the bulk aqueous concentration. This consideration, however, does not explain the fact that D_2 is sensitive to low aqueous concentrations while D_3 requires high neuroleptic concentrations.

B. D_2 and D_3 Differ in Affinity for Ergot Alkaloids

In general the D_2 sites are more sensitive to ergot alkaloids than the D_3 sites (tables 9, 10; 427, 1154, 129, 88a), suggesting physically different sites.

TABLE 13

IC_{50} (nM) values for rat striatum

	^{3}H-apo (250a)	^{3}H-apo (668)	^{3}H-DA (1148)	^{3}H-apo (1148)	^{3}H-apo* (1070a)
Dopamine	300	40	5		19
Spiperone	0.4	0.6	1200	1000	1700
Haloperidol	30	5	200	200	1100
Chlorpromazine	65	10	500	850	
Receptor type	D_2; D_4	D_4	D_3	D_3	D_3

* With 6 nM ^{3}H-apomorphine in the presence of 200 nM domperidone to preclude the ^{3}H-apomorphine from binding to "class I" sites, which had a very low affinity for dopamine (1070a). Abbreviations used are: apo, apomorphine; DA, dopamine.

TABLE 14

*^{3}H-apomorphine binding conditions**

	This Lab.	Creese et al., 1978	Leysen, 1979
Rat	m. Wistar	Spr.-Daw.	f. Wistar
Tissue washes	4 times	2 times	4 times
Tissue/filter	~4 mg	4 mg	20 mg
Preinc. at 37°C	0 min	0 min	10 min
^{3}H-apomorphine	0.5 nM	4 nM	4 nM
Incubation (min)	30; 20°C	10; 37°C	30; 22°C
Tris-HCl	15 mM	50 mM	15 mM
pH at 25°C	7.4	7.7	7.6
EDTA	5 mM	0	1 mM
Ascorbate	0.02%	0.01%	0.01%
Nialamide	12 μM	0	0
Na^+	10 mM	120 mM	0
K^+	0	5 mM	0
Ca^{++}	0	2 mM	0
Mg^{++}	0	1 mM	0
Rinse vol.	10 ml	15 ml	10 ml
Baseline drug	1 μM DA	10 μM B	1 μM DA
% of total	68%–85%	60%	50%

* Comparison of conditions for the binding of ^{3}H-apomorphine to homogenates of rat striatum. Abbreviations used are: Preinc., preincubation; Spr.-Daw., Sprague-Dawley; DA, dopamine; B, (+)-butaclamol; m., male; f., female; EDTA, ethylenediamine tetraacetate.

C. D_2 and D_3 Differ in Densities (B_{max})

As summarized in table 6, the density of D_2 receptors is generally about two or three times greater than the density of D_3 sites. Thal et al. (1136), however, found similar densities. Leysen (669) finds that ^{3}H-apomorphine and ^{3}H-spiperone yield a similar drug profile (table 14) for the D_2 receptor, except that the density of ^{3}H-spiperone sites exceeds that for ^{3}H-apomorphine by a factor of 2.

D. D_3 Can Be Separately Labeled by ^{3}H-NPA

Titeler and Seeman (1153) have demonstrated that it is possible to label D_4 receptors and D_3 sites selectively with the same agonist ^{3}H-ligand, ^{3}H-NPA. When an excess concentration of dopamine was present to occlude D_3 sites, then ^{3}H-NPA labeled D_4 receptors. However, when an excess concentration of spiperone was present to occlude D_4 receptors, then ^{3}H-NPA labeled only D_3 sites. This type of experiment is illustrated in figure 6b. Creese et al. (241) did not use such a selective labeling procedure and found a pattern of IC_{50} values approximately intermediate between those for the D_4 and D_3 sites (cf. 241 and 1153).

E. D_2 and D_3 Can Be Separately Labeled by ^{3}H-LSD

Burt et al. (117) found that ^{3}H-LSD could label D_2 receptors. Along the same lines as just mentioned for the binding of ^{3}H-NPA, Whitaker and Seeman (1240) have found that it is possible to label D_3 sites with ^{3}H-LSD, while occluding the D_2 receptor with excess spiperone (100 nM).

F. Differential Separation of D_2 and D_3

It is possible to centrifuge the D_2 and D_3 binding sites differentially (1156), although other work on D_2 sites (669) indicates that these two ^{3}H-ligands continue to bind to the same D_2 sites in different subcellular fractions (669; see also 75).

G. D_2 and D_3 Differ in Thermal Sensitivity

Lew and Goldstein (666) have demonstrated that the D_3 site (bovine striatum, labeled by ^{3}H-dopamine) became denatured by about 75% upon exposure to 53°C for 2 min, while only 10% of the D_2 sites (labeled by ^{3}H-spiperone) became denatured under the same conditions.

H. Differential Alkylation of D_2 and D_3 Sites

Titeler (1147a) has found it possible to alkylate (and protect) D_2 receptors independently of the D_3 sites, providing additional evidence for the separate existence of these two sets of sites. Costall et al. (221a) alkylated these two sites differentially and selectively with [−]-N-(2-chloroethyl)norapomorphine ((−)-NCA). They found that 15 min preincubation with (−)-NCA (10^{-9} to 10^{-5} M) antagonized the binding of 0.25 nM ^{3}H-NPA, but that much higher concentrations of (−)-NCA (10^{-5} to 10^{-4} M) were needed to antagonize the binding of 0.25 nM ^{3}H-spiperone.

I. Differential Solubilization of D_2 and D_3 Sites

Although the evidence is rather preliminary at present, Clement-Cormier and colleagues (190, 1090a) have reported solubilization of different sites for ^{3}H-spiperone, ^{3}H-apomorphine, and ^{3}H-NPA.

J. D_2 and D_3 Have Different Structural Requirements for Agonists

The IC_{50} values for many dopamine agonists and antagonists on the binding of ^{3}H-dopamine or ^{3}H-apomorphine to striatum tissue are listed in tables 9 and 10. As discussed elsewhere in this review, some of these data presumably reflect the binding of ^{3}H-apomorphine to D_2 or D_4 sites while others represent values at D_3 sites. For a consistent comparison of these IC_{50} values, therefore, it is best to restrict the analysis on the D_3 site to those IC_{50} values from this laboratory (data indicated by "s" in table 2; 691a, 690a, 690, 1148, 1152–1155, 1157, 1159).

In general, the structure-activity relationships for the D_3 site are qualitatively similar to those for the D_2 dopamine receptor: 1) (+)-6,7-ADTN was more potent than (−)-6,7-ADTN; 2) (±)-6,7-ADTN was more potent than (±)-5,6-ADTN; 3) (−)-5-hydroxy-N,N-dipropyl-2-aminotetralin was more potent than the (±)-7-hydroxy congener, which in turn was more potent than the (±)-6-hydroxy congener; and 4) in general, the (−)-aporphines were more potent than their (+)-enantiomers (see also refs. 1245 and 923).

An exception to this, however, was aporphine, where the (−)- and (+)-compounds were about equally potent on the D_3 site, and the (+)-enantiomer was several times more potent than the (−)- form at the D_2 receptor. Aporphine, however, elicits no stereotyped behaviour even when injected i.p. at doses up to 20 mg/kg (874).

Thus, these qualitatively similar stereoselective features suggest that the D_2 receptor and the D_3 site may have a common core structure, despite the fact that they must be distinctly separate sites. There were many quantitative differences, however, between the stereoselectivity patterns for the D_2 and D_3 sites. For example, although (±)-6,7-ADTN was only about three times more potent than (±)-5,6-ADTN on the D_2 receptor, it was over 75 times more potent on the D_3 site.

A more complete quantitative comparison between the IC_{50} values of dopamine agonists on D_2 receptors and D_3 sites is given in figure 7. It can be seen therein that the ratio between the two IC_{50} values varied from agonist to agonist. For example, the ratio was 0.00003 for dopamine while the ratio for apomorphine was 0.005; this indicated that dopamine was disproportionately more selective than apomorphine on the D_3 site compared to the actions of these two agonists at the D_2 receptor. These quantitative differences further justify the D_2 and D_3 sites as distinct and separate entities.

Finally, another important structural difference between the D_2 and D_3 sites is reflected in the fact that the D_3 site is occupied by high concentrations of neuroleptics (100 to 10,000 nM) in contrast to the D_2 site where only 0.1 to 100 nM of the neuroleptic is required. This may suggest that the D_2 receptor has a more hydrophobic environment than the D_3 site.

XII. Differences between D_1 Sites and D_2 Receptors

The existence of dopamine-sensitive adenylate cyclase was first reported in 1972 (571, 567). It is convenient to refer to this dopaminergic site as the D_1 site (570). Since there have been many reviews of the biochemical properties of this site (567, 568, 570, 537, 1036, 540), the purpose of this section is limited to the comparison of the similar and different features between the D_1 sites and the D_2 receptors.

A. Similar Sensitivity to Dopamine

The definition of D_1 and D_2 as dopaminergic is based primarily on the fact that dopamine is generally about 1 order of magnitude more potent than (−)-noradrenaline at both these sites (e.g. compare tables 9 and 10). The absolute concentrations of dopamine that are effective on both sites, however, are of the same order of magnitude. For example, dopamine causes 50% stimulation of the D_1 site at about 3000 nM, and causes 50% inhibition of ^{3}H-haloperidol binding to the D_2 site at about 700 to 7000 nM (table 9). Approximately 10 times higher concentrations of dopamine are required for 50% inhibition

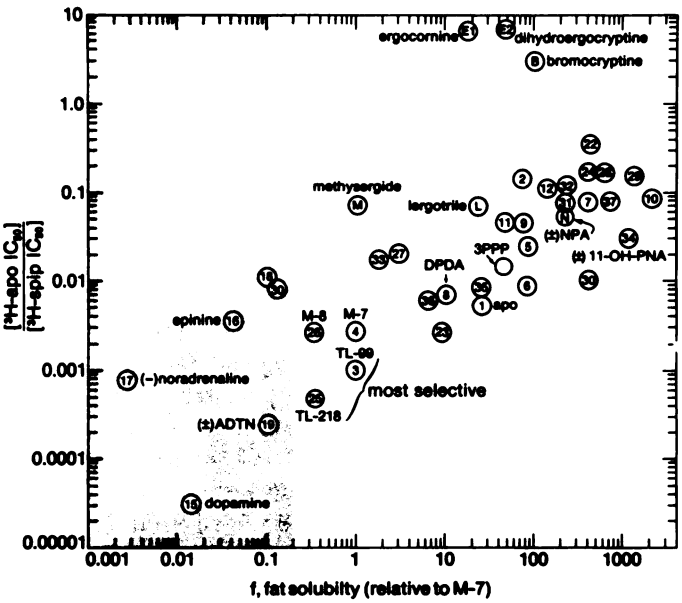

FIG. 7. The ordinate indicates the selectivity of a dopamine agonist for the D_3 dopamine site relative to the D_2 dopamine receptor. Drugs with low ordinate values were those with high selectivity for the D_3 site. The abscissa indicates the octanol/water solubility of each drug relative to M-7 [(±)-5,6-dihydroxy-N,N-dimethyl-2-aminotetralin]. The solubility ratios were calculated by using the partition rules of Hansch (987), where the octanol/water solubility ratio was increased by a $-CH_2$ group (factor of 3), but decreased by a double bond (factor of 0.5), a ring closure (factor of 0.9), or a -OH group (factor of 0.2). The shaded zone indicates the drugs that do not permeate the blood-brain barrier because of their low fat solubility (see 494a, 1232a). Thus, for example, two drugs that would be expected to permeate the blood-brain barrier and that had the most selective action on D_3 dopamine receptors were TL-218 and TL-99 (see tables 9, 10 for structures). The ordinate values were calculated from the IC_{50} values for calf striatum (indicated by the letter "s" in tables 9 and 10). The encircled numbers and letters used are: 1, (−)-apomorphine; 2, TL-140 (see fig. 12 for structure); 3, (±)-6,7-dihydroxy-N,N-dimethyl-2-aminotetralin (TL-99); 4, (±)-5,6-dihydroxy-N,N-dimethyl-2-aminotetralin (M-7); 5, (±)-5,6-dihydroxy-N,N-dipropyl-2-aminotetralin (TL-102); 6, (±)-6,7-dihydroxy-N,N-dipropyl-2-aminotetralin (TL-232); 7, (±)-5-hydroxy-N,N-dipropyl-2-aminotetralin (JGC-174); 8, N,N-dipropyl-dopamine (DPDA); 9, TL-308 (see fig. 12 for structure); 10, N,N-dipropyl-2-aminotetralin (TL-68); 11, 3-hydroxy-N,N-dipropyl-tyramine (VI-182); 12, (±)-5-hydroxy-6-methyl-N,N-diethyl-2-aminotetralin (DK-121); 15, dopamine; 16, epinine; 17, (−)-noradrenaline; 18, N-cyclopropyl-dopamine; 19, (±)-6,7-dihydroxy-2-aminotetralin [(±)-ADTN]; 20, (−)-5-hydroxy-N,N-dipropyl-2-aminotetralin; 21, (+)-6,7-dihydroxy-2-aminotetralin [(+)-ADTN]; 22, (±)-7-hydroxy-N,N-dipropyl-2-aminotetralin; 23, (±)-5,6-dihydroxy-N,N-diethyl-2-aminotetralin; 24, (+)-5-hydroxy-N,N-dipropyl-2-aminotetralin; 25, (±)-6,7-dihydroxy-N-methyl-2-aminotetralin; 26, (±)-5,6-dihydroxy-N-methyl-2-aminotetralin; 27, (±)-5,6-dihydroxy-N-propyl-2-aminotetralin; 28, (±)-6-hydroxy-N,N-dipropyl-2-aminotetralin; 29, (±)-5-hydroxy-6-methyl-N,N-dipropyl-2-aminotetralin; 30, (±)-5,6-dihydroxy-2-aminotetralin; 31, N-methyl-N-propyl-2-aminotetralin; 32, (±)-5-hydroxy-6-methyl-N,N-diethyl-2-aminotetralin; 33, (±)-5,6-dihydroxy-N-isopropyl-2-aminotetralin; 34, (±)-11-hydroxy-N-n-propyl-noraporphine; 35, TL-121 (see fig. 12 for structure); 36, GJH-166 (see fig. 12 for structure); 37, dipropyl-aminoindane (DR 4-7); B, bromocriptine; L, lergotrile; N, (±)-N-propyl-norapomorphine; E1, ergocornine; E2, dihydroergocryptine; M, methysergide; 3PPP, N-n-propyl-3-(3-hydroxyphenyl)-piperidine.

of ^{3}H-spiperone binding to the D_2 receptor, however, partly because ^{3}H-spiperone has a higher affinity than ^{3}H-haloperidol for the D_2 receptor and partly because ^{3}H-spiperone also binds to nondopaminergic sites in the striatum for which dopamine has a low affinity.

B. Different Sensitivities to Neuroleptics

As summarized in figure 2, the neuroleptic drugs inhibit the D_1 site at concentrations between 100 and 10,000 nM, while inhibiting the D_2 receptor at concentrations between 0.1 and 100 nM. As explained elsewhere (991), the high molarities of neuroleptics (that inhibit the D_1 site) are over 100 times higher than the therapeutic concentrations detected in the plasma water (or cerebrospinal fluid) of patients managed clinically by the drugs. It is true, however, that the widely used K_i values for the neuroleptics on the D_1 site are much lower than their IC_{50} values. These K_i values are between 1 and 100 nM and indicate the concentrations acting on the D_1 site in the absence of any dopamine. However, since the dopamine concentration in the synaptic space is expected to be between 10^{-6} M to 10^{-4} M (991, 1157), it would require a neuroleptic concentration of between 100 and 10,000 nM to inhibit the D_1 activity, a concentration range that is not seen clinically. Consistent with this view is the observation by Nakahara et al. (810) that neuroleptics inhibit D_1 in vivo only if given i.p. in massive supraclinical doses of over 25 mg/kg of chlorpromazine and over 5 mg/kg of haloperidol.

There is no correlation between the clinical doses of the neuroleptics and the neuroleptic IC_{50} values on the D_1 site (fig. 2). There is some correlation for the phenothiazine neuroleptics (fig. 2; 542), but this appears to be related simply to their different fat or membrane solubilities (985–988, 991, 993, 1000, 1013, 1017).

There are different sensitivities of D_1 and D_2 to some of the different neuroleptics (fig. 2). The most notable differences occur in the case of sulpiride, sultopride, and metoclopramide, all of which have extremely weak or no action on D_1 (958, 946, 553a, 1077) yet have considerable potency on D_2, particularly human and rat striatum; these drugs are weaker in inhibiting the binding of ^{3}H-spiperone to calf striatum, presumably because this ^{3}H-ligand binds to a slightly different combination of D_2, S_2, and "other" sites for ^{3}H-spiperone (see section IX and table 9).

Finally, it is interesting to note that some of the chlorpromazine metabolites are almost as active as chlorpromazine on D_2 (240), but much weaker than chlorpromazine on D_1 (764, 848).

C. Different Cellular Locations of D_1 and D_2

The D_1 sites are not found in dopamine-containing neurones, but are located on neurones postsynaptic to the dopamine cells. For example, although the substantia nigra contains D_1 (871, 984, 572), specific lesions of the dopamine-containing cells have no effect on the nigral D_1

activity (382, 870, 880). This indicates that the D_1 sites are located on the terminals of GABA-ergic neurones originating within the striatum and/or globus pallidus and terminating in the nigra (880). Thus, lesions of these striatal cells by electrolytic means (1078) or by kainic acid (737) markedly reduce the D_1 activity in the nigra.

Different alterations occur, however, in the D_1 and D_2 sites after lesions of striatal neurones. For example, 2 weeks after a kainic acid lesion of the striatum, D_1 sites were not detectable, but about 40% of ^{3}H-spiperone binding remained in the striatum (766). However, 1 year after such a kainic lesion, the D_1 sites were fully restored, while the binding of 0.4 nM ^{3}H-spiperone to the D_2 receptors was still 50% reduced (976a).

The conclusions of several lesion studies may be summarized as follows:

1. About 50% to 60% of the ^{3}H-neuroleptic-binding sites (mostly D_2 sites) in the striatum are situated on cell bodies residing in the striatum; these sites are eliminated by intrastriatal kainic acid (802a, 766, 976a, 244, 974).

2. About 20% to 30% of the ^{3}H-neuroleptic binding sites (mostly D_2 sites) in the striatum are situated on nerve terminals coming from the cerebral cortex; these sites are eliminated by decortication (974, 244, 386).

3. All the D_1 sites in the striatum are situated on cell bodies within the striatum; these sites, therefore, are completely eliminated in the first few weeks after kainic lesion (766, 386, 974, 244).

4. About 50% of the ^{3}H-spiperone-binding sites (composed of both D_2 and S_2 sites) in the nigra are on cell bodies residing in the nigra; these sites, therefore, are eliminated by lesions that destroy the nigral dopamine-containing cells (802a, 892).

5. All the D_1 sites in the nigra are situated on terminals from cells arising from the striatum or elsewhere; these sites, therefore, are 75% reduced by lesions of striatal neurones (892, 1078, 737).

D. Different Regional Distribution of D_1 and D_2 Sites

1. Brain. A separate existence of the D_1 and D_2 sites is further supported by the lack of any correlation between the numbers of these sites within the striatum itself (665) or in different brain regions (675, 894, 1167, 194). The ventral tegmental area (A-10 cell region of the mesolimbic pathway), for example, has considerable ^{3}H-spiperone binding (D_2 and/or S_2 sites) but no D_1 activity (706, 707, 90).

The cerebral frontal cortex has appreciable D_1 activity (9, 767, 90). The D_2 sites, however, are discretely localized (717a) in accordance with the localization of the dopamine nerve terminals (85). Such observations indicate that it is essential to distinguish between the various catecholamine-adenylate cyclases (89, 362, 558, 1037).

2. Retina. Another example is the retina, wherein ^{3}H-spiperone binding occurs (711) but ^{3}H-domperidone binding does not (1225). Since domperidone does not inhibit D_1 (1225) but is potent on D_2, the absence of ^{3}H-domperidone binding suggests that there are no D_2 receptors in the retina (1225).

3. Pituitary. The presence of D_1 activity in the anterior pituitary is uncertain, since most workers have not detected the enzyme there (1278, 966; further refs. in 735, 568), although one group has reported its existence (7). There is complete agreement, however, on the existence of D_2 receptors in the anterior pituitary, whether measured by the binding of ^{3}H-haloperidol (106), ^{3}H-spiperone (243, 256, 295a), or ^{3}H-dihydroergocryptine (164).

4. Neuroblastoma cells. Hartley et al. (466) have found that neuroblastoma A_2(1) cells (879, 950) have D_1 activity but no D_2 receptors.

E. Different Behavioural Correlations of D_1 and D_2

In animals that are made unilaterally supersensitive to dopamine, there is a good correlation between the rotational responses (to apomorphine) and the number of D_2 sites but not with the D_1 activities (1216, 1217).

In all cases where nigrostriatal lesions have resulted in at least a 90% depletion of striatal dopamine there has been a significant increase in the density of D_2 sites in the striatum (table 15). Such lesions, however, usually had no effect on striatal D_1 activity (607), although Mishra et al. (768, 769) reported an elevation in D_1. Based on the data of Krueger et al. (607), wherein the D_1 activity of the slice was elevated but that of the homogenate was not, Iversen (538) concludes that the apparent elevation of D_1 in the denervated slices may be attributed to the loss of presynaptic dopamine terminals with their dopamine uptake sites.

F. Different Subcellular Distributions of D_1 and D_2

Convincing evidence for the separate existence of D_1 and D_2 has been provided by the subcellular studies of Leysen and coworkers (630, 675, 624). The D_1 sites equilibrated at 0.95 M sucrose (630, 675), while the D_2 sites equilibrated at about 0.6 M sucrose (624). There are additional data on subcellular distribution (189, 193, 1047, 388, 629).

G. Different Susceptibilities of D_1 and D_2 to Detergents

Circumstantial evidence for different biochemical composition of the D_1 and D_2 sites is the fact that cholate and lubrol PX appear to solubilize the D_1 site (481, 954a) while inhibiting or denaturing the D_2 receptors (1114, 432–434, 621).

H. Different Selective ^{3}H-Ligands for The D_1 and D_2 Sites

The D_1 sites appear to be labeled selectively by ^{3}H-*cis*-flupenthixol, since clebopride, sultopride, sulpiride, and metoclopramide exert little inhibition of the binding of this ^{3}H-ligand (520–522b). This pattern of ^{3}H-*cis*-flupenthixol binding is different from that of ^{3}H-haloperidol or ^{3}H-spiperone, which label D_2 receptors.

Bromocriptine is an agonist at the D_2 receptor, but

TABLE 15

*Effects of lesions on dopamine receptors**

^{3}H-Ligand	Receptor Type	Lesion Site*	Depletion of Dopamine (%)	Binding Change	Refs.
Effects of 6-OH-DA lesions on D_2 receptors in rat striatum					
^{3}H-halo. (3 nM)	D_2	MFB		+87%	(1069)
^{3}H-spip. (B_{max})	D_2	SN	>95%	+63%	(1138)
^{3}H-spip. (80 pM)	D_2	MFB	>90%	+55%	(915)
^{3}H-halo. (B_{max})	D_2	MFB		+50%	(237)
^{3}H-spip. (0.8 nM)	D_2	MFB	~83%	+42%	(1217)
^{3}H-spip. (B_{max})	D_2	?	?	+40%	(388a)
^{3}H-spip.	D_2	MFB		+40%	(429)
^{3}H-halo. (B_{max})	D_2	SN	>95%	+38%	(1138)
^{3}H-spip.	D_2	MFB		+26%	(802a)
^{3}H-halo.	D_2	MFB		+28%	(769)
^{3}H-spip. (B_{max})	D_2	MFB	>90%	+25%	(914)
^{3}H-halo. (3 nM)	D_2	MFB	>90%	+22%	(808)
^{3}H-spip. (0.2 nM)	D_2	MFB	>90%	+18%	(250)
^{3}H-spip. (0.5 nM)	D_2	MFB	>90%	+18%	(808)
^{3}H-spip.	D_2	SN	~67%	+ 3% ns	(669)
^{3}H-ADTN (2 nM)	D_2	SN	?	+59%	(475a)
^{3}H-apo. (3 nM)	D_2	MFB	>90%	+52%	(250)
^{3}H-ADTN (B_{max})	D_2	SN		+27%	(378)
^{3}H-apo. (4 nM)	D_2	SN	~67%	− 4% ns	(669)
^{3}H-apo. (B_{max})	D_2	SN	>80%	−18%	(372a)
Effects of 6-OH-DA lesions on D_2 receptors in nigra					
^{3}H-spip.	D_2?	str.		−48%	(802a)
^{3}H-spip. (80 pM)	D_2?	MFB	90%	−40%	(915)
^{3}H-spip. (0.5 nM)	D_2?	SN		−36%	(892)
Effects of 6-OH-DA or PD lesions on D_3 sites in striatum					
^{3}H-apo. (B_{max})	D_3	MFB	>90%	−47%	(808)
^{3}H-apo. (3 nM)	D_3	str.		−47%	(1228)
^{3}H-apo. (6 nM)	D_3	MFB	>80%	−50%	(1070a)
^{3}H-apo. (6 nM)	D_3	SN	>80%	−37%	(1070a)
^{3}H-apo. (3 nM)	D_3	PD	>90%	−55%	(651)
^{3}H-DA (B_{max})	D_3	PD	>90%	−40%	(649c)
^{3}H-DA (B_{max})	D_3	i.c.	>99%	−50%	(WSS)
Effects of kainic acid lesions on dopamine receptors in striatum					
^{3}H-spip. (0.1 nM)	D_2	str.		−75%	(351)
^{3}H-spip.	D_2	str.		−61%	(802a)
^{3}H-spip. (0.4 nM)	D_2	str.		−53%	(976a)
^{3}H-spip. (B_{max})	D_2	str.		−49%	(766)
^{3}H-spip. (B_{max})	D_2	str.		−45%	(378)
^{3}H-spip.	D_2	str.		−54%	(251)
^{3}H-spip. (B_{max})	D_2	str.		−48%	(1228)
^{3}H-halo. (1 nM)	D_2	str.		−40%	(386)
^{3}H-halo. (B_{max})	D_2	str.		−36%	(974)
^{3}H-spip. (2 nM)	D_2	str.		−30%	(669)
^{3}H-ADTN (B_{max})	D_2	str.†		−90%	(378)
^{3}H-apo. (4 nM)	D_2	str.		−64%	(251)
^{3}H-ADTN (8 nM)	D_2	str.		−60%	(976a)
^{3}H-apo. (B_{max})	D_2	str.		−64%	(372a)
^{3}H-apo. (4 nM)	D_2	str.		−30%	(669)
^{3}H-apo. (B_{max})	D_3	str.		0%	(1228)
^{3}H-apo. (3 nM)	D_3	str.		0%	(50a)

* Abbreviations used are: MFB, medial forebrain bundle; SN, substantia nigra; str., striatum; ns, not significant; PD, Parkinson's disease (human); ADTN, (±)-6,7-dihydroxy-2-aminotetralin; APO., apomorphine; DA, dopamine; spip., spiperone; halo., haloperidol; i.c., intracisternal into 5-day old rats; done on days 25 to 35; WSS, Watanabe, Seeman and Shaywitz, to be published.

† Ibotenic acid lesion.

primarily an antagonist of D_1 (196a, 845). ^{3}H-Bromocriptine binds to sites in the striatum identical to those for ^{3}H-spiperone (196a).

I. Different Changes in D_1 and D_2 in Schizophrenic Brain

The D_2 receptors in postmortem brains from schizophrenic patients are higher than normal by about 50% to 100% (646–649a, 652, 1003, 259, 842, 843, 710). No such elevation, however, is seen in the D_1 sites in schizophrenic brain tissue (148).

J. Different Structural Requirements for a Dopamine Agonist at the D_1 and D_2 Sites

There are some similarities and some differences between the structure-activity relations for the D_1 site and

the D_2 receptor. For example, both sites are: (a) much more affected by (+)-6,7-ADTN than (−)-6,7-ADTN (tables 3 and 9); (b) considerably more affected by (±)-6,7-ADTN than by (±)-5,6-ADTN (tables 3 and 9); (c) more affected by (−)-apomorphine than by dopamine; (d) unaffected by (±)-isoapomorphine.

These similar stereoselectivity patterns suggest that the D_1 and D_2 dopaminergic site receptors may have a similar core structure. There are also, however, numerous differences that indicate that the overall composition and/or environment of the two sites are very different. These differences include the following:

1. Although the behavioural effects of dopamine agonists correlate with their IC_{50} values on the D_2 site (see section XIV), there is no correlation with their action on the D_1 site. Many of the clinically important ergot alkaloids (e.g. bromocriptine and lergotrile), for example, do not stimulate the D_1 receptors at all (718, 966; table 3) but merely inhibit this site (table 3).

2. There is no correlation between the inhibitory concentrations of the aporphines on the D_1 site with their IC_{50} values on D_2 receptors (P. Seeman and H. Sheppard, unpublished data).

3. The molarities of the butyrophenones for inhibiting the D_1 sites (i.e. IC_{50} values) are generally between 1000 and 10,000 nM (191, 537, 563, 564, 571, 620, 762, 991), which are about 1000 times higher than the IC_{50} values on the D_2 receptors (table 9).

Because of the partial agonist action of (−)-apomorphine on dopamine-sensitive adenylate cyclase (571, 539, 761, 1118), and because of the selective antagonism (without any agonist action) of certain ergot alkaloids, it is difficult to develop a coherent picture of the key binding sites of the D_1 site, as can be done for the D_2 receptor (fig. 15). There is additional discussion of this topic by McDermed and Miller (735) and Sheppard (1036).

XIII. Effects of Ions and Nucleotides on Dopaminergic ^{3}H-Ligand Binding

The role of ions and nucleotides in the binding properties of dopaminergic ^{3}H-ligands is still unsettled, with different workers obtaining different results. Usdin et al. (1193a) have found that the binding sites for ^{3}H-spiperone in the rat striatum are unstable at 37°C (pH 7.1, 0.1% ascorbate), with a fall of 60% in the amount of ^{3}H-spiperone bound after 20 min of incubation. They found that 100 mM NaCl or 5 mM EDTA or 1 mM $MnCl_2$ could prevent this loss in binding activity; there did not seem to be any particular ion selectivity in this protective action, since Na^+ and K^+ were both effective. Jenner et al. (554a), on the other hand, have reported that NaCl (25 to 200 mM) but not KCl (1 to 100 mM) enhances the specific binding of ^{3}H-(+)-sulpiride with a much smaller effect on ^{3}H-spiperone binding.

Creese and Sibley (244a) have summarized studies (1193, 1275, 1045, 252, 710a) indicating that guanine nucleotides decrease the binding of ^{3}H-apomorphine but not ^{3}H-butyrophenones in striatum (see also 954). They also summarize reports that guanine nucleotides decrease the ability of agonists to displace the binding of ^{3}H-butyrophenones to striatum. In other studies (17), however, it has not been possible to detect these effects of nucleotides, despite the fact that such effects are readily detected on beta adrenoceptors by the same workers (712; see 573, 786, 656, 659, 809, 787, 1190). As Creese and Sibley (244a) have pointed out, nucleotide sensitivity of ^{3}H-ligand binding to D_2 sites does not necessarily mean that the D_2 sites are linked to the D_1 sites.

There may be other factors involved in modulating either D_1 or D_2 sensitivity (947, 216, 100). It should also be noted that the binding of ^{3}H-haloperidol is considerably reduced by 0.1 to 1 mM ascorbic acid (664a; see also 1139a); this destructive effect, however, is prevented by EDTA at concentrations over 0.1 mM (664a).

XIV. Correlations between Behaviour and the Binding of Dopaminergic ^{3}H-Ligands

There is now an enormous literature on the behavioural potencies of various dopaminergic agonists. As summarized in figures 8 to 11, it is now clear that the behavioural potencies of these agonists correlate reasonably well with their IC_{50} values on D_2 receptors only, and not on the D_3 or D_1 sites. This conclusion holds for agonists that alleviate Parkinson's disease (fig. 8), elicit rotational behaviour (fig. 9), produce emesis (fig. 10), and elicit stereotypy (fig. 11).

Such correlations are necessary, but not by themselves sufficient, for ascribing a role or function to the D_2

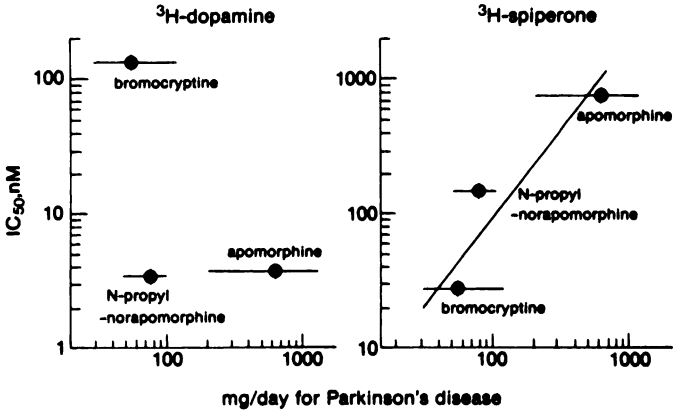

FIG. 8. Indicating that the clinical doses for anti-parkinsonian action correlated directly with the IC_{50} values for ^{3}H-spiperone (D_2 dopamine receptors), but not with the IC_{50} values for ^{3}H-dopamine (D_3 dopamine receptors) [adapted from Titeler and coworkers (1149, 1157)]. The IC_{50} values were obtained in this laboratory on calf striatum (data indicated by the letter "s" in tables 9 and 10). The ranges of anti-parkinsonian doses (p.o.) are: apomorphine, 200 to 1400 mg/day, with a mean of 600 mg/day (228, 230, 305); (±)-N-n-propyl-norapomorphine, 60 to 90 mg/day (230, 851); bromocriptine, 42 mg/day (136), 79 mg/day (565), 70 mg/day (682), 120 mg/day (390), 26 mg/day (684), 26 mg/day (853), approximately averaging 50 mg/day (see also 5, 334, 683, 906, 1134, 137, 606, 446, 135, 138, 184, 663). Lergotrile has not been included, since the average dose of 49 mg/day (681) required considerably higher supplementary doses of L-DOPA; presumably, therefore, the lergotrile by itself would be much higher than 49 mg/day (cf. 186, 377, 134, 1135).

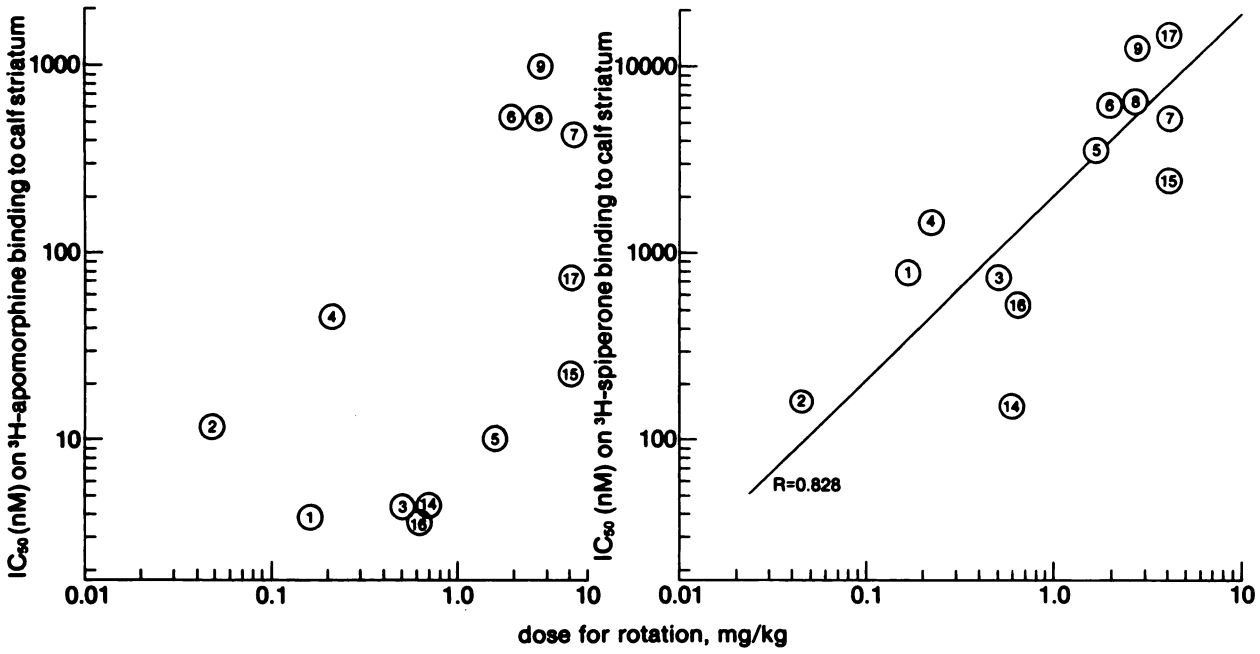

FIG. 9. Correlation between the IC_{50} values for dopamine agonists on ^{3}H-spiperone binding (D_2 receptors) and the doses of these agonists to elicit contralateral turning in 6-OH-dopamine-lesioned rats (unilateral lesions of the substantia nigra). A standard dose of apomorphine (0.16 mg/kg s.c.; 701, 702, 948) elicited 328 ± 85 turns (mean ± S.E.). The above doses had been those that elicited average turning rates equal to that caused by 0.16 mg/kg apomorphine. All doses had been given s.c. except drugs 2, 4, and 7 (i.p.). The agonist doses did not correlate with the IC_{50} values for the D_3 sites that were labeled by ^{3}H-apomorphine (left side of figure). The IC_{50} values for ^{3}H-spiperone and ^{3}H-apomorphine were from this laboratory (calf striatum; indicated by the letter "s" in tables 9 and 10). The encircled numbers are: 1, apomorphine (701, 702, 819, 948); 2, (±)-N-propyl-norapomorphine (819); 3, GJH-166 (702; see fig. 12 for structure); 4, (±)-11-OH-N-propyl-noraporphine (819); 5, M-7, 5,6-dihydroxy-N,N-dimethyl-2-aminotetralin (701); 6, DR-4-7, dipropylaminoindane (701); 7, (±)-10-hydroxy-N-propyl-noraporphine (819); 8, TL-68, N,N-dipropyl-2-aminotetralin (701); 9, DR-4-9, N-methyl-N-propyl-2-aminotetralin (701); 14, TL-140, (702; see fig. 12 for structure); 15, TL-137 (702; see fig. 12 for structure); 16, TL-121 (702; see fig. 12 for structure); 17, DPDA; dipropyldopamine (701, 702).

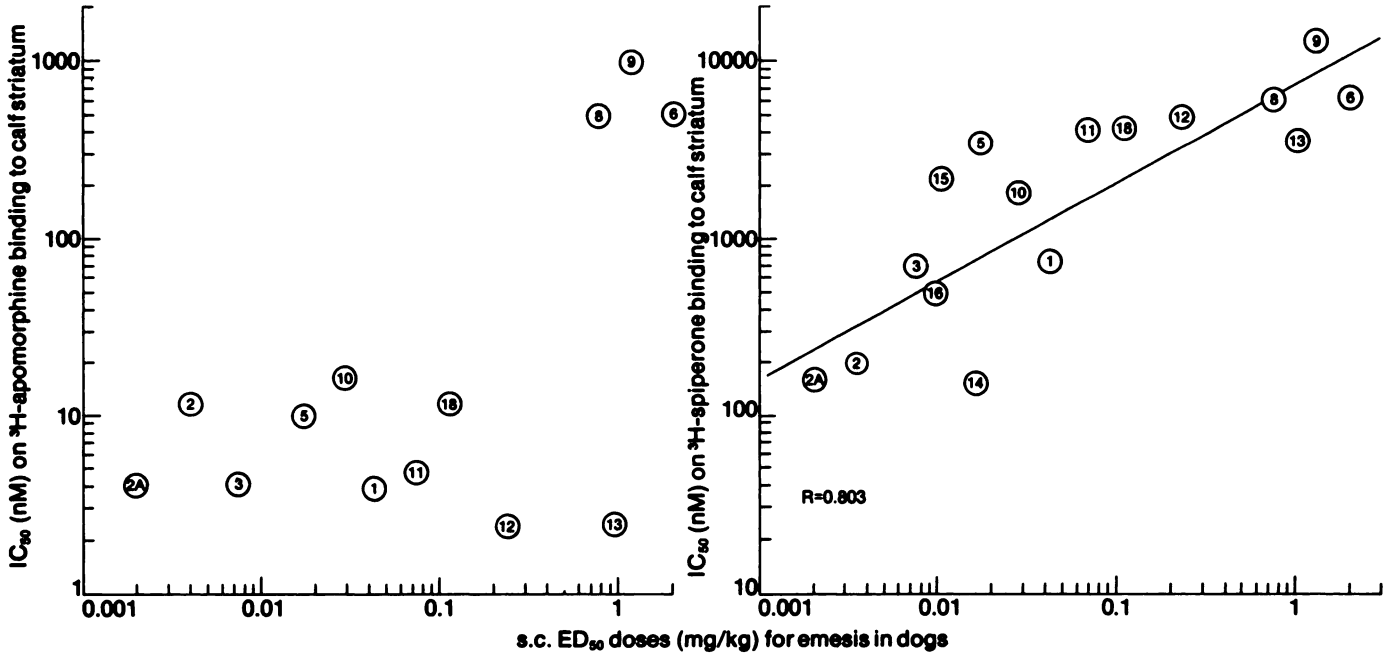

FIG. 10. Correlation between the IC_{50} values for dopamine agonists on ^{3}H-spiperone binding and the ED_{50} doses to elicit emesis in dogs (701, 702, 818). The emetic dose for (−)-N-propyl-norapomorphine (drug no. 2A in this figure) was calculated on the basis that this compound is known to be 20 times more potent than (−)-apomorphine (818). The agonist doses did not correlate with the IC_{50} values for the D_3 dopamine receptor which was labeled by ^{3}H-apomorphine (left side of figure). The IC_{50} values for ^{3}H-spiperone and ^{3}H-apomorphine were obtained in this laboratory (calf striatum; indicated by the letter "s" in tables 9 and 10). The encircled numbers are: 1, (−)-apomorphine; 2, (±)-N-propyl-norapomorphine; 2A, (−)-N-propyl-norapomorphine (818); 3, GJH-16 (see fig. 12 for structure); 5, M-7, 5,6-dihydroxy-N,N-dimethyl-2-aminotetralin; 6, DR-4-7, dipropylaminoindane; 8, TL-68, N,N-dipropyl-2-aminotetralin; 9, DR-4-9, N-methyl-N-propyl-2-aminotetralin; 10, TL-232, (±)-6,7-dihydroxy-N,N-dipropyl-2-aminotetralin; 11, TL-99, (±)-6,7-dihydroxy-N,N-dimethyl-2-aminotetralin; 12, TL-218, (±)-6,7-dihydroxy-N-methyl-2-aminotetralin; 13, (±)-ADTN, (±)-6,7-dihydroxy-2-aminotetralin; 14, TL-140 (see fig. 12 for structure); 15, TL-137 (see fig. 12 for structure); 16, TL-121 (see fig. 12 for structure); 18, M-8, (±)-5,6-dihydroxy-N-methyl-2-aminotetralin.

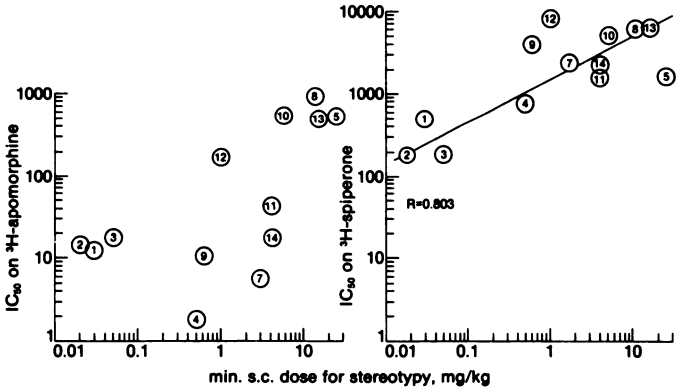

FIG. 11. The minimum doses of dopamine agonists for eliciting stereotypy in rats correlated with the IC_{50} values for ^{3}H-spiperone (D_2 dopamine receptors), but not with the IC_{50} values for ^{3}H-apomorphine (D_3 binding sites). The doses refer to minimum doses required to produce a consistent motor response (i.e. sustained for at least 30 min). Most of the doses had been given s.c. (733, 734, 140). The minimum s.c. doses were about half the ED_{50} doses administered i.p. (968); thus, doses taken from Schoenfeld et al. (968) were halved for purposes of this figure. The IC_{50} values for ^{3}H-spiperone and ^{3}H-apomorphine were obtained in this laboratory (calf striatum; indicated by the letter "s" in tables 9 and 10). The encircled numbers are: 1, (±)-5,6-dihydroxy-N,N-dipropyl-2-aminotetralin (TL-102); 2, (±)-N-propyl-norapomorphine; 3, (−)-5-hydroxy-N,N-dipropyl-2-aminotetralin; 4, (−)-apomorphine; 5, (±)-7-hydroxy-N,N-dipropyl-2-aminotetralin; 7, (±)-5,6-dihydroxy-N,N-diethyl-2-aminotetralin; 8, (±)-6-hydroxy-N,N-dipropyl-2-aminotetralin; 9, (±)-5,6-dihydroxy-N,N-dimethyl-2-aminotetralin (M-7); 10, (±)-10-hydroxy-N-propyl-aporphine; 11, (±)-11-hydroxy-N-propyl-aporphine; 12, (±)-5,6-dihydroxy-N-propyl-2-aminotetralin; 13, N,N-dipropyl-2-aminotetralin (TL-68); 14, (±)-6,7-dihydroxy-N,N-dipropyl-2-aminotetralin (TL-232).

receptor. There are, of course, a number of difficulties in determining clinical doses (229, 305, 274, 1186), in behavioural tests (205, 825, 410, 882), in genetics (355, 356, 471a), in circadian rhythm (807, 35), in pharmacokinetics (45, 2, 371), and in mixed agonist-antagonist effects, particularly with ergot alkaloids (375, 576, 24, 361, 694, 1223, 412, 1072, 872, 1211, 1075, 182, 743), which undermine the significance of such correlations. Nonetheless, at least the correlations (figs. 8 to 11) suggest that the D_2 receptor is more functionally linked to behaviour than is the D_3 site. The situation may be even more complicated than this, because Köhler et al. (594, 595) have found that apomorphine elicited stereotypies at low doses that had no effect on the amount of ^{3}H-spiperone bound to the striatum in vivo; it is possible that this in vivo method is not sufficiently sensitive, or, alternatively, there may be many spare receptors.

XV. Structural Requirements for a Dopamine Agonist at the D_2 Receptor

It is possible to outline the structural features required for a potent dopamine agonist acting on the D_2 receptor. These structural requirements have emerged as a result of two important developments. First, a wide variety of dopamine congeners have been synthesized in recent years in the laboratories of J. G. Cannon (Iowa City), J. L. Neumeyer (Boston), J. D. McDermed (Research Triangle Park, N.C.), J. Z. Ginos (Upton, N.Y.), and E. C. Kornfeld (Indianapolis), permitting the testing of various models of the dopamine receptor. Second, the correlations shown in figures 8 to 11 indicate that the D_2 dopamine receptor (as labeled by ^{3}H-neuroleptics) is the primary dopamine receptor associated with stereotypy, rotation, anti-parkinsonian locomotion, prolactin inhibition (section XXVIII), emesis, and antipsychotic action (fig. 2). Thus, a detailed structure-activity analysis becomes convenient by using the IC_{50} values for the binding of ^{3}H-spiperone to the D_2 receptor (see structures of dopamine-related agonists in figs. 12 and 13).

Previous structure-activity analyses have considered a variety of dopaminergic responses (401a, 206, 139, 1257, 270, 1261, 732). These past analyses have been limited, however, by insufficient biological data for many dopamine congeners and by the problem that many congeners

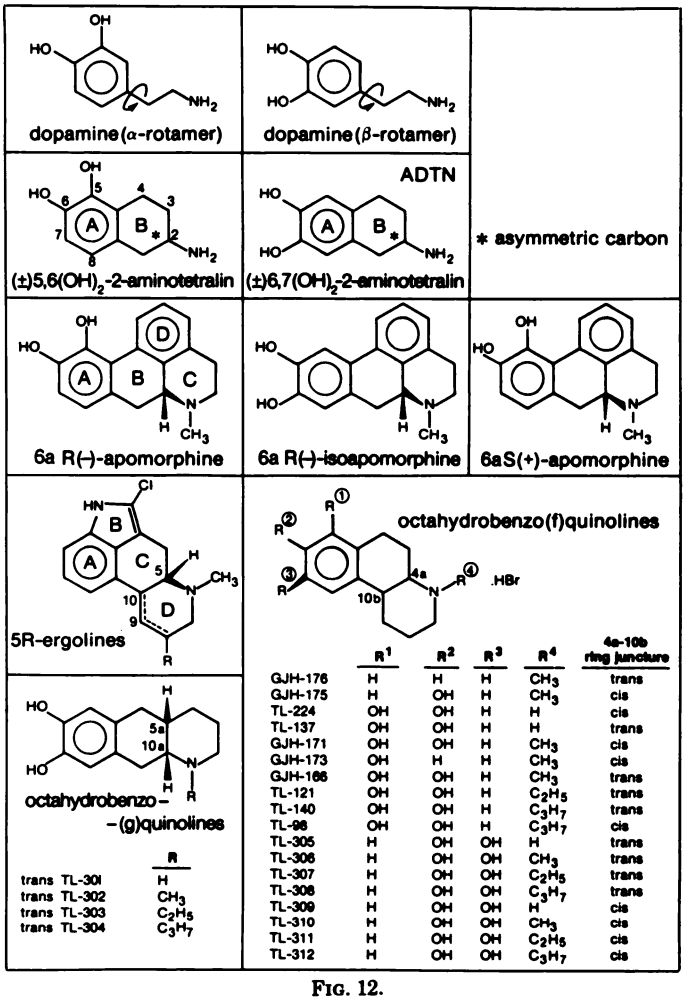

FIG. 12.

Figs. 12, 13. Structures of dopamine-related compounds. Although (−)-isoapomorphine is here drawn in the 6aR conformation, this compound is only generally available as the racemate, 6aS, 6aR (±)-isoapomorphine (761, 817, 875). Each octahydrobenzo(g)quinoline has two asymmetric carbon atoms (at positions 5a and 10a), and so has four isomers. TL-301 to TL-304 all have the 5a to 10a hydrogens *trans* to each other, so that each compound is a racemate of the (±)-*trans*-isomers. Similarly, each octahydrobenzo(*f*)quinoline is a racemate of the (±)-HBr salts.

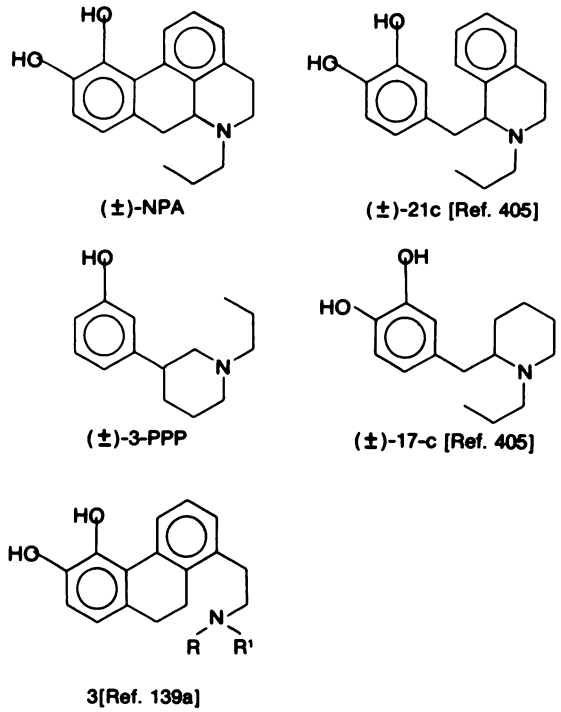

FIG. 13.

are not sufficiently fat-soluble to permeate into the brain. It is known, for example, that an i.p. injection of (±)-ADTN [or (±)-6,7-dihydroxy-2-aminotetralin] as high as 50 mg/kg does not elicit any dopaminergic behaviour, such as stereotypy, gnawing, or licking (875, 494a, 1232a). (±)-ADTN is a potent dopamine agonist, however, in those instances where the blood-brain barrier has been bypassed, as in the case of direct intracerebral injection (144, 220, 1262) or in cerebral tissues where there is no blood-brain barrier [pituitary gland (918); vomiting center (701, 702)], or where a brain-permeating fat-soluble ester of (±)-ADTN has been employed (494a). Furthermore, there are additional problems in comparing the biological potencies of congeners that are directly injected into the brain. The injected drugs cannot be expected to distribute identically within the neuropile, and, secondly, different congeners may have a different metabolic fate. As an example of the latter, (±)-5,6-ADTN [or (±)-5,6-dihydroxy-2-aminotetralin] was about 100 times more potent than (±)-6,7-ADTN when injected into the nucleus accumbens (220) but was only four times more potent when injected into the nucleus accumbens of the nialamide-pretreated rat (220). Woodruff et al. (1262), on the other hand, found that (±)-6,7-ADTN was slightly more potent than (±)-5,6-ADTN upon intracerebral injection. Such complications, therefore, may account for the fact that, although intracerebral injections suggested that (±)-5,6-ADTN was up to 100 times more potent than (±)-6,7-ADTN (220), in vitro systems (where the concentrations can be controlled) have generally revealed that (±)-6,7-ADTN was 10 to 20 times more potent than (±)-5,6-ADTN (tables 9, 10; 140, 1016, 1018), including pituitary cells, where (±)-6,7-ADTN was between 8 and 100 times more potent than (±)-5,6-ADTN (918). Therefore, in order to compare the potencies of dopamine congeners on brain dopamine receptors, it is desirable to know the local brain region concentrations of the congeners at a time when the brain effect is observed. Such an approach was taken by Westerink et al (1232a), who thereby concluded that (±)-6,7-ADTN was at least 13 times more potent than (±)-5,6-ADTN on dopamine autoreceptors, in agreement with the in vitro relative potencies for these congeners.

The structural requirements for a dopamine agonist at the D_2 dopamine receptor are summarized in figures 14 to 16. In addition to several essential requirements, there are also nonessential but desirable features that assist in enhancing the potency of a dopamine agonist. These are detailed as follows:

A. Presence of a Hydrogen-Bonding Group

As illustrated in figure 14, one of the requirements is for the agonist to have a hydrogen-bonding group (at position 3 in dopamine) to interact with the receptor. A hydroxyl group serves this function for practically all dopamine agonists. The hydroxyl group is located at ring position 3 in dopamine or in an equivalent position in the other dopamine agonists (see top of fig. 14). There are two excellent examples indicating that the 3 (in dopamine) position is the most effective location for the -OH group. The first example is (−)-5-N,N-dipropyl-2-aminotetralin, which was considerably more potent than the (±)-6 or (±)-7 congeners (see table 9). The second example is that of meta-tyramine, which has an IC_{50} value about half that of para-tyramine (see table 9). In the case of ergot alkaloids (e.g. *d*-LSD, lergotrile, dihydroergocyrptine, etc.), however, the hydrogen-bonding group is an -NH- group, as drawn in figure 16.

Although it appears essential to have at least one hydroxyl group (or one hydrogen-bonding group) on the agonist, a second hydroxyl group is desirable but not essential for dopaminergic activity. For example, the monohydroxylated compound, (±)-11-hydroxy-N-n-propylnoraporphine (816, 819), was potent, revealing an IC_{50} of 1500 nM on ^{3}H-spiperone binding (fig. 15). Similarly, as shown in figure 15, the monohydroxylated aminotetralin [i.e. (−)-5-hydroxy-N,N-dipropyl-2-aminotetralin] was very potent both in vivo (733) and in vitro (IC_{50} of 190 nM on ^{3}H-spiperone; fig. 15). The addition of a second hydroxyl (at ring position 4 in dopamine) generally enhances potency. For example, (−)-N-n-propylnorapomorphine, with its two hydroxyls, was approximately 5 to 10 times more potent than (±)-11-hydroxy-N-n-propylnoraporphine (see fig. 15). For the aminotetralin, however, this second hydroxyl is not particularly helpful. For example, the IC_{50} of (−)-5-hydroxy-N,N-dipropyl-2-aminotetralin (on ^{3}H-spiperone) was 190 nM, while that for (±)-5,6-dihydroxy-N,N-dipropyl-2-aminotetralin was 490 nM (see table 9); thus, the second hydroxyl did not

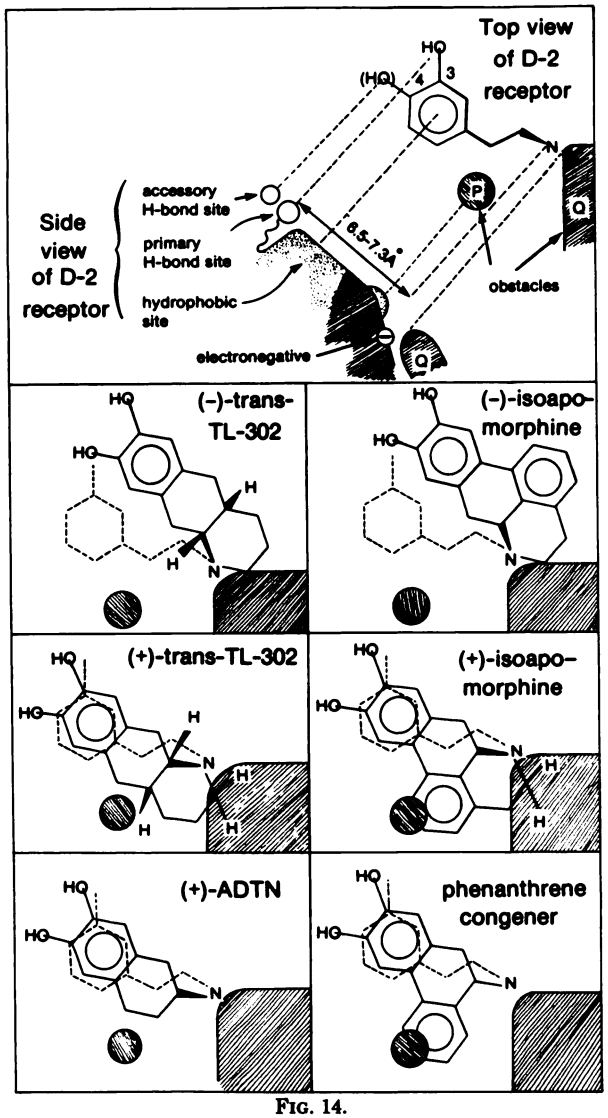

FIG. 14.

FIGS. 14–16. Interpretation of the structure-activity data for dopamine agonists acting on the D_2 dopamine receptor. The potency of a dopamine agonist appears to depend on several requirements. These are:

1. Hydrogen-bonding group. The hydrogen-bonding group of the agonist is almost always a hydroxyl located at ring position 3 in dopamine. In the case of ergot alkaloids, however, the hydrogen-bonding group is an -NH- (see example for lergotrile). In general, a second hydroxyl at ring position 4 is helpful, but not essential. For example, as shown in figure 15, (−)-5-OH-DPAT [or (−)-5-hydroxy-N,N-dipropyl-2-aminotetralin] has only one hydroxyl group but had a potent IC_{50} value of 190 nM against ^{3}H-spiperone binding. Thus, the D_2 receptor appears to have a primary site (fig. 14, top), as well as an accessory site, for hydrogen bond formation. (The IC_{50} values in fig. 15 are indicated immediately above the drug name and are taken from table 9 for calf striatum, as noted by the letter "s" in table 9).

2. High fat solubility. Although not essential, it is helpful to have high fat solubility in order to enhance potency. For example, as shown at the top of figure 15, potency varied directly with fat solubility, providing that the compound contained the active conformation; thus, (−)-N,n-propyl-norapomorphine [or (−)-NPA] was more potent than (−)-apomorphine, which in turn was more potent than (±)-5,6-dihydroxy-2-aminotetralin.

3. Nitrogen atom positioned 0.6 Å from plane of ring (see fig. 16). The highest potencies occurred when the nitrogen atom was positioned about 0.6 Å from the plane of the ring (fig. 16). For example, as shown in figure 15, R(−)-apomorphine was more potent than S(+)-apomorphine, and (−)-5-hydroxy-N,N-dipropyl-2-aminotetralin [or (−)-5-OH-DPAT] was 10 times more potent than (+)-5-OH-DPAT. In order to position the nitrogen properly, most dopamine agonists have an aromatic ring positioned as shown in figure 14. This is not met by (−)-trans-TL-302 or by (−)-isoapomorphine.

4. Distance of less than 7.3 Å between -OH and -N. The most potent compounds were those wherein the distance between the hydroxyl group and the nitrogen atom was 7.3 Å or less. For example, providing the compound had the nitrogen atom positioned ~ 0.6 Å from the plane of the ring, the most potent compounds were those that had a distance of 6.5 Å [e.g. (−)-5-OH-DPAT and (±)-11-OH-NPA]. Those congeners with a distance of 7.3 Å (and N below the ring) were weaker [e.g. (±)-7-OH-DPAT)], while those having a distance of 7.8 Å were extremely weak [e.g. (±)-6-OH-DPAT and (±)-10-OH-NPA]. As analyzed by McDermed (732), the case of ADTN (or 6,7-dihydroxy-2-aminotetralin) is interesting. (+)-ADTN was about 10 times more potent than (−)-ADTN. This fact is in keeping with the above requirements. The interesting feature is that the requirement of 7.3 Å is met by the hydroxyl in the 7 position and not that in the 6 position (see bottom of figs. 14 and 15).

5. Steric hindrance factors. It is necessary to postulate an obstacle (Q) that must hinder the attachment of the (+)-enantiomers of (±)-*trans*-TL-302 and (±)-isoapomorphine, as above. (It should be noted that [±]-TL-302 has not been resolved into its enantiomers, and that the mention of each enantiomer separately is merely for illustrative purposes.) There is likely to be a second obstacle (P) to hinder the attachment of the phenanthrene congener shown (145a). These obstacles are avoided by all the other bioactive congeners.

significantly alter or enhance the biological potency of the (−)-5-monohydroxy compound, assuming all the potency resided in the (−)-enantiomer.

B. High Fat Solubility

A nonessential but desirable feature is for the dopamine agonist to have high fat solubility. This is illustrated at the top of figure 15, where it can be seen that potency at the D_2 receptor varied directly with the fat solubility of the compound. For example, (−)-N-n-propylnorapomorphine (IC_{50} of 190 nM on ^{3}H-spiperone) was considerably more potent than R(−)-apomorphine (IC_{50} of 750 nM), which in turn was much more potent than (±)-5,6-dihydroxy-2-aminotetralin (IC_{50} of 9000 nM for the racemate), even though all these three compounds have identical conformations. Presumably, therefore, additional carbon atoms, appropriately placed, enhance the biomembrane solubility (987, 991, 1013) such that the agonist more readily enters the brain (494a) and more readily associates hydrophobically with the D_2 receptor.

A second example of this nonspecific role of fat solubility may be detected in the IC_{50} values (on ^{3}H-spiperone) for the dialkyl derivatives of (±)-5,6-dihydroxy-N,N-dialkyl-2-aminotetralin; the dipropyl congener had an IC_{50} of 490 nM, the diethyl congener had a value of 2100 nM, while the dimethyl compound had an IC_{50} of 3600 nM (see table 9 for data).

The same phenomenon may be seen in the aporphine homologues (855); (−)-N-n-propyl-norapomorphine was more potent in vivo (postural asymmetry test) than the N-ethyl compound, which was more potent than the N-methyl compound (855). The N-butyl compound, how-

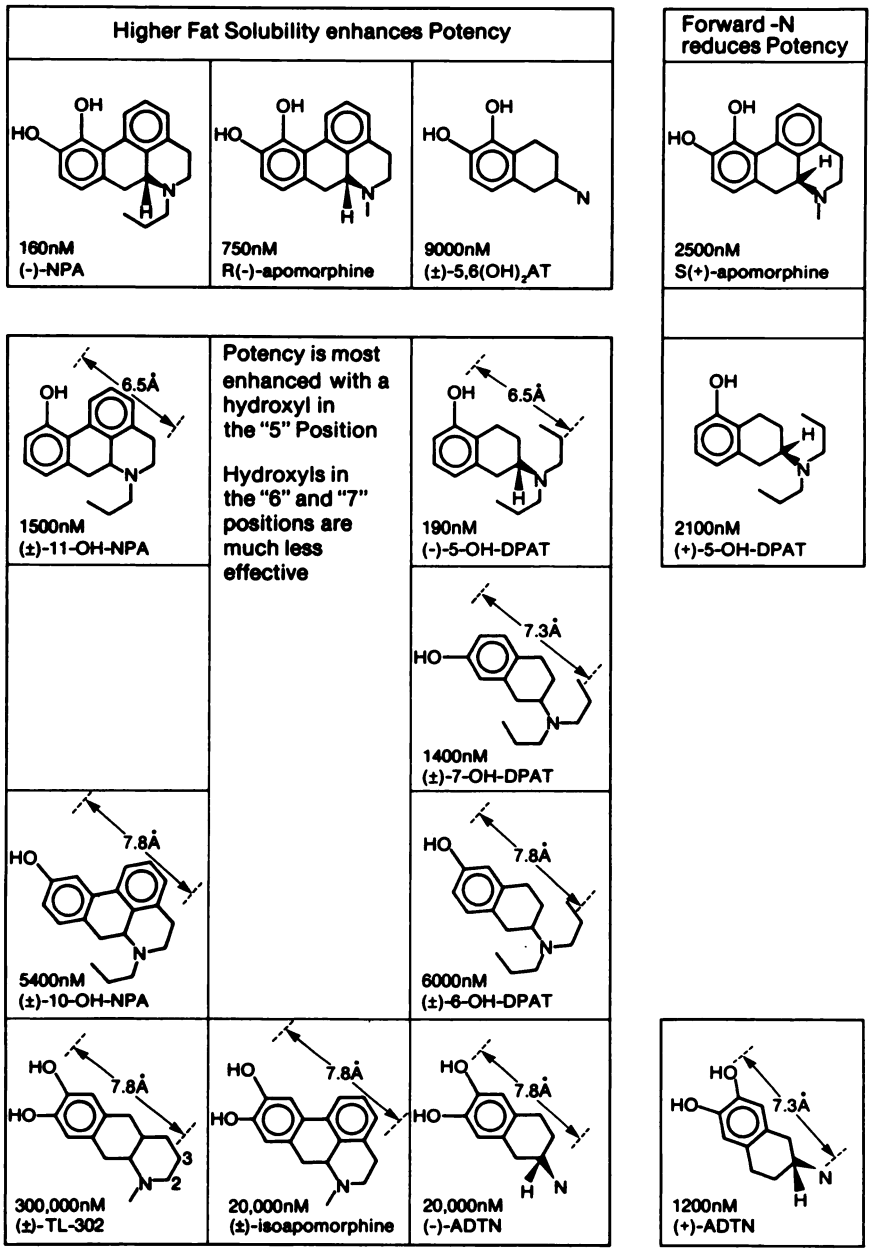

FIG. 15.

ever, was completely inactive (855), despite its high fat solubility. This inactivity of the N-butyl derivative most likely stems from a steric hindrance factor (see section XV C).

C. *Nitrogen Atom Positioned about 0.6 Å from Plane of Ring*

An essential feature for dopaminergic potency is for the nitrogen atom to be positioned away (~ 0.6 Å) from the plane of the ring, as shown in figures 14 and 16. For example, R(−)-apomorphine was more potent than S(+)-apomorphine (see 950), and (−)-5-hydroxy-N,N-dipropyl-2-aminotetralin [or (−)-5-OH-DPAT] was 10 times more potent than (+)-5-OH-DPAT (fig. 15).

In order to position the nitrogen atom properly, most dopamine agonists have an aromatic ring in the position depicted in figure 14. It has long been known that (±)-isoapomorphine has little, if any, biological activity (761, 817, 875); this is compatible with the extremely high IC_{50} value of 20,000 nM for (±)-isoapomorphine (fig. 15). The inactivity of (−)-isoapomorphine can be explained by the fact that this enantiomer cannot appropriately position its aromatic ring in order to position the nitrogen atom; this difficulty is drawn in figure 14. (Its enantiomer, (+)-isoapomorphine, has another difficulty, and this is discussed in section XV E).

Similarly, the (−)-enantiomer of *trans*-TL-302 (figs. 14, 15; 143, 144a, 1054) also cannot simultaneously fulfill the requirements for a properly positioned nitrogen atom, and a length of less than 7.3 Å for the OH-N distance, as indicated in figure 14.

As shown in figure 16, the ergolines are also compatible

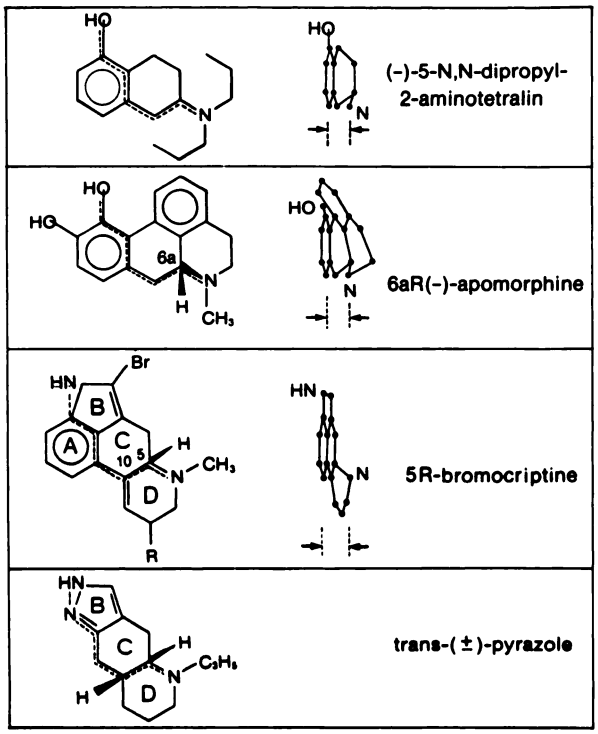

FIG. 16. The dotted line indicates the important portion of dopamine required for biological activity. The pyrazole compound is a partial segment of an ergoline and demonstrates that the benzene ring A is not essential for biological activity (36a). The molecular structures on the right give the view of each molecule as seen from the aromatic end of the molecule, using Dreiding models. Each pair of arrows thus indicate that the nitrogen atom in each case is approximately 0.6 Å from the main plane of the molecule.

with the model of the D_2 receptor illustrated in figure 14. Partial structures of the ergolines are also strongly dopamine-mimetic, particularly *trans*-(±)-4,4a,5,6,7,8,8a, 9-octahydro-5-propyl-2H-pyrazolo[3,4-g]quinoline (36a; see fig. 16 for structure). These interesting pyrazoles demonstrate that the phenyl ring of dopamine (or A ring of the ergolines) is not essential for biological activity. The phenyl ring apparently serves only to assist in positioning the relation between OH and N (in dopamine) or between NH and N (in ergolines).

It is not essential that the asymmetric carbon atom have an identical absolute configuration in all the active dopamine-mimetic compounds, as long as the nitrogen atom is positioned away from the plane of the phenyl ring holding the -OH or the -NH group. For example, the asymmetric carbon atom 6a in (−)-apomorphine has the R configuration, while that in the bioactive (+)-6,7-ADTN has the S configuration. The active ergolines have an asymmetric carbon at position 5 that is in the R configuration (fig. 16). Thus, the superposition of an ergoline (with the H at C5 below the ring) with that of (−)-apomorphine (with the H at C6a above the ring) results in opposite configurations at the asymmetric carbon, as has been pointed out by Bach et al. (36a). There is no need, however, for the absolute configuration to be identical, as long as the ergoline is sufficiently flexible to permit the nitrogen atom to be positioned by ~ 0.6 Å away from the plane of the A or B ring. Camerman et al. (138a) have demonstrated a good fit between (−)-apomorphine and bromocriptine.

D. Distance of Less Than 7.3 Å between -OH and -N Groups

The highest potencies occurred in those compounds wherein the distance between the hydroxyl group and the nitrogen atom was 7.3 Å or less. This is best exemplified in the monohydroxylated aminotetralin series prepared by McDermed et al. (733). The most potent compound, (−)-5-hydroxy-N,N-dipropyl-2-aminotetralin, had a distance of 6.5 Å (fig. 15), and this gave an IC_{50} value (on ^{3}H-spiperone) of 190 nM. Considerably less potent was (±)-7-hydroxy-N,N-dipropyl-2-aminotetralin with a distance of 7.3 Å and an IC_{50} value of 1400 nM (fig. 15). The least potent was (±)-6-hydroxy-N,N-dipropyl-2-aminotetralin, with a long distance of 7.8 Å and a high IC_{50} value of 6000 nM.

The above interpretation helps explain why (+)-6,7-ADTN was more potent (IC_{50} value of 1200 nM) than (−)-6,7-ADTN (IC_{50} value of 20,000 nM). This is illustrated at the bottom of figures 14 and 15. The requirements of 7.3 Å together with a nitrogen atom below the ring plane are met only by (+)-ADTN (see 19).

E. Steric Hindrance Factors

Finally, it is necessary to account for the inactivity of (+)-isoapomorphine. Although it has been suggested by Grol and Rollema (445), as well as by McDermed et al. (732), that the nonhydroxylated phenyl ring of isoapomorphine sterically hindered attachment to the receptor, Cannon et al. (144a) noted that this explanation was not by itself sufficient to explain the inactivity of (±)-isoapomorphine. Cannon et al. observed that (±)-*trans*-TL-302 (figs. 14, 15) was inactive, despite the fact that it had the identical conformation of (±)-isoapomorphine but without the nonhydroxylated phenyl ring.

A possible explanation, therefore, for the inactivity of (+)-*trans*-TL-302, as well as (+)-isoapomorphine, may be that there is an obstacle (indicated by "Q" in fig. 14) in the receptor near the binding site for the nitrogen atom. This obstacle would sterically hinder a tilted ring, but would have little or no effect on the ergot alkaloids or on the octahydrobenzo(f) quinolines. Such an obstacle, furthermore, would also be expected to prevent a compound like (−)-N-n-butyl-norapomorphine (855) from attaching to the receptor, since the butyl group cannot fold up like a propyl group to avoid the obstacle; the terminal carbon atom of the butyl group would bump into either the 7 carbon atom of apomorphine or the receptor obstacle.

At the same time, moreover, it is necessary to explain the fact that a phenanthrene congener, 2,3-dihydroxy-9-amino-9,10-dihydrophenanthrene, (fig. 14) did not stimulate or inhibit dopamine-sensitive adenylate cyclase (D_1 receptor) and did not elicit vasodilation (820). It is likely, therefore, that this particular phenanthrene congener

would be weak or inactive on the D_2 dopamine receptor (^{3}H-spiperone binding), although in general the D_2 dopamine receptor has a different dopamine structure-activity pattern than the D_1 receptor or the vascular dopamine receptor. The biological inactivity of this congener may be explained by the presence of an obstacle situated at point P in figure 14. This obstacle P would also hinder the attachment of (+)-isoapomorphine but would not interfere with the binding of the other dopamine agonists, including the related phenanthrene congener, 3,4-dihydroxy-9-N,N-dimethylamino-9,10-dihydrophenanthrene (145a), which has about 25% of the potency of apomorphine in eliciting emesis (145a). Other phenanthrenes, however, such as the 9,10-dihydrophenanthrene-4-ethylamines (fig. 13; 139a), are approximately equipotent to apomorphine (pigeon emesis) and these compounds fit the D_2 receptor model.

The presence of an obstacle at point P also explains the inactivity of the recently synthesized octahydrobenz[h]isoquinolines (144b), since carbon atoms 5 and 6 of those compounds directly collide with obstacle P.

F. Unresolved Difficulties

While the model for the D_2 receptor in figure 14 fits the majority of dopaminergic agonists, there are a few dopamine-related congeners which ought to fit into that receptor but which apparently do not have any effect on the D_2 receptor. For example, no dopaminergic-like rotation was elicited by compound (±)-17c (405, fig. 13; 1-*n*-propyl-2-(3′,4′-dihydroxybenzyl)-piperidine), by compound (±)-21c (405; 1-(3′,4′-dihydroxybenzyl)-2-*n*-propyl-1,2,3,4-tetrahydroisoquinoline), or by compound 3-PPP (478; N-*n*-propyl-3-(3-hydroxyphenyl)-piperidine) (fig. 13). Although these compounds have a somewhat lower fat solubility than (−)-apomorphine, this factor does not appear to be sufficient to account for their low potency at the D_2 site. Since each of these three congeners has an asymmetric carbon atom, it is theoretically conceivable that one of the enantiomers from each pair might act as an antagonist at the receptor. A more likely possibility is that the position of the nitrogen atom with respect to the plane of the hydroxylated phenyl ring may not be as required. The rotational freedom of the hydroxylated phenyl ring confers a very low probability for the appropriate position of the nitrogen atom, a problem that does not arise in the aporphines or in the aminotetralins. Since 3-PPP is a very potent agonist at dopamine autoreceptors (478), it appears that the autoreceptors may not require such a precise positioning of the nitrogen atom.

G. References for Pharmacology of Dopamine Agonists

Further information on the chemistry and pharmacology of various dopaminergic agonists may be obtained from the following references:

Phenylethylamine-related	92, 225, 324, 403, 404, 405, 407, 758, 701, 142, 145, 580, 526, 525, 697–699, 528, 478, 599
Aporphines	78, 635, 816, 819, 855, 874, 1039
Apomorphine	32, 44, 47, 113, 114, 206, 325, 551, 739, 818, 429a, 526, 528, 1062, 770
Isoapomorphine	761, 817, 875
N-n-propyl-norapomorphine	32, 221, 749–751, 815, 816, 818, 752, 819, 855, 968
phenanthro-azepine analogue	73
bulbocapnine	527, 1171
(+)-aporphines	950
isoquinolines	815
Aminotetralins	524, 581, 528, 494a, 1232a, 113, 144, 173, 220, 222, 224, 490, 494, 731, 733–735, 918, 1040, 1260, 1262, 429a, 701, 702, 948, 145, 700, 529
Aminoindanes	173, 701, 948
Octahydrobenzo(f)-quinolines	734, 1054, 143, 146, 144a, 702, 141, 703, 1029
Octahydrobenzo(g)-quinolines	1054, 143, 144a
Phenanthrene analogue	820
Imidazoline derivative	1106

XVI. Localization of D_2 Receptors and D_3 Sites

As summarized in table 15, there is general agreement that D_2 receptors are situated on postsynaptic processes in the striatum. This conclusion is based on the general observation (table 15) that lesions of these postsynaptic processes by kainic acid invariably reduces the density of the D_2 receptors, and that lesions of the presynaptic (dopamine-containing) neurones by 6-OH-dopamine almost invariably result in an elevation of the D_2 receptors (compatible with denervation supersensitivity) (see also 554b, 913, 388a, 1147). There are also reports that there are binding sites for ^{3}H-butyrophenones on the terminals of axons arising from extrastriatal regions, such as the cerebral cortex (244, 974, 386); it is not yet clear whether these presynaptic sites, labeled by ^{3}H-butyrophenones, are D_2, S_2, or NSS sites in character. There is also a possibility that some of the ^{3}H-butyrophenone binding may be to glial cells (472, 473).

The anatomical location of the D_3 sites, however, is only now being resolved. Our earlier work on this subject (808) revealed that the density of ^{3}H-apomorphine binding sites was reduced by 47% in the rat striatum after a 6-hydroxy-dopamine-induced lesion of the left medial forebrain bundle. This had suggested that about half of the high-affinity sites for ^{3}H-apomorphine were located on presynaptic terminals of nigral dopamine neurones. Although recent experiments (1228, 724a, 372a) are com-

patible with and support the original observation (808), there are two reports (250, 378) indicating that lesions of the nigral dopamine neurones *elevated* the binding of ^{3}H-apomorphine by 52% (250) and of ^{3}H-ADTN by 27% (378) in the rat striatum. Because of these different findings we decided to repeat our earlier experiments (808), but this time with ^{3}H-dopamine instead of ^{3}H-apomorphine. Although others report serious difficulty working with ^{3}H-dopamine (250a), we have found that this ^{3}H-ligand gives extremely reliable results under our conditions, particularly when ^{3}H-dopamine of very high specific activity is used (690a, 1148) and when one uses a low concentration of ascorbate (0.02% or less) and 1 to 5 mM Na_2EDTA. The properties of ^{3}H-dopamine binding are similar to those for the binding of ^{3}H-apomorphine or ^{3}H-ADTN under our conditions (690a, 1148, 1024, 1016). Our current work indicates that ^{3}H-dopamine binding in the striatum becomes reduced by 40% after lesioning the nigral neurones, in agreement with our earlier work with ^{3}H-apomorphine (808).

This reduction in ^{3}H-dopamine binding sites in the nigral-lesioned striata agrees with some reports (808, 1228, 724a), but not with others (250); ^{3}H-apomorphine was used in all of these studies. It is possible to resolve the fact that Creese and Snyder (250) found elevated ^{3}H-apomorphine binding, while we found decreased ^{3}H-apomorphine and ^{3}H-dopamine binding in the nigral-lesioned striata, by considering that Creese and Snyder (250) were primarily labeling D_2 dopamine receptors with ^{3}H-apomorphine, while we have been labeling D_3 dopamine sites with either ^{3}H-apomorphine (808) or ^{3}H-dopamine (690a, 1148). This possibility could be expected, since the assay conditions were different. As presented elsewhere in detail (690a, 1148), the properties of the D_2 and D_3 dopamine sites are considerably different. For example, D_2 sites [which can be labeled by ^{3}H-neuroleptics (1023, 118, 671), ^{3}H-ergot alkaloids (1151, 196a), or ^{3}H-N-propyl-norapomorphine (1153)] have a very high affinity for neuroleptics (generally between 0.1 and 50 nM) but a low affinity for dopamine (about 500 to 5000 nM). D_3 dopamine sites, on the other hand, have a very high affinity for dopamine (between 1 and 7 nM; 690a, 1148, 1022), but a low affinity for neuroleptics (about 200 to 2000 nM).

The sites being labeled by ^{3}H-apomorphine under the conditions of Creese and Snyder (250) had properties more resembling the D_2 sites; for example, they found that ^{3}H-apomorphine was displaced by low concentrations of spiperone (0.4 nM) and haloperidol (30 nM), but high concentrations of dopamine (300 nM) (250a). However, the sites being labeled by ^{3}H-apomorphine or ^{3}H-dopamine under our present working conditions were occupied by high concentrations of neuroleptics (spiperone 1200 nM; haloperidol 200 nM; 690a, 1148) and low concentrations of dopamine (5 nM; 690a, 1148). Thus, if ^{3}H-apomorphine primarily labels the D_2 receptors under the conditions of Creese and Snyder (250), it is reasonable to expect the binding of ^{3}H-apomorphine and ^{3}H-neuroleptics to go up or down together, since under those conditions both ^{3}H-ligands are labeling the same D_2 receptors. Under our present conditions, however, ^{3}H-apomorphine or ^{3}H-dopamine labels D_3 sites, which differ from the D_2 sites labeled by ^{3}H-neuroleptics.

There are other considerations (1215) involved in lesion studies, including receptor synthesis (125b, 36) and receptor selectivity (1081). Such experiments have been very useful, however, in the field of serotonin receptors, where lesions of serotonin neurones did not reduce S_1 sites (69) but resulted in an increase in both the density of S_1 sites (1020, 813) and S_2 sites (36, 379; see also 547, 1096, 1253).

XVII. Dopamine Autoreceptors; Possible Relation to Binding Sites for Dopaminergic ^{3}H-Ligands

Between 1970 and 1972 considerable evidence emerged for the existence of presynaptic alpha-adrenoceptors on adrenergic terminals (637, 1098, 638, 468). Stimulation of these alpha receptors inhibits the release of noradrenaline, while blockade of these receptors increases the release of noradrenaline; these effects have been found not only in whole tissues (640, 1087–1089, 1230, 27, 301, 76, 1145, 1146, 207, 77, 1221, 62, 1243, 1244, 927, 719, 866, 70), but also in slices (297, 1130) and synaptosomes (788, 279a).

Likewise, dopamine-containing neurones have dopamine receptors (autoreceptors) that can inhibit the release of dopamine (575, 151–155, 158–160, 4, 939, 574, 834, 938). These dopamine autoreceptors may be situated either on the dopamine cell processes within the substantia nigra (109, 448, 1252, 86, 267, 601, 828, 1224, 447, 110) or on the preterminal endings (presynaptic receptors) within the striatum (110, 542, 1235). Activation of these autoreceptors by dopamine or apomorphine results in less dopamine being released as well as less dopamine being synthesized by tyrosine hydroxylase (940; but see 708). Neuroleptics block these dopamine autoreceptors, contributing further to the neuroleptic-induced acceleration of release and synthesis of dopamine (161, 983, 1277).

The doses of apomorphine that activate these biochemical actions of autoreceptors are very low (0.05 to 0.5 mg/kg i.p.). Such low doses produce behavioural effects compatible with a reduction in the release of dopamine, in contrast to the classical dopamine-mimetic effects (stereotypy, locomotion, etc.; 882, 410) of high doses of apomorphine (1 to 10 mg/kg i.p.). In animals these low-dose effects include sedation (292, 293) and hypomotility (1103, 1104, 293; see also 920).

Clinically, the effects of low doses of apomorphine or L-DOPA in patients also result in behaviour compatible with a reduction in the release of endogenous dopamine. For example, very low doses of these and other dopamine-mimetic drugs cause sedation (134), suppress dys-

kinetic (291, 168, 1163, 1116, 1061) or choreiform movement (214, 1162), have a distinct antipsychotic action (530–532, 634, 212, 392, 747, 1060, 157, 1115, 156; but see 133), potentiate parkinsonism (212, 213), and reduce ethanol-withdrawal symptoms (965).

A current problem is to identify these dopamine autoreceptors in vitro by a selective ^{3}H-ligand (1150). This type of problem has already received much attention in the case of alpha-adrenoceptors (1255, 243). The postsynaptic alpha$_1$ sites can be labeled by ^{3}H-WB4101 (1185, 863, 561, 1274), while presynaptic alpha$_2$ sites are possibly labeled by ^{3}H-clonidine (1185, 1180, 1227), by ^{3}H-noradrenaline or ^{3}H-adrenaline (1188, 1189, 1183, 1187, 1192), or by ^{3}H-para-aminoclonidine (1274). It had been suggested earlier (442) that ^{3}H-clonidine and ^{3}H-WB4101 labeled two different states (agonist and antagonist states) of the alpha receptor. The prevailing view (861), however, is that these ^{3}H-ligands label entirely separate sites. It appears that both these sites can also be labeled by ^{3}H-dihydroergocryptine (861; see 1151, 276, 1249, 439, 1247, 10, 1170, 1181, 451, 441, 440, 1035, 756, 479 for further data on this ^{3}H-ligand). As mentioned in an earlier section, however, ^{3}H-ergot alkaloids are not selective (298, 428), since in addition to labeling alpha-adrenoceptors, they can also bind to dopamine receptors (165, 1158) and serotonin receptors (197). Thus, when using an ^{3}H-ergot alkaloid to label a particular neurotransmitter receptor, it would be best to include other drugs in the assay to occlude receptors that are not under study and to which the ^{3}H-ergot alkaloid may bind (see section IX E on D_2 and S_2 receptors).

In order to identify presynaptic binding sites for either dopaminergic (1226) or adrenergic ^{3}H-ligands (1227), one must obtain evidence that lesions of these presynaptic neurones result in a diminution of these sites. Since clonidine is highly selective on effects mediated by presynaptic adrenoceptors (108, 1230, 301, 76, 125a, 1146, 927, 207, 719), it is reasonable to expect that ^{3}H-clonidine would preferentially label these presynaptic receptors. However, lesions of such noradrenaline-containing neurones have generally resulted in an increase in the density of sites for ^{3}H-clonidine (1180, 460, 916) with the important exceptions of the septum and the amygdala, where the densities were reduced (916). Such lesions also produce a decrease in the amount of ^{3}H-dihydroergocryptine that binds to heart tissue (1030). Thus, it appears that ^{3}H-clonidine may bind to both pre- and postsynaptic sites. Many of these lesion-type experiments may have to be repeated in the presence of protein synthesis-inhibitors, in order to preclude the possibility of rapid synthesis of alpha$_2$ receptors by the postsynaptic cell.

Somewhat similar difficulties have been encountered in trying to identify dopamine autoreceptors by means of ^{3}H-ligands. The following points indicate that approximately 50% of the D_3 sites are situated on presynaptic dopamine-containing neurones.

A. Lesions of Dopamine Neurones in Adult Rats

As summarized in section XVI (table 15), lesions of dopamine neurones in adult rats resulted in approximately a 50% reduction in the density of D_3 sites, as measured either by ^{3}H-apomorphine (808, 724a, 372a) or by ^{3}H-dopamine.

B. Lesions of Dopamine Neurones in Immature Rats

Lesions of maturing dopamine neurones can be made in 5-day-old rats by means of an intracisternal injection of 6-OH-dopamine into animals that have been pretreated with imipramine (1033, 1034). Such lesions result in a depletion of striatal dopamine (after 2 to 3 weeks) of well over 90%. These striata have a density of D_3 sites that has become reduced by 20% to 50% (S. Watanabe, P. Seeman, and B. A. Shaywitz, unpublished data).

C. Lesions of Dopamine Neurones in Parkinson's Disease

The densities of the D_3 sites were reduced by about 30% to 50% in the postmortem striata from patients who had died with Parkinson's disease (650, 651). Although these findings had been obtained with ^{3}H-apomorphine, a similar reduction in the density of D_3 sites in these diseased tissues has also been found with ^{3}H-dopamine (649a, 1002a).

In order to determine the function of the D_3 sites and to examine whether they may have a presynaptic function, it is essential to compare the pharmacological properties of these sites (IC_{50} values) with those for presynaptically mediated effects. The D_3 sites and the presynaptic biological effects have the following features in common:

D. Pre- and Postsynaptic Action of Apomorphine

As reviewed in the beginning of this section XVII, low doses of dopamine-mimetic drugs produce a variety of behaviours that are just the opposite of those behaviours occurring at high doses. The behavioural effects of high doses (stereotypy, locomotion, etc.) are compatible with stimulation of the postsynaptic D_2 receptors (figs. 8 to 11). The behavioural effects of the low doses (sedation, antidyskinesia, antipsychotic action, etc.) are compatible with activation of the presynaptic receptors (see refs. cited at beginning of this section).

Quantitatively, these low-dose actions of apomorphine occur at doses that are 0.01 to 0.001 of those that elicit the high-dose actions.

In agreement with this quantitative difference is the fact that the D_3 site has an apomorphine IC_{50} value of 2 to 4 nM (1148; table 10; 1015), while the D_2 site has an apomorphine IC_{50} value of about 1000 nM (1023; table 9); the two sites thus differ by about 300-fold in their sensitivity to apomorphine. It is conceivable, therefore, that the D_3 site may be the one selectively activated at low doses of apomorphine, while the D_2 receptors are

activated (and dominant) at apomorphine doses 300-fold higher. It is important to note that the dopamine autoreceptors can vary greatly in their sensitivity to apomorphine; those in the olfactory tubercle are about six times more sensitive to apomorphine than those in the striatum (833).

These considerations are compatible with the important observations made by Skirboll, Grace, and Bunney (1052) that the dopamine-containing nigral neurones are one or two orders of magnitude more sensitive to dopamine or apomorphine than the postsynaptic striatal cells.

E. Pre- and Postsynaptic Action of Neuroleptics

In a complicated and careful series of experiments, Andén and Grabowska-Andén (13a) have shown that some neuroleptics (haloperidol, clozapine, and pimozide) were much more effective in blocking rotational behaviour (i.e. postsynaptic dopamine receptors) than inhibiting the presynaptic actions of apomorphine. It is known, furthermore, that high concentrations of 200 nM haloperidol (542) or 1000 nM fluphenazine (1235) are needed to inhibit the presynaptic dopamine receptors in striatal synaptosomes (542) or slices (1235).

These high molarities of neuroleptics are consistent with the high haloperidol IC_{50} value (200 nM; 1148) or the high fluphenazine IC_{50} value (500 nM; 1148) on the D_3 site (see table 10). Clozapine and pimozide are also weak on the D_3 site (table 10). The high molarities are in sharp contrast to the very low molarities (1 to 50 nM) required for these neuroleptics on the postsynaptic D_2 receptors.

The situation cannot be so simple, however, since it has also been reported that low doses of haloperidol (of the order of 0.05 mg/kg; 1104, 293) antagonize the low-dose hypomotility action of apomorphine, an effect apparently mediated by dopamine autoreceptors. Sulpiride and pimozide, however, have been reported to be very weak in antagonizing this low-dose effect of apomorphine (292, 293). It will be important to do more experimental work on the neuroleptic sensitivity of the behavioural effects that are mediated by dopamine autoreceptors.

F. Pre- and Postsynaptic Action of Bromocriptine

The effect of bromocriptine is somewhat weaker on dopamine autoreceptors than on postsynaptic dopamine receptors. For example, bromocriptine at 1 to 4 mg/kg (i.p.) causes appreciable rotational behaviour in rats (377, 299), and 1 mg/kg (p.o.) gives optimum benefit to patients with Parkinson's disease (1135; fig. 8). Effects mediated by dopamine autoreceptors, however, require somewhat higher doses of bromocriptine (2.5 to 10 mg/kg; 717b, 51).

Other clinical observations suggest that bromocriptine is weaker in its effect on dopamine autoreceptors than on postsynaptic dopamine receptors. For example, bromocriptine (15 to 38 mg/day) exerts no antipsychotic action, unlike apomorphine, but only produces the postsynaptic actions of nausea and vomiting (1165). Low doses of bromocriptine, therefore, would not be expected to suppress tardive dyskinesia by means of autoreceptors (55).

These behavioural data with bromocriptine are in line with the bromocriptine IC_{50} values on the D_3 and D_2 sites. As can be seen in figure 7, bromocriptine has a 3-fold greater affinity for the D_2 receptor than for the D_3 site.

G. Pre- and Postsynaptic Actions of Various Dopamine Agonists

A variety of dopamine agonists have now been tested for their potencies on dopamine autoreceptors (947a) and on the D_2 receptors (table 9) and the D_3 sites (table 10). As shown in figure 17, there is a good correlation between the autoreceptor ED_{50} doses and the IC_{50} values on the D_2 receptors (fig. 17A). However, as detailed in the figure legend, each dopamine agonist has only a limited duration of action (40 min) such that it appears reasonable to compare the doses as if these drugs had identical fat solubility. When this is done (see fig. 7; also see 709a), then it can be seen that the normalized doses correlate much better with the IC_{50} values for the D_3 site (fig. 17D) than for the D_2 receptor. In future experiments it will be necessary to measure the brain or striatum concentrations of each of these agonists in order to relate the striatum concentrations with the IC_{50} values. This approach will provide more direct evidence as to whether these various dopamine agonists activate D_2-type or D_3-type sites for the eventual production of the autoreceptor action.

H. Dopamine Receptors in Peripheral Tissues

There are pre- and postsynaptic dopamine receptors in peripheral tissues as well (421). The postjunctional dopamine receptors mediate vasodilation in many tissues (979, 1209, 859, 416–420, 422–424, 692, 1113, 79, 1141, 596, 597, 917, 928, 266, 1270, 800, 277, 104, 204, 314, 730, 1160, 172, 858, 783, 781, 66; but see 328). Some of these tissues have dopaminergic innervation (52, 291). The potencies of various dopamine agonists that produce this vasodilatory action are summarized in table 16.

There are also presynaptic dopamine-sensitive sites on adrenergic nerve terminals that also result in vasodilation or cardiodeceleration because these sites inhibit the release of noradrenaline (338, 1242, 1241, 289, 25, 147, 780, 474, 1048, 696, 300, 643, 695, 124, 1071, 91, 125, 969, 1194, 384, 421, 106a).

The sensitivities of these peripheral dopamine receptors to agonists and antagonists (table 16), however, seem to be very different in all cases than the D_2 receptors in the brain or the pituitary gland. For the postsynaptic dopamine receptor in vascular tissue, the (+)-form of sulpiride is about five times more potent than (−)-sulpiride (421); on the presynaptic receptor, (−)-sulpiride is

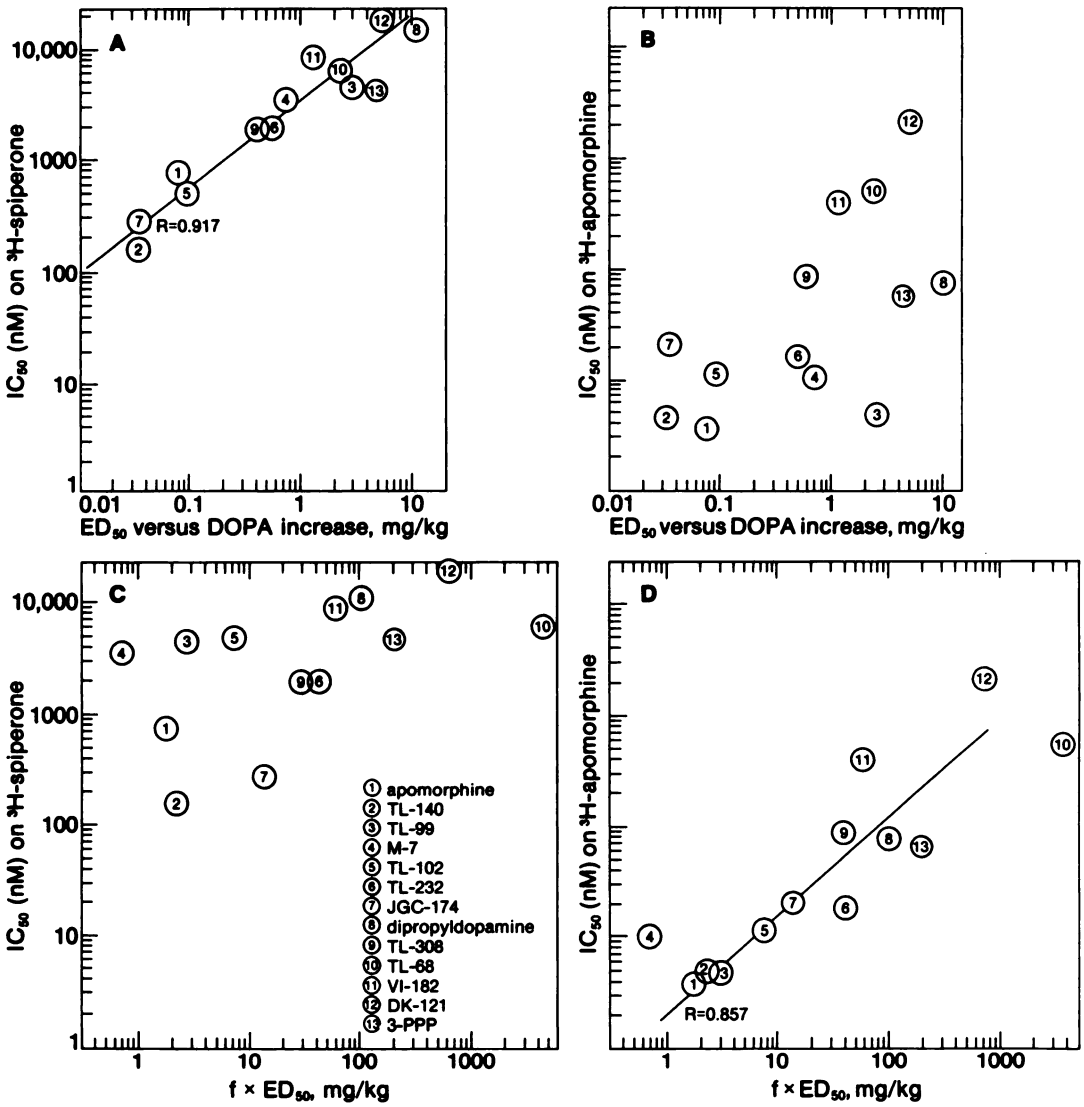

FIG. 17. Showing that it is possible to correlate the autoreceptor actions of dopamine agonists with their effects on D_3 dopamine sites, providing that one takes into account the ease of permeation into the brain (i.e. fat solubility) of the dopamine agonists. The IC_{50} values were obtained in this laboratory on calf striatum (from tables 9 and 10, indicated by the letter "s"). The ED_{50} values were the doses that reversed the gammabutyrolactone-induced elevation of DOPA by 50% [data from Rusterholz et al. (947a), Goodale et al. (429a), and Dr. J. P. Long (personal communication)]; the standard procedure for this type of experiment (833) is for the dopamine agonist to be given first, followed 5 min later by gammabutyrolactone, followed 5 min later by a DOPA decarboxylase inhibitor (Ro4-4602); the rat is killed 30 min later. The duration of action for each dopamine agonist, therefore, was fixed at 40 min. The elevation of brain DOPA by gammabutyrolactone is thought to be a result of disinhibition of dopamine autoreceptors (833); dopamine agonists prevent the DOPA elevation. Figures A and B illustrate that, although there was a good correlation (fig. A) between the ED_{50} doses and the ^{3}H-spiperone IC_{50} values (D_2 dopamine receptors), there was a poor correlation (fig. B) between the ED_{50} doses and the ^{3}H-apomorphine IC_{50} values (D_3 dopamine binding sites). However, because of the limited duration of action of each dopamine agonist (40 min), it appears reasonable to normalize the ED_{50} values such as to be able to compare the doses of the different drugs *as if* they had identical fat solubility and, thus, *as if* they had a similar ease of permeation into the brain. This normalization can be done by multiplying each ED_{50} by a fat solubility factor, f, the derivation of which is given in figure 7. It can be seen, therefore, in figures C and D that the $f \cdot ED_{50}$ doses correlated much better with the ^{3}H-apomorphine IC_{50} values (fig. D) than with the ^{3}H-spiperone IC_{50} values (fig. C). The chemical structures of the compounds are given in figure 12 and 13. It is important to emphasize that such fat solubility corrections would only be expected to be meaningful in experiments such as these where there was a brief and fixed time (40 min) to the experiment, thus limiting the amount of drug that actually reaches the brain; such corrections would not be meaningful, for example, in experiments where the animal's behaviour is monitored for several hours (figs. 9 and 11) or where there is no blood-brain barrier involved (data on emesis in fig. 10 and data on pituicytes in fig. 18).

active while (+)-sulpiride is not (421, 304).

In order to distinguish between presynaptic adrenoceptors and presynaptic dopamine receptors in the periphery, it has usually been necessary to add excess amounts of phentolamine or phenoxybenzamine (304, 307, 399) to block adrenoceptors; it is also necessary to add cocaine to prevent the uptake or reuptake of the catecholamines into the nerve terminals (489, 814, 1092, 642). These factors presumably determine the IC_{50} values. For example, it requires 200 nM haloperidol to block the pre-

synaptic action of dopamine on the rabbit ear artery nerve (489); when cocaine is present, lower concentrations of haloperidol (approximately 10 nM) are effective in blocking the actions of dopamine (1092). It is difficult to find a similar pharmacological pattern between central and peripheral dopamine receptors (cf. tables 16, 9, and 10). Either these receptors are truly different or the methods are presently not sufficiently discriminating in order to characterize the peripheral dopamine receptors. Finally, it is interesting to note that a variety of presynaptically-acting drugs, which produce cardiodeceleration and which are dopamine-related, correlate much better with the IC_{50} values on ^{3}H-clonidine binding rather than with the IC_{50} values for either D_2 or D_3 sites (1227). It is possible, therefore, that many of these actions of dopamine congeners on peripheral nerves may actually be actions of special types of adrenoceptors rather than dopamine receptors.

XVIII. Use of D_2 Receptors for Measuring Neuroleptics in Serum

The procedure for measuring neuroleptic/dopamine receptors (i.e. D_2 receptors) by means of ^{3}H-haloperidol (1023) was later developed into a radioreceptor assay for measuring the concentrations of neuroleptics in the sera of patients (247). The advantages of this radioreceptor assay for determining the neuroleptic concentrations in serum are as follows:

A. Simplicity of the Method

The radioreceptor assay is very simple to do. It merely requires an aliquot of D_2 receptors (fresh or frozen or freeze-dried from the brain striatum of any species), an aliquot of ^{3}H-spiperone, and an aliquot of serum from the patient. The neuroleptic in the serum inhibits the binding of ^{3}H-spiperone to the D_2 receptors in proportion to the amount of neuroleptic in the serum. This procedure is much simpler than the elaborate extraction procedure necessary for precise analysis of neuroleptics (838). The result is best expressed in units of "% inhibition of ^{3}H-spiperone binding." Some workers convert this "% inhibition" into nanograms per milliliter of chlorpromazine-equivalent (931b, 132, 202b), although such a conversion is not really needed and may be confusing to readers.

B. Low Cost and Speed of the Method

The radioreceptor assay entails trivial expense compared to the costly equipment required for the gas chromatographic methods (838). The radioreceptor assay is also very rapid.

C. Active Metabolites of Neuroleptics

There are large amounts of neuroleptic metabolites that are also active as neuroleptics, particularly in the case of chlorpromzine (240) and thioridazine (202b). The radioreceptor assay readily detects these active metabolites since they also compete against ^{3}H-spiperone for binding to the D_2 receptors (240, 202b, 247). It is likely that these active metabolites readily permeate the blood-brain barrier, since it can be readily shown that their membrane/buffer partition coefficients are still sufficiently high to permit them to enter into the brain (cf. fig. 7).

D. Therapeutic Benefit and Neuroleptic Concentration in Serum

Clinical studies are only now beginning to appear indicating that there is a qualitative relation between the clinical response of the patient and the serum concentration of the neuroleptic as measured by these radioreceptor assays (931b, 132; B. M. Cohen, personal communication; 931b).

Disadvantages of the radioreceptor assay include the following:

E. Inhibitory Effect of Normal Serum on ^{3}H-Spiperone Binding

There are factors in normal serum that inhibit the binding of ^{3}H-spiperone to D_2 receptors (247). For example, 100 μliters of normal serum diluted in a total final volume of 600 μliters (in the incubation tube) inhibits approximately 40% of the ^{3}H-spiperone bound to the D_2 receptors (this laboratory, unpublished data). Although Creese and Snyder (247) found that this amount of inhibition was constant for different sera from different human volunteers, it is not yet known whether this control inhibition is similar for a larger population of nonmedicated people or patients whose blood samples are taken at different times of the day and under different conditions.

F. Total and Free Concentrations of Neuroleptic in Serum

Ideally, it would be desirable to know the free concentration of the neuroleptic in the serum water of the patient, since this is the concentration found in the cerebrospinal water (see 991). The radio-receptor assay, however, measures the total amount of neuroleptic in the serum, because the neuroleptic that is adsorbed to the serum proteins dissociates and exchanges during the incubation (247).

Hence, it is necessary to calculate the free concentration of neuroleptic in the serum by correcting for the amount of neuroleptic bound to the serum proteins. For example, approximately 95% of the serum chlorpromazine and thioridazine and 92% of the serum haloperidol are bound to serum proteins (see refs. in 991). Freedberg et al. (367) found that about 99.9% of 8 μM chlorpromazine was bound to serum proteins. This is an unusually high value that may have resulted from the low temperature (4°C) used for dialysis, since Kwant and Seeman (617) found that the binding of chlorpromazine to hydrophobic sites was highly temperature-dependent. Another explanation for this high value of 99.9% may be that the

total concentration of 8 μM chlorpromazine (which was much higher than that found in patients; see 991) was sufficiently high to expose many new binding sites for chlorpromazine in the serum proteins (see 987 for discussion on protein expansion by neuroleptics).

Since this bound proportion can vary considerably from patient to patient, it would be ideal if the fraction bound could be measured in all samples of sera. Alternatively, an even better approach would be to centrifuge the patient's serum at about 200,000 × *g* for 1 or 2 hr, such that the top 100 μliter of the serum becomes colourless and free of protein. This top 100 μliter would contain the true free concentration of neuroleptic in the serum water (see 985 for further analysis of this problem). No investigators have yet adopted this simple, precise technique. Admittedly, the free concentrations of neuroleptic may be too low to be detected by the radioreceptor assay (see 991).

G. Interfering Drugs and Reproducibility of the Radioreceptor Assay

Since various ergot alkaloids are highly active on D_2 receptors (table 9), patients taking these drugs will have sera that will reveal neuroleptic-like activity in the radioreceptor assay. Finally, there are a variety of practical pitfalls in this assay stemming from the fact that the neuroleptics are very surface-active and adhere to all glass and rubber surfaces; thus, extensive mixing and shaking the test tubes is sufficient to adsorb the drug onto the glass wall, removing it permanently from the bulk fluid (see 985 for discussion).

XIX. Parkinson's Disease and D_2 Receptors

It has been suggested that one of the critical factors compensating for the loss of dopamine neurones in Parkinson's disease may be the development of denervation supersensitivity in the striatum, since severe cases of Parkinson's disease are more sensitive to L-dopa than milder cases (83; also see papers by Bernheimer et al. in 651, 501, 582). Direct evidence supporting this concept was obtained in this laboratory. We found that the number of D_2 (postsynaptic) receptors was elevated by 50% to 100% in the postmortem brain striata of patients with Parkinson's disease who had not been on L-DOPA therapy (651, 1002a). The binding of ^{3}H-haloperidol was within normal limits, however, in those striata where the patients had been on L-DOPA until their death (651).

Rinne et al. (922a, 922b), as well as Reisine et al. (909, 912), found that the density of D_2 sites was either normal or low in striata from patients who had been on L-DOPA. Rinne et al. (922a) found that the patients who had been greatly disabled and unresponsive to L-DOPA had striata with low densities of D_2 receptors. Of the series of 21 patients with Parkinson's disease studied by Rinne et al (922b), 10 also suffered from psychotic episodes. These psychotic patients were treated with neuroleptics. The striata of these 10 revealed densities of D_2 receptors that were from 50% to 100% higher than normal. Since psychosis is associated with increased densities of D_2 receptors (see section XXI), it is difficult to determine in the report of Rinne et al. (922b) whether the extra numbers of D_2 receptors were associated with the psychotic process or were induced by the neuroleptic administration.

As for D_1 sites (dopamine-sensitive adenylate cyclase) in the striatum of patients with Parkinson's disease, one report (1042) indicates no differences from normal (eight brains), while a second report (806) describes an elevation of D_1 activity for three brains, of which the value for one brain was in the normal range.

XX. L-DOPA Holidays and Rehypersensitization of D_2 Transmission

Prolonged L-DOPA therapy for Parkinson's disease might lead to desensitization of the D_2 receptor system. Compatible with this is the observation that the binding of ^{3}H-haloperidol was elevated in the striata from untreated patients, normal in L-DOPA-treated patients, and low in tissues from patients who had been responding poorly to L-DOPA.

Long-term administration of dopamine agonists in animals also generally reduces the density of D_2 receptors in the striatum by 10% to 50% (689, 691, 893, 507; see also table 17). This goes along with behavioural desensitization to L-DOPA (368, 333).

It is possible, therefore, that those patients who lose their response to L-DOPA or who begin to respond adversely to L-DOPA (e.g. "on-off" effects, etc.) may have become desensitized to L-DOPA. A prolonged holiday from L-DOPA (2 or 3 weeks, if possible) apparently rehypersensitizes the D_2 receptor system, permitting a marked reduction in the daily requirement for L-DOPA and alleviating the movement fluctuations (296).

XXI. Schizophrenia and D_2 Receptors

Once having identified the specific ^{3}H-haloperidol-binding site as dopaminergic in nature (1023), it became feasible to test this aspect of the dopamine hypothesis of schizophrenia (section II G).

Our first data in 1977 (1001a) reported on 20 brains from schizophrenics, wherein we found elevations in the binding of ^{3}H-butyrophenones of between 50% and 75% in both the striatum and the nucleus accumbens (646; see also 649, 652). Our more recent work confirmed and extended these previous findings to an enlarged series of 50 schizophrenic and 59 normal brains (649, 1003, 1004, 1008, 1002a, 649a, 649b).

Further confirmation of elevated densities in D_2 receptors in the brains from schizophrenics has been provided by Owen et al. (842), Crow et al. (264), and Cross et al. (257, 258a). Although Mackay et al. (710) in their first report did not find any significant elevation in D_2 density in the schizophrenics' tissues, they now do find such an elevation (915a).

There is no significant alteration in the D_1 sites in

schizophrenia, as measured by the binding of ^{3}H-*cis*-flupenthixol (258a) or by the activity of dopamine-sensitive adenylate cyclase (148). There is also no change in the D_3 sites, as measured by the binding of ^{3}H-apomorphine (652, 649), ^{3}H-dopamine (1002a), or ^{3}H-ADTN (258).

Although it is conceivable that the elevated density of D_2 receptors are totally induced by the long-term administration of neuroleptics, there are reasons for thinking that this is not a major factor. For example, in our series of schizophrenic brains, 11 were from patients who had received no (or negligible amounts of) long-term neuroleptic medication (649, 1003). These 11 brains, however, also revealed extra amounts of D_2 receptors. Owen et al. (842) have observed this as well, and they have not been able to detect any relation between the increased density of D_2 sites and the amount of neuroleptic administered during the lifetime of the patient. Although the presence of neuroleptics in brain tissue can alter the K_D, their short-term presence has no effect on the density of the D_2 sites (841).

The only evidence that might possibly indicate that long-term neuroleptic administration may elevate the D_2 density is from that of Rinne et al. (922a, 922b). Ten of the patients with Parkinson's disease studied by Rinne et al. had become psychotic, and these 10 patients were treated by neuroleptics. The postmortem striata of the 10 patients had elevations of 50% to 100% in their densities of D_2 receptors. While it is possible that the neuroleptics had produced the elevation in D_2 receptors, it is also possible that the psychosis had developed during the course of disease and/or treatment and that the elevated D_2 density reflected the psychosis quite apart from the neuroleptic administration.

With respect to future research in this area, it is important to note that ^{3}H-spiperone binds to S_2 sites in addition to D_2 receptors. It will be necessary to measure these S_2 sites separately in diseased tissues, since there may be abnormalities in the serotonin system in schizophrenia (983, 68). Since many patients with Huntington's disease exhibit schizophrenia-like signs in the early stages of their illness, it would also be important to measure D_2 receptors in these early stages rather than in the late degenerative stages where the D_2 density falls (910, 911). Tourette's disease is another condition that might be expected to have an elevated density of D_2 receptors in the striatum (344). In addition, it would be desirable to measure alpha$_2$-adrenoceptors in Tourette's disease since clonidine can successfully control some of the signs in this syndrome (203). It would be desirable, furthermore, to develop a human brain region receptor "atlas" of normal values (cf. 323).

Finally, it would be important to investigate the state of various opiate receptors in schizophrenic brain. While it is true that opiate and neuroleptic receptors are distinctly different entities (677; see table 9), opiates can indirectly control the release of dopamine (see refs. in 614, 329, 612, 953, 80, 1195). Although it has apparently been difficult to replicate reports of abnormal neuropeptides in schizophrenia (849), there is one neuropeptide (des-tyrosine-gamma-endorphin) that has neuroleptic-like activity (288, 1204); the site of action of this peptide is unlikely to be a dopamine receptor (1198, 856a).

The elevated number of dopamine receptors in postmortem brains from schizophrenic patients is compatible with the hyperdopaminergic hypothesis of schizophrenia. The elevated number of receptors would be similar to excessive dopaminergic transmission and would give rise to psychotic-like symptoms such as those reported by Parkinson patients who are overdosed with L-DOPA. Such an elevated number of dopamine receptors would also be compatible with the work of Bowers (97), who found a reduction in the amount of cerebrospinal HVA in schizophrenic patients. Presumably this lower production of HVA may represent a homeostatic response to the elevated number of dopamine receptors. It is not presently possible, however, to determine whether these extra dopamine receptors became developed before or after the onset of the schizophrenic disease.

XXII. Dopaminergic Supersensitivity after Neuroleptic Administration

A. Tardive Dyskinesia

Tardive dyskinesia is an insidiously slow-developing syndrome of involuntary motor movements appearing as a late effect of neuroleptic therapy (see reviews in refs. 582, 46, 1125, 336, 391, 330, 331). The syndrome is transiently increased upon withdrawal of the neuroleptic, while reintroduction of the neuroleptic or an increase in dose can mask the signs. Although tardive dyskinesia may be associated with some nigrostriatal degeneration (181, 822, 552, 389), the syndrome generally gradually disappears (over many months), occasionally persisting in older persons (897, 556, 330). It appears, therefore, that the syndrome may develop secondarily to the nigrostriatal degenerative changes (which are accelerated by the neuroleptics; 1014) and/or as a result of the long-term blockade of brain dopamine receptors (D_2 receptors) by the neuroleptics. This present section reviews studies indicating that such long-term receptor-blockade elicits dopaminergic supersensitivity in animals in association with an elevated number of dopamine (D_2) receptors.

It has been difficult to test directly whether patients who have tardive dyskinesia are supersensitive to dopamine or dopamine-mimetic drugs. This question has been examined indirectly in the study of Tamminga et al. (1117) wherein it was found that dyskinetic patients were equally responsive as nondyskinetic schizophrenic patients to the prolactin-suppressing actions of apomorphine or L-DOPA. Bowers et al. (98) found that the HVA levels in cerebrospinal fluid of tardive dyskinetic patients was only slightly (and not significantly) lower than in nondyskinetic patients. Ideally, the most direct test for

determining dopaminergic supersensitivity in tardive dyskinesia would be to measure whether such patients are more sensitive to apomorphine in lowering the cerebrospinal HVA level.

B. Early Supersensitivity after a Single Dose of Neuroleptic

It is known that animals become superresponsive to dopamine-mimetic drugs within 1 to 2 days after a single dose of haloperidol or within 3 to 6 days after a single dose of a highly fat-soluble neuroleptic such as teflutixol (516–523, 774, 641). No changes have been found in any of the catecholaminergic neurotransmitter receptors to account for this early phase of supersensitivity (522a). Although the biochemical basis for this early change in sensitivity is not clear, a possible explanation may be that a residual amount of neuroleptic remains in dopaminergic presynaptic terminals (798a). Such residual neuroleptics could block autoreceptors and enhance the release of dopamine (cf. 978, 883).

C. Behavioural Dopaminergic Supersensitivity after Long-Term Neuroleptics

Long-term administration (weeks or months) of all neuroleptics results in behavioural supersensitivity to dopamine-mimetic drugs. Stereotypy provoked by apomorphine (or other dopamine-mimetics) is enhanced after long-term chlorpromazine or haloperidol (1123–1126, 454, 546, 584, 455, 316, 358, 398, 57, 275, 1110, 395, 394, 956), trifluoperazine, thioridazine or clozapine (200, 1055, 1059; but see 956), fluphenazine (1207, 178), penfluridol (319, 545), pimozide, and sulpiride (326, 223).

D. Biochemical and Electrophysiological Aspects of Dopaminergic Supersensitivity

As reviewed in detail elsewhere (796), there are a variety of biochemical and neurophysiological concomitants of neuroleptic-induced dopaminergic supersensitivity. These include supersensitive electrical responses of caudate cells to iontophoretic dopamine (1266, 1267, 1050, 1051), and enhancement of the apomorphine-induced inhibition of striatal dopamine turnover (396, 1058).

It appears that supersensitivity to apomorphine develops simultaneously with biochemical and behavioural tolerance to neuroleptics (725, 559, 31, 885, 776, 961, 949, 775, 1219, 332, 959, 957, 37, 453, 39). Neuroleptic tolerance generally develops for the extrapyramidal and striatum-associated movements (332, 717) but rarely to the antipsychotic actions of neuroleptics (717, 932). Thus, it is of considerable interest that the HVA-elevating action of neuroleptics does not become tolerant in the frontal cortex (622).

E. Dopamine Receptors and Neuroleptic-Induced Dopaminergic Supersensitivity

D_1 activity (dopamine-sensitive adenylate cyclase) was increased in some studies (560, 718a), but unchanged in others (1214, 944), after long-term haloperidol or chlorpromazine. Overall, therefore, the changes in D_1 following long-term neuroleptics are small (see 796 for summary) and are probably not the basis of neuroleptic-induced supersensitivity (see also 413, 414).

D_2 receptors invariably increase in density in the striatum after long-term administration of various neuroleptics, as summarized in table 16 (see papers by Muller and Seeman in 789, 792–796; also see 199–202b, 116, 370). The receptor densities increase by approximately 20% to 70%, except in the case of five rat striata that exhibited an unusually high increase of 128% (311). Long-term haloperidol to rats with partial lesions of their striata (lesioned by kainic acid) also results in an elevation of D_2 receptors, as measured by ^{3}H-sulpiride (554b); such a result was not obtained in another study (931a) wherein ^{3}H-spiperone was used.

The D_2 receptors are also increased in the striatum or limbic tissue of young rats who receive the neuroleptic through their mother's milk (934, 318a). However, if the mother rat receives a neuroleptic during the pregnancy, the resultant D_2 sites in the offspring's striatum are lower than normal; in this case the neuroleptic presumably had suppressed the maturation of the nigrostriatal system.

The D_3 sites increase as well after long-term neuroleptic administration, as detailed in table 16. It is known, furthermore, that the dopamine autoreceptor system becomes supersensitive to dopamine agonists after long-term fluphenazine (833, cf. 177).

Although neuroleptic-induced dopaminergic supersensitivity may be mostly ascribed to alterations in D_2 receptors (794), the long-term effects of neuroleptics may also include changes in synapses for GABA (374, 411, 693, 381b, 347a), acetylcholine (393, 397, 307), serotonin (794), noradrenaline (308, 794, 309), substance P (487), and endogenous opiates (488; see also 794, 543, 544, 613, 316, 94, 150, 409, 964, 887, 886).

Long-term neuroleptic drugs may also affect metabolic factors, which can in turn modify receptor synthesis (586, 753, 577, 183, 1248, 226, 381). It will be important, therefore, to study the effects of kindling (387b), sleep deprivation (1172), and other types of nondrug stimulation in order to test whether a selective elevation in D_2 receptors is by itself a sufficient condition for dopaminergic supersensitivity.

XXIII. Dopaminergic Supersensitivity after Denervation of Dopamine Neurones

Denervation of the dopamine-containing nigral neurones results in dopaminergic supersensitivity of the postsynaptic neurones in the striatum (1175, 1176, 239, 639, 1177, 348, 778, 535). Such nigral-lesioned rats rotate at doses of apomorphine that are about 5 to 10 times lower than those doses that elicit locomotion in normal rats (1144).

It has often been mentioned that it is not appropriate to compare locomotion in normal animals with rotation in lesioned animals (721, 1179, 972). It is necessary to

TABLE 16

Effect of long-term drugs on dopamine receptors in rat striatum

Drug	mg/kg/day*	^{3}H-Ligand	Conditions	Change (%)	Ref.
Antagonists					
Haloperidol	1; 10 wk.	^{3}H-spip.†	B_{max}	+128%	(311)
Haloperidol	1½; 9 mo.	^{3}H-spip.	B_{max}	+ 65%	(841a)
Haloperidol	10; 3 wk.	^{3}H-spip.	1 nM	+ 45%	(689)
Haloperidol	4; 1 wk.	^{3}H-domp.	B_{max}	+ 38%	(977)
Haloperidol	1½; 3 wk.	^{3}H-spip.	B_{max}	+ 37%	(718a)
Haloperidol	5; 3 wk.	^{3}H-spip.	0.8 nM	+ 36%	(593)
Haloperidol	5; 1 wk.	^{3}H-halo.	0.8 nM	+ 36%	(119)
Haloperidol	10; 3 wk.	^{3}H-halo.	2 nM	+ 34%	(793, 794)
Haloperidol	4; 1 wk.	^{3}H-pimo.	B_{max}	+ 30%	(977)
Haloperidol	0.2; 3 wk.	^{3}H-spip.	2 nM	+ 19%	(668)
Haloperidol	0.4; 2 wk.	^{3}H-spip.	B_{max}	+ 6%	(380)
Haloperidol	10; 3 wk.	^{3}H-apo.	3 nM	+ 77%	(794)
Haloperidol	0.5; 3 wk.	^{3}H-DA	B_{max}	+ 67%	(476)
Haloperidol	2; 4 wk.	^{3}H-DA	10 nM	+ 58%	(368)
Haloperidol	1½; 3 wk.	^{3}H-ADTN	B_{max}	+ 37%	(718a)
Haloperidol	10; 3 wk.	^{3}H-apo.	3 nM	+ 28%	(689)
Haloperidol	0.2; 3 wk.	^{3}H-apo.	4 nM	+ 18%	(668)
Haloperidol	0.4; 2 wk.	^{3}H-ADTN	B_{max}	+ 11%	(380)
Trifluoperazine	3; 12 mo.	^{3}H-spip.	B_{max}	+ 50%	(202a)
Thioridazine	35; 12 mo.	^{3}H-spip.	B_{max}	+ 40%	(202a)
Metoclopramide	45; 39 days	^{3}H-spip.	?	+ 22%	(1086a)
Clozapine	30; 3 wk.	^{3}H-spip.	0.8 nM	+ 14%	(593)
Agonists and miscellaneous drugs					
Estradiol	0.01; 6 days	^{3}H-spip.	B_{max}	+ 20%	(510)
Amphetamine	5; 3 wk.	^{3}H-spip.	0.2 nM	+ 25%	(926)
Amphetamine	30; 3 wk.	^{3}H-spip.	B_{max}	− 35%	(507)
Bromocriptine	5; 2 wk.	^{3}H-spip.	2 nM	0%	(429)
Bromocriptine	15; 4 days	^{3}H-spip.	B_{max}	− 20%	(1229)
Bromocriptine	15; 1 wk.	^{3}H-halo.	B_{max}	− 38%	(541)
Bromocriptine	15; 1 wk.	^{3}H-spip.	B_{max}	− 52%	(893)
Morphine	50; 2 wk.	^{3}H-spip.	B_{max}	− 24%	(886)
Pergolide	0.2; 2 wk.	^{3}H-spip.	B_{max}	− 21%	(667a)
Cocaine	20; 1 wk.	^{3}H-spip.	2 nM	+ 42%	(1130a)
Cocaine	20; 2 wk.	^{3}H-spip.	2 nM	+ 32%	(1130a)

* Dose; duration.

† Abbreviations as in footnote, table 15.

compare the apomorphine sensitivities for rotation caused by denervated and nondenervated striata. One such approach indicates that the unilateral nigral cell lesion results in 10- to 40-fold enhancement to the rotational effects of apomorphine (721). A different approach was taken recently by Schwarcz et al. (976), who found that the intact striatal dopamine receptor responded to apomorphine doses of 0.23 mg/kg (ED_{50}), while the supersensitive animal responded to 0.044 mg/kg, a 5-fold increase in sensitivity.

Since dopamine is primarily an inhibitory neurotransmitter, more spontaneously firing neurones are detected in the striatum after nigral cell denervation (1178, 973, 28). Any remaining dopamine neurones also become hyperactive (6). Electrophysiologically, the denervated striatal cells become 10 to 80 times more sensitive to the impulse-suppressing actions of apomorphine given intravenously (972, 1179). These striatal cells are generally also more sensitive to the inhibitory action of iontophoretic dopamine (345, 1080; but see 831).

D_1 activity (dopamine-sensitive adenylate cyclase) was unchanged in homogenates of denervated striatum (1213, 607; cf. 101). The D_1 activity is 10-fold more sensitive to dopamine in denervated striatal slices (607), while there is no such difference in homogenates (607). Because the results are so sensitive to the manner of preparing the tissue, Krueger et al. (607) have suggested that D_1 differences observed between normal and denervated striata (768, 933) could be attributed to differences in dopamine uptake in residual nerve terminals in either slices or loosely homogenized tissues.

D_2 receptors invariably increase in the striatum after nigral cell lesions, as summarized in table 15 (see also section XVI). The density of D_2 receptors increases 20% to 90%, provided that the depletion of dopamine is greater than 90%. Although not listed in table 15, the dissociation constant for the denervated D_2 receptors is generally the same as normal. This is similar to other forms of supersensitivity (1276, 1267), where the density of receptors (B_{max}) increases but the dissociation constant (K_D) remains the same (1082, 1191, 844, 631). It is likely, therefore, that the extra D_2 receptors in the denervated tissue are similar in properties to the D_2 receptors in the normal tissue. Setler et al. (1027) have reported on a benzazepine (SK & F 38393) that stimulates cyclase activity and elicits rotation in nigral-lesioned animals but does not

TABLE 16A

Dopamine receptors in postmortem brains of schizophrenics

^{3}H-Ligand	nM Baseline	Normal (fmol/mg protein)	Schizophrenic (fmol/mg protein)	Difference (%)		Ref.
			D_2 Receptors			
Caudate nucleus						
^{3}H-halo. (1.7 nM)	100 B*	45 ± 2 (N = 21)	78 ± 3 (N = 18)	+74%		(1018, 646, 1001a, 652)
^{3}H-spip. (1 nM)	1,000 B	99 ± 15 (N = 5)	159 ± 18 (N = 9)	+59%		(652)
^{3}H-spip. (0.8 nM)	100 B	95 (N = 18)	150 (N = 19)	+58%		(842, 264)
^{3}H-spip. (B_{max})	100 B	167 ± 50 (N = 15)	340 ± 120 (N = 15)	+103%	+ 69%	(842, 264)
^{3}H-halo. (2 nM)	100 B	45 ± 1 (N = 39)	86 ± 4 (N = 29)	+93%		(649)
^{3}H-spip. (1 nM)	1,000 B	101 ± 5 (N = 29)	149 ± 7 (N = 27)	+47%		(649)
^{3}H-spip. (0.1 nM)	100 B	90 ± 9 (N = 11)	124 ± 11 (N = 11)	+38%		(915a)
^{3}H-spip. (B_{max})	10,000 Su	127 ± 15 (N = 5)	204 ± 47 (N = 3)	+61%		(L&S)
Putamen						
^{3}H-halo. (1.7 nM)	100 B	50 ± 3 (N = 21)	75 ± 4 (N = 18)	+15%		(1018, 646, 1001a, 652)
^{3}H-spip. (1 nM)	1,000 B	(N = 5)	(N = 9)	+75%		(652)
^{3}H-spip. (0.8 nM)	100 B	90 ± (N = 19)	136 (N = 19)	+51%		(842, 264)
^{3}H-halo. (2 nM)	100 B	47 ± 2 (N = 39)	77 ± 3 (N = 30)	+64%		(649)
^{3}H-spip. (1 nM)	1,000 B	104 ± 4 (N = 33)	150 ± 8 (N = 37)	+45%	+55%	(649)
^{3}H-spip. (B_{max})	1,000 B	66 ± 9 (N = 6)	136 ± 14 (N = 8)	+105%		(649)
^{3}H-spip. (0.1 nM)	100 B	75 ± 13 (N = 11)	114 ± 8 (N = 11)	+52%		(915a)
^{3}H-spip. (B_{max})	100 B	213 ± 21 (N = 3)	308 ± 11 (N = 3)	+45%		(915a)
^{3}H-FPT				+75%		(258a)
^{3}H-spip. (B_{max})	10,000 Su	244 ± 39 (N = 13)	327 ± 136 (N = 13)	+34%		(L&S)
^{3}H-spip. (B_{max})	10,000 Su	159 ± 9 (N = 4)	275 ± 88 (N = 4)	+73%		(L&S)
Nucleus accumbens						
^{3}H-halo. (1.7 nM)	100 B	37 (N = 2)	63 (N = 2)	+71%		(1018, 646, 1001a, 652)
^{3}H-halo. (2 nM)	100 B	38 (N = 2)	79 ± 7 (N = 9)	+110%	+38%	(649)
^{3}H-spip. (1 nM)	1,000 B	55 (N = 2)	118 ± 18 (N = 4)	+115%		(649)
^{3}H-spip. (0.8 nM)	100 B	79 (N = 17)	108 (N = 17)	+37%		(842, 264)
^{3}H-spip. (0.5 nM)	10,000 ADTN	54 (N = 16)	64 (N = 26)	[+19% ns]		(710)
^{3}H-spip. (B_{max})	10,000 Su	124 (N = 5)	161 (N = 3)	+30%		(L&S)
			D_3 Sites			
Caudate nucleus						
^{3}H-apo. (3.2 nM)	1,000 B	28 ± 3 (N = 13)	27 ± 4 (N = 7)	+0%		(1018, 646, 1001a, 652)
^{3}H-DA (B_{max})	100 Apo	68 ± 8 (N = 4)	61 ± 5 (N = 3)	−10% ns		(L&S)
Putamen						
^{3}H-apo. (3.2 nM)	1,000 B	25 ± 3 (N = 13)	26 ± 2 (N = 7)	+0%		(1018, 646, 1001a, 652)
^{3}H-ADTN (7.5 nM)	1,000 DA	42 ± 6 (N = 17)	49 ± 4 (N = 19)	+17% ns		(258)
^{3}H-DA (B_{max})	100 Apo	70 ± 7 (N = 17)	66 ± 6 (N = 16)	−6% ns		(649b)
Nucleus accumbens						
^{3}H-apo. (3.2 nM)	1,000 B	23 ± 3 (N = 4)	19 ± 4 (N = 3)	+0%		(1018, 646, 1001a, 652)

* Abbreviations used are: ADTN, (±)-6,7-dihydroxy-2-aminotetralin; B, (+)-butaclamol; ns, Not statistically significant; DA, dopamine; FPT, cis-flupenthixol; L&S, T. Lee and P. Seeman, to be published; Su, sulpiride; Apo., apomorphine.

cause stereotypy, emesis, or inhibition of prolactin release. Since the rotating rat is a supersensitive preparation, these authors have suggested that this drug may selectively affect a different class of dopamine receptors appearing in the supersensitive state. It is more likely, however, that this drug acts on nondopaminergic neurones, since many other neurone systems modify dopaminergic behaviours, including rotation (16, 888, 1142).

XXIV. Relation between Density of D_2 Receptors and Dopamine Sensitivity

There is no reason to expect a linear relation between the increase in the density of D_2 receptors and the extent of dopaminergic supersensitivity. It can be shown, for example, that a 40% increase in D_2 receptors can account for a 4-fold increase in the dopamine sensitivity of tissue, provided that one makes only a single reasonable assumption (691), as follows.

The receptors occupied (R_{occ}) by the drug concentration (D) can be expressed as a fraction (f) of the total number of receptors present (R_{tot}) by the standard equation of mass action:

$$f = \frac{R_{occ}}{R_{tot}} = \frac{D}{D + K_D} \quad (1)$$

where K_D is the dissociation constant. It is important to note that f is independent of the absolute number of receptors existing in the tissue. The biological response, however, is dependent on R_{occ} rather than f. Hence, if there is an elevation in R_{tot} (as in the supersensitive animal), then the value of f must become lower if R_{occ} is to remain constant in order to elicit the same absolute response as in the normal animal. It is only assumed that

the efficacy remains constant. For example, if a 40% increase in R_{tot} occurs (tables 15, 17), then the value of f must fall by a factor of 1/1.40 or 0.71 in order to keep R_{occ} constant. Consider the case of a near maximum response that may require 90% occupancy of the receptors in the normal animal (i.e., $f = 0.9$). This same response in the supersensitive animal would require the same absolute R_{occ} as in the normal animal, but the f value need only be 0.71×0.9 or 0.64. Continuing, the drug concentration required for any particular value of f is given by equation 2 (from equation 1):

$$D = \frac{f}{f-1} \times K_D \qquad (2)$$

Thus, to produce identical responses with f values of 0.9 (normal animal) and 0.64 (supersensitive animal) one requires drug concentrations of 9 K_D units and 1.8 K_D units, respectively, a difference of about 4-fold. This explains the way in which a 40% increment in R_{tot} may yield up to a 4-fold reduction in the drug concentration (or dose) required to elicit a given response in the supersensitive animal compared to the normal animal. Such an analysis, furthermore, also predicts steepened dose-response curves (691), precisely as seen experimentally (976) in the supersensitive animal.

Finally, it is also possible that some (say, 10%) of the D_2 receptors are more "effective" than others, by being situated, for example, more closely to the neurotransmitter output. A 40% increase in such receptors could be equivalent to a 400% increase in the entire population of receptors with an ensuing dramatic increment in overall dopamine sensitivity.

As mentioned in section XXII D, supersensitivity to apomorphine develops simultaneously with biochemical and behavioural tolerance to neuroleptics. It is perfectly reasonable to expect a priori that a 40% elevation in the density of dopamine receptors would also be associated with tolerance to neuroleptics. This is simply because many more neuroleptic molecules would be needed to occlude the extra numbers of dopamine receptors.

XXV. D_2 Receptors, Dopamine Sensitivity, and Role of Estrogen

Any relation between the density of D_2 receptors and the dopaminergic sensitivity of the response should take into account the fact that estrogens have a strong anti-dopaminergic action (619). For example, estrogens inhibit the prolactin-lowering action of dopamine (295a, 918), inhibit apomorphine-induced rotation (64), potentiate neuroleptic-induced parkinsonism (64), alleviate dopaminergic dyskinesia (see refs. in 64; 431), and inhibit dopamine-sensitive adenylate cyclase (1120).

This neuroleptic-like quality of estrogens also results in dopaminergic supersensitivity (431) and an elevated number of D_2 receptors (295a, 510) after long-term estrogen administration (see table 17). For some unknown reason, guinea pigs are anomalous in this respect, insofar as estrogen enhances dopaminergic behaviours in this species (811).

The molecular mechanism may be that estrogen (or a close derivative, 2-hydroxyestradiol; 963) may directly compete with dopamine at the D_2 receptor (963), or that the estrogen may reverse the electrical inhibition of the membrane action potentials by dopamine (305a). The latter mechanism seems more likely since the tissue level of 2-hydroxyestrogen (see refs. in 963) is of the order of 10^{-7} M, a concentration that inhibits the binding of ^{3}H-spiperone by only 15% (963).

In addition to the direct action of estrogen on the brain (in eliciting more D_2 receptors; 863a), there is also an indirect action of estrogen in its elevation of prolactin, which in turn separately also elevates D_2 receptors (508a; 708a; 863a, 1265). Although in one study it was found that hypophysectomy prevented the haloperidol-induced elevation of D_2 receptors (708a), another study (863a) revealed that 3 weeks of haloperidol treatment approximately doubled the number of D_2 receptors in the hypophysectomized animal (both studies in rats).

XXVI. Reversal of Elevated D_2 Receptors: Effects of Dopamine Agonists

Upon withdrawal of neuroleptics, there is a spontaneous decay in the behavioural dopaminergic supersensitivity concordant with a spontaneous reversal of the elevated density of D_2 receptors (see refs. in 796; 202a). In the case of rats treated with long-term neuroleptics, the time required for full reversal is of the order of 50% to 75% of the time during which the animal had been maintained on neuroleptics. For example, after 1 month of neuroleptic administration, it required approximately 2 to 3 weeks for a full reversal of the supersensitive behaviour (956, 1055) and the extra number of D_2 receptors (593, 119). After 1 year of neuroleptic administration (trifluoperazine or thioridazine), the behavioural supersensitive responses to apomorphine returned to normal after 3 months and the density of D_2 receptors returned to normal at some time between 3 and 6 months (202a).

Repeated administration of dopamine-mimetic drugs can result in either dopaminergic desensitization (1222, 54, 1164, 962, 598, 1264, 722, 149, 587) or "sensitization" (also termed "behavioural facilitation," "reverse tolerance," etc.). Such sensitizing drugs include L-DOPA (450, 53, 585, 589; but see 890), apomorphine (369, 42; but see 360), bromocriptine (812, 1063), amphetamine (1220, 1025, 590, 583, 1044, 578, 42, 312, 313), cocaine (578, 1130a), and phenylethylamine (93).

Repeated administration of dopamine-mimetics generally results in a lowering of the density of D_2 receptors in the striatum, as summarized in table 16 (see also 769). This decrease could account for those instances of dopaminergic desensitization that occur after long-term administration of dopamine-mimetic drugs. There are a

variety of cellular mechanisms that may account for this reduction in receptors (757, 364, 365, 170, 1102, 645, 437, 854, 847, 176, 653, 461), the most likely being a reduction in the steady-state synthesis of receptors.

Tardive dyskinesia can be alleviated in principle, therefore, by giving the patient high doses of L-DOPA for short periods of time (days or weeks) in order to reduce the number of D_2 receptors (29, 368, 333, 689, 691, 88, 890). This approach appears to alleviate tardive dyskinesia in approximately 50% of patients (88; M. Alpert and A. J. Friedhoff, personal communication).

The cellular mechanism of dopaminergic sensitization, however, is not clear. Although there are some studies in which an increased binding of dopaminergic ^{3}H-ligands after prolonged exposure to dopamine agonists in vitro (741, 926a) or in vivo was found (926, 1130a, 1251a), none of these studies characterized whether the binding pattern was to D_2, D_3, or NSS sites. To explain this sensitization, it has been suggested (724, 58, 227, 978, 797) that the long-term dopamine agonist desensitizes the dopamine autoreceptors, possibly by a reduction in D_3 sites (797). The net effect would be less autoregulation and more postsynaptic stimulation by the dopamine agonist (i.e. sensitization). It has recently been suggested that this mechanism may also occur in long-term antidepressant therapy (1026a).

Other drugs also block the development of neuroleptic induction of more D_2 receptors. These drugs include D-ala^2-methionine-enkephalin (290), amantadine (290), *d*-phenylalanine (290), and Li^+ salts (864, 931, 1169, 383, 368a, 865, 907, 359, 310, 388, 363).

XXVII. Development and Aging of Brain Dopamine Receptors: Hyperactivity Syndrome

The onset of synthesis of D_2 receptors in the striatum may possibly be triggered by the arrival of the dopamine-containing neurones from the nigra. This is only indirectly suggested by the finding that neuroleptic administration during pregnancy results in an abnormally low number of D_2 receptors in the striatum of the pups at birth (934). Since neuroleptic administration to young or adult animals invariably elevates D_2 receptors (table 17), the inhibition of maturation of D_2 receptors during gestation suggests that the neuroleptic inhibits the growth and development of dopamine neurones into the striatum. If this concept is true, it would differ from that of muscarinic cholinergic receptors, which appear before the arrival of cholinergic nerve terminals (see refs. in 852).

It will be important to examine whether there is a relation between the development of either D_2 receptors or adrenoceptors and the maturation of locomotor activity in both the human and animal brain. In the case of the rat, it is known that locomotor activity sharply increases at day 10 (after birth), reaches peak activity at days 14 to 19, and then declines to adult values by days 25 to 27 (see refs. in 324a, 1034). A time-course of this sort has been found by Pardo et al. (852) for the binding of 1 nM ^{3}H-haloperidol to striata of rats of different ages. It will be necessary to confirm that the density of D_2 receptors (i.e., B_{max}, as determined by using a range of ^{3}H-butyrophenone concentrations for each tissue) follows the pattern reported by Pardo et al. for 1 nM ^{3}H-haloperidol. Using the in vivo method of ^{3}H-spiperone binding, Murrin (802) has found qualitatively similar data to those of Pardo et al. in rats at days 5 and 15 (see 801, 802).

It is difficult to attribute the full development of locomotion solely to D_2 receptors, since there are parallel developments in dopamine terminals (579a, 852), D_1 activity (852), and other neurotransmitter systems (see refs. 889, 324a, 41), including autoreceptors. It is possible, for example, that the full expression and/or persistence of hyperlocomotor behaviour may depend on a balance between pre- and postsynaptic receptors. Persistently hyperactive rats can be produced by selective destruction of dopamine neurones (1034, 1033, 324a, 127). Such lesioned rats are more sensitive to apomorphine (832), as expected, because of the extra density of D_2 receptors.

More important, however, is the interesting observation that the locomotion of such hyperactive rats can be reduced by methylphenidate, the medication used for the hyperactivity syndrome (Attention-Disorder syndrome or Minimum Brain Dysfunction syndrome) in children (1033). Since such lesions of dopamine neurones reduce dopamine autoreceptors, including D_3 sites (table 15), the hypothesis now emerges that persistent locomotion (or persistent "inattentiveness") stems from a deficiency in dopamine autoreceptors (or possibly D_3 sites). Matthysse (728) has already emphasized the role of dopamine in selective attention. This hypothesis is being pursued in this laboratory by examining the development of pre- and postsynaptic dopamine and alpha-adrenoceptors in both the rat and human postmortem brain tissue (S. Watanabe, E. J. Hartley, and P. Seeman, unpublished data). Further work on this subject should also explore the possible relation between receptors and behaviour by examining animals of different genetic strains (1119, 356, 471a, 1028).

After adulthood, the aging process is associated with a degeneration of the nigral dopamine neurones (see refs. in 152, 503). Furthermore, the density of D_2 receptors (436) is 40% lower in the striata of senescent rats (30 months old), in qualitative agreement with other studies (1057, 1028, 1027b); D_1 activity is also reduced (435). In the human brain striatum, the density of D_2 sites falls by about 3% per decade of life (1027a).

Older persons as well as older animals are supersensitive to dopamine compared to the younger ones. This is supported by the observations that 10% to 20% of elderly patients in nursing homes exhibit oro-buccal-lingual dyskinesias, and aged rats are more responsive to apo-

morphine or amphetamine (1056, 1105, 720). It is possible to account for the behavioural dopaminergic supersensitivity in the older person or animal on the proposition that the number of presynaptic dopamine receptors has fallen more than the number of postsynaptic (D_2) receptors. The older brain might have a high ratio of D_2/D_3 with a lower dopamine content. Partial experimental support for this comes from the work of Severson and Finch (1027b), who found that the binding of ^{3}H-ADTN to rat striata declined much more quickly with age than did the D_2 receptors. As outlined in previous sections in this review, there is reason to consider that ^{3}H-ADTN binds to presynaptic neural (D_3) elements. Thus, this elevated D_2/D_3 ratio is similar to those patients or animals who have neuroleptic-induced dyskinesias (see section XXII). Finally, although the emphasis has here been on striatal dopamine receptors, it is also clear that there are important alterations in adrenoceptors in hyperactivity states (127) as well as in the aging process (967, 443).

XXVIII. Dopamine Receptors in the Pituitary and Peripheral Tissues

The anterior pituitary gland contains dopamine receptors (425, 426) that meet the criteria of the D_2 receptor, as summarized in table 17. As shown in figure 18, furthermore, there is a fair correlation between the physiological actions of dopamine agonists (i.e. inhibition of prolactin release) with their IC_{50} values on the D_2 receptor. There is no such correlation between these prolactin-release-inhibiting potencies and the IC_{50} values on either

TABLE 17A

Inhibition of ^{3}H-neuroleptic binding (to anterior pituitary)

	^{3}H-Spiperone IC_{50} (nM)		^{3}H-Haloperidol IC_{50} (nM)	
	Sheep (r:rat)	Bovine	Rat	Monkey
Neuroleptics				
Spiperone	2.1 (255)	0.6 (243)		
(+)-Butaclamol	3.8 (256)	2.1 (243)		
(−)-Butaclamol	41,000 (256)	20,000 (243)		
Fluphenazine		4.5 (243)		
Pimozide	9.6 (256)			
Haloperidol	29 (255)	7 (243)	6 (102)	0.7 (106)
		9.7 (746)		
Chlorpromazine	41 (255)	39 (243)		10 (106)
Metoclopramide		158 (746)	12 (102)	
(−)-Sulpiride	5,300 (256)			
	r: 700 (788a)			
(+)-Sulpiride	>100,000 (256)			
	r:80,000 (788a)			
Agonists				
Bromocriptine	47 (255)	5.4 (243)		
Apomorphine	560 (255)	525 (243)		
Dopamine	3,400 (255)	16,000 (243)	1,000 (102)	
Adrenaline	56,000 (255)	140,000 (243)		
Noradrenaline	46,000 (255)	450,000 (243)		
Phentolamine	66,000 (255)			
Serotonin	>100,000 (255)	120,000 (243)		

TABLE 17B

Inhibition of ^{3}H-agonist binding (to anterior pituitary)

	^{3}H-DHEC* IC_{50} (nM)		^{3}H-Dopamine IC_{50} (nM)
	Sheep	Bovine	Bovine
Neuroleptics			
Fluphenazine		15.6 (164)	
Haloperidol	154 (254)	55 (164)	880 (131)
Chlorpromazine		200 (164)	
Agonists			
Bromocriptine	160 (254)	110 (164)	~10 (131)
Apomorphine	190 (254)	360 (164)	25 (131)
Dopamine	1,500 (254)	2,260 (164)	107 (131)
Adrenaline	>10,000 (254)	7,800 (164)	
Noradrenaline	10,000 (254)	14,700 (164)	750 (131)
Phentolamine	10,000 (254)	14,700 (164)	
Serotonin	>100,000 (254)	106,000 (164)	

* DHEC, dihydroergocryptine.

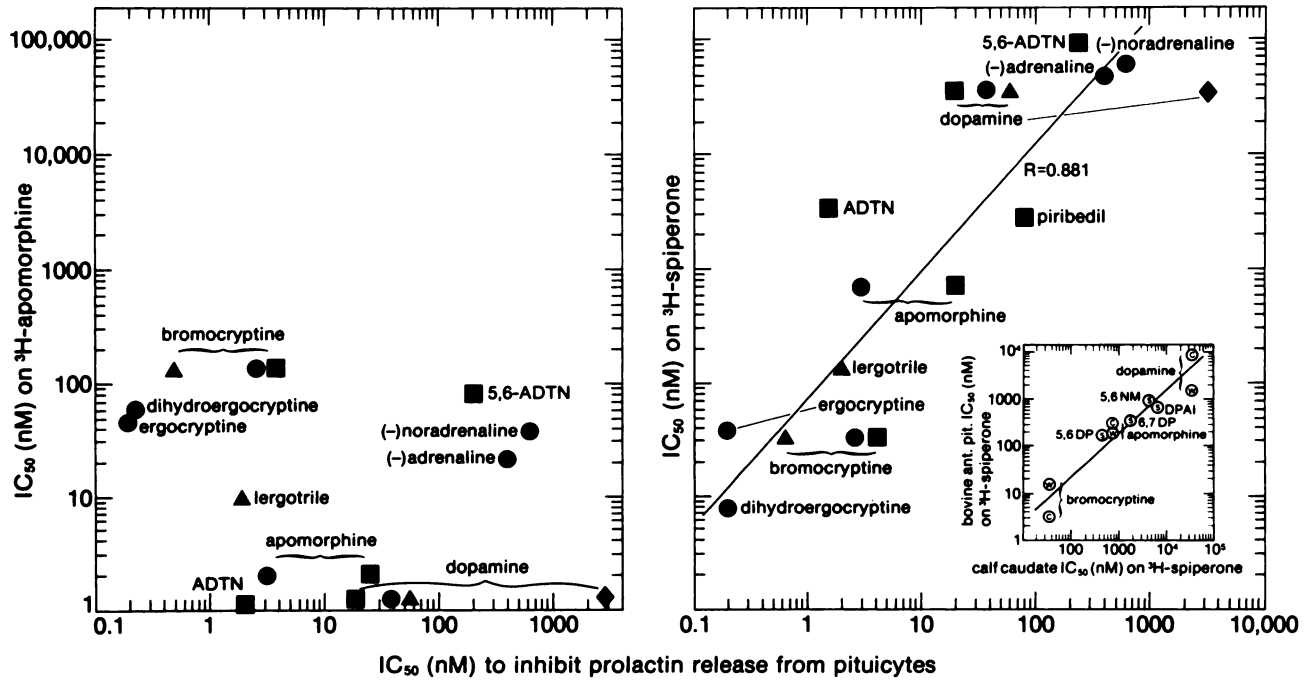

FIG. 18. The concentrations of dopamine agonists that inhibited the release of prolactin (from rat pituicytes) correlated with the ^{3}H-spiperone IC_{50} values (D_2 dopamine receptors) but not with the ^{3}H-apomorphine IC_{50} values (D_3 binding sites). All the IC_{50} values were obtained in this laboratory on calf striatum (indicated by the letter "s" in tables 9 and 10). The drug concentrations for 50% inhibition of prolactin release were from Caron et al. (●; 164), Rick et al. (■; 918), Yeo et al. (▲; 1271) and Mowles et al. (◆; 782). As shown in the inset, the ^{3}H-spiperone IC_{50} values for anterior pituitary tissue closely correlated with those for calf caudate tissue; data indicated by "s" were from this laboratory, by "c" from Creese et al. (243) and by "w" (for sheep anterior pituitary) from Cronin and Weiner (256). The abbreviations used are: DPAI, dipropylaminoindane; 5,6NM, (±)-5,6-dihydroxy-N-methyl-2-aminotetralin; 6,7DP, (±)-6,7-dihydroxy-N,N-dipropyl-2-aminotetralin; 5,6DP, (±)-5,6-dihydroxy-N,N-dipropyl-2-aminotetralin; 5,6ADTN, (±)-5,6-dihydroxy-2-aminotetralin; ADTN, (±)-6,7-dihydroxy-2-aminotetralin.

the D_3 site (fig. 18, left side) or the D_1 site (278, 1278, 966, 7, 111, 1046, 1091).

Although the pituitary D_2 receptor has been known for some time (106), it is still not clear what the physiological concentration of dopamine is in order to inhibit the release of prolactin. The concentrations of dopamine that have been reported to inhibit the release of prolactin in vitro are 35 nM (164), 500 nM (1271, 1043), and 3000 nM (782) (see also fig. 18). The physiological concentration of dopamine in the pituitary stalk plasma in vivo, however, is very low: 1.7 nM in male Long-Evans rats (449a), and about 40 nM in ovariectomized female Charles River CD rats (279). Pituitary tumour cells are particularly insensitive to dopamine (715, 252a).

Thus, the physiologically relevant concentration of dopamine in the pituitary stalk plasma is 2 nM to 40 nM, a range that is in excellent agreement with the property of the D_4 site (fig. 1a) in the intermediate pituitary cells (754a). It may be, therefore, that both the D_2 receptors and the D_4 sites in the pituitary are activated by dopamine. A major problem in this area is that no one has found a reliable binding site in the pituitary that is sensitive to dopamine (i.e. IC_{50} value for dopamine between 2 and 40 nM against any ^{3}H-ligand).

The pattern of binding of ^{3}H-DHEC (dihydroergocryptine) (164, 165, 167, 254) to D_2 pituitary sites is similar to that for the binding of the ^{3}H-butyrophenones (table 17). The binding of ^{3}H-dopamine (131, 579, 253, 130) to anterior pituitary tissue, although not yet fully characterized, is very different from the D_2 site (table 17; see also 61). In our own laboratory, although we readily detect specific binding of ^{3}H-dopamine to rat striata (D_3 sites; 690–691b), we have not been able to detect any specific binding of ^{3}H-dopamine in either rat or calf anterior pituitary tissue (1155a); this negative observation is compatible with the idea that high-affinity binding of ^{3}H-dopamine may be restricted to nerve terminals (which are not found in the pituitary), suggesting that such sites might be detected in the median eminence (483).

Because of this clear separation between the pre- and postjunctional elements in the pituitary system, it is very suitable for studying the correspondence between receptor properties and clinical potencies of various drugs (636, 449, 664, 20, 745) as well as possible changes in dopaminergic sensitivity (327, 175, 633, 63, 107, 805, 171). Although dopamine inhibits prolactin release between 10^{-9} M and 10^{-6} M, the pituitary cells are alleged to have the peculiar property of being stimulated to release prolactin at dopamine concentrations of 10^{-10} M to 10^{-9} M (1043, 287a, 284), although this effect has not been found by F. Labrie (personal communication). It is also important to be aware of the fact that very high concentrations of neuroleptics can inhibit the release of prolactin by a mechanism not involving the D_2 receptor, but presum-

TABLE 18

*Renal, femoral, and brain dopamine receptors**

	nmoles (i.a.) to Alter Renal Blood Flow† (266; 421; 597; 1209)	nmoles (i.a.) to Alter Femoral Blood Flow‡ (125)	IC_{50} (nM) on ^{3}H-Spiperone (calf caudate) (this lab)	IC_{50} (nM) on ^{3}H-Apomorphine (calf caudate) (this lab)
Agonists				
5,6(OH)$_2$-N-DPAT		0.07	490	11
Dopamine	16		37,000	2
(+)-ADTN	16		1,200	1.7
(±)-ADTN	10–22		3,700	2.4
Epinine	25		730	2.5
6,7(OH)$_2$-N-MAT	60		5,000	2.4
(−)-ADTN	320		20,000	18
(±)-N-P-norapomorphine	350	0.14	85	12
D-P-dopamine	377	5.5	10,500	74
R(−)-apomorphine	1,000	1.0	750	3.8
5,6(OH)$_2$-N-DMAT [M-7]	≫1,000		3,600	10
6,7(OH)$_2$-N-DMAT [TL-99]	≫1,000		4,400	4.8
Dimethyldopamine	≫1,000		Not tested	10.5
Antagonists				
Sulpiride	29§	~3‖	8,000	250,000
Haloperidol	140		19	650
Chloropromazine	250		41	1100
Fluphenazine	250		2.3	70 (250a)
Metoclopramide	1,500		3,000 (250a)	35,000 (919)

* There is no correlation between the intraarterial doses of congeners that increase renal blood flow and the IC_{50} values of these congeners (on either ^{3}H-spiperone or ^{3}H-apomorphine binding to calf caudate homogenates). Abbreviations used are: AT, 2-aminotetralin; others as in table 9.

† Agonit doses that increased the renal blood flow by 50%; antagonist doses that shifted the dopamine dose-response curve by 3- to 4-fold to the right. Done on phenoxybenzamine-pretreated (5 or 10 mg/kg i.a.) dogs, wherein 100% response was the increase in renal blood flow caused by 190 nmoles dopamine i.a.

‡ Agonist doses that increased the femoral blood flow by 50%. The antagonist doses were those that antagonized the dipropyldopamine-induced increase in flow by 50% (421).

§ (+)-sulpiride was about five times more potent than (−)-sulpiride (421).

‖ (−)-sulpiride was active; (+)-sulpiride was not active (421).

ably by simply inhibiting stimulus-secretion coupling (287, 1234).

XXIX. Future Work on Dopamine Receptors

As summarized in table 18, there are substantial differences between dopamine receptors in the brain and those in peripheral tissues (294), particularly vascular tissue (415, 123, 1093). It is necessary to study further the properties of dopamine receptors in the stomach (1196), the retina (456, 315, 305, 604, 605, 970, 971, 711, 352, 381a, 960), the carotid body (295, 736), and the superior cervical ganglion (306, 602, 1251, 679).

Further research is indicated in dopamine receptor changes seen with long-term ethanol treatment (790, 1111; cf. 49). Long-term effects of neuroleptics should also be studied on histamine receptors, since the neuroleptics are potent on these receptors (475, 1168, 891a). These findings may have implications for the understanding of the sedative side-effects of neuroleptics. Long-term effects of antidepressants should be tested for possible changes in the density of D_2 or D_3 receptors in the brain (1121–1122a), since it has recently been suggested that dopamine autoreceptors become desensitized with long-term antidepressants (1026a). It is already known that antidepressants are potent on alpha$_1$-adrenoceptors (1184, 1182), as well as on ^{3}H-antidepressant-binding sites (898, 533), and that long-term antidepressant administration (particularly desipramine) results in a reduction in the density of beta-adrenoceptors (48, 1026, 955, 195, 72, 1182; cf. 366, 1169, 1108, 283, 821).

A formidable current challenge is to isolate the D_2 receptor. These receptors have already been solubilized from calf brain (1114), dog brain (434, 432, 621, 710b, 710c), rat brain (433, 361a), and human brain (272b), by using the digitonin method worked out by Caron and Lefkowitz for the beta-adrenoceptor (166, 685, 873, 591, 686, 33; see also 387, 387a, 80, 1256). It is not presently clear whether the method of using a saturated KCl solution results in membrane solubilization or disruption of the membrane into small pieces (99, 188, 192). The binding of ^{3}H-dopamine to lubrol-solubilized tissue (cf. 480) appears to be associated with the D_1 site (dopamine-sensitive adenylate cyclase) and not the D_2 receptor or the D_3 sites (954a). In order to isolate the D_2 receptor, it may be possible to use an alkylating dopamine derivative such as (−)-N-(chlorethyl)norapomorphine (216a). Such a compound, however, would be likely to have an affinity for both the D_2 and the D_3 sites, as has already been shown for ^{3}H-(±)-N-propyl-norapomorphine (1153).

In the case of the beta-adrenoceptor, experience has shown that a successful resolution of many questions depended on the development of progressively more se-

lective ^{3}H-ligands (34, 12, 784, 11, 655, 716, 1250, 654, 408, 658, 444, 1031, 438, 50) with progressively higher specific activity (463, 105, 660, 1231, 785, 713, 126, 661, 557, 1053, 1097, 657, 127, 462). Since there has been difficulty with ^{3}H-dopamine binding, it would be desirable to develop a selective dopamine ^{3}H-agonist with very high specific activity.

The isolation of such D_2 receptors will permit the preparation of antibodies to these receptors for use in refining the cellular location of these receptors in the brain. The isolated receptors would also permit the reconstitution of the receptor into liposomes such as to be able to study the ionic mechanism that the receptor may induce in an accompanying ionophoric channel (cf. 1101, 1102, 1218, 1273).

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