Dopamine receptors in the central nervous system[1,2]

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ABSTRACT

Dopamine receptors in the central nervous system can be studied by measuring the specific binding of [^{3}H]dopamine, [^{3}H]haloperidol, *d*-[^{3}H]LSD, [^{3}H]dihydroergocryptine or [^{3}H]apomorphine. The receptors are stereoselectively blocked by (+)-butaclamol, a neuroleptic. All neuroleptics inhibit the specific binding of [^{3}H]haloperidol in relation to their clinical potencies. The radioligand that desorbs most slowly from the receptor is [^{3}H]apomorphine, thus making it a reliable ligand for dopamine receptors. Dopamine agonists that compete for [^{3}H]apomorphine binding do so at concentrations that correlate with their potency in stimulating striatal adenylate cyclase. Structure–activity analysis, using [^{3}H]apomorphine, confirms that the active dopamine-mimetic conformation is the beta rotamer of dopamine. Prolonged exposure in vitro of caudate homogenate to high concentrations of dopamine leads to increased binding of [^{3}H]apomorphine or [^{3}H]haloperidol, suggesting receptor "sensitization." Chronic haloperidol treatment of rats leads to an increased number of dopamine/neuroleptic receptors in the striatum, but a decrease in the pituitary.—**Seeman, P., J. L. Tedesco, T. Lee, M. Chau-Wong, P. Muller, J. Bowles, P. M. Whitaker, C. McManus, M. Tittler, P. Weinreich, W. C. Friend and G. M. Brown.** Dopamine receptors in the central nervous system. *Federation Proc.* 37: 130–136, 1978.

Abnormal dopaminergic transmission occurs or has been implicated in a wide variety of diseases, including Parkinson's disease (43, 44), schizophrenia (59, 62, 90), Huntington's disease (54, 96), Gilles de la Tourette's syndrome (98), neuroleptic-induced tardive dyskinesia (2, 3, 49), various choreas and torsion dystonias (58), the Lesch-Nyhan syndrome (98), minimal brain dysfunction in children (hyperkinesis), and some neuroendocrine disorders associated with prolactin control, growth hormone control, and obesity (95).

Since some of these disorders may be associated with abnormalities in brain dopamine receptors, it is necessary to have a reliable assay for measuring such receptors in small amounts of human brain tissue. Second, drug treatment of these diseases is not very satisfactory. The drugs produce many undesirable effects, such as dyskinesias and the "on-off" phenomenon (4) (with L-dopa). It is also desirable, therefore, to have a simple in vitro receptor assay to screen new and potentially better drugs for therapeutic purposes.

DOPAMINE RECEPTOR ASSAY

In the past 5 years six new in vitro assays for dopamine receptors have been described. They are: determination of dopamine-sensitive adenylate cyclase, and radioreceptor assays for measuring the binding of [^{3}H]dopamine, [^{3}H]haloperidol, [^{3}H]LSD, [^{3}H]dihydroergocryptine, and [^{3}H]-apomorphine.

Dopamine-sensitive adenylate cyclase

Dopamine-sensitive adenylate cyclase was first detected in homogenates of bovine superior cervical ganglion (38). This enzyme has now been found in all dopamine-sensitive tissues (basal ganglia (46, 47, 51, 52, 65), olfactory tubercle and nucleus accumbens (20, 40)), with the important exception of the pituitary (74). Although the pituitary is known to be dopamine-sensitive and to contain dopamine receptors (6, 12, 17, 18, 28, 74), Schmidt and Hill (74) could not detect dopamine-sensitive adenylate cyclase in either the intact pituitary or homogenates of this tissue, using 100 μM dopamine, 10 μM apomorphine, or 10 μM lergotrile.

A second problem with dopamine-sensitive cyclase is that the butyrophenone neuroleptics, such as haloperidol, are weaker inhibitors of this enzyme than the phenothiazines, such as chlorpromazine or trifluoperazine (20, 46–48, 51, 63, 73). Clinically or experimentally (in vivo), however, the butyrophenones are much more potent than the phenothiazines in antagonizing the actions of dopamine. This problem has been extensively reviewed elsewhere (78, 82).

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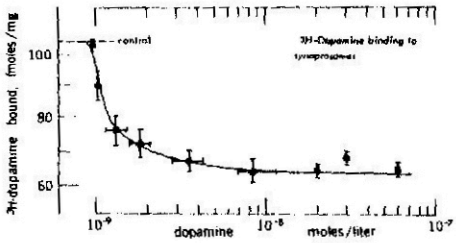


Figure 1. Early results for the binding of [^{3}H]dopamine to synaptosomes (rat striatum), using the centrifugation method (adapted from (80, 81)). The K_D was approximately 1 nM and the total number of specific dopamine sites was about 40 fmole/mg.

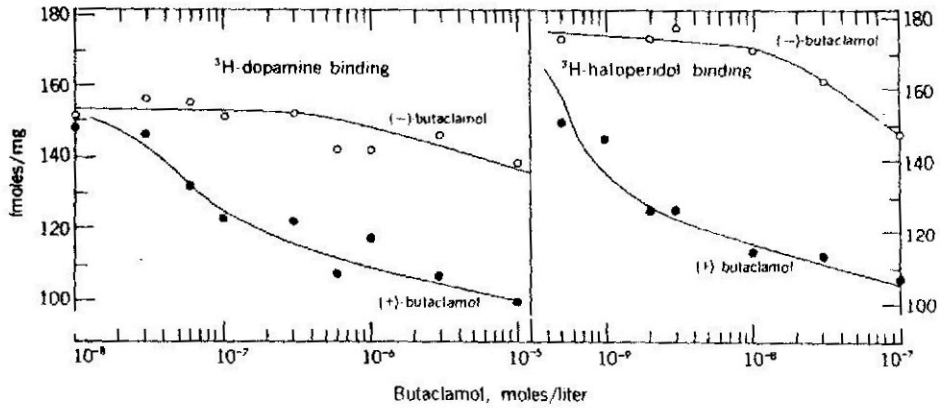


Figure 2. Stereoselective inhibition of [^{3}H]dopamine binding by butaclamol (adapted from (81)).

[^{3}H]Dopamine radioreceptor assays

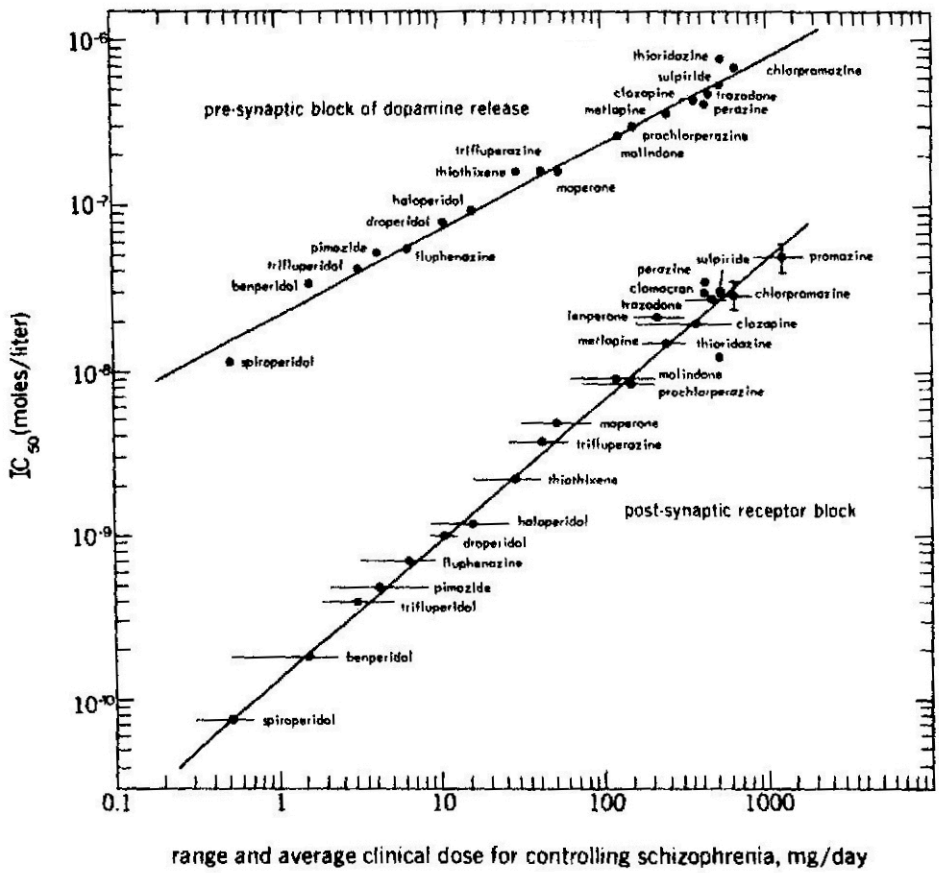
The first reports on the specific binding of [^{3}H]dopamine to tissues appeared in early 1974 (76, 77, 80), and an example of this work is shown in Fig. 1. These early experiments were done either by a centrifugation method or by a Millipore filtration method using [^{14}C]inulin as a marker for trapped water containing [^{3}H]-dopamine. The results revealed a dissociation constant (K_D) of 6×10^{-10} M for dopamine (77, 80).

These early methods were time consuming, since many replicates were needed to obtain statistical significance for each point. The situation changed considerably in late 1974 when Humber and Bruderlein (45) reported the synthesis of the butaclamol enantiomers, of which only (+)butaclamol is the active neuroleptic (7, 99, 100).

The butaclamol enantiomers facilitated a direct test of the 1966 hypothesis that neuroleptic drugs specifically blocked dopamine receptors (16, 42, 50, 97). In addition to having a stereospecific presynaptic action on dopamine neurons (82, 83), it was soon found that (+)butaclamol stereoselectively inhibited the binding of [^{3}H]dopamine (12, 27, 81, 85) (see Fig. 2).

In distinguishing between specific and nonspecific binding of [^{3}H]dopamine, therefore, the usual current practice is to define nonspecific binding as any binding of [^{3}H]dopamine that occurs in the presence of 1 μM (+)butaclamol (11, 81, 85, 86) or 10 μM (+)butaclamol (9, 10, 25, 26) or 1 μM dopamine (9, 10, 25, 26). It has been pointed out by Enna et al. (32) that butaclamol stereoselectively inhibits not only the binding of dopamine and haloperidol, but also the binding of serotonin, *d*-LSD, quinuclidinyl benzilate and dihydroergocryptine. The isomeric ratio of potencies ((+)butaclamol/(−)butaclamol), however, is highest in blocking the binding of [^{3}H]dopamine, [^{3}H]-haloperidol or [^{3}H]apomorphine, while the ratios for blocking the binding of the other ligands are much lower (32, 78).

Figure 3. Neuroleptics inhibit the binding of [^{3}H]haloperidol (to calf striatal homogenate) in direct relation to the clinical potencies (lower line) (adapted from (81, 84, 85)). The upper line indicates that neuroleptics also block the stimulated release of [^{3}H]dopamine (from rat striatal slices) in relation to their clinical potency; however, the neuroleptic concentrations needed for this presynaptic action are much higher than those that inhibit [^{3}H]haloperidol binding (adapted from (83)).



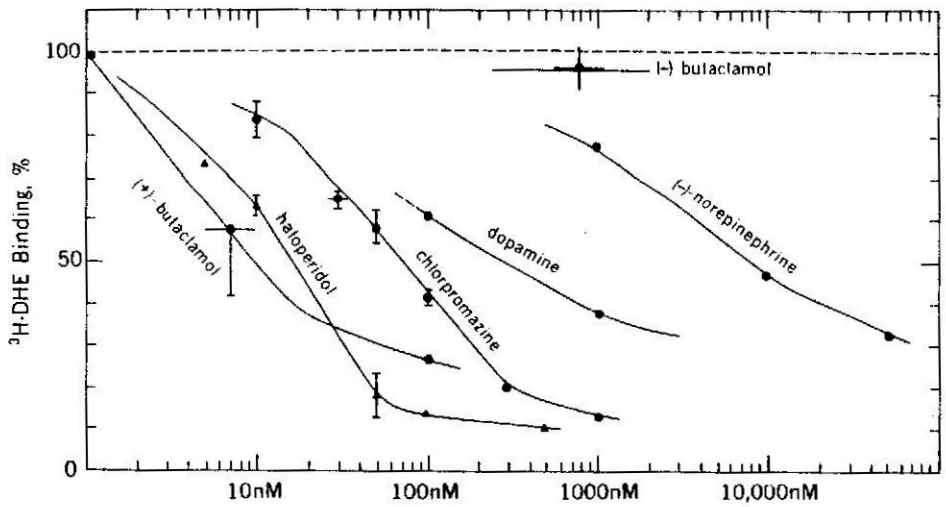


Figure 4. In the presence of 100 nM phentolamine (to block the alpha-noradrenergic sites), it is possible to use [^{3}H]DHE as a ligand for dopamine receptors. (Calf caudate homogenate; [^{3}H]DHE concentration was 0.7 nM; M. Tittler, P. Weinreich and P. Seeman, in preparation.)

[^{3}H]Haloperidol radioreceptor assays

Since neuroleptics readily adsorb to all biological cell membranes in relation to their high surface-activity (79) and high fat solubility (75, 87), the clear identification of specific binding sites for neuroleptics was not possible (94) until the advent of the butaclamol enantiomers, since these latter substances have identical solubilities.

Using 100 nM (+)-butaclamol to define nonspecific [^{3}H]haloperidol binding, the specific binding of haloperidol exhibits a K_D of between 1.3 and 3.3 nM (10, 25, 26, 81, 86, 88). All clinically effective antipsychotic drugs block the stereospecific binding of [^{3}H]haloperidol at concentrations that correlate directly with the clinical potencies (see Fig. 3) and that are actually found to occur in the plasma water of patients under neuroleptic treatment (85) (see also (27, 63, 92)). Although there is no simple direct proof that [^{3}H]haloperidol is binding to the dopamine receptor site (in whatever conformation), it is true that dopamine is more effective than (−)-noradrenaline, serotonin, or other neurotransmitters in competing for [^{3}H]haloperidol binding (10, 81, 85).

[^{3}H]LSD and [^{3}H]dihydroergocryptine (DHE) as ligands for dopamine receptors

Since *d*-LSD and the ergot alkaloids (ergotamine, ergocryptine, etc.) inhibit the binding of [^{3}H]dopamine at low concentrations (40 to 90 nM (11)), radioligands of such drugs can be used to tag dopamine receptors (9, 17, 18). The binding of [^{3}H]LSD is complicated since it also attaches to serotonin receptors (5, 9, 103).

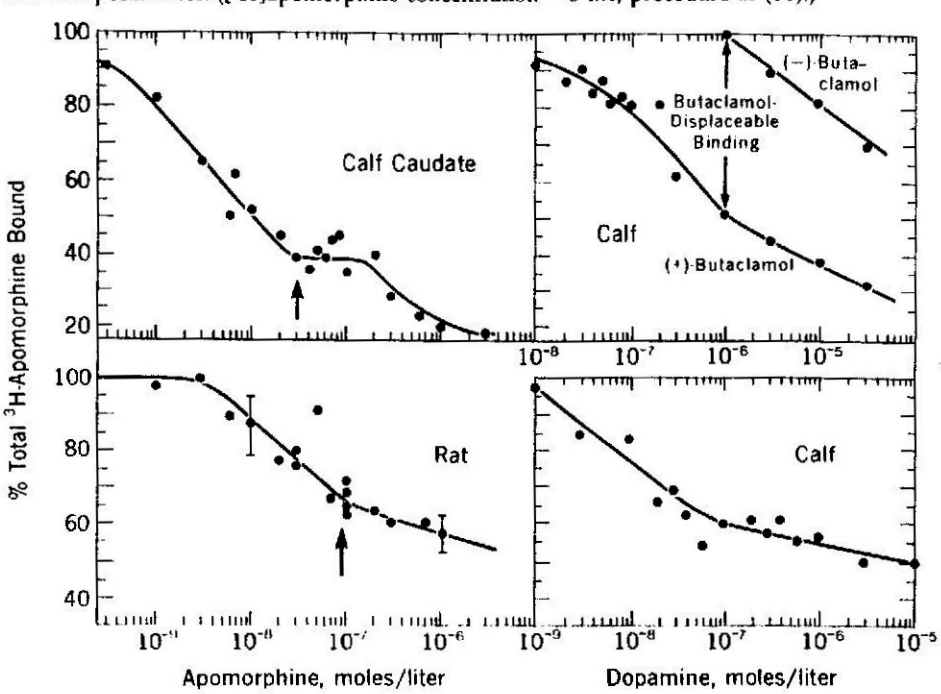
The case with [^{3}H]dihydroergocryptine is rather interesting, since it has been used for alpha-noradrenergic (31, 39, 104, 105), serotoninergic (21) as well as dopaminergic receptors (17, 18). The successful identification of [^{3}H]DHE as a valid ligand for dopamine receptors in the pituitary (17, 18) was aided by the fact that the pituitary has few, if any, noradrenaline or serotonin receptors. Studies in this laboratory (M. Tittler, P. Weinreich and P. Seeman, in preparation) indicate that it is also possible to use [^{3}H]DHE as a dopamine receptor ligand in caudate tissue if one blocks all the noradrenergic sites with 100 nM phentolamine (Fig. 4).

[^{3}H]Apomorphine as a dopamine receptor ligand

Apomorphine has been well characterized as a dopamine agonist (1, 33, 41). In many instances, however, it acts as a partial agonist (74), and can thus antagonize the more powerful agonists such as dopamine itself (22, 36, 37, 70).

[^{3}H]Apomorphine is an excellent ligand for dopamine receptors (86). In crude homogenates of the calf caudate or the rat striatum there are both high and low affinity sites for apomorphine; the K_D for the high affinity site is 2 nM in the cow and 15 nM in the rat (see Fig. 5). All these high affinity sites are occupied at either 100–200 nM apomorphine or 1 μM (+)butaclamol (Fig. 5).

Figure 5. Evidence for high and low affinity sites of [^{3}H]apomorphine binding in calf caudate and rat striatal homogenates. Generally 40–60% of the total binding is associated with the specific sites. ([^{3}H]apomorphine concentration = 3 nM; procedure of (86).)



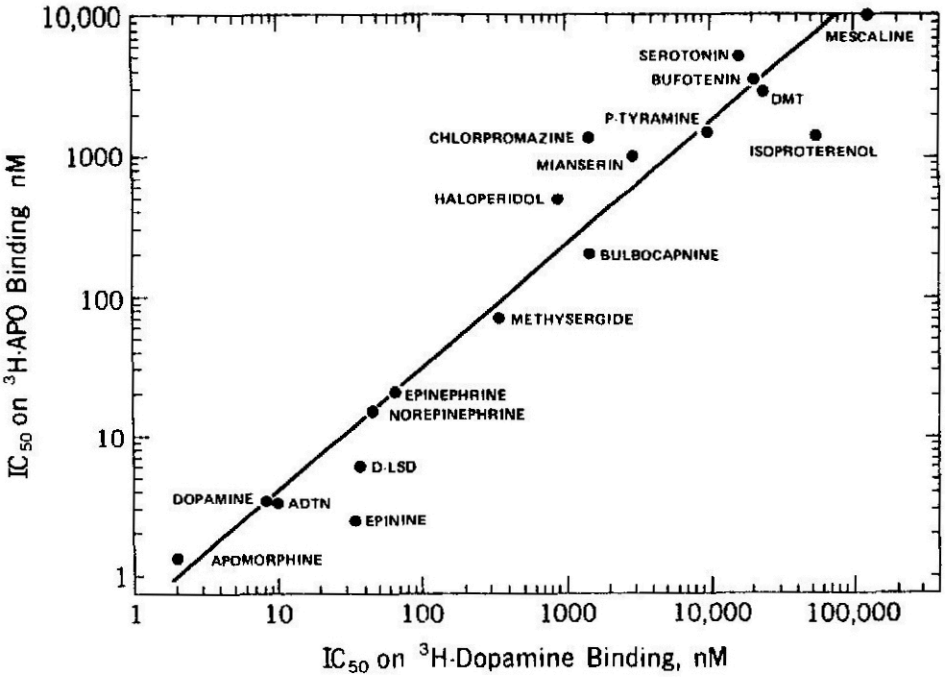


Figure 6. The IC_{50} values of various drugs for inhibiting the specific binding of [^{3}H]apomorphine (APO) correlated with the IC_{50} values for inhibition of [^{3}H]dopamine binding (calf caudate homogenate). Specific binding of [^{3}H]apomorphine is defined as that which is displaceable by 1 μM (+)butaclamol (for data from (86) for apomorphine, dopamine, norepinephrine, epinephrine, chlorpromazine, haloperidol and isoproterenol and from (103) for serotonin, bufotenin, DMT or dimethyltryptamine, mescaline, mianserin, methysergide and *d*-LSD) or by 200 nM apomorphine (for data from J. Tedesco and P. Seeman (in preparation) for epinine, ADTN (6,7-dihydroxy-2-aminotetralin), bulbocapnine and *p*-tyramine). Specific binding of [^{3}H]dopamine is here defined as that which is displaceable by 1 μM (+)butaclamol (for data from (86) for apomorphine, dopamine, norepinephrine, and epinephrine, or from (11) for ADTN, epine, bulbocapnine, chlorpromazine, haloperidol, *p*-tyramine, and isoproterenol) or by either 1 μM dopamine or 10 μM (+)butaclamol (for data from (9) for *d*-LSD, methysergide, mianserin, serotonin, bufotenin, DMT and mescaline).

In general, the results obtained for the IC_{50} values (i.e., concentrations that inhibit ligand binding by 50%) of various agonists and antagonists for inhibiting [^{3}H]apomorphine binding correlate very well with those for inhibiting [^{3}H]dopamine binding (Fig. 6).

The IC_{50} values for a variety of dopamine agonists (in blocking the binding of [^{3}H]apomorphine) also correlate with their potencies in stimulating the rat caudate dopamine-sensitive adenylate cyclase (Fig. 7).

Thus, it appears valid to use [^{3}H]-apomorphine as a ligand to study the structure–activity relations of dopamine-mimetic drugs, such as the 2-aminotetralins (60, 61), the aporphines (13, 71), and the dopamine analogues (89). The preliminary structure–activity relation study shown in Fig. 8 (J. Tedesco, J. Bowles, J. D. McDermed and P. Seeman, in preparation) indicate that the active conformation of dopamine is the beta rotamer form (13, 22, 30). In general, there is a fair relation between in vivo (19, 22, 29, 106) and in vitro (i.e., versus binding) actions, particularly within a set of closely related congeners (e.g., the 2-dipropylaminotetralins; (60)). Better correspondence is seen for drugs injected directly into the brain (23) than for those injected intraperitoneally (24, 64, 71).

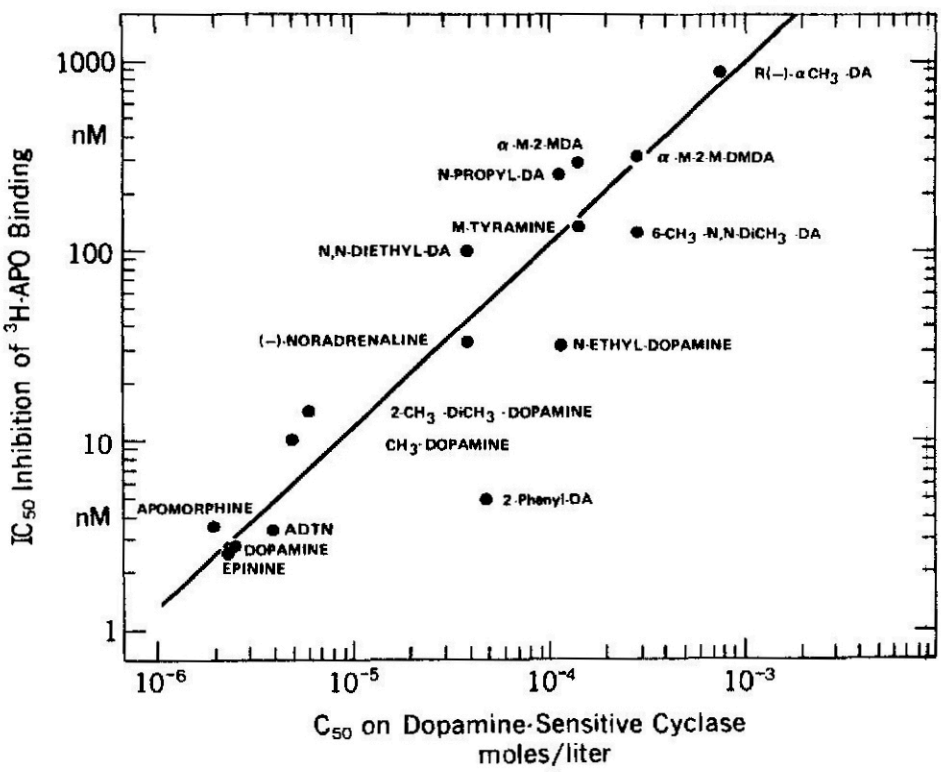


Figure 7. The IC_{50} values of dopamine agonists in blocking the specific binding of [^{3}H]apomorphine (to calf caudate homogenate) correlate with the concentrations (C_{50} values) for stimulating dopamine-sensitive adenylate cyclase in rat caudate homogenate. Specific [^{3}H]apomorphine binding was defined as that displaceable by 200 nM apomorphine (J. Tedesco and P. Seeman (in preparation)). The C_{50} values for dopamine-sensitive adenylate cyclase were taken from (52) (for apomorphine), from (66) and (47) (for noradrenaline, ADTN and dopamine) and from (89) for all other drugs (N.B.: the average C_{50} for dopamine was 2.5 μM, combining (66) and (89)). The dopamine antagonists do not fit along this correlation, and it is not known whether 2-phenyl-dopamine is an agonist or an antagonist.

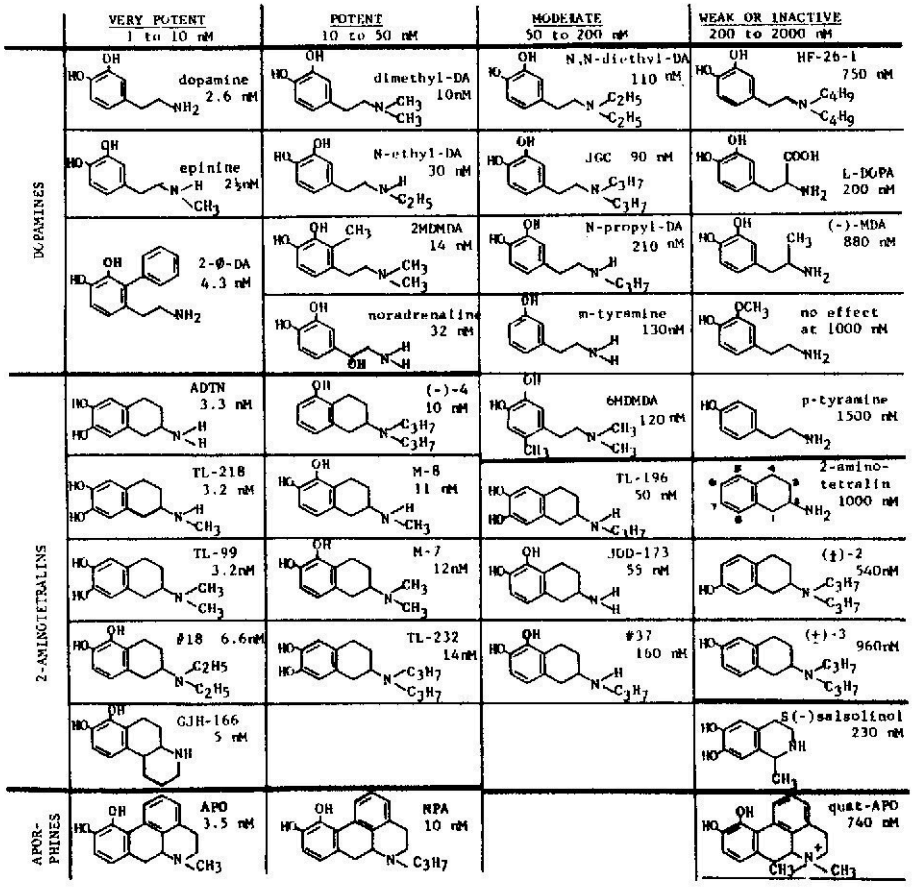


Figure 8. The potencies (IC_{50} values) for various dopamine analogues, 2-aminotetralins, and aporphines for inhibiting the specific binding of [^{3}H]apomorphine to calf caudate homogenate. Specific binding of [^{3}H]apomorphine is defined as that which is displaceable by 200 nM apomorphine. 2-Ø-DA (2-phenyl-dopamine), *S*(−)salsolinol, *N*-ethyl-DA, 2MDMDA (2-methyl-*N*,*N*-dimethyl-dopamine),*N*,*N*-diethyl-DA, *N*-propyl-DA, 6MDMDA (6-methyl-*N*,*N*-dimethyl-dopamine), and (−)-MDA (methyl-dopamine) were donated by Dr. Herbert Sheppard (Hoffman-La Roche Inc., New Jersey). Compounds #18, (−)-4, #37, (±)-2 and (±)-3 were donated by Dr. John D. McDermed (Wellcome Research Labs., North Carolina). ADTN, TL-218, TL-99, GJH-166, dimethyl-DA, M-8, M-7, TL-232, JGC, TL-196, JOD-173, HF-26-1, 2-aminotetralin, TL-68 and quat-APO (or apomorphine methoiodide) were donated by Drs. J. P. Long and J. G. Cannon (Iowa University); NPA (or *N*-propyl-norapomorphine) was donated by Dr. J. L. Neumeyer (Northeastern University).

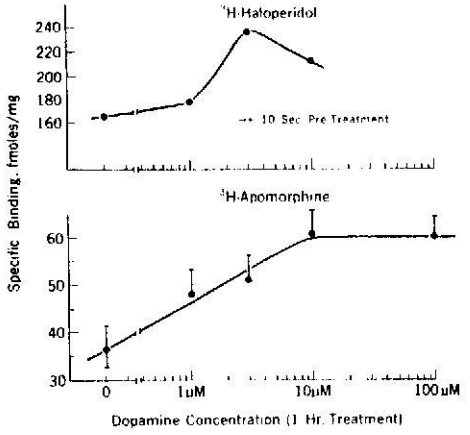
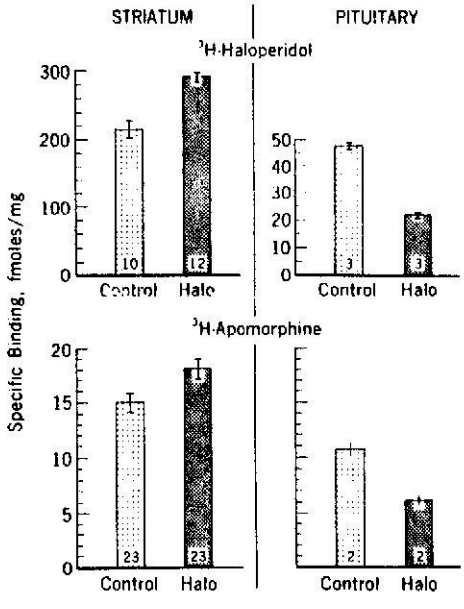


Figure 9. Pretreatment of calf caudate homogenate with high concentrations of dopamine (1 to 100 μM) for 1 hr followed by at least 4 washes (resuspension and recentrifugation) with 80 volumes of buffer (per wash) leads to an increasing binding of [^{3}H]apomorphine and [^{3}H]haloperidol. Separate experiments with [^{3}H]dopamine indicated little residual dopamine. Brief (10 sec) exposure to dopamine did not produce this effect.

Figure 10. Effect of chronic haloperidol on the dopamine/neuroleptic receptors in rat striatum and pituitary. The rats received haloperidol 0.32 mg/kg i.p. twice per day (BID) for 4 days, then 0.64 mg/kg i.p. BID for 4 days, then 1.25 mg/kg i.p. BID for 4 days, and then 2.5 mg/kg i.p. BID for 8 days; the animals were killed after a 6-day drug-free period. At least 30 animals were included in each group; each rat striatum was assayed separately. The number in each column indicates the number of separate assays; at least 6 pituitaries were needed for each assay. Vertical bars indicate standard errors, except in the lower right where the bar indicates the range of values. Differences in [^{3}H]haloperidol binding were significant at the 0.001 level, while those for [^{3}H]apomorphine were significant at the 0.05 level.



MODULATION OF DOPAMINE RECEPTORS

Sensitization and desensitization of dopamine receptors

Desensitization of adrenergic receptors (in vitro) has now been extensively described (56). Little information exists on whether dopamine receptors can be desensitized. However, Walters et al. (102) have found that cells in the pars compacta of the substantia nigra become resistant to intravenously administered dopamine-mimetics (apomorphine or piribedil) after intraperitoneal or intravenous injections of these drugs, and they review both presynaptic and postsynaptic sites as possible explanations for the tachyphylaxis. Clinically, it is possible that the "on-off" phenomenon and other diphasic phenomenons associated with high-dosage L-dopa therapy may reflect acute phases of desensitization of striatal dopamine receptors.

In vitro, however, pretreatment (see (72)) of the caudate homogenate with high concentrations of dopamine (in the μM region), followed by extensive washing (such that less than 1 nM subsequently remains, as monitored directly with [^{3}H]dopamine), surprisingly leads to an increased binding of both [^{3}H]apomorphine and [^{3}H]haloperidol (Fig. 9). Although the specificity of this effect

has not yet been examined, this type of short-term "sensitization" may underlie the short-term sensitization (in stereotyped behavior) that occurs over a matter of a few days in guinea pigs receiving amphetamine daily (53). The L-dopa-induced dyskinesias that quickly develop over a matter of the first weeks of therapy in patients with Parkinson's disease (4, 53) may possibly arise from such a dopamine-induced sensitization. It has also been found that repeated treatment with apomorphine actually enhances the dopaminergic supersensitivity brought on by reserpine (35). The interpretation of such L-dopa-induced or apomorphine-induced sensitization effects in vivo are complicated because of the existence of presynaptic dopamine receptors (on dopamine neurons) which are inhibited by dopamine-mimetic drugs (14, 15, 48).

Dopaminergic supersensitivity

Behavioral supersensitivity to dopamine-mimetic drugs occurs after nigrostriatal lesions (91) and after chronic neuroleptic treatment (3, 34, 68, 69). In both instances the number of striatal receptors increases. Rats treated chronically with haloperidol exhibit an increased binding of [^{3}H]haloperidol (20–25% in ref 8 and 30–35% in ref 69 and Fig. 10), and of [^{3}H]apomorphine in the striatum (Fig. 10). In the pituitary, however, the number of these receptors goes down (Fig. 10).

After nigrostriatal lesions, a decrease in the electrophysiological neuronal sensitivity to dopamine has been reported (93). Dopamine-sensitive adenylate cyclase, however, has been reported both to rise (55, 67) and to be unchanged (55, 101), following nigrostriatal lesions. We have found that such lesions lead to an enhanced striatal binding (by 60–80%) of [^{3}H]haloperidol. FP

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