Chapter 2. Antipsychotic Agents and Dopamine Agonists

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A large body of indirect but compelling pharmacological data implies the existence of dopaminergic defects in the brains of patients suffering from schizophrenic psychosis. Direct demonstration of a causative biochemical lesion in this disorder is still almost completely lacking, and other neurohumoral systems may be involved.[1,2] However, the dopamine (DA) hypothesis has provided fertile soil from which much of the recent progress in the understanding and treatment of schizophrenia and other diseases of the CNS has grown.

Dopamine Receptors. The use of receptor binding assays, which was reviewed by Creese and Snyder[3] in the previous volume of this series, has accounted for much of the progress of the past year in the characterization of the DA receptor in normal and disease states. The tritiated DA agonists and antagonists which have now been successfully used to label DA receptors in vitro include ^{3}H-DA, ^{3}H-apomorphine (APO), ^{3}H-dihydroergotamine, ^{3}H-haloperidol, and ^{3}H-spiroperidol.[3-12] However, it is not clear that all these label the same population of receptors. It has been previously reported that DA agonists are more effective in displacing ^{3}H-DA than ^{3}H-haloperidol from binding sites in rat and calf caudate and that DA antagonists have the opposite effect, although these binding sites are closely associated.[3,13] This has been explained by suggesting that agonists and antagonists selectively interact with different conformations of the same DA receptor.[14] More recently Seeman, et al. have examined the abilities of drugs to displace the binding of five different ligands from DA receptors in calf caudate.[7] They obtained biphasic displacement curves in some cases which led them to suggest the existence of two entirely separate receptor populations in brain. Further data from the same group suggest that these distinct receptors may represent pre- and postsynaptic dopaminergic receptors. Thus it has been found that 6-hydroxydopamine lesions in the nigro-striatal pathway of the rat decrease the binding of ^{3}H-APO but increase the binding of ^{3}H-haloperidol.[15] The authors therefore suggested that APO selectively labels presynaptic sites (destroyed by the lesion) and haloperidol selectively labels postsynaptic (supersensitive) receptors. It should also be noted that other groups have also proposed the existence of functionally distinct classes of DA receptors in brain to explain behavioral[16,17] and electrophysiological[18] data.

Several groups have begun to examine the changes in DA receptors in various pathological states or in experimental models of them. For example, rats may be treated chronically with neuroleptic drugs to produce a model of tardive dyskinesia. In such animals, it is found that there is an increase in the total number of DA receptors in the basal

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ganglia.[19,20] However, similar increases do not occur in the number of opiate or noradrenergic receptors in the same animals.[20] Animal models of Parkinson's disease may also be produced by 6-hydroxydopamine lesions of the nigrostriatal DA pathways or by electrocoagulation of the substantia nigra.[21] Behavioral supersensitivity to DA agonists is seen in such animals, together with an increase in the number of binding sites for ^{3}H-haloperidol.[21] It is highly significant that postmortem samples of caudate nucleus from brains of parkinsonian patients show similar increases over controls.[22] In these same samples ^{3}H-APO binding is reduced, which is entirely consistent with results in rats with 6-hydroxydopamine lesions noted above. Decreases in ^{3}H-spiroperidol binding have also been recorded from brains of patients with Huntington's chorea.[23] In such cases a decrease in the concentration of choline acetylase in the basal ganglia was also seen, leading to the suggestion that some of the haloperidol binding sites may be on cell bodies of cholinergic neurons of the basal ganglia. In support of this suggestion it has also been found that injection of kainic acid into the basal ganglia, which selectively destroys cell bodies of cholinergic and GABAergic neurons, also leads to a decrease of haloperidol binding in this area.[24] It also leads to a decrease in DA-sensitive adenylate cyclase activity.

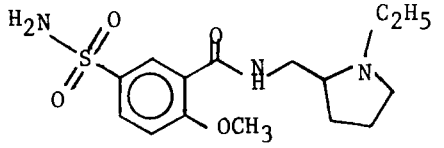
A very important observation has been made with respect to the state of DA receptors in the basal ganglia and elsewhere in the brains of patients with schizophrenia.[25] Lee and Seeman found that in the postmortem samples of brains from such patients there was an increased number of receptors for haloperidol binding in the putamen, caudate nucleus, and nucleus accumbens, but not in the frontal cortex. This provocative observation suggests that an increased number of DA receptors could be the biochemical defect responsible for the symptoms of schizophrenia. However, more work is required in this system, particularly to determine if this result was from a primary lesion characteristic of the disease or a secondary one resulting from long term treatment with neuroleptic drugs.

Another novel use of binding assays has been reported by Creese and Snyder, who have used this technique to assay for neuroleptic drugs in the sera of schizophrenic patients undergoing drug therapy. In this system the amount of circulating drug is monitored by observing the ability of the patient's plasma to inhibit the binding of ^{3}H-spiroperidol to calf caudate membranes.[26] This single procedure is simultaneously applicable to all the commonly used antipsychotic drugs and even any active metabolites, and should be a considerable aid to psychiatrists trying to establish optimal drug regimens for their patients.

One other DA-linked system has been increasingly investigated over the past year. That is the ability of DA agonists to decrease, and of DA antagonists to increase, the secretion of prolactin from the anterior pituitary.[27] This is believed to be a direct effect of dopaminergic agents on the prolactin-secreting cells of the anterior lobe. In fact, binding of tritiated ligands to such cells has been observed.[28,29] It is quite clear that the ability of DA antagonists to act as antipsychotic drugs correlates well with their ability to increase prolactin secretion

in the rat. It may therefore be that this is another important and useful system for monitoring DA antagonists both in vitro and in the clinic.[30] In addition, one paper has reported very interesting dopaminergic effects in cells of the bovine parathyroid gland.[31] However, the pharmacology of this system has not as yet been extensively elucidated.

Antipsychotic Agents. Considerable interest in recent years has been focused on the mode of action of sulpiride (1), because this antipsychotic is generally believed to be largely free from the liabilities of extrapyramidal side effects and tardive dyskinesia encountered with the classical neuroleptics. Recent clinical studies have confirmed the antischizophrenic efficacy of sulpiride,[32-4] though it should be noted that in the largest of these[33] (76 inpatients, double-blind vs. haloperidol) sulpiride did produce a significant number of "extrapyramidal disturbances" (8 cases vs. 12 for haloperidol). Several pharmacological studies have provided evidence that sulpiride exhibits many, although not all, of the effects of classical neuroleptics. In common with other neuroleptics sulpiride inhibits APO-induced behavior in animals,[35] increases dopamine turnover and accumulation of metabolites,[35-36] increases prolactin secretion,[34,37] and inhibits binding of ^{3}H-haloperidol to dopamine receptors in homogenates of rat caudate.[38] Rather high doses are required in some of these systems as well as for antischizophrenic activity in man. On the other hand, sulpiride is apparently atypical in other regards. It does not produce catalepsy and does not block the DA-sensitive adenylate cyclase in striatum and nucleus accumbens.[39] In the periphery it has been shown to have an unusually high specificity for DA receptors vs. α-adrenergic receptors,[40] in comparison to other neuroleptics. There are particularly interesting reports that sulpiride is atypical in producing selective effects on DA metabolism in the limbic system,[41] entorhinal cortex,[42] and retina,[43] rather than in the striatum. It should also be noted that sulpiride may be acting at the presynaptic level to an unusual degree.[44]

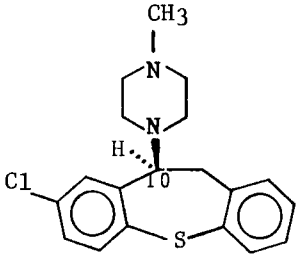


1

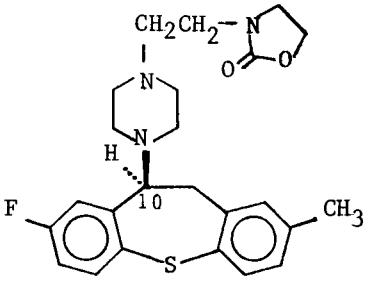
Perhaps the most intensively studied subject of neurobiology during very recent years has been the endogenous opioids, the endorphins and enkephalins.[45,46] The profound behavioral effects of endorphins injected into the brain have led some authors to speculate that endogenous opiate peptide systems may be involved in the pathogenesis of schizophrenia.[47] Consequently, it has also been suggested that opiate peptides may be effective antipsychotic agents in certain cases. Several studies have pointed to interaction of enkephalinergic systems with central dopaminergic pathways. For example, β-endorphin and analogs of enkephalin, as well as classical narcotics, have been shown to produce typically "dopaminergic" responses such as hypermotility and catalepsy.[48] Moreover, high concentrations of these peptides have been found in the regions of the basal ganglia which are also densely innervated by dopaminergic neurons.[49] At the biochemical level, it has been shown that β-endorphin and

enkephalins increase the turnover of DA and accumulation of metabolites in the basal ganglia and decrease the turnover of DA in the hypothalamus.[50] It is well known that opiates and opiate peptides are effective in increasing the release of prolactin from the pituitary.[51] In spite of the evidence above, it should be stressed that antipsychotic efficacy has not yet been demonstrated in any opioids.

Some information has recently appeared on chiral neuroleptics which may ultimately provide new insights into receptor topography. Although numerous neuroleptics have been resolved into optical isomers and many of these show a high degree of stereoselectivity, the absolute configurations of very few of these are yet known. The best studied of these is butaclamol, whose DA receptor blocking activity is exclusively a property of the dextro enantiomer.[52] Recently the structures of two resolved dibenzothiepins have been determined by X-ray diffraction. These are octoclothepin (2)[53] and the related compound 3.[54] In each case neuroleptic activity is found only in the (+)-10S enantiomer. However, it might be noted that some controversy exists over whether or not some related dibenzothiepins are completely stereospecific in their biological activities.[55-57]

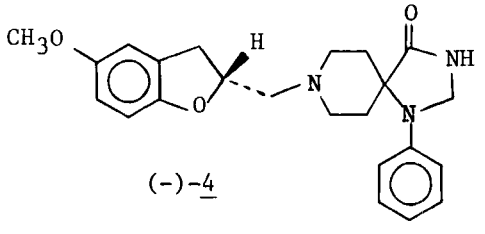


(+)-2

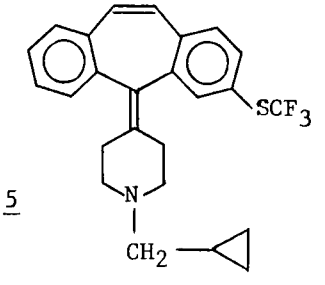


(+)-3

The absolute configuration of SU 23397 (4), a stereospecifically active neuroleptic of a very different structural type, has been determined by chiral synthesis.[58] Comparison of the structures and configurations of these chiral antagonists with each other and with chiral DA agonists should offer an improved understanding of the mode of interaction of these drugs with their receptors.[52]



(-)-4

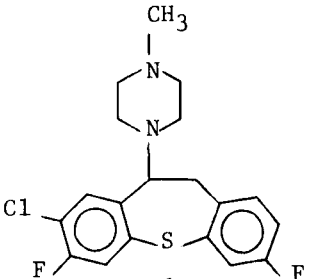


5

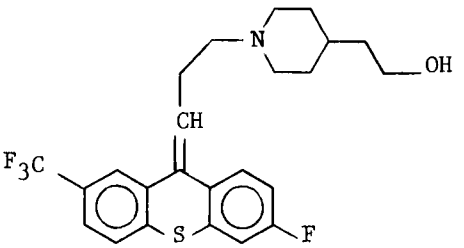
From the standpoint of chirality, the novel compound 5 is interesting.[59] This drug, which was made as an analog of cyproheptadine, is

optically active. Although it lacks a chiral carbon atom, severely hindered inversion of the non-planar 7-membered ring renders it permanently asymmetric. (-)-5 blocks the conditioned avoidance response (CAR) in squirrel monkeys (0.6 X haloperidol) and APO-induced stereotypy in rats (0.1 X haloperidol). Its enantiomer, (+)-5, blocks neither the CAR nor the stereotypy, but it appears to possess central anticholinergic activity.

Protiva's group has reported[60] that the compound VUFB-10699 (6) is an orally-active cataleptic and blocks APO-induced emesis. Although it is obviously a derivative of octoclothepin (2), those workers noted that it also bears some structural resemblance to drugs of the pimozide type.

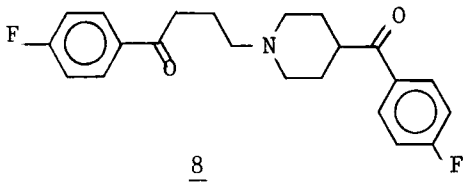


6



7

A Lundbeck group has reported that piflutixol (7), the 6-fluoro derivative of flupenthixol, is even more potent that its distinguished parent as a neuroleptic in animal models.[61] This compound, whose geometrical isomerism is unstated, is more potent (4-10x) than cis-flupenthixol in blocking APO- and amphetamine-induced stereotypy and in inducing catalepsy. It is the most potent blocker known for the DA-sensitive adenylate cyclase of striatum (IC_{50}=9.7 x 10^{-10}M). It is a potent and long-acting sedative. Typical of neuroleptic drugs, 7 increases DA turnover and elevates the metabolites HVA and DOPAC in rodent brain.[62]



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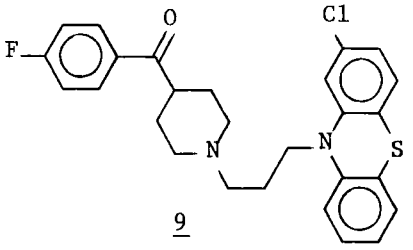
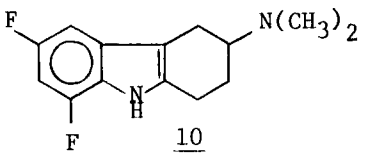


9

An approach to drug design which is often attempted but rarely rewarded is the incorporation of two separate pharmacophores into the same molecule. This approach appears to have succeeded twice in the case of neuroleptics. Lenperone (AHR 2277; 8) may be viewed as containing two butyrophenone moieties in the same molecule. It is an effective antipsychotic drug in man and has a rapid onset of action with minimal extrapyramidal and autonomic side effects.[63] It appears to show greater selectivity than haloperidol in blocking APO-induced behavior in animals.[64] Using this as a model, Boswell, et al.,[65] have combined butyrophenone and phenothiazine groups to produce compound 9, which is the most interesting of a series of five. It is long-acting in suppression of CAR

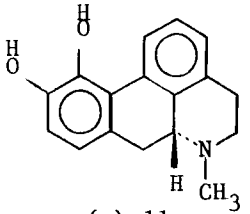
in mice and in protection against amphetamine toxicity in aggregated mice.



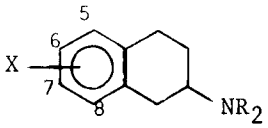
10

One of the more novel structures reported this year to have neuroleptic potential is 10, which was the only active analog in a large series.[66] It was active (6x chlorpromazine) in blocking amphetamine-induced stereotypy, but no further indications of neuroleptic activity were reported. Removal of the fluorine groups gave a compound with imipramine-like activity.

Dopamine Agonists. APO (11) is easily the most thoroughly investigated DA agonist and is the basis for a large number of widely used pharmacological models. It is the subject of a valuable recent review by Colpaert, et al.[67] Subsequent to this review, some papers have appeared which are pertinent to the use of APO in pharmacological models. Ljundberg and Ungerstedt[68] reported that APO elicits two distinguishable patterns of behavior in rats (gnawing vs. locomotion, sniffing, etc.), depending on apparently trivial change in the point of s.c. injection, and that such behavioral changes are not merely dose-dependent intensity changes as is commonly assumed. Cools, et al., have made similar observations and have noted rapid conditioning with APO.[69] Additional evidence has accumulated that various behavioral and neurochemical effects of APO are mediated at presynaptic sites,[70] whose existence is supported by binding studies.[21] Corsini, et al., have demonstrated that low (non-emetic) doses of APO have a paradoxical antipsychotic effect in schizophrenics.[71] This could be explained by selective action of APO at low doses at the presynaptic level which inhibits release of DA into the synapse and thus decreases the activity of the neuron. This may be an attractive target for future drug design.

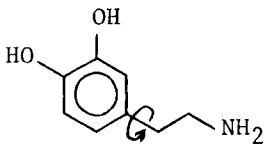


(-)-11

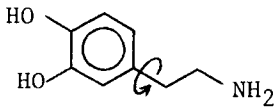


12

a. X=5,6-(OH)$_2$
b. X=6,7-(OH)$_2$
c. X=5-OH



DA, α-rotamer

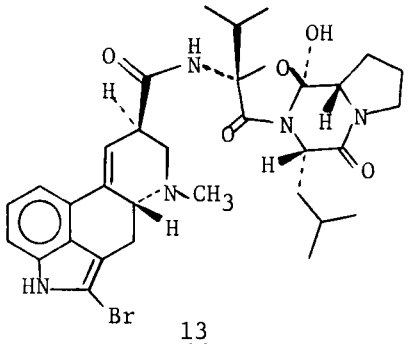


DA, β-rotamer

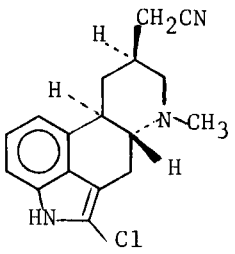
In recent years 2-aminotetralins (12) have received considerable attention as DA agonists. They were envisioned to be the principal pharmacophore of APO and have lately been used to infer conformational preferences of DA at its receptors. Cannon, et al.,[72] have now reported that the pattern of stereotypy-hyperactivity induced by numerous compounds of types 12a and 12b depends on the mode of administration (see also refs. 68, 69) and on the substitution pattern. Compound 12a, R=Pr,[73,74] was the most potent of all. They suggest that compounds of type 12a (α-rotamer of DA) may act via a mechanism different from that of 12b

(β-rotamer of DA), and that the α-rotamer represents the preferred conformation of DA in the caudate. This latter suggestion stands in interesting contrast to the effects of these compounds in stimulation of DA-sensitive adenylate cyclase from striatum,[75] in dilation of the canine renal artery,[76] and in binding studies,[77] in which models the β-rotamer is preferred. Of course, the possibility of different receptors in different models must be considered.[40] The earlier report[78] that *in vivo* activity of compound 12c, R=Pr, is an exclusive property of the levo enantiomer has been subsequently found to have biochemical correlates in stimulation of DA-sensitive adenylate cyclase from retina[79] and in binding to striatal membranes.[77] A compound possibly related to 12c which has been reported to have dopaminergic agonist activity in mice is 3-[2-(dipropylamino)ethyl]phenol,[80] a homolog of m-tyramine.

Ergot alkaloids, which bear little structural resemblance to the dopaminergic aporphines and tetralins, continue to be a rich source of therapeutically useful DA agonists. Parkinson's disease is a condition in which a functional deficit of DA has been clearly established.[81] Reports demonstrating the benefit of bromocriptine (CB 154; 13) in this condition have been rapidly accumulating.[82-87] Of particular interest are the observations in these reports that patients who fail or cease to respond to L-Dopa may respond well to 13. More limited clinical experience with lergotrile (14) in Parkinson's disease[88] appears to parallel that with 13. It would appear that the efficacy of 13 is indeed due to a



13



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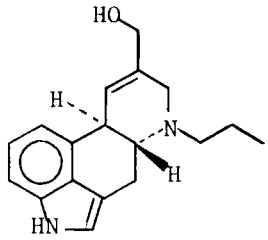

15

DA agonist effect. For example, 13 inhibits release of prolactin.[89] Like APO, it raises secretion of growth hormone from normal pituitary, but paradoxically, 13 lowers it in the condition of benign pituitary adenoma. This last property has made it the drug of choice for treatment of acromegaly.[90,91] The pharmacology of 13 and 14 is complex and appears to include both post- and presynaptic activity[92-96] and possible metabolic activation.[92] Interestingly, while both inhibit binding of agonists *in vitro*,[94] 14 is an antagonist in the DA-sensitive adenylate cyclase preparation.[97]

Two reports describing synthetic analogs of ergot alkaloids have appeared using inhibition of prolactin secretion in rats to assess activity. Compound 15 was found to be very active in this model.[98] Simpler fragments of the ergoline structure were generally inactive.[99]

L-Dopa, of course, remains the classic treatment of Parkinson's disease. Two groups have reported attempts to improve the bioavailability of L-Dopa, itself a prodrug of DA, by a prodrug approach. Bodor, et al.,[100] systematically prepared derivatives of L-Dopa with one or more of the functional groups blocked, and dipeptides of L-Dopa with multiple protecting groups. Plasma levels of L-Dopa and DA in dogs given such prodrugs orally were found to be significantly higher than after oral L-Dopa. A different approach was taken by Maeda, et al.[101-102] They showed that 3,4-dihydroxyphenylpyruvic acid was rapidly metabolized to L-Dopa by transamination in homogenates of liver and kidney. However, this particular prodrug appears to be hampered by poor absorption in vivo.

L-Dopa has been reported to reverse DA receptor supersensitivity,[103, 104] and this finding may have implications for the treatment of tardive dyskinesia[104,106]. L-Dopa has also been found to induce recovery from septal lesion-induced rage.[105]

There is a very provocative report by Cotzias, et al.,[107] that chronic L-Dopa treatment produces a dose-dependent increase in longevity of normal mice. This is particularly interesting in view of recent epidemiological studies which indicate that L-Dopa treatment may increase longevity of parkinsonian patients.[108]

Virtually all of the preceeding discussion has pertained to DA agonists and antagonists in the CNS, but more recently the importance of DA mechanisms in the periphery has been noted and reviewed.[40,109] Hypertension is a particular focus of attention.[110] There is an interesting report that prolactin levels in 19 young men with essential hypertension were consistently and significantly higher than in 8 normotensive controls.[111] Bromocriptine was effective in reducing both prolactin levels and blood pressure in these hypertensives. The involvement and possible therapeutic relevance of DA control of cerebral blood flow is also being examined.[112-114]

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