Dopamine Receptors and Their Behavioral Correlates
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Dopamine Autoreceptor Stimulation: Clinical Significance[1]

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MELTZER, H. Y. *Dopamine autoreceptor stimulation: Clinical significance.* PHARMAC. BIOCHEM. BEHAV. 17: Suppl. 1, 1–10, 1982.—Recent studies of the effects of low doses of dopamine agonists, designed to stimulate dopamine autoreceptors and hence diminish the synthesis and release of dopamine, were based on a series of basic research studies which demonstrated the existence of autoreceptors on dopamine neurones of the nigrostriatal, mesolimbic and mesocortical dopaminergic neurones. Evidence for autoreceptors on the tuberoinfundibular dopamine neurones which participate in the regulation of prolactin and growth hormone secretion is lacking. Some recent reports have questioned the existence of dopamine autoreceptors on the mesolimbic and nigrostriatal dopamine neurones. Specificity of various dopamine agonists and antagonists for the dopamine autoreceptor will be reviewed. The sedative, anxiolytic, antipsychotic, antidyskinetic and neuroendocrine effects of low dose dopamine agonists in man will be described. Low dose apomorphine, N-propylapomorphine and bromocriptine have been reported to have antipsychotic effects in the major psychoses, to diminish tardive dyskinesia and to enhance extrapiramidal insufficiency. A unique depressive state which developed in a small proportion of psychiatric patients after low dose apomorphine will be described. Further evidence for the lack of dopamine autoreceptors on the tuberoinfundibular dopamine neurones in man will be presented. Strategies for further study of the dopamine autoreceptor concept in man will be discussed.

Dopamine neurons Autoreceptors Dopamine agonists

DOPAMINE (DA) neurons, in some but not all areas of the brain, have been shown to possess receptors sensitive to DA itself over all parts of the neuron, including the cell body, dendrites and preterminal axons. These receptors were termed "autoreceptors" by Carlsson [20]. Stimulation of the DA autoreceptors on the cell body by DA or DA agonists has been shown by electrophysiological methods to inhibit the tonic firing of the DA neurons [1, 2, 18, 84] and to inhibit the synthesis and release of DA [26, 44, 59, 65, 88, 115]. Through the latter mechanisms, DA released from nerve endings at those DA neurons which have autoreceptors plays a major role in the regulation of the activity of these neurons. There is controversy as to the relative importance of the feedback loops from postsynaptic neurons to the cell bodies of DA neurons and the terminal autoreceptor mechanism for the regulation of the activity of various DA neurons, but there appears to be strong agreement that the autoreceptor mechanism plays a critical role in the regulation of the activity of DA neurons [41, 47, 104, 109].

EFFECTS OF STIMULATION

Since the terminal autoreceptors inhibit the synthesis and release of DA, it would be expected that those behaviors believed to be dependent upon the release of DA, e.g., locomotor activity and stereotyped movements in rodents and psychotic phenomenology and extrapyramidal movement disorders in man, would be diminished by stimulation of DA autoreceptors. This, of course, would depend upon selective stimulation of DA autoreceptors without stimulation of postsynaptic DA receptors which would have the opposite effect, e.g., increased locomotor activity and stereotypy in rodents, and increased psychotic symptoms and extrapyramidal movement disturbance in man. This selective effect on autoreceptors might occur if the DA autoreceptors were more sensitive than the postsynaptic DA receptors to drugs which stimulate both types of receptors, if there were DA agonists which stimulated the autoreceptors selectively, or if there were antagonists which acted only at the postsynaptic DA receptor. The potential clinical usefulness of DA autoreceptor stimulation in clinical psychiatry is mainly based upon the evidence that increased dopaminergic activity is important in psychosis and tardive dyskinesia. In this paper, we will review some of the more important recent basic science information concerning the DA autoreceptor, especially the presence of these receptors on particular DA neurons but not others, and the pharmacology of the DA autoreceptor. We will then discuss some of the clinical studies concerning DA autoreceptor stimulation. Some of these studies have previously been reviewed elsewhere [71,79].

LOCALIZATION OF DA AUTORECEPTORS

Autoreceptors which modulate DA synthesis and release have been identified on the cell bodies and terminals of the

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nigrostriatal and mesolimbic DA systems [79]. They have also been demonstrated on the tuberohypophyseal neurons which innervate the neural lobe of the pituitary gland [37]. Autoreceptors are not present in terminal regions of the tuberoinfundibular neurons which release DA directly into the hypophyseal portal circulation [38]. There is some recent evidence that in contrast to the nigrostriatal neurons, some mesocortical DA neurons in the rat lack autoreceptors. Thus, Bannon *et al.* [11,12] reported that apomorphine and bromocriptine did not reverse the increase in DA content in the prefrontal cortex, produced by gammabutyrolactone (GBL), which inhibits firing in the DA neurons, whereas they did reverse the effect of GBL on DA content in the striatum. GBL also did not increase DOPA accumulation in the prefrontal cortex. Pericic and Walters [75] had previously reported that apomorphine pretreatment did reverse the increase in prefrontal cortical DA which they observed 60 min after GBL administration. The reason for the discrepancy is unclear. Roth (personal communication) using the GBL technique, has also found no autoreceptors on the DA terminals of the mesocortical DA neurons which terminate in the cingulate gyrus whereas those which innervate the entorhinal cortex do possess autoreceptors. If these results are verified by other laboratories, preferably using independent methods, they should have considerable importance for clinical research because of the possible involvement of frontal cortical DA neurons in psychosis. The decreased frontal blood flow and metabolic activity reported in schizophrenia [16,58] could conceivably reflect abnormalities in the DA neurons in this region. If man, like the rat, lacked autoreceptors on these DA neurons, it would reduce the likelihood that administration of DA autoreceptor agonists would diminish psychotic symptoms. However, the cell bodies in the ventral tegmentum of the mesolimbic DA neurons appear to have autoreceptors [2,116]; the terminals of the nigrostriatal DA neurons as well as limbic DA terminals in the nucleus accumbens also have DA autoreceptors [11]. Since both the mesolimbic and nigrostriatal DA neurons appear to play an important role in the action of neuroleptic drugs and probably in the psychopathology and motor disturbances of the psychiatric psychoses, the likelihood that stimulation of DA autoreceptors could have important clinical effects is not seriously challenged by their possible absence in the frontal cortex and cingulate gyrus.

PHARMACOLOGY OF THE DA AUTORECEPTOR

The pharmacology of the DA autoreceptor in the striatum has not been as well studied as that of the postsynaptic DA receptors. It has been proposed that ^{3}H-DA agonists such as ^{3}H-apomorphine have a much greater affinity for the DA autoreceptor than for the postsynaptic DA receptor [105], but this is quite controversial. Studies of the ability of DA or DA antagonists to displace ^{3}H-DA agonist ligand from the autoreceptor may provide at least a rough idea of their potency *in vivo* at this site, but formation of active metabolites and distribution within the brain could affect this. There is, of course, no reason to expect that drugs would have the same effect at all DA autoreceptors in the central nervous system relevant to psychosis or extrapyramidal disorders.

The relative ability of neuroleptics to block the effect of DA agonists on putative autoreceptor-dependent effects on cell bodies and terminal areas compared to postsynaptic DA receptor blockade has been studied by a variety of mechanisms [79]. This is of clinical importance since the combination of a selective postsynaptic DA receptor antagonist and DA autoreceptor agonist would produce the greatest interference in dopaminergic activity. Walters and Roth [113] reported that loxapine, haloperidol, and spiroperidol were much more potent than chlorpromazine, fluphenazine, or thioridazine in blocking the effect of apomorphine on striatal DOPA accumulation in GBL-treated rats, a classical DA autoreceptor model. Pimozide was quite weak and clozapine had no effect at all. Gianutsos *et al.* [50] reported similar findings for pimozide. However, McMillan *et al.* [69] demonstrated that pimozide was an effective autoreceptor antagonist in the GBL model and with electrophysiological techniques, if it was given 60 min before apomorphine and proposed this as the explanation of the difference between their results and those of Walters and Roth [113], who had given it 30 minutes prior to sacrifice. However, Di Chiara *et al.* [40] and Summers *et al.* [93] reported that pimozide given 15 to 20 min before apomorphine blocked low dose apomorphine-induced hypomotility in mice, suggesting that time factor is not the crucial factor. However, it appears that the hypomotility due to apomorphine may not simply be due to stimulation of DA autoreceptors. Stimulation of alpha$_2$ adrenergic receptors may also be involved in the apomorphine-induced hypomotility in mice since it is partially blocked by the adrenergic blockers yohimbine and piperoxane [92,93].

There is also conflicting evidence concerning the DA autoreceptor blocking effects of the benzamide drugs such as sulpiride. Walters and Roth [113] found sulpiride to be inactive in the GBL model, but Di Chiara *et al.* [40] reported that sulpiride blocked apomorphine-induced hypomotility, and Arbilla and Langer [8] have found that (S)-sulpiride was ten times more effective than (R)-sulpiride in blocking the DA receptors involved in modulation of the calcium-dependent electrically evoked release of ^{3}H-DA from slices of rabbit caudate nucleus. Similar results were reported with (S)- and (R)-butaclamol, indicating these effects are mediated through the blockade of DA receptors. Molindone has been reported, on the basis of biochemical and behavioral studies, to be more potent at blocking the DA autoreceptor in the cell bodies and terminals of the nigrostriatal pathway than the postsynaptic DA receptor [5]. At low doses, it appears to increase the release of DA. It is conceivable that molindone or a drug which was a relatively more potent autoreceptor antagonist would be useful in treating psychoses in which there might be decreased dopaminergic activity, e.g. some forms of chronic schizophrenia with defect and negative symptoms [72].

All chemical classes of DA agonists so far studied have been reported to stimulate the DA autoreceptor in some but not all models: DA and its analogs; apomorphine; the amino tetralins such as α-amino-6,7-dihydroxy-1,2,3,4-tetrahydronapthalene (ADTN), the ergots such as bromocriptine and ergolines such as pergolide [39, 42, 43, 52, 65, 79, 92]. Haubrich and Pfleuger [54] reported the following order of potency of DA agonists as autoreceptor agonists *in vivo* in the GBL model: N-n-propylnorapomorphine > pergolide > apomorphine > lergotrile > RU-24926 (a tertiary amine) > bromocriptine > CF 25-397 (an ergot) > 3-PPP (a DA derivative, see below). Their effects were blocked by haloperidol. Very different orders of potency were found in an *in vitro* system to assess effects on tyrosine hydroxylase. Thus, ADTN did not reverse the increase in tyrosine hydroxylase in GBL-treated rats. The ergot alkaloids and 3-PPP were weak or inactive in this system both as agonists or

antagonists. Haubrich and Pfleuger [54] considered that metabolites of the ergots could be responsible for the *in vivo* effect.

This currently available DA autoreceptor agonists also stimulate postsynaptic DA receptors. However, there is extensive evidence that the terminal autoreceptor is more sensitive to DA than the postsynaptic receptor [84] which is consistent with the observation that administration of low doses of these agents produces behavioral suppression [90]. Drugs with relatively specific action at the DA autoreceptor are being sought. Such agents can be identified by screening drugs in various putative autoreceptors models, such as neuroleptic-antagonized behavioral suppression in rodents, antagonism of DOPA accumulation after DOPA-decarboxylase inhibitor, antagonism of DA or L-DOPA accumulation after GBL and inhibition of DA release from slices or synaptosomes; these results are then compared with the potency of these drugs in models for postsynaptic DA receptor stimulation such as the stimulation of locomotor activity and behavior, or direction and rate of turning in rats with unilateral lesions of the substantia nigra. The most promising such compound is 3-(3-hydroxy-phenyl)-N-n-propylpiperidine; (3-PPP), which is effective in decreasing locomotor activity in blocking DA synthesis after DOPA-decarboxylase inhibition [55] and inhibiting the firing of DA neurons in the nigra [17] but with limited postsynaptic effects [55]. However, 3-PPP does not block the release of ^{3}H-DA from electrically-stimulated caudate slices [54,64], reported that 3-PPP was a very weak antagonist of the GBL-induced increase in DA synthesis in the mouse brain. Recently, 3-PPP has been found to be a racemic mixture, and each of the enantiomers has a different profile of action at pre- and postsynaptic DA receptors. Both (+)- and (−)-3-PPP and DA autoreceptor agonists. However, (+)-3-PPP is also a postsynaptic DA receptor agonist while (−)-3-PPP is a postsynaptic DA receptor antagonist. In the racemic mixture, these postsynaptic effects cancel each other out so that 3-PPP does not stimulate locomotor activity in the reserpine-treated rat or cause ipsilateral turning in unilaterally striatal lesioned rats [55]. However, (+)-3-PPP does produce some of the effects of a postsynaptic DA receptor agonist, albeit weakly. (−)-3-PPP is of potential clinical interest because it can reduce dopaminergic activity by two mechanisms: autoreceptor stimulation and postsynaptic DA receptor blockade. Another drug with relatively selective DA autoreceptor agonist properties is 6,7-dihydroxy-2-dimethylaminotetralin (TL-99) [53] but 3-PPP appears to be more selective [67].

Dopamine autoreceptors may become supersensitive following chronic neuroleptic administration [12, 74, 89] or chronic GBL treatment [74]. Possible subsensitivity of DA autoreceptors after chronic electroshock treatment [81] and antidepressant treatment has been reported by Serra *et al.* [82] and Antleman and Chiodo [7]. Such changes in sensitivity would have obvious impact upon the effects of administration of DA autoreceptor agonists.

With this background, it is possible to consider the evidence for DA autoreceptors in man and the effect of DA agonists on these receptors in patients with psychoses or movement disorders, or both.

EVIDENCE OF DOPAMINE AUTORECEPTORS IN MAN

There have been numerous clinical studies involving the administration of DA agonists to normal volunteers or patients with various types of psychiatric and neurologic disorders which have yielded results that are consistent with the presence of a class of DA receptors which are more sensitive to the action of DA agonists than postsynaptic dopamine receptors and which mediate effects that generally are the opposite of what might be expected from stimulation of postsynaptic DA receptors. These receptors have been thought to be of the same type and location as the DA autoreceptors in rodents just discussed. The behavioral effects following DA agonist administration consistent with DA autoreceptors include the following responses to low doses of dopamine agonists: (1) relaxation, sedation, and sleep in a variety of excited psychiatric and neurologic conditions as well as in normal volunteers; (2) antipsychotic effects in manics, schizoaffectives, and schizophrenics; (3) reduction in the abnormal movements in tardive dyskinesia; (4) reduction in the abnormal movements in Huntington's disease; (5) reduction in the symptoms of Tourette's syndrome; (6) production of parkinsonian symptoms in schizophrenics by low doses of a DA agonist and antagonist which have no discernible effect alone; (7) reduction of symptoms in spasmodic torticollis; and (8) reduction of the craving for alcohol. Some of these effects will be reviewed here in addition to presenting some of our own heretofore unpublished studies.

ABILITY OF APOMORPHINE TO INDUCE RELAXATION, SEDATION AND SLEEP IN MAN

Feldman *et al.* [46] reported that apomorphine, in doses of 1.5 mg, SC, with or without additional anticholinergic treatment (scopolamine), rapidly produced drowsiness and even sleep in excited schizophrenic or manic patients, in patients with agitated depression, as well as in patients with excitement and confusion due to delerium tremens, bromism, senile and general paresis, or toxic psychoses. It also reduced excitement and confusion in patients with a variety of supratentorial lesions or following electroconvulsive therapy.

Lal and de la Vega [62] reported drowsiness in 5 of 20 alcoholic patients who received apomorphine chronically. Angrist *et al.* [6] reported that low doses of piribedil given intravenously produced sedation and dysphoria which could be antagonized by low doses of haloperidol in 5 nonpsychotic volunteer subjects, four of whom had an alcoholic history. Corsini *et al.* [31] reported that apomorphine (1 mg) produced sedation and sleep in comparable proportions of unmedicated schizophrenic patients and normal controls. Sulpiride was more effective than haloperidol in blocking these effects. Corsini *et al.* [29] also found that apomorphine caused sedation and sleep in patients with Parkinson disease. These results suggest that it is unlikely that the sedative effects of apomorphine are due to an action on the nigrostriatal neurons which presumably had degenerated in Parkinson disease patients.

Bassi *et al.* [14] reported that apomorphine (1.5 mg SC) produced sleep in 10 normal volunteers and 10 Parkinson disease patients who had not previously been treated with L-DOPA. Sleep latency and total sleep time did not differ between the two groups—evidence that nigrostriatal DA neurons or their receptors are not relevant to this effect of apomorphine. However, in 10 Parkinson disease patients who had been treated with L-DOPA plus carbidopa for at least 18 months, apomorphine induced sleep in only three subjects; in two of these, the latency of sleep onset was much longer than in the other two groups of subjects. In two

of these subjects, apomorphine induced some excitation. Bassi *et al.* [14] attributed the sleep-inducing effect of apomorphine to its neuroendocrine actions. The attenuated effect of apomorphine in the L-DOPA treated patients suggests that the receptors which mediate apomorphine-induced sleep could become subsensitive after chronic stimulation.

Corsini *et al.* [32] have reported that the ability of apomorphine in doses of 20 μg/kg to produce nausea, arterial hypotension, sedation and sleep in Parkinson disease patients was blocked by pretreatment with domperidone, a DA receptor blocker which is believed to act mainly peripherally because it does not pass the blood brain barrier [34]. The improvement in rigidity and tremor due to apomorphine in four Parkinson disease patients was not blocked, nor was yawning, another possible central effect of apomorphine. On this basis, Corsini *et al.* [32] raised the possibility that apomorphine-induced drowsiness, which they had previously attributed to stimulation of brain DA autoreceptors [30], might be due to stimulation of DA receptors in peripheral organs such as the pituitary or stomach rather than central DA receptors.

Before this conclusion can be accepted, it must be shown that domperidone does not penetrate the blood-brain barrier in man or that it does not interfere with apomorphine absorption. Costall *et al.* [34] have found that levels of domperidone in several mesolimbic areas of the rat, including the nucleus accumbens and tuberculum olfactorium, as well as the globus pallidus, were approximately equivalent to or greater than those of blood. The lack of worsening of parkinsonian symptoms or blockade of yawning by domperidone suggests that it does not reach the striatum in man, but this does not rule out the possibility that other central dopaminergic receptors could be blocked by domperidone. Nevertheless, the findings of Corsini *et al.* [32] do indicate that considerable caution is needed before attributing the central effects of low doses of DA agonists to an action at brain DA autoreceptors. The possibility that peripheral DA receptors could induce sedation is most intriguing. However, it seems unlikely that a peripheral mechanism could affect psychotic symptoms or abnormal movements.

Cianchetti *et al.* [27] reported that continuous IV infusion of nonemetic doses of apomorphine (0.17–0.20 μg/kg/min) during sleep abolished REM sleep, reduced stage 4 sleep and increased stage 2 sleep. This effect was prevented by haloperidol or sulpiride but not by domperidone. Similar results were obtained with piribedil. Cianchetti *et al.* [27] attribute these effects to postsynaptic DA receptor stimulation rather than to an autoreceptor effect since they are opposite to those produced by inhibition of DA synthesis.

EFFECTS OF APOMORPHINE ON MANIC AND DEPRESSIVE SYMPTOMS

Arbuthnott and Murray [9] reported that one or two of seven manic patients improved while receiving the DA agonist piribedil. Although the dose administered (up to 240 mg/day) was sufficiently high that it might be expected to produce postsynaptic effects, the dose received by the patients who improved was not specified and may have been lower. Furthermore, interindividual variations in blood levels are likely so that the responders may have been those with blood levels sufficient to stimulate autoreceptors, not postsynaptic receptors. Post *et al.* [76] reported that piribedil, 60 mg/day, produced marked improvement in two manic patients whereas the same group reported a higher dose of piribedil activated mania [49]. DiChiara *et al.* [39] reported that low-dose apomorphine produced a marked antimanic effect in three of seven manic patients and 6 of 18 schizoaffective manic patients. As will be discussed subsequently, the Cagliari investigators reevaluated the data of Corsini *et al.* [30] on the antipsychotic effects of a single apomorphine injection in schizophrenic patients and concluded that it was mainly effective in schizoaffective manic patients (Research Diagnostic Criteria; [36]). During the course of a study of the effect of apomorphine at a dose of approximately 0.01 mg/kg on prolactin and GH secretion in psychotic patients, we found that 2 of 28 (7%) became severely depressed within 30 min; a third became slightly depressed (Meltzer and Bucht, unpublished data). Two became more elated.

In uncontrolled studies [101–103], apomorphine produced severe depression in mentally normal subjects and neurotic patients. This was not confirmed by Lal and De La Vega [62] who administered apomorphine, 1 mg, or water subcutaneously three times a day for 14 days to groups of 20 alcoholics. We have found slightly increased severity of depression in 3 of 22 (13.6%) patients with primary depressive disorders given approximately 0.01 mg/kg apomorphine SC (Meltzer and Bucht, unpublished data). Similar results have been reported by Maany *et al.* [66].

Post *et al.* [77] treated 16 depressed patients with piribedil. Twelve of the 16 patients showed improvement with moderate doses of piribedil (range 100 to 200 mg per day) for an average of approximately five weeks' duration. Two showed an exacerbation of depression. The possibility that the antidepressant effect of chronic piribedil administration could be due to gradual desensitization of DA autoreceptors leading to increased dopaminergic activity was considered. Several recent studies have also reported an antidepressant action of high doses of the mixed DA agonist/antagonist bromocriptine [4, 28, 73, 112].

ANTI-SCHIZOPHRENIC EFFECT OF DOPAMINE AGONISTS

There is provocative evidence that low doses of DA agonists can produce transient improvement in some schizophrenic patients. Thus, the administration of 1 mg apomorphine SC to unmedicated schizophrenics has been reported to produce a rapid, transient improvement of many psychotic symptoms [30, 39, 86]. For example, Di Chiara *et al.* [30] reported that eight of 24 paranoid schizophrenics and seven of 12 hebephrenic schizophrenics given apomorphine, 1 mg, IM, showed a rapid loss of most of their psychotic symtpoms, including delusions, cognitive disturbances, bizarre behavior, suspiciousness and aggressiveness for a brief period (20–50 min), after which their symptoms returned. Improvement in nearly all aspects of psychotic symptomatology was reported even in subjects who did not become sedated. No effect was observed in four catatonic schizophrenics. This group reexamined its previous reports [30] and determined that seven of the nine patients who responded best to apomorphine met Research Diagnostic Criteria for schizoaffective disorder, manic type, whereas eight out of nine non-responders were schizophrenic. They did not however specify which subtype of schizoaffective manic patients were included in the responder group. The responders more frequently fell asleep after apomorphine, had better premorbid functioning and were subsequently more likely to be treated with lithium carbonate than the

non-responders. The two groups did not differ in age at onset or age at time of receiving apomorphine.

Smith *et al.* [86] also noted improvement in some psychotic symptoms in 3 of 14 otherwise unmedicated schizophrenic patients given apomorphine in doses of 1.5–6 mg. We have administered approximately 0.01 mg/kg apomorphine (0.75 mg) SC to 47 unmedicated acutely ill schizophrenics and not observed any marked change in psychosis (Meltzer and Bucht, unpublished data) but the difference in dosage and route of administration between our studies and those of Corsini *et al.* [30,31] and Smith *et al.* [86] may account, in part, for this. Seven of the 47 (14.9%) schizophrenic patients given apomorphine became slightly to moderately depressed and three became slightly elated. We have already presented some evidence that the DA autoreceptors in some schizophrenics may be subsensitive to apomorphine, if apomorphine-induced sedation and sleep are indeed due to autoreceptor stimulation [70]. No clinical improvement was noted in chronic schizophrenics following prolonged treatment with bromocriptine [15]. Tamminga and Schaffer [96] also found no clinical improvement after chronic treatment with bromocriptine or CF 25-397, an ergot alkaloid which was reported to have dopamine agonist properties without having antiparkinsonian effects.

We have administered bromocriptine in doses of 0.5–6.0 mg/day in divided doses to 7 unmedicated chronic schizophrenic and 2 schizoaffective patients at the end of a 2–4 week placebo period during which psychotic and affective symptoms remained stable. Marked improvement in both psychotic and affective symptoms occurred in one schizoaffective depressed patient who received 0.25–0.50 mg/day for three weeks. Withdrawal and then reinstatement of bromocriptine led to relapse and restoration of improvement, suggesting this was a drug response. A much more modest improvement occurred in 1 schizoaffective manic and 3 chronic schizophrenic patients, most of whom had a very slight exacerbation of symptoms by the third week of treatment. Two chronic schizophrenic patients also worsened slightly and 2 showed no change. Clinical improvement was associated with side effects such as nausea and drowsiness but was unrelated to age or duration of illness. Serum prolactin levels decreased in some but not all subjects even at doses of 0.5 or 1.0 mg. Serum GH levels increased only at the 1.0 mg dose, 60–90 min after bromocriptine. There were no persistent increases in serum GH levels due to bromocriptine.

These results suggest systematic study of the antipsychotic action of low-dose bromocriptine in schizoaffective patients might prove worthwhile; low-dose bromocriptine appears unlikely to be clinically useful in chronic schizophrenia. Our results agree with those of Corsini *et al.* [31] who reported that apomorphine was most effective in schizoaffective manic patients but had little effect in chronic schizophrenia or on schizoaffective depressed patients. The mild relapse noted after subchronic bromocriptine administration in our study could have been due to the development of subsensitivity of DA autoreceptors leading to increased release of endogenous DA. However, Bannon *et al.* [11] have reported bromocriptine produced an irreversible blockade of DA autoreceptors in the rat striatum. Such a persistent action, if it occurred in man, might be expected to have a profound effect on both pre- and postsynaptic dopaminergic mechanisms, the results of which would vary from individual to individual.

Tamminga *et al.* [96] have recently studied N-n-propylnorapomorphine (NPA), a potent DA agonist, as a treatment of schizophrenia. Using an increasing dosage schedule in a placebo controlled double-blind study, NPA produced some improvement in BPRS scores in 5/9 subjects. Those who improved after NPA subsequently had a good response to neuroleptic drugs.

Tamminga *et al.* [95] have also reported that administration of apomorphine (3 mg SC) produced improvement in 9/18 neuroleptic-treated chronic schizophrenics. Furthermore, Cutler *et al.* [35] reported that a dose of 0.005 mg/kg apomorphine produced significant improvement in the BPRS in 2 of 5 chronic schizophrenic patients receiving a daily dose of the equivalent of chlorpromazine, 1.1 gm. Moreover, apomorphine decreased plasma homovanillic acid (HVA), the DA metabolite, which may have indicated that apomorphine inhibited DA release and subsequent metabolism, peripherally, centrally, or both. Cutler *et al.* [35] postulated that chronic neuroleptic administration may have induced DA autoreceptor sensitivity. In addition to the study of Small *et al.* [85] cited above, Corsini *et al.* [30,31] have reported that the sedative and antipsychotic effects of as much as a 10 mg dose of apomorphine was prevented either by chronic treatment with haloperidol or sulpiride. Hollister [56] was also unable to demonstrate any benefit from addition of apomorphine to neuroleptics for the treatment of schizophrenia. There is extensive evidence that the autoreceptor-stimulating properties of neuroleptics in laboratory animals are blocked by neuroleptics [39, 50, 78, 91]. There appears to be no development of tolerance to the ability of neuroleptics to block dopamine autoreceptors [50]. There is also some evidence that neuroleptics can produce variable decreases in the levels of DA agonists such as apomorphine in some regions of rat brain [111,114]. If this also occurred in man, it would interfere with the ability of apomorphine to produce autoreceptor stimulation in neuroleptic-treated patients. Further study seems indicated to verify the results of Tamminga *et al.* [95]. If they can be replicated, this would indicate the possibility of utilizing autoreceptor agonists as complementary therapy to neuroleptics, rather than as a substitute.

REDUCTION IN THE ABNORMAL MOVEMENTS IN TARDIVE DYSKINESIA

There have been a number of studies reporting that DA agonists can alleviate tardive symptoms. Thus, Carroll *et al.* [22] reported that apomorphine in doses of 2–6 mg SC caused a marked reduction in tardive movements within 10 min lasting for up to 60 min, after which they rapidly returned to full intensity. Improvement occurred following repeated injections every 2–6 hours over a 2–4 week period but after 5–7 days, the extent and duration of improvement began to diminish. Apomorphine was also able to prevent the severe dyskinesia which occurred after high-dosage L-DOPA treatment. Tarsy *et al.* [100] reported that apomorphine, 1.0–1.5 mg SC, produced striking improvement in two patients, worsening in one patient, and no change in seven patients. Placebo produced no significant change. Tolosa and Tolosa and Sparber [106–108] reported the same rate and extent of improvement following apomorphine as noted by the previously cited investigators.

Carroll *et al.* [22] also reported that L-DOPA in doses between 2 and 4 grams per day reduced the severity of tardive symptoms but higher doses worsened the movement disorder and exacerbated psychosis. Tarsy *et al.* [100] re-

ported that L-DOPA plus carbidopa produced improvement in tardive symptoms in lower doses, whereas higher doses produced no change or worsening. Chase and Shoulson [25] reported that piribedil at a maximum daily dose of 240–300 mg produced 40–60% improvement in tardive symptoms in three patients. This is a rather high dose for a presynaptic effect considering the findings of Post *et al.* [76] and Gerner *et al.* [49] for piribedil administration to manic patients. Chase and Shoulson [25] attribute this to possible dopamine receptor blocking effects of piribedil. Pharmacokinetic considerations might also account for relatively low blood levels despite the high dosages. Persistence of neuroleptics in these subjects could also account for diminished efficacy.

In a recent study, bromocriptine and the ergot CF 25-397 were used in low doses, 2.5 mg, to treat tardive Huntington's chorea and a small group of other movement disorders, including tardive dyskinesia, with a dystonic component [47]. Bromocriptine was more effective in Huntington's chorea than in the dyskinetic-dystonic syndromes. The reverse was true for CF 25-397, but it did not produce clinically significant changes.

We recently studied the ability of saline and apomorphine in doses of 1.5 and 5.0 mg intramuscularly, on a double-blind basis, to diminish severe truncal and limb dyskinesia of 11 months, duration in a 25 year-old schizophrenic male who was receiving thioridazine, 400 mg bid, which was essential to provide some control over psychotic symptoms and self destructive and aggressive behavior. Neither dose of apomorphine produced any significant effect on the dyskinesia or psychotic symptoms.

While the pathophysiology of tardive dyskinesia is far from clear, and like schizophrenia, is probably of diverse etiology [99], the efficacy of low doses of DA agonists, at least in some patients, does tend to support the concept of DA autoreceptors.

REDUCTION IN THE ABNORMAL MOVEMENTS IN HUNTINGTON'S DISEASE

Lal *et al.* [63] reported that apomorphine, 1 mg SC had no effect on the abnormal involuntary movements (AIM) of two patients with Huntington's disease. However, Tolosa and Sparber [108] reported that apomorphine in a dose of 1–3 mg SC produced slight to marked diminution of the AIM in four Huntington's patients as well as in a fifth patient with a similar but non-hereditary syndrome. Corsini *et al.* [30] confirmed these findings. They studied the effect of 1–4 mg apomorphine IM in four patients with Huntington's disease and found marked reduction of the AIM in all four patients studied whereas saline treatment produced no significant effect. The improvement produced by apomorphine was dose related, indicating that an autoreceptor effect can still be achieved even at dosages as high as 4 mg. No worsening of the choreic symptomatology was noted even at the highest dose tested. Whereas Tolosa and Sparber [108] noted drowsiness in their patients, Corsini *et al.* [30], who, as discussed above, had previously reported sedation and sleep in normal controls and many types of psychiatric patients given apomorphine, reported no sedation or sleep following apomorphine in any of the Huntington's patients. Corsini *et al.* [29] reported that the ability of apomorphine to reduce the AIM in their subjects was blocked by sulpiride and haloperidol but that sulpiride was more potent than haloperidol. Agnoli *et al.* [3] reported that acute treatment with apomorphine, 0.002 mg/kg SC, produced moderate improvement in eight patients with choreiform disorders, three of whom were diagnosed as having Huntington's disease. Chronic treatment with bromocriptine (7.5–15 mg per day) produced marked improvement in three of four patients studied. These results were replicated by Frattola *et al.* [47] using lower doses of bromocriptine.

There is also some evidence that L-DOPA and amantadine, which may enhance the release of dopamine, may not exacerbate and may even improve the AIM of some Huntington's disease patients [3, 80, 98]. In light of the evidence that the AIM in Huntington's disease are related to an increased dopaminergic activity in the striatum [23], both Tolosa and Sparber [108] and Corsini *et al.* [32] interpreted their findings with apomorphine as supportive of the concept of DA autoreceptors in man.

EFFECT OF APOMORPHINE IN TOURETTE'S SYNDROME

Tourette's syndrome is characterized by the childhood onset of abnormal movements of the head, trunk and limbs and involuntary vocalizations [83]. Increased dopaminergic activity is thought to play a role in this disorder because the symptoms tend to respond to haloperidol and AMPT treatment [87,94]. Drugs which increase dopaminergic activity such as L-DOPA [61], methylphenidate [52] and *d*-amphetamine [45] tend to exacerbate the disorder or are associated with its onset. Hence, one might expect DA agonists such as apomorphine to increase the severity of the movements or vocalizations in patients with Tourette's syndrome. However, Feinberg and Carroll [45] reported that apomorphine, in doses of 0.01–0.04 mg/kg produced a decrease in both types of symptoms lasting for 45 to 60 minutes. In one subject who received a variety of doses on a blind basis, the improvement in symptoms was dose-related. No nausea or vomiting was produced at these doses. Piribedil also at a dose of 60 mg four times a day also alleviated the tics and vocalizations in one patient. Stimulation of DA autoreceptors was one of the mechanisms suggested as the explanation for this phenomenon.

Since cerebrospinal fluid levels of homovanillic acid (HVA), the major metabolite of DA appear to be decreased in Tourette children, it has been proposed that the basis for the increased dopaminergic activity may be supersensitivity of postsynaptic DA receptors [19]. If so, then there is even reason to have expected apomorphine to exacerbate the symptoms in the Feinberg and Carroll [45] study unless the dose of apomorphine was so low that it did not stimulate even supersensitive DA receptors.

EFFECT OF LOW DOSE HALOPERIDOL AND PIRIBEDIL ON PARKINSONISM

It is well-established that Parkinson's disease and parkinsonian symptoms which result from neuroleptic treatment are the result of reduced dopaminergic activity in the striatum [57]. Thus, increased dopaminergic activity following high doses of L-DOPA, bromocriptine, lisuride or piribedil alleviates many of the disturbances of extrapyramidal function of the natural and drug-induced syndromes [24]. In an effort to utilize the presynaptic DA receptor agonist strategy to achieve an antipsychotic effect, Corsini *et al.* [30] administered piribedil (60 mg), haloperidol (3 mg) or a combination of the two drugs, in three divided doses daily, to 15 acutely psychotic schizophrenics. Two of the four patients treated with haloperidol alone developed mild EPS whereas none of the four patients treated with piribedil alone had any

EPS. However, all seven of the patients treated with a combination of the two drugs developed severe EPS, mainly akinetic and hypertonic in nature, within a few days of beginning treatment. Other side effects, such as sweating, hypersalivation, and dysphoria, were worse in the group given combined treatment. Treatment was discontinued within 7 days without any apparent change in mental status. These results were interpreted as the result of stimulation of DA autoreceptors by piribedil counteracting the increase in impulse flow of nigral dopamine neurons which usually follows blockade of DA receptors in the striatum [21].

DOPAMINE AGONIST EFFECTS IN SPASMODIC TORTICOLLIS

The etiology of spasmodic torticollis is not known with any degree of certainty, but there is some evidence suggesting that dopaminergic dysfunction in the basal ganglia may be involved. L-DOPA can induce torticollis in patients with Parkinson's disease [13] while haloperidol has been reported to partially alleviate the spasmodic torticollis [51]. Low doses of apomorphine have been reported to temporarily and partially alleviate some of the symptoms of spasmodic torticollis in a small number of patients in a placebo-controlled study [107]. This was attributed to inhibition of DA autoreceptors. However, bromocriptine in doses of 2.5–50 mg was found to be no different than placebo in another study [60]. This may suggest that apomorphine has greater specificity for DA autoreceptors than does bromocriptine. The very limited efficacy reported for apomorphine by Tolosa [107] suggests that stimulation of DA autoreceptors—if indeed that is the mechanism of low dose apomorphine in spasmodic torticollis—is not a promising strategy for the treatment of this condition, which is also relatively insensitive to blockade of postsynaptic DA receptors.

CONCLUSIONS

The clinical evidence in support of DA autoreceptors is, at this time, far from conclusive. Some of the findings which have been attributed to stimulation of DA autoreceptors are well-documented such as sleep and sedation, but the evidence that those effects are due to autoreceptor stimulation is weak. Furthermore, there is some intriguing evidence that these effects may be due to stimulation of DA receptors outside of the central nervous system [32]. The antimanic effects of DA agonists are somewhat better documented than the antischizophrenic effects, but, in both instances, only a small number of subjects have been studied and the clinical assessment procedures have not been ideal. There is need for further replications of the reports of Tamminga *et al.* [95] and Cutler *et al.* [35] that apomorphine has an antipsychotic effect in some neuroleptic-treated schizophrenic patients. The clinical evidence that low doses of DA agonists can influence the AIM of Huntington's chorea to Tourette's syndrome is based on studies from several laboratories and seems more certain than the antipsychotic action.

The known functions of the nigro-striatal dopaminergic neurons would suggest that the inhibitory effect of low doses of DA agonists in AIM disorders is due to stimulation of autoreceptors on these neurons, if it is due to stimulation of DA autoreceptors at all. The anti-psychotic effects of low doses of apomorphine could be due to stimulation of autoreceptors on the mesolimbic or cortical dopaminergic neurons. McCulloch *et al.* [68] have recently described marked stimulation of glucose metabolism of many areas of rat cortex by high doses of apomorphine. Whether low doses of apomorphine could have the opposite effects on cerebral energy metabolism of many cortical areas remains to be determined. Postmortem studies have recently focused attention on the cortex as the site of the antipsychotic action of neuroleptics [10].

Further human studies with drugs which are more specific for autoreceptors, both as agonists and antagonists, are to be eagerly awaited. They should provide needed information about the many intriguing questions which have emerged in this early phase of investigation. It seems likely that such drugs will prove valuable as tools to better understand the regulation of brain dopaminergic neurons. They may also be highly useful in the treatment of hyperarousal, sleep disturbance, psychoses of various etiologies, and AIM disorders.

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