Dopamine Agonists in Parkinson's Disease

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ABSTRACT: Dopamine agonists have yielded two important advances to our understanding of the basal ganglia — they have facilitated the subdivision of different classes of dopamine receptors, and they have established the fact that important dopaminergic effects can be achieved by activation of dopamine receptors in a manner that is unrelated to anoxal impulse traffic in dopaminergic neurons — a phenomenon similar in its diffuse, slow, characteristics to an endocrine effect.

The tangible clinical benefit of dopamine agonists has been evident in patients with prominent dyskinesia or wearing off reactions. It is possible that earlier use of agonists, in low doses combined with similarly low doses of levodopa, may improve the long term treatment of Parkinson's disease, but as yet there is no firm evidence.

In the future, we can expect to see agonists with more prolonged effects, deriving from the formation of active metabolites. We can also hope to gain further insight into the correlations between the various animal models of dopaminomimetic activity, and specific aspects of drug efficacy and toxicity in parkinsonian patients. Such information should allow the design of improved pharmacotherapy.

RÉSUMÉ: Les agonistes de la dopamine ont permi deux progrès importants dans notre compréhension des noyaux gris centraux: la sous division de différentes classes de récepteurs dopaminergiques; l'observation que des effets dopaminergiques importants peuvent être obtenus par l'activation des récepteurs dopaminergiques d'une façon non reliée au flot axonal dopaminergique — un phénomène semblable dans ses caractéristiques de lente diffusion à un effet endocrinien.

Les bénéfices cliniques tangibles des agonistes de la dopamine furent évidents chez les patients avec des dyskinésies importantes et des réactions de fin de dose. Il n'est pas impossible que l'emploi précoce simultané de petites doses d'agonistes et de Lévodopa puisse être bénéfique aux Parkinsoniens, mais ceci n'a encore été prouvé.

Dans l'avenir nous pouvons nous attendre à voir des agonistes à effet prolongé dérivant de la formation de métabolites actifs. Il nous faudra également mieux comprendre les divers modèles animaux d'activité dopaminergique, d'efficacité et de toxicité des médicaments.

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The Drugs

Although apomorphine and N-propylnoraporphine were the first dopamine agonists to be employed in the treatment of Parkinson's disease (Schwab et al., 1969; Cotzias et al., 1976), these drugs never achieved a sufficiently high therapeutic index for acceptance in anything other than a research context. Both drugs were demonstrated to possess efficacy, but both had such a high incidence of adverse effects that they were abandoned. Subsequently, a series of dopaminomimetic ergot derivatives were produced, and while some have fallen by the wayside, several have been shown to possess therapeutic properties with unwanted actions sufficiently mild for either acceptance into routine treatment, or continuing clinical study with a view to widespread application.

Bromocriptine is the prototype clinically useful dopamine agonist, and considerable experience has accrued since it was first employed to treat parkinsonism (Calne et al., 1974). It has become the reference compound, against which the newer agents are compared. Table 1 summarizes the dopaminomimetic drugs that are currently prescribed for parkinsonism, together with those undergoing study with a view to general release. Table 1 also shows the average daily dose of each drug that we have found appropriate for the treatment of Parkinson's disease.

The logical sequence of producing new molecules is pharmacological screening for dopamine agonism, followed by toxicity testing, and finally clinical experiment. This has not always proceeded smoothly for these compounds. Lergotrile came to clinical investigation with an impeccable record of laboratory studies to support its anticipated efficacy and safety, yet clinical experience revealed significant and unacceptable hepatotoxicity in over 50% of patients (Teychenne et al., 1979); a cautionary episode that reaffirms the importance of careful monitoring and surveillance in the clinic, that is probably more important than endless batteries of preclinical tests.

Theoretical justification for dopamine agonists

Since levodopa is a physiological aminoacid that is the normal precursor of dopamine, it is reasonable to ask the question "Why develop artificial dopamine agonists?" There are several reasons. First, it should be possible to stimulate a more selective population of receptors than can be achieved with levodopa, which has actions on serotonin and noradrenaline synapses; it might even be advantageous to activate a subpopulation of dopamine receptors, and thereby perhaps decrease some of the centrally induced adverse reactions of levodopa. Another potential benefit would emerge if dopamine agonists had a longer biological half life in the striatum, than levodopa. A further argument for the use of dopamine agonists stems from the reduction of dopa decarboxylase — the enzyme converting levodopa to dopamine — in the brain of parkinsonian patients. Since artificial dopamine

agonists are not dependent upon such an enzymic transformation, they can be assured of more certain action on dopamine receptors. Finally, there is theoretical concern that the metabolism of levodopa may generate an excess of free radicals, such as superoxide, which might accelerate the demise of dopaminergic neurons (Calne and Langston, 1983); artificial dopaminomimetics can not be saddled with this possible drawback.

The impact of dopamine agonists on theoretical issues

One of the most important consequences of the advent of dopamine agonists is their application to the problem of classifying dopamine receptors. Prior to the development of dopamino-mimetic ergot derivatives, the only dopamine receptor to be characterized was the recognition site linked to a dopamine sensitive adenylate cyclase demonstrable in homogenates of striatum (Kebabian and Greengard, 1971). Bromocriptine and lergotrile allowed the firm identification of another dopamine receptor that is not involved in activating the formation of cyclic AMP. The former receptor was classified as D1 type, and the latter as D2 type (Kebabian and Calne, 1979; Spano et al., 1978). Subsequently, there was much controversy, deriving largely from binding studies, that led to proposals of up to four categories of dopamine receptor (Seeman, 1980). However, the present consensus is that the classification of dopamine receptors into types D1 and D2 is acceptable, though each may exist in more than one conformation (Leff and Creese, 1983; Grigoriadis and Seeman, 1984). Following the subdivision of dopamine receptors into two types, the obvious questions that arise are: (1) do interactions occur between D1 and D2 receptors, and (2), which receptors are involved in the deficits of Parkinson's disease, the efficacy of treatment, and the side effects of therapy?

Work by Kebabian and Stoof (1981) indicates that interactions do occur, such that stimulation of D2 receptors decreases the response to activation of D1 receptors. A comparison of the pharmacological and therapeutic actions of dopamine agonists and antagonists (Table 1) indicates that the D2 receptor is of central importance in the alleviation of neurological deficits in Parkinson's disease, and excessive drive of the D2 system provokes psychiatric reactions very similar to schizophrenia. Another point of interest is that the ergot dopaminomimetics produce less dyskinesia than levodopa. However, it is not easy to draw simple conclusions from this finding in terms of D1 and D2 actions, because a similar profile of clinical activity is shared by drugs that are both agonists and antagonists of the D1 receptor (eg. pergolide and bromocriptine).

A final concept emerging from experience with artificial dopamine agonists is the very unusual nature of the nigrostriatal dopaminergic projection. Since all the D2 agonists are anti-parkinson agents, and several exert their pharmacological actions without any effect on the release of dopamine, we have an explicit conflict with traditional ideas of neuronal interaction. The therapeutic response to dopamine agonists implies that function can be altered irrespective of axonal impulse traffic; in a sense, the behaviour of the dopaminoceptive striatal neurons, that re-establish coherent patterns of motor activity when the parkinsonian brain is flooded with dopamine agonists, resemble an endocrine rather than a neurological system. The dopamine projection seems to have some "enabling" role, rather than a precisely wired spatial and temporal orientation to specific motor control.

Table 1: Profiles of activity and dose equivalents of dopamine agonists

Dopamine agonist	D1	D2	Oral dose equivalent (mg)
Bromocriptine	−	+	30
Mesulergine	−	+	20
Lisuride	−	+	2.5
Pergolide	+	+	2.5

− = receptor antagonist
+ = receptor agonist

The impact of dopamine agonists on practical issues

The cumulative experience of treating parkinsonian patients with dopamine agonists for a decade has led to general agreement that these drugs are efficaceous (Calne et al., 1978; Lieberman et al., 1984; Lang et al., 1983). However, like most potent therapeutic agents, they also have significant adverse effects, and there is still an absence of general agreement of how and when to use them. A critical factor in this controversy is the unresolved question of whether the cummulative exposure of parkinsonian patients to levodopa contributes to some of the late management problems such as fluctuations in response, increasing dyskinesia, dementia, or declining efficacy. The range of views on this topic have been expressed in this symposium by Meunter and Fahn. However, in spite of the wide areas of disagreement, there is some common ground between the proponents of early and late use of levodopa — it is generally agreed that the dose of levodopa should be kept at the minimal level compatible with adequate motor function.

This issue, of how to use levodopa, is crucial for establishing the background against which dopamine agonists are to be prescribed. Few would disagree with the contention that dopamine agonists are useful in managing parkinsonian patients who have prominent dyskinesia or wearing off reactions, common problems after several years of levodopa therapy; most neurologists would combine a slow increase of a dopamine agonist with a concomittant gradual reduction of levodopa intake to about 50% of its previous level. However, the controversies over the potential toxicity of levodopa raise the question of whether dopamine agonists should be given as an alternative, by themselves, for Parkinson's disease; a further option is the early use of dopamine agonists in low doses combined with a correspondingly small intake of levodopa.

Our limited experience with the treatment of Parkinson's disease with dopamine agonists without levodopa has not been encouraging; our findings are similar to but less extensive than those of Stern and Lees (1983). In contrast, we consider that small doses of dopamine agonists, in combination with low doses of levodopa (combined with carbidopa or benserazide) may be a worthwhile early approach to treatment. We are currently keeping the dose of levodopa low when we start treatment with this drug, and we add bromocriptine after 4-6 weeks, again in low dosage. This approach is in keeping with the hypothesis that minimizing the cumulative dose of levodopa will facilitate the long term treatment of patients; it will take at least five years to confirm or refute the value of this strategy.

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Before leaving the subject of practical management of patients with dopamine agonists, it is appropriate to comment on the extensive and sometimes conflicting literature on the dosage of bromocriptine. We have not found it possible to pursue the very low dosages advocated by Teychenne et al. (1982), because patients are unwilling to spend several weeks at a level of bromocriptine intake that does not induce any benefit. We have found that patients with mild or moderate Parkinson's disease usually benefit from a dose of 20-40 mg bromocriptine daily, in combination with 500-1000 mg of levodopa combined with carbidopa or benserazide. We have found that patients with substantial or severe Parkinson's disease generally require 40-80 mg of bromocriptine daily, combined with the same levodopa regimen mentioned above.

In discussions of the dosage of dopaminomimetic ergot derivaties it is appropriate to introduce a note of caution. All ergolines are extremely susceptible to extensive but individually variable first pass metabolism by the liver. Ergopeptines, such as bromocriptine, are also subject to widely disparate rates of gastrointestinal absorption. These factors mean that the same dose of dopaminomimetic ergot derivative can lead to a broad spectrum of plasma concentrations ranging tenfold, in different individuals.

New concepts with dopamine agonists

The quest for a long acting dopamine agonist for treating Parkinson's disease has not been particularly successful. Certainly, these drugs have more prolonged effects than levodopa, but the theoretical expectations for some, such as pergolide (Lemberger and Crabtree, 1979), have not been realized in a clinical setting. An approach to extending the action of agonists is the development of compounds that gradually undergo transformation to one or more metabolites that also possess dopaminomimetic properties. One of the newest agonists, mesulergine, is thought to generate at least one active metabolite (Fluckiger et al., 1983), so it will be of interest to see whether this drug can elicit a more sustained clinical response than previous agonists.

Another recent concept (Enz, 1981; Wachtel, 1983), is the suggestion that agonists may have an advantage if they possess certain additional antagonistic properties, leading to decreased adverse reactions. A specific example is transidhydrolisuride, a drug that has not yet been studied in Parkinson's disease. The development of drugs with mixed agonist-antagonist features in different tests of dopaminomimetic function will shed light in a crucial area of ignorance. At present, we have no good evidence to discuss the relative clinical relevance of turning in rodents with unilateral nigral lesions, stereotyped behaviour, increased locomotor activity, or suppression of prolactin. We do not know the importance of each of these responses to predicting various types of clinical efficacy (eg. improvement in akinesia, rigidity, tremor or posture), neither can we relate the pharmacological paradigms to particular adverse reactions to treatment (eg. dyskinesia, psychosis, or emesis). Transdihydrolisuride will be a particularly interesting drug to study in this context (Wachtel, 1983); its agonist features include induction of turning in rodents with unilateral nigral lesions and suppression of prolactin. Antagonistic properties of transdihydrolisuride comprise production of catalepsy, and inhibition of stereotyped behaviour, locomotor activity and hypothermia caused by apomorphine. It is not clear whether this mixed profile derives from differential activity at various dopamine receptors, partial agonism, or involvement at synapses that employ neurotransmitters other than dopamine. Whatever the mechanism, it is important to determine what this drug does in parkinsonian patients. As experience accummulates with a new range of drugs having disparate dopaminomimetic properties, we should be able to establish a library of information from which correlations will emerge between clinical effects and particular animal models of dopaminomimetic activity. From this knowledge, it will be possible to generate a more rational approach to the development of new therapy.

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