The Significance of Continuous Dopaminergic Stimulation in the Treatment of Parkinson's Disease.

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Summary

Levodopa continues to be the most effective agent for the symptomatic treatment of Parkinson's disease. No other drug matches its ability to suppress parkinsonian symptoms, especially in patients with advanced disease. But over time, initial benefits begin to wane, not so much because of a decline in efficacy against core symptoms, but rather because of a rise in adverse effects. Most common are the motor response complications that appear within a few years of treatment initiation and ultimately affect most parkinsonian patients. These progressively disabling complications include response fluctuations and abnormal involuntary movements.

Current evidence indicates that 'wearing-off' fluctuations, typically the first motor complication to become clinically evident, initially reflect the loss of buffering normally provided by striatal dopaminergic terminals. Thus, with increasing degeneration of the nigrostriatal system, swings in plasma levodopa concentrations associated with standard dosage regimens produce nonphysiological fluctuations in intrasynaptic dopamine. As a result of long term discontinuous stimulation, secondary changes occur at sites downstream from the dopamine system and now appear to underlie the progressive worsening of 'wearing-off' phenomena as well as the eventual appearance of other response complications.

Chronic intermittent stimulation of normally tonically active dopaminergic receptors activates specific signalling cascades in striatal dopaminoceptive medium spiny neurons, and this evidently results in long term potentiation of the synaptic efficacy of glutamate receptors of the *N*-methyl-D-aspartate (NMDA) subtype on these GABAergic efferents. As a consequence of their increasing sensitivity to excitation by cortical glutamatergic projections, it would, however, appear that medium spiny neuron function changes to favour the appearance of response fluctuations of the 'on-off' type and peak dose dyskinesias.

The inability of standard levodopa treatment to restore striatal dopaminergic function in a more physiological manner clearly contributes to the appearance of motor complications. Continuous dopaminergic replacement not only reverses these complications in parkinsonian patients but also prevents their development in animal models of Parkinson's disease. Thus, pharmaceutical approaches that provide relatively continuous dopamine receptor stimulation might confer both prophylactic and palliative benefit to parkinsonian patients. Several such strategies are currently under development, and include various methods to prolong the duration of action of levodopa as well as the use of transdermally administered or very long acting dopamine agonists.

Parkinson's disease is a central nervous system disorder characterised by the progressive degeneration of dopamine-containing neurons that have their cell bodies in the substantia nigra and their synaptic terminals in the corpus striatum. Once striatal dopaminergic transmission is sufficiently impaired, the disease manifests primarily with motor abnormalities, especially hypokinesia, rigidity, tremor and postural instability. Symptomatic treatment attempts to restore transmission at hypofunctional dopaminergic synapses. Currently, this goal can be approached by administering either levodopa, which requires decarboxylation to dopamine for activity, or a dopamine agonist, which can act directly to stimulate postsynaptic dopaminergic receptors.

Dopamine agonists have several theoretical advantages over levodopa for the treatment of Parkinson's disease (table I).[1] Since most nigrostriatal dopaminergic neurons are lost prior to symptom onset[2] and residual cells continue to degenerate, it would seem preferable to administer a direct acting drug rather than a prodrug, which depends, once converted to the active amine, on the declining number of dopaminergic neurons for vesicular storage and regulated release. Dopamine agonists have the additional advantage that they may be chosen to interact relatively selectively with one or more subtype of dopaminergic receptor and thus possibly achieve a higher therapeutic index than levodopa.

Stimulation of D_2 family receptors has generally been considered crucial for antiparkinsonian activity, and all agonists currently marketed for the treatment of Parkinson's disease fall into this category. However, some animal model studies suggest that D_1 family receptor stimulation may also be effective.[3,4] Definitive clinical evaluation of this possibility is dependent on the results of ongoing trials using relatively selective, fully effective D_1 agonists in patients with Parkinson's disease.

Table I. Potential advantages of a dopamine agonist over levodopa, for the treatment of Parkinson's disease

Act independently of the degenerating dopaminergic system
Improve therapeutic index by selectively interacting with certain dopamine receptor subtypes
Limit risk of exacerbating oxidative stress, by reducing free-radical production
Provide more continuous stimulation of postsynaptic dopaminergic receptors

Furthermore, dopamine agonists may avoid the risk of promoting free-radical induced damage due to increased dopamine metabolism.[5,6] Levodopa and dopamine can be broken down by enzymatic and nonenzymatic mechanisms to neurotoxic free-radicals. Conceivably, levodopa administration exacerbates the potentially deleterious consequences of accelerated dopamine turnover in residual dopaminergic neurons that accompanies nigrostriatal system degeneration. In contrast, dopamine agonists, at least in part because of their ability to stimulate presynaptic dopaminergic receptors, tend to retard this compensatory process.[1,7,8] Some agonists may, in addition, possess neuroprotective activity for reasons not yet fully understood.[9]

Finally, dopamine agonists with relatively long half-lives can provide relatively continuous stimulation to postsynaptic dopaminergic elements and thus, as described below, possibly diminish the danger of motor response complications.[10,11]

1. Striatal Dopaminergic Transmission

Under normal conditions, the nigrostriatal pathway is generally a tonically active system. Dopaminergic neurons that constitute this pathway generally fire at a rate of about 5Hz, except when interrupted by bursts of higher frequency activity associated with salient sensory stimuli but not with volitional movement.[12] Since intrasynaptic transmitter levels reflect nerve impulse activity rates, it would thus appear that dopaminergic regulation of motor function requires the maintenance of rather stable levels of dopamine in contact with its postsynaptic receptors. Relief of core parkinsonian symptoms clearly depends on the restoration of normal dopaminergic function. Accordingly, the goal of antiparkinsonian therapy should be to provide relatively constant stimulation to striatal dopaminergic receptors.

At early stages of disease, exogenous levodopa is taken up by residual dopaminergic neurons, where it is decarboxylated to dopamine and stored in vesicles for subsequent release onto its postsynaptic receptors. Under such circumstances, swings in levodopa concentrations resulting from its periodic administration are smoothed out by the vesicular storage and neuronally regulated release of the newly synthesised amine from residual dopaminergic terminals. Accordingly, striatal dopamine receptors continue to be exposed to the relatively constant transmitter levels found under physiological conditions.

However, in patients with advanced disease most dopamine terminals have degenerated.[2] Consequently, exogenous levodopa largely accumulates in other decarboxylase-containing cells, where it is converted to dopamine and leaked to the extracellular space without intervening storage or regulated release.[13] As a result, intrasynaptic dopamine levels do not remain constant, but begin to reflect the wide shifts in levodopa concentrations associated with the intermittent administration (usually every 2 to 6 hours) of this rapidly metabolised (half-life approximately 90 minutes) prodrug.[10,14,15] Thus, soon after levodopa ingestion, striatal dopamine levels rise quickly through the physiological range and probably well beyond[16] (fig. 1). This peak is followed by a rapid decline to subthreshold levels until the next dose is administered. Recent observations suggest that the chronic inability of standard levodopa regimens to provide more physiological dopaminergic stimulation contributes to the appearance of motor complications.

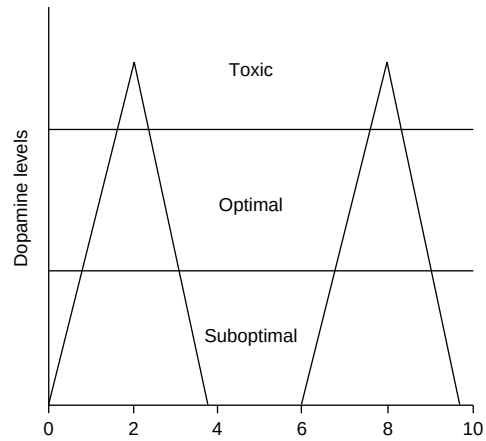

Fig. 1. Theoretical level of dopamine in the brain, 0 and 6 hours after levodopa administration.

2. Altered Responses to Dopaminergic Stimulation

Levodopa remains the mainstay for treating Parkinson's disease. This situation largely reflects its superior ability to alleviate symptoms, especially in patients with advanced disease.[17] But the initially favourable response enjoyed by most parkinsonian patients normally does not last.[17,18] Deterioration relates less to a decline in levodopa's antiparkinsonian efficacy, and more to an increase in adverse effects.

The most common, and often the most disabling, complications reflect a progressive alteration in motor response. Within 5 years of symptom onset, about half of levodopa-treated patients begin to experience one or more motor complication, including response variations, and various dystonic and choreatic dyskinesias.[19] Motor fluctuations of the 'wearing-off' type are usually the first to appear.[20,21] They occur in relation to dosage and reflect a shortening in the duration of levodopa's antiparkinsonian action (fig. 2). In addition, a more complex response fluctuation, usually termed 'on-off' phenomena, can often be distinguished in patients in a relatively advanced stage of the disease.[22] These are characterised by abrupt, seemingly random switches between the relatively treated (hyperkinetic) and untreated (hypokinetic) states. They appear to arise as a result of the increasing steepness of the relation between levodopa dose and motor response that attends disease progression (fig. 2). Under such circumstances, small changes in striatal dopamine levels produce large shifts in motor responses.

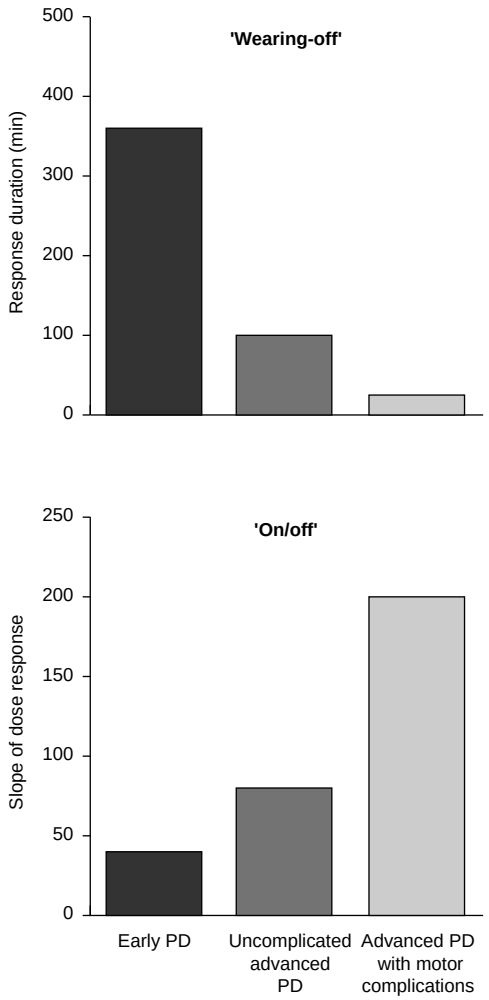

Fig. 2. Severity of motor fluctuation at different stages of Parkinson's disease (PD).

Late stage parkinsonian patients also commonly manifest abnormal involuntary movements, especially when brain dopamine levels peak. These choreiform dyskinesias reflect the fact that the levodopa dose able to induce dyskinesias progressively declines, while the dose needed to ameliorate parkinsonian symptoms remains constant (fig. 3). Thus, with advancing disease the difference between these amounts (i.e. the therapeutic window) essentially vanishes, and no dose of levodopa can be found that adequately controls symptoms without also inducing dyskinesias. All these motor complications tend to worsen with continued disease progression and dopaminomimetic therapy.[10]

3. Pathogenesis of Motor Complications

Recent studies have begun to provide insight into mechanisms underlying the appearance of motor complications. Fluctuations of the 'wearing-off' type initially reflect the swings in intrasynaptic dopamine produced by levodopa administration. As might be expected, if patients manifesting early 'wearing-off' fluctuations when levodopa is given according to standard intermittent schedules are switched to constant infusion therapy, these fluctuations immediately disappear.[23] However, 'wearing-off' fluctuations progressively worsen, and 'on-off' fluctuations as well as peak dose dyskinesias appear as a consequence of secondary changes postsynaptic to the dopamine system. Under such circumstances, conversion from intermittent to continuous levodopa treatment has a gradual rather than an immediate ameliorative effect.[15]

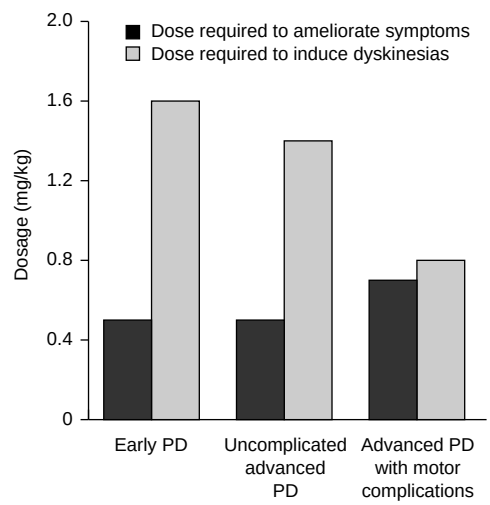

Fig. 3. Difference between the clinically effective dose of levodopa and the dose causing dyskinesias (i.e. the therapeutic window) at different stages of Parkinson's disease (PD).

Dopamine agonist studies in animals and humans have provided the most direct evidence implicating postsynaptic changes. Rats rendered parkinsonian with 6-hydroxydopamine and then given levodopa by twice-daily injection soon begin to show response alterations resembling human 'wearing-off' and 'on-off' fluctuations.[24,25] Thus with intermittent, but not continuous levodopa administration, both a progressive shortening in response duration and an increasing frequency of 'off' responses to an otherwise effective dose of levodopa occur. In these parkinsonian rats as well as in parkinsonian patients, an acute challenge dose of a direct dopamine agonist such as apomorphine replicates all the response changes occurring with levodopa. Since the motor effects of apomorphine, unlike levodopa, reflect only its interaction with postsynaptic dopaminergic receptors, changes underlying motor response complications must be occurring downstream from the dopamine system.[26]

4. Striatal Mechanisms

Studies to determine possible sites of these changes have focused on the population of striatal GABAergic neurons that receive dopaminergic projections from the substantia nigra. An initial evaluation of neuropeptides used by these medium spiny neurons revealed characteristic alterations, presumably indicative of functional change.[27,28]

Striatal GABAergic neurons that largely express the D_2 dopamine receptor subtype primarily project to the internal segment of globus pallidus via the external globus pallidus and subthalamic nucleus; they utilise enkephalin and neurotensin as peptide cotransmitters.[29] On the other hand, striatal GABAergic neurons that mainly express D_1 dopamine receptors largely project directly to the internal globus pallidus and contain dynorphin, neurotensin and substance P. Lesioning the dopamine system with 6-hydroxydopamine significantly increases enkephalin and neurotensin levels. Subsequent intermittent levodopa treatment produces additional changes, most conspicuously a substantial rise in both dynorphin and neurotensin.[28]

Pharmacological studies suggest that these peptide alterations, which do not occur with continuously administered levodopa, reflect functional modifications that could have important implications for motor performance.[30] This view is further supported by the finding that parkinsonian rats evidencing motor response alterations have a profoundly decreased reaction to agonists that preferentially stimulate D_1 dopamine receptors and a markedly increased response to selective D_2 agonists.[31] Thus, dopaminergic responsivity of the direct striatonigral pathway is attenuated, while responsivity of the indirect striatopallidal pathway is augmented, possibly indicating that an imbalance between striatal output pathways influenced by D_1 and by D_2 dopamine receptor stimulation might contribute to the pathogenesis of motor complications. Importantly, changes in both peptide levels and motor responses were evident only when levodopa treatment was given intermittently (as occurs in parkinsonian patients) and did not occur when the same daily dose of levodopa was infused around-the-clock.

5. Glutamatergic Response Changes

Both laboratory and clinical studies have begun to elucidate changes occurring in striatal GABAergic neurons that accompany the response modifications associated with long term dopaminomimetic treatment.[32] In parkinsonian rats, chronic intermittent stimulation of dopaminergic receptors on GABAergic medium spiny neurons modifies responses mediated by co-expressed glutamate receptors of the *N*-methyl-D-aspartate (NMDA) subtype.[33,34] Thus, systemically administered drugs that selectively inhibit NMDA receptors act prophylactically as well as palliatively to prevent or reverse all motor response alterations occurring in this rodent model.[25,33,34] Direct injection studies suggest that these effects of systemically administered NMDA antagonists are primarily mediated in the striatum,[34] presumably at the dendrites of GABAergic neurons expressing dopamine as well as NMDA receptors.[35]

In MPTP-lesioned parkinsonian primates, co-treatment with certain NMDA antagonists has also been found to reduce the dyskinesiogenic but not the antiparkinsonian effects of levodopa.[36] Furthermore, observations in parkinsonian patients treated with various NMDA receptor antagonists support the view that glutamatergic hyperstimulation of striatal GABAergic neurons may be a factor contributing to the appearance of motor complications in human Parkinson's disease.[37,38]

6. Signal Transduction Alterations

Recent investigations have attempted to discern the basis for the apparently excessive glutamatergic influence on striatal GABAergic neurons. Preliminary evidence from one such study suggests that the binding affinity of striatal NMDA receptors increases rather than decreases in parkinsonian rats that develop levodopa-induced response modifications. These results seem more compatible with the hypothesis that upregulation of NMDA receptor sensitivity, not hyperfunction of cortical glutamatergic afferents, explains the beneficial effects of NMDA antagonists on motor complications.

Components of signal transduction pathways that might explain how intermittent stimulation of dopaminergic receptors enhances the synaptic efficacy of co-expressed NMDA receptors have recently begun to be identified.[39,40] Current evidence suggests that a cyclic adenosine monophosphate (cAMP)-protein kinase A-mediated pathway contributes to D_1 receptor associated activation of NMDA receptors, while a calcium-calmodulin-dependent kinase II pathway participates in the signalling cascade linked to D_2 receptors. Conceivably, activation of these signal transduction cascades, as a consequence of chronic nonphysiological dopaminergic stimulation, results in changes in NMDA receptor subunit composition and phosphorylation state leading to long term potentiation of their synaptic efficacy. As a result, striatal GABAergic efferent system function changes to favour the appearance of motor response complications.

7. Clinical Relevance

Levodopa-associated motor response changes can be reliably induced by intermittent, but not by continuous, dopaminergic stimulation in rodent and primate models of Parkinson's disease. Clinical observations suggest that the same may be true for parkinsonian patients, although data from definitive evaluations of the prophylactic value of relatively continuous dopaminomimetic administration are not yet available.

Attempts to assess the palliative benefit of converting parkinsonian patients who developed motor complications while receiving a standard (usually 3 to 6 times daily) levodopa regimen to a continuous levodopa infusion have, however, been carried out (fig. 4). Ten days of round-the-clock, optimal-dose, intravenous administration tends to reduce all motor complications.[15] A continuous infusion of a dopamine agonist lasting 3 months has even more dramatic beneficial effects on pre-existing motor complications.[41] Taken together, these studies indicate that motor fluctuations and peak dose dyskinesias complicating dopaminomimetic therapy of Parkinson's disease are attributable, at least in part, to the intermittent administration of levodopa and can be partially reversed by treatments that provide more physiological (i.e. uninterrupted, optimal level) dopamine replacement.

Conceivably, the continuous stimulation of striatal dopaminergic receptors from the outset of dopaminomimetic treatment will confer prophylactic benefit by limiting changes that occur in striatal GABAergic neurons as a consequence of chronic intermittent stimulation.

8. Future Therapeutic Goals

The foregoing observations suggest that the intermittent stimulation of striatal dopaminergic receptors may play a role in the pathogenesis of the most common forms of levodopa-associated motor response complications. In parkinsonian animals, the response alterations associated with standard levodopa regimens can be prevented by approaches

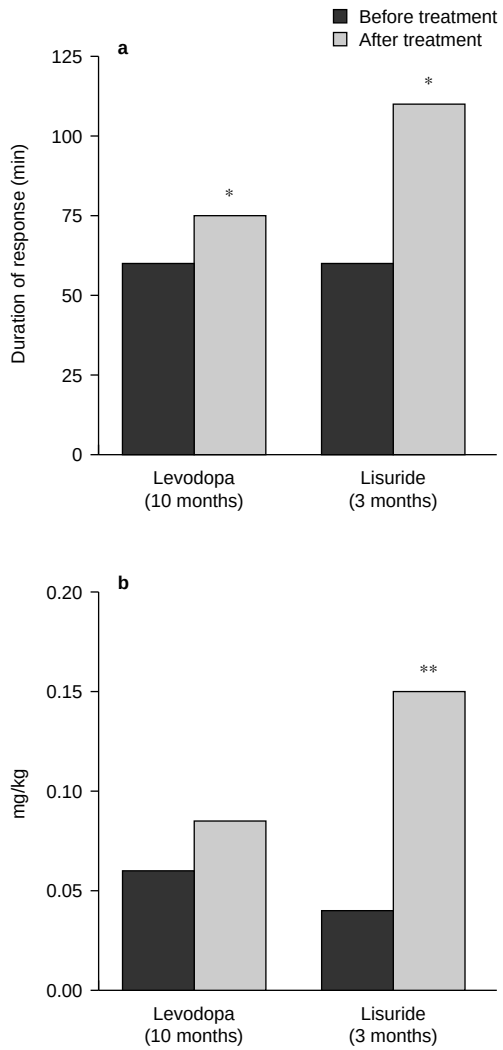

Fig. 4. Effect of continuous dopamine treatment on (**a**) the anti-parkinsonian response duration and (**b**) the therapeutic window for levodopa. * p = 0.05; ** p < 0.01 *vs* before treatment.

that provide continuous dopaminergic stimulation.[27] In patients with advanced Parkinson's disease, continuous levodopa administration has documented palliative value and thus might be expected to confer prophylactic benefit at earlier stages of disease.[10,15]

Translation of these theoretical concepts and experimental results to clinical practice are now beginning to show promise (table II). The palliation or prevention of motor response complications could, in theory, involve targeting relevant internal signalling pathways or cell-surface receptors. Although pharmaceuticals that selectively interact with components of transduction cascades in striatal GABAergic neurons are not yet available for clinical study, preliminary trials of NMDA receptor antagonists have recently begun to yield encouraging results.[37,38]

At present, however, most developmental efforts remain directed towards new approaches to more continuously stimulate striatal dopaminergic receptors. Chronic enteral or parenteral infusions of levodopa, its more soluble analogues, or of dopamine agonists have not proven generally useful. On the other hand, pharmaceutical approaches to prolonging levodopa's duration of action, such as with controlled release formulations (e.g. Sinemet-CR) or by the addition of a catechol-*O*-methyltransferase (COMT) inhibitor (e.g. tolcapone or entacapone) can be expected to confer some benefit.[42,43]

Most orally administered dopamine agonists now marketed for Parkinson's disease also have relatively short durations of action (plasma half-lives ranging from about 4 to 12 hours); accordingly, while better than levodopa, they still fall short of providing continuous stimulation. Dopamine agonists with a much longer duration of action (e.g. cabergoline) or sufficient lipid solubility to permit transcutaneous administration (e.g. N-0923) currently have the clearest potential for restoring normal dopaminergic function in parkinsonian patients.[44-46]

Table II. Strategies for continuous dopaminergic replacement

Continuous infusions of levodopa (intravenous/subcutaneous/enteral)
Oral sustained release formulations of levodopa
Dopamine metabolism inhibitors, e.g. monoamine oxidase inhibitors (selegiline) or catechol-*O*-methyltransferase (COMT) inhibitors (tolcapone, entacapone)
Long-acting dopamine agonists (e.g. cabergoline)

9. Conclusions

The principal symptoms of Parkinson's disease reflect deficient striatal dopaminergic transmission. In the later stages of disease, standard levodopa therapy only transiently replaces physiological intrasynaptic dopamine levels. Accordingly, normal dopaminergic transmission is not restored and motor response complications eventually ensue. Several promising approaches to the prevention or mitigation of these disabling adverse effects are under development. Determination of whether any of these strategies is capable of conferring significant patient benefit awaits completion of ongoing clinical studies.

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