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Dopamine receptor agonists in the treatment of advanced Parkinson's disease

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ABSTRACT

The symptoms of Parkinson's disease (PD) can become increasingly difficult to control as the disease advances. L-Dopa is the most efficacious therapy; however, with long-term therapy, motor and non-motor complications develop.

There is now accumulating evidence that the progressive pathology of PD, the change in drug pharmacodynamics, and the pulsatile manner in which short-acting dopaminergic agents stimulate striatal dopamine receptors combine as key contributing factors to the priming of the basal ganglia for induction of motor complications. Dopamine receptor agonists have been extensively used as add-on therapy to L-dopa to treat motor complications. In this article we review the role of dopamine receptor agonists in the treatment of advanced parkinsonian patients.

1. Introduction

After 40 years of clinical use, L-dopa therapy still offers the best symptomatic control of Parkinson's disease (PD), and virtually all patients will require it during the course of their disease [1,2,2–5]. However, with each year of L-dopa treatment, about 10% of patients will develop L-dopa-associated motor complications [6,7]. These include motor fluctuations and different types of dyskinesia [8–10]. In many patients, "off" periods (motor difficulty) are associated with pain, panic attacks, severe depression, confusion, and a sense of death, which makes this clinical status even more distressing for patients and their caregivers. Sometimes these non-motor symptoms can appear without a clear worsening of motor performance (non-motor "off") [11].

Different drugs and therapeutic strategies have been tested in the course of the last 30 years to improve motor complications. Dopamine receptor agonists have played a prominent role in this scenario and remain a very effective treatment in combination with L-dopa to improve motor and non-motor fluctuations. Moreover, because of their pharmacokinetic characteristics, dopamine receptor agonists can provide a more continuous dopaminergic stimulation [12].

2. The concept of continuous dopaminergic stimulation

Substantia nigra pars compacta (SNc) dopaminergic neurons normally fire tonically at a rate of 3–6 Hz independent of movement, although phasic firing activity or bursting can be seen in association with reward or novel stimuli [13,14]. This, in turn, is associated with relatively constant striatal dopamine levels as demonstrated by both microdialysis and amperometry [15,16].

The situation changes in the dopamine denervated state. Here, the loss of nigral neurons impairs dopaminergic modulation of corticostriatal activity [17], resulting in plastic changes and an impaired capacity to form long-term potentiation and long-term depression [17–19]. While surviving dopaminergic cells show little change in firing rate, autoregulatory mechanisms are impaired and there is a loss of stability associated with non-renewal. This implies that small fluctuations in firing rate are not compensated for, leading to less stable dopaminergic nigrostriatal activity [20]. Further, dendritic spines on striatal neurons, which are the sites of glutamate–dopamine interactions, are reduced in density and size in the denervated striatum [21,22]. As a consequence of these changes, there is a loss of the somatotopic selectivity of neuronal firing and reduced inhibitory centre-surround in response to peripheral stimuli in both the striatum and globus pallidus internus (GPi) [23,24]. These changes fundamentally impair basal ganglia function and its capacity to appropriately select and facilitate normal movement.

Standard replacement of L-dopa does not restore basal ganglia physiology to normal. The exogenous administration of repeated doses of a short-acting formulation of L-dopa (half-life of about 60–90 minutes) results in large and uncontrolled oscillations in striatal dopamine levels [25]. These oscillations increase with disease progression [26] due to the progressive loss of striatal dopamine terminals and their capacity to buffer fluctuations in plasma L-dopa levels. This leads to a change from the normal situation in which dopamine receptors are continuously exposed to dopamine, to one in which they are exposed to alternating high

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and low concentrations of dopamine. This discontinuous activation of dopamine receptors is referred to as pulsatile stimulation, and further destabilizes a denervated and already unstable basal ganglia network.

2.1. Evidence that pulsatile stimulation contributes to the development of motor complications

Both the degree of dopamine denervation and the half-life of the dopaminergic agent employed contribute to the likelihood that pulsatile stimulation of dopamine receptors will occur. In early PD patients who have an estimated 40–60% loss of SNc dopamine neurons, dyskinesias typically develop after months or years of L-dopa treatment, whereas patients initiated on treatment with more severe dopaminergic lesions develop dyskinesias within weeks of starting L-dopa [27].

The half-life of the dopaminergic agent employed is also a critical factor in the development of dyskinesia. In 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned monkeys, short-acting dopaminergic agents such as L-dopa and some dopamine receptor agonists (e.g. PHNO, apomorphine), rapidly induce severe dyskinesias. In contrast, long-acting dopaminergic agents (e.g. ropinirole, bromocriptine), matched to provide comparable motor benefit to L-dopa-treated animals, result in a markedly reduced frequency and severity of dyskinesias [28–30]. Indeed, treatment with intermittent injections of a short-acting dopamine receptor agonist, such as U-91356A or apomorphine, induces dyskinesia, whereas continuous infusion of the same agent does not [31,32]. Dyskinesia induced by pulsatile stimulation is also associated with a series of gene and protein changes in striatal neurons. Studies in dopamine denervated rats and monkeys demonstrate altered regulation of preproenkephalin, cFos, delta FosB, JunB, preprodynorphin, [S]GTP gammas, Cdk5 (cyclin-dependent protein kinase 5), and DARPP32 [33–36]. Interestingly, these gene changes do not occur with long-acting or continuous administration of dopaminergic agents where animals do not develop dyskinesia. Similar changes have been demonstrated in post-mortem PD brains where preproenkephalin expression is significantly increased in L-dopa-treated PD patients with dyskinesia compared with L-dopa-treated PD patients who do not have dyskinesia and normal controls [37]. The pattern of neuronal firing in basal ganglia output neurons is also influenced by pulsatile administration of a dopaminergic agent. Changes in the number and duration of pauses as well as in firing frequency have been observed with pulsatile dopaminergic stimulation in subthalamic nucleus and GPi neurons of MPTP monkeys as well as PD patients [38,39]. Similar evidence supports the concept that motor fluctuations and "wearing off" are related to pulsatile stimulation. In 6-hydroxydopamine-lesioned rats, chronic intermittent or pulsatile L-dopa therapy is associated with a progressive reduction in the duration of the motor response that can be avoided by administering L-dopa in a continuous manner [40,41]. In this model, pulsatile L-dopa treatment and shortening of the motor response duration were also associated with altered expression of striatal preprodynorphin and pro-Met-enkephalin, whereas these changes did not occur with continuous L-dopa administration and therefore a more continuous dopaminergic stimulation [42].

These examples illustrate that nonphysiological, pulsatile or discontinuous replacement of dopamine to the denervated striatum induces further disruptions of basal ganglia activity leading to the development of motor complications [12].

These experimental observations have been extended to the clinic. Several prospective double-blind controlled trials support continuous dopaminergic stimulation-based treatment approaches in early untreated PD patients. Each has demonstrated that patients randomized to initiate therapy with a long-acting dopamine receptor agonist have a reduced risk of developing motor complications in comparison to patients randomized to initiate therapy with a short-acting formulation of L-dopa [43–46]. Indeed, very few patients, if any, treated exclusively with a dopamine receptor agonist experience dyskinesia.

Long-lasting and dramatic reductions in motor complications have also been observed in advanced PD patients, where treatment with continuous infusion of L-dopa or a dopamine receptor agonist (apomorphine, lisuride) is associated with reduced "off" periods and dyskinesias [47]. For example, patients randomized to receive a continuous subcutaneous infusion of lisuride have marked reductions in both "off" periods and dyskinesias in comparison to those randomized to treatment with standard oral formulations of L-dopa [48].

3. Dopamine receptor agonists

Since the introduction of bromocriptine in the early 1980s, several dopamine receptor agonists have become available for the treatment of PD. Dopamine receptor agonists are frequently employed in the management of early PD based on their having a relatively low potential to induce dyskinesia [43–46], but were initially developed as an adjunct to L-dopa for more advanced patients. The addition of a dopamine receptor agonist such as pergolide, ropinirole, pramipexole or cabergoline to L-dopa in patients with motor complications can reduce "off" time by about 1.1–1.5 hours per day [49–52]. These benefits can be obtained in conjunction with a reduction of dyskinesia, probably by allowing a reduction of about a 30% in L-dopa dose.

Talati et al. [53] performed a meta-analysis of randomized placebo-controlled trials evaluating the use of dopamine receptor agonist or placebo added to pre-existing L-dopa therapy for the treatment of advanced PD. They included a total of 15 trials (N = 4,380). Adjunctive dopamine receptor agonist use resulted in greater improvement as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) for activities of daily living (weighted mean difference [WMD] –2.20, 95% confidence interval [CI] –2.64 to –1.76; $p < 0.0001$) and motor score reduction (WMD –5.56, 95% CI –6.82 to –4.31; $p < 0.0001$), as well as reduction of "off" time measured in hours/day (WMD –1.20, 95% CI –1.78 to –0.62; $p < 0.0001$) and reduction of L-dopa dose (WMD –128.5 mg, 95% CI –175.0 to –82.1; $p < 0.0001$) versus placebo. Incidence of dyskinesia (odds ratio [OR] 3.27, 95% CI 2.65 to 4.03; $p < 0.0001$) and hallucinations (OR 3.34, 95% CI 2.44 to 4.58; $p < 0.0001$) were higher with dopamine receptor agonists. Non-ergot dopamine receptor agonists were qualitatively better, although both ergot and non-ergot dopamine receptor agonists showed significant improvements in all UPDRS scores. The authors concluded that adjunctive dopamine receptor agonist use with L-dopa is superior to L-dopa alone at reducing PD symptoms in patients not controlled with monotherapy.

Some physicians have advocated the simultaneous use of two different dopamine receptor agonists, and the addition of cabergoline to pramipexole or ropinirole has been reported to reduce "off" time [54], but it has not been established that it would have been impossible to achieve these benefits with further manipulation of a single dopamine receptor agonist.

4. Innovative dopamine receptor agonists

Continuous delivery of dopamine receptor agonists is now available by way of a 24-hour prolonged-release (PR) formulation of ropinirole and a transdermal formulation of rotigotine. Double-blind placebo-controlled trials in PD patients with motor complications have demonstrated significantly decreased "off" time