An Approach to the Continuous Dopaminergic Stimulation in Parkinson's Disease

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ABSTRACT: Dopaminergic neurons in the basal ganglia normally fire in a continuous manner, maintaining the striatal dopamine concentration at a relatively constant level. In Parkinson's disease, dopaminergic treatment produces a discontinuous stimulation, inducing an intermittent pulsatile activation of the striatal receptors. It is likely that the oscillations in the dopamine level in the striatum contribute to the development of motor complications. Treatment with long-acting dopaminergic agents, or providing a more continuous dopaminergic effect in the striatum, has been associated with fewer clinical motor complications. This review describes the state-of-the-art approach to achieve the desired continuous dopaminergic stimulation, providing patients with the best clinical effect and probably minimal motor complications.

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L-dopa is the most effective treatment of Parkinson's disease. However, this treatment is associated with side effects, mainly in chronic patients after prolonged treatment. More than 50% of patients were found to develop motor complications 5 years after continuous L-dopa treatment [1]. The motor complications mainly comprise "wearing-off" phenomena, dyskinesias and "on-off" phenomena. The reason for these complications is still unclear. The pathophysiological changes in the dopamine pathways in the basal ganglia, probably due to extracellular L-dopa, could be the key to this process. These include the loss of presynaptic dopamine neurons, changes in the response of postsynaptic receptors, and changes in the pharmacokinetic and pharmacodynamic metabolism of extracellular L-dopa. Moreover, changes in the buffering function of the dopamine receptors could be among the factors responsible for the motor fluctuations. Finally, other non-dopaminergic pathways are also involved in the pathogenesis of the motor side effects.

Fahn et al. showed in the ELLDOPA study [2] that motor complications are related to the L-dopa dose and appear relatively early after treatment with L-dopa. To explain the pathophysiological changes we refer to the dopamine pathways in the basal ganglia. There are two different pathways in the basal ganglia-thalamus-cortex circuit: direct and indirect. The interactions between these two pathways induce an inhibitory or excitatory effect on the different structures implied in the circuit.

In normal activity, the dopaminergic neurons in the substantia nigra pars compacta modulate the glutamate inputs in the striatum (via medium spiny neurons), activate the D1 and D2 receptors and, respectively, the direct and indirect pathways. Activation of these pathways in normal subjects produces an inhibitory (direct pathway) or excitatory effect (indirect pathway) on the globus pallidum pars interna and the substantia nigra pars reticularis [Figure 1]. In Parkinson's disease, this activation is disrupted by the dopaminergic cell loss, resulting in increased excitation on the GPi/SNr circuit and excessive inhibition of the thalamic projection with a con-

Gpi = globus pallidum pars interna
SNr = substantia nigra pars reticularis

Figure 1. Normal projections to/from basal ganglia

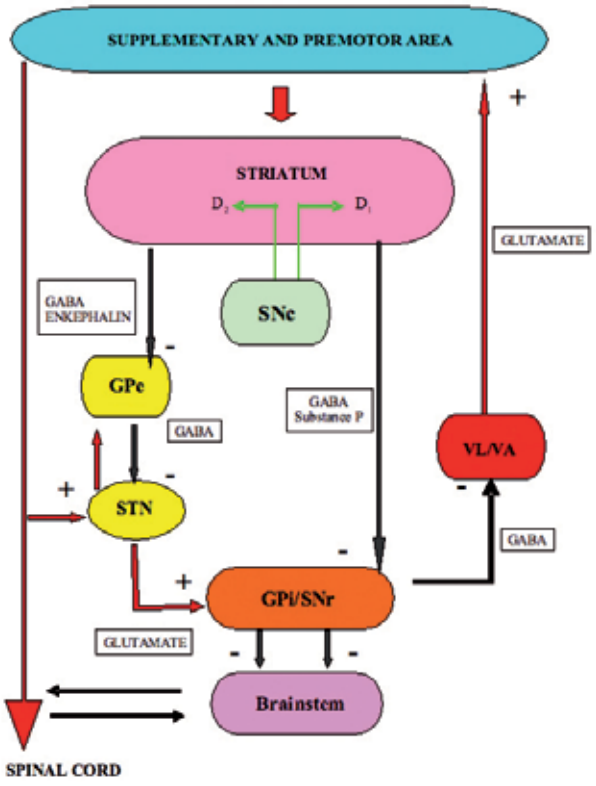
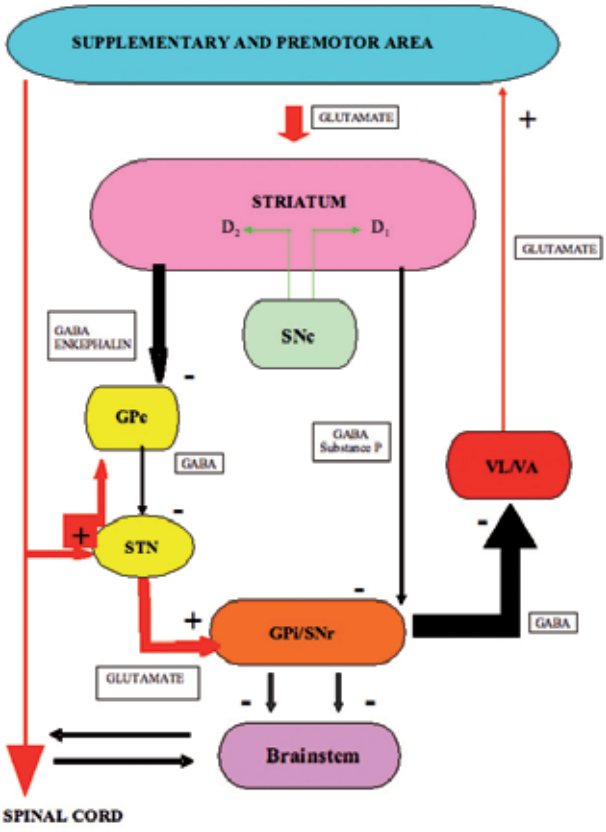


Figure 2. Projections to/from basal ganglia in Parkinson's disease



secutive inhibition of the cortical centers [Figure 2]. The result is abnormal firing of the neurons, producing the motor clinical signs of Parkinson's disease.

Under normal conditions the dopaminergic neurons in the substantia nigra pars compacta fire continuously and the dopamine concentrations in the striatum are maintained at a relatively constant level [3]. The firing is elicited in two ways: tonic and phasic. Tonic stimulation consists of a continuous low frequency release of dopamine, whereas in phasic stimulation there is a high frequency burst (in planning a movement). Normally the dopamine neurons fire in the tonic mode at a rate of about three to four cycles per second. The reason for this difference in stimulation (tonic or phasic) is to provide, constantly, the necessary concentration of dopamine according to the motor activity of the individual.

Continuous dopaminergic stimulation, a novel treatment in Parkinson's disease, prevents pulsatile stimulation in the striatum and probably also motor complications

Neurophysiological studies in Parkinson's disease have demonstrated differences in how the neurons fire: there is an increased firing rate of the subthalamic nucleus, GPi and SNr cells, with changes in the pattern of activity and synchronization in the GPe and GPI, whereas in L-dopa-treated patients the firing rate is lower than in normal subjects [4]. On the other hand, in PD patients with dyskinesia, there is decreased firing in GPi and SNr. Most probably other interconnections in the basal ganglia system as well as alterations in additional neurotransmitter pathways (such as glutamate, adenosine and acetylcholine) are implied in the pathophysiology of dyskinesia. [5].

In the early stage of PD, there are compensatory mechanisms to counteract the reduction of dopamine (such as increased activity of the remaining dopamine neurons, changes in the response of the postsynaptic receptors, and/or increased firing rates in the dopamine neurons). This buffered capacity in the dopaminergic terminals in the striatum fails later on to modify the dopamine decrease.

One of the important consequences of this buffered failure in treated patients is the fluctuations of the L-dopa concentration in the striatum. Probably oscillations in the dopamine level in the striatum after long-term treatment contribute to the dysfunction of the dopamine pathways in PD patients, leading to the motor fluctuations.

Dyskinesia is a motor side effect of dopaminergic treatment. It does not occur in untreated PD patients. As mentioned above, this undesirable side effect appears months after treatment with L-dopa or dopaminergic agents.

In normal subjects and animals receiving L-dopa, the buffered capacity of the dopaminergic terminals in the striatum prevents abnormal activity of the dopaminergic receptors as well as fluctuations of the dopamine levels in the synapsis. Only after extremely high doses of L-dopa does this buffering capacity not function appropriately, presumably because of pulsatile stimulation of the dopamine receptors, which induce dyskinesia [6].

The risk of motor fluctuations developing in PD patients is related to two principal factors: the clinical state of the disease, and the treatment.

- **Clinical state:** Motor fluctuation occurs more frequently in patients with advanced Parkinson's disease, probably because the buffering capacity of the dopaminergic terminals in the striatum of these patients is not effective. Activation of the postsynaptic dopamine receptors depends on the L-dopa concentration in the synapsis or other dopaminergic agents given to the patient. PD patients with severe clinical symptoms (reflecting the marked reduction of dopamine neurons in the nigro-striatal system) could develop dyskinesia after a relatively short time (days or weeks) of exposure to L-dopa, in contrast to patients at an early stage of the disease who develop dyskinesia after months of treatment.

PD = Parkinson's disease

- **Treatment:** A large proportion of PD patients treated with L-dopa agents develop motor complications. The same clinical effect can occur with intermittent doses of short-acting dopamine agonists such as apomorphine. In contrast, the use of long-acting dopamine agonists in long term-treated PD patients reduces the risk of dyskinesia developing [7]

The reason for these different responses to the dopamine agents remains unclear. It might be related to the pharmacodynamic physiological effect of the dopamine on the dopaminergic receptors in the striatum, and also to the changes in the firing of the dopaminergic neurons. In Parkinson's disease, when the level of dopamine is markedly reduced, the response of the denervated dopamine receptors in the striatum changes according to the exogenous treatment – tonically or phasically.

When a patient receives L-dopa or short-acting dopamine agonists, the receptor is intermittently stimulated (pulsatile stimulation), rapidly reaching a maximum concentration and quickly declining under threshold concentrations. The effect on the postsynaptic receptor is sharp oscillations in dopamine concentrations. In the early stages of Parkinson's disease the buffering functions are preserved and could prevent the marked changes in dopamine concentrations in the synapsis. In advanced stages these buffering capacities are not capable of preventing this effect. Each single dose of L-dopa produces this non-physiological shift in dopamine concentrations. These phenomena may occur in the patient several times a day, resulting in motor fluctuations [8,9]. On the other hand, when long-acting dopamine agonists are given, the patient rarely develops dyskinesia. The same effect is seen when short-acting dopamine agonists are administered continuously [10,11]. Studies in MPTP-treated monkeys showed that treatment with short-acting dopamine agonists (giving phasic or pulsatile stimulation) induces motor fluctuations whereas continuous administration of the same agents does not.

The challenge is to develop a long-acting formulation of levodopa or dopamine agonists to achieve continuous dopaminergic stimulation

Another clinical observation is the possible role of the D1 receptor in the induction of dyskinesia. Dopamine agonist drugs (such as ropinirole and bromocriptine) acting selectively on D2 dopamine receptors produce less dyskinesia than unselective D1 and D2 dopamine receptor agonist drugs (such as pergolide and apomorphine) [12,13].

The purpose of continuous dopaminergic stimulation is to prevent sharp oscillations in the dopamine level and the motor complications caused by the exogenous dopaminergic treatment.

The state-of-the-art approach to the continuous dopamine stimulation in Parkinson's disease includes mainly the dopamine agonist agents, given alone or in combination with L-dopa.

DOPAMINE AGONIST AGENTS

This group of medications includes the following agents: apomorphine, bromocriptine, pergolide, ropinirole, pramipexole, cabergoline. Open-label studies and double-blind studies showed fewer motor complications in patients treated with dopamine agonists (pergolide, ropinirole, pramipexole, cabergoline, bromocriptine, lisuride), as compared to L-dopa.

The various dopamine agonists differ in their effect on the dopamine receptors and their half-life. For example, the half-life of ropinirole ranges from 6 to 8 hours while that of cabergoline exceeds 24 hours. According to these pharmacodynamic data, theoretically cabergolide could provide the best efficient CDS. However, certain side effects of some of these dopamine agonists, such as pathological gambling [14] and valvular heart disease [15-17], limit their clinical use.

Apomorphine is a potent non-ergot dopamine agonist with a very strong affinity to D1 and D2 receptors. It has a very short action onset, and the effect lasts for 2 hours. Apomorphine could theoretically obviate the need for L-dopa, but as noted before it has a very short-lived effect and a high potential for inducing dyskinesia. For this reason, apomorphine as an intermittent bolus is not suitable for patients in the early stages of Parkinson's disease. Apomorphine is available in two therapeutic forms: intermittent bolus (pen) or continuous subcutaneous administration (pump). The former can provide rapid relief of off-symptoms. Apomorphine continuous infusion can provide continuous dopaminergic stimulation [18-20]. We recommend the continuous form of administration (by pump) for patients with advanced Parkinson's disease and motor complications who require more than 10 intermittent injections (pen) of apomorphine for controlling motor fluctuations. The regional side effects at the site of administration and the potential induction of early motor fluctuation probably limit the use of apomorphine in the early stage of Parkinson's disease. Nausea and vomiting are other common effects of apomorphine. Concomitant treatment with domperidone reduces these undesirable effects, and once the treatment has been established the domperidone dosage can be gradually reduced.

Because of the neuropsychiatric side effects (similar to those with other dopamine agonists), we do not recommend apomorphine in PD patients who have cognitive impairment or neuropsychiatric complications. In conclusion, apomorphine can provide clinical benefit in patients in advanced stages of Parkinson's disease with motor fluctuations (such as disabling dyskinesia, dystonia, or freezing in the off-state), with potential rapid reversal of the motor complications.

CDS = continuous dopamine stimulation

Among the new products emerging in the market that could provide CDS in patients with Parkinson's disease is the prolonged-release drug ropinirole [21,22]. Recently the Food and Drug Administration approved pramipexole, extended-release, a once-daily treatment in patients with early-onset Parkinson's disease. This medication is not indicated for the advanced stage of the disease.

Another new long-acting dopamine receptor agonist is the rotigotine transdermal patch (a non-ergolinic D1/D2/D3 dopamine receptor agonist) which was recently approved for clinical use in Europe but is still unavailable in Israel.

All dopamine agonists have proven successful in the early stages of Parkinson's disease, but they are contraindicated in patients with cognitive impairment and psychiatric manifestations due to increased psychotoxicity. Moreover, ergot-derived dopamine agonists have recently been associated with cardiac valvulopathy (with the use of pergolide and less with cabergoline). This side effect could limit the use of ergot-derived dopamine agonists. Strict cardiological follow-up is required in these patients [17,23,24].

Another unusual side effect of dopamine agonist agents is pathological gambling. A few reports in recent years have described the gambling effect that develops after treatment with pramipexole and ropinirole [25,26]. All the effects mentioned above limit the use of dopamine agonists and require close follow-up of patients treated with these agents.

COMBINED L-DOPA AGENTS

Continuous-release levodopa: L-dopa 200 mg/carbidopa 50 mg (Sinemet CR®, MSD, Israel) does not reduce the risk of motor complications, probably due to pharmacokinetic factors. The absorption of this product is unpredictable and the administration of the drug is problematic due to the fluctuating plasma level of L-dopa. Finally, continuous-release levodopa does not provide the desirable effect of continuous dopamine stimulation. Probably the best combination of L-dopa treatment is with COMT (catechol-O-methyltransferase) inhibitors (Stalevo®, Novartis Pharma, USA)

The COMT inhibitor (such as entacapone and tolcapone) can be given in combination with L-dopa or with continuous-release levodopa. COMT inhibitors increase the absorption and decrease the metabolism of the L-dopa in the central nervous system and slow down the rapid metabolism of levodopa, resulting in a more sustained response to dopaminergic therapy. The co-administration of L-dopa with a COMT inhibitor is associated with increased availability of L-dopa, which is higher than when L-dopa is administered alone. In theory, it seems to provide more continuous dopamine stimulation in the striatum, with fewer fluctuations in dopaminergic firing, and probably reduces the risk of dyskinesia. Moreover, COMT inhibitors reduce the formation of 3-OMD, which competes with L-dopa at both sites – blood and brain – and provide greater availability of the L-dopa [27-30].

COMT inhibitors are available as entacapone (Comtan®, Novartis Pharma, USA, alone or in combination with different doses of L-dopa, Stalevo®) and tolcapone. Tolcapone is related to severe hepatotoxicity and was withdrawn from clinical use. However, recently, tolcapone was reintroduced into the European market. The use of tolcapone should be under strict hepatic function monitoring.

Another option is continuous duodenal levodopa administration (Duodopa®, Abbott, UK). When given as continuous intraduodenal infusion, marked reductions in dyskinesia were observed [31]. However, this strategy is currently limited by the high cost and the need for percutaneous gastrostomy. Other routes of levodopa treatment such as transdermal or transnasal are currently under investigation.

MAO-B INHIBITORS

In recent years, a new generation of MAO-B inhibitors has been introduced in the treatment of Parkinson's disease. Rasagiline, a second-generation, selective, reversible MAO-B inhibitor, is associated with benefit in patients at an early disease stage (ADAGIO study) and reduced "off" time in patients with motor fluctuations. The LARGO study [32] compared the effect of entacapone and rasagiline in advanced Parkinson's disease. A significant mean reduction in "off" time was reported in patients with mild to moderate dyskinesia, but there was no mention of a possible mechanism through dopaminergic stimulation. The effect of rasagiline on dopaminergic stimulation has not been established. New MAO-B inhibitor agents such as safinamide are currently in different developmental phases [33].

ADDITIONAL OPTIONAL TREATMENTS

We have not yet considered the role of other non-dopaminergic systems in the development of motor complications and non-dopaminergic related dyskinesias in PD patients, or the potential role of deep brain stimulation in the treatment of patients with advanced Parkinson's disease. Deep brain stimulation is a promising treatment; however, it requires invasive surgery and is appropriate for a limited population of PD patients. Subthalamic nucleus-deep brain stimulation has been associated with behavioral changes and cognitive difficulties.

With regard to non-dopaminergic systems, some therapeutic approaches are still at the developmental level while others are in different stages of clinical trials; these include adenosine A2a antagonists [34], serotonin receptor agonists, and others. Other strategies include direct cell replacement and gene transfer through viral vectors [35]. Cell replacement represents a way to provide dopamine directly to the striatum, while gene therapy restores the dopamine function in the striatum. These strategies

showed promising results in rodents and non-human primates. However, in clinical studies the attenuation in PD symptoms have been rather modest and in some cases were associated with severe dyskinesias. Further development of these techniques is necessary to improve clinical efficacy and safety.

CONCLUSIONS

Experimental and clinical experience supports the fact that pulsatile stimulation of the dopamine receptors in the basal ganglia contributes to the development of motor complications in patients with Parkinson's disease. At the present time, long-acting dopaminergic agents (such as ropinirole 24 hour release and cabergoline), as well as combinations of L-dopa and COMT inhibitors (Stalevo®) might provide a clinical anti-parkinsonian effect with reduced risk of motor complications, perhaps providing more tonic stimulation in the striatum. Short-acting dopaminergics such as apomorphine given in continuous infusion (pump) in the advanced stages of the disease can provide continuous dopaminergic stimulation with a potential reduction of L-dopa dose and reduction of motor fluctuations.

Despite recent improvements and the emerging new strategies, further innovations and development of neuroimaging techniques are required. Concerning cell transplantation and gene therapy, the future of these techniques in Parkinson disease treatment remains unknown. Future technical advancements and patient selection will be critical when deciding on any cell or gene therapy.

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