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Chapter 2

Postural instability in Parkinson’s disease: the adrenergic hypothesis and the locus coeruleus

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ABSTRACT

Parkinson’s disease (PD) is traditionally viewed as a mainly hypodopaminergic syndrome, with symptoms resulting predominantly from loss of dopamine-producing neurons in the substantia nigra. However, while most of the cardinal motor features of PD respond well to dopaminergic therapy, many other features of the disease do not. Balance impairment and the associated risk of falling represent one of the most prominent and potentially disabling features that are typically refractory to dopaminergic treatment. Therefore, it is possible that lesions in non-dopaminergic systems contribute to the pathophysiology of postural instability in PD. Such non-dopaminergic lesions are well recognized, certainly in advanced stages of PD where postural instability and falls dominate the clinical presentation. However, it remains unclear which of the identified non-dopaminergic lesions is specifically responsible for postural instability and balance impairment. In this review, we argue that cell loss in the locus coeruleus and a resultant central norepinephrine deficit are intimately involved in the pathophysiology of postural instability in PD. If proven to be correct, this link between defective noradrenergic neurotransmission and postural instability could have important implications for the future development of new symptomatic treatments aimed to correct postural instability and preventing falls. Studies in the next 5 years could test this hypothesis, using a battery of complementary research techniques, including advanced neuroimaging (structural, functional imaging and nuclear), neurochemical studies of cerebrospinal fluid, post-mortem clinicopathological analyses, and detailed clinical balance evaluations supplemented by posturography studies.
INTRODUCTION

Idiopathic Parkinson’s disease (PD) is traditionally said to be characterized by a varying combination of at least two of the following core features: bradykinesia, tremor, rigidity and postural instability, although there is increasing evidence that these features are just a part of a much broader clinical complex. Postural disturbances represent one of the most disabling features of the disease. They are typically a late manifestation of PD and include the distinctive stooped posture, the shuffling gait disorder and progressive balance impairment. Postural instability leads to frequent falls, often with devastating consequences, such as fractures or long-term hospitalization.

The pathophysiology of postural instability in PD remains insufficiently understood, but is likely complex and multifactorial. It is good to realize that what patients and clinicians perceive as “a poor balance” actually encompasses a fairly broad range of pathophysiological processes, and this makes it difficult to easily correlate any given factor to “balance impairment”. Indeed, it is now broadly accepted that deficiencies in many of the afferent and efferent postural systems that normally contribute to balance control can contribute to the complex pathophysiology underlying postural instability in PD. Examples include inadequately organized automatic postural reactions, poor anticipatory postural responses, a slowing of compensatory stepping reactions, inappropriately directed protective arm movements, and a defective somatosensory integration of afferent sensory information. The net result is that patients frequently fall (or nearly so), which is defined as inadvertently landing on any lower surface (the definition usually also states that this should not be caused by an overwhelming external force).

Clinically based studies have underscored the magnitude of the problem and the impact on quality of life, but to date have failed to provide good pathophysiological insights, mainly because bedside balance tests are relative crude and subjective techniques. For example, the widely used retropulsion test of the UPDRS (Unified Parkinson’s Disease Rating Scale) provides only a gross measure of overall balance disturbances in PD, but is not designed to unravel the complex underlying pathophysiology. This situation has improved with the advent of posturography, which is an umbrella term for a variety of techniques that entail an objective electrophysiological assessment of human balance. In this review, we will refer to papers that used either static or dynamic posturography. Static posturography refers to all those techniques that measure quiet standing, with or without an instrumented fixed support surface, and without any physical body perturbation. By contrast, dynamic posturography techniques employ physical perturbations of stance, using either an unstable or motorized support surface, or an external force applied to one or more body parts. Technological advances such as these have allowed this field to progress at a relatively rapid pace, helping to clarify fundamental disturbances at
the neurophysiological level when PD patients begin to fall. Thus, researchers using this approach have identified various factors that can each contribute to postural instability, including impairment of automatic postural responses (both reactive and anticipatory), bradykinesia of corrective stepping movements, abnormally directed protective arm movements, and axial stiffness.⁸,⁹,¹⁰ These improved neurophysiological insights now need to be backed up by a clear understanding of the underlying neurochemical and neuropathological changes. However, this is where much work remains to be done.

**PD: A HYPODOPAMINERGIC SYNDROME?**

The cardinal symptoms of PD are generally conceived as the clinical offprint of a central dopamine loss, for several reasons. First, progressive destruction of dopaminergic neurons in the substantia nigra pars compacta is a neuropathological hallmark of PD. Second, both neurochemical analyses of the cerebrospinal fluid (CSF) and positron emission tomography (PET) imaging of the nigrostriatal pathway indicate that nigral cell loss leads to decreased levels of dopamine and its metabolites in the central nervous system (CNS).¹¹,¹² Interestingly, nigral cell loss – as documented with fluorodopa PET scans – shows and excellent correlation with bradykinesia, but much less so with postural instability.¹³ Third, symptomatic treatment of PD with dopaminergic drugs (especially levodopa) generally leads to marked alleviation of most cardinal symptoms. Bradykinesia and rigidity usually respond best, particularly in early stages of the disease. (Note that tremor responds less well to dopaminergic treatment, and PET studies have in fact associated tremor with serotonergic lesions¹⁴). Finally, fairly selective nigrostriatal neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) can induce a hypokinetic-rigid syndrome in both humans and animals which shares many clinical, neuropathological and biochemical features of idiopathic PD, including prominent postural instability.¹⁵,¹⁶,¹⁷,¹⁸ Treatment with levodopa also markedly alleviates the symptoms of MPTP-induced parkinsonism.¹⁹ Taken together, these different lines of evidence imply that PD is largely a hypodopaminergic syndrome.

**POSTURAL INSTABILITY AND DOPAMINERGIC DEFICITS IN PD**

There is reason to believe that not all clinical manifestations of PD result solely from dopamine loss in the nigrostriatal pathway. While this is particularly true of the nonmotor features of this disease, it also applies to some of the motor features, including including balance impairment and freezing of gait – although other signs (such as rigidity or bradykinesia) do continue to improve with dopaminergic treatment within the same patients²⁰,²¹ (figure 1). Indeed, once present, postural instability is notoriously refractory
Balance problems are sometimes even aggravated by the adverse effects of dopaminergic drugs, such as dyskinesias (which can be sufficiently violent to throw patients off balance), orthostatic hypotension or confusion.

Studies using dynamic posturography have therefore taken these clinical observations one step further, trying to unravel the contribution of dopaminergic and non-dopaminergic lesions using two different approaches. First, postural responses can be assessed in patients with presumably selective hypodopaminergic syndromes and in patients with PD (where lesions are known to extend beyond the substantia nigra). Responses that are abnormal in both groups might be influenced by supraspinal dopaminergic control (because dopamine loss occurs in both conditions), whereas responses that are merely abnormal in PD could be under non-dopaminergic influence. Following this line of reasoning, automatic postural responses have been assessed in patients with what are presumed to be relatively pure hypodopaminergic syndromes such as neuroleptic-induced parkinsonism, MPTP-induce parkinsonism and young-onset PD. Some postural abnormalities that are commonly present in patients with late-onset PD were found to be absent in these hypodopaminergic syndromes, suggesting that non-dopaminergic lesions probably contributed to their development in PD. However, other
postural abnormalities were present in patients with a selective dopamine deficiency as well as typical late-onset PD, raising the interesting proposition that balance impairment in PD might be related to a combination of both dopaminergic and non-dopaminergic abnormalities. We should note that MPTP-induced parkinsonism is not a perfect model for idiopathic PD, because the onset is subacute and the syndrome does not have the same inevitable process of progressive neurodegeneration. A limitation to studying neuroleptic induced parkinsonism is that postural deficits are often only mild, so this syndrome may not fully reflect the severity of balance impairment in PD.

A second approach to assessing postural responses in patients with PD involves examining patients both before and after administration of dopaminergic drugs. Using this approach, some postural abnormalities (for example, the defective voluntary postural corrections) have been found to be responsive to dopaminergic medication, whereas other abnormalities (including the overall instability during dynamic posturography testing, as measured by excursions of the center of mass following a sudden platform movement) persist despite antiparkinson treatment. These observations confirm the results obtained in patients with hypodopaminergic syndromes described and, again, a concept emerged of postural instability as a combined dopaminergic and hypodopaminergic syndrome.

**NON-DOPAMINERGIC LESIONS IN PD**

It appears that postural instability and other poorly dopa-responsive symptoms are likely to be the clinical results of ‘extra-nigral’ or ‘non-dopaminergic’ lesions. Post-mortem studies have clearly identified the presence and extent of these non-dopaminergic lesions, and also shown that these typically develop in elderly patients with long-lasting PD. Affected neurotransmitters include, among others, noradrenaline, serotonin and acetylcholine. For example, cell loss in the noradrenergic locus coeruleus, the cholinergic basal nucleus of Meynert and the mixed cholinergic-glutaminergic pedunculopontine nucleus (PPN) has been demonstrated. The latter has recently been studied as a new target for stereotactic surgery, aimed specifically to improve walking and freezing of gait in PD. Animal studies have shown that the PPN is normally responsible for gait initiation and stepping maintenance, and a recent paper reported a patient with freezing after a bilateral infarction of the PPN, thus suggesting a clinical correlation in humans.
POSTURAL INSTABILITY AND THE LOCUS COERULEUS

In the remainder of this review, we propose the hypothesis that postural disturbances in PD are closely related to cell loss in one specific non-dopaminergic nucleus, namely the locus coeruleus and the resultant norepinephrine deficit in the CNS. We realize that evidence supporting a link between balance impairment in PD and the locus coeruleus is only indirect. However, to support our hypothesis, we will carefully address all circumstantial evidence, first by reviewing the normal functions of the locus coeruleus. We then discuss how and when the locus coeruleus is likely to become involved in the pathophysiology of PD, drawing mainly on neuropathological and neurochemical evidence. We conclude by summarizing the available data that therapeutic correction of the central norepinephrine deficit might reduce postural disturbances in neurodegenerative disorders, including PD.

ANATOMY OF THE LOCUS COERULEUS

The locus coeruleus is a small nucleus (the rostrocaudal extent approximates 16 mm) which is situated bilaterally in the pontine tegmentum. Its neurons are pigmented due to presence of neuromelanin in the cell bodies. In the CNS, the locus coeruleus is the main source of norepinephrine\textsuperscript{36}, an excitatory neurotransmitter which is metabolized mainly to 3-methoxy-4-hydroxy-phenyleneglycol (MHPG). The locus coeruleus also uses various neurotransmitters other than norepinephrine, and this includes among others glutamate, dopamine and GABA.\textsuperscript{37} However, these other neurotransmitters and their corresponding pathways are thought to be less important for the functions of the locus coeruleus. In humans, the locus coeruleus has been mapped through immunocytochemical labeling of the biosynthetic enzymes tyrosine hydroxylase (TH) and dopamine-beta-hydroxylase\textsuperscript{38,39}, as well as by visualizing neuromelanin content.\textsuperscript{38,40,41}

Despite its relatively small size, the locus coeruleus innervates widespread areas in the CNS, including the spinal cord, neocortex, hippocampus and cerebellum.\textsuperscript{42,43} Retrograde tracer transport studies in rats have identified a topographic arrangement of these projections within the locus coeruleus. The more caudal and ventral part, which consist of densely packed small cells, contain neurons that project to the spinal cord and cerebellum. The more rostral and dorsal part, which are formed by large multipolar cells, project mainly to the neocortex.\textsuperscript{42,44} A single neuron originating within the locus coeruleus may branch to widely divergent areas, for example with one fiber to the spinal cord and another to the neocortex.
NORMAL FUNCTIONS OF THE LOCUS COERULEUS

In accordance with these widespread projections, the locus coeruleus and its transmitter, norepinephrine, have rather diverse functions, including the regulation of autonomic responses, cognition and motor control. Interestingly, most functions could be important for normal balance control. First, studies of cats with acute spinal cord lesions suggest that noradrenergic systems are involved in gait initiation. As this may involve the coeruleo-spinal noradrenergic pathway this raises the interesting question whether dysfunction of the locus coeruleus could underlie, at least in part, the freezing of gait phenomenon that, in turn, is one of the leading causes of falls in PD. Second, studies in rats, cats and monkeys found evidence that the locus coeruleus is activated in situations demanding immediate attention and coping responses. Although the link is only very indirect, this function of the locus coeruleus could be relevant for balance control, because immediate handling of unexpected postural perturbations is of vital importance to prevent falls. The locus coeruleus is known to have various firing patterns: tonic activity is positively correlated with the arousal state, while phasic activity is aroused by sensory stimuli. In this respect, one might speculate that the phasic patterns of the locus coeruleus are more task-oriented and related to immediate action, whereas the tonic firing patterns would reflect a more continuous exploration of the environment and thereby help regulate postural control. Third, involvement of the locus coeruleus in autonomic regulation could also be relevant for balance control, because dysfunction could lead to orthostatic hypotension and thereby cause falls. Syncopal falls in PD appear to be relatively rare (perhaps because of inadequate ascertainment), but do occur in more advanced states of PD. Fourth, the coeruleospinal pathway appears to contribute to gain control of vestibulospinal limb reflexes. For example, work in decerebrate cats subjected to passive neck rotation has shown that activation of coeruleo subcoeruleospinal neurons is opposite to that of the lateral vestibulospinal neurons projecting to the same segments of the spinal cord. Together, this functional coupling could assist in regulating the excitability of limb extensor motoneurons to neck stimulation. A link to human balance may be placed because gain control of vestibulospinal responses is important for regulating upright stance in healthy subjects, particularly when the head is being displaced. Although direct evidence is lacking, it is possible that the influence of coeruleospinal pathways on excitability of limb extensor motoneurons may also affect other automatic balance responses in the legs that are involved in regulation of upright stance in response to externally imposed postural perturbations. Gain control of these automatic balance reactions is severely impaired in PD, possibly due to loss of descending coeruleospinal influence. The controlling action of the locus coeruleus on the cerebellum may also be relevant in this respect, because cerebellar output is required to optimally tune postural reflexes. Finally, given its widespread projections, the locus coeruleus may play a coordinating role in linking different brain functions. As balance
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Neuropathological studies

Post-mortem brain studies of PD patients have identified substantial cell loss in the locus coeruleus, particularly in its caudal part. As this caudal part projects mainly to the spinal cord and cerebellum, it could well be related to balance impairment in PD. This cell loss is likely superimposed upon the normal age-related decline of locus coeruleus cell volume, which relatively spares the caudal part of the locus coeruleus. If the locus coeruleus is indeed involved in postural control, the combination of these two processes could explain why postural disturbances are a late manifestation of PD.

To support this latter contention, it would be interesting to investigate whether cell loss in the locus coeruleus occurs mainly in advanced PD. Unfortunately, most post-mortem studies did not specifically investigate the influence of duration or severity of the disease. Two studies found no relation between disease duration and total cell loss within the locus coeruleus. However, total cell loss is possibly a poor parameter because, as stated earlier, cell loss in PD occurs especially in the caudal part of the locus coeruleus. According to the Braak staging of neuropathology of PD, lesions in the caudal brainstem precede pathology in the mesencephalon. This would argue against a role in producing postural instability, as this is typically a late feature of PD. In fact, this raises the interesting question whether an isolated lesion in the locus coeruleus would suffice to produce postural abnormalities or balance impairment, even in the absence of a concurrent lesion in the substantia nigra. Answering this question would require selective lesioning studies in primates, which is technically possible. In fact, this raises the interesting question whether an isolated lesion in the locus coeruleus would suffice to produce postural instability, as this is typically a late feature of PD.

Accelerated cell loss in progressive supranuclear palsy (PSP) where early, severe postural instability and high fall rates are prominent features has been reported, but the extent to which cell loss occurs in the locus coeruleus of PSP has been controversial and cell counts have not been directly studied in relation to postural instability in these patients.

THE LOCUS COERULEUS IN PD (AND OTHER NEURODEGENERATIVE DISORDERS)

Accelerated cell loss in the locus coeruleus has also been reported in other neurodegenerative diseases, including both motor and cognitive functions. The locus coeruleus could be adequate positioned to serve as “coordinator” again, dysfunction would lead to postural instability.
**Neurochemical studies**

Consistent with the reported cell loss in the locus coeruleus of PD patients, most CSF analyses and post-mortem studies have shown reduced levels of norepinephrine. However, a few studies did not find such a reduction, perhaps because of differences in patient material or the techniques that were used. Unlike norepinephrine itself, CSF levels of its main metabolite MHPG are not significantly reduced. However, MHPG does not reflect adrenergic activity accurately because, unlike norepinephrine, MHPG is rapidly exchanged across the blood-brain barrier (BBB).

The post-mortem brain studies rarely reported a clinical correlate of the observed pathological changes. The possible clinical relevance was addressed in several CSF studies, but postural disturbances were only mentioned rarely. However, one study reported a significant correlation between the reduced concentration of norepinephrine and the severity of clinically rated gait and postural disturbances in PD. In another study, levels of norepinephrine were significantly reduced in PD patients with a frozen gait, again linking the locus coeruleus to falling via freezing of gait.

**Neuroimaging studies**

Nuclear imaging techniques using position emission tomography (PET) or single photon emission computed tomography (SPECT) can assess various neurotransmitter functions. There is increasing attention for specific markers of non-dopaminergic functions, including the noradrenergic system. A PET study that examined the uptake of \(^{11}\)C-RTI 32 (a combined marker for noradrenaline and dopamine transporter binding) showed a lower uptake in the locus coeruleus of depressed patients with PD, suggesting an influence of noradrenergic function on mood. Balance was not assessed in this study. Based on the hypothesis put forth in the article, we would argue that attempts to explore the role of noradrenergic dysfunction in PD by developing imaging techniques that could assess the integrity of the locus coeruleus are both needed and fully warranted.

**CORRECTION OF THE CENTRAL NOREPINEPHRINE DEFICIT**

Another way to demonstrate a role for the locus coeruleus on balance control is to explore the therapeutic effects of pharmacologically replenishing the central norepinephrine deficiency. Noradrenergic drugs have mainly been tested because of their potential to suppress levodopa-induced dyskinesias. However, several investigators have used noradrenergic drugs with the specific aim of improving gait or balance (Table 1).
**Table 1** Therapeutic studies examining the effect of norenergic compounds on postural disturbances and gait.

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Patients</th>
<th>Controls</th>
<th>Outcome</th>
<th>CSF</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>L</em>-threo-DOPS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600-900 mg/day</td>
<td>202 PD</td>
<td>Yes, double blind</td>
<td>Retropulsion improved, freezing tended to improve</td>
<td>Not assessed</td>
<td>97</td>
</tr>
<tr>
<td>6 weeks</td>
<td>24 pure akinesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>100-900 mg/day</td>
<td>6 PD</td>
<td>No</td>
<td>Freezing improved in 3 out of 6 patients</td>
<td>NE concentrations increased (dose related)</td>
<td>94</td>
</tr>
<tr>
<td>Unknown treatment period</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100-900 mg/day</td>
<td>13 PD</td>
<td>No</td>
<td>Freezing improved in 7 out of 13 patients</td>
<td>NE concentrations increased (dose related)</td>
<td>95</td>
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<tr>
<td>Unknown treatment period</td>
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<tr>
<td>D(L)-threo-DOPS</td>
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<tr>
<td>200-2400 mg</td>
<td>6 PD</td>
<td>Placebo-controlled, crossover</td>
<td>No benefit in freezing</td>
<td>Not assessed</td>
<td>96</td>
</tr>
<tr>
<td>single dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>750 mg - max?</td>
<td>4 PD</td>
<td>No</td>
<td>Freezing mildly improved in 3 out of 4 patients</td>
<td>No change in DA, noradrenergic metabolites</td>
<td>88</td>
</tr>
<tr>
<td>10 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Idazoxan</em></td>
<td></td>
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<tr>
<td>1-40 mg</td>
<td>8 PSP</td>
<td>Placebo-controlled, double blind</td>
<td>Postural stability and gait improved (UPDRS items)</td>
<td>Not assessed</td>
<td>104</td>
</tr>
<tr>
<td>4 weeks</td>
<td></td>
<td></td>
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<tr>
<td><em>Methylphenidate</em></td>
<td></td>
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<tr>
<td>20 mg</td>
<td>21 older adults</td>
<td>No, open</td>
<td>Gait speed, timed up and go and stride time variability improved</td>
<td>Not assessed</td>
<td>109</td>
</tr>
<tr>
<td>single dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 mg</td>
<td>5 PD</td>
<td>No, open</td>
<td>Freezing improved</td>
<td>Not assessed</td>
<td>110</td>
</tr>
<tr>
<td>single dose</td>
<td></td>
<td></td>
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<tr>
<td>1 mg/kg/day</td>
<td>17 PD, with STN-stimulation</td>
<td>Not controlled, videos blindly assessed</td>
<td>Freezing improved</td>
<td>Not assessed</td>
<td>111</td>
</tr>
<tr>
<td>3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.2 mg/kg/day</td>
<td>12 PD</td>
<td>Placebo-controlled, double blind</td>
<td>No significant effects on walking time</td>
<td>Not assessed</td>
<td>112</td>
</tr>
<tr>
<td>2 weeks</td>
<td></td>
<td></td>
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</tbody>
</table>

Only studies with sufficient information (e.g. concerning trial design and dose of medication) are included in this table.

CSF: Cerebrospinal fluid; DA: Dopamine; DOPS: Dihydroxyphenylserine; NE: Norepinephrine; PD: Parkinson’s disease; PSP: Progressive nuclear palsy; STN: Subthalamic nucleus; UPDRS: Unified Parkinson’s disease rating scale.

**Dihydroxyphenylserine**

There are several possibilities to correct the central norepinephrine deficit. Thus far, the compound dihydroxyphenylserine (DOPS), a synthetic precursor of norepinephrine, has been studied most extensively. DOPS has four different stereoisomers that are termed...
L-threo-, D-threo-, L-erythro and D-erythro-DOPS. The L-isomer is converted directly to natural (-)-norepinephrine by aromatic L-amino acid decarboxylase. By contrast, D-threo-DOPS inhibits the decarboxylation of L-threo-DOPS in vitro\(^6\) and is therefore theoretically unsuitable for restoring norepinephrine levels. Nonetheless, both L-threo-DOPS and racemic mixtures of both D- and L-threo-DOPS have been used in therapeutic trials. (D) L-threo-DOPS can restore depleted norepinephrine levels in plasma of both rats\(^4,3\) and humans, including patients with postprandial hypotension\(^4\), DBH deficiency\(^5\), multiple system atrophy\(^6\) or PD\(^7,8\). (D) L-threo-DOPS can pass across the BBB of PD patients.\(^8\)\(^,8\)\(^,9\)

However, there is disagreement as to whether (D) L-threo-DOPS can actually increase norepinephrine concentrations in the CSF. Several investigators could not detect an increase in norepinephrine or its metabolites in the CSF after administration of L-threo- or (D) L-threo-DOPS to rats\(^9\)\(^,10\) and patients with PD.\(^8\)\(^,8\)\(^,9\) Conversely, others have found increased MHPG-levels in the brains of mice after administration of L-threo-DOPS.\(^8\)\(^,4\) Significantly, Tohgi and colleagues found a dose-dependent increase in norepinephrine concentrations in the CSF after long-term administration of L-threo-DOPS to patients with PD.\(^8\)\(^,8\)

Several investigators have studied the influence of L-threo-DOPS on various ‘non-dopaminergic’ manifestations of PD, including freezing, gait impairment, retropulsion and postural disturbances. Quinn et al. found no improvement of freezing of gait in a single-dose, placebo-controlled study of (D) L-threo-DOPS in six PD patients.\(^9\) Narabayashi et al. studied the effect of oral L-threo-DOPS in a prospective, double blind and placebo-controlled study of 226 patients with longstanding PD (Hoehn and Yahr stages 3 and 4) and related disorders.\(^8\) After six weeks of treatment, gait, retropulsion and festination had improved according to the clinical impression of a neurologist. Unfortunately this study did not ascertain balance changes with objective assessments as dynamic posturography. Another study reported that administration of (D) L-threo-DOPS during 10 days improved clinically rated gait impairment in a small group of four patients with longstanding PD in an open uncontrolled study.\(^9\) Tohgi et al. noted a moderate to marked improvement of freezing in three out of six PD patients (Hoehn and Yahr stage 3 and 4) treated with L-threo-DOPS.\(^7\) In a later extended study, freezing improved significantly in 7 out of 13 patients, but again this was not a controlled study.\(^8\) Freezing was assessed in four grades while watching the patient walk 10 meters up and down; an improvement by more than one grade was considered significant. Other Japanese investigators reported improvement of postural control and freezing of gait by L-threo-DOPS in Parkinson patients, but these were open trials and details on the outcome parameters of these studies are difficult to obtain.\(^8\)\(^,9\)\(^,10\)
(D) L-threo-DOPS has also been tested in patients with other neurodegenerative disorders. For example, (D) L-threo-DOPS can reduce orthostatic hypotension in patients with severe autonomic failure\textsuperscript{101}, and such effects could also be relevant for patients with PD suffering from syncopal falls. Its effect on orthostatic hypotension has never been compared directly with other anti-orthostatic measures. Autonomic failure is particularly problematic in patients with multiple system atrophy (MSA), and one study found an increased upright blood pressure after administration of L-threo-DOPS to four patients with MSA.\textsuperscript{86} In a single blind placebo-controlled study of two patients with DBH deficiency, stance ability was prolonged after DL-threo-DOPS administration.\textsuperscript{85} Interestingly, (D) L-threo-DOPS may also ameliorate orthostatic hypotension in PD patients. One preliminary report mentioned a significant increase in standing blood pressure in PD patients.\textsuperscript{102} In addition, subjective complaints of orthostatic hypotension disappeared in seven out of twelve patients.

One caveat to using L-threo-DOPS needs to be mentioned. While it may elevate norepinephrine levels, (D) L-threo-DOPS may adversely affect dopamine levels. Thus, cerebral dopamine levels were significantly decreased in rats after administration of L-threo-DOPS.\textsuperscript{103} It is unclear whether norepinephrine levels were actually increased. Similar mechanisms may exist in humans, as the raised dopamine plasma concentration of a patient with DBH deficiency was reduced during treatment with DL-threo-DOPS.\textsuperscript{104} By contrast, norepinephrine concentration in plasma was raised and the patient was free of orthostatic symptoms. However, in another study, dopamine concentrations in the CSF did not change in patients treated with levodopa prior to L-threo-DOPS administration.\textsuperscript{71,96} In fact, dopamine levels actually increased in patients who received only L-threo-DOPS. Therefore, the precise effects of L-threo-DOPS on dopamine metabolism remain unresolved. However, the potential inhibition of dopamine by L-threo-DOPS could obviously limit its use in the treatment of PD and could partially explain the thus far disappointing results with this compound.

**Idazoxan**

Another pharmacological strategy aimed at restoring central norepinephrine deficit is to use the selective alpha-2 adrenoreceptor inhibitor idazoxan. Activation of the presynaptic alpha-2 receptor decreases norepinephrine transmission in the locus coeruleus. Hence, inhibition of this receptor with compounds such as idazoxan should boost norepinephrine neurotransmission. The first relevant experiment with idazoxan involved a double-blind crossover study of nine patients with PSP. Treatment over 4 weeks resulted in significant improvement in the ability to rise from a chair, as well as in gait and postural instability.\textsuperscript{105} This improvement was scored by a physician according to, among others, the UPDRS and global assessment by patients on a 4-point scale. Thus far, idazoxan has not been tested in PD with a specific focus on assessing gait and postural instability. A
drawback could be the dose-dependent side-effects, such as hypertension and headache. A study on the effects of idazoxan on levodopa-induced dyskinesias showed a drop-out rate of 50% at a dose of 60 mg/day. Moreover, a large phase III trial that aimed to examine the effects of idazoxan on levodopa-induced dyskinesias was terminated early for unpublished reasons, but perhaps this was owing to tolerability problems.

**Methylphenidate**

Methylphenidate, a drug traditionally used to combat attention-deficit/hyperactivity disorder, has predominantly dopaminergic effects through blocking presynaptic dopamine re-uptake. However, it may also improve noradrenergic neurotransmission by presynaptic inhibition of the norepinephrine transporter. Recent work has shown that methylphenidate can decrease fall risks in community dwelling older adults, either by increasing the availability of central dopamine and norepinephrine or by improving attention. Three further trials have shown that methylphenidate can also improve gait and freezing in patients with PD. However, another double-blind, randomized placebo-controlled cross-over study in 13 PD patients failed to demonstrate a clinically relevant effect on walking speed, but these are very small numbers. Furthermore, postural stability was not specifically tested in any of these studies, so the jury is still undecided with respect to methylphenidate.

**COULD OTHER NON-DOPAMINERGIC NEUROTRANSMITTERS BE INVOLVED?**

Of course there the possibility remains that loss of other non-dopaminergic neurotransmitters also play a role in the pathophysiology of postural disturbances in PD. Biochemical analyses of CSF and post-mortem neuropathological studies of PD brains have identified various other ‘non-dopaminergic’ lesions, besides the lesion in the locus coeruleus. We previously mentioned the mixed cholinergic-glutaminergic PPN and its presumed role in gait disturbances. Other examples include serotonin and choline acetyltransferase, whose levels are also reduced in patients with PD. Serotonin is an interesting candidate player in the pathophysiology of postural instability in PD, because in one study, serotonin levels in the CSF were significantly lower in PD patients with severe postural instability and gait disorders, compared with a control group of PD patients with predominantly hyperkinetic symptoms. However, a 4-week treatment with L-5-hydroxytryptophan, a biosynthetic precursor of serotonin, did not improve balance in a small group of six PD patients in an open label trial. Therefore, at the current time there is no compelling evidence that correction of the serotonergic deficit would be likely to improve postural disturbances in PD. Acetylcholine is the second interesting candidate, mainly because cholinergic deficiencies seem responsible for at least some of the cognitive deficits in PD. This is relevant because gait and balance are now increasingly seen as
a’ cognitive disorder’, and it has been speculated that cholinesterase inhibitors should be tested as adjunctive treatment for gait and balance deficits in PD. However, at the present time there is no compelling evidence to suggest that cholinesterase inhibitors lead to significant improvements of gait and balance. Once again, this leaves cell loss in the locus coeruleus as the prime suspect.

A COMBINATION OF DOPAMINERGIC AND NON-DOPAMINERGIC LESIONS?

Before concluding, we wish to reiterate that postural disturbances in PD are most likely related to the combined presence of both non-dopaminergic lesions – in particular a central norepinephrine depletion due to cell loss in the locus coeruleus – and a concurrent dopaminergic lesion. This view is supported by our severely affected patients with MPTP-induced parkinsonism, whose gait and balance were markedly compromised, yet they almost certainly had a selective nigrostriatal lesion and a severe hypodopaminergic syndrome. Indeed, CSF studies in these patients confirmed the presence of a selective central dopamine deficiency, possibly even with a compensatory increase in norepinephrine turnover. Gait and balance also improved considerably when these patients first received levodopa, and this is also common clinical experience in early stages of PD, a situation in which gait bradykinesia can improve with dopaminergic therapy. Freezing of gait is typically seen in the ‘off’ state, and most patients with freezing improve with dopaminergic therapy (‘on’ state freezing is a relatively rare phenomenon). Finally, although balance impairment is usually refractory to dopaminergic treatment, careful analyses using dynamic posturography have shown that some postural abnormalities can be at least partially dopa-responsive. Thus, static sway (in some reports, but not all), voluntary weight shifts, some automatic postural responses, anticipatory postural adjustments, voluntary toe rises and compensatory steps improved to some extent in PD patients after levodopa administration, albeit typically not to normal levels. One might even speculate that some of the balance abnormalities in PD are only seemingly refractory to dopaminergic treatment, because by the time postural instability emerges, the central dopamine loss has become so severe that it can no longer be overcome by mounting doses of oral levodopa. Furthermore, in this stage of the disease, the cumbersome side effects of levodopa become an important dose-limiting factor. For practicing clinicians, it is therefore always worth trying to treat postural instability with a judicious trial of levodopa, certainly while we await the advent of efficacious non-dopaminergic drugs.
EXPERT COMMENTARY AND FIVE-YEAR REVIEW

In this review, we have argued for the hypothesis that postural disturbances in advanced PD may well be related to a combination of a severe central dopamine loss, plus a concurrent norepinephrine deficiency caused by cell loss in the locus coeruleus. This adrenergic hypothesis should now be tested directly in prospective, randomized and placebo-controlled trials, designed to investigate the influence of norepinephrine precursors on postural instability in PD. Ideally, such trials should be controlled and include appropriate (relevant and reliable) outcome measures. Evaluation of treatment effects should not just rely on clinically based measures of balance impairment (such as the retropulsion test), because clinical judgments are subjective and difficult to standardize.\textsuperscript{5} Additional outcome measures should include a prospective assessment of fall rates during a sufficient time frame (at least six months), standardized balance and gait rating scales, and objective measures of postural instability using dynamic posturography. Quality of life, as a reflection of regained mobility and confidence, should also be an outcome measure. If successful, such studies would provide a much welcome therapeutic approach to a hitherto poorly treatable and incapacitating feature of PD, and one of the leading causes of disability as the disease progresses.

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