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Parkinson's Disease: What role do pedunculopontine nucleus cholinergic neurons play?

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There is increasing evidence that cholinergic systems dysfunction contributes significantly to both non-motor and motor morbidities in Parkinson's disease (PD) [1]. Important brain cholinergic projection systems include the well characterized basal forebrain corticopetal system (BF) and cholinergic neurons within the pedunculopontine-lateral dorsal tegmental complex (hereafter labeled as PPN). Located at the mesopontine border, the PPN is a phylogenetically ancient structure composed of a number of different neuronal populations [2]. Cholinergic projection neurons are prominent PPN components with strong interconnections with the basal ganglia and the thalamus, and substantial descending projections to important medullary motor centers. The PPN is a key node in the regulation of both consciousness and motor function. The midbrain locomotor region (MLR), a physiologically defined region crucial for normal gait and posture, encompasses the PPN [3].

Positron emission tomography (PET) ligands targeting markers of cholinergic terminals enable *in vivo* assessment of the integrity of cholinergic projections. Combined with post-mortem studies and experimental animal work, a much clearer picture of the nature of cholinergic projection system changes and their clinical correlates is now emerging. Non-motor symptoms like REM sleep behavior disorder and possibly visual hallucinations may reflect degeneration of PPN cholinergic neurons and their thalamic afferents in Parkinson's disease.

Degeneration of basal forebrain cholinergic neurons and their centripetal cortical projections is a determinant of cognitive decline in PD and Alzheimer's disease (AD) [1]. A major distinction in cholinergic systems degeneration between PD and AD is that PPN neurons and

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their thalamic projections degenerate in PD but remain relatively spared in AD [4]. Rapid eye movement sleep behavior disorder (RBD) is a parasomnia that has been linked almost exclusively to α-synucleinopathies [5]. We showed recently that PD subjects reporting symptoms of RBD had evidence of more prominent cholinergic terminal loss, including within the thalamus, reflecting impaired integrity of PPN-thalamic projections [6]. These findings help explain not only why the presence of RBD is a risk factor for dementia in PD [7], but also why this parasomnia is quite uncommon in AD [5].

RBD is a risk factor also for visual hallucinations in PD [7]. A recent MRI-morphometric study found that PD and PD with dementia patients with visual hallucinations showed grey matter reductions of the PPN region and the thalamus compared to PD patients without hallucinations [8]. These preliminary data suggest that cholinergic projections to the visual thalamus may play a role in visual hallucinations in PD but need further confirmation.

Consistent with the role of the PPN as a key node in the regulation of sleep and gait and posture, the presence of RBD in PD is associated with the motor complications of freezing of gait [9]. Several lines of evidence implicate degeneration of cholinergic PPN projections to the thalamus in gait and balance disorders in PD. Our *in vivo* PET imaging findings are consistent with post-mortem results showing more severe PPN cholinergic cell losses in PD fallers compared to PD non-fallers [10]. A small placebo-controlled clinical trial showed that cholinesterase inhibitors reduced falls in frequently falling PD patients [11]. Recently, we showed that declining ability to integrate sensory information during postural control is specifically associated with PPN-thalamic cholinergic terminal losses but not BF-cortical cholinergic terminal losses in PD [12]. These data provide converging evidence for a role of cholinergic PPN neurons and their thalamic afferents in postural control and falls in PD.

In addition to the known efferent cholinergic projections from caudal PPN to thalamus, including to ventral anterior-ventral lateral thalamic relay nuclei in the cerebello-dentato-thalamocortical tract (reviewed in [2]), it is plausible that PPN cholinergic efferents may influence cerebellar function directly. A diffusion tensor MRI study of normal human subjects showed connectivity between PPN and the declive and folium regions of cerebellum [13]. The presence of afferents to PPN from deep cerebellar nuclei reinforces the notion of a functional connection between these structures [14]. PPN cholinergic efferents may function as the first link in a PPN-cerebellothalamic circuit, the degeneration of which may disrupt gait or balance by impairing directly the role of cerebellum in postural control. This direct impact on cerebellar function may synergize with the loss PPN-derived thalamic cholinergic innervation, which we found to correlate with defects in postural control in subjects with PD [12].

Preclinical studies provide further support for PPN cholinergic neuron degeneration in PD-related postural dysfunction [10]. It is remarkable that selective lesioning of PPN cholinergic neurons in the monkey can induce a parkinsonian syndrome with prominent balance and postural defects in the absence of nigral dopaminergic degeneration. Karachi and colleagues reported that MPTP induced clinical parkinsonism in both young and old monkeys, but postural deficits were exclusively observed in the older monkeys. Although nigral dopaminergic losses were similar between young and old MPTP-lesioned monkeys, loss of

PPN cholinergic neurons were seen exclusively in the older monkeys. In parallel experiments, isolated lesions of PPN cholinergic neurons induced components of a parkinsonian syndrome with prominent balance and postural defects despite preserved dopaminergic nigral neurons. Similar to the dopamine replacement resistant gait and posture deficits in PD, these parkinsonian features did not improve with dopaminergic replacement therapy. These cumulative data indicate that selective PPN cholinergic neuron degeneration in PD contributes to important motor deficits.

Progressive supranuclear palsy (PSP) is an atypical parkinsonian syndrome with severe dopamine replacement nonresponsive gait and balance impairments where patients have a much greater frequency of falls compared to PD. Cholinergic terminal PET imaging in PSP subjects indicates greater loss of thalamic cholinergic terminals in patients with PSP compared to PD [15]. These results are consistent with striking and severe loss of cholinergic PPN neurons in PSP [16]. The much higher incidence of falls in PSP compared to PD may be a correlate of more severe cholinergic PPN pathology in PSP [15].

Management of gait and balance impairments in PD represents a clinically unmet need as postural deficits are largely dopamine replacement therapy resistant and gait problems ultimately become resistant to dopaminergic replacement therapy. Recognition of the unique role of PPN cholinergic neurons and their thalamopetal projections in postural control and fall risk provides an opportunity to develop new therapeutic approaches for PD patients with these motor problems. As degeneration of PPN cholinergic neurons varies among PD patients [17], we suggest a personalized medicine approach to select hypocholinergic PD subjects for targeted cholinergic augmentation therapy. It is not yet clear what class of cholinergic drugs would be the best candidates for targeted therapies. Cholinesterase inhibitors showed modest efficacy in a small clinical trial in frequently falling PD subjects [11]. Penetrance of cholinesterase inhibitors into brain may be limited and may preclude a robust clinical response [18]. Targeting of nicotinic cholinergic receptors (nAChRs) may be a useful alternative approach. Increasing interest from the pharmaceutical industry in nAChRs has resulted in a considerable number of subtype specific nAChR agonists and antagonists [19]. α4β2 nAChRs are the most highly expressed nAChR subtype in brain and it is noteworthy that expression of α4β2 nicotinic receptors is most prominent in the thalamus [20]. This particular pattern of biodistribution raises the possibility that selective pharmacological targeting of α4β2 nicotinic receptors may act specifically on thalamic cholinergic synapses innervated by PPN cholinergic afferents. In this respect, it is also noteworthy that the midbrain and thalamus show prominent losses of this class of receptors in PD [20].

In summary, degeneration of PPN cholinergic neurons and their thalamic projections associates with the important clinical phenomena of RBD, falls, and abnormal sensory integration during postural control. These specific motor and non-motor features may be the clinical signature of a combined dopaminergic-brain cholinergic denervation phenotype in PD that is associated with increased risk of dementia. A subgroup of PD subjects with prominent cholinergic PPN neuron degeneration may be preferred targets for some form of cholinergic augmentation therapy to mitigate falls. The emergence of the cholinergic PPN-thalamus system as a brain center related to some of the disabling motor and non-motor

features of Parkinson's disease calls for new clinical trials using preferably nicotinic receptor agonist drugs in selected patients based on cholinergic hypofunction.

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