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Review

The cholinergic system and Parkinson disease

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ABSTRACT

Although Parkinson disease (PD) is viewed traditionally as a motor syndrome secondary to nigrostriatal dopaminergic denervation, recent studies emphasize non-motor features. Non-motor comorbidities, such as cognitive impairment, are likely the result of an intricate interplay of multi-system degenerations and neurotransmitter deficiencies extending beyond the loss of dopaminergic nigral neurons. The pathological hallmark of parkinsonian dementia is the presence of extra-nigral Lewy bodies that can be accompanied by other pathologies, such as senile plaques. Lewy first identified the eponymous Lewy body in neurons of the nucleus basalis of Meynert (nbM), the source of cholinergic innervation of the cerebral cortex. Although cholinergic denervation is recognized as a pathological hallmark of Alzheimer disease (AD), *in vivo* neuroimaging studies reveal loss of cerebral cholinergic markers in parkinsonian dementia similar to or more severe than in prototypical AD. Imaging studies agree with post-mortem evidence suggesting that basal forebrain cholinergic system degeneration appears early in PD and worsens coincident with the appearance of dementia. Early cholinergic denervation in PD without dementia appears to be heterogeneous and may make specific contributions to the PD clinical phenotype. Apart from well-known cognitive and behavioral deficits, central, in particular limbic, cholinergic denervation may be associated with progressive deficits of odor identification in PD. Recent evidence indicates also that subcortical cholinergic denervation, probably due to degeneration of brainstem pedunculopontine nucleus neurons, may relate to the presence of dopamine non-responsive gait and balance impairments, including falls, in PD.

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1. Introduction

Although Parkinson disease (PD) is viewed traditionally as a motor syndrome secondary to nigrostriatal dopaminergic denervation, recent studies emphasize non-motor features. Non-motor comorbidities, such as cognitive impairment, are explained better by multi-system neurodegeneration that extends beyond the loss of dopaminergic nigral neurons [73]. Several decades of neuropathology research has generated considerable evidence for altered cholinergic neurotransmission in PD, even in the absence of dementia. Lewy first identified the eponymous Lewy body in neurons of the nbM [77], the source of cholinergic innervation of the cerebral cortex. Cholinergic denervation may occur early in PD. In the Braak et al. staging scheme of PD pathology, nigral and basal forebrain pathology occur simultaneously [18]. More recently, neurochemical PET (positron emission tomography) and SPECT (single photon emission computed tomography) imaging studies have complemented neuropathology studies by allowing *in vivo* assessment of the regional distribution and quantitative measurement of cholinergic terminal markers or receptors in the brain of patients with PD or related syndromes. These imaging technologies offer the opportunity to study cholinergic innervation *in vivo* at early stages of PD and other neurodegenerative disorders.

2. Pathology of the cholinergic system in Parkinson disease and parkinsonian dementia

2.1. Cholinergic system anatomy and markers

There are three major sources of cholinergic projections in the brain. The basal forebrain complex provides the principal cholinergic input of the entire cortical mantle and degenerates in PD [91]. The pedunculopontine nucleus-laterodorsal tegmental complex (PPN-LDTC; hereafter referred to as the PPN), a brainstem center, provides cholinergic inputs to the thalamus, cerebellum, several brainstem nuclei, some striatal fibers, and the spinal cord [55]. The striatum contains a population of cholinergic interneurons. While striatal cholinergic interneurons are only a small fraction (1–2%) of striatal neurons, the high density of striatal cholinergic markers indicates a robust role for cholinergic neurotransmission in striatal function. Small populations of cholinergic neurons are present in the cortex, the medial habenula, and parts of the reticular formation [29,38,74,90].

Neurochemical, histochemical, immunohistochemical, and radiotracer imaging identification of cholinergic neurons and pathways depends on cholinergic neuron expression of proteins dedicated to acetylcholine synthesis, storage, and degradation. Acetylcholine is synthesized via acetylation of choline by the cytosolic enzyme Choline Acetyltransferase (ChAT) and then pumped into synaptic vesicles by the vesicular acetylcholine transporter (VAChT). After exocytosis, acetylcholine is degraded within the synapse by acetylcholinesterase (AChE) located on both pre- and postsynaptic membranes. The free choline can be recycled back into cholinergic neuron terminals via a plasmalemmal high affinity choline transporter. Cholinergic terminals also express some subtypes of nicotinic cholinergic receptors as presynaptic autoreceptors and ligand binding to these receptors has been used also as a marker for cholinergic terminals.

2.2. Early emphasis of the cholinergic pathology research paradigm on Alzheimer disease

Most of the original pathologic research on neurodegeneration of the cholinergic system in neurodegeneration was performed in AD. Substantial loss of cholinergic innervation in the cerebral cortex is accepted universally as an aspect of advanced AD [43]. Losses are most severe in the temporal lobes, including the entorhinal cortex, where up to 80% of cholinergic axons are depleted [44]. Depletion of cholinergic axons is associated with neurofibrillary degeneration and cell loss in the nbM [45]. Neuronal loss is most severe in the posterior sector of the nbM, where neurons preferentially innervating parts of the temporal lobes are located [45,91]. In contrast to the degeneration of the basal forebrain complex, the cholinergic innervation of the striatum (mainly originating from striatal interneurons) and of the thalamus (mainly originating from the brainstem) remain relatively intact. Therefore, there is no general cholinergic lesion in AD [89], but rather, selective cholinergic denervation of the cerebral cortex, most severe in the temporal lobes as well as in adjacent limbic and paralimbic areas [89]. Although the initial neuropathology studies indicated profound cortical reduction of ChAT activity and cholinergic nbM neuronal loss in patients with AD [16,27,105,136], more recent evidence indicates that cholinergic deficits are not severe in mild AD, and become significant only in more advanced stages of AD [28,30,94,128,129].

2.3. Cholinergic pathology in Parkinson disease and parkinsonian dementia

A key pathologic hallmark of PD is loss of midbrain dopaminergic neurons of the substantia nigra, pars compacta, and of their terminals in the striatum. In addition to the well-known reductions in dopamine, there is convergent evidence for early alterations in cholinergic neurotransmission in PD. Braak et al. note early accumulation of a-synuclein deposition within basal forebrain cholinergic neurons in PD, apparently coincident with the occurrence of Lewy bodies and neuronal loss in the substantia nigra [18].

2.3.1. Cholinergic forebrain pathology

Significant loss of nbM cholinergic neurons is reported in PD brains [19,97,111,126,134]. Arendt et al. found greater neuronal loss of nbM neurons in PD compared to AD [3], suggesting that cholinergic deficits may be at least as prominent in PD as in AD. Dysfunction of the basal forebrain cholinergic system is accompanied by a consistent loss of presynaptic cholinergic markers in cortex, sometimes accompanied by loss of muscarinic receptor binding sites. For example, muscarinic binding and ChAT activity are reduced in the pars compacta of the substantia nigra [112], hippocampus, and especially in the neocortex in PD [72].