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REVIEW

Pharmacotherapies for Parkinson's disease symptoms related to cholinergic degeneration

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ABSTRACT

Introduction: Dopamine depletion is one of the most important features of Parkinson's Disease (PD). However, insufficient response to dopaminergic replacement therapy suggests the involvement of other neurotransmitter systems in the pathophysiology of PD. Cholinergic degeneration contributes to gait impairments, cognitive impairment, psychosis, and REM-sleep disturbances, among other symptoms.

Areas covered: In this review, we explore the idea that enhancing cholinergic tone by pharmacological or neurosurgical procedures could be a first-line therapeutic strategy for the treatment of symptoms derived from cholinergic degeneration in PD.

Expert opinion: Rivastigmine, a drug that increases cholinergic tone by inhibiting the enzyme cholinesterase, is effective for dementia, whereas the use of Donepezil is still in the realm of investigation. Interesting results suggest the efficacy of these drugs in the treatment of gait dysfunction. Evidence on the clinical effects of these drugs for psychosis and REM-sleep disturbances is still weak. Stimulation of the pedunculo-pontine tegmental nuclei (which provide cholinergic innervation to the brain stem and subcortical nuclei) has also been used with some success for the treatment of gait dysfunction. Anticholinergic drugs should be used with caution in PD, as they may aggravate cholinergic symptoms. Notwithstanding, in some patients they might help control parkinsonian motor symptoms.

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1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder affecting about 1 person out of every 1000 in their fifth decade and 19 out of every 1000 in their eighth decade or older [1]. Its principal epiphenomenological clinical symptoms are abnormal involuntary movements, bradykinesia, rigidity, and tremor. Patients also frequently present non-motor symptoms, including cognitive impairment, mood disorders, sleep alterations, dysautonomia and hallucinations, among others [2].

Histopathological changes are mainly, but not exclusively, characterized by the progressive loss of the nigrostriatal dopaminergic pathway because of degeneration of dopaminergic neurons in the substantia nigra pars compacta, which explain the most typical motor symptoms [3]. Administration of levodopa to parkinsonian patients has been considered the most effective symptomatic treatment for the past 40 years [4].

Nigrostriatal cell loss may be related to loss of redox control, alteration of lysosomal activity, abnormal protein control mechanisms in the endoplasmic reticulum (ER), and perturbation of the ER-Golgi trafficking mechanisms. These cellular abnormalities are the main factors leading to abnormal accumulation of misfolded protein aggregates [5]. Lewy bodies constitute a characteristic pathological finding resulting from protein aggregation, second only to the neurofibrillary tangles in Alzheimer´s disease (AD). Early work suggested that Lewy bodies were mainly constituted by α-synuclein [6]. One major target of α-synuclein is Rab1, a key component of the endoplasmic ER-Golgi trafficking pathway [7]. It has been suggested that dysfunction of the endoplasmic reticulum due to stress might lead to an adaptive reaction known as the unfolded protein response [8]. When activated to a supraphysiological level, this response might be deleterious, triggering the apoptotic death of the damaged neuron [9,10].

There are many features of PD that are unresponsive to levodopa, such as gait disorders and cognitive impairment or dementia, indicating the involvement of other neurotransmitter systems [11]; in this context, recent evidence suggests that degeneration of adrenergic, serotoninergic, glutamatergic and cholinergic neurons, among others, may play a role [11].

Cholinergic dysfunction is a major feature of PD. For example, antagonists of the muscarinic acetylcholine receptors, derived from *Atropa belladonna*, were used to treat akinetorigid disorders in the XIXth century [12], well before recognition of the role of dopaminergic degeneration in PD and the use of dopaminergic agents. Indeed, acetylcholine dysfunction is involved in a myriad of PD symptoms [13]. The possibility of

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