The Putative Neuroprotective Role of Dopamine Agonists in Parkinson’s Disease

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INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disorder. It may affect up to 1.6% of the population over the age of 65 years (De Rijk et al., 1997). The classical clinical syndrome of PD consists of rest tremor, akinesia-bradykinesia, muscle rigidity, postural abnormalities and gait disturbances. These cardinal signs may lead to an important motor dysfunction, impairing markedly the quality of life of parkinsonian patients.

The pathologic picture of PD is characterized by degeneration of pigmented brainstem nuclei, especially the substantia nigra pars compacta, with loss of dopamine-containing neurons, and the presence of eosinophilic inclusions in the residual neurons. These inclusions, named Lewy bodies, are regarded as the pathological hallmark of PD. Within the substantia nigra pars compacta the cell loss is greater in the ventrolateral part (Fearnley and Lees, 1991) and appears to follow a spatiotemporal progression. A recent study has found, applying calbindin D28-K immunostaining to subdivide the substantia nigra pars compacta...
in calbindin-rich regions (matrix) and calbindin-poor pockets (nigrosomes), that the maximal neuronal depletion occurred in the main pocket (nigrosome 1), located in the caudal and medial part of this nucleus. Neuronal loss begins in nigrosome 1 and then spreads to other nigrosomes and matrix (Damier et al., 1999). The topographical selectivity and the orderly temporal progression of neuronal depletion suggests a differential neuronal vulnerability to the primary neurodegenerative process.

Loss of dopamine-containing neurons of substantia nigra results in a severe depletion of dopamine in the striatum, mainly in the putamen and the tail of the caudate nucleus. Some postmortem and functional neuroimaging studies have pointed out that the threshold for onset of clinical parkinsonian symptoms is around 30% loss of nigral dopaminergic cells (Fearnley and Lees, 1991; Morrish et al., 1995; Paulus and Jellinger, 1991), although other authors suggest a loss of around 60% (Riederer and Wuketich, 1976). Thus, PD has a preclinical phase which may last several years, before neurological signs become evident. This presymptomatic stage should be the main target for any neuroprotective therapy for this disorder.

PD is probably a multicausal disorder. Mutations in the α-synuclein gene have been found in several families in which the disease was inherited as an autosomal dominant trait (Kruger et al., 1998; Polymeropoulos et al., 1997), and mutations in the “parkin” protein gene have also been described in patients with autosomal recessive juvenile parkinsonism (Kitada et al., 1998). α-Synuclein may be relevant in the pathogenesis of PD, since this protein is located in Lewy bodies (Spillantini et al., 1997). Mutated α-synuclein can experience conformational changes which may lead this protein to aggregate to form insoluble fibrils (Borden, 1998).

However, α-synuclein mutations have not been detected in the majority of familial cases or in patients with sporadic PD, who are by far the largest proportion of PD cases. In these patients a combination of both genetic (still unknown) and environmental factors have been suggested as the most likely etiology. Nevertheless, although from epidemiological studies have emerged several potential environmental risk factors such as rural living, well-water consumption or exposure to pesticides, no specific agents have been yet identified (Langston, 1998).

PATHOGENESIS OF PARKINSON'S DISEASE

Whatever the cause or causes of PD are, they trigger a cascade of events that finally lead to the cell death of dopaminergic neurons of the substantia nigra pars compacta. It appears that a number of interacting processes are involved in nigral cell degeneration.

Oxidative Stress

The substantia nigra pars compacta seems to be particularly vulnerable to such process. Dopamine metabolism, especially its enzymatic oxidation by monoamine oxidase leads to the formation of hydrogen peroxide (H₂O₂) and other reactive oxygen species. In addition, dopamine autoxidation can lead to the formation of superoxide radicals and reactive quinones and semiquinones. Under normal conditions H₂O₂ is inactivated by catalase or by reduced glutathion in a chemical reaction catalyzed by glutathion peroxidase. However, H₂O₂ can react with iron, via the Fenton reaction, and form hydroxyl radicals.

Free radicals may damage lipids, proteins and DNA, potentially promoting the cell death (Wolf et al., 1986) and reactive oxygen species can signal the initiation of apoptosis (Ratan et al., 1994).

There are evidences which highlight the role of oxidative stress in the pathogenesis of PD. In postmortem studies it has been found in the substantia nigra of PD patients increased malondialdehyde (Dexter et al., 1986) and high levels of hydroperoxides (Dexter et al., 1994) suggesting lipid peroxidation.

There has also been described an increase of reactive carbonyles (Alam et al., 1997) and