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Progress in Neurobiology 81 (2007) 29–44

progress in Neurobiology

www.elsevier.com/locate/pneurobio

Advances in the treatment of Parkinson's disease

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Received 29 June 2006; received in revised form 14 November 2006; accepted 22 November 2006

Abstract

Parkinson's disease (PD) affects one in every 100 persons above the age of 65 years, making it the second most common neurodegenerative disease after Alzheimer's disease. PD is a disease of the central nervous system that leads to severe difficulties with body motions. The currently available therapies aim to improve the functional capacity of the patient for as long as possible; however they do not modify the progression of the neurodegenerative process. The need for newer and more effective agents is consequently receiving a great deal of attention and consequently being subjected to extensive research. This review concisely compiles the limitations of currently available therapies and the most recent research regarding neuroprotective agents, antioxidants, stem cell research, vaccines and various surgical techniques available and being developed for the management of PD.

Keywords: Parkinson's disease (PD); Current therapies; Neuroprotective agents; Non-pharmacological treatments; Drug delivery; Levodopa; Nicotine; PD vaccine; Cell transplantation

Contents

Abbreviations: PD, Parkinson's disease; DA, dopamine; MAO-B, monoamine oxidase-B; COMT, catechol-*O*-methyl transferase

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0301-0082/$ – see front matter
doi:10.1016/j.pneurobio.2006.11.009

1. Introduction

> 'Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects uninjured' (Parkinson, 1817).

Parkinson's disease (PD) or *Paralysis Agitans* was first documented in 1817 by Dr. James Parkinson as the ''shaking palsy'' that afflicted his gardener who led a life of ''sobriety'' (Critchley, 1955). Since then the relationship between personality and the potential for developing PD has been extensively investigated. The inverse relationship between the ''novelty-seeking'' personality (versus the law-abiding, contentious and cautious ''reduced-novelty seeking'' personality displaying a 'certain intellectual and moral rigidity' (Critchley, 1955)) and subsequent development of PD is widely documented (Benedetti et al., 2000). Smoking, alcohol, coffee, cocaine, amphetamine and opiate abuse have all been shown to have somewhat of a preventative effect in the onset of PD in the population (Paulson and Dadmehr, 1991; Menza et al., 1993; Fujii et al., 2000). As a direct paradox, to this phenomenon, currently prescribed drugs for managing this condition have now been demonstrated to have a link between patients seeking a ''reward-seeking'' lifestyle subsequent to initiating therapy (Uitti et al., 1989; Dodd et al., 2005; Klos et al., 2005; Stocchi, 2005). Such etiological data only confirms the pathological affliction associated with PD by depletion of the 'rewarding' dopaminergic neurons in the brain.

PD is a disease of the central nervous system (CNS) that leads to severe difficulties with body motions. Typical symptoms include tremor, rigidity, slowed body movements (bradykinesia), unstable posture and difficulty in walking (characterized by the patient's shuffling gait). To date PD remains an incurable disease. The currently available pharmacological and non-pharmacological treatments are able to offer only symptomatic relief for patients (Katzung, 2001). Available therapies aim to improve the functional capacity of the patient for as long as possible; however they do not modify the progression of the neurodegenerative process. The need for newer and more effective agents is consequently receiving a great deal of attention and consequently being subjected to extensive research, many of which are discussed in detail in this review.

In neuropathological terms, PD is characterized by the presence of intracytoplasmic inclusions from protein aggregates called Lewy bodies (LBs) (Burke, 1998) and the depletion of pigmented DA-containing neurons in the region known as the substantia nigra pars compacta (Forno, 1996). LBs consist of a heterogeneous mixture of proteins and lipids. The lipoidal core of these inclusions is surrounded by the peripheral filamentous elements which can comprise a variety of proteins, including ubiquitin, neurofilament, various proteasomal elements, and α-synuclein, which may be oxidatively modified (Fahn and Cohen, 1992; Zhang et al., 2000). Approximately 80% of dopaminergic neurons in the susbtantia nigra are already irreversibly destroyed when the first symptoms of PD become significantly visible.

Affecting one in every 100 persons above the age of 65 years, it is the second most common neurodegenerative disease after Alzheimer's disease (de Rijk et al., 2000). Apart from a documented relationship between personality-type, PD generally presents itself in the population as a sporadic condition. However an atypical presentation arising from gene defects inherited, by Mendelian trait have also been observed (Lev and Melamed, 2001; Vila and Przedborski, 2004). Among such inherited forms, abnormalities in the genes coding for the protein α-synuclein have been documented (Polymeropulous et al., 1997). Secondary causes of this condition include infection (post-encephalitic PD), drugs (e.g. antipsychotics such as haloperidol and thioridazine, antiemetics such as promethazine and metaclopramide (Standaert and Young, 2001)), chronic intoxication (among many substances, manganese and more rarely carbon bisulphide or carbon monoxide (Critchley, 1955) and stroke.

Over the past few decades a large volume of data generated from clinical studies, autopsies and *in vitro* and *in vivo* experimental models have been accumulated, which has allowed us to gain some understanding of the pathogenesis of sporadic PD. Studies that have investigated this multifactorial cascade have thus far been primarily, if not exclusively, studied in toxic experimental animal models of PD, in particular from models that have been produced by the parkinsonian neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Emborg, 2004).

Studies demonstrated that soon after the systemic administration of MPTP, its active metabolite, MPP^+, (1-methyl-4-phenylpyridinium ion) (Srivastava et al., 1993), concentrates in the mitochondrial matrix, where it binds to complex I of the electron transport chain (ETC) (Gluck et al., 1994). This binding interrupts the movement of electrons along the ETC, leading to an increased production of reactive oxygen species (ROS), particularly superoxide radicals (Fig. 1). This MPP^+-related disruption in electron flow is consequently associated with a drop in adenosine triphosphate (ATP) production. This phenomenon is found only in susceptible areas of the brain such as the ventral midbrain and striatum (Khan et al., 2005).