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Parkinson disease: primacy of age as a risk factor for mitochondrial dysfunction

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Abstract

In 1983, it was reported that certain drug users with a history of exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a contaminant of an illicitly produced meperidine analogue, developed an irreversible syndrome resembling idiopathic Parkinson disease (PD). Soon thereafter, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine's active metabolite, 1-methyl-4-phenylpyridine, was shown to be a complex I inhibitor. Activity of complex I (the point of entry for most electrons that traverse the mitochondrial electron transport chain) has been found to be impaired in the substantia nigra pars compacta and also in other brain tissues in PD patients. In 2006, high temporal and spatial resolution phosphorous functional magnetic resonance spectroscopy was used to demonstrate that, in 20 PD patients, mitochondrial dysfunction extended to the visual cortex. Epidemiologic studies have implicated a number of apparently disparate exogenous factors in the causation of PD. For example, exposure to certain pesticides and herbicides (many known to inhibit electron transport chain activity) increases PD risk. Parkinson disease risk can be doubled, tripled, or more in individuals with repeated head injuries. Over time, PD risk is almost doubled in men and women with prior type 2 diabetes mellitus. Nevertheless, despite evidence that certain exogenous and/or developmental factors play a role in causation of PD, their potential effect on PD incidence is greatly overshadowed by that of advancing age. In 1 prospective study, PD incidence rate in subjects at least 85 years old was about 14 times that observed in subjects aged 56 to 65 years. The dramatic effect of aging on PD risk may be explained in part by the fact that mitochondrial DNA deletions are abundant and cause functional impairment in aged human substantia nigra pars compacta neurons. High levels of these mutations are associated with electron transport chain deficiency, a situation that favors increased oxidative damage, Lewy body formation, and apoptotic cell death. Systematic study of the effects of putative risk factors in animal models of parkinsonism may be expected to improve our understanding of PD's complex pathogenesis.

1. Mitochondria: normal physiology and vulnerability

This review focuses on the contribution of certain putative Parkinson disease (PD) risk factors to the mitochondrial dysfunction that is associated with the illness. However, to be meaningful, any discussion of "dysfunction" requires, and should be preceded by, a brief consideration of the normal physiology of the mitochondria and the vulnerability of these complex organelles to endogenous or exogenous damage.

The mitochondria are tiny intracellular powerhouses that, collectively, provide the energy that makes metazoan life possible. They produce such energy by mitochrondial adenosine triphosphate (ATP) generation. The ATP is the energy currency that cells use to power their work. Mitochondrial ATP generation in neurons involves 3 distinct but coordinated processes: (1) degradation of certain nutrient fuels (glucose [via pyruvate] and/or ketones) to their 2-carbon intermediates, which then enter the Krebs tricarboxylic acid (TCA) cycle and are combusted to CO_2, with salvage of their reducing equivalents as mitochondrial reduced nicotinamide adenine dinucleotide (NADH), reduced flavoprotein, and H^+; (2) oxidation, with molecular oxygen, of these salvaged reducing equivalents to water in the mitochondrial electron transport chain (concurrently, a proton gradient is created across the membrane separating the mitochondrial intermembrane space and the matrix); and (3) reentry of protons into the negative intramitochondrial matrix phase through reversible F1 ATPase complex. One ATP is produced for each one-third turn of the ATPase and requires 4 protons per ATP and an augmented electrical

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potential between the mitochondrial matrix and intermembrane phases. The energy of ATP hydrolysis conforms to the Nernst potential energy between the matrix and intermembrane phases (Fig. 1).

Because of their high level of metabolic activity and complex structure, mitochondria, particularly as they age [1,2], are vulnerable to a variety of functional impairments, including those arising from either nuclear or mitochondrial DNA mutations, or from a host of exogenous factors such as drugs, infections, metabolic burdens (such as those imposed by obesity and type 2 diabetes mellitus), toxins, certain dietary factors, and episodes of cerebral hypoxia. Finsterer [3] has emphasized that tissues or organs with a high oxygen and energy demand, such as the brain, heart, liver, epithelium, gut, and renal tubules, are the ones predominantly affected by mitochondriopathies.

Damage to mitochondrial enzymes of the TCA cycle, mitochondrial membranes, or the electron transport chain—from whatever source—will ultimately interfere with the generation of ATP and either kill the cell or reduce its ability to function properly. If insufficient electrons are transferred via the chain to reduce molecular oxygen and form water, dangerous reactive oxygen species (ROS) such as the highly reactive hydroxyl radical are likely to be produced [4]. The rate of ROS formation may exceed the ability of enzymes such as superoxide dismutase, catalase, and other protective mechanisms to convert them to less reactive forms or render them harmless. Uncontrolled oxidative stress may then trigger sequences that result in excessive rates of programmed cell death [5,6].

2. Evidence for impaired electron transport chain function in PD

In 1983, it was reported that certain drug abusers with a history of exposure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, a contaminant of an illicitly produced meperidine analogue, developed an irreversible chronic syndrome resembling idiopathic PD [7]. Soon thereafter, it was demonstrated that 1-methyl-4-phenylpyridine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine's active metabolite, is a

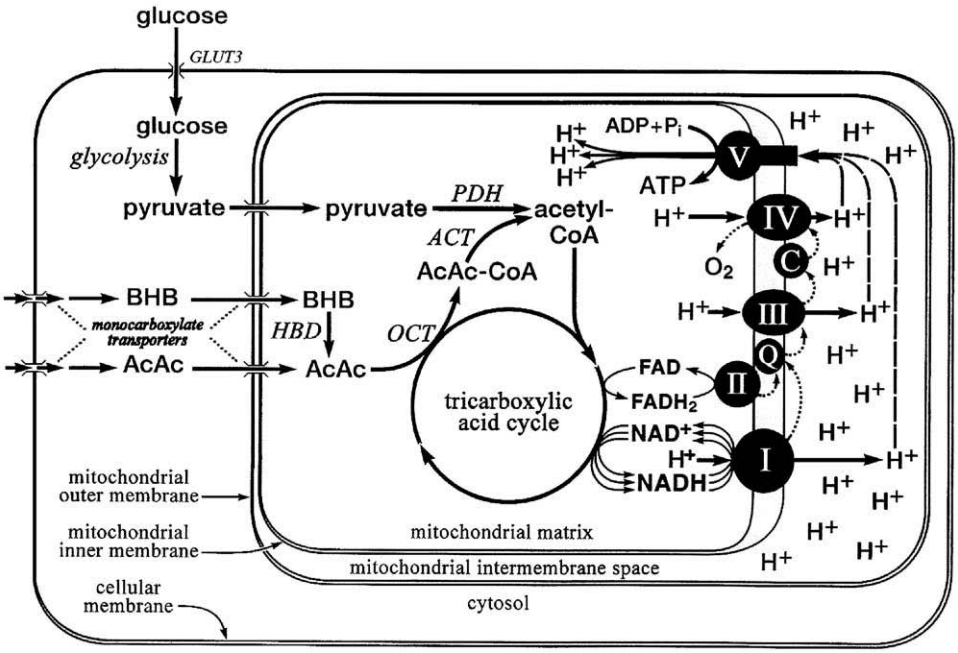

Fig. 1. Mitochondrial generation of ATP in a representative neuron. Acetyl-CoA undergoes oxidative degradation in the TCA (tricarboxylic acid) cycle with reduction of the electron carriers NAD + (nicotinamide adenine dinucleotide) and FAD (flavin adenine dinucleotide) to NADH and $FADH_2$, respectively. NADH and $FADH_2$ donate electrons to the protein complexes I (NADH-ubiquinone oxidoreductase) and II (succinate-ubiquinone reductase) of the mitochondrial electron transport chain. Energy derived from the transfer of electrons down the electron transport chain to oxygen (O2) is used by complexes I, III (Q-cytochrome c oxidoreductase [cytochrome reductase]), and IV (cytochrome c oxidase) to pump protons (shown as H+) out of the matrix into the intermembrane space, thereby generating a proton motive force (pmf) between the intermembrane space and the matrix. The pmf (reflecting the electrochemical proton gradient across the mitochondrial inner membrane) drives protons back through F1 ATP synthase (sometimes called complex V), thereby providing the energy to produce ATP from ADP (adenosine diphosphate) and Pi (inorganic phosphate). Glucose transporter protein type 1 (GLUT1) enables glucose transfer across the blood-brain barrier (BBB), being expressed at high levels in endothelial cells of the BBB. Because GLUT1 is consistently expressed at high levels in brain microvessel endothelial cells, it could affect access of glucose to neurons nourished by such microvessels. Glucose transporter protein type 3 (GLUT3) is the principal glucose transporter isoform in adult brain, being preferentially situated in neurons. Transfer of the ketone bodies (BHB and AcAc) across cell membranes is enabled by monocarboxylate transporters (MCTs). Abbreviations: BHB = β-hydroxybutyrate; AcAc = acetoacetate; HBD = β-hydroxybutyrate dehydrogenase; OCT = 3-oxoacid-CoA transferase; ACT = acetoacetyl-CoA thiolase; PDH = pyruvate dehydrogenase multienzyme complex. Adapted, with permission, from T. B. Vanltallie and T. H. Nufert. Ketones: Metabolism's Ugly Duckling, Nutrition Reviews 2002;61:327-41 (International Life Sciences Institute), and from S.W. Fowkes, who created and rendered the original figure.

complex I inhibitor [8]. Subsequently, it was found that, in idiopathic PD, there is a 30% to 40% decrease in complex I activity in the substantia nigra pars compacta (SNpc), a defect that could contribute to energy failure of the cell [9]. As shown in Fig. 1, complex I is the point of entry for most of the electrons that traverse the electron transport chain.

In 2006, Rango et al [10], using high temporal and spatial resolution ^{31}P functional magnetic resonance spectroscopy, demonstrated that, in the visual cortex of 20 PD patients, high-energy phosphates fell by an average of 36% in the recovery period after visual activation. In marked contrast, an equal number of non-PD control subjects exhibited a *rise* in high-energy phosphates in the visual cortex during the recovery phase. Rango and associates were the first to use an in vivo procedure to disclose impairment of mitochondrial function in PD patients. Their observations also showed that such dysfunction is not limited to the SNpc but can involve the visual cortex (and probably other parts of the brain) as well. Interestingly, with progression of the disease, there is a deterioration of color discrimination and contrast sensitivity in patients with PD [11].

As Finsterer [3] has emphasized, PD qualifies as a mitochondriopathy, given the evidence that, in this illness, complex I dysfunction is systemic [12].

3. Pathogenic role of exogenous factors

The evidence that developmental and/or exogenous factors might play a role in the pathogenesis of PD is largely epidemiologic in nature. Often, the clues provided by such studies are followed up in the laboratory or the clinic. Epidemiologic findings reported to date are quite heterogeneous. However, despite their apparently disparate nature, many of the exogenous "insults" implicated in the pathogenesis of PD share the common property of having a damaging effect on mitochondrial function. Examples of factors that may increase risk of developing PD are considered below.

3.1. Host factors

3.1.1. Familial PD

Most cases of PD are sporadic, with late onset. A small minority of PD cases are seen in family clusters [13]. Because of the likelihood that members of such family clusters have a genetic basis for their illness, genetic studies often target such individuals. Although the risk of developing PD is significantly increased among individuals with first- and second-degree relatives who have PD, families tend to share the same environment and lifestyle; therefore, environmental factors (like exposure to pesticides) may also contribute to PD aggregation in certain families [14].

3.1.2. Genetic determinants

Only a relatively small proportion of PD cases can be directly attributed to purely genetic factors. High levels of mitochondrial DNA deletions have been shown to be important in the selective SNpc neuronal loss in aging and PD cases [15]. By 2006, 11 forms of "familial Parkinson disease" had been mapped to different chromosomal loci, of which 6 genes were identified as being causative [16]. However, despite the difficulty in identifying genes that directly cause PD, genetic factors may well increase an individual's susceptibility to environmental toxins, various metabolic stresses, and other insults implicated in the phenotypic expression of PD.

3.1.3. Age

The prevalence of PD increases after the age of 50 years and accelerates dramatically between 65 and 90 years. Among those at least 65 years old, PD prevalence is much greater than that of the general population [17]. Five percent to 10 percent of patients have symptoms before the age of 40 years ("young-onset PD").

3.1.4. Sex

The disease occurs somewhat more frequently in men than in women [18].

3.1.5. Depression

Ishihara and Brayne [19] made a systematic review of depression and mental illness preceding PD. They found that premorbid depression was significantly more common in PD patients than in those without a diagnosis of PD in 5 of 6 case-control studies and 3 cohort studies.

3.2. Head trauma

Several studies have reported that episodes of head trauma in the past are associated with an increased risk of developing PD later. Risk may be doubled or tripled in individuals with repeated head injuries (eg, those related to boxing) [20] or in individuals whose head injury was severe enough to require hospitalization [21]. In a study of twins, one of whom experienced a head injury, Goldman et al [22] found a relative risk of 3.8 to be associated with head injury, with an increasing risk associated with more severe injuries.

3.3. Environmental toxins

Herbicides, pesticides, fungicides, and other chemicals used in agriculture may play a role in the pathogenesis of PD. There is evidence that PD prevalence is increased among people who have occupational exposure to herbicides and insecticides and to farming [14,23,24].

In addition to epidemiologic studies linking chronic exposure to pesticides, farming, well-water use, and rural living to increased PD risk, related laboratory investigations have implicated (in varying degrees) an array of agricultural chemicals as being capable of targeting and damaging the SNpc. Examples include the herbicide paraquat [25,26], the pesticide rotenone [24], the organophosphate pesticide parathion [23], and other less well-known pesticides [27]. Studies in mice have suggested that prenatal exposure to the pesticide maneb produces selective, permanent alterations of

the nigrostriatal dopaminergic system and enhances adult susceptibility to paraquat [28].

Iron is another putative environmental toxin implicated in the causation of PD. A consistent increase in SN iron has been reported to occur in cases of PD [29]. Iron deposits appear to be toxic to SNpc neurons and have been observed in conjunction with protein inclusions. Iron may cause synuclein aggregation (α-synuclein is a major constituent of Lewy bodies) because of its propensity to generate excessive or untoward ROS [30].

3.4. Metabolic factors

3.4.1. Type 2 diabetes mellitus and obesity

The finding in Finland that type 2 diabetes mellitus is a risk factor for PD [31] raises the suspicion that the chronic metabolic stress associated with the illness contributes to the PD development. Of 52 552 men and women 25 to 74 years of age, 633 (1.2%) developed PD over an 18-year follow-up period. After statistical adjustments for age, study years, and such known modifying factors as smoking status, coffee and alcohol consumption, and body weight, the 1098 men and women with prior diabetes were found to be 1.85 times more likely to develop PD than the 50 454 men and women without prior diabetes. In an earlier study, the same population had been used to demonstrate that *excess weight* (defined as a body mass index $\geq$23 kg/m^2) is associated with an elevated risk of PD [32].

3.5. Neuroinflammation

Whitton [33] has called attention to the fact that, in both PD patients and experimental models of PD, "…neuroinflammation appears to be a ubiquitous finding…with all the classic features of inflammation including phagocyte activation, increased synthesis and release of proinflammatory cytokines and complement activation." He theorizes that "…in the etiology of PD this process may spiral out of control with overactivation of microglia, overproduction of cytokines and other proinflammatory mediators, as well as the release of destructive molecules such as reactive oxygen species. Given that dopaminergic neurons in the SNpc are relatively vulnerable to 'stress' and the region has a large population of microglia in comparison with other CNS structures, these events may easily trigger neurodegeneration."

Some support for the notion that inflammation is involved in the causation of PD may be found in reports that individuals who take the nonsteroidal anti-inflammatory drug ibuprofen appear to have a reduced incidence of PD [34].

3.6. Neuroprotective factors

There is insufficient space in this review to consider in any detail several factors that have been reported to give some protection against PD, such as tobacco use [35], caffeine consumption [36], an elevated plasma urate concentration [37], and a high level of physical exercise in the early years [38].

4. The overarching effect of advancing age on PD risk

Despite growing evidence that impairment of the mitochondria's energy-generating machinery contributes to the etiology of idiopathic PD, the importance of environmental and developmental factors in the pathogenic process remains uncertain. There are at least 3 reasons for this uncertainty: (*a*) a number of disparate environmental factors have been implicated in the causation of PD, providing an overall epidemiologic picture that lacks coherence and consistency; (*b*) no one environmental factor appears to be able to account for more than a small proportion of sporadic PD cases; and (*c*) much of the epidemiologic evidence that implicates certain environmental factors in the causation of PD is preliminary, unconfirmed, and lacking in the kind of corroborative support that can be provided by appropriate laboratory and clinical investigations.

When one considers the possible role of various exogenous and/or developmental factors in the development of PD, their quantitative effect on PD incidence—even if the claims for their importance are taken at face value—is greatly overshadowed by that of advancing age. In 1 prospective study of a population followed in the Netherlands (the Rotterdam Study), the PD incidence rate in subjects 85 years and older was found to be about 14 times that observed in subjects aged 56 to 65 years [39]. In a study of the brains of individuals without apparent PD, Gibb and Lees [40] determined that the age-specific prevalence of Lewy bodies—an important diagnostic feature of typical PD—increased from 3.8% to 12.8% between the sixth and ninth decades. According to Lang and Lozano [6], the pathologic changes associated with this "incidental Lewy-body disease" look very much like a presymptomatic stage of PD. If this interpretation is correct, subclinical PD in the aging population is much more pervasive than previously estimated.

In the attempt to explain why the prevalence of PD increases so rapidly during the 3 decades after the age of 60 years, one has to ask whether aging by itself can explain most—if not all—aging-related PD or whether aging makes the mitochondria increasingly vulnerable to environmental toxins and other factors that might contribute to the impairment of SNpc mitochondrial function.

There have been many attempts to explain why a decline in mitochondrial function occurs with aging. The problem has not been resolved; however, it has been reported that mitochondrial deletions are abundant and cause functional impairment in aged human substantia nigra neurons [15,41].

A major goal in PD research is to determine why some individuals are more susceptible than others to the illness. Is such susceptibility primarily an inherited trait, or does it result from some kind of interaction between susceptibility genes and an effect (for example) of aging-associated oxidative damage to the mitochondria? What proportion of cases of sporadic PD can one attribute to risk factors such as

exposure to insecticides, transition metals, "metabolic stress," and episodes of brain hypoxia? Are there vulnerabilities to demonstrated risk factors that can be identified; and if so, are there measures that can be taken to reduce risk?

In conclusion, given the association of PD with type 2 diabetes mellitus, obesity, neuroinflammation, and impaired mitochondrial function, PD may now be considered to be a manifestation of a disordered cerebral metabolism, with pathologic features that extend well beyond the region of the SNpc. Aging-associated impairments in mitochondrial function appear to play the dominant role in PD's pathogenesis; however, a number of different exogenous and developmental factors appear capable of contributing (singly or in concert) to the SNpc dopaminergic neuronal damage and death that, in susceptible individuals, could result in the emergence of clinically manifest PD. Appropriate clinical and epidemiologic investigations, together with a systematic examination of the effects of implicated exogenous and developmental factors in in vitro preparations and animal models of parkinsonism, can be expected to continue to improve our understanding of the complex pathogenesis of idiopathic PD.

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