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ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

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NAD METABOLISM IN THE PATHOPHYSIOLOGY AND THERAPY OF PARKINSON'S DISEASE

Illia Koval *(Corresponding Author, Email: illiakoval.pl@gmail.com)*
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0002-1109-6354

Klaudia Romejko
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0003-6452-1323

Barbara Kujawa
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0000-3951-965X

Jagoda Saniuk
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0006-3193-8634

Sandra Sienkiewicz
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0000-0002-4454-9498

Justyna Rajczyk
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0003-1307-931X

Weronika Kielińska
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0009-0006-4901-0332

Joanna Osmólska
Provincial Hospital in Poznań, Poznań, Poland
ORCID ID: 0000-0002-8754-7222

Michał Dorota
Central Clinical Hospital of the Medical University of Lodz, Lodz, Poland
ORCID ID: 0009-0008-7481-0045

Kacper Wojtala
Medical Center HCP, Poznań, Poland
ORCID ID: 0009-0009-8100-8074

ABSTRACT

This paper explores the rapidly increasing incidence of Parkinson's disease (PD) and the limitations of current dopamine-based therapies, which only address symptoms rather than underlying causes. This has spurred research into novel treatment approaches rooted in the disease's pathophysiology. A key pathological hallmark of PD is mitochondrial dysfunction, particularly affecting complex I, a critical component of cellular energy metabolism. This discovery has directed investigations toward individual elements of mitochondrial pathways, including the NAD+/NADH redox balance. Studies indicate reduced NAD+ levels in the brains of individuals with PD, prompting research into the therapeutic effects of NAD+ supplementation. This review summarizes recent scientific findings on how augmenting NAD+ and its derivatives may influence Parkinson's disease. It discusses the impact of NAD+ precursor supplementation on mitochondrial function and NAD+ levels in neurons carrying the GBA mutation. The paper also covers defects in PINK1 expression, their link to PD development, and the potential role of Nicotinamide (vitamin B3) in this context. Additionally, it assesses the safety of oral NAD+ precursor supplementation and its effects on brain NAD+ levels and metabolism in PD patients. A deeper understanding of PD pathophysiology and continued research into raising NAD+ levels are vital for developing novel therapeutic strategies. Modulating NAD+ holds significant promise as a supportive or disease-modifying therapy for this neurodegenerative condition.

KEYWORDS

Parkinson Disease, Nicotinamide Adenine Dinucleotide, Mitochondria, Complex I, Nicotinamide Riboside, PINK1 Protein, Human, GBA Gene, Neurodegenerative Diseases, Oxidative Stress, Mitochondrial Dysfunction

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Introduction & Background

Parkinson's disease (PD) is the world's fastest-growing neurodegenerative disorder, with projections indicating that the number of affected individuals will double from 6 million in 2015 to 12 million by 2040 [1]. In most populations, 3 to 5% of Parkinson's disease cases are caused by genetic mutations in single genes associated with the disease, which is defined as the monogenic form. In contrast, about 90 genetic variants collectively account for 16-36% of the hereditary susceptibility to the non-monogenic form. Additional factors that increase the risk of developing the disease include: having a close relative with Parkinson's disease or essential tremor, chronic constipation, and not smoking tobacco - each of these factors at least doubles the risk of the disease [2]. Despite its prevalence, current therapeutic strategies are fundamentally limited. Standard treatments, such as levodopa, function by replenishing dopamine levels in the brain, effectively alleviating motor symptoms like tremors and rigidity. However, these therapies are purely symptomatic; they do not slow or halt the progressive underlying neurodegeneration that defines the disease [3]. This critical therapeutic gap-the absence of a disease-modifying treatment-has created an urgent need for new approaches that target the root causes of PD. Consequently, research has shifted focus toward the core pathophysiological mechanisms driving the disease. These include oxidative stress, protein aggregation (notably of alpha-synuclein), impaired autophagy, and neuroinflammation [4]. Central to these interconnected pathways is the dysfunction of mitochondria, the organelles that function as the cell's "power plants." Neurons, with their high energy demands, are exceptionally vulnerable to mitochondrial failure. The first reports linking mitochondrial impairment to PD emerged in 1989, demonstrating a deficiency of mitochondrial complex I in the brains of patients [5]. Properly functioning mitochondria are responsible for the process leading to the formation of ATP (adenosine triphosphate), thus playing a crucial role in the cell's energy supply. During the process of oxidative phosphorylation leading to ATP synthesis, metabolites generated by the tricarboxylic acid cycle (Krebs cycle) are utilized via the electron transport system, also known as the respiratory chain [6].

Review

Methods

A literature search was conducted using the PubMed, Scopus, and Google Scholar databases for articles published between January 2010 and October 2023. The search strategy combined keywords related to Parkinson's disease (e.g., "Parkinson's disease," "parkinsonism") with terms related to NAD+ metabolism (e.g., "NAD+," "nicotinamide adenine dinucleotide," "nicotinamide riboside," "NR," "NMN," "niacin") and pathophysiology (e.g., "mitochondria," "Complex I," "GBA," "PINK1"). Foundational and highly cited articles published before this period were also included for historical context. Studies were included if they were original research articles (in vitro, animal models, or human clinical trials) or review articles published in English in peer-reviewed journals. Priority was given to studies that directly investigated the link between NAD+ metabolism and PD pathology or tested the effects of NAD+ precursor supplementation. Case reports, conference abstracts, and non-peer-reviewed articles were excluded.

As this is a narrative review, a formal meta-analytic risk of bias assessment was not performed. However, the findings from selected studies were critically evaluated, considering study design, sample size, and the statistical significance of the reported outcomes. A clear distinction between preclinical evidence and human clinical data is maintained throughout the review.

Mitochondrial Dysfunction as a Central Hub in PD Pathogenesis

Mitochondria are responsible for producing the vast majority of cellular ATP (adenosine triphosphate) through a process called oxidative phosphorylation. This process utilizes metabolites generated by the tricarboxylic acid (Krebs) cycle via the electron transport chain (ETC) [6]. The first and often rate-limiting enzyme in this chain is Complex I, which serves as the main entry point for electrons into the ETC. It is a large multi-subunit enzyme crucial for cellular respiration and energy production, and its dysfunction is increasingly recognized in various neurodegenerative conditions beyond Parkinson's disease [7]. It functions by oxidizing NADH, releasing energy that is used to pump protons from the mitochondrial matrix to the intermembrane space. This action generates a proton motive force that ultimately drives ATP synthesis. An indirect but vital result of this process is the regeneration of oxidized NAD+, which is then available for subsequent metabolic reactions. The deficiency of mitochondrial complex I in PD, first described by Schapira et al. [5], has been documented extensively over the years and is considered a key biochemical hallmark of the disease [8]. The pathophysiological relevance of this finding was powerfully demonstrated in an in vivo model using rotenone, a known inhibitor of complex I. Recent research continues to leverage models of mitochondrial complex I inhibition to elucidate mechanisms of neurodegeneration and evaluate potential therapeutic interventions for PD, highlighting its ongoing significance in the field [9]. These studies solidified mitochondrial dysfunction, particularly of complex I, as a critical starting point for investigating the pathogenesis and potential therapies for PD.

The NAD+/NADH Redox Couple: A Critical Bioenergetic Sensor

Maintaining cellular energy balance is a primary role of mitochondria, making the homeostasis of metabolites involved in their reactions crucial. The intricate interplay between mitochondrial function and cellular metabolism underscores the importance of various factors, including the precise regulation of reactive oxygen species (ROS) and antioxidant systems, in maintaining overall cellular health and preventing pathological states [10]. A key aspect of this homeostasis is the NAD+/NADH ratio, which reflects the cell's redox state. NAD is a coenzyme essential for hundreds of metabolic reactions, existing in two forms: oxidized (NAD+) and reduced (NADH) [11, 12]. NAD pools are maintained in the body through endogenous synthesis from dietary niacin or through recycling from metabolic pathways [13]. Numerous studies suggest that NAD+ metabolism is deeply intertwined with brain aging and neurodegeneration, with evidence of an age-dependent decline in brain NAD+ concentrations and further reductions in neurodegenerative diseases like PD [14].

Parkinson's Disease Associated with a Mutation in the GBA Gene

The most significant genetic risk factor for Parkinson's disease is a mutation in the GBA1 gene, which encodes the lysosomal enzyme β-glucocerebrosidase (GCase) [15]. A mutated GCase impairs chaperone-mediated autophagy, a cellular waste-clearing process, leading to the accumulation of toxic substrates, including alpha-synuclein [16]. A pivotal study by Schöndorf et al. investigated the link between GBA mutations, mitochondrial function, and NAD+ metabolism [17]. Using neurons derived from PD patients with a GBA mutation, they observed impaired mitochondrial morphology and function, alongside significant reductions in key elements of NAD+ metabolism. To test if these defects could be reversed, they administered

the NAD+ precursor nicotinamide riboside (NR). NR supplementation significantly increased both NAD+ and NADH levels in the patient-derived neurons. Consequently, mitochondrial mass increased and mitochondrial function improved. To validate these findings in vivo, the researchers used a Drosophila (fruit fly) model carrying a human GBA mutation. These flies exhibited age-dependent loss of dopaminergic neurons and progressive motor deficits. Feeding the flies NR significantly prevented this neuronal loss and the decline in climbing ability compared to untreated controls [17]. This study provides a compelling preclinical rationale for testing NR supplementation in humans with PD, particularly those with GBA mutations.

ATP and NAD+ Deficiency in Parkinson's Disease

Mounting evidence suggests that PD is a systemic metabolic syndrome rather than a disease confined to the brain. A study by Mischley et al. investigated bioenergetic markers in the muscles of individuals with mid-stage PD [18]. They found that people with PD had significantly lower maximal mitochondrial ATP production (ATPmax) and reduced NAD levels in their leg muscles (tibialis anterior) compared to age- and sex-matched controls. Furthermore, muscular endurance and strength were lower in both hand and leg muscles of the PD cohort. This research underscores that energetic deficits are present in peripheral tissues and suggests that skeletal muscle mitochondrial function could serve as a valuable biomarker for understanding disease mechanisms and guiding clinical management [18].

The Role of PINK1 in the Development of Parkinson's Disease

Mutations in the PINK1 and PARKIN genes are responsible for over 50% of autosomal recessive juvenile parkinsonism cases [19]. The PINK1 protein is a kinase that plays a critical role in mitochondrial quality control, primarily by initiating mitophagy-the selective degradation of damaged mitochondria. The loss of PINK1 function leads to the accumulation of defective mitochondria, which generate excessive reactive oxygen species and ultimately trigger the death of dopaminergic neurons [20]. Research by Lehmann et al. has shown that enhancing the NAD+ salvage pathway can be neuroprotective in a PINK1 model of PD [20]. Other studies suggest that nicotinamide (vitamin B3), another NAD+ precursor, can increase the activity of the PINK1 signaling pathway, potentially reducing nerve cell damage [21]. This line of evidence indicates that boosting NAD+ levels may offer a therapeutic benefit by compensating for defects in mitochondrial quality control pathways.

NADPARK study and NOPARK study

Brakedal et al.'s research focused on determining whether adjuvant therapy with nicotinamide adenine dinucleotide (NAD) via oral nicotinamide riboside (NR) is safe, increases NAD levels in the brain, and influences cerebral metabolism in Parkinson's disease (PD). A double-blind, phase I clinical trial was conducted in which thirty newly diagnosed, previously untreated patients received 1000 mg of NR or placebo for 30 days. The clinical trial determined that orally administered NR is safe, leads to increased NAD levels in the brain, and also alters cerebral metabolism in PD patients. Cerebral penetration was further confirmed by detecting an increase in the metabolite Me-2-PY in the cerebrospinal fluid of participants receiving NR. Nicotinamide riboside increased NAD metabolism and the expression of genes related to mitochondrial, lysosomal, and proteasomal function in blood and muscle, and also reduced inflammatory cytokine levels in serum and CSF. Phosphorus 31-magnetic resonance spectroscopy detected a significant increase in brain NAD levels. However, this effect was not present in all patients in the NR group. Three patients demonstrated a metabolic response only in CSF, blood, and muscle, with no evidence of an increase in brain NAD. Despite the variable effect of supplementation on brain NAD, this study confirms treatment compliance and the impact on the NAD metabolome. The variable brain NAD response likely reflects interindividual variability in brain NAD metabolism as well as the limited sensitivity of NAD measurement by MRS, with increases occurring below the detection limits of the method. The findings of Brakedal et al. indicate that assessment of NAD levels in the brain may be an important monitoring parameter in clinical trials evaluating NR supplementation in brain health and disease. Furthermore, it was shown that an increase in NAD levels in the brain was indeed associated with neurometabolic and clinical response in patients. The study results undoubtedly justify further testing in a much larger number of PD patients [22]. The NOPARK study is a randomized, double-blind, placebo-controlled phase III clinical trial designed to determine whether high-dose NR (1000 mg daily) delays progression of Parkinson's disease, as measured by change in the MDS-UPDRS scale over 52 weeks. The study design assumed the participation of 400 patients with early-stage Parkinson's disease (diagnosed within two years before the study) and their randomization to receive NR or placebo, followed by one year of follow-up. It was also planned to collect biological material from the participants to check whether nicotinamide riboside supplementation corrects NAD deficiency and affects its metabolism [23].

Nicotinamide riboside supplementation and safety

Nicotinamide riboside (Niagen, NR) is a naturally occurring form of vitamin B3, composed of nicotinamide and ribose. Studies have shown that supplementation with this vitamin is effective and safe. The first study assessed changes in the weight of organs such as the liver, kidneys, and brain, and histological analysis of these tissues, except the brain, was performed. During this study, no treatment-related mortality or adverse effects were observed after a single dose of 5000 mg/kg of Niagen. A different effect (adverse effects) was achieved at a dose of 1000 mg/kg/day; they were not observed at a dose of 300 mg/kg/day [24]. In the second randomized, double-blind, placebo-controlled clinical trial, participants received either Niagen (500 mg, twice daily) or placebo for 6 weeks, followed by a reverse treatment regimen. The results of this study indicate that Niagen is very well tolerated and increases NAD levels in the blood of patients. The best effects were observed in middle-aged and older subjects compared to the placebo group [25]. The third, randomized, double-blind, placebo-controlled study conducted by Elysium Inc. enrolled 120 healthy older patients (60-80 years old) to evaluate the safety of Basis-NRPT (NR + pterostilbene). Subjects receiving standard doses of Basis for one month experienced a 40% increase in NAD levels in their blood. Those receiving double the recommended doses of Basis experienced a 90% increase [26]. Considering the above, nicotinamide riboside supplementation demonstrates high efficacy and safety. Due to the pathophysiology of Parkinson's disease, a vitamin B3 derivative could be more widely used in the treatment of this pathology.

Conclusions

This review highlights the critical importance of understanding the pathophysiology of Parkinson's disease. Knowledge of the molecular mechanisms driving neurodegeneration has enabled the investigation of therapies, such as NAD+ precursor supplementation, that directly target brain metabolism. As the presented studies demonstrate, nicotinamide and nicotinamide riboside show significant potential, protecting dopaminergic neurons in preclinical models and favorably influencing NAD+ metabolism in human-derived cells. These findings provide a strong foundation for further research in this area.

However, clinical research into the efficacy and safety of NAD+ precursors in PD patients is still in its early stages. While some results are promising, larger, placebo-controlled clinical trials are necessary to definitively clarify their therapeutic value. It is important to note that while these compounds are available as over-the-counter supplements, they should not be used for therapeutic purposes without medical consultation due to potential side effects and drug interactions. Mitochondria are the powerhouses of the cell, and the biomolecule NAD+ is a key component of their energy production process. Given that mitochondrial dysfunction and the resulting oxidative stress are fundamental drivers of Parkinson's disease, improving mitochondrial health represents a highly promising therapeutic avenue. Modulating NAD+ levels targets the very core of this cellular energy crisis, offering hope for the development of a truly disease-modifying therapy for this devastating condition.

Disclosures

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Illia Koval, Klaudia Romejko, Barbara Kujawa, Jagoda Saniuk, Sandra Sienkiewicz, Justyna Rajczyk, Weronika Kielińska, Joanna Osmólska

Acquisition, analysis, or interpretation of data: Illia Koval, Klaudia Romejko, Barbara Kujawa, Jagoda Saniuk, Sandra Sienkiewicz, Justyna Rajczyk, Weronika Kielińska, Joanna Osmólska

Drafting of the manuscript: Illia Koval, Klaudia Romejko, Barbara Kujawa, Jagoda Saniuk, Sandra Sienkiewicz, Justyna Rajczyk, Weronika Kielińska, Joanna Osmólska

Critical review of the manuscript for important intellectual content: Illia Koval, Klaudia Romejko, Barbara Kujawa, Jagoda Saniuk, Sandra Sienkiewicz, Justyna Rajczyk, Weronika Kielińska, Joanna Osmólska

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