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NAD^+ metabolism and retinal degeneration (Review)

ANDREEA SILVIA PÎRVU[1*], ANA MARINA ANDREI[2], ELENA CAMELIA STĂNCIULESCU[2*], ILEANA MONICA BANIȚĂ[3], CĂTĂLINA GABRIELA PISOSCHI[2*], SANDA JURJA[4*] and RADU CIULUVICA[5]

[1]Department of Biochemistry, Faculty of Medicine; [2]Department of Pharmaceutical Biochemistry, Faculty of Pharmacy; [3]Department of Histology, Faculty of Dentistry, University of Medicine and Pharmacy of Craiova, 200349 Craiova; [4]Department of Ophthalmology, Faculty of Medicine, 'Ovidius' University of Constanta, 900527 Constanta; [5]Faculty of Dentistry, 'Carol Davila' University of Medicine and Pharmacy, 050474 Bucharest, Romania

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Abstract. The recent years has revealed an intense interest in the study of nicotinamide adenine dinucleotide (NAD^+), particularly in regards to its intermediates, such as nicotinamide and nicotinic acid known as niacin, and also nicotinamide riboside. Besides its participation as a coenzyme in the redox transformations of nutrients during catabolism, NAD^+ is also involved in DNA repair and epigenetic modification of gene expression and also plays an essential role in calcium homeostasis. Clinical and experimental data emphasize the age-dependent decline in NAD^+ levels and its relation with the onset and progression of various age-related diseases. Maintaining optimal levels of NAD^+ has aroused a therapeutic interest in such pathological conditions; NAD^+ being currently regarded as an important target to extend health and lifespan. Based on a systematic exploration of the experimental data and literature surrounding the topic, this paper reviews some of the recent research studies related to the roles of the pyridine nucleotide family focusing on biosynthesis, NAD^+ deficiency-associated diseases, pathobiochemistry related to retinal degeneration and potential therapeutic effects on human vision as well.

Contents

Correspondence to: Dr Ana Marina Andrei, Department of Pharmaceutical Biochemistry, Faculty of Pharmacy, University of Medicine and Pharmacy of Craiova, 2-4 Petru Rareș Street, 200349 Craiova, Romania
E-mail: marinafusaru@yahoo.com

*Contributed equally

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1. Introduction

Nicotinamide adenine dinucleotide (NAD^+) is considered the precursor for the pyridine nucleotide family constituted by NADH and two phosphorylated forms, nicotinamide adenine dinucleotide phosphate in its oxidized ($NADP^+$) and reduced (NADPH) forms (1). All of these nucleotides are well-known cofactors in numerous cellular processes. NAD^+ is the substrate for major redox transformations of nutrients during the catabolic phase of metabolism. Its reduced form, NADH, is the main source of electrons for mitochondrial oxidative chain and production of adenosine triphosphate through oxidative phosphorylation. NAD^+ is also involved in DNA repair, as a substrate for poly(ADP-ribose) polymerases (PARP) (2), epigenetic modification of gene expression, also having an important influence on immunological function (3). NAD^+ also has a critical role in calcium homeostasis, as the substrate for NAD^+ glycohydrolases, enzymes related to the production of cyclic ADP-ribose, a calcium efflux effector (4).

Since the original discovery of NAD^+ by Harden and Young in 1906 in cell-free yeast juices as a factor that enhanced the rate of fermentation, many studies have been developed to reveal the NAD^+ biosynthetic pathway as a key player in cellular metabolism (5). NAD^+ is currently regarded as an important target with which to extend lifespan and health span. Accurate evaluation of the NAD^+ metabolome is of great interest due to its association with cognitive impairment, cancer, normal aging and age-related disorders (1).

Research conducted to date has elucidated the signaling pathways and cellular processes that contribute to the maintenance of pyridine nucleoside and nucleotide homeostasis; the regulation of molecular mechanisms underlying NAD^+ metabolism is known but the use of its precursors in therapy are still incompletely explained.

2. NAD+ biosynthesis, metabolism and effects on the human body

NAD+ biosynthesis in mammals involves five important intermediates including tryptophan, niacin, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), through three biosynthetic pathways: i) Nucleotide salvage from nicotinamide (NAM), NR and NMN; ii) *de novo* synthesis from tryptophan and iii) Preiss-Handler pathway from nicotinic acid (NA) (6).

In mammals, the salvage pathway is the major route to generate NAD+. Conversion of NMN, one of the forms of the water-soluble vitamin B3, to NAD+ is catalyzed by nicotinamide mononucleotide adenylyltransferase (Nmnat) (Fig. 1). NMN can be synthesized by nicotinamide phosphoribosyltransferase (Nampt) from NAM. Bieganowski and Brenner revealed an alternative NAD+ salvage biosynthesis pathway, in which NR, another form of vitamin B3 that enters cells through nucleoside transporters, could be converted to NAD+ by nicotinamide riboside kinases (NMRK1 and NMRK2) and Nmnat via phosphorylation reactions (7).

In recent years, NMN and NR have been extensively investigated in various experiments on rodents and humans and evidence suggests that with age NAD+ levels decline at a systemic level (8,9), causing profound metabolic changes (10). These precursors of NAD+ have an essential influence on the elevation of NAD+ concentration in a variety of tissues, automatically suggesting a beneficial therapeutic effect (8,11,12).

The metabolic balance of NAD+ in the cellular environment can be accomplished in several ways and involves multiple metabolites in an oxidized and reduced form such as NADP+, NADH, NADPH, and nicotinic acid adenine dinucleotide phosphate (NAADP), all with an essential role in energy production and cellular metabolism, acting as one proton-accepting or donating coenzymes. NAD+ derivatives are important for regulating cellular redox status, intracellular Ca^{2+} pools, DNA damage and repair, cell cycle timing and lipid and energy metabolism (13). NAD+ is a major cofactor for mitochondrial ATP production and for NAD-dependent enzymes including sirtuins and poly-ADP-ribosylpolymerases, essential players in fundamental processes such as cell division and proliferation, apoptosis, aging, senescence and stress resistance (14). Lin and Guarente argued that sirtuins can sense the NADH/NAD+ ratio in cells by the recognition of the oxidized dinucleotides, but it seems that other cellular factors also respond to the alterations within NADH levels (15).

For many years it was believed that NAD+ breakdown is a nonspecific process but in the last decade evidence has shown that NAD+ consumption is linked with the signaling reactions inside and outside the cells (16). For example, the oxidation of glucose and fatty acids lead to the reduction of oxidized NAD+ to NADH and alterations in its concentration were found to be involved in multiple pathogenic signaling pathways, including heart failure (17). The last two decades generated multiple discoveries regarding NAD+ and its precursors, identifying the important role in DNA repair, immune activation and epigenetic control through protein deacetylation (3). Even if the metabolism of NAD+ has been the subject of numerous research studies in various cells, tissues, and organs, those regarding pyridine nucleotide metabolism in eye structures and its involvement in visual dysfunctions are scarce.

3. Diet and NAD+ level

Dietary supplementation is the only way to increase body NAD+ levels. Since NAD+ administration is not efficient enough to increase NAD+ levels, its precursors, such as NAM and NA known as niacin, NMN and NR could be useful to increase NAD+ levels in animal models and humans (18).

Most raw foods provide these substances which can regulate cellular activities and the timing of changes that lead to aging phenotypes (13). Another important precursor of NAD+ is the amino acid tryptophan which is synthetized via the kynurenine pathway. While NR is the form of vitamin B3 found in humans and cow milk and other foods, NA is produced by plants and algae, and tryptophan is the most abundant amino acid found in animal and plant proteins (19).

Many of the biochemical studies performed recently have shown that a poor diet lacking niacin and tryptophan intake or a chronic immune activation can lead to inefficient production of NAD+, where catabolism exceeds anabolism producing a consequent cellular dysfunction (20). By contrast, a reduced energy load due to activities such exercise, calorie restriction, fasting and glucose deprivation can increase the concentration of NAD+ (8).

Although studies on rodents have shown that both NMN and NR enhance NAD+ biosynthesis and have beneficial effects in multiple disorders (21-23), it still remains unclear what mechanisms mediate their beneficial effect. Presently, the pharmacokinetics and metabolic fates of NAD+ precursors are still under investigation, multiple human clinical trials being conducted to study and understand the safety of NAD+ precursor supplementation, mainly NR and NMN (24-26). The concentrations of NAD+ and NAM in blood are in the micromolar range and can be boosted by oral administration of their precursors, NR and NMN. In their study, Trammell *et al* showed that a daily dose of 1000 mg NR leads to a 2.7-fold rise in blood NAD+ after one dose of NR (24). Another clinical study demonstrated that daily doses of NR up to 1000 mg are well tolerated and efficient to increase NAD+ levels by almost 60% in peripheral blood mononuclear cells (25). Irie *et al* conducted a human study regarding the safety of a single oral NMN dose (100, 250 or 500 mg) in healthy Japanese men by investigating the pharmacokinetics of NMN metabolites for 5 h after each intervention and found that NMN supplementation is safe without causing any significant deleterious effects (27).

4. NAD+ and diseases

Multiple studies strongly confirm that deficiencies in NAD+ levels can lead to degenerative diseases and multiple pathologies such as metabolic disorders, heart and renal diseases, cognitive impairment and even cancer (28,29).

In the past few years, research on the biology of NAD+ has provided many critical insights into the pathogenesis of age-associated functional decline (30).

Studies on rodents have demonstrated that under normal and pathophysiological conditions, systemic NMN administration enhanced NAD+ biosynthesis in various peripheral tissues

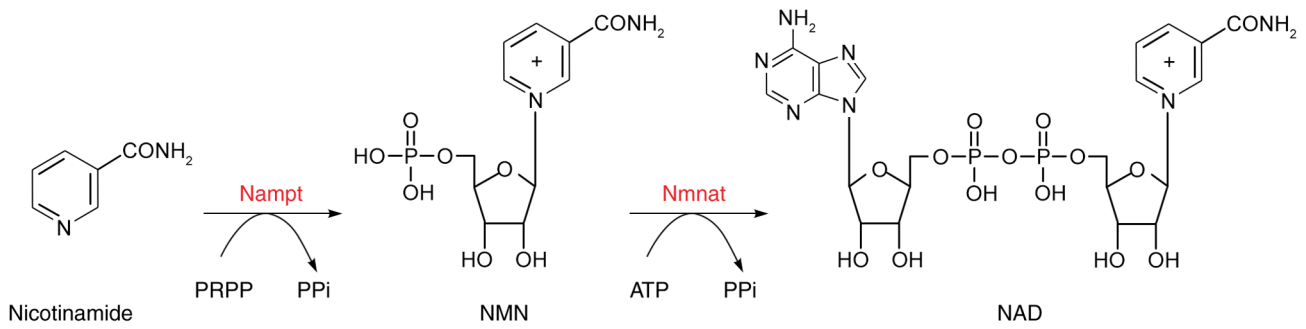

Figure 1. Reactions involved in NAD+ synthesis through the salvage pathway. NAD+, nicotinamide adenine dinucleotide; NMN, nicotinamide mononucleotide; PPi, inorganic pyrophosphate; PRPP, phosphoribosyl pyrophosphate; Nampt, nicotinamide phosphoribosyltransferase; Nmnat, nicotinamide mononucleotide adenylyltransferase; ATP, Adenosine triphosphate.

such as the pancreas, liver and white adipose tissue of diabetic mice (21), heart (31,32), skeletal muscle (33), kidney (34,35), eyes (36) and blood vessels (37,38). Recent studies on mouse and rat models suggest that NMN improves the neuronal function with visible benefits on cognition and memory (39-41).

NR is also a direct factor involved in NAD+ metabolism with a recognized efficacy in metabolic and skeleton-muscular disorders. Similar to NMN, NR also exhibits protective effects against aging and age-related diseases, improves liver health and protects against diabetic and chemotherapy induced neuropathy (42).

In the past few years, metabolic syndrome has become a global health concern due to its critical risk in regards to the development of various life-threatening conditions such as cardiovascular disease, stroke and cancer (43). Obesity, diabetes, dyslipidemia, fatty liver and hypertension are common diseases linked with the metabolic syndrome and are closely associated with impaired nutrient status and lifestyle (44). A number of studies have demonstrated that NAD+ levels decline with aberrant nutritional status and its prevention is regarded as a promising strategy with which to combat metabolic disorders (18). Administration of NMN and NR can ameliorate diet-associated weight gain, dietary intervention, their use being a promising treatment against obesity (45). In addition, the administration of NR in mice was found to increase fatty acid oxidation and energy expenditure and also to improve insulin sensitivity (45). On other hand, studies on various diabetic rodent models, have revealed that NAM administration ameliorates hyperglycemia by increasing β-cell proliferation (46).

Recent studies indicate that NAD+ is involved in tumor cell progression being considered a promising therapeutic target for cancer (47-49). NAD+-metabolizing enzymes play an important role in conditioning several aspects of cancer and immune cell fate and functions (50). Cancer cells display a unique energy metabolism and the continuous replenishment of NAD+ promotes the proliferation and survival of fast-dividing cancer cells as elevated NAD+ levels enhance anaerobic glycolysis (51). Increased intracellular NAD+ levels accompanied by overexpression of NAD+ salvage biosynthesis pathway enzymes sustain tumor cell proliferation and promote survival against anticancer cell agents (52).

Overexpression of Nampt is frequently observed in several types of malignant tumors, for example, breast, colorectal, gastric, ovarian, prostate cancers, and malignant lymphomas (48,52). A recent study showed that high expression of Nampt and Naprt predicts a poor prognosis in colorectal cancer and was associated with vascular invasion. This finding suggests that these two enzymes of the NAD+ salvage synthesis pathway may be novel markers for the diagnosis and treatment of colorectal cancer (53).

5. NAD+ in normal and abnormal function of the retina

The retina is a highly organized eye structure, light-sensitive, intensively innervated and vascularized. It consists of numerous cell types that function in a coordinated manner to give rise to a signal transmitted to the brain. To create an image, light photons are sensed by the retinal receptors and the signal from the photoreceptors is then transmitted to secondary neurons before being transmitted to the retinal ganglion cells. Retinal photoreceptor death is a common cause of blindness in retinal degenerative diseases (54-56).

Retinal degenerative diseases are a major cause of morbidity because visual impairment significantly decreases the quality of life of patients. These have different etiologies, being either acquired, clinical manifestation of a systemic problem or inherited (54).

Despite their diversity, these diseases focus on the death of photoreceptors. The huge metabolic and energetic requirements of the retinal photoreceptors and their progressive impairment in various retinal degenerative diseases have been for a long time the subject of research.

Given the key metabolic role of NAD+ and the high metabolism in photoreceptor cells, there is a growing interest in debating the role of the 'NADome' in controlling retinal metabolism and mediating the pathogenesis of retinal degeneration.

The involvement of NAD+ biosynthesis pathways in retinal photoreceptor dysfunction has been previously investigated. The mutation of Nmnat1, one of the key enzymes involved in NAD+ biosynthesis, was identified as a cause of a childhood blinding disease (57). Rodent studies that replicated this mutation showed the same alterations (for example, rapidly photoreceptor degeneration, retinal pigment epithelial cell loss, retinal vasculature attenuation) and confirm its importance for retinal survival (58).

Data reported by Kaja and colleagues showed that altered circulating levels of Nampt were also significantly associated with risk for retinal vein occlusion, ischemia and metabolic

alteration (59). Other studies confirmed the relevance of Nampt for retinal function proving its importance for maintenance of functional retinal pigment epithelial and endothelial cells. For example, inhibition of Nampt with pharmacological inhibitors or deficits in NAD^+ bioavailability promoted an early senescent phenotype in these cells (60,61).

NAD^+ metabolism is also important for cell longevity. Age-dependent decline in NAD^+ levels reported for multiple human organs has been demonstrated to occur also in the retina, especially in photoreceptor, ganglion, endothelial, and retinal pigment epithelial cells (62). That is why extensive research has focused on the role of NAD^+ as a modulator of sirtuin activity, known that sirtuins play important roles in the retina, confer protection against oxidative stress and retinal degeneration being able to increase lifespan (63). All seven mammal sirtuins (SRT1-SRT7) are highly expressed in the mouse retina (64) and could enhance retinal metabolism, reduce photoreceptor death, and improve vision.

Given the roles of sirtuins in retinal function, pharmacological modulation of sirtuin activation may be a therapeutic strategy for preventing retinal degeneration. The supply with NAD^+ precursors, such as NMN and NR, represent an interesting approach to this condition. In a mouse model of light-induced acute retinal degeneration, Zhang and colleagues found that NR treatment prevented NAD^+ diminution following toxic light exposure (65). Maintenance of NAD^+ levels allowed continued activity of enzymes for which NAD^+ is a substrate, for example mitochondrial sirtuins, on which optimal activity relies NAD^+-dependent retinal homeostasis (66). Supplementation with these precursors was found to lead to increased intracellular NAD^+ bioavailability and enhanced sirtuin function, especially in contexts of cellular stress when NAD^+ requirements may be increased and have been shown to be critical to retinal health. Further studies are important to ensure the development of new safe and efficient therapeutic strategies.

6. Conclusions

While the first century of NAD^+ research has revealed multiple discoveries which prove that NAD^+ plays a key role in the regulation of cell metabolism, stress and immune responses to physiological or pathological signals, it is widely recognized that additional research is required to fully reveal the complex metabolic fate of the 'NADome' in order to sustain the paramount importance of the supplementation of NAD^+ precursors to promote health and improve therapeutic safety in various diseases, including retinal disturbances.

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Availability of data and materials

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Authors' contributions

ASP, AMA, ECS, IMB, CGP, SJ and RC made equal contributions to the conception and editing of this manuscript. ASP, AMA, ECS, CGP, SJ and RC contributed to the acquisition of the data. ASP, AMA, ECS, CGP, IMB, SJ and RC selected, processed the data acquired and wrote appropriate parts of this manuscript. SJ, RC, CGP and IMB revised its contents. All authors read and approved the final manuscript to be published.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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