Nicotinamide Riboside for Healthy Aging and Longevity

Subjects: Pharmacology & Pharmacy

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Nicotinamide riboside (NR) is widely used as a dietary supplement. Structurally, it is a form of vitamin B_3 (nicotinic acid, niacin, NA), incorporating into its structure more elements of nicotinamide adenine dinucleotide (in its oxidized form, NAD^+). NR influences, in particular, energy metabolism and neuroprotection.

nicotinamide riboside | vitamin B3 derivative | efficacy

1. Nicotinamide Riboside for Healthy Aging

NAD^+ metabolism and homeostasis are important in aging and disease [1][2]. Declining NAD^+ levels induce the augmentation of hypoxia-inducible factor-1alpha (HIF-1α) and a pseudohypoxic state disrupting PGC-1α/-1β-independent nuclear–MT communication during aging [3].

Thus, in recent preclinical studies, managing NAD^+ deficits with NAM, NA, NR, and NMN provided healthy aging [4]. In the Caco-2 cell line and NIAAA mouse model, NAD^+ supplementation by NR alleviated intestinal barrier injury induced by ethanol via protecting epithelial MT function [5]. NRS increased the formation of human leukocytes from hCD34+ progenitors in the immunodeficient mice model. Thus, through increased MT clearance, NR potently stimulated the hematopoiesis [6] and the lymphoid potential of $Atm^{-/-}$ and old mice HSCs [7][8]. Moreover, NMN can be used to activate SIRT1 and improve the pathophysiology of diet- and age-induced diabetes in mice [9].

Likewise, reduced NMN is a newly analyzed and potent NAD^+ precursor in mammalian cells and mice blood and internal organs [10]. In randomized, double-blind, PLA-controlled clinical trials in healthy middle-aged and older adults, chronic NRS (500 mg twice daily) is safe and well tolerated, and it is recommended for (i) increasing NAD^+ level [11] and (ii) treating elevated systolic blood pressure (SBP) and arterial stiffness having initial above-normal (120–159 mmHg) SBP [12].

In aging and disease, a close connection relates NAD^+ levels and the activation of SIRTs, as seen in murine models: (i) NR alleviates CPT-induced peripheral neuropathy (CIPN) and neuronal death via SIRT2 activation and enhancement of nucleotide excision repair in Lewis lung carcinoma model [13]; (ii) SIRT3 is required for regeneration of WT or mutant liver but not for the beneficial effect of NR [14]; (iii) SIRT3 deficiency aggravates contrast-induced acute kidney injury (CIAKI) in vitro (HK-2 cells) and in vivo (WT and SIRT3 KO mice) [15]; (iv) NR

attenuates inflammation and OXS by activation of SIRT1 and normalization of NAD^+/NADH ratio in alcohol-stimulated RAW 264.7 macrophages and in mouse bone marrow-derived macrophages [16].

NRS could be a missing piece in the puzzle of exercise therapy for older adults. Short-term oral NR treatment, 300 mg/kg or 600 mg/kg daily, improves muscle quality and function in middle-aged male C57BL/6J mice and increases cellular energetics and differentiating capacity of myogenic progenitors [17]. A randomized, PLA-controlled trial of safe and well-tolerated daily NRPT supplementation (1 g NR and 0.2 g PT) improved skeletal muscle regeneration after experimental muscle injury in 23 elderly individuals (55–80 years) [18]. Moreover, in a double-blind, crossover study, acute NRS improved redox homeostasis and exercise performance in 12 old individuals compared with the same number of young men [19].

Recent studies have highlighted that senotherapeutic NRS could contribute to healthy aging and longevity. As a sample of results: (i) the effects of senolytic drugs, including NR, were tested on human mesenchymal stromal cells (MSCs) with no significant action on molecular markers for replicative senescence [20]; (ii) the senotherapeutic NR triflate improved the NAD^+ levels of buffy coat-derived platelet concentrates, but cannot prevent storage lesion for 23 days [21]; (iii) 17-α-estradiol late in life extends lifespan in aging UM-HET3 heterogeneous male mice, but NRS does not affect lifespan in either sex [22].

In this regard, NAD^+ supplementation (NR, NAM, NA) exhibited emerging roles in replicative and chronological aging in fungi and mammals. For example: (i) *Saccharomyces cerevisiae YOR071C* gene encodes the high-affinity NR transporter Nrt1 polypeptide [23]; (ii) *S. cerevisiae* unicellular organism probably represents one of the most recognized experimental aging models for the study of replicative lifespan (RLS, proliferating cells) and chronological lifespan (CLS, non-proliferating cells) [24][25][26].

2. Brain Aging, Cognitive Impairment, and Neurodegenerative Diseases

Supplements of NAD^+ precursors (NR, NRH, NMN) are a potential way to prevent cognitive decline within aging-associated diseases, such as neurodegenerative disorders [27][28][29]. For example, in models of murine dementia, NRS decreased neuroinflammation, DNA damage, and apoptosis while contributing to maintaining synaptic plasticity, integrity of the blood–brain barrier (BBB), and gut microbiota functionality. It also improved hippocampal synaptic plasticity, learning, and memory in AD. Aβ forming in the brain can be prevented by NRS partly through the upregulation of ubiquitination and proteasomal degradation of PGC-1α-mediated beta-secretase 1 (BACE1) [30] [31].

These studies have extended for over a decade. For example, in Tg2576 mice, NR dietary supplementation (250 mg/kg/day) for three months significantly alleviated cognitive damage, increased the NAD^+/NADH ratio in the cerebral cortex, and reduced Aβ production [32]. A further study examines DNA repair-deficient 3xTgAD/Polβ$^{+/-}$ mice that exhibited cognitive impairment, synaptic dysfunction, phosphorylated *tau* (p-*tau*) pathologies, and neuronal death, the main characteristics of human AD. Here, NRS decreased neuroinflammation, DNA damage,

and hippocampal neurons' apoptosis, increased SIRT3 activity in the brain, improved cognitive function, and restored hippocampal synaptic plasticity [33]. NRS (2.5 g/kg in food for three months) in APP/PS1 transgenic AD and aged mice inhibited serum NAMPT elevation, astrocyte activation, neuroinflammation, senescence, Aβ accumulation, and astrocyte migration to Aβ, as well as improving locomotor activity, cognitive function, behavior, and dementia progression [34][35]. Inhibition of CD38 and NRS alleviated LPS-induced microglial and astrocytic neuroinflammation/neurodegeneration by increasing NAD^+ levels in mice brains and by suppressing the NF-κB signaling pathway at the microglia level [36]. In APP/PS1 transgenic (AD) mice, NRS for eight weeks normalized gut dysbiosis for *Adlercreutzia*, *Akkermansia*, *Bacteroides*, *Bifidobacterium*, *Butyricicoccus*, *Desulfovibrio*, *Lactobacillus*, *Olsenella*, and *Oscillospira* microbiota species [37]. In late-onset AD patients, NR and caffeine co-administration partially restores diminished NAD^+ availability but does not alter bioenergetic metabolism [38]. In a randomized, double-blinded, PLA-controlled, phase II clinical trial, combined metabolic activators (CMAs) administered in a single dose during the first 28 days and twice daily between days 28 and 84 significantly increased the cognitive capacity and alleviated NAD^+ plasma levels and GSH metabolism of AD patients. CMA complex included 12.35 g L-serine (61.75%), 3.73 g L-carnitine tartrate (18.65%), 2.55 g *N*-acetyl-L-cysteine (12.75%), and 1 g NR (5%) [39].

NR food supplementation for 28 days rescues Ang II-induced cerebral small vessel disease (CSVD) in C57BL/6 mice. NRS significantly reduced glial activation, neuroinflammation, and white matter injury that is associated with cognitive dysfunction. It also supported BBB integrity and vascular remodeling, and improved Ang II-induced CSVD [40].

Further, treatment with NAD^+ precursor NRS rescues MT defects in induced pluripotent stem cells (iPSCs) and aging-associated dopaminergic neuronal loss and motor decline and *Drosophila* models of glucocerebrosidase (GBA)-related Parkinson's disease (PD) [41]. In a randomized, PLA-controlled, phase I clinical trial in 30 newly diagnosed, treatment-naïve PD patients (NADPARK study), oral NRS 1 g for 30 days significantly increased the level of NAD^+ and its related metabolites in the CSF and decreased the inflammatory cytokines amounts also in serum and CSF [42]. In a recent randomized, PLA-controlled crossover trial in 22 healthy older adults using oral NRS (500 mg, twice daily, six weeks), the levels of NAD^+ in neuronal-origin enriched plasma extracellular vesicles (NEVs) were increased, and levels of kinases (Aβ42, pJNK, pERK1/2) implicated in neuroinflammation and insulin resistance pathways were inhibited [43]. Moreover, in a double-blind, PLA-controlled trial of 29 PD patients, including cases with common pathogenic mutations in the methylenetetrahydrofolate reductase (*MTHFR*) gene, it was found that high-dose NRS for 30 days was not associated with altered DNA methylation homeostasis [44].

3. Aging and Cancer

NAD^+ metabolism is a major feature of cancer pathogenesis (tumorigenesis), being closely related to genome integrity provided by efficient redox homeostasis, MT metabolism, and signal transduction [45]. The anti-tumoral effect of NR was studied in experimental models of hepatocellular carcinoma (HCC), such as the subcutaneous transplantation of tumors in Balb/c nude mice (xenograft) and C57BL/6J mice (allograft) and hematogenous metastatic tumor in nude mice. Daily administration of NR (400 mg/kg) by oral gavage extended the overall survival

of HCC mice and decreased the size of allografted tumors and lung, liver, and bone metastases. Also, in vitro TGF-β-induced migration/invasion of HepG2 cells was inhibited by NRS [46].

In a mouse model of C26 adenocarcinoma, NR pellet dietary supplementation significantly improved cancer cachexia and inflammation through the inhibition of specific molecular markers, such as IL-6, TNF-α, PCG-1α, and muscle-specific ubiquitin-proteasome ligases (e.g., mitofusin-2, atrogin-1, muscle RING-finger protein-1 (MuRF-1)) [47]. Oral administration of 200 mg/kg NR in female tumor-bearing rats in a preclinical model of mammary gland cancer induced by *N*-methyl-nitrosourea (MNU) and previously treated with PTX i.v. injections (three doses of 6.6 mg/kg) led to a decrease in tumor growth and the Ki67 index of tumoral cells and to an improvement in peripheral neuropathy symptoms [48]. In high-risk skin cancer patients, boosting NAD^+ with NR, MNM, and NAM p.o. supplements decreased the incidence of keratinocyte carcinoma. This presumably occurred through its cellular protective effects, mainly targeting DNA repair and prevention of possible activation of oncogenic mutations [49].

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